

## FOCUS ISSUE: CARDIAC RESYNCHRONIZATION THERAPY

### Editorial Comment

# Cost Effectiveness of Cardiac Resynchronization Therapy\*

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Cardiac resynchronization therapy (CRT) is a promising new approach for improving outcomes among patients who have heart failure, reduced left ventricular (LV) systolic function, and a wide QRS complex. Cardiac resynchronization therapy devices are quite expensive, however, so their cost effectiveness is of concern now that the costs of health care are increasing rapidly once again. Randomized clinical trials can provide unbiased measures of the economic outcomes of new therapies, just as they do for clinical outcomes. However, the short-term results of trials do not provide a complete picture of health and economic outcomes, especially for devices and procedures. Consequently, many investigators now use a model to extrapolate trial results and analyze cost effectiveness (1). In this issue of the *Journal*, this approach has been taken to evaluate the economic outcomes of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial (2).

See page 2311

The COMPANION trial randomized patients to either CRT with implantable cardioverter-defibrillator (ICD) capability, CRT without ICD capability, or optimal medical therapy (3). The COMPANION trial found that CRT, either with or without ICD capability, significantly improved patient functional status and quality of life compared with optimal medical therapy. The COMPANION trial also found that the combined CRT-ICD device, but not CRT alone, reduced mortality significantly compared with medical therapy. The COMPANION investigators now report that the costs of CRT alone and of combined CRT-ICD therapy are substantially higher than the cost of medical therapy (2). Because the observed follow-up in the COMPANION trial was much too brief to give a fair picture of the cost effectiveness of these devices, the investigators used a model to extrapolate their results to seven years, and suggest that CRT therapy is cost effective. Before

accepting this conclusion, it is important to examine how their results were achieved and consider the relevance of these findings to current clinical decision-making.

### PRINCIPLES OF COST EFFECTIVENESS

Cost-effectiveness analysis is an analytic tool that organizes information about medical interventions and facilitates judgments about whether a therapy improves outcomes sufficiently to justify the added cost. One of the key principles of cost-effectiveness analysis is that a new therapy should be compared with the next best alternative therapy. The costs and benefits of the new therapy compared with the best alternative are used to calculate the incremental cost-effectiveness ratio:

$$CE = \frac{\text{Cost}_{\text{CRT}} - \text{Cost}_{\text{MED}}}{\text{Life Years}_{\text{CRT}} - \text{Life Years}_{\text{MED}}}$$

Cost-effectiveness ratios of <\$50,000 per life-year added are generally considered acceptable in the U.S., whereas values >\$100,000 are generally considered too expensive, and the middle range of \$50,000 to \$100,000 is a “gray zone.”

### COSTS

The net cost of any device includes more than the price of the hardware and the cost of implantation. Device complications will increase the net cost, whereas prevention of disease complications by the device may reduce the net cost. The COMPANION investigators estimated the initial implantation costs to be \$20,500 for CRT alone and \$29,500 for the combined CRT-ICD device (2). They projected that post-implantation costs over the next seven years would be \$39,400 in the CRT-alone group and \$52,700 in the CRT-ICD group, compared with \$46,000 in the medical therapy group. Thus, the long-term cost of the combined CRT-ICD device (\$82,200) was much higher than the cost of CRT alone (\$59,900) or of medical therapy (\$46,000).

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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## EFFECTIVENESS

Although CRT therapy is costly, the increased cost may be acceptable if outcomes are sufficiently improved. A therapy is considered effective if it either increases life expectancy or improves quality of life, or both. The length and quality of life can be combined as quality-adjusted life-years (QALYs), a measure of effectiveness that underscores that improving either outcome is desirable.

The evidence from several clinical trials shows that CRT significantly improves quality of life for the average patient eligible for randomization (4). The degree of improvement in quality of life is clinically meaningful and certainly contributes to the overall effectiveness of CRT. The effect of CRT alone on mortality has been uncertain, but the recently published Cardiac Resynchronization Heart Failure (CARE-HF) trial showed CRT reduced mortality significantly compared with medical therapy (5). The weight of evidence now suggests that CRT devices without ICD capability reduce mortality and improve quality of life in patients with heart failure.

The combined CRT-ICD device in the COMPANION trial reduced mortality and improved quality of life significantly compared with medical therapy (3). The COMPANION trial did not formally compare the combined CRT-ICD with CRT alone, but the small differences in mortality and quality of life between these devices are almost certainly not statistically significant (3). The data from the COMPANION trial suggest that CRT therapy in patients with heart failure yields better outcomes than medical therapy, but that neither device is clearly superior to the other.

## COST EFFECTIVENESS

The CRT device alone in the COMPANION trial was much less expensive than the combined CRT-ICD device and had very similar clinical outcomes. A prudent buyer would first look at the less expensive CRT-alone device, and then ask whether the combined CRT-ICD device is worth the considerable added expense. A formal cost-effectiveness analysis similarly first compares CRT alone with medical therapy, and then compares the combined CRT-ICD device with the next best alternative, which is CRT alone.

Compared with optimal medical therapy, CRT alone in the COMPANION trial had a cost-effectiveness ratio of \$19,600 per QALY added, which is well within the range of other generally accepted interventions. The overall benefit of 0.71 QALYs resulted from the significant improvement in quality of life and the trend toward improved survival. The COMPANION trial therefore provides direct evidence that CRT without ICD capability can be a cost-effective therapy in properly selected patients with heart failure, low ejection fraction, and a wide QRS.

Does the more costly combined CRT-ICD device improve outcomes sufficiently to be worthwhile? The appropriate comparison is against CRT alone, the next best alternative, and not with medical therapy. The COMPANION

trial data show that the combined CRT-ICD had only slightly better outcomes than CRT alone (3.15 vs. 3.01 QALYs) but cost much more (\$82,200 vs. \$59,900). The cost effectiveness calculated from these data is \$160,000 per QALY, which is expensive compared with standard benchmarks. The COMPANION trial data suggest that adding ICD capability to a CRT device may not improve outcomes sufficiently to justify the considerable additional expense.

## CLINICAL CONTEXT

The CRT device aims to improve the efficiency of cardiac contraction and thereby ameliorate the underlying physiologic defect in patients with heart failure. Clinical trials of CRT initially assessed the effect of CRT on symptoms and functional capacity, and only recently examined whether CRT reduces mortality in patients with heart failure. The totality of evidence from clinical trials suggests that CRT alone reduces mortality by roughly 20% compared with medical therapy.

While CRT was being developed, an independent avenue of investigation has tested whether prophylactic implantation of an ICD reduces mortality in patients with a reduced ejection fraction, with or without heart failure. Large trials such as Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) suggest that an ICD alone can reduce mortality by 23% or more (6).

Because the mechanisms of action of CRT and ICD devices are quite different, it is reasonable to hypothesize that they may have an additive effect on mortality. It is important to recognize, however, that the effects of these devices may not be additive—that the 20% mortality reduction from CRT may overlap the 23% mortality reduction from an ICD. The only way to prove that the combined CRT-ICD device leads to better outcomes than either CRT alone or ICD alone is to perform head-to-head comparison trials. The ongoing Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT CRT) and REsynchronization reVERses Remodeling in Systolic left vEntricular dysfunction (REVERSE) trial are comparing ICD alone with combined CRT-ICD therapy; these studies, along with previous trials (7–9), should provide adequate power to test the hypothesis. By contrast, the combined CRT-ICD device has been compared with CRT alone only in the COMPANION trial, and that single study was not large enough to show a difference between these devices in clinical outcomes.

## EVIDENCE

Evidence is accumulating to show that device therapy improves outcomes compared with medical therapy in patients with heart failure. There are clearly differences among devices in their capabilities, reliability, and cost. Too few head-to-head comparisons have been done among the various devices to show clearly whether one has significantly better clinical outcomes in this patient population. Al-

though it is seductive to believe that devices with more features should lead to better outcomes than simpler and cheaper devices, recent experience with dual-chamber pacing (10,11) should warn us that this supposition is often incorrect. The more complex CRT-ICD devices are significantly more costly, but there is no solid evidence showing that they lead to significantly better outcomes than CRT alone. Are they really a good value? Only properly sized comparative clinical trials can answer this question.

Medical technology is a moving target, with constantly improving therapies and outcomes. Cost-effectiveness analysis compares the newest therapy with the next best alternative, just as prudent clinicians do. The CRT-alone device seems to be cost effective compared with medical therapy for patients with heart failure, reduced ejection fraction, and a wide QRS. The combined CRT-ICD device has only marginally better outcomes than CRT alone, at a significantly higher cost. The question of which device is the most cost effective for patients with heart failure remains open.

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