REVIEW ARTICLE

CURRENT CONCEPTS

Implantable Cardioverter–Defibrillators after Myocardial Infarction

Robert J. Myerburg, M.D.

From the Division of Cardiology, University of Miami Miller School of Medicine, Miami. Address reprint requests to Dr. Myerburg at the Division of Cardiology (D-39), University of Miami Miller School of Medicine, P.O. Box 016960, Miami, FL 33101, or at rmyerbur@med.miami.edu.

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Persons who survive a myocardial infarction are at increased risk for sudden death from cardiac causes, owing largely to ventricular tachyarrhythmias.[1,2] The risk of sudden death after a myocardial infarction is highest during the first 12 months and then declines.[3-6] Although survival during the acute and early convalescent phases after a myocardial infarction has improved as a result of therapies introduced during the past 25 years,[7] a delayed increase in the risk of sudden death from cardiac causes after the initial convalescent phase has become evident. Those in whom ventricular remodeling and heart failure develop are at greatest risk[8,9] (Fig. 1).

In studies from the 1980s, a low ejection fraction was shown to predict the risk of death after a myocardial infarction. In addition, the presence of spontaneous ventricular arrhythmias that occur during ambulatory monitoring (termed ambient ventricular arrhythmias) was shown to be associated with an increased risk of sudden death.[4,10] On the basis of these observations, therapy with antiarrhythmic drugs was evaluated for its efficacy in preventing sudden death from cardiac causes among patients who had a low ejection fraction and ambient arrhythmias after a myocardial infarction.[11] However, therapy with the class 1-C antiarrhythmic agents encainide and flecainide was shown to increase mortality among patients in the Cardiac Arrhythmia Suppression Trial (CAST),[12,13] and no survival benefit was seen with amiodarone treatment after a myocardial infarction in two subsequent trials[14,15] These findings discouraged the use of antiarrhythmic drugs for reducing the risk of sudden death from cardiac causes. Attention turned to the rapidly evolving technology of the implantable cardioverter–defibrillator (ICD) as a potential approach to this unresolved clinical problem.

Evidence of the Benefit and Reliability of ICDs

ICDs are designed to sense life-threatening arrhythmias and are reported to be more than 97% successful in responding with electrical therapy to terminate them.[16] However, early evidence supporting a survival benefit of ICDs was based largely on observations from relatively small cohorts of very-high-risk patients. Seventeen years elapsed between the first implantation of an ICD and the publication in 1996 of the results of the first randomized trial of ICD therapy.[17] During that interval, debates continued between proponents of drug therapy that was guided by information from ambulatory monitoring or electrophysiological testing and supporters of the empirical use of ICDs.[18-20] Subsequent data from clinical trials established the benefit of ICD therapy and led to more widespread acceptance of the device and broader indications for its use for various categories of tachyarrhythmic risk.[21-27]

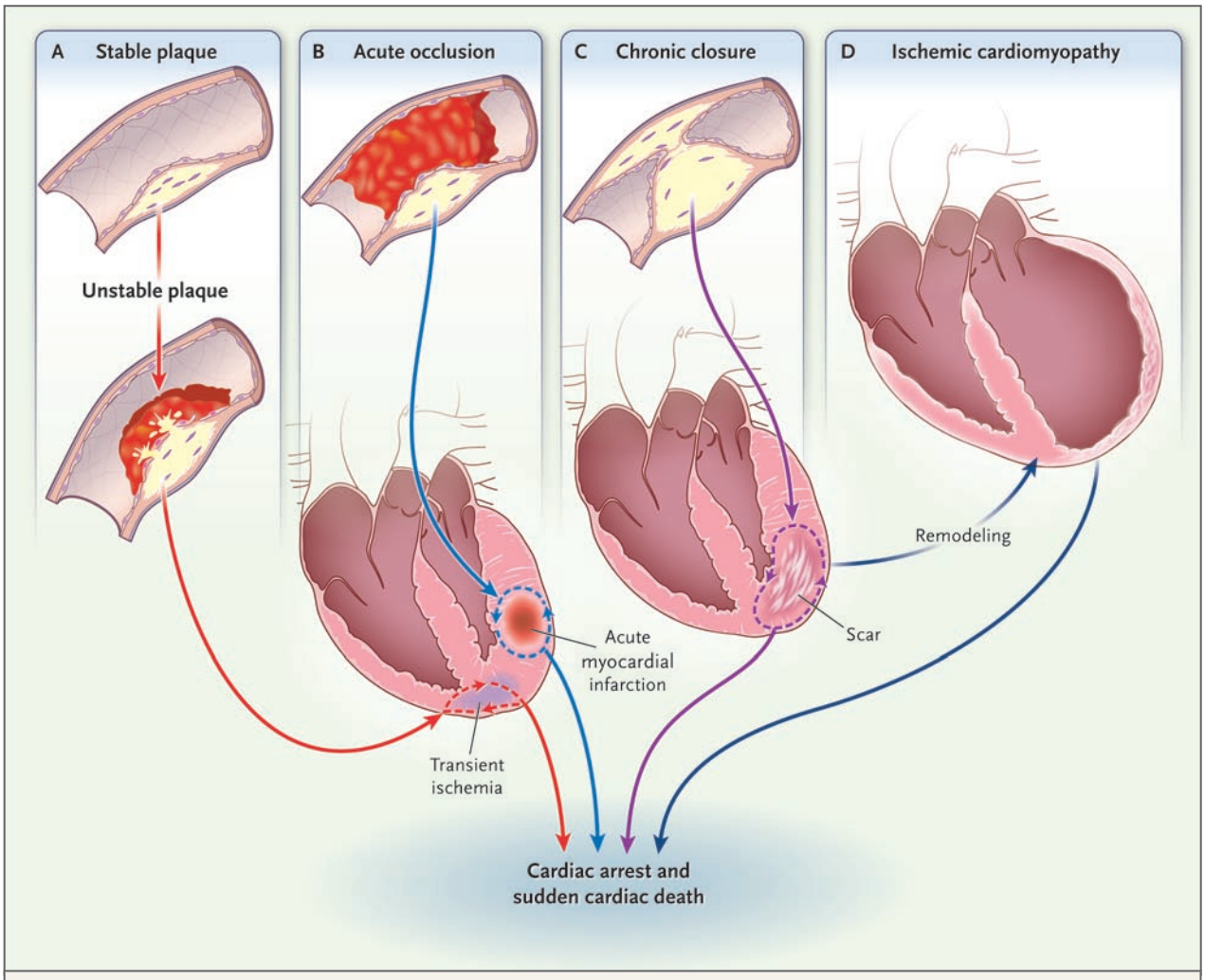

Figure 1. Pathophysiology of Life-Threatening Tachyarrhythmias in Coronary Heart Disease.

Short- and long-term risks of ventricular tachycardia or ventricular fibrillation, and of recurrent events, are related to the presence of transient or persistent physiological factors. Ventricular tachycardia or ventricular fibrillation caused by transient ischemia (Panel A) and the acute phase of myocardial infarction (24 to 48 hours after onset) (Panel B) are not predictive of recurrent events if recurrent ischemia is preventable. In contrast, ventricular tachycardia or ventricular fibrillation associated with healed myocardial tissue, with or without acute transient ischemia (Panel C), is associated with the risk of recurrence. Long-standing ischemic cardiomyopathy (Panel D), especially when accompanied by heart failure, establishes a substrate associated with the long-term risk of ventricular tachycardia or ventricular fibrillation. (Modified from Huikuri et al.[1])

Randomized trials have investigated the use of an ICD for both primary and secondary prevention.[28] ICD therapy for secondary prevention targets patients who have survived a life-threatening ventricular arrhythmia, as well as selected high-risk patients who have unexplained syncope that is thought to be due to tachyarrhythmias. Primary prevention targets high-risk patients in whom life-threatening arrhythmias have not yet occurred.

The cumulative results of three secondary-prevention trials have led to a general acceptance of ICD therapy for most survivors of tachyarrhythmic cardiac arrest.[22,24,25] The major exceptions are patients in whom arrhythmias are triggered by transient or reversible conditions. For example, ventricular fibrillation or ventricular tachycardia that occurs during the acute phase of a myocardial infarction (the first 24 to 48 hours) is caused by electrophysiological changes that are due to acute ischemia and injury, and the condition stabilizes as the infarct evolves (Fig. 1B).

Such arrhythmias do not predict future arrhythmic events and are not an indication for implantation of an ICD.[29]

PRIMARY PREVENTION OF SUDDEN DEATH AFTER MYOCARDIAL INFARCTION

In contrast to the fairly clear role of ICD therapy for secondary prevention, the optimal approach to the appropriate selection of patients for primary prevention has been more difficult to define. Several major trials, including the Multicenter Automatic Defibrillator Implantation Trial (MADIT),[17] the Multicenter Unsustained Tachycardia Trial (MUSTT),[23] the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II),[26] the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (ClinicalTrials.gov number, NCT00000609),[27] and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT),[30] have addressed this issue (see Table 1 for summaries of individual trials, and the Supplementary Appendix, available with the full text of this article at www.nejm.org, for further details). Although the results of most of these studies have confirmed a significant benefit of ICD therapy, these trials, especially MADIT II and SCD-HeFT, had broad enrollment criteria, with limited stratification of the study populations, and have shown relatively small absolute improvements in the outcomes (Table 1).

In 2005, the Centers for Medicare and Medicaid Services (CMS) estimated that as many as 500,000 Medicare beneficiaries might be eligible for an ICD on the basis of the available trial criteria, at a cost of $30,000 per case.[31] These estimates, and the challenge of predicting individual risk, have led to concerns that ICDs may be used too broadly and perhaps in some subgroups for which the actual benefit from therapy will be very modest.

According to current CMS policy, ICD therapy is approved for patients who have ejection fractions of 35% or less, ambient episodes of nonsustained ventricular tachycardia, and inducible ventricular tachycardia. These criteria are based on data from MADIT[17] and MUSTT[23] (Table 1). In addition, ICDs are approved for patients with ejection fractions of 30% or less and for those who have New York Heart Association (NYHA) class II or III heart failure with ejection fractions

Table 1. Summary of Major Randomized Trials of ICD Therapy for Primary Prevention of Sudden Death after Myocardial Infarction.*

Trial	Defined Entry Criteria	Time from Qualifying MI		Ejection Fraction of Enrolled Patients	All-Cause Mortality		Reduction in Mortality with ICD Therapy	
		Entry Criterion	Actual		Control Group	ICD Group	Relative	Absolute
				%	*% of patients*		*% reduction*	
MADIT (2-yr analysis)	EF ≤35%, previous MI, nonsustained VT, inducible VT not suppressed by intravenous administration of antiarrhythmic agents	≥3 wk	≥6 mo in 75% of cases	26±7	32	13	59	19
MUSTT (5-yr analysis)†	EF ≤40%, previous MI, nonsustained VT, inducible VT	Not defined	≥1 mo in 16% of cases; ≥3 yr in 49% of cases	Median, 30 (interquartile range, 21–35)	55	24	58	31
MADIT II (2-yr analysis)	EF ≤30%, previous MI	≥1 mo	≥6 mo in 88% of cases	23±5	22	16	28	6
SCD-HeFT (5-yr analysis)	EF ≤35%, NYHA class II or III congestive heart failure due to coronary heart disease or nonischemic cardiomyopathy	Not defined	Median, 4.3 yr	Median, 25 (interquartile range, 20–30)	36	29	23	7
DINAMIT (2.5-yr analysis)	EF ≤35%, recent MI, abnormal HRV	6–40 days	Mean, 18 days	28±5	17	19	—	—

* Plus–minus values are means ±SD. DINAMIT denotes Defibrillator in Acute Myocardial Infarction Trial,[30] EF ejection fraction, HRV heart-rate variability, MADIT Multicenter Automatic Defibrillator Implantation Trial,[17] MADIT II Multicenter Automatic Defibrillator Implantation Trial II,[26] MI myocardial infarction, MUSTT Multicenter Unsustained Tachycardia Trial,[23] NYHA New York Heart Association, SCD-HeFT Sudden Cardiac Death in Heart Failure Trial,[27] and VT ventricular tachycardia.

† For the MUSTT results listed here, all-cause mortality and relative and absolute risk reductions are for the group that received antiarrhythmic treatment based on electrophysiological guidance, as compared with the ICD subgroup, in most of whom drug therapy failed, as assessed by electrophysiological testing.

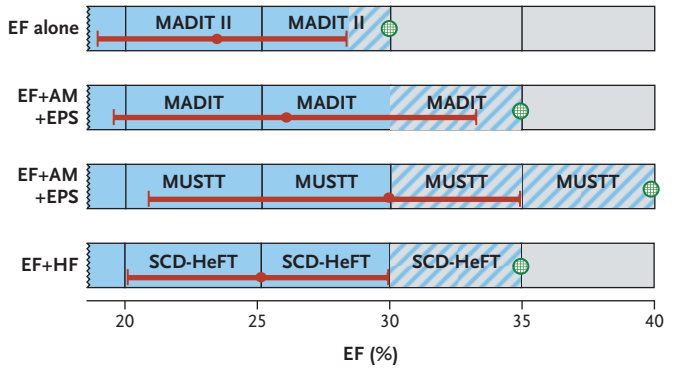

Figure 2. Ejection Fractions of Subjects Enrolled in the ICD Trials.

The figure shows defined entry criteria for ejection fraction (EF) and EFs of subjects enrolled in ICD trials. Each of these four primary prevention trials had a qualifying EF cutoff (green circles), above which patients were not enrolled in the trials (gray boxes). In each study, the EF subgroup that dominated enrollment (solid blue boxes [mean ±SD for MADIT and MADIT II and median and interquartile ranges for MUSTT and SCD-HeFT]) received a measurable benefit from ICD therapy, whereas those whose EF extended to the upper limit of entry criterion (striped blue boxes) were underrepresented, received no benefit, or received an uncertain benefit. AM denotes ambulatory monitor, EPS electrophysiological study, and HF heart failure.

of 35% or less. These criteria are based on data from MADIT II[26] and SCD-HeFT,[27] respectively. In all these cases, implantation of an ICD is approved only after 40 days or more have elapsed from the time of the myocardial infarction, on the basis of data from DINAMIT.[30]

The available practice guidelines, although substantially similar to the CMS criteria, differ in some specifics. The 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death from the American College of Cardiology, the American Heart Association, and the European Society of Cardiology[29] use ranges of ejection fraction to define the limits for consideration of ICD therapy. They set the upper limit of the ejection fraction in a range of 30 to 35% among patients who do not have heart failure and in a range of 30 to 40% among patients with NYHA class II or III heart failure. Patients in both categories qualify for implantation 40 days or more after a myocardial infarction. The 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities from the American College of Cardiology, the American Heart Association, and the Heart Rhythm Society[32] adhere more closely to the specific ejection-fraction limits used in the major ICD studies, avoiding ranges but also adhering to the 40-day rule.

SELECTION OF PATIENTS FOR PRIMARY PREVENTION

The ICD trials showed a benefit of ICD implantation for high-risk patients who have had a myocardial infarction. However, they did not define specific criteria for the use of ICDs in individual patients or in subgroups. Neither the CMS criteria nor the practice guidelines are able to provide a clear consensus about the way in which the data should be applied selectively, on the basis of the characteristics of the individual patient. The following discussion outlines some of the factors that should be taken into consideration in the selection of patients for ICD therapy.

EJECTION FRACTION

The one entry criterion that is common to all of the ICD studies is a qualifying ejection fraction. Each of the trials used a single ejection-fraction threshold, most often 35%, with a range of 30 to 40% (Table 1). However, the differences between the entry criteria and the mean or median values for patients who were actually enrolled in the trial were large (7 to 10%) (Table 1 and Fig. 2). Yet it is the upper limit that is the basis for current treatment recommendations. For example, in SCD-HeFT, the ejection-fraction threshold for entry into the trial was 35%, but the enrolled patients had a median ejection fraction of 25%, with an interquartile range of 20 to 30%. A subgroup analysis of participants who had ejection fractions higher than 30% suggested no benefit from ICD therapy. A similar trend was seen in the MADIT and MADIT II study populations.[17,26,33]

HEART FAILURE

A history of heart failure influences the likelihood that a patient will benefit from ICD therapy.[33-35] Whereas SCD-HeFT was designed to study ICD therapy in patients with stable NYHA class II or III heart failure, MADIT II required only a low ejection fraction and did not require the presence of clinical heart failure for enrollment. Nonetheless, hospitalization for episodic heart failure was a strong indicator of future ICD use and of death among patients enrolled in MADIT II.[36] Thus, if

implantation of an ICD is questioned because the ejection fraction is in the range of uncertainty (Fig. 2), a history of heart failure tips the scale in favor of ICD therapy.

QRS DURATION

In a subgroup analysis from MADIT II, a prolonged duration of the QRS interval on the electrocardiogram was associated with a benefit from ICD therapy, whereas a normal duration of the QRS interval was associated with an uncertain benefit (if any).[26] The first set of ICD indications approved by the CMS after the MADIT II criteria were published included a QRS duration of 120 msec or more.[31] Subsequently, this criterion was removed from the CMS approval policy on the basis of the results of SCD-HeFT[27] and a reassessment of the predictive value of the QRS duration.[37] It is nonetheless reasonable to take a prolonged duration of the QRS complex into account in making decisions about the treatment of individual patients (Fig. 2).

TIME-DEPENDENT BENEFIT

All of the patients in MADIT and MADIT II, and almost all of those in MUSTT, were enrolled more than 3 weeks after they had had a myocardial infarction (Table 1). The DINAMIT trial[30] specifically addressed the potential benefit of ICD implantation in patients with a reduced ejection fraction in the early period after a myocardial infarction. Patients were randomly assigned to a study group 6 to 40 days after a myocardial infarction, with a mean interval of 18 days between the myocardial infarction and enrollment. Despite the higher risk of sudden death from cardiac causes in the early period after a myocardial infarction, there was no reduction in all-cause mortality in the group that received an ICD.

One possible explanation of the results from DINAMIT is that the prognostic value of an ejection fraction depends on when it is measured. The DINAMIT study population had a mean (±SD) ejection fraction (28±5%) that was similar to the mean ejection fraction in the other primary-prevention trials. However, some patients with early left ventricular dysfunction may have partial or complete recovery of function when they are restudied at 7 months, particularly if they receive acute reperfusion therapy.[38] This issue awaits clarification from additional research.

Physicians are also commonly confronted with the need to decide whether a patient who meets indication criteria for ICD therapy many months or years after a myocardial infarction is still considered a candidate for implantation of an ICD, even though he or she has had no events for a substantial length of time. Subgroup analyses from the ICD trials suggest that there is an increased benefit at 3, 4, or more years after a myocardial infarction,[26,27,39] probably because the risk of arrhythmia may increase over time as a result of progressive remodeling and its hemodynamic consequences (Fig. 1D). Accordingly, a long interval from the most recent myocardial infarction should not preclude consideration of ICD therapy.

COEXISTING CONDITIONS AND AGE

Patients who have serious coexisting conditions and an expected survival of 1 year or less and patients with NYHA class IV heart failure are not considered candidates for ICD therapy according to both practice guidelines and current CMS-approved indications. Patients with heart failure who have moderate-to-severe renal dysfunction have a very poor prognosis, regardless of whether they receive an ICD.[40] Studies suggest that such patients do not have a survival benefit from ICDs.[36,41] The effect of other coexisting conditions (e.g., chronic lung disease and cancer) has not been systematically studied.

Age limits for ICD therapy are not specified in the practice guidelines or by the CMS. The majority of patients who were enrolled in the trials of ICD therapy after a myocardial infarction were between 60 and 70 years of age at entry. On the basis of life-table data for 2004 in the United States, the average number of additional years of life expected for people who reach the age of 70 years is 15.1, and the average number for people who reach the age of 80 is 9.1.[42] Although participants in ICD trials are not likely to be representative of people in the general elderly population, an analysis from MADIT II suggests that patients 75 years of age or older are no less likely to have a survival benefit from an ICD than younger patients.[43] Age limitations for ICD implantation should be considered in the context of coexisting conditions and the quality of life of the candidate, with recommendations individualized through discussions with the patient and family members.

OTHER CONSIDERATIONS

Implantation of an ICD is a minor surgical procedure that is accompanied by a small risk of surgical complications, primarily bleeding, infection, and vascular lacerations or cardiac perforations. The reported incidence of procedure-related complications does not substantially affect the expected benefit of the device for appropriate candidates. However, the risk of surgery should be taken into consideration when patients with marginal indications are referred for ICD therapy and in the rare circumstances when there are increased risks of bleeding or infection as a result of concomitant bleeding diatheses or immunodeficient states.

During long-term follow-up, optimal treatment requires coordination between the patient's primary physicians (generalists, internists, and cardiologists) and the electrophysiologist.[44] The requirement for repeated routine and event-related downloading of the information from the ICD is an inconvenience, rather than a risk, but compliance is important for long-term management of the device and for patient safety. Remote-monitoring technology is likely to alleviate much of this inconvenience.

A malfunction of the ICD can be life-threatening and may require replacement of the pulse generator or leads.[45,46] However, because device malfunction is infrequent, and because some types of malfunction can be tracked or modified by reprogramming, the possibility of future malfunction should not influence the decision about whether to implant an ICD. Efforts to reduce the risk of complications resulting from malfunction of the device should include improved detection of malfunction by means of better surveillance methods,[45] communication of information to physicians and patients by manufacturers and the Food and Drug Administration, and clear definition of the indications for early replacement of devices or leads.[46] Decisions about elective replacement of the ICD are complex and should be guided by an electrophysiologist, in consultation with the treating physician and the patient.

AREAS OF UNCERTAINTY

The decision to proceed with the implantation of an ICD requires consideration of the clinical-trial criteria, the society guidelines, and CMS policies; consideration of all these factors must be modulated by an understanding of the issues discussed above and by clinical judgment. Unfortunately, there is no established approach for synthesizing the various elements of the risk of sudden death and the benefit of ICD therapy for the individual patient. Although recent analyses from MADIT II[36] and MUSTT[47] describe scoring systems that could be used for risk stratification, these algorithms

Table 2. Variables That May Increase the Strength of the ICD Indication Based on Ejection Fraction.*

Modifier of EF	Increase in Strength of Indication			
	EF ≤25% (strong indication)	EF 26%–35% (variable indication)		EF >35% (no indication or no data available)
		EF 26%–30% (probable indication)	EF 31%–35% (uncertain indication)	
Heart failure	Uncertain	Likely	Uncertain	Unknown
Ambient nonsustained VT; induced VT†	Possible	Likely	Probable	Possible
QRS interval ≥0.12 sec	Possible	Likely	Possible	Unknown
Deteriorating EF over time	Uncertain	Possible	Likely	Probable

* Data on ejection-fraction (EF) indicators and other variables are derived from data in published randomized trials of ICDs.[17,23,26,27,30] EF indication is based on EF measured more than 2 weeks after a myocardial infarction. Classifications of added value modifiers of EF data are as follows: likely refers to strong support from subgroup data; probable, to support from subgroup data or other sources; possible, to limited support from subgroup data; uncertain, to equivocal or unlikely support from subgroup data or other sources; unknown, to the lack of available data. The values assigned to the modifiers are intended as guides to decision making and are the author's opinion derived from subgroup analyses of published trials and other sources of risk data. They do not necessarily align exactly with practice guidelines and are subject to modification as new clinical research dictates in the future.

† Induced ventricular tachycardia (VT) refers to VT induced by programmed electrical stimulation.

have not been prospectively validated and can serve only as partial guides to clinical decision making.

One area of uncertainty is the reliability of the measurement of the ejection fraction. Although there are methods available for quantitating echocardiographic, nuclear, or angiographic estimates of the ejection fraction, the use of such methods in clinical practice is limited. In fact, many reported ejection fractions are visual estimates, which are subject to bias and reader error. If we are to use the ejection fraction as the major objective criterion for ICD implantation, we will need better methods and practice standards to provide uniform measurements.

We also lack sufficient information about the evolution of the ejection fraction over time and the way in which this influences risk. The interval between myocardial infarction and study enrollment varied widely among patients in the ICD trials (except in DINAMIT). In addition, the interval between myocardial infarction and measurement of the ejection fraction was not uniform. Thus, the optimal time for measurement of the ejection fraction is uncertain. Until further data are available, patients with initially marginal indications for ICD therapy in whom the ejection fraction deteriorates over time should be considered for ICD therapy, especially if they have other risk factors (Table 2).

Efforts to identify additional measures of risk with independent or additive predictive power are under way. These include techniques such as microvolt T-wave alternans[48] and magnetic resonance imaging with the use of contrast material to define the anatomy of the infarct,[49,50] as well as measures of QT variability,[51] derivatives of measures of heart-rate variability,[52-54] and studies of familial clustering of sudden death as the first clinical expression of coronary artery disease[55-57] and the possible value of genetic risk profiling.[58] With the possible exception of T-wave alternans testing, which some practitioners have adopted as a means of further risk stratification, these measures are all in their infancy with respect to their application in clinical practice.

RECOMMENDATIONS

Because of the limitations of the available data and current guidelines, the selection of patients to receive an ICD for primary prevention is not uniform in clinical practice.[59,60] A reasonable approach is to begin with an assessment of the ejection fraction and then consider the modifying factors discussed above (Table 2).

Patients with ejection fractions higher than 35% after a myocardial infarction are not currently considered to be candidates for ICD implantation. Although one of the studies did set an ejection-fraction threshold of 40%,[23] there was no suggested benefit for patients with ejection fractions higher than 35%. For patients with ejection fractions in the range of 30 to 40%, a reassessment of ventricular function every 6 to 12 months is prudent.

For patients with ejection fractions between 25 and 35%, additional factors should be considered. Within this range, there is some evidence of greater benefit among patients with ejection fractions that are closer to 25%, and less, if any, benefit for those with ejection fractions closer to 35%. Modifying factors include symptomatic heart failure or a history of heart failure, documented nonsustained or inducible ventricular tachycardia, and a prolonged duration of the QRS interval (Table 2). For patients with none of these modifying factors, implantation of an ICD may be deferred, particularly when the ejection fraction is in the range of 30 to 35%. Decision making involving patients in this category should include a discussion with the patient and his or her referring physician to gauge their preferences. Finally, patients with ejection fractions of 25% or less should generally be considered suitable candidates, even in the absence of the modifying factors.

As noted above, patients with NYHA class IV heart failure were not included in the major trials and are not considered to meet standard criteria for implantation of an ICD. Candidates for heart transplantation may receive an ICD in order to reduce the risk that sudden death will occur during the time the patient is awaiting a donor heart. Some patients with relatively stable, early class IV heart failure may also be considered for ICD therapy, usually in combination with resynchronization pacing, but patients with unstable class IV heart failure are typically hospitalized for more urgent heart transplantation, support with a ventricular assist device, or palliative care.

These principles are tempered by consideration of the overall clinical picture. In order to be suitable candidates, patients over the age of 75 years,

and especially those over the age of 80, must have no other life-limiting coexisting condition and should be in reasonably robust physical condition (to the extent that their heart condition allows) and have normal or near-normal cognition. Patients with poorly controlled bleeding diatheses, systemic immunosuppression, or persistent compliance problems should be considered on an individual basis but may not be appropriate candidates for ICD therapy. In all of these cases, a detailed discussion of the issues with the patient and his or her referring physician is an essential part of appropriate care.

These recommendations are provisional and are likely to change as more information becomes available. Additional objective stratifying criteria are needed and are likely to emerge from further research. In the meantime, ICD therapy should be neither denied nor overextended while we are awaiting better evidence-based algorithms. Physicians familiar with the current criteria and their limitations are in the best position to exercise reasonable judgment. Patients should be advised of the issues involved and included in the discussion of the appropriateness of ICD implantation for them.

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REFERENCES

1. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Engl J Med 2001;345:1473-82.
2. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Libby P, Bonow RO, Mann DL, Zipes DP, eds. Braunwald's heart disease. 8th ed. Philadelphia: Saunders Elsevier, 2008:933-74.
3. Mukharji J, Rude RE, Poole WK, et al. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. Am J Cardiol 1984;54:31-6.
4. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N Engl J Med 1983;309:331-6.
5. Ross AM, Coyne KS, Moreyra E, et al. Extended mortality benefit of early postinfarction reperfusion. Circulation 1998; 97:1549-56.
6. Solomon SD, Zelenkofske S, McMurray JJV, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. N Engl J Med 2005;352:2581-8. [Erratum, N Engl J Med 2005;353:744.]
7. Braunwald E. Shattuck Lecture — Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities. N Engl J Med 1997;337:1360-9.
8. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. Circulation 1990;81:1161-72.
9. Pfeffer MA, Braunwald E, Moyé LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement trial. N Engl J Med 1992;327: 669-77.
10. Bigger JT Jr, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM. The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984;69:250-8.
11. The Cardiac Arrhythmia Pilot Study (CAPS) Investigators. Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after acute myocardial infarction: the CAPS. Am J Cardiol 1988;61:501-9.
12. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 1989;321:406-12.
13. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo: the Cardiac Arrhythmia Suppression Trial. N Engl J Med 1991;324:781-8.
14. Julian DG, Camm AJ, Frangin G, et al. Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. Lancet 1997;349:667-74. [Errata, Lancet 1997;349:1180, 1776.]
15. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Lancet 1997;349:675-82. [Erratum, Lancet 1997; 349:1776.]
16. Zipes DP, Roberts D. Results of the international study of the implantable pacemaker cardioverter-defibrillator: a comparison of epicardial and endocardial lead systems. Circulation 1995;92:59-65.
17. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 1996;335:1933-40.
18. Buxton AE, Marchlinski FE, Flores BT, Miller JM, Doherty JU, Josephson ME. Nonsustained ventricular tachycardia in patients with coronary artery disease: role of electrophysiologic study. Circulation 1987;75:1178-85.
19. Wilber DJ, Olshansky B, Moran JF, Scanlon PJ. Electrophysiological testing and nonsustained ventricular tachycardia: use and limitation in patients with coronary artery disease and impaired ventricular function. Circulation 1990;82:350-8.
20. Bourke JP, Richards DAB, Ross DL, Wallace EM, McGuire MA, Uther JB. Routine programmed electrical stimulation in survivors of acute myocardial infarction for prediction of spontaneous ventricular tachyarrhythmias during follow-up: results, optimal stimulation protocol and cost-effective screening. J Am Coll Cardiol 1991;18:780-8.
21. Bigger JT. Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. N Engl J Med 1997;337:1569-75.
22. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997; 337:1576-83.
23. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-90. [Erratum, N Engl J Med 2000;342:1300.]

24. Connolly SJ, Gent M, Roberts RS, et al. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.
25. Kuck KH, Cappato R, Siebels J, Rüppel R. Randomized comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 2000; 102:748-54.
26. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
27. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37. [Erratum, N Engl J Med 2005;352:2146.]
28. Myerburg RJ, Castellanos A. Emerging paradigms of the epidemiology and demographics of sudden cardiac arrest. Heart Rhythm 2006;3:235-9.
29. Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC 2006 guidelines 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 and the European Society of Cardiology Committee for Practice Guidelines. Circulation 2006;114: e385-e484.
30. Hohnloser SH, Kuck KH, Dorian P, et al. Prophylactic use of an implantable cardioverter–defibrillator after acute myocardial infarction. N Engl J Med 2004;351: 2481-8.
31. McClellan MB, Tunis SR. Medicare coverage of ICDs. N Engl J Med 2005;352: 222-4.
32. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary — a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;51:e1-e62.
33. Moss AJ, Fadl Y, Zareba W, Cannom DS, Hall WJ. Survival benefit with an implanted defibrillator in relation to mortality risk in chronic coronary heart disease. Am J Cardiol 2001;88:516-20.
34. Huikuri HV, Tapanainen JM, Lindgren K, et al. Prediction of sudden cardiac death after myocardial infarction in the beta-blocking era. J Am Coll Cardiol 2003;42: 652-8.
35. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). J Am Coll Cardiol 2004;43: 1459-65.
36. Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2008;51:288-96.
37. Buxton AE, Sweeney MO, Wathen MS, et al. QRS duration does not predict occurrence of ventricular tachyarrhythmias in patients with implanted cardioverter-defibrillators. J Am Coll Cardiol 2005;46: 310-6.
38. Halkin A, Stone GW, Dixon SR, et al. Impact and determinants of left ventricular function in patients undergoing primary percutaneous coronary intervention in acute myocardial infarction. Am J Cardiol 2005;96:325-31.
39. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. Circulation 2004;109:1082-4.
40. Cuculich PS, Sanchez JM, Kerzner R, et al. Poor prognosis for patients with chronic kidney disease despite ICD therapy for the primary prevention of sudden death. Pacing Clin Electrophysiol 2007;30: 207-13.
41. Amin MS, Fox AD, Kalahasty G, Shepard RK, Wood MA, Ellenbogen KA. Benefit of primary prevention implantable cardioverter-defibrillators in the setting of chronic kidney disease: a decision model analysis. J Cardiovasc Electrophysiol 2008 July 25 (Epub ahead of print).
42. Arias E. United States life tables, 2004. National vital statistics reports. Vol. 56. No. 9. Hyattsville, MD: National Center for Health Statistics, 2007.
43. Huang DT, Sesselberg HW, McNitt S, et al. Improved survival associated with prophylactic implantable defibrillators in elderly patients with prior myocardial infarction and depressed ventricular function: a MADIT-II substudy. J Cardiovasc Electrophysiol 2007;18:833-8.
44. Linzer M, Myerburg RJ, Kutner JS, et al. Exploring the generalist-subspecialist interface in internal medicine. Am J Med 2006;119:528-37.
45. Myerburg RJ, Feigal DW Jr, Lindsay BD. Life-threatening malfunction of implantable cardiac devices. N Engl J Med 2006;354:2309-11.
46. Maisel WH. Safety issues involving medical devices: implications of recent implantable cardioverter-defibrillator malfunctions. JAMA 2005;294:955-8.
47. Buxton AE, Lee KL, Hafley GE, et al. Limitations of ejection fraction for prediction of sudden death risk in patients with coronary artery disease: lessons from the MUSTT study. J Am Coll Cardiol 2007; 50:1150-7.
48. Bloomfield DM, Steinman RC, Namerow PB, et al. Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation 2004;110:1885-9.
49. Yan AT, Shayne AJ, Brown KA, et al. Characterization of the peri-infarct zone by contrast-enhanced cardiac magnetic resonance imaging is a powerful predictor of post-myocardial infarction mortality. Circulation 2006;114:32-9.
50. Schmidt A, Azevedo CF, Cheng A, et al. Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. Circulation 2007;115:2006-14.
51. Haigney MC, Zareba W, Gentlesk PJ, et al. QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol 2004;44:1481-7.
52. Bauer A, Kantelhardt JW, Barthel P, et al. Deceleration capacity of heart rate as a predictor of mortality after myocardial infarction: cohort study. Lancet 2006;367: 1674-81.
53. Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 2003;108:1221-6.
54. Mäkikallio TH, Barthel P, Schneider R, et al. Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. Eur Heart J 2005;26:762-9.
55. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. Circulation 1999;99:1978-83.
56. Dekker LR, Bezzina CR, Henriques JP, et al. Familial sudden death is an important risk factor for primary ventricular fibrillation: a case-control study in acute myocardial infarction patients. Circulation 2006;114:1140-5.
57. Kaikkonen KS, Kortelainen ML, Linna E, Huikuri HV. Family history and the risk of sudden cardiac death as a manifestation of an acute coronary event. Circulation 2006;114:1462-7.
58. Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. J Cardiovasc Electrophysiol 2002;13: 709-23.
59. Buxton AE. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter-defibrillator? Not everyone with an ejection fraction < or = 30% should receive an ICD. Circulation 2005;111:2537-42.
60. Moss AJ. Should everyone with an ejection fraction less than or equal to 30% receive an implantable cardioverter-defibrillator? Everyone with an ejection fraction < or = 30% should receive an implantable cardioverter-defibrillator. Circulation 2005;111:2542-8.