Progressive reverse remodeling in patients with mild or asymptomatic heart failure with previous symptoms in the REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study.

Clinical Trial Update III

Session number:
4484-4485

Session title:
Clinical Trial Update III

Authors:
Linde, Cecilia & Vardas, Panagiotis

Presenter report:

Linde, Cecilia (Sweden)

The REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study is the first multi-center, randomized, double-blind controlled trial to assess whether CRT plus optimal medical therapy (CRT ON) can attenuate heart failure (HF) progression compared to optimal medical therapy alone (CRT OFF), in patients (pts) with NYHA I or II HF, QRS-duration ≥ 120 ms and LV ejection fraction ≤ 40%. At 12 months, the HF clinical composite endpoint indicated 16% worsened in CRT ON compared to 21% in CRT OFF (p=0.10). Pts assigned to CRT ON experienced a greater improvement in LVESVi (-18.4 versus -1.3 ml/m², p<0.0001) and other measures of LV remodeling. Time to first HF hospitalization was significantly delayed in CRT ON (hazard ratio 0.47, p=0.03).

Methods: 610 pts in NYHA II (82%) or I (18%) were randomized in 73 centers in the US, Canada and Europe. 262 pts were randomized in Europe where randomized follow-up continues for 24 months. We now present the 18 month results in European pts with special regard to reverse left ventricular remodelling.

Hypothesis: We hypothesized that reverse remodeling continues to evolve over time. Therefore, the 18 month follow-up in European countries could reveal meaningful differences in pts randomized between CRT ON and CRT OFF, concerning progressive reverse remodeling and possibly a continued divergence in the time to first HF hospitalization survival curves as a sign of delayed disease progression by CRT.
Results: There was a progressive reduction in LVESVI (-27 versus -7 ml/m², p<0.0001) and LVEDVi (-28 versus -6 ml/m², p<0.0001) over 18 months in the CRT ON compared to OFF groups. Mean LVEF increased by 7.6% in CRT ON versus +2.4% in CRT OFF, p<0.0001. The HF clinical composite response endpoint indicated 15% worsened in CRT ON compared to 29% in CRT OFF (p=0.007).

The study was not powered to demonstrate differences in healthcare utilization but important long-term implications of CRT have emerged. Although there was no difference in mortality between treatment assignments, the time to first HF hospitalization was significantly reduced in the CRT ON compared to OFF group (CRT ON (3.9%) and CRT OFF (11.2%) (hazard ratio 0.34, p=0.03).

Conclusions: The long-term (18 month) findings from REVERSE show that CRT in combination with optimal medical therapy (± defibrillator), induces progressive reverse remodeling in mildly symptomatic HF patients, which in turn reduces the risk for heart failure hospitalization in NYHA I and NYHA II (ACC/AHA stage C) patients with previous HF symptoms. This means that CRT may modify disease progression in such patients.

<table>
<thead>
<tr>
<th>Discussant report:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vardas, Panagiotis (Greece)</strong></td>
</tr>
</tbody>
</table>

Cardiac Resynchronization Therapy (CRT) has been found to improve both morbidity and mortality and reverse the remodeling of the left ventricle in patients with NYHA functional class III-IV having intraventricular conduction disturbances.

To date, two non-randomized trials have shown that CRT might be beneficial in patients with less severe heart failure too. The REVERSE study is the first randomized study designed to examine the role of CRT in patients with NYHA class I-II heart failure symptoms and reduced systolic LV function (mean LVEF was 26.7±7.0% and the mean LVEDD was 66.9±8.9 mm).

During the first 12 months, no differences were noted regarding the primary end point; that is the HF clinical composite response (all-cause mortality, heart failure hospitalizations, CRT activation due to worsening heart failure, worsened NYHA class and patient global assessment). It was found though that CRT improves LV remodeling and the time-to-first-hospitalization.

Regarding the effect of CRT on the incidence of ventricular arrhythmias, no beneficial effect was established; indeed it seems that there was a non-significant trend towards an increase in VT/VF episodes in patients with CRT ON.

However, the data analysis of the patients enrolled in Europe (who were followed-up for a longer period) shows a significant improvement, both in the clinical composite score and LV remodeling, at 18 months follow-up. It seems that in such patients with mild heart failure, the benefit of CRT requires a longer period of time to become apparent and thus, the results of the 24 month follow-up
are of particular interest. Nevertheless, before reaching hasty conclusions concerning the role of CRT in mild HF, care must be exercised to take cost-effectiveness and the incidence of side effects and complications into account that would justify the CRT device implantation, a relatively expensive and potentially dangerous procedure.

**Notes to editor**

This congress report accompanies a presentation given at the ESC Congress 2008. Written by the author himself/herself, this report does not necessarily reflect the opinion of the European Society of Cardiology.

LIVE from ESC Congress