DEBATE

# CRT-P is sufficient in Most Patients Needing Resynchronization

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## Introduction

The recent 2012 updated device guidelines (1) state that cardiac resynchronization therapy (CRT) is Class IA indication in patients with left ventricular ejection fraction (LVEF) < 0.35, in SR, LBBB with QRS width of >150 ms, those who are in NYHA III-IV, despite optimal medical therapy. The dilemma clinicians face is, should CRT be supplemented with implantable cardioverter defibrillator (ICD) (as primary prophylaxis). In this review, we apply evidence based knowledge and rationale to address this question.

## Evidence for CRT-P (pacemaker) vs. CRT-D (defibrillator)

Till date there is paucity of literature comparing CRT-P vs. CRT-D. The COMPANION trial (2) is the only randomized study of 1520 patients with advanced heart failure having three arms of optimal medical therapy alone or optimal medical therapy along with either CRT-P or CRT-D device. The device group – CRT-P and CRT-D revealed a similar reduction in all-cause death or hospitalization. CRT-P reduced the risk of death and hospitalization for heart failure by 34% ($p$<0.002) and all-cause death by 24% ($p$=0.06) compared to optimal medical therapy. CRT-D had a greater impact with reduction in risk of death and hospitalization by 40% (p< 0.001) and all-cause mortality by 36% ($p$=0.003). These results have been largely interpreted as CRT-D is better than CRT-P. However, both the CRT arms showed similar benefit compared to medical therapy and there is no statistically significant difference between CRT-P and CRT-D arms. It is argued that the trial was underpowered and not designed to compare the device arms with each other and also the duration of follow-up is short. This is precisely the reason we cannot conclude that CRT-D is better than CRT-P from the COPMANION trial.

### Real-life practice

In the US, amongst the CRT device implanted, 85% patients receive CRT-D and in Europe CRT-D use is about 75% (3). These practice patterns prevail despite any proven clinical evidence. The argued logic behind such practice is that there is an overlap in the indications for CRT-P and CRT-D. Hence every patient eligible for CRT is also in need for a defibrillator. There is a need to rationalize this logic with indepth dissection of this seemingly overlapping indication for CRT-P and CRT-D.

## Is it rational to have ICD as back up for primary prophylaxis in patients needing CRT?

One of the important roles of CRT is to improve symptom status and quality of life of patients with heart failure. This has been amply proven in trials done so far (4,5). It is simultaneously clear that there is no added advantage with an ICD in improving either the symptoms or quality of life. The only reason for an ICD is then to improve mortality.

CRT is primarily recommended in NYHA III & IV heart failure patients. Majority of the ICD trials have excluded class IV patients (6,7). The SCD-HeFT trial (8) is the only study to show benefit with ICD in the heart failure population. The results need to be scrutinized as the study had to be extended for 1 year to show a modest absolute risk reduction of 7.2% at 5 years. It was further known that only NYHA class II patients in SCD-HeFT benefited from ICD and 30% patients in NYHA III did not derive any benefit.

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Thus the seemingly similar indications for CRT-P and CRT-D devices are not true i.e., CRT-P benefits class III and IV heart failure patients and ICD benefits are restricted to NYHA II patients. The MADIT-CRT (9) and RAFT (10) trials have shown CRT-D benefits in class II patients but there was no CRT-P only arm to definitively conclude the benefits are because of ICD. In fact the superiority of CRT-D in MADIT-CRT was primarily due to a 41% reduction in risk of heart failure events and mortality was no different in the CRT-D *vs*. ICD arms.

The CARE-HF (5), showed a mortality benefit with CRT-P alone with 37% relative risk reduction in the composite end-point of death and hospitalization and 36% in risk of death. Also the ICD trials, SCD-HeFT and MADIT II start showing mortality reduction only after 12-18 months. Within this time frame patients receiving CRT, show improvement in their ejection fraction and at least two-thirds of the responders will no longer be candidates for ICD. In fact few of them are super-responders and these patients having an ICD is a waste. Women, patients with idiopathic dilated cardiomyopathy and hypertensive heart disease are likely to have a high responder rate or be super-responders and therefore in this sub-group only CRT-P should be considered.

This data sufficiently suggests that there is no real overlap of indication of CRT-P and CRT-D. Only a new randomized study directly comparing CRT-P and CRT-D is likely to resolve this issue.

*Some of the patients with chronic right ventricular apical pacing for bradycardia, over-time result in dyssynchrony and LV dysfunction due to the LBBB effect of pacing. These patients, if have symptomatic heart failure and LVEF < 0.35 or during their generator replacement, are candidates for upgrade to CRT. In these patients, it would be logical to consider only CRT-P, as the LV dysfunction is a result of RV apical pacing and therefore LV function is very likely to improve with additional LV pacing and would not require ICD back-up. Recently presented BLOCK HF study, has in fact recommended only CRT-P, in patients with LV function < 0.50, needing pacemaker for bradycardia indication.*

## Why should ICD be avoided if avoidable?

If there were only incremental benefits and no downside to ICD, CRT-D would be the preferred choice. However in reality that is not the case.

**ICD lead complications** - It is well recognized from various registries that there is a definite attrition with ICD leads, such that across board all device manufacturers report more than 20% lead malfunction cumulatively over a 5-10 year follow-up (11). Also, infections are more likely to happen with bulkier devices like CRT-D than CRT-P (12).

**Inappropriate shocks** - Almost 10-20% patients are going to experience inappropriate shocks (13). This continues despite the improvement in algorithms to identify supra-ventricular tachyarrhythmia and even the dual chamber ICDs are not able to prevent it completely. Interestingly, any shocks, appropriate or inappropriate result in higher mortality, thus negating the perceived benefit with an ICD (13).

**Cost** - The device cost in the Indian context, nearly doubles with CRT-D compared to CRT-P. This is a major deterrent, especially in India as most patients are either not insured or reimbursed for such high priced devices. Scant resources need to be utilized judiciously and avoid unnecessary financial burden.

**Device longevity** - Addition of ICD to CRT devices result in decreased longevity by at least one to two years i.e., nearly 25% reduction of the battery life. Early replacement only adds to the overall cost. Also, repeat procedures add to the infection risk.

**Older patients** - The mean age of patient in SCD-HeFT trial (8), which should benefit with ICD in heart failure population, was 60 years. Therefore one can, if at all, interpret that the younger patients are likely to benefit from ICD. The older patients are more sick with worse NYHA class and co-morbid conditions and unlikely to benefit from ICD. It is ethical to consider end of life issues in the elderly with many co-morbid conditions. We surely need to strive for a symptom free and better quality of life as long as they live (CRT-P would do this); yet allow a more peaceful, sudden death (which CRT-D might prevent). This often is the wish and desire of many elderly patients.

## When should ICD be considered in patients undergoing CRT?

The obvious answer seems to be those with secondary prophylaxis i.e., patients with aborted sudden cardiac death, documented ventricular tachycardia or unexplained syncope.

One should also attempt to determine who are at high risk for sudden cardiac death. Further risk stratification in terms of etiology, non-invasive and invasive tests might be useful. Patients with ischemic heart disease with scar are prone to arrhythmic events. Non-sustained VT and abnormal heart rate variability with T wave alternans are the non-invasive tests helpful to identify the high-risk group. MADIT I (6) and MUSTT (14) trials proved the utility of electrophysiology study to identify patients with inducible VT, who derive the most benefit from ICD.

## Conclusion

CRT-P suffices in vast majority of patients requiring resynchronization. Women, idiopathic dilated cardiomyopathy, hypertension, extremely wide QRS of LBBB morphology with significant dyssynchrony are likely to be responders and super-responders to CRT, mitigating any benefit from ICD. Heart failure patients with NYHA III and IV do not derive benefit from ICD and CRT-P is enough. There is to date, no randomized trial evaluating the two therapies and therefore any recommendation for CRT-D should be weighed against the cost, device longevity, lead issues etc.

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