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REVIEW

Natriuretic peptides: Ready for prime-time in hypertension?

Peptides natriurétiques : prêts à entrer en scène dans l'hypertension ?

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Summary Over the past years, natriuretic peptides have been recognised not only as important contributors to cardiovascular regulation but also as valuable markers in overt cardiac disease, including heart failure or coronary disease. More recently, these markers have shown their ability to detect preclinical cardiac alterations in different settings. In this respect, natriuretic peptides offer a new perspective for risk stratification in hypertension. They are correlated to various features of cardiac remodelling provoked by hypertension. They also depend on vascular properties, including blood pressure level and aortic stiffness. In addition to being integrative markers of cardiovascular alterations, several studies have shown their value in predicting all-cause mortality or cardiovascular mortality and morbidity in the general population. At least three consistent studies are now available in hypertension also showing this prognostic value. This performance, together with the ease of measurement, low cost and widespread availability, should prompt the wide use of natriuretic peptides for risk stratification in hypertension, at least in patients with normal electrocardiography, but also in most hypertensive patients.

MOTS CLÉS
Hypertension ;
NT-proBNP ;
Survie;

Résumé Ces dernières années, l'importance des peptides natriurétiques a été reconnue non seulement pour leur contribution à la régulation cardiovasculaire mais surtout comme des marqueurs dans l'insuffisance cardiaque et la maladie coronaire. Plus récemment, ces marqueurs ont été utilisés pour détecter des atteintes cardiaques infracliniques. Dans ce contexte,

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Stratification du risque ;
Hypertrophie ventriculaire gauche

ils offrent de nouvelles perspectives pour la stratification du risque dans l'hypertension. Leurs taux plasmatiques sont corrélés à différents aspects du remodelage cardiaque induit par l'hypertension. Ils dépendent également des propriétés vasculaires, incluant la pression et la rigidité aortique, et de la fonction rénale. Au-delà de l'aspect de marqueurs intégratifs des dysfonctionnements cardiovasculaires, plusieurs études ont récemment montré leur valeur dans la prédiction de la mortalité globale ou la morbi-mortalité cardiovasculaire dans la population générale. Au moins trois études sont maintenant disponibles confortant cette valeur pronostique dans l'hypertension artérielle. Cette performance associée à la facilité de la mesure, au coût modéré et à sa large disponibilité devraient accélérer l'utilisation du dosage des peptides natriurétiques pour la stratification du risque dans l'hypertension artérielle, au moins chez les patients avec un ECG normal si ne n'est chez la plupart des hypertendus.

Abbreviations

ANP	atrial natriuretic peptide
BNP	brain natriuretic peptide
ECG	electrocardiography
LVH	left ventricular hypertrophy
NT	N-terminal

Introduction

In response to volume expansion and pressure load, ventricular myocytes release cardiac hormones with potent natriuretic effect associated with vasodilation and strong antifibrotic effects. Theses hormones oppose the sympathetic and renin-angiotensin-aldosterone system in blood pressure control and cardiovascular remodelling [1] (Fig. 1). The two main peptides, ANP and BNP, stem from different genes and have specific spatiotemporal expression; they are differentially expressed in the heart [2]. Both hormones are small cyclic peptides with very similar amino acid compositions, acting on the same membrane receptor (natriuretic peptide receptor-A), which is a membrane guanylate cyclase. Both are generated by proteolytic cleavage from a prohormone, which gives rise to an equimolar amount of the remnant peptide, NT-ANP or NT-BNP, and of each active ANP or BNP hormone (Fig. 2). They are each of great interest, both in terms of pathophysiology and as potential drug targets [3,4]. The availability of reliable plasma assays for the different players has identified BNP, together with its amino-terminal fragment (NT-proBNP), as the most promising markers for cardiac diseases. Over the past years, as a result of a tremendous amount of work in this field, these hormones have profoundly changed the management of heart failure and are now recommended for diagnosis, prognostic stratification, and treatment adjustment.

More recently, the potential of these markers in hypertension has been questioned. Why so? Reasons are numerous, ranging from the physiopathology of hypertension where 'salt sensitivity' is a key mechanism in hypertension and has to be related to the natriuretic peptide system, to detection of hypertension consequences in terms of target organ damage. In hypertension, detection of cardiac damage is critical for risk stratification, as emphasized by most guidelines [5]. This is usually done by searching for LVH and more generally by identifying pathological cardiac remodelling. The ideal marker for screening should be easy to measure, widely available, reproducible, correlated with cardiac status and, most of all, correlated with outcomes.

ECG, which is recommended by most guidelines, apparently fits all these requirements, except that it is rarely performed in clinical practice [6] because of either the lack of ECG devices or insufficient skills in the interpretation of ECG recordings. Echocardiography, which remains the 'gold standard' in clinical practice, suffers from a lack of availability for all hypertensive patients and from its cost, making this investigation not indicated for risk stratification of hypertensive patients in general. Thus, there is still room for new cardiac markers to be used for risk stratification.

Why are natriuretic peptides of potential interest in hypertension?

As mentioned above, some prerequisites should be met before a marker is considered as potentially interesting for risk stratification in hypertension. In this respect, assays of natriuretic peptides in plasma are easily available, independent of the operator's skills, and their cost (€22.95 in France) compares with the cost of ECG. We have recently looked at the distribution of plasma NT-proBNP concentrations in a large cohort of hypertensive patients; while the plasma concentrations were, on average, much lower than in overt cardiac disease — namely, heart failure — they covered a wide range, from undetectable values to fairly high ones [7]. Despite this wide interindividual variability, the intrapatient reproducibility of NT-proBNP measured at arrival in the hospital (ambulatory) and in decubitus after one night's rest in hospital was very satisfactory, with a coefficient of variation around 5%. The fact that expression and secretion of BNP by ventricular myocytes is a landmark of cardiac remodelling is, of course, of particular interest in hypertension. In this context, NT-proBNP may be more suitable than BNP because of its longer half-life, lower intraindividual variability, and better ability to detect subtle preclinical cardiac changes [8]. The secretion of natriuretic peptides mainly correlates with left ventricular wall stress, either systolic or diastolic [9], which is a complex interplay between pressure, left ventricular diameter, and wall thickness. Consistently,

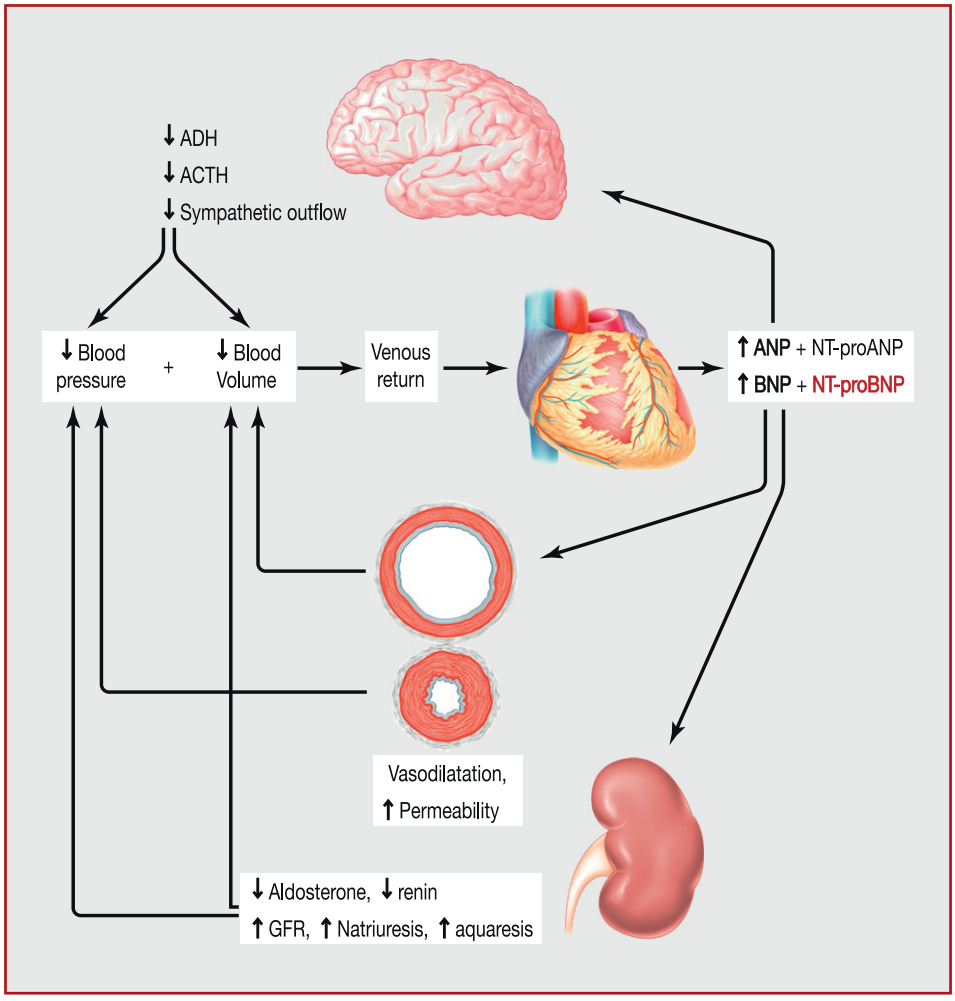

Figure 1. Physiological actions of natriuretic peptides in different tissues contribute to decreased venous return and decreased heart stress in a classical negative regulatory loop. ACTH: adrenocorticotrophic hormone; ADH: antidiuretic hormone; ANP: atrial natriuretic peptide; BNP: B-type natriuretic peptide; GFR: glomerular filtration rate; NT: N-terminal.

most studies have found an increased concentration of plasma natriuretic peptides associated with LVH; NT-proBNP was also found to be related to systolic dysfunction [8], diastolic dysfunction, and increased filling pressure [10], while BNP is secreted in response to myocardial ischaemia [11]. Additional non-cardiac factors influence natriuretic peptide release. This is the case with ventricular afterload, particularly blood pressure [12] and aortic stiffness [13,14]. Finally, plasma natriuretic peptide concentrations are raised with renal failure [15,16], as a result of both insufficient clearance and increased blood volume or an impaired cardiovascular system (Fig. 3). In this respect, natriuretic peptides act as integrative markers of cardiac, vascular, and even renal status, i.e. three major targets of elevated blood pressure. Indeed, it has been suggested that natriuretic peptides represent markers of cardiorenal distress [17].

Evidence available in hypertension

In animal models, the increased cardiac expression and secretion of natriuretic peptides is a landmark of cardiac overload and associated remodelling. In a previous work, we showed that, in hypertensive patients, the relationship between left ventricular mass and NT-proBNP was strong enough to propose this marker as a test for LVH with a reasonable diagnostic performance (area under the curve 0.816 [confidence interval 0.72—0.91]) [12]. By using a receiver operating characteristic (ROC) regression model, we demonstrated that this performance was independent of several confounders, including age, systolic blood pressure, and creatinine clearance, while the effect of body mass index was of borderline significance. Of interest was the fact that the performance of the test was statistically better in women than in men. The value of natriuretic peptides for the diagnosis of LVH has been variably confirmed by other teams. Morillas et al. found a very similar performance compared with magnetic resonance imaging [18], as did a second report [19] when C-reactive protein was included. Nishikimi et al. showed that plasma ANP and BNP concentrations increased in essential hypertensive patients with LVH. Furthermore, BNP secretion was augmented to a greater extent in concentric hypertrophy. They suggested that these markers may be useful for the detection of concentric LVH in patients with

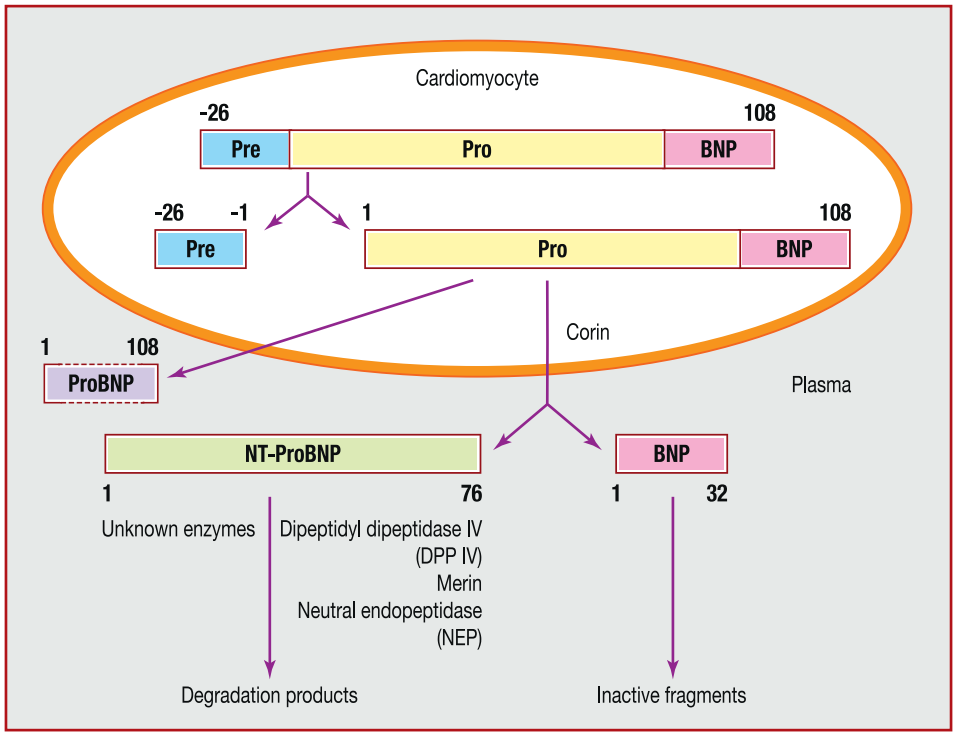

Figure 2. Metabolic aspects of BNP and NT-proBNP secretion in blood. Contrary to ANP, which is stored in secretory granules and released upon stretch in atria myocytes, BNP is constitutively secreted in an equimolar ratio with NT-proBNP. ProBNP, the complete form of the precursor, can also be directly released from cardiomyocytes into the circulation. While the metabolism of BNP via a set of proteases is relatively well characterized, the mechanisms of NT-proBNP metabolism are less well-defined. ANP: atrial natriuretic peptide; BNP: B-type natriuretic peptide; NT: N-terminal.

essential hypertension [20]. On the contrary, Vasan et al. [21] and Nakamura et al. [22] showed that BNP was of limited value for the detection of LVH. These discrepancies can probably be explained by the fact that natriuretic peptides not only depend on left ventricular mass but also on diastolic function, as previously mentioned. They may also be influenced by mild systolic impairment assessed, for example, by midwall shortening fraction (unpublished personal observation). Several reports have addressed the value of these markers for detecting preclinical cardiac abnormalities. The ability of BNP as a screening test for preclinical systolic or diastolic dysfunction has been found to be either good [23] or suboptimal [24]. Because of the various possible combinations of mass and diastolic/systolic dysfunction, it is not surprising that the relationship of natriuretic peptides with one of these variables may vary and that an elevation of these markers does not always reflect the same feature of cardiac remodelling. Far from being a limitation, this characteristic may be used in hypertension to provide a tool that can detect any form of cardiac injury. This usefulness may even go beyond cardiac remodelling, as high blood pressure and aortic stiffness per se are also able to raise plasma natriuretic peptides [12].

Prognostic data in hypertension

An increasing number of reports have confirmed the value of natriuretic peptides as predictors of outcomes in patients free from heart failure, on top of classical Framingham-type risk factors. In a subset of 270 hypertensives from the general population with no left ventricular dysfunction, Pedersen et al. showed that NT-proBNP was predictive of a composite endpoint of death, stroke/transient ischaemic attack or myocardial infarction [25]; this was independent of traditional cardiovascular risk factors. The median NT-proBNP concentration in the study population was 103.8 pg/mL; this threshold was associated with a marked increased risk for those patients with concentrations above it. Olsen et al. [26,27] showed that NT-proBNP had a significant prognostic value in two complementary analyses of the LIFE substudy, i.e. in highly severe hypertensive subjects with electrical LVH. In the latter report, NT-proBNP predicted a composite endpoint of cardiovascular death, non-fatal stroke or non-fatal myocardial infarction after adjustment for traditional risk factors, urinary albumin/creatinine ratio, and history of diabetes or cardiovascular disease. In this case, the proposed concentration threshold was around 170 pg/mL; of note, all these patients had electrical LVH. McKie et al. showed in a community-based cohort of 2042 subjects free from heart or renal failure, 29% of whom were hypertensives, that BNP and NT-proBNP were independent predictors of all-cause death [28]. Again, a similar NT-proBNP concentration threshold of 109 pg/mL was of prognostic value. Depending on the technique used, the cutoff for BNP lay between 23.0 and 39.7 pg/mL. More recently, in a community-based cohort of 5063 participants free of cardiovascular disease and aged greater or equal to 55 years, circulating NT-proBNP concentrations appeared predictive of a first major fatal

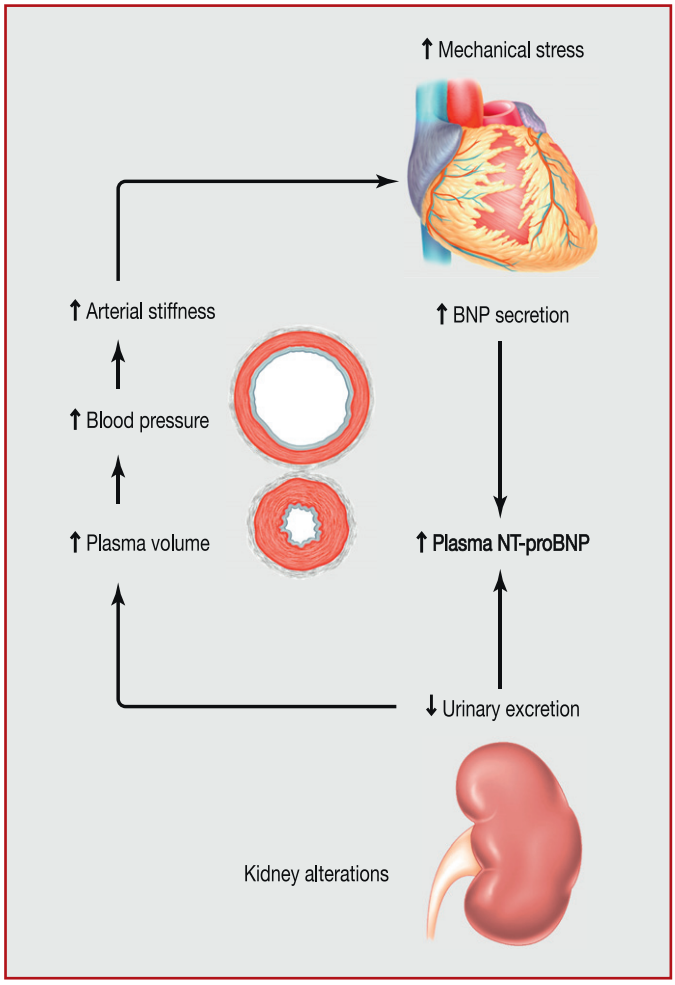

Figure 3. Integrative aspects of NT-proBNP plasma concentration in cardiovascular risk assessment. BNP: B-type natriuretic peptide; NT: N-terminal.

or non-fatal cardiovascular event. When analysed in more detail, NT-proBNP was predictive of coronary heart disease, heart failure, and ischaemic stroke. This risk prediction was verified beyond classical risk factors [29]. In this study, the proposed thresholds were much lower than the aforementioned ones, probably because the population came from the general population with less hypertensive patients.

The last contribution in this field was made by our group. In 684 patients with hypertension of varying severities followed for an average duration of 5.7 years, NT-proBNP appeared again to be significantly associated with all-cause death [7] (Fig. 4). This predictive value was observed on top of classical risk factors, and was also independent of renal function, and ECG LVH estimated either by the Sokolov index or by the amplitude of the R wave in the aVL lead. Finally, even the inclusion of ambulatory blood pressure in the model did not influence the prognostic value of NT-proBNP, which in all cases remained the second most predictive variable after age. This study confirmed for the first time in a cohort of hypertensive patients who were fairly representative of everyday hypertensive patients, the value of this marker, which had already been documented in more severe hypertensive patients or in the general population, beyond traditional risk factors. Interestingly, a concentration threshold of around 130 pg/mL was again associated with a substantial increase of risk and could be proposed as an acceptable cutoff.

Effect of treatment on natriuretic peptides

Nowadays, most hypertensive patients are treated with a variety of antihypertensive drugs including diuretics, beta-blockers, and renin-angiotensin system blockers. This raises two important points: (1) the extent to which the prognostic value is affected by the treatment; (2) whether the change in NT-proBNP can be used as a target for therapy, as in heart failure patients.

In our recently published study, the presence of a treatment did not interact with the prognostic value of NT-proBNP but we were unable to test for a differential effect of drug classes [7]. On the other hand, renin-angiotensin system inhibitors usually decrease natriuretic peptide concentrations, as do diuretics or any drug that tends to lower blood volume [30]. This was confirmed in the LIFE substudy, as NT-proBNP levels decreased in the group treated with losartan but increased in the group treated with atenolol [31].

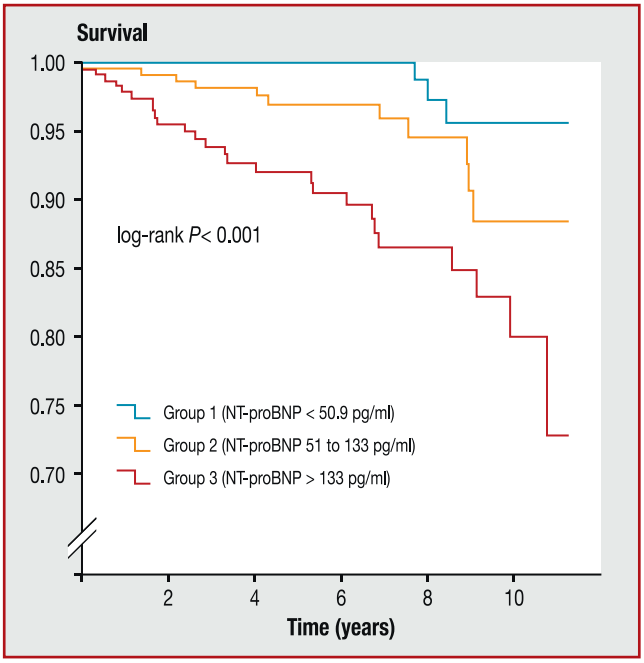

Figure 4. Survival curves relative to three terciles of plasma NT-proBNP concentrations ($n = 684$). Modified from [7]. BNP: B-type natriuretic peptide; NT: N-terminal.

The explanation is not, however, unique. While a direct effect of angiotensin II on natriuretic peptide synthesis can be advocated, there is a case for a better haemodynamic profile characterized by a decrease in vascular resistances leading to decreased left ventricular afterload and circumferential wall stress. In any case, natriuretic peptides (ANP and NT-proBNP) kept their prognostic value with both beta-blockers and angiotensin II antagonists, which is of utmost importance in proposing these markers for large-scale screening in hypertension. A slight difference in prognostic cutoff according to ongoing treatments cannot be ruled out. Yet this difference, if any, would be expected to be very small, as suggested by the small but significant absolute differences in NT-proBNP concentrations between the two treatment groups in the LIFE substudy [31].

Concerning the second aspect, the fact that, in the same study, the concentrations of NT-proBNP under treatment were on average more predictive than the basal concentrations also suggests that it could be used as a surrogate criterion for treatment adjustment, with the aim of decreasing NT-proBNP concentration together with lowering blood pressure; this strategy is already well accepted in the management of heart failure patients. In view of the difficulties in precisely measuring blood pressure and the fact that, on average, the effect of antihypertensive drugs on blood pressure is smaller than spontaneous fluctuations, it would be of great value for the physician to be able to adjust therapy on the basis of a more stable surrogate marker in hypertension follow-up. Of course, this deserves further study to compare the gain of targeting NT-proBNP over blood pressure in terms of morbi-mortality, compared with blood pressure only. Lessons from heart failure treatment should help to identify the therapeutic strategies that can decrease both blood pressure and NT-proBNP plasma concentrations.

Conclusions

The history of natriuretic peptides in blood pressure regulation, water, and salt homeostasis continues and new applications are regularly reported. Natriuretic peptides are variably elevated in hypertension, reflecting various degrees of cardiac, vascular, and renal injuries. The potential of this marker to detect one particular aspect of cardiac remodelling (namely LVH) may be suboptimal and not sufficient to be proposed for large-scale screening of hypertensive patients, contrary to what has been suggested earlier. This might not be the major point, however, as what we critically need is a marker that can predict events rather than organ damage. Here, the picture is totally different, as we and others have reported a strong predictive value for hard endpoints such as all-cause death or cardiovascular mortality and morbidity. In our view, it is not a tool to replace echocardiography, which will still have to be performed to gain insights into the components of heart remodelling. On the other hand, systematic use of echocardiography, which is not recommended, would be neither feasible nor desirable on an economic basis [32]. On the contrary, it could replace ECG in general practice. Considering NT-proBNP, we have reported that it adds significant prognostic information to the conventional Framingham-type risk factors and, in our hands, performed better than ECG. In addition, it may be extended to all patients more easily than ECG. Furthermore, it was not sensitive to renal impairment or body mass index. On the basis of the literature, a reasonable concentration threshold would be around 130 pg/mL. Despite similar prognostic capabilities in men and women, the usefulness of different thresholds cannot be excluded, as previously suggested for the diagnosis of LVH [12].

This performance, together with the ease of measurement, low cost and widespread availability, should prompt wide use of this marker for risk stratification in hypertension in most hypertensive patients. Of course, the economic impact of implementing this measurement in the management of the hypertensive patient in general should be evaluated.

New questions are also raised, such as the potential interest of these markers as surrogates to optimize therapeutic strategies; this deserves further work.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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