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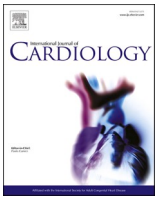

Beta-blocking patients with cardiac amyloidosis: *Adelante cum juicio*

Once upon a time, beta-blockers (BB) were simply forbidden for the treatment of patients with heart failure (HF): they were thought to worsen clinical severity of the disease, eliciting salt/water retention, reducing myocardial contractility, impairing hemodynamics. [1] Therefore, although the first evidence of metoprolol efficacy was given in 1975, only 20 years after, in 1993, the first randomized study paved the way to a widespread use, finally guideline-recommended since 1999 up to 2021. [2] In the meanwhile, Packer's neurohormonal model of HF overcame the cardiocirculatory and cardiorenal ones. Nowadays, the antiadrenergic strategy is a pillar of therapeutics of HF with reduced ejection fraction (HFrEF), while the use in HF with preserved EF (HFpEF) is still controversial. [2]

More recently, a European Consensus document on diagnosis and treatment of cardiac amyloidosis (CA) has stated as a rule the "deprescription" of the use of BB, as well as the "avoidance" of renin-angiotensin-aldosterone system (RAAS) antagonists in CA patients, without giving any evidence-based explanation. [3] An apparent justification is the fear for a poor tolerance due to the hypotensive effect of these drugs in patients with a stiff left ventricle typical of a restrictive cardiomyopathy. However, CA: a) may present with either HFpEF or HFrEF, with a prevalence of 12% and 10%, respectively, [4] b) recognizes, as underlying anatomo-pathological substrate, not only amyloid accumulation in the interstitium, but also fibrosis, likely elicited by profibrotic pathways including adrenergic and RAAS system axes activation, [5] c) is accompanied by a striking neuro-hormonal activation, namely with sympathetic overactivity. [6] All these premises make of beta-blockade a rationale treatment of HF accompanying CA, given also the evidence of a safe, tolerated use from several reports, [7] with even an impact on prognosis, at moderate doses, as it is the case for the use of aldosterone. [8] Though underlying disease-modifying drugs targeting the amyloid cascade are available for light chain-CA (AL-CA) and transthyretin CA (ATTR-CA), [3] both subsets need a rationale HF-disease/cardiac remodeling modifying drug treatment, targeting fibrosis and consequence of chronic maladaptive neurohormonal activation, combined with device implantation and intervention on valve disease, when needed.

The systematic review published in the current issue of the International Journal of Cardiology, conducted by Kang et al. represents a significant advancement in elucidating the role of BBs in CA management. [9] Through careful analysis of observational studies, the review provides crucial insights into real-world prescription patterns and the association between BB use and outcomes in this complex patient cohort. One salient observation from this review, apparently divergent from current consensus advice, is the widespread utilization of BBs among CA patients. This may be due to the clinical imperative to address HF together with concurrent cardiovascular comorbidities such as hypertension and arrhythmias. However, alongside prevalent BB use, the review also highlights considerable variability in BB tolerability within the CA population. A significant proportion of patients experienced adverse events necessitating BB discontinuation, ranging from hypotension to HF exacerbation. Alarmingly, the review reports withdrawal rates of up to 47.2%, underscoring challenges in achieving optimal tolerability and adherence to BB therapy in this patient cohort. Nevertheless, rates of BB prescription and discontinuation vary widely, in between 23% and 87%, not entirely explained by heterogeneity of enrolled populations among studies, possibly reflecting differing perspectives on systematic BB prescription in this patient category and, also, heterogeneity in BB up-titration regimen, with slower increases being better tolerated.

The study by Kang et al. also provides valuable insights into the association between BB use and patient outcomes in ATTR-CA. The analysis did not reveal a significant reduction in all-cause mortality associated with BB use across the overall CA population. However, findings diverged when stratified by left ventricular ejection fraction (LVEF), suggesting potential heterogeneity in treatment response among CA subgroups. Notably, while one study hinted at a survival benefit with BB use in patients with LVEF $\leq$40%, conflicting results were observed in another study, indicative of the complexity underlying treatment effects in this subset of patients. Nevertheless, the former study excluded patients with ATTR polyneuropathy, a possible cause of BB intolerance.

Despite the seminal effort of this systematic review in synthesizing current evidence on BB therapy in CA, it is essential to acknowledge its limitations. Reliance on observational studies inherently limits the strength of evidence, emphasizing the need for prospective interventional trials to rigorously validate these findings. Furthermore, the predominance of studies focusing on ATTR-CA patients may restrict the generalizability of results to other CA subtypes, namely AL-CA. Furthermore, the systematic review solely focused on assessing prognostic outcomes in terms of all-cause mortality, neglecting, likely because of the absence of data in the literature, important endpoints such as HF hospitalization and exercise capacity, which significantly contribute to the disease burden, as demonstrated by studies on HFpEF.

In summary, HF therapy must be per se considered a disease-modifying and life-saving treatment as well as the one addressing the amyloid cascade, and the use of BBs in CA has a strong rationale, though still controversial in the context of HFpEF. While evidence suggests potential benefits of BBs in reducing neurohormonal activation and, possibly, myocardial fibrosis in CA, observational studies reveal variability in tolerability and outcomes. Prospective trials are needed to clarify the role of BB therapy in CA management and to assess its impact

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on disease progression. All in all, we make ours the Antonio Ferrer's sentence in the Promessi Sposi "*Adelante… con juicio*". [10]

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