Economic Value and Cost-Effectiveness of Cardiac Resynchronization Therapy Among Patients With Mild Heart Failure

Projections From the REVERSE Long-Term Follow-Up

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ABSTRACT

OBJECTIVES This study investigated the cost effectiveness of early cardiac resynchronization therapy (CRT) implantation among patients with mild heart failure (HF). The differential cost effectiveness between CRT using a defibrillator (CRT-Ds) and CRT using a pacemaker (CRT-P) was also assessed.

BACKGROUND Cardiac resynchronization has been shown to be cost effective in New York Heart Association (NYHA) functional classes III/IV but is less studied in class II HF. The incremental costs of early CRT implementation in mild HF compared with the costs potentially avoided because of delaying disease progression to advanced HF are also unknown. Finally, combined biventricular pacing and defibrillator (CRT-D) devices are more expensive than biventricular pacemakers (CRT-P), but the relative cost effectiveness is controversial.

METHODS Data from the 5-year follow-up phase of REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) were used. The economics were evaluated from the U.S. Medicare perspective based on published clinical projections.

RESULTS Probabilistic estimates yielded $8,840/quality-adjusted life year (QALY) gained (95% confidence interval [CI]: $6,705 to $10,804/QALY gained) for CRT-ON versus CRT-OFF (i.e., programmed “ON” or “OFF” at pre-specified post-implantation timings) and $43,678/QALY gained for CRT-D versus CRT-P (95% CI: $35,164 to $53,589/QALY gained) over the patient’s lifetime. Results were robust to choice of patient subgroup and alterations of ±10% to key model parameters. An “early” CRT-D class II strategy totaled $95,292 compared with $91,511 for a “late” implantation. An “early” implant offered on average 1.00 year of additional survival for $3,781, resulting in an ICER of $3,795/LY gained.

CONCLUSIONS This study demonstrates CRT cost effectiveness in mild HF. The incremental CRT-D costs are justified by the anticipated benefits, despite increased procurement costs and shorter generator longevities. “Early” CRT-D implants have essential cost parity with “late” implants while increasing the patient’s survival. (REsynchronization reVERses Remodeling in Systolic Left vEntricular Dysfunction [REVERSE]; NCT00271154) (J Am Coll Cardiol HF 2017;5:204–12) © 2017 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
he risk of developing heart failure (HF) is approximately 20% among patients over 40 years of age, and more than 650,000 new cases are diagnosed annually in the United States. Heart failure patients generate more than a million hospital admissions per year and have a short-term readmission risk of 25%. This leads to an annual economic burden of more than $30 billion (1). Clinical (2-4) and cost (5) effectiveness of cardiac resynchronization therapy (CRT) have been demonstrated in patients with New York Heart Association (NYHA) functional classes III/IV HF and QRS prolongation. However, there remain uncertainties regarding the incremental cost effectiveness of CRT devices with defibrillation therapy (CRT-D) compared with that with CRT devices that provide only pacing (CRT-P) (6).

Multiple trials demonstrated patients with mild HF (NYHA functional class II) benefit from CRT (7–9). Much less is known about the cost effectiveness in this population. An analysis from the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial CRT) (10) determined that CRT-D implantation was cost effective by conventional thresholds in patients with New York Heart Association (NYHA) functional classes III/IV HF and QRS prolongation. Moreover, a cost effectiveness evaluation of CRT-P was not possible because these devices were not included in that trial. To address this, a cost effectiveness analysis was performed from the REVERSE (Resynchronization reVeRses Remodeling in Systolic Left vEntricular Dysfunction) trial. Importantly, long-term follow-up (11) enabled several analyses (12) that, along with enhanced statistical techniques (13–15), addressed many issues regarding the cost effectiveness of CRT in mild HF.

METHODS

TRIAL POPULATION. REVERSE enrolment criteria have been detailed elsewhere (11). In short, 610 North American and European subjects were randomized. Key inclusion criteria included NYHA functional classes I/II HF, QRS ≥120 ms, left ventricular ejection fraction ≤40%, and optimal medical therapy (OMT) for HF. Subjects received CRT devices that were randomly assigned (2:1) to be “CRT-ON” or “CRT-OFF.” Randomization ended when all patients had CRT programmed “ON” at pre-specified post-implantation timing (12 months in North America and 24 months in Europe). The trial was approved by an institutional review committee, and all subjects gave informed consent (NCT00271154).

ECONOMIC MODEL DESIGN. A “proportion-in-state” model, with a 1-month cycle length was used to evaluate lifetime costs and benefits (16,17). Health states were defined by survival (“alive” and “dead”) and NYHA functional class. Given the dataset’s very small number of class IV patients at any time, this subgroup was combined with class III patients. All patients received biventricular pacing devices, with the controls having CRT initially off, whereas some received implants with a combined biventricular pacing and defibrillator device. All patients designated “alive” were assumed to receive OMT regardless of NYHA functional class. A 3-stage process was subsequently implemented, using statistical models generated and previously published in REVERSE outcome extrapolation (13).

Monthly, a parametric survival function was used to estimate the original cohort proportion still alive at a particular time. Conditional on being “alive,” the second statistical model allocated patient proportions to each NYHA functional class subgroup. The final statistical model predicted the number of HF hospitalizations occurring at every time point, using NYHA functional class allocation information.

The covariates examined were: etiology (ischemic/non-ischemic), left bundle branch block (LBBB) morphology, median QRS duration (<128 ms, ≥138 ms). A subanalysis of CRT-ON-randomized patients informed the impact of a defibrillator and was used for CRT-D versus CRT-P.

The primary outcome measure was incremental cost effectiveness ratio (ICER), defined as the cost to offer an additional quality-adjusted life year (QALY). Discounting of 3% was applied (18). Probabilistic sensitivity analysis (PSA) was undertaken in main and subgroup analyses, using 1,000 Monte Carlo simulations. Cost effectiveness acceptability curves (CEACs) were also provided. Mean PSA results were presented with 95% credible intervals (CrIs). The model was coded in Excel 2010 software (Microsoft Corp., Redmond, Washington).

MORTALITY, HF DISEASE PROGRESSION AND HF HOSPITALIZATION. Analytical methods to estimate survival, disease progression, and HF hospitalization have been detailed elsewhere (13). In summary, statistical techniques (19) used for the first time in cardiology allowed an estimate of how CRT-OFF patients would have performed had they not turned biventricular pacing “ON” at the pre-specified time points.

ABBREVIATIONS AND ACRONYMS

CRT = cardiac resynchronization therapy
CRT-D = cardiac resynchronization therapy defibrillator
CRT-P = cardiac resynchronization therapy pacemaker
HF = heart failure
ICD = implantable cardioverter-defibrillator
ICER = incremental cost effectiveness ratio
NYHA = New York Heart Association
QALY = quality-adjusted life year
OMT = optimal medical therapy
PSA = probabilistic sensitivity analysis
TABLE 1 Selected Inputs, Costs, and Resource Use

<table>
<thead>
<tr>
<th>Input Name</th>
<th>Value</th>
<th>Ref. #</th>
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<tbody>
<tr>
<td>Starting age, yrs</td>
<td>62.55</td>
<td>7</td>
</tr>
<tr>
<td>Cost and benefit annual discounting rate</td>
<td>3%</td>
<td>18</td>
</tr>
<tr>
<td>Cycle length, months</td>
<td>1</td>
<td>Convention*</td>
</tr>
<tr>
<td>Proportion of patients with combined biventricular pacing and defibrillator devices (CRT-Ds)</td>
<td>83.84%</td>
<td>7</td>
</tr>
<tr>
<td>Number of annual outpatient device follow-ups</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>NYHA functional class allocation at baseline</td>
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<tr>
<td>Class I</td>
<td>17.30%</td>
<td>7</td>
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<tr>
<td>Class II</td>
<td>82.70%</td>
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<tr>
<td>Classes III/IV</td>
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<tr>
<td>Healthcare utility by NYHA functional class</td>
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<tr>
<td>Class I</td>
<td>0.850</td>
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<tr>
<td>Class II</td>
<td>0.773</td>
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<tr>
<td>Classes III/IV</td>
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<td>24,25</td>
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<tr>
<td>Costs</td>
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<td>CRT-D implantation, initial/replacement</td>
<td>$36,263.73/$32,688.24</td>
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<tr>
<td>CRT-P implantation, initial/replacement</td>
<td>$16,218.44/$13,375.22</td>
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</tr>
<tr>
<td>ICD implantation, initial/replacement</td>
<td>$35,795.41/$32,379.14</td>
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<tr>
<td>HF hospitalization</td>
<td>$6,511.47</td>
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<tr>
<td>CRT-D/ICD follow-up</td>
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<tr>
<td>CRT-P follow-up</td>
<td>$104.71</td>
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<tr>
<td>Monthly medication use</td>
<td>$50.84</td>
<td>22,35</td>
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<tr>
<td>Generator longevity, yrs</td>
<td>6.92</td>
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<tr>
<td>CRT-D</td>
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<tr>
<td>CRT-P</td>
<td>10.58</td>
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<tr>
<td>ICD</td>
<td>7.83</td>
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</tr>
<tr>
<td>Successful CRT implantation rate</td>
<td>95.11%</td>
<td>36</td>
</tr>
<tr>
<td>Post-implant device-related AE rate</td>
<td>10.56%</td>
<td>36</td>
</tr>
</tbody>
</table>

*The value was selected because of customary reasons and without any particular reference (it is common for these analyses to employ monthly cycles). AE = adverse event; CRT-D = cardiac resynchronization defibrillator; CRT-P = cardiac resynchronization pacemaker; HF = heart failure; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

ANALYTICAL PERSPECTIVE AND DEVICE IMPLANTATION COSTS. In all analyses, a Centers for Medicare and Medicaid Services (CMS) perspective was used. Device implantation costs (Table 1) were based on fiscal year 2014 (FY2014) national average payment rate. Calculations weighted average mixtures of inpatient Medicare Severity Diagnosis-Related Groups and outpatient ambulatory payment classification for device implantation payments and the anticipated physician-related payments for each type of device based on 2014 values. The mixture of inpatient and outpatient implantations was determined by the 2012 physician/supplier procedure summary master file (20). Sequestration was also considered.

SUCCESSFUL DEVICE IMPLANTATION RATE. Successful implants were ones of a functional system consisting of right atrium, right ventricle, and left ventricle (LV) leads, and the generator. The successful implantation rate reported in this trial (Table 1) was used in the CRT-ON patients, and equal rates were applied to CRT-Ds and CRT-Ps. Second attempts were assumed to be successful.

DEVICE-RELATED ADVERSE EVENTS. Adverse events (AEs) for patients who received a biventricular pacing device were based on clinical trial data over the full follow-up period. All patients were used to calculate these rates, regardless of randomization allocation. Adverse event rates were assumed to be zero for patients not receiving biventricular pacing in this analysis; they were assumed to happen immediately after implantation and were paid at the same rate as for HF-related hospitalization. Adverse events actually observed during implantation were assumed to be covered within the implantation.

GENERATOR BATTERY LONGEVITY. The factor of time to battery depletion was integrated using actual data from the cardiac clinical audit database (21) that collected information from all device implants across the United Kingdom, including 22,259 implantable cardioverter-defibrillators (ICDs), 10,062 CRT-Ds, and 7,968 CRT-Ps implanted between January 1, 2000 and April 14, 2011.

MEDICATION USE BY NYHA CLASS AND UNIT COSTS. Medication usage was based on trial data and was assumed constant for all. Exact costing used the patient proportion receiving each HF-related medication class at baseline, as reported in REVERSE. Proportions were applied to the generic wholesale acquisition cost price (22). The 2014 national average payment rates were used to estimate facility costs per HF hospitalization. Associated physicians’ payments were calculated from the 2010 PREMIER Hospital Database (Premier Inc., Charlotte, North Carolina).

HEALTH RELATED QUALITY OF LIFE AND UTILITY ESTIMATES. REVERSE included 2 health-related quality of life (HRQoL) questionnaires, neither of which were transferrable to healthcare utility values, a requirement for cost effectiveness analysis (23). Age- and sex-adjusted data from the U.S. general population informed the utility value for NYHA functional class I (24). The impact on HRQoL of NYHA functional classes II and III, relative to NYHA functional class I, were taken from a published study (25). The distribution of patients across classes at baseline was taken from REVERSE. The model dynamically calculated QALYs based on projected NYHA functional class allocation and proportion of patients alive at any moment in time. Heart failure-related hospitalizations had no impact on utility.

PROBABILISTIC SENSITIVITY ANALYSIS. Probabilistic sensitivity analysis was implemented to understand the impact of parameter uncertainty on the model.
results. For each parameter, 95% confidence intervals (CI) were used to inform the uncertainty estimate. In the absence of CIs, we used the simplifying assumption that the standard error was 10% of the mean. Beta distributions were used to quantify uncertainty in utility values. Log-normal distributions were used for uncertainty in device longevity and cost/resource parameters. Relationships between coefficients in all regression equations were maintained within the PSA via the use of multinomial distributions.

**SPECIFIC DEVICE TYPE AND CLINICAL PATHWAY ANALYSES.** To compare the cost effectiveness of CRT-D versus that of ICD and CRT-P versus that of OMT, we used the CRT-D versus CRT-P analysis and benefits of the CRT-OFF group, assuming the device-related costs in the latter were zero. In “real-world” clinical practice, these would either be ICD patients or patients without a device.

A separate analysis examined the cost differential between CRT-D implantation immediately upon class II diagnosis and a more “conventional”/“early” pathway of implanting a dual-chamber ICD and changing to CRT-D upon patient progression to class III. Discounting of 3% per year was incorporated in this analysis but not in CRT-P devices.

**RESULTS**

**ALL PATIENTS.** Probabilistic results, from the mean of 1,000 simulations, are detailed in Table 2. Cardiac resynchronization therapy–ON (CRT-D or CRT-P) offered a mean benefit of 1.39 QALYs (6.58 vs. 5.19, respectively) per patient versus CRT-OFF. Mean additional costs were $12,250 ($78,452 vs. $66,202, respectively), resulting in $8,840/QALY gained. No additional costs were $12,250 ($78,452 vs. $66,202, respectively) per patient versus CRT-OFF. Mean longevities, acquisition costs, and device-related costs in the latter were zero. In “real-world” clinical practice, these would either be ICD patients or patients without a device. A separate analysis examined the cost differential between CRT-D implantation immediately upon class II diagnosis and a more “conventional”/“early” pathway of implanting a dual-chamber ICD and changing to CRT-D upon patient progression to class III. Discounting of 3% per year was incorporated in this analysis but not in CRT-P devices.

**ADDITIONAL SENSITIVITY ANALYSES.** Univariate deterministic sensitivity analyses were run with mean device longevities, acquisition costs, and NYHA functional class utilities being varied by ±10%. The impact of these analyses was marginal (highest ICERs for CRT-ON/CRT-OFF and CRT-D/CRT-P were $10,976/QALY and $51,614/QALY, respectively [utility values: 10%]). Running the model using utility values solely from Gohler (24) also had a marginal impact.

**CLINICAL SUBGROUPS.** Results for all clinical subgroups are presented in Online Table S1. Deterministic results comprise mean estimates calculated for the “average” patient, assuming mean values for all inputs. Results are very similar to the “all patient” values reported in Table 2, suggesting little variation in cost effectiveness across subgroups. Subgroup-specific CEACs for CRT-ON versus CRT-OFF and CRT-D versus CRT-P are provided in Figures 2 and 3.

**EARLY” VERSUS “LATE” CRT-D SCENARIO ANALYSIS.** Discounted results are presented in Table 3. In the “early” versus “late” analysis, total treatment strategy cost, including an immediate CRT-D device implant for NYHA functional class II subjects, was projected to be $95,511. This was in contrast to $91,511 for an NYHA functional class II patient with an upgrade to CRT-D upon progression to NYHA functional class III. In this analysis, projected survival with an early implant was 8.11 years versus 7.12 years with a late implant, yielding an ICER of $3,785 per life year gained. Undiscounted results for the same scenario analysis are presented in Online Table S2.

**EXPLORATORY CRT-D VERSUS ICD AND CRT-P VERSUS OMT.** Cardiac resynchronization therapy using a pacemaker versus OMT generated an ICER of $17,413/QALY gained (95% CrI: $10,053 to $50,706). Cardiac resynchronization therapy using a defibrillator versus an ICD yielded $7,557/QALY (95% CrI: -$5,044 to $9,353). Thus, CRT devices can be regarded as cost effective in these comparisons (Online Table S3).

**TABLE 2**

<table>
<thead>
<tr>
<th>Table 2 Probabilistic Cost Effectiveness Results</th>
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<tbody>
<tr>
<td>Interval</td>
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</tr>
<tr>
<td>CRT-ON/CRT-OFF</td>
</tr>
<tr>
<td>LCrI</td>
</tr>
<tr>
<td>UCrI</td>
</tr>
<tr>
<td>Average</td>
</tr>
<tr>
<td>CRT-D/CRT-P</td>
</tr>
<tr>
<td>LCrI</td>
</tr>
<tr>
<td>UCrI</td>
</tr>
<tr>
<td>Average</td>
</tr>
</tbody>
</table>

LCrI = lower credible interval; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life years; UCrI = upper credible interval; other abbreviations as in Table 1.
DISCUSSION

The benefit of CRT in HF with a reduced ejection fraction is well established (2–4,7–9) and is part of the updated U.S. and E.U. guidelines for device-based therapy (26,27). However, this therapy’s cost effectiveness has been primarily demonstrated only in advanced HF (5,6), and these studies have several limitations. HF therapy has high initial costs, which may yield a cost effectiveness underestimation whenever the study duration is shorter than generator battery lifespan. Most of these studies were not double-blinded, which may influence treatments. Cost comparisons of CRT-P and ICD devices have not

FIGURE 1 Cost-Effectiveness Plane for “All Patient” Analysis for CRT-ON/CRT-OFF and CRT-D/CRT-P

CRT-D/CRT-P = cardiac resynchronization therapy defibrillator/cardiac resynchronization therapy pacemaker; CRT-ON/CRT-OFF = cardiac resynchronization therapy-ON/cardiac resynchronization therapy defibrillator-OFF.

FIGURE 2 Cost-Effectiveness Acceptability Curves (CRT-ON/CRT-OFF)

Abbreviations as in Figure 1.
been performed. Finally, little is known regarding the relative costs of early CRT use in mild HF versus postponing device implantation until disease severity progressed further (6).

To address these issues, a detailed analysis of REVERSE was performed. REVERSE was designed to ensure double-blinding and to maximize bias mitigation (14,15). We used the preplanned 5-year follow-up phase of this trial (11), as well as the separate analysis of subjects with CRT-P and CRT-D devices.

The main finding of these analyses was that CRT is cost effective compared with that of OMT in mild HF (CRT-ON vs. CRT-OFF) for the whole cohort. In addition, CRT-D represented a cost effective alternative to CRT-P. Finally, the incremental cost of an early class II CRT-D implant was minimal compared to that of an ICD followed by upgrade to CRT-D after the patient deteriorated to a NYHA functional class III status.

A previously published analysis of the MADIT-CRT study (10) compared CRT-D with ICD over 4 years. The ICER was $58,330/QALY, above the $50,000/QALY acceptability threshold. This investigation did not include CRT-P and was closer to a “health care system” perspective in its cost accounting (28,29), in contrast to the more common “payer” perspective used here (18). Therefore, our results cannot be compared with other reported ICERS.

Use of the device-cost accounting methods from MADIT-CRT (10) in our model yielded a 4-year ICER of $73,890/QALY (CRT-D vs. ICD). This demonstrates our modelling methods were equivalently conservative, and if the MADIT-CRT analyses extrapolated lifetime clinical benefits, a highly cost effective ICER would have likely also been demonstrated. Our analysis indicated that, compared to no CRT, CRT was highly cost effective in NYHA functional class II HF patients over a patient’s lifetime, which was implied previously in a European health care environment (29). MADIT-CRT (10) showed improved cost effectiveness among the subgroup with LBBB, which guidelines suggest is the subgroup most likely to benefit from

TABLE 3 Cost-Effectiveness Results*

<table>
<thead>
<tr>
<th></th>
<th>Total Cost</th>
<th>Total LYG</th>
<th>Total QALYs gained</th>
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<tbody>
<tr>
<td>Immediate CRT-D Implant</td>
<td>$95,292</td>
<td>8.11</td>
<td></td>
</tr>
<tr>
<td>Delayed CRT-D Implant</td>
<td>$91,511</td>
<td>7.12</td>
<td>Not Evaluated</td>
</tr>
<tr>
<td>Incremental</td>
<td>$3,795</td>
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</tr>
<tr>
<td>ICER ($/QALY Gained)</td>
<td>$3,795</td>
<td></td>
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</table>

*“Early” versus “late” CRT-D implantation. LYG = Life Years Gained; other abbreviations as in Tables 1 and 2.
CRT. Recent studies have suggested that QRS duration may be more important than QRS morphology (i.e., bundle branch type) (30). Thus, the benefit noted in REVERSE is important if further studies support CRT guideline broadening as the cost-effectiveness was noted with all subjects included.

Probabilistic methods were used to include and quantify the uncertainty around results. Probabilistic sensitivity analysis revealed that CRT likely is a cost effective option compared to non-biventricular pacing. Cardiac resynchronization therapy with a defibrillator, even if the average ICER compared to CRT-P is close to the $50,000/QALY threshold, the probability exceeded is < 10%. As battery longevity continues to improve, CRT-Ds are highly likely to be more cost effective in this patient population.

Cardiac resynchronization therapy with pacemakers (4) and CRT-Ds (3,9) have been shown to reduce mortality among patients with HF with a reduced ejection fraction and QRS prolongation. Limited data are available directly comparing both of these device types. Of the current large prospective, randomized trials, only the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial and REVERSE included both CRT-Ps as well as CRT-Ds. In COMPANION, subjects were randomized to CRT-P, CRT-D, or OMT (3). There was a trend toward better survival with CRT-D, but the study was statistically underpowered. In REVERSE (7), device choice was based on local guidelines at time of implantation, and subjects were randomized to CRT-ON or CRT-OFF groups. We recently showed CRT-D was associated with better long-term survival in REVERSE (11). The guidelines recommend that device choice should be based in part on costs and on patient life expectancy (25).

Despite common use of CRT-D devices in clinical practice, incremental cost effectiveness has until now not been adequately addressed. MADIT-CRT and CARE-HF (Cardiac Resynchronization-Heart Failure) trial evaluations were unable to evaluate this issue due to lack of appropriate data as only 1 device type was included in each study. The COMPANION analysis (5) did not report CRT-D versus CRT-P values. Calculations based on the published data suggest that comparative ICERs may have been in the “expensive” or “economically unattractive” ranges (31,32). This is not surprising, because COMPANION (3) did not show a survival benefit of CRT-D versus CRT-P. Regardless, optimal CRT device choice remains difficult and controversial (6), as a recent assessment demonstrates (31). The National Institute for Health and Care Excellence (29) concluded that both of the device types were acceptable based on clinical and cost effectiveness data. The present results support and extend this conclusion to mild HF, as we report ICERs remain below the $50,000/QALY threshold for CRT-D compared with CRT-P in REVERSE.

Finally, our analyses strongly support use of CRT as an early intervention in NYHA functional class II patients rather than withholding such therapy until more advanced HF is present. The indication for ICD use in mild HF is well-established, and the beneficial effects on mortality in these patients have been clearly shown (33). Moreover, it was established that ICD device implantation was more cost-effective than medication (34). The RAFT results (9) showed a mortality benefit of CRT-D versus ICD. This analysis extends these observations showing that early CRT-D use essentially has cost parity compared with ICD implantation and CRT-D at a later time point in those subjects with HF progression. It is noteworthy that this analysis accounted for the shorter battery life and increased complications associated with CRT-D.

**STUDY LIMITATIONS.** Our analysis should be interpreted in light of several methodological limitations. The OMT comparator was based on patients randomized to CRT-OFF, and most had back-up defibrillation and pacing (VVI at 35 beats/min). In “real-world” practice, these would certainly not be patients with an inactivated CRT device. In this analysis, CRT-OFF patients were treated as medication-only and incurred no device-related costs but accumulated ICD benefits (85% of subjects with CRT-Ds). This may improve the performance in the control group by reducing sudden cardiac death, making the CRT-D/ICD analysis highly conservative.

On the other hand, 15% of the patients (28 of 191) randomized to CRT-OFF were programmed to backup VVI/DDD pacing without a pacing indication. These patients could have worse outcomes than nondevice patients. The programmed lower rate by protocol was ≤35 beats/min (sometimes 30 beats/min). During the randomization period that informed our statistical modelling the pacing was <1% in all such patients. Therefore, even if backup pacing could have introduced bias, this did not actually occur.

Lead implant location has also been shown to be important in clinical outcomes after CRT. An analysis from REVERSE suggested significantly better outcomes with LV lateral and nonapical locations (35). More recent studies have shown that pacing at LV sites with late mechanical or electrical activation are associated with better outcomes (36,37). Of the 346 patients with implant location data, 66.18% (n = 229) had lateral LV leads, and 71% had nonapical locations.
We did not adjust for implant location in our analyses. Therefore, the results may underestimate the cost effectiveness of CRT when newer techniques to choose implant locations are used.

For the “early” versus “late” analysis, we assumed patients who received implants when progressing to class III, received benefits (and costs) mimicking those of CRT-ON. With CRT-ON patients being class I/II at time of implantation, we might have overestimated the benefits associated with delayed implantation and been biased against early implantation.

The limitations of the extrapolated clinical data we used have been described previously (13). The applicability of the statistical models used has been well validated in clinical trials. Importantly, 508 of 610 (83.27%) patients had CRT-D devices. This adds to the uncertainty of the results in the CRT-D versus CRT-P comparison.

The costing methods we used also erred on the side of caution. We assumed all AEs observed in REVERSE post-implantation (approximately 10.5% per patient, excluding generator change-outs that were cost separately, over an average follow-up period of 4.49 years) happened at the same time as the implantation. This meant minimal discounting of what in reality would be future costs. We also assumed all AEs would be paid as a HF hospitalization, when many were not hospitalized. Some of these AEs would have also been accounted as adjudicated HF-related hospitalizations, leading to double-counting in the analysis, working against CRT.

CONCLUSIONS

Cardiac resynchronization therapy using CRT-D and CRT-P devices represent a highly cost-effective option for patients with mildly symptomatic HF compared to ICD and OMT, respectively. In addition, CRT-D devices are below the U.S. acceptability threshold of $50,000/QALY compared with CRT-Ps. Finally, a clinical strategy of immediate CRT-D device implantation when the patient has mild HF (NYHA functional class II) is projected to have essentially similar overall payer costs compared with waiting to implant this device until the patients develops more advanced HF.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: CRT is established as beneficial in NYHA functional class II HF patients. Recent studies have also demonstrated benefits in disease progression, reduced hospitalization rates and increased survival in mild HF. We reaffirm the cost effectiveness of CRT in NYHA functional class II patients under the Medicare setting and additionally demonstrate how the incremental cost of CRT-D devices is justified by their additional benefit over CRT-Ps. Last, we demonstrate that delaying referral for CRT does not significantly save costs because savings realized are offset by the increased costs of hospitalizations. This holds true despite shorter longevity of CRT devices and increased CRT recipient survival.

TRANSLATIONAL OUTLOOK: These data can be used to inform optimal decision making in patients with a guideline-based indication for device implantation. They can also be used as important inputs in environments where economic value plays a role, especially alternative payment models gradually being introduced.

REFERENCES

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**KEY WORDS** cardiac resynchronization therapy, cost effectiveness, health economics, health policy, heart failure

**APPENDIX** For supplemental tables, please see the online version of this article.