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Lessons from the trials

REVERSE 5-year follow up: CRT impact persists

Mohamed ElMaghawry*, Mahmoud Farouk

Department of Cardiology, Aswan Heart Centre, Kasr ElHajjar, Aswan, Egypt
*Email: Maghawry79@gmail.com

ABSTRACT

The role of cardiac resynchronization therapy (CRT) in patients presenting with mild manifestations of heart failure (HF), depressed left ventricular ejection fraction (LV EF), and wide QRS complex, has been addressed in four previous trials: MIRACLE ICD II,[1] MADIT-CRT,[2] RAFT,[3] and REVERSE.[4] The consistent observed benefits in reverse cardiac remodelling and reduction of heart failure adverse events have resulted in guideline recommendations for CRT in NYHA Class II patients. The guidelines also recommend further studies to determine whether survival is increased by CRT in patients with mild symptoms. The 5-year analysis of the REsynchronization reVErses Remodeling Systolic left vEntricular (REVERSE) trial, which was designed prospectively for 5-year follow-up to specifically assess the long term benefits of CRT, were recently published in the *European Heart Journal*.[5]

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STUDY DESIGN AND RESULTS

The REVERSE trial was a prospective, randomized, double blind, parallel-controlled multinational study designed to determine whether CRT limited the progression of HF compared with optimal medical therapy alone. The study included 610 patients with ACC/AHA stage C, NYHA Class I or II HF patients with QRS more than 120 msec, and LVEF less than 40% on optimal medical therapy. Patients were implanted with a CRT-device with (CRT-D) or without (CRT-P) defibrillator and randomized 2:1 to CRT ON ($n = 419$) or CRT OFF ($n = 191$). Patients were then programmed as randomized through 12 months in North America and through 24 months in Europe. By the study design, all patients were programmed to CRT ON after the randomization period and followed for 5 years from implantation. First enrollment occurred in September 2004, and enrollment was completed in September 2006.The final 5-year follow-up was in November 2011.The primary end point was HF clinical composite response, which scores patients as improved, unchanged, or worsened. The prospectively powered secondary end point was LV end-systolic volume index. Hospitalization for worsening HF was evaluated in prospective secondary analysis of health care use.

The initial results were published in 2009 in the *Journal of American College of Cardiology*. They showed The HF clinical composite response end point, which compared only the percent worsened, indicated 16% worsened in CRT-ON compared with 21% in CRT-OFF (p 0.10). Patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index (18.4 29.5 ml/m 2 vs. 1.3 23.4 ml/m 2, 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).[4]

The five-year follow up analysis was confined to 419 subjects randomized to CRT ON, who received up to 5 years of CRT therapy. The mean follow up time was 54.8 ± 13.0 months. After 2 years, the functional and LV remodelling were maximal. The 6-min hall walk increased by 18.8 ± 102.3 minutes and the Minnesota and Kansas City scores improved by 8.2 ± 17.8 and 8.2 ± 17.2 unites, respectively. The mean decrease in left ventricular end-systolic volume index and left ventricular end-diastolic volume index was 23.5 ± 34.1 mL/m^2 and 25.4 ± 37.0 mL/m^2 and the mean increase in LVEF 6.0 ± 10.8% with sustained improvement thereafter (Figure 1). The annualized and 5-year mortality was 2.9 and 13.5% and the annualized and 5-year rate of death or first HF hospitalization 6.4, and 28.1%. The 5-year LV-related complication rate was 12.5%.[5]

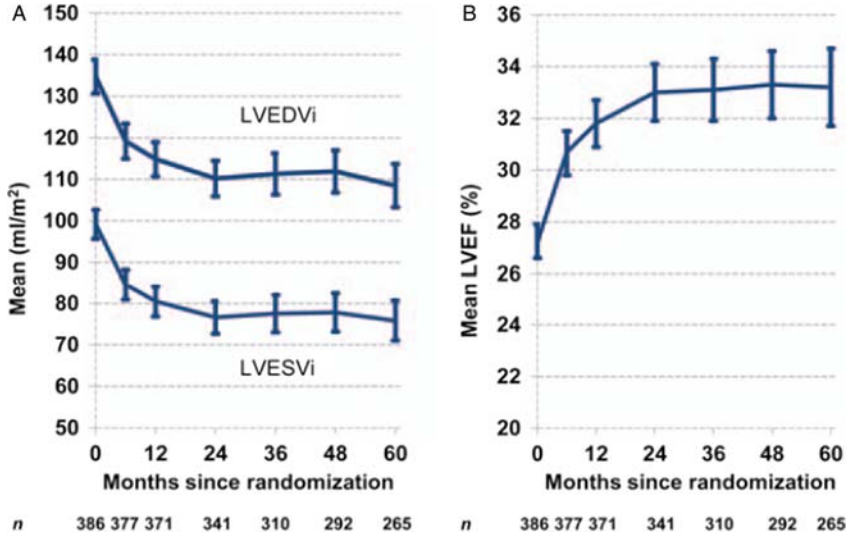

Figure 1. Left ventricular end-systolic volume index, left ventricular end-diastolic volume index (A), and left ventricular ejection fraction (B) over the follow up period of 60 months.[2]

CRITIQUE

The 5-year results of REVERSE confirmed that CRT in mildly symptomatic HF and wide QRS reverses remodeling and is associated with low rates of HF hospitalization and all-cause mortality over the entire follow-up.

CRT effect in mildly symptomatic HF patients was first tested on 186 patients (101 control and 85 CRT) in the MIRACLE ICD II trial, which was published in 2004. The results from the study demonstrated that CRT significantly improved the cardiac structure and function over a 6-month period of follow up in optimally treated patients. In the larger MADIT-CRT, published in 2009, the use of CRT combined with an ICD in asymptomatic or mildly symptomatic patients with heart failure and a reduced ejection fraction and wide QRS complex was associated with 34% reduction in the risk of death or heart failure events, as compared with the use of an ICD alone. This benefit was driven by 41% reduction in the risk of heart failure events, a finding that was evident primarily in subgroup of patients with a QRS duration of 150 msec or more. Similarly, the RAFT trial, published in 2010, found the addition of CRT to an ICD and optimal medical therapy reduced rates of death and hospitalization for HF among patients with mild-to-moderate HF, a reduced LV EF, and a wide QRS complex over a period of 40 months of follow-up.

The echocardiographic studies from REVERSE, MADIT-CRT, and CARE-HF[6] showed substantial improvements in LV size and function, LVEF, RV function, left atrial size and mitral regurgitation severity in patients treated with CRT compared with ICD only. These findings were strongly concordant with and predictive of the primary outcome of death or a HF event and suggest a compelling cardiac structural and functional mechanism by which CRT therapy improves outcomes. These results suggest that in the long term, CRT lowers the risk of HF-related adverse clinical events and prevents or reduces the progression of disease by reverse LV remodelling.[2,5,6]

Four trials have studied the effect of CRT on rates of death among patients with HF. CARE-HF and COMPANION[7] included patients with moderate –to-severe NYHA Class III and ambulatory class IV HF. RAFT and MADIT-CRT included less symptomatic patients with NYHA class II and III in the RAFT and NYHA class I or II in the MADIT-CRT. The RAFT trial found a significant reduction in the rate of death from any cause associated with the use of CRT in addition to ICD and optimal medical therapy. The relative risk of death was reduced by 25%, resulting in an absolute mortality reduction of 6 percentage points at 5 years. Possible reasons for the differences in mortality rates between RAFT and MADIT CRT are that RAFT had longer follow up period and that patients had slightly more advanced disease with a slightly lower EF and a higher proportion of the RAFT patients and ischemic heart disease.

Although REVERSE was not designed as a morbidity and mortality trial, its 5-year follow-up confirmed the RAFT findings that CRT in mild HF patients over a longer treatment period provided benefits in morbidity and mortality. This positive impact on mortality was in fact predicted by the REVERSE authors in their 2009 publication as they observed a delay in time to first HF hospitalization in the active CRT group in the 24 months follow-up.[4] However, the investigators were not blinded to the follow-up cohort and this could represent a potential bias to the results.

Like the MADIT-CRT, the positive REVERSE findings were greatest in patients with a QRS width of more than 150 msecs, left bundle branch block (LBBB), and of non-ischemic aetiology. In fact, this finding was confirmed in a meta-analysis of five randomized controlled trials. A detailed non-invasive 3-dimensional electrocardiographic mapping, in 33 consecutive CRT candidates, demonstrated that patients with LBBB had uniform patterns of activation, whereas in patients with nonspecific interventricular conduction delay, conduction patterns were highly variable. Left ventricular electrical uncoupling was consistently elevated in all LBBB patients, and properly identified clinical CRT responders.[8]

Among the 419 patients, 51 (12.2%) experienced 63 LV lead-related complications. Most events occurred within the first 3 months of implant with a rate of 7.9% (95% CI: 5.7–10.9%), and a rate of 12.5% (95% CI: 9.6–16.2%) at 5 years. The majority were due to LV lead dislodgment ($n = 33$) and/or diaphragmatic stimulation ($n = 10$). Over the course of the 5-year follow-up, 132 of the 419 patients (31.5%) underwent device replacement. These findings were relatively fewer than the 16% complication rate (LV 11%, RV 5%) reported in NYHAClass III and IV patients with 6-month follow-up and comparable to the reported European CRT Survey with 1-year follow-up (10.3%).

Despite the low mortality rates, the cost effective analysis from REVERSE showed that compared with CRT-OFF, 0.94 life years or 0.80 QALYs were gained in the CRT ON group at an additional cost of € 11,455 - yielding an incremental cost-effectiveness ratio of € 14,278 per quality-adjusted life year (QALY) gained. At a threshold of € 33,000 (£ 30,000) per QALY gained, the probability that CRT is cost-effective is 79.6%. Cardiac resynchronization therapy becomes cost-effective after 4.5 years.[9]

WHAT HAVE WE LEARNT?

In the USA ~5 million individuals - from a total population of nearly 294 million - have HF. In Europe the numbers are 10 million from a total of 666 million people. Asymptomatic left ventricular dysfunction

is estimated to have at least the same prevalence as congestive HF. Overt HF symptoms generally follow the asymptomatic phase and are linked to increased morbidity and mortality. The clinical efficacy of CRT in patients with moderate to severe HF has been established in a number of trials. In contrast, for patients with asymptomatic or mildly symptomatic HF, CRT represents a relatively novel treatment option. Evidence on the efficacy of CRT in this patient group has recently been demonstrated with the publication of the REVERSE and MADIT-CRT trials. The long term follow up confirmed the initial findings of REVERSE by showing that cardiac reverse remodelling lowers HF related events and mortality rates with longer follow up time. The possibility of long-lasting benefit of CRT on HF progression outweighs the risk, as the complication rate related to CRT remained acceptable after 5 years. This also confirms the cost effectiveness of CRT in mildly symptomatic HF patients. However, these results are exclusive to patients with LBBB and wide QRS complex more than 150 milliseconds, emphasizing a specific electrophysiological process that takes place in CRT responders.

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