This editorial refers to ‘Effects of cardiac resynchronization therapy on overall mortality and mode of death: a meta-analysis of randomized controlled trials’ by M. Rivero-Ayerza et al., on page 2682.

The failing heart suffers not only from alterations in cardiac structure and contractile function but also from severe damage to its electrical system. Conduction disturbances leading to asynchronous atrial and ventricular activation, and rhythm disorders, particularly atrial fibrillation and malignant ventricular arrhythmia, are common and account for a substantial proportion of morbidity and mortality in heart failure. Although the link between conduction abnormalities and left ventricular dysfunction has been established already decades ago, the true magnitude of hemodynamic and clinical detriment associated with cardiac dyssynchrony has not been recognized until recently. Moreover, despite the advances of modern drug treatment, sudden cardiac death (SCD) continues to be the main killer in heart failure, accounting for ~50% of deaths. In this scenario, cardiac resynchronization therapy (CRT) and the implantable cardiac defibrillator (ICD) do not only improve the specific substrates of electromechanical asynchrony and arrhythmic death, respectively, but also cause a substantial reduction in all-cause mortality when applied in patients with drug refractory moderate-to-severe heart failure.

In their meta-analysis, Rivero-Ayerza et al. evaluated the effect of CRT alone on overall mortality comparing altogether 1343 CRT-treated patients with 1028 controls treated by optimal pharmacological therapy. CRT reduced all-cause mortality by 29% (16.9 vs. 20.7%; odds ratio 0.71; 95% confidence interval 0.57–0.88), corresponding to a 3.8% absolute risk reduction. Although this finding could be expected in view of the Cardiac Resynchronization-Heart-Failure trial (CARE-HF) and previous meta-analyses in the field, it is still important, mainly for three reasons: first, none of the previous CRT-trials assessed total mortality as a primary endpoint; second, as so far only one study demonstrated a significant effect on survival by CRT alone, and third, previous meta-analyses included trials with background ICD therapy and may, therefore, represent a different patient population. Thus, the present paper adds substantially to the evidence for CRT as a live prolonging treatment in chronic heart failure.

Beyond this, the authors report on differential CRT effects with regard to the mode of death—an effort with well-known limitations mainly due to difficulties and inconsistencies in classifying a death as sudden. Notably, the finding that SCD is not affected by CRT contrasts with recent data from the extended 37-month CARE-HF follow-up, suggesting an equal effect of CRT in reducing both sudden and worsening heart failure death. In the latter study, the effect size of CRT on SCD increased over time and became more prominent following 2 years of treatment. A possible and reasonable explanation for this pattern of long-term response is that antiarrhythmic effects of CRT are related to time-dependent reverse remodelling processes, while the relative risk for SCD increases as patients improves from NYHA classes III–II. Accordingly, the duration of follow-up appears to play a critical role in the analysis of CRT effects on SCD. This is also supported by the fact that the relative reduction of the risk to die suddenly improved from 29 to 34% when the results from the CARE-HF extension study were considered for the present meta-analysis. Thus, as far as general conclusions on SCD prevention by CRT are concerned, the study is limited by the relatively short follow-up duration of the trials included. The statement that CRT does not affect SCD is only applicable to the limited follow-up of mean 18.4 months covered by the meta-analysis.

Nevertheless, even after long-term treatment, CRT cannot abolish SCD. Instinctively, adding an ICD component appears as the obvious solution to close the gap. However, there is an ongoing lively debate as to the actual magnitude of survival improvement and the relationship between risks, costs, and the clinical benefits of this approach. CRT–ICD protagonists emphasize the ease of giving a complete electrical therapy unit at once when the patient is subjected to the risk of implantation anyway. Eventually, the ICD will further improve prognosis if the probability of long-term survival is not clearly limited by co-morbidities and/or age. Contrarily, ICD critics refer to the issues related to quality of life (QoL) and inappropriate shock delivery associated with defibrillator use. Yet, studies addressing QoL find no general deterioration among ICD recipients when compared with antiarrhythmic treatment and technical progress continues to decrease the burden of painful shocks. In our clinical practice, most well-informed patients rather accept the hazard of inappropriate ICD shocks than taking the fatal risk of a lacking appropriate therapy in case of life threatening arrhythmia.
As a matter of fact, definite trial evidence for the additional survival benefit of CRT–ICD over CRT alone is still lacking. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, the only study evaluating CRT and CRT–ICD both devices were equally effective in reducing the primary composite endpoint of death or hospitalization for any cause (relative-risk reduction 56%).\(^2\) CRT–ICD and CRT alone reduced the secondary endpoint of total mortality by 36% and 24%, respectively. This 12% difference in relative-risk reduction did not reach statistical significance, despite the fact that COMPANION had greater power to detect differences between the two device arms than between either of them and the control group. Moreover, Kaplan–Meier estimates suggest a time window of additional ICD effects on survival between 6 months after device implantation and 2 years of follow-up—the latter observation being limited by the small sample size (n = 200) at that time point. In primary prevention trials of ICD, a delay of defibrillator effectiveness by 1–1.5 years has been noted during the initial phase of treatment,\(^1\)\(^3\) when defibrillation capabilities would be most needed to compensate for lacking CRT effects on SCD, as reported by the present meta-analysis.

Clearly, a proper assessment of the clinical and economic impact of implantable device therapies on the chronic heart failure population requires a long-term perspective. This is essential not to overlook time-dependent aspects of effects, side effects, and the front-loaded cost–benefit profile.\(^10\) A randomized mortality trial to investigate CRT–ICD vs. CRT would require a long-term follow-up of at least 3200 device patients\(^8\) and is not likely to be performed in the near future. For the time being, the choice between CRT and CRT–ICD remains a matter of careful physician judgment and informed patient preference. According to sales statistics, CRT–ICD is the increasingly preferred choice, although geographic differences are striking. Since limited health-care budgets seem to be a key player in this process and often initiate complex priority discussions, the large group of NYHA II–III patients with a class I (level of evidence A) recommendation for a primary prophylactic ICD,\(^11\) about 3–5 times the target volume of CRT–ICD candidates, needs also to be taken into serious consideration.

CRT and ICD devices, alone and in combination, provide effective therapies to treat the deleterious consequences of ‘electrical heart failure’. Cardiologists should be mindful of the continued need to build up the evidence for their appropriate use in specific clinical situations. The present meta-analysis is an important contribution to this process and highlights the impressive survival benefit by CRT compared with optimal medical therapy in selected patients with chronic heart failure. Bearing in mind the concomitant marked improvements in exercise capacity and QoL, CRT should not be withheld any longer from patients with a guideline approved indication. On today’s evidence, CRT clearly stands out as the most valuable component of device therapies for heart failure in terms of clinical efficacy and cost effectiveness.

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**References**