

FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY**VIEWPOINT AND COMMENTARY**

Why Should We Care About CARE-HF?

Kenneth A. Ellenbogen, MD, FACC,* Mark A. Wood, MD, FACC,* Helmut U. Klein, MD, FACC†
Richmond, Virginia; and Magdeburg, Germany

Previous trials of cardiac resynchronization therapy (CRT) have suggested that this therapy can significantly improve functional class and exercise capacity during short-term follow-up. The impact of this therapy on morbidity and mortality has only recently been reported. The Cardiac Resynchronization-Heart Failure (CARE-HF) study has definitively shown that CRT significantly reduces mortality (36%, $p < 0.002$) in patients with NYHA functional class III and IV heart failure and ventricular dyssynchrony. This study also shows that CRT reverses ventricular remodeling and improves myocardial performance progressively for at least 18 months. In heart failure patients, the CARE-HF and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) (the earlier major morbidity/mortality trial) studies together show the unequivocal benefit for CRT therapy and CRT therapy with back-up defibrillation to significantly reduce mortality and hospitalization compared with optimal medical therapy. Both studies suggest the benefit of adding the implantable cardiac defibrillator to CRT devices, as over one-third of deaths in the CRT-pacemaker arm of both the COMPANION and CARE-HF studies were sudden. (J Am Coll Cardiol 2005;46:2199–203) © 2005 by the American College of Cardiology Foundation

The Cardiac Resynchronization-Heart Failure (CARE-HF) trial (1) is the latest in a series of prospective randomized clinical trials that evaluate the benefits of cardiac resynchronization therapy (CRT). Early trials dating back more than a decade have shown significant improvement in New York Heart Association (NYHA) functional class, exercise time, quality of life, and oxygen consumption during metabolic testing (2–11). These early trials followed patients for up to six months in a blinded fashion. Non-invasive cardiac testing showed an increase in ejection fraction as well as a decrease in left ventricular end diastolic and end systolic volumes. These early trials enrolled an insufficient number of patients to look at hard clinical end points, including total mortality, cardiovascular mortality, and hospitalization. A meta-analysis suggested a benefit of CRT therapy with respect to mortality and hospitalization (12).

In March 2005, the results of the CARE-HF trial were presented at the American College of Cardiology by Dr. John Cleland on behalf the CARE-HF study investigators (1). This is an important trial that adds significantly to our knowledge about the effects of CRT therapy. As a starting point, we wish to recognize several “firsts” accomplished by the CARE-HF study: 1) the first study to show a benefit for CRT pacemaker (CRT-P) alone with respect

to survival as a single end point; 2) the first study to show a benefit for CRT-P for up to 18 months, and continued improvement over time; 3) the first study to show that neurohormonal measures (e.g., N-terminal pro-brain natriuretic peptide) improve dramatically with CRT, and 4) the first study to use direct measures of dyssynchrony as an inclusion criteria. At the same time, it is important and comforting to us, who have begun using CRT therapy routinely for appropriately selected patients, to see that the results of the CARE-HF study are entirely consistent with those of other major trials. The benefits of CRT shown in the CARE-HF study with regard to improved functional class, improved ventricular function, improved quality of life, and reduced mitral regurgitation have now been established by so many previous CRT trials that we will focus our attention almost entirely on the reduction in mortality and morbidity, which were the primary end points of this trial. Here the major contribution to cardiovascular science of the CARE-HF study is the reinforcement and extension of the results from the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (13). The COMPANION trial randomized 1,520 patients with NYHA functional class III to IV congestive heart failure (just as in the CARE-HF study) to optimal pharmacologic therapy (OPT) versus OPT plus CRT-P (biventricular pacing alone) versus CRT-D (biventricular pacing plus back-up defibrillation by implantable cardiac defibrillator [ICD]). The COMPANION trial showed a 20% reduction ($p = 0.01$) in the combined end point of hospitalization and mortality for both CRT and CRT-D, compared with OPT, and showed that CRT-D reduced all-

From the *Department of Medicine, Virginia Commonwealth University School of Medicine, Richmond, Virginia; and the †Division of Cardiology, University Hospital, Magdeburg, Germany. Dr. Ellenbogen has received honoraria and research grants from Medtronic, Guidant, and St. Jude Medical. Dr. Wood has served as a consultant to Medtronic, and has received research grants from Medtronic and St. Jude Medical. Manuscript received March 29, 2005; revised manuscript received July 12, 2005, accepted July 18, 2005.

Abbreviations and Acronyms

CARE-HF	= Cardiac Resynchronization-Heart Failure study
COMPANION	= Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure study
CRT	= cardiac resynchronization therapy
CRT-D	= cardiac resynchronization therapy pacemaker plus back-up defibrillation (implantable cardiac defibrillator)
CRT-P	= cardiac resynchronization therapy pacemaker
ICD	= implantable cardiac defibrillator
MERIT-HF	= Metoprolol Randomized Intervention Trial in Congestive Heart Failure
NYHA	= New York Heart Association
OPT	= optimal pharmacologic therapy

cause mortality by 36% ($p = 0.003$) with respect to OPT. Because the COMPANION trial was not designed and powered to be able to show mortality reduction with CRT-P alone, and its results only showed a trend toward mortality reduction with CRT-P (hazard ratio, 0.76; $p = 0.059$), uncertainty remained regarding whether CRT-P did indeed reduce mortality, and that question has now been unequivocally resolved by the CARE-HF study.

Another important message from the CARE-HF study is the reassuring finding that the advantages of CRT therapy, vis-a-vis best medical management, continue to increase over time, at least through 18 months. This information is over and above what we learned from the COMPANION trial, because that trial had too few patients in follow-up past 12 months to be able to conclude anything beyond one year. The follow-up was shorter in the COMPANION trial than in the CARE-HF study because the COMPANION trial was stopped by the data and safety monitoring committee when the number of primary end points was achieved. This occurred relatively early in follow-up because the patients had much more advanced heart failure and left ventricular dysfunction in the COMPANION trial than in the CARE-HF study. The control group mortality at 12 months in the CARE-HF study was 12.6%, and in the COMPANION trial was 19%. The combined incidence of hospitalization for congestive heart failure plus mortality is almost two times higher in the COMPANION trial than it was in the CARE-HF study. Most importantly, this is the first large trial to show a benefit in a biomarker with CRT therapy (e.g., a surrogate measure of congestive heart failure severity). Prior large studies have failed to show improvements in neurohormonal measures, including epinephrine, norepinephrine, dopamine, endothelin, and brain natriuretic peptide levels. The reason that prior trials failed to show a consistent improvement in biomarkers with CRT therapy may be partially explained by small sample size or inadequate follow-up. What is interesting about the CARE-HF study is that there was a non-significant de-

crease in N-terminal pro-brain natriuretic peptide at three months that was dramatically lowered by over 1,100 pg/ml at 18 months. This change should be dramatic enough to convince even the biggest skeptics of CRT therapy.

Clearly, one of the most important contributions of the CARE-HF study is that it has answered the question of whether CRT-P reduces mortality. It does. A thorough analysis of the CARE-HF study and the COMPANION trial together shows that we now understand better the meaning of add-on therapies (in terms of CRT-D therapy, adding defibrillation). The modern management of heart failure began with randomized clinical trials showing the value of first adding angiotensin-converting enzyme inhibitors to the then standard medical therapy for heart failure (e.g., diuretics and digoxin), which reduced mortality by 15% to 31% (14,15). Next a large number of studies showed the value of adding beta-blockers to angiotensin-converting enzyme inhibitors, achieving an additional approximately 33% reduction in mortality (16–18). The CARE-HF study, and the COMPANION trial, as well as virtually every CRT trial, added CRT on top of OPT medical therapy, now also including aldosterone antagonists. The CARE-HF study shows that CRT on top of medical therapy (70% with beta-blockers, 95% with angiotensin-converting enzyme or angiotensin receptor blocker inhibitors, and 50% with aldosterone inhibitors) will further reduce mortality by approximately one-third. The COMPANION trial, on the other hand, showed that the inclusion of an ICD integrated within the CRT system—CRT-D—substantially decreases the non-negligible sudden death mortality that remains, despite OPT and CRT-P.

There is a note of caution that we feel obliged to emphasize with regard to interpretation and clinical implications of the CARE-HF study. Based on the fact that the relative mortality reduction with CRT alone in the CARE-HF study was approximately the same as with CRT-D in the COMPANION trial, some people may infer that a CRT-P alone suffices. That would be an incorrect understanding of the key findings of the two studies: one-third of the deaths that occurred in the CARE-HF study were sudden. A back-up defibrillator, i.e., CRT-D, would have prevented many of these sudden deaths. Figure 1 shows the percentage of deaths that were sudden in these two studies. In the COMPANION trial, 36% of the deaths in the CRT-P arm were sudden, very similar to the 35% in the CARE-HF study. In the absence of ICD back-up, both studies showed that despite the evident benefits of CRT-P therapy, one-third of the fatalities were attributable to sudden death. As seen in Figure 1, the CRT-D arm of the COMPANION trial reduced the sudden cardiac death incidence to 16%, a 55% relative risk reduction for sudden cardiac death. In terms of absolute mortality, 7% of patients in the CRT arm of the CARE-HF study died suddenly, compared with only 2.9% in the CRT-D arm of the COMPANION trial. A comparison of the cost effectiveness of CRT-P with CRT-D has not yet

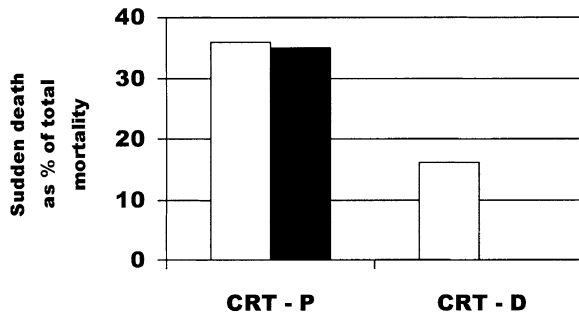


Figure 1. Comparison of percentage of mortality attributable to sudden cardiac death in Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial and in Cardiac Resynchronization-Heart Failure (CARE-HF) study. **Open bars** = the COMPANION trial; **solid bars** = the CARE-HF study. CRT-D = cardiac resynchronization therapy pacemaker plus back-up defibrillation (implantable cardiac defibrillator); CRT-P = cardiac resynchronization therapy pacemaker.

been performed, but has important implications in countries with limited health care budgets. It is highly unlikely, however, that future trials will be done in this population comparing patients with CRT-P and CRT-D devices to better quantitate the improvement in sudden cardiac death because of ethical concerns and difficulty with patient enrollment. Finally, one cannot exclude the possibility that long-term CRT-P therapy may reduce the incidence of sudden cardiac death by slowing the progression of congestive heart failure, improving the autonomic milieu, and causing anatomic remodeling.

Therefore, it becomes clear that the CARE-HF study confirms and reinforces the message of the COMPANION trial, namely that: 1) CRT alone confers a mortality benefit: a strong trend is seen in the COMPANION trial, hazard ratio, 0.76; $p = 0.059$; a significant trend is seen in the CARE-HF study, hazard ratio, 0.66; $p < 0.002$. 2) Therapy with CRT-D adds substantial survival benefit, attributable to reduction of sudden death, the COMPANION trial: hazard ratio, 0.64; $p = 0.01$.

Finally it is worth pointing out that some of the minor differences between the CARE-HF study and the COMPANION trial can be explained by the different patient populations included in the two studies as summarized in Table 1. The differing populations probably explain the different risks for mortality. The most important differences are that: 1) only 38% of the patients in the CARE-HF study had coronary artery disease, compared with 56% in the COMPANION trial; 2) the mean left ventricular ejection fraction was 25% in the CARE-HF study, compared with 21% in the COMPANION trial; and 3) a higher percentage of the patients in the COMPANION trial were in NYHA functional class IV (16% vs. 6.5%). Thus, clearly the patients in the COMPANION trial represent a cohort at higher risk of heart failure and arrhythmic death than those in the CARE-HF study, and this point is confirmed by the significantly higher control group mortality: at one year, 19% in the COMPANION trial and 12.6% in the CARE-HF study. The far fewer patients with coronary

Table 1. Patient Characteristics of Patients Enrolled in CARE-HF and in COMPANION

	CARE-HF		COMPANION	
	OPT	CRT-P	OPT	CRT-P
Age (yrs)	66	67	68	67
Male (%)	73	74	69	67
NYHA IV (%)	7	6	18	13
QRS (ms)	160	160	158	160
EF (%)	25	25	22	20
CAD (%)	35	41	59	54

CAD = coronary artery disease; CARE-HF = Cardiac Resynchronization-Heart Failure; COMPANION = Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure; CRT-P = cardiac resynchronization pacemaker; EF = left ventricular ejection fraction; NYHA = New York Heart Association functional class; OPT = optimal pharmacologic therapy; QRS = width of QRS.

artery disease etiology in the CARE-HF study also warrants comment. Based on the results of multiple ICD studies in patients with chronic ischemic disease (19–23), some of the potential candidates for the CARE-HF study were considered candidates for ICDs, and therefore were excluded from the CARE-HF study. In fact, the message of another important recently reported large clinical trial is that patients with NYHA functional class II or III heart failure and a low ejection fraction have better survival when an ICD is implanted (23). This observation reinforces our earlier comment that in a population with advanced heart failure, such as that studied in both the CARE-HF study and the COMPANION trial, the risk of sudden death remains substantial, thus the necessity for considering ICD for back-up in many of these patients.

Actually, the strategy of add-on therapies, illustrated schematically in Figure 2, has been commonplace in treating heart failure patients. Now, the COMPANION trial and the CARE-HF study have shown CRT (and CRT-D) as the next “new molecule,” providing a further one-third incremental protection against all-cause mortality and sudden death mortality over and above optimal medical therapy. Thus, with regard to the very specific question of using CRT-P alone or CRT-D, the question (thanks to the

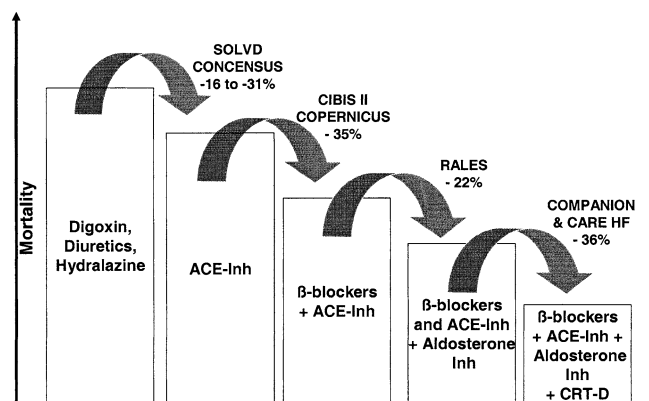


Figure 2. Add-on therapy in heart failure. Each added therapy incrementally decreases mortality when added on top of previous therapy. See text for explanation and references. ACE-Inh = acetylcholinesterase inhibitor; other abbreviations as in Figure 1.

CARE-HF study) is not whether CRT-P saves lives, but whether substantially more lives may be saved by combining CRT therapy with an ICD. These results should not surprise us. The MERIT-HF trial has shown that the degree of sudden death risk is higher in patients with less severe heart failure than in those with very advanced heart failure (18). There has been no evidence showing that CRT alone reduces the arrhythmic risk (11). The data from the CARE-HF study do not refute this point because the incidence of sudden death in the CRT arm is nearly identical to that in the control arm: 35% versus 32%, respectively. Thus, because CRT improves functional class, it is likely that the relative risk for sudden death remains elevated and provides a rationale for ICDs as an excellent complement to CRT therapy. These results are further confirmed by two single-center non-randomized series that have shown significant mortality reductions with CRT-D compared with CRT-P, very similar to the difference we have highlighted earlier (24–25).

It has been noted that 20% to 30% of patients who receive CRT therapy show no measurable clinical benefit. One explanation for this finding is that patients are selected for CRT therapy on the basis of the electrocardiogram duration, which is an imperfect measure of ventricular dyssynchrony. This is the first large clinical trial to select patients on the basis of the presence of either a very wide QRS (e.g., >149 ms, and most of these patients are thought to have dyssynchrony) or a QRS interval between 120 and 149 ms and the presence of two of three additional criteria for dyssynchrony. It is likely that the selection of patients for CRT therapy using measures of dyssynchrony serves to better identify candidates for CRT therapy and may increase the response rate and improve the outcome for patients receiving CRT.

In conclusion, the CARE-HF study and the COMPANION trial together show unequivocal benefit for CRT in NYHA functional class III and IV congestive heart failure with QRS >150 ms or QRS >120 ms plus dyssynchrony. The CARE-HF study trial showed ventricular remodeling and improved myocardial performance, which continued up to at least 18 months. Both studies confirm the need of adding the ICD to CRT devices, because more than one-third of deaths in the CRT-alone arm of both the COMPANION trial and the CARE-HF study were sudden. The implications of these results for the care of patients with moderate to severe heart failure should be immediately translated into clinical practice. Future research in CRT therapy will focus on patients with less severe degrees of heart failure. We can only eagerly anticipate these results in the coming years.

Reprint requests and correspondence: Dr. Kenneth A. Ellenbogen, Medical College of Virginia, P.O. Box 980053, Richmond, Virginia 23298-0053. E-mail: kaellenb@vcu.edu.

REFERENCES

- Cleland J, Daubert J-C, Erdmann E, et al., for the Cardiac Resynchronization–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–49.
- Cazeau S, Ritter P, Bakdach S, et al. Four-chamber pacing in dilated cardiomyopathy. *Pacing Clin Electrophysiol* 1994;17:1974–9.
- Cazeau S, Ritter P, Lazarus A, Gras D, Backdach H, Mundler O, Mugica J. Multisite pacing for end-stage heart failure: early experience. *Pacing Clin Electrophysiol* 1996;19:1748–57.
- Bakker P, Meijburg H, deVries J, et al. Biventricular pacing in end-stage heart failure improves functional capacity and left ventricular function. *J Interv Cardiovasc Electrophysiol* 2000;4:395–404.
- Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873–80.
- Auricchio A, Stellbrink C, Sack S, et al. Long-term clinical effect of hemodynamically optimized cardiac resynchronization therapy in patients with heart failure and ventricular conduction delay. *J Am Coll Cardiol* 2002;39:1895–8.
- Abraham WT, Fisher WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–53.
- Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the Multisite Stimulation in Cardiomyopathy (MUSTIC) Study. *J Am Coll Cardiol* 2002;40:111–8.
- Gras D, Leclercq C, Tang ASL, et al. Cardiac resynchronization therapy in advanced heart failure: the Multicenter InSync clinical study. *Eur J Heart Fail* 2002;4:311–20.
- Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure. *JAMA* 2003;289:2685–94.
- Higgins SL, Hummel JD, Niazi IK, et al. Cardiac resynchronization therapy for the treatment of heart failure in patients with intraventricular conduction delay and malignant ventricular tachyarrhythmias. *J Am Coll Cardiol* 2003;42:1454–9.
- Bradley DJ, Bradley EA, Baughman KL, et al. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;289:730–40.
- Bristow MR, Saxon LA, Boehmer J, et al., for the Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–50.
- The SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fraction and congestive heart failure. *N Engl J Med* 1991;325:293–302.
- CONSENSUS: Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med* 1987;316:1429–35.
- CIBIS-II Investigators and Committees. CIBIS II: the Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999;353:9–13.
- Packer M, Coats A, Fowler M, et al. COPERNICUS: Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001;344:1651–8.
- The MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure (MERIT-HF). *JAMA* 2000;283:1295–302.
- Moss A, Hall J, Cannom D, et al., for the MADIT Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk of ventricular arrhythmias. *N Engl J Med* 1996;335:1933–40.
- Buxton A, Lee K, Fisher J, Josephson M, Prystowsky E, Hafley G, for the Multicenter UnSustained Tachycardia Trial (MUSTT) Investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341:1882–90.
- Moss A, Zareba W, Hall J, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877–83.

22. Nanthakumar K, Epstein A, Kay N, et al. Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. *J Am Coll Cardiol* 2004;44:2166–72.
23. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
24. Ermis C, Lurie K, Zhu A, et al. Biventricular implantable cardioverter defibrillators improve survival compared with biventricular pacing alone in patients with severe left ventricular dysfunction. *J Cardiovasc Electrophysiol* 2004;15:862–6.
25. Pappone C, Augello G, Vicedomini G, et al. Backup defibrillation prolongs survival in patients with indications for CRT by reducing sudden cardiac death (abstr). *Circulation* 2004;110:III461.