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EDITORIAL COMMENT

N-Terminal Pro–B-Type Natriuretic Peptide

A Risk Predictor for All*

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"Superior doctors prevent the disease;
mediocre doctors treat the disease before evident;
inferior doctors treat the full-blown disease."
—Huang Dee: Nai-Ching (1)

The most common cause of death in the United States for more than a century, cardiovascular disease (CVD), is now the most common cause of death worldwide. The magnitude of the problem, coupled with a high rate of sudden death as a first presentation, mandates effective primary prevention. However, given the large numbers of patients involved and the high cost of long-term preventive treatment, efforts must be targeted to those at highest risk. But, the questions remain: how can we best predict risk, and what can we do about it?

The 2013 American College of Cardiology/American Heart Association guideline on the treatment of blood cholesterol (2) was released simultaneously with a set of recommendations addressing cardiovascular (CV) risk assessment (3). The pairing provoked considerable controversy upon release, because the new guidelines discarded treatment targets, setting a relatively low threshold for treatment, and it used the new risk algorithm on the basis of more recent multiethnic data, which may misclassify a sizable percentage of patients. In reality, all currently available primary prevention risk assessment tools—including Framingham, European HeartScore, Reynolds Risk Score, National Health and Nutrition Examination Survey, and so on—are only moderately predictive of CV events, as most report a c-statistic <0.80. In the real world, this means that our current efforts at risk prediction, even if consistently following current recommendations, are inaccurate in millions of individuals.

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An important effort to improve risk prediction (and hopefully enhance the cost-effectiveness of primary prevention strategies) is presented in this issue of the *Journal* by Everett et al. (4), who analyzed the relationship between N-terminal pro-B-type natriuretic peptide (NT-proBNP) and CV events in women without known CVD enrolled in the WHI (Women's Health Initiative). Although very few individuals had an NT-proBNP level above the diagnostic threshold for heart failure (HF) (900 ng/l), there was a consistent, albeit modest, relationship between NT-proBNP and incident CV events. Several features suggest that these findings are significant: there was a linear relationship between risk and NT-proBNP values; the hazard ratios were consistent across several methods of adjustment; NT-proBNP levels predicted each individual component of the composite endpoint; and there were no interactions with any other cardiac risk factor or patient descriptor.

This study boasts several important strengths. Data focusing on the utility of NT-proBNP in women are clearly welcomed, as natriuretic peptide (NP) values are generally higher in women and with aging, factors that might confound these biomarkers' predictive ability in women. Prior data supporting NT-proBNP as a risk predictor have been predominantly derived from male cohorts (5). The recent publication of 2 randomized controlled trials (6,7) demonstrating the efficacy of primary

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prevention strategies focused on patients with elevated NP levels heightens the potential utility of NP-based risk prediction. Using the WHI is also a strength; as a large, carefully characterized cohort with a high prevalence of events, it provides tremendous power to investigate risk prediction in women, who are otherwise under-represented in current literature.

The choice of a composite of CV death, myocardial infarction, and stroke provides a "hard" endpoint; omitting HF is perhaps understandable because of its potentially more subjective ascertainment. However, given previous data clearly linking NP levels to incident HF (8), the omission is notable, because including incident HF as an endpoint might have further strengthened the relationship between NT-proBNP and risk. Because subjects were not screened for asymptomatic heart disease nor were they excluded for a history of angina, it is unclear whether the presence of undiagnosed structural heart disease might, in part, explain the association between NT-proBNP and events.

Most important, though, are concerns about implementation. Because Everett et al. (4) did not estimate the incremental value of adding NT-proBNP to the recently recommended atherosclerotic CVD risk score (3), these data are hard to interpret in the context of current guideline recommendations. Similarly, the reclassification analysis performed by the authors evaluated the incremental information provided beyond traditional risk factors and Reynolds Risk Scores using cut points of <5%, 5% to <10%, 10% to <20%, and >20% rather than including the currently recommended cut point of 7.5% risk to initiate statin therapy.

Everett et al. (4) rightly justify considering risk prediction in men and women separately on the basis of substantial differences between the sexes in CVD epidemiology. Indeed, refinements of risk prediction in women can enhance refined risk algorithms in men, as application of the female-derived Reynolds Risk Score in men shows (9). Most importantly, the acute coronary syndromes (ACS) literature provides ample evidence regarding the importance of a separate consideration of biomarkers in women. The 2007 American College of Cardiology/American Heart Association guidelines for the management of non-ST-elevation MI (10) differentiates between the sexes in recommending the use of troponin levels to decide between an early invasive versus conservative trial in women but not in men. Further, a multimarker approach (combining troponin, high-sensitivity C-reactive protein, and NT-proBNP) is more predictive when used for ACS risk assessment in women than any single biomarker (11).

Although the present study contributes important information to help refine risk prediction, many questions remain, including those related to pathophysiology and clinical translation. Although associated with many CV abnormalities, our current understanding of NPs is that they primarily reflect ventricular wall stress (12). Given that, it is unclear why NT-proBNP should be predictive of the primary endpoint components, especially those not clearly etiologically related to this physiology, such as hemorrhagic stroke. If detection of asymptomatic atrial fibrillation (and presumably subsequent embolic events) is the postulated mechanism for NT-proBNP's relationship to incident stroke (13), then what is the causal relationship with myocardial infarction? Are both related to asymptomatic structural heart disease? Perhaps further investigation into the underlying mechanism of the association will shed some much-needed light on cardiovascular event pathogenesis, a welcome "side effect" of efforts to improve risk prediction.

Other questions include the potentially additive value of using multiple versus single biomarkers and the relative value of different types of emerging biomarkers in this setting.

Finally, as with any diagnostic test, we must question its impact on relevant patient-related health and economic outcomes. The diagnostic test hierarchy originally proposed by Fryback and Thornbury (14) applies here: to demonstrate efficacy, an NT-proBNP assay would need to first demonstrate technical excellence, followed by high test performance, then significant changes in diagnostic thinking, and finally, an alteration in therapeutic strategy. The first 3 of these tenets are clearly met by NT-proBNP, and the present study nicely validates the role of NT-proBNP in changing diagnostic thinking in women. However, these data cannot take us further in implementing this knowledge to improve patient care. Recent studies suggest that targeting intensified CV care on the basis of NP levels can reduce events, but these were in populations at higher risk than in the present study (6,7). Although this is a high evidentiary standard, it is required if we are truly to practice evidence-based medicine in diagnostic tests and not just medications and devices.

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