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EDITORIAL COMMENT

Putting Together the Pieces of the Natriuretic Peptide Puzzle*

D.H. Frank Gommans, MD,[a] Antoni Bayés-Genís, MD, PhD,[b,c] Roland R.J. van Kimmenade, MD, PhD[a]

"Sometimes something has to happen before something can happen."
—Johan Cruyff (1947-2016), soccer player/philosopher (1)

Brain natriuretic peptide (BNP) and its amino-terminal cleavage equivalent, NT-proBNP, are the cornerstones of biomarker analysis in heart failure (HF) (2). In this issue of *JACC: Heart Failure*, Zhou et al. (3) present a study that focuses on the enzyme corin, another component in the natriuretic peptide (NP) cascade. Corin plays an important role in the conversion of NP precursors into BNP and NT-proBNP. As such, the concentration of circulating NPs most likely depends not only on myocardial wall

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stress (i.e., NP production), but also on the concentrations of corin and other mediators, such as furin, neprilysin, and proBNP glycosylation (i.e., NP metabolization) (**Figure 1**) (4-6). With regard to corin, low corin concentrations may lead to low concentrations of circulating NPs and are associated with the development of hypertension, hypertrophy, and HF in both preclinical and clinical studies (3). Hence, corin seems a promising piece of the NP puzzle that may help clinicians elucidate the mechanisms underlying HF and thereby improve HF treatment.

Zhou et al. (3) are the first to report that corin might be a valuable adjunct to current risk stratification in more than 1,000 HF patients admitted. Specifically, Zhou et al. (3) showed that low corin concentrations are associated with higher cardiovascular mortality and with more HF admissions during follow-up. Also, after correction for well-known risk factors in HF, including NT-proBNP concentrations, corin remained independently associated with adverse outcome. This led the authors to conclude that assessing corin concentrations might substantially improve risk stratification in patients with chronic HF.

A few things should be kept in mind when interpreting these results. First, the authors chose to use integrated discrimination improvement to assess the additional value of corin in conventional risk stratification in HF. However, the use of the net reclassification index would have provided more insights into the potential implications of corin for daily clinical practice. With a demonstrated integrated discrimination improvement of about 2% in an HF cohort with an a priori risk of 50% of reaching the composite endpoint, it is debatable whether corin will help clinicians classify HF patients into high- or low-risk groups. Second, the patients were included at the time of hospital admission, so it is uncertain how these results translate to the outpatient clinic setting. Third, only 64% of the HF patients in the study were treated with a beta blocker. Intriguingly, fewer patients with low corin concentrations received guideline-recommended HF therapy compared to those with high corin concentrations.

Keeping these considerations in mind, more research is needed to demonstrate whether corin measurement could lead to improved risk stratification for HF patients. The major value of this study is that it generates interesting hypotheses with regard to interpreting NP release in HF and HF treatment.

The first hypothesis is that the interpretation of "NPs as biomarkers" in HF is influenced by corin concentrations. As mentioned previously, the

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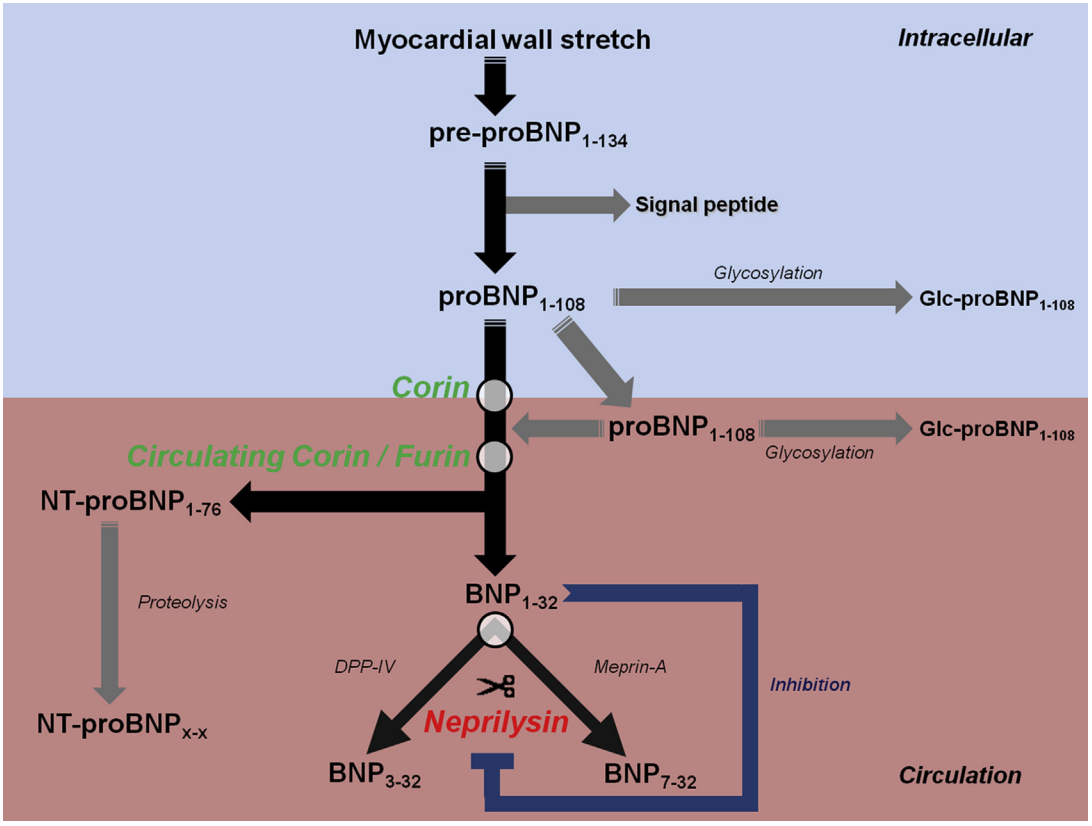
From the [a]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands; [b]Heart Failure Clinic, Cardiology Service, Hospital Universitari Germans Trias i Pujol Badalona, Barcelona, Spain; and the [c]Department of Medicine, Universitat Autonoma de Barcelona, Barcelona, Spain. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

FIGURE 1 Schematic Summary of the Natriuretic Peptide Cascade



BNP = brain natriuretic peptide; DPP-IV = dipeptidyl peptidase-IV; NP = natriuretic peptide.

discovery of mediators in the NP cascade, such as corin, raises the question whether NP concentrations are solely a measure of myocardial wall stretch (i.e., NP production) or whether they are also related to the capacity of a particular patient to increase and maintain circulating NPs, based on, for example, the amount of corin present (i.e., NP metabolization).

The survival curves provided by Zhou et al. (3) support this hypothesis, demonstrating that among the patients with high NT-proBNP, those who had low corin concentrations fared worse. Hypothetically, a patient with a low corin concentration might need a larger stimulus in terms of increased myocardial wall stretch to achieve the same concentrations of circulating NPs as a patient with a high corin concentration. In other words, patients with high NT-proBNP *and* low corin concentrations have the most severe form of HF, which is in accordance with their poorer survival during follow-up. Moreover, the survival curve of patients with low NT-proBNP concentrations and low corin concentrations is similar to the survival curve of patients with high NT-proBNP concentrations and high corin concentrations. It is plausible that the myocardial stretch is the same in both groups, whereas the difference in NT-proBNP simply reflects the difference in the patients' capacities to convert proBNP into NT-proBNP. In daily clinical practice, this would suggest that NT-proBNP values should be interpreted bearing this in mind and that the NT-proBNP-to-corin ratio might be important.

A second hypothesis is that a patient's capacity to increase and maintain active "NPs as biotarget" in HF is important for determining the effects of medications that target the NP cascade (i.e., NP analogues and angiotensin-renin-neprilysin-inhibitors, ARNIs). Increasing the concentrations of active NPs is an intriguing target for medical treatment in HF patients (7,8). In theory, increased natriuresis should lower the circulatory volume and, consequently, myocardial wall stretch, which could improve myocardial contractility and patient outcomes. Inhibiting NP degradation via neprilysin inhibition was shown