"Echocardiographic response" to sacubitril-valsartan: does it decrease defibrillation implantation, as well as the incidence of malignant arrhythmias?

«Respuesta ecocardiográfica» al sacubitrilo-valsartán: disminución de la implantación de desfibriladores, pero ¿también de la incidencia de arritmias malignas?

To the Editor,

We have read with great interest the scientific letter by Belarte-Tornero et al.[1] The introduction of the most recent pharmacological novelties in the treatment of heart failure with reduced ejection fraction, such as sacubitril-valsartan (SV), have represented a therapeutic advance, which has been shown to significantly improve the prognosis and quality of life of heart failure patients.

The authors[1] conclude that a strategy providing SV before consideration of a cardiac implantable device could likely avoid the need for almost 60% of cardiac implantable devices, thus decreasing the short- and long-term associated complications and allowing for lower health care expenditure without compromising patient outcomes. These conclusions are strong but not sustained by the study design, the results obtained, or current knowledge on the risk of ventricular arrhythmias (VA) and sudden cardiac death (SCD).

Because this was a single center retrospective study, its results do not imply causality and are merely hypothesis-generating. The echocardiographic measurements of left ventricular ejection fraction (LVEF) were not performed blind in a core lab, which is a major limitation for a technique with high interobserver variability. Importantly, patients who died during SV titration were excluded, a decision that is difficult to understand since those patients could have died because they had no cardiac implantable device. Other important limitations of the study include the exclusion of high-risk patients, and those who were lost to follow-up. Finally, a mean follow-up of 16 months is too short for any study on primary prevention of SCD.

There is increasing evidence of the limitations of LVEF for arrhythmia risk stratification.[2,3] In this regard, contrast-enhanced cardiac magnetic resonance (ce-CMR) has been shown to be a useful technique to improve arrhythmic risk stratification, both for ischemic and nonischemic cardiomyopathies.[2,3] CMR allows detection the amount of myocardial scar and characterization of its components (core, border zone), thus permitting identification of the arrhythmogenic substrate related to the development of scar-related VA.[4]

A related consideration is that, because there are no randomized trials comparing the outcomes of cardiac resynchronization (CRT)-pacemakers vs CRT-defibrillators in primary prevention, prior studies[5,6] have assessed the impact of the presence of myocardial scar, as analyzed by ce-CMR, on the occurrence of appropriate implantable cardiac defibrillator therapies and SCD. The presence, extent, heterogeneity, and qualitative distribution of the scar border zone independently predicted appropriate implantable cardiac defibrillator therapies and SCD in the CRT population, whereas LVEF did not, for both ischemic and nonischemic etiologies.[5,6] Later, the occurrence of VA and SCD depended on the presence of myocardial scar but not on CRT response (ie, improvement of LVEF and left ventricular volume reduction).[5,6] Echocardiographic response to CRT is only weakly associated with the size of the myocardial scar and is influenced by several other parameters, such as preload and afterload, autonomic factors, and medication itself.

In a similar way, the 'echocardiographic response' to SV therapy could incorrectly place many patients at a theoretical low risk for VA/SCD which, in many cases, may not correspond to the actual underlying risk, similarly to what was observed prospectively in CRT responders with underlying arrhythmogenic scars.[5,6] In this regard, the direct measurement and characterization of the scar using ce-CMR could likely be more precise to assess the VA/SCD risk, and could improve the selection of patients suitable for ICD implantation.

Similarly, pharmacological advances will undoubtedly lead to a prognostic improvement in terms of overall mortality and hospital admissions for heart failure, but further prospective studies with longer follow-up times would still be required for accurate arrhythmia risk stratification. In our opinion, clinical decision-making based purely on echocardiographic response to SV should be avoided, and patient custom-tailored assessment of arrhythmia risk should be preferred.

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AUTHORS' CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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«Respuesta ecocardiográfica» al sacubitrilo-valsartán: disminución de la implantación de desfibriladores, pero ¿también de la incidencia de arritmias malignas? Respuesta

To the Editor,

We greatly appreciate the letter by Jáuregui et al.[1] regarding our recent publication. However, we would like to take the opportunity to clarify certain points.

Due to the retrospective and observational design of our study, we agree that causality cannot be assumed. Patients who were lost to follow-up discontinued sacubitril-valsartan (SV) early, or died before completing titration were excluded because no follow-up evaluation to assess the impact of SV can be made in these circumstances. Of 30 patients excluded, 7 patients (23%) died before completing titration. All of them died due to heart failure progression. No other exclusion criteria related to patients' risk were used.

Currently, SV is an essential part of heart failure treatment because of its proven prognostic benefit in reducing cardiovascular death, including sudden cardiac death and arrhythmic events.[2,3] The prognostic benefits of SV are probably mediated by reduced wall stress, ventricular dilatation, cardiomyocyte injury, hypertrophy, and fibrosis, which are factors related to arrhythmias.[2,4] Therefore, through these positive effects on reverse remodelling, myocardial stretch and fibrosis progression, the arrhythmic risk might be modified by SV treatment.[3] Of note, some of the recent studies evaluating arrhythmic risk cited by Jáuregui et al. included patients from retrospective cohorts who were not treated with SV.[5]

Interestingly, the authors focus on the fact that accurate arrhythmic risk stratification, especially in dilated cardiomyopathy, may include parameters other than left ventricular ejection fraction $\leq$ 35% as late-gadolinium enlargement detected by cardiac magnetic resonance.[5] Although this new approach is exciting and will probably change future clinical practice, it is not yet validated in external populations or included in current guideline recommendations. In our opinion, these new clinical algorithms of arrhythmic risk stratification are not incompatible with the fact that heart failure disease-modifying therapies such as SV should be implemented as early as possible and preferably before consideration of implantation of cardiac devices.

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L.C. Belarte-Tornero and N. Farré contributed to the conceptualization and writing of the manuscript. All authors discussed and approved the final version of the manuscript.

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