A Guide to Device Selection: Cardiac Resynchronization Therapy Alone or in Combination with an Implantable Cardioverter Defibrillator

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The most recent estimates show an apparent increase in sudden cardiac death (SCD) in the United States. A major reduction in SCD will depend on developing effective methods to identify and prevent risk factors for SCD. This article reviews the research milestones that have resulted in our current approach to risk stratification and treatment of patients at high risk for SCD. One of the earliest attempts to prevent SCD involved suppression of premature ventricular complexes (PVCs) in high-risk patients, but trials using a variety of antiarrhythmic drugs with the aim of suppressing PVCs and reducing mortality demonstrated negative survival results. In the case of amiodarone, clinical trial data to date suggest that it should not be used for primary prevention of SCD or to prolong survival in patients with congestive heart failure secondary to coronary artery disease. The implantable cardioverter defibrillator (ICD) has been demonstrated in multiple studies to be the most significant therapy for life-threatening ventricular arrhythmias and for primary and secondary prevention of SCD. It is recommended that the majority of patients who receive cardiac resynchronization therapy should have an ICD unit implanted in order to include defibrillator therapy.
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Key words: Sudden cardiac death • Ventricular fibrillation • Ventricular tachycardia • Premature ventricular complexes • Antiarrhythmic drugs • Cardiac resynchronization therapy • Implantable cardioverter defibrillator

Sudden cardiac death (SCD) remains a major epidemiologic problem in the United States. The most recent estimates show an alarming trend, with an apparent increase in SCD.[1] Of 728,743 cardiac disease deaths that occurred in 1999, 462,340 (63.4%) were due to SCD. The most common pathologic finding in SCD victims is coronary artery disease.[2] The cause of SCD is not always obvious. Some patients may succumb to an acute ischemic event that precipitates ventric-

ular fibrillation (VF), whereas other patients with coronary artery disease have no definable ischemia at the time of death. Decades of research seeking to define patients at highest risk for sudden death after myocardial infarction have uncovered a patient subgroup that appears most vulnerable: those with a left ventricular ejection fraction (LVEF) of 40% or less who have nonsustained ventricular tachycardia (VT).[2] Because survival rates for out-of-hospital cardiac arrest are so low, ranging from 2% to 25% in the United States,[3] much effort has been directed at trying to identify patients at highest risk for sudden death and at formulating plans for prevention and treatment that will result in a reduction of mortality.[2] There will likely be a small survival gain with greater access to the automated external defibrillator, but a major reduction in SCD will more likely depend on developing effective methods to identify and treat patients with risk factors for SCD and, more importantly, to reduce the prevalence of coronary artery disease in the population.

This article will review the research milestones that have resulted in our current approach to risk stratification and treatment for patients who are at high risk for SCD and will apply these data to determine whether patients should receive a stand-alone, biventricular pacemaker or a biventricular pacemaker combined with an implantable cardioverter defibrillator (ICD).

Primary Prevention of SCD: Antiarrhythmic Drugs and ICD Trials

Antiarrhythmic Drugs

One of the earliest attempts to prevent SCD was suppression of premature ventricular complexes (PVCs) in patients "apparently" at high risk for SCD.[2,4–7] Patients were considered to be at increased risk if they had complex ventricular arrhythmias associated with significant left ventricular dysfunction. In fact, Lown and Wolf[7] developed a classification to identify varieties of PVCs that they considered "warning arrhythmias," that is, those arrhythmias that would lead to either VF or sustained VT. This classification scheme was demonstrated to have many shortcomings but, nonetheless, became a standard approach to ventricular arrhythmias for many years.[2]

Many small and large trials using a variety of antiarrhythmic drugs with the aim of suppressing PVCs and reducing mortality in patients after acute myocardial infarction have been performed.[2] In retrospect, there was a trend toward increased mortality in patients receiving antiarrhythmic drugs, but this was not made clear until the Cardiac Arrhythmia Suppression Trial (CAST) was performed.[8] In CAST (a randomized, placebo-controlled study), patients received either placebo or one of three antiarrhythmic drugs known to suppress PVCs: encainide, flecainide, or moricizine. CAST was stopped prematurely because patients receiving encainide and flecainide had a higher mortality rate than those in the placebo group. Moricizine was studied further in CAST-II, but this trial was also prematurely discontinued because of an increased mortality rate in patients treated with moricizine compared with placebo in the early phase of drug initiation. During further observation over time, there was no survival benefit with moricizine.[9]

Multiple theories emerged as to the reason why CAST and CAST-II demonstrated negative survival results, and in one fell swoop the PVC suppression hypothesis was invalidated. It is possible that these drugs did help some patients, but the overall effect was an increase in mortality, possibly due to the known proarrhythmic actions of these antiarrhythmic agents.[10,11] Another potential explanation is a negative interaction of drugs such as flecainide and encainide with myocardial ischemia.[12] Most importantly, there appears to be a fundamental flaw with the PVC suppression hypothesis. The assumption is that a PVC "triggers" sustained VT or VF and that suppression of these triggers will prevent lethal arrhythmias. In fact, this simplistic concept is not consistent with much published data. For example, sustained monomorphic VT often starts with a mid-cycle PVC that frequently has the same appearance as the rest of the arrhythmia, which suggests that it may actually be the first beat of tachycardia. In addition, VF unrelated to ischemia often is initiated by a run of rapid VT that degenerates to the VF, and not by a single PVC. Finally, there are no good data to suggest why, at a given point in time on a given day, VF will occur in a patient who has stable but decreased heart function and nonsustained VT and PVCs all day long. The missing link between substrate and trigger is a fundamental area requiring further research.

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Empiric Amiodarone Therapy

For physicians who still believed that antiarrhythmic drugs could prevent

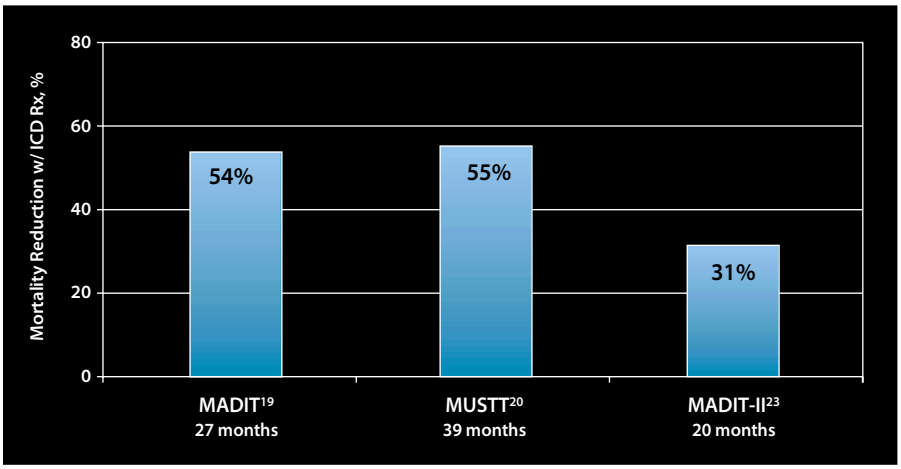

Figure 1. *Primary prevention post–myocardial infarction trials: reduction in mortality with implantable cardioverter defibrillator (ICD) therapy. MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial. Data from Moss et al,[19] Buxton et al,[20] and Moss et al.[23]*

sudden death, amiodarone provided the answer. The literature was replete with studies involving small numbers of patients that suggested that amiodarone given to high-risk patients after myocardial infarction could reduce mortality. In fact, amiodarone became popular among these physicians as empiric therapy for secondary prevention of SCD in patients who had documented sustained VT or were survivors of a cardiac arrest.[2] To test the hypothesis that empiric amiodarone therapy would be useful in the primary prevention of SCD, two large, randomized, placebo-controlled trials were undertaken.[13,14] The European Myocardial Infarction Amiodarone Trial (EMIAT) enrolled 1486 patients with LVEF ≤ 40% within 5 to 21 days of an acute myocardial infarction.[13] Amiodarone had no effect on all-cause mortality in EMIAT. The Canadian Myocardial Infarction Amiodarone Trial (CAMIAT) enrolled 1202 patients who had a criterion of more than 10 PVCs per hour, but no LVEF cutoff was mandated.[14] CAMIAT demonstrated an 18% reduction in all-cause mortality, which did not reach statistical significance. These two large-scale trials clearly demonstrated that empiric amiodarone therapy could no longer be recommended for asymptomatic patients after myocardial infarction to improve survival.

Amiodarone has also been investigated as empiric therapy to reduce mortality in patients with clinically significant congestive heart failure.[15,16] Doval and colleagues[15] evaluated amiodarone in a prospective, parallel, randomized trial in patients with congestive heart failure stratified to the presence of nonsustained VT. Patients were required to have a marked reduction in left ventricular systolic function (LVEF ≤ 35%). After a brief oval loading dose of amiodarone, the drug was administered at 300 mg daily for 2 years in one group of patients. Of note, only 39% of patients had a prior history of a myocardial infarction. During follow-up there were 106 deaths in the control group and 87 in the amiodarone group, demonstrating a relative risk reduction of 28% in patients who received amiodarone. The actual reduction in mortality was relatively modest.

Singh and colleagues[16] performed a double-blind, placebo-controlled prospective study in patients with congestive heart failure using amiodarone with a brief oval loading dose and a long-term dose of 300–400 mg/d. In comparison with the trial of Doval and colleagues,[15] a much greater percentage of patients had an ischemic cardiomyopathy (71%), and nearly two thirds had LVEF < 30%. Singh and colleagues concluded that amiodarone effectively suppressed ventricular arrhythmias but did not prolong survival in the patients studied. They did note a trend, though not significant, toward a reduction in mortality among patients with non-ischemic cardiomyopathy.

These two trials of amiodarone in patients with congestive heart failure reported opposite conclusions. The trial by Singh and colleagues[16] was consistent with previous studies in patients with ischemic heart disease (the major patient population of this trial), showing no survival advantage. The results from Doval and colleagues,[15] demonstrating a small benefit from amiodarone treatment, might be explained by the inordinately high number of patients with non-ischemic cardiomyopathy in their study group. A reasonable conclusion based on the clinical trial data to date is that amiodarone should not be used for primary prevention of SCD or to prolong survival in patients with congestive

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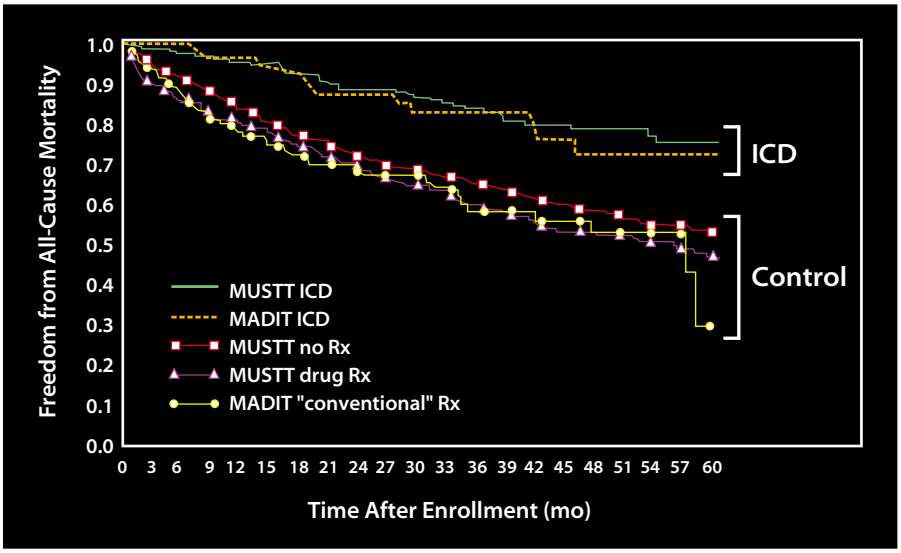

Figure 2. *Kaplan-Meier survival curves for MUSTT and MADIT. These curves depict the freedom from all-cause mortality for the control and treated patient groups in the two studies. The three lower curves represent conventional (mostly amiodarone) therapy (in MADIT) and electrophysiologically guided antiarrhythmic drug therapy or nonspecific antiarrhythmic therapy (in MUSTT). The two upper curves show survival outcomes for patients treated with ICDs in the two studies. The risk ratio for reduction in mortality for the ICD-treated patients compared with the controls was 0.49 (P = .0001) for MUSTT and 0.46 (P < .009) for MADIT. MUSTT, Multicenter Unsustained Tachycardia Trial; MADIT, Multicenter Automatic Defibrillator Implantation Trial; ICD, implantable cardioverter defibrillator. Reproduced from Prystowsky EN. Screening and therapy for patients with nonsustained ventricular tachycardia.* Am J Cardiol. *2000;86 (suppl):34K–39K, with permission from Elsevier Science.*

heart failure secondary to coronary artery disease. There may be some benefit, albeit small, in patients with non-ischemic cardiomyopathy. This latter group of patients requires further study before firm conclusions can be drawn.

Implantable Cardioverter Defibrillator

The ICD has been demonstrated in multiple studies to be the most significant therapy available to treat life-threatening ventricular arrhythmias and to prevent SCD.[2,17–23] Three randomized, prospective, controlled trials have demonstrated conclusively that the ICD is the therapy of choice in the primary prevention of SCD for patients with a history of previous myocardial infarction (Figure 1).[19–21,23]

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) enrolled patients who had had a myocardial infarction at least 3 weeks before study entry, nonsustained VT, and LVEF ≤ 35%. Eligible patients underwent electrophysiologic testing; if sustained VT was induced and not suppressed with intravenous procainamide administration, they were eligible for randomization. Patients were randomized to receive either an ICD or conventional medical therapy, which was not prespecified but left to the discretion of the investigator. In this trial, amiodarone was the conventional medical treatment of choice. MADIT was prematurely terminated after a follow-up of 27 months because the ICD group had a 54% reduction in mortality compared with patients in the conventional medical treatment group.

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The Multicenter Unsustained Tachycardia Trial (MUSTT) investigated the hypothesis that antiarrhythmic therapy guided by electrophysiologic testing could reduce the risk of cardiac arrest and sudden death.[20,21] Eligible patients had coronary artery disease, nonsustained VT, and LVEF ≤ 40%. Standard practice among electrophysiologists prior to MUSTT was to use serial electrophysiologic–pharmacologic testing to evaluate the effectiveness of antiarrhythmic drug therapy in patients with inducible sustained VT or VF.[24] This concept had never been evaluated in a large group of patients in a prospective, randomized manner. Thus, MUSTT evaluated not only the concept of serial electrophysiologic testing but also whether therapy using this concept would reduce sudden death and cardiac arrest. Eligible patients underwent electrophysiologic study; if sustained monomorphic VT was induced with three or fewer extrastimuli or if sustained polymorphic VT was initiated with two or fewer extrastimuli, they were eligible for participation in MUSTT. Patients were randomized to either no specific antiarrhythmic treatment, that is, a true control group, or to electrophysiologically guided therapy. The selection of a specific antiarrhythmic agent was randomized, and an ICD could be implanted if the drugs proved ineffective.

Inducible, sustained VT occurred in 767 (35%) of 2202 patients screened, and 704 agreed to randomization. The nonrandomized patients were followed in a registry. The mean time from myocardial

infarction to enrollment in MUSTT was 39 months, and the mean LVEF was 30%. Of note, New York Heart Association (NYHA) Class II or III congestive heart failure was present in 64% of patients. The median follow-up was 39 months. The overall mortality after 2 and 5 years, respectively, was 22% and 42% for patients randomized to electrophysiologically guided therapy, compared with 28% and 48% for patients in the control group (P = .06). Cardiac arrest or arrhythmic death at 2 and 5 years, respectively, was 12% and 25% for patients randomized to electrophysiologically guided therapy, compared with 18% and 32% in the control group (P = .04). Most importantly, a subsequent analysis in the treatment group demonstrated that the ICD was responsible for the lower rates of arrhythmic deaths and total mortality. For patients who received an ICD, the 5-year cardiac arrest or arrhythmic death rate was 9%, compared with 37% for patients who received antiarrhythmic drugs. In addition, the overall 5-year mortality rate was 24% for patients who received an ICD, compared with 55% for those who received antiarrhythmic drugs. Importantly, the type of antiarrhythmic drug used, including amiodarone, did not alter the results.[25]

For MUSTT patients who received an ICD, the 5-year cardiac arrest or arrhythmic death rate was 9%, compared with 37% for patients who received antiarrhythmic drugs.

A composite of the Kaplan-Meier survival curves for all-cause mortality has been developed for the MUSTT and MADIT studies (Figure 2).[17] It is remarkable how similar the survival curves are from these two trials, even though there were important differences in trial design. Overall, the ICD conferred an approximate 50% reduction in overall mortality compared with either conventional therapy in MADIT or no specific antiarrhythmic therapy or antiarrhythmic drug treatment in MUSTT.

The latest primary prevention ICD trial completed and published was MADIT II,[23] which included 1132 patients with a prior history of myocardial infarction and LVEF ≤ 30%. Patients were randomized to receive an ICD or conventional medical therapy, trying to avoid the use of any antiarrhythmic drugs. For the average follow-up of 20 months, the mortality rates were 19.8% in the conventional-therapy group and 14.2% in the ICD group. The hazard ratio for the risk of all-cause mortality in the ICD group compared with the conventional treatment group was 0.69 (P = .016). Thus, the ICD was clearly superior for prolonged survival in this group of patients.

In a recent review of primary prevention of SCD we opined, "Can we afford to do it? (Can we afford not to?)."[22] Without a doubt, the ICD has provided clinicians with a powerful tool to prevent SCD in many high-risk patients. In my opinion, in the appropriate patient, we can ill afford not to use it.

Secondary Prevention of SCD: ICD Trials

Before the approval of the ICD, serial electrophysiologic–pharmacologic testing was the invasive means to guide drug therapy; noninvasive tests, such as suppression of PVCs, were also used.[2] Empiric amiodarone was often used in these patients. Several randomized, controlled, clinical trials have shed new light on the appropriate therapy to prevent secondary SCD (Figure 3).[2,22,26–29] The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial enrolled patients who either survived a cardiac arrest, had sustained VT with syncope, or had sustained VT with LVEF ≤ 40% with either hypotension, chest pain, or presyncope during VT.[26] More than half of the patients had congestive heart failure, and the mean LVEF of the overall population was 31%. Patients were randomized to receive an ICD or empiric medical therapy with either amiodarone or sotalol. In reality, few patients received sotalol, and the trial was essentially a comparison of ICD versus amiodarone. AVID was prematurely terminated because the overall survival in the ICD group was significantly better than in the amiodarone-treated patients, with a decrease in death rates of 39%, 27%, and 31% at 1, 2, and 3 years, respectively, for patients who received an ICD. The survival benefit was most profound in patients with LVEF ≤ 35%; in patients with a higher LVEF, the survival benefit was not statistically different.

The Cardiac Arrest Study Hamburg (CASH) trial randomized cardiac arrest survivors who had documented ventricular arrhythmias to receive drug therapy or an ICD.[27] Amiodarone, propafenone, and metoprolol were the initial drug therapy options, with propafenone being discontinued because of safety concerns. Amiodarone was given empirically. A total of 288 patients were continued in the study after propafenone use was stopped. There was a 23% reduction in all-cause mortality with patients who received an ICD compared with the amio-

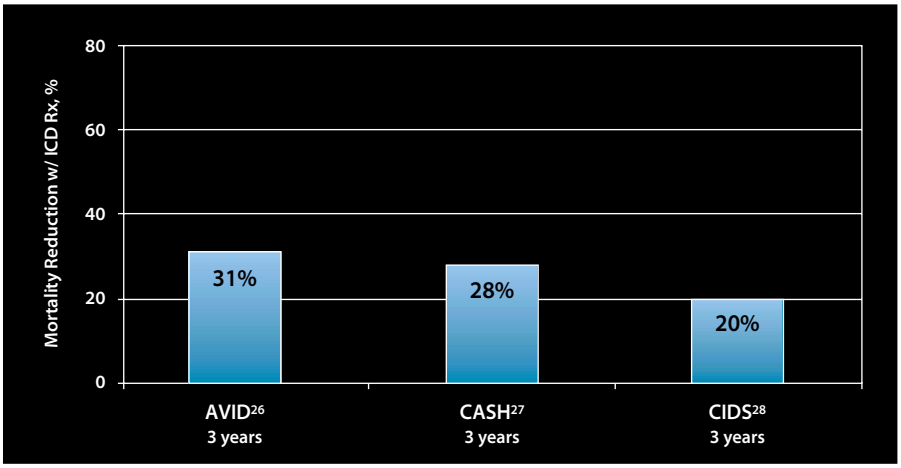

Figure 3. *Secondary prevention trials: reduction in mortality with implantable cardioverter defibrillator (ICD) therapy. AVID, Antiarrhythmics Versus Implantable Defibrillators trial; CASH, Cardiac Arrest Study Hamburg trial; CIDS, Canadian Implantable Defibrillator Study. Data from the AVID investigators,[26] Kuck et al,[27] and Connolly et al.[28]*

darone or metoprolol groups. This did not reach statistical significance, but the study population was quite small.

A third trial, the Canadian Implantable Defibrillator Study (CIDS) randomized patients to receive an ICD or amiodarone.[28] There was a reduction in all-cause mortality of 19.7% in patients who received an ICD compared with amiodarone, which did not reach statistical significance. Of note, an important update from the CIDS trial was recently reported and published in abstract form.[29] In a single center that did not alter the original treatment in their CIDS patients, 60 patients in each group were followed from 1991 to 2002. Deaths occurred in 28 patients who received amiodarone, compared with 16 deaths in the ICD patients. In addition, 82% of patients receiving amiodarone had at least some side effects related to the drug, and 50% of those required discontinuation or reduction of the dose. These authors concluded that, in their CIDS patients, there was a benefit of the ICD over amiodarone, which accrued over time.

Consistent with the superiority of an ICD in the primary prevention of SCD in patients with coronary artery disease and left ventricular dysfunction, the ICD has also been proved to be the treatment of choice in the secondary prevention of SCD. In this latter group, patients had ischemic as well as non-ischemic forms of heart disease, and some even had no demonstrable signs of heart disease.

Indications for ICD Therapy

The indications for ICD therapy have been codified by the American College of Cardiology, the American Heart Association, and the North American Society of Pacing and Electrophysiology.[30] A Class I indication is for conditions in which there is general agreement that an ICD is warranted, and a Class IIa condition implies that the weight of evidence or opinion favors usefulness/efficacy of treatment. Class I indications for an ICD are listed in Table 1. Regarding the fourth recommendation under Class I, most electrophysiologists no longer feel that it is necessary to test an antiarrhythmic drug at electrophysiologic study but merely to demonstrate inducible sustained VT or VF. The Class IIa indication is for patients with LVEF ≤ 30%, at least 1 month post–myocardial infarction, and 3 months post–coronary artery revascularization surgery.

Cardiac Resynchronization Therapy Alone Versus CRT Plus ICD

For this discussion, it is assumed that clinical indications for cardiac resynchronization therapy (CRT) are present and, therefore, the patients are candidates for CRT. Thus, all of these patients have NYHA Class III or IV symptoms resulting

Table 1
American College of Cardiology/American Heart Association Guideline Update: Recommendations for Implantable Cardioverter Defibrillator Therapy, Class I

1. Cardiac arrest due to VF or VT not due to transient or reversible cause
2. Spontaneous sustained VT in association with structural heart disease
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiologic study when drug therapy is ineffective, not tolerated, or not preferred
4. Nonsustained VT in patients with coronary artery disease, prior myocardial infarction, left ventricular dysfunction, and inducible VF or sustained VT at electrophysiologic study that is not suppressible by a Class I antiarrhythmic drug
5. Spontaneous sustained VT in patients without structural heart disease that is not amenable to other treatments

VF, ventricular fibrillation; VT, ventricular tachycardia. Adapted from Gregoratos et al.[30] Available at http://www.acc.org/clinical/guidelines/pacemake/pacemaker.pdf.

from congestive heart failure and left ventricular systolic dysfunction. A decision to implant a CRT device has been made, and the question remaining is whether to implant one with pacemaker function only or to include defibrillation therapy. For me, the choice is rather simple and straightforward: these are all high-risk patients who are at risk for sudden death, and the choice should be CRT in combination with ICD therapy. At the very least, a CRT-ICD should be given to any patient who meets criteria for MADIT, MADIT II, and MUSTT (Table 2). Furthermore, any patient with a Class I indication for an ICD should receive a CRT-ICD.

Supporting the concept that those patients who receive CRT for heart failure indications need a device with defibrillator capabilities are the recently reported but not published results from the Comparison of Medical Therapy, Pacing, and Defibrillation in Chronic Heart Failure (COMPANION) trial.[31] This was a randomized, controlled trial using three treatment arms. Patients were randomized to optimal pharmacologic therapy alone, CRT plus optimal pharmacologic therapy (CRT-P), or CRT with defibrillator backup (CRT-D) in addition to optimal pharmacologic therapy. Inclusion criteria were NYHA Class III or IV for symptomatic heart failure, prior heart failure hospitalization in the 12 months before enrollment, QRS duration ≥ 120 ms, and LVEF ≤ 35%. The trial was terminated prematurely and, at the time of this writing,

Table 2
MADIT, MADIT II, and MUSTT Inclusion Criteria

MADIT
• New York Heart Association functional Class I, II, or III with prior myocardial infarction
• LVEF ≤ 35%
• Asymptomatic, unsustained ventricular tachycardia
• Inducible, nonsuppressible ventricular tachyarrhythmia at electrophysiologic study
MADIT II
• Prior myocardial infarction and LVEF ≤ 30%
MUSTT
• Coronary artery disease
• LVEF ≤ 40%
• Asymptomatic, unsustained ventricular tachycardia
• Inducible sustained ventricular tachycardia (1–3 extra stimuli) or ventricular fibrillation (1–2 extra stimuli) at electrophysiologic study

MADIT, Multicenter Automatic Defibrillator Implantation Trial; MUSTT, Multicenter Unsustained Tachycardia Trial; LVEF, left ventricular ejection fraction.

Main Points

- One of the earliest attempts to prevent sudden cardiac death (SCD) was suppression of premature ventricular complexes (PVCs) in patients "apparently" at high risk for SCD; patients were considered to be at increased risk if they had complex ventricular arrhythmias associated with significant left ventricular dysfunction.
- Many small and large trials using a variety of antiarrhythmic drugs with the aim of suppressing PVCs and reducing mortality in patients after acute myocardial infarction have been performed but, in retrospect, these trials showed a trend toward increased mortality in patients receiving antiarrhythmic drugs.
- Despite many small-scale studies that suggested that amiodarone given to high-risk patients after myocardial infarction could reduce mortality, two large-scale trials (EMIAT and CAMIAT) clearly demonstrated that empiric amiodarone therapy could no longer be recommended for asymptomatic patients after myocardial infarction to improve survival.
- Three randomized, prospective, controlled trials (MADIT, MADIT II, and MUSTT) have demonstrated conclusively that the implantable cardioverter defibrillator (ICD) is the therapy of choice in the primary prevention of SCD for selected patients with a history of previous myocardial infarction.
- Consistent with the superiority of an ICD in the primary prevention of SCD in patients with coronary artery disease and left ventricular dysfunction, the ICD has also been proved to be the treatment of choice in the secondary prevention of SCD.
- In patients for whom a decision to implant a cardiac resynchronization therapy (CRT) device has been made and the question remains whether to implant one with pacemaker function only or to include defibrillation therapy, the choice should be CRT in combination with ICD therapy; evidence from the randomized, controlled COMPANION trial supports this concept.

has yet to be presented or published. Certain data were reported recently at the American College of Cardiology meeting in Chicago. Both CRT-P and CRT-D with optimal pharmacologic therapy demonstrated a statistically significant 19% reduction in the composite end point of all-cause mortality and all-cause hospitalization compared with optimal pharmacologic therapy only. There was a nonsignificant 23.9% reduction in all-cause mortality with CRT-P, but a significant 43.4% reduction in all-cause mortality with addition of the defibrillator (CRT-D). In essence, this study shows that the long-term mortality benefit in patients with advanced heart failure is maximized with combination CRT-defibrillation therapy.

Are there indications for CRT therapy with pacing only? I think there may be, but not in patients with significant left ventricular systolic dysfunction who are at high risk for sudden death. Future studies will be needed to determine whether CRT is superior to traditional right ventricular pacing for patients who require chronic ventricular pacing and who have some left ventricular dysfunction or possibly mitral regurgitation. It is also conceivable that CRT therapy given to patients with NYHA Class II heart failure may be able to prevent further deterioration of cardiac function, but this certainly requires further study.

In summary, until further studies demonstrate a significant indication for CRT only, the vast majority of patients who receive CRT should have a unit implanted that includes defibrillator therapy. ■

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