EDITORIAL COMMENT

Natriuretic Peptides, Ejection Fraction, and Prognosis

Parsing the Phenotypes of Heart Failure*

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Since the first pivotal studies introduced the natriuretic peptides as biomarkers for the diagnosis of heart failure (HF), use of both B-type natriuretic peptide (BNP) and its N-terminal equivalent (NT-proBNP) has grown not only for this indication, but also for establishing HF prognosis as well. Indeed, a vast array of studies has established the natriuretic peptides as the biomarker gold standard to prognosticate risk for a wide array of relevant complications in HF (ranging from ventricular arrhythmias to pump failure) (1,2). In these studies, the prognostic information provided by BNP and NT-proBNP in HF was independent of a number of relevant covariates, including left ventricular ejection fraction (LVEF).

Despite the utility BNP or NT-proBNP concentrations for risk prediction in HF, it is necessary to recognize the potential pitfalls in the interpretation of these versatile biomarkers. Whereas the severity of HF itself is a prime factor responsible for the elevation of both, BNP and NT-proBNP are nonetheless subject to a large number of factors that may independently influence their values either upward or downward. These factors (that clinicians should always keep in mind) include noncardiac aspects (age, body mass index, renal function, and hemoglobin levels, to name a few), as well as cardiac structure and function. Among the most relevant cardiac variables, determining natriuretic peptide concentrations is LVEF (3). Because LV systolic dysfunction is typically associated with larger ventricular chamber radius and greater wall stress—a prime determinant of natriuretic peptide synthesis and release—patients so affected typically have higher natriuretic peptide values than those with normal LV function. In this regard, it has been known for quite a while that patients with heart failure and preserved ejection fraction (HFpEF) typically have lower natriuretic peptide values than do those with heart failure and reduced ejection fraction (HFrEF) (4). A conundrum is thus present: whereas both BNP and NT-proBNP tend to be lower in HFpEF, when these peptides are elevated in this setting, they remain prognostic; this intriguing circumstance has been relatively poorly studied.

It is in this setting that van Veldhuisen et al. (5) examined the impact of LVEF on the prognostic merits of BNP in the COACH (Coordinating Study Evaluating Outcomes of Advising and Counseling in Heart Failure) study in the present issue of the Journal. The investigators found—as expected—that BNP levels were lower in HFpEF, but for a given BNP concentration, prognosis of those with HFpEF in COACH was just as poor as those with HFrEF at matched BNP values. Stated differently, a high BNP in a patient with HFpEF imparted similar prognostic information as it would in someone with HFrEF. Actually, whereas LVEF was not obviously prognostically impactful, when considered across the range of ventricular function, an elevated BNP concentration in the most normal range of LVEF seemed to be associated with a higher risk than at the lower ranges of pump function. Although it is previously established that BNP or NT-proBNP are prognostic independently of LVEF (1,2,6), the well-executed analysis by van Veldhuisen et al. (5) allows for a more in-depth examination of this phenomenon and raises some important questions.

On the one hand, how do we interpret a low natriuretic peptide concentration in a patient with symptomatic HFpEF? Do they have a forme fruste of HF? Are they a different type of HF? Should they be treated differently? Could some such patients not have the syndrome that we call HF at all (as argued by the investigators)? Clearly, clinical experience would dictate that many patients with HFpEF and a low BNP do in fact have HF, but aggregate experience suggests such patients often have a lower risk for complications.

On the other hand, how do we reconcile the fact that those with HFpEF and a high natriuretic peptide are at least at comparable risk to those with HFrEF? Should we evaluate and manage such patients the same way as we do a patient with HFrEF? Clearly not. van Veldhuisen et al. (5) show that, compared with those with HFrEF, patients with HFpEF and markedly elevated concentration of BNP had more medical comorbidities such as anemia, renal dysfunction, ischemic heart disease, and atrial arrhythmias. Thus, BNP testing allows for the identification of a specific HF phenotype, which may merit considerably different evaluation and management.

Thus, whereas establishment of prognosis is important, it is reasonable to argue the ultimate goal for measuring physiologically and prognostically meaningful biomarkers in...
this setting is ultimately to allow for personalization of risk assessment, with the hope for better treatment for the individual from whom the blood was drawn.

To this point, the investigators rightfully consider how the results of this and the other studies showing prognostic merit of BNP or NT-proBNP in HFpEF might be harnessed for the betterment of patient care. This is of great importance, as we sadly do not yet have therapies that clearly benefit those with the clinical diagnosis of HFpEF. This may be because HF itself is a syndrome, not a specific diagnosis, and patients with HFpEF are a mixed bag of clinical and risk phenotypes, vastly more heterogeneous than are those with HFrEF. Thus, biomarkers may be of some use to sort out these phenotypes in HFpEF; in this regard, early—though somewhat conflicting—data have recently emerged.

For example, in the PEP-CHF (Perindopril in Elderly People with Chronic Heart Failure) trial, only those HFpEF patients with elevated NT-proBNP concentrations showed potential benefit from allocation to angiotensin-converting enzyme inhibition (6). On the other hand, Anand et al. (7) reported that among those treated in the I-PRESERVE (Irbesartan in Heart Failure With Preserved Ejection Fraction) study, only those with lower BNP values demonstrated benefit from angiotensin receptor blockade. In both trials, however, natriuretic peptides strongly predicted risk.

It is hard to reconcile these divergent findings, and the results from I-PRESERVE should make us take pause. Are some patients with HFpEF and markedly elevated natriuretic peptide values so medically complex or prognostically challenged that they have an immutable risk? Very clearly, more data are needed before the various “faces” of HF are defined, and the approach will be much more complex than using a single biomarker such as BNP to clarify care. To this extent, it is most likely the way to individually phenotype patients with HFpEF will involve a spectrum of tools, including clinical variables, blood testing, imaging, and hemodynamic factors, all integrated to inform specific aspects about the individual, and lead to better care (Fig. 1). Biomarkers are only a part of this parsing out of who our patients are.

Whereas natriuretic peptide “guided” HF care has promise in the management of patients with chronic HFrEF (8), we have many miles to go before biomarkers may be used to trigger better care in HFpEF. Given the broad-based futility of therapeutic trials for this heterogeneous syndrome, directing therapies toward specific HFpEF phenotypes is worth considering, with the hope to better inform treatment strategies for these patients. Recent studies have explored this concept (9); more trials should follow.

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Key Words: heart failure • natriuretic peptides • preserved ejection fraction • prognosis.