Natriuretic Peptides as Markers of Cardiovascular Risk: The Story Continues

And it appears to me that one ought also know what diseases arise in man from the powers, and what from the structures. What do I mean by this? By powers, I mean intense and strong juices; and by structures, whatever conformations there are in man

Hippocrates[1]

In his teachings, Hippocrates inferred the importance of dynamic circulatory factors in mediating illness. The search for these "intense and strong juices" has led to the discovery of biomarkers in cardiovascular medicine. Today, in patients with known or suspected cardiovascular disease, biomarkers are reported to be associated with the risk, presence, and severity of disease. Additionally, they have prognostic implications and serve as guides for potential therapeutic interventions. The cardiac natriuretic peptides, atrial (ANP) and B-type (BNP), are secreted in response to various signals, including myocardial stretch and volume overload. Both ANP and BNP are produced with their inactive amino-terminal fragments NT-proANP and NT-proBNP.[2,3] These peptides play an important role in the regulation of electrolytes, water balance, and blood pressure; promotion of vasodilatation and natriuresis; and, in effect, modulation of homeostasis. Other research has discovered that ANP and BNP modulate the renin-angiotensin-aldosterone axis, inhibit the sympathetic nervous system, inhibit cardiac fibrosis and hypertrophy, improve diastolic function, and introduce metabolic protective properties.[2,4,5]

Several studies have demonstrated the clinical applications of the cardiac natriuretic peptides in the diagnosis and risk stratification of both acute and chronic heart failure.[6-8] Recently, these peptides have been discovered to have utility beyond standard risk factors for determining outcome prognosis for cardiovascular morbidity and mortality in patients with chronic heart failure,[7,8] hypertension,[9,10] acute coronary syndromes,[11,12] prior myocardial infarction,[13,14,] stable coronary artery disease,[15] vascular disease, or high coronary risk[16,17] and in community-based cohorts.[18,19]

In this issue of *Mayo Clinic Proceedings*, McKie et al[20] report on the relative predictive value of several of the natriuretic peptides as markers of cardiovascular morbidity and mortality in the Prevalence of Asymptomatic Ventricular Dysfunction (PAVD) cohort of the Rochester Epidemiology Project. Specifically, their research evaluated 2042 patients from Olmsted County, Minnesota, with a median follow-up of 9 years. In that study, the authors delineated the predictive utility of NT-proANP and ANP for mortality and cardiovascular events beyond standard risk factors and ventricular structure and function. In addition, they compared the diagnostic utility of ANP, NT-proANP, and NT-proBNP for assessing cardiovascular morbidity and mortality.

Several inferences can be reached with the data reported by McKie et al. The population is of interest in that at time of entry most participants were women, relatively young, and with minimal background chronic disease processes (eg, diabetes, 7%). These factors, coupled with the duration of follow up, make these data new, unique, and powerful.

The study by McKie et al is the first to analyze and compare the predictive value of NT-proANP, ANP, and NT-proBNP in a large community-based cohort without heart failure. The data demonstrate that ANP has no predictive value for either cardiovascular mortality or morbidity, whereas NT-proANP has the ability to predict mortality further than conventional clinical risk factors. Additionally, the results of that study confirm once more that minimally elevated NT-proBNP is independently predictive for death, heart failure, and myocardial infarction after adjustment for clinical risk factors and remains predictive for death and heart failure even after adjustment for echocardiographic structural and functional abnormalities. Of interest, adding NT-proANP to conventional clinical risk factors did not alter the predictive significance of NT-proBNP for death or heart failure. This suggests that, in the general population without heart failure, NT-proBNP is a superior biomarker compared to either ANP or NT-proANP for predicting death and cardiovascular morbidity.

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These collective findings continue to call into question the conventional viewpoint that natriuretic peptides concentrations are merely hemodynamic markers of worsening heart failure or left ventricular dysfunction.

How can a biomarker of myocardial stretch, measured at a single point, predict a long-term outcome of a wide variety of cardiovascular events within an asymptomatic population? It is plausible that natriuretic peptides may re-

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flect a variety of different factors, all resulting in increased hormonal release from stretched myocardium. However, if these peptide biomarkers are all related to myocardial stretch, their ability to predict cardiovascular events should decline after adjustment for either biochemical or echocardiographic and functional factors. That may be the case of ANP because in unadjusted models it was significantly associated with death and cardiovascular morbidity but did not provide incremental predictive value beyond age, sex, and body mass index. Therefore, ANP may be a significant predictor of outcome only when heart failure is present, denoting that its activation is related to myocardial dysfunction only.[20]

In contrast, NT-proANP is a significant predictive biomarker of death, heart failure, and myocardial infarction in the general population after adjustment for basic confounders, including age, sex, and body mass index. Adjustment for additional clinical cardiovascular risk factors did not attenuate the predictive significance of NT-proANP for mortality.

As in previous studies,[7-19] NT-proBNP was highly predictive of death and heart failure in a cohort without heart failure, even after adjustment for structural and functional abnormalities, including diastolic function. Although speculative, these results suggest that minimal elevation in NT-proBNP is due to other factors besides myocardial stretch, and thus it may serve as a biomarker for preclinical cardiovascular disease and may aid in identifying disease progression and patients who may benefit from preemptive therapies. A variety of other factors have been found to stimulate secretion of BNP in vitro, including myocardial ischemia, endothelin A, angiotensin II, and tumor necrosis factor α.[2,4] These observations suggest that the predictive value of plasma NT-proBNP concentration in a population of patients without heart failure is not only associated with acute myocardial stretch but also to factors that are related to inflammation, fibrosis, and hypertrophy at the circulation and vascular level.

The findings by McKie et al[20] lend credence once more to the notion that patients with elevated plasma concentrations of natriuretic peptides in the absence of clinical heart failure should be considered as study participants when evaluating novel interventions designed to prevent progression of cardiovascular disease. Research using this type of study design could, in the long term, provide valuable information regarding the utility of biomarker use for longitudinal risk assessment.

Until such studies are completed and the concepts proven, one should be cautious in using NT-proBNP as a reason for initiating a therapeutic intervention. Fortunately, these types of studies are currently under way in patients with clinical heart failure.[21]

It was Arthur Conan Doyle, speaking through the famous detective Sherlock Holmes, who wrote, "It is a capital mistake to theorize before one has data."[22] The data of McKie et al emphasize the value of the natriuretic peptides to predict cardiovascular morbidity and mortality beyond standard risk factors and in patients without heart failure. These data will help us further refine the theories underlying cardiovascular disease outcomes. Future investigations need to be focused on the value of these peptides to guide therapy in patients with cardiovascular disease and, perhaps more importantly, those at risk of future disease.

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