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EDITORIAL COMMENT

Do we need to EVALUATE multiple biomarkers and/or the same biomarkers multiple times in patients with heart failure?

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This article refers to 'Changes in cardiac biomarkers in association with alterations in cardiac structure and function, and health status in heart failure with reduced ejection fraction: the EVALUATE-HF trial' by P.L. Myhre *et al.*, published in this issue on pages 1200–1208.

The concept of biomarker encompasses all indicators of 'normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention',[1] but this term is usually employed to define circulating molecules measurable with accurate assays.[2] Biomarker research on heart failure (HF) has led to the identification of many potential biomarkers related to different aspects of HF pathophysiology. Nonetheless, only natriuretic peptides (NPs) are employed on a routine basis in clinical practice. NPs are produced by cardiomyocytes subjected to stress from volume and/or pressure overload. They are incorporated in the same definition of HF,[3] and their diagnostic value is acknowledged by both European[4] and American guidelines.[5] All other possible applications of NPs, namely prediction of future development of HF, risk stratification, assessment of the response to therapy and disease trajectory, are not contemplated by the European guidelines[4] and only partially by the American ones,[5] reflecting the fragmentary evidence on these points.[2] The picture is even more nebulous for high-sensitivity cardiac troponin T (hs-cTnT) and soluble suppression of tumorigenesis-2 (sST2). The main stimuli to hs-cTnT release are cardiomyocyte death (mostly by necrosis), while sST2 is produced mainly in extracardiac sites following the activation of inflammatory and profibrotic pathways as well as haemodynamic overload.[2] hs-cTnT and sST2 are not accurate enough to discriminate HF from other conditions, but have emerged as powerful prognostic biomarkers in patients with either chronic or acute HF, with an additive value over N-terminal pro-B-type NP (NT-proBNP) in the chronic setting,[6,7] possibly because they are surrogates of different pathways involved in the HF syndrome.[2]

The use of multiple biomarkers for risk prediction in chronic HF has typically focused on single measures.[6,8] The prognostic role of changes in biomarkers has been quite extensively investigated in acute HF,[9] where changes in NT-proBNP are even been used as a surrogate endpoint.[10] Nonetheless, most trials have not performed repeated measures of HF biomarkers other than NPs (usually NT-proBNP), which is regarded as the universal HF biomarker. Therefore, the impact of even guideline-directed medical therapy (GDMT) on biomarkers reflecting different aspects of HF pathophysiology, and the relationship between changes in biomarkers, clinical status and cardiac remodelling remains to be elucidated.

The EVALUATE-HF trial

The Study of Effects of Sacubitril/Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction (EVALUATE-HF) trial enrolled patients with HF and reduced ejection fraction (HFrEF), with the requirement of GDMT, and excluding those with persistent or permanent atrial fibrillation (AF).[11] These patients were randomized to sacubitril/valsartan or enalapril, with target doses of 97/103 mg or 10 mg twice daily, respectively. After 12 weeks, all patients were transitioned to open-label sacubitril/valsartan for further 12 weeks. Compared with enalapril, therapy with sacubitril/valsartan did not significantly reduce central aortic stiffness over 12 weeks, as well as several secondary endpoints including left ventricular (LV) ejection fraction, although an improvement in LV volumes and diastolic function was observed.[11]

In this issue of the Journal, Myhre and colleagues assess patients with serial biomarker measurements available (n = 410, 88%).[12] NT-proBNP, sST2 and hs-cTnT at 24 weeks decreased by median −31% (interquartile range −55%, +6%), −6% (−19%, +8%) and −3% (−13%, +8%), and, at 12 weeks, to a significantly greater

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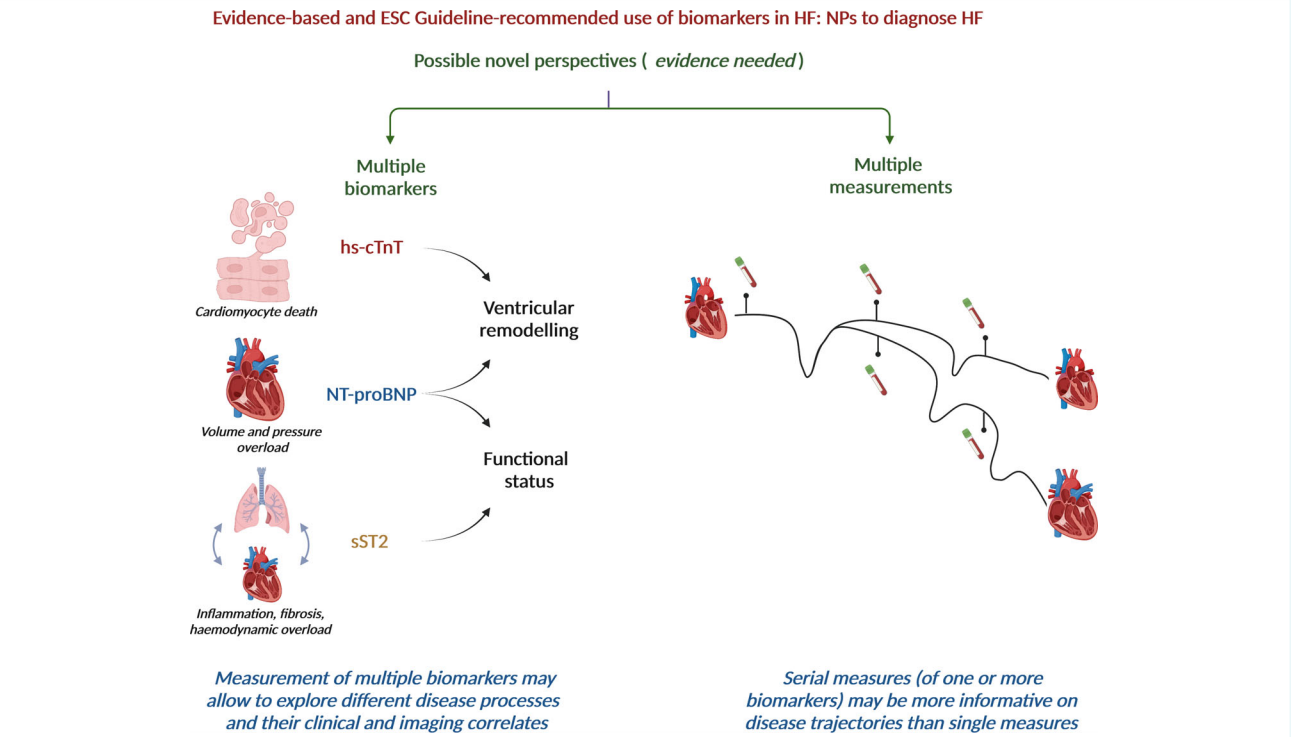

Figure 1 Rationale for a multi-marker approach and repeated biomarker measurement in heart failure (HF) patients. ESC, European Society of Cardiology; hs-cTnT, high-sensitivity cardiac troponin T; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sST2, soluble suppression of tumorigenesis-2.

extent in patients on sacubitril/valsartan than those on enalapril.[11] Changes in the three biomarkers displayed weak correlations between them, and rather few relationships with other variables: specifically, decreases in NT-proBNP were associated with reductions in cardiac volumes and improvement in systolic and diastolic function and health status, decreases in hs-cTnT with reductions in LV mass, and decreases in sST2 with improvements in health status. All these associations were not influenced by treatment with sacubitril/valsartan versus enalapril.[12]

The authors should be congratulated for this well-conducted analysis, with potential implications in trial design and clinical practice, as discussed below. Possible limitations are a therapy strategy still not relying on the four pillars, with just 25% of patients on mineralocorticoid receptor antagonists, and obviously none on sodium–glucose cotransporter inhibitors.[12] Confirmation of these results could be searched in patients on current GDMT, as well as in patients with different aetiologies (ischaemic vs. non-ischaemic), and in subgroups like women (accounting for just 25% of the total cohort),[12] and those with persistent or permanent AF, which is very common in HFrEF and it is known to have an impact on NP levels.[2] Additionally, baseline biomarker values were quite low, which suggests a highly selected, very stable subset of patients, in line with the apparent lack of HF rehospitalizations over 24 weeks.[11,12] Despite these possible issues, the study messages are clear and prompt two fundamental questions regarding (i) the need for a multi-marker approach to HF, or at least to move from the 'one-size-fits-all' approach relying exclusively on NPs, and (ii) the possibilities and challenges of repeated biomarker measurements.

Do we really need multiple biomarkers?

In the study by Myhre *et al.*,[12] the decrease of all three biomarkers suggests a positive effect of sacubitril/valsartan on congestion (translating into NT-proBNP and sST2 decreases), cardiomyocyte death (with hs-cTnT reductions), and the activation of inflammatory and profibrotic pathways (driving sST2 decreases). The other findings are reasonable from a pathophysiological perspective: for example, the relationship between sST2 variations and metrics of health status, but not with measures of cardiac structure or function,[12] may reflect the link between congestion and sST2 production as well as the extra-cardiac production of this biomarker. The strong point of a multi-marker approach is that it can capture an effect on different elements of HF pathophysiology. While some drugs, like sacubitril/valsartan, may have a wide spectrum of action, other drugs may have a more specific action on one or few disease pathways. Changes in biomarkers exploring these specific pathways (such as biomarkers of fibrosis for anti-fibrotic drugs) are well-suited to act as surrogate endpoints. Instead of focusing only on NPs in clinical trials, future studies should use

specific biomarkers reflective of the mechanism of action of each drug. These patterns could be employed for risk enrichment and to assess the response to treatment. A panel of biomarkers reflecting different cardiac alterations, such as collagen peptides or sST2 associated with fibrosis, C-reactive protein and interleukins with inflammation, endothelin or adrenomedullin with endothelial dysfunction, carbohydrate antigen 125 or bio-adrenomedullin with fluid overload, urinary sodium for monitoring decongestion, or direct renin for renin–angiotensin–aldosterone system activation could provide additional useful information. An unbiased -omic approach could be even more accurate than the simple evaluation of biomarkers more closely associated with specific disease mechanisms.[13] The heterogeneous setting of HF with preserved ejection fraction seems particularly well-suited for this kind of approach.[14]

Which are the possibilities and challenges of repeated biomarker measurements?

Interpreting the magnitude of changes in NT-proBNP, hs-cTnT and sST2 observed in EVALUATE-HF is more challenging than one may expect because NT-proBNP has a much larger intrinsic variability than hs-cTnT and sST2.[2] For this reason, 'an increase in NT-proBNP levels of >42% or a decrease of >30% is needed to indicate a reliable short-term change; and for a long-term change an increase of up to >76% or a decrease of >43% is required',[15] while much smaller hs-cTnT and sST2 changes can be reliably attributed to changes in the disease status rather than random fluctuations. While a single NT-proBNP value may be adequate to diagnose HF in patients with a suggestive clinical and imaging picture,[4] interpreting the magnitude of change of two NT-proBNP measures taken several weeks apart is more difficult because of the fluctuations in NT-proBNP levels due to the many factors affecting volume status and the relatively short half-life of NT-proBNP.[2] The effect of this variability is greatly reduced in a study on 410 patients, but this notion is important when repeated NT-proBNP measures are evaluated in single patients as indicators of disease evolution. The possible options to make this assessment more reliable are: (i) to consider just large variations as significant, (ii) to add further measurements and to assess the general trend over time, and (iii) to stick to couples of measures, but add biomarkers with a lower intrinsic variability, such as hs-cTnT or sST2, which can more easily capture subtle changes in the disease state.

In conclusion, NT-proBNP, hs-cTNT and sST2 can be measured using robust and validated assays, which have been approved by the Food and Drug Administration and have the *Conformitè Europëenne* Mark for clinical use. The combined use of these biomarkers could give insight on multiple disease mechanisms, which are related to clinical and imaging findings and future disease evolution. Furthermore, serial measurements of a single or multiple biomarkers inform on disease evolution over time (*Figure 1*). Future prospective studies are needed to clarify the possible implications for trial design and clinical practice.

Conflict of interest: none declared.

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