Series Editors • Craig T. Basson and Bruce B. Lerman

Emerging Concepts in Cardiology

Topics in Arrhythmias and Ischemic Heart Disease

Bruce B. Lerman
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To my wife, Karen,
my children, Josh, Jessica, Rachel and Jennifer,
and my parents, Lillian and Philip Lerman.

—Bruce B. Lerman

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Preface

Cardiology continues to be a dynamic field, one fueled in part by innovation in mechanical and cell-based therapies. This makes the field fascinating to observe but challenges one to remain au courant. Therefore, the task before the editors is to strike a balance in a single source that is authoritative, current, and readily absorbed. This is the goal of the current volume. We have organized this text to reflect the most current thinking in the field. To accomplish this mission, we have solicited the efforts of recognized authorities in ischemic heart disease and cardiac arrhythmias from the Weill Medical College of Cornell University, Division of Cardiology.

Although this volume, *Topics in Arrhythmias and Ischemic Heart Disease*, emphasizes state-of-the-art modalities in the treatment of coronary artery disease and arrhythmias, we are mindful that any coherent and integrated approach to the treatment of such patients must incorporate the impressive advances made in risk stratification. To that end, we have included a chapter that deciphers the myriad and sometimes contradictory data regarding biomarkers and their prognostic significance in ischemic heart disease. Prognostication for sudden cardiac death has become more sophisticated with the completion of several large randomized studies. The chapter dealing with this subject guides the reader through the nuances of the data, allowing one to incorporate the information into sound clinical decisions.

Impressive advancements in the treatment of acute coronary syndromes and congestive heart failure have been introduced in recent years. This has relied on a better understanding of the underlying pathogenesis and the introduction of novel therapeutic approaches. Pulmonary hypertension is an area that was relatively dormant until recent advances promoted new approaches to patients with this disorder. The chapter on this topic synthesizes the striking developments in this area. Likewise, cardiac resynchronization therapy has provided dramatic symptomatic relief for appropriately screened patients. Familiarity with understanding who benefits from such therapy and the determinants of such an outcome are essential for the clinician.

Interventional cardiology no longer refers to just percutaneous coronary procedures. Peripheral vascular procedures are now a well-established part of the armamentarium. Perhaps the most exciting innovation in the interventional domain is percutaneous valvular repair for treatment of aortic stenosis and mitral regurgitation. This area has the potential to be transformative. Finally, in the field of electrophysiology, percutaneous ablation to isolate the pulmonary veins in patients with atrial fibrillation achieves success in the majority of patients. Whether this procedure will replace antiarrhythmic therapy as a first-line approach remains to be seen, but for time being this approach at the very least can offer dramatic symptomatic relief for debilitated patients.

We wish to express appreciation to Demos Medical Publishing for their professionalism and expertise. It is our hope that this book serves as a useful guide and supplement for clinicians treating patients with ischemic heart disease and cardiac arrhythmias.

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1 Risk Stratification of Sudden Cardiac Death

APOOR PATEL
SEI IWAI

OUTLINE

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH

Heart disease is the leading cause of death in the United States and is responsible for approximately 870,000 deaths per year (1). Sudden cardiac death (SCD) is responsible for almost half of these deaths, claiming 350,000 to 400,000 lives per year (2). SCD is defined by the World Health Organization as death due to any cardiac disease that occurs out of hospital, in an emergency room, or a patient who is dead on arrival to a care facility. Of note, the death must occur within one hour after the onset of symptoms. The majority of SCD is likely arrhythmic in etiology. In women, up to 88% of sudden cardiac arrests may be due to arrhythmic causes (3). Of SCD due to cardiac arrhythmias, greater than 80% of events are due to ventricular tachycardia (VT) and ventricular fibrillation (VF), with the remainder due to bradyarrhythmias and asystole (4). Coronary artery disease (CAD), manifesting acutely as ischemic ventricular arrhythmias or chronically as scar-mediated arrhythmias, is responsible for 80% of SCD. Idiopathic dilated cardiomyopathies and hypertrophic cardiomyopathy are the next most common causes (5). While certain inherited ion channel disorders and acquired forms of structural heart disease are important etiologies of SCD, these entities are beyond the scope of this chapter, which will focus on risk stratification in patients with ischemic heart disease and nonischemic cardiomyopathies.

While medical therapy and the advent of the implantable cardioverter-defibrillator (ICD) have conferred a survival benefit to high-risk patients for SCD, there remains a substantial portion of the population at risk who do not meet current guidelines for ICD implantation. High-risk subgroups have a higher incidence of SCD but a lower absolute number of deaths, while low-risk subgroups have a low incidence of SCD but contribute a higher absolute number of deaths, as they represent a larger proportion of the overall population (Figure 1.1) (6). Liberalizing ICD implantation criteria to all patients in lower risk subgroups would, by definition, lead to an increase in the number needed to treat to save one life. Even utilizing current ICD implant criteria, most patients considered high risk do not benefit from defibrillator therapy and are exposed to the possibility of experiencing inappropriate ICD shocks as well as other device complications. Thus, identification of markers with better sensitivity and specificity for patients who would benefit from ICDs is critical.

A number of potential methods for risk stratification exist, including use of clinical parameters such as left ventricular ejection fraction (LVEF), electrophysiologic markers, imaging assessments, biochemical and genetic markers, and functional assessments (Table 1.1). A number of these methods will be discussed below. Some of the initial lessons were learned from ICD trials involving secondary prevention of SCD; that is, trials in patients

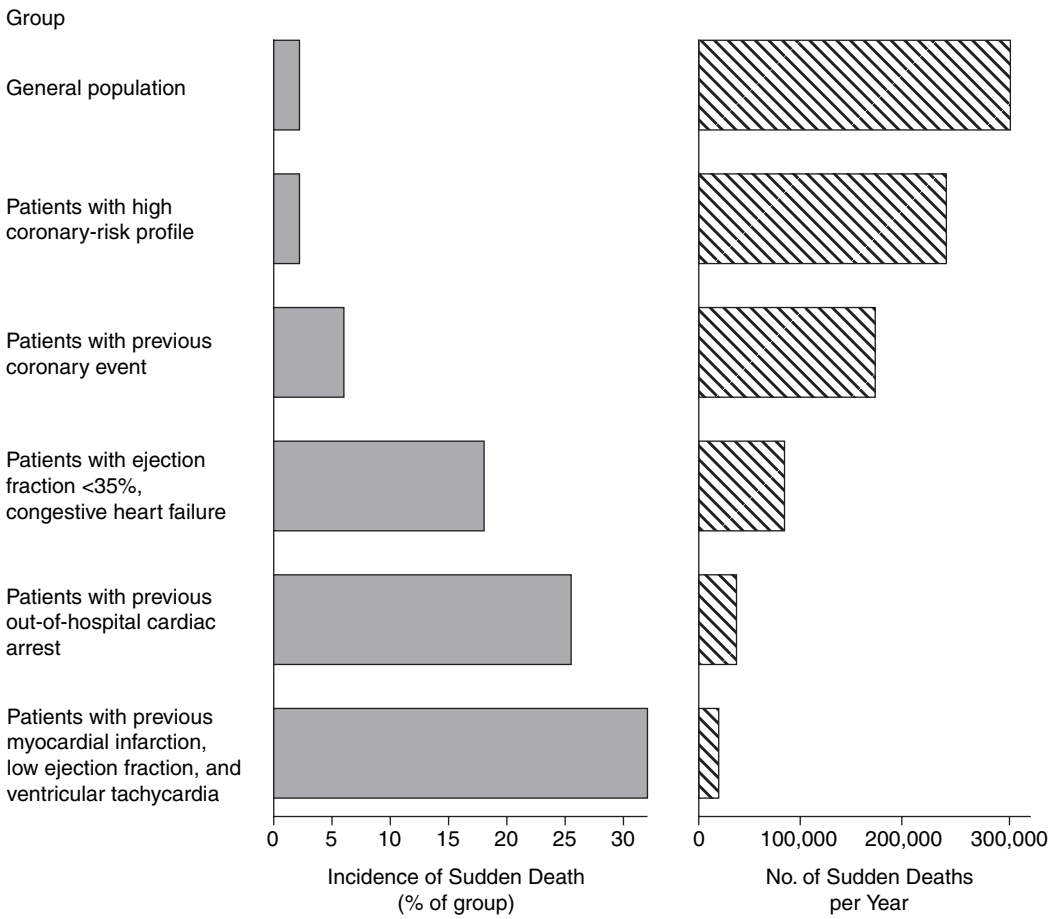


FIGURE 1.1 The incidence of sudden death in specific populations and the annual number of deaths in those populations. (Adapted from Ref. 6, with permission.)

Table 1.1 Methods of risk stratification for sudden cardiac death

Electrophysiologic markers	Anatomic markers
Electrophysiologic study	Left ventricular ejection fraction
T wave alternans	MRI for scar burden
Signal averaged ECG	Genetic markers
QRS duration	Functional markers
Measures of autonomic tone	Exercise testing
	Biochemical markers

EF, ejection fraction; MRI, magnetic resonance imaging; SCD, sudden cardiac death.

who had already survived cardiac arrest and were therefore identified to be in a high-risk subgroup. We will discuss these trials before continuing on to the utility of risk stratification tools in primary prevention of SCD.

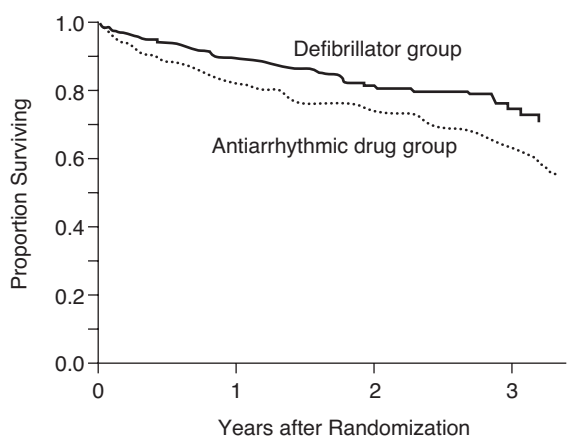
SUDDEN CARDIAC DEATH SURVIVORS

Secondary Prevention ICD Trials

The Antiarrhythmics versus Implantable Defibrillators (AVID) trial (7) was the largest secondary prevention trial, and helped define ICD implant indications for patients with a history of ventricular arrhythmias. In AVID, 1013 patients who presented with VF, sustained VT with syncope, or sustained VT with a LVEF of ≤40% were randomized to either an ICD or antiarrhythmic

therapy. The antiarrhythmic therapy was predominantly amiodarone (97%). Importantly, patients with VT/VF deemed to be due to reversible causes, VT/VF within five days of a myocardial infarction (MI) or revascularization, and with class IV heart failure (HF) were excluded from the trial. Over a mean follow-up of 18 months, the unadjusted total mortality for the ICD group and the antiarrhythmic drug group was 16% and 24%, respectively (Figure 1.2). Furthermore, the ICD group had better survival throughout the course of the study. As expected, the ICD reduced total mortality mainly via prevention of arrhythmic death, which was 4.7% in the ICD group and 10.8% in the antiarrhythmic group. Subgroup analysis of AVID based on LVEF demonstrated that patients with an LVEF of 20% to 34% had a survival benefit from ICD implantation compared to antiarrhythmic therapy (8). In patients with an LVEF of ≥35% there was no significant mortality difference between the ICD group and the antiarrhythmic group, and in patients with an LVEF of <20% there was only a trend towards benefit with an ICD. While some have used this data to question the benefit of an ICD in patients with an LVEF <20% or LVEF ≥35%, subgroup analysis should be interpreted with caution. Thus, current guidelines (9) call for ICD implantation in all survivors of SCD with a life expectancy of more than one year.

The Cardiac Arrest Study Hamburg (CASH) randomized 349 cardiac arrest survivors due to documented ventricular arrhythmias to an ICD, amiodarone, propafenone, or metoprolol (10). Propafenone was discontinued early when an interim analysis showed a 61% higher mortality in this group compared to the ICD group. ICD patients had a nonsignificant 23% reduction in all-cause mortality at a mean follow-up of 57 months, with the most benefit derived in the first five years. Of note, there was no significant difference in mortality between the patients assigned to metoprolol versus amiodarone, questioning the utility of amiodarone therapy for SCD prevention. Similar to CASH, the Canadian Implantable Defibrillator Study (CIDS) randomized 659 patients with resuscitated VT/VF or unmonitored syncope to an ICD or amiodarone (11). After a five-year follow-up, a nonsignificant decrease in risk of total mortality and arrhythmic death was observed in the ICD group versus the amiodarone group.



Patients at risk	1016	644	333	104
Percent surviving				
Defibrillator group		89.3	81.6	75.4
Antiarrhythmic-drug group		82.3	74.7	64.1

FIGURE 1.2 Overall survival in AVID. Unadjusted for baseline characteristics. (From Ref. 7, with permission.)

While AVID was the largest of these trials, it was stopped early (because the difference in the primary outcome variable between the two groups had crossed the statistical boundary for early termination). CASH and CIDS had fewer patients but longer follow-up, and thus a meta-analysis that was performed of the three trials is instructive (12). It demonstrated that ICD implantation resulted in a significant 27% reduction in total mortality driven by a 50% reduction in arrhythmic mortality. The analysis showed that the ICD was beneficial mainly in low LVEF (<35%) patients and those with advanced HF. Based on the demonstration of significant risk of recurrent SCD in patients in these secondary prevention trials, the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities assign a class I indication for ICD implantation in cardiac arrest survivors of VF or hemodynamically unstable VT not felt to be due to reversible causes (9). Patients with structural heart disease and sustained VT, whether hemodynamically stable or unstable, and patients with syncope of unknown origin with hemodynamically significant sustained VT or VF induced at electrophysiologic study (EPS) also meet class I indications for ICD therapy (9).

■ PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

Since SCD can be the first manifestation of heart disease in 50% of men and 63% of women (1), relying solely on a strategy of secondary prevention of SCD

would be ineffective in substantially reducing the event rates. In addition, the median reported survival to hospital discharge after out-of-hospital cardiac arrest with any first recorded rhythm is 7.9% (13). Therefore, it is important to identify patients at risk prior to their first episode in order to have the biggest impact on reducing the number of SCDs that occur.

Ejection Fraction, Nonsustained VT, and Inducibility of Sustained VT

ICD Trials in Ischemic Cardiomyopathy

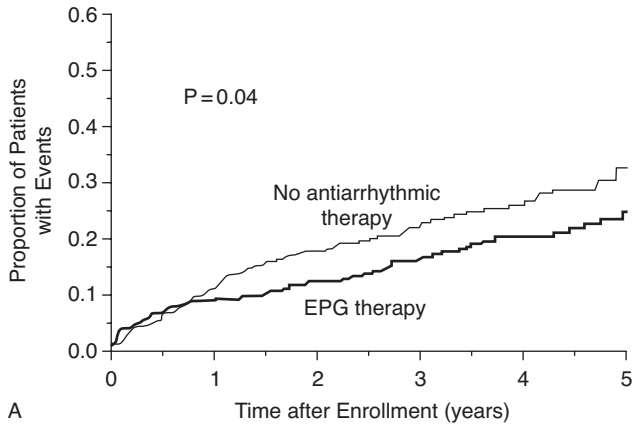
Primary prevention ICD trials initially focused on patients post-MI with significantly reduced LVEF, due to the high mortality rates in this population (14). Early primary prevention trials also utilized arrhythmic markers of nonsustained ventricular tachycardia (NSVT) and inducibility of sustained VT/VF at EPS as inclusion criteria in an attempt to identify the highest risk patients, based on prior studies (15). After these initial trials demonstrated mortality benefit to ICD implantation, subsequent studies evaluated patients post-MI with a low LVEF alone; presence of NSVT and inducibility at EPS were no longer utilized as inclusion criteria. These later trials also showed survival benefit, leading to current guidelines for ICD implantation in primary prevention candidates.

The Multicenter Automatic Defibrillator Trial (MADIT) randomized 196 patients with prior MI, class I–III congestive HF, a LVEF ≤35%, NSVT, and inducible VT on EP study that was not suppressible with procainamide, to an ICD or conventional therapy (16). Most patients in the conventional therapy arm received amiodarone. The trial was stopped early as it demonstrated a statistically significant, and impressive, 54% reduction in total mortality in the ICD arm at 27 months (16% and 39% in the ICD and conventional therapy groups, respectively). MADIT is notable in that it only enrolled a small number of patients and did not have a control group. In addition, more patients in the ICD group received beta-blockers.

The Multicenter Unsustained Tachycardia Trial (MUSTT) was not designed as an ICD trial per se, but rather to test whether EP-guided antiarrhythmic therapy would decrease the risk of SCD (17). The trial enrolled patients with CAD, LVEF 40% or less, NSVT, HF class I–III, and inducible VT during EP study. NSVT had to occur four days or more post-MI or revascularization. 704 inducible patients were randomized to EP-guided therapy (351 patients) or no therapy (353 patients). Of the patients randomized to EP-guided therapy, 29% received antiarrhythmic drugs and 58% received an ICD. Patients only qualified for an ICD if they failed one antiarrhythmic agent and remained inducible for VT/VF at repeat EP testing. MUSTT showed a decrease in the combined endpoint of cardiac arrest or death from arrhythmia at five years with EP-guided therapy compared to no antiarrhythmic therapy (25% versus 32%, respectively). Overall mortality was also reduced from 48% to 42% among patients receiving EP guided therapy (Figure 1.3). Subgroup analysis revealed that the benefit from EP-guided therapy was entirely due to the survival benefit of the ICD group. The ICD arm demonstrated a 31% reduction in mortality compared with those receiving antiarrhythmic therapy and a 24% mortality reduction compared to those receiving no therapy. Together, MADIT and MUSTT clearly demonstrated the benefit of ICD therapy in patients with a low LVEF, NSVT, and inducible ventricular arrhythmias on EP study.

The MUSTT trial also created a registry of the 1435 patients who had a low LVEF and NSVT, but were not inducible for VT/VF at EP study (18). They compared these patients with the 353 patients who received no antiarrhythmic therapy. Although, overall mortality at five years was significantly lower at 44% in the noninducible registry patients compared with 48% in the inducible patients not receiving antiarrhythmic therapy, it was still quite high overall. In addition, it was significantly higher than the 24% mortality in the ICD treated arm. Thus, results from the MUSTT registry suggested that even noninducible patients were at high risk and may benefit from ICD therapy.

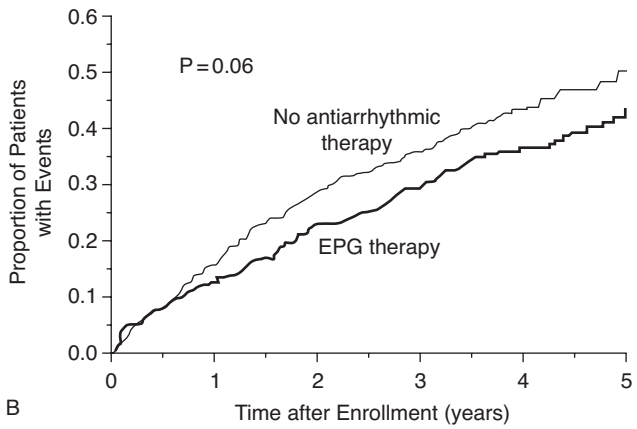
Of the 2202 patients screened in the MUSTT trial, only 35% were inducible. Inducibility in the MUSTT trial was defined as monomorphic VT with up to three extrastimuli or burst pacing, or polymorphic VT or VF with up to two extrastimuli. The negative predictive value of an EP study was only 88% at two years and 76% at five years for cardiac arrest or death due to arrhythmia among the registry patients. Thus, while the EP study provides some utility in risk stratification, it appears to be inadequate in isolation to classify patients with CAD and LV dysfunction into a sufficiently low-risk category. Another substudy of the MUSTT trial examined the relationship between LVEF and inducibility to the risk of cardiac arrest or arrhythmic death (19). It found that patients with a



A

No. at Risk

No antiarrhythmic therapy	353	290	242	178	118	67
EPG therapy	351	301	265	199	119	68



B

No. at Risk

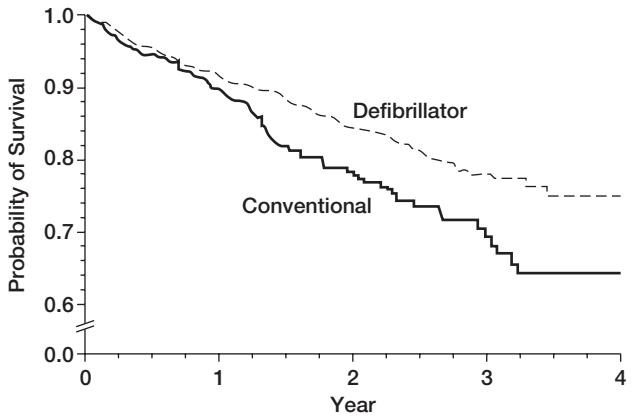
No antiarrhythmic therapy	353	296	248	185	122	71
EPG therapy	351	306	270	203	121	70

FIGURE 1.3 A: Kaplan–Meier estimates of the rates of cardiac arrest or death from arrhythmia. B: Death from all causes from the MUSTT trial. EPG notes electrophysiologically guided therapy. (From Ref. 17, with permission.)

LVEF <30% who were noninducible had the same rate of arrhythmic death or cardiac arrest as patients with a LVEF of 30% to 40% who were inducible. The only patients with a low event rate were those with an LVEF >30% who were noninducible. This implies that EPS may be of limited utility in higher risk patients—that is, those with severely decreased LVEF. The lower predictive power of EPS in patients with a lower LVEF might be due to these patients having more severe HF. Severe HF predisposes patients to having hormonal and electrolyte abnormalities, myocardial stretch, and repolarization abnormalities, all of which may predispose to arrhythmias (20,21). These conditions are dynamic, and thus may not be accurately assessed by an EP study that occurs at one point in time.

The MADIT-II trial addressed the possibility raised from the MUSTT registry data that patients with CAD and a low LVEF were at sufficiently high risk of SCD, and thus would benefit from an ICD (22), regardless of inducibility at EPS. In MADIT-II, 1232 patients with prior MI, LVEF ≤30%, and NYHA class I–III HF were randomly assigned in a 3:2 ratio to receive an ICD or conventional therapy. Patients were excluded if they had an MI within the past month, or if they were revascularized via percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG) in the past three months. The mean time from MI to enrollment in the trial was 6.5 years. During an average follow-up of 20 months, the mortality rates were 19.8% in the conventional therapy group and 14.2% in the ICD group, representing a 31% relative risk reduction for death with ICD therapy (Figure 1.4). The mortality benefit was due to a reduction in sudden death (3.8% versus 10.0% in the ICD and conventional therapy arms, respectively). Interestingly, there was a higher rate of hospitalization for HF in the ICD group (20%) than in the conventional therapy group (15%). Potential explanations for this include the ICD preventing arrhythmic death thus leading to more HF, or the effects of right ventricular pacing leading to ventricular dyssynchrony.

While MADIT-II excluded patients who were less than 30 days post-MI, data from a substudy of the Valsartan in Acute Myocardial Infarction Trial (VALIANT) showed that the risk of sudden death was highest in the first 30 days post-MI (23). VALIANT was a trial of 14,609 patients with an ejection fraction of <40% or HF post-MI who were randomized to an angiotensin converting enzyme inhibitor, an angiotensin receptor blocker, or both (24). The trial also examined SCD rates and found that patients had a 1.4% event rate in the first month post-MI, which then diminished over time (23). The event rate was higher in the patients with an ejection fraction of <30%, with an event rate of 2.3% in the first month. Each decrease of LVEF by 5% was associated with a 21% increase in the risk of sudden death in the first month. At one year, the rates of SCD merged, regardless of LVEF, suggesting that the



No. at Risk

Defibrillator	742	503 (0.91)	274 (0.84)	110 (0.78)	9
Conventional	490	329 (0.90)	170 (0.78)	65 (0.69)	3

FIGURE 1.4 Kaplan–Meier estimates of the probability of survival in the group assigned to receive an implantable defibrillator and the group assigned to receive conventional therapy in MADIT-II. (From Ref. 22, with permission.)

discriminatory effect of LVEF to distinguish patients at risk for SCD declines over time.

Further evidence of the dynamic temporal relationship of SCD and MI was presented in a surveillance study of 2997 post-MI patients (25). They reported an incidence of SCD of 1.2% in the 30 days posthospital discharge, and a subsequent 1.2% per year, with a five-year rate of 6.9%.

Contrasting evidence was found by the Defibrillation in Acute Myocardial Infarction Trial (DINAMIT) investigators, who assessed the utility of ICD implantation after recent MI (26). In their study, 674 patients with an MI within 6 to 40 days, LVEF ≤35%, and impaired cardiac autonomic function (manifest as either depressed heart rate variability or an elevated average 24-hour heart rate on Holter monitoring) were randomized to either medical therapy or an ICD. During a mean follow-up of 30 months, there was no difference in overall mortality between the two groups. While the ICD was effective in reducing death from arrhythmia by 58%, a prespecified secondary outcome, this was offset by a 75% increase in nonarrhythmic death in this group. Most of the nonarrhythmic deaths in the ICD group were due to cardiac causes, suggesting that ICD implantation shifted the mode of death from arrhythmia to HF in this population. As only 10% of patients were revascularized in the ICD group, recurrent ischemia leading to VT/VF—which would have normally led to cardiac arrest—was prevented by the ICD, but infarction and pump failure was not. However, the trial had a low event rate overall, which may have prevented detection of a difference between the control group and ICD group. It is also possible that the use of impaired autonomic tone as an inclusion criterion may have somehow selected for patients that had a higher propensity to die from HF and not sudden death. Ultimately, the results of DINAMIT suggest that immediate risk stratification of post-MI patients by LVEF and impaired autonomic tone may not be helpful, as the LVEF can recover over time, or scar formation may occur, thus changing the risk of SCD as time progresses.

In addition to DINAMIT, the Coronary Artery Bypass Graft (CABG)-Patch Trial failed to show the utility of ICD in primary prophylaxis (27). In CABG-Patch, 900 patients scheduled for a CABG with an LVEF ≤35% and a positive signal average electrocardiogram (SAECG) were randomized to CABG and an epicardial ICD or CABG and conventional therapy. There was no reduction in total mortality with the ICD after an average follow-up of 32 months, but the ICD group did have a reduction in arrhythmic death (4% versus 6.9% in the control group). Since the majority of the deaths were nonarrhythmic, the reduction in arrhythmic death did not affect total mortality. Reasons proposed for the lack of benefit include the beneficial effects of revascularization, including protection against arrhythmia and possible improvement of postoperative LVEF, thereby creating a lower risk patient population for SCD.

Given the results of MADIT-II, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), MUSTT, as well as DINAMIT and CABG-Patch, current guidelines for patients post-MI with a LVEF ≤35% with class II–III HF advocate waiting 40 days post-MI before ICD implantation, and waiting three months postrevascularization before ICD implantation (Figure 1.5a) (9). Post-MI patients with class I HF must have an LVEF ≤30% as only MADIT-II specifically included this group of patients. Based on MUSTT, patients with an LVEF ≤40% and NSVT may undergo EPS and receive an ICD if inducible for VF or sustained VT.

ICD Trials in Nonischemic Cardiomyopathy

Risk stratification of patients with nonischemic cardiomyopathy has proven to be more challenging than in their counterparts with CAD. The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation

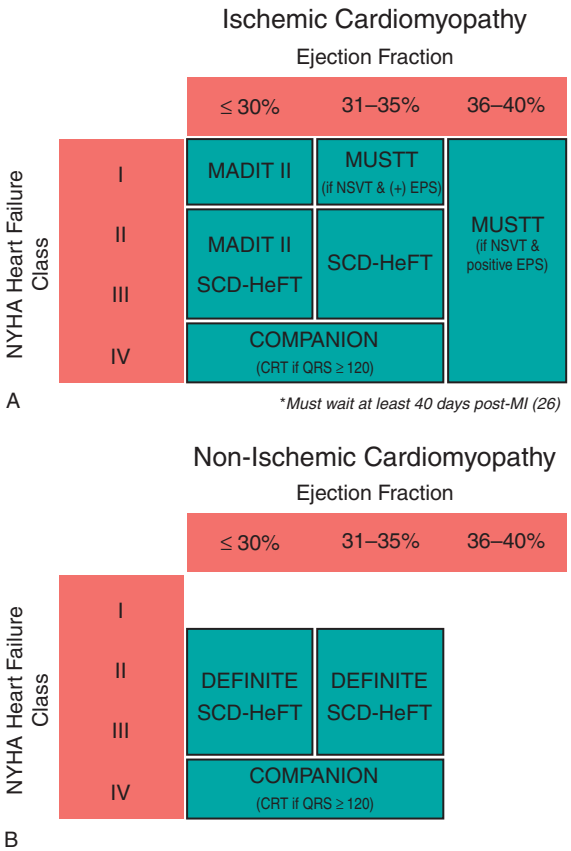


FIGURE 1.5 Summary of evidence supporting defibrillator implantation as stratified by ejection fraction and heart failure class in patients with ischemic cardiomyopathy (A) and nonischemic cardiomyopathy (B). For details of COMPANION trial, see Chapter 5. (CRT, cardiac resynchronization therapy; EPS, electrophysiology study; NYHA,New York Heart Association.)

(DEFINITE) Trial (28) randomized 458 patients with nonischemic dilated cardiomyopathy, LVEF <36%, and premature ventricular complexes or NSVT to standard medical therapy or standard medical therapy plus a single-chamber ICD. Of these patients, 86% were on an ACE inhibitor and 85% were on a beta-blocker. The ICD group had a significant reduction in arrhythmic death, but a nonsignificant reduction in total mortality. The trial was underpowered as the mortality rate in the medical therapy arm was lower than what the trial design had anticipated, and thus the primary endpoint may have reached statistical significance if there were a larger number of study subjects.

SCD-HeFT enrolled 2521 patients with ischemic or nonischemic cardiomyopathy with class II or III HF and an LVEF ≤35% (29). Patients were randomized to conventional therapy plus placebo, conventional therapy plus amiodarone, or conventional therapy plus a single-lead ICD. Placebo and amiodarone were administered in double-blind fashion. Amiodarone had no effect on the risk of death (28%) compared to placebo (29%). In contrast, ICD therapy was associated with an absolute decrease in mortality of 7.2% over amiodarone and medical therapy with ACE inhibitors and beta-blockers (Figure 1.6). These results held true for patients with both ischemic and nonischemic cardiomyopathies, a prespecified subgroup analysis. While MADIT-II had a follow-up period of 20 months, SCD-HeFT bolstered the MADIT-II findings with a follow-up of up to five years, demonstrating that beneficial effects of ICD implantation were not short-lived.

Subgroup analysis by HF class demonstrated that patients with class II HF derived benefit with ICD therapy, but not those with class III HF. Given that MADIT-II showed a greater benefit of ICD therapy the lower the LVEF, and that DEFINITE showed a greater benefit in class III patients, it is unlikely that this post-hoc subgroup analysis of SCD-HeFT represents a valid finding.

The results of these primary prevention trials in nonischemic cardiomyopathy patients led to an indication for ICD implantation in patients with a nonischemic cardiomyopathy, LVEF ≤35%, and class II or III HF (Figure 1.5b) (9). Importantly in SCD-HeFT, patients had to have a diagnosis of HF for at least three months and be on appropriate medical therapy.

■ OTHER METHODS OF RISK STRATIFICATION

Limitations of the LVEF in Risk Stratification

Based on data including the ICD trials described above, LVEF is the most well-established method for risk stratification for SCD. Furthermore, its accessibility and ease of measurement offers advantages over other risk stratification methods. The prognostic value of LVEF has remained strong despite improvements in treatments for acute MI, including beta-blocker therapy (30,31). However, while LVEF predicts both total mortality and arrhythmic death, it is poor at discriminating between the two (19). The results of DINAMIT and CABG-Patch also suggest that LVEF may be as much a