Multipoint pacing for cardiac resynchronisation therapy in patients with heart failure: A systematic review and meta-analysis

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Abstract
Introduction: Multipoint pacing (MPP) has been proposed as an effective way to improve cardiac resynchronisation therapy (CRT) response. We performed a systematic review and meta-analysis evaluating the efficacy of CRT delivered via MPP compared to conventional CRT.

Methods: A literature search was performed from inception to January 2021 for studies in Medline, Embase and Cochrane databases, comparing MPP to conventional CRT with a minimum of 6 months follow-up. Randomised and nonrandomised studies were assessed for relevant efficacy data including echocardiographic (left ventricular end systolic volume [LVESV] and ejection fraction) or functional changes (New York Heart Association [NYHA] class/Clinical Composite Score). Subgroup analyses were performed by study design and programming type.

Results: A total of 7 studies with a total of 1390 patients were included in the final analysis. Overall, MPP demonstrated greater echocardiographic improvement than conventional CRT in nonrandomised studies (odds ratio [OR]: 5.33, 95% confidence interval [CI]: [3.05–9.33], \( p < .001 \)), however, was not significant in randomised studies (OR: 1.86, 95% CI: [0.91–3.79], \( p = .086 \)). There was no significant difference in LVESV reduction >15% (OR: 1.96, 95% CI: [0.69–5.55], \( p = .20 \)) or improvement by ≥1 NYHA class (OR: 2.49, 95% CI: [0.74–8.42], \( p = .141 \)) when comparing MPP to conventional CRT. In a sub analysis, MPP programmed by widest anatomical separation (MPP-AS) signalled greater efficacy, however, only 120 patients were included in this analysis.

Conclusion: Overall MPP was more efficacious in nonrandomised studies, and not superior when assessed in randomised studies. There was considerable heterogeneity in study design making overall interpretation of results challenging. Widespread MPP programming in all CRT patients is currently not justified. Further large, randomised studies with patient-specific programming may clarify its effectiveness.
1 | INTRODUCTION

Cardiac resynchronisation therapy (CRT) is an effective treatment for patients with heart failure (HF) and electrical dyssynchrony characterised by left bundle branch block (LBBB), however, between 30% and 50% fail to respond. CRT nonresponse is multifactorial, however, placement of the left ventricle (LV) pacing lead away from scar may play a significant role in determining response.\(^1\) Multipoint pacing (MPP) is achieved when multiple pacing stimuli are delivered via a single quadripolar lead placed in a branch of the coronary sinus to achieve CRT.\(^2\) Early feasibility and single-centre studies demonstrated positive results with improvements in acute and short-term measures of dyssynchrony and haemodynamic response.\(^3\)–\(^5\) Determining efficacy of MPP is essential as this technology has been demonstrated to reduce battery longevity.\(^6\) Small randomised studies,\(^7\) and a nonrandomised prospective registry\(^8\) has demonstrated significant symptomatic and echocardiographic improvements when comparing MPP to conventional CRT. Subsequently the MPP trial by Niazi et al.\(^9\) demonstrated noninferiority of MPP to conventional CRT with significant benefit in a nonspecified subgroup analysis of maximally separated programming (MPP-AS). More recently, the MORE-CRT MPP study by Leclercq et al.,\(^10\) failed to demonstrate benefit of MPP compared to CRT in terms of volumetric response, however, it did show improvement in a nonprespecified subgroup with MPP-AS programming. A prior meta-analysis evaluating MPP included 11 studies and concluded that MPP reduced HF hospitalisation (odds ratio [OR]: 0.41, 95% confidence interval [CI]: [0.33–0.5], \(p < .001\)), increased CRT response (OR: 3.64, 95% CI: [1.68–7.87], \(p < .001\)) and decreased cardiovascular mortality (OR: 0.21, 95% CI: [0.11–0.4], \(p < .001\)).\(^11\) The authors concluded that MPP was more effective than standard CRT, however the meta-analysis included studies which did not only employ MPP, but rather the effects of single site stimulation from a quadripolar lead. Since this prior metaanalysis, two further major randomised trials evaluating MPP have been published\(^12\)–\(^10\) and a meta-analysis incorporating the data from these randomised trials is needed to evaluate the utility of this treatment.

2 | METHODS

2.1 | Literature search

The systematic review and meta-analysis were conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for all stages of the design and implementation (see Table S1).\(^12\) We systematically reviewed the relevant literature, comparing MPP to conventional CRT, by searching EMBASE, CENTRAL, and MEDLINE databases from inception to January 2021 without language restriction. The Quality of Reporting of Meta-Analyses statement\(^13\) and the empiric study by McAuley\(^14\) indicate the exclusion of unpublished studies produces a systematic positive bias, and therefore “grey literature” in the form of poster presentations, unpublished data from Cochrane reviews or other meta-analyses, conference abstracts and preprints were included. In addition, references of review articles, meeting abstracts, pre-prints, letters, editorials, and previous meta-analyses were searched. The robustness of the decision to include “grey literature” in the final analysis will be tested by a sensitivity analysis. The following keywords were used for search: “multipoint pacing” OR “multipoint left ventricular pacing” OR “Multi-point pacing” OR “multi-point left ventricular pacing” OR “MPP pacing.”

2.2 | Selection criteria

We included all eligible studies that met the following inclusion criteria: (i) CRT-Pacemaker/Defibrillator (CRT-P/D), (ii) MPP (defined as two or more pacing sites from a single quadripolar lead) versus control group (i.e., conventional CRT), (iii) human studies only, (iv) minimum of 6 months mean follow-up. We excluded studies that only assessed acute haemodynamic and/or electrical metrics. For each included study, data of the following efficacy endpoints were used and evaluated: (i) echocardiographic volumetric response (change in ejection fraction (EF) or left ventricular end systolic volume [LVESV]), and symptomatic response (change in New York Heart Association [NYHA] class or Clinical Composite Score [CCS]). Observational and randomised trials were included.

2.3 | Data extraction

All data from included studies were independently extracted and assessed for further analysis by two reviewers (CAR and VSM). Any discrepancies were resolved through a third reviewer (MKE). From each study, relevant information regarding reported baseline patient characteristics (age, aetiology of HF, QRS duration), follow-up time, and baseline prespecified efficacy endpoints (LVEF, LVESV) were extracted and tabulated. Characteristics of studies, including study design, number of patients included in the analysis, inclusion criteria, primary and secondary efficacy endpoints, and MPP configuration, are reported. MPP configuration was defined as: (i) MPP-AS: study participants programmed to anatomically separated MPP, (ii) MPP-Other: study participants programmed by implant preference, (iii) MPP-Mixed: study participants programmed to either MPP-AS or MPP-Other.
| Author, year | Trial registration number | Study design | Period of active run-in (months) | Total included in analysis (n) | Notable inclusion criteria | CRT device and LV lead implanted | Primary efficacy end point | Secondary efficacy endpoint | Final MPP Programme (MPP-AS/MPP-Other/MPP-Mixed) |
|--------------|---------------------------|-------------|---------------------------------|-----------------------------|---------------------------|-------------------------------|---------------------------|-------------------------------|------------------------------------------|
| Papone et al. (2015) | NCT01564186 | Parallel RCT (with active run-in) | 3 | 42 | CRT implant as per ESC/EHRA guidelines | CRT Device: Unify Quadra MP™ or Quadra Assura MP™, SJM | Reduction in LVEF >15% | -LVEF (absolute & relative change) | MPP-Other |
| Zanon et al. (2016) | NR | Retrospective observational registry | NA | 74 | CRT Implant as per ESC/EHRA guidelines | CRT Device: Quadra Assura MP™, SJM | Reduction in LVEF >15% | -ESVI (absolute) | MPP-Other |
| Forteo et al. (2016) | NCT02606071 | Prospective observational registry | NA | 232 | Any patient following CRT-D implant | CRT Device: Unify Quadra MP™ or Quadra Assura MP™, SJM | Clinical Composite Score (Death, hospitalization for HF, increase in NYHA class) | -Increase in LVEF >5% | MPP-Other |
| Niazi et al. (2017) | NCT01786993 | Parallel RCT (with active run-in) | 3 | 381 | De novo CRT-D incl. upgrades | CRT Device: Quadra MP™ CRT-D, SJM | Clinical Composite Score (All-cause mortality, HF-related hospitalization, NYHA class, Patient Global Assessment (PGA) score) | -Nil | MPP-Mixed (MPP-AS & MPP-Other) |
| Leclercq et al. (2019) | NCT02006069 | Parallel RCT (with active run-in) | 6 | 467 | CRT implant as per ESC/EHRA guidelines | CRT Device: Quadra Assura MP™, SJM | Reduction in LVEF >15% | -LVEF (absolute & relative) | MPP-Mixed (MPP-AS & MPP-Other) |

(Continues)
| Author, year | Trial registration number | Study design | Period of active run-in (months) | Total included in analysis (n) | Notable inclusion criteria | CRT device and LV lead implanted | Primary efficacy end point | Secondary efficacy endpoint |
|-------------|--------------------------|--------------|---------------------------------|-------------------------------|---------------------------|-------------------------------|-----------------------------|-----------------------------|
| AlMusaad et al. (2020) | NR | Parallel RCT (without active run-in) | NA | 142 | De Novo CRT-D LBBB | CRT Device: Unify Quadra MP™ or Quadra Assura MP™, SJM | LV lead: | Final MPP Programme (MPP-AS/MPP-Other/MPP-Mixed) |
|             |              |              |                                |                              |                           | Quartet™ quadripolar lead, SJM | Reduction in LVESV >15% | -HF events per 100 patient years |
|             |              |              |                                |                              |                           |                             |                             |                             |
| Ferreira et al. (2020) | NR | Parallel RCT (with active run-in) | 6 | 52 | NR | CRT Device: NR LV Lead: | Quartet™ quadripolar lead, SJM | Reduction in LVESV >30% | Final MPP Programme (MPP-AS) |
|             |              |              |                                |                              |                           |                             | -LVESV (absolute & relative) | -LVEF (absolute & relative) |
|             |              |              |                                |                              |                           |                             | -QoL – ESQD, MLWHF, 6MWT | -NT-Pro BNP |

Abbreviations: AF, atrial fibrillation; CRT, cardiac resynchronisation therapy; EHRA, European Heart Rhythm Association; ESQD, EuroQol; ESC, European Society of Cardiology; HF, heart failure; LBBB, left bundle branch block; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV(i), left ventricular end systolic volume (indexed); MLWHF, Minnesota Living with Heart Failure; MPP, multipoint pacing; 6MWT, six minute walk test; NA, not applicable; NR, not recorded; NT-Pro BNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Failure; QoL, Quality of Life; QRSd, QRS duration; RCT, randomised controlled trial; SJM, St Jude Medical/Abbott.
TABLE 2  Baseline characteristics of participants included by study

| Author, year               | Age (years) | Ischaemic aetiology (%) | Male (%) | LVEF (%) | LVESV (ml) | LBBB (%) | QRSd (ms) | Follow-up (months) |
|----------------------------|-------------|--------------------------|----------|----------|------------|----------|----------|-------------------|
| Papone et al. (2015)       | 67 ± 8      | 36.0                     | 55.0     | 73.0     | 86.0       | 30 ± 6   | 28 ± 5   | 170 ± 104/177 ± 56 |
| Zanon et al. (2016)        | 69.7 ± 10.4 | 50.0                     | 80.5     | 27.2 ± 4.3| 76.6 ± 25.4| 61.1     | NR       | 26.5 ± 23.4 |
| Forleo et al. (2016)       | 71.0 ± 10.0 | 47.0                     | 81.0     | 28.1 ± 6.0| 72.9 ± 28.2| 78.0     | 71.0     | 157 ± 23/164 ± 3   |
| Niazi et al. (2017)        | 68 ± 10     | 48.9                     | 64.8     | NR       | NR         | 77.2     | 73.4     | 158 ± 24/9.0 |
| Leclercq et al. (2019)     | 68 ± 10     | 51.5                     | 79.7     | 26 ± 8   | 26 ± 8     | 65.1     | 68.4     | 156 ± 25/157 ± 25  |
| Al-Musaad et al. (2020)    | 59 (IQR: 52.1–67.0) | 30.4         | 35.6     | 25.7 (IQR: 21.7–32.5) | 140 (IQR: 102–191) | 100.0    | 158 (IQR: 100–170) | 6.0/6.0 |
| Ferreira et al. (2020)     | NR          | NR                      | NR       | NR       | NR         | NR       | NR       | 12.0/12.0 |

Abbreviations: IQR, interquartile range; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; NR, not recorded; QRSd, QRS duration.

LVESV is recorded as ml/m².
2.4 **Data synthesis, sensitivity, and statistical analysis**

Intention-to-treat data were used for evaluating clinical endpoints from included studies whenever possible. It was anticipated that there would be considerable variation in the efficacy endpoints reported, therefore an echo volumetric endpoint (either reduction in LVEF >15% or increase in LVEF >5%) and clinical improvement endpoint (either CCS or NYHA class improvement by 1) was considered. The OR and respective 95% CIs were computed for categorical variables (study pooled echo volumetric and clinical endpoints, reduction in LVEF >15%, and improvement in NYHA class or CCS) and as appropriate, the standardised mean distance (SMD) and respective 95% CIs were computed for continuous variables (LVEF, LVESV). As an aid to interpretation of the results, we conducted a sensitivity analysis to assess the role that inclusion of “grey literature” had on observed results and to evaluate the robustness of the inclusion criteria. To estimate prespecified efficacy endpoints of continuous data, only those publications that contained both baseline and follow-up means ± SDs were used. Significant heterogeneity was expected, and so a random effects meta-analytical approach was applied to all analyses. Heterogeneity was assessed by calculating $I^2$ and $R^2$, and was considered low, moderate, and high for $R^2$ values of <30%, 30%–60% and >60%, respectively. Sub-group analysis according to the study design and MPP pacing configuration versus conventional CRT was performed. Analyses were performed using R version 1.3.1093 with the “metafor” package. A significance level of 0.05 was used for testing and confidence intervals, and all testing was two-tailed. Risk of bias for the individual studies was performed with the Cochrane Risk of Bias 2 tool and presented graphically. As less than 10 studies were included in the final analysis, no test for funnel plot asymmetry was performed.

### RESULTS

A total of 203 unique records were identified through the database and bibliographic searches. Of these, 151 were excluded based on title and abstract content. After screening the full texts of the remaining 52 articles, 7 met inclusion criteria (Figure S1). A total of 5 randomised controlled trials (3 multicentre) were included, of which 3 had an active run-in period of conventional CRT for a period of at least 3 months, and 2 did not. A total of 2 were observational registry analyses, of which 1 was prospective, and 1 was retrospective. A total of 5 were fully published results, 1 was an abstract, and 1 was a full-text preprint of an earlier published abstract (Table 1). In total 1390 patients were included in the final analysis (669 undergoing MPP, and 721 undergoing conventional CRT). In the MPP programming sub-analysis, 519 patients were included (217 undergoing MPP-AS, 205 undergoing MPP-Other, and 97 undergoing conventional CRT). All patients had either a Unify Quadra MP™ or Quadra Assura MP™ (St Jude Medical) CRT device implanted alongside a Quartet™ quadripolar LV lead (St Jude Medical). Mean follow-up ranged between 6 and 26.5 months (Table 1). Baseline

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**TABLE 1** | **Outcome** | **OR (95% CI)** | **Favours Control** | **Favours Treatment**
---|---|---|---

**A**

| Source | OR (95% CI) | Favours Control | Favours Treatment |
|---|---|---|---|
| Papone et al, 2015 | 2.40 [0.64; 9.03] | | |
| Zanon et al, 2016 | 7.20 [1.52; 34.14] | | |
| Forleo et al, 2016 | 5.10 [2.80; 9.29] | | |
| Leclercq et al, 2019 | 0.91 [0.62; 1.34] | | |
| AlMusaad et al, 2020 | 2.11 [1.07; 4.18] | | |
| Ferreira et al, 2020 | 4.64 [1.40; 15.32] | | |
| Total (fixed effect) | 1.88 [1.45; 2.44] | | |
| Total (random effects) | 2.70 [1.38; 5.30] | | |
| 95% PI | [0.32; 23.13] | | |
| Heterogeneity: $I^2 = 29.30$ ($P < .001$), $R^2 = 83$

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**B**

| Source | OR (95% CI) | Favours Control | Favours Treatment |
|---|---|---|---|
| Papone et al, 2015 | 0.56 [0.08; 3.79] | | |
| Zanon et al, 2016 | 6.19 [1.30; 29.40] | | |
| Forleo et al, 2016 | 3.88 [2.22; 6.76] | | |
| Niazi et al, 2017 | 0.78 [0.50; 1.23] | | |
| AlMusaad et al, 2020 | 2.88 [1.35; 6.12] | | |
| Total (fixed effect) | 1.73 [1.29; 2.32] | | |
| Total (random effects) | 2.04 [0.89; 4.71] | | |
| 95% PI | [0.11; 36.54] | | |
| Heterogeneity: $I^2 = 25.50$ ($P < .001$), $R^2 = 84$
characteristics of study participants are reported in Table 2. Graphical risk of bias assessment is reported (Figure S2).

3.1  Primary efficacy endpoint and study design sub-analysis

Overall, MPP was found to be more effective than conventional CRT (OR 2.70, 95% CI: [1.38–5.30], p = .004; I² = 83%) of achieving an echocardiographic improvement, and only trended towards significance of achieving functional improvement (OR: 2.40, 95% CI: [0.89–4.71], p = .19; I² = 37%) (Figure 1). Sub-group analyses with regards to echocardiographic response were performed by study design: (i) randomised versus nonrandomised, and (ii) with active run-in versus without active run-in (Figure 2). MPP was effective in the nonrandomised analysis [OR: 5.33, 95% CI: [3.05–9.33], p < .001; I² = 0%] and not-effective in the randomised analysis [OR: 1.86, 95% CI: [0.91–3.79], p = .086; I² = 71%]. 3 studies had an active run-in of at least 3 months with conventional CRT before randomisation9,10,20 of which 1 study by Leclerq et al.,10 only randomised CRT non-responders after 6 months. Studies with an active run-in demonstrated no significant difference in efficacy of MPP [OR: 1.86, 95% CI: [0.38–9.01], p = .442; I² = 84%] whereas those without an active run-in did demonstrate MPP efficacy (OR: 3.50, 95% CI: [1.85–6.28], p < .001; I² = 37%).

3.2  Sub-analysis by programming type

A sub-analysis was performed of studies depending on type of MPP programming (as defined above), in the participants randomised to MPP vs conventional CRT. Two studies compared MPP-AS only,20,22 and two compared a combined cohort of MPP programming (MPP-Mixed).9,10 to conventional CRT. Three studies did not specify degree of final programming separation (MPP-Other).7,8,19 Of those, Zanon et al.19 optimised MPP
Subgroup

MPP–AS
AlMusaad et al, 2020
Ferreira et al, 2020
Random effects model
$\chi^2 = 2.58$ ($P = .26$), $I^2 = 20$

MPP–Mixed
Leclerq et al, 2019
Random effects model
not applicable

MPP–Other
Papone et al, 2015
Zanon et al, 2016
Forleo et al, 2016
Random effects model
$\chi^2 = 1.35$ ($P = .51$), $I^2 = 0$ [0%; 85%]
Fixed effects (plural) model

# Table 3

| Author, year | Efficacy endpoint evaluated | No. of MPP-AS patients | No. of MPP-other patients | OR (95% CI) | p value |
|--------------|----------------------------|------------------------|---------------------------|-------------|---------|
| Niazi et al. (2017) | CCS improvement by >1 | 52 | 37 | 6.79 (2.44–18.90) | <.001 |
| Leclerq et al. (2019) | Reduction in LVESV >15% | 68 | 168 | 2.36 (1.31–4.25) | .004 |

Abbreviations: CCS, clinical composite score; CI, confidence interval; LVESV, left ventricular end systolic volume; OR, odds ratio.

(A)

| Source         | OR (95% CI)     |
|----------------|-----------------|
| Zanon et al, 2016 | 7.20 [1.52; 34.14] |
| Leclerq et al, 2019 | 0.91 [0.62; 1.34] |
| AlMusaad et al, 2020 | 2.11 [1.07; 4.18] |
| Total (fixed effect) | 1.27 [0.92; 1.75] |
| Total (random effects) | 1.96 [0.69; 5.55] |
| 95% PI           | [0.00; 401213.89] |
| Heterogeneity: $\chi^2 = 9.62$ ($P = .008$), $I^2 = 79$%

(B)

| Source         | SMD (95% CI)     |
|----------------|-----------------|
| Papone et al, 2015 | -0.13 [-0.74; 0.47] |
| Zanon et al, 2016 | -0.08 [-0.60; 0.43] |
| Leclerq et al, 2019 | -0.06 [-0.24; 0.13] |
| Ferreira et al, 2020 | -0.29 [-0.84; 0.25] |
| Total (fixed effect) | -0.08 [-0.24; 0.07] |
| Total (random effects) | -0.08 [-0.24; 0.07] |
| 95% PI           | [-0.43; 0.26] |
| Heterogeneity: $\chi^2 = 0.69$ ($P = .88$), $I^2 = 0$%
programming by pressure-volume haemodynamic measurements, and Forleo et al.\textsuperscript{8} by seven different methods. Of the studies evaluating MPP-AS mixed programming when compared to conventional CRT, Niazi et al.\textsuperscript{9} reported no clinical improvement (OR: 0.78, 95% CI: [0.50–1.23], p = .291) and Leclercq et al. reported no echocardiographic improvement (OR: 0.91, 95% CI: [0.62–1.34], p = .647) (Figure 3). A further sub analysis was performed of studies where efficacy of MPP-AS was compared to MPP-Other. Niazi et al provided an improvement in CCS as an endpoint when comparing MPP-AS to MPP-Other, and MPP-AS was more efficacious (OR: 6.79, 95% CI: [2.44–18.90], p < .001). Similarly Leclercq et al.\textsuperscript{10} demonstrated greater efficacy with MPP-AS when evaluating a reduction in LVESV >15% (OR: 2.36, 95% CI: [1.31–4.25], p = .004). However, only 52 and 68 patients were programmed to MPP-AS in these respective studies, representing a small sample size (Table 3).

### 3.3 | Echocardiographic changes

Echo response was reported in different ways in the studies. There was no significant difference at follow-up in absolute LVESV value [SMD: -0.084, 95% CI: [-0.24–0.074], p = .30; I² = 0%] or absolute EF (SMD: 0.22, 95% CI: [-0.32–0.77], p = .42; I² = 75%) when comparing MPP vs conventional CRT in studies that reported these outcomes (Figure 4). Similarly there was no significant difference in LVESV reduction of >15% (OR: 1.96, 95% CI: [0.69–5.55], p = .20; I² = 79%). The number of “super-response” cases, as defined as >30% reduction

### Table 4: Sensitivity analysis based on publication status

| Endpoint                          | Calculation method | Including abstract and preprint (7 studies) | Excluding abstract and preprint (5 studies) |
|-----------------------------------|--------------------|--------------------------------------------|---------------------------------------------|
|                                   | OR (95% CI)        | SMD (95% CI)                               | SMD (95% CI)                               |
| Pooled echocardiographic response | Random effects     | 2.70 (1.38–5.30)                           | 2.70 (1.01–7.20)                           |
| Pooled clinical response          | Random effects     | 2.40 (0.89–4.71)                           | 1.85 (0.62–5.51)                           |
| Reduction in LVESV >15%           | Random effects     | 1.96 (0.69–5.55)                           | 2.22 (0.30–16.48)                          |
| Clinical Composite Score          | Random effects     | 2.42 (0.99–5.90)                           | 2.37 (0.68–8.28)                           |
| Improvement by at ≥1 NYHA class   | Random effects     | 2.49 (0.74–8.42)                           | 2.23 (0.14–35.70)                          |

Abbreviations: CI, confidence interval; OR, odds ratio; SMD, standardised mean difference.
in LVESV following MPP trended towards significance (OR: 2.51, 95% CI: [0.99–6.37], p = .054; I² = 48%).

3.4 | NYHA and CCS change

CCS was defined as per the descriptions for relevant studies in Table 1. There was no significant difference in improvement in NYHA class of ≥1 (OR: 2.49, 95% CI: [0.74–8.42], p = .141; I² = 50%) or improvement in CCS of ≥1 (OR: 2.37, 95% CI: [0.68–8.28], p = .178; I² = 91%) (Figure 5).

3.5 | Sensitivity analysis

In the sensitivity analysis, excluding the abstracts by Al Mussad and Ferreira, resulted in no differences in the odds ratios and significance of results with regards to the prespecified endpoints20,22 (Table 4).

4 | DISCUSSION

The current meta-analysis adds important new data on the role of MPP from a quadripolar lead in the improvement of outcomes of CRT response and represents a critical addition to the literature evaluating the efficacy of MPP. Since the publication of a previous metanalysis by Hu et al there have been two major randomised trials9,10 and two further preliminary randomised studies of MPP efficacy published.20–22 The prior meta-analysis of Hu et al incorporated smaller, non-randomised studies with a high risk of bias. The current analysis demonstrates superiority of MPP over conventional CRT when evaluating both randomised and nonrandomised studies together. Notably, the benefit of MPP is not significant when including randomised studies only. This is an important finding as MPP activation will adversely affect battery life and therefore, there needs to be a robust clinical reason to consider its activation.6 Additionally, not all mechanistic studies have demonstrated benefit with MPP compared to single site optimised LV stimulation.23,24

4.1 | Variability in study design and efficacy outcomes

There was considerable variability and heterogeneity in the studies with differing patient populations and end points that make it difficult to draw firm conclusions as to the therapeutic benefit of MPP. We did not specifically compare the effects of MPP in ischemic and nonischemic patients as there was insufficient data to allow results to be included in the final analysis. Of the studies included, Papone et al identified that ischaemic patients underwent significant improvements in EF, however no improvement at 12 months with respect to LVESV, with MPP compared with conventional CRT, however only 9 patients had ischaemic aetiology. Leclercq et al.10 did not identify any improvement in ischaemic individuals with respect to reduction in LVESV >15% in ischaemic patients (OR: −0.8 [−12.1–10.4]), in a much larger group of 215 patients. Further analysis of this may be important as MPP could be particularly beneficial in this group by avoiding areas of slow conduction or scar.25,26 Likewise, we did not compare the effects in patients with LBBB and non-LBBB conduction disorders due to insufficient sub-group data. In addition, final LV lead position was not universally described in the studies included. Of those that did describe this, Leclercq et al did not identify any significant difference in position between groups (p = .621); and neither did Zanon et al, who identified similar basal and mid lateral LV lead position proportions between groups. Similarly, Papone et al did not identify a significant difference in final LV lead position, however, there was a tendency to more basal LV position in the conventional CRT group (27% vs. 9%, p = .09). MPP was used to treat both CRT naive patients and those patients that had already been identified as CRT nonresponders and this may have confounded the results. To address this there are ongoing multicentre randomised studies which aim to assess the effect of MPP in previously CRT naïve patients that may address this.27

4.2 | MPP programming

The results of the current analysis suggest a signal towards improved response when MPP is programmed with maximal anatomical separation (MPP-AS). It could be argued that the results of MPP may be dependent on programming and that MPP-AS may capturing a wider area of myocardium, and potentially avoiding scar may result in better electrical synchronization and improved outcomes. In keeping with this hypothesis, the two large published randomised studies of Niazi9 and Leclercq10 both found a signal for benefit of MPP-AS. It should, however, be noted that in both cases the sub-groups were neither significant in sample size, prespecified, nor randomised, and therefore, we cannot draw firm conclusions from these findings. Based on the initial findings of phase I of the MORE-CRT MPP, where the widest anatomical spacing was not prespecified but programming was left to the discretion of the implanter,10 phase II of the MORE-CRT MPP study has been undertaken recruiting over 4000 additional patients in whom MPP-AS is the mandated programming.28,29 The results of phase II are not yet available but when published should be able to address the question as to whether MPP-AS results in improved clinical outcomes compared to standard CRT.

4.3 | Clinical perspective

Since their initial introduction, quadripolar leads have revolutionised CRT with initial studies demonstrating reduced PNS and reintervention.30 Subsequent studies have shown cost effectiveness31 and mortality benefit,22 and as such they have become standard of care. The ability to program vectors from multiple poles of an LV lead has potential advantages in terms of improving CRT response, however
initial positive findings in small, single centre acute studies and nonrandomised studies have not, to date, been reflected in larger randomised studies with lower risk of bias. MPP may also have a deleterious effect with a significant reduction in battery longevity. Few studies have specifically assessed the impact of MPP on battery longevity compared to conventional CRT. Of the included studies, Leclercq et al is the only to comment that MPP can reduce battery longevity by approximately 1 year (or approximately 15%), with a separate sub-study of Spanish participants in the MORE-CRT study demonstrated similar reductions in battery capacity of 15 ± 14% in those programmed to MPP-AS.33 A sub-analysis of the IRON-MPP study concluded that out of 237 patients followed up, MPP was associated with 0.44 years reduction in projected battery longevity.34 In a separate dataset, a small observational study of 46 patients by Akerstrom et al, demonstrated that MPP-AS programming significantly shortened battery longevity compared with conventional CRT at three pacing capture thresholds (≤1.5 V, −5.6%; ≤4.0 V, −16.9%; ≤6.5 V, −21.3%; p < 0.001).35 This is an important point to consider, due to the increased risk associated with repeated device intervention, as illustrated by the REPLACE registry demonstrating a 4% risk of major complication 6 months following generator change.36

It also may not be possible to program MPP in all patients due to high capture thresholds or phrenic nerve stimulation (PNS). Of the included studies that evaluated capture threshold (CT), varying levels of CTs in patients randomised to MPP were identified. Forleo et al reported that whilst 97% of patients were programmable to MPP, this was at a CT of 5 V, however only 87% were programmable at 3 V without PNS. In addition, 4% of patients were not programmable to MPP due to PNS. Niazi et al reported that 3.2% of patients were not programmable to MPP, whilst similar results were noted by Leclercq et al, with only 2.8% not being able to be programmed to MPP due to PNS or high CT.

Given these uncertainties it is difficult to justify the widespread use of MPP programming in all CRT patients and its use may be better restricted to certain groups of patients where there is a good reason to believe that its activation may be beneficial, although based on the current data it is unclear as to which group of patients this may relate to. In addition, alternative technologies including multisite pacing in the form of multilead CRT with an additional right or left ventricular lead may offer an alternative solution to higher rates of nonresponse in certain patient groups. However, published results involve trials with a small number of participants with softer outcomes.37–39 It is hoped that further large, randomised studies will help clarify in which patients this treatment may be beneficial and how it should be programmed in those patients.

5 LIMITATIONS

The current meta-analysis has important limitations. Several of the studies were nonrandomised, and observational cohort studies or registries, and such studies have inherent confounders and biases as highlighted in the risk of bias assessment that we performed. In addition, there were two studies which were not fully peer reviewed. As stated in the methodology, the inclusion of so-called “grey literature” is encouraged to avoid selection and publication bias, these should be approached with caution. To mitigate this and justify their inclusion a sensitivity analysis was performed which justified inclusion of grey literature. Notably, the weighting assigned to studies that are fully peer reviewed and are considered high quality were given greater weighting in the final ROB assessment (figure S2). There were multiple different measures of MPP outcome and follow-up duration was not standardised across the studies. This may have affected the outcome, as the marginal benefits of MPP over conventional CRT may require longer therapy duration than the follow-up periods allowed in the current studies. In several studies MPP was assessed only in nonresponders to CRT and in fact, this was the case in the largest major published randomised trial by Leclercq et al.10 It could be argued that MPP in this group of patients who have already failed to respond to conventional CRT may not be of benefit, as response is unlikely due to underlying unfavourable substrate in this patient group which is not amenable to CRT.

Furthermore, MPP programming varied across studies, and was often at the discretion of the implantator making it difficult to systematically assess the electrical benefit of MPP and evaluate an individual effect of each programming type. We mitigated this risk by assuming high levels of heterogeneity, and so a random effects meta-analytical approach was applied to all analyses. In the future, as further studies are performed with more detailed information on programming type, a network meta-analysis may be an appropriate way to evaluate types of MPP programming better. Delivery of MPP was via two different models of CRT devices and not consistently personalised to the patient’s cardiac substrate and it is possible that such measures may optimise electrical resynchronisation and improve response. Specifically, ensuring that both pacing sites are outside of scar, may improve response.

6 CONCLUSION

The current meta-analysis represents the largest to date on the use of MPP. There appears to be a signal for benefit for MPP mainly derived from nonrandomised trials, whilst more recent larger randomised studies have failed to show a clear benefit. The results of ongoing large scale randomised studies will be required to better assess the potential benefit of MPP. At present it is difficult to justify widespread use of MPP in the CRT population.

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CONFLICT OF INTERESTS

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