DEVICES

VVI pacing with normal QRS duration and ventricular function: MOST trial findings relevant to leadless pacemakers

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Abstract

Background: Leadless pacemakers (LPs) provide ventricular pacing without the risks associated with transvenous leads and device pockets. LPs are appealing for patients who need pacing, but do not need defibrillator or cardiac resynchronization therapy. Most implanted LPs provide right ventricular pacing without atrioventricular synchrony (VVIR mode). The Mode Selection Trial in Sinus Node Dysfunction (MOST) showed similar outcomes in patients randomized to dual-chamber (DDDR) versus ventricular pacing (VVIR). We compared outcomes by pacing mode in LP-eligible patients from MOST.

Methods: Patients enrolled in the MOST study with an left ventricular ejection fraction (LVEF) >35%, QRS duration (QRSd) <120 ms and no history of ventricular arrhythmias or prior implantable cardioverter defibrillators were included (LP-eligible population). Cox proportional hazards models were used to test the association between pacing mode and death, stroke or heart failure (HF) hospitalization and atrial fibrillation (AF).

Results: Of the 2010 patients enrolled in MOST, 1284 patients (64%) met inclusion criteria. Baseline characteristics were well balanced across included patients randomized to DDDR (N = 630) and VVIR (N = 654). Over 4 years of follow-up, there was no association between pacing mode and death, stroke or HF hospitalization (VVIR HR 1.28 [0.92-1.75]). VVIR pacing was associated with higher risk of AF (HR 1.32 [1.08-1.61], $P = .007$), particularly in patients with no history of AF (HR 2.38 [1.52-3.85], $P < .001$).

Conclusion: In patients without reduced LVEF or prolonged QRSd who would be eligible for LP, DDDR, and VVIR pacing demonstrated similar rates of death, stroke or HF hospitalization; however, VVIR pacing significantly increased the risk of AF development.

KEYWORDS
atrial fibrillation, heart failure, leadless pacing, outcomes, pacemaker

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1 | INTRODUCTION

Complications occur in approximately 10% of traditional transvenous pacemaker implantations with the majority of complications are related to lead.[1] Leadless pacemakers (LP) are a safe and effective method of ventricular pacing without the need for implantation of transvenous leads and pulse generators.[2–5] Currently, LPs do not have the ability to function as implantable cardioverter-defibrillators (ICDs) or deliver cardiac resynchronization therapy (CRT). Therefore, patients who have a need for a pacemaker and do not meet indications for either ICD or CRT are the ideal candidates for LPs.

First-generation LPs are self-contained pacemakers that provide asynchronous right ventricular (RV) pacing, although a very recently approved second-generation device is able to provide VDD pacing in some patients with AV block.[6,7] LPs that provide atrial pacing are in development but are not yet commercially available. In patients with sinus node dysfunction, implantation of an LP would provide asynchronous RV pacing only. The effect of pacing mode in patients with sinus node dysfunction was evaluated in the Mode Selection Trial in Sinus Node Dysfunction (MOST), which randomized patients to dual-chamber pacing (DDDR mode) or single chamber pacing (VVIR mode). The MOST trial demonstrated similar rates of stroke-free survival in both arms; however, DDDR paced patients had lower rates of atrial fibrillation (AF) and heart failure (HF) hospitalizations.[8] In patients with QRS duration (QRSd) <120 ms, a high amount of ventricular pacing in DDDR was also associated with higher rates of AF and HF hospitalizations.[9] Frequent ventricular pacing has also been associated with the development of pacemaker syndrome among patients with sinus rhythm treated with VVIR pacing.[10] Understanding how pacing mode affects these outcomes in patients without indications for an ICD or CRT will inform clinical decision making regarding the risks and benefits of LP implantation for patients with sick sinus syndrome. In this study, we analyzed patients enrolled in the MOST trial without substantial left ventricular (LV) dysfunction and QRSd <120 ms to evaluate the effect of pacing mode on clinical outcomes in a LP-eligible population.

2 | METHODS

2.1 | Study population

The details of the MOST trial have been previously published.[8] Briefly, 2010 patients with sick sinus syndrome were enrolled at 91 US sites between September 25, 1995 and October 13, 1999 and implanted with a dual-chamber pacing system. Patients were randomized to VVIR or DDDR pacing mode (patient blinded) at the time of implantation and were followed up four times during the first year and biannually thereafter. To better emulate an LP-eligible population, we applied additional exclusion criteria. Patients with moderately reduced or unknown LV function at baseline (LV ejection fraction [EF] ≤35%, or "moderate" or "severe" dysfunction, or LVEF unknown), a personal history of ventricular tachycardia or ventricular fibrillation, or those with a previous ICD

implantation were excluded due to their need for defibrillation capabilities from their device. Additionally, patients with a QRSd ≥120 ms or unknown were excluded due to their potential need for CRT. After these exclusions were applied, 1284 patients enrolled from 89 sites remained (630 randomized to VVIR and 654 randomized to DDDR). This study was approved by the Duke University Institutional Review Board.

2.2 | Outcomes

The primary outcome of interest was the composite of death, stroke, or HF hospitalization. Secondary outcomes included the components of the composite endpoint as well as the diagnosis of pacemaker syndrome, and the first episode of AF. The occurrence of AF subsequent to device implantation was stratified by patient's history of AF prior to device implantation. Pacemaker syndrome was only reported on patients assigned to VVIR mode. Thus, this outcome was not compared across pacing modes, but rather the rate of pacemaker syndrome in this population is reported.

2.3 | Statistical analyses

Demographic and patient baseline characteristics among included patients were compared between patients randomized to VVIR and DDDR pacing modes. Categorical variables were compared using chi-square tests, and continuous variables were compared with the Wilcoxon rank sum test. All analyses were conducted using an intention to treat approach.

Outcomes were compared by pacing mode using Kaplan-Meier curves and Cox proportional hazards models adjusted for variables identified as significant predictors of outcomes using backward selection and an inclusion threshold of alpha = 0.05. For the outcome of AF occurrence, independent models were generated for patients with and without a clinical history of AF at the time of randomization. A robust covariance estimate was included in each model to account for within site correlation. Because pacing percentage is typically not known at the time of device implantation, it was not included as a covariate in the multivariable Cox models; however, because this variable is known to have a significant impact on the key outcomes of HF hospitalization and AF,[9] we conducted a sensitivity analysis in which pacing percentage was included in the above described models. Ventricular pacing percentage data were treated as a time-dependent covariate with last recorded value carried forward to the last date of follow up.

3 | RESULTS

3.1 | Study population

Among 1284 patients with LVEF >35%, QRSd <120 ms, and no history of ventricular arrhythmias or prior ICD, 630 were randomized to

TABLE 1 Baseline characteristics by pacing mode

Characteristic	Overall N = 1,284	VVIR N = 630	DDDRN = 654	P value
Age (years)	74 (67-80)	74 (67-80)	73 (66-79)	.3839
Female	667 (51.9)	339 (53.8)	328 (50.2)	.1898
Non-white race	202 (15.7)	96 (15.2)	106 (16.2)	.6333
Hypertension	789 (61.4)	377 (59.8)	412 (63.0)	.2455
Hypercholesterolemia	478 (37.4)	231 (36.8)	247 (37.9)	.7004
Current smoker	115 (9.0)	55 (8.8)	60 (9.2)	.5406
Prior myocardial infarction	261 (20.3)	117 (18.6)	144 (22.0)	.1285
Prior heart failure	178 (13.9)	81 (12.9)	97 (14.9)	.3008
New York Heart Association class I or II heart failure	1092 (86.3)	545 (87.8)	547 (84.8)	.1268
Cardiomyopathy	63 (4.9)	22 (3.5)	41 (6.3)	**.0209**
Prior stroke	134 (10.4)	60 (9.5)	74 (11.3)	.2940
Diabetes	250 (19.5)	108 (17.1)	142 (21.7)	**.0387**
Chronic obstructive pulmonary disease	125 (9.7)	56 (8.9)	69 (10.6)	.3153
Percutaneous transluminal coronary angioplasty	158 (12.3)	73 (11.6)	85 (13.0)	.4360
Coronary-artery bypass grafting	212 (16.5)	105 (16.7)	107 (16.4)	.8827
Other cardiac surgery	29 (2.3)	16 (2.5)	13 (2.0)	.5030
Any supraventricular tachycardia	706 (55.0)	337 (53.5)	369 (56.4)	.2914
Atrial fibrillation	573 (44.6)	267 (42.4)	306 (46.8)	.1122
Other atrial tachycardia	123 (9.6)	60 (9.5)	63 (9.6)	.9470
Complete heart block	49 (3.8)	29 (4.6)	20 (3.1)	.1486
Second-degree heart block	82 (6.4)	38 (6.0)	44 (6.7)	.6101
Prolonged atrioventricular interval	122 (9.5)	65 (10.3)	57 (8.7)	.3278
Other heart block	22 (1.7)	12 (1.9)	10 (1.5)	.6040
Vasovagal syndromes	41 (3.2)	23 (3.7)	18 (2.8)	.3591

Continuous variables are presented as median (interquartile range).
Categorical variables are presented as frequencies (percentages).

VVIR mode, and 654 were randomized to DDDR mode. Demographics and baseline characteristics by pacing mode are shown in Table 1. The median age was 74 years (interquartile range 67-80), and 51.9% of patients were female. Mild HF symptoms (New York Heart Association [NYHA] class I or II) were present in 86.3% of patients. Compared with the overall MOST trial population, this subpopulation had less cardiomyopathy (4.9% vs 11.9%) but was otherwise similar. Baseline characteristics were well balanced by pacing mode with the exceptions of higher rates of cardiomyopathy (6.3% vs 3.5%, P = .021) and diabetes (21.7% vs 17.1%, P = .039) among patients randomized to DDDR mode.

3.2 | Clinical outcomes by pacing mode

Over 4 years of follow-up, there were 198 deaths, 54 strokes, and 112 HF hospitalizations. Of the 630 patients randomized to VVIR mode, 120 (19.0%) developed pacemaker syndrome. A total of 303 (23.6%) patients experienced one of the primary endpoints (death,

stroke, or HF hospitalization). Event rates according to the randomized pacing mode are shown in Figure 1. The multivariable Cox-proportional hazard model for the primary endpoint was adjusted for Charlson Comorbidity Index,[11] age, Karnofsky performance status score,[12] mini-mental state exam score, presence of lower extremity edema, heart rate, sex, prior congestive HF, NYHA class, antiarrhythmic use at admission, and prior myocardial infarction. There was no association between pacing mode and the primary outcome (VVIR hazard ratio [HR]: 1.28 [0.92-1.75], P = .14) (Table 2A). Similarly, no relationship was shown between pacing mode and the individual components of the composite endpoint, including death (HR 1.11 [0.77-1.61]), stroke (HR 1.33 [0.81-2.17]), and HF hospitalization (HR 1.35 [0.94-1.96]).

AF occurred in a total of 313 patients (24.4%), including 66 patients (9.9%) who had no known history of AF. AF event rates are shown for all patients (Figure 2A) and those with no known history of AF (Figure 2B). The multivariable Cox-proportional hazard model for the occurrence of AF was adjusted for prior AF/flutter, mitral regurgitation murmur,
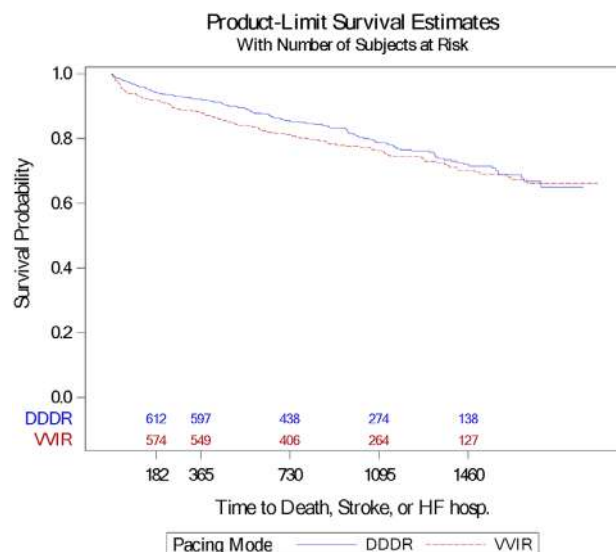
FIGURE 1 Product-limit survival curves by pacing mode for death, stroke, or heart failure hospitalization

weight, hypercholesterolemia, age, prior atrioventricular (AV) block, and hypertension. Among patients with no history of AF, the model was adjusted for Charlson Comorbidity Index, age, hypercholesterolemia, African-American race, prior AV block, and cardiomyopathy. VVIR pacing mode was associated with a higher risk of AF (HR 1.32 [1.08-1.61],

TABLE 2A Adjusted hazard models (baseline variables only)

Outcome	VVIR HR (95% CI)	P value
Primary outcome	1.28 (0.92-1.75)	.14
Death	1.11 (0.77-1.61)	.56
Stroke	1.33 (0.81-2.17)	.25
HF hospitalization	1.35 (0.94-1.96)	.09
AF- all patients	1.31 (1.08-1.61)	**.007**
AF- patients with no AF history	2.38 (1.52-3.85)	**.0002**

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio.

TABLE 2B Adjusted hazard models (including %V pacing)

Outcome	VVIR HR (95% CI)	P value
Primary outcome	1.32 (0.97-1.78)	.07
Death	1.01 (0.74-1.39)	.94
Stroke	1.33 (0.76-2.33)	.32
HF hospitalization	1.69 (1.11-2.56)	**.02**
AF- all patients	1.47 (1.12-1.92)	**.005**
AF- patients with no AF history	3.22 (1.96-5.26)	**<.0001**

Abbreviations: AF, atrial fibrillation; CI, confidence interval; HF, heart failure; HR, hazard ratio.
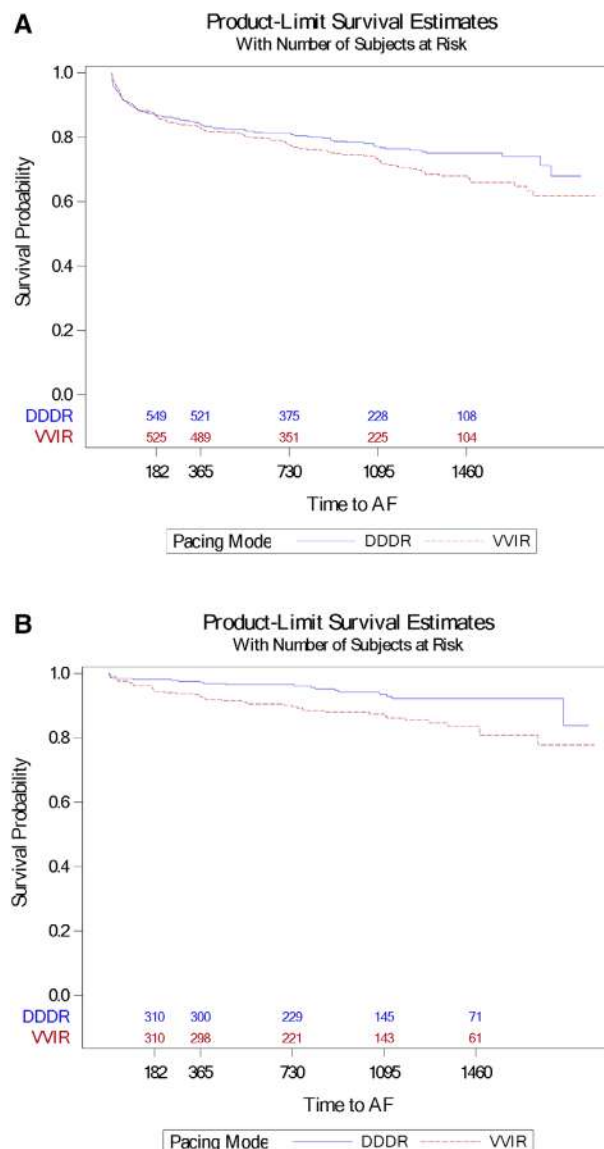

FIGURE 2 A, Product-limit survival curves by pacing mode for atrial fibrillation episodes among all patients. B, Product-limit survival curves by pacing mode for atrial fibrillation episodes among patients with no known history of atrial fibrillation

P = .007), particularly among those with no history of AF (HR 2.38 [1.52-3.85], P < .001) (Table 2A).

3.3 | Sensitivity analysis

Frequency of ventricular pacing data was available in 1198 (93.3%) of the 1284 included patients. The average pacing burden in the study population was 65 ± 33%. Patients in the DDDR mode had an average ventricular pacing burden of 74 ± 31%, whereas patients in the VVIR mode had a pacing burden of 55 ± 34%. When the multivariable hazards models were adjusted for pacing burden there were no differences in the primary outcome, death, or stroke (Table 2B); however, there was

a higher rate of HF hospitalization among patients randomized to VVIR pacing (HR 1.69 [1.11-2.56], $P = .02$).

When adjusted for ventricular pacing burden, multivariable models for AF occurrence showed similar trends as the base model. VVIR pacing mode was associated with a higher risk of AF (HR 1.47 [1.12-1.92], $P = .005$), particularly among those with no history of AF (HR 3.22 [1.96-5.26], $P < .0001$) (Table 2B).

4 | DISCUSSION

In this retrospective analysis of the MOST study focused on patients without reduced LVEF or prolonged QRSd, pacing mode was not associated with the composite endpoint of death, stroke, or HF hospitalization. However, VVIR pacing was associated with a higher hazard of AF and a greater than two-fold increase in hazard of the development of new-onset AF. In patients with sick sinus syndrome who might be considered for an LP, VVIR pacing may not influence the risk of death, stroke, or HF hospitalization, but may carry an increased risk of AF particularly among those with no known history of AF.

In many respects, LP is an innovation that simplifies device implant and pacing but provides RV-only pacing. Prospective studies of LPs have demonstrated good safety profiles and acute implant success rates with low procedural complication rates; however, there have been no randomized outcome studies comparing single RV LPs to dual-chamber devices. Currently, LPs are used primarily to treat patients with persistent AF and bradycardia; however, a significant minority of LPs are implanted for sinus node dysfunction, bradycardia with infrequent pauses or syncope (15% of patients in LEADLESS, 35.4% in LEADLESS-II, 17.5% in the Micra Transcatheter Pacing Study, and 8% in the Micra Post Approval Registry).[2–5] We took advantage of the randomized treatments inherent to the MOST study and examined outcomes in those patients who would have been eligible for RV LP. The results of this analysis in MOST suggest that use of VVIR pacing with LP in this population would likely not have impacted death, stroke, or HF hospitalization rates, but may have increased the risk of AF. Interestingly, sick sinus syndrome patients in the DANPACE trial randomized to AAIR pacing also demonstrated higher rates of AF compared with those randomized to DDDR pacing.[13] The authors of that study hypothesized that this finding was driven by prolonged AV conduction and possibly more AV dyssynchrony in the AAIR arm highlighting the importance of the AV relationship in the risk of developing subsequent AF. In the model controlling for pacing burden, VVIR pacing was associated with a higher hazard of HF hospitalization despite a lower overall pacing burden compared with DDDR pacing; however, this was a sensitivity analysis using data not always available at the time of pacemaker implantation (ventricular pacing burden) and is hypothesis generating. The majority of patients enrolled in these trials and post-approval registries had a history of AF (67% in LEADLESS, 77% in LEADLESS-II, 73% in the Micra Transcatheter Pacing Study, and 67% in the Micra Post Approval Registry); however, a substantial minority of patients did not have a history of AF.[14] These patients may be at increased risk for developing AF with a VVIR LP pacing system. Additionally, the lack of an atrial lead may delay identification of subclinical AF which carries a substantial risk of ischemic stroke or systemic embolism.[15]

The MARVEL study demonstrated that using an accelerometer-based pacing algorithm designed to detect atrial contraction (VDD pacing) in LPs resulted in significantly higher AV synchrony compared to patients with VVI pacing.[6] The MARVEL-2 study evaluated an updated algorithm which showed an improvement in median AV synchrony from 27% to 94% using VDD pacing compared to VVIR pacing.[7] We were unable to directly compare VVI pacing to VDD pacing in this study as only seven patients randomized to DDDR had 0% atrial pacing (which would be the equivalent of VDD pacing). Our results reflect a comparison of VVI pacing and DDDR pacing with an average amount of atrial pacing (58% $\pm$ 32% in this population). While there have not yet been cardiovascular outcomes studies of this algorithm, the results of the present study suggest that maintenance of AV synchrony may help reduce the risk of developing AF. Due to the lower burden of intravascular foreign material, LPs are an attractive option for patients at higher risk for infection (e.g., immunocompromised patients) and those for whom vascular access is of critical importance (e.g., renal failure patients with a need for current or future dialysis). Current generation LPs do not routinely identify AF episodes[16]; therefore, consideration of AF risk when selecting a pacing device and mode is of particular importance in these patients who are often at high risk for thromboembolic events given AF paroxysms may remain undetected and not appropriately treated with anticoagulation therapy.[17]

4.1 | Limitations

This is a sub-study of a randomized trial and the introduction of additional exclusion criteria may have introduced additional confounding. While the balance of baseline characteristics was similar to the trial as a whole, there were differences in rates of cardiomyopathy and diabetes. However, patients randomized to DDDR had more of these comorbidities which would bias the results toward the null. Additionally, the MOST study was conducted before the advent of algorithms designed to reduce RV pacing burden.[18] Modern devices using these algorithms may have even lower RV pacing percentages, which could result in an even larger benefit with DDDR pacing. For patients in the VVIR group, AF incidence was based on clinical presentation with AF; thus, the incidence of asymptomatic AF may be underestimated in this group, and the association between VVIR pacing and AF incidence may be more substantial than shown in this study.

5 | CONCLUSION

In patients without reduced LVEF or prolonged QRSd, DDDR and VVIR pacing demonstrated similar rates of death, stroke, and HF hospitalization. VVIR pacing was associated with a significantly higher risk of developing AF, particularly among patients without a history of AF. Atrial-asynchronous ventricular pacing in an LP-eligible population

may not affect the risk of death, stroke, or HF hospitalization, but may confer an increased risk of AF development.

AUTHOR CONTRIBUTIONS

Study concept and design: Loring. Analysis and interpretation of data: North and Hellkamp. Drafting of the manuscript: Loring. Critical revision of the manuscript for important intellectual content: North, Hellkamp, Atwater, Frazier-Mills, Jackson, Pokorney, Lamas, and Piccini. Statistical analysis: North and Hellkamp. Approval of article: Loring, North, Hellkamp, Atwater, Frazier-Mills, Jackson, Pokorney, Lamas, and Piccini. Data collection: Lamas.

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