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Prognostic Benefit of Optimum Left Ventricular Lead Position in Cardiac Resynchronization Therapy

Follow-Up of the TARGET Study Cohort (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy)

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Objectives This study was conducted to assess the impact of left ventricular (LV) lead position on longer-term survival after cardiac resynchronization therapy (CRT).

Background An optimal LV lead position in CRT is associated with improved clinical outcome. A strategy of speckle-tracking echocardiography can be used to guide the implanter to the site of latest activation and away from segments of low strain amplitude (scar). Long-term, prospective survival data according to LV lead position in CRT are limited.

Methods Data from a follow-up registry of 250 consecutive patients receiving CRT between June 2008 and July 2010 were studied. The study population comprised patients recruited to the derivation group and the subsequent TARGET (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy) randomized, controlled trial. Final LV lead position was described, in relation to the pacing site determined by pre-procedure speckle-tracking echocardiography, as *optimal* (concordant/adjacent) or *suboptimal* (remote). All-cause mortality was recorded at follow-up.

Results An optimal LV lead position ($n = 202$) conferred LV remodeling response superior to that of a suboptimal lead position (change in LV end-systolic volume: $-24 \pm 15\%$ vs. $-12 \pm 17\%$ [$p < 0.001$]; change in ejection fraction: $+7 \pm 8\%$ vs. $+4 \pm 7\%$ [$p = 0.02$]). During long-term follow-up (median: 39 months; range: <1 to 61 months), an optimal LV lead position was associated with improved survival (log-rank $p = 0.003$). A suboptimal LV lead placement independently predicted all-cause mortality (hazard ratio: 1.8; $p = 0.024$).

Conclusions An optimal LV lead position at the site of latest mechanical activation, avoiding low strain amplitude (scar), was associated with superior CRT response and improved survival that persisted during follow-up.
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Cardiac resynchronization therapy (CRT) has been an important advance in the treatment of patients with heart failure, leading to improvements in symptoms, left ventricular (LV) function, and survival (1–3). However, a significant proportion of recipients, up to 30%, still do not achieve a favorable response. In addition to patient selection and device optimization, LV lead position is of fundamental importance in delivering effective CRT, and as such was included in recent international CRT guidelines (4).

Early retrospective studies indicated that an LV lead placed at the site of latest mechanical activation, away from scar, and in a nonapical location conferred greatest benefit (5–7). Characterization of both myocardial substrate (8) and mechanical activation pattern (9) in the LV using speckle-tracking echocardiography (STE) can be applied to determine the optimal LV pacing site in individual patients (10). The utility of this approach to guide the implanter has been demonstrated in 2 prospective, randomized trials: TARGET (Targeted Left Ventricular Lead Placement to guide Cardiac Resynchronization Therapy) (11) and STARTER (Speckle Tracking Assisted Resynchronization Therapy for Electrode Region) (12). Benefits observed in the echo-guided groups in both studies included a larger proportion of patients with a favorable LV lead position, greater LV remodeling response, and improved survival at up to 2 years' follow-up.

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Abbreviations and Acronyms

2D = 2-dimensional

CRT = cardiac resynchronization therapy

EF = ejection fraction

LV = left ventricle

LVEDV = left ventricular end-diastolic volume

LVESV = left ventricular end-systolic volume

NYHA = New York Heart Association

STE = speckle-tracking echocardiography

On the basis of previous studies, it was observed that the initial beneficial effects of CRT are maintained, and that the impact on survival persists over a longer duration of follow-up (13). Therefore, we examined the effects of LV lead position on all-cause mortality following CRT in a prospective cohort of patients.

Methods

Patient population. We studied data from a total of 250 patients who underwent CRT implantation between June 2008 and July 2010. An initial group of 50 patients participated in an open-label study that assessed the feasibility of using STE to guide LV lead placement to achieve the greatest increase in LV performance. A randomized trial was then undertaken that compared conventional LV lead placement to a targeted approach in which the LV lead was placed in a segment defined on echocardiography (TARGET [11]). This registry comprises data from the 50 patients in the derivation group studied prospectively from June 2008 to March 2009, and 200 patients from the TARGET randomized, controlled trial, which enrolled from April 2009 to July 2010 (Fig. 1). There were no differences in the baseline characteristics between the 2 groups, including age, etiology, ejection fraction (EF), and dyssynchrony. Patient characteristics, study methods, and results from the TARGET study (11) have been published previously in detail; although 247 patients were initially screened, 27 were not eligible for inclusion in the trial due to suboptimal echocardiographic imaging. Echocardiographic image quality was satisfactory for STE in all patients in the derivation group. Patients who died before CRT implantation or in whom there was failure to implant an LV lead were not included in this cohort follow-up study.

All patients met standard indications for CRT implantation, with impaired LV function (EF ≤35%), left branch bundle block or intraventricular conduction delay (QRS duration ≥120 ms), and New York Heart Association (NYHA) functional class III/IV symptoms despite optimal medical therapy, and had satisfactory echocardiographic

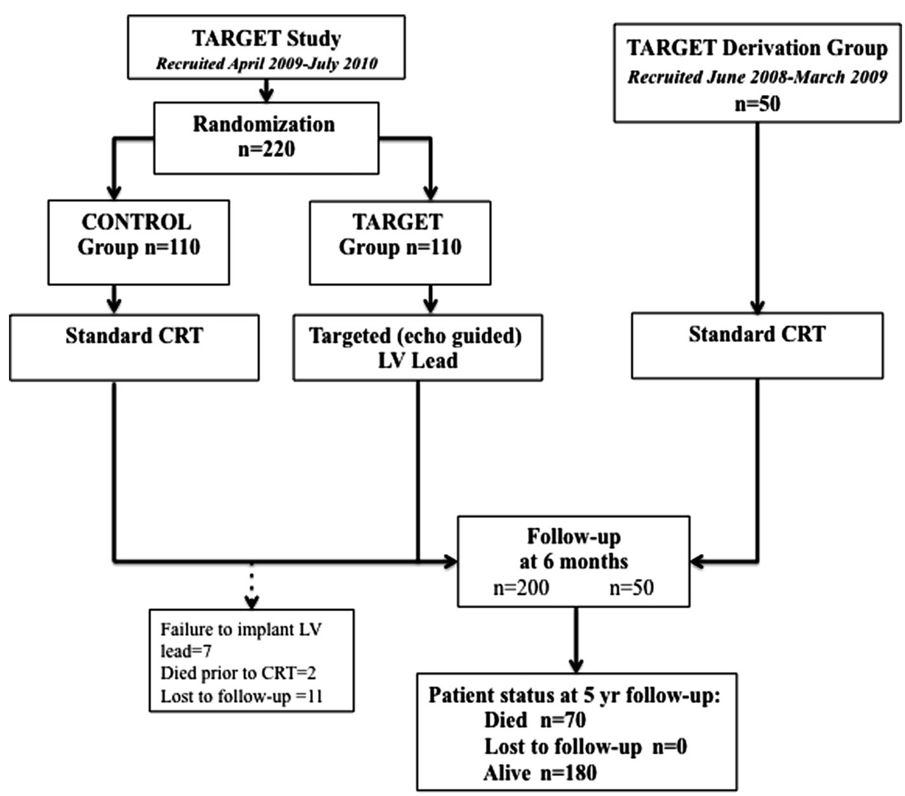

Figure 1 **The TARGET Registry**

Diagram illustrating the TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) registry which includes subjects from the TARGET randomized control trial and derivation group. Subjects excluded from the study included those who did not receive CRT due to either failure to implant an LV lead or death prior to scheduled procedure, and those lost to follow-up.

Table 1 Baseline Characteristics According to Final LV Lead Position

	All Patients (n = 250)	Concordant/Adjacent LV Lead (n = 202)	Remote LV Lead (n = 48)	p Value
Age, yrs	72 (64–77)	71 (63–77)	74 (69–79)	0.02
Male	193 (77)	152 (75)	41 (85)	0.18
NYHA functional class IV	30 (12)	22 (11)	8 (17)	0.5
Ischemic etiology	135 (54)	107 (53)	28 (58)	0.5
Cardiac parameters				
QRS duration, ms	157 (146–170)	160 (146–176)	155 (136–171)	0.09
LVEDV, ml	187 (152–220)	187 (152–223)	190 (152–213)	0.8
LVESV, ml	143 (112–175)	143 (112–177)	140 (119–165)	0.85
LVEF, %	23 (19–29)	24 (19–29)	23 (18–29)	0.6
LV filling time, ratio	0.4 (0.35–0.46)	0.4 (0.34–0.46)	0.4 (0.35–0.5)	0.45
IVMD, ms	40 (22–57)	40 (22–57)	39 (20–66)	0.64
AS-PW delay, ms	167 (56–324)	193 (68–321)	110 (26–240)	0.08
Treatment history				
ACEI or ARB	232 (93)	189 (94)	43 (90)	0.4
Beta-blocker	178 (71)	144 (71)	34 (71)	0.95
Spironolactone	140 (56)	116 (57)	24 (50)	0.4
CRTD	92 (37)	77 (38)	15 (31)	0.5

Values are median (interquartile range) or n (%). p Value for comparison of concordant/adjacent and remote groups.
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AS-PW = anteroseptal to posterior wall delay; CRTD = cardiac resynchronization therapy defibrillator; IVMD = interventricular mechanical delay; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association functional classification.

image quality for STE analysis. *Ischemic etiology* was defined as the presence of coronary stenosis >50% by invasive coronary angiography. All patients underwent detailed clinical assessment, including a 6-min walk test, a quality-of-life questionnaire (Minnesota Living with Heart Failure Questionnaire), and echocardiography before and 6 months after CRT device implantation. *LV remodeling response* was pre-defined as a ≥15% reduction in left ventricular end-systolic volume (LVESV) at 6 months. Ongoing data on all-cause mortality were collected, with a maximal follow-up duration of 5 years. The study protocol was approved by the local ethics committee.

Echocardiography. Standard 2-dimensional (2D) echocardiography was performed using a commercially available ultrasound system (Vivid 7, GE Healthcare Vingmed, Wauwatosa, Wisconsin) and a 3.5-MHz transducer. Standard grayscale images and color Doppler data were acquired in a cine-loop format and digitally stored for off-line analysis (EchoPac version 7.0, GE Medical Systems, Horten, Norway). LVESV, left ventricular end-diastolic (LVEDV), and EF according to the biplane Simpson method, were derived from standard 2- and 4-chamber apical views. Intraventricular dyssynchrony was assessed by speckle-tracking radial strain as the time delay between the anteroseptal and posterior segments. A previously defined cutoff ≥130 ms was considered significant (14). The echocardiographic data were analyzed by assessors blinded to all other patient-related data.

Speckle-tracking radial strain analysis was performed on the pre-implantation basal and mid-LV short-axis images (frame rate ≥40 Hz) using a standardized approach, as previously described (15). The endocardial border was traced in end-systole using a point-and-click technique, with care taken to adjust tracking of all segments. A second, larger, concentric circle was then automatically generated and manually adjusted near the epicardium so that the area of interest included the entire myocardial wall. Tracking was fine-tuned by visual assessment of the cine image to ensure appropriate tracking of all segments throughout the cardiac cycle. Time-strain curves for each of the 12 nonapical

Table 2 Final Anatomic LV Lead Position

	Concordant/Adjacent LV Lead (n = 202)	Remote LV Lead (n = 48)
Anterior	8 (4%)	10 (21%)
Basal	1	0
Mid	7	10
Apical	0	0
Lateral	92 (46%)	27 (56%)
Basal	8	1
Mid	79	23
Apical	5	3
Posterior	87 (43%)	10 (21%)
Basal	2	0
Mid	68	8
Apical	17	2
Inferior	15 (7%)	1 (2%)
Basal	0	0
Mid	14	1
Apical	1	0

Values are n or n (%).
LV = left ventricular.

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segments were analyzed for time to peak strain and strain amplitude. Time to peak strain was recorded to identify the latest segment (most delayed peak) from the onset of the QRS. If >1 latest segment was identified, all late segments were reported to the implanter. A segmental strain amplitude of <10% was considered to represent scar, as previously described (11).

Optimal LV pacing site was defined, on the basis of both timing and amplitude of segmental radial strain, as the segment with the longest time to peak strain, with preserved strain amplitude ≥10%.

CRT implantation and final LV lead position. CRT implantation was undertaken via a transvenous approach in accordance with the TARGET study protocol. In the group randomized to echo-guided CRT, an attempt was made to position the LV lead at the optimal site, defined by 2D speckle-tracking radial strain. The remaining patients underwent standard CRT implantation, without echocardiographic guidance, with the LV lead placed preferentially in a posterolateral or lateral vein. Optimization of atrioventricular and interventricular delays using echocardiography was performed on the day after implantation. Further optimization was performed subsequently according to clinical need.

Final LV lead position was determined by an independent assessor using biplane fluoroscopy and post-implantation chest radiography, as previously reported (16). LV lead position was described as *basal, mid,* or *apical* on the basis of anteroposterior and right anterior oblique views, and as *anterior, lateral, posterior,* or *inferior* on the basis of the left anterior oblique view. The agreement between optimal pacing site, defined on echocardiography, and final LV lead position was described as *concordant* if positioned at the optimal site, *adjacent* if placed within 1 segment of the optimal site, or *remote* if ≥2 segments from the optimal site. In cases in which the final LV lead position was apical, this was also described as either *adjacent* or *remote* with respect to the optimal site defined on echocardiography.

Data from patients with a concordant (n = 139) or adjacent (n = 63) (i.e., optimal) LV lead position were combined for further analysis and compared to those from the group with a remote (suboptimal) lead position. This was undertaken to reflect clinical practice, in which achieving a concordant lead position may be limited by venous anatomy, lead stability, or phrenic nerve stimulation and an adjacent lead position may be the only feasible option. Furthermore, optimization in patients with an adjacent LV lead position can enhance response and negate potential deleterious effects, in contrast to optimization in patients with a remote LV lead position (17).

Statistical analysis. Continuous data are presented as median (interquartile range) or mean ± SD, and categorical data, as n (%). Continuous variables were compared using the Mann-Whitney *U* and Student *t* tests as appropriate. Categorical variables were compared by the use of the chi-square test. Kaplan-Meier curves were plotted to describe all-cause mortality according to LV lead position (either concordant/adjacent or remote from the optimal pacing site), and data from these 2 groups were compared using the log-rank test. Cox univariate proportional hazards analysis

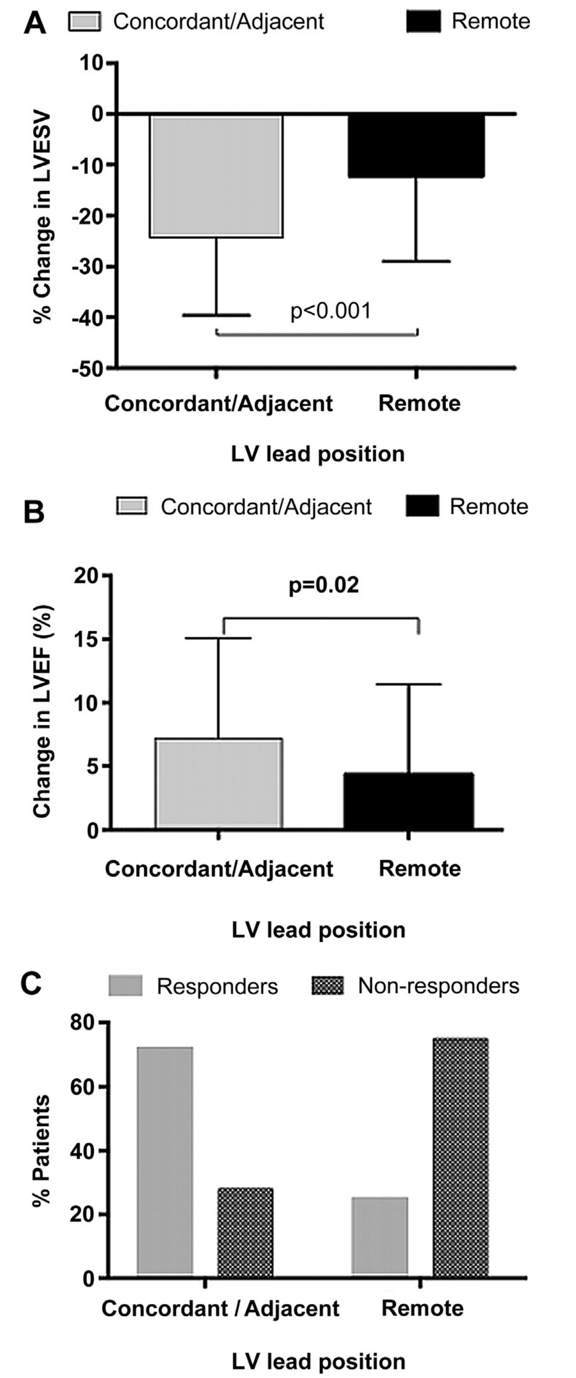

Figure 2 **LV Remodeling Response to CRT at 6 Months According to LV Lead Position**

Comparison of change in left ventricular end-systolic volumes (LVESV) **(A)** and left ventricular ejection fraction (LVEF) **(B),** according to final LV lead position. A greater proportion of patients with a concordant/adjacent LV lead position were categorized as cardiac resynchronization therapy (CRT) responders **(C).**

Table 3 Clinical Parameters at Baseline and 6-Month Follow-Up According to LV Lead Position

	All Patients (n = 250)	Concordant/Adjacent LV Lead (n = 202)	Remote LV Lead (n = 48)	p Value
NYHA functional class				
Baseline	3.12 ± 0.33	3.12 ± 0.32	3.2 ± 0.41	0.33
Follow-up	2.17 ± 0.79	2.0 ± 0.7	2.5 ± 0.8	
Change	–0.96 ± 0.78	–1.04 ± 0.73	–0.58 ± 0.92	0.002
6MWT, m				
Baseline	224 ± 96	229 ± 95	216 ± 89	0.31
Follow-up	275 ± 105	284 ± 105	233 ± 104	
Change	48.0 ± 72.7	54 ± 73	17 ± 63	0.005
MLHFQ				
Baseline	54 ± 19.9	57 ± 19	50 ± 21	0.04
Follow-up	36 ± 21	35 ± 21	43 ± 19	
Change	–19.0 ± 19.8	–21.5 ± 19.0	–7 ± 19	<0.001

Values are mean ± SD. p Value for comparison of concordant/adjacent and remote groups.
6MWT = 6-min walk test; MLHFQ = Minnesota living with heart failure questionnaire; other abbreviations as in Table 1.

was performed to identify the baseline characteristics that predicted all-cause mortality. Important clinical and echocardiographic characteristics ($p < 0.1$) were then included in a forward stepwise multivariate model. Analysis was performed using SPSS statistical software version 19.0 (IBM SPSS Statistics, IBM Corporation, Armonk, New York) and GraphPad Prism version 6 (GraphPad Software, Inc., San Diego, California). A p value of <0.05 was considered significant.

Results

Baseline patient characteristics according to final LV lead position are presented in Table 1. Patients with a remote LV lead were older than those with a concordant/adjacent LV lead position. Clinical and echocardiographic characteristics were otherwise similar between the 2 groups, and there was no difference in the proportions of patients receiving a CRT defibrillator.

The distribution of final LV lead anatomic location is shown in Table 2, stratified according to concordant/adjacent or remote position. Although a greater proportion of LV leads in the remote group were of anterior location (21% vs. 4%; $p < 0.001$) the proportion of remote LV leads (77%) located either laterally or posteriorly was similar to that in the concordant/adjacent group (89%; $p = 0.06$). The majority of patients had a nonapical LV lead position (88% vs. 11%). The proportions of patients in whom the LV lead was placed at the apex did not differ between the 2 groups (11% in the adjacent group vs. 10% in the remote group; $p = 0.8$).

Clinical and LV remodeling response to CRT. At 6-month follow-up, there were overall improvements in LVEDV (193 ± 65 ml vs. 162 ± 59 ml; $p < 0.001$), LVESV (149 ± 56 ml vs. 116 ± 49 ml; $p < 0.001$), and EF (23 ± 7% vs. 30 ± 10%; $p < 0.001$) compared with baseline, and 63% (n = 157) of patients were considered CRT responders (≥15% reduction in LVESV). Patients with a concordant/adjacent LV lead position demonstrated a superior response to CRT (72% vs. 25% response rate in the remote group; $p < 0.001$) (Fig. 2), with a greater relative reduction in LVESV (–24 ± 15% vs. −12 ± 17%; $p < 0.001$) and greater absolute increase in EF (+7 ± 8% vs. +4 ± 7%; $p = 0.02$). Patients with a concordant/adjacent LV lead also had a greater improvement in NYHA functional class, heart failure questionnaire score, and 6-min walk test score (Table 3).

Long-term survival according to LV lead location and scar. During a median follow-up duration of 39 months (range: <1 to 61 months) there were 70 deaths (49 in the concordant/adjacent group, 21 in the remote group). The survival rate in the group with concordant/adjacent LV lead position was 70% compared with 38% in the group with a remote LV lead position (log-rank $p = 0.003$) (Fig. 3). A total of 7 patients (15%) in the remote LV lead group had died before 6-month follow-up compared with 4 patients (2%) in the concordant/adjacent group ($p < 0.001$). Analysis according to the presence of low strain amplitude (scar) at the LV lead position demonstrated an impact on longer-term survival. At 5-year follow-up, patients *without* low strain amplitude at the LV lead site had a higher survival rate (log-rank $p < 0.01$) (Fig. 4). An apical (n = 28) versus nonapical (n = 222) LV lead position did not affect survival (log-rank $p = 0.48$). On Cox proportional hazards analysis, remote LV lead position was an independent predictor of impaired survival (Table 4).

Discussion

The beneficial effect of CRT on all-cause mortality in patients with a concordant or adjacent LV lead position persisted during long-term follow-up. Our definition of *optimum LV lead position* combines the assessment of both dyssynchrony (the latest segment of mechanical activation) and absence of scar (preserved strain amplitude). This is the

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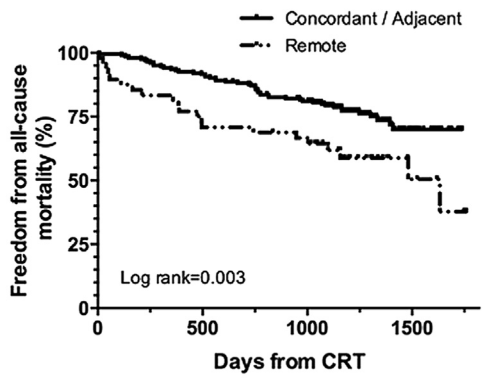
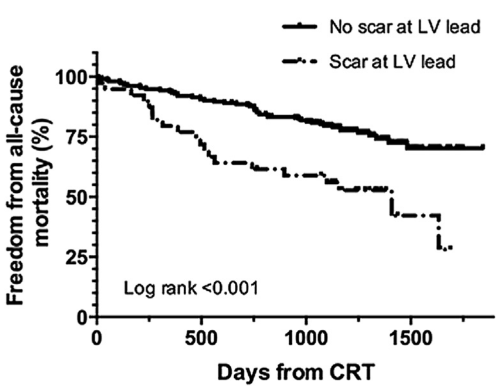


No. at risk				
Concordant/ Adjacent	202	186	156	27
Remote	48	36	32	6

Figure 3 **Kaplan-Meier Curves According to LV Lead Position**

Kaplan-Meier curves comparing estimates of time to all-cause mortality, according to LV lead position, showing a significant difference between the concordant/adjacent LV lead and the remote LV lead. Abbreviations as in Figure 2.



No. at risk				
No scar	211	190	165	30
Scar	39	29	23	4

Figure 4 **Kaplan-Meier Curves Comparing All-Cause Mortality According to the Presence or Absence of Low-Amplitude Strain (Scar) at the LV Lead**

Kaplan-Meier curves comparing estimates of time to all-cause mortality according to presence or absence of low amplitude strain at the LV lead position show impaired survival in the group with low amplitude strain. Abbreviations as in Figure 2.

longest reported prospective follow-up using this definition of *optimum pacing site* and extends previous findings from our group and those of others (5,6). In addition, a greater extent of LV remodeling, resulting in a greater proportion of CRT volume responders, and greater symptomatic improvement were observed in the concordant/adjacent group after 6 months. A remote LV lead position was an independent predictor of all-cause mortality.

The early divergence of the Kaplan-Meier curves, stratified according to LV lead position, suggests that the disadvantageous effect of a remotely placed LV lead occurs soon after implantation. After a follow-up duration of 46 months, survival in the remote group was 54.3%, qualitatively this is comparable to that in the medical-therapy arm in the CARE-HF (Cardiac Resynchronization–Heart Failure) trial (1). Data to support the concept that correction of mechanical dyssynchrony is the major mechanism of benefit from CRT are accumulating (14,18,19); however, the potential for CRT to worsen mechanical dyssynchrony remains largely unaddressed. It is conceivable that a suboptimal (remote) LV lead position may increase electromechanical activation time, leading to either no change or even deterioration in dyssynchrony and LV performance.

This potential for a deleterious effect of CRT has been alluded to in retrospective observational data from Auger et al. (20) and Sanderson and Yu (21) showing that mechanical dyssynchrony (defined by tissue Doppler imaging) not present at baseline can actually be induced in some patients after CRT and results in less favorable outcomes. Further mechanistic insight can be derived from the dyssynchrony data presented in the STARTER trial (12), in which greater mechanical resynchronization was observed in a group of patients receiving an echo-guided LV lead, comprising a smaller proportion of remote leads than that in the control group. In addition, a reduction in mechanical dyssynchrony was associated with reduced mortality and heart failure–related hospitalizations (12).

Clinical implications. Our current findings add further support for an individualized lead-targeting strategy to optimize CRT device implantation, matching the LV lead position to the underlying ventricular mechanical dysfunction. The importance of this concept is emphasized by the high proportion of patients categorized in the remote group with either a lateral or posterior LV lead, which is in contrast with early data regarding anatomic LV lead placement that would actually favor these sites. The corollary is that an anterior LV lead position may in fact be optimal in some cases, although in the majority of patients it should be avoided. A pacing strategy on the basis of pre-procedure STE is one approach that, with supporting randomized data, can be used to achieve a prospectively targeted LV lead to the latest activated myocardial segment while avoiding scar. Our group is experienced in this analysis, which is performed on routinely acquired 2D grayscale short-axis echocardiographic views. The available published reports suggest that achieving satisfactory image quality to perform this type of analysis in this patient group is feasible in the vast majority (~85% to 90%) of cases, in keeping with our clinical experience (12,15). The performance of this approach in a nonspecialist center and in a more general setting is unknown. An alternative strategy using cardiac magnetic resonance imaging to avoid pacing segments of

Table 4 Cox Univariate and Multivariate Regression Analyses on the Effect of Baseline Characteristics and LV Lead Position on All-Cause Mortality

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	95% CI	p Value
Age (per 1 yr)	1.05	1.02–1.08	<0.001	1.05	1.02–1.10	0.001
Male	2.11	1.08–4.10	0.03	1.95	0.99–3.83	0.053
ICM	1.68	1.02–2.77	0.04			
DM	1.10	0.65–1.86	0.73			
QRS duration	1.00	0.98–1.01	0.28			
CRTD	1.70	1.00–3.02	0.05			
Remote LV lead position	2.11	1.27–3.52	0.004	1.80	1.08–3.04	0.024
Dyssynchrony AS-PW >130	0.86	0.50–1.47	0.58			
Baseline EF	0.98	0.94–1.01	0.17			

CI = confidence interval; DM = diabetes mellitus; EF = ejection fraction; HR = hazard ratio; ICM = idiopathic cardiomyopathy; other abbreviations as in Table 1.

scar has also been shown to improve clinical outcomes, including all-cause mortality, cardiovascular disease–related death, and heart failure–related hospitalization (22). A multimodality imaging approach incorporating cardiac magnetic resonance scar and dyssynchrony assessment integrated with fluoroscopy has also been utilized to facilitate lead targeting (23). Ultimately, the optimum imaging modality may depend on local availability and expertise. The fundamental concept underpinning this approach is that CRT implantation is enhanced when tailored to treat patient-specific LV mechanical dysfunction.

Using the current standard transvenous implantation technique, final LV lead position is inherently dependent on coronary venous anatomy, accessibility, and lead stability. In the echo-guided LV lead groups in both the TARGET and STARTER studies, 10% and 15% of patients, respectively, had a remotely positioned LV lead. For this relatively small proportion of patients, an alternative implantation strategy may be advantageous. For example, a surgically placed epicardial LV lead, or the emerging approach of an endocardial LV lead, may overcome constraints relating to the coronary sinus and its tributaries. Given that a remotely placed LV lead may be no better than medical therapy alone when considering long-term survival, the option of avoiding implantation of a remote LV lead, or using one of these less conventional approaches, warrants consideration. This may be particularly important as CRT guidelines have been extended to include less symptomatic patients in NYHA functional class II (24,25).

Study limitations. The limitations of the TARGET study were described in the publication, and we have subsequently reported the utility of 2D radial strain imaging to identify the optimal LV pacing site to enhance response to CRT (11). Recent advances in imaging technology were not used as the initial characterization of subjects was based on echocardiographic analysis at the time of recruitment into the The TARGET study in 2008 to 2010. The data at 5 years was complete, aided by the fact that the subjects were attending 2 teaching hospitals for device follow-up and accurate recording of death through the primary care system in the United Kingdom.

Conclusions

We have shown that the initial benefits derived from CRT according to final LV lead position are sustained over longer-term follow-up. Remote placement of the LV lead was associated with early reduction in survival after implantation and was an independent predictor of impaired prognosis. Optimal device implantation requires a strategy incorporating the assessment of myocardial substrate and underlying myocardial dysfunction to guide LV lead position, and this can be readily achieved using pre-procedure 2D STE. In patients in whom anatomic or lead-stability constraints prevent an optimal location being achieved, an alternative strategy is perhaps warranted.

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REFERENCES

1. Cleland JG, Daubert JC, Erdmann E, et al., Cardiac Resynchronization–Heart Failure (CARE-HF) Study Investigators. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
2. Abraham WT, Fisher WG, Smith AL, et al., Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346: 1845–53.
3. Bristow MR, Saxon LA, Boehmer J, et al., Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
4. Daubert JC, Saxon L, Adamson PB, et al., European Heart Rhythm Association (EHRA); European Society of Cardiology (ESC); Heart Rhythm Society; Heart Failure Society of America (HFSA); American Society of Echocardiography (ASE); American Heart Association (AHA); European Association of Echocardiography (EAE) of ESC; Heart Failure Association of ESC (HFA). 2012 EHRA/HRS expert consensus statement on cardiac resynchronization therapy in heart failure: implant and follow-up recommendations and management. Europace 2012;14:1236–86.
5. Ypenburg C, van Bommel RJ, Delgado V, et al. Optimal left ventricular lead position predicts reverse remodeling and survival after cardiac resynchronization therapy. J Am Coll Cardiol 2008;52:1402–9.

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: 70–8.
7. 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;123:1159–66.
8. Becker M, Hoffmann R, Kuhl HP, et al. Analysis of myocardial deformation on the basis of ultrasonic pixel tracking to determine transmurality in chronic myocardial infarction. Eur Heart J 2006;27: 2560–6.
9. Geyer H, Caracciolo G, Abe H, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr 2010;23:351–69, quiz 453–5.
10. Becker M, Zwicker C, Kaminski M, et al. Dependency of cardiac resynchronization therapy on myocardial viability at the LV lead position. J Am Coll Cardiol Img 2011;4:366–74.
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;59:1509–18.
12. Saba S, Marek J, Schwartzman D, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region (STARTER) trial. Circ Heart Fail 2013;6: 427–34.
13. Cleland JG, Freemantle N, Erdmann E, et al. Long-term mortality with cardiac resynchronization therapy in the Cardiac Resynchronization-Heart Failure (CARE-HF) trial. Eur J Heart Fail 2012;14:628–34.
14. Gorcsan J 3rd, Oyenuga O, Habib PJ, et al. Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. Circulation 2010;122:1910–8.
15. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. Circulation 2006;113: 960–8.
16. Molhoek SG, Bax JJ, Bleeker GB, et al. Long-term follow-up of cardiac resynchronization therapy in patients with end-stage heart failure. J Cardiovasc Electrophysiol 2005;16:701–7.
17. Khan FZ, Virdee MS, Read PA, et al. Impact of VV optimization in relation to left ventricular lead position: an acute haemodynamic study. Europace 2011;13:845–52.
18. Tanaka H, Nesser HJ, Buck T, et al. Dyssynchrony by speckle-tracking echocardiography and response to cardiac resynchronization therapy: results of the Speckle Tracking and Resynchronization (STAR) study. Eur Heart J 2010;31:1690–700.
19. van Bommel RJ, Gorcsan J 3rd, Chung ES, et al. Effects of cardiac resynchronisation therapy in patients with heart failure having a narrow QRS Complex enrolled in PROSPECT. Heart 2010;96:1107–13.
20. Auger D, Bleeker GB, Bertini M, et al. Effect of cardiac resynchronization therapy in patients without left intraventricular dyssynchrony. Eur Heart J 2012;33:913–20.
21. Sanderson JE, Yu CM. Can cardiac resynchronization therapy cause harm? Eur Heart J 2012;33:816–8.
22. Leyva F, Foley PW, Chalil S, et al. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13:29.
23. Shetty AK, Duckett SG, Ginks MR, et al. Cardiac magnetic resonance-derived anatomy, scar, and dyssynchrony fused with fluoroscopy to guide LV lead placement in cardiac resynchronization therapy: a comparison with acute haemodynamic measures and echocardiographic reverse remodelling. Eur Heart J Cardiovasc Imaging 2013;14:692–9.
24. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2012;60:1297–313.
25. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33:1787–847.

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