Letter to the Editor

The benefit of cardiac resynchronization therapy is not hindered by the number of comorbidities

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Financial support: None
Conflicts of interest relevant to the purpose of this study: None declared

Word count: 489

We read with great interest the study by Zeitler et al of patients enrolled in the *Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy* (MADIT-CRT) trial, in which the authors demonstrated that, in patients with left bundle branch block, the relative benefit of CRT in addition to the implantable cardioverter-defibrillator (ICD) did not significantly change according to the burden of comorbidity (1). To the best of our knowledge, this was the first large study demonstrating that CRT may be beneficial regardless of the number of comorbidities.

To which extent those findings, from a randomized controlled trial, are replicable in a "real life" setting remains to be determined. To the best of our knowledge, there are no data available in the literature. We took the opportunity to test this hypothesis in a large French registry of primary prevention ICDs and CRT-Ds (*Défibrillateur Automatique Implantable Prévention Primaire* – DAI-PP) through the analysis of 3,573 patients with prolonged QRS (>120 ms) (2, 3). We assessed the association of multiple comorbidities (coronary artery disease, atrial fibrillation, cerebrovascular disease, respiratory disease, renal dysfunction and previous malignancy) with the benefits of CRT-D (n=2459) compared with single- or dual-chamber ICD alone (n=1114). As expected, unadjusted overall mortality increased with increasing comorbidity burden (41.2 deaths per 1000 patient-years in patients with 0-1 comorbidities, vs. 48.3 and 70 per 1000 patient-years in those with 2 or ≥3 comorbidities, respectively, $p<0.001$), with non-cardiovascular death accounting for much of the difference between comorbidity groups. Likewise, the probability of CRT response decreased with increasing number of comorbidities, but even those with multiple comorbidities had a good probability of responding (82.6% in patients with 0-1 comorbidities, compared with 77% in 1560 patients with 2 comorbidities and 71.1% in individuals with ≥3 comorbid conditions ($p<0.001$). Proportional hazards regression with adjustment on the propensity score and mortality predictors was performed to compare CRT-D vs. ICD alone. During a mean follow-up of 3.4±2.2 years, CRT responders derived a pronounced benefit from CRT-D (HR 0.58, 95% CI 0.43-0.78, $p<0.001$). The survival benefit of CRT-D was evident in those with small number of comorbidities (HR 0.50, 95% CI 0.28-0.90, $p=0.021$ in those with 0-1 comorbidities; HR 0.48, 95% CI 0.27-0.87, $p=0.017$ in patients with 2 comorbidities), but attenuated in the smaller group of patients with ≥3 comorbid

conditions (HR 0.82, 95% CI 0.44-1.52, p=0.5; unpowered comparison) [p-value for interaction 0.53] (**Figure 1**).

In summary, our real world data support the findings of Zeitler et al (1). As expected, there were differences in the risk of death and probability of CRT response among comorbidity groups but, as seen in the long-term follow-up of MADIT-CRT, the burden of comorbidity did not appear to significantly influence the probability of response to CRT, despite a potentially smaller survival benefit in patients with ≥3 comorbidities. Although ICD implantation should be carefully considered in patients with multiple comorbidities, CRT should not be withhold in this context of heart failure patient with enlarged QRS.

FIGURE LEGENDS

Figure 1 – Adjusted survival in CRT responders and ICD patients according to number of comorbidities

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