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Letter to Editor

Could Comorbidities Contraindicate Cardiac Resynchronization Therapy Devices Implantation? - @

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ABSTRACT

Cardiac Resynchronization Therapy (CRT) is a valuable therapy for Heart Failure (HF), that has proved effective not only in improving symptoms, exercise capacity, quality of life (QoL) and systolic function of the Left Ventricle (LV), but also in determining an increase in survival and a reduction of hospitalizations for exacerbations of HF. However only 70% of patients respond favorably to such treatment, attracting therefore the attention on the appropriateness of indications and correct selection of patients, also in relation to comorbidities.

Cardiac Resynchronization Therapy (CRT) has proved to be effective not only in improving symptoms, exercise capacity, Quality of Life (QoL) and systolic function of the Left Ventricle (LV), but also in determining an increase in survival and a reduction of hospitalizations, among patients with Heart Failure (HF). However, the data obtained from the various studies on CRT have shown that only 70% of patients respond favorably to such treatment, attracting therefore the attention on the appropriateness of indications and correct selection of patients, also in relation to comorbidities that can both make the implantation difficult and impair its long-term benefit. In patients undergoing CRT, in a single-center observational study, the prevalence of COPD, CKD and diabetes resulted respectively of 27.7%, 65.2% and 33.8%, while in patients aged >75 years the prevalence of these comorbidities was respectively of 40%, 82% and 31.3% [1].

Most of the patients have many comorbidities and the burden of comorbidities correlate with an increased mortality.

Keywords: Heart Failure; Cardiac Resynchronization Therapy; Chronic Kidney Disease

RENAL FAILURE

CKD is a major determinant of mortality in patients with HF and is associated with a poor long term prognosis. Data of Medicare published in 2014 show that, after ICD/CRT implantation, the rate of survival in patients with HF is worse among those with CKD [2].

A retrospective analysis of the MIRACLE showed that implantation of CRT was associated with an improvement in renal function in patients with moderate CKD [3]. Fung et al. showed that, in patients who enjoyed reverse remodeling after CRT, a slight increase in GFR was registered [3]. In addition, the post CRT improvement of renal function can allow a safer use of medical therapies, such as ACE-inhibitors, which may further contribute to the survival of patients with CKD. In the study of Verbrugge, reverse remodeling was not influenced by the presence of comorbidities, including CKD [4].

Subgroup analysis in CARE-HF, which included patients with and without CKD (GFR ≥ 60 and < 60 ml/min/1.73m²), showed a substantial uniformity in the effects of CRT in terms of death from any cause and hospitalization for cardiovascular events [3]. Bogdan et al. have demonstrated that the functional response to CRT occurred in 63% of patients with no significant difference between patients with and without CKD. The presence of CKD was associated with a lower rate of long-term survival. Despite the poor prognosis, responders with CKD have still a greater benefit in terms of long-term survival after CRT [5].

Few retrospective and observational studies compared the clinical outcomes in patients with CKD, with and without a CRT implantation. In CARE HF, RAFT and MADIT-CRT studies patients with CKD who underwent implantation of CRT-D enjoyed a greater benefit in terms of mortality and/or hospitalization for HF than those who received only an ICD [3].

All these observations suggest that, despite the higher mortality risk in patients with CKD, the benefits from CRT are also evident in the presence of moderate renal impairment.

COPD

COPD frequently coexists with HF, determining not only a poorer prognosis but also a challenge from the standpoint of diagnostic and therapeutic. The prevalence of COPD in patients with HF may have been overestimated by previous studies with important therapeutic implications (eg. unnecessary treatment for COPD, failure to

therapy with beta-blockers). There are not many studies that have attempted to define the influence of COPD on the CRT. In the study of Verbrugge, at the multivariate analysis, COPD was independently associated with an increased mortality from all causes and an increase in hospitalization for HF [4]. Although the assessment of the effects of COPD on the outcome of CRT has not been evaluated in detail, this study showed that, despite the negative weight of COPD as well as that of other major comorbidities on the prognosis, the positive effect of CRT on echocardiographic parameters and clinical improvement was unchanged [4].

ANEMIA

Only few study have explored the possible effect of anemia and iron deficiency on CRT outcomes. Anemia is frequent in patients with HF, with a prevalence ranging from 5% to 70%, depending on the various definitions used (the most used is the WHO definition that identifies anemia as Hb < 12 g/dL in women and < 13 g/dL in men) [6]. The pathophysiology of anemia in HF is complex and sees the interaction of several factors such as hemodilution, occult blood loss, inflammation, renal disease, and iron deficiency [7]. A recent study has suggested a direct link between anemia and cardiac remodeling, with low Hb levels independently associated with increases in LV size and other echocardiographic markers of LV remodeling [8]. In Venkateswaran and Freeman study, Hb levels significantly impact prognosis in terms of survival free from hospitalization, left ventricular assist device implantation and heart transplantation [9,10]; however, in the first one, no significant difference were recorded in baseline to follow-up changes in LVEF, LVESV, or LVEDV between the anemic and non-anemic group [9]. Iron Deficiency (ID) has been identified as comorbidity frequently complicating natural course of HF, since it deteriorates energy production, resulting in impaired function of many tissues and organs, in particular cardiomyocytes [11]. In Bojarczuk and Martens study, it has been demonstrated that ID not only can affect clinical outcomes but also can be associated with lack of favorable response to CRT. In Authors' opinion, this effect is probably linked to the key role of iron in maintaining systemic homeostasis and proper functioning of almost all cells and tissues [11,12].

FRAILITY

Frailty represents a state of increased vulnerability described as a clinical phenotype of: slowed walking speed, low physical activity; unintentional weight loss; low energy; low grip strength (weakness).



The presence of three of five criteria indicates frailty, and one or two criteria represents prefrail status [13]. To date, there is a clear under-representation of older adults across trials and no studies that specifically target the frail. Trials have strict exclusion criteria which, probably, contributed to the exclusion of elderly and frail patients. Nevertheless, frailty is extremely common in elderly HF patients [14]. In a Spanish multicentre study, frailty was associated with an increased risk of 1-year mortality, hospital readmission and functional decline among very old ambulatory patients with HF [15]. Dominguez-Rodriguez et al. reported that the frailty phenotype was associated with a higher risk of admission after CRT in advanced HF [16]. Post-hoc analyses of CRT clinical trials and large device registries suggest that CRT benefits are largely independent of age, and that eligible older HF patients derive additional benefit from CRT use when compared to defibrillator-only implantation. In elderly patients enrolled in the MIRACLE and MIRACLE-ICD trials, CRT resulted in significant improvements in NYHA class and LVEF, regardless of age [17]. Beside this, Fumagalli et al. found a benefit in terms of functional and cognitive profile after only 6 months of resynchronization therapy, given to the increased cardiac index. 18 Patients appropriately selected for implantation can benefit from CRT.

CRT-P VS CRT-D

Randomized trial comparing CRT-D VS CRT-P are lacking. Indeed, most of the trial compared CRT-D and ICD, except for COMPANION study that included both CRT modalities. However it was not powered for this analysis [19]. The appropriate selection of patients who may benefit from CRT-P or CRT-D is important, since CRT-D is associated with elevated costs and with the risk of inappropriate therapy [20]. According to current ESC guidelines, CRT-P should be favored in presence of frailty, multiple comorbidities and older patients [21]. In a recent retrospective study from Martens et al. the Authors compared CRT-P and CRT-D: patients implanted with CRT-P were older and experienced predominantly non cardiac deaths. They also experienced less episodes of ventricular arrhythmias [22]. Given that, the choice between CRT modalities should be driven by clinical judgement since old patients with multiple comorbidities run the risk of dying before CRT-D benefits become evident. So in this group, CRT-P could be the best choice in order to improve symptoms and lower the risk of HF hospitalization.

CONCLUSION

Answering to the question in the title, in our opinion comorbidities are not a contraindication to CRT, since CRT related benefits seem to be independent from comorbidities. The real challenge is choosing correctly between CRT modalities. In the absence of randomized trial, the good clinical sense could help us, basing choice on the single patient's status and favoring CRT-P in those patients with a burden of comorbidities that constitute per se a limit to their survival.

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