DEBATE

CRT-D Should be the Device of Choice in Patients Undergoing Resynchronization Therapy

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ABSTRACT

The addition of cardiac resynchronization to medical therapy alleviates heart failure, and improves mortality in certain patient subsets. Whether a combination device that is additionally capable of cardioversion-defibrillation would further improve outcomes has not been systematically studied in most patient subgroups. The proven benefit of implantable cardioverter defibrillators in milder forms of heart failure should make a combined device the therapy of choice in NYHA Class I and II heart failure. Sufficient data exist to show that a combined device is more beneficial than a resynchronization-only device in NYHA III heart failure. The device of choice should be individualized in NYHA IV heart failure; among these patients, it may be easier to implant a combined device and turn off tachyarrhythmia therapies if and when not desired, than to have a resynchronization-only device. Cost considerations should be individualized as far as possible while choosing these devices.

Key Words: Resynchronization, CRT, CRTD, heart failure

Introduction

Randomized clinical trials have shown that the addition of cardiac resynchronization therapy (CRT) to medical treatment improves heart failure symptoms, reverses left ventricular remodeling and, in certain patient subsets, reduces mortality (1-4). Sudden cardiac death (SCD) is a major cause of mortality in heart failure (5). Implantable cardioverter defibrillators (ICD) reduce mortality in heart failure by preventing SCD. Hence, it would seem logical that a combined cardiac resynchronization therapy-defibrillator (CRT-D) device should be able to provide incremental mortality benefit over CRT in heart failure. However, data and viewpoints regarding this continue to be controversial (6,7). This paper presents arguments as to why it would be prudent to choose a CRT-D device over a CRT device in most patients requiring cardiac resynchronization.

The Role of ICD in Mild Heart Failure – NYHA Class I and II

The relative contribution of SCD (versus "pump failure death") as the cause of mortality in heart failure is higher in milder forms of heart failure (5). In the MERIT-HF study, at one year of follow up, all-cause mortality of heart failure patients on optimal medical treatment (OMT) was 5.3%, 8.1% and 16.7% respectively in patients in NYHA Class II, III and IV functional status, respectively. In the cohort of 1636 patients in NYHA Class II heart failure, SCD was responsible for 64% of the mortality, as compared to 59% and 33% SCD-related mortality in patients with NYHA Class III and NYHA Class IV heart failure, respectively. Therefore, it is not surprising that ICDs implanted for a primary prevention indication have demonstrated a greater mortality benefit in patients with milder forms of heart failure. The MADIT-II study randomized 1232 patients with a past history of myocardial infarction and a left ventricular ejection fraction (LVEF) of ≤ 30% to OMT alone, or to ICD + OMT; 70% of these patients were in NYHA Class I or Class II heart failure (8). There was a 31% relative reduction in mortality at 20 months in the overall study group. The mortality curves began to diverge at 9 months, and continued to do so at an extended follow up of 8 years (9). On extended follow up, patients in NYHA Class I had greater mortality reduction than those in NYHA Class II and Class III (hazard ratio of 0.59 *vs.* 0.68). The SCD-HeFT study analyzed the effect of ICD for primary prevention in NYHA Class II and NYHA Class III patients with an LVEF of ≤ 35%, and had a cohort which included 48% patients with non-ischemic cardiomyopathy (NICMP) (10). The mortality reduction was more in patients in NYHA Class II as compared to

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those in NYHA Class III. A longer duration of follow up (median duration: 45.5 months) was required to demonstrate the mortality benefit, and the absolute mortality reduction achieved was less than that achieved in MADIT-II. Together, these data indicate that ICDs provide a greater mortality reduction in milder forms of heart failure, possibly a greater mortality reduction in ischemic cardiomyopathy (ICMP) as compared to NICMP, and that a long duration of follow-up is required for the mortality benefit to accrue in milder forms of heart failure.

The Case for CRTD in Milder Heart Failure – NYHA Class I and II

Much of the data regarding the use of CRT in NYHA I or NYHA II heart failure is derived from the MADIT-CRT and the RAFT studies. The MADIT-CRT study compared the effect of OMT + ICD *vs.* OMT + CRT-D in patients with NYHA Class I and NYHA Class II heart failure, LVEF ≤ 30%, and a QRS duration (QRSd) of > 130 ms (3). In this study, 45% of the patients had NICMP. At 2.4 years of follow up, as compared to ICD + OMT, CRTD + OMT offered a significant reduction in heart failure related events; there was no difference in mortality between the two groups. This effect was similar in NYHA I, NYHA II, NICMP and ICMP. The relatively short duration of follow up of 2.4 years of the MADIT-CRT study may have been inadequate to demonstrate a mortality benefit, especially in NYHA Class I patients. The RAFT study randomized 1798 patients with NYHA Class II or Class III heart failure, LVEF ≤ 30%, and a wide QRS (QRSd > 120 ms in native QRS, and > 200 ms in paced QRS) to OMT + ICD or OMT + CRTD (4). Nearly two-thirds of the patients had ICMP. At a mean follow up of 40 months, CRT-D significantly reduced both death and heart failure hospitalization in NYHA Class II heart failure. Among patients in NYHA Class III, there was a significant reduction in heart failure hospitalization in the CRTD group, without a significant reduction in mortality.

Meta-analyses of available studies on resynchronization in NYHA I/ NYHA II heart failure concur with the results of the MADIT-CRT and RAFT trials (11). The available evidence thus suggests that the addition of CRT-D to OMT reduces heart failure hospitalization and mortality among patients in NYHA II heart failure, and reduces heart failure hospitalization among patients in NYHA I heart failure. There is no data available to compare the effect of CRT *vs.* CRT-D in NYHA I and NYHA II heart failure and as such, evidence-based recommendations cannot be made for the use of CRT in these patients. This, plus the demonstrated mortality benefit of ICD in these patients, make CRT-D the resynchronization device of choice among patients with an LVEF ≤ 35% and NYHA I or NYHA II heart failure.

Various authors have analyzed available data to identify a patient subset likely to show "super-response" to CRT. An analysis of the MADIT-CRT study included patients with an absolute LVEF improvement of ≥ 14.5% as super-responders; many of the super-responders improved their LVEF to ≥ 45% (12). Once this happens to patients receiving CRT, they would no longer be ICD candidates for a primary prevention indication. However, there is no consensus on parameters predicting super-response (12-15). Moreover, the time frame taken for super-response to happen is also not delineated, exposing patients to the risk of SCD during this time frame. Besides, in MADIT-CRT, even the super-responders had a 5.2% incidence of death or ICD therapy for ventricular tachycardia or ventricular fibrillation (12). Had these patients been implanted with a CRT instead of a CRT-D, then, even among the super-responders, 5.2% would have been indicated for upgradation to a CRT-D for secondary prevention; the corresponding numbers for the responder and hypo-responder groups in MADIT-CRT are 11.9% and 23.7%, respectively. If we are able to consistently foresee super-response in a subset of NYHA Class I patients with NICMP then, in future, it may be possible to offer only CRT and not CRT-D to them. The available data is insufficient to make such predictions.

The Case for CRT-D in More Severe Heart Failure – NYHA III and IV

The COMPANION study randomized 1520 patients with NYHA III/ NYHA IV heart failure, LVEF ≤ 35%, and QRSd > 120 ms to OMT, or OMT + CRT, or OMT + CRT-D (1). At 12 months of follow, both CRT and CRT-D significantly and similarly decreased heart failure hospitalization compared to OMT. However, whereas the mortality reduction in the OMT + CRT arm was only marginally significant, there was a highly significant 36% reduction in mortality in the OMT + CRT-D arm compared to OMT. The CARE-HF study randomized 813 patients with NYHA III/ NYHA IV heart failure, LVEF ≤ 35%, QRSd > 150 ms or QRSd 120-150 ms plus additional evidence of dyssynchrony to OMT *vs.*

OMT + CRT (2). The patients were followed up for a mean duration of 29.4 months; 94% of the patients were in NYHA Class III. In addition to the original study, an extended follow up of 37 months was also later made available (16). At 29.4 months of follow up, in addition to a reduction in heart failure, there was also a significant 10% absolute reduction in mortality in the OMT + CRT arm as compared to the OMT arm (30% and 20% overall mortality in the OMT and OMT + CRT arms, respectively). This was driven predominantly by a reduction in heart failure mortality (14% and 8% heart failure mortality in the OMT and OMT + CRT arms, respectively). There was no significant reduction in the SCD mortality between the two arms (9% and 7% SCD mortality in the OMT and OMT + CRT arms respectively). This means that the relative contribution of SCD as a cause of death actually increased in the OMT + CRT arm in the initial 29.4 months (32% in the OMT arm, and 35% in the OMT + CRT arm), an effect which could perhaps have been negated had a CRT-D device been used. In the extension phase, OMT + CRT was able to significantly both heart failure mortality (9% *vs.* 16%), as well as SCD mortality (8% *vs.* 13%). Together, these data imply that once CRT reverses heart failure, SCD also reduces. However, in the early phase of CRT response, while the heart failure is still in the process of reversing, the SCD risk persists, and may even be magnified on a relative scale.

No randomized control trial of CRT/CRT-D has predominantly included patients with NYHA Class IV heart failure; hence conclusions need to be based on sub analyses of studies. The largest data on this patient group comes from an analysis of the 14% (217 patients) NYHA Class IV patients included in the COMPANION study (17). Compared to OMT, both OMT + CRT and OMT + CRT-D increased the time to death and the time to heart failure hospitalization; there was no significant difference between CRT and CRT-D in this regard. CRT-D decreased SCD mortality and increased heart failure mortality in this subset, effectively changing the mode of death. This being a sub analysis, the results should be interpreted with caution. Besides, the decision regarding implanting a CRT-D in a patient with NYHA Class IV symptoms also involves several non-medical considerations, as discussed later.

Choosing a CRT-D – Safety Considerations

Two of the major negative concerns regarding ICDs are lead failures over time, and the risk of inappropriate shocks. There is a large variation among reported lead failure rates, with specific leads and smaller diameter leads being significantly more implicated (18). There are also lead models for which failure rates are not reported (19). Both appropriate and inappropriate shocks can be minimized using several programming strategies (20,21). Neither of these seem compelling enough arguments to warrant withholding the implant of a life-saving device such as an ICD.

Choosing a CRTD – Non-medical Considerations

Improvement of heart failure by CRT in itself reduces the risk of SCD to some extent. Hence, the "number-needed-to-treat" to show an incremental mortality benefit of CRT-D over CRT would be very high. CRT-D is also a significantly more expensive therapy than CRT. However, the decision to implant or withhold a potentially life-saving therapy like an ICD should be an individualized decision which is not based predominantly on cost considerations or "number-needed-to-treat". The debate regarding the value of an individual's life versus the cost required to preserve that life should, as far as possible, be adjudicated by the individual and his/her close confidantes, rather than by medical care providers. This principle may be even more relevant in societies where health care costs are predominantly borne out-of-pocket, as is the case with the majority of the world's population.

There may be situations in patients with end stage, non-CRT responsive heart failure where SCD may be the most humane form of death. There may be patients with end stage heart failure who are willing to accept a poorer quality of life accorded by ICD shocks in order to have the possibility of extending their lives for a few more crucial months. Decisions such as these, which involve more than science and medical evidence can only be taken by the patient and his/her closest confidantes. In such patients, it may be more appropriate on the physician's part to implant a CRT-D after due discussion, so that the patient and surrogate decision-makers are aware that should it be required, they have the option to request that tachyarrhythmia therapies be turned off. This is a better option than hoping that a potential CRT responder will be spared of SCD in the initial phase while he/she is still responding to CRT. This is also far easier than keeping the CRT recipient with runs of non-sustained ventricular

tachycardia "under close follow up". This is certainly easier than upgrading to CRT-D in the small minority of CRT recipients who survive a sustained ventricular arrhythmia. Finally, for a CRT responder and his/her associates who might have lived through symptomatic heart failure for months to years and has now received new hope in life through this therapy, a preventable tachyarrhythmic death may be the worst thing to happen. For the treating physician, who has nurtured the patient through his/her heart failure, there could be no worse feeling than such a death. The impact of a death cannot be measured in numbers; and there is no worse thing in life than to give hope and to then take it away.

Conclusion

Most CRT candidates are also ICD candidates for prevention of sudden cardiac events (22,23). Unless the individual under consideration for a CRT implant falls in a subgroup where the benefit of ICD is unproven, it would be prudent to implant a CRT-D rather than a CRT.

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