Targeting the latest site of left ventricular mechanical activation is associated with improved long-term outcomes for recipients of cardiac resynchronization therapy

Rasmus Borgquist, MD, PhD,* William R. Barrington, MD,† Zoltan Bakos, MD, PhD,‡ Anna Werther-Evaldsson, PhD,§ Samir Saba, MD, FHRS†

From the *Arrhythmia Section, Department of Cardiology, Lund University, Skane University Hospital, Lund, Sweden, †Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, ‡Department of Cardiology, Kristianstad Hospital, Kristianstad, Sweden, and §Heart Failure and Transplant Section, Department of Cardiology, Lund University, Skane University Hospital, Lund, Sweden.

BACKGROUND Previous studies have suggested that targeting the site of latest mechanical activation of the left ventricle (LV) results in improved cardiac resynchronization therapy (CRT) outcomes. It is not known whether these benefits are sustained over medium-term follow-up.

OBJECTIVE To assess the clinical outcome of imaging-guided LV lead position.

METHODS We sought to assess the medium-term clinical outcome by performing a patient-level meta-analysis of 2 previously published randomized controlled trials (the “STARTER” trial and the “CRT Clinic” trial). These 2 trials compared imaging-guided LV lead placement in the latest activated scar-free segment (intervention group) to standard of care (control). Mortality and heart failure hospitalization outcomes over extended follow-up were gathered from the medical records and merged. Results were stratified for native electrocardiogram (ECG) morphology.

RESULTS A total of 289 patients were followed for a median of 6.3 years. Seven years post implant, 47 (28%) in the intervention group had died, vs 47 (38%) in the control group (P = .13); 49 (30%) vs 53 (42%) had been hospitalized for heart failure (P = .035); and 47% vs 59% (P = .057) had reached the combined endpoint. In Kaplan-Meier analysis, patients in the intervention group had better survival free of heart failure hospitalization (P = .045) and lower risk of heart failure hospitalization (P = .019).

CONCLUSION Targeting the latest mechanically activated segment in CRT results in better medium-term clinical outcome, mainly driven by a reduced risk of hospitalization for heart failure. The effect was seen regardless of native ECG morphology.

KEYWORDS Cardiac resynchronization therapy; Latest mechanical activation; Heart failure hospitalization; Mortality

Clinical Trial Registration: Clinicaltrials.gov numbers NCT00156390 and NCT01426321. Address reprint requests and correspondence: Dr Rasmus Borgquist, Arrhythmia Section, Skane University Hospital, 221 85, Lund, Sweden. E-mail address: rasmus.borgquist@med.lu.se.

Introduction
Cardiac resynchronization therapy (CRT) is an effective treatment for reducing mortality and risk for heart failure hospitalization in patients with systolic heart failure and wide QRS complex.1–3 The rationale for resynchronization is that by placing the left ventricular (LV) lead on the free wall of the left ventricle, earlier and more synchronized activation of the ventricle is achieved. However, there may be several anatomical options for placing the LV lead in a suitable epicardial vein, and it is unclear what is the best selection method for choosing the final pacing site.

Previous observational data have suggested that a lateral, nonapical position may be preferable, but this has not been proven prospectively.4–8 In principle, LV lead position can be chosen based on anatomical location, maximized interlead distance from the right ventricular (RV) lead, late electrical activation, or late mechanical activation. In addition, lead stability and local pacing properties are important, since scar tissue, high thresholds, and diaphragmatic stimulation all need to be avoided.6,9,10 Targeting the mechanically latest activated LV segment is theoretically appealing, since it enables early activation of the part of the ventricle that is contracting last during intrinsic activation. High-frame-rate imaging is needed to correctly discriminate between the timing of contraction of the various LV segments, and echocardiography is therefore the most suitable modality. Four randomized...
KEY FINDINGS

- Imaging-guided left ventricular (LV) lead placement targeting the latest mechanically activated segment is feasible and results in a higher proportion of LV leads placed concordant to, or adjacent to, the latest mechanically activated segment.

- Early benefits in reverse remodeling for patients with targeted LV lead placement in the latest mechanically activated segment transform into medium-term benefit in hard clinical endpoints.

- Targeting the latest mechanically activated segment for LV lead placement in cardiac resynchronization therapy reduces medium-term risk of heart failure hospitalization and mortality.

controlled trials (RCTs) have used speckle-tracking radial strain for evaluation of mechanical activation timing and guiding LV lead placement—the TARGET, STARTER, Imaging CRT, and CRT Clinic studies.\textsuperscript{11–14}

However, there is so far no published data to show if targeting the latest LV site of mechanical activation leads to better medium-term clinical results. We therefore sought to evaluate this by looking at extended data from 2 of the above-mentioned randomized studies, the STARTER and CRT Clinic trials (clinical trials identifier NCT00156390 and NCT01426321, respectively). The research reported in this paper was approved by the local ethics committees and adhered to the Helsinki Declaration.

Methods

The methodology of both studies has been published previously.\textsuperscript{12,14} In brief, patients fulfilling guideline indications for CRT treatment (LV ejection fraction [LVEF] ≤35%, QRS >120 ms, NYHA class II–IV, optimal medical therapy) were recruited and randomly assigned to image-guided LV lead placement vs standard of care. Both studies used GE Echopac (Vivid 7 or E9; GE Medical, Horten, Norway) for analysis of radial strain. Speckle tracking–based strain analyses were performed using short-axis views of the mid and basal segments of the left ventricle, leaving the apical segments out. Frame rate was set at between 60 and 90 frames per second, and all images were collected at 3 heart cycles and stored digitally for off-line analysis. The segment with the latest mechanical activation was chosen as the optimal segment. Segments with scar were avoided in both studies. In the STARTER study, scar was defined as thin-walled segments (≤5 mm) with hyperacoustic appearance. In the CRT Clinic study scar was defined either by cardiac magnetic resonance imaging (CMR) showing accumulation of gadolinium contrast, or (in the absence of CMR) by peak radial strain ≤9.5%.

Prior to the implant procedure, the implanting physician was presented with the imaging data results, including which segment should be targeted for patients in the intervention group. For patients in the control group, imaging data were not available to the implanting physician, and the LV lead was targeted at the discretion of the implantaner, as standard of care. Patients received a CRT-defibrillator or CRT-pacemaker; no patients had a secondary prevention indication for an implantable cardioverter-defibrillator. A right atrial lead was placed in the right atrial appendage, and an RV lead was placed in the RV apex or in the interventricular septum.

Determination of LV lead concordance was done using a combination of fluoroscopy or chest radiograph in the right

### Table 1 Demographic data and lead positions

|                          | Control | Image-guided LV lead placement | \( P \) value |
|--------------------------|---------|-------------------------------|---------------|
| Age, years               | 67 ± 11 | 66 ± 10                       | .24           |
| Female sex, n (%)        | 29 (23) | 47 (29)                       | .35           |
| Ischemic cardiomyopathy, n (%) | 76 (60) | 77 (47)                       | .06           |
| ECG morphology, n (%)    |         |                               | .75           |
| LBBB                     | 88 (70) | 117 (72)                      |               |
| Paced                    | 24 (19) | 28 (17)                       |               |
| Non-LBBB                 | 14 (11) | 18 (11)                       |               |
| QRS duration (ms)        | 165 ± 25| 162 ± 25                      | .31           |
| Diabetes, n (%)          | 37 (29) | 47 (29)                       | 1.0           |
| Renal failure, n (%)     | 13 (10) | 11 (7)                        | .40           |
| Atrial fibrillation, n (%) | 33 (26) | 51 (31)                       | .43           |
| Beta-blocker therapy, n (%) | 105 (83) | 148 (91)                    | .07           |
| ACEi or ARB therapy, n (%) | 113 (90) | 153 (88)                     | .70           |
| Aldosterone antagonist therapy, n (%) | 39 (31) | 51 (31)                | .97           |
| Loop diuretic therapy, n (%) | 98 (78) | 116 (71)                     | .43           |
| NYHA class, n (%)        |         |                               | .37           |
| II                       | 19 (15) | 33 (20)                       |               |
| III                      | 82 (65) | 106 (65)                      |               |
| IV                       | 25 (20) | 24 (15)                       |               |
| LVEF, % [IQR]            | 25 [20–29] | 25 [20–29]                  | .59           |
| LVESV, mL [IQR]          | 138 [112–183] | 147 [106–185]              | .77           |
| LVEDV, mL [IQR]          | 189 [155–234] | 196 [145–234]             | .96           |
| Follow-up time, years [IQR] | 6 [3.4–8.9] | 6.5 [3.7–8.7]              | .40           |
| Biventricular pacing, % [IQR] | 99 [97–99] | 99 [98–99]               | .88           |
| Left ventricular lead placement, n (%) | 0.004 |
| Concordant               | 18 (14) | 44 (27)                       |               |
| Adjacent                 | 70 (56) | 93 (57)                       |               |
| Remote                   | 38 (30) | 26 (16)                       |               |

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor antagonist; LV = left ventricular; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association classification of heart failure.
Data analysis was performed with SPSS (Version 27; IBM, Armonk, NY). Continuous variables are expressed as mean ± standard deviation or median [interquartile range, IQR]. Categorical variables are presented as percentages. Differences between groups were assessed using Student t tests for continuous variables and Mann-Whitney U test, 1-way ANOVA, χ² test, or Fisher exact test for ordinal variables, as appropriate. We used the Kaplan-Meier method to estimate the cumulative hospitalization and death rates, both for the primary groups and as a secondary on-treatment analysis. The assumption of proportional hazard was tested using visual inspection of the curves. Stratified log-rank statistic was used to compare groups. Cox regression was used to evaluate continuous or multinomial predictors of clinical outcome. A P value of <.05 was considered statistically significant.

Results
A total of 289 patients at the 2 sites were randomized to image-guided intervention (n = 163) or standard of care (n = 126) and were followed for a median of 6.3 [IQR 3.6–8.5] years. Baseline characteristics are presented in Table 1 and did not differ between groups. The majority of patients were male (n = 214, 74%), had symptoms corresponding to NYHA class III (n = 191, 66%) and had left bundle branch block morphology on electrocardiogram (ECG) (n = 205, 71%).

Echocardiography strain evaluation indicated that the optimal segment was most often located in the posterolateral part of the left ventricle, but in a substantial proportion of patients another segment was indicated as the latest activated (Figure 1). Patients in the image-guided group were more likely to have the LV lead placed in the optimal or an immediately adjacent segment (134 [84%] in the intervention group vs 88 [70%] in the control group, P = .004, Table 1).

Clinical outcome parameters are presented in Table 2. LVEF improved by a median of 8% [IQR 0%–16%] in the total cohort, 9% [IQR 1%–18%] in the intervention group vs 7% [IQR 0%–14%] in the control group, P = .24.
Table 2 Clinical outcome

|                     | Control | Image-guided LV lead placement group |
|---------------------|---------|-------------------------------------|
|                     | N = 126 | N = 163                             |
| LVEF improvement ≥5%| 71 (56%)| 79 (63%)                            |
| Hospitalized for heart failure | 57 (45%)| 61 (37%)                            |
| Died                | 68 (54%)| 81 (50%)                            |
| Cardiac cause       | 23 (34%)| 14 (17%)                            |
| Noncardiac cause    | 5 (7%)  | 16 (20%)                            |
| Unknown cause       | 40 (59%)| 51 (63%)                            |
| Hospitalized for heart failure or died | 83 (67%)| 102 (63%)                          |

LV = left ventricular; LVEF = left ventricular ejection fraction.

Image-guided intervention resulted in a numerically higher proportion of echocardiographic responders at 6–12 months (defined as ≥5% absolute increase in LVEF compared to baseline), 103 (63%) in the intervention group vs 71 (56%) in the control group, but this difference was not statistically significant (P = .34). Symptoms improved by 0.9 ± 0.7 NYHA class on average, with 223 (77%) patients showing improvement of at least 1 NYHA class (n = 127 [78%] in the intervention group vs n = 95 [75%] in the control group, P = .24).

During the entire follow-up period 149 (52%) patients died, 118 (41%) were hospitalized for heart failure, and 185 (64%) were either hospitalized for heart failure or died. The cause of death was known in 58 of the 149 deceased patients. Among those, heart failure was the most common cause of death (30/58) and cardiac death (heart failure, arrhythmia) was significantly less common in the intervention group than in the control group (47% vs 82%, P = .007).

Seven years post implant, 47 (28%) patients in the intervention group vs 47 (38%) in the control group (P = .13) had died, 49 (30%) vs 53 (42%) (P = .035) had been hospitalized for heart failure, and 77 (47%) vs 73 (59%) (P = .057) had experienced the combined endpoint. In time-dependent survival analysis there was a significantly higher risk for reaching the combined endpoint of all-cause mortality or heart failure hospitalization (hazard ratio [HR] 1.39 confidence interval [CI] 1.01–1.91, P = .046) or hospitalization for heart failure (HR 1.59 [CI 1.07–2.34], P = .020), but for all-cause mortality alone there was no significant difference (HR 1.33 [CI 0.89–2.00], P = .16; see Figure 2 for Kaplan-Meier curves).

In subgroup analysis focusing on different ECG morphologies, the relation between latest activated segment and baseline ECG appearance was further explored. The percentage of left bundle branch block (LBBB) was similar in both groups (70% vs 72%), and ECG morphology was not in itself a predictor of clinical outcome (P = .58), whereas QRS duration (HR 0.93 [CI 0.87–0.99] per 10 ms increase in QRS duration) and ischemic etiology (HR 2.3 [1.6–3.2]) were. Numerically, patients with paced QRS were less likely to have the latest activated segment in an inferior location, whereas those with LBBB and non-LBBB native QRS had a similar distribution of segments (Table 3). The success rate in targeting the latest activated segment was similar in the intervention group regardless of the ECG morphology, but in the control group fortuitous optimal/adjacent placement was numerically more common for those with paced QRS pre-CRT. In multivariate Cox regression analysis (adjusting for age, sex, NYHA class, etiology, atrial fibrillation, diabetes, and ECG morphology) imaging-guided strategy was not an independent predictor of outcome (HR 0.88 [CI 0.62–1.2], P = .41).

Discussion

In this aggregated pool of 289 patients from 2 RCTs, we show that during a 7-year follow-up, targeting of the latest mechanically activated LV segment resulted in better clinical outcome. While this effect was primarily driven by a reduction in heart failure hospitalizations, the combined endpoint of survival free from heart failure hospitalization was also significantly improved for the intervention group.

Prior published trials

Two additional studies have evaluated the benefit of targeting areas of late LV activation (the Imaging CRT trial and the TARGET trial).11,13 These show comparable results to our analysis combining the STARTER and the CRT Clinic Trials. The individual results of the 4 trials are summarized in Table 4. Even though there were differences with regard to which of the individual endpoints (echocardiographic, clinical response, or hard endpoints) were significant in the 4 studies, the results are overall congruent and point in the same direction. The rationale for reaching a better clinical outcome by targeting the latest mechanically activated segment is that the most effective resynchronization would be achieved by recruiting the latest contracting free wall segment first, and then spreading activation from this point simultaneously with the septal activation wavefront emerging from the RV electrode. Optimal resynchronization would in turn result in more pronounced reverse remodeling of the left ventricle, which over time will transform into better clinical outcome. It is therefore likely that some of the beneficial effects of optimized resynchronization have a gradual effect, which increases over time during the first years post implant. The magnitude of the effect also depends partly on the prognosis of the control arm who receives standard of care, where concordant LV lead placement may occur fortuitously. Furthermore, starting from the 2013 CRT guidelines, targeting a posterolateral nonapical location (also the most common optimal location in the present meta-analysis) was specifically recommended, and this recommendation may have helped to eliminate “remote” LV lead locations in patients where no imaging is performed.15

Adding these medium-term results for the targeted LV lead strategy is an important step toward a more general recommendation on individualized LV lead placement for CRT therapy. Even though short-term results from the 4
Figure 2  Kaplan-Meier curves showing A: survival free of heart failure (HF) hospitalization, B: freedom from HF hospitalization, and C: overall survival.
published RCTs generally were positive, the effect on surrogate endpoints such as reverse remodeling were ambiguous, with Imaging CRT and CRT Clinic showing no difference on reverse remodeling between groups. It is, however, well known that agreement between reverse remodeling after CRT and clinical outcome is relatively poor,\textsuperscript{16} and the positive results of the present medium-term follow-up including the CRT Clinic database strengthens the notion that targeting the latest mechanical activation is beneficial.

The result was mainly driven by heart failure hospitalizations, but for the subgroup of diseased patients where cause of death was known, there seemed to be strong signal for lower risk of death from heart failure in the intervention group. Considering the substantial number of missing data on cause of death, this finding should be interpreted with caution and will need to be further explored and validated in other studies.

Even though all 4 studies showed a higher proportion of concordant LV leads in the intervention group, the percentage of patients with remote LV leads differed between studies, as did the magnitude of difference between intervention and control groups. This may have affected the results, since the largest differences in actual LV lead position between groups were seen in the TARGET and STARTER studies, which coincides with a positive effect on clinical endpoints within 2 years.

### Identifying the latest mechanically activated segment

Several other strategies for targeted LV lead placement have been suggested, including targeting the latest electrically delayed segment or any of the posterolateral segments without scar.\textsuperscript{6,17–19} Even though all these strategies seem theoretically appealing, it is still unclear if they are equally good, or which is the optimal strategy. Electrical and mechanical activation patterns may vary depending on the underlying substrate for the widened QRS, such as presence and location of myocardial scar, size of the LV cavity, and surface ECG morphology.\textsuperscript{20} In addition, the activation pattern during simultaneous RV pacing may change significantly compared to intrinsic LBBB pattern, thus conferring an additional confounder for targeting the optimal pacing segment.\textsuperscript{21,22} Only 1 study has so far prospectively studied the latter strategy.

### Table 3

| Optimal lead location | LBBB (N = 186) | Paced (N = 48) | Non-LBBB (N = 31) | \(P\) value |
|-----------------------|----------------|----------------|-------------------|-------------|
| Anterior              | 11 (6%)        | 5 (10%)        | 3 (9%)            | .19         |
| Anterolateral         | 60 (31%)       | 16 (31%)       | 10 (31%)          |             |
| Posterolateral        | 93 (47%)       | 28 (55%)       | 13 (41%)          |             |
| Inferior              | 33 (17%)       | 2 (4%)         | 6 (19%)           |             |

### Table 4

| Trial          | LV lead placement (optimal/adjacent/distant), % | Reverse remodeling (LVESV reduction ≥15%) | Clinical responder (NYHA class improvement ≥1) | Freedom from death or heart failure hospitalization after 2 years |
|----------------|-----------------------------------------------|------------------------------------------|-----------------------------------------------|---------------------------------------------------------------|
|                | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control |
| STARTER\textsuperscript{12} | 30/55/15 | 12/44/33 | 57% | 35%\textsuperscript{3} | 82% | 80% | 77% | 57%\textsuperscript{3} |
| TARGET\textsuperscript{11}  | 61/25/10 | 45/28/24 | 70% | 55%\textsuperscript{3} | 83% | 65%\textsuperscript{3} | 86% | 78%\textsuperscript{3} |
| Imaging CRT\textsuperscript{13} | 49/50/1 | 43/54/2 | N/r | N/r | 60% | 51%\textsuperscript{2} | 78% | 80% |
| CRT Clinic\textsuperscript{14} | 21/62/17 | 15/58/27 | 56% | 55% | 74% | 67% | 80% | 96% |

\(\text{LV} = \) left ventricular; \(\text{LBBB} = \) left ventricular; \(\text{LVESV} = \) left ventricular end-systolic volume; \(\text{N/r} = \) not reported; \(\text{NYHA} = \) New York Heart Association classification of heart failure.

\textsuperscript{1}Imaging CRT used a definition that included either NYHA class improvement or ≥10% improvement at 6-min walk test, in absence of heart failure hospitalization or death.

\textsuperscript{2}P < .05.
compared electrically guided LV lead implantation with mechanically guided LV lead implantation and found no significant difference on clinical endpoints.23

**Clinical implications and patient selection regarding ECG criteria**

In the absence of other prospectively validated strategies, targeting the latest mechanically activated segment is a reasonable strategy to improve prognosis for CRT recipients for the time being. There are several imaging strategies available to evaluate mechanical activation, including CMR with several subtypes, cardiac computed tomography, and echocardiography using either tissue Doppler or speckle-tracking technique. All methods have their strengths and weaknesses, including feasibility, validation, reproducibility, and temporal resolution.24 Differences in mechanical activation times are relatively short, and a high time resolution is therefore essential. Echocardiography-based strain has the best temporal resolution (60–90 fps) and is the only modality that so far has been prospectively validated for CRT regarding segmental strain. CMR-based strain, however, allows for better reproducibility and global strain by CMR has been shown to associate with reverse remodeling.25

Observational and randomized trial data have indicated that patients with non-LBBB morphology obtain less benefit from CRT, compared to those with LBBB or strict LBBB fulfilling Strauss’ criteria.26,27 Since LV activation sequence is more unpredictable in non-LBBB, there may be a higher potential gain for individualized LV lead placement in this patient group. We therefore performed sub-analyses to determine if there was a difference in latest activated segment, or a prognostic difference, depending on native ECG morphology. Our results in this respect indicate that there is no such difference and that the distribution of latest activated segments was similar for LBBB and non-LBBB, as was the success rate of placing the LV lead at the intended site in the intervention group.

**Limitations**

The present study includes data from 2 separate randomized controlled trials. Even though every effort was made to ensure consistency in each presented variable, the studies did not have a joint case report form or protocol for the original data collection. Therefore, there may be minor discrepancies between the datasets, which have not been detected or corrected for. The total number of patients is limited (n = 289), although this is the largest published analysis so far. Data collection was done during the period 2005–2016. Since then, contemporary guidelines for CRT have changed (eg, QRS duration must now be ≥130 ms instead of ≥120 ms), and optimal medical therapy has evolved to include more classes of drugs. Furthermore, there was a relatively high incidence of ischemic cardiomyopathy in the cohort (53% overall), which may have adversely impacted CRT response in the entire group. These factors could limit the generalizability of our results in a contemporary cohort of CRT-eligible patients. We performed predetermined sub-group analyses stratified for ECG morphology; however, the total number of non-LBBB patients in this cohort was relatively low, and therefore these results should be interpreted with caution. The technical tools nowadays provide better opportunities for targeted lead placement, and if the study were repeated today this could have impacted the results.

**Conclusion**

In this patient-level meta-analysis, we show that targeting the LV site of latest mechanical activation in CRT results in improved medium-term survival free from heart failure hospitalizations. This benefit is mainly driven by a reduced risk of hospitalization for heart failure. In the absence of other prospectively validated targeting modalities with proven clinical benefit, it may be reasonable to target the site of latest LV mechanical activation during CRT device implantation.

**Funding Sources:** This work was supported by an ALF grant (R.B.) within the Swedish National Health Care system.

**Disclosures:** RB has received speaker’s fees from Medtronic and Biotronik, and research grant from Boston Scientific.

**Authorship:** All authors attest they meet the current ICMJE criteria for authorship.

**Patient Consent:** Subjects gave written informed consent.

**Ethics Statement:** The research reported in this paper was approved by the local ethics committees and adhered to the Helsinki Declaration.

**References**

1. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–1549.
2. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–2150.
3. Goldenberg I, Kuttyfa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med 2014;370:1694–1701.
4. Singh JP, Klein HU, Huang DT, et al. Left ventricular lead position and clinical outcome in the multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT) trial. Circulation 2011;123:1159–1166.
5. Kronborg MB, Johansen JB, Riahi S, et al. An anterior left ventricular lead position is associated with increased mortality and non-response in cardiac resynchronization therapy. Int J Cardiol 2016;222:157–162.
6. Delgado V, van Bommel RJ, Bertini M, et al. Relative merits of left ventricular dyssynchrony, left ventricular lead position, and myocardial scar to predict long-term survival of ischemic heart failure patients undergoing cardiac resynchronization therapy. Circulation 2011;123:70–78.
7. Bleeker GB, Schalij MJ, Bax JJ. Importance of left ventricular lead position in cardiac resynchronization therapy. Eur Heart J 2007;28:1182–1183.
8. Becker M, Aliot E, Ockengren C, et al. Analysis of LV lead position in cardiac resynchronization therapy using different imaging modalities. JACC Cardiovasc Imaging 2010;3:472–481.
9. Bleeker GB, Schalij MJ, Van Der Wall EE, Bax JJ. Posterolateral-scar tissue resulting in non-response to cardiac resynchronization therapy. J Cardiovasc Electrophysiol 2006;17:899–901.
10. Bilchick KC, Kuruvilla S, Hamirani Y, et al. Impact of mechanical activation, scar, and electrical timing on cardiac resynchronization therapy response and clinical outcomes. J Am Coll Cardiol 2014;63:1657–1666.
11. Khan FZ, Virdee MS, Palmer CR, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. J Am Coll Cardiol 2012;59:1509–1518.
12. Saba S, Marek J, Schwartzman D, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle
13. Sommer A, Kronborg MB, Norgaard BL, et al. Multimodality imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial. Eur J Heart Fail 2016;18:1365–1374.
14. Borgquist R, Carlsson M, Markstad H, et al. Cardiac resynchronization therapy guided by echocardiography, MRI, and CT imaging: a randomized controlled study. JACC Clin Electrophysiol 2020;6:1300–1309.
15. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–2329.
16. Fornwalt BK, Sprague WW, Bedell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation 2010;121:1985–1991.
17. Del Greco M, Zorzi A, Di Matteo I, et al. Coronary sinus activation patterns in patients with and without left bundle branch block undergoing electroanatomic mapping system-guided cardiac resynchronization therapy device implantation. Heart Rhythm 2017;14:228–233.
18. Sohal M, Chen Z, Sammut E, et al. New developments in the delivery of cardiac resynchronization therapy: targeted lead placement, multi-site and endocardial pacing. Expert Rev Med Devices 2014;11:295–304.
19. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J 2017;38:1463–1472.
20. Strik M, Regoli F, Auricchio A, Prinzen F. Electrical and mechanical ventricular activation during left bundle branch block and resynchronization. J Cardiovasc Transl Res 2012;5:117–126.
21. Varma N. Left ventricular electrical activation during right ventricular pacing in heart failure patients with LBBB: visualization by electrocardiographic imaging and implications for cardiac resynchronization therapy. J Electrocardiol 2015;48:53–61.
22. Mail R, Blauw Y, et al. Different regions of latest electrical activation during left bundle-branch block and right ventricular pacing in cardiac resynchronization therapy patients determined by coronary venous electro-anatomic mapping. Eur J Heart Fail 2014;16:1214–1222.
23. Stephansen C, Sommer A, Kronborg MB, et al. Electrically vs. imaging-guided left ventricular lead placement in cardiac resynchronization therapy: a randomized controlled trial. Europace 2019;21:1369–1377.
24. Amzulescu MS, De Craene M, Langel H, et al. Myocardial strain imaging: review of general principles, validation, and sources of discrepancies. Eur Heart J Cardiovasc Imaging 2019;20:605–619.
25. van Everdingen WM, Zweerink A, Nijveldt R, et al. Comparison of strain imaging techniques in CRT candidates: CMR tagging, CMR feature tracking and speckle tracking echocardiography. Int J Cardiovasc Imaging 2018;34:443–456.
26. Strauss DG, Selvester RH, Wagner GS. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol 2011;107:927–934.
27. Goldstein RE, Haigney MC, Krone RJ, McNitt S, Zareba W, Moss AJ. Differing effects of cardiac resynchronization therapy on long-term mortality in patient subgroups of MADIT-CRT defined by baseline conduction and 1-year post-treatment left ventricular remodeling. Heart Rhythm 2013;10:366–373.