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Cardiac Resynchronization Therapy in Mild Heart Failure/ REVERSE, MADIT-CRT & RAFT studies & Meta-analyses / Expanding CRT-D Indications to Lower Risk Patients

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ABBREVIATIONS
CRT = cardiac resynchronization therapy
EF = ejection fraction
HF = heart failure
ICD = implantable cardioverter defibrillator
LV = left ventric-le (-ular)
NYHA = New York Heart Association

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ABSTRACT

Cardiac resynchronization therapy (CRT), effected via biventricular pacing, has been shown to improve symptoms and left ventricular (LV) systolic function and to reduce mortality and hospitalizations among patients with moderate to severe heart failure symptoms (class III and IV), reduced LV ejection fraction (EF), and a wide QRS complex on electrocardiogram, usually in the form of left bundle branch block. Recent evidence from randomized clinical trials and meta-analyses demonstrate that the beneficial effects of CRT on LV remodeling, heart failure symptoms, hospitalizations, and mortality also extend to patients with milder heart failure symptoms (class II). These data support the expansion of indications for CRT to less symptomatic patients with heart failure who have LVEF <0.35 and wide QRS duration in sinus rhythm. Accordingly the guidelines for CRT therapy by the European Society of Cardiology (ESC) and the American heart Association (AHA) have been updated to expand CRT indications to patients with milder heart failure symptoms.

Heart failure (HF) is a major international health problem with a substantial personal and economic impact. In the United States alone, there are approximately 6 million HF patients, with >500,000 newly diagnosed patients each year. The estimated direct expenditure for healthcare cost approach $40 billion annually in the US. Recent advances in pharmacologic and nonpharmacologic therapies have improved outcomes in HF patients. Cardiac resynchronization therapy (CRT), effected via biventricular pacing, has been demonstrated to provide additional benefit in selected patients on guideline based optimal medical therapy with advanced heart failure symptoms.[1-7] Multiple clinical trials have demonstrated that CRT improves symptoms and left ventricular (LV) systolic function and reduces mortality and hospitalizations among patients with moderate to severe HF symptoms, reduced LV ejection fraction (EF), and a wide QRS complex on electrocardiogram.[1–7] Cardiac resynchronization therapy also improves echocardiographic parameters, symptoms, hospitalizations, and mortality in patients with NYHA Class III or IV symptoms with left ventricular systolic

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dysfunction, sinus rhythm, and a prolonged QRS duration.[1-7] These trials demonstrate a 22% relative risk reduction in all-cause mortality and 37% relative risk reduction in heart failure hospitalization with CRT.[1-7]

Based on the improved outcomes in Class III and IV HF patients, clinical trials have been performed more recently to evaluate the role of CRT therapy in patients with less advances HF including patients with NYHA Class I and II symptoms.[8-12] Recent evidence from randomized clinical trials and meta-analyses demonstrate that the beneficial effects of CRT on LV morphology, HF symptoms, hospitalizations, and mortality also extend to patients with mild HF.[8-12]

In the REVERSE trial, 600 patients with Class I or II heart failure, LVEF $\leq$40% and QRS $\geq$120 ms received a CRT-device.[8] In a 2:1 fashion, they were randomized to CRT-ON or CRT-OFF for 12 months. The primary endpoint was a composite heart failure response. This demonstrated a trend toward benefit with biventricular pacing.[8] However, patients assigned to CRT-ON experienced a greater improvement in LV end-systolic volume index and other measures of LV remodeling. In addition, time-to-first HF hospitalization was significantly delayed in CRT-ON.[8]

In the larger MADIT-CRT trial, 1820 patients with Class I or II heart failure, LVEF $\leq$30%, and QRS duration $\leq$130 ms were randomized to implantation with CRT-D or ICD only.[9] Enrollment criteria included patients with class I and II symptoms with ischemic cardiomyopathy (ICMP) and class II symptoms with non-ischemic cardiomyopathy (NICMP). In follow-up of 2.4 years, the primary end point of heart failure hospitalization or death occurred in 187 of 1089 patients in the CRT-D group (17.2%) compared to 185 of 731 patients in the ICD-only group (25.3%).[9] Mortality was low, thus the result was primarily driven by heart failure.[9] In addition, LVEF was more likely to be improved in CRT patients (0.11 compared to 0.03). There was no difference in benefit between the ICMP and NICMP groups. Although no significant effect was seen in mortality, there were salutary effects seen on remodeling and heart failure events when CRT was utilized.[9] In the MADIT-CRT Trial, CRT-D was associated with a 34% reduction in the risk of death or heart failure events in asymptomatic or mildly symptomatic patients with ischemic or non-ischemic cardiomyopathy.[9] This CRT-D benefit was driven by a 41% reduction in the risk of HF events.[9] Subsequent analysis of the impact of CRT on echocardiographic parameters demonstrates that CRT improves LV end-systolic volume, LV end-diastolic volume and LVEF.[9,12] Based on the MADIT-CRT Trial, CRT therapy is more effective in women than men, and in patients with wider than narrower QRS complexes.[9] While this trial demonstrated that CRT-D is effective in preventing heart failure in mildly symptomatic at-risk cardiac patients with a 29% reduction in heart failure hospitalization, a mortality benefit was not found.[9]

More recently CRT was evaluated in mild to moderate heart failure in the RAFT trial.[10] This trial enrolled patients with NYHA Class II and III heart failure patients who were receiving ICD implantation for primary or secondary prevention of SCD. Inclusion criteria were patients with LVEF $\leq$30%, ICMP or NICMP, and intrinsic QRS duration $\geq$120 ms or paced QRS duration $\geq$200 ms.[10] Patients were randomized to ICD only versus CRT-D in a 1:1 ratio.[11] In the ICD group, patients were programmed to minimize pacing while the converse was true in the CRT-D group.[10] Of note, because of published data during enrollment revealing decreased mortality with CRT alone in NYHA Class III heart failure, after 2006, the investigators of RAFT limited enrollment to Class II heart failure only.[10] Thus, of the total 1798 patients enrolled, the vast majority (1438 patients) had NYHA Class II heart failure. The primary outcome of death or hospitalization for heart failure occurred in 40.3% of patients in the ICD group compared to 33.2% of patients in the CRT-D group (hazard ratio-HR 0.75, 95% confidence intervals-CI 0.64-0.87).[10] When only NYHA Class II heart failure patients were analyzed, there was also a decrease in the primary outcome (34.7% versus 27.3%, HR 0.73, 95% CI 0.61-0.88).[10] Moreover, in Class II patients, unlike the MADIT-CRT and REVERSE trial, there was a significant decrease in death from any cause when CRT-D was placed rather than ICD alone (21.1% versus 15.5%, HR 0.71, 95% CI 0.56-0.91).[10]

A recent meta-analysis was published including analysis of the REVERSE, MADIT-CRT, RAFT, and three smaller trials evaluating CRT in Class I and II heart failure.[11] The analysis showed improvement in all-cause mortality (6 trials, 4572 participants, pooled RR 0.83, 95% CI 0.72-0.96) and heart failure hospitalizations (4 trials, 4349 participants, pooled RR 0.71, 95% CI 0.57-0.87) when CRT was utilized. There was no improvement in functional outcomes or quality of life which is not surprising as these patients had minimal symptoms at the time of implantation.[11] Importantly, REVERSE, MADIT-CRT, and RAFT drove the findings based on much larger population. Control patients in trials including NYHA class I or II symptoms had an ICD thus and optimal medical therapy, thus the benefits of CRT represent incremental benefits.

Important insights into the mechanisms of the beneficial effect of CRT have come from echocardiographic studies that have consistently demonstrated reverse remodeling in all HF functional classes.[12] In patients with an increased QRS duration, especially left bundle-branch block, dysfunctional cardiac remodeling progresses over time.[12] This results in an increased left ventricular volume and a decreased ejection fraction.[12] The dyssynchronous cardiac contraction and increased myocardial strain is an essential pathophysiologic component of this remodeling.[12] Cardiac resynchronization therapy provides more synchronous contraction with restoration of the left ventricular systolic contraction, including the torque motion that is an important part of normal cardiac contractility. This improvement in contractile efficiency with CRT is associated with a

reduction in myocardial energy cost and oxygen consumption.[12]

Based on the available trials it is evident that CRT reduces all-cause mortality and heart failure hospitalization in patients with milder symptoms of heart failure (NYHA class I or II), left ventricular systolic dysfunction, and prolonged QRS duration. Randomized controlled trials provide sufficient evidence to support the expansion of indications for CRT to less symptomatic patients with heart failure who have LVEF less than 0.35 and wide QRS duration in sinus rhythm. Accordingly the guidelines for CRT therapy by the European Society of Cardiology (ESC) and the American heart Association (AHA) have been updated to expand the indications for CRT therapy to prevent HF progression in patients with both ischemic and non-ischemic cardiomyopathy, with impaired left ventricular function and bundle branch block.

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