Sites of left and right ventricular lead implantation and response to cardiac resynchronization therapy observations from the REVERSE trial

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Objectives
The objective of this study is to ascertain the effects of the left (LV) and right (RV) ventricular lead tip position in response to cardiac resynchronization therapy (CRT).

Background
The REVERSE randomized trial examined the effects of CRT in patients with asymptomatic or mildly symptomatic heart failure (HF).

Methods
We analysed data collected from the active group (CRT-ON) of REVERSE in whom the precise locations of the LV and RV ventricular lead tips were determined from postoperative chest roentgenograms as part of a prespecified sub-study. LV position was classified as lateral or non-lateral, and apical or non-apical. RV position was classified as apical or non-apical. Echocardiographic LV end-systolic volume index (LVESVI), QRS duration, and clinical outcomes at 12–24 months of follow-up were evaluated with respect to the lead tip position. The primary trial endpoint was the proportion of patients with a worsened HF clinical composite response, scored as improved, unchanged, or worsened.

Results
 Totally 346 patients included in this analysis were followed for a median of 12.6 months (interquartile range: 11.9–23.9 months). The proportion of worsened HF clinical composite response did not correlate with lead position, whereas a significantly greater decrease in the powered secondary endpoint of LVESVI was observed with the non-apical vs. the apical LV lead positions. CRT-paced QRS duration was significantly shorter than at baseline in patients with lateral vs. non-lateral LV position, as well non-apical vs. apical LV position. The incidence of composite endpoint of death and first hospitalization for HF was lower in the LV lateral than in the non-lateral (HR 0.44; 95% CI 0.19–0.99; P = 0.04), and in the LV non-apical than in the apical group (HR 0.27; 95% CI 0.11–0.63; P = 0.001). No significant differences were observed between RV apical and non-apical positions of the lead tip.

Conclusions
A more favourable outcome of CRT with regard to LV reverse remodelling and the composite of time to death or first HF hospitalization was observed when the LV lead tip was implanted in the lateral wall, away from the apex, while the position of the RV lead tip was indifferent. The long-term change in QRS duration was significantly associated with the position of the LV lead tip.

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Keywords
Cardiac resynchronization ● Left ventricular stimulation ● Right ventricular stimulation ● Ventricular dyssynchrony ● Heart failure

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Stimulation site and response to CRT

Introduction

The influence of the left (LV) and right (RV) ventricular positions of the lead tips on the clinical outcomes of, and response to cardiac resynchronization therapy (CRT) remains unclear. It is presumed that an LV lateral wall position of the lead tip is optimal,¹,² though this has not been confirmed by a controlled study including the analysis of the data by a core centre.³ Recent observations from the MADIT CRT trial revealed that the outcomes of patients whose LV lead was in a position other than at the apex were more favourable than when it was in an apical position, though the superiority of a lateral, compared with a non-lateral LV lead position could not be confirmed.⁴ However, the influence of the RV lead tip position was not examined.

We report the results of a prespecified sub-analysis of the active group (CRT-ON) of the REVERSE trial,⁴ in whom the precise locations of the LV and RV lead tips were determined by a core centre, based on postoperative antero-posterior and lateral chest roentgenograms. The effects of the lead tip positions were ascertained by the 12-month clinical and echocardiographic responses, and the death and heart failure (HF) hospitalizations at the end of follow-up according to a prespecified protocol of the study in patients assigned to CRT-ON.

The REVERSE trial

The design and results of this international, multicentre, double-blinded randomized clinical trial have been reported in detail.⁵,⁶ Briefly, in the main study, 610 adults presenting with a QRS duration ≥ 120 ms and an LV ejection fraction (EF) ≤ 40% received a CRT defibrillator (CRT-D) or CRT pacemaker (CRT-P) device, and were randomly assigned in a 2:1 ratio to CRT-ON (active group) or CRT-OFF (control group) for 12 months. The position of the LV lead was not randomly assigned. The investigators were recommended to place the LV lead in a lateral or postero-lateral position, when possible, though had received no precise recommendation regarding the placement of the RV lead.

The 262 patients enrolled by European medical centres remained in the randomized arm for a total of 24 months. All patients had suffered from New York Heart Association (NYHA) functional class II or class I, American College of Cardiology/American Heart Association stage C stable HF for ≥ 3 months before entry into the trial, and were optimally treated according to the published international practice guidelines.⁷,⁸ The primary trial endpoint was the proportion of patients with a worsened HF clinical composite response, scored as improved, unchanged, or worsened, according to Packer.⁹ The prospectively powered secondary trial endpoint was the change in LV end-systolic volume index (LVESVi)—an index of reverse ventricular remodelling. The combination of hospitalization for management of decompensated HF or all-cause mortality was another secondary clinical endpoint.

At 1 year, the proportion of worsened patients was similar (P = 0.10) in both randomized groups of the main trial.⁹ LVESVi decreased significantly in the CRT-ON (P < 0.001) but remained unchanged in the CRT-OFF group. At 2 years, in the European sample, the proportion of worsened patients was significantly lower in the CRT-ON when compared with the CRT-OFF group (P = 0.01).⁹ The effect on LVESVi increased over 18 months and remained stable thereafter, indicating progressive reverse remodelling by CRT (P < 0.001). Furthermore, the incidence of first hospitalization for HF or to death from any cause was significantly lower in the CRT-ON than in the CRT-OFF group (P < 0.001).

Data collection and analysis by the Core Centre

Antero-posterior and lateral chest roentgenograms were obtained before discharge of the patients from the hospitals. Digital images were sent to the core laboratory for analysis (Rennes University Medical Centre, Rennes, France). Each image was analysed by an expert radiologist (C.M.) and an expert cardiologist (R.G.) not otherwise involved in the REVERSE study. The inter-observer concordance was re-evaluated after the interpretation of 50 images.

The position of the LV lead tip was ascertained in the lateral view, using an original model with a 12-box diagram (Figure 1), and classified.

1. On the longitudinal axis, as posterior, lateral, antero-lateral, or anterior. In the final analysis, posterior and lateral were combined as ‘lateral’ and antero-lateral and anterior were combined as ‘non-lateral’.

2. On the vertical axis as superior (boxes 1–4), mid (boxes 5–8), or inferior (boxes 9–12). The diagonal (hatched) line separated the LV apical from the non-apical position.

The position of the RV lead tip was ascertained on the antero-posterior and lateral views, and classified as apex, mid-septum, high-septum, or free wall (Figure 2). In the statistical analysis, all RV non-apical positions were classified as ‘non-apical’.

Surface electrocardiogram

The 12-lead surface electrocardiograms (ECGs) were recorded at 25 and 50 mm/s during spontaneous rhythm, before implantation of the CRT device and at 12 months with biventricular pacing, and analysed by Rennes’ University Core Centre. The QRS duration was measured on a tracer table from nine consecutive cycles in leads II, V₆, and V₆. The intra- and inter-observer reproducibilities were evaluated by a second measurement of 50 randomly selected ECGs, prepared by another expert interpreter, who was unaware of the first expert’s interpretation. The intra- and inter-observer coefficients of variability of the non-paced and paced QRS complexes were 1.6% and 1.4%, and 6.4% and 2.6%, respectively.

Study endpoints

The clinical, echocardiographic, and ECG responses in the CRT-ON group were evaluated with respect to the lead tip position at 12 months of follow-up. The clinical outcome was evaluated by the proportion of patients experiencing the composite of: (i) % worsened by the clinical composite; (ii) LVESVi defined as the proportion of patients whose LVESVi had decreased by ≥ 15% at 12 months; (iii) the ECG response, defined as the
CRT-paced QRS duration at 12 months when compared with the intrinsic QRS duration at baseline; (iv) time to first hospitalization for management of HF; (v) time to death from any cause; and (vi) combined endpoints of time to hospitalization for HF or death during follow-up.

**Statistical analysis**

Continuous variables are expressed as means ± standard deviations (SD). Categorical data are presented as counts and percentages. Between-group comparisons of the baseline clinical characteristics and echocardiographic and ECG endpoints, stratified by the LV and RV lead position, were made using Student’s t-test for continuous variables and Fisher’s exact test for dichotomous variables. Additionally, LVEF was compared between combinations of RV–LV lead using ANOVA. Curves of cumulative probability of death and hospitalization for management of HF were constructed according to the Kaplan–Meier method, and the cumulative event rates were compared by the log-rank test. Hazard ratio (HR) estimates with 95% confidence intervals (CI) were calculated by Cox proportional hazards regression analysis. Time to event was analysed over 1 year of randomization for non-European, and 2 years for European patients. All tests were two-sided and a P-value < 0.05 was considered statistically significant. All analyses were performed using the SAS statistical package, version 9.2 (SAS Institute Inc., Cary, NC, USA).
Results

The 346 patients included in this analysis were followed for a median of 12.6 months (interquartile range: 11.9–23.9 months).

Distribution of the left ventricular and right ventricular lead tip positions

Chest roentgenograms of acceptable quality were available in 346 of the 419 patients randomly assigned to the CRT-ON group. Ultimately, the precise lead-tip position could be ascertained in 345 patients for the RV lead and in 285 patients for the LV lead. The main reasons for missing data were poor quality images (two of three cases), absence of lateral view (one of three cases), and presence of two LV leads in three patients. The LV lead tip position was classified as postero-lateral in 60.0%, lateral in 20.4%, antero-lateral in 15.8%, and anterior in 3.8% of patients along the longitudinal axis. Based on the bisector-separation, the position of the LV lead tip was classified as apical in 13.7% and non-apical in 86.3%. The position of the RV lead tip was apical in 68.7% and non-apical in 31.3% of patients, including the high septum in 4.3%, mid-septum in 24.0%, and free wall in 2.9%. The lateral LV position was associated with an RV apical position in 54.9% and RV non-apical position in 25.7% of configurations. The non-lateral LV position was associated with an RV apical position in 13.4% and RV non-apical position in 6% of configurations.

Lead-tip position and baseline clinical characteristics

The baseline characteristics of the patients were classified according to the position of the LV and RV lead tips. Table 1 shows the clinical characteristics of (i) the whole study population, (ii) LV lateral vs. non-lateral groups, (iii) LV apical vs. non-apical groups, (iv) RV apical vs. non-apical groups, and (v) LV and RV combined. The main baseline characteristics, including age, gender, NYHA class, disease aetiology, QRS duration, LVEF, LV dimensions, and drug treatment were similar among groups. Furthermore, recipients of CRT-D were more likely, as expected, to receive an apical than a non-apical RV lead ($P < 0.0001$).

Response to cardiac resynchronization therapy at 12-month and left ventricular–right ventricular lead tip position

There was a significantly higher proportion of echocardiographic responders ($P = 0.016$) in recipients of non-apical vs. apical LV lead tips. Otherwise, the 12-month rates of clinical and echocardiographic responders were similar regardless of the positions of the LV or RV leads (Table 2). Similarly, no difference was found among the four LV and RV combinations (respectively, $P = 0.69$ and $P = 0.65$, for the clinical and echocardiographic responses). In contrast, a highly significant shortening of the QRS was observed at 12 months in the LV lateral and in the LV non-apical, compared with the LV non-lateral and LV apical groups. The changes in QRS duration width at 12 months and RV apical vs. non-apical groups were not significantly different.

Clinical outcome in relation to left ventricular and right ventricular lead-tip position

The % of worsened patients (the primary study endpoint) evaluated by the clinical composite was not correlated with the lead position. However, a significantly greater decrease in LVEFSi (the powered secondary endpoint) was observed in the non-apical as opposed to the apical LV position. The CRT-paced QRS duration was significantly smaller than the intrinsic QRS duration at baseline in recipients of lateral vs. non-lateral LV lead tips, and in recipients of non-apical vs. apical LV tips (Table 3). The estimated incidence of death or more than one hospitalization for management of HF at 1 and 2 years of follow-up for different positions of the LV and RV lead tip is also shown in Table 3. The incidence of the composite endpoint was significantly lower in the LV lateral than in the non-lateral group (HR 0.44; 95% CI 0.19–0.99; $P = 0.04$; Figure 3), and in the LV non-apical than in the apical group (HR 0.27; 95% CI 0.11–0.63; $P = 0.001$; Figure 4). The difference was mainly attributable to lower rates of hospitalizations for management of HF. No significant differences were observed between the RV apical and non-apical positions and among the four LV and RV configurations ($P = 0.16$).

Discussion

Our study shows that the clinical outcome and LV reverse remodeling of patients undergoing CRT for mildly symptomatic HF depends on the position of the LV but not the RV lead tip. The lateral and non-apical LV positions were associated with a significantly lower 1–2 years risk of hospitalization for management of HF or of death from any cause, though had no effect on the 1-year rate of clinical and echocardiographic response, as defined in this study indicating that the effect of LV lead-tip position develops over ≤24 months.

Position of the left ventricular lead tip

This is the second, large multicentre study that examined the impact of the LV lead location on the clinical outcome of CRT, which included the prospective acquisition of cardiac images and analysis by an independent core centre. In the MADIT CRT trial, the lead position was ascertained from perioperative venograms in the right and left anterior oblique views.3 The LV lead position was classified as anterior, lateral, or posterior along the short axis, and basal, mid-ventricular, or apical along the long axis. The primary endpoint was HF event or all-cause mortality during a mean follow-up of 29 months. No significant differences were observed among the anterior, lateral, and posterior locations. However, an apical LV position was associated with a significantly higher rate of primary endpoint than a non-apical lead position.4 While the primary endpoint in REVERSE was different, this observation is concordant with ours, supporting the recommendation to avoid placing the lead at the apex in clinical practice.

Unlike the MADIT CRT trial, we found that a lateral LV position was associated with a significantly lower risk of hospitalization for management of HF or of all-cause mortality than a non-lateral position. These discordant results might be explained by different methodologies and proportions of leads placed in ‘lateral’ positions.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All enrolled patients (n = 419)</th>
<th>Patients in analysis (n = 346)</th>
<th>LV lateral vs. non-lateral</th>
<th>LV apical vs. non-apical</th>
<th>RV apical vs. non-apical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>Age (years)</td>
<td>62.9 ± 10.6</td>
<td>62.6 ± 10.7</td>
<td>62.9 ± 10.5</td>
<td>63.9 ± 11.7</td>
<td>62.9 ± 10.8</td>
<td>0.56</td>
</tr>
<tr>
<td>Men</td>
<td>327 (78%)</td>
<td>261 (75%)</td>
<td>173 (76%)</td>
<td>44 (79%)</td>
<td>29 (74%)</td>
<td>0.73</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>85.1 ± 17.8</td>
<td>84.5 ± 17.7</td>
<td>83.8 ± 17.5</td>
<td>82.3 ± 15.3</td>
<td>83.6 ± 18.2</td>
<td>0.57</td>
</tr>
<tr>
<td>NYHA functional class II</td>
<td>344 (82%)</td>
<td>282 (82%)</td>
<td>184 (80%)</td>
<td>42 (75%)</td>
<td>29 (74%)</td>
<td>0.36</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>236 (56%)</td>
<td>194 (56%)</td>
<td>134 (59%)</td>
<td>29 (52%)</td>
<td>20 (51%)</td>
<td>0.37</td>
</tr>
<tr>
<td>Diabetes</td>
<td>91 (22%)</td>
<td>76 (22%)</td>
<td>49 (21%)</td>
<td>15 (27%)</td>
<td>11 (28%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Intrinsic QRS duration (ms)</td>
<td>153 ± 21</td>
<td>154 ± 21</td>
<td>154 ± 22</td>
<td>154 ± 22</td>
<td>154 ± 23</td>
<td>0.94</td>
</tr>
<tr>
<td>LV Ejection fraction (%)</td>
<td>26.8 ± 7.0</td>
<td>26.6 ± 7.0</td>
<td>26.7 ± 7.3</td>
<td>25.2 ± 6.1</td>
<td>25.9 ± 6.4</td>
<td>0.15</td>
</tr>
<tr>
<td>Diameter (cm)</td>
<td>6.7 ± 0.9</td>
<td>6.7 ± 0.9</td>
<td>6.7 ± 0.9</td>
<td>6.7 ± 0.8</td>
<td>6.8 ± 0.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>268 ± 89</td>
<td>267 ± 87</td>
<td>265 ± 91</td>
<td>275 ± 83</td>
<td>280 ± 71</td>
<td>0.46</td>
</tr>
<tr>
<td>Glomerular filtration rate (mL/min)</td>
<td>84.2 ± 31.3</td>
<td>83.6 ± 30.6</td>
<td>83.0 ± 29.5</td>
<td>76.3 ± 33.6</td>
<td>79.6 ± 34.2</td>
<td>0.14</td>
</tr>
<tr>
<td>Minnesota living with heart failure score</td>
<td>27.0 ± 20.1</td>
<td>27.5 ± 20.2</td>
<td>27.4 ± 20.0</td>
<td>24.8 ± 20.3</td>
<td>28.4 ± 22.9</td>
<td>0.41</td>
</tr>
<tr>
<td>Distance covered in 6-min hall walk (m)</td>
<td>398 ± 125</td>
<td>396 ± 127</td>
<td>398 ± 135</td>
<td>398 ± 111</td>
<td>374 ± 131</td>
<td>0.98</td>
</tr>
<tr>
<td>Drug therapy</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ACE-inhibitors or ARB</td>
<td>404 (96%)</td>
<td>331 (96%)</td>
<td>218 (95%)</td>
<td>53 (95%)</td>
<td>36 (92%)</td>
<td>0.74</td>
</tr>
<tr>
<td>β-adrenergic blocker</td>
<td>401 (96%)</td>
<td>330 (95%)</td>
<td>218 (95%)</td>
<td>53 (95%)</td>
<td>37 (95%)</td>
<td>0.74</td>
</tr>
<tr>
<td>At least 50% of target dose of β-adrenergic blocker</td>
<td>255 (61%)</td>
<td>213 (62%)</td>
<td>146 (64%)</td>
<td>34 (61%)</td>
<td>24 (62%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Diuretic</td>
<td>339 (81%)</td>
<td>276 (80%)</td>
<td>181 (79%)</td>
<td>50 (89%)</td>
<td>34 (87%)</td>
<td>0.09</td>
</tr>
<tr>
<td>CRT-D implanted</td>
<td>345 (82%)</td>
<td>280 (81%)</td>
<td>181 (79%)</td>
<td>42 (75%)</td>
<td>32 (82%)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Values are means ± SD (compared with Student's t-test) or numbers (%) of observations (compared with Fisher's exact test).
### Table 2  Clinical, echocardiographic and electrocardiographic responses to CRT classified according to the positions of the left ventricular (LV) and right ventricular (RV) lead tips

<table>
<thead>
<tr>
<th>Measurement</th>
<th>All patients in analysis</th>
<th>LV</th>
<th>Non-lateral</th>
<th>P-value</th>
<th>Apical</th>
<th>Non-apical</th>
<th>P-value</th>
<th>RV</th>
<th>Apical</th>
<th>Non-apical</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>346</td>
<td>229</td>
<td>56</td>
<td></td>
<td>39</td>
<td>246</td>
<td></td>
<td>237</td>
<td>108</td>
<td></td>
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</tr>
<tr>
<td>Worsened</td>
<td>57 (16)</td>
<td>40 (17)</td>
<td>10 (18)</td>
<td>1.00*</td>
<td>9 (23)</td>
<td>41 (17)</td>
<td>0.36*</td>
<td>35 (15)</td>
<td>21 (19)</td>
<td>0.27*</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>101 (29)</td>
<td>64 (28)</td>
<td>21 (38)</td>
<td></td>
<td>9 (23)</td>
<td>76 (31)</td>
<td></td>
<td>72 (30)</td>
<td>29 (27)</td>
<td></td>
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<tr>
<td>Improved</td>
<td>188 (54)</td>
<td>125 (55)</td>
<td>25 (45)</td>
<td>1.00*</td>
<td>21 (54)</td>
<td>129 (52)</td>
<td>0.36*</td>
<td>130 (55)</td>
<td>58 (54)</td>
<td></td>
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<tr>
<td>Number of patients with paired observations</td>
<td>291</td>
<td>189</td>
<td>52</td>
<td></td>
<td>34</td>
<td>207</td>
<td></td>
<td>197</td>
<td>93</td>
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<tr>
<td>12-month change in LVESVi</td>
<td></td>
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<tr>
<td>△ (mL/m²)</td>
<td>−18.7 ± 29.1</td>
<td>−19.5 ± 27.2</td>
<td>−15.0 ± 29.4</td>
<td>0.30</td>
<td>−11.9 ± 26.4</td>
<td>−19.6 ± 27.8</td>
<td>0.13</td>
<td>−18.2 ± 30.4</td>
<td>−19.9 ± 26.2</td>
<td>0.64</td>
<td></td>
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<tr>
<td>≥15% relative decrease</td>
<td>157 (54)</td>
<td>108 (57)</td>
<td>24 (46)</td>
<td>0.21</td>
<td>12 (35)</td>
<td>120 (58)</td>
<td>0.016</td>
<td>101 (51)</td>
<td>56 (60)</td>
<td>0.17</td>
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<td>QRS duration (ms)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>151 ± 22</td>
<td>152 ± 22</td>
<td>149 ± 23</td>
<td>&lt;0.0001</td>
<td>149 ± 24</td>
<td>152 ± 22</td>
<td>0.57</td>
<td>152 ± 22</td>
<td>151 ± 23</td>
<td>0.63</td>
<td></td>
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<tr>
<td>12 months</td>
<td>148 ± 23</td>
<td>145 ± 22</td>
<td>163 ± 24</td>
<td>&lt;0.0001</td>
<td>149 ± 23</td>
<td>146 ± 23</td>
<td>&lt;0.001</td>
<td>147 ± 23</td>
<td>149 ± 23</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>△</td>
<td>−4.2 ± 26.8</td>
<td>−8.4 ± 26.0</td>
<td>14.3 ± 24.0</td>
<td>&lt;0.0001</td>
<td>11.3 ± 28.3</td>
<td>−5.9 ± 26.3</td>
<td>&lt;0.001</td>
<td>−5.3 ± 27.3</td>
<td>−1.5 ± 25.5</td>
<td>0.29</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD or numbers (%) of observations. LVESvi, left ventricular end-systolic volume index; △, change between baseline and 12 months.

*aFisher’s exact test.
We ascertained the position of the LV lead tip along the long axis on a lateral view, which can influence the ultimate identification of the lead location. More importantly, the proportion of ‘lateral’ positions, including true lateral and postero-lateral, was 80.4% in REVERSE compared with 59% in MADIT CRT. A higher proportion of lateral and postero-lateral LV lead position in our study was not surprising as this was the pacing site recommended by the study protocol, and since we only allowed expert CRT
operators for safety reasons. This >20% difference may have influenced the overall clinical outcome and increased the probability of finding a significant difference between ‘lateral’ and non-lateral positions. Our data support the superior response by stimulation of the LV free wall observed in short-term studies of CRT, an observation, however, not confirmed thus far in long-term studies. The significant shortening of the QRS duration at 12 months in patients whose leads had been implanted in lateral vs. non-lateral, and in non-apical vs. apical positions is noteworthy. In contrast, the position of the RV lead tip had no significant effect on the width of the paced QRS. This could be interpreted as the result of less electrical dyssynchrony, as well as an indicator of less mechanical dyssynchrony. Early studies found a close relationship between the immediate haemodynamic benefit conferred by CRT and changes in electrical dyssynchrony. Furthermore, a delayed activation at the site of LV lead predicted a response to CRT.

**Standard vs. targeted left ventricular lead placement**

As in the MADIT CRT trial, our LV lead implantation technique hinged mainly on the anatomy of the coronary venous network and on the accessibility of the veins. However, in the REVERSE trial, as opposed to MADIT CRT, it was recommended to implant the lead in the lateral or postero-lateral wall, whenever possible, and no attempt was made to find an optimal LV stimulation site. In addition, since REVERSE focused on patients suffering from mild HF, in whom the risk of CRT-related complications might have been larger than the benefits, participation in the study was limited to experienced centres, which might not represent the ‘real-world’ practices. However, several studies have found a considerable variability in the sequence of ventricular activation and distribution of mechanical dyssynchrony among recipients of CRT systems. Consequently, the optimal LV pacing site varies widely among patients depending on several factors, including the type of conduction delay and, in patients with ischaemic heart disease, on the location and size of myocardial scars. Echocardiographic imaging techniques, speckle tracking in particular, seem able to identify the latest site of LV contraction with acceptable accuracy and reproducibility in individual patients. Preoperative echocardiography has been proposed, in recent years, as a guide to implantation of the LV lead at the optimal or near-optimal site. Preliminary studies showed improvements in the echocardiographic responses to CRT with targeted lead placement. TARGET, a recent randomized, parallel-arms trial, compared the echocardiogram-guided vs. empirical lead placement in patients with standard indications for CRT. The LV lead was placed at or near the optimal site identified by speckle tracking in 86% of patients in the echocardiogram-guided arm vs. 73% of patients in the control group. Despite these small differences, the proportion of echocardiographic responders at 6 months was 70% in the echocardiogram-guided vs. 55% in the control group ($P = 0.01$), and a trend towards better clinical outcomes was observed. By multiple variable analysis, a concordant LV lead placement and stimulation away from areas of scar were correlated with improved CRT outcomes. These observations might explain the difficulty to demonstrate, when applying the standard

**Figure 4** Cumulative incidence of composite clinical endpoint associated with implant of the left ventricular lead in an apical vs. non-apical position.
approach, an incremental benefit conferred by a specific stimulation site,\textsuperscript{3,4} which, depending on the patient, might be a mix of optimal and suboptimal lead tip position. Nevertheless, the technical feasibility and long-term merit of LV lead targeting remains to be proven. For the time being, we find the general recommendation to favour a lateral, and avoid an apical implantation of the LV lead, most appropriate.

**Position of the right ventricular lead tip**

In previous, short-term studies, the RV stimulation site seemed to have an effect on the pattern and degree of LV dyssynchrony in CRT candidates.\textsuperscript{30} We evaluated prospectively the impact of the RV lead tip position on the long-term outcome of CRT. The REVERSE trial made no recommendations regarding the placement of the RV lead, though the apex was preferred in 78% of recipients of CRT-D to optimize the stability of the lead and of the energy required to defibrillate. The RV lead was ultimately placed at the apex in 68%, and in the septum or elsewhere in 32% of patients. No significant differences were observed between an RV apical vs. non-apical lead placement with respect to the clinical and echocardiographic responses or clinical outcomes. These observations are concordant with those made in a relatively large observational study published recently.\textsuperscript{31} They do not support the use of alternate RV stimulation sites for CRT, though this remains to be definitively addressed in a randomized trial.

**Strengths and limitations of the study**

The main strength of our study was the independent analysis, by a core centre, of the prospectively collected, postoperative chest roentgenograms. The method we used to determine the LV and RV lead tips locations, based on post-operative roentgenograms, is simple and widely applicable, though has some limitations. It has been suggested that the radiographic lead position does not invariably correspond to the true anatomic position ascertained by perioperative venous angiograms, used as a reference.\textsuperscript{4} Our means of determination of the LV lead-tip position in the lateral view did not take into account the rotation of the apex associated with left heart enlargement.\textsuperscript{32} However, the risk of misclassification was mitigated by a combined analysis of the antero-posterior view. The LV lead positions were not randomly assigned. In the REVERSE trial, placement of the lead in a lateral position was systematically attempted, and other positions accepted only when a lateral position was not attained. Leads in non-lateral positions were, therefore, implanted in a particular subgroup of patients, a selection which may have influenced the results.

Finally, the relatively high proportion of patients with missing data, the small number of patients in some subgroups, and the follow-up limited to 12 or 24 months, depending on where the patients were recruited, are limitations of our study.

**Conclusion**

A more favourable outcome of CRT with significantly prolonged time to HF-related hospitalizations or deaths was observed when the LV lead tip was implanted in the lateral wall, away from the apex, while the position of the RV lead tip was indifferent. These observations suggest that these are the preferred LV lead positions for CRT.

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**References**


29. Khan FZ, Virdee MS, Pugh PJ, O’Halloran D, Elsk M, Read PA, Begley D, Fynn SP, Dutka DP. Targeted left ventricular lead placement using speckle tracking echocardiography improves the acute hemodynamic response to cardiac resynchronization therapy: a randomized controlled trial. J Am Coll Cardiol 2011;57:E2033 (Abstract).

