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NEW RESEARCH PAPERS

Safety and Efficacy of Multipoint Pacing in Cardiac Resynchronization Therapy

The MultiPoint Pacing Trial

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ABSTRACT

OBJECTIVES The MultiPoint Pacing (MPP) trial assessed the safety and efficacy of pacing 2 left ventricular sites with a quadripolar lead in patients with heart failure indicated for a CRT-D device.

BACKGROUND Cardiac resynchronization therapy nonresponse is a complex problem where stimulation of multiple left ventricular sites may be a solution.

METHODS Enrolled patients were indicated for a CRT-D system. Bi-ventricular (Bi-V) pacing was activated at implant. Three months later, clinical response was assessed and the patient was randomized (1:1) to receive Bi-V pacing or MPP. Patients were followed for 6 months post-randomization and clinical response was again assessed.

RESULTS The CRT-D system was successfully implanted in 455 of 469 attempted implants (97%). A total of 381 patients were randomized to Bi-V or MPP at 3 months. The primary safety endpoint was met with freedom from system-related complications of 93.2%. The primary efficacy endpoint of the noninferiority comparison of nonresponder rates between the 2 arms was met. Patients randomized to MPP arm and programmed to pace from anatomically distant poles (MPP-AS) responded to therapy at significantly higher rates than MultiPoint pacing–other programmed settings (MPP-Other). Within this group, 87% were responders at 9 months, 100% designated as nonresponders at 3 months converted to responders at 9 months, and 54% experienced an incremental response compared to MPP-Other. Also within MPP-AS, 92% of patients with de novo CRT-D implant were classified as responders compared with patients with MPP-Other.

CONCLUSIONS MPP is safe and effective for treating heart failure. The study met the pre-specified hypothesis that response to MPP is noninferior to Bi-V pacing with a quadripolar left ventricular lead. (MultiPoint Pacing IDE Study [MPP IDE]; NCT01786993) (J Am Coll Cardiol EP 2017;3:1510–8) © 2017 by the American College of Cardiology Foundation.

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Cardiac resynchronization therapy (CRT) is a well-established therapy for heart failure (HF) and has been shown to produce significant clinical benefits, including reduced mortality, reduced HF hospitalizations, and improved symptoms and quality of life (1,2). However, despite technological advances, a significant proportion of patients fail to respond (3). The mean responder rate from the 15 largest contemporary CRT studies has been approximately 59% to 80%, with a 44% to 78% rate based on echocardiographic parameters (4). In the MIRACLE study, 34% of patients did not demonstrate improvement based on the clinical composite score (CCS), a composite measure defined by all-cause mortality, HF-related hospitalization, New York Heart Association (NYHA) functional class, and Patient Global Assessment (PGA) score (5).

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Although the cause of nonresponse to CRT is multifactorial, complex, and not completely understood, stimulation of multiple left ventricular (LV) sites may be an effective solution. This has been attempted by the use of 2 separate LV leads (6,7) but at the cost of increased technical difficulty and increased chance of major procedure-related adverse events. An alternative approach is to pace multiple LV sites using a single quadripolar lead, achieved by using a CRT-D system enabled with MultiPoint Pacing (MPP) programming (Quartet LV Quadripolar Lead with a Quadra CRT-D, Abbott, Sylmar, California). In this system, dual-site LV pacing using 2 different vectors can be selected. Additionally, a programmable delay (5 to 80 ms) can be introduced between the 2 LV pacing pulses (intraventricular delay) and the 2 LV pulses can be delivered either before or immediately after the right ventricular pacing pulse (V-V delay).

Small prospective studies have shown CRT with MPP can result in acute improvements in contractility, hemodynamics, and dyssynchrony compared with standard bi-ventricular (Bi-V) pacing (8–11). In a study by Pappone et al. (12), MPP therapy was shown to result in both mid-term (3 months) and long-term (12 months) improvements in LV reverse remodeling and clinical response compared with standard Bi-V pacing. Recent studies by Forleo et al. (13) and Zanon et al. (14) have shown MPP is associated with improved clinical status and an additional increase in ejection fraction, with reverse remodeling, beyond the effect caused by traditional Bi-V CRT. The present trial was designed to assess the safety and effectiveness of MPP stimulation in patients indicated for a CRT-D device.

METHODS

STUDY DESIGN AND OVERSIGHT. The MPP trial was a prospective, randomized, double-blind, multicenter clinical trial sponsored by the manufacturer of the quadripolar CRT-D system (Abbott) and approved by the Food and Drug Administration and institutional review board at each of the participating centers. All investigators agreed to abide by the conflict-of-interest guidelines described by Healy et al. (15). This trial was designed in collaboration with the Food and Drug Administration to prove the safety and efficacy of the MPP feature. Furthermore, a steering committee, with the participation of the sponsor, was responsible for the design and conduct of the trial and reporting of the findings. Clinical events were adjudicated by an independent, blinded events committee. Monitoring and collection of the data and data analyses were performed by the sponsor in partnership with the steering committee. The authors confirm the accuracy and completeness of the reported findings.

STUDY PARTICIPANTS. After obtaining written informed consent, eligible patients with a standard clinical indication for implantation of a CRT-D system (16) were enrolled. **Table 1** lists the study inclusion and exclusion criteria.

Enrolled patients had cardiac performance (2-dimensional echocardiography) and other clinical and demographic variables assessed within 30 days before implant. Patients who had the CRT-D system successfully implanted had Bi-V pacing with a quadripolar LV lead activated at that time. The LV pacing vector, atrioventricular delay, and V-V delay settings

ABBREVIATIONS AND ACRONYMS

Bi-V = bi-ventricular
CCS = clinical composite score
CRT = cardiac resynchronization therapy
EA VTI = velocity-time integral of the transmitral flow
HF = heart failure
ITT = intention-to-treat
LCB = lower confidence bound
LV = left ventricular
MPP = MultiPoint pacing
MPP-AS = MultiPoint pacing–anatomic separation/minimal intraventricular timing delay
MPP-Other = MultiPoint pacing–other programmed settings
NYHA = New York Heart Association
PGA = Patient Global Assessment

Medtronic and Abbott. Dr. Varma is on the advisory board and is a consultant for Abbott. Dr. Lee is an employee at Abbott. Dr. Tomassoni is an advisor, speaker, and on the Medical Device Board for Abbott, Biosense Webster, Medtronic, Boston Scientific, Biotronik, Siemens, STXS, Topera, Atricure, CPI, Johnson & Johnson, and Pfizer.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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TABLE 1 Inclusion and Exclusion Criteria

Inclusion
Meets current clinical indication for implantation of a CRT-D system for treatment of heart failure or life-threatening ventricular tachyarrhythmia
Receiving a new cardiac resynchronization therapy implant or undergoing an upgrade from an existing implantable cardioverter-defibrillator or pacemaker implant with no prior left ventricular lead placement
Have the ability to provide informed consent for study participation and are willing and able to comply with the prescribed follow-up tests and schedule of evaluations
Exclusion
Have had a recent cerebrovascular accident or transient ischemic attack within 3 months of enrollment
Have an existing class I recalled lead
Have a hypersensitivity to a single 1.0-mg dose of dexamethasone sodium phosphate
Have a classification of status 1 for cardiac transplantation or consideration for transplantation over the next 9 months
Have permanent atrial fibrillation
Have undergone a cardiac transplantation within 40 days of enrollment
Have had a recent myocardial infarction, unstable angina within 40 days, or cardiac revascularization (percutaneous transluminal coronary angioplasty, stent, or coronary artery bypass graft) within 3 months of implant
Are currently participating in a clinical investigation that includes an active treatment arm
Are pregnant or planning to become pregnant during the duration of the study
Have a life expectancy of <9 months because of any condition
Are <18 years of age

at implant were programmed at the discretion of the implanting physician.

STUDY BLINDING. The participating site's staff (e.g., electrophysiologist and electrophysiology nurses) performed all tests requiring viewing of the programmed pacing mode and therefore were unblinded to the patient's randomization. Other site personnel were designated as blinded assessors and authorized to assess NYHA functional class and PGA, which are components of the CCS (17). Patients were also blinded to randomization assignment and carried a card identifying them as clinical trial patients to minimize the risk of unblinding by other health care providers. All efforts were made to minimize potential bias by maintaining the blind until the trial endpoint visit at 9 months. Blinding was confirmed by questioning both assessor and patient at the completion of the trial.

DEFINITION OF RESPONSE TO CRT. Response to CRT was evaluated at 3 months and 9 months post-implant using the CCS. The CCS includes objective and subjective measures of clinical status (17). A patient's CCS was classified as worsened, improved, or unchanged based on the following definitions:

- Worsened: the patient died because of cardiovascular reasons OR experienced a HF event OR demonstrated worsening in NYHA functional class, or had worsening of PGA score compared with the last observation
- Improved: the patient survived without an HF event AND demonstrated either improvement in NYHA functional class or improvement in PGA score or both compared with the last observation
- Unchanged: the patient was neither improved nor worsened

An HF event was defined as a hospitalization for HF of ≥24 h, or any inpatient or outpatient treatment requiring the intravenous administration of diuretics, inotropes, and/or vasodilators. Cardiovascular death was defined as sudden unexpected death; death caused by HF, myocardial infarction, pulmonary embolism, peripheral thromboembolism, stroke; death caused by a vascular procedure; or other major cardiovascular event.

At the 3-month visit, patients who were "improved" were classified as CRT responders, and those who were "worsened" or "unchanged" were grouped together as nonresponders. At the 9-month trial endpoint visit, CRT response status was again evaluated using the CCS (Figure 1). The NYHA class and PGA score at the 9-month visit were compared with the 3-month visit for the evaluation of the primary efficacy endpoint. Patients who were responders at the 3-month visit (following 3 months of Bi-V CRT), with "improved" and "unchanged" statuses between 3 and 9 months, were classified as responders, whereas those with "worsened" status were grouped together as nonresponders. Under this definition, arresting the progression of HF after randomization in these patients (following 3 months of Bi-V CRT) was considered a success. Patients who were nonresponders at the 3-month visit, with "improved" status, were classified as responders, whereas those with "worsened" and "unchanged" statuses were grouped together as nonresponders.

POST-IMPLANT SCREENING AND RANDOMIZATION. At 3 months post-implant, patients were screened to determine response status to Bi-V CRT and subsequently had acute Doppler echocardiographic measurements performed (velocity-time integral of the transmitral flow [EA VTI]) at various MPP combinations to provide programming guidance. EA VTI was specifically used because it is the echocardiography measurement shown to have the closest correlation with LV dP/dtmax (18). The EA VTI results with MPP were then compared with the EA VTI results with Bi-V pacing.

Only patients in whom the EA VTI during MPP were equal to or better than Bi-V pacing were randomized (1:1) to either the Bi-V arm or the MPP arm (Figure 1). The randomized patients included both CRT responders and nonresponders based on the CCS.

Patients who did not have any tested MPP combinations yield an acute EA VTI with an equal or better value compared with the Bi-V configuration tested were not randomized. Instead they were assigned to an observational arm and followed with Bi-V pacing until the 9-month follow-up visit. This trial design was chosen in concert with regulatory bodies to reduce the risk of harm to the patient as a potential result of a new therapy, namely MPP. For patients randomized to the MPP arm, MPP was programmed by the physician to any of the vectors that yielded an equal or better acute EA VTI value compared with Bi-V pacing. There was no further MPP programming requirement mandated by the protocol. For patients randomized to the Bi-V arm, programming was left to physician discretion.

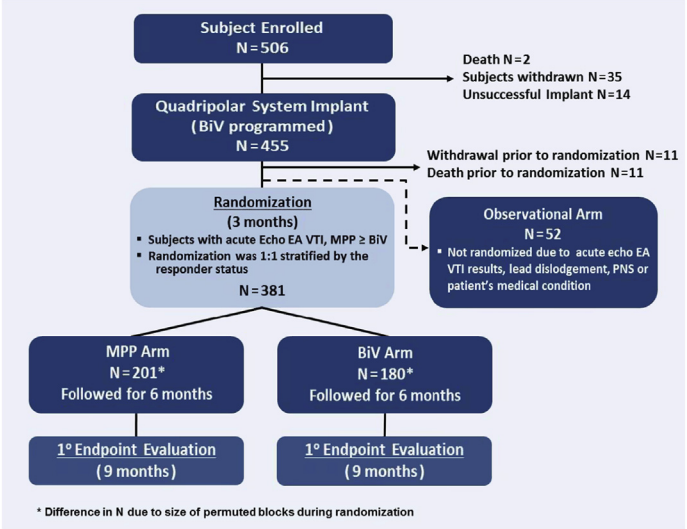
FOLLOW-UP AND ENDPOINTS. Patients returned for study visits at 6 and 9 months post-implant (Figure 1). The primary safety endpoint, freedom from system-related complications through 9 months of follow-up, was evaluated by a performance goal. A complication was defined as an adverse event caused by or associated with the investigational device, system components, and/or procedure requiring invasive intervention. For the primary efficacy endpoint, a noninferiority test was used to compare the percentage of nonresponders in the 2 arms between 3 and 9 months of follow-up. Because the trial was not powered to show superiority, no predefined superiority analysis is included. The primary efficacy endpoint was carried out on the intention-to-treat (ITT) and as-treated populations. The ITT population included all randomized patients. A total of 381 patients were randomized at 3 months, of whom 180 were in the Bi-V arm and 201 were in the MPP arm. The as-treated population included randomized patients receiving MPP or Bi-V pacing at 9 months or at the last follow-up before 9 months.

STATISTICAL ANALYSIS. In the multicenter FREEDOM study, the proportion of nonresponders (as defined by the CCS in this study) between 3 and 9 months was 44%. Therefore, assuming a binomial distribution with a 44% probability for nonresponse between 3 and 9 months in both study arms, the sample size required for 85% power to reject the null hypothesis at the 5% significance level was 394 patients. To adjust for a potential net crossover of 15%, the effective sample size was increased from 394 patients to 404 patients. An overall attrition rate of 20% was assumed. Because the primary efficacy endpoint required 404 patients, the total number of patients required for enrollment in this trial was 506.

For the primary safety endpoint, freedom from system-related complications through 9 months of follow-up, all patients who had an attempted implant or a successful CRT-D system implant were included. This endpoint was evaluated using the Kaplan-Meier method, and the 97.5% lower confidence bound (LCB) was calculated for freedom from system-related complications on the log-survival scale. The null hypothesis was rejected if the observed 97.5% LCB was greater than the performance goal of 75%. Poolability across investigational sites was verified by a log-rank test. Poolability was assessed by statistical significance of site category effect at the 15% significance level.

The efficacy objective of the trial was addressed through a noninferiority study design enrolling CRT-D indicated patients and was not limited to symptomatic HF. Treatment efficacy with MPP versus Bi-V pacing with a quadripolar lead was evaluated by a test for noninferiority for the proportion of 9-month nonresponders (by the CCS) in the MPP arm versus

FIGURE 1 Study Flow Diagram and Definition of Clinical Response



Responder Definition at 3 and 9 Months
*Relative to 3-month status

3-Month Responder Definition	9-Month Responder Definition*
Improved = Responder	Improved/Unchanged = Responder
	Worsened = Nonresponder
Unchanged/Worsened = Nonresponder	Improved = Responder
	Unchanged/Worsened = Nonresponder

Progress of enrolled patients in the study. The table outlines cardiac resynchronization therapy response definitions at 3 months following quadripolar Bi-V pacing and at 9 months, following 6 months of MPP therapy or continued Bi-V pacing.
Bi-V = bi-ventricular; EA VTI = velocity-time integral of the transmitral flow; MPP = MultiPoint pacing; PNS = phrenic nerve stimulation.

TABLE 2 Baseline Demographics Between Bi-V and MPP Arms

	All Randomized Subjects (n = 381)	Bi-V Arm (n = 180)	MPP Arm (n = 201)	p Value
Age, yrs	68 ± 10 (381)	68 ± 10 (180)	67 ± 10 (201)	0.5433*
Gender				
Male	247/381 (64.8)	119/180 (66.1)	128/201 (63.7)	0.6200†
Ethnicity				
Hispanic or Latino	15/381 (3.9)	5/180 (2.8)	10/201 (5.0)	0.2709†
Non-Hispanic or Latino	366/381 (96.1)	175/180 (97.2)	191/201 (95.0)	
NYHA functional class at enrollment per blinded assessor				
I	36/381 (9.4)	11/180 (6.1)	25/201 (12.4)	0.0622‡
II	111/381 (29.1)	59/180 (32.8)	52/201 (25.9)	
III	218/381 (57.2)	105/180 (58.3)	113/201 (56.2)	
IV	16/381 (4.2)	5/180 (2.8)	11/201 (5.5)	
QRS duration, ms	156 ± 22 (355)	154 ± 20 (168)	158 ± 24 (187)	0.0510§
QRS morphology				
LBBB	285/379 (75.2)	139/180 (77.2)	146/199 (73.4)	0.4652†
RBBB	41/379 (10.8)	20/180 (11.1)	21/199 (10.6)	
IVCD	53/379 (14.0)	21/180 (11.7)	32/199 (16.1)	
Cardiomyopathy etiology				
Ischemic	184/381 (48.3)	88/180 (48.9)	96/201 (47.8)	0.9675‡
Nonischemic	194/381 (50.9)	91/180 (50.6)	103/201 (51.2)	
None	3/381 (0.8)	1/180 (0.6)	2/201 (1.0)	

Values are mean ± SD (N) or n/N (%). *Wilcoxon rank sum test. †Pearson chi-square test. ‡Fisher exact tests. §Student's t-test.

Bi-V = bi-ventricular; IVCD = interventricular conduction delay; LBBB = left bundle branch block; MPP = MultiPoint pacing; NYHA = New York Heart Association; RBBB = right bundle branch block.

the Bi-V arm. A noninferiority margin of 15 percentage points was applied. This was a 1-sided hypothesis, which was to be tested at the 2.5% significance level, if the lower 1-sided 97.5% confidence bound for the difference in the proportion of nonresponders between 3 months and 9 months in the Bi-V and MPP group was above −15%. Poolability across investigational sites was verified by fitting a logistic regression model for the 9-month nonresponder status of each subject, where the terms in the model were randomization arm (BiV or MPP), site, and randomization arm by site interaction. Poolability was assessed by statistical significance of the interaction effect of site category by randomization arm at the 15% significance level.

RESULTS

PATIENTS. From April 25, 2013, through July 2, 2014, a total of 506 patients were enrolled at 49 centers in the United States. Of the 506 patients enrolled in the trial, 2 (0.4%) died and 35 (6.9%) were withdrawn before an attempted implant; 469 (92.7%) patients underwent an implant attempt with a CRT-D system, of whom 455 (97%) were successfully implanted. Of the 455 patients who were successfully implanted, 11 died (2.4%), 11 (2.4%) were withdrawn before the 3-month randomization, and 433 (95.2%) completed the 3-month visit. Of the 433 patients who completed the 3-month visit, 52 (12%) were assigned to the observational arm per study protocol and 381 (88%) were randomized, 180 patients to the Bi-V arm and 201 patients to the MPP arm (Figure 1). The reasons for assignment of the 52 patients to the observational arm include EA VTI not equal to or better with MPP versus Bi-V (30 of 433; 6.9%), elevated capture threshold and/or phrenic nerve stimulation (14 of 433; 3.2%), medical condition (3 of 433; 0.7%), lead dislodgement (2 of 433; 0.5%); EA VTI not collectable (1 of 433; 0.2%); and other (2 of 433; 0.5%).

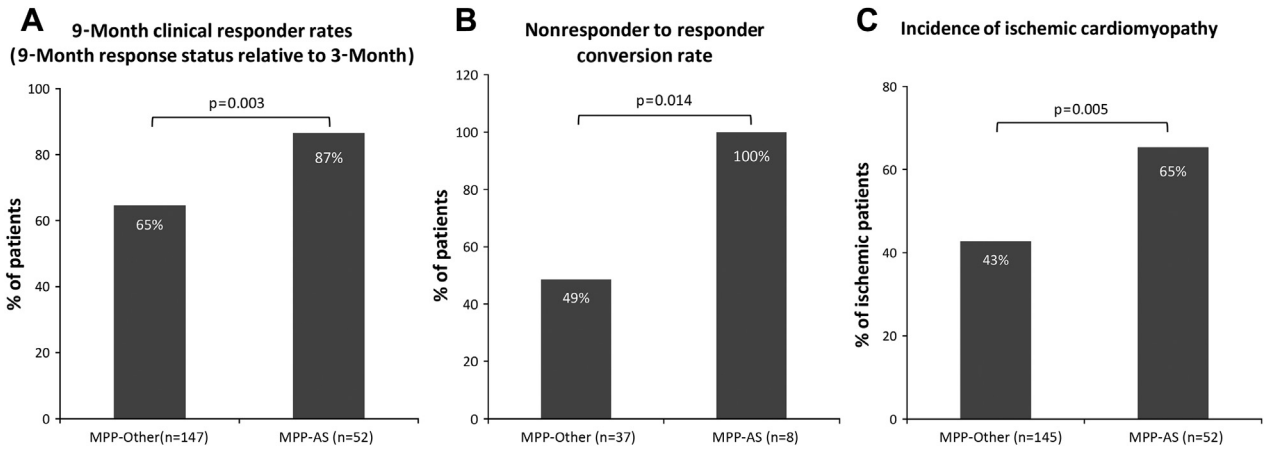
Baseline characteristics were similar between the 2 groups (Table 2). There were no differences in cardiovascular history and arrhythmia history between the 2 groups ($p > 0.24$). After 3 months of Bi-V pacing with a quadripolar LV lead, only 22% of patients remained in NYHA functional class III/IV (vs. 61% at baseline) and the overall responder rate was 77%.

Of the 180 patients who were randomized to the Bi-V arm at 3 months, 7 died between 3 and 9 months and 3 missed the 9-month follow-up visit. Of the 201 patients who were randomized to the MPP arm, 6 died between 3 and 9 months and 2 missed the 9-month follow-up visit. All randomized patients continued to receive the assigned therapy for the intended duration of the trial, except for 8 patients in the MPP arm who were reprogrammed to BiV pacing and for 3 patients (1, MPP arm; 2, Bi-V arm) who were programmed to right ventricular-only pacing because of clinical reasons per investigator, before the 9-month follow-up visit. Therefore, in the as-treated population, 8 patients who received Bi-V pacing between 3 and 9 months were analyzed in the Bi-V arm and 3 patients who were programmed to right ventricular-only pacing were excluded.

PRIMARY ENDPOINTS (SAFETY AND EFFICACY). Thirty-one patients experienced system-related complications through 9 months. The Kaplan-Meier freedom from system-related complications through 9 months was estimated as 93.2% and the 97.5% LCB was 90.4%, which was above the performance goal of 75%. A total of 1.7% of patients in the Bi-V arm experienced a complication between 3 months and 9 months, as compared with 1.5% of patients in the MPP arm ($p = 0.89$). Poolability of the primary safety endpoint across sites was verified ($p = 0.90$).

A total of 381 patients were randomized at 3 months, of whom 180 in the Bi-V arm and 201 in the MPP arm were included in the ITT population. Likewise, a total of 378 patients randomized at 3 months were included in the as-treated population, of whom

FIGURE 2 Impact of MPP Programming on Cardiac Resynchronization Therapy Responder Classification



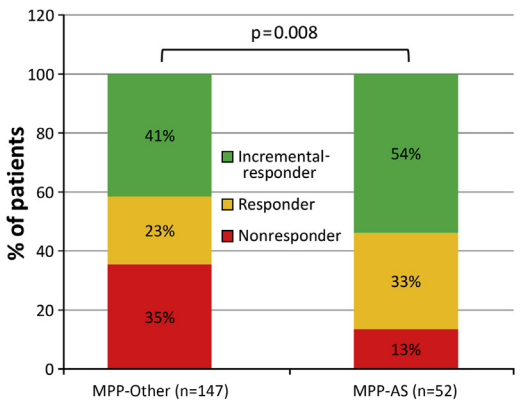
(A) Comparison of 9-month responder rates relative to the 3-month responder status between the MPP-AS and MPP-Other subgroups. Response is defined as a change in clinical composite score during MPP (from 3-month visit to 9-month visit). **(B)** Comparison of conversion rates from 3-month nonresponder to 9-month responder during MPP between the MPP-AS and MPP-Other subgroups. **(C)** Comparison of the incidence of ischemic cardiomyopathy in the MPP-AS subgroup compared with the MPP-Other subgroup. MPP-AS = MultiPoint pacing–anatomic separation/minimal intraventricular timing delay; MPP-Other = MultiPoint pacing–other programmed settings.

186 were in the Bi-V arm and 192 were in the MPP arm. In both ITT and as-treated populations, there were no statistically significant differences at the 5% significance level in any of the demographic or baseline characteristics between the Bi-V and MPP arms and a significant proportion of patients were in NYHA functional class I or II (~78%) at the 3-month visit. The difference in 9-month nonresponder rates between the Bi-V and MPP arms was −4.9% (45 of 180 [25%] and 60 of 201 [29.9%], nonresponder rate in Bi-V and MPP) for the ITT population and −3.9% (48 of 186 [25.8%] and 57 of 192 [29.7%] nonresponder rate in Bi-V and MPP) for the as-treated population. The 97.5% LCB for the difference in 9-month nonresponder rates between the Bi-V and MPP arms in the ITT and as-treated populations were −13.8% and −12.9%, respectively, which were both greater than the noninferiority margin of −15%. The primary efficacy endpoint was therefore met for both ITT and as-treated populations. Poolability of the primary efficacy endpoint across sites was verified (p value for the interaction effect was >0.95).

IMPORTANCE OF MPP PROGRAMMING: RESPONDER RATE, CONVERSION RATE, INCREMENTAL-RESPONDER RATE. In the MPP IDE trial, a selection of MPP combinations to be tested was determined by the investigator's discretion (i.e., phrenic nerve stimulation, high capture threshold) or Q-LV measurements. Analyses were conducted to determine if there were potential differences in responder rate, nonresponder to responder conversion rate, and incremental-responder rate in patients randomized to the MPP arm, in whom MPP was programmed with maximal anatomic separation (i.e., distance between 2 cathodal LV electrodes ≥30 mm) and the shortest intraventricular timing delay of 5 ms (i.e., virtually simultaneous stimulation of both LV pacing sites) (MPP-AS). An incremental-responder was defined as a patient who responded (i.e., improved in the CCS) with standard Bi-V pacing using a quadripolar LV lead during the first 3 months (before randomization) and showed further improvement in CCS at 9 months compared with the 3 month value. Of the 199 patients who were randomized to the MPP arm, 52 patients were programmed with MPP-AS and 147 patients were programmed with other MPP settings (MPP-Other).

For patients in the MPP-AS subgroup, MPP therapy provided a significantly higher clinical responder rate at 9 months of 87% (45 of 52) (Figure 2A) versus 65% (95 of 147) in MPP-Other ($p = 0.003$) and converted 100% (8 of 8) of patients who were nonresponders at 3 months to responders at the 9-month assessment (Figure 2B) versus 49% (18 of 37) in MPP-Other ($p = 0.014$), despite having a significantly higher number of patients with ischemic cardiomyopathy (Figure 2C), 65% (34 of 52) versus 43% (62 of 145) ($p = 0.005$). The incidence of incremental response

FIGURE 3 Impact of MPP Programming on Incremental Response

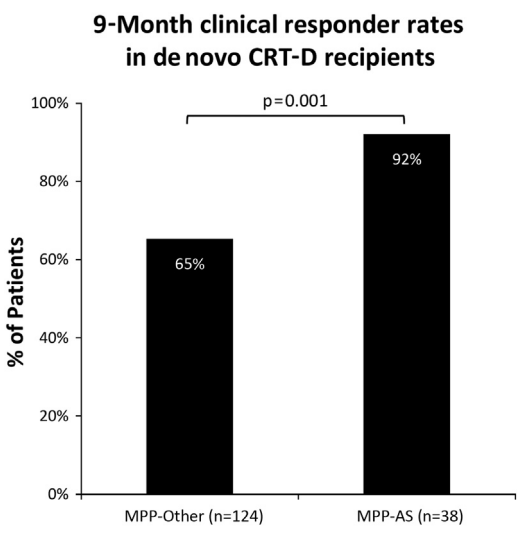


Proportion of responders, nonresponders, and incremental responders among the MPP-AS and MPP-Other subgroups. Abbreviations as in Figure 2.

was significantly higher in patients with MPP-AS versus with MPP-Other (Figure 3), 54% (28 of 52) versus 41% (61 of 147) ($p = 0.008$).

Additionally, in patients with de novo CRT-D implants, the MPP-AS subgroup had a significantly higher clinical responder rate (35 of 38; 92%) compared with MPP-Other (81 of 124; 65%) (Figure 4) ($p = 0.001$).

FIGURE 4 Impact of MPP Programming on Cardiac Resynchronization Therapy Response in De Novo Implants



Comparison of responder rates between the MPP-AS and MPP-Other subgroups for patients with de novo implants. Abbreviations as in Figure 2.

DISCUSSION

The present trial is the first large-scale clinical trial examining the safety and efficacy of multisite LV pacing with a single LV lead to treat patients with HF. The results of this trial indicate the use of MPP therapy in treating patients with HF is safe and effective and not inferior to standard Bi-V pacing with a quadripolar LV lead. It suggests MPP, with certain programming settings, may be superior to standard single-site LV CRT, particularly in those who fail to respond to standard CRT.

Although conventional CRT has been shown to improve HF signs and symptoms in appropriate patients, failure to respond in a significant proportion (generally one-third in large trials using bipolar leads) remains a clinical challenge. Multiple LV leads placed in different coronary sinus branches have been used to improve response, presumably by depolarizing large segments of the LV simultaneously (19,20). This technique significantly increases the time, radiation exposure, and risk compared with implanting a single LV lead, making it clinically unattractive. Pacing multiple sites using a single quadripolar LV lead is a more appealing alternative (8–14,21).

Delivering pacing pulses at multiple LV sites is more likely to capture a larger volume of cardiac muscle and therefore the site of latest electrical activation within the LV may be more likely to be depolarized early, resulting in superior resynchronization. Multisite LV stimulation may also more closely mimic normal LV depolarization in patients with conduction system abnormalities, because a larger portion of the LV is simultaneously depolarized compared with single-site LV stimulation. Sohal et al. (22) have demonstrated more rapid activation of the bulk of the LV myocardium with multisite LV pacing in patients with myocardial scar. Wide separation of the 2 pacing sites may be important: when pacing sites are close, the area of myocardium simultaneously depolarized is necessarily smaller than pacing 2 widely separated sites. Wider separation also makes it more likely at least 1 of the pacing sites is not overlying previous myocardial scar (23).

The trial results indicate a higher response rate in patients programmed with MPP-AS. This makes theoretical sense: pacing widely separated areas more closely resembles multibranch pacing, whereas pacing adjacent poles is similar to conventional bipolar CRT. Indeed, it has been shown with conventional bipolar LV leads, the identical surface area of the anode and cathode electrodes result in unwitting anodal capture in at least half of all cases (24). Thus, dual-site LV pacing from adjacent poles occurs in

about half of patients with standard bipolar pacing; this cathodal-anodal pacing of 2 adjacent LV lead poles may not, in effect, be different from multisite LV cathodal pacing of adjacent poles.

It has been shown there is a lower response rate to CRT in patients with ischemic cardiomyopathy as compared with nonischemic cardiomyopathy, possibly related to repetitive episodes of ischemia or to the presence of scar tissue (25). The MPP-AS subgroup showed a significantly higher rate of response than patients with other programmed MPP settings, despite having a significantly higher proportion of patients with ischemic cardiomyopathy. This suggests optimal MPP programming overcomes anatomic and/or electrical barriers by capturing a larger volume of LV, resulting in more rapid LV conduction and possibly further reduction in mechanical dyssynchrony.

Better response with MPP-AS was discovered in patients with a de novo indication for CRT implantation. This may have been caused by the de novo population being slightly healthier than patients previously implanted with a pacemaker or defibrillator. It is also possible the response to MPP therapy is higher in patients with intrinsic left bundle branch block compared with pacing-induced left bundle branch block, because the LV activation sequence may be different in the 2 situations (26).

This trial also represents the first report of clinical outcomes using conventional CRT with the Quartet quadripolar LV lead, as distinct from CRT with a conventional bipolar or unipolar lead. The Bi-V response rate using the Quartet quadripolar LV lead is relatively higher than in CRT trials using bipolar/unipolar leads in similar populations (27–29), possibly because the quadripolar lead design allows pacing from a more basal pacing site in a higher proportion of patients. Moreover, the CRT response rate (using the CCS) at 3 months during standard Bi-V pacing with the Quartet quadripolar LV lead in this trial was marginally superior, at 77%, than the 6-month response rate of 74% (using the same CCS) in the Adaptive CRT trial (30,31). The latter was a recent CRT trial conducted in a similar population with similar endpoints but with an "adaptive" atrioventricular delay. Of note, the unexpectedly high response rate with standard CRT using the Quartet LV lead rendered demonstration of further improvement with MPP difficult.

STUDY LIMITATIONS. This trial used a complex design to evaluate the safety and effectiveness of the MPP technology. Study design was partially at the behest of regulatory bodies to ensure a new therapy (MPP) should not impact patient safety. All patients underwent an acute assessment of EA VTI before randomization with the MPP feature turned on, to ensure MPP did not impair hemodynamics and could therefore be safely programmed for the study duration. Only patients with improved or equal EA VTI were eligible for randomization, thus potentially selecting long-term clinical responders. Nevertheless, this comprised most (88%) trial subjects, with only 30 patients (6.9%) showing deterioration in EA VTI with MPP. Moreover, acute hemodynamic response to CRT may not predict long-term clinical response (3,32). The improved CRT response identified based on MPP programming was the result of post hoc analyses. These results should be confirmed in future prospective studies designed and powered to evaluate potential superiority of MPP, which has now been proven safe in the present trial. Finally, MPP was shown to be safe and effective for the 9-month duration of this trial, but long-term follow-up data are warranted.

CONCLUSIONS

MPP therapy using a quadripolar LV lead is safe and effective for treating appropriate patients with HF. The subgroup of patients with MPP-AS had the highest response rate. Patients in this specific MPP programming subgroup, and those with a de novo CRT implant indication, had an incremental improvement in CRT response over 9 months. These results add to the body of evidence indicating MPP technology provides physicians with an additional tool for improving response to CRT.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: MPP is safe and effective. When MPP is programmed optimally, CRT response was greatest and all nonresponders were converted to responders.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to confirm the superiority of optimal MPP programming, which may help further guide the use of evidence-based therapies among patients with HF.

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