Cause of death and CRT device selection: striving for certitude?

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This editorial refers to ‘Causes-of-death analysis of patients with cardiac resynchronization therapy: an analysis of the CeRtiTuDe cohort study’†, by E. Marijon et al., on page 2767.

‘More important than the quest for certainty is the quest for clarity’.
— Francois Gautier

Implantable cardiac defibrillators (ICDs) and cardiac resynchronization therapy (CRT) devices have had a significant favourable impact on hospitalization and mortality among patients with heart failure (HF). Despite some degree of overlap, the therapeutic rationales for these two forms of device-based therapies are distinct, where ICDs abort arrhythmic death and CRT devices improve cardiac function. The efficacy of ICDs and CRT has been clearly established after large-scale randomized controlled trials (RCTs).¹–⁴ However, as with most invasive therapies, there is a constant quest to minimize harm while enhancing the value of the care being delivered. Notably, the majority of patients who are candidates for CRT are also eligible for an ICD by virtue of low left ventricular ejection fraction (LVEF). If only ICDs were totally benign and an inexpensive add-on, this difference might not have been clinically significant. Inappropriate shock therapy from ICDs has been associated with higher mortality,⁵,⁶ and therefore the relative benefit of adding defibrillator therapy to CRT (i.e. CRT-D), particularly in patients whose highest risk of dying is from pump failure, has been questioned.

The only large RCT which compared CRT-D and pacemaker CRT (CRT-P) vs. optimal medical therapy (COMPANION), was not powered to examine differences in mortality between these two arms of device therapy. The median age of enrolled patients was 69 years, of which the majority was New York Heart Association (NYHA) class III (86%) and the remaining ambulatory class IV. Cardiac death was reduced in CRT-D patients as compared with optimal pharmacologic therapy (P = 0.006) driven by a significant reduction in sudden cardiac death (SCD).³,⁷ No difference was found between non-cardiac deaths in patients with CRT-D, CRT-P or medical therapy. CRT-P was associated with a non-significant trend towards reduced pump failure deaths and overall cardiac deaths. In part, it was due to this ‘lingering uncertainty’ regarding the role of CRT-P in addressing survival that the results of the Cardiac Resynchronization in Heart Failure (CARE-HF) trial came as a welcome relief one year later, convincingly demonstrating a 36% relative risk (RR) reduction for death with CRT-P vs. medical therapy.⁴ Anecdotal reports of CRT-induced proarrhythmia have caused some degree of concern for the potential risk of innate and induced SCD in this cohort of CRT-P patients. Longer-term data from CARE-HF, however, have shown that improved pump function from CRT-P can actually halve the risk of SCD.⁵ Nevertheless, in the absence of an RCT with a head-to-head comparison of CRT-D vs. CRT-P, there is a lack of consensus regarding the choice of device and consequently there remains considerable variability in practice. In addition, there is also little comparative data on the mode of death between these two cohorts of patients.

In this issue of the European Heart Journal, Marijon et al.⁹ present results from the CeRtiTuDe registry, analysing causes of death after CRT therapy. Enrolling patients in 41 centres across France between January 2008 and December 2010, CRT implantation and choice of therapy (CRT-D or CRT-P) was left to the discretion of the treating physician based on the 2007 or 2010 update of the Guidelines of the European Society of Cardiology and European Heart Rhythm Association. Patients were followed at 6-month intervals for 2 years by the implanting centre until the close of the study on 1 January 2013. A standardized form was used to record major clinical events, and vital status was ascertained through use of national registries.

Causes of death were pre-specified for data collection in CeRtiTuDe. Sudden death was defined as occurring within 1 hour of symptoms in the absence of cardiac deterioration, unexpected death during sleep, or unexpectedly dying within 24 h of last being seen alive. Importantly, fatal arrhythmias associated with end-stage heart failure were classified as non-sudden deaths. Other cardiovascular deaths included myocardial infarction (MI), HF, acute aortic

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syndrome (AAS), stroke and pulmonary embolism (PE). Non-cardiovascular deaths included cancer, infectious disease and renal or respiratory failure. In total, 1705 patients were studied with an average age of 69 years, 77% male, and 47% with a history of ischaemic heart disease. CRT-D was implanted in 68% of patients, with no significant differences in perioperative complications between CRT-D and CRT-P. These groups demonstrated significantly different baseline characteristics. Of note, CRT-P patients were older, had a higher proportion of women, higher rates of non-ischaemic cardiomyopathy, wider QRS, more severe NYHA functional class, more atrial fibrillation, and higher rates of renal insufficiency. It should come as no surprise that CRT-P patients demonstrated two-fold increased all-cause mortality. The excess of mortality in this cohort of CRT was driven by heart failure, ‘other’ cardiovascular deaths (MI, AAS, stroke and PE), and non-cardiovascular deaths.

A non-significant trend for a higher risk of sudden death was observed in CRT-P vs. CRT-D patients that persisted to some extent even after propensity matching [adjusted RR 2.33 (95% CI 0.43, 12.71)]. From an absolute perspective, 11.8 deaths/1000 patient-years of the total mortality of 130.8 deaths/1000 patient-years in CRT-P patients were attributable to sudden death. In the case of CRT-D patients, 7.5 deaths/1000 patient-years of a total mortality of 65.1 deaths/1000 patient-years were associated with sudden death. The authors concluded that since the sudden death rates were comparable, the excess was driven by non-sudden causes and therefore CRT-D may not provide incremental benefit for ‘that subset of patients’ receiving CRT-P. It does need to be emphasized that in the absence of a randomized controlled study, any direct comparison of CRT-D and CRT-P from these data is not possible. The classification of a fatal arrhythmia in end-stage HF as a non-sudden event further confounds interpretation of the data. It is unclear how many of these lives in the CRT-P cohort could have been saved—or perhaps prolonged beyond the 2-year cut-off mark of this study—if they had a defibrillator. Further, the absence of uniformity in device programming could have impacted the true classification of arrhythmic events and thereby the impact of the intervention.

Understanding the mode of death has been central to parsing out which patients might benefit most from which type of device. Recent data have highlighted the importance of gender in prognostication. In a patient-level analysis combining the data of five studies, women were found to demonstrate a 30% lower risk of SCD than men, but with a 54% higher proportion of pump failure death.10 These data might help partially explain the reason women, despite being more likely to respond to CRT, still appear to benefit less than men for all-cause mortality reduction after ICD therapy. In a recent analysis of the MADIT-CRT trial, an association between CRT response and reduction in arrhythmia was explored. Specifically, patients with LVEF normalization (>50%) and the presence of favourable prognostic factors (i.e. female gender, no history of MI, left bundle branch block, baseline LVEF >30%, lower baseline LV systolic volume and left atrial volumes), demonstrated no ventricular tachyarrhythmias in follow-up. Indeed, the authors argued that patients with favourable characteristics might be considered for downgrade from CRT-D to CRT-P at the time of generator change to reduce the risk of inappropriate therapies.11

Marjon et al.9 have to be congratulated on attempting to provide a closer lens with which to view the cause of death, and therefore the potential for benefit of a particular type of therapy (i.e. CRT-P vs. CRT-D). Similar to earlier work, this study shows that aging and worsening of heart failure are associated with a higher preponderance of non-arrhythmic and non-cardiac causes of death. Also paradoxically, it is the sickest patient who may not only be at the highest risk for arrhythmias, but may also have the lowest chance of survival. Over and above this, we know that ICDs may be associated with inappropriate therapies, which can add to the morbidity and emotional distress while worsening clinical outcomes. This study indirectly emphasizes the need for an individualized, patient-centric decision-making model (Figure 1). A prospectively constructed risk scoring systems within this study population could have potentially provided better insight into the value proposition of CRT-P vs. CRT-D, and seems to have been a missed opportunity.

Of note, the authors observed that in the real-world setting, subjects chosen for CRT-P were ‘appropriately’ usually older, women, had less ischaemic heart disease, more advanced HF and a higher comorbidity burden (i.e. renal dysfunction, atrial fibrillation, etc.) compared with CRT-D patients.9 In essence, this registry highlights that individuals with more risk factors for pump failure, stroke or infection (vs. arrhythmias) as a cause of death would benefit from a CRT-P device. Nonetheless, rates of sudden death are not insignificant within the CRT-P cohort of the CeRtiTuDe population, thus suggesting that a thoughtful discussion with the patient should still highlight the potential risk of sudden death, among other conceivable causes. It is worth remembering that death, like life, comes with no guarantees.

References


