Cost-Effectiveness of Cardiac Resynchronization Therapy in Patients with Symptomatic Heart Failure

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Background: Heart failure is a common, costly, and debilitating illness. Resynchronization of ventricular contraction in patients with heart failure improves ejection fraction. The long-term morbidity and costs associated with such cardiac resynchronization therapy remain unclear.

Objective: To assess the incremental cost-effectiveness of cardiac resynchronization therapy.

Design: Markov model with Monte Carlo simulation. Future costs and effects were discounted at 3%.

Data Sources: Effects data were obtained from a concurrent systematic review. Health-related quality-of-life and cost data were obtained from publicly available data or from surveys.

Target Population: Patients with reduced ventricular function and prolonged QRS.

Time Horizon: Lifetime.

Perspective: U.S. health care system.

Interventions: Cardiac resynchronization therapy versus medical therapy.

Outcome Measures: Quality-adjusted life-years (QALYs), costs, and incremental cost-effectiveness.

Methods

Congestive heart failure is a common, costly, and debilitating illness. It affects an estimated 4.8 million patients in the United States, and 400 000 new cases are identified every year (1). Approximately 30% to 50% of patients with heart failure have major intraventricular conduction delay, which is associated with higher risk for adverse events (2, 3). Biventricular pacemakers resynchronize the ventricular contraction to improve ejection fraction and relaxation of the left ventricle (4). However, not all therapies that improve functional outcomes in patients with heart failure reduce mortality (5).

The long-term mortality, morbidity, and costs associated with cardiac resynchronization therapy remain unclear. Economic evaluation of an intervention assesses its effectiveness and costs so that decision makers can decide whether it is good value for the money. If cardiac resynchronization is effective and inexpensive, then the lives of thousands will be improved annually. If not, then limited health care resources can be invested in other interventions that are better value for the money. We used decision analysis to estimate the incremental cost-effectiveness of cardiac resynchronization therapy versus medical therapy.

Results of Base-Case Analysis: Medical therapy yielded a median of 2.64 (interquartile range, 2.47 to 2.82) discounted QALYs and a median discounted lifetime cost of $34 400 (interquartile range, $31 100 to $37 700). Cardiac resynchronization therapy was associated with a median incremental cost of $107 800 (interquartile range, $79 800 to $156 500) per additional QALY.

Results of Sensitivity Analysis: Results were sensitive to changes in several variables, including the relative risk for death or hospitalization.

Limitations: These results apply to patients who meet the inclusion criteria of the currently completed trials.

Conclusions: The incremental cost per QALY for cardiac resynchronization is similar to that of other commonly used interventions but is sensitive to changes in several key variables. Resynchronization therapy should not be considered in patients with comorbid illness that shortens life expectancy.


See related article on pp 381-390 and editorial comment on pp 399-400.
Assigning the utility for the health state before hospitalization to the remainder of the cycle. Finally, age-specific mortality due to unrelated causes was based on life tables (11).

Structure of the Decision Model

The base-case analysis considered patients with New York Heart Association (NYHA) class III heart failure. The analysis considered the lifetime horizon, as recommended elsewhere (12). A state-transition Markov model compared costs and outcomes of congestive heart failure treated with cardiac resynchronization therapy versus medical therapy. A cycle length of 1 month was used.

During each cycle, patients who received medical therapy could die, be hospitalized for heart failure, or remain stable (Figure 1). Patients who underwent insertion of a device capable of cardiac resynchronization could die during the initial implantation; experience lead infection, lead failure, and battery failure; or experience any of the health states associated with medical therapy for heart failure (Figure 2).

Figure 1. Markov model of medical therapy for heart failure.

The reference-case analysis considered only the effect of resynchronization on all-cause mortality, since it is difficult to subclassify causes of death in patients with cardiovascular disease (13). The concurrent systematic review (14) considered death due to any cause, cardiac death, and sudden cardiac death separately. However, the pooled relative risk for cardiac death and sudden cardiac death was based on retrospective subgroup analyses of data observed in the randomized trials of cardiac resynchronization therapy. Such post hoc determinations may be susceptible to bias. Therefore, cardiac and noncardiac death were considered only in secondary economic analyses that accounted for patient age at implantation (that is, differences in mortality due to unrelated causes).

Decision analyses were performed by using DATA Pro (TreeAge Software, Inc., Williamstown, Massachusetts) and Excel 2000 (Microsoft Corp., Redmond, Washington). Statistical analyses were performed with S-PLUS (Insightful Corp., Seattle, Washington).

Input Data

Survival and Hospitalization

We obtained the probabilities of cardiovascular death, arrhythmic death, death from heart failure, hospitalization for heart failure, and adverse effects associated with either therapy from a concurrent systematic review (14). Nine trials were included in the efficacy analysis: a study from the Multisite Stimulation in Cardiomyopathies (MUSTIC) Study Investigators examining sinus rhythm (4); a study from the MUSTIC Study Investigators examining atrial fibrillation (15); a trial by Garrigue and colleagues (16); the Pacing Therapies for Congestive Heart Failure (PATH-CHF) trial (17); a trial examining the safety and effectiveness of the Guidant Cardiac Resynchronization Therapy Defibrillator System (CONTAK-CD) (18); the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) (19, 20); the Multicenter InSync Randomized Clinical Evaluation Implantable Cardioverter Defibrillator (MIRACLE-ICD) (21); the Comparison of Medical Therapy, Pacing and Defibrillation in Chronic Heart Failure (COMPANION) (22); and 1 trial that remains unpublished (Leclercq C, Alonso F, d’Alonnes FR, et al. Effets à moyen terme de la stimulation multisite biventriculaire dans l’insuffisance cardiïque séveé. Personal communication. May 2003).

We annualized the rate of events observed among patients randomly assigned to medical therapy by using an exponential approximation (23, 24). Transition probabilities incorporated into the Markov model were adjusted for the cycle length. Pooled relative risks were calculated by using fixed-effects methods (25).

Quality of Life

We estimated the health-related quality of life of patients with heart failure by eliciting utilities (Appendix, available at www.annals.org), since current standards sug-
gest that use of such outcome measures (7) and the relative cost-effectiveness of some cardiac therapies are sensitive to the difference between the utilities associated with either treatment (8). The general public was surveyed because the analysis considered resource allocation among different types of interventions (that is, medical therapy vs. resynchronization) rather than allocation for a single intervention (7).

**Costs**

The economic analysis was conducted from a health care perspective, including costs of hospitalization, procedures, and laboratory tests. Costs were expressed in 2003 U.S. dollars (Table 1). The costs of insertion of a resynchronization-capable device were based on a survey of manufacturers’ list prices. Physician costs related to cardiac resynchronization were based on Current Procedural Terminology codes (26). The costs of hospitalizations associated with congestive heart failure were based on estimates derived from a cohort study of health resource use by patients participating in a previous randomized trial of medical therapy for heart failure (9). All costs were adjusted for inflation by using the U.S. Consumer Price Indexes (27).

**Uncertainty and Variability Analyses**

The analysis distinguished between parameter uncertainty (that is, variation in costs and effects due to sampling and measurement error) and variability (that is, heterogeneity in costs and effects between groups of patients with systematic differences in cost or effects). Uncertainty was assessed by using 10 000 probabilistic Monte Carlo simulations (28, 29). Empirical cost variables were assigned
Table 1. Input Data*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Best Estimate</th>
<th>Lowest Estimate</th>
<th>Highest Estimate</th>
<th>Threshold Value</th>
<th>Strategy Favorable by Values Higher Than Threshold</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of patient, y</td>
<td>60</td>
<td>50</td>
<td>70</td>
<td>NA</td>
<td>Assumed</td>
<td></td>
</tr>
<tr>
<td>Annual rate of death without CRT, %</td>
<td>24.7</td>
<td>20.7</td>
<td>29.2</td>
<td>0.78</td>
<td>Medical</td>
<td>6</td>
</tr>
<tr>
<td>Relative risk for death with CRT</td>
<td>0.79</td>
<td>0.66</td>
<td>0.96</td>
<td>0.78</td>
<td>Medical</td>
<td>6</td>
</tr>
<tr>
<td>Annual rate of heart failure hospitalization without CRT, %</td>
<td>56.0</td>
<td>47.6</td>
<td>66.2</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Relative risk for heart failure hospitalization with CRT</td>
<td>0.68</td>
<td>0.41</td>
<td>1.12</td>
<td>0.68</td>
<td>Medical</td>
<td>6</td>
</tr>
<tr>
<td>Annual rate of cardiac death without CRT, %</td>
<td>20.3</td>
<td>15.1</td>
<td>27.0</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Relative risk for cardiac death with CRT</td>
<td>0.60</td>
<td>0.36</td>
<td>1.01</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Relative risk for death due to unrelated causes with CRT</td>
<td>1.0</td>
<td>0</td>
<td>1.1</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Annual rate of lead infection, %</td>
<td>2.0</td>
<td>1.1</td>
<td>3.2</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Annual rate of lead failure, %</td>
<td>13.7</td>
<td>11.7</td>
<td>16.1</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Annual rate of battery replacement, %</td>
<td>10.8</td>
<td>8.7</td>
<td>13.4</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
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<tr>
<td>Probability of death during insertion, %</td>
<td>0.4</td>
<td>0.2</td>
<td>0.7</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Probability of death during lead infection, %</td>
<td>1.0</td>
<td>0</td>
<td>10</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Probability of death during lead failure, %</td>
<td>1.0</td>
<td>0</td>
<td>10</td>
<td>2.3</td>
<td>Medical</td>
<td>Assumed</td>
</tr>
<tr>
<td>Probability of death during battery replacement, %</td>
<td>1.0</td>
<td>0</td>
<td>10</td>
<td>2.0</td>
<td>Medical</td>
<td>Assumed</td>
</tr>
<tr>
<td>Utility of NYHA class III heart failure</td>
<td>0.84</td>
<td>0.71</td>
<td>0.98</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Utility of NYHA class IV heart failure</td>
<td>0.74</td>
<td>0.58</td>
<td>0.91</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
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<tr>
<td>Utility of hospitalization for heart failure</td>
<td>0.57</td>
<td>0.48</td>
<td>0.80</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Relative utility of heart failure with CRT</td>
<td>1.0</td>
<td>0.9</td>
<td>1.1</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Duration of hospitalization for CRT implantation</td>
<td>5 d</td>
<td>0</td>
<td>1 mo</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Duration of hospitalization for lead failure</td>
<td>5 d</td>
<td>0</td>
<td>1 mo</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Duration of hospitalization for lead infection</td>
<td>5 d</td>
<td>0</td>
<td>1 mo</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Duration of hospitalization for battery replacement</td>
<td>5 d</td>
<td>0</td>
<td>1 mo</td>
<td>NA</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>Discount rate for future costs and effects, %</td>
<td>3</td>
<td>0</td>
<td>10</td>
<td>NA</td>
<td>Medical</td>
<td>7</td>
</tr>
<tr>
<td>Cost of CRT insertion, $</td>
<td>33 495</td>
<td>16 747</td>
<td>50 242</td>
<td>31 000</td>
<td>Medical</td>
<td>Survey</td>
</tr>
<tr>
<td>Monthly cost of CRT, $</td>
<td>771</td>
<td>385</td>
<td>1 216</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Cost of hospitalization for lead infection, $</td>
<td>30 997</td>
<td>15 499</td>
<td>46 496</td>
<td>NA</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Cost of hospitalization for lead failure, $</td>
<td>30 997</td>
<td>15 499</td>
<td>46 496</td>
<td>25 800</td>
<td>Medical</td>
<td>8</td>
</tr>
<tr>
<td>Cost of battery replacement, $</td>
<td>28 835</td>
<td>14 417</td>
<td>43 252</td>
<td>23 200</td>
<td>Medical</td>
<td>8</td>
</tr>
<tr>
<td>Cost of heart failure hospitalization, $</td>
<td>15 427</td>
<td>10 660</td>
<td>20 193</td>
<td>NA</td>
<td>NA</td>
<td>9</td>
</tr>
</tbody>
</table>

* CRT = cardiac resynchronization therapy; NA = not applicable; NYHA = New York Heart Association.
† Considered only in secondary analysis of age at implantation.

Table 1. Input Data

We replaced the value of each variable in the decision model with its upper and lower limits while holding all other values constant (Table 1) (35, 36). For empirical variables, these limits were the 95% CIs for each variable. For assumed variables (for example, cost of insertion of the cardiac resynchronization device and discount rate), these limits were based on reasonable possible limits (that is, ±50%). Threshold analyses identified the value of each variable across its range (if any) at which the decision maker should be indifferent between medical therapy or cardiac resynchronization (that is, when the incremental cost per QALY was $100 000) (36). Sensitivity analyses considered lower incidences of device-related adverse effects than those observed in the trials. The duration of study follow-up in each trial was relatively short, and the observed incidence of adverse effects was higher than is generally accepted for implantable cardioverter defibrillator use (10), which may reflect relative inexperience with devices capable of cardiac resynchronization.

A structural sensitivity analysis considered cardiac death and death due to unrelated causes simultaneously, in log-normal distributions, and empirical probability variables were assigned β distributions (28). Variables without a known distributional form (that is, those with assumed values or those with values based on a range of published reports) were assigned triangular distributions (30). Since there is no absolute cost-effectiveness criterion (31), the results of the Monte Carlo simulation were illustrated as a scatter plot of incremental effects in quality-adjusted life-years (QALYs) versus incremental costs. In such a plot, the incremental cost-effectiveness ratio is represented by the slope of incremental costs to incremental effects. The uncertainty in costs and effects was also illustrated as a cost-effectiveness acceptability curve (32–34). An acceptability curve is a conditional probability plot showing the proportion of the observed incremental cost-effectiveness density that lies below a threshold ratio (λ), which represents the monetary value of a QALY. The plot is conditional on λ, and therefore the decision maker can interpret the data relative to the threshold willingness to pay for the incremental health outcome.

Variability was assessed by using sensitivity analyses.
order to assess the robustness of the results to changes in the age of the patient at implantation. Finally, subgroup analyses considered the incremental cost-effectiveness of cardiac resynchronization for patients with NYHA class IV heart failure by substituting the appropriate weight for health-related quality of life.

Role of the Funding Sources
The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS
Effectiveness of Medical Therapy
Nine trials randomly assigned 1131 patients (median per study, 154 [interquartile range, 18 to 230]) to medical therapy. The mean annual mortality rate was 24.7% (95% CI, 20.7% to 29.2%) during a mean follow-up of 26.2 weeks. The mean annual rate of heart failure hospitalization was 56.0% (CI, 47.6% to 66.2%) during a mean follow-up of 18.5 weeks, and the mean annual rate of cardiac death was 20.3% (CI, 15.1% to 27.0%) during a mean follow-up of 15.8 weeks.

Effectiveness of Cardiac Resynchronization Therapy
Nine trials randomly assigned 2041 patients (median per study, 228 [interquartile range, 25 to 35]) to cardiac resynchronization. The pooled relative risks for death, heart failure hospitalization, and cardiac death were 0.79 (CI, 0.66 to 0.96), 0.68 (CI, 0.41 to 1.12), and 0.84 (CI, 0.56 to 1.25), respectively.

Model Validation
In these trials, the estimated mean annual mortality rate among controls was 24.7%. The mortality rate within 1 year was 22.9% among patients who received medical therapy, as estimated by the Markov model. Conversely, the estimated mean annual mortality rate among patients allocated to the control group in recent large long-term trials ranged from 11% to 20% (37–39).

Cost-Effectiveness of Cardiac Resynchronization Therapy
In patients with heart failure, medical therapy yielded a median of 2.64 (interquartile range, 2.47 to 2.82) discounted QALYs and a median discounted lifetime cost of $34 400 (interquartile range, $31 100 to $37 700) (Table 2). Cardiac resynchronization therapy yielded a median of 2.92 (interquartile range, 2.72 to 3.14) discounted QALYs with a median discounted lifetime cost of $64 400 (inter-

### Table 2. Potential Cost-Effectiveness of Cardiac Resynchronization Therapy Compared with Medical Therapy*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median Discounted QALYs (Interquartile Range)</th>
<th>Median Discounted Lifetime Cost (Interquartile Range), $</th>
<th>Median Incremental Cost-Effectiveness (Interquartile Range), $/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical therapy</td>
<td>2.64 (2.47–2.82)</td>
<td>34 400 (31 100–37 700)</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac resynchronization therapy</td>
<td>2.92 (2.72–3.14)</td>
<td>64 400 (59 000–70 200)</td>
<td>107 800 (79 800–156 500)</td>
</tr>
</tbody>
</table>

* NA = not applicable; QALY = quality-adjusted life-year.
† 2003 U.S. dollars rounded to the nearest hundred.

Uncertainty Analyses
Figure 3 is a scatter plot that illustrates the uncertainty in the expected incremental costs and QALYs for resynchronization versus medical therapy in the reference case. Data points from Monte Carlo simulation illustrate that compared with medical therapy, resynchronization is consistently associated with a gain in QALYs and additional cost.

The cost-effectiveness acceptability curve illustrates a probability of less than 45% that resynchronization is cost-effective compared with medical therapy, given a maximum willingness to pay of $100 000 per QALY (Appendix Figure, available at www.annals.org).

Variability Analyses
The incremental cost-effectiveness of resynchronization was sensitive to reasonable changes in the value of several variables, including the relative risk for death or hospitalization with resynchronization and the probability of death during lead failure or battery replacement (Table 1). Also, when resynchronization therapy was associated with greater health-related quality of life or lower risk for device-related adverse effects than medical therapy, then the incremental cost-effectiveness of resynchronization was reduced (data not shown; details available from the authors).

DISCUSSION
To our knowledge, this is the first published economic evaluation of the long-term costs and effects of cardiac resynchronization therapy compared with medical therapy in patients with heart failure. The point estimate for the incremental cost per QALY is similar to that of other common medical interventions (40). The results were sensitive to changes in the relative risks for death or hospitalization, as well as other factors. Our results should be interpreted cautiously, given the magnitude in the uncertainty of incremental costs and incremental effects, the sensitivity of the results to changes in the value of several variables, and the recognition that patients with heart failure in clinical trials may not be representative of those in everyday practice (41, 42).

Our analysis has several strengths. It used currently

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recommended methods of economic evaluation (7), and the effectiveness estimates incorporated into the decision analysis were based on a high-quality systematic review (14). Long-term effects and costs were considered. The analysis was based on the framework of a previously published economic analysis (10) in order to facilitate comparison of the economics of different interventions in patients with cardiovascular disease.

Our analysis also has limitations. The concurrent systematic review demonstrated a differential effect of resynchronization therapy on all-cause mortality versus cardiac death alone. However, the analysis of cardiac death alone is susceptible to bias because it is difficult to assign cause of death in cardiovascular trials (13). In a separate but related patient sample, insertion of implantable cardioverter defibrillators was associated with increased rates of early death (43). Although the pooled effect of implantable cardioverter defibrillators in patients at risk for sudden death is beneficial (44, 45), use of a combined implantable cardioverter defibrillator and biventricular pacemaker will not necessarily decrease mortality rates (46). Since patients with heart failure experience fatal bradyarrhythmia and tachyarrhythmia, a large randomized trial is evaluating the effect of devices with implantable cardioverter defibrillator and biventricular pacemaking capability (Tang AS. Personal communication).

The experience observed with these patients and providers may not be applicable to other settings since only selected patients and experienced physicians participated in the randomized trials of the effectiveness of cardiac resynchronization. If the results are not applicable to other settings, our analysis overestimates survival and underestimates the incremental cost of resynchronization in patients with heart failure. Conversely, if adverse effects become less frequent as providers gain experience, our analysis underestimates survival and overestimates the incremental cost of resynchronization in patients with heart failure. This consideration is important since our results were sensitive to death associated with complications of resynchronization. The incidence of adverse events should be monitored as cardiac resynchronization becomes more broadly used.

The incidence of complications associated with cardiac resynchronization probably decreases over time, whereas our analysis assumed that it was constant. If the former is true, then the model underestimates survival and overestimates the incremental cost-effectiveness of resynchronization. Long-term follow-up of patients enrolled in the previously completed trials will determine whether the incidence of complications does decline over time.

Resynchronization is associated with significant improvements in health-related quality of life compared with medical therapy (6). If we had assumed that such trial-related short-term benefits persisted, it would have biased our results in favor of the intervention. Instead, the reference-case analysis assumed no difference in quality of life. Secondary analyses demonstrated that if resynchronization improves quality of life, then it is an even better value compared with medical therapy. Also, it is unlikely that the relative benefit of resynchronization will remain constant as the severity of heart failure increases. Therefore, as results from trials of resynchronization become available, our analysis should be revised to reflect better estimates of this therapy’s true effectiveness and costs.

Our model did not consider short-term or long-term

Figure 3. Distribution of incremental costs versus incremental effects for cardiac resynchronization therapy versus medical therapy.

For the base-case point estimate (white X), incremental costs $30,252 and incremental effect 0.282 quality-adjusted life-year (QALY).
benefits and costs of selected surgical interventions for patients with heart failure. Cardiac transplantation is widely available but is infrequently used because of supply constraints and is associated with many long-term complications that were outside the scope of our analysis. Ventricular assistance devices increase survival and improve quality of life (47) but have frequent side effects and are expensive. A large trial sponsored by the National Institutes of Health is currently evaluating surgical remodeling. None of these interventions have been shown to be effective in patients with moderate heart failure (that is, NYHA class II to III), similar to the patients studied in the trials of cardiac resynchronization. We assumed that heart failure costs were constant. However, resynchronization will decrease these costs if any associated ventricular remodeling decreases the use of outpatient drug therapy or the duration of hospital stays.

Another limitation of our study is that it uses a health care system perspective rather than the recommended societal perspective (7). This is an important limitation for health interventions that have significant cost sharing or a major impact on other sectors of the economy (such as maternal care). However, heart failure mainly affects individuals' health or health system costs, since most patients with heart failure are eligible for Medicare. While there could be other burdens on patients’ households, such as informal care, these would be highly correlated with health function. Estimation of the impact of such additional effects, usually referred to as process utility, is often difficult. Appropriate techniques to estimate them are only now emerging (48). Process disutility can be associated with new technology, such as resynchronization (49), and would reduce its incremental cost-effectiveness. However, this effect would dissipate over time as the technology became more widely used. Therefore, use of a health care system perspective rather than a societal perspective does not meaningfully affect our estimates of the incremental cost of resynchronization.

Finally, our input data were derived from several sources and may be confounded by information that was not incorporated into the model. For example, the effectiveness of resynchronization was not adjusted for comorbid conditions. Until additional data on the long-term effectiveness and costs of cardiac resynchronization are available, device implantation should be limited to patients who meet the current trials' inclusion criteria in the absence of comorbid illness.

Cardiac resynchronization has similar incremental costs per QALY when compared with other commonly used health interventions for patients with heart failure. Resynchronization therapy should not be considered in patients with comorbid conditions that shorten life expectancy. These findings should be reevaluated when the long-term incidence of complications of resynchronization is known.

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**References**

Cardiac Resynchronization Therapy in Patients with Symptomatic Heart Failure

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ior. Princeton, NJ; Princeton Univ Pr; 1944.
APPENDIX: HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH HEART FAILURE

Overview

The health-related quality of life of hypothetical patients with heart failure was estimated by using utilities, as part of an ongoing decision analysis of the cost-effectiveness of medical therapy for patients with heart failure (Heart and Stroke Foundation of Canada grant no. NA4443). Health-related quality of life was valued as utilities because current standards suggest that use of such outcome measures (7) and the relative cost-effectiveness of some cardiac therapies are sensitive to the magnitude of the difference between the utilities associated with either treatment (8).

Sampling Frame

An interesting methodologic issue is whether such utilities should be obtained from persons with the condition of interest or from members of the general public. A generic source of preferences is recommended, since the purpose of a decision analytic model is to consider an intervention in the context of choosing among interventions for different target disorders (that is, cancer vs. cardiovascular disease) (7). Therefore, we recruited a convenience sample of members of the general public from persons living in the community in Ottawa, Ontario, Canada. Inclusion criteria were fluency in English, ability to consent, age older than 40 years, and no known cardiac disease.

Creation of Descriptive Scenarios

Four health states were considered: NYHA functional class II, III, and IV heart failure and heart failure severe enough to require hospitalization (although the resynchronization therapy considered class III or IV heart failure but not class II). These hypothetical scenarios described what patients would typically feel and experience if living with each of these health states. The scenarios included a short text describing the health state followed by a systematic presentation of the attributes of the Health Utilities Index Mark III (50, 51), in point form.

The scenarios were structured similarly, and differences between each health state were highlighted in bold font. The scenarios were written in second person singular at a grade 6 reading level. Labels were carefully avoided. For example, *NYHA class II heart failure was described as “Condition A,” and terms such as heart attack or chest pain were avoided so that the nature of each condition was unknown to the respondent. The use of such labels introduces bias in generating utilities (52). To avoid double-counting life expectancy in the QALY measure, an estimate of prognosis or life expectancy was not provided in the descriptions of the health states. Respondents were simply told that each health state would last for the rest of their lives. An expert panel of 4 cardiologists with experience in treatment of heart failure developed the content of the scenarios.

Instrumentation

The standard gamble technique of eliciting preferences was used for the following reasons. First, it is based on the axioms of utility theory (53). Second, it places the respondent in a situation of uncertainty and forces him or her to make a trade that simulates the context of decision making in health care. The standard gamble offers a choice between 2 alternatives: living in a less-than-perfect health state or taking a gamble with a probability chance of perfect health (p) and a chance of immediate painless death (1 − p). The probabilities of perfect health and death were varied in a converging “ping-pong” order until the respondent was indifferent between either option (54). The utility score was defined as being equal to this indifference probability p'.

Interview Format

Eliciting patient preference through the standard gamble technique has been criticized because it is time-consuming, is conceptually difficult for the respondent to understand, and requires both well-trained interviewers and carefully designed props (55). To overcome these potential limitations, we created a computerized interview with voice, text, and a graphic display of the standard gamble. The structure of the interview was as follows.

A research assistant was present throughout the interview process to ensure its proper conduct. Each respondent read and signed a consent form that explained the purpose and the nature of the interview. The consent form emphasized the hypothetical nature of the health states that would be described and stressed that there was no right or wrong answer.

The following characteristics were elicited from each respondent: age, sex, level of education, and number of comorbid illnesses (56). The presentation continued with 2 examples of health states: “blind in 1 eye” and “blind in both eyes.” Each of these was followed by a standard gamble. The use of such examples is intended to ensure that respondents understand the standard gamble, since it is reasonable to expect that “blind in 1 eye” would yield higher utilities than “blind in both eyes.” Respondents who reported a higher utility for “blind in both eyes” than “blind in 1 eye” were excluded from the analysis.

Next, respondents completed a standard gamble for each of

Appendix Table. Characteristics of Respondents*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>49 ± 7†</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>36 (60)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
</tr>
<tr>
<td>High school</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Diploma</td>
<td>20 (33.3)</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>19 (31.7)</td>
</tr>
<tr>
<td>Master’s degree</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Earned doctorate</td>
<td>2 (3.3)</td>
</tr>
<tr>
<td>Comorbid conditions, n (%)</td>
<td></td>
</tr>
<tr>
<td>Angina or ischemic chest pain</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Peripheral vascular disease or claudication</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Emphysema or COPD</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Peptic ulcer disease or stomach ulcers</td>
<td>6 (10.0)</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Kidney disease or renal failure</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Cancer</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Unable to move one side of the body</td>
<td>3 (5.0)</td>
</tr>
<tr>
<td>Stayed in the hospital for heart failure</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stayed in the hospital for myocardial infarction</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Stayed in the hospital for a stroke</td>
<td>1 (1.7)</td>
</tr>
</tbody>
</table>

* COPD = chronic obstructive pulmonary disease.
† Mean ± SD.
the 4 health states successively. An interesting methodologic issue was whether scenarios should be presented in a fixed or random order. The latter approach would have required use of a Latin-square design to test for possible order effects (57). However, it is easier for respondents to form a coherent preference structure if scenarios are presented in a logical sequence (58, 59). Therefore, the scenarios were presented to each respondent in order of increasing severity of illness, from NYHA class II heart failure to hospitalization for heart failure. At the end of the process, the computer program generated a printed output of the respondent’s data. Qualitative data were gathered about any comments or difficulties expressed by respondents.

Sample Size and Statistical Analysis
We elicited utility values primarily to develop input data for decision analysis rather than to test for significant differences between states. For the pilot phase of this study, we interviewed a convenience sample of 6 respondents. In the pilot study, the mean (±SD) utility of each health state was 0.96 ± 0.08 for NYHA class II heart failure, 0.92 ± 0.07 for NYHA class III heart failure, 0.86 ± 0.20 for NYHA class IV heart failure, and 0.80 ± 0.24 for hospitalization for heart failure. On the basis of the results of the pilot study, a sample size of 66 would be associated with a precision of ±0.010 for NYHA class II heart failure, ±0.008 for NYHA class III heart failure, ±0.024 for NYHA class IV heart failure, and ±0.029 for hospitalization for heart failure. Utilities for each health state were summarized as the mean (±SD).

Human Participants
Informed consent was obtained before interviews were conducted, and strict participant confidentiality was maintained at all times. The research ethics committee of the Ottawa Health Research Institute approved the protocol for this study before any patient data were collected.

Results
Respondents (n = 66) were predominantly middle-aged women with no previous experience of cardiovascular disease (Appendix Table). Mean utilities (±SD) for each health state were 0.82 ± 0.16 for NYHA class II heart failure, 0.72 ± 0.21 for NYHA class III heart failure, and 0.58 ± 0.25 for NYHA class IV heart failure.

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