Implantable Cardioverter-Defibrillator Therapy in Clinical Practice

David A. Cesario, MD, PhD,* G. William Dec, MD†
Irvine, California; and Boston, Massachusetts

Advances in the pharmacological therapy of chronic heart failure have led to significantly improved survival and enhanced quality of life (1–3). Nonetheless, the risk of sudden cardiovascular death remains high in this growing population. Current estimates of the annual incidence of sudden cardiac death varies between 20% and 30% among patients with depressed left ventricular systolic function. Further, the risk of sudden death increases in a nearly exponential manner as ejection fraction falls below 30% (10).

In addition to the severity of left ventricular dysfunction, the degree of functional impairment by New York Heart Association (NYHA) functional classification has also been shown to be a powerful independent predictor of SCD (11,12). Although the absolute number of sudden deaths is greatest for patients with NYHA functional class IV symptoms, sudden death accounts for only 35% of all-cause mortality in this group of patients. Conversely, SCD accounts for 64% of deaths among patients with compensated NYHA functional class II heart failure symptoms (11,13,14). Thus, patients with mildly symptomatic (i.e., well-compensated) heart failure should not be viewed as being at low risk for sudden death. A growing list of clinical, electrocardiographic, neurohumoral, and electrophysiologic (EP) parameters may be useful for sudden cardiac death risk stratification (10,15) (Table 1).

SUBSETS OF PATIENTS AT THE HIGHEST RISK OF SCD: PRIOR CARDIAC ARREST PATIENTS

The ICD remains the only evidence-based therapeutic strategy for patients who have survived a life-threatening ventricular arrhythmic event (i.e., out-of-hospital cardiac arrest). Table 2 lists the American College of Cardiology/American Heart Association/North American Society for Pacing and Electrophysiology 2002 guidelines for ICD implantation. Three prospective, controlled secondary prevention trials have specifically examined this population (Table 3) (16–18). The Antiarrhythmics Versus Implantable Defibrillators (AVI D) trial enrolled 1,016 patients who were resuscitated from either ventricular fibrillation, sustained ventricular tachycardia with syncope, or sustained ventricular tachycardia with an ejection fraction of ≤40%, and symptoms suggesting severe hemodynamic compromise (19). Eligible patients were randomized to receive an ICD or treatment with a class III antiarrhythmic drug, primarily amiodarone, at empirically determined doses. The primary end point of this trial was all-cause mortality. Overall survival was greater for patients receiving ICD treatment compared with antiarrhythmic drug therapy at 1, 2, and 3 years (p < 0.02) (19). Similar results have been reported in two small, randomized trials—the Canadian Implantable Defibrillator Study (CIDS) (17) and the Cardiac Arrest Study Hamburg (CASH) (18). Pooled data from these three secondary prevention trials indicate that ICD therapy reduces mortality risk by 35%. Absolute two-year mortality was reduced from 23% in the medically treated cohort to...
15.5% in the ICD cohort. Finally, a recent large retrospective observational study of over 6,900 patients admitted to Veteran’s Administration hospitals evaluated the efficacy of ICD therapy versus medical management alone among patients with new-onset ventricular arrhythmias (ventricular tachycardia, fibrillation, or cardiac arrest) and known ischemic heart disease (20). Multivariate regression analysis that adjusted for demographics, illness acuity, and medical comorbidities showed ICD treatment to significantly lower all-cause mortality (odds ratio, 0.52; 95% confidence interval, 0.45 to 0.60) at three-year follow-up. However, no significant differences were noted between groups in cardiovascular mortality rates. The greatest benefit of ICD therapy in all studies was observed among patients with advanced left ventricular systolic dysfunction (16,19) (Table 3). Little advantage over drug therapy has been observed in patients with an ejection fraction that exceeds 35% (21). Electrophysiological studies, performed after resuscitation, are insensitive predictors of risk for recurrent life-threatening arrhythmias during long-term follow-up.

**INHERITED ION CHANNELOPATHIES (LONG QT AND BRUGADA SYNDROMES)**

Long QT syndrome (LQTS) is a group of inherited disorders caused by mutations of the genes encoding the structure of cardiac ion channels. To date, mutations affecting seven genes on six different chromosomes have been identified in this disorder. Affected patients classically have a prolonged corrected QT interval on surface electrocardiogram (ECG) associated with a propensity to syncope, aborted cardiac arrest, and sudden cardiac death (22–25). Recent data indicate that beta-blocker therapy is effective in about 70% of LQTS patients; however, 30% of these patients are still at increased risk for adverse cardiac events despite optimal treatment including aggressive beta-blockade (26). A recent study evaluated ICD implantation in high-risk LQTS patients, defined as those with a history of prior cardiac event (either cardiac arrest, recurrent syncope, or LQTS-related sudden cardiac death in a close family member). In this study, there was a 1.3% death rate among patients receiving ICDs during an average follow-up of three years, whereas non-ICD patients experienced a

<table>
<thead>
<tr>
<th>Indicators of an Increased Risk of Sudden Death From Ventricular Arrhythmia</th>
<th>Risk Factors</th>
<th>Predictive Power</th>
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<tbody>
<tr>
<td>Conventional coronary risk factors</td>
<td>High cholesterol, High blood pressure, Smoking, Diabetes</td>
<td>Low power to discriminate the individual person at risk for sudden death</td>
</tr>
<tr>
<td>Clinical markers</td>
<td>NYHA functional class, Ejection fraction</td>
<td>High power to predict death from cardiac causes; relatively low specificity to predict death from arrhythmia</td>
</tr>
<tr>
<td>Baseline ventricular arrhythmia</td>
<td>Premature ventricular depolarizations, Non-sustained ventricular tachycardia, Sustained ventricular tachycardia</td>
<td>Low overall power if not combined with other variables; higher predictive power with low ejection fraction</td>
</tr>
<tr>
<td>Electrocardiographic variables</td>
<td>Standard ECG, Left ventricular hypertrophy, Widened QRS complex, QT dispersion, Specific abnormalities (e.g., prolonged QT interval, right bundle branch block, ST-segment elevation in V1 [Brugada syndrome], ST- and T-wave abnormalities in V1 and V2 [right ventricular dysplasia], delta waves [Wolf-Parkinson-White syndrome])</td>
<td>Higher degree of accuracy in identifying specific electrical abnormalities</td>
</tr>
<tr>
<td>High-resolution ECG</td>
<td>Late potentials on signal-averaged ECG, T-wave alternans</td>
<td>High negative predictive value but low positive predictive value; Primary predictive value unknown</td>
</tr>
<tr>
<td>Markers of autonomic nervous function</td>
<td>Heart rate variability, Baroreflex sensitivity</td>
<td>Exact predictive value unknown</td>
</tr>
<tr>
<td>Electrophysiologic testing</td>
<td>Inducibility of sustained tachyarrhythmia by programmed electrical stimulation</td>
<td>High degree of accuracy in specific high-risk subgroups</td>
</tr>
</tbody>
</table>

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ECG = electrocardiogram; NYHA = New York Heart Association.
16% death rate during a mean follow-up time of eight years (27). The results of this study strongly suggest that ICDs should be implanted in LQTS patients with prior cardiac arrest or recurrent syncope despite beta-blocker therapy. Because of the small number of patients with LQTS, our understanding of which patients require protection via ICD implantation remains incomplete; thus, standard guidelines for ICD implantation in LQTS patients are currently unavailable. Additional subgroups of LQTS patients at high risk of SCD who may benefit from ICD therapy include patients with known SCN5A mutations (these patients tend to have more lethal events and less efficacy from beta-blocker therapy) (28), those with a strong family history of sudden cardiac death, and those intolerant of beta-blockers.

Brugada syndrome is an inherited disorder associated with increased cardiac arrhythmias caused by loss of function mutations in the SCN5A sodium channel gene. This disorder is characterized by the typical surface ECG pattern of incomplete right bundle branch block and ST-segment elevation in leads V1 to V3, and an increased risk of sudden cardiac death as the result of ventricular fibrillation (29). Patients with Brugada syndrome have been reported to have
a cardiac arrest risk as high as 30% during a three-year follow-up period (30). Currently, there are no standard practice guidelines describing ICD implantation recommendations for patients with Brugada syndrome. Patients at high risk for sudden cardiac death have been identified by the presence of ST-segment elevation on surface ECG leads V1 to V3 at baseline and a history of syncope (31). These patients should be seriously considered for ICD implantation. Low-risk patients have been identified as silent mutation carriers or patients who have diagnostic ECG characteristics only after a provocative challenge (31). The cardiac arrest rate in these patients has been reported as only 5% during four decades of follow-up. Finally, Priori et al. have defined a group of Brugada patients at intermediate risk for cardiac arrest. These patients have spontaneous ST-segment elevation $\geq 2$ mm without a previous history of syncope; 14% of them had a cardiac arrest during follow-up (31). Treatment recommendations for intermediate-risk Brugada patients must be evaluated on an individual case basis with family history and patient preference playing a key role in the decision-making process.

### HYPERTROPHIC CARDIOMYOPATHY

Hypertrophic cardiomyopathy (HCM) is the most common genetic cardiac disorder with an incidence of about 1 in 500 persons in the general population (32–34). Hypertrophic cardiomyopathy is caused by a variety of gene mutations in the proteins encoding components of the cardiac sarcomere (35,36). This disorder is characterized by widely heterogeneous clinical, morphologic, and genetic expressions (37). Sudden death occurs in affected patients as a consequence of an electrically unstable myocardial substrate with re-entrant ventricular tachyarrhythmias brought on by the presence of myocardial architectural disarray, interstitial scarring, microvascular insufficiency, and myocardial ischemia. Hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young athletes and accounts for 40% to 50% of the sudden deaths in this population (38). Drug therapy, including beta-blockers and amiodarone, alcohol septal ablation, or septal myomectomy have not been shown to be effective in lowering the risk of sudden death in HCM patients. Although there is a predilection for sudden death in younger patients (<30 years of age), older age alone does not confer immunity from this complication.

Risk stratification should be undertaken for all patients with known HCM, especially those <50 years of age. Evaluation should comprise a detailed personal and family history, physical examination including provocative maneuvers, 12-lead ECG, two-dimensional echocardiography with assessment of resting and provoked ventricular outflow tract gradients, 24-h ambulatory ECG monitoring, and exercise testing. The strongest risk factors for sudden death are summarized in Table 4. Massive left ventricular hypertrophy (intraventricular septal wall thickness $>30$ mm) is a powerful independent marker for sudden death, even in the absence of demonstrable ventricular arrhythmias (39). Although approximately 50% of clinically identified hypertrophic cardiomyopathy patients have one or more markers of increased SCD risk, almost 50% of those who ultimately experience SCD have no risk factors (40).

An ongoing challenge is the more precise identification of patients who should be targeted for primary prevention via ICD implantation. Table 5 outlines one proposed scoring system to identify high-risk HCM patients. The development of genetic markers of sudden death risk holds great promise as a potential future risk stratifier for this population. However, it remains unclear whether identifying specific disease-causing mutations will prove useful in predicting prognosis and designing effective treatment strategies for individual HCM patients (41,42). A multi-center retrospective analysis of high-risk HCM patients confirmed the efficacy of ICD therapy (43). The ICD reliably aborted potentially lethal ventricular arrhythmias in almost 25% of patients over a three-year period. Appropriate device interventions occurred at a rate of 11% per year for secondary prevention, and about 5% per year for primary prevention (43). The ratio of devices implanted to lives saved in this study was calculated at 4:1. At present, ICD placement remains a class IIb indication for primary prevention in this population.

### Table 4. Predictors of High Risk for Sudden Cardiac Death in Hypertrophic Cardiomyopathy

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>Prior cardiac arrest (VF)</td>
<td>20.0 (9.6–41.4)</td>
</tr>
<tr>
<td>Spontaneous sustained ventricular tachycardia (VT)</td>
<td>10.0 (5.7–17.4)</td>
</tr>
<tr>
<td>Familial history of sudden death (particularly first-degree or multiple relatives)</td>
<td>6.0 (3.2–11.5)</td>
</tr>
<tr>
<td>Syncope (particularly recurrent, exertional, or occurring in the young)</td>
<td>5.0 (2.8–8.7)</td>
</tr>
<tr>
<td>Non-sustained VT on ambulatory monitoring</td>
<td>4.0 (2.6–6.2)</td>
</tr>
<tr>
<td>Abnormal blood pressure response to aerobic exercise testing (decrease or failure to augment by $&gt;20$ mm Hg in patients &lt;50 years old)</td>
<td>3.0 (1.8–5.0)</td>
</tr>
<tr>
<td>Extreme left ventricular hypertrophy ($&gt;30$ mm by echocardiography)</td>
<td>3.0 (1.8–5.0)</td>
</tr>
<tr>
<td>Specific lethal molecular mutations of myosin heavy chain (Arg403Gln; Arg19Trp), troponin T (intron 15 G, to A; Ile79Asm; Arg92Gln) and $\alpha$-troponymysin</td>
<td>2.0 (1.2–3.3)</td>
</tr>
</tbody>
</table>

Reprinted, with permission, from Elliot et al. (40).

### Table 5. Hypertrophic Cardiomyopathy: Scoring System for Identification of High-Risk Patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR</th>
<th>(95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise BP</td>
<td>2.4</td>
<td>(1.0–5.5)</td>
</tr>
<tr>
<td>Syncope</td>
<td>2.0</td>
<td>(0.8–4.9)</td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td>1.8</td>
<td>(0.7–4.7)</td>
</tr>
<tr>
<td>Family history of sudden death</td>
<td>1.9</td>
<td>(0.8–4.1)</td>
</tr>
<tr>
<td>LV wall thickness $&gt;30$ mm</td>
<td>4.1</td>
<td>(1.7–9.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Score (No. of Risk Factors)</th>
<th>6-Year Sudden Cardiac Death Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5% (1%–9%)</td>
</tr>
<tr>
<td>1</td>
<td>7% (1%–13%)</td>
</tr>
<tr>
<td>2</td>
<td>18% (4%–33%)</td>
</tr>
<tr>
<td>3</td>
<td>35% (25%–100%)</td>
</tr>
</tbody>
</table>

$BP =$ blood pressure decrease or failure to augment during exercise testing; CI = confidence interval; LV = left ventricular; RR = relative risk; VT = ventricular tachycardia.
population by the ACC/AHA/NASPE 2002 Practice Guidelines (44).

**ARRHYTHMOGENIC RIGHT VENTRICULAR DYSPLASIA**

Arrhythmogenic right ventricular dysplasia (ARVD) is characterized by varying degrees of patchy replacement of right ventricular myocardium with fatty or fibrous-fatty tissue (45). It is frequently transmitted in an autosomal-dominant manner, with disease-causing mutations identified in genes encoding the cell adhesion proteins, plakoglobin and desmoplakin (46,47). A family history is present in 30% to 50% of affected patients (47–49), and male patients seem to be disproportionately affected. The ARVD patients most frequently suffer from palpitations or syncope associated with a left bundle branch block pattern of ventricular tachycardia that originates in the right ventricle.

An ARVD has been reported to be the underlying cause for 3% to 10% of unexplained sudden cardiac deaths in patients <65 years old (45,50); ECG abnormalities are detected in up to 90% of patients diagnosed with ARVD (51). T-wave inversion in leads V1 to V3 is the most common finding; however, these repolarization abnormalities are not pathognomonic for ARVD and may be seen in normal children or may be secondary to right bundle branch block. Additional ECG abnormalities that may be seen in ARVD and result from delayed right ventricular activation include right bundle branch block and epsilon waves (small amplitude potentials occurring immediately after the QRS complex at the beginning of the ST-segment) (45,52).

Previously, the diagnosis of ARVD was made by endomyocardial biopsy, showing typical fibro-fatty replacement of the right ventricular muscle (52). However, endomyocardial biopsy has a low sensitivity because samples are usually taken from the ventricular septum to avoid cardiac perforation, and this region is uncommonly involved in ARVD. Additionally, it can be difficult to differentiate ARVD from other causes of right ventricular myocardial fatty infiltration. Thus, endomyocardial biopsy should be reserved for selected patients in whom the final diagnosis depends on the histological exclusion of other cardiomyopathic conditions.

Evaluation of the heart by one of the common imaging modalities is an integral part of the diagnostic workup. The diagnosis of ARVD can be supported by cardiac magnetic resonance imaging, and the risk of sudden cardiac death seems to be related to the extent of fatty replacement of the right and/or left ventricles, as well as the degree of systolic dysfunction. However, the fibro-fatty replacement in ARVD can sometimes be microscopic, rendering a definitive diagnosis even by magnetic resonance imaging difficult in some borderline cases (53).

Identification of ARVD patients at high risk for sudden cardiac death is critical in deciding which patients should receive ICD therapy. Several retrospective studies have shown potential predictors of adverse outcomes in ARVD patients (Table 6) (54). In a recent multicenter trial, ICD therapy resulted in a significant improvement in survival rates among selected ARVD patients (55). Patients with a history of syncope or frequent runs of ventricular tachycardia should generally have an ICD implanted. Predictors of appropriate ICD firing have been reported to include inducible ventricular tachycardia during EP testing, detection of spontaneous ventricular tachycardia, male gender, and marked right ventricular dilatation (56). The EP studies have uncertain predictive value among asymptomatic patients despite documented disease. The current ACC/AHA/NASPE practice guidelines do not yet offer specific recommendations on the management of asymptomatic individuals once the diagnosis of ARVD has been established.

**PRIMARY PREVENTION OF SUDDEN DEATH IN ISCHEMIC CARDIOMYOPATHY**

Several randomized clinical trials have evaluated ICD treatment for primary prevention of sudden cardiac death among patients with impaired left ventricular systolic function due to underlying ischemic heart disease. The first Multicenter Automatic Defibrillator Implantation Trial (MADIT I) randomized 196 patients with coronary artery disease, spontaneous non-sustained ventricular tachycardia during EP testing, a left ventricular ejection fraction ≤35%, and inducible ventricular tachycardia that was not suppressed during intravenous procainamide administration to an implantable defibrillator or conventional medical therapy (57). The ICD implantation resulted in a significant reduction in overall mortality: there were 15 deaths in the defibrillator group compared with 39 deaths in the EP-guided conventional treatment group (risk reduction, 54%) (57).

The Coronary Artery Bypass Graft Trial (CABG Patch) randomized 900 patients already scheduled for elective coronary revascularization surgery who also had a left ventricular ejection fraction below 36% and an abnormal signal-averaged ECG to undergo ICD implantation versus no ICD (control group) at the time of their coronary artery bypass graft surgery (58). In this trial, there were 101 deaths among the 454 patients who received defibrillators (22%) versus 95 deaths among the 446 control patients (21%).

Table 6. Proposed Risk Factors for Poor Prognosis in Arrhythmogenic Right Ventricular Dysplasia

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
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<tbody>
<tr>
<td>Previous cardiac arrest</td>
</tr>
<tr>
<td>Syncope or sustained ventricular tachycardia with impairment of consciousness</td>
</tr>
<tr>
<td>Increased QT dispersion (a difference of ≥40 ms between the maximum and minimum QRS values occurring in any of the 12 electrocardiographic leads)</td>
</tr>
<tr>
<td>Early onset of symptoms</td>
</tr>
<tr>
<td>Severe right ventricular dilatation</td>
</tr>
<tr>
<td>Right heart failure</td>
</tr>
<tr>
<td>Left ventricular involvement (regional wall motion abnormalities or dilatation and impairment of left ventricular systolic function)</td>
</tr>
</tbody>
</table>

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confidence interval, 0.81 to 1.42; p = not significant). It should be noted that the majority of deaths in the ICD group occurred in the peri-operative period; further, 10% of the control group eventually crossed over to receive ICD therapy during the trial (58).

The Multicenter Unsustained Tachycardia Trial (MUSTT) enrolled a patient population similar to that of the MADIT I trial and evaluated the efficacy of EP-guided antiarrhythmic therapy. Patients with inducible ventricular tachycardia on EP testing (n = 704) were assigned to receive either conventional medical therapy or antiarrhythmic therapy as guided by serial EP testing (8). Individuals could receive an ICD without randomization (n = 161) if one or more drug trials showed inadequate arrhythmia suppression. At 5-year follow-up, all-cause mortality was 24% in the ICD group, 55% for patients who received EP-guided antiarrhythmic therapy and 48% in patients who did not receive any antiarrhythmic treatment (p < 0.001) (8).

The second MADIT II trial enrolled 1,232 patients with ischemic cardiomyopathy and ejection fractions ≤30%. No documentation of spontaneous or inducible arrhythmias was required for enrollment (58). Antiarrhythmic therapy was prescribed in <20% of both groups. During an average follow-up of 20 months, all-cause mortality was 20% in the control group versus 14.2% in the defibrillator group (59). The hazard ratio for death in the ICD group was 0.69 (95% confidence interval, 0.51 to 0.93; p = 0.016). A recent meta-analysis of all major primary prevention sudden cardiac death trials showed a significant benefit in favor of ICD placement with a risk reduction for all-cause mortality of 34% (p = 0.03) (60). Current practice guidelines support ICD implantation as a primary prevention strategy in patients with a prior myocardial infarction, left ventricular ejection fraction <30%, and QRS duration >120 ms (Table 2) (44).

It should be noted that the recently published Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) randomized 674 patients who had recently suffered a myocardial infarction (6 to 40 days after myocardial infarction), had a left ventricular ejection fraction ≤35%, and had impaired cardiac autonomic function (decreased heart rate variability or elevated average heart rate as determined by 24-h ambulatory monitoring) to receive either ICD implantation or no ICD therapy (61). A percutaneous coronary intervention on the infarct-related artery was performed in only 36% of study patients. During a follow-up period of 30 ± 13 months, there was no significant difference in overall mortality between the two treatment groups (61). However, annual mortality rates were low in both groups, 7.5% for ICD-treated patients and 6.9% for control patients. These results suggest that the prophylactic use of ICD placement within the first month after acute myocardial infarction remains of unproven benefit.

**PRIMARY PREVENTION OF SUDDEN DEATH IN NON-ISCHEMIC CARDIOMYOPATHY**

The role of defibrillator therapy for the primary prevention of sudden death in patients with non-ischemic cardiomyopathy has remained controversial; however, several recent trials suggest a beneficial role for ICDs in this population. The Cardiomyopathy Trial (CAT) enrolled 104 patients with recent onset of non-ischemic dilated cardiomyopathy (<9 months) and an ejection fraction ≤30% (62). Patients were assigned to either ICD implantation or conventional therapy. The primary end point was all-cause mortality at one year of follow-up. The trial was terminated after enrollment of only 104 patients because the all-cause mortality at one year did not reach the expected 30% in the control group. No significant difference in survival was noted among patients undergoing ICD implantation compared with control patients in this underpowered trial (62). Similarly, the recently published Amiodarone Versus Implantable Cardioverter Defibrillator Trial (AMIOVIRT) showed no improvement in survival or arrhythmia-free survival with ICD therapy as compared with amiodarone treatment in 103 patients with non-ischemic dilated cardiomyopathy, left ventricular ejection fractions ≤35%, and asymptomatic non-sustained ventricular tachycardia (63). It should be noted that Fonarow et al. (64) in a non-controlled, retrospective, observational study have reported that patients with heart failure due to non-ischemic cardiomyopathy and a prior history of syncope have a significant reduction in sudden death risk and improvement in overall survival after ICD implantation when compared with historical control patients. The prognostic importance of syncope was confirmed in a small study by Knight et al. (65) that reported a high incidence of appropriate ICD firings among patients with non-ischemic cardiomyopathy and prior unexplained syncope, even when non-inducibility was present during initial EP testing. Additionally, Grimm et al. found that ICDs implanted for primary prevention in patients with idiopathic dilated cardiomyopathy and reduced left ventricular ejection fractions (≤30%) had an appropriate ICD firing rate similar to that of patients with a history of syncope or sustained ventricular tachycardia/ventricular fibrillation (66).

The Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial randomized 458 patients with non-ischemic dilated cardiomyopathy, left ventricular ejection fractions <36%, and >10 premature ventricular complexes per hour or non-sustained ventricular tachycardia on 24-h ambulatory monitoring to receive standard medical therapy alone, or in combination with a single-chamber ICD (67). All patients had NYHA functional class II or higher heart failure symptoms within six months of randomization. Patients who had NYHA functional class IV heart failure, who were not candidates for ICD implantation, had undergone EP testing within the
previous three months, or had a permanent pacemaker were excluded. Over 95% of enrolled patients were receiving either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Additionally, 85% of enrolled patients received beta-blockers. The primary end point of the trial was all-cause mortality; patients were followed up for a mean of 29 ± 14.4 months. There was a trend toward improved overall 24-month survival in patients undergoing ICD implantation (hazard ratio, 0.65; 95% confidence interval, 0.40 to 1.06); however, this failed to reach statistical significance (p = 0.08) (65). This trial did show a significant and striking reduction in a key secondary end point, the risk of sudden death from arrhythmia (hazard ratio, 0.20; 95% confidence interval, 0.06 to 0.71) in ICD patients.

The recently completed Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) was a three-armed study that randomized 2,521 patients with left ventricular ejection fractions <35%, ischemic (52%) or non-ischemic (48%) cardiomyopathy, and NYHA functional class II (70%) or III (30%) heart failure symptoms to conventional pharmacological therapy alone, or in combination with either amiodarone or a single-lead ICD (9). Median follow-up averaged 45.5 months. The SCD-HeFT trial showed a significant reduction in total mortality in the ICD cohort (hazard ratio, 0.77; 97.5% confidence interval, 0.62 to 0.96). Amiodarone therapy failed to improve survival (hazard ratio, 1.06; 97.5% confidence interval, 0.86 to 1.30). The survival benefit was similar in magnitude between ischemic patients (hazard ratio, 0.79; p = 0.05) and non-ischemic cardiomyopathy patients (hazard ratio, 0.73; p = 0.06), but remained of marginal statistical significance. Curiously, the mortality benefit was confined to patients with mild (NYHA functional class II) symptoms in the SCD-HeFT and moderate symptoms (NYHA functional class III) in the DEFINITE trial (9,67). At present, prophylactic ICD therapy is not recommended by AHA/ACC/NASPE guidelines for primary prevention in patients with moderate heart failure symptoms due to non-ischemic cardiomyopathy (Table 2) (44); however, the recent DEFINITE and SCD-HeFT findings will almost certainly result in a change in these recommendations favoring more widespread use of ICDs in the non-ischemic heart failure population when left ventricular ejection fraction is <35%, as reflected in the recent Centers for Medicare and Medicaid Services guidelines.

**HEART FAILURE SUBSETS IN WHICH IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR THERAPY IS NOT CLINICALLY INDICATED**

Implantable cardioverter-defibrillator therapy should not be used for patients with advanced heart failure symptoms (NYHA functional class IV) that remain refractory to optimal medical therapy for whom cardiac transplantation is not an option. However, some of these patients may still be considered for cardiac resynchronization therapy with ICD backup capability. Sweeney et al. have shown little improvement in survival after ICD implantation for these patients, most of whom die of progressive pump failure (68). Further, ICD treatment is contraindicated in the presence of medically intractable ventricular tachycardia or ventricular fibrillation. Implantable cardioverter-defibrillator implantation remains unproven for patients with substantially impaired systolic function and coronary artery disease, who lack evidence of sustained or non-sustained ventricular tachycardia and are scheduled to undergo coronary revascularization.

**CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE**

Evidence of ventricular dyssynchrony can be noted on the surface ECG as prolongation of the QRS interval, most often with a left bundle branch block pattern. Prolongation of the QRS complex has been associated with diminished cardiac function, more advanced heart failure symptoms, and increased mortality (69–71). Approximately 30% of patients with NYHA functional class III or IV heart failure symptoms will have significant QRS prolongation. Unlike traditional right ventricular pacing, cardiac resynchronization uses a left ventricular lead that is positioned on the lateral wall of the left ventricle via the coronary sinus or a lead surgically placed directly on the left ventricle epicardium. This additional ventricular lead ensures stimulation of the left ventricle at or near the time of right ventricular depolarization. Resynchronization therapy is associated acutely with improved contractility, decreased mitral regurgitation, and lower left ventricular filling pressures.

Proper selection of those patients most likely to benefit from resynchronization therapy is imperative (Table 7). The published literature suggests that only 60% to 70% of patients currently undergoing biventricular pacing experience measurable clinical improvement from this therapy. In most series, biventricular pacing does not improve patients when left ventricular ejection fraction exceeds 40%, because heart failure is largely due to diastolic dysfunction in this population. Ambulatory patients with severe (NYHA functional class III or IV) symptoms despite optimized oral

<table>
<thead>
<tr>
<th>Table 7. Potential Predictors of Patient Responsiveness to Cardiac Resynchronization Therapy Based on Published Studies</th>
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<tr>
<td><strong>Clinical/electrocardiographic</strong></td>
</tr>
<tr>
<td>NYHA functional class III or IV symptoms</td>
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<tr>
<td>Sinus rhythm</td>
</tr>
<tr>
<td>Wide QRS (&gt;120 ms)</td>
</tr>
<tr>
<td><strong>Measures of contractility</strong></td>
</tr>
<tr>
<td>Ejection fraction (≤35%)</td>
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<tr>
<td>Basal dP/dtmax</td>
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<tr>
<td>Doppler diastolic-to-cycle length ratio</td>
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<tr>
<td><strong>Dysynchrony analysis</strong></td>
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<tr>
<td>MRI</td>
</tr>
<tr>
<td>Tissue Doppler/strain rate analysis</td>
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<tr>
<td>Contrast echocardiography</td>
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<tr>
<td>Phase analysis (Φ)</td>
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<tr>
<td>Septal/posterior wall motion delay</td>
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</tbody>
</table>

MRI = magnetic resonance imaging; NYHA = New York Heart Association.
pharmacological therapy (including a flexible diuretic regimen, an angiotensin-converting enzyme inhibitor, and a beta-blocker, with or without an aldosterone antagonist) seem to derive the most benefit. Within that population, clinical trials have generally focused on patients in normal sinus rhythm who have a QRS duration >130 ms. Clinical, electrocardiographic, echocardiographic, and other imaging modalities have been explored to better predict those most likely to benefit from resynchronization therapy. Biventricular pacing is not indicated as rescue therapy for patients with cardiogenic shock and has not been validated for patients who require intermittent or continuous inotropic support or those supported by intra-aortic balloon counterpulsation. Successful biventricular pacing typically results in an improvement in symptoms by one NYHA functional class and at least 20% improvement in Minnesota Living with Heart Failure Questionnaire scores.

Cardiac resynchronization therapy has also been shown to enhance both submaximal and maximal exercise capacity (as assessed by 6-min walk distance and peak oxygen uptake on cardiopulmonary exercise testing, respectively). The Multisite Stimulation in Cardiomyopathies (MUSTIC) trial enrolled 67 patients with NYHA functional class III symptoms in a single-blind, randomized, controlled crossover study (72). All patients were in sinus rhythm and had a QRS duration >150 ms. Patients underwent three months of biventricular pacing and three months of inactive pacing (VVI backup at 40 beats/min). A significant improvement in six-minute walk distance (+30 m or more) was observed only during active pacing (72).

Similarly, the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial randomized 453 patients with moderate to severe heart failure symptoms to biventricular pacing or continued medical therapy for six months (73). Patients assigned to cardiac resynchronization experienced an improvement in their six-minute walk distance when compared with the control group (+39 m vs. +10 m) (p = 0.005) (73). Cardiac resynchronization therapy has also been shown to reduce hospitalizations for heart failure in the CONTAK-CD, InSync ICD (74), and MIRACLE trials (73). A meta-analysis of these three pivotal studies showed a reduction in heart failure hospitalizations by 29% (odds ratio, 0.71; 95% confidence interval, 0.53 to 0.96) (75).

The MIRACLE trial was the first to show that cardiac resynchronization therapy could decrease the time to death or hospitalization for worsening heart failure (73). In this study, death from any cause was reduced by 27% (p = 0.4). However, the composite end point of death or worsening heart failure requiring hospitalization was reduced by 40% (p = 0.03) (73). A recent meta-analysis reported cardiac resynchronization therapy to be associated with a trend toward reduced all-cause mortality (odds ratio, 0.77; 95% confidence interval, 0.51 to 1.18) (75). Absolute rates of all-cause mortality, based on pooled data over three to six months of follow-up, were 4.9% in the resynchronization group versus 6.3% in the control group.

The Comparison of Medical Therapy, Pacing and Defibrillators in Chronic Heart Failure (COMPANION) trial was the first large-scale prospective trial of cardiac resynchronization therapy to directly examine its effects on all-cause mortality (76). A total of 1,520 patients with ischemic or non-ischemic cardiomyopathy, left ventricular ejection fractions ≤35%, and NYHA functional class III or IV symptoms were randomized to optimal medical therapy, biventricular pacing alone, or biventricular pacing combined with ICD. There was a trend toward reduction in all-cause mortality in patients assigned to biventricular pacing (absolute mortality, 14.4% for pacing alone versus 19% for control patients). However, patients who received biventricular pacing plus an ICD had a statistically significant reduction in all-cause mortality (absolute mortality, 11%; p < 0.01). The recently published Cardiac Resynchronization-Heart Failure (CARE-HF) study further confirmed the mortality benefit of cardiac resynchronization therapy in 813 patients with advanced symptomatic heart failure caused by left ventricular systolic dysfunction (77). Among patients with severe heart failure (NYHA functional class III or IV) and evidence of ventricular dyssynchrony, cardiac resynchronization resulted in a significant improvement over standard pharmacological therapy in the composite primary end point of death from any cause or unplanned hospitalization for a major cardiovascular event (p < 0.001) (77). Additionally, cardiac resynchronization therapy resulted in significant reductions in the interventricular mechanical delay, end-systolic volume index, and mitral regurgitant jet area when compared with medical therapy (77). Additional trials are underway to determine whether biventricular pacing alone will provide a long-term survival benefit. Thus, current practice guidelines support the use of biventricular pacing in patients with advanced (NYHA functional class III or IV) heart failure symptoms due to either ischemic or primary cardiomyopathy when sinus rhythm, QRS prolongation (>120 ms), left ventricular enlargement (left ventricular end-diastolic dimension >55 mm), and left ventricular systolic dysfunction (left ventricular ejection fraction ≤35%) exist (79).

**PRE-EXISTING PACER UPGRADE TO CARDIAC RESYNCHRONIZATION THERAPY**

The utility of revising standard VVI or DDD pacemakers for patients who are pacer dependent and have chronic heart failure symptoms is being re-examined in light of the results of the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial (79). When patients with DDD rate-responsive pacing (set at 70 beats/min) were compared with a cohort with VVI pacing (set at 40 beats/min), there was a trend toward increased mortality and hospitalizations for new-onset heart failure in the DDRD group (78). These findings suggest that unnecessary right ventricular apical pacing may induce ventricular dyssynchrony and should be
avoided whenever possible among patients with significantly impaired systolic function. Similarly, an increased incidence of heart failure was noted in the MADIT-II trial cohort randomized to ICD therapy who showed a high frequency of right ventricular pacing. Both studies represent retrospective post-hoc analyses and should be interpreted cautiously. Prospective controlled trials are necessary to determine whether heart failure patients who require frequent conventional pacing from a standard pacer or ICD may benefit from an upgrade to a biventricular model. Finally, cardiac resynchronization therapy has been largely studied among patients with advanced (NYHA functional class III or IV) heart failure symptoms. Echocardiographic studies have shown substantial reverse remodeling in this population. Whether this approach should be applied earlier to patients with asymptomatic left ventricular dysfunction or mild heart failure (NYHA functional class I or II) requires further clinical trials.

CONCLUSIONS

Over the past two decades, multiple clinical trials have documented the dramatic survival benefit of ICD therapy in certain subsets of patients. The ICDs should be considered first-line therapy for survivors of life-threatening ventricular arrhythmic events. Additionally, subsets of patients with inherited pro-arrhythmic syndromes, such as long QT syndrome, Brugada syndrome, hypertrophic cardiomyopathy, and arrhythmogenic right ventricular dysplasia have shown substantial survival benefits after undergoing ICD implantation. Recent trials have also clearly defined specific subsets of patients with both ischemic and dilated/non-ischemic cardiomyopathies who benefit from ICDs. It is clear from the studies summarized in this review that ICD therapy has an increasing role in the management of a diverse population of cardiac patients. A reduced left ventricular ejection fraction predicts an increased risk for sudden cardiac death and identifies many subpopulations that benefit from ICD therapy. Reduced left ventricular ejection fraction as an indication for ICD implantations as well as the supporting clinical trials are summarized in Figure 1. Finally, cardiac resynchronization therapy has also been shown to produce substantial symptomatic improvement and survival benefits in a subgroup of chronic heart failure patients. This therapy should be considered in all patients undergoing ICD implantation who have evidence of ventricular dyssynchrony. Table 7 lists variables that may potentially predict patients likely to have a response to cardiac resynchronization therapy.

Reprint requests and correspondence: Dr. G. William Dec, Cardiology Division, Massachusetts General Hospital, Heart Failure and Transplantation Unit, Bigelow 800, Mailstop 817, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: gdec@partners.org.

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