MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy): cardiac resynchronization therapy towards early management of heart failure

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This commentary refers to ‘Cardiac-resynchronization therapy for the prevention of heart-failure events’, by A.J. Moss et al., published in the New England Journal of Medicine, 2009; 361:1329–1338

Randomized clinical trials have firmly established the role of cardiac resynchronization therapy (CRT) in chronic heart failure patients in New York Heart Association (NYHA) class III or IV who have left ventricular dysfunction and a prolonged QRS complex. CRT improves symptoms, reduces the need for hospitalizations, and improves survival by reversal of left ventricular remodelling and by slowing of disease progression.

In these CRT trials, patients were selected on the basis of the degree of heart failure. COMPANION included 86% class III and 14% class IV patients. CARE-HF included 94% NYHA class III and 6% class IV patients. Thus, the data on the beneficial effects of CRT, based on large trials, are restricted to class III and to a lesser degree to class IV patients. In contrast, in primary prevention implantable cardioverter defibrillator (ICD) trials, the spectrum of patients was broader. Although SCD-HeFT also selected heart failure patients in class III (30%), the majority were in class II (70%).3 The two post-myocardial infarction trials, MADIT and MADIT II, included an even broader spectrum of heart failure patients although primary inclusion was on the basis of ejection fraction and history of prior myocardial infarction. MADIT included 35% of patients in class I, and 65% in class II–III. In MADIT II, 37% of patients were in NYHA class I, 35% in class II, 24% in class III, and 5% in class IV.5

Since CRT induces progressive reverse left ventricular remodelling and slows disease progression in patients with NYHA class III or IV heart failure, it might also be beneficial in patients with less severe heart failure. Small studies have suggested that CRT may indeed reverse left ventricular remodelling in NYHA class II patients.6–8 However, the impact of CRT in class I and II patients on various outcome parameters has been a matter of debate.

Only recently, this issue was addressed in a larger randomized trial that tested whether CRT is effective in reducing clinical endpoints in either asymptomatic (class I) but previously symptomatic, or less symptomatic patients (class II). The REVERSE trial (RESynchronization reVErses Remodeling in Systolic left vEntricular dysfunction)9 randomly assigned 610 patients with NYHA functional class I or II heart failure with a QRS duration of ≥0.12 s and a left ventricular ejection fraction of ≤40% (mean 27%) who all received a CRT device (with or without an ICD) to active CRT (CRT-ON, n = 419 patients) or control (CRT-OFF, n = 191) for 12 months. All patients had to be on a stable heart failure medication for at least 3 months before enrolment. REVERSE failed to reach the primary endpoint of a heart failure clinical composite response which compared only the percentage of patients worsened (16% worsened in CRT-On vs. 21% in CRT-Off, P = 0.10). However, patients assigned to CRT-ON experienced a greater change in echocardiographic left ventricular end-systolic volume index and other measures of left ventricular remodelling. The time to first hospitalization was significantly delayed in patients randomized to CRT-ON [hazards ratio (HR) 0.47, P = 0.003]. The mortality rate at 1 year was 2.2% for the CRT-ON group and 1.6% for the CRT-OFF group (P = 0.63). The authors concluded from this relatively small trial that CRT may delay disease progression in heart failure patients with less severe symptoms through left ventricular remodelling.
MADIT-CRT: new evidence for the benefit of CRT

At the Hot Line Session of the 2009 ESC Congress, on 1 September 2009, Arthur Moss, Rochester, NY, presented for the first time the results of the MADIT-CRT trial (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). The trial recruited a population similar to REVERSE, but three times more patients were included (1820 vs. 610 patients). Both trials had started in 2004. Recruitment in REVERSE ended in 2006 (follow-up 12 months) whereas MADIT-CRT, due to its larger patient numbers, ended recruitment in 2008 (average follow-up 2.4 years).

During follow-up, 17.2% of patients in the resynchronization group and 25.3% in the ICD group experienced the primary endpoint of all-cause mortality or a heart failure event, whichever occurred first [HR 0.66, 95% confidence interval (CI) 0.52–0.84; P = 0.001], with similar benefit in patients with ischaemic and non-ischaemic cardiomyopathy. Superiority of resynchronization therapy was driven by a 41% reduction in the risk of a first heart failure event without an effect on the 3% annual mortality in each treatment group. Resynchronization therapy was associated with significant reduction in left ventricular volumes and improvement in ejection fraction.

Comparison between REVERSE and MADIT-CRT: the same message?

Apart from the number of patients included, the baseline clinical characteristics such as age, gender, NYHA class I or II, ischaemic vs. non-ischaemic, diabetes mellitus, use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), β-blockers, diuretics, systolic and diastolic blood pressure, and end-systolic and end-diastolic volumes on echocardiography were almost identical. The inclusion criteria differed between REVERSE and MADIT-CRT, respectively, with regard to QRS width (≥0.12 vs. ≥0.13 s) and ejection fraction (≤0.40 vs. ≤0.30). This may explain that for patients without and with CRT, mean QRS duration in MADIT-CRT (159 and 158 ms, respectively; A. Moss, personal communication) was slightly longer than in REVERSE (154 and 153 ms). This may be related to the somewhat lower ejection fraction in MADIT-CRT (24% in both groups) vs. 26.4 and 26.8% (in patients without and with CRT) in REVERSE. The slightly higher mortality in MADIT-CRT (3% in both groups) than in REVERSE (2.2% for CRT-ON and 1.6% for CRT-OFF; P = 0.63) is in line with the slightly broader QRS complexes and the somewhat lower ejection fraction in MADIT-CRT.

Looking at subgroups may only help to generate hypotheses. Doing so, it is remarkable that both trials did not show an effect either on the ‘heart failure clinical composite response of worsening’ (as used in REVERSE) or for ‘death or heart failure’ (in MADIT-CRT) in those patients with a QRS width <0.15 s, whereas a benefit was found in both trials in those with a broader QRS.

Although there were differences in endpoints between these trials, both came up with a similar message, i.e. that in class I or II patients CRT improves the function and structure of the left ventricle, and leads to a decrease in the need for hospitalization due to heart failure, but that it has no effect on mortality. Indeed, mortality was low in both trials, as can be expected from a NYHA class I and II population, despite the low ejection fraction of the left ventricle.

In REVERSE, 85% (CRT-OFF group) and 82% (CRT-ON group) received an ICD, whereas all patients in MADIT-CRT did so. Thus, it can be assumed that the populations were comparable with previous ICD trials such as MADIT II and SCD-HeFT with regard to ejection fraction and other clinical characteristics. Both trials suggest—although MADIT-CRT presents the strongest evidence—that CRT is able to halt the progression of heart failure but does not have an effect on mortality (which was low anyway), at least not during the follow-up period of 1 year (REVERSE) or 2.4 years (MADIT-CRT).

Open issues

Is the evidence similarly strong for class I and II patients? This and other questions might be answered by merging the original data from both trials into a meta-analysis.

Patient characteristics were not much different from previous ICD trials, especially with regard to ejection fraction. Should we re-define the present guidelines for primary ICD implantation to include CRT and, if so, to all patients with a QRS duration of ≥0.12 s (or ≥0.13 s)? Or should there be a cut-off of ~0.15 s as suggested by the subgroup analyses in both trials? Should parameters of dyssynchrony be added?

Another question is what makes some patients with a low ejection fraction less symptomatic than others with similar low ejection fractions and why do they have a better clinical outcome.

Mortality in class I and II heart failure patients is low. However, if progression of the disease in the long term is retarded by CRT, does this translate into a lower mortality as the disease would normally progress and as long as no competing risks occur?11 It may be difficult to find an answer to this issue since the present data from MADIT-CRT but also from REVERSE may make it at least difficult if not impossible to carry out another randomized trial with and without CRT which, as a mortality trial, would require a very large population.

Conclusions

CRT is an effective therapy in improving heart failure-related manifestations in patients with poor left ventricular function who frequently are eligible for primary prevention ICD implantation with an ischaemic or non-ischaemic aetiology and broad QRS complexes of ≥0.12 s (REVERSE) or ≥0.13 s (MADIT-CRT) but with no or only minimal symptoms.

The MADIT-CRT investigators are to be congratulated that they have carried out this large and convincing trial.
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