FOCUS ISSUE: BIOMARKERS IN CARDIOVASCULAR DISEASE

Editorial Comment

B-Type Natriuretic Peptide Testing in the General Population

Are We Ready for Prime Time?*

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Since the discovery of brain natriuretic peptide (BNP) in 1988 (1), both BNP and its inactive metabolite N-terminal pro–B-type natriuretic peptide (NT-proBNP) have played a prominent role in furthering our understanding of cardiovascular pathophysiology. Clinically, both assays now have a firmly established role in the diagnosis of acute heart failure, and have been incorporated in the most recent American College of Cardiology Foundation/American Heart Association guidelines for use in the urgent care setting, when the diagnosis of heart failure is uncertain (2). The role of these biomarkers in prognostication and risk prediction is also expanding. Prior studies have shown that BNP and/or NT-proBNP are independent predictors of mortality in patients with stable coronary artery disease (3), acute coronary syndromes (4), and congestive heart failure (5). The utility of testing in the general population, however, remains less well established. In the Framingham Heart Study, BNP values above the 80th percentile (but well below thresholds used to diagnose heart failure) were independently associated with death and cardiovascular events in subjects without prevalent heart failure (6). Similar results were found in a community-based cohort from Olmsted County (7).

McKie et al. (8) now report an extension of data from Olmsted County in this issue of the *Journal*. Whereas their previous study reported overall results for the full cohort of 1,991 participants, this new analysis takes on a different and novel focus. Rather than examining the overall sample, participants were divided into subgroups. The healthy normal subgroup included participants without heart disease or its major risk factors including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, history of cardiovascular drug use, peripheral vascular disease, hyperlipidemia, atrial

fibrillation, or structural heart disease on echocardiography. The remaining subjects with clinical heart disease, 1 or more heart disease risk factors, or subclinical heart abnormalities on echocardiography were classified as stage A/B heart failure. The authors then examined the utility of an NT-proBNP value exceeding the 80th percentile (age- and sex-specific) as a predictor of all-cause mortality and cardiovascular events in each subgroup. Interestingly, NT-proBNP was not predictive of clinical outcomes in the healthy normal subgroup, whereas in the stage A/B heart failure subgroup, mortality and incident heart failure, cerebrovascular accident, and myocardial infarction were all higher in patients with elevated NT-proBNP levels.

While it is not surprising that NT-proBNP was not associated with cardiovascular outcomes in the healthy normal subgroup in whom the pre-test probability of an event is already exceedingly low based on the absence of traditional clinical and echocardiographic risk factors, this still represents an important finding. Within the larger field of cardiovascular biomarkers, identifying persons who would not benefit from a diagnostic test may be just as important as knowing who to test, making this study unique and novel in that regard. However, several points need to be considered before convincingly rejecting any role of natriuretic peptide measurements in the general "healthy" population. First, the healthy normal subgroup in this study differs from the general healthy population, because subjects with subclinical echocardiographic abnormalities were excluded (i.e., they were already pre-screened with echocardiography, a more expensive modality to detect subclinical structural heart disease). We know that echocardiographic features such as asymptomatic left ventricular systolic dysfunction portend a worse cardiovascular prognosis (9), and treatment with angiotensin-converting enzyme inhibitors has been shown to prevent progression to overt heart failure in this patient population (10). Yet, it is not routine to screen the general population with echocardiography because of cost considerations. Could natriuretic peptide levels be a useful and cost-effective screening tool in apparently healthy persons, when echocardiography has not already screened out those with structural abnormalities? This question remains

unanswered by this study, and should be considered before dismissing the utility of natriuretic peptides as a screening tool in the general population. Finally, it is also important to consider that with just over 700 healthy normal participants, the study may be underpowered to detect a potential moderate difference in outcomes as a function of NT-proBNP levels within the healthy normal subgroup. Thus, it may be somewhat premature to definitively conclude that there is no utility to natriuretic peptide measurements in the general population.

While the identification of a subgroup in which NT-proBNP testing may not be indicated is novel, its significance in populations akin to the stage A/B heart failure subgroup identified in this study has been examined previously. In the present study, NT-proBNP was an independent predictor of cardiovascular events in participants with stage A/B heart failure, a group that included people with prevalent coronary artery disease, in whom BNP testing already has been shown to predict prognosis (11). While natriuretic peptides are clearly associated with cardiovascular outcomes in high-risk populations, the incremental benefit of NT-proBNP testing to already known clinical and echocardiographic risk factors remains unclear. Prior studies in risk prediction have focused on the combination of several biomarkers and their potential incremental utility in risk prediction, with mixed results. In the Framingham Heart Study (12), the addition of a combination of 10 biomarkers (including natriuretic peptides) added only moderately to standard risk factors in persons free of major cardiovascular disease at baseline. In contrast, in a study by Zethelius et al. (13), there appeared to be significant improvement in cardiovascular risk stratification in a cohort of elderly men from a combination of 4 biomarkers, although men with prevalent disease at baseline were included.

The present study (8) demonstrates a negligible change in the c-statistic with the addition of natriuretic testing to a model with clinical risk factors for each of the clinical outcomes. Furthermore, the incremental increase in integrated discrimination improvement ranged from 0.5% to 1.3% for the various cardiovascular outcomes, which, while statistically significant in a model including only clinical but not echocardiographic factors, is a very modest increase, and so the true utility and cost effectiveness of natriuretic peptide testing in this group with a substantial burden of risk factors remains to be elucidated. It may be that incremental improvement in risk prediction with natriuretic peptide testing is limited to a subset of patients within the stage A/B heart failure subgroup, given a relatively heterogenous group with respect to clinical risk factors. For example, in participants with known coronary artery disease for whom echocardiography is already indicated and aids in risk stratification, additional testing with NT-proBNP may not be cost effective. However, it certainly is possible that in participants with hypertension or diabetes mellitus for whom screening echocardiography may not be indicated in routine clinical practice, natriuretic peptide testing may aid in risk stratification and may be more cost effective than echocardiography in that setting.

With the growing burden of heart failure and its associated morbidity and mortality in the U.S., identifying high-risk patients before the development of overt symptoms is an important clinical challenge, as it may facilitate early prevention efforts at a time when intervention is most likely to succeed. Understanding the role of biomarkers as tools to identify high-risk groups will allow us to effectively target prevention strategies, and the present study by McKie et al. (8) is an important step in the right direction. By identifying low-risk groups in which NT-proBNP testing is not informative, the role of natriuretic peptides in cardiovascular risk stratification will become slightly less complex.

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