Relationship of the Implantable Cardioverter Defibrillator and Chronic Resynchronization Therapy: The Perfect Marriage?

David S. Cannom, M.D., and Morton Mower, M.D.

Good Samaritan Hospital Los Angeles, Los Angeles, California

Background: The two major modes of death in the patient with a reduced ejection fraction (EF) are death due to heart failure and death due to lethal arrhythmia, essentially the two sides of the same coin. Over the last 20 years, two therapies—cardiac resynchronization therapy (CRT) and the implantable cardioverter defibrillator (ICD)—have been developed and tested in clinical trials. They are now, in conjunction with appropriate medical therapy, the mainstays of therapy for these two commonly encountered clinical problems.

Method and Results: Both of these therapies were conceived and patented by two Baltimore cardiologists, Michel Mirowski and Morton Mower (Table I). The path to everyday acceptance of both therapies was remarkably similar. The concept and early success of both devices was accomplished but the proof of concept depended on a series of carefully designed randomized clinical trials that showed that both the CRT and ICD devices saved lives in the low EF population, especially when used together. These trials overcame substantial skepticism on behalf of elements of the cardiology and electrophysiology establishment.

Conclusion: We are now at a crossroads in the further extension of either therapy. The majority of the indications for either device alone or in combination are established. In the next few years, assuming the continued commitment on the part of regulatory agencies to fully embrace evidence-based medicine, we will see indications extended but only by the careful clinical trials that became the bedrock of their initial acceptance.

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Three major advances in electrophysiology (EP) occurred between 1990 and 2005: radiofrequency ablation of tachyarrhythmias and a series of clinical trials that supported the efficacy of the implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT) in high-risk patients with congestive heart failure (CHF). This exciting era that employed ingenious devices to reduce mortality and improve patient's quality of life followed the 1980s when clinical EP was really a form of invasive electrocardiography, and was becoming stagnant with essentially only serial drug testing being offered as a therapeutic entity. The everyday life of the electrophysiologist has been transformed and we now talk in terms of "cure" and clinical improvement, not palliation.

A fascinating story of innovation and persistence is responsible for the ICD and CRT. Mirowski and

Mower developed both concepts, patented both ideas, and lived to see their ingenuity reap clinical benefits far beyond what most thought possible. This manuscript will outline both the early beginnings and increasing interrelationships of the technologies.

THE RELATIONSHIP BETWEEN HEART FAILURE, SUDDEN DEATH AND THE ICD

For decades, electrophysiologists have worked to better understand the causes and treatment of the arrhythmic complications of CHF. A variety of clinical studies completed in the 1990s demonstrated that heart failure patients have a high annual cardiac mortality.¹ In NYHA class II heart failure

Table 1. Mirowski/Mower Legacy of Pivotal Therapies

	ICD	CRT
Concept	1970	Mid 1970s
Patent	1971	1990
First implant	1981	1991
FDA/CMS approval	1984	2004
Pivotal trials	MADIT I & II SCD-HeFT AVID CIDS	COMPANION CARE-HF

ICD = implantable cardioverter defibrillator; MADIT = Multicenter Automatic Defibrillator Implantation Trial; COMPANION = Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial; AVID = Antiarrhythmics versus Implantable Defibrillator; CIDS = Canadian Implantable Defibrillator Study.

patients, 5–15% die annually and one-half to two-thirds of these deaths are sudden.^{2–5} In NYHA class III patients the annual mortality increases to 20–50% and in NYHA class IV the annual patient mortality can exceed 50%.^{6–10} As the NYHA class heart failure worsens, the relative number of deaths due to arrhythmia declines. While 50% of NYHA class II deaths are sudden, this percentage falls to 30% in class III patients.^{11,12} These studies did not distinguish between the natural history of ischemic versus dilated cardiomyopathy (DCM) patient (see below).

Packer stated in 1985, “The frequency of sudden death is greater in patients with CHF than in any other definable subset of patients in cardiovascular medicine.” He further notes (somewhat pessimistically):

There remains no clear means of identifying patients who are likely to die suddenly before the terminal event occurs. Ventricular ectopic activity on Holter monitor, especially the presence of non-sustained ventricular tachycardia (VT), predicts total mortality rather than the occurrence of sudden unexpected death. Because the frequency of sudden death in the overall heart failure population is substantial (20% per year), I view all patients with CHF as being at high risk and would suggest that all such patients are candidates for long-term prophylactic treatment were an effective and well tolerated therapeutic approach available.¹

There is still no single best way to identify the patient with heart failure who will die from an arrhythmia rather than from progressive left ventricular dysfunction. Attempts at identifying which heart failure patients are at an increased risk of sudden cardiac death (SCD) have met with limited success. To date, there is still no single best measurement to identify which heart failure patients will die from an arrhythmia rather than progressive left ventricular systolic dysfunction (LVSD). Simple clinical markers such as greater age, degree of LVSD, and severity of heart failure predict overall mortality but have low specificity for the mode of death. Syncope has been reported to be one specific clinical marker associated with increased SCD.^{13–15} High frequency ventricular ectopy does indicate a worse prognosis, yet controversy remains as to whether this is predictive of the mode of death rather than a reflection of the degree of LVSD.^{16–17} Inducibility of VT/ventricular fibrillation (VF) during electrophysiology testing (EPS) has a low sensitivity in nonischemic or DCM patients. However, it does predict an increased risk of SCD in ischemic cardiomyopathy but does not predict overall mortality.^{18,19}

It is noteworthy that many of the initial ICD multicenter studies were deliberately crafted to have a very narrow patient profile since the challenge at that time was to show that the ICD was indeed effective in a high risk population. Notwithstanding this, the results of the recently completed ICD trials—including Multicenter Automatic Defibrillator Implantation Trial (MADIT) I & II, Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE), SCD in Heart Failure Trial (SCD-HeFT) and Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION)—do establish a survival advantage in implanting ICDs in selected patients with heart failure. However, all of these trials recruited patients on the basis of their ejection fraction (EF), not their heart failure status. The purest heart failure trial is COMPANION, which enrolled patients with advanced heart failure (NYHA class II and IV) and a low EF: here the survival benefit of both cardiac resynchronization therapy (CRT) and ICD was clearly seen. In less advanced heart failure (NYHA class I and II), the dominant risk stratifier seems to be EF rather than CHF.

THE ROLE OF THE ICD IN PREVENTING SCD IN CAD PATIENTS

Several randomized, prospective trials have proven the efficacy of the prophylactic ICD in improving survival in patients who have survived SCD.^{20–22} A meta-analysis of these trials reported that the ICD was associated with a 28% reduction in the risk of death due almost entirely to a 50% reduction in arrhythmic mortality.²³ Patients with an EF $\geq 35\%$ derived the most benefit from the ICD. This data provides strong evidence to support ICD use in all patients who have survived SCD or sustained VT regardless of the degree or etiology of heart failure.

The inventors of the ICD (Drs. Mirowski and Mower) anticipated a prophylactic use for the ICD. They wrote in the Archives of Internal Medicine in 1970 that "It is too early to determine exactly the indications and contraindications for the standby automatic defibrillator. For use outside the hospital this device might be implanted on a permanent base in selected patients with coronary artery disease identified as belonging to high-risk populations."²⁴

Three well-designed primary prevention trials in patients with reduced EF and coronary disease support a role for the ICD in low EF patients.^{25–27} The MADIT I and The Multicenter Unsustained Tachycardia Trial (MUSTT) examined similar patients with CAD, EF $< 36\%$ (MADIT I) or 40% (MUSTT) and inducible VT/VF at EPS. MADIT I reported a 54% mortality reduction, with most of the benefit seen in patients with a history of heart failure ($\sim 40\%$ of patients), EF $< 26\%$, or LBBB. MUSTT showed a 27% risk reduction in SCD solely attributed to use of the ICD and not antiarrhythmic drug therapy.²⁶ Approximately 2 of 3 of the enrolled patients were either NYHA class II or III. MADIT II evaluated patients with CAD and EF $< 30\%$ and did not require inducibility of VT/VF by EPS. The ICD produced a 31% risk reduction in overall mortality, with the majority of the benefit occurring in patients with a QRS duration > 120 ms.²⁷ Approximately 60% of the patients were either NYHA class II or III.

THE DEFINITE AND SCD-HeFT TRIALS

Previous small studies examining the role of prophylactic ICDs among patients with DCM did

not define the role of the ICD. The Amiodarone versus Cardioverter Study (AMIOVIRT) reported no mortality difference among patients with DCM and asymptomatic nonsustained VT (NSVT).²⁸ Similarly, the German Cardiomyopathy Trial (CAT) was stopped when interim statistical analysis suggested the impossibility of any mortality difference emerging between ICDs and medical therapy among patients with DCM diagnosed within 12 months of enrollment.²⁹ The neutral results of these studies were due to inadequate sample size and the absence of a requirement for symptomatic heart failure that in turn contributed to lower than expected event rates. In contrast, the recently reported DEFINITE trial, which randomized 458 patients with DCM, left ventricular EF $> 35\%$, and asymptomatic NSVT to ICD or conventional medical therapy, demonstrated a 34% reduction in all-cause mortality in ICD patients, but that did not reach statistical significance.³⁰ A post hoc analysis of NYHA Class III patients showed a 67% relative reduction in all-cause mortality, again showing that patients with left ventricular dysfunction and more advanced heart failure symptoms are most likely to benefit from ICD therapy as in MADIT I.

The hypothesis of SCD-HeFT was to determine, by intention-to-treat analysis, whether either ICD or Amiodarone reduced all-cause mortality compared with placebo in patients with ischemic or DCM, NYHA Class II-III heart failure, and left ventricular EF $\leq 35\%$.³¹ Event estimates were based on an estimated 10% per year all-cause mortality rate in the control arm at a minimum follow-up of $2\frac{1}{2}$ years. A total of 2521 patients were enrolled between September 16, 1997, and July 18, 2001, at 148 sites in North American and New Zealand. Follow-up terminated on October 31, 2003, yielding a median (25th, 75th percentile) follow-up duration of 40.8 (29.7, 53.0) months. In addition to SCD-HeFT being an extremely large classic fixed-sample-size study, this long follow-up duration exceeds any prior study of ICDs or drug therapy for prevention of SCD.

Fifty-two percent of enrolled patients had an ischemic cardiomyopathy and 48% had a DCM, 70% were NYHA Class II and 30% were Class III. A high standard for optimal medical management of heart failure was maintained, which countered a historical criticism of prior ICD trials. At last follow-up, 87% of patients were taking either an ACE or ARB, 78% were taking beta blockers, 80% were taking diuretics, and 31% were taking spironolactone. There

Figure 1. The Kaplan–Meier estimates of death from any cause in the SCD-HeFT trial is shown. Note the 5-year reduction in mortality by the ICD of 23% compared to either placebo or amiodarone. This difference was noted irrespective of the cause of the cardiomyopathy (ischemic or dilated) but was limited to NYHA CI II patients only. CI denotes confidence interval.

were no important differences for baseline demographic variables, substrate, NYHA class, or medical therapy among treatment groups, with the exception of slightly more beta-blocker use in Class II (71%) versus Class III (64%) patients.

The primary result of SCD-HeFT was a significant reduction in all-cause mortality with ICD therapy compared to amiodarone or placebo (Fig. 1). Five-year all-cause mortality was 35.8% in the placebo group. Thus, ICD therapy conferred a 23% relative reduction in all-cause mortality (hazard ratio: 95% confidence interval 0.77; $P = 0.007$). This difference in mortality emerged within 18 months of enrollment and was sustained throughout follow-up. The majority of deaths were cardiac (68%, similarly distributed among treatment groups) and the mortality benefit of ICD therapy was due entirely to a reduction in arrhythmic deaths (39% in the placebo arm vs 20% in the ICD arm).

The reduction of mortality among patients with ischemic cardiomyopathy approximates that observed in MADIT II and serves to validate the findings of that study. More important, the equivalent mortality of reduction among patients with DCM demonstrates that the primary prevention mortality benefits of ICD therapy seen in ischemic myopathy are identical to DCM populations.

There were many peculiarities in the SCD trial design that, while present, do not distract from the

overall results. DFT testing was minimal and even if DFTs under 30 joules could not be obtained, the device was still implanted. Also, the device was programmed as a “shock only” device, without any of the benefits of antitachycardia pacing programmed “on.” Finally, the hazard ratio for those patients with a left ventricular EF more than 30% (285 patients) was 1.08. The hazard ratio for patients with EFs equal to or under 30% (1390 patients) was 0.73. Thus, there was no benefit of the ICD in patients with an EF between 30 and 35%. The benefit of ICD therapy was greater in patients with a QRS duration of greater than or equal to 120 ms (hazard ratio: 0.67). This finding was also noted in the MADIT II trial. While there was a significant reduction in mortality in patients with NYHA class II CHF (7.9% at 5 years), patients with NYHA class III CHF had no apparent reduction in the risk of death (hazard ratio of ICD vs Placebo 1.16). Despite this data, the authors state in the discussion that “we do not believe that the unanticipated subgroup effect will be found as a sufficient basis for withholding ICD therapy from patients in NYHA class III.”

Recently presented data from SCD-HeFT showed that in surviving patients the NYHA class actually improved over time for the surviving population within each treatment group.³² This occurred despite the associated mortality in each arm. One possible explanation for this finding is that more intense pharmacologic therapy improved these patients and that they were misassigned at enrollment due to undertreatment with CHF medication.

Heart failure is probably not as relevant a way to select patients as the presence of a low EF alone. Of course most of these low EF patients will have heart failure. But the inconsistency of benefit from the ICD across studies (e.g., the differences between benefit in class III patients between DEFINITE and SCD-HeFT) reinforces the importance of a low EF rather than an attempt to categorize heart failure, which relies on a subjective interpretation of symptoms. Other causes of heart failure, for example, diastolic dysfunction and a high EF, would not qualify for an ICD. Medicare has recently agreed to fund the SCD-HeFT indications in a broad decision that includes all patients with an EF $\leq 35\%$ due to either an ischemic or nonischemic cause and irrespective of NYHA, heart failure studies, or QRS duration (CMS memo accessible at <http://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?d=139>).

Not all ICD trials turned out to show a survival advantage for the ICD. A large surprise, in this regard, were the results of a DINAMIT trial.³³ In this trial a different group of patients was studied, those having an infarction within 6–40 days prior to randomization to an ICD or best medical therapy. The mean EF of the population was 28% versus 23% in MADIT II. A total of 332 patients were randomized to the ICD and 342 patients to no ICD. After 30 ± 13 months, there were 12 arrhythmic deaths in the ICD group compared to 29 in the control group (HR in the ICD group 0.42: 95% confidence interval 0.22 to 0.83, $P = 0.009$). However, this survival advantage was offset by 50 deaths due to nonarrhythmic causes on the ICD group compared to 29 in the control group. Of these 50 deaths, 78% were cardiovascular in nature. Thus, the patients being saved from SCD by the ICD were dying at a high rate from other causes, thereby negating the benefit of the ICD. Perhaps this should not have been too surprising. The authors of this paper think that if a CRT-ICD device had been used in this study that might have improved LV function, this difference might have been negated. Such a trial should be done.

A similar finding was also noted in the CABG-PATCH trial.³⁴ In this trial, 900 patients with ischemia and an EF $<36\%$ underwent revascularization and half of the patients received an ICD. Again, the ICD reduced arrhythmic mortality (22 deaths in controls vs 13 in the ICD arm) but this was offset by 30 deaths in the ICD arm due to myocardial pump failure versus only 23 such deaths in the control arm. No overall survival benefit was afforded by the ICD. A similar trend was noted in the MADIT II population despite an overall improvement in survival in the ICD arm. In the conventional group, 19 deaths were due to a primary mechanical (i.e., a nonarrhythmic cause, mostly CHF) while there were 40 such deaths in the ICD arm. Again, this difference might be neutralized by using CRT in some or all of these patients.³⁵ This hypothesis should be the subject of another clinical trial.

CARDIAC RESYNCHRONIZATION THERAPY

A common finding in patients with CHF is the presence of electrical conduction disturbances on EKG. These have been considered an ancillary finding attributed to disrupted connections between the working myocardium and conducting cells.³⁶ The

most common conduction disturbance is LBBB, found in 25% of patients with advanced heart failure.³⁷ Both naturally occurring and experimentally induced ventricular conduction delay may generate uncoordinated ventricular contraction patterns that reduce the effectiveness and contribute to left ventricular (LV) systolic dysfunction. There is a correlation between the degree of ventricular conduction disturbance and mortality with depressed LVEF. Previous investigators described the relationship between QRS width and mortality post-MI: a QRS wider than 150 ms with advanced CHF predicts a poor outcome.^{38,39}

Acute hemodynamic studies demonstrate significant improvement in LV systolic function with maintained diastolic function when both right ventricle (RV) and LV are preexcited.^{40–43} Biventricular or univentricular left ventricular contraction synchronized to sinus rhythm resynchronizes RV and LV contraction. Acute hemodynamic benefits of ventricular resynchronization therapy pacing include increased pulse pressure and improved LV contractility with decreased LV filling pressure.^{41–43} In addition, there is decreased myocardial oxygen consumption presumably by decreasing LV wall stress through improved coordination of LV wall segmental contraction.^{44–46} Longer-term clinical trials have shown decreased LV end-diastolic volume and LV end-systolic volume and improved myocardial performance index.^{47,48}

Clinical studies have shown encouraging results in improving symptom-limited endpoints of the type used in heart failure trials.^{49–51} Patients have shown increased 6-minute walk distances and oxygen uptake at peak exercise. In addition, resting serum norepinephrine levels have decreased⁵² and NYHA class and quality of life scores have improved.

The mechanism by which biventricular stimulation influences the risk for malignant VT in patients with CHF is unknown—if it has this effect at all.⁵³ Nevertheless, the measured improvement in LV pumping function, the reduction in wall stress, measured reverse remodeling, the decrease in myocardial oxygen consumption, the reduction in neurohormone activation and improvement in myocardial efficiency is similar to what occurs after long-term beta blocker therapy through biological mechanisms. Such data imply that ventricular resynchronization therapy (VRT) may extend a benefit similar to that of beta blockade with a comparable improvement in LV mechanics.^{54–58}

Drs. Mower and Mirowski knew that preventing arrhythmic death would reduce cardiac mortality significantly but not completely. Thus, they began work on the technology of CRT as early as 1974 in dogs being tested with the ICD. They found that multisite ventricular pacing acutely benefited left ventricular function.

In 1986, they had a number of patients with the implanted defibrillator, and had occasion to take one of them with severe heart failure to the cath lab at Sinai Hospital in Baltimore for diagnostic purposes. They were able to do acute bi-ventricular pacing from the LV and RV cavities. This was done very gingerly because they did not want to take the chance of displacing any of the defibrillator leads. They were not impressed with any BP changes but did find that the urine output markedly increased during the half hour or so of the pacing.

In 1988, they described a pacing model in dogs for distinguishing VT from SVT (i.e., with both ventricles being stimulated by the intrinsic conduction system as opposed to eccentric stimulation), which ends up making diagnoses on the basis of hemodynamic differences.⁵⁹ They also did a series of studies on dogs then which was finally published in 1990 after Dr. Mower had gone to Cardiac Pacemaker, Inc., as Vice President of Medical Sciences.⁶⁰ This work eventuated into patent no. 4,928,688.⁶¹

In 1991, Dr. Mower worked with Patricia Bakker on a series of 12 class III/IV long-term implants of a biventricular pacer, using both extended bipole and split cathode configurations, Leslie Saxon at UCLA added 4 cases, and Michael Gold added 2 patients at University of Maryland. This work gave rise to a number of abstracts, but only a few papers.^{62–65} Unfortunately, it was very difficult to get a full-length paper published on this early work. There were many rejections. One finally appeared a decade later.⁶⁶ But early on after the Bakker poster session, the Val d'Or group reported on a single case, and they had to rush a letter into publication warning of the dangers of rising thresholds with the extended bipole lead configuration.⁶⁷

A series of early CRT trials studied patients with LBBB and low EF and found that symptom-limited endpoints improved.^{50–52} Other trials quickly addressed the addition of the ICD to CRT, but failures in design and small numbers did not establish the role of the ICD. More recently a series of elegant, randomized trials have shown both survival

improvement and quality of life improvement with CRT-D and CRT alone.

THE COMPANION TRIAL

The COMPANION trial expanded the earlier studies of CRT that analyzed only functional endpoints. These earlier trials, including those with an ICD, were intended primarily for U.S. Food and Drug Administration approval for a specific device. However, the COMPANION trial was a serious scientific trial designed by some of the top experts in the heart failure and ICD world. Its design features and endpoints were chosen to clarify whether CRT alone or in combination with an ICD will improve mortality and morbidity in heart failure patients.

The COMPANION enrollment criteria included patients in NYHA class III or IV heart failure, normal sinus rhythm, QRS duration 120 ms or more, PR interval 150 ms or more, LVEF 35% or less, and left ventricular end-diastolic dimension 60 mm or more.⁵³ Enrolled patients were required to be taking optimal pharmacologic therapy (OPT) including a beta-blocker for at least 3 months, a diuretic, ACE inhibitor or ARB, and spironolactone for 1 month. Furthermore, patients had to have a history of a hospitalization for heart failure in the year before enrollment. Patients were randomized in a 1:2:2 strategy to OPT alone, OPT with CRT, or OPT with CRT-D. The primary end point of the trial was the time to all-cause mortality or all-cause hospitalization. A secondary end point was all-cause mortality.

The randomization was very consistent across all three groups. More than 80% of the patients were in NYHA class III rather than class IV heart failure. Also, the mean EF of the enrolled population was between 20% and 22%, which is only slightly lower than that of MADIT II (which was 23%). QRS duration averaged 158–160 ms, with approximately 70% of the patients having LBBB rather than right bundle branch block. Despite the fact that the use of beta-blockers and ACE inhibitors was required for enrollment, only 70% of the population was on ACE inhibitors, and 66–68% were on beta-blockers at the time of randomization. This demonstrates the difficulty in maintaining patients on these drugs even in a carefully controlled research environment.

The main reason that the primary endpoint of the COMPANION trial was met was the very high event rate (68%) in the OPT group. Both CRT and CRT-D reduced the primary endpoint by 20%

Figure 2. The Kaplan–Meier estimates of death from any cause for the prespecified subgroups of NYHA Class II (Panel A) and Class III (Panel B) in the SCD-HeFT Trial is shown. There was no apparent risk reduction of death in ICD therapy in Class III patients compared with placebo (HR 1.16)

(P value 0.008 for CRT and 0.007 for CRT-D). Although only 1600 patients were enrolled, the high event rate of the OPT group allowed the primary end point to be successfully reached. This was a fortuitous outcome as enrollment in the COMPANION trial slowed significantly after the commercial release of CRT-ICDs based on the aforementioned trial data.

The end point of greatest interest to the EP community was the effect of CRT-D on the secondary endpoint of all-cause mortality. The 12-month mortality of the OPT group was 19% and was double that at 24 months. CRT alone reduced 1-year mortality by 24% ($P = 0.06$), and CRT-D reduced the 1-year mortality by 43% ($P = 0.003$) compared to OPT (Fig. 2).

It is important for the clinician to appreciate that only 54% to 59% of the patients in this trial (depending on which arm is being considered) had an ischemic cardiomyopathy. It also appears that the CRT benefit was equal for NYHA class III and class IV patients. QRS width affected survival, with the greatest benefit for those patients with the widest QRS (>168 ms) and those with LBBB rather than RBBB. ACE inhibitor use had little impact on outcome, although β -blocker use was associated with a significantly more favorable outcome.

Based on these data, there is now scientific evidence to support the concept that CRT-D reduces heart failure mortality. The COMPANION trial showed that two thirds of this effect can be attributed to CRT alone, whereas one third is attributable to the ICD. Thus, all patients considered for CRT in 2005 are candidates for a back-up ICD as well.

Two additional trials have been completed that further extended the role of CRT. The Cardiac Resynchronization Heart Failure (CARE-HF) trial showed that in low EF patients, CRT both improved quality of life and reduced mortality.⁶⁸ A total of 813 patients with systolic dysfunction and cardiac dyssynchrony were randomized to either CRT or medical therapy. The primary end point was time to death from any cause or an unplanned hospitalization of a major cardiovascular event, primarily heart failure: total mortality was a secondary end point. There were a total of 82 deaths in the CRT group compared to 120 deaths in the medical therapy group (hazard ratio: 0.64; 95% confidence interval 0.48–0.85; $P < 0.002$). Quality-of-life end points were also improved with CRT. This trial extended the impact of COMPANION by showing that CRT alone (not CRT with an ICD as in COMPANION) improved survival. Most electrophysiologists have been implanting ICDs with CRT although this varies from country to country. The COMPANION trial clearly showed an additional survival impact of the ICD with CRT, which should also apply to the CARE-HF population.

The recently completed MIRACLE ICD II trial studied patients with NYHA Class II heart failure and $EF \leq 35\%$ and a $QRS \geq 130$ ms as well as a Class I indication for an ICD.⁶⁹ This was a small trial of 186 patients randomized to either medical therapy or CRT; both received an ICD. Although some indices improved in the CRT group at 6 months (remodeling indices, e.g., LV systolic and diastolic volumes, and LVEF), there was no difference in quality of life or 6-minute walk (Fig. 3). Larger trials will determine the impact of CRT and mortality and heart failure in NYHA Class I and II patients.

CONCLUSION

Few, if any, technological breakthroughs in clinical EP have evolved as quickly as the ICD and CRT. The impact of these devices on patients with end-stage heart failure has been an important clinical adjunct to routine background medical therapy. This field has changed so rapidly that the clinician still wrestles with the problems of how far to extend prophylactic ICD therapy to the heart failure population and which patients should be selected for CRT therapy and, in turn, for CRT-D therapy. A North American Society of Pacing and Electrophysiology (NASPE) Consensus Conference on Resynchronization Therapy for Heart Failure held in 2002

Figure 3. The Kaplan–Meier estimates of the time to the primary end point (Panel A) and the principal secondary end point (Panel B) is shown. The primary end point was death from any cause or an unplanned hospitalization for a major cardiovascular event. The principal secondary outcome was death from any cause. Note that CRT alone (Panel B) improved survival in this study in contrast to the COMPANION study.

noted that although much progress has been made, there are many issues that still must be resolved.⁷⁰ These include the long-term benefit of device therapy, the need for further evolution of the devices themselves to assure successful implantation, studies to help optimize programmability, identification of the patient population most likely to benefit, the importance of the economic and ethical ramifications, and the critical full buy-in on the part of the Government to the importance of good science in this regard.

One of the major challenges for the next few years is to ascertain whether we can extend the indications for CRT by implanting these devices in patients with CAD, a low EF (in the 30% range), a wide QRS (≥ 120 ms), and in NYHA class I or

II. Such a study is MADIT CRT, which will test the hypothesis that these high-risk patients who receive CRT will have a reduced rate of heart failure or all-cause mortality. This important protocol was initiated in December 2004 and will enroll 1700 patients over 2 years. A similar study called Biventricular Pacing to Inhibit Heart Failure Progression (BLOCK-HF) will evaluate the potential benefit of CRT on heart failure progression. There are important design differences between MADIT CRT and BLOCK-HF, although both seek to answer the question as to whether CRT benefits patients before they progress to NYHA class III or IV heart failure. Trials such as these will further enhance our knowledge and ability to treat SCD in heart failure.

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Michel Mirowski and Morton Mower

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