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**META-ANALYSIS**

# Targeted left ventricular lead positioning to the site of latest activation in cardiac resynchronization therapy: a systematic review and meta-analysis

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**Aims** Several studies have evaluated the use of electrically- or imaging-guided left ventricular (LV) lead placement in cardiac resynchronization therapy (CRT) recipients. We aimed to assess evidence for a guided strategy that targets LV lead position to the site of latest LV activation.

**Methods and results** A systematic review and meta-analysis was performed for randomized controlled trials (RCTs) until March 2023 that evaluated electrically- or imaging-guided LV lead positioning on clinical and echocardiographic outcomes. The primary endpoint was a composite of all-cause mortality and heart failure hospitalization, and secondary endpoints were quality of life, 6-min walk test (6MWT), QRS duration, LV end-systolic volume, and LV ejection fraction. We included eight RCTs that comprised 1323 patients. Six RCTs compared guided strategy ($n = 638$) to routine ($n = 468$), and two RCTs compared different guiding strategies head-to-head: electrically- ($n = 111$) vs. imaging-guided ($n = 106$). Compared to routine, a guided strategy did not significantly reduce the risk of the primary endpoint after 12–24 (RR 0.83, 95% CI 0.52–1.33) months. A guided strategy was associated with slight improvement in 6MWT distance after 6 months of follow-up of absolute 18 (95% CI 6–30) m between groups, but not in remaining secondary endpoints. None of the secondary endpoints differed between the guided strategies.

**Conclusion** In this study, a CRT implantation strategy that targets the latest LV activation did not improve survival or reduce heart failure hospitalizations.

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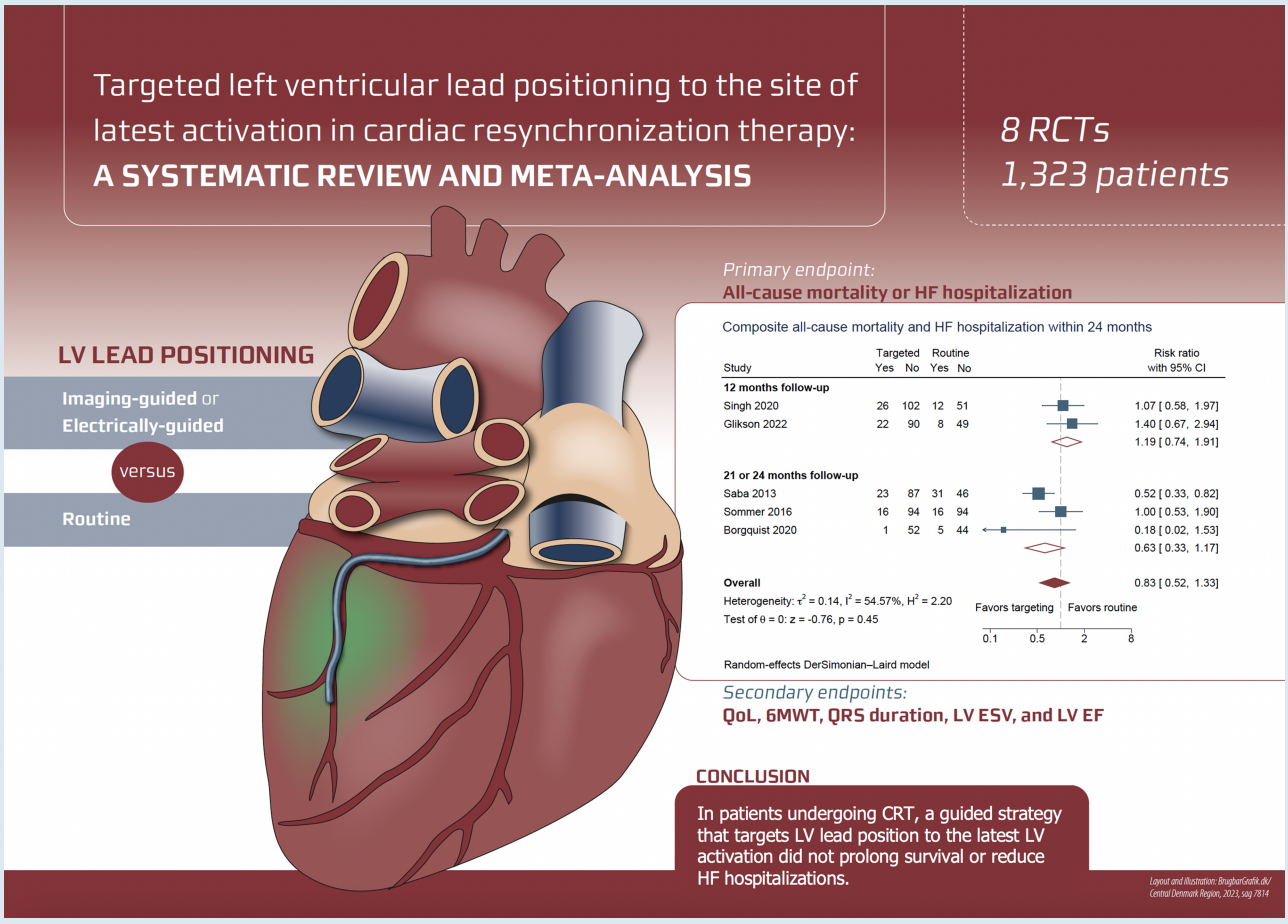
## Graphical Abstract




**Keywords** Cardiac resynchronization therapy • Targeting left ventricular lead position • Guided • Electrically • Imaging • Latest activation • Echocardiographic outcomes • Clinical outcomes

## What's new?

- This was a comprehensive meta-analysis and systematic review with additional data from included trials comparing targeted (electrically- or imaging-guided) to routine left ventricular (LV) lead positioning.
- Compared to routine LV lead positioning, a targeted strategy did not reduce the risk of all-cause mortality or heart failure hospitalization up to 24 months of follow-up.
- A targeted strategy yielded a numerically small improvement in walking distance at 6-month follow-up, but did not improve quality of life, reduce QRS duration, or lead to left ventricular reverse remodelling as compared to routine LV lead positioning.

# Introduction

Cardiac resynchronization therapy (CRT) is a guideline-recommended therapy for patients with symptomatic heart failure (HF), left ventricular (LV) ejection fraction (EF) ≤ 35%, and prolonged QRS duration despite optimal medical treatment.[1] Despite its well-established effect on effect on morbidity and mortality,[2] only one-third of eligible patients receive a CRT device,[3] and up to one-third of those patients derive no measurable benefit from CRT.[4] The LV lead position has been identified as an important determinant of favourable CRT outcome[5] and observational data support positioning the LV lead towards the non-apical posterolateral region.[6–8] An LV lead position discordant with the site of latest activation or within myocardial scar has been associated with increased long-term mortality.[9] Therefore, individualized strategies have been proposed to identify and target the optimal LV lead position i.e. the site of the latest activation free from myocardial scar. Targeted LV lead positioning can be achieved by imaging modalities identifying the latest mechanical activation or by electrophysiological mapping identifying the latest electrical activation. Previous randomized controlled trials (RCTs) had relatively small sample sizes and reported diverging results.[10–17] Five reviews and meta-analyses[18–22] have been published previously. These are however subject to limitations including missing data and dissimilar study selection. Therefore, it remains unanswered if a targeted strategy is superior to routine LV lead positioning and if so, whether electrically- or imaging-guided LV lead positioning is the best strategy.

In this systematic review and meta-analysis, we aimed primarily to assess evidence for a guided strategy for CRT that targets LV lead position to the site of latest LV activation, and secondarily to assess evidence between the strategies. We hypothesized that a targeted strategy would

be superior to routine LV lead positioning in terms of clinical and echocardiographic parameters, and we hypothesized that electro- and imaging-guided LV lead placement would provide similar improvements.

# Methods

## Sources

We designed this systematic review and meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered the review protocol with the International Prospective Register of Systematic Reviews (PROSPERO, registration number CRD42022355716). The primary endpoint was a composite of all-cause mortality and HF hospitalization. Secondary endpoints were changes in Minnesota Living with Heart Failure Questionnaire (MLHFQ) score, 6-min walk test (6MWT) distance, QRS duration, LV end-systolic volume (ESV), and EF. An online literature search of PubMed and EMBASE databases was performed from inception through 1 March 2023, using the Medical Subject Heading (MeSH) terms 'cardiac resynchronization therapy', 'guided', 'targeted', 'positioning', 'placement', and 'latest activation' with no restrictions on publication dates, language, or article type. The search was performed independently by two authors (D.B.F. and H.L.B.).

## Study selection

Randomized controlled trials comparing targeted LV lead positioning to routine LV lead positioning, or comparing different targeting strategies, were eligible if they included patients with LV EF $\leq$ 35%, QRS duration $\geq$ 120 ms, and New York Heart Association (NYHA) functional classes II–IV. Trials were eligible if they reported on the primary or any secondary endpoints.

The study selection followed an independent screening of titles and abstracts, and a full-text review by two authors (D.B.F. and H.L.B.) using the online platform Covidence (Melbourne, Australia). Disagreements were resolved by consensus or via consultation with a third author (M.H.J.P.F or J.C.N.) when necessary. Finally, the reference lists of included RCTs were also reviewed for additional potentially relevant studies.

All pre-defined data of interest from the included RCTs were extracted by two independent authors (D.B.F. and H.L.B.) using the module Extraction 2.0 (Covidence, Melbourne, Australia). The corresponding authors of all included trials were contacted to inquire additional data that were not reported in the original papers to limit missing data and to enable robust endpoint analysis.

Two authors (D.B.F. and H.L.B.) assessed study quality using the Jadad quality scale, which evaluates randomization, blinding, and accounting of all patients.[23] A score of 0–2 reflects low quality, a score of 3–4 indicates moderate quality, and a score of 5 represents a high-quality study.[23]

## Statistics

Values are reported as mean ± standard deviation (SD) for continuous variables and number (%) for categorical variables. If a study did not report or provide the pairwise change from baseline to follow-up in mean ± SD, we estimated the value using available baseline and follow-up values in accordance with the Cochrane Handbook for Systematic Reviews of Interventions.[24] Intention-to-treat meta-analyses were conducted for all outcomes of interests that were reported in at least two RCTs. For each outcome, we report an overall estimate for trials investigating a targeted strategy compared to routine positioning. This estimate comprises trials that investigated imaging-guided strategy compared to routine and trials investigating electrically-guided strategy compared to routine. Separately, we report an overall estimate for trials that compared the two guiding strategies head-to-head i.e. electrically- compared to imaging-guided strategy. Categorical outcomes were pooled and presented as a risk ratio (RR) with 95% confidence interval (CI), while continuous outcomes were pooled and presented as mean difference (MD) with 95% CI and illustrated in forest plots. Heterogeneity was assessed using a standard $\chi^2$ test and the $I^2$ statistic, with significance set at $P < 0.05$ and $I^2 > 50\%$, respectively. Recognizing the diversity of the trials regarding design, intervention, follow-up time, and outcomes, meta-analyses were performed using a DerSimonian–Laird random-effects model. Publication bias was estimated by visual inspection of funnel plots. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed in Stata (StataCorp, TX, USA).

# Results

## Study characteristics

The literature search strategy retrieved a total of 457 studies (*Figure 1*). Titles and abstracts were reviewed, and 39 articles were subject to full-text assessment. This yielded a total of eight studies eligible for inclusion in the meta-analysis. Of these, six RCTs[11–14,16,17] contributed additional data not published previously in the original publications or subsequent analyses, and two RCTs could not contribute additional data[10,15] (see Supplementary material online, *Table S1*). The present meta-analysis comprised a total of 1323 patients. Six RCTs compared a targeted LV lead placement ($n = 638$ patients) to routine LV lead placement ($n = 468$ patients),[10–15] and two RCTs compared electrically- ($n = 111$ patients) with imaging-guided ($n = 106$ patients) LV lead placement.[16,17] Study characteristics are summarized in *Table 1*, and patient baseline characteristics in *Table 2*.

## All-cause mortality and heart failure hospitalization

Five studies reported the primary composite endpoint of all-cause mortality and HF hospitalization at an intermediate follow-up time; two studies after 12 months,[14,15] one study after 21 months,[11] and two studies after 24 months.[12,13] This yielded a total of 160 events. We found an estimated reduction of 17% in the primary composite endpoint at 12 to 24 months of follow-up but it did not reach statistical significance (RR 0.83, 95% CI 0.52–1.33, *Figure 2*). The primary composite endpoint was also reported after 6 months of follow-up, where no benefit of a targeted strategy was observed compared to routine positioning (RR 0.92, 95% CI 0.57–1.48; see Supplementary material online, *Figure S1*).[12–14] In the two studies comparing electrically- vs. imaging-guided strategies, there was a difference favouring imaging-guided strategy within the first 6 months (RR 3.43, 95% CI 1.16–10.17; see Supplementary material online, *Figure S1*), while no data were available beyond this follow-up. No sign of publication bias was found in any of the analyses (see Supplementary material online, *Figures S2* and *S3*).

## Quality of life, exercise capacity, and QRS duration

Quality of life assessed by MLHFQ score was available from all studies. Targeted LV lead positioning provided no additional improvement in quality of life (absolute MD −1 point, 95% CI −6 to 4, *Figure 3A*). Similar results were found in the two studies comparing electrically- vs. imaging-guided LV lead implantation (absolute MD 0 points, 95% CI −5 to 6, *Figure 3A*).

Improvement in 6MWT was examined in five studies comparing targeted vs. routine LV lead placement.[10–14] There was a small difference between the two strategies favouring targeted LV lead positioning (absolute MD 18 m, 95% CI 6–30, *Figure 3B*). There was a similar difference between electrically- vs. imaging-guided LV lead placement (absolute MD 15 m, 95% CI −6 to 35, *Figure 3B*), but this did not reach statistical significance.

Absolute QRS reduction after 6 months was examined in three studies comparing targeted vs. routine strategy,[11,12,14] and two studies comparing electrically- vs. imaging-guided strategy, but none of them showed a difference between the strategies (absolute MD −1 ms, 95% CI −6 to 4 and absolute MD 0 ms, 95% CI −6 to 6, respectively; see Supplementary material online, *Figure S4*).

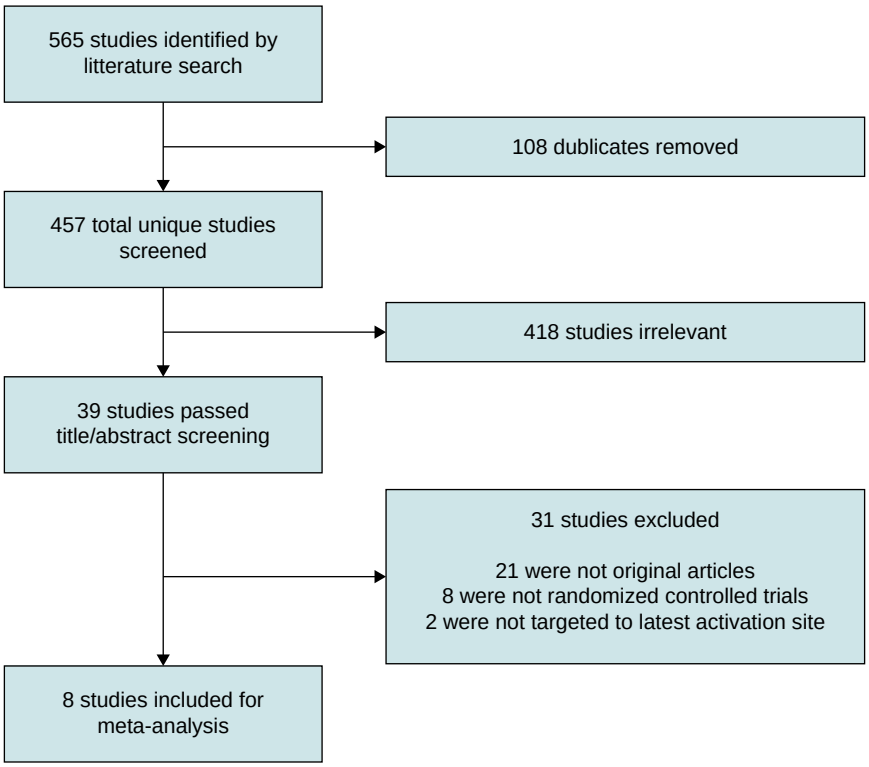



**Figure 1** Literature search and study selection.

No sign of publication bias was found in any of the analyses (see Supplementary material online, *Figures S5–S7*).

## Echocardiographic improvement

There were no differences between the targeted strategy and routine LV lead implantation in terms of absolute increase in LV EF (absolute MD 1%, 95% CI −1 to 2, *Figure 4A*). At 6 months, there was a slightly larger absolute difference in relative LV ESV reduction favouring a targeted strategy compared to routine but it did not reach statistical significance (absolute MD −5 percentage point, 95% CI −10 to 1, *Figure 4B*). Similar results were found between electrically- vs. imaging-guided strategies for both LV EF and LV ESV (*Figures 4A and B*). Both LV EF and LV ESV analyses were without signs of publication bias (see Supplementary material online, *Figures S8* and *S9*, respectively).

## Remote left ventricular lead placement

Five studies comparing targeted vs. routine LV lead positioning reported on *de facto* LV lead position and relation to the latest LV activated area.[10–14] This analysis showed a reduced risk of remote LV lead positioning in the patients randomized to targeted LV lead placement (RR 0.60, 95% CI 0.47–0.76, see Supplementary material online, *Figure S10*). No publication bias was found (see Supplementary material online, *Figure S11*).

# Discussion

We found no differences in the primary composite endpoint of all-cause mortality and HF hospitalization, as well as in the secondary endpoints of quality of life, QRS reduction, or echocardiographic parameters favouring targeted as compared to routine LV lead positioning. We observed a statistically significant but numerically relatively small difference in the improvement of walking distance 6 months post-implant in favour of targeted LV lead positioning.

The primary composite endpoint was reported at various time points in the studies. Only three studies reported on the endpoint within the first 6 months post-implant, yielding a total of eight deaths and 20 HF hospitalization.[12–14] With this small number of events, the result favouring an imaging-guided strategy as compared to an electrically-guided strategy may not necessarily pertain to the overall CRT population. In our meta-analysis, five studies comparing targeted and routine LV lead implantation reported on the primary composite endpoint at 12, 21, or 24 months, comprising an intermediate follow-up time. Unfortunately, intermediate follow-up data from the studies comparing the electrically- and imaging-guided strategies head-to-head were not available. It is debateable whether a potential difference between strategies on hard endpoints would be evident at an intermediate follow-up time of 12–24 months, or if any benefit would only show on long-term follow-up. In a recent patient-level combined analysis of 'The Speckle Tracking Assisted Resynchronization Therapy for Electrode Region' (STARTER) and 'Cardiac Resynchronization Therapy Guided by Echocardiography, MRI, and CT Imaging' (CRT Clinic) with a total of 289 patients followed for a median of 6.3 years, the authors found a reduced risk of all-cause death and HF hospitalization among patients with imaging-guided LV lead implantation,[25] mainly driven by a reduced risk of HF hospitalization. In contrast, the recent long-term follow-up of 'Multimodality Imaging-guided Left Ventricular Lead Placement in Cardiac Resynchronization Therapy' (ImagingCRT) with a median follow-up of 6.7 years reported no difference in this composite endpoint between the imaging-guided and control group (hazard ratio 1.22, 95% CI 0.83–1.81).[26] This divergence between the long-term follow-up studies may be due to several factors. First, the long-term

**Table 1** Study characteristics

| Author, year | Study acronym | Country | Guidance modality compared | Singlecentre or multicentre | Sample size | Randomization ratio | Inclusion criteria | Follow-up | Primary endpoint | Jadad score |
|---|---|---|---|---|---|---|---|---|---|---|
| Khan *et al.*, 2012[10] | TARGET | UK | Imaging (echocardiography) vs. routine | Multicentre | 220 | 1:1 | NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms | 6 months | Relative reduction of LV ESV by ≥15% | 5 |
| Saba *et al.*, 2013[11] | STARTER | USA | Imaging (echocardiography) vs. routine | Singlecentre | 187 | 3:2 | NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms | 1.8 ± 1.3 years | HF hospitalization or all-cause mortality | 4 |
| Sommer *et al.*, 2016[12] | ImagingCRT | Denmark | Imaging (cardiac CT, SPECT, echocardiography) vs. routine | Singlecentre | 182 | 1:1 | NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms or RV-paced QRS > 180 ms, and age > 40 years | 1.8 ± 0.9 years | All-cause mortality, HF hospitalization, no NYHA functional class improvement or <10% increase in 6MWT | 5 |
| Borgquist *et al.*, 2020[13] | CRT Clinic | Sweden | Imaging (CMR, echocardiography) vs. routine | Singlecentre | 102 | 1:1 | NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms | 47 ± 21 months | Relative reduction of LV ESV by ≥15% | 5 |
| Singh *et al.*, 2020[15] | ENHANCE-CRT | USA | Electrically (QLV) vs. routine | Multicentre | 243 | 2:1 | NYHA functional class II despite OMT, LV EF ≤ 35%, prolonged QRS > 120 ms and non-LBBB | 12 months | Clinical composite: ≥1 NYHA functional class improvement, patient global score, no HF hospitalization or all-cause mortality | 4 |
| Glikson, 2022[14] | Raise CRT | Israel | Imaging (echocardiography) vs. routine | Singlecentre | 172 | 2:1 | IHD, NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms | 12 months | Relative reduction of LV ESV | 3 |
| Kockova, 2018 | CMR-CRT | Czech Republic | Electrically (QLV) vs. imaging (CMR) | Singlecentre | 95 | 1:1 | NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms | 47 (35–56) months | Cardiovascular mortality or HF hospitalization | 2 |

*Continued*

**Table 1** *Continued*

| Author, year | Study acronym | Country | Guidance modality compared | Singlecentre or multicentre | Sample size | Randomization ratio | Inclusion criteria | Follow-up | Primary endpoint | Jadad score |
|---|---|---|---|---|---|---|---|---|---|---|
| Stephansen *et al.*, 2019[17] | ElectroCRT | Denmark | Electrically (QLV) *vs.* imaging (cardiac CT, SPECT, echocardiography) | Singlecentre | 122 | 1:1 | NYHA functional class II despite OMT, LV EF ≤ 35%, and prolonged QRS > 120 ms or RV-paced QRS > 180 ms, and age > 40 years | 6 months | Absolute increase in LV EF | 5 |

Values are mean ± SD and median (interquartile range).
6MWT, 6-min walk test; CMR, cardiac magnetic resonance; CT, computed tomography; EF, ejection fraction; ESV, end-systolic volume; HF, heart failure; IHD, ischaemic heart disease; LBBB, left bundle branch block; LV, left ventricular; NYHA, New York Heart Association; OMT, optimal medical treatment; RV, right ventricular; SPECT, single photon emission computed tomography.

follow-up of STARTER and CRT Clinic included 187 patients from STARTER between 2005 and 2011 and 102 patients from CRT Clinic between 2012 and 2017. The positive effect of a targeted strategy reported in this long-term follow-up study may partly be explained by the larger proportion of patients and risk time from the STARTER population, in which the control group may have been treated differently from the control groups in more recent studies. Second, the modalities used for the targeting strategy differed; STARTER used speckle-tracking echocardiography, while CRT Clinic and ImagingCRT used multimodality imaging. Third, none of the trials were sufficiently powered for these long-term outcomes.

Among the additional clinical endpoints, we observed a small but statistically significant longer 6MWT distance after 6 months of follow-up in patients having targeted LV lead implantation. It is, however, debateable whether an absolute difference of 18 m reflects a meaningful clinical difference.

Implantation of a CRT device usually induces QRS narrowing because of a faster electrical activation of the ventricles. In this meta-analysis, we did not observe any *additional* change in QRS duration when utilizing a targeted compared to routine strategy, or between the electrically- vs. imaging-guided targeting strategies. Studies applied dissimilar inclusion criteria regarding QRS morphology: the early 'Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy' (TARGET) and STARTER trials included any patient with prolonged QRS duration > 120 ms irrespective of QRS morphology, while the 'Targeted Left Ventricular Lead Implantation Strategy for Non-Left Bundle Branch Block Patients' (ENHANCE-CRT) study included patients exclusively with non-LBBB, and most patients in CRT Clinic, ImagingCRT, and 'Radial Strain Imaging-guided Lead Placement for Improving Response to Cardiac Resynchronization Therapy in Patients with Ischaemic Cardiomyopathy' (Raise CRT) trials had LBBB (74%, 86%, and 74%, respectively). Considering the superior effect of CRT in classic LBBB compared to non-LBBB, this heterogeneity may have masked any potential beneficial effect of targeted positioning in patients with LBBB.[8]

On echocardiographic parameters, we observed no significant difference between targeted and routine LV lead implantation, or between electrically- vs. imaging-guided targeting strategies. The TARGET and STARTER trials, published in 2012 and 2013 respectively, reported significantly improved, or a tendency towards more pronounced LV remodelling with a targeted strategy, while the later studies were all neutral, with mean differences in these parameters close to zero. The studies were published over an approximate 10-year timespan, comprising changes in patient selection criteria, medical therapy and guideline recommendations, implant experience, and evolution in methodology and technical equipment. This development could have reduced the risk of remote lead positioning with routine positioning, thereby diminishing the potential additional effect that can be achieved by employing a targeted strategy.

Among the studies included, we did find a reduced risk of having the LV lead implanted in a remote position to the latest mechanically activated site as compared to a concordant/adjacent position. When inspecting the Forest Plot (see Supplementary material online, *Figure S10*), this effect size seems to gradually abate in more recent studies, supporting the notion that routine positioning in the control group improved over time. A reduced risk of all-cause death was found in patients with concordant/adjacent LV lead position to optimal pacing sites in both STARTER, TARGET, and CRT Clinic.[10,11,13] This beneficial effect persisted in the substudy of TARGET with a follow-up of median 39 months, where the authors found that suboptimal LV lead placement independently predicted all-cause mortality (HR 1.8, 95% CI 1.08–3.04).[27] Similar results were found in sub-studies from the STARTER population and CRT Clinic.[13,28,29]

One of the major determinants of the measurable effect of CRT is LV lead position in a non-scarred area[30] with an electromechanical

**Table 2** Patient baseline characteristics

| Author, year | Study acronym | Guidance modality evaluated | No. of participants enrolled | | Age | | Female | | IHD | | NYHA functional class, II/III/IV | | MLHFQ, points | | 6MWT, m | | QRS duration, ms | | LV EF, % | | LV ESV, mL | | Medical therapy, ACEi or ARB/BB/MRA/LD | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control |
| Khan *et al.*, 2012[10] | TARGET | Imaging vs. routine | 110 | 110 | 72 (65–76) | 72 (64–80) | 25 (28) | 22 (24) | 62 (56) | 61 (56) | 0/95/15 (0/86/14) | 0/93/17 (0/85/15) | 55 ± 21 | 53 ± 20 | 282 ± 101 | 268 ± 112 | 157 ± 16 | 159 ± 18 | 23 ± 6 | 23 ± 7 | 157 ± 56 | 154 ± 52 | 104/78/63/110 (95/71/57/100) | 103/77/59/110 (94/70/54/100) |
| Saba *et al.*, 2013[11] | STARTER | Imaging vs. routine | 110 | 77 | 66 ± 11 | 67 ± 13 | 33 (30) | 17 (22) | 64 (58) | 52 (67) | 16/64/20 (15/58/18) | 8/71/21 (10/92/27) | 49 ± 28 | 52 ± 29 | 234 ± 141 | 245 ± 120 | 157 ± 27 | 162 ± 27 | 26 ± 6 | 26 ± 7 | 140 ± 59 | 144 ± 63 | NA | NA |
| Sommer *et al.*, 2016[12] | ImagingCRT | Imaging vs. routine | 89 | 93 | 71 ± 9 | 71 ± 9 | 20 (22) | 19 (20) | 46 (52) | 44 (47) | 44/44/1 (49/49/1) | 40/48/5 (43/52/5) | 38 ± 23 | 35 ± 21 | 378 ± 137 | 389 ± 102 | 167 ± 22 | 165 ± 22 | 25 ± 6 | 24 ± 6 | 190 ± 70 | 198 ± 69 | 84/82/42/64 (95/92/48/73) | 85/85/41/61 (91/91/44/66) |
| Borgquist *et al.*, 2020[13] | CRT Clinic | Imaging vs. routine | 53 | 49 | 67 ± 8 | 70 ± 8 | 14 (26) | 13 (27) | 22 (42) | 25 (51) | 14/36/3 (26/68/6) | 12/28/9 (25/57/18) | 39 ± 21 | 44 ± 26 | 413 ± 119 | 375 ± 138 | 171 ± 16 | 169 ± 22 | 23 ± 7 | 23 ± 7 | 184 ± 82 | 167 ± 55 | 53/46/29/31 (100/87/55/59) | 47/43/30/37 (96/88/61/76) |
| Singh *et al.*, 2020[15] | ENHANCE-CRT | Electrically vs. routine | 161 | 82 | 66 ± 12 | 64 ± 13 | 27 (17) | 21 (26) | 100 (62) | 45 (55) | 0/157/4 (0/98/2) | 1/72/9 (1/88/11) | 54 ± 26 | 55 ± 26 | NA | NA | NA | NA | 25 ± 8 | 25 ± 7 | NA | NA | 104/139/22/125 (65/86/14/78) | 59/69/20/66 (72/84/24/81) |
| Glikson *et al.*, 2022[14] | Raise CRT | Imaging vs. routine | 115 | 57 | 69 ± 9 | 71 ± 8 | 5 (4) | 4 (7) | 115 (100) | 57 (100) | 36/74/5 (31/64/4) | 22/34/1 (39/60/2) | 47 ± 25 | 36 ± 24 | 324 ± 116 | 353 ± 120 | 155 ± 19 | 155 ± 17 | 30 ± 9 | 29 ± 8 | 203 ± 67 | 203 ± 53 | NA | NA |
| Kockova *et al.*, 2018[16] | CMR-CRT | Electrically vs. imaging | 51 | 44 | 64 ± 9 | 64 ± 12 | 17 (33) | 13 (30) | 18 (35) | 17 (39) | 21/26/2 (41/51/4) | 17/26/0 (39/59/0) | 29 ± 21 | 27 ± 18 | 391 ± 102 | 384 ± 124 | 165 ± 17 | 165 ± 14 | 27 ± 7 | 28 ± 7 | 155 ± 70 | 133 ± 51 | 50/50/43/44 (98/98/84/86) | 44/42/32/33 (100/95/73/75) |
| Stephansen *et al.*, 2019[17] | ElectroCRT | Electrically vs. imaging | 60 | 62 | 72 ± 8 | 70 ± 10 | 14 (23) | 17 (27) | 32 (53) | 28 (47) | 35/24/1 (58/40/2) | 41/19/2 (66/31/3) | 32 ± 20 | 31 ± 20 | 379 ± 106 | 410 ± 105 | 170 ± 17 | 169 ± 23 | 29 ± 8 | 31 ± 8 | 142 ± 56 | 132 ± 54 | 58/54/38/44 (97/90/63/73) | 56/59/40/47 (90/95/65/76) |

Values are mean ± SD, median (interquartile range), and *n* (%).

6MWT, 6-min walk test; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; EF, ejection fraction; ESV, end-systolic volume; IHD, ischaemic heart disease; LD, loop diuretics; LV, left ventricular; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

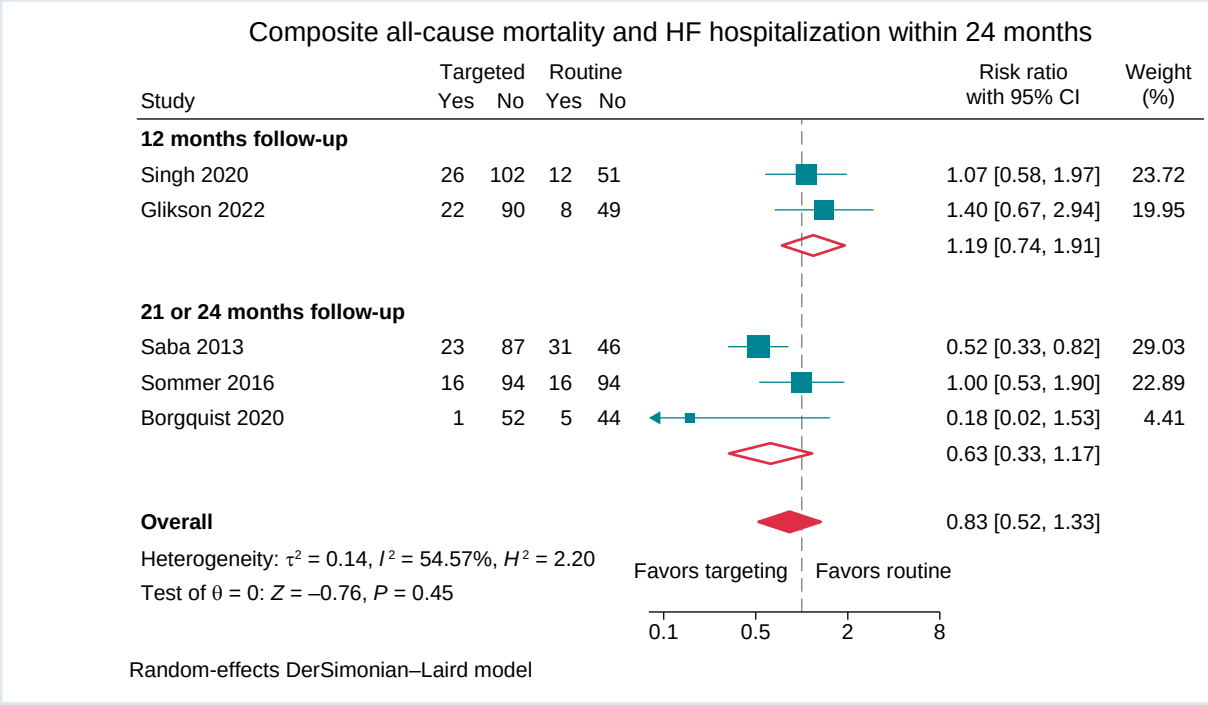



**Figure 2** Risk of the primary composite endpoint of all-cause mortality or heart failure hospitalization within 24 months between patients having the LV lead implanted either by targeting the latest activation site or by routine placement (targeted vs. routine). HF, heart failure.

substrate,[31] which also seems related to reduced arrhythmogenicity.[32] To target this optimal LV lead position, several guidance techniques have been investigated, including the strategies included in this meta-analysis. The imaging-guided strategy is costly and time-consuming, especially if including multimodality-imaging techniques. In contrast, the electrically-guided strategy without the need for pre-procedural imaging may present a more feasible option. However, we could include only two small studies with no longer than 6 months of follow-up comparing the two strategies, and these results thus should be interpreted very cautiously. Both studies used the local LV electrical delay (QLV) measured by invasive electrophysiological mapping to target the site of latest electrical activation. The QLV was previously shown to be associated with favourable CRT response in the 'The SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy' (SMART-AV) substudy,[33] and Varma *et al.* recently showed that *non-invasive* three-dimensional electrical activation mapping to assess the QLV was a strong predictor for CRT response.[34] In the substudy of ImagingCRT however, QLV was not able to discriminate between CRT responders and non-responders.[35] Instead, a longer inter-electrical delay of ≥100 ms was found to be independently associated with more pronounced LV reverse remodelling after 6 months of follow-up,[35] and was associated with reduced all-cause death and HF hospitalization during long-term follow-up.[26] Other methods to assess electrical dyssynchrony have been investigated, including the body surface mapping and ECG belts.[36,37] The 'Electrocardiogram Belt Guidance for Left Ventricular Lead Placement and Biventricular Pacing Optimization' (ECG Belt Trial) was a multicentre RCT with 408 patients comparing the ECG Belt System (EBS)-guided LV lead implantation or routine CRT care, showing no added value of targeted positioning.[36] The EBS is a surface mapping system designed to measure electrical dyssynchrony of the LV, and not to specifically target the latest electrical activated region. Another recent study evaluated the impact of atrioventricular (AV) timing algorithms using non-invasive epicardial electrocardiographic imaging (ECGi).[38] The authors found that dynamic AV delay programming targeting fusion with intrinsic conduction significantly reduced electrical dyssynchrony, as quantified by ECGi and QRS duration for all evaluated pacing modes.[38] In addition, optimization of CRT is associated with improved clinical and echocardiographic outcomes when using intracardiac electrocardiograms, which are less time-consuming, as compared to echocardiography-based methods.[39]

Previous meta-analyses investigating targeted LV lead placement in CRT recipients have certain limitations.[18–22] No previous meta-analyses included additional data by contacting the corresponding authors of original trials. This unavoidably entails some missing data, fewer reported endpoints, and fewer studies contributing data to each endpoint analysis. Hence, our meta-analysis with additional data from most included RCTs provides an extended and comprehensive perspective. The most recent meta-analysis is not in agreement with our results,[22] which may be due to diverse study selection criteria. We decided only to include fully published RCTs, while the previous meta-analysis prioritized to also include data from three abstracts; one with preliminary data from the recently published Raise CRT study,[14] and two unpublished studies.[40,41] Furthermore, the 'A Multicenter Prospective Randomized Controlled Trial of Cardiac Resynchronization Therapy Guided by Invasive dP/dt" (RADI-CRT) comparing haemodynamically-guided or routine LV lead placement based on invasive LV dP/dt measurements was included,[42] as well as a study comparing surface ECG-guided LV lead placement with routine LV lead placement.[43] These five studies reported results favouring a guided strategy as compared to routine CRT implantation, driving the potential difference between our two meta-analyses. The different study selection criteria applied by the different meta-analyses provide valuable complementory insights into the field. Another recent meta-analysis reported solely on echocardiographic parameters and NYHA functional class improvement,[21] one investigated exclusively imaging-guided strategy compared to

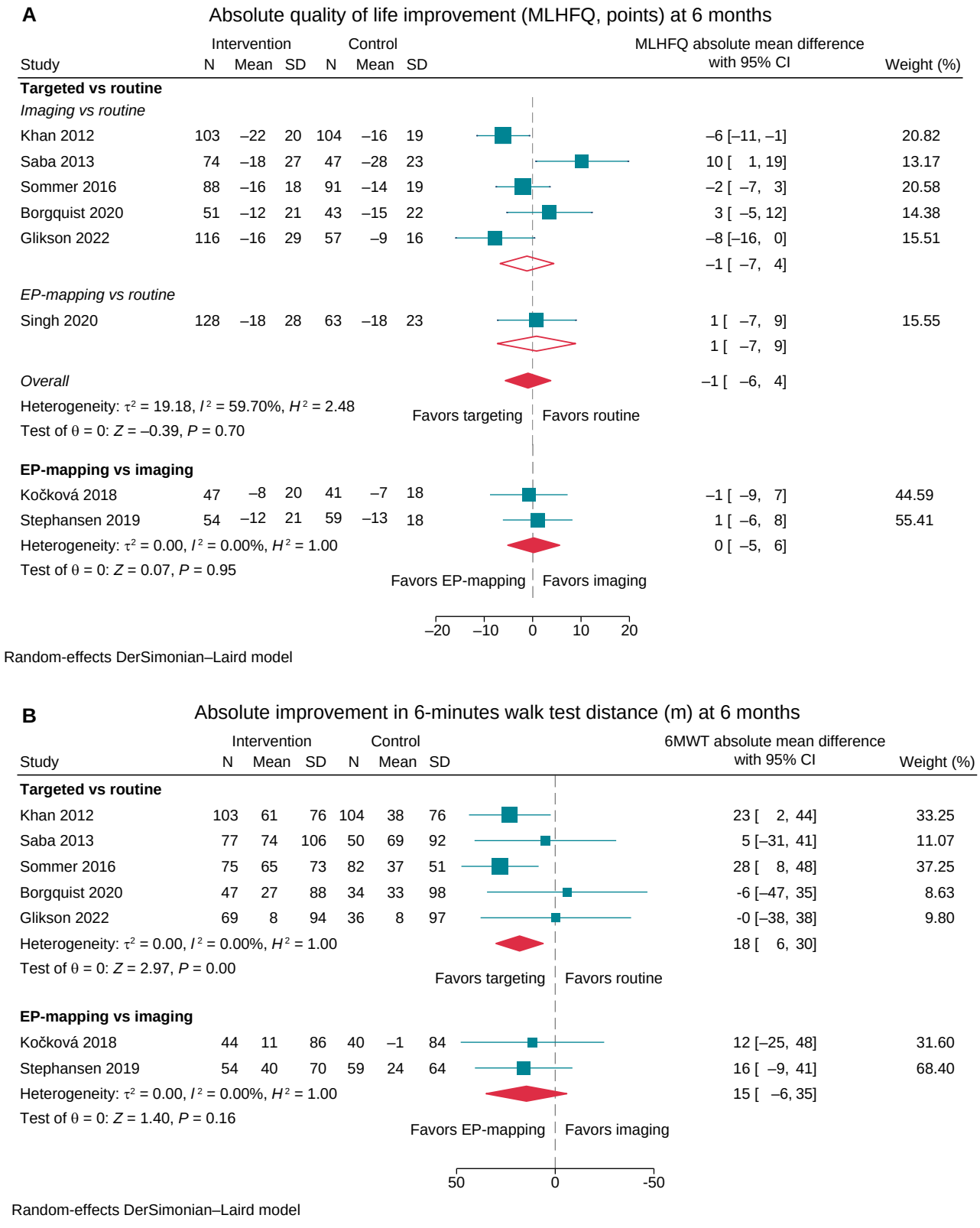
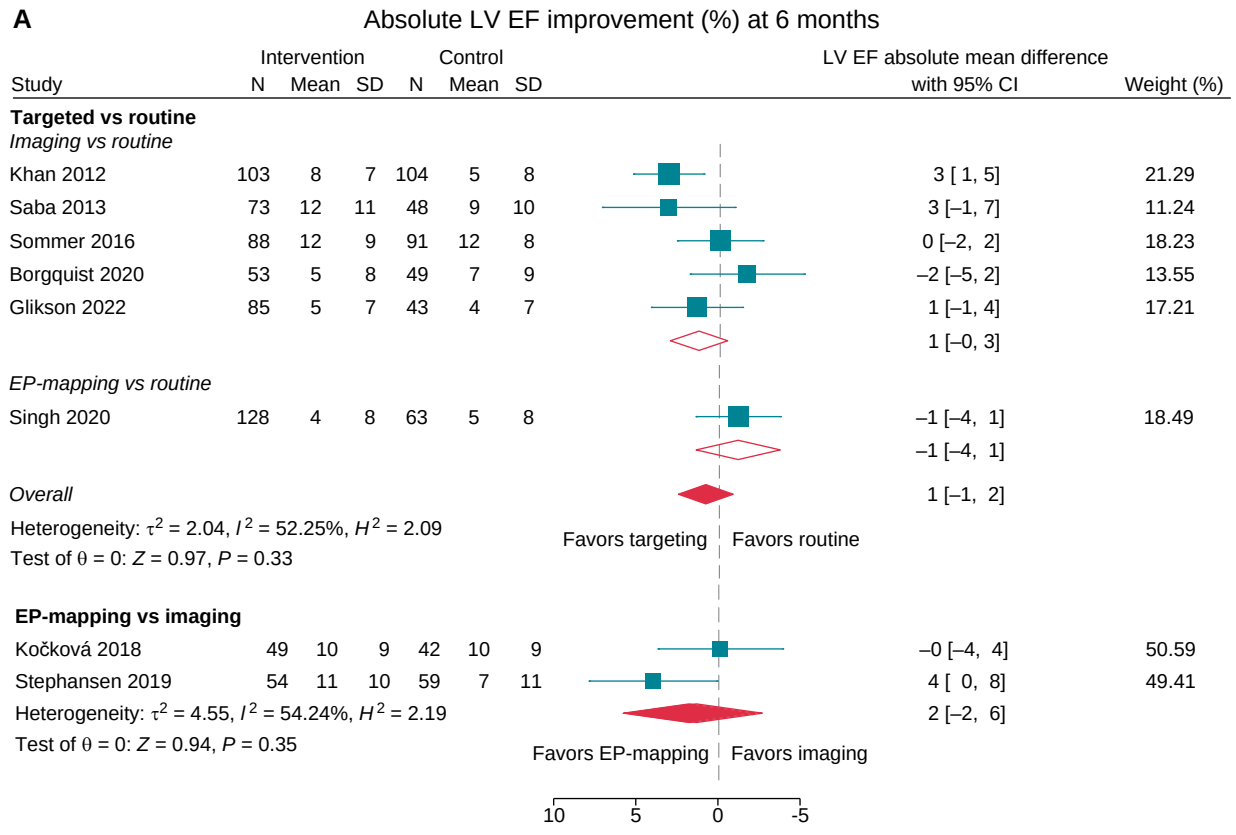



**Figure 3** Clinical improvement after 6 months as assessed by Minnesota Living with Heart Failure Questionnaire (*A*) and 6-min walk test (*B*) between patients having the LV lead implanted either by targeting the latest activation site or by routine placement (targeted vs. routine) or by an electrically- vs. imaging-guided strategy (EP-mapping vs. imaging).



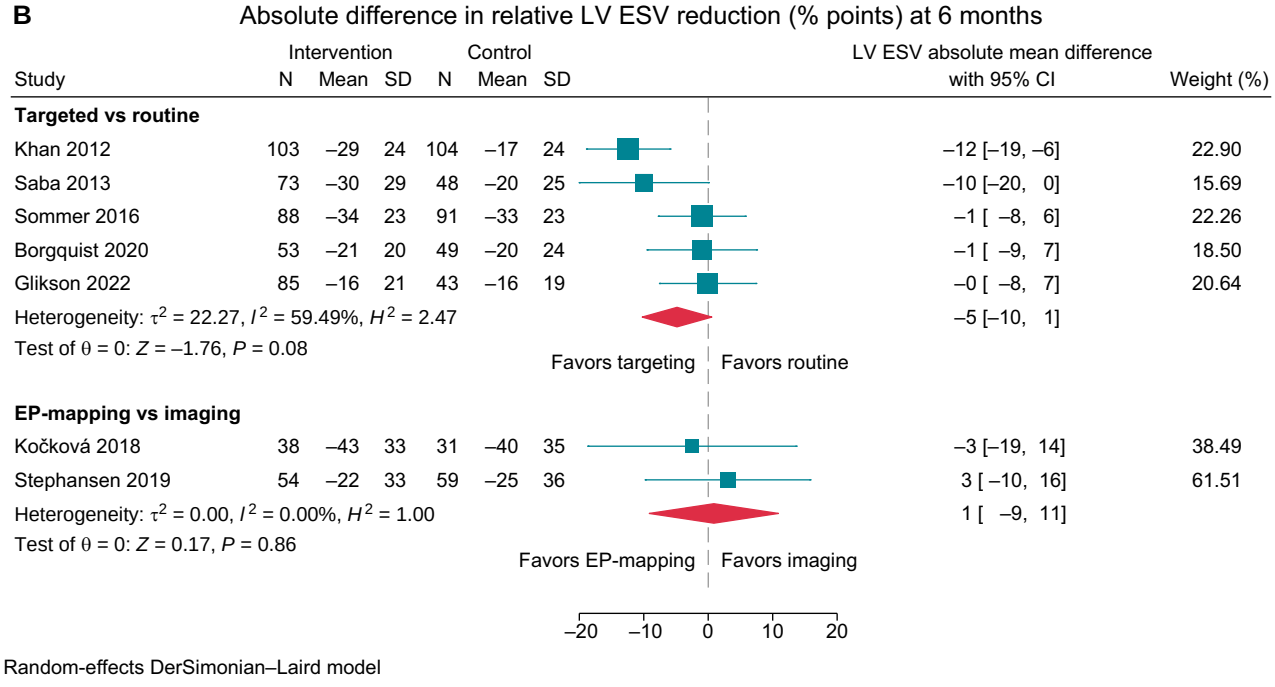




**Figure 4** Echocardiographic changes after 6 months as evaluated by LV EF (*A*) and LV ESV (*B*) between patients having the LV lead implanted either by targeting the latest activation site or by routine placement (targeted vs. routine) or by an electrically- vs. imaging-guided strategy (EP-mapping vs. imaging). EF, ejection fraction; ESV, end-systolic volume; LV, left ventricular.

routine positioning[20] and two[18,19] included non-randomized observational studies,[44–47] making them subject to risk of selection bias and residual confounding.

## Limitations

This systematic review and meta-analysis is subject to several limitations, including the relatively small number of studies eligible for inclusion, particularly those comparing electrically-guided with imaging-guided LV lead implantation, and the variability of outcome measures and differences in techniques used to detect latest activated regions. Follow-up was in a clinical context short or moderate, and number of clinically hard endpoints not high. Only two of the eight studies included were multicentre studies, and therefore generalizability of the findings may be questioned. The CRT Clinic was terminated early due to equivocal results between study arms, which potentially could introduce bias.[13] We included published data and additional data provided by investigators from six of eight included trials, but we did not use patient-level data as this was not available. Only intention-to-treat analyses were available. Patient-level analysis of outcomes stratified for remote vs. concordant lead position, LBBB, and QRS duration > 150 ms could have provided further insights but these data were not available. The present meta-analysis highlights the need for larger multicentre studies investigating the role of electrically- and imaging-guided strategies. Currently, two ongoing multicentre trials are comparing cardiac MRI-guided implantation with routine implantation (Clinical Trials, registration numbers NCT03992560 and NCT05053568),[48] and an ongoing multicentre trial is comparing electrically-guided LV lead implantation with routine implantation (Clinical Trials, registration number NCT0328 0862).[49] These larger trials will provide us with greater insights into targeted LV lead implantation and its impact on patient outcomes as compared with routine CRT implantation. Furthermore, the potential of alternative methods for delivering CRT, including conduction system pacing and LV endocardial pacing, is being investigated and may form a new era in CRT if they turn out to be superior to conventional biventricular pacing.[50]

# Conclusion

This comprehensive meta-analysis and systematic review suggests that a CRT implantation strategy that targets the latest LV activation does not improve survival or HF hospitalizations.

# Supplementary material

Supplementary material is available at *Europace* online.

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## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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