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CLINICAL RESEARCH | Clinical Trial

Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy

The TARGET Study: A Randomized, Controlled Trial

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Objectives This study sought to assess the impact of targeted left ventricular (LV) lead placement on outcomes of cardiac resynchronization therapy (CRT).

Background Placement of the LV lead to the latest sites of contraction and away from the scar confers the best response to CRT. We conducted a randomized, controlled trial to compare a targeted approach to LV lead placement with usual care.

Methods A total of 220 patients scheduled for CRT underwent baseline echocardiographic speckle-tracking 2-dimensional radial strain imaging and were then randomized 1:1 into 2 groups. In group 1 (TARGET [Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy]), the LV lead was positioned at the latest site of peak contraction with an amplitude of >10% to signify freedom from scar. In group 2 (control) patients underwent standard unguided CRT. Patients were classified by the relationship of the LV lead to the optimal site as concordant (at optimal site), adjacent (within 1 segment), or remote (≥2 segments away). The primary endpoint was a ≥15% reduction in LV end-systolic volume at 6 months. Secondary endpoints were clinical response (≥1 improvement in New York Heart Association functional class), all-cause mortality, and combined all-cause mortality and heart failure–related hospitalization.

Results The groups were balanced at randomization. In the TARGET group, there was a greater proportion of responders at 6 months (70% vs. 55%, p = 0.031), giving an absolute difference in the primary endpoint of 15% (95% confidence interval: 2% to 28%). Compared with controls, TARGET patients had a higher clinical response (83% vs. 65%, p = 0.003) and lower rates of the combined endpoint (log-rank test, p = 0.031).

Conclusions Compared with standard CRT treatment, the use of speckle-tracking echocardiography to the target LV lead placement yields significantly improved response and clinical status and lower rates of combined death and heart failure–related hospitalization. (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy [TARGET] study); ISRCTN19717943) (J Am Coll Cardiol 2012;59:1509–18) © 2012 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) reduces both morbidity and mortality in selected patients with heart failure who remain symptomatic despite optimal medical therapy, exhibit intraventricular conduction delay, and have left ventricular (LV) dysfunction (1–3). However, a significant proportion of patients fail to achieve benefit from CRT (4). The position of the LV lead is increasingly recognized as an important determinant of response together with mechanical dyssynchrony at baseline and the extent and distribution of myocardial scar (5–8). The primary therapeutic target of CRT is restoration of coordinated myocardial contraction, and the current preferred method to achieve this is to position the LV lead at a lateral

See page 1519

or posterolateral branch of the coronary sinus based on the results of early hemodynamic studies. Recent reports have challenged this view and suggest that there is great individual variation in the optimal LV pacing site and that the effects of resynchronization may be optimally facilitated when the left ventricle is paced at the most delayed site (concordance), avoiding myocardial scar (9–11). Pacing the

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Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
2D = 2-dimensional
LV = left ventricular
LVESV = left ventricular end-systolic volume
NYHA = New York Heart Association

most delayed LV region appears to result in a better clinical response, greater LV reverse remodeling, and reduced mortality and heart failure–related hospitalization (6,12,13). Similarly, LV lead placement at areas of scar is associated with attenuated clinical and echocardiographic response (14,15). We report the findings of a randomized, controlled trial comparing the impact of prospectively targeting the LV lead at the most delayed viable segment defined by speckle-tracking echocardiography to usual treatment.

Methods

Patient population and study protocol. The TARGET (Targeted Left Ventricular Lead Placement to Guide Cardiac Resynchronization Therapy) study was a 2-center, randomized, controlled trial that enrolled patients between April 2009 and July 2010. A total of 247 consecutive patients with advanced heart failure who were eligible for CRT underwent baseline speckle-tracking echocardiography. All patients were in sinus rhythm with impaired LV systolic function (LV ejection fraction ≤35%), intraventricular conduction delay (QRS duration ≥120 ms), and New York Heart Association (NYHA) functional class III or IV symptoms despite maximal tolerated optimal medical treatment. In 27 patients (11%), image quality was not suitable for 2-dimensional (2D) radial strain analysis, and these patients were therefore excluded. The remaining 220 patients were randomized in a 1:1 ratio to 1 of 2 groups. In group 1 (TARGET), an attempt was made to position the LV lead to the optimal site as defined by 2D radial strain imaging. In group 2 (control), the patients underwent standard CRT without echocardiographic guidance. The study was approved by the local ethics committee, and the study protocol complied with the guidelines set out in the Declaration of Helsinki. All participants gave fully informed written consent, and the trial was registered on a national database (ISRCTN19717943).

Randomization and masking. Randomization was performed by a computer-generated system, and group assignment used a central fully independent system. Masking was maintained throughout the study, with all patients in both groups undergoing the same baseline and follow-up assessments and all assessors of the primary and secondary endpoints remaining blinded to group assignment.

Baseline assessment. All participants underwent detailed baseline clinical assessment including a 6-min walk test, Minnesota Living with Heart Failure Questionnaire, and echocardiography to ascertain LV volumes and function before and 6 months after device therapy. Ischemic etiology was defined as the presence of coronary stenoses of >50% by invasive coronary angiography. Standard 2D echocardiography was performed using a commercial machine (Vivid 7, General Electric Medical Systems, Horten, Norway) equipped with a 3.5-MHz phased-array transducer. The gray-scale and color Doppler data were acquired in a cine-loop format and digitally stored for post-processing offline (EchoPAC, version 7.0, GE Ultrasound, Horten, Norway). LV end-diastolic volume and left ventricular end-systolic volume (LVESV) and LV ejection fraction were calculated using Simpson's biplane method according to the guidelines of the American Society of Echocardiography (16). Interventricular dyssynchrony was determined as the difference in time from QRS onset of the continuous Doppler recordings in the pulmonary and aortic outflow tracts. Intraventricular dyssynchrony was defined using radial strain speckle analysis as the delay between the anteroseptal and posterior segments (anteroseptal-posterior wall delay) using the mid LV short-axis images, and, as previously reported, a value of >130 ms was considered significant (17). All baseline and follow-up clinical and echocardiographic data were acquired and analyzed by assessors blinded to the assigned group and to all other patient-related data.

Identification of optimal sites for LV pacing. Speckle-tracking 2D radial strain analysis of the baseline gray-scale basal and mid LV short-axis was performed in all patients as previously described (17). The data were made available to the CRT implanters to guide LV lead placement only in the TARGET group. All images were recorded with a frame rate of >40 Hz, and the endocardial border was traced using a point-and-click technique in end-systole followed by automatic generation of a second larger concentric circle that was manually adjusted to the epicardium. Speckle-tracking software automatically analyzed frame-by-frame movement of the stable patterns of natural acoustic markers (speckles) to generate time-strain curves over the cardiac cycle of the 12 nonapical segments. The latest segment of contraction was identified as the most delayed peak from the onset of the QRS duration in both the basal and mid short-axis views. When >1 segment was equally delayed, then placement of the LV lead at either site was considered to be concordant. Scar was identified using 2D radial strain as previously reported (13,18), and those segments with radial strain amplitude <10% at the LV pacing site were regarded as nonviable. This figure was chosen based on our previous work suggesting that this figure has a very high negative predictive value to identify the presence of scar in patients being assessed for CRT (19). The optimal pacing site was therefore defined using both the timing and amplitude of 2D radial strain in the basal or mid LV segment with the latest timing to peak contraction and deformation amplitude of ≥10% (Fig. 1).

CRT implantation and LV lead placement. LV lead placement at the coronary sinus was attempted using an 8-French guiding catheter (Easytrak 2/3, Aquity Guidant Corporation, St. Paul, Minnesota or Attain-SD 4194,

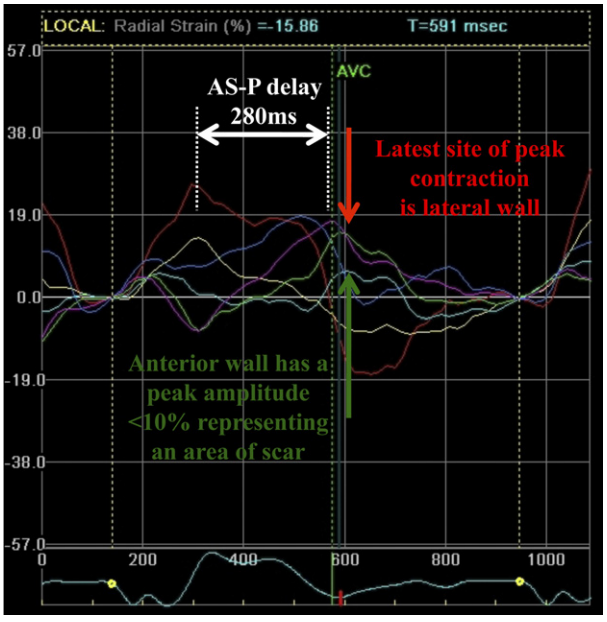

Figure 1 **Speckle-Tracking Echocardiography to Determine Optimal Sites**

Example of echocardiographic speckle-tracking 2-dimensional radial strain applied to the mid short-axis left ventricle of a single patient with ischemic cardiomyopathy and previous myocardial infarction to identify optimal pacing sites. The latest segment of peak contraction is the lateral wall **(green line)**, and left ventricular (LV) lead placement at this site would ensure a concordant lead. The peak amplitude of contraction of the anterior wall **(light blue)** is <10%, representing an area of scar, and hence this represents a segment to be avoided for LV lead placement. Significant dyssynchrony is also seen, with the time delay of peak contraction between the anteroseptum **(red line)** and posterior wall **(purple line)** (anteroseptal-posterior wall delay [AS-P]) >130 ms. Inferoseptum **(yellow line)**, inferior wall **(dark blue line)**. AVC = aortic valve closure.

Medtronic Inc., Minneapolis, Minnesota) in all patients. In the control group, this was performed according to standard clinical practice without echocardiographic guidance, preferentially at a lateral or posterolateral vein. In the TARGET group, LV lead placement was performed in a 2-step process at the pre-defined optimal site. First, the coronary venous anatomy was delineated using balloon occlusive coronary sinus venography in a steep left anterior oblique orientation (50° to 90°) such that the coronary sinus encircles the mitral valve with the tributaries radiating out (20). This left anterior oblique fluoroscopic image approximates to the short-axis parasternal echocardiographic view, enabling the coronary vein that traverses the optimal segment defined by echocardiography (anterior, lateral, posterior, or inferior segments) to be readily discernible. The appropriate vein was then selected by the operator, and an attempt was made to place the LV lead with due consideration for standard pacing parameters such as threshold, sensing, and stability. In all patients, the final position of the LV lead was determined by an independent assessor blinded to the echocardiographic data using the post-implantation chest radiographs and biplane fluoroscopy and categorized as either basal, mid, or apical in the anteroposterior and right anterior oblique projections and as anterior, lateral, posterior, or inferior in the left anterior oblique views. The LV lead was described as concordant if the LV lead paced the optimal site, adjacent if within 1 segment, or remote if ≥2 segments from the optimal site. The right ventricular lead was placed according to operator preference at either the right ventricular septum or right ventricular apex. The day after implantation, atrioventricular and interventricular delays were optimized in all patients by echocardiography. Devices were programmed in DDD mode (lower rate limit, 40) to achieve atrial synchronous biventricular pacing.

Follow-up and study endpoints. Response to CRT was defined by LV reverse remodeling as a ≥15% reduction in LVESV) at 6 months. The primary endpoint was a comparison of response between the TARGET and control groups. Secondary endpoints included clinical response (defined as ≥1 improvement in NYHA functional class), all-cause mortality, and the combined endpoint of all-cause mortality and heart failure–related hospitalization.

Statistical analysis. Analyses were conducted according to the intention-to-treat principle. The study had a statistical power of 80% to identify a 20% absolute difference in response rates between the 2 groups given a conventional 1-sided α value of 0.05. Statistical analysis was performed

Table 1 **Baseline Characteristics of Patients in Both Randomized Groups**

	Target Group (n = 110)	Control Group (n = 110)
Age, yrs	72 (65/76)	72 (64/80)
Male	85 (77)	88 (80)
NYHA functional class III/IV	95/15	93/17
Ischemic cardiomyopathy	62 (56)	61 (56)
Diabetes mellitus	30 (27)	29 (26)
Previous CABG	35 (32)	29 (26)
Previous MI	56 (51)	58 (53)
QRS duration, ms	157 (148/170)	159 (146/170)
LVEDV, ml	198 (152/231)	198 (166/221)
LVESV, ml	152 (118/183)	149 (130/176)
LVEF, %	23 (19/28)	24 (18/29)
Moderate/severe mitral regurgitation	24 (22)	27 (25)
ACEI	80 (73)	77 (70)
ARB	24 (22)	26 (24)
ACEI or ARB	104 (95)	103 (94)
Beta-blockers	78 (71)	77 (70)
Spironolactone	63 (57)	59 (54)
Loop diuretics	100 (100)	100 (100)
LV filling time, ratio	0.41 (0.37/0.46)	0.40 (0.35/0.46)
IVMD, ms	43 (22/61)	41 (25/57)
AS-P wall delay, ms	187 (101/320)	177 (120/336)

Values are median (25th/75th percentile) or n (%).

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; AS-P = anteroseptal-posterior; CABG = coronary artery bypass grafting; IVMD = interventricular mechanical delay; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; NYHA = New York Heart Association.

using commercially available software (GraphPad Prism 5 for Windows, GraphPad, San Diego, California, and SPSS statistical software, version 17.0, SPSS Inc., Chicago, Illinois). Continuous variables are expressed as mean ± SD. Categorical variables are presented as frequencies and percentages. Differences were assessed using paired and unpaired Student *t* tests for continuous variables, the chi-square test for trend for ordinal variables, or the Fisher exact test for unordered categorical variables as appropriate. A p value of <0.05 was considered statistically significant. Univariable and, to adjust for age, sex, and other baseline parameters, multivariable logistic regression analyses were used to assess the relationship of LVESV change at follow-up to the LV lead position, scar presence at the LV pacing site, and baseline LV dyssynchrony. Kaplan-Meier curves were plotted to describe all-cause mortality with and without combining with cause-specific hospitalization, and the log-rank test used to compare the groups.

Results

Patient population and baseline characteristics. No statistically significant differences were produced by the randomization process in any of the recorded baseline characteristics between patients in the TARGET and control groups (Table 1). The implantation of the LV lead failed in 7 patients (3%) (4 in the TARGET group), despite repeated attempts, due to coronary sinus dissection (n = 2), failure to intubate the coronary sinus (n = 2), absence of an appropriate coronary sinus tributary (n = 2), and intractable phrenic nerve stimulation (n = 1). Eleven patients (5%) (6 in the TARGET group) did not return for echocardiographic and clinical assessment at 6 months. Three patients in the TARGET group and 4 patients in the control group died within 6 months of device implantation and were classified as nonresponders. The proportion of patients receiving defibrillators was similar in each group (control vs. TARGET, 39.4% vs. 43.7%; p = 0.549). For the primary and secondary endpoints, data were excluded for all patients lost to follow-up in both groups and from 1 patient in each of the assigned groups who died between randomization and scheduled device therapy (time delay, 3 and 5 days, respectively). Data for all other patients were included on an intention-to-treat principle, giving 103 patients in the TARGET and 104 patients in the control groups (Fig. 2). Survival and heart failure–related hospitalization data were available for all participants.

LV lead targeting and procedural success. There were no differences in the distribution of the latest segment of activation or the overall LV lead position between the groups. However, on an individual basis, when relating the LV lead

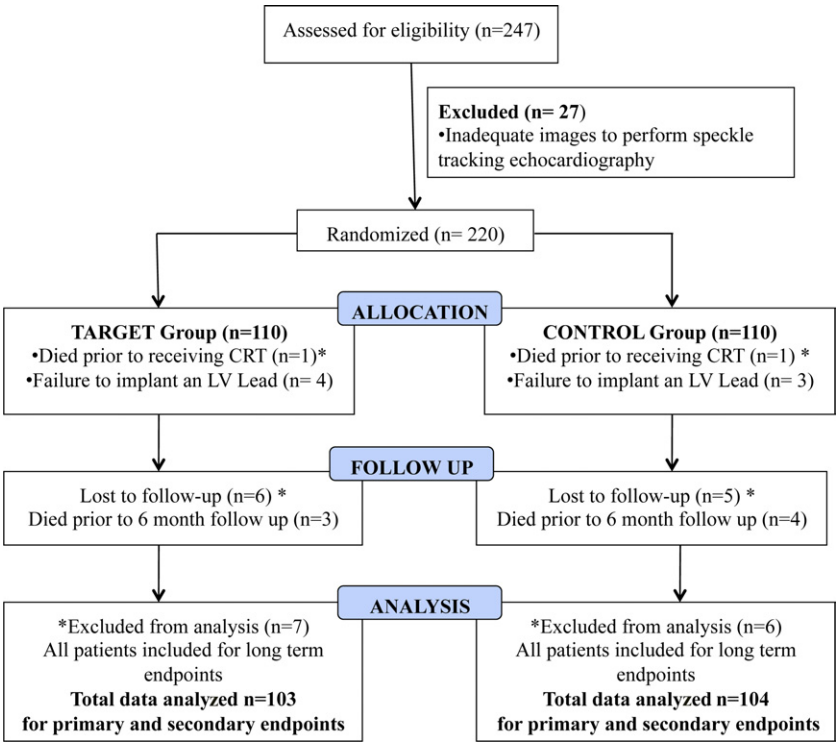

Figure 2 Consort Diagram for the TARGET Study

Consort diagram for the TARGET study illustrating the recruitment, group allocation, follow-up, and analysis of all patients. Patients excluded from the analysis of the primary endpoint were those who failed to receive a cardiac resynchronization therapy (CRT) device due to death between randomization and scheduled device implantation and those patients lost to follow-up. All other patients were included on an intention-to-treat basis. LV = left ventricular.

Table 2 Distribution of Latest Site of Activation, LV Lead Position, Implant-Related Complications, and Procedural Characteristics Between Both Treated Groups

	Target Group (n = 103)	Control Group (n = 104)	p Value
Latest site of activation, % (% basal/mid)			0.962
Inferior	13 (13) [4/9]	14 (15) [5/9]	
Posterior	38 (39) [14/24]	41 (43) [15/26]	
Lateral	32 (33) [13/19]	31 (32) [11/20]	
Anterior	9 (9) [3/6]	7 (7) [3/4]	
Anteroseptal	4 (4) [1/3]	4 (4) [1/3]	
Inferoseptal	4 (4) [1/3]	3 (3) [0/3]	
LV lead position, % (% basal/mid/apical)			0.442
Inferior	12 (12) [4/7/1]	6 (6) [1/4/1]	
Posterior	35 (36) [12/20/3]	38 (40) [14/22/2]	
Lateral	46 (47) [16/29/1]	47 (49) [13/31/3]	
Anterior	3 (3) [1/2]	6 (6) [2/4]	
Failed implantation	4 (4)	3 (3)	
Relationship of LV lead to late site			0.011
Concordant	61 (63)	45 (47)	
Adjacent	25 (26)	28 (29)	
Remote	10 (10)	24 (25)	
Failed implantation	4 (4)	3 (3)	
Scar at LV lead site	8 (8)	16 (15)	0.131
Implant-related complications			0.993
Total	13 (13)	14 (13)	
Failure to implant LV lead	4 (4)	3 (3)	
LV lead displacement requiring repositioning	5 (5)	6 (6)	
Device infection requiring extraction and reimplantation	1 (1)	1 (1)	
Pneumothorax requiring chest drain	1 (1)	1 (1)	
Myocardial perforation	1 (1)	1 (1)	
Phrenic nerve stimulation (LV lead reposition)	1 (1)	2 (2)	
Procedural characteristics			
Procedural length, min	139 ± 36	138 ± 42	0.823
Screening time, min	25 ± 14	19 ± 13	0.033
Screening dose, mGy/cm^2	133 ± 107	91 ± 69	0.024

Values are absolute numbers (%) or mean ± SD.
LV = left ventricular.

position to the latest site of activation, in the TARGET group, there more concordant leads, a similar number of adjacent leads, and fewer remote leads. The total procedural time was similar in the 2 groups, although in the target group, screening time was longer. Implant-related complications were similar in both groups (Table 2).

Primary endpoint: echocardiographic response. In the TARGET group after 6 months of CRT, 70% of the subjects (n = 72) were classified as responders compared with 55% of the subjects (n = 57) in the control group (p = 0.031). The absolute difference in primary response rates is 15% (95% confidence interval: 2% to 28%), and the number need to treat by using a targeted approach to LV lead placement to gain an additional responder is 6.6 (95% confidence interval: 4 to 49). The changes in LV end-diastolic volume, LVESV, and LV ejection fraction between both the groups at baseline and follow-up are shown in Figure 3 and Table 3.

Secondary endpoints. In the TARGET group, NYHA functional class improved by ≥1 in 83% of patients (n = 85) compared with only 65% of patients (n = 68) in the control group (p = 0.003). NYHA functional class was unchanged in 10 patients and deteriorated in 8 patients in the TARGET group; in the control group, NYHA functional class was unchanged in 24 patients and deteriorated in 12 patients. The improvement in the 6-min walk test performance and Minnesota Living with Heart Failure Questionnaire scores was greater in the TARGET group (Table 3).

Over a 2-year follow-up period, there were 22 deaths (10%) in total and 18 episodes (8%) of heart failure–related hospitalization. The 2-year all-cause mortality rates were similar in the TARGET and control groups (log-rank test, p = 0.301). The rate of the combined endpoint was, however, higher in the control group (log-rank test, p = 0.031) (Fig. 4) driven by a higher rate of heart failure–related hospitalization. In the entire cohort, long-term endpoints were evaluated according to the LV lead position and the presence of scar at the LV pacing site. Four of the deaths occurred in patients who did not receive CRT due to death before implantation or failure to implant an LV lead.

JACC Vol. 59, No. 17, 2012
April 24, 2012:1509–18

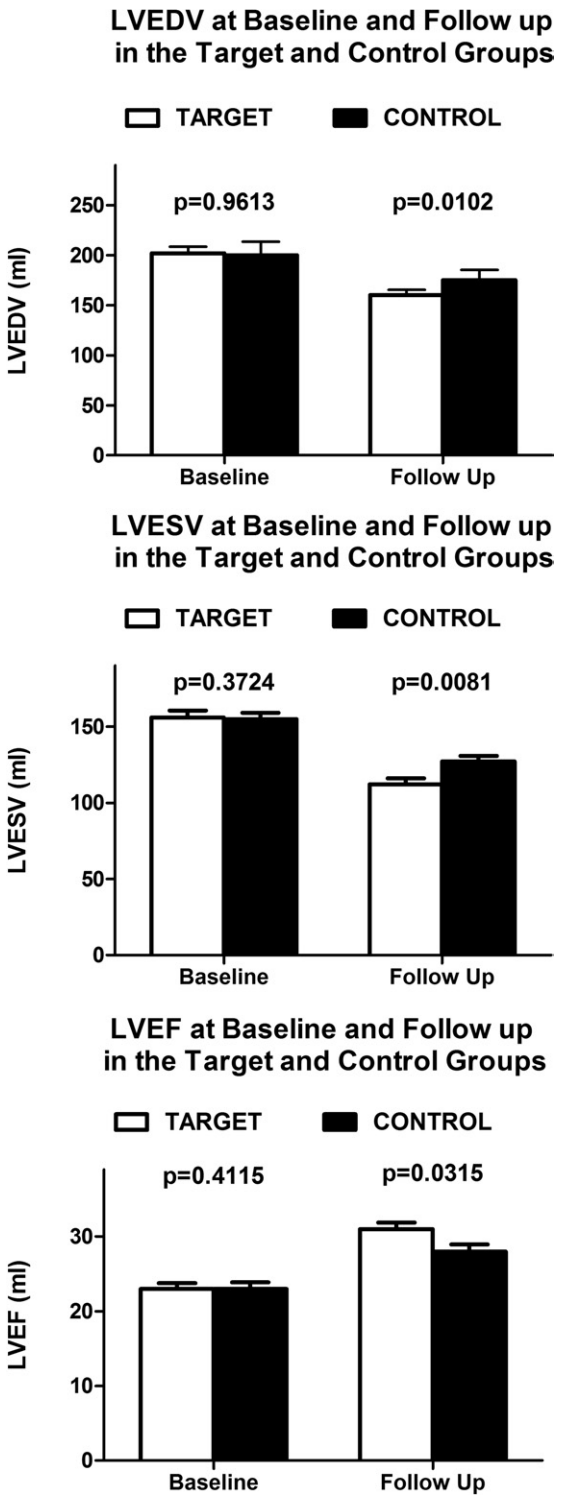

Figure 3 Comparison of LV Volumes and Function at Baseline and 6-Month Follow-up Between Both Groups

Comparison of changes in left ventricular (LV) volumes and LV function between both study groups at baseline and at 6-month follow-up showing greater improvements in LV reverse remodeling and improvements in ejection fraction in the TARGET population. LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume.

In patients with a concordant LV lead, there were 6 deaths (5%) and 12 combined deaths and heart failure–related hospitalizations (10%). This was much lower than patients with an adjacent LV lead (5 [9%] and 12 [21%], respectively) or a remote LV lead (7 [24%] and 12 [15%], respectively) (Fig. 5). In patients in whom scar was present at the LV pacing site, there were 6 deaths (29%) and 9 combined deaths and heart failure–related hospitalizations (38%). This was much higher than in patients with no scar at the LV pacing site in whom there were 12 deaths (6%) and 9 combined deaths and heart failure–related hospitalizations (5%) (Fig. 6).

Univariable and multivariable regression analyses. Univariable and multivariable regression analyses were used to determine which parameters predict LV reverse remodeling (Table 4), and increasing age, male sex, LV lead concordance, presence of scar at the LV pacing site, and dyssynchrony but not QRS duration or etiology were significantly associated with response to CRT.

Discussion

The present study prospectively demonstrates the feasibility and improved outcome associated with a targeted approach to LV lead placement during CRT implantation. Greater LV reverse remodeling, better clinical response, and a lower

Table 3 Echocardiographic and Clinical Parameters at Baseline and Follow-Up Between Both Randomized Groups

	Target (n = 103)	Control (n = 104)	p Value
NYHA functional class			
Baseline	3.1 ± 0.3	3.1 ± 0.3	
Follow-up	2.0 ± 0.7	2.3 ± 0.7	
Change	−1.1 ± 0.7	−0.8 ± 0.7	0.002
6MWT, m			
Baseline	222 ± 92	229 ± 95	
Follow-up	282 ± 101	268 ± 112	
Change	61 ± 76	38 ± 76	0.011
MLHFQ			
Baseline	55 ± 21	53 ± 20	
Follow-up	33 ± 21	38 ± 22	
Change	−22 ± 20	−16 ± 19	0.024
LVEDV, ml			
Baseline	202 ± 66	200 ± 58	
Follow-up	160 ± 51	176 ± 56	
Change	−41 ± 34	−23 ± 23	0.001
LVESV, ml			
Baseline	157 ± 56	154 ± 52	
Follow-up	111 ± 43	128 ± 50	
Change	−46 ± 33	−26 ± 23	0.001
LVEF, %			
Baseline	23 ± 6	23 ± 7	
Follow-up	31 ± 9	28 ± 10	
Change	8 ± 7	5 ± 8	0.001

Values are mean ± SD.

6MWT = 6-min walk test; MLHFQ = Minnesota Living With Heart Failure Questionnaire; other abbreviations as in Table 1.

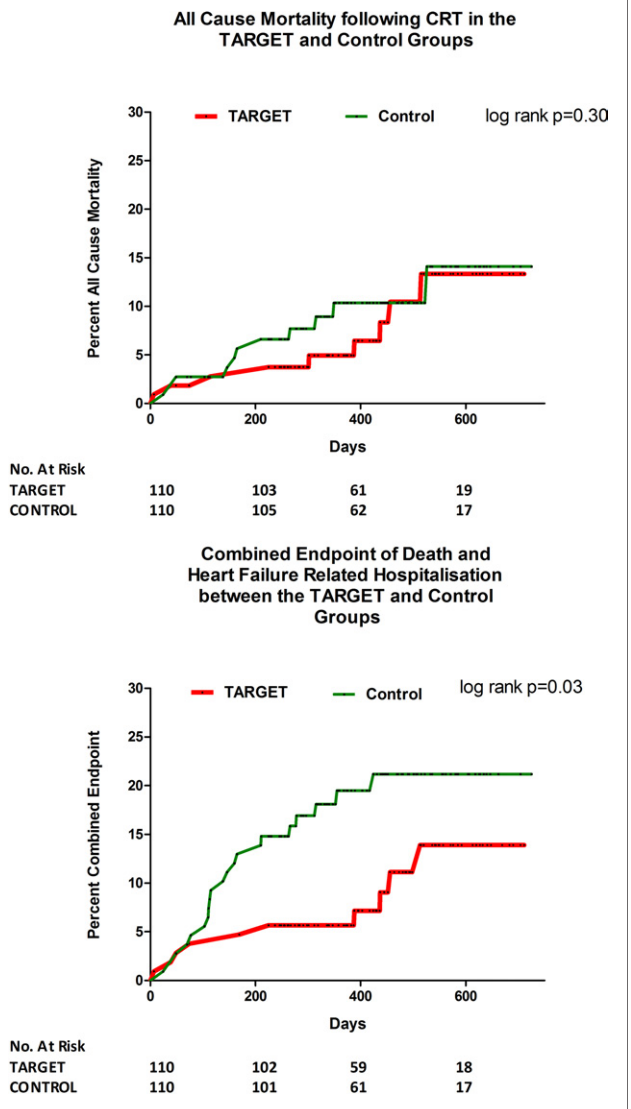

Figure 4 **Kaplan-Meier Curves Comparing Both Randomized Groups**

Kaplan-Meier curves for the outcomes of all-cause mortality and the combined endpoint of all-cause mortality and heart failure–related hospitalization for both groups are shown. There were no significant differences in all-cause mortality, although there were significant differences in the combined endpoint driven by lower rates of heart failure–related hospitalization. CRT = cardiac resynchronization therapy.

rate of the combined endpoint of death and heart failure–related hospitalization (largely driven by the latter) was found with guided LV lead implantation using echocardiographic speckle-tracking 2D radial strain imaging. Multivariate analysis suggests that the greatest benefit is demonstrated in patients with a concordant LV lead at sites free of scar, with significantly lower responses in patients with either an LV lead remote to the latest site of contraction or when pacing scar.

A number of studies reported that CRT is superior to optimal medical treatment in patients with advanced heart failure (1,2,21,22). Consistent in all of these reports is a failure to derive any significant benefit in a substantial minority of all recipients of device therapy. A number of factors have been implicated in this lack of response to CRT including mechanical dyssynchrony, but defining the abnormal LV function at echocardiography has not enhanced clinical response. However, the underlying pathophysiology of bundle branch block and contractile dysfunction results in

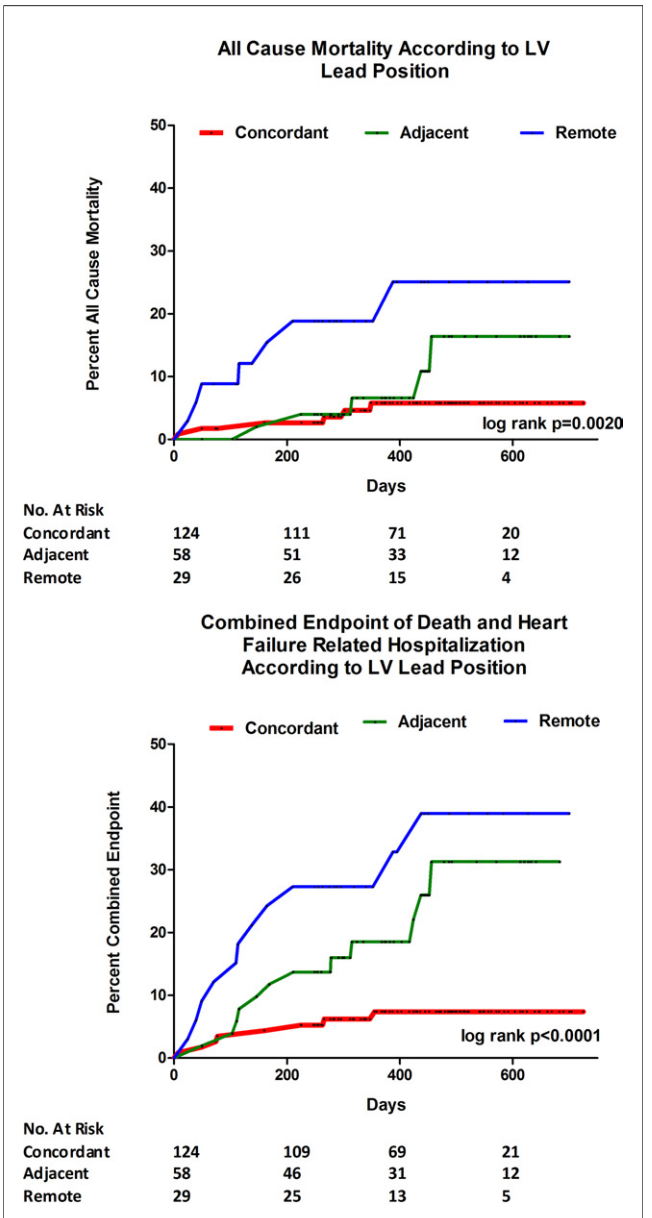

Figure 5 **Kaplan-Meier Curves Comparing Groups According to LV Lead Position**

Subgroup analysis of all patients across both groups was conducted to assess the effect of left ventricular (LV) lead position on outcomes. Kaplan-Meier curves for the outcomes of all-cause mortality and the combined endpoint of all-cause mortality and heart failure–related hospitalization for all 3 groups (concordant, adjacent, and remote LV lead positions) are shown. There were significant differences in all-cause mortality and the combined endpoint in all 3 groups.

JACC Vol. 59, No. 17, 2012
April 24, 2012:1509–18

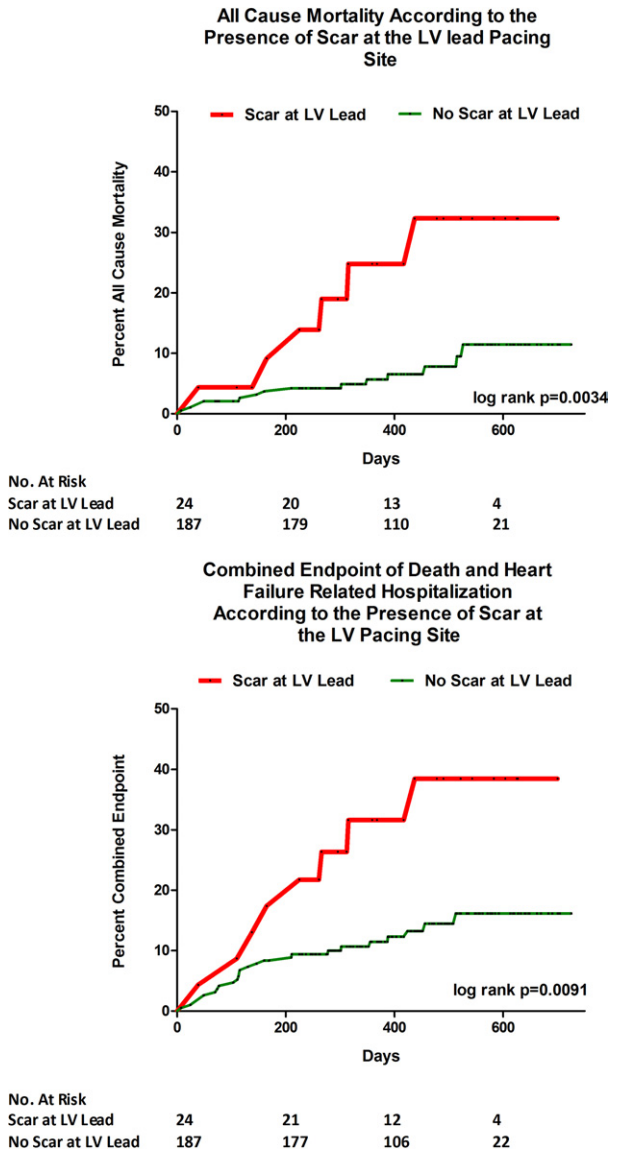

Figure 6 Kaplan-Meier Curves Comparing Groups According to Presence or Absence of Scar at LV Pacing Site

Subgroup analysis of all patients across both groups was conducted to assess the effect of the presence or absence of scar at the left ventricular (LV) pacing site. Kaplan-Meier curves for the outcomes of all-cause mortality and the combined endpoint of all-cause mortality and heart failure–related hospitalization are shown. There were significant differences in all-cause mortality and the combined endpoint according to the presence or absence of scar at the LV pacing site.

intraventricular conduction delay that generates regions of both early and delayed activation within the left ventricle leading to wasted work, increased end-systolic volume, wall stress, and a further decline in myocardial efficiency (23–25). The reversal of these deleterious effects through coordination of myocardial contraction is the primary target of CRT. However, the extent to which this may be achieved has not been previously assessed in a randomized trial of LV lead location and the underlying myocardial substrate with respect to the delayed LV segments and distribution of myocardial scar.

The conventional approach to resynchronization has been to direct the LV lead to the lateral and posterior wall based on the benefit shown in early hemodynamic studies and the observation that delayed segments predominate at these sites. However, recent data support a more individualized approach to LV lead placement with significant interindividual and intraindividual variation in the optimal LV lead position (9,11). In addition to such acute hemodynamic data, a number of reports using imaging techniques demonstrated that pacing the latest segment of contraction leads to more energetically efficient ventricular ejection, greater LV reverse remodeling, improved survival, and reduced heart failure–related hospitalization compared with those patients with discordant pacing leads (12,26,27). Similarly, patients with extensive scar or scar in the region of the LV pacing site show lower response rates to CRT and a poorer prognosis (15,28). Deformation imaging by speckle-tracking radial strain imaging can identify myocardial scar, and in this study, we used a value of <10% to define scar because this figure has been derived and validated by our group in a CRT population and related to LV lead position (19). Avoiding nonviable myocardium is important, but being able to identify the optimal pacing site but not reach it via a suitable coronary vein is an inherent limitation of transvenous CRT implantation (29). In this study, the targeted approach achieved the aim of a higher proportion of concordant LV leads with fewer remote leads and leads over regions of scar with low lead complication rates. Furthermore, in this randomized study, subgroup analyses confirm previous reports that the greatest clinical response is seen in patients with a concordant LV lead, together with

Table 4 Univariate and Multivariate Regression Analyses on the Effect of Each Variable on LV Reverse Remodeling at 6 Months

	OR	95% CI	p Value
Univariate regression analysis			
Age	1.05	1.01–1.80	0.007
Male	2.09	0.99–4.43	0.054
Ischemic etiology	1.74	0.97–3.12	0.064
QRS duration	1.00	0.98–1.01	0.474
No scar at LV pacing site	2.40	1.02–5.70	0.046
Dyssynchrony	5.51	2.90–10.40	0.010
Concordant LV lead	5.30	2.80–9.96	0.010
Multivariate regression analysis			
Age	1.06	1.01–1.11	0.018
Male	2.85	1.02–7.96	0.045
Ischemic etiology	1.54	0.69–3.43	0.293
QRS duration	0.99	0.97–1.01	0.224
No scar at LV pacing site	3.06	1.01–9.26	0.048
Dyssynchrony	5.95	2.78–12.7	0.009
Concordant LV lead	4.43	2.09–9.40	0.009

CI = confidence interval; LV = left ventricular; OR = odds ratio.

improved survival and a reduction in the combined endpoint of death and heart failure–related hospitalization.

Despite targeting, the limitations of coronary venous anatomy appear to have restricted concordance to only two thirds of patients, and 8% of all patients still had LV lead placement at areas of scar. Our data suggest that as many as one third of all patients may require additional assessment to guide and achieve optimal LV lead placement including coronary venous anatomy and precise delineation of scar, areas of late contraction, or late electrical activation. Although this approach may restrict implantation to more specialized centers, it may enable CRT to achieve its full potential in the therapeutic armamentarium of advanced heart failure. It is also important to identify those patients in whom it will not be possible to place the LV lead appropriately to enable alternative routes to be considered. The present study demonstrated that a relatively simple investigative tool can be used to guide LV lead placement with significant benefits over and above usual LV lead placement.

Study limitations. Two-dimensional radial strain imaging was used to determine the optimal LV pacing site based on the delayed segment and lowest amplitude associated with the highest negative predictive value in those being considered for CRT. However, radial strain may not be the best technique, and further work related to examining changes in circumferential strain or combined patterns of strain may have had superior results. Furthermore, 3-dimensional speckle tracking, which was not widely available at the commencement of this study, may better define the optimal site with greater potential for coregistration of different imaging techniques. Importantly, not everyone will be able to undergo speckle-tracking echocardiography as 11% of patients were excluded from this study due to inadequate image quality. Dyssynchrony is one of the major underlying abnormalities within the left ventricle of this group of patients with heart failure, and yet despite the results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study, it is clear that adequate and clinically relevant characterization of such abnormal contraction is not readily offered by a single investigation. Speckle-tracking echocardiography offers additional information regarding myocardial function and may predict the benefit from CRT by radial strain analysis (13,30–32), but further studies using more recent technological developments may increase our understanding of how to use device therapy to treat ventricular dysfunction. In our study, we made no attempt to pre-select patients on the basis of dyssynchrony parameters, nor was consideration given to the extent of total scar burden. The presence of both of these parameters would tend to reduce the overall benefit, although this would be distributed in both groups. CRT response may therefore be enhanced by integrating measures of dyssynchrony and total scar burden with a targeted approach to lead placement, and such an approach should be tested in future studies.

Conclusions

The TARGET study is the first randomized, controlled study to demonstrate the benefit of a targeted approach to LV lead placement in CRT, resulting in significant benefit defined by LV reverse remodeling, clinical status, and the long-term endpoint of combined death and heart failure–related hospitalization. The study prospectively confirms the importance of the LV lead position in CRT outcomes and demonstrates the feasibility of LV lead targeting using speckle-tracking radial strain imaging as a modality to guide lead placement. Given this randomized trial's observed number needed to treat for a response of approximately 7 (95% confidence interval: 4 to 49), an individualized approach to LV lead placement should be considered in all patients undergoing CRT for advanced heart failure to yield a significant improvement over current routine practice.

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