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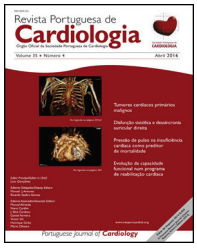

LETTER TO THE EDITOR

Response to the Letter to the Editor ''When sacubitril/valsartan met neprilysin and B-type natriuretic peptide in the labyrinth of biochemistry''

Resposta à Carta ao Editor «Quando o sacubitril/valsartan encontra a neprilisina e o peptídeo natriurético auricular tipo B no labirinto da bioquímica»

We read with interest the letter by Siniorakis et al. referring to our paper, ''Sacubitril/valsartan: a practical guide'' published in the *Journal*,[1] and we do agree that biochemical issues on natriuretic peptides in the context of sacubitril/valsartan treatment are complex and controversial. Nevertheless, we have to keep in mind that our purpose was to provide physicians with clear and practical guidance to everyday practice, and our recommendations are based on the evidence of clinical arguments.

There is ample literature about the effects of neprilysin and its inhibition by neprilysin inhibitors like sacubitril on the natriuretic peptide system – protein modifications, endopeptide scissions – and their identification by immunoassays from different manufacturers. The effects of neprilysin inhibition are variable and poorly predictable in BNP assays from different manufacturers; change in one BNP assay may not necessarily be comparable to another one and there is definitely heterogeneity across assays with respect to how much change is observed. This variation is logical because neprilysin cleaves the BNP molecule in several places, which also reflect binding sites for the various BNP immunoassays. Sacubitril/valsartan leads to a somewhat more predictable decrease in NT-proBNP, as measured by different assays.[2]

There is also wide between-patient variability in BNP response to sacubitril/valsartan, including the initial variable increase in BNP after initiation of the ARNi in HFrEF patients – no increase in BNP in some patients, variable increases in others – compared to a more homogeneous NT-proBNP decrease.[3,4]

Because of these two effects, investigators recommend the use of NT-proBNP after sacubitril/valsartan initiation to avoid clinical confusion. This is reflected in the 2017 American College of Cardiology expert consensus decision pathway for optimization of heart failure (HF) treatment and in the 2019 Heart Failure Association practical guidance on the use of natriuretic peptides. The Task Forces consider NT-proBNP ''the preferred biomarker to quantify HF severity and monitor prognosis in patients on sacubitril/valsartan''.[5–7]

Moreover, the European Medicines Agency package clearly states that BNP is not a suitable biomarker of HF in patients treated with sacubitril/valsartan because BNP is a neprilysin substrate. NT-proBNP is not a neprilysin substrate and is therefore a more suitable biomarker.[8,9]

The US Food and Drug Administration has recently approved sacubitril/valsartan in pediatric HF based on its effect on NT-proBNP levels; NT-proBNP is therefore considered a valid surrogate efficacy endpoint for regulatory approval of sacubitril/valsartan.[10]

Therefore, although we do understand the biochemical issues reported by Siniorakis et al., our practical recommendation may be more prudent and probably limit clinical confusion, at least until BNP reaches a steady state during the maintenance phase of ARNi treatment.[4] However, in hospitals where BNP is the only natriuretic peptide assay available, its measurement during maintenance treatment with sacubitril/valsartan reliably reflects clinical prognosis with comparable performance to NT-proBNP. BNP should not however be used to determine treatment adherence or degree of treatment response, or lack thereof, in individual patients, during the initial phases of treatment.[4]

The response of natriuretic peptides to sacubitril/valsartan and comparisons of different BNP and NT-proBNP assays that target different regions on the BNP molecule, as well as NT-proBNP and proBNP1–108 assays, have been prospectively tested in PROVE-HF, and should provide a more comprehensive picture.[11,12] Until then, our practical recommendation is consistent with current international guidelines and expert consensus statements.

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