



HAL
open science

Cardiac resynchronization therapy non-responder to responder conversion rate in the MORE-CRT MPP trial

Christophe Leclercq, Haran Burri, Peter Paul Delnoy, Christopher A Rinaldi, Johannes Sperzel, Leonardo Calò, Joaquin Fernandez Concha, Luigi Antonio Fusco, Faisal Al Samadi, Kwangdeok Lee, et al.

► To cite this version:

Christophe Leclercq, Haran Burri, Peter Paul Delnoy, Christopher A Rinaldi, Johannes Sperzel, et al.. Cardiac resynchronization therapy non-responder to responder conversion rate in the MORE-CRT MPP trial. EP-Europace, 2023, 25 (10), pp.1-11. 10.1093/europace/euad294 . hal-04266693

HAL Id: hal-04266693

<https://hal.science/hal-04266693>

Submitted on 31 Oct 2023






HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

Cardiac resynchronization therapy non-responder to responder conversion rate in the MORE-CRT MPP trial

Christophe Leclercq ^{1*}, Haran Burri ², Peter Paul Delnoy³, Christopher A. Rinaldi ⁴, Johannes Sperzel⁵, Leonardo Calò ⁶, Joaquin Fernandez Concha ⁷, Antonio Fusco⁸, Faisal Al Samadi⁹, Kwangdeok Lee¹⁰, and Bernard Thibault¹¹ on behalf of the MORE-CRT MPP Investigators

¹Service de Cardiologie et Maladies Vasculaires, Université de Rennes I, CICIT 804, CHU Pontchaillou Rennes, 2, rue Henri le Guilloux 35033 Rennes Cédex 09, Rennes 35033, France;

²Department of Cardiology, University of Geneva, Geneva, Switzerland; ³Isala Hospital, Department of Cardiology, Isala Klinieken, Zwolle, The Netherlands; ⁴King's College, London, UK;

⁵The Kerckhoff Heart and Thorax Center, Bad Nauheim, Kerckhoff Klinik, Bad Nauheim, Germany; ⁶Division of Cardiology, Policlinico Casilino, Rome, Italy; ⁷Cardiólogo en Servicio

Extremeño De Salud, Hospital Universitario de Badajoz, Badajoz, Spain; ⁸Ospedale Dott. Pederzoli, Italy; ⁹King Fahad Medical City, Saudi Arabia; ¹⁰Abbott, Plano, USA; and

¹¹Electrophysiology Service Department of Cardiology, Université de Montréal, Montreal, Canada

Received 9 May 2023; editorial decision 26 July 2023; accepted after revision 26 July 2023; online publish-ahead-of-print 30 September 2023

Aims

To assess the impact of MultiPoint™ Pacing (MPP) in cardiac resynchronization therapy (CRT) non-responders after 6 months of standard biventricular pacing (BiVP).

Methods and results

The trial enrolled 5850 patients who planned to receive a CRT device. The echocardiography core laboratory assessed CRT response before implant and after 6 months of BiVP; non-response to BiVP was defined as <15% relative reduction in left ventricular end-systolic volume (LVESV). Echocardiographic non-responders were randomized in a 1:1 ratio to receive MPP (541 patients) or continued BiVP (570 patients) for an additional 6 months and evaluated the conversion rate to the echocardiographic response. The characteristics of both groups at randomization were comparable. The percentage of non-responder patients who became responders to CRT therapy was 29.4% in the MPP arm and 30.4% in the BiVP arm ($P = 0.743$). In patients with ≥ 30 mm spacing between the two left ventricular pacing sites (MPP-AS), identified during the first phase as a potential beneficial subgroup, no significant difference in the conversion rate was observed.

Conclusion

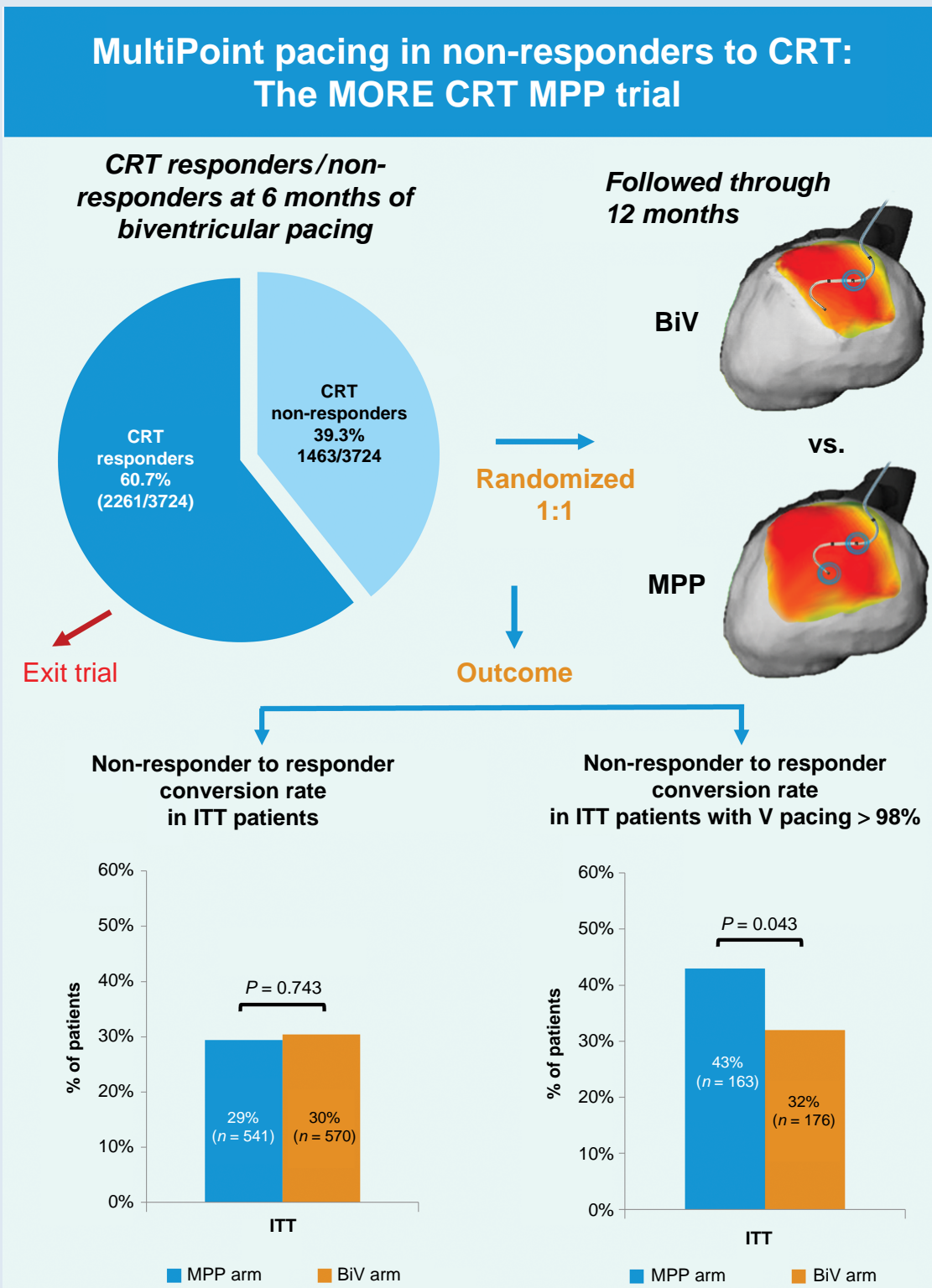
Our trial shows that ~30% of patients, who do not respond to CRT in the first 6 months, experience significant reverse remodelling in the following 6 months. This finding suggests that CRT benefit may be delayed or slowly incremental in a relevant proportion of patients and that the percentage of CRT responders may be higher than what has been described in short-/middle-term studies. MultiPoint™ Pacing does not improve CRT response in non-responders to BiVP, even with MPP-AS.

* Corresponding author. Tel: +33 2 99 28 25 17, +33 6 23 80 85 60, E-mail address: christophe.leclercq@chu-rennes.fr

© The Author(s) 2023. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Graphical Abstract



Keywords

MultiPoint Pacing • MPP • Heart failure • Biventricular pacing • Cardiac resynchronization • Randomized controlled study • Quadripolar left ventricular pacing

What's New?

- In echocardiographic non-responders after 6 months of biventricular pacing (BiVP), MultiPoint™ Pacing (MPP) providing two pacing pulses in the left ventricle (LV) with a large anatomical separation through a quadripolar lead did not improve the LV end-systolic volume as compared to BiVP during the next 6 months. It is not recommended to use MPP systematically in patients who do not respond to cardiac resynchronization therapy (CRT). However, it has been observed that MPP could be beneficial for CRT non-responders who have a considerable amount of ventricular pacing (>98%).
- In patients receiving CRT with BiVP, the response to BiVP may be delayed over 6 months, 30% of patients who were not responders at 6 months became responders during the following 6 months.

Introduction

Cardiac resynchronization therapy (CRT) is an established heart failure therapy; however, up to 30–40% of conventional CRT patients do not respond.^{1–4} Failure to respond to CRT has been attributed, in part, to suboptimal left ventricular (LV) lead placement and device programming.^{1,5–7} CRT response may improve when the LV pacing site is selected based on delayed electrical activation, acute haemodynamic response, scar burden/location, and electrical or mechanical mapping.^{8–10} Nevertheless, approaching the target vein(s) has been limited, mainly due to unfavourable coronary venous anatomy, phrenic nerve stimulation, high capture thresholds, or pacing lead instability. Pacing multiple LV sites using a single quadripolar lead in a vein of the coronary sinus has been achieved using a CRT system enabled with MultiPoint™ Pacing (MPP). Studies have shown that MPP improves contractility, haemodynamics, and dyssynchrony,^{11–18} as well as longer-term improvements in LV reverse remodelling and clinical response compared with biventricular pacing (BiVP).^{11,19,20} However, the impact of MPP on conventional CRT non-responders is not well defined. The More Response on Cardiac Resynchronization Therapy with MultiPoint Pacing (MORE-CRT MPP) trial was designed to assess MPP in the treatment of non-responders to 6 months of standard BiVP, based on LV reverse remodelling. More Response on Cardiac Resynchronization Therapy with MultiPoint Pacing constituted a two-part trial, with phase II serving as a direct extension of phase I, aimed at assessing the potential advantage of MPP with a large (≥ 30 mm) anatomic separation (MPP-AS) over BiVP in CRT non-responders based on the observations made during the initial phase of the trial.²¹

Methods

Study design and progress

The MORE-CRT MPP trial was a prospective, randomized, multi-centre study designed to assess the impact of MPP on treating echocardiographic non-responders to 6 months of standard BiVP.²² MultiPoint™ Pacing was evaluated in two phases; phase I allowed physicians to program MPP according to their discretion (467 evaluable non-responder subjects from 1921 enrolments), while in phase II, the protocol required to programme MPP-AS between any of the LV pacing electrodes as long as capture threshold did not exceed 4.5 V at 0.5 ms pulse width in CRT-D devices and 0.4 ms pulse width in CRT-P devices (644 evaluable non-responder subjects from 3929 enrolments). This setting was associated with a trend in improved response to CRT in phase I.²² The study was approved by the institutional ethics committees.

The present report includes patients from both phases. The study sponsor performed data monitoring and performed data analyses in partnership with the steering committee. The steering committee had final authority on data interpretation, presentation, and writing of the manuscript.

The sponsor prematurely closed the MORE-CRT MPP trial in 2020 in consultation with the study steering committee and an independent review committee because a pre-specified interim analysis showed a low probability of the study meeting the primary endpoint. There were no safety concerns with activating MPP. Following the closure decision, sites followed all randomized subjects to collect the 12-month data as outlined in the protocol. In addition, sites withdrew patients who were enrolled but not yet randomized in the study.

The data underlying this article cannot be shared publicly due to the privacy of individuals that participated in the study.

Study participants, randomization, and endpoint evaluation

The study enrolled eligible patients with a standard CRT indication after obtaining written informed consent. The study inclusion and exclusion criteria have been previously reported.^{21,22} The implanting physician programmed BiV pacing at implant in those patients who had the quadripolar CRT system successfully implanted (Quartet LV lead with a Quadra CRT device, Abbott, Sylmar, CA, USA). The implanting physician programmed the LV pacing vector, A-V delay, and V-V delay settings at their discretion until the patient's randomization at 6 months. During the first 6 months following implant, all subjects received standard BiVP (MPP OFF).

Following standard BiVP for the first 6 months post-implant, patients with a LV end-systolic volume (LVESV) relative reduction $\geq 15\%$ compared to implant were classified as echocardiographic responders and exited the trial. Echocardiographic non-responder patients based on LV reverse remodelling (i.e. LVESV relative reduction from implant to 6 months $< 15\%$) were randomized in a 1:1 ratio to either the MPP arm or BiV arm. The primary endpoint was the percentage of non-responders after 6 months of BiVP who converted to responders at 12 months, as measured by $\geq 15\%$ reduction in LVESV. Patients who died due to cardiac causes post-randomization were considered non-responders. An independent Echocardiography Core Laboratory (Cardialysis, The Netherlands) analysed all measurements before implant, 6, and 12 months and evaluated CRT response based on the LVESV reduction.

Secondary endpoints included heart failure events (defined as a hospitalization or emergency department visit for heart failure of ≥ 24 h or hospitalization or emergency department visit for heart failure of < 24 h requiring intravenous administration of inotropes or diuretics), cardiac death, LVESV at 12 months, and mean reduction in LVESV at 12 months compared to 6 months and before implant.

To evaluate the impact of BiVP percentage on MPP, we assessed the association between non-responder to responder conversion rate and percent BiVP between the two arms after randomization. To evaluate the effect of MPP programming on the study endpoint, we assessed the association between baseline characteristics/ BiVP % and the difference in echocardiographic non-responder to responder conversion rates between the two arms using multivariable logistic regression analysis.

Intention-to-treat analysis

Intention-to-treat (ITT) analysis was conducted according to the treatment to which they were randomized. The ITT population includes all patients from both phases of the study who were echocardiographic non-responders at 6 months confirmed by the Echocardiography Core Laboratory and were randomized into either the MPP or BiV arm and completed the 12-month visit with evaluable endpoint data.

As-treated MultiPoint™ Pacing with a large (≥ 30 mm) anatomic separation analysis

As-treated analysis for the subgroup of patients with MPP-AS was conducted as pre-defined in the revised version of the study protocol. The as-treated population included patients who were echocardiographic non-responders at 6 months, were programmed with MPP-AS for the treatment arm compared to the whole BiVP control arm, and completed the 12-month visit with evaluable endpoint data.

Study blinding

Patients were blinded to the treatment they received in the trial. An independent Echocardiography Core Laboratory, blinded to device programming, analysed all measurements before implant, at 6, and at 12 months and evaluated CRT response based on the LVESV reduction.

Statistical analysis

The conversion rate from non-responders to responders was compared using χ^2 test. The non-responder to responder conversion rate differences as a function of characteristics at randomization were derived from multivariable logistic regression models. Other comparisons were analysed using descriptive statistics, χ^2 test, or Fisher's exact test according to the expected number of crossings for categorical variables and Wilcoxon rank sum test. Analyses were conducted using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

Patients

The study enrolled 5850 patients (1921 in phase I and 3929 in phase II) at 215 centres worldwide (Figure 1). After 6 months of BiVP from implant to randomization, 39.3% (1463/3724) of the patients with evaluable echocardiography data failed to respond to CRT per echocardiography. A total of 1111 CRT non-responder patients at 6 months, who had LVESV measurements at 12 months, were included in the ITT analysis population: 541 randomized to the MPP arm (of whom 236 stemmed from phase 1, [Supplementary material online, Table](#)) and 570 to the BiV arm (of whom 231 stemmed from phase 1). Of subjects randomized to the MPP arm, 20 crossed-over to BiVP. Of subjects randomized to the BiV arm, four crossed-over to MPP-AS. A total of 271 patients with MPP-AS programmed (of whom 68 stemmed from phase 1, [Supplementary material online, Table](#)) and 555 with BiVP (of whom 231 stemmed from phase 1) were included in the as-treated analysis population.

In the ITT population, patients in the two study arms had comparable demographic characteristics at randomization (Table 1). The two arms showed no significant differences in mean reduction of LVESV at 6 months compared to implant ($1.0 \pm 13.5\%$ in MPP arm and $0.2 \pm 12.6\%$ in BiV arm, $P = 0.305$). Heart failure events (events per patient-year) from implant through randomization (i.e. implant to 6 months) were also comparable between the two arms (0.21 ± 0.70 in MPP arm and 0.21 ± 0.73 in BiV arm, $P = 0.584$).

In the as-treated analysis, patients had comparable demographic characteristics, except for the use of anticoagulants (Table 2) and for a slightly greater reduction of LVESV at 6 months compared to implant which was observed in the MPP-AS arm ($2.1 \pm 11.2\%$ in MPP-AS arm and $0.1 \pm 12.6\%$ in BiV arm, $P = 0.023$). Heart failure events (events per patient-year) from implant through randomization were comparable between the two arms (0.22 ± 0.72 in MPP-AS arm and 0.19 ± 0.70 in BiV arm, $P = 0.422$).

Primary endpoint (intention-to-treat analysis)

Overall, there was no difference in non-responder to responder conversion rate between the MPP and BiV arms at 12 months ($P = 0.743$). The percentage of patients who were CRT non-responders at 6 months and became responders to CRT therapy at 12 months was 29.4% (159/541 patients) in the MPP arm and 30.4% (173/570 patients) in the BiV arm. Cardiac death was a criterion of CRT non-response; eight patients died due to cardiac causes in the MPP arm and 15 in the BiV arm ($P = 0.130$).

In both arms, LVESV decreased after randomization at 6 months to 12 months follow-up (161 ± 70 mL in MPP and 160 ± 67 mL in BiV at 6

months, $P = 0.817$, to 157 ± 72 mL in MPP and 154 ± 69 mL in BiV at 12 months, $P = 0.473$). There was no difference in a mean reduction in LVESV at 12 months compared with implant ($2 \pm 26\%$ in MPP, $4 \pm 23\%$ in BiV, $P = 0.326$) nor at 12 months compared to six months ($1 \pm 22\%$ in MPP, $3 \pm 21\%$ in BiV, $P = 0.074$).

This remained true in all but one of the pre-defined subgroups (Figure 2A). In a subgroup analysis of ventricular pacing in $>98\%$ of the time, MPP was associated with a significant improvement in converting echocardiographic non-responders to responders compared to BiV ($P = 0.034$, Figure 2A) and the MPP arm showed a significant improvement in the conversion rate compared to the BiV arm (43% in MPP arm, 32% in BiV arm, $P = 0.043$) (Figure 3A). However, the difference in percentage reduction in LVESV did not reach statistical significance. There was no significant difference in improvement in NYHA class at 12 months compared to baseline between MPP and BiV groups (including patients who had $>98\%$ ventricular pacing).

The difference in patients who experienced adverse events (both serious and non-serious) between the two study arms was not statistically significant (23.1% in MPP arm and 19.3% in BiV arm, $P = 0.120$). Specifically, the per patient-year heart failure event rates were similar between the two arms (0.28 ± 1.20 in MPP arm and 0.38 ± 1.58 in BiV arm, $P = 0.096$).

As-treated MultiPoint™ Pacing with a large (≥ 30 mm) anatomic separation analysis

In the as-treated population, the results showed no difference in echocardiographic non-responder to responder conversion rate between the MPP-AS and BiV arms at 12 months (84/271, 31.0% in MPP-AS arm and 170/555, 30.6% in BiV arm, $P = 0.915$). Four patients died due to cardiac causes in the MPP-AS arm and 17 in the BiV arm ($P = 0.173$).

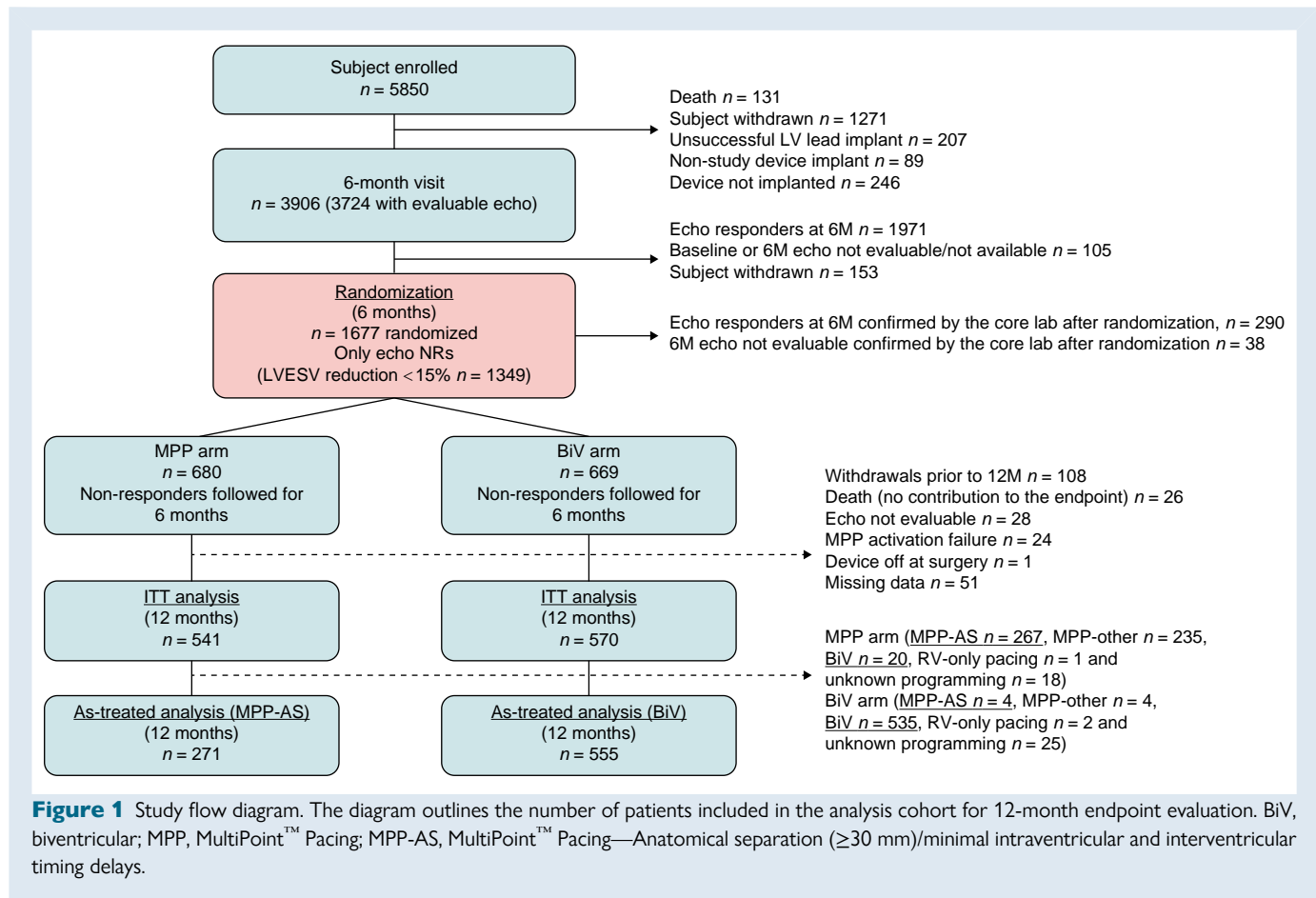
In both arms, LVESV decreased after randomization at 6 months to 12 months follow-up (164 ± 70 mL in MPP and 159 ± 66 mL in BiV at 6 months, $P = 0.318$, to 160 ± 71 mL in MPP and 152 ± 67 mL in BiV at 12 months, $P = 0.109$). There was no difference between the arms in a mean reduction in LVESV at 12 months compared to before implant ($3 \pm 24\%$ in MPP-AS, $4 \pm 23\%$ in BiV, $P = 0.620$) and at 12 months compared to 6 months ($1 \pm 23\%$ in MPP-AS, $4 \pm 21\%$ in BiV, $P = 0.069$).

In a pre-defined subgroup analysis of ventricular pacing in $>98\%$ of the time, MPP-AS was associated with a significant improvement in converting echocardiographic non-responders compared to BiVP ($P = 0.034$, Figure 2B) and the MPP-AS arm showed a significant improvement in the conversion rate compared to the BiV arm (44% in MPP arm, 31% in BiV arm, $P = 0.036$) (Figure 3B). However, the difference in percentage reduction in LVESV did not reach statistical significance. There was no significant difference in improvement in NYHA class at 12 months compared to baseline between MPP-AS and BiV groups (including patients who had $>98\%$ ventricular pacing).

Following the 6-month randomization point, heart failure event rates in the As-Treated population tended to decrease slightly in the MPP-AS arm compared to those in the BiV arm without a statistical significance (per patient-year, MPP-AS arm: 0.31 ± 1.08 ; BiV arm: 0.44 ± 1.82 , $P = 0.356$). The difference in patients who experienced adverse events (both serious and non-serious) between the two study arms was not statistically significant (23.1% in MPP-AS and 19.3% in BiV, $P = 0.120$).

Feasibility of MultiPoint™ Pacing with a large (≥ 30 mm) anatomic separation programming

During phase II of the MORE CRT MPP trial, MPP-AS programming was required per protocol. Nevertheless, of the 305 patients randomized to MPP-AS programming (Su), 72 patients were programmed to



MPP-Other, rather than MPP-AS, due to phrenic nerve stimulation/high capture threshold (57%, 41/72), inadvertent programming error (12.5%, 9/72), physician's discretion due to medical reasons (2.8%, 2/72), and unknown reasons (28%, 20/72). At the time of the study launch, the Quartet 1458QL lead with a distance of 60 mm between poles 1 and 4 was not available (only a maximal space of 47 mm was available), limiting the programming to ensure MPP-AS.

Effect of MultiPoint™ Pacing on longevity

Longevity calculations at nominal device settings indicated that the difference in the estimated battery longevity between the MPP and BiV arms at 12 months was approximately 0.9 years—the projected longevity impact if MPP programming were to be continued until battery depletion.

Discussion

The MORE-CRT MPP trial, with 5850 patients enrolled by 215 centres over five continents, is the largest randomized clinical trial ever conducted on CRT response. With 1677 patients randomized, it is also the largest randomized study dedicated to assessing the potential benefit of any pacing configuration in converting CRT echocardiographic non-responders to responders. The main findings of this trial are (i) the actual echocardiographic response rate at 6 months after implant was high at around 60%; (ii) out of the 39.3% of echocardiographic non-responders at 6 months, about 30% of them showed an echocardiographic reverse remodelling response at 12 months in both study arms—accounting for an overall 72% echocardiographic response

Death $n = 131$
 Subject withdrawn $n = 1271$
 Unsuccessful LV lead implant $n = 207$
 Non-study device implant $n = 89$
 Device not implanted $n = 246$

Echo responders at 6M $n = 1971$
 Baseline or 6M echo not evaluable/not available $n = 105$
 Subject withdrawn $n = 153$

Echo responders at 6M confirmed by the core lab after randomization, $n = 290$
 6M echo not evaluable confirmed by the core lab after randomization $n = 38$

Withdrawals prior to 12M $n = 108$
 Death (no contribution to the endpoint) $n = 26$
 Echo not evaluable $n = 28$
 MPP activation failure $n = 24$
 Device off at surgery $n = 1$
 Missing data $n = 51$

MPP arm (MPP-AS $n = 267$, MPP-other $n = 235$, BiV $n = 20$, RV-only pacing $n = 1$ and unknown programming $n = 18$)
 BiV arm (MPP-AS $n = 4$, MPP-other $n = 4$, BiV $n = 535$, RV-only pacing $n = 2$ and unknown programming $n = 25$)

rate at 12 months, which is positioned at the upper end of CRT response rate compared to previously reported results;^{23,24} (iii) however, there was no difference in the echocardiographic conversion rate from non-responders to responders between MPP and BiV in both the ITT and as-treated MPP-AS analysis; and (iv) in the pre-specified sub-group analysis, when $>98\%$ of ventricular pacing was achieved, the conversion rate (from 6 to 12 months) was superior with MPP and MPP-AS compared to BiV.

Long-term cardiac resynchronization therapy response

Our study shows that within 6 months, standard BiVP induces a positive LV reverse remodelling in about 60% of patients. This result is aligned with previous publications.^{23,24} Our study design, which followed patients who were non-responders to CRT for additional 6 months, allowed us to evaluate long-term (12 months) CRT response. Approximately 30% of patients, who did not initially respond to CRT, actually experienced delayed significant reverse remodelling in the following 6 months which was an unexpected finding and thus questioned the timeline for assessing echocardiographic response to CRT. This finding suggests that CRT benefit may be delayed or slowly incremental in a relevant proportion of patients and that the percentage of CRT responders may be higher than what has been measured in short-middle term studies, accounting for an overall 72% echocardiographic response rate at 12 months. This is positioned at the upper end of the reverse remodelling-based CRT response rate compared to previously reported results.^{23,24}

Table 1 Demographics of MultiPoint™ Pacing and biventricular (BiV) arms [cardiac resynchronization therapy (CRT) non-responders per left ventricular end-systolic volume (LVESV), intention-to-treat (ITT) population] at randomization

Demographic variable	All randomized subjects (n = 1111)	MPP arm (n = 541)	BiV arm (n = 570)	P-value
Age (years)				
Mean ± SD	68 ± 10	68 ± 10	68 ± 11	0.982 ^a
Gender, (%)				
Male	79.3	81.0	77.7	0.183 ^b
NYHA class at enrolment (%)				
Class II	48.6	49.8	48.9	0.673 ^b
Class III	49.1	50.1	48.2	
Class IV	2.0	1.7	2.3	
NYHA class at 6 months (%)				
Class I	17.5	16.5	18.4	0.426 ^b
Class II	62.9	64.0	61.9	
Class III	18.8	19.2	18.4	
Class IV	0.2	0.0	0.4	
QRS duration (ms)				
Mean ± SD (n)	154 ± 25	155 ± 26	153 ± 25	0.300 ^a
QRS morphology (%)				
LBBB	62.0	61.6	62.3	0.825 ^b
Non-LBBB	38.0	38.4	37.7	
Cardiomyopathy aetiology (%)				
Ischaemic	52.0	53.0	51.1	0.505 ^b
Non-ischaemic	48.0	47.0	48.9	
LVESV (ml)				
Mean ± SD	163 ± 68	164 ± 68	163 ± 68	0.763 ^a
LVEF (%)				
Mean ± SD	26 ± 8	26 ± 8	26 ± 7	0.774 ^a
Device type (%)				
CRT-P	10.3	10.0	10.5	0.765 ^b
CRT-D	89.7	90.0	89.5	
LV lead location (%)				
Anterior	1.4	1.3	1.4	
Anterior lateral	13.0	13.0	12.9	
Lateral	39.4	38.2	40.5	0.858 ^b
Posterior lateral	40.1	40.6	39.6	
Posterior	6.2	6.9	5.5	
Medical treatment (%)				
Diuretics	80.6	80.6	80.5	0.978 ^b
ACE inhibitor or ARB	87.5	87.2	87.7	0.812 ^b
β-Blocker	87.2	87.8	86.7	0.572 ^b
Aldosterone antagonist	39.4	40.1	38.8	0.648 ^b
Anticoagulant	32.6	33.3	31.9	0.633 ^b
Calcium channel blockers	6.8	7.0	6.7	0.814 ^b
Nitrates	8.7	8.7	8.8	0.960 ^b

LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, interventricular conduction delay; LAFB, left anterior fascicular block; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

^aWilcoxon rank sum test.

^bPearson chi-square test.

Table 2 Demographics of MultiPoint™ Pacing (MPP) [MultiPoint™ Pacing—Anatomical separation (≥ 30 mm)/minimal intraventricular and interventricular timing delays (MPP-AS)] and biventricular (BiV) arms [cardiac resynchronization therapy (CRT) non-responders per LVESV, as-treated population] at randomization

Demographic variable	All randomized subjects (n = 826)	MPP arm (MPP-AS) (n = 271)	BiV arm (n = 555)	P-value
Age (years)				
Mean \pm SD	68 \pm 10	68 \pm 10	68 \pm 11	0.748 ^a
Gender, (%)				
Male	79.7	83.4	77.8	0.063 ^b
NYHA class at enrolment (%)				
Class II	48.5	47.6	49.0	0.629 ^b
Class III	49.0	50.6	48.3	
Class IV	2.1	1.5	2.3	
NYHA class at 6 months (%)				
Class I	17.7	14.0	19.5	0.182 ^b
Class II	63.1	66.4	61.4	
Class III	18.4	19.2	18.0	
Class IV	0.2	0.0	0.4	
QRS duration (ms)				
Mean \pm SD (n)	154 \pm 25	155 \pm 25	154 \pm 25	0.584 ^a
QRS morphology (%)				
LBBB	61.7	60.3	62.4	0.599 ^b
Non-LBBB	38.3	39.7	37.6	
Cardiomyopathy aetiology (%)				
Ischaemic	51.5	54.2	50.1	0.262 ^b
Non-ischaemic	48.5	45.8	49.9	
LVESV (ml)				
Mean \pm SD	163 \pm 68	168 \pm 66	161 \pm 68	0.169 ^a
LVEF (%)				
Mean \pm SD	26 \pm 7	26 \pm 7	26 \pm 7	0.831 ^a
Device type (%)				
CRT-P	11.0	12.2	10.5	0.457 ^b
CRT-D	89.0	87.8	89.5	
LV lead location (%)				
Anterior	1.2	1.1	1.3	
Anterior lateral	13.0	12.5	13.3	
Lateral	40.7	43.5	39.3	0.845 ^b
Posterior Lateral	39.3	37.3	40.4	
Posterior	5.7	5.5	5.8	
Medical treatment (%)				
Diuretics	80.5	80.4	80.5	0.973 ^b
ACE inhibitor or ARB	88.0	88.9	87.6	0.571 ^b
β -Blocker	87.8	88.9	87.2	0.478 ^b
Aldosterone antagonist	40.4	41.7	39.8	0.606 ^b
Anticoagulant	34.4	39.1	32.1	0.045 ^b
Calcium channel blockers	7.1	8.9	6.3	0.182 ^b
Nitrates	9.6	11.1	8.8	0.304 ^b

LBBB, left bundle branch block; RBBB, right bundle branch block; IVCD, interventricular conduction delay; LAFB, left anterior fascicular block; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

^aWilcoxon rank sum test.

^bPearson chi-square test.

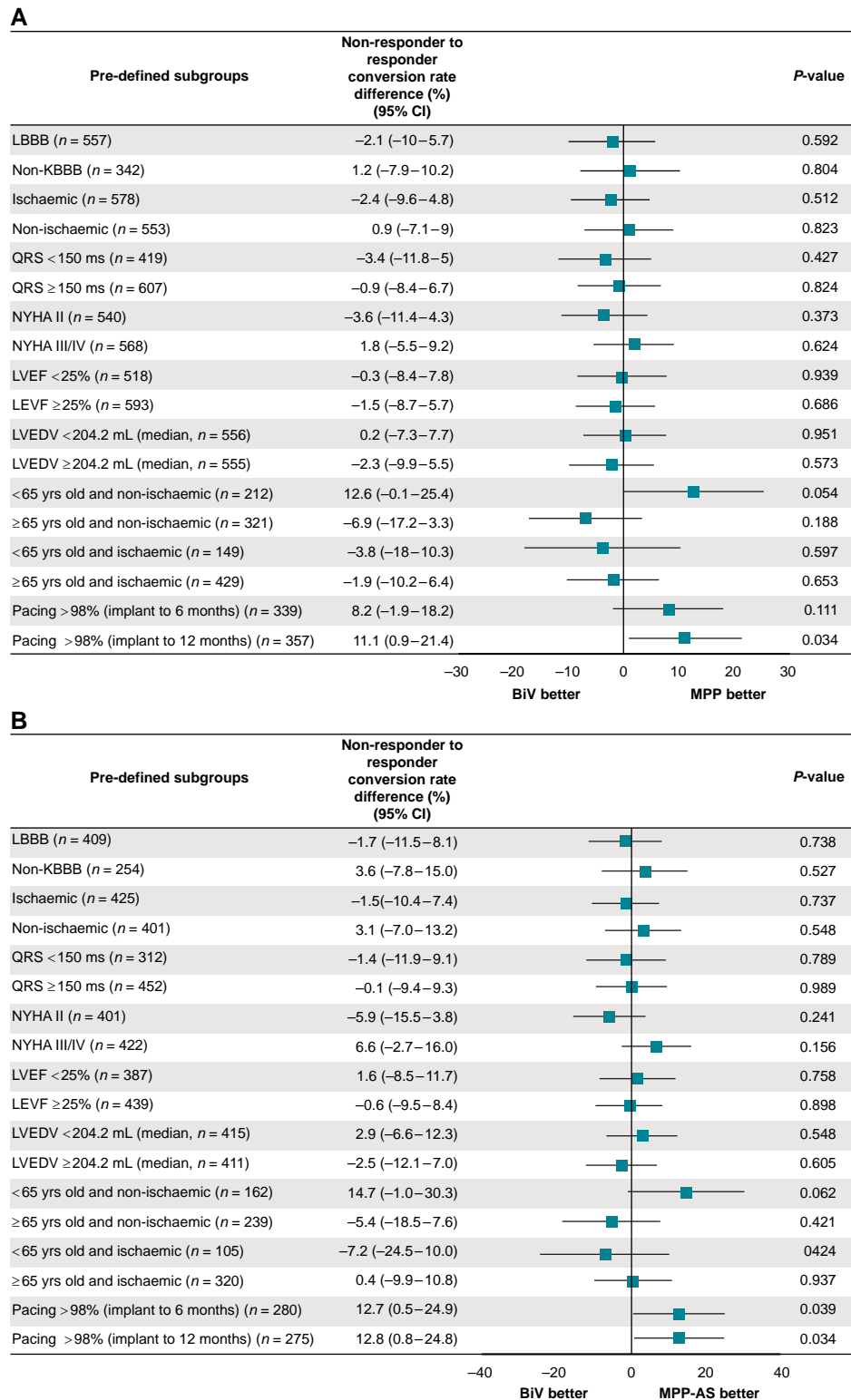


Figure 2 Effect of MultiPoint™ Pacing (MPP) programming on the study endpoint in pre-defined subgroups. The graph displays the non-responder to responder conversion rate difference (%) per echocardiogram between MPP and biventricular (BiV) in intention-to-treat (ITT) population (2.A) and between MPP-AS (MultiPoint™ Pacing—Anatomical separation (≥30 mm)/minimal intraventricular and interventricular timing delays) and BiV in as-treated (2.B) population. The subgroups of left bundle branch block (LBBB), non-LBBB, ischaemic, non-ischaemic, QRS < 150 ms, QRS ≥ 150 ms, NYHA II, NYHA III/IV, LVEF < 25%, LVEF ≥ 25%, LVEDV < median, LVEDV ≥ median, <65 years old and non-ischaemic, ≥65 years old and non-ischaemic, <65 years old and ischaemic, ≥65 years old and ischaemic, pacing > 98% (between implant and 6 months), and pacing > 98% (between implant and 12 months) are included in the analyses.

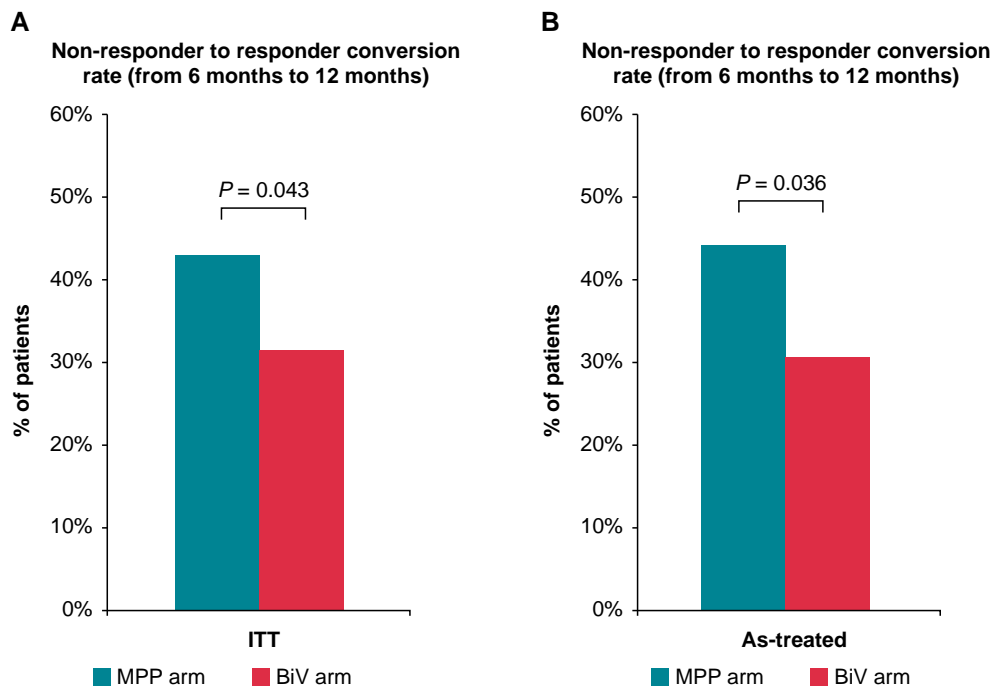


Figure 3 Non-responder to responder conversion rate: subgroup analysis. The graph displays the proportion of patients converted from non-responders at 6 months to responders at 12 months among patients with ventricular pacing > 98% in both intention-to-treat (ITT) (A) and as-treated MultiPoint™ Pacing—Anatomical separation (≥ 30 mm)/minimal intraventricular and interventricular timing delays (MPP-AS) populations (B).

Role of MultiPoint™ Pacing in improving cardiac resynchronization therapy response

The rationale for MPP is that pacing at two different LV sites in the same coronary vein might decrease LV activation time, resulting in an improvement in LV synchrony and contractility. A few non-randomized studies did show that MPP improved clinical outcomes. However, most of these studies had limitations, mainly due to the lack of randomization.^{11,19,20}

The first acute studies did show a significant benefit of MPP on haemodynamic and echocardiographic responses.^{13,16} These very encouraging findings had to be confirmed by long-term clinical and echocardiographic evaluation. The MPP IDE study showed that MPP was not superior to BiVP in CRT response as measured by the clinical composite score.²⁴ However, MPP-AS programming was suggested to have a better outcome than MPP-Other programming with a non-responder to responder conversion rate of 100% compared to 49% in the BiV group. Furthermore, this finding was substantiated by dichotomizing patients based on heart size and demonstrated that MPP-AS programming in patients with a larger heart had a significantly higher responder rate compared to BiV (92% in MPP-AS vs. 65% in BiV, $P=0.023$), but the difference was not significant when patient's heart size is smaller (79% in MPP-AS vs. 79% in BiV, $P=1.000$).²⁵ Phase 1 of the MORE CRT MPP trial also showed a non-significant benefit in the echocardiographic conversion rate from non-responder to responder in the overall population but with the same trend in increased conversion with MPP-AS (45.6% MPP-AS vs. 33.8% BiV, $P=0.102$) and with a significant difference between MPP-AS and MPP-Other (45.6% MPP-AS vs. 26.2% MPP-Other, $P=0.006$).²¹ These observations led to Phase 2 of the MORE-CRT MPP trial, comparing MPP-AS with BiVP, but we failed to show any advantage of MPP-AS except in the subgroup of patients with >98% ventricular pacing (with all the caveats of subgroup analysis).

The recent non-randomized SMART-MSP trial showed that using the clinical composite score (CCS), the conversion rate was 51.3%. However, the main limitation of this study was the lack of a control arm, and improvement may have simply been related to the delayed response, as we have found in both groups in our study.^{26,27} Interestingly, the best response was observed in patients with Multisite Pacing (MSP) involving the proximal LV electrode.

Probability of cardiac resynchronization therapy response as a function of biventricular pacing percentage

Cardiac resynchronization therapy requires steady, effective capture of the LV. Even small decrements in pacing percentage can reduce CRT benefits.²⁸ In our study, the patients with ventricular pacing rate > 98% seem to benefit more from MPP than from conventional BiVP, where therapy was delivered as intended for the entire duration of the study from implant to 12 months. These findings are in concordance with those of Hayes *et al.*²⁹ who demonstrated with a large cohort of ~37 000 patients the importance of a high pacing rate with a significant reduction in mortality achieved with BiVP > 98%. There is no inordinate amount of pacing percentage in CRT—which should be as close as possible to 100%, and a complete resynchronization with substantially high pacing percentage results in improved echocardiographic reverse remodelling, reduced heart failure hospitalization, and/or all-cause mortality.^{30–32}

Limitations associated with MultiPoint™ Pacing programming

The high rate of the inability of programming MPP-AS (i.e. ≥ 30 mm separation and minimal timing delays, required per protocol) was

observed in Phase II of the trial and was due to the following reasons: (i) the original Quartet lead has 20-10-17 mm inter-electrode spacing making it mandatory to use the distal electrode (i.e. D1) to achieve at least 30 mm distance between two electrodes. The new generation of a Quartet lead with an interelectrode spacing of up to 60 mm allows more programming options for anatomical separation. (ii) MPP programming, using multiple LV vectors, could be limited partly because of high pacing thresholds and/or phrenic nerve stimulation, which explains the lower than expected rate of MPP-AS programming in the trial.

Impact on battery longevity

If MPP were turned on for the whole duration of the device, the impact on battery longevity would be significant: estimated at 0.9 years, an 11% drop on an 8-year device. This is comparable to what was reported in the MSP study; they projected a decrease of 9.8 months (0.8 years).²⁹ With the relatively shorter device lifespan, the absence of benefits demonstrated in our trial contradicts using this feature in all non-responder patients, with the possible exception of those patients for whom a very high % of ventricular pacing (>98%) can be guaranteed.

Limitations

Our trial has some limitations. First, the trial was prematurely closed because a pre-specified interim analysis showed a low probability of the study meeting the primary endpoint. Second, there was no requirement for device programming other than MPP/MPP-AS or BiVP. Especially, atrioventricular (AV) delay was left to the physician's discretion. Our results may have differed had AV optimization with fusion pacing with and without MPP being considered.^{33,34} Third, CRT responders during the first 6 months who were withdrawn from the trial may have become non-responders during the following 6 months, which may neutralize the effect of the supposed late remodelling. Fourth, the analysis populations were limited to randomized patients who were echocardiographic non-responders, confirmed by the echocardiography core laboratory, at 6 months compared to baseline, and had evaluable endpoint data at 12 months. The effect of selection bias on patients with evaluable data cannot be excluded. Fifth, the two-dimensional echocardiographic evaluation of LVESV has limited reproducibility and may have confounded the results. Sixth, the CRT pacing percentage recorded by the device may not reflect consistent capture.²⁸ Lastly, phase II was a continuation of phase I, where the comparison of MPP-AS to BiVP was not a pre-specified endpoint, which might introduce a bias when the patients from both phases merged for the purpose of analysing the endpoints.

Conclusions

The MORE-CRT MPP study failed to provide a better conversion rate of non-responders compared to BiVP, defined by reverse LV remodelling (LVESV). The conversion rate was approximately 30% in both groups. Due to the negative impact on device longevity, our data do not support using MPP in non-responders in general. However, MPP could be considered an alternative in the sub-group of patients who fare poorly with BiVP and for whom a very high percentage of ventricular pacing (>98%) can be achieved.

Clinical perspectives

In echocardiographic non-responders after 6 months of BiVP, MPP providing two pacing pulses in the LV with a large anatomical separation through a quadripolar lead did not improve the LVESV as compared to BiVP during the next 6 months. It is not recommended to use

MPP systematically in patients who do not respond to CRT. However, it has been observed that MPP could be beneficial for CRT non-responders who have a considerable amount of ventricular pacing (>98%). Enhanced monitoring through device programming and optimizing medication regimens could effectively help in keeping patients within the upper range of ventricular pacing. Continuous dynamic optimization and effective LV pacing could help achieve BiVP close to 100%.^{17,33,35}

In patients receiving CRT with BiVP, the response to BiVP may be delayed over 6 months, 30% of patients who were not responders at 6 months became responders during the following 6 months.

Supplementary material

Supplementary material is available at *Europace* online.

Funding

This study is sponsored by Abbott (ClinicalTrials.gov Identifier: NCT02006069)

Conflict of interest: Dr. Leclercq has received honoraria from Abbott, Medtronic, Boston Scientific, Biotronik, and Livanova. Dr. Burri has received institutional fellowship support and research grants from Abbott. Dr. Delnoy serves as a consultant to Abbott. Dr. Rinaldi has received research grants and honoraria from Abbott. Dr. Sperzel serves as a consultant to Abbott, in addition to receiving honoraria and currently conducting research sponsored by Abbott. Dr. Calò has none declared. Dr. Joaquin Fernandez Concha serves as a consultant to Abbott, Dr. Antonio Fusco has nothing to disclose. Dr. Faisal Al Samadi has received honoraria from Abbott, Medtronic, and Boston Scientific. Dr. Lee is an employee of Abbott. Dr. Thibault has received research support and honoraria from Abbott and Medtronic.

Data availability

All relevant data are within the manuscript and its Supporting Information files.

References

1. Glikson M, Nielsen JC, Kronborg MB, Michowitz Y, Auricchio A, Barbash IM et al. Corrigendum to: 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: developed by the task force on cardiac pacing and cardiac resynchronization therapy of the European Society of Cardiology (ESC): with the special contribution of the European Heart Rhythm Association (EHRA). *Europace* 2022;**24**:699.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;**37**:2129–200.
3. Kamdar R, Frain E, Warburton F, Richmond L, Mullan V, Berriman T et al. A prospective comparison of echocardiography and device algorithms for atrioventricular and inter-ventricular interval optimization in cardiac resynchronization therapy. *Europace* 2010; **12**:84–91.
4. Kronborg MB, Albertsen AE, Nielsen JC, Mortensen PT. Long-term clinical outcome and left ventricular lead position in cardiac resynchronization therapy. *Europace* 2009; **11**:1177–82.
5. Macias A, Gavira JJ, Alegria E, Azcarate PM, Barba J, Garcia-Bolao I. [Effect of the left ventricular pacing site on echocardiographic parameters of ventricular dyssynchrony in patients receiving cardiac resynchronization therapy]. *Rev Esp Cardiol* 2004;**57**: 138–45.
6. Gasparini M, Mantica M, Galimberti P, Bocciolone M, Genovese L, Mangiacavchi M et al. Is the left ventricular lateral wall the best lead implantation site for cardiac resynchronization therapy? *Pacing Clin Electrophysiol* 2003;**26**:162–8.
7. Aktaa S, Abdin A, Arbelo E, Burri H, Vernooij K, Blomstrom-Lundqvist C et al. European Society of Cardiology Quality Indicators for the care and outcomes of cardiac pacing: developed by the Working Group for Cardiac Pacing Quality Indicators in collaboration with the European Heart Rhythm Association of the European Society of Cardiology. *Europace* 2022;**24**:165–72.
8. Ansalone G, Giannantonio P, Ricci R, Trambaiolo P, Fedele F, Santini M. Doppler myocardial imaging to evaluate the effectiveness of pacing sites in patients receiving biventricular pacing. *J Am Coll Cardiol* 2002;**39**:489–99.

9. Chalil S, Stegemann B, Muhyaldeen SA, Khadjooi K, Foley PW, Smith RE *et al.* Effect of posterolateral left ventricular scar on mortality and morbidity following cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2007;**30**:1201–9.
10. Ypenburg C, Schalij MJ, Bleeker GB, Steendijk P, Boersma E, Dibbets-Schneider P *et al.* Impact of viability and scar tissue on response to cardiac resynchronization therapy in ischaemic heart failure patients. *Eur Heart J* 2007;**28**:33–41.
11. Forleo GB, Santini L, Giammaria M, Potenza D, Curnis A, Calabrese V *et al.* Multipoint pacing via a quadripolar left-ventricular lead: preliminary results from the Italian registry on multipoint left-ventricular pacing in cardiac resynchronization therapy (IRON-MPP). *Europace* 2017;**19**:1170–7.
12. Gutleben KJ, Kranig W, Barr C, Morgenstern MM, Simon M, Lee K. Multisite left ventricular pacing is safe and improves cardiac hemodynamic in heart failure patients—results from a 1-month follow-up study. *Heart Rhythm* 2013;**5**:S134–68.
13. Pappone C, Calovic Z, Vicedomini G, Cuko A, McSpadden LC, Ryu K *et al.* Multipoint left ventricular pacing improves acute hemodynamic response assessed with pressure-volume loops in cardiac resynchronization therapy patients. *Heart Rhythm* 2014;**11**:394–401.
14. Rinaldi CA, Kranig W, Leclercq C, Kacet S, Betts T, Bordachar P *et al.* Acute effects of multisite left ventricular pacing on mechanical dyssynchrony in patients receiving cardiac resynchronization therapy. *J Card Fail* 2013;**19**:731–8.
15. Rinaldi CA, Leclercq C, Kranig W, Kacet S, Betts T, Bordachar P *et al.* Improvement in acute contractility and hemodynamics with multipoint pacing via a left ventricular quadripolar pacing lead. *J Interv Card Electrophysiol* 2014;**40**:75–80.
16. Thibault B, Dubuc M, Khairy P, Guerra PG, Macle L, Rivard L *et al.* Acute haemodynamic comparison of multisite and biventricular pacing with a quadripolar left ventricular lead. *Europace* 2013;**15**:984–91.
17. Waddingham PH, Mangual JO, Orini M, Badie N, Muthumala A, Sporton S *et al.* Electrocardiographic imaging demonstrates electrical synchrony improvement by dynamic atrioventricular delays in patients with left bundle branch block and preserved atrioventricular conduction. *Europace* 2023;**25**:536–45.
18. van Everdingen WM, Zweerink A, Salden OAE, Cramer MJ, Doevendans PA, van Rossum AC *et al.* Atrioventricular optimization in cardiac resynchronization therapy with quadripolar leads: should we optimize every pacing configuration including multipoint pacing? *Europace* 2019;**21**:e11–9.
19. Pappone C, Calovic Z, Vicedomini G, Cuko A, McSpadden LC, Ryu K *et al.* Multipoint left ventricular pacing in a single coronary sinus branch improves mid-term echocardiographic and clinical response to cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2015;**26**:58–63.
20. Zanon F, Marcantoni L, Baracca E, Pastore G, Lanza D, Fracarro C *et al.* Optimization of left ventricular pacing site plus multipoint pacing improves remodeling and clinical response to cardiac resynchronization therapy at 1 year. *Heart Rhythm* 2016;**13**:1644–51.
21. Leclercq C, Burri H, Curnis A, Delnoy PP, Rinaldi CA, Sperzel J *et al.* Cardiac resynchronization therapy non-responder to responder conversion rate in the more response to cardiac resynchronization therapy with MultiPoint Pacing (MORE-CRT MPP) study: results from Phase I. *Eur Heart J* 2019;**40**:2979–87.
22. Leclercq C, Burri H, Curnis A, Delnoy PP, Rinaldi CA, Sperzel J *et al.* 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). *Am Heart J* 2019;**209**:1–8.
23. Sieniewicz BJ, Gould J, Porter B, Sidhu BS, Teall T, Webb J *et al.* Understanding non-response to cardiac resynchronization therapy: common problems and potential solutions. *Heart Fail Rev* 2019;**24**:41–54.
24. Niazi I, Baker J II, Corbisiero R, Love C, Martin D, Sheppard R *et al.* Safety and efficacy of multipoint pacing in cardiac resynchronization therapy: the MultiPoint Pacing trial. *JACC Clin Electrophysiol* 2017;**3**:1510–8.
25. Varma N, Baker J II, Tomassoni G, Love CJ, Martin D, Sheppard R *et al.* Left ventricular enlargement, cardiac resynchronization therapy efficacy, and impact of MultiPoint Pacing. *Circ Arrhythm Electrophysiol* 2020;**13**:e008680.
26. Saba S, Nair D, Ellis CR, Ciuffo A, Cox M, Gupta N *et al.* Usefulness of multisite ventricular pacing in nonresponders to cardiac resynchronization therapy. *Am J Cardiol* 2022;**164**:86–92.
27. Mehta VS, Elliott MK, Wijesuriya N, Niederer S, Rinaldi CA. Reply to usefulness of multisite ventricular pacing in nonresponders to cardiac resynchronization therapy. *Am J Cardiol* 2022;**169**:158.
28. Varma N, Stadler RW, Ghosh S, Kloppe A. Influence of automatic frequent pace-timing adjustments on effective left ventricular pacing during cardiac resynchronization therapy. *Europace* 2017;**19**:831–7.
29. Hayes DL, Boehmer JP, Day JD, Gilliam FR III, Heidenreich PA, Seth M *et al.* Cardiac resynchronization therapy and the relationship of percent biventricular pacing to symptoms and survival. *Heart Rhythm* 2011;**8**:1469–75.
30. Daubert JC, Saxon L, Adamson PB, Auricchio A, Berger RD, Beshai JF *et al.* 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. *Heart Rhythm* 2012;**9**:1524–76.
31. Ruwald AC, Kutyla V, Ruwald MH, Solomon S, Daubert JP, Jons C *et al.* The association between biventricular pacing and cardiac resynchronization therapy-defibrillator efficacy when compared with implantable cardioverter defibrillator on outcomes and reverse remodelling. *Eur Heart J* 2015;**36**:440–8.
32. Ruwald MH, Mittal S, Ruwald AC, Aktas MK, Daubert JP, McNitt S *et al.* Association between frequency of atrial and ventricular ectopic beats and biventricular pacing percentage and outcomes in patients with cardiac resynchronization therapy. *J Am Coll Cardiol* 2014;**64**:971–81.
33. Thibault B, Ritter P, Bode K, Calo L, Mondesert B, Mangual JO *et al.* Dynamic programming of atrioventricular delay improves electrical synchrony in a multicenter cardiac resynchronization therapy study. *Heart Rhythm* 2019;**16**:1047–56.
34. Trucco E, Tolosana JM, Arbelo E, Doltra A, Castel MA, Benito E *et al.* Improvement of reverse remodeling using electrocardiogram fusion-optimized intervals in cardiac resynchronization therapy: a randomized study. *JACC Clin Electrophysiol* 2018;**4**:181–9.
35. Varma N, O'Donnell D, Bassiouny M, Ritter P, Pappone C, Mangual J *et al.* Programming cardiac resynchronization therapy for electrical synchrony: reaching beyond left bundle branch block and left ventricular activation delay. *J Am Heart Assoc* 2018;**7**:e007489.