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Atrial fibrillation and quality of life after pacemaker implantation for sick sinus syndrome: Data from the Mode Selection Trial (MOST)

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Background In the Mode Selection Trial (MOST) of 2,010 patients with sinus node dysfunction, dual-chamber–paced patients had less atrial fibrillation (AF) and heart failure and had slightly improved health-related quality of life (QOL) compared with rate modulated right ventricular–paced patients. Our objective was to assess the impact of AF on QOL within MOST.

Methods We analyzed serial QOL measures (Short Form-36, Specific Activity Scale, time trade-off) in 3 groups: (1) those without AF; (2) those with paroxysmal AF (PAF), but not chronic AF (CAF); and (3) those with CAF. We carried forward the last known QOL before crossover for all subsequent time points in patients randomized to rate modulated right ventricular pacing who crossed over to dual-chamber pacing for severe pacemaker syndrome.

Results Three hundred seventeen patients (15.8%) had AF in the year after implantation, 206 patients within 3 months (191 PAF, 15 CAF), and another 159 (124 PAF, 35 CAF) between 3 and 12 months. There were no significant differences among groups in individual Short Form-36 subscales or time trade-off scores at 12 months as compared with baseline or 3 months. Cardiovascular health status was better at 12 months as compared with baseline or 3 months in those without AF.

Conclusions Atrial fibrillation after pacemaker implantation in elderly patients with sick sinus syndrome was not a major determinant of QOL. However, there was a trend toward better cardiovascular functional status in patients without AF. (Am Heart J 2009;158:78-83.e2.)

Dual-chamber pacemakers are recommended for patients with sick sinus syndrome and sinus rhythm (SR) given their potential for preserving atrioventricular synchrony as compared with single-chamber ventricular pacemakers.[1] Large randomized studies of pacing mode have not shown significant differences in mortality,[2,3] but most studies, including Mode Selection Trial (MOST), have demonstrated a reduction in rates of development of atrial fibrillation (AF). A meta-analysis of 8 randomized trials of pacing mode performed at the patient level found a 20% reduction in the risk of AF with dual-chamber pacing.[4] Newer modalities of dual-chamber pacing, which reduce the proportion of ventricular-paced beats, have further reduced the incidence of persistent AF.[5] In addition, MOST and some, but not all, other studies of this issue have suggested that dual-chamber pacing improves some aspects of health-related quality of life (QOL),[2,6,7] an important metric of treatment efficacy.

How any beneficial effects of dual-chamber pacing on QOL are mediated remains unclear. Therefore, we analyzed the serial QOL data from the MOST study, a large trial of 2,010 patients with sick sinus syndrome randomized to single-chamber ventricular (rate modulated right ventricular pacing [VVIR]) or dual-chamber (DDDR) pacing,[8] to assess the effect of AF on QOL. We hypothesized that QOL would be adversely affected in patients who developed AF during the trial and that cardiovascular functional status would also be adversely affected.

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Methods

From 1995 to 1999, MOST randomized patients (n = 2,010) with sick sinus syndrome to DDDR or VVIR.[2,8] Subjects were followed regularly for clinical outcomes 4 times during the first year and biannually thereafter until January 2001. Procedures for subject enrollment and data collection have been outlined in previous reports.[2] Briefly, MOST enrolled patients who were >21 years of age, in SR with sick sinus syndrome without major comorbidities but meeting standard indications for pacemaker implantation. Demographic and clinical data as well as health-related QOL, measured by means of the Medical Outcomes Study 36-item Short Form (SF-36) General Health Survey,[9,10] were collected at baseline. Subscale scores were constructed for 8 major domains, each scored from 0 points (worst) to 100 points (best). These included physical function, physical role, social function, emotional role, mental health, vitality, bodily pain, and general health perception. Summary scores for physical (PCS) and mental (MCS) components with a standardized mean of 50 and an SD of 10 points were also calculated for each patient. Cardiac-related functional status was assessed using the Specific Activity Scale (SAS),[11] a validated multilevel scale that stratifies subjects from 1 (best) to 4 (worst) cardiac-related functional status by asking about their ability to perform everyday tasks. Utilities were assessed with the standard time trade-off methodology,[12] in which patients were asked how much time in their current state of health they would trade for perfect health. The QOL and functional status measures (SF-36, SAS, and time trade-off) were assessed at baseline and then again at 3 and 12 months and yearly thereafter. We also attempted to reassess QOL when patients crossed from 1 pacing mode to another.

We performed a primary analysis of the change scores for each individual's QOL measures at 12 months after pacemaker implantation as compared with baseline in 3 groups: (1) those without AF; (2) those who developed paroxysmal AF (PAF) but not chronic AF (CAF); and (3) those with CAF. Atrial fibrillation was diagnosed at each follow-up visit based on electrocardiographic information in patients presenting with symptoms of AF or flutter or from evidence of mode switching on pacemaker interrogation. Sites did not distinguish atrial flutter from AF. Chronic AF was diagnosed in subjects whose AF was considered chronic or permanent, whereas PAF was diagnosed in those with AF but not CAF. After initial unadjusted analyses, change in QOL measures was stratified by clinical factors including age, sex, treatment arm, and baseline QOL score for each measure. These multivariable analyses were performed in SAS (Version 8, Cary, NC) with PROC GLM.

To avoid any confounding effect of the pacemaker implantation itself, we then examined the effect of AF on the change scores in QOL measures between 3 and 12 months of follow-up. In patients who crossed over from VVIR to DDDR for severe pacemaker syndrome, we carried forward the last known QOL before crossover (either from reassessment at the time of crossover, if available, or the last prior assessment) for all subsequent data points. This approach was designed to account for the improvement in QOL scores anticipated after crossover, which would tend to overestimate QOL scores in the VVIR arm. We also performed similar pairwise comparisons between subjects with PAF and those who remained in SR as well as those with CAF and those who remained in SR. Finally, to assess the impact of crossovers on our results, we repeated our analyses of the change scores between 3 and 12 months while excluding subjects who experienced crossover, either for severe pacemaker syndrome or for other reasons.

Table I. Baseline characteristics of the cohort

Variable	VVIR (n = 996)	DDDR (n = 1014)
Age (±SD)	73.1 ± 11.0	72.9 ± 11.1
Male sex (%)	52	53
Nonwhite race (%)	14	16
Diabetes (%)	20	24
Hypertension (%)	61	63
Prior MI (%)	24	28
Prior PAF (%)	44	47
Prior HF (%)	18	22

MI, Myocardial infarction.

Results

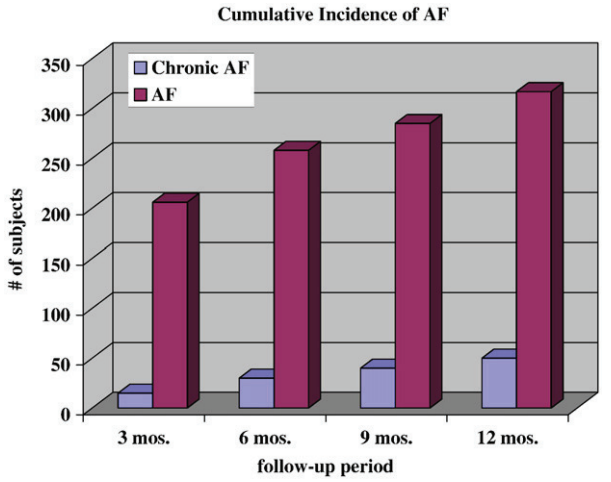
Baseline characteristics

Average age was 73 years, with a slight male predominance (Table I). Most participants were white. Hypertension was common, and approximately 20% of patients had a history of diabetes. Prior stroke was present in 11% and prior myocardial infarction in 26% of patients. Patients with CAF were excluded from the trial, but >40% of patients in both VVIR and DDDR groups reported a prior history of PAF. Eighteen percent of VVIR patients and 22% of DDDR patients had a history of heart failure (HF; P = .05). Over the course of the study, 182 (18%) crossed over from VVIR to DDDR due to severe pacemaker syndrome. Another 131 (13%) crossed over for other reasons such as refractory HF, chronotropic incompetence, or physician preference. Within 3 months after pacemaker implantation, 206 patients had AF (191 with PAF and 15 with CAF), and another 159 patients (124 with PAF, 35 with CAF) had AF between 3 and 12 months of follow-up (Figure 1).

Effect of AF on QOL

Pacemaker implantation was associated with significant improvement in multiple domains of QOL at 12 months[2,7] (data not shown). After adjustment for age, gender, history of AF, history of HF, treatment arm, and baseline QOL score, none of the subscale scores were significantly different among AF groups, although physical function and role physical function scores at 12 months were generally lower in those with PAF and CAF than those with SR (Table II). In combination, this led to a statistically significant difference among groups in the PCS score of the SF-36 at 12 months (P = .04). Specifically, improvement in the PCS score, denoting improvement in QOL as compared with baseline, was greatest in the group without AF at 12 months (mean change [MC] +2.50 pts, standard error of the mean [SEM] 0.44 pts), as opposed to those with PAF (MC +0.90 pts, SEM 0.77) or CAF (MC −0.30 pts, SEM 1.62), suggesting that AF might blunt the improvement in physical functioning associated with

Figure 1



Cumulative incidence of CAF and any AF by time from enrollment.

Table III. Difference in QOL scores at 12 months as compared with 3 months stratified by the presence or absence of AF*†

Scale	No AF (n = 1737)	PAF (n = 75)	CAF (n = 29)
Physical function	−2.21	−4.36	−3.45
Role physical	+2.44	−1.80	+0.83
Mental health	+0.25	+0.50	−3.31
Role emotional	+0.99	−0.34	+1.66
Vitality	−1.21	−1.43	−0.95
Pain	−0.92	−3.13	−7.09
Health perception	+3.28	+2.27	+0.79
Social function	−1.24	+0.15	−1.06
PCS	−0.60	−2.49	−0.50
MCS	0.11	+0.80	−0.74
Time trade-off	−0.00	−0.02	+0.03
SAS‡	+0.05	+0.12	+0.44§

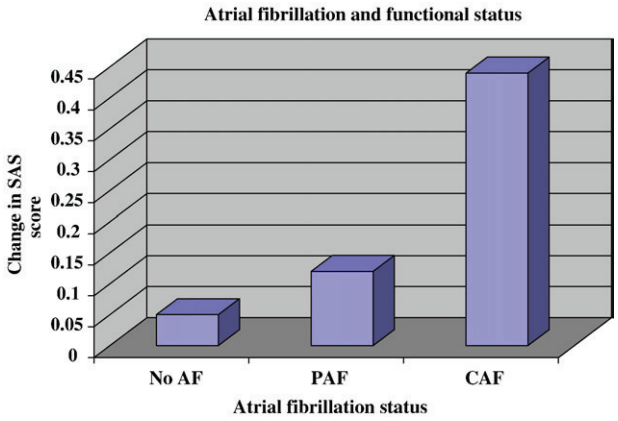
*Occasional data unavailable for each analysis.
†Higher scores denote improvement in QOL for all measures except for the SAS score, where lower scores denote improvement in cardiovascular functional status.
‡ $P < .05$ among groups, after adjustment for age, gender, history of AF, history of HF, treatment arm, baseline score.
§ $P < .05$ in pairwise comparison between those with CAF and those without AF.

Table II. Change in QOL scores at 12 months as compared with baseline stratified by the presence or absence of AF*†

Scale	No AF	PAF	CAF
Physical function	+0.06	−2.92	−3.29
Role physical	+22.22	+16.88	+14.32
Mental health	+2.55	+1.57	+2.09
Role emotional	+6.85	+4.10	+12.39
Vitality	+7.68	+7.04	+4.46
Pain	+3.46	+1.46	−3.20
Health perception	−1.29	−2.96	−1.29
Social function	+6.80	+4.98	+6.61
PCS‡	+2.50	+0.90	−0.30
MCS	+2.50	+2.32	+2.87
Time trade-off	+0.07	+0.06	+0.11
SAS‡	+0.03	+0.15	+0.21

*Occasional data unavailable for each analysis.
†Higher scores denote improvement in QOL for all measures except for the SAS score, where lower scores denote improvement in cardiovascular functional status.
‡ $P \leq .05$ among groups, after adjustment for age, gender, history of AF, history of HF, treatment arm, baseline score.

Figure 2



Worsening in SAS scores from 3 to 12 months in relation to AF status ($P = .02$).

pacemaker implantation. This was echoed by a similar trend of borderline statistical significance ($P = .05$) in SAS scores. Specifically, MC scores were only 0.03 points higher (SEM 0.03 pts) at 12 months as compared with baseline in those without AF, reflecting relatively stable functional status but worsened by 0.15 and 0.21 points (SEM 0.06 and 0.12), respectively, in those with PAF and CAF post pacemaker implantation.

Effect of AF on serial QOL

In analyses of the difference in QOL measures between 3 and 12 months follow-up, AF was not a significant predictor of SF-36 subscale scores, PCS or MCS summary scores, or of time trade-off utilities (adjusted for age, gender, history of AF, history of HF, treatment arm, and baseline score for each measure) (Table III). However, there was still better cardiovascular functional status in those without AF as compared with those who had PAF or CAF ($P = .02$). Specifically, patients without AF had a mean worsening in SAS score of 0.05 points (SEM 0.03) on a 4-point scale from 3 to 12 months of follow-up. In contrast, those with PAF and CAF had a worsening of 0.12 and 0.44 points (SEM 0.10

and 0.14), respectively (adjusted for age, gender, history of AF, history of HF, treatment arm, and baseline SAS score) (Figure 2).

Effect of AF on pairwise comparisons between those with PAF or CAF compared with no AF

In pairwise comparisons of QOL differences between 3 and 12 months stratified by the presence or absence of PAF over that period, the presence of PAF was not a significant predictor of any SF-36 subscale or summary score, of time trade-off scores, or of SAS scores (adjusted for age, gender, history of AF, history of HF, treatment arm, and baseline score for each measure). Similarly, pairwise-adjusted comparisons of the difference in QOL scores between 3 and 12 months after implantation between those who developed CAF and those who remained in SR showed no significant difference in SF-36 subscales or summary scores or time trade-off values. However, SAS scores were worse in those with CAF than those without AF (MC +0.18 pts; $P = .007$).

Discussion

Recent large randomized studies of elderly patients with sick sinus syndrome have not demonstrated significant differences in the rate of survival between patients who receive dual-chamber pacemakers versus single-chamber pacing. MOST, however, in contrast to the other large pacemaker trials, found a slight improvement in QOL among patients receiving dual-chamber compared with single-chamber pacemakers.[2,7] Perhaps important as a reason for this QOL improvement, the PASE, the CTOPP, and MOST trials reported a reduction in AF.[2,3,6,13] A meta-analysis of randomized trials of pacing mode performed at the patient level documented a hazard ratio of 0.8 for AF, corresponding to a significant 20% reduction in the risk of AF with DDDR.[4] More recently, newer algorithms for dual chamber pacing in sinus node dysfunction that target reduction in percent ventricular pacing have demonstrated further improvements on postimplant AF rates.[5] Thus, an analysis of QOL in paced patients with and without AF is timely because it may both explain QOL differences between pacing modes, and calibrate our expectations of improvements in QOL in elderly patients receiving new technology.

Moreover, because dual chamber pacing is not associated with a survival benefit, it becomes vital to quantify and understand the effects of pacing mode on the patient's functional status and sense of well-being, as measured by validated QOL instruments. In this report of the effect of AF on health-related QOL within MOST, AF was not a major determinant of most QOL measures, although AF did appear to blunt the improvement in PCS scores (which combine various components of HRQOL) associated with pacemaker placement. When the change scores in QOL from 3 to 12 months were analyzed to reduce potential confounding from the pacemaker implantation itself, AF was not a significant driver of QOL, suggesting that this is not a major component of the differences seen between treatment arms in MOST. Perhaps not surprisingly, though, there was a trend toward better cardiovascular functional status in patients without PAF or CAF, driven largely by worse cardiovascular status scores in those with CAF.

Relatively little is known about the effect of AF on QOL in patients with pacemakers. In keeping with our results, a prospective randomized MOST substudy of the efficacy of a mode switching algorithm for atrial high rate events to reduce rapid right ventricular pacing, a potential cause for poor QOL in AF, found that mode switching reduced the need for pacemaker reprogramming but was not associated with significant improvement in QOL.[14] Similarly, the ADOPT study, a randomized trial of atrial dynamic overdrive pacing to suppress AF in patients with DDDR pacing, showed that overdrive pacing substantially reduced the burden of symptomatic AF in patients with sick sinus syndrome and AF, but QOL scores improved similarly in both groups.[15] The CTOPP study randomized >2,500 patients with symptomatic bradycardia to ventricular or "physiologic" (dual-chamber or atrial) pacing.[3] Physiologic pacing was associated with a decrease in AF during the trial,[3,13] but there were no significant differences in QOL detected between treatment arms,[16] although the specific effect of AF on QOL has not been reported.

The larger question of the degree to which AF itself impacts QOL is more controversial, in part due to difficulties in accurately assessing and quantifying the effects of AF on this end point.[17-19] Early studies, which suggested that AF had substantial effects on QOL, akin to other chronic diseases such as coronary artery disease or HF, were often limited by small size, design, or the use of nonvalidated instruments.[17,19] Studies in highly symptomatic patients with AF undergoing atrioventricular node ablation and often subsequent pacemaker placement also reported marked improvement in QOL in these selected patient populations.[20-23] However, in the older, less selected population enrolled in the AFFIRM QOL substudy, QOL was comparable between rate and rhythm control strategies and was also similar in SR versus AF,[24,25] suggesting that effects on QOL associated with AF were quite modest in an older, medically managed population.

Our results should be interpreted in light of possible limitations in our study. The presence or absence of AF at each follow-up was detected in some cases by surface electrocardiography, in others by atrial electrograms and pacemaker interrogation, although we believe detection of mode switching to be quite sensitive for detecting AF, minimizing bias. The exact duration of each episode of AF was not determined and did not allow classification as paroxysmal or persistent according to the most recent practice guidelines.[26] In addition, for the purposes of

this analysis, we could not distinguish between AF and atrial flutter. Our QOL measures did not include a symptom scale specific to AF. Comparisons with baseline QOL measures may have been affected by the pacemaker insertion itself, and therefore, an additional analysis of the change in QOL measures from the 3-month to the 12-month time point was added. Access to mode switching in patients with AF may have lessened differences in QOL between the 2 groups**.** Other pacemaker parameters such as degree of pacemaker dependency or percentage of ventricular pacing may have influenced our results. Finally, multiple analyses were conducted, which may influence the probability of a significant result being obtained.

Conclusion

In summary, AF after pacemaker implantation in elderly patients with sick sinus syndrome was not a major determinant of QOL. However, there was a trend toward better cardiovascular functional status in patients without PAF or CAF.

Disclosures

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Dr Lamas reports receiving research grants and acting as a consultant and speaker for Medtronic; a speaker and consultant for Astra-Zeneca (Wilmington, DE) and CVT (Foster City, CA); a consultant for Astellas (Tokyo, Japan); and a speaker for Novartis (Washington, DC) and Glaxo-Smith-Kline (Philadelphia, PA). Dr Fleischmann has participated in CME and QI initiatives sponsored by Pfizer.

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Appendix A

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