

## Indications for Implantable Cardioverter-Defibrillators Based on Evidence and Judgment

Robert J. Myerburg, MD, Vivek Reddy, MD, Agustin Castellanos, MD

*Miami, Florida*

Implantable cardioverter-defibrillators (ICDs) are generally reliable medical devices that have the potential to add quality years of life for appropriate candidates. Indications for ICDs have emerged from a series of randomized clinical trials, observational data from cohorts of high-risk patients with less common diseases, and expert opinion based on limited data in uncommon disorders. The randomized trials are limited by inadequate stratification designs that resulted from insufficient funding availability. The result was outcomes that led to uneven applications, based in part on post-implant experience of device utilization. In this document, we explore the basis for the features of the evidence available to support ICD use, the role of clinical judgment in circumstances in which data are limited or lacking, and the need for additional research to improve the specificity of indications. Directions for new research initiatives are considered. In addition, a general overview of a clinical research paradigm is presented, in which the research and health care delivery arms of the health care enterprise combine in research design and funding, as the latter bears the impact of the outcomes of the former. Impact estimates during the design of trials, considering reasonable contingencies for outcomes, are suggested as a means of justifying the size, scope, and appropriate costs of studies. If we who are involved in clinical research and health care delivery do not resolve this problem, for both ICDs and other new therapies that appear in the future, society will do it for us. (J Am Coll Cardiol 2009;54:747-63) © 2009 by the American College of Cardiology Foundation

The implantable cardioverter-defibrillator (ICD) has emerged as generally accepted therapy for prevention of sudden cardiac death (SCD) in selected categories of patients. Indications are derived from 3 sources of data: 1) randomized clinical trials; 2) observational data from cohorts of high-risk patients with less common diseases; and 3) expert opinion on potential benefit for clinical conditions or specific circumstances in which data are limited or uncertain. For all 3 categories of clinical guidance, there are limitations in available data that reinforce the importance of physician judgment in decision making, based on circumstances of individual cases. Understanding the value and limitations of current information is important not only for the clinical electrophysiologist, but also for general cardiologists and primary care physicians because of their roles in

referring appropriate patients for consideration of ICD therapy.

Categories of disease that have achieved confirmation of ICD benefit from randomized trials, primarily coronary artery disease (CAD) with a prior myocardial infarction (MI), non-ischemic cardiomyopathy, and cardiac arrest survivors generally, have done so within the restrictions of clinical trial designs that provide broad sweeps of statistical benefit. The clinical trial data are hampered by the uncertainties of risk-benefit impact for subgroups within study populations and for individual patients. This is, at least in part, a consequence of funding available for the trials. The purpose of this document is to explore the current scientific basis for clearly defined indications, as well as uncertainties based on limitations of data from randomized clinical trials, observational data, and expert opinions. Opportunities for improving risk prediction and therapeutic efficacy and efficiency by means of new investigative strategies are also explored.

### Evolution of the ICD

Nearly 4 decades elapsed between the original notion that an ICD might be a useful clinical strategy, its subsequent development, and its current acceptance in various clinical settings based on randomized trial data (Fig. 1). Each decade played a distinctive role in the evolution of ICD therapy. From the late 1960s until the first patient implant

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From the Division of Cardiology, University of Miami Miller School of Medicine, Miami, Florida. Dr. Myerburg is supported in part by a grant from the Leducq Foundation (Network on Sudden Cardiac Death), by the Florida Heart Research Foundation, and by the American Heart Association Chair in Cardiovascular Research at the University of Miami Miller School of Medicine; he has also received consulting fees during the past 24 months from Boston Scientific Corporation, Proctor and Gamble, GlaxoSmithKline Pharmaceuticals, and Sanofi-Aventis, and lecture fees from Boston Scientific Corporation, General Electric Company, and St. Jude Medical Corporation. Dr. Reddy has received consulting fees and grants from St. Jude, and speaker honoraria from Medtronic and Boston Scientific.

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**Abbreviations and Acronyms**

- CAD** = coronary artery disease
- CMS** = Center for Medicare and Medicaid Services
- EF** = ejection fraction
- HCM** = hypertrophic cardiomyopathy
- ICD** = implantable cardioverter-defibrillator
- MI** = myocardial infarction
- NYHA** = New York Heart Association
- PVC** = premature ventricular complex
- SCD** = sudden cardiac death
- VF** = ventricular fibrillation
- VT** = ventricular tachycardia

in 1980 (1), Mirowski's concept of a "standby automatic defibrillator" (2,3) met with skepticism (4) and concern about the practical difficulties in designing and manufacturing such a device (5,6). After the first human device implant in 1980, clinical acceptance of the concept was initially slow, but began to accelerate after Food and Drug Administration approval in 1985 and Medicare coverage for limited indications in 1986.

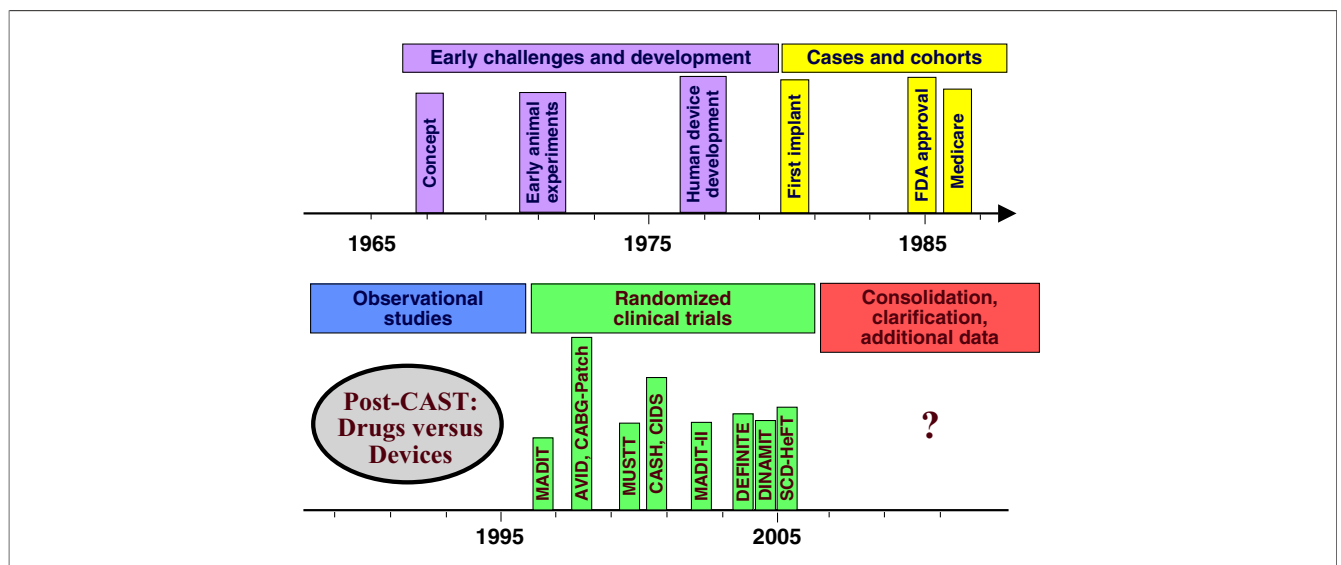
The early scientific support for the clinical value of the ICD was limited to a series of nonrandomized observational studies involving cohorts of high-risk patients. They were counterbalanced by contemporary interest in studies exploring the value of antiarrhythmic drug therapy guided by ambulatory arrhythmia monitoring

or electrophysiological testing, and antiarrhythmic surgical techniques. This created uncertainty and intense debate in the electrophysiology community that continued even after the publication of the CAST (Cardiac Arrhythmia Suppression Trial) study (7,8) highlighted the potential dangers of empiric treatment with membrane-active antiarrhythmic drugs. Nonetheless, the CAST study was seminal in both constituting a turning point of the concept of antiarrhythmic drug therapy for prevention of SCD and serving as a catalyst for the recognition of the importance of randomized trial data to validate the potential for ICD benefit. The vacuum for evidence-based identification of benefits and limitations of ICDs remained until the first randomized clinical trials evaluating efficacy were designed and implemented in the early 1990s and reported in the later part of that decade (9-14), with the first published study appearing nearly 17 years after the first implant (Fig. 1). After 2000, additional clinical trials broadened the indications for, and acceptance of, the device for prophylactic use in post-MI patients (15,16) and in patients with nonischemic cardiomyopathy and heart failure (17,18), as well as for other categories of diseases with tachyarrhythmic risk. Since the publication of the most recent of the major randomized ICD trials in 2005 (18), there has been a pause in the rapid growth of enthusiasm for the device in the clinical community, likely based upon a need for better understanding of the specifics of indications and insights into the magnitude of benefit for some subsets of patients.

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**Randomized Trial Support for ICD Therapy**

The randomized clinical trials of ICD benefit are classified into 2 categories: primary and secondary prevention strate-



**Figure 1** Timeline of Evolution of ICDs From Original Concept to Present

The concept of an implantable cardioverter-defibrillator (ICD) originated in the late 1960s, and the development of the technology and proof of concept leading to the first clinical implant extended to 1980. From 1980 until late 1996, data supporting ICD benefit were largely observational, or based on small high-risk cohorts or case-control studies. The first true randomized trials were designed in the late 1980s and early 1990s, and all of the major trials for both primary and secondary indications were published during an interval of <10 years between late 1996 and early 2005. Additional studies since then have aided in the interpretation of the outcomes from the clinical trials, but there remains a need for consolidation and clarification and for additional data to better define efficiency of therapy and targeted selection of individual candidates who have a high likelihood of benefit. AVID = Antiarrhythmic Versus Implantable Defibrillator; CABG-Patch = Coronary Artery Bypass Graft-Patch; CASH = Cardiac Arrest Study of Hamburg; CAST = Cardiac Arrhythmia Suppression Trial; CIDS = Canadian Implantable Defibrillator Study; DEFINITE = Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation; DINAMIT = Defibrillator In Acute Myocardial Infarction Trial; FDA = Food and Drug Administration; MADIT = Multi-center Automatic Defibrillator Implantation Trial; MUSTT = Multicenter Unsustained Tachycardia Trial; SCD-HeFT = Sudden Cardiac Death-Heart Failure Trial.

gies. Primary prevention of SCD has been interpreted, by common usage, to mean a reduction in mortality among a category of patients known to be at high risk for cardiac arrest due to defined pre-existing disease, but without clinical expression of potentially fatal arrhythmias. Secondary prevention has been used to refer to reduction of mortality risk in patients who have survived cardiac arrests due to ventricular tachyarrhythmias. Although these classifications, as used in the electrophysiological literature, are not conventional epidemiological definitions (19) (Table 1), they have become ingrained in the ICD literature and will therefore be applied in this document.

Although the preferred strategy of randomized trial support for defining indications and benefits is feasible for the common diseases, the less common disorders do not generate sufficient numbers to adequately power clinical trials. The ICD indications for these conditions must derive guidance from more limited observational data, registries, and/or expert opinion.

### Secondary Prevention Trials

The secondary prevention strategy emerged from observational data recognizing that survivors of documented life-threatening ventricular tachyarrhythmias (ventricular fibrillation [VF], pulseless ventricular tachycardia [VT]) are at high risk for recurrent arrhythmic events and death (20,21). This category has been extended to include patients with unexplained syncope suspected to be due to high-risk tachyarrhythmic mechanisms in the presence of advanced structural heart disease. High recurrence rates were likely

when a cardiac arrest was associated with uncontrollable arrhythmogenic pathophysiology or recurring triggers.

The cumulative results of 3 randomized trials have led to the general acceptance of ICD therapy for survivors of cardiac arrest when the arrhythmia was not due to transient and/or reversible factors, such as acute MI, proarrhythmic drug effects, or electrolyte disturbances. The occurrence of cardiac arrest during the acute phase of MI, defined as from the onset of symptoms to 24 to 48 h, is not an indication for an ICD and does not contribute to the decision of whether an ICD is indicated, based upon post-MI risk markers. While this statement is generally accepted and incorporated into the guidelines documents addressing management of ventricular arrhythmias and SCD (22), limited data have begun to question the validity of this conclusion (23). Until further data are forthcoming, this generally accepted exclusion still stands.

The 3 secondary prevention trials, the AVID (Antiarrhythmic Versus Implantable Defibrillator) trial in the U.S. (11), CIDS (Canadian Implantable Defibrillator Study) in Canada (13), and CASH (Cardiac Arrest Study of Hamburg) in Germany (14), were initiated between the late 1980s and early 1990s (Table 2). The AVID trial was the first to be completed and demonstrated a statistically significant survival benefit of the ICD over antiarrhythmic drug therapy (primarily amiodarone), with a 2-year relative risk reduction of 27%, corresponding to an absolute risk reduction of 7% (Table 2). Because of the similarities between the AVID and CIDS trials, the latter was terminated after the AVID trial was reported. Although the CIDS trial did not achieve a statistically significant all-cause mortality benefit, possibly because it was stopped early, it

**Table 1 Terminology for Preventive Strategies**

Epidemiological Definition	Examples of General Applications in Clinical Research and Epidemiology	Common Usage in Strategies to Prevent Cardiac Arrest and SCD	Proper Usage in Strategies to Prevent Cardiac Arrest and SCD
<b>Primary prevention</b> Target Prevent underlying disease Strategies Public education Screening for risk factors Preventive medicine	Prevention of atherogenesis	Prevention of SCD in post-MI, heart failure, or uncommon arrhythmogenic syndrome patients who are profiled at high risk but have not had prior cardiac arrests or clinical events equivalent to cardiac arrests	Prevention of SCD in some high-risk uncommon arrhythmogenic syndrome patients who have not had any prior events
<b>Secondary prevention</b> Target Early progression and onset of clinical events Strategies Therapy to prevent clinical expression Prophylaxis against recurrences or complications	Prevention of myocardial infarction, progression of LV dysfunction, or SCD in post-MI patients	Prevention of SCD in survivors of prior cardiac arrests or who have had clinical events equivalent to cardiac arrests	Prevention of SCD in post-MI, heart failure, or some uncommon arrhythmogenic syndrome patients who are at high risk for SCD but have not had a prior cardiac arrest or its equivalent
<b>Tertiary prevention</b> Target Complications of clinically expressed disease Strategies Control of transient risk factors Treatment of disease-associated risk factors Responses to acute syndromes	Prevention of SCD in survivors of cardiac arrest, or SCD or heart failure deaths in patients at very high risk due to extent or expression of disease (e.g., heart failure, ischemia, arrhythmias)		Prevention of SCD in survivors of prior cardiac arrests

LV = left ventricular; MI = myocardial infarction; SCD = sudden cardiac death.

**Table 2 Secondary Prevention Trials**

Trial (Follow-Up Analysis) Year Published	Study Group Defined Entry Criteria	Time From Diagnosis of Qualifying Condition to Randomization	Ejection Fraction of Enrolled Patients	All-Cause Mortality		Benefit	
				Control	ICD	ReIRR	AbsRR
AVID (2-yr analysis) 1997	VF, VT with syncope, VT with EF ≤40%	Entry criterion: interval not defined Actual: interval not reported EF: 3 days after qualifying event, median	32 ± 13%	25%	18%	-27%	-7%
CIDS (2-yr analysis) 2000	VF, out-of-hospital cardiac arrest due to VF or VT, VT with syncope, VT with symptoms and EF ≤35%, unmonitored syncope with subsequent spontaneous or induced VT	Entry criterion: interval not defined Actual: time from qualifying event to randomization not reported; median time from randomization to ICD 7 days (>90% in ≤21 days) EF: interval not reported	34 ± 14%	21%	15%	-30%	-6%
CASH (9-yr analysis) 2000	VF, VT	Entry criteria: interval not defined Actual: interval not reported EF: interval not reported	46 ± 18%	44%	36%	-23%	-8%

AbsRR = absolute risk reduction; EF = ejection fraction; ICD = implantable cardioverter-defibrillator; ReIRR = relative risk reduction; VF = ventricular fibrillation; VT = ventricular tachycardia; other abbreviations as in Figure 1.

did demonstrate a similar trend toward benefit, with a 2-year relative risk reduction of 30%, corresponding to an absolute risk reduction of 6%. The CASH study, which was smaller and had some intervening design changes because 1 of the arms in the study suggested an adverse outcome, was started before the AVID and CIDS trials and were reported later (14). It too failed to achieve statistically significant benefit, but showed magnitudes of relative and absolute risk reduction similar to the other 2 studies. Thus, only 1 of the 3 secondary prevention trials achieved independent statistical significance, but that 1 has dominated opinion because of its larger size and clarity of outcome. Moreover, a meta-analysis of the pooled data from the 3 trials did demonstrate statistical significance (24).

The secondary prevention trials tracked, but did not stratify, ejection fraction (EF). The AVID and CIDS studies' populations had mean EFs <35% in the study groups, but there remain uncertainties of the relationship between EF measured shortly after cardiac arrest and ICD benefit over time. The mean interval between qualifying event and EF measurement in the AVID study was 3 days (11), a time at which transient myocardial injury may be a consequence of cardiac arrest. A subgroup analysis of the AVID trial (25) suggested the possibility that the benefit of ICDs is absent (or at least is equivalent to amiodarone) for patients with EFs >35%. Because this was a secondary analysis that was not pre-specified, the validity of that possibility remains uncertain. It has not been re-evaluated prospectively, but the same finding emerged from the meta-analysis of the secondary prevention trials (24). Because of the limitations of relying on post-hoc subgroup analyses, and the principle that meta-analyses are considered exploratory rather than definitive (26), the observations questioning secondary prevention benefit for patients with EF >35% have not had an impact on recommendations in practice guidelines.

### Primary Prevention of SCD in Patients With Coronary Artery Disease and Prior Myocardial Infarction

During the 1980s and early 1990s, there was intense interest in the use of programmed electrical stimulation techniques for determining whether inducibility of life-threatening arrhythmias (VT or VF) was a reliable method for profiling risk of SCD in patients with CAD who have survived an MI (27–29). In addition to risk profiling, the questions of suppression of inducibility of ventricular arrhythmias in the electrophysiology laboratory and of suppressibility of ambient arrhythmias were also explored for their potential as indicators of protection against spontaneous life-threatening arrhythmias by antiarrhythmic drugs. The combination of the emergence of ICDs as a practical therapy, concern about adverse effects of antiarrhythmic drugs based in part upon the CAST study (7,8), and insufficient data on efficacy of device or pharmacological therapies for protection against SCD, led to the design of randomized trials testing defibrillator therapy against “conventional” therapy, the latter including antiarrhythmic drugs in many of the studies. The first of the randomized primary prevention ICD trials was MADIT (Multicenter Automatic Defibrillator Implantation Trial) (Table 3). MADIT compared ICD therapy to antiarrhythmic drugs (75% amiodarone) in a population of post-MI patients with EFs <35%, nonsustained VT on ambulatory monitoring, inducible VT by programmed stimulation, and failure of intravenous procainamide to prevent inducibility. The study was small, but a 59% difference in the relative risk of death was observed between the ICD group and the active controls at 2 years of follow-up (13% versus 32%) (9). Another study, MUSTT (Multicenter Unsustained Tachycardia Trial) (12), was designed to determine whether inducibility of VT identified SCD risk in patients with CAD, ≈95% of whom had a prior MI, documented nonsustained VT ≥4 days after the most

**Table 3 Primary Prevention ICD Trials**

Trial (Follow-Up Analysis) Year Published	Study Group Defined Entry Criteria	Time From Diagnosis of Qualifying Condition to Randomization	Ejection Fraction of Enrolled Patients*	All-Cause Mortality		Benefit	
				Control	ICD	ReIRR	AbsRR
MADIT (2-yr analysis) 1996	Prior MI, EF ≤35%, NS VT, inducible VT, failed IV PA	Entry criterion: ≥3 weeks Actual: 75% ≥6 months Qualifying EF: interval not reported	26 ± 7%	32%	13%	-59%	19%
CABG-Patch (2-yr analysis) 1997	Coronary artery bypass surgery, EF <36%, SAECG(+)	Diagnosis of CAD: interval not reported Qualifying EF: interval not reported SAECG: day of randomization	27 ± 6%	18%	18%	N/A	N/A
MUSTT (5-yr analysis) 1999	CAD (prior MI ~95%), EF ≤40%, NS VT, inducible VT	Qualifying NS VT: ≥4 days from MI Time from MI: 17% ≤1 month; 50% ≥3 yrs Qualifying EF: interval not reported	30% (21%, 35%)	55%	24%	-58%	-31% [EP guided arm: AAD vs. ICD at 60 m]
MADIT-II (2-yr analysis) 2002	Prior MI (>1 month), EF ≤30%	Entry criteria: ≥1 month Actual: 88% ≥6 months Qualifying EF: interval not reported	23 ± 5%	22%	16%	-28%	-6%
DEFINITE (2.5-yr analysis) 2004	Nonischemic CM, history of HF, EF ≤35%, ≥10 PVCs/h, or NS VT	Heart failure onset, mean: Controls = 3.27 yrs ICD group = 2.39 yrs	21% (7%-35%)	14%	8%	-44%	-6%
DINAMIT (2.5-yr analysis) 2004	Recent MI (6-40 days), EF ≤35%, abnormal HRV, or mean 24 heart rate ≥80 beats/min	Entry criteria: 6-40 days Actual: mean 18 days	28 ± 5%	17%	19%	N/A	N/A
SCD-HeFT (5-yr analysis) 2005	NYHA functional class II-III CHF, EF ≤35%	Entry criteria: interval not reported Qualifying EF: interval not reported	25% (20%, 30%)	36%	29%	-23%	-7%

\*Values are presented as mean ± SD, median (25th, 75th percentile), and mean (range).

AAD = antiarrhythmic drug; CAD = coronary artery disease; CHF = congestive heart failure; CM = cardiomyopathy; EP = electrophysiologically; HF = heart failure; HRV = heart rate variability; IV PA = intravenous procainamide; N/A = not available; NS = nonsustained; NYHA = New York Heart Association; PVC = premature ventricular complex; SAECG = signal-averaged electrocardiogram; other abbreviations as in Tables 1 and 2 and Figure 1.

recent MI, and an EF ≤40%. The MUSTT trial did not randomize ICD therapy, but patients failing suppression of inducibility received ICDs at the option of treating physicians. The ICD subgroup achieved a 58% reduction in relative risk of death (24% vs. 55%) over 5 years of observation (12). The MADIT and MUSTT results were interpreted to indicate that electrophysiological inducibility in patients with low EFs and nonsustained VT was a predictor of SCD, with improvement in outcome by implantation of ICDs compared with antiarrhythmic drugs. The lack of survival benefits attributable to antiarrhythmic drugs in these studies were reinforced by 2 other randomized, placebo-controlled post-MI amiodarone trials that showed no survival benefit, EMIAT (European Myocardial Infarct Amiodarone Trial) (30) and CAMIAT (Canadian Amiodarone Myocardial Infarction Arrhythmia Trial) (31).

The CABG-Patch (Coronary Artery Bypass Graft-Patch) trial (10) was carried out concurrent with the MADIT and MUSTT trials. The CABG-Patch trial tested for a potential benefit of ICDs in patients undergoing nonemergent coronary bypass surgery, with EFs <36% and positive signal-averaged electrocardiograms. Prior MIs and/or a heart failure history were not required for entry but were very prevalent among the enrolled subjects (82% and 50%, respectively). The mean EF was 27%. Despite these features, ICDs demonstrated no survival benefit in this study, possibly because of a parallel benefit of revasculariza-

tion (10). A subsequent study, MADIT II, was designed to test the hypothesis that an EF ≤30% in post-MI patients was a sufficient marker of risk to justify ICD therapy, without relying on ambient or inducible arrhythmias (15). In the MADIT II trial, the ICD group performed better than a conventional therapy control group, with a 28% reduction in relative risk of mortality at 2 years, considerably less than the relative benefit for the MADIT and MUSTT trials. The absolute risk reduction was 6% at 2 years.

Whereas the MADIT, MUSTT, and MADIT II studies enrolled patients many months after the qualifying MI on average, the DINAMIT (Defibrillator In Acute Myocardial Infarction Trial) study was designed to evaluate the potential for ICD benefit when implanted early after a MI in patients with EFs ≤35% (16). Even though both old (32,33) and recent (34,35) data suggest a higher risk for SCD early after MI, the DINAMIT study suggested no overall survival benefit attributable to early implantation of ICDs in patients randomly allocated at 6 to 40 days after MI (mean 18 days), despite a reduced arrhythmic mortality. In addition, there was an unexplained increase in nonarrhythmic mortality compared with conventional therapy that needs to be explored in future studies. The inconsistency between early SCD risk and absence of early ICD benefit observed in the DINAMIT study has led some to call for further studies of this question.

## ICDs for Prevention of SCD in Nonischemic Cardiomyopathy

Several small randomized trials carried out to evaluate the potential for ICD benefit among patients with nonischemic cardiomyopathy were inconclusive. Another study, the DEFINITE (Defibrillators In Non-Ischemic Cardiomyopathy Treatment Evaluation), was designed to test ICD benefit in a cohort of 458 patients with nonischemic cardiomyopathy, a history of heart failure, EFs  $\leq 35\%$ , and PVCs or nonsustained VT (17) (Table 3). The study compared ICD therapy to conventional therapy and demonstrated a strong trend ( $p = 0.08$ ) toward ICD benefit, with a 2-year mortality of 7.9% in the ICD group compared with 14.1% with standard therapy. Although a threshold of significance for total survival benefit was not reached, likely because of insufficient numbers, certain subgroups, such as those with prolonged QRS durations, EF  $>20\%$ , and New York Heart Association (NYHA) functional class III heart failure performed better with ICD therapy.

The SCD-HeFT (Sudden Cardiac Death-Heart Failure Trial) study (18) enrolled patients with both nonischemic and ischemic cardiomyopathies with EFs  $\leq 35\%$ , and required stable NYHA functional class II or III heart failure. The study was unique in design in that it had an ICD arm, a drug arm (amiodarone), and a usual-therapy control group. The study was nearly equally balanced between patients with nonischemic cardiomyopathy and those with ischemic cardiomyopathy, 85% of whom had a prior MI (G. Bardy, personal communication, previously unpublished data from SCD-HeFT, May 2008). Both groups were large enough to do meaningful subgroup analyses of benefit. The study was underpowered for a 3-way analysis, so the ICD and amiodarone groups were compared with the control group independently. There was no difference between usual therapy and amiodarone, whereas an ICD survival benefit became apparent after the first 2 years and continued to increase at 5 years. The magnitude of absolute benefit was relatively small at 1.4% per year (cumulative 7% over 5 years), but there was a relative risk reduction of 23% (29% vs. 36%). Although there remains some uncertainty regarding ICD benefit for nonischemic cardiomyopathy patients without heart failure, regardless of EF (Table 3), the cumulative information available from clinical trials and observational data, in conjunction with opinions of experts in the field, supports prophylactic ICD therapy among the subgroup of patients with nonischemic cardiomyopathy who remain in NYHA functional class II or III heart failure on optimal medical therapy. Subgroup analysis suggested that NYHA functional class II patients benefited more, in contrast to the observation in the DEFINITE study that class III heart failure patients performed better (17).

## ICD Indications in Less Common and Rare Disorders

The major categories of cardiovascular diseases, which generate cohorts large enough to accommodate randomized clinical trial designs, dominate the cumulative number of indications for ICDs. Nonetheless, physicians must also evaluate patients with less common disorders about which available data on ICD benefit are less robust. The less common diseases associated with SCD risk are a heterogeneous group of clinical entities, none of which is large enough to support a randomized clinical trial. Thus, the decision-making process for ICD indications is derived from registry and small cohort data, and interpreted by expert opinion provided in practice guideline documents (22,36) (Table 4). In the absence of sufficient data to generate uniformly agreed-upon expert opinions, decision making defaults to physician judgment. Under such circumstances, it is incumbent upon the physician to explain the limits of knowledge to the potential candidates, so that they can make informed decisions.

The less common and rare disorders that may be indications for ICDs include acquired, congenital, and inherited conditions. Among the acquired diseases, myocarditis, various infiltrative disorders, and the acquired valvular diseases dominate (22). Congenital disease indications include valvular diseases and arrhythmic risk that appears late after surgical correction of complex anomalies (22,36,37), and the inherited diseases include both genetically based primary arrhythmia disorders (long-QT syndromes, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia) and structural diseases with a lethal arrhythmia risk (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia).

**Myocarditis.** Cardiac arrest is a well-established complication of acute viral myocarditis (38,39). Its incidence appears to be very low, although the precise frequency of cardiac arrest or symptomatic sustained VT among those affected with myocarditis is unknown. Although arrhythmias during the acute phase of myocarditis are generally not considered decisive for immediate ICD indications, the determination of whether, and under what circumstances, the post-myocarditis patient should receive an ICD remains challenging (22). Despite limited data, recurrent or persistent life-threatening arrhythmias (sustained VT, and possibly long runs of nonsustained VT, especially if polymorphic) after healing are commonly considered indications, regardless of EF, based on pathological data on unanticipated SCDs in minimally symptomatic or unrecognized myocarditis (39). It is generally agreed that post-myocarditis cardiomyopathy that meets ICD criteria for nonischemic cardiomyopathy is an ICD indication, but ICDs are not generally recommended for patients whose EFs return to normal or near-normal, and who are free of arrhythmias other than PVCs after healing, regardless of prior acute phase arrhythmias. The middle ground—patients with EFs

**Table 4 ICD Indications in Genetic Disorders Associated With SCD Risk**

Diagnosis	ICD Indication	Primary Source of Data	Risk Indicators	Guidelines	
				Classification	Evidence
HCM	Secondary SCA protection	Registries; cohorts	Prior SCA, pulseless VT	Class I	Level B
	Primary SCA protection	Registries; cohorts	Sustained VT, unexplained syncope LV thickness >30 mm, high LV outflow gradient, family history of SCD, NS VT, blunted BP response to exercise	Class IIa	Level C
ARVD/RVCM	Secondary SCA protection	Registry; case series	Prior SCA, sustained VT	Class I	Level B, C
	Primary SCA protection	Registry; case series	Unexplained syncope Induced VT, ambient NS VT, extensive disease	Class IIa	Level C
Congenital LQT	Secondary SCA protection	Registry; cohorts	Prior SCA, symptomatic VT	Class I	Level B
	Primary SCA protection	Registry; cohorts	VT or syncope on beta-blocker, QTc >500 ms, family history premature SCA (?)	Class IIa, IIb	Level B
Familial SQT	Secondary SCA protection	Small case series	Prior SCA, "idiopathic" VF	Class I	Level C
	Primary SCA protection	Small case series	Unknown; family history of SCD (?)	Class IIb, III	Level C
Brugada syndrome	Secondary SCA protection	Case cohorts	Prior SCA, pulseless VT	Class I	Level B
	Primary SCA protection	Case cohorts	Symptomatic VT, unexplained syncope, family history of premature SCA with type I ECG pattern	Class IIa	Level C
CPVT/F	Secondary SCA protection	Small case series	Prior SCA, pulseless VT	Class I	Level C
	Primary SCA protection	Small case series	Syncope or VT while receiving beta-blockers, family history premature SCA (?)	Class IIa	Level C

Guideline classifications and levels of evidence are derived from an amalgamation of narrative and tabular statements in 2 recent guideline documents (22,37), with variations in the documents adjudicated by the authors. Definitions are the standard usages provided in guideline documents.

ARVD/RVCM = arrhythmogenic right ventricular dysplasia/cardiomyopathy; BP = blood pressure; CPVT/F = catecholaminergic polymorphic ventricular tachycardia/idiopathic ventricular fibrillation; ECG = electrocardiographic; HCM = hypertrophic cardiomyopathy; LQT = long-QT syndrome; PVT = polymorphic ventricular tachycardia; QTc = corrected QT interval; SCA = sudden cardiac arrest; SQT = short-QT syndrome; VA = ventricular arrhythmias; (?) = uncertain; other abbreviations as in Tables 1 and 2.

in the range of 35% to 45% and ambient nonsustained arrhythmias—remains uncertain because of an absence of data.

**Infiltrative disorders.** Cardiac sarcoidosis is a generally accepted indication when accompanied by VT (sustained and possibly nonsustained), regardless of EF (40). The other infiltrative disorders have indication criteria that are variable and not well defined, as outlined in the guideline documents (22,37). However, the data are not extensive, and to a significant degree, indications are determined by life expectancy based on multiorgan involvement, as in amyloidosis.

**Inherited disorders.** The inherited disorders that may be indications for ICDs are a heterogeneous group characterized by primary expressions that are either structural substrate-based or arrhythmic. An example of the former is hypertrophic cardiomyopathy (HCM) for which categorically defined SCD risk has been recognized for many years (41). Unfortunately, although HCM is relatively more common among the less common disorders, it is not sufficiently common to support a reasonably sized randomized clinical trial. Thus, the data favoring the use of ICDs for at-risk patients in this category are derived from retrospective analysis of observational data from a registry of patients with HCM who received ICDs (42) (Table 4). In the absence of randomized controls, outcomes were measured as rates of appropriate ICD discharges, rather than

survival benefit. Despite the limitations of such an approach, and the fact that an ICD shock is not a surrogate for death (43), it is generally accepted that ICDs are indicated for specific subgroups within the HCM cohort.

The ICD strategies for HCM are separated into primary and secondary indications. Among patients who received ICDs for secondary indications after surviving a documented or strongly suspected life-threatening arrhythmia, the end point of appropriate ICD discharges occurred at an annualized rate of 10.6%, or a cumulative rate of 39% over 5 years (44). Primary prevention indications are based upon risk profiling, also derived largely from retrospective data and expert opinion. The ICD utilization rate of 3.6% per year (cumulative 5-year rate of 17%) suggests a less dramatic benefit, but nonetheless supports the use of ICDs in patients with the defined risk markers. The major risk markers for primary prevention include one or more of the following: LV wall thickness  $\geq$ 30 mm, syncope, family history of SCD, and nonsustained VT. A high LV outflow gradient and blunted blood pressure response to exercise have also been suggested as risk markers for primary prevention (42,45).

A second structurally based inherited condition is arrhythmogenic right ventricular dysplasia, which has attracted a great deal of interest in recent years because of recognition that it is more common than previously thought, although it still remains properly classified among

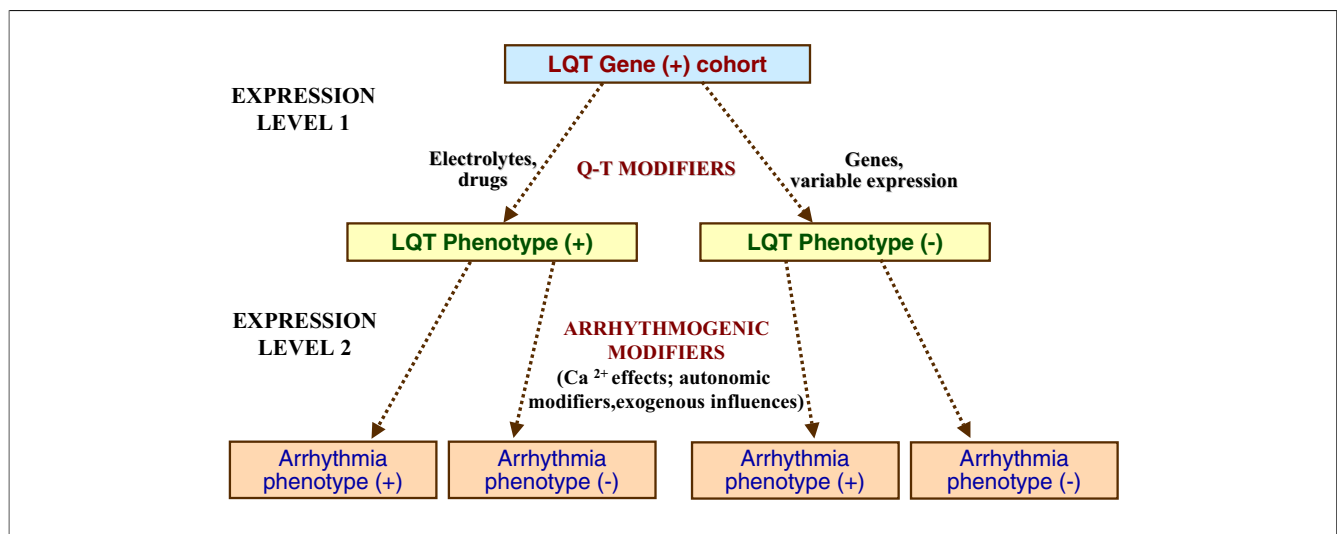
the less common disorders. SCD is commonly the first clinical manifestation, particularly in association with exercise triggers. While accurate diagnosis can be difficult (46), early recognition offers the potential for improved SCD prevention strategies. To this end, ICD therapy has become accepted for patients arrhythmogenic right ventricular dysplasia who have symptomatic arrhythmias (Table 4), as well as for those with documented disease thought to be at high risk, although the cut-point for ICD indications for primary prevention is not yet clearly defined (47,48). As with other entities in this category, the secondary prevention strategy for ICDs is clear, but criteria for ICDs for primary prevention use of ICDs are less well defined.

The inherited disorders that express as primary arrhythmias include congenital long-QT interval syndrome, Brugada syndrome, and very rare conditions such as catecholaminergic polymorphic VT (49), short-QT interval syndrome (50), and a recently described variant of early repolarization (51). These uncommon disorders may have extremely variable clinical expression, and reliable cohort data are also difficult to acquire, further defaulting to expert opinion that is based on limited data. For each of these entities, it is generally accepted that ICDs are indicated for high-risk subgroups that can be identified with varying degrees of confidence.

Among patients with congenital long-QT syndrome, ICDs are generally accepted as secondary prevention therapy for those who have had cardiac arrest or documented symptomatic ventricular tachyarrhythmias, based largely upon experiences from a sizable international registry (52)

(Table 4). Beta-blockers are generally recommended as the first choice of therapy for patients who are asymptomatic or have syncope without beta-blocker therapy. For patients who experience syncope while on beta-blocker therapy, particularly if suspected to be due to ventricular tachyarrhythmias, ICDs are generally recommended (53). However, an ICD may be recommended in other circumstances, based on the judgment of the physician.

A more difficult decision-making process in the congenital long-QT syndrome population regards management of asymptomatic family members who carry the mutation identified in a related proband who has expressed life-threatening arrhythmias or SCD. Beta-blockers are generally advised as first-line therapy. However, while it has been thought in the past that a family history of SCD, cardiac arrest, or symptomatic ventricular tachyarrhythmias suggested increased risk of such events in asymptomatic relatives who are mutation carriers, the magnitude of risk is lower than in probands, and the power of the carrier state as an independent predictor for individual risk has recently been questioned (54,55). Variability of risk in individual carriers within a family may be based upon modifier genes migrating in a parallel but separate inheritance patterns, random environmental factors, or even a statistical aberration due to selection bias or limited numbers observed over time (Fig. 2) (56). Individual variability creates a dilemma for treating physicians, and it is now suggested that individual risk profiles be considered in related carriers. One of the potential limiting factors is the observation that among the clinical expressions of long-QT syndrome, syncope is by



**Figure 2** Variable Phenotypic Expression in Gene-Positive LQT Syndrome Patients

Variable expression confounds the interpretation of the genetics of the inherited long-QT (LQT) syndrome and can be viewed as a multistage expression algorithm. Expression level I in gene-positive subjects refers to whether and to what extent the corrected QT interval lengthens predictably based on the presence of a genetic variant plus environmental influences. At expression level II, referring to phenotypic expression of clinical events, such as syncope, arrhythmias, cardiac arrest, and sudden cardiac death, variability occurs with both physiological and environmental modifiers. This feature of long-QT syndrome influences the difficulty in the decision-making process for implantable cardioverter-defibrillators in gene-positive carriers of related probands, with and without baseline expression of corrected QT prolongation. No quantitative distribution of the various patterns of electrocardiographic (ECG) phenotype/arrhythmia phenotype is intended because of lack of sufficient data. However, ECG(-)/arrhythmia(+) is likely far less common than ECG(+)/arrhythmia(-). Modified, with permission, from Myerburg and Castellanos (56).

far the more common, and mortality rates, while large enough to warrant concern, are statistically lower than nonfatal events. New strategies for risk profiling, both clinical and genetic, will be needed to unravel these uncertainties.

Brugada syndrome has attracted world-wide interest since its original description in Europe in the 1990s (57) and subsequent recognition that it was the basis for a group of variously named disorders in the Far East, many if not all of which turned out to be based on Brugada pathophysiology (58,59). The ICD indications among patients with Brugada syndrome have run a contentious course, in part because of difficulties in establishing risk based upon various electrocardiographic patterns of expression and risk profiling according to clinical expression. At one point, it was proposed that virtually all patients with an electrocardiographic phenotype should be considered ICD candidates; but over time, with clarification of profiles of risk, the indications have been more limited (Table 4) (60,61). Once again, the secondary prevention indications are uncontested and generally accepted, as are the primary prevention indications based on type I electrocardiographic manifestations with suspected ventricular tachyarrhythmias and/or syncope. The values of positive programmed electrical stimulation studies or positive pharmacological challenge with flecainide or intravenous procainamide in patients who do not have the typical type I Brugada electrocardiographic pattern at baseline are less certain.

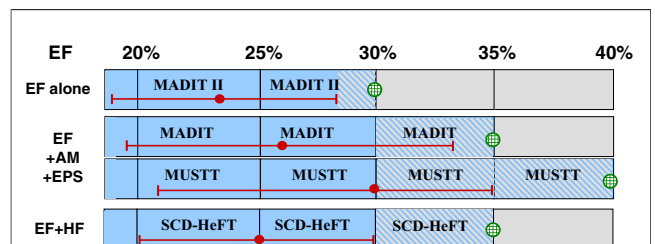
Catecholaminergic polymorphic ventricular tachycardia, the short-QT-interval syndrome, and early repolarization patterns associated with risk of SCD (51) are additional conditions in which ICDs are indicated for secondary prevention. Patients with early repolarization patterns associated with life-threatening arrhythmias have some clinical features similar to those of patients with Brugada syndrome (62). However, the pathophysiological basis for this entity has yet to be defined and, most importantly, our current inability to prospectively differentiate the rare persons at risk from the very large population with “normal” early repolarization confounds attempts at primary prevention with ICDs.

### Limitations of Clinical Trial Designs

The sources of data for establishing ICD benefits, particularly those for primary prevention strategies, are limited in their ability to identify strata of risk and ICD survival benefits for individual patients or concentrated subgroups. This derives in part from the fact that none of the studies, regardless of the number of entry criteria, stratified the 1 continuous variable common to each—namely, a qualifying EF. By dichotomizing entry based on a single pre-specified value of EF, analyses of the outcomes are limited to cumulative effects on heterogeneous populations. This is further impacted by emergence of qualifying EF as a dominant focus for ICD indications, in a sense minimizing other qualifications or clinical criteria.

Whenever an entry cut-off is used for a continuous variable, it is axiomatic that the enrolled population will have a mean or median value that deviates from the defined threshold value. This variance was especially prominent in the primary prevention ICD trials for post-MI and non-ischemic cardiomyopathy patients, in which enrollees had broad ranges of EF values skewed away from the entry threshold (63) (Fig. 3). However, it is the threshold values that are generally linked to recommendations, even though subgroup analyses have generally suggested reduced benefit for patients closer to the entry limits. The effect of failing to stratify the entry criteria such as EF, accumulating patient populations that deviate significantly from the outer limit of qualification, and suggestions of limited benefit in certain defined subgroups is a loss of efficiency in application of the results of these clinical trials as they are applied to the general population (63,64). While conventional analysis of most of the trials demonstrate statistically significant benefit, the actual magnitudes of the benefits among subgroups, and their impact on individual patients, remain uncertain. Without placing a value on a particular length of added life based upon numbers needed to treat, it is sufficient to recognize the need for better stratification so that greater numbers of patients receiving ICDs will achieve benefit and those not reasonably expected to achieve benefit can be excluded from consideration.

**Entry criteria based on study design versus exit data based on enrollment.** The post-MI primary prevention trials have led to a general consensus that there is a survival benefit attributable to ICD therapy among those with low EFs. However, interpretation of indications based on the benefit (and its magnitude) identified in the randomized trials are intricately woven into contrasts between trial designs and details in outcome data (63,64). Strict reliance on indications based solely on defined entry thresholds leads to conclusions that are not perfectly aligned among peer-



**Figure 3** Entry Criteria for EF and EFs of Subjects Enrolled in ICD Trials

Each of these 4 primary prevention trials had a qualifying ejection fraction (EF) cutoff (green circles), above which patients were not enrolled (grey bars). In each study, the EF subgroup that dominated enrollment (solid blue bars) (mean  $\pm$  SD for MADIT and MADIT II and median and interquartile ranges for MUSTT and SCD-HeFT) received a measurable benefit from implantable cardioverter-defibrillator (ICD) therapy, whereas those with EFs closer to the threshold entry criterion (cross-hatched blue bars) achieved no benefit or an uncertain benefit (see text on ejection fraction data). Used with permission, from Myerburg (63). AM = ambulatory monitor; EPS = electrophysiological study; HF = heart failure; other abbreviations as in Figure 1.

reviewed reports of the actual data, 2 guideline documents that analyze the data and conclusions (22,36), and with current Center for Medicare and Medicaid Services (CMS) approvals. The CMS approval policies come closest to strict alignment with entry criteria defined in the trials, approving ICD therapy for patients who have EFs  $\leq 35\%$ , ambient episodes of nonsustained VT, and inducible VT as ICD candidates 40 or more days after a qualifying MI, and those with EFs  $\leq 30\%$  without further qualifiers also at 40 or more days after MI (65,66). The 2 practice guidelines documents (22,36), and several thoughtful reviews and analyses of the topic (67–72), critically explore the subtleties in available data. Comparisons between entry criteria, actual enrollment, and survival data lead to a distinction between “entry criteria” and “exit data.” The intent of the latter term is to highlight the patterns of patients actually enrolled in the studies and the need for physician judgment in applying the results of these trials in clinical practice. In addition to the difficulties inherent in the EF data and recognition of the need for additional risk stratifiers, other subgroup metrics also raise important questions (73).

**Ejection fraction data from ICD trials.** A pre-specified qualifying EF limit was the 1 categorical entry criterion common to all of the primary prevention ICD trials. Most of the trials set enrollment at an EF  $\leq 35\%$ , with entry cut-offs ranging from  $\leq 30$  to  $\leq 40\%$  (Table 3). Although the absolute differences between the EF entry thresholds, and mean or median values of those actually enrolled, ranged from 7% to 14% in these trials (Table 3), the threshold entry criterion is generally linked, directly or indirectly, to treatment recommendations. As an example of the limitations of this approach, the maximum qualifying EF in the SCD-HeFT study was 35%, whereas the enrolled patients had a median EF of 25%, with an interquartile range of 20% to 30% (18). Subgroup analysis of the 17% of study patients enrolled with EFs  $>30\%$  suggested no ICD benefit. The MADIT and MADIT II study populations had similar trends for EF subgroups close to the upper limit cut-off for entry (9,15,74). While such nonpre-specified subgroup analyses usually lack the power to prove absence of benefit, particularly if apparent differences are trends that do not achieve statistical significance, such trends raise important questions about generalizability of the magnitude of benefit across all strata of the study populations. Consistency of this pattern in multiple ICD trials reinforces the plausibility of this concern (75) and supports the need for additional data.

In contrast to the CMS approval values for EF, the ventricular arrhythmias and sudden cardiac death guidelines document (22) uses EF ranges derived from (but not identical to) entry criteria, rather than values observed among the enrolled subjects, to establish recommendations for ICD therapy. The recommended upper limit of EF in post-MI patients ranges from 30% to 35% in the absence of heart failure, and from 30% to 40% with class II or III heart failure. The 2008 update of the 2002 device guidelines links

more closely to specific EF limits used in study designs, avoiding ranges, but does not integrate commentary on the potential confounding influence of observed values. The recommendations developed in both documents reinforce the generally accepted principle of inserting clinical judgment into decision making for the individual patient.

Additional limitations of EF data include a lack of a uniform methodology and reliability of EF measurements and of time from infarct to determination of a qualifying EF. In regard to the former, while many large clinical trials establish uniform reading criteria or core centers for analysis of imaging data, giving somewhat more credibility to the reported values, they still allow measurement to be made by multiple modalities which are inherently variable. Of greater concern is the lack of any standard for interpretation of data, particularly echocardiographic EFs, during the general application of the outcomes in the practice communities. Reader variability in interpreting data is a general problem to which ICD decision making is not immune.

**Heart failure and ICD benefit.** Because a history of heart failure is among the clinical variables that add dimensions beyond EF for potential benefit of ICD therapy (74,76–78), it is important for the clinician to distinguish cardiomyopathy as an expression of myocardial damage and measured as a reduced EF, from clinical heart failure as the functional consequence of muscle damage, expressed as NYHA functional classification. The role of heart failure as an indicator for ICD benefit enters trial strategies and influences outcomes analyses in 3 different patterns: 1) persistent heart failure on medical therapy as an entry criterion in study design, as exemplified in the SCD-HeFT study; 2) a high prevalence of manifest heart failure at entry in studies in which only a history of heart failure was included in entry criteria, such as in the DEFINITE study; and 3) a high prevalence of either a history of heart failure or manifest heart failure in studies in which neither was an entry criterion, such as in the MADIT II trial. In the latter 2 models, subgroup analyses suggest that a history of heart failure is likely an indicator of potential ICD benefit, exceeding that of the qualifying EF alone.

Although the SCD-HeFT study (18) was designed to determine whether patients with heart failure and an EF  $\leq 35\%$  benefit from ICD therapy, requiring stable NYHA functional class II and III for enrollment, the MADIT II trial required only a low post-MI EF. Based upon subgroup analysis of EFs dichotomized at 25%, the 33% of subjects with EFs  $>25\%$  did not appear to achieve the same magnitude of ICD benefit suggested for the cumulative group or for those with EF  $\leq 25\%$ . Moreover, hospitalization for episodic heart failure was a strong indicator of future ICD use and of mortality among patients enrolled into the MADIT II trial (15). In addition, emergence of heart failure was more common in the ICD group, particularly after ICD therapy (78,79), suggesting (among other possibilities) that the underlying pathophysiology of heart failure predisposes to life-threatening arrhythmias. In the

SCD-HeFT study, ICD shocks predicted a higher mortality rate than observed in ICD recipients who did not have shocks (80). At least 30% of the deaths among patients who had appropriate shocks occurred within 24 h of a first appropriate shock, suggesting end-stage pathophysiology in a substantial minority of those with a shock/death relationship.

Subgroup analysis of the MADIT population also suggested that an EF  $\leq 25\%$  and/or a history of heart failure were better predictors of ICD use and mortality during follow-up than EF  $\geq 26\%$  without heart failure (73). This general principle appears in other trials as well (12,15,17,18), suggesting interactions between EF and heart failure, with the likelihood that presence or absence of heart failure modulates the implications of risk and benefit attributable to EF (63). An exception is the CABG-Patch study (10), which demonstrated no ICD survival benefit despite a mean EF of 27% and a high prevalence of heart failure history (50%) and functional classification impairments (72% NYHA functional class II or III).

**QRS duration.** In the MADIT II study, subgroup analysis indicated that a prolonged QRS duration increased the probability of ICD benefit, with uncertainty if the QRS duration was normal (15). This observation controlled CMS-approved ICD indications based on MADIT II data until the SCD-HeFT study (18), and reassessment of the QRS-duration indicator (81,82), superceded the requirement of a QRS duration  $\geq 0.12$  s (66). Although the QRS duration no longer limits CMS indications for MADIT-II candidates, a prolonged QRS duration may be a modifier supporting ICD use in patients with a marginal EF indication. This role for QRS duration is debated (83).

**Time after MI and ICD benefit.** The presence of temporal heterogeneity in most of the studies, both in regard to time from qualifying MI or onset of heart failure to enrollment and to timing of a qualifying EF determination, are confounding influences for interpreting EF significance and outcomes data generally. With the exception of DINAMIT, the qualifying EF may have been recorded as early as within 3 to 4 weeks or as remotely as several years from the qualifying MI or onset of heart failure (Table 3). In those studies in which timing of qualifying EF was defined, it was linked to a time before randomization (e.g., 3 to 6 months before enrollment), rather than to time from the qualifying MI or heart failure onset.

The combined observations of the defined time to enrollment in the post-MI ICD trials (9,12,15,18), and the absence of benefit from earlier ICD implantation in the DINAMIT trial (16), have led to the current recommendations for ICD implants 40 days or more after the qualifying MI. In addition, time after a MI influences decision making for an ICD recommendation, in that it is often necessary to decide whether an indication is durable over a long period after MI in a patient free of recurrent events. That is relevant because subgroup differences in outcomes in the primary prevention trials suggest that ICD benefit increases as the interval from the MI to ICD

implant increases (84). Because of such subgroup data on delayed risk and benefit, ICD therapy should be considered for the chronic post-MI patient who fulfills criteria, even when there is a long time interval from the most recent MI.

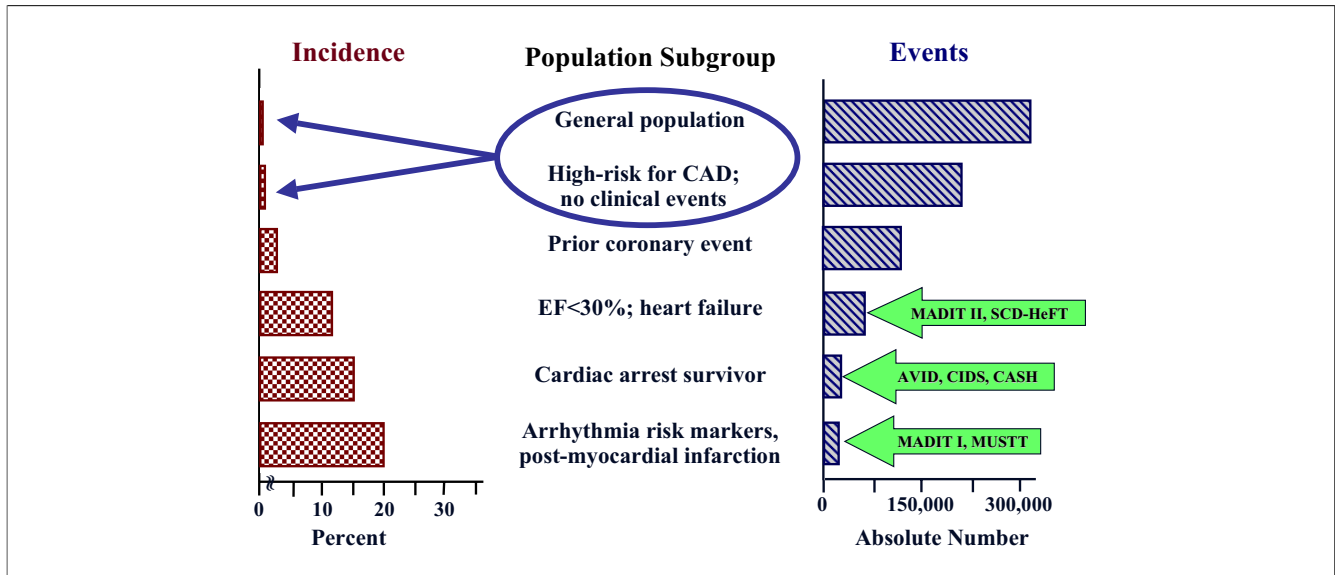
### The Low Risk–High Number Dilemma

A major population dynamic, the number of SCDs that occur among lower risk subgroups of patients with common disorders, remains a dilemma for reducing the numbers of SCDs. A large majority of the SCDs due to CAD come from the segment of the general population with undiagnosed disease and those who are profiled to be at low absolute risk based on conventional risk markers (85) (Fig. 4). It has been estimated that more than one-third of all SCDs occur among patients with known heart disease, whose EFs are  $>35\%$ , without other known arrhythmia risk markers. Thus, they are difficult to identify individually based on current ability to profile risk, but generate large numbers among the total SCD population. Another 30% or more are first clinical expressions of unrecognized underlying disease (86) (Fig. 5). At present, the general adult population, those with markers for coronary atherosclerosis and those with low risk profiles after expression of a coronary event, cannot be subgrouped into numbers small enough to warrant ICD therapy. The denominator for the total population class described above is much too large, with event rates too small, to warrant such an approach. New methods of risk profiling will be needed to work within these categories to identify high-risk subgroups among whom primary prevention ICD therapy can be justified (63,71,72,87). Such an approach would have a much greater impact on the public health issue of SCD than does the focus on the small, very high-risk subgroups included in the randomized clinical trials to date (Table 4).

### New Risk Markers and Dynamic Risk Profiling

Despite the intent of many of the investigators responsible for the designs of the series of trials summarized here, and the limitations of the nonstratified threshold EFs used in these clinical trials, the practice has evolved of placing disproportionate emphasis on EF for determining ICD indications in post-MI and nonischemic cardiomyopathy patients (63,88). This practice has led to limited power of prediction for individual patients or small subgroups of patients, and a low statistical benefit for individual patients, despite high relative benefits (63) (Tables 2 and 3). Thus, the need for better risk profiling is self-evident.

The ICD trials incorporated only limited strategies for linking the time interval between the qualifying infarct and EF measurement, or between the qualifying EF and randomization. Neither was there provision for repeated measures of EF or other qualifiers over time. The static nature of these designs does not take into account that the pathophysiologies of ischemic heart disease and nonischemic cardiomyopathy are dynamic, encompassing changes



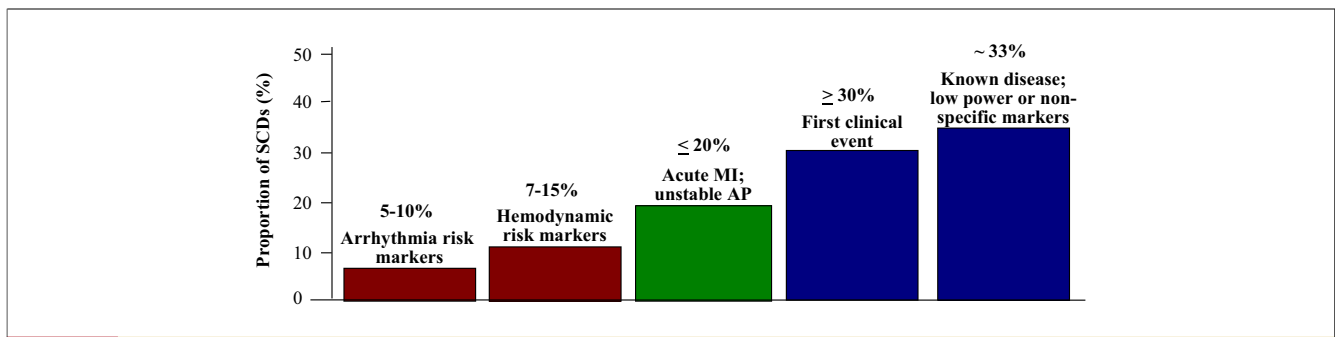
**Figure 4** Estimates of Incidence and Total Annual Population Burden for General Adult Population and Increasingly High-Risk Subgroups

The overall adult population has an estimated sudden death incidence of 0.1% to 0.2% per year, accounting for a total of >300,000 events per year. With the identification of increasingly powerful risk factors, the incidence increases progressively, but it is accomplished by a progressive decrease in the total number of events represented by each group. The inverse relationship between incidence and total number of events occurs because of the progressively smaller denominator pool in the highest subgroup categories. The **blue-hatched incidence bars** for the higher risk groups represent estimates from the original analysis in the 1990s; the superimposed **red-hatched bars** reflect more recent estimates based on the effects of newer multimodal therapies. Successful interventions among larger population subgroups require identification of specific markers to increase the ability to identify specific patients who are at particularly high risk for a future event. (Note: The horizontal axis for the incidence figures is not linear.) Modified, with permission, from Myerburg et al. (86). CAD = coronary artery disease; EF = ejection fraction.

over time that may influence the presence and stability of risk markers. That results in conflicts between entry criteria and outcomes data that can be difficult to resolve for routine clinical applications (63).

**Dynamic risk profiling.** The concept of dynamic risk profiling is intended to take into account time-dependent changes in both the presence and the power of risk markers. It is based on the hypothesis that markers such as remodeling after MI, anatomic properties of scarred areas, progression of disease, and variations in hemodynamic and electrophysiological substrates are active processes, and their predictive power for adverse events may change over time.

Because of the dynamic nature of post-infarction pathophysiology, a low EF shortly after an acute MI may improve over time (especially if there has been an intervention) (89,90), or an EF >35% may deteriorate over time as a result of remodeling or recurrent ischemic injury. It is, therefore, intuitively treacherous to accept a priori that a single measurement at an ill-defined point in time is necessarily a durable predictor of either low or high long-term risk at some future point in time. Since the stability of risk markers over time has not been systematically studied in the ICD trials, the potential value of repeated measures as a strategy for dynamic risk profiling will require further research.



**Figure 5** Distribution of Clinical Status of Victims at Time of SCD

Nearly two-thirds of cardiac arrests occur as the first clinically manifest event or in the clinical setting of known disease in the absence of strong risk predictors. Less than 25% of the victims have high-risk markers based on arrhythmic or hemodynamic parameters. Modified, with permission, from Epstein (87). AP = angina pectoris; MI = myocardial infarction; SCD = sudden cardiac death.

**Additional markers under study.** Reliance on EF as a sole or dominant indicator for ICD implantation has been challenged (88) and debated (91,92), and efforts are under way to identify alternative measures of risk that have independent or added predictive power. These include microvolt T-wave alternans (93), contrast magnetic resonance imaging for imaging the post-infarct anatomy and border zone (94,95), measures of QT variability (96), heart rate variability methods (97-99), familial clustering of SCD as the first expression of CAD (100-102), and the potential for genetic risk profiling (103). None of these have yet worked their way into general clinical applications. For some, available studies have not yet confirmed a generalizable value, and others are still in their infancy.

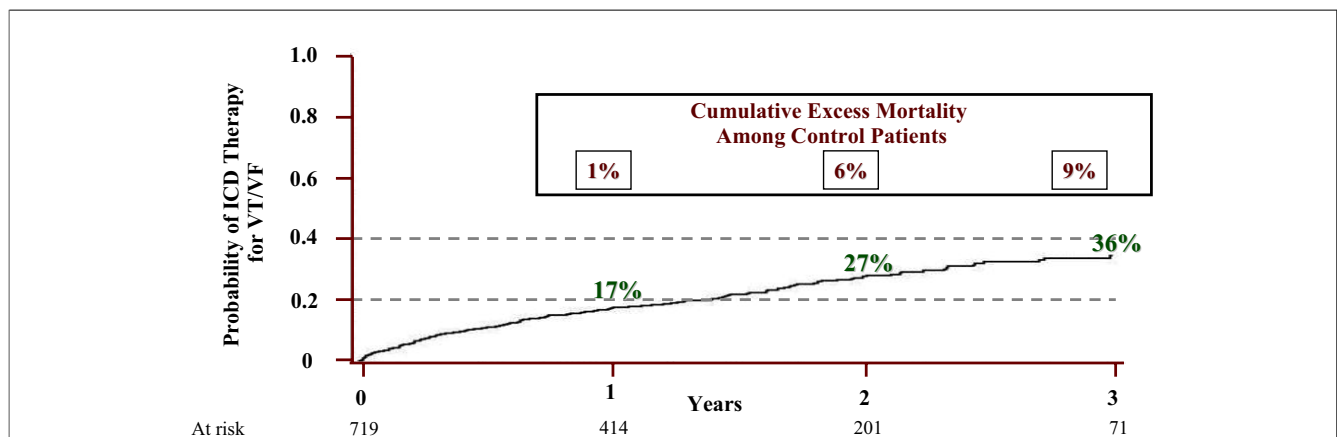
### Risk Stratification and Economic Impact

**The funding paradox.** While clinical investigators, practicing physicians, and patients focus primarily on the risk-benefit equation for evaluating the applicability of clinical research to the practice of medicine, other segments of society add a third dimension—cost—to the equation. The expanded equation, risk-benefit-cost, has become increasingly visible to physicians as major trials now commonly include cost-efficacy studies as part of the research design and outcome statements. Such studies, while increasingly important to a financially stressed health care delivery system, appear to have had little impact on health care practice attitudes.

The economic challenges linked to ICD therapy are defined by the facts that ICDs provide reliable therapy, for which the cost is high and the indications are inefficient, as a consequence of limitations of clinical trial designs and observational data. Cost-effectiveness analyses have suggested differing levels of benefit, some falling within ac-

cepted ranges for cost-effective medical therapies and others falling outside those ranges (72,104-109). Levels of benefit related to cost are expressed in terms of variables such as length of extended life, complications, need for interim hospitalizations, and most important, the ability to identify the most suitable individual candidates.

**The multiplier effect and economic impact.** The impact of ICDs on medical economics is driven by the integration of individual and group efficiencies, which should be adjusted for a multiplier effect based upon prevalence of disease. ICD therapy that is not cost effective by standard criteria, but intended for a rare disorder such as long-QT-interval syndrome, will place a limited economic burden on society because of the infrequency of the disease. In contrast, a common disorder with inefficient guidelines, in which the multiplier effect is large, can have significant economic impact. As an example, the adjustments in CMS approvals after publication of the SCD-HeFT study results (65) for patients in primary prevention categories of ischemic and nonischemic heart disease was estimated to have a potential economic impact of as much as \$10 to \$15 billion for initial implants only. This was based upon estimates of disease prevalence and then-current costs of ICDs (66). The inefficiencies in ICD prescription, particularly for primary prevention after MI, are reflected in appropriate shock rates of only 20% to 30% and relatively low survival benefits (Fig. 6) (110), as discussed earlier. These limitations derive from restrictions in the designs of clinical trial designs because of funding limitations. The cumulative direct cost (exclusive of ICDs) for the major trials underpinning the primary prevention indications was <\$120 million (personal communication with the principle investigators of MADIT, MUSTT, MADIT-II, SCD-HeFT, and DINAMIT, October 2008). Even if the cost of defibrillators are included



**Figure 6** Comparison of Appropriate ICD Discharge Rate and Survival Benefit From MADIT II

The survival curve demonstrates the probability of appropriate implantable cardioverter-defibrillator (ICD) therapy at 1, 2, and 3 years of follow-up. The insert demonstrates the excess mortality among control patients without ICDs at the same 3 points in time. These figures demonstrate that appropriate ICD discharges cannot be considered a surrogate for survival, and do not accurately indicate the magnitude of benefit expected from ICD recipients. VT/VF = ventricular tachycardia/fibrillation. Modified, with permission, from Moss AJ et al. (110).

(estimated cost based on 2,159 patients receiving ICD devices at \$30,000 per initial implant = \$65 million), and primary prevention indications derived from these study designs were implemented in only one-third of the estimated number of candidates, the initial cost to the health care delivery system would be >25 times the cumulative 1-time expenditure for the clinical trials. Further, additional candidates are added into the health care pool annually.

The conceptual inconsistency in this economic model is that the scope and the stratification of the clinical trials for therapies that might have broad utilization are limited by their conventional sources of funding, while the economic burden of the outcomes of those trials is borne by another segment of the health care enterprise, namely, the health care delivery systems. The absence of a formal interaction between the clinical research enterprise and the health care delivery enterprise, in view of the large impact that the former has upon the latter, is inconsistent with rational health care policy planning and optimal medical care. Impact estimates during the design of trials, based on reasonable contingencies for outcomes, could be used to justify the size and scope of studies. Relatively modest increases in funding for research that has the potential for large economic impact on clinical practice, in order to provide clinical trial data that are more comprehensive and yield better guidelines by using stratified designs, would avoid such false economies. There are now attempts to better define candidates by additional research and post hoc registries, but this will be a complicated challenge because of difficulties in accumulating comprehensive post hoc data, ethical issues, and existing guidelines for care.

For the future, those of us involved in clinical research and health care delivery, including clinicians and clinical investigators, the insurance industry, funding agencies, and the biomedical manufacturing industries, must work on a resolution of the problem of appropriate funding for clinical research, for both ICDs and other new therapies that are on the horizon. As we learned in the 1980s, failure to consider and address the economic context of our actions will leave us without a meaningful voice as society addresses these issues through other channels (111,112). A societal revolution against perceived excesses or inefficiencies, once started, will be beyond control by any elements of the medical complex (111), and political forces will ultimately prevail.

## Conclusions

ICDs are reliable medical devices that have the potential to add quality years of life for appropriate candidates. There are scientifically-derived guidelines for their prescription that are limited by the scope of the clinical trials and observational data available. Further studies on risk profiling are needed, but in the interim, practicing physicians should recommend devices to their individual patients based upon available data, which they should interpret in the light of individual patient profiles and their patients' preferences.

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**Reprint requests and correspondence:** Dr. Robert J. Myerburg, Professor of Medicine and Physiology, Division of Cardiology (D-39), University of Miami Miller School of Medicine, P.O. Box 016960, Miami, Florida 33101. E-mail: rmyerbur@med.miami.edu.

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## REFERENCES

1. Mirowski M, Reid PR, Mower MM, et al. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med* 1980;303:322–44.
2. Mirowski M, Mower MM, Staewen WS, Tabatznik B, Mendeloff AI. Standby automatic defibrillator. An approach to prevention of sudden coronary death. *Arch Intern Med* 1970;126:158–61.
3. Mirowski M, Mower MM, Mendeloff AI. Implanted standby defibrillators. *Circulation* 1973;47:1135–6.
4. Lown B, Axelrod P. Implanted standby defibrillators. *Circulation* 1972;46:637–9.
5. Langer A, Heilman MS, Mower MM, Mirowski M. Considerations in the development of the automatic implantable defibrillator. *Med Instrum* 1976;10:163–7.
6. Mirowski M, Mower MM, Langer A, Heilman MS, Schreibman J. A chronically implanted system for automatic defibrillation in active conscious dogs. Experimental model for treatment of sudden death from ventricular fibrillation. *Circulation* 1978;58:90–4.
7. 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;321:406–412.
8. 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.
9. 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. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933–40.
10. Bigger JT Jr., for the Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. 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.
11. 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;337:1576–80.
12. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G, for the Multicenter Unsustained Tachycardia Trial Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882–90.
13. Connolly SJ, Gent M, Roberts RS, et al., on behalf of the CIDS Investigators. Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation* 2000;101:1297–302.
14. Kuck KH, Cappato R, Siebels J, Ruppel 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.
15. 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.
16. Hohnloser SH, Kuck KH, Dorian P, et al., for the DINAMIT Investigators. Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. *N Engl J Med* 2004; 351:2481–8.
17. Kadish A, Dyer A, Daubert JP, et al., for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *N Engl J Med* 2004;350:2151–8.
18. Bardy GH, Lee KL, Mark DB, et al., for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.

19. Myerburg RJ, Castellanos A. Emerging paradigms of the epidemiology and demographics of sudden cardiac arrest. *Heart Rhythm* 2006;3:235-9.
20. Schaffer WA, Cobb LA. Recurrent ventricular fibrillation and modes of death in survivors of out-of-hospital ventricular fibrillation. *N Engl J Med* 1975;293:259-62.
21. Cobbe SM, Dalziel K, Ford I, Marsden AK. Survival of 1476 patients initially resuscitated from out of hospital cardiac arrest. *Br Med J* 1996;312:1633-7.
22. 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—executive summary: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol* 2006;48:1064-108.
23. Wyse DG, Friedman PL, Brodsky MA, et al., and the AVID Investigators. Life-threatening ventricular arrhythmias due to transient or correctable causes: high risk for death in follow-up. *J Am Coll Cardiol* 2001;38:1718-24.
24. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. *Antiarrhythmics Vs. Implantable Defibrillator Study*, *Cardiac Arrest Study Hamburg*, *Canadian Implantable Defibrillator Study*. *Eur Heart J* 2000;21:2071-8.
25. Domanski MJ, Saksena S, Epstein AE, et al., for the AVID Investigators. Relative effectiveness of the implantable cardioverter-defibrillator and antiarrhythmic drugs in patients with varying degrees of left ventricular dysfunction who have survived malignant ventricular arrhythmias. *J Am Coll Cardiol* 1999;34:1090-5.
26. Feinstein AR. Meta-analysis: statistical alchemy for the 21st century. *J Clin Epidemiol* 1995;48:71-9.
27. 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.
28. 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.
29. 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.
30. 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.
31. 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.
32. Mukharji J, Rude RE, Poole WK, Gustafson N, et al. Risk factors for sudden death after acute myocardial infarction: two-year follow-up. *Am J Cardiol* 1984;54:31-6.
33. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. *N Engl J Med* 1983;309:331-6.
34. Ross AM, Coyne KS, Moreyra E, et al. Extended mortality benefit of early postinfarction reperfusion. *Circulation* 1998;97:1549-56.
35. Solomon SD, Zelenkofske S, McMurray JJV, et al., for the Valsartan in Acute Myocardial Infarction Trial (VALIANT) Investigators. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med* 2005;352:2581-8.
36. 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;51:2085-105.
37. Oechslin EN, Harrison DA, Connelly MS, et al. Mode of death in adults with congenital heart disease. *Am J Cardiol* 2000;86:1111-6.
38. Myerburg RJ, Castellanos A. Cardiac arrest and sudden cardiac death. In: Libby P, Bonow RO, Mann DL, Zipes DP, editors. *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*. 8th edition. Philadelphia, PA: Elsevier, 2008:933-74.
39. Diaz FJ, Loewe C, Jackson A. Death caused by myocarditis in Wayne County, Michigan: a 9-year retrospective study. *Am J Forensic Med Pathol* 2006;27:300-3.
40. Winters SL, Cohen M, Greenberg S, et al. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. *J Am Coll Cardiol* 1991;18:937-43.
41. Frank S, Braunwald E. Idiopathic hypertrophic subaortic stenosis. Clinical analysis of 126 patients with emphasis on the natural history. *Circulation* 1968;37:759-88.
42. Maron BJ, Shen WK, Link MS, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med* 2000;342:365-73.
43. Ellenbogen KA, Levine JH, Berger RD, et al., for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. Are implantable cardioverter defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation* 2006;113:776-82.
44. Maron BJ, Spirito P, Shen WK, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy (erratum in: *JAMA* 2007;298:1516). *JAMA* 2007;298:405-12.
45. Maron MS, Olivetto I, Betocchi S, et al. Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. *N Engl J Med* 2003;348:295-303.
46. Calkins H, Marcus F. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: an update. *Curr Cardiol Rep* 2008;10:367-75.
47. Bujá G, Estes NA III, Wichter T, Corrado D, Marcus F, Thiene G. Arrhythmogenic right ventricular cardiomyopathy/dysplasia: risk stratification and therapy. *Prog Cardiovasc Dis* 2008;50:282-93.
48. Wichter T, Paul M, Wollmann C, et al. Implantable cardioverter/defibrillator therapy in arrhythmogenic right ventricular cardiomyopathy: single-center experience of long-term follow-up and complications in 60 patients. *Circulation* 2004;109:1503-8.
49. Liu N, Ruan Y, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. *Prog Cardiovasc Dis* 2008;51:23-30.
50. Gaita F, Giustetto C, Bianchi F, et al. Short QT syndrome. A familial cause of sudden death. *Circulation* 2003;108:965-70.
51. Haissaguerre M, Derval N, Sacher F, et al. Sudden cardiac arrest associated with early repolarization. *N Engl J Med* 2008;358:2016-23.
52. Moss AJ, Schwartz PJ. 25th anniversary of the International Long-QT Syndrome Registry: an ongoing quest to uncover the secrets of long-QT syndrome. *Circulation* 2005;111:1199-201.
53. Zareba W, Moss AJ, Daubert JP, Hall W, Robinson J, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003;14:337-41.
54. Goldenberg I, Moss AJ, Peterson DR, et al. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008;117:2184-91.
55. Kaufman E, McNitt S, Moss AJ, et al. Risk of death in the long QT syndrome when a sibling has died. *Heart Rhythm* 2008;5:831-6.
56. Myerburg RJ, Castellanos A. Sudden cardiac death. In: Zipes DP, Jalife J, editors. *Cardiac Electrophysiology: From Cell to Bedside*. 5th edition. New York, NY: Elsevier, 2009. In press.
57. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. A multicenter report. *J Am Coll Cardiol* 1992;20:1391-6.
58. Nademanee K, Veerakul G, Nimmannit S, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. *Circulation* 1997;96:2595-600.
59. Alings M, Wilde A. "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. *Circulation* 1999;99:666-73.

60. Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. *Circulation* 2002;105:1342-7.
61. Antzelevitch C, Brugada P, Borggrefe M, et al. Brugada syndrome. Report of the Second Consensus Conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation* 2005;111:659-70.
62. Myerburg RJ, Castellanos A. Early repolarization and sudden cardiac arrest: theme or variation on a theme? *Nat Clin Pract Cardiovasc Med* 2008 Oct 7 [Epub ahead of print].
63. Myerburg RJ. Implantable cardioverter-defibrillators after myocardial infarction. *N Engl J Med* 2008;359:2245-53.
64. Myerburg RJ, Castellanos A. Clinical research designs and implantable defibrillator indications: spend in the beginning or pay at the end. *J Am Coll Cardiol* 2006;47:108-11.
65. Phurrough SE, Salive ME, Baldwin JF, Chin J, and the Centers for Medicare and Medicaid Services. Decision memorandum for implantable defibrillators (CAG-00157R3), January 27, 2005. Available at: <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=148>. Accessed November 20, 2008.
66. McClellan MB, Tunis SR. Medicare coverage of ICDs. *N Engl J Med* 2005;352:222-4.
67. Nanthakumar K, Epstein AE, Kay GN, Plumb VJ, Lee DS. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. *J Am Coll Cardiol* 2004;44:2166-72.
68. Buxton AE. Sudden death after myocardial infarction who needs prophylaxis, and when? *N Engl J Med* 2005;352:2638-40.
69. Passman R, Kadish A. Sudden death prevention with implantable devices. *Circulation* 2007;116:561-71.
70. Ezekowitz JA, Rowe BH, Dryden DM, et al. Implantable cardioverter defibrillators for adults with left ventricular systolic dysfunction. *Ann Intern Med* 2007;147:251-62.
71. Goldberger JJ, Cain ME, Hohnloser SH, et al., for the American Heart Association; American College of Cardiology Foundation; Heart Rhythm Society. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on Clinical Cardiology Committee on Electrocardiography and Arrhythmias and Council on Epidemiology and Prevention. *J Am Coll Cardiol* 2008;52:1179-99.
72. Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. *J Am Coll Cardiol* 2008;52:1111-1121.
73. Stein KM. Noninvasive risk stratification for sudden death: signal-averaged electrocardiography, nonsustained ventricular tachycardia, heart rate variability, baroreflex sensitivity, and QRS duration. *Prog Cardiovasc Dis* 2008;51:106-17.
74. Moss AJ, Faddl Y, Zareba W, Cannom DS, Hall WJ, for the Defibrillator Implantation Trial Research Group. Survival benefit with an implanted defibrillator in relation to mortality risk in chronic coronary heart disease. *Am J Cardiol* 2001;88:516-20.
75. Hill AB. The environment and disease. Association or causation? *Proc Royal Soc Med* 1965;58:295-300.
76. 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.
77. 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.
78. Goldenberg I, Moss AJ, Hall WJ, et al., for the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II Investigators. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation* 2006;113:2810-7.
79. Goldenberg I, Vyas AK, Hall WJ, et al., for the MADIT-II Investigators. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008;51:288-96.
80. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. *N Engl J Med* 2008;359:1009-17.
81. Buxton AE, Sweeney MO, Wathen MS, et al., for the PainFREE Rx II Investigators. QRS duration does not predict occurrence of ventricular tachyarrhythmias in patients with implanted cardioverter defibrillators. *J Am Coll Cardiol* 2005;46:310-6.
82. Singh JP, Hall WJ, McNitt S, et al. Factors influencing appropriate firing of the implanted defibrillator for ventricular tachycardia/fibrillation: findings from the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). *J Am Coll Cardiol* 2005;46:1712-20.
83. Wang NC, Maggioni AP, Konstam MA, et al. Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. *JAMA* 2008;299:2656-66.
84. Wilber DJ, Zareba W, Hall WJ, et al. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. *Circulation* 2004;109:1082-4.
85. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: structure, function, and time-dependence of risk. *Circulation* 1992;85 Suppl 1:2-10.
86. Myerburg RJ. Sudden cardiac death: exploring the limits of our knowledge. *J Cardiovasc Electrophysiol* 2001;12:369-81.
87. Epstein AE. Benefits of the implantable cardioverter-defibrillator. *J Am Coll Cardiol* 2008;52:1122-7.
88. Buxton AE, Lee KL, Hafley GE, et al., for the MUSTT Investigators. 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.
89. Solomon SD, Glynn RJ, Greaves S, et al. Recovery of ventricular function after myocardial infarction in the reperfusion era: the healing and early afterload reducing therapy study. *Ann Intern Med* 2001;134:451-8.
90. 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.
91. Buxton AE. Not everyone with an ejection fraction <30% should receive an implantable cardioverter-defibrillator. *Circulation* 2005;111:2537-42.
92. Moss AJ. Everyone with an ejection fraction less than or equal to 30% should receive an implantable cardioverter-defibrillator. *Circulation* 2005;111:2542-8.
93. 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.
94. 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.
95. 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.
96. 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.
97. 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.
98. Barthel P, Schneider R, Bauer A, et al. Risk stratification after acute myocardial infarction by heart rate turbulence. *Circulation* 2003;108:1221-6.
99. Makikallio 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.
100. Jouven X, Desnos M, Guerot C, Ducimetière P. Predicting sudden death in the population: the Paris Prospective Study I. *Circulation* 1999;99:1978-83.
101. 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.

102. 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.
103. Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. *J Cardiovasc Electrophysiol* 2002;13:709-23.
104. Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med* 2005;353:1471-80.
105. Mark DB, Nelson CL, Anstrom KJ, et al., for the SCD-HeFT Investigators. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2006;114:135-42.
106. Zwanziger J, Hall WJ, Dick AW, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006;47:2310-8.
107. Buxton M, Caine N, Chase D, et al., for the Health Economics Research Group. A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modeling of cost-effectiveness and cost-utility for these groups in a UK context. *Health Technol Assess* 2006;10:1-164.
108. Reynolds MR, Cohen DJ, Kugelmass AD, et al. The frequency and incremental cost of major complications among Medicare beneficiaries receiving implantable cardioverter-defibrillators. *J Am Coll Cardiol* 2006;47:2493-7.
109. Groeneveld PW, Farmer SA, Suh JJ, Matta MA, Yang F. Outcomes and costs of implantable cardioverter-defibrillators for primary prevention of sudden cardiac death among the elderly. *Heart Rhythm* 2008;5:646-53.
110. Moss AJ, Greenberg H, Case RB, et al. Long-term clinical course of patients after termination of ventricular tachyarrhythmia by an implanted defibrillator. *Circulation* 2004;110:3760-5.
111. Thurow LC. The implosion of medicine, ethics, and economics. *N Engl J Med* 1984;311:1569-72.
112. Fuchs VR. The "rationing" of medical care. *N Engl J Med* 1984;311:1572-3.

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