



## LETTER TO THE EDITOR

### When sacubitril/valsartan met neprilysin and B-type natriuretic peptide in the labyrinth of biochemistry



### Quando o sacubitril/valsartan encontra a neprilisina e o peptídeo natriurético auricular tipo B no labirinto da bioquímica

To the Editor,

We read with interest the article by Fonseca and colleagues, which provides a practical guide on sacubitril/valsartan (SV).<sup>1</sup> We noted that in accordance with the suggestions of the PARADIGM-HF study, the authors discourage the use of B-type natriuretic peptide (BNP) in monitoring the effectiveness of SV during heart failure (HF) treatment.<sup>2</sup>

SV is at the same time an angiotensin receptor blocker and a neprilysin (NEP) inhibitor. NEP is a metalloprotease that catalyzes several peptides, including BNP. Inhibition of NEP by SV is expected to cause a transient increase in BNP, giving the erroneous impression of failed treatment. To avoid misinterpretations, PARADIGM-HF proposes the exclusive use of the terminal form NT-proBNP, which is resistant to NEP, instead of BNP. The novel drug SV is expanding worldwide as a promising and revolutionary treatment in the previously stagnant environment of pharmaceutical HF treatment. However, the establishment of SV threatens BNP as a diagnostic and prognostic biomarker.

BNP is a well-established biomarker of HF, with significant diagnostic and prognostic properties. It is secreted during myocardial stress and promotes diuresis and vasodilatation while expressing anti-fibrotic and anti-inflammatory characteristics. Furthermore, BNP inhibits the renin-angiotensin-aldosterone system and regulates cardiorenal interactions. The precursor of BNP is proBNP, which when split also forms the inactive terminal form NT-proBNP. NT-proBNP and BNP are used interchangeably as biomarkers in

clinical practice, and have been used extensively in recent decades in modern cardiology.<sup>3</sup> Before sending BNP into exile, its complex relationship with NEP should be reviewed from a laboratory point of view, in biochemical terms.

Only immunoreactive forms of BNP are assessed by common commercial assays, which contain monoclonal or polyclonal antibodies targeting specific epitopes.<sup>4</sup> Immunoreactive BNP is conjugated to proBNP, so both forms are inseparably included in the final result.<sup>5</sup> In humans, the proBNP-BNP complex is a poor substrate for NEP, which cleaves only a limited number of bonds, depending on the type of assay used.<sup>6,7</sup> Apart from NEP, the proBNP-BNP complex is also degraded by other exogenous and endogenous proteases including insulin-degrading enzyme, proteases of the kallikrein family and natriuretic peptide receptors of the guanylate cyclase family.<sup>5</sup> All these catalysts remain unaffected by the inhibitory action of SV on NEP, and therefore do not provoke a drug-mediated change in BNP.

Interestingly, human BNP itself is a NEP inhibitor. Recently, *in vitro* as well as *in vivo*, it was found that BNP values >900 pg/ml degrade NEP decisively.<sup>8</sup> In this light, the methodology of PARADIGM-HF should be re-evaluated. The majority of enrolled patients were in NYHA class II, with average BNP values of 255 pg/ml. In these patients NEP is expected to be overactive, prone to be catalyzed by SV. In NYHA III and IV patients, higher values of BNP seem to be involved in reduced NEP activity, raising questions about SV's further synergistic action.

The complex relationship between BNP and NEP is not amenable to simplifications. The results of PARADIGM-HF concerning the validity of BNP may be reconsidered after a thorough re-exploration of the study methodology from a biochemical point of view. The concept of HF is currently moving from the classic renin-angiotensin-aldosterone system theory to the context of proteases and their substrates. Withdrawing BNP from the investigation of these novel mechanisms is a challenge we should not surrender to. In the meanwhile appropriate algorithms for estimating the dynamic of natriuretic peptides in HF treated with SV are awaited with considerable interest.<sup>9</sup>

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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