PERSONS WHO SURVIVE A MYOCARDIAL INFARCTION ARE AT INCREASED risk for sudden death from cardiac causes, owing largely to ventricular tachyarrhythmias. The risk of sudden death after a myocardial infarction is highest during the first 12 months and then declines. 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, 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 (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. 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. 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), and no survival benefit was seen with amiodarone treatment after a myocardial infarction in two subsequent trials. 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. 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. 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. 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.
Randomized trials have investigated the use of an ICD for both primary and secondary prevention. 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. The major exceptions are patients in whom arrhythmias are triggered by transient or reversible conditions. For example, 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.)

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.)
Such arrhythmias do not predict future arrhythmic events and are not an indication for implantation of an ICD.\textsuperscript{20}

**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),\textsuperscript{17} the Multicenter Unsustained Tachycardia Trial (MUSTT),\textsuperscript{23} the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II),\textsuperscript{26} the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (ClinicalTrials.gov number, NCT00000609),\textsuperscript{27} and the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT),\textsuperscript{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.\textsuperscript{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\textsuperscript{17} and MUSTT\textsuperscript{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** |
| | | | | **Reduction in All-Cause Mortality with ICD** | **Relative Absolute % of patients % reduction** | **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 | ≥2 wk | ≥6 mo in 75% of cases | 26±7 | 13 | 2 | 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) | 22 | 16 | 6 |
| MADIT II (2-yr analysis) | EF ≤30%, previous MI ≥1 mo | ≥6 mo in 88% of cases | 23±5 | 15 | 7 |
| SCD-HeFT (5-yr analysis) | EF ≤35%, NYHA class I or II congestive heart failure due to coronary heart disease or nonischemic cardiomyopathy | Not defined | Median, 4 yr | Median, 25 (interquartile range, 20–30) | 23 | 19 |
| DINAMIT (2.5-yr analysis) | EF ≤35%, recent MI abnormal HRV | 6–40 days | 28±5 | 17 | — |

* Plus–minus values are means ±SD. DINAMIT denotes Defibrillator in Acute Myocardial Infarction Trial, HRV heart-rate variability, MADIT Multicenter Automatic Defibrillator Implantation Trial, MADIT II Multicenter Automatic Defibrillator Implantation Trial II, MUSTT Multicenter Unsustained Tachycardia Trial, NYHA New York Heart Association, SCD-HeFT Sudden Cardiac Death in Heart Failure Trial, 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 testing.
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

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**

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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). 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. Subsequently, this criterion was removed from the CMS approval policy on the basis of the results of SCD-HeFT and a reassessment of the predictive value of the QRS duration. 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 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. 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, 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. Studies suggest that such patients do not have a survival benefit from ICDs. 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. 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. 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. 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. 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, 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. 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 and MUSTT describe scoring systems that could be used for risk stratification, these algorithms require adjustment to fit local clinical practice and resource availability.

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

<table>
<thead>
<tr>
<th>Modifier of EF</th>
<th>Increase in Strength of Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF ≤25% (strong indication)</td>
<td>EF 26%–35% (variable indication)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Uncertain</td>
</tr>
<tr>
<td>Ambient nonsustained VT; induced VT†</td>
<td>Possible</td>
</tr>
<tr>
<td>QRS interval ≥0.12 sec</td>
<td>Possible</td>
</tr>
<tr>
<td>Deteriorating EF over time</td>
<td>Uncertain</td>
</tr>
</tbody>
</table>

* Data on ejection-fraction (EF) indicators and other variables are derived from data in published randomized trials of ICDs. The 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 limited support from subgroup data; uncertain, to equivocal or unlikely 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 and magnetic resonance imaging with the use of contrast material to define the anatomy of the infarct, as well as measures of QT variability, derivatives of measures of heart-rate variability, and studies of familial clustering of sudden death as the first clinical expression of coronary artery disease and the possible value of genetic risk profiling. 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. 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%, 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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