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REVIEW ARTICLE

Primary Prevention of Sudden Cardiac Death in Heart Failure: Will the Solution Be Shocking?

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Sudden cardiac death (SCD) may occur in as many as 40% of all patients who suffer from heart failure. This review describes the scope of the problem, risk factors for SCD, the effect of medications used in heart failure on SCD and the potential effect of the implantable cardioverter-defibrillator in primary prevention.

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Families and physicians of ambulatory heart failure (HF) patients have shared the grief engendered by patients who die suddenly and unexpectedly. Sadness is compounded by frustration and anger, as the patient may finally have been "stabilized" on a medical regimen and "doing well." With symptomatically advancing HF, the patient, the patient's loved ones and the physician often change their attitude, viewing sudden death as the most merciful mode of death. This report reviews the current knowledge of sudden cardiac death (SCD) in HF and strategies for primary prevention. It also considers which patient subsets are most suitable for treatment and the potential benefits and costs, including the financial, resource utilization and quality-of-life ones.

It should be emphasized that the bulk of data on preventing SCD in HF is derived from studies of secondary prevention in patients with varying degrees of left ventricular dysfunction. However, the stratification of functional severity has rarely been concomitantly analyzed. As such, data on primary prevention in HF populations are sparse.

Sudden Cardiac Death in HF: Scope of the Problem

More than 2 million patients experience HF, with over 400,000 new cases annually. Many studies of patients with HF have described the incidence of SCD in the HF population (Table 1). In symptomatically mild HF (New York Heart Association functional class II), the overall annual mortality is in the range of 5% to 15%, with approximately one-half to two-thirds being classified as sudden (1–3). In functional class III HF, annual mortality rises to 20% to 50% (4–6), and in class IV, it often exceeds 50% (7,8). As symptoms worsen, the proportion of deaths that are classified as sudden decrease; in functional class III it has been reported to be 20% to 50% and in class IV, 5% to 30% of all deaths. Sudden cardiac death occurs in HF from both coronary artery disease and nonischemic causes, and in most but not all studies the incidence of SCD in these two groups has been similar (6).

Causes of SCD in HF. Most studies of HF have described the major, if not exclusive, cause of sudden death as arrhythmic. In some studies a small percentage of cases of sudden deaths (usually <2%) are the result of nonarrhythmic causes, such as cerebrovascular accident or pulmonary embolism. The myopathic ventricle is extremely arrhythmogenic, which in part may be related to mechanical factors, including chronic stretch, remodeling and other less well understood factors (9). The incidence of various initiating arrhythmias in SCD in HF is not precisely known. There are a limited number of actual electrocardiographic (ECG) recordings at the onset of SCD. As such, most estimates of the initiating arrhythmia incidence are theoretically rather than empirically based. Meissner et al. (10) have estimated that in ischemic heart disease, monomorphic ventricular tachycardia from structural heart disease and reentrant tachycardia (but not due to acute ischemia) may account for 20% to 60% of all initiating arrhythmias, whereas polymorphic ventricular tachycardia or ventricular fibrillation may account for 20% to 40% and bradyarrhythmias for <5% to 25%. Davies' data (11), based on pathologic examinations in patients with ischemic heart disease dying suddenly (not necessarily with an antecedent history of HF), have shown a potentially anatomic basis for an ischemically mediated arrhythmia in >80% of cases (occlusive thrombus in 29.8%, mural thrombus in 43.5% and plaque fissure in only 7.7%). Farb et al. (12) have provided similar data in a recent study. Particularly relevant for the patient with HF is the possibility that further myocardial necrosis, coupled with previous myocardial damage, may produce enough additional pump dysfunction that if sudden death does not occur, rapidly developing myocardial failure will (Fig. 1). This point is especially important in considering shock therapy, if prolongation of life

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
ECG = electrocardiographic, electrocardiogram
HF = heart failure
ICD = implantable cardioverter-defibrillator
LV = left ventricular
MI = myocardial infarction
PES = programmed electrical stimulation
SAECG = signal-averaged electrocardiogram
SCD = sudden cardiac death

is measured in days to weeks rather than months to years. Also, if arrhythmias are primarily ischemia mediated, more aggressive anti-ischemia therapy may be worthwhile in a setting where other therapeutic modalities are typically stressed.

The initiating arrhythmia for SCD in nonischemic cardiomyopathy is even less well documented and understood. One frequently quoted study has suggested that up to 25% of patients may die of a bradyarrhythmia; in this study, there were actual precollapse ECG recordings, but they were taken on patients admitted to the hospital and "stabilized" with severe heart failure (13). The relevance of these data to the ambulatory outpatient with heart failure is unclear. Also, bundle branch reentrant ventricular tachycardia may be somewhat more prevalent in this group (14).

Identification of at-risk patients for SCD in HF. There are several clinical variables that identify the patient with HF at higher risk of dying. There are no undisputedly accepted markers to identify the patient with HF who is most prone to die suddenly, compared with the patient who will die from progressive pump failure. The degree of functional impairment, typically classified by the New York Heart Association schema, is the simplest variable to predict overall survival. Mortality rates vary somewhat between studies, but the range of values in Table 1 reflects the consensus in the published data and points out the major differences in survival among the various functional classes. Although classification of symptoms is subjective and differentiation of patients in functional class II versus III may have a relatively high interobserver variability, the patient with severe symptoms at rest (class IV) is unlikely to be confused with the ambulatory patient who gets winded by climbing one flight of stairs or by doing heavy housework. Left ventricular dysfunction has been established as a major predictor of long-term outcome in many studies evaluating therapies in coronary artery disease in patients without HF and in secondary prevention trials of sudden death, as well as in multiple HF studies (15–17). The combination of poor LV function and severe functional impairment portends a worse prognosis than either alone.

Table 1. Sudden Death by Severity of Heart Failure Symptoms

NYHA Functional Class	Annual Mortality (%)	Sudden Death (%)
II	5–15	50–80
III	20–50	30–50
IV	30–70	5–30

These data summarize mortality estimates from the published data. NYHA = New York Heart Association.

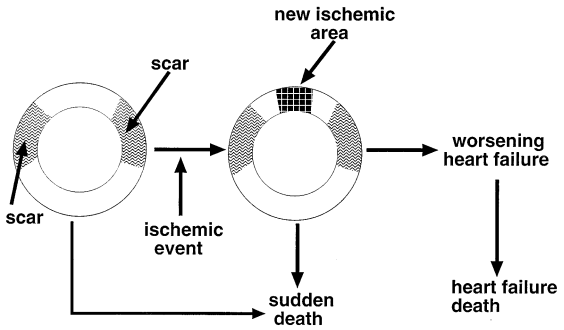

Figure 1. In the patient with HF from ischemic cardiomyopathy, a small infarction may tip the balance into profound and terminal myocardial failure if the acute ischemic event does not produce a fatal arrhythmia. This possibility must be considered in determining a strategy of sudden death prevention in the individual patient.

Other factors relate to worsened prognosis, particularly when stratified in the setting of a certain functional class and range of LV function. Nonsustained ventricular tachycardia and complex ventricular ectopy, which increase in incidence with worsening functional class in most studies, portend a worse prognosis within that functional class, but for overall mortality rather than specifically for SCD (5,18–22). In a subgroup analysis of the Gruppo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina (GESICA) trial, nonsustained ventricular tachycardia appeared to identify patients with a higher propensity to have SCD as well as total mortality (23). The level of plasma norepinephrine can be used to stratify the risk of death (22), but it rarely is, probably because in part of the expense and technical requirements. Furthermore, the plasma level is linked in part to functional impairment and ejection fraction, although it also has some independent predictive value (22,24). Other neurohormones, including plasma renin activity in some but not all studies and atrial natriuretic peptide, have been related to prognosis (25,26). The same issues as with plasma norepinephrine have precluded wider use of these variables in clinical decision-making. Hyponatremia ("poor man's plasma renin activity") has also shown some prognostic value (27). All of these blood levels tend to be abnormal in the most functionally impaired patient, so they tend to separate the patient with a very bad prognosis from a bad prognosis. Objective measures of functional impairment, particularly oxygen consumption at peak exercise, predict mortality (28). By combining an objective measure with subjective feelings of functional impairment, a sharper risk profile may emerge.

Direct evaluation of electrical disturbances in the dysfunctional heart has provided conflicting data on the predictive value of various tests. The signal-averaged electrocardiogram (SAECG) in the time domain may have value in predicting SCD in the routine post–myocardial infarction (MI) patient (29–31); its value in patients with HF from ischemic cardio-

Table 2. Angiotensin-Converting Enzyme Inhibitors for the Prevention of Sudden Death in Heart Failure

Study (ref. no.)	NYHA Functional Class	Follow-Up (mo)	Overall Mortality Decrease (%)	p Value	Sudden Death Mortality (%)		
					ACE Inhiitors*	No ACE Inhibitors	p Value
CONSENSUS (7)	IV	12	27	0.003	11.0 (14/127)	11.0 (14/126)	>0.25
SOLVD RX (1)	II, III	41	16	0.004	8.2 (105/1,284)	8.8 (113/1,285)	>0.25
SOLVD PRE (2)	I, II	37	8	0.30	4.6 (98/2,111)	5.0 (105/2,117)	0.10
Overall					6.2 (217/3,522)	6.6 (232/3,528)	0.09

*Enalapril was used in all studies cited. ACE = angiotensin-converting enzyme; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; NYHA = New York Heart Association; ref = reference; SOLVD RX and PRE = Studies of Left Ventricular Dysfunction, treatment and prevention, respectively.

myopathy is less clear (28). The SAECG does not have clear prognostic value in patients with nonischemic cardiomyopathy (32–36). Provocation of sustained arrhythmias, particularly monomorphic ventricular tachycardia, by programmed electrical stimulation (PES) has identified patients at higher risk for SCD in secondary prevention studies of patients with coronary disease (16,37–41). Patients with coronary artery disease who have had a resuscitated SCD, syncope or documented sustained monomorphic ventricular tachycardia and who have inducible and nonsuppressible ventricular arrhythmias by class IA agents, particularly procainamide, seem to have the worst prognosis (37,39,41). Patients who are not inducible or "easily suppressed" by a class Ia antiarrhythmic agent seem to have a better prognosis (37,38). Studies evaluating groups of patients with HF with PES as a prognostic factor are few and results are mixed. The consensus may be summarized as follows: for predicting SCD in patients with HF with ischemic cardiomyopathy, PES probably has some incremental value, although what it may be in relation to the major determinants already mentioned is not as clear; for patients with HF with nonischemic cardiomyopathy, present PES protocols do not seem to be predictive. We are left with the situation that the high-risk patient can be easily determined clinically, and that more sophisticated and expensive studies *may* improve risk stratification for overall mortality.

Effect of Therapeutic Agents Used in HF on the Incidence of SCD

Angiotensin-converting enzyme inhibitors. Substantial data confirm the efficacy of angiotensin-converting enzyme (ACE) inhibitors in decreasing mortality in patients with varying degrees of functional impairment (Table 2). In addition, after a myocardial infarction (MI) patients both with and without HF symptoms have shown a decrease in mortality with long-term (1 to 5 years) follow-up (42–45). The effect of ACE inhibitors on SCD is less clear. In the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) of patients in functional class IV, ~20% of patients died suddenly, without a difference between the enalapril and placebo groups (7). In patients with less severe functional impairment in the Studies of Left Ventricular Dysfunction (SOLVD) treatment trial and in asymptomatic or minimally symptomatic patients in the SOLVD prevention trial, there was a slight (<1%), nonsignificant decrease in SCD (1,2). Thus, the effect of ACE inhibitors on the prevention of SCD, although theoretically attractive, is small in patients with established HF.

The situation is somewhat different in patients without HF in the post-MI setting (Table 3). The Survival And Ventricular Enlargement (SAVE) trial, which recruited patients 3 to 14 days after infarction with an ejection fraction <35% to receive captopril or placebo, showed a decrease of 19% in the overall mortality rate (43). There were somewhat fewer SCDs in the ACE inhibitor group, but the difference was not statistically significant. The Trandolapril Cardiac Evaluation (TRACE) trial used the ACE inhibitor trandolapril in post-MI patients (ejection fraction <35%) with or without mild HF (45). A significant reduction in overall deaths, SCDs and myocardial failure deaths was seen. Likewise, in the Survival of Myocardial Infarction: Long-Term Evaluation (SMILE) trial using the ACE inhibitor zofenopril in patients with an anterior MI, there were fewer overall deaths, SCDs and HF deaths at 6 weeks in the zofenopril compared with the placebo group (44). The possibility of a small effect of ACE inhibitors on the prevention of SCD is strengthened from data from the Veterans Administration Heart Failure Trial II (V-HeFT II) trial (46) comparing enalapril with the combination of isosorbide dinitrate and hydralazine. An overall reduction in mortality with enalapril was significant at 2 years. At the end of the trial (average 2.5 years), there was still a borderline ($p = 0.08$) difference in mortality, primarily related to fewer sudden deaths with the ACE inhibitors.

Digoxin. There has been ongoing concern that digoxin is particularly arrhythmogenic in the setting of LV dysfunction. Survival data are limited to the recently published Digitalis Investigation Group (DIG) trial (47). This study compared

Table 3. Angiotensin-Converting Enzyme Inhibitors for the Prevention of Sudden Death in Post–Myocardial Infarction Patients With Left Ventricular Dysfunction

Study (ref no.)	NYHA Functional Class	Follow-Up (mo)	Overall Mortality Decrease (%)	p Value	Sudden Death Mortality (%)		
					ACE Inhibitors	No ACE Inhibitors	p Value
SAVE (43)*	I	42	19	0.019	5.6	6.7	>0.25
					(62/1,115)	(75/1,116)	
					(sudden unexpected)		
					3.9	4.5	
					(43/1,115)	(50/1,116)	
					(sudden, preceding sxs)		
TRACE (45)†	I, II	24–50	22	0.001	12.0	15.2	0.025
SMILE (44)‡	I, II	1.5	22	0.17	0.5	1.4	0.17
					(4/772)	(11/784)	
Overall					7.7	9.7	0.015
					(214/2,763)	(269/2,773)	

*Captopril. †Trandolapril. ‡Zofenopril. SAVE = Survival and Ventricular Enlargement; SMILE = Survival of Myocardial Infarction: Long-Term Evaluation; sxs = symptoms; TRACE = Trandolapril Cardiac Evaluation; other abbreviations as in Table 2.

survival among ambulatory patients with HF (predominantly functional classes II and III), most taking an ACE inhibitor and a diuretic, who received either placebo or digoxin. Digoxin had a neutral effect on survival. Interestingly, deaths classified by the investigator as secondary to pump failure showed a trend to decrease with digoxin, as did hospital admissions for HF. Deaths considered "other cardiac" (presumably, in part, SCD) were not statistically different between the two groups, although they were somewhat higher in the digoxin group. These findings have raised the concern that digoxin's neutral effect on mortality is the sum of a decrease in pump failure deaths and a slight increase in arrhythmic deaths.

The study protocol did not provide for an independent events committee to review the cause of death. The investigator at each site was responsible for assigning the causative event. Even with guidelines provided to the investigators by the study protocol, there was likely to have been significant variations in interpretation of cause of death. Because of the known difficulties in categorizing the cause of death, even when analyzed rigorously, the effects of digoxin on SCD based on the DIG data must be interpreted cautiously.

Diuretic agents. There are no data on the effect of diuretic agents on survival in HF. This fact should not be surprising because congestion often requires the use of diuretic agents to maintain clinical stability. Withdrawing diuretic agents in the stable ambulatory patient have not met with much success (48). With these caveats in mind, diuretic agents do have the theoretic potential to increase the risk of SCD by producing hypokalemia and hypomagnesemia and activating the renin-angiotensin system. Thus, a reasonable provisional strategy in the absence of definitive clinical trial data is to minimize the diuretic dose to a level that allows the patient to be congestion-free as an outpatient.

Beta-adrenergic blocking agents. In post-MI studies, beta-blockers have been shown to decrease mortality (49). The incidence of SCD also decreases (Table 4); this effect is particularly striking in patients with presumed or documented LV dysfunction. The results in patients with established HF are

Table 4. Beta-Blockers for Prevention of Sudden Death After Myocardial Infarction and Heart Failure

Trial	NYHA Functional Class	Sudden Death Mortality (%)		
		BB	No BB	p Value
After MI				
BHAT, hx CHF				
Yes	II	5.5 (19/345)	10.4 (38/365)	<0.05
No	I	2.9 (45/1,541)	3.4 (53/1,556)	NS
Timolol, heart size				
Normal		5.1 (31/608)	7.3 (43/591)	NS
Borderline		6.9 (9/131)	13.7 (18/131)	NS
Enlarged		12.9 (26/202)	22.7 (49/216)	<0.05
Heart failure				
MDC	II, III	9.8 (18/184)	6.3 (12/189)	NS
CIBIS	III, IV	4.9 (15/320)	5.3 (17/321)	NS
Carvedilol	II, III	1.7 (12/696)	3.8 (15/398)	<0.01

BB = beta-blockers; BHAT = Beta-Blocker Heart Attack Trial; CHF = congestive heart failure; CIBIS = Cardiac Insufficiency Bisoprolol Study; hx = history of; MDC = Metoprolol in Dilated Cardiomyopathy trial; MI = myocardial infarction; NYHA = New York Heart Association.

therefore somewhat paradoxic. In the Metoprolol in Dilated Cardiomyopathy (MDC) trial (50) using metoprolol in patients with noncoronary cardiomyopathy, SCD was not decreased, nor was it significantly decreased in the Cardiac Insufficiency B Isoprolol Study (CIBIS) (not powered as a mortality trial) (51). In contrast, the combination of three trials using carvedilol in patients with mostly mild to moderate HF showed a significant reduction in all-cause, heart failure, and SCD mortality rates (52). The ongoing Beta-Blocker Evaluation of Survival Trial (BEST) survival trial using bucindolol may further clarify the value of beta-blockers in preventing SCD.

Calcium channel blockers. Studies with the first-generation dihydropyridines, verapamil and diltiazem, have failed to show survival benefit in the setting of HF or LV dysfunction, or both, and in some cases, worsening (53–55). The second-generation, "vascular-specific" dihydropyridine, amlodipine, has been subjected to a placebo-controlled survival trial (Prospective Randomized Amlodipine Survival Evaluation [PRAISE]) in patients with ischemic and nonischemic cardiomyopathy (56). Overall, survival rates were similar for amlodipine- and placebo-treated groups, with an improved survival in the nonischemic cardimyopathy group. The reason for the decrease in deaths in this subgroup has not been described to date. These data have prompted PRAISE II, a survival study limited to a nonischemic cardiomyopathy cohort.

Antiarrhythmic agents. No class I antiarrhythmic agent has shown evidence of preventing SCD in HF (or in any other setting). It is unlikely that such a trial will proceed because of the propensity for proarrhythmia in this class of antiarrhythmic agents in patients with LV dysfunction and HF and the results of the Cardiac Arrhythmia Suppression Trials (CAST) I and II (57,58). These trials addressed primary prevention of SCD in patients after they had an MI with ventricular ectopy and in most cases LV dysfunction. The active drug arms, either encainide or flecainide, demonstrated a significant increase in mortality compared with placebo (57), whereas moricizine showed a nonsignificant increase in mortality (58). The increase in mortality was seen for both SCD and non-SCD, suggesting a more widespread deleterious effect of these agents, rather than a proarrhythmogenic effect only.

These data may be contrasted with the results with amiodarone. No study in post-MI patients has shown an increase in mortality and some have shown a decrease (59–64). Results of primary sudden death prevention in HF have been mixed. The American Congestive Heart Failure–Survival Trial of Antiarrhythmic Therapy (CHF-STAT) (~40% mortality at 2 years) showed no difference in mortality between amiodarone and placebo, with ~50% of the deaths being sudden (65). In this study, patients with nonischemic cardiomyopathy showed a trend toward improved survival, but the causes of death were not reported in this subgroup analysis. The Argentinian GESICA trial (66) did show a significant mortality reduction with amiodarone (overall risk reduction 27% over 2 years). Two-thirds of the study patients had nonischemic cardiomyopathy. The decrease in mortality was due to a decrease in both SCD and pump failure deaths, suggesting that amiodarone, in contrast to the class I agents tested in CAST, had salutary actions in addition to its antiarrhythmic effect. More recently, in two large randomized trials of amiodarone after MI, there was a significant reduction in SCD (~35%) but no reduction in overall mortality (62,63). This somewhat perplexing result may be related to problems in death classification or, more ominously, a deleterious component of amidarone (64). In the latter regard, the recently published Survival With Oral D-Sotalol (SWORD) trial comparing the class III agent D-sotalol with placebo in post-MI patients also showed a significant increase in mortality with the active agent (67).

Implantable Cardioverter-Defibrillator

There is much enthusiasm that the implantable cardioverter-defibrillator (ICD) can prevent SCD in HF (68,69). This attitude is aptly stated in a recent editorial: "The real and legitimate question concerning ICD therapy is no longer 'Do ICDs prolong life?' but rather 'Which patients benefit most?' and 'What is the cost effectiveness of the ICD in the prevention of sudden death and prolongation of life?' " (69). The remainder of this report will address these issues as they relate to the patient with HF.

First, it must be admitted, even by the most enthusiastic advocate of ICD therapy, that scientific data for ICD use in primary prevention in the setting of HF are not available. Data used to suggest that the ICD saves lives include studies in patients who have had a cardiac arrest or syncope (secondary prevention) (16,70,71), studies using historic control subjects (72) and studies in which LV function but not functional impairment from HF has been characterized (16,68). Published survival results have not uniformly favored the ICD (73–75). For example, in one study of SCD survivors with an ICD who had no inducible arrhythmias by PES, the SCD-free interval was significantly prolonged but overall survival was not (74).

There are reasons to be concerned that the benefit from an ICD in the HF setting may indeed be limited. The primary reason is that a large percentage of deaths from myocardial failure may be expected over time (ranging from 4% to 50% per year depending on the severity of symptoms). In a study of patients awaiting heart transplant, the majority of deaths (approximately two-thirds) were nonsudden (75). Although SCD was significantly decreased, overall mortality was not. Second, in all ICD studies, SCD continues to occur (typical 1% to 2% per year in patients who do *not* have HF). If we hypothesize that some of these deaths are ischemic with further myocardial necrosis, salvage from SCD may, within a short period of time, convert the patient to a pump failure death. The issue of operative mortality has fortunately been avoided by the use of transvenous devices, particularly for patients with a very dilated, structurally deranged heart (76). We may consider a "best case" scenario for ICD therapy constructed from the published data as follows: in functional class II, mortality will be decreased by 50% of its baseline; class III, 30% of its baseline; and class IV, 8%. Because the annual mortality of functional class III is much higher than class II,

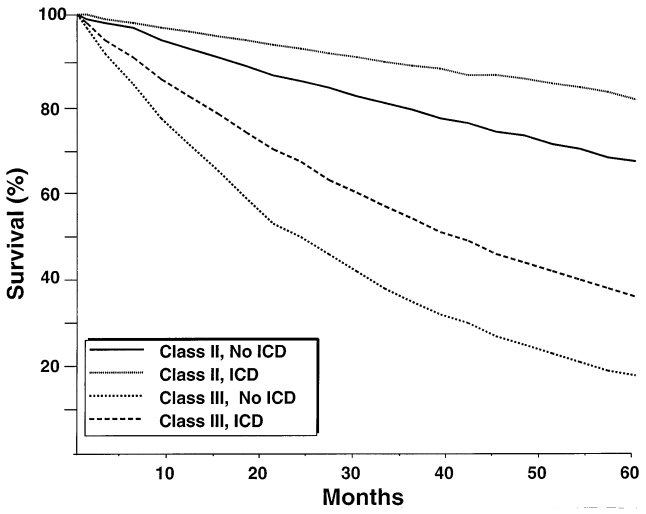

Figure 2. This figure shows the potential of the ICD to prolong life in patients in functional class II or III. It assumes that the yearly mortality rate in functional class II is 8% and that the sudden death percentage is 50% in this class. It also assumes an annual mortality rate in functional class III of 30% and that 30% of all deaths are sudden. Finally, it assumes that the ICD can prevent *all* sudden deaths (refer to text).

more patients will actually be saved from SCD if a general strategy of implanting ICDs is targeted for this group. However, many more patients in this class will progress to terminal HF and the patient will be defibrillated by the device in the throes of terminal pump failure or the physician will prepare for the terminal event by deactivating the device. Applying a general strategy may indeed save lives if applied to less functionally limited patients (class II), but fewer patients may be expected to use the device. Figure 2 illustrates the potential life-saving effects of placing an ICD solely on the basis of functional class. In theory, the ICD could provide an improvement in long-term survival comparable or superior to agents that have been shown to improve survival in HF, particularly ACE inhibitors.

If trial data are forthcoming in support of the use of the ICD for primary prevention, then the question will emerge whether we can afford such a strategy. Actual study data are required to answer this question; a first-order approximation of costs may estimate the cost of each life-year saved. These assumptions are the "best case" scenario for ICD costs. Assumptions include an annual mortality rate of 8% in functional class II, with 50% of these deaths being sudden and preventable, and an annual mortality of 30% in functional class III, with 30% of these deaths being sudden and preventable. Furthermore, we assume that all SCDs can be prevented and that SCD in the HF group costs no money to treat (i.e., no resuscitative efforts, hospital admissions). The incremental costs of the ICD are considered limited to implantation and follow-up costs, and all ICDs perform flawlessly without the need for a battery change for 5 years. We also assume that there are no implantation deaths or morbidity, that the average hospital stay is ≤3 days, that no electrophysiologic testing is performed and that no new antiarrhythmic drugs are used after implantation. Finally, we assume a cost for ICD placement and follow-up of $40,000 over an approximate period of 5 years (77).

Applying this model to 100 patients followed for 5 years, 30 life-years will be saved in patients in functional class II and 65 life-years in those in class III. The cost per life-year saved will be approximately $133,000 for patients in functional class II and $62,000 for those in class III. Owens et al. (78), using a sophisticated Markovian model comparing the incremental cost of ICD with amiodarone in SCD survivors, concluded a somewhat similar cost for ICD per life-year saved (average cost approximately $74,000). In the high risk group in the Multicenter Automatic Defibrillator Implantation Trial (MADIT), a preliminary report has suggested that the cost per life-year saved ranged from $23,000 to $38,000 based on the statistical model used (77). These results demonstrate that costs are sensitive to the patient's mortality risk and that ICD therapy applied on a large scale is likely to be an expensive approach for society as a whole.

How expensive will this be compared with other life-saving therapies? It has been estimated that the incremental cost per life-year saved for outpatient dialysis is approximately $40,000 to $60,000 (79); that of the thrombolytic agent streptokinase as compared with placebo is estimated to be $3,500 to $21,000; and that of tissue-type plasminogen activator over streptokinase is $16,000 to $60,000 (80,81). It has recently been reported that primary prevention of coronary events with the hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitor pravastatin costs in the range of $15,000 to $30,000 per life-year saved (82). Thus, ICD placement for all, although life-saving in patients of a certain functional class, will be an expensive strategy. It will then become a societal question if this strategy is worth the money.

Two presently ongoing or imminent studies are addressing primary SCD prevention in HF. One is the German-Austrian CArdiomyopathy Trial (CAT) (83,84). The primary study group is limited to patients with nonischemic cardiomyopathy with an assumed mortality rate of 30%, and 40% of that mortality rate is assumed to be sudden, which is a predicted absolute reduction in mortality of 6% in the ICD arm with a follow-up time of 1 year. That trial assumes that there will be almost complete elimination of SCD and that there will be significant operative mortality from thoracotomy-placed ICD (21% of all ICD deaths). Although the use of the transvenous approach will decrease mortality in the ICD arm, the assumption that 40% of deaths will be SCD in this group, in order to reach statistical significance, may be too optimistic, because many studies have shown fewer SCDs when the yearly overall mortality rate is as high as 30%. The other major study is the Sudden Cardiac Death in Heart Failure: Trial of prophylactic amiodarone versus implantable defibrillator therapy (SCD-HeFT) study, which uses the strategy of ICD placement in ambulatory patients with HF (85). It is a three-arm trial: "optimal" medical therapy alone; optimal medical therapy and amiodarone; and medical therapy and ICD. The sample size (n = 2,500) assumes a 25% annual mortality rate in the

medical therapy alone arm and a mortality reduction of 20% in the ICD arm. The SCD rate of 20% to 25% and the longer follow-up of 2 to 3 years in SCD-HeFT provide a somewhat better opportunity to find a difference than in CAT.

The recently published MADIT trial (41) showed that in a highly selected high risk post-MI group, primary prevention of SCD could be achieved (with a risk reduction of 54% over an average of 27 months) (Fig. 3A). This study, by design, tried to recruit a very high risk patient group by using post-MI patients with severe LV dysfunction (ejection fraction <35%) and nonsustained ventricular tachycardia on Holter monitoring (note that these two variables are risk factors for increased mortality in patients within any functional class). Patients were then further stratified according to their inducibility by PES and their suppressibility with procainamide. This study was *not* a primary prevention in HF trial. Nevertheless, valuable insights may be gleaned from this study in that the patient group was very similar to an average HF group. Two-thirds of the patient group had a history of HF with either functional class II or III symptoms; over half of the patients were taking an ACE inhibitor and a diuretic agent; and ~40% to 50% were taking digoxin. Based on the percentage of the patients in functional classes I, II and III (86) and the mortality assumptions used for Figure 2, we may calculate 5-year mortality on the basis of HF symptoms alone (Fig. 3B). The actual higher mortality seen in the non-ICD group represents the successful selection process of recruiting very high risk patients for SCD. Although screening with PES is formidable and possibly prohibitive, the MADIT trial points out that a very high risk group can be obtained, which may in turn help to maximize the life-saving potential of the ICD (38).

The ICD as an initial treatment for secondary prevention of SCD in patients with severe symptomatic ventricular arrhythmias (very high risk group) has been shown in the National Heart, Lung and Blood Institute–sponsored Antiarrhythmics Vs Implantable Defibrillators (AVID) trial to decrease overall mortality in comparison with antiarrhythmic therapy (87). This study, which was discontinued early because of the favorable effect of ICD on mortality, showed a 38% reduction at 1 year and a 25% reduction at 2 and 3 years in comparison with amiodarone or sotalol (87). There are two ongoing randomized clinical trials comparing ICD with amiodarone therapy in patients who have survived an episode of SCD (Cardiac Arrest Study Hamburg [CASH]) or had hemodynamically unstable sustained ventricular tachycardia (Canadian Implantable Defibrillator Study [CIDS]) (88,89). The AVID data and the anticipated results of the CASH and CIDS will likely increase the momentum to consider ICD use for primary prevention in patients with HF, although the risk-benefit ratio is at present unknown.

Conclusions. Data from studies on pharmacologic therapy suggest that the greatest benefit in preventing SCD occurs in patients with LV dysfunction with at most mild to moderate symptoms. As functional impairment increases, drugs become less effective. Angiotensin-converting enzyme inhibitors provide only modest, if any, protection against SCD in patients with established HF. In patients with asymptomatic LV dysfunction after MI, a small benefit in decreasing SCD may be present. No data support the proposition that digoxin or diuretic agents decrease SCD, and hypothetically may increase it, although data are insufficient to support this either. The possibility that beta-blockers and amiodarone decrease the risk of SCD is supported by some but not all data.

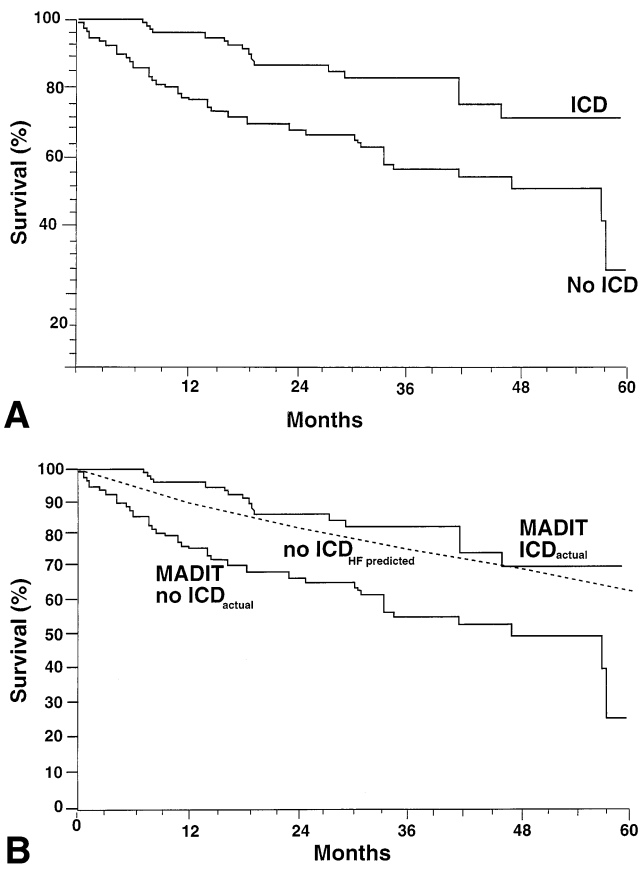

Figure 3. A, Results of the MADIT trial. **B,** Superimposition of the expected mortality in the conventional arm based on functional class alone, assuming an annual mortality rate of 4% in functional class I, 8% in class II and 30% in class III, or an annual aggregate mortality rate of 14% (refer to text).

Although several arrhythmic markers of SCD can be identified, the results of antiarrhythmic therapy aimed at primary prevention of SCD have been disappointing.

The most encouraging prospect, at present, for preventing sudden death is the transvenous ICD, where technologic advances have been remarkable. The generator size and technology of the ICD allow for a minimally invasive procedure and in many cases a brief (<24 h) hospital stay. These improvements will reduce the costs per implantation. The developments of electrogram storage and retrieval and remote ICD interrogation will further reduce the costs of ICD management. Recently approved ICD devices have expected battery longevity of >7 years. With the increasing number of ICD placements, it is anticipated that unit costs will decrease. All of these changes will decrease the cost per life-year saved.

Furthermore, interrogating electrograms before shocking will further our understanding of the initiating arrhythmias of SCD, including the role of bradyarrhythmias. In addition, current devices have bradycardia pacing capabilities. Newer devices with dual-chamber pacing capabilities will soon be approved.

Similar to data from pharmacologic trials, secondary ICD prevention studies suggest that less functionally impaired patients with HF will have the greatest gain in overall survival from prophylactic ICD placement. This fact underscores the importance of developing a more exact risk profile for SCD in this large group of patients.

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