ORIGINAL ARTICLE

Minimizing Ventricular Pacing to Reduce Atrial Fibrillation in Sinus-Node Disease

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ABSTRACT

BACKGROUND

Conventional dual-chamber pacing maintains atrioventricular synchrony but results in high percentages of ventricular pacing, which causes ventricular desynchronization and has been linked to an increased risk of atrial fibrillation in patients with sinus-node disease.

METHODS

We randomly assigned 1065 patients with sinus-node disease, intact atrioventricular conduction, and a normal QRS interval to receive conventional dual-chamber pacing (535 patients) or dual-chamber minimal ventricular pacing with the use of new pacemaker features designed to promote atrioventricular conduction, preserve ventricular conduction, and prevent ventricular desynchronization (530 patients). The primary end point was time to persistent atrial fibrillation.

RESULTS

The mean (±SD) follow-up period was 1.7±1.0 years when the trial was stopped because it had met the primary end point. The median percentage of ventricular beats that were paced was lower in dual-chamber minimal ventricular pacing than in conventional dual-chamber pacing (9.1% vs. 99.0%, P<0.001), whereas the percentage of atrial beats that were paced was similar in the two groups (71.4% vs. 70.4%, P=0.96). Persistent atrial fibrillation developed in 110 patients, 68 (12.7%) in the group assigned to conventional dual-chamber pacing and 42 (7.9%) in the group assigned to dual-chamber minimal ventricular pacing. The hazard ratio for development of persistent atrial fibrillation in patients with dual-chamber minimal ventricular pacing as compared with those with conventional dual-chamber pacing was 0.60 (95% confidence interval, 0.41 to 0.88; P=0.009), indicating a 40% reduction in relative risk. The absolute reduction in risk was 4.8%. The mortality rate was similar in the two groups (4.9% in the group receiving dual-chamber minimal ventricular pacing vs. 5.4% in the group receiving conventional dual-chamber pacing, P=0.54).

CONCLUSIONS

Dual-chamber minimal ventricular pacing, as compared with conventional dual-chamber pacing, prevents ventricular desynchronization and moderately reduces the risk of persistent atrial fibrillation in patients with sinus-node disease. (ClinicalTrials.gov number, NCT00284830.)

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Despite nearly 20 years of clinical research involving thousands of patients, the optimal pacing strategy for patients with symptomatic bradycardia due to sinus-node disease has yet to be defined. Atrial pacing is associated with a reduced incidence of atrial fibrillation, as compared with ventricular pacing,[1] but atrioventricular block may occur even in carefully selected patients.[2,3] Conventional dual-chamber pacing maintains a coordinated atrioventricular relationship by synchronizing ventricular paced beats to atrial activity, prevents syncope during atrioventricular block, and slightly reduces the risk of atrial fibrillation as compared with ventricular pacing. Dual-chamber pacing, however, does not reduce mortality and has a minimal effect on the risk of stroke and heart failure.[4-8] Furthermore, in patients with an implantable cardioverter–defibrillator, dual-chamber pacing paradoxically led to increased risks of heart failure and death.[9]

These findings led to the hypothesis that right ventricular stimulation during dual-chamber pacing has adverse effects on left ventricular pump function that negate the physiological advantage of atrioventricular synchrony. Retrospective analyses support this hypothesis by linking an increased frequency of right ventricular paced beats to increased risks of atrial fibrillation and heart failure in patients with sinus-node disease.[10,11] We report on a trial that prospectively tested the hypothesis that in patients with sinus-node disease, dual-chamber pacing incorporating a strategy to minimize right ventricular stimulation would lead to a lower risk of persistent atrial fibrillation than would conventional dual-chamber pacing.

METHODS

STUDY ORGANIZATION

The Search AV Extension and Managed Ventricular Pacing for Promoting Atrioventricular Conduction (SAVE PACe) trial was a randomized, controlled clinical trial, sponsored by Medtronic, to compare a strategy of dual-chamber minimal ventricular pacing with conventional dual-chamber pacing in patients with sinus-node disease. The trial was designed by the sponsor and a physician advisory committee that included the academic authors. The data were analyzed by statisticians employed by the sponsor, who were overseen by two of the academic authors. The academic authors wrote all drafts of the manuscript and vouch for the accuracy and completeness of the reported data. From January 15, 2003, to December 19, 2006, a total of 1065 patients from 72 centers in the United States and Canada underwent randomization. The institutional review boards of all participating centers approved the research protocol, and all participants gave written informed consent. An independent data and safety monitoring committee reviewed safety data on March 20, 2006, and interim results on December 9, 2006.

PATIENT POPULATION

Eligible patients had symptomatic bradycardia due to sinus-node disease and met criteria for treatment with permanent implantation of a pacemaker,[12] were more than 18 years old, had a QRS interval of 120 msec or less, and passed a test of atrial pacing (an atrioventricular conduction ratio of 1:1 during atrial pacing at 100 beats per minute[1]). Patients were excluded from enrollment if they had persistent atrial fibrillation, two or more cardioversions for atrial fibrillation within a 6-month period, second- or third-degree atrioventricular block, or a life expectancy of less than 2 years.

RANDOMIZATION, PROGRAMMING, AND FOLLOW-UP

After written informed consent was provided, baseline demographic characteristics and medical history were obtained. All patients received dual-chamber pacemakers (Kappa 700, Kappa 900, EnPulse, or EnRhythm; Medtronic) approved by the Food and Drug Administration. On satisfactory completion of the atrial pacing test, patients were randomly assigned in a 1:1 ratio to dual-chamber minimal ventricular pacing or conventional dual-chamber pacing using sealed sequentially numbered envelopes at each center. Patients, but not investigators, were unaware of the treatment assignment.

Prespecified pacemaker-programming prescriptions were used to deliver the randomized treatment assignment. Dual-chamber minimal ventricular pacing was achieved with new pacemaker features designed to permit automatic lengthening of, or elimination of, the pacemaker's atrioventricular interval in order to withhold ventricular pacing and prevent ventricular desynchronization.[13,14] These new pacemaker features can maintain dual-chamber pacing in the event of atrioventricular block. For patients randomly assigned to conventional dual-chamber pacing, the atrioventricular interval was between 120 msec and

180 msec, which maximizes cardiac output during right ventricular stimulation.[15] Features for monitoring atrial fibrillation, including storage of atrial electrograms, were activated in the pacemakers of all patients.

Patients were seen at 1 month after enrollment and every 6 months thereafter for downloading of stored diagnostic data from the pacemaker to a diskette. The status of atrial rhythm was evaluated by the examination of atrial electrograms, surface electrocardiograms, or both, and the interim medical history was reviewed.

END POINTS

The primary end point was the time to persistent atrial fibrillation, which was defined as the occurrence of any of the following three circumstances: two consecutive visits in which atrial fibrillation was present[1,5-7]; at least 22 hours of atrial fibrillation for at least 7 consecutive days, detected by means of diagnostic data stored in the pacemaker; and at least 22 hours of atrial fibrillation per day for fewer than 7 consecutive days if an interruption by electrical or pharmacologic cardioversion occurred.[16] The second circumstance listed was consistent with published guidelines for the management of atrial fibrillation[16] in both specifics and intent at the time the study was designed; it also takes into account that pacemakers objectively and accurately quantify both symptomatic and asymptomatic atrial fibrillation.[17-22] In addition, two expert cardiologists who were unaware of the treatment assignment reviewed all catheter-ablation procedures for evidence of persistent atrial fibrillation. Secondary end points included hospitalizations for heart failure and the percentages of atrial and ventricular paced beats over time.

STATISTICAL ANALYSIS

The study was designed to have an overall power of 80% to detect a 6.4% reduction in the 2-year rate of the primary end point, or an estimated 32% reduction in relative risk. All analyses were performed according to the intention-to-treat principle.

The time to development of persistent atrial fibrillation was analyzed with the use of Cox proportional hazards models[23] adjusted for age and for the presence or absence of a history of atrial fibrillation, myocardial infarction, coronary artery disease, hypertension, diabetes, and the use of antiarrhythmic drugs for atrial fibrillation. Relative risks were expressed as hazard ratios with 95% confidence intervals. The time to the first occurrence of persistent atrial fibrillation was compared visually with the use of Kaplan–Meier curves[24] and assessed with the log-rank test. The percentages of atrial and ventricular beats that were paced were not normally distributed and were analyzed with the use of the Wilcoxon rank-sum test. Categorical variables were compared with the chi-square test, and continuous variables with Student's t-test.

The study used a group-sequential design with one interim analysis to evaluate the primary end point. Stopping rules based on an O'Brien–Fleming spending function[25] were prespecified for the interim analysis, which evaluated the primary end point at a significance level of 0.01 and a hazard ratio of greater than 1.61 for treatment superiority. At the recommendation of the data and safety monitoring committee, the trial was stopped on December 21, 2006, shortly after an interim analysis revealed that the difference in persistent atrial fibrillation between the two groups had passed the prespecified efficacy boundary (P=0.007).

RESULTS

ENROLLMENT

Of 1321 patients who underwent screening, 256 (19.4%) were not enrolled for the following reasons: 214 (83.6%) did not pass the atrial pacing test, 13 (5.1%) had QRS intervals that were greater than 120 msec, and 29 (11.3%) had other reasons (Fig. 1). The remaining 1065 patients were enrolled and underwent randomization after the successful implantation of pacemakers.

STUDY POPULATION

Most patients were elderly and had hypertension, normal ventricular function, and no history of heart failure. Men and women were approximately equally represented, and 38% of patients had documented paroxysmal atrial fibrillation before enrollment. The remaining clinical characteristics, including various cardiac medications, were similar between treatment groups (Table 1).

The mean (±SD) follow-up period was 1.7±1.0 years (range, 0 days to 3.6 years). Crossovers were observed in 59 patients (44 patients [8.2%] crossed over from conventional dual-chamber pacing to dual-chamber minimal ventricular pacing, and 15 patients [2.8%] crossed over from dual-chamber minimal ventricular pacing to conventional dual-

chamber pacing; P<0.001). Thirteen patients (1.2%) were lost to follow-up after a mean follow-up period of 1.5 months.

OUTCOMES

The median percentage of ventricular beats that were paced was significantly less in the group assigned to dual-chamber minimal ventricular pacing than in the group assigned to conventional dual-chamber pacing (9.1% vs. 99.0%, P<0.001). However, the median percentage of atrial beats that were paced was similar in the two groups (71.4% vs. 70.4%, P=0.96).

During the follow-up period, persistent atrial fibrillation developed in 110 patients — 68 of 535 patients in the group assigned to conventional dual-chamber pacing (12.7%), and 42 of 530 in the group assigned to dual-chamber minimal ventricular pacing (7.9%) (P=0.004 by the log-rank test). Kaplan–Meier estimates of time to persistent atrial fibrillation showed absolute reductions in the rates of persistent atrial fibrillation associated with dual-chamber minimal ventricular pacing as compared with conventional dual-chamber pacing of 3.8% at 1 year (95% confidence interval [CI], 0.4 to 7.3), 6.9% at 2 years (95% CI, 2.4 to 11.4), and 7.0% at 3 years (95% CI, −0.3 to 14.4) (Fig. 2).

Prespecified multivariable analyses showed that dual-chamber minimal ventricular pacing remained an independent predictor of persistent atrial fibrillation (hazard ratio, 0.60; 95% CI, 0.41 to 0.88; P=0.009). The hazard ratio of 0.60 indicates a 40% decrease in the relative risk of persistent atrial fibrillation at any time interval among patients randomly assigned to dual-chamber minimal ventricular pacing as compared with those assigned to conventional dual-chamber pacing. There was no significant difference among selected clinical subgroups in the effect of dual-chamber minimal ventricular pacing as compared with conventional dual-chamber pacing on reducing the risk of persistent atrial fibrillation (Fig. 3).

Other independent predictors of persistent atrial fibrillation included age (hazard ratio for each 1-year increment, 1.02; 95% CI, 1.00 to 1.04; P=0.05) and the presence or absence of previous atrial fibrillation (hazard ratio, 3.56; 95% CI, 2.23 to 5.67; P<0.001) and antiarrhythmic drug use (hazard ratio, 1.51; 95% CI, 0.99 to 2.32; P=0.06). There was no significant interaction between any of these variables and the treatment group.

Mortality was not significantly different between treatment groups (4.9% in the group assigned to dual-chamber minimal ventricular pacing vs. 5.4% in the group assigned to conventional dual-chamber pacing; hazard ratio, 0.85; 95% CI, 0.50 to 1.44; P=0.54), nor was the rate of hospitalization for heart failure (2.8% in the group assigned to dual-chamber minimal ventricular pacing vs. 3.1% in the group assigned to conventional dual-chamber pacing; hazard ratio, 0.84; 95% CI, 0.42 to 1.68; P=0.62). Given the observed event rates, the study had only 22% power to detect a clinically plausible 25% reduction in the relative risk of death and 16% power for the same reduction in the relative risk of heart failure. Nonprespecified analyses showed that the proportion of patients who underwent catheter ablation of the atrioventricular node or pulmonary-vein isolation was greater in the group assigned to conventional dual-chamber pacing (13 of 535 [2.4%]) than in the group assigned to dual-chamber minimal ventricular pacing (2 of 530 [0.4%], P=0.005). The numbers of cardioversions performed were similar in the conventional dual-chamber pacing

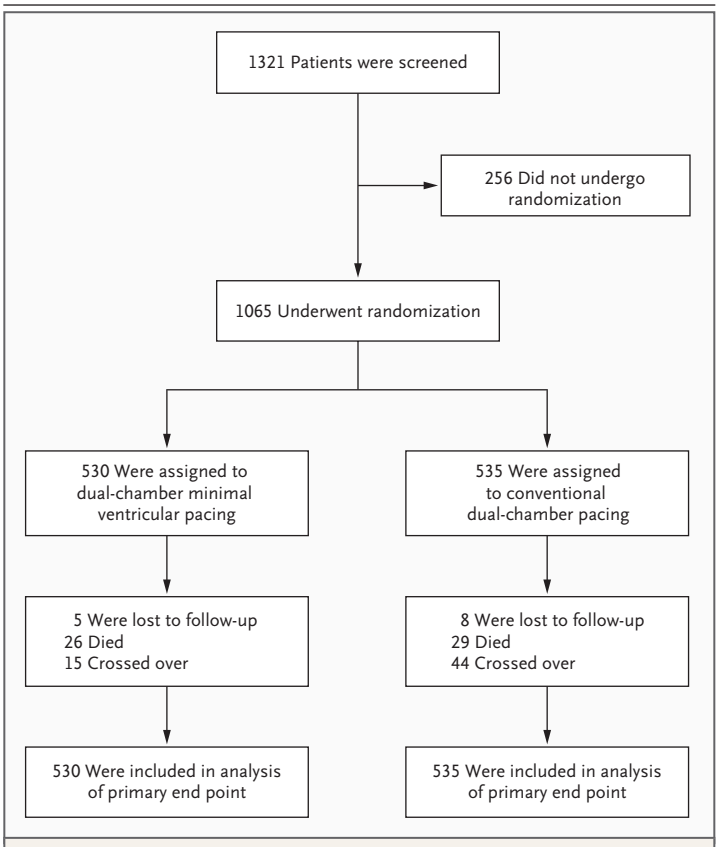

Figure 1. Enrollment, Randomization, and Analysis of Patients.

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Dual-Chamber Minimal Ventricular Pacing (N=530)	Conventional Dual-Chamber Pacing (N=535)	P Value
Age — yr	72.1±11.9	72.6±11.5	0.49
Male sex — no. (%)	266 (50.2)	254 (47.5)	0.38
Ejection fraction — %	58.1±9.5	58.0±10.0	0.91
Medical history — no. (%)			
Previous myocardial infarction	104 (19.6)	101 (18.9)	0.76
Previous heart failure	99 (18.7)	118 (22.1)	0.17
Previous atrial fibrillation	192 (36.2)	211 (39.4)	0.28
Hypertension	394 (74.3)	387 (72.3)	0.46
Diabetes	115 (21.7)	124 (23.2)	0.56
Percutaneous coronary intervention	121 (22.8)	118 (22.1)	0.76
Coronary-artery bypass grafting	92 (17.4)	81 (15.1)	0.33
Valvular surgery	12 (2.3)	18 (3.4)	0.28
Medication at randomization — no. (%)			
Beta-blockers	227 (42.8)	225 (42.1)	0.80
Calcium-channel blockers	140 (26.4)	157 (29.3)	0.29
Antiarrhythmic agents	93 (17.5)	122 (22.8)	0.03
Angiotensin-converting–enzyme inhibitors	175 (33.0)	182 (34.0)	0.73
Angiotensin-receptor blockers	69 (13.0)	86 (16.1)	0.16
Digoxin	35 (6.6)	39 (7.3)	0.66
Diuretics	195 (36.8)	202 (37.8)	0.74
First-degree atrioventricular block — no. (%)	111 (20.9)	116 (21.7)	0.77
Pacemaker programming			
Minimum pacing rate — beats/min	61.4±4.8	61.5±5.7	0.70
Detection of atrial fibrillation — beats/min	178.7±4.0	178.4±4.9	0.24

* Plus–minus values are means ±SD.

group (26 of 535 patients [4.9%]) and in the dual-chamber minimal-ventricular-pacing group (22 of 530 patients [4.2%], P=0.58). The time to first cardioversion, catheter ablation of the atrioventricular node, or pulmonary-vein isolation showed a difference of borderline significance favoring dual-chamber minimal ventricular pacing (hazard ratio, 0.62; 95% CI, 0.37 to 1.03; P=0.06) (Fig. 4).

Non-prespecified analyses comparing patients in whom persistent atrial fibrillation developed with those in whom it did not showed no significant difference in mortality (6.4% vs. 5.0%, P=0.55) but a higher rate of hospitalizations for heart failure (7.3% vs. 3.2%, P=0.03). Patients in whom persistent atrial fibrillation developed had more strokes than did those in whom persistent atrial fibrillation did not develop, but the difference was not significant (4.5% vs. 1.8%, P=0.18).

ADVERSE EFFECTS

Forty-three subjects (4.0%) had problems related to the leads. Three patients (0.3%) had nonfatal infections requiring removal of the pacemaker; pacemakers were not reimplanted in two of the patients, who left the study. There was one intraoperative death.

DISCUSSION

This prospective, randomized clinical trial tested the hypothesis that, in patients with sinus-node disease and bradycardia requiring permanent pacing devices, a pacing strategy to minimize ventricular pacing while maintaining support for bradycardia reduces the risk of persistent atrial fibrillation. Dual-chamber minimal ventricular pacing conferred a 4.8% absolute reduction in

risk, which yielded a 40% reduction in the relative risk of the development of persistent atrial fibrillation, as compared with conventional dual-chamber pacing. After two decades of randomized clinical trials involving nearly 7000 patients,[1,4-7] this study shows that newer forms of dual-chamber pacing for sinus-node disease are superior to older pacemaker technology.

The conceptual underpinning of the strategy to minimize unnecessary and potentially harmful right ventricular pacing originates from physiological and clinical data spanning more than 80 years. In 1925, Wiggers showed that ventricular pacing results in reduced ventricular-pump function in mammals.[26] The cause of this reduction in pump function is a left ventricular electrical-activation sequence resembling left bundle-branch block. The resulting electrical asynchrony is manifested by prolonged QRS intervals due to slow myocardial conduction. Consequently, left ventricular contraction is altered and dyssynchrony may occur.[27] Ventricular desynchronization imposed by pacing results in chronic left ventricular remodeling, including asymmetric hypertrophy and dilatation[28,29] and reduced ejection fraction.[3,30,31]

The importance of this trial is that it prospectively links a reduction in clinical events (persistent atrial fibrillation) to a reduction in ventricular pacing. This reduction in persistent atrial fibrillation was associated directly with fewer invasive ablation procedures and fewer hospitalizations for heart failure in post hoc analyses.

The frequent occurrence of paroxysmal atrial fibrillation and sinus bradycardia brings clinical relevance to this study. The sudden change from one to the other is termed the "tachy-brady" or the sick sinus syndrome. At least 40 to 50% of patients with sinus-node disease have paroxysmal atrial fibrillation,[6] as in our study, and bradycardia that complicates medical management of atrial fibrillation is the reason for pacemakers in up to 83% of these patients.[6]

Atrial fibrillation continues to dominate the treatment of patients with sinus-node disease after the correction of symptomatic bradycardia with pacemakers. Indeed, modern pacemakers with advanced rhythm-monitoring capabilities detect atrial fibrillation in 50 to 65% of patients.[17,19] These episodes, which are asymptomatic in the majority of patients,[21] are a powerful, independent predictor of stroke, death, and persistent atrial fibrillation.[17] Therefore, the observation that selecting a pacing strategy to minimize ventricular pacing reduces the risk of persistent atrial fibrillation should inform changes in clinical practice.

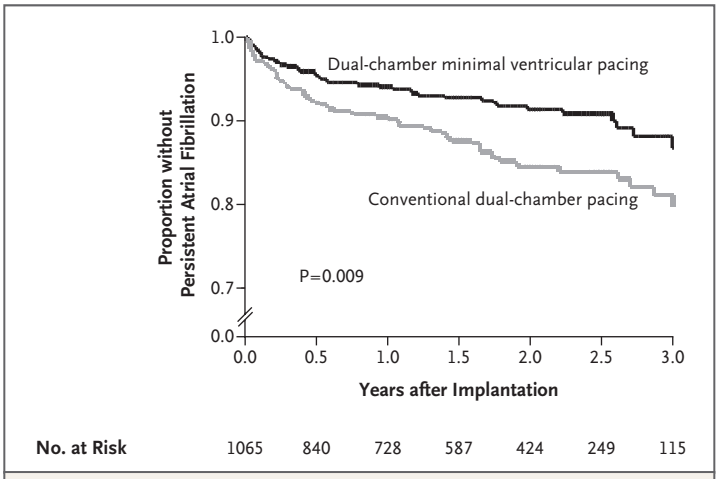

Figure 2. Kaplan–Meier Estimates of Time to Development of Persistent Atrial Fibrillation According to Treatment Group.

The hazard ratio of 0.60 (95% CI, 0.41 to 0.88) indicates a 40% decrease in the relative risk of persistent atrial fibrillation at any time interval among patients in the group assigned to dual-chamber minimal ventricular pacing as compared with those in the group assigned to conventional dual-chamber pacing.

The physiological mechanisms by which ventricular pacing (including atrial synchronous ventricular pacing) induces atrial fibrillation have not been fully determined. There is some evidence that electromechanical feedback may be important. Altering the relationship between atrial and ventricular timing during atrial synchronous ventricular pacing has been shown to cause increases in atrial pressure and size, as well as to favor the development of electrophysiological properties that could facilitate the development of atrial fibrillation.[3,32,33] Mitral regurgitation due to papillary muscle desynchronization may also be important.[34]

The rates of mortality and heart failure were very low in the present study, and there was no sign of benefit or harm for these end points from dual-chamber minimal ventricular pacing. These low event rates do not necessarily imply a highly selected patient population, since they are similar to rates in other trials of cardiac pacing for sinus-node disease.[5,6] Patients with pacemakers who have sinus-node disease are, on average, at low risk for heart failure that is attributable to pacing-induced ventricular desynchronization (approximately 1.2% at 2 years after implantation of the pacemaker).[11]

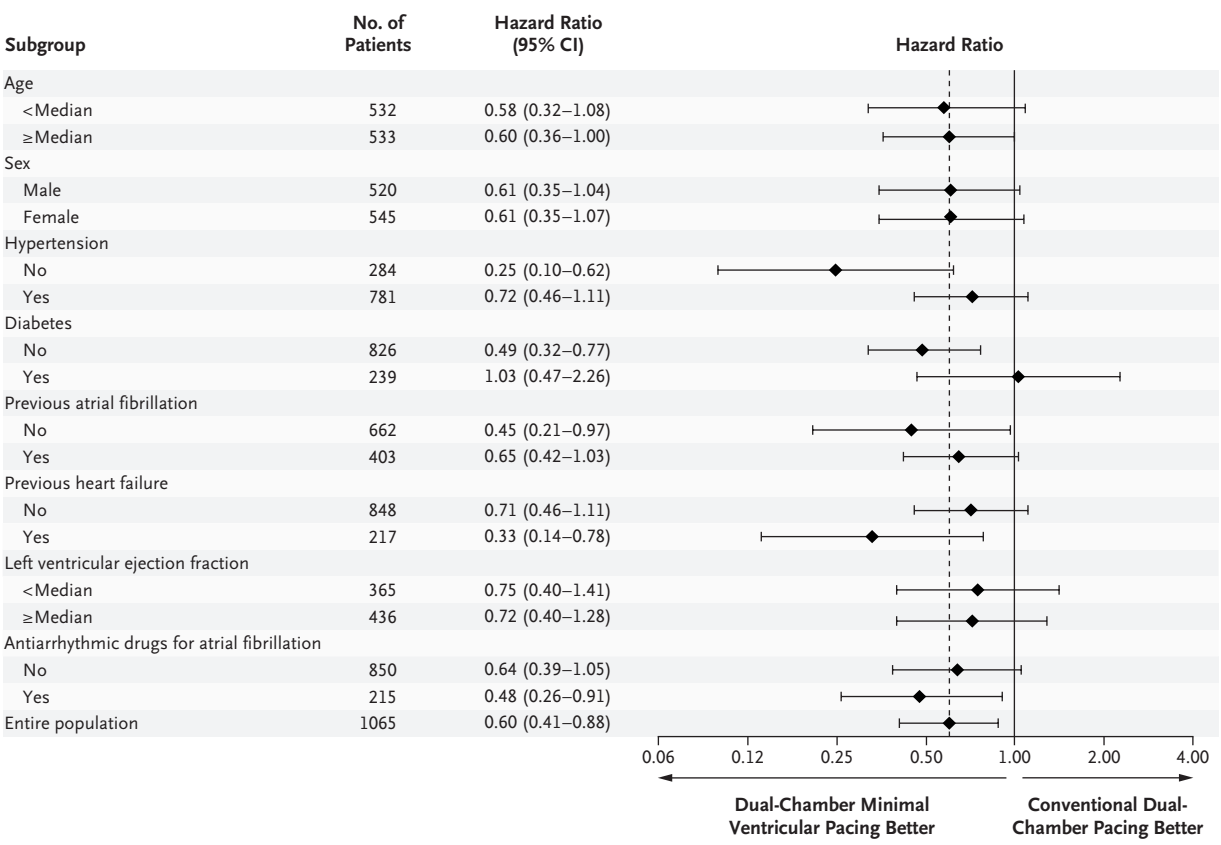

Figure 3. Hazard Ratios and 95% Confidence Intervals for Persistent Atrial Fibrillation According to Clinical Subgroup.

The dashed vertical line indicates the hazard ratio for the entire population. None of the differences between subgroups were significant. The left ventricular ejection fraction was not documented in 264 patients.

Studies other than the Mode Selection Trial (MOST)[6] have suggested that the avoidance of right ventricular pacing altogether, by the use of atrial pacemakers, is associated with a lower incidence of atrial fibrillation than is conventional dual-chamber or ventricular pacing in sinus-node disease.[1,3] Unfortunately, concern about the late development of atrioventricular block generally discourages the frequent use of atrial pacemakers, and most patients receive conventional dual-chamber pacemakers. Conventional dual-chamber pacemakers result in a high frequency of ventricular pacing in the majority of patients despite intact atrioventricular conduction.[10] This occurs because the most frequently recommended atrioventricular intervals for a pacemaker are similar to spontaneous PR intervals.[9,13] Conventional dual-chamber pacing therefore subjects most patients with sinus-node disease to a lifetime of "forced" ventricular desynchronization.[10] In contrast, the new pacemaker features for minimizing ventricular pacing that we used in this trial reduced the percentage of ventricular paced beats by 90 percentage points, to a median value of 9%, while maintaining high levels of atrial paced beats.

On the basis of the post hoc analyses of MOST and the results of some trials involving defibrillators, albeit in a very different population, older pacemaker algorithms to reduce ventricular pacing have been used to attenuate adverse effects among patients with implantable cardioverter–defibrillators who do not have symptomatic bradycardia.[35] The newer programming for dual-chamber minimal ventricular pacing that was used in our study was developed specifically to yield "functional" pacing of the atrium in the safe context of a dual-chamber pacemaker. These new pacemaker features selectively uncouple atrial from ventricular paced beats without sacrificing atrial support or atrioventricular synchrony.[13,14] We are

not aware that these new pacemaker features have been tested prospectively in large-scale trials until now, and long atrioventricular intervals may invoke clinical concern in some patients.[36] None of these concerns materialized in this or other[13,14] trials of dual-chamber minimal ventricular pacing. In conclusion, prevention of ventricular desynchronization with the use of new pacemaker features for dual-chamber minimal ventricular pacing as compared with conventional dual-chamber pacing moderately reduces the risk of the development of persistent atrial fibrillation in patients with sinus-node disease.

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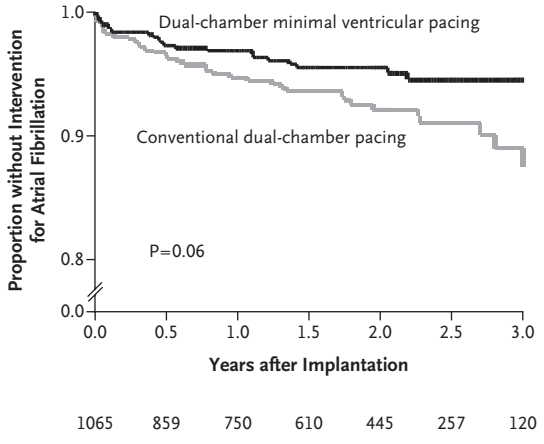

Figure 4. Time to First Cardioversion, Catheter Ablation of the Atrioventricular Node, or Pulmonary-Vein Isolation According to Treatment Group.

The time to first cardioversion, catheter ablation of the atrioventricular node, or pulmonary-vein isolation showed a difference of borderline significance favoring dual-chamber minimal ventricular pacing (hazard ratio, 0.62; 95% CI, 0.37 to 1.03).

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