2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Heart Failure Society of America

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Preamble

Since 1980, the American College of Cardiology (ACC) and American Heart Association (AHA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cardiovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a cornerstone for quality cardiovascular care. The ACC and AHA sponsor the development and publication of guidelines without commercial support, and members of each organization volunteer their time to the writing and review efforts. Guidelines are official policy of the ACC and AHA.

Intended Use

Practice guidelines provide recommendations applicable to patients with or at risk of developing cardiovascular disease. The focus is on medical practice in the United States, but guidelines developed in collaboration with other organizations may have a global impact. Although guidelines may be used to inform regulatory or payer decisions, their intent is to improve patients' quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances and should not replace clinical judgment.

Clinical Implementation

Guideline-recommended management is effective only when followed by healthcare providers and patients. Adherence to recommendations can be enhanced by shared decision-making between healthcare providers and patients, with patient engagement in selecting interventions based on individual values, preferences, and associated conditions and comorbidities.

Methodology and Modernization

The ACC/AHA Task Force on Clinical Practice Guidelines (Task Force) continuously reviews, updates, and modifies guideline methodology on the basis of published standards from organizations including the Institute of Medicine (1, 2) and on the basis of internal reevaluation. Similarly, the presentation and delivery of guidelines are reevaluated and modified on the basis of evolving technologies and other factors to facilitate optimal dissemination of information at the point of care to healthcare professionals.

Toward this goal, this guideline heralds the introduction of an evolved format of presenting guideline recommendations and associated text called the "modular knowledge chunk format". Each modular "chunk" includes a table of related recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. References are provided within the modular chunk itself to facilitate quick review. This format also will facilitate seamless updating of guidelines with focused updates as new evidence is published, and content tagging for rapid electronic retrieval of related recommendations on a topic of interest. This evolved format was instituted when this guideline was near completion; therefore, the current document represents a transitional formatting that best suits the text as written. Future guidelines will fully implement this format, including provisions for limiting the amount of text in a guideline.

Recognizing the importance of cost–value considerations in certain guidelines, when appropriate and feasible, an analysis of the value of a medication, device, or intervention may be performed in accordance with the ACC/AHA methodology (3).

To ensure that guideline recommendations remain current, new data are reviewed on an ongoing basis, with full guideline revisions commissioned in approximately 6-year cycles. Publication of new,

potentially practice-changing study results that are relevant to an existing or new medication, device, or management strategy will prompt evaluation by the Task Force, in consultation with the relevant guideline writing committee, to determine whether a focused update should be commissioned. For additional information and policies regarding guideline development, we encourage readers to consult the ACC/AHA guideline methodology manual (4) and other methodology articles (5-8).

Selection of Writing Committee Members

The Task Force strives to avoid bias by selecting experts from a broad array of backgrounds. Writing committee members represent different geographic regions, sexes, ethnicities, races, intellectual perspectives/biases, and scopes of clinical practice. The Task Force may also invite organizations and professional societies with related interests and expertise to participate as partners, collaborators, or endorsers.

Relationships With Industry and Other Entities

The ACC and AHA have rigorous policies and methods to ensure that guidelines are developed without bias or improper influence. The complete relationships with industry and other entities (RWI) policy can be found online http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/relationships-with-industry-policy. Appendix 1 of the current document lists writing committee members' relevant RWI. For the purposes of full transparency, writing committee members' comprehensive disclosure information is available online (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000549/-/DC1), as is the comprehensive disclosure information for the Task Force http://www.acc.org/guidelines/about-guidelines-and-clinical-documents/guidelines-and-documents-task-forces.

Evidence Review and Evidence Review Committees

When developing recommendations, the writing committee uses evidence-based methodologies that are based on all available data (4-7). Literature searches focus on randomized controlled trials (RCTs) but also include registries, nonrandomized comparative and descriptive studies, case series, cohort studies, systematic reviews, and expert opinion. Only key references are cited.

An independent evidence review committee (ERC) is commissioned when there are ≥1 questions deemed of utmost clinical importance that merit formal systematic review. This systematic review will strive to determine which patients are most likely to benefit from a test, medication, device, or treatment strategy and to what degree. Criteria for commissioning an ERC and formal systematic review include: a) the absence of a current authoritative systematic review; b) the feasibility of defining the benefit and risk in a time frame consistent with the writing of a guideline; c) the relevance to a substantial number of patients; and d) the likelihood that the findings can be translated into actionable recommendations. ERC members may include methodologists, epidemiologists, healthcare providers, and biostatisticians. When a formal systematic review has been commissioned, the recommendations developed by the writing committee on the basis of the systematic review are marked with "SR".

Guideline-Directed Management and Therapy

The term *guideline-directed management and therapy* (GDMT) encompasses clinical evaluation, diagnostic testing, and pharmacological and procedural treatments. For these and all recommended medication treatment regimens, the reader should confirm the dosage by reviewing product insert material and evaluate

the treatment regimen for contraindications and interactions. The recommendations are limited to medications, devices, and treatments approved for clinical use in the United States.

Class of Recommendation and Level of Evidence

The Class of Recommendation (COR) indicates the strength of the recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to risk. The Level of Evidence (LOE) rates the quality of scientific evidence that supports the intervention on the basis of the type, quantity, and consistency of data from clinical trials and other sources (Table 1) (4, 6, 8).

Glenn N. Levine, MD, FACC, FAHA
Chair, ACC/AHA Task Force on Clinical Practice Guidelines

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Table 1. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — **Benefit >>> Risk**

Suggested phrases for writing recommendations:
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) — **Benefit >> Risk**

Suggested phrases for writing recommendations:
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) — **Benefit ≥ Risk**

Suggested phrases for writing recommendations:
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well established

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

Suggested phrases for writing recommendations:
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

CLASS III: Harm (STRONG) — **Risk > Benefit**

Suggested phrases for writing recommendations:
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE‡

LEVEL A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

LEVEL B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

LEVEL B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

LEVEL C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

1. Introduction

1.1. Methodology and Evidence Review

The recommendations listed in this clinical practice guideline are, whenever possible, evidence-based. An initial extensive evidence review, which included literature derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline, was conducted from April 2016 to September 2016. Key search words included, but were not limited, to the following: sudden cardiac death, ventricular tachycardia, ventricular fibrillation, premature ventricular contractions, implantable cardioverter-defibrillator, subcutaneous implantable cardioverter-defibrillator, wearable cardioverter-defibrillator, and catheter ablation. Additional relevant studies published through March 2017, during the guideline writing process, were also considered by the writing committee, and added to the evidence tables when appropriate. The final evidence tables are included in the Online Data Supplement (http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000549/-/DC2) and summarize the evidence used by the writing committee to formulate recommendations. Additionally, the writing committee reviewed documents related to ventricular arrhythmias (VA) and sudden cardiac death (SCD) previously published by the ACC, AHA, and the Heart Rhythm Society (HRS). References selected and published in this document are representative and not all-inclusive.

As noted in the Preamble, an independent ERC was commissioned to perform a formal systematic review of 2 important clinical questions for which clear literature and prior guideline consensus were felt to be lacking or limited (Table 2). The results of the ERC review were considered by the writing committee for incorporation into this guideline. Concurrent with this process, writing committee members evaluated other published data relevant to the guideline. The findings of the ERC and the writing committee members were formally presented and discussed, then guideline recommendations were developed. The "Systematic Review for the 2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death" is published in conjunction with this guideline (1).

Table 2. Systematic Review Questions on SCD Prevention

Question Number	Question	Section Number
1	For asymptomatic patients with Brugada syndrome, what is the association between an abnormal programmed ventricular stimulation study and SCD and other arrhythmia endpoints?	7.9.1.3
2	What is the impact of ICD implantation for primary prevention in older patients and patients with significant comorbidities?	9.3

ICD indicates implantable cardioverter-defibrillator; and SCD, sudden cardiac death.

The ACC and AHA have acknowledged the importance of value in health care and have called for eventual development of a Level of Value for clinical practice recommendations (2). Available cost-effectiveness data were determined to be sufficient to support 2 specific recommendations in this guideline (see Sections 7.1.1 and 7.1.2). As a result, a Level of Value was assigned to those 2 recommendations on the basis of the "ACC/AHA Statement on Cost/Value Methodology in Clinical Practice Guidelines and Performance Measures," as shown in Table 3 (2). Available quality of life (QoL) data were deemed to be insufficient to support specific recommendations in this guideline.

Table 3. Proposed Integration of Level of Value Into Clinical Practice Guideline Recommendations*

Level of Value
High value: Better outcomes at lower cost or ICER <$50,000 per QALY gained **Intermediate value:** $50,000 to <$150,000 per QALY gained **Low value:** ≥$150,000 per QALY gained **Uncertain value:** Value examined but data are insufficient to draw a conclusion because of no studies, low-quality studies, conflicting studies, or prior studies that are no longer relevant **Not assessed:** Value not assessed by the writing committee
Proposed abbreviations for each value recommendation: *Level of Value: H to indicate high value; I, intermediate value; L, low value; U, uncertain value; and NA, value not assessed*

*Dollar amounts used in this table are based on U.S. GDP data from 2012 and were obtained from WHO-CHOICE Cost-Effectiveness Thresholds (3).
GDP indicates gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years; and WHO-CHOICE, World Health Organization Choosing Interventions that are Cost-Effective.
Reproduced from Anderson, et al. (2).

1.2. Organization of the Writing Committee

The writing committee consisted of cardiac electrophysiologists (including those specialized in pediatrics), general adult and pediatric cardiologists (including those specialized in critical care and acute coronary syndromes [ACS], genetic cardiology, heart failure, and cost-effectiveness analyses), a geriatrician with expertise in terminal care and shared decision-making, and a lay representative, in addition to representatives from the ACC, AHA, HRS, and the Heart Failure Society of America (HFSA).

1.3. Document Review and Approval

This document was reviewed by 2 official reviewers nominated by the ACC, AHA, and HRS; 1 official lay reviewer nominated by the AHA; 1 organizational reviewer nominated by the HFSA; and 28 individual content reviewers. Reviewers' RWI information was distributed to the writing committee and is published in this document (Appendix 2).

This document was approved for publication by the governing bodies of the ACC, the AHA, and the HRS; and endorsed by the HFSA.

1.4. Scope of the Guideline

The purpose of this AHA/ACC/HRS document is to provide a contemporary guideline for the management of adults who have VA or who are at risk for SCD, including diseases and syndromes associated with a risk of SCD from VA. This guideline supersedes the "ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death" (4). It also supersedes some sections of the "ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities" (5), specifically those sections on indications for the implantable cardioverter-defibrillator (ICD); and, it updates the SCD prevention recommendations in the "2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy" (6). Some recommendations from the earlier guidelines have been updated as warranted by new evidence or a better understanding of existing evidence, and irrelevant or overlapping recommendations were deleted or modified.

In the current guideline, sudden cardiac arrest (SCA) is defined as the "sudden cessation of cardiac activity so that the victim becomes unresponsive, with no normal breathing and no signs of circulation" (7). If corrective measures are not taken rapidly, this condition progresses to SCD. Cardiac arrest is used to signify

an event that can be reversed, usually by cardiopulmonary resuscitation (CPR), administration of medications and/or defibrillation or cardioversion. SCA and SCD can result from causes other than VA, such as bradyarrhythmias, electromechanical dissociation, pulmonary embolism, intracranial hemorrhage, and aortic dissection; however, the scope of this document includes only SCA and SCD due to VA.

This guideline includes indications for ICDs for the treatment of VA and prevention of SCD, but it does not delve into details on individual device selection and programming, including considerations relevant to cardiac resynchronization therapy (CRT), bradycardia pacing, and hemodynamic monitoring. These important aspects of ICD management have been covered in an HRS expert consensus statement (8). An AHA science advisory discusses the use of wearable cardioverter-defibrillators (9). The findings of that document were reviewed; however, recommendations on this topic were developed independently of that document. This guideline includes indications for catheter ablation of VA, but does not provide recommendations on specific techniques or ablation technologies, which were beyond the scope of this document.

Recommendations for interventional therapies, including ablation and the implantation of devices, apply only if these therapies can be implemented by qualified clinicians, such that outcomes consistent with published literature are a reasonable expectation. The writing committee agreed that a high degree of expertise was particularly important for performance of catheter ablation of VA, and this point is further emphasized in relevant sections. In addition, all recommendations related to ICDs require that meaningful survival of >1 year is expected; meaningful survival means that a patient has a reasonable quality of life and functional status.

Although this document is aimed at the adult population (≥18 years of age) and offers no specific recommendations for pediatric patients, some of the literature on pediatric patients was examined. In some cases, the data from pediatric patients beyond infancy helped to inform this guideline.

The writing committee recognized the importance of shared decision-making and patient-centered care and, when possible, it endeavored to formulate recommendations relevant to these important concepts. The importance of a shared decision-making process in which the patient, family, and clinicians discuss risks and benefits of diagnostic and treatment options and consider the patients' personal preferences is emphasized (see Section 15).

In developing this guideline, the writing committee reviewed previously published guidelines and related statements. Table 4 contains a list of guidelines and statements deemed pertinent to this writing effort and is intended for use as a resource, obviating repetition of existing guideline recommendations.

Table 4. Associated Guidelines and Statements

Title	Organization	Publication Year (Reference)
Guidelines		
Syncope	ACC/AHA/HRS	2017 (10)
Heart failure	ACCF/AHA	2017 (11) 2016 (12), and 2013 (13)
Valvular heart disease	AHA/ACC	2017 (14) and 2014 (15)
Supraventricular tachycardia	ACC/AHA/HRS	2015 (16)
Ventricular arrhythmias and the prevention of sudden cardiac death	ESC	2015 (17)
Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care	AHA	2015 (18)
Atrial fibrillation	AHA/ACC/HRS	2014 (19)
Non–ST-elevation acute coronary syndromes	AHA/ACC	2014 (20)
Assessment of cardiovascular risk	ACC/AHA	2013 (21)
ST-elevation myocardial infarction	ACCF/AHA	2013 (22)
Acute myocardial infarction in patients presenting with ST-segment elevation	ESC	2012 (23)
Device-based therapies for cardiac rhythm abnormalities	ACCF/AHA/HRS	2012 (24)
Coronary artery bypass graft surgery	ACCF/AHA	2011 (25)
Hypertrophic cardiomyopathy	ACCF/AHA	2011 (6)
Percutaneous coronary intervention	ACCF/AHA/SCAI	2011 (26)
Secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease	AHA/ACCF	2011 (27)
Scientific Statements		
Wearable cardioverter-defibrillator therapy for the prevention of sudden cardiac death	AHA	2016 (9)
Optimal implantable cardioverter defibrillator programming and testing	HRS/EHRA/APHRS/ SOLAECE	2016 (8)
Treatment of cardiac arrest: current status and future directions: strategies to improve cardiac arrest survival	IOM	2015 (28)
Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities	ACC/AHA	2015 (29)
Ventricular arrhythmias	EHRA/HRS/APHRS	2014 (30)
Arrhythmias in adult congenital heart disease	PACES/HRS	2014 (31)
Implantable cardioverter-defibrillator therapy in patients who are not included or not well represented in clinical trials	HRS/ACC/AHA	2014 (32)
Cardiac sarcoidosis	HRS	2014 (33)
Inherited primary arrhythmia syndromes	HRS/EHRA/APHRS	2013 (34)

ACC indicates American College of Cardiology; ACCF, American College of Cardiology Foundation; AHA, American Heart Association; APHRS, Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; ESC, European Society of Cardiology; HRS, Heart Rhythm Society; PACES, Pediatric and Congenital Electrophysiology Society; SCAI, Society for Cardiovascular Angiography and Interventions; and, SOLAECE, Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia.

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1.5. Abbreviations

Abbreviation	Meaning/Phrase
ACS	acute coronary syndromes
AED	automated external defibrillator
AMI	acute myocardial infarction
BNP	B-type natriuretic peptide
CABG	coronary artery bypass graft
CKD	chronic kidney disease
CPR	cardiopulmonary resuscitation
CRT	cardiac resynchronization therapy
CT	computed tomography
ECG	electrocardiogram
ERC	evidence review committee
ESRD	end-stage renal disease
GDMT	guideline-directed management and therapy
HCM	hypertrophic cardiomyopathy
HF	heart failure
HF*p*EF	heart failure with preserved ejection fraction
HF*r*EF	heart failure with reduced ejection fraction
ICD	implantable cardioverter-defibrillator
LV	left ventricular
LVAD	left ventricular assist device
LVEF	left ventricular ejection fraction
MI	myocardial infarction
NICM	nonischemic cardiomyopathy
NSVT	nonsustained ventricular tachycardia
PET	positron emission tomography
PCI	percutaneous coronary intervention
PVC	premature ventricular complex
QoL	quality of life
RCT	randomized controlled trial
RV	right ventricular
RVOT	right ventricular outflow tract
SCA	sudden cardiac arrest
SCD	sudden cardiac death
SVT	supraventricular tachycardia
TOF	tetralogy of Fallot
VA	ventricular arrhythmia
VT	ventricular tachycardia

2. Epidemiology

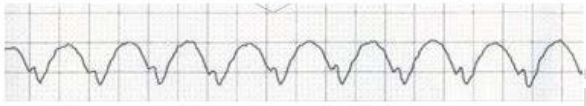
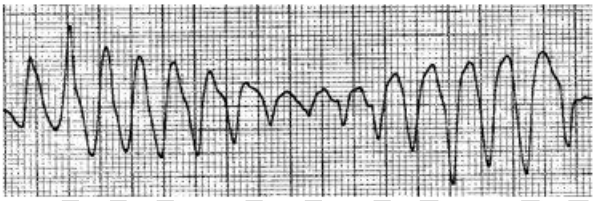
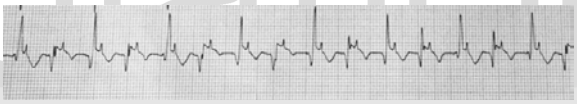
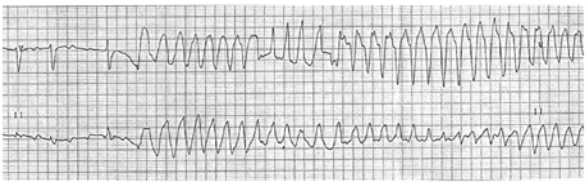
2.1. General Concepts

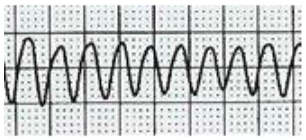
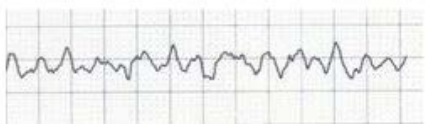
Table 5

VA include a spectrum that ranges from premature ventricular complex (PVC) to ventricular fibrillation (VF), with a clinical presentation that ranges from a total lack of symptoms to cardiac arrest. Most life-threatening

VA are associated with ischemic heart disease, particularly in older patients (1). The risks of VA and SCD vary in specific populations with different underlying cardiac conditions, and with specific family history and genetic variants, and this variation has important implications for studying and applying therapies.

Table 5. Table of Definitions of Commonly Used Terms in this Document

Term	Definition or Description
Ventricular tachycardia (2)	Cardiac arrhythmia of ≥3 consecutive complexes originating in the ventricles at a rate >100 bpm (cycle length: <600 ms). Types of VT: ● Sustained: VT >30 s or requiring termination due to hemodynamic compromise in <30 s. ● Nonsustained/unsustained: ≥3 beats, terminating spontaneously. ● Monomorphic: Stable single QRS morphology from beat to beat. ● Polymorphic: Changing or multiform QRS morphology from beat to beat. ● Bidirectional: VT with a beat-to-beat alternation in the QRS frontal plane axis, often seen in the setting of digitalis toxicity or catecholaminergic polymorphic VT Monomorphic VT  Polymorphic VT  Bidirectional VT 
Torsades de pointes (2)	Torsades de pointes is polymorphic VT that occurs in the setting of a long-QT interval and is characterized by a waxing and waning QRS amplitude. It often has a long-short initiating sequence with a long coupling interval to the first VT beat and may present with salvos of NSVT. The twisting of the points, although characteristic, may not always be seen, especially if the episode is nonsustained or if only a limited number of leads are available. Torsades de pointes can result from bradycardia including high-grade AV block that leads to a long-short sequence initiating torsades de pointes. 
Ventricular flutter (2)	A regular VA ≈300 bpm (cycle length: 200 ms) with a sinusoidal, monomorphic appearance; no isoelectric interval between successive QRS complexes.

	
Ventricular fibrillation (2)	Rapid, grossly irregular electrical activity with marked variability in electrocardiographic waveform, ventricular rate usually >300 bpm (cycle length: <200 ms). 
Sudden cardiac arrest (2)	SCA is the sudden cessation of cardiac activity such that the victim becomes unresponsive, with either persisting gasping respirations or absence of any respiratory movements, and no signs of circulation as manifest by the absence of a perceptible pulse. An arrest is presumed to be of cardiac etiology unless it is known or likely to have been caused by trauma, drowning, respiratory failure or asphyxia, electrocution, drug overdose, or any other noncardiac cause.
Sudden cardiac death (2)	Sudden and unexpected death occurring within an hour of the onset of symptoms, or occurring in patients found dead within 24 h of being asymptomatic and presumably due to a cardiac arrhythmia or hemodynamic catastrophe.
VT/VF storm (3)	VT/VF storm (electrical storm or arrhythmic storm) refers to a state of cardiac electrical instability that is defined by ≥3 episodes of sustained VT, VF, or appropriate shocks from an ICD within 24 h.
Primary prevention ICD (2)	ICD placement with the intention of preventing SCD in a patient who has not had sustained VT or SCA but who is at an increased risk for these events.
Secondary prevention ICD (2)	ICD placement in a patient with prior SCA, sustained VT, or syncope caused by VA.
Structural heart disease*	This term encompasses IHD, all types of cardiomyopathy, valvular heart disease, and adult congenital heart disease.
Cardiac channelopathy (4)	Arrhythmogenic disease due to a genetic abnormality that results in dysfunction of a cardiac ion channel (e.g., long-QT syndrome, catecholaminergic polymorphic VT).

*The definition of this term may differ across publications. Refer to the entry for the definition used in this document.
AV indicates atrioventricular; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; NSVT, nonsustained ventricular tachycardia; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; VF, ventricular fibrillation; and VT, ventricular tachycardia.

2.1.1. Premature Ventricular Complexes and Nonsustained VT

PVCs are common and increase in frequency with age. Although PVCs were found in a healthy military population in only 0.6% of those <20 years of age and 2.7% of those >50 years of age (5) on 12-lead ECGs, longer term monitoring shows PVCs in about 50% of all people with or without heart disease (6). The presence of PVCs on 2 minutes of monitoring of middle-aged patients in the ARIC (Atherosclerosis Risk In Communities) study was associated with increased risk of both ischemic heart disease events and mortality, with or without prevalent ischemic heart disease (7, 8). In the general population, frequent PVCs, which are defined as the presence of at least 1 PVC on a 12-lead ECG or >30 PVCs per hour, are associated with increased cardiovascular risk and increased mortality (9). In a study from Taiwan of patients without sustained VT or structural heart disease who had 24-hour Holter monitoring for clinical evaluation, multifocal PVCs were associated with increased risk of death and nonfatal cardiovascular adverse outcomes (10). In the same population, nonsustained ventricular tachycardia (NSVT) was independently associated with increased risk of death and other cardiovascular adverse outcomes, including stroke (11). An association of PVCs with increased risk of stroke was also seen in the ARIC population (8).

Because some studies have shown an association of PVCs with adverse outcomes, the detection of PVCs, particularly if multifocal and frequent, is generally considered a risk factor for adverse cardiovascular outcomes, and such patients are generally evaluated to ensure they do not have underlying conditions (e.g., ischemic heart disease, left ventricular [LV] dysfunction) that warrant further treatment to reduce risk. PVC and NSVT in patients with cardiovascular disease are common and have been associated with adverse outcomes (12, 13). In CAST (Cardiac Arrhythmia Suppression Trials), treatment of patients with post-myocardial infarction (MI) who took antiarrhythmic medications (e.g., flecainide, encainide, moricizine) increased the risk of death despite suppression of VA (14, 15). Treatment of PVCs with antiarrhythmic medications has not been shown to reduce mortality and, in the post- MI population, treatment with class I sodium channel–blocking medications (e.g., quinidine, flecainide) increases the risk of death (15, 16). Likewise, in patients with a reduced LVEF class I, sodium channel–blocking medications and d-sotalol increase the risk of death (16, 17). Beta blockers, nondihydropyridines calcium channel blockers, and some antiarrhythmic medications may relieve symptoms of palpitations (18).

PVCs that occur during an exercise test are associated with a higher risk of death (19). In 1 study, PVCs that occur during recovery are a stronger predictor of death than PVCs occurring only during exercise (20). However, PVCs are common in trained athletes who have palpitations, in whom there does not appear to be increased risk of death based on studies of small numbers of athletes, at least in those without other cardiovascular abnormalities (21, 22). Complex PVCs may not represent a benign finding in endurance athletes. An electrophysiological study may be needed to assess patients' arrhythmogenic risk (22). Very frequent PVCs, >10,000 to 20,000 a day, can be associated with depressed LV function in some patients that is reversible with control of the PVCs, and has been referred to as PVC-induced cardiomyopathy (23, 24). (See also Section 8.5. PVC-Induced Cardiomyopathy.) Very rarely, idiopathic PVCs from the outflow tract may trigger malignant VA in patients without structural heart disease (25, 26).

2.1.2. VT and VF During ACS

Approximately half of patients with out-of-hospital cardiac arrest with the first rhythm identified as VF and who survive to hospital admission have evidence of acute MI (AMI) (27). Of all out-of-hospital cardiac arrests, >50% will have significant coronary artery lesions on acute coronary angiography (27). Of patients hospitalized with AMI, 5% to 10% have VF or sustained VT prior to hospital presentation, and another 5% will have VF or sustained VT after hospital arrival, most within 48 hours of admission. A study of patients with non–ST-elevation ACS who underwent cardiac catheterization within 48 hours found VT/VF in 7.6% of patients, with 60% of those events within 48 hours of admission (28). Accelerated idioventricular rhythm is a common arrhythmia in patients with acute MI, including patients with ST-segment elevation MI undergoing primary percutaneous coronary intervention (PCI). Accelerated idioventricular rhythm is more closely related to the extent of infarction than to reperfusion itself (29).

Sustained VA that occurs in the setting of an ACS is more often polymorphic VT or VF than monomorphic VT. Risk factors for VT/VF include prior history of hypertension, prior MI, ST-segment changes at presentation, and chronic obstructive pulmonary disease (30). A nationwide Danish study found that 11.6% of patients with ST-segment elevation MI who underwent PCI had VF prior to the PCI, and that VF was associated with alcohol consumption, preinfarction angina, anterior infarct location, and complete coronary occlusion at the time of coronary angiography (31). In a select group of patients undergoing primary PCI in a clinical trial, 5.7% developed sustained VT or VF, with two thirds of these events occurring prior to the end of the catheterization, and 90% within 48 hours from the procedure. VT or VF after primary PCI was associated with lower blood pressure, higher heart rate, poor coronary flow at the end of the procedure, and incomplete resolution of ST elevation (32). Importantly, and in contrast to some earlier studies, VT or VF at any time was associated with a substantially higher risk of death within 90 days. Late VT or VF (after 48 hours of hospital presentation) was associated with a higher risk of death than early VT or VF (within 48 hours of hospital presentation) (33).

2.1.3. Sustained VT and VF Not Associated With ACS

Patients with structural heart disease are at an increased risk for sustained VT and VF. Sustained VT that is not associated with an ACS is often monomorphic as it is usually due to scar-related reentry, but it may degenerate to VF (34). The risk and predictors of VT in patients with structural heart disease depend on the type, severity, and duration of structural heart disease, increasing with the severity of ventricular dysfunction and the presence of symptomatic HF. Monomorphic VT occurring in the absence of structural heart disease is commonly referred to as idiopathic VT and is often due to an automatic focus in a characteristic location, giving rise to typical electrocardiographic appearances. Polymorphic VT and VF occurring in the absence of structural heart disease are rare and may be due to a cardiac channelopathy (35, 36), medication-induced long QT syndrome (36), or they may be idiopathic (37, 38).

2.2. Sudden Cardiac Death

2.2.1. Incidence of SCD

SCA and its most common consequence, SCD, constitute major public health problems, accounting for approximately 50% of all cardiovascular deaths (1, 39), with at least 25% being first symptomatic cardiac events (1, 40, 41). In addition, analyses of the magnitude of SCD are limited, in part because of the broad range of estimates of the risk based on different epidemiological methods (42). During the past 20 to 30 years, SCD accounted for approximately 230,000 to 350,000 deaths per year in the United States, with a range of <170,000 to >450,000, depending on epidemiological methods, data sources, and inclusion criteria (41, 43). The lowest of these extremes came from national extrapolation of data from specific local programs, while the highest rates included noncardiac causes of sudden death such as pulmonary embolism or intracranial bleeding. The mid-range numbers were largely based on death certificate studies that required a code inclusive of ischemic heart disease.

The 2017 update of cardiovascular statistics from the AHA estimated the total annual burden of out-of-hospital cardiac arrest at 356,500 (44). An additional 209,000 in-hospital cardiac arrests occur annually (45). Among the out-of-hospital cardiac arrest group, approximately 357,000 events trigger emergency rescue response, with 97% occurring in adults >18 years of age.

The survival statistics for out-of-hospital cardiac arrest remain disappointing, with an estimated 10% overall survival rate (44). Among the subgroup of 70% of out-of-hospital cardiac arrests that occur in the home, survival is 6%. The best reported outcomes are from locations with highly developed and publicly visible emergency rescue response, along with the combination of public location of cardiac arrest, bystander witnesses willing to provide CPR, first responders arriving quickly, shockable rhythm at initial contact, availability of automated external defibrillators (AEDs), and possibly a benefit from telecommunication-directed CPR (46, 47). Survival to hospital discharge after in-hospital cardiac arrests is estimated to be 24% (48). In all settings, survival statistics appear to be better when rhythms recorded by responders are shockable (VF, pulseless VT), compared with pulseless electrical activity or asystole (49). Although the apparent increase in the incidence of pulseless electrical activity or asystole could be due to the later arrival of medical care, the decrease in the incidence of shockable rhythm has also been attributed, in part, to improvements in diagnosis and treatment of structural heart disease (40).

2.2.2. Population Subgroups and Risk Prediction

Risk prediction for SCA and SCD is complex. Risk analysis is divided into 2 general categories: population risk prediction and individual risk prediction (41, 50). Conventional epidemiological markers provide insight into probabilities for the development of ischemic heart disease within a general class of subjects, but adequately tested and validated profiles for SCA risk stratification of individuals in the general population do not presently exist. The challenge of defining SCA risk in individuals derives from a population model characterized by large

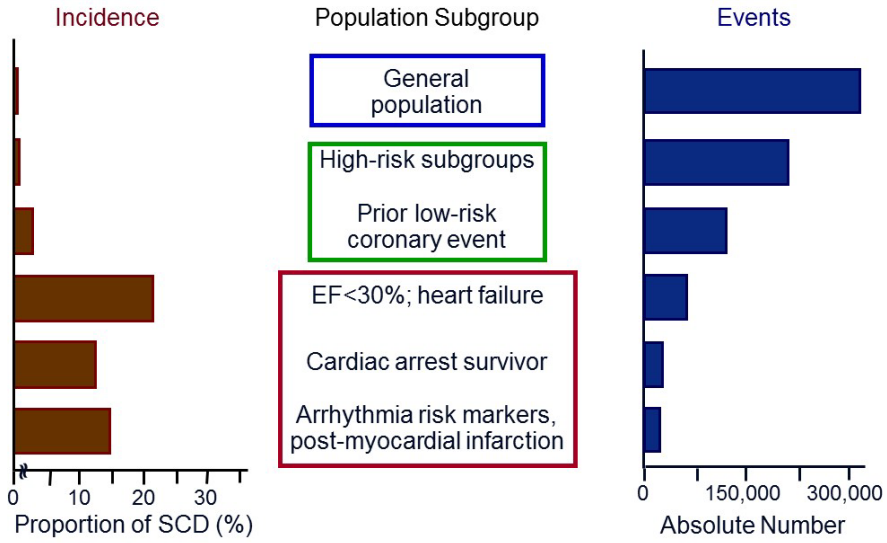
numbers of events diluted into a very large denominator (Figure 1). The overall population can be subgrouped into categories based on integration of age, presence and extent of disease, and identification of small, high-risk subgroups within the large denominator general population.

Increasing age is a strong predictor of risk for SCA, but it is not linear. Risk in the general population, over time, beginning at 35 years of age has been estimated at 1 per 1000 population per year, increasing from a risk <1000 at the younger end of that spectrum to a higher risk in the elderly (41). However, an analysis of lifetime risk of SCD, derived from the Framingham data, suggested that the incidence of SCD decreases in later years, especially in people >75 years of age (51). The data also suggested that SCD is uniformly more common in men than in women at all age groups. In contrast, the population of children, adolescents, and young adults has an overall annual risk of 1 per 100,000, and there is somewhat a higher risk of SCD at the younger end of that age range (41). An age-associated transition range, from the mid-20s to 35 to 40 years of age, is characterized by a steep increase in risk from that of the adolescent group to the middle-aged group, corresponding to the emergence of ischemic heart disease.

Although ischemic heart disease remains the most common underlying substrate associated with SCD, the incidence of ischemic heart disease-related SCD appears to be decreasing (52), with various forms of cardiomyopathy associated with myocardial fibrosis and LV hypertrophy increasing (53). In addition, a trend over time has suggested that out-of-hospital cardiac arrest patients who are admitted alive to a hospital are becoming more likely to have high-risk clinical profiles, as opposed to manifest disease (54). The younger population—children, adolescents, and young adults—is affected by a series of disorders that manifest earlier in life, including the genetic structural disorders and cardiac channelopathies, myocarditis, congenital heart disease, and other rare disorders (43). During the transition range, from the mid-20s to the mid-30s, causes of SCA and SCD include a lower proportion of inherited diseases and increasing proportion of ischemic heart disease (>40% of cases) (43).

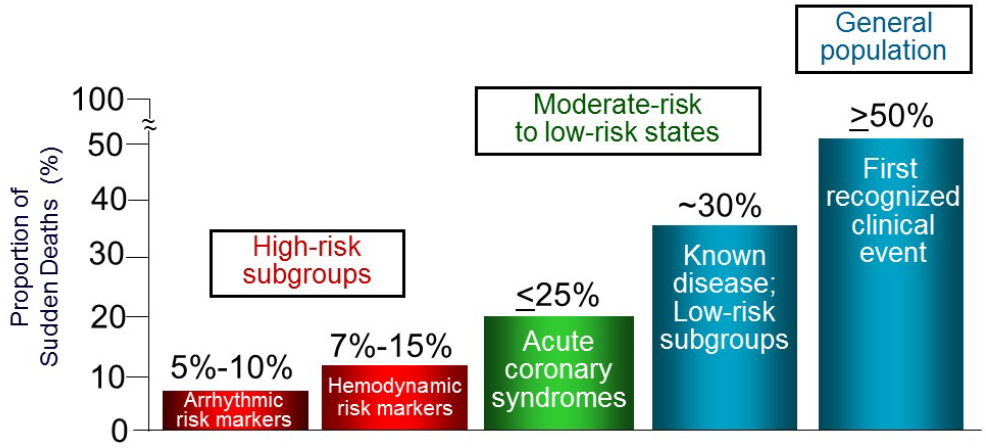
Despite the small progress that has been made in risk prediction of SCA and SCD, the greatest challenge is to identify the relatively small, high-risk subgroups concealed within the large general population who have no identified disease but are at risk of SCA as their first cardiac event (Figure 1) (50).

Figure 1A. SCD Incidence and Total Events (1)



EF indicates ejection fraction; and SCD, sudden cardiac death.

Figure 1B. SCD and Clinical Subsets (1)



SCD indicates sudden cardiac death.

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3. Mechanisms of VA

3.1. Cellular Mechanisms and Substrates

Mechanisms of VA include enhanced normal automaticity, abnormal automaticity, triggered activity induced by early or late afterdepolarizations, and reentry (1-3). Reentry requires a trigger to initiate the arrhythmia and a substrate to sustain it. The trigger may be a PVC, which may be due to automaticity. The substrate may be structural remodeling secondary to an underlying disease process, and often includes a scar secondary to a prior MI or surgical repair, or patchy fibrosis in the setting of cardiomyopathy or hypertrophy. Changes in ion channel or transporter function and/or expression and cell to cell coupling secondary to the underlying pathology may alter the initiation or propagation of the cardiac action potential. The electrophysiological substrate is dynamically influenced by a variety of factors including cardiac metabolism, electrolytes, signaling pathways and autonomic effects. Enhanced automaticity or abnormal automaticity causing VA may arise from subordinate pacemaker cells in the His-Purkinje system or ventricular myocardium.

3.2. Automaticity

Normal automaticity results from phase 4 spontaneous depolarization of the transmembrane action potential arising from a normal resting potential, reaching threshold and initiating an action potential (1, 3). An initiating current (I_f) is responsible for spontaneous phase 4 depolarization in the sinus node. The rate is determined by the integration of the maximum diastolic potential at the end of repolarization, the slope of phase 4 depolarization, and the threshold potential. In contrast, abnormal automaticity arises from a partially depolarized membrane potential that is usually close to the activation potential for calcium channels in the cell membrane (1, 3). In the acute phase of an MI or during transient ischemia, increased extracellular potassium causes partial depolarization of the resting membrane potential creating injury currents between the infarcted/ischemic tissue and healthy myocardium. These injury currents may initiate spontaneous activity. In ischemia, abnormal automaticity may occur in both ventricular myocytes and Purkinje fibers, and may also enhance normal automaticity in Purkinje fibers in the ischemic zone.

3.3. Triggered Activity

Early afterdepolarizations occur during late phase 2 or early phase 3 of the action potential (3-5), usually in the setting of action potential prolongation due to an increase in inward currents (the late sodium current, the inward calcium current or the sodium calcium exchange current) or a decrease in repolarizing potassium currents. Under these conditions, early afterdepolarizations may be initiated when reactivation of the inward L-type calcium channel occurs before the membrane has returned to a more negative potential than that required for calcium channel reactivation. Spontaneous calcium release from the sarcoplasmic reticulum may also result in activation of a depolarizing sodium/calcium exchange current. Early afterdepolarizations are the trigger for torsades de pointes VT associated with QT prolongation either induced by medications or other acquired factors or due to mutations of ion channels causing the long QT syndrome. In these cases, it is possible that the early afterdepolarization/triggered activity sequence is the trigger that culminates in polymorphic VT/VF.

Delayed afterdepolarizations occur after complete membrane repolarization and develop under conditions of intracellular calcium overload. Factors contributing to elevated intracellular calcium load include tachycardia, catecholamines, hypokalemia, digoxin toxicity, cardiac hypertrophy, and HF (6, 7). Elevated sarcoplasmic calcium content or increased sensitivity of the ryanodine receptor can initiate spontaneous

calcium release, which activates a transient inward current driven predominantly by the sodium–calcium exchange current. If the membrane depolarization is sufficiently large, the inward sodium current is activated resulting in a triggered action potential. Delayed afterdepolarizations are the underlying mechanism for VT in the setting of digoxin toxicity, catecholaminergic polymorphic VT, and idiopathic outflow tract VA. Delayed afterdepolarizations are also considered to be an important trigger of VA in the setting of HF. Purkinje cells are more susceptible to spontaneous sarcoplasmic reticulum calcium release than ventricular myocytes suggesting that delayed afterdepolarizations may be an important mechanism for some Purkinje fiber-related VA (3, 8, 9).

3.4. Reentry

Reentry is the underlying mechanism for most sustained VA in the presence of structural heart disease (1-3, 10-12). Reentry may occur around a fixed anatomical obstacle, such as scar after an MI or surgically repaired congenital heart disease. In this setting, an excitable gap separates the excitation wavefront from its tail of refractoriness. The existence of structural reentrant substrates provide the rationale for VT ablation in scar-related VTs (11, 12).

Functional reentry around areas of functional block without anatomical obstacles can also occur. Two main models of functional reentry have been proposed (2, 3). The leading circle model has a functionally refractory core and no excitable gap. Spiral wave reentry is driven by a rotor with a curved wavefront and wavetail pivoting around an excitable but unexcited core. There remains much debate about the precise mechanism(s) of VF (rotor versus multiple wavelet reentry). Both mechanisms may be operational in different phases of VF (10).

Phase 2 reentry may occur due to heterogeneity of ventricular repolarization. Electrotonic currents may flow from endocardial sites with longer action potential durations to the epicardium with shorter action potential durations which can result in reexcitation when these sites have recovered from refractoriness. This is believed to be one potential mechanism of VT/VF in Brugada syndrome (3) and may also be operative during ischemia.

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4. General Evaluation of Patients With Documented or Suspected VA

4.1. History and Physical Examination

Recommendation for Syncope* Referenced studies that support the recommendation are summarized in Online Data Supplement 1.		
COR	**LOE**	**Recommendation**
I	**B-NR**	**1. Patients presenting with syncope for which VA is documented, or thought to be a likely cause, should be hospitalized for evaluation, monitoring, and management (1-4).**

*This section covers practices that are well accepted, and a new recommendation was determined to only be warranted for syncope.

Table 6

Synopsis

VA can produce a wide spectrum of symptoms, and the severity of symptoms does not necessarily reflect the extent of structural heart disease or the potential risk of SCD. Symptoms of VA include palpitations, either skipped or extra beats or sustained palpitations, shortness of breath, chest pain, dizziness, near syncope, and syncope (5, 6). Palpitations may correlate with VA but are frequently reported during normal rhythm (7). The differential diagnosis of exercise intolerance, chest pain, dyspnea, presyncope, and syncope includes VA but also includes other etiologies. Nonetheless, more dramatic symptoms, particularly in patients with known or discovered structural or electrical heart disease should prompt focused investigation for possible association with VA (Table 6).

The elucidation of precipitating factors, such as exertional or emotional stress, concurrent medications or illness, and alleviating factors is important. The presence of a family history of SCD, ischemic heart disease, valvular heart disease, nonischemic cardiomyopathy (NICM), or HF raises concern for the presence of one of these disorders associated with VA. Obtaining a complete medication history is important. Various antiarrhythmic and other medications can cause QT prolongation and torsades de pointes (www.crediblemeds.org) (8); some medications can also induce Brugada type I electrocardiographic pattern and VF (www.brugadadrugs.org) (9, 10).

Table 6. Important Considerations in the Evaluation of Patients With Known or Suspected VA

Component	Assessment and Findings Relevant for VA and/or SCD Risk
History	1. Symptoms/events related to arrhythmia: Palpitations, lightheadedness, syncope, dyspnea, chest pain, cardiac arrest 2. Symptoms related to underlying heart disease: Dyspnea at rest or on exertion, orthopnea, paroxysmal nocturnal dyspnea, chest pain, edema 3. Precipitating factors: Exercise, emotional stress 4. Known heart disease: Coronary, valvular (e.g., mitral valve prolapse), congenital heart disease, other 5. Risk factors for heart disease: Hypertension, diabetes mellitus, hyperlipidemia, and smoking 6. Medications: • Antiarrhythmic medications • Other medications with potential for QT prolongation and torsades de pointes • Medications with potential to provoke or aggravate VA

	➢ Stimulants including cocaine and amphetamines ➢ Supplements including anabolic steroids • Medication-medication interaction that could cause QT prolongation and torsades de pointes 7. Past medical history: • Thyroid disease • Acute kidney injury, chronic kidney disease, or electrolyte abnormalities • Stroke or embolic events • Lung disease • Epilepsy (arrhythmic syncope can be misdiagnosed as epilepsy) • Alcohol or illicit drug use • Use of over-the-counter medications that could cause QT prolongation and torsades de pointes • Unexplained motor vehicle crashes
Family History	1. SCD, SCA, or unexplained drowning in a first-degree relative 2. SIDS or repetitive spontaneous pregnancy losses given their potential association with cardiac channelopathies 3. Heart disease • IHD • Cardiomyopathy: Hypertrophic, dilated, ARVC • Congenital heart disease • Cardiac channelopathies: Long QT, Brugada, Short QT, CPVT • Arrhythmias • Conduction disorders, pacemakers/ICDs 4. Neuromuscular disease associated with cardiomyopathies • Muscular dystrophy 5. Epilepsy
Examination	1. Heart rate and regularity, blood pressure 2. Jugular venous pressure 3. Murmurs 4. Pulses and bruits 5. Edema 6. Sternotomy scars

ARVC indicates arrhythmogenic right ventricular cardiomyopathy; CPVT catecholaminergic polymorphic ventricular tachycardia; IHD, ischemic heart disease; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SIDS, sudden infant death syndrome; and VA, ventricular arrhythmia.

Patients with bigeminy and trigeminy can present with effective bradycardia, an apical-radial pulse deficit and relative hypertension with a wide pulse pressure. Effective bradycardia from PVCs can result in inaccurate estimation of the heart rate. Although premature beats on auscultation of the heart can be detected, the physical examination is focused largely on finding evidence of structural heart disease. Carotid bruits or diminished peripheral pulses may be indicators of atherosclerotic disease associated with ischemic heart disease. Jugular venous distention, rales, gallops, and peripheral edema provide evidence of HF. Auscultation may reveal cardiac murmurs consistent with valvular heart disease, such as aortic stenosis or mitral regurgitation, and may be associated with HF and VA. A midsystolic click may indicate mitral valve prolapse that can be associated with VA (11-13). Many VA are asymptomatic and detected only on an ECG or telemetry. Such cases highlight the need to search for evidence of underlying heart disease.

Recommendation-Specific Supportive Text

1. Rapid, sustained VT may result in syncope secondary to marked reduction in cardiac output, followed by spontaneous recovery if VT terminates, or SCA if VT persists and is not treated promptly. Syncope or SCA may

be the first manifestation of structural or electrical heart disease (14), and some SCA victims have preceding "sentinel" syncope episodes (15). Syncope, or its forewarnings of dizziness, lightheadedness, or near-syncope, may constitute a risk factor for SCA and SCD (2). The initial evaluation at any age focuses on detection or exclusion of heart disease. Syncope during exercise should prompt thorough evaluation to rule out cardiac causes. Cardiac evaluation with echocardiography, ambulatory monitoring, and exercise testing may be warranted depending on the clinical information elicited (3, 4). Cardiac causes of syncope include sustained VT, high-grade atrioventricular block or severe sinus bradycardia or prolonged sinus pauses, supraventricular tachycardia (SVT), malfunction of pacemakers, VA from cardiac channelopathies or structural heart disease syndromes, such as hypertrophic cardiomyopathy (HCM) or congenital heart disease (3, 4, 16). Cardiac channelopathies and HCM are particularly important to consider in adolescents and young adults. Arrhythmic causes of syncope are often associated with very short periods of premonitory symptoms, or palpitations, and known preexisting heart disease, especially a history of a low LVEF or HF (1). Among nonarrhythmic cardiac causes, considerations should include myocardial ischemia, severe aortic stenosis, HCM, HF, and prosthetic valve malfunction, pulmonary embolism, medications, and illicit drug use (3).

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4.2. Noninvasive Evaluation

4.2.1. 12-lead ECG and Exercise Testing

Recommendations for 12-lead ECG and Exercise Testing References studies that support the recommendations are summarized in Online Data Supplement 2.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with sustained, hemodynamically stable, wide complex tachycardia, a 12-lead ECG during tachycardia should be obtained (1-3).**
I	**B-NR**	**2. In patients with VA symptoms associated with exertion, suspected ischemic heart disease, or catecholaminergic polymorphic ventricular tachycardia, exercise treadmill testing is useful to assess for exercise-induced VA (4, 5).**
I	**B-NR**	**3. In patients with suspected or documented VA, a 12-lead ECG should be obtained in sinus rhythm to look for evidence of heart disease (6).**

Recommendation-Specific Supportive Text

1. A 12-lead ECG during tachycardia is the first diagnostic test that should be done in any patient found to be in a stable wide QRS complex tachycardia on a monitor. VT is the diagnosis in most adults with wide complex tachycardia and underlying structural heart disease (3). Criteria that support a diagnosis of VT include AV dissociation, a QRS complex >0.14 s, monophasic R wave in aVR, specific QRS morphologies (e.g., positively or negatively concordant QRS complexes in the precordial leads), the absence of an RS complex in all precordial leads and an RS interval >100 ms in at least 1 precordial lead (2). Exceptions occur, particularly in patients with advanced heart disease and with the use of certain antiarrhythmic medications (1). For patients with preexisting bundle branch block, comparison of the QRS morphology during sinus rhythm with that during wide complex tachycardia is often relevant.

2. For exertion-related arrhythmic symptoms, exercise in a monitored setting may reproduce the symptoms and/or the related arrhythmia, allowing for diagnosis. Exercise testing is particularly important when catecholaminergic polymorphic ventricular tachycardia is a possibility. However, exertion-related symptoms and findings may not be reliably reproducible with exercise testing, and long-term electrocardiographic monitoring with external or implantable recorders may be necessary.

3. A 12-lead ECG may indicate the presence of structural heart disease such as prior MI or chamber enlargement that would increase the likelihood that a patient's symptoms might be due to VA, or it may provide evidence of the underlying substrate for documented VA. An ECG may also reveal evidence of inherited arrhythmia disorders, such as long QT syndrome, Brugada syndrome, and arrhythmogenic right ventricular cardiomyopathy. In patients with structural heart disease, QRS duration and the presence of conduction abnormalities provide prognostic information (7-14). Data on the use of microvolt T wave alternans and the signal averaged ECG are inconclusive, as such these tests are not routinely used in clinical practice (15-19); the one exception is the potential use of signal averaged ECG in patients with arrhythmogenic right ventricular cardiomyopathy (see Section 7.3).

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4.2.2. Ambulatory Electrocardiography

Recommendation for Ambulatory Electrocardiography Referenced studies that support the recommendation are summarized in Online Data Supplement 3 and 4.		
COR	**LOE**	**Recommendation**
I	**B-NR**	**1. Ambulatory electrocardiographic monitoring is useful to evaluate whether symptoms, including palpitations, presyncope, or syncope, are caused by VA (1-4).**

Recommendation-Specific Supportive Text

1. Ambulatory electrocardiographic monitoring is often used to assess the effectiveness of treatments to suppress arrhythmias, but more robust data are needed on the clinical use of this practice. Continuous or intermittent ambulatory electrocardiographic recording with a Holter monitor or an event recorder is helpful

in diagnosing suspected arrhythmias, establishing their frequency, relating them to symptoms, and assessing the response to therapy. Although the yield of these tests is relatively low , VT is occasionally documented (4). A 24-hour continuous Holter recording is appropriate when symptoms occur at least once a day or when quantitation of PVCs/NSVT is desired to assess possible VA-related depressed ventricular function. For sporadic symptoms, event or "looping" monitors are more appropriate because they can be activated over extended periods of time and increase diagnostic yield (2, 3). Adhesive patch electrocardiographic monitors can record for weeks and allow for continuous short-term 1-lead monitoring and patient activation for symptoms. Studies have shown satisfactory patient compliance, and arrhythmia detection; however, with some monitors, detected arrhythmias are not discovered until the patch is returned for analysis (1, 4). Serial evaluations with exercise testing and/or 24-hour ambulatory monitoring are also used to assess rhythm burden and response of VA to therapy. Notably, implantable monitors are covered in Section 4.2.3. Importantly, when the suspicion of VA in a patient is high, outpatient ambulatory monitoring is inappropriate as prompt diagnosis and prevention of VA are warranted. It is important to accurately correlate the symptoms with the arrhythmias detected by ambulatory ECG monitoring.

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4.2.3. Implanted Cardiac Monitors

Recommendation for Implanted Cardiac Monitors Referenced studies that support the recommendation are summarized in Online Data Supplement 5.		
COR	**LOE**	**Recommendation**
IIa	**B-R**	**1. In patients with sporadic symptoms (including syncope) suspected to be related to VA, implanted cardiac monitors can be useful (1-4).**

Recommendation-Specific Supportive Text

1. Implanted cardiac monitors provide continuous rhythm monitoring and stored recordings of electrograms based on patient activation or preset parameters, allowing a prolonged monitoring period of a few years. These devices require a minor invasive procedure with local anesthesia for implantation. In patients with sporadic symptoms, including syncope, implantable recorders are useful in diagnosing serious tachyarrhythmias (including VA) and bradyarrhythmias (2-4). They are generally reserved for patients in whom other ambulatory monitoring is nonrevealing due to the infrequency of events. A 25% added yield in diagnosis has been described after an unrevealing external ambulatory monitor (5). In a study of patients with syncope, the implantable monitor had a greater diagnostic yield than "conventional" testing with external monitoring, tilt table testing and electrophysiological study (2). A systematic review in patients with syncope concluded that use of these devices provide a higher rate of diagnosis and a trend toward reduction in syncope relapse after diagnosis, as compared with conventional management (3). A prospective study of patients after MI, with LVEF <40%, demonstrated NSVT (>16 beats long) in 13%, VT (>30 s) in 3% and VF in 3% of patients (1). It

is important to accurately correlate the symptoms with the arrhythmias detected by implanted cardiac monitors.

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4.2.4. Noninvasive Cardiac Imaging

Recommendations for Noninvasive Cardiac Imaging Referenced studies that support the recommendations are summarized in Online Data Supplement 6.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with known or suspected VA that may be associated with underlying structural heart disease or a risk of SCA, echocardiography is recommended for evaluation of cardiac structure and function (1, 2).**
IIa	**C-EO**	**2. In patients presenting with VA who are suspected of having structural heart disease, cardiac magnetic resonance imaging (MRI) or computed tomography (CT) can be useful to detect and characterize underlying structural heart disease.**

Recommendation-Specific Supportive Text

1. Assessment of global and regional myocardial function, valvular structure and function, along with assessment for adult congenital heart disease is required in patients with or at high risk for VA or SCD, including patients with cardiomyopathy, HF, prior MI, family history of cardiomyopathy or SCD, or an inherited structural heart disease associated with SCD. Echocardiography is the most readily available and commonly used imaging technique (1, 2). LVEF is a strong, independent predictor of SCD and cardiovascular mortality and a determinant of eligibility for ICD implantation for primary prevention of SCD (1). In SCD-HeFT (the Sudden Cardiac Death in Heart Failure Trial) (2), the benefit of the ICD was not dependent on the modality (i.e., echocardiography, radionuclide angiography, or contrast angiograms) by which the LVEF was assessed. In clinical practice, if cardiac CT (3) or cardiac MRI has been performed and provides sufficient evaluation, echocardiography may be unnecessary. This recommendation for imaging differs from that of the 2017 ACC/AHA/HRS syncope guideline (4) that applies to patients who may not have VA.

2. VA or SCA can be an initial manifestation of ischemic heart disease, cardiomyopathic processes, or myocarditis. Cardiac CT and cardiac MRI allow for evaluation of structural heart disease and assessment of LV and RV function including quantification of LVEF, LV mass and volume, valvular structure and coronary anatomy including anomalous coronary origins. Cardiac MRI can be useful in the evaluation for myocardial scar and infiltrative processes evident as late gadolinium enhancement (5-9). Cardiac MRI also provides high-

quality assessment of LV and RV function, size, and degree of fibrosis and is particularly useful in arrhythmogenic right ventricular cardiomyopathy and HCM.

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4.2.5. Biomarkers

Recommendation for Biomarkers Referenced studies that support the recommendation are summarized in Online Data Supplement 7.		
COR	**LOE**	**Recommendation**
IIa	**B-NR**	**1. In patients with structural heart disease, measurement of natriuretic peptides (BNP or N-terminal pro-BNP) can be useful by adding prognostic information to standard risk factors for predicting SCD or SCA (1-4).**

Recommendation-Specific Supportive Text

1. Elevated levels of natriuretic peptides—B-type natriuretic peptide (BNP) or N-terminal pro-BNP—are associated with increased risk of SCA and appropriate ICD therapies, even after adjustment of LVEF and other risk factors (1-4). These biomarkers are also predictive of nonsudden cardiovascular mortality and thus are not specific to SCD risk alone. Natriuretic peptides have also been evaluated for predicting SCD in the general population (5, 6). In the Nurses' Health Study, an elevated N-terminal pro-BNP was an independent risk marker for SCD in presumably healthy women (5). In an older adult population, higher baseline levels of N-terminal pro-BNP were associated with SCD over a 16-year follow-up period (6). These biomarkers may also have a potential role in facilitating the identification of individuals at increased risk of SCD and VA in the general population, particularly in those at intermediate or high risk of ischemic heart disease, but further studies are needed. Use of biomarkers has not been shown to be useful for selecting patients for ICDs. A study of 4431 patients found high-sensitivity troponin to be only weakly predictive of SCD (7). However, there are no data on whether high-sensitivity troponin can improve the current SCD prediction algorithms.

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4.2.6. Genetic Considerations in Arrhythmia Syndromes

Recommendation for Genetic Counselling*		
COR	**LOE**	**Recommendation**
I	**C-EO**	**1. In patients and family members in whom genetic testing for risk stratification for SCA or SCD is recommended, genetic counseling is beneficial.**

*Please refer to section 7.9 for disease-specific recommendations.

Synopsis

The diagnosis of most inherited arrhythmia syndromes is based on clinical features and family history. The availability of genetic testing for inherited arrhythmia syndromes can: 1) provide opportunity to confirm a suspected clinical diagnosis and sometimes provide prognostic information for the proband and 2) offer cascade screening of potentially affected family members when a disease-causing mutation is identified in the proband. The yield of genetic testing varies by disease. The verification of pathogenicity of suspected mutations is an evolving field, and exome sequencing has identified an increasing number of variants of uncertain significance in the general population (1-5). Genotyping can have therapeutic implications for some arrhythmogenic phenotypes such as long QT syndrome and Fabry's disease (6-9), where a monogenic pathogenic mutation has been clearly identified, the risk to mutation positive individuals has been extensively studied, and effective therapy relevant to the mutation can be instituted. In other diseases, such as Brugada syndrome, the role of a clear monogenic disease-causing mutation is less certain, and the genotype does not provide therapeutic or prognostic information for the proband (5, 10-12). In arrhythmogenic right ventricular cardiomyopathy, some desmosomal mutation positive individuals do not develop disease, indicating that additional mutations and environmental interactions likely influence the clinical development of disease (13-16). Importantly, the absence of an identified disease-causing genetic mutation does not exclude the presence of disease, and as such, ongoing monitoring and decision-making are done based on the clinical phenotype. Genotyping is frequently most useful when a pathogenic mutation is identified in the proband, such that screening can be applied to relatives who are in a preclinical phase, allowing institution of lifestyle changes, therapy, or ongoing monitoring for those who are gene mutation positive (7). Refer to Section 7.9 for disease-specific recommendations.

In young patients (<40 years of age) without structural heart disease who have unexplained cardiac arrest, unexplained near drowning, or recurrent exertional syncope, genetic testing may be important to identify an inherited arrhythmia syndrome as a likely cause (17-23).

Recommendation-Specific Supportive Text

1. The decision to proceed with genetic testing requires discussion regarding the clinical use of genetic information to be obtained for both the proband and family members, as well as consideration of the important psychological, financial, employment, disability, and life insurance implications of positive genotyping (17, 18, 20, 24). Balancing privacy of health care information for the proband with the "right to know" for family members, and the ability to provide appropriate communication of information to all potentially affected family members can be challenging on many levels, including family dynamics, geographic proximity, and access to health care (25). For these reasons, genetic counseling generally occurs before proceeding with genetic testing, and, from a patient's perspective, is optimally provided by genetic counselors, if available, in collaboration with physicians (26, 27). A combined approach of genetic counseling with medical guidance may appropriately balance the decision as to whether genetic testing would be beneficial on an individual basis.

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4.3. Invasive Testing

4.3.1. Invasive Cardiac Imaging: Cardiac Catheterization or CT Angiography

Recommendation for Invasive Imaging: Cardiac Catheterization		
COR	**LOE**	**Recommendation**
I	**C-EO**	**1. In patients who have recovered from unexplained SCA, CT or invasive coronary angiography is useful to confirm the presence or absence of ischemic heart disease and guide decisions for myocardial revascularization.**

Recommendation-Specific Supportive Text

1. Although randomized studies are unavailable, coronary angiography has an important role in establishing or excluding the presence of significant obstructive ischemic heart disease in patients with SCA or those with life-threatening VA (1-4). Recurrent polymorphic VT or VF can be due to ongoing myocardial ischemia that resolves with coronary revascularization. Presence of ST-elevation on preresuscitation or early postresuscitation ECG suggests ischemia and potential ACS warranting urgent angiography and revascularization (5). ST-elevation can also result from coronary spasm or DC shocks. The absence of ST-elevation after cardiac arrest does not exclude obstructive or thrombotic coronary lesions. A coronary angiogram may not be warranted if a nonischemic cause of SCA is established. Coronary and CT angiography also have an important role excluding the presence of anomalous origin of the coronary arteries that may cause SCD.

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4.3.2. Electrophysiological Study for VA

Recommendations for Electrophysiological Study References that support the recommendations are summarized in Online Data Supplement 8 and 9.		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**1. In patients with ischemic cardiomyopathy, NICM, or adult congenital heart disease who have syncope or other VA symptoms and who do not meet indications for a primary prevention ICD, an electrophysiological study can be useful for assessing the risk of sustained VT (1-7).**
III: No Benefit	**B-R**	**2. In patients who meet criteria for ICD implantation, an electrophysiological study for the sole reason of inducing VA is not indicated for risk stratification (8-11).**
III: No Benefit	**B-NR**	**3. An electrophysiological study is not recommended for risk stratification for VA in the setting of long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or early repolarization syndromes (12-16).**

Synopsis

Electrophysiological study can be used to induce sustained VA in patients with known or suspected VA. With the advent of the ICD and its proven benefit in the primary and secondary prevention of SCD, there are fewer indications for programmed stimulation to provoke VA. Patients with HF and LVEF ≤35% generally will have an indication for an ICD and specific induction of VT/VF before implantation is not necessary. Patients with LVEF >35% and unexplained syncope or near-syncope may benefit from an electrophysiological study to determine if VT/VF is the cause of symptoms and to guide further therapy. Induction of VT/VF is often attempted before catheter ablation of the arrhythmia substrate to guide the procedure and to determine the success of the intervention after ablation is performed. An electrophysiological study can be used to determine the mechanism of a wide complex tachycardia. See Sections 7.3, 7.4, 7.6, 7.9.1.3, and 10.8 for recommendations regarding electrophysiological study for specific disease states.

Recommendation-Specific Supportive Text

1. A study of electrophysiological testing in patients with symptomatic NICM found inducible VT/VF in 28% of patients which was associated with a higher rate of ICD events during follow-up (17). In a prospective cohort of 180 patients with ischemic or NICM and syncope, induction of VT or VF at electrophysiological study correlated with cardiac mortality only in patients with ischemic heart disease. In patients with NICM, cardiac mortality correlated with LVEF but not with inducibility on electrophysiological study (18).

2. In patients who meet criteria for ICD implantation (i.e., HF and LVEF ≤35%), data do not support the routine use of electrophysiological study solely for risk stratification, as such patients have been shown to derive survival benefit from the ICD (8-11). An electrophysiological study may be helpful, however, in selected patients suspected to have preexcitation or supraventricular arrhythmias as the cause of symptoms or wide complex tachycardias that warrant definitive diagnosis and management. SVT leading to VT/VF or aberrantly

conducted SVT may also be suspected in younger patients or those with a preserved LVEF. Induction of SVT and ablation may then be curative, with no need for an ICD. In such cases, failure to induce VT/VF after elimination of the substrate for SVT would be expected.

3. Risk stratification for channelopathies is generally made on the basis of symptoms, the ECG (13, 19-24), exercise treadmill testing (25-27), and the results of genetic testing (28-32). The electrophysiological study (i.e., programmed ventricular stimulation) does not have prognostic value for risk stratification in patients with these cardiac channelopathies (12-15).

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5. Therapies for Treatment or Prevention of VA

5.1. Medication Therapy

With the exception of beta blockers (e.g., metoprolol succinate, carvedilol), there is no evidence from RCTs that antiarrhythmic medications for VA improve survival when given for the primary or secondary prevention of SCD. However, the use of these medications is essential in some patients to control arrhythmias and improve symptoms. Medication use for VA is discussed, and any recommendations are listed, in subsequent sections. Further, medication-induced proarrhythmia is addressed in Section 10.7.

Antiarrhythmic medications are often categorized by the Vaughan Williams 4-level schema (class I: fast sodium channel blockers; class II: beta blockers; class III: repolarization potassium current blockers; class IV: nondihydropyridines calcium channel blockers) (1). This system does not address the complexities in antiarrhythmic medications, since nearly every agent has multiple effects. Table 7 shows uses, electrophysiological effects, pharmacological effects, and common adverse effects of antiarrhythmic medications.

Table 7. Pharmacological Characteristics of Available Antiarrhythmic Medications for Treating VA

Antiarrhythmic Medication (Class) and Dose	Uses in VA/SCA	Target	Electrophysiological Effects	Pharmacological Characteristics	Common Adverse Effects
Acebutolol PO 200–1200 mg daily or upto 600 mg bid	VT, PVCs	Beta 1, Mild intrinsic sympathomimetic activity	Sinus rate slowed AV nodal refractoriness increased	Active metabolite $t_{1/2}$: 8–13 h pProlonged with renal impairment) Metab: H Excr: F 60%, U 40%	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, fatigue, anxiety, impotence, hyper/hypoesthesia
Amiodarone (III) IV: 300 mg bolus for VF/ pulseless VT arrest; 150-mg bolus for stable VT; 1 mg/min x 6 h, then 0.5 mg/min x 18 h PO: 400 mg* q 8 to 12 h for 1–2 wk, then 300-400 mg daily; reduce dose to 200 mg daily if possible	VT, VF, PVC,	I_{Na}, I_{Ca}, I_{Kr}, I_{K1}, I_{Ks}, I_{to}, Beta receptor, Alpha receptor nuclear T3 receptor	Sinus rate slowed QRS prolonged QTc prolonged AV nodal refractoriness increased; increased DFT	$t_{1/2}$: 26-107 d Metab: H Excr: F	Cardiac: Hypotension, bradycardia, AVB, TdP, slows VT below programmed ICD detection rate, increases defibrillation threshold Other: Corneal microdeposits, thyroid abnormalities, ataxia, nausea, emesis, constipation, photosensitivity, skin discoloration, ataxia, dizziness, peripheral neuropathy, tremor, hepatitis, cirrhosis, pulmonary fibrosis or pneumonitis
Atenolol (II) PO: 25–100 mg qd or bid	VT, PVC, ARVC, LQTS	Beta 1	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$: 6–7 h (prolonged with renal impairment) Metab: H Excr: F 50%, U 40%	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, fatigue, depression, impotence
Bisoprolol (II) PO: 2.5–10 mg once daily	VT, PVC	Beta 1 receptor	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$: 9–12 h Metab: H Excr: U	Cardiac: Chest pain, bradycardia, AVB Other: Fatigue, insomnia, diarrhea
Carvedilol (II) PO: 3.125–25 mg q 12 h	VT, PVC	Beta 1 and 2 receptors, Alpha	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$: 7–10 h Metab: H Excr: F	Cardiac: Bradycardia, hypotension, AVB, edema, syncope Other: Hyperglycemia,

					dizziness, fatigue, diarrhea
Diltiazem (IV) IV: 5-10 mg qd 15-30 min Extended release: PO: 120–360 mg/day	VT specifically RVOT, idiopathic LVT	I_{Ca-L}	Sinus rate slowed PR prolonged AV nodal conduction slowed	$t_{1/2}$: Injection 2–5 h, immediate release 4.5–12 h, extended release 12 h, and severe hepatic impairment 14–16 h Metab: H Excr: U	Cardiac: Hypotension, edema, HF, AVB, bradycardia, exacerbation of HF*r*EF Other: Headache, rash, constipation
Esmolol (II) IV: 0.5 mg/kg bolus, 0.05 mg/kg/min	VT	Beta 1 receptor	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$: 9 min Metab: RBC esterases Excr: U	Cardiac: Bradycardia, hypotension, HF, AVB Other: Dizziness, nausea
Flecainide (IC) PO: 50–200 mg q 12 h	VT, PVC (in the absence of structural heart disease). Has a role in treating patients with CPVT	I_{Na}, I_{Kr}, I_{Kur}	PR prolonged QRS prolonged; increased DFT	$t_{1/2}$: 7–22 h Metab: H Excr: U	Cardiac: Sinus node dysfunction, AVB, drug-induced Brugada syndrome. monomorphic VT in patients with a myocardial scar, exacerbation of HF*r*EF Other: Dizziness, tremor, vision disturbance, dyspnea, nausea
Lidocaine (IB) IV: 1 mg/kg bolus, 1–3 mg/min 1-1.5 mg/kg. Repeat 0.5–0.75 mg/kg bolus every 5–10 min (max cumulative dose 3 mg/kg). Maintenance infusion is 1–4 mg/min although one could start at 0.5 mg/min	VT, VF	I_{Na}	No marked effect on most intervals; QTc can slightly shorten	Initial $t_{1/2}$ 7–30 min; terminal 90–120 min. Prolonged in HF, liver disease, shock, severe renal disease Metab: H Excr: U	Cardiac : Bradycardia, hemodynamic collapse, AVB, sinus arrest Other: Delirium, psychosis, seizure, nausea, tinnitus, dyspnea, bronchospasm
Metoprolol (II)	VT, PVC	Beta 1 receptor	Sinus rate slowed	$t_{1/2}$: 3–4 h Metab: H Excr: U	Cardiac: Bradycardia, hypotension, AVB

IV: 5 mg q 5 min up to 3 doses PO: 25–100 mg Extended release qd or q 12 h			AV nodal refractoriness increased		Other: Dizziness, fatigue, diarrhea, depression, dyspnea
Mexiletine (IB) PO: 150–300 mg q 8 h or q 12 h	T, VF, PVC, has a role in patients with LQT3	I_{Na}	No marked effect on most intervals; QTc can slightly shorten	$t_{1/2}$: 10–14 h Metab: H Excr: U	Cardiac: HF, AVB Other: Lightheaded, tremor, ataxia, paresthesias, nausea, blood dyscrasias
Nadolol (II) PO: 40–320 mg daily	VT, PVC, LQTS, CPVT	Beta 1 and 2 receptors	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$: 20–24 h Metab: none Excr: U	Cardiac: Bradycardia, hypotension, HF, AVB Other: Edema, dizziness, cold extremities, bronchospasm
Procainamide (IA) IV: loading dose 10–17 mg/kg at 20–50 mg/min Maintenance dose: 1–4 mg/min PO (SR preparation): 500–1250 mg q 6 h	VT	I_{Na}, I_{Kr}	QRS prolonged QTc prolonged; increased DFT	Metab: H $t_{1/2}$: 2–5 h; NAPA 6–8 h $t_{1/2}$ prolonged in renal dysfunction. Anephric: proc 11 h and NAPA 42 h Excr: U	Cardiac: TdP; AVB, hypotension and exacerbation of HF*r*EF Other: Lupus symptoms, diarrhea, nausea, blood dyscrasias
Propafenone (IC) PO: Immediate release 150–300 mg q 8 h Extended release 225–425 mg q 12 h	VT, PVC (in the absence of structural heart disease)	I_{Na}, I_{Kr}, I_{Kur}, Beta receptor, Alpha receptor	PR prolonged QRS prolonged; increased DFT	$t_{1/2}$: 2–10 h or 10–32 h $t_{1/2}$: extensive metabolizers 2–10 h; poor metabolizers 10–32 h. Metab: H Excr: U	Cardiac: HF, AVB, drug-induced Brugada syndrome Other: Dizziness, fatigue, nausea, diarrhea, xerostomia, tremor, blurred vision
Propranolol (II) IV: 1–3 mg q 5 min to a total of 5 mg PO: Immediate release 10–40 mg q 6 h;	VT, PVC, LQTS	Beta 1 and 2 receptors, I_{Na}	Sinus rate slowed AV nodal refractoriness increased	$t_{1/2}$: Immediate release 3–6 h Extended release 8–10 h Metab: H Excr: U	Cardiac: Bradycardia, hypotension, HF, AVB Other: Sleep disorder, dizziness, nightmares, hyperglycemia, diarrhea, bronchospasm

Extended release 60–160 mg q 12 h					
Quinidine (IA) PO: sulfate salt 200–600 mg q 6 h to q 12 h gluconate salt 324–648 mg q 8 h to q 12 h IV: loading dose: 800 mg in 50 mL infused at 50 mg/min	T, VF, (including short QT syndrome, Brugada)	I_{Na}, I_{to}, I_{Kr}, M, Alpha receptor	QRS prolonged QTc prolonged; increased DFT	$_{1/2}$: 6-8 h longer in HF, liver cirrhosis, and with older age Metab: H Excr: U	Cardiac: Syncope, TdP, AVB Other: Dizziness, diarrhea, nausea, esophagitis, emesis, tinnitus, blurred vision, rash, weakness, tremor; blood dyscrasias
Ranolazine (not classified) PO: 500–1000 mg q 12 h	VT	I_{Na}, I_{Kr}	Sinus rate slowed Tc prolonged	$t_{1/2}$: 7 h Metab: H Excr: U 75%, F 25%	Cardiac: Bradycardia, hypotension Other: Headache, dizziness, syncope, nausea, dyspnea
Sotalol (III) IV: 75 mg q 12 h PO: 80–120 mg q 12 h, may increase dose every 3 d; max 320 mg/d	VT, VF, PVC	I_{Kr}, Beta 1 and 2 receptor	Sinus rate slowed QTc prolonged AV nodal refractoriness increased; decreased DFT	$t_{1/2}$: 12 h Metab: none Excr: U	Cardiac: Bradycardia, hypotension, HF, syncope, TdP Other: Fatigue, dizziness, weakness, dyspnea, bronchitis, depression, nausea, diarrhea
Verapamil (IV) IV: 2.5–5 mg q 15–30 min Sustained release PO: 240–480 mg/d	VT (specifically RVOT, verapamil-sensitive idiopathic LVT)	$I_{Ca\text{-}L}$	Sinus rate slowed PR prolonged AV nodal conduction slowed	$t_{1/2}$: 3–7 h Metab: H Excr: U	Cardiac: Hypotension, edema, HF, AVB, bradycardia, exacerbation of HFrEF Other: Headache, rash, gingival hyperplasia, constipation, dyspepsia

*Although up to 800 mg every 8 h might be used, higher doses of amiodarone are associated with a higher risk of adverse events.

Alpha indicates alpha-adrenergic receptor; ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; AVB, atrioventricular block; Beta, beta-adrenergic receptor; HF, heart failure; CPVT, catecholaminergic polymorphic ventricular tachycardia; DFT, defibrillation threshold; F, feces; H, hepatic; I_{Ca}, L-type calcium channel current; I_{K1}, inward rectifier potassium channel; I_{KACh}, muscarinic receptor-gated potassium channel; I_{KATP}, adenosine-activated potassium channel; I_{Kr}, rapid delayed rectifier potassium current; I_{Ks}, slow delayed rectifier potassium current; I_{Kur}, ultra-rapid delayed rectifier potassium current; I_{Na}, fast inward sodium current; I_{to}, transient outward potassium current; LQTS, long-QT syndrome; LVT, left ventricular tachycardia; M, muscarinic; Metab, metabolism; NAPA, n-acetyl procainamide; PVC,

premature ventricular complex; QTc, corrected QT interval; $t_{1/2}$, half-life; RVOT, right ventricular outflow tract; T3, triiodothyronine; TdP, torsades de pointes; U, urine; VT, ventricular tachycardia; and VF, ventricular fibrillation. Modified from Shleifer JW, et al. (2).

5.1.1. Medications With Prominent Sodium Channel Blockade

Except in specific circumstances, sodium channel blockers (Vaughn-Williams class I agents) have a limited role in the prevention of VT/SCD; this is based on a lack of survival benefit and increased mortality observed during chronic therapy in patients with ischemic heart disease (see Section 10.7). Specific circumstances where sodium channel blockers have been used to treat VT/SCA include: intravenous lidocaine for patients with refractory VT/cardiac arrest (especially witnessed) (3); oral mexiletine for congenital long QT syndrome (4); quinidine for patients with Brugada syndrome; and flecainide for patients with catecholaminergic polymorphic ventricular tachycardia (5). These medications could also be used in ICD patients with drug- and ablation-refractory VT.

One newer medication of potential benefit, based on very limited data, is ranolazine. This medication, developed and FDA-approved as an antianginal agent, provides relatively specific late sodium channel current blockade in addition to less potent blockade of the phase 3 repolarizing potassium current; that is, the rapid delayed rectifier potassium current; IKr. The potential for clinical antiarrhythmic efficacy is supported by basic studies and experimental models (6). Clinical data are scant. In a study of 12 patients, ranolazine reduced ICD shocks in otherwise medication-resistant VT/VF in 11 patients (7). In MERLIN TIMI-36 (Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST-Elevation Acute Coronary Syndromes-Thrombolysis In Myocardial Infarction 36), ranolazine did not reduce SCD but did reduce VT in the first few days after a non-ST-segment elevation ACS (8). In 1 RCT, high-risk ICD patients with ischemic or NICM were randomly assigned to ranolazine 1000 mg twice a day versus placebo (9). High risk was defined as: 1) having a primary prevention ICD without a history of documented VT/VF and with one of the following conditions: BUN ≥26 mg/dL, QRS >120 msec, atrial fibrillation, or NSVT or >500 VPBs on 24-hour Holter recording; 2) having a primary prevention ICD with a history of documented VT/VF appropriately treated with ICD therapy or untreated NSVT; or 3) having a secondary prevention ICD after documented VT/VF or cardiac arrest. Ranolazine did not significantly reduce the primary endpoint of VT/VF requiring appropriate ICD therapy or death. In a prespecified secondary analysis, ranolazine was associated with a significant reduction in VT events treated with anti-tachycardia pacing (9).

5.1.2. Beta Blockers

Because of their excellent safety profile and effectiveness in treating VA and reducing the risk of SCD, beta blockers are often first-line antiarrhythmic therapy (10, 11). Their antiarrhythmic efficacy is related to the effects of adrenergic-receptor blockade on sympathetically mediated triggering mechanisms, slowing of the sinus rate, and possibly inhibition of excess calcium release by the ryanodine receptor (12).

Beta blockers reduce all-cause mortality and SCD in patients with HF with reduced EF (HF*r*EF) (13-15). Although beta blockers have long been proven to reduce mortality after MI (16), registry data confirm that early beta blocker use in patients with MI and risk factors for shock (>70 years of age, symptoms <12 hours [ST-elevation MI patients], systolic blood pressure <120 mm Hg, and heart rate >110 beat/min on presentation) is associated with an increased risk of shock or death (17). In the setting of polymorphic VT after MI, beta blockers reduce mortality (18). Beta blockers suppress VA in some patients with structurally normal hearts (19). When used in combination with membrane-stabilizing antiarrhythmic medications, beta blockers can enhance antiarrhythmic efficacy (20). Beta blockers (e.g., nadolol, propranolol) are also first-line therapy for some cardiac channelopathies (e.g., long QT syndrome, catecholaminergic polymorphic ventricular tachycardia).

5.1.3. Amiodarone and Sotalol

Amiodarone possesses a wide spectrum of actions that include blockade of beta receptors and sodium, calcium and potassium currents (i.e., a multichannel blocker). Its overall long-term effect on survival is controversial, with most studies showing no clear advantage over placebo. A few studies and a meta-analysis of several large studies have shown a reduction in SCD using amiodarone in patients with LV dysfunction due to prior MI and NICM (21-23), but SCD-HeFT showed no survival benefit from amiodarone compared with placebo (24). A secondary analysis of the SCD-HeFT showed increased risk of mortality with amiodarone in patients with New York Heart Association (NYHA) class III symptoms (25). A systematic review of the literature in high-risk patients (LVEF <40%, with or without coronary disease), concluded that, for primary prevention, amiodarone, compared with no treatment or placebo, decreased the risk of SCD (Risk ratio: 0.76; 95% CI: 0.66–0.88) and all-cause mortality (Risk ratio: 0.88; 95% CI: 0.78–1.00), but the quality of the supporting evidence was very low (26). For secondary prevention of SCD, the same systematic review identified neither risk nor benefit with amiodarone (26). Compared with beta-blocker therapy and other antiarrhythmic medications (including sotalol), amiodarone appears to reduce the risk of SCD and all-cause mortality (26). Intravenous amiodarone has a role in reducing recurrent VF/VF during resuscitation (3, 27-29).

Chronic administration of amiodarone is associated with complex medication interactions and a host of adverse effects involving the lung, liver, thyroid, skin, and nervous system. As a general rule, the longer the therapy and the higher dose of amiodarone, the greater the likelihood of adverse effects that will require discontinuance of the medication (26). For this reason, chronic treatment of young patients with amiodarone should be reserved as a bridge to more definitive treatment options such as catheter ablation. Baseline evaluation of patients may include ECG, liver function tests, thyroid function tests, chest x-ray, and pulmonary function tests (including diffusing capacity of the lungs for carbon monoxide). Monitoring for toxicity generally includes periodic history and physical examination, as well as evaluation of the ECG, chest x-ray, and thyroid, liver, and lung function. High-resolution chest CT is generally reserved for suspected pulmonary toxicity (30).

Although sotalol has some efficacy in suppressing VA, it has significant proarrhythmic effects and has not been shown to improve survival (31). D-sotalol was shown in the SWORD (Survival With Oral d-Sotalol) trial to increase the risk of death in patients with heart failure (32). Unlike amiodarone and many other antiarrhythmic agents, sotalol appears to reduce the defibrillation threshold (33). Also, sotalol may lead to HF decompensation, and so its use in patients with an LVEF <20% is generally avoided.

5.1.4. Calcium Channel Blockers

For the treatment of most VA, nondihydropyridines calcium channel blockers have no role. In fact, intravenous verapamil given for sustained VT has been associated with hemodynamic collapse, especially in patients with prior MI (34, 35). For patients with a structurally normal hearts, verapamil or diltiazem can suppress some outflow tract origin (35-39). Oral and intravenous verapamil are effective in treating idiopathic interfascicular reentrant LVT (38). Calcium channel bloickers should not be given to patients with VT in the settin of HF*r*EF.

5.1.5. Nonantiarrhythmic Medications and Therapies

5.1.5.1. Electrolytes

Administration of potassium and magnesium has been proposed as helpful adjuncts in the prevention of VA (40, 41). Hypokalemia and hypomagnesemia are common consequences of diuretic therapy in HF, both have been associated with VA during an acute MI (41, 42), and can increase the risk of torsades de pointes in patients on medications or with conditions known to prolong the QT interval (43). In fact, in patients with torsades de pointes, intravenous magnesium is first-line therapy (44). In patients who are deficient in both magnesium and potassium, magnesium should be repleted to facilitate replacement of the potassium (45). In the case of potassium, some recommend keeping the potassium level between 4.5 mmol/L and 5 mmol/L to

prevent VA and SCD (46, 47). A large observational study of patients with an acute MI found that the lowest rates of death were seen in patients with serum potassium concentrations between 3.5 mmol/L and <4.5 mmol/L (48). Interestingly, the rates of VA did not rise unless the potassium was <3 mmol/L or ≥5 mmol/L. Likewise, a large randomized, double-blind trial of intravenous magnesium in the post-MI period demonstrated no benefit in 30-day mortality (40). It remains quite reasonable to monitor potassium and magnesium during aggressive diuresis and in the post-MI period.

5.1.5.2. n-3 Fatty Acids and Lipids

Both n-3 poly-unsaturated fatty acids and statin therapies may have a role in the prevention of SCD, thought to be due to a stabilization of the bilipid myocyte membrane involved in maintaining electrolyte gradients (49).

Early data were promising regarding the effects of n-3 polyunsaturated fatty acids on the reduction of cardiovascular events and SCD. In 2006, a large meta-analysis of 19 observational and RCTs demonstrated a significant association between the consumption of n-3 polyunsaturated fatty acids and prevention of SCD (50). The randomized GISSI (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto)-Prevenzione trial in people with recent MI, found that fish oil 1 g/d reduced mortality, due to fewer SCD (51). However, subsequent RCTs have not replicated these benefits and have shown n-3 polyunsaturated fatty acids to be ineffective (52-56). Because studies showed a consistent lack of harm from n-3 polyunsaturated fatty acids, patients can be reassured of their safety. Longer-term data will hopefully clarify the conflicting results.

In contrast, statin medications clearly reduce mortality and appear to reduce the risk of SCD related to ischemic heart disease (57). The predominant mechanism remains uncertain. Prevention of coronary plaque rupture or a direct cardioprotective effect reducing VA has been suggested. Experimental ischemia/reperfusion models demonstrate a cardioprotective effect of statins, and a large observational analysis observed this effect in humans (42, 56-58). This was explored further in HF in several secondary analyses of patients on statins in ICD prevention trials, including the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy), SCD-HeFT, AVID (Antiarrhythmics versus Implantable Defibrillators) (59), and DEFINITE (DEFibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation) trials that showed less SCD risk among the patients on statins (58, 60-62). However, this general effect in HF was not confirmed in 2 prospective RCTs of rosuvastatin in HF; the CORONA (Controlled Rosuvastatin Multinational Trial in Heart Failure) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca-Heart Failure) (63, 64). It appears that the beneficial effects of statins are confined to the population with or at risk for atherosclerotic cardiovascular disease and/or ischemia, and not HF generally.

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5.2. Preventing SCD With HF Medications

Recommendation for Pharmacological Prevention of SCD References that support the recommendation are summarized in Online Data Supplement 10.		
COR	**LOE**	**Recommendation**
I	**A**	**1. In patients with HF*r*EF (LVEF ≤40%), treatment with a beta blocker, a mineralocorticoid receptor antagonist and either an angiotensin-converting enzyme inhibitor, an angiotensin-receptor blocker, or an angiotensin receptor-neprilysin inhibitor is recommended to reduce SCD and all-cause mortality (1-8).**

Recommendation-Specific Supportive Text

1. For patients with HF and depressed LV function, appropriate medical therapy is important to reduce SCD. These therapies have various beneficial effects on arrhythmia mechanisms. Beta blockers reduce myocardial oxygen demand and electrical excitability, and counter arrhythmogenic effects of sympathetic stimulation. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers decrease preload and afterload, decreasing myocardial oxygen demand, blocking the formation of angiotensin II, and slowing the progression of ventricular remodeling and fibrosis. Mineralocorticoid receptor antagonists limit potassium loss, decrease fibrosis, and increase the myocardial uptake of norepinephrine (7).

RCTs in patients with HF*r*EF have consistently demonstrated that chronic therapy with beta blockers reduces all-cause mortality, VA, and SCD (2, 4, 5, 9). Three beta blockers (i.e., bisoprolol, carvedilol, sustained-release metoprolol succinate) have been proven to reduce mortality in patients with current or prior symptoms of HF*r*EF without beta-blocker contraindications. Angiotensin-converting enzyme inhibition also reduces mortality and SCD (3). Angiotensin-receptor blockers added to angiotensin-converting enzyme inhibitor showed additional benefit to angiotensin-converting enzyme inhibitors in some (10) but not other RCTs (8, 11). Therapy with the mineralocorticoid-receptor antagonists, spironolactone and eplerenone, have also demonstrated reductions in both all-cause mortality and SCD (6, 12, 13). Recent studies of the angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan) versus angiotensin-converting enzyme inhibitor demonstrated a reduction in SCD and cardiac mortality (14).

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5.3. Defibrillators for Treatment of VA and SCD

See Sections 7, 10.2, 10.3, 10.8, and 10.9.

Defibrillation is highly effective in terminating life-threatening VA. This therapy can be delivered by a transvenous ICD, a subcutaneous implantable cardioverter-defibrillator, a wearable cardioverter-defibrillator or an external defibrillator. These devices monitor the heart rhythm continuously and deliver therapy in response to a tachycardia that meets preprogrammed detection rates and arrhythmia duration. The vast majority of transvenous ICDs are implanted in the subclavicular area under fluoroscopy guidance. subcutaneous implantable cardioverter-defibrillators are implanted in the left side of the chest over the sixth rib between the left midaxillary and left anterior axillary lines. ICDs with epicardial sensing and pacing leads are still being implanted in some patients especially those with certain forms of congenital heart disease.

The transvenous ICD has been in clinical use for >3 decades, and robust data from high-quality RCTs support its use in various patient populations including survivors of cardiac arrest, patients with VT and structural heart disease, and patients with significant LV dysfunction.

5.4. Catheter Ablation

5.4.1. General Considerations

Catheter ablation is an important treatment option for patients with VA when antiarrhythmic medications are ineffective, not tolerated, or not desired by the patient. Monomorphic VA usually have an origin or substrate

that can be targeted for ablation. Ablation is an option for selected patients with polymorphic VT/VF only if an initiating PVC focus or substrate can be identified. The ablation strategy, risks and outcomes are related to the mechanism and location of the VA. Most VA originate close to the subendocardium and are approached through a transvenous (for the right ventricle) or transaortic/transeptal (for the left ventricle) catheterization. Some diseases give rise to VA from the subepicardium, which may be approached by epicardial mapping and ablation. Pericardial access is usually achieved by a percutaneous subxiphoid puncture. The catheter ablation procedure usually involves attempts to induce VT by programmed electrical stimulation to confirm the diagnosis and guide ablation. Problems limiting success include inability to induce an arrhythmia for mapping (common with idiopathic VA), or origin of the arrhythmia from an inaccessible location in the myocardium (common in some cardiomyopathies).

5.4.2. VA in Patients With No Apparent Structural Heart Disease

See Section 8.

VA that are not associated with underlying structural heart disease or a genetic arrhythmia syndrome are commonly referred to as idiopathic. Most idiopathic VA are monomorphic and based on a focal mechanism of triggered activity or abnormal automaticity; a few are due to reentry. For patients who are symptomatic, and in whom antiarrhythmic medications are ineffective, not tolerated, or not desired by the patient, catheter ablation is a treatment option. The ablation strategy is to identify the site of origin manifested by the earliest site of electrical activation, or when this is not practical, by pace mapping. Catheter ablation of idiopathic VA is usually accomplished with endocardial catheterization, though an epicardial approach through the coronary venous circulation or a subxiphoid pericardial puncture may occasionally be required. Ablation failure for idiopathic VA is often due to inability to provoke the arrhythmia to allow mapping in the electrophysiological laboratory or origin from an inaccessible region.

5.4.3. Scar-Related VT

See Section 8.

For most patients with structural heart disease, sustained monomorphic VT is due to reentry through regions of surviving myocardial fibers associated with areas of fibrous scar. The ablation strategy for these reentry circuits is to identify and eliminate channels of surviving myocardium within the scar that are often associated with slow conduction facilitating reentry. For most VTs that are related to prior MI, the substrate is on the subendocardial surface of the left ventricle. In NICM, the reentrant circuits are more variable in location, often involve the epicardial surface of either ventricle and frequently extending into the midmyocardium where ablation may be difficult to achieve from either surface. In tetralogy of Fallot specific reentry paths have been defined (1). Electroanatomical mapping that helps clarify the relation of electrophysiological abnormalities to cardiac anatomy is commonly employed. Areas of scar can be appreciated as regions of relatively low electrogram voltage. For scar-related VTs, hemodynamic intolerance often limits mapping during VT. Ablation is then often guided by substrate mapping, in which areas of scar and potential reentry circuit substrate are delineated in electroanatomic maps based on electrocardiographic and pacing characteristics assessed during hemodynamically stable sinus or paced rhythm. Catheter ablation of scar-related VT requires an advanced level of experience by the operator, electrophysiological laboratory staff, and anesthesiologists as well as availability of surgical back-up and specialized mapping, imaging, and ablation equipment (2, 3).

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5.5. Surgery and Revascularization Procedures in Patients With Ischemic Heart Disease

Recommendations for Surgery and Revascularization Procedures in Patients With Ischemic Heart Disease

References that support the recommendations are summarized in Online Data Supplement 11.

COR	LOE	Recommendations
I	B-NR	**1. Patients with sustained VA and survivors of SCA should be evaluated for ischemic heart disease, and should be revascularized as appropriate (1-4).**
I	C-EO	**2. In patients with anomalous origin of a coronary artery suspected to be the cause of SCA, repair or revascularization is recommended.**

Recommendation-Specific Supportive Text

1. Myocardial ischemia is a cause of sustained polymorphic VT/VF, and revascularization is an effective treatment to prevent myocardial ischemia. For patients with life-threatening VA, observational studies show that patients undergoing coronary artery bypass graft (CABG) had substantially better survival after accounting for other predictors (1, 5). The risk of SCD appears comparable for patients with complex ischemic heart disease randomized to treatment with PCI versus CABG (6). For patients with low LVEF and ischemic heart disease amenable to CABG, the risk of SCD is lower with CABG than medical therapy (2, 7). Observational studies show an association between a lower likelihood of death with revascularization for survivors of SCA and CABG (3) or PCI (4). Revascularization alone is usually insufficient to prevent recurrence of sustained monomorphic VT; further evaluation for inducible VT is generally considered if ventricular function is depressed and/or scar is present.

2. Anomalous aortic origin of the coronary arteries is detected in approximately 1% of patients undergoing routine coronary angiography, and <0.2% of children and adolescents undergoing echocardiography (8). Although ischemic heart disease is detected in as many as 24% to 55% of SCD cases in young patients <35 years of age (9, 10), anomalous aortic origin of the coronary arteries is an important cause of SCD in the young, reported in 10% to 17% of patients included in postmortem studies (10, 11). Anomalous origin of the coronary arteries can be identified by echocardiography, invasive coronary angiography, CT angiography or cardiac MRI. In patients with SCA or life-threatening VA presumed related to ischemia caused by anomalous origin of a coronary artery, repair or revascularization is performed to alleviate ischemia and reduce the recurrence of VA (6, 7, 12-14).

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5.5.1. Surgery for Arrhythmia Management

Recommendation for Surgery for Arrhythmia Management References that support the recommendation are summarized in Online Data Supplement 12.		
COR	**LOE**	**Recommendation**
IIb	**C-LD**	**1. In patients with monomorphic VT refractory to antiarrhythmic medications and attempts at catheter ablation, surgical ablation may be reasonable (1-7).**

Recommendation-Specific Supportive Text

1. Cardiac surgery as a standalone procedure for VT is rarely performed, but has a role in some highly symptomatic patients, when antiarrhythmic medications and catheter ablation fails or are not possible, particularly if the failure of ablation is due to an arrhythmia arising from an area that is inaccessible to catheter ablation, such as deep in the myocardium, beneath epicardial fat, or near the coronary arteries. Surgical ablation of tachycardia can also be performed at the time of other cardiac surgical interventions, such as during surgical resection of large aneurysms due to prior MI in which the border zone is often a substrate for VT, or placement of an LV assist device (LVAD) (5-7). The procedure requires detailed characterization of the arrhythmia usually with preoperative imaging and mapping, therefore, surgical ablation is best undertaken at tertiary referral centers and with collaboration between experienced surgeons and electrophysiologists.

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5.6. Autonomic Modulation

Recommendations for Autonomic Modulation References that support the recommendations are summarized in Online Data Supplement 13 and 14.		
COR	**LOE**	**Recommendations**
IIa	**C-LD**	**1. In patients with symptomatic, non–life-threatening VA, treatment with a beta blocker is reasonable (1).**
IIb	**C-LD**	**2. In patients with VT/VF storm in whom a beta blocker, other antiarrhythmic medications, and catheter ablation are ineffective, not tolerated, or not possible, cardiac sympathetic denervation may be reasonable (2-4).**

Synopsis

Sympathetic activation is proarrhythmic and parasympathetic activation is generally antiarrhythmic in VT/VF. Modulating the autonomic nervous system for the purpose of preventing arrhythmias is an emerging therapeutic modality. For the prevention of VA, autonomic modulation can be done either through interruption of sympathetic outflow to the heart, pharmacological beta blockade, or through stimulation of the parasympathetic pathway (e.g., vagal nerve stimulators, spinal cord stimulators). Although autonomic modulation has proven efficacy for certain conditions such as long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (see Section 7.9), evidence is limited for its applicability to the broader group of VA, but studies are ongoing. Currently, there are limited data on the role of vagal nerve stimulators and spinal cord stimulators for the prevention of VA/SCD in humans, and thus no formal recommendation could be supported (5).

Recommendation-Specific Supportive Text

1. Many patients with non–life-threatening VA require only reassurance, but others have symptoms that warrant therapy. A small RCT of patients with symptomatic VA demonstrated a significant reduction in the arrhythmic burden with atenolol (1).

2. VT/VF storm causes significant morbidity and is associated with increased mortality. For VT/VF storm refractory to treatment (medications, catheter ablation), cardiac sympathetic denervation has been shown in several small, observational studies (3, 6) and 1 RCT (4) to reduce the arrhythmia burden. This has been shown for left or bilateral cardiac sympathetic denervation, and it has been suggested that bilateral cardiac sympathetic denervation may be superior (3). Although data are limited, the significant morbidity and limited options in these patients make cardiac sympathetic denervation a reasonable option in selected patients.

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6. Acute Management of Specific VA

Recommendations for Management of Cardiac Arrest References that support the recommendations are summarized in Online Data Supplement 15 and 16.		
COR	**LOE**	**Recommendations**
I	A	1. CPR should be performed in patients in cardiac arrest. according to published basic and advanced cardiovascular life support algorithms (1-3).
I	A	2. In patients with hemodynamically unstable VA that persist or recur after a maximal energy shock, intravenous amiodarone should be administered to attempt to achieve a stable rhythm after further defibrillation (1, 4-6).
I	A	3. Patients presenting with VA with hemodynamic instability should undergo direct current cardioversion (1-3).
I	B-NR	4. In patients with polymorphic VT or VF with ST-elevation MI, angiography with emergency revascularization is recommended (7-10).
I	C-EO	5. Patients with a wide-QRS tachycardia should be presumed to have VT if the diagnosis is unclear.
IIa	A	6. In patients with hemodynamically stable VT, administration of intravenous procainamide can be useful to attempt to terminate VT (11-13).
IIa	B-R	7. In patients with a witnessed cardiac arrest due to VF or polymorphic VT that is unresponsive to CPR, defibrillation, and vasopressor therapy, intravenous lidocaine can be beneficial (1, 4, 5, 14, 15).
IIa	B-R	8. In patients with polymorphic VT due to myocardial ischemia, intravenous beta blockers can be useful (16, 17).
IIa	B-NR	9. In patients with a recent MI who have VT/VF that repeatedly recurs despite direct current cardioversion and antiarrhythmic medications (VT/VF storm), an intravenous beta blocker can be useful (17, 18).
IIb	A	10. In patients in cardiac arrest, administration of epinephrine (1 mg every 3 to 5 minutes) during CPR may be reasonable (1, 19-24).
IIb	B-R	11. In patients with hemodynamically stable VT, administration of intravenous amiodarone or sotalol may be considered to attempt to terminate VT (5, 13, 25, 26).
III: No Benefit	A	12. In patients with cardiac arrest, administration of high-dose epinephrine (>1 mg boluses) compared with standard doses is not beneficial (19, 21).
III: No Benefit	A	13. In patients with refractory VF not related to torsades de pointes, administration of intravenous magnesium is not beneficial (27, 28).
III: Harm	B-R	14. In patients with suspected AMI, prophylactic administration of lidocaine or high-dose amiodarone for the prevention of VT is potentially harmful (16, 29).
III: Harm	C-LD	15. In patients with a wide QRS complex tachycardia of unknown origin, calcium channel blockers (e.g., verapamil and diltiazem) are potentially harmful (30, 31).

Figure 2

Recommendation-Specific Supportive Text

1. The most common electrical mechanisms for cardiac arrest are VF and pulseless VT, but substantial numbers of cardiac arrests begin as severe bradyarrhythmias or asystole. Survival is better for patients presenting with VT or VF than for those with bradyarrhythmic or asystolic mechanisms (32). Rapid arrival of

paramedical personnel is the major determinant of survival. A number of strategies for responding to unexpected cardiac arrest, including rapid defibrillation and initiation of CPR for a witnessed cardiac arrest, have improved survival probabilities for cardiac arrest victims (2, 3). Nonetheless, the absolute number and proportion of survivors remain low, except in unique circumstances where there is an extraordinarily rapid response time to victims in VF or VT such as in monitored intensive care units, where survival is >90% (33-36). Survival decreases rapidly after the initial 2 minutes from the onset of cardiac arrest, so that by 4 to 5 minutes, survival may be ≤25%, and by 10 minutes it is 0% (33, 35, 36). Advanced life support activities, other than those directly related to cardioversion and defibrillation for control of tachyarrhythmias, have led to the generation of comprehensive protocols to guide responders. These AHA documents cover the broad expanse of clinical circumstances and considerations of mechanisms (1, 37).

2. Paramedic administration of amiodarone after at least 3 failed shocks and administration of epinephrine improved hospital admission rates when compared with placebo (6) or 1.5 mg/kg lidocaine (1, 4) in RCTs in adults with out-of-hospital cardiac arrest due to refractory VF or polymorphic VT, although survival to hospital discharge and survival with favorable neurologic outcome were not improved with amiodarone or lidocaine (5). However, in the subset of patients with witnessed cardiac arrest due to initial shock-refractory VF or pulseless VT, survival to hospital discharge after amiodarone administration was higher than with placebo (5). The administration of procainamide in out-of-hospital cardiac arrest due to VF or pulseless VT has been associated with more shocks, more pharmacologic interventions, longer resuscitation times, and lower survival (38).

3. VA with hemodynamic instability, including VF and pulseless monomorphic or polymorphic VT, causes loss of consciousness and leads to death if untreated. A short time to direct current cardioversion is the major determinant of survival, and defibrillation should be performed as quickly as possible. CPR is used until a perfusing rhythm is restored. If defibrillation is unsuccessful in returning spontaneous circulation, responders follow advanced cardiovascular life support activities (1-3).

4. Quickly identifying and treating patients with out-of-hospital cardiac arrest related to acute coronary occlusion is associated with improved survival and better functional recovery (37). Coronary occlusion as a cause of cardiac arrest is not reliably predicted by clinical and electrocardiographic findings (7), and emergency coronary angiography should be considered (rather than later in the hospital stay or not at all) for unstable patients with a suspected cardiac etiology regardless of whether the patient is comatose or awake (9, 39). In 1 observational study of patients resuscitated from SCA who did not have ST elevation and had angiography, one third were found to have a culprit lesion and coronary intervention appeared to be associated with a greater likelihood of favorable neurologic outcome (10).

5. The initial management of any tachycardia should proceed according to published AHA advanced cardiovascular life support guidelines (40). Immediate cardioversion should be performed for hemodynamic instability at presentation or if it develops subsequently. An ECG should be obtained for stable rhythms. Wide-complex tachycardias, defined by a QRS duration ≥0.12 s (37), can be due to VT, SVT with aberrancy, preexcited tachycardia, or a paced rhythm such as pacemaker-mediated tachycardia. An irregular wide-complex tachycardia may be AF with aberrancy, preexcited AF (i.e., AF using an accessory pathway for anterograde conduction), atrial flutter, or VT (37). A diagnosis should be established, and consultation with an arrhythmia expert considered (37).

6. In 1 study, amiodarone was more effective than lidocaine in terminating incessant VT with improved survival at 24 hours (26). For patients with recurrent, stable VT not in the setting of an AMI, intravenous procainamide has been shown to be superior to lidocaine for terminating the arrhythmia (11). One randomized trial of 62 patients found procainamide superior to amiodarone for termination of stable VT (13). Adverse events, including hypotension were more common with amiodarone, but the difference was not statistically significant. Procainamide and its metabolite n-acetylprocainamide have potassium channel blocking

properties that may prolong the QT interval. In patients who already have QT prolongation, administration of procainamide may further prolong the QT interval and lead to torsades de pointes (11, 12, 26).

7. Intravenous lidocaine is an alternative antiarrhythmic medication of long-standing and widespread familiarity. Compared with no antiarrhythmic medication, lidocaine did not consistently increase a return of spontaneous circulation after defibrillation and was not associated with improvement in survival to hospital discharge (4, 14, 41). In prospective, blinded, RCTs, lidocaine was less effective than amiodarone in improving hospital admission rates after out-of-hospital cardiac arrest due to shock-refractory VF or polymorphic VT; but there were no differences between the 2 medications in survival to hospital discharge (4, 5). However, in the subset of patients with witnessed SCA due to initial shock-refractory VF or pulseless VT, a subgroup analysis showed that survival to hospital discharge with lidocaine was better than with placebo (5, 42).

8. In a large meta-analysis of antiarrhythmic medications in the setting of AMI, beta blockers were associated with a significant reduction in mortality (16). Beta blockers can be effective in suppressing recurrent VF in patients with recent MI, with an associated improvement in survival (17).

9. In patients with recurrent VT/VF (VT/VF storm) in the setting of a recent MI that is refractory to amiodarone and/or lidocaine and repeated cardioversion, administration of a beta blocker has been shown to improve survival at 1 week. For those who did not survive, mortality was mostly due to recurrent VF. Survival at 1 year was also better in those treated with a beta blocker (17, 18). Other measures to reduce sympathetic tone including sedation and general anesthesia are also often used.

10. Epinephrine produces beneficial effects in patients during cardiac arrest, primarily because of its alpha-adrenergic (i.e., vasoconstrictor) effects (1). These alpha-adrenergic effects can increase coronary and cerebral perfusion pressure during CPR. The value and safety of the beta-adrenergic effects of epinephrine are controversial because they may increase myocardial work and reduce subendocardial perfusion (1). One trial assessed short-term and longer-term outcomes when comparing standard-dose epinephrine to placebo (23). Standard-dose epinephrine was defined as 1 mg given intravenously or intraosseously every 3 to 5 minutes. For both survival to discharge and survival to discharge with good neurologic outcome, there was no benefit with standard-dose epinephrine; however, the study was underpowered for analysis of either of these outcomes. There was, nevertheless, improved survival to hospital admission and improved return of spontaneous circulation with the use of standard-dose epinephrine. A number of trials have compared outcomes of standard-dose epinephrine with those of high-dose epinephrine. These trials did not demonstrate any benefit for high-dose epinephrine over standard-dose epinephrine in relation to survival to discharge with a good neurologic recovery, survival to discharge, or survival to hospital admission (1, 19, 21, 22).

11. Amiodarone was more effective than lidocaine in terminating incessant VT with improved survival at 24 hours (26). For patients with recurrent, stable VT not in the setting of an AMI, intravenous procainamide has been shown to be superior to lidocaine for terminating the arrhythmia (11). One RCT in 62 patients found procainamide superior to amiodarone for termination of stable VT (13). Adverse events, including hypotension, were more common with amiodarone, but the difference was not statistically signficant. Procainamide and its metabolite n-acetylprocainamide have potassium channel blocking properties that may prolong the QT interval. In patients who already have QT prolongation, administration of procainamide may further prolong the QT interval and lead to torsades de pointes (11). A single RCT of 33 patients comparing sotalol with lidocaine for treating patients with hemodynamically stable VT showed that VT was terminated in 69% of patients using sotalol and 18% using lidocaine (25). Intravenous sotalol has been approved for use in the United States. Sotalol has potassium channel blocking properties that may prolong the QT interval. In patients who already have QT interval prolongation, administration of sotalol may further prolong the QT interval and lead to torsades de pointes (25).

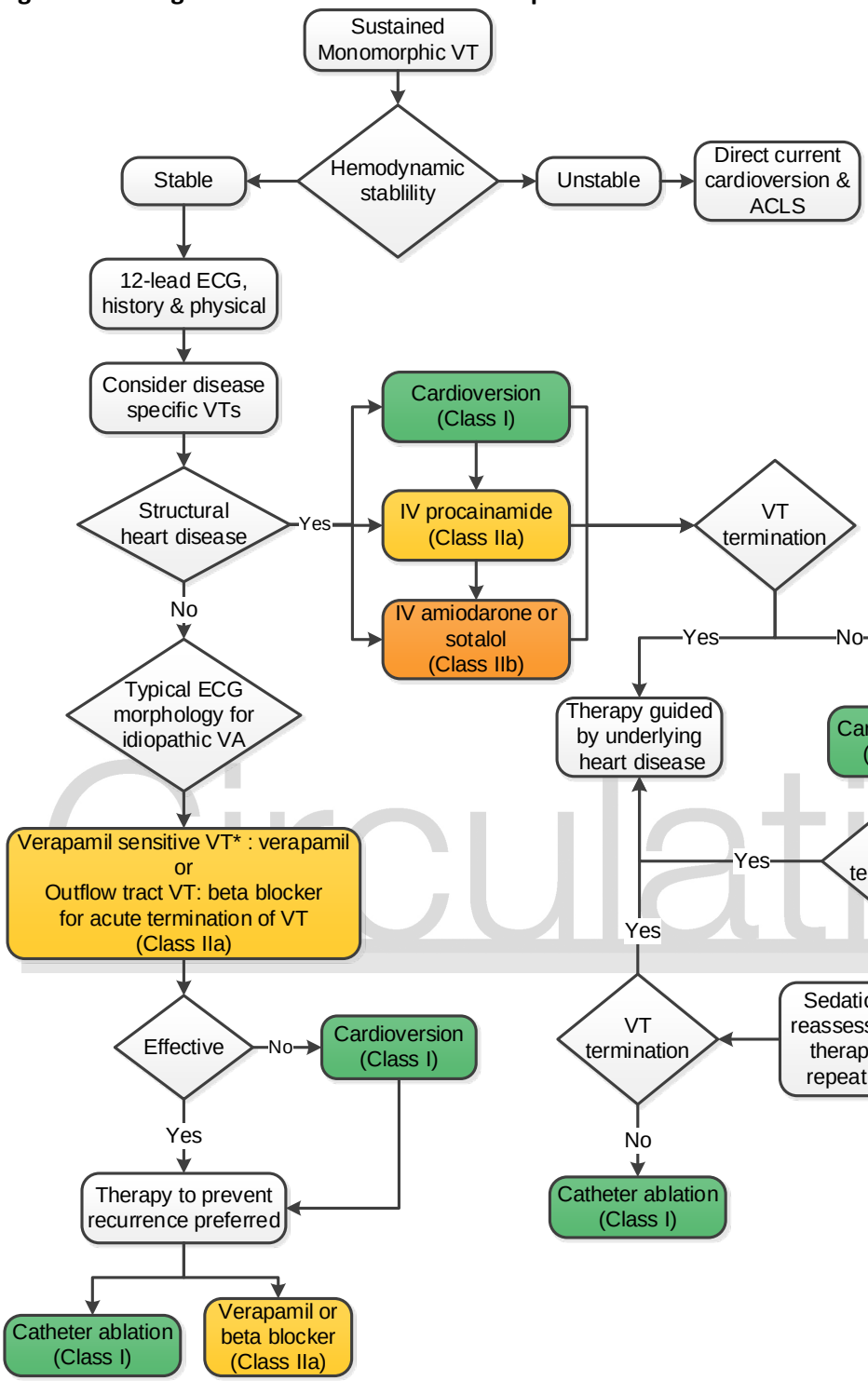
12. Epinephrine may increase coronary and cerebral perfusion pressure during CPR because of its vasoconstrictive effects. High doses of epinephrine (0.1 to 0.2 mg/ kg IV, as opposed to a standard dose of 1 mg) have been studied in RCTs. In out-of-hospital cardiac arrest unresponsive to defibrillation, administration of high-dose epinephrine improved survival to hospital admission, but there was no difference compared to standard dose epinephrine in survival to hospital discharge (19). There was also no improvement in long-term survival (21). Of note, the administration of vasopressin is no longer recommended in the most recent advanced cardiovascular life support algorithms (1).

13. Magnesium may suppress automaticity, suppress early and late after-depolarizations, and inhibit calcium flux into cardiomyocytes. It is effective in suppressing VA related to acquired long QT syndrome. However, 2 RCTs that investigated the use of intravenous magnesium in patients with cardiac arrest and refractory VF found no benefit (27, 28). In a study of out-of-hospital cardiac arrest, administration of 2 to 4 g magnesium intravenously did not improve survival to hospital admission (27). In a similar study involving inpatient cardiac arrest, magnesium did not improve return of spontaneous circulation, survival to 24 hours, or survival to hospital discharge (28). There are exceptions such as marked hypokalemia or medication-induced torsades de pointes in which administration of intravenous magnesium is warranted.

14. Several studies have tested the hypothesis that prophylactic administration of antiarrhythmic medications could reduce the incidence of post-MI VA and lead to better outcomes. One meta-analysis assessed studies in which beta blockers, class I antiarrhythmic agents such as lidocaine and procainamide, and amiodarone were given in the setting of AMI. The routine use of lidocaine and procainamide was associated with increased mortality, whereas beta blockers were associated with a significantly lower mortality rate (16). Limited data with amiodarone appeared to be promising, but a subsequent RCT involving 1073 patients found that administration of high-dose amiodarone led to a higher mortality rate, although a moderate dose of amiodarone was not superior to placebo (29).

15. With a stable, wide QRS complex tachycardia, differentiation between SVT with aberrancy and VT is often possible by review of the patient's history and the 12-lead ECG during tachycardia. Patients with wide QRS complex tachycardia and known structural heart disease should be presumed to have VT until proven otherwise. Administration of a calcium channel blocker such as verapamil to a patient with VT may result in severe hypotension or syncope (31). The exception is verapamil-sensitive VT (interfascicular reentry) that occurs in a structurally normal heart; but this is often difficult to recognize on initial presentation (30).

Figure 2. Management of Sustained Monomorphic VT



Colors correspond to Class of Recommendation in Table 1.
See Sections 7, 8.1.3, 8.2.3, and 10 for discussion.
*Known history of verapamil sensitive or classical electrocardiographic presentation.
ACLS indicates advanced cardiovascular life support; ECG, electrocardiogram; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

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7. Ongoing Management of VA and SCD Risk Related to Specific Disease States

7.1. Ischemic Heart Disease

7.1.1. Secondary Prevention of SCD in Patients With Ischemic Heart Disease

Recommendations for Secondary Prevention of SCD in Patients With Ischemic Heart Disease References that support the recommendations are summarized in Online Data Supplement 17 and 18.		
COR	**LOE**	**Recommendations**
I	B-R	**1. In patients with ischemic heart disease, who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) (1-4) or stable VT (LOE: B-NR) (5) not due to reversible causes, an ICD is recommended if meaningful survival greater than 1 year is expected.**
	B-NR	
Value Statement: Intermediate Value (LOE: B-R)		**2. A transvenous ICD provides intermediate value in the secondary prevention of SCD particularly when the patient's risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status (6).**
I	B-NR	**3. In patients with ischemic heart disease and unexplained syncope who have inducible sustained monomorphic VT on electrophysiological study, an ICD is recommended if meaningful survival of greater than 1 year is expected (7).**

Figure 3

Recommendation-Specific Supportive Text

1. In the AVID trial (1), the ICD improved overall survival compared with antiarrhythmic medication therapy (primarily amiodarone) in patients who survived SCD or with hemodynamically unstable VT, with a 2-year relative risk reduction in mortality of 27% and an absolute risk reduction of 7%. CIDS (Canadian Implantable Defibrillator Study) (2), which was stopped early after the results of the AVID trial were released, showed a similar, but not statistically significant, benefit of the ICD over antiarrhythmic medication therapy. A subsequent meta-analysis using data from 3 RCTs showed a statistically significant reduction in both arrhythmic and all-cause mortality with secondary prevention ICDs (3).

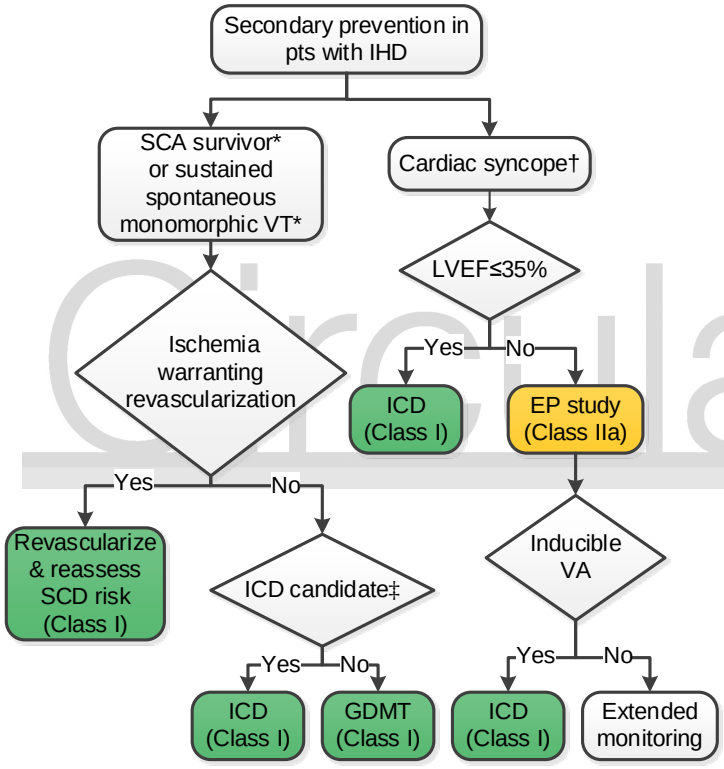
In survivors of life-threatening VA that may be due to transient or reversible factors, such as AMI, proarrhythmic medication effects, or electrolyte disturbances, an ICD is not implanted if the cause may be correctable. This is a population of patients that still requires thorough evaluation, treatment, and close follow-up and, as in the AVID registry, mortality was still high in the population that may have had a reversible cause for their arrest (8). Small increases in troponin present a challenge in selecting patients for an ICD, as it often cannot be determined whether troponin elevation is due to ischemia from VT/VF and resuscitation, in which case an ICD is likely warranted, or an indication that ischemia caused the arrhythmia, in which case prevention of ischemia would be the therapeutic focus.

ICDs may improve the outcomes of patients with hemodynamically tolerated sustained VT and structural heart disease (5); however, this has not proved in any RCT. VT ablation has been used as an alternative in selected patients with well-tolerated VT and appears to reduce recurrences, but the impact on long-term mortality is unknown; there is not yet sufficient evidence to recommend this approach as an alternative to ICD implantation (9, 10).

2. Economic outcomes of ICD implantation for secondary prevention of SCD were assessed in the AVID and CIDS trials (11, 12), as well as in a simulation model (13) and an observational study of Medicare beneficiaries (14). All studies compared ICD recipients with non-ICD recipients, and all found that ICD recipients had longer overall survival and higher lifetime costs of medical care. All studies reported incremental cost-effectiveness ratios between $64,000 and $100,000 per year of life added by an ICD (11-14), which is in the range of intermediate value by the benchmarks applied in the ACC/AHA cost/value statement (15).

3. VAs are an important cause of syncope or near syncope in patients with ischemic heart disease, particularly those with prior infarction. A study of 70 patients with unexplained syncope who underwent an electrophysiological study identified positive findings in 37 patients; 31 with VT. During 3 years of follow-up, patients with a positive electrophysiological study had higher rates of SCD and 3-year total mortality (61% versus 15%, respectively) than those with a negative electrophysiological study (7). An ICD is warranted for patients with syncope and inducible sustained monomorphic VT even if they do not otherwise meet criteria for primary prevention (Figure 4).

Figure 3. Secondary Prevention Patients With Ischemic Heart Disease



Colors correspond to Class of Recommendation in Table 1.
See Sections 4.3.1 and 7.1.1 for discussion.
*Exclude reversible causes.
†History consistent with an arrhythmic etiology for syncope.
‡ICD candidacy as determined by functional status, life expectancy, or patient preference.
EP indicates electrophysiological; GDMT, guideline-directed management and therapy; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; pts, patients; SCA, sudden cardiac arrest; SCD, sudden cardiac death; and VT, ventricular tachycardia.

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7.1.1.1. Coronary Artery Spasm

Recommendations for Patients With Coronary Artery Spasm References that support the recommendations are summarized in Online Data Supplement 20.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with VA due to coronary artery spasm, treatment with maximally tolerated doses of a calcium channel blocker and smoking cessation are indicated to reduce recurrent ischemia and VA (1, 2).**
IIa	**B-NR**	**2. In patients resuscitated from SCA due to coronary artery spasm in whom medical therapy is ineffective or not tolerated, an ICD is reasonable if meaningful survival of greater than 1 year is expected (3-6).**
IIb	**B-NR**	**3. In patients resuscitated from SCA due to coronary artery spasm, an ICD in addition to medical therapy may be reasonable if meaningful survival of greater than 1 year is expected (3-6).**

Recommendation-Specific Supportive Text

1. Coronary artery spasm results from vasomotor dysfunction and can occur in the presence or absence of atherosclerotic ischemic heart disease. Vasospasm episodes can lead to VA, syncope, and SCD. Treatment includes risk factor elimination including smoking cessation, and treatment with vasodilators including dihydropyridine calcium channel blockers with or without nitrates. A more detailed summary of treatments for coronary artery spasm can be found in other guideline documents (7, 8).

2. Patients with coronary artery spasm who survive an SCA are a high-risk population (5). Recurrent VA, even life-threatening, may be prevented if coronary artery spasm can be effectively addressed with risk factor modification, smoking cessation, and ongoing treatment with nitrates and dihydropyridine calcium channel blockers (9). However, SCA or VA can recur despite medical therapy or if compliance is poor. Whether a wearable cardioverter-defibrillator may provide protection while medical therapy is being evaluated has not been assessed but is of interest (10). An ICD can terminate VT/VF initiated by spasm, potentially preventing SCD.

3. Patients with coronary vasospasm who survive an SCA are a high-risk population, and some support the use of an ICD in those patients based on the reported event rates from observational studies (5) even before determining the patient's response to or compliance with medical therapy. Recurrent SCA can occur despite medical therapy. Regardless of the approach, risk factor modification (e.g., illicit drug use), smoking cessation, and ongoing treatment with dihydropyridine calcium channel blockers with or without nitrates represent essential treatments (9).

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7.1.1.2. Post CABG VT/VF

The incidence of sustained VT or VF early after CABG is low, but these VAs are associated with high in-hospital mortality (1). VF occurring very early (intraoperatively or within 24 hours postoperatively) may be due to the transient effects of reperfusion, electrolyte and acid base disturbances, and the use of inotropes. Patients who present with VF or polymorphic VT in the postoperative period more often have associated ischemia, while patients presenting with monomorphic VT usually have an old infarct and ventricular scar (2). Polymorphic VT/VF occurring after CABG warrants a therapeutic approach targeting treatment of myocardial ischemia, including a possible need for assessment of graft patency, as well as identification and treatment of mechanical complications and acute electrolyte or acid base disturbances. Risk factors for occurrence of monomorphic VT early after CABG include prior MI, ventricular scar, LV dysfunction, and placement of a bypass graft across a noncollateralized occluded coronary vessel to a chronic infarct zone (3). Unlike polymorphic VT and VF, sustained monomorphic VT is typically not due to acute ischemia. Many of these patients have inducible sustained VT at electrophysiological study. Management of symptomatic VA in the early period after CABG follows the recommendations for acute and ongoing management of VT detailed elsewhere in this document. In patients without sustained VT or VF but with LV dysfunction prior to undergoing CABG, implantation of an ICD did not improve survival (4). For patients with LV dysfunction who are undergoing revascularization, there is a possibility that the LV function may improve, so many advocate for reassessment of the LV function 3 months after revascularization before a decision about ICD implantation is made (5). For patients with a high burden of NSVT and reduced LVEF, an electrophysiological study may be helpful for risk stratification; those with inducible sustained VT may benefit from an ICD (6). The wearable cardioverter-defibrillator may play a role in patients at risk of SCD in the early phase after revascularization to allow time for recovery of ventricular function (7).

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7.1.2. Primary Prevention of SCD in Patients With Ischemic Heart Disease

Recommendations for Primary Prevention of SCD in Patients With Ischemic Heart Disease References that support the recommendations are summarized in Online Data Supplement 21.		
COR	**LOE**	**Recommendations**
I	A	1. In patients with LVEF of 35% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class II or III HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1, 2).
I	A	2. In patients with LVEF of 30% or less that is due to ischemic heart disease who are at least 40 days' post-MI and at least 90 days postrevascularization, and with NYHA class I HF despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (2, 3).
Value Statement: High Value (LOE: B-R)		3. A transvenous ICD provides high value in the primary prevention of SCD particularly when the patient's risk of death due to a VA is deemed high and the risk of nonarrhythmic death (either cardiac or noncardiac) is deemed low based on the patient's burden of comorbidities and functional status (4).
I	B-R	4. In patients with NSVT due to prior MI, LVEF of 40% or less and inducible sustained VT or VF at electrophysiological study, an ICD is recommended if meaningful survival of greater than 1 year is expected (5).
IIa	B-NR	5. In nonhospitalized patients with NYHA class IV symptoms who are candidates for cardiac transplantation or an LVAD, an ICD is reasonable if meaningful survival of greater than 1 year is expected (6-9).
III: No Benefit	C-EO	6. An ICD is not indicated for NYHA class IV patients with medication-refractory HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities.

Figure 4

Recommendation-Specific Supportive Text

1. The rationale for recommending that an ICD be offered to patients with NYHA class II or III HF, in addition to LVEF ≤35%, is based on the survival benefit observed in SCD-HeFT and MADIT-II (which used LVEF cutoff of below 35% and 30%, respectively). Selection for implantation of an ICD must be individualized. Patients with serious comorbidities associated with a survival of <1 year are generally not considered ICD candidates. The recommendation to wait at least 40 days after an MI before implanting a primary prevention ICD is based on the fact that such patients were excluded from MADIT-II and SCD-HeFT and 2 other RCTs showed no survival benefit from ICDs implanted early after an acute MI (10, 11).

2. In the MADIT-II trial (2), which randomized patients with LVEF ≤30% and prior MI to an ICD or not, approximately one third of the patients had NYHA class I symptoms. A subgroup analysis supported benefit of the ICD on survival in this subgroup (2).

3. Economic outcomes of ICD implantation for primary prevention of SCD were assessed in 3 RCTs [MADIT-I (12), MADIT-II (13), and SCD-HeFT (14)], 1 observational study (15), and 4 simulation models (16-19), which all had generally consistent results. All studies reported increased survival and life expectancy, and higher lifetime costs of medical care with an ICD than without an ICD. The incremental cost-effectiveness ratios were

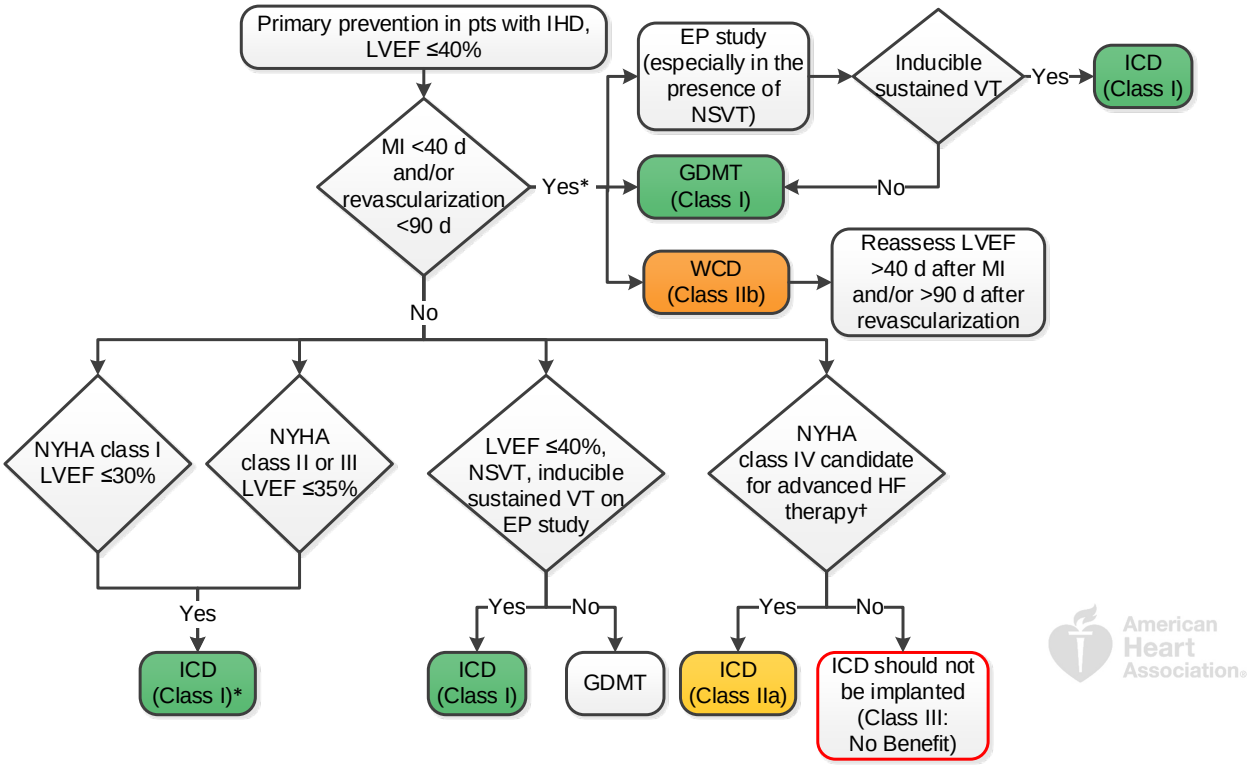
generally <$50,000 per year of life added by an ICD, which provides high value according to the benchmarks adopted for the current guideline (20). The value provided by an ICD was consistently high when life expectancy was projected to increase by >1.4 years (18). In contrast, when survival was not increased by ICD implantation, as in the CABG-Patch trial (18), the ICD did not provide value, because the higher costs were unaccompanied by a gain in life expectancy.

4. MUSTT (Multicenter Unsustained Tachycardia Trial) demonstrated that patients with prior MI, NSVT, and reduced LVEF with inducible VT at electrophysiological study have a higher overall mortality rate than similar patients without inducible sustained VT (21). Patients who received an ICD after failing to have inducible VT suppressed by an antiarrhythmic medication had lower mortality rate than those who did not receive an ICD. Although the entry criteria into MUSTT required an LVEF of ≤40%, the average LVEF in enrolled patients was 30%, and ICD placement was not randomized but rather was selected by the treating physician for patients with VT that could not be suppressed with antiarrhythmic medication therapy. MUSTT allowed enrollment of patients who were ≥4 days after an acute MI or revascularization. The ICD was of no benefit in 2 other RCTs that examined the efficacy of the ICD in the acute phase of an MI (10, 11). In a single center observational study, an electrophysiological study was performed a median of 9 days after acute MI in 115 patients with LVEF <40% and ICDs recommended for those with inducible VT. Median follow-up was 12 months. Sustained VT was induced in 27% of patients, and 22% of those who received ICDs had spontanous VT terminated by the ICD during follow-up. None of the patients without inducible VT had VT or SCD during follow-up (22).

5. In a retrospective analysis of the UNOS (United Network for Organ Sharing) registry that extended from 1999 to 2014, data on 32,599 patients showed that during a median follow-up of 154 days, 3,638 patients (11%) died while on the waitlist for cardiac transplantation (9% in the ICD group versus 15% in the non-ICD group; p<0.0001). The presence of an ICD at listing was associated with an adjusted 13% relative risk reduction in mortality. In the subgroup of patients with an LVAD (n=9,478), an ICD was associated with an adjusted 19% relative risk reduction in mortality (9). In another study of 380 patients listed for heart transplantation between 2005 and 2009 at 1 tertiary heart transplant center, 122 patients received an ICD before or within 3 months after being listed for heart transplantation. Non-ICD patients were more likely to die while on the transplant list. In a multivariable model, the ICD was not associated with improved survival; however, that analysis was limited by the small sample size (8). Another small study (n=79) conducted at 1 institution suggested that ICDs reduce the risk of SCD in patients with LVEF ≤30% who are awaiting heart transplantation; however, this study was limited by the small number of patients (6). In a retrospective multicenter study of 1,089 patients listed for heart transplantation, 550 patients (51%) had an ICD. In 216 patients, the ICD was for primary prevention of SCD and, in 334 patients, the ICD was for secondary prevention. The remaining 539 patients did not receive an ICD. During a median time on the waiting list of 8 months, the ICD was associated with a reduction in all-cause mortality in the primary and secondary prevention cohorts (estimated 1-year: 88±3% versus 77±3% versus 67±3%; p=0.0001). This relationship between the ICD and improved survival persisted even after adjusting for potential confounders (7).

6. There are insufficient data from RCTs regarding the value of the ICD in patients with NYHA class IV HF. Ambulatory class IV patients with HF were included in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, which showed an overall improved functional status and survival with a CRT defibrillator (23). Unless such a patient is a candidate for CRT or advanced HF therapies such as heart transplantation or an LVAD, an ICD is not expected to meaningfully prolong survival (23).

Figure 4. Primary Prevention of SCD in Patients With Ischemic Heart Disease



Colors correspond to Class of Recommendation in Table 1.
See Section 7.1.2 for discussion.
*Scenarios exist for early ICD placement in select circumstances such as patients with a pacing indication or syncope
†Advanced HF therapy includes CRT, cardiac transplant, and LVAD.
thought due to VT. These are detailed elsewhere in an HRS/ACC/AHA expert consensus statement (24).
CRT indicates cardiac resynchronization therapy; EP, electrophysiological; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; pts, patients; SCD, sudden cardiac death; VT, ventricular tachycardia; and WCD, wearable cardioverter-defibrillator.

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7.1.3. Treatment and Prevention of Recurrent VA in Patients With Ischemic Heart Disease

Recommendations for Treatment of Recurrent VA in Patients With Ischemic Heart Disease References that support the recommendations are summarized in Online Data Supplement 22 and 23.		
COR	**LOE**	**Recommendations**
I	**B-R**	**1. In patients with ischemic heart disease and recurrent VA, with significant symptoms or ICD shocks despite optimal device programming and ongoing treatment with a beta blocker, amiodarone or sotalol is useful to suppress recurrent VA (1-3).**
I	**B-R** **B-NR**	**2. In patients with prior MI and recurrent episodes of symptomatic sustained VT, or who present with VT or VF storm and have failed or are intolerant of amiodarone (LOE: B-R) (4) or other antiarrhythmic medications (LOE: B-NR) (5-9), catheter ablation is recommended (10-12).**
IIb	**C-LD**	**3. In patients with ischemic heart disease and ICD shocks for sustained monomorphic VT or symptomatic sustained monomorphic VT that is recurrent, or hemodynamically tolerated, catheter ablation as first-line therapy may be considered to reduce recurrent VA (10, 11).**
III: Harm	**B-R**	**4. In patients with prior MI, class IC antiarrhythmic medications (e.g., flecainide and propafenone) should not be used (13).**
III: Harm	**C-LD**	**5. In patients with incessant VT or VF, an ICD should not be implanted until sufficient control of the VA is achieved to prevent repeated ICD shocks (14).**
III: No Benefit	**C-LD**	**6. In patients with ischemic heart disease and sustained monomorphic VT, coronary revascularization alone is an ineffective therapy to prevent recurrent VT (15, 16).**

Figure 5

Recommendation-Specific Supportive Text

1. The most common antiarrhythmic medications used for suppression of VA include amiodarone and sotalol, while mexiletine, quinidine, and ranolazine are occasionally used (17, 18). Amiodarone appears to be more effective than sotalol and has a low rate of ventricular proarrhythmia, but has an increased risk of medication-related adverse effects that lead to its discontinuation in many patients within 18 to 24 months from initiation of therapy (1, 19). Data supporting effectiveness of sotalol for suppression of VA are conflicting, but given its more favorable adverse effect profile than amiodarone, it may be a better first-line antiarrhythmic medication in appropriate patients (1-3). However, sotalol is generally avoided in patients with a severely reduced LVEF <20% due to its negative inotropic effects and the risk of torsades de pointes. In a double-blind placebo-controlled study of 674 patients with HF and ≥10 PVCs/h and an LVEF ≤40% randomly assigned to receive amiodarone (336 patients) or placebo (338 patients), there was no significant difference in overall mortality or SCD between the 2 arms. There was a trend toward a reduction in overall mortality among the patients with NICM who received amiodarone (p=0.07) (20).

2. Patients with prior MI may present with frequent episodes of sustained monomorphic VT or recurrent VF episodes that are initiated by PVCs arising from Purkinje Fibers in the peri-infarct zone. VA storms are associated with increased mortality (12). The arrhythmia substrate is usually in the subendocardium. The randomized VANISH (Ventricular Tachycardia Ablation versus Escalated Antiarrhythmic Drug Therapy in Ischemic Heart Disease) trial (4) compared escalating antiarrhythmic medication therapy versus catheter

ablation for patients with prior MI and recurrent sustained monomorphic VT despite antiarrhythmic medications. The primary outcome, a composite of death, VT storm, or ICD shocks occurred in 59.1% in the ablation group and in 68.5% in the escalated-therapy group. There was no difference in mortality between the groups. Recurrent ICD shocks and VT storm and treatment-related adverse events were lower in the ablation group. In a subgroup analysis, patients having VT on amiodarone had better outcomes with ablation compared with increasing amiodarone or adding mexiletine to amiodarone. For patients receiving medications other than amiodarone, catheter ablation did not reduce the risk of ICD shocks or VT storm compared with switching to amiodarone. Although recurrent VT after catheter ablation is associated with increased mortality (9), whether mortality is reduced by catheter ablation has not been established. Procedural complications occur in approximately 6% of patients, most of which are related to vascular access but stroke, tamponade, and atrioventricular block can occur. Procedure mortality is <1% in experienced centers (4, 9).

Sustained monomorphic VT often occurs as occasional isolated episodes in patients with prior MI. Several nonrandomized studies have shown that catheter ablation reduces recurrent VT or ICD shocks (5, 7, 8). A meta-analysis of 5 VT ablation studies (5) reported that VT recurred in 35% of patients after catheter ablation compared with 55% on antiarrhythmic medications. In a multicenter study of catheter ablation (7) for patients with ≥3 episodes of sustained VT in the prior 6 months, 53% were free from recurrent VT at 6 months follow-up; the median number of VT episodes was reduced from 11.5 to 0. Superiority of ablation over escalating medication therapy was shown in the composite endpoint of death, VT storm, or ICD shocks by the VANISH trial (4).

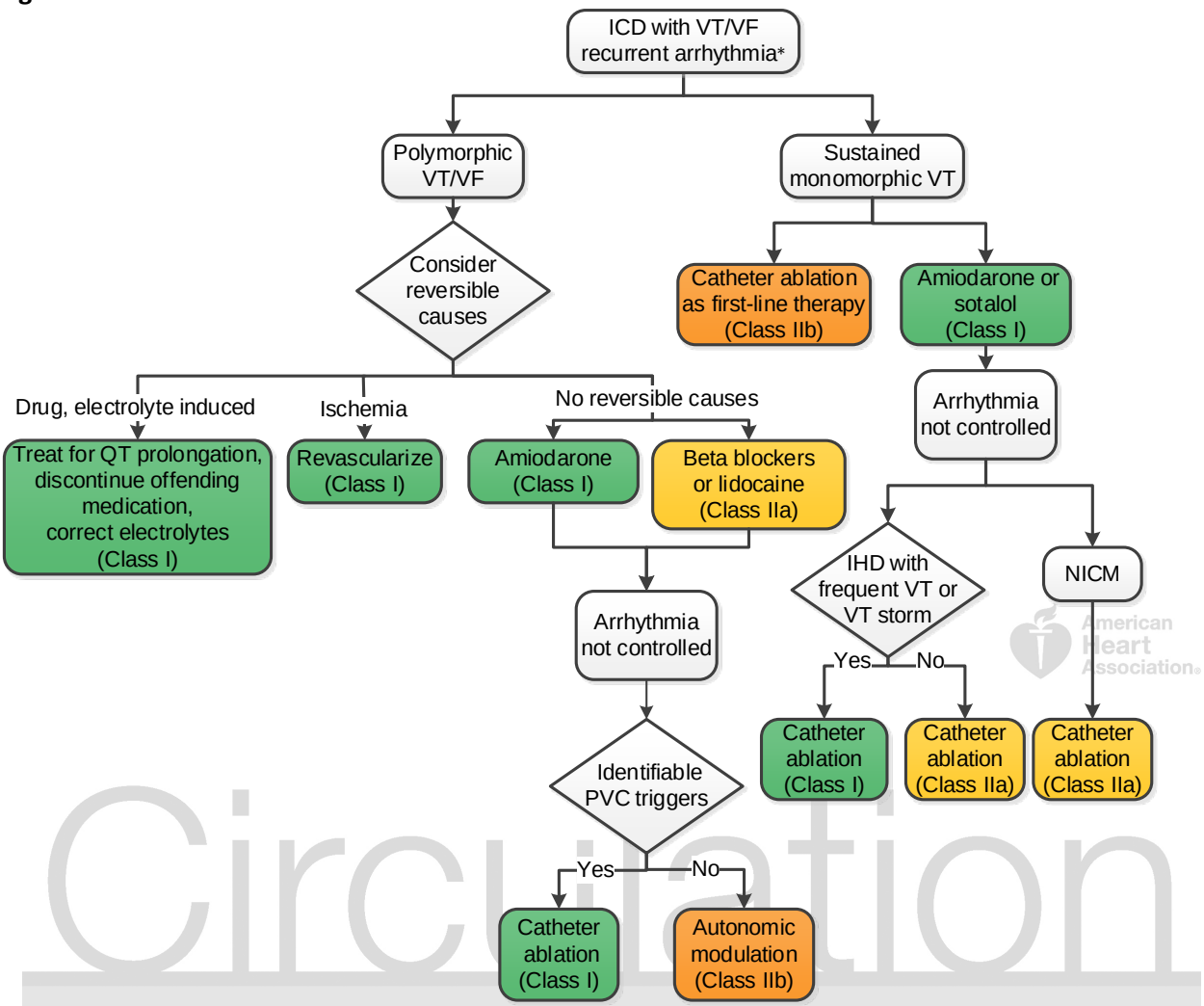
3. Patients with prior MI who develop sustained monomorphic VT often have recurrent episodes. The VTACH (Ventricular Tachycardia Ablation in Addition to Implantable Defibrillators in Coronary Heart Disease) trial (11) randomized patients undergoing ICD implantation for stable sustained monomorphic VT, who had not failed antiarrhythmic medication therapy, to catheter ablation versus ICD implantation alone. At 2 years, any VT had recurred in 53% of the ablation group and 71% of the control group. Ablation prolonged the time to recurrent VT from a median of 5.9 months to 18.6 months (11). Several nonrandomized studies have shown that catheter ablation reduces the risk of recurrent VT or ICD shocks in patients with sustained VT related to prior MI (5, 7, 8). In a multicenter study of catheter ablation (7) for patients with ≥3 episodes of sustained VT in the prior 6 months, 53% were free from recurrent VT at 6 months follow-up; the median number of VT episodes was reduced from 11.5 to 0. A meta-analysis of 5 VT ablation studies (5) reported that VT recurred in 35% of patients after catheter ablation compared with 55% on antiarrhythmic medications. Another study of 63 patients with recurrent VT after MI demonstrated acute success with catheter ablation in 83% of mappable VTs and 40% of nonmappable VTs (8). Superiority of ablation over escalating medication therapy for patients with recurrent VT despite antiarrhythmic medications was shown by the VANISH trial (4). See Section 5.6.

4. CAST (21) demonstrated higher rates of mortality or nonfatal cardiac arrest in post-MI patients treated with encainide or flecainide when used to suppress PVCs and NSVT (13). Propafenone is associated with increased mortality in SCA survivors compared with beta blockers, amiodarone, and the ICD (22).

5. Implantation of an ICD prior to achieving suppression of frequent or incessant VA places the patient at high risk of repetitive shocks, which can be psychologically detrimental and has been associated with increased mortality (23, 24).

6. Sustained monomorphic VT in the setting of prior MI is typically due to scar-related reentry and is not due to acute ischemia. Although it may be appropriate to recommend revascularization when another indication for revascularization exists, revascularization alone is unlikely to reduce the recurrence of monomorphic VT and specific therapies such as antiarrhythmic medications or ablation may be needed to prevent recurrence (16). On the contrary, revascularization might be beneficial in patients with ischemic heart disease and VF, polymorphic VT, or exercise-induced arrhythmias associated with ischemia (25).

Figure 5. Treatment of Recurrent VA in Patients With Ischemic Heart Disease or NICM



Colors correspond to Class of Recommendation in Table 1.
See Sections 5.6, 6, 7.1.3, and 7.2 for discussion.
*Management should start with ensuring that the ICD is programmed appropriately and that potential precipitating causes, including heart failure exacerbation, are addressed. For information regarding optimal ICD programming, refer to the 2015 HRS/EHRA/APHRS/SOLAECE expert consensus statement (26).
APHRS indicates Asia Pacific Heart Rhythm Society; EHRA, European Heart Rhythm Association; HRS, Heart Rhythm Society; IHD, ischemic heart disease; ICD, implantable cardioverter-defibrillator; PVC, premature ventricular complex; NICM, nonischemic cardiomyopathy; SOLAECE, Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología; VF, ventricular fibrillation; and VT, ventricular tachycardia.

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7.2. Nonischemic Cardiomyopathy

Recommendations for Patients With NICM References that support the recommendations are summarized in Online Data Supplement 24.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with suspected NICM from myocardial infiltrative processes, cardiac MRI with late gadolinium enhancement is useful for diagnosis (1-3).**
IIa	**B-NR**	**2. In patients with suspected NICM, cardiac MRI with late gadolinium enhancement can be useful for assessing risk of SCA/SCD (1-3).**
IIa	**C-EO**	**3. In patients with NICM who develop conduction disease or LV dysfunction at less than 40 years of age, or who have a family history of NICM or SCD in a first-degree relative (<50 years of age), genetic counseling and genetic testing are reasonable to detect a heritable disease that may clarify prognosis and facilitate cascade screening of relatives (4, 5).**

Recommendation-Specific Supportive Text

1. Cardiac MRI allows for evaluation of structural heart disease and assessment of LV and RV function including quantification of LVEF, LV mass and volume, and valvular structure. Cardiac MRI can help in the evaluation for myocardial infiltrative processes and evidence of scar, indicated by delayed hyperenhancement, associated with VA (1-4, 6).

2. The presence of delayed hyperenhancement has been associated with worse outcomes, including SCD (1-3).

3. It is important to consider genetic etiologies for NICM. Goals of genetic testing for NICM are to identify at-risk relatives who host a disease-causing mutation and to help clarify prognosis. *Lamin A/C* and *NKX 2.5* mutations (7-12) are associated with a particularly high risk of early conduction disease, arrhythmias, and SCD, and their identification often prompts consideration of early use of an ICD. It is unknown, however, whether early pharmacological treatment of mutation-positive, asymptomatic subjects can prevent or delay manifestation of the disease or whether genetic testing ultimately improves survival.

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7.2.1. Secondary Prevention of SCD in Patients With NICM

Recommendations for Secondary Prevention of SCD in Patients With NICM References that support the recommendations are summarized in Online Data Supplement 25 and 26.		
COR	**LOE**	**Recommendations**
I	**B-R** **B-NR**	**1. In patients with NICM who either survive SCA due to VT/VF or experience hemodynamically unstable VT (LOE: B-R) (1-4) or stable VT (LOE: B-NR) (5) not due to reversible causes, an ICD is recommended if meaningful survival greater than 1 year is expected.**
IIa	**B-NR**	**2. In patients with NICM who experience syncope presumed to be due to VA and who do not meet indications for a primary prevention ICD, an ICD or an electrophysiological study for risk stratification for SCD can be beneficial if meaningful survival greater than 1 year is expected (6-11).**
IIb	**B-R**	**3. In patients with NICM who survive a cardiac arrest, have sustained VT, or have symptomatic VA who are ineligible for an ICD (due to a limited life-expectancy and/or functional status or lack of access to an ICD), amiodarone may be considered for prevention of SCD (12, 13).**

Figure 6

Recommendation-Specific Supportive Text

1. Three prospective RCTs compared the ICD with pharmacological therapy in patients resuscitated from SCA due to VT/VF or hemodynamically significant VT (1, 2, 4). The antiarrhythmic medications most commonly used were amiodarone, a beta blocker, or both, although in the CASH (Cardiac Arrest Study Hamburg) trial (4), there was also a propafenone arm that was terminated early due to increased mortality. The 3 trials enrolled 1,963 patients, but only 292 (14.8%) had NICM. A meta-analysis in which data from AVID and CIDS were pooled found a nonsignificant 31% reduction in all-cause mortality relative to medical therapy in patients with NICM (3). Although this analysis was underpowered, the observed mortality reduction was consistent with the observed benefit in the entire study population. In the AVID trial (1), patients who were ineligible for the RCT were included in a registry, and sustained VT without serious symptoms or hemodynamic compromise was associated with a mortality rate similar to that of patients with unstable VT who were assigned to medical therapy. Therefore, stable VT is likely a marker for a substrate capable of producing subsequent lethal arrhythmias (5).

2. Small observational studies demonstrated high mortality and frequent appropriate ICD shocks in patients with syncope and NICM (7-9). The assumption that malignant VAs are the likely cause of syncope and that the ICD would be protective has recently been challenged. In a subgroup analysis of SCD-HeFT that included 472 patients, the ICD did not reduce either recurrent syncope or the increased risk of mortality associated with syncope (10). A subgroup analysis of the MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy) trial found syncope to be arrhythmic only in 39% of patients (11). These studies

suggest that syncope in some HF patients may be an indicator of an end-stage cardiomyopathy associated with a poor prognosis (11). In a substudy of DEFINITE, inducible sustained VT/VF was found in a minority of patients, but it was associated with appropriate ICD therapy (14). Another study of electrophysiological testing in NICM found inducible VT/VF in 27.8% of patients, which was associated with future ICD events (15). In a study of patients with NICM, cardiac mortality correlated with LVEF but not with inducibility on electrophysiological study (16). Based on these data, many experts are uncomfortable withholding an ICD from patients with NICM who experience syncope potentially due to a VA even if the electrophysiological study shows no inducible sustained VT.

3. Access to ICDs may be limited by financial, medical, or personal considerations. In addition, not all patients at high risk of SCD meet ICD indications, such as those with class IV HF without CRT possibility or with a life expectancy <1 year. A meta-analysis of RCTs, which examined the use of amiodarone for the prevention of SCD, included 15 studies with 8522 patients assigned to amiodarone or placebo/control (12). Amiodarone reduced the risk of SCD by 29%; however, it did not reduce all-cause mortality and was associated with an increased risk of pulmonary and thyroid toxicity. In a subgroup analysis, the benefit of amiodarone appeared similar in patients with ischemic cardiomyopathy and those with NICM (12). In a separate meta-analysis (13), the evidence was insufficent to support amiodarone's efficacy for reduction of SCD and all-cause mortality in survivors of cardiac arrest or those with syncope due to VA. A subgroup analysis of the VALIANT (Valsartan in Acute Myocardial Infarction) trial found that amiodarone was associated with increased mortality in patients with NYHA class III HF (17). These data call for a careful and nuanced approach to using amiodarone for the secondary prevention of SCD in patients with NICM.

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7.2.2. Primary Prevention of SCD in Patients With NICM

Recommendations for Primary Prevention of SCD in Patients With NICM References that support the recommendations are summarized in Online Data Supplement 27 and 28.		
COR	**LOE**	**Recommendations**
I	**A**	**1. In patients with NICM, HF with NYHA class II–III symptoms and an LVEF of 35% or less, despite GDMT, an ICD is recommended if meaningful survival of greater than 1 year is expected (1-6).**
IIa	**B-NR**	**2. In patients with NICM due to a *Lamin A/C* mutation who have 2 or more risk factors (NSVT, LVEF <45%, nonmissense mutation, and male sex), an ICD can be beneficial if meaningful survival of greater than 1 year is expected (7-10).**
IIb	**B-R**	**3. In patients with NICM, HF with NYHA class I symptoms and an LVEF of 35% or less, despite GDMT, an ICD may be considered if meaningful survival of greater than 1 year is expected (5).**
III: No Benefit	**C-EO**	**4. In patients with medication-refractory NYHA class IV HF who are not also candidates for cardiac transplantation, an LVAD, or a CRT defibrillator that incorporates both pacing and defibrillation capabilities, an ICD should not be implanted.**

Figure 6

Recommendation-Specific Supportive Text

1. For all patients with NICM, it is imperative that patients be on GDMT for HF for at least 3 months before a primary prevention ICD is offered. Four prospective RCTs (1, 2, 5, 6) initially evaluated ICDs for primary prevention of SCD in patients with NICM. Two (2, 6) were small studies that were terminated early due to a low event rate. In DEFINITE (5), an ICD reduced the risk of SCD, with a trend toward reduced all-cause mortality. SCD-HeFT included 792 NICM patients (1). Total mortality at 5 years was 27% in the placebo group and 21% in the ICD group (p=0.06). A pooled analysis of these studies demonstrated a significant 31% reduction in all-cause mortality for ICD relative to medical therapy (4). The DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial (11) raised questions about the role of primary pevention ICDs in patients with NICM. This trial randomized 1116 patients with NICM LVEF <35% and class II, III, or IV (if CRT was planned) HF to an ICD or no ICD. CRT (either ICD or pacemaker) was present in 58% of patients in the ICD and medical therapy arms. Therefore, the results of DANISH should not be generalized to patients with NICM who are ineligible for CRT. During a median follow-up of 5.6 years, ICD reduced SCD from 8.4% to 4.3%, but there was no difference in all-cause mortality (11). Several meta-analyses have been published (12, 13). One provided data on ICDs with and without CRT and showed survival

benefit from the ICD (13). The second used patient level data from 2 trials and adopted a more robust approach to reducing heterogeneity by excluding patients with CRT and those randomized to antiarrhythmic medications; a 25% relative risk reduction in mortality with an ICD was shown (12).

2. Laminopathies are diseases caused by mutations mainly in the *Lamin A/C* gene that produce various inherited diseases including subtypes of muscular dystrophy and progeria. Isolated cardiac involvement is also observed and is an important cause of familial cardiomyopathy (9). The disease is highly penetrant such that all affected individuals have evidence of disease by 60 years of age. Cardiac manifestations may include atrial fibrillation, conduction disturbances, VA, and NICM. A number of observational studies reported a high risk of SCD when cardiac involvement is present (7-10). One study reported SCD as the most frequent mode of death (46%) in both the isolated cardiac and the neuromuscular phenotypes of *Lamin* diseases (9). In a cohort of 269 *LMNA* mutation positive individuals (10), NSVT during ambulatory electrocardiographic monitoring, LVEF <45% at first evaluation, male sex, and nonmissense mutations were independent risk factors for VA. Malignant VA were observed only in persons with ≥2 of these risk factors (10). No studies have tested the effect of the ICD on long-term survival.

3. Patients with NICM and class I HF symptoms were not included in SCD-HeFT or DANISH (1, 11). Although such patients were included in the DEFINITE trial, only 99 (21.6%) of 458 patients in the DEFINITE trial had class I HF (5). Therefore, it is uncertain whether a primary prevention ICD in such patients improves survival.

4. There are insufficient data from RCTs regarding the value of the ICD in patients with NYHA class IV. Ambulatory class IV HF patients were included in the COMPANION trial that, overall, showed improved functional status and survival with a CRT defibrillator (3). Unless such a patient is a candidate for CRT or advanced HF therapies such as heart transplantation or an LVAD, an ICD is not expected to meaningfully prolong survival (3).

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7.2.3. Treatment of Recurrent VA in Patients With NICM

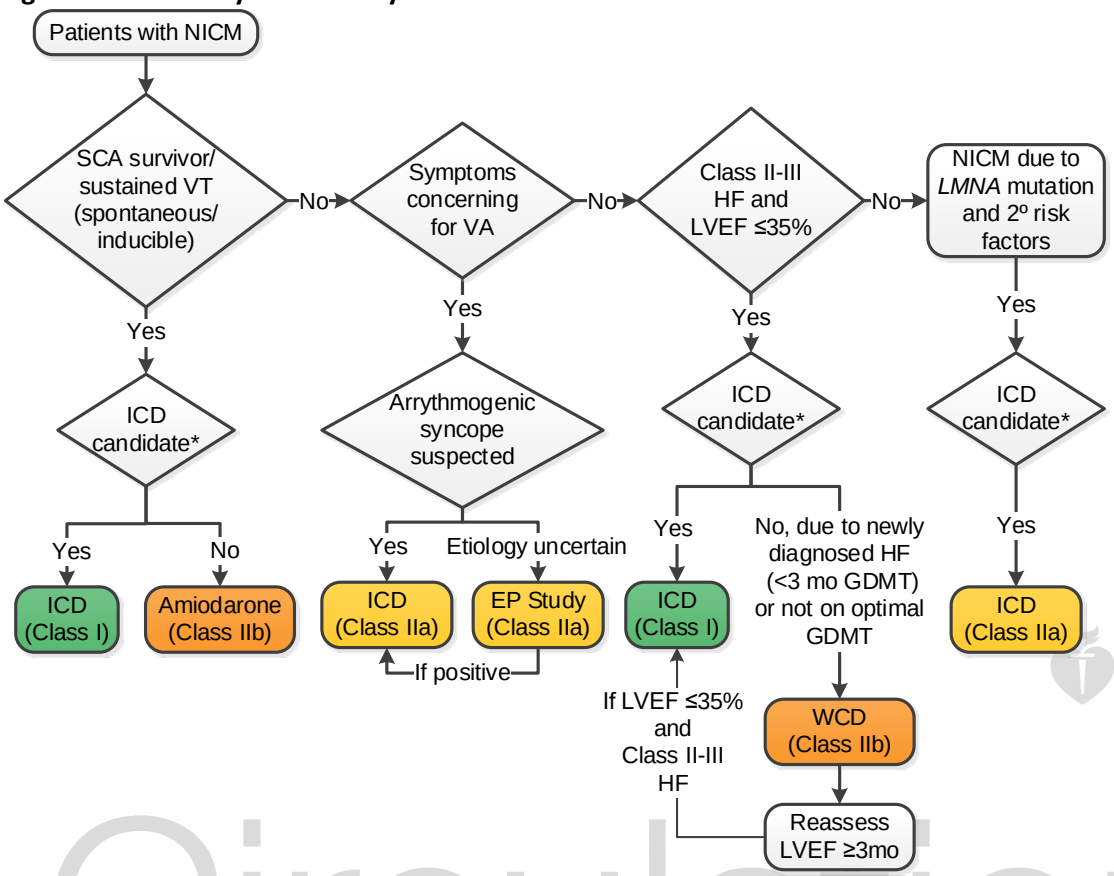
Recommendations for Treatment of Recurrent VA in Patients With NICM References that support the recommendations are summarized in Online Data Supplement 29.		
COR	**LOE**	**Recommendations**
IIa	**B-R**	**1. In patients with NICM and an ICD who experience spontaneous VA or recurrent appropriate shocks despite optimal device programming and treatment with a beta blocker, amiodarone or sotalol can be beneficial (1).**
IIa	**B-NR**	**2. In patients with NICM and recurrent sustained monomorphic VT who fail or are intolerant of antiarrhythmic medications, catheter ablation can be useful for reducing recurrent VT and ICD shocks (2, 3).**

Recommendation-Specific Supportive Text

1. ICDs reduce mortality from VA, yet ICD shocks are painful and associated with significant morbidity and poor QoL. Although ICDs are highly programmable and provide antitachycardia pacing therapy that can terminate most VT episodes without the need for a shock, prevention of shocks, both appropriate and inappropriate, remains an important concern. In the OPTIC (Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients) study, 412 patients with documented VT and VF who received an ICD within 21 days of the documented arrhythmia (1) were randomized to amiodarone plus beta blocker, sotalol alone, or beta blocker alone. Over 1 year, shocks occurred in 38.5% assigned to beta blocker alone, 24.3% assigned to sotalol, and 10.3% assigned to amiodarone plus beta blocker. The rates of study medication discontinuation at 1 year were 18.2% for amiodarone, 23.5% for sotalol, and 5.3% for beta blocker alone. Adverse pulmonary and thyroid events and symptomatic bradycardia were more common among patients randomized to amiodarone. Thus, amiodarone plus beta blocker were more effective than sotalol in preventing ICD shocks but at the expense of increased risk of medication-related adverse effects (1). Sotalol should not be used in patients with an LVEF <20% due to its negative inotropic effects.

2. Sustained monomorphic VT due to NICM is most often due to scar-related reentry. Cardiac MRI often indicates scar location, which tends to be basal along the mitral annulus or in the septum (4, 5). The VT substrate can be subendocardial, subepicardial, or intramyocardial, and all locations may be affected and require endocardial and epicardial ablation. In the HELP-VT (Heart Center of Leipzig VT) study (2), successful ablation of all VT morphologies was achieved in 66.7% of patients with NICM, compared with the 77.4% success rate in ischemic cardiomyopathy. An epicardial approach to ablation was required in 30.2% of NICM patients, compared with only 1.2% with ischemic cardiomyopathy. Epicardial ablation was an independent predictor of successful ablation. Acute and long-term success of ablation is lower for NICM, compared with post-MI patients. The long-term survival-free of VT recurrence after catheter ablation appears to be better for patients with ischemic than NICM (57% versus 40.5% at 1 year) (2). Risks are similar to those observed for post-MI VT ablation, with additional risks of epicardial access and ablation when required. Although any NICM can produce scar-related VT, cardiac sarcoidosis (see Section 7.6) and *Lamin* mutations are particularly associated with sustained monomorphic VT (6).

Figure 6. Secondary and Primary Prevention of SCD in Patients With NICM



Colors correspond to Class of Recommendation in Table 1.
See Section 7.2 for discussion.
*ICD candidacy as determined by functional status, life expectancy or patient preference.
2° indicates secondary; EP, electrophysiological; GDMT, guideline-directed management and therapy; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NICM, nonischemic cardiomyopathy; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; and WCD, wearable cardiac-defibrillator.

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7.3 Arrhythmogenic Right Ventricular Cardiomyopathy

Recommendations for Arrhythmogenic Right Ventricular Cardiomyopathy References that support the recommendations are summarized in Online Data Supplement 30.		
COR	**LOE**	**Recommendations**
I	B-NR	1. In selected first-degree relatives of patients with arrhythmogenic right ventricular cardiomyopathy, clinical screening for the disease is recommended along with genetic counseling and genetic testing, if the proband has a disease causing mutation (1-4).
I	B-NR	2. In patients with suspected arrhythmogenic right ventricular cardiomyopathy and VA or electrocardiographic abnormalities, cardiac MRI is useful for establishing a diagnosis and for risk stratification (5-8).
I	B-NR	3. In patients with arrhythmogenic right ventricular cardiomyopathy and an additional marker of increased risk of SCD (resuscitated SCA, sustained VT, significant ventricular dysfunction with RVEF or LVEF ≤35%), an ICD is recommended if meaningful survival greater than 1 year is expected (9-13).
I	B-NR	4. In patients with arrhythmogenic right ventricular cardiomyopathy and VA, a beta blocker is recommended (11, 14, 15).
I	B-NR	5. In patients with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy , avoiding intensive exercise is recommended (11, 12, 16-21).
IIa	B-NR	6. In patients with clinically diagnosed or suspected arrhythmogenic right ventricular cardiomyopathy , genetic counseling and genetic testing can be useful for diagnosis and for gene-specific targeted family screening (1, 4, 22-26).
IIa	B-NR	7. In patients with arrhythmogenic right ventricular cardiomyopathy and syncope presumed due to VA, an ICD can be useful if meaningful survival greater than 1 year is expected (10, 11, 13).
IIa	B-NR	8. In patients with clinical evidence of arrhythmogenic right ventricular cardiomyopathy but not VA, a beta blocker can be useful (14, 15).
IIa	B-NR	9. In patients with arrhythmogenic right ventricular cardiomyopathy and recurrent symptomatic sustained VT in whom a beta blocker is ineffective or not tolerated, catheter ablation with availability of a combined endocardial/epicardial approach can be beneficial (27-33).
IIa	B-NR	10. In patients with suspected arrhythmogenic right ventricular cardiomyopathy , a signal averaged ECG can be useful for diagnosis and risk stratification (14, 34, 35).
IIb	B-NR	11. In asymptomatic patients with clinical evidence of arrhythmogenic right ventricular cardiomyopathy , an electrophysiological study may be considered for risk stratification (9, 36).

Synopsis

Arrhythmogenic right ventricular cardiomyopathy is an inherited cardiomyopathy that predominantly affects the right ventricle but can affect the left ventricle causing areas of myocardial replacement with fibrosis and adipose tissue that frequently causes VA and SCD.

Recommendation-Specific Supportive Text

1. Selected first-degree relatives refers to relatives who are willing to undergo further testing and who could benefit from further screening and testing (and not the terminally ill patients or those who do not want to be

screened and tested). Arrhythmogenic right ventricular cardiomyopathy is often due to a mutation involving a desmosomal protein, and it usually has autosomal dominant inheritance with variable penetrance. SCD can be the initial manifestation of arrhythmogenic right ventricular cardiomyopathy. Clinical screening with ECG, cardiac imaging, and ambulatory rhythm monitoring and/or exercise testing may identify family members at risk for arrhythmogenic right ventricular cardiomyopathy. Arrhythmogenic right ventricular cardiomyopathy is detected clinically in approximately 35% to 40% of first-degree relatives (3, 4), most commonly in siblings or symptomatic first-degree relatives (4). When a proband is identified with a disease-causing mutation, targeted genotype screening can identify mutation positive relatives (1), with approximately 35% of mutation positive individuals ultimately developing progressive disease expression (1, 4). In studies of arrhythmogenic right ventricular cardiomyopathy mutation-positive individuals who do not initially manifest the disease, 8% to 16% have a major arrhythmic event over the next 7 to 39 years (1, 4, 26). Early identification of affected or potentially affected family members can allow lifestyle modifications in sports participation and serial monitoring for development of electrocardiographic abnormalities, symptoms, ventricular dysfunction, or arrhythmia. As genetic testing for arrhythmogenic right ventricular cardiomyopathy has subtle complexities, the decision to proceed with family screening is facilitated by informed genetic counseling to discuss the cost of testing, the potential lack of a single gene as the determinant for disease expression, psychological implications of uncertain disease progression, and implications for lifestyle modification, screening, and potential treatment.

2. Cardiac MRI provides high-quality assessment of ventricular function, size, regional wall motion abnormalities, and extent of scar and fibrosis (late gadolinium enhancement) that are seen in 30% to 95% of patients with the clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy (5, 6, 37, 38). Cardiac MRI detects biventricular involvement in 34% to 56% of patients, with isolated LV involvement noted in 4% to 9% of patients (37-40). Cardiac MRI should include assessment of late gadolinium enhancement with quantification of fibrosis. Application of the 2010 Task Force Criteria to cardiac MRI criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy has improved the specificity of this test (5, 8). Electrocardiographic and Holter findings precede detectable cardiac MRI abnormalities in arrhythmogenic right ventricular cardiomyopathy mutation-positive individuals, with only 4% of patients with normal electrocardiographic and Holter results having cardiac MRI abnormalities, suggesting that evaluation of cardiac structure and function using cardiac MRI may be unnecessary in mutation-positive individuals who do not have electrical abnormalities (7). The presence of both electrocardiographic abnormalities and abnormal cardiac MRI findings may identify patients at an increased risk for developing sustained VA (7, 38). Areas of scar identified on cardiac MRI have correlated with the location of VT substrate identified by endocardial and epicardial mapping (38). During early stages of disease, a baseline cardiac MRI may provide useful information along with electrocardiographic and rhythm abnormalities to monitor disease progression over time. Experience and expertise in interpretation of cardiac MRI are important (5, 8).

3. Arrhythmogenic right ventricular cardiomyopathy is characterized by progressive ventricular myocyte loss with replacement by fatty or fibrous tissue, and is associated with progressive ventricular dysfunction that may involve both ventricles. VA, syncope, and SCD may occur at a relatively young age, particularly in the second and third decades of life and often occurring during physical activity (1, 16, 22, 41). Sustained VT is an important predictor of SCA and SCD or appropriate ICD shocks in patients with arrhythmogenic right ventricular cardiomyopathy (10, 13). In patients receiving an ICD for primary prevention, appropriate ICD shocks are reported in 24% to 48% of patients (9, 10, 12, 13). As sustained VT in arrhythmogenic right ventricular cardiomyopathy patients is monomorphic in 55% to 90% of episodes based on ICD interrogation or electrophysiological studies (12, 36), antitachycardia pacing algorithms are used to terminate VT.

4. Frequent PVCs, >760 to 1000 per 24 hours during ambulatory rhythm monitoring, correlate with arrhythmic risk (9, 23). The presence of NSVT or sustained VT is an important predictor of adverse cardiac events (9, 12, 13, 42, 43). The increased arrhythmia risk conferred by intense exercise is consistent with beta-adrenergic

modulation of disease expression (17, 20, 21). An observational registry reported that treatment with atenolol or amiodarone was associated with less clinically relevant VA, while sotalol was associated with no effect or increased arrhythmia (15). Ambulatory monitoring to assess VA burden and adequacy of beta-blocker therapy is usually used (9, 14, 23, 42).

5. Patients with arrhythmogenic right ventricular cardiomyopathy have a significantly increased risk of SCD during exertion (16, 17, 20, 21). Vigorous exercise in patients with arrhythmogenic right ventricular cardiomyopathy has been shown to impair myocardial function by echocardiography and cardiac MRI (19). Participation in high intensity/duration or endurance physical activity accelerates the penetrance/disease progression and arrhythmic risk for arrhythmogenic right ventricular cardiomyopathy patients and mutation positive individuals, as well as mutation positive family members (17, 19-21). Patients with arrhythmogenic right ventricular cardiomyopathy who participate in competitive sports are at increased risk for VT or SCD, compared with those who participate in recreational sports or are inactive (17-19, 21). Exercise influences disease progression in a linear manner; family members who limited activity to less than the AHA recommended minimum for activity guidelines (<650 metabolic equivalent hours per year [MET-Hr/year]) were less likely to develop VA or disease progression (21). In a study of arrhythmogenic right ventricular cardiomyopathy probands and exercise, athletes (defined as subjects with ≥4 h vigorous exercise/week) were found to have reduced biventricular function compared with nonathletes in arrhythmogenic right ventricular cardiomyopathy patients and in mutation-positive family members (19). Many advise limiting exercise intensity and duration to <650 MET-Hr/year, or 12.5 MET-Hr/week (21).

6. The proband with arrhythmogenic right ventricular cardiomyopathy is usually diagnosed by the presence of clinical symptoms along with the presence of arrhythmogenic right ventricular cardiomyopathy Task Force criteria including: abnormalities on ECG, structural and functional changes of either ventricle, arrhythmias, and arrhythmogenic right ventricular cardiomyopathy in first-degree relatives (6). A pathogenic genetic mutation was added to the major Task Force criteria in 2010 (44). The yield of genetic testing in probands with suspected arrhythmogenic right ventricular cardiomyopathy is generally 30% to 54%, and is up to 58% among patients with a strong family history of SCD in multiple members (3, 25, 45). A negative genetic test for arrhythmogenic right ventricular cardiomyopathy does not exclude the disease, and a positive genetic test currently does not guide therapy (22). For the proband with a clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy, identification of pathogenic mutations provides limited prognostic information relative to the risk of VT/VF (22, 26) or development of HF (22). In a large multicenter study, the presence of positive mutations among probands was not associated with a difference in mortality or cardiac transplantation (1). However, the identification of a pathogenic mutation facilitates targeted genetic screening for that mutation in first-degree relatives, that may identify approximately 60% to 70% as gene positive (1), highest among siblings, and those with symptoms (4). Screening for the specific mutation can identify some gene positive family members prior to disease expression, while relieving others from the need for lifestyle changes and long-term monitoring (2, 3).

7. Syncope is reported in 16% to 39% of arrhythmogenic right ventricular cardiomyopathy patients at the time of diagnosis (13, 14, 16, 41, 43), is frequently exercise-related, and has been associated with high arrhythmic risk in some studies (10, 41). Among patients with arrhythmogenic right ventricular cardiomyopathy and implanted ICDs, syncope was an important predictor of appropriate shocks in 1 study (10), but not in other studies (9, 12, 13, 43). Studies have not provided information about ventricular function or abnormalities on ECG in patients with syncope, limiting its assessment as an independent risk factor. Syncope may be a harbinger of progression of underlying disease and should be integrated into the decision-making process for ICD implantation with the patient.

8. Asymptomatic patients with arrhythmogenic right ventricular cardiomyopathy and no VA or ventricular dysfunction are generally observed without antiarrhythmic therapy other than beta-blocker therapy, with ongoing periodic reassessment for the development of arrhythmias or ventricular dysfunction (46, 47).

Atenolol was shown to reduce VA in 1 study (15). Ambulatory monitoring and/or exercise testing can be performed to assess adequacy of beta-blocking dosing.

9. Interrogation of ICDs shows that >90% of spontaneous sustained VTs in arrhythmogenic right ventricular cardiomyopathy are monomorphic (12), while sustained monomorphic VT is inducible at electrophysiological study in 55% of patients (36). VT is usually related to scar-related reentry, and the subepicardium usually has more extensive scar than the endocardium (27). In experienced centers, use of epicardial mapping and ablation is associated with better outcomes (27, 28, 30, 31, 33). Important complications including pericardial tamponade, MI, and death occur in 2.3% to 3.3% of ablation cases (27-29), emphasizing the need for performance in centers with specialized expertise in epicardial procedures. Ablation reduces the frequency of recurrent VT, although 27% to 55% of patients (27, 28) have at least 1 recurrence; ablation of VT in arrhythmogenic right ventricular cardiomyopathy patients does not eliminate the need for an ICD in appropriate candidates. The potential risk of VT recurrence due to disease progression should be reviewed with patients when considering ablation. There are no randomized comparisons of antiarrhythmic therapy to suppress recurrent VT. Beta blockers, sotalol and amiodarone have been used (15). In an observational series, sotalol suppressed inducible VT in 58% of patients with <10% of patients experiencing arrhythmia recurrence during follow-up (48). Effectiveness of the different medications appears to be variable, and so more studies are needed.

10. In arrhythmogenic right ventricular cardiomyopathy, areas of fibrofatty scar in the RV free wall create areas of delayed ventricular activation causing fractionated deflections following the QRS, known as epsilon waves on the surface ECG (a major criterion) and late potentials in the signal averaged ECG (minor criterion) in the 2010 Task Force Criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy (6). When the standard ECG QRS duration is ≤110 ms, criteria for abnormal signal-averaged ECG include any 1 of the following: filtered QRS duration ≥114 ms, duration of the terminal QRS <40 uV exceeding 37 ms, or a root mean square voltage in the terminal 40 ms of ≤20 uV (6). Abnormal findings on signal averaged ECG correlated with disease severity on cardiac MRI (35), and increased adverse events in males (34). In an assessment of the diagnostic use of testing for arrhythmogenic right ventricular cardiomyopathy, signal averaged ECG was of greater value than cardiac MRI or biopsy (14).

11. The value of an electrophysiological study is uncertain in asymptomatic arrhythmogenic right ventricular cardiomyopathy patients with preserved ventricular function in predicting subsequent risk for SCD. Studies of programmed ventricular stimulation in patients with definite or probable arrhythmogenic right ventricular cardiomyopathy include most symptomatic patients, making recommendations on asymptomatic patients difficult. Electrophysiological studies induce sustained VT in approximately 60% of patients (10, 36); many of whom have had prior spontaneous episodes of sustained VT. In patients with primary prevention ICDs, inducible sustained VT did not predict subsequent appropriate ICD shocks (13). In 1 study including symptomatic patients, patients without inducible VT were less likely to receive appropriate ICD shocks (9). In asymptomatic patients without evidence of VA on ambulatory monitoring, a negative electrophysiological study may have limited value in decision-making for an ICD.

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7.4. Hypertrophic Cardiomyopathy

Recommendations for HCM References that support the recommendations are summarized in Online Data Supplement 31.		
COR	**LOE**	**Recommendations**
I	B-NR	1. In patients with HCM, SCD risk stratification should be performed at the time of initial evaluation and periodically thereafter (1-8).
I	B-NR	2. In patients with HCM who have survived an SCA due to VT or VF, or have spontaneous sustained VT causing syncope or hemodynamic compromise, an ICD is recommended if meaningful survival greater than 1 year is expected (1, 6, 9, 10).
I	B-NR	3. In first-degree relatives of patients with HCM, an ECG and echocardiogram should be performed (11-17).
I	B-NR	4. In first-degree relatives of patients with HCM due to a known causative mutation, genetic counseling and mutation-specific genetic testing are recommended (13-15, 18, 19).
IIa	B-NR	5. In patients with clinically suspected or diagnosed HCM, genetic counseling and genetic testing are reasonable (13-15, 18-22).
IIa	B-NR C-LD C-LD	6. In patients with HCM and 1 or more of the following risk factors, an ICD is reasonable if meaningful survival of greater than 1 year is expected: a. Maximum LV wall thickness ≥30 mm (LOE: B-NR) (2, 3, 23, 24). b. SCD in 1 or more first-degree relatives presumably caused by HCM (LOE: C-LD) (25, 26). c. 1 or more episodes of unexplained syncope within the preceding 6 months (LOE: C-LD) (8, 26).
IIa	B-NR C-LD	7. In patients with HCM who have spontaneous NSVT (LOE: C-LD) (2, 26, 27) or an abnormal blood pressure response with exercise (LOE: B-NR) (5, 28, 29), who also have additional SCD risk modifiers or high risk features, an ICD is reasonable if meaningful survival greater than 1 year is expected.
IIb	B-NR B-NR	8. In patients with HCM who have NSVT (LOE: B-NR) (2, 26, 27) or an abnormal blood pressure response with exercise (LOE: B-NR) (5, 28, 29) but do not have any other SCD risk modifiers, an ICD may be considered, but its benefit is uncertain.
IIb	C-LD	9. In patients with HCM and a history of sustained VT or VF, amiodarone may be considered when an ICD is not feasible or not preferred by the patient (30, 31).
III: No Benefit	B-NR	10. In patients with HCM, an invasive electrophysiological study with programmed ventricular stimulation should not be performed for risk stratification (32, 33).
III: No Benefit	B-NR	11. In patients with an identified HCM genotype in the absence of SCD risk factors, an ICD should not be implanted (7, 34, 35).

Table 8 and Figure 7

Refer to the ACCF/AHA HCM guideline for the definition of HCM (36).

Recommendation-Specific Supportive Text

1. Patients with HCM have approximately a 1% risk of SCD per year (1, 6). Selection of patients who are appropriate candidates for implantation of an ICD can be a difficult clinical decision because of the individuality of each patient and family, variable definitions of risk factors and risk modifiers, sparse clinical data, the relative infrequency of both HCM and SCD in most clinical practices, and the potential complications of living

with an ICD. Table 8 lists risk factors and risk modifiers associated with SCD in patients with HCM. ICD risk stratification should be performed every 1 to 3 years in patients with HCM. There is increasing evidence supporting the association of late gadolinium enhancement on cardiac MRI with the risk of sudden death and it is included as a risk modifier (37-39). LV aneurysm may be associated with a risk of sustained monomorphic VT (40). Age is also an important consideration, as sudden death risk is greater in those <30 years of age, and low in patients whose initial presentation is after the age of 60 years (5, 26), (41).

2. HCM is the most common cause of SCD in individuals <40 years of age (26). Individuals who have survived an episode of SCD, VF, or sustained VT resulting in syncope or hemodynamic compromise warrant ICD implantation (1, 6, 9, 10). Although there are no RCTs assessing the use of the ICD in patients with HCM who have survived SCD, 1 study reported that 54% of patients with an ICD placed for secondary prevention received appropriate ICD therapy during an average follow-up of 4.6 years (10). Select patients with HCM may be candidates for implantation of the subcutaneous implantable cardioverter-defibrillator (42); however, more data on this group are needed especially given their higher risk of T wave oversensing that may increase the risk of inappropriate ICD shocks.

3. Clinical and/or genetic screening of first- and second-degree family members of patients with HCM is important to identify those with unrecognized disease. Genetic counseling should precede genetic testing of family members to enhance their understanding of the usefulness and cost of testing (18, 20, 43). On the basis of family history, clinical screening, and pedigree analyses, the pattern of inheritance is ascertained to identify and manage relatives at risk (13, 14, 18, 19, 43-45). Because familial HCM is a dominant disorder, the risk that an affected patient will transmit disease to each offspring is 50%. When a pathogenic mutation is identified in an index patient, the genetic status of each family member can be readily ascertained. Relatives with overt HCM will have the same pathogenic HCM mutation as the index patient. Pathogenic mutations may also be identified in other relatives with unknown clinical status. These mutation-positive individuals should be evaluated by physical examination, electrocardiography (11, 17), and echocardiography (12, 16, 17) and, if HCM is identified, these individuals should undergo risk stratification. Gene-positive subjects without evidence of HCM may be at risk for future development of HCM and benefit from ongoing clinical evaluation (15, 46, 47). If the proband's implicated mutation is the bona fide disease–causing mutation, then mutation-negative family members and their descendants are not at an increased risk for developing HCM and do not need further evaluation. However, such mutation-negative family members must have an echocardiogram to ensure genotype and phenotype concordance.

4. In a study of 1,053 unrelated patients with clinically manifest HCM, 359 patients (34%) were genotype positive for an HCM-associated mutation in ≥1 HCM-associated genes (22). Whether the results of genetic testing in the proband improve outcomes is uncertain, but identification of a mutation can help inform screening of relatives.

5. Genetic counseling is important in patients with HCM, and genetic screening of relatives is also important unless there are no living first- or second-degree relatives. Most HCM is caused by an autosomal dominant mutation in genes that encode sarcomere proteins or sarcomere-associated proteins. Presence of a pathogenic sarcomere protein gene mutation in patients with HCM identifies risk of LV dysfunction and adverse outcome irrespective of the myofilament involved (13-15, 18, 19, 22). A single mutation in 1 of the 2 alleles (or copies) of a gene is sufficient to cause HCM; however, 5% of patients with HCM have ≥2 mutations in the same gene or different genes, which can be a marker for worse outcomes (13, 34, 48). When genetic testing reveals a mutation in the index patient, ascertainment of genetic status in first- and second-degree relatives can be predictive of risk for developing HCM (14, 49). Relatives with overt HCM will have the same pathogenic HCM mutation as the index patient.

6. Several studies have described an independent relationship between hypertrophy and SCD when the magnitude of hypertrophy is ≥30 mm (2, 3, 23, 24). Risk does not abruptly increase for patients with a ≥30 mm wall thickness, but it rather increases in a linear manner (24) and appears to carry more prognostic significance

in younger patients. A young adult with hypertrophy that approaches 30 mm may have similar or greater SCD risk than an older patient with maximum wall thickness ≥30 mm (23, 50).

Patients with HCM are at an increased risk for SCD if they have a first-degree relative who experienced SCD presumably caused by HCM. Family history appears to be an independent predictor of SCD although the supportive studies are small and observational (25, 26). Syncope can be neurally mediated or medication-related as well as due to VA and requires a careful evaluation before considering it a risk factor for SCD (8, 26). In an analysis, syncope that was unexplained or thought not to be neurally mediated was associated with SCD risk only when it occurred within the past 6 months but not if the most episode occurred >5 years previously (8).

7. Although sustained VT is clearly associated with SCD, the data for NSVT are less robust. Most studies do not support NSVT as an independent risk factor for SCD in patients with HCM (2, 26, 27), but the risk increases if risk modifiers are present, especially in patients <30 years of age (27). Up to one third of patients with HCM have an abnormal blood pressure response during exercise testing (defined variably as either a 20 mm Hg decrease in blood pressure or a failure to increase systolic blood pressure by at least 20 mm Hg during effort) (28, 29). This finding has been postulated to be a risk factor for SCD; however, it is unclear how this relates to the increase in dynamic LV outflow tract obstruction that occurs with exertion, a hemodynamic condition that is readily modifiable with medication or mechanical procedures. The significance of an abnormal blood pressure response with exercise predicting SCD risk increases in the presence of risk modifiers (Table 8).

8. Most studies have found that NSVT alone has a low positive predictive value for SCD (2, 26, 27); therefore, use of an ICD is more appropriate if risk modifiers are also present. An abnormal blood pressure response to exercise has also been associated with the risk of sudden death (5, 28, 29), but it is unclear how this relates to the increase in dynamic LV outflow tract obstruction that occurs with effort, which is often treatable. The significance of an abnormal blood pressure response with exercise for predicting SCD risk increases when risk modifiers are present (Table 8).

9. The ICD is recommended for the prevention of SCD in patients with HCM who have survived sustained VT or VF as antiarrhythmic medications have limited effectiveness (31). Amiodarone has been associated with improved survival in observational studies and is an option for patients for whom an ICD is not feasible due to limited expectation for survival or patient preference (30, 31).

10. Approximately one third of consecutive patients with HCM undergoing an electrophysiological study have polymorphic VT or VF induced by programmed ventricular stimulation, but the results of programmed stimulation do not predict SCD risk. Programmed ventricular stimulation in patients with HCM has low predictive value and a nontrivial risk of complications (32, 33, 51). Electrophysiological studies can help to clarify the diagnosis of wide complex tachycardia or guide therapy for supraventricular tachycardia or bundle branch reentry.

11. SCD may cluster in certain families with HCM, and the possibility that specific sarcomere mutations may confer SCD risk has been hypothesized. However, subsequent studies of selected patients with HCM (34, 35) were unable to establish a clinically useful relation between genotype and SCD risk. In some cases, the rate of adverse events (and prevalence of associated SCD risk factors) was lower in patients with mutations initially felt to be malignant than it was in those with mutations believed to be benign (34, 35). Data from series of unselected consecutive outpatients suggest that most mutations are novel and limited to particular families (34, 35). Therefore, routine mutation screening would appear to be of little prognostic value in HCM (52). The short-term risk of sudden death in patients who are genotype positive but have no other manifestations of the disease appears to be low (53). Therefore, an ICD is not indicated in these individuals.

Table 8. Major Clinical Features Associated With Increased Risk of SCD in Patients With HCM

Established risk factors*

- Survival from a cardiac arrest due to VT or VF (1, 5, 6)
- Spontaneous sustained VT causing syncope or hemodynamic compromise (1, 5, 6)
- Family history of SCD associated with HCM (25, 26)
- LV wall thickness ≥30 mm (2, 3, 23, 24)
- Unexplained syncope within 6 mo (8, 26)
- NSVT ≥3 beats (2, 26, 27)
- Abnormal blood pressure response during exercise† (5, 28, 29)

Potential risk modifiers‡

- <30 y (5, 26)
- Delayed hyperenhancement on cardiac MRI (37-39, 54)
- LVOT obstruction (2, 4)
- Syncope >5 y ago (8, 26)

High-risk subsets§

- LV aneurysm (40, 55, 56)
- LVEF <50% (52)

*There is general agreement in the literature that these factors independently convey an increased risk for SCD in patients with HCM.

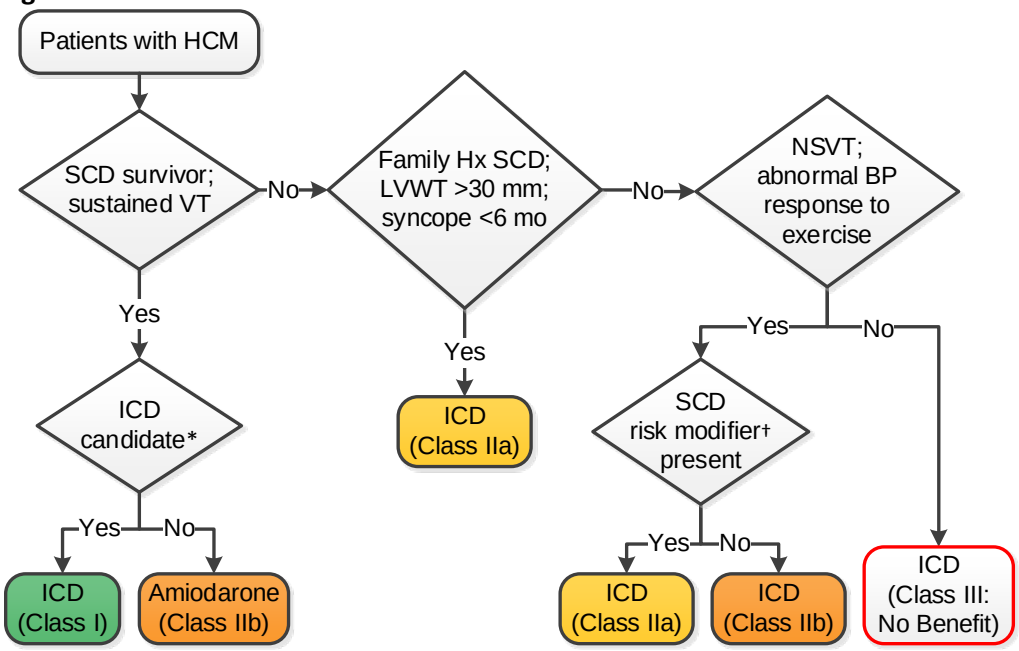
†Decrease in blood pressure of 20 mm Hg or failure to increase systolic blood pressure >20 mm Hg during exertion.

‡There is a lack of agreement in the literature that these modifiers independently convey an increased risk of SCD in patients with HCM; however, a risk modifier when combined with a risk factor often identifies a patient with HCM at increased risk for SCD beyond the risk conveyed by the risk factor alone.

§A small subset of patients with an LVEF <50% (end-stage disease) or an LV aneurysm warrant consideration for ICD implantation (52).

HCM indicates hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Figure 7. Prevention of SCD in Patients With HCM



Colors correspond to Class of Recommendation in Table 1.
See Section 7.4 for discussion.
*ICD candidacy as determined by functional status, life expectancy, or patient preference.
†Risk modifiers: Age <30 y, late gadolinium enhancement on cardiac MRI, LVOT obstruction, LV aneurysm, syncope >5 y.
BP indicates blood pressure; HCM, hypertrophic cardiomyopathy; Hx, history; ICD, implantable cardioverter-defibrillator; LVOT, left ventricular outflow tract; LVWT, left ventricular wall thickness; MRI, magnetic resonance imaging; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; and VT, ventricular tachycardia.

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7.5. Myocarditis

Recommendations for Myocarditis References that support the recommendations are summarized in Online Data Supplement 32.		
COR	**LOE**	**Recommendations**
I	**C-LD**	**1. In patients with life-threatening VT or VF associated with confirmed or clinically suspected myocarditis, referral to centers with mechanical hemodynamic support and advanced arrhythmia management is recommended (1).**
IIb	**C-LD**	**2. In patients with giant cell myocarditis with VF or hemodynamically unstable VT treated according to GDMT, an ICD and/or an antiarrhythmic medication may be considered if meaningful survival of greater than 1 year is expected (2-4).**

Recommendation-Specific Supportive Text

1. Myocarditis is an inflammatory process often related to infection (1, 5-9). When patients are treated in centers with the availability of mechanical hemodynamic support procedures, cardiac catheterization, endomyocardial biopsy, advanced cardiac imaging procedures, and arrhythmia management including ICD implantation, outcomes appear improved (1). The acute course of myocarditis varies ranging from an asymptomatic finding of transient ST-T changes noted on ECG to cardiogenic shock and recurrent VA (10-12). Acute management is largely supportive and can rapidly advance to requiring mechanical support (13, 14). Cardiac arrhythmias range from conduction abnormalities to life-threatening VT and VF (15-17). Arrhythmias may require antiarrhythmic medications and/or device therapy (18). Giant cell myocarditis is fairly uncommon, but it is of particular importance because it typically affects young individuals and is usually fatal if untreated (2-4, 19). VT may require antiarrhythmic medications such as amiodarone and/or an ICD that in some instances can be used as a bridge to more advanced HF therapies such as LVAD or transplant. Myocarditis and SCD have been reported with HIV infection (20, 21). Systemic lupus erythematous can cause myocarditis but only rarely VT or VF (8, 22). In patients with Chagas disease, acute myocarditis is rare but more than one third of affected patients develop late myocardial damage with progressive HF. Conduction defects with progression to complete heart block and VT or VF are common. Amiodarone appears to be effective in treating VA (23). An ICD is frequently used in the late phase of myocarditis (24), and radiofrequency catheter ablation has been successfully used to control recurrent VA in some patietnts (25).

2. Giant cell myocarditis is fairly uncommon, but it is of particular importance as it typically affects young individuals and is usually fatal if untreated. The diagnosis is confirmed by endomyocardial biopsy. Patients may develop heart block, requiring a temporary or a permanent pacemakers. An ICD and antiarrhythmic medications, such as amiodarone are often used in the acute phase to treat VT or VF and reduce the risk of SCD (2-4, 19, 26-28).

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7.6. Cardiac Sarcoidosis

Recommendations for Cardiac Sarcoidosis References that support the recommendations are summarized in Online Data Supplement 33.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with cardiac sarcoidosis who have sustained VT or are survivors of SCA or have an LVEF of 35% or less, an ICD is recommended, if meaningful survival of greater than 1 year is expected (1-5).**
IIa	**B-NR**	**2. In patients with cardiac sarcoidosis and LVEF greater than 35% who have syncope and/or evidence of myocardial scar by cardiac MRI or positron emission tomographic (PET) scan, and/or have an indication for permanent pacing implantation of an ICD is reasonable, provided that meaningful survival of greater than 1 year is expected (6-10).**
IIa	**C-LD**	**3. In patients with cardiac sarcoidosis and LVEF greater than 35%, it is reasonable to perform an electrophysiological study and to impant an ICD, if sustained VA is inducible, provided that meaningful survival of greater than 1 year is expected (11, 12).**
IIa	**C-LD**	**4. In patients with cardiac sarcoidosis who have an indication for permanent pacing, implantation of an ICD can be beneficial (13).**
IIa	**C-LD**	**5. In patients with cardiac sarcoidosis with frequent symptomatic VA and evidence of myocardial inflammation, immunosuppression in combination with antiarrhythmic medication therapy can be useful to reduce VA burden (14-16).**

Figure 8

Recommendation-Specific Supportive Text

1. Sarcoidosis is a systemic granulomatous disease of unknown cause. Pulmonary involvement is most frequent but any organ can be affected. Cardiac involvement, diagnosed by cardiac MRI or positron emission tomography (PET), has been reported in up to 55% of patients with extracardiac disease, while isolated cardiac sarcoidosis was seen in most patients diagnosed with cardiac sarcoidosis in 1 report (17). Cardiac manifestations include conduction abnormalities, VA, and depressed ventricular function with or without HF, and these contribute greatly to a higher mortality in cardiac sarcoidosis compared with sarcoidosis without cardiac involvement (2). In a 25-year study of 110 patients with cardiac sarcoidosis in Finland with HF at presentation, marked LV dysfunction at diagnosis (LVEF <35%), and isolated cardiac sarcoidosis predicted an adverse outcome (1). VA can also occur in patients with relatively normal LV function, some of whom have RV involvement that can mimic arrhythmogenic right ventricular cardiomyopathy. Several reports of patients with cardiac sarcoidosis and ICDs implanted for either primary or secondary prevention of SCD show a high frequency of appropriate ICD therapies (3-5), supporting use of ICDs for primary and secondary prevention of SCD according to the indications applied for other cardiomyopathies. The frequency of conduction abnormalities often warrants a device that provides bradycardia pacing as well.

2. Patients with cardiac sarcoidosis can experience VA and SCD, even if the LVEF is normal, and approaches to identification of patients at risk of SCD despite preserved LV function are not well defined. A number of studies have evaluated the role of cardiac MRI for predicting VA and SCD. A meta-analysis (6), which included 760 patients in 10 studies, found that late gadolinium enhancement was associated with increased all-cause mortality and more VA compared with those without late gadolinium enhancement. Applicability is limited by the lack of precise quantification of late gadolinium enhancement burden that may allow for more nuanced risk stratification. Some studies suggested that a threshold effect exists, with extensive LV and RV involvement

being a particularly high-risk feature (7, 8). However, late gadolinium enhancement can be present even if the LVEF is >50% and was associated with a risk of death or VT of 4.9% per year compared to 0.24% per year when late gadolinium enhancement was absent in 1 observational study (7). PET for assessing inflammation and scar is also being increasingly used, but data are limited. In 1 report, the presence of inflammation and RV involvement on PET scanning was associated with increased risk of death or (10). Electrophysiological studies in a series of 76 patients with evidence of cardiac sarcoid found that 11% had inducible VT. During a median follow-up of 5 years, 75% of patients with inducible VT had spontaneous VT or death compared with 1.5% of those who did not have inducible VT (18).

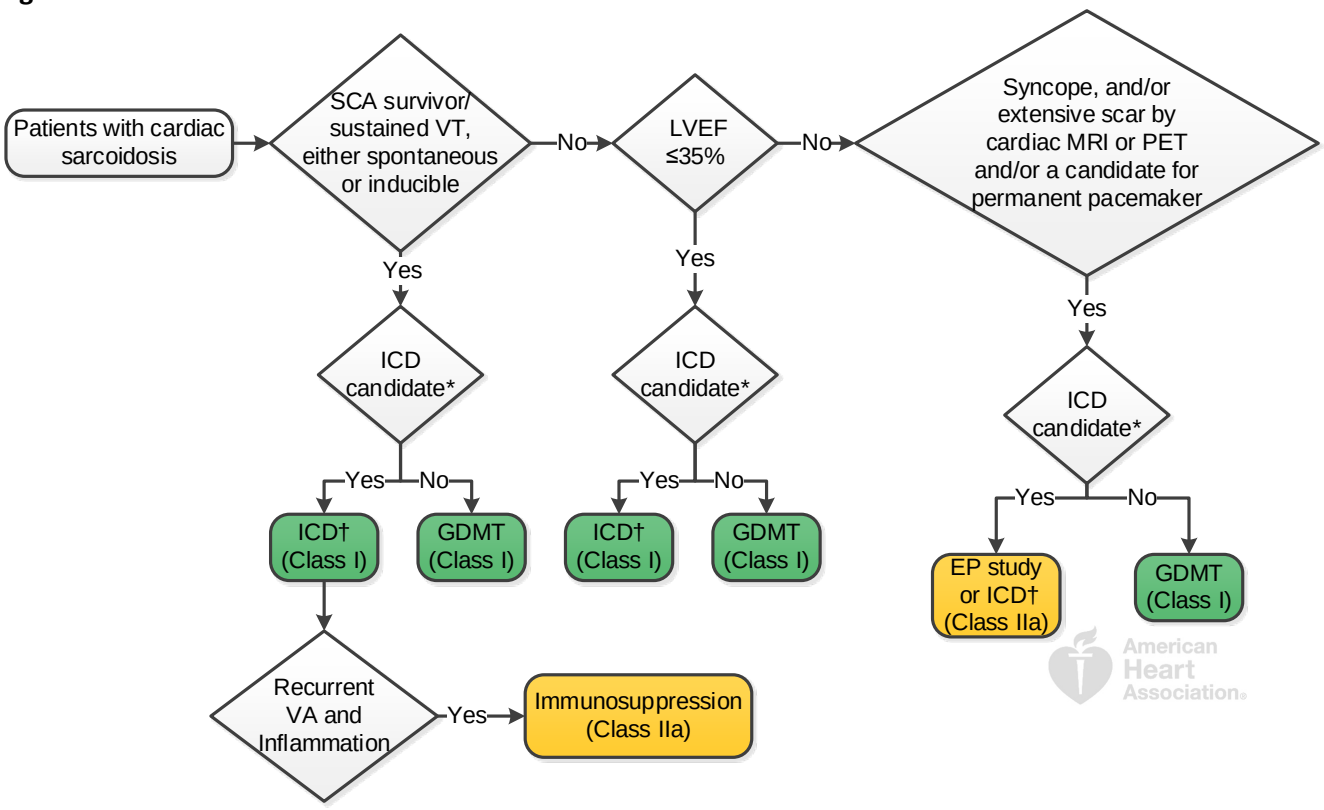
3. Electrophysiological study has been proposed as a potential tool for risk stratification of VA and SCD in patients who had demonstrable evidence of cardiac sarcoidosis based on imaging studies or biopsy, but do not have documented arrhythmias or arrhythmic symptoms nor meet standard primary prevention criteria for ICD implantation.

One study evaluated 76 patients with documented cardiac sarcoidosis by PET or cardiac MRI who underwent electrophysiological study (12). Eight (11%) were inducible for sustained VAs and received an ICD, while the rest did not receive an ICD because they were not inducible. LVEF was lower in patients with inducible VA (36.4 + 4.2% versus 55.8 + 1.5%). Over a median follow-up of 5 years, 6 of 8 patients in the group with inducible VA had VA or died, compared with 1 death in the negative group (12). An important caveat is that it remains unclear if electrophysiological study is more predictive than LVEF alone, because inducibility appears to reversely correlate with LVEF. Furthermore, in this study the average LVEF of the inducible patients declined further during the followup period (12).

4. In addition to VA and LV dysfunction, conduction abnormalities, including heart block, can also be a common manifestation of cardiac sarcoidosis. Patients with documented VA and LV dysfunction are at increased risk of cardiac events including cardiac death. One study compared outcomes in 22 patients with high-degree atrioventricular block as the initial manifestation of cardiac sarcoidosis, to 31 patients who initially presented with VT and/or HF. After a median follow up of 34 months, the patients who presented with heart block had fewer HF hospitalization, yet fatal cardiac events, including sustained VAs, were similar to those with VT and/or HF, suggesting that the risk of fatal cardiac events is high regardless of the initial clinical presentation (13). In the same study, administration of steroids led to some clinical improvement, with some patients recovering conduction, yet steroid effectiveness was not universal and did not seem to be protective against adverse cardiac events (13).

5. Several studies have attempted to evaluate the role of immunosuppression for reducing VA in patients with cardiac sarcoidosis, but results have been inconsistent (14-16). Furthermore, a worsening of VA has been reported with immunosuppressive therapy (usually glucocorticoids) in a number of patients, including electrical storm developing in some within 12 months of initiating therapy (15). One study reported a decrease of arrhythmia burden with steroid therapy but only when given in the early stages of the disease; those with advanced LV dysfunction did not experience benefit (16). A systematic combined treatment approach was successful in 63% of patient in a series in which medical therapy included both steroids and antiarrhythmic medications, followed by radiofrequency catheter ablation if needed (14). Immunosuppressive therapy may serve a dual purpose beyond arrhythmia effects as it may help stabilize disease progression and prevent further deterioration of LV function, although this has yet to be demonstrated in RCTs. Steroids do not appear to reverse advanced ventricular dysfunction once present, which supports the importance of early diagnosis and intervention (1). PET scanning for assessing inflammation and scar is being increasingly used in sarcoidosis as well, but data supporting its use for guiding therapy of arrhythmias are limited.

Figure 8. Prevention of SCD in Patients With Cardiac Sarcoidosis



Colors correspond to Class of Recommendation in Table 1.
See Section 7.6 for discussion.
*ICD candidacy as determined by functional status, life expectancy, or patient preference.
†For recurrent sustained monomorphic VT, refer to Figure 2.
CEP indicates electrophysiological; GDMT, guideline-directed management and therapy; ICD, implantable cardiac-defibrillator; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; PET, positron emission tomography; SCA, sudden cardiac arrest; SCD, sudden cardiac death; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

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7.6.1. Other Infiltrative Cardiomyopathies

Infiltrative cardiomyopathies are a heterogeneous group of uncommon systemic diseases with associated cardiac involvement. In some infiltrative cardiomyopathies, such as Fabry's disease, VAs are uncommon. Some, such as hemochromatosis, are highly treatable especially when diagnosed early. In all cases, treatment of the underlying condition must accompany management of cardiac arrhythmias. Most studies of infiltrative cardiomyopathies and arrhythmias are small and observational (1) but, in general, unless contraindications are present, VAs should be treated as in any other cardiomyopathy. See Section 7.6 for sarcoidosis. Until recently, cardiac amyloidosis was associated with a very poor prognosis with patients ultimately succumbing to progressive HF (2). This perception is changing with advances in medical therapy for light-chain amyloidosis, which have led to improved outcomes (3). Yet, decisions must be individualized because data remain too limited to allow formal recommendations as published reports on ICD effectiveness in amyloidosis are small, observational and with limited follow up (4). Whether there is greater benefit to ICD placement in light chain amyloidosis versus transthyreitin-related amyloidosis remains uncertain, because most studies included mainly patients with amyloid light-chain amyloidosis for which the rate of VA may be greater and prognosis is generally worse. Whether ICDs are effective for primary prevention of SCD is uncertain, but many deaths in patients with cardiac amyloidosis do not appear to be preventable by an ICD (2).

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7.7. Heart Failure

7.7.1. HF With Reduced Ejection Fraction

Recommendation for HF*r*EF References that support the recommendation are summarized in Online Data Supplement 35.		
COR	**LOE**	**Recommendation**
IIa	**B-NR**	**1. In patients with HF*r*EF who are awaiting heart transplant and who otherwise would not qualify for an ICD (e.g., NYHA class IV and/or use of inotropes) with a plan to discharge home, an ICD is reasonable (1-5).**

Synopsis

Patients with HF*r*EF are at an increased risk for VA and SCD. The risk is increased irrespective of HF*r*EF etiology (6). SCD makes up a greater proportion of deaths in patients with milder HF symptoms and lesser proportion in those with moderate/severe HF symptoms (7). The reported incidence of SCD varies depending on the definition used and the population studied. Although many deaths, classified as sudden, are indeed due to lethal VA, others may be due to bradyarrhythmias, pulseless electrical activity, and sudden hemodynamic deterioration (7-9).

Medical therapy with neurohormonal agents decreases the risk of SCD by reducing both the incidence of VA and disease progression (7, 10-12). Despite GDMT for HF*r*EF, some patients remain at risk for SCD, and an ICD may be helpful. See Sections 7.1 and 7.2 for the indications on ICDs in patients with reduced LVEF. CRT, in appropriate patients, has also been shown to reduce the incidence of SCD (13).

The pathophysiology of SCD in HF is complex, resulting from interactions between both functional and structural changes that occur in patients with HF*r*EF that result in increased susceptibility to SCD (14). Although many of the risk factors are shared among HF*r*EF patients, the reason that SCD strikes a particular individual is usually unknown; however, some individuals may have a genetic susceptibility (15). Varying degrees of myocardial fibrosis, neurohormonal activation, and increased wall stress alter the electrophysiological properties with changes in cell coupling, ionic currents (electrical remodeling), and calcium handling that likely contribute to the development of lethal VA (16). Contributing factors extrinsic to the heart include electrolyte abnormalities related to volume shifts and diuretic use, sympathetic activation, hemodynamic stress, and hypoxia.

Recommendation-Specific Supportive Text

1. Many patients with advanced HF listed for heart transplant would not otherwise qualify for ICD given the severity of illness including NYHA class IV status and/or use of inotropic infusion. Although no randomized data on ICD use in this population exist, data from observational and large registry studies of patients awaiting heart transplant suggest improved survival in patients with an ICD (1, 4, 5). One alternative to ICD in this population is the wearable cardioverter-defibrillator (2, 3). The recommendation in this section is relevant to those patients without an ICD where there is a plan to discharge the patient to home to await cardiac transplant and not, for example, to those patients who remain hospitalized with no intention to discharge home until transplant occurs. For those patients with an LVAD, the decision to place an ICD is generally independent of whether they are awaiting heart transplant but rather the indication in those patients is generally based on the need to treat VA (17).

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7.7.2. HF With Preserved Ejection Fraction

Nearly half of the patients with HF have a preserved LVEF (1). These patients tend to be older and have more comorbidities than patients with HF*r*EF. However, although the rate of SCD is lower in patients with HF with preserved ejection fraction (HF*p*EF) than in patients with HF*r*EF (2), nearly a quarter of all deaths among patients with HF*p*EF are sudden (3-5). The challenge in preventing SCD in patients with HF*p*EF is identifying which patients are at a high enough risk to benefit from preventive therapies. Studies exploring noninvasive risk factors for SCD in patients with HF*p*EF do not identify consistent factors with the exception of ischemic heart disease (2, 6). Consequently, there is no accepted noninvasive test to identify high-risk patients with HF*p*EF. Invasive risk stratification with an electrophysiological study shows promise in this population (7, 8). This topic is currently being studied in the PRESERVE-EF (Risk Stratification in Patients With Preserved Ejection Fraction) trial (NCT02124018).

Whether to include a recommendation related to an electrophysiological study in patients with HF*p*EF and ischemic heart disease was carefully considered by the writing committee. However, evidence was deemed insufficient to support a formal recommendation. Still, the pros and cons of an electrophysiological study can reasonably be considered in select patients with HF*p*EF and ischemic heart disease who are experiencing symptoms suggestive of a VA.

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7.7.3. Left Ventricular Assist Device

Recommendation for Patients With an LVAD References that support the recommendation are summarized in Online Data Supplement 36.		
COR	**LOE**	**Recommendation**
IIa	**C-LD**	**1. In patients with an LVAD and sustained VA, an ICD can be beneficial (1).**

Recommendation-Specific Supportive Text

1. Patients with an LVAD have a high risk of VA, particularly those with a history of arrhythmias (2-4). The increased risk of VA may be due to myocardial irritation from insertion of the LVAD inflow cannula, LV compression due to a suctioning effect from the LVAD, inotropic support frequently needed by some patients, and repolarization changes that can occur after LVAD placement. Although VT/VF is tolerated by some patients with an LVAD, others experience a decrease in flow as the RV is unsupported; syncope and hypoperfusion can result. Having an ICD can allow for prompt termination of VA before significant hemodynamic consequences occur. Data on ICDs in patients with an LVAD are from observational series. A systematic review of 6 observational studies observed that within 7 months, 26% of patients with an LVAD had died (1). The death rate was lower among patients who previously had an ICD (16% versus 32%), suggesting a 39% relative-risk reduction in all-cause mortality in an adjusted analysis (1). Patients with a history of pre-LVAD VA have nearly a ≥10-fold risk of post-LVAD VA (2-4). In many of the initial studies demonstrating ICD benefit, older pulsatile LVAD devices were in use (2, 5). Studies of ICD use with the newer, continuous flow LVADs have inconsistently shown benefit (1, 4, 6, 7). Of note, approximately 2 of 10 patients with an LVAD develop an LVAD related infection in the first year(8, 9).

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7.7.4. ICD Use After Heart Transplantation

Recommendation for ICD Use After Heart Transplantation References that support the recommendation are summarized in Online Data Supplement 37.		
COR	**LOE**	**Recommendation**
IIb	**B-NR**	**1. In patients with a heart transplant and severe allograft vasculopathy with LV dysfunction, an ICD may be reasonable if meaningful survival of greater than 1 year is expected (1-3).**

Recommendation-Specific Supportive Text

1. Development of disease in the transplanted heart places some patients at an increased risk of SCD that has ranged from 10% to 35% in observational studies (4, 5). Both rejection and a decreased LVEF are predictors of SCD. The mechanisms underlying SCD in patients with a heart transplant include damage to the conduction system itself and VA due to coronary vasculopathy or during episodes of acute rejection. Several small case series observing appropriate ICD termination of VA suggest that an ICD can be beneficial in selected patients, particularly those with severe allograft vasculopathy, unexplained syncope, a history of SCA, and severe LV dysfunction (1-3). Additionally, a patient with severe allograft vasculopathy who is being considered for retransplant may be appropriate for an ICD as a bridging device. Secondary prevention indications for an ICD in patients with a heart transplant are identical to those in other patients.

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7.8. Neuromuscular Disorders

Recommendations for Neuromuscular Disorders References that support the recommendations are summarized in Online Data Supplement 38.		
COR	**LOE**	**Recommendations**
I	B-NR	**1. In patients with neuromuscular disorders, primary and secondary prevention ICDs are recommended for the same indications as for patients with NICM if meaningful survival of greater than 1 year is expected (1, 2).**
IIa	B-NR	**2. In patients with Emery-Dreifuss and limb-girdle type IB muscular dystrophies with progressive cardiac involvement, an ICD is reasonable if a meaningful survival of greater than 1 year is expected (3-8).**
IIa	B-NR	**3. In patients with muscular dystrophy, follow-up for development of cardiac involvement is reasonable, even if the patient is asymptomatic at presentation (9-12).**
IIb	B-NR	**4. In patients with myotonic dystrophy type 1 with an indication for a permanent pacemaker, an ICD may be considered to minimize the risk of SCA from VT if meaningful survival of greater than 1 year is expected (9, 13, 14).**

Table 9

Synopsis

The muscular dystrophies are a group of inherited diseases affecting skeletal and cardiac muscle. Some present primarily as a NICM (e.g., Duchenne, Becker, and limb-girdle types 2C, 2F, and 2I), while others present primarily as conduction system degeneration with a variable association with cardiomyopathy (e.g., myotonic dystrophy types 1 and 2, Emery-Dreifuss, limb-girdle type 1B; summarized in Table 9) (15). Because SCD can occur either due to VA or due to bradyarrhythmias from rapid and unpredictable progression of conduction system disease, the clinician is faced with the challenge of identifying those patients who would benefit from prophylactic pacemaker or ICD implantation. There should be a high level of concern for those patients with muscular dystrophy who present with arrhythmia symptoms (15). The current guideline focuses on VA and indications for implantation of an ICD. The indications for permanent pacemaker are discussed in another ACC/AHA/HRS guideline (16).

Recommendation-Specific Supportive Text

1. In general, the indications for an ICD in patients with muscular dystrophy should follow standard ICD recommendations for patients with NICM (see Section 7.2.1 on Secondary Prevention and Section 7.2.2 on Primary Prevention of SCD with NICM). A high index of suspicion for bundle-branch reentrant tachycardia is warranted in patients with myotonic dystrophy who exhibit wide QRS complex tachycardia or tachycardia-related symptoms (2).

2. In patients with Emery-Dreifuss and limb-girdle type 1B muscular dystrophies associated with *Lamin A/C* mutations, SCD accounts for about one third of all deaths (4). Observational studies show a significant rate of appropriate ICD therapy in patients with cardiac conduction disorders who are gene positive for *Lamin A/C* mutation even if LV function is preserved (3, 5, 17). In an observational study in which 38% had isolated skeletal muscular involvement but included patients with conduction defects and other risk factors (including PR interval >240 ms, left bundle-branch block, NSVT, or bradycardia requiring a permanent pacemaker) life-threatening VAs were relatively common; with 52% of patients receiving appropriate ICD therapy including approximately 40% of those patients with an LVEF ≥45% (3). A study of patients who had *Lamin A/C* mutation, in which approximately 21% had a skeletal muscular dystrophy phenotype, SCD and appropriate ICD therapy were associated with NSVT, LVEF <45%, male sex, and *Lamin A/C* nonmissense mutations (4). These

observational studies support the use of an ICD when a pacing indication is present and likely also when evidence of progressive cardiac involvement such as cardiac conduction defects, NSVT or reduced LVEF is present (8).

There is a paucity of data regarding the rare form of x-linked recessive Emery-Dreifuss muscular dystrophy (related to the *Emerin* gene mutation), but arrhythmias may be less frequent than for the *Lamin A/C* mutations (15).

3. Cardiac involvement can occur in a number of neuromuscular dystrophies (Table 9). To determine cardiac involvement, a 12-lead ECG and echocardiogram are important for the initial clinical assessment, independent of symptom status. In general, the more extensive the cardiac involvement, including evidence of distal conduction disease, ventricular dysfunction, and atrial arrhythmias, the more likely a VA will occur. The initial evaluation for myotonic dystrophy patients includes ambulatory monitoring. In asymptomatic patients, some experts advocate for annual follow-up during the concealed phase of the disease with an annual 12-lead ECG to screen for development of conduction abnormalities. However, the optimal frequency of electrocardiographic screening is unknown (18). Once cardiac involvement is present, either on the basis of conduction delay, atrial arrhythmias, or ventricular dysfunction, a low threshold for investigating symptoms or electrocardiographic findings by the clinician to determine the need for pacemaker implantation, invasive electrophysiological studies, or ICD implantation is optimal.

4. Up to one third of deaths in myotonic dystrophy patients are sudden(9). Although commonly attributed to conduction block and asystole, SCD due to VT/VF has been recognized in patients with functioning permanent pacemakers, and spontaneous VA have been documented in some (13, 19). The risk of SCD in patients with pacemakers suggests that an ICD may be preferred to a pacemaker. However, these patients are also at high risk of respiratory failure as a competing cause of death. Therefore, in patients with severe skeletal muscle involvement, a pacemaker or ICD may not improve outcomes (15). A shared decision-making approach to selecting ICD or pacing therapy is warranted. Compared with myotonic type 1 patients, myotonic dystrophy type 2 patients are not well studied but may also benefit from the same approach.

Table 9. Neuromuscular Disorders Associated With Heart Disease

Muscular Dystrophy	Inheritance	Gene/ Protein Affected	Primary Cardiac Pathology	Frequency of Cardiac Involvement	Causes of Death	Associated With Sudden Death?
Duchenne	X-linked recessive	Dystrophin	NICM	>90%	Respiratory, HF	Yes, uncertain etiology
Becker	X-linked recessive	Dystrophin	NICM	60%–75%	HF, respiratory	Yes, uncertain etiology
Limb-girdle type 1B	Autosomal dominant	*Lamin A/C*	Conduction system disease and NICM	>90%	Sudden, HF	Yes
Limb-girdle type 2C-2F	Autosomal recessive	Sarcoglycan	NICM	<25%	Respiratory, HF	Uncertain
Limb-girdle type 2I	Autosomal recessive	Fukutin-related protein	NICM	20%–80%	Respiratory, HF	Uncertain
Myotonic type 1	Autosomal dominant	CTG repeat expansion	Conduction system disease and NICM	60%–80%	Respiratory, sudden, HF	30% of deaths, uncertain bradycardia versus tachycardia

Myotonic type 2	Autosomal dominant	CCTG repeat expansion	Conduction system disease	10%–25%	Normal causes	Reported
Emery-Dreifuss	X-linked and autosomal dominant or recessive	Emerin, *Lamin A/C*	Conduction system disease and NICM	>90%	Sudden, HF	Yes
Facioscapulohumeral	Autosomal dominant	D4Z4 repeat contraction	Possibly conduction disease	5%–15%	Normal causes, respiratory rarely	Not reported

HF indicates heart failure; and NICM, nonischemic cardiomyopathy.
Adapted with permission from Groh, et al. (15).

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7.9. Cardiac Channelopathies

Recommendations for Cardiac Channelopathies References that support the recommendations are summarized in Online Data Supplement 39.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In first-degree relatives of patients who have a causative mutation for long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, short QT syndrome, or Brugada syndrome, genetic counseling and mutation-specific genetic testing are recommended (1-6).**
I	**B-NR**	**2. In patients with a cardiac channelopathy and SCA, an ICD is recommended if meaningful survival of greater than 1 year is expected (7-13).**

Synopsis

Implantation of an ICD in asymptomatic low-risk patients with a cardiac channelopathy for a positive family history of SCD as the sole indication is unsupported by published data (13-18).

Recommendation-Specific Supportive Text

1. Clinical screening of first-degree relatives of patients with inherited arrhythmia syndromes is crucial to identifying affected family members. Due to the increased risk of adverse cardiac events in genotype positive patients with long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome, targeted screening for the identified family-specific mutation can identify individuals who are at risk for these adverse outcomes (2-5). Screening ECGs may be insufficient for diagnosis, because the resting ECG in patients with catecholaminergic polymorphic ventricular tachycardia is normal, and as many as 25% of genotype-positive patients with long QT syndrome have QTc intervals ≤440 ms (2). Due to the increased risk of adverse cardiac events in young patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia (2, 19-22), screening infants and young children is particularly important to guide therapy and institute preventive measures, including the avoidance of possible provocative medications (www.crediblemeds.org) (23). However, because up to 15% of mutations previously associated with catecholaminergic polymorphic ventricular tachycardia do not appear to cause disease (24), caution is advised to avoid unnecessary treatment or sports restriction in phenotype-negative catecholaminergic polymorphic ventricular tachycardia mutation positive individuals. Notably, some patients may prefer not to undergo genetic testing, so genetic counseling should focus on this issue.

2. Patients with cardiac channelopathies (i.e., long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, early repolarization syndrome, and short QT syndrome) and prior SCA have a significantly increased risk of subsequent SCA or SCD (7-13, 25-28). Implantation of an ICD reduces the risk of death in high-risk patients (9, 29-31). Appropriate ICD therapy for VF/fast VT is reported in 8% to 33% of channelopathy patients, while inappropriate shocks and device complications are reported in 8% to 35% (10, 29, 30, 32-36). To minimize inappropriate shocks, concurrent beta blockers in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia patients, optimal device programming, and appropriate lead selection are necessary. Ventricular pacing without ICD implantation was associated with a significant risk of recurrent SCA or SCD in long QT syndrome patients (37-39). In selected patients with LQT1 in whom the SCA occurred in the absence of beta-blocker treatment, beta-blocker therapy is offered as an alternative to ICD implantation in patients who refuse to receive an ICD (40).

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7.9.1. Specific Cardiac Channelopathy Syndromes

7.9.1.1. Congenital Long QT Syndrome

Recommendations for Long QT Syndrome References that support the recommendations are summarized in Online Data Supplement 40.		
COR	**LOE**	**Recommendations**
I	B-NR	1. In patients with long QT syndrome with a resting QTc greater than 470 ms, a beta blocker is recommended (1-5).
I	B-NR	2. In high-risk patients with symptomatic long QT syndrome in whom a beta blocker is ineffective or not tolerated, intensification of therapy with additional medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation, and/or an ICD is recommended (2, 6-12).
I	B-NR	3. In patients with long QT syndrome and recurrent appropriate ICD shocks despite maximum tolerated doses of a beta blocker, intensification of medical therapy with additional medications (guided by consideration of according to the particular long QT syndrome type) or left cardiac sympathetic denervation, is recommended (6, 7, 10, 13-16).
I	B-NR	4. In patients with clinically diagnosed long QT syndrome, genetic counseling and genetic testing are recommended (17-21).
IIa	B-NR	5. In patients with suspected long QT syndrome, ambulatory electrocardiographic monitoring, recording the ECG lying and immediately on standing, and/or exercise treadmill testing can be useful for establishing a diagnosis and monitoring the response to therapy (22-29).
IIa	B-NR	6. In asymptomatic patients with long QT syndrome and a resting QTc less than 470 ms, chronic therapy with a beta blocker is reasonable (3, 30, 31).
IIb	B-NR	7. In asymptomatic patients with long QT syndrome and a resting QTc greater than 500 ms while receiving a beta blocker, intensification of therapy with medications (guided by consideration of the particular long QT syndrome type), left cardiac sympathetic denervation or an ICD may be considered (2, 8, 11, 30).
III: Harm	B-NR	8. In patients with long QT syndrome, QT-prolonging medications are potentially harmful (5, 12, 32-34).

Table 10 and Figures 9, 10, 11, and 12

Recommendation-Specific Supportive Text

1. Beta blockers reduce adverse cardiac events for long QT syndrome type 1 (Figure 10) (>95%), long QT syndrome type 2 (Figure 11) (>75%), and females with long QT syndrome type 3 (Figure 12) by >60% (1-5). There are limited data regarding efficacy of beta blockers in males with long QT syndrome type 3 (3, 35, 36) but, in selected patients, beta blockers can be protective against SCA (36, 37). Several observational studies have reported effectiveness for risk reduction in long QT syndrome with propranolol, atenolol, and nadolol with appropriate dosing (26, 28, 38-40), while metoprolol appears less effective (41). RCTs to assess comparative efficacy of specific beta blockers are unavailable, although many centers favor the use of nadolol. For long QT syndrome type 1, 1 study reported atenolol reduced risk of VA while nadolol was not associated with risk reduction (2). For long QT syndrome type 2, nadolol was reported to show superior efficacy (1, 2). Patients receiving a beta blocker should undergo ongoing monitoring to assess changes in QTc over time, and adequacy of beta blockade with exertion (26, 28).

2. High-risk patients with long QT syndrome include those with QTc >500 ms, genotypes long QT syndrome type 2 and long QT syndrome type 3, females with genotype long QT syndrome type 2, <40 years of age, onset

of symptoms at <10 years of age, and patients with prior cardiac arrest or recurrent syncope (3, 8, 11, 30, 38). Women with long QT syndrome type 2 are at a higher risk of postpartum cardiac arrest/SCD (42, 43) and should receive prepregnancy counseling. Patients with long QT syndrome and recurrent syncope while receiving a beta blocker have an increased risk of SCA or appropriate ICD shocks (9) and escalation of therapy is warranted to prevent SCD. Earlier studies reported benefit of antibradycardia pacing, with recurrent syncope or cardiac arrest reported in 7% to 24% of patients (44-47). In high-risk patients, observational studies support effectiveness of the ICD in preventing SCD, with consideration of left cardiac sympathetic denervation to reduce the frequency of ICD shocks (16, 48, 49). Left cardiac sympathetic denervation can reduce VA burden, but up to 27% of high-risk patients experience at least 1 recurrence (16, 48, 50). Left cardiac sympathetic denervation may be more effective in patients with long QT syndrome type 1 and long QT syndrome type 3 (16). Complications related to left cardiac sympathetic denervation occur in 8% to 20% of patients (48, 51). Syncope in patients with long QT syndrome may occur due to vasovagal syncope, noncompliance with medications, or proarrhythmia from concurrent medications (5). Clinical evaluation that incorporates consideration of genotype, QTc interval, medication compliance, and shared decision-making regarding the need to change or escalate therapy is important. Use of additional medications is guided by long QT syndrome type. In long QT syndrome type 3 ranolazine, mexiletine, and flecainide shorten the QTc and have been used to reduce recurrent arrhythmias (6, 7, 10).

3. Mexiletine is an additional medication that can be used in patients with long QT syndrome and recurrent ICD shocks. Left cardiac sympathetic denervation is associated with a reduction the number of appropriate ICD shocks and VA burden (13-16). Reduction of the QTc to <500 ms after left cardiac sympathetic denervation has been correlated with reduced risk of recurrent ICD shocks and frequency of symptoms (16, 52); however, SCD or SCA is reported in 3% to 10% of patients (15, 16, 48, 50). Although arrhythmia burden is often reduced, up to 27% of high-risk patients experience at least 1 recurrence (13, 14, 48). Patient outcomes are improved if the left cardiac sympathetic denervation is performed in centers with surgical expertise in this procedure. Use of additional medications is guided by long QT syndrome type. In long QT syndrome type 3, ranolazine, mexiletine, and flecainide shorten the QTc and have been used to reduce recurrent arrhythmias (6, 7, 10).

4. Genetic testing for disease-causing mutations in long QT syndrome offers important diagnostic, prognostic, and therapeutic information in addition to the clinical evaluation, and a positive test can facilitate establishing risk for family members. The yield of genetic testing in long QT syndrome phenotype-positive patients is 50% to 86%, with the higher range present in patients with marked QT prolongation or positive family history of SCD (17, 21, 53). A negative genetic test does not exclude the diagnosis of long QT syndrome, which relies on the clinical evaluation. In asymptomatic patients with otherwise unexplained prolonged QTc ≥480 ms on serial ECGs, genetic testing may help confirm the diagnosis and supplement prognostic information in addition to clinical symptoms and QTc duration (5, 18-20, 30, 35, 54-56).

5. In a prospective, observational study of patients with suspected long QT syndrome, patients with a history of syncope or cardiac arrest and either an affected first-degree relative or a borderline or prolonged QTc interval underwent exercise treadmill testing and bicycle exercise, with ECGs recorded before, during, and after exercise, as well as in different positions (27). long QT syndrome was confirmed by genetic testing in all affected individuals. Among patients with borderline-to-normal resting QTc intervals, prolongation of the 4-minute recovery QTc ≥445 ms had high sensitivity for correctly identifying patients with long QT syndrome (27). A study in younger patients demonstrated QTc prolongation >460 ms at 7 minutes of recovery predicted long QT syndrome type 1 or long QT syndrome type 2 patients versus controls (23). In a study using burst bicycle exercise, patients with latent long QT syndrome had a significantly greater increase in QTc with exercise than either controls or those with QTc prolongation at baseline (24). These findings can be useful in establishing whether long QT syndrome is present. Monitoring adequacy of beta-blocker therapy using exercise testing can be beneficial, particularly in school-aged patients (26, 28). Beta-blocker therapy may be

associated with a decrease in supine and peak exercise QTc, with the exception of long QT syndrome type 1 patients with C-loop mutations (25).

6. Approximately 10% to 36% of genotype-positive patients with long QT syndrome have QTc intervals ≤440 ms, most commonly patients with long QT syndrome type 1 (31, 35). Patients with long QT syndrome and normal QTc have a lower risk of VA and SCD compared to those with prolonged QTc (35), but still have an increased risk of SCA or SCD compared with genotype-negative, age- and sex-matched general patients (31). Beta blockers reduce the risk of adverse cardiac events substantially (1-5, 30, 36, 38, 41, 57). During the periods of highest risk in the first 3 decades of life (11, 18), treatment with a beta blocker may reduce risk of SCA (26, 28, 36, 38). Changes in QTc occur over time, particularly during puberty and during and after pregnancy, indicating the need for assessment of QTc on ECG annually or with medication changes, and assessing medication efficacy with exercise testing as feasible. Asymptomatic adult (male) long QT syndrome patients with normal QTc intervals may choose to decline beta-blocker therapy (11, 34).

7. The risk of adverse cardiac events from VA is influenced by the patient's resting QTc interval, age, sex, and long QT syndrome genotype/mutation. For asymptomatic males with long QT syndrome, the risk of cardiac events is highest in childhood (2, 8, 11, 30), during a time when medication compliance is challenging. Young women with LQT2 and QTc >500 ms are at increased risk of SCA (2, 11, 18-20, 30, 35) especially in the 9 months postpartum, and may be candidates for primary prevention ICD placement or use of a wearable cardioverter-defibrillator (30).

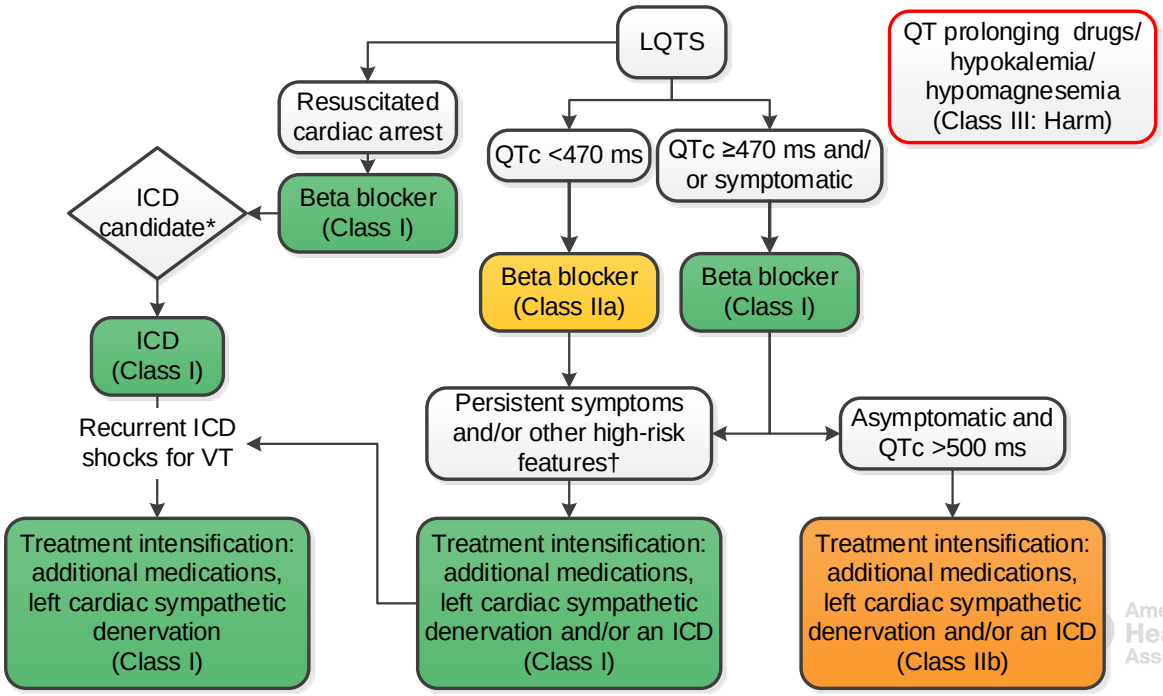
8. The risk of adverse events increases in patients with long QT syndrome with prolongation of the QTc >500 ms (2, 12, 26, 35, 41, 58). QT-prolonging medications (www.crediblemeds.org) (59) should not be used in patients with long QT syndrome unless there is no suitable alternative; careful monitoring of the QTc during therapy is recommended, with consideration for discontinuing therapy with marked QTc prolongation. Concurrent use of stimulant or nonstimulant attention deficit/hyperactivity medications was associated with an increased risk of syncope/cardiac arrest in long QT syndrome, particularly males, in 1 study (34), but it did not appear to be associated with increased risk in another retrospective study (60). Episodes of torsades de pointes can be precipitated by exposure to a QT prolonging medication, or hypokalemia induced by diuretics or gastrointestinal illenss. Attention to maintaining normal potassium and magnesium balance when medications or situations that promote depletion are encountered is an important component of management. Rare case reports exist of fever prolonging the QT interval in patients with long QT syndrome type 2; fever should be reduced with antipyretics (61) (Table 10).

Table 10. Commonly Used QT-Prolonging Medications (59, 62)

Examples of QT Prolonging Medications*			
Antiarrhythmic Medications	**Psychotropic Medications**	**Antibiotics**	**Others**
Disopyramide Procainamide (N-acetylprocainamide) Quinidine Dofetilide Dronedarone Ibutilide Sotalol Amiodarone†	Haloperidol Phenothiazines Citalopram Tricyclic antidepressants	Erythromycin Pentamidine Azithromycin Chloroquine Ciprofloxacin Fluconazole Levofloxacin Moxifloxacin Clarithromycin Itraconazole Ketoconazole	Methadone Probucol Droperidol Ondansetron

*A more complete list is maintained at: www.crediblemeds.org (59).
†Amiodarone rarely causes torsades de pointes.

Figure 9. Prevention of SCD in Patients With Long QT Syndrome



Colors correspond to Class of Recommendation in Table 1.
See Section 7.9.1.1 for discussion.
*ICD candidacy as determined by functional status, life expectancy, or patient preference.
†High-risk patients with LQTS include those with QTc >500 ms, genotypes LQT2 and LQT3, females with genotype LQT2, <40 years of age, onset of symptoms at <10 years of age, and patients with recurrent syncope.
ICD indicates implantable cardioverter-defibrillator; LQTS, long-QT syndrome; VT, ventricular tachycardia.

Figure 10. Long-QT Syndrome Type 1

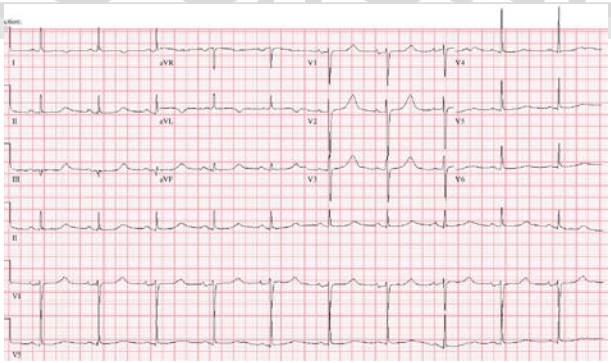


Figure 11. Long-QT Syndrome Type 2

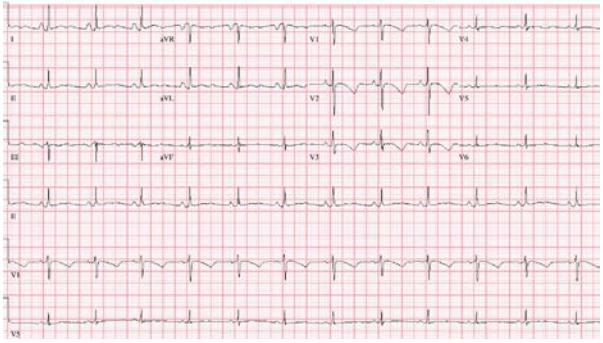
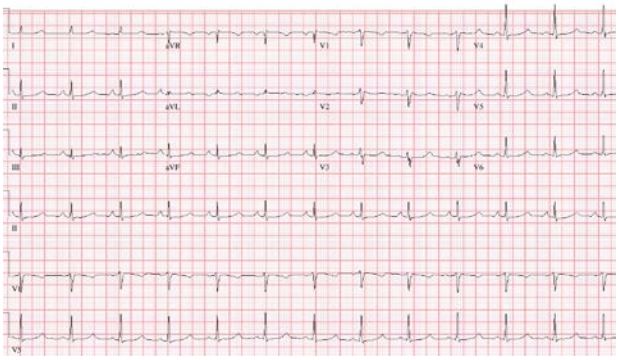


Figure 12. Long-QT Syndrome Type 3



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7.9.1.2. Catecholaminergic Polymorphic Ventricular Tachycardia

Recommendations for Catecholaminergic Polymorphic Ventricular Tachycardia References that support the recommendations are summarized in Online Data Supplement 41.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with catecholaminergic polymorphic ventricular tachycardia, a beta blocker is recommended (1, 2).**
I	**B-NR**	**2. In patients with catecholaminergic polymorphic ventricular tachycardia and recurrent sustained VT or syncope, while receiving adequate or maximally tolerated beta blocker, treatment intensification with either combination medication therapy (e.g., beta blocker, flecainide), left cardiac sympathetic denervation, and/or an ICD is recommended (2-6).**
IIa	**B-NR**	**3. In patients with catecholaminergic polymorphic ventricular tachycardia and with clinical VT or exertional syncope, genetic counseling and genetic testing are reasonable (7).**

Figure 13

Recommendation-Specific Supportive Text

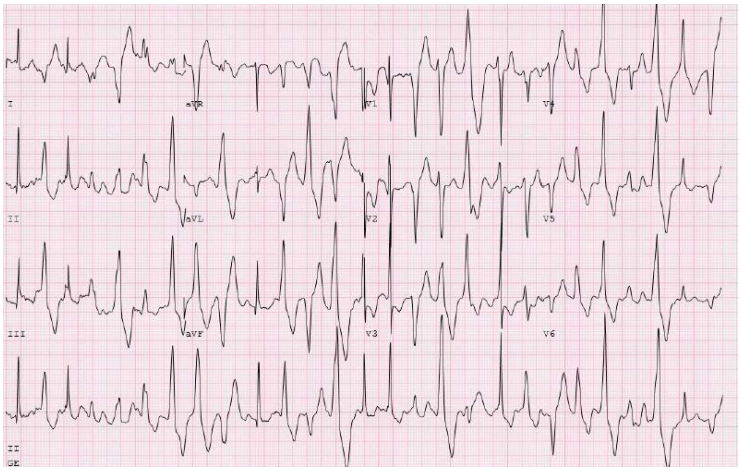
1. Catecholaminergic polymorphic ventricular tachycardia is characterized by exertion-related polymorphic or bidirectional VT (Figure 13), associated with syncope and SCA. SCA/SCD is reported in 3% to 13% of patients (1, 2, 8). Treatment with beta blockers is associated with a reduction in adverse cardiac events (1, 2). Some experts prefer the use of nadolol over other types of beta blockers; direct comparison data among beta blockers are unavailable. Use of a maximally tolerated dose of a beta blocker is important. Small observational studies suggest possible benefit of nondihydropyridine calcium channel blockers in the treatment of catecholaminergic polymorphic ventricular tachycardia (9, 10).

2. Flecainide in combination with a beta blocker can suppress ventricular ectopy by as much as 76% in patients with catecholaminergic polymorphic ventricular tachycardia during exercise testing or clinical follow-up (2, 6, 11). For refractory VA, verapamil or propafenone may also be effective (9, 10, 12). ICD implantation in patients with catecholaminergic polymorphic ventricular tachycardia should be reserved for patients with prior SCA, or patients with refractory VAs on combination medical therapy. Inappropriate shocks are reported in 20% to 30% of catecholaminergic polymorphic ventricular tachycardia patients with ICDs (2, 13-16) . ICD programming in patients with catecholaminergic polymorphic ventricular tachycardia should be optimized to deliver therapy for VF and to minimize inappropriate shocks and the risk of potentially fatal electrical storms (13, 15). Left cardiac sympathetic denervation for catecholaminergic polymorphic ventricular tachycardia may reduce the frequency of recurrent ICD shocks by 32% to 75% (3-5, 17, 18) although recurrent syncope, SCA, or SCD is reported in 9% to 32% of patients, with other minor complications in 20% to 70% of patients. It is best if the left cardiac sympathetic denervation is performed in centers with expertise in this procedure. Intensification of medical therapy or left cardiac sympathetic denervation is important in treating patients who present with recurrent appropriate ICD shocks (19).

3. Genetic testing may be useful to confirm the diagnosis of catecholaminergic polymorphic ventricular tachycardia, which is suggested by the development of bidirectional VT with exertion or stress. Recognition of catecholaminergic polymorphic ventricular tachycardia as the cause for exertional symptoms should prompt aggressive therapy to prevent the significant risk of SCD. Therapy for catecholaminergic polymorphic ventricular tachycardia is not guided by genotype status, but screening of first-degree relatives may be facilitated with genetic testing (20). Ryanodine receptor mutations have been reported in 47% of probands, which were de novo mutations in >70% (7). Ryanodine genotype status has not correlated with disease severity or response to medications (7). In very young patients presenting with idiopathic VF, mutations in calmodulin have been identified and are associated with high lethality (21-24). Studies of proposed pathogenic

mutations in catecholaminergic polymorphic ventricular tachycardia genes report up to 15% of variants were present in exome databases of the general population, raising questions as to the monogenic cause of catecholaminergic polymorphic ventricular tachycardia (20, 25).

Figure 13. Exercise-Induced Polymorphic VT in Catecholaminergic Polymorphic Ventricular Tachycardia



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7.9.1.3. Brugada Syndrome

Recommendations for Brugada Syndrome References that support the recommendations are summarized in Online Data Supplement 42 and Systematic Review Report.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In asymptomatic patients with only inducible type 1 Brugada electrocardiographic pattern, observation without therapy is recommended.**
I	**B-NR**	**2. In patients with Brugada syndrome with spontaneous type 1 Brugada electrocardiographic pattern and cardiac arrest, sustained VA or a recent history of syncope presumed due to VA, an ICD is recommended if a meaningful survival of greater than 1 year is expected (4, 6).**
I	**B-NR**	**3. In patients with Brugada syndrome experiencing recurrent ICD shocks for polymorphic VT, intensification of therapy with quinidine or catheter ablation is recommended (7-11).**
I	**B-NR**	**4. In patients with spontaneous type 1 Brugada electrocardiographic pattern and symptomatic VA who either are not candidates for or decline an ICD, quinidine or catheter ablation is recommended (7, 9-11).**
IIa	**B-NR**	**5. In patients with suspected Brugada syndrome in the absence of a spontaneous type 1 Brugada electrocardiographic pattern, a pharmacological challenge using a sodium channel blocker can be useful for diagnosis (12-14).**
IIb	**B-NR^{SR}**	**6. In patients with asymptomatic Brugada syndrome and a spontaneous type 1 Brugada electrocardiographic pattern, an electrophysiological study with programmed ventricular stimulation using single and double extrastimuli may be considered for further risk stratification (1, 6, 13, 15-17).**
IIb	**C-EO**	**7. In patients with suspected or established Brugada syndrome, genetic counseling and genetic testing may be useful to facilitate cascade screening of relatives (18-20).**

SR indicated systematic review.

Figures 14 and 15.

Synopsis

Refer to the "Systematic Review for the 2017 ACC/AHA/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death" for the complete systematic evidence review for additional data and analyses (15). The results from the question "For asymptomatic patients with Brugada syndrome, what is the association between an abnormal EP study and SCD and other arrhythmia endpoints? (Part 1)" and the writing committee's review of the totality of the literature were used to frame decision-making. Recommendations that are based on a body of evidence that includes the systematic review conducted by the ERC are denoted by the superscript SR (e.g., LOE: B-R^{SR}).

Factors identified as potential triggers of VF and SCA in Brugada syndrome include some psychotropic medications, and anesthetic agents, cocaine, excessive alcohol intake, and fever (www.brugadadrugs.org) (21, 22). These agents should be avoided, and fever warrants early and aggressive measures to reduce temperature (23).

Recommendation-Specific Supportive Text

1. The risk of major adverse cardiac events in asymptomatic patients without spontaneous type 1 electrocardiographic changes of Brugada syndrome (Figure 15), or with only medication-induced

electrocardiographic changes, is low (1-5). A positive family history of Brugada syndrome or SCA is not a significant predictor of adverse events in Brugada syndrome (1, 2, 4, 5). Implantation of an ICD in an asymptomatic patient without a spontaneous type 1 Brugada electrocardiographic has not been shown to confer any benefit.

2. Brugada syndrome is characterized by coved ST elevation in leads V1 or V2 positioned in the second, third, or fourth intercostal space either spontaneously or induced by administration of a sodium channel–blocking drug in the absence of other causes of ST elevation (24) and negative T waves in the right precordial leads, and is associated with syncope or SCA due to VF, predominantly in young males, although it has been reported in all age groups. The type 1 Brugada ECG with coved ST elevation in right precordial leads may be present spontaneously, during fever or vagotonic states, or after medication challenge with sodium channel blockers. QRS complex fractionation is seen in a minority of patients. Patients with spontaneous coved type ST elevation and a history of syncope or prior SCA are at the highest risk for potentially lethal VA. ICD implantation has been shown to reduce mortality in symptomatic patients with Brugada syndrome (25, 26).

3. Ablation of abnormal areas of epicardial late activation in the RV can suppress recurrent VA as shown in a small number of patients (8, 9, 11, 27). In these reports, the spontaneous type 1 Brugada pattern on ECG may be eliminated in >75% of patients, and recurrences of VT/VF are markedly reduced (9-11). Experience and follow-up after ablation are limited, and an ICD for patients who have had syncope or SCA is recommended. A series of patients with Brugada syndrome treated with quinidine had no deaths during a mean follow-up of over 9 years, although adverse effects of quinidine were reported in 38% of patients, these authors felt that quinidine could be used as an alternative to the ICD in selected patients (7).

4. Observational studies show that quinidine can suppress VF storm in patients with Brugada syndrome, and a low risk of arrhythmia was observed in a long-term observational study (681). No patient treated with quinidine experienced SCD. Adverse effects of quinidine occur in up to 37% of patients. Catheter ablation targeting the epicardial right ventricular areas of abnormality has also been shown to reduce recurrent VF episodes and normalize the ECG (682, 684, 685).

5. Administration of procainamide, flecainide, or ajmaline may be useful to provoke type 1 ST elevation in patients suspected to have Brugada syndrome as a cause of symptoms but who do not have a type 1 electrocardiographic pattern at baseline. Medication challenge should be terminated with the development of VA, marked QRS widening, or type 1 Brugada electrocardiographic pattern (14, 28). The use of high electrocardiographic electrode positioning in the second and third interspaces for electrocardiographic recording improves detection of a type 1 Brugada ECG (29). Asymptomatic patients with a family history of Brugada syndrome may be offered sodium channel blocker challenge for diagnostic evaluation, although a positive test does not require chronic therapy due to a low risk in this setting (12). In asymptomatic patients with type 1 Brugada electrocardiographic findings, medication challenge does not offer additional diagnostic value.

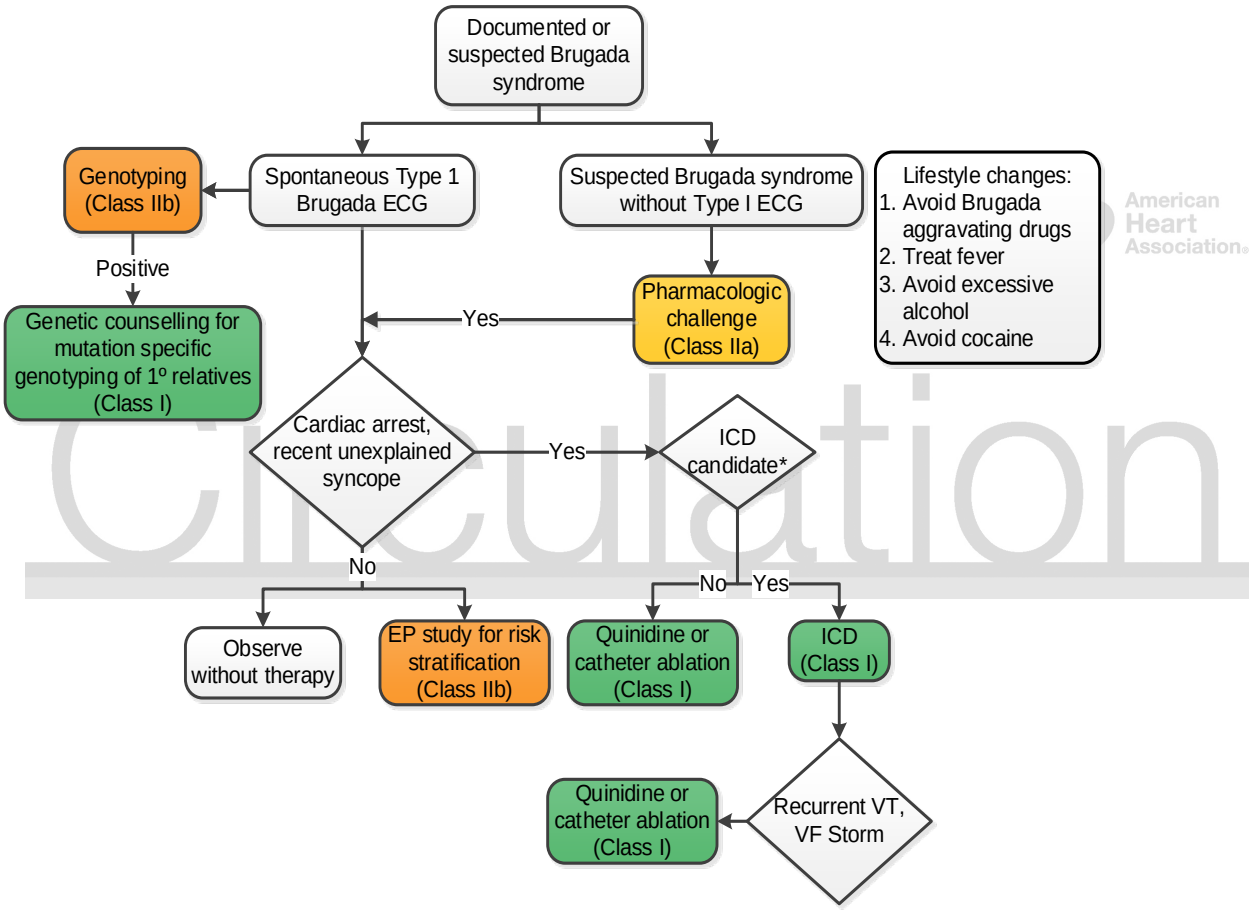
6. Polymorphic VT/VF induced by programmed stimulation has been associated with an increased risk of VA in some patients with spontaneous type 1 Brugada ECG (13).The specificity of programmed stimulation for assessing risk decreases with the inclusion of triple extrastimuli (6, 13). The value of programmed stimulation in asymptomatic patients with spontaneous type 1 Brugada ECGs has been the subject of multiple studies (1, 2, 4, 5). A report found that the prognostic value has decreased over time, possibly as patients with less severe phenotypes have been recognized and studied (1). Some experts use the results of programmed ventricular stimulation for informing shared decision-making in consideration of the ICD. In symptomatic patients with Brugada syndrome, programmed ventricular stimulation for risk stratification does not add anything to the evaluation of the patients as an ICD is warranted (2, 4, 6).

7. The yield of genetic testing in phenotype positive patients is approximately 20% to 30% in Brugada syndrome (4, 16, 18, 19, 30, 31). *SCN5A* variants account for most of this subset of genotype positive Brugada

syndrome. However, 2% to 10% of otherwise healthy individuals host a rare variant of *SCN5A* (20, 31). A negative genetic test does not exclude the diagnosis of Brugada syndrome, which is usually based on electrocardiographic and clinical characteristics. Risk stratification is based on symptoms and clinical findings (32); genotype status is not correlated with the risk of adverse events (5, 18, 19, 33). Identification of a pathogenetic mutation may help facilitate recognition of carrier status in family members, allowing for lifestyle modification and potential treatment.

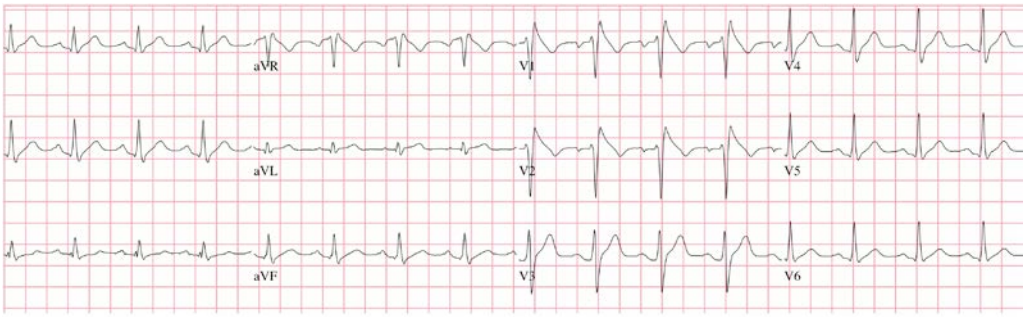
8. Factors identified as potential triggers of VF and SCA in Brugada syndrome include some psychotropic medications, and anesthetic agents, cocaine, excessive alcohol intake, and fever (www.brugadadrugs.org) (21, 22). These agents should be avoided and fever warrants early and aggressive measures to reduce temperature. (23).

Figure 14. Prevention of SCD in Patients With Brugada Syndrome



Colors correspond to Class of Recommendation in Table 1.
See Section 7.9.1.3 for discussion.
*ICD candidacy as determined by functional status, life expectancy or patient preference.
1° indicates primary; ECG, electrocardiogram; EP, electrophysiological; ICD implantable cardioverter-defibrillator; SCD, sudden cardiac death; VT, ventricular tachycardia; and VF, ventricular fibrillation.

Figure 15. Brugada Syndrome



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7.9.1.4. Early Repolarization "J-wave" Syndrome

Recommendations for Early Repolarization Syndrome References that support the recommendations are summarized in Online Data Supplement 43.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In asymptomatic patients with an early repolarization pattern on ECG, observation without treatment is recommended (1, 2).**
I	**B-NR**	**2. In patients with early repolarization pattern on ECG and cardiac arrest or sustained VA, an ICD is recommended (3, 4).**
III: No Benefit	**B-NR**	**3. In patients with early repolarization pattern on ECG, genetic testing is not recommended (5).**

Recommendation-Specific Supportive Text

1. The prevalence of an early repolarization pattern on ECG with J point elevation in the inferior or lateral leads of at least 0.1 mV has been reported to be as high as 5.8% in adults (1) and is more common in males. The early repolarization pattern was lost during 10-year follow-up in >60% of young males (2). Patients are determined to have an early repolarization syndrome when, in addition to having early repolarization pattern on an ECG, they either have symptoms such as syncope or present with an arrhythmia. When patients present

with an early repolarization pattern on an ECG, it is important to rule out reversible causes such as ischemia. Patients with early repolarization are more susceptible to the development of VF during acute cardiac ischemia and/or in the presence of QRS abnormalities due to LV hypertrophy or bundle-branch block (6-8).

2. Patients with cardiac arrest or VF in the setting of an electrocardiographic pattern of early repolarization are at increased risk for subsequent recurrent episodes of VF, occurring in at least 40% of patients (3, 4, 9). Antiarrhythmic medications, with the exception of quindine/hydroquinidine, have limited efficacy in preventing recurrent VA (3, 4).

3. To date, genetic testing has not reliably identified mutations predisposing to early repolarization (5).

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7.9.1.5. Short QT Syndrome

Recommendations for Short QT Syndrome References that support the recommendations are summarized in Online Data Supplement 44.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In asymptomatic patients with a short QTc interval, observation without treatment is recommended (1, 2).**
I	**B-NR**	**2. In patients with short QT syndrome who have a cardiac arrest or sustained VA, an ICD is recommended if meaningful survival greater than 1 year is expected (3-5).**
IIa	**C-LD**	**3. In patients with short QT syndrome and recurrent sustained VA, treatment with quinidine can be useful (3, 5, 6).**
IIa	**C-LD**	**4. In patients with short QT syndrome and VT/VF storm, isoproterenol infusion can be effective (7).**
IIb	**C-EO**	**5. In patients with short QT syndrome, genetic testing may be considered to facilitate screening of first-degree relatives (4).**

Recommendation-Specific Supportive Text

1. The prevalence of short QTc ≤340 ms is estimated to be 5 in 10,000 in persons <21 years of age and is more common in males (1, 4, 8, 9). An incidental finding of a short QTc ≤320 ms in an asymptomatic patient warrants monitoring and follow-up without prophylactic medication treatment (1, 2).

2. Patients with cardiac arrest in the setting of short QT syndrome are known to be at increased risk for recurrent cardiac arrest (3-5). Approximately 18% of the small number of reported patients with short QT and implanted ICDs have experienced appropriate ICD therapies during short-term follow-up (3, 5, 6). Therapy with quinidine may reduce the number of ICD shocks (3, 5, 6).

3. Markedly shortened QTc values ≤300 ms are associated with increased risk of SCD, especially during sleep or rest, in young persons, in whom the median QTc was 285 ms (5, 9). A clinical score including QTc duration, clinical history of documented polymorphic VT or VF, unexplained syncope, family history of autopsy-negative SCD or sudden infant death syndrome, and positive genotype results has been proposed to identify patients at increased risk for SCD (4, 10). Treatment with quinidine results in lengthening of the QTc and, in selected patients, may be an alternative to ICD implantation (3, 5, 6).

4. In the setting of electrical storm with refractory VF and short QT syndrome, infusion of isoproterenol can be effective in restoring/maintaining sinus rhythm (7).

5. Pathogenic mutations in potassium channels have been identified in approximately 10% to 20% of patients with short QT syndrome including in *KCNH2* (SQT1), *KCNQ1* (SQT2), and *KCNJ2* (SQT3) (4). Due to the rarity of the disease, genotype/phenotype correlations are unavailable, limiting the use of knowledge of genotype status.

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8. VA in the Structurally Normal Heart

Recommendations for VA in the Structurally Normal Heart References that support the recommendations are summarized in Online Data Supplement 45.		
COR	**LOE**	**Recommendation**
I	**B-R**	**1. In patients with symptomatic PVCs in an otherwise normal heart, treatment with a beta blocker or nondihydropyradine calcium channel blocker is useful to reduce recurrent arrhythmias and improve symptoms (1, 2).**
IIa	**B-R**	**2. n patients with symptomatic VA in an otherwise normal heart, treatment with an antiarrhythmic medication is reasonable to reduce recurrent symptomatic arrhythmias and improve symptoms if beta blockers and nondihydropyradine calcium channel blockers are ineffective or not tolerated (3, 4).**

Synopsis

Most idiopathic VA are due to a focal mechanism of triggered activity or abnormal automaticity, some, notably interfascicular reentrant LV tachycardias, are due to reentry. The clinical manifestations of idiopathic VA are highly variable and range from benign, asymptomatic PVCs to sustained VT or even VF. On initial discovery, an evaluation for structural heart disease is warranted with physical examination, an ECG, and imaging, usually with echocardiography. In the absence of any abnormality or a family history of SCD, further assessment and treatment are guided by symptoms. If the patient is asymptomatic and does not have evidence of a cardiac channelopathy, reassurance as to the benign nature is sufficient. If the arrhythmia is suspected of being sufficiently frequent to cause ventricular dysfunction over time, periodic follow-up with reassessment of ventricular function is warranted (see Section 10.8). For mild symptoms, avoidance of aggravating factors such as excessive consumption of caffeine or sympathomimetic agents, may be sufficient. Therapy with a beta blocker or nondihydropyradine calcium channel blocker reduces symptoms for some patients. Class I antiarrhythmic medications can be effective, but those are generally avoided due to concerns for adverse effects. For patients who require arrhythmia suppression for whom antiarrhythmic medications are ineffective, not tolerated, or undesired, catheter ablation can be a highly effective treatment (see Section 9). The ablation strategy is to identify the site of origin manifested by the earliest site of electrical activation or, when this is not feasible, by pace-mapping. The most common site of origin for idiopathic VA is from the right ventricular outflow tract (RVOT) or the ostium of the LV, which is comprised of the oval opening of the LV to which the aorta is attached anteriorly and the left atrium is attached posteriorly. The likely origin can be reasonably predicted from the QRS morphology of the VA, which provides a good indication of the type of approach required and the likelihood of success and risks. Ablation failure is often related to the absence of the VA for mapping at the time of the procedure, or origin of the VA in an inaccessible region of the heart. These foci occasionally produce sustained monomorphic VT (5-7).

Recommendation-Specific Supportive Text

1. In a randomized, double-blinded, placebo-controlled study of 52 patients with symptomatic VA and a mean PVC count of 21,407±1740 beats per 24 hours, atenolol significantly decreased symptom frequency (p=0.03) and PVC count (p=0.001), whereas placebo had no effect on PVC count (p=0.78) or average heart rate (p=0.44) (8). A prospective randomized comparison of antiarrhythmic medications versus catheter ablation, metoprolol or propafenone had modest efficacy to suppress RVOT VA although with a far higher rate of recurrence than catheter ablation (9).
2. In an RCT of 233 patients with ≥30 PVCs per hour, d-sotalol was shown to reduce frequent PVCs, but only racemic dl-sotalol is presently available (10). In a prospective randomized comparison of antiarrhythmic medications versus catheter ablation, therapy with metoprolol or propafenone was shown to have modest

efficacy when used to suppress RVOT PVCs although with a far higher rate of recurrence than catheter ablation (9). Nondihydropyridine calcium channel blockers reduce arrhythmias (1, 2, 11, 12).

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8.1. Outflow Tract and Atrioventricular Annular VA

Recommendations for Outflow Tract VA References that support the recommendations are summarized in Online Data Supplement 46.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with symptomatic outflow tract VA in an otherwise normal heart for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful (1-3).**
I	**B-NR**	**2. In patients with symptomatic outflow tract VT in an otherwise normal heart, a beta blocker or a calcium channel blocker is useful (1-3).**

Recommendation-Specific Supportive Text

1. In 1 RCT, catheter ablation was superior to antiarrhythmic medications at suppressing frequent PVCs arising from the RVOT (4). Observational studies have shown that radiofrequency catheter ablation is effective in the treatment of idiopathic VA arising from the RVOT and LV outflow tract (2, 5-16). The site of ablation may be below or above the pulmonic valve in the RVOT (9, 13). Although most RVOT VA can be ablated within the RV, 10% may require ablation within the pulmonic sinus cusps (9). Serious complications are infrequent. For LV outflow tract VA, the site of ablation may be within the aortic cusp sinuses (11, 14, 16), below the aortic valve (2, 6), at the aorto-mitral continuity (1-3) or on the epicardial surface of the LV summit (3, 17, 18). The mitral

and tricuspid annulae are less common sites of idiopathic VA, but these VA can also be effectively treated with catheter ablation (1, 19, 20). Approximately 10% of idiopathic VA may arise from the summit of the LV. Some can be ablated from the great cardiac vein or the epicardial surface, but others arise from an inaccessible region in close proximity to the left coronary artery precluding effective ablation (14). Intramural sites of origin are infrequent but may require ablation on both the endocardial and epicardial surfaces of the LV ostium (3). Complications from ablation of outflow tract VA are infrequent, but bleeding complications related to arterial and venous access, pericardial tamponade, and damage to the coronary arteries can occur.

2. In a prospective randomized comparison of antiarrhythmic medications versus catheter ablation, metoprolol or propafenone was shown to have modest effectiveness when used to suppress RVOT PVCs, though with a far higher rate of recurrence than catheter ablation (4). Non-dihydropyradine calcium channel blockers suppress arrhythmia in some patients (4).

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8.2. Papillary Muscle VA

Recommendation for Papillary Muscle VA (PVCs and VT) References that support the recommendation are summarized in Online Data Supplement 47.		
COR	**LOE**	**Recommendation**
I	**B-NR**	**1. In patients with symptomatic VA arising from the papillary muscles for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful (1-5).**

Recommendation-Specific Supportive Text

1. The papillary muscles of the LV or RV can be the site of origin of VA in the presence or absence of structural heart disease (1-5). Idiopathic left and right ventricular papillary muscle VA are most commonly PVCs and NSVT, and are usually exercise-related and may be induced by intravenous epinephrine or isoproterenol administration (3). These arrhythmias have a focal, nonreentrant mechanism. Any of the 3 RV papillary muscles may be the site of origin and catheter ablation is usually effective (2). In 1 study, successful ablation was achieved in all 8 patients with a reduction in PVC burden from 17±20% to 0.6±0.8% (2). In the left ventricle, the site of origin may be either the posteromedial or the anterolateral papillary muscles (1, 4, 5). Multiple VA QRS morphologies were observed in 47% of patients, and ablation on both sides of the papillary muscle is required in some patients (4). Achieving adequate catheter stability can be challenging. Acute ablation success is high, but recurrences are more frequent than for idiopathic outflow tract VA. Serious complications, including valve injury, appear to be infrequent. The risks of catheter ablation include bleeding related to arterial and venous access and a low risk of pericardial tamponade.

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8.3. Interfascicular Reentrant VT (Belhassen Tachycardia)

Recommendations for Interfascicular Reentrant VT (Belhassen Tachycardia) References that support the recommendations are summarized in Online Data Supplement 48.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with verapamil-sensitive, idiopathic LVT related to interfascicular reentry for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful (1-3).**
I	**B-NR**	**2. In patients with sustained hemodynamically tolerated verapamil-sensitive, idiopathic LVT related to interfascicular reentry, intravenous verapamil is recommended for VT termination (3-6).**
IIa	**C-LD**	**3. In patients with recurrent verapamil-sensitive idiopathic LVT, chronic therapy with oral verapamil can be useful (7-10).**

Recommendation-Specific Supportive Text

1. Idiopathic LVT is due to reentry involving a portion of the LV Purkinje system, usually the left posterior fascicle as the retrograde limb of the circuit and an incompletely defined segment of LV tissue as the anterograde limb, a portion of which is verapamil sensitive (1-3). These VTs are typically sustained with a QRS that has a right bundle-branch block configuration with a superior axis. Less frequently an inferior axis VT or a relatively narrow QRS VT occurs as a result of alternate reentry paths, also involving a part of the Purkinje system. Beta blockers or verapamil typically terminate these arrhythmias, but they fail to prevent recurrences in some patients (1-3). The target of catheter ablation for the most common form is usually the distal insertion of the anterograde limb of the Purkinje system along the inferior portion of the LV septum near its junction with the left posterior fascicle. Catheter ablation is acutely successful in >90% of patients with a risk of recurrence of approximately 10%. This VT may resemble fascicular VA that are due to a focal mechanism in the left anterior or left posterior fascicles of the LV His-Purkinje system. These fascicular arrhythmias usually have a focal mechanism with the target of catheter ablation being the site of earliest electrical activation recorded with a presystolic fascicular potential. Catheter ablation is highly effective for intrafascicular and fascicular VA. Serious complications are infrequent and include bleeding at the site of arterial or venous access and a small risk of bundle branch block or atrioventricular block.

2. Idiopathic LVT is based on reentrant mechanism involving tissue with slow conduction properties along the LV septum as the anterograde limb and the normal left posterior fascicle of the His-Purkinje system as the retrograde limb. The slow conduction zone is verapamil-sensitive (3-6). These arrhythmias typically have a right bundle-branch block morphology with superior axis, though reversal of the circuit may produce a relatively narrow QRS during VT. Verapamil typically terminates these arrhythmias in the anterograde slow conduction zone (3-6).

3. Although no RCTs have been published, the chronic use of oral verapamil for verapamil-sensitive idiopathic LVT has been reported to control this tachycardia in many patients, including both adults and children (5, 8-10).

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8.4. Idiopathic Polymorphic VT/VF

Recommendations for Idiopathic Polymorphic VT/VF References that support the recommendations are summarized in Online Data Supplement 49.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In young patients (<40 years of age) with unexplained SCA, unexplained near drowning, or recurrent exertional syncope, who do not have ischemic or other structural heart disease, further evaluation for genetic arrhythmia syndromes is recommended (1-8).**
I	**B-NR**	**2. In patients resuscitated from SCA due to idiopathic polymorphic VT or VF, an ICD is recommended if meaningful survival greater than 1 year is expected (9-13).**
I	**B-NR**	**3. For patients with recurrent episodes of idiopathic VF initiated by PVCs with a consistent QRS morphology, catheter ablation is useful (11, 14).**

Recommendation-Specific Supportive Text

1. When combined with clinical evaluation, genetic testing can provide a diagnosis in up to 13% to 60% of younger (<40 years of age) survivors of SCA (3), with the most common genotypes identified associated with long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome (8). Drowning/near drowning events are particularly associated with LQT1 and catecholaminergic polymorphic ventricular tachycardia; genetic mutations in long QT syndrome and catecholaminergic polymorphic ventricular tachycardia have been identified in 23% of patients with unexplained near-drowning episodes (15). In 1 study (6), exertion-related cardiac arrest, particularly in children, may be related to long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, or to calmodulin/triadin-mediated long QT syndrome/catecholaminergic polymorphic ventricular tachycardia mutations, which may require additional specialized genetic testing (1, 2, 4, 16-18). Single-driver auto crashes should prompt the consideration of arrhythmic causes. The yield of genetic testing is higher if a family history of SCD at a young age is present. Referral to specialized genetic testing centers is important if local expertise is unavailable.

2. VF in the absence of identifiable structural heart disease or known genetic arrhythmia syndromes such as catecholaminergic polymorphic ventricular tachycardia, long QT syndrome, short QT syndrome, Brugada syndrome, or J wave syndromes is usually the result of short coupled PVCs arising from the Purkinje system in either the right or left ventricles or, less commonly, from the ventricular myocardium (9-13). The recurrence risk after resuscitation of idiopathic VF is very high (12). Among 38 consecutive patients from 6 different centers who underwent ablation of primary idiopathic VF initiated by short coupled PVC, 87% had experienced

≥2 VF episodes in the preceding year (12). Because idiopathic VF is associated with a very high risk of recurrent VF, an ICD is indicated to prevent SCD. Catheter ablation of the triggering focus has proved to be highly effective in eliminating the repetitive PVCs which induce VF in these patients (11). During a median postprocedural follow-up of 63 months, 7 (18%) of 38 patients undergoing catheter ablation of idiopathic VF induced by short coupled PVCs experienced VF recurrence at a median follow-up of 4 months. Five of these 7 patients underwent repeat ablation without VF recurrence. Thus, although catheter ablation is very effective in idiopathic VF, the recurrence risk remains substantial after an apparently successful procedure and the patient should be protected with an ICD. The subcutaneous ICD may not be a good therapy for these patients due to the higher risk of T-wave oversensing seenin this population; however, data are limited (10).

3. Idiopathic VF may be initiated by PVCs that arise from the outflow tracts or the His-Purkinje system within either the right ventricle or left ventricle (11, 14, 19-21). Some patients have clusters of VF episodes (electrical storm) that typically present as PVCs initiating polymorphic VT/VF. The PVCs usually have a consistent QRS morphology and a short coupling interval and can be targeted for ablation to control the arrhythmia (11). For PVCs from the Purkinje system, the ablation target is a high-frequency Purkinje potential preceding the PVCs. When episodes are induced by short-coupled PVCs arising from the outflow tracts, the ablation target is the site of earliest ventricular activation. Patients with idiopathic VF often have periods of frequent VT/VF interspersed with periods of relative quiescence (11, 14). To maximize the probability of successful ablation, the procedure is best performed during periods of frequent PVCs. Less-frequent episodes of VF may be amenable to ablation if frequent PVCs with a consistent QRS morphology are present. When the PVCs can be identified, ablation is highly successful, but late recurrences are observed in approximately 10% of patients such that implantation of an ICD is prudent even if ablation is acutely successful. The risks of catheter ablation include bleeding at the site of arterial or venous access and a small risk of pericardial tamponade. Therapy with quinidine acutely and chronically can suppress recurrent VF episodes in some patients (22).

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9. PVC-Induced Cardiomyopathy

Recommendations for PVC-Induced Cardiomyopathy References that support the recommendations are summarized in Online Data Supplement 50.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. For patients who require arrhythmia suppression for symptoms or declining ventricular function suspected to be due to frequent PVCs (generally >15% of beats and predominately of 1 morphology) and for whom antiarrhythmic medications are ineffective, not tolerated, or not the patient's preference, catheter ablation is useful (1, 2).**
IIa	**B-NR**	**2. In patients with PVC-induced cardiomyopathy, pharmacological treatment (e.g., beta blocker, amiodarone) is reasonable to reduce recurrent arrhythmias and improve symptoms and LV function (3, 4).**

Recommendation-Specific Supportive Text

1. Frequent PVCs (usually >15% of the total number of beats) may produce a reversible form of LV dysfunction (5-18). However, it is sometimes difficult to ascertain whether the PVCs caused LV dysfunction or whether progressive LV dysfunction caused frequent PVCs. LV dysfunction has been associated with greater PVC burden (>10% and usually >20%), NSVT, a retrograde P-wave after the PVCs, and interpolated PVCs (6, 15). In a prospective study of catheter ablation for PVC-induced cardiomyopathy, ablation was completely successful in 80% of patients (19). LV function normalized within 6 months in 82% of the 22 patients who had depressed ventricular dysfunction at baseline. Thus, frequent PVCs may be a reversible cause of LV dysfunction that can be effectively treated with catheter ablation. It is often difficult to determine if apparent LV dysfunction reflects impaired LV function or inability to accurately assess LV function due to the frequent ectopic activity. In patients who have a high density of PVCs with normal ventricular function, optimal treatment and surveillance for prevention and detection of decline in ventricular function have not been established.

2. In a double-blind parallel study of 30 patients with or without ischemic heart disease with >30 PVCs per hour comparing sotalol to propranolol, proarrhythmic effects were present in 1 patient on sotalol. There was no significant difference in suppression of PVCs (sotalol 65%, propranolol 44%), with reduction in ventricular couplets being 99% for sotalol and 49% for propranolol. There was a significant increase in QTc in patients on sotalol (20). In a double-blind, randomized, placebo-controlled study of 674 patients with HF and LVEF <0.40 attributed to ischemic or NICM and ≥10 PVCs per hour, amiodarone significantly reduced VA, slowed heart rate, and was associated with an increase in LVEF by 42% at 2 years with a nonsignificant trend toward reduction in mortality (4). Whether the VA was contributing to ventricular dysfunction in these patients is unknown.

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10. VA and SCD Related to Specific Populations

10.1. Athletes

In athletes, VAs range from isolated PVCs, couplets, and NSVT, to sustained VT and SCA leading to SCD (1). Infrequent PVCs and short runs of repetitive NSVT, especially in the absence of structural heart disease, are more common in nonathletes, but they are generally benign, requiring only a limited workup and rarely lead to disqualification for sports (2, 3). In contrast, longer runs of NSVT, especially when exercise-induced, and sustained VT and SCA/SCD are infrequent, but they have a higher incidence in athletes than that reported for the general population in the corresponding age groups. Reported estimates of SCD range from 1 per 53,703 athlete-years in the National Collegiate Athletic Association database (4) to <1 per 200,000 in Minnesota high school students (5). Among those studies judged to have better epidemiological protocols, estimates were in the range of 1 per 40,000 to 1 per 80,000 (6). These figures compare with a general population risk of 1.0 to 1.9/100,000 in adolescents and young adults (7, 8). Moreover, there appears to be both sport and sex differences in the magnitude of risk, with males being at higher risk than females in most sports (7, 9), blacks at higher risk than whites, and male basketball players being the single highest risk group in the United States, 1 per 5200 athlete-years (4).

A study that included both competitive and recreational athletes showed that both groups are at a higher risk for SCD than the general population, with recreational athletes having greater cumulative numbers (7), SCD occurring at an older age, and a different distribution of diseases. Postmortem data on SCD in athletes reveal that 25% to 40% are autopsy-negative, suggesting a role for genetic molecular disorders in these victims (4, 10, 11) and for family members (12).

Another limitation of SCD data analysis in athletes centers on noncardiac causes, some of which mimic cardiac events. Noncardiac causes include acute neurological disorders, drug abuse, heat stroke, rhabdomyolysis, sickle cell disorders, suicides, and accidents (13, 14). Nonetheless, arrhythmias in athletes remain the most common medical cause of death and many occur as the first cardiac event.

The most common structural cause of SCAs and SCDs in athletes in the United States is HCM, followed by anomalous origins of coronary arteries, with myocarditis contributing a smaller but significant proportion (15). Beyond these, the other inherited disorders contribute to the distribution of causes of a SCD in athletes, many of which can be suspected or identified by a careful family history and preparticipation ECGs.

In general, management of arrhythmias in athletes follows that in nonathletes. In regard to interventions, it is now generally recommended that AEDs be available at training and facilities for competitive athletes (16), with less specific statements for AED availability at venues (e.g., tennis courts) or circumstances (e.g., jogging or small group runs) in which recreational athletics are occurring.

Many athletes who have had corrective procedures (repair of congenital or developmental defects such as anomalous origins of coronary arteries) (17, 18) are on therapy for inherited disorders (19) or have ICD implants (1) and are able to participate in athletics depending on the nature and severity of the disease and with appropriate precautions and counseling regarding potential residual risks (19, 20). For example, athletes with acquired disorders such as myocarditis are advised against exercise for at least 3 to 6 months after disease resolution.

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10.2. Pregnancy

Recommendations for Pregnancy References that support the recommendations are summarized in Online Data Supplement 51.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In mothers with long QT syndrome, a beta blocker should be continued during pregnancy and throughout the postpartum period including in women who are breastfeeding (1).**
I	**C-EO**	**2. In the pregnant patient with sustained VA, electrical cardioversion is safe and effective and should be used with standard electrode configuration (2, 3).**
IIa	**B-NR**	**3. In pregnant patients needing an ICD or VT ablation, it is reasonable to undergo these procedures during pregnancy, preferably after the first trimester (4, 5).**

Recommendation-Specific Supportive Text

1. Women with long QT syndrome should be counseled about maternal and fetal risks prior to pregnancy to ensure ongoing beta-blocker therapy. The risk of SCA or SCD is significantly higher during the 9 months after delivery, most notably among women with LQT2 (1, 6, 7). A large retrospective analysis from the long QT syndrome registry demonstrated an odds ratio of 40.8 for syncope, SCA, or SCD among women with long QT syndrome in the 9 months' postpartum; treatment with beta blockers during pregnancy was independently associated with decreased risk (7). Overall arrhythmic events during pregnancy are not increased among women receiving beta-blocker therapy (1, 6, 7). In a case-control study, women with LQT1 who did not receive beta blockers during pregnancy, particularly those with prior syncope, were at significantly increased risk of SCA or syncope (8). Frequency of events returned to prepregnancy levels after 9 months (1). Maternal use of beta blockers during pregnancy is associated with decreased newborn birth weight and hypoglycemia (9), but it is not associated with increased risk of miscarriage (8, 10). Fetal bradycardia is associated with fetal long QT syndrome and should not independently provoke discontinuation of beta-blocker therapy (11-14); these infants are at increased risk of death and require careful neonatal monitoring and treatment (13). As 50% of offspring may be affected with long QT syndrome, with highest risk of adverse events in infancy and childhood, screening of the newborn at birth and during infancy for long QT syndrome is important (8).

2. Available data on electrical fields associated with properly applied AED patches suggest that the fetus is safe; no observational data are available to the contrary. Anterolateral defibrillator pad placement is preferred with the lateral pad/paddle placed under the breast tissue, which is an important consideration in the pregnant patient.

3. The ICD in pregnant women is safe and effective (4). For the rare circumstance of pregnant women with an immediate indication for an ICD, or less common indications for VT ablation during pregnancy, the radiation risk to the fetus is minimal (5, 15). The procedure is usually performed after the first trimester unless there are circumstances that demand an earlier procedure. Wearable cardioverter-defibrillators have been used in peripartum cardiomyopathy while awaiting repeat assessment of recovery of ventricular function (16).The subcutaneous implantable cardioverter-defibrillator is a potential alternative to conventional ICDs, although data are unavailable to support a recommendation.

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10.3. Older Patients With Comorbidities

Recommendation for Older Patients With Comorbidities See Systematic Review Report (1).		
COR	**LOE**	**Recommendation**
IIa	**B-NR^{SR}**	**1. For older patients and those with significant comorbidities, who meet indications for a primary prevention ICD, an ICD is reasonable if meaningful survival of greater than 1 year is expected (1).**

SR indicates systematic review.

Synopsis

Refer to the "Systematic Review for the 2017 ACC/AHA/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death" for the complete systematic evidence review for additional data and analyses (1). The results from the question "What is the impact of ICD implantation for primary prevention in older patients and patients with significant comorbidities? (Part 2)" and the writing committee's review of the totality of the literature were used to frame our decision-making. Recommendations are based on a body of evidence that includes the systematic review conducted by the ERC and are denoted by the superscript SR (e.g., LOE: B-R^{SR}). Comorbidities included various combinations of renal disease, chronic obstructive pulmonary disease, atrial fibrillation, and heart disease, among others.

Recommendation-Specific Supportive Text

1. Older age is defined as ≥75 years.

The ERC's analyses are helpful in clearly demonstrating that neither age nor comorbidities alone should be exclusions for an ICD. However, the data included in the analysis are limited. Firstly, most data are from nonrandomized studies and "both selection and unidentified confounding biases can never be fully

adjusted for." It is likely that the more frail patients are already appropriately not offered ICDs and are thus not included. Secondly, because most of the studies are nonrandomized, these findings signify only an association and not causality.

Also, older adults are prone to higher complication rates, shorter life expectancies (and thus, fewer years during which they could derive benefit from an ICD), and varying preferences (2). For these reasons, it is important to take a particularly nuanced and patient-centered approach to treating these patients.

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10.4. Chronic Kidney Disease

Patients with chronic kidney disease (CKD) are at an increased risk of SCD compared with the general population, yet the risk versus benefit of primary prevention ICDs has been unclear; data from observational studies have been conflicting, and patients with moderate or severe CKD, especially patients with end-stage renal disease (ESRD) on dialysis were not included in the pivotal RCTs of ICDs (1-5). Furthermore, prior data had significant limitations given that patients who received ICDs have been compared inconsistently with a control group with CKD that did not receive primary prevention ICDs and the degree of renal insufficiency likely influences survival benefit (6). Patients with CKD, especially ESRD on dialysis, appear to be at increased risk of ICD-related complications. A significant number of sudden deaths are unassociated with VA in this population (7). Therefore, the ERC was asked to address the impact of ICDs on mortality in patients with CKD.

The ERC conducted a specific analysis of 5 studies that explored renal dysfunction. A meta-analysis of these studies suggested that an association exists between ICD implantation and improved survival (8) . An important limitation is that only 2 studies specifically studied patients with ESRD and most data analyzed were from observational studies (8, 9). In view of these limitations, the writing committee concluded there was not enough data to inform a recommendation on ICD implantation in patients with ESRD on dialysis. Decisions regarding ICDs in patients with CKD, especially those with ESRD, should be individualized and take into consideration the patient's functional status, number of comorbidities, and preferences, among other factors.

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10.5. Valvular Heart Disease

Patients with valvular heart disease should be evaluated and treated according to GDMT for valvular heart disease and, when LVEF is depressed, GDMT that applies to NICM to reduce the risk of SCD (23). VA in patients with valvular heart disease can be caused by any of the mechanisms responsible for VA in other cardiac disease including ischemic heart disease, MI, severe LV hypertrophy, adrenergic-dependent rhythm disturbances, or an inherited molecular abnormality. Patients with valvular heart disease and VA are generally evaluated and treated using current recommendations for each disorder (1). The presence of a VA alone does not constitute an indication for valve repair or replacement. In general, there is more knowledge on the risk for SCD in patients with aortic stenosis than other valvular lesions with a risk of 1% to 1.5% per year (2). Most patients who die suddenly have been symptomatic from their valve disease (3, 4). Although recurrent NSVT may place a patient with severe aortic stenosis at risk for syncope, the management of such a patient is guided by the severity of the valvular lesion.

Mitral valve prolapse has been implicated as a cause of SCD, although a study of 18,786 patients found no increased risk of SCA for patients with bileaflet mitral valve prolapse versus single leaflet mitral valve prolapse or no mitral valve prolapse (5). LV fibrosis in the papillary muscles has been described in some mitral valve prolapse patients with VA or SCD (6). Further, a possible syndrome for SCD has been described that includes bileaflet mitral valve prolapse, female sex, T wave abnormality, and complex ventricular ectopy (7). Guidance for treatment of patients with NICM, whether valvular or otherwise in origin, is provided in the current guideline (see Sections 7.2.1 and 7.2.2 for primary and secondary prevention).

10.6. Sex-Related Differences in the Risk of SCD

The information on associations between sex and VA and SCD is largely limited to epidemiological, cohort, and observational studies. Various population studies, primarily focused on SCD due to ischemic heart disease, have demonstrated age gradients in SCD risk among men and women (8-10). These include a 10-year lag in SCD incidence in women compared with men. However, risk factor burden among women has the same proportional effect as in men, with a 17-fold increase in risk from the lowest to highest deciles (9). Importantly, 69% of the SCDs in women were first cardiac events (8). A study of lifetime risk of SCD stratified at 45, 55, 65, and 75 years of age identified persistently lower and similar proportions of lifetime risk of SCD among women versus men in each of the strata (10). The difference between women and men is somewhat smaller at ages below and above 75 years, largely because of a reduced risk in men. The overall lifetime risk of SCD was 1 in 9 among men and 1 in 30 among women (10).

In studies of outcomes after out-of-hospital cardiac arrest, women were older, had more SCAs in homes, and fewer shockable rhythms (VT/VF) than men (11, 12). This was associated with a somewhat lower probability of survival overall; however, women with VT/VF and those with pulseless electrical activity had better outcomes than men (12). A retrospective analysis of out-of-hospital cardiac arrest reported that survival improved over a 10-year period, with more favorable outcomes in men as well as younger women (13). Two studies demonstrated better outcomes in women with VT/VF, despite adverse risk factor profiles in women (14, 15). Another large study demonstrated that despite similar prehospital return of spontaneous circulation and survival to discharge, younger women had lower 1-month neurologically intact survival than the 50 to 60 age group (16). A 17-year retrospective analysis did not demonstrate any difference between men and women, although total outcomes improved (17).

The proportion of ischemic heart disease-associated SCAs among women surviving out-of-hospital cardiac arrest was significantly lower than in men, but ischemic heart disease remained the most powerful predictor etiologically (18), and women were also significantly less likely to have severe LV dysfunction (LVEF ≤35%) or previously recognized ischemic heart disease (19). Women appear to be less likely to benefit from therapeutic hypothermia postcardiac arrest; however, in the younger age group, neurologic recovery in women was better than in older women (20). Women are less likely to have SCA during competitive athletic events. A large study including both recreational and competitive athletes across a large age range noted that SCA in women during athletic events was 1 in 20 of that in men (21).

A large literature review from 1980 to 1992 demonstrated that women accounted for 70% of recorded cases of cardiovascular medication–related arrhythmias (22). This is consistent with QT interval differences among men and women. A retrospective analysis of quinidine discontinuation reported a significant difference in discontinuation between men and women (66% versus 84%) largely due to prolonged QT (23). A study of catheter ablation for VT reported that overall outcome was similar between men and women (24). The only sex difference was the greater probability of women having RVOT VT and a greater probability of men having LV outflow tract VT.

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10.7. Medication-Induced Arrhythmias

Recommendations for Medication-Induced Arrhythmias References that support the recommendations are summarized in Online Data Supplement 52 and 53.		
Digoxin		
COR	**LOE**	**Recommendation**
I	**B-NR**	**1. Administration of digoxin antibodies is recommended for patients who present with sustained VA potentially due to digoxin toxicity (1, 2).**
Medication-Induced QT Prolongation and Torsades de Pointes		
COR	**LOE**	**Recommendations**
I	**B-NR**	**2. In patients with recurrent torsades de pointes associated with acquired QT prolongation and bradycardia that cannot be suppressed with intravenous magnesium administration, increasing the heart rate with atrial or ventricular pacing or isoproterenol are recommended to suppress the arrhythmia (3).**
I	**C-LD**	**3. For patients with QT prolongation due to a medication, hypokalemia, hypomagnesemia, or other acquired factor and recurrent torsades de pointes, administration of intravenous magnesium sulfate is recommended to suppress the arrhythmia (4, 5).**
I	**C-LD**	**4. For patients with torsades de pointes associated with acquired QT prolongation, potassium repletion to 4.0 mmol per L or more and magnesium repletion to normal values (e.g., ≥2.0 mmol/L) are beneficial (6, 7).**
Sodium Channel Blocker–Related Toxicity		
COR	**LOE**	**Recommendations**
IIa	**C-LD**	**5. In patients taking sodium channel blockers who present with elevated defibrillation or pacing thresholds, discontinuing the presumed responsible medication or reprogramming the device can be useful to restore effective device therapy (8, 9).**
III: Harm	**B-NR**	**6. In patients with congenital or acquired long QT syndrome, QT-prolonging medications are potentially harmful (10).**

Recommendation-Specific Supportive Text

1. Typical arrhythmias related to digoxin toxicity include enhanced atrial, junctional, or ventricular automaticity (with ectopic beats or tachycardia) often combined with atrioventricular block (11). VT that is fascicular or bidirectional in origin is suggestive of digoxin toxicity (12). Severe digoxin overdose causes hyperkalemia and cardiac standstill. The diagnosis is established by the combination of characteristic rhythm disturbances, ancillary symptoms (visual disturbances, nausea, changes in mentation), and elevated serum concentrations. Potentiating factors may include hypothyroidism, hypokalemia, or renal dysfunction (12). Treatment of digoxin toxicity is based on the severity. In mild cases, discontinuing the medication, monitoring rhythm, and maintaining normal serum potassium may be sufficient (11). Intravenous magnesium is often administered if VAs are present (12). Occasionally, temporary pacing may be needed for atrioventricular block or asystole (13). For more severe intoxication (serum digoxin concentrations exceeding 4 ng/ mL and with serious arrhythmias such as VT), the treatment of choice is digoxin-specific Fab antibody (1). In 1 series of 150 severely intoxicated patients, response was rapid (30 minutes to 4 hour), and 54% of patients presenting with a cardiac arrest survived hospitalization (1). Adverse effects include worsening of the underlying disease (increased ventricular rate during AF, exacerbation of HF) and hypokalemia. Doses lower (and less expensive)

than the full neutralizing dose are sufficient as long as cardiac arrest is not imminent (2). Digoxin concentration monitoring is unreliable after antidigoxin antibody administration.

2. Monitoring high-risk patients during initiation of QT-prolonging antiarrhythmic medications and recognition of the syndrome when it occurs are the first steps. Temporary pacing is highly effective in managing torsades de pointes that is recurrent after potassium and magnesium supplementation (3). Isoproterenol can also be used to increase heart rate and abolish postectopic pauses (3).

3. Intravenous magnesium can suppress episodes of torsades de pointes without necessarily shortening QT, even when serum magnesium is normal (4, 5). Repeated doses may be needed, titrated to suppress ectopy and nonsustained VT episodes while precipitating factors are corrected (4). Magnesium toxicity (areflexia progressing to respiratory depression) can occur at high serum concentrations, but this risk is very small with the doses usually used to treat torsades de pointes, 1 to 2 g intravenously (14).

Allelic variants in clinical long-QT disease genes have been identified in patients with medication-induced torsades de pointes (7, 15-18). Further, whole exome sequencing implicates an increased burden of rare potassium channel variants in the risk of medication-induced torsades de pointes (17, 19). These findings do not yet support general genetic screening for prediction of medication-induced torsades de pointes. In long QT syndrome, genetic testing may be performed in the index case who experienced medication-induced torsades de pointes and, if he/she did not survive that event, electrocardiographic screening of first-degree relatives may be performed.

4. Maintaining serum potassium between 4.5 mEq/L and 5 mEq/L shortens QT and may reduce the chance of recurrent torsades de pointes (6, 7).

5. In large clinical trials, sodium channel blockers increased mortality among patients convalescing from MI (20), but similar trends were also seen with earlier trials of mexiletine (21) and disopyramide (22). Based on CAST, flecainide is contraindicated in patients with ischemia, prior MI, and is avoided in patients with other structural heart diseases (20).

Sodium channel blockers increase defibrillation energy requirement and pacing thresholds (8, 9); as a consequence, patients may require reprogramming or revision of pacing or ICD systems or changes in their medication regimens (although modern pacing systems that provide automatic pacing threshold testing and adjustment of pacing output have mitigated the risk of loss of capture). Sodium channel blockers can "convert" AF to slow atrial flutter, which can show 1:1 atrioventricular conduction with wide QRS complexes that can be confused with VT (23).

Sodium channel blockers, like procainamide and flecainide, can occasionally precipitate the typical Brugada syndrome ECG (24, 25). This has been reported not only with antiarrhythmic medications but also with tricyclic antidepressants (26) and cocaine (27) (www.brugadadrugs.org) (28). Whether this represents unmasking individuals with clinically unapparent Brugada syndrome (see Section 7.9.1.3) or one end of a broad spectrum of responses to sodium channel blockers is unknown.

In the setting of sodium-channel blocker toxicity, limited animal data suggest that administration of sodium, as sodium chloride or sodium bicarbonate, may improve conduction slowing or suppress frequent or cardioversion-resistant VT (29). Successful treatment with beta blockers (30) and intravenous fat emulsion and/or extracorporeal membrane oxygenation has also been reported (31).

6. QT-prolonging medications (www.crediblemeds.org) (32) are not used in patients with congenital or acquired long QT syndrome unless there is no suitable alternative or the benefit greatly exceeds the risk. Episodes of torsades de pointes can be precipitated by exposure to a QT-prolonging medication, and underlying prolongation of the QT (from genetic and clinical risk factors) increases this risk (10). Medications implicated in torsades de pointes are found in several medication classes, including antiarrhythmics,

antihistamines, antibiotics, antifungals, antidepressants, antipsychotics, opiates, and anticancer agents (10) (Table 10).

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10.8. Adult Congenital Heart Disease

Recommendations for Adult Congenital Heart Disease References that support the recommendations are summarized in Online Data Supplement 54.		
COR	**LOE**	**Recommendations**
I	B-NR	1. Adult patients with repaired complex congenital heart disease presenting with frequent, complex, or sustained VA, or unexplained syncope should undergo evaluation for potential residual anatomic or coronary abnormalities (1-6).
I	B-NR	2. In patients with adult congenital heart disease and complex or sustained VA in the presence of important residual hemodynamic lesions, treatment of hemodynamic abnormalities with catheter or surgical intervention as feasible is indicated prior to consideration of ablation or an ICD (3, 7-12).
I	B-NR	3. In patients with adult congenital heart disease and hemodynamically unstable VT, an ICD is recommended after evaluation and appropriate treatment for residual lesions/ventricular dysfunction if meaningful survival of greater than 1 year is expected (13-17).
I	B-NR	4. In patients with adult congenital heart disease with SCA due to VT or VF in the absence of reversible causes, an ICD is recommended if meaningful survival of greater than 1 year is expected (13-17).
IIa	B-NR	5. In adults with repaired tetralogy of Fallot physiology with high-risk characteristics and frequent VA, an electrophysiological study can be useful to evaluate the risk of sustained VT/VF (18, 19).
IIa	B-NR	6. In adults with repaired tetralogy of Fallot physiology and inducible VT/VF or spontaneous sustained VT, implantation of an ICD is reasonable (1, 19, 20).
IIa	B-NR	7. In patients with adult congenital heart disease with recurrent sustained monomorphic VT or recurrent ICD shocks for VT, catheter ablation can be effective (21-25).
IIa	B-NR	8. In adults with repaired severe complexity adult congenital heart disease and frequent or complex VA, a beta blocker can be beneficial to reduce the risk of SCA (26).
IIa	B-NR	9. In patients with repaired moderate or severe complexity adult congenital heart disease with unexplained syncope and at least moderate ventricular dysfunction or marked hypertrophy, either ICD implantation or an electrophysiological study with ICD implantation for inducible sustained VA is reasonable if meaningful survival of greater than 1 year is expected (5, 16, 27-29).
IIb	B-NR	10. In patients with adult congenital heart disease and severe ventricular dysfunction (LVEF <35%) and symptoms of heart failure despite GDMT or additional risk factors, ICD implantation may be considered if meaningful survival of greater than 1 year is expected (14-16, 20).
III: Harm	B-NR	11. In patients with adult congenital heart disease who have asymptomatic VA, prophylactic antiarrhythmic therapy with class Ic medications (i.e., flecainide, propafenone) or amiodarone is potentially harmful (30-32).

Table 11 and Figure 16

Synopsis

Tetralogy of Fallot (TOF) is defined as, congenital heart disease with RVOT obstruction and ventricular septal defect, often requiring right ventricle to pulmonary artery conduit placement or pulmonary valve replacement; includes TOF and double-outlet right ventricle. Moderate complexity congenital heart disease is defined as congenital heart disease requiring intracardiac surgical repair, other than isolated atrial and ventricular septal defects; includes TOF, aortic stenosis, coarctation of aorta, and Ebstein anomaly of the tricuspid valve. Severe complexity congenital heart disease is defined as cyanotic congenital heart disease requiring intracardiac repair in infancy, often with staging procedures; includes transposition of the great arteries, truncus arteriosus, and single ventricle anatomy (Figure 16).

Recommendation-Specific Supportive Text

1. The association of VT with RV hemodynamic abnormalities was first established in patients with repaired TOF (33). Multiple studies since that time have demonstrated the correlation of hemodynamic residue and ventricular dysfunction with risk of VT or SCD in patients with congenital heart disease (1, 3-6, 18, 34-36). Presentation with frequent or complex VA may indicate worsening hemodynamic function, coronary artery compromise, or decreased perfusion in the setting of ventricular hypertrophy. Evaluation may also include exercise testing to assess functional capacity (35). Careful evaluation of hemodynamic status for optimization of management is important (9). Potentially treatable residual hemodynamic problems may be identified during hemodynamic evaluation, such as outflow tract stenosis or significant regurgitation, which may benefit from either catheter or surgical intervention (3, 7, 10, 12, 37). Patients with markedly reduced ventricular function, elevated end-diastolic pressures, or pulmonary hypertension should be treated for underlying hemodynamic problems as part of their arrhythmia management.

2. The correlation of residual hemodynamic abnormalities with VA has been most extensively studied in patients with repaired TOF, where RV hypertension, residual pulmonary outflow tract obstruction or regurgitation, and RV dilation are risk factors for VT/SCD (1, 2, 4, 8, 33, 34, 36) . In these studies, frequent PVCs correlated with risk of clinical or inducible sustained VT. A combined approach of surgery for structural abnormalities with map-guided arrhythmia surgery has been used with success (3, 8, 10, 12) , but elimination of VT circuits may be limited by deep endocardial or LV origin of VT and limitations of operative mapping; an empiric approach to VT surgery is generally not recommended as it has limited effectiveness and carries risk of ventricular proarrhythmia (38). Pulmonary valve replacement in patients with TOF may result in improved hemodynamics and functional status, but it may not eliminate the risk of VT (3, 12); postoperative reassessment for the need for an ICD is performed after the early recovery period.

3. Correction of residual hemodynamic/structural abnormalities contributing to VT may improve ventricular function and reduce symptoms, but it may inadequately prevent the risk of subsequent VT or SCA. The use of ICDs in adult congenital heart disease patients for secondary prevention accounts for approximately 50% of implantations presently, at a mean age of 36 to 41 years (13-17). Patients with adult congenital heart disease experience appropriate shock rates of 3% to 6% per year, with equivalent or slightly increased frequency of appropriate shocks for secondary prevention indications (14, 15, 17). Patients with adult congenital heart disease experience a higher rate of complications and inappropriate shocks compared with other adult populations (13-17, 39).

4. Challenges of ICD implantation in patients with adult congenital heart disease may include anatomic complexity, intracardiac shunts, and limited vascular access to the ventricle. Patients with adult congenital heart disease receiving an ICD have an increased rate of complications of 26% to 45%, as well as inappropriate shocks in 15% to 25% of patients (13-16, 40). Limited studies on the use of subcutaneous implantable cardioverter-defibrillator implantation, particularly in patients with single ventricle anatomy (41), report improved success by using right in addition to left parasternal lead positioning for screening (42). Patients with a single ventricle or a systemic right ventricle may not tolerate defibrillation threshold testing, resulting in

multiorgan system failure. Patients with complex anatomy, such as older patients with univentricular physiology, or patients with significantly reduced ventricular function, marked hypertrophy, or multiple prior surgeries, may benefit from earlier consideration of heart transplantation before renal or liver dysfunction progresses.

5. Patients with repaired TOF who are at an increased risk of sustained VT include those with prior palliative systemic to pulmonary shunts, unexplained syncope, frequent PVCs, atrial tachycardia, QRS duration ≥180 ms, decreased LVEF or diastolic dysfunction, dilated right ventricle, severe pulmonary regurgitation or stenosis, or elevated levels of BNP. Patients with TOF physiology and suboptimal hemodynamic status are more likely to have inducible sustained VT (18, 19, 33, 35), and inducible sustained VT correlated with an increased risk of SCA in a multicenter cohort study (19). Evaluation of hemodynamics for residual abnormalities is important, with catheter or surgical treatment of important lesions prior to consideration of ICD implantation.

6. In a multicenter cohort, inducible sustained VT in patients with TOF was an independent risk factor for subsequent clinical VT or SCD (19); patients in that early study had cardiomegaly and prior palliative shunts. Patients with repaired TOF account for approximately 50% of ICD implantations in adult congenital heart disease (13-16, 40). Appropriate ICD shocks occur in up to 7.7% per year of patients with TOF receiving the ICD for primary prevention, compared with 9.8% per year in patients with a secondary prevention ICD (20). In another study including patients with TOF as well as other lesions, inducible sustained VT did not correlate with subsequent appropriate ICD shocks (14). Because of the high incidence of inappropriate shocks in 20% to 30% and complications in at least 30% of patients with adult congenital heart disease (14-17, 39, 40, 43), in addition to financial and psychological burdens, shared decision-making regarding primary prevention ICDs is essential.

7. In patients with recurrent sustained monomorphic VT, catheter ablation of VT can be effective (21-25). Hemodynamic repair, at the time that an arrhythmia is being ablated surgically, should be considered. For patients with complex adult congenital heart disease, care should be provided at experienced centers. After successful catheter ablation of VT, implantation of an ICD for those who do not have an ICD is an individualized decision based on overall functional and physiological status and shared decision making. Careful monitoring during follow-up for recurrent arrhythmias is essential.

8. The highest risk of SCD associated with repaired congenital heart disease reported from large contemporaneous cohorts is in patients with transposition of the great arteries with atrial baffle repair, Ebstein anomaly of the tricuspid valve, aortic stenosis, and univentricular physiology (44-47). Patients with Senning or Mustard atrial baffle repairs are at an increased risk for SCA, particularly during exertion (48). The atrial baffle is noncompliant restricting ability to augment volume and may be associated with pulmonary vein stenosis and increased end-diastolic pressures. RV ischemia and infarction occur, with perfusion defects identified by myocardial perfusion studies in >40% of patients in this population (49, 50). Risk factors for cardiac arrest in patients with transposition and atrial baffle repairs include prior ventricular septal defect closure, symptoms of HF, atrial arrhythmia, RVEF <30% to 35%, and QRS duration ≥140 ms (48, 51). In the single multicenter study assessing outcomes after implantation of an ICD in patients with prior atrial baffle repair of transposition of the great arteries, the lack of beta blockers was associated with a high risk of appropriate ICD therapy (26). Atrial arrhythmias frequently precede VT in transposition patients, and treatments for atrial tachycardia including catheter ablation, antitachycardia pacing algorithms, and beta blockers are important to reduce ICD shocks (26, 52, 53).

9. The risk of SCD is increased among patients with adult congenital heart disease compared with the general population, with the median age at death ranging from 30 to 49 years of age (27, 44, 47, 54, 55). The risk of SCD is highest among patients with moderate or severe complexity congenital heart disease, and accounts for approximately 25% of cardiac causes of death (5, 27, 28, 44-46, 55, 56). Patients with septal defects and a positive family history of septal defects, cardiomyopathy, or bundle-branch block/conduction defects may have the gene mutation *NKX2.5*, which portends an increased risk of early SCD; genetic testing and early

consideration of ICD implantation if positive is warranted (57-59). Patients with repaired complex forms of congenital heart disease have undergone multiple intracardiac surgeries in the first few decades of life with resultant hypertrophy and risk for subendocardial ischemia as well as scar formation contributing to VT/VF. Risk factors for SCD include increasing complexity of heart disease, VA, SVT, progressive increase in QRS duration, systemic ventricular dysfunction, and subpulmonary ventricular dysfunction (1, 5, 6, 14, 28, 29, 36, 45-47, 55). Extrapolation of data regarding specific measures of ventricular function warranting implantation of primary prevention ICDs from adult patients with NICM is unrealistic. The development of unexplained syncope in patients with moderate or severe complexity adult congenital heart disease may be a harbinger of risk for SCD; electrophysiological study with consideration for an ICD as primary prevention can be beneficial.

10. ICDs implanted in patients with adult congenital heart disease, who are in their 40s and 50s, for primary prevention indications now account for >40% to 67% of implanted devices in patients with adult congenital heart disease (13, 15, 16, 41). In these patients, appropriate shocks are delivered in 14% to 22% of patients in the first 3 to 5 years of follow-up (13, 15, 16). In patients with congenital heart disease and severely depressed ventricular function, or single ventricle anatomy, defibrillation threshold testing may pose excessively high risk. In patients without vascular access or prior Fontan repairs, the risk of reoperation with sternotomy for epicardial ICD implantation may outweigh the potential benefits, and consideration for transplant evaluation may be preferable. Subcutaneous implantable cardioverter-defibrillator implantation may be an appropriate option for some patients (42, 53).

11. Adult patients with complex adult congenital heart disease typically have hypertrophy and ventricular dysfunction of varying degrees, increasing their risk for worsening ventricular function with antiarrhythmic medications. In the only large study of antiarrhythmic medications for congenital heart disease, the use of flecainide was associated with proarrhythmia in 5.8% of patients and SCA in 3.9% of patients (30). The use of amiodarone is generally reserved for refractory symptomatic VA or asymptomatic VA that can aggravate ventricular dysfunction, due to the high risk of adverse effects including thyroid dysfunction, particularly among females and patients with univentricular physiology (31, 32).

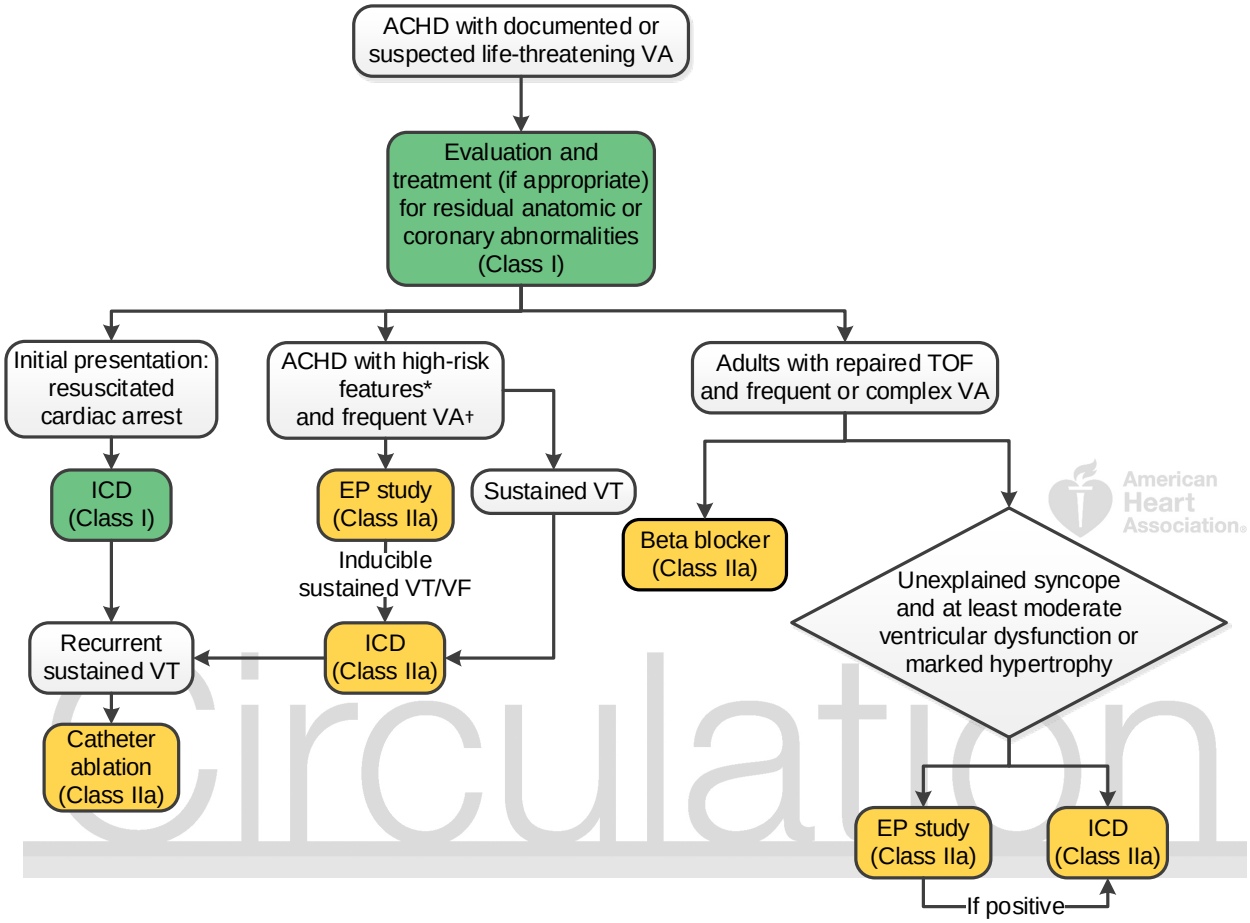
Table 11. Congenital Heart Disease: Risk Factors for VA/SCD

Congenital Heart Disease	Incidence of VA	Incidence of SCD	Higher Risk Characteristics
Simple complexity			
ASD (44,47,57-62)	2%–6%	<1.5%	Ventricular pacing RV dilatation Pulmonary hypertension *NKX2.5* gene
VSD (27,44,47,57-63)	3%–18%	<3%	
Moderate complexity			
Tetralogy of Fallot (1,2,5,6,28,34,36,44,46,47,54-56,62-65)	14%–31%	1.4%–8.3%	Unexplained syncope Frequent or complex VA Sustained VT QRS duration ≥180 ms Inducible sustained VT Atrial tachycardia Decreased LVEF Dilated right ventricle Severe PR Severe PS
Aortic stenosis (27,44,56)	10%–34%	3%–20%	Unexplained syncope Severe LV hypertrophy Aortic stenosis mean pressure gradient >40 mm Hg Ventricular dysfunction
Coarctation of aorta (28,29,44,46,56,62)	2%	2%	Aneurysm at repair site Aortic stenosis Systemic hypertension Premature coronary artery disease
Ebstein's anomaly (45,47,55)	2%	3%–6%	Cardiomegaly Atrial fibrillation Wide complex tachycardia Mitral regurgitation Dilated RVOT
Severe complexity			
Transposition of the great arteries (27,44-48,51,55,56,62)			Atrial switch Mustard repair Prior VSD closure Unexplained syncope Atrial tachycardia Coronary orifice stenosis Systemic ventricular dysfunction Severe tricuspid regurgitation
Atrial switch	2%	3%–9.5%	
Arterial switch	2%	1%	
cc-TGA	10%	17%–25%	
Truncus arteriosus (66,67)	10%	4%	Multiple surgical repairs Coronary anomalies Ventricular dysfunction and/or hypertrophy
Fontan repair for univentricular physiology* (27,37,44,45,47,55,68)	5%–17%	2.8%–5.4%	Atrial tachycardia Longer duration of follow-up Ascites Protein-losing enteropathy

*Univentricular physiology includes: Tricuspid atresia, Double inlet left ventricle, Mitral atresia, Hypoplastic left heart, Unbalanced AV septal defect.

ASD indicates atrial septal defect; cc-TGA, congenitally corrected transposition of the great arteries; LV, left ventricular; LVEF, left ventricular ejection fraction; PR, pulmonary regurgitation; PS, pulmonary stenosis; RV, right ventricular; RVOT, right ventricular outflow tract; SCD, sudden cardiac death; VA, ventricular arrhythmia; VSD, ventricular septal defect; and VT, ventricular tachycardia.

Figure 16. Prevention of SCD in Patients With Adult Congenital Heart Disease



Colors correspond to Class of Recommendation in Table 1.
See Section 10.8 for discussion.
*High-risk features: prior palliative systemic to pulmonary shunts, unexplained syncope, frequent PVC, atrial tachycardia, QRS duration ≥180 ms, decreased LVEF or diastolic dysfunction, dilated right ventricle, severe pulmonary regurgitation or stenosis, or elevated levels of BNP.
†Frequent VA refers to frequent PVCs and/or nonsustained VT.
ACHD indicates adult congenital heart disease; BNP, B-type natriuretic peptide; EP, electrophysiological; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; PVC, premature ventricular complexes; SCD, sudden cardiac death; TOF, tetralogy of Fallot; VA, ventricular arrhythmia; and VT, ventricular tachycardia.

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11. Defibrillators Other than Transvenous ICDs

11.1. Subcutaneous Implantable Cardioverter-Defibrillator

Recommendations for Subcutaneous Implantable Cardioverter-Defibrillator References that support the recommendations are summarized in Online Data Supplement 55.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. n patients who meet criteria for an ICD who have inadequate vascular access or are at high risk for infection, and in whom pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated, a subcutaneous implantable cardioverter-defibrillator is recommended (1-5).**
IIa	**B-NR**	**2. In patients who meet indication for an ICD, implantation of a subcutaneous implantable cardioverter-defibrillator is reasonable if pacing for bradycardia or VT termination or as part of CRT is neither needed nor anticipated (1-4).**
III: Harm	**B-NR**	**3. In patients with an indication for bradycardia pacing or CRT, or for whom antitachycardia pacing for VT termination is required, a subcutaneous implantable cardioverter-defibrillator should not be implanted (1-4, 6-8).**

Synopsis

In patients being considered for a subcutaneous implantable cardioverter-defibrillator, a preimplant ECG to establish QRS-T wave morphology is needed to reduce the risk of under sensing of VT/VF and the risk of inappropriate shocks (9-11). The subcutaneous implantable cardioverter-defibrillator is implanted using primarily anatomical landmarks, thereby minimizing the need for fluoroscopy. The subcutaneous implantable cardioverter-defibrillator consists of a pulse generator that is placed at the midaxillary line between the fifth and sixth intercostal spaces and a lead with 2 sensing electrodes and a shocking coil, positioned subcutaneously adjacent to the sternum. As with the transvenous ICD, the pulse generator housing serves as an electrode for defibrillation but, in addition, it can also serve as an optional electrode for sensing. The subcutaneous implantable cardioverter-defibrillator cannot achieve adequate arrhythmia sensing for all patients, and electrocardiographic screening to assess sensing is required prior to implantation (10, 11). Some advocate exercise testing after device implantation to ensure proper sensing with exercise.

Both transvenous and subcutaneous implantable cardioverter-defibrillators have SVT-VT discriminators that can be programmed to facilitate discrimination of SVT from VT; however, these discriminators do not always work. If sustained VT is confirmed, therapy to terminate the arrhythmia is delivered. All ICDs provide shocks to terminate VT or VF, but shocks in an awake patient are painful and associated with decreased QoL. Transvenous ICDs are capable of bradycardia pacing as well as antitachycardia pacing that can terminate many VTs painlessly. Subcutaneous implantable cardioverter-defibrillators provide limited postshock bradycardia pacing but do not provide either bradycardia or antitachycardia pacing.

The subcutaneous implantable cardioverter-defibrillator recommendations supplant, but do not nullify, the need for waiting periods and other requirements to be satisfied for ICD/CRT implantation specified in other parts of this document.

Recommendation-Specific Supportive Text

1. The subcutaneous implantable cardioverter-defibrillator was designed to avoid the need for venous access and some of the complications of inserting transvenous lead(s) (1-4) that include pneumothorax, hemothorax, and cardiac tamponade (12). Difficulties in achieving venous access can prolong the implantation procedure and occasionally result in failed ICD implantation. These difficulties are more likely to be encountered in patients with limited venous access such as patients with ESRD. In a study of 27 patients with ESRD, the

subcutaneous implantable cardioverter-defibrillator was not associated with an increased risk of procedural complications or inappropriate shocks (5). The risk of infection appears to be lower with subcutaneous implantable cardioverter-defibrillators than with transvenous ICDs (1-4).Therefore, a subcutaneous implantable cardioverter-defibrillator may be preferred in patients who are at high risk of infection, such as those with a prior device infection, ESRD, diabetes mellitus, or who are chronically immunosuppressed.

2. Nonrandomized studies show that the subcutaneous implantable cardioverter-defibrillator reliably detects and converts VF during defibrillation threshold testing and successfully terminates spontaneous sustained VT that occurs during follow-up (1, 13). In 1 study of 314 patients, the 180-day complication-free rate was 99%, and the success of VF termination with first shock was >90% (2). All spontaneous episodes of VT/VF recorded in 21 patients (6.7%) were successfully converted, and there were no lead failures, endocarditis or bacteremia, tamponade, cardiac perforation, pneumothorax, or hemothorax associated with the subcutaneous implantable cardioverter-defibrillator (2). In 472 patients enrolled in the EFFORTLESS (Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD) registry (3), the complication-free rate was 94%, at 360 days. First shock conversion efficacy was 88% with 100% overall successful clinical conversion after a maximum of 5 shocks. In 882 patients enrolled in investigational device exemption trials and the EFFORTLESS registry (4), 111 spontaneous VT/VF events were treated in 59 patients; 90.1% were terminated with 1 shock, and 98.2% were terminated within the 5 available shocks. The estimated 3-year inappropriate shock rate was 13.1% most due to oversensing of cardiac signals, and mortality was 4.7%. Device-related complications occurred in 11.1% of patients. An ongoing trial will compare the effect of the subcutaneous implantable cardioverter-defibrillator with that of the transvenous ICD on the outcomes of inappropriate shocks, complications, shock efficacy, and mortality (13).

3. The subcutaneous implantable cardioverter-defibrillator is incapable of bradycardia pacing, biventricular pacing, or antitachycardia pacing. Therefore, patients who need any of these types of pacing from an ICD should not be offered a subcutaneous implantable cardioverter-defibrillator (6). Some clinical scenarios may come up in which a transvenous pacemaker for bradycardia pacing in a patient with a subcutaneous implantable cardioverter-defibrillator- which is needed; this can be performed as long as the pacing is not unipolar. Leadless pacing devices for patients who require bradycardia pacing will be evaluated with the subcutaneous implantable cardioverter-defibrillator in the near future.

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11.2. Wearable Cardioverter-Defibrillator

Recommendations for Wearable Cardioverter-Defibrillator References that support the recommendations are summarized in Online Data Supplement 56.		
COR	**LOE**	**Recommendations**
IIa	**B-NR**	**1. In patients with an ICD and a history of SCA or sustained VA in whom removal of the ICD is required (as with infection), the wearable cardioverter-defibrillator is reasonable for the prevention of SCD (1-4).**
IIb	**B-NR**	**2. In patients at an increased risk of SCD but who are not ineligible for an ICD, such as awaiting cardiac transplant, having an LVEF of 35% or less and are within 40 days from an MI, or have newly diagnosed NICM, revascularization within the past 90 days, myocarditis or secondary cardiomyopathy or a systemic infection, wearable cardioverter-defibrillator may be reasonable (1-5).**

Synopsis

The wearable cardioverter-defibrillator is a vestlike device worn under the clothing that continuously monitors the heart rhythm and automatically delivers an electric shock when VF or VT is detected. This device is intended to be worn continuously, 24 hours per day, except when the wearer is bathing or showering. The wearable cardioverter-defibrillator has been approved in the United States by the U.S. Food and Drug Administration for patients who are "at risk for SCA and are not candidates for or refuse an implantable defibrillator" (6). A science advisory from the AHA summarizes the data and recommendations for the use of the wearable cardioverter-defibrillator (4). Effectiveness of the wearable cardioverter-defibrillator in recognition and defibrillation of VF has been demonstrated in a number of studies, although no RCTs support the use of the wearable cardioverter-defibrillator. Among 3569 patients who received the device for various reasons, for at least 1 day in the U.S. manufacturer registry, there were 80 VT/VF events in 59 patients, with a frequency of 1.7% per patient-year. First shock efficacy was 99%, with postshock survival of 90%. Overall, 2% of the patients received an inappropriate shock (1).

Recommendation-Specific Supportive Text

1. Removal of an ICD for a period of time, most commonly due to infection, exposes the patient to risk of untreated VT/SCD unless monitoring and access to emergency external defibrillation is maintained. In 1 series of 354 patients who received the wearable cardioverter-defibrillator, the indication was infection in 10% (3). For patients with a history of SCA or sustained VA, the wearable cardioverter-defibrillator may allow the patient to be discharged from the hospital with protection from VT/SCA until the clinical situation allows reimplantation of an ICD.

2. The patients listed in this recommendation are represented in clinical series and registries that demonstrate the safety and effectiveness of the wearable cardioverter-defibrillator. Patients with recent MI, newly diagnosed NICM, recent revascularization, myocarditis, and secondary cardiomyopathy are at increased risk of VT/SCA. However, the wearable cardioverter-defibrillator is of unproven benefit in these settings, in part

because the clinical situation may improve with therapy and time. In patients awaiting transplant, even with anticipated survival <1 year without transplant, and depending on clinical factors such as use of intravenous inotropes and ambient VA, a wearable cardioverter-defibrillator may be an alternative to an ICD.

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11.3 Automated External Defibrillator

External defibrillation can save lives when used within minutes of the onset of VF. The AED is an efficient method of delivering defibrillation to persons experiencing out-of-hospital cardiac arrest, and its use by first responders is safe and effective (1-3). Federal efforts have been effective in placing AEDs in airports/airplanes and federal buildings, while varying efforts at the state and community levels have been effective in placing AEDs in many. but not all, schools, sporting events, high-density residential sites, and airports as well as in police and fire department vehicles (4-7). Resuscitation protocols with or without AED placement are required in most states for fitness clubs, although alternate indoor exercise facilities may have higher rates of arrest and provide for increased survival over other indoor public sites (8). In a study population of 21 million, survival to hospital discharge was nearly twice as high when an AED was applied for out-of-hospital cardiac arrest (9). Expanded and coordinated placement of AEDs in the community, including in high-risk geographic locations such as schools and organized sports arenas, can substantially increase the proportion of patients with cardiac out-of-hospital cardiac arrest who receive AED therapy (10). The U.S. Food and Drug Administration has approved over-the-counter sales of AEDs. Approximately 70% of SCAs occur in the home, and the rate of survival to hospital discharge after AED placement by emergency medical services is significantly lower for arrest at home (12%) versus public settings (34%) (11). However, in an RCT of AEDS, home AED placement did not improve the survival of patients recovering from an anterior MI (12). Appropriate device location to reduce time delay after onset of SCA is critical. In addition to prevention, critical components of survival from SCA include immediate recognition and activation of the emergency response system, early high-quality CPR, and rapid defibrillation for shockable rhythms (13).

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12. Special Considerations for Catheter Ablation

Recommendations for Catheter Ablation References that support the recommendations are summarized in Online Data Supplement 57.		
COR	**LOE**	**Recommendations**
I	**C-LD**	**1. In patients with bundle-branch reentrant VT, catheter ablation is useful for reducing the risk of recurrent VT and ICD shocks (1-3).**
IIa	**B-NR**	**2. In patients with structural heart disease who have failed endocardial catheter ablation, epicardial catheter ablation can be useful for reducing the risk of recurrent monomorphic VT (4-6).**

Synopsis

Bundle-branch reentrant VT is due to reentry involving the bundle branches. Catheter ablation is the preferred therapy for this VT, which is encountered in <10% of patients with recurrent sustained monomorphic VT and structural heart disease (see Section 7.2.3).

Recommendation-Specific Supportive Text

1. Bundle-branch reentrant VT can occur in any form of heart disease associated with slow infra-Hisian conduction. The most common mechanism involves antegrade conduction over the right bundle branch and retrograde conduction over the left bundle branch, thereby producing left bundle-branch block QRS morphology during VT, which is often rapid and poorly tolerated. Catheter ablation of the right or left bundle branch interrupts the circuit and is usually curative (1-3). After ablation, severely impaired atrioventricular conduction can be present, requiring permanent pacing, which can have hemodynamic consequences (4, 6). Many patients have other inducible scar related VTs or meet eligibility for an ICD due to severity of associated heart disease.

2. Endocardial catheter ablation failure can be due to location of the arrhythmia substrate in the midmyocardium or epicardium, and this is more likely in patients with nonischemic rather than ischemic cardiomyopathy, and in arrhythmogenic right ventricular cardiomyopathy (7-9). In the HELP-VT trial (4),

epicardial ablation was required in 30% of patients with VT related to NICM compared with 1.2% of patients with ischemic cardiomyopathy. A wide QRS with marked slurring of the initial portion of the QRS and a QS complex in the lateral or inferior leads during VT suggests an epicardial circuit in NICM, but the ECG does not reliably predict epicardial VT locations in patients with prior MI. Preprocedural cardiac MRI and intraprocedural electroanatomic mapping are useful tools to guide the localization of epicardial scar that may be the source of reentrant VT (8, 10). Pericardial adhesions prevent percutaneous access in some patients, notably many with prior cardiac surgery. Percutaneous pericardial access for mapping and ablation is associated with a serious complication rate of approximately 5% and tamponade from RV puncture or laceration that can require emergent surgery or be fatal, coronary artery injury and phrenic nerve injury can occur (11, 12). Reported experience is from tertiary referral centers.

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13. Postmortem Evaluation of SCD

Recommendations for Postmortem Evaluation of SCD References that support the recommendations are summarized in Online Data Supplement 58.		
COR	**LOE**	**Recommendations**
I	B-NR	**1. In victims of SCD without obvious causes, a standardized cardiac-specific autopsy is recommended (1, 2).**
I	B-NR	**2. In first-degree relatives of SCD victims who were 40 years of age or younger, cardiac evaluation is recommended, with genetic counseling and genetic testing performed as indicated by clinical findings (3).**
IIa	B-NR	**3. In victims of SCD with an autopsy that implicates a potentially heritable cardiomyopathy or absence of structural disease, suggesting a potential cardiac channelopathy, postmortem genetic testing is reasonable (4-7).**
IIa	C-LD	**4. In victims of SCD with a previously identified phenotype for a genetic arrhythmia-associated disorder, but without genotyping prior to death, postmortem genetic testing can be useful for the purpose of family risk profiling (8).**

Recommendation-Specific Supportive Text

1. A comprehensive postmortem protocol has been recommended for the routine evaluation of subjects (typically <40 years of age) who die suddenly without a prior diagnosis of a condition and circumstances of death that could be reasonably implicated in the cause of unexpected SCD (1). One study documented the added value of postmortem examination at a specialized cardiac pathology center (2), with particular value for clarifying an apparent overdiagnosis of cardiomyopathy by nonspecialized centers. Pathological findings limited to the specialized conduction system were demonstrated in 22% of cases (9). A misdiagnosis of cardiomyopathy was reported in 37% of referred cases that were ultimately determined to be structurally normal. The etiologic data for specialized cardiac evaluation are not generalizable to the overall population because of skewing of age at the time of SCD. In another study of SCD patients at ages ranging from <1 year to >80 years (mean, 38.2 years; median, 38 years), the peak incidence of SCD occurred between the ages of 31 and 60 years, with a 5- to 7-fold excess of males/females in that age range (10). For the overall group, 42% of SCD were due to ischemic heart disease, 12% viral myocarditis, and 5% cardiomyopathy, with 15% being unexplained by autopsy. For the subgroup <35 years of age, 13.5% were attributed to ischemic heart disease and 24.9% were unexplained. In the subgroup >55 years of age, only 0.8% were unexplained. In patients who die suddenly despite an ICD, interrogation of the ICD is important to confirm proper device functioning and can provide information on the mechanism of death.

2. Comprehensive cardiac screening including 12-lead ECG, possible signal averaged ECG, echocardiogram, and ambulatory rhythm monitoring or exercise testing of first-degree relatives of decedents with sudden unexpected death may identify a probable heritable cardiac cause of death in up to 30% of cases (11-13). Genetic testing should be targeted based on the results of initial evaluation (3). Genetic testing in selected first-degree relatives may result in identification of inherited conditions including long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy, and HCM in 4% to 30% of families (11, 12, 14).

3. For the purpose of family risk profiling, it is important to use the disease-specific genetic test panel that corresponds to the autopsy findings. Risk profiling of family members of an SCD victim suspected of having an inherited cardiomyopathy at autopsy is important. Although phenotyping of surviving family members is crucial, genotyping of the SCD proband provides a mechanism for efficient follow-up evaluation of those relatives with the disease-causing mutation found in the proband. To be able to harvest quality DNA for such testing, medical examiners, hospital pathologists, and private pathologists need standards for harvesting and

storing samples for later genetic testing. Family members of SCD probands who died suddenly (first cardiac event, death from natural causes, last seen alive and well within 12 hours), with autopsy findings showing structural abnormalities of uncertain significance (e.g., ventricular hypertrophy, myocardial fibrosis, or minor ischemic heart disease [n=41]) had a 51% prevalence of genetic variants associated with sudden arrhythmic deaths, compared with 47% among a comparison group in which proband autopsies were completely negative (15).

4. Identification of the genotype can facilitate family screening (16).

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14. Terminal Care

Recommendations for Terminal Care References that support the recommendations are summarized in Online Data Supplement 59,		
COR	**LOE**	**Recommendations**
I	**C-EO**	**1. At the time of ICD implantation or replacement, and during advance care planning, patients should be informed that their ICD shock therapy can be deactivated at any time if it is consistent with their goals and preferences.**
I	**C-EO**	**2. In patients with refractory HF symptoms, refractory sustained VA, or nearing the end of life from other illness, clinicians should discuss ICD shock deactivation and consider the patients' goals and preferences.**

Synopsis

A particularly challenging area of medicine is recognizing when life-prolonging therapies may become burdensome or even harmful. This is particularly true near the end of life for patients with ICDs in whom once life-prolonging shocks may only cause unnecessary morbidity and distress to both patients and loved ones.

Recommendation-Specific Supportive Text

1. Current evidence suggests that many patients are unaware of the possibility that their ICD can be deactivated without surgery (1-3). During decision-making, clinicians do not routinely inform patients about ICD deactivation (4). Clinicians even disagree on whether discussions of deactivation should occur when patients are making a decision about an ICD-related procedure (5). As a result, patients often do not include wishes about deactivation in advance care planning documents (6). Consequently, surrogates usually make decisions about ICD deactivation without any prior discussions with the patient (6). In hypothetical scenarios, patients with ICDs were able to identify scenarios in which they might choose to deactivate their ICD (1, 7). This discussion can occur at any time, but it is particularly important to have it at the time of initial ICD implantation, at the time of reimplantation, and during preparation of advance care plans.

2. When ICDs are not deactivated at the end of life, patients and families suffer unnecessarily. Families have had unpleasant experiences of watching their loved one die while getting shocked repeatedly by an ICD (8). In 1 survey of hospice staff, half of those surveyed noted that a deceased patient had been shocked by an ICD during the year prior to the survey (9). This is unnecessary and easily preventable by having caring, patient-centered discussions with patients and their loved ones. In general, patients want their clinicians to initiate these discussions (2, 10), so this recommendation is carefully worded to put the responsibility of initiating the discussion on the clinician. Ethically, patients and surrogates are free to choose to deactivate antitachycardia function (11-13). Most patients only elect deactivation of the antitachycardia functions while leaving the pacing function on. Even at the end of life, pacing (either for bradycardia or for resynchronization therapy) may be an important aspect of the patient's QoL and may facilitate more alert and meaningful personal interactions. These differences are easily misunderstood, so they need careful explanation.

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15. Shared Decision-Making

Recommendations for Shared Decision-Making References that support the recommendations are summarized in Online Data Supplement 60.		
COR	**LOE**	**Recommendations**
I	**B-NR**	**1. In patients with VA or at increased risk for SCD, clinicians should adopt a shared decision-making approach in which treatment decisions are based not only on the best available evidence but also on the patients' health goals, preferences, and values (1-5).**
I	**B-NR**	**2. Patients considering implantation of a new ICD or replacement of an existing ICD for a low battery should be informed of their individual risk of SCD and nonsudden death from HF or noncardiac conditions and the effectiveness, safety, and potential complications of the ICD in light of their health goals, preferences and values (1-5).**

Synopsis

During most of their lives, people prefer to do everything possible to prevent SCD and prolong life. However, many people may get to a point in their lives where SCD is not the worst outcome. Patients may report a desire to die in their sleep (6). Decisions related to SCD can be quite emotional; according to the patient's wishes, shared decision regarding end-of-life therapy making may involve caregivers such as family members or friends.

Recommendation-Specific Supportive Text

1. Consideration of patient preferences is important for VA diagnosis and management decisions. Patient preferences for invasive therapies and acceptance of SCD risk vary and may evolve throughout the course of their illness. The writing committee endorses a shared decision-making approach as part of the general care for patients at risk for VA and SCD. A commonly accepted definition of the shared decision-making (7) includes 4 components: 1) at least 2 participants, the clinician and patient, be involved; 2) both parties share information; 3) both parties take steps to build a consensus about the preferred treatment; and 4) an agreement is reached on the treatment to implement. Sharing a decision does not mean giving a patient a list

of risks and benefits and telling them to make a decision—a practice some authors have called "abandonment" (8). Notably, a recommendation based on evidence or guidelines alone is not shared decision-making. Rather, a recommendation based both on the evidence as well as an understanding of the patients' health goals, preferences, and values is essential to achieving true shared decision-making. Also, the possibility of deactivation of an existing ICD should be discussed with patients who have terminal illnesses.

2. ICDs prolong lives as highlighted in many places within this guideline. However, a patient with HF or advanced noncardiac illness may elect to forgo replacement of an ICD when faced with the prospect of continual decline in health and functional status from either progressive HF or some other competing morbidity.

Unfortunately, research suggests that patients are ill-informed when faced with understanding the risks, benefits, and downstream burdens of their ICDs. Patients with an ICD tend to overestimate the benefit of this therapy and underestimate its risks (1-3). Likewise, patients who decline an ICD also frequently underestimate their personal risk of VA and SCD (4, 5). Studies of clinician decision-making demonstrate that clinicians often overestimate the benefits while downplaying the potential harms (3).

In kind, ICD replacement is also an important point in time where patients and clinicians should discuss whether replacing an ICD is still consistent with the patients' goals. What made sense at 70 years of age may not make sense at 80 years of age. Patients may have had progressive disease or developed poor QoL. These factors can all change the risk/benefit ratio of the ICD and the patients' preferences.

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16. Cost and Value Considerations

The key principles of value assessment as part of clinical practice guidelines have been discussed in detail (1). Economic outcomes of clinical management strategies can be documented empirically using the same research designs as used in establishing clinical outcomes, including RCTs and observational comparisons. In addition, simulation models are often used to assess the value of management strategies, because the standard for cost-effectiveness studies is to compare life-time outcomes, and clinical studies usually have follow-up of a few years at most. Standards for economic modeling in health care have been published by an expert group (2).

Economic assessments of alternative management strategies for VA and prevention of SCD have primarily evaluated ICDs, including several RCTs (3-7) and observational studies (8, 9), and simulation models (10-14). In all studies, patients who received ICDs had higher long-term costs. The high initial cost of the ICD

device and the implantation procedure leads to higher long-term costs, because there are few, if any, subsequent cost-savings from implanting an ICD. ICDs without resynchronization capability do not reduce hospital readmissions and may increase late costs due to device monitoring, complications, and replacement. However, the cost of the device and the procedure may change significantly over time.

The trial based assessments of the cost-effectiveness of the ICD are based on 3 to 6 years of follow-up, which is considerably shorter than the lifetime perspective that is standard in cost-effectiveness models. Because most of the incremental cost of the ICD is incurred immediately, while most of the potential effectiveness (life-years of survival added by the ICD) is accrued over many years, estimates of ICD cost-effectiveness based on limited trial follow-up have a systematic bias toward showing lower value. Trial based economic studies that projected long-term ICD outcomes have consistently found more favorable cost-effectiveness ratios than estimates restricted to the duration of trial follow-up (4-7). A lifetime simulation model applied to each major trial of primary prevention ICDs also reported consistently more favorable estimates of cost-effectiveness than the estimates based on limited trial follow-up (11). Because the framework proposed for assessing value in ACC/AHA clinical practice guidelines uses benchmarks based on lifetime estimates (1), we have generally relied on the model-based estimates of ICD cost-effectiveness in applying value ratings to recommendations in this guideline.

The initial cost of an ICD device is similar regardless of the clinical indication, so variations in ICD cost-effectiveness are driven primarily by potential differences in clinical effectiveness in extending survival in different patient populations. The effect of the years of life added by an ICD on its incremental cost-effectiveness ratio is illustrated in Figure 17: the cost-effectiveness ratio becomes rapidly unfavorable as the extension in survival time falls below 1 year, particularly below 0.5 year. This inverse relation strongly suggests that the value provided by an ICD will be highest when the risk of arrhythmic death due to VT/VF is relatively high and the risk of nonarrhythmic death (either cardiac or noncardiac) is relatively low, such that a meaningful increase in survival can be expected from the ICD. Thus, appropriate patient selection is fundamental to high value care in using the ICD to prevent SCD. It should also be recognized that cost-effectiveness is also influenced by the costs for the ICD and implantation procedure, which are likely to change significantly over time.

The empirical evidence suggests that ICDs are not effective for primary prevention of SCD when implanted early after CABG (15) or an acute myocardial infarction (16, 17). An analysis of individual patient level data from 3 secondary prevention trials (18) showed a significant variation (p=0.011) in the clinical effectiveness of ICDs between patients with an LVEF ≤35% (hazard ratio: 0.66) and an LVEF >35% (hazard ratio: 1.2). Some studies and simulation models suggest that ICDs might prolong life expectancy to a greater extent when used in higher-risk patients than in lower-risk patients (19). In contrast, there is little evidence of variation in the effectiveness or cost-effectiveness of the ICD based on factors such as age or sex (20). Most studies of ICD effectiveness and value have been performed on patients with reduced LV function due to prior MI or NICM. There are few data on the effectiveness or value of an ICD for other potential clinical indications, such as cardiac channelopathies or HCM, although studies have suggested that their potential cost effectiveness in such patients will depend on their underlying risk of SCD, with little evidence of value in low-risk patients (14).

Figure 17. Incremental Cost-Effectiveness of ICD by Years of Life Added* (Example)

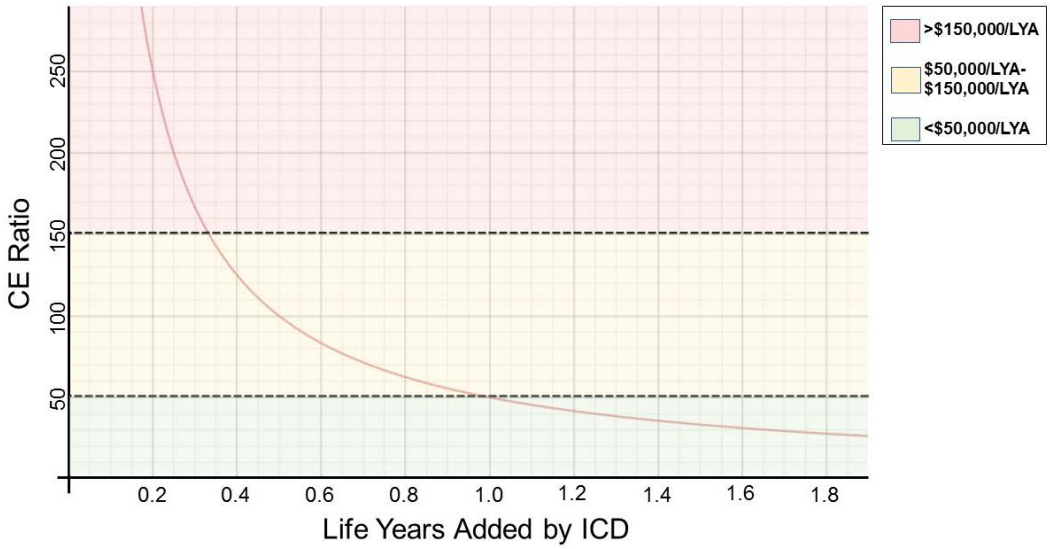

*Figure based on formula: Incremental cost-effectiveness ratio = $50,000/QALYs.
CE indicated cost effectiveness, ICD, implantable cardioverter-defibrillator; LYA, life year added; and QALYs, quality-adjusted life-years

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17. Quality of Life

ICD implantation has not had a significant effect on QoL in the overall population of patients enrolled in RCTs (1-3). Several studies have, however, demonstrated that the subset of patients who receive inappropriate ICD shocks have worse QoL than patients who have an ICD but have not had inappropriate shocks (2). Because an ICD is designed to prevent SCD rather than to reduce symptoms, it would not be expected to improve QoL or functional status directly, but may have indirect, negative effects in some patients due to device complications, or indirect, positive effects in some patients due to reassurance of having a protective device in place.

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18. Evidence Gaps and Future Research Needs

Despite the numerous advances in risk stratification for SCD and prevention and treatment of SCD and VA, many gaps in knowledge remain. These gaps include:

- Identification of patients who are most likely to benefit from an ICD among all ICD-eligible patients. The role of novel markers (including genetic and imaging markers) and combinations of markers should be studied.
- Characterizing the role of the ICD in patient subgroups not well-represented in the pivotal ICD trials. Such subgroups include patients ≥80 years of age and those with kidney disease, especially patients with ESRD on dialysis, or multiple comorbidities.
- Methods to identify and treat patients at high individual risk for SCD who are not identified by current ICD eligibility criteria, including those who are within 40 days of an MI.

- Defining the role of the ICD in patients with HCM, arrhythmogenic right ventricular cardiomyopathy, cardiac sarcoidosis, and inherited cardiac channelopathies in prospective studies (preferably RCT).
- Determining the best approach to patients due for elective ICD generator replacement due to battery depletion, but who may now be at low risk for SCA, such as if significant LVEF improvement has occurred.
- Obtaining more data on the efficacy and effectiveness of the subcutaneous implantable cardioverter-defibrillator, compared with transvenous ICDs and on the extent of testing required, and its use with other novel technologies, including leadless pacemakers.
- Conducting RCTs on catheter ablation of VT in ischemic heart disease and cardiomyopathies that evaluates procedural end points, mortality, arrhythmia suppression, QoL, and costs.
- Improving identification of individuals without significant ventricular dysfunction who are at risk of SCD.
- Identifying mechanisms and risk factors for SCD in patients with HF*p*EF.
- Improving emergency response to out-of-hospital cardiac arrest.
- Developing better methods for identifying and ablating the arrhythmia substrate in structural heart disease.
- Developing better risk stratification of diseases and syndromes associated with sudden death, including ischemic heart disease, NICM, adult congenital heart disease, and Brugada syndrome.
- Identifying what causes different types of long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome, HCM, and arrhythmogenic right ventricular cardiomyopathy and advancing the genotype-phenotype relationships, genotype-dependent risk, and genotype-based tailoring of therapies for patients with inherited cardiomyopathies and inherited channelopathies.
- Defining the most appropriate and beneficial use of wearable cardioverter-defibrillators.
- Developing methods to identify and treat patients at high personal risk for SCD who are not identified by current ICD eligibility criteria.
- Defining the role of CMR in enhancing risk stratification for SCD.

Increasing research funding in this area, through existing and new mechanisms is critically important. Some have proposed research funding strategies that would offer business incentives to the insurance industries, while providing support for unresolved research goals. Such approaches should be tested.

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Appendix 1. Author Relationships With Industry and Other Entities (Relevant)—2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (October 2017)

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness	Voting Recusals by Section*
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Anne B. Curtis	University at Buffalo—SUNY Distinguished Professor; Charles and Mary Bauer Professor and Chair	• Medtronic • St. Jude Medical	None	None	None	None	None	4.1, 4.2.2, 4.2.3, 5.1.1, 5.1.2, 5.1.3, 5.1.4, 5.2, 5.4, 5.6, 6, 7, 8, 9, 10, 12, 13, 15

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Richard L. Page	University of Wisconsin Hospital and Clinics—Chair, Department of Medicine	None	None	None	None	None	None	None

This table represents the relationships of committee members with industry and other entities that were determined to be relevant to this document. These relationships were reviewed and updated in conjunction with all meetings and/or conference calls of the writing committee during the document development process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the *document*, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household*, has a reasonable potential for financial, professional or other personal gain or loss as a result of the issues/content addressed in the *document*.

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply.
†Significant relationship.
‡No financial benefit.

ACC indicates American College of Cardiology; AHA, American Heart Association; EP, Electrophysiology; HRS, Heart Rhythm Society; IMPROVE-HF, Improve the Use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; PI, principle investigator; SUNY, State University of New York; and UT, University of Texas.

Appendix 2. Reviewer Relationships With Industry and Other Entities (Comprehensive)—2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death (July 2017)

Reviewer	Representation	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Salary	Expert Witness
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Andrew E. Epstein	Content Reviewer	Professor of Medicine—Cardiovascular Division University of Pennsylvania—Chief of Cardiology Section—Philadelphia VA Medical Center	• Zoll*	None	None	• Biotronik* • Boston Scientific* • Boston Scientific (DSMB)* • Medtronic* • Medtronic (DSMB) • St Jude Medical/ Abbott* • St Jude Medical/ Abbott (DSMB)*	None	None	• Defendant, Amiodarone pulmonary toxicity, 2016 • Defendant, Appropriateness of pacemaker implantation, 2016*
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‡This disclosure was entered under the Clinical Trial Enroller category in the ACC's disclosure system. To appear in this category, the author acknowledges that there is no direct or institutional relationship with the trial sponsor as defined in the ACC/AHA Disclosure Policy for Writing Committees.

ABIM indicates American Board of Internal Medicine; ACC, American College of Cardiology; ACGME, Accreditation Council for Graduate Medical Education; AHA, American Heart Association; ARTESiA, Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; BEAT-HF, Better Effectiveness After Transition–Heart Failure DSMB, data safety monitoring board; ENDEAVOUR, carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma; EP, electrophysiology; FDA, U.S. Food and Drug Administration; HFSA, Heart Failure Society of America; HRS, Heart Rhythm Society; ICD, implantable cardioverter-defibrillator; JACC, Journal of the American College of Cardiology; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; and PACE, Programs of All-Inclusive Care for the Elderly.

2017 AHA/ACC/HRS Guideline for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

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ACC indicates American College of Cardiology; ACTION, Acute Coronary Treatment and Intervention Outcomes Network; AHA, American Heart Association; AFAR, American Federation for Aging Research; CABANA; Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation; DSMB, data safety monitoring board; EP, Electrophysiology; GWTG, Get With The Guidelines; FDA, Food and Drug Administration; HRS, Heart Rhythm Society; IMPROVE-HF, Registry to Improve the use of Evidence-Based Heart Failure Therapies in the Outpatient Setting; JAMA, Journal of the American Medical Association; NIH, National Institutes of Health; NHLBI, National Heart, Lung, and Blood Institute; NIAID, National Institute of Allergy and Infectious Diseases; PACES, Pediatric and Congenital Electrophysiology Society; PCORI, Patient Centered Outcomes Research Institute; PI, principle investigator; PRT, pharmaceutical round table; SADS, Sudden Arrhythmia Death Syndromes Foundation; SMDM, Society for Medical Decision Making; UK, United Kingdom; and VANISH, Vasopressin Versus Noradrenaline as Initial Therapy in Septic Shock.

2017 VA/SCD Guideline Data Supplement

Table of Contents

Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence based. An extensive evidence review was conducted from April through September 2016, that included literature published through September 2016. Other selected references published through March 2017 were incorporated by the writing committee. Literature included was derived from research involving human subjects, published in English, and indexed in MEDLINE (through PubMed), EMBASE, the Cochrane Library, the Agency for Healthcare Research and Quality, and other selected databases relevant to this guideline. Key search words included but were not limited to the following: *accelerated idioventricular rhythm, advanced cardiac life support, ambulatory electrocardiography, amiodarone, amyloidosis, Antiarrhythmic drugs ARNI – Angiotensin Receptor-Neprilysin Inhibitor, arrhythmias, arrhythmogenic right ventricular dysplasia, atenolol, autonomic modulation, biomarkers, CABG, cardiac, catheter ablation, cardiac arrest, cardiac arrhythmia, cardiac catheterization, cardiac magnetic resonance imaging, cardiac sympathetic denervation, cardiac troponin, cardiomyopathy, catecholaminergic polymorphic ventricular tachycardia, carvedilol, choice behavior, coronary artery bypass surgery, coronary stent, cryoablation deactivation, decision-making, digoxin toxicity, dilated cardiomyopathy, dilated non ischemic cardiomyopathy, disease management, Dor Procedure, drug induced arrhythmia, drug induced long QT, emergency medical services, electrical storm, electrocardiography, electrophysiologic study, electrophysiologic techniques, electrophysiological testing, emergency management, end of life, endocardiectomy exercise test, Fabry's disease, fibrillation, flecainide,heart arrest, heart disease, hemochromatosis, hemodynamically stable ventricular tachycardia*, *holter monitor, hypertrophic, implantable cardiac monitor, incessant, infiltrative heart disease, intervention,* lamin a/c *left ventricular assist device, left ventricular reconstruction, lidocaine, long QT syndrome, loop recorder, LV dysfunction, metoprolol, monomorphic, muscular dystrophies, myocardial infarction/therapy, myotonic dystrophy*, *nadolol, natriuetic peptides, papillary muscle, patient perspective, patient preference, percutaneous coronary, polymorphic, Polymorphous Ventricular Tachycardia, premature ventricular contractions, procainamide, propranolol, pulseless electrical activity, PVC induced cardiomyopathy, resting ecg, renal denervation, resuscitation, risk stratification, secondary prevention, shared decision making, sotalol, spinal cord stimulation, subcutaneous implantable cardioverter defibrillators, sudden cardiac death, sudden death, syncope, tachycardia, torsades de pointes, vagal nerve stimulation ventricular, ventricular arrhythmias, ventricle extrasystole, ventricular fibrillation, ventricular premature complexes, ventricular tachycardia*

Abbreviations: 1° indicates primary; 2°, secondary; AAD, antiarrhythmic drugs; ACA, aborted cardiac arrest; ACC, American College of Cardiology; ACHD, adult congenital heart disease; ACLS, advanced cardiac life support; ACS, acute coronary syndrome; AF, atrial fibrillation; AHA, American Heart Association; AMI, acute myocardial infarction; ARVC, arrhythmogenic right ventricular cardiomyopathy; AS, atrial stenosis; AT, atrial tachyarrhythmias; AV, atrioventricular; AVID, antiarrhythmics versus implantable defibrillators; BB, beta blocker; BBB, bundle branch block; BBRVT, bundle branch reentrant ventricular tachycardia; BID, two times a day; BNP, brain natriuretic peptide; BP, blood pressure; BrS, Brugada syndrome; CA, cardiac arrest; CABG, coronary artery bypass graft; CABG-PATCH, coronary artery bypass graft patch trial; CAD, coronary artery disease; CASH, cardiac arrest study Hamburg; CASS, coronary artery surgery study; CE, cardiac event; CHF, congestive heart failure; CHFSTAT, survival trial of antiarrhythmic therapy in congestive heart failure; CI, confidence interval; CIBIS II, cardiac insufficiency bisoprolol study II; CIDS, Canadian implantable defibrillator; ICD, cardiovascular implantable electronic device; CMRI, cardiac magnetic resonance imaging; COPD, chronic obstructive pulmonary disease; CPR, cardiopulmonary resuscitation; CPVT, catecholaminergic polymorphic ventricular tachycardia; CRT, cardiac reshynchronization therapy; CS, carotid sarcoidosis; CT, computed tomography; CV, cardiovascular; CVD, cardiovascular disease; CXR, chest x-ray; DCM, dilated cardiomyopathy; DEFINITE, defibrillator in nonischemic cardiomyopathy treatment evaluation; DFT, defibrillation threshold; DINAMIT, defibrillator in acute myocardial infarction trial; DM1, myotonic dystrophy 1; DM2, myotonic dystrophy; DYS, dystrophin;ECG, electrocardiogram; EDMD2, Emery-Dreifuss muscular dystrophy type 2; EF, ejection fraction; EFFORTLESS S-ICD, evaluation of factors impacting clinical outcome and cost effectiveness of the S-ICD; EGM, electorgram EMD, electromechanical dissociation; EP, electrophysiological; EPS, electrophysiological study; ERP, effective refractory period; ESRD, end stage renal disease; EURO-VT Study, Euro–ventricular tachycardia study; GDMT, guideline-directed management and therapy; GFR, glomerular filtration rate; HCM, hypertrophic cardiomyopathy; HELP-VT, heart center of Leipzig VT study; HF, heart failure;

HPS, His-Purkinje system; HR, hazard ratio; HTN, hypertension; Hx, history; HV, His Purkinje conduction rate; ICD, implantable cardioverter-defibrillator; ICU, intensive care unit; IDCM, idiopathic dilated cardiomyopathy; IDE, investigational device exemption; ILR, implantable loop recorder; IRIS, insulin resistance intervention after stroke; IV, intravenous; KM, Kaplan-Meier; LBBB, left bundle branch block; LCSD, left cardiac sympathetic denervation; LGE, late gadolinium enhancement; LQTS, long QT syndrome; LV, left ventricle; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVOT, left ventricular outflow tract; MACE, major adverse cardiac event; MADIT, multicenter automatic defibrillator implantation trial; MAGIC, magnesium in coronaries; MD, muscular dystrophy; MI, myocardial infarction; MR, mitral regurgitation; MRI, magnetic resonance imaging; MTWA, microvolt T-wave alternans; MUSTT, multicenter unsustained tachycardia trial; N/A, not available; NICM, nonischemic dilated cardiomyopathy; NPV, negative predictive value; NS, not significant; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association classification for heart failure; NT-proBNP, N-terminal pro b-type natriuretic peptide; OHCA, out-of-hospital cardiac arrest; OPTIC, optimal pharmacological therapy in cardioverter defibrillator patients; OR, odds ratio; PainFREE Rx II, pacing fast ventricular tachycardia reduces shock therapies; PARADIGM-HF, prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial; PCI, percutaneous coronary intervention; PE, physical examination; PES, programmed electrical stimulation; PM, papillary muscle; PMCD, Perimortem Cesarian Delivery; PMCS, Perimortem Cesarian Section; PMVT, polymorphic ventricular tachycardia; PO, per os; PROCAT, Parisian region out of hospital cardiac arrest; PVC, premature ventricular contractions; PVR, pulmonary valve replacement; QoL, quality of life; RBB, right bundle branch; RBBB, right bundle branch block; RCSD right cardiac sympathetic denervation; RCT, randomized controlled trials; RNA, radionuclide angiography; RR, relative risk; RRR relative risk ratio; RyR2, Ryanodine receptor type 2; S-ICD, subcutaneous implantable cardioverter-defibrillator; SAECG, signal averaged ECG; SBP, systolic blood pressure; SCA, sudden cardiac arrest; SCD, sudden cardiac death; SCD-HeFT, sudden cardiac death in heart failure trial; SCS, spinal cord stimulation; SHD, structural heart disease; SMASH VT, substrate mapping and ablation in sinus rhythm to halt ventricular tachycardia; SND, sinus node dysfunction; SQTS, short QT syndrome; STICH, surgical treatment for ischemic heart failure; STICHES, surgical treatment for ischemic heart failure extension study; SVT, supraventricular tachycardia; SYNTAX, synergy between PCI with Taxus and cardiac surgery; TdP, torsades de pointes; TIA, transient ischemic attack; TOF, tetralogy of Fallot; VA, ventricular arrhythmias; VALIANT, valsartan in acute myocardial infarction; VANISH, ventricular tachycardia ablation versus escalated antiarrhythmic drug therapy in ischemic heart disease; VERP, ventricular effective refractory period; VF, ventricular fibrillation; VFL, ventricular flutter; VHD, valvular heart disease; VT, ventricular tachycardia; VTE, ventricular tachyarrhythmic events; and WCD, wearable cardiac defibrillator.

Data Supplement 1. Nonrandomized Trials, Observational Studies, and/or Registries for History and Physical Examination – (Section 4.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Ruwald, et al. 2012 (1) ● 22588456	**Study type:** Retrospective observational study from a registry cohort with matched controls. **Size:** 127,508 patients with first episode of syncope. Each subject paired with 5 age and sex matched controls.	**Inclusion criteria:** Patients hospitalized or seen in emergency department with first episode of syncope between 1997 and 2009. **Exclusion criteria:** Not specified	**1° endpoint:** Incidence of syncope and associations with comorbidities and pharmacotherapy **Results:** Age distribution peaked at 20, 60, and 80 y. Incidence was higher in women in all age groups, although the peak in the oldest age group occurred 5–7 y earlier in men. CVD was present in 28% of the subjects, and drug therapy was being used by 48%. There was an association between CVD and admission for syncope, inversely related to age - 0–29 y (OR: 5.8); 30–49 y (OR: 4.4); 50–79 y (OR: 2.9), and ≥80 y (OR: 2.0). Cardiovascular pharmacotherapy associated with age and risk of syncope was similar.	● The incidence rates observed are higher than previously reported and the age distribution of syncope is widely different according to gender. Syncope is more common in females, in the elderly, is generally a diagnosis associated with considerable comorbidity. ● The data may be influenced by the fact that the study is dominated by syncope leading to hospitalization and emergency department visits.
● Soteriades et al. 2002 (2) ● 12239256	**Study type:** Retrospective analysis of a prospectively enrolled long term population cohort (Framingham) **Size:** 727 patients with reported syncope and long term follow up from a population of 7814 participants (3563 men and 4251	**Inclusion criteria:** Reported episodes of syncope by subjects in Framingham study population examined between 1971 and 1998. Reports coded as “yes,” “no,” or “maybe.” **Exclusion criteria:** Equivocal reports of syncope (N=120), participants who had not	**1° endpoint:** Death from any cause, MI or death from coronary heart disease, and fatal or nonfatal stroke. **Results:** Overall incidence of a first report of syncope was 6.2 per 1000 person-y, with an increase with increasing age, most prominent at 70 y. Age-adjusted incidence was 7.2 per 1000 person-y among both men and women. Causes among men and women were: cardiac causes (13.2% and 6.7%), unknown (31.0% 40.7%),	● Cardiac syncope constitutes a high-risk group for morbidity and premature mortality from CVD. ● Patients with unknown cause are a mixed group at apparent increased risk for death and warrant further diagnostic testing. ● Vasovagal syncope has a benign prognosis.

	women) followed for an average of 17 y in the outcome analysis.	had an examination within 4 y of the report (N=101), syncope due to head trauma (N=47), incomplete records (N=7).	stroke or TIA (4.3%and 4.0%), seizure disorder (7.2% and 3.2%), vasovagal (19.8% 22.2%), orthostatic (8.6% and 9.9%), medication (6.3% and 7.2%), and "other" (9.5% and 6.1%). Recurrences were reported in 21.6%). There were 847 deaths from all causes, 263 MI or deaths from coronary heart disease, and 178 fatal or nonfatal strokes during a mean follow-up of 8.6 y (median, 7.7). Participants with cardiac syncope had lower survival than those without syncope.	
● Middlekauff et al. 1993 (3) ● 8417050	**Study type:** Retrospective analysis of a consecutive patient cohort **Size:** 491 patients	**Inclusion criteria:** Consecutive series of patients with advanced HF without a Hx of CA referred for optimization of medical therapy, often in conjunction with pre-transplant evaluation, between 1983 and 1991 **Exclusion criteria:** Prior Hx of CA.	**1° endpoint:** SCD **Results:** After a mean follow-up of 365±419 d, 165 patients (35%) were alive, 148 (30%) had undergone heart transplantation, 69 (14%) had died suddenly, 66 (13%) had died of progressive HF, 19 (4%) had died of noncardiac or unknown causes and 24 (4%) were lost to follow-up. All-causes at I y was 29% and sudden death was 15%. All cause mortality was greater in patients with syncope (65% vs. 25%, p<0.00001). SCD risk was significantly greater in patients with syncope (45% vs. 12%, p <0.00001).	● Patients with advanced HF and syncope are at increased risk of all cause mortality, largely associated with an increased risk of SCD.

Data Supplement 2. Nonrandomized Trials, Observational Studies, and/or Registries of Noninvasive Evaluation (12-lead ECG, Exercise Testing and Electrocardiographic Monitoring) – (Section 4.2.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Steinman et al. 1989 (4) ● 2915409	**Study type:** retrospective cohort **Size**: 20 patients	**Inclusion criteria:** regular wide QRS tachycardia in conscious adults **Exclusion criteria:** hemodynamic instability	**1° endpoint:** diagnosis of VT **Results:** 75% of patients had atherosclerotic heart disease, with remote MI in 73% Diagnosis of VT established in 17/20 patients, by AV dissociation or the use of Wellens'criteria. EP testing in 17 patients confirmed the diagnosis of VT in 94%.	● VT is the most common diagnosis in adults with stable, wide complex tachycardia
● Brugada et al. 1991 (5) ● 2022022	**Study type:** prospective cohort **Size**: 554 tachycardias	**Inclusion criteria:** ECGs with wide QRS (≥0.12 s) **Exclusion criteria:** AAD treatment	**1° endpoint:** mechanism confirmed by EPS **Results:** New criteria had sensitivity of 0.987 and specificity of 0.965.	● Absence of RS in all precordial leads was highly specific for VT ● When RS is present in 1 or more precordial leads, RS interval of >100 ms is highly specific for VT ● Other criteria included AV dissociation and morphology in leads V1-2 and V6
● Wellens HJ et al. 1978 (6) ● 623134	**Study type:** Prospective cohort **Size:** 140 ECGs, 70 of sustained VT and 70 SVT with aberrancy, in 122 patients	**Inclusion criteria:** Diagnosis confirmed by His bundle ECG recording **Exclusion criteria**: Atrial fibrillation or flutter in patients with SVT	**1° endpoint:** development of algorithm for differentiation of VT from SVT **Results:** Findings suggestive of VT: QRS >0.14 s; left axis deviation; QRS morphology; AV dissociation	● Capture or fusion beats seen only infrequently
● Elhendy et al. 2002 (7) ● 12106835	**Study type:** retrospective cohort analysis **Size:** 1460	**Inclusion criteria:** intermediate pre-test probability of CAD **Exclusion criteria:** Hx of MI or revascularization,	**1° endpoint:** cardiac death or nonfatal MI **Results:** Exercise-induced VA occurred in 146 patients (10%).	● 41 patients had NSVT. ● Study was aimed more at ischemic outcomes than arrhythmias.

		CAD documented on angiography, or LBBB	During follow-up (median 2.7 y), 1° endpoint occurred in 36 patients. In multivariate analysis, independent predictors of cardiac events were exercise-induced VA (chi-square 4.7, p=0.03) and exercise heart rate (chi-square 18, p=0.0001).	
● Grady et al. 1998 (8) ● 9440667	**Study type:** retrospective matched control cohort study **Size:** 70 cases and 70 matched controls	**Inclusion criteria:** Exercise-induced LBBB **Exclusion criteria:** preexcitation or permanent pacemakers	**1° endpoint:** All-cause mortality, PCI, open heart surgery, nonfatal MI, documented symptomatic or sustained VT, or implantation of a permanent pacemaker or an ICD. **Results:** 37 events (28 in LBBB, 9 in controls) occurred during mean 3.7 y follow-up Adjusted relative risk in LBBB was 2.78 (95% CI: 1.16–6.65, p=0.02)	● Exercise-induced LBBB predicts a higher risk of death and major cardiac events.
● **ABCD** ● Costantini et al. 2009 (9) ● 19195603	**Study type:** prospective, non-randomized cohort **Size:** 566 patients	**Inclusion criteria:** ischemic cardiomyopathy, EF≤40%, and NSVT **Exclusion criteria:** unstable CAD, NYHA class IV HF, prior CA, sustained VA, unexplained syncope; recent (<28 d) MI, CABG, or PCI; permanent AF; taking AAD at baseline	**1° endpoint:** appropriate ICD discharge or SCD **Results:** 39 patients (7.5%) met the 1° endpoint after a median follow-up of 1.9 y; MTWA had a positive predictive value of 9% and NPV of 95%, comparable to EPS (11% and 95% respectively) Event rate with both positive MTWA and EPS was 12%, vs. 2% with both negative (p=0.017)	● Combination of MTWA and EPS identifies a subset of patients most likely to benefit from ICD. ● Negative predictive value is not 100%, indicating that a small subset of patients may still have events even if both tests are negative.
● Desai et al. 2006 (10) ● 16828632	**Study type:** retrospective **Size:** 46,933 consecutive patients with ECGs	**Inclusion criteria:** Patients with ECGs at a single center **Exclusion criteria:** preexcitation; BBB or	**1° endpoint:** cardiovascular death **Results:** After adjustment in the Cox model for age, gender, and heart rate, the QRS duration score was a strong independent predictor of cardiovascular	● 801 patients (1.8%) had a QRS>120 ms; another 2300 had BBB No specific information on arrhythmic death

		paced patients considered separately	mortality. For every 10ms increase in QRS duration, there was an 18% increase in cardiovascular risk.	
● Freedman et al. 1987 (11) ● 3597997	**Study type:** retrospective **Size:** 15,609 patients from the CASS study (Coronary Artery Surgery Study); 522 with BBB	**Inclusion criteria:** All patients from CASS; BBB patients compared to those without **Exclusion criteria:** preexcitation, ventricular pacing, nonspecific IVCD, previous myocardial surgery	**1° endpoint:** mortality **Results:** LBBB associated with 5-fold greater mortality; RBBB 2-fold greater mortality ($p<0.0001$ for both)	● Mean EF in LBBB patients 40% vs. 49% in RBBB and 57% in patients without BBB
● Baldasseroni et al. 2002 (12) ● 11868043	**Study type:** retrospective analysis of outpatient registry **Size:** 5517 patients	**Inclusion criteria:** unselected outpatients with HF **Exclusion criteria:** N/A	**1° endpoint:** mortality **Results:** LBBB was present in 1391 patients (25.2%) and was associated with an increased 1y mortality rate from any cause (HR 1.70; 95% CI: 1.41–2.05) and sudden death (HR: 1.58; 95% CI: 1.21–2.06).	● LBBB Is associated with higher mortality in CHF
● **MUSTT** ● Zimetbaum et al. 2004 (13) ● 15289365	**Study type:** retrospective substudy **Size:** 431	**Inclusion criteria:** CAD, EF<40%, NSVT **Exclusion criteria:** treatment with AAD or an ICD	**1° endpoint:** CA or arrhythmic death **Results:** LBBB and intraventricular conduction delay were associated with a 50% increase in the risk of both arrhythmic and total mortality. RBBB was not associated with arrhythmic or total mortality. LVH was the only ECG predictor of arrhythmic (HR 1.35; 95% CI: 1.08–1.69) but not total mortality.	● Likely reflects the effect of ventricular dyssynchrony

● Buxton et al. 2005 (14) ● 16022960	**Study type:** retrospective substudy from PainFREE Rx II **Size:** 431 patients	**Inclusion criteria:** patients in the study with CAD and a baseline ECG. **Exclusion criteria:** HCM, BrS, LQTS	**1° endpoint:** recurrence of VT/VF **Results:** QRSd was ≤120 ms in 291 of 431 (68%) patients (LBBB 65, RBBB 48, IVCD 124). Over 12mo follow-up, VT/VF occurred in 95 (22%) patients (22% of patients with QRSd ≤120ms vs. 23% of patients with QRSd >120ms, p=NS).	● QRS duration is not useful in predicting recurrent VT/VF.
● **MADIT-II** ● Monasterio et al. 2013 (15) ● 24028998	**Study type:** substudy of prospective clinical trial **Size:** 175 patients	**Inclusion criteria:** CAD, EF ≤30% **Exclusion criteria:** AF; heart rate <80 beats/min	**1° endpoint:** appropriate ICD therapy and SCD **Results:** Neither QTV nor TWA predicted SCD. Appropriate ICD therapy was predicted by combining IAA90 from T wave alternans testing and QTVN after adjusting for relevant correlates.	● Increased TWA and QTV are independent predictors of appropriate ICD therapy in MADIT-II patients with elevated heart rate at baseline.
● **MASTER** ● Chow et al. 2008 (16) ● 18992649	**Study type:** prospective, non-randomized cohort study of MTWA testing **Size:** 575 patients; all received ICDs	**Inclusion criteria:** post-MI, EF≤30% **Exclusion criteria:** AF or atrial flutter, Hx of sustained VT/VF or CA, MI in past mo, revascularization within 3 mo, class IV CHF, advanced cerebrovascular disease	**1° endpoint:** SCD or appropriate ICD therapy **Results:** SCD or appropriate ICD therapy occurred in 48 of 361 (13%, 6.3%/y) MTWA non-negative and 22 of 214 (10%, 5.0%/y) MTWA negative patients. A non-negative MTWA test result was not associated with 1° endpoint (HR: 1.26; 95% CI 0.76–2.09; p=0.37)	● Total mortality was significantly increased in MTWA non-negative patients (HR: 2.04; 95% CI: 1.10–3.78; p=0.02). MTWA did not identify patients at a higher risk of a VT.
● Gupta et al. 2012 (17) ● 22424005	**Study type:** meta-analysis	**Inclusion criteria:** predominantly prior MI	**1° endpoint:** VT events were defined as the total and	● Negative MTWA result would decrease the annualized risk of VTE from 8.85% to 6.37% in MADIT-II–

	Size: 20 prospective cohort studies consisting of 5,945 subjects	or left ventricular dysfunction **Exclusion criteria:** healthy patients; BrS; LQTS	arrhythmic mortality and nonfatal sustained or ICD-treated VT **Results:** Although there was a modest association between positive MTWA and VTE (RR: 2.45; 95% CI:1.58-3.79) and nonnegative MTWA and VTE (RR: 3.68; 95% CI: 2.23–6.07), test performance was poor (positive MTWA: LR+ 1.78, LR− 0.43; nonnegative MTWA: LR+ 1.38, LR− 0.56)	type patients and from 5.91% to 2.60% in SCD-HeFT–type patients. ● Despite a modest association, results of spectrally derived MTWA testing do not sufficiently modify the risk of VTE to change clinical decisions
● **MADIT-II** ● Dhar et al. 2008 (18) ● 18534364	**Study type:** substudy of randomized clinical trial that estimated the association of prolonged QRSd ≥140ms with arrhythmic outcomes **Size:** 1232 patients	**Inclusion criteria:** prior MI, EF ≤30% **Exclusion criteria**: indicated for an ICD; NYHA class IV; coronary revascularization within the preceding 3 mo; MI within the past mo; advanced cerebrovascular disease; other potentially life-threatening conditions	**1° endpoint:** SCD in the medically treated arm and SCD or first appropriate ICD therapy for rapid VT/VF in the ICD-treated arm **Results**: In the medically treated arm, prolonged QRS was a significant independent predictor of SCD (HR: 2.12; 95% CI1.20–3.76, p=0.01). In the ICD-treated arm, prolonged QRS did not predict SCD or rapid VT/VF (HR: 0.77; 95% CI 0.47–1.24, p=0.28).	● Prolonged QRS does not predict SCD/VT/VF in ICD treated patients but does predict SCD in medically treated patients.
● Bloomfield et al. 2004 (19) ● 15451804	**Study type:** prospective cohort **Size:** 177 patients	**Inclusion criteria:** prior MI, EF≤30% **Exclusion criteria:** AF or atrial flutter; requirement for ventricular pacing; unstable CAD; NYHA class IV HF; unable to exercise on a bicycle or treadmill	**1° endpoint:** 2y all-cause mortality **Results:** For abnormal MTWA compared to normal (negative) test, the HR: 4.8; p=0.02; for QRS >120ms compared to ≤120ms, the HR for 2y mortality was 1.5 (p=0.367). The actuarial mortality rate was substantially lower among patients with normal MTWA (3.8%; 95% CI: 0–9.0) than	● Among MADIT II–like patients, MTWA is better than QRS duration at identifying a high-risk group; it is also better at identifying a low-risk group unlikely to benefit from ICD therapy.

			the mortality rate in patients with a narrow QRS (12.0%; 95% CI: 5.6–18.5).	
● Iuliano et al. 2002 (20) ● 12075267	**Study type:** retrospective analysis of CHF-STAT **Size:** 669 patients	**Inclusion criteria:** ischemic or nonischemic cardiomyopathy, NYHA class II-IV, ≥10 PVCs/h, EF <40% **Exclusion criteria:** recent MI, Hx of ACA, QRS >180ms, or a QTc >500ms	**1° endpoint:** total mortality and sudden death **Results:** Prolonged QRS (≥120 ms) was associated with a significant increase in mortality (49.3% vs 34.0%, p=0.0001) and sudden death (24.8% vs 17.4%, p=0.0004). LBBB was associated with worse survival (p=0.006) but not sudden death	● QRS prolongation is an independent predictor of both increased total mortality and sudden death in patients with HF.
● Perez-Rodon, et al. 2014 (21) ● 24993462	**Study type:** Retrospective observational study, aimed at studying the association between specific ECG abnormalities and mortality in patients with syncope from the GESINUR study. **Size:** 524 patients	**Inclusion criteria:** Patients in the GESINUR study who had syncope and had available, readable ECG and 12 mo follow-up data	**1° endpoint:** all-cause mortality **Results**: Abnormal ECGs in 344 patients (65.6%). 33 Patients died during follow-up (6.3%): - 1 due to SCD - Atrial fibrillation (OR: 6.8; 95% CI: 2.8–16.3, p<0.001) - intraventricular conduction disturbances (OR: 3.8; 95% CI: 1.7–8.3; p=0.001), - LV hypertrophy ECG criteria (OR: 6.3, 95% CI: 1.5–26.3; p=0.011) - ventricular pacing (OR 21.8, 95% CI 4.1–115.3, P <.001)	● Although an abnormal ECG in patients with syncope is a common finding, only the presence of atrial fibrillation, intraventricular conduction disturbances, left ventricular hypertrophy ECG criteria, and ventricular pacing is associated with 1-year all-cause mortality.

Data Supplement 3. RCTs Comparing Ambulatory Electrocardiography – (Section 4.2.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Barrett et al. 2014 (22) ● 24384108	**Aim:** Compare Holter to a 14 d patch electrode **Study type:** Head to head comparison, simultaneous **Size:** 146 pt	**Inclusion criteria:** patients for evaluation of cardiac arrhythmia **Exclusion criteria:** skin allergies, conditions, or sensitivities to any of the components of the adhesive patch monitor, receiving or anticipated to receive pacing or external direct current cardioversion, or the anticipation of being exposed to high-frequency surgical equipment during the monitoring period	**Intervention:** 24 h Holter and 14 d adhesive patch **Comparator:** Detection of arrhythmia over total wear time. Any 1 of 6 arrhythmias, including supraventricular tachycardia, AF/flutter, pause greater than 3s, AV block, VT, or polymorphic VT/VF.	**1° endpoint:** Adhesive 96, Holter 61 events (p<0.001)	● Prolonged duration monitoring for detection of arrhythmia events using single lead, less-obtrusive, Adhesive-patch monitoring platforms could replace conventional Holter monitoring in patients referred for ambulatory ECG monitoring.
● de Asmundis et al. 2014 (23) ● 24574492	**Aim:** head to head comparison of 24 h Holter and hand held patient-activated even monitor (not loop) **Study type:** Sequential comparison (Holter, then monitor)	**Inclusion criteria:** Indication for monitor (palpitations 92.3%, dizziness 7.7%) **Exclusion criteria:** presence of a pacemaker or an ICD, syncope, structural heart diseases, ECG abnormalities, and a Hx of documented arrhythmia.	**Intervention:** 24 h monitor and 15 d HeartScan **Comparator:** Percent diagnosis of symptom-related arrhythmias	**1° endpoint:** Clinical diagnosis for symptoms: Holter 1.8% HeartScan 89% (p<0.01)	● Longer time and patient-activated monitor improved yield. This was NOT a loop recorder

	Size: 625				

Data Supplement 4. Nonrandomized Trials, Observational Studies, and/or Registries of Ambulatory Monitors – (Section 4.2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Turakhia et al. 2013 (24) ● 23672988	**Study type:** observational **Size:** 26,751	**Inclusion criteria:** Zio placed **Exclusion criteria:** N/A	**1° endpoint:** evaluated compliance, analyzable signal time, interval to arrhythmia detection, and diagnostic yield of the Zio Patch, COMPARED: first 48h with later (mean 7.6 d) **Results:** Any arrhythmia: 62.2% vs 43.9% Symptomatic arrhythmia: 9.7% vs 4.4% VT 187 pt (0.7%) PMVT, TdP, VF 6 pt (0.0%)	● Demonstrates yield and compliance with patch monitor although VT/VF not a major issue here
● Linzer et al. 1990 (25) ● 2371954	**Study type:** observational **Size:** 57	**Inclusion criteria:** Syncope with negative Holter **Exclusion criteria:** Patients who had undergone EPS	**1° endpoint:** Monitor up to 1 mo with Loop **Results:** arrhythmia was the cause of symptoms (diagnostic yield 25%; 95% CI: 14–38%). VT (1 patient), high grade AV block (2 patients), SVT (1 patient), asystole or junctional bradycardia from neutrally mediated syncope (3 patients) and normal cardiac rhythms (the remaining 7 patients).	● 25% yield for syncope Dx after negative Holter ● VT/VF uncommon (1 pt)

Data Supplement 5. Nonrandomized Trials, Observational Studies, and/or Registries of Implanted Cardiac Monitors – (Section 4.2.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Turakhia et al. Am J Car 2013 (24) ● 23672988	**Study type:** observational **Size:** 26,751	**Inclusion criteria:** Zio placed **Exclusion criteria:** N/A	**1° endpoint:** evaluated compliance, analyzable signal time, interval to arrhythmia detection, and diagnostic yield of the Zio Patch COMPARED: first 48 h with later (mean 7.6 d) **Results:** Any arrhythmia: 62.2% vs 43.9% Symptomatic arrhythmia: 9.7% vs 4.4% VT 187 pt (0.7%) PMVT, TdP, VF 6 patients (0.0%)	● Demonstrates yield and compliance with patch monitor although VT/VF not a major issue here
● **CARISMA** ● Bloch Thomsen et al. 2010 (26) ● 20837897	**Study type:** observational **Size:** 297 participants	**Inclusion criteria:** AMI and reduced LVEF **Exclusion criteria:** Refusal; inability of the patient to participate in the study because of other serious illness (N=312), planned coronary bypass graft surgery (N=184), or death (N=89).	**1° endpoint:** incidence and prognostic significance of arrhythmias post MI with reduced LVEF **Results:** Brady and tachyarrhythmia's seen in 137 patients (46%), with 86% asymptomatic. 13% incidence of NSVT (≥16 bts), 3% sustained VT (≥30 sec), 3% VF (≥16 bts). Also 28% AF with fast vent response; 10% high degree AV block;	● Intermittent AV block was associated with "very high risk of cardiac death"

			7% sinus brady, 5% sinus arrest	
● Linzer et al. 1990 (25) ● 2371954	**Study type:** observational **Size:** 57 participants	**Inclusion criteria:** Syncope with negative Holter **Exclusion criteria:** Prior EPS.	**1° endpoint:** Monitor up to 1 mo with Loop **Results:** arrhythmia was the cause of symptoms (diagnostic yield 25%; 95% CI 14–38%). VT (1 patient), high grade AV block (2 patients), SVT (1 patient), asystole or junctional bradycardia from neutrally mediated syncope (3 patients) and normal cardiac rhythms (the remaining 7 patients).	● 25% yield for syncope diagnosis after negative Holter
● Volosin et al. 2013 (27) ● 23439867	**Study type:** Observational, for CareLink monitoring service **Size:** 2190 patients overall who transmitted data. Also studied induced arrhythmias	**Inclusion criteria:** Patients who transmitted data studied with induced VA at time of ICD implant testing. **Exclusion criteria:** Patients who did not transmit over 4 mo period	**1° endpoint:** Evaluate tachycardia detection of device and software **Results:** 15.1% had VT or FVT detected, although true VT was seen in only 10.4%. For induced 1909 tachycardia episodes reviewed. Sensitivity of VT/VF was 99.3%	● Sensitivity is high (96.5% or 99.3% if programmed for slower VT. ● Shows excellent detection in artificial environment.
● Krahn et al. 1999 (28) ● 9918528	**Study type:** Observational **Size:** 85	**Inclusion criteria:** recurrent undiagnosed syncope **Exclusion criteria:** unlikely to survive 1y, were unable to give informed consent, had a previously implanted programmable medical device, were pregnant, or	**1° endpoint:** Detection of arrhythmias related to recurrent syncope, with prior Holter **Results:** 68% had syncope. Arrhythmia seen in 42% who transmitted rhythm during symptoms.	● Demonstrates utility of loop although no VT/VF seen in this relatively small study.

		were women of childbearing potential not on a reliable form of contraception.	Bradyarrhythmia in 18, tachyarrhythmia in 3 (SVT 2, AFL 1; no VT/VF)	
● Solbiati et al. 2016 (29) ● 27092427	**Study type:** Systematic review, Meta-analysis **Size:** 579 participants in 4 trials	**Inclusion criteria:** Unexplained Recurrent Syncope, evaluation of loop recorder vs no loop recorder **Exclusion criteria:** N/A	**1° endpoint:** To assess the incidence of mortality, QoL, adverse events and costs of ILRs vs. conventional diagnostic workup in people with unexplained syncope **Results:** No difference in long-term mortality 2 studies showed trend of reduction in syncope relapse after diagnosis with the ILR Higher rate of diagnosis (RR: 0.61; 95% CI: 0.54–0.68)	● This confirmed the advantage of the ILR in making a diagnosis in unexplained syncope, with trend seen in reduction of relapse.

Data Supplement 6. Nonrandomized Trials, Observational Studies, and/or Registries Comparing Noninvasive Cardiac Assessment– (Section 4.2.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **VALIANT** ● Solomon et al. 2005 (30) ● 15972864	**Aim:** To evaluate risk and predictors of SCD in patients post MI with left ventricular dysfunction and/or HF	**Inclusion criteria:** patients with first or subsequent MI with HF, LV dysfunction, or both **Exclusion criteria:** ICD in place prior to randomization	**Intervention:** Analysis of rates of SCD. Evaluation of EF determined by echocardiography as well as other parameters.	**1° endpoint:** The risk of sudden death was greatest in the first 30 d after MI: 1.4% per mo, 95% CI: 1.2%–1.6% and decreased to 0.14% per mo 95% CI: 0.11%–0.18% after 2 y after MI. Patients	● Each 5% lower LVEF was associated with a 21% increase in adjusted risk of SCD or CA with resuscitation.

	Study type: Observational study of patients enrolled in a RCT **Size:** 14,609 patients		**Comparator:** N/A	with LVEF <30% were at the greatest risk for SCD	
● **SCD-HEFT** ● Gula et al. 2008 (31) ● 19033019	**Aim:** To determine with baseline assessment of EF being performed using echocardiography, RNA, or contrast angiography impacted the likelihood of survival. **Study type:** Observational analysis of patients enrolled into a RCT **Size:** 2,521 patients	**Inclusion criteria:** Patients with HF, NYHA class II-III and LVEF ≤35% **Exclusion criteria:** Contraindication to amiodarone or 1° prevention ICD	**Intervention:** Type of modality to evaluate LVEF and clinical outcomes. **Comparator:** N/A	**1° endpoint:** Multivariable analysis showed that there was no significant difference in survival between patients enrolled based on LVEF determined RNA vs. echocardiography (HR: 1.06; 95% CI: 0.88–1.28), RNA Vs. angiography (HR: 1.25; 95% CI: 0.97–1.62), or echocardiography vs. angiography (HR: 1.18; 95% CI: 0.94–1.48).	● Among HF patients with an LVEF between 20% and 35%, each 5% increase in LVEF was associated with a lower mortality risk (HR: 0.81; 95% CI: 0.75–0.88). The findings were similar for each initial EF imaging modality, with the interaction term combining imaging method and LVEF in the Cox model was NS (p=0.71).

Data Supplement 7. Nonrandomized Trials, Observational Studies, and/or Registries Comparing Biomarkers – (Section 4.2.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Korngold et al. 2009 (32) ● 19470888	**Aim:** Evaluate baseline NT-proBNP levels to predict risk of SCD in a general population of women.	**Inclusion criteria:** Women nurses 30–55 y of age **Exclusion criteria:** Blood sample not collected	**Intervention:** NT-proBNP data at baseline. 99 SCD cases and 294 matched controls. **Comparator:** N/A	**1° endpoint:** Relationship of NT-proBNP and SCD (RR for 1-standard deviation increment 1.49; 95% CI: 1.09–2.05; p=0.01)	● Women with NT-proBNP levels above the cut point of 389 pg/mL were at increased risk of SCD (RR 5.68; 95% CI: 1.78–18.2; p=0.003).

	Study type: Case Control **Size:** 32,826 women with biomarker data out of 121,700 enrolled				
● Patton et al. 2011 (33) ● 21044699	**Aim:** Evaluate risk of SCD as function of baseline NT-proBNP in a community cohort of older men and women **Study type:** Cohort study **Size:** 5,447 men and women	**Inclusion criteria:** Men and women 65 y of age and older randomly selected from 4 communities **Exclusion criteria:** NT-proBNP levels not available	**Intervention:** NT-proBNP levels were analyzed both as a continuous variable, where the natural log of NT-proBNP was used, and as categorized into quintiles **Comparator:** N/A	**1° endpoint:** Higher NT-proBNP levels were associated with SCD, with an unadjusted HR: 4.2; 95% CI: 2.9, 6.1; p=0.001 for the highest vs. lowest quintile	● NT-proBNP was associated with SCD after adjustment for clinical characteristics and risk factors (age, sex, race, and other associated conditions), with an adjusted HR for the fifth vs. the first quintile of 2.5 (95% CI: 1.6, 3.8; p=0.001).
● Scott et al. 2009 (34) ● 19789399	**Aim:** Evaluate whether BNP levels can predict SCD and VA in patients without ICDs **Study type:** Meta-Analysis of Observational Studies **Size:** 14 studies (6 studies with 3,543 patients without ICD and 8 studies of 1,047 patients with ICD)	**Inclusion criteria:** Studies evaluating BNP or NT-proBNP levels for SCD or VA **Exclusion criteria:** Overlapping studies	**Intervention:** BNP and NT-proBNP levels evaluated for SCD risk in patients without ICD or VA risk in patients with ICD **Comparator:** N/A	**1° endpoint:** Increased BNP or NT-proBNP predicted SCD with a RR: 3.68; 95% CI: 1.90–7.14 in patients without ICDs. Increased BNP or NT-proBNP predicted VA with a RR: 2.54; 95% CI: 1.87–3.44.	● The risk of SCD associated with increased BNP or NT-proBNP tended to be higher in patients with a lower LVEF. However, there was not a significant interaction between BNP level and LVEF on risk prediction.

● Blangy et al. 2007 (35) ● 17526509	**Aim:** Evaluate biomarkers on VT risk in patients with ICD post MI **Study type:** Observational **Size:** 121 men and women	**Inclusion criteria:** Patients with spontaneous sustained VT post MI receiving ICD **Exclusion criteria:** N/A	**Intervention:** Serum BNP, hs-CRP, and procollagen levels measures at baseline **Comparator:** N/A	**1° endpoint:** In a multivariate analysis, an increased serum BNP (OR: 3.75; 95% CI: 1.46–9.67), an increased hs-CRP (OR: 3.2; 95% CI: 1.26–8.10, and an increased PINP (OR: 3.71; 95% CI: 1.40–9.88 were associated with a higher VT incidence.	● In addition, LVEF <0.35 (OR 2.19; 95% CI: 1.00–4.79) was associated with a higher VT incidence.
● **HF ACTION** ● Ahmad et al. 2014 (36) ● 24952693	**Aim:** Evaluate biomarkers in prediction of sudden deathand progressive HF death in patients with HF with reduced EF **Study type:** Observational analysis of subjects enrolled in a RCT **Size:** 813 subjects	**Inclusion criteria:** NYHA class II to IV chronic HF with EF≤35% **Exclusion criteria:** • Biomarker data not obtained • Inability to exercise	**Intervention:** NT-proBNP, galectin-3, and ST2 levels were assessed at baseline in patients enrolled in the trial of exercise training vs. usual care **Comparator:** N/A	**1° endpoint:** Elevations in each biomarker was associated with increased risk for SCD death in both adjusted and unadjusted analyses. However, increases in the biomarkers had stronger associations with pump failure than SCD. Clinical variables along with NT-proBNP levels were predictors sudden cardiac death (C statistic: 0.73).	● NT-proBNP was more strongly predictive of pump failure (C statistic: 0.87) ● Addition of ST2 and galectin-3 led to improved net risk classification of 11% for SCD. ● There was no improvement in net risk reclassification for pump failure death with ST2 or galectin-3
● Levine et al. 2014 (37) ● 24837348	**Aim:** To evaluate the ability of BNP or NT-proBNP to predict VA in patients with 1° prevention ICDs **Study type:** Observational **Size:** 564 patients	**Inclusion criteria:** BNP or NT-proBNP levels and 1° prevention ICD **Exclusion criteria:** BNP or NT-proBNP not available within 12mo of ICD implantation.	**Intervention:** BNP or NT-proBNP levels to predict risk of VA **Comparator:** N/A	**1° endpoint:** In multivariate analysis NT-proBNP was associated with increased risk of VA with HR: 5.75; p<0.001 and BNP was associated with increased risk with HR: 3.40; p<0.01.	● Quartile analyses showed higher relative risk of VA compared to the relative risk of all-cause mortality for both BNP and NT-proBNP.

● Berger et al. 2002 (38) ● 12021226	**Aim:** To evaluate role of BNP in predicting SCD in patients with HF with LVEF ≤35% **Study type:** Observational **Size:** 452 patients	**Inclusion criteria:** Patients with HF and reduced EF with BNP level measured at baseline **Exclusion criteria:** Patients with heart transplantation or VAD	**Intervention:** BNP levels at baseline and association with subsequent SCD **Comparator:** N/A	**1° endpoint:** In multivariate analysis, log BNP level was the only independent predictor of sudden death	● Using a cutoff point of log BNP 2.11 (130 pg/mL), the KM sudden death–free survival rates were significantly higher in patients below (99%) compared with patients above (81%) this cutoff point (p=0.0001)

Data Supplement 8. RCTs Evaluating EP Study for VA – (Section 4.3.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Buxton AE, et al. Circ 2002 (39) ● 12417544	**Aim:** to analyze the relationship of EF and inducible VA to mode of death **Study type:** Prospective, randomized, RCT **Size:** 1791 patients	**Inclusion criteria:** CAD, EF≤40%, and asymptomatic, unsustained VT **Exclusion criteria:** History of syncope, sustained VT/VF more than 48 h after AMI, unsustained VT only in the setting of drug-induced LQTS or AMI or that was attributable to acute metabolic disorders or drug toxicity, or symptomatic, unsustained VT	**Intervention:** AAD or ICD for inducible patients **Comparator:** EF 30–40% vs. <30%	**1° endpoint:** ● Total mortality and arrhythmic deaths/cardiac arrests more common in patients with EF <30% ● Arrhythmic deaths similar in patients with EF <30% and 30–40% ● Relative contribution of arrhythmic deaths to total mortality was higher in inducible patients (58% of deaths vs. 46% of deaths in noninducible patients, p=0.004	● 61% of events were arrhythmic among inducible patients with EF ≥30% and only 42% among noninducible patients, p=0.002

● **MUSTT** ● Buxton AE, et al NEJM 1999 (40) ● 10601507	**Aim:** to test the usefulness of EPS for risk stratification for SCD **Study type:** Prospective, randomized, RCT **Size:** 704 patients with inducible, sustained VA	**Inclusion criteria:** CAD, EF≤40%, and asymptomatic, unsustained VT **Exclusion criteria:** History of syncope, sustained VT/VF more than 48 h after AMI, unsustained VT only in the setting of drug-induced LQTS or AMI or that was attributable to acute metabolic disorders or drug toxicity, or symptomatic, unsustained VT	**ntervention:** AAD or ICD **Comparator:** Patients with inducible VT/VF at EPS randomized to treatment with AAD or ICD vs. no specific antiarrhythmic treatment	**1° endpoint:** CA or arrhythmic death ● At 5 y, inducible patients treated with AAD/ICD had a significantly lower risk of arrhythmic death or CA (25%) than patients not receiving antiarrhythmic therapy (32%) (RR: 0.73; 95% CI: 0.53–0.99)	● The risk of cardiac arrest or death from arrhythmia among patients who received treatment with ICDs was significantly lower than that among the patients discharged without receiving defibrillator treatment (RR: 0.24; 95% CI: 0.13–0.45; p<0.001). ● Reduction in 1° endpoint in AAD/ICD arm was due to reduction in events in patients treated with ICDs, not AAD
● **MUSTT** ● Buxton et al. 2000 (41) ● 10874061	**Aim:** to test the usefulness of EPS for risk stratification for SCD **Study type:** Prospective, randomized, RCT **Size:** 1750 patients (353 inducible; 1397 noninducible)	**Inclusion criteria:** CAD, EF ≤40%, and asymptomatic, unsustained VT **Exclusion criteria:** History of syncope, sustained VT/VF more than 48 h after AMI, unsustained VT only in the setting of drug-induced LQTS or AMI or that was attributable to acute metabolic disorders or drug toxicity, or symptomatic, unsustained VT	**Intervention:** EPS **Comparator:** Inducible VT/VF at EPS and not treated with AAD or ICD compared to noninducible patients	**1° endpoint:** CA or arrhythmic death At 2 and 5 y, noninducible patients had a significantly lower risk of arrhythmic death or CA (12%, 24%) than inducible patients (18%. 32%) (adjusted p<0.001). Overall mortality at 5 y was lower in noninducible patients (44% vs. 48%, adjusted p=0.005). **Safety endpoint (if relevant):** N/A	● Patients with ischemic cardiomyopathy and asymptomatic, unsustained VT with inducible VT have a significantly greater risk of SCD or CA and higher overall mortality than similar patients who are noninducible

● **MADIT-I** ● Moss et al. 1996 (42) ● 8960472	**Aim:** To evaluate whether prophylactic ICD, as compared with conventional medical therapy, would improve survival in a high-risk group of patients with NSVT, reduced LVEF and previous MI. **Study type:** prospective multicenter RCT **Size:** 196 patients	**Inclusion:** Previous MI, LVEF ≤35%, NSVT, inducible VT at EPS that was non-suppressed with IV procainamide or equivalent AAD **Exclusion:** previous CA or VT causing syncope that was not associated with an AMI; symptomatic hypotension while in a stable rhythm; and MI <3 wk, prior CABG <2 mo or PCI <3 mo, as were women of childbearing age who were not using medically prescribed contraceptives, patients with advanced cerebrovascular disease, patients with any condition other than cardiac disease that was associated with a reduced likelihood of survival for the duration of the trial, and patients who were participating in other clinical trials	**Comparator**: Control (101 patients) **Intervention:** ICD (95 patients)	**All-cause mortality**: Control 32% vs. ICD 13% (RRR -59% ARR -19%)	● In patients with a prior MI, low EF who are at high risk for VT, prophylactic therapy with an ICD leads to improved survival as compared with conventional medical therapy.
● **SCD-HeFT** ● Bardy et al. 2005 (43) ● 15659722	**Aim:** Evaluate whether amiodarone or a conservatively programmed shock-only, single-lead ICD would decrease the	**Inclusion:** NYHA class I-III HF, LVEF≤35% **Exclusion:** <18 y, unable to give consent	**Intervention 1:** GDMT plus a ICD (829 patients) **Intervention 2:**	**All-cause mortality:** control 36% vs. ICD 29% (RRR -23% and ARR -7%)	● In patients with NYHA class II or III HF and LVEF≤35%, amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall

	risk of death from any cause in a broad population of patients with mild-to-moderate HF **Study type:** prospective multicenter RCT **Size:** 2521 patients		GDMT plus amiodarone (845 patients) **Comparator 1:** GDMT plus Placebo (847 patients)		mortality. This was the longest and largest ICD trial.
● **MADIT-II** ● Moss et al. 2002 (44) ● 11907286	**Aim:** To evaluate the benefit of ICD in patients with prior MI and reduced LVEF **Study type:** RCT **Size:** 1232 patients	**Inclusion:** Prior MI (>1 mo), EF ≤30% **Exclusion:** existing indication for ICD; NYHA class IV at enrollment; had undergone coronary revascularization <3 mo; MI <30 d, advanced cerebrovascular disease, childbearing age and not using contraceptive, presence of any condition other than cardiac disease that was associated with a high likelihood of death during the trial, or unwilling to provide consent	**Comparator**: Control (490 patients) **Intervention:** ICD (742 patients)	**All-cause mortality:** control 22% vs. ICD 16% (RRR -28% and ARR -6%)	● In patients with a prior MI and advanced left ventricular dysfunction, prophylactic ICD improves survival and should be considered as a recommended therapy.

Data Supplement 9. Nonrandomized Trials, Observational Studies, and/or Registries of EP Study for VA - (Section 4.3.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Hilfiker et al. 2015 (45) ● 26131339	**Study type:** prospective cohort **Size:** 265 patients	**Inclusion criteria:** Patients who underwent EPS for SCD risk evaluation because of structural or functional heart disease and/or electrical conduction abnormality and/or after syncope/CA. **Exclusion criteria:** Not specified	**1° endpoint:** SCD or appropriate ICD therapy **Results:** Sustained VT was induced in 125 patients (47.2%) and non-sustained VT in 60 patients (22.6%) 153 patients (57.7%) underwent ICD implantation 1° endpoint event occurred in 49 patients (18.5%). Cox regression analysis showed that both sustained VT during EPS (HR: 2.26; 95% CI: 1.22–4.19, p=0.009) and EF<5% (HR: 2.00; 95% CI: 1.13–3.54, p=0.018) were independent predictors of 1° endpoint events.	● Mixed population of patients ● EPS identifies patients who are likely to have recurrent VA or SCD.
● Bourke et al. 1991 (46) ● 1907984	**Study type:** prospective cohort **Size:** 1209 patients	**Inclusion criteria:** recent AMI **Exclusion criteria:** early recurrence of angina requiring treatment; spontaneous VT or VF more than 48 h after MI; CHF not controlled with furosemide; significant noncardiac disease	**1° endpoint:** documented sustained VT/VF or witnessed sudden death **Results:** Sustained monomorphic VT was inducible by programmed electrical stimulation in 75 (6.2%). 14 infarct survivors (19%) with inducible VT experienced spontaneous VT or VF compared with 34 (2.9%) of those without inducible VT (p<0.0005).	● EPS predicts VT/VF in follow-up of survivors of AMI

● Bailey et al. 2001 (47) ● 11738292	**Study type:** meta-analysis **Size:** 4022 post-MI patients	**Inclusion criteria:** 44 reports for which incidence of major arrhythmic events and predictive accuracy could be inferred **Exclusion criteria:** N/A	**1° endpoint:** sustained VT/VF, CA, sudden death **Results:** positive EPS had 61.6% sensitivity and 84.1% specificity 2 y probability of event was 25.5% RR 6.6; OR 8.5	● Multiple tests evaluated: SAECG; heart rate variability; severe VA on ambulatory electrocardiography; EF; and EPS. ● Results for all tests evaluated were similar ● EPS has moderate predictive value for life-threatening VA.
● Schmitt et al. 2001 (48) ● 11401129	**Study type:** prospective cohort **Size:** 98 post-MI patients identified as high risk by noninvasive markers	**Inclusion criteria:** post-MI patents identified as high risk by scoring system including EF, PVCs, and abnormal SAECG **Exclusion criteria:** Hx of spontaneous sustained VT	**1° endpoint:** sudden death, symptomatic VT, CA **Results:** Patients underwent EPS. Event rate was 33% with a positive EPS vs. 2.6% (p<0.0001) with a negative EPS.	● A subgroup of 96 high-risk patients declined ● EPS. In this non-consent group, cardiac mortality (combined sudden and nonsudden) was significantly higher (log-rank chi-square 9.38 RR 4.7; 95% CI: 1.6–13.9, p=0.0022) compared to group treated according to results of EPS. 20/21 patients with a positive EPS had ICD implanted.
● Brembilla-Perrot et al. 2004 (49) ● 15358027	**Study type:** Prospective observational **Size:** 180 patients (119 CAD, group 1; 61 DCM, group 2)	**Inclusion criteria:** EF<40% and syncope **Exclusion criteria:** unstable angina; recent AMI; recent coronary angioplasty or CABG; second- or third-degree AV block; sustained supraventricular or ventricular arrhythmia; clinical HF not controlled by furosemide; uncontrolled electrolyte abnormalities; significant noncardiac disease; or amiodarone treatment.	**1° endpoint:** cardiac mortality **Results:** Sustained VT was induced in 44 group I patients (37%) and 13 group II patients (21%); VFL (>270 beats/min) or VF was induced in 24 group I patients (19%) and 9 group II patients (15%) VT or VF induction was predictive of mortality in CAD and identified a group with high cardiac mortality (46%), compared with patients with a negative study, who had a lower mortality (6%;	● EPS may be useful to determine mechanism of syncope in patients with ischemic cardiomyopathy.

			p<0.001). Cardiac mortality was only correlated with EF in DCM.	
● Bhandari AK Circ 1985 (50) ● 2856866	**Study type:** retrospective single center **Size:** 15	**Inclusion criteria:** LQTS with syncope or ACA Mean QTc 550 msec 11 control subjects, normal QTc **Exclusion criteria:** N/A	**1° endpoint:** EP testing in LQTS **Results:** RV and LV EPS, 3 extrastimuli, with and without isuprel Rapid polymorphic VT: 40% No pt with inducible sustained VT or VF	● Inducibility of nonsust VT did not provide prognostic information. ● EP studies of limited value in diagnosis, treatment of LQTS patients.
● Giustetto C EHJ 2006 (51) ● 16926178	**Study type:** Retrospective single center **Size:** 29	**Inclusion criteria:** Short QTc ≤340 msec and personal or family Hx of CA. 73% males. **Exclusion criteria:** N/A	**1° endpoint:** outcomes with AICD or hydroquinidine **Results:** Median age dx 30y (4-80); 62% symptomatic: syncope 24%, AF 31%. 34% ACA (10 patients); 2/10 had CA in infancy. In 28% ACA was initial symptom. ICD implanted in 14; 10 hydroquinidine. Median followup 23 mo (9-49), one pt with appropriate ICD shock. No pt on hydroquinidine had SCD or syncope. ES 18/29: Ventricular ERP 140-180 msec. VF induced in 61% (11/18); 3/6 with documented VF had inducible VF: sensitivity 50%. AERP CL 600: 120-180 ms, mean 157.	●Short QTS may be a cause of SCD in infancy ● Hydroquinidine may be proposed in children or patients not suitable for AICD ● PES sensitivity 50%
● Mahida S JACC 2015 (52) ● 25593056	**Study type:** multicenter observational **Size:** 81	**Inclusion criteria:** Patients with ER and ACA due to VF underwent EPS. Mean age 36 ± 13y. Followup with ICD interrogations.	**1° endpoint:** Inducibility of VF in patients with ACA and ER on ECG and outcomes. Followup 7±4.9 y **Results:** VF inducible in 22%.	● EPS not useful to risk stratify patients with prior VF arrest and ER

		Exclusion criteria: N/A	Recurrent VF in 33% of inducible VF, vs. 33% of those with non-inducible VF. p=NS, 0.93. VF inducibility did not correlate with max J wave amplitude or distribution	
● Giustetto C JACC 2011 (53) ● 21798421	**Study type:** retrospective multi-center **Size:** 53	**Inclusion criteria**: European Short QT Registry patients with QTc ≤360 msec with Hx sudden death, ACA, syncope; patients with QTc ≤340 msec included without symptoms. 75% males. Family Hx SCD/CA (11). Genotype positive 23% of probands: HERG in 4 families (N588K in 2, T6181 in 2; CACNB2b in one family) **Exclusion criteria:** N/A	**1° endpoint:** syncope, CA or approp ICD shocks SQTS **Results:** Mean Followup 64±27 mo. Median age 26 y (IQR 17–39). 62% symptomatic: 32% with ACA (13 patients) or sudden death (4), syncope (8), AF (6), palpatations (13). Age at CA 3 mo–62 y. Males: >90% of CA occurred between 14–40 y. Prevalence CA males 35%, females 30%. AICD in 24, hydroquinidine in 12. 11/12 with prior CA received ICD: 2 approp ICD shocks. 58% complications of ICD, inapprop shocks due to T wave oversensing 4/14. PES: 28 patients. VERP CL 600-500: mean 166 msec. AERP 166 msec. VF induced in 16/28: 3/28 with prior CA = sensitivity 37%, NPVs 58%. Overall event rate 3.3%/y: 4.9% in patients without AA drugs. Asymptomatic patients: 27. ICD implanted in 9 due to + family Hx or induced VF. Two long term	● SQTS assoc with SCD in all ages ● Symptomatic patients have high risk of recurrent arrhythmic events ● Patients treated with Hydroquinidine did not have arrhythmic events ● Asymptomatic patients: no CA/ICD shocks. ● PES not sensitive

			quinidine. One syncope; 2 nonsust VT on ICD.	
● Raczak et al. 2004 (54) ● 15226627	**Study type:** prospective cohort **Size:** 112 patients	**Inclusion criteria:** post-MI patients with documented VF, sustained VT, or syncope and NSVT **Exclusion criteria:** AF, SND or AV block, insulin-dependent DM, frequent (>5%) ectopic beats	**1° endpoint:** appropriate ICD shock or sudden or unwitnessed death **Results:** Sustained VT induced in 84% and 77% of patients who did or did not develop arrhythmia in follow-up (p=0.34) Baroreflex sensitivity <3.3 ms/mmHg was only predictor of arrhythmia recurrence in patients with EF <35% (sensitivity 79%, specificity 74%, positive and NPVs 83% and 68%)	● 97 patients had ICDs implanted ● EPS not useful in predicting arrhythmias in follow-up
● **AVID** ● Brodsky et al. 2002 (55) ● 12228785	**Study type:** substudy from prospective clinical trial **Size:** 572 patients	**Inclusion criteria:** patients with VF, VT with syncope, or sustained VT in the setting of LV dysfunction who underwent EPS **Exclusion criteria:** N/A	**1° endpoint:** death or recurrent VT/VF **Results:** 384 (67%) had inducible sustained VT or VF. Inducible patients were more likely to have CAD, previous infarction, and VT as their index arrhythmic event. Inducibility of VT or VF did not predict death or recurrent VT or VF.	● EPS is of limited value in patients with a Hx of sustained VA.
● **MADIT II** ● Daubert et al. 2006 (56) ● 16386671	**Study type:** substudy from prospective clinical trial **Size:** 593 patients	**Inclusion criteria:** Patients from MADIT II (previous MI, EF≤30%) who received ICDs and underwent EPS **Exclusion criteria:** control patients; ICD patients with no EPS	**1° endpoint:** sustained VT/VF **Results:** The 2 y KM event rate for VT or VF was 29.4% for inducible patients and 25.5% for noninducible patients (p=0.280, by log-rank analysis).	● ICD therapy for spontaneous VF was less common (p=0.021) in inducible patients than in noninducible patients.

			Inducible patients had a greater likelihood of experiencing ICD therapy for VT than noninducible patients (p=0.023).	
● **ABCD** ● Costantini et al. 2009 (9) ● 19195603	**Study type:** Prospective cohort; patients underwent EPS and T wave alternans testing; ICDs were implanted if either test was positive **Size:** 566 patients	**Inclusion criteria:** ischemic cardiomyopathy (EF ≤40%) and NSVT **Exclusion criteria:** unstable CAD; NYHA class IV; prior CA, sustained VT, or unexplained syncope; <28 d from MI, CABG, or PCI; permanent AF; on an AAD.	**1° endpoint:** appropriate ICD discharge or sudden death **Results:** 39 (7.5%) met the 1° end point at 1y T wave alternans achieved 1 y positive (9%) and negative (95%) predictive values comparable to EPS (11% and 95%). Event rate with both tests negative was 2% vs. 12% with both tests positive (p=0.017).	● Both tests somewhat helpful in risk stratification, but NPV is not 100%
● **DEFINITE** ● Daubert et al. 2009 (57) ● 19545338	**Study type:** substudy of DEFINITE **Size:** 204 patients	**Inclusion criteria:** dilated cardiomyopathy (EF≤35%), NSVT or frequent PVCs, and NYHA class I-III, randomized to ICD arm; noninvasive EPS performed through ICD **Exclusion criteria:** NYHA class IV or permanent pacemaker	**1° endpoint:** appropriate ICD therapy for VT/VF or arrhythmic death **Results:** Inducibility was found in 29 of 204 patients (VT in 13, VF in 16). 34.5% of the inducible group (10 of 29) experienced ICD therapy for VT or VF or arrhythmic death vs. 12.0% (21 of 175) of the noninducible patients (HR: 2.60; p=0.014).	● Inducibility of either VT or VF was associated with an increased likelihood of subsequent ICD therapy for VT or VF.
● Gold et al. 2000 (58) ● 11127468	**Study type:** prospective, multicenter **Size:** 215 patients	**Inclusion criteria:** patients undergoing diagnostic EPS who were in sinus rhythm and able to do bicycle exercise; reasons for EPS included syncope, CA, sustained VT, SVT	**1° endpoint:** SCD, sustained VT/VF or appropriate ICD therapy **Results:** KM survival analysis of the 1° end point showed that T-wave alternans predicted events	● Both T-wave alternans testing and EPS predicted VT.

		Exclusion criteria: not specified	with a RR:10.9; EPS had a RR: 7.1; and SAECG had a RR: 4.5. Multivariate analysis of 11 clinical parameters identified only T-wave alternans and EPS as independent predictors of events.	
● Gatzoulis et al. 2013 (59) ● 23588627	**Study type:** prospective cohort **Size:** 158 patients	**Inclusion criteria:** symptomatic idiopathic DCM >6 mo **Exclusion criteria:** Hx of aborted SCD or sustained VT; NYHA class IV; Hx of MI or myocarditis; significant VHD; hypertrophic or restrictive cardiomyopathy; alcohol-associated disease; cardiac toxicity	**1° endpoint:** total mortality and appropriate ICD activation **Results:** EPS performed in all patients; 44 (27.8%) had inducible VT/VF. ICDs implanted in 41/44 inducible patients and 28/114 noninducible patients. No difference in mortality Inducibility was associated with ICD activation events (30/41 inducible patients (73.2%) vs. 5/28 noninducible patients (17.9%), p=0.001.	● EPS inducibility of sustained VT/VF is predictive of future ICD activation but not total mortality in patients with CDM

Data Supplement 10. RCTs for Preventing SCD with HF Medications - (Section 5.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **CAPRICORN** ● Dargie et al. 2001 (60) ● 11356434	**Study type:** RCT **Aim:** to test whether carvedilol added to standard AMI care in	**Inclusion criteria:** Recent MI (3-12 d); EF <40% **Exclusion criteria**	**Intervention:** Carvedilol up to 25mg BID **Comparator:** Placebo	**1° endpoint:** All-cause mortality 12% vs 15%, HR: 0.77; 95% CI 0.60–0.98, p=0·03).	● BB improve mortality post-MI in patients with LV dysfunction ● VT/VF significantly reduced.

	patients with left ventricular dysfunction would improve outcomes. **Size:** 1959	Uncontrolled HF, unstable angina, hypotension, bradycardia		VT/VF: 3.9% vs. 0.9%. HR: 0.24; 95% CI 0.11–0.49; p<0.0001.	
● **US CARVEDILOL** ● Packer et al. 1996 (61) ● 8614419	**Study type:** RCT **Aim:** To determine the effects of carvedilol on survival and hospitalization **Size:** 1094	**Inclusion criteria:** CHF, LVEF<35% **Exclusion criteria** Major procedure or surgery within 3 mo.	**Intervention:** Carvedilol **Comparator:** Placebo	**1° endpoint:** survival and hospitalization - Mortality: 7.8% vs. 3.2 % - SCD 3.8% vs. 1.7%	● BB have a large effect on all cause and SCD mortality.
● **CIBIS II** ● No Authors listed (62) ● 10023943	**Study type:** RCT **Aim:** To investigate the efficacy of bisoprolol in decreasing all-cause mortality in chronic HF **Size:** 2647	**Inclusion criteria:** EF <35%, class III, IV, standard therapy, **Exclusion criteria** N/A	**Intervention:** Bisoprolol **Comparator:** Placebo	**1° endpoint:** all-cause mortality CIBIS-II was stopped early, All-cause mortality 11.8% vs 17.3%. p<0.0001. SCD 3.6% vs 6.3% p=0.0011.	● Bisoprolol reduces all-cause mortality and mortality from SCD.
● **MERIT HF** ● Hjalmarson et al. (63)2000 ● 10714728	**Study type:** RCT **Aim:** To examine the effects of metoprolol CR/XL on mortality,	**Inclusion criteria:** NYHA class II to IV, EF<40%; optimum standard therapy. **Exclusion criteria**	**Intervention:** Metoprolol succinate **Comparator:** Placebo	**1° endpoint:** mortality and hospitalization (time to event). - All-cause mortality: 34% - SCD: 41% RR	● BB reduce mortality in patients with HF.

	hospitalization, symptoms, and QoL in patients with HF. **Size:** 3991	N/A			
● **V-HEFT-II** ● Cohn et al. 1991 (64) ● 2057035	**Study type:** RCT **Aim:** To better define vasodilator therapy in HF **Size:** 804	**Inclusion criteria:** NYHA Class II-III **Exclusion criteria** N/A	**Intervention:** Enalapril **Comparator:** Isosorbide Dinitrite	**1° endpoint:** mortality Mortality 18% vs. 25% p=0.016. SCD: 14% vs. 23%, p<0.05 favoring enalapril	● Enalapril in patients with HF reduces mortality and SCD compared to Isosorbide Dinitrite
● **Val-HeFT** ● Cohn et al. 2001 (65) ● 11759645	**Study type:** RCT. **Aim:** To explore the efficacy of the addition of ARB to ACE-I therapy. **Size:** 5010	**Inclusion criteria:** NYHA II, III **Exclusion criteria** N/A	**Intervention:** Valsartan (added to ACE-I) **Comparator**: Placebo	**1° endpoint:** all-cause mortality Result: no difference in all-cause mortality.	● ARB added to ACE-I are not additionally helpful
● **VALIANT** ● Pfeffer et al. 2003 (66) ● 14610160	**Study type:** RCT **Aim:** To explore the effects of ARB added to ACE-I therapy. **Size:** 14,703	**Inclusion criteria:** Post-MI, LVEF<35%. Class I or II HF. **Exclusion criteria** N/A	**Intervention:** Valsartan 160 BID **Comparator:** Valsartan 80 BD Both added to enalapril	**1° endpoint:** all-cause or CV mortality No difference in either all-cause or CV related mortality	● ARB added to ACE-I are not additionally helpful
● **ELITE**	**Study type:** RCT	**Inclusion criteria:**	**Intervention:** Losartan **Comparator:** Captopril	**1° endpoint:** tolerability measure	● ARB better than ACE,

● Pitt et al. Lancet 1997 (67) ● 9074572	**Aim:** To determine the relative efficacy of ACE vs. ARB in HF **Size:** 722	NYHA II – IV, EF <40%, age >65 y **Exclusion criteria** N/A		2° measure: mortality All-cause mortality 4.8% vs. 8.7% (p=0.035) 36% relative risk reduction in SCD	● Only ARB trial to show a difference in SCD. ● Small trial, ● Mortality was a 2° end-point.
● **ELITE II** ● Pitt et al. 2000 (68) ● 10821361	**Study type:** RCT **Aim:** To confirm whether losartan is superior to captopril **Size:** 3152	**Inclusion criteria:** Age >60 y, class II-IV HF, EF <40%. **Exclusion criteria** N/A	**Intervention:** Losartan **Comparator:** Captopril	**1° endpoint:** all-cause mortality and SCD all-cause mortality (11.7 vs 10.4%) p=0.16 or sudden death or resuscitated arrests (9.0 vs 7.3%) p=0.08	● There were no significant differences in all-cause mortality or sudden death or resuscitated arrests
●**RALES** ●Pitt et al. 1999 (69) ● 10471456	**Study type:** RCT **Aim:** To explore whether a mineralocorticoid antagonist could reduce mortality in patients with HF. **Size:** 1663	**Inclusion criteria:** Class III, IV HF, EF <35%, **Exclusion criteria** N/A	**Intervention:** spironolactone **Comparator:** placebo	**1° endpoint:** all-cause mortality Death: 46% vs. 35%. p<0.001 SCD: 13% vs. 10%, p=0.02	● Spironolactone reduced all-cause mortality and SCD in patients with HF.
● **EPHESUS** ● Pitt et al. 2003 (70) ● 12668699	**Study type:** RCT **Aim:** To determine the effect of eplerenone on mortality among patients with AMI and LV dysfunction **Size:** 6632	**Inclusion criteria:** 3-14 d post-MI LVEF <40% **Exclusion criteria** Creatinine >2.5	**Intervention:** Eplerenone **Comparator:** Placebo	**1° endpoint:** All-cause mortality. Death: 14% vs. 17%. RR 0.85, p=0.008. SCD: 5% vs. 6% (p=0.03) **Safety endpoint (if relevant):**	● Eplerenone reduced all-cause and SCD in patients with HF

				Hyperkalemia: 5.5% eplerenone vs. 3.9% Hypokalemia: 8.4% eplerenone vs. 13.1%	
● **EMPHASIS** ● Zannad et al. 2011 (71) ● 21073363	**Study type:** RCT **Aim:** To evaluate the effect of eplerenone on patients with chronic systolic HF. **Size:** 2737	**Inclusion criteria:** Class II HF EF <35% **Exclusion criteria** AMI, NYHA III, IV, GFR <30	**Intervention:** Eplerenone **Comparator**: Placebo	**1° endpoint:** composite – death and HF hospitalization 1° composite endpoint: 18.3% vs. 25.9% (p<0.001) SCD: 4.4% vs. 5.5%, p=0.12 **Safety endpoint (if relevant):** Hyperkalemia: 11.8% vs. 7.2%	● Significant reduction on composite endpoint. Non-significant reduction in SCD.
● **PARADIGM** ● Desai et al. 2015 (72) ● 26022006	**Study type:** RCT **Aim:** 2° analysis of the original PARADIGM-HF trial to explore mode of death. **Size:** 8399	**Inclusion criteria:** Class II-IV HF EF <40% Guideline rec. med therapy **Exclusion criteria** AMI, NYHA III, IV, GFR <30	**Intervention:** Eplerenone **Comparator**: Placebo	**1° endpoint:** CV death (2° analysis exploring mode of death) CV death: HR: 0.80; 95% CI 0.72–0.89, p<0.001. Among CV deaths, SCD: HR: 0.80; p=0.008 death due to worsening HF: HR: 0.79; p=0.034	

Data Supplement 11. RCTs and Nonrandomized Trials, Observational Studies, and/or Registries Related to Surgery and Revascularization Procedures – (Section 5.5)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **STICH** ● Carson et al. 2013 (73) ● 24621972	**Aim:** Cause of death analysis for the 462 deaths during the original follow-up period of a median of 56 mo of the parent trial that compared CABG plus medical therapy to medical therapy alone to reduce death from any cause **Study type:** RCT **Size:** 1212 patients	**Inclusion criteria:** age ≥18 y, CAD amenable to CABG, and LVEF ≤35% **Exclusion criteria:** left main coronary stenosis ≥50% or Canadian Cardiovascular Society III-IV angina while receiving medical therapy	**Intervention:** CABG (plus medical therapy) **Comparator:** medical therapy alone	CABG therapy tended to reduce cardiovascular deaths (HR: 0.83; 95% CI: 0.68–1.03; p=0.09) and significantly reduced the most common modes of death: sudden death (HR: 0.73; 95% CI: 0.54–0.99; p=0.041) and fatal pump failure events (HR: 0.64; 95% CI: 0.41–1.00; p=0.05). Time-dependent estimates indicated that the protective effect of CABG principally occurred after 24 mo in both categories.	
● **STICHES** ● Velazquez et al. 2016 (74) ● 27040723	**Aim:** Compare CABG plus medical therapy to medical therapy alone to reduce death from any cause **Study type:** RCT **Size:** 1212 patients, with 9.8 y median followup	**Inclusion criteria:** age ≥18 y, CAD amenable to CABG, and LVEF ≤35% **Exclusion criteria:** left main coronary stenosis ≥50% or Canadian Cardiovascular Society III-IV angina while receiving medical therapy	**Intervention:** CABG (plus medical therapy) **Comparator:** medical therapy alone	**1° endpoint:** lower mortality with CABG (58.9%) than the medical therapy (66.1%) group. CABG vs. medical therapy, HR: 0.84; 95% CI: 0.73–0.97; p=0.02 by log-rank test.	● **Cardiac arrest outcomes:** ● Sudden/arrhythmic death 116 (19%) CABG, 154 (26%) medical therapy ● Within 30 d after randomization ● CA requiring CPR, 25 (4%) CABG and 2 (0.3%) medical therapy.

● **AVID Registry** ● Cook et al. 2002 (75) ● 12040343	**Aim:** determine whether patients with CAD who underwent revascularization after a life-threatening VA have improved survival rate when compared with those who did not undergo revasc; and evaluate the interaction of revascularization with ICD therapy **Study type:** observational **Size:** 3117 patients with life-threatening VA, of whom 2321 (77%) had CAD and 281 (17%) underwent CABG after the index event	**Inclusion criteria:** Ventricular fibrillation or symptomatic VT (defined as VT with syncope or VT with symptoms and LVEF ≤0.40 [VT/VF]). Also, patients with unexplained syncope who had inducible and symptomatic VT during EPS.	**Intervention:** revascularization; ICD	Patients who underwent revascularization had better survival than those who did not after the index event (HR: 0.67; p=0.002). With a mean follow-up period of 24.2±13.5 mo, crude death rates (with 95% confidence limits) were 21.4%±4.8% in the revascularization group and 29.4%±2.0% in the medically treated group. After adjustment, HR unchanged at 0.67, significance decreased to p=0.01. The association of better survival with ICD was consistent regardless of revascularization status	
● Mondésert et al. 2016 (76) ● 26806581	**Aim:** determine the impact of revascularization on recurrent VA or death **Study type:** observational	**Inclusion criteria:** LVEF ≥40%, first clinical sustained VA, without ACS	**Intervention:** coronary revascularization	Revascularization was not associated with significantly lower rate of recurrent VA or death (multivariable HR: 0.86; 95% CI 0.60–1.24, p=0.43) regardless of whether complete or incomplete (HR: 0.65; 95% CI 0.25–	

	Size: 274 patients, mean follow-up 6.2 y			1.69, p=0.37) or PCI or CABG (HR: 1.02; 95% CI 0.53–1.94, p=0.96). ICD associated with significantly lower mortality (HR: 0.23; 95% CI 0.09– 0.55, p=0.001).	
● Ngaage et al. 2008 (77) ● 18355509	**Aim:** assess the outcomes in patients undergoing CABG after ischemic VT/VF (after MI, with exercise, with CA) **Study type:** observational **Size:** 93 patients undergoing CABG	**Inclusion criteria:** patients who underwent CABG with preceding VT or VF	**Intervention:** CABG	Perioperative mortality was 6.5%, and 5 y survival rate was 88%, comparable to patients without prior VT/VF.	
● Every et al. 1992 (78) ● 1593036	**Aim:** estimate the possible effect of CABG on the subsequent outcome of patients who have been resuscitated from CA **Study type:** observational **Size:** 265 patients, 85 treated with CABG, 180 medical management,	**Inclusion criteria:** OHCA survivors, neurologically recovered, coronary disease, no prior CABG or other revascularization		Significant association of CABG with lower risk of subsequent CA during follow-up RR: 0.48; 95% CI 0.24–0.97, p=0.04). Also, lower cardiac mortality (RR: 0 .65; 95% CI 0.39–1.10, p=0.10).	

● van der Burg et al. 2003 (79) ● 14530201	**Aim:** determine relation between ischemia, viability, scar tissue (and revascularization), and the incidence of VA (and survival) in patients with CA and coronary disease **Study type:** observational **Size:** 153 patients, follow-up up to 3 y	**Inclusion criteria:** VA CA survivors with CAD	**Intervention:** N/A	Patients with ischemic/viable myocardium (N=73) were revascularized if possible. ICD in 112 (72%) patients. 15 cardiac deaths occurred and 42 (29%) patients had recurrent VA. Patients with events (death or recurrence) exhibited more often a severely depressed LVEF (≤30%), more extensive scar tissue, and less ischemic/viable myocardium on perfusion imaging and less frequently underwent revascularization. Multivariate analysis identified extensive scar tissue and LVEF ≤30% as the only predictors of death/recurrent VA	
● **PROCAT** ● Dumas et al. 2010 (80) ● 20484098	**Aim:** assess the effect of an invasive strategy for patients with OHCA on hospital survival. **Study type:** observational **Size:** 435 patients treated with an	**Inclusion criteria:** patients with OHCA with presumed cardiac etiology and with coronary angiogram performed at admission	**Intervention:** immediate PCI	At least 1 significant coronary lesion was found in 304 (70%) patients, in 128 (96%) of 134 patients with ST-segment elevation, and in 176 (58%) of 301 patients without ST-segment elevation. Multivariable analysis showed successful coronary	

	immediate coronary angiogram at admission with coronary angioplasty if possible			angioplasty to be an independent predictor of survival, regardless of the post resuscitation ECG pattern (OR: 2.06; 95% CI: 1.16–3.66).	
● **PROCAT II registry** ● Dumas et al. 2016 (81) ● 27131438	**Aim:** assess the association between early PCI and favorable outcome (cerebral performance category 1 to 2 at discharge) **Study type:** observational **Size:** 695 patients treated with an immediate coronary angiogram at admission without ST elevation on post-resuscitation ECG	**Inclusion criteria:** patients with OHCA with presumed cardiac etiology and with coronary angiogram performed at admission	**Intervention:** immediate PCI	At least 1 significant coronary lesion was found in 403 of 695 patients (58%). A PCI was performed in 199 of 695 (29%). A favorable outcome was observed in 87 of 200 (43%) in patients with PCI compared with 164 of 495 (33%) in patients without PCI (p=0.02). After adjustment, PCI was associated with a better outcome (adjusted OR: 1.80; 95% CI: 1.09–2.97, p=0.02).	
● **SYNTAX** ● Serruys et al. 2009 (82) ● 19228612	**Aim:** To show PCI is noninferior to CABG for major adverse cardiac or cerebrovascular event (i.e., death from any cause, stroke, MI, or repeat revascularization) during 12 mo	**Inclusion criteria:** previously untreated three-vessel or left main CAD (or both) with stable/unstable angina or atypical chest pain **Exclusion criteria:**	**Intervention:** PCI with Taxus Express paclitaxel-eluting stents **Comparator:** CABG	**1° endpoint:** rates of major adverse cardiac or cerebrovascular events at 12 mo were significantly higher in the PCI group (17.8%, vs. 12.4% for CABG; p=0.002)	● At 12 mo, the rates of death and MI were similar between the 2 groups; stroke was significantly more likely to occur with CABG (2.2%, vs. 0.6% with PCI; p=0.003).

	Study type: RCT **Size:** 1800 patients with 12 mo follow-up	Previous PCI or CABG, AMI, or the need for concomitant cardiac surgery			
● **SYNTAX** ● Milojevic et al. 2016 (83) ● 26764065	**Aim:** to investigate specific causes of death, and its predictors, after revascularization for complex CAD in patients **Study type:** RCT **Size:** 1800 patients with 12 mo follow-up	**Inclusion criteria:** previously untreated 3-vessel or left main CAD (or both) with stable/unstable angina or atypical chest pain **Exclusion criteria:** Previous PCI or CABG, AMI, or the need for concomitant cardiac surgery	**Intervention:** PCI with Taxus Express paclitaxel-eluting stents **Comparator:** CABG	**1° endpoint:** 97 deaths after CABG and 123 deaths after PCI during a 5 y followup. After CABG, 49.4% of deaths were cardiovascular, with the greatest cause being heart failure, arrhythmia, or other causes (24.6%). After PCI, the majority of deaths were cardiovascular (67.5%) and as a result of MI (29.3%). Treatment with PCI vs. CABG was an independent predictor of cardiac death (HR: 1.55; 95% CI: 1.09–2.33; p = 0.045).	● SCD: 24 (2.8%) with PCI, 15 (1.9%) with CABG, HR: 1.61; 95% CI: 0.83–3.11, p=0.16.
● **SCD-HeFT** ● Al-Khatib et al. 2008 (84) ● 18479330	**Aim:** examine the effect of the ICD on the outcomes of patients with prior coronary revascularization enrolled in SCD-HeFT	**Inclusion criteria:** Overall SCD-HeFT, NYHA class II or III CHF symptoms and a LVEF ≤35% due to ischemic or nonischemic heart disease.	**Intervention:** ICD **Comparator:** no ICD	There was no significant difference in ICD benefit across the revascularization subgroups (all p>0.1). There was a trend toward improved survival with an ICD in patients who had	

	Study type: RCT **Size:** of the 882 patients who met these inclusion criteria, 255 (29%) had no prior revascularization, 178 (20%) had prior PCI only, 284 (32%) had prior CABG only, and 165 (19%) had prior PCI and CABG.	This substudy, patients with ischemic heart disease who were not randomized to amiodarone (N= 884) and who had complete revascularization data (revascularization data were missing on 2 patients).		their CABG >2 y before randomization (HR: 0.71; 95% CI: 0.49–1.04) that was not observed in patients who had their CABG ≤2 y before randomization (HR:1.40; 95% CI: 0.61–3.24)	
● Nageh et al. 2014 (85) ● 25146702	**Aim:** assess the role of ICD in cardiac surgery patients with perioperative resuscitated VA arrest <3 mo post revascularization, and the role of ICDs in patients who had revascularization after SCD **Study type:** observational, evaluating total mortality and/or appropriate ICD therapy **Size:** 164 patients had cardiac surgery	**Inclusion criteria:** cardiac surgery and ICD within 3 mo	Overall group rates	The 1° endpoint of total mortality and appropriate shocks were observed in 52 35 (38%) and 28 (30%) of patients, respectively Conclusion was that recurrent VA are not prevented by CABG	

	and ICD within 3 mo; 93/164 had an ICD for sustained pre- or postoperative VT or fibrillation requiring resuscitation, mean follow-up 49 mo				

Data Supplement 12. Nonrandomized Trials, Observational Studies, and/or Registries of Arrhythmic Surgery and Revascularization for Arrhythmia Management – (Section 5.5.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Kumar et al. 2015 (86) ● 25925229	**Aim:** To characterized the reasons for VT ablation failure and describe alternative interventional procedures. **Study type:** Single center experience **Size:** 62	**Inclusion criteria:** Sixty-seven patients with VT refractory to 4±2 AAD and 2±1 previous endocardial/epicardial catheter ablation attempts underwent transcoronary ethanol ablation, surgical epicardial window (Epi-window), or surgical cryoablation **Exclusion criteria:** N/A	**1° endpoint:** abolishment of at least 1 inducible VT, complete success, partial success (abolishment of at least 1 spontaneous VT), and failure (residual inducibility of spontaneous VT). **Results:** Transcoronary ethanol ablation alone was attempted in 37 patients, OR-Cryo alone in 21 patients, and a combination of transcoronary ethanol ablation and OR-Cryo (5 patients), or transcoronary ethanol ablation and Epi-window (4 patients), in the remainder. Overall, alternative interventional procedures abolished ≥1 inducible VT and terminated	● The conclusion was that a collaborative strategy of alternative interventional procedures offers the possibility of achieving arrhythmia control in high-risk patients with VT that is otherwise uncontrollable with AAD and standard percutaneous catheter ablation techniques.

			storm in 69% and 74% of patients, respectively, although 25% of patients had at least 1 complication. By 6 mo post procedures, there was a significant reduction in ICD shocks (from a median of 8/mo to 1; p<0.001) and AAD requirement although 55% of patients had at least 1 VT recurrence, and mortality was 17%.	
● Anter et al. 2011 (87) ● 21673018	**Aim:** Evaluate the efficacy of preoperative electroanatomic and EP characterization of the VT substrate and circuit to guide surgical ablation in patients with NICM **Study type:** Single center experience **Size:** 62	**Inclusion criteria:** Eight patients with recurrent sustained VT refractory to AAD underwent endocardial and/or epicardial ablation procedures. After the unsuccessful percutaneous approach, surgical cryoablation was applied to the sites previously identified and targeted during the percutaneous procedure. **Exclusion criteria:** N/A	**1° endpoint:** Clinical VT and ICD shocks **Results:** During a mean followup period of 23 ± 6 mo (range, 15– 34 mo), 6 patients had significant reduction in VT burden as evident by a reduced number of ICD shocks after ablation (6.6–0.6 shocks per pt; p=0.026). Two patients died, 1 of progressive HF and 1 of sepsis.	• The authors concluded that VT circuits inaccessible to percutaneous ablation techniques are rare but can be encountered in patients with nonischemic cardiomyopathy. These VTs can be successfully targeted by surgical cryoablation guided by preoperative electroanatomic and EP mapping.
● Bhavani et al. 2007 (88) ● 18039225	**Aim:** To present variety of ablation strategies and technologies for surgical cryoablation of VT	**Inclusion criteria:** 3 patients who underwent succeesful surgical cryoablation after catheter failed. **Exclusion criteria:** N/A	**1° endpoint:** Successful elimination of VT **Results:** Case report. The specific approach (endocardial vs. epicardial, beating heart vs. arrested) and ablation device must be	● Patient with intraoperatively CARTO

	Study type: Single center experience-case report **Size:** 3		tailored to the patient's anatomy and presentation	
● Sartipy et al. 2006 (89) ● 16368337	**Aim:** The aim of this study was to evaluate the Dor procedure including VT surgery **Study type:** Single center experience **Size:** 53	**Inclusion criteria:** From July 1997 to December 2003, 53 consecutive patients with left ventricular aneurysm and VT underwent surgical ventricular restoration including nonguided endocardiectomy and cryoablation. Twenty-four patients had at least 1 preoperative episode of spontaneous VT, and 29 patients had inducible-only VT. **Exclusion criteria:** N/A	**1° endpoint:** Mortality and Vt inducible or spontaneous **Results:** Early mortality was 2 of 53 (3.8%). Mean followup was 3.7 y. At 1, 3, and 5 y overall actuarial survival was 94%, 80%, and 59%, respectively. Surgical success rate in patients with preoperative spontaneous VT was 91%. Inducible VT was found in 5 of 35 patients who underwent postoperative programmed stimulation. There was no arrhythmia-related late death and there was no loss to follow-up.	● Authors concluded that the Dor procedure including endocardiectomy and cryoablation yields a very high (90%) freedom from spontaneous VT and eliminates the need for an ICD in most patients ● Karolinska Institute is a specialized center.
● Choi et al. 2015 (90) ● 25697752	**Aim:** The aim is to describe surgical cryoablation of VA from the LVOT region inaccessible for ablation because of epicardial fat or overlying coronary arteries **Study type:** Single center experience **Size:** 4	**Inclusion criteria:** During the period from March 2009 to March 2014, 190 consecutive patients with focal VA originating from the LVOT underwent ablation at Brigham and Women's Hospital, Boston. The study describes 4 patients (2%) who underwent surgical cryoablation.	**1° endpoint:** Patients outcomes. **Results:** Surgical cryoablation was successful in 3 of the 4 patients. The 4th patient subsequently had successful endocardial catheter ablation. During a mean followup of 22 ± 16 mo (range 4–42 mo), all patients showed abolition of or marked reduction in symptomatic VA. However, 1 patient subsequently required	● The authors concluded that surgical cryoablation is an option for highly symptomatic drug-resistant VAs emanating from the LVOT region. Yet, the procedure is not effective for all patients, and coronary injury is a risk.

		Exclusion criteria: N/A	percutaneous intervention to the LAD; another developed progressive left ventricular systolic dysfunction caused by NICM; and a third patient underwent permanent pacemaker implantation because of complete AV block after concomitant aortic valve replacement.	
● Patel et al. 2016 (91) ● 26377813	**Aim:** to determine effectiveness of hybrid surgical epicardial mapping and ablation at the time to LVAD placement **Study type:** Single center experience. Retrospective review. **Size:** 5	**Inclusion criteria:** From March 2009 to October 2012, 5 patients (4 men and 1 woman, age range 52–73 y) underwent open chest EPS and epicardial mapping for recurrent VT while the heart was exposed during the period of LVAD implantation **Exclusion criteria:** N/A	**Endpoint:** post LVAD VA. **Results:** Epicardial mapping was considered if patients had recurrent VT despite failed prior endocardial ablation and/or electrocardiogram (EKG) features of an epicardial exit. Activation and/or a substrate mapping approach were employed during all procedures. 3 of 5 patients (60%) had acute procedural success. In all patients, VT was either eliminated or significantly reduced with epicardial ablation. 1 patient had mediastinal bleeding delaying sternal closure. During a follow-up period of 363±368 d, 4 patients died due to nonarrhythmic causes.	● Open-chest hybrid epicardial mapping and ablation for recurrent VT is feasible and can be considered in select patients during the period of LVAD implantation.
● Mulloy et al. 2013 (92) ● 22520722	**Aim:** to determine whether intraoperative cryoablation in select	**Inclusion criteria:** 50 consecutive patients undergoing implantation of the HeartMate II LVAD	**1° endpoint:** post LVAD ventricualr arrhythmias.	● Postoperative VA can be minimized by preoperative risk assessment and intraoperative treatment. Localized cryoablation in select patients offers

	patients reduces the incidence of postoperative VA after LVAD. **Study type:** Single center experience. Retrospective review. **Size:** 14	were examined. 14 of these patients had recurrent preoperative VA. Of those patients with recurrent VA, half underwent intraoperative cryoablation (Cryo: N=7) and half did not (NoCryo: N=7). **Exclusion criteria:** N/A	**Results:** Compared with NoCryo, the Cryo group had significantly decreased postoperative resource use and complications (p<0.05). Recurrent postoperative VA did not develop in any of the Cryo patients (p=0.02).	promising early feasibility when performed during HeartMate II LVAD implantation. ● None of the Cryo patients had recurrent postoperative VA compared with 4 (57%) of the NoCryo group (p=0.02).

Data Supplement 13. RCTs for Autonomic Modulation – (Section 5.6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Schwartz PJ et al. 1992 (93)	**Study type:** RCT **Aim:** To explore the influence of BB vs. LCSD in patients at high risk for SCD. **Size:** 144 high risk; 869 low risk	**Inclusion criteria:** Patients post-MI (30 d); High risk (evidence of Vfib or Vtach); low risk (no evidence of VF or VT. **Exclusion criteria** N/A	**Intervention:** High risk: 1:1:1 BB (oxprenolol) vs. LCSD; Low risk: BB vs. placebo. **Comparator:** Placebo	**1° endpoint:** SCD. 22 mo High Risk: Placebo 21.3% Oxprenolol 2.7% LCSD 3.6% Low Risk: Placebo: 5.2% Oxprenolol: 1.6%	● LCSD may be considered as a possible alternative for high-risk patients with contraindications to BB.
● Krittayaphong et al. 2002 (94) ● 12486439	**Study type:** RCT **Aim:** To determine the efficacy of atenolol in the treatment of symptomatic VA	**Inclusion criteria:** VA with LBBB, inferior axis morphology. Symptomatic (VA disturbed their daily activities) **Exclusion criteria**	**Intervention:** Atenolol 50-100mg/day **Comparator:** Placebo	**1° endpoint:** Atenolol significantly decreased PVC count (p=0.001) and average heart rate (p<0.001) compared to placebo. Both placebo and	● BB may be useful for patients with RVOT and symptomatic VA.

	from RVOT compared with placebo **Size:** 52	SHD.		atenolol decreased symptom frequency.	

Data Supplement 14. Nonrandomized Trials, Observational Studies, Guidelines, and/or Registries for Autonomic Modulation – (Section 5.6)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Vaseghi et al. 2014 (95) ● 24291775	**Study type:** retrospective chart review **Aim:** To describe the experiences of patients with VT storm who underwent cardiac sympathetic denervation. **Size:** N= 41 (14 LCSD; 27 BCSD)	**Inclusion criteria:** VT storm (>3 events requiring treatment in 24 h) or refractory VA and ICD shocks who underwent cardiac sympathetic denervation between April 2009 and December 2012. **Exclusion criteria:** N/A	**1° endpoint:** Survival free of ICD shocks. **Results:** • Survival free of ICD shocks: 30% in LCSD; 48% in the BCSD. (p=0.04) • number of shocks decrease from Mean of 19 pre CSD to 2.3 (p<0.001)	● Bilateral cardiac sympathetic denervation appears better than LCSD
● Ajijola et al. 2012 (96) ● 22192676	**Study type:** Case Series **Aim:** To describe the experiences of patients with bilateral cardiac sympathetic denervation (or RCSD after unsuccessful LCSD) **Size:** N=6	**Inclusion criteria:** Patients with ongoing VAs with LCSD and maximal med therapy **Exclusion criteria:** N/A	**1° endpoint:** Reduction in Ventricular events **Results:** • Complete response in 4/6 • Partial response in 1/6 • No response in 1/6 (PMVT)	● Our study suggests that patients with incessant VA for whom no other therapeutic options exist, bilateral cardiac sympathetic denervation may be beneficial.
● Ukena et al. (97) ● 27364940	**Study type:** Multicenter (5) Case Series **Aim:** To describe the effect of renal denervation on refractory VT	**Inclusion criteria:** CHF; Recurrent VA refractory to medications and ablation **Exclusion criteria:** N/A	**1° endpoint:** Reduction in Ventricular events **Results:** Median VT/VF: • 4 wk prior =21 • 1 mo post =2 (p=0.004) • 3 mo post =0 (p=0.006)	● Renal sympathetic denervation appeared safe and was associated with a reduction in VT/VF events.

	Size: N=13		No peri-procedural adverse events Baseline BP was low but no change in BP.	
● Grimaldi et al. 2012 (98) ● 22877745	**Study type:** Case Series (from patients enrolled in an under-enrolled RCT – trial was a 2 mo alternating on/off design.) **Aim:** To describe the experiences of patients with SCS on **Size:** N=2	**Inclusion criteria:** Patients with CM, ICDs and previous VF or 2xVT **Exclusion criteria:** N/A	**1° endpoint:** Ventricular arrhythmia **Results:** Patient 1 had a 75% reduction in VA with SCS on Patient 2 had a 100% reduction in VA with SCS on. (These are the authors reports, numbers in the table don't quite add to this. Not sure how the math was done)	● SCS may decrease the rate of VA.

Data Supplement 15. RCTs Comparing Acute Management of Specific Arrythmias - (Section 6)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Kudenchuk et al. 2016 (99) ● 27043165	**Aim:** Compare amiodarone, lidocaine, placebo in OHCA with shock-refractory VF or pulseless VT **Study type:** RCT double-blind, placebo controlled **Size:** 3,026 patients	**Inclusion criteria:** 18 y or older with OHCA and shock refractory VF or pulseless VT. IV access **Exclusion criteria:** Already received lidocaine or amiodarone, hypersensitivity to these drugs	**Intervention:** IV amiodarone or lidocaine; repeated once if VF/VT persisted after initial dose and repeat shocks **Comparator:** IV normal saline repeated once if VF/VT persisted after	**1° endpoint:** No difference in survival to hospital discharge: amiodarone (24.4%), lidocaine (23.7%), placebo (21.0%). Amiodarone vs. placebo 3.2% points (95% CI: -0.4–7.0; p=0.08); lidocaine vs. placebo 2.6% points (95% CI: -1.0–6.3; p=0.16); Amiodarone vs. lidocaine	● Neurologic outcomes similar More amiodarone patients required temporary pacing; otherwise, no difference in drug related adverse events ● Trial may have been underpowered to show amiodarone benefit over placebo Note: An editorial (100) suggesting use of amiodarone

			initial dose and repeat shocks	0.7% points (95% CI: -3.2–4.7; p=0.70) In witnessed arrest, survival to hospital discharge with amiodarone and lidocaine was higher than with placebo. The absolute risk difference for amiodarone vs. placebo was (5.0 % points, p=0.04) and for lidocaine vs. placebo was (5.2 % points, p=0.05)	or lidocaine for witnessed arrest as there was a significant reduction in shocks and fewer CPR events in hospital.
● Jacobs et al. 2011 (101) ● 21745533	**Aim:** Compare epinephrine with normal saline during OHCA treated following ACLS guidelines **Study type:** RCT double blind, placebo controlled **Size:** 601 patients	**Inclusion criteria:** Age ≤18 y with OHCA, CPR started by paramedics **Exclusion criteria:** Traumatic OHCA	**Intervention:** 1 ml aliquots of epinephrine 1:1000 following current ACLS guidelines **Comparator:** 1 ml aliquots of 0.9% sodium chloride following current ACLS guidelines	**1° endpoint:** Survival to hospital discharge not different: 1.9% for placebo and 4% for epinephrine (OR: 2.2; 95% CI: 0.7–6.3). Return of spontaneous circulation 8.4% for placebo and 23.5% for epinephrine (OR: 3.4; 95% CI: 2.0–5.6)	● Epinephrine improved return to spontaneous circulation but not survival to hospital discharge ● Limitations: Inadequate sample size to access hospital survival. ● Quality of ACLS not evaluated ● Adverse events not listed

● Piccini et al. 2008 (102) ● 19026290	**Aim:** Compare outcomes in patients with MI and sustained VT/VF treated or not treated with BB **Study type:** Prospective, multicenter registry of patients with acute MI **Size:** 306 patients with sustained VT/VF	**Inclusion criteria:** acute MI with sustained VT/VF and/or high Killip classification **Exclusion criteria:** N/A	**Intervention:** BB within 24 h of MI **Comparator:** No BB	**1° endpoint:** BB therapy within 24 h was associated with decreased in-hospital mortality in patients with sustained VT/VF (RR: 0.28; 95% CI: 0.10–0.75, p=0.013) without evidence of worsening HF ● 55.2% of patients with sustained VT/VF were treated with BB within 24 h of MI	● Sustained VT/VF was a major predictor of in-hospital death (RR: 4.18; 95% CI: 2.91–5.93)
● Dorian et al. 2002 (103) ● 11907287	**Aim:** Compare IV lidocaine with IV amiodarone as adjunct to defibrillation in OHCA **Study type:** RCT placebo controlled **Size:** 347 patients	**Inclusion criteria:** Age ≤18 y with OHCA due to VF. **Exclusion criteria:** traumatic, or OHCA	**Intervention:** Patients randomized to IV amiodarone plus IV lidocaine placebo or IV lidocaine plus IV amiodarone placebo to treat VF resistant to 3 shocks, at least 1 dose of IV epinephrine, and then 4th shock. Or, recurrent VF after successful initial shock. **Comparator:** 1 ml aliquots of 0.9% sodium chloride following current ACLS guidelines	**1° endpoint:** Amiodarone had higher survival to hospital admission than lidocaine: 28% with amiodarone vs. 12% with lidocaine (OR: 2.17; 95% CI: 1.21–3.83; p=0.009). Of 42 patients surviving to hospital admission, 9 (5%) survived to hospital discharge in the amiodarone group and of 20 initial survivors in the lidocaine group, 5 (3%) were discharged (p=0.34).	● Increased survival with shorter interval from dispatch to receiving study drugs. ● Patients with VF had better survival than those with asystole or PEA. ● Amiodarone did not improve survival to hospital discharge ● Limitation: not powered to show amiodarone improved survival to discharge. ● No adverse events noted.

● Hassan et al. 2002 (104) ● 11777881	**Aim:** IV magnesium given early during CPR for VF will improve survival. **Study type:** RCT, double blind, placebo controlled **Size:** 105 patients	**Inclusion criteria:** Patients ≥18 y with OHCA and refractory or recurrent VF **Exclusion criteria:** Traumatic OHCA	**Intervention:** Patients received 2–4 g of magnesium **Comparator:** Placebo	**1° endpoint:** IV magnesium did not improve survival to hospital admission: 17% for magnesium and 13% for placebo (OR: 1.69; 95% CI: -10%–18%)	● No benefit from magnesium ● Limitations: Possible inadequate magnesium dose ● No adverse effects listed
● **MAGIC** ● Thel et al. 1997 (105) ● 9357406	**Aim:** Determine if IV magnesium improves return to spontaneous circulation (measurable BP and pulse) for 1 h after in-hospital CA **Study type:** RCT, placebo controlled **Size:** 156 patients	**Inclusion criteria:** Adult patients with CA in the ICU or hospital wards **Exclusion criteria:** Patients in emergency department. Advanced heart block, chronic renal failure, already on magnesium	**Intervention:** IV magnesium bolus followed by a 24 h infusion **Comparator:** Normal saline	**1° endpoint:** Magnesium did not improve return to spontaneous circulation: 54% with magnesium and 60% with placebo (95% CI: 0.41–0.47; p=0.44)	● No benefit of magnesium for survival to 24 h or hospital discharge ● No adverse effects
● Somberg et al. 2002 (106) ● 12372573	**Aim:** Establish the effectiveness of IV amiodarone for shock resistant VT. **Study type:** RCT, double-blinded, parallel design **Size:** 29 patients	**Inclusion criteria:** Patients with incessant (shock resistant) VT not treated with prior antiarrhythmics **Exclusion criteria:** Already on AAD	**Intervention:** IV amiodarone (or IV lidocaine) followed by a 24 h infusion. If the first medication failed to terminate VT, patients were crossed over to the alternative medication. **Comparator:** Lidocaine	**1° endpoint:** Amiodarone was more effective than lidocaine: amiodarone terminated VT in 78% and lidocaine 27% (p<0.01). OR and CI not listed. 24 h survival 39% on amiodarone and 9% on lidocaine (p<0.01). More hypotension with lidocaine than amiodarone (28% vs. 7%,	● Amiodarone was more effective than lidocaine for terminating VT with improved 24 h survival. ● Limitations: Drug related hypotension with amiodarone less frequent than with lidocaine.

				p=0.06). Bradycardia equal	
● Kudenchuk et al. 1999 (107) ● 10486418	**Aim:** Determine if amiodarone improves the rate of successful resuscitation after OHCA **Study type:** RCT, double blinded, placebo controlled **Size:** 504 patients	**Inclusion criteria:** Patients <18 with OHCA due to VF or pulseless VT that remained present after ≥3 shocks, with IV access **Exclusion criteria:** Absence of IV access, VF, or pulseless VT	**Intervention:** IV amiodarone (single dose) after receiving 1 mg epinephrine **Comparator:** Placebo (polysorbate 80, dilutant, single dose) after receiving 1 mg epinephrine	**1° endpoint:** Amiodarone improved survival to hospital admission: 44% on amiodarone and 34% on placebo (OR: 1.6; 95% CI: 1.1–2.4; p=0.02)	● Amiodarone improved survival to hospital with no difference in duration of resuscitation, number of shocks, need for other antiarrhythmics ● Limitations: lack for power to detect treatment effect on survival to hospital discharge ● More hypotension with amiodarone (59% vs. 48%, p=0.04)
● Callaham et al. 1992 (108) ● 1433686	**Aim:** To determine the relative efficacy of high vs. standard dose catecholamines in initial treatment of OHCA **Study type:** RCT, double blind **Size:** 816 patients	**Inclusion criteria:** Adults with OHCA who would receive epinephrine by AHA ACLS guidelines **Exclusion criteria:** None listed	**Intervention:** High dose epinephrine (15 mg), high dose norepinephrine (11 mg), or standard dose epinephrine blindly substituted for ACLS doses of epinephrine **Comparator**: standard dose epinephrine (no placebo)	**1° endpoint:** High dose epinephrine significantly improved the rate of return of spontaneous circulation: 13% for high dose epinephrine, 8% receiving standard dose epinephrine (p=0.01). 18% of high dose epinephrine and 10% of standard dose epinephrine patients admitted to hospital (p=0.02)	● High dose epinephrine improved admission to hospital but no difference in dismissal from hospital ● Trends for norepinephrine were not different ● Limitations: low hospital dismissal rate ● No adverse effects

● Gueugniaud et al. 1998 (109) ● 9828247	**Aim:** compare repeated low dose vs high dose epinephrine in OHCA **Study type:** Prospective, multicenter, randomized **Size**: 3327 patients	**Inclusion criteria**: OHCA patients with VF/VT despite defibrillation shocks, or asystole /hypotensive VT **Exclusion criteria:** Inadequate data	**Intervention:** High dose epinephrine, 5 mg, up to 15 doses **Comparator**: standard dose epinephrine, 1 mg, following ACLS protocol	**1° endpoint:** 40.4% of 1677 patients in the high dose group had a return of spontaneous circulation compared to 36.4% of 1650 patients in the standard dose group (p=0.02). There was no difference in survival to hospital discharge (2.3% vs 2.8%. p=0.34).	● Long-term survival after OHCA was no better with repeated high doses of epinephrine than with repeated standard doses.
● Gorgels et al. 1996 (110) ● 8712116	**Aim:** Determine the relative efficacy of procainamide and lidocaine for treating spontaneous monomorphic VT **Study type:** Randomized, open label, parallel study **Size:** 29 patients	**Inclusion criteria:** Adult patients with spontaneous monomorphic VT **Exclusion criteria:** Patients with AMI and those with poor hemodynamic tolerance	**Intervention:** IV procainamide (10 mg/kg at 100 mg/min) or lidocaine (1.5 mg/kg over 2 min) **Comparator:** Procainamide or lidocaine (no placebo)	**1° endpoint:** Procainamide was more effective than lidocaine: 27% of VT episodes responded to lidocaine and 77% to procainamide (p<0.01)	● Procainamide was superior to lidocaine for terminating VT ● Limitations: No patients with AMI or ischemia ● Significant lengthening of QRS and QT on procainamide
● Ho et al. 1994 (111) ● 7912296	**Aim:** Determine the relative efficacy of lidocaine and sotalol for terminating spontaneous VT not causing CA **Study type:** RCT, double blind **Size:** 33 patients	**Inclusion criteria:** Adult patients with sustained VT **Exclusion criteria:** Already on an antiarrhythmic, hypotension requiring immediate cardioversion, known adverse reaction to either medicantion	**Intervention:** IV sotalol (100 mg) **Comparator:** IV lidocaine (100 mg) Cross-over to second drug if VT persisted after 15 min	**1° endpoint:** Sotalol was more effective than lidocaine for terminating VT: 69% with sotalol and 18% with lidocaine (95% CI: 22%–80%; p=0.003)	● No 2° endpoints ● Limitations: no placebo control; small number of patients ● 1 death in each drug group after the first drug and 1 death in each group after both drugs

● Levine et al., 1996 (112) ● 8522712	**Aim:** Response rate and safety of intravenous amiodarone in patients with VT refractory to standard therapies. **Study type:** prospective, controlled **Size:** 273 patients	**Inclusion criteria:** Patients with recurrent hypotensive VT refractory to lidocaine, procainamide and bretylium. **Exclusion criteria:** Cardiogenic shock; significant hepatic dysfunction or pulmonary disease; Hx of TdP; congenital QT prolongation; bradyarrhythmias or AV block (unless pacemaker present).	**Intervention:** Patients were randomized to receive 1 of 3 doses of intravenous amiodarone: 525, 1,050 or 2,100 mg/24 h by continuous infusion over 24 h. **Comparator:** As above	**1° endpoint:** 110 patients (40.3%) survived 24 h without another hypotensive VT episode **Safety endpoint:** Adverse events requiring drug discontinuation	● Significantly longer time to first recurrence in the 2 higher dose groups ● Hypotension required vasopressor therapy in 38 patients (14%) and led to death in 6 (2%).
● Teo et al. 1993 (113) ● 8371471	**Aim:** Assess the effectiveness of AAD on mortality in patients with AMI **Study type:** Metanalysis **Size:** 138 randomized trials, 98,000 patients	**Inclusion criteria**: Patients with AMI randomized to AAD therapy **Exclusion criteria:** Inadequate study design	**Intervention:** AAD **Comparator**: Placebo, standard agents	**1° endpoint:** 660 deaths in 11,712 patients receiving Class I agents and 571 deaths in 11,517 controls (OR: 1.14; 95% CI: 1.01–1.28; p=0.03). 778 patients received amiodarone and 77 died, compared with 101 deaths in 779 control patients (OR, 0.71; 95% CI, 0.51–0.97, p=0.03). 26,973 patients received BB and 1,464 died compared with 1,727 deaths in 26,295 controls (OR: 0.81; 95% CI, 0.75–0.87, p=0.00001)	● The routine use of Class I agents (lidocaine, procainamide) was associated with increased mortality after MI. ● BB reduced morality ● The amiodarone data was limited “but promising”

● Elzari et al. 2000 (114) ● 10639301	**Aim:** Assess the mortality associated with amiodarone in patients with AMI **Study type:** Single center, randomized **Size:** 1,073 patients	**Inclusion criteria**: Acute MI, no contraindications to study drug **Exclusion criteria:** Contraindication to amiodarone	**Intervention**: IV or PO amiodarone **Comparator**: Placebo	**1° endpoint:** The study was modified after the first 516 patients showed higher mortality on amiodarone than placebo (16.30% vs. 10.16%; p=0.04). **Safety endpoint**: Increased mortality on high dose amiodarone	● Amiodarone given by IV and PO to a total of 2,700 mg in the first 48 h after MI was associated with increased mortality. ● Reducing the dose by half showed amiodarone and placebo mortality were similar

Data Supplement 16. Nonrandomized Trials, Observational Studies, and/or Registries Comparing Acute Management of Specific Arrythmias – (Section 6)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Piccini et al. 2008 (102) ● 19026290	**Study type:** Registry of patients in the VALsartan In Acute myocardial iNfarcTion trial (VALIANT) **Size:** 306 patients	**Inclusion criteria:** Patients with AMI who experienced sustained VT/VF **Exclusion criteria**: inadequate data	**1° endpoint:** death **Results** 306 of 5,391 patients (5.7%) in the VALIANT registry had sustained VT/VF with a mortality of 20.3%. 55.2% were treated with IV or oral BB which were associated with decreased in-hospital mortality (RR: 0.28; 95% CI: 0.10–0.75, p=0.013)	● Sustained VT/VF was common with AMI ● In patients with sustained VT/VF, BB therapy in the first 24 h after AMI was associated with decreased early mortality without worsening HF.
● Link et al 2015 (115) ● 26472995	**Study type:** Guidelines	**Inclusion criteria:** Acute treatment of patients with VA	Expert developed guidelines Reviews role of direct current cardioversion, epinephrine, magnesium, and AAD therapy for the treatment of acute VA	● Electrical cardioversion is recommended for the initial treatment of VF, poorly tolerated VT, and polymorphic VT. ● The appropriate use of AAD, epinephrine, and magnesium for the treatment of acute VA is discussed

● Herlitz et al.1997 (116) ● 9044490	**Study type:** Retrospective, observational study of patients with OHCA due to VF **Size:** 1,212 cases; 405 receiving lidocaine	**Inclusion criteria:** All patients with OHCA due to VF. CPR by single center emergency department **Exclusion criteria:** Traumatic cause of OHCA	**1° endpoint:** Survival to hospital discharge **Results:** Patients receiving lidocaine had a higher return of spontaneous circulation ($p<0.001$) and hospitalized alive (38% vs. 18%; $p<0.01$). Survival to discharge did not differ	● Lidocaine improved the return to spontaneous circulation and hospitalization ● Lidocaine did not improve rate of discharge from hospital
● Markel et al. 2010 (117) ● 20624142	**Study type:** Retrospective, observational, cohort **Size:** 665 patients, 176 received procainamide	**Inclusion criteria:** Witnesses, OHCA due to VF or pulseless VT treated by King County, WA, emergency services. **Exclusion criteria:** Traumatic cause of OHCA, asystolic OHCA	**1° endpoint:** The association between procainamide and survival **Results:** Procainamide associated with a lower survival to hospital discharge (OR: 0.52; 95% CI: 0.36–0.75)	● Procainamide associated with more shocks, pharmacologic interventions, and longer resuscitations. ● Procainamide did not improve survival
● Stiell et al. 2004 (118) ● 15306666	**Study type:** Multicenter, controlled prospective trial **Size:** 5638 patients; 1391 enrolled in the rapid defibrillation phase and 4247 in the ACLS phase	**Inclusion criteria:** OHCA **Exclusion criteria:** traumatic cause of SCD	**1° endpoint:** survival to hospital admission and discharge **Results:** The rate of hospital admission increased from the defibrillation phase to the ACLS phase (10.9% vs 14.6%, $p<0.001$). Survival after rapid defibrillation (OR: 3.4; 95% CI: 1.4–8.4) was better than ACLS (OR: 1.1; 95% CI: 0.8–1.5) and bystander CPR (OR: 3.7; 95% CI: 2.5–5.4)	● The addition of ACLS did not improve the rate of survival over the use of rapid defibrillation in OHCA.
● Haqihara et al. 2012 (119) ● 22436956	**Study type:** Prospective, observational	**Inclusion criteria:** Age ≥18 y with OHCA treated by emergence medical service personnel	**1° endpoint:** Return of spontaneous circulation, survival at 1 mo, neurologic outcome	● Pre-hospital epinephrine for OHCA was associated with improved return to spontaneous circulation.

	Size: 417,188 patients	**Exclusion criteria:** Traumatic cause of OHCA	**Results:** Epinephrine improved return of spontaneous circulation (OR: 2.36; 95% CI: 2.22–2.50; p<0.001); but had an adverse effect on long-term outcome measures (1 mo survival, OR: 0.46; 95% CI: 0.42–0.51; and neurologic, OR: 0.31; 95% CI: 0.26–0.36)	● Pre-hospital epinephrine for OHCA was associated with worse 1 mo survival and neurologic outcomes.
● Donnino et al. 2014 (120) ● 24846323	**Study type:** Prospective data collection, observational **Size:** 25,095 patients	**Inclusion criteria:** Adults with CA in hospital with asystole or pulseless VT as the initial rhythm **Exclusion criteria:** Cardiac arrest in emergency department, ICU, missing data, received vasopressin	**1° endpoint:** Survival to hospital discharge **Results:** Survival was increased by early administration of epinephrine: 1–3 min (reference group) (OR: 1.0); 4–6 min (OR: 0.91; 95% CI: 0.82–1.0; p=0.055); 7–9 min (OR: 0.63; 95% CI: 0.52–0.76; p<0.001).	● Patients with non-shockable CA in hospital had improved return of spontaneous circulation, survival in hospital, and neurologically intact survival with earlier administration of epinephrine
● Koscik et al. 2013 (121) ● 23523823	**Study type:** Retrospective database analysis **Size:** 686 patients	**Inclusion criteria:** Adults with OHCA **Exclusion criteria:** Traumatic cause of OHCA	**1° endpoint:** Does timing of epinephrine administration improve outcome **Results:** Early epinephrine was more likely to have return of spontaneous circulation (32% vs. 23.4%; OR: 1.59; 95% CI: 1.07–2.38)	● Early administration of epinephrine improved return of spontaneous circulation ● Early administration of epinephrine did not increase survival to admission or discharge ● Similar results were reported with PEA
● Spaulding et al. 1997 (122) ● 9171064	**Study type:** Retrospective, observational, consecutive patients	**Inclusion criteria:** OHCA survival **Exclusion criteria:** Non-cardiac cause of arrest	**1° endpoint:** Incidence of acute coronary occlusion and role of reperfusion therapy	● Acute coronary occlusion is frequent in survivors of OHCA and is predicted poorly by clinical and ECG findings ● Coronary angioplasty may improve survival

	Size: 84 patients		**Results:** 71% had significant CAD and 48% had coronary artery occlusion. In-hospital survival 38%. Successful angioplasty predicted survival (OR: 5.2; 95% CI: 1.1–24.5; p=0.04)	
● Cronier et al. 2011 (123) ● 21569361	**Study type:** Retrospective, observational, consecutive patients **Size:** 111 patients	**Inclusion criteria:** OHCA survivor, age <80 y, treated with mild hypothermia, hemodynamically stable **Exclusion criteria:** Non-cardiac cause of arrest	**1° endpoint:** Prognostic impact of routine PCI **Results:** 73% had CAD. Time from collapse to return of spontaneous circulation associated with mortality (OR: 1.05; 25th–75^{tth} percentile range, 1.03–1.08; p<0.001); Percutaneous intervention associated with survival (OR: 0.30; 25th–75th percentile range, 0.11–0.79; p=0.01)	● Routine coronary angiography with percutaneous intervention may improve survival following OHCA in patients treated with mild hypothermia who are hemodynamically stable
● Zanuttini et al. 2012 (124) ● 22975468	**Study type:** Retrospective, observational, consecutive patients **Size:** 93 patients	**Inclusion criteria:** OHCA survival, remained unconscious soon after recovery of spontaneous circulation **Exclusion criteria:** Non-cardiac cause of OHCA	**1° endpoint:** Independent determinants of in-hospital survival **Results:** Coronary angiography performed in 66 patients (71%); 48 emergent and 18 at 13±10 d. PCI in 52%; in hospital survival 54%. Emergency angiography (HR: 2.32; 95% CI: 1.23–4.38; p=0.009) and PCI (HR: 2.54; 95% CI: 1.35–4.8; p=0.004) related to in hospital survival	● Emergency coronary angiography and PCI, if indicated, appeared to improve survival. ● The study has significant limitations: no control group; and unconscious patients who had delayed procedures 18 d after OHCA is a poor comparative group.
● Dumas et al. 2016 (81) ● 27131438	**Study type:** Observational, multicenter registry	**Inclusion criteria:** OHCA survivor without an ST-elevation MI	**1° endpoint:** Favorable neurologic outcome	● 1/3 of OHCA patients without ST elevation had a culprit lesion and had a

	Size: 695 patients	**Exclusion criteria:** Inadequate data	**Results:** 199 patients (29%) had a PCI. 43% with PCI had a favorable outcome and 33% without PCI. (OR: 1.80; 95% CI: 1.09–2.97; p=0.02).	nearly 2-fold increase in favorable neurologic outcome. ● A favorable outcome was also predicted by a shockable rhythm, lower epinephrine dose, and shorter resuscitation.
● Kudenchuk et al. 2013 (125) ● 23743237	**Study type:** retrospective, cohort of patients with OHCA who did or did not receive prophylactic lidocaine **Size:** 1721 patients with OHCA due to VF or VT	**Inclusion criteria:** OHCA due to VF or VT. Age ≥18 y **Exclusion criteria:** Missing data points, no chance of survival when paramedics arrived	**1° endpoint:** re-arrest, hospital admission, survival **Results:** 1296 patients received prophylactic lidocaine and 425 did not. Prophylactic lidocaine reduced re-arrest from VF/VT (OR: 0.34; 95% CI: 0.26–0.44); non-shockable arrhythmias (OR: 0.47;95% CI: 0.29–0.78); higher hospital admission (OR: 1.88;95% CI, 1.28–2.76); and improved survival to discharge (OR, 1.49;95% CI: 1.15–1.95)	● Patients receiving lidocaine had a shorter time to a return of spontaneous circulation and higher BP ● Use of prophylactic lidocaine upon return to a spontaneous circulation after OHCA was associated with less recurrent VF/VT and higher rates of admission to hospital and survival to discharge.
● Nademanee et al., 2000 (126) ● 10942741	**Study type:** retrospective, observational **Size:** 49 patients	**Inclusion criteria:** ES with recent (72 h–3 mo) MI **Exclusion criteria:** MI <72 h	**1° endpoint:** Effect of beta blockade (left stellate ganglion blockade, esmolol, propranolol) on outcome (survival) **Results:** 1-wk mortality rate was higher in group not treated with beta blockade: 18 (82%) of the 22 patients died, all of refractory VF, compared to 6 (22%) of the 27 patients with beta blockade, 3 of refractory VF	● Sympathetic blockade is superior to standard ACLS therapy in treating ES patients.

			(p<0.0001). Patients who survived the initial ES event did well over the 1 y followup period: Overall survival was 67% with beta blockade compared with 5% without it (p<0.0001).	
● Sasson et al. 2010 (127) ● 20123673	**Study type:** Meta-analysis OF OHCA studies **Size:** 79 studies reporting 142,740 patients	**Inclusion criteria**: OHCA	**1° endpoint:** survival **Results:** Survival to hospital discharge was more likely among OHCA patients witnessed by a bystander (6.4% to 13.5%); witnessed by EMS (4.9% to 18.2%), received bystander CPR (3.9% to 16.1%), or were found in VF/VT (14.8% to 23%).	● Witnessed OHCA and arrest due to VF/VT treated with defibrillation had improved survival.
● Buxton et al 1987 (128) ● 3578051	**Study type:** single center, observational **Size:** 25 patients	**Inclusion criteria:** Sustained VT treated with IV verapamil	**1° endpoint:** adverse hemodynamics **Results:** 44% of 25 patients with sustained VT receiving IV verapamil had severe hypotension of loss of consciousness.	IV verapamil should not be used in patients with sustained VT
● Pellis et al. 2009 (129) ● 19010581	**Study type:** prospective, observational **Size:** 144 patients	**Inclusion criteria:** OHCA **Exclusion criteria**: Inadequate data	**1° endpoint:** return of spontaneous circulation and hospital discharge **Results:** Precordial thump had no effect on heart rhythm in 96% of patients. with return of spontaneous circulation in only 3 patients.	A pre-cordial thump did not delay other aspects of CPR and had no adverse effects; but efficacy was lacking.

● Volkman et al. 1990 (130) ● 2087859	**Study type**: single center, observational, consecutive patients **Size:** 47 patients	**Inclusion criteria:** patients with VT	**1° endpoint:** VT conversion following a pre-cordial thump **Results:** VT with a heart rate ≤160 BPM converted in 17 of 22 cases, and VT >160 bpm converted in 3 of 15 cases. 3 cases of VF and 7 cases of VFL failed to convert.	A pre-cordial thump converted VT in 77% of patients with a rate ≤160 bpm but only 20% if the rate was faster. VF and VFL did not convert.

Data Supplement 17. RCTs Secondary Prevention Sudden Death in Ischemic Heart Disease – (Section 7.1.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint and Results	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **AVID** ● The AVID Investigators 1997 (131) ● 9411221	**Aim:** To examine the effect on overall survival of initial therapy with an ICD as compared with amiodarone or sotalol in patients resuscitated from VF or symptomatic, sustained VT with hemodynamic compromise. **Study type:** RCT **Size:** 1016 patients	**Inclusion criteria:** patients who were resuscitated from near-fatal VF; sustained VT with syncope; or sustained VT with an LVEF ≤0.40 and symptoms suggesting severe hemodynamic compromise. **Exclusion criteria:** arrhythmia was judged to have a transient or correctable cause, excessively high risk (life expectancy <1 y, class IV HF, awaiting a heart transplant, or	**Intervention:** Therapy with ICD **Comparator:** Antiarrhythmic drugs - amiodarone or sotalol, (only 2.6% received sotalol)	**1° endpoint:** Overall survival was greater with the ICD, with unadjusted estimates of 89.3% as compared with 82.3% in the antiarrhythmic-drug group at 1 y, 81.6% vs. 74.7% at 2 y, and 75.4% vs. 64.1% at 3 y ($p<0.02$). The corresponding reductions in mortality (with 95% CI) with the ICD were 39±20%, 27±21%, and 31±21%	● Study terminated early after 1016 of 1200 patients enrolled ● 81% of patients had CAD ● **Conclusion:** Among survivors of VF or sustained VT causing severe symptoms, ICD is superior to AAD therapy for reducing overall mortality.

		requiring a balloon pump, other mechanical means, or inotropic drug administration for hemodynamic support) or excessively low risk (event occurring within 5 d of cardiac surgery or angioplasty, or occurring in-hospital <5 d after MI), previous ICD implant (or attempted implant), chronic serious bacterial infection, or were unable to give verbal assent due to neurologic impairment, or a contraindication to amiodarone			
● **CIDS** ● Conolly et al. 2000 (132) ● 10725290	**Aim:** To compare the efficacy of the ICD and amiodarone for the prevention of death in patients with previous sustained VA **Study type:** RCT	**Inclusion criteria:** in the absence of either recent AMI or electrolyte imbalance, they manifested any of the following: (1) documented VF; (2) OHCA requiring defibrillation or cardioversion; (3) documented,	**Intervention:** ICD **Comparator:** Amiodarone	**1° endpoint:** Death from any cause. A nonsignificant reduction in the risk of death was observed with the ICD, from 10.2%/y to 8.3%/y (RRR 19.7%; 95% CI: -7.7%–40%; p=0.142). A nonsignificant reduction in the risk of arrhythmic death was observed, from	● 82% had ischemic etiology ● **Conclusions:** CIDS provides further support for the superiority of the ICD over amiodarone in the treatment of patients with symptomatic sustained VT or resuscitated CA.

	Size: 659 patients	sustained VT causing syncope; (4) other documented, sustained VT at a rate ≥150 beats/min, causing presyncope or angina in a patient with a LVEF ≤35%; or (5) unmonitored syncope with subsequent documentation of either spontaneous VT≥10 s or sustained (≥30 s) monomorphic VT induced by programmed ventricular stimulation. **Exclusion criteria:** (1) ICD or amiodarone not considered appropriate, (2) excessive perioperative risk for ICD implantation; (3) previous amiodarone therapy for ≥6 wk; (4) nonarrhythmic medical condition making 1y survival unlikely, and (5) long-QT syndrome.		4.5%/y to 3.0%/y (RRR 32.8%; 95% CI, -7.2%–57.8%; p=0.094).	

● **CASH** ● Kuck et al. 2000 (133) ● 10942742	**Aim:** to study the impact on overall survival of initial therapy with an ICD as compared with that with 3 AAD **Study type:** RCT **Size:** 288 patients	**Inclusion criteria:** patients resuscitated from CA 2° to documented sustained VA **Exclusion criteria:** If CA occurred within 72 h of an AMI, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect.	**Intervention:** ICD therapy **Comparator:** amiodarone, metoprolol, or propafenone. Assignment to propafenone was in March 1992, after an interim analysis showed a 61% higher all-cause mortality rate than in 61 ICD patients during a followup of 11.3 mo.	**1° endpoint:** The 1° end point was all-cause mortality. Over a mean followup of 57±34 mo, the death rates were 36.4% (95% CI 26.9% to 46.6%) in the ICD and 44.4% (95% CI 37.2% to 51.8%) in the amiodarone/metoprolol arm. Overall survival was higher, though not significantly, in patients assigned to ICD than in those assigned to drug therapy (1-sided p=0.081, HR: 0.766; 97.5% CI upper bound 1.112)	● In ICD patients, the percent reductions in all-cause mortality were 41.9%, 39.3%, 28.4%, 27.7%, 22.8%, 11.4%, 9.1%, 10.6%, and 24.7% at y 1 to 9 of followup. ● Coronary disease was etiology in 73%. A much larger reduction of 61%, for SCD was observed
● Connolly et al. 2000 (134) ● 11102258	**Aim:** To obtain the most precise estimate of the efficacy of the ICD, compared to amiodarone, for survival in patients with malignant VA. **Study type:** Meta-analysis of RCTs **Size:** 3 RCTs	**Inclusion criteria:** RCTs evaluating the ICD vs. AAD therapy in patients with sustained VA or SCD	**Intervention:** ICD (934 patients) **Comparator:** Amiodarone (932 patients)	**1° endpoint:** Reduction in death from any cause with the ICD, HR 0.72; 95% CI 0.60-0.87; p=0.0006).	● **2° endpoints:** Arrhythmic death, HR 0.50 (95% CI 0.37-0.67; p<0.0001). Survival was extended by a mean of 4.4 mo by the ICD over a followup period of 6 y. ● P heterogeneity=0.306 Patients with LVEF ≤35% derived more benefit from ICD therapy than those with more preserved left ventricular function.
● **MAVERIC** Lau et al. 2004 (135) ● 15172648	**Aim:** to test the possibility of prospectively identifying patients who would benefit most ICD by EPS in	**Inclusion criteria:** survivors of sustained VT, VF or SCD in the absence of an AMI in the last 48 h.	**Intervention:** EP-guided interventions (AAD, coronary revascularization, and ICD) (106	**1° endpoint:** Of the 108 EP arm patients, 31 (29%) received an ICD, 46 (43%) received AAD only (mainly amiodarone or sotalol) and 18 (17%) received	● 61% of patients had prior MI EPS has a minimal impact on the diagnosis of patients presented with VT, VF or SCD. The trial does not support a role for EP testing in risk stratification.

	the context of 2° prevention. **Study type:** RCT **Size:** 214 patients	**Exclusion criteria:** life expectancy of <6 mo from a non-arrhythmic cause or child-bearing age	patients assigned to this arm) **Comparator:** therapy with amiodarone (108 patients assigned to this arm)	coronary revascularization but no ICD. No significant differences in survival or arrhythmia recurrence existed between the two treatment arms after 6 y. However, ICD recipients had a lower mortality than non-ICD recipients, regardless of allocated treatment (HR=0.54, p=0.0391).	
● Claro et al. 2015 (136) ● 26646017	**Aim:** To evaluate the effectiveness of amiodarone for 1° or 2° prevention of SCD compared with placebo or no intervention or any other antiarrhythmic. **Study type:** meta-analyses using a random-effects model **Size:** 24 studies (9,997 participants) with 6 studies identified as 2° prevention trials.	**Inclusion criteria:** Randomized assessing the efficacy of amiodarone vs. placebo, no intervention, or other antiarrhythmics in adults, either for 1° prevention or 2° prevention of SCD.	**Intervention:** Amiodarone **Comparator:** placebo, no intervention, ICD or other antiarrhythmics	**1° endpoint:** For 2° prevention, amiodarone compared to placebo or no intervention (two studies, 440 participants) appeared to increase the risk of SCD (RR: 4.32; 95% CI: 0.87–21.49) and all-cause mortality (RR: 3.05;95% CI: 1.33–7.01). Compared to other AAD (four studies, 839 participants) amiodarone appeared to increase the risk of SCD (RR: 1.40; 95% CI: 0.56–3.52; very low quality of evidence), but there was no effect in all-cause mortality (RR: 1.03; 95% CI: 0.75–1.42; low quality evidence).	● **Conclusions:** With very low quality evidence, amiodarone leads to a statistically non-significant increase in the risk of SCD and all-cause mortality (by 33% to 600%) when compared to placebo or no intervention. This meta-analysis did not effectively rule out benefit or harm for 2° prevention with amiodarone. ● **Side effects:** Amiodarone was associated with an increase in pulmonary and thyroid adverse events. ● **Limitations:** For 2° prevention, the evidence is inconsistent and the quality of the evidence was very low, so the authors concluded that there is uncertainty on the findings. There are some methodological issues that warrant certain caution when interpreting these results.

Data Supplement 18. Nonrandomized Trials, Observational Studies, and/or Registries for Secondary Prevention Sudden Death in Ischemic Heart Disease – (Section 7.1.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Endpoint and Results	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Raitt et al. 2001 (137) ● 11208684	**Aim:** To determine prognostic implications of stable VT **Study type:** Observational, registry of patients with hemodynamically stable VT **Size:** The study population consisted of 440 patients with stable VT and 1029 patients with unstable VT. Of the 1029 patients with unstable VT, 330 had therapy determined by randomization in the AVID trial: 52% received an ICD, 47% amiodarone, and 2% sotalol. Therapy for the remaining 699 patients with unstable VT and the 440 patients with stable VT was determined at the discretion of the attending physician.	**Inclusion criteria:** Patients with stable VT that were not enrolled in AVID, were included in a registry of patients screened for the study. **Exclusion criteria:** Patients who had an arrhythmia within 5 d of a MI, cardiac surgery, or coronary intervention were excluded, as were patients with class IV HF or those who were on a heart transplant list, had a prior ICD implant or attempted implant, or had a life expectancy of <1 y.	**1° endpoint:** Mortality **Results:** The mortality in 440 patients with stable VT tended to be greater than that observed in 1029 patients presenting with unstable VT (33.6% vs. 27.6% at 3 y; RR:1.22; p=0.07). After adjustment for baseline and treatment differences, the RR was little changed (RR: 1.25, p=0.06).	● Sustained VT without serious symptoms or hemodynamic compromise is associated with a high mortality rate and may be a marker for a substrate capable of producing a more malignant arrhythmia.

● Bass EB et al. 1988 (138) ● 3195480	**Study type:** retrospective cohort **Size:** 70 patients	**Inclusion:** unexplained syncope EP study between April 1981 and April 1986. **Exclusion:** N/A	**Results:** EP study had positive results in 37 patients--31 with VT, 3 with SVT and 3 with abnormal conduction. No difference in the 3 y recurrence rate between the ± studies (32 vs 24%, respectively). At 3 y, patients + had higher rates of SCD than patients with - results (48% vs 9%, respectively, p<0.002). 3 y total mortality rate was also higher with + results than among those with - (61% vs 15%, respectively, p<0.001).	● **Conclusion:** patients with electrophysiologically positive results had high rates of SCD and total mortality
● Owens DK et al. 2002 (139) ● 12228780	**Aim:** Evaluated whether risk stratification based on risk ofSCD alone was sufficient to predict the effectiveness and cost-effectiveness of the ICD.	Markov model to evaluate the cost-effectiveness of ICD implantation compared with empiric amiodarone treatment. The model incorporated mortality rates from sudden and nonsudden cardiac death, noncardiac death and costs for each treatment strategy. Model assumed that the ICD reduced total mortality rates by 25%, relative to use of amiodarone.	**Results:** cost-effectiveness becomes unfavorable at both low and high total cardiac mortality rates. If the annual total cardiac mortality rate is 12%, the cost-effectiveness of the ICD varies from $36,000 per quality-adjusted life-year (QALY) gained when the ratio of sudden cardiac death to nonsudden cardiac death is 4 to $116,000 per QALY gained when the ratio is 0.25.	● The cost-effectiveness of ICD use relative to amiodarone depends on total cardiac mortality rates as well as the ratio of sudden to nonsudden cardiac death.

Data Supplement 19. Nonrandomized Trials, Observational Studies, and/or Registries for Coronary Artery Spasm – (Section 7.1.1.1)

Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Ahn et al. 2016 (140) ● 27386766	**Study type:** retrospective multicenter cohort **Size:** 188 patients with aborted SCD Median followup of 7.5 y	188 patients with variant angina with aborted SCD and 1,844 patients with variant angina without aborted SCD from 13 heart centers in South Korea.	**1° endpoint:** The 1° end point cardiac death Cardiac death was significantly higher in aborted SCD patients (24.1 /1,000 patient-y vs. 2.7/ 1,000 patient-y (HR: 7.26; 95% CI: 4.21-12.5; p<0.001) Predictors included family Hx of SCD (OR: 3.67; 95% CI: 1.27-10.6; p=0.016), multivessel spasm (OR: 2.06; 95% CI: 1.33-3.19; p=0.001), and LAD artery spasm (OR: 1.40; 95% CI: 1.02-1.92; p=0.04) A total of 24 aborted SCD patients received ICD 6 ICD patients experienced VF and 1 died due to intractable VF. In the aborted SCD patients who received an ICD, mortality was 4.3% compared with 19.3% of those that did not receive an ICD (trend but nonsignificant p=0.15)	● **Conclusions:** The prognosis of patients with variant angina with ASCD was worse than other patients with variant angina. In addition, our findings supported ICDs in these high-risk patients as a 2° prevention because current multiple vasodilator therapy appeared to be less optimal. ● **Limitations:** Retrospective study and no accurate information for response to medical therapy or compliance. This is an ethnically homogenous group raising questions about extrapolation to other ethnicities. It is unknown what factors might have led physicians to implant an ICD.
● Yamashina et al. 2014 (141) ● 23906527	**Study type:** retrospective single center cohort **Size:** 18 patients in Japan between 1992 and 2012	Resuscitated from CA with 1) documented VF/VT or PEA and 2) the absence of significant narrowing due to coronary atherosclerosis or any structural cardiac	**1° endpoint:** recurrent VT/VF **Results:** No recurrent VA, syncope, or CA during a mean followup of 67 mo (1 of 18 died during the initial hospitalization and another cancer). All are treated with long-acting	● **Conclusions:** Medical therapy associated with favorable long-term outcomes for patients with vasospastic angina associated with CA.

		abnormalities possibly causing CA; 3) absence of identifiable or reversible causes of lethal VA 4) documented ST elevation during chest pain or positive provocation test	CCBs/nitrates and successfully quit smoking. 6 received ICD – none received therapies	● **Limitations:** small, retrospective, and non-randomized study in a single Japanese center.
● Eschalier et al. 2014 (142) ● 24373622	**Study type:** case reports **Size:** 3 patients.	Patients with CA related to coronary artery vasospasm	**Results:** 2/3 patients underwent ICD implantation because of recurrent VT despite medical therapy. None had ICD shocks in follow-up.	**Conclusions:** Very small case series demonstrating ICD use in patients with coronary vasospasm.
● Matsue et al. 2012 (143) ● 22840527	**Study type:** retrospective observational cohort **Size:** 23 patients. from 3 Japanese hospitals Mean followup period of 2.9 y	23 patients with aborted SCD receiving a 2° prevention ICD in the absence of SHD or CAD who had spasm of a major epicardial coronary artery induced with acetylcholine challenge	**Endpoints:** Appropriate ICD therapy, sudden CA, or death from all causes 26% of patients experienced event 4 patients had an episode of VF appropriately treated by their ICD and survived (all but 1 patient was compliant with vasodilator therapy). After the first episode of appropriate ICD therapy in these 4 patients, none received recurrent therapy during the limited follow-up. 1 additional patient survived CA 2° to pulseless electrical activity	● **Results:** The average time for appropriate ICD therapy from ICD insertion was about 1 y and only 2/5 patients with recurrent lethal arrhythmia had symptoms of chest pain prior to ICD therapy. ● **Conclusions:** These data support the use of ICD therapy in patients with coronary artery vasospasm who have survived an episode of life-threatening VT/VF ● **Limitations:** Non-randomized and relatively small number of Japanese patients in only 3 cardiovascular centers. ● The cohort in the present study included only patients with coronary vasospasm who had SCD, and thus the data shown here cannot be extrapolated to the whole coronary vasospasm population. ● Medication compliance was evaluated only by medical interview with patients, and that

				may have caused over-estimation of compliance.
● Takagi et al. 2011 (144) ● 21406685	**Study type:** nationwide registry of patients with vasospastic angina **Size:** 35 patients with OHCA.	30 men and 5 women had OHCA within a registry of 1429 patients in Japan with vasospastic angina (definition: an angina attack at rest and/or on effort, accompanied by a transient ECG ST-segment elevation or depression of >0.1mV or a newly appearance of negative U wave in at least 2 related leads, and/or a total or subtotal coronary artery narrowing during the provocation test of coronary spasm, accompanied by chest pain and/or ischemic ECG changes mentioned above)	**1° endpoint:** The 1° end point MACE included cardiac death, nonfatal MI, hospitalization for unstable angina pectoris and HF, and appropriate ICD shocks during the follow-up period, which began at the date of original VSA diagnosis. **2° endpoint:** The 2° end point was all-cause mortality. **Results:** Survival rate free from MACE was significantly lower in the OHCA survivors compared with the non-OHCA patients (72% vs. 92% at 5 y, p<0.001). There was no difference in all-cause mortality between the groups.	● **Results (continued):** In the 35 OHCA survivors, 14 patients underwent ICD implantation while intensively treated with calcium channel blockers. Appropriate ICD shocks for VF in 2 of 14 patients despite intensive medical treatment. SCD occurred in 1 patient without an ICD who self-discontinued medication prior to the fatal event. ● Rate of cardiac death and nonfatal MI in patients in whom medications were reduced or discontinued (8%, 2 of 25 patients) was 10-fold higher than that in the patients with continued medications (0.7%, 10 of 1404 patients, p=0.017). ● **Limitations:** Appropriate ICD therapy is used as surrogate for sudden death. Retrospective observational study and there the association found in the present study is not necessarily causal and follow-up duration was variable possible many arrhythmic events were missed.
● Meisel et al. 2002 (145) ● 11988204	**Study type:** Retrospective case review with multicenter survey	**Inclusion criteria:** (1) typical chest pain at rest associated with transient ST-segment elevations not present on the baseline ECG and disappearing with relief of pain; (2)	**Results:** All patients were treated with maximum tolerated calcium channel antagonists. Ventricular arrhythmia reoccurred after discharge in all patients. Median time to the first arrhythmia recurrence	● **Conclusions:** VF complicating variant angina is a higher risk population. Raises possibility that some patients such as those remaining symptomatic despite medical therapy should be considered for an ICD.

	Size: 8 patients with vasospastic angina complicated by VF	documented VF immediately after the ischemic episode; (3) survival of the index episode of VF; (4) angiographically normal coronary arteries defined as patent arteries with no irregularities; (5) angiographic evidence of coronary spasm defined as transient narrowing of arterial lumen or recurrent episodes of ECG documented ischemia especially if occurring in different coronary territories; and (6) recurrent angina despite medical therapy **Exclusion criteria:** N/A	was 15 mo (range 2-112). An ICD was subsequently implanted in 7 patients. After ICD implantation, 4 patients received appropriate ICD shocks for VT/VF. 1 patient died with ICD and recurrent chest pain with EMD. 1 patient with recurrent VF and no ICD had recurrent VF out of hospital and subsequent brain damage and died several years later.	
● Chevalier et al. 1998 (146) ● 9426018	**Study type:** retrospective case review **Size:** 7 patients	**Inclusion criteria:** survivors of CA with positive ergonovine provocation test Mean age was 44 y; 3 were male and 4 females. All of them were habitual cigarette smokers. **Exclusion criteria:** N/A	**Results:** At a mean follow-up 58 mo, 6 patients remained free of symptoms. 1 patient who continued smoking had a new CA despite 10 y after and was discovered to have a new LAD and RCA stenosis and underwent CABG and ICD placement.	● **Conclusions:** medical treatment with calcium channel antagonists appears to be associated with an event-free clinical course. Stopping smoking is important.
● Myerburg et al. 1992 (147) ● 1574091	**Study type:** retrospective cohort **Size:** 5 patients	**Inclusion:** From 356 patients, included were 5 survivors of OHCA between 1980 and 1991	**Results:** Titration of calcium channel blocking drugs (verapamil, diltiazem, or nifedipine) against the ability of ergonovine to provoke spasm was	● **Conclusions:** Silent MI due to coronary artery spasm can initiate potentially fatal

		without epicardial CAD with induced or spontaneous focal coronary artery spasm (or both) **Exclusion criteria:** N/A	successful in preventing recurrent arrhythmias in all 4 patients. 1/5 patients had a positive EPS with ventricular flutter despite propranolol so ICD was implanted.	arrhythmias in patients without flow-limiting CAD. In patients with OHCA due to coronary vasospasm, treatment with calcium channel blocking agents appears to prevent recurrent arrhythmias.

Data Supplement 20. Nonrandomized Trials, Observational Studies, and/or Registries for Post CABG VT/VF – (Section 7.1.1.2)

Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Saxon et al. 1995 (148) ● 7856540	**Study type:** retrospective single center cohort **Size:** 17 patients	17 patients UCLA medical center with new-onset sustatined VT/VF within 30 d of CABG between 1981-1993 compared to 119 control patients 1992-1993 without VT/VF post-CABG	VT/VF patients had lower LVEF, more likely to have had MI <2 w before CABG, graft to chronically occluded vessel Sustained MMVT 11/17 patients (65%) and most (64%) had no evidence of peri-op MI. Those with MMVT, 80% inducible at EPS Polymorphic VT/VF 6/17 patients (35%) and most had peri-op MI (67%) and only 2/6 (33%) had inducible VT at EPS	● **Conclusions:** New onset MMVT is usually associated with old infarct/scarring (and many inducible at EPS) ● Polymorphic VT/VF usually associated with ischemia. ● Polymorphic VT/VF occurring after CABG warrants a therapeutic approach targeting treatment of MI.
● Ascione et al. 2004 (149) ● 15120824	**Study type:** retrospective single center cohort **Size:** 4411 patients undergoing CABG	Cases CABG patients 4/1996-9/2001 with VT/VF post-op compared to controls without. Assessed	Factors associated with VT/VF age <65 y, female, low BMI, unstable angina, reduced LVEF, and need for inotrope or IABP	● **Results (cont.):** 5/12 (42%) intraoperative VT/VF died in the hospital, as compared with 10/55 (18%) with VT/VF in post-op period (p=0.08). Those with post-op VT/VF, 27

	including 69 patients with post op VF/VT	factors associated with post-op VT/VF None of the VT/VF patients underwent ICD placement.	Off-pump CABG associated with protective effect (OR: 0.53; 95% CI: 0.25–1.13) Long term survival was similar between groups (2 y 98.2% VT/VF surviving to discharge vs. 97% for control (HR: 0.96; 95% CI: 0.4–2.3)	(47.4%) had the event within the first 24 h. ● **Conclusion:** incidence of VT/VF is low in patients undergoing CABG but associated with high in-hospital mortality. The late survival of those discharged is similar to controls.
● Steinberg et al. 1999 (150) ● 10027813	**Study type:** cohort study **Size:** 12 patients	Patient with sustained post-op VT ≥24 hrs but <30 d after CABG among consecutive patients 382 patients undergoing CABG at a single institution Variables associated with the occurrence of VT was performed	Results: 12 patients (3.1%) experienced ≥1 episode of sustained VT 4.1±4.8 d after CABG In 11 /12 patients, no postoperative complication explained the VT. 1 patient had a perioperative MI. The in-hospital mortality rate was 25%. Among the 9 survivors, 5 had EPS with all inducible sustained monomorphic VT (matching clinical VT). 3/9 patients received an ICD before hospital discharge. Other 6/9 patients received chronic therapy with AAD (primarily amiodarone). All 9 patients are alive, with a mean followup of 2.5 y. 2 patients (1 with an ICD and 1 on amiodarone) had recurrent VT during follow-up.	● Results (cont.): Patients with VT were more likely to have prior MI (92% vs. 50%, p<0.01), severe CHF (56% vs. 21%, p<0.01), and LVEF <0.40 (70% vs. 29%, p<0.01). By multivariate analysis, the number of bypass grafts across a noncollateralized occluded vessel to an infarct zone was the only independent factor predicting VT. ● Conclusions: (1) Patients who developed VT had a high in-hospital mortality rate of 25% (2) However, long-term outcome was good (possibly related to antiarrhythmic or ICD). (3) predictors are MMVT previous MI scar and associated severe LV dysfunction. (4) Relationship was found between the development of VT and the placement of a bypass graft across a noncollateralized occluded coronary vessel to a chronic infarct zone. (5) The development of MMVT was typically not due to a detectable postoperative complication or ischemia.

Data Supplement 21. RCTs and Nonrandomized Trials, Observational Studies, and/or Registries of ICDs Primary Prevention Ventricular Arrhythmias and Sudden Death in Patients with Ischemic Cardiomyopathy – (Section 7.1.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Randomized Subjects	Endpoint and Results	Conclusion:
● **MADIT-I** ● Moss et al.1996 (42) ● 8960472	**Aim:** To evaluate whether prophylactic ICD, as compared with conventional medical therapy, would improve survival in a high-risk group of patients with NSVT, reduced LVEF and previous MI. **Study type:** prospective multicenter RCT **Size:** 196 patients	**Inclusion:** Previous MI, LVEF ≤35%, NSVT, inducible VT at EPS that was non-suppressed with IV procainamide or equivalent AAD **Exclusion:** previous CA or VT causing syncope that was not associated with an AMI; symptomatic hypotension while in a stable rhythm; and MI <3 wk, prior CABG <2 mo or PCI <3 mo, as were women of childbearing age who were not using medically prescribed contraceptives, patients with advanced cerebrovascular disease, patients with any condition other than cardiac disease that was associated with a reduced likelihood of survival for the duration of the trial, and patients who were participating in other clinical trials	**Comparator**: Control (101 patients) **Intervention:** ICD (95 patients)	**All-cause mortality**: Control 32% vs. ICD 13% (RRR -59% ARR -19%)	● In patients with a prior MI, low EF who are at high risk for VT, prophylactic therapy with an ICD leads to improved survival as compared with conventional medical therapy.
● **CABG-Patch** ● Bigger et al.1997 (151) ● 9371853	**Aim:** To evaluate the role of ICD in patients after CABG with high risk of SCD **Study type:** RCT **Size:** 900 patients	**Inclusion:** Coronary artery bypass surgery, EF <36, SAECG positive **Exclusion:** sustained VT/VF, diabetes mellitus with poor blood glucose control or recurrent infections, previous or concomitant aortic- or mitral-valve surgery, concomitant cerebrovascular surgery, a serum creatinine concentration greater than 3 mg/dl, emergency CABG, a	**Comparator**: Control (454 patients) **Intervention:** ICD (446 patients)	**All-cause mortality**: Control 18% vs. ICD 18%	● No evidence of improved survival among patients with CAD, reduced LVEF, and abnormal SAECG receiving prophylactic ICD after CABG

		noncardiovascular condition with expected survival of less than 2 y, or an inability to attend followup visits			
● **MUSTT** ● Buxton et al. 2000 (41) ● 10874061	**Aim:** To evaluate the usefulness of EPS for risk stratification among patients with CAD, abnormal ventricular function, and NSVT **Study type:** RCT **Size:** 704 patients	**Inclusion:** CAD, LVEF ≤40%, NSVT, inducible at EPS **Exclusion:** H/o of syncope or had sustained VT/VF >48 h after the onset of AMI, NSVT that occurred only in the setting of drug-induced LQTS or AMI or that was attributable to acute metabolic disorders or drug toxicity, or if they had symptomatic NSVT	If sustained VT/VF were induced by EPS, patients were randomized to antiarrhythmic therapy, including AAD and possible ICD, as indicated by the results of EP testing, or no antiarrhythmic therapy. **Comparator**: Control (353 patients) Inducible but no antiarrhythmic **Intervention:** Inducible and failed suppression with AAD and given ICD (161 patients)	Risk of CA or death from arrhythmia among the patients who received treatment with ICDs was lower than that among the patients discharged without (HR: 0.24; 95% CI: 0.13–0.45; p<0.001) **All-cause mortality**: Control 55% vs. ICD 24% (RRR -58% and ARR -31%)	● Patients with CAD, left ventricular dysfunction, and asymptomatic, NSVT in whom sustained VAs cannot be induced have a significantly lower risk of SCD and lower overall mortality than similar patients with inducible sustained tachyarrhythmias. Important to point out that receipt of an ICD was not randomized treatment.
● **MADIT-II** ● Moss et al. 2002 (44) ● 11907286	**Aim:** To evaluate the benefit of ICD in patients with prior MI and reduced LVEF **Study type:** RCT **Size:** 1232 patients	**Inclusion:** Prior MI (>1 mo), EF ≤30% **Exclusion:** existing indication for ICD; NYHA class IV at enrollment; had undergone coronary revascularization <3 mo; MI <30 d, advanced cerebrovascular disease, childbearing age and not using contraceptive, presence of any condition other than cardiac disease that was associated with a high likelihood of death during	**Comparator**: Control (490 patients) **Intervention:** ICD (742 patients)	**All-cause mortality:** control 22% vs. ICD 16% (RRR -28% and ARR -6%)	● In patients with a prior MI and advanced left ventricular dysfunction, prophylactic ICD improves survival and should be considered as a recommended therapy.

		the trial, or unwilling to provide consent			
● **DINAMIT** ● Hohnloser et al. 2004 (152) ● 15590950	**Aim:** To assess the benefit of ICD in patients with recent MI and reduced LVEF **Study type:** RCT **Size:** 674 patients	**Inclusion:** Recent MI (6-40 d), EF ≤35%, standard deviation of normal-to-normal RR intervals of 70 msec or less or a mean RR interval of 750 msec or less, mean heart rate ≥80 beats/min **Exclusion:** CHF class IV; noncardiac disease that limited life expectancy; CABG performed since the qualifying infarction or planned to be performed within 4 wks after randomization; three-vessel PCI performed since the qualifying infarction; name on a waiting list for a heart transplant; current, ongoing ICD therapy; prior implantation of a permanent pacemaker; requirement for an ICD (i.e., sustained VT or fibrillation more than 48 h after the qualifying infarction); low probability that the study ICD could be implanted within 7 d after randomization; and expected poor compliance with the protocol	**Comparator**: Control (342 patients) **Intervention:** ICD (332 patients)	**All-cause mortality:** control 17% vs. ICD 19% **2° outcome:** arrhythmic death: 12 ICD group vs. 29 in the control group (HR ICD group, 0.42; 95 95% CI 0.22 to 0.83; p=0.009)	● Prophylactic ICD therapy does not reduce overall mortality in high-risk patients who have recently had a MI. ● Although ICD therapy was associated with a reduction in the rate of death due to arrhythmia, that was offset by an increase in the rate of death from nonarrhythmic causes.
● **SCD-HeFT** ● Bardy et al. 2005 (43) ● 15659722	**Aim:** Evaluate whether amiodarone or a conservatively programmed shock-only, single-lead ICD would decrease the risk of death from any cause in a broad	**Inclusion:** NYHA class I-III HF, LVEF ≤35% **Exclusion:** Age <18 y, unable to give consent	**Intervention 1:** GDMT plus a ICD (829 patients) **Intervention 2:** GDMT plus amiodarone (845 patients) **Comparator 1:**	**All-cause mortality:** control 36% vs. ICD 29% (RRR: -23% and ARR: -7%)	● In patients with NYHA class II or III HF and LVEF≤35%, amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality. This was the longest and largest ICD trial.

	population of patients with mild-to-moderate HF **Study type:** prospective multicenter RCT **Size:** 2521 patients		GDMT plus Placebo (847 patients)		
● **IRIS** ● Steinbeck et al. 2009 (153) ● 19812399	**Aim:** Test whether patients at increased risk who are treated early with an ICD will live longer than those who receive GDMT alone **Study type:** prospective RCT **Size:** 898 patients	**Inclusion:** Recent MI (5-31 d) plus HR >90 bpm and LVEF ≤40% or NSVT **Exclusion:** VAs that occurred before the index MI or >48 h after the MI and that required treatment, NYHA class IV drug-refractory HF, an interval of >31 d between MI and presentation, no ECG documentation within <48 h after the onset of chest pain, an indication for CABG before study entry, a psychiatric disorder, severe concomitant disease, a Hx of poor compliance with treatment, either the inability to participate in this trial or current participation in another trial, and an unstable clinical condition	**Comparator**: Control (453 patients) **Intervention:** ICD (445 patients)	**All-cause mortality:** control 23% vs. 22%	● Prophylactic ICD therapy did not reduce overall mortality among patients with AMI and clinical features that placed them at increased risk.
● Piccini et al. 2009 (154) ● 19336434	**Aim:** To evaluate the cumulative evidence regarding the safety and efficacy of amiodarone in prevention of SCD **Study type:** Meta-analysis of all RCT examining the use	**Inclusion criteria:** Studies in which patients were randomized to amiodarone and placebo or inactive control. Additional inclusion criteria included: treatment for >30 d, followup >6 mo, and availability of all-cause mortality as an endpoint **Exclusion criteria:** Studies	**1° endpoint:** SCD, CVD, all-cause mortality, and the incidences of drug toxicities. **Results:** Amiodarone decreased the incidence of SCD (7.1% vs. 9.7% [OR: 0.71; 95% CI: 0.61–	● Amiodarone reduces the risk of SCD by 29% and CVD by 18%, however, amiodarone therapy is neutral with respect to all-cause mortality	● **Conclusions:** Amiodarone reduced the risk of SCD but is neutral with respect to all-cause mortality. ● Authors suggested amiodarone as a viable alternative in patients who are not eligible for or who do not have

	of amiodarone vs. placebo/control for the prevention of SCD **Size:** 15 trials, which randomized 8,522 patients	of patients with shock-refractory VA, OHCA, patients <18 y, randomization to amiodarone vs. a class Ic or class III AAD (without a placebo or standard of care arm). Studies of patients with ICDs were excluded unless used on both arms.	0.84, p<0.001]) and cardiovascular death (14.0% vs.16.3% [OR: 0.82;0.71–0.94, p=0.004]). There was a 1.5% absolute risk reduction in all-cause mortality which did not meet statistical significance (p=0.093). Amiodarone therapy increased the risk of pulmonary (2.9% vs. 1.5% [OR: 1.97;95% CI:1.27–3.04, p=0.002]), and thyroid (3.6% vs. 0.4%; [OR: 5.68; 95% CI :2.94–10.98, p<0.001]) toxicity.	Adverse events: associated with a 2- and 5-fold increased risk of pulmonary and thyroid toxicity.	access to ICD therapy for the prevention of SCD.
● Claro et al. 2015 (136) ● 26646017	**Aim:** To evaluate the effectiveness of amiodarone for 1° or 2° prevention of SCD compared with placebo or no intervention or any other antiarrhythmic. **Study type:** meta-analyses using a random-effects model	**Inclusion criteria:** Randomized assessing the efficacy of amiodarone vs. placebo, no intervention, or other antiarrhythmics in adults, either for 1° prevention or 2° prevention of SCD.	**Intervention:** Amiodarone **Comparator:** placebo, no intervention, ICD or other antiarrhythmics	**1° endpoint:** There was a beneficial effect with amiodarone reducing the risk of SCD by 12%-34% and may reduce the risk of all-cause mortality by up to 22% when compared with placebo or no intervention in a 1° prevention setting.	● **Conclusions:** There is low quality evidence that amiodarone reduces the risk of SCD and may reduce the risk of all-cause mortality when compared with placebo or no intervention in a 1° prevention setting. ● The evidence regarding the comparison with other antiarrhythmics is of moderate quality and goes in the same direction.

	Size: 24 studies (9,997 participants) with 17 studies with 8383 patients identified as relevant 1° prevention trials.			**Adverse events:** Amiodarone was associated with increased adverse effects, both thyroid and pulmonary (based on 12 studies), and increased risk of discontinuation (based on 13 studies) when compared with placebo.	● Stresses the importance for people in low-income countries, where an ICD may not be available.
● Owens DK et al. 2002 (139) ● 12228780	**Aim:** Evaluated whether risk stratification based on risk ofSCD alone was sufficient to predict the effectiveness and cost-effectiveness of the ICD.	Markov model to evaluate the cost-effectiveness of ICD implantation compared with empiric amiodarone treatment. The model incorporated mortality rates from sudden and nonsudden cardiac death, noncardiac death and costs for each treatment strategy. Model assumed that the ICD reduced total mortality rates by 25%, relative to use of amiodarone.	**Results:** cost-effectiveness becomes unfavorable at both low and high total cardiac mortality rates. If the annual total cardiac mortality rate is 12%, the cost-effectiveness of the ICD varies from $36,000 per quality-adjusted life-year (QALY) gained when the ratio of sudden cardiac death to nonsudden cardiac death is 4 to $116,000 per QALY gained when the ratio is 0.25.		● The cost-effectiveness of ICD use relative to amiodarone depends on total cardiac mortality rates as well as the ratio of sudden to nonsudden cardiac death.
● Cantero-Pérez EM, et al. 2013 (155) ● 24314988	**Aim:** To evaluate the effectiveness of ICDs for primary prevention in patients with LVEF ≤30% included on the heart transplantation list **Size:** Patients who received ICDs for primary prevention (N=28)	**Inclusion criteria:** Records from patients accepted for heart transplantation from January 1, 2006, to July 30, 2012, and whose LVEF was <31% were reviewed	**Results:** Median follow-up of 77 d overall mortality in the ICD group was 7.1% (2/28) and in the non-ICD group was 17.6% (9/51; p=0.062). Cause of death in patients without ICDs: Sudden death (5/9, 55.6%), HF (4/9, 44.4%). Cause of death in patients with ICDs: HFheart		● Appropriate ICD therapies were recorded in 42.9% (12/28) in this population.

	were compared with patients without ICDs (N=51)			
● Fröhlich GM, et al. 2013 (156) ● 23813845	**Aim:** To delineate the role of ICD therapy for the primary and secondary prevention of SCD in patients listed for heart transplantation **Size:** N=1089	**Inclusion criteria:** Patients listed for heart transplantation in 2 tertiary heart transplant centres were enrolled. Of 550 patients (51%) on the transplant list with an ICD: primary prevention ICD: N=216 secondary prevention ICD: N=334	**Results:** Median time on the waiting list = 8 mo (estimated 1-year: 88±3% vs. 77±3% vs. 67±3%; p=0.0001). An independent beneficial effect of ICDs that was most pronounced in patients who had received an ICD for primary prevention (HR: 0.4, 95% CI: 0.19–0.85; p=0.016).	● ICDs appear to be associated with a reduction in all-cause mortality in patients implanted with the device for primary and secondary prevention compared to those without an ICD.
● Gandjbakhch E, et al. 2016 (157) ● 27344378	**Aim:** To evaluate the ICD benefit on mortality in patients with end-stage HF listed for heart transplantation **Size:** N=380 consecutive patients listed for heart transplantation between 2005 and 2009 in A tertiary heart transplant centre	**Inclusion criteria:** Patients with end-stage HF receiving an ICD before or within 3 mo after being listed for heart transplantation	**Results:** 15.6% of patients died while awaiting heart transplantation. Non-ICD patients presented more often haemodynamic compromise. ICD did not remain an independent predictor of death. Death by haemodynamic compromise (76.3% of deaths), which occurred more frequently in the non-ICD group (14.7% vs. 5.8%; log-rank p=0.002). Unknown/arrhythmic deaths did not differ significantly between the two groups (3.9% vs. 1.7%; log-rank p=0.21).	● Need for mechanical circulatory support (p<0.001), low EF (p=0.001) and registration on the regular list (p=0.008) were the only independent predictors of death. ● ICD-related complications occurred in 21.4% of patients, mainly as a result of postoperative worsening of HF (11.9%).
● Vakil K, et al. 2016 (158)	**Aim:** To assess the impact of ICD on waitlist mortality in patients listed	**Inclusion criteria:** Adults (age ≥18 y) listed for first-time heart transplantation in the US between January 1, 1999, and September 30, 2014, were	**Results:** Median follow-up of 154 days, 3,638 patients (11%) died on the waitlist (9% in ICD group vs. 15% in no-ICD group;	● In the subgroup of patients with LVAD (N= 9,478), having an ICD was associated with an adjusted 19% relative

	for heart transplantation **Size:** N=32,599	retrospectively identified from the United Network for Organ Sharing registry.	p<0.0001), whereas 63% underwent heart transplantation. An ICD at listing was associated with an adjusted 13% relative reduction in mortality (HR: 0.87; 95% CI: 0.80–0.94).	reduction in mortality (HR: 0.81; 95% CI: 0.70–0.94).

Data Supplement 22. RCTs Evaluating Treatment and Prevention of Recurrent Ventricular Arrhythmias in Patients with Ischemic Heart Disease – (Section 7.1.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **OPTIC** ● Connolly et al. 2006 (159) ● 16403928	**Aim:** Determine whether amiodarone plus BB or sotalol are better than BB alone for prevention of ICD shocks. **Study type:** RCT **Size:** 412 patients	**Inclusion criteria:** Patients who had received an ICD within 21 d for inducible or spontaneous VT/VF **Exclusion criteria:** Long QT syndrome, corrected QT interval of more than 450 ms, already receiving or recent treatment with a class I or class III antiarrhythmic agent, creatinine clearance less than 30 mL/min, AF likely to require use of a class I or class III antiarrhythmic agent, absence of SHD, NYHA class IV HF	**Intervention:** amiodarone plus BB or sotalol **Comparator:** BB alone	**1° endpoint:** ICD shock for any reason. Shocks occurred in 41 patients (38.5%) assigned to BB alone, 26 (24.3%) assigned to sotalol, and 12 (10.3%) assigned to amiodarone plus BB (HR: 0.44; 95% CI: 0.28–0.68; p<0.001). **Safety endpoint:** NA	● Amiodarone plus BB significantly reduced the risk of shock compared with BB alone (HR: 0.27; 95% CI: 0.14–0.52; p<0.001) and sotalol (HR: 0.43; 95% CI: 0.22–0.85; p=0.02). There was a trend for sotalol to reduce shocks compared with BB alone (HR: 0.61; 95% CI: 0.37–1.01; p=0.055). ● Adverse pulmonary and thyroid events and symptomatic bradycardia were more common among patients randomized to amiodarone. ● **Conclusions:** Despite use of advanced ICD technology and treatment with a BB, shocks occur commonly in the first year after ICD implant. Amiodarone plus BB is effective

					for preventing these shocks and is more effective than sotalol but has an increased risk of drug-related adverse effects.
● Pacifico et al. 1999 (160) ● 10369848	**Aim:** Efficacy and safety of sotalol to prevent shocks from ICDs **Study type:** prospective, RCT double-blind **Size:** 302 patients	**Inclusion criteria:** age >18 y, life-threatening VT that were not due to a reversible cause; had received their first or a replacement ICD within 3 mo before enrollment (patients with replacement defibrillators had to have received at least one shock during the preceding 6 mo); had a ICD that provided tiered therapy with EGM and separate logging of shocks **Exclusion criteria: i**ncessant VT; had received AAD therapy <5 half-lives of the drug before randomization in the case of class I and III agents (and <3 mo before randomization in the case of amiodarone); had a QT interval of more than 450 msec (or a JT interval of more than 360 msec) in the absence of drug therapy; had a LQTS, including prolongation of the QT interval in response to specific drugs; had unstable coronary syndromes or had	**Intervention:** 160 to 320 mg of sotalol per day **Comparator:** matching placebo	**1° endpoint:** Treatment with sotalol was associated with a lower risk of death from any cause or the delivery of a first shock for any reason (reduction in risk 48%; p<0.001; first appropriate shock for a va or death from any cause was also reduced (reduction in risk, 44%; p=0.007), **Safety endpoint:** Bradycardia was more common in sotalol group, but only 2 patients discontinued therapy because of it; 3 patients in each group had HF.	● First inappropriate shock for a SVT or death from any cause was reduced with sotalol (reduction in risk, 64%; p=0.004). ● Sotalol also reduced the mean frequency of shocks due to any cause (1.43±3.53 shocks/y, as compared with 3.89±10.65 in the placebo group; p=0.008). ● **Conclusions:** Oral sotalol was safe and efficacious in reducing the risk of death or the delivery of a first defibrillator shock whether or not ventricular function was depressed.

		had an AMI less than two weeks before screening; had intractable HF (NYHA class IV); were candidates for heart transplantation; or had a medical condition that was likely to be fatal in less than 2 y.			
● Kettering et al. 2002 (161) ● 12494613	**Aim:** Efficacy of metoprolol vs. sotalol in preventing recurrent VT in patients with ICDs **Study type:** prospective, RCT **Size:** 100 patients	**Inclusion criteria:** ICD implanted for sustained VT or VF **Exclusion criteria:** Contraindications for metoprolol or sotalol; AMI within the last 4 wk; unstable angina; severe concomitant diseases	**Intervention:** 40-480 mg sotalol daily **Comparator:** 25-200 mg daily metoprolol tartrate	**1° endpoint:** VT/VF recurrence requiring ICD intervention; 33 events in patients treated with metoprolol vs. 30 in patients receiving sotalol (p=0.68) **Adverse Events:** 5 metoprolol and 6 sotalol patients required dose reduction for fatigue, dizziness, HF	● **Conclusions:** No significant difference in freedom from ICD therapies between metoprolol and sotalol group (p=0.68)
● Echt et al. 1991 (162) ● 1900101	**Aim:** Examine the mortality and morbidity after randomization to encainide or flecainide or their respective placebo. **Study type:** RCT **Size:** 1498 patients	**Inclusion:** 6 d - 2 y after MI if they had an average of ≥6 PVCs/h on ambulatory electrocardiographic monitoring of at least 18 h duration, and no runs of VT of ≥15 beats at a rate of ≥120 beats/mim. EF ≤0.55 if recruited within 90 d of the MI, or EF ≤0.40s if recruited 90 d or more after the MI. **Exclusion:** as above	**Intervention:** encainide or flecainide **Comparator:** placebo	**1° endpoint:** arrhythmic death or cardiac arrest After a mean followup of 10 mo, 89 patients had died: 59 of arrhythmia (43 receiving drug vs. 16 receiving placebo; p=0.0004)	● **Conclusions:** Excess of deaths due to arrhythmia and deaths due to shock after acute recurrent MI in patients treated with encainide or flecainide. Nonlethal events, however, were equally distributed between the active-drug and placebo groups.

● Seidl et al.1998 (163) ● 9761084	**Aim:** efficacy of d,l-sotalol and metoprolol in preventing recurrence of arrhythmic events after ICD implantation. **Study type:** prospective, RCT **Size:** 70 patients	**Inclusion criteria:** Patients with ICD and Hx of VT/VF **Exclusion criteria:** AMI within 1 wk; contraindications for BB; Hx of proarrhythmia caused by d,l-sotalol	**Intervention:** metoprolol (mean dosage 104±37 mg/d) **Comparator**: d,l-sotalol (mean dosage 242± 109 mg/d)	**1° endpoint:** Actuarial rates for absence of VT recurrence at 1 and 2 y were significantly higher in the metoprolol group compared with the d,l-sotalol group (83% and 80% vs 57% and 51%, respectively, p=0.016). **Safety endpoint:** HF led to drug discontinuation in 9% in each group. ● 2 episodes of proarrhythmia in sotalol group.	● **Conclusions:** The recurrence rate of VT in patients treated with metoprolol was lower than in patients treated by d,l-sotalol. No difference in overall survival
● Kuhlkamp et al. 1999 (164) ● 9935007	**Aim:** Evaluate efficacy of sotalol in preventing recurrences of VT **Study type:** prospective, RCT **Size:** 146 patients	**Inclusion criteria:** Patients with inducible sustained VT or VF **Exclusion criteria:** non-syncopal sustained VT; contraindications to BB; limited projected survival due to comorbid disease	**Intervention:** Patients whose VT was suppressed on sotalol were treated with it; patients whose VT was not suppressed on sotalol received an ICD and were randomized to treatment with sotalol or no antiarrhythmic therapy **Comparator:** no antiarrhythmic	**1° endpoint:** 25 patients (53.2%) in the ICD-only group had a VT/VF recurrence in comparison to 15 patients (28.3%) in the sotalol group and 15 patients (32.6%) in the ICD/sotalol group (p 5 0.0013). **Safety endpoint:** Intolerance to treatment with d,lsotalol (overt	No difference in total mortality among the 3 groups **Conclusion:** Sotalol significantly reduces the incidence of recurrences of sustained VT in comparison to no AAD treatment

				cardiac failure, symptomatic hypotension or Bradycardia)	
● **MADIT-II substudy** ● Brodine et al. 2005 (165) ● 16125497	**Study type:** Retrospective, observational **Size:** 720 patients who received ICDs	**Inclusion criteria:** ischemic cardiomyopathy, EF≤30%, randomized to ICD arm **Exclusion criteria:** Patients who were not randomized to ICD therapy	**1° endpoint:** Appropriate ICD therapy for VT/VF; survival **Results:** Patients in the top quartile of BB doses had a significant reduction in the risk of VT or VF requiring ICD therapy compared with patients not receiving BB (HR: 0.48; p=0.02). BB use was also associated with significant improvement in survival compared with the nonuse of BB (HR: 0.4; p<0.01).	The frequency of inappropriate ICD therapy for SVT was not significantly different among the 3 treatment groups (p=0.32).	● **Conclusion:** Beta blockers reduce the risk for VT or VF and improve survival in ICD-treated patients with ischemic cardiomyopathy.
● **SMASH VT** ● Reddy et al. 2007 (166) ● 18160685	**Aim:** To determine whether prophylactic substrate based catheter ablation in sinus rhythm decreases ICD therapies after MI **Study type:** RCT prospective **Size:** 128 patients	**Inclusion criteria:** age ≥18 y with MI at least 1 mo previously and a Hx of VF, Hemodynamically unstable VT, or Syncope with inducible VT and ICD implantation **Exclusion criteria:** Treatment with AAD, ischemia induced VT/VF, or incessant VT or VF	**Intervention:** Substrate based catheter ablation of arrhythmogenic myocardium during sinus rhythm (N=64) **Comparator:** Standard ICD follow-up (N=64)	**1° endpoint** After 2 y of follow-up, ICD therapies occurred in 12% of patients randomized to catheter ablation and 33% in the control group (HR 0.35; CI 0.15–0.78, p=0.007)	● Trend towards reduced mortality after 2 y in the ablation group (9% vs 17%, p=0.06) ● No difference in left ventricular function or NYHA functional class during follow-up.

● **VANISH** ● Sapp J. et al. 2016 (167) ● 27149033	**Aim:** To determine whether catheter ablation decreases ICD therapies in patients with ischemic cardiomyopathy with a Hx of VT or VF despite the use of AAD **Study type:** randomized, prospective **Size:** 259 patients	**Inclusion criteria:** Prior MI, ICD implantation, at least 1 episode of VT during treatment with amiodarone or another class I or class III AAD within the previous 6 mo **Exclusion criteria:** Failure to give informed consent	**Intervention:** Randomized 1:1 to catheter ablation or escalated AAD therapy (escalated-therapy group), (N=132) **Comparator:** Escalated drug therapy: Amiodarone loading then amio 200 mg/d (if on Sotalol) or Amiodarone reloading then 300 mg/d if on amiodarone <300 mg/d, Or addition of mexiletine 200 mg TID to amiodarone 300 mg/d if on amiodarone 300 mg/d (N=127)	**1° endpoint** The 1° outcome occurred in 78 of 132 patients (59.1%) in the ablation group and in 87 of 127 patients (68.5%) in the escalated-therapy group. The rate of the 1° outcome was significantly lower in the ablation group than in the escalated-therapy group (HR:0.72; 95% CI:0.53–0.98; p=0.04) This difference was driven by trends toward reductions in rates of appropriate shocks and episodes of VT storm	● VT storm occurred in 32 patients (24.2%) in the ablation group and 42 patients (33.1%) in the escalated-therapy group (HR: 0.66; 95% CI: 0.42–0.05 p=0.08). Appropriate ICD shocks occurred in 50 patients (37.9%) and 54 patients (42.5%), respectively (HR: 0.77; 95% CI: 0.53–1.14; p=0.19). ● 36 patients (27.3%) in the ablation group and 35 (27.6%) in the escalated-therapy group died (HR: 0.96; 95% CI: 0.60–1.53; p=0.86).
● **VTACH Trial** ● Kuck KH, et al. 2010 (168) ● 20109864	To determine whether catheter ablation reduces the risk of VT recurrence in patients with Ischemic Cardiomyopathy, stable VT, and an ICD compared with ICD and continued medical Rx alone **Study Type** RCT	**Inclusion Criteria:** Patients age 18-80 y with prior MI, CAD, clinically hemodynamically stable VT, reduced LVEF <0.50, ICD indication **Exclusion Criteria** MI or Cardiac Surgery within 1 mo, LV thrombus, artificial heart valve, incessant VT, impaired renal function, life expectancy <1 y.	**Study Intervention** ICD plus catheter ablation of all inducible VTs or elimination of substrate for non-inducible VT (N=52) **Comparator** ICD and continued medical therapy (N=55)	After 24 mo, 47% of patients in the ablation group and 29% of controls were free of recurrent VT (HR: 0.61;95% CI 0.37–0.99, p=0.044).	● Patients with LVEF >0.30 had greater reduction of VT with catheter ablation than did patients with more severe LV dysfunction (freedom from VT in 48% with ablation vs 27% of controls, (HR:0.47; 95% CI 0.24–0.88, p=0.016). ● No difference in VT storm, syncope, or death between ablation and controls.

	Study Size 107 patients				
● **CALYPSO** ● Al-Khatib S. et al. 2015 (169) ● 25332150	**Aim** Pilot study to determine feasibility of RCT of catheter ablation of VT vs. AAD when used early in the course of patients with CAD who experience ICD therapies. **Study Type** Pilot RCT **Study size** 27 patients	**Inclusion Criteria** Patients with CAD, ICDs, who had received ≥1 ICD shock or ≥3 ATP therapies for VT **Exclusion Criteria** Present AAD, Incessant VT, VT due to reversible cause	**Intervention** Catheter ablation of VT (N=13) **Comparator** AAD(N=14)	**1° Endpoint** Mean time to recurrent VT was 75 d in ablation arm and 57 d in AAD arm. There were 2 deaths in both arms of the study	● Of 243 screened patients, 27 were enrolled. ● Presently on AAD (88, 41%), VT due to reversible cause (23, 11%), and incessant VT (20, 9%).

Data Supplement 23. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Recurrent Arrhythmias in IHD – (Section 7.1.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Conclusions
● Blanck et al. 1993 (170) ● 8269297	**Study type:** Single Center Review **Size:** 48 patients	**Inclusion criteria:** All patients at single center with BBRVT diagnosed at EPS between 1980-1992 **Criteria:** 1) Typical RBBB or LBBB QRS morphology during VT	**Results:** 45 of 48 patients had SHD SHD was NICM in 16 patients, ischemic cardiomyopathyin 23 patients, V HD in 2 patients Mean LVEF 23.2%	● BBRVT typically occurs in patients with SHD from a variety of causes in patients with prolonged HV conduction intervals. ● BBRVT is associated with aborted SCD, Syncope, and Palpitations

		2) QRS preceded by His and appropriate bundle branch potential **3)** Stable HV, RB-V, or LB-V interval **4)** Induction dependent on HV delay **5)** Termination by block in HPS **6)** Noninducibility after RBB ablation	**Clinical Presentation** Aborted SCD in 26% Syncope in 51% Sustained palpitations in 10% Mean HV interval in sinus 80.4 msec **QRS morphology in VT** LBBB in 46 patients RBBB in 5 patients Interfascicular reentry in 2 patients **Catheter Ablation** Performed in 28 patients targeting the RBB in 26 patients and LBB in 2 patients Successful ablation of VT in 100% No Complications observed.	● BBRVT is most commonly associated with a LBBB QRS morphology, and less commonly with RBBB or Interfascicular QRS morphologies ● Catheter ablation targeting the RBB or LBB is highly effective and associated with a low risk of serious complications.
● Brugada J et al. 2001 (171) ● 11216974	**Study type:** prospective **Size:** 61 patients	**Inclusion:** prior MI, spontaneous VA not related to an acute ischemic event and coronary lesions requiring revascularization **Exclusion:** n/a **Protocol:** EP performed before and after revascularization	**Results:** 61 patients were inducible into sustained VA. After revascularization, 52 of 59 patients previously inducible were still inducible (group A), and 10 patients were noninducible (group B). No differences were found in clinical, hemodynamic, therapeutic and electrophysiological characteristics between both groups. During 32 +/- 26 mo followup, 28/52 patients in group A (54%)	● In patients with VA in the chronic phase of MI, probability of recurrence is high despite coronary artery revascularization, but mortality is low if combined with appropriate AAD. ● Recurrences: lower EF predicted higher recurrence rate but not ischemia before revascularization, amiodarone or BB therapy or EP study after revascularization. An EF <30% predicted recurrent arrhythmic events (p=0.02), but not the presence of demonstrable ischemia before revascularization (p=0.42), amiodarone (p=0.69) or

			and 4/10 patients in group B (40%) had arrhythmic events (p =0.46). Total mortality was 10% in both groups.	beta-adrenergic blocking agent therapy (p=0.53).
● Sears et al. 1999 (172) ● 10410293	**Study type:** literature review	**Inclusion:** studies assessing psychological impact of ICD and shocks	**Results:** 13-38% of recipients experiencing diagnosable levels of anxiety. Specific ICD-related concerns such as fear of shock, fear of device malfunction, fear of death, and fear of embarrassment have been identified.	● **Conclusions:** Psychosocial adjustment risk profiles indicate that young ICD recipients and those with high discharge rates may experience the most adjustment difficulties
● Lopera et al. 2004 (173) ● 15028072	**Study type:** Single Center Review **Size:** 20 patients	**Inclusion criteria:** His Bundle, LBB, or RBB potential closely associated with QRS with any of the following: 1) H-H interval variation preceding similar V-V interval variation; 2) Anterograde activation of the bundle branches during tachycardia; or, 3) Abolition of VT by bundle branch ablation. **Exclusion criteria:** None	**Results:** HPS VT induced in 20 of 234 consecutive patients referred for VT ablation NICM: 9 of 81 patients (11%) had HPS VT ICM: 11 of 153 patients (7.1%) had HPS VT Mean LVEF 29±17% 2 of 20 patients had normal LVEF **Clinical Presentation** ICD Shocks in 10 patients Syncope in 3 patients Other symptoms in 7 patients **Typical BBRVT** in 16 of 20 patients (all had LBBB QRS morphology) 13 of 16 patients BBRVT successfully ablated by RBB	● BBRVT occurs in patients with both NICM and ischemic cardiomyopathy, usually with impaired LVEF. ● BBRVT is most commonly associated with a LBBB QRS morphology, and less commonly with RBBB or Interfascicular QRS morphologies ● Catheter ablation targeting the RBB or LBB is highly effective and associated with a low risk of serious complications if only one BB is targeted and a higher risk of AV block if both BBs are targeted for ablation.

			ablation and 3 of 16 by LBB ablation. HV interval prolonged from 70±5.9 msec to 83±17 msec after ablation. **Typical BBRVT and Interfascicular VT** in 2 of 20 patients. Ablation of both the RBB and portion of LBB eliminated VT in both patients, complicated by AV block in 1 pt. **Focal Mechanism from BBs** in 2 patients, one in RBB, one in LBB. Ablation eliminated focal VT in both patients, complicated by AV block in 1 pt.	
● Mehdirad et al.1995 (174) ● 8771124	**Study type:** Single Center Review **Size:** 16 patients	**Inclusion criteria:** All patients undergoing RF catheter ablation of the RBB for BBRVT	**Results:** HV interval 68±8 msec at baseline LVEF mean 31±15% RBBB developed in 15/16 patients after RBB ablation AV block occurred in 1 pt After mean of 19±10 mo, one patient died suddenly, 2 received cardiac transplantation, and 1 died of CHF.	● Catheter ablation of the RBB is effective for the treatment of BBRVT ● BBRVT is associated with prolonged HV conduction intervals. ● The medium term followup after catheter ablation of the RBB is overall quite good.
● **HELP-VT** ● Dinov B, et al. 2014 (175) ● 24211823	**Aim:** To determine the outcome of VT catheter ablation in patients with NICM to those with ICM **Study type:** Prospective, non-randomized **Size:** 227 patients	**Inclusion criteria:** Patients with SHD referred for catheter ablation of VT with either NICM (N=63) or ischemic cardiomyopathy(N=164) **Exclusion criteria:** Failure of informed consent	**1° endpoint:** At 1 y follow-up, VT free survival was 57% for ischemic cardiomyopathyand 40.5% for NICM patients (HR: 1.62; 95% CI 1.12–2.34, p=0.01). ischemic cardiomyopathyrequired epicardial ablation in only 2 of 164 (1.2%) whereas NICM required epicardial ablation in 30.8% (p=0.0001).	**Complications** Complications occurred in 11.1% of NICM and 11.1% of ischemic cardiomyopathypatients, including death in 4.8% of NICM and 3.7% of ischemic cardiomyopathy

		Intervention: Catheter ablation for patients with NICM **Comparator:** Catheter ablation in patients with ICM		
● **Euro-VT Study** ● Tanner H 2010 (176) ● 19656251	**Aim** To determine the safety and efficacy of electroanatomic mapping and irrigated RF catheter ablation for VT after MI **Study Type:** Multicenter, non-randomized **Study Size** 63 patients	**Inclusion Criteria** Drug and device refractory, recurrent sustained VT after MI. ≥4 episodes of sustained VT in prior 6 mo. **Exclusion Criteria** Age <18 y MI within 2 mo LV Thrombus Unstable Angina Severe AS or MR Unwillingness to participate **Intervention** Electroanatomic mapping and ablation with open-tip irrigated catheter.	**1° endpoint:** Acute success with ablation was achieved in 83% of mappable VTs and 40% of non-mappable VTs ($p<0.0001$). During 12mo follow-up, VT recurred in 49% of patients. The mean number of therapies dropped from 60±70 prior to ablation to 14±15 in the same period of time (6 mo) after ablation ($p= 0.02$).	**Complications** Major complications occurred in 1.5% and minor complications in 5% of patients, particularly groin hematomas, with no procedural deaths.
● **Post-approval Thermocool Trial** ● Marchlinski F 2016 (177) ● 26868693	**Aim** To evaluate long-term safety and effectiveness of RF catheter ablation for VT in patients with CAD **Study Type:** Multicenter, non-randomized	**Inclusion Criteria** Patient with coronary disease, age ≥18 y and LVEF ≥10% with recurrent VT (either ≥4 episode documented by ICD, ≥2 episode documented by ECG in patients without ICD, incessant VT or symptomatic VT despite AAD treatment **Exclusion Criteria**	**1° endpoint:** At 6 mo: 62% without VT recurrence, proportion of patients with ICD shock reduced from 81.2 (pre) to 26.8% and ≥50% reduction in VT episodes in 63.8% of patients. **Safety Endpoint** CV specific AE in 3.9% with no stroke	● **Comments** ● Reduction in amiodarone usage and hospitalization ● Improvement in QoL

	Study Size 249 patients	Mobile LV thrombus, MI within 3 mo, idiopathic VT, class IV HF, creatinine ≥2.5, recent cardiac surgery, unstable angina, severe AS or MR. **Intervention** Electroanatomic mapping and ablation with open-tip irrigated catheter.		
● **International VT Collaborative Group Study** ● Tung R 2015 (178) ● 26031376	**Aim:** to determine the association of VT recurrence after ablation and survival in scar related VT **Study type:** Multicenter observational **Size:** 2061	**Inclusion criteria:** SHD with ischemic and non-ischemic cardiomyopathies with monomorphic VT and myocardial scar by electroanatomic mapping **Exclusion criteria:** absence of scar on electroanatomical mapping **Intervention:** Catheter ablation, either endocardial or epicardial, guided by EAM. End point of ablation with elimination of all induced VTs	**1° endpoint:** Freedom from VT recurrence, Heart Transplant, or death was 70% at 1 y follow-up. VT recurred in 55% of patients who died vs. 22% of patients who survived. Transplant free survival was 90% for patients without VT recurrence and 71% for those with VT recurrence (HR: 6.9; 95% CI: 5.3–9.0, p<0.001).	● Procedural complications occurred in 6%, including 2 deaths (0.1%), hemopericardium in 1.7%, and vascular access complications in 1.6%
● **Meta-Analysis of Randomized and Non-Randomized Trials of Catheter Ablation for VT** ● Mallidi J 2011 (179) ● 21147263	**Aim:** To determine the relative risk of VT recurrence in patients undergoing catheter ablation compared with medical therapy **Study type:** Meta-Analysis of 5 Trials of VT Ablation	PubMed, Embase, Cochrane searches of both randomized and nonrandomized clinical trials of catheter ablation of VT compared with a control group receiving AAD treatment alone **Intervention:** Catheter ablation with or without AAD	**1° endpoint:** VT recurred in 93 of 266 patients (35%) after Catheter Ablation compared with 105 of 191 (55%) on AAD (HR: 0.62; 95% CI: 0.51–0.76, p<0.001) **Safety endpoint:** Complications occurred in 6.3% after ablation, including death	● Electrical Storm occurred in 17 of 116 (15%) after catheter ablation and 29 of 119 (25%) on AAD therapy (HR: 0.61; 95% CI: 0.36–1.03, p<0.066). ● Mortality occurred in 12% of patients treated with ablation and 14% on AAD.

	Size: 457 patients	**Comparator:** AAD alone.	(1%), tamponade (1%) and AV block (1.6%)	
● **Cooled Tip Ablation of VT** ● Calkins 2000 (180) ● 10841242	**Aim:** To determine the safety and efficacy of an internally cooled RF ablation catheter used for VT in SHD in patients with ≥2 episodes of VT in the prior 2 mo despite ≥2 AAD **Study type:** Non-Randomized trial of Cooled Tip ablation catheter for VT **Size:** 147 patients	**Inclusion criteria:** >2 episodes of hemodynamically stable VT in previous 2 mo, CAD, ICD implantation, failure of ≥2 AAD. **Exclusion criteria:** Failure to give informed consent **Intervention:** Catheter ablation using the Cooled RF catheter system **Comparator:** VT recurrence Hx prior to ablation	**1° endpoint:** Acute success with elimination of all mappable VTs in 75%, At a mean of 243±153 d of follow-up, VT recurred in 46% of patients Acute success defined by noninduciblity of VT after ablation did not predict VT recurrence	● **Complications** Complications occurred in 8% including death in 2.7%
● **Multicenter ThermoCool Ventricular Tachycardia Ablation Trial** ● Stevenson WG, et al. 2008 (181) ● 19064682	**Aim:** To determine the outcome after catheter ablation of VT **Study type:** Non-randomized **Size:** 231 patients	**Inclusion criteria:** ≥4 episodes of sustained VT requiring cardioversion or AAD for termination in past 6 mo despite ICD or AAD THERAPY, age >18 y. **Exclusion criteria:** LVEF <0.10, LV thrombus, Creatinine >2.5, NYHA Class IV CHF, severe AS, unstable angina, pregnancy. **Intervention:**	**1° endpoint:** Freedom from recurrent VT at 6 mo follow-up in 123/231 patients (53%). VT ablation reduced the median number of VT episodes in 6 mo before ablation from 11.5 to 0 after ablation (p<0.0001) **Safety endpoint:** Complications occurred in 7%, including 7 patients (3%) who died within 3 d of ablation, and groin complications in 4.7%.	● 1 y mortality was 18%

		Catheter ablation with the BioSense ThermoCool ablation catheter **Comparator:** Prior Hx of VT recurrences		
● Steinberg et al. 1999 (150) ● 10027813	**Study type:** cohort study **Size:** 12 patients	Patient with sustained post-operational VT ≥24 h but <30 d after CABG among consecutive patients 382 patients undergoing CABG at a single institution Variables associated with the occurrence of VT was performed	**1° endpoint:** 12 patients (3.1%) experienced ≥1 episode of sustained VT 4.1±4.8 d after CABG In 11 /12 patients, no postoperative complication explained the VT. 1 patient had a perioperative MI. The in-hospital mortality rate was 25%. Among the 9 survivors, 5 had EPS with all inducible sustained monomorphic VT (matching clinical VT). 3/9 patients received an ICD before hospital discharge. Other 6/9 patients received chronic therapy with AAD (primarily amiodarone). All 9 patients are alive, with a mean follow-up of 2.5 y. 2 patients (1 with an ICD and 1 on amiodarone) had recurrent VT during followup.	● Results (cont.): Patients with VT were more likely to have prior MI (92% vs. 50%, p<0.01), severe CHF (56% vs. 21%, p<0.01), and LVEF <0.40 (70% vs. 29%, p<0.01). ● By multivariate analysis, the number of bypass grafts across a noncollateralized occluded vessel to an infarct zone was the only independent factor predicting VT. ● Conclusions: (1) Patients who developed VT had a high in-hospital mortality rate of 25% (2) However, long-term outcome was good (possibly related to antiarrhythmic or ICD). (3) predictors are MMVT previous MI scar and associated severe LV dysfunction. (4) Relationship was found between the development of VT and the placement of a bypass graft across a noncollateralized occluded coronary vessel to a chronic infarct zone. (5) The development of MMVT was typically not due to a detectable postoperative complication or ischemia.

Data Supplement 24. Nonrandomized Trials, Observational Studies, and/or Registries of NICM – (Section 7.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Ackerman MJ 2011 (182) ● 21810866	**Study type:** HRS/EHRA consensus statement.	Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies **Panel:** geneticists, arrhythmia specialists Agreement ≥ 84%	**General: Class I:** 1) sound clinical suspicion when positive predictive value > 40%, signal/noise ratio >10; 2) AND/OR genetic test result provides either diagnostic or prognostic info, or influences therapeutic choices. Screening of family members: when genetic testing leads to the adoption of therapy/protective measures/ lifestyle adaptations. LQTS: Class I: 1) any pt with strong clinical index of suspicion for LQTS; 2) any asymptomatic pt with QT prolongation on serial ECGs: QTc >480 ms prepuberty; >500 ms, adult; 3) Mutation specific genetic testing for family members and other appropriate relatives Class IIb: any asymptomatic pt with otherwise idiopathic QTc values >460 ms (puberty) or 480 ms (183) on serial ECGs CPVT: Class I: 1) any pt w strong clinical index of suspicion of CPVT;	● LQTS: Note difference between Class I if QTc >480 or 500 ms, and Class IIb if QTc >460/480 ms

			2) Mutation specific genetic testing is recommended for family members and appropriate relatives Brugada: Class I: Mutation specific genetic testing is recommended for family members and appropriate relatives **Class IIa:** any pt w strong clinical index of suspicion of BrS, including with procainamide challenge **Class III:** not indicated in the setting of an isolated type 2 or 3 Brugada ECG pattern **Short QTS: Class I:** Mutation specific genetic testing is recommended for family members and appropriate relatives **Class IIb:** any pt with strong clinical index of suspicion **ARVC: Class I:** Mutation specific genetic testing is recommended for family members and appropriate relatives **Class IIa:** can be useful for patients satisfying task force diagnostic criteria **Class IIb:** may be considered for patients with possible ACM/ARVC **Class III:** not recommended for patients with only a single minor	

			criterion according to the 2010 task force criteria **SCD/SIDS: Class I: 1)** Collection of tissue sample recommended (blood or heart/liver/spleen tissue); 2) Mutation specific genetic testing is recommended for family members and appropriate relatives **Class IIb:** testing may be considered if circumstantial evidence suggests LQTS or CPVT specifically **ACA/resuscitated: Class I:** Genetic testing should be guided by the results of medical evaluation and is used for the 1° purpose of screening at-risk family members for sub-clinical disease **Class III:** Routine genetic testing, in the absence of a clinical index of suspicion for a specific cardiomyopathy or channelopathy, is not indicated for the survivor of unexplained OHCA **HCM: Class I: 1)** any pt in whom the clinical dx of HCM is established. 2) Mutation specific genetic testing is recommended for family members and appropriate relatives	

			DCM: Class I: 1) DCM and significant cardiac conduction disease and/or family Hx of premature unexpected sudden death. 2) Mutation specific genetic testing is recommended for family members and appropriate relatives **LVNC: Class I:** Mutation specific genetic testing is recommended for family members and appropriate relatives **Class IIa:** can be useful if clinical dx of LVNC is established **PCCD: Class I:** Mutation specific genetic testing is recommended for family members and appropriate relatives **Class IIb:** may be considered as part of diagnostic evaluation for patients with either isolated CCD or CCD with concomitant congenital heart disease, especially w post family Hx of CCD.	
● Hershberger RE et al. 2010 (184) ● 20864896	**Study type:** This is a review on clinical and genetic issues in DCM	N/A	N/A	● Idiopathic DCM, has been shown to have a familial basis in 20-35% of cases. Genetic studies in familial dilated cardiomyopathy have shown dramatic locus heterogeneity with mutations identified in >30 mostly autosomal genes showing primarily dominant transmission.

● Piers et al 2013 (185) ● 24036134	**Study type:** single center, observational **Size:** 45	**Inclusion criteria:** Patients with NICM and VT treated with catheter ablation **Exclusion criteria:** N/A	**1° endpoint:** VT recurrence over mean follow up of 25±15 mo **Results:** VT occurred in 24 patients (53%), but the 6 mo VT burden was reduced by ≥75% in 79%. Recurrence rates were low after complete procedural success (18%), but high after both partial success (77%) and failure (73%).	● VT recurrence is high in NICM patients, but significant reduction in the frequency of VT episodes is observed in the majority of patients following ablation. ● There was a suggestion that patients treated with ablation early (first VT or VT ICD therapy) had better outcome than those treated late.
● Greulich et al. 2013 (186) ● 23498675	**Aim:** study aimed to demonstrate that the presence of late gadolinium enhancement is a predictor of death and other adverse events in patients with suspected CS **Study type:** Multicenter prospective **Size:** 155 patients	**Inclusion criteria**: 155 consecutive patients with systemic sarcoidosis who underwent CMR for workup of suspected cardiac sarcoid involvement. The median follow-up time was 2.6 y. **Exclusion criteria:** N/A	**1° endpoint:** 1° endpoints were death, aborted SCD, and appropriate ICD discharge. **Results:** LGE was present in 39 patients (25.5%). The presence of LGE yields a HR of 31.6 for death, aborted SCD, or appropriate ICD discharge, and of 33.9 for any event. This is superior to functional or clinical parameters such as left LVEF, LV end-diastolic volume, or presentation as HF, yielding HRs between 0.99 (per % increase LVEF) and 1.004 (presentation as HF), and between 0.94 and 1.2 for potentially lethal or other adverse events, respectively.	● Could not tell on additional LGE parameters due to low numbers.
● Kuruvilla et al. 2014 (187) ● 24363358	**Aim:** To assess the relation between CMR LGE and cardiovascular outcomes in NICM patients	**Inclusion criteria:** NICM **Exclusion criteria:** Ischemic cardiomyopathy, HCM **Intervention:** CMR-LGE findings and subsequent	**1° endpoint:** Patients with LGE had an increased risk of SCA events (OR: 5.32; p<0.00001) compared with those without LGE.	● Patients with LGE had increased overall mortality (OR: 3.27; p<0.00001) and increased HF hospitalization (OR: 2.91; p=0.02), ● The annualized event rates for SCA was 6.0% in LGE detected patients vs. 1.2% for those without LGE (p<0.001).

	Study type: Meta-Analysis **Size:** 9 studies and 1,488 patients	clinical outcomes in patients with NICM **Comparator:** N/A		
● **HELP-VT** ● Dinov B et al. 2014 (175) ● 24211823	**Study type:** single center, observational **Size:** 227 (63 NICM)	**Inclusion criteria:** Patients with SHD referred for catheter ablation of VT with either NICM (N=63) or ischemic cardiomyopathy (N=164) **Exclusion criteria:** Failure of informed consent	**1° endpoint:** VT free survival at 1 y **Results:** VT free survival 40.5% in NICM vs. 57% in ICM HR for VT recurrence for NICM 1.62 (p=0.01)	● VT free survival worse in NICM compared to ICM. ● Complete noninducibility after index procedure predicted better outcome
● Tokuda et al 2012 (188) ● 22942218	**Study type:** single center, observational **Size:** 226	**Inclusion criteria:** Patients with NICM and sustained monomorphic VT referred for catheter ablation **Exclusion criteria:** N/A	**1° endpoint:** All cause death or heart transplantation following ablation; 2° endpoint: composite of death, heart transplantation and admission for VT recurrence **Results:** After a mean of 1.4 ablation procedures 1° endpoint (4.4±3.3 y follow-up) reached in 66 (29%) patients reached the 1° end point: death in 50 (21%) and transplant in 16 (7%) 2° endpoint (12 mo): death 10%, transplant 3%, VT admission 18%	● Outcomes of ablation differ in individual etiologies of NICM. ARVC had better outcomes than DCM for 1° (p=0.002) and 2° end points (p=0.004). Sarcoidosis had worse outcome than DCM for 2° end point (p=0.002).
● Cantero-Pérez EM, et al. 2013 (155) ● 24314988	**Aim:** To evaluate the effectiveness of ICDs for primary prevention in patients with LVEF ≤30%	**Inclusion criteria:** Records from patients accepted for heart transplantation from January 1, 2006, to July	**Results:** Median follow-up of 77 d overall mortality in the ICD group was 7.1% (2/28) and in the non-	● Appropriate ICD therapies were recorded in 42.9% (12/28) in this population.

	included on the heart transplantation list **Size:** Patients who received ICDs for primary prevention (N=28) were compared with patients without ICDs (N=51)	30, 2012, and whose LVEF was <31% were reviewed	ICD group was 17.6% (9/51; p=0.062). Cause of death in patients without ICDs: Sudden death (5/9, 55.6%), HF (4/9, 44.4%). Cause of death in patients with ICDs: HFheart	
● Fröhlich GM, et al. 2013 (156) ● 23813845	**Aim:** To delineate the role of ICD therapy for the primary and secondary prevention of SCD in patients listed for heart transplantation **Size:** N=1089	**Inclusion criteria:** Patients listed for heart transplantation in 2 tertiary heart transplant centres were enrolled. Of 550 patients (51%) on the transplant list with an ICD: primary prevention ICD: N=216 secondary prevention ICD: N=334	**Results:** Median time on the waiting list = 8 mo (estimated 1-year: 88±3% vs. 77±3% vs. 67±3%; p=0.0001). An independent beneficial effect of ICDs that was most pronounced in patients who had received an ICD for primary prevention (HR: 0.4, 95% CI: 0.19–0.85; p=0.016).	● ICDs appear to be associated with a reduction in all-cause mortality in patients implanted with the device for primary and secondary prevention compared to those without an ICD.
● Gandjbakhch E, et al. 2016 (157) ● 27344378	**Aim:** To evaluate the ICD benefit on mortality in patients with end-stage HF listed for heart transplantation **Size:** N=380 consecutive patients listed for heart transplantation between 2005 and 2009 in A tertiary heart transplant centre	**Inclusion criteria:** Patients with end-stage HF receiving an ICD before or within 3 mo after being listed for heart transplantation	**Results:** 15.6% of patients died while awaiting heart transplantation. Non-ICD patients presented more often haemodynamic compromise. ICD did not remain an independent predictor of death. Death by haemodynamic compromise (76.3% of deaths), which occurred more frequently in the non-ICD group (14.7% vs. 5.8%; log-rank p=0.002). Unknown/arrhythmic deaths did not differ significantly between	● Need for mechanical circulatory support (p<0.001), low EF (p=0.001) and registration on the regular list (p=0.008) were the only independent predictors of death. ● ICD-related complications occurred in 21.4% of patients, mainly as a result of postoperative worsening of HF (11.9%).

			the two groups (3.9% vs. 1.7%; log-rank p=0.21).	
● Vakil K, et al. 2016 (158)	**Aim:** To assess the impact of ICD on waitlist mortality in patients listed for heart transplantation **Size:** N=32,599	**Inclusion criteria:** Adults (age ≥18 y) listed for first-time heart transplantation in the US between January 1, 1999, and September 30, 2014, were retrospectively identified from the United Network for Organ Sharing registry.	**Results:** Median follow-up of 154 days, 3,638 patients (11%) died on the waitlist (9% in ICD group vs. 15% in no-ICD group; p<0.0001), whereas 63% underwent heart transplantation. An ICD at listing was associated with an adjusted 13% relative reduction in mortality (HR: 0.87; 95% CI: 0.80–0.94).	● In the subgroup of patients with LVAD (N= 9,478), having an ICD was associated with an adjusted 19% relative reduction in mortality (HR: 0.81; 95% CI: 0.70–0.94).
● Oloriz et al 2014 (189) ● 24785410	**Study type:** single center, observational **Size:** 87	**Inclusion criteria:** Patients with NICM and drug refractory VT treated with ablation **Exclusion criteria:** N/A	**1° endpoint:** VT recurrence, stratified to scar location (anteroseptal vs. basal lateral) determined by unipolar voltage mapping **Results:** Over a mean 1.5 y follow up, VT recurred in 44 patients (51%) during a median follow-up of 1.5 y. Anteroseptal scar was associated with higher VT recurrence (74% vs. 25%; log-rank p<0.001) Death occurred in 15%	● Multivariate predictors of VT recurrence included electrical storm (HR: 3.211; p=0.001) and NHYA class (HR: 1.608; p=0.018), anteroseptal scar pattern (HR: 5.547; p<0.001)
● Proietti et al 2015 (190) ● 25488957	**Study type:** single center, observational **Size:** 142 (55 NICM)	**Inclusion criteria:** Patients with ischemic cardiomyopathyand NICM referred for catheter ablation for VT **Exclusion criteria:** N/A	**1° endpoint:** VT recurrence, determined by ICD interrogations over 641±301 d. **Results:** Recurrent VT occurred more frequently in the NICM group 51% than in the ischemic	● Results of substrate guided ablation less favorable in NICM than ischemic cardiomyopathy patients

			cardiomyopathy group 26% (p=0.03) Acute results (defined by response to PES) correlated with likelihood of recurrence: for the NICM group, recurrence was observed in 7, 75 and 100% of successful, partially successful and failed ablations	
● Haqqani et al 2011 (191) ● 21392586	**Study type:** single center, observational **Size:** 31	**Inclusion criteria:** Patients with NICM and VT treated with catheter ablation who had isolated intra-septal scar (11.65% of total) **Exclusion criteria:** N/A	**1° endpoint:** VT recurrence over mean followup of 20±28 mo **Results:** Following a mean of 1.6 ablation procedures, VT recurrence was observed in 32%; death and heart transplant occurred in 26% and 16% respectively	● Isolated septal substrate in NICM portended a poor outcome, both in terms of VT recurrence and transplant free survival in followup
● Kuhne et al 2010 (192) ● 20384656	**Study type:** single center, observational **Size:** 35	**Inclusion criteria:** Patients with NICM and VT treated with catheter ablation **Exclusion criteria:** N/A	**1° endpoint:** VT recurrence over mean followup of 18±13 mo **Results:** Recurrence was observed in 57%. In patients who had isolated late potentials (targeted for ablation), freedom from VT and major arrhythmia related adverse events was improved compared to those without identified isolated late potentials	
● Cano et al 2009 (193) ● 19695457	**Study type:** single center, observational **Size:** 22	**Inclusion criteria:** Patients with NICM and VT suspected to be epicardial in origin (Prior failed endocardial	**1° endpoint:** VT recurrence over mean follow up of 18±7 mo following endocardial and epicardial ablation	● The VT substrate in NICM is often more prominent on the epicardial than the endocardial surface. Epicardial ablation may improve outcome in selected patients with VT in the setting of NICM.

		ablation or ECG characteristics during VT) **Exclusion criteria:** N/A	**Results:** Freedom from VT recurrence was observed in 15 of 21 patients in whom any ablation was performed, and 14 of 18 with epicardial ablation	
● Delacretaz et al 2000 (194) ● 10695454	**Study type:** single center, observational **Size:** 26	**Inclusion criteria:** Patients with NICM and VT treated with catheter ablation **Exclusion criteria:** N/A	**1° endpoint:** VT recurrence over mean followup of 15±12 mo **Results:** VT recurrence was observed in 23%, but differed depending on VT mechanism: 40, 0 and 14% in scar related VT, focal VT and bundle branch reentry, respectively.	● Recurrent monomorphic VT in NICM can be focal or reentrant; reentrant causes can be scar related or 2° to bundle branch reentry.

Data Supplement 25. RCTs Secondary Prevention SCD in NICM – (Section 7.2.1)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **AVID** ● The AVID Investigators 1997 (131) ● 9411221	**Aim:** To examine the effect on overall survival of initial therapy with an ICD as compared with amiodarone or sotalol in patients resuscitated from VF or symptomatic, sustained VT with hemodynamic compromise. **Study type:** RCT	**Inclusion criteria:** patients who were resuscitated from near-fatal VF; sustained VT with syncope; or sustained VT with an LVEF ≤0.40 and symptoms suggesting severe hemodynamic compromise. **Exclusion criteria:** arrhythmia was judged to have a transient or correctable cause, excessively high risk (life expectancy <l y, class IV CHF, awaiting a heart transplant, or requiring a balloon pump, other mechanical means, or inotropic drug administration for hemodynamic support) or excessively low risk (event occurring within 5 d of cardiac surgery or angioplasty,	**1° endpoint:** Survival **Results:** Overall survival was greater with the ICD, with unadjusted estimates of 89.3 percent, as compared with 82.3% in the AAD group at 1 y, 81.6% vs 74.7% at 2 y, and 75.4% vs 64.1% at 3 y (p<0.02). The corresponding reductions in mortality (with 95% confidence limits) with the ICD were 39±20%, 27±21%, and 31±21%.	● Study terminated early after 1016 of 1200 patients enrolled ● 81% of patients had CAD

	Size: 1016 patients	or occurring in-hospital within 5 d after MI), had a previous ICD implant (or attempted implant), chronic serious bacterial infection, or were unable to give verbal assent due to neurologic impairment. Contraindications to amiodarone. **Intervention:** Therapy with ICD **Comparator:** AAD amiodarone or sotalol, but only 2.6% received sotalol, most received amiodarone		
● **CIDS** ● Conolly et al. 2000 (132) ● 10725290	**Aim:** To compare the efficacy of the ICD and amiodarone for the prevention of death in patients with previous sustained ventricular arrhythmia **Study type:** RCT **Size:** 659 patients	**Inclusion criteria:** in the absence of either recent AMI or electrolyte imbalance, they manifested any of the following: (1) documented VF; (2) OHCA requiring defibrillation or cardioversion; (3) documented, sustained VT causing syncope; (4) other documented, sustained VT at a rate ≥150 beats/min, causing presyncope or angina in a patient with a LVEF ≤35%; or (5) unmonitored syncope with subsequent documentation of either spontaneous VT ≥10 s or sustained (≥30 s) monomorphic VT induced by programmed ventricular stimulation. **Exclusion criteria:** (1) ICD or amiodarone not considered appropriate, (2) excessive perioperative risk for ICD implantation; (3) previous amiodarone therapy for ≥6 wk; (4) nonarrhythmic medical condition making 1 y survival unlikely, and (5) LQTS. **Intervention:** ICD **Comparator:** Amiodarone	**1° endpoint:** Death from any cause. **Results:** A nonsignificant reduction in the risk of death was observed with the ICD, from 10.2%/y to 8.3%/y (RRR: 19.7; 95% CI: -7.7%–40%; p=0.142). A nonsignificant reduction in the risk of arrhythmic death was observed, from 4.5%/y to 3.0%/y (RRR :32.8%; 95% CI: -7.2%–57.8%; p=0.094).	● 82% had ischemic etiology

● **CASH** ● Kuck et al. 2000 (133) ● 10942742	**Aim:** to study the impact on overall survival of initial therapy with an ICD as compared with that with 3 AAD. **Study type:** RCT **Size:** 288 patients	**Inclusion criteria:** patients resuscitated from CA 2° to documented sustained VA **Exclusion criteria:** If CA occurred within 72 h of an AMI, cardiac surgery, electrolyte abnormalities, or proarrhythmic drug effect. **Intervention:** ICD therapy **Comparator:** amiodarone, metoprolol, or propafenone. Assignment to propafenone was in March 1992, after an interim analysis showed a 61% higher all-cause mortality rate than in 61 ICD patients during a followup of 11.3 mo.	**1° endpoint:** The 1° end point was all-cause mortality. **Results:** Over a mean follow-up of 57±34 mo, the death rates were 36.4% (95% CI: 26.9%–46.6%) in the ICD and 44.4% (95% CI: 37.2%–51.8%) in the amiodarone/metoprolol arm. Overall survival was higher, though not significantly, in patients assigned to ICD than in those assigned to drug therapy (HR: 0.766, 97.5% CI:1.112, p=0.081).	● In ICD patients, the percent reductions in all-cause mortality were 41.9%, 39.3%, 28.4%, 27.7%, 22.8%, 11.4%, 9.1%, 10.6%, and 24.7% at 1 y to 9 of follow-up. ● CAD was etiology in 73% ● A much larger reduction of 61%, for SCD was observed
● Desai et al. 2004 (195) ● 15598919	**Aim:** To determine whether ICD therapy reduces all-cause mortality in patients with NICM. **Study type:** meta-analysis of RCT **Size:** 8 randomized trials enrolling a total of 2146 patients with NICM were included.	**Inclusion criteria:** prospective RCT of ICD or combined CRT defibrillator vs medical therapy enrolling at least some individuals with NICM and reporting all-cause mortality as an outcome. **Intervention:** ICD **Comparator:** Medical therapy.	**1° endpoint:** Two of the 3 2° prevention trials presented subgroup estimates for ICD efficacy in NICM. Pooled analysis of these 2° prevention trials (N=256 patients with NICM) indicated an equivalent to 1 y prevention but nonsignificant mortality reduction with ICD therapy (RR: 0.69; 95% CI: 0.39–1.24; p=0.22).	● Analysis of all 7 trials (1° and 2° prevention) combined demonstrated a statistically significant 31% overall reduction in mortality with ICD therapy (RR: 0.69; 95% CI: 0.56–0.86; p=0.002).
● **MAVERIC** ● Lau et al. 2004 (135) ● 15172648	**Aim:** to test the possibility of prospectively identifying patients who would benefit most ICD by EPS in	**Inclusion criteria:** survivors of sustained VT, VF or sudden cardiac death in the absence of an AMI in the last 48 h. **Exclusion criteria:** life expectancy of <6 mo from a non-arrhythmic cause or child-bearing age	**1° endpoint:** Survival and arrhythmia recurrence **Results:** Of the 108 EP arm patients, 31 (29%) received an ICD, 46 (43%) received AAD only (mainly amiodarone or sotalol) and 18 (17%)	● 61% of patients had prior MI ● EPS has a minimal impact on the diagnosis of patients presented with VT, VF or SCD.

	the context of 2° prevention. **Study type:** RCT **Size:** 214 patients	**Intervention:** EP-guided interventions (AAD, coronary revascularization, and ICD) (106 patients assigned to this arm) **Comparator:** therapy with amiodarone (108 patients assigned to this arm)	received coronary revascularization but no ICD. No significant differences in survival or arrhythmia recurrence existed between the 2 treatment arms after 6 y. However, ICD recipients had a lower mortality than non-ICD recipients, regardless of allocated treatment (HR:0.54, p=0.0391).	● The trial does not support a role for EP testing in risk stratification.
● Claro et al. 2015 (136) ● 26646017	**Aim:** To evaluate the effectiveness of amiodarone for 1° or 2° prevention of SCD compared with placebo or no intervention or any other antiarrhythmic. **Study type:** meta-analyses using a random-effects model **Size:** 24 studies (9,997 participants)	**Inclusion criteria:** Randomised and quasi-randomised trials assessing the efficacy of amiodarone vs. placebo, no intervention, or other antiarrhythmics in adults, either for 1° prevention or 2° prevention of SCD. **Exclusion criteria:** NA **Intervention:** Amiodarone **Comparator:** placebo, no intervention, or other antiarrhythmics	**1° endpoint:** SCD and overall mortality **Results:** For 2° prevention, amiodarone compared to placebo or no intervention (2 studies, 440 participants) appeared to increase the risk of SCD (RR: 4.32; 95% CI: 0.87–21.49) and all-cause mortality (RR:3.05;95% CI 1.33–7.01). However, the quality of the evidence was very low. Compared to other antiarrhythmics (4 studies, 839 participants) amiodarone appeared to increase the risk of SCD (RR:1.40; 95% CI: 0.56–3.52; very low quality of evidence), but there was no effect in all-cause mortality (RR: 1.03; 95% CI: 0.75–1.42; low quality evidence).	● For 2° prevention, the quality of the evidence was very low, so the authors concluded that there was uncertainty on the findings. ● Amiodarone was associated with an increase in pulmonary and thyroid adverse events.
● **OPTIC Study** ● Connolly et al. 2006 (159) ● 16403928	**Aim:** To determine whether amiodarone plus BB or sotalol are better than BB alone for prevention of ICD shocks.	**Inclusion criteria:** Patients were eligible if they had received an ICD within 21 d for inducible or spontaneously occurring VT or VF. **Exclusion criteria:** Patients were excluded if they had LQTS, corrected QT interval of more than 450 millisec, were receiving a	**1° endpoint:** ICD shock for any reason. **Results:** Shocks occurred in 41 patients (38.5%) assigned to BB alone, 26 (24.3%) assigned to sotalol, and 12 (10.3%) assigned to amiodarone plus BB. A reduction in	● Amiodarone plus BB is effective for preventing these shocks and is more effective than sotalol but has an increased risk of drug-related adverse effects

	Study type: multicenter RCT **Size:** 412 patients	class I or class III antiarrhythmic agent, had received amiodarone or sotalol for more than 20 consecutive d at anytime (patients who had received >10 d of amiodarone had to be taken off amiodarone for 10 d before randomization), a calculated creatinine clearance of less than 30 mL/min (<0.50 mL/s), symptomatic AF likely to require use of a class I or class III antiarrhythmic agent, absence of SHD, contraindications to amiodarone or a β-blocker, or NYHA class IV symptoms of HF. **Intervention:** amiodarone plus BB, sotalol alone **Comparator:** BB alone.	the risk of shock was observed with use of either amiodarone plus BB or sotalol vs BB alone (HR: 0.44; 95% CI: 0.28–0.68; p<0.001). Amiodarone plus BB significantly reduced the risk of shock compared with BB alone (HR: 0.27; 95% CI: 0.14–0.52; p<0.001) and sotalol (HR: 0.43; 95% CI: 0.22–0.85; p=0.02). There was a trend for sotalol to reduce shocks compared with BB alone (HR: 0.61;95% CI, 0.37–1.01; p=0.055). The rates of study drug discontinuation at 1y were 18.2% for amiodarone, 23.5% for sotalol, and 5.3% for BB alone.	● Adverse pulmonary and thyroid events and symptomatic bradycardia were more common among patients randomized to amiodarone.
● Piccini et al. 2009 (154) ● 19336434	**Aim:** To evaluate the cumulative evidence regarding the safety and efficacy of amiodarone in prevention of SCD **Study type:** Meta-analysis of all RCT examining the use of amiodarone vs. placebo/control for the prevention of SCD **Size:** 15 trials, which randomized 8,522 patients	**Inclusion criteria:** Studies in which patients were randomized to amiodarone and placebo or inactive control. Additional inclusion criteria included: treatment for >30 d, follow-up >6 mo, and availability of all-cause mortality as an endpoint **Exclusion criteria:** Studies of patients with shock-refractory VA, OHCA, patients <18 y, randomization to amiodarone vs. a class Ic or class III AAD (without a placebo or standard of care arm). Studies of patients with ICDs were excluded unless used on both arms.	**1° endpoint:** SCD, CVD, all-cause mortality, and the incidences of drug toxicities. **Results:** Amiodarone decreased the incidence of SCD (7.1 vs. 9.7%; OR: 0.71; 95% CI: 0.61–0.84; p<0.001) and cardiovascular death (14.0% vs.16.3%; OR: 0.82; 95% CI: 0.71–0.94, p=0.004). There was a 1.5% absolute risk reduction in all-cause mortality which did not meet statistical significance (p=0.093). Amiodarone therapy increased the risk of pulmonary (2.9% vs. 1.5%; OR: 1.97; 95% CI: 1.27–3.04, p=0.002), and thyroid (3.6% vs. 0.4%; OR: 5.68; 95% CI: 2.94–10.98, p<0.001) toxicity.	● Amiodarone reduces the risk of SCD by 29% and CVD by 18%, however, amiodarone therapy is neutral with respect to all-cause mortality and was associated with a two- and five-fold increased risk of pulmonary and thyroid toxicity. ● Authors suggested amiodarone as a viable alternative in patients who are not eligible for or who do not have access to ICD therapy for the prevention of SCD.

Data Supplement 26. Nonrandomized Trials, Observational Studies, and/or Registries of Secondary Prevention SCD in NICM – (Section 7.2.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Raitt et al. 2001 (137) ● 11208684	**Aim:** To determine prognostic implications of stable VT **Study type:** Observational, registry of patients with hemodynamically stable VT **Size:** The study population consisted of 440 patients with stable VT and 1029 patients with unstable VT. Of the 1029 patients with unstable VT, 330 had therapy determined by randomization in the AVID trial: 52% received an ICD, 47% amiodarone, and 2% sotalol. Therapy for the remaining 699 patients with unstable VT and the 440 patients with stable VT was determined at the discretion of the attending physician.	**Inclusion criteria:** Patients with stable VT that were not enrolled in AVID, were included in a registry of patients screened for the study. **Exclusion criteria:** Patients who had an arrhythmia within 5 d of MI, cardiac surgery, or coronary intervention were excluded, as were patients with NYHA class IV HF or those who were on a heart transplant list, had a prior ICD implant or attempted implant, or had a life expectancy of <1y.	**1° endpoint:** Mortality **Results:** The mortality in 440 patients with stable VT tended to be greater than that observed in 1029 patients presenting with unstable VT (33.6% vs 27.6% at 3 y; RR:1.22; p=0.07). After adjustment for baseline and treatment differences, the RR was little changed (RR:1.25, p=0.06).	● Sustained VT without serious symptoms or hemodynamic compromise is associated with a high mortality rate and may be a marker for a substrate capable of producing a more malignant arrhythmia
● Ruwald et al. 2014 (196) ● 24201303	**Aim:** to evaluate (1) the effects of innovative ICD programming with either a high-rate cutoff VT zone or delayed therapy on risk of syncope compared with conventional programming; (2) the independent prognostic factors associated	**Inclusion criteria:** 1500 patients from 98 hospital centers with a 1° prevention guideline indication to receive an ICD or CRT-D. **Exclusion criteria:** Patients were excluded	**1° endpoint:** Syncope was a prespecified safety end point that was adjudicated independently. Multivariable Cox models were used to identify risk factors associated with syncope and to analyze subsequent risk of mortality.	● 21 syncopal events (33%) were classified as caused by VT or VF and 4 (6%) as caused by other or unspecified arrhythmias, whereas a total of 39 events (61%) were classified as nonarrhythmogenic. ● Syncope in HF patients (with a defibrillator) is primarily vasovagal, orthostatic, or otherwise

	with syncope; and (3) the association between syncope, the cause of syncope, and the risk of death in patients enrolled in MADIT-RIT **Study type:** Subgroup analysis of MADIT-RIT. **Size:** 64 of 1500 patients (4.3%) had syncope	if they had experienced AF within 1 mo before implantation; if they previously had been implanted with a pacemaker, ICD, or CRT-D; or if they had a recent MI or revascularization procedure (within 3 mo).	**Results:** Prognostic factors for all-cause syncope included the presence of ischemic cardiomyopathy (HR: 2.48; 95% CI 1.42–4.34; p=0.002), previous VA (HR: 2.99; 95% CI 1.18–7.59; p=0.021), LVEF ≤25% (HR: 1.65; 95% CI 0.98–2.77; p=0.059), and younger age (by 10 y; HR: 1.25; 95% CI1.00–1.52; p=0.046). Syncope was associated with increased risk of death regardless of its cause (arrhythmogenic syncope: HR: 4.51; 95% CI 1.39–14.64, p=0.012; nonarrhythmogenic syncope: HR 2.97; 95% CI 1.07–8.28, p=0.038).	nonarrhythmogenic in mechanism and underscores the fact that the presence of heart disease (in this case, ischemic or nonischemic HF) does not dictate that syncope has a cardiac cause ● Syncope in HF patients is related to an increased cardiovascular risk profile and is associated with an increased risk of death regardless of its cause
● Middlekauff et al.1993 (3) ● 8417050	**Study type:** Retrospective cohort **Size:** 491 patients with CHF, of which 60 had a Hx of syncope; the condition had a cardiac origin in 29 (48%) and was due to other causes in 31 (52%).	**Inclusion criteria:** 491 consecutive patients with advanced CHF (NYHA functional class III or IV), no Hx of CA and a mean LVEF of 0.20 ± 0.07. **Exclusion criteria:** N/A	**1° endpoint:** Mortality **Results:** The actuarial incidence of sudden death by 1 y was significantly greater in patients with (45%) than in those without (12%, p<0.00001) syncope. In the Cox proportional hazards model, syncope predicted sudden death independent of AF, serum sodium, cardiac index, angiotensin-converting enzyme inhibition and patient age. The actuarial risk of sudden death by 1 y was similarly high in patients with either cardiac syncope or syncope from other causes (49% vs. 39%, p=NS).	● Authors concluded that patients with advanced HF and syncope are at especially high risk for sudden death regardless of the etiology of syncope.
● Knight et al.1999 (197) ● 10362200	**Study type:** Observational **Size:** 14 patients	**Inclusion criteria** consecutive patients who had a NICM,	**1° endpoint:** Mortality	● The authors conclude that the high incidence of appropriate ICD shocks and the association of

		unexplained syncope and a negative electrophysiology test and who underwent defibrillator implantation (Syncope Group).19 consecutive patients with a NICM and a CA who were treated with a ICD (Arrest Group) served as a control group. **Exclusion criteria:** N/A	**Results:** Seven of 14 patients (50%) in the Syncope Group received appropriate shocks for VA during a mean follow-up of 24±13 mo, compared with 8 of 19 patients (42%) in the Arrest Group during a mean follow-up of 45±40 mo (p=0.1).	recurrent syncope with VA support the treatment of patients with NICM unexplained syncope and a negative electrophysiology test with ICD.
● Brilakis et al. 2001 (198) ● 11816631	**Study type:** Observational **Size:** 54 patients	**Inclusion criteria:** Between 1990 and 1998, 54 (mean age 67±11 y, 76% men) patients presented with IDCM and syncope. **Exclusion criteria:** N/A	**Results:** An EPS was done in 37 of the 54 patients. In the 17 patients who received an ICD, incidence of appropriate shocks at 1 and 3 y was 47% and 74%, respectively, in the inducible sustained monomorphic VT group, and 40% and 40%, respectively, in the group without inducible sustained monomorphic VT (p=0.29, log-rank test)	● The authors conclude that programmed ventricular stimulation is not useful in risk stratification of patients with IDCM and syncope and may delay necessary ICD implantation.
● Fonarow et al. 2000 (199) ● 10760339	**Study type:** Observational **Size:** 147 patients	**Inclusion criteria:** 147 patients with Hx of syncope and no prior Hx of sustained VT or CA were identified. Outcomes were compared for the 25 patients managed with an ICD and 122 patients managed with	**Results:** During a mean follow-up of 22 mo, there were 31 deaths, 18 sudden, in patients treated with conventional therapy, whereas there were 2 deaths, none sudden, in patients treated with an ICD. An appropriate shock occurred in 40% of the ICD patients. Actuarial survival at 2 y was 84.9% with ICD therapy and	● The authors conclude in patients with nonischemic cardiomyopathy and syncope, therapy with an ICD is associated with a reduction in sudden death and an improvement in overall survival.

		conventional medical therapy. **Exclusion criteria:** N/A	66.9% with conventional therapy (p=0.04).	
● Olshansky et al. 2008 (200) ● 18371559	**Study type:** Subgroup analysis of SCD-HeFT trial. **Size:** 472 patients	**Inclusion criteria:** Patients in the SCD-HeFT trial who reported syncope prior of after randomization. **Exclusion criteria:** N/A	**1° endpoint:** Outcomes, including mortality, ICD discharges and SCD. **Results:** In SCD-HeFT, 162 (6%) patients had syncope before randomization, 356 (14%) had syncope after randomization (similar incidence in each randomized arm), and 46 (2%) had syncope before and after randomization. In the ICD arm, syncope, before and after randomization, was associated with appropriate ICD discharges (HR: 1.75;95% CI: 1.10–2.80, p=0.019 and HR: 2.91;95% CI: 1.89–4.47, p=0.001, respectively). Post-randomization syncope predicted total and cardiovascular death (HR: 1.41; 95% CI: 1.13–1.76, p=0.002 and HR: 1.55; 95% CI: 1.19–2.02, p=0.001, respectively). The elevated relative risk of mortality for syncope vs. nonsyncope patients did not vary significantly across treatment arms (ICD, HR: 1.54; 95% CI: 1.04–2.27; amiodarone, HR: 1.33; 95% CI: 0.91–1.93; and placebo, HR: 1.39; 95% CI: 0.96–2.02, test for difference p=0.86).	● Syncope was common in the SCD-HeFT population. Post-randomization syncope was associated with increased risk of all-cause mortality, cardiovascular mortality, and SCD (despite randomization to an ICD). Those patients randomized to an ICD, who had syncope, were more likely to receive appropriate ICD shocks than those without syncope; yet, did not protect patients against recurrent syncope and did not protect against the risk of death.

Data Supplement 27. RCTs Primary Prevention SCD in NICM – (Section 7.2.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **CAT** ● Bänsch D et al. 2002 (201) ● 11914254	**Aim:** Multicenter RCT of ICD vs. conventional Therapy in NIDCM **Study type:** RCT **Size:** 104 patients	**Inclusion criteria:** Recent onset of DCM (≤9 mo) and an EF ≤30% and class II-III **Exclusion criteria:** CAD, excessive alcohol intake, prior MI or myocarditis.	**Intervention:** ICD (N=50) **Comparator:** Conventional therapy (N=54)	**1° endpoint:** The 1° end point of the trial was all-cause mortality at 1 y. • Cumulative survival was 92%, 86%, and 73% in the ICD treatment group vs. 93%, 80%, and 68% in the control group after 2, 4, and 6 y, respectively (log rank p=0.554)	● Enrollment was terminated early because the interim analysis showed that the overall1 y mortality rate for all patients was only 5.6%, well below the assumed value of 30%. ● Because the overall mortality rate was too low, the study was stopped for futility after the pilot phase. Even if 1,348 patients had been included, as initially planned, the trial would have been underpowered.
● **AMIOVIRT** ● Strickberger et al. 2003 (202) ● 12767651	**Aim:** Multicenter RCT of ICD vs. amiodarone Therapy in NIDCM and NSVT **Study type:** RCT **Size:** 103 patients	**Inclusion criteria:** EF ≤0.35, asymptomatic NSVT, NYHA class I to III. **Exclusion criteria:** Syncope, pregnancy, a contraindication to amiodarone or ICD or concomitant therapy with a Class I AAD	**Intervention:** ICD (N=51) **Comparator:** Amiodarone (N=52)	**1° endpoint:** Total Mortality • Survival at 1 y (90% vs. 96%) and 3 y (88% vs. 87%) was similar in the amiodarone and ICD groups respectively (p=0.8).	● Trial terminated early for futility in view of lower than expected mortality. ● With the observed mortality rates, approximately 12,000 patients would have been required to achieve a power of 80%.

● **DEFINITE** ● Kadish A, et al. 2004 (203) ● 15152060	**Aim:** Multicenter RCT of ICD vs. standard medical therapy in NIDCM and ambient VA **Study type:** RCT **Size:** 458 patients	**Inclusion criteria:** EF ≤35%, and >10 PVCs/h or NSVT. **Exclusion criteria:** NYHA class IV HF, familial cardiomyopathy associated with sudden death, acute myocarditis or congenital heart disease.	**Intervention:** ICD (N=229) **Comparator:** Conventional therapy (N=229)	**1° endpoint:** Total Mortality Fewer patients died in the ICD group than in the Control group (28 vs. 40), but the difference in survival was NS (p=0.08)	● There were 3 sudden deaths from arrhythmia in the ICD group, as compared with 14 deaths in the ● Control group (HR: 0.20; 95 % CI: 0.06–0.71; p=0.006)
● **SCD-HeFT** ● Bardy et al. 2005 (43) ● 15659722	**Aim:** Multicenter RCT of ICD vs amiodarone vs. optimal medical therapy **Study type:** RCT **Size:** 2,521 patients	**Inclusion criteria:** Ischemic or non ischemic DCM, NYHA class II or III HF and LVEF ≤35% **Exclusion criteria:** N/A	**Intervention:** Amiodarone (N=845) ICD therapy (N= 829) **Comparator:** Optimal medical therapy (N=847)	**1° endpoint:** After a median follow-up of 4 y, the mortality rate was 22% in the ICD group, 28% in the amiodarone group, and 29% in the control group. This resulted in a 22% RR reduction and a 7.2% absolute risk reduction in the all-cause mortality in the ICD group as compared with optimized medical therapy alone (p=0.007)	● Amiodarone showed no benefit in survival ● Non-ischemic DCM 48% of cohort. ● Similar benefit ischemic vs. non-ischemic.
● **COMPANION** ● Bristow et al. 2004 (204) ● 15152059	**Aim:** Multicenter RCT of CRT vs. CRT-D vs. optimized medical therapy **Study type:** RCT **Size:** 1,520 patients	**Inclusion criteria:** 1,520 Ischemic or non ischemic DCM, NYHA class III or IV, LVEF ≤35% and QRS >120 msec **Exclusion criteria:** N/A	**Intervention:** CRT-D (N=595) CRT Pacer (N=617) **Comparator:** Optimal medical therapy (N=308)	**1° endpoint:** The 1° end point was a composite of death or hospitalization for any cause. CRT-P decreased the risk of the 1° end point (HR: 0.81; p=0.014), as did CT-D (HR: 0.80; p=0.01).	● A CRT pacemaker reduced the risk of the 2° end point of death from any cause by 24% (p=0.059), and a CRT pacemaker–defibrillator reduced the risk by 36% (p=0.003) ● Non ischemic 44% of cohort

• Desai et al. 2004 (195) • 15598919	**Aim:** To determine whether ICD therapy reduces all-cause mortality in patients with NICM. **Study type:** meta-analysis of RCTs **Size:** 8 RCTs enrolling a total of 2146 patients with NICM were included. 7 trials reported subgroup estimates for ICD efficacy in NICM	**Inclusion criteria:** prospective RCTs of ICD or combined cardiac resynchronization therapy and defibrillator (CRT-D) vs medical therapy enrolling at least some individuals with NICM and reporting all-cause mortality as an outcome	**Intervention:** ICD **Comparator:** Medical therapy	**1° endpoint:** Five 1° prevention trials enrolling 1854 patients with NICM were identified; pooled analysis suggested a significant reduction in total mortality among patients randomized to ICD or CRT-D vs medical therapy (RR: 0.69; 95% CI: 0.55–0.87; p=0.002). Mortality reduction remained significant even after elimination of CRT-D trials.	• Analysis of all 7 trials combined demonstrated a statistically significant 31% overall reduction in mortality with ICD therapy (RR: 0.69; 95% CI: 0.56–0.86; p=0.002).
• **DANISH** • Kober L, et al. 2016 (205) • 27571011	**Aim:** To evaluate the benefit of prophylactic ICDs in patients with systolic HF that is not due to CAD **Study type**: RCT **Size:** 1116 patients	**Inclusion criteria:** Symptomatic patients (NYHA class II or III, or NYHA class IV if CRT was planned) with nonischemic systolic HF (LVEF ≤35%) and an increased level (>200 pg/mL) of N-terminal pro–brain natriuretic peptide (NT-proBNP). **Exclusion criteria**: Patients who had permanent atrial fibrillation with a resting heart rate higher than	**Intervention**: ICD (N=556) **Comparator:** Usual care for CHF (N=560)	**1° endpoint:** Death from any cause. After a median follow-up period of 67.6 mo, the 1° outcome had occurred in 120 patients (21.6%) in the ICD group and in 131 patients (23.4%) in the control group (HR: 0.87; 95% CI: 0.68–1.12; p=0.28).	• SCD (a 2° outcome) occurred in 24 patients (4.3%) in the ICD group and in 46 patients (8.2%) in the control group (HR: 0.50; 95% CI: 0.31–0.82; p=0.005) • 58% of patients received CRT system, which could have influenced overall results. • Younger patients did show survival benefit.

		100 beats per minute or renal failure that was being treated with dialysis.			

Data Supplement 28. Nonrandomized Trials, Observational Studies, and/or Registries of Primary Prevention of SCD in NICM – (Section 7.2.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● **Marburg Cardiomyopathy Study** ● Grimm et al. 2003 (206) ● 14623812	**Aim:** To determine the clinical value of potential noninvasive arrhythmia risk predictors in a large patient cohort with IDC **Study type:** Prospective observational monocenter study **Size:** 343 patients	**Inclusion criteria:** Men and women with IDC between 16 and 70 y of age and LVEF <45% and a LV end-diastolic diameter >56 mm by echocardiography. **Exclusion criteria:** CHF NYHA functional class IV; a Hx of sustained VT or VF); an episode of unexplained syncope within the previous 12 mo; class I or class III AAD therapy that could not be withdrawn for at least 5 drug half-lives; amiodarone therapy within the previous 6 mo; pacemaker dependency; CAD diagnosed by evidence of any coronary artery stenosis >50% by angiography; or a Hx of MI, systemic arterial hypertension, active myocarditis, alcohol abuse, drug dependency, severe liver or kidney disease, thyroid disease, malignancies, or systemic diseases.	**1° endpoint:** During 52±21 mo of follow-up, major arrhythmic events were observed in 46 patients (13%), including sudden cardiac death in 23 patients and sustained VT or VF in another 23 patients **Results:** On multivariate analysis, LVEF was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10% decrease of LVEF (95% CI: 1.5–3.3; p=0.0001). NSVT on Holter was associated with a trend toward higher arrhythmia risk (RR: 1.7; 95% CI: 0.9–3.3; p=0.11), whereas BB therapy was associated with a trend toward lower arrhythmia risk (RR: 0.6; 95% CI: 0.3–1.2; p=0.13).	● Non invasive tests such as signal-averaged ECG, baroreflex sensitivity, heart rate variability, and T-wave alternans did not seem to be helpful for arrhythmia risk stratification.

● Goldberger et al. 2014 (207) ● 24445228	**Aim:** To estimate performance of 12 common risk stratification test as predictors of arrhythmic events in patients with DNICM **Study type:** meta-analysis of 12 commonly reported risk stratification tests as predictors of arrhythmic events **Size:** 45 studies enrolling 6,088 patients	**Inclusion criteria:** 45 studies involving human subjects of the following tests: baroreflex sensitivity, heart rate turbulence, heart rate variability, LV end-diastolic dimension, LVEF, electrophysiologic study, NSVT, LBBB, signal-averaged electrocardiogram, fragmented QRS, QRS-T angle, and T-wave alternans **Exclusion criteria:** N/A	**Results:** Test sensitivities ranged from 28.8% to 91.0%, specificities from 36.2% to 87.1%, and odds ratios from 1.5 to 6.7. Odds ratio was highest for fragmented QRS and TWA (OR: 6.73 and 4.66; 95% CI: 3.85–11.76 and 2.55–8.53, respectively) and lowest for QRS duration (OR: 1.51; 95% CI: 1.13–2.01). None of the autonomic tests (heart rate variability, heart rate turbulence, baroreflex sensitivity) were significant predictors of arrhythmic outcomes.	● Techniques incorporating functional parameters, depolarization abnormalities, repolarization abnormalities, and arrhythmic markers provide only modest risk stratification for sudden cardiac death in patients with NICM. ● At best, the OR for any 1 predictor is generally in the range of 2 to 4, precluding their usefulness in isolation for individual patient decisions
● Anselme et al. 2013 (208) ● 23811080	**Aim:** To evaluate a strategy of prophylactic ICD in LMNA mutation carriers with significant cardiac conduction disorders **Study type:** Prospective single center observational **Size:** 47 patients with LMNA mutations	**Inclusion criteria** ICD implant at any time during follow-up when any of the following prespecified significant conduction disorders was encountered: (1) requirement for permanent ventricular pacing for bradycardia; (2) PR interval >0.24 s and either complete LBBB (LBBB) or NSVT; (3) patients already implanted with a pacemaker at presentation to our center. **Exclusion criteria:** N/A	**1° endpoint:** Malignant VA **Results:** ICD was implanted in 21 out of the 47 patients. Among ICD recipients, no patient died suddenly and 11 (52%) patients required appropriate ICD therapy during a median follow-up of 62 mo. LVEF was ≥45% in 9 patients at the time of the event. Among the 10 patients without malignant VA, device memory recorded NSVT in 8 (80%). The presence of significant conduction disorders was the only factor related to the occurrence of malignant VA (HR: 5.20; 95% CI: 1.14–23.53; p=0.03).	● Life-threatening VAs are common in patients with LMNA mutations and significant cardiac conduction disorders, even if LVEF is preserved

● van Rijsingen et al. 2012 (209) ● 22281253	**Aim:** The purpose of this study was to determine risk factors that predict malignant VA in Lamin A/C mutation carriers **Study type:** Multicenter, retrospective analysis **Size:** 269 patients	**Inclusion criteria:** Mutation carriers older than 15 y of age with a previously published pathogenic *LMNA* mutation with cardiac involvement and persons with a newly identified *LMNA* mutation with clinical or family evidence of a laminopathy with possible cardiac involvement. **Exclusion criteria:** N/A	**1° endpoint:** First occurring MVA. MVA were defined as appropriate ICD treatment, CPR, or SCD **Results:** At median follow-up period of 43 mo (interquartile range: 17–101 mo), 48 (18%) persons experienced a first episode of MVA. Independent risk factors for MVA were NSVT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing). MVA occurred only in persons with at least 2 of these risk factors. There was a cumulative risk for MVA per additional risk factor.	● Carriers of *LMNA* mutations with a high risk of MVA can be identified using these risk factors. ● Conduction disturbances were not a risk factor in this study. ● The 4 independent risk factors were NSVT, LVEF <45% at the first clinical contact, male sex, and non-missense mutations (ins-del/ truncating or mutations affecting splicing).
● Pasotti et al. 2008 (210) ● 18926329	**Aim:** The aim of this study was to analyze the long-term follow-up of dilated cardiolaminopathies in patients with LAMIN gene mutations **Study type:** Retrospective observational longitudinal study **Size:** 94 patients	**Inclusion criteria:** 27 consecutive families in which *LMNA* gene defects were identified in the probands, all sharing the DCM phenotype. Of the 164 family members, 94 had LMNA gene mutations **Exclusion criteria:** N/A	**1° endpoint:** Events were death from any cause, death from HF, heart transplantation, and SCD, including appropriate ICD interventions **Results:** • 60 of 94 (64%) were phenotypically affected whereas 34 were only genotypically affected. • Of the 60 patients, 40 had DCM with AVB, 12 had DCM with VT/VF, 6 had DCM with AVB and EDMD2, and 2 had AVB plus EDMD2.	● Authors concluded that dilated cardiomyopathies caused by *LMNA* gene defects are highly penetrant, adult onset, malignant diseases characterized by a high rate HF and life-threatening arrhythmias. ● Neither AVB nor pacemaker implantation turned out to be predictors of events. ● NYHA class III to IV and highly dynamic ● Competitive sports for 10 y were independent predictors of total events.

			•During a median of 57 mo there were 49 events in 43 DCM patients. •The events were related to HF (15 heart transplants, 1 death from end-stage HF) and VA (15 SCDs and 12 appropriate ICD interventions).	
● van Berlo et al. 2005 (211) ● 15551023	**Aim:** To evaluate common clinical characteristics of patients with lamin A/C gene mutations that cause either isolated DCM or DCM in association with skeletal muscular dystrophy. **Study type:** Meta-analysis (pooled data) **Size:** 299 carriers of lamin A/C mutations	**Inclusion criteria:** 21 publications between March 1999 and March 2002 reporting lamin A/C gene mutations **Exclusion criteria:** Patients with familial partial lipodystrophy, progeria, axonal neuropathy and mandibuloacral dysplasia caused by mutations in the lamin A/C gene were excluded	**1° endpoint:** Arrhythmias and sudden death **Results:** • Cardiac dysrhythmias were reported in 92% of patients after the age of 30 y; HF was reported in 64% after the age of 50. • 76 of the reported 299 patients (25%) died at a mean age of 46 y. • Sudden death was the most frequently reported mode of death (46%) in both the cardiac and the neuromuscular phenotype.	● Authors conclude that carriers of lamin A/C mutations carry a high risk of sudden death. ● Presence of pacemaker did not protect against sudden death.
● Piccini et al. 2009 (154) ● 19336434	**Aim:** To evaluate the cumulative evidence regarding the safety and efficacy of amiodarone in prevention of SCD **Study type:** Meta-analysis of all RCT examining the use of amiodarone vs. placebo/control for	**Inclusion criteria:** Studies in which patients were randomized to amiodarone and placebo or inactive control. Additional inclusion criteria included: treatment for >30 d, follow-up >6 mo, and availability of all-cause mortality as an endpoint **Exclusion criteria:** Studies	**1° endpoint:** SCD, CVD, all-cause mortality, and the incidences of drug toxicities. **Results:** Amiodarone decreased the incidence of SCD [7.1 vs. 9.7%; OR: 0.71; 95% CI 0.61–0.84; p<0.001] and cardiovascular death (CVD) [14.0% vs.16.3%; OR: 0.82; 95% CI 0.71–0.94, p=0.004]. There was a 1.5% absolute risk	● Amiodarone reduces the risk of SCD by 29% and CVD by 18%, however, amiodarone therapy is neutral with respect to all-cause mortality and was associated with a 2- and 5-fold increased risk of pulmonary and thyroid toxicity. ● Authors suggested amiodarone as a viable alternative in patients who are not eligible for or who do not have access to ICD therapy for the prevention of SCD.

	the prevention of SCD **Size:** 15 trials, which randomized 8,522 patients	of patients with shock-refractory VA, OHCA, patients <18 y, randomization to amiodarone vs. a class Ic or class III AAD (without a placebo or standard of care arm). Studies of patients with ICDs were excluded unless used on both arms.	reduction in all-cause mortality which did not meet statistical significance (p=0.093). Amiodarone therapy increased the risk of pulmonary [2.9% vs. 1.5%; OR: 1.97; 95% CI 1.27–3.04, p=0.002], and thyroid [3.6% vs. 0.4%; OR: 5.68; 95% CI 2.94–10.98, p<0.001] toxicity.	
● **WEARIT-II** ● Kutyifa et al. 2015 (212) ● 26316618	**Study type:** Observational **Size:** 2000	**Inclusion criteria:** All patients with LifeVest offered patients with LVEF and a high risk for SCD after MI, following coronary revascularization, with a new-onset dilated NICM, with high risk for SCD until stabilization, or with inherited or congenital heart disease **Exclusion criteria:** refused consent	**1° endpoint:** **Results:** 805 patients (40%) had ischemic cardiomyopathy, 927 patients (46%) had nonischemic cardiomyopathy, and 268 (14%) patients were diagnosed with congenital or inherited heart disease The median age was 62 y; the median LVEF was 25%. The median WCD wear time was 90 d, with median daily use of 22.5 h.	● There was a total of 120 sustained ventricular tachyarrhythmias in 41 patients, of whom 54% received appropriate WCD shock. Only 10 patients (0.5%) received inappropriate WCD therapy. ● The rate of sustained ventricular tachyarrhythmias by 3 mo was 3% among patients with ischemic cardiomyopathy and congenital/inherited heart disease, and 1% among nonischemic patients (p=0.02). ● 90 sustained VT events in 22 patients were withheld from therapy, whereas 30 events in 22 patients required WCD shock therapy owing to hemodynamic instability (corresponding to 5 events per 100 patient y). ● All patients who required shock delivery had their VT/VF episodes successfully terminated with the first shock. ● 10 patients (0.5%, 2 per 100 patient-y) had inappropriate WCD

				therapy during the follow-up because of ECG artifacts. ● Inappropriate shocks did not induce VT or VF.
● Singh et al. 2015 (213) ● 26670060	**Study type:** observational single center **Size:** 691 (254 new NICM and 271 new ICM	**Inclusion criteria:** All consecutive patients prescribed a WCD between June 1, 2004 and May 30, 2015 at the hospitals comprising the University of Pittsburgh Medical Center to which access to clinical data was available. **Exclusion criteria:** Patients with an explanted ICD awaiting reimplantation, prior cardiac arrest unrelated to AMI, or elevated risk of SCD for reasons other than ICM or NICM.	**1° endpoint:** Appropriate WCD therapy **Results:** During 56.7 patient-y, 0 NICM patients received an appropriate WCD shock During 46.7 patient-y, 6 (2.2%) ischemic cardiomyopathypatients received an appropriate shock; 5 survived the episode, and 4 survived to hospital discharge	● Single center study
● Uyei et al. 2014 (214) ● 24893969	**Study type:** Systematic review **Size:**	N/A	**1° endpoint:** N/A **Results:** It appears that wearable defibrillator use compared with no defibrillator use reduces the chance of VT/VF associated deaths by an absolute risk reduction of approximately 1%, achieved by averting approximately 4/5th of all VT/VF associated deaths.	● The quality of evidence was low to very low quality, such that our confidence in the reported estimates is weak.
● Al-Khatib et al. JAMA Cardiology 2017 (215) ● 28355432	**Study type:** meta-analysis of RCTs **Size:** N=1,874	**Inclusion criteria:** 1° prevention ICDs in patients with NICM **Exclusion criteria:**	**1° endpoint:** all-cause mortality **Results:** Pooling data with fixed and RE models from these 4 studies	• 1° prevention ICDs are efficacious at reducing all-cause mortality in patients with NICM

		CRT Antiarrhythmic medication arm	showed a significant reduction in all-cause mortality with an ICD (HR: 0.75; 95% CI 0.61-0.93, p= 0.008; p for heterogeneity=0.873)	

Data Supplement 29. RCTs and Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Recurrent VA in Patients With NICM – (Section 7.2.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● **OPTIC Study** ● Connolly et al. 2006 (159) ● 16403928	**Aim:** To determine whether amiodarone plus BB or sotalol are better than BB alone for prevention of ICD shocks. **Study type:** multicenter RCT **Size:** 412 patients	**Inclusion criteria:** Patients were eligible if they had received an ICD within 21 d for inducible or spontaneously occurring VT or VF. **Exclusion criteria:** Patients were excluded if they had LQTS, corrected QT interval of more than 450 millisec, were receiving a class I or class III antiarrhythmic agent, had received amiodarone or sotalol for more than 20 consecutive days at anytime (patients who had received >10 d of amiodarone had to be taken off amiodarone for 10d before randomization), a calculated creatinine clearance of less than 30 mL/min (<0.50 mL/s), symptomatic AF likely to require use of a class I or	**1° endpoint:** ICD shock for any reason. **Results:** Shocks occurred in 41 patients (38.5%) assigned to BB alone, 26 (24.3%) assigned to sotalol, and 12 (10.3%) assigned to amiodarone plus BB. A reduction in the risk of shock was observed with use of either amiodarone plus BB or sotalol vs BB alone (HR: 0.44; 95% CI: 0.28–0.68; p<0.001). Amiodarone plus BB significantly reduced the risk of shock compared with BB alone (HR: 0.27; 95% CI: 0.14–0.52; p<0.001) and sotalol (HR: 0.43; 95% CI: 0.22–0.85; p=0.02). There was a trend for sotalol to reduce shocks compared with BB alone (HR: 0.61;95% CI, 0.37–1.01; p=0.055). The rates of study drug discontinuation at 1y were 18.2% for amiodarone, 23.5% for sotalol, and 5.3% for BB alone.	● Amiodarone plus BB is effective for preventing these shocks and is more effective than sotalol but has an increased risk of drug-related adverse effects ● Adverse pulmonary and thyroid events and symptomatic bradycardia were more common among patients randomized to amiodarone.

		class III antiarrhythmic agent, absence of SHD, contraindications to amiodarone or a β-blocker, or NYHA class IV symptoms of HF. **Intervention:** amiodarone plus BB, sotalol alone **Comparator:** BB alone.		
● **International VT Collaborative Group Study** ● Tung R 2015 (178)	**Aim:** to determine the association of VT recurrence after ablation and survival in scar related VT **Study type:** Multicenter observational **Size:** 2061	**Inclusion criteria:** SHD with Ischemic and Non-Ischemic cardiomyopathies with monomorphic VT and myocardial scar by electroanatomic mapping **Exclusion criteria:** absence of scar on electroanatomical mapping **Intervention:** Catheter ablation, either endocardial or epicardial, guided by EAM. End point of ablation with elimination of all induced VTs	**1° endpoint:** Freedom from VT recurrence, Heart Transplant, or death was 70% at 1 y follow-up. VT recurred in 55% of patients who died vs. 22% of patients who survived. Transplant free survival was 90% for patients without VT recurrence and 71% for those with VT recurrence (HR 6.9; 95% CI 5.3–9.0, p<0.001).	● Procedural complications occurred in 6%, including 2 deaths (0.1%), hemopericardium in 1.7%, and vascular access complications in 1.6%
● **HELP-VT** ● Dinov 2014 (175) ● 24211823	**Aim:** To determine the outcome of VT catheter ablation in patients with NICM to those with Ischemic Cardiomyopathy (ICM) **Study type:** Prospective, non-randomized	**Inclusion criteria:** Patients with SHD referred for catheter ablation of VT with either NICM (N=63) or ischemic cardiomyopathy(N=164) **Exclusion criteria:** Failure of informed consent **Intervention:**	**1° endpoint:** At 1y follow-up, VT free survival was 57% for ischemic cardiomyopathyand 40.5% for NICM patients (HR: 1.62; 95% CI: 1.12–2.34, p=0.01). ischemic cardiomyopathyrequired epicardial ablation in only 2 of 164 (1.2%) whereas NICM required epicardial ablation in 30.8% (p=0.0001).	● **Complications** Complications occurred in 11.1% of NICM and 11.1% of ischemic cardiomyopathypatients, including death in 4.8% of NICM and 3.7% of ischemic cardiomyopathy

	Size: 227 patients	Catheter ablation for patients with NICM **Comparator:** Catheter ablation in patients with ischemic cardiomyopathy		

Data Supplement 30. Nonrandomized Trials, Observational Studies, and/or Registries of Arrhythmogenic Right Ventricular Cardiomyopathy – (Section 7.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Quarta G, et al. Circ 2011 (216) ● 21606390	**Study type:** national cohort **Size:** 255	**Inclusion criteria:** 100 families with ARVC evaluated 2003-2009 first degree: 210 second degree: 45 **Exclusion criteria:** N/A	**1° endpoint: Familial evaluation for ARVC**; followup 3.4±1.6 y. Deceased proband in 51 families **Results:** in 88% of deceased: dx of ARVC made at autopsy SCD most common in young: 31% died between 14-20 y Definite or probable gene mutations; 58% of families, 73% of living probands 42% of first degree relatives had disease expression 62% of gene carriers had phenotypic expression Progressive disease expression beyond age 40 in 50%	● >50% probands died suddenly ● Desmosomal gene complexity in 10% of relatives, assoc with 5-fold increased risk of disease expression
● Kapplinger JD JACC 2011 (217) ● 21636032	**Study type:** Multi-center Netherlands, retrospective **Size:** 93 probands and 427 controls	**Inclusion criteria:** ARVC patients and 427 unrelated healthy controls	**1° endpoint:** Determine prevalence of background “noise” in ARVC genetic testing **Results:** Mutations present in 58% of ARVC and 16% of controls Radical mutations: 43% of ARVC, vs 0.5% controls	● Radical mutations are high-probablility ARVC associated mutations ● R Missense mutation should be interpreted in context of race, ethnicity, mutation location, sequence conservation; more likely

<table>
<tr><td></td><td></td><td>Tested for PKP2, DSP, DSG2, DSC2, TEME43

Added data from 82 patients in ARVD/C Registry in USA

<u>Exclusion criteria</u>:
N/A</td><td>Missense mutations: 21% of ARVC, 16% of controls</td><td>positive if Caucasian, within DSP and DSG2 hotspot, and conserved in PKP2 and DSG2 residue
● R Background mutation rate = 16% (vs 5% for LQT1-3)</td></tr>
<tr><td>● Bhonsale A, et al. CAE 2013 (218)
● 23671136</td><td><u>Study type</u>:

<u>Size</u>: 215</td><td><u>Inclusion criteria</u>:
ARVC patients with positive genotype: desmosomal mutation carriers
PKP2 85%
53% males, mean age 32 ±18 y
Presentation VT/VF 23%

<u>Exclusion criteria</u>:
N/A</td><td><u>1° endpoint</u>: Risk stratification in ARVC genotype positive: sustained VT, SCD/ADA, appropriate ICD shock
Mean followup 7 y

<u>Results:</u> 40% ACE
ECG: high risk ≥3 inverted precordial T waves; intermediate risk = T wave inversion in leads V1, V2 + late depol; low risk = 02 T wave inversion without depol changes
PVC count on holter higher in arrhythmic outcomes, p<0.0001
Event free survival lowest among probands p<0.001, and symptomatic patients p<0.001
Incremental risk: Proband, HR: 7.7; ≥3 T wave inversions, HR: 4.2; male gender, HR: 1.8</td><td>● ARVC desmosomal mutation carriers risk stratification:
● High risk: ECG ≥3 T wave inversions, Holter, proband status
● Increasing PVC’s on holter c/w arrhythmic events, > 760 PVC’
● “Benign” ECG conferred low arrhythmic risk</td></tr>
<tr><td>● Marcus FI, et al. JACC 2013 (219)
● 23500315</td><td colspan="2">Review paper for physicians summarizing genetics of ARVC

5 genes:<table><tr><td>Plakophilin- 2</td><td>73-78%</td></tr><tr><td>Desmoglein -2</td><td>10-13%</td></tr><tr><td>Desmocollin-2</td><td>4-6%</td></tr><tr><td>Desmoplakin</td><td>3-8%</td></tr><tr><td>Junctional plakoglobin</td><td>1-4%</td></tr></table></td><td><u>ARVC:</u> aut dominant, Desmosomes: cardiac, skin, hair
30-50% of patients with ARVC have abnormal gene, range 26-58%, highest in clinical familial disease. 20-30% family Hx sudden death

Negative genetic tesing ≠ no disease, as >50% gene negative to date.
Abnormal gene = risk, but not disease; modified by additional gene modifiers, virus, athletics</td><td>● Proband may not benefit from gene testing, does not alter therapy. Patients with >1 gene abnormality may have more severe course; earlier ICD.
● Benefits genetic testing ARVC: understand cause of disease, identify family members at risk, family planning, limited prognostic information.</td></tr>
</table>

	Cost ~$5400		PKP2 may require a second mutation to cause disease. The second mutation may not be tested in relatives, leading to false negative. ~48% of patients with ARVC have at least 2 different mutations; these patients have more severe disease. Truly abnormal gene should not be present in >1:400 controls; However, 1:200 Finnish have desmosomal mutation of ARVC; 6% of Asians carry PKP2 mutations. "the interpretation of genetic results for ARVC is not an exact science and is more complex than for other heart disorders caused by only a single gene and for which most patients will have an abnormal gene identified".	● For gene carriers: Recommend cardiac eval beginning at 10-12 y: ECG, SAECG, echo, holter, ± CMR ● Evaluate q 2 y between 10-20 y; then every 5 y, may stop at age 50-60 y.
● Bhonsale A et al. Eur Heart J 2015 (220) ● 25616645	**Study type:** Retrospective multicenter, Dutch, US **Size:** 577	**Inclusion criteria:** Genotype positive desmosomal and non-desmosomal mutations in ARVC. PKP2 80% Males 55%, mean age 35±17 y. 541 presenting alive: Presentation SCD= 6% 41% probands. **Exclusion criteria:** non-genotyped ARVD	**1° endpoint:** Impact of genotype on clinical course in ARVC mutation carriers. Mean followup 6±7 y. **Results:** Presentation with SCD were younger (median 23 y) than those presenting with VT (36 y) ($p<0.001$). Death 2%, transplant 2%; Sustained VT/VF 30%, LVEF < 55 14%; CHF 5%. Compound mutations: earlier onset of symptoms, higher incidence VT/VF. PKP2 least ventricular dysfunction, 9%; Desmoplakin (DSP) mutations had more ventricular dysfunction/HF than PKP2 carriers: 40% ventricular dysfunction; more likely to present with SCD (11% of SCD) Male gender higher arrhythmic outcome, 53% vs 29%	● Among ARVC patients with known genotype: specific genotype affects clinical course and disease expression. ● Gene specific variation in SCD, LV dysfunction, HF. ● Males worse outcome: more likely to be probands, symptomatic earlier and more severe arrhythmic expression. ● Phenotypic variability—modifier genes/environmental influences.

● Rigato I et al. Circ CV Genetics 2013 (221) ● 24070718	**Study type:** Prospective Observational **Size:** 134	**Inclusion criteria:** Desmosomal gene mutations carriers Desmoplakin 39%, plakophilin 2 34%, desmoglein 2 26%, desmocolliln 2 1% 16% complex genotype: compound or dignenic heterozygosity **Exclusion criteria:** N/A	**1° endpoint:** ARVC gene carriers risk of arrhythmic outcome **Results:** Median observation 39 y (22-52) 16% major arrhythmic events. Independent predictors: Multiple desmosomal gene mutations HR: 3.71; 95 CI:1.54–8.92, p=0.003. Male gender HR: 2.76; 95% CI: 1.19–6.41, p=0.02.	● Multiple DS gene mutation status was powerful predictor for major arrhythmic events.
● Groeneweg JA et al. Circ CV Genetics 2015 (222) ● 25820315	**Study type:** retrospective multicenter, Europe and USA **Size:** 1001	**Inclusion criteria:** ARVC patients Probands 44%, family members 56%. Probands: 416/439 presented alive (5% presented SCD). Overall 63% mutation positive**:** PKP2 46%. Family members: 73% mutation carriers. **Exclusion criteria:** N/A	**1° endpoint:** outcomes of ARVC patients median followup 7 y **Results:** Sustained VT developed in 72% of probands. Probands with positive mutations presented at younger age. Mortality 6%, transplantation 4%, not different based on mutation status in probands. Family members: 1/3 developed ARVC. Sustained VT 8%, cardiac mortality 2%. Mutations in family members modified course: 8x increase in VT, increased cardiac mortality. ICD improved survival in index patients: SCD 0.6% vs 16% without ICD.	● ARVC: 10% death/heart transplantation during median followup 7y. ● Probands: Mutations altered age of disease expression but not outcomes. ● Family members: mutation carriers had more VA and increased cardiac mortality.

● te Riele AS, et al. EHJ 2016 (223) ● 26314686	**Study type:** Multicenter retrospective **Size:** 274	**Inclusion criteria:** First degree relatives of ARVC proband 46% male, age 36±19 y **Exclusion criteria:** N/A	**1° endpoint:** ARVC first degree relatives: risk of ARVC dx and outcomes Mean followup 6.7±3.7 y **Results:** 35% developed ARVC Risk of ARVC dx: sibling, HR: 3.11; p<0 .001, symptoms, p<0.001, pathogenic mutation p<0.001, female, p=0.01. 8% developed sustained VA: neither relatedness to proband nor malignant family Hx were predictive of arrhythmic events.	● ARVC first degree relatives' with increased likelihood of dx: symptoms, sibling, pathogenic mutation, female gender. ● Malignant family Hx was not associated with arrhythmic events
● Kamath GS, et al., HR 2011 (224) ● 20933608	**Study type:** retrospective single center **Size:** 87	**Inclusion criteria:** ARVC probands compared with 103 controls Mean age 37 y, 54% male **Exclusion criteria:** N/A	**1° endpoint:** SAECG abnormalities in ARVC Abnormal: fQRSD ≥114 ms, LASD >38 ms, RMS-40 <20 μV **Results:** SAECG sensitivity/specificity: 1-criteria 69%/ 92%; 2-criteria 47%/95%; 3-criteria 33%/100%	● SAECG: using 1/3 criteria increased sensitivity and maintained specificity ● SAECG correlated with disease severity on CMR, but not VT
● Marcus FI, et al., Circ 1982 (225) ● 7053899	**Study type:** Single center **Size:** 22	**Inclusion criteria:** 22 adults with recurrent VT w/ LBBB 21/22 Mean age 39 y, Males 2.7:1 **Exclusion criteria:** N/A	**1° endpoint:** right ventricular abnormalities in ARVC **Results:** inverted T waves right precordium, cardiac enlargement, delayed ventricular potentials RV dysplasia– inferior, apical or diaphragmatic-diagnosed with angiography. 1 death.	● Characterize RV pathology in LBBB VT ● Consider dx in patients with VT of unknown cause, particularly if LBBB pattern
● Corrado D et al. JACC 1997 (226) ● 9362410	**Study type:** retrospective multicenter **Size:** 42	**Inclusion criteria:** Pathologic dx of ARVC at autopsy or heart transplant Mean age 29.6±18 y (9–65 y)	**1° endpoint:** ARVC clinic-pathologic manifestations **Results:** 80% died suddenly: 47% of SCD died during exertion SCD first symptom in 35%. CHF 24%	● LV involvement in 76% of ARVC: ● age dependent, ● more severe cardiomegaly ● More CHF ● Prior syncope in 26% ● SCD exercise related in 47%

		Exclusion criteria: N/A	Syncope 26% Exercise related in 64% LV fibrofatty involvement 76% Isolated RV involvement 24%	
● Link MS ert al. JACC 2014 (227) ● 25011714	**Study type:** Prospective multi-center North American ARVC Registry **Size:** 137	**Inclusion criteria:** ARVC patients enrolled in registry 79% (108 patients) received ICD's Mean age enrollment 40±14 y. Prior symptoms, sustained VT or CA 41% **Exclusion criteria:** N/A	**1° endpoint**: Sustained VA in ARVC during followup 3.3±1.7 y **Results:** 44% (48 patients) had 502 episodes of sustained VT: 97% monomorphic VT. Inapprop shocks 17%. Independent predictors sust VT: prior spontaneous VT, inferior T wave inversion. Independent predictor life threatening VT (rate ≥240bpm or VF): younger age at enrollment. ATP successfully terminated 92% of VT Patients without ICD implantation: no SCD or SVT -followup 2.4 y	● ARVC predictors of VT: sustained VT prior to ICD, inferior T wave inversion, younger age at enrollment ● 48% received ICD therapy ● Recommend programming ATP for termination of VT: successful 92% ● Syncope, family Hx SCD did not predict ICD therapy
● Corrado D et al. Circ 2015 (228) ● 26216213	International Task Force Treatment of ARVC: International Task Force Recommendations		No competitive or endurance sports; AAD's as adjunct in patients w frequent AICD shocks; BB for patients with recurrent VT, appropriate ICD rx, or ICD therapy for SVT; epicardial ablation for patients who fail endocardial approach; ICD for patients with hemo unstable sustained VT/ VF. EPS for suspected ARVC; restrict athletics to low intensity; BB for all ARVC patients irrespective of arrhythmias; cath ablation for recurrent VT fail meds other than amio. Vstim for risk stratification asymptomatic; endocardial voltage mapping; restrict comp sports in phenotype neg patients; cath ablation without ICD for selected patients	● ICD implantation: ● Hemodynamically unstable sust VT, or VF; severe systolic dysfunction RV or LVEF ≤ 35%; ● Hemodynamically stable sustained VT; unexplained syncope; mod vent dysfunction RV EF= 36-40% or LVEF= 36-45%; or NSVT ● Minor risk factors ● Prophylactic ICD in asymptomatic patients with no risk factors of healthy gene carriers.

			with drug refractory hemo stable single morphology VT. No BB for healthy gene carriers; cath ablation as alternative to ICD for prevention of SCD.	
● Corrado D et al. Circ 2003 (229) ● 14638546	**Study type:** multicenter retrospective **Size:** 132	**Inclusion criteria:** ARVC patients with ICD Mean age 40 y 70% males ICD indication: ACA 10%, sustained VT 62%, syncope 16%; nonsust VT 9%; family Hx 3% 83% on AA drugs prior to ICD **Exclusion criteria:** N/A	**1° endpoint:** ARVC appropriate ICD shocks Mean followup 39 mo **Results:** Approp shocks 48%, comps 14%, inapprop shocks 16% 84% underwent PES: 69% inducible sust VT: neither sensitive nor specific: 51% no appropr shock, 54% of non-inducible had approp rx Syncope: 21 patients: none died, one underwent OHT; 38% approp shocks; multivariate analysis p=0.07 for approp shock **Independent predictors of VF:** ACA, VT with hemodynamic compromise, younger age, LV involvement	● 48% approp ICD shocks ● Predictors: ACA, unstable VT, younger age, lower LVEF ● PES not predictive of approp shock ● Syncope not statistically important as risk factor in multivariable analysis. ● 4 patients implanted due to family Hx SCD: no approp shocks
● Piccini JP et al. Heart Rhythm 2005 (230) ● 16253908	**Study type:** single center retrospective **Size:** 67	**Inclusion criteria:** Patients with definite or probable ARVC with ICD's Mean age 36±14 y; 52% male 1° prevention 42%, 2° 58% Sustained VT: 52%, syncope 36%, ACA 58/5 **Exclusion criteria:** N/A	**1° endpoint:** ARVC clinical + EP characteristics that predict appropriate ICD shocks. Mean followup 4.4±2.9 y **Results:** Appropriate shocks in 94% of 2° prevention, 39% of 1° prevention (p=0.001), overall 66% approp shocks: Definite ARVC: 73%; probable:33% Overall 21% received shock for life threatening VT/VF >240 bpm; no difference in 1° or 2° prevention patients EPS did not predict ICD approp use in patients with 1° prevention All patients with VF had inducible VT/VF	● Multivariate predictor approp shock: sustained VT/VF, OR:11.4; p=0.015; ● NSVT, OR: 6.29, p=0.051 ● EPS did not predict ICD shocks in patients with 1° prevention ICD ● Further research to identify low risk patients who do not need ICD placement ● Syncope not statistically significant

			Syncope: 43% approp shocks, 22% no rx, p=0.08	
● Bhonsale A et al. JACC 2011 (231) ● 21939834	**Study type:** Retrospective single center **Size:** 84	**Inclusion criteria:** Definite or probable ARVC with ICD implantation for 1° prevention 63 patients genotyped: 43% + desmosomal mutations 76% symptomatic, 63% >1000 PVC's on holter Syncope: 27% **Exclusion criteria:** N/A	**1° endpoint**: Incidence and predictors of appropriate ICD shocks for ARVC undergoing ICD for 1° prevention Mean followup 4.7±3.4 y. **Results:** 48% approp ICD shocks. Predictors: Multivariable analysis: Positive VT inducibility at PES, HR: 4.5; 95% CI: 1.4–15, p=0.013), clinical nonsust VT, HR:10.5; 95% CI: 2.4–46.2, p=0.002); PVC's >1000/24 h, HR: 3.48; proband, HR:1.62. Syncope: approp shocks 9%/y. 25% approp shocks, vs 30% no approp shocks Recent syncope <6 mo: 63% appropr shocks vs 20% remote, p=0.046	● 48% ARVC patients undergoing 1° prevention ICD received appropr shocks Approp shocks: proband, inducible at EPS, clinical nonsust VT, PVCs >1000/24 hrs ● Syncope NS predictor, HR: 0.91 ● Non-inducible: 1/20 appropr ICD shock
● Dalal D et al. JACC 2007 (232) ● 17662396	**Study type:** retrospective single center **Size:** 24	**Inclusion criteria:** ARVC patients undergoing ablation at Hopkins. Mean age 36±9 y, 46% males **Exclusion criteria:** N/A	**1° endpoint:** Efficacy of ablation for ARVC. Mean followup 32 mo. **Results:** 48 procedures. 46% eliminated all inducible VT Recurrence: overall 85%. One procedural death 4%. VT recurrence free survival: 50% at 5 mos, 25% at 14 mo. Did not vary by procedural success, mapping, repeat procedures.	● High rate of recurrent VT after ablation for ARVC ● "diffuse cardiomyopathy with evolving electrical substrate"

● Garcia FC et al. Circ 2009 (233) ● 19620503	**Study type:** retrospective single center **Size:** 13	**Inclusion criteria:** ARVC patients undergoing epicardial ablation after failed endocardial ablation VT **Exclusion criteria:** N/A	**1° endpoint:** Endocardial vs epicardial ablation in ARVC **Results:** 27 VT's in 13 patients 85% epi ablation opposite endocardial ablation sites 77% no VT with 18±13 mo followup	● Epicardial ablation in ARVC after failed endocardial ablation results in VT control
● Philips B et al. Circ AE 2012 (234) ● 22492430	**Study type:** Retrospective multicenter **Size:** 87	**Inclusion criteria:** ARVC patients undergoing ablation 1992-2011 at 80 centers. Mean age 33±11 y, 53% male 50% failed endocardial ablation **Exclusion criteria:** N/A	**1° endpoint:** ARVC Efficacy of epicardial ablation of VT. **Results:** 175 ablations in 87 patients: 53% repeat procedures. 27% recurrent VT; VT reduction Freedom from VT at 1, 5, 10y: 47%, 21%, 15%. Epicardial ablation: freedom from VT at 1, 5 y: 64%, 45% Burden of VT reduced irrespective of ablation strategy: $p<0.001$ Complications: 2.3% major: death; delayed MI/occlusion RCA. Related to pericardial access.	● Epicardial ablation of VT in ARVC associated with high recurrence rate, but reduces VT burden. ● Majority of VT circuits were epicardial.
● Bai R, et al. CAE 2011 (235) ● 21665983	**Study type:** Multicenter prospective **Size:** 49	**Inclusion criteria:** Consecutive ARVC patients undergoing ablation All sust monomorphic VT; all with AICD's **Exclusion criteria:** N/A	**1° endpoint:** Comparison of outcomes for ARVC ablation, endocardial vs endo-epicardial: non-inducibility of VT with isuprel. Followup 3 y **Results:** Freedom from VA or ICD therapies: Endocardial: 52%, endo-epi 85%, $p=0.029$	● Combined endocardial-epicardial ablation approach in ARVC achieves longer term freedom from VA or shocks. ● Patients with frequent PVC's more likely to have recurrences
● Berruezo A et al. Circ AE 2012 (236) ● 22205683	**Study type:** retrospective single center	**Inclusion criteria:** ARVC patients undergoing endo +	**1° endpoint:** ARVC patients: recurrence of VT after ablation endo + epicardial	● ARVC combined endo + epi ablation reveals wider substrate, with good short/mid-term success

	Size: 11	epicardial ablation of VT **Exclusion criteria:** N/A	**Results:** ablation eliminated all clinical and induced VT 64% continued on sotalol 9% VT recurrence with median 11 mo followup	
● Philips B Heart Rhythm 2015(237) ● 25530221	**Study type:** retrospective single center **Size:** 30	**Inclusion criteria:** ARVC undergoing epicardial ablation at tertiary center **Exclusion criteria:** N/A	**1° endpoint:** Safety and efficacy of epicardial ablation at tertiary center for ARVC **Results:** VT circuits: 69% on epicardial surface, most sub-tricuspid. VT recurrence: 27%. Reduced VT burden (p<0.001) VT free survival at 1,2 y: 76%, 70% Complications: 3.3%, pericarditis. Fluoro 82 min (40-135)	● Epicardial ablation for VT in ARVC safe in tertiary center ● Freedom from VT 70% at 2 y. ● Reduces VT burden
● Santangeli P et al. Circ AE 2015 (238) ● 26546346	**Study type:** Retrospective single center **Size:** 62	**Inclusion criteria:** ARVC patients undergoing ablation Endo + epi: 63% **Exclusion criteria:** N/A	**1° endpoint:** ARVC ablation outcomes, followup 56±44 mos Epicardial ablation if failed endocardial ablation **Results:** VT recurrence: 29%; VT free survival 71% 64% on BB or no rx	● ARVC VT ablation outcomes 'good'; most have VT control
● James CA et al. JACC 2013 (239) ● 23871885	**Study type:** Single center retrospective **Size:** 87	**Inclusion criteria:** ARVC patients interviewed about exercise from 10 y of age. Mean age 44±18 y **Exclusion criteria:** N/A	**1° endpoint:** ARVC exercise and VT/VF **Results:** Endurance athletes developed symptoms at younger age (30±13 y) vs 40 y, p=0.05; Increasing exercise Lower lifetime survival free of VT/VF p=0.013	● Endurance and frequent exercise increase the risk of VT/VF, HF in ARVC patients.
● Sawant AC et al. JAHA 2014 (240) ● 25516436	**Study type:** single center retrospective **Size:** 82	**Inclusion criteria:** ARVC patients interviewed re exercise	**1° endpoint:** ARVC: exercise and impact on desmosomal and gene-elusive patients	● Gene-elusive non-familial ARVC is assoc with very high intensity exercise ● Recommend exercise restriction

		Desmosomal mutations: 39 Gene-elusive 43 **Exclusion criteria:** N/A	**Results:** all gene-elusive patients were endurance athletes; more intense exerscie, p<0.001 Family Hx more often neg in gene-elusive Gene-elusive patients with most intense exercise had younger age at presentation, p=0.025, shorter survival free of VEA, p=0.002	
● Ruwald AC et al. EHJ 2015 (241) ● 25896080	**Study type:** North Americal ARVC registry, 18 centers US, Canada **Size:** 108 probands	**Inclusion:** ARVC Registry probands. **Exclusion criteria:** Age <12 y; ICD >2 y before enrollment; unknown exercise level before dx	**1° endpoint:** ARVC exercise and VT/VF/SCD followup 3 y **Results:** Patients in competitive sports: Younger at age of Dx, 71% inducible VT/VF, increased risk death/VT.	● Competitive sports associated with HR: 2.05 for VTA/death and earlier presentation of symptoms, c/w recreational sports or inactive
● Sawant AC Heart Rhythm 2016 (242) ● 26321091	**Study type:** Single center retrospective **Size:** 28	**Inclusion criteria:** ARVC first degree relatives of probands with PKP2 mutation, interview re exercise since age 10 y; exercise vs AHA recommendations to restrict to 390-650 MET-HR/y **Exclusion criteria:** N/A	**1° endpoint:** ARVC and outcomes with exercise intensity (MET-HR/y) **Results:** After adjusting for age, sex, family; participation in endurance athletics, (OR: 7.4, p=0.03), higher intensity exercise (OR: 4.2, p=0.004) were associated with dx of ARVCD. Family members restricting exercise to ≤650 MET-Hr/yr (AHA upper limits) were sig less likely to have ARVC dx (OR: 0.07, p=0.002); no VT/VF (AHA/AC Sports Med recommend healthy adults participate in minimum, 450-750 MET-min weekly =390–650 MET-Hr/y)	● Recommend restricting unaffected desmosomal mutation carriers from endurance and high-intensity athletics, but not from AHA recommended minimum levels of exercise for heatlhy adults
● Saberniak J et al. Eur J Heart F 2014 (243) ● 25319773	**Study type:** single center **Size:** 110	**Inclusion criteria:** ARVC probands and mutation positive family members	**1° endpoint:** ARVC assess exercise ventricular function with echo, CMR Athlete: intensity ≥6 METS, duration ≥4 h/wk **Results:** Function reduced in athletes' vs non-athletes by echo and MRI, all p<0.01.	● ARVC athletes showed reduced biventricular function compared with non-athletes and mutation-positive family members

		Genotyping in 100 patients 75% mutation positive, PKP 91%, Syncope 44%, ICD 47% **Exclusion criteria:** N/A	METs x min/wk correlated with reduced RV and LV function p<0.01 LVEF by MRI reduced in athletes, index and family members Exercise induced VA in 37% of patients, more likely in athletes p<0.001 and in those w increased duration exercise ≥2.5 h/wk x 6 y	● Amount and intensity of exercise was assoc with impaired LV and RV function ● Exercise aggravates, accelerates myocardial dysfunction in ARVC
● Sen-Chowdry S et al. JACC 2008 (244) ● 19095136	**Study type:** observational cohort **Size:** 42	**Inclusion criteria:** ARVC patients w clinical suggestion of LV involvement: one or more: RBBB morphology arrhythmia, isolated (infero) lateral T wave inversion, proven family dx LV ARVC or idiopathic myocardial fibrosis Clinical eval: includes CMR (41 patients): consensus >2 readers; echo, holter, exercise test, mutation screening **Exclusion criteria:** HCM, ischemia, other structural heart/lung/systemic disease	**1° endpoint:** ARVC presenting as LV dominant arrhythmogenic cardiomyopathy (LDAC): CMR & clinical **Results:** Desmosomal mutations present in 45% of probands, 33% of families Arrhythmia of RBBB morphology exceeding degree of ventricular dysfunction distinguished ARVC from dilated cardiomyopathy CMR: 88% RV segmental dil and/or wall motion abnormality; 27% low RVEF; LV involvement 34% dilation or decreased EF. LV late gadolinium enhancement Inflammatory myocarditis on genetic basis: 10% prior “myocarditis”	● LV dominant ARVC subtype under-recognized ● Unexplained T wave inversion V5, V6± V4, I, aVL ● VT of RBBB morphology, ● LV aneurysms ● LV dilation and/or systolic impairment with arrhythmic presentation ● Extensive LGE of LV myocardium ● “inflammatory myocarditis part of nat Hx of ARVC”

● Vermes E et al. JACC CV Imaging 2011 (245) ● 21414577	**Study type:** retrospective cohort, single center **Size:** 294	**Inclusion criteria:** Patients referred for ARVC evaluation by CMR 2005–2010 **Exclusion criteria:** N/A	**1° endpoint:** Compare ARVC CMR criteria from 1994–2010; also, assessed 134 patients with full diagnostic evaluation for ARVC Results: original CMR criteria: 23.5% major; using 2010: 6.5% major Of 69 patients with major criteria 1994, only 23% had major criteria 2010 Of 172 with minor---only 1.1% minor criteria 2010 Also, assessed 10 patients with proven ARVC on complete evaluation: 4/10 met major criteria, none met minor Specificity for major/minor criteria: 1994-78/39%; 2010: 94/96%	● 2010 criteria reduced major + minor CMR criteria: from 23.5% to 6.5% ● new TFC for CMR improved specificity, but may have reduced sensitivity
● te Riele AS et al. JCE 2013(246) ● 23889974	**Study type:** multicenter retrospective: international registry ARVC **Size:** 80	**Inclusion criteria:** ARVC mutation positive patients undergoing CMR, EPS. CMR 74, EPS in 11 patients PKP2 83% **Exclusion criteria:** N/A	**1° endpoint:** ARVC electro-anatomical correlates CMR, EPS Mean followup 6 y **Results:** CMR: abnl RV 96%, biventricular: 52%, LV only: 4%. ACE 41%: VT 67%, approp ICD shock 23%, ACA 10%. Arrhythmia free survival lower in patients with more abnormal RV segments 24 patients with advanced structural abnormalities: 1,5, 10 y arrhythmia free survival= 57%, 42%, 35% EPS: scar more extensive in epicardium vs endocardium, p<0.0001; scar map correlated with CMR locations: RV epicardial scar subtricuspid 100%, RV basal anterior wall 64%	● CMR: basal inferior (94%) and basal anterior RV (87%) and posterolateral LV involvement (80% subepicardial fat infiltration). ● RV apex involved only in advanced disease. ● Epicardial delayed activation particularly in perivalvar RV area and LV posterolat wall. ● RVOT involved late in disease.

			Ablation successful in 18/19 VT: 84% were from RV; no VT from RV apex	
● te Riele AS et al. JACC 2013 (247) ● 23810894	**Study type:** prospective registry based **Size:** 69	**Inclusion criteria:** ARVC mutation carriers without sustained VA 78%: first degree relatives 83% PKP2 mutations Mean age 27±15 y **Exclusion criteria:** ARVC with prior sustained VA	**1° endpoint:** ARVC mutation carriers undergoing risk stratification: incremental value of ECG, Holter, CMR. Mean followup 6 y **Results:** 78% holter; ECG, CMR in all 68% asymptomatic at presentation Abnormal ECG: 57%, abnormal Holter 26% (PVC's >500/24 h, or nonsust VT >100 bpm Abnormal CMR 30% patients with abnormal ECG/Holter: 48% had abnormal CMR, vs 4% in patients with normal ECG/Holter, p<0.0001 Only 1 pt with normal ECG/holter had abnormal CMR. Development of sust VA: 16% mean time to arrhythmia 4.5 y All patients with sust VA presented with electrical abnormalities; all had abnormal CMR. Patients with both electrical and CMR abnormalities: higher VA, p <0.0001: arrhythmia free survival at 1,5,10 y: 89%, 54%, 36%.	● Presence of mutation alone did not confer arrhythmia risk. ● ECG & holter abnormalities preceded detectable CMR abnormalities in ARVC mutation carriers ● ECG PLUS CMR abnormalities identify high risk group; ●**?** ICD for 1° prevention ● "Evaluation of cardiac structure and function using CMR is probably not necessary in the absence of baseline electrical abnormalities"
● Liu T et al. J Cardiovasc magn Reson 2014 (248) ● 24996808	**Study type:** retrospective cohort **Size:** 968	**Inclusion criteria:** patients referred 1995-2010 for CMR with clinical suspicion of ARVC If quantitative RV measures not avail, repeat CMR performed Mean age 42 y	**1° endpoint:** ARVC: effect of revised TFC on CMR criteria vs 1994 criteria. **Results:** 2010 criteria reduced no. of total patients meeting diagnostic CMR criteria from ~23% to 2.6%: 2.2% met major criteria, 0.4% met minor CMR identified alternatic dx in 9.2% of patients, and 4.4% of dx were "potential	● 2010 criteria reduced number of total patients meeting diagnostic CMR criteria ● Only 2.6% met diagnostic criteria on CMR ● More objective, quantified criteria in ARVC dx by CMR

		Males 52% **Exclusion criteria:** N/A	mimics" af ARVC-sarcoidosis, other cardiomyopathies.	
● Marcus FI et al. Circ 2010 (249) ● 20172911	Modifications of Task Force criteria for ARVC		**1° endpoint**: Quantification, specificity of ARVC diagnostic criteria. Structural, ECG, arrhythmic and genetic features as major and minor, with quantitative criteria. SAECG: fQRS fQRSD >114 ms, LASD ≥38 ms, RMS-40 ≤20 μV, terminal activation duration QRS ≥55 ms V1,2, or 3 See major criteria at right Dx: 2 major, or 1 major plus 2 minor, or 4 minor from different groups RV fat not part of CMR criteria Added mutation status in proband	● Major criteria ● Dysfunction: echo, MRI, angio regional dyskinesia, akinesia, dyssynchrony AND dilation; echo FAC ≤33%, ● CMR RVEF ≤40%; RVEDVI ≥100–110 ml/m^2 (Female/male); localized RV aneurysms or severe segmental dilatiom ● Tissue bx: residual myocytes <60%● ECG Repol: age >14 y: Twave inversion V1, V2, and V3; ● Depolarization: epsilon V1-3; ● Arrhythmia: nonsust/sust VT of LBBB, superior axis ● Family hx: ARVC confirmed in first degree relative by TFC, surgery or autopsy; or pathogenic mutation in proband
● Corrado D et al. Circ 2010 ● 20823389	**Study type**: Multicenter retrospective **Size:** 106	**Inclusion criteria:** consecutive ARVC patients with ICD implanted for 1° prevention Mean age 36 y Males 67% Syncope 39% NSVT 53%, family Hx SCD 46% **Exclusion criteria:** Prior sust VT/VF	**1° endpoint:** ARVC appropr ICD shocks in 1° prevention Mean followup 58 mo **Results:** approp shocks: 24%; inapprop shocks 19%; comps 17% PES: performed in 60% of patients: 40 patients (60%) inducible. 65% did not receive approp therapy; of non-inducible 30% received approp rx. PES PPV 35%, neg PV 70% Syncope: 43% approp shocks, 4 had recurrent syncope without arrhythmia	● Overall group had high arrhythmic risk: Univariate analysis: approp shocks: younger, syncope, NSVT, LV dysfunction ● Multivar analysis: syncope only predictor, HR: 3.16, p=0.005 ● No pt with ICD implanted for family Hx only had appropriate shocks
● Marcus GM et al. JACC 2009	**Study type:** Retrospective multi-	**Inclusion criteria:** ARVC patients in	**1° endpoint:** Suppression of VEA on AA meds in ARVC	● Overall BB not associated with increase or decrease in VEA;

● 19660690	center North American ARVC Registry **Size:** 95	Registry treatment with ICD and AA drugs **Exclusion criteria:** N/A	**Results:** BB: used in 61%, (58 patients): no increase or decrease in VEA; atenolol (20 patients) assoc with decreased risk VEA, HR: 0.25; 95% CI: 0.08–0.80, p=0.018. Sotalol 38 patients: increased risk ICD shock; in high dose 320 mg (6 patients) VEA HR: 14.0; 95%CI: 1.6–125, p=0.018. Amio (10 patients) lower risk VEA, HR: 0.25; 95% CI: 0.07–0.95.	Atenolol associated with decreased risk VEA ● Sotalol increased risk ICD shock Amio lower risk VEA
● Hershberger RE J Card Fail 2009 (250) ● 19254666	Genetic evaluation of Cardiomyopathy		Guideline restricts the indication for genetic testing to that of facilitation of family screening and management. Ie, Testing is used for risk stratification of family members who have little or no clinical evidence of disease. Recommendations: Careful family Hx for ≥3 generations, for all patients. Clinical screening recommended at intervals for asymptomatic at-risk relatives who are mutation carriers; Clinical screening for asymptomatic first degree relatives when genetic testing has not been performed/or mutation not identified. Genetic screening for Fabry disease in all men w unexplained cardiac disease. Referral to centers expert in genetic evaluation and family based management.	● Details of clinical screening & intervals given: ● SAECG in ARVC only ● CMR in ARVC ● Childhood: screening intervals specified relative to ages and mutation status ● Especially LMNA mutations

			Genetic testing for the one most clearly affected person in a family to facilitate family screening and management. ICD may be considered before the LVEF falls below 35% in patients with CM and significant arrhythmia or known risk of arrhythmia.	
● Marcus FI et al. HR 2009 ● 19560088	**Study type:** Multicenter retrospective **Size:** 108	**Inclusion criteria:** North American ARVC/D Registry probands 57% male Mean age at dx 38 y 34% competitive athletes Symptoms: ~ all Syncope 21% VA 70% Sustained VT 35% Genotype: 100 patients: 33% positive: PKP2 present in 22% **Exclusion criteria:** N/A	**1° endpoint:** Study ARVC clinical eval and diagnostic utility of 7 tests: ECG, SAECG, holter, echo, MRI, RV angio, biopsy in 108 probands referred to core center. Followup mean 27 mo. **Results:** 78% of probands classified as affected after evaluation Biopsy performed in 59%: should not target septum but should target RV free wall; sarcoidosis found in 3 patients 15% viral infection: Parvovirus 4; enterovirus not found: ARVC may predispose to viral myocarditis and accelerate disease progression Among 86 patients referred with diagnosis, 23% did not meet TFC, reclassified as borderline, or not ARVC (2 patients)-mainly due to CMR interpretation at referring vs core lab-only 63% confirmed	● Biopsy and CMR least helpful ● Diagnostic eval favors: ECG, SAECG, echo, RV angio ● Recommend minimum diagnostic eval: ECG, SAECG, Holter, echo, RV angio Diagnostic performance of CMR and biopsy was less than with other tests
● Choudhary N et al. JCE 2016 ● 26840461	**Study type:** Multicenter **Size:** 125	**Inclusion criteria:** ARVC probands in North American ARVC Registry Males 56% 109 genotype testing **Exclusion criteria:** N/A	**1° endpoint:** Presentation, outcomes ARVC by gender Mean followup 37 mo **Results:** ACE more likely in “affected” vs “borderline” ICD VT/VF or SCD: no difference Fast VT/VF or death in women trend to lower risk, HR: 0.41	● No major gender differences in outcomes ● Women highest risk age: 31-40 y ● ARVC females: increased PVC’s on Holter, 2200 vs 1089, p=0.016 ● SAECG: ACE in females-equal in patients w or w/out abnl SAEC ● In males, ACE more likely if abnl SAECG

			Males: Increase in Abnormal SAECG 81% vs 48%, p<0.001, inducible VT/VF 60% vs 40%, p=0.026 Overall VT/VF shocks: 27% women, 41% men Genotype positive: 38%, of positive: PKP-2 71%; genotype = gender ≥2 mutations: 8%	● cardiac events not different in genotype positive vs negative
● Saguner AM AJC 2013 ● 23103200	**Study type:** Prospective single center **Size:** 62	**Inclusion criteria:** ARVC patients undergoing EPS **NOTE** prior to study 39% had clinical hemodynamically compromised VT or VF; 32% sust VT stable; 50% syncope; NYHA Class II-III 31%; LVEF <50% in 24% RV FAC <33% in 48% **Exclusion criteria:** N/A	**1° endpoint:** ARVC utility of V-stim to predict outcomes: positive EP = sustained monomorphic VT only, triple VEST, =/- isuprel **Results:** 55% sustained monomorphic VT inducible at PES correlated with increased risk adverse outcome Inducibility of sust monomorphic VT (HR: 2.52; 95% CI:1.03–6.16, p=0.043) and nonadherence to meds and activity restrictions (HR: 2.34; 95% CI: 1.1–4.99, p=0.028) PPV 65%, NPV 71% Anti-tach pacing successfully terminated VT > 90% of cases	● study included symptomatic patients with clinical VT/VF/syncope and ventricular dysfunction ● Cannot identify how many patients were asymptomatic with normal ventricular function

Data Supplement 31. Nonrandomized Trials, Observational Studies, and/or Registries of Hypertrophic Cardiomyopathy – (Section 7.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Maron et al. 2000 (251) ● 10666426	**Study type:** Retrospective, multicenter, observational **Size:** 128 patients	**Inclusion criteria:** HCM patients at high risk for SCD treated with ICD **Exclusion criteria:** Inadequate data	**1° endpoint:** ICD shock from VT or VF **Results:** At 3.1 y follow up, the ICD delivered appropriate therapy in 23% of patients (7%/y). 25% of patients had an inappropriate shock. Therapy for 1° prevention patients was 5%/y; and for 2° prevention 11%/y.	● VT or VF are the principal mechanisms of SCD in HCM ● ICDs are highly effective in high risk patients
● Christiaans et al. 2009 (252) ● 19533783	**Study type:** observational, single center **Size:** 143 patients	**Inclusion criteria:** Predictively tested HCM mutation carriers followed by questionnaire **Exclusion criteria:** inadequate data	**1° endpoint:** satisfaction with genetic counseling **Results:** Genetic counseling was valued positively and only 4 carriers would rather not have known that they were a mutation carrier.	● The majority of genetic carriers of HCM gene(s) were satisfied with genetic counseling ● Receiving information by mail was satisfactory
● Hamang et al 2012 (253) ● 21773878	**Study type:** Prospective, multi-center observational study **Size:** 126 patients	**Inclusion criteria:** Norwegian patients with a clinical diagnosis or genetic risk of HCM attending genetic counseling **Exclusion criteria:** inadequate data	**1° endpoint:** Development of heart-focused anxiety **Results:** 1 y of follow-up questionnaires after genetic counseling. Patients with a clinical diagnosis of HCM compared to genetic risk had higher avoidance ($p<0.002$), attention ($p<0.005$) and fear ($p<0.007$).	● Patients with a clinical diagnosis of HCM receiving genetic counseling continue to experience anxiety. ● Patients with a genetic risk for HCM had less anxiety if they experienced satisfaction with genetic counseling

●Bos JM et al 2014 (254) ● 24793961	**Study type:** Single center, observational data registry **Size:** 1053 patients	**Inclusion criteria:** Established clinical HCM diagnosis **Exclusion criteria:** Inadequate data	**1° endpoint:** Genetic testing for HCM **Results:** 1053 patients with clinical HCM (mean age 44.4±19 y) had genetic testing evaluating 9 HCM-associated myofilament genes. 34% were positive or a HCM mutation. .	● Predictors of a positive genetic test were reverse curve morphological subtype, age <45 y, LV wall thickness ≥20 mm, family history of HCM, and family history of SCD. Hypertension was not predictive. ● A positive genetic test was predicted in 6% of patients with only hypertension and 80% with all 5 predictor markers.
● O'Mahony et al. 2014 (255) ● 24126876	**Study type:** Prognostic model derived from a retrospective, multicenter longitudinal cohort study Clinical risk prediction model for SCD in HCM **Size:** 3,675 patients	**Inclusion criteria:** HCM patients **Exclusion criteria:** inadequate data	**1° endpoint:** SCD or appropriate ICD shock **Results:** Median follow-up 5.7 y; 5% of patients had SCD/ICD shock. 8 pre-specified predictors were associated with SCD/ICD shock at 15% significance level. Model developed to estimate probability of SCD at 5 y. For every 16 ICDs implanted in patients with a ≥4% 5-y SCD risk, potentially 1 pt will be saved.	● Risk modifiers for SCD used in the model were age, maximal LV wall thickness, left atrial diameter, LV outflow tract gradient, family Hx of SCD, non-sustained VT, and unexplained syncope ● This is the first validated SCD risk prediction model for patients with HCM and provides accurate individualized estimates for the probability of SCD using clinical parameters.
● Elliott et al. 1999 (256) ● 10334430	**Study type:** single center, observational Survival after SCD or sustained VT in HCM: treated with amiodarone or ICD **Size:** 16 patients	**Inclusion criteria:** HCM patients surviving resuscitated VF or syncopal sustained VT **Exclusion criteria:** inadequate data	**1° endpoint:** Survival free from SCD or appropriate ICD shock **Results:** 8 patients on amiodarone and 6 received an ICD. Mean follow-up 6.1±4 y 2 patients on amiodarone with SCD and 3 patients had appropriate ICD shock.	● ICD therapy was better than amiodarone at preventing recurrent SCD ● Small numbers and purely observational without controls reported.

● Maron et al. 2007 (257) ● 17652294	**Study type:** Retrospective, multicenter, registry ICD to prevent SCD in HCM **Size:** 506 patients	**Inclusion criteria:** HCM patients at high risk for SCD treated with ICD **Exclusion criteria:** Inadequate data	**1° endpoint:** ICD shock from VT or VF **Results:** 20% had appropriate treatment of VT/VF: 10.6% per y for 2° prevention and 3.6%/y for 1° prevention. Time to 1st appropriate shock was 10 y. Appropriate discharge was similar in patients with 1, 2, or 3 risk factors (p=0.77)	● ICDs are highly effective in high risk patients ● One death due to VT/VF when ICD failed to function ● Inappropriate shocks in 27% of patients ● A single modifier of high risk for SCD may be sufficient to justify ICD placement
● Lin G et al. 2009 (258) ● 19282314	**Study type:** Retrospective, single center, registry Complications and inappropriate ICD shocks in HCM patients **Size:** 181 patients	**Inclusion criteria:** Patients with HCM receiving ICD **Exclusion criteria:** Inadequate data	**1° endpoint:** Inappropriate shocks and device complications **Results:** Mean follow up 4.92 y. 36% of patients had complications and 23% inappropriate shocks (5.3% per y). Appropriate shocks 4%/y.	● Inappropriate shocks and device complications are significant in HCM patients receiving an ICD ● Younger patients and those with AF more likely to have problems
● Syska et al. 2010 (259) ● 20132378	**Study type:** Retrospective, observational, single center Efficacy and complications of ICD therapy in HCM **Size:** 104 patients	**Inclusion criteria:** HCM patients at high risk for VT/VF treated with ICD **Exclusion criteria:** Inadequate data	**1° endpoint:** ICD therapy and relation to clinical risk profile **Results:** Average follow up 4.6 y. 53.8% of 2° prevention patients received an appropriate therapy and 16.7% of 1° prevention patients. Complications: inappropriate shocks (33.7%), lead dysfunction (12.5%), and infections (4.8%).	● ICD therapy is effective in HCM, although the complication rate is significant. ● 1, 2, or more risk modifiers did not predict appropriate ICD therapies

● O'Mahony et al. 2012 (260) ● 21757459	**Study type:** Retrospective, observational, single center, cohort Efficacy and complications of ICD therapy in HCM **Size:** 334 patients	**Inclusion criteria:** HCM patients at high risk for VT/VF treated with ICD **Exclusion criteria:** Inadequate data	**1° endpoint:** ICD therapy and complications **Results:** 8% of patients received appropriate shocks (2.3%/y). 16% of patients received inappropriate shocks (4.6%/y). 18% had implant complications (5.1%/y) and 30% had inappropriate shocks (8.6%/y).	● HCM patients with an ICD are exposed to frequent inappropriate shocks and implant complications
● Melacini et al. 2007 (261) ● 17502652	**Study type:** Retrospective, single center, observational Pharmacological treatment to prevent SCD in HCM **Size:** 173 patients	**Inclusion criteria:** HCM patients on AAD **Exclusion criteria:** Inadequate data	**1° endpoint:** Risk of sudden death **Results:** 10% of patients had SCD over an average of 62 mo: 20% on amiodarone (6/30), 9% on verapamil (4/46) and BB (7/76), and 0% on sotalol (0/21)	● Medical treatment is not absolutely protective against risk of SCD in HCM.
● McKenna et al. 1985 (262) ● 4039188	**Study type:** single center, observational Improved survival with amiodarone in HCM and VT **Size:** 86 patients	**Inclusion criteria:** HCM patients with NSVT on Holter **Exclusion criteria:** inadequate data	**1° endpoint:** SCD, recurrent VT **Results:** 24 patients during 1976-1977 had NSVT and received conventional AAD: 7 patients had SCD during 3 y follow-up. 21 patients from 1978-1979 with NSVT received amiodarone: no SCD on amiodarone during 3 y follow-up.	● Amiodarone was better than conventional medications for preventing SCD. Study design was purely observational
● Olivotto et al.1999 (263) ● 10362212	**Study type:** Prospective, single center observational	**Inclusion criteria:** Patients with HCM who underwent exercise testing	**1° endpoint:** Mortality **Results:** 22% had an abnormal BP response (9	● An abnormal BP response during exercise in HCM was associated with CV mortality

	Prognostic value of BP response during exercise in HCM **Size:** 128 patients	**Exclusion criteria:** Inadequate data	with hypotension, 19 with failed BP rise). 4.7±3.7 y follow up, 7% died (3 SCD, 6 HF). An abnormal BP response predicted increased risk for CV mortality (OR: 4.5; 95% CI: 1.1–20.1).	● However, the positive predictive value was only 14%. Negative predictive value 95%
● Sadoul et al.1997 (264) ● 9386166	**Study type:** Prospective, single center observational Prognostic value of BP response during exercise in HCM **Size:** 161 patients	**Inclusion criteria:** Patients with HCM who underwent exercise testing **Exclusion criteria:** Inadequate data	**1° endpoint:** Mortality **Results:** 37% had an abnormal BP response. During 44±22 mo follow up, SCD occurred in 12 patients: 3% in normal BP group and 15% in abnormal BP response group.	● A normal BP response during exercise identifies low risk young patients with HCM. ● An abnormal response had a low (15%) positive predictive value and a high (97%) predictive value.
● Sorajja et al. 2006 (265) ● 16762758	**Study type:** Single center, retrospective, longitudinal data base. Clinical implications of massive hypertrophy in HCM **Size:** 107 patients	**Inclusion criteria:** HCM patients with LVH ≥ 30 mm **Exclusion criteria:** inadequate data	**1° endpoint:** Survival **Results:** 10-y outcome assessed. Survival less than general population (77% vs 95%, p<0.001). SCD most common cause of mortality in younger patients (overall survival 80%)	● Patients with HCM and massive LVH are at increased risk of SCD, especially in the young.
● Maki et al. 1998 (266) ● 9761089	**Study type:** single center, retrospective, data base analysis Hemodynamic predictors of SCD in HCM **Size:** 309 patients	**Inclusion criteria:** Patients with HCM **Exclusion criteria:** Inadequate data	**1° endpoint:** SCD **Results:** Mean follow-up 9.4 y; SCD in 9%. Independent predictors of SCD were a smaller difference between peak and rest SBP during exercise (p=0.006), and higher LV outflow tract pressure gradient at rest (p=0.003). Exercise-related	● Patients with exercise-related SCD were younger and had smaller increases in SBP during exercise.

			SCD in 8 patients and exercise-unrelated SCD in 20 patients (mean age 28 vs 47 y, p<0.05).	
● Elliott et al. 2006 (267) ● 16754630	**Study type:** Single center, retrospective, data base LV outflow track obstruction and SCD risk in HCM **Size:** 917 patients	**Inclusion criteria:** HCM patients with LV outflow tract gradient measured **Exclusion criteria:** inadequate data	**1° endpoint:** SCD **Results:** 31.4% had LV outflow tract gradient ≥ 30 mmHg, followed median of 61 mo, 5.9% had SCD, VF, or appropriate ICD shock. LV outflow tract gradient ≥30 mmHg associated with reduced survival free from SCD and ICD shock (91.4% vs 95.7%. p=0.004)	● LV outflow tract gradient ≥ 30 mmHg was an independent risk modifier for SCD/ICD shock with a 2.4-fold (p=0.003) increase in the risk of SCD/ICD shock that is increased if other risk modifiers are present. ● Risk of SCD/ICD shock low (0.37% annual risk) if the only risk modifier is an increased LV outflow tract gradient
● Monserrat et al. 2003 (268) ● 12957435	**Study type:** Retrospective, single center, observational NSVT and risk for SCD in young HCM patients **Size:** 531 patients	**Inclusion criteria:** HCM with Holter monitoring **Exclusion criteria:** Inadequate data	**1° endpoint:** Sudden cardiac death **Results:** 19.6% had NSVT. Mean follow up 70±40 mo. 32 died from SCD, 21 had an ICD placed with 4 appropriate shocks. The OR of SCD in HCM 30 y or younger was 4.35 (95% CI: 1.54–12.28; p=0.006); compared with 2.16 (95% CI: 0.82–5.96; p=0.1) in patients older than 30 y.	• NSVT was associates with a substantial increased risk of SCD in young patients with HCM • No relationship between duration, frequency and rate of NSVT runs and adverse events.
● Spirito et al. 2000 (269) ● 10853000	**Study type:** Retrospective, single center, observational LVH and risk of SCD in HCM **Size:** 480 patients	**Inclusion criteria:** HCM patients **Exclusion criteria:** Inadequate data	**1° endpoint:** SCD **Results:** 23 patients (4.8%) had SCD with a mean follow up of 6.5 y. The risk of SCD increased with wall thickness: 0 per 1,000 pt y if	● The cumulative risk of SCD was nearly 0 for a wall thickness of 19 mm or less; and was 40% The sudden death risk in HCM was increased for a left ventricular wall thickness of 30 mm or more.

			15 mm or less, to 18.2 per 1,000 pt y if 30 mm or more (95% CI: 7.3–37.6).	
● Elliott et al. 2001 (270) ● 11273061	**Study type:** Retrospective, single center, observational Severe hypertrophy and SCD in HCM **Size:** 630 patients	**Inclusion criteria:** HCM patients **Exclusion criteria:** Inadequate data	**1° endpoint:** Sudden cardiac death **Results:** 39 patients (6.2%) had SCD or appropriate ICD shock; 10 had a wall thickness of 30 mm or more. Wall thickness of 30 mm or more had a higher probability of SCD or shock: (RR: 2.07; 95% CI: 1.0–4.25; p=0.049)	● A wall thickness in HCM of 30+ mm was associated with SCD. ● Most sudden deaths occur in patients with a thickness less than 30 mm so the presence of other risk factors is important
● Elliott et al. 2000 (271) ● 11127463	**Study type:** Retrospective, single center, observational Risk factors for SCD in HCM **Size:** 368 patients	**Inclusion criteria:** HCM patients **Exclusion criteria:** Inadequate data	**1° endpoint:** Sudden cardiac death **Results:** Follow up 3.6±2.5 y. The SCD free survival was 95% with 0 risk factors, 93% for 1, 82% for 2, and 36% for 3. Six y SCD risk was 72% (95% CI: 56%–88%) for 2+ risk factors and 94% (95% CI: 91%–98%) for 1 or 0.	● Risk factors for SCD include NSVT, syncope, exercise BP response, family Hx of SCD, left ventricular wall thickness ● 2 or more risk factors had a high risk for SCD
● Ackerman et al. 2002 (272) ● 12084606	**Study type:** Genetic analysis in unrelated HCM patients Malignant mutations in HCM **Size:** 293 patients	**Inclusion criteria:** HCM patients consenting to genetic analysis **Exclusion criteria:** Inadequate data	**1° endpoint:** Genetic abnormalities **Results:** 4 beta myosin heavy chain and one troponin T gene mutation assessed. 3 of the 293 patients had one of the 5 mutations and all 3 <25 y.	● There is profound heterogeneity in HCM ● Only1% of unrelated individuals had one of the 5 “malignant” mutations.
● Lopes et al. 2013 (273)	**Study type:** Meta-analysis	**Inclusion criteria:** Studies evaluating	**1° endpoint:** Genetic mutation	● HCM is a heterogeneous disease.

● 23674365	Meta-analysis of genetic mutations in HCM **Size:** 18 publications, 2,459 patients	genetic mutations in HCM **Exclusion criteria:** Poor study design	**Results:** Sarcomere gene mutation associated with younger age (p<0.0005), family Hx of HCM (p<0.0005), family Hx of SCD (p<0.0005) and greater wall thickness (p=0.03).	● The establishment of precise genotype-phenotype relationships could not be established
● Bos et al. 2010 (274) ● 21059440	**Study type:** Multicenter, consecutive patients, prospective data base, observational Family Hx and SCD in HCM **Size:** 177 patients	**Inclusion criteria:** HCM patients with and without a family Hx of SCD in 1st degree relatives who received an ICD. **Exclusion criteria:** Inadequate data	**1° endpoint:** SCD or appropriate ICD discharge **Results:** 4.6±3 y follow up, 25 patients (14%) had an appropriate ICD therapy. Patients with a family Hx of SCD experience ICDs shocks at a rate (3.7/100 person-y) similar to patients with other risk factors (3.1/100 pt y).	● Patients receiving ICD for 1° prevention because of a family Hx of SCD whether as an isolated risk factor or combined with other markers, experience rates of appropriate ICD discharge comparable to that of other risk factors.
● Spirito et al. 2009 (275) ● 19307481	**Study type:** Observational, prospective data base entry Syncope and risk of SCD in HCM **Size:** 1,511 patients	**Inclusion criteria:** HCM patients **Exclusion criteria:** Inadequate data	**1° endpoint:** Relationship between syncope and SCD **Results:** 205 patients (14%) had unexplained or neurally-mediated syncope. 5.6±5.2 y follow up, 74 patients (4.9%) had SCD. Relative risk of SCD was 1.78 (95% CI: 0.88–3.51; p=0.08) in unexplained syncope and 0.91 (95% CI: 0.0– 3.83; p=1.0) in neurally-mediated syncope.	● Unexplained syncope was a risk factor for SCD in HCM ● Patients ≤40 y with syncope occurring >5 y before evaluation did not show an increased risk of SCD. ● Neurally mediated syncope was not predictive of SCD
● Maron et al. 2009 (276) ● 19221222	**Study type:** Retrospective, registry data	**Inclusion criteria** Athletes who died suddenly	**1° endpoint:** cause of SCD	● Athletes confined to United States ● CVD was found in 54% of the deaths

	Sudden deaths in young competitive athletes. **Size:** 1,866 patients	**Exclusion criteria:** inadequate data	**Results:** Average age 19±6 y. The most common cardiovascular cause was HCM (36%)	● HCM was the most common finding in young athletes experiencing SCD due to a cardiac cause.
● Kuck et al. 1988 (277) ● 3280318	**Study type:** observational, single center, consecutive Role of PVS in HCM **Size**: 54 patients	**Inclusion criteria:** symptomatic and asymptomatic patients with HCM **Exclusion criteria:** inadequate data	**1° endpoint:** results of PVS **Results** 11 symptomatic and 43 asymptomatic patients. 33% of had inducible rabid monomorphic or polymorphic VT, VF.	● PVS induced VA in 33% of both symptomatic and asymptomatic HCM patients.
● Zhu et al. 1998 (278) ● 9474693	**Study type:** observational, single center, consecutive Role of PVS in HCM **Size**: 53 patients	**Inclusion criteria:** HCM patients with no Hx of SCD **Exclusion criteria:** inadequate data	**1° endpoint:** results of PVS and long term follow-up **Results:** Sustained polymorphic VT or VF induced in 35%. Mean follow-up 47±31 mo: no events (VT, VF, or ICD shock) in 34 patients with a negative PVS, 3 events in 19 patients with positive PVS.	● Sustained polymorphic VT/VFinducible in 1/3 of patients with HCM with a low subsequent event rate.
● Christiaans et al. 2010 (279) ● 20019025	**Study type:** observational, single center, registry data The yield of risk stratification for SCD in HCM myosin-binding C gene mutation carriers; focus on predictive screening **Size:** 245 patients	**Inclusion criteria:** Asymptomatic carriers of an MYBPC3 gene mutation **Exclusion criteria:** inadequate data	**1° endpoint:** diagnosis of HCM, long-term outcome **Results:** Clinical HCM was diagnosed in 53 of 235 mutation carriers (22.6%). Women were affected less than men (15% and 32% respectively, p=0.003)25 carriers (11%) with one or more risk factors for SCD and manifest HCM could be at risk for SCD.	● At first cardiac evaluation 22.6% of asymptomatic carriers were diagnosed with HCM ● Risk factors for SCD were frequently present and 11% of carriers could be at risk for SCD. ● Predictive genetic testing in HCM families and frequent cardiac evaluation for the presence of HCM and risk factors for SCD are justified until advanced age.
● Olivotto et al. 2008 (280)	**Study type:** Multicenter, prospective, cohort	**Inclusion criteria:** Unrelated patients with	**1° endpoint:** clinical outcomes related to HCM	● Screening for sarcomere protein gene mutations in HCM identifies a

● 18533079	Myofilament protein gene mutation screening and outcome of patients with HCM **Size:** 203 patients	HCM with genetic testing of the 8 HCM-susceptibility genes **Exclusion criteria:** inadequate data	**Results:** Mean follow-up 4 y. 62% of patients had mutations (Myofilament-positive HCM) and 38% were myofilament-negative. Myofilament-positive patients at increased risk for CV death, stroke, Class III or IV HF (25% vs 7% HR: 4.27; p=0.008)	broad subgroup of patients with increased propensity toward long-term impairment of LV function and adverse outcome ● These findings were irrespective of the myofilament (thick, intermediate, or thin) involved.
● Ingles et al. 2013 (281) ● 23598715	**Study type:** Multicenter, retrospective, data base analysis Clinical predictors of genetic testing outcomes in HCM **Size:** 265 patients	**Inclusion criteria:** Probands with HCM and genetic testing **Exclusion criteria:** inadequate data	**1° endpoint:** Identify clinical variables that can predict probands with HCM in whom a pathogenic mutation will be identified **Results:** 52% of 265 patients had at least one mutation. Detection rate was higher with positive family Hx (72 vs 29%, p<0.0001) and positive family Hx of SCD (89 vs 59%, p<0.0001).	● Family Hx is a key clinical predictor of a positive genetic diagnosis and has direct clinical relevance, particularly in the pretest genetic counseling setting. ● Multivariate analysis identified female gender, increased LV wall thickness, family Hx of SCD as being associated with the greatest chance of identifying a gene mutation.
● Jensen et al 2013 (282) ● 23197161	**Study type:** single center, observational, data registry Penetrance of HCM in children and adolescents: a 12-y follow-up study of clinical screening and predictive genetic testing **Size:** 90 probands and 361 relatives	**Inclusion criteria:** HCM patients and their relatives with clinical screening and predictive genetic testing **Exclusion criteria:** inadequate data	**1° endpoint:** Penetrance of HCM of child relatives of patients with HCM **Results:** After a mean follow-up of 12 y, 2 of the 36 (6%; 95% CI: 2-18) at-risk child relatives who were phenotype negative at conclusion developed HCM phenotype at 26 and 28 y of age.	● The penetrance of HCM in phenotype-negative child relatives at risk of developing HCM was 6% after 12 y of follow-up. ● The finding of phenotype conversion in the mid-20s warrants continued screening into adulthood. ● 42% of the child relatives were non-carriers, and repeat clinical follow-up could be safely limited to the remaining children.

● Bos JM et al 2013 (274) ● 24793961	**Study type:** Single center, observational data registry Characterization of a phenotype-based genetic test prediction score for unrelated patients with HCM **Size:** 1053 patients	**Inclusion criteria:** Established clinical HCM diagnosis **Exclusion criteria:** Inadequate data	**1° endpoint:** Genetic testing for HCM **Results:** 1053 patients with clinical HCM (mean age 44.4 ± 19 y) had genetic testing evaluating 9 HCM-associated myofilament genes. 34% were positive or a HCM mutation. .	● Predictors of a positive genetic test were reverse curve morphological subtype, age <45y, LV wall thickness ≥20mm, family Hx of HCM, and family Hx of SCD. Hypertension was not predictive. ● A positive genetic test was predicted in 6% of patients with only hypertension and 80% with all 5 predictor markers.
● Girolami F et al 2010 (283) ● 20359594	**Study type:** Multicenter, observational data registry Clinical features and outcome of HCM associated with triple sarcomere protein gene mutations **Size:** 488 patients	**Inclusion criteria:** Patients with clinical HCM undergoing genetic testing **Exclusion criteria:** Inadequate data	**1° endpoint:** The presence of triple sarcomere gene mutations **Results:** Of 488 unrelated index HCM patients, 4 (0.8%) had triple mutations and significant events during follow up.	● 4 patients with HCM (0.8% of cohort) had triple sarcomere gene mutations ● The clinical outcome in the 4 patients included resuscitated SCD in 1; ICD implantation due to risk factors in all 4 with appropriate shocks in 2; and 3 progressed to end-stage HCM by 4th decade with transplant in 1 and biventricular pacing in 2.
● Hershberger RE J Card Fail 2009 (250) ● 19254666		Genetic evaluation of Cardiomyopathy	Guideline restricts the indication for genetic testing to that of facilitation of family screening and management. Ie, Testing is used for risk stratification of family members who have little or no clinical evidence of disease. Recommendations: Careful family Hx for ≥3 generations, for all patients. Clinical screening recommended at intervals for asymptomatic at-risk	● Details of clinical screening & intervals given: SAECG in ARVC only CMR in ARVC ● Childhood: screening intervals specified relative to ages and mutation status ● Especially LMNA mutations

			relatives who are mutation carriers; Clinical screening for asymptomatic first degree relatives when genetic testing has not been performed/or mutation not identified. Genetic screening for Fabry disease in all men w unexplained cardiac disease. Referral to centers expert in genetic evaluation and family based management. Genetic testing for the one most clearly affected person in a family to facilitate family screening and management. ICD may be considered before the LVEF falls below 35% in patients with CM and significant arrhythmia or known risk of arrhythmia.	
● Klues HG, et al. 1995 (284) ● 7594106	**Aim:** To achieve an understanding of the true structural heterogeneity of HCM **Size:** N=600 patients	**Inclusion criteria:** Patients with LV hypertrophy	**Results:** LV wall thickness = 15–52 mm (mean 22.3±5). Various patterns of asymmetric LV hypertrophy were identified Hypertrophy involved:	● In HCM the distribution ofLV hypertrophy is characteristically asymmetric and particularly heterogeneous, encompassing most possible patterns of wall thickening and with no single morphologic expression considered typical or classic.

			2 left ventricular segments (228 patients [38%]) or ≥3 segments (202 patients [34%]) 1 segment in a substantial number of patients (170 [28%]). The anterior portion of the ventricular septum: most frequently showed thickening (573 patients [96%]), and the predominant site of hypertrophy in most patients (492 patients [83%]).	● A greater extent of LV hypertrophy was associated with younger age and more marked mitral valve systolic anterior motion and outflow obstruction but showed no relation to either magnitude of symptoms or gender.
● Adabag AS, et al. (285) ● 17126660	**Aim:** To determine the clinical circumstances under which HCM is identified **Size:** N=711	**Inclusion criteria:** HCM patients who underwent a diagnostic echocardiography	**1° endpoint:** Clincail trigger **Results:** HCM was initially suspected only after the onset of cardiac symptoms or acute cardiac events in 384 patients. In 327 patients, HCM was recognized while patients were asymptomatic: 225 by routine medical evaluations, 27 of whom HCM was recognized during preparticipation examinations for competitive sports or other activities.	● Patients with extreme hypertrophy (wall thickness ≥30 mm) and those at high risk for sudden death were more often asymptomatic and identified by routine or family screenings ($p<0.0001$ and $p=0.004$, respectively).

			Women, older patients (age ≥50 years), and those with outflow obstruction at rest (gradient ≥30 mm Hg) were more likely suspected to have HCM by virtue of cardiac symptoms or events (p<0.0001).	
● Afonso LC, et al. 2008 ● 19356516	**Aim:** To profile the utility and pitfalls of established echocardiographic modalities and discuss the evolving role of novel echocardiographic imaging modalities such as tissue Doppler, Doppler-based strain, 2-dimensional strain (speckle tracking imaging), and 3-dimensional imaging in the assessment of HCM.			● At the time of this paper, tissue Doppler-derived strain and 2D strain or speckle tracking imaging represent robust and rapidly evolving technologies that have advanced our understanding of regional myocardial mechanics in HCM. ● Ongoing refinements and additional research will define the incremental role and clinical utility of these promising techniques, including the identification of preclinical disease in carriers of HCM mutations, improvement of diagnostic accuracy, risk stratification, planning therapeutic strategies, and monitoring treatment.

Data Supplement 32. Nonrandomized Trials, Observational Studies, and/or Registries of Myocarditis – (Section 7.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Cooper et al.1997 (286) ● 9197214	**Study type:** observational, multicenter data base Natural Hx of giant-cell myocarditis **Size:** 63 patients	**Inclusion criteria:** Giant cell myocarditis **Exclusion criteria:** inadequate data	**1° endpoint:** survival **Results:** Rate of death or cardiac transplantation 89%; median survival from onset of symptoms 5.5 mo.	● Giant cell myocarditis is often fatal due to HF and VA
● Kandolin et al. 2013 (287) ● 23149495	**Study type:** observational, retrospective, single center Management of giant-cell myocarditis with immunosuppression **Size:** 32 patients	**Inclusion criteria:** giant-cell myocarditis treated with immunosuppression **Exclusion criteria:** inadequate data, unable to use immunosuppression	**1° endpoint:** survival **Results:** Transplant-free survival 69% at 1 y, 58% at 2 y, 52% at 5y. 59% experienced sustained VA during follow up and 3 received ICD shocks for VT or VF.	● 2/3 of patients with giant-cell myocarditis are free from severe HF or transplantation on immunosuppression ● 59% experience life-threatening VT or VF
● Maleszewski et al. 2015 (288) ● 25882774	**Study type:** retrospective, observational, multicenter data base Long-term risks in giant cell myocarditis **Size:** 26 patients	**Inclusion criteria:** Patients with giant-cell myocarditis surviving >1 y without heart transplantation **Exclusion criteria:** inadequate data, need for transplantation	**1° endpoint:** Survival free from death, transplant **Results:** mean age 54.6±13.9 y, follow up 5.5 y starting 1 y after diagnosis. 12% died; 19% transplanted; 23% had 19 episodes of VT or VF	● The risk of disease recurrence and progression is high in giant-cell myocarditis treated with immunosuppression ● Life-threatening VT or VF occurred in 23% of patients during long-term follow up
● **WEARIT/BIROAD** ● Feldman et al. 2004 (289) ● 14720148	**Study type:** Prospective registries were combined Use of the wearable defibrillator. **Size:** 289 patients	**Inclusion criteria:** symptomatic HF and EF <0.30 (WEARIT) or patients at high risk for SCD after MI or bypass surgery (BIROAD)	**1° endpoint:** appropriate shock form the wearable defibrillator **Results:** 4 mo follow up. 6 of 8 defibrillation attempts successful; 6 inappropriate	● The wearable defibrillator was successful in defibrillating 75% of events ● 24% of patients did not tolerate the device

		Exclusion criteria: inadequate data	shocks. 6 SCD during study: 5 not wearing and 1 incorrectly wearing device. 68 did not tolerate vest	
● Kao et al. 2012 (290) ● 23234574	**Study type:** multicenter, prospective registry Wearable defibrillator in HF **Size:** 82 patients	**Inclusion criteria:** HF patients awaiting transplantation, dilated cardiomyopathy, or receiving inotropic medicines **Exclusion criteria:** inadequate data	**1° endpoint:** sudden death **Results:** 75±58 d follow up. No episodes of sudden CA.	● The event rate was too low to allow assessment of the wearable defibrillator

Data Supplement 33. Nonrandomized Trials, Observational Studies, and/or Registries of Cardiac Sarcoidosis – (Section 7.6)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Naruse et al. 2014 (291) ● 24837644	**Aim:** This study sought to describe both clinical and EP characteristics and outcomes of systematic treatment approach to VT associated with CS. **Study type:** Single center observational **Size:** 37 patients	**Inclusion criteria:** 37 consecutive patients (11 men; age, 56±11 y) with a diagnosis of sustained VT associated with CS. Clinical effects of a systematic treatment approach including medical therapy (both steroid and antiarrhythmic agents), in association with radiofrequency catheter ablation, were evaluated. **Exclusion criteria:** N/A	**1° endpoint:** freedom from any VT **Results:** During a 39 mo follow-up, 23 (62%) patients were free from any VT episodes with medical therapy. Fourteen patients who experienced VT recurrences even while on drug therapy underwent radiofrequency catheter ablation. After a 33 mo follow-up subsequent to the radiofrequency catheter ablation, 6 of 14 patients experienced VT recurrence. The number of VTs sustained during EPS was higher in the patients with VT recurrence than in those without (3.7±1.4 vs 1.9±0.8; $p<0.01$).	

● Takaya Y, et al. 2015 (292) ● Am J Cardiol. 2015 Feb 15 ● 25529542	**Aim:** to assess outcomes in patients with AVB as an initial manifestation of cardiac sarcoidosis compared with those in patients with VT and/or HF. **Study type:** single center observational **Size:** 53 pts	**Inclusion criteria:** Fifty-three consecutive patients with cardiac sarcoidosis, who had high-degree AVB (N=22) or VT and/or HF (N=31), were enrolled **Exclusion criteria:** N/A	**1° endpoint:** major adverse cardiac events, including cardiac death, VF, sustained VT, and hospitalization for HF. **Results:** Over a median follow-up period of 34 mo, the outcomes of major adverse cardiac events were better in patients with high-degree AVB than in those with VT and/or HF (log-rank test, p=0.046). However, this difference was due mainly to HF hospitalization. The outcomes of fatal cardiac events, including cardiac death, VF, and sustained VT, were comparable between the 2 groups (log-rank test, p=0.877	● Positive myocardial uptake of ^{67}Ga or ^{18}F-FDG disappeared after the initiation of steroid treatment in all patients, and high-degree AVB recovered in some patients, indicating that steroid treatment was effective but might not be sufficient for preventing the fatal cardiac events in patients with high-degree AVB.
● Kandolin et al. 2015 (293) ● 25527698	**Aim:** assess the epidemiology, characteristics, and outcome of CS in Finland **Study type:** Retrospective **Size:** 110 patients	**Inclusion criteria:** adult (>18y of age) patients diagnosed with histologically confirmed CS in Finland between 1988 and 2012. A total of 110 patients (71 women) 51±9 y of age (mean±SD) were found and followed up for outcome events to the end of 2013. **Exclusion criteria:** N/A	**1° endpoint:** serious cardiovascular events **Results:** Altogether, 102 of the 110 patients received immunosuppressive therapy, and 56 received an ICD. Left ventricular function was impaired (LVEF <50%) in 65 patients (59%) at diagnosis and showed no overall change over 12 mo of steroid therapy. During follow-up (median, 6.6 y), 10 patients died of a cardiac cause, 11 patients underwent transplantation, and another 11 patients suffered an aborted SCD. The KM estimates for 1-, 5-, and 10-y transplantation-free cardiac survival were 97%, 90%, and 83%, respectively. HF at presentation predicted poor outcome (log-rank p=0.0001) with a 10 y transplantation-free cardiac survival of only 53%.	● With current therapy, the prognosis of CS appears better than generally considered, but patients presenting with HF still have poor long-term outcome. ● Steroids appeared to stabilize disease but not reverse it. 10-y estimate of transplantation-free cardiac survival was as high as 91% in patients who were diagnosed clinically and received contemporary immunosuppressive and device therapy. ● EF <35% was most important predictor of outcomes

● Yazaki et al. 2001 (294) ● 11703997	**Aim:** To determine the significant predictors of mortality and to assess the efficacy of corticosteroids **Study type:** retrospective multicenter in Japan **Size:** 95 patients	**Inclusion criteria:** 95 Japanese patients with CS. Twenty of the 95 patients had never received corticosteroid therapy because the sarcoidosis had not been diagnosed before their deaths; sarcoidosis was proved at autospy. The other 75 patients treated with corticosteroids were classified into 2 cohorts according to initial LVEF obtained by contrast left ventriculography or echocardiography: LVEF ≥50% (N=39) or LVEF <50% (36). **Exclusion criteria:** N/A	**1° endpoint:** predictors of mortality **Results:** During the mean follow-up of 68 mo, 29 patients (73%) died of CHF and 11 (27%) experienced sudden death. KM survival curves showed 5-y survival rates of 75% in the steroid-treated patients and of 89% in patients with a LVEF ≥ 50%, whereas there was only 10% 5 y survival rate in autopsy subjects. Multivariate analysis identified NYHA functional class HR: 7.72 per class I increase, p=0.0008), left ventricular end-diastolic diameter (HR: 2.60/10 mm increase, p=0.02), and sustained VT (HR: 7.20, p=0.03) as independent predictors of mortality.	● Authors concluded that the severity of HF was one of the most significant independent predictors of mortality for CS. Starting corticosteroids before the occurrence of systolic dysfunction resulted in an excellent clinical outcome
● Aizer A, et al. 2005 (295) ● Am J Cardiol. 2005 ● 16018857	**Aim:** To evaluate the utility of programmed ventricular stimulation to predict future arrhythmic events in patients with cardiac sarcoidosis **Study type:** Single center **Size:** 32 pts	**Inclusion criteria:** Consecutive patients with cardiac sarcoidosis underwent programmed ventricular stimulation. Patients with spontaneous or inducible sustained ventricular arrhythmias (N=12) underwent ICD insertion **Exclusion criteria:** NA	**1° endpoint:** appropriate ICD therapies or sudden death **Results:** 5 of 6 patients (83%) with spontaneous sustained ventricular arrhythmias and 4 of 6 patients (67%) without spontaneous but with inducible sustained ventricular arrhythmias received appropriate ICD therapy. 2 of 20 patients (10%) with neither spontaneous nor inducible sustained ventricular arrhythmias experienced sustained ventricular arrhythmias or sudden death. Programmed ventricular stimulation predicted subsequent arrhythmic events in the entire population (relative HR: 4.47; 95% CI: 1.30–15.39) and in patients	● Most patients had syncope, NSVT or presysncope and mean EF in the inducible was 33.2±17.0

			who presented without spontaneous sustained ventricular arrhythmias (relative HR: 6.97; 95% CI: 1.27–38.27).	
● Mehta D., et al. 2011 (296) ● Circ Arrhythm Electrophysiol. 2011 ● 21193539	**Aim: to** assess the value of programmed electric stimulation of the ventricle (PES) for risk stratification in patients with sarcoidosis **Study type:** Single center 1998-2008 **Size:** 76 pts	**Inclusion criteria**: Patients with biopsy-proven systemic sarcoidosis but without cardiac symptoms who had evidence of cardiac sarcoidosis on PET or CMR were included **Exclusion criteria:** prior history of ventricular arrhythmias or ICD	**1° endpoint:** survival and arrhythmic events. **Results:** Eight (11%) were inducible for sustained VA and received an ICD. None of the noninducible patients received a defibrillator. LVEF was lower in patients with inducible VA (36.4±4.2% vs 55.8±1.5%, p<0.05). Over a median follow-up of 5 y, 6 of 8 patients in the group with inducible VA had VA or died, compared with 1 death in the negative group	● Authors mention that based on present clinical indications, a significant proportion of patients with CS and LVEF of <35% would qualify for ICD implantation. There are no data to guide management of patients with minimal or mild LV dysfunction who lack evidence of VA or conduction system disease.
● Coleman et al. 2016 (297) ● 27450877	**Aim:** This study sought to perform a systematic review and meta-analysis to understand the prognostic value of myocardial scarring as evidenced by late gadolinium enhancement (298) on CMR imaging in patients with known or suspected CS. **Study type:** Meta analysis **Size:** Ten studies were included, involving a total of 760 patients.	**Inclusion criteria**: Studies were considered eligible for inclusion if CMR was used to assess for myocardial scarring from biopsy-proven or clinically suspected sarcoidosis; in cohorts of >5 patients; with >1 y of prognostic follow-up data, including event data for ventricular arrhythmia, SCD, aborted cardiac death and/or appropriate ICD discharge, hospital admission for congestive HF, cardiac mortality, and allcause mortality. **Exclusion criteria:** Studies with populations known to	**1° endpoint:** all-cause mortality and a composite outcome of arrhythmogenic events plus all-cause mortality. **Results:** The average EF was 57.8±9.1%. Patients with LGE had higher odds for all-cause mortality (OR: 3.06; p<0.03) and higher odds of the composite outcome (OR: 10.74; p<0.00001) than those without LGE. Patients with LGE had an increased annualized event rate of the composite outcome (11.9% vs. 1.1%; p<0.0001).	● This analysis shows that the presence of LGE in sarcoid patients with normal or near-normal LVEF is prognostically significant and greatly increases the likelihood of adverse events.

		have CAD or cardiomyopathies of nonsarcoid etiology.		
● Murtagh et al. 2016 (299) ● 26763280	**Aim:** The aim of this study was to establish whether CMR with LGE imaging can be used to risk stratify patients with known extracardiac sarcoidosis and preserved LVEF (>50%). **Study type:** Single center retrospective **Size:** 205 patients	**Inclusion criteria**: 205 patients with LVEF >50% and extracardiac sarcoidosis who underwent cardiovascular magnetic resonance for LGE evaluation **Exclusion criteria:** N/A	**1° endpoint:** death or any VT **Results:** Forty-one of 205 patients (20%) had LGE; 12 of 205 (6%) died or had VT during follow-up; of these, 10 (83%) were in the LGE+ group. In the LGE+ group (1) the rate of death/VT/y was >20× higher than LGE- (4.9 vs. 0.2%, p<0.01); (2) death/VT were associated with a greater burden of LGE (14±11 vs. 5±5%, p<0.01) and right ventricular dysfunction (right ventricular EF 45±12 vs. 53±28%, p=0.04). LGE burden was the best predictor of death/VT (area under the receiver-operating characteristics curve, 0.80); for every 1% increase of LGE burden, the hazard of death/VT increased by 8%.	● The burden of LGE and the severity of RV dysfunction further refine the risk of death/VT in patients with CS
● Crawford et al. 2014 (300) ● 25266311	**Aim:** to assess whether delayed enhancement (DE) on MRI is associated with VT/VF or death in patients with CS and LVEF>35%. **Study type:** Retrospective analysis from multicenter registry **Size:** 51 patients	**Inclusion criteria**: Fifty-one patients with CS and LVEF >35% underwent DE-MRI. DE was assessed by visual scoring and quantified with the full-width at half-maximum method. The patients were followed for 48.0±20.2 mo. **Exclusion criteria:** N/A	**1° endpoint:** death or VT/VF **Results:** Twenty-two of 51 patients (63%) had DE. Forty patients had no prior Hx of VT (1° prevention cohort). Among those, 3 patients developed VT and 2 patients died. DE was associated with risk of VT/VF or death (p=0.0032 for any DE and p<0.0001 for right ventricular DE). The positive predictive values of the presence of any DE, multifocal DE, and right ventricular DE for death or VT/VF at mean follow-up of 48 mo were 22%, 48%, and 100%, respectively.	● A cut-off value of ≥9 involved segments separated patients with and without future VTs, suggesting that a threshold effect may be present. Right ventricular involvement seems to be particularly important for arrhythmogenesis; it was predictive of adverse events in 1° prevention patients and for the group as a whole. Patients without DE on MRI have a low risk of VT.

● Greulich et al. 2013 (186) ● 23498675	**Aim:** study aimed to demonstrate that the presence of late gadolinium enhancement (298) is a predictor of death and other adverse events in patients with suspected CS **Study type:** Multicenter prospective **Size:** 155 patients	**Inclusion criteria**: 155 consecutive patients with systemic sarcoidosis who underwent CMR for workup of suspected cardiac sarcoid involvement. The median follow-up time was 2.6 y. **Exclusion criteria:** N/A	**1° endpoint:** 1° endpoints were death, aborted SCD, and appropriate ICD discharge. **Results:** LGE was present in 39 patients (25.5%). The presence of LGE yields a Cox HR: 31.6 for death, aborted SCD, or appropriate ICD discharge, and of 33.9 for any event. This is superior to functional or clinical parameters such as LVEF, LV end-diastolic volume, or presentation as HF, yielding HRs between 0.99 (per % increase LVEF) and 1.004 (presentation as HF), and between 0.94 and 1.2 for potentially lethal or other adverse events, respectively.	● Could not tell on additional LGE parameters due to low numbers.
● Blankstein et al. 2014 (301) ● 24140661	**Aim:** to relate imaging findings on positron emission tomography (PET) to adverse cardiac events in patients referred for evaluation of known or suspected CS. **Study type:** Single center observational **Size:** 118 patients	**Inclusion criteria**: consecutive patients with no Hx of CAD, who were referred for PET, using (18)F-fluorodeoxyglucose to assess for inflammation and rubidium-82 to evaluate for perfusion defects (PD), following a high-fat/low-carbohydrate diet to suppress normal myocardial glucose uptake **Exclusion criteria:** N/A	**1° endpoint:** Death or VT **Results:** Among the 118 patients (age 52±11 y; 57% males; mean EF: 47±16%), 47 (40%) had normal and 71 (60%) had abnormal cardiac PET findings. Over a median follow-up of 1.5 y, there were 31 (26%) adverse events (27 VT and 8 deaths). Cardiac PET findings were predictive of AE, and the presence of both a PD and abnormal FDG (29% of patients) was associated with HR:3.9; p<0.01 and remained significant after adjusting for LVEF and clinical criteria. Extra-cardiac FDG uptake (26% of patients) was not associated with AE.	● Conclusion was that presence of focal PD and FDG uptake on cardiac PET identifies patients at higher risk of death or VT.
● Kron et al. 2013 (302) ● 23002195	**Aim:** to evaluate the efficacy and safety of ICDs in patients with CS	**Inclusion criteria:** consecutive patients with CS and an ICD at 13 academic centers.	**1° endpoint:** appropriate ICD therapy **Results:** Over a mean follow-up of 4.2±4.0 y, 85 of 234 (36.2%) patients	● Patients receiving appropriate therapies were more likely to be male, have a Hx of syncope, have a lower LVEF, a 2° prevention ICD indication

	Study type: multicentre retrospective data review **Size:** 235 patients from 13 institutions	147 patients (62.6%) had their devices implanted for 1° prevention while 88 patients (37.5%) were implanted for 2° prevention, including 7 for VF (3.0%), 63 for VT (26.8%), and 18 for syncope presumed to be due to an arrhythmia (7.7%). **Exclusion criteria:** N/A	received an appropriate ICD therapy (shocks and/or anti-tachycardia pacing) and 67 of 226 (29.7%) received an appropriate shock.	● Most patients receiving appropriate therapies had an LVEF >35%, suggesting that CS patients with mild or moderately reduced LVEF may be at risk for VA
● Mohsen et al. 2014 (303) ● 24433308	**Aim:** to identify the predictors of life-threatening VA in patients with CS and to evaluate the role of the ICD in this patient population. **Study type:** multicentre retrospective data review **Size:** 32 patients. 84% received the ICD for symptoms.	**Inclusion criteria:** Patients with biopsy-proven systemic sarcoidosis but without cardiac symptoms who had evidence of CS on positron emission tomography (PET) or CMR were included **Exclusion criteria:** N/A	**1° endpoint:** appropriate ICD therapy **Results:** The mean LVEF was 41±18%. Thirty patients received an ICD. Twelve patients (36.3%) had sustained VA. Eleven patients received appropriate therapies and 9 patients received inappropriate shocks, representing 36.7% and 30.0% of the ICD population, respectively. Patients who received appropriate ICD therapies were younger with mean age 47.4±7.8, and had a lower mean LVEF 33.0±12.0 compared to those who did not receive ICD therapies (p=0.0301 and 0.0341, respectively).	● CS is strongly associated with malignant VA. No specific predictors of such tachyarrhythmias emerged, other than young age and low LVEF. ● Over 2/3 received ICD for 2° prevention
● Schuller et al. 2012 (304) ● 22812589	**Aim:** identify the incidence and characteristics of ICD therapies in patients with CS **Study type:** multicentre observational	**Inclusion criteria:** Patients with CS and an ICD implanted for 1° or 2° prevention of sudden death. Additionally, authors included a comparison with historical controls of ICD therapy rates reported in clinical trials evaluating the	**1° endpoint:** Any ICD therapy **Results:** Of the 112 CS subjects identified, 36 (32.1%) received appropriate therapies VT over a mean follow-up period of 29.2 mo. VT storm (>3 episodes in 24 h) occurred in 16 (14.2%) CS subjects. Inappropriate therapies occurred in 13 CS subjects (11.6%).	● Appropriate ICD therapies were higher than in historical control

	Size: 32 patients. 84% received the ICD for symptoms.	ICD for 1° and 2° prevention of sudden death. **Exclusion criteria:** N/A	Covariates associated with appropriate ICD therapies included LVEF <55% (OR 6.52; 95% CI: 2.43–17.5), right ventricular dysfunction (OR: 6.73; 95% CI: 2.69–16.8), and symptomatic HF (OR: 4.33; 95% CI: 1.86–10.1).	
● Yodogawa et al. 2011 (305) ● 21496164	**Aim:** to evaluate the efficacy of corticosteroid therapy VA in CS **Study type:** Single center observational **Size:** 31 patients	**Inclusion criteria:** Patients presenting premature ventricular contractions (PVCs ≥300/d) were investigated. All were treated with steroids. **Exclusion criteria:** N/A	**1° endpoint:** PVCs and NSVT burden before and after steroid therapy. **Results:** The group with less advanced LV dysfunction patients (EF ≥35%, N=17) showed significant reduction in the number of PVCs (from 1820±2969 to 742±1425, p=0.048) and in the prevalence of NSVT (from 41 to 6%, p=0.039). Late potentials on SAECG were abolished in 3 patients. The less advanced LV dysfunction group showed a significantly higher prevalence of gallium-67 uptake compared with the advanced LV dysfunction group (EF <35 %, N=14). In the advanced LV dysfunction patients, there were no significant differences in these parameters.	● Steroid therapy may be effective for VA in the early stage, but less effective in the late stage
● Segawa et al.2016 (306) ● 27301264	**Aim:** to evaluate time course and factors correlating with VT after introduction of corticosteroid therapy in patients with CS remain to be elucidated. **Study type:** Single center observational	**Inclusion criteria:** Patients presenting with CS treated with steroids. **Exclusion criteria:** N/A	**1° endpoint:** Sustained VA. **Results:** During a mean follow-up of 5.5 y, 20 out of 68 patients (29%) experienced VTs after initiation of corticosteroid therapy, especially in the first 12 mo in 14 patients (70%). A multivariable analysis revealed that positive gallium scintigraphy had a significant correlation with VTs (HR: 11.33; 95% CI: 3.22–39.92; p<0.001), in addition to reduced LVEF (HR: 0.94; 95% CI: 0.90–0.97; p=0.001). Furthermore,	● These results indicate that VTs and electric storm frequently occur in the first 12mo after initiation of corticosteroid therapy, presumably because of inflammatory conditions, and that the positive gallium scintigraphy is a significant and independent predictor of VTs

	Size: 68 patients		electrical storm was noted in 10 patients (14.7%), 8 within the first 12mo of treatment, whereas the recurrence of electric storm was relatively less.	

Data Supplement 34. Nonrandomized Trials, Observational Studies, and/or Registries of Other Infiltrative Cardiomyopathies – (Section 7.6.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Varr et al. 2014 (307) ● 24121001	**Aim:** To test whether there is a specific population of patients with cardiac amyloidosis at risk of SCD owing to VA (vs EMD) who would benefit from ICD **Study type:** Retrospective registry Database analysis **Size:** 31	**Inclusion criteria:** The Stanford Amyloid Center's database to identify all patients with AL or ATTR who had ambulatory cardiac monitoring. This included patients who had undergone interrogation of an ICD or pacemaker and those who had ambulatory monitoring in the outpatient setting with either a Holter monitor or Ziopatch (iRhythm technologies, San Francisco, CA). **Exclusion criteria:** patients who did not have any form of telemetry monitoring available	**1° endpoint:** VA **Results:** NSVT was common and occurred in 23 of 31 (74%) patients. Sustained VT or VF occurred in 6 of 31 (19%) patients over the study period. Of the 6 patients with VT/VF, 1 patient had spontaneous resolution of VT before the delivery of ICD therapy. The remaining 5 patients had ICD therapies used, either antitachycardia pacing (ATP) or defibrillation. All patients had had documented NSVT before ICD therapy for VT/VF.	● Of the 6 patients who received ICD therapies, 4 died within 18 mo and 3 received the ICD initially for 1° prevention. ● The authors proposed criteria for ICD implant ● That included syncope, VT or NSVT.
● Kristen et al. 2008 (308)	**Aim:** to test whether prophylactic placement	**Inclusion criteria:** patients with	**1° endpoint:** mortality	● Authors concluded that patients with cardiac amyloidosis predominantly die as

● 18242546	of an ICD reduces SCD in patients with cardiac amyloidosis **Study type:** Single center observational **Size:** 19	histologically proven cardiac amyloidosis and risk of sudden death as demonstrated by a Hx of syncope and/or ventricular extra beats (Lown grade IVa or higher) **Exclusion criteria**: N/A	**Results:** During a mean follow-up of 811±151 d, 2 patients with sustained VT were successfully treated by the ICD. Two patients underwent heart transplantation, and 7 patients died due to electromechanical dissociation (N=6) or glioblastoma (N=1).	a result of electromechanical dissociation and other diagnoses not amenable to ICD therapy. Selected patients with cardiac amyloidosis may benefit from ICD placement.
● Lubitz et al. 2008 (309) ● 18634918	**Study type:** Review Article on SCD in infiltrative cardiomyopathies: sarcoidosis, scleroderma, amyloidosis, hemachromatosis. **Size:** NA	**Inclusion criteria:** Review article on infiltrative cardiomyopathis and sudden death. Studies related to sudden death and sudden death prevention were discussed. **Exclusion criteria:** N/A	**1° endpoint:** NA **Results:** It is difficult to draw substantive conclusions regarding the appropriate risk stratification and therapy of patients with the infiltrative cardiomyopathies. Few studies are prospective, many use different diagnostic criteria, and therapies are rarely randomized. Furthermore, sample sizes are small, studies are typically single center, and the heterogeneity of disease manifestations may preclude the generalization of results. Patients in high-risk groups, especially those with significantly reduced left ventricular function may be best treated with prophylactic ICD.	● Data on sudden death prevention in diseases other than sarcoidosis is very scant

Data Supplement 35. Nonrandomized Trials, Observational Studies, and/or Registries of Use of ICD and WCD in Patients with HFrEF - (Section 7.8.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Gandjbakhch E, et al. 2016 (157) ● 27344378	**Study type:** single center retrospective observational study **Size:** 380 patients (122 with ICD)	**Inclusion criteria:** consecutive patients listed for heart transplantation at 1 center. ICD patients characterized as having ICD before or within 3 mo after being listed for heart transplant **Exclusion criteria:** N/A	**1° endpoint:** all-cause mortality **Results:** Patients with ICD were less likely to die on the waiting list (8.3% ICD patients and 19.0% non-ICD, p=0.001). However, in multivariable model, ICD did not remain an independent predictor. ICD-related complications 21% of patients of which 11.9% was post-op worsening of HF.	● **Conclusion:** Patients with ICD were less likely to die on the waiting list but this did not appear in the multivariable model to be independently associated with mortality.
● Frohlich GM, et al. Heart 2013 (156) ● 23813845 .	**Study type:** retrospective observational study **Size:** 1089 consecutive patients listed for heart transplantation of which 550 (51%) with ICD (216 1° and 334 2° prevention indcations)	**Inclusion criteria:** consecutive patients listed for heart transplantation in two tertiary centers **Exclusion criteria:** N/A	**1° endpoint:** all-cause mortality **Results:** estimated 1 y survival 88% ICD vs. 77% without ICD (p=0.0001). Model adjustment suggested ICD independently associated with survival most pronounced for those with 1° prevention indication (HR: 0.4; 95% CI: 0.19–0.85; p=0.016)	● Conclusion: ICD appears to be associated with a reduction in all-cause mortality compared to those without an ICD on the waiting list

● Sandner SE, et al. 2001 (310) ● 11568051	**Study type:** Retrospective observational study **Size:** 854 patients on the waiting list for heart transplant (102 patients with ICD, 11.9%). All patients had ICD implanted before listing for transplant	**Inclusion criteria:** Consecutive patients listed for heart transplant 1/1992 and 3/2000 **Exclusion criteria:** N/A Patient demographics: Indication for ICD was SCA (63%), 60% non-ischemic etiology Only 24% overall were on BB	**1° endpoint and results:** Total mortality while waiting for transplant was 13.2% with ICD and 25.8% without ICD (p=0.03). Rate of 12 mo sudden death was 20% in the non-ICD group and 0% in the ICD group. Cox proportional hazard model showed absence of ICD associated with increased mortality and sudden death.	● Limitations: retrospective, older study with MADIT I and MUSTT type indications for ICD and ICD patients were highly selected introducing confounding and baseline clinical variables were not comparable. Low use of BB. ● Conclusions: supports the use of ICD for improving survival to transplant
● Kao AC, et al. 2012 (290) ● 23234574	**Study type:** Observational multicenter cohort study **Size:** 82	**Inclusion:** WCD prescribed for either listed for cardiac transplantation, diagnosed with dilated cardiomyopathy, or receiving inotropic medications. Mean age 56.8±13.2, and 72% were male. Most patients (98.8%) were diagnosed with DCM with a low EF (<40%) and 12 were listed for cardiac transplantation.	Device worn for 75±58 d. 4 patients were on inotropes. There were no sudden cardiac arrests or deaths during the study. 41.5% of patients were much improved after WCD use, while 34.1% went on to receive an ICD.	● **Conclusions:** WCD monitored HF patients until further assessment of risk. The leading reasons for end of WCD use were improvement in LVEF or ICD implantation if there was no significant improvement in LVEF.

● Opreanu M et al. 2015 (311) ● 26094085	**Study type:** registry of patients awaiting heart transplant with WCD **Size:** 121 patients Patient Demographics: consisting of 83 (69%) men and 38 (31%) women. The mean age was 44±18 y. Mean EF was 25 ± 15%. Non-ischemic cardiomyopathy (CMP) was the underlying diagnosis in 67 (55%) patients, whereas 21 (17%) patients had ischemic CMP and 33 (27%) had a mixed or uncharacterized CMP. NYHA Class III HF was present in 32% and 34% were in Class IV.	**Inclusion:** patients awaiting heart transplant with WCD	The patients wore the WCD for an average of 127±392 d (median 39d) with average daily use of 17±7 h (median 20h). Seven patients (6%) received appropriate WCD shocks. Fifty-one patients (42%) ended use after ICD implantation and 13 patients (11%) after HT. There were 11 deaths (9%).	● **Conclusions:** A significant proportion of patients on the heart transplant waiting list will have VA. WCD use in this registry associated with a high compliance and efficacy and a low complication rate, suggesting that the WCD is a reasonable bridge therapy for preventing SCD in patients awaiting HT.

Data Supplement 36. Nonrandomized Trials, Observational Studies, and/or Registries Related to LVAD – (Section 7.8.3)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)
● Vakil, et al. JACCCEP 2016 (312) ● 27395347	**Study type:** retrospective national registry **Size:** 32,599 patients	**Inclusion criteria:** Adults (age ≥18 y) listed for first-time HT in the United States between January 1, 1999, and September 30, 2014, were retrospectively identified from the United Network for Organ Sharing registry. Median follow-up of 154 d, 3,638	**1° endpoint:** all-cause waitlist mortality. **Results:** 9% died on the wait list in ICD group vs. 15% in no-ICD group (p<0.0001), An ICD at listing was associated reduction in mortality (HR: 0.87; 95% CI: 0.80–0.94). In the subgroup of patients with LVAD (N=9,478), having an ICD was associated with relative reduction in mortality (HR: 0.81; 95% CI 0.70–0.94).	● **Conclusion:** ICD use was associated with improved survival on the HT waitlist in patients with or without LVADs

Data Supplement 37. Nonrandomized Trials, Observational Studies, and/or Registries Related to ICD Use After Heart Transplantation – (Section 7.8.4)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)
● Tsai et al. 2009 (313) ● 19808340	**Study type:** Retrospective cohort of Heart Tx. Patients with ICDs across 5 centers. 1995-2005	**Inclusion criteria:** Patients with heart transplants and ICDs **Exclusion criteria:** N/A	**1° endpoint:** Descriptive: Indications for ICDs and shocks (appropriate/inappropriate) **Results:** indications for ICD 1) severe allograft vasculopathy (N=12),	● Use of ICDs after heart transplantation may be appropriate in selected high-risk patients. ● Very small number, no control group, Pre-SCD-HeFT.

	Size: 36 (2612 patients with heart transplants, 36, with ICDs)		2) unexplained syncope (N=9), 3) Hx of CA (N=8), 4) severe LV dysfunction (N=7). Shocks: 22 shocks in 10 patients (28%), Appropriate: 8 patients/12 shocks (100% - allograft vasculopathy) Inappropriate: 3 patients of whom 8 (80%) received 12 appropriate shocks for either rapid VT or VF. The shocks were effective in terminating the VA in all cases. Three (8%) patients received 10 inappropriate shocks.	
● McDowell et al. 2009 (314) ● 19632584	**Study type:** Survey of transplant program directors. Asked about all transplant patients with an ICD **Size:** 44 patients with heart transplants with ICD	**Inclusion criteria:** Survey responses about heart transplant patients. With ICDs **Exclusion criteria:** N/A	**1° endpoint:** Indication, **Results:** Indication for implant* • 1° VT/VF arrest 6 (13.3) • Unexplained syncope 3 (6.7) • CAV with LV dysfunction 20 (44.4) • CAV without LV dysfunction 3 (6.7) • Non-specific graft dysfunction 5 (11.1) • High-grade arrhythmia determined by • Non-invasive monitor 3 (6.7) Patients with appropriate therapies 6 (13.6); Total 19 Patients with inappropriate therapies 3 (6.8) Total 15	● Most common reason was allograft vasculopathy with LV dysfunction
● Neylon et al. 2016 (315) ● 26856670	**Study type:** Single center review of transplant patients with ICDs	**Inclusion criteria:**	**1° endpoint:** Descriptive **Results:**	● ICDs in transplant patients – inconclusive.

	Size: 10 patients	Review of all transplant patients with ICDs between 1983 and 2012. **Exclusion criteria:** N/A	• Allograft vasculopathy in 8/10 • 1/10 shocked, • 1/10 ATP	

Data Supplement 38. Nonrandomized Trials, Observational Studies, and/or Registries Evaluating the Risk of Sudden Death or Ventricular Arrhythmias in Patients with Neuromuscular Disorders – (Section 7.8)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Study Size (N); Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Tanawuttiwat T, et al. 2017 (316) ● 27829084	**Study type:** Observational retrospective cohort referred for risk stratification at a single referral center **Size:** 155 patients	**Inclusion criteria:** 136 patients with DM1 and 28 patients with DM2 with genetically confirmed diagnosis and baseline ECG between January 1997 and August 2014. **Exclusion criteria:** Exclusion of ECG's with paced or non-sinus rhythm	**1° endpoint:** Conduction abnormalities were defined as PR of at least 240 msec and QRS of at least 120 msec **Results:** In DM1, incidences of PR ≥240 ms and QRS ≥120 ms during a mean 5.54 y were 19.2% and 11.7%, respectively. In contrast, DM2 patients there were no incident PR abnormalities, despite similar incidence of QRS abnormalities. An incident 10 ms increase in QRS duration was associated with 3.5% decrease in EF in the subsequent year (−3.45; 95% CI: −4.87–−2.03; p<0.001).	● Prevalence of critically prognostic conduction abnormalities >20% and LV dysfunction > 10% (defined LVEF <55%) ● Incident QRS prolongation > 10 ms is associated with decreased LV function the subsequent year. ● Supports serial ECG examinations and symptom / QRS prolongation–prompted evaluation of LV function. ● Limitations include retrospective design with potential for selection bias, differential clinical follow-up among subgroups.
● Merino et al. 1998 (317) ● 9714111	**Aim**: To assess the mechanism of sustained VT in myotonic dystrophy	**Inclusion:** Consecutive patients with myotonic dystrophy and	**1° endpoint:** N/A **Results:** Clinical tachycardia was inducible in all patients and were	● Summary – A high clinical suspicion for bundle-branch reentry tachycardia is reasonable in patients with wide

	Study type: Case series **Size:** 6 patients	sustained VT referred for EPS **Exclusion:** N/A	bundle branch reentry. VT was no longer inducible after bundle branch ablation except for a nonclinically documented and NSVT in a patient with SHD	complex tachycardia and myotonic dystrophy ● Limitations – small case series. Does not prove a link between bundle branch reentry and sudden death in this population
● Diegoli et al. 2011 (318) ● 21851881	**Aim**: To describe the outcome of patients with dilated cardiomyopathy and DYS defects **Study type:** Cohort study **Size:** 34 patients with DYS defects	**Inclusion:** 1/1995 – 12/2009, screened DYS in 436 unrelated male probands diagnosed with DCM who were male sex **Exclusion:** females, families with male to male transmission	**1° endpoint:** N/A **Results:** Of the 34 affected patients, 8 patients underwent heart transplant and 8 patients received an ICD (indications depressed LVEF). There were no appropriate interventions during a median follow-up 14 mo (IQR 5–25 mo).	● DYS-related DCM is characterized by severe impairment of LV function, marked LV dilation, and low arrhythmogenic risk; the only factor that impacts survival seems to be end-stage HF. ● Limitations: relatively small number of patients and short follow-up, referral center.
● Anselme et al. 2013 (208) ● 23811080	**Aim:** To evaluate a strategy of prophylactic ICD implantation in lamin A/C mutation carriers with significant cardiac conduction disorders **Study type:** Cohort study, single center **Size:** 47 patients	**Inclusion criteria:** • LMNA mutation carriers seen between 3/1999 and 4/2009 • 47 patients (mean age 38±11 y; 26 men) with LMNA mutation. • 21 (45%) had significant conduction disorders (defined as bradycardia requiring pacemaker or a PR interval of >240 ms and either complete LBBB or NSVT) and received a prophylactic ICD **Exclusion criteria**: N/A	**1° endpoint:** N/A **Results:** • In those with ICD, 11/21 (52%) had appropriate ICD therapy during a median follow-up of 62 mo • LVEF was ≥45% in 9/11 patients with appropriate therapy • The presence of significant conduction disorders is associated with malignant VA (HR: 5.20; 95% CI: 1.14–23.53; p=0.03)	● Life-threatening VAs are common in patients with lamin A/C mutations and significant cardiac conduction disorders, even if LVEF is preserved. ● ICD is an effective treatment and should be considered in this patient population.

• van Rijsingen et al. 2012 (209) • 22281253	**Aim:** To identify risk factors that predict malignant VAs in lamin A/C mutation carriers **Study type:** Cohort, multicenter **Size:** 269 patients	**Inclusion criteria:** Pathogenic lamin A/C mutation carriers between 2000 and 2010 **Exclusion criteria:** • Patients ≤15 y of age • Median follow up of 43 mo	**1° endpoint:** Occurrence of malignant VAs **Results:** • 48 (18%) had malignant VAs (11 successful CPR, 25 appropriate ICD treatment, and 12 died suddenly) • Risk factors for VAs were NSVT, LVEF <45%, male sex, and non-missense mutations (ins-del/truncating or mutations affecting splicing). VA occurred only in persons with at least 2 of these risk factors.	• Patients with lamin A/C mutations with ≥2 risk factors may benefit from prophylactic ICD
• Meune et al. 2006 (319) • 16407522	**Aim:** To assess whether ICD is beneficial for 1° prevention of SCD in patients with lamin A/C gene mutations with preserved LVEF referred for pacing due to presence of progressive conduction delay or SND **Study type:** Cohort study **Size:** 19 patients	**Inclusion criteria:** Lamin A/C mutations associated with cardiac conduction defects **Exclusion criteria:** • 19 patients received ICD (Muscular phenotype: 9 Emery-Dreifuss, 8 DCM plus conduction disease, 1 Limb-girdle, 1 shoulder-muscle amyotrophy) • Mean age 41.7±13.4 y • Sex: 73% Male • Mean LVEF 58%±12%	**1° endpoint:** Not specified **Results:** • 8/19 (42%) received appropriate ICD therapy • Follow up 33.9±21 mo • No factor (including LVEF, spontaneous or induced VA or drug therapy) predicted VA events • LVEF not reduced in patients receiving ICD therapies	• 1 inappropriate shock • Summary: ICD rather than pacemaker should be considered in patients with conduction disorders and lamin A/C mutation
• Pasotti et al. 2008 (210) • 18926329	**Aim:** The aim of this study was to analyze the long-term follow-up of dilated cardiolaminopathies in	**Inclusion criteria:** 27 consecutive families in which *LMNA* gene defects were identified	**1° endpoint:** Events were death from any cause, death from HF, heart transplantation, and SCD,	• Authors concluded that dilated cardiomyopathies caused by *LMNA* gene defects are highly penetrant, adult onset, malignant diseases

	patients with Lamin A/C gene mutations **Study type:** Retrospective observational longitudinal study **Size:** 94 patients	in the probands, all sharing the DCM phenotype. Of the 164 family members, 94 had LMNA gene mutations **Exclusion criteria:** N/A	including appropriate ICD interventions **Results:** • 60 of 94 (64%) were phenotypically affected whereas 34 were only genotypically affected. • Of the 60 patients, 40 had DCM with AVB, 12 had DCM with VT/fibrillation, 6 had DCM with AVB and EDMD2, and 2 had AVB plus EDMD2. •During a median of 57 mo there were 49 events in 43 DCM patients. •The events were related to HF (15 heart transplants, 1 death from end-stage HF) and VA (15 SCDs and 12 appropriate ICD interventions).	characterized by a high rate of HF and life-threatening arrhythmias.
● van Berlo et al. 2005 (211) ● 15551023	**Aim:** To evaluate common clinical characteristics of patients with lamin A/C gene mutations that cause either isolated DCM or DCM in association with skeletal muscular dystrophy. **Study type:** Meta-analysis (pooled data) **Size:** 299 carriers of lamin A/C mutations	**Inclusion criteria:** 21 publications between March 1999 and March 2002 reporting lamin A/C gene mutations **Exclusion criteria:** Patients with familial partial lipodystrophy, progeria, axonal neuropathy and mandibuloacral dysplasia caused by mutations in the lamin	**1° endpoint:** Arrhythmias and sudden death **Results:** • Cardiac dysrhythmias were reported in 92% of patients after 30 y of age; HF was reported in 64% after 50 y of age. • 76 of the reported 299 patients (25%) died at a mean of 46 y of age. • Sudden death was the most frequently reported mode of death (46%) in both the cardiac and the neuromuscular phenotype.	● Authors conclude that carriers of lamin A/C mutations carry a high risk of sudden death. ● Presence of pacemaker did not protect against sudden death.

		A/C gene were excluded		
● Lallemand et al. 2012 (320) ● 22038543	**Aim:** To analyze the natural Hx and predictors of change in infra-Hisian conduction time in myotonic dystrophy patients with normal baseline EPS **Study type:** Cohort study **Size:** 127 patients	**Inclusion criteria:** Patients with muscular dystrophy of which 25 underwent a second EPS for new symptoms, new AV conduction abnormalities on ECG, changes on SA-ECG, ord asymptomatic patients >60 mo from first EPS **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** Mean HV interval increased between the baseline and follow-up EP • Study – 52.1±1.6 ms to 61.4±2.2 ms. • Predictors of increased HV interval were change in resting ECG and SA-ECG (QRSd ≥100 ms or low amplitude signal <40 microvolts) • 5 patients with HV ≥70 ms received prophylactic pacemaker	● In patients with normal initial EPS, changes in the resting ECG and/or SA-ECG on annual follow-up were associated with change in infra-Hisian conduction
● Wahbi et al. 2012 (321) ● 22453570	**Aim:** To determine whether an invasive strategy based on EPS and prophylactic pacemaker is associated with longer survival in patients presenting with myotonic dystrophy type 1 and infranodal conduction delays compared to a noninvasive strategy using propensity adjustments **Study type:** Cohort study **Size:** 486 patients	**Inclusion criteria:** Genetically confirmed myotonic dystrophy type 1 with PR >200 ms and/or QRS >100 ms between 1/2000 to 12/2009 **Exclusion criteria:** N/A	**1° endpoint:** All-cause mortality **Results:** 341 (70.2%) - EPS compared to 145 (29.8%) - noninvasive strategy • Median follow-up 7.4 y (322) • 50 patients died in EPS strategy group 30 died in the noninvasive strategy group (HR: 0.74; 95% CI: 0.47–1.16; p=0.19) • Difference attributable to a lower incidence of SCD (10 patients invasive strategy group vs. 16 patients noninvasive strategy group, HR: 0.24; 95% CI: 0.10–0.56; p=0.001])	● In patients with myotonic dystrophy type 1, an invasive strategy was associated with a higher rate of 9y survival than a noninvasive strategy

● Ha et al. 2012 (323) ● 22385162	**Aim:** To define predictors of cardiac conduction disease in myotonic dystrophy patients **Study type:** Cohort study, single-center **Size:** 211 patients	**Inclusion criteria:** Patients with DM1 and 25 DM2 after 2003 **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Follow-up 57±46 mo • A severe ECG abnormality was defined as a PR interval of ≥240 ms or QRS duration of ≥120 ms • Severe ECG abnormality present in 24% of DM1 patients and 17% of DM2 patients • Pacemaker or ICD implanted in 14% of all patients, including 65% of patients with severe ECG abnormalities. • 13 patients died (1.16%/y), including 3 sudden (2 of whom had pacemakers)	● Despite identification of conduction disease and prophylactic pacing, mortality remains high in patients with a severe ECG abnormality (most deaths non-sudden, suggesting that a severe ECG abnormality is also general marker of risk for all-cause mortality.) ● Of 3 patients who died suddenly, 2 had pacemakers, suggesting that a severe ECG abnormality does not simply predict sudden death from AV block
● Laurent et al. 2011(324) ● 20227121	**Aim:** To determine whether implantation of prophylactic pacemaker in myotonic dystrophy patients with HV interval ≥70 lowers the risk of sudden death (due to complete AV block) **Study type:** Cohort study **Size:** 100 patients	**Inclusion criteria:** Genetically confirmed MD1 between 1994 and 2008 at single institution **Exclusion criteria:** • Infantile form of MD • 100 patients enrolled and 49 implanted with pacemaker for HV interval ≥70 • Mean follow up 74±39 mo • 46% had 1 or more Groh criteria (rhythm other than sinus, PR ≥240 ms, QRS ≥120 ms,	**1° endpoint:** All-cause mortality **Results:** • 10 deaths (9 respiratory failure, 1 sudden). 1 SCD occurred in a patient with pacemaker who had no spontaneous VT suggesting a non-cardiac etiology for this event. • 1/51 with HV interval <70 developed complete AV block • 19/49 patients with HV ≥ 70 developed AV block	● Implantation of a pacemaker when HV interval ≥70 seemed to identify a population likely to progress to high grade AV block. A higher rate of sudden death would have been expected based on previous studies of comparable populations, implying that prophylactic pacemaker implantation, based on these criteria, may have prevented some deaths due to asystole.

		2nd or 3rd degree AV block)		
● Bhakta et al. 2011 (325) ● 22035077	**Aim:** To assess implant rates and indications for pacemaker and ICDs and outcomes in patients with DM1 **Study type:** Cohort study, multicenter **Size:** 406 patients	**Inclusion criteria:** Genetically confirmed DM1 **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** Follow up 9.5±3.2 y 46 (11.3%) received a pacemaker and 21 (5.2%) an ICD Devices were primarily implanted for asymptomatic conduction abnormalities or LV systolic dysfunction 7 (15.2%) pacemakers were implanted for third-degree AV block and 6 (28.6%) ICDs were implanted for VAs 5 (10.9%) pacemaker patients underwent upgrade to an ICD (3 for LV systolic dysfunction, 1 for VAs, and 1 for progressive conduction disease). 17 (27.4%) of the 62 patients with devices were pacemaker-dependent at last follow-up 3 (14.3%) ICD patients had appropriate therapies 24 (52.2%) pacemaker patients died including 13 of respiratory failure and 7 of sudden death 7 (33.3%) ICD patients died including 2 of respiratory failure and 3 of sudden death (1 death was documented due to inappropriate therapies)	● Adult DM1 patients commonly receive pacemakers and ICDs. ● The risk of SCD in patients with pacemakers suggests that the ICD may warranted but SCD was still observed in ICD patients raising uncertainty benefit. ● DM1 patients are at high risk of respiratory failure. Therefore, pacemaker or ICDs in asymptomatic patients moderate conduction disease and also severe skeletal muscle involvement may not improve outcomes.

● Nazarian et al. 2011 (326) ● 20946286	**Aim:** To characterize the trends and predictors of time-dependent ECG changes in patients with DM1 **Study type:** Cohort study, single center **Size:** 70 patients	**Inclusion criteria:** Patients with DM1 baseline ECG and then routine follow-up **Exclusion criteria:** • History of second or third degree AV block, VAs, resuscitated SCD, or persistent supraVA • Mean follow-up 956 d • Clinical predictors of conduction disease progression were assessed using multivariate analysis	**1° endpoint:** Time dependent PR or QRS prolongation during follow-up **Results:** • Age, h/o AF or flutter, and number of cytosine-thymine-guanine (CTG) repeats were predictors of time-dependent PR and QRS prolongation • Lower LVEF associated greater QRS progression	● Patients with DM1 can develop rapid changes in cardiac conduction intervals. ● AF or flutter, older age, and larger CTG expansions predict greater time-dependent PR and QRS interval prolongation and warrant particular attention in the arrhythmic evaluation of this high-risk patient subset.
● Bhakta et al. 2010 (327) ● 21146669	**Aim:** To assess the prevalence of conduction disease and LVEF in population of patients with DM1 **Study type:** cohort study, multicenter **Size:** 406 patients	**Inclusion criteria:** Patients with DM1 with confirmed abnormal CTG repeat sequence (one or both alleles ≥ 38 repeats) **Exclusion criteria:** Patients <18 y or unconfirmed DM1 diagnosis as above	**1° endpoint:** N/A **Results:** Cardiac imaging was performed on 180 (44.3%) • Prevalence of LV systolic dysfunction and HF in 41 (10.1%) of 406 (risk factors were increasing age, male sex, ECG conduction abnormalities, presence of atrial and VA, and implanted devices) • Presence of decreased LVEF was associated with all-cause death (RR: 3.9; 95% CI: 2.3–6.4; p<0.001) and cardiac death (RR: 5.7; 95% CI: 2.6–12.4; p<0.001).	● There is a notable incidence of LV systolic dysfunction and HF exists in patients with DM1. ● The presence of LVSD/HF in DM1 is significantly associated with all-cause and cardiac death.

● Groh et al. 2008 (328) ● 18565861	**Aim:** To identify whether the ECG is useful for prediction of SCD risk in patients with DM1 **Study type:** Cohort study, multicenter **Size:** 406 patients	**Inclusion criteria:** Genetically confirmed DM1 (only patients with abnormal CTG repeat sequence ≥38 repeats) **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** • Defined: Severe abnormality on ECG includes rhythm other than sinus, PR interval ≥ 240 ms, QRS ≥ 120 ms, or 2nd or 3rd degree AV block • 96/406 had severe abnormality on ECG – 9 received ICD and 23 pacemakers • Follow-up 5.7 y during which 81/406 (20%) died (27 SCD, 32 respiratory failure, 5 non-sudden cardiac deaths, 17 deaths from other causes) • Of the 27 SCD, 17 had post-collapse rhythm documented of which only 9 was VT/VF • Severe abnormality on ECG (RR: 3.3; CI: 1.25–8.78) and diagnosis of atrial tachyarrhythmia (RR: 5.18; CI: 2.28–11.77) predictive of sudden death in patients with DM1 • Rates of prophylactic pacing increased during the study period and we not associated with decreased rates of SCD	● Patients with DM1 are at high risk for sudden death (up to 1/3 of deaths are sudden) ● Severe abnormality on ECG (RR: 3.3; 95% CI: 1.25–8.78) and diagnosis of atrial tachyarrhythmia (RR: 5.18; 95% CI: 2.28–11.77) predictive of sudden death in patients with DM1 ● Severe abnormality on ECG PPV 12.1% and NPV 97.1% for prediction of SCD
● Laforêt P et al. 1998 (329) ● 9818880	**Aim:** Evaluate the incidence of cardiac involvement in facioscapulohumeral muscular dystrophy **Study type:** Cohort, single center	**Inclusion criteria:** Patients exhibiting clinical and molecular features of facioscapulohumeral muscular dystrophy	**1° endpoint:** N/A **Results:** 5 patients had conduction defects or arrhythmia (IVCD or AF/flutter induced by EPS), 1 case of AV block requiring	● Patients with FSHMD may have cardiac involvement. ● Significant clinical cardiac involvement is rather rare in this form of muscular dystrophy, specific monitoring or treatment recommendations are not well defined.

	Size: 100 patients	**Exclusion criteria:** N/A	pacemaker, 1 case of VT possibly related to co-existing ARVC	● Discussion of arrhythmia- related symptoms and yearly electrocardiograms has been recommended.
● Stevenson et al. 1990 (330) ● 2299071	**Aim:** Evaluate incidence of cardiac involvement in fascioscapulohumeral muscular dystrophy **Study type:** cohort, single center **Size:** 30 patients	**Inclusion criteria:** Patients with fascioscapulohumeral muscular dystrophy (autosomal dominant inheritance, characteristic facial involvement, scapular/deltoid muscle weakness > biceps/triceps, myopathic changes on biopsy or EMG) **Exclusion criteria:** Elbow contractures, absence of scapular winging, and X-linked heredity	**1° endpoint:** Evidence of cardiac involvement **Results:** • 30/30 had 12-lead ECG, 22/30 had 24 hr Holter, 15 had echocardiogram, 10 patients had 12 EP studies • P wave abnormalities were common (60%) • AF or Aflutter induced at EPS in 10/12 • Evidence of abnormal AV node conduction or infranodal conduction present on EPS or ECG in 27% of patients • Sinus node function abnormal in 3 patients	● Evidence supporting cardiac involvement in this condition with minority of cases having abnormal sinus node function or AV conduction.

Data Supplement 39. Nonrandomized Trials Related to Cardiac Channelopathies – (Section 7.9)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Costa J et al. HR 2012 (331) ● 22293141	**Study type:** multicenter **Size:** 1051	**Inclusion criteria:** LQT1 gentoype, age 0-40 y **Exclusion criteria:**	**1° endpoint: LQT1 gender and mutation specific risk** stratification ACA/SCD **Results:** Increased risk: Age 0-13 y: males; >13, Males =females Loop mutations: HR: 2.7 for females, not males	● Combined assessment of clinical and mutation location can identify gender specific risk factors for life-threatening events

			Time-dependent syncope increased risk for males, HR: 4.73 QTc ≥500 ms: higher risk for women	
● Bai R, et al. CAE 2009 (332) ● 19808439	**Study type:** Sigle center retrospective **Size:** 1394	**Inclusion criteria:** consecutive probands referred with confirmed or suspected LQTS, BrS, or CPVT, or idiopathic VF/ACA **Exclusion criteria:** N/A	**1° endpoint:** Yield of genetic testing and cost **Results:** Yield and cost in US $ per diagnosis: LQTS: 40%, $13402 Br S: 8%, $33,148 CPVT: 35%, $9170 Idiopathic VF: 9%, $71,430	● Yield in LQTS higher if confirmed dx present: 64% ● Yield in BrS increased if type 1 BrS ECG with AV block present ● Yield in CPVT increased in males, prior CA, or confirmed bidirectional VT present ● LQTS, CPVT reasonable cost if strong clinical suspicion ● BrS less cost effective ● Idiopathic VF ineffective, costly
● Gehi AK, et al. JCE 2006 (333) ● 16836701	**Study type:** Meta-analysis: retrieved 30 prospective studies on Brugada ECG **Size:** 1545	**Inclusion:** Publications 1/1990-3/2005 on prognosis of patients with a Brugada ECG: Prospective cohort studies, >10 subjects, primary data on syncope, SCD, ICD shocks; followup >6 mo and >90% followup **Exclusions:** non-English; presence of cardiac disease	**1° endpoint:** Identify risk predictors of adverse natural history in patients with Brugada ECG **Results:** Risk increased with prior hx syncope or ACA, spont type 1 Br ECG, and male gender **NOT sig risk factors:** Fam hx SCD SCN5A mutation, or inducibility by PES: (not a risk factor but heterogeneity of studies)	● BrS ACE risk increased with prior syncope or SCD, RR: 3.24 ● Males, RR: 3.47 ● Spont type 1 ECG RR: 4.65
● Kim JA et al. HR 2010 (334) ● 20850565	**Study type:** multicenter retrospective **Size:** 634	**Inclusion criteria:** genotype + LQT2 **Exclusion criteria:** N/A	**1° endpoint:** LQT2 genotype: trigger specific risk factors for SCD/ACA **Results:** arousal 44%, exercise 13%, non-exercie/non-arousal 43% Risk for arousal: female >13 y, pore-loop mutation	● Pore-loop mutations assoc with arousal events; ● BB not significanty protective for this subset

			Non-pore loop assoc with exercise events, HR:6.84 Beta-bl reduced risk for exercise events but not arousal/non-exercise events	
● Migdalovich D et al. HR 2011 (335) ● 21440677	**Study type:** multicenter retrospective **Size:** 1166	**Inclusion criteria:** LQT2 genotype **Exclusion criteria:** N/A	**1° endpoint:** LQT2 genotype vs outcome ACA/SCD by age 40 y Pore-loop vs non-pore loop mutations **Results:** women w LQT2 much higher risk: 26% vs. men; For women, no sig difference in mutation site Risk similar at age <13 y; Age >13 y, females HR: 2.23 ACA/SCD vs males Males: pore loop mutations >2-fold increased risk Increased risk: QTc ≥ 500 msec (males 2x, females 4-fold increase) Highest risk: 5.3/1000 patient-y: prior syncope plus QTc ≥ 500 ms, pore loop male, or female >13 y old, HR: 17 BB: 61% reduced risk	● Women w LQT2 much higher risk v men ● Overall, pore loop mutations sig increased risk ACA, SCD, greater risk for males vs females ● Pore loop mutations LQT2 males, HR:2.18 for ACA/SCD
● Ackerman MJ 2011 (182) ● 21810866	**Study type:** HRS/EHRA consensus statement.	Expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies **Panel:** geneticists, arrhythmia specialists Agreement ≥ 84%	**General:** Class I: 1) sound clinical suspicion when positive predictive value > 40%, signal/noise ratio >10; 2) AND/OR genetic test result provides either diagnostic or prognostic info, or influences therapeutic choices. Screening of family members: when genetic testing leads to the adoption of therapy/protective measures/ lifestyle adaptations. LQTS: Class I: 1) any pt with strong clinical index of suspicion for LQTS; 2) any asymptomatic pt with QT prolongation on	● LQTS: Note difference between Class I if QTc >480 or 500 ms, and Class IIb if QTc > 460/480 ms

			serial ECGs: QTc >480 ms prepuberty; >500 ms, adult; 3) Mutation specific genetic testing for family members and other appropriate relatives Class IIb: any asymptomatic pt with otherwise idiopathic QTc values >460 ms (puberty) or 480 ms on serial ECGs CPVT: Class I: 1) any pt w strong clinical index of suspicion of CPVT; 2) Mutation specific genetic testing is recommended for family members and appropriate relatives Brugada: Class I: Mutation specific genetic testing is recommended for family members and appropriate relatives Class IIa: any pt w strong clinical index of suspicion of BrS, including with procainamide challenge Class III: not indicated in the setting of an isolated type 2 or 3 Brugada ECG pattern Short QTS: Class I: Mutation specific genetic testing is recommended for family members and appropriate relatives Class IIb: any pt with strong clinical index of suspicion ARVC: Class I: Mutation specific genetic testing is recommended for family members and appropriate relatives Class IIa: can be useful for patients satisfying task force diagnostic criteria Class IIb: may be considered for patients with possible ACM/ARVC	

			Class III: not recommended for patients with only a single minor criterion according to the 2010 task force criteria SCD/SIDS: Class I: 1) Collection of tissue sample recommended (blood or heart/liver/spleen tissue); 2) Mutation specific genetic testing is recommended for family members and appropriate relatives Class IIb: testing may be considered if circumstantial evidence suggests LQTS or CPVT specifically ACA/resuscitated: Class I: Genetic testing should be guided by the results of medical evaluation and is used for the 1° purpose of screening at-risk family members for sub-clinical disease Class III: Routine genetic testing, in the absence of a clinical index of suspicion for a specific cardiomyopathy or channelopathy, is not indicated for the survivor of unexplained OHCA HCM: Class I: 1) any pt in whom the clinical dx of HCM is established. 2) Mutation specific genetic testing is recommended for family members and appropriate relatives DCM: Class I: 1) DCM and significant cardiac conduction disease and/or family Hx of premature unexpected sudden death. 2) Mutation specific genetic testing is recommended for family members and appropriate relatives	

			LVNC: Class I: Mutation specific genetic testing is recommended for family members and appropriate relatives Class IIa: can be useful if clinical dx of LVNC is established PCCD: Class I: Mutation specific genetic testing is recommended for family members and appropriate relatives Class IIb: may be considered as part of diagnostic evaluation for patients with either isolated CCD or CCD with concomitant congenital heart disease, especially w post family Hx of CCD.	
● Nannenberg EA Circ CV Genetics 2012 (336) ● 22373669	**Study type:** Retrospective single center, Netherlands **Size:** 1170	**Inclusion criteria:** Genotype positive 6 inherited arrhythmia syndromes analyzed with Family Tree Mortality Ratio (FTMR): LQT1,2,3; Brugada Syndrome, SCN5A overlap syndrome (LQT3, BrS, conduction disease); RYR2 CPVT. **Exclusion criteria:** N/A	**1° endpoint:** Using FTMR method to achieve Standardized Mortality Ratio(SMR) (observed to expected mortality by genotype and age in inherited arrhythmias **Results:** LQTS1: in first 10 y of life SMR 2.9 (1.5–5.1) LQTS2: age 30-39 y, SMR 4.0 (1.1–10) LQTS3: age 15-19 y, SMR 5.8(1.2–16.9) SCN5A overlap syndrome: 20-39 y, SMR 3.8 (2.5–5.7) CPVT: age 20-39 y, SMR 3.0 (1.3–6.0) BrS: 40-59 y, SMR 1.79 (1.2–2.4), especially males	● Identify age ranges of highest risk for specified inherited arrhythmia syndromes ● Asymptomatic patients over age ranges may not require rx
● Kimbrough J Circ 2001 (337) ● 11479253	**Study type:** Retrospective multi-center **Size:** 791	**Inclusion criteria:** 791 first degree relatives of 211 LQTS probands **Exclusion criteria:** N/A	**1° endpoint:** Risk of ACE for family members of proband with LQTS **Results:** Severity of proband symptoms did not significantly influence family member's symptoms, although more likely to receive BB.	● Affected female parents have increased risk of cardiac event before age 40 y. ● Severity of proband symptoms did not significantly influence family members' symptoms.

			Female gender and duration of QTc important risk factors	
● Kaufman ES Heart Rhythm 2008 (338) ● 18534367	**Study type:** Retrospective registry: International LQTS Registry **Size:** 1915	**Inclusion criteria:** Patients with QTc ≥450 msec in registry, who had a sibling with SCD **Exclusion criteria:** N/A	**1° endpoint:** risk of death in LQTS when a sibling has died: ACA, SCD, or syncope **Results:** 270 patients with sibling SCD Sibling death did not correlate with risk ACA/SCD Was associated with increased risk of syncope Associations with increased risk death: QTc ≥530 msec, syncope, gender	● SCD of sibling did not predict risk of death or ACA ● Did correlate with increased risk of syncope ~6% ● Hx of syncope, QTc≥ 530 msec, female gender correlated with increased risk ACA/SCD
● Wedekind H Eur J Ped 2009 (339) ● 19101729	**Study type:** Retrospective single center **Size:** 83	**Inclusion criteria:** Genotype positive **probands**, age ≤16 y LQTS: 89% LQT1, 2,3 Mean QTc 510±74 ms 61% symptoms: syncope 49%, ACA 33%, SCD 18% 78% with BB rx **Exclusion criteria:** N/A	**1° endpoint:** Recurrent syncope, ACA or SCD after dx LQTS. Mean followup 5.9±4.7 y **Results:** 92% treated: Followup: Propranolol 79%, atenolol 20%, metoprolol 12%, bisoprolol 8%, pindolol 2%; mexiletine 4% ICD 8%, pacer 5%. 31% recurrent symptoms: 14% ACA or SCD; syncope 86% Significant predictors: QTc >500 ms (HR: 2.9; 95% CI: 1.2–7.3 p=0.02); prior syncope HR: 4.04; 95% CI: 1.1–15, ACA HR:11.7; 95% CI: 3.1–43.4, p<0.001	● Risk predictors: QTc > 500 msec, prior syncope or ACA ● LQT2 highest rate SCD vs other
● Goldenberg I JACC 2011 (340) ● 21185501	**Study type:** Multicenter international registry, retrospective **Size:** 469	**Inclusion criteria:** Genotyped patients with LQTS: 3386 patients Normal QTc: ≤440 ms Prolonged QTc >440 ms Unaffected: negative genotype	**1° endpoint:** LQTS with normal QTc: risk for ACE: ACA or SCD **Results:** Normal QTc =14% of total LQTS patients in study. Normal QTc risk ACA/SCD =4%, lower than those with prolonged QTc (15%) but higher than genotype neg family members.	● Genotype positive patients with normal QTc =25% of genotype positive patients. ● 4% ACA/SCD with normal QTc vs 15% if prolonged QTc

		Exclusion criteria: N/A	Increased risk: mutation characteristics; LQT1 vs LQTS 2, HR: 9.88; p=0.03; Duration of QTc and gender important only in those with prolonged QTc.	
● Tester DJ JACC 2006 (341) ● 16487842	**Study type:** retrospective single center **Size:** 541	**Inclusion criteria:** consecutive patients undergoing Genetic testing LQTS 1997-2004 **Exclusion criteria:** N/A	**1° endpoint:** yield of LQTS genetic testing vs. clinical genotype **Results:** 50% positive genotype. Yield correlated with duration of QTc and phenotype: 0%: QTc<400 62%: QTc >480 ms (p<0.0001) Schwartz score ≥4: 72% positive	● Genotype results more likely to be positive with QTc >480ms or with higher Schwartz score
● Priori S Circ 2002 (342) ● 11901046	**Study type:** Multicenter retrospective **Size:** 200	**Inclusion criteria:** Brugada S with ECG changes, spont (51%) or induced 130 probands **Exclusion criteria:** N/A	**1° endpoint:** Brugada risk stratification for SCD PES performed in 86 **Results:** SCN5A identified in 22% probands, 46% of family members Risk analysis: gender; ECG, family hx, mutation status, symptoms Syncope without ST elevation on baseline ECG: not a risk Syncope AND ST elevation: increased risk SCD, HR: 6.4; p <0.002	● Multivariable risk predictor: spontaneous ST elevation V1-V3 and Hx of syncope ● Syncope without spontaneous ST elevation not a risk factor ● PES not predictive ● Mutation carriers without phenotype: low risk
● **FINGER** ● Probst V Circ 2010 (343) ● 20100972	**Study type:** Multi-center registry, 11 centers in Europe **Size:** 1029	**Inclusion criteria:** Brugada Syndrome ECG spont (45%) or with drug challenge. Median 45 y (35-55). Hx ACA 6%, syncope 30%, asymptomatic 64% (654 patients). SCN5A positive 22%. **Exclusion criteria:** N/A	**1° endpoint:** ACE outcomes in BrS **Results:** PES performed in 62%: 41% positive, higher in symptomatic patients 46% vs 37%, p=0.02. PES performed in 369 asymptomatic patients: 37% positive (137/369); 85% (117/137) inducible asyx patients had ICD implanted ICD's implanted: 433/1029 patients (42%): of 433: 54 ACA (12.5%), 208 syncope (48%),	● Low event rate in asymptomatic patients 0.5%/y. ● Inducibility w PES or family Hx SCD or SCN5A mutation not predictors of ACE ● Predictors of ACE: symptoms, ACA, syncope, presence of ICD, spont type 1 ECG. ● Among asymptomatic patients: 37% positive PES; of these 85% had ICD implanted.

			171 asymptomatic (39%). 118/171 asymptomatic patients with ICD (69%) implanted due to positive EPS. ACE 51: approp ICD shocks 44, SCD 7. Mean ACE rate 1.6%/y: 7.7% in patients w Hx ACA;1.9% w prior syncope; 0.5% in asymp patients Predictors: symptoms (p<0.001): ACA (HR: 11; 95% CI: 4.8–24.3, p<0.001), syncope (HR: 3.4; 95% CI 1.6–7.4, p=0.002), ICD implantation (HR: 3.9; 95% CI: 1.4–10.6, p=0.007). spont type 1 ECG (HR: 1.8;95% CI: 1.03–3.33, p=0.04); NOT predictive: gender, family Hx SCD, +PES (p=0.48), presence SCN5A mutation	● ICD implantation in asymptomatic patients was significant in multivariable analysis as predictor of ACE: HR:10.1; 95% CI: 1.7–58.7, p=0.01). ● No independent predictive value of PES (p=0.09), males (p=0.42, spont type 1 ECG (p=0.38) age (p=0.97)
● Moss AJ Circ 2000(344) ● 10673253	**Study type:** Retrospective observational **Size:** 869	**Inclusion criteria:** LQTS registry, Rochester, patients treatment w BB age <41 y, 80% syncope or ACA prior to rx. Atenolol, metoprolol, nadolol, propranolol. 139/869 genotyped: LQT 1(69), LQT 2 (42), LQT 3 (28) **Exclusion criteria:** age >41 y start rx	**1° endpoint:** Recurrent CE on b-bl in LQTS **Results:** B-Bl significantly reduce risk LQT 1 and 2; LQT 3: no effect For symptomatic patients, HR 5.8 for recurrent CE: 32% ACE within 5 y. Prior syncope: HR: 3.1. Prior ACA, HR: 12.9 for ACA or sudden death: 14% recurrent CA.	• For LQT 1 and 2, BB reduce risk • Highly symptomatic patients prior to treatment at high risk for recurrent events. • LQT 3 patients: BB did not reduce risk
● Zareba JCE 2003 (345) ● 12741701	**Study type:** Single center retrospective **Size:125**	**Inclusion criteria:** 125 LQTS patients with ICD's compared with LQTS with similar risk and no ICD. ICD Indications: 54 ACA, 19 recurrent syncope on b-bl; 52 "other" (syncope; + family Hx SCD) **Exclusion criteria:** N/A	**1° endpoint:** Mortality of LQTS patients treated with/without ICD: 73 patients with syncope on treatment or prior ACA and ICD compared with 161 LQTS patients without ICD (89 ACA, 72 rec syncope on b-bl) **Results:** Deaths: ICD 1.3% (1 pt), followup av 3 y, vs. 16% (26 patients) in non-ICD patients during 8 y mean followup.	● Prior ACA or recurrent syncope on b-bl treatment assoc with significant mortality without ICD during 8 y followup

● Monnig G Heart Rhythm 2005 (346) ● 15840474	**Study type:** single center retrospective **Size:** 27	**Inclusion criteria:** symptomatic **LQTS patients** undergoing ICD implant. Mean QTc 540±64; 85% famle, 63% ACA, 33% recurrent syncope on b-bl, 4% "severe phenotype 81 genotype pos: LQT 1 28, LQT2 39; LQT3 1, LQT5 13. **Exclusion criteria:** N/A	**1° endpoint:** LQTS Appropriate ICD shocks or death during followup. **Results:** Mean followup 65±34 mo. Death 1 pt, non-cardiac. Approp shocks: 37%; 30% multiple shocks. Logistic regression: QTc >500 ms, prior ACA predictive. Shocks reduced from av 7.1 to 0.75 shocks annually by adding b-bl, increased rate anti-brady pacing, rate smoothing algorithm.	● Predictors of approp ICD shocks: QTc >500 msec, prior ACA ● Approp shocks reduced by anti-brady pacing, b-bl rx, rate-smoothing
● Hayashi M Circ 2009 (347) ● 19398665	**Study type:** single center retrospective **Size:** 101	**Inclusion criteria:** CPVT 50 probands, 51 family members, age at dx 15±10 y. Symptoms 60% (61 patients), all probands, 22% family members 93% symptomatic <21 y old 77% detection of mutations: RYR2 CASQ2 **Exclusion criteria:** N/A	**1° endpoint:** ACE in CPVT patients: syncope, ACA, approp ICD shocks, SCD **Results:** followup 7.9 y 8 y total event rate 32% total, 27% with b-bl, 58% without b-bl. 8 y event ACA/SCD 13% (8 patients) Increased risk: Absence BB HR: 5.54; 95% CI: 1.17–16.15, p=0.003), Hx ACA HR: 13.01; 95% CI: 2.48–68.21, p=0.002); younger age at dx (HR: 0.54/decade; 95% CI: 0.33–0.89, p=0.02) 32% with events on b-blockers did not take meds on day of event. Nadolol: ACE 19%	● Higher risk for lack of BB, Hx ACA ● Prior syncope not associated with increased risk
● Delise P EHJ 2011(348) ● 20978016	**Study type:** Multi- center prospective **Size:** 320	**Inclusion criteria:** Type 1 **Brugada ECG:** spontaneous 54%, drug-induced 46%. Median age 43 y. Males 81% Asymptomatic 66%, syncope 33% NO prior ACA	**1° endpoint:** predictors in Brugada S of ACE (approp ICD shocks, sudden death) **Results:** Median followup 40 mos (IQR 20-67) 5.3 % MACE (17 patients): VF on ICD (14), sudden death3 MACE occurred in 10.4% of symptomatic and 2.8% of asymptomatic patients (p=0.004) ICD's implanted in 34%(110 patients)	● Combining 2 or more risk factors was useful risk stratification: • Spontaneous type 1 ECG • Family Hx sudden death, syncope, positive PES ● MACE occurred only in patients with 2 or more risk factors. MACE event rates: • 3.0%/pt/yr in symptomatic, • 0.8%/pt/yr in asymptomatic

		Exclusion criteria: N/A	PES performed in 245 (76%): positive in 50% of symptomatic and 32% of asymptomatic patients. MACE in 14% of positive PES, 0% of negative, 5.3% of no EPS: positive predictive values 14%, negative pred value 100% VF occurred in 15.5% of patients with inducible VF using doubles, 8.6% of triples Combination of risk factors most significant: spont ECG, family Hx sudden death, syncope, positive EPS: no events occurred in patients without any of above or with only one risk factor. Spontaneous type 1 ECG: if additional risk factors, 30% MACE (p<0.001)	● PES can be useful in patients with spontaneous type 1 ECG and no other risk factors; may be helpful to identify low risk patients
● Hiraoka M JE 2013 (349) ● 23702150	**Study type:** Prospective single center **Size:** 69	**Inclusion criteria:** Brugada S patients ages 18–35 y Mean age 30±6 y No genetic testing **Exclusion criteria:** N/A	**1° endpoint:** Brugada S ages 18-35 y at dx, outcomes of VF or SCD Followup 43±27 mos. **Results:** Based on presenting symptoms: VF 42%, syncope 12%, asymptomatic 2.5% Not predictive: gender, family Hx SCD, abnl SAECG, spontaneous vs drug-induced ECG, inducible VT/VF All ages 460 patients symptoms at presentation vs outcomes: VF 8.4%/y, Syncope 1.7%/y, asymptomatic 0.3%/y	● Brugada outcomes in young adults vs presenting symptoms: ● Events: VF 11.2% /y, syncope 3.3% y, asymptomatic 0.7%/y
● **PRELUDE** ● Priori SG et al. JACC 2012 ● 22192666	**Study type:** Prospective registry **Size:** 308	**Inclusion criteria:** Age >18 y, BrS type 1 ECG spont (56%, 171/308) or drug-induced, without prior ACA;	**1° endpoint:** Predictive accuracy of PES for sustained VT/VF or approp ICD shock in Brugada. **Results:** PES performed at enrollment; followup every 6 mo. Mean age 45±12 y.	● PES did not predict high risk ● Predictors: spontaneous type BrS ECG and symptoms; f-QRS, VERP <200 msec VERP <200 msec was predictive: this data would only be obtained at EPS.

		21% with prior syncope (65 patients: 16/65 {25%} > 1 syncope). SCN5A positive 20% of tested patients. (f-QRS =2 or more spikes within QRS leads V1-V3: present 8.1%) **Exclusion criteria:** N/A	Cardiac arrest 4.5% (14/308), 13/14 resuscitated with ICD, EMS 1. PES positive in 41% (126/308); of these: single stimulation 5.5%, double 44.5%, triples 50%. ICD's implanted in 137 patients (78% of inducible patients {98/126} and 21% of non-inducible patients {39/182}. Annual event rate 1.5%: Multivariable predictors: spont type 1 ECG and Hx of syncope (HR: 4.20; 95% CI: 1.38–12.79, p=0.012), Ventricular ERP <200 msec (HR: 3.91; 95% CI: 1.03–12.79, p=0.045), QRS fractionation (HR: 4.94, 95% CI: 1.54–15.8, p=0.007). Positive PES not predictive (HR: 1.03; 95% CI: 0.34–3.16, p=0.96)	● NOTE that + PES used in decision to implant ICD's: 13/137 patients (9.5%) with ICD's were resuscitated with ICD. Note 1/14 patients with VF had only spont type 1 ECG and no prior syncope, neg family hx, neg EPS, VERP >200 msec but + SCN5A mutation and received ICD after EPS. Only 1 pt without ICD had ACA: pt had spont type 1 ECG, VRP <200 msec, and fQRS.
● Wilde A et al. Circ 2016 ● 27566755	**Study type:** multicenter observational **Size:** 391	**Inclusion criteria:** LQT3 SCN5A mutation carriers In 8%, first cardiac symptom: ACA, SCD **Exclusion criteria:** symptoms during first year of life-12 patients; Lost to followup after age 1: 3 patients; Patients with 2 mutations	**1° endpoint:** LQT3 ACE outcomes: syncope, ACA, SCD Median followup 7 y **Results:** Rx: B-bl 29%; LCSD 2%; pacer 5%; ICD 18%. Time dependent increase in ACE: by age 40yrs, ~40% with ACE. ~ 50% of ACE =ACA or SCD B-blocker rx: 83% risk reduction in females (p=0.015); 49% risk reduction in males (not sig; too few events in males to assess) BB not pro-arrhythmic 3% died on BB during followup Multivariate risk factors: QTc, syncope:	● High risk LQT3: Females; syncope, QTc 450-490 ● Hx of syncope—doubled risk ● BB therapy significantly reduced risk for ACE, especially in females Mutation type/location did not have sig effect on outcome

			Each 10 msec increase in QTc up to 500 msec associated with 19% increase in ACE (no further risk with QTc >500 msec)	
● Probst V et al. Circ CV Gen 2009 ● 20031634	**Study type:** multicenter retrospective **Size:** 115	**Inclusion criteria:** BrS families with at least 5 family members genotype carries **Exclusion criteria:** N/A	**1° endpoint:** BrS assoc with SCN5A **Results:** BrS ECG present in 47% of mutation carriers Mutation carriers had longer PR and QRS intervals SCN5A mutations are not directly causal of Br pattern ECG	● Poor genotype phenotype correlation for BrS SCN5A
● Crotti L et al. ACC 2012 ● 22840528	**Study type:** Multicenter retrospective **Size:** 129	**Inclusion criteria:** BrS	**1° endpoint:** Genotype results Brugada S **Results:** 20% putative pathogenic mutations, (95% in SCN5A; 5% other genes) Yield similar with type 1 Brugada ECG only (23%) and those with symptoms (17%) Prolonged PQ interval > 200 msec: 38% positive vs 11% if PQ < 200 ms, (OR 8, 1.5-16)	● Brugada: no genotype/phenotype correlation
● Risgaard B et al. Clin Genet 2013 ● 23414114	**Study type:** Exome Sequencing Project (ESP) analysis **Size:** 6258	**Inclusion criteria:** Genetic variants of Brugada Syndrome searched for in exome data **Exclusion criteria:** N/A	**1° endpoint:** Identify prevalence of mutations associated with BrS in general exome BrS prevalence ~ 1:2000 to 1:100,000 **Results:** 10% of variants identified in ESP, a frequency of 1:23	● ~10% of variants associated with BrS are present in Exome, raising doubt about monogenic role in pathogenicity of BrS ● Recommend using Exome data to establish gene frequency in population

Data Supplement 40. Nonrandomized Trials Related to Congenital LQTS – (Section 7.9.1.1.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)

● Garson AJ Circ 1993 (350) ● 8099317	**Study type:** Retrospective multicenter **Size:** 287	**Inclusion criteria**: Age <21y, QTc >0.44, unexplained syncope, seizures, ACA triggered by emotion or exercise, or family Hx LQTS. Mean age presentation 8.8 y 61% symptoms 9% ACA was first symptom **Exclusion criteria:** N/A	**1° endpoint:** ACA or SCD for LQTS children during Mean followup 5 y. **Results**: Rx 68% BB, 8% other meds, LCSD 2%, ICD 1% Med treatment effective for symptoms in 76%, and for VEA 60% Symptoms in first mo of life high risk group: 16% died. Asymptomatic patients with normal QTc and positive family Hx may be low risk group (no genotyping results) Predictors highest risk: symptoms at presentation, propranolol failure	● QTc at presentation >0.60 highest risk group ● no difference between propranolol and atenolol ● consider prophylactic treatment in asymptomatic patients with QTc >0.44
● Hobbs JB et al. JAMA 2006 (351) ● 16968849	**Study type:** Retrospective multicenter **Size:** 2772	**Inclusion criteria:** Adolescents in LQTS Registry alive at age 10 y, followed until age 20 y **Exclusion criteria:** N/A	**1° endpoint:** ACA or SCD in adolescents with LQTS **Results:** 81 patients w ACA, 45 SCD Significant risk factors: recent syncope in prior 2 y, HR: 11.7; QTc ≥ 530 msec HR: 2.3; males age 10-12 y, HR: 4; males = females ages 13–20 y Beta blocker therapy ↓by 64% in patients with syncope in last 2 y	● Risk factors: syncope, QTc ≥ 530 msec, males age 10–12 y
● Goldenberg I JACC 2011 (340) ● 21185501	**Study type:** Multicenter international registry, retrospective **Size:** 469	**Inclusion criteria:** Genotyped patients with LQTS: 3386 patients Normal QTc: ≤440 ms Prolonged QTc >440 ms Unaffected: negative genotype **Exclusion criteria:** N/A	**1° endpoint:** LQTS with normal QTc: risk for ACE: ACA or SCD **Results:** Normal QTc =14% of total LQTS patients in study. Normal QTc risk ACA/SCD =4%, lower than those with prolonged QTc (15%) but higher than genotype neg family members. Increased risk: mutation characteristics; LQT1 vs LQTS 2, HR: 9.88; p=0.03; Duration of QTc and gender important only in those with prolonged QTc.	● Genotype positive patients with normal QTc =25% of genotype positive patients. ● 4% ACA/SCD with normal QTc vs 15% if prolonged QTc

● Priori SG NEJM 2003 (352) ● 12736279	**Study type:** Retrospective **Size:** 647	**Inclusion criteria:** Genotyped patients: LQT1 60%, LQT2 32%, LQT3 8%, mean followup 28 y **Exclusion criteria:** N/A	**1° endpoint:** LQTS risk of ACE age <40 y and before rx: syncope, ACA, sudden deathbefore **Results:** Incidence ACE: LQT1 30%, LQT2 46%, LQT3 42%. 13% ACA or sudden deathbefore age 40 y, Events highest among LQT2	● Genetic locus and QTc independent risk factors ● QTc risk factor for LQT1 and LQT2, not LQT3 ●
● Wedekind H Eur J Ped 2009 (339) ● 19101729	**Study type:** Retrospective single center **Size:** 83	**Inclusion criteria:** Genotype positive probands, age ≤16 y LQTS: 89% LQT1, 2,3 Mean QTc 510±74 ms 61% symptoms: syncope 49%, ACA 33%, SCD 18% 78% with BB rx **Exclusion criteria:** N/A	**1° endpoint:** Recurrent syncope, ACA or SCD after dx LQTS. Mean followup 5.9±4.7 y **Results:** 92% treated: Followup: Propranolol 79%, atenolol 20%, metoprolol 12%, bisoprolol 8%, pindolol 2%; mexiletine 4% ICD 8%, pacer 5%. 31% recurrent symptoms: 14% ACA or SCD; syncope 86% Significant predictors: QTc >500 ms, p=0.02, HR: 2.9; 95% CI: 1.2–7.3; prior syncope HR: 4.04; 95% CI: 1.1–15, ACA HR: 11.7; 95% CI: 3.1–43.4, p<0.001	● Risk predictors: QTc >500 msec, prior syncope or ACA ● LQT2 highest rate SCD vs other
● Jons C et al. JACC 2010 (353) ● 20170817	**Study type:** Retrospective International LQTS Registry **Size:** 1059	**Inclusion criteria:** LQTS patients, QTc ≥ 450 msec with syncope as first symptoms 20% with ICD 52 patients LCSD **Exclusion criteria:** N/A	**1° endpoint:** Risk of ACE in LQTS patients with syncope Severe = ACA, approp ICD shock, SCD **Results:** Lowest risk in patients with single syncope before rx; intermediate risk: multiple syncope before rx, HR: 1.8 Higher risk: syncope after BB rx: HR:3.6 p<0.001. Does not state how many patients died/aca.	● Recurrent syncope during BB treatment assoc with increased risk of recurrent events ●BB failure highest in children and females
● Barsheshet Circ 2012 (354) ● 22456477	**Study type:** Retrospective observational	**Inclusion criteria:** LQT1 genotyped patients, mutations KCNQ1, ages birth-40	**1° endpoint:** Risk for ACA/SCD vs. mutation location in LQT1 **Results:** 105 events: 27 ACA, 78 SCD	● LQT1 patients with C-loop mutations are at high risk for ACA/SCD, and derive pronounced benefit from b-blocker rx

	Size: 860 patients	**Exclusion criteria:** N/A	C-loop mutations highest risk (HR: 2.75; 95% CI: 1.29–5.86, p=0.009) B-bl treatment sig greater risk reduction in C loop mutations (HR: 0.12; 95% CI: 0.02–0.73, p=0.02) vs all other mutations (HR: 0.82; 95% CI: 0.31–2.13, p=0.68) C-loop mutations showed sig reduction in channel activation in response to b-adrenergic stimulation	
● Vincent GM Circ 2009 (355) ● 19118258	**Study type:** Retrospective observational **Size:** 216	**Inclusion criteria:** Genotype + LQT1 patients treatment with BB for minimum 2 y (unless CA/SCD), median followup 10 y. Median age 26 y (4–76 y); 73% symptomatic; prior CA in 12% (26 patients). Mean QTc 495±48 ms **Exclusion criteria:** N/A	**1° endpoint:** ACE (syncope, CA, SCD) in LQT 1 treatment with BB **Results:** 75% asymptomatic. ACE 25%. 5.5% CA/SCD (12 patients) after rx: 11/12 non-compliant or on QT prolonging med. None of 26 patients with prior CA had SCD on beta-bl, one had CA. Risk for CE reduced to 0.06 CE/y (0.05–0.07)	● Risk for CA in compliant patients <<< non-compliant (OR:0.03; 95% CI: 0.003–0.22, p=0.001) ● Beta-bl meds approp treatment for asxy patients, and symptomatic patients who have not had CA before b-bl rx. ● Risk of CA/SCD on beta bl not assoc with baseline QTc nor prior syx nor gender ● LQT1 patients with prior CA had very low risk CA/SCD on BB
● Moss AJ Circ 2000 (344) ● 10673253	**Study type:** Retrospective observational **Size:** 869	**Inclusion criteria:** LQTS registry, Rochester, patients treatment w BB age <41 y, 80% syncope or ACA prior to rx. Atenolol, metoprolol, nadolol, propranolol. 139/869 genotyped: LQT 1(69), LQT 2 (42), LQT 3 (28) **Exclusion criteria:** age >41 y start rx	**1° endpoint:** Recurrent CE on b-bl in LQTS **Results:** B-Bl significantly reduce risk LQT 1 and 2; LQT 3: no effect For symptomatic patients, HR 5.8 for recurrent CE: 32% ACE within 5 y. Prior syncope: HR: 3.1. Prior ACA, HR: 12.9 for ACA or sudden death: 14% recurrent CA.	● For LQT 1 and 2, BB reduce risk ● Highly symptomatic patients prior to treatment at high risk for recurrent events. ● LQT 3 patients: BB did not reduce risk

● Abu-Zeitone JACC 2014 (356) ● 25257637	**Study type:** Retrospective multicenter **Size:** 1530	**Inclusion criteria:** Patients in LQTS registry, Rochester, NY treatment with BB: atenolol (441), metoprolol (151), propranolol (679), nadolol (259), age <40 y, no AICD **Exclusion criteria:** simultaneous use of 2 beta Blockers	**1° endpoint:** First cardiac event: syncope, CA, sudden deathafter starting b-bl **Results:** LQT 1: risk reduction 57% any b-bl, no differential efficacy. LQT2: nadolol only med with sig risk reduction (HR: 0.4)	● All BB reduce risk of events, without difference ● In LQT 2 nadolol appeared superior (HR: 0.40) ● For patients with recurrent events on beta-bl, propranolol offered least protection (HR: 0.52)
● Goldenberg I JCE 2010 (357) ● 20233272	**Study type:** Retrospective observational Multi-center **Size:** 1393	**Inclusion criteria:** Genotyped LQT1 (971) and LQT2 (422) patients in International LQTS registry. Ages Birth-40 y. ICD 129 patients (LQT1 50, 9%; LQT2 79, 19%) LCSD 31 patients, LQT1 3%, LQT2 4% **Exclusion criteria:** N/A	**1° endpoint:** Age related, gender and genotype specific risk factors for ACE (syncope, approp shock, ACA, or SCD) **Results:** ACE LQT1 39%, LQT2 46% Risk for ACE: • Ages 0–14 y, LQT1 genotype vs LQT2 (HR: 1.49; 95% CI: 1.14–1.93, p<0.003); males vs females (HR: 1.31, p=0.04) • Ages 15–40 y, LQT2 vs LQT1, (HR 1.67; 95% CI: 1.31–2.13, p<0.001); females vs. males HR: 2.58; 95% CI: 1.90–3.49, p<0.001) • QTC≥500 msec at increased risk in both age groups: 0–14 y, HR: 2.3 (p<0.0001); age 15–40 y, HR: 2.22 (p<0.001) • Treatment in LQT1: atenolol decreased risk HR: 0.23; 95% CI: 0.08–0.67, p=0.008) nadolol was not associated with sig risk reduction (HR: 0.4; 95% CI: 0.14–1.16, p=0.09) • Treatment in LQT2: nadolol reduced risk (HR: 0.13; 95% CI: 0.03–0.62, p=0.01); atenolol did not (HR: 0.69; 95% CI: 0.32–1.49, p=0.34) • ACA or SCD rarely occurred during treatment with beta-bl	● B-blockers reduced risk in LQT1 and 2: o LQT1 atenolol > nadolol o LQT2 nadolol > atenolol ● ACA/SCD rarely occurred as presenting symptom in patients treatment with b-bl ● QTc ≥ 500 msec increased risk HR: 2.2–2.3 ● Syncope during b-bl treatment assoc with increased risk ACA/SCD ● Recommend BB therapy routinely to all high-risk LQT1 and LQT2 patients without contraindications as first rx ● 1° AICD therapy recommended for those with syncope during b-bl therapy

			• Patients with syncope during b-bl treatment had rel high rate subsequent ADA/SCD (>1 event per 100 pt-y.	
● Sauer AJ JACC 2007 (358) ● 17239714	**Study type:** retrospective **Size:** 812	**Inclusion criteria:** Genotype positive LQTS adults ≥18 y old 8% prior ACA **Exclusion criteria:** N/A	**1° endpoint:** ACE: syncope, ACA, SCD between ages 18-40 y in LQTS **Results:** Risk predictors: ACA or SCD: female gender HR: 32.68; QTc ≥500 ms HR: 3.34; QTc ≥550 msec HR: 6.35; syncope after age 18y, HR: 5.10 LQT2 33% recurrent ACE. LQT1 highest prior events 34%. BB reduced risk ACA, SCD by 60%; highest benefit in QTc ≥500 msec, LQT1 and LQT2.	● Highest risk: females, QTc >500 msec, syncope after age 18 y ● LQT2 higher risk ● QTc ≤499 msec did not contribute to higher risk lethal event
● Steinberg C J Interv Card EP 2016 (359) ● 27394160	**Study type:** retrospective cohort **Size:** 114	**Inclusion criteria:** Genotype positive LQT1 (62%) or LQT2 (38%) treated with bisoprolol 52%, (59 patients), nadolol 14%, (16 patients) or atenolol 34%, (39 patients) 59% females **Exclusion criteria:** N/A	**1° endpoint:** syncope, SCD, ACA, documented polymorphic VT LQT1 or 2, on BB Median followup 3 y for bisoprolol and nadolol; 6 y for atenolol (p=0.03) **Results:** Symptoms: 29%: syncope 27%, ACA 3.5%, documented VT; ICD's 7%. Dosing: bisoprolol 5 mg, nadolol 65–80 mg, atenolol 55 mg Nadolol patients highest proportion of probands vs bisoprolol (p=0.007) QTc shortening greater with bisoprolol and nadolol, vs. atenolol; QTc reduction greater in nadolol vs. atenolol, similar to bisoprolol	● Bisoprolol (selective b-1 antagonist) well-tolerated, and shortened QTc similar to nadolol ● not powered to assess difference in BB

			Cumulative incidence ACE 0.5%/pt-y. ACA in one pt on bisoprolol; syncope in 2 patients with atenolol; no events with nadolol NO difference events bisoprolol 0.4% vs other b-blocker 0.6%	
● Nannenberg EA Circ CV Genetics 2012 (336) ● 22373669	**Study type:** Retrospective single center, Netherlands **Size:**	**Inclusion criteria:** Genotype positive 6 inherited arrhythmia syndromes analyzed with Family Tree Mortality Ratio (FTMR): LQT1,2,3; Brugada Syndrome, SCN5A overlap syndrome (LQT3, BrS, conduction disease); RYR2 CPVT. **Exclusion criteria:** N/A	**1° endpoint:** Using FTMR method to achieve Standardized Mortality Ratio(SMR) (observed to expected mortality by genotype and age in inherited arrhythmias **Results:** LQTS1: in first 10 y of life SMR 2.9 (1.5–5.1) LQTS2: age 30-39 y, SMR 4.0 (1.1–10) LQTS3: age 15-19 y, SMR 5.8(1.2–16.9) SCN5A overlap syndrome: 20-39 y, SMR 3.8 (2.5–5.7) CPVT: age 20-39 y, SMR 3.0 (1.3–6.0) BrS: 40-59 y, SMR 1.79 (1.2–2.4), especially males	● Identify age ranges of highest risk for specified inherited arrhythmia syndromes ● Asymptomatic patients over age ranges may not require rx
● Villain E EHJ 2004 (360) ● 15321698	**Study type:** retrospective single center **Size:** 122	**Inclusion criteria:** LQTS in pt <18 y treated with BB, dx 1984-2002; 86% genotype pos. 26 patients dx in first mo of life; for others, median age 6y at dx 54% symptomatic probands **Exclusion criteria:** N/A	**1° endpoint:** ACA or SCD in LQTS patients <18yr old during followup median 7.5 y **Results:** BB: nadolol 50 mg/m^2/d given bid; Propranolol 3-5 mg/kg/d, acebutolol 10 mg/kg/d., atenolol 50 mg/d, bisoprolol 10 mg/d. Monitored at least yearly with ecg, exercise test and/or holter, goal peak HR <130-150 bpm. Symptomatic patients w longer QTc. 3 neonates died; one pt died after pacemaker implantation. One pt died after meds discontinued. 4.5% recurrent syncope. Cumulative event-free survival 94%	● BB highly effective in children, particularly in LQT1 ● Double mutations or LQT2,3 higher risk ● no LQT1 patient died while receiving BB

● Moltedo JM Ped Cardiol 2011 (361) ● 20960185	**Study type:** retrospective **Size:** 57	**Inclusion criteria:** Pediatric patients with LQTS treated with atenolol. Genotyping not available **Exclusion criteria:** N/A	**1° endpoint:** Death, recurrent symptoms in young LQT1 ps treatment with atenolol during followup 5.4±4.5 y **Results:** Mean age dx 9 ±6 y, 60% females. Mean QTc 521± 54 msec Mean dose atenolol 1.5±0.5 mg/kg/d twice daily; dose titrated to achieve peak HR <150 bpm on holter and exercise. + family Hx sudden death22%. ICD's 10% Symptoms 42%: VT: 18%, syncope 10%, ACA 7%, AV block 4%. One death, non-compliant with meds. Recurrent symptoms: 8%, 4 patients: ¾ received ICD. All patients with recurrences had QTc > 500 msec 6% side effects (1 pt) or inadequate heart rate control—change b-blocker	● Atenolol in twice daily dosing effective in pediatric patients in reducing events ● Assessing adequacy of beta-blockade by blunting peak HR recommended ● Recurrent syncope occurred in patients with QTc >500 msec
● Schwartz et al.2004 (362) ● 15051644	**Aim:** To assess the long-term efficacy of LCSD in a group of high-risk patients. **Study type:** Multicenter global registry **Size:** 147 patients	**Inclusion criteria:** 162 LQTS patients who underwent LCSD between 1970 and 2002 were identified. Among them, 15 underwent left stellectomy that we regarded as inadequate denervation and therefore insufficient therapy. Accordingly, the analysis is on the 147 patients who underwent LCSD **Exclusion criteria:** N/A	**1° endpoint:** Cardiac events and on survival free of cardiac events **Results:** Their QT interval was very prolonged (QTc, 543±65 ms); 99% were symptomatic; 48% had a CA; and 75% of those treated with BB remained symptomatic. The average follow-up periods between first CE and LCSD and post-LCSD were 4.6 and 7.8 y, respectively. After LCSD, 46% remained asymptomatic. Syncope occurred in 31%, ACA in 16%, and sudden death in 7%. The mean yearly number of CEs per patient dropped by 91% (p<0.001). Among 74 patients with only syncope before LCSD, all types of CEs decreased significantly as in the entire group, and a post-LCSD QTc <500 ms predicted very low risk. The percentage of patients with >5 CEs declined	● LCSD is associated with a significant reduction in the incidence of ACA and syncope in high-risk LQTS patients when compared with pre-LCSD events. However, LCSD is not entirely effective in preventing cardiac events including SCD during long-term follow-up. ● The study population included the vast majority of LQTS patients treated with LCSD worldwide. ● Among 51 genotyped patients, LCSD appeared more effective in LQT1 and LQT3 patients.

			from 55% to 8% (p<0.001). In 5 patients with preoperative implantable defibrillator and multiple discharges, the post-LCSD count of shocks decreased by 95% (p=0.02) from a median number of 25 to 0 per patient.	
● Bos JM Circ Arrhythm Elect 2013 (363) ● 23728945	**Study type:** Single center retrospective **Size:** 52	**Inclusion criteria:** LQTS patients undergoing LCSD 2005-2010, mean QTc 528±74 msec; 33% 1° prevention. Mean age 14.1±10 y. **Exclusion criteria:** N/A	**1° endpoint:** LCSD for LQTS: ACE: syncope, ACA, SCD, approp ICD shock for VF F/U 3.6±1.3 y. **Results:** 23% recurrent ACE (not specified). 15% no reduction in events. No recurrence in patients with b-bl intolerance as indication (vs. recurrent events). (0/12 vs 17/40, p<0.001) Ptosis: 8%, pneumothorax 6%	• 23% recurrent ACE after LCSD
● Schneider, HE Clin Res Cardiol 2013 (364) ● 22821214	**Study type:** Retrospective single center **Size:** 10	**Inclusion criteria:** LQT 5, CPVT 5, with recurrent syncope, VT, ICD shocks or ACA on BB. Mean age 14 y (3.9–42 y). 2 ICD pre-surg; 6 ICD at LSCD. **Exclusion criteria:** N/A	**1° endpoint:** LCSD for LQT, CPVT: ACE LOS 3-9 d; followup median 2.3 y (0.6–3.9 y) **Results:** Decrease in arrhythmia burden, ACE No ICD discharges for VT ACA: 10% Horner syndrome 70%, 20% pleural effusion	● Reduction in ICD discharges ● 10% ACA ● Minor comps frequent
● Collura CA Heart Rhythm 2009 (365) ● 19467503	**Study type:** single center retrospective **Size:** 20	**Inclusion criteria:** LCSD 2005-2008, video-assisted. Mean age 9.1±9.7 y, (2mo-42 y) LQTS 12 geno +, 4 geno – LQT; CPVT 2 **Exclusion criteria:** N/A	**1° endpoint:** LCSD for LQTS and CPVT: ACE followup mean 17 mo **Results:** 2° prev: ICD shocks eliminated 72%; 18% ineffective 2° prev 11, mean QTc 549 msec; 1° 9, mean QTc 480 msec.	● LCSD reduced shocks in 72% during short term followup ● 18% ineffective
● Hofferberth SC JTCS 2014(366) ● 24268954	**Study type:** single center retrospective	**Inclusion criteria:** LCSD 2000-2011. LQTS 13	**1° endpoint:** ACE after LCSD: LQTS, CPVT, VF Median followup 28 mo, (4–131 mo)	● LCSD recommended in patients with recurrent symptoms refractory to meds

	Size: 24	(median age 8 y), CPVT 9 (age 17 y), VF 2 (age 23). **Exclusion criteria:** N/A	**Results:** 73% marked reduction in arrhythmia burden; 55% arrhythmia free. 27% persistent symptoms	● 27% recurrent symptoms, non-responders
● Chattha IS Heart Rhythm 2010 (367) ● 20226272	**Study type:** Retrospective single center **Size:** 75	**Inclusion criteria:** Exercise testing done on 3 groups: LQT1, LQT2, and controls **Exclusion criteria:** N/A	**1° endpoint:** Genotypic specific changes in QTc with exercise **Results:** Changes in QTc: LQT1: longer corrected QTc at peak and early recovery LQT2: QTc increased during recovery Controls: normal QTc during recovery	● End of recovery QTc >445 msec, usually at 4 min of recovery, distinguished 92% of LQTS from controls ● Start of recovery QTc >460 msec correctly identified 80% of LQT1 and 92% of LQT2
● Aziz PF CAE 2011 (368) ● 21956039	**Study type:** Single center retrospective **Size:** 158	**Inclusion criteria:** LQT1, LQT2, and controls undergoing cycle ergometer exercise testing **Exclusion criteria:** N/A	**1° endpoint:** QTc changes during exercise in LQTS **Results:** LQT1 and LQT2 with sig increase in QTc during recovery. Recovery delta QTc- (7 min-1 min) > 30 msec predicted LQT2	● QTc >460 msec at 7min of recovery predicted LQT1 or LQT2 vs controls with 96% sensitivity, 86% specificity, 91% PPV.
● Laksman ZW JCE 2013 (369) ● 23691991	**Study type:** Single center retrospective **Size:** 123	**Inclusion criteria:** LQT1 patients undergoing exercise testing; 28% with C-loop mutations **Exclusion criteria:** N/A	**1° endpoint:** LQT1 patients undergoing exercise: assess QTc and response to BB **Results:** no difference in QTc response based on mutation location in LQT1; however, BB did not reduce QTc in c-loop mutation patients	● LQT1 patients with c-loop mutations did not increase QTc with exercise ● BB reduced supine, standing and peak exercise QTc
● Sy RW Heart Rhythm 2011 (370) ● 21315846	**Study type:** single center retrospective 33% presented <21 y **Size:** 27	**Inclusion criteria:** 27 patients with CPVT Median age 35 y 65% female CA 33%, syncope 56%, asymptomatic 11% ICD's in 15 patients with CA or recurrent syncope on b-blockers; **Exclusion criteria:** N/A	**1° endpoint:** CPVT outcomes: recurrent syncope, death or appropr shocks **Results:** followup 6.2±5.7y 63% exercise induced, 83% adrenalin induced; polymorphic VT more common than bidirectional. SVT in 26%, (AF in 3, focal LA tach in 1) caused ICD shocks	● SVT occurred frequently (AF) and caused ICD shocks ● Patients presenting <21 y appeared to have increased risk death during followup ● Two deaths despite medications and ICD therapies

			2 deaths, both in patients with ICD's: one VF triggered by inappropriate shocks; one incessant VT not-responding to ICD 4 appropr shocks; 19% inappropriate shocks 5 y risk ACE on b-blockers 4.9% all CPVT, 5.8% for RYR2 carriers	
● Spazzolini C JACC 2009 (371) ● 19695463	**Study type:** Retrospective International LQTS Registry **Size:** 212	**Inclusion criteria:** LQTS patients with ECG during first year of life **Exclusion criteria:** N/A	**1° endpoint:** Outcome of LQTS patients with ACA during infancy **Results:** 70 patients events <1y: 20 SCD, 16 ACA, 34 syncope. Risk of ACE: HR <100, QTc ≥500 msec ACA in first year: HR: 23.4 for ACA/SCD in first 10y. BB reduced risk in patients with syncope but not ACA/SCD	• ACA in first year of life are at very high risk of subsequent ACA/SCD during next 10 y of life • BB not effective in preventing SCD/ACA in patients with prior ACA
● Zhang C, et al. JCE 2015 (372) ● 26149510	**Study type:** LQT registry retrospective **Size:** 548	**Inclusion criteria:** LQTS patients 1979-2003, with followup to 2015, treated with Attention deficit/hyperactivity disorder (ADHD) medications **Exclusion criteria:** other LQT; patients with ICD's	**1° endpoint:** Identify major ACE (syncope, ACA, SCD) in patients with LQTS treatment with ADHD meds; mean followup 7.9y **Results:** 62% cumulative probablility of ACE in ADHD group, vs 28% in non-ADHD group. Time dependent use increased risk, HR: 3.07, p=0.03; increased riks in males, HR: 6.8	● ADHD meds-stimulant or non-stimulants-associated with increased risk majory ACE, particularly in mlaes
● Choy et al. 1997 (373) ● 9337183	**Study type:** Double-blind comparison of potassium infusion after quinidine and placebo sequentially in 12 healthy subjects.	**Inclusion criteria:** healthy subjects (12) and CHF (mean EF 17%) with age-matched controls without CHF **Exclusion criteria:** N/A	**1° endpoint:** Effect on QTUc from KCl after quinidine or placebo. **Results:** KCl was IV, 0.5 mEq/kg (to maximum of 40 meEq) over 60-70 min resulted in normalization of quinidine-induced and CHF-related QTU prolongation	• "Potentially arrhythmogenic QT abnormalities during quinidine treatment and in CHF can be nearly normalized by modest elevation of serum potassium"

	Also, study on QTU in patients with CHF and age-matched controls who receive IV KCl **Size:** 12 healthy, 8 CHF plus 8 age-matched controls			
● Kannankeril P Pharmacol Rev 2010 (374) ● 21079043	**Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** N/A Lists drugs associated with torsades de pointes Genetic background-polymorphisms- may contribute to risk	● Associated factors for drug induced LQTS; bradycardia, hypokalemia; hypomagnesemia by modulating L-type calcium channel function ● Drugs prolonging QT: block rapid component of delayed rectifier potassium current, IKr

Data Supplement 41. Nonrandomized Trials Related to Catecholaminergic Polymorphic Ventricular Tachycardia – (Section 7.9.1.2.)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Hayashi M Circ 2009 (347) ● 19398665	**Study type:** single center retrospective **Size:** 101	**Inclusion criteria:** CPVT 50 probands, 51 family members, age at dx 15±10 y. Symptoms 60% (61 patients), all probands, 22% family members 93% symptomatic <21 y old	**1° endpoint:** ACE in CPVT patients: syncope, ACA, approp ICD shocks, SCD **Results:** followup 7.9 y 8 y total event rate 32% total, 27% with b-bl, 58% without b-bl. 8 y event ACA/SCD 13% (8 patients)	● Higher risk for lack of BB, Hx ACA ● Prior syncope not associated with increased risk

		77% detection of mutations: RYR2 CASQ2 **Exclusion criteria:** N/A	Increased risk: Absence BB HR: 5.54; 95% CI: 1.17–16.15, p=0.003), Hx ACA HR: 13.01; 95% CI: 2.48–68.21, p=0.002); younger age at dx (HR: 0.54/decade; 95% CI: 0.33–0.89, p=0.02) 32% with events on b-blockers did not take meds on day of event. Nadolol: ACE 19%	
● Roston TM Circ Arrh EP 2015 (375) ● 25713214	**Study type:** multicenter retrospective cohort **Size:** 226	**Inclusion criteria:** age <19 y dx with CPVT Symptomatic 78%; 211 treatment with meds: B-blockers: 91% AICD: 54% Flecainide 24%, calcium channel blockers LCSD 8% **Exclusion criteria:** N/A	**1° endpoint:** ACE during followup in CPVT Treatment failure: syncope, CA **Results:** Median followup 3.5y (1.4–5.3 y) Deaths 3% (6 patients): 2 patients receiving b-blocker; one previously asymptomatic B-blockers: 25% recurrent events; 2% deaths Flecainide: 38% persistent VA, 16% failure (non-complaince, suboptimal dose); LCSD: 18 patients: 16% complications; 67% asymptomatic after rx; 11% recurrent VT, 5% CA (1 pt) ICD: electrical storm 18%; 46% approp shocks, 22% inappropriate shocks; complications 23%	● CPVT 25% recurrent events on BB—compliant, non-compliant, inadequate dosing ● High complications with ICDs
● Chattha IS Heart Rhythm 2010 (367) ● 20226272	**Study type:** Retrospective single center **Size:** 75	**Inclusion criteria:** Exercise testing done on 3 groups: LQT1, LQT2, and controls **Exclusion criteria:** N/A	**1° endpoint:** Genotypic specific changes in QTc with exercise **Results:** Changes in QTc: LQT1: longer corrected QTc at peak and early recovery LQT2: QTc increased during recovery Controls: normal QTc during recovery	● End of recovery QTc >445 msec, usually at 4 min of recovery, distinguished 92% of LQTS from controls ● Start of recovery QTc >460 msec correctly identified 80% of LQT1 and 92% of LQT2
● Wilde AA NEJM 2008(376) ● 18463378	**Study type:** Single center observational **Size:** 3	**Inclusion criteria:** CPVT patients, treatment BB, multiple ICD shocks: LCSD performed RYR2 mutations	**1° endpoint:** CPVT patients and LCSD: ACE after ICD implantation **Results:** no symptoms after LCSD	● LCSD does not preclude ICD implantation ● LCSD Reduced symptoms and shocks

		Exclusion criteria: N/A		● LCSD recommended in CPVT patients with symptoms on b-bl therapy
● Li J ATS 2008 (377) ● 19022016	**Study type:** Single center retrospective **Size:** 11	**Inclusion criteria:** 11 patients LCSD for LQT 2002-2007, BB not tolerated or refractory; followup time 37±26 mos. **Exclusion criteria:** N/A	**1° endpoint:** LQTS treatment with LCSD: outcomes **Results:** 7/11 no symptoms; 2 recurrent syncope; 1 SCD	● LCSD reduced syncopal episodes by 82%; ● Mortality: 9.1%
● Collura CA Heart Rhythm 2009 (365) ● 19467503	**Study type:** single center retrospective **Size:** 20	**Inclusion criteria:** LCSD 2005-2008, video-assisted. Mean age 9.1±9.7 y, (2mo–42y) LQTS 12 geno +, 4 geno – LQT; CPVT 2 **Exclusion criteria:** N/A	**1° endpoint:** LCSD for LQTS and CPVT: ACE followup mean 17 mos **Results:** 2° prev: ICD shocks eliminated 72%; 18% ineffective 2° prev 11, mean QTc 549 msec; 1° 9, mean QTc 480 msec.	● LCSD reduced shocks in 72% during short term followup ● 18% ineffective
● Schneider HE Clin Res Cardiol 2013 (364) ● 22821214	**Study type:** Retrospective single center **Size:** 10	**Inclusion criteria:** LQT 5, CPVT 5, with recurrent syncope, VT, ICD shocks or ACA on BB. Mean age 14 y (3.9–42 y). 2 ICD pre-surg; 6 ICD at LSCD. **Exclusion criteria:** N/A	**1° endpoint:** LCSD for LQT, CPVT: ACE LOS 3–9 d; followup median 2.3y (0.6–3.9 y) **Results:** Decrease in arrhythmia burden, ACE No ICD discharges for VT ACA: 10% Horner syndrome 70%, 20% pleural effusion	● Reduction in ICD discharges ● 10% ACA ● Minor comps frequent
● Hofferberth SC JTCS 2014 (366) ● 24268954	**Study type:** single center retrospective **Size:** 24	**Inclusion criteria:** LCSD 2000-2011. LQTS 13 (median age 8 y), CPVT 9 (age 17 y), VF 2 (age 23 y). **Exclusion criteria:** N/A	**1° endpoint:** ACE after LCSD: LQTS, CPVT, VF Median followup 28mo, (4–131 mo) **Results:** 73% marked reduction in arrhythmia burden; 55% arrhythmia free. 27% persistent symptoms	● LCSD recommended in patients with recurrent symptoms refractory to meds ● 27% recurrent symptoms, non-responders
● Van der Werf C JACC 2011 (378) ● 21616285	**Study type:** multicenter retrospective **Size:** 33	**Inclusion criteria:** Flecainide treatment for genotype positive CPVT patients, 8 European centers prior to 12/2009;	**1° endpoint:** reduction of VA in CPVT with flecainide during exercise testing. Median followup 20mo	● Flecainide suppresses VA in CPVT, up to 76%

		Exclusion criteria: N/A	**Results:** Median age 25 y (7–68y); 73% females 29/33 underwent exercise testing Median dose flecainide in responders 150 mg (100–300mg). 76% partial or complete suppression VA with exercise (p<0.001); no worsening of VA Appropr ICD shock in 1 pt, low serum flec level	
● Watanabe H Heart Rhythm 2013 (379) ● 23286974	**Study type:** Single center retrospective **Size:** 12	**Inclusion criteria:** Genotype negative CPVT with VA, syncope or ACA **Exclusion criteria:** N/A	**1° endpoint:** Flecainide efficacy for suppressing VA in CPVT during exercise testing **Results:** Mean followup 48 mo Reduced arrhythmias 8/12 patients, prevented VA 7/12 2/12 ACA/SCD, non-compliance	● Flecainide suppressed VA on exercise testing in 75% of patients
● Priori S circ 2002(342) ● 12093772	**Study type:** multicenter retrospective **Size:** 148	**Inclusion criteria:** CPVT probands (30) underwent genotyping; and 118 family members screened **Exclusion criteria:** N/A	**1° endpoint:** CPVT genotype RyR2 vs outcome **Results:** RyR2 identified in 47% of probands, and 9 family members, 4 clinically silent 71% of gene positive were de novo; 29% familial: of familial, 75% asymptomatic, 55% VA on exercise test; 44% no syx or VA on exercise testing RyR2: events at younger age, males increased syncope Genotype positivity did not correlate with VA, SCD, beta-bl rx	● Genotype positive RyR2 did not correlate with VA, SCD, or response to BB

Data Supplement 42. Nonrandomized Trials Related to Brugada Syndrome – (Secction7.9.1.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Gehi AK, et al. JCE 2006 (333) ● 16836701	**Study type:** Meta-analysis: retrieved 30 prospective studies on Brugada ECG **Size:** 1545	**Inclusion:** Publications 1/1990-3/2005 on prognosis of patients with a Brugada ECG: Prospective cohort studies, >10 subjects, primary data on syncope, SCD, ICD shocks; followup >6 mo and >90% followup **Exclusions:** non-English; presence of cardiac disease	**1° endpoint:** Identify risk predictors of adverse natural history in patients with Brugada ECG **Results:** Risk increased with prior hx syncope or ACA, spontaneous type 1 Br ECG, and male gender **NOT sig risk factors:** Fam hx SCD SCN5A mutation, or inducibility by PES: (not a risk factor but heterogeneity of studies)	● BrS ACE risk increased with prior syncope or SCD, RR: 3.24 ● Males, RR: 3.47 ● Spontaneous type 1 ECG, RR: 4.65
● Somani R, et al. HR 2014 (380) ● 24657429	**Study type:** Multicenter prospective **Size: 174**	**Inclusion criteria:** CASPER study of probands and first degree relatives of Unexplained cardiac arrest, SCD <60 y, VT or VF undergoing cardioversion or defibrillation, syncope with polymorphic VT **Exclusion criteria:** decreased LVEF, HCM, CHD, overt Brugada ECG pattern, prolonged QTc	**1° endpoint:** Provocation of Brugada ECG with procainamide infusion 15 mg/kg, maximum 1 gm **Results:** Mean age 47 yrs Procainamide: increased HR, prolongation of QT. Brugada ECG provoked in 12/174 = 6.9% 10/12 pts with ECG changes had SCN5A mutation.	● Procainamide infusion provoked Brugada ECG changes in ~7% of CASPER population.
● Mizusawa Y, et al. HR 2016 (381) ● 27033637	**Study type:** multicenter retrospective	**Inclusion criteria:** Brugada S pts with fever 88 asymptomatic (79%) 26% SCN5A mutation	**1° endpoint:** compare effects of fever and drugs on BrS ECG Subgroup of asymptomatc pts, (N=52), serial ECG's	● 3 aymptomatic patients developed VF/SCA during followup; 1/3 with spontaneous BrS ECG,

	Size: 112	Mean age 46 y 76% males **Exclusion criteria:** N/A	followup **Results:** fever shortened PR, drug challenge prolonged PR and QRS Drug challenge in 36 pts: ajmaline 24, pilsicainide 7, flecainide 5	● Paper is hard to interpret
● **FINGER** ● Probst V Circ 2010 (343) ● 20100972	**Study type:** Multi-center registry, 11 centers in Europe **Size:** 1029	**Inclusion criteria:** Brugada Syndrome ECG spont (45%) or with drug challenge. Median 45 y (35-55). Hx ACA 6%, syncope 30%, asymptomatic 64% (654 patients). SCN5A positive 22%. **Exclusion criteria:** N/A	**1° endpoint:** ACE outcomes in BrS **Results:** PES performed in 62%: 41% positive, higher in symptomatic patients 46% vs 37%, p=0.02. PES performed in 369 asymptomatic patients: 37% positive (137/369); 85% (117/137) inducible asyx patients had ICD implanted ICD's implanted: 433/1029 patients (42%): of 433: 54 ACA (12.5%), 208 syncope (48%), 171 asymptomatic (39%). 118/171 asymptomatic patients with ICD (69%) implanted due to positive EPS. ACE 51: approp ICD shocks 44, SCD 7. Mean ACE rate 1.6%/y: 7.7% in patients w Hx ACA;1.9% w prior syncope; 0.5% in asymp patients Predictors: symptoms (p<0.001): ACA (HR: 11; 95% CI: 4.8–24.3, p<0.001), syncope (HR: 3.4; 95% CI 1.6–7.4, p=0.002), ICD implantation (HR: 3.9; 95% CI: 1.4–10.6, p=0.007). spont type 1 ECG (HR: 1.8;95% CI: 1.03–3.33, p=0.04); NOT predictive: gender, family Hx SCD, +PES (p=0.48), presence SCN5A mutation	● Low event rate in asymptomatic patients 0.5%/y. ● Inducibility w PES or family Hx SCD or SCN5A mutation not predictors of ACE ● Predictors of ACE: symptoms, ACA, syncope, presence of ICD, spont type 1 ECG. ● Among asymptomatic patients: 37% positive PES; of these 85% had ICD implanted. ● ICD implantation in asymptomatic patients was significant in multivariable analysis as predictor of ACE: HR:10.1; 95% CI: 1.7–58.7, p=0.01). ● No independent predictive value of PES (p=0.09), males (p=0.42, spont type 1 ECG (p=0.38) age (p=0.97)
● Hiraoka M JE 2013 (349) ● 23702150	**Study type:** Prospective single center	**Inclusion criteria:** Brugada S patients ages 18–35 y	**1° endpoint:** Brugada S ages 18-35 y at dx, outcomes of VF or SCD Followup 43±27 mos.	● Brugada outcomes in young adults' vs presenting symptoms:

	Size: 69	Mean age 30±6 y No genetic testing **Exclusion criteria:** N/A	**Results:** Based on presenting symptoms: VF 42%, syncope 12%, asymptomatic 2.5% Not predictive: gender, family Hx SCD, abnl SAECG, spontaneous vs drug-induced ECG, inducible VT/VF All ages 460 patients symptoms at presentation vs outcomes: VF 8.4%/y, Syncope 1.7%/y, asymptomatic 0.3%/y	● Events: VF 11.2%/y, syncope 3.3%/y, asymptomatic 0.7%/y
● **PRELUDE** ● Priori SG et al. JACC 2012 (382) ● 22192666	**Study type:** Prospective registry **Size:** 308	**Inclusion criteria:** Age >18 y, BrS type 1 ECG spont (56%, 171/308) or drug-induced, without prior ACA; 21% with prior syncope (65 patients: 16/65 {25%} >1 syncope). SCN5A positive 20% of tested patients. (f-QRS = 2 or more spikes within QRS leads V1-V3: present 8.1%) **Exclusion criteria:** N/A	**1° endpoint:** Predictive accuracy of PES for sustained VT/VF or approp ICD shock in Brugada S **Results:** PES performed at enrollment; followup every 6 mo. Mean age 45±12 y. Cardiac arrest 4.5% (14/308), 13/14 resuscitated with ICD, EMS 1. PES positive in 41% (126/308); of these: single stimulation 5.5%, double 44.5%, triples 50%. ICD's implanted in 137 patients (78% of inducible patients {98/126} and 21% of non-inducible patients {39/182}. Annual event rate 1.5%: Multivariable predictors: spont type 1 ECG and Hx of syncope (HR: 4.20; 95% CI: 1.38–12.79, p=0.012), Ventricular ERP < 200 msec (HR: 3.91; 95% CI: 1.03–12.79, p=0.045), QRS fractionation (HR: 4.94' 95% CI: 1.54–15.8, p=0.007).	● PES did not predict high risk ● Predictors: spontaneous type BrS ecg AND symptoms; f-QRS, VERP <200 msec VERP <200 msec was predictive: this data would only be obtained at EPS. ● NOTE that + PES used in decision to implant ICD's: 13/137 patients (9.5%) with ICD's were resuscitated with ICD. Note 1/14 patients with VF had only spont type 1 ECG and no prior syncope, neg family hx, neg EPS, VERP >200 msec but + SCN5A mutation and received ICD after EPS. Only 1 pt without ICD had ACA: pt had spont type 1 ECG, VRP < 200 msec, and fQRS.

			Positive PES not predictive (HR: 1.03; 95% CI: 0.34–3.16, p = 0.96)	
● Casado-Arroyo R JACC 2016 (383) ● 27491905	**Study type:** Single center retrospective **Size:** 447	**Inclusion criteria:** Compare BrS early period ≤2002 vs. 2003-2014 Early: 165 Latter: 282 ICD's: 48% early, 44% latter **Exclusion criteria:** N/A	**1° endpoint:** Long term trends Brugada S EPS **Results:** Early group more severe phenotype ACA 12% early, 4.6% latter, p =.005 PES positive 34% early, 19% latter, p<0.001 Spontaneous type 1 ECG: early 50%, latter 26%, p=0.0002 Recurrent VA: early 19%, latter 5%, p=0.007	● Brugada s: changes over time ● Decrease in ACA over time as presentation ● PES predictive in early group but not latter
● Belhassen B et al, CAE 2015 (384) ● 26354972	**Study type:** retrospective single center **Size:** 96	**Inclusion criteria:** Brugada S patients undergoing PES and treated with Class IA drugs Mean age 39±16 y 88% males **Exclusion criteria:** N/A	**1° endpoint:** Brugada S outcomes treated with IA drugs Mean followup 113±71 mo **Results:** Prior ACA 10, syncope 27, 59 asymptomatic PES: VF induced in 69% (100% of prior ACA, 74% of syncope, 61% of asymptomatic), PES RVA and RVOT in most, ≤3 extrastimuli. PES positive in 77% males, 9% females; in 88% with spont ECG vs 59% without spont ECG. Tested (60 patients) w quinidine (54), disopyramide (2), both (4). Quinidine prevented re-induction of VF in 90%; disopyramide 50% 30 Patients with neg PES were not treated: all remained asymptomatic. ICD implanted in 20 patients after PES (30% of inducible VF patients): complications 55% of patients.	● Brugada S: Class IA meds: ● No deaths on quinidine; 40% of ACA patients remained arrhythmia free off AAD (3 treatment with quinidine for many years then discontinued rx ● 38% side effects

			4 died of non-cardiac causes. Recurrent syncope: vasovagal 10, non-arrhythmic 2. 2/96 had recurrent arrhythmia: both with prior ACA**;** both discontinued quinidine and had VF storms.	
● Nademanee K et al. Circ 2011(385) ● 21403098	**Study type:** Retrospective single center **Size:** 9	**Inclusion criteria: 9** Brugada patients, symptomatic with recurrent VF median 4 episodes/mon; median age 38 y; all with ICD's **Exclusion criteria:** N/A	**1° endpoint:** mapping and ablation of RVOT in Brugada **Results:** Anterior aspect of RVOT epicardium with late fractionate egms Ablation successful in 78% (7/9) VF not inducible, normalization of Brugada ECG in 89% Followup 20±6 mo, no recurrent VT/VF in all patients off meds (except one on amiodarone)	● BrS shows delayed repolarization over anterior RVOT epicardium. ● Ablation normalizes ECG and reduces VT/VF
● Sunsaneewitaykul B et al. JCE 2012 (386) ● 22988965	**Study type:** Retrospective single center **Size:** 10	**Inclusion criteria:** BrS patient's EP mapping and ablation. between 8/07-12/08 VF storm (4) and no VF storm (6) **Exclusion criteria:** N/A	**1° endpoint:** Ablation of zone of late activation in RVOT **Results:** Patients with VF storm: ablation modified Brugada ECG in 75% (3/4) and suppressed VF in all 4 during followup of 12–30 mo. RBBB in ¼ patients	● Ablation of late activation zone in RVOT may suppress VF storm and reduce VF recurrence
● Zhang et al. HR 2016 (387) ● 27453126	**Study type:** Two center retrospective **Size:** 11	**Inclusion criteria:** BrS patients, 9 spont, 2 induced **Exclusion criteria:** N/A	**1° endpoint:** Brugada mapping and ablation of RVOT epicardium **Results:** Normalization of spont Brugada ECG pattern in all 73% free of VT/VF at 25±11 mo	● Ablation epicardial RVOT results in normalization of Brugada ECG and reduces VT/VF ● ICD needed despite ablation
● Brugada J et al. Circ A E 2015 (388) ● 26291334	**Study type:** Single center retrospective **Size:** 14	**Inclusion criteria:** BrS, spont ECG, median age 39 y **Exclusion criteria:** N/A	**1° endpoint:** Epicardial mapping and ablation RVOT in Brugada **Results:** Ablation resolved spontaneous Brugada ECG 5 mo, no recurrence	● Ablation may eliminate spontaneous Brugada ECG pattern

● McNamara DA ● Cochrane Database Syst Rev 2015 (389)	**Study type:** Cochrane search for randomized trials of ICD vs medical treatment ion channelopathy **Size:** 86	**nclusion criteria:** **patients** >18 y, ion channelopathies, randomized to ICD vs medical rx, identified 2 studies including Brugada patients **Exclusion criteria:** N/A	**1° endpoint:** All-cause mortality, ACE in BrS and ICD **Results:** 2 studies identified, Brugada Syndrome, same authors. ICD: assoc with decreased risk mortality RR: 0.11; 95% CI: 0.01–0.83) Adverse events higher in ICD: 28% vs 10%, RR: 2.44; 95% CI: 0.92–6.44) Non-fatal ACE higher in ICD: 26% vs 0%, RR: 11.4; 95% CI: 1.57–83.3)	● Decreased mortality in patients randomized to ICD in BrS: 9-fold reduction ● Brugada patients with prior ACA: ICD treatment reduced mortality
● Delise P et al. EHJ 2011 (348) ● 20978016	**Study type:** Multi-center prospective **Size:** 320	**Inclusion criteria:** Type 1 Brugada ECG: spontaneous 54%, drug-induced 46%. Median age 43 y. Males 81% Asymptomatic 66%, syncope 33% No prior ACA **Exclusion criteria:** N/A	**1° endpoint:** predictors in Brugada S of ACE (approp ICD shocks, sudden death) **Results:** Median followup 40 mos (IQR 20–67) 5.3 % MACE (17 patients): VF on ICD (14), sudden death3 MACE occurred in 10.4% of symptomatic and 2.8% of asymptomatic patients (p=0.004) ICD's implanted in 34%(110 patients) PES performed in 245 (76%): positive in 50% of symptomatic and 32% of asymptomatic patients. MACE in 14% of positive PES, 0% of negative, 5.3% of no EPS: positive predictive values 14%, negative pred value 100% VF occurred in 15.5% of patients with inducible VF using doubles, 8.6% of triples Combination of risk factors most significant: spont ECG, family Hx sudden death, syncope, positive EPS: no events occurred in patients without any of above or with only one risk factor.	● Combining ≥2 risk factors was useful risk stratification: Spontaneous type 1 ECG Family Hx sudden death, syncope, positive PES ● MACE occurred only in patients with ≥2 risk factors ● MACE event rates: 3.0%/pt/yr in symptomatic, 0.8%/pt/yr in asymptomatic ● PES can be useful in patients with spontaneous type 1 ECG and no other risk factors; may be helpful to identify low risk patients

			Spontaneous type 1 ECG: if additional risk factors, 30% MACE (p<0.001)	
● Sieira J et al. Circ Arrhyth EP 2015 (390) ● 26215662	**Study type:** Single center retrospective **Size:** 363	**Inclusion criteria:** Asymptomatic patients type 1 BrS ECG, spont (11%) or drug-induced. Mean age 40.9±17 y, 55% males. 321 patients underwent PES. 22% genotype + SCN5A. **Exclusion criteria:** N/A	**1° endpoint:** Event-free survival in Brugada S. Mean followup 73±59 mo. **Results:** PES positive in 10% (32 patients) ICD's implanted 17% (61 patients), 6 approp rx. Event free survival: 99% 1 y, 96% at 5 y, 95.4% at 10 and 15 y. Arrhythmic events: 9, annual incidence 0.5% Multivariate analysis: Positive PES only significant predictor (HR: 9.1, 95% CI: 1.8–46.8, p<0.01)	● Brugada S: Positive PES predictor of adverse events, HR: 9.1. ● Event free survival 95.4% at 10 and 15 y
● Konigstein M et al. Heart Rhythm 2016 (391) ● 27131070	**Study type:** multicenter retrospective **Size:** 74	**Inclusion criteria:** Brugada database non-cardiac drug-induced Brugada patients; each with 5 healthy controls Mean age 39±16 y. 77% males **Exclusion criteria:** N/A	**1° endpoint:** Outcomes of non-cardiac drug-induced BrS **Results:** By definition: "spontaneous type 1" ECG: 49% psychotropic meds (lithium, amitriptyline), 27% anesthetic/analgesic, 24% other; of total, 20% propofol occurred predominantly in adult males, frequently due to drug toxicity, occurs late after onset of treatment Off-drug ECG's: 33% type IIC Brugada ECG	● Non-cardiac drug induced type 1 Brugada ECG: ● 26% VF/pulseless VT ● 13.5% mortality
● Sroubek J et al. Circ 2016 (392) ● 26797467	**Study type:** Systematic review and pooled analysis of prospective observational studies **Size:** 8 studies, 1312 patients	**Inclusion criteria**: BrS patients without ACA who underwent PES Mean age 44.9 ±13.3 yrs; 79% male; 53% spont type 1 ECG Prior Syncope 33%;	**1° endpoint:** CA or appropriate ICD shock in Brugada S. **Results:** PES induced sust VEA (40%).with up to triple extrastimuli in 527 patients (2%, single; double 18%; triples 28% AICD's implanted in 576 patients: 77% of ICD implanted in PES positive patients	● Positive PES associated with increased risk ACE during followup; induction with 1–2 extrastimuli associated with higher risk. ● Specificity of induction as risk predictor decreased with triple VEST

		Exclusion criteria: N/A	65 patients experienced ACE during median followup 38 mo: 5 CA, appropriate ICD shock 60. Positive PES assoc with increased risk ACE: HR: 2.66, 95% CI: 1.44–4.92, p <0.001); greatest risk in those induced with single (HR: 1.99, 95% CI: 0.52–7.68, p=0.32); or double extrastimuli (HR: 2.55, 95% CI: 1.34–4.88, p=0.005), vs. triples (HR: 2.08, 95% CI: 0.98–4.39, p=0.06) Clinical variables useful: annual event rates for no syncope, drug induced type 1 ECG: 0.27% (95% CI: 0.07–0.68); Positive syncope and spont type 1 ECG 3.22%; (95% CI: 2.23–4.5) Highest risk: + syncope, spont type 1 ECG: neg PES HR: 2.55; 95% CI: 1.58–3.89; positive PES HR: 5.6; 95% CI: 2.98–9.58 Annual incidence rates of CA or VT: Asymptomatic, spont type 1 ECG: annual events 1.04 (95% CI: 0.61–1.67): positive PES 1.70 (95% CI: 0.73–3.35); negative PES 0.78 (95% CI: 0.36–1.47) Asymptomatic, drug ind ECG: overall 0.27, neg PES 0.23 (95% CI: 0.05–0.68), pos PES 0.45 (95% CI: 0.01–2.49) Spont type 1 ECG: asymptomatic, with neg PES: annual event incidence 0.78% (95% CI: 0.36–1.47); pos PES 1.70 (95% CI: 0.73–3.35). Prior syncope and neg PES 2.55% (95% CI: 1.58–3.89); Positive PES 5.60 (95% CI: 2.98–9.58) Drug induced ECG: asymptomatic: neg PES 0.23% (95% CI: 0.05–0.68); positive PES 0.45 (95% CI: 0.01–2.49); prior syncope and negative PES 1.29 (95% CI:	● Negative PES did not identify low risk individuals ● Annual event rates varied based on syncope, spontaneous type 1 ECG, and positive PES: ● Asymptomatic patients with spont type ECG and positive PES: annual incidence 1.70 (0.73–3.35) ● Aymptomatic patients with drug ind ECG and + PES: annual incidence 0.45 (0.01–2.49) ● Clinical factors important determinants of risk: syncope; spont type 1 ECG ● Asymptomatic patients with drug induced ECG patterns: “PES may not be warranted” ● Symptomatic patients: increased risk with positive PES, but risk exists with neg PES: higher if spont type 1 ECG: ? value of PES

			0.52–2.67); positive PES 1.96 (95% CI: 0.40–5.73)	
● Sieira J et al. Heart 2016 (393) ● 26740482	**Study type:** Single center retrospective **Size:** 228	**Inclusion criteria:** Women with BrS, spontaneous 8%, or induced **Exclusion criteria:** N/A	**1° endpoint:** Brugada outcomes in women, mean followup 73 mo **Results:** Mean age 41.5± 17.3 y women = 42% of Brugada population Spontaneous type 1 ECG 7.9% vs males 23%, p<0.01 ICD implanted in 28%, event rate 0.7%/y vs 1.9% males	● BrS Females: ● Less severe than males, less spont type 1 ECG ● Event rate 0.7%/y (males 1.9%/y) Higher risk: prior ACA, SND
● Priori S et al. Circ 2002 (394) ● 11901046	**Study type:** Multicenter retrospective **Size:** 200	**Inclusion criteria:** Brugada S with ECG changes, spont (51%) or induced 130 probands **Exclusion criteria:** N/A	**1° endpoint:** Brugada risk stratification for SCD PES performed in 86 **Results:** SCN5A identified in 22% probands, 46% of family members Risk analysis: gender; ECG, family hx, mutation status, symptoms Syncope without ST elevation on baseline ECG: not a risk Syncope AND ST elevation: increased risk SCD, HR: 6.4, p<0.002	● Multivariable risk predictor: spontaneous ST elevation V1-V3 and Hx of syncope ● Syncope without spontaneous ST elevation not a risk factor ● PES not predictive Mutation carriers without phenotype: low risk
● Fauchier L et al. IJC 2013 (395) ● 23642819	**Study type:** meta-analysis **Size:** 1789	**Inclusion criteria:** Brugada S patients undergoing PES ACA 11%, syncope 31%, asymptomatic 57% **Exclusion criteria:** N/A	**1° endpoint:** utility of PES in Brugada S: adverse event = sust VT/VF, appropriate ICD shock, sudden death) **Results:** Inducible VT/VF associated with higher risk arrhythmic event in patients with prior syncope (OR: 3.30, 95% CI: 1.68–6.51, p=0.0006) and in asymptomatic patients (OR: 4.62, 95% CI: 2.14–9.97, p<0.0001)	• Inducibility of VT in Brugada S patients with syncope or asymptomatic may identify an increased risk of subsequent events
● Rodriguez-Manero M et al. Heart Rhythm 2016 (396) ● 26538325	**Study type:** retrospective multi center	**Inclusion criteria:** BrS patients with implantable ICD 1993-2014	**1° endpoint:** ICD usage and comps in Brugada S. followup mean 69 ± 54 mo **Results:** 13.7% at least one approp rx	BrS: ● ICD approp use in ~14% ● Monomorphic VT in 4.2%

	Size: 834	mean age 45±13.9 y 24% women **Exclusion criteria:** N/A	Monomorphic VT recorded in 4.2% (35 patients), sensitive to anti-tach pacing in 43% Monomorphic VT from RVOT 6, LVOT 2, BBR 2 successfully ablated in 80%	● Successful ablation in 80% of 10 patients with outflow tract VT
● Sacher F et al. Circ 2013 (397) ● 23995538	**Study type:** Retrospective multi-center **Size:** 378	**Inclusion criteria:** BrS patients with ICD Mean age 46±13 y ACA 31, syncope 181, asymptomatic 166 **Exclusion criteria:** N/A	**1° endpoint:** ICD outcomes in BrS, followup mean 77±42 mo **Results:** appropriate shocks 12%, Shock rates highest for ACA patients (48%), syncope 19%, 12% asymptomatic Inaapropriate shocks 24%; due to lead failure, SVT, T wave oversensing or sinus tach. Lead failure 29%	● Approp ICD shocks more prevalent in symptomatic BrS; Asymptomatic patients had approp shocks 1%/y ● Optimal programming may reduce inapprop shocks ● Lead failure a significant problem
● Rosso R et al. Isr Med Assoc J 2008 (398) ● 18669142	**Study type:** retrospective multi-center, 12 centers, 1994-2007 **Size:** 59	**Inclusion criteria:** BrS patients with ICD Mean age 44.1 y **Exclusion criteria:** N/A	**1° endpoint:** Followup efficacy and comps of ICD in Brugada; followup 45±35 mo **Results:** Symptoms 71%: ACA 19%, syncope 53%, inducible VF in asymptomatic patients 24%, family Hx SCD 0.5%. Appropriate shocks 8.4%, all with prior ACA Comps 32% Inappropriate shocks 27% Psych problems 13.5%, mainly related to inappropriate shocks	● Appropriate shocks occurred only in symptomatic patients with prior ACA ● VF inducibility did not predict approp shocks ● High complication rate
● Conte G et al. JACC 2015 (399) ● 25744005	**Study type:** Prospective single center **Size:** 176	**Inclusion criteria:** BrS patients with ICD's **Exclusion criteria:** N/A	**1° endpoint:** Long term followup ICD in BrS, mean followup 84±57 mo **Results:** Spontaneous VA in 17%. Appropriate shocks 15.9% Inappropriate shocks 18.7% Electrical storm 2.3% SCN5A mutation (22%) did not correlate with approp shocks	● ACA and VT inducibility on EPS were multi-variate predictors of appropriate shocks ● Appropriate shocks occurred in 13% of asymptomatic patients

● Miyazaki S et al. AJC 2013 (400) ● 23433764	**Study type:** single center retrospective **Size:** 41	**Inclusion criteria:** Brugada S patients with ICD Mean age 48±12 y 93% males **Exclusion criteria:** N/A	**1° endpoint:** Brugada S ICD outcomes Median followup 76 mo **Results:** Complications 37%: device related 20%, inappropriate shocks in 24% Appropriate shocks: 12%	● Brugada S + ICD's: Complications 37%
● Takaqi M et al. Heart Rhythm 2014(401) ● 24981871	**Study type:** retrospective single center **Size:** 213	**Inclusion criteria:** Brugada S patients undergoing ICD implantation, Mean age 53±14 y Males 93% **Exclusion criteria:** N/A	**1° endpoint:** ACE documented VT or SCD in Brugada S with ICD Mean followup 60±31 mo **Results:** indications classified as IIa (66): spontaneous type 1 ECG and Hx of cardiac syncope, or IIb (147): spont or drug induced type ECG and inducible VF by PES. Event rates: IIa 12%, 2.2%/y; IIb 3%, 0.5%/y p=0.01	● ICD implantation in Brugada: ● Higher events in IIa vs IIb ● Spontaneous type 1 ECG AND syncope useful for identifying intermediate risk

Data Supplement 43. Nonrandomized Trials Related to Early Repolarization "J-wave" Syndrome – (Secction 7.9.1.4)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Rosso R et al. JACC 2008 (398) ● 18926326	**Study type:** Retrospective single center **Size:** 45	**Inclusion criteria:** Idiopathic VF patients compared with 123 age/gender matched controls. Mean age 38±15 y, 71% male 2/45 dx with Brugada **Exclusion criteria:** N/A	**1° endpoint:** Assess frequency of ER on ECG vs controls **Results:** ER more common among VF patients, 42% vs 13%, p=0.001 J point elev in inferior leads: 27% vs 8%, p=0.006 J point elev in leads I-aVL 13% vs 1%, p=0.009 J point elev in V4-V6 equal among groups, 6.7 vs 7.3%	● J point elevation occurs more frequently in idiopathic VF patients than healthy controls ● Athletes intermediate frequency of J point elevation between normal adults and idiopathic VF patients ● ST segment elevation or QRS slurring did not add diagnostic values

			Males more often had J point elev vs females; young athletes more frequent than controls but less than VF patients	
● Haissaguerre M, et al. JACC 2009 (402) ● 19215837	**Study type:** multicenter cohort **Size:** 122	**Inclusion criteria:** Idiopathic VF survivors with ER assessed for recurrent VF All pts had AICDs implanted Mean age of diagnosis 39 y **Exclusion criteria:**	**1° endpoint:** Recurrent VF >3 episodes **Results:** overall 27% with multiple (>3 episodes) of recurrent VF Inducible VF 28% in entire cohort Pts with >3 episodes recurrent VF: inducible VF 48%, p<0.01, prior syncope 58%, p<0.001 compared with pts with <3 episodes of recurrent VF. Anti-arrhythmic meds not highly effective in preventing recurrent VF 1 death due to refractory VF	● Recurrent VF high: 40% with mult episodes in 27% ● Meds not effective other than quinidine or hydroquinindine (9 pts)
● Tikkanen JT ET AL. NEJM 2009 (403) ● 19917913	**Study type:** retrospective community based screen of ECG's in Finnish population 1962-1972 **Size:** 10864	**Inclusion criteria:** ECG's obtained in general population reviewed, **Exclusion criteria:** N/A	**1° endpoint:** Death from cardiac causes; 2°: death from any cause and from arrhythmia before end of 2007; mean followup 30±11 y. **Results:** Prevalence J point elev of at least 0.1 mV: 5.8%: inferior leads 3.5 %, 70% male; Lateral leads 2.4%, 58% male J point elev at least 0.2 mV inferior leads 0.3%, lateral 0.3% Cardiac death: ER patients (RR: 1.28, 95% CI: 1.04–1.59, p=0.03); arrhythmia death J point elev 0.2 mV: cardiac death RR: 2.98, 95% CI: 1.85–4.92, p=0.01; arrhythmic death RR: 2.92, 95% CI: 1.45–5.89, p=0.01 QTc (RR: 1.2, 95% CI: 1.02–1.42, p=0.03) and LVH (RR: 1.16, 95% CI: 1.05–1.27, p=0.004) weaker predictors cardiac death	● ER pattern in inferior leads of ECG is associated with an increased risk of death from cardiac causes in middle-aged adults ● ER transmural heterogeneity in vent repolarization, increases risk during cardiac ischemia

● Sinner MF et al. Heart Rhythm 2012 (404) ● 22683750	**Study type:** 3 community based ECG cohorts **Size:** 7482	**Inclusion criteria:** 452 patients with ER underwent genome wide association studies **Exclusion criteria:** N/A	**1° endpoint:** Combined meta-analysis failed to reach genome wide significance **Results:** ER: 70% male	● Unable to reliably identify genetic variants predisposing to ER
● Adhikarla C et al. AJC 2011 (405) ● 21907947	**Study type: retrospective** Screening ECG's on veterans for ER 1987-99 **Size:** 29281	**Inclusion criteria:** ER > 0.1 mV with ST segment elevation, J wave as upward defection, slurs as delay on R wave downstroke: first 250 patients selected. Mean 42±10 y **Exclusion criteria:** other ECG abnormalities	**1° endpoint:** assess changes in ER on ECG during 10 y followup **Results:** 122/244 patients had second ECG ER persisted in 38%**;** most no longer filled criteria.	● ER pattern lost in over half of young male cohort over 10 y period, not related to death
● Siebermair J, et al. Europace 2016 (406) ● 26759124	**Study type:** Single center retrospective **Size:** 35	**Inclusion criteria:** Idiopathic VF survivors assessed for ER and ICD interventions during follow-up median 8.8 y **Exclusion criteria:** N/A	**1° endpoint:** Appropriate VF shocks on ICD in idiopathic VF pts; compare ER to non-ER **Results:** overall 43% recurrent VF after median 6.6 yrs. VF more frequent in ER patients: (HR: 3.9, 95% CI: 1.4–11.0, p=0.01) 40% inappropriate shocks: 66% due to AF	● Recurrent VF high: 43% ● Recurrent VF higher in ER patients ● High incidence AF in VF survivors
●Cheng YJ, et al. JAHA 2016 ● 27671315	**Study type:** meta-analysis **Size:** 16 studies including 334,524 patients identified	**Inclusion criteria:** studies assessing link between ER and risk of SCA, cardiac death, and eath from any cause **Exclusion criteria:** N/A	**1° endpoint:** risk of SCA, cardiac death, death any cause associated with early repolarization pattern on ECG **Results:** Increased risk of SCA (RR:2.18, 95% CI: 1.29–3.68), and cardiac death (RR: 1.48, 95% CI: 1.06–2.07) in patients with early repolarization. Increased risk predominantly in Asians and whites but not African Americans. J-point elevation in inferior leads, notching configuration, and harizaontal	● Early repolarization associated with absolute risk increase of 139.6 additional SCAs/100,000 pt y and responsible for 7.3% of SCA in general poulation

			or descending ST segement connote higher risk.	
● Tikkanen JT et al. Circ AE 2012 (407) ● 22730409	**Study type:** Retrospective population based **Size:** 432	**Inclusion criteria:** Prevalence of ER in Baseline ECG's of 432 consecutive cases of SCD due to ischemia compared with 532 survivors of acute ischemic event **Exclusion criteria:** N/A	**1° endpoint:** Prevalence of ER in SCD vs survivors of acute ischemia **Results:** Prevalence ER ≥0.1 mV in at least 2 inf or lateral leads: 14.4% cases vs 7.9% controls. ER with horizontal or descending ST segment assoc with SCD 10.2% vs 5.3%, p=0.004; ER with ascending ST NS. SCD patients younger, more often male, smokers, lower BMI, elevated HR, prolonged QRS complex, lower prevalence of Hx of CVD	● Higher prevalence of ER in SCD ischemic patients than in survivors of acute coronary event ● ER increases vulnerability to fatal arrhythmia during acute myocardial ischemia
● Junttila MJ et al. Heart Rhythm 2014 (408) ● 24858812	**Study type:** Community based ECG's Finnish population, mean 44±8 yrs **Size:** 10,846	**Inclusion criteria:** arrhythmic outcomes and cardiac deaths in patients with ER on community screening **Exclusion criteria:** N/A	**1° endpoint:** Sustained VT or VF, arrhythmic death, non-arrhythmic cardia death, AF, CHF, CAD; mean followup 30±11 y **Results:** Inferior ER 3.5% prevalence: predicted VF-VT events (N=108), HR: 2.2 (1.1–4.5, p=0.03), not not nonarrhythmic cardiac death, CHF, or CAD Inferior ER predicted arrhythmic death in cases without other QRS abnormalities (HR: 1.68, 95% CI: 1.1–2.58, p=0.02) but not in those with coexisting abnormalities in QRS morphology (HR: 1.3, 95% CI: 0.86–1.96, p=0.22)	● Inferior ER without other QRS morphology changes predicted occurrence of VT-VF but not non-arrhythmic cardiac events ● Suggests ER sign of increased vulnerability to ventricular tachyarrhythmias

Data Supplement 44. Nonrandomized Trials Related to Short-QT Syndrome – (Secction 7.9.1.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Gaita F et al. JACC 2004 (409) ● 15093889	**Study type:** single center retrospective **Size:** 6	**Inclusion criteria:** Symptomatic patients with QTc <380 undergoing drug testing. One prior ACA age 6 y. PES 5 adult patients: 4/5 inducible VF. 5 adults received ICD's. **Exclusion criteria:** N/A	**1° endpoint:** Prolongation of QTc with medications **Results:** Flecainid, sotalol, ibutilide, hydroquinidine tested. Only hydroquinidine prlonged QTc from 263±12 to 363±25, prolonged VERP to ≥200 msec, and no VF induced.	● Hydroquinidine prolonged QTc and resulted in non-inducible VF ● use dependent block fast inward Na, blocks rapid IKr and IKs, IKATP, Ito.
● Giustetto C et al. EHJ 2006 (51) ● 16926178	**Study type:** Retrospective single center **Size:** 29	**Inclusion criteria:** Short QTc ≤340 msec and personal or family Hx of CA. 73% males. **Exclusion criteria:** N/A	**1° endpoint:** outcomes with AICD or hydroquinidine **Results:** Median age dx 30 yrs (4-80); 62% symptomatic: syncope 24%, AF 31%. 34% ACA (10 patients); 2/10 had CA in infancy. In 28% ACA was initial symptom. AICD implanted in 14; 10 hydroquinidine. Median followup 23 mo (9-49), one pt with appropriate ICD shock. No pt on hydroquinidine had SCD or syncope. PES 18/29: VERP 140-180 msec. VF induced in 61% (11/18); 3/6 with documented VF had inducible VF: sensitivity 50%. AERP CL 600: 120-180 ms, mean 157.	● Short QTS may be a cause of SCD in infancy ● Hydroquinidine may be proposed in children or patients not suitable for AICD PES sensitivity 50%
● Gollob MH et al. JACC 2011 (410) ● 21310316	**Study type:** Medline database search **Size:** 61	**Inclusion criteria:** review details of reported cases of SQTS **Exclusion criteria:** non-English journals	**1° endpoint:** review reported cases of Short QTS: 61 cases worldwide **Results:** Increased in males: 75% mean QTc 397 msec, 248–381 msec in symptomatic cases.	• Gollob criteria for SQTS, ≥4 points very likely • QTc duration <370, <350, <330 J point-Tpeak <120 msec Clinical hx: ACA, SCD, AF, unexplained syncope;

				Family hx; Genotype results
● Giustetto C et al. JACC 2011 (53) ● 21798421	**Study type:** retrospective multi-center **Size:** 53	**Inclusion criteria:** European Short QT Registry **patients** with QTc ≤360 msec with Hx sudden death, ACA, syncope; patients with QTc ≤340 msec included without symptoms. 75% males. Family Hx SCD/CA (11). Genotype positive 23% of probands: HERG in 4 families (N588K in 2, T6181 in 2; CACNB2b in one family) . **Exclusion criteria:** N/A	**1° endpoint:** syncope, CA or approp ICD shocks SQTS **Results:** Mean Followup 64±27 mo. Median age 26 y (IQR 17–39). 62% symptomatic: 32% with ACA (13 patients) or sudden death(4), syncope 8, AF 6, palps 13. Age at CA 3 mos–62 y. Males: >90% of CA occurred between 14-40 yrs. Prevalence CA males 35%, females 30%. AICD in 24, hydroquinidine in 12. 11/12 with prior CA received ICD: 2 approp ICD shocks. 58% complications of ICD, inapprop shocks due to T wave oversensing 4/14. PES: 28 patients. VERP CL 600-500: mean 166 msec. AERP 166 msec. VF induced in 16/28: 3/28 with prior CA = sensitivity 37%, NPVs 58%. Overall event rate 3.3%/y: 4.9% in patients without AA drugs. Asymptomatic patients: 27. ICD implanted in 9 due to + family Hx or induced VF. Two long term quinidine. One syncope; 2 nonsust VT on ICD.	● SQTS assoc with SCD in all ages ● Symptomatic patients have high risk of recurrent arrhythmic events ● Patients treated with Hydroquinidine did not have arrhythmic events ● Asymptomatic patients: no CA/ICD shocks. ● PES not sensitive
● Villafane J et al. JACC 2013 (411) ● 23375927	**Study type:** Multicenter retrospective **Size:** 25	**Inclusion criteria:** patients <21 y old with short QTc <360 msec. Median age 15 y **Exclusion criteria:** N/A	**1° endpoint:** ACE in short QT; Assess Gollob score Mean followup 6 y. **Results:** Symptoms 56%: ACA 24%, syncope 16% 84% personal or family Hx ACA/SCD 24% genotype + AICD 11: 2 approp shocks; 64% inappropriate shocks	● modified Gollob score >5 associated with likely clinical events ● High rate inappropriate shocks

			10 patients med rx: quinidine Gollob score <5 remained event free (excluding patients for symptoms)	
● Mazzanti A et al. JACC 2014 (412) ● 24291113	**Study type:** Registry **Size:** 73	**Inclusion criteria:** Short QTS: asymptomatic ≤340 msec, or QTc 340–360 msec Plus ACA, family Hx SCD or family Hx SQTS 53% symptomatic at referral **Exclusion criteria:** N/A	**1° endpoint:** SQTS patients followed for median 56 mo **Results:** 84% male Mean age 26±15 y, QTc 329±22 msec. 40% presented with ACA, range 1 mo–41 y. CA during sleep 83%, 17% emotion/exertion Rate CA 4% first yr of life, 1.3%/y between 20-40 y. Probability first occurrence CA by 40 y: 41%. ACA only predictor of recurrence: p<0.0000001	● SQTS highly lethal at young age ● 11% genotype positive ● Prior ACA predicts recurrent CA: recommend ICD for these patients ● Gollob score did not predict risk
● Iribarren C et al. Ann Noninv ECG 2014 (413) ● 24829126	**Study type:** Retrospective **Size:** 1026	**Inclusion criteria:** Screened 6,387,070 ECG's in population of 1.7 million persons for QTc ≤300 msec **Exclusion criteria:** N/A	**1° endpoint:** Prevalence, risk of death associated with Short QT during 8.3 y median followup **Results:** Prevalence 2.7/100,000**,** or 1/141,935 ECG's. Associations: age >65 y, AA race, prior Hx VA, COPD, ST changes QTc ≤300 msec assoc w increased mortality: HR: 2.6 (95% CI: 1.9–3.7)	● QTc ≤300 msec: 2.6 fold increased risk death
● Guerrier K et al. Circ Arrh EP 2015 (414) ● 26386018	**Study type:** Single center retrospective **Size:**	**Inclusion criteria:** Screened 272, 504 ECG's <21 y for QTc≤340 msec **Exclusion criteria:** N/A	**1° endpoint:** Prevalence short QTc ≤340 msec in patients <21 y old, deaths **Results:** Prevalence 0.05%, 76% males Females shorter QTc 312 vs 323 msec, p=0.03 2 deaths: respiratory; dilated cardiomyopathy	● Short QTc ≤340 msec prevalence 0.05% in <21 y old ● Short QT rare, increased prevalence in males

● Bun SS et al. JCE 2012 (415) ● 22493951	**Study type:** case report **Size:** 1	**Inclusion criteria:** 28 y old ACA while asleep, QTc 320 msec, admitted with electrical storm, 8 VF arrests while sedated/hypothermia **Exclusion criteria:** N/A	**1° endpoint:** treatment electrical storm in short QTS **Results:** isoproterenol infusion resulted in sinus rhythm	● Case report efficacy of isoproterenol in treating recurrent VF in short QT
● Dhutia H et al. Br J Sports Med 2016 (416) ● 26400956	**Study type:** single center retrospective **Size:** screening 18,825 patients	**Inclusion criteria:** Healthy people ages 14–35 y undergoing screening with hx, PE, ECG **Exclusion criteria:** N/A	**1° endpoint:** Prevalence and significance of short QTS among healthy young individuals **Results:** QTc ≤320 msec: 0.1%, 26 patients QTc ≤330 msec: 0.2%, 44 patients QTc <380 msec: 7.9%, 1478 patients QTc <390 msec: 15.8%, 2973 patients Followup 5.3±1.2 y, no deaths	● Males, Afro-Caribbean ethnicity had strongest association with short QT ● Short QTc ≤320 msec: excellent medium term prognosis in young patients ● Recommend using QTc ≤320 **msec** to prevent over-diagnosis

Data Supplement 45. RCTs Related to VA in the Structurally Normal Heart – (Section 8)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Ling et al. 2014 (417) ● 24523413	**Aim:** to compare the efficacy of radiofrequency catheter ablation (RFCA) vs.	**Inclusion criteria**: (1) frequent symptomatic VPBs from the RVOT	**Intervention:** RF catheter ablation of RVOT **Comparator:** Antiarrhythmic medications	**1° endpoint:** The 1° end point was recurrence of RVOT VPBs at a rate of	● RF Catheter ablation is more effective than AAD for treatment of frequent premature beats arising from the RVOT.

	AAD for treatment of patients with frequent ventricular premature beats (VPBs) originating from the right ventricular outflow tract (RVOT). **Study type:** Prospective, RCT **Size:** 330 patients	documented by 12-lead ECG to have inferior axis and left bundle-branch block (LBBB) QRS morphology (2) >6000 VPBs per 24h on Holter monitoring. **Exclusion criteria**: (1) the presence of non-RVOT origin for VPBs indicated by an S wave in lead I, R-wave duration index in V1 and V2≥0.5, and R/S wave amplitude index in V1 and V2≥0.311; (2) previous AAD therapy; (3) evidence of any structural heart disease; (4) hyperthyroidism or electrolyte disturbance; (5) drug toxicity; (6) diabetes mellitus; (7) BP>165/100 mm Hg;		≥300 beats per day documented by 24 h Holter monitoring. The 2° variables of interest including the number of VPBs, the burden of VPBs (the number of VPBs/ total QRS complexes×100%), and LVEF at each follow-up time point were collected During the 1y follow-up period, VPB recurrence was significantly lower in patients randomized to RFCA group (32 patients, 19.4%) vs. AAD group (146 patients, 88.6%; p<0.001, log-rank test). In a Poisson generalized estimating equations regression model, RFCA was associated with a greater decrease in the burden of VPBs (incidence rate ratio: 0.105; 95% CI: 0.104–0.105; p<0.001) compared with AAD. In a liner GEE model, the LVEF had a tendency to increase after the treatment in both groups (coefficient, 0.584; 95% CI: 0.467–0.702; p<0.001).	

		(8) significant impairment of renal function; (9) QT interval>450 ms in the absence of bundle-branch block; (10) significant AV conduction disease and left or right bundle-branch block			
● Krittayaphong et al. 2002 (94) ● 12486439	**Study type:** RCT **Aim:** To determine the efficacy of atenolol in the treatment of symptomatic VA from RVOT compared with placebo **Size:** 52	**Inclusion criteria:** VA with LBBB, inferior axis morphology. Symptomatic (VA disturbed their daily activities) **Exclusion criteria** SHD.	**Intervention:** Atenolol 50-100mg/day **Comparator:** Placebo	**1° endpoint:** Atenolol significantly decreased PVC count (p=0.001) and average heart rate (p<0.001) compared to placebo. Both placebo and atenolol decreased symptom frequency.	● BB may be useful for patients with RVOT and symptomatic VA.

Data Supplement 46. Nonrandomized Trials, Observational Studies, and/or Registries Related to Outflow Tract and AV Annular VA – (Section 8.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Liao et al. 2015 (418) ● 26670064	**Study type:** Single Center Observational **Size:** 24 patients	**Inclusion criteria:** Patients with idiopathic VAs that were successfully ablated within the pulmonic valve sinus cusps	**Results:** Among 244 patients with LBBB and inferior QRS axis VAs, 24 patients required ablation within the pulmonic sinus cusps.	● Right ventricular outflow tract VAs may require ablation within the pulmonic valve sinus cusps.

		Exclusion criteria: none	Successful ablation within the right PV sinus in 10 patients, the left sinus in 8, and anterior sinus in 6. There were no complications.	
● Morady et al. 1990 (419) ● 2242533	**Study type:** Single Center observational **Size:** 10 patients	**Inclusion criteria:** Consecutive patients undergoing DC Shock catheter ablation of RVOT VT **Exclusion criteria:** none	**Results:** DC shock ablation in the RVOT rendered 9 of 10 patients free of VT over a mean follow-up of 33±18 mo. There were no complications.	● RVOT VT can be successfully ablated with DC shock ablation with high efficacy and low complications.
● Yamada et al. 2008 (420) ● 18598894	**Study type:** Single Center Observational **Size:** 265 patients	**Inclusion criteria:** Idiopathic VAs undergoing catheter ablation 44 patients with VAs mapped and ablated within the aortic sinuses	**Results:** Left coronary cusp in 24 patients (54.5%), Right coronary cusp in 14 patients (31.8%), Right-Left cusp junction in 5 patients (11.4%), and Noncoronary cusp in 1 pt. Successful catheter ablation in 44/44 patients (100%). No complications.	● The aortic valve sinuses are a common location of outflow tract arrhythmias that can be effectively and safely ablated with RF current.
● Yamada et al. 2010 (421) ● 20855374	**Study type:** Single Center Observational **Size:** 27 patients	**Inclusion criteria:** Among 221 consecutive patients with LV Idiopathic VAs, 27 patients had VAs mapped and ablated on the Summit of the LV **Exclusion criteria:** N/A	**Results:** Successful ablation from the Great Cardiac Vein in 14 patients and on the epicardial surface of the LV in 4. In 5 patients ablation abandoned because of origin in the inaccessible region. In 4 patients ablation abandoned due to close proximity to epicardial coronary artery.	● LV summit VAs may be ablated within the GCV or inferior to the GCV on the epicardial surface, though sites superior to the GCV are often inaccessible to ablation.

● Mountantonakis et al. 2010 (422) ● 20855374	**Study type:** Single Center Observational **Size:** 47 patients	**Inclusion criteria:** Among 511 consecutive patients with non-scar related VAs, 47 patients were found to have a site of origin within the Coronary Venous System (CVS). **Exclusion criteria:** N/A	**Results:** Twenty-five (53%) were in the great cardiac vein, 19 (40%) in the anterior interventricular vein, and 3(7%) in the middle cardiac vein. Successful ablation achieved in 17 of 18 (94%) ablated at the earliest CVS site and in 16 of 29 (55%) ablated at adjacent CVS or non-CVS sites.	● Although ablation at the earliest CVS site is effective, it is often (62%) precluded, mainly because of proximity to coronary arteries. Ablation at adjacent CVS and non-CVS sites can be successful in 55% of these anatomically challenging cases, for an overall ablation success rate of 70%.
● Doppalapudi et al. 2009 (423) ● 19121799	**Study type:** Single Center Observational **Size:** 4 patients	**Inclusion criteria:** Among 340 patients with idiopathic VT referred for ablation, four were identified with VT that was mapped to the epicardium at the crux. **Exclusion criteria:** N/A	**Results:** VT was sustained and rapid (mean cycle length 264 msec) in all patients and was associated with syncope or presyncope in three. VT was induced with programmed stimulation or burst pacing in all 4 patients but required isoproterenol infusion in three.	Idiopathic VT may arise by a focal mechanism from the epicardium at the crux in close proximity to the posterior descending coronary artery. This syndrome can result in rapid, catecholamine-sensitive VT and requires careful attention to the posterior descending coronary artery during ablation.
● Konstantinidou et al. 2011 (424) ● 21307021	**Study type:** Single Center Observational **Size:** 13 patients	**Inclusion criteria:** 13 patients presenting with VT suggestive of RVOT origin with ablation guided by Magnetic Navigation **Exclusion criteria:** N/A	**Results:** The RVOT was reached in all patients utilized solely with the Magnetic Navigation System. Successful RVOT ablation was achieved in (135) (92.3%) patients. No Complications occurred. During a mean follow-up of 252±211 d, clinical arrhythmia recurrence was observed in 1 of 13 (7.7%) patients.	● RVOT access is feasible with the Magnetic Navigation System, while RVOT mapping and ablation appear to be safe, fast, and effective.

● Ouyang et al. 2002 (425) ● 11823089	**Study type:** Single Center Observational **Size:** 15 patients	**Inclusion criteria:** Consecutive patients with VAs from the right ventricular outflow tract or aortic sinuses **Exclusion criteria:** N/A	**Results:** The RVOT was site of origin in 7 patients and aortic sinuses in 8 patients. The left coronary cusp was the site of origin in 5 of 7 patients and the right coronary cusp in 2 of 7 patients with aortic sinus VAs	● VAs may arise in either the right or left ventricular outflow tracts and can be safely ablated with RF current.
● Tada et al. 2005 (426) ● 15766824	**Study type:** Single Center Observational **Size:** 19 patients	**Inclusion criteria:** Consecutive patients with VAs mapped to the mitral valve annulus **Exclusion criteria:** N/A	**Results:** Among 352 patients with idiopathic VAs, 19 (5%) had mitral annular VAs. 11 (58%) originated from the anterolateral mitral annulus, 2 from the posterior mitral annulus, and 6 from the posteroseptal mitral annulus. Successful ablation achieved in 19/19 patients (100%). No complications observed. Over a follow-up period of 21±15 mo, there were no recurrences of VAs after ablation.	● VAs may arise from the anterolateral, posterior, and posteroseptal regions of the mitral annulus and can be effectively and safely ablated with RF current.
● Tada et al. 2008 (427) ● 18313601	**Study type:** Single Center Observational **Size:** 12 patients	**Inclusion criteria:** Cases of VAs mapped and ablated within the Pulmonary Artery. **Exclusion criteria:** N/A	**Results:** Among 276 patients with VAs referred for RF ablation, 12 patients were identified with a successful site of catheter ablation within the pulmonary artery. All 12 patients had attempted ablation within the RVOT with	● A site of origin in the Pulmonary artery should be suspected when mapping and ablation of apparent RVOT VAs is not successful within the RVOT. Ablation within the pulmonary artery is safe and effectifve.

			a change in the QRS morphology after ablation. A characteristic prepotential was recorded within the pulmonary artery in all patients. Ablation was successful within the pulmonary artery in 12/12 patients (100%). There were no complications. No recurrences of VAs were observed over a follow-up period of 27±13 mo.	
● Tada et al. 2007 (428) ● 18313601	**Study type:** Single Center Observational **Size:** 38 patients	**Inclusion criteria:** Consecutive patients with idiopathic VAs mapped and ablated on the tricuspid annulus **Exclusion criteria:** N/A	**Results:** Among 454 consecutive patients with idiopathic VAs, 38 patients (8%) were found to originate from the tricuspid annulus. 28 (74%) originated from the septal tricuspid annulus 10 (26%) from the freewall portion of the annuls. Catheter ablation eliminated 90% of freewall VAs but only 57% of septal tricuspid annular VAs. There were no complications.	● Tricuspid annular VAs are not rare and ablation has a higher efficacy for freewall than septal sites.
● Kamioka et al. 2015 (429) ● 25633492	**Study type:** Single Center Observational **Size:** 34 patients	**Inclusion criteria:** Consecutive patients with LVOT Vas **Exclusion criteria:** N/A	**Results:** Twelve patients had VAs mapped in the Aortic cusps, and 22 patients had VAs mapped below the Aortic valve.	● LVOT VAs may arise above or below the aortic valve. Prepotentials are recorded at the site of successful ablation in the majority of patients with origin within the aortic sinuses but are rarely recorded below the aortic valve.

			Pre-potentials recorded in 91% of Aortic Sinus VAs and 13% below the aortic valve. VAs successfully ablated in 34/34 patients (100%)	
● Nagashima et al. 2014 (430) ● 25110163	**Study type:** Single Site observational **Size:** 30 patients	**Inclusion criteria:** 30 patients with VAs with early activation within the Great Cardiac Vein (GCV). **Exclusion criteria:** N/A	**Results:** Angiography in 27 patients showed earliest GCV site within 5 mm of a coronary artery in 20 (74%). Ablation was performed in the GCV in 15 patients and abolished VA in 8. Ablation was attempted at adjacent non-GCV sites in 19 patients and abolished VA in 5 patients (4 from the left ventricular endocardium and 1 from the left coronary cusp). After a median of 2.8 mo, 13 patients remained free of VA. Major complications occurred in 4 patients, including coronary injury requiring stenting.	● Ablation within the GCV requires careful attention to the proximity of coronary arteries with the potential for coronary arterial injury.
● Yamada et al. 2015 (431) ● 25637597	**Study type:** Single Center observational study **Size:** 64 patients	**Inclusion criteria:** 64 consecutive patients with symptomatic idiopathic sustained VTs (VTs) (N=14), NSVT (N=15), or premature ventricular contractions (PVCs) (N=35), which presumed origins identified in the AMC, LV	**Results:** Among 64 patients, 14 patients were identified with intramural foci between the endocardium and epicardium which required sequential or simultaneous irrigated unipolar radiofrequency ablation from the endocardial	● LVOT VAs originating from intramural foci could usually be eliminated by sequential unipolar radiofrequency ablation and sometimes required simultaneous ablation from both the endocardial and epicardial sides.

		summit, or intramural sites between the endocardium and epicardium. **Exclusion criteria:** N/A	and epicardial sides for their elimination. Simultaneous ablation was most likely to be required when the distance between the endocardial and epicardial ablation sites was >8 mm and the earliest local ventricular activation time relative to the QRS onset during the VAs was <30 ms at both ablation sites.	
● Hai et al. 2015 (432) ● 25637597	**Study type:** Single Center observational study **Size:** 21 patients	**Inclusion criteria:** All patients who underwent successful catheter ablation of VAs at the Aortomitral Continuity (AMS) **Exclusion criteria:** N/A	**Results:** Among 21 patients, prepotentials (PPs) were found at the ablation sites preceding the ventricular EGM during arrhythmias in 13 (61.9%) patients and during sinus rhythm in 7 (53.8%) patients. VAs with PPs were associated with a significantly higher burden of premature ventricular complexes (PVCs; 26.1±10.9% vs. 14.9±10.1%, p=0.03), shorter ventricular EGM to QRS intervals (9.0±28.5 msec vs. 33.1±8.8 msec, p=0.03), lower pace map scores (8.7±1.6 vs. 11.4±0.8, p=0.001), and a trend toward shorter V-H intervals during VA (32.1± 8.6 msec vs. 76.3±11.1 msec, p=0.06) as compared to those without PP.	● Specific identification and targeting of PPs when ablating VAs at the AMC may improve procedural success.

● Yamada et al. 2010 (433) ● 19804552	**Study type:** Single Center observational study **Size**: 21 patients	**Inclusion criteria:** All patients who underwent successful catheter ablation of VAs at the Aortomitral Continuity (AMS) **Exclusion criteria:** N/A	**Results:** 48 consecutive patients undergoing successful catheter ablation of idiopathic VAs originating from the left coronary cusp (LCC, N= 29), aortomitral continuity (AMC, N=10) and great cardiac vein or anterior interventricular cardiac vein (Epi, N= 9). An S wave in lead V5 or V6 occurred significantly more often during both the VAs and pacing from the AMC than during that from the LCC and Epi ($p<0.05$ vs. $p=0.0001$). For discriminating whether VA origins can be ablated endocardially or epicardially, the maximum deflection index (MDI = the shortest time to the maximum deflection in any precordial lead/QRS duration) was reliable for VAs arising from the AMC (100%), but was less reliable for LCC (73%) and Epi (67%) VAs. In 3 (33%) of the Epi VAs, the site of an excellent pace map was located transmurally opposite to the successful ablation site (LCC = 1 and AMC = 2).	● The MDI has limited value for discriminating endocardial from epicardial VA origins in sites adjacent to the LSOV probably due to preferential conduction, intramural VA origins or myocardium in contact with the LCC.

Data Supplement 47. Nonrandomized Trials, Observational Studies, and/or Registries of Catheter Ablation in Papillary Muscle VA - (Section 8.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Doppalapudi et al. 2008 (434) ● 19808390	**Study type:** Single Site Observational **Size:** 9 patients	**Inclusion criteria:** VT mapped to the Posterior Papillary Muscle of the LV **Exclusion criteria:** none	Among 290 patients with idiopathic VAs, 7 were found to have origin in the Posteromedial PM. All patients had RBBB and Superior QRS axis. No patient had SHD. VT had focal mechanism, sensitive to catecholamines **Results:** Successful catheter ablation in all patients without complications.	● Posteromedial papillary muscle VT is catecholamine sensitive with a focal mechanism that is amendable to catheter ablation. Catheter stability may be difficult and multiple RF applications are usually required.
● Yamada et al. 2010 (435) ● 20558848	**Study type:** Single Site Observational **Size:** 19 patients	**Inclusion criteria:** VT mapped to the Posteromedial or Anterolateral Papillary Muscles of the LV **Exclusion criteria:** none	Among 159 consecutive patients with idiopathic VAs mapped to the LV, the site of origin was in the Posteromedial PM in 12 and the Anterolateral PM in 7. **Results:** Successful ablation was achieved in 19/19 patients. Multiple QRS morphologies were observed in 47% of patients and in 7 patients ablation on both sides of the PM were required. No complications were observed. Recurrence of PM VAs was observed in 2/19 patients.	● VT of focal origin may occur in either the posteromedial of the anterolateral PMs of the LV. Catheter ablation often requires multiple RF applications over a wide area suggesting an origin deep within the PM. ● The recurrence risk after initially successful ablation is higher than for many other forms of idiopathic VT.

● Yokokawa et al. 2010 (436) ● 20637311	**Study type:** Single Site Observational **Size:** 40 patients	**Inclusion criteria:** VT mapped to the Posteromedial or anterolateral Papillary Muscles of the LV **Exclusion criteria:** None	**Results** 40 consecutive patients referred for ablation of symptomatic premature ventricular complexes (PVCs) (N=19) or VT (VT) (N=21) originating from a Papillary muscle in the LV (N=32) or RV (N=8). Antiarrhythmic drugs failed to control the VAs in 24 patients. 20 of 40 patients (50%) had SHD: prior MI in 10 patients, dilated cardiomyopathy in 9, and VHD in 1 pt. Catheter ablation was acutely successful in 33 of 40 patients (83%). Pleomorphic QRS morphologies observed in 31/40 patients. By MRI, the mass of the arrhythmogenic PM was greater in patients with failed than successful ablations. In follow-up, the PVC burden was reduced from 15%±11% to 3%±3%; p<0.01) after successful ablation.	● VAs may originate in the papillary muscles of both the LV and the RV. PVCs from the papillary muscles are often pleomorphic. ● Catheter ablation is successful in over 80% of cases, with greater mass of the papillary muscle predicting lower efficacy of ablation.
● Crawford et al. 2010 (437) ● 20206325	**Study type:** Single Site observational	**Inclusion criteria:**	**Results:** A total of 15 distinct PAP VAs was mapped to the posterior	● PVCs and VT may originate in the RV PAPs. Radiofrequency ablation is effective in eliminating these

	Size: 8 patients	VAs mapped to the papillary muscles in the right ventricle. **Exclusion criteria:** none	(N=3), anterior (N=4), or septal (N=8). Successful ablation achieved in all 8 patients. The PVC burden was reduced from 17%±20% preablation to 0.6%±0.8% postablation.	arrhythmias with low risk of complications.
● Ban et al. 2013 (438) ● 24385992	**Study type:** Single Site Observational **Size:** 12 patients	**Inclusion criteria:** Among 284 patients with idiopathic VAs undergoing ablation, 12 patients were identified with VAs originating from the Papillary Muscles of the LV.	**Results:** Successful catheter ablation was achieved in 7 of 8 (87.5%) patients with high amplitude electrograms at the earliest site of origin. The 4 patients with low amplitude and fractionated electrograms had recurrences of VAs after ablation. The mean duration from onset to peak downstroke (Δt) on the unipolar electrogram was significantly longer in the successful group than in the recurrence group (58±8 ms vs. 37±9 ms, p=0.04). A slow downstroke >50 ms of the initial Q wave on the unipolar electrogram at ablation sites was also significantly associated with successful outcome (85.7% vs. 25.0%, p=0.03).	● In PMVT, a high-amplitude, discrete potential before the QRS and slow down-stroke of the initial Q wave on the unipolar electrogram at ablation sites are related to favorable outcome after RF catheter ablation.

Data Supplement 48. Nonrandomized Trials, Observational Studies, and/or Registries Related to Interfascicular Reentrant VT (Belhassen Tachycardia)- (Section 8.3)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Nogami et al. 2000 (439) ● 10987604	**Study type:** Multicenter Observational **Size:** 20 patients	**Inclusion criteria:** 20 consecutive patients with verapamil-sensitive left VT exhibiting a RBBB and left-axis deviation QRS who underwent RF ablation. **Exclusion criteria:** None	**Results:** Sustained VT could be induced by programmed electrical stimulation, entrained by rapid ventricular pacing, and terminated by verapamil in all patients. Two discrete potentials could be recorded on the LV septum with antegrade conduction (P1) and retrograde conduction (P2). RF current applied to the exit site of P1 terminated VT in all patients. The interval between the LV and the P1 potential demonstrated decremental conduction and verapamil sensitivity.	● Verapamil sensitive idiopathic LV VT is a reentrant tachycardia involving a discrete longitudinal pathway in the LV septum and retrograde conduction over the His Purkinje network. Catheter ablation is highly successful with a low risk of complications.
● Liu et al. 2015 (440) ● 10987604	**Study type:** Single Center Observational **Size:** 120 patients	**Inclusion criteria:** Consecutive patients with Idiopathic fascicular VT undergoing catheter ablation. **Exclusion criteria:** None	**Results:** 120 patients with idiopathic fascicular VT (mean age, 29.3±12.7 y; 82% men; all with normal EF). Catheter ablation acutely successful in 117 of 120 patients. Over median follow-up of 55.7 mo, VT recurred in 17 patients, all successfully re-ablated.	Ablation of FVT guided by activation mapping is associated with a single procedural success rate of 80.3% without the use of AAD. 23 patients (20%) developed new onset LPF block, whereas 67 patients (58.3%) exhibited rightward shift in their frontal axis compared with baseline. There were no complications from the procedure.

● Lin et al. 2005 (441) ● 26386017	**Study type:** Single Center Observational **Size:** 15 patients	**Inclusion criteria:** Consecutive patients with idiopathic fascicular VT undergoing catheter ablation **Exclusion criteria:** N/A	**Results:** Among 15 patients with idiopathic fascicular VT, 6 (40%) had VT that was not inducible with programmed stimulation and isoproterenol. For these patients, a linear lesion was placed perpendicular to the long axis of the ventricle approximately midway from the base to the apex in the region of the mid to mid-inferior septum. Left posterior fascicular block developed in 2 of 6 patients. No spontaneous arrhythmias occurred during follow-up to 16±8 mo (range 6–30 mo).	● A linear ablation lesion perpendicular to the long axis of the LV across the left side of the interventricular septum is an effective ablation strategy for patients with idiopathic fascicular VT that is non-inducible.

Data Supplement 49. Nonrandomized Trials, Observational Studies, and/or Registries Related to Idiopathic Polymorphic VT/VF - (Section 8.5)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Haïssaguerre et al. 2002 (442) ● 11879868	**Study type:** Multi-Center Observational **Size:** 16 patients	**Inclusion criteria:** 16 patients with idiopathic VF treated with catheter ablation **Exclusion criteria:** N/A	Results: 16 patients with idiopathic VF triggered by short coupled PVCs (mean 300 msec). The mean PVC frequency per day was 9618. The initiating focus was in the RVOT in 4 patients, the RV Purkinje in 4 patients, the LV Purkinje in 7 patients, and both the RV and LV Purkinje in 1 pt.	● Idiopathic VF is often triggered by short coupled PVCs from the RVOT or the Purkinje system. The initiating focus can be successfully ablated with low risk of complications.

			Initially successful ablation of the triggering PVC focus in 16/16 patients. Long term freedom from VF observed in 13 patients.	
● **VALIANT** ● Solomon et al. 2005 (30) ● 15972864	**Aim:** To evaluate risk and predictors of SCD in patients post MI with left ventricular dysfunction and/or HF **Study type:** Observational study of patients enrolled in a RCT **Size:** 14,609 patients	**Inclusion criteria:** Patients with first or subsequent MI with HF, LV dysfunction, or both **Exclusion criteria:** ICD in place prior to randomization	**Intervention:** Analysis of rates of SCD. Evaluation of EF determined by echocardiography as well as other parameters. **Comparator:** N/A **1° endpoint:** The risk of sudden deathwas greatest in the first 30 d after MI: 1.4% per mo, 95% CI: 1.2%–1.6% and decreased to 0.14% per mo 95% CI: 0.11%–0.18% after 2 y after MI. Patients with LVEF <30% were at the greatest risk for SCD	● Each 5% lower LVEF was associated with a 21% increase in adjusted risk of SCD or CA with resuscitation.
● Linzer et al. 1990 (25) ● 2371954	**Study type:** observational **Size:** 57	**Inclusion criteria:** Syncope with negative Holter **Exclusion criteria:** Patients who had undergone electrophysiology study	**1° endpoint:** Monitor up to 1mo with Loop **Results:** arrhythmia was the cause of symptoms (diagnostic yield 25%; 95% CI: 14–38%). VT (1 patient), high grade AV block (2 patients), supraventricular tachycardia (1 patient), asystole or junctional bradycardia from neutrally mediated syncope (3 patients) and normal cardiac rhythms (the remaining 7 patients).	● 25% yield for syncope Dx after negative Holter ● VT/VF uncommon (1 pt)
● Noda et al. 2005 (443)	**Study type:** Single Center Observational	**Inclusion criteria:**	**Results:**	● PVCs from the RVOT may trigger VF when the coupling interval is short (<320

● 16198845	**Size:** 16 patients	16 patients who had documented VF or syncope out of a total of 101 patients with RVOT VAs undergoing catheter ablation	Holter monitoring showed frequent PVCs with LBBB inferior QRS axis with mean coupling interval of 245± 28 msec. RF ablation targeting the initiating PVC focus acutely successful in 16/16 patients. Over mean follow-up period of 54±39 mo, no recurrences of syncope or VF.	msec). The long term outcome after ablation of the triggering focus is excellent.
● Haissaguerre et al. 2002 (444) ● 12186801	**Study type:** Multicenter Observational **Size:** 27 patients	**Inclusion criteria:** 27 patients undergoing catheter ablation of idiopathic VF without SHD	**Results:** Premature beats were elicited from the Purkinje conducting system in 23 patients: from the left ventricular septum in 10, from the anterior right ventricle in 9, and from both in 4, and from the RVOT in 4 patients. The interval from the Purkinje potential to the following myocardial activation varied from 10–150 ms during premature beat but was 11±5 ms during sinus rhythm, indicating location at peripheral Purkinje arborization. The accuracy of mapping was confirmed by acute elimination of premature beats during local radiofrequency delivery. During a follow-up of 24±28 mo, 24 patients (89%) had no recurrence of VF without drug	● Idiopathic VF can be successfully ablated by targeting the initiating focus which is usually in the Purkinje system or RVOT.
● Van Herendael et al. 2014 (445) ● 24398086	**Study type:** Single Center Observational **Size:** 30 patients	**Inclusion criteria:** 30 patients from among 1132 consecutive patients undergoing	**Results:** In 21 patients, VF/PMVT occurred in the setting of cardiomyopathy; in 9 patients, VF/PMVT was	● Catheter ablation of VPD-triggered VF/PMVT is highly successful. Left ventricular outflow tract and papillary muscles are common and are previously

		catheter ablation of VAs of all types	idiopathic. The origin of VPD trigger was from the Purkinje network in 9, papillary muscles in 8, left ventricular outflow tract in 9, and other low-voltage areas unrelated to Purkinje activity in 4. Acute VPD elimination was achieved in 26 patients (87%), with a decrease in VPDs in another 3 patients (97%). During median follow-up of 418 d (interquartile range [IQR] 144-866), 5 patients developed a VF/PMVT recurrence after a median of 34 d.	unrecognized sites of origin of these triggers in patients with and without SHD.
● Sadek et al. 2015 (446) ● 25240695	**Study type:** Single Center Observationa. **Size:** 10 patients	**Inclusion criteria:** 10 patients with VAs mapped to moderator band in the RV undergoing catheter ablation	**Results:** VF was the clinical arrhythmia in 7 patients and monomorphic VT in 3 patients. Six patients required a repeat procedure. After mean follow-up of 21.5±11.6 mo, all patients were free of sustained VAs, with only 1 patient requiring AAD therapy and 1 patient having isolated PVCs no longer inducing VF. There were no procedural complications.	● VAs originating from the moderator band may present with VF. Catheter ablation is effective, though the risk of requiring more than one procedure may be higher than for other sites.
● Tester DJ et al. Mayo Clinic Proc 2011 (447) ● 21964171	**Study type:** retrospective single center **Size:** 35	**Inclusion criteria:** Unexplained drowning patients 1988-2010 molecular autopsy, mean age 17±12 y (4-69 y). 28 swimming (age 15.7 y), 7 bathtub (age 23 y). PCR	**1° endpoint:** genetic mutation yield in unexplained drowning victims **Results:** 23% positive mutations, 8/28 swimming, 0/7 bathtub Pos family Hx 43%: syncope, seizures, CA, near-drowning or	● Recommend genetic screening for unexplained drowning, especially if positive family Hx of drowning, prolonged QTc

		DNA sequencing for LQTS 1-3, RYR2 **Exclusion criteria:** N/A N/A	drowning. Among 11 patients with positive personal or family hx, 64% gene positive	
● Tzimas I et al. Int J Legal Med 2016 (448) ● 27460199	**Study type:** retrospective **Size:** 171	**Inclusion criteria:** Genotyping performed in corpses found in water: drowning, unclear deaths. **Exclusion criteria:** N/A	**1° endpoint:** Testing mutations in 19 variants in drowning/water related deaths. **Results:** one SNP of KCNQ1 noted NOS1AP significance	● NOS1AP mutation of KCNq1 may be significant in drowning victims. ● Recommend molecular autopsy in unexplained water deaths.
● Anderson JH et al. Circ CV Gen 2016 (449) ● 27114410	**Study type:** retrospective single center **Size:** 32	**Inclusion criteria:** Exertion related SUDY decedents (sudden unexplained death in young) ages 1-19 y Mean age 11±5 y Family Hx SCD age <50 y in 10% Molecular autopsy 1998-2010. DNA sequencing (PCR) followed by whole-exome sequencing **Exclusion criteria:** N/A	**1° endpoint:** yield of genetic testing in decedents with exercise related sudden death **Results:** PCR DNA testing putative mutation in 34% (11 patients, LQTS, CPVT). Subsequent WES performed in 21 patients, yield 3/21, 14% (calmodulin 2, PKP2 1-ARVC). Calmodulin deaths 2, 5 y. Yield higher among decedents aged 1–10 y (91%) vs. 11–19 y (19%), p=0.0001	● In decedents with exertion related **SUD** <20 y, overall yield 44%, ● Yield higher in probands <11 y.
● Wang D et al. Forensic Sci Int 2014 (450) ● 24631775	**Study type:** Retrospective cohort **Size:** 274	**Inclusion criteria:** SUD channelopathy genetic testing in NYC 2008-2012. LQTS, RYR2 testing. Ages ≤1 y, 141 patients, 51%, Age 1–58 y, 133 cases,	**1° endpoint:** Yield of channelopathy genetic screening in ethnically diverse population of SUCD **Results:** Gene positive: 13.5% infants, 19.5% older	● Overall genetic testing positive in 13.5%–19.5% of autopsy negative sudden death ● "Genetic testing information should be provided to the family members with proper counseling along with the choices of further clinical evaluation"

		African Americans 48%, Hispanic 22%, Caucasian 16% **Exclusion criteria:** autopsy positive	SCN5A positive, 68% infants, 50% non-infants AA carried more SCN5A, KCNQ1 variants vs other ethnic groups; Whites: more RYR2 LQTS more prevalent during sleep related deaths, RYR2 active	
● Kumar S et al. Heart Rhythm 2013 (451) ● 23973953	**Study type:** **Size:** 502	**Inclusion criteria:** Autopsy negative sudden unexplained death syndrome (SADS) and unexplained CA (UCA) (patients resuscitated successfully), mean age 32 y. Clinical evaluation (ECG, EST, echo) w targeted genetic testing. SADS mean age 24 y, UCA 32 y. **Exclusion criteria:** N/A	**1° endpoint:** Evaluate yield of comprehensive evaluation of SADS and UCA **Results:** SADS: yield 18%; LQTS in young ≤20 y; Brugada in age ≥40 y. UCA: yield 62%: mainly LQTS and BrS; CPVT, ER, ARVC, Short QT. Targeted genetic tesing in patients with proven or suspected phenotype: molecular dx SADS 35%, UCA 48%.	● Clinical + targeted genetics yield: SADS: 18%, UCA 62% ● Inherited cardiac disease diagnosed only in families with multiple events ● Recommend ongoing periodic clinical evaluation of children/young family members for developing disease

Data Supplement 50. Nonrandomized Trials, Observational Studies, and/or Registries of PVC-induced Cardiomyopathy - (Section 9)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population		1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Ban et al. 2013 (452) ● 23194696	**Study type:** Single Site Observational **Size:** 127 patients	**Inclusion criteria:** PVC burden >10% per 24 h and no known SHD		**Results:** Left ventricular dysfunction (EF <50%) was present in 28 of 127 patients (22.0%). The mean PVC burden (31±11 vs. 22±10%, p<0.001), the presence of non-	● A PVC burden >26%/d predicts LV dysfunction with sensitivity of 70% and specificity of 78%. Thus, PVC induced LV dysfunction is reversible

		Exclusion criteria: SHD		sustained VT (53.6 vs. 33.3%, p<0.05), and the presence of a retrograde P-wave following a PVC (64.3 vs. 30.3%, p=0.001) were significantly greater in those with LV dysfunction than in those with normal LV function. The cut-off PVC burden related to LV dysfunction was 26%/day, with a sensitivity of 70% and a specificity of 78%. The origin sites of PVCs, the acute success rate, and the recurrence rate during follow-up after RFCA were similar. In a multivariate analysis, the PVC burden (OR: 2.94; 95% CI: 0.90–3.19, p=0.006) and the presence of retrograde P-waves (OR: 2.79; 95% CI: 1.08–7.19, p=0.034) were independently associated with PVC-mediated LV dysfunction.	with catheter ablation though there is wide variability in the PVC burden associated with reduced LVEF.
● Haïssaguerre et al. 2002 (442) ● 11879868	**Study type:** Multi-Center Observational **Size:** 16 patients	**Inclusion criteria:** 16 patients with idiopathic VF treated with catheter ablation **Exclusion criteria:** N/A		**Results:** 16 patients with idiopathic VF triggered by short coupled PVCs (mean 300 msec). The mean PVC frequency per day was 9618. The initiating focus was in the RVOT in 4 patients, the RV Purkinje in 4 patients, the LV Purkinje in 7 patients, and both the RV and LV Purkinje in 1 pt. Initially successful ablation of the triggering PVC focus in 16/16 patients. Long term freedom from VF observed in 13 patients.	● Idiopathic VF is often triggered by short coupled PVCs from the RVOT or the Purkinje system. The initiating focus can be successfully ablated with low risk of complications.

• Haissaguerre et al. 2002 (444) • 12186801	**Study type:** Multicenter Observational **Size:** 27 patients	**Inclusion criteria:** 27 patients undergoing catheter ablation of idiopathic VF without SHD		**Results:** Premature beats were elicited from the Purkinje conducting system in 23 patients: from the left ventricular septum in 10, from the anterior right ventricle in 9, and from both in 4, and from the RVOT in 4 patients. The interval from the Purkinje potential to the following myocardial activation varied from 10–150 ms during premature beat but was 11±5 ms during sinus rhythm, indicating location at peripheral Purkinje arborization. The accuracy of mapping was confirmed by acute elimination of premature beats during local radiofrequency delivery. During a follow-up of 24±28 mo, 24 patients (89%) had no recurrence of VF without drug	• Idiopathic VF can be successfully ablated by targeting the initiating focus which is usually in the Purkinje system or RVOT.
• Lee et al. 2015 (453) • 25940215	**Study type:** Single Center, Retrospective review, 2004–2013 **Size:** 100	**Inclusion criteria:** Continuous Flow LVAD only **Exclusion criteria:** N/A		**1° endpoint:** All cause mortality **Results:** • 64 patients. Had ICDs. • Death occurred in 15 (38%) patients in the no ICD group vs. 18 (30%) in the ICD group. Univariate analysis demonstrated a marginal early survival benefit at up to 1 y. No difference after 1 y. • Multivariate analysis did not show any significant predictor of survival.	• ICD was not associated with improved survival.

				• No patients died of SCD.	
• Carballeira Pol et al. 2014 (454) • 24184787	**Study type:** Single Site Observational **Size:** 45 patients	**Inclusion criteria:** Consecutive patients without SHD who had >10% PVCs/d and normal LVEF (>0.55) who were observed. **Exclusion criteria:** Structural Heart Disease		**Results:** Of the 45 patients studied, 28 patients (62%) developed PVC-related LV dysfunction and 17 patients (38%) remained with normal LV function. The PVC burden was similar (26.5% vs 26%) between the two groups (p=NS). The QRS duration was significantly greater for those who developed LV dysfunction than those who did not (159 vs 142 msec, p<0.001). A PVC QRS duration >153 msec best predicted the development of LV dysfunction (sensitivity 82% and specificity 75%). A non-outflow tract site of origin was also an independent predictor of LV dysfunction.	• A QRS duration >153 msec of high frequency PVCs and a non-outflow tract site of origin are predictors of developing PVC-induced LV dysfunction.
• Deyell et al. 2012 (455) • 22640894	**Study type:** Single Center observational **Size:** 114 patients	**Inclusion criteria:** 114 consecutive patients with PVC burden >10%/d undergoing catheter ablation. 66 patients had preserved LV function and 48 patients had impaired LV function **Exclusion criteria:**		**Results:** Over a median follow-up of 10.6 mo, 24 of 48 patients with LV dysfunction were classified as reversible and 13 of 48 as irreversible and 11 of 44 were excluded due to failed ablation. There was a gradient of VPD QRS duration between the control, reversible, and irreversible groups (mean VPD QRS 135, 158, and 173 ms, respectively; p<0.001). This gradient persisted even for the same site of origin. In multivariate	• For patients with a PVC burden >10%/d, LV dysfunction may reverse after successful catheter ablation. The more prolonged the QRS duration of the PVC the higher the risk that LV dysfunction will not improve.

		Structural Heart Disease		analysis, the only independent predictor of irreversible LV function was VPD QRS duration OR: 5.07; 95% CI: 1.22–21.01 per 10-ms increase).	
● Del Carpio Munoz et al. 2011(456) ● 21332870	**Study type:** Single Center Observational **Size:** 70 patients	**Inclusion criteria:** 70 patients undergoing PVC ablation without SHD. **Exclusion criteria:** Known SHD		**Results:** Patients with reduced LVEF (N=17) as compared to normal LVEF (N=53) had an increased burden of PVCs (29.3±14.6% vs 16.7±13.7%, p=0.004), higher prevalence of NSVT (VT) [13 (76%) vs 21 (40%), p=0.01], longer PVC duration (154.3±22.9 vs 145.6±20.8 ms, p=0.03) and higher prevalence of multiform PVCs [15 (88%) vs 31 (58%), p=0.04]. There was no significant difference in prevalence of sustained VT, QRS duration of normally conducted complexes, PVC coupling interval, or delay in PVC intrinsicoid deflection.	● A higher PVC burden and prolonged QRS duration during PVCs may predict patients with reversible, PVC-induced CM.
● Olgun et al. 2011 (457) ● 21376837	**Study type:** Single Center Observational **Size:** 51 patients	**Inclusion criteria:** 51 consecutive patients with PVCs undergoing 24 h Ambulatory Monitoring, including 21 patients with PVC-induced cardiomyopathy and 30 patients without cardiomyopathy.		**Results:** Fourteen of the 21 patients (67%) with cardiomyopathy had interpolated PVCs, compared with only 6 of 30 patients (20%) without PVC-induced cardiomyopathy (p<0.001). Patients with interpolated PVCs had a higher PVC burden than patients without interpolation (28%±12% vs. 15%±15%; p=0.002). The burden of interpolated PVCs correlated with	● The presence of interpolated PVCs was predictive of the presence of PVC -related cardiomyopathy. Interpolation may play an important role in the generation of PVC-induced cardiomyopathy.

		Exclusion criteria: Structural Heart Disease		the presence of PVC cardiomyopathy (21%±30% vs. 4%±13%; p=0.008). Both PVC burden and interpolation independently predicted PVC-induced cardiomyopathy (OR: 1.07; 95% CI: 1.01–1.13, p=0.02; and OR: 4.43; 95% CI: 1.06–18.48, p=0.04, respectively). The presence of ventriculoatrial block at a ventricular pacing cycle length of 600 ms correlated with the presence of interpolation (p=0.004). Patients with interpolation had a longer mean ventriculoatrial block cycle length than patients without interpolated PVCs (520±110 ms vs. 394±92 ms; p=0.01).	
● Hasdemir et al. 2011 (458) ● 21235667	**Study type:** Single Center Observational **Size:** 247 patients	**Inclusion criteria:** Seventeen of 247 patients with PVCs (6.8%) who had Ambulatory monitoring and ECHO had tachycardia induced cardiomyopathy (TICMP) **Exclusion criteria:** Structural Heart Disease		**Results:** Patients with TICMP compared to patients with preserved LVEF were more likely to be male (65% vs 39%, p=0.043) and asymptomatic (29% vs 9%, p=0.018), and were more likely to have higher PVC burden (29.4±9.2 vs 8.1±7.4, p<0.001), persistence of PVCs throughout the day (65% vs 22%, p=0.001), and repetitive monomorphic VT (24% vs 0.9%, p<0.001). PVC burden of 16% by ROC curve analysis best separated the patients with TICMP compared to patients with preserved LVEF (sensitivity 100%,	● TICMP was relatively common (~1 in every 15 patients) in our study population. The predictors of TICMP were male gender, absence of symptoms, PVC burden of ≥16%, persistence of PVCs throughout the day, and the presence of repetitive monomorphic VT

				specificity 87%, area under curve 0.96).	
● Baman et al. 2010 (459) ● 20348027	**Study type:** Single Center Observational **Size:** 174 patients	**Inclusion criteria:** Consecutive group of 174 patients referred for ablation of frequent idiopathic PVCs **Exclusion criteria:** Structural Heart Disease		**Results:** A reduced LVEF (mean 0.37±0.10) was present in 57 of 174 patients (33%). Patients with a decreased EF had a mean PVC burden of 33%±13% as compared with those with normal left ventricular function 13%±12% ($p<0.0001$). A PVC burden of >24% best separated the patient population with impaired as compared with preserved left ventricular function (sensitivity 79%, specificity 78%, area under curve 0.89) The lowest PVC burden resulting in a reversible cardiomyopathy was 10%.	● A PVC burden of >24% was independently associated with PVC-induced cardiomyopathy.
● Kanei et al. 2008 (460) ● 20348027	**Study type:** Single Center Observational **Size:** 108 patients	**Inclusion criteria:** Consecutive group of 108 patients referred for evaluation of frequent idiopathic PVCs from the RVOT **Exclusion criteria:** Structural Heart Disease		**Results:** 24 patients had <1000 PVCs/24 h, 55 patients had 1000–10,000 PVCs/24 h, and 29 patients had ≥10,000 PVCs/24 h. The prevalence of LV dysfunction was 4%, 12%, and 34%, respectively ($p=0.02$). With logistic regression analysis, non-sustained VT was an independent predictor of LV dysfunction with OR: 3.6; 95% CI: 1.3–10.1).	● A new index, which incorporates PVC burden, QRS width and presence of SHD or suspected EPI origin that best predicted PVC-CMP.
● Hamon et al. 2016 (461) ● 26924618	**Study type:** Single Center Observational	**Inclusion criteria**: 107 consecutive patients (69 men; mean age =		**Results:** Patients with decreased LV function had a greater PVC burden on a 24-hour Holter	● LV dysfunction in the setting of frequent, idiopathic PVCs may represent a form of

	Size: 107 patients	56±16 y) with frequent PVC (23.1±11.5%) referred for PVC ablation. **Exclusion criteria:** Structural Heart Disease		monitor than patients with normal EF (37%±13% vs. 11%±10% of all QRS complexes; p<0.0001). There was a significant inverse correlation between the PVC burden and the EF before ablation (r=0.73, p<0.0001). PVCs originated in the right ventricular outflow tract in 31 (52%) of 60 patients, the LV outflow tract in 9 (15%) of 60 patients, and in other sites in 13 (22%) of 60 patients. The site of PVC origin could not be determined in seven patients. Ablation was completely successful in 48 (80%) patients. In patients with an abnormal EF before ablation, LV function normalized in 18 (82%) of 22 patients from a baseline of 34% to 59%±7% (p<0.0001) within 6 mo. In the 4 patients in whom ablation was ineffective, the EF further declined from 34%±10% to 25%±7% (p=0.06) during follow-up. In a control group of 11 patients with a similar PVC burden (30%±8%) and a reduced EF (28%±13%) who did not undergo ablation, the EF remained unchanged in 10/11 patients over 19±17 mo of follow-up and one patient underwent heart transplantation.	cardiomyopathy that can be reversed by catheter ablation of the PVCs.

● Bogun et al. 2007 (462) ● 17599667	**Study type:** Single Center Observational **Size**: 60 patients	**Inclusion criteria:** 60 consecutive patients with idiopathic, frequent PVCs (>10/h), a reduced LV EF (EF; mean 34%±13%) was present in 22 (37%) patients **Exclusion criteria:** Structural Heart Disease		**Results:** Patients with decreased LV function had a greater PVC burden on a 24 h Holter monitor than patients with normal EF (37%±13% vs. 11%±10% of all QRS complexes; p<0.0001). There was a significant inverse correlation between the PVC burden and the EF before ablation (r=0.73, p<0.0001). PVCs originated in the right ventricular outflow tract in 31 (52%) of 60 patients, the LV outflow tract in 9 (15%) of 60 patients, and in other sites in 13 (22%) of 60 patients. The site of PVC origin could not be determined in seven patients. Ablation was completely successful in 48 (80%) patients. In patients with an abnormal EF before ablation, LV function normalized in 18 (82%) of 22 patients from a baseline of 34% to 59%±7% (p<0.0001) within 6 mo. In the 4 patients in whom ablation was ineffective, the EF further declined from 34%±10% to 25%±7% (p=0.06) during follow-up. In a control group of 11 patients with a similar PVC burden (30%±8%) and a reduced EF (28%±13%) who did not undergo ablation, the EF remained unchanged in 10/11	● LV dysfunction in the setting of frequent, idiopathic PVCs may represent a form of cardiomyopathy that can be reversed by catheter ablation of the PVCs

				patients over 19±17 mo of follow-up	
● Zhong et al. 2014 (463) ● 24157533	**Study Type:** Single Center Prospective observational **Size:** 510 patients	**Inclusion Criteria:** 510 patients with frequent PVCs (>1000/24 h) were treated either by RFA or with AAD from January 2005 through December 2010. Data from 24 h Holter monitoring and echocardiography before and 6–12 mo after treatment were compared between the treatment 2 groups **Exclusion criteria:** Structural Heart Disease		**Results:** Of 510 patients identified, 215 (40%) underwent RFA and 295 (60%) received AAD. The reduction in PVC frequency was greater by RFA than with AAD (-21,799/24 h vs -8,376/24 h; p<0.001). The LVEF was increased significantly after RFA (53%–56%; p<0.001) but not after AAD (52%–52%; p=0.6) therapy. Of 121 (24%) patients with reduced LVEF, 39 (32%) had LVEF normalization ≥50%. LVEF was restored in 25 of 53 (47%) patients in the RFA group compared with 14 of 68 (21%) patients in the AAD group (p=0.003). PVC coupling interval less than 450 ms, less impaired left ventricular function, and RFA were independent predictors of LVEF normalization performed by using multivariate analysis.	● RFA appears to be more effective than AAD in PVC reduction and LVEF normalization
● Kawamura et al. 2014 (464) ● 24157533	**Study type:** Single Center Observational **Size**: 214 patients	**Inclusion criteria:** 214 patients undergoing successful ablation of PVCs who had no other		**Results:** Among these patients, 51 (24%) had reduced LVEF and 163 (76%) had normal LV function. Patients with LV dysfunction had significantly longer coupling interval (CI) dispersion	● In addition to the PVC burden, the CI-dispersion and BMI are associated with PVC-induced cardiomyopathy

		causes of cardiomyopathy **Exclusion criteria:** Structural Heart Disease		(maximum-CI-minimum-CI) and had significantly higher PVC burden compared to those with normal LV function (CI-dispersion: 115±25 msec vs. 94±19 msec; p<0.001; PVC burden: 19% vs. 15%; p=0.04). Furthermore, patients with LV dysfunction had significantly higher body mass index (BMI) compared to those with normal LV function (BMI>30 kg/m^2; 37% vs. 13%; p=0.001). Logistic regression analysis showed that CI-dispersion, PVC burden, and BMI (>30 kg/m^2) are independent predictors of PVC-induced cardiomyopathy.	
● Yokokawa et al. 2013 (465) ● 24612052	**Study Type:** Single Center observational **Size:** 264 patients	**Inclusion Criteria:** A consecutive series of 264 patients with frequent idiopathic PVCs referred for PVC ablation, including 87 with LV dysfunction **Exclusion criteria:** Structural Heart Disease		**Results:** The majority of patients (51 of 75, 68%) with PVC-induced LV dysfunction had a recovery of LV function within 4 mo. In 24 (32%) patients, recovery of LV function took more than 4 mo (mean 12±9 mo; range 5-45 mo). An epicardial origin of PVCs was more often present (13 of 24, 54%) in patients with delayed recovery of LV function than in patients with early recovery of LV function (2 of 51, 4%; p<0.0001). The PVC-QRS width was significantly longer in patients with delayed recovery than in patients with recovery within 4 mo (170±21 ms vs 159±16 ms; p=0.02). In multivariate analysis, only an	● PVC-induced cardiomyopathy resolves within 4 mo of successful ablation in most patients. In about one-third of the patients, recovery is delayed and can take up to 45 mo. An epicardial origin predicts delayed recovery of LV function.

				epicardial PVC origin was predictive of delayed recovery of LV function in patients with PVC-induced cardiomyopathy	

Data Supplement 51. Nonrandomized Trials, Observational Studies, and/or Registries Related to Pregnancy - (Section 10.2)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Jeejeebhoy et al. 2015(466) ● 26443610	**Study type:** Scientific Statement of the AHA **Size:** N/A	**Inclusion criteria:** Comprehensive review and recommendations for management of CA during pregnancy **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** Specific recommendation for management of CA during late pregnancy and delivery. There are 2 of major importance that are given the force of Recommendations in the absence of supporting data on outcomes (LOE-C): Left Uterine Displacement during CPR when the uterus is above the umbilicus; and the 4-5 min rule for emergency C-section during CA PMCD.	● Both this Scientific Statement on Cardiac Arrest in Pregnancy and the 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care; Part 10: Special Circumstances of Resuscitation, recommend that in CA when the uterus is above the umbilicus, left uterine displacement (142) should be performed to relieve aortocaval compression during CPR. While there is limited data on the relief of aortocaval compression by this maneuver, there is no data on the effect of LUD on outcomes. This is a Class I Recommendation, with LOE C. ● There is no specific data to support these recommendations from the point of view of outcomes yet they are woven in to two recommendation documents recently released. ● The 4-5 min window for PMCD is also based on limited theoretic information, but does not have any scientific basis supporting improved maternal or fetal outcomes. It is a Class IIa

				recommendation, LOE C. It is led to the recommendation that a scalpel be available for response teams on the obstetrical units, and a recommendation against moving the patient to operating room or delivery suite, but rather doing the PMCD on site.
● Creagna A A, et al 2014 (467) ● 3880915	**Study type:** Analysis of surveillance data accumulated by CDC (Division of Reproductive Health) **Size:** Absolute numbers not specified	**Inclusion criteria:** De-identified maternal and related fetal deaths reported to CDC by 52 voluntary reporting areas (50 U.S. states, New York City, and District of Columbia); based upon death certificate data **Exclusion criteria:** None specified	1° endpoint: Deaths during or within 1 y after pregnancy, with causes based upon death certificate data. Results: Pregnancy-related mortality ratio increased steadily from 7.2 deaths/100,000 live births in 1987 to 17.8 deaths/100,000 live births in 2009. The reasons for this increase are unclear. In parallel with this, there has been a decline in the contribution of the traditional causes of pregnancy-related mortality (i.e., hemorrhage, sepsis, hypertensive disorders of pregnancy), and the emergence of CV and other medical conditions as important contributors to mortality. For the most recent surveillance period shown (2006–2009), CV conditions alone accounted for over 1/3 of all pregnancy-related deaths.	● Pregnancy-related mortality ratios are 3–4 times higher among black than white women ● The data do not distinguish CA from other mechanisms of CV death; nor do they distinguish tachyarrhythmic CA from other mechanisms.
● **ZAHARA II** ● Kampman et al. 2015 (468) ● 25641540	**Study type:** Prospective cohort **Size:** 172	**Inclusion criteria:** Pregnant women with known congenital heart disease **Exclusion criteria:** N/A	**1° endpoint:** Cardiovascular events within 1 y postpartum **Results:** Women with events during pregnancy were 7.1 times more likely to have events postpartum	● Postpartum risk is low among women free of events during pregnancy ● Women who have events during pregnancy should be followed postpartum for changes in cardiovascular status.

				● Arrhythmias were most common events, mostly atrial; others not specified
● **ZAHARA** ● Drenthen et al. 2010 (469) ● 20584777	**Study type:** retrospective analysis of registry data **Size:** 1302 pregnancies in 714 women with congenital heart disease	**Inclusion criteria:** Pregnant women with known congenital heart disease **Exclusion criteria:** Miscarriages at <20 wk of gestation; elective abortions.	**1° endpoint:** Cardiovascular events during pregnancy **Results:** Cardiovascular complications occurred in 7.6% of pregnancies, with "clinically significant" arrhythmias most common events – 4.7%; type not specified.	● Presence of cyanotic heart disease (corrected/uncorrected), use of cardiac medication before pregnancy, left heart obstruction, aortic or pulmonic regurgitation, and mechanical valves were most closely associated with cardiovascular complications.
● Mhyre et al. 2014 (470) ● 24694844	**Study type:** Retrospective cohort study of CA during admissions for delivery from the Nationwide Inpatient Sample (NIS) **Size:** 56,900,512 hospitalizations for delivery between 1998 and 2011	**Inclusion criteria:** Diagnosis code indicating delivery or a procedure code related to delivery **Exclusion criteria:** Diagnosis code indicating abnormal products of conception or a procedure code indicating abortion.	**1° endpoint:** Cardiac arrest during hospitalization for delivery in the United States between 1998 and 2011. 2° outcomes included: (1) survival to hospital discharge; (2) the association between CA and demographic and socioeconomic characteristics, and medical and obstetric diagnoses and procedures; and (3) association between CA and the annual hospital delivery volume. **Results:** 4,843 cardiopulmonary arrests (CPA) between 1998 and 2011 (event rate = 8.5 CPA/100,000 hospitalizations, or 1: 12,000). Incidence was higher for older subjects (≥35 y), black women, and Medicaid patients. The conditions most strongly associated with CPA were pulmonary hypertension, malignancy, CVD (i.e., ischemic heart disease, congenital heart disease, cardiac valvular disease, and pre-existing hypertension), liver disease,	● CPA is rare among patients hospitalized for delivery, but considerably higher than the age adjusted incidence of CPA in general population. ● There is a trend towards improving survival to hospital discharge over the 14 y observation period, but the incidence has not changed significantly. ● The most common etiologies numerically are those that are not associated with the tachyarrhythmic CA, but the incidence is highest among those conditions that are more likely to be associated with tachyarrhythmic events. ● The cumulative number of CPAs in the sample was 4,843 over 14 y (average = 346/y), but this number is based on the limitations of the sample size in the NIS.

			and systemic lupus erythematosus. However, the absolute numbers were highest for postpartum or antepartum hemorrhage combined = 44.7%, HF, amniotic fluid embolism, and sepsis.	
● Siu et al. 2001 (471) ● 11479246	**Study type:** Retrospective analysis of a multicenter consecutive series of pregnant women with a Hx a heart disease. **Size:** 599 pregnancies in 562 consecutive referrals	**Inclusion criteria:** Congenital or acquired cardiac lesions or cardiac arrhythmias. Patients in whom cardiac arrhythmia was the 1° diagnosis must have had symptomatic sustained tachyarrhythmias or bradyarrhythmias requiring treatment before pregnancy. **Exclusion criteria:** Isolated mitral valve prolapse (moderate or mild mitral regurgitation) or those referred for termination of pregnancy.	**1° endpoint:** Prepartum (2nd and 3rd trimesters), peripartum, and postpartum 1° cardiac, 2° cardiac, neonatal, or obstetric complications. **Results:** The principal cardiac lesion was congenital in 445 pregnancies (74%), acquired in 127 pregnancies (22%), and arrhythmic in 27 pregnancies (4%, with the majority being SVT's). 1° cardiac events occurred in 80 pregnancies (13%); 55% of which occurred prepartum. Pulmonary edema and/or cardiac arrhythmia accounted for most of the cardiac events, the majority SVT's. Predictors of 1° cardiac events were HF, TIA, CVA, or arrhythmia before pregnancy; baseline NYHA class >II or cyanosis; left heart obstruction; and LV EF<40%. A 2° cardiac event occurred in 37 (6%). Worsening of NYHA class by >2 classes occurred in 26 of the 579 pregnancies in which the baseline NYHA class was I or II.	● A subgroup at high risk for 1° or 2° cardiac complications of pregnancy is identifiable, with a combined incidence of 17%. Among 1° events, 55% occurred during the 2nd and 3rd trimesters. ● The majority of arrhythmias were SVT's. ● Careful scrutiny of high risk cardiac patients during pregnancy, beginning no later than the second trimester, is warranted for both arrhythmic and non-arrhythmic 1° and 2° complications.
● Einav et al. 2012 (472) ● 22613275	**Study type:** Retrospective analysis of published original	**Inclusion criteria:** (1) At least 5 clinical details regarding the case (e.g. age,	**1° endpoint:** Maternal and neonatal survival to hospital discharge and the	● Maternal outcomes may not be as poor as in other CA populations. Mortality rates were higher among women who underwent PMCD compared

	articles, case series, case reports and letters to the editor regarding PMCD during CA in pregnancy **Size:** 94 cases selected from 108 publications that met review criteria.	gravidity, parity, obstetric and medical Hx, presenting rhythm, location of arrest), and the care provided (e.g. chest compression, ventilation, monitoring, drugs given); (2) At least one of the following outcomes: (a) maternal non-return/return of spontaneous circulation or non-survival/survival to hospital discharge; (b) fetal/neonatal outcome. **Exclusion criteria** Maternal arrest post-delivery, no data enabling relation of case details to outcome, or if both outcomes were unclear.	relationship between PMCD and this outcome. **Results:** ROSC was achieved in 60.6% of mothers (N=57), among whom 89.5% survived to hospital discharge (51/57). Time from arrest to PMCD was reported for only 57 cases of the 76 (75%) receiving PMCD; the average time was 16.6±12.5 min (median 10, range 1–60, IQR 8–25), with only 4 cases achieving the recommended 4-min target. Overall survival to hospital discharge was 54.3%. Among 23 with VT/VF, 15 survived to discharge. Overall, in-hospital location and PMCD <10 min were statistically significant. Neurological outcomes of surviving mothers (N=51) were described as CPC 1/2 in 78.4% (40/51). The overall neonatal survival rate was 63.6% (42/66). Neurological outcomes of surviving neonates were CPC 1/2 in 52.3% (22/42),	with those who did not, possibly because of a subgroup with spontaneous or rapid ROSC. ● The 4-min time goal for PMCD usually remains unmet (4 of 57, 7%), yet neonatal survival is still likely if delivery occurs within 10 or even 15 min of arrest and neonatal survival was most-powerfully associated with maternal arrest occurring in-hospital, regardless of the cause of arrest.
● Citro et al. 2013 (473) ● 23519095	**Study type:** Case reports identified in systematic literature review **Size:** 15	**Inclusion criteria:** Diagnostic criteria for tako-tsubo syndrome based upon modified Mayo criteria **Exclusion criteria:** Preexisting cardiomyopathy or	**1° endpoint:** Diagnosis of TTS **Results:** 13 of 15 cases of TTS had onset 24 h after a C-section. 13 patients had cardiac complications (pulmonary edema, cardiogenic shock, or CA [N=1]) All patients had return of LV function in 13.43±10.96 d.	• Acute medical/surgical stressors are increasingly recognized as a trigger for TTS • Distinction from peripartum cardiomyopathy is important for prognostic reasons. • Cardiac arrest is infrequent in TTS. • LQT2 more likely to have ACE postpartum vs LQT1 or 3

		other known cardiac defects		• Risk greatest during 9 mo postpartum: HR: 2.7, 95% CI: 1.8–4.3, p<0.001 • risk reduced by using beta-bl, HR: 0.34, 95% CI: 0.14-0.84, p=0.02.
● Seth et al. 2007 (474) ● 17349890	**Study type:** Retrospective analysis of data from the International LQTS Registry **Size:** 391	**Inclusion criteria:** First live birth pregnancy in women with identified LQTS-related gene mutation or considered to be affected with LQTS on the basis of a QTc>470 ms **Exclusion criteria:** First live birth prior to 1980.	**1° endpoint:** LQTS-related death, ACA, and/or syncope before, during, and after pregnancy **Results:** Compared to frequency of endpoint events prior to pregnancy, event rates during pregnancy were lower, but significantly higher during the 9 mo postpartum period. Frequency of events returned to pre-pregnancy levels after 9 mo. The post-partum increase was greatest among those with HERG mutations.	● The data have implications for observation and pharmacological management during the 9 mo post-partum.
● Katz et al. 2005 (475) ● 15970850	**Study type:** Systematic MEDLINE review of outcomes from perimortem cesarian deliveries **Size:** 38	**Inclusion criteria:** Case reports of pregnant CA victims between 25 and 42 wk of gestation who underwent PMCD. **Exclusion criteria:** Cesarean deliveries performed on mothers who were dying from mortal injuries, but still had vital signs, were excluded.	**1° endpoint:** Outcomes for fetus and mothers as a result of PMCD **Results:** In 30 of 38 PMCD's surviving infants were delivered. One of the twins died in the neonatal period from anoxic injury and complications of prematurity. In 12 of 22 cases in which hemodynamic data was reported, sudden return of pulse and BP occurred when the uterus was emptied.	● The data reviewed supports, but does not prove, that PMCD within 4 minutes of onset of maternal CA improves maternal and neonatal outcomes. A controlled trial will never be feasible. The conclusion is based upon general data on survival free of neurological injury during CA as a function of down-time.
● Dijkman et al. 2010 (476) ● 20078586	**Study type:** Retrospective cohort study of CA during pregnancy, with and without	**Inclusion criteria:** All cases of maternal CA during the second half of pregnancy in The Netherlands	**1° endpoint:** Frequency of use of PMCD over time and case fatality rate of those with PMCD (N=12) compared to those without PMCD (N=43).	● Use of PMCD is increasing over time. Outcome for pregnant women with CA and PMCD remains dismal, but this study is limited by small numbers and apparent long delays to initiation of PMCD.

	PMCD during a 15 y period. **Size:** 55 CA among 2,929,289 women, 12 of whom underwent PMCD.	identified by survey from 1993-2008. **Exclusion criteria:** None specified	**Results:** A total of 8 of 55 mothers survived (15%). Among the 12 women in whom PMCS was performed, there were two maternal survivors (17%). In the 43 women in whom no PMCS was performed, there were six maternal survivors (14%). No PMCD's were performed prior to 2000, and the use progressively increased after 2000. The maternal case fatality rate for PMCS for the entire 15 y period was 83% (10/12). For the period of August 2004 to August 2006 the case fatality rate for PMCS was 75% (3/4) and the case fatality rate for resuscitation without PMCS was 67% (6/9). Neonatal case fatality rate with PMCD was 58%. Corresponding data for no PMCD is not provided.	● The data are reasonable for trend to increased used of PMCD, but outcomes cannot be relied upon because of factors cited above.
● Colletti et al. 2013 (477) ● 23436839	**Study type:** Review and opinion article on radiation during pregnancy **Size:** Not specified	**Inclusion criteria:** Studies of radiation exposure to fetus as a result of cardiovascular procedures in pregnant women. **Exclusion criteria:** N/A	**1° endpoint:** Magnitude of exposure risk to fetus based upon nature of radiation-associated procedure and stage of pregnancy **Results:** Most procedures entail a fetal dose well below the fetal risk threshold of 50 mGy. For the specific issue of fluoroscopic radiation for ICD implants, no specific data is available. However, for groin-to-heart catheter procedures, the fetal exposure is 0.094–0.244 mGy/min. Thus, a	● Even in light of these numbers, it is generally recommended that fluoroscopic procedures be avoided until after the first trimester, unless clinical circumstances, based on risk/potential benefit considerations, warrant an earlier intervention.

			fluoroscopic time of 1 h falls well-below the fetal risk threshold.	
● Natale et al. 1997 (478) ● 9386142	**Study type:** Multicenter retrospective analysis of women with an ICD who became pregnant. **Size:** 44	**Inclusion criteria:** Women with an ICD who completed a pregnancy or was currently pregnant. (1). The clinical presentation and indication for ICD implantation were sudden cardiac death in 33 patients, VT in 9 patients, and VT with syncope in 2 patients. **Exclusion criteria:** N/A	**1° endpoint:** Use, efficacy and safety of ICD's during pregnancy. **Results:** The EF at the time of ICD implantation was 49.8±9.7% (present EF was 51.4±9.5%). Underlying cardiac diseases were long-QT syndrome (N=13), idiopathic VF (17), cardiomyopathy (8), congenital heart disease (3), CAD with an ischemic cardiomyopathy (1), HCM (1), and ARVC (1). The indications for the ICD were VF in 33 patients, VT in 9, and VT/syncope in 2. During the first pregnancy after implant, 33 women experienced no ICD discharge, 8 received one shock; 1 experienced 5 firings in Afib; and 2 had 11 and 5 discharges, respectively, for monomorphic VT. During delivery, in the women in whom the ICD remained active, none received any shocks. In the 24 to 48 h period after delivery, 1 patient had an ICD discharge for VF. Overall, the total number of ICD discharges during pregnancy ranged from none to 11, with an average of 0.66±1.9 shocks (0.07 shock per mo). There were no apparent adverse effects on the fetus among the 11 shocks delivered during pregnancy	● ICD's are effective and safe for the pregnant female ● There were no apparent adverse effects on the fetus.

● Damilakis et al. 2001 (479) ● 11514375	**Study type:** Radiation exposure and fluoroscopy tines to a theoretical fetus during simulated pregnancies during ablation procedures in female patients of childbearing age. Estimated radiation exposure was carried out for each projection of the cardiac ablation procedure, using fetal phantoms simulating pregnancy in the first, second, and third trimesters. **Size:** 20 women	**Inclusion criteria:** Women of childbearing age undergoing catheter ablation procedures for supraventricular tachycardias. **Exclusion criteria:** N/A	**1° endpoint:** Radiation exposure and fluoroscopy times estimated for phantom simulated fetus, calculated for first, second, and third trimesters. **Results:** The average radiation dose to the fetus was <1 mGy in all periods of gestation. Average excess fatal cancer was $14.5/10^6$ fetuses exposed during the first trimester. Corresponding values for the second and third trimesters were 30 and $55.7/10^6$, respectively. The risk for hereditary effects in future generations was $1.5/10^6$ cases for irradiation during the first trimester. Corresponding values for the second and third trimesters were 3.0 and $5.6/10^6$, respectively.	● Catheter ablation procedures result in a very small increase in risk of potentially harmful radiation effects to the fetus.

Data Supplement 52. RCTs Comparing Medication-Induced Arrhythmias - (Section 10.7)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● **CAST** ● The Cardiac Arrhythmia Suppression Trial Investigators. 1989 (480) ● 2473403	**Aim:** Test hypothesis that suppression of ventricular ectopy post MI reduces incidence of SCA n patients whose ectopy was suppressed by encainide, flecainide or moricizine **Study type:** Randomized contolled, double-bllind **Size: 1498**	**Inclusion criteria:** Post MI, 6 d to 2 y; six or more PVCs/h and no VT over 15 beats at 120 bpm. 80% suppressioin of PVCs and 90% suppression of NSVT. **Exclusion criteria:** No flecainide for EF<30%. Moricizine was second choice if EF>30%	**Intervention:** Drugs as listed Encainide 432, placebo 425 Flecainide 323, placebo 318. **Comparator:** Placebo	**1° endpoint:** after 10 mo there was an excess in deaths due to arrhythmia (p=0.0004) in patients treated with encainide or flecainide. **Safety endpoint (if relevant):** n/a	● Excess in deaths due to shock due to recurrent MI.
● **CAST II** ● The Cardiac Arrhythmia Suppression Trial II Investigators. 1992 (481) ● 1377359	**Aim:** test hypothesis that suppression of ventricular ectopy post MI reduces incidence of SCA n patients whose ectopy was suppressed by moricizine	**Inclusion criteria:** Post MI, 6 d to 2 y; six or more PVCs/h and no VT over 15 beats at 120 bpm. 80% suppressioin of PVCs and 90% suppression of NSVT. **Exclusion criteria:** patients with any runs lasting 30 sec or	**Intervention:** Moricizine **Comparator:** Placebo,	**1° endpoint:** Terminated early due to excess mortality (17 of 665 with death or SCA with moricizine vs 3 of 660 with placebo) **Safety endpoint: n/a**	● N/A

	Study type: Randomized contolled, double-bllind **Size:** 1335	longer at a rate of ≥120 complexes/min			

Data Supplement 53. Nonrandomized Trials, Observational Studies, and/or Registries of Medication-Induced Arrhythmias (Section 10.7)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Wyse et al. 2001 (482) ● 11704386	**Study type:** Prospective study of the registry of AVID, examining the outcome of patients with "transient" or "correctable" causes of VT/VF **Size** 278 patients with transient or correctable cause, of 4450 in registry; only 18 (6.5%) had an AAD reaction	**Inclusion criteria:** Patients with "transient" or "correctable" VT/VF, compared with patients with high risk in AVID registry. Patients in registry could have EF >40% **Exclusion criteria:** N/A	**1° endpoint:** Mortality **Results:** mortality of patients with a transient or correctable cause of VT/VF was no different or perhaps even worse than that of the 1° VT/VF.	● Mortality of patients with a transient or correctable cause of VT/VF was no different or perhaps even worse than that of the 1° VT/VF. However, the small number of patients with AAD reaction seemed to "most likely to presage better survival"
● Monnig et al. 2012 (483) ● 21979994	**Study type:** Single center observational trial **Size** 43 patients	**Inclusion criteria:** survival of CA due to acquired QT prolongation/TdP who received an ICD. 79% had drug-induced TdP from an AAD. sotalol N=17; amiodarone N=12; quinidine	**1° endpoint: ICD shock** **Results:** Over mean followup of 84 mo, 44% had appropriate shocks and inappropriate shocks in 30% (Only inappropriate in 3 of 43)	● ICD therapy was appropriate in 44% of patients with drug-induced QT prolongation/TdP, (where DI-TdP was due to an AAD in 79%). ● However, EF was not normal (mean 41±12)

		N=3; propafenone N=1; ajmaline N=1] **Exclusion criteria:** N/A		● Appropriate shocks were most common in those with structural disease. ● Beta blockers did not seem to reduce risk
● Antman et al. 1990 (484) ● 2188752	**Study type:** An open-label multicenter clinical trial of Fab treatment for life-threatening digitalis intoxication **Size** 150	**Inclusion criteria:** Digitalis intoxication with actual or potentially life-threatening cardiac rhythm disturbances, hyperkalemia, or both caused by digitalis intoxication; refractory to or likely to be refractory to treatment with conventional therapeutic modalities. 46% had refractory VT and 33% had VF. **Exclusion criteria:** N/A	**1° endpoint:** Resolution of toxicity and time course. Dosing requirements **Results:** 80% had resolution of all signs and symptoms of toxicity, 10% improved, and 10% showed no response. Median initial response time was 19 min. Time to complete response was 88 min median (30–360 min). 54% of those with CA survived hospitalization. Adverse events in 14/148, with hypokalemia or worsening CHF.	● 90% of patients had a treatment response in the setting of advanced and potentially life-threatening digitalis toxicity.
● Chan et al. 2014 (485) ● 25089630	**Study type:** Review of 10 case series **Size** 2080	**Inclusion criteria:** digoxin poisoning **Exclusion criteria:** N/A	**1° endpoint:** Resolution of toxicity, time course to effect. **Results:** Response varied from 80-90% to 50%. Reversal of toxicity 30–45 min. Adverse events <10% (exacerbated CHF, increased HR and hypokalemia) Lower dose requirements (1/2 of the full neutralizing dose) are appropriate unless CA is imminent.	● Confirms efficacy, onset of action. Suggests that lower doses (at lower cost) are appropriate in many situations due to pharmacokinetics of digoxin (unless CA is imminent).

● Hauptman et al. 1999 (486) ● 10069797	**Study type:** Review of treatment of digoxin toxicity **Size** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint**: N/A **Results:** N/A	• More common manifestations (including occasional ectopic beats, marked first-degree AV block, or AF with a slow ventricular response) require only temporary withdrawal of the drug and monitoring. Administration of potassium salts is recommended for ectopic VA, even when the serum potassium is within the "normal" range.
● Kelly et al. 1992 (487) ● 1626485	**Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint** N/A **Results:** N/A	● Describes VT with digoxin toxicity. ● Notes exacerbation of digoxin toxicity with low and high K, hypothyroidism, Notes benefit of magnesium administration.
● Osmonov et al. 2012 (488) ● 22530749	**Study type:** Single center observational series. **Size:** 108	**Inclusion criteria:** drug-related symptomatic type 2 second degree or third degree AV block **Exclusion criteria:** MI, electrolyte abnormalities, digitalis toxicity, and vasovagal syncope. Digoxin toxicity (a digoxin level from a blood test of higher than 2 nmol/L with symptoms such as nausea, vomiting, and color vision abnormalities or Above 2.5 nmol/L with or without symptoms.	**1° endpoint:** improvement or need for pacer. **Results:** 39 patients had AV block with digoxin dosing, with 28 of them improving after withdrawal of the drug.	● Digoxin-induced AV block (without "toxicity") usually improved (28 of 39) after withdrawal of the drug.
● Tzivoni et al. 1988 (489)	**Study type:** Consecutive series	**Inclusion criteria:** TdP (9/12 due to AAD)	**1° endpoint** Abolition of TdP	● This established MgSO4 as treatment for TdP

● 3338130	Provided 2 gm IV with second bolus of 2 g after 5-15 min. 9 received infusion at 3-20 mg/min for 7-48 h. **Size** 12	**Exclusion criteria:** N/A	**Results:** In nine of the patients a single bolus of 2 g completely abolished the TdP within 1 to 5 min, and in three others complete abolition of the TdP was achieved after a second bolus was given 5 to 15 min later.	
● Keren et al. 1981 (490) ● 7296791	**Study type:** Single center series **Size:** 10 (9 on AAD, 4 treated with pacing)	**Inclusion criteria:** TdP, QTc>600 ms **Exclusion criteria:** N/A	**1° endpoint:** response to therapy of isoproterenol and/or ventricular pacing. **Results:** Pacing effective in 4 of 4 patients, 2 who had not responded to isoproterenol. Continued up to 48 h and pacer removed after another 24 h. Pacing rate was "lowest effective rate", 88-105 bpm. In 2 cases atrial pacing was tried, initially effective but unstable so V pacing provided. Lidocaine was given in 4 cases without improvement. Isoproterenol (2-8 microgram/min) was given in 7 cases: effective in 5/7.	● This confirmed the effectiveness of V pacing for DI-TdP, even after isoproterenol was ineffective. ● This confirms the effectiveness of isoproterenol as a first line treatment. ● Magnesium was not given in this series.
● Choy et al. 1997 (373) ● 9337183	**Study type:** Double-blind comparison of potassium infusion after quinidine and	**Inclusion criteria:** healthy subjects (12) and CHF (mean EF 17%) with age-matched controls without CHF	**1° endpoint:** Effect on QTUc from KCl after quinidine or placebo. **Results:**	● "Potentially arrhythmogenic QT abnormalities during quinidine treatment and in CHF can be nearly normalized by modest elevation of serum potassium"

	placebo sequentially in 12 healthy subjects. Also, study on QTU in patients with CHF and age-matched controls who receive IV KCl **Size:** 12 healthy, 8 CHF plus 8 age-matched controls	**Exclusion criteria:** N/A	KCl was IV, 0.5 mEq/kg (to maximum of 40 meEq) over 60-70 min resulted in normalization of quinidine-induced and CHF-related QTU prolongation	
● Yang et al. 1996 (491) ● 8565156	**Study type:** Basis EP (cardiac myocytes) **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** Change in IC50 for dofetilide and quinidine according to the extracellular K concentration **Results**: Elevating [K+]o from 1 to 8 mmol/L increased the IC50 for dofetilide block from 2.7±0.9 to 79±32 nmol/L and for quinidine block from 0.4±0.1 to 3.8±1.2 µmol/L.Increased K blunted drug effect of dofetilide and quinidine	● Extracellular potassium is a critical determinant of drug block of IKr, with substantial clinical implications. The increase in drug block with low [K+]o provides a mechanism to explain the link between hypokalemia and torsade de pointes
● Hellestrand et al. 1983 (492) ● 6195608	**Study type:** Clinical research study **Size:** 28	**Inclusion criteria:** Group I:11 with temporary pacer; Group II:10 with chronic pacer at generator change; Group III: 7 with programmable pacer with pacing threshold testing **Exclusion criteria:** N/A	**1° endpoint:** Results: Given IV flecainide 2 mg/kg over 10 min. 7 with programmable pacers given oral 100-400 mg per day. I: 0.66–1.44 V II: 1.73–2.13 V III: 10 min: at 2.7 V: 0.14–0.22 msec; at 4.9 V 0.06–0.11 After 3 wk: at 2.7V 0.09–0.28 msec, at 4.9 V 0.06–0.16	● Flecainide significantly increased both acute and chronic thresholds and the most marked rise (>200%) occurred during chronic oral therapy.

• Echt et al. 1989 (493) • 2469545	**Study type: Basic canine study** **Size:** 78 protocols total	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** change in defibrillation threshold (DFT) **Results:** ED90 increased from 11 to 22 Joules (p<0.01)	• Lidocaine doubled the defibrillation energy requirement
• Crijns et al. 1988 (494) 3143257	**Study type:** observational trial **Size:** 6 of 79 patients treated with flecainide developed this wide complex tachycardia	**Inclusion criteria:** Rate – related BBB giving wide QRS tachycardia **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** 6 patients developed WCT, rates 145-200 BPM	• Wide complex tachycardia resulted from tachycardia and flecainide slowing conduction. This can appear to be VT but is not.
• Bajaj et al. 1989 (495) 2551538	**Study type:** Basic canine **Size:** 30	**Inclusion criteria:** N/A **Exclusion criteria**: N/A	**1° endpoint:** After infusion of ODE, a potent metabolite of encainide, shortening in intervals (HV and QRS) with NaHCO3 or NaCl **Results:** With NaHCO3, QRS: 92–76 msec; HV 44 to 37 msec.	• Short-term administration of NaHCO3 or NaCl can partially reverse ODE-induced conduction slowing, which may be an important factor in arrhythmia aggravation
• Myerburg et al. 1989 (496) 2480856	**Study type:** Case series **Size:** 4 (3 flecainide, 1 encainide)	**Inclusion criteria:** Prior CA or symptomatic sustained VT, treated with a Ic medication who developed runs of sustained VT, NSVT or increased ectopy **Exclusion criteria:** N/A	**1° endpoint:** suppression of drug-induced arrhythmias **Results:** Drug-induced arrhythmias were suppressed in all 4 patients	• Propranolol had failed to prevent inducibility of sustained VT during previous programmed stimulation studies in three of the four patients, but it reproducibly suppressed drug-induced arrhythmias that appeared only after administration of the IC agents in each patient.
• Schwartz PJ et al. 2016 (497) • 27150690	**Study type:** Review	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	N/A	• Review of Hx of drug-induced QT prolongation and TdP. • crediblemeds.org categorizes drugs as possible, conditional and known TdP risk. • Drugs associated with prolonged QT and TdP fall into a number of different

				pharmacologic classes, and the risk of TdP increases according to clinical and genetic factors. • Clinical decision support systems reduce prescription of QT prolonging drugs in patients at risk of TdP due to clinical or genetic factors.
• Kannankeril P, et al. Pharcological Reviews 2010. (374)	**Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint** N/A **Results:** N/A	• Hypokalemia worsens risk of TdP Although no randomized prospective trial has been conducted, intravenous magnesium has become a first-line therapy for drug-induced TdP.

Data Supplement 54. Nonrandomized Trials, Observational Studies, and/or Registries Related to ACHD - (Section 10.8)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
• Basso C, et al. Virchows Arch 2008 (498) • 17952460	**Study type:** Review **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A Role of autopsy to establish cause of SCD: Assoc of European Cardiovascular Pathology developed guidelines Includes ARVC, athlete's heart, HCM, myocarditis **Results:** N/A	• Discussed gross and microscopic pathologic findings • "Further tests in future": molecular or toxicology
• Thorne SA, et al. Circ 1999 (499) • 10402444	**Study type:** Retrospective multicenter **Size:** 92 pts	**Inclusion criteria:** ACHD, mean age 34.9 y, receiving amiodarone for ≥6 mo; case-control group. Mean duration 3 y, mean dose 191 mg **Exclusion criteria:** N/A	**1° endpoint:** Review side effects of chronic oral amiodarone **Results:** 36% developed thyroid dysfunction: 19 hyper, 14 hypothyroid. Sig risk factors: Female gender (OR: 3.0) cyanotic HD (OR: 7.0); Fontan (OR: 4.0); dosage >200 mg/d (OR: 4.0)	• Patients with CHD at higher risk for amio adverse effects, esp women, cyanosis, Fontan, or dose >200 mg
• Deal B, et al. AJC 1987 (500) • 3591695	**Study type:** single center retrospective	**Inclusion criteria:** TOF pts undergoing cath + EPS and drug testing Sust VT: 4	**1° endpoint:** Induction of VT in TOF, response to drug rx Mean 3.3 drugs/pt tested. Followup mean 2.2 y	• TOF EPS reproduces clinical sustained VT Pts with freq PVC's: 60% inducible sust VT

	Size: 9	PVC's: 5 **Exclusion criteria:**	**Results:** all pts with clinical sust VT had inducible sustained VT 60% pts with frequent PVC's had inducible sust VT Pts with RV hypertension did not respond to any medications 4 pts underwent surgery: no recurrent VT	Surgery to improve hemodynamics eliminated VT • Elevated RV pressure: did not respond to medicationss
• Gatzoulis MA et al. Circ 1995 (501) • 7600655	**Study type:** Single center prospective **Size:** 41	**Inclusion criteria:** TOF survivors **Exclusion criteria:** N/A	**1° endpoint:** TOF mechano-electrical interaction Mean followup 24 y **Results:** 41/178 patients evaluated serially, + reviewed 4 SCD QRS duration correlated with RV size on Echo and heart size on CXR VT 9 patients: QRS mean 199 msec, CTR 0.67; significantly different than those without VT	• TOF: QRS duration ≥ 180 msec predicts VT and SCD • All patients with documented sustained VT and patients with SCD had QRS duration ≥ 180 msec (100% sensitivity) • Chronic RV volume overload related to diastolic dysfunction
• Koyak Z et al. Circ 2012 (502) • 22991410	**Study type:** Retrospective multi-center with case-controls **Size:** 213	**Inclusion criteria:** ACHD patients in Canadian database **Exclusion criteria:** N/A	**1° endpoint:** SCD in ACHD **Results:** 1,189 deaths among 25,790 ACHD patients: 19% SCD (213 patients) Arrhythmic cause 80% SCD vs severity of congenital heart disease Mild 12%, mod 33%, severe 55%	• Risk for SCD in ACHD: SVT (OR: 3.5), mod-severe systemic ventricular dysfunction (OR: 3.4), mod-severe sub-pulmonary vent dysfunction (OR: 3.4), increased QRS duration (OR: 1.34 per 10 msec increase)
• Diller GP et al. Circ 2012 (503) • 22496160	**Study type:** Single center retrospective **Size:** 413	**Inclusion criteria:** TOF patients Mean age 36 y Median followup 2.9 y **Exclusion criteria:** N/A	**1° endpoint:** TOF: sustained VT, ACA/SCD, approp ICD shock **Results:** 4.6% sust VT/SCD/ACA (SCD 1.2%, Sustained VT, 2.2%, ICD shock 1.2%) Combination echo variables c/w poor outcome: RA area, RV fractional area change, LV global longitudinal strain, mitral annular systolic excursion	• TOF: sust VT/SCD1.2/ACA 4.6% • LV longitudinal function associated with greater risk SCD/VT
• Harrison DA et al. JACC 1997 (504) • 9350941	**Study type:** Single center retrospective **Size:** 18	**Inclusion criteria** TOF and VT, compared with 192 TOF patients without arrhythmia	**1° endpoint:** TOF and sustained VT **Results:** Patients with VT had frequent PVC's, low CI, RVOT aneurysms/PR/TR	• TOF patients with VT have anatomic aneurysms of RVOT or PR • Combined approach of correcting structural abnormalities + intra-op map-guided VT ablation may

		Exclusion criteria: N/A	14 patients reoperated: 10/14 cryoablation map-guided: recurrent VT in 3/10 Two patients with VT developed severe CHF, died.	reduce risk of deteriorating function and optimize VT management
• Knauth Al et al. Heart 2008 (505) • 17135219	**Study type:** Single center retrospective **Size:** 88	**Inclusion criteria:** TOF patients with CMR Median postop interval: 21 y **Exclusion criteria:** N/A	**1° endpoint: TOF major ACE:** death, sustained VT, NYHA Class III/IV, clinical predictors **Results:** MACE: 20.5%: death 5%, Sustained VT 10%, worsening NYHA class 11% QRS duration ≥180 msec correlated with RV size	• TOF adverse outcomes predictors: RVEDV z score ≥7, OR: 4.55 LVEF <55%, OR: 8.05 RVEF <45% QRS duration ≥180 msec
• Therrien J et al. Circ 2001 (506) • 11369690	**Study type:** cohort study **Size:** 70	**Inclusion criteria:** PVR for TOF VT preop 22% AT preop 17% **Exclusion criteria:** N/A	**1° endpoint:** Impact of PVR in TOF on QRS duration and VT, AT Mean followup 4.7 y **Results:** Cryoablation 15 patients with intraop mapping: 9 VT, 6 AFL: none had recurrence of pre-existing arrhythmia VT post PVR 9% from 22%, p<0.001 AFL/AF decreased from 17% to 12%, p=0.32	• PVR in TOF: QRS duration stabilized Concurrent cryoablation decreased incidence of VT
• Therrien J et al. AJC 2005 (507) • 15757612	**Study type:** Single center retrospective **Size:** 17	**Inclusion criteria** adult TOF undergoing pulmonary valve replacement (PVR) **Exclusion criteria:** N/A	**1° endpoint:** TOF and PVR: effect on RV volume Mean followup 21 mo **Results:** PVR decreased RV volume: RVEDV: From 163 ml/m^2–107 ml/m^2 RVESV: 109 to 69 ml/m^2 RVEF did not change: EF 32–34 Patients with RVEDV >170 ml/m^2 or RVESV >85 ml/m^2: no pt had normalization of RV volume after surgery	• TOF and PVR: Decreases RV volumes RVEF did not change • PVR before marked RV volume increase?
• Harrild DM et al. Circ 2009 (508) • 19139389	**Study type:** Single center retrospective **Size:** 98	**Inclusion criteria** TOF patients with late pulmonary valve replacement for RV dilation; matched controls with TOF, RV dilation but no PVR	**1° endpoint:** Impact of PVR in TOF on major adverse events followup median 1.4 y **Results:** Freedom from death or VT: 5 y: 80%, 10 y: 41%	• TOF with late PVR: VT or death every 20 patient-y • In matched comparison with TOF controls, PVR did not reduce the incidence of VT or death • NOTE: advanced RV enlargement, empiric cryoablation

		Median age 21 y 6% preop VT QRS duration >180 msec: 19% **Exclusion criteria:** N/A	Empiric cryoablation: 7 patients: 5/7 VT during followup Incidence death, VT, or both: 4.8/100 pt yrs All cause mortality: 6.1% No sig change in QRS duration after surgery	
• Adamson L et al. Interact CTS 2009 (509) • 19567499	**Study type:** meta-analysis medline 1950-2009 **Size:** 1070	**Inclusion criteria** PVR after TOF repair: 19 papers analyzed **Exclusion criteria:** N/A	**1° endpoint:** Effect of PVR in TOF on RV size and function **Results:** summarizes all 19 papers' conclusions	• PVR in TOF: Low mortality Reduces RV volumes RV function improves Symptoms and functional status improves
• Sabate Rotes A et al. CAE 2015 (510) • 25416756	**Study type:** Single center retrospective **Size:** 205	**Inclusion criteria:** TOF patients with late pulmonary valve replacement for RV dilation between 1988-2010 Median age 33 y Prior VT 8% LVEF <50%: 16% **Exclusion criteria:** N/A	**1° endpoint:** Impact of PVR in TOF on major adverse events: VT, SCD/ACA, appropriate ICD shock **Results:** Freedom from MACE: 5 y: 95%, 10 y: 90%, 15 y: 79% More events occurred in patients without cryoablation Cryoablation of VT: 22 patients: (11%) 1/22 event after 7 y. Empiric Cryo performed in patients with VT, inducible VT at EPS not ablated, or Hx of unexplained syncope/pre-syncope; not map-guided	• TOF and PVR: Hx of VT and LV dysfunction associated with higher risk, HR: 4.7 •QRS duration ≥180 msec predictive of arrhythmic event • Surgical cryoablation of VT may be protective Recommend patients with risk factors for VT undergo pre-or postop EPS
• Tsai SF et al. AJC 2010 (511) • 20723654	**Study type:** single center retrospective **Size:** 80	**Inclusion criteria:** ACHD patients ≥ 18y undergoing V stim Mean age 30 y **Exclusion criteria:** patients with clinical ventricular arrhythmias	**1° endpoint:** Inducible VT in ACHD patients without clinical VA **Results:** Inducible sust VT: 29% (TOF 52%, TGA 26%) Predictors: increased QRS, decreased VO2 on exercise, ventricular fibrosis on MRI ($p < .05$)	• Inducible VT: 29% • Combined fibrosis on MR and peak oxygen uptake <80% predicted had 100% sensitivity for sustained VT • Consider using MRI, ex test as screening for V stim studies

• Garson A et al. JACC 1983 (512) • 6853902	**Study type:** single center retrospective **Size:** 27	**Inclusion criteria:** TOF patients undergoing EP **Exclusion criteria:** N/A	**1° endpoint:** Induction of VT in TOF **Results:** patients with syncope had inducible sustained or non-sust VT	• TOF with inducible VT: more frequent PVC's, longer HV interval, elevated RV pressure, reduced RV EF • Poor hemodynamics correlated with VT induction
• Chandar JS et al. AJC 1990 (513) • 1689935	**Study type:** Multicenter retrospective **Size:** 359	**Inclusion criteria:** TOF patients undergoing EPS Mean age repair 5 y Mean followup 7 y **Exclusion criteria:** N/A	**1° endpoint:** Inducible VT in TOF **Results:** Induced VT correlated with delayed age at repair, longer followup, syncope, elevated RV pressure, frequent PVC's on holter	• Correlation poor hemodynamics with inducible VT
• Koyak Z et al. Circ 2012 (502) • 22991410	**Study type:** Retrospective multi-center with case-controls **Size:** 213	**Inclusion criteria:** ACHD patients in Canadian database **Exclusion criteria:** N/A	**1° endpoint:** SCD in ACHD **Results:** 1189 deaths among 25790 ACHD patients: 19% SCD (213 patients) Arrhythmic cause 80% SCD vs severity of congenital heart disease Mild: 12%, mod: 33%, severe: 55%	• Risk for SCD in ACHD: SVT (OR: 3.5) mod-severe systemic ventricular dysfunction (OR: 3.4) mod-severe sub-pulmonary vent dysfunction (OR: 3.4) increased QRS duration (OR: 1.34 per 10 msec increase)
• Kella DK et al. PCE 2014 (514) • 24889130	**Study type:** Retrospective single center **Size:** 59	**Inclusion criteria:** ICD in ACHD patients TOF 56% TGA 25% **Exclusion criteria:** N/A	**1° endpoint:** ICD outcomes in ACHD Median followup 3.2 y **Results:** 1° prevention 53% Approp ICD therapies 20% 22% inapprop shocks TOF: 27% approp shocks, non-TOF: 11% (p=0.043)	• Non-TOF patients less likely to receive appropriate shocks • ICD implantation indications should be ACHD lesion specific
• Santharam S et al. Europace 2016 (515) • 27234868	**Study type:** Retrospective single center **Size:** 42	**Inclusion criteria:** ACHD patients with ICD 2000-2014 Mean age 41 y TOF 50%, TGA 12% **Exclusion criteria:** N/A	**1° endpoint: ICD outcomes in ACHD** Mean followup 5 y **Results:** Indications: 2° prev: 62% 1° 38%. Appropriate shocks 14% Complications: 45%	• ACHD and ICD: 2.9%/y shock rate Complications 9%/y • Disease specific indications, risks must be clearly discussed • alternatives for 1° prevention ablation

• Vehmeijer JT et al. EHJ 2016 (516) • 26873095	**Study type:** Meta-analysis EMBASE, MEDLINE, Google Scholar **Size:** 2162	**Inclusion criteria:** 24 studies with 2162 ACHD patients with ICD: Mean age 36 y TOF 50% **Exclusion criteria:** N/A	**1° endpoint:** ICD implants in ACHD Mean followup 3.6 y **Results:** 1° 53%, 2° 47% Approp intervention (ATP or shock): 24%; 1° 22%, 2° 35%. Inapprop shocks 25%; Complications: 26% All-cause mortality 10%	• High rate appropriate ICD therapy in both 1° and 2° ACHD • High rates inappropriate shocks and complications • Case-by-case analysis costs/benefits essential
• Moore JP et al. CAE 2016 (517) • 27635073	**Study type:** Retrospective multi-center 7 centers **Size:** 21	**Inclusion criteria:** subcut ICD in ACHD starting 2011. Median age 33.9 y Indication: limited venous access (10), right-to-left cardiac shunt 5 **Exclusion criteria:** N/A	**1° endpoint:** Subcutaneous ICD in ACHD outcomes. Single ventricle 52%. Median followup 14 mo. **Results:** 1ary prevention: 67%, 2ary 33%. Implant: VT induced 81%, converted ≤ 80 joules in all. Infection: 1 (5%); Shocks: inapprop 21%, appropriate 1 (5%). One death due to asystole.	• Subcut ICD feasible in ACHD, most commonly single ventricle patients with limited venous access • Successful conversion of induced VT • "reasonable" rhythm discrimination
• Okamura H et al. Circ J 2016 (518) • 27109124	**Study type:** Retrospective single center **Size:** 100	**Inclusion criteria:** ACHD patients undergong screening for subcutaneous ICD Mean age 48 y **Exclusion criteria:** N/A	**1° endpoint:** screening for suitability for subcutaneous ICD use in ACHD patients **Results:** Left parasternal: failure 21%, reduced to 12% using right parasternal.	• for use of subcutaneous ICD in ACHD, screening of left and right parasternal position may improve; QT interval and T wave inversion V2-V6 independent predictors of left parasternal screening.
• Yap SC et al. EHJ 2007 (519) • 17030523	**Study type:** Multicenter retrospective, Dutch national registry **Size:** 64	**Inclusion criteria:** ACHD patients ≥18 y receiving ICD Mean age 37±13 y 2° prevention 60% **Exclusion criteria:**	**1° endpoint:** ICD outcomes in ACHD patients: median followup 3.7 y **Results:** Early comps 13%, late 17% Approp shocks 23%, inapprop 41% -mainly SVT. TOF fewer approp shocks vs other congenital heart disease, HR 0.29	• ACHD Appropriate shocks 6%/yr, no difference in 1° or 2° prevention • Inappropriate shocks 41%
• Khairy P et al. Circ 2004 (520) • 15051640	**Study type:** Multicenter cohort **Size:** 252	**Inclusion criteria:** TOF patients undergoing V stim followup 6.5 y **Exclusion criteria:** N/A	**1° endpoint:** TOF: correlate V stim with outcomes **Results:** sust monomorphic VT 30%, polymorphic VT 4.4% Independent risk factors: age ≥18 y (OR: 3.3), palpitations (OR: 2.8), frequent PVCs (OR: 5.6), CT ratio ≥0.6, prior shunt (OR: 3.1)	• Multivariate analysis: inducible sustained VT independent risk for subsequent clinical VT or SCD (RR: 4.7)

				• Older age, prior shunts, frequent PVC's, cardiomegaly—increased likelihood of inducible VT
• Khairy P et al. Circ 2008 (521) • 18172030	**Study type:** Retrospective multicenter, 11 sites **Size:** 121	**Inclusion criteria:** TOF patients receiving ICD Median age 33 y **Exclusion criteria:** N/A	**1° endpoint:** TOF ICD outcomes Median followup 3.7 y **Results:** 2° prevention: 44% Comps: total 30%, 5% early Approp shocks: 30% Annual rate approp: 1° 7.7%, 2° 9.8% (p=0.11)	• TOF ICD shocks annual rate 7.7–9.8%, approx. equal for 1° and 2° prevention • Approp shocks: elevated EDP (HR: 1.3), nonsust VT (HR: 3.7) • Inappropriate shocks 5.8%/y • Comps 30%: 21% leads, 6% generator
• Zeppenfeld K et al. Circ 2007 (522) • 17967973	**Study type:** Single center retrospective **Size:** 11	**Inclusion criteria:** repaired congenital heart disease patients with sustained VT, undergoing voltage map, ablation **Exclusion criteria:** N/A	**1° endpoint:** Ablation of VT in congenital heart disease followup 30 mo **Results:** SR voltage map, identify scar: anatomic isthmus: between TV-RVOT, pulm annulus and RV free wall, pulm annulus and septal scar, septal scar and TV Ablation of isthmus (most common between TV and anterior RVOT) abolished all 15 VT circuits.	• VT ablation of anatomic isthmus successful: 91% without recurrence during 30 mo followup
• van Zyl M et al. HR 2016 (523) • 26961296	**Study type:** single center retrospective **Size:** 21	**Inclusion criteria:** repaired congenital heart disease patients with VT undergoing ablation Mean age 45 y 71% males **Exclusion criteria:** N/A	**1° endpoint:** outcome VT ablation in congenital heart disease: SCD or appropriate ICD shock Mean followup 33 mo **Results:** Reentrant VT 67%, Focal 33% Isthmus dependent VT mechanism in 67%, conduction block confirmed in 8	• VT ablation in ACDH: reentrant VT targets anatomic isthmus: with confirmed block, no recurrent VT
• Kapel GF et a. CAE 2014 (524) • 25151630	**Study type:** Retrospective, 2 centers **Size:** 28	**Inclusion criteria:** TOF patients with VT ablation **Exclusion criteria:** N/A	**1° endpoint:** TOF VT ablation in LV outcomes **Results:** Left sided mapping/ablation if right side RFA failed, part of circuit in LV 4/28 VT ablations used LV approach Target anatomic isthmus with transection	• TOF VT ablation in LV successful in 4 patients: no recurrence during 20 mos • Rt side failure: septal hypertrophy 2, pulmonary homograft 1, VSD patch 1

• Kapel GF, et al. Circ AE 2015 (525) • 25422392	**Study type:** 2 centers, retrospective **Size**: 34	**Inclusion criteria:** repaired CHD pts undergoing ablation Mean age 48 y 74% male TOF 82% TGA; VSD, AVSD, PS Sustained VT 79% **Exclusion criteria:** N/A	**1° endpoint:** Ablation of VT in CHD followup 46 mo. 41% prior ICD **Results:** complete success 25/34 pts: 74%; 18/25 had preserved fxn Procedural failure: hypertrophy, pulm homograft, prox to HBE, no critical reentry 79% discharged with ICD 15/18 complete success + preserved function d/c on no AAD—no recurrences 4 late deaths, 2 CHF, 2 CA	• Predictors of lack of success: No complete procedural success, decreased LV function • Transection of VT isthmus feasible in 74%
• Kapel GF et al. EHJ 2017 (526) • 27233946	**Study type:** Single center **Size:** 74	**Inclusion criteria:** repaired TOF patients with VT induction/mapping 63% male Mean age 40 y **Exclusion criteria:** N/A	**1° endpoint:** TOF VT isthmus identification **Results:** slow conducting anatomic isthmus identified by electroanatomical mapping: targeted for ablation 28 patients with inducible VT. Ablation in 18 of isthmus	• TOF VT: slow conducting anatomic isthmus is dominant substrate
• Khairy P et al. CAE 2008 (527) • 19808416	**Study type:** Retrospective multicenter, 7 sites **Size:** 37	**Inclusion criteria:** TGA s/p atrial baffle with ICD Mean age 28 y, 89% male **Exclusion criteria:** N/A	**1° endpoint:** TGA s/p atrial baffle ICD outcomes **Results:** 2° prevention: 38% Annual rates approp shocks: 1° 0.5%, 2° 6% Independent predictors: 2° prevention, lack of BB Approp shocks: None with inducible VT; 37% of patients without inducible VT (p=0.043) Comps 38%, 33% lead, 3% generator	• TGA s/p atrial baffle: ICD appropriate shocks mainly in patients with 2° prevention, (HR: 18; p=0.034) and lack of BB, (HR: 16.7; p=0.03) • SVT preceded VT in 50% of approp shocks • Inducible VT did not predict appropriate shock treatment in TGA • Protective effect of BB
• Tutarel O et al. Eur H J 2014 (528) • 23882067	**Study type:** retrospective cohort, Royal Brompton **Size:** 375	**Inclusion criteria:** ACHD patients ≥60 y at entry, followed 1/2000-3/2012, mean age 65 y, median followup 5.5 y **Exclusion criteria:** N/A	**1° endpoint:** all-cause mortality ACHD **Results:** 14.6% died (55/375) Cardiac deaths: 40% CHF, CAD Independent predictors mortality: CAD (HR: 5.05); CHF (HR: 2.36); NYHA class (HR: 1.96); mod-severe systemic vent dysfunction (HR: 1.90)	• 9-fold (864%) increase in ACHD patients >60 y between 2000 and 2011

• Koyak Z et al. Europace 2017 (529) • 27247006	**Study type:** Multicenter case-control: CONCOR, Toronto, Leuven **Size:** 25,000	**Inclusion criteria:** ACHD; age matched controls; mean followup 7 y **Exclusion criteria:** N/A	**1° endpoint: SCD in ACHD** **Results:** 131 SCD, mean age 36±14 y Increased risk: increase in QRS duration ≥5 ms/y (OR: 1.9), change in systemic vent fxn to severe (OR: 16.9; 95% CI: 1.8–120.1, p=0.008)	• Increased risk SCD: severe ventricular dysfunction, increase QRS duration ≥5 ms/y
• Engelfriet P et al. EHJ 2005 (530) • 15996978	**Study type:** multicenter retrospective **Size:** 4110	**Inclusion criteria:** ACHD patients in Europe: ASD, VSD, TOF, coA, TGA, Marfan, Fontan, cyanotic **Exclusion criteria:** 8 lesions included	**1° endpoint: ACHD morbidity** Median followup 5 y **Results:** Ventricular arrhythmias: TOF 14%, cyanotic 6%, VSD 3%, others 2% except Fontan: 0 SVT: Fontan 45%, ASD 28%, TGA 26%, TOF 20%, cyanotic 16% Endocarditis: VSD 7%, cyanotic 6%, TOF 4%, others 0-2%	• VEA highest in TOF 14%; Cyanotic 6%, VSD 3%,
• Gallego P et al. AJC 2012 (531) • 22464215	**Study type:** single center retrospective **Size:** 22	**Inclusion criteria:** 936 ACHD patients followed single center 8387 patient-y of followup **Exclusion criteria:** N/A	**1° endpoint:** Causes SC arrest in ACHD **Results:** SCA 2.6/1000 pt y SCA occurred in 23% of severe subaortic ventricular dysfunction, vs 0.7% with nonsevere dysfunction, p<0.001 80% of SCA occurred in TGA, UVH, coarctation, TOF	• Highest SCA: TGA 10/1000 UVH, coarctation, TOF • Severe subaortic ventricular dysfunction (HR: 29)
• Engelings CC et al. Int J Cardiol 2016 (532) • 26970963	**Study type:** National cohort **Size:** 2596	**Inclusion criteria:** ACHD patients >18 y, mean followup 3.7 y; between 1/01-1/15 **Exclusion criteria:** N/A	**1° endpoint:** Identify cause of death in ACHD **Results:** 239 deaths, 9.2%, mean age 39.8±17.8 y Related to Cong HD: 72%: CHF 28%, SCD 23% Leading causes: CHF-UVH, TGA SCD: Eisenmenger, TOF, Marfan, AS Comparing 2001-2008 with 2009-2015: CHF increased from 23-30%, SCD decreased from 29-20%	• Leading causes of cardiac death: CHF 28%, Sudden 23% • Sudden death highest: Marfan's, AS, Eisenmenger syndrome, cc TGA, TGA, TOF, VSD, UVH • AICD under-utilized

• Fish FA (533) • JACC 1992 • 1906902	**Study type:** Retrospective multi-center **Size:** 124 (entire study, 579)	**Inclusion criteria:** Use of class Ic AA meds in 124/579 young patients with VA Flecainide 103, encainide 21 **Exclusion criteria:** N/A	**1° endpoint:** Adverse events during treatment with flecainide or encainide for VA: Pro-arrhythmia, CA/SD **Results: Flecainide**: Pro-arrhythmia: 5.8%, CA 3.9%, sudden death4.9% Encainide: pro-arrhythmia 9.5%, CA 9.5%, sudden death9.5% Efficacy 71-76% 10 patients CA/Death: most on flecainide	• Deaths 5.6%, CA 4.8%, pro-arrhythmia 6.4% for patients treatment for VA with either flecainide or encainide • for SVT patients, risk higher if structural HD, not for VT
• Stan MN et al., 2014 (534) • 22518347	Retrospective single center 23	ACHD patients developing amio-induced thyrotoxicosis after ≥ 3 mos amio, Mayo Clinic 1987-2009; median followup3.1 yrs.	**1° endpoint:** Identify incidence and risk factors amio **Results:** Thyrotoxicosis13.6% (23/169) ACHD patients developed amio thryrotoxicosis.	•Highest Risk: low BMI <21, cyanotic HD
• Silka MJ et al. JACC 1998 (535) • 9669277	**Study type:** Retrospective statewide registry **Size:** 41	**Inclusion criteria:** congenital heart disease surgery in Oregon 1958-1996 3589 patients **Exclusion criteria:** single ventricle not included	**1° endpoint:** Population based risk of SCD in congenital heart disease **Results:** SCD 1/1118 patient-y 37/41 late sudden deathoccurred in 4 lesions Causes SCD: arrhythmia 75%, CHF 10%, other cardiac 17% (embolic, aneurysm rupture)	• Late SCD: 4 lesions: 1/454 patient-y Aortic stenosis Coarctation TGA TOF • Cause SCD: arrhythmia 75%, CHF 10%
• Oechslin EN et al. AJC 2000 (536) • 11074209	**Study type:** single center retrospective **Size:** 197	**Inclusion criteria:** ACHD patients followed Toronto, 2609 adults **Exclusion criteria:** N/A	**1° endpoint:** Mortality causes in ACHD **Results:** Mean age death 37 y Causes: sudden 26%, CHF 21%, periop 18% Youngest age at death: TGA, tricuspid atresia, PA, aortic coarc <30 y >50 y; ASD, PDA	• Highest mortality lesions congenital heart disease: univentricular 41%; ccTGA 26%, TOF or PA 16%, Ebstein 9% AVSD 7%,
• Nieminen HP et al. JACC 2007 (537)	**Study type:** National	**Inclusion criteria:** Finland national registry of congenital	**1° endpoint:** Causes of death in ACHD during 45 y followup	• Causes of late death in congenital heart disease: cardiac 67%: CHF

• 17888844	registry, retrospective **Size:** 592	heart disease, 6024 patients surviving first operation **Exclusion criteria:** N/A	**Results:** 45 y survival 89%, lower than gen population Highest risk CD: TGA, UVH, TOF, VSD Other CVD: stroke, arrhythmia, pulm emboli, endocarditis, aortic rupture Increased non-cardiac mortality	40%, periop 26%, SCD 22% other CV 12% • Highest risk of SCD: coA 42%, TOF and TGA: 30% • Increased non-cardiac death 2 fold: neurologic, respiratory
• Verheugt C et al. IJC 2008 (538) • 18687485	**Study type:** Meta-analysis MEDLINE 1980-2007 **Size:** 7894	**Inclusion criteria:** ASD, VSD, PS, TOF, coarctation, TGA **Exclusion criteria:** univentricular heart	**1° endpoint:** Complications in ACHD **Results:** Vent arrhythmias: TOF 14%, VSD 2.9%, TGA 1.9% SVT: TGA 26%, ASD 28%TOF 20% Summarizes endocarditis, CHF, CVA, MI, SVT by lesion	• Ventricular arrhythmias overall 7%, highest TOF 14% • MI highest" coarctation 5% • SVT: all lesions: 18%
• Pillutla P et al. AHJ 2009 (539) • 19853711	**Study type:** CDC registry causes of death **Size:**	**Inclusion criteria:** CDC registry 1979-2005, congenital heart disease in USA **Exclusion criteria:** N/A	**1° endpoint:** ACHD death trends **Results:** Cyanotic lesions: arrhythmia, then HF Non-cyanotic lesions, MI after 1990, arrhythmia prior to 1990	• Decline in mortality among TGA, TOF • MI leading cause of death in patients with non=cyanotic lesions
• Verheugt CL et al. EHJ 2010 (540) • 20207625	**Study type:** Dutch CONCOR national registry, retrospective **Size:** 197	**Inclusion criteria:** 6933 ACHD patients: 197 deaths: 2.8% **Exclusion criteria:** N/A	**1° endpoint:** ACHD causes of death **Results:** Median age death 49 yrs 77% CV cause: CHF 26% age 51 yrs, sudden death19% age 38 yrs Ventricular arrhythmias predicted SCD, HR 1.5 SVT and VT predicted CHF, HR 5.1 and 4.5 *See complications by lesion analysis!*	• Lesions with highest mortality: Univentricular heart 25%, DORV + TOF 13% ccTGA 6% Ebstein 5% AVSD 5% TGA 3%
• Zomer AC et al. IJC 2012 (541) • 20934226	**Study type:** Retrospective national registry **Size:** 231	**Inclusion criteria:** causes of death in ACHD patients **Exclusion criteria:** N/A	**1° endpoint:** ACHD causes of death Total followup 26,500 pt y **Results:** Median age at death 48 y Causes of death: CHF 26%, SCD 22%, malignancy 9%, pneumonia 4% SCD exercise 8%, Lower risk-ASD 3%, VSD 1.3%, AS 1% Youngest age: TGA 33 y, AVSD 37 y, ASD age 61 y	• SCD: 10% with exertion • Highest mortality: univentricular hearts 26%, TOF/DORV/PA 20%, TGA and cc TGA 10%, AVSD 6%, Ebstein 6%,

• Diller GP et al. Circ 2015 (542) • 26369353	**Study type:** Single center cohort **Size:** 6969	**Inclusion criteria:** ACHD patients followed 1991-2013, median followup 9.1 yrs **Exclusion criteria:** N/A	**1° endpoint:** Cause of death ACHD compared with general age/gender matched, calculate SMR (standardized mortality ratio) **Results:** 7.7% died, 0.72%/pt y Leading causes: CHF 42%, pneumonia 10%, **SCD 7%,** cancer 6%, hemorrhage 5% SCD highest: TGA arterial switch 33%, AVSD 14%, Fontan and single RV 13% each, complex congenital heart disease 11%, Eisenmenger 9%, TOF 6%	• Highest mortality: Eisenmenger, complex congenital heart disease, UVH • SMR, p<0.001: Fontan: 23.4, Complex congenital heart disease 14.1, Eisenmenger 12.8, systemic RV 4.9, Ebstein 3.3, TGA arterial switch 2.6 (0.08), TOF 2.3, Marfan 2.2, coarctation 1.7
• Raissadati A et al. JACC 2016 (543) • 27470457	**Study type:** Nationwide cohort study, Finland **Size:** 10,964	**Inclusion criteria:** Patients undergoing cardiac surgery <15 y old between 1953-2009 **Exclusion criteria:** N/A	**1° endpoint:** ACHD Late mortality causes **Results:** early mortality 5.6%; late 10.4% congenital heart disease related deaths: 6.6%: causes-CHF 28%, reop 14%, SCD 13%, other CV 8% Sudden deaths: arrhythmia/unknown 78%, MI 7%, aortic dissection 5% Sudden death ages: ASD 40 y, TOF 30 y, coarc 29 y, Cancer higher than general population, especially females, (RR: 5.9)	• Late 40 yr survival: simple defects 87%, complex 65% • 40 y freedom sudden death: 99% simple, 91% severe, (HR: 9.9) Highest CV mortality: UVH, TGA, TOF, VSD, coarc • Increased lung, neuro, infectious diseases
• Teuwen CP et al. IJC 2016 (544) • 26805391	**Study type:** retrospective cohort **Size:** 145	**Inclusion criteria:** **ACHD** patients with VA: Nonsust VT 71% Sustained VT 17% VF 12% **Exclusion criteria:** N/A	**1° endpoint:** ACHD Non-sustained VT: risk for sustained VT/VF Mean age 40±14 y **Results:** 5/103 nonsust VT patients developed sustained VT/VF	• Sustained VT/VF developed rarely in patients with only non-sust VT • Recurrent sust VT/VF frequent in patients presenting with sust VT/VF • recommend "wait and see approach" for nonsust VT; aggressive treatment for sust VT/VF

• Wells R et al. 2009 (545) • 19691680	**Study type:** Retrospective multicenter **Size:** 20 patients	**Inclusion criteria:** ACHD, mean age 34.9 y, receiving amiodarone for ≥6 mo; case-control group. Mean duration 3 y, mean dose 191 mg **Exclusion criteria:** N/A	Review side effects of chronic oral amio 36% developed thyroid dysfunction: 19 hyper, 14 hypothyroid. Sig risk factors: Female gender (OR: 3.0) cyanotic HD (OR: 7.0); Fontan (OR: 4.0); dosage >200 mg/d (OR: 4.0)	Patients with congenital heart disease at higher risk for amio adverse effects, esp women, cyanosis, Fontan, or dose >200 mg
• Afilalo J et al. JACC 2011 (546) • 21939837	**Study type:** Quebec database 1993-2005 **Size:** 3239	**Inclusion criteria:** ACHD patients ≥65 y old at entry, followed up to 15 y **Exclusion criteria:** N/A	**1° endpoint:** all-cause mortality ACHD **Results:** most common types congenital heart disease: shunt lesions 60%, valvar 37%, severe 3% Arrhythmias present: AF 25%, Ventricular arrhythmias 3–4% Mortality driven by co-morbidity: dementia (HR: 3.24), GI bleed (HR: 2.79), chronic kidney disease (HR: 2.5); CHF (HR: 1.98), diabetes (HR: 1.76), COPD (HR: 1.67)	• Current ACHd populations surviving to age 65 y or greater, co-morbid diseases most powerful predictors of mortality; increased CAD 7% vs 5% age matched • Ventricular arrhythmias present in 3–4% • Prevalence ACHD in geriatrics: 3.7 /1000 (vs 4.2/1000 in non-geriatric)
• El Malti R et al. EJ Human Genetics 2016 (547) • 26014430	**Study type: retrospective** **Size:** 154	**Inclusion criteria:** familial congenital heart disease genetic screening **Exclusion criteria:** N/A	**1° endpoint:** Screening congenital heart disease for FATA4, NKX2.5, ZIC3 **Results:** 10.4% identified with causal gene NKX2.5 identified in ASD/VSD and conduction disorders; 6/154, 3.9% ZIC3 1.9%, GATA4, 0.7%	• Familial AV block/ASD correlated with NKX2.5 • Can be used to screen high risk SCD families
• Abou Hassan OK et al. Sci Rep 2015 (548) • 25742962	**Study type:** retrospective **Size:** 188	**Inclusion criteria:** congenital heart disease in Lebanon: high incidence of cosanguinity **Exclusion criteria:** N/A	**1° endpoint:** Screening NKX 2.5 gene defect in congenital heart disease **Results:** Familial ASD: 60% with NKX 2.5 Diversity of phenotypes: congenital heart disease, AV block, SCD, coronary sinus disease	• Familial septal defects and conduction disorders: high prevalence NKX2.5, SCD
• Ellesoe SG et al. CHD 2016 (549) • 26679770	**Study type:** **Size:** 39	**Inclusion criteria:** Probands with familial	**1° endpoint:** NKX 2.5 occurrence in familial congenital heart disease	• Screen familial ASD patients for NKX 2.5, esp if conduction disorders

		congenital heart disease **Exclusion criteria:** N/A	**Results:** NKX 2.5 found 2.5% of probands	
• Cuypers JA et al. Heart 2013 (550) • 23886606	**Study type:** Longitudinal cohort **Size:** 135	**Inclusion criteria:** ASD surgical repair 1968-1990 **Exclusion criteria:** N/A	**1° endpoint:** ASD surgical repair long-term **outcomes** Mean Followup 35 y **Results:** SVT: 16%, late SCD 1.5% Pacemaker 6%. LVEF 58%, RVEF 51%. Low RVEF 31%, **d**ilated RV 20%	• Surgical repair ASD: late SCD 1.5%
• Kuijpers JM et al. EHJ 2015 (551) • 25883174	**Study type:** Dutch national registry **Size:** 2207	**Inclusion criteria: ASD secundum** in Dutch registry Mean age 45 y Males 33% **Exclusion criteria:** N/A	**1° endpoint:** ASD secundum outcomes: gender differences Cumulative followup 13584 pt-y **Results:** Median survival: men 79.7 y, women 85.6 y. Compared w age/sex matched gen pop, survival for males lower; equal for females.	• ASD secundum outcomes: males higher risk conduction disturbances, SVT, CVA, CHF; decreased life expectancy c/w general population
• Khairy P et al. Circ 2010 (552) • 20713900	**Study type:** Retrospective multi-center **Size:** 556	**Inclusion criteria:** TOF repair Female 54% Mean age 37 y **Exclusion criteria:** N/A	**1° endpoint:** TOF arrhythmia outcomes & correlates **Results:** Sustained arrhythmia: 43%. Prevalence AT 20%: RAE, HTN, number of surgeries ventricular 14.6%: number of surgeries, QRS duration, LV diastolic dysfunction (OR: 3.3)	• TOF Ventricular arrhythmias 15%, increased with LV diastolic dysfunction • AF and Vent arrhythmias increased after age 45 y
• Valente AM et al. Heart 2014 (553) • 24179163	**Study type:** Prospective multi-center **INDICATOR** cohort **Size:** 873	**Inclusion criteria**: TOF adults Median age 24 y **Exclusion criteria:** N/A	**1° endpoint:** TOF risk factors death, VT **Results:** 3.7% death/VT, median age 38 y Cos regression outcomes predictors: RV mass/volume ratio ≥0.3, (HR: 5.04) LVEF z score <2, (HR: 3.34) AT, (HR: 3.65)	• TOF predictors SCD, VT: RVH, ventricular dysfunction (RV or LV), and AT Higher RV systolic pressure, HR 1.39

• Arya S et al. CHD 2014 (554) • 24314315	**Study type:** Retrospective single center **Size:** 109	**Inclusion criteria:** TOF Late followup Male 49% Ages 17-58 y **Exclusion criteria:** N/A	**1° endpoint:** TOF outcomes: risk changing? **Results:** Arrhythmias 54%: older postop interval, wide QRS mean 158 msec. No correlation with surgical era, gender RV pressure, RVOT gradient, RVEDV	• TOF late SCD: 1.8%
• Wu MH et al. HR 2015 (555) • 25461497	**Study type:** National database Taiwan retrospective (national health insurance! Easily accessible care!) **Size:** 4781	**Inclusion criteria:** TOF repair Taiwan; database those born 2000-2010 reviewed for late outcomes 58% males **Exclusion criteria:** N/A	**1° endpoint:** TOF late arrhythmia outcomes **Results:** Prevalence TOF in adults 0.06/1000 Survival 10 y: 78% Arrhythmias 4.6%: 73% tachycardia Overall tachycardia: 3.3% (6.6% adults, 1.8% peds). AF 29%. AVB 0.6% SVT/AT/AFL/AF = 80%, VT 18%, VF 3% Mortality with VT: 24%, VF 60%.	• TOF tachycardia in adults: 6.6%: VT 18%, VF 3%, • Median age VT/VF 23–25 y • Interventions for tachycardia 2.4% annually, adults
• Heng EL et al. Heart 2015 (298) • 25351509	**Study type:** Single center prospective **Size:** 90	**Inclusion criteria:** TOF patients with age/gender matched controls. BNP 1pmol/L = 3.472 pg/ml **Exclusion criteria:** N/A	**1° endpoint:** TOF outcomes and biomarkers Median followup 10 y Measured aldosterone, ANP, BNP, renin, endothelin **Results:** Late deaths: 9% BNP ≥15 pmol/L: increased mortality (HR: 5.4), sustained VT, (HR: 2.06)	• TOF: BNP level ≥15 pmol/L associated with 5 fold increased risk death • Incorporate BNP into risk stratification
• Drago F et al. IJC 2016 (556) • 27505328	**Study type:** Retrospective single center **Size:** 146	**Inclusion criteria:** **Exclusion criteria:**	**1° endpoint:** TOF voltage mapping of ventricular endocardium **Results:** 97% with scar in RVOT. Total scar extension c/w: QRS ≥180 ms, LV and RV dysfunction, PVC, prior shunt, re-intervention, duration of post surgical followup	• TOF scar extension correlates with risk factors for life-threatening arrhythmias
• Kriebel T et al. JACC 2007 (557) • 18036455	**Study type:** single center retrospective **Size:** 10	**Inclusion criteria:** repaired TOF patients with VT undergoing ablation Males 75%; Age 52 y	**1° endpoint:** TOF patients undergoing ablation, contact mapping, RF ablation **Results:** 13 VT circuits, 2 focal ICD pre in 2, recommended post in all	• TOF VT Ablation acute success 100% (8 patients) • Recurrence 25% in 35 mo

		Exclusion criteria: N/A		
• Witte KK et al. Europace 2008 (558) • 18442962	**Study type:** single center retrospective **Size:** 20	**Inclusion criteria:** TOF patients with ICD compared with dilated CM **Exclusion criteria:**	**1° endpoint:** TOF patients with ICD vs dilated CM **Results:** TOF appropr shocks 25%; inapprop 20%	• TOF patients: higher risk inapprop shocks 25% vs 4%, • Death rate for TOF 5%, < DCM, 21%
• Lange R et al. Circ 2006 (559) • 17060385	**Study type:** Single center retrospective **Size:** 417	**Inclusion criteria:** TGA with atrial repair: Senning 79% Mustard 21% **Exclusion criteria:** N/A	**1° endpoint:** TGA atrial switch outcomes. Mean followup 19 y **Results:** 25 y survival: Mustard 76%, Senning 91% (p=0.002) Mustard: die more often of arrhythmia (p<0.001), reop baffles (p<0.0001); Independent risk SCD: VSD closure (HR: 2.3), Mustard (HR: 2.0)	• TGA atrial baffle risk factors SCD: Prior VSD closure, Mustard repair
• Schwerzmann M et al. EHJ 2009 (560) • 19465439	**Study type:** Single center retrospective **Size:** 149	**Inclusion criteria:** TGA s/p Mustard repair Mean age 28 y **Exclusion criteria:** N/A	**1° endpoint:** TGA s/p Mustard outcomes Mean followup 9 y **Results:** Sustained VT/SCD 9%: risk factors: Associated anatomic lesion (HR: 4.9), NYHA ≥ III (HR: 9.8), impaired subaortic RVEF (HR: 2.2) AT 44%, not predictor of VT/SCD (HR: 2.7; 95% CI: 0.6–13)	• TGA s/p Mustard: late SCD or sustained VT: 9% • QRS duration ≥140 msec highest risk sVT/SCD (HR: 13.6; 95% CI: 2.9–63.4)
• Wheeler M et al. CHD 2014 (561) • 24151816	**Study type:** Single center retrospective **Size:** 89	**Inclusion criteria:** TGA patients, s/p atrial switch, Mustard or Senning **Exclusion criteria:** N/A	**1° endpoint:** TGA atrial switch late outcomes **Results:** SCD 5.6% ICD 5.6% 1° prevention: no appropriate therapy Patients with SCD: all with AT vs 29% AT in survivors	• TGA s/p atrial switch: 1° prevention ICD-no appropriate rx • Higher risk: older age at surgery, presence of AT, earlier era of surgery

• Bouzeman A et al. IJC 2014 (562) • 25499397	**Study type:** Retrospective multicenter, **Size:** 12	**Inclusion criteria:** TGA s/p atrial switch with ICD Median age 34 y **Exclusion criteria:** N/A	**1° endpoint:** TGA atrial switch and ICD outcomes Median followup 19 mo **Results:** 2° prevention 33%; Implant: one death during DFT (8%) All patients with severe vent dysfunction; 54% worsening CHF, 5/11 (45%) transplanted. 50% sustained AT during followup	• TGA atrial switch and ICD: • 9% appropriate therapy (1 pt, 1° prevention, successful ATP without shock) •complications: 27% • HF determines outcomes
• Buber J et al. Europace 2016 (563) • 26705566	**Study type:** Retrospective single center **Size:** 18	**Inclusion criteria:** TGA s/p atrial switch with ICD implanted for 1° prevention Median age 26 y **Exclusion criteria:** N/A	**1° endpoint:** TGA s/p atrial switch: ICD outcomes Median followup 4 y **Results:** EPS performed 72%: sust VT 54%, AFL 31%. VT inducibility did not predict appropriate shock. One pt received shock for VT; 39% for SVT, Inappropriate shocks: 61%, mainly SVT/AFL	• AT most common cause for ICD shocks in 1° prevention TGA s/p atrial switch • NOT predictive: VT inducibility, QRS duration, age • 50% complications
• Backhoff D et al. PCE 2016 (564) • 27503213	**Study type:** Retrospective multicenter, 4 German centers **Size:** 33	**Inclusion criteria:** TGA s/p atrial switch with ICD. Median age 27 y, 85% male. **Exclusion criteria:** N/A	**1° endpoint:** TGA s/p atrial switch: ICD rx Median followup 4.8 y **Results:** 2° prev 12%. Shocks: Approp 9%, inapprop 24% Annual incidence approp rx: 1.9%/pt/yr. Inducible VT/VF: no approp shock 2° prev: no approp shock No predictors of approp rx	• TGA s/p atrial switch: low rate of appropriate ICD shocks 9% <<<inapprop shocks 24% • AT main cause of inappropriate shocks • Vigorous treatment of AT, careful ICD programming (inactivation VT zone, program VF zone 220-230 bpm) • Complications 21%
• Pundi KN et al. CHD 2016 (565) • 27545004	**Study type:** Retrospective single center **Size:** 996	**Inclusion criteria:** Fontan patients operated at Mayo 1973-2012, with questionnaire sent **Exclusion criteria:** arrhythmia prior to Fontan surgery	**1° endpoint:** Fontan arrhythmia outcomes **Results:** Freedom from arrhythmia requiring treatment: 10 y: 71%; 20 y: 42%; 30 y 24%. AFL /AT 48%, AF 19%, SVT AC /AVN 4%, VT 5%, SND 13%. Predictors arrhythmia: AP Fontan, age at surgery >16 y, AT postoperatively.	• Fontan late outcomes: 5% VT, 5% late SCD • Risk factors: arrhythmias (65%), AVV replacement, post bypass Fontan pressure >20 mm Hg •Preop sinus rhythm was protective

• Sakamoto T et al. Asian CVTS 2016 (566) • 27563102	**Study type:** Retrospective single center **Size:** 40	**Inclusion criteria:** Fontan patients operated 1974-1986 Surgery: AP 70%, RA-RV 25% **Exclusion criteria:** N/A	**1° endpoint:** Late outcomes Fontan 20/40 (50%) died **Results:** Causes of death in 20 patients: CHF 30%, SCD 20%, arrhythmia 20%, other 30%	• Late SCD in Fontan: 10% overall • Timely conversion of AP Fontan, medication to decrease ventricular volume and pressure load needed
• Alexander ME et al. JCE 1999 (567) • 10466482	**Study type:** single center **Size:** 130	**Inclusion criteria:** congenital heart disease patients undergoing V-stim TOF 33%, TGA 25%, LVOT lesions 12% Median age 18 y **Exclusion criteria:** N/A	**1° endpoint:** Sustained VT inducibility in congenital heart disease **Results:** Sust VT inducible 25% Non-sust VT 12%, AFL or SVT: 32%	• Positive V stim correlated decreased survival (HR: 6), arrhythmic events (HR: 3) • Patients with documented clinical VT: 33% negative V stim—frequent false negative
• Silka MJ et al. Circ 1993 (568) • 8443901	**Study type:** Multicenter retrospective **Size:** 125	**Inclusion criteria:** 177 patients age <20 y undergoing ICD; 125 with data available. Mean age 14.5 y Cardiomyopathy 54%, electrical 26%, congenital heart disease 18% **Exclusion criteria:** N/A	**1° endpoint:** ICD outcomes in younger patients Mean followup 2.6 y **Results:** 2°: ACA 76%, refractory VT 10%. 1°: Syncope with HD and inducible sustained VT: 10% Shocks: appropriate 68% of patients, inapprop 20%. 5 late SCD. Predictors late mortality: abnormal vent fxn	• Early ICD study: 2° prevention 86% • 5 y survival: 85% SCD free survival 5 yrs: 90%
• Berul CI et al. JACC 2008 (569) • 18436121	**Study type:** Multicenter retrospective **Size:** 443	**Inclusion criteria:** Pediatric and congenital heart disease patients receiving ICD in 4 centers 1992-2004 Median age 16 y; 69% structural HD: TOF 19%, HCM 14%	**1° endpoint:** ICD comps & therapies young Mean followup 7.5 y **Results:** 2° prev 48% Comps: early 14%, late 29%, electrical storm 5% Appropriate shocks 26%, inapprop 21%--higher in electrical disease (31%) vs cardiomyopathy (13%), congenital heart disease (28%) SCD 1%	• ICD in young patients: high inappropriate shocks 28% in congenital heart disease • Complications 43%

		Electrical 31% **Exclusion criteria:** N/A		
• Khanna AD et al. AJC 2011 (570) • 21684513	**Study type:** Retrospective single center, Mayo **Size:** 73	**Inclusion criteria:** ACHD patients with ICD TOF 44% cc-TGA 17% **Exclusion criteria:** N/A	**1° endpoint:** ACHD patients with ICD outcomes Mean followup 2.2 y **Results:** 1° prevention 64% Approp shock 19%, inapprop 15%	• Appropriate ICD shock more likely in patients with elevated subpulmonary pressure
• Koyak Z et al. CAE 2012 (571) • 22095638	**Study type:** Multicenter retrospective 10 centers Netherlands, Belgium **Size:** 136	**Inclusion criteria:** ACHD patients receiving ICD Mean age 41 y TOF 51%, Septal defect 20%, ccTGA 13% **Exclusion criteria:** N/A	**1° endpoint:** ACHD ICD approp shock risk score. Median followup 4.6 y **Results:** 2° prevention 50% Shocks: approp 29%, inapprop 30%, (SVT 69%) Comps 29% 63% underwent PES: 73% inducible sust VT/pmVT, VF: no difference in appropriate shocks: 33% with induc VT, 32% w/out In 1° prev patients, univariable risks symptomatic nonsust VT HR: 8; 95% CI: 2.3–27.1, p=0.001 and subpulmonary ventricular dysfunction, HR: 3.0; 95% CI: 1.2–12.6, p=0.02	• Appropriate shocks for ACHD: 2° prevention, (HR: 3.6) CAD, (HR: 2.7), and symptomatic nonsust VT (HR: 9.1) • High morbidity with ICD • No assoc between ICD treatment and QRS duration • Inducible sustained VT did not correlate with appropr shock •TGA patients: appropriate therapy: 29% 2° prev, 4.3% 1° • TOF patients: not at higher risk approp rx
• Khairy P et al. HR 2014 (572) • 24814377	PACES/HRS Expert Consensus Statement on recognition and management of arrhythmias in ACHD		**1° endpoint:** **Results:**	

Data Supplement 55. Nonrandomized Trials, Observational Studies, and/or Registries of S-ICD - (Section 11.1)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Bardy et al. 2010 (573) ● 20463331	**Study type:** Prospective non-randomized clinical trials (covered 4 trials) **Size:** N=78 in temporary S-ICD implantation for testing 4 electrode configurations and DFT testing; N=49 in a trial that compared the best of the tested S-ICD in the first trial with a transvenous ICD system, comparing DFTs; N=6 followed by N=55 in trials that tested permanent S-ICD implantation.	**Inclusion criteria:** Meeting class I, IIa, IIb criteria for an ICD **Exclusion criteria:** GFR <30 ml/min, need for antibradycardia pacing, Hx of VT at rates <170 bpm and documented VT known to be reliably terminated with ATP	**1° endpoint:** Successful immediate conversion of 2 consecutive episodes of induced VF each with a single 65-j shock. **Results:** ● Mean age of the 78 patients was 61±11 y ● All 6 patients underwent successful implantation of the S-ICD, and in all the patients, defibrillation with 65-J submaximal shocks was successful during 2 consecutive episodes of induced VF. Of 18 induced VF episodes, all were successfully detected by the device. After 488 d of FU, there were no complications. ● In the 4th trial, 53 patients were evaluated for sensing and defibrillation during implantation. Of 137 episodes of induced VF, 100% were detected by the S-ICD. After 10 mo of FU, 53 of 55 patients were alive. Pocket infection developed in 2 patients. 12 episodes of VT in 3 patients were successfully treated during followup	● In small, nonrandomized studies, an entirely S-ICD consistently detected and converted VF induced during EP testing. ● The device also successfully detected and treated all 12 episodes of spontaneous, sustained VT
● Olde Nordkamp et al. 2012 (574) ● 23062537	**Study type:** Retrospective study **Size:** N=118	**Inclusion criteria:** Class I or IIa indication for a 1° or 2° prevention ICD **Exclusion criteria:** None	**1° endpoint:** Effectiveness and safety of the S-ICD **Results:** Mean age=50 y. After 18 mo of followup, 8 patients experienced 45 successful appropriate shocks (98% first shock conversion efficacy). No	● The S-ICD is effective at terminating VA ● Rate of inappropriate shocks was 13% ● The rate of complications decreased with improved technology and implanter's experience.

			sudden deaths occurred. Fifteen patients (13%) received inappropriate shocks, mainly due to T-wave oversensing, which was mostly solved by a software upgrade and changing the sensing vector of the S-ICD. Sixteen patients (14%) experienced complications. Adverse events were more frequent in the first 15 implantations/center compared with subsequent implantations.	
● Kobe et al. 2013 (575) ● 23032867	**Study type:** Retrospective case-control study (matching was done on the basis of sex and age) **Size:** N=138	**Inclusion criteria:** Patients with a 1° or 2° prevention indication for an ICD **Exclusion criteria:** None mentioned	**1° endpoint:** Short and long term effectiveness and safety **Results:** Conversion rates of induced VF were 89.5% with a 65J shock, and 95.5% including reversed shock polarity in the study group. Termination of induced VF was successful in 90.8% of the control patients (p=0.815). Procedural complications were similar between the 2 groups. During a mean follow-up of 217 d, 3 patients with S-ICD were appropriately treated for VA. Three inappropriate shokcks (5.2%) occurred in 3 S-ICD patients due to T-wave oversensing, whereas AF with rapid conduction was the predominant reason for inappropriate therapy in conventional devices (p=0.745).	● Failure of conversion of induced VF with the S-ICD set to standard polarity was 10.4%, and there were comparable inappropriate shock rates during short-term follow-up.
● de Bie et al. 2013 (576) ● 23704324	**Study type:** Retrospective study **Size:** N=1,345	**Inclusion criteria:** All patients who received a single- or dual chamber ICD in the Leiden University Medical Center between 2002 and 2011.	**1° endpoint:** Suitability for an S-ICD defined as not reaching one of the following endpoints during follow-up: (1) an atrial and/or right ventricular pacing indication, (2) successful anti-tachycardia pacing without a	● After 5 y of follow-up, approximately: i. 55% of the patients would have been suitable for an S-ICD. ii. Significant predictors of unsuitability for an S-ICD were: 2°

		Exclusion criteria: Patients with a pre-existent indication for cardiac pacing were excluded.	subsequent shock or (3) an upgrade to a CRT-defibrilator device. **Results:** During a median follow-up of 3.4y, 463 patients (34%) reached an endpoint. The cumulative incidence of ICD recipients suitable for an initial S-ICD implantation was 55.5% after 5 y. Appropriate ATP and the necessity of cardiac pacing resulted in the unsuitability for an S-ICD in approximately 94% of the cases, whereas device upgrade was responsible for the unsuitability in approximately 6% of the cases.	prevention, severe HF and prolonged QRS duration. iii. No mention of patients with ESRD (mean GFR 85-89 ml/min)
● Weiss R. et. al 2013 (577) ● 23979626	**Study type:** Prospective non-randomized multicenter trial **Size:** N=321 (314 were implanted successfully)	**Inclusion criteria:** Adult patients with a standard indication for an ICD. **Exclusion criteria:** Patients who required pacing or had documented pace terminable VT.	**1° endpoint:** The 180 d S-ICD system complication-free rate compared with a pre-specified performance goal of 79%. The 1° effectiveness end point was the induced VF conversion rate compared with a pre-specified performance goal of 88%, with success defined as 2 consecutive VF conversions of 4 attempts. **Results:** Followup was for 11 mo. Mean age was 52 y. The 180 d system complication-free rate was 99%, and sensitivity analysis of the acute VF conversion rate was >90% in the entire cohort. There were 38 discrete spontaneous episodes of VT/VF recorded in 21 patients (6.7%), all of which successfully converted. Forty-one patients (13.1%) received an inappropriate shock.	● This study supports the efficacy and safety of the S-ICD System for the treatment of life-threatening VA.

			There were no cases of lead failures, endocarditis or bacteremia, tamponade, cardiac perforation, pneumothorax, hemothorax, or subclavian vein occlusion associated with the S-ICD System. There was no electrode or pulse generator movement in 99% of implanted patients throughout the followup period.	
● Olde Nordkamp et al. 2014 (578) ● 24320684	**Study type:** Prospective non-randomized study **Size:** N=230	**Inclusion criteria:** Patients more than 18 y old with a prior ICD implantation visiting the ICD outpatient clinic. **Exclusion criteria:** Patients who were pacemaker-dependent or had an indication for pacing during implantation (i.e., ICD settings other than VVI ≤40 or DDI ≤40). Also patients with an indication for resynchronization pacing.	**1° endpoint:** To determine the prevalence of patients who are not suitable for a S-ICD according to the QRS-T morphology screening-ECG; (2) to identify clinical characteristics of these patients; and (3) to analyze whether standard 12-lead ECG parameters can be used to predict QRS-T morphology screening failure. Patients were defined suitable when at least 1 sensing vector was considered appropriate in both supine and standing position. **Results:** In total, 7.4% of patients, who were all male, were considered not suitable for a S-ICD according to the QRS-T morphology screening-ECG. Independent predictors for TMS failure were HCM (HCM; OR: 12.6), a heavy weight (OR: 1.5), a prolonged QRS duration (OR: 1.5) and a R:T ratio <3 in the lead with the largest T wave on a standard 12-lead surface ECG (OR: 14.6).	● In patients without an indication for bradycardia- or resynchronization pacing, 7.3% were not suitable for S-ICD implantation according to the QRS-T morphology screening-ECG. This indicates that this prerequisite screening method is not limiting S-ICD selection for most patients.

● Randles et al. 2014 (579) ● 24351884	**Study type:** Prospective non-randomized study **Size:** N=196	**Inclusion criteria:** ICD patients with no ventricular pacing. **Exclusion criteria:** Patients with an S-ICD, patients with a paced QRS complex, and patients who were unable to stand for the time required to record an erect ECG.	**1° endpoint:** S-ICD eligibility that required ≥2 leads to satisfy the S-ICD screening template in both erect and supine positions. **Results:** Overall, 85.2% of patients (95% CI: 80.2–90.2%) fulfilled surface ECG screening criteria. The proportion of patients with 3, 2, 1, and 0 qualifying leads were 37.2% (95% CI: 30.4–44.0%), 48.0% (95% CI: 41.0–55.0%), 11.2% (95% CI: 6.8–15.6%), and 3.6% (95% CI: 1.0–6.2%). The S-ICD screening template was satisfied more often by Lead III (1° vector, 83.7%, 95% CI: 78.5–88.9%) and Lead II (2° vector, 82.7%, 95% CI: 77.4–88.0%) compared with Lead I (alternate vector, 52.6%, 95% CI: 45.6–59.6%).	● About 85.2% of patients with an indication for a 1° or 2° prevention ICD have a surface ECG that is suitable for S-ICD implantation when assessed with an S-ICD screening template. A prolonged QRS duration was the only baseline characteristic independently associated with ineligibility for S-ICD implantation.
● **EFFORTLESS S-ICD Registry** ● Lambiase et al. 2014 (580) ● 24670710	**Study type:** Prospective and retrospective observational study **Size:** N=472 (241 studied prospectively)	**Inclusion criteria:** Patients receiving a S-ICD **Exclusion criteria:** Specific contraindications include class I indications for permanent pacing, pace-terminable VT, and previously implanted functional unipolar pacing system.	**1° endpoint:** Effectiveness and safety of the S-ICD. **Results:** Complication-free rates were 97 and 94%, at 30 d and 360 d, respectively. 317 spontaneous episodes were recorded in 85 patients during the follow-up period. Of these episodes, 169 (53%) received therapy, 93 for VT/VF. One patient died of recurrent VF and severe bradycardia. First shock conversion efficacy was 88% with 100% overall successful clinical conversion after a maximum of five shocks. The 360d inappropriate shock rate was 7% with the vast majority occurring for oversensing	● This study showed appropriate system performance with clinical event rates and inappropriate shock rates comparable with those reported for transvenous ICDs.

			(62/73 episodes), primarily of cardiac signals (94% of oversensed episodes).	
● Groh et al. 2014 (581) ● 24755323	**Study type:** Prospective non-randomized study **Size:** N=100	**Inclusion criteria:** Patients who had previously undergone implantation of a transvenous ICD for 1° or 2° prevention and who were not receiving bradycardia pacing and did not have an indication for pacing were identified. **Exclusion criteria:** See above.	**1° endpoint:** Rate of passing screening test and predictors of failure. **Results:** 8% of patients failed the screening test. Patients with T-wave inversions in the inferior leads had a 45% chance of failing the screening.	● More work is needed on sensing algorithms on S-ICDs to increase pt eligibility for this device.
● **EFFORTLESS/ IDE Registry** ● Burke et al. 2015 (582) ● 25908064	**Study type:** Prospective and retrospective **Size:** N=882 (568 from EFFORTLESS and 308 from the IDE trials)	**Inclusion criteria:** Patients indicated for an ICD. **Exclusion criteria:** Patients with recurrent VT reliably terminated with ATP and patients in need of pacing. Patients with ESRD were excluded from the IDE trials.	**1° endpoint:** Safety and effectiveness of the S-ICD **Results:** Followup was for 651 d. Spontaneous VT/VF events (N= 111) were treated in 59 patients; 100 (90.1%) events were terminated with 1 shock, and 109 events (98.2%) were terminated within the 5 available shocks. The estimated 3 y inappropriate shock rate was 13.1%. Estimated 3 y, all-cause mortality was 4.7% (95% CI: 0.9%–8.5%), with 26 deaths (2.9%). Device-related complications occurred in 11.1% of patients at 3 y. There were no electrode failures, and no S-ICD–related endocarditis or bacteremia occurred. Three devices (0.3%) were replaced for right ventricular pacing. Themo complication rate decreased by quartile of enrollment (Q1: 8.9%; Q4: 5.5%), and there was a trend toward a reduction in	● S-ICD demonstrated high efficacy for VT/VF. Complications and inappropriate shock rates were reduced consistently with strategic programming and as operator experience increased.

			inappropriate shocks (Q1: 6.9% Q4: 4.5%).	

Data Supplement 56. Nonrandomized Trials, Observational Studies, Guidelines, and/or Registries for WCD – (Section 11.2)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Endpoint Results (Absolute Event Rates, P values; OR or RR; & 95% CI)	Summary/Conclusions Comment(s)
● Chung MK. Cardiol Clin. 2014. (583) ● 24793801	Review article **Study size:** N/A	N/A	N/A	Description of WCD indications, efficacy and limitations.
● Chung MK, et al. J Am Coll Cardiol. 2010. (584) ● 20620738	**Study type:** observational, post-market registry and Social Security Death Index **Size:** 3569	**Inclusion criteria:** All patients implanted and signed consent post-market **Exclusion criteria:** N/A	**1° endpoint:** Observational study of compliance and effectiveness	Asystole was an important cause of mortality in SCA events. Compliance was satisfactory with 90% wear time in >50% of patients and low sudden death mortality during usage. 80 sustained VT/VF events occurred in 59 patients (1.7%). First shock success was 76/76 (100%) for unconscious VT/VF and 79/80 (99%) for all VT/VF. 8 patients died after successful conversion of unconscious VT/VF (survival 89.5% of VT/VF events). Asystole occurred in 23 (17 died), PEA in 2 and respiratory arrest in 1 (3 died), representing 24.5% of SCA. During WCD use, 3541/3569 patients (99.2%) survived overall. Survival occurred in 72/80 (90%) VT/VF events. Survival was comparable to that of implantable ICD patients.
● Klein HU et al. Pacing Clin Electrophysiol. 2010. (585) ● 19889186	Review article **Study size:** N/A	N/A	N/A	Description of WCD indications, efficacy and limitations.

Data Supplement 57. Nonrandomized Trials, Observational Studies, Guidelines, and/or Registries for Special Considerations for Catheter Ablation – (Section 12)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Relevant 2° Endpoint (if any); Study Limitations; Adverse Events
● Blanck et al. 1993 (170) ● 8269297	**Study type:** Single Center Review **Size:** 48 patients	**Inclusion criteria:** All patients at single center with BBRVT diagnosed at EPS between 1980-1992 **Exlcusion Criteria:** 7) Typical RBBB or LBBB QRS morphology during VT **8)** QRS preceded by His and appropriate BB potential **9)** Stable HV, RB-V, or LB-V interval **10)** Induction dependent on HV delay **11)** Termination by block in HPS **12)** Noninducibility after RBB ablation	**Results:** 45 of 48 patients had SHD SHD was NICM in 16 patients, Ischemic CM in 23 patients, VHD in 2 patients Mean LVEF=23.2% **Clinical Presentation** Aborted SCD in 26% Syncope in 51% Sustained palpitations in 10% Mean HV interval in sinus 80.4 msec **QRS morphology in VT** LBBB in 46 patients RBBB in 5 patients Interfascicular reentry in 2 patients **Catheter Ablation** Performed in 28 patients targeting the RBB in 26 patients and LBB in 2 patients Successful ablation of VT in 100% No Complications observed.	● BBRVT typically occurs in patients with SHD from a variety of causes in patients with prolonged HV conduction intervals. ● BBRVT is associated with aborted SCD, Syncope, and Palpitations ● BBRVT is most commonly associated with a LBBB QRS morphology, and less commonly with RBBB or Interfascicular QRS morphologies ● Catheter ablation targeting the RBB or LBB is highly effective and associated with a low risk of serious complications.

● Lopera et al. 2004 (173) ● 15028072	**Study type:** Single Center Review **Size:** 20 patients	**Inclusion criteria:** His Bundle, LBB, or RBB potential closely associated with QRS with any of the following: 4) H-H interval variation preceding similar V-V interval variation; 5) Anterograde activation of the bundle branches during tachycardia; or, 6) Abolition of VT by bundle branch ablation. **Exclusion criteria:** None	**Results:** HPS VT induced in 20 of 234 consecutive patients referred for VT ablation NICM: 9 of 81 patients (11%) had HPS VT ICM: 11 of 153 patients (7.1%) had HPS VT Mean LVEF 29±17% 2 of 20 patients had normal LVEF **Clinical Presentation** ICD Shocks in 10 patients Syncope in 3 patients Other symptoms in 7 patients **Typical BBRVT** in 16 of 20 patients (all had LBBB QRS morphology) 13 of 16 patients BBRVT successfully ablated by RBB ablation and 3 of 16 by LBB ablation. HV interval prolonged from 70±5.9 msec to 83±17 msec after ablation. **Typical BBRVT and Interfascicular VT** in 2 of 20 patients. Ablation of both the RBB and portion of LBB eliminated VT in both	● BBRVT occurs in patients with both NICM and ICM, usually with impaired LVEF. ● BBRVT is most commonly associated with a LBBB QRS morphology, and less commonly with RBBB or Interfascicular QRS morphologies ● Catheter ablation targeting the RBB or LBB is highly effective and associated with a low risk of serious complications if only one BB is targeted and a higher risk of AV block if both BBs are targeted for ablation.

			patients, complicated by AV block in 1 pt. **Focal Mechanism from BBs** in 2 patients, one in RBB, one in LBB. Ablation eliminated focal VT in both patients, complicated by AV block in 1 pt.	
● Mehdirad et al.1995 (174) ● 8771124	**Study type:** Single Center Review **Size:** 16 patients	**Inclusion criteria:** All patients undergoing RF catheter ablation of the RBB for BBRVT	**Results:** HV interval 68±8 msec at baseline LVEF mean 31±15% RBBB developed in 15/16 patients after RBB ablation AV block occurred in 1 pt After mean of 19+10 mo, one patient died suddenly, 2 received cardiac transplantation, and 1 died of CHF.	● Catheter ablation of the RBB is effective for the treatment of BBRVT ● BBRVT is associated with prolonged HV conduction intervals. ● The medium-term follow-up after catheter ablation of the RBB is overall quite good.
● **HELP-VT** ● Dinov 2014 (175) ● 24211823	**Aim:** To determine the outcome of VT catheter ablation in patients with NICM to those with ischemic cardiomyopathy **Study type:** Prospective, non-randomized **Size:** 227 patients	**Inclusion criteria:** Patients with SHD referred for catheter ablation of VT with either NICM (N=63) or ischemic CM (N=164) **Exclusion criteria:** Failure of informed consent **Intervention:** Catheter ablation for patients with NICM	**1° endpoint:** At 1y follow-up, VT free survival was 57% for ischemic cardiomyopathy and 40.5% for NICM patients (HR: 1.62; 95% CI: 1.12–2.34, p=0.01). ischemic cardiomyopathy required epicardial ablation in only 2 of 164 (1.2%) whereas NICM required	● **Complications** Complications occurred in 11.1% of NICM and 11.1% of ischemic cardiomyopathy patients, including death in 4.8% of NICM and 3.7% of ischemic cardiomyopathy

		Comparator: Catheter ablation in patients with ischemic cardiomyopathy	epicardial ablation in 30.8% (p=0.0001).	
● **Euro-VT Study** ● Tanner H 2010 (176) ● 9656251	**Aim** To determine the safety and efficacy of electroanatomic mapping and irrigated RF catheter ablation for VT after MI **Study Type:** Multicenter, non-randomized **Study Size** 63 patients	**Inclusion Criteria** Drug and device refractory, recurrent sustained VT after MI. ≥4 episodes of sustained VT in prior 6 mo. **Exclusion Criteria** Age <18 y MI within 2 mo LV Thrombus Unstable Angina Severe AS or MR Unwillingness to participate **Intervention** Electroanatomic mapping and ablation with open-tip irrigated catheter.	**1° Endpoint** Acute success with ablation was achieved in 83% of mappable VTs and 40% of non-mappable VTs (p<0.0001). During 12 mo follow-up, VT recurred in 49% of patients. The mean number of therapies dropped from 60±70 prior to ablation to 14±15 in the same period of time (6 mo) after ablation (p=0.02).	● **Complications** Major complications occurred in 1.5% and minor complications in 5% of patients, particularly groin hematomas, with no procedural deaths.
● **Post-approval Thermocool Trial** ● Marchlinski F 2016 (177) ● 26868693	**Aim** To evaluate long-term safety and effectiveness of RF catheter ablation for VT in patients with coronary disease **Study Type:** Multicenter, non-randomized **Study Size:** 249 patients	**Inclusion Criteria** Patient with coronary disease, age ≥18 y and LV EF ≥10% with recurrent VT (either ≥4 episode documented by ICD, ≥2 episode documented by ECG in patients without ICD, incessant VT or symptomatic VT despite AAD treatment **Exclusion Criteria**	**1° Endpoint** At 6 mo: 62% without VT recurrence, proportion of patients with ICD shock reduced from 81.2 (pre) to 26.8% and ≥ 50% reduction in VT episodes in 63.8% of patients. **Safety Endpoint** CV specific AE in 3.9% with no stroke	**Comments** Reduction in amiodarone usage and hospitalization Improvement in QoL

		Mobile LV thrombus, MI within 3 mo, idiopathic VT, class IV HF, creatinine ≥2.5, recent cardiac surgery, unstable angina, severe AS or MR **Intervention** Electroanatomic mapping and ablation with open-tip irrigated catheter.		

Data Supplement 58. Nonrandomized Trials, Observational Studies, and/or Registries Related to Post-Mortem Evaluation of SCD - (Section 13)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● de Noronha et al. 2014 (586) ● 24148315	**Study type:** consecutive prospective observational study **Size:** 720	**Inclusion criteria:** SCD cases referred by general pathologist to specialized cardiac pathology center; SCD defined as witnessed SCA or unwitnessed SCD in an individual alive and well up to 24 hs prior; non-cardiac causes ecluded at initial autopsy **Exclusion criteria:** Non-sudden death; sudden-death in the context of worsening CHF; absence of age, sex, and circumstances of death	**1° endpoint:** Determine cause of SCD and compare initial diagnosis with that determined at specialized center. **Results:** Data were skewed by age (median 32 y, range 1-98 y, 58% ≤35 y. Approximately 1/3 of the cases had a "cardiomyopathy", including idiopathic LVH (26%), HCM (20%) and ARVC (14%), and a category of obesity CM (14%) Coronary artery abnormalities accounted for 10%, with 79% of those being ASHD. In a comparison of diagnoses of 200 autopsies examined after referral, a disparity in final diagnosis was observed in 41% of the cases. A misdiagnosis of cardiomyopathy was reported in 37% referred cases, ultimately determined to have to be structurally normal.	● The specialized cardiac pathology exam appears to have value for determining specific causes of SCD in this population. ● Referring pathologists tended to have a more difficult time identifying anatomically normal hearts, and over-diagnoses cardiomyopathies. ● The etiological data are not generalizable to the overall population because of skewing of age at time of SCD for specialized cardiac evaluation.

● Wu et al. 2016 (587) ● 26844513	**Study type:** Retrospective observational cohort study of anatomic and histopathological findings in SCD victims between 1998 and 2013 **Size:** 1656 SCD identified from a total of 3770 sudden deaths (43.9%) from all causes during the study period	**Inclusion criteria:** Deaths that occur within 1 h of the sudden loss of consciousness due to various CVD, or during sleep or unwitnessed, in which the affected persons were considered healthy 24 h before the event. **Exclusion criteria:** Deaths due to non-cardiac conditions, such as injuries, poisonings, epilepsy, acute pulmonary embolisms, and allergies.	**1° endpoint:** Causes of SCD, sub-grouped according to circumstances, sex and age groups **Results:** The peak incidence occurred between the ages of 31 and 60, with a 5-7-fold excess of males/females in that age range. Both incidence and male preponderance markedly decreased in younger and older age groups. Overall, 42% were due to CAD, 12% viral myocarditis, and 5% cardiomyopathy, with 15% being unexplained by autopsy. In age group <35, CAD was 17% of cases, viral myocarditis 27%, and unexplained 32%. At age >55, CAD accounted for 86%, viral <2%, and unexplained <1%.	● The proportion of SCDs that were autopsy negative was strongly age-dependent, as was the common autopsy-provable causes. ● The proportion of SCDs attributed to dilated cardiomyopathy was surprisingly low, especially in the age group older than 35 y.
● Vassalini et al. 2016 (588) ● 25575272	**Study type:** Retrospective cohort autopsy study **Size:** 54	**Inclusion criteria:** SCD in subjects aged 1-40 y. **Exclusion criteria:** Prior Hx of heart disease; sudden infant death syndromes (under 1 y of age), extracardiac causes at autopsy; drug or alcohol abuse found at postmortem toxicology.	**1° endpoint:** Clinical and postmortem findings of patients who died suddenly without a Hx of prior heart disease. **Results:** Coronary artery abnormalities in 18.5% (including one with an anomalous coronary artery origin); ARVD/C in 11.1%; LVH in 5 cases (9.2%), 3 of whom had myocyte disarray; VHD in 7.4%; myocarditis in 7.4%; pathological changes in the specialized conducting system in 22.2%, in the absence of any other anatomic or histopathological findings; in 12 cases (22.2%), autopsy was completely negative in 22.2%. No postmortem genetics done in this group	● Although this is a small study, the exclusion of a prior Hx of heart disease restricts this study to SCD that occurred as a first cardiac event. ● One important finding is the association of SCD with the only abnormalities at postmortem found in the specialized conducting system in 22.2% ● A second is the autopsy being completely negative in another 22.2%. No postmortem genetics were done in this subgroup
● Tester et al. 2012 (589) ● 22677073	**Study type:** Prospective cohort study **Size:** 173	**Inclusion criteria:** Autopsy-negative SUDs referred for molecular autopsy. Candidate genes restricted to KCNQ1, KCNH2, SCN5A, KCNE1,	**1° endpoint:** Identification of SUD-associated variants in KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, or RYR2. **Results:** Pathogenic mutations were identified in 45 autopsy-negative SUD cases (26.0%). LQT	● Molecular autopsy provides a reasonable yield of putative SUD-associated variants, recognizing that the candidate genes were restricted to the common LQTS-

		KCNE2, and RYR2. SUD-associated variants had to be nonsynonymous, involve a highly conserved residue, and absent from reference normal populations **Exclusion criteria:** A prior documented Hx of a channelopathy in either probands or family members (Exception: History of long QT on an ECG mentioned in autopsy)	variants more likely to be associated with SUD during sleep; CPVT (RyR2) more like associated with SUD during exercise. Family Hx of SCD positive among relatives of 11 of 45 variant-positive probands.	associated genes and the most common CPVT-associated gene. ● It is likely that broader panels, including other genetic disorders, including structural disorders that may not be identified on routine autopsy, would increase this yield.
● Tang et al. 2014 (590) 24157219	**Study type:** Review article on molecular diagnostic protocol for SCD **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° endpoint:** N/A **Results:** N/A	● Comprehensive review on postmortem molecular studies of SUD and autopsy-defined structural genetic disorders
● Papadakis et al. 2013 (591) ● 23671135	**Study type:** Retrospective cohort study, with prospective cardiogenetic evaluation of family members. **Size:** 340 families	**Inclusion criteria:** Family members of SCD probands who died suddenly and had been apparently healthy, death from natural causes, last seen alive and well within 12 h, with autopsy findings showing structural abnormalities of uncertain causal effect (e.g., ventricular hypertrophy, myocardial fibrosis, or minor CAD (N=41).	**1° endpoint:** Identification of genetic variants associated with inherited arrhythmia syndrome in ≥1 relative(s) of probands who had structural findings of uncertain significance (such as ventricular hypertrophy, myocardial fibrosis, and minor CAD). Comparison group was the cohort of 163 families in whom the findings were consistent with SUD based on normal autopsy. **Results:** 51% of the study group had genetic variants associated with SADS; for the comparison group, consistent with SADS, the proportion with positive genetic findings was 47%.	● Victims of SCD with structural findings of uncertain significance are as likely to have genetic variants associated with inherited arrhythmia syndromes as are those with normal autopsies. ● Findings call for caution in interpreting uncertain structural findings, with particular regard to implications for family members of probands.

		Exclusion criteria: Incomplete postmortem report, presence of an extracardiac cause of death, or positive toxicology screen.		
● Harmon et al. 2014 (592) ● 24585715	**Study type**: Cohort study from NCAA registry of athletes who died suddenly **Size:** 45	**Inclusion criteria:** 36 of 45 athlete SCDs with sufficient autopsy information **Exclusion criteria**: N/A	**1° endpoint:** Autopsy-defined cause of SCD **Results:** Autopsy-negative SUD in 11 (31%); coronary artery abnormalities in 5 (14%), dilated CM in 3 (8%), myocarditis in 3 (8%), aortic dissection in 3 (8%), and idiopathic LVH (possible HCM) in 3 (8%). There was 1 case each (3%) of HCM, ARVC, LQTS, commotio cordis, commotio cordis, and Kawasaki disease. There was 1 case of death in a sickle cell positive athlete who also had LVH. There was 1 case of death in a sickle cell positive athlete who also had LVH.	● The adjudicated diagnosis agreed with the official pathology report in only 59% of cases. ● Autopsy-negative SUD was common (31%)
● Bagnall et al. 2014 (593) ● 24440382	**Study type:** Retrospective analysis of de-identified cases of autopsy-negative SUDs **Size:** 28	**Inclusion criteria**: SUD in the 1–40 y age group, classified as SUD based upon sudden unexpected death with a negative autopsy. **Exclusion criteria:** Previous Hx of systemic disease or alternative cause of death identified after a complete autopsy, including histopathologic and toxicologic analysis	**1° endpoint**: Comparison of the yield of whole exome sequencingto common candidate gene sequencing for identifying a potentially relevant variant associated with autopsy-negative SUDs in a population age 1–40 y. **Results**: Based upon likely variants identified by WES, the yield increased from approximately 10% of cases to as much as 30%.	● Study suggests the WES increases the yield of molecular autopsy in SUD by as much as 3-fold, compared to common candidate genes for LQTS and CPVT. ● Nonetheless, the majority of molecular autopsies still fail to identify a highly-likely or known disease-causing mutation.
● Anderson et al. 2016 (449) ● 27114410	**Study type:** Whole exome sequencing of stored DNA from	**Inclusion criteria:** Stored DNA from SUD victims with previous negative molecular autopsies	**1° endpoint**: Putative variants identified by WES, excluding the previously studied common candidate genes.	● There appears to be added valve to WES, compared to a limited candidate gene approach

	referred cases of SUDY with negative autopsies **Size:** 32	(21/32, 66%) using a common candidate gene protocol (KCNQ1, KCNH2, SCN5A, RYR2) **Exclusion criteria:** Previous identification of a putativelt significant variant in KCNQ1, KCNH2, SCN5A, or RYR2 (11/32, 34%)	**Results**: WES increased the yield compared to the candidate genes, to 44% from 34%.	for molecular autopsies following SUD. ● Whether a broader candidate gene panel might achieve the same yield requires further study. ● The data suggest that the yield from WES is greater for the age group 1-10 y, compared to 11-19 y, but this is not conclusive based upon the small numbers.
● Bagnall et al. 2016 (594) ● 27332903	**Study type:** Prospective, population-based, clinical, toxicological, autopsy, and genetic study of sudden cardiac death among children and young adults, age 1–35 y. **Size:** 490	**Inclusion criteria:** 292 subjects with clinical and autopsy confirmed causes of SCD (60%), and 198 (40%) subjects without identified cause based on clinical or autopsy information, among whom 113 underwent genetic testing. **Exclusion criteria:** De-identified cases; DNA unavailable	**1° endpoint**: Identification of relevant genetic variants among subjects without autopsy or clinical identification of cause of SCD. **Results**: Among the total cohort, 292 subjects had clinical and/or autopsy identified causes of SCD (60%). The most common identified causes were CAD (24%) and inherited cardiomyopathies (16%), while unexplained SCD accounted for 40% overall (N=198). Among the 113 of 198 unexplained cases that had post-mortem genetic testing, 31 (27%) were identified as having a clinically genetic variant.	● 40% of SCDs in children, adolescents and young adults are classified as unidentified causes based on autopsy and clinical information. ● In the age group 30–35 y, a greater proportion of causes are identified, and CAD is the dominant cause. ● Based on a partial sample of cases with unidentified causes that underwent post-mortem genetic testing, an estimated 27% of such cases yielded evidence of a clinically relevant genetic variant.

Data Supplement 59. Nonrandomized Trials, Observational Studies, Guidelines, and/or Registries of Terminal Care - (Section 14)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
• Hill et al. 2015(595) • 25239128	**Study type:** Systematic narrative review of	**Inclusion criteria:** Empirical studies published in English	**1° endpoint:** N/A – concept mapping was performed for	• Three broad themes (1) Diverse preferences regarding discussion and deactivation.

	published studies (2008 – 2014) **Aim:** to evaluate the evidence on patients' perception of implantable cardioverter defibrillator deactivation at end of life. **Size:** N=18 studies	language between 2008 and 2014, primarily related to adults (above 18 y) with an implanted ICD and primarily related to the deactivation of ICDs at end of life	emergent themes from the set of studies **Results:** See conclusions	(2) Ethical and legal considerations were predominant in Canadian and American literature. Advance directives were uncommon in Europe. (3) 'Living in the now' was evident among patients.
• Lewis et al. 2014 (37) • 24668214	**Study type:** Integrative review **Aim:** To explore patients' decision-making experiences regarding ICDs from the decision to implant to the consideration of deactivation at end of life. **Size:** N=25 studies	**Inclusion criteria:** original quantitative and qualitative research articles that directly studied the patient response regarding ICD decision-making. 18 y of age orolder, **Exclusion criteria** articles that did not incorporate the patient's perspective, if they solely focused on living with or adjusting to the ICD.	**1° endpoint:** N/A – integrative review **Results:** See conclusions.	• A significant degree of misunderstanding and inaccurate recall of information regarding ICD function at all decision • In terms of deactivation decisions, the majority of patients were not aware of this option.
• Kramer et al. 2016 (596) • 27016104	**Study type:** Retrospective cohort study (NCDR linked to Medicare) **Aim:** to describe the incidence and features	**Inclusion Criteria:** Patients >65 y who had ICDs inserted between January 1, 2006 through March 31, 2010 **Exclusion criteria:**	**1° endpoint:** Descriptive **Results:** 5 y after device implantation, 50.9% of patients were either deceased or in hospice.	• Half of patients over age 65 y don't survive 5 y. • 1/3 of the decedents utilize hospice services.

	of hospice use in a large, nationally representative sample of older patients following ICD implantation, and to identify factors associated with hospice enrollment in this cohort. **Size:** N=194,969	Not fee-for-service Medicare patients. Patients enrolled in hospice before device placement.	Among decedents, 36.8% received hospice services. Factors most strongly associated with shorter time to hospice enrollment were: older age HR: 1.77; class IV HF HR: 1.79; EF <20% HR: 1.57 Greater regional hospice use	
• Buchhalter et al. 2014 (597) • 24276835	**Study type:** retrospective chart review – Mayo clinic **Aim:** To describe features and outcomes of patients who underwent ICD deactivation. **Size:** N=150	**Inclusion criteria:** Patients with ICD referred to the cardiac service for deactivation. **Exclusion criteria** N/A	**1° endpoint:** Descriptive **Results:** 150 patients who had their ICD deactivated. Median of 2 d between deactivation and death. Advance directives were present for 85 (57%) of these patients, but only 1 of these made any mention of the ICD. 6 of the ICD deactivations were for pacemaker-dependent patients, Surprisingly, surrogates were responsible for over half (51%) of the deactivation decisions. Palliative care consultation was obtained in 43% of patients.	• Patients have deactivation decisions very close to delay (median 2 d) • Over half the time, this decision falls to a surrogate. • Devices were not mentioned in advance directives.

• Goldstein et al. 2004 (598) • 15583224	**Study type:** Telephone survey with next-of-kin of deceased patients **Aim:** To describe the frequency, timing, and correlates of ICD deactivation discussions **Size:** 100	**Inclusion criteria:** Deceased patients: median age 76 y at death; 27% women; median implant time 27 mo. Interviewed next-of-kin: median age 67; majority were spouses.	**1° endpoint:** Descriptive **Results:** 27% of next of kin recalled a discussion regarding deactivation of the ICD with their clinician. 21% chose to deactivate. These discussions all took place in the last few d or h of the patient's life. 27 patients received shocks in the last mo of life, 8 patients received a shock from their ICD in the min before death.	• Deactivation discussions were not common and occurred late in the illness • **Limitations** 12 y old Relied on reports from the next-of-kin Recall bias (interviews occurred a median of 2.3 y after patient death)
• Goldstein et al. 2010 (599) • 20194235	**Study type:** Nationwide survey of hospice providers **Aim:** To determine whether hospices are admitting patients with ICDs, whether such patients are receiving shocks, and how hospices manage ICDs. **Size:** 414	**Inclusion criteria:** Hospice directors (nursing, clinician, or administrative)	**1° endpoint:** Descriptive **Results:** 97% of hospices admitted patients with ICDs 58% reported that in the past year, a patient had been shocked. Only 10% of hospices had a policy that addressed deactivation. On average, 42% (95% CI, 37% to 48%) of patients with ICDs had the shocking function deactivated.	• Over half of hospices had had a patient get shocked by their ICD in the year prior to their death. • Older survey: more hospices have a policy now.

• Berger et al. 2006 (600) • 16689116	**Study type:** self-administered survey **Aim:** To assess whether ICD recipients have considered preferences for disabling the ICD. **Size:** N=57	**Inclusion criteria:** Patients with ICDs **Exclusion criteria:** N/A	36/57 did not have preferences for disabling. 21/57 described situations in which they would want deactivation. Advanced directives were prepared by 35/57 subjects, none addressed the ICD.	• Patients infrequently consider deactivation and rarely consider them in advance directives • **Limitations:** Retrospective Selection bias
• Dodson et al. 2013 (601) • 23358714	**Study type:** telephone survey. **Aim:** To examine preferences for ICD deactivation in hypothetical scenarios **Size:** N=95.	**Inclusion criteria:** Patients with ICDs, >50 y, English speaking **Exclusion criteria:** N/A	Following an informational script regarding the benefits and harms of ICD therapy, 67/95 (71%) subjects wanted ICD deactivation in 1 or more scenarios.	• Patients endorse preferences for ICD deactivation in hypothetical scenarios • **Limitations:** Single center
• Goldstein et al. 2008 (602) • 18095037	**Study type:** Qualitative focus groups. **Aim:** To identify barriers to ICD deactivation discussions in patients with advanced illness. **Size:** N=15	**Inclusion criteria:** Patients with ICDs	No participant had ever discussed deactivation with their physician, nor knew that deactivation was an option. Some subjects expressed that the physician should make the decision.	• Patients did not consider and had some confusion about ICD deactivation • **Limitations:** Single center Small sample size
• Habal et al. 2011 (603) • 21514785	**Study type:** semi-structured survey study	**Inclusion criteria:** N=41 total patients N=19 with ICD	Focused on subset of patients with ICDs 2/19 (11%) reported discussing the possibility of	• Patients expressed varied impressions about deactivation • **Limitations:**

	Aim: To determine HF patients' awareness, comprehension and utilization of advanced care directives **Size:** 41 (19 with ICDs)		ICD deactivation with their physician. Following clarification, 9/19 (47%) stated they would want their ICD turned off should their condition deteriorate. 5/19 (26%) would not want it deactivated.	Convenience sampling Single center Small sample size
• Kirkpatrick et al. 2012 (604) • 21943937	**Study type:** Non-experimental, descriptive, telephone survey. **Aim:** To explore patients' preferences for ICD deactivation in the setting of a do not resuscitate order and/or admission to hospice. **Size:** N=278	30% women; 85% Caucasian; median age 61 y; mean implant time 61 mo; 100% 2° education and higher; 38% with prior shock(s); mean number of shocks 4.69.	**1° endpoint:** Descriptive **Results:** 140 subjects either had a living will or a power of attorney. Only 3 (2%) of these subjects included a plan for their ICD. 96% had never discussed what to do with their ICD at end-of-life with a medical professional. Nearly all wanted their physician to bring up the topic of deactivation.	• Majority of patients are not addressing their ICD in advance directives. Patients want their doctors to have the conversation about deactivation. • **Limitations:** Study objectives not explicitly stated Single center
• Kramer et al. 2011 (605) • 21296323	**Study type:** Non-experimental, descriptive, online survey. **Aim:** To identify the ethical beliefs and legal knowledge of patients with HCM relating to end-of-life care and the withdrawal of implantable cardiac device therapy.	**Inclusion criteria:** Members of Hypertrophic Cardiomyopathy Association	**1° endpoint:** Descriptive **Results:** Widespread uncertainty and confusion regarding the legal status on implantable cardiac device deactivation was found. 57% were unsure if ICD deactivation was legal. 198 patients with an ICD had advanced directives, and only 15 (8%) specifically addressed their ICD.	• Legality of ICD deactivation is not well-known among patients

	Size: N=546			

Data Supplement 60. Nonrandomized Trials, Observational Studies, Guidelines, and/or Registries for Shared Decision Making – (Section 15)

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	1° Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
● Lewis et al. 2014 (606) ● 24668214	**Study type:** Integrative review **Aim:** To explore patients' decision-making experiences regarding ICDs from the decision to implant to the consideration of deactivation at end of life. **Size:** 25 studies	**Inclusion criteria:** Original quantitative and qualitative research articles that directly studied the patient response regarding ICD decision-making. age ≥18y **Exclusion criteria** articles that did not incorporate the patient's perspective, if they solely focused on living with or adjusting to the ICD.	**1° endpoint:** N/A – integrative review **Results:** See conclusions	● A significant degree of misunderstanding and inaccurate recall of information regarding ICD function at all decision points. ● The majority of patients were not aware of deactivation. ● The desire to live trumped inconveniences for most patients but this appeared to be a function of health state.
● Dodson et al. 2013 (601) ● 23358714	**Study type:** telephone survey. **Aim:** To examine preferences for ICD deactivation in hypothetical scenarios **Size:** N=95.	**Inclusion criteria:** Patients with ICDs, age >50 y, English speaking **Exclusion criteria:** N/A	Following an informational script regarding the benefits and harms of ICD therapy, 67/95 (71%) subjects wanted ICD deactivation in 1 or more scenarios.	● Patients endorse preferences for ICD deactivation in hypothetical scenarios ● **Limitations:** Single center
● Lewis et al. 2014 (607) ● 25070249	**Study type:** mailed survey	**Inclusion criteria:** Adult patients with ICDs	**1° endpoint:** 55 of 106 patients (51.9%) were unaware that ICD	● Over half of patients were unaware that there was an

	Aim: To assess patient awareness that ICD generator replacement is optional, to gauge their understanding of the risks and benefits of ICD replacement, and to gain insight into their decision-making process. **Size:** N=106 (response rate 72%).	**Exclusion criteria:** CRT	generator replacement was not compulsory. **Results:** If given the option, 15 of 55 (27.2%) stated that they would have considered nonreplacement. For 88 of 106 patients (83.0%), it was "important" or "very important" to discuss risks and benefits of continued therapy before deciding.	option to not replace the ICD and a portion of them would have considered it. ● **Limitations:** Single center and Recall bias
● Hauptman et al. 2013 (608) ● 23420455	**Study type:** Focus groups; standardized patients (providers) **Aim:** To examine patient-physician communication at the time the decision is made to implant an ICD. **Size:** 41 patients, 11 providers	**Inclusion criteria:** • Adult patients with ICDs • Cardiologists **Exclusion criteria:** N/A	**1° endpoint:** Patient focus group findings and the results of standardized patient interviews **Results - Patients:** 33/41 patients could not recall a discussion about complications. Patients felt a score of 5.7 on a scale of 1-10 on "feeling informed" Mean number of patients out of 100 who would be saved by the ICD was 87.9 **Results - Clinicians:** • In 17 of 22 of interviews, cardiologists did not address or minimized or denied QOL issues and long-term consequences of ICD placement • In 15 of 22 of the standardized patient interviews, cardiologists	● Patients overestimated the benefits and felt uninformed regarding the risks. ● Patient-physician communication about ICDs is characterized by unclear representation and omission of information to patients

			used unexplained medical terms or jargon.	
● Stewart et al. 2010 (609) ● 20142021	**Study type:** Survey **Aim:** To examine patient expectations from ICDs for 1° prevention of sudden death in HF. **Size:** 105	**Inclusion criteria:** • Patients with EF <35% • Symptomatic HF **Exclusion criteria:** N/A	**1° endpoint/Results** Most patients anticipated more than 10 y survival. 54% expected an ICD to save ≥50 lives per 100 during 5 y. 70% of ICD recipients indicated they would keep the ICD on even if dying of cancer, 55% even if having daily shocks, None would inactivate even if suffering constant dyspnea at rest.	● Study demonstrated that patients overestimate the benefits of ICD therapy.
● Ottenberg et al. 2014 (610) ● 24889010	**Study type:** Qualitative Focus Group **Aim:** To describe the reasons why patients decline ICD implantation **Size:** 13 patients (3 groups)	**Inclusion criteria:** Patients who had declined ICD (12 ICD, one CRT) **Exclusion criteria:** N/A	**1° endpoint/Results:** 5 Themes: (1) don't mess with a good thing; (2) my health is good enough; (3) independent decision making; (4) it's your job, but it's my choice; and (5) gaps in learning	● Interviews identified significant gaps for some patients in their understanding about the ICD.
● Yuhas et al. 2012 (611) ● 22897624	**Study type:** Qualitative interview **Aim:** To explore patients' attitudes and perceptions of ICDs to better understand potential patient-related barriers to appropriate utilization. **Size:** N=25. 12 who accepted referral, 13	**Inclusion criteria:** outpatient cardiology patients with EF ≤35% and without an ICD. **Exclusion criteria:** N/A	**1° Endpoint/Results**: 5 Themes: (1) Patients who refused ICD referral had a lack of insight into their own risk. (2) Many patients who accepted ICD referral perceived that this was strongly recommended by their physicians. (3) Concerns over recall, malfunction, and surgical risk were common in both.	● People who decline had misunderstandings about their personal risk.

	who declined referral (note: none had ICDs)		(4) Many patients demonstrated inaccurate perceptions of ICD-related risks (5) Feelings regarding invasive life-prolonging interventions played an important role in ICD referral refusal for some individuals.	

Data Supplement 61. Randomized Trials, Observational Studies, and/or Registries Related to Cost and Value Considerations - (Section 16)

Study Name	Study Design Study Size	Patient Population	Costs	Effectiveness	Value	Summary/Conclusions
● **AVID** ● Larsen G, et al. 2002 (612) ● 11980684	**Study type:** RCT of ICD vs. antiarrhythimic drug therapy (largely amiodarone). Within trial costs and outcomes to 3 y; lifetime projection. **Size:** 1,008 patients	2° prevention: resuscitated CA or sustained VT, EF ≤40%.	Within trial: ICD $87,479, Antiarrythmic drug Tx $73,564	Within trial: ICD 2.48 y, Antiarrythmic drug Tx 2.27 y	Lifetime ICER= $67,100 Within-trial ICER= $66,700	● Intermediate value based on ACC/AHA benchmarks. ● Authors concluded: ICD was "moderately cost-effective for 2° prevention."
● **CIDS** ● O'Brien BJ, et al. 2001 (613) ● 11245646	**Study type:** RCT of ICD vs. amiodarone. Within trial cost and survival to 6 y; 12 y projection of cost and survival. 430 patients in economic substudy. **Size:** 659 total patients	2° prevention: Resuscitated VF or VT.	Within trial: ICD C$87,715; amiodarone C$38,600	Within trial: ICD 4.58 y; amiodarone 4.35 y	12 year ICER; C$99,400 (US$67,600) (with continued ICD benefit) Within trial ICER= C$213,500 (US$145,200)	● Intermediate value based on ACC/AHA benchmarks. ● Authors concluded that "ICD therapy is not attractive" based on Canadian standards. ● No lifetime projections of cost and life expectancy.

● Weiss, et al. 2002 (614) ● 12015242	**Study type:** Propensity score matched analysis of Medicare patients. Costs and outcomes to 8 y. **Size:** 7,619 matched pairs	2° prevention. Hospitalized with 1° diagnosis of VT or VF.	Within study: ICD $78,700; conventional therapy $37,200	Within study: ICD 4.6 y; conventional therapy 4.1 y	Within study ICER= $78,400	● Intermediate value based on ACC/AHA benchmarks. ● No lifetime projections of cost and life expectancy.
● Buxton et al. 2006 (615) ● 16904046	**Study type:** Markov model, 20 y time horizons. Effectiveness inputs from RCTs, cost inputs from UK. **Size:** Cost data from 535 patients with ICD implants in Liverpool.	2° prevention.	ICD: £87,184; amiodarone: £18,379	Life-y: ICD 9.87; amiodarone 8.41 Quality-adjusted life-y: ICD 7.41, amiodarone 6.35	£48,700/life-y gained ($64,700) £65,000/QALY gained ($86,200)	● Intermediate value based on ACC/AHA benchmarks. ● Authors concluded that ICDs were not cost-effective at the UK benchmark (<£30,000).
● **SCD-HeFT** ● Mark DB, et al. (616) ● 16818817	**Study type:** RCT of ICD vs. amiodarone or placebo. Costs and outcomes to 5 y; lifetime projection of costs and life expectancy. 1,692 patients in economic substudy (US centers), **Size:** 2,521 total patients	1° prevention: HF (NYHA II or III) and EF ≤35%.	Within trial: ICD $61,938; placebo $42,971 Lifetime: ICD $158,840; placebo $79,028	Life expectancy: ICD 10.87 y; placebo 8.41 y	Lifetime ICER= $38,400 Within trial ICER= $127,500	● High value based on ACC/AHA benchmarks. ● Authors concluded that ICD was "economically attractive" compared with placebo as long as ICD benefit was maintained for ≥8 y.
● **MADIT-II** ● Zwanziger J, et al. 2006 (617) ● 16750701	**Study type:** RCT of ICD vs conventional medical therapy. Within trial costs and survival to 3.5 y; 12 y projection of cost and survival.	1° prevention: Patients with prior MI, EF ≤30%.	Within trial: ICD $84,100, conventional $44,900; 12 year projections: ICD $173,700 to $180,300,	Within trial: ICD 2.89 y, conventional 2.72 y	12 y ICER= $78,600 to $114,000 Within trial ICER =$235,000;	● Intermediate value based on ACC/AHA benchmarks, based on long-term projections of ICD outcomes.

	Size: 1,095 patients in economic substudy (US patients), 1,232 total patients		conventional $97,900			
● **MADIT-I** ● Mushlin AI, et al. 1998 (618) ● 9626173	**Study type:** RCT of ICD or medical therapy. Costs and outcomes to 4 y. **Size:** 181 patients in economic study (US centers), 196 total patients.	1° prevention. Prior MI, asymptomatic non-sustained VT, EF ≤35%, inducible VT not suppressed by procainamide.	Within trial: ICD $97,560; medical therapy $78,980	Within trial: ICD 3.66 y, medical therapy 2.80 y	Within trial ICER= $27,000	● High value based on ACC/AHA benchmarks. ● Authors concluded that "ICD is cost-effective in selected individuals at high risk" for sudden cardiac death.
● Al-Khatib, et al. 2005 (619) ● 15838065	**Study type:** Duke database outcomes and costs for 15 y. Llifetime extrapolation by Markov model. **Size:** 1,285 patients	1° prevention. Post-MI, EF ≤30%.	ICD: $131,490; medical: $40,661	Life expectancy: ICD 8.59 y, medical 6.79 y	$50,500 per life-y gained	● Intermediate value by ACC/AHA benchmarks ● Authors concluded: ICD therapy for patients eligible for MADIT-II was "economically attractive" by conventional standards.
● Sanders, et al. 2005 (620) ● 16207849	**Study type:** Markov model, lifetime projection, applied to data from each of eight randomized trials. **Size:** Not applicable	1° prevention. Trial subjects in CABG-PATCH, COMPANION, DEFINITE, DINAMIT, MADIT-I, MADIT-II, MUSTT, and SCD-HeFT.	ICD had higher costs in each population: $55,700 to $100,500	ICD had higher life expectancy in six trials, ranging from 1.46 to 4.14 life-y added	≤$39,000 for COMPANION, DEFINITE, MADIT I, MADIT II, MUSTT; $50,700 for SCD-HeFT Higher cost, worse outcomes for	● High value by ACC/AHA benchmarks when projected life expectancy was increased by >1.4 y

					CABG-PATCH, DINAMIT.	
● Smith, et al. 2013 (621) ● 22584647	**Study type:** Markov model, lifetime projection. Effectiveness from meta-analysis of 6 RCTs. **Size:** Not applicable	1° prevention. Patients with EF <40%, due to either ischemic or non-ischemic causes.	ICD €86,759; conventional therapy €50,685	ICD 7.08 QALY; conventional therapy 6.26 QALY	ICER= €44,000 ($49,200)	● High value by ACC/AHA benchmarks. ● Authors concluded: 1° prophylactic ICD therapy had high value in the European setting for patients with EF <40%.
● Cowie, et al.2009 (622) ● 19359333	**Study type:** Markov model, lifetime projection. Effectiveness from meta-analysis of 6 RCTs. European costs. **Size:** Not applicable	1° prevention. Patients with EF <35%, ischemic or non-ischemic etiology.	ICD €64,600; conventional therapy €18,187	ICD 8.58 life-y (7.27 QALY); conventional therapy 6.71 life-y (5.70 QALY)	ICER= €24,800/ life-y gained ($27,700) €29,500/QALY gained ($33,000)	● High value by ACC/AHA benchmarks. ● Authors concluded: Prophylactic ICD implantation had high value if current guidelines for patients with EF <35% are followed.

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