Rationale and design of a randomized clinical trial to assess the safety and efficacy of multipoint pacing therapy: MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP–PHASE II)

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Background Although cardiac resynchronization therapy (CRT) is beneficial in most heart failure patients, up to 40% do not respond to CRT. Data from the MultiPoint Pacing (MPP) IDE trial and MORE-CRT MPP–PHASE I study suggest improved response in subjects in the MPP arm—programmed with wide left ventricular (LV) electrode anatomical separation (≥30 mm) and shortest timing delays of 5 milliseconds (MPP-AS)—compared with quadripolar biventricular (BiV) pacing.

Study design The MORE-CRT MPP–PHASE II trial is a prospective, randomized, multicenter study to assess the 6-month impact of MPP programmed to mandated MPP-AS settings in subjects who do not respond to 6 months of BiV pacing (MPP OFF). Approximately 5,000 subjects with a standard CRT indication will be enrolled and implanted with a quadripolar CRT system (Abbott) capable of delivering MPP. Only BiV pacing is activated at implant. At 6 months, subjects classified as CRT nonresponders (<15% reduction in LV end-systolic volume) are randomized (1:1) to MPP or continued BiV pacing. The mandated MPP parameters (eg, MPP-AS) are programmed to subjects randomized to the MPP arm. At 12 months, the 2 groups will be compared to determine if there is a difference in CRT response rate.

Conclusions This trial will evaluate whether MPP programmed to mandated MPP-AS settings improves LV reverse remodeling and clinical response to CRT in patients who fail to respond to 6 months of BiV pacing (www.clinicaltrials.gov identifier NCT02006069). (Am Heart J 2019;209:1-8.)

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Cardiac resynchronization is a well-established therapy for heart failure and has been shown to produce significant clinical benefits, including reduced mortality, fewer heart failure hospitalizations, and improved symptoms and quality of life.[1-6] Conventional cardiac resynchronization therapy (CRT) with the Quartet quadripolar left ventricular (LV) lead (eg, quadripolar biventricular [BiV] pacing) has demonstrated significantly lower LV lead–related event and improved clinical response rates compared with those with a bipolar or unipolar lead possibly because the quadripolar lead design allows more pacing configurations and pacing from a more basal pacing site in a higher proportion of patients.[7-9]

However, the proportion of patients who fail to respond to CRT remains significant.[10] The cause of CRT nonresponse is not completely understood and involves multiple interrelated factors; in those patients with atrial fibrillation (AF), there is limited evidence (retrospective

Figure 1

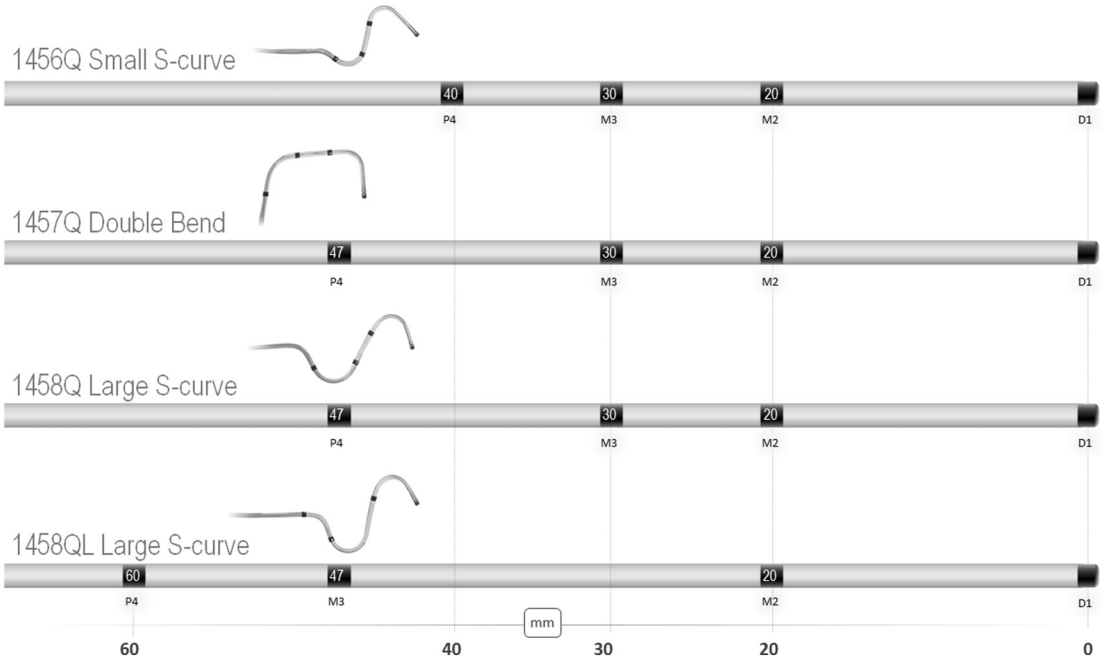


Diagram of Quartet family of LV quadripolar leads. The diagram shows electrode location and spacing.

and observational data) for the benefits of CRT in the absence of sinus rhythm, which may suggest that CRT patients with AF who undergo atrial ventricular junctional ablation respond similarly as to those patients in normal sinus rhythm. However, there is a general consensus that suboptimal LV lead placement is one of the main contributing reasons to nonresponse.[11]

In an effort to improve CRT response rate, clinicians have proposed the implantation of multiple LV leads to improve LV synchrony. Although technically feasibile, this approach can increase CRT implant procedure time, fluoroscopic exposure, and procedure-related adverse events.[12-14] An alternative approach is to use a quadripolar lead (Figure 1) for multipoint pacing (MPP) of the LV from 2 of 10 possible vectors in a CRT-D or from 2 of 14 possible vectors in a CRT-P (Table I). In addition, a programmable delay (5-80 milliseconds) can be introduced between the 2 LV pacing pulses, thereby delivering sequential pacing either before or after the right ventricular stimulation.

Small prospective studies have shown that CRT with MPP results in acute improvements in contractility, hemodynamics, and dyssynchrony compared with quadripolar BiV pacing.[15-19] A recent study demonstrated both midterm (3 months) and long-term (12 months) LV reverse remodeling and an improved CRT response rate with MPP compared with quadripolar BiV pacing.[20] In addition, an ad hoc analysis of the MPP IDE study has shown an 87% CRT response rate by programming 2 MPP vectors with wide 2-cathode anatomic spacing (≥ 30 mm) and minimal timing delay (5 milliseconds), that is, MPP-AS programming.[21,22] Data from the MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint Pacing Phase I trial have been recently published.[23] MPP-AS elicited a significantly higher nonresponder conversion rate compared to MPP-Other (45.6% vs 26.2%, $P = .006$) and a trend in a higher conversion rate compared to biventricular pacing (45.6% vs 33.8%, $P = .10$).

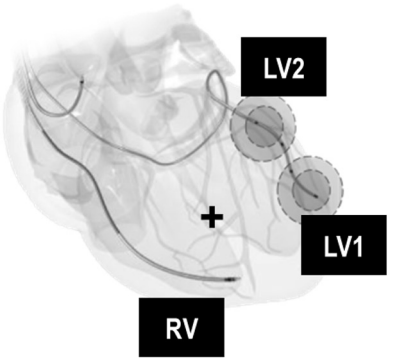
However, there is still a need for larger trials to confirm the long-term efficacy of CRT with MPP and to prospectively evaluate the impact of MPP programming. Moreover, it is important to specifically evaluate the effects of MPP in patients who do not respond to quadripolar BiV pacing. Therefore, the objective of the present report is to describe the design of the MOre REsponse on Cardiac Resynchronization Therapy with MultiPoint Pacing Phase II (MORE-CRT MPP–PHASE II) trial. This is a prospective, randomized, multicenter trial to assess the impact of MPP programmed with MPP-AS in subjects who do not respond after an initial 6 months of BiV pacing.

Methods

Patient selection

The trial will enroll approximately 5,000 subjects at up to 250 centers worldwide. Subjects are eligible for enrollment if they meet the current Class I or IIa criteria of the European Society of Cardiology or American College of Cardiology Foundation/American Heart

Table I. The pacing configurations available in the Abbott Quadripolar CRT-D system (10) and Quadripolar CRT-P system (14)



Vector	Cathode to Anode
1	D1 → M2
2	D1 → P4
3	D1 → RV Coil
4	M2 → P4
5	M2 → RV Coil
6	M3 → M2
7	M3 → P4
8	M3 → RV Coil
9	P4 → M2
10	P4 → RV Coil
11	D1 → Can
12	M2 → Can
13	M3 → Can
14	P4 → Can

D1, distal tip; *M2*, middle ring 2; *P4*, proximal ring; *M3*, middle ring 3.

Table II. Inclusion and exclusion criteria

Inclusion criteria (all must be present)
- Meets the current European Society of Cardiology guidelines or American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society class I or class IIa indications for CRT implant (including upgrades from single- or dual-chamber ICDs)
- Must be willing and able to comply with study requirements
- Must indicate their understanding of the study and willingness to participate by signing an appropriate informed consent form

Exclusion criteria (all must be absent)
- Already had a CRT device implanted
- Myocardial Infarction, unstable angina within 40 d prior to the enrollment
- Recent cardiac revascularization (PTCA, stent, or CABG) in the 4 wk prior to enrollment or planned for the 3 m following
- Cerebrovascular accident or transient ischemic attack in the 3 m prior to the enrollment
- Primary valvular disease requiring surgical correction
- AF:
  - Persistent AF at the time of enrollment
  - Permanent AF not treated with AV node ablation within 2 wk from the CRT implant
  - History or incidence of paroxysmal or persistent AF within 30 d prior to the enrollment
- Unable to comply with the follow-up schedule
- Less than 18 y of age
- Pregnant or are planning to become pregnant during the duration of the investigation
- Classification of status 1 for cardiac transplantation or consideration for transplantation over the next 12 m
- Undergone a cardiac transplantation
- Life expectancy <12 m
- Currently participating in any other clinical investigation

Association/Heart Rhythm Society guidelines for CRT device implantation (including upgrades from single- or dual-chamber ICDs or pacemakers). A complete list of the MORE CRT MPP–PHASE II trial inclusion and exclusion criteria appears in Table II. Subjects are considered enrolled in the study after giving informed consent; sites then assess the subject's cardiac performance—via 2-dimensional echocardiography—and other clinical and demographic variables at a baseline visit (Table III).

Implant procedure

Within 30 days following enrollment, the clinician implants the subject with a regulatory-approved Abbott CRT-D or CRT-P device with the MPP feature and an Abbott quadripolar LV lead. Any commercially available right atrial and right ventricular leads may be implanted. The clinicians activate BiV pacing at implant and programs the subject's device—including atrioventricular and interventricular delays—based on their discretion. Clinical sites must obtain

Table III. Summary of all scheduled evaluations and procedures

	Enroll	Baseline	Implant procedure	Patient classification	6-m follow-up	12-m follow-up
Informed consent procedure	X					
Inclusion/exclusion criteria check	X					
Implant procedure details			X			
Fluoroscopy images collection (LAO and RAO)			X			
Implant procedure success confirmation				X		
MPP vector test				X	X‡	
Patient data and medical history		X				
Current cardiac medications		X				
Changes in cardiac medications					X	X
Patient global assessment					X	X
NYHA class evaluation		X			X	X
Randomization procedure (only for nonresponders to CRT)					X	
12-Lead ECG (EDC upload)		X			X	X
BNP/pro-BNP/NT-pro-BNP test *		(X*)			(X*)	(X*)
6-min hall walking test		X			X	X
EQ-5D questionnaire		X			X	X
MLWHF questionnaire		X			X	X
Echocardiography	X§				X	X
Preliminary LVESV evaluation		X			X	
Conduction delays test†			X	X	X	X
Device test and programming (EDC upload)			X	X	X	X

LAO, left anterior oblique; *RAO*, right anterior oblique; *BNP*, brain natriuretic peptide; *EQ-5D*, European Quality of Life–5 Dimensions; *MLWHF*, Minnesota Living with Heart Failure.
* If performed as standard of care at the site.
† CRT device-based test that measures the conduction delay between the right and left ventricles.
‡ Testing of mandated MPP settings before randomization.
§ Can be performed at any time from 3 months prior CRT implant (by an echo qualified study center).

postimplant fluoroscopic images in 2 views (left anterior oblique 45° ± 10° and right anterior oblique 45° ± 10°) to document lead location (Table III). Subjects enrolled in the trial but who do not have a successful implant of the MPP CRT device terminate their participation in the trial.

Subject classification

Within 7 days of the implant procedure, all subjects have a classification visit (Table III) at clinical sites to evaluate the success of the implant procedure and to perform the required MPP vector test. The MPP vector test consists of measuring pacing thresholds using each of the 4 electrodes on the quadripolar lead as the cathode and various other electrode combinations as the anode (Table I). The test is considered successful if at least any 2 of the 4 LV cathodes are free from phrenic nerve stimulation at 1 V above the pacing capture threshold and *high capture threshold*, defined as >4.5 V at the device default pulse width. Subjects implanted with an appropriate device but who do not have a successful MPP vector test at a classification visit terminate their participation in the trial. All subjects with a successful MPP vector test are considered "qualified" subjects and continue in the trial.

Subject follow-up and randomization

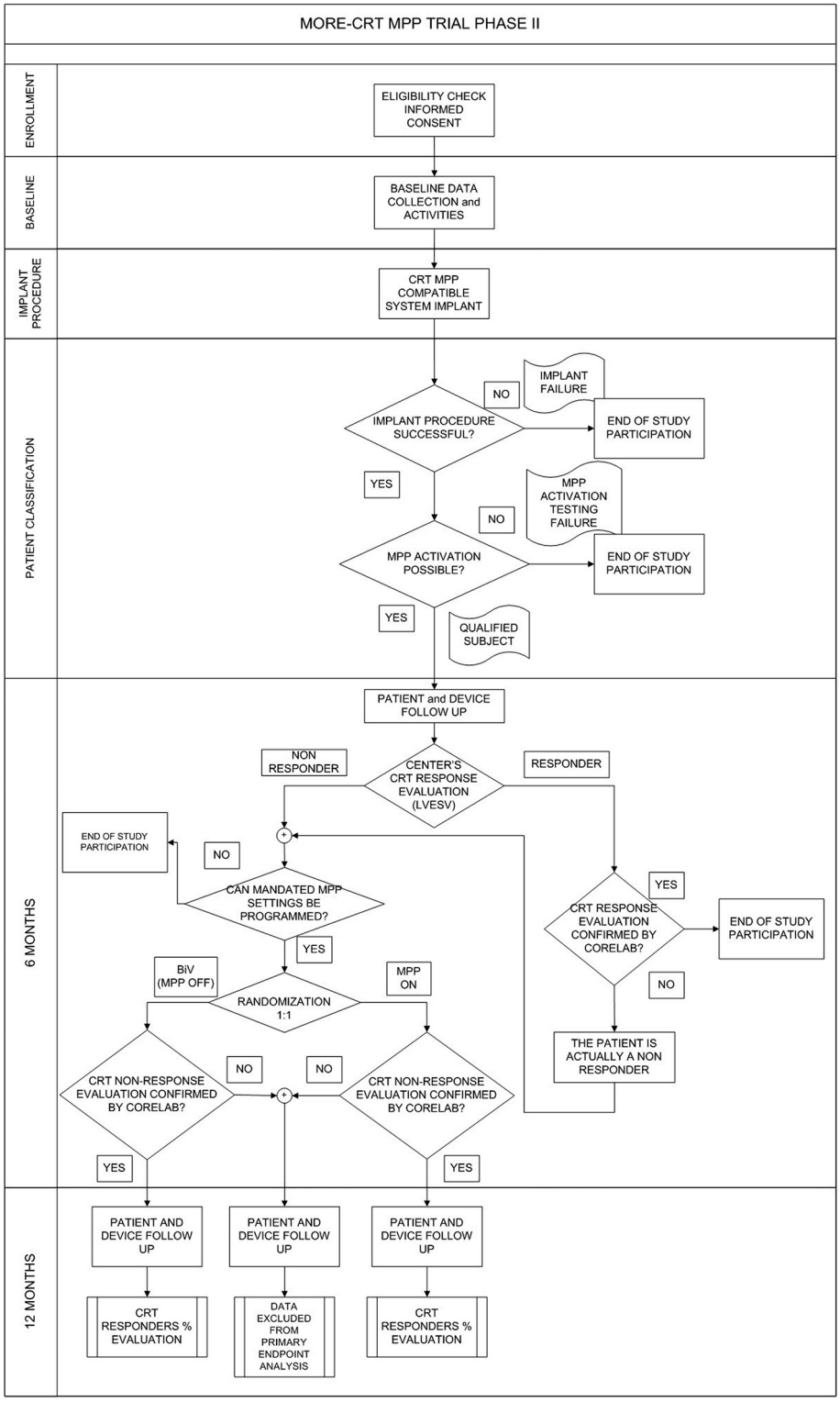
During the first 6 months following implant, all subjects receive quadripolar BiV pacing (MPP OFF). At the 6-month follow-up visit, clinical sites perform a 2-dimensional echocardiogram on qualified subjects and evaluate *CRT response*, defined as a reduction of at least 15% in left ventricular end-systolic volume (LVESV) compared with baseline. An independent echocardiogram core laboratory (Cardialysis, the Netherlands) provides a final, blinded evaluation of CRT response via changes in LVESV using the modified Simpson method in the apical 4- and 2-chamber views according to standard methods recommendations of the American Society of Echocardiography.[24] If the biplane method is not feasible, a single view is analyzed. Contrast LV opacification is used when indicated for subjects with poorly defined endocardial borders.

Subjects who have an LVESV reduction of at least 15% compared with baseline by both the site and the core laboratory are classified as responders, and these subjects terminate their participation in the trial. If the core laboratory assesses a subject as a responder but the clinical site assesses the same subject as a nonresponder, the subject will continue follow-up until 12 months; data from these subjects are excluded from the primary end point analysis. Subjects who have an LVESV reduction of less than 15% as assessed by the core laboratory are classified as nonresponders.

Subjects classified as nonresponders at the 6-month visit undergo acute testing to determine if their device can be programmed to protocol-mandated MPP settings. The mandated MPP-AS settings are defined as follows,

- MPP vector combination: 2 programmable MPP vectors with wide spacing (≥30 mm between 2 cathodes, corresponding to D1-M3/P4 of any Quartet lead, or of M2-P4 of the 1458QL lead, see Figure 1)

Figure 2



Study flow diagram. The diagram outlines patient flow of screening, implant, randomization, and follow-up in the MORE-CRT MPP–PHASE II trial.

- LV1-LV2 timing delay: 5 milliseconds
- LV2-RV timing delay: 5 milliseconds

Subjects unable to have their device programmed with the mandated MPP settings terminate their participation in the trial. Subjects with a successful acute MPP test at 6 months are randomized in a 1:1 ratio to a group with MPP (MPP arm) or a group with continued BiV pacing (BiV arm) for an additional 6 months of follow-up. Subjects randomized to the BiV arm receive BiV pacing per the clinician's discretion; subjects randomized to the MPP arm receive MPP with the mandated parameters.

During the 12-month visit, clinical sites perform a final 2-dimensional echocardiogram and evaluate CRT response compared with baseline. The independent core laboratory again provides a final, blinded assessment of CRT response at 12 months. The study will be terminated after all qualified subjects complete the 12-month follow-up visit (Figure 2).

Primary and secondary end points

The primary end point of the trial is the percentage of nonresponder subjects converted to responders after 6 months of CRT with MPP or BiV pacing. A response to CRT is a reduction in LVESV of at least 15% at 12 months compared with baseline. Subjects who die because of cardiac reasons postrandomization are considered a nonresponder. Assuming that 34% of subjects in the BiV arm versus 43.9% of subjects in the MPP arm will become responders at 12 months compared to baseline, at least 380 subjects with analyzable data at 12 months are required in each arm (using a 1-sided significance level of 2.5% and a power of 80%). Assuming a dropout rate of 21% after randomization, at least 482 randomized subjects are required in each arm. Further, assuming 37% of qualified subjects are nonresponders at 6 months postimplant—with a dropout rate of 6.4% during the first 6 months following the classification visit—and considering approximately 35% of qualified subjects are unable to receive protocol-mandated MPP settings due to phrenic nerve stimulation or high thresholds, the trial is required to include at least 4,286 qualified subjects. To obtain 4,286 qualified subjects and taking into account implant failures (7.3%), dropout before implant (2.4%), and MPP activation failure following implant (5%), the trial requires enrollment of approximately 5,000 subjects.

The primary end point analysis will be carried out on an "as-treated" basis—subjects will be analyzed accordingly to their programming (MPP or BiV) at 12 months or at the last follow-up before 12 months. The analysis population for the primary end point will include all 6-month nonresponders randomized at 6 months and who complete the trial with analyzable data, or who die because of cardiac reasons prior to 12 months. In addition, for the MPP arm, the subjects programmed with the protocol-mandated MPP settings will be included in the primary end point analysis. The number and proportion of responders will be reported, as well as comparisons between the samples using the χ^2 test.

In addition to the primary analyses, subgroup analyses on the primary end point will be performed by gender, cardiomyopathy classification (ischemic or nonischemic), device type (CRT-P or CRT-D), conduction delay types (LBBB or non-LBBB), tQRS width $\geq$150 or <150, LV ejection fraction $\geq$25 or <25, LV end-diastolic volume $\geq$ median or < median, and by New York Heart Association (NYHA) class (III/IV or II).

Secondary end point analyses will be performed once all subjects have completed or crossed the 12-month visit window. For the MPP arm, subjects programmed with the protocol-mandated MPP settings will be included. Changes in the following outcomes will be compared between baseline and 12 months, and between the 6- and 12-month visits: reduction of LVESV; Packer's Clinical Composite Score[25]; reverse LV remodeling—measured as percent changes in LVESV, LV end-diastolic dimension, and LV ejection fraction; NYHA class; 6-minute hall walk test; and quality of life (Minnesota Living with Heart Failure and European Quality of Life–5 Dimensions).

Statistical analysis

The trial hypothesis will be tested at the 1-sided 2.5% significance level for the primary end point. The null hypothesis will be rejected if the 97.5% lower confidence bound for the difference between the proportion of subjects who are responders in the treatment arm (MPP) and the proportion of subjects who are responders in the control arm (BiV)—$P_{MPP} - P_{BiV}$—is greater than 0. The 97.5% lower confidence bound will be calculated using the Wald asymptotic confidence limits with continuity correction method for difference of binomial proportions. Subjects with missing responder status will be excluded from analysis.

Discussion

Newer CRT pacing strategies have been developed to address the inconsistent response to CRT in a substantial number of patients. One such strategy is the use of multiple LV pacing leads to activate larger areas of the myocardium.[12-14,26] Previous experimental and clinical work has shown that simultaneously activating a larger volume of ventricular tissue results in an increased depolarization velocity and shorter interventricular conduction times.[20,27] In addition, by capturing a larger volume of ventricular muscle, the site of latest LV intrinsic activation may undergo earlier activation, resulting in better synchronization and improved cardiac output. Multisite LV pacing using multiple leads has been evaluated in numerous small trials, but the results have been inconsistent.[12,14,26,28] Furthermore, the use of multiple LV leads significantly increases the complexity,

duration, and risk of the procedure. Thus, MPP using a single quadripolar lead is an attractive alternative to the use of multiple LV leads.

Compared with traditional BiV pacing, several small studies have shown that MPP delivered through a quadripolar LV lead improves LV dP/dtmax (maximum rate of rise of LV pressure),[17] LV dyssynchrony,[16,29] LV peak radial strain,[19] LV pressure-volume loop parameters,[18] and LV electrical activation.[26] Studies also demonstrated that MPP provides effective stimulation of the LV and results in both midterm and long-term LV reverse remodeling and improvements in LV function compared with quadripolar BiV pacing.[20,30]

Although these previous studies indicate MPP may offer advantages over BiV pacing in patients who need CRT, the long-term clinical effects of MPP and the impact of MPP programming have not yet been evaluated in large randomized, prospective trials. The MORE-CRT MPP trial is the first large, randomized, multicenter trial to evaluate the long-term effects of MPP. Given the trial design, the results should provide more definitive information on whether there is a clinical benefit of CRT with MPP at 12 months when MPP is activated at 6 months in patients who have failed to respond to BiV pacing.

Because the patient population eligible for inclusion into the trial includes patients who receive CRT via defibrillators and pacemakers, this enables observation of potential effectiveness of the MPP feature in a wider audience. Response is assessed after a 6-month period and is defined using an echocardiographic measure which is objective in nature (LVESV reduction $\geq$15%) and will moreover be validated by an independent core laboratory blinded to the site's assessment of the patient's response. One limitation in determining response to CRT is that the LVESV measure used to determine response is most likely a continuum and may not necessarily be a simple "cutoff" point. The randomization aspect of the trial should produce comparable groups of nonresponders who will either have MPP or BiV pacing. Randomization should also reduce effects of potential confounding factors and result in a more unbiased testing of treatment efficacy.

A post hoc analysis from the MPP IDE study showed that patients programmed with a distance between LV1 and LV2 $\geq$30 mm and a minimal programmable delay of 5 milliseconds (MPP-AS) had a significantly higher responder rate and nonresponder to responder conversion rate compared to other MPP configurations.[21] Furthermore, the results from the recent MORE CRT MPP–PHASE I study were consistent with a 2-fold response in conversion rate with MPP-AS compared to MPP-other based on LV reverse remodeling, and a trend in a higher conversion rate with MPP-AS compared to BiV pacing (46% vs 34%).[23] The finding from the Phase I study underscores the importance of proper MPP programming and significance of assessing the impact of mandated MPP-AS programming compared with BiV pacing in converting nonresponders to responders in the Phase II study.

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