Device Trials in Heart Failure: A Focused Summary

Olaf Hedrich, MD, Jonathan Weinstock, MD, Mark Link, MD, Munther Homoud, MD, N.A. Mark Estes, III, MD

The New England Cardiac Arrhythmia Center, Division of Cardiology, Tufts-New England Medical Center, Boston, MA

Despite considerable progress in heart failure management with pharmacologic agents, measures to bring about significant improvements in morbidity and mortality are still needed. Cardiac resynchronization therapy (CRT) is a means to enhance myocardial function by stimulating the failing left ventricle at or near the time of right ventricular activation to synchronize ventricular depolarization. Current data from randomized, controlled trials suggest that CRT benefits patients with moderate to severe heart failure and have shown that this therapy significantly reduces mortality and hospital admissions in this group. In addition to CRT, implantable cardioverter-defibrillators have been evaluated in heart failure patients with significantly reduced left ventricular function and have been shown to reduce mortality from sudden cardiac death. This article summarizes recent device trials and discusses how best to apply their results to clinical practice.

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The problem of heart failure (HF) is formidable in scope, both in terms of prevalence and incidence. Almost 5 million Americans have HF, a further 550,000 are diagnosed with HF annually, and HF represented the primary diagnosis for approximately 1 million hospital discharges in 2001.[1] The growth of this epidemic appears to be correlated with an increasingly aged population and the increasing survival of patients presenting with large

myocardial infarctions, and is associated with significant morbidity, mortality, and expense.[2] Despite considerable progress made in the management of HF utilizing several pharmacologic agents (including β-blockers, angiotensin-converting enzyme inhibitors, and aldosterone antagonists), measures to bring about significant additional improvements in morbidity and mortality are still needed.

Ventricular dyssynchrony manifests as abnormal ventricular electromechanical coupling, usually (but not always) associated with an intraventricular conduction delay (QRS ≥ 120 milliseconds on surface electrocardiogram, most commonly in a left bundle branch block [LBBB] pattern). Such crude estimation of ventricular dyssynchrony has been applied to several large HF cohorts, and, in this manner, has been shown to occur in 27% to 53% of patients with HF with reduced left ventricular ejection fraction (LVEF).[3] Moreover, ventricular dyssynchrony appears to imply an increased risk for mortality. In a recent Italian study of 5517 HF outpatients, 1391 (25%) had an LBBB, which was associated with a 1-year total mortality hazard rate of 1.7, and a 1-year hazard rate of mortality by sudden cardiac death of 1.6, when compared with patients without LBBB.[4]

Sufficient evidence exists supporting the deleterious effects of ventricular dyssynchrony, which is both a result of, and a contributor to, the syndrome of HF.[5,6] Dyssynchrony (by whatever mechanism, intrinsic or pacer induced) may promote remodeling in such patients, as supported by observations made in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial.[7] In this trial, patients with an implantable cardioverter-defibrillator (ICD) who were paced in a dual-chamber rate-responsive mode ≥ 70 beats per minute (bpm) experienced greater mortality and HF hospitalizations at 1 year than did the group randomized to ventricular backup pacing at 40 bpm.

Cardiac resynchronization therapy (CRT) improves symptoms, quality of life (QOL), and exercise capacity by stimulating the failing left ventricle at or near the time of right ventricular activation in order to synchronize ventricular depolarization. CRT has been demonstrated to reverse ventricular remodeling consistently in randomized, placebo-controlled, prospective trials,[8] and an extensive body of data has been assembled about this new therapy. The following paragraphs aim to summarize these trials in a structured manner to allow greater understanding of the evolution of the principles guiding the development of CRT, as well as how best to apply their results to clinical practice.

It is of note that trial endpoints (clinical status/New York Heart Association functional class, quality-of-life scores, distance covered in 6-minute walk tests, and hemodynamic parameters) showed significant improvement with CRT in both observational and randomized cohort trials.

CRT Trials

Early Observational Trials

In the 1990s, several observational cohort trials were conducted to evaluate atrial-synchronized biventricular pacing. Overall, patient numbers were small and trials were mostly conducted over a short period of time without long-term follow-up. These trials are well described in summary elsewhere,[9] but it is of note that trial endpoints (clinical status/New York Heart Association [NYHA] functional class, quality-of-life [QOL] scores, distance covered in 6-minute walk tests [6MWT], and hemodynamic parameters) showed significant improvement with CRT in all these trials. As a result of these favorable outcomes, randomized, controlled trials have been conducted subsequently to evaluate the long-term effects of biventricular pacing.

Contemporary Trial Designs

Two broad groups of randomized, controlled CRT trials have emerged in the recent era of intensified device therapy for HF. Whereas some trials have aimed to solidify the notion that clinical improvement occurs with CRT, others have attempted to demonstrate the effect of CRT on mortality and other hard outcomes. Accordingly, trial endpoints to be kept in mind when interpreting their findings include NYHA functional class, QOL scores, 6MWT, peak oxygen consumption (VO_2), and echocardiographic parameters (including LVEF, cardiac output, ventricular filling patterns, and wall motion indices), as well as effects on hospital admissions for HF (accepted to represent a surrogate for clinical improvement or decline) and mortality rates.

Recent trials have been designed either as crossover trials, in which patients receive biventricular pacing for a period of time followed by a period of no (or univentricular) pacing (or vice versa), or as parallel trials, in which 2 groups of patients are assigned different therapies and are followed concurrently. Both have limitations and advantages.

Table 1
Cardiac Resynchronization Therapy: Crossover Trials

Study	Patients, N*	NYHA Functional Class (Baseline)	CAD, %	Patient Characteristics	Results
PATH CHF[10,11]	42	III, IV	30	Ischemic or nonischemic CMP; Moderate to severe HF with IVCD; Univentricular vs biventricular pacing (epicardial LV)	Trend toward improvement in peak VO_2, 6MWT, and secondary endpoints (NYHA class, QOL, HF hospitalization frequency)
MUSTIC SR[12,13]	47	III	37	Ischemic or nonischemic CMP; Moderate HF; Biventricular vs no pacing; Normal sinus rhythm	Significant improvement in primary endpoint of 6MWT; All secondary endpoints improved significantly (QOL, NYHA class, peak VO_2, hospital admissions, worsening HF, total mortality)
MUSTIC AF[14]	41	III	43	Ischemic or nonischemic CMP; Moderate HF; Biventricular vs no pacing; Chronic atrial fibrillation; RV paced QRS > 200 ms	All primary and secondary endpoints in MUSTIC AF also improved to statistically significant degree, although magnitude of improvement was less than in MUSTIC SR

*Number of patients completing crossover protocol.
CAD, proportion of patients with coronary artery disease; CMP, cardiomyopathy; HF, heart failure; ICD, implantable cardioverter-defibrillator; IVCD, intraventricular conduction delay; LV, left ventricle; LVEF, left ventricular ejection fraction; MUSTIC AF, Multisite Stimulation in Cardiomyopathy, Atrial Fibrillation; MUSTIC SR, Multisite Stimulation in Cardiomyopathies, Sinus Rhythm; 6MWT, 6-minute walk test distance; NYHA, New York Heart Association; PATH CHF, Pacing Therapies in Congestive Heart Failure; QOL, quality of life; RV, right ventricle; VO_2, oxygen uptake; VT/VF, ventricular tachycardia/fibrillation.

Crossover Trials

A comparison of the crossover CRT trials is given in Table 1.

Pacing Therapies in Congestive Heart Failure (PATH CHF) Trial

The PATH CHF trial[10,11] was a small single-blinded, randomized crossover controlled trial (42 patients) that assigned patients with NYHA class III and IV HF (mean LVEF 21%) and intraventricular conduction delay to best univentricular pacing versus biventricular pacing. This study demonstrated a trend toward improvement in peak VO_2, 6MWT, and secondary endpoints including NYHA class, QOL, and HF hospitalization frequency. Its results complement several other crossover studies.

Multisite Stimulation in Cardiomyopathy (MUSTIC) Studies

The MUSTIC trial[12,13] was also a single-blinded, randomized crossover trial that comprised 2 subsets of patients. It was designed to evaluate the safety and efficacy of CRT in patients with moderate HF (NYHA class III, LVEF < 35%), ventricular dyssynchrony (QRS > 150 milliseconds), and left ventricular cavity enlargement (left ventricular end-diastolic dimension > 60 mm) whose medical regimen had been optimized, and who had no standard indication for pacing. Patients were randomized to 3 months of active biventricular pacing (MUSTIC was the first randomized, controlled trial to use a transvenous approach for left ventricular lead placement) or no pacing, then were crossed over to the alternative assignment for 3 months.

Forty-seven patients in sinus rhythm completed both phases (MUSTIC SR group). The primary endpoints were measures of exercise tolerance (6MWT and peak VO_2). During the active-pacing phase, the mean 6MWT increased by 23% compared with the inactive phase ($P < .001$). All other measured parameters, including endpoints for improvement in QOL, NYHA class, need for rehospitalization, or drug therapy modification for worse HF, showed significant improvement in the active-paced phase.

A further 41 patients with chronic atrial fibrillation completed the trial (MUSTIC AF group). These patients had indications for pacing because of

slow ventricular rate and consequently were assigned to biventricular ventricle-paced, ventricle-sensed, inhibited, rate-responsive (VVIR) pacing versus single-site right ventricular VVIR pacing. Ventricular dyssynchrony in this group was determined by a paced QRS > 200 milliseconds. Similar endpoints were evaluated in the atrial fibrillation group, which showed smaller, although still significant, improvements in primary and secondary endpoints.

In long-term follow-up of the MUSTIC SR population, results reveal that the benefits apparent after short-term therapy persist over 1 year of therapy compared with baseline: 6MWT increased by 20%, peak VO_2 increased by 11%, QOL increased by 36%, NYHA class improved by 25%, LVEF improved by 5%, and mitral regurgitation improved by 45%.[14] All of these were highly significant. Again, lesser yet still significant improvements persisted in the atrial fibrillation group.

Parallel Trials

A comparison of the parallel CRT trials is given in Table 2.

Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Trial

The randomized, double-blinded, parallel-controlled MIRACLE trial[15] was completed in 2000 and attempted to confirm the results of previous CRT studies and to assess efficacy and safety of biventricular pacing in a group of 453 patients with either ischemic or nonischemic cardiomyopathy, moderate to severe HF (NYHA class III or IV), LVEF ≤ 35%, and QRS duration ≥ 130 milliseconds. Patients (who did not meet traditional criteria for permanent pacing or ICD) were

Table 2
Cardiac Resynchronization Therapy (CRT): Parallel Trials

Study	Patients, N	NYHA Functional Class (Baseline)	CAD, %	Patient Characteristics	Results
MIRACLE[15]	453	III, IV	54	Ischemic or nonischemic CMP; Moderate to severe HF, LVEF ≤ 35%, QRS ≥ 130 ms; 228 in CRT group, 225 in control group	Significant improvement in NYHA class, exercise capacity, QOL, cardiac function, and chamber dimensions (echocardiographically); reduced HF events; improvement in combined morbidity and mortality outcome
MIRACLE ICD[16]	369	III, IV	69	Ischemic or nonischemic CMP; Moderate to severe HF, LVEF ≤ 35%, LVEDd > 55 mm, QRS ≥ 130 ms, with indication for ICD	Improvement in NYHA class, exercise capacity, QOL
COMPANION[17,18]	1520	III, IV	55	Ischemic or nonischemic CMP; Moderate to severe HF, QRS ≥ 120 ms, without indication for ICD or permanent pacemaker	CRT-P 34% reduction in total mortality and HF hospitalizations ($P < .001$); CRT-D 40% reduction in total mortality and HF hospitalizations ($P < .001$)
CONTAK CD[19,20]	581	II-IV	69	Ischemic or nonischemic CMP; Symptomatic HF, IVCD, LVEF < 35%, indication for ICD	Trends toward improvement in combined primary endpoint of mortality, HF hospitalization, and VT/VF; Significant improvement in peak VO_2, 6MWT, QOL, NYHA class, LV end-diastolic and end-systolic dimensions
MIRACLE ICD II[21]	186	II	55	LVEF ≤ 35%, QRS ≥ 130 ms, class I ICD indication	Significant improvement in cardiac structure and function and composite clinical response over 6 months; no alteration of exercise capacity

CAD, proportion of patients with coronary artery disease; CMP, cardiomyopathy; COMPANION, Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure; CRT-D, CRT with ICD; CRT-P, CRT pacing; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; LVEDd, left ventricular end-diastolic dimension; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MIRACLE ICD, Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator; NYHA, New York Heart Association; QOL, quality of life.

randomized to a cardiac resynchronization group (n = 228) or to a control group without pacing (n = 225). Patients were followed in their respective groups for 6 months, after which the control patients were allowed to cross over to active pacing. Primary endpoints included change in NYHA class, QOL score, and 6MWT distance. A secondary endpoint measured a composite of several indicators of HF response, including metabolic testing, cardiac structural and functional changes, and cytokine and neurohormone levels, as well as a combined measure of HF morbidity and all-cause mortality (the trial was not sufficiently powered to allow evaluation of mortality endpoints alone). The CRT patients demonstrated significant improvement in all primary and secondary outcomes. The CRT group required fewer hospitalizations (8% vs 15%, $P < .05$) or intravenous medications (7% vs 15%, $P < .05$) for worsening HF and experienced a 77% decrease in total hospitalization days ($P = .012$ for difference in hospital days) over the 6-month observation period. These effects were sustained beyond the initial 6-month follow-up period and were still evident at 12 months.

Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) Trial

The prospective, randomized, multicenter, double-blind, parallel-controlled MIRACLE ICD trial[16] was designed with inclusion criteria identical to those for the MIRACLE trial, with the exception that participants also met standard indications for ICD implantation. The aim was to determine the efficacy and safety of a combined biventricular pacing and ICD system in HF patients. Endpoints were the same as in the MIRACLE trial, with additional measures of ICD function, including the efficacy of antitachycardia pacing with biventricular therapy. Three hundred sixty-nine participants were randomized either to active resynchronization therapy (n = 187, ICD active and biventricular pacing on) or to a control group (n = 182, ICD active and biventricular pacing off). The extent of improvement in HF endpoints was similar to that observed in MIRACLE. After a 6-month follow-up period, the CRT group showed significant improvement in NYHA class, QOL score, peak VO_2, and treadmill exercise duration. Trends toward benefit were recorded for survival and rates of hospitalization, but these studies were not powered to report comparisons of these parameters. From the standpoint of ICD function, important observations included the lack of proarrhythmia, lack of impairment of arrhythmia-terminating capability, and significantly greater efficacy of biventricular antitachycardia pacing than that seen in univentricular systems. These observations taken as a whole indicate that HF patients with an ICD indication benefit from CRT to a degree equivalent to those without an ICD indication.

Observations such as lack of proarrhythmia, lack of impairment of arrhythmia-terminating capability, and significantly greater efficacy of biventricular antitachycardia pacing than that seen in univentricular systems, taken as a whole, indicate that HF patients with an ICD indication benefit from CRT to a degree equivalent to those without an ICD indication.

Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) Trial

With the publication of data from the COMPANION trial,[17,18] important and powerful information regarding the mortality benefit of CRT in HF patients became available. This multicenter, prospective, randomized, controlled trial was event driven and designed to randomize 2200 patients into 1 of 3 treatment groups in a 1:2:2 scheme. Inclusion criteria were NYHA class III or IV HF with LVEF $\leq$ 35%, QRS duration $\geq$ 120 milliseconds and PR interval $>$ 150 milliseconds, and left ventricular end-diastolic diameter $\geq$ 60 mm. Three patient groups received optimal medical therapy as tolerated (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 90%; β-blockers, 68%; and spironolactone, 55%), but one of the groups also received a CRT device (CONTAK TR pacemaker; Guidant Corp., Indianapolis, IN) and another received a CRT device with defibrillation capability (CONTAK CD device; Guidant Corp.). The primary endpoint was a composite of all-cause mortality and all-cause hospitalization; secondary endpoints included all-cause mortality alone and indices of cardiovascular morbidity. The trial was terminated prematurely by a data and safety monitoring board after 1520 patients had been randomized, when a significant reduction of nearly 20% in the primary endpoint in the resynchronization groups compared with medical therapy alone was noted. This significant improvement was believed to be driven by a high event rate. As compared with optimal medical therapy alone, CRT decreased the risk of the primary endpoint (hazard ratio, 0.81; $P = .014$), as did CRT with ICD (hazard ratio, 0.80; $P = .01$). The risk

of the primary endpoint was reduced by 34% in the CRT group ($P < .002$) and by 40% in the CRT-ICD group ($P < .001$). Death by any cause was reduced by 24% in the CRT group ($P = .059$) and by 36% by CRT-ICD therapy ($P = .003$). Hence, COMPANION demonstrated that in patients with advanced HF and prolonged QRS duration, CRT decreases the combined risk of death from any cause and hospitalization and, when combined with an ICD, significantly reduces mortality.

CONTAK CD Trial

The CONTAK CD study (also known as the VENTAK CHF study)[19,20] was a randomized, controlled, double-blinded placebo-controlled trial comparing active CRT with no pacing in HF patients who had an established indication for an ICD. Patients had NYHA class II-IV (mostly III and IV) HF, LVEF ≤ 35%, and QRS > 120 milliseconds. The study was initially designed to be a 3-month crossover trial but was later changed to a 6-month parallel study. The primary composite endpoint comprised mortality, HF hospitalizations, and occurrence of ventricular tachycardia or fibrillation. Two hundred forty-eight patients were randomized into the 3-month crossover study and a further 333 into the 6-month parallel controlled trial. The primary endpoint failed to reach statistical significance in the CRT group, but there was a trend favoring the resynchronization group. Secondary endpoints, however, including peak VO_2, 6MWT, QOL score, NYHA class, and left ventricular dimensions, showed a clear, statistically significant improvement in the group randomized to active CRT.

Multicenter InSync ICD Randomized Clinical Evaluation II (MIRACLE ICD II) Trial

The MIRACLE ICD II Trial[21] was designed to evaluate the safety and efficacy of CRT in patients with mildly symptomatic heart failure. Specifically, patients with NYHA class II HF who were on optimal medical therapy with an LVEF less than or equal to 35%, a QRS at 130 ms or greater, and a Class I indication for an ICD were enrolled. The aim was to determine whether a CRT-ICD system in this population with mild HF would limit disease progression and improve exercise performance. Although the trial was not powered to detect hard clinical endpoint data, results at 6 months suggested improved ventricular remodeling indices (specifically LV diastolic and systolic volumes) and LV ejection fraction in the CRT-ICD group (85 patients) when compared to a control group of 101 patients (medical therapy and ICD only). Although no significant differences were noted in 6-minute walk distance or QOL scores, CRT patients did show significant improvement in NYHA class, a clinical composite response, and ventilatory response to exercise (V_E/V_{CO2}). These results may support the notion that CRT acts to limit disease progression in patients with mild HF symptoms.

COMPANION demonstrated that in patients with advanced HF and prolonged QRS duration, CRT decreases the combined risk of death from any cause and hospitalization and, when combined with an ICD, significantly reduces mortality.

In a further effort to determine whether minimally symptomatic HF patients might benefit from CRT, the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) Trial is presently enrolling patients. Five hundred patients with NYHA class I to II symptoms in US, Canadian, and European centers will be randomized to CRT-ICD therapy or ICD therapy alone, against a background of optimal medical therapy. After a follow-up period of 1 year, the patients in the ICD-only control group will begin receiving CRT therapy. The primary endpoint is a clinical composite score that measures key outcomes such as mortality, hospitalization for worsening HF, QOL, and symptoms. Secondary endpoints will include ventricular volumes and a cost analysis will be undertaken.

Meta-Analysis of Randomized, Controlled Trials

Before the publication of the COMPANION trial's findings, an effort to determine whether CRT reduces mortality from progressive HF (sudden cardiac death, one of the predominant modes of death in HF, accounting for the majority of the rest) was undertaken. Bradley and colleagues[22] published a meta-analysis of data from 4 randomized, controlled trials evaluating CRT in 1634 patients (CONTAK CD, MIRACLE, MUSTIC, and MIRACLE ICD). According to this analysis, CRT reduced death from progressive HF by 51% relative to controls and reduced HF hospitalization by 29%. Progressive HF mortality was 1.7% for CRT patients compared with 3.5% for controls. There was no statistically significant effect on non-HF mortality, although there was a trend toward reduction in all-cause mortality. It is hoped that ongoing mortality trials will yield data that will consolidate

our understanding of the impact of CRT on HF outcomes.

Indications for and Complications of CRT

Based on the available evidence to date, the rate of implantation of CRT devices may be expected to increase in the future. Accordingly, careful patient selection to ensure appropriate therapy and minimization of adverse events is mandated. This selection may be assisted by newer echocardiographic Doppler techniques, such as tissue Doppler imaging, to identify potential responders. The current criteria for selecting patients for CRT are determined primarily by the inclusion and exclusion criteria of the trials outlined above, as well as by U.S. Food and Drug Administration (FDA) labeling, particularly because sufficient cost-efficacy data are as yet not available. Table 3 summarizes the current American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology guidelines for CRT in patients with congestive HF.[23] Most existing data on complications are derived from individual trial reports. Although indications are that complication rates (particularly implantation failure and lead-related problems) are decreasing with improved devices and techniques as well as greater operator experience, important observations to be made in this regard are that 1) potential complications (involving the procedure or the hardware or programming of the device) are multiple and require expertise to diagnose and correct, 2) in combination with ICD backup, inappropriate shocks may be delivered as a result of double-counting, and 3) with appropriate candidate selection and device programming, complications may be minimized.[6-18]

Based on these studies, the FDA has currently approved CRT for patients with class III-IV HF on optimal medical therapy, provided they have a QRS duration $\geq$ 120 milliseconds and LVEF $\leq$ 35% in normal sinus rhythm. With this background of improvement in outcomes in patients with class III or IV HF with CRT therapy, a new trial—the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-CRT—has been designed. This study will test the hypothesis that CRT combined with ICD therapy will reduce all-cause mortality and HF hospitalizations by 25% in MADIT II–type patients and in patients with non-ischemic cardiomyopathy, with ejection fractions $\leq$ 30%, NYHA class I-II HF and a QRS duration $\geq$ 120 milliseconds. Patients will be randomized to a single-chamber ICD versus an ICD with CRT. Accordingly, this trial will determine if CRT can delay the onset or worsening of HF as opposed to treatment of the condition.

Beyond all of these findings and indications, the newly-published CARE-HF trial showed further benefit from CRT coupled with standard medical therapy in patients with NYHA class III and IV heart failure due to LV systolic dysfunction and cardiac dyssynchrony. Cleland and associates[24] reported favorable effects from CRT, based on symptoms, quality of life, ventricular function, and blood pressure, which were similar to those reported in previous trials. However, they also found CRT to reduce risk of death (20% at 29.4 months follow-up vs 30% in the medical therapy-only group). This effect was judged to be separate from and in addition to the benefits of standard pharmacologic therapy and was a new finding, not proved conclusively in earlier trials.

ICD Therapy Without CRT

Additional patient populations have been shown to benefit from ICD therapy without CRT for primary prevention of sudden cardiac death and improvement in total mortality.[25-29] The patient populations in the MADIT I trial include those with ischemic heart disease, LVEF $\leq$ 35%, spontaneous nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia.[25] In the MADIT II trial, patients with prior myocardial infarction and an LVEF $\leq$ 30% and no arrhythmia qualifier benefited from ICD therapy without CRT.[26] This mortality benefit was also seen in similar patients

Table 3
ACC/AHA/NASPE Guidelines for Cardiac Resynchronization Therapy in Patients With Congestive Heart Failure (Class IIA/Level of Evidence: A)*

Medically refractory advanced heart failure (NYHA class III/IV)
Optimal pharmacologic regimen
LVEF $\leq$ 35%
QRS complex duration $>$ 120 ms
Normal sinus rhythm
With or without indication for ICD

ACC/AHA/NASPE, American College of Cardiology/American Heart Association/North American Society of Pacing and Electrophysiology; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

*Data from Moss et al.[25]

in the Multicenter Unsustained Tachycardia Trial (MUSTT).[27] In this study, patients with prior myocardial infarction, LVEF ≤ 40%, spontaneous nonsustained ventricular tachycardia, and inducible sustained ventricular tachycardia were randomized to no therapy or antiarrhythmic therapy guided by electrophysiologic studies or ICD. The ICD in this trial also was found to result in a reduction in arrhythmic death and cardiac arrest.[27] In MADIT I, MADIT II, and MUSTT, more than 60% of the patients had class II or III HF.[25-27]

More recently, ICD therapy without CRT for primary prevention of sudden cardiac death demonstrated a mortality benefit in those with class II-III HF, LVEF < 35%, and ischemic or nonischemic cardiomyopathy in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[28] The SCD-HeFT trial was designed to evaluate the hypothesis that amiodarone or a single-chamber ICD (model # 7223, Medtronic, Inc., Minneapolis, MN) would decrease the risk of death from any cause in a broad population of patients with mild to moderate HF. Patients (n = 2521) were randomly assigned to conventional therapy for HF plus placebo, conventional therapy plus amiodarone, or conventional therapy plus a single-chamber ICD. The primary endpoint was death from any cause and median follow-up was 45.5 months. Seventy percent of patients were in NYHA class II, with the remainder in class III HF. As compared with placebo, ICD therapy was associated with a 23% decrease in relative risk of death (hazard ratio 0.77, $P = .007$) and a 7.2% absolute decrease in mortality. Amiodarone had no favorable effect on survival.

Among patients with NYHA class III HF, there was a relative 44%

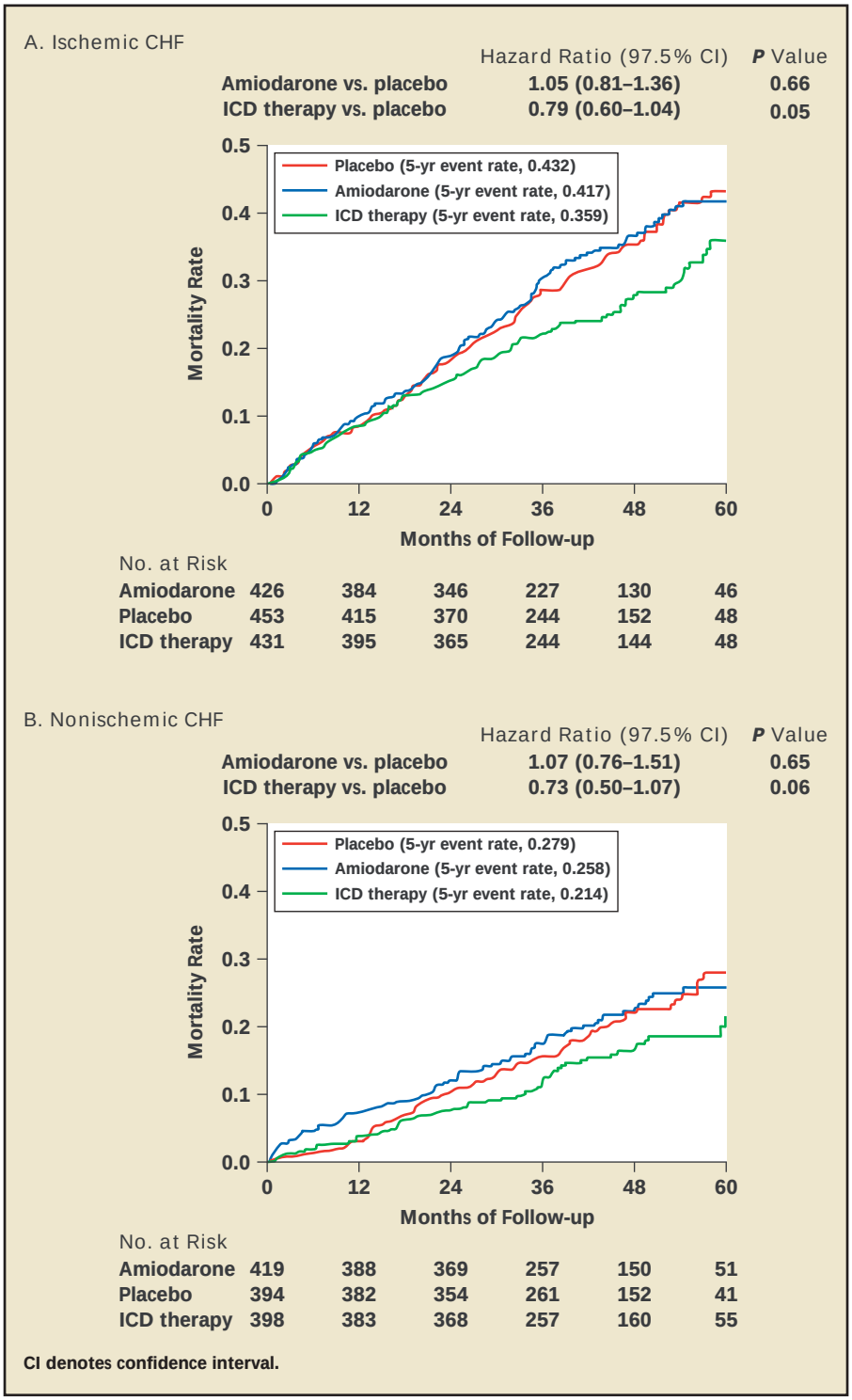

Figure 1. *Kaplan-Meier estimates of death from any cause for the prespecified subgroups of ischemic* **(A)** *and nonischemic* **(B)** *chronic heart failure. Reproduced with permission from Bardy et al.*[28]

increase in the risk of death in the amiodarone group compared to placebo whereas there was no excess mortality risk among patients with NYHA class II HF. ICD therapy in class II patients led to a 46% relative reduction in mortality whereas patients in class III had no apparent reduction in mortality risk. Thereby, SCD-HeFT substantiated previous clinical trial evidence showing a benefit of ICD therapy in patients with ischemic cardiomyopathy and provided new data showing mortality benefit in patients with non-ischemic cardiomyopathy (Figure 1).

Interestingly, NYHA subgroup analysis revealed a significant benefit in NYHA class II but not class III HF patients. This unanticipated subgroup effect should probably be interpreted cautiously, as other large trials (MADIT II, DEFINITE) reported survival benefit in NYHA class III patients. These data should therefore not be seen as sufficient basis for withholding ICD therapy from patients in NYHA class III. A further point to be emphasized in this study is that ICD device selection was particularly conservative, and it is not clear (although it seems intuitive) that one can extrapolate the results in SCD-HeFT to other permutations of ICD therapy involving dual-chamber or biventricular pacing.

There was also a strong trend toward improved survival in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial with ICD therapy in patients with nonischemic cardiomyopathy.[29] Patients (n = 458) with non-ischemic dilated cardiomyopathy with an LVEF of 35% or lower and premature ventricular complexes or nonsustained ventricular tachycardia were enrolled. The majority of patients were in NYHA class II (57.4%), but class I (21.6%) and class III (21.0%) patients were included. Patients were randomized to conventional medical therapy alone or to conventional medical therapy plus a single-chamber ICD, and were followed for a mean of 29 (± 14.4) months. Fewer patients died in the ICD group than in the standard-therapy group (28 vs 40), and the overall difference in survival approached statistical significance but did not attain it ($P = 0.08$). The implantation of an ICD did, however, seem to reduce the risk of death from arrhythmia significantly. Of the seventeen sudden deaths adjudicated as being arrhythmic in etiology, only 3 occurred in the ICD group (hazard ratio 0.20, $P = .006$). Although the study was not powered to detect differences within subgroups, implantation of an ICD most significantly reduced the risk of death among patients with NYHA class III HF and among men. Again, these data must be applied cautiously, and may highlight the need for case-by-case consideration prior to ICD implantation.

The U.S. Centers for Medicare and Medicaid Services (CMS) recently issued a long-awaited decision proposal that significantly expands ICD coverage in the Medicare population.

The U.S. Centers for Medicare and Medicaid Services (CMS) recently issued a long-awaited decision proposal that significantly expands ICD coverage in the Medicare population.[30] The proposal is based largely on results from SCD-HeFT and extends ICD coverage to include patients with ischemic cardiomyopathy, a history of prior myocardial infarction, and an LVEF ≤ 35%, as well as those with nonischemic cardiomyopathy of > 9 months' duration with an LVEF ≤ 35%. In addition, this criterion does eliminate the previously imposed criterion of a long QRS duration following the publication of MADIT II, which limited ICD coverage to patients with QRS duration > 120 milliseconds.

Device Selection

Whereas individual patient characteristics and reimbursement policy play a role in directing the clinician's ultimate choice of whether to implant an ICD alone or a CRT system with or without defibrillator capability, contemporary data suggest that the patient subset likely to benefit from CRT will also likely derive benefit from an ICD. This may minimize the indication for biventricular pacing alone.

An as yet unanswered question is whether mild to moderate HF symptoms warrant therapy with CRT, the derived benefit ostensibly being a survival advantage. If this is indeed the case (as may be answered in trials such as MADIT-CRT and PRESERVE), current guidelines for CRT may be expanded to include less symptomatic patients. Whether crude estimations of dyssynchrony (such as QRS duration) will prevail will likely be determined by future trial inclusion criteria, which may incorporate more refined methods of quantifying ventricular dyssynchrony. Conceivably, CRT may demonstrate benefit in future study populations with mild or asymptomatic HF and narrow QRS width.

Using the best available current evidence, HF patients who derive benefit from an ICD include those with ischemic cardiomyopathy, a history of prior myocardial infarction,

and an LVEF of 35% or lower, as well as those with nonischemic cardiomyopathy of greater than 9 months' duration with an LVEF of 35% or lower. CRT is currently approved only for patients with class III-IV HF on optimal medical therapy, provided they have a QRS duration greater than 120 milliseconds and LVEF less than 35% in normal sinus rhythm.

Conclusion

In this era of aggressive HF management, targeted device therapy holds the potential for significant improvement in both clinical status and hard outcomes when appropriately added to optimum medical therapy. Current data derived from randomized, controlled trials suggest that CRT benefits patients with moderate to severe HF, and CRT has been shown to significantly reduce mortality and hospital admission in this group. This benefit is likely to be driven by reduced death from progressive HF. In addition to CRT, ICD therapy has been applied in patients with significantly reduced left ventricular function and has been shown to significantly reduce mortality from sudden cardiac death. Current recommendations for CRT and ICD in HF are limited to patients with moderate to severe HF who exhibit the specific inclusion criteria of subjects enrolled in recent clinical trials. Future directions include incorporating exciting advances in technology, identifying further patient populations who may benefit from these device therapies, identifying therapies suited to patients in atrial fibrillation, and identifying indications for combination CRT and ICD therapy. ■

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Main Points

- Cardiac resynchronization therapy (CRT) has been developed as a means to enhance myocardial function and improve symptoms, quality of life, and exercise capacity in heart failure patients by stimulating the failing left ventricle at or near the time of right ventricular activation in order to synchronize ventricular depolarization.
- Two broad groups of randomized, controlled CRT trials have emerged in the recent era of intensified device therapy for heart failure. Whereas some trials have aimed to solidify the notion that clinical improvement occurs with CRT, others have attempted to demonstrate the effect of CRT on mortality and other hard outcomes.
- Trial endpoints (clinical status/New York Heart Association functional class, quality-of-life scores, distance covered in 6-minute walk tests, and hemodynamic parameters) showed significant improvement in both observational and randomized controlled trials.
- The SCD-HeFT trial showed an overall mortality reduction of 23%. ICD therapy in NYHA class II patients led to a 46% relative reduction in mortality whereas patients with class III had no apparent reduction in mortality risk. SCD-HeFT thereby substantiates previous clinical trial evidence showing a benefit of ICD therapy in patients with ischemic cardiomyopathy and provides new data showing mortality benefit in patients with non-ischemic cardiomyopathy.
- Using the best available current evidence, HF patients that derive benefit from an implantable cardioverter-defibrillator include those with ischemic cardiomyopathy, a history of prior myocardial infarction, and an LVEF of 35% or lower, as well as those with nonischemic cardiomyopathy of greater than 9 months' duration with an LVEF of 35% or lower.

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