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EDITORIAL COMMENT

BNP/NT-proBNP Levels Are Sensitive Markers of Impaired Prognosis in Patients Without Heart Failure*

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Over the last decades, extraordinary progress has deeply modified and improved the management of cardiovascular diseases (CVDs) based on the availability of new technologies and innovative diagnostic and therapeutic strategies. However, besides the effective control of conventional cardiovascular risk factors, the screening and prevention of CVD still present several gaps to fill, and consequently, CVD continues to represent a major issue for health care systems around the world.[1]

Since their discovery in the early 80s and their identification and characterization in the human heart natriuretic peptides (NPs) have been regarded as potential biomarkers of cardiac function and of the severity of CVD, especially in view of the regulated expression and secretion from myocytes.

Hence, NPs have progressively become a cornerstone of integrated strategies aimed to predict the development and progression of heart failure (HF). Subsequently, the potential diagnostic and prognostic role of NPs has been investigated in the general population and in a wide variety of CVD patients including asymptomatic subjects and high-risk patients.[2]

The synthesis and secretion of NPs are promoted by pressure and volume overload, and the effects of increased levels of NPs have presumably beneficial hemodynamic functions.[2] B-type NP (BNP) and N-terminal-proBNP (NT-proBNP) are well-established markers of HF. They are routinely used, in combination with clinical and imaging tests, to diagnose HF, assess the severity of the disease, evaluate the effectiveness of treatment, and guide the titration of long-term medical therapy.[3] Studies have demonstrated that the incorporation of NPs levels may significantly improve the prediction of HF development in asymptomatic individuals with one or more CVD and drive the clinical decision to intensify treatment strategies and improve outcomes.[4,5]

NPs levels increase in different cardiovascular conditions where they behave as markers of disease progression and may help for prognostic purposes. In the context of hypertension, individuals with stage 1 hypertension and elevated NT-proBNP levels have higher risk of cardiovascular and all-cause mortality compared to patients with stage 2 hypertension and lower NP levels.[6] In patients with coronary artery disease (CAD), higher NPs levels predict recurrent myocardial infarction and angina, and they represent a prognostic marker in both chronic and acute coronary syndromes.[7-9] NP levels are associated with the severity of both aortic stenosis and mitral regurgitation, where they can contribute to monitor the hemodynamic changes as well as the risk of HF, hospitalizations, death from cardiovascular causes, and the need of surgical intervention.[10,11] In patients with atrial fibrillation, NP levels are related to an enhanced risk of stroke and cardiovascular death.[12] NP levels also correlate with mean pulmonary artery pressure and increased risk of mortality in patients with pulmonary arterial hypertension.[13]

Despite the great advantage offered by NP level assessment for CVD screening and prevention, several uncertainties remain to be solved, most

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importantly the lack of validated cutoff levels in non-HF patients, in contrast to what has been clearly established for the diagnosis of both acute and chronic HF.[3]

In this issue of *JACC: Advances*, Jehn et al[14] attempted to explore the appropriate NP cutoff levels for risk stratification by investigating NP thresholds in non-HF patients from the cohort of the Essen Coronary Artery Disease registry. Patients with known HF or elevated BNP/NT-proBNP levels (BNP >100 pg/ml, NT-proBNP >400 pg/ml) were excluded from their analysis. The final study sample included 3.690 individuals with a large percentage of males (71%), mean age of 63 years, history of CAD (70%), median BNP level of 36 pg/ml, and NT-proBNP level of 120 pg/ml. The primary endpoint was all-cause mortality; this information was acquired from available hospital records. During a mean follow-up of 2.6 years, the study outcome occurred in 169 patients. As a result, BNP levels >9.6 pg/ml in men and >29 pg/ml in women and NT-proBNP thresholds of 65 and 77 pg/ml for men and women, respectively, were associated with a 2.5-fold increased all-cause mortality independently from hypertension, CAD, and body mass index. The results were confirmed in a validation group. In subgroup analyses, the association between BNP/NT-proBNP levels above the thresholds and all-cause mortality was stronger in patients older than 60 years, females, and those with a known cardiac diagnosis, although without significant interaction. No-significant association between elevated BNP/NT-proBNP levels and all-cause mortality was observed in patients with impaired renal function without a plausible explanation.[14] The low threshold levels of both BNP and NT-proBNP, which are within the normal values or just at the upper limit, identified for risk stratification in this study underscore the ability of NPs in capturing initial, meaningful signs of CVD impairment.

In spite of the unquestionable merits of these authors investigation of a clinically relevant area of application of the measurement of NPs, several limitations of this study deserve to be discussed. First, the only endpoint investigated was all-cause mortality, excluding other potentially relevant cardiovascular outcomes such as cardiovascular death, HF hospitalizations, and acute cardiovascular events. Secondly, the duration of follow-up was relatively short and was likely too short to properly detect the impact on mortality. Although numerically higher effect sizes were observed for patients with follow-up duration of <2.6 years as compared to ≥2.6 years, suggesting a stronger association between elevated BNP values and short-term mortality, a longer observational follow-up would have been more appropriate to achieve more solid information on the predictive value of death. Third, no information is available about the presence of left ventricular hypertrophy, diastolic dysfunction, and subclinical atherosclerotic organ damage as detected by echocardiography or vascular imaging, which are known to be associated with a higher cardiovascular risk. Fourth, a significant proportion of patients received treatment with beta-blockers, diuretics, and renin-angiotensin-aldosterone-system inhibitors with consequent potential impact on the study objectives. Although the population had no overt acute or chronic HF, it cannot be definitely excluded that some patients had asymptomatic HF. Earlier or milder stages of HF may recognize different alert thresholds of NP levels. Fifth, the analysis considered only the primary discharge diagnosis available in the Essen Coronary Artery Disease registry, with limited information about developed comorbidities that might have played a relevant prognostic role. Finally, the study included a large proportion of Caucasian participants, thus limiting the possibility to extend the results to other ethnic groups.

Based on the results of the current analysis,[14] the measurement of NP levels may represent a valuable tool to promote the introduction of tailored approaches in non-HF patients[15] to identify worse cardiovascular risk profiles, which may benefit from a more effective control of cardiovascular risk factors and an earlier initiation of medical therapy. More studies are needed to confirm the currently identified threshold values of NPs in the blood to be used for prognostic purposes in patients without HF.

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