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Natriuretic Peptide and Cardiovascular Risk: Is It About "U"?

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Natriuretic peptides have established indications for the diagnosis of acute decompensated heart failure in patients presenting with dyspnea, and for prognosis in patients with an established diagnosis of heart failure (American College of Cardiology/American Heart Association stage C heart failure).[1] Furthermore, there is increasing evidence to suggest that natriuretic peptide levels may be an important adjunct to clinical judgment in the chronic management of ambulatory heart failure patients to reduce readmissions and death.[2] A large multicenter National Institutes of Health–funded trial that focuses on ambulatory patients with heart failure with reduced ejection fraction is ongoing to more definitively answer this question.[3] Perhaps equally exciting has been the role of natriuretic peptides, particularly amino terminal B-type natriuretic peptide (NT-proBNP), for heart-failure risk stratification in asymptomatic populations. Though natriuretic peptide levels are associated with underlying structural heart disease such as left ventricular systolic dysfunction and left ventricular hypertrophy (American College of Cardiology/American Heart Association stage B heart failure), they still have relatively modest accuracy for discriminating asymptomatic patients with and without underlying left ventricular hypertrophy and left ventricular systolic dysfunction.[4] In contrast to use for diagnosis, NT-proBNP has emerged as a powerful prognostic marker in patients with known left ventricular hypertrophy or coronary disease.[5–7] In multiple general population cohort studies, natriuretic peptide levels were highly prognostic for new-onset heart failure and cardiovascular death across the spectrum of sex, age, and race.[6,8,9] For these asymptomatic patients with cardiovascular risk factors (American College of Cardiology/American Heart Association stage A heart failure), natriuretic peptide measurement not only can risk-stratify, but potentially can be used as part of a strategy to guide further evaluation and medical treatment to reduce incident cardiovascular events.[10,11] Though there is gradation of risk in asymptomatic subjects based on progressively higher natriuretic peptide levels, there also appears to be a risk threshold generally encompassing the upper tertile, quartile, or quintile of the general population cohort of middle- to older-age adults.[6,8,9] These higher-risk portions of the cohorts consistently have a greater burden of measurable subclinical cardiovascular disease and likely represent a transition zone from American College of Cardiology/American Heart Association stage A to stage B.[6,8]

Given the low cardiovascular event rate in the majority of participants with lower natriuretic peptide levels, less attention has been focused on risk stratification in this majority other than potentially retesting of natriuretic peptides after several years, recognizing that an upward trajectory is associated with an increased risk of left ventricular dysfunction and future new-onset heart failure events.[12] However, it may be at levels well below these risk thresholds that natriuretic peptides exert important protective metabolic effects. For example, in the MESA cohort without overt cardiovascular disease, NT-proBNP levels are inversely associated with several metabolic risk factors such as low-density lipoprotein and total cholesterol, but these inverse associations are present primarily below an inflexion point at about 100 pg/mL.[13] The ARIC study also showed an inverse relationship between baseline NT-proBNP levels and the development of diabetes, again where most of the benefit was also seen across a range of levels below an NT-proBNP <100 pg/mL.[14] Based on these observations, could there then be individuals whose levels of natriuretic peptides are too low, at least from a metabolic perspective?

Recent studies suggest that genetic factors may explain the lower natriuretic peptide levels observed in some subgroups. For example, Wang et al showed in the Framingham Heart Study that 40% of the population-based variation in BNP levels could be explained on a genetic basis, which was comparable to the amount of variation explained by age,

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clinical variables, and echocardiography combined.[15] In that particular cohort, however, African Americans are underrepresented compared to the United States population at-large. Interestingly, in other middle age and older adult population cohorts, African Americans are significantly more likely than whites to have the lowest NT-proBNP levels.[6,8]

In this issue of *JAHA*, Gupta et al now directly investigate and explain these racial differences of natriuretic peptide levels using the ARIC cohort of 9137 adults (22% African American) without prevalent cardiovascular disease.[16] They find that African Americans have, on average, a 40% adjusted lower level of NT-proBNP than whites. Further confirming a genetic basis of these racial differences is their finding that for every 10% greater European genetic ancestry in self-identified African Americans, there is an associated 7% higher level of NT-proBNP. This finding may have particular relevance for the premature heart disease often seen in African Americans versus whites that cannot be explained on the basis of socioeconomic or cardiovascular risk factors alone.

The ramifications of these lower natriuretic peptide levels among asymptomatic African Americans in terms of long-term risk of heart failure are not clear. Most studies support a markedly greater heart failure risk among African Americans versus whites even among low-risk populations. In the Dallas Heart Study, using cardiac magnetic resonance imaging, African Americans have a 2- to 3-fold higher prevalence of left ventricular hypertrophy compared to whites. This difference persists even after adjustment for systolic blood pressure, age, gender, and measures of socioeconomic status.[17] In the CARDIA study of younger adults between 18 and 30 years, African Americans were much more likely to develop heart failure over 20 years compared to whites (0.9% of African American men versus 0% of white men).[18] In the MESA study, African Americans had nearly twice the incidence of heart failure as whites, with 75% of the cases not related to myocardial infarction, the highest nonischemic etiologies of all the ethnicities.[19]

A number of genetic variants in natriuretic peptide production and processing have been identified in African Americans.[20,21] In particular, a genetic variation in corin (T555I/Q568P) is common, with the heterozygous haplotype seen in ≈11% to 14% of African Americans and nearly absent in whites.[20,22] Corin is an important enzyme for the intracellular processing of proBNP to BNP. African Americans with this variant have lower BNP levels, higher blood $proBNP_{132}$/BNP_{32} ratios, and more clinical manifestations including more prevalent hypertension, higher systolic blood pressure, and greater left ventricular mass than those without this mutation.[20,23] Rats bred with the corin gene variant (T555I/Q568P) mutation, when given a high-sodium diet, had a rapid increase in blood pressure that persisted after discontinuation of the high-sodium diet with a marked progression in left ventricular mass compared to similarly treated wild-type controls, suggesting a dysfunctional natriuretic response.[24] For those African Americans with established systolic heart failure, the presence of the corin mutation was associated with increased heart failure hospitalizations and death. This was mitigated by treatment with a fixed combination of isosorbide dinitrate and hydralazine.[22]

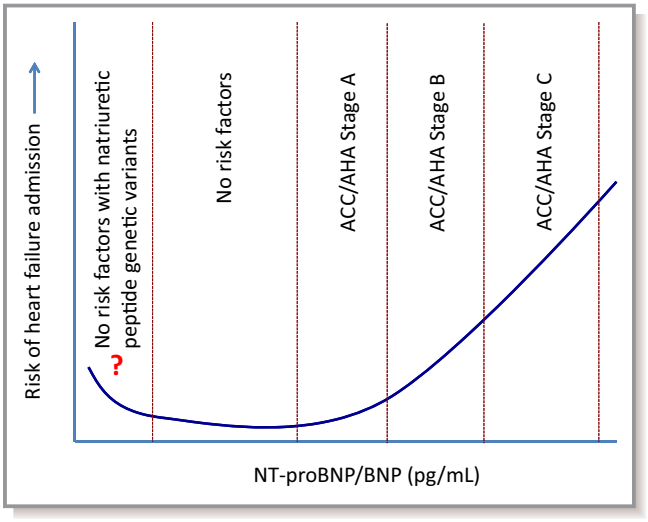

Figure. Hypothesized "U"-shaped relationship of risk for heart failure based on NT-proBNP level. ACC indicates American College of cardiology; AHA, American Heart Association; NT-proBNP, amino terminal B-type natriuretic peptide.

In summary, there is a range of risk associated with NT-proBNP and BNP levels in ambulatory patients, with higher levels being progressively associated with cardiovascular risk factors, structural heart disease, and symptomatic heart failure. While low levels of natriuretic peptides are traditionally considered an indicator of low to very low cardiovascular risk, Gupta et al show that substantially lower levels are found disproportionately in African Americans, a group with a paradoxically higher incidence of nonischemic heart failure at a young age. While further work is needed to confirm increased clinical risk in African Americans with very low natriuretic peptide levels, the spectrum of risk across a broad range of levels and risk factors may in fact be a "U"-shaped relationship (Figure). With this in mind, it may in the future be reasonable to consider genetic testing, evaluating the $proBNP_{132}$/BNP_{32} ratio or both to guide closer monitoring of blood pressure, more intensive dietary counseling, and perhaps early initiation of pharmacologic therapy to reduce progression of left ventricular mass and ultimately reduce the risk of heart failure.

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