Cost-Effectiveness of Dual-Chamber Pacing Compared With Ventricular Pacing for Sinus Node Dysfunction

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Background—Compared with single-chamber ventricular pacing, dual-chamber pacing can reduce adverse events and, as a result, improve quality of life in patients paced for sick sinus syndrome. It is not clear, however, how these benefits compare with the increased cost of dual-chamber pacemakers.

Methods and Results—We used 4-year data from a 2010-patient, randomized trial to estimate the incremental cost-effectiveness of dual-chamber pacing compared with ventricular pacing and then projected these findings over the patients’ lifetimes by using a Markov model that was calibrated to the first 5 years of in-trial data. To assess the stability of the findings, we performed 1000 bootstrap analyses and multiple sensitivity analyses. During the first 4 years of the trial, dual-chamber pacemakers increased quality-adjusted life expectancy by 0.013 year per subject at an incremental cost-effectiveness ratio of $53 000 per quality-adjusted year of life gained. Over a lifetime, dual-chamber pacing was projected to increase quality-adjusted life expectancy by 0.14 year with an incremental cost-effectiveness ratio of $50 000 per quality-adjusted year of life gained. In bootstrap analyses, dual-chamber pacing was cost-effective in 91.9% of simulations at a threshold of $50 000 per quality-adjusted year of life and in 93.2% of simulations at a threshold of $6800 per quality-adjusted year of life gained. Its cost-effectiveness ratio was also below this threshold in numerous sensitivity analyses that varied key estimates.

Conclusions—For patients with sick sinus syndrome requiring pacing, dual-chamber pacing increases quality-adjusted life expectancy at a cost that is generally considered acceptable. (Circulation. 2005;111:165-172.)

Key Words: pacing | pacemakers | sinoatrial node | cost-benefit analysis | quality of life

Dual-chamber pacemakers maintain atrioventricular synchrony and preserve normal physiological function compared with single-chamber ventricular pacemakers. Although this physiological advantage has not translated into improved survival in several large, randomized trials, it has resulted in a reduced incidence of atrial fibrillation, pacemaker syndrome, and heart failure and an improvement in quality of life. Whether the increased cost of dual-chamber pacemakers is warranted by these modestly improved outcomes is unknown. This analysis assessed cost, quality of life, and cost-effectiveness on the basis of data from a large, randomized trial to address this question.

Methods

Study Sample
The Mode Selection in Sinus Node Dysfunction Trial (MOST) enrolled patients (median age, 74 years; 48% female) who gave informed consent, had sinus node dysfunction, and were in sinus rhythm. Patients were excluded if they had serious concurrent illnesses, scored <17 on the Mini–Mental State Examination, or were in heart failure at the time of implantation. After lead placement but before generator implantation, devices were randomly programmed to rate-modulated, dual-chamber (DDDR, 1014 patients) or right ventricular (VVIR, 996 patients) pacing. By 4 years, 19.4% of patients who were randomized to VVIR had been reprogrammed to DDDR because of severe pacemaker syndrome, as diagnosed by the physicians caring for them and confirmed by an end point–adjudication committee.

Costs
Costs were estimated predominantly on the basis of detailed medical care resource utilization data that were collected prospectively in the trial (Table 1). Included were the direct medical cost of pacemaker implantation (hardware, hospitalization costs, professional fees), follow-up outpatient costs (emergency department visits, unscheduled outpatient visits, and 50% of scheduled visits during the trial), medication costs, and costs due to rehospitalization for cardiovascu...
lar events (eg, atrial fibrillation, heart failure, stroke). Time costs and out-of-pocket costs were not collected, because they were expected to be very small compared with medical care costs. Costs of lost productivity also were not considered. Given that hospital reimbursement is currently equal for dual- and single-chamber pacemakers despite very different actual medical care costs, our analysis is best defined as being from the societal perspective.10

Although all trial patients received 2 leads and a dual-chamber pacemaker (to facilitate blinding), our analysis assumed that in real life, patients assigned to VVIR pacing would undergo placement of a single ventricular lead and a less expensive generator and that they would require a new DDDR generator and an atrial lead if they developed severe pacemaker syndrome. On the basis of expert opinion and the literature, outpatient generator replacements were assumed to be necessary every 8 years for DDDR pacemakers and every 11 years for VVIR pacemakers.11,12

For 54% of hospitalizations, diagnosis-related group (DRG) data13 were collected prospectively. For other cases, International Classification of Diseases 9 diagnosis14 or Current Procedural Terminology15 information or text descriptions of primary and secondary diagnoses were converted to DRGs by experienced coders. Costs for each hospital admission were assigned on the basis of national averages for the appropriate DRG. Costs were measured in 2001 US dollars unless otherwise noted. To account for physician fees, inpatient costs were inflated by 16.6%, which is the weighted arithmetic average of the individual geometric means for cardiac dysrhythmias, heart failure, and stroke for 1996 to 2001 in a ratio of 4:1:1, respectively.16

We assumed that costs for emergency department visits without admission included physician and technical fees for a level 4 visit, cardiac monitoring, an intravenous line, pulse oximetry, noninvasive blood pressure monitoring, and 2 electrocardiograms. Professional fees for the emergency department visit were obtained from the Medicare fee schedule.17 Outpatient follow-up visits were presumed to be of moderate complexity.18 For outpatient, nonscheduled testing, we assigned costs on the basis of Medicare-allowed charges.17,18 We estimated a “typical” medication for each class of prescription drug on the case-report form and an “average” dose on the basis of clinical grounds. Medication costs were based on wholesale prices, determined as the midrange of 2001 Red Book costs19 for compatible generic drugs when available and patented drugs otherwise.

**Death and Clinical Events**

During the 4 years of the trial,3 the clinical outcomes of patients randomized to DDDR pacing were consistently better than those of patients randomized to VVIR pacing, but the differences were statistically significant only for the development of atrial fibrillation (adjusted hazard ratio [HR] 0.77, P<0.01) and for hospitalization for heart failure (adjusted HR 0.73, P=0.02). Nonsignificant reductions were found in stroke (adjusted HR 0.81; 95% confidence intervals [CIs], 0.54 to 1.23) and death (0.95; 95% CI, 0.78 to 1.16), with the more modest reduction in death explained by slightly higher mortality rates among patients with cardiovascular events in the DDDR group.
of nonfatal cardiac events (atrial fibrillation, new heart failure, stroke).

The Markov model was then compared with the actual proportion of patients in each specific health state for each year during the trial to guide the selection of values for parameters in the model. Age-specific background mortality rates were obtained from US life tables, adjusted for the sex distribution in our study. Mortality rates were calculated as the sum of age-specific background mortality and health state-specific rates according to the number of previous cardiovascular events (as specified earlier).\(^23\) Calibration to within 1% of the absolute actual survival and event rates during the 5 years of the trial was achieved by estimating parameters from selected combinations of trial follow-up years. For example, 5-year life-table mortality rates were 31.3% for DDDR and 32.4% for VVIR in the trial and were 31.8% and 32.5% in our calibrated model. Projections of costs and utilities after completion of the trial were based on this final calibrated model. The result was a model in which overall mortality during and after the trial was very similar in the 2 groups, despite the observed reduction in nonfatal events that improved quality of life in DDDR patients.

### State-Specific Annual Costs and Utilities

Yearly increments in costs and time tradeoff values, as well as single-time costs and decrements of time tradeoff values at the time of events, crossover, or death were calculated by using multiple linear regression models with the following independent variables: initial pacing mode, first year of the trial (versus year 2 to 5), crossover in a prior year, crossover during a given year, nonfatal event during a given year, 1 prior nonfatal event, 2 or more prior nonfatal events, and death during the year.

### Baseline, Uncertainty, and Sensitivity Analyses

For the baseline cost-effectiveness analysis, we used the actual data during the first 4 years of the trial because only 424 patients were followed up beyond that time, and then we used the calibrated Markov model to predict follow-up costs, life expectancy, and quality of life for each surviving trial participant thereafter. All costs and years of life were discounted at 3% per year\(^{24}\) unless stated otherwise. Cost-effectiveness was calculated as discounted differences in costs divided by discounted differences in quality-adjusted life years.\(^{10}\)

To examine the stability of the results, we used the bootstrap method\(^{25,26}\) to generate 1000 different study simulations by resampling with replacement from the study population. For practical reasons, it was not feasible to reestimate the parameters for the

### In-Trial Cost-Effectiveness

The in-trial analyses covered 4 years because median follow-up was 33 months (range up to 65 months), and only 424 patients were followed up beyond 4 years. Survival-adjusted cost and utility were calculated by multiplying year-specific costs and utilities by the Kaplan-Meier estimate of survival.

### Estimated Costs and Effectiveness After Completion of the Trial

For patients who survived beyond the end of the trial or were lost to follow-up during the trial, a Markov model\(^21\) was used to estimate subsequent costs and quality-adjusted life expectancy on the basis of randomized assignment, duration of follow-up, occurrence of nonfatal events (new atrial fibrillation, stroke, heart failure), or crossover because of adjudicated severe pacemaker syndrome during the trial.\(^22\) For total mortality and other outcomes, we applied incidence density analysis (Table 2) to the trial data to estimate rates of events, mortality, and crossover. In patients with missing data on costs (2.3% of 4583 interviews) or quality of life (8.1% of 4583 interviews) before completion of the trial, predicted values from regression models with parameters in Table 1 were used to estimate cumulative costs and quality of life. The Markov model classified all individuals according to their actual mode of pacing and their history of nonfatal cardiac events (atrial fibrillation, new heart failure, stroke).

### Health-Related Quality of Life

A standard time tradeoff instrument\(^20\) was administered in person at baseline and by phone at 3 and 12 months after enrollment and yearly thereafter. This instrument asks individuals how much of their life expectancy they would trade for thereafter. This instrument asks individuals how much of their life expectancy in their current state of health they would trade for replaced it. This one difference was explicitly considered in our analysis.

### Cost-Effectiveness

Cost-effectiveness was assessed from a societal perspective by using prespecified and prospectively designed methods, supported by a specific grant from the National Institutes of Health. We assumed that the MOST patients, who were broadly representative of elderly patients with sick sinus syndrome, provided data applicable to the clinical question at hand because they received standard care, with the one caveat that crossover from single- to dual-chamber pacing could be accomplished by reprogramming the generator rather than by replacing it. This one difference was explicitly considered in our analysis.

### TABLE 2.  Annual Event Probabilities and Other Time-Dependent Estimates According to Initial Pacing Mode

<table>
<thead>
<tr>
<th>Event Type</th>
<th>DDDR</th>
<th>VVIR</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>First nonfatal event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1</td>
<td>0.1975</td>
<td>0.2469</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.1068</td>
<td>0.0956</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Annually after year 2</td>
<td>0.0799</td>
<td>0.0933</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Second nonfatal event</td>
<td>0.0721</td>
<td>0.0902</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Death as first event*</td>
<td>0.0510</td>
<td>0.0470</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Death after 1 event*</td>
<td>0.1112</td>
<td>0.1233</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Death after 2 events*</td>
<td>0.1485</td>
<td>0.1306</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Crossover from VVIR to DDDR</td>
<td>...</td>
<td>0.1600</td>
<td>Calibrated trial data</td>
</tr>
<tr>
<td>Delay for generator replacement</td>
<td>8 years</td>
<td>11 years</td>
<td>Expert opinion and References 11 and 12</td>
</tr>
</tbody>
</table>

Abbreviations are as defined in text. Data shown are for a 74-year-old patient but were age-adjusted in the analysis.

*Annual probability = \(1 - e^{-\text{event-specific rate} \times \text{background mortality rate based on age and sex}}\).
Markov model for each individual bootstrap simulation. Therefore, long-term survival and cost estimates for each surviving patient were based on the observed in-trial events and the original calibrated Markov model for each bootstrap sample. We also performed 1-way sensitivity analyses on the discount rate, implantation costs, generator replacement cost and delay, impact of a history of crossover on quality of life or costs, effect of pacing mode on quality of life, mortality rates, and age.

**Statistical Analyses**

Treatment groups were compared on an intention-to-treat basis. Kaplan-Meier methods were used to calculate cumulative event rates. Absolute differences during the first 4 years and their 95% CIs were calculated. All statistical analyses, including multiple linear regression models to derive costs and utilities for the Markov model as well as the bootstrap analysis, were performed with SAS for Windows (version 8, SAS Institute). We used DATA 3.5 for Healthcare (TreeAge Software) to develop the Markov model, project future costs and quality-adjusted life expectancy, and perform sensitivity analyses.

**Results**

**First 4 Years: Actual Trial Data**

As noted previously, patients who received DDDR pacemakers were significantly less likely to develop atrial fibrillation or to be hospitalized for heart failure than were patients who received VVIR pacemakers, and the former also had a slightly lower risk of death and of the combined end point of death or stroke. Furthermore, DDDR patients had significantly better results on a heart failure score and relatively small but significantly better results on several measures of health-related quality of life.

During the first 4 years, patients who received DDDR pacemakers had cumulative costs of $27,441 compared with $26,760 in VVIR patients (Table 3). Cumulative undiscounted (difference = $681 = 0.0131) and discounted (difference = 0.0129) quality-adjusted years of life gained were slightly but not significantly higher in patients randomized to DDDR pacing, primarily because of differences in quality of life rather than improved survival itself. Detailed analysis of observed trial outcomes demonstrated that although DDDR patients had lower rates of nonfatal events, their rates of death as a first event and case-fatality rates after 2 events were slightly higher than in the VVIR group (Table 2). Thus, the absence of a net mortality benefit with dual-chamber pacing was explained by the countervailing nature of these 2 effects. On the basis of the absolute discounted differences, the cost-effectiveness of dual-chamber pacing (versus VVIR) after 4 years was $53,000 per quality-adjusted year of life gained.

**Projected Lifetime Costs, Effectiveness, and Cost-Effectiveness**

Many of the benefits of DDDR pacing in the first 4 years would be expected to result in better long-term quality of life even if DDDR pacing did not appreciably affect longevity. As a result, analyses that projected lifetime quality-adjusted life expectancy and costs were more favorable than those observed during the limited follow-up period encompassed by the trial. Using observed data for the first 4 years and the Markov model to project costs and outcomes for the remain-

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**TABLE 3. Mean Costs,* Quality of Life, and Survival During the First 4 Years of the Trial**

<table>
<thead>
<tr>
<th>Year</th>
<th>DDDR</th>
<th>VVIR</th>
<th>Difference (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>Mean total costs $17,981</td>
<td>$17,048</td>
<td>$933 (−266, 2178)</td>
</tr>
<tr>
<td></td>
<td>Mean utility score 0.8250</td>
<td>0.8207</td>
<td>0.0043 (−0.0221, 0.0307)</td>
</tr>
<tr>
<td></td>
<td>Survival probability 0.9365</td>
<td>0.9303</td>
<td>0.0062 (−0.0157, 0.0281)</td>
</tr>
<tr>
<td>Year 2</td>
<td>Mean total costs $4784</td>
<td>$5220</td>
<td>$−436 (−1435, 563)</td>
</tr>
<tr>
<td></td>
<td>Mean utility score 0.8284</td>
<td>0.8280</td>
<td>0.0004 (−0.0280, 0.0279)</td>
</tr>
<tr>
<td></td>
<td>Survival probability 0.8762</td>
<td>0.8732</td>
<td>0.0030 (−0.0266, 0.0326)</td>
</tr>
<tr>
<td>Year 3</td>
<td>Mean total costs $4572</td>
<td>$4544</td>
<td>$28 (−967, 1099)</td>
</tr>
<tr>
<td></td>
<td>Mean utility score 0.8309</td>
<td>0.8221</td>
<td>0.0088 (−0.0251, 0.0416)</td>
</tr>
<tr>
<td></td>
<td>Survival probability 0.8111</td>
<td>0.8234</td>
<td>−0.0123 (−0.0250, 0.0496)</td>
</tr>
<tr>
<td>Year 4</td>
<td>Mean total costs $4425</td>
<td>$4300</td>
<td>$125 (−1020, 1361)</td>
</tr>
<tr>
<td></td>
<td>Mean utility score 0.8414</td>
<td>0.8367</td>
<td>0.0047 (−0.1074, 0.1442)</td>
</tr>
<tr>
<td></td>
<td>Survival probability 0.7500</td>
<td>0.7492</td>
<td>0.0008 (−0.0472, 0.0488)</td>
</tr>
<tr>
<td>Cumulative 4-year results</td>
<td>Cumulative mean total costs $27,441</td>
<td>$26,760</td>
<td>$681 (−1426, 2964)</td>
</tr>
<tr>
<td></td>
<td>Cumulative quality-adjusted years of life 2.690</td>
<td>2.677</td>
<td>0.0129 (−0.1074, 0.1442)</td>
</tr>
<tr>
<td></td>
<td>Incremental cost per quality-adjusted year of life gained* $52,814</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Discounted at 3% per year.
†One-year costs also include costs of pacemaker implantation.
der of each patient’s life expectancy, we estimated that a patient who had the median age (74 years) in the randomized trial and who received a DDDR pacemaker would incur $59 104 in discounted lifetime costs, with a quality-adjusted, undiscounted life expectancy of 7.64 years and a discounted life expectancy of 6.49 years. By comparison, we projected that the same patient randomized to VVIR pacing would accumulate $58 160 in costs, with a quality-adjusted, undiscounted life expectancy of 7.47 years and discounted life expectancy of 6.35 years. With an incremental cost of $944 and an incremental, discounted quality-adjusted life expectancy of 0.14 year, the incremental cost-effectiveness ratio for DDDR pacing was $6800 per quality-adjusted year of life gained (Table 4).

Uncertainty Analyses

Bootstrap Analysis
In bootstrap analyses, DDDR pacing saved money and prolonged quality-adjusted life expectancy in 15.9% of simulations, and it was more costly but associated with better quality-adjusted life expectancy in another 73.4% of simulations (Figure 1). DDDR pacing was cost-effective in 91.9% of simulations at a threshold of $50 000 per quality-adjusted year of life and in 93.2% of simulations at a threshold of $100 000 (Figure 2).

Sensitivity Analyses
The results of 1-way and structural sensitivity analyses are summarized in Table 4. If the Markov model was substituted for the first 4 years of observed data, the incremental cost-effectiveness ratio rose only slightly to $12 200 per quality-adjusted year of life. The ratio was $14 000 at a 5% per year discount rate and dropped to $7600 without discounting. With a discount rate of 3%, the ratio remained $<50 000 per quality-adjusted year of life at a DDDR implantation cost up to $13 500, whereas DDDR saved costs and prolonged life expectancy if its implantation cost was $10 400.

Table 4. Sensitivity Analyses on Lifetime Cost-Effectiveness Estimates

<table>
<thead>
<tr>
<th>Sensitivity analyses</th>
<th>Baseline Value</th>
<th>Incremental Cost-Effectiveness Ratio for DDDR Pacing Compared With VVIR Pacing ($/QALY Gained)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline analysis</td>
<td>$6800</td>
<td></td>
</tr>
<tr>
<td>Model data for first 4 years</td>
<td>Actual data for first 4 years</td>
<td>$12 000</td>
</tr>
<tr>
<td>5% per year discount rate</td>
<td>3%</td>
<td>$14 000</td>
</tr>
<tr>
<td>No discounting</td>
<td>3%</td>
<td>$7600</td>
</tr>
<tr>
<td>DDDR implantation cost &gt;$13 500</td>
<td>$11 203</td>
<td>&gt;$50 000</td>
</tr>
<tr>
<td>DDDR implantation cost &lt;$10 400</td>
<td>$11 203</td>
<td>DDDR saves costs and increases QALYS</td>
</tr>
<tr>
<td>DDDR replaced every 6 years</td>
<td>8 years</td>
<td>$39 000</td>
</tr>
<tr>
<td>DDDR replaced every 5 years</td>
<td>8 years</td>
<td>$60 000</td>
</tr>
<tr>
<td>DDDR replacement cost $10 000</td>
<td>$7100</td>
<td>$29 000</td>
</tr>
<tr>
<td>DDDR replacement cost &lt;$5000</td>
<td>$7100</td>
<td>DDDR saves costs and increases QALYS</td>
</tr>
<tr>
<td>Crossover to DDDR carries the same incremental yearly follow-up cost as if a DDDR pacemaker had been implanted initially ($662)</td>
<td>$1264</td>
<td>$29 000</td>
</tr>
<tr>
<td>No quality-of-life difference by pacemaker type except for events avoided (no decrement with DDDR pacing, no persistent decrement after crossover)</td>
<td>$0.001 for DDDR; $0.019 for VVIR after crossover to DDDR</td>
<td>$18 000</td>
</tr>
</tbody>
</table>

QALY indicates quality-adjusted life-year. All other abbreviations are as defined in text.

Figure 1. Scatterplot of differences in cost and quality-adjusted life expectancy from 1000 bootstrap simulations based on observed trial results and lifetime extrapolation. Dashed line indicates hypothetical cost-effectiveness threshold of $50 000 per quality-adjusted year of life gained. Percent of simulations in each region is as follows: region A, DDDR yields higher cost, fewer quality-adjusted years of life—5.2%; region B, DDDR more costly, more effective, cost-effectiveness ratio >$50 000—2.0%; region C, DDDR more costly, more effective, cost-effectiveness ratio <$50 000—71.4%; region D, DDDR yields lower cost, more quality-adjusted years of life—15.9%; region E, DDDR less costly, less effective, cost-effectiveness ratio for VVIR >$50 000—0.8%; region F, DDDR less costly, less effective, cost-effectiveness ratio for VVIR <$50 000—4.6%.
of bootstrapped cost-effectiveness ratios were based on observed 4-year results of MOST trial and lifetime Markov model (see text for details). As indicated by arrow, 92% of bootstrapped cost-effectiveness ratios were <$50 000 per quality-adjusted year of life gained.

If the implantation cost of VVIR was >$9400, DDDR pacemakers saved costs.

If the DDDR generator had to be replaced every 6 years on average rather than every 8 years, the cost-effectiveness ratio would rise to $39 000 per quality-adjusted year of life. Even if the cost of a DDDR generator replacement increased to $10 000, the cost-effectiveness ratio for DDDR remained <$30 000 per quality-adjusted year of life. Variations on the estimated replacement cost of VVIR generators within reasonable ranges had little impact on cost-effectiveness.

Our analysis assumed, on the basis of the first 4 years of trial data, that a history of crossing over from VVIR to DDDR pacing was associated with increased subsequent yearly costs compared with patients who initially received DDDR pacemakers. If this differential were eliminated, the cost-effectiveness ratio remained <$30 000 per quality-adjusted year of life. If the crossover rate at 4 years was assumed to be 10% instead of the observed 19.4% (with otherwise identical quality-of-life and clinical outcomes to those observed in the trial), the cost-effectiveness ratio would rise only to $49 000 per quality-adjusted year of life even if the outcomes in the VVIR group would not be adversely affected by the lower crossover rate.

In the 4-year follow-up of the randomized trial, there was a small, nonsignificant yearly decrement (0.001) in quality of life with DDDR pacing compared with VVIR pacing among patients who had no adverse events. Also, among patients who crossed over from VVIR to DDDR, utility values remained lower (by 0.019) during each of the subsequent years compared with patients initially randomized to DDDR. If pacing per se was assumed to have no effect on quality of life other than its prevention of cardiovascular events, the cost-effectiveness ratio for DDDR was $18 000 per quality-adjusted year of life.

Finally, we performed a series of sensitivity analyses to evaluate the extent to which the cost-effectiveness of DDDR was driven by improved survival or quality of life. If mortality rates for DDDR and VVIR pacing were assumed to be identical, conditional on cardiac events, the cost-effectiveness ratio of DDDR pacemakers was $9700 per quality-adjusted year of life gained. Under these assumptions, DDDR pacing was projected to improve life expectancy by 0.13 year with a cost-effectiveness ratio of ~$11 000 per year of life saved. If we assumed that the only difference between DDDR and VVIR pacing was the observed reduction in nonfatal events during the first 4 years of the trial (with no other differences in cost or quality of life), the cost-effectiveness ratio for dual-chamber pacing remained favorable at $3200 per quality-adjusted year of life gained. On the other hand, when we reanalyzed the data with the original mortality rates but excluding any quality-of-life benefits (by setting all utility scores to 1), the life-expectancy gain with DDDR fell to 0.002 life-years with a cost-effectiveness ratio of $334 000 per life-year saved.

**Discussion**

Compared with ventricular pacemakers, dual-chamber pacemakers in the MOST trial significantly reduced the rates of atrial fibrillation and hospitalization for heart failure and were associated with somewhat lower rates of stroke. This reduction in nonfatal events with dual-chamber pacing resulted in better quality of life observed during the trial on a number of measures and projected to an even greater extent beyond the trial because of the life expectancy of affected patients. The result was a projected gain of 0.17 quality-adjusted life-years with dual-chamber pacing compared with single-chamber pacing, despite very little prolongation of life expectancy. Although this increase in quality-adjusted years of life may seem modest, it compares favorably with other medical advances, including recombinant tissue-type plasminogen activator versus streptokinase for suspected acute myocardial infarction (~0.06 to 0.29 years of life), β-blockers for low-risk survivors of myocardial infarction (~0.10 year of life), and stenting versus balloon angioplasty for single-vessel coronary revascularization (~0.03 quality-adjusted year of life). By comparison, implantable cardioverter-defibrillators are reported to increase life expectancy by ~0.23, 0.37, or 0.86 years of life in various trials. When weighed against a small increase in lifetime costs, the cost-effectiveness of dual-chamber pacing over the first 4 years was of borderline attractiveness, but the benefits during these 4 years projected to a lifetime cost-effectiveness ratio of $6800 per quality-adjusted year of life gained.

In our study, in which crossover from ventricular pacing to dual-chamber pacing could be performed by reprogramming the already-implanted, dual-chamber pacemaker, the rate of crossing over from ventricular to dual-chamber pacing for severe pacemaker syndrome was 19.6% at 4 years by life-table analysis. This crossover rate was similar to that for a smaller study of 407 patients with a mean age of 76 years who received pacemakers for sinus node dysfunction or atrioventricular block. However, the crossover rates for these 2 US-based trials were substantially higher than the <5% rate in a Canadian trial of 2568 patients randomized to ventricular pacing or atrially based, dual-chamber pacing, a study that reported no significant differences in quality of life among
the 269 patients in whom this outcome was assessed in detail analogous to our study.5,33 Severe pacemaker syndrome in our ventricularly paced patients was associated with a higher percentage of paced beats, a higher programmed escape rate, a slower underlying sinus rate,22 and a substantial decrement in quality of life, which improved by crossing over to dual-chamber pacing. For patients who crossed over without severe pacemaker syndrome, we assumed that any lesser benefits54,35 occurred without any accompanying costs; as a result, we believe our estimates regarding the benefits of dual-chamber pacemakers are consistent with the clinical data.

The incidence of atrial fibrillation was significantly lower in our patients who received dual-chamber pacing,5,36 a finding similar to that in other large, randomized trials.4,37,38 Although dual-chamber pacing reduced hospitalization for heart failure in our study,5 frequent, direct pacing of the right ventricle, whether by dual-chamber or ventricular pacemakers, is associated with an increased risk of hospitalization for heart failure in patients with a normal QRS duration before pacemaker implantation.8 These findings are consistent with clinical data that atrially based pacing, in patients with a normal, native QRS duration and preserved atrioventricular conduction, provides better systolic function than dual-chamber pacing with ventricular capture.4,39,40 Atrial pacing is not widely used, however, because of the fear that patients with sick sinus syndrome will subsequently develop brady-atrioventricular block.

Although initial implantation costs more for dual-chamber pacemakers,1,6 their cumulative, incremental lifetime costs were estimated to be modest, $944, because they reduced subsequent cardiovascular events and because a substantial proportion of patients who initially received a ventricular pacemaker developed severe pacemaker syndrome.3,5 This lifetime narrowing of the cost differential between dual-chamber and ventricular pacemakers was more notable than previously estimated.6

To put our results in perspective, the cost-effectiveness of implantable cardioverter-defibrillators has been reported to be as favorable as $27 000 per year of life saved or as high as $68 000 to $214 000 per year of life saved, with even less favorable ratios in low-risk patients.30–32,41,42 Comparative cost-effectiveness ratios of other invasive cardiac therapies include $13 000 per year of life gained for invasive management of non-ST-segment elevation acute coronary syndromes43 and $23 000 per quality-adjusted year of life gained for stenting (versus balloon angioplasty) for symptomatic single-vessel coronary disease.29

Our analysis has several limitations. First, the observed differences in costs and utilities were relatively small. However, to minimize the effect of outliers, we performed bootstrap analyses and extensive sensitivity analyses, which confirmed favorable cost-effectiveness ratios in most simulations. Second, we included only healthcare costs. However, noncovered costs associated with events and pacemaker syndrome likely would have further reduced the incremental cost of DDDR pacing; thus, our analysis is probably conservative. Third, our Markov model was based on the observed differences in cost and outcomes data during the trial period, regardless of their statistical significance. However, this model was within 1% of trial data for all cumulative event probabilities, and our findings were little changed by sensitivity analyses in which all death rates were assumed to be equal. Furthermore, the model specifically considered the long-term implications of the benefits of DDDR pacing during the course of the trial, some of which, such as lower rates of atrial fibrillation, better heart failure scores, and better scores on a number of measures of health-related quality of life, were statistically significant.5 Fourth, given the small values in both the numerator and denominator of our cost-effectiveness ratios, it was not possible to obtain stable cost-effectiveness ratios for patient subgroups by age or sex. Nonetheless, there was no evidence of a significant interaction between age or sex and the composite clinical outcome,5 suggesting that a true difference in cost-effectiveness across the subgroups was unlikely. Finally, the bootstrap analysis reflects uncertainty only during the within-trial period of time and not the uncertainty owing to the estimation of model parameters. We relied on 1-way, deterministic sensitivity analysis to check for uncertainty in the model assumptions, which were robust to wide variations on the tested parameters.

Although current dual-chamber pacemakers induce ventricular dyssynchrony, their benefits compared with single-chamber ventricular pacing seem worth the costs. Pure atrial pacing for sick sinus syndrome is not considered safe for most patients, so dual-chamber pacing usually remains the preferred option. Future investigations should evaluate biventricular pacing for patients whose underlying conduction-system disease may require frequent ventricular pacing.

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