

## FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

# There Is Plenty of Room for Cardiac Resynchronization Therapy Devices Without Back-Up Defibrillators in the Electrical Treatment of Heart Failure

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Patients with chronic heart failure might benefit from electrical therapy with a view to resynchronize the heart and improve its mechanical performance by cardiac resynchronization therapy (CRT) or to prevent the risk of sudden death by automatic defibrillation. These two therapies can be applied separately or with a combined device, the biventricular implantable cardioverter-defibrillator (CRT-D). There is currently no strong scientific evidence indicating that a CRT-D must be offered to all candidates for CRT. Plain common sense should limit the prescription of these costly devices for patients in need of secondary prevention or for younger patients without major comorbidities. The preferential choice of CRT pacemakers in the remainder of patients is currently a logical one. (*J Am Coll Cardiol* 2005;46:2204-7)  
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Patients with chronic heart failure (CHF) might benefit from electrical therapy with a view to: 1) resynchronize the heart and improve its mechanical performance, or 2) prevent the risk of sudden death by automatic defibrillation. These two therapies can be applied separately with dedicated devices, using a specific pacemaker for cardiac resynchronization therapy (CRT-P), or an implantable cardioverter-defibrillator (ICD), or a combined device, the cardiac resynchronization therapy by biventricular defibrillation (CRT-D). The article by Ellenbogen et al. (1) in this issue of the *Journal* is a strong plea in favor of the preferential, if not exclusive, prescription of CRT-D for patients with CHF and cardiac dyssynchrony. We have a different opinion, which we share here in the light of available scientific information, and on the basis of plain common sense.

### **SHOCK-ONLY ICD THERAPY LOWERS MORTALITY IN CHF: YES. . . BUT!**

The use of ICDs for primary prevention is based on the high proportion of cardiac sudden deaths in CHF. This percentage, observed in the control groups of large drug trials on New York Heart Association (NYHA) functional class II to IV patients ranges between 35% and 50%, reaching a maximum of 58% in the Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF) (2), which is probably explained by its inclusion of 41% of patients in NYHA functional class II.

As the severity of CHF increases, the proportion of sudden death relative to overall mortality decreases, and conversely, the percentage of deaths attributed to worsening heart failure increases (2). Therefore, the potentially greatest benefit of ICDs is likely to be conferred to patients with mild to moderate heart failure. The Sudden Cardiac Death in Heart Failure (SCD-HeFT) trial is thus far the only trial showing a lowering of all-cause mortality by ICD therapy in patients with CHF and a left ventricular (LV) ejection fraction (EF) <35% (3). In that study, which enrolled patients optimally treated for CHF, ICD therapy was compared with amiodarone or placebo. Although amiodarone conferred no benefit compared with placebo, a significant 23% relative reduction in the risk of overall mortality (RRR) was observed among the ICD recipients. These apparently spectacular results must be interpreted cautiously. The demographic characteristics of the SCD-HeFT population were quite peculiar (see later text). In addition, the trial had to include over 2,500 patients followed up for a median of 45.5 months and had to be extended for one year to show a statistically significant albeit modest absolute risk reduction (ARR) of 7.2% at five years. Finally, in agreement with the epidemiologic data mentioned earlier, a subgroup analysis showed that the risk reduction was limited to functional class II patients (RRR, 46%; ARR, 11.9% at five years). No treatment benefit was observed among the 30% of patients who were in NYHA functional class III (hazard ratio, 1.16). These latter observations, which place the impact of ICD therapy in perspective, must also have been considered when choosing a device for a cardiac resynchronization therapy (CRT) candidate, because CRT has only been validated in NYHA functional class III to IV patients.

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#### Abbreviations and Acronyms

ARR	= absolute risk reduction
CHF	= chronic heart failure
CRT-D	= cardiac resynchronization therapy by biventricular defibrillation
CRT-P	= pacemaker for cardiac resynchronization therapy
EF	= ejection fraction
ICD	= implantable cardioverter-defibrillator
LV	= left ventricular
NYHA	= New York Heart Association
RRR	= relative reduction in the risk of overall mortality

### **CRT IS THE ONLY ELECTRICAL THERAPY PROPERLY VALIDATED IN PATIENTS WITH MODERATE TO SEVERE CHF**

Several randomized trials have been conducted to ascertain the clinical impact of CRT in patients with advanced CHF and in sinus rhythm, with or without indications for an ICD (4-11). Two meta-analyses have also been published (12,13). The usual enrolment criteria have been: 1) NYHA functional class III or IV function despite optimal drug treatment, 2) LVEF <35%, and 3) QRS duration >120 or >150 ms.

The concordant results of these studies have confirmed that in this patient population, CRT combined with optimal pharmacologic therapy has a highly favorable and sustained impact (13,14) on all of the treatment objectives: 1) improvement of symptoms and exercise capacity with a mean decrease in NYHA functional class by 0.5 to 0.8 points, a mean increase in exercise capacity by 10% ( $\text{VO}_2$  peak) to 20% (6-min walking distance) and a highly significant improvement in quality-of-life score; 2) major reduction in heart failure-related morbidity with, in particular, a 30% to 52% decrease in the number of hospitalizations for worsening heart failure (10-13); 3) reverse ventricular remodeling: a consistent finding in the randomized trials designed with  $\geq 6$  months of follow-up has been an up to 15% absolute reduction in LV end-diastolic diameter, and an up to 6% increase in LVEF, conferred by CRT (11,14,15)—these effects were significantly greater in patients with non-ischemic than in patients with ischemic heart disease (14,15); and 4) impact of CRT on mortality: the CARE-HF and Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trials examined the effects of CRT on morbidity and mortality (10,11). In the COMPANION trial (10), CRT-P and CRT-D were both associated with a 20% reduction in the primary combined end point of all-cause mortality and all-cause hospitalization ( $p < 0.01$ ). However, only CRT-D, compared with controls, was associated with a significant decrease in total mortality at one year (RRR, 36%; ARR, 7%;  $p = 0.003$ ), whereas the 24% relative

(absolute, 4%) reduction in mortality associated with CRT-P was nearly statistically significant ( $p = 0.059$ ). The CARE-HF trial enrolled 813 patients (11). The CRT-P plus standard CHF pharmacologic treatment was compared with pharmacologic treatment alone. At the end of a mean follow-up of 29 months, a 37% relative risk reduction in the composite end point of death and hospitalization for major cardiovascular events ( $p < 0.001$ ) and 36% in the risk of death (ARR, 10%;  $p < 0.002$ ) were observed. The effect on mortality was mainly attributable to a marked reduction in CHF-related deaths. It is, however, noteworthy that the absolute number of sudden cardiac deaths was lower in the CRT group ( $n = 29$ ) than in the control group ( $n = 38$ ).

Recently, this scientific evidence has allowed the issue of a class I recommendation for CRT in the European Society of Cardiology guidelines on the diagnosis and treatment of chronic CHF to be formulated as follows: "CRT using bi-ventricular pacing can be considered in patients with reduced ejection fraction and ventricular dyssynchrony (QRS width  $\geq 120$  ms), who remain symptomatic in NYHA functional class III to IV despite optimal medical therapy to improve symptoms (class or recommendation I, level of evidence A), hospitalizations (class I, level A) and mortality (class I, level B)" (16).

### **IN CHF PATIENTS WITH INDICATION FOR CRT, WHICH TYPE OF DEVICE TO IMPLANT IN 2005: CRT-D OR CRT-P?**

In practice, the question is whether the more complicated and costly device (i.e., CRT-D) offers a significant additional benefit compared with CRT-P. The COMPANION trial is the only trial that has addressed this question, although it, unfortunately, remains unresolved (10). This failure is explained by: 1) a median follow-up limited to 14 months per study design, and 2) the absence of a direct comparison between the two therapies, because the analysis compared CRT-P and CRT-D each with the control group. Therefore, the only tenable conclusion is that compared with controls, CRT-D and CRT-P had a similar effect on all-cause mortality and hospitalization. It is also noteworthy that a putative superiority of CRT-D was short-lived, because the survival curves of patients treated with CRT-P and CRT-D became parallel beyond the ninth month of follow-up. Only a new randomized study comparing the two treatment modalities might resolve this issue. Based on the results of the CARE-HF trial (11), and assuming that the combination of CRT and defibrillation back-up could prevent two-thirds of sudden deaths, a study would require 1,300 patients per group and a follow-up period equivalent to that of the CARE-HF trial to have a statistical power of 90% to detect a 5% absolute relative risk reduction of death from any cause with the use of combined therapy compared with CRT alone. Who will undertake such a study?

## DID THE PATIENTS INCLUDED IN THE COMPANION TRIAL HAVE CHF THAT WAS TOO ADVANCED TO SHOW A BENEFIT FROM THE ICD?

As suggested by the SCD-HeFT study, the benefit conferred by ICDs might have been greater in a population suffering from less severe CHF. On the other hand, the efficacy of CRT has not been established in patients in NYHA functional class I to II function. Such demonstration is likely to be lengthy and arduous because, a priori, these patients have few or no symptoms, are rarely hospitalized for decompensation, and have a low death rate when optimally treated. In fact, the main goals of treatment for patients in NYHA functional classes I to II are largely different from those set for patients in class III to IV, consisting primarily of: 1) preventing disease and CHF progression and 2) lowering cardiac mortality, mainly sudden. These specific objectives need to be achieved by the pursuit of specific end points, the most relevant being: 1) a composite of symptoms, morbidity, and mortality (17) and 2) reverse remodeling. In the study by Higgins *et al.* (7), a significant degree of reverse remodeling was observed after six months of CRT in a small subgroup of patients in NYHA functional class I to II, although the benefits were less prominent than in the much larger group of patients in NYHA functional class III to IV (7). Similar observations were made in the Multicenter Insync Randomized Clinical Evaluation (MIRACLE ICD II) study (9). This small trial randomly assigned NYHA functional class II patients to CRT versus no CRT, who all received a CRT-D for an accepted ICD indication. At the end of the six-month blinded period, there was no significant difference in the primary study objective, although a significant improvement in the clinical composite end point was observed in the group assigned to CRT compared with the controls. These observations suggest that CRT might have a favorable impact on the outcome of patients with less advanced CHF and ventricular dyssynchrony. This issue now needs to be further examined in large randomized trials. The ongoing Resynchronization Reverses Remodeling in Asymptomatic Left Ventricular Dysfunction (REVERSE) (18) and Multicenter Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy (MADIT-CRT) trials are not expected to yield their results before three to five years.

## ARE THE RESULTS OF RANDOMIZED TRIALS APPLICABLE TO THE REAL WORLD OF CHF MANAGEMENT?

Randomized trials are often criticized for their enrollment of highly selected patients, unlike those encountered in real life. This criticism is particularly applicable in the treatment of CHF. Considering the large randomized studies of drugs or devices in CHF conducted in the last three years, the mean age of the populations was relatively young, between 60 and 67 years, and the proportion of women was small,

between 20% and 32%. The most striking example is the SCD-HeFT trial, with a population 60.1 years old on average and 23% women (3). These demographic characteristics are vastly different from those of registries in which the mean ages range between 71 and 78 years and the proportion of women approaches 50% (19,20). It is therefore problematic to apply recommendations issued from randomized trials to the general population of patients with CHF. Common sense dictates that these recommendations would have to be applied to similar or identical patients. In the case of the SCD-HeFT trial example, the treatment should be offered to young or relatively young patients without serious comorbidity. However, the majority of patients with advanced CHF are older and have various concomitant disorders (19,20).

It is not morally wrong to address the issue of priority of therapeutic objectives in this majority of patients with CHF, whose prognosis remains poor despite all efforts. Improving quality of life, lowering the rates of hospitalizations for management of CHF, and preserving patient autonomy are probably priorities. A treatment that moreover lowers mortality and prolongs life under comfortable conditions, which the CRT-P achieves at a modest cost, may be viewed as successful.

## CONCLUSIONS

Both CRT-P and CRT-D are electrical treatment modalities that have been validated for the management of CHF. There is currently no strong scientific evidence indicating that a CRT-D must be offered to all candidates for CRT. Plain common sense should limit the prescription of these costly and complicated devices for patients in need of secondary prevention, or for the purpose of primary prevention in younger patients without major comorbidities. The preferential choice of CRT-P in the remainder of patients, who represent the large majority of potential candidates for CRT, is currently a logical one.

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## REFERENCES

1. Ellenbogen KA, Wood MA, Klein HU. Why should we care about CARE-HF? *J Am Coll Cardiol* 2005;46:2199–203.
2. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL, Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999;353:2001–7.
3. Bardy G, Lee KL, Mark DB, *et al.* Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225–37.
4. 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.
5. Abraham WT, Fisher WG, Smith AL, *et al.* Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845–53.

6. 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;39:2026–33.
7. 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.
8. Young JB, Abraham WT, Smith AL, et al. Combined cardiac resynchronization and implantable cardioversion defibrillation in advanced chronic heart failure: the MIRACLE ICD trial. *JAMA* 2003;289:2685–94.
9. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left ventricular dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic heart failure. *Circulation* 2004;110:2864–8.
10. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140–50.
11. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization therapy on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539–49.
12. 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.
13. McAlister EA, Ezekowitz JA, Wiebe N, et al. Systematic review: cardiac resynchronization in patients with symptomatic heart failure. *Ann Intern Med* 2004;141:381–90.
14. Linde C, Leclercq C, Rex S, et al. Long-term benefits of biventricular pacing in congestive heart failure: results from the MUSTIC study. *J Am Coll Cardiol* 2002;40:111–8.
15. St. John Sutton MG, Plappert T, Abraham WT, et al. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. *Circulation* 2003;107:1985–90.
16. Swedberg K, Cleland JGF, Dargie H, et al., and the Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. Guidelines for the diagnosis and treatment of chronic heart failure: update 2005. *Eur Heart J* 2005;26:1115–40.
17. Packer M. Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Card Fail* 2001;7:176–82.
18. Linde C, Abraham W, Gold M, Daubert C. Rationale and design of a randomized controlled trial to assess the safety and efficacy of cardiac resynchronization therapy in patients with asymptomatic or mild heart failure: the REVERSE study. *Am Heart J* 2005. In press.
19. Cleland JG, Swedberg K, Follath F, et al. The European Heart Failure Survey Programme—a survey on the quality of care among patients with heart failure in Europe. *Eur Heart J* 2003;24:442–63.
20. McMurray JJ, Pfeffer MA. The year in heart failure. *J Am Coll Cardiol* 2004;44:2398–405.