New Drugs and Technologies

Heart Failure Devices

Implantable Cardioverter-Defibrillators and Biventricular Pacing Therapy

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Although the age-adjusted mortality from heart disease has declined in the United States, cardiovascular disease remains the No. 1 cause of death.1,2 Patients with cardiac disease generally die of one of 2 causes: sudden, unexpected cardiac death or progressive heart failure. Chronic heart failure (CHF) has become an epidemic in the United States. Implantable cardioverter-defibrillator (ICD) therapy has had a major impact on the treatment of heart failure in the United States. The ICD has been shown to decrease mortality relative to the best medical therapy in patients who have survived an episode of sustained ventricular tachycardia (VT) or ventricular fibrillation (VF).3 Unfortunately, only a small minority of patients who experience an out-of-hospital cardiac arrest in the United States are successfully resuscitated.4 Thus, ICD therapy has been applied for the primary prevention of sudden death in patients at high risk of cardiac arrest. Once thought to be a “bystander” curiosity in the progression of heart failure, electrical-conduction disturbances are now recognized to be important causes of left ventricular (LV) dysfunction. Cardiac resynchronization therapy (CRT) can restore more-normal electrical contraction and, when combined with defibrillation (CRTD), can have a major impact on the mortality and morbidity of heart failure. Although there remain many limitations and challenges to the appropriate application of ICDs or CRTD, there is no question that device therapy has had a major impact on the management of patients with LV dysfunction.

ICD Therapy

The ICD was developed in the 1970s as a device to detect and automatically terminate ventricular tachyarrhythmias.5,6 Early ICDs were large devices that required a thoracotomy to implant. Improvements in batteries, capacitors, and microprocessors7 have resulted in the rapid evolution of ICD technology. Current-generation ICDs are small enough to be easily implanted in the pectoral region and can perform a variety of sophisticated functions, including atrial8 and ventricular de-\n
The development of the ICD was a revolutionary advance in the treatment of heart disease. Its development represented something of a paradox. It was the work of a small group of individuals, but its evolution has represented an extraordinary collaboration between technology, industry, and medicine. The ICD was conceived and developed by Dr Michel Mirowski (Figure 1) and Dr Morton Mower working in a small laboratory at a hospital affiliated with a major medical center. Dr Mirowski’s thoughts were widely criticized in the mainstream medical literature as being unrealistic. Dr Mirowski’s vision and perseverance in the face of criticism were remarkable, and the ICD represented the culmination of the work of lone visionaries. In contrast, the development of the ICD has also been emblematic of the tremendous change that advanced technology has produced in medical care. The ICD incorporates technological advances, such as tiny microprocessors with hundreds of programmable features, batteries, and capacitors specifically designed for the ICD and novel miniaturization techniques. These advances would have been completely unimaginable 2 decades ago and exemplify the role that industry and technology play in modern medical care.

Basic ICD Components and Function

The basic components of ICDs have not changed in the past 20 years.7,8 ICDs contain batteries, capacitors, a microprocessor, and a “header” that contains a site to attach leads. Although ICDs have millions of programmable features, advanced microprocessor technology has allowed these features to be seamlessly incorporated without an increase in device size. ICD leads are constructed in a fashion similar to pacemaker leads, except that a shocking coil or coils are also included. In a single-chamber ICD, one lead is placed in the right ventricle at a site that can pace and also defibrillate the heart. The ICD generator and microprocessors are encased in a titanium can that may be as small as 30 cm3 and can weigh as little as 50 g.

The essential features of ICD function include detecting tachyarrhythmia, classification of a tachyarrhythmia as a treatable arrhythmia, delivering therapy, monitoring of heart rhythm after treatment, and storage of diagnostic results from the episode. Sensing of tachyarrhythmias occurs via a dedicated bipole of small electrodes near the catheter tip (dedicated sensing) or via a bipole from a tip electrode to a coil electrode that is also used to deliver defibrillation shocks.
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range from 21% to 25%. The most common cause of therapy in almost all series is inappropriate ICD shocks that individual patients. The most common complication of ICD evaluating the risk-benefit ratio of ICD implantation for complications have been described with the use of ICD therapy, and these need to be carefully considered in appropriate ICDs, dual-chamber ICDs, and CRT ICDs. Single-chamber ICDs have only a right ventricular lead, dual-chamber ICDs have a right atrial and a right ventricular lead, and CRTDs also have an LV lead that is placed via the coronary sinus (Figure 3) or epicardially. At present, no firm guidelines exist for implantation of single- versus dual-chamber ICDs. Although several clinical trials have compared single-chamber with dual-chamber pacemakers, few trials have examined comparisons between single-chamber and dual-chamber defibrillators. Although dual-chamber defibrillators provide additional flexibility when added to old diagnostic information, clear clinical benefit has not been demonstrated in prospective, randomized trials, except for patients who have bradycardia pacing indications. It has also become clear that electrical disturbances may be a cause of CHF, rather than just an effect of CHF. This results in progressive LV dysfunction, not due to permanently necrotic myocardium but due rather to electrical dysynchrony. CRT, by restoring mechanical synchrony, can reverse signs and symptoms of heart failure and in some patients improve ejection fraction.

Complications
A number of complications have been described with the use of ICD therapy, and these need to be carefully considered in evaluating the risk-benefit ratio of ICD implantation for individual patients. The most common complication of ICD therapy in almost all series is inappropriate ICD shocks that range from 21% to 25%. The most common cause of these shocks is atrial fibrillation, other supraventricular tachyarrhythmias, or sinus tachycardia. Although atrial fibrillation is not a contraindication to ICD implantation, a careful assessment of heart rate during fibrillation should be performed to minimize the incidence of inappropriate shocks. Inappropriate ICD shocks due to oversensing can also occur but are less frequent in current ICDs. Although the effects of inappropriate shocks can be psychologically devastating in individual patients, in most cases, changes in ICD programming or adjustment of medical therapy can eliminate or decrease the incidence of inappropriate shocks. More serious complications can occur during ICD implantation, such as pneumothorax, hemothorax, infection, lead dislodgment, and cardiac tamponade. The overall incidence of significant complications, with the exception of inappropriate ICD shocks, should be well under 5%. Unless patients are acutely ill, have severe CHF, or are undergoing lead extraction, death from ICD implantation should be uncommon.

Cost-Effectiveness
Healthcare costs in the United States have risen at a rate faster than inflation for the past 20 years. Although ICD therapy accounts for only a very small percentage of current healthcare costs, the cost of ICD implantation including the device, lead or leads, and hospitalization for ICD implantation may be as high as $30 000 to $40 000. Thus, careful analysis of ICD cost-effectiveness is appropriate. At present, there are no hard guidelines for cost-effectiveness application of medical therapy. However, a carefully thought-out, case-by-case approach should be utilized when considering expanding ICD indications to patients in whom the clinical benefit may be small. If ICD costs can be decreased, it will allow the therapy to be applied to larger numbers of patients without dramatic increases in healthcare expenditures for ICDs.

ICD Therapy for Secondary Prevention of Sudden Cardiac Death
Initial observational studies suggested that the ICD was effective in preventing recurrent cardiac arrest in survivors of sudden arrest. However, no comparative trials validating the relative effectiveness of ICD therapy compared with other forms of therapy were performed until the late 1990s. Three randomized, controlled trials compared the best antiarrhythmic therapy with ICD therapy for the treatment of ventricular tachyarrhythmias in patients resuscitated from a cardiac arrest. Although the trials differed slightly in inclusion criteria and study design, the major results were similar. In the Antiarrhythmic versus Implantable Defibrillator trial (AVID), 1016 patients with life-threatening arrhythmias were randomized to receive an ICD or antiarrhythmic therapy. More than 75% of the patients who were randomized to receive antiarrhythmic therapy were treated with amiodarone. There was an 30% relative decrease in overall mortality in the group who received the ICD compared with antiarrhythmic drugs. Absolute mortality at 2 years was 25.3% in the control (drug) group and 18.4% in the ICD group. The Canadian Implantable Defibrillator trial (CIDS) randomized 328 patients to receive an ICD and 331 to receive amiodarone. There was a 20% relative risk reduction and a
2% absolute annual mortality benefit in the group who received an ICD. However, this difference did not reach significance. In the Cardiac Arrest Study Hamburg (CASH), patients were randomized to receive an ICD, amiodarone, or metoprolol.30 Two hundred twenty-eight patients were included in the study. There was an $\approx 30\%$ reduction in mortality in the group who received the ICD. The absolute mortality benefit was difficult to calculate because the primary end point of the study was sudden death mortality rather than total mortality. There was no significant difference between the effect of amiodarone and that of metoprolol. Although the results of the study were of borderline significance, the patient population was small. Taken together and evaluated in a meta-analysis, the results suggest that ICDs are superior to medical therapy for the treatment of patients who have experienced a cardiac arrest.3 Subgroup analysis has suggested that some patients who have survived a cardiac arrest, such as those $>65$ years or with well-preserved...
ventricular function, may not have as great a benefit from ICD therapy.\textsuperscript{31-36} However, trials that are adequately powered to detect differences among such subgroups have not been completed.\textsuperscript{36} Although the data suggesting lower mortality in patients who receive an ICD are clear, there are many patients who experience a cardiac arrest in whom less-aggressive medical therapy may be appropriate because of an overall poor prognosis or comorbid conditions.

### ICD Therapy for Primary Prevention of Sudden Cardiac Death

#### Risk Stratification

A multifactorial approach to the prevention of sudden cardiac death is clearly needed. Components of this approach include modifying risk factors for coronary disease, identifying genetic predispositions to sudden death, improving community-based cardiopulmonary resuscitation training, and using technological advances, such as the automatic external defibrillator\textsuperscript{37} and the wearable defibrillator. Despite substantial efforts, however, survival rates from cardiac arrest in the United States remain low.\textsuperscript{1} Although survival rates >30\% were briefly achieved in some local areas such as Seattle and continue to be achieved in areas such as casinos and airports, the overall survival rate from cardiac arrest in the United States is probably <10\%.\textsuperscript{38} Thus, identifying patients at high risk for cardiac arrest and treating them with pharmacological or nonpharmacological therapy to prevent cardiac arrest is appropriate.

The most important risk factor for determining the risk of cardiac arrest in patients with acquired heart diseases is the extent of myocardial damage.\textsuperscript{39} The risk of cardiac arrest increases moderately with ejection fractions <40\% and more significantly with ejection fractions <30\%. Other factors that have been shown to be associated with the risk of sudden cardiac death include the extent of heart failure, QRS width, and neurohormone levels. Some studies have suggested that the inducibility of ventricular arrhythmias at electrophysiological testing, heart rate variability, signal-averaged ECGs, and T-wave alternans may provide independent prognostic information. However, for many of these risk-stratification tests, high positive and negative predictive values have not been consistently obtained. A multifactorial model\textsuperscript{40} may be scientifically most appropriate to determine the risk of cardiac arrest, but it is unclear whether such a model can be widely applied clinically. Thus, selection of patients for trials examining the efficacy of the ICD in the primary prevention of sudden death has typically been based on ejection fraction and, at most, 1 or 2 other risk-stratification tests.

### Clinical Trials

Several recently completed, large-scale trials have examined the use of ICD therapy in patients with underlying structural heart disease at risk for sudden death. Six large trials have examined the use of the ICD in patients with coronary artery disease. The CABG-PATCH trial\textsuperscript{41} randomized 900 patients who were undergoing cardiac surgery for adjunctive epicardial ICD placement. The inclusion criteria for the CABG-PATCH trial were the presence of LV dysfunction and an abnormal signal-averaged ECG. There was no difference in survival between the patients who received the epicardial ICD and those who did not. The negative results of this study could potentially be attributed to deleterious effects of epicardial ICD implantation or to improvements in ventricular function occurring as a result of bypass surgery. In contrast, 4 other trials that used the ICD for the primary prevention of sudden death in patients with chronic coronary disease and LV dysfunction all showed benefits of the ICD. The MADIT-I study, published in 1996, randomized patients with an LV ejection fraction of \( \leq 35\% \), coronary artery disease, nonsustained VT, and inducible VT to receive an ICD or standard therapy.\textsuperscript{42} Only 196 patients were enrolled. There were 15 deaths in the ICD arm and 39 in the conventional-therapy arm. The hazard ratio for overall mortality was 0.46 (\( P=0.009 \)). Although the study was small and limited by an imbalance in \( \beta \)-blocker use in the 2 groups, the dramatic clinical benefit of the ICD in this patient population led to approval of ICD use for this indication. The Multi-center, Unsustained Tachycardia Trial (MUSTT) had a complex study design.\textsuperscript{43} Two thousand two hundred two patients were screened and 704 were randomized to be treated with an electrophysiology-guided approach or a medical approach. No difference was seen between the 2 arms. However, a subpopulation who was randomized to the electrophysilog-
ically guided approach received an ICD. The risk of cardiac arrest or death from arrhythmia among patients who received the ICD was significantly lower than in those without the ICD (hazard ratio, 0.24; \( P<0.001 \)). Analyzing the effect of the ICD in a trial that was designed to compare an electrophysiologically to a nonelectrophysiologically guided approach is complex. However, the dramatic reduction in mortality seen and the consistency with the results of the MADIT-I trial were important observations that the ICD would benefit patients with coronary disease and LV dysfunction. The MADIT-II trial did not use electrophysiologically testing or signal-averaged ECGs to stratify patients for enrollment.\(^{18} \)

Patients were randomized if they had a prior myocardial infarction and an LV ejection fraction \( \leq 30\% \). The crude mortality rate was 19.8\% in the control arm and 14.2\% in the ICD arm. The hazard ratio for reduction of all-cause mortality was 0.69 (\( P=0.016 \)). These results confirmed that patients with coronary disease and LV dysfunction would benefit from the ICD for the primary prevention of sudden death. One limitation to these trials is that in some, medical therapy was not optimal by current standards. The most recent trial examining the effectiveness of the ICD in the primary prevention of sudden death in patients without coronary artery disease was the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), which has been presented in abstract form.\(^{44} \)

This trial randomized patients with all types of LV dysfunction to an ICD, placebo, or conventional therapy. The results in patients with nonischemic cardiomyopathy are discussed in the next section. Approximately 1300 patients with coronary disease were randomized. Amiodarone had no effect on mortality. The ICD reduced overall mortality by 23\%. The ICD had a significant benefit in the overall patient population. In patients with coronary disease, the hazard ratio crossed 1, but an impressive trend to reduction in overall mortality was seen.

One study on ICD therapy soon after infarction failed to show a benefit. In the Defibrillator in Acute Myocardial infarction Trial (DINAMIT), 675 patients were randomized to receive an ICD or standard medical therapy.\(^{45} \) Patients were randomized 4 to 40 days after myocardial infarction and had LV dysfunction and abnormal heart rate variability. Survival was similar in the 2 groups. The reasons for the failure to demonstrate benefits of prophylactic ICD implantation are not yet fully apparent but suggest that ICD implantation soon after myocardial infarction does not yield dramatic clinical benefit. Taken together, the results of these trials suggest that the transvenous ICD substantially reduces mortality in patients with chronic coronary disease and severe LV dysfunction.

Although small trials failed to show ICD benefit in patients with nonischemic dilated cardiomyopathy,\(^{30,46} \) 2 large, multicenter, randomized trials have been performed. The Defibrillators in Non Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) study randomized 458 subjects with nonischemic dilated cardiomyopathy and LV ejection fractions <36\% to receive the best medical therapy or the best medical therapy plus an ICD.\(^{17} \) After 2 years, 14.1\% of the patients in the standard-therapy group and 7.9\% of the patients in the ICD group had died of all causes (6.2\% absolute mortality reduction, \( P=0.08 \)). Although statistical significance was not reached in the primary end point, the results of the study did suggest that the ICD might have utility in selected patients with nonischemic dilated cardiomyopathy. In the SCD-HeFT trial, 1100 patients with nonischemic cardiomyopathy were randomized into 3 arms.\(^{44} \) There was a 27\% relative risk reduction in patients who received an ICD. The difference in patients with nonischemic cardiomyopathy did not quite reach significance, but a strong trend to mortality reduction was observed.

The results of these studies suggest that in judiciously selected patients with significant LV dysfunction that persists despite optimal medical therapy, ICD implantation may be appropriate. A group with moderately high risk for cardiac arrest in whom ICD implantation may be justified is probably defined by those patients with ejection fractions \( \leq 35\% \). In patients with less severe ventricular function, additional assessments such as electrophysiological or noninvasive testing may be appropriate to further risk-stratify patients.

### Primary Prevention of Sudden Death in Other Diseases

A number of diseases other than dilated cardiomyopathy have been associated with an increased incidence of sudden cardiac death. These include inherited diseases of ion channels, such as long-QT syndrome,\(^{47} \) Brugada syndrome,\(^{48} \) and catecholaminergic VT.\(^{49} \) In addition, other structural heart diseases, such as right ventricular dysplasia,\(^{50} \) hypertrophic cardiomyopathy,\(^{51} \) and certain types of congenital heart disease, may be associated with an increased risk of sudden death. The frequency of these conditions is not as high as that of ischemic or nonischemic dilated cardiomyopathy, making prospective, randomized, control trials difficult to perform. Nonrandomized, observational studies suggest that subgroups of high-risk patients may benefit from ICD therapy. One randomized trial was performed in Thailand on patients with an inherited risk of sudden cardiac death (DEBUT).\(^{52} \) In that trial, patients with an inherited syndrome of sudden death that probably represents the Brugada syndrome were randomized to receive \( \beta \)-blockers or an ICD. Patients who received an ICD had better survival.

In the absence of large-scale trials for most of these conditions, risk-stratification algorithms based on retrospective studies have been created in an attempt to help select appropriate patients for ICD therapy. Although criteria suggesting an increased risk differ among different conditions, a family history of sudden death in almost all of the diseases mentioned earlier appears to be associated with an increased risk of sudden death. In addition, there are disease-specific markers, such as septal wall thickness in hypertrophic cardiomyopathy,\(^{51} \) the length of the QT interval in the inherited long-QT syndrome,\(^{47} \) and the presence of persistent rather than intermittent right precordial ST-segment elevation in Brugada syndrome,\(^{48} \) that appear to portend an increased risk of sudden death and may make aggressive use of the ICD for the primary prevention of sudden death appropriate.

### Cardiac Resynchronization Therapy

Physiologically, the presence of electrical-conduction defects in heart failure is associated with a decrease in contractile
performance, development or prolongation of mitral regurgitation, and wasted cardiac work as a result of development of mechanical asynchrony. Intraventricular asynchrony, characterized by regional contractile phase delay in the anteroseptal and posterolateral walls of the LV, and interventricular asynchrony, characterized by a phase delay in contraction between the right and left ventricles, are the typical manifested consequences of electrical remodeling in the cardiac conduction system. These electrical alterations translate into abnormal myocardial metabolism, redirection of regional coronary perfusion, and cellular changes characterized by abnormalities in cellular calcium handling and upregulation of stress kinases. Thus, restoring electrical synchrony could potentially improve cardiac function by reversing these cellular, physiological, and hemodynamic aberrations.

**Resynchronization Pacing in Heart Failure**

The first clinical report of biventricular pacing is credited to Cazeau et al in 1994. That study was followed by a series of uncontrolled studies demonstrating marked short-term improvements in hemodynamics and symptoms with biventricular stimulation.

The European and Canadian InSync Study was designed to test the safety and efficacy of a multisite pacemaker (Medtronic InSync) in the treatment of refractory heart failure. The trial was conducted without a control group and thus, was observational. Significant improvements in exercise capacity, New York Heart Association (NYHA) functional class, and quality-of-life score were also noted at each of these time points. The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial randomized 453 patients to activation or nonactivation of cardiac resynchronization in a double-blind study design. Inclusion criteria were NYHA class III/IV, QRS >130 ms, ejection fraction <35%, and LV end-diastolic dimension >55 mm (echocardiographic). Resynchronization improved symptoms, quality of life, and exercise capacity (6-minute walk test increased by 39 m and $V_{O_2}$ increased by 1 mL · min⁻¹ · kg⁻¹) while reducing LV dimension (LV end-diastolic dimension decreased by 5 mm) and improving ejection fraction. There were also improvements in the numbers of patients requiring hospitalization (8% versus 15%) or intravenous medications (7% versus 15%) for the treatment of heart failure ($P<0.05$).

The biggest drawback of that study is that it was not subjected to an intention-to-treat analysis, because randomization assignment was made only after initial successful device implantation was secured.

**Long-Term Studies of Multisite Pacing (With ICD)**

The CONTAK CD trial enrolled 581 patients, who also met conventional indications for ICD implantation, to active CRT or not. Initially, patients were randomized (in a double-blind design) to either biventricular or no pacing for 3 months and then crossed over to the opposite assignment for the next 3 months (n=248), but the scheme was later changed to a 6-month parallel control design (n=333). The primary end point was a composite of mortality, heart failure hospitalizations, and episodes of ventricular arrhythmias. The primary end point favored CRT but was not statistically significant. However, the 6-minute walk test, NYHA class, and peak aerobic capacity were significantly improved with CRT, particularly in patients with NYHA III/IV heart failure.

The MIRACLE ICD trial was designed in a similar manner to the original MIRACLE study, the only exception being that all patients were to have an indication for ICD. In addition to the primary heart failure–related efficacy variables, this trial also assessed the efficacy of ICD function in the presence of CRT. At 6 months, significant improvements in NYHA class and peak aerobic capacity (but not in the 6-minute walk test) were noted. Furthermore, no significant differences were noted in overall heart failure status, LV size or function, hospitalizations, or survival. More important, this study demonstrated that arrhythmia recognition and ICD function were preserved, and no proarrhythmia was noted. The CRTD trials as a group showed functional improvement after biventricular pacing.

**Morbidity and Mortality Studies of Multisite Pacing**

COMPANION (comparison of medical therapy, pacing, and defibrillation in CHF) enrolled patients with CHF and NYHA class III or IV symptoms, despite maximized medical therapy. Inclusion criteria included a QRS duration >120 ms and a PR interval >150 ms. The trial had 3 treatment arms: One of 5 patients was to receive optimal pharmacological therapy, 2 of 5 were to receive optimal pharmacological therapy plus biventricular pacing, and the remaining 2 of 5 were to receive biventricular pacing plus backup ICD therapy. In contrast to all others, this study was sufficiently powered to evaluate a primary end point of combined all-cause mortality and hospitalization. Peak oxygen consumption was the other (functional) primary end point. Data were analyzed by an intention-to-treat statistical approach. Patients (n=1520) were randomized (93%), and 1080 patients were implanted with a CRT pacer or defibrillator (CRTD); 118 patients failed the initial implantation (88% implantation success for CRT and 92% for CRTD). LV lead dislodgment was seen in 2% and 2.5% in the CRT and CRTD groups, respectively. Compared with patients treated by medical therapy only, there was a statistically significant event rate reduction in the primary combined end point of total hospitalization and total mortality at 1 year in the CRT/CRTD group (odds ratio, 0.82; $P=0.05$ and 0.81; $P=0.015$, respectively), as well as in the combined end point of hospitalization for CHF and death (odds ratio, 0.64 and 0.60, respectively; $P=0.05$). Mortality at 1 year decreased by 24% ($P=0.059$, NS) in the CRT group and by 36% ($P=0.003$) in the CRTD group. The effects of CRT on hospitalization due to CHF appeared to be more pronounced in patients with left bundle-branch block (as opposed to intraventricular conduction defect or right bundle-branch block), patients with a longer QRS duration (>148 ms), and patients receiving β-blockers.

**Meta-Analyses of CRT**

Two published meta-analyses have attempted to evaluate the collective effect of CRT on the end points of progressive heart failure mortality or total mortality. The first meta-analysis by Bradley and colleagues suggested that biventricular
pacemakers decreased deaths due to progressive heart failure. The other analysis by McAlister and colleagues reviewed 9 trials (3216 patients) for efficacy and suggested that this technique improves LV ejection fraction and quality of life and reduces heart failure hospitalizations. Additionally, these authors suggested an improvement in survival, but this was largely accounted for by the inclusion of the ICD arm from the COMPANION trial. Thus, the meta-analyses suggest but do not definitively answer the question of mortality reduction by CRT when used in isolation from an ICD.

Unresolved Issues With CRT

The evidence supporting CRT in severe heart failure is compelling; however, device placement exerts a substantial placebo response, with evidence of improved functional capacity and quality-of-life parameters in those randomized to the control group and carries with it a significant nonresponder rate (no improvement in functional capacity and well-being). Furthermore, a marked heterogeneity of response (differences in magnitude of observed benefit between trials presumably enrolling similar heart failure populations) has also been noted. One of the most important advances in CRT must accrue from diminishing the implantation risks and redefining successful implantation to include correlation of the site and magnitude of mechanical asynchrony.

An increasing evidence base points to the use of echocardiography (and, in particular, tissue Doppler imaging) to help identify potential responders to CRT based on assessment of mechanical asynchrony. At present, several echocardiographic methods to assess dyssynchrony have been proposed, varying from conventional to advanced approaches, primarily involving tissue Doppler imaging, strain, strain rate, and tissue tracking. It is currently unclear which of these parameters provides optimal information on asynchrony and which parameters may actually allow prospective identification of responders to CRT. It is uncertain whether optimization of atriventricular delay, interventricular resynchronization, or intraventricular resynchronization should be the principal goal of CRT.

The underlying etiology of heart failure may be important. Patients with ischemic cardiomyopathy frequently have large areas of scar tissue, and not infrequently, these are the areas of latest activity. It is unclear whether pacing of nonviable (scar) tissue results in clinical improvement.

Another issue of importance relates to extrapolation of resynchronization therapy to mild (NYHA II) heart failure. Abraham and colleagues have reported on a subgroup of NYHA II patients in sinus rhythm enrolled at the Multicenter InSync ICD II trial. In that study, a significant improvement in cardiac structure and function was noted, but no improvement in exercise capacity or neurohormones was evident. As more information about mechanisms of benefit from resynchronization accumulate and patient selection evolves, further large-scale, adequately powered, clinical trials will be needed to assess effects on morbidity and mortality as well as functional outcomes in patients with less severe heart failure.

It is also unclear whether an ICD must accompany a cardiac resynchronization device (CRTD therapy) or whether it should be performed in isolation. Taking the recent SCD-HeFT results in context, one could argue that CRT therapy should ideally be accompanied by ICD placement in those with NYHA III symptoms. As in the SCD-HeFT investigation, results also suggest that ICDs might be beneficial in heart failure patients with advanced symptoms, irrespective of ischemic or nonischemic etiology. In the COMPANION trial, there was a trend for CRT to decrease mortality, but CRTD significantly decreased mortality. The point estimate for mortality reduction by the addition of the ICD was similar in class III and class IV heart failure. Thus, carefully selected patients with NYHA class IV heart failure may also derive benefit from concomitant ICD therapy.

Atrial Defibrillation

ICD therapy is effective for the treatment of atrial fibrillation. An atrial-only defibrillator was developed and tested in early clinical trials. However, development of a stand-alone atrial ICD has not progressed. Instead, atrial ATP and defibrillation capabilities have been incorporated in current-generation dual-chamber ICDs. Adequate atrial defibrillation thresholds have been obtained in almost all patients undergoing implantation. The main limitation to the use of the ICD is the painful nature of ICD shocks. Self-administered sedation and shock timing have been used to minimize the morbidity of atrial defibrillation shocks. In addition, atrial fibrillation may often begin as atrial tachycardia, and thus, atrial ATP may be effective at terminating arrhythmias soon after they begin and prevent the progression to atrial fibrillation.

The Future

A summary of current recommendations for ICD and CRT is shown in the Table. The ICD (including CRT) has already had a major impact on the treatment of heart failure. Future-
generation ICDs will likely become cardiac disease management devices. Sensors that can monitor the progression of heart failure and potentially be incorporated in future generations of ICDs. Each of these features should be carefully evaluated for its clinical benefit and cost-effectiveness before routine application to the management of all patients.

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