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### Authors

Fleischmann, Kirsten E

Orav, E John

Lamas, Gervasio A

et al.

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# Pacemaker implantation and quality of life in the Mode Selection Trial (MOST)

Kirsten E. Fleischmann, MD, MPH,<sup>a</sup> E. John Orav, PhD,<sup>b</sup> Gervasio A. Lamas, MD,<sup>c</sup>  
Carol M. Mangione, MD, MSPH,<sup>d</sup> Eleanor Schron, MS, RN,<sup>e</sup> Kerry L. Lee, PhD,<sup>f</sup> Lee Goldman, MD, MPH<sup>a</sup>

From the <sup>a</sup>Department of Medicine, the University of California, San Francisco, San Francisco, California, <sup>b</sup>Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, <sup>c</sup>Division of Cardiology, Mount Sinai Medical Center, Miami Heart Institute, Miami Beach, Florida, <sup>d</sup>Department of Medicine, David Geffen School of Medicine at University of California, Los Angeles, California, <sup>e</sup>National Heart, Lung, and Blood Institute, Bethesda, Maryland, and <sup>f</sup>Duke Clinical Research Institute and Duke University School of Medicine, Durham, North Carolina.

**BACKGROUND** Dual-chamber pacemakers restore AV synchrony compared with ventricular pacemakers, but the effects on health-related quality of life (QOL) are uncertain.

**OBJECTIVES** The purpose of this study was to assess the effect of pacemaker implantation, clinical factors, and pacing mode on QOL.

**METHODS** The Mode Selection Trial (MOST) randomized 2,010 patients with sinus node dysfunction to rate-modulated right ventricular (VVIR) or dual-chamber (DDDR) pacing. A longitudinal analysis of serial QOL measures (Short Form-36 [SF-36], Specific Activity Scale, and time trade-off utility) was performed. In patients who crossed over from VVIR to DDDR because of severe pacemaker syndrome, the last known QOL prior to crossover was carried forward.

**RESULTS** Pacemaker implantation resulted in substantial improvement in almost all QOL measures. Subjects 75 years or older experienced significantly less improvement in functional status and physical component summary scores than did younger sub-

jects. In longitudinal analyses of the effect of pacing mode on QOL, significant improvement in three SF-36 subscales was observed with DDDR pacing compared with VVIR pacing: role physical [62.8 points (95% confidence interval [CI] 60.2, 65.5) vs 56.4 (95% CI 53.7, 59.1)], role emotional [85.0 (95% CI 82.9, 87.0) vs 81.9 (95% CI 79.9, 84.0)], and vitality [51.8 (95% CI 50.3, 53.3) vs 49.3 (95% CI 47.8, 50.7)], but not in other SF-36 subscales, the Specific Activity Scale, or utilities. The gains in QOL were larger than the declines associated with 1 year of aging but smaller than those associated with heart failure.

**CONCLUSION** Pacemaker implantation improved health-related QOL. The mode selected was associated with much smaller, but significant, improvements in several domains, particularly role physical function.

**KEYWORDS** Pacemakers; Pacing; Sinoatrial node; Arrhythmia (Heart Rhythm 2006;3:653–659) © 2006 Heart Rhythm Society. All rights reserved.

Dual-chamber pacemakers have the potential for preserving physiologic AV synchrony compared with single-chamber ventricular pacemakers in patients with sick sinus syndrome.<sup>1</sup> Although large, randomized trials of pacing mode have demonstrated no significant differences in mor-

ality,<sup>2,3</sup> some studies have demonstrated a reduction in adverse events such as atrial fibrillation, heart failure, and pacemaker syndrome. In addition, some, but not all, studies have suggested improvement in aspects of health-related quality of life (QOL) in patients assigned to dual-chamber pacing.<sup>2,4</sup>

Health-related QOL is an important metric of the efficacy of treatment, particularly in assessing treatments that do not clearly influence survival, and especially in older patients likely to suffer from sick sinus syndrome. Therefore, we collected and analyzed serial QOL in the Mode Selection Trial (MOST), a large trial of patients with sick sinus syndrome who were randomized to dual-chamber, rate-modulated (DDDR) or single-chamber, rate-modulated ventricular (VVIR) pacing<sup>5</sup> to assess the effect of pacemaker implantation, clinical factors, and mode on QOL. We hypothesized that dual-chamber pacing would be associated with greater improvement in QOL after pacemaker implantation. Partial results from the QOL data in MOST have been published.<sup>2</sup> This report expands on prior publications by including analyses of the effect of (1) pacemaker im-

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plantation on QOL in clinically important subgroups within the trial, (2) clinical factors on serial QOL, (3) pacing mode on QOL using adjudicated crossovers for severe pacemaker syndrome, and (4) performing analyses both with and without carrying forward QOL measurement after adjudicated crossover. This study also places the magnitude of the observed changes in QOL in context with other common events, such as aging, and with chronic disease, such as heart failure.

## Methods

MOST randomized 2,010 patients with sick sinus syndrome to VVIR or DDDR pacing between 1995 and 1999.<sup>2,5</sup> Follow-up for clinical outcomes occurred four times during the first year and twice per year thereafter and ended in January 2001. Enrollment and data collection have been outlined in detail.<sup>2</sup> Trained research coordinators enrolled patients older than 21 years with sick sinus syndrome who were in sinus rhythm and had standard indications for pacemaker implantation but no serious comorbid illness. Baseline demographic and clinical data were collected. Multidimensional health-related QOL was assessed with the Medical Outcomes Study 36-Item Short-Form (SF-36) General Health Survey.<sup>6,7</sup> Individual SF-36 components were used to construct subscale scores in eight health-related domains: physical function, physical role, social function, emotional role, mental health, vitality, bodily pain, and general health perception. For each domain, scores range from 0 to 100 points, where 100 is the best score possible and 0 is the worst. Physical component summary (PCS) and mental component summary (MCS) scales also were calculated for each patient. These scores have a standardized mean of 50 and standard deviation of 10 points. Cardiac-specific functional status was assessed using the Specific Activity Scale,<sup>8</sup> a multilevel scale that ranges from 1 (worst) to 4 (best) status depending on the patients' ability to perform everyday tasks. Patients' utilities were assessed using standard time trade-off methodology,<sup>9</sup> in which patients were asked how much time in their current state of health they would trade for perfect health. All three QOL measures (SF-36, Specific Activity Scale, and time trade-off) were repeated at the 3-month and 12-month visits and yearly thereafter. We also attempted to obtain an assessment of QOL at the time of crossover from one pacing mode to another, as QOL commonly was improved when crossing over from VVIR to DDDR because of pacemaker syndrome.

QOL measures (including each SF-36 subscale and summary score, Specific Activity Scale, and time trade-off utility) were selected *a priori* as endpoints for analysis. Each was assessed for differences related to pacemaker implantation using a paired t-test comparing scores at 3 months postimplantation to values at baseline as well as a linear regression of the change score between the 3-month and baseline timepoints. Change in QOL measures was stratified by clinical factors, which included age, sex, history of congestive heart failure, comorbidity as assessed by the Charlson comorbidity index, and treatment arm. Multivari-

able analyses were performed using SAS (version 8, SAS Institute, Cary, NC, USA) with PROC GLM, which uses the method of least squares to fit linear models to the data, and PROC MIXED, which fits mixed effects linear models. Significant differences in QOL over time were assessed in longitudinal analyses using PROC MIXED. The effect of sex was measured in models adjusted for age and treatment arm. The effects of a history of heart failure, Charlson comorbidity score, and mode on serial QOL in analyses adjusted for age, sex and baseline QOL score also were examined. Patients were truncated from the analysis at the time of death. Patients who could not complete the QOL questionnaire were considered to have missing data unless data from surrogate interviews were available. In patients who crossed over from single-chamber to dual-chamber pacing because of severe pacemaker syndrome, a primary analysis was performed in which the last known QOL prior to crossover was carried forward for all subsequent data-points. This was designed to account for the improvement in QOL scores anticipated after crossover, which tends to overestimate QOL scores in the VVIR arm. A secondary analysis using the measured QOL data after crossover also was performed.

To provide context for these analyses, the effect of 1 year of aging on QOL measures in this cohort was assessed. Differences in each QOL measure from the 1-year to the 2-year follow-up timepoint were assessed using PROC GLM in analyses adjusted for baseline score and stratified by sex. These timepoints were chosen to maximize the completeness of the follow-up data while avoiding the confounding effects of pacemaker implantation on QOL at earlier timepoints. The effect of a common chronic disease, in this case a history of heart failure at the time of enrollment into the trial, was assessed in analyses of baseline QOL data using PROC GLM adjusted for age and sex. In addition, serial QOL in subjects who experienced heart failure during the trial was compared with serial QOL in patients who did not experience heart failure using PROC MIXED, adjusting for age, sex, treatment arm, and baseline score.

## Results

### Baseline characteristics

The average age of the cohort was 73 years; 52% of patients were male (Table 1). The majority of patients were white, and 22% had a history of diabetes. Prior myocardial infarction was reported in 26% and prior stroke in 11%. Prior heart failure was present in 18% of VVIR patients and 22% of DDDR patients, a difference of borderline significance ( $P = .05$ ).

### Effect of pacemaker implantation

In unadjusted analyses, pacemaker implantation was associated with significant improvement in multiple domains of QOL. Specifically, significant improvement was seen in all subscales of the SF-36 except for the health perception subscale, resulting in higher PCS scores (mean 2.7 points,  $P$

**Table 1** Baseline characteristics of the cohort

Characteristic	VVIR (n = 996)	DDDR (n = 1,014)
Age (yr)	73.1 ± 11.0	72.9 ± 11.1
Male	519 (52%)	536 (53%)
Nonwhite race	144 (14%)	162 (16%)
Diabetes	204 (20%)	246 (24%)
Hypertension	608 (61%)	640 (63%)
Hypercholesterolemia	340 (34%)	376 (37%)
Current smoker	85 (9%)	84 (8%)
Prior angina	280 (28%)	288 (28%)
Prior myocardial infarction	243 (24%)	279 (28%)
Prior heart failure	183 (18%)	221 (22%)
Prior stroke	108 (11%)	116 (11%)
Charlson comorbidity index	1.46 ± 1.65	1.54 ± 1.67

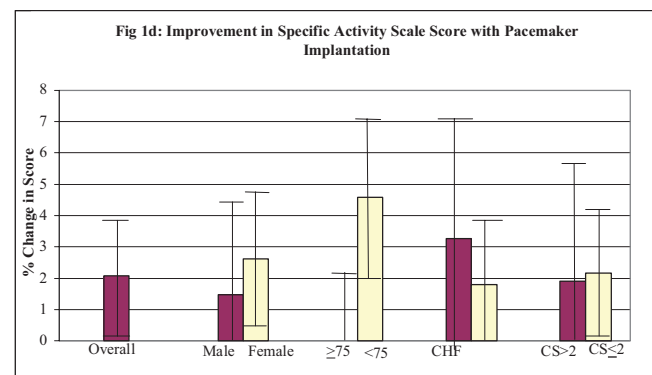
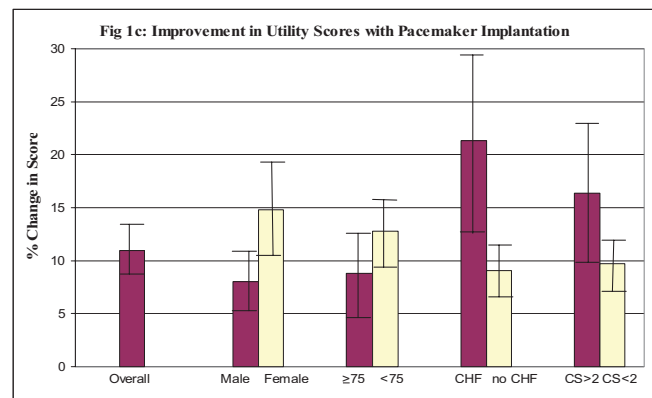
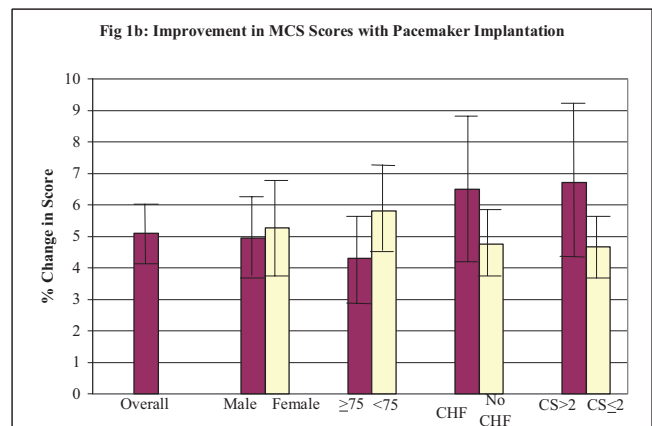
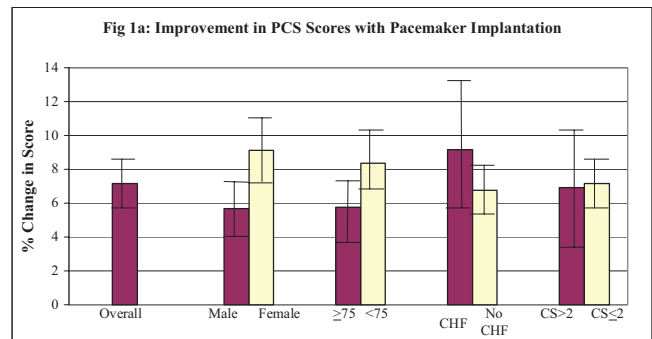
Values are given as number (%) or mean ± SD.

DDDR = dual-chamber pacing; VVIR = rate-modulated right ventricular pacing.

< .0001) and MCS scores (mean 2.5 points,  $P < .0001$ ; Figures 1a and 1b). Time trade-off values and Specific Activity Scale scores also were significantly improved (Figures 1c and 1d). The benefits were similar regardless of sex, history of heart failure, or comorbidity score. Paired t-tests showed a trend toward greater improvement in functional status, as measured by the Specific Activity Scale, in patients younger than 75 years (Figure 1d). In linear regression analyses of the change in QOL score between the baseline and 3-month postimplantation timepoints, this trend became significant, with less negative change scores connoting less improvement in functional status, among subjects 75 years or older (parameter estimate 0.09, 95% CI [confidence interval] 0.02, 0.17). The PCS score of the SF-36 also improved significantly less in the older patients than in the patients younger than 75 years (parameter estimate -1.09, 95% CI -2.04, -0.14). Even after adjustment for sex, a history of heart failure, Charlson score, and treatment arm, age remained a significant predictor of the change in PCS score (parameter estimate -1.21, 95% CI -2.16, -0.25) and Specific Activity Score (parameter estimate 0.10, 95% CI 0.02, 0.17).

**Serial QOL**

In analyses adjusted for age and sex, pacemaker implantation was associated with improvements in several subscales of the SF-36, particularly the role physical (Table 2). In longitudinal analyses of QOL, sex was an independent predictor of functional status by Specific Activity Scale ( $P < .0001$ ) and of all SF-36 subscale scores ( $P < .03$ ) except role physical function and health perception in analyses adjusted for age and treatment arm. QOL scores were generally higher, and reported functional status was better in men. Most aspects of QOL were significantly worse in subjects with Charlson comorbidity scores >2, including Specific Activity Scale scores [1.56 (95% CI 1.48, 1.63) vs 1.30 (95% CI 1.25, 1.36),  $P < .0001$ ], health utilities [0.78 (95% CI 0.75, 0.81) vs 0.83 (95% CI 0.81, 0.84),  $P = .001$ ], and all SF-36 subscales ( $P < .03$ ) except mental health in adjusted analyses (data not shown).



**Figure 1** Improvement in quality of life associated with pacemaker implantation. CHF = congestive heart failure; CS = Charlson comorbidity score; MCS = mental component summary; PCS = physical component summary.

**Table 2** Quality-of-life scores before and after pacemaker implantation

Scale	Mode	Mean scores adjusted for age and gender					
		Baseline (n* = 1,935)	3 mo (n* = 1,736)	12 mo (n* = 1,639)	24 mo (n* = 1,208)	36 mo (n* = 748)	48 mo (n* = 392)
Physical function	DDDR	58.9	63.0	61.6	61.0	59.0	58.6
	VVIR	58.9	61.5	61.4	59.0	57.4	58.3
Role physical†	DDDR	34.6	61.0	64.0	65.5	68.6	65.3
	VVIR	35.7	55.5	60.5	56.2	56.5	59.9
Mental health	DDDR	72.1	75.9	76.8	76.7	79.6	78.7
	VVIR	72.0	75.5	75.4	74.7	75.8	77.1
Role emotional†	DDDR	74.0	82.9	85.8	85.9	86.2	89.1
	VVIR	74.1	81.2	81.5	81.9	81.6	80.1
Vitality†	DDDR	42.6	54.8	53.4	51.5	54.1	52.1
	VVIR	41.9	50.8	51.7	49.2	48.5	49.8
Pain	DDDR	67.0	72.4	72.4	71.1	72.1	73.0
	VVIR	67.6	72.4	72.9	69.9	72.9	76.7
Health perception	DDDR	60.3	62.3	61.1	58.4	59.0	58.6
	VVIR	60.0	60.4	61.0	57.0	58.0	56.2
Social function	DDDR	62.6	73.1	73.5	71.4	72.5	73.8
	VVIR	63.5	71.1	72.3	70.5	70.9	71.6
Time trade-off	DDDR	0.72	0.83	0.83	0.83	0.86	0.83
	VVIR	0.73	0.82	0.82	0.81	0.83	0.87
Specific Activity Scale	DDDR	1.97	1.92	1.99	1.99	2.01	2.01
	VVIR	2.00	1.94	1.97	2.01	1.98	2.03

DDDR = dual-chamber pacing; VVIR = rate-modulated right ventricular pacing.

\*Occasional data unavailable for each analysis.

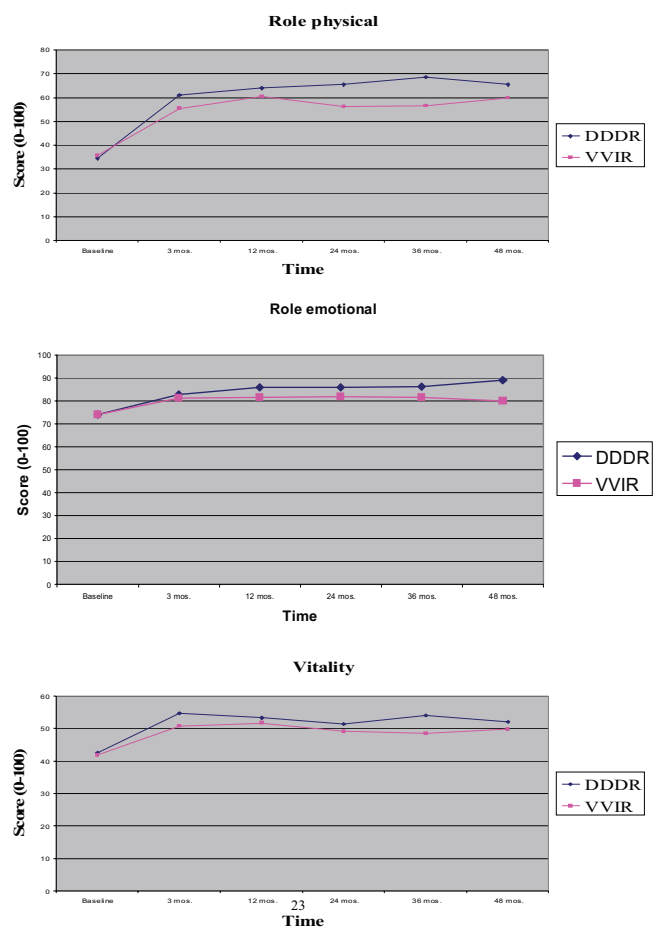
† $P < .05$  in longitudinal analyses of subscale score by treatment arm.

### Effect of pacemaker mode on serial QOL

One hundred eighty-two patients (18%) crossed over from single-chamber to dual-chamber pacing because of severe pacemaker syndrome. In addition, 131 patients (13%) crossed over for other reasons but did not meet the protocol's prespecified definition of severe pacemaker syndrome. Most crossovers occurred early, predominantly within 3 months of pacemaker placement.

In longitudinal analyses by pacemaker mode adjusted for age and sex, dual-chamber pacing was associated with significantly greater improvement in three of the eight SF-36 subscales compared with single-chamber pacing: role physical [62.8 points for DDDR (95% CI 60.2, 65.5) vs 56.4 for VVIR (95% CI 53.7, 59.1),  $P < .0001$ ], role emotional [DDDR 85.0 (95% CI 82.9, 87.0) vs VVIR 81.9 (79.9, 84.0),  $P = .009$ ], and vitality [DDDR 51.8 (95% CI 50.3, 53.3) vs VVIR 49.3 (95% CI 47.8, 50.7),  $P = .002$ ]; (Figure 2). The relationship between pacing mode and QOL remained significant for these three subscales even after adjustment for heart failure or atrial fibrillation during the study, both of which were significantly reduced by dual-chamber pacing in MOST.<sup>2</sup> There were no significant differences in the five other subscales or in scores on the time trade-off or Specific Activity Scale. In no case was single-chamber pacing associated with significantly better QOL.

If health-related QOL measures were carried forward for all crossovers rather than for just those meeting the prespecified endpoint of severe pacemaker syndrome, qualitatively similar results were obtained. Significant improvement in serial QOL again was seen in role physical [62.3 points (95% CI 59.6, 65.0) vs 54.5 points (95% CI 51.7,



**Figure 2** Effect of pacing mode on serial quality of life.



57.2),  $P < .0001$ ], role emotional [85.2 (95% CI 83.1, 87.3) vs 81.9 (95% CI 79.8, 84.0),  $P = .006$ ], and vitality [52.0 (95% CI 50.5, 53.5) vs 48.7 (95% CI 47.2, 50.2),  $P < .0001$ ] subscales of the SF-36, as well as in the social function subscale [72.1 (95% CI 70.5, 73.6) vs 70.1 (95% CI 68.5, 71.6),  $P = .02$ ] in subjects randomized to the DDDR treatment arm compared with those in the VVIR arm.

In the analysis using the measured health status throughout the trial, regardless of crossover status, health status commonly improved after crossover from VVIR to DDDR. By ascribing this benefit of DDDR to the VVIR treatment arm, no significant differences in serial health-related QOL were detected between treatment arms, indicating that the two strategies—DDDR pacing or VVIR pacing converted to DDDR when advised by the physician—were equivalent.

### Magnitude of QOL changes

The decline in health status scores associated with 1 year of aging within the trial was 0.6 points (95% CI  $-3.7, 4.9$ ,  $P = .78$ ) in women and 1.7 points (95% CI  $-2.5, 5.9$ ,  $P = .43$ ) in men for role physical, 1.0 point (95% CI  $-2.4, 4.4$ ,  $P = .56$ ) in women and 0.1 point (95% CI  $-3.2, 3.5$ ,  $P = .94$ ) in men for role emotional, and 3.6 points (95% CI 1.7, 5.4,  $P = .0002$ ) in women and 2.4 points (95% CI 0.5, 4.2,  $P = .01$ ) in men for vitality (adjusted for age and baseline score). Patients with a history of heart failure had significantly lower baseline role physical [24.3 (95% CI 19.7, 29.0) vs 37.4 (95% CI 34.7, 40.1),  $P < .0001$ ], role emotional [69.9 (95% CI 65.5, 74.3) vs 74.9 (95% CI 72.3, 77.5),  $P = .03$ ], and vitality [33.4 (95% CI 30.7, 36.1) vs 44.1 (95% CI 42.5, 45.7),  $P < .0001$ ] scores compared with those without antecedent heart failure, adjusted for age and sex. Patients who experienced heart failure over the course of the trial also had significantly lower mean role physical [44.8 (95% CI 40.1, 49.5) vs 61.3 (95% CI 59.1, 63.6)], role emotional [77.8 (95% CI 74.1, 81.4) vs 84.1 (95% CI 82.3, 85.8)], and vitality [44.2 (95% CI 41.6, 46.8) vs 51.2 (95% CI 50.0, 52.5)] scores in longitudinal analyses adjusted for age, sex, treatment arm, and baseline score.

### Discussion

For at least 2 decades, clinicians have recommended dual-chamber pacemakers for preserving or restoring AV synchrony. However, controversy has persisted about the effect of pacing mode on the clinical outcomes of elderly patients with sick sinus syndrome. Large randomized studies have not shown significant differences in survival or stroke between patients receiving dual-chamber pacing and those receiving single-chamber pacing. However, randomized trials such as Pacemaker Selection in the Elderly (PASE), the Canadian Trial of Physiologic Pacing (CTOPP), and MOST have reported a reduction in atrial fibrillation.<sup>2,3,4,10</sup> Moreover, MOST, but not the other trials, found a reduction in hospitalizations for heart failure.<sup>2</sup>

Given that pacing mode appears not to affect survival, quantifying the effects of pacing mode on the patient's own

sense of health, well-being, and functional status is a vital part of the overall critical analysis of pacing mode. In this detailed report of health-related QOL within MOST, pacemaker implantation itself was associated with significant improvement in health-related QOL scores. This improvement extended to almost all domains and was of similar magnitude irrespective of sex, the presence of heart failure, or comorbidity level, all of which also influenced QOL over the course of the study. Younger patients appeared to benefit more from pacemaker implantation than did their older counterparts in terms of functional status and PCS scores. Although this study did not have a sham-operated control group for comparison, these data confirm that when pacemakers are implanted in patients with sinus node dysfunction and standard bradycardia indications, direct and measurable benefits of pacemaker implantation on QOL and functional status are observed, particularly in younger patients.

The effects of pacing mode on the various QOL measures were much smaller than those associated with pacing itself. Modest but measurable improvement for dual-chamber rate-modulated pacing compared with rate-modulated single-chamber pacing was most notable for the physical role, vitality, and emotional role subscales. Interestingly, pacing mode was associated with nonsignificant differences in the physical function subscale of the SF-36 and in cardiovascular functional status as measured by the Specific Activity Scale. This finding suggests that dual-chamber pacing significantly improves patients' ability to fulfill expectations at work or in other daily activities at the margins despite only small differences in overall physical capacity itself, as measured by either the physical function subscale or the Specific Activity Scale. In contrast to pacemaker implantation itself, no significant differences in time trade-off utilities were seen between pacing modes, indicating that subjects were reluctant to accept even small reductions in survival for the modest gains in QOL seen.

The vitality subscale reflects general levels of energy and fatigue, so the improved scores might represent the effect of more physiologic dual-chamber pacing on hemodynamics and cardiac output. The emotional role subscale measures "problems with work or other daily activities as a result of emotional problems"<sup>6,7</sup> and may be an indirect reflection of improved well-being. Generally, these improvements in QOL were larger than the declines associated with 1 year of aging in the trial but smaller than those associated with chronic illness, such as heart failure.

Early studies suggested improved QOL for patients with dual-chamber pacemakers compared with single-chamber pacemakers,<sup>11-16</sup> but the studies were limited by small size, design, nonstandardized instruments, or inconsistent blinding. PASE, a 30-month, controlled, single-blind study of 407 patients randomized to ventricular or dual-chamber pacing for sinus node dysfunction or AV block, showed that QOL improved significantly after pacemaker implantation but found no significant differences in QOL, cardiovascular

events, or death by pacing mode.<sup>4</sup> However, analysis of QOL by mode in the prespecified subgroup of patients with sinus node dysfunction revealed significant improvement in the role physical, role emotional, and social function subscales at 3 months in patients randomized to dual-chamber pacing compared with ventricular pacing, results that are consistent with those in the current study of patients with sinus node dysfunction.

CTOPP randomized more than 2,500 patients with symptomatic bradycardia to ventricular or “physiologic” (dual-chamber or atrial) pacing.<sup>3</sup> QOL was assessed in two ways: (1) a substudy of 269 patients in whom detailed QOL data, including SF-36 and pacemaker-specific and pacemaker syndrome scales, were measured at baseline and at 6-month follow-up; and (2) a larger QOL study in which 1,721 patients underwent a briefer 12-item assessment only once at 6 months postimplantation.<sup>17</sup> Pacing was associated with significant improvement in QOL in the substudy, but no significant differences in QOL were discerned between treatment arms. The larger QOL study also failed to detect significant differences in QOL when comparing ventricular and physiologic pacing. These results differ from those of the current study, possibly because a relatively small number of participants in CTOPP underwent QOL assessment to the same level of detail as in MOST, or possibly because more than 50% of patients enrolled in the Canadian study received a pacemaker for AV node disease rather than for sinoatrial node disease, limiting power for differences within the sinoatrial node dysfunction subgroup.

Our results should be interpreted in light of design features that may have affected the results. Patients randomized to ventricular pacing had access to rate modulation, which may have lessened differences in QOL between the two groups. In addition, programming mode rather than the pacemaker itself was randomized, making crossover from ventricular to dual-chamber pacing relatively easy. Because QOL commonly improves after crossover, crossovers tend to minimize any differences between groups. To account for this design feature in our trial, baseline analysis was structured to carry forward the last known QOL prior to crossover for subsequent timepoints. Finally, although all endpoints were selected *a priori*, multiple analyses were performed in this cohort, which may influence the probability of obtaining statistically significant results.

## Conclusion

Pacemaker implantation is associated with substantial improvement in health-related QOL in patients with sick sinus syndrome. Pacing mode is associated with much more modest improvements in some (but not most) QOL domains, most notably the role physical, energy/vitality, and role emotional domains. The magnitude of the QOL difference between modes of pacing is slightly larger than that associated with 1 year of aging within the trial but smaller than that associated with chronic disease, such as heart failure. Although these improvements in QOL may not be substantial enough, in and of themselves, to sway decisions on

pacemaker mode, cost-effectiveness analysis suggests that these changes, in conjunction with effects on clinical events such as atrial fibrillation and heart failure, are associated with favorable cost-effectiveness ratios for routine implantation of dual-chamber pacing systems in elderly patients with sinus node dysfunction.<sup>18</sup>

## APPENDIX

### Clinical Coordinating Center:

Gervasio A. Lamas MD (Study Chairman), Division of Cardiology, Mount Sinai Medical Center, and the University of Miami School of Medicine, Miami Beach FL

### Data Coordinating Center:

Kerry L. Lee PhD (Principal Investigator), Anne S. Hellkamp MS (Statistician); Duke Clinical Research Institute and Duke University School of Medicine, Durham NC

### Quality of Life and Economic Analysis Coordinating Center:

Lee Goldman MD (Principal Investigator), Department of Medicine, University of California, San Francisco (LG), E. John Orav PhD (Statistician) Brigham and Women's Hospital and Harvard Medical School Boston MA.

### Project Office:

Eleanor Schron RN MS (Project Officer); Division of Epidemiology and Clinical Applications, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda MD

### Participating Investigators

Advanced Cardiac Specialists, Gilbert, AZ: R. Siegel, S. Cantor, and P. Underwood; Alamance Regional Medical Center, A. Paraschos, B. Fath, and B. Kowalski; Austin Heart, Austin, TX: Stephen Greer MD, D. Pederson and J. Black; Baptist Medical Center, Princeton, NJ: T. Gaskin, A. Bouchard, and M. Nilensky; Baptist Medical Center, Little Rock, AR: S. Greer; Baylor College of Medicine, Houston, TX: A. Blaustein, M. Nadir Ali, J. Nattama; Baystate Medical Center, Springfield, MA: J. Cook, and G. Kabell, and J. Kirchoffer; Brigham & Women's Hospital, Boston, MA: M. O. Sweeney and G. Mitchell; Brooklyn Veterans Affairs Medical Center, Brooklyn, NY: N. El-Sherif; Cardiac Disease Specialists, Atlanta, GA: T. Deering; Catholic Medical Center, Manchester, NH: B. Hook; The Christ Hospital, Cincinnati, OH: R. Henthorn, S. Behrens, J. Burroughs, and T. Waller; Christiana Hospital, Newark, DE: B. Sarter, R. Miller, M. Stillabower, A. Vigh, and R. Vitullo; Cleveland Clinic Foundation, Cleveland, OH: B. Wilkoff, R. Augustine, L. Castle, M. Chung, F. Jaeger, G. Kidwell, V. Morant, M. Niebauer, and P. Tchou; Columbia Presbyterian Medical Center, New York, NY: D. Bloomfield, J. Dizon, and H. Spotnitz; Crawford Long Hospital and Emory University Hospital, Atlanta, GA: A. Leon, D. Delurgio, and J. Langberg; Danville Regional Medical Center, Danville, VA: G. Miller; Deaconess Nashoba Hospital, Ayer, MA: T. Hack; Deborah Heart and Lung Center, Browns Mills, NJ: C. Dennis and R. Corbisiero; Duke University Medical Center, Durham, NC: J. M. Wharton, R. Greenfield, and R. Sorrentino; Easton Hospital, Easton, PA: K. Khalighi; Gaston Memorial Hospital, Gastonia, NC: M. Silver; Geisinger Medical Center, Danville, PA: R. Storm and J. Oren; Good Samaritan Hospital, Lombard, IL: M. O'Toole and M. Nora; Good Samaritan Hospital, Los Angeles, CA: R. Matthews, and R. Lerman; Hackensack Medical Center, Hackensack, NJ: J. Zimmerman and T. Glotzer; Harbin Clinic, Rome, GA: A. S. Gursoy, G. Floyd, G. Myers, F. Stegall, and R. Young; Harper Hospital/Detroit Medical Center, Detroit, MI: M. Meissner; Heart Clinics Northwest, Spokane, WA: T. Lessmeir and W. Pochis; Henry Ford Hospital, Detroit, MI: C. Schuger, M. Lehmann, L. Pires, and R. Steinman; Hospital of the University of Pennsylvania, Philadelphia, PA: D. Kocovic, D. Callans, C. Gottlieb, F. Marchlinski and B. Pavri; Howard University Hospital: O. Randall, and D. Williams; John F. Kennedy Medical Center, Atlantis, FL: R. Fishel; Lahey Hitchcock Medical Center, Burlington, MA: D. Martin, R. John, and F. Venditti; Lanckenau Hospital, Wynnewood, PA: R. Marinchak, D. Bharucha, M. Hernandez, P. Kowey, S. Rials, and J. Shuck; Lovelace Health Systems, Albuquerque, NM: M. West and F. Kusumoto; Maine Medical Center, Portland, ME: J. Love, J. Cutler, W. Dietz, and G. Leask; Marshfield Clinic, Marshfield, WI: J. Hayes, and H. Vidaillet Jr; Medical College of Philadelphia-Hahnemann University, Philadelphia, PA: S. Kutalek, J. Caplan, J. Fontaine, S. Hessen, C. Movsowitz, F. Samuels, S. Wilbur; Medical College of Virginia, Richmond, VA: K. Ellenbogen and M. Wood; Michael Reese Hospital, Chicago, IL: D. Lieb, and M. Siddiqi; Milton S. Hershey Medical Center, Hershey, PA: J. Luck, J. Dell'Orfano, G. Naccarelli, H. Patel, and D. Wolbrette; Montefiore Medical Center, Bronx, NY: J. Gross and S. Furman; Montreal General Hospital, Montreal, Canada: T. Hadjis and M. Sami; Mount Sinai Medical Center, New York, NY: J. Camuñas and J. Halperin; Mount

Sinai Medical Center, Miami Beach, FL: J. Zebede, E. Lieberman; Mt. Auburn Hospital, Cambridge, MA: S. Forwand and P. Voukydis; New England Medical Center, Boston, MA: N. A. M. Estes III and M. Link; Northeast Medical Center, Fayetteville, NY: R. Silverman; Ohio State University Medical Center, Columbus, OH: C. Love and A. Mehdirdad; Oregon Health Sciences University, Portland, OR: J. McAnulty, B. Halperin and J. Kron; Peninsula Regional Medical Center, Salisbury, MD: E. Nsah; Phoebe Putney Memorial Hospital, Albany, GA: S. Souther; Presbyterian Medical Center/University of Pennsylvania, Philadelphia, PA: A. Russo and H. Waxman; Providence Hospital, Southfield, MI: C. Machado; Regional Cardiology Associates, Sacramento, CA: G. O'Neill and A. Sharma; Ruby Memorial Hospital, Morgantown, WV: S. Schmidt and J. Lobban; Rush Presbyterian-St. Luke's Medical Center, Chicago, IL: P. Santucci and E. Sgarbossa; Saint Joseph's Hospital of Atlanta, Atlanta, GA: M. Cohen, H. Kopelman, and S. Prater; Sentara Norfolk General Hospital, Norfolk, VA: R. Bernstein and J. Herre; Shands Hospital, Gainesville, FL: J. Conti; St. Elizabeth's Hospital of Boston, Boston, MA: C. Haffajee and G. M. Chandrahy; St. Joseph Mercy Hospital, Ypsilanti, MI: J. Kappler, and S. Winston; St. Joseph's Hospital & Medical Center, Paterson, NJ: N. Tullo, M. Biehl, and S. Fishberger; St. Luke's/Roosevelt Hospital Center, New York, NY: F. Ehlert and J. Steinberg; Sunnybrook Health Sciences Center, Toronto, Canada: C. Lau; Susquehanna Health System, Willamsport, PA: J. Burks, and E. Keating; Tampa General Hospital, Tampa, FL: H. Fontanet; Thomas Jefferson University Hospital, Philadelphia, PA: A. Greenspon, D. Kleinman and S. Sloan; Tri-City Cardiology, Mesa, AZ: A. Kaplan; University Cardiology Consultants, PA: R. Schneider; University Community Hospital/Pepin Heart Centre, Tampa, FL: S. Elchahal; University Hospital, London, Canada: R. Yee, G. Klein, and A. Krahn; The University of California at Los Angeles, Los Angeles, CA: Z. Feliciano, N. Boyle, and B Long; University of Chicago Hospitals, Chicago, IL: D. Wilber and D. Kopp; University of Kentucky, Lexington, KY: F. Leonelli, C S. Kuo, and A. Natale; University of Massachusetts Medical Center, Worcester, MA: L. Rosenthal, R. Mittleman, and P. Spector; University of Missouri Hospital and Clinics, Columbia, MO: G. Flaker, P. McLaughling, and R. Tummula; University of New Mexico School of Medicine, Albuquerque, NM: C. Cadman; University of Pittsburgh Medical Center, Pittsburgh, PA: D. Schwartzman, K. Anderson, D. Contrafatto, and V. Gottipaty; University of Utah Health Sciences Center, Salt Lake City, UT: R. Freedman and S. Compton; University of Virginia Health Sciences Center, Charlottesville, VA: J. DiMarco, D. Haines, and S. Nath; Veterans Affairs Medical Center, Washington, DC: S. Singh, R. Fletcher, and P. Karasik; Virginia Beach General Hospital, Virginia Beach, VA: J. Griffin and L. Kanter; Watson Clinic, Lakeland, FL: S. Keim, D. Ebersole, J. Messina, W. Moore III, G Tyson, and R. Vlietstra; Welborn Baptist Hospital, Evansville, IN: S. Muftic; West Los Angeles Veterans Affairs Medical Center, Los Angeles, CA: M. Bersohm, B. Cohen and D. Gallik; West Roxbury Veterans Affairs Medical Center, Brookline, MA: M. Katcher; William Beaumont Hospital, Royal Oak, MI: H. Frumin and J. Stewart; Wilson Regional Medical Center of United Health Services Hospitals, Johnson City, NY: N. Stamato; Winthrop University Hospital, Mineola, NY: B. Ibrahim and R. Steingart; William Jennings Bryan Dorn Veterans Affairs Hospital, Columbia, SC: A. Saenz; Yale University School of Medicine, New Haven, CT: W. Batsford, C. McPherson, and L. Rosenfeld.

#### ECG Core Laboratory:

A. Tolentino MD, A. Montanez MD, J. Zebede MD

#### Clinical Events Committee:

G. Flaker MD (Chair), A. J. Greenspon, R. Marinchak, J. McAnulty, M.O. Sweeney, N.A.M. Estes, B. Tardiff, F. Marchlinski

#### Data and Safety Monitoring Board:

M. Pfeffer MD PhD (Chair), E. Antman MD, A. Curtis MD, K. Davis PhD, S. Saksena MD, M.Hlatky MD, D. Sherman MD

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