

## VENTRICULAR PACING OR DUAL-CHAMBER PACING FOR SINUS-NODE DYSFUNCTION

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FOR THE MODE SELECTION TRIAL IN SINUS-NODE DYSFUNCTION\*

### ABSTRACT

**Background** Dual-chamber (atrioventricular) and single-chamber (ventricular) pacing are alternative treatment approaches for sinus-node dysfunction that causes clinically significant bradycardia. However, it is unknown which type of pacing results in the better outcome.

**Methods** We randomly assigned a total of 2010 patients with sinus-node dysfunction to dual-chamber pacing (1014 patients) or ventricular pacing (996 patients) and followed them for a median of 33.1 months. The primary end point was death from any cause or nonfatal stroke. Secondary end points included the composite of death, stroke, or hospitalization for heart failure; atrial fibrillation; heart-failure score; the pacemaker syndrome; and the quality of life.

**Results** The incidence of the primary end point did not differ significantly between the dual-chamber group (21.5 percent) and the ventricular-paced group (23.0 percent,  $P=0.48$ ). In patients assigned to dual-chamber pacing, the risk of atrial fibrillation was lower (hazard ratio, 0.79; 95 percent confidence interval, 0.66 to 0.94;  $P=0.008$ ), and heart-failure scores were better ( $P<0.001$ ). The differences in the rates of hospitalization for heart failure and of death, stroke, or hospitalization for heart failure were not significant in unadjusted analyses but became marginally significant in adjusted analyses. Dual-chamber pacing resulted in a small but measurable increase in the quality of life, as compared with ventricular pacing.

**Conclusions** In sinus-node dysfunction, dual-chamber pacing does not improve stroke-free survival, as compared with ventricular pacing. However, dual-chamber pacing reduces the risk of atrial fibrillation, reduces signs and symptoms of heart failure, and slightly improves the quality of life. Overall, dual-chamber pacing offers significant improvement as compared with ventricular pacing. (N Engl J Med 2002;346:1854-62.)

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SINCE the first implantation of a cardiac pacemaker in a human in 1958,<sup>1</sup> technological advances have enhanced the sophistication of cardiac pacemakers, but there has been no clear evidence of the advantages of more complex devices.<sup>2-4</sup> For example, dual-chamber pacing maintains atrioventricular synchrony and may better preserve normal physiologic function as compared with single-chamber ventricular pacemakers,<sup>5-7</sup> but dual-chamber pacemakers are more expensive, are more complex to implant and program, and have a higher rate of complications.<sup>8</sup> Although retrospective studies and case series suggest benefits of dual-chamber or atrial-based pacing,<sup>9,10</sup> randomized trials have had divergent results with regard to rates of death and stroke, particularly in patients with sinus-node dysfunction.<sup>11-14</sup> We investigated whether dual-chamber pacing would provide better event-free survival and quality of life than single-chamber ventricular pacing in patients with sinus-node dysfunction.

### METHODS

The Mode Selection Trial in Sinus-Node Dysfunction (MOST) was designed as a five-year trial to compare single-chamber (ventricular), rate-modulated pacing with dual-chamber (atrioventricular), rate-modulated pacing in patients whose sinus-node dysfunction required permanent pacing for bradycardia.<sup>15</sup> The first patient was enrolled on September 25, 1995, and the last patient on Octo-

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ber 13, 1999. Follow-up ended on January 31, 2001. The 2010 patients enrolled at 91 clinical sites had a median follow-up of 33.1 months.

### Selection of Patients

Patients were eligible if they were at least 21 years old; were undergoing initial implantation of a dual-chamber, rate modulated pacing system for sinus-node dysfunction; and were in sinus rhythm when randomly assigned to treatment. To be eligible for the quality-of-life analyses, patients had to score 17 or higher on the Mini-Mental State Examination<sup>16</sup> before implantation. Patients with serious concurrent illnesses, as determined by the investigator at each site, were excluded.

### Collection of Data before Implantation

Written informed consent was obtained before implantation. Trained research coordinators collected base-line demographic, clinical, and quality-of-life data. Coexisting conditions were assessed with the Charlson comorbidity index.<sup>17</sup> Multidimensional health-related quality of life was assessed with the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36).<sup>18</sup> The individual components of the SF-36 were used to calculate summary scores for the physical and mental components.<sup>19</sup> Cardiovascular functional status was measured with the Specific Activity Scale.<sup>20</sup> Utilities were assessed with the time-tradeoff approach, in which patients are asked a series of questions to determine how much time in their present state of health they would trade for perfect health.<sup>21</sup>

### Implantation, Randomization, Programming of Pacemakers, and Monitoring of Patients

After both atrial and ventricular leads were positioned, a 24-hour randomization line was called, and the pacemaker was programmed to the randomly assigned mode (rate-modulated dual-chamber pacing or rate-modulated ventricular pacing) before implantation. Patients were unaware of the pacing assignment. Randomization was stratified according to the history of stroke and the clinical site. For both assigned modes, the lower heart rate was programmed to be at least 60 beats per minute, and the upper rate to be at least 110 beats per minute.

Follow-up evaluations occurred four times during the first year and twice yearly thereafter. Quality-of-life assessments were performed 3 and 12 months after enrollment and yearly thereafter, with use of the SF-36 scales,<sup>18,19</sup> the time-tradeoff utility score,<sup>21</sup> and the Specific Activity Scale class.<sup>20</sup>

### Primary and Secondary End Points

The primary end point was death from any cause or nonfatal stroke. Prespecified secondary end points included the composite of death from any cause, a first occurrence of stroke, or a first occurrence of hospitalization for heart failure; death from any cause; death from cardiovascular causes; atrial fibrillation; the Minnesota Living with Heart Failure score<sup>22</sup>; the pacemaker syndrome<sup>23</sup> with a need for permanent reprogramming to dual-chamber pacing; and health-related quality of life. A clinical-events committee that was unaware of the assigned pacing mode classified deaths according to cause and adjudicated all suspected strokes and hospitalizations for heart failure. An electrocardiographic core laboratory reviewed electrocardiograms and confirmed diagnoses of atrial fibrillation. Investigators at each site categorized patients as having chronic atrial fibrillation if they had atrial fibrillation without intervening sinus rhythm on more than one visit. The heart-failure score, which assigns points for symptoms and signs as well as intensification of medical therapy for heart failure, correlates with exercise capacity<sup>22</sup> and mortality after myocardial infarction (unpublished data). Higher points indicate more severe disease. The diagnosis of the pacemaker

syndrome required signs and symptoms of elevated right-sided or left-sided filling pressures or hypotension with ventricular pacing.<sup>13,15</sup>

### Statistical Analysis

The study was designed to have over 90 percent power to detect a 25 percent reduction in the rate of the primary end point and over 80 percent power to detect a 25 percent reduction in mortality in the dual-chamber group. Unless otherwise specified, treatment groups were compared on an intention-to-treat basis. All statistical tests were two-tailed. Cumulative event rates were calculated by the Kaplan-Meier method,<sup>24</sup> and differences between the treatment groups were assessed with the log-rank test.<sup>25</sup> Relative risk was expressed as a hazard ratio (with a 95 percent confidence interval).<sup>26</sup> As specified in the study protocol, supplemental analyses adjusted for selected base-line characteristics with the use of the Cox proportional-hazards model.<sup>26</sup> An independent data and safety monitoring board monitored interim analyses with two-sided, symmetric O'Brien-Fleming<sup>27</sup> boundaries generated with the Lan-DeMets<sup>28</sup> spending-function approach to group-sequential testing. The heart-failure score, calculated as an average score per visit, was analyzed with the use of the Wilcoxon rank-sum test.

Each of the SF-36 scale and summary scores, the time-tradeoff utility scores, and the score on the Specific Activity Scale were compared with the use of a repeated-measures analysis of variance. An unstructured correlation matrix was used to adjust for dependence across the five time points, and the model included covariates for age group, sex, and base-line quality of life. Since there were no significant interactions between time and the effect of treatment, significance testing considered only the single-effect estimate across all time points. Analyses are presented as the adjusted average change from base line in each study group. For patients who crossed over from single to dual pacing, health status at the time of the crossover was carried forward; in a secondary analysis, actual health status, which commonly was improved by crossing over, was assessed. The principal investigators had full access to the data and independently performed all data analyses.

## RESULTS

### Base-Line Characteristics

The median age of the 2010 patients was 74 years; 48 percent were women (Table 1). Hypertension was reported by 62 percent, and diabetes by 22 percent. A history of myocardial infarction was reported by 26 percent of patients, and a history of heart failure by 20 percent. Over 80 percent of patients were in New York Heart Association class I or II at base line. Over 50 percent of patients had a history of supraventricular tachycardia, generally atrial fibrillation or flutter that had occurred within the past three weeks. The indication for pacemaker implantation was sinus-node dysfunction in all cases, but 21 percent of patients also had atrioventricular block. A total of 1014 patients were assigned to dual-chamber pacing, and 996 patients were assigned to ventricular pacing.

### Primary End Point

The primary end point, death or nonfatal stroke, occurred in 447 patients (22.2 percent). There were no significant differences between patients receiving dual-chamber pacing (21.5 percent) and those receiving ventricular pacing (23.0 percent,  $P=0.48$ ) (Fig. 1 and Table 2).

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS ACCORDING TO TREATMENT GROUP.

CHARACTERISTIC	VENTRICULAR PACING (N=996)	DUAL-CHAMBER PACING (N=1014)	P VALUE*
Age (yr)			0.58
Median	74	74	
Interquartile range	68–80	67–80	
	no. (%)		
Female sex	477 (48)	478 (47)	0.74
Nonwhite race	144 (14)	162 (16)	0.34
Hypertension	608 (61)	640 (63)	0.34
Hypercholesterolemia	340 (34)	376 (37)	0.17
Current smoker	85 (9)	84 (8)	0.87
Prior myocardial infarction	243 (24)	279 (28)	0.11
Prior heart failure	183 (18)	221 (22)	0.05
New York Heart Association class I or II heart failure	841 (84)	822 (81)	0.05
Cardiomyopathy	106 (11)	133 (13)	0.09
Prior stroke	108 (11)	116 (11)	0.67
Diabetes	204 (20)	246 (24)	0.04
Chronic pulmonary disease	109 (11)	109 (11)	0.89
Percutaneous transluminal coronary angioplasty	119 (12)	131 (13)	0.50
Coronary-artery bypass grafting	215 (22)	222 (22)	0.87
Other cardiac surgery	88 (9)	83 (8)	0.63
Implantation of cardioverter-defibrillator	6 (1)	13 (1)	0.17
Any supraventricular tachycardia	514 (52)	545 (54)	0.34
Atrial fibrillation	440 (44)	477 (47)	0.20
Other atrial tachycardia	92 (9)	94 (9)	0.99
Any atrioventricular block	209 (21)	204 (20)	0.62
Complete heart block	52 (5)	39 (4)	0.16
Second-degree heart block	62 (6)	72 (7)	0.48
Prolonged atrioventricular interval	102 (10)	101 (10)	0.83
Other heart block	23 (2)	25 (2)	0.88
Vasovagal syndromes	33 (3)	28 (3)	0.52
Ventricular tachycardia or ventricular fibrillation	24 (2)	42 (4)	0.03

\*P values for categorical variables present in less than 10 percent of patients were calculated with Fisher's exact test; for other categorical variables, P values were calculated with the likelihood-ratio chi-square test. For continuous variables, P values were calculated with the Wilcoxon rank-sum test.

### Death, Nonfatal Stroke, or Hospitalization for Heart Failure

Stroke occurred in 4.5 percent of the study population, death from any cause in 20.1 percent, and the composite end point — death, stroke, or hospitalization for heart failure — in 28.8 percent. Death from cardiovascular causes occurred in 8.9 percent. Unadjusted analyses did not reveal any significant differences between the treatment groups in the rate of any of the end points (Fig. 1 and Table 2).

### Atrial Fibrillation

Atrial fibrillation occurred in 24.2 percent of the study population, including 4.8 percent in whom it developed for the first time. The incidence of atrial fibrillation after randomization was significantly lower in the dual-chamber group (hazard ratio, 0.79; 95 percent confidence interval, 0.66 to 0.94;  $P=0.008$ )

(Fig. 1 and Table 2). Of 487 patients in whom atrial fibrillation developed after randomization, 105 (21.6 percent) had chronic atrial fibrillation (15.2 percent of patients with dual-chamber pacing, as compared with 26.7 percent of patients with ventricular pacing; hazard ratio for chronic atrial fibrillation in the overall study population, 0.44; 95 percent confidence interval, 0.29 to 0.67;  $P<0.001$ ). Patients receiving dual-chamber pacing who had no history of atrial fibrillation had a 50 percent lower incidence of atrial fibrillation after randomization (hazard ratio as compared with ventricular pacing, 0.50; 95 percent confidence interval, 0.32 to 0.76;  $P=0.001$ ), whereas patients receiving dual-chamber pacing who had a history of atrial fibrillation had a smaller, nonsignificant 14 percent reduction (hazard ratio, 0.86; 95 percent confidence interval, 0.70 to 1.04;  $P=0.12$ ).

### Heart Failure

Hospitalization for heart failure occurred in 10.3 percent of the patients receiving dual-chamber pacing and 12.3 percent of the patients receiving ventricular pacing (hazard ratio, 0.82; 95 percent confidence interval, 0.63 to 1.06;  $P=0.13$ ). Patients who did not have a history of heart failure at the time of enrollment accounted for 51 percent of hospitalizations for heart failure, and the hazard ratios for the treatment groups were similar in patients with a history of heart failure (0.74; 95 percent confidence interval, 0.51 to 1.07) and without such a history (0.79; 95 percent confidence interval, 0.55 to 1.13). During follow-up, patients receiving dual-chamber pacing accumulated fewer points per visit on the heart-failure score than did patients receiving ventricular pacing (average points per visit during follow-up: ventricular pacing, 1.75; dual-chamber pacing, 1.49;  $P<0.001$ ).

### Adjusted Analyses

Multivariable analyses were performed to control for slightly higher proportions of patients with a history of myocardial infarction, diabetes, congestive heart failure, and supraventricular tachycardia in the group receiving dual-chamber pacing. Adjusted analyses had minimal influence on the estimate of the effect of treatment on the primary end point. However, the adjusted hazard ratio was 0.73 (95 percent confidence interval, 0.56 to 0.95;  $P=0.02$ ) for hospitalization for heart failure and 0.85 (95 percent confidence interval, 0.72 to 1.00;  $P=0.05$ ) for death, stroke, or hospitalization for heart failure (the combined clinical end point).

### Prespecified Subgroups

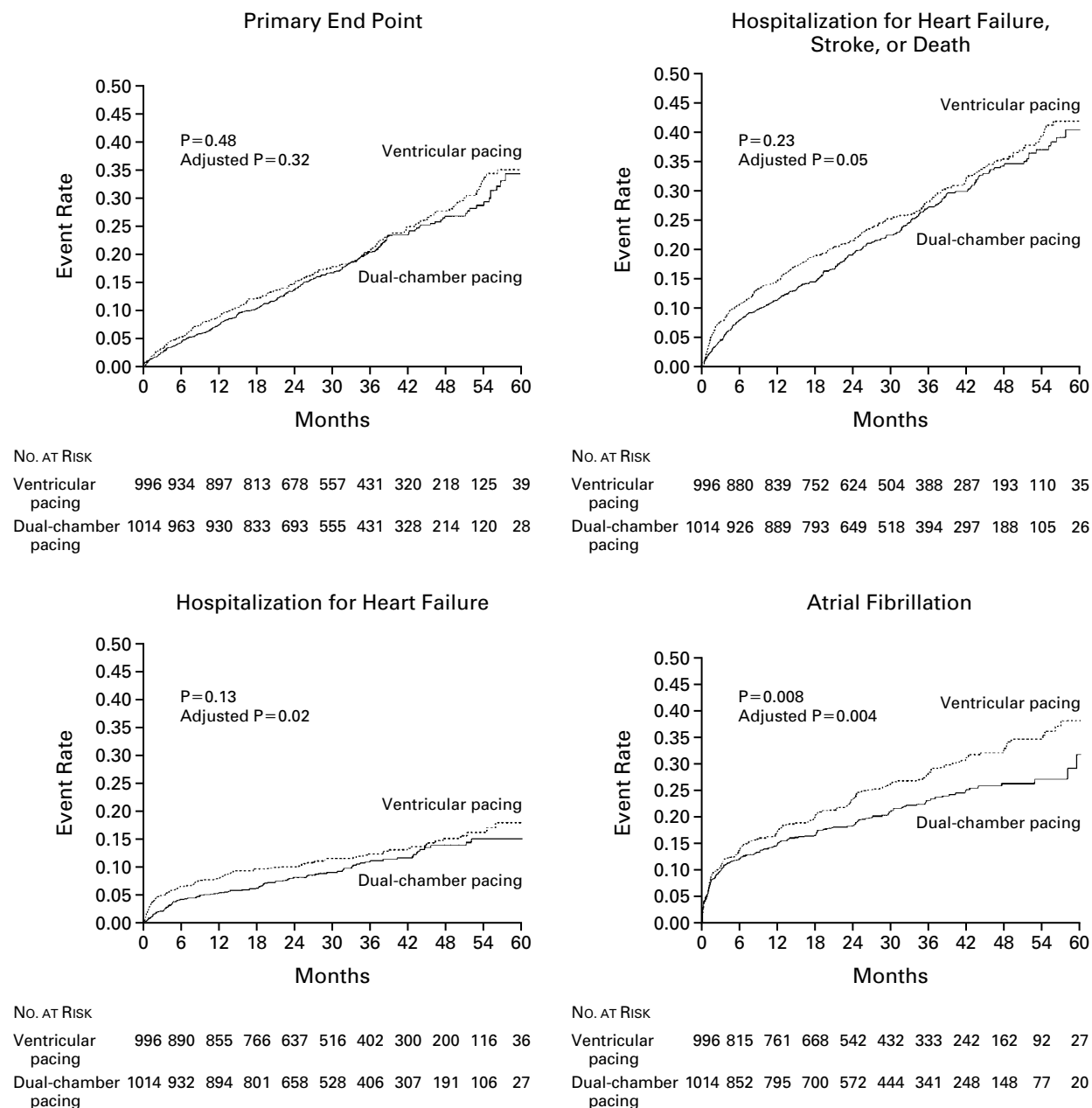
There were no statistically significant differences in the risk of death, stroke, and hospitalization for heart failure between the two treatment groups among

patients over 75 years of age, women, nonwhite patients, or patients with a history of supraventricular tachycardia (Fig. 2).

**Quality of Life**

At three months, both ventricular pacing and dual-chamber pacing led to substantial improvement in

the SF-36 physical role (18 points for ventricular pacing, about 1.3 times the effect of a history of angina or heart failure in study patients), but a much smaller 1.9-point change in the SF-36 physical function (only about 10 to 15 percent of the effect of a history of angina or heart failure in study patients). Over a period of four years, dual-chamber pacing provided



**Figure 1.** Rates of Clinical Events According to the Mode of Pacing.

An explanation of adjusted and unadjusted analyses is provided in the Methods section. Unadjusted P values were derived with the log-rank test.

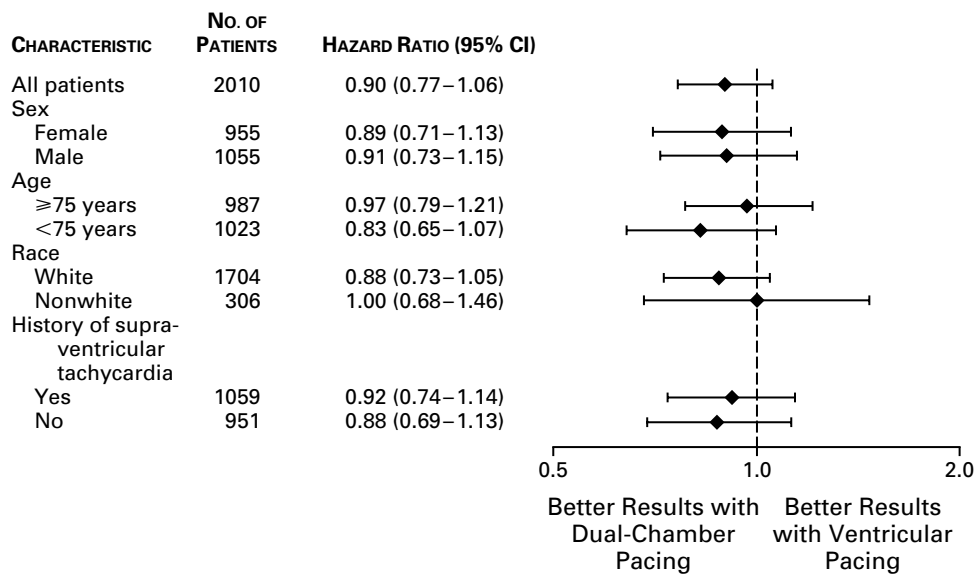
**TABLE 2.** CLINICAL EVENTS AND CLINICAL END POINTS.\*

EVENT OR END POINT	VENTRICULAR PACING	DUAL-CHAMBER PACING	UNADJUSTED HAZARD RATIO	UNADJUSTED 95% CI	P VALUE	ADJUSTED HAZARD RATIO	ADJUSTED 95% CI†	P VALUE
	percent							
Death or stroke	23.0	21.5	0.93	0.78–1.13	0.48	0.91	0.75–1.10	0.32
Combined clinical end point‡	29.9	27.6	0.90	0.77–1.06	0.23	0.85	0.72–1.00	0.05
Death	20.5	19.7	0.97	0.80–1.18	0.78	0.95	0.78–1.16	0.64
Stroke	4.9	4.0	0.82	0.54–1.25	0.36	0.81	0.54–1.23	0.33
Death from cardiovascular causes	9.2	8.5	0.93	0.69–1.24	0.61	0.87	0.65–1.18	0.37
Hospitalization for heart failure	12.3	10.3	0.82	0.63–1.06	0.13	0.73	0.56–0.95	0.02
Atrial fibrillation	27.1	21.4	0.79	0.66–0.94	0.008	0.77	0.64–0.92	0.004

\*CI denotes confidence interval.

†Values have been adjusted for age, sex, history of stroke, history of supraventricular arrhythmia, history of heart failure, history of myocardial infarction, history of ventricular tachycardia or ventricular fibrillation, and score on the Charlson comorbidity index.

‡The combined clinical end point included death from any cause, a first occurrence of nonfatal stroke, or a first hospitalization for heart failure.



**Figure 2.** Unadjusted Subgroup Comparisons According to the Mode of Pacing.

Shown are the unadjusted hazard ratios for the secondary composite end point (death, stroke, or hospitalization for heart failure) for the patients assigned to dual-chamber pacing as compared with those assigned to ventricular pacing. CI denotes confidence interval.

significant improvements in health-related quality of life, as compared with ventricular pacing, for six of eight SF-36 subscales in the carry-forward analysis (Table 3). Summary scores for both physical and mental components also improved significantly. If health status after crossover was included in the analysis, there were no significant differences between the two groups.

**Pacemaker Syndrome**

During the course of the trial, 374 patients receiving ventricular pacing (37.6 percent) had their pacemakers reprogrammed to dual-chamber pacing; 61 of the patients were subsequently switched back to the originally assigned mode. Thus, at the last follow-up, 313 patients (31.4 percent) assigned to ventricular pacing were receiving dual-chamber pacing. The pace-

TABLE 3. CHANGES FROM BASE LINE IN QUALITY OF LIFE AFTER PACING.\*

QUALITY-OF-LIFE SCALE†	BASE LINE		3 MONTHS		12 MONTHS		24 MONTHS		36 MONTHS		48 MONTHS		CHANGE FROM BASE LINE AFTER 48 MONTHS‡	
	VENTRICULAR	DUAL	VENTRICULAR	DUAL	VENTRICULAR	DUAL	VENTRICULAR	DUAL	VENTRICULAR	DUAL	VENTRICULAR	DUAL	SCORE	P VALUE
Physical function	58.8	58.9	+1.9	+4.3	+0.5	+1.8	-1.7	+0.7	-2.9	-0.7	-3.2	-0.1	+1.9	0.04
Physical role	35.7	34.6	+17.8	+25.5	+21.5	+27.7	+17.1	+28.4	+17.1	+32.7	+18.0	+26.7	+8.6	<0.01
Social function	63.5	62.6	+6.3	+9.1	+6.7	+9.3	+4.3	+6.3	+4.3	+7.8	+6.4	+9.8	+2.5	<0.01
Energy	41.9	42.6	+7.1	+11.6	+6.3	+9.3	+4.0	+7.1	+1.7	+8.3	+3.6	+5.2	+4.1	<0.01
Mental health	72.0	72.0	+2.2	+2.8	+1.7	+3.1	+1.6	+3.2	+1.6	+5.6	+4.7	+4.6	+1.2	0.05
Emotional role	74.0	74.0	+5.0	+6.9	+4.6	+9.1	+4.3	+9.2	+4.7	+11.4	+4.8	+12.3	+3.6	<0.01
Pain	67.5	67.0	+4.2	+4.4	+3.3	+3.7	+0.4	+2.4	+3.5	+4.6	+6.9	+5.1	+0.5	0.57
Health perception	60.0	60.2	0.0	+1.9	-0.8	-0.2	-3.4	-3.1	-3.4	-3.1	-3.5	-2.5	+1.1	0.09
Mental-component summary	48.4	48.4	+1.8	+2.6	+1.5	+2.8	+1.4	+2.3	+1.4	+3.6	+2.4	+3.5	+1.1	<0.01
Physical-component summary	38.5	38.4	+2.2	+3.7	+2.1	+2.7	+0.6	+2.0	+0.7	+2.3	+1.0	+2.2	+1.2	<0.01
Specific Activity Scale	2.01	1.97	-0.04	-0.06	0.00	+0.02	+0.03	+0.05	+0.04	+0.11	+0.16	+0.13	+0.002	0.94
Time-tradeoff utility (%)	73	72	+7	+8	+5	+8	+4	+7	+4	+8	+6	+6	+2	0.06

\*P values (which are not shown) for comparisons with base line were all less than 0.05 except for perception of health and score on the Specific Activity Scale.

†All are SF-36 scales except for the Specific Activity Scale and the time-tradeoff utility scale. For all SF-36 scales and component summaries, a positive number denotes improved quality of life. For the score on the Specific Activity Scale, a lower number denotes improved quality of life. For time-tradeoff utility, a positive number denotes improvement.

‡The score represents the difference between the group of patients assigned to ventricular pacing and the group assigned to dual-chamber pacing, where a plus sign indicates a better result in the group assigned to dual-chamber pacing. P values are for the comparison between the two groups.

maker syndrome as strictly defined by the protocol was present in 113 of these patients, whereas an additional 69 had symptoms of severe pacemaker syndrome but did not fully meet the strict definition. Consequently, clinical pacemaker syndrome was the principal reason for crossover in 18.3 percent of patients assigned to ventricular pacing and in 48.9 percent of all patients who crossed over. Most crossovers due to the pacemaker syndrome occurred early (69 percent by 3 months and 73 percent by 6 months; median time to crossover, 58 days). Other reasons for crossover are listed in Table 4.

#### Complications

The rate of complications within 30 days after pacemaker implantation was 4.8 percent. The most frequent complications were dislodgement or failure of the atrial lead in 1.8 percent, pneumothorax in 1.5 percent, and complications associated with the ventricular lead in 1.1 percent. There were no instances of death as a complication of implantation of a permanent pacemaker.

#### DISCUSSION

In 2000, over 225,000 pacemakers were implanted in the United States, and over 600,000 were implanted worldwide. Historically, sinus-node dysfunction, a disorder of unknown cause, represents the diagnosis leading to implantation in about one half of all pacemaker recipients in the United States.<sup>10</sup> To date, clinical recommendations and guidelines regarding the selection of pacing systems have been based on small clinical studies and retrospective analyses of existing data bases.<sup>29</sup>

When viewed in aggregate, the first randomized trials comparing ventricular with dual-chamber pacing<sup>11-14</sup> suggested that dual-chamber pacing reduces the rates of death, stroke, and heart failure, particularly among patients with sinus-node dysfunction. These small trials led to the expectation that larger trials would confirm the superiority of dual-chamber pacing for sinus-node dysfunction.

The Canadian Trial of Physiologic Pacing (CTOPP)<sup>8</sup> compared physiologic (i.e., atrial or dual-chamber) pacing with ventricular pacing in 2568 patients and reported no differences in the rates of death, stroke, or hospitalizations for heart failure. CTOPP included 1077 patients with sinus-node dysfunction and thus did not have sufficient statistical power to exclude a moderate benefit of physiologic pacing. In the present trial in 2010 patients, we also found no statistically significant differences when comparing dual-chamber with ventricular pacing in terms of death from any cause, death from cardiovascular causes, or stroke.

The loss of atrioventricular synchrony with ventricular pacing is associated with enlargement of the

**TABLE 4.** REASONS FOR PERMANENT CROSSEVERS FROM VENTRICULAR TO DUAL-CHAMBER PACING.

REASON	NO. OF PATIENTS
Severe pacemaker syndrome requiring permanent reprogramming	182
Refractory heart failure	39
Chronotropic incompetence*	27
Physician's preference or refusal	22
Supraventricular arrhythmias	19
Possible pacemaker syndrome	8
Patient's refusal	4
Rate response causing angina	2
Vasovagal syndrome	2
Physician's error or programming error	1
Recurrent syncope	1
Unknown	6
Total	313

\*Chronotropic incompetence was defined as the failure to increase heart rate with exercise.

left atrium,<sup>30</sup> and retrospective studies noted a marked reduction in atrial fibrillation<sup>31</sup> with dual-chamber pacing. A more moderate reduction, principally in patients with sinus-node disease, was found in two small prospective trials<sup>12,13</sup> and confirmed by CTOPP. In contrast to CTOPP, 21 percent of whose patients had a history of supraventricular arrhythmia, the prevalence of prior supraventricular tachycardia in our trial was over 50 percent, and we found a 56 percent reduction in the subsequent development of chronic atrial fibrillation with dual-chamber pacing than with ventricular pacing.

The preservation of atrioventricular synchrony has been thought to be central to the maintenance of optimal cardiac performance.<sup>5-7</sup> Signs and symptoms of heart failure, as assessed by the heart-failure score,<sup>22</sup> were less severe with dual-chamber pacing than with ventricular pacing. Unadjusted comparisons of hospitalizations for heart failure reflected an insignificant 18 percent reduction in risk, whereas multivariable analyses that adjusted for base-line imbalances revealed a marginally significant reduction in hospitalizations for heart failure with dual-chamber pacing.

A high incidence of the pacemaker syndrome, which is thought to be due to loss of atrioventricular synchrony, was observed in the group receiving ventricular pacing.<sup>32</sup> In observational studies, the incidence of the pacemaker syndrome has been reported to be as high as 83 percent.<sup>33</sup> In the Pacemaker Selection in the Elderly (PASE) trial, the pacemaker syndrome occurred in 26 percent of patients during an average follow-up of 18 months.<sup>13</sup> In our trial, 16.5 percent of the patients receiving ventricular pacing

crossed over to dual-chamber pacing because of the pacemaker syndrome. In both the PASE trial and our study, about 75 percent of crossovers occurred within six months.

The high incidence of the pacemaker syndrome reported here is in sharp contrast to the low incidence (1.7 percent) reported by Andersen et al.<sup>11,12</sup> and the 2.7 percent rate at three years reported in CTOPP.<sup>8</sup> In our study and the PASE trial,<sup>13,31</sup> only reprogramming was required to change from ventricular to physiologic pacing, whereas reoperation was necessary in the other two studies. Nonetheless, we cannot exclude the possibility that there are different clinical thresholds for the diagnosis of such a subjective condition in different countries.

The quality-of-life benefits of dual-chamber pacing over ventricular pacing were generally small in comparison with the differences based on the presence of angina or heart failure. Although physical role improved by an amount equivalent to about 60 percent of the improvement associated with a change of one class on the Specific Activity Scale, the changes were much smaller for physical function and perception of health. These data suggest that dual-chamber pacing has incremental benefits in terms of the ability to perform physical tasks at the margin of a person's own capacity but does not have dramatic incremental benefits over ventricular pacing in terms of the number of blocks walked or stairs climbed. In addition, the incremental benefits of dual-chamber pacing were, in part, offset by age-related declines in function over the course of the study.

Limitations in the design of the study may have affected our results. We randomly assigned programming, not the type of pacemaker. Since mode changes are easier with this design, we may have overestimated the true incidence of the pacemaker syndrome and reduced the number of clinical events in the ventricular-pacing group. Dual-chamber pacing, by necessity, led to atrial synchronous ventricular pacing in many patients. There is increasing recognition that a ventricular-paced beat, with a wide QRS interval and left bundle-branch block morphology, may be hemodynamically disadvantageous and may even blunt the benefits of atrial pacing. Finally, given the study design, it is impossible to determine whether atrial-based pacing prevents atrial fibrillation or whether ventricular pacing is arrhythmogenic and thus causes atrial fibrillation.

We conclude that for patients with sinus-node dysfunction, dual-chamber pacing, as compared with single-chamber ventricular pacing, did not improve the rate of our primary end point of stroke-free survival. However, when compared with ventricular pacing, dual-chamber pacing reduces newly diagnosed and chronic atrial fibrillation, reduces signs and symp-

toms of heart failure, and slightly improves the quality of life.

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## APPENDIX

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