Cardiac resynchronization therapy reduced all-cause death and hospitalization in chronic heart failure

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.

QUESTION

In patients with advanced chronic heart failure (HF), is cardiac resynchronization therapy (CRT) with a biventricular pacemaker with or without a defibrillator in addition to optimal pharmacotherapy (OPT) better than OPT alone for reducing death and hospitalization?

METHODS

Design: Randomized controlled trial (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure [COMPANION]).

Allocation: Concealed.*

Blinding: Unblinded.*

Follow-up period: 12 months.

Setting: 128 centers in the United States.

Patients: 1520 patients (mean age 67 y, 68% men) with advanced New York Heart Association (NYHA) class III or IV HF resulting from either ischemic or nonischemic cardiomyopathy, left ventricular (LV) ejection fraction ≤ 0.35, QRS interval ≥ 120 ms and PR interval > 150 ms, sinus rhythm, no clinical indication for a pacemaker or implantable defibrillator, and hospitalization for the treatment of HF or equivalent in the previous 12 months.

Intervention: All patients received OPT (diuretics, if needed); angiotensin-converting enzyme inhibitors (or angiotensin-receptor blockers, if not tolerated); β-blockers, if tolerated or not contraindicated; and spironolactone, if tolerated), and digoxin or other medications for HF. Patients were allocated to OPT (n = 308), OPT plus CRT with a biventricular pacemaker (n = 617), or OPT plus CRT and a pacemaker-defibrillator (n = 595).

Outcomes: Composite endpoint of all-cause death or hospitalization. Unscheduled intravenous inotropic or vasoactive drugs for > 4 hours in the emergency department or on an outpatient basis was considered an instance of the primary endpoint with respect to hospitalization. Secondary endpoints included all-cause death, and death from or hospitalization for cardiovascular (CV) causes or HF.

Patient follow-up: 97% (intention-to-treat analysis).

MAIN RESULTS

Compared with OPT alone, CRT with or without a defibrillator reduced risk for the composite endpoint (Table). Fewer patients who received CRT and a pacemaker–defibrillator died from all causes than did those who received a pacemaker alone (Table). Compared with OPT, death from or hospitalization for CV causes or HF were reduced in CRT groups with a defibrillator (hazard ratio [HR] 0.72, 95% CI 0.60 to 0.86) and without a defibrillator (HR 0.75, CI 0.63 to 0.90). More moderate or severe all-cause adverse events occurred in the CRT defibrillator group than the OPT group (69% vs 61%, P = 0.03).

CONCLUSION

In patients with advanced chronic heart failure, cardiac resynchronization therapy with a biventricular pacemaker with or without a defibrillator reduced all-cause death or hospitalization.

Source of funding: Guidant.

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*See Glossary.

Cardiac resynchronization therapy with a pacemaker (P) or pacemaker–defibrillator (PD) vs optimal pharmacologic therapy (OPT) for advanced chronic heart failure at mean 12 months†

Outcomes	P	PD	OPT	RRR (95% CI)	NNT (CI)
Composite endpoint	56%	—	68%	11% (2 to 20)	13 (8 to 68)
	—	56%	68%	12% (3 to 21)	13 (8 to 54)
All-cause death	15%	—	19%	22% (–0.9 to 39)	Not significant
	—	12%	19%	34% (13 to 49)	16 (11 to 42)

†Composite endpoint = all-cause death or hospitalization. Other abbreviations defined in Glossary; RRR, NNT, and CI calculated from data in article.

COMMENTARY

Despite major improvements in treating HF, mortality remains high. Newer therapeutic approaches have focused on the benefits of such electrical therapies as CRT and ICDs. CRT is aimed at restoring the desynchronization that is usually associated with conduction delays (characterized by left-bundle branch block), and ICDs primarily prevent arrhythmic deaths.

The COMPANION trial by Bristow and colleagues further supports and extends the beneficial effects of CRT in patients with advanced HF and QRS > 120 ms and reinforces the importance of OPT. In addition, all-cause mortality was reduced by 36% when CRT and an ICD were combined (HR 0.64, 95% CI 0.48 to 0.86). A limitation of this study was the disproportionately high rate of withdrawal from the OPT group, which was reported once the Multicenter Automatic Defibrillator Implantation II (MADIT-II) trial results became available (1). It remains unclear whether the reduction in mortality is solely attributable to the ICD or the combination of CRT and ICD.

The extent of benefit derived from CRT with or without an ICD was similar in both ischemic and nonischemic patients. Interestingly, in patients with nonischemic cardiomyopathy, CRT combined with an ICD was associated with a lower risk for all-cause mortality than CRT combined with OPT (HR 0.50, CI 0.29 to 0.88). These findings support the use of CRT with or without an ICD also in patients with advanced HF secondary to nonischemic cardiomyopathy.

The main issue related to electrical therapy of HF remains its cost-effectiveness. Although not reported, the 20% reduction in the composite endpoint in both groups may indicate a reduction in health costs (primarily driven by hospitalizations). The 13 patients needed to treat to prevent 1 primary outcome is comparable to the treatment cost of other chronic conditions (2). However, in the COMPANION trial, the effect on all-cause mortality was only seen in the group that received both CRT and an ICD.

Despite the major effect of CRT on quality of life, hospital admissions, and mortality secondary to the progression of HF, 20% to 40% of patients do not respond to this therapy (3–5). Similarly, not all

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A prophylactic cardioverter–defibrillator prevented sudden death from arrhythmia in nonischemic cardiomyopathy

Kadish A, Dyer A, Daubert JP, et al. **Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy.** N Engl J Med. 2004;350:2151-8.

QUESTION

In patients with nonischemic dilated cardiomyopathy, is a prophylactic implantable cardioverter–defibrillator (ICD) more effective than standard pharmacotherapy (SP) for reducing all-cause death?

METHODS

Design: Randomized controlled trial (Defibrillators in Non-Ischemic Cardio-myopathy Treatment Evaluation [DEFINITE]).
Allocation: Concealed.*
Blinding: Blinded (events committee). *
Follow-up period: Mean 29 months.
Setting: 40 centers in the United States and 5 centers in Israel.
Patients: 458 patients (mean age 58 y, 71% men) with left-ventricular (LV) ejection fraction < 36%, presence of ambient arrhythmias (an episode of nonsustained ventricular tachycardia on Holter or telemetric monitoring [3 to 15 beats at > 120 beats/min] or an average of ≥ 10 premature ventricular complexes/h on 24-h Holter monitoring), history of symptomatic heart failure (HF), and presence of nonischemic dilated cardiomyopathy. Exclusion criteria were New York Heart Association class IV congestive HF, unsuitability for a cardioverter–defibrillator, electrophysiologic testing within the previous 3 months, permanent pacemakers, imminent cardiac transplantation, familial cardiomyopathy associated with sudden death, or acute myocarditis or congenital heart disease.
Intervention: Patients were stratified by center and use or nonuse of amiodarone for supraventricular arrhythmias. 229 patients were allocated to SP (angiotensin-converting enzyme inhibitors [unless contraindicated; or hydralazine or nitrates or angiotensin II-receptor blockers, if not tolerated], and β-blockers [if tolerated]) at doses adjusted to levels recommended for HF or to the highest tolerated doses. 229 patients were allocated to SP plus an ICD (a single-chamber device approved by the Food and Drug Administration and programmed to back up VVI pacing at a rate of 40 beats/min and to detect ventricular fibrillation at a rate of 180 beats/min). Patients in the SP group received ICD if they had a cardiac arrest or an episode of unexplained syncope that was consistent with the occurrence of an arrhythmic event.
Outcomes: All-cause death. Secondary outcome was sudden death from arrhythmia.
Patient follow-up: 100% (intention-to-treat analysis).
Main results: Of the 229 patients in the SP group, 23 (10%) received ICD for syncope or HF with a prolonged QRS interval. Fewer patients in the ICD group died than did patients in the SP group; the difference did not reach statistical significance (P = 0.08) (Table). Death from arrhythmia occurred in fewer patients who received ICD than those who received SP (Table).

CONCLUSION

In patients with nonischemic dilated cardiomyopathy, a prophylactic implantable cardioverter–defibrillator showed a trend toward a mortality benefit and prevented more sudden deaths from arrhythmia than standard pharmacotherapy.

Source of funding: St. Jude Medical.

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*See Glossary.

Implantable cardioverter–defibrillator (ICD) vs standard pharmacotherapy (SP) for nonischemic dilated cardiomyopathy at mean 29 months†

Outcomes	ICD	SP	RRR (95% CI)	NNT (CI)
All-cause mortality	12%	17%	33% (–5 to 58)	Not significant
Sudden death from arrhythmia	1%	6%	79% (28 to 94)	21 (18 to 59)

†Abbreviations defined in Glossary; RRR, NNT, and CI calculated from hazards ratios in article.

COMMENTARY *(continued from page 60)*

patients with an LV ejection fraction < 30% will benefit from insertion of an ICD. Better methods of identifying CRT responders as well as patients with higher risk for sudden death are needed to reduce unnecessary costs (6, 7). Treatment decisions may depend on whether the purpose of therapy with CRT is primarily for symptomatic relief, prolongation of life, or both. The critical question is whether all patients with poor LV function (associated with some degree of desynchrony, regardless of cause) should undergo the insertion of CRT with an ICD.

The DEFINITE trial by Kadish and colleagues showed a trend toward reducing all-cause mortality in patients with nonischemic cardiomyopathy who received an ICD. Conversely, an impressive reduction in sudden death from arrhythmia was reported in the group that received ICD. Aggressive medical therapy in patients with depressed LV function secondary to nonischemic cardiomyopathy should be reinforced. The recently presented Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) randomized patients with poor LV function (ejection fraction < 35%) and moderate-to-severe HF (NYHA II-III) to placebo, amiodarone, or an ICD. SCD-HeFT showed that an ICD reduced all-cause mortality regardless of cause by 23% (HR 0.77, 97.5% CI 0.62 to 0.97) (8). These studies support prophylactic insertion of an ICD in patients with moderate-to-severe LV dysfunction.

The COMPANION and DEFINITE trials expand the indications of CRT and ICDs in high-risk patients with LV dysfunction regardless of cause. Further risk stratification is needed to appropriately select responders to either therapy. Given the impact of electrical therapy for HF on health economics, judicious use of these technological advances is warranted.

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References

1. **Moss AJ, Zareba W, Hall WJ, et al.** N Engl J Med. 2002;346:877-83.
2. Special report: cost-effectiveness of implantable cardioverter-defibrillators in a MADIT-II population. Technol Eval Cent Asses Program Exec Summ. 2004; 19:1-2.
3. **Bradley DJ, Bradley EA, Baughman KL, et al.** JAMA. 2003;289:730-40.
4. **Young JB, Abraham WT, Smith AL, et al.** JAMA. 2003;289:2685-94.
5. **Abraham WT, Fisher WG, Smith AL, et al.** N Engl J Med. 2002;346: 1845-53.
6. **Abraham WT.** Rev Cardiovasc Med. 2003;4 Suppl 2:S30-7
7. **Hohnloser SH, Ikeda T, Bloomfield DM, Dabbous OH, Cohen RJ.** Lancet. 2003;362:125-6.
8. **Shah SH, Dery JP, Fischi MC, et al.** Am Heart J. 2004;148:254-62.