B-Type Natriuretic Peptides and the Promise of Improved Cardiovascular Risk Prediction

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Since the discovery of the natriuretic peptides in the 1980s and their subsequent introduction into clinical laboratory testing in the 2000s, assays of B-type natriuretic peptides (BNPs)2 have gained widespread acceptance as important tools for diagnosis and risk stratification in the acute-care setting. Tests for natriuretic peptides accurately diagnose heart failure in patients presenting to emergency rooms with dyspnea (1, 2) and stratify risk in patients presenting with unstable angina or acute myocardial infarction. In some studies of stable patients, natriuretic peptides have shown strong associations with cardiovascular events, raising the possibility that their use as a screening tool in asymptomatic patients may help clinicians prevent heart attack and stroke. Such a finding would have enormous public health implications and would likely lead to a vast expansion in the use of these diagnostic markers and a shift from the acute-care setting to the outpatient clinic. Therefore, what we do and do not know about natriuretic peptides as predictors of cardiovascular events in stable patients is of considerable interest to clinicians, clinical chemists, and the manufacturers and marketers of the diagnostic tests. To address these issues and to make comparing studies more straightforward, Di Angelantonio and colleagues systematically assessed the relationship between natriuretic peptide concentrations and cardiovascular events in studies of populations that represented a wide range of baseline cardiovascular risk (3). Their recently published metaanalysis is the subject of this perspective.

BNPs and Cardiovascular Events in Stable Patients

Di Angelantonio and colleagues analyzed results from 40 studies that included 87,474 participants and 10,625 cardiovascular events. Of these events, the largest number (n = 7314) was observed in populations with preexisting cardiovascular disease (CVD); fewer events were observed among those with increased markers of CVD risk (n = 2040) and among general populations (n = 1271). The vast majority of the events were observed in studies that measured N-terminal proBNP (NTproBNP) (n = 9940) rather than BNP (n = 685). The range of measured values was 30–750 pg/mL for NTproBNP and 9–142 pg/mL for BNP. Although the authors reported a high degree of heterogeneity across studies, the estimate of the adjusted relative risk (RR) for those in the top tertile vs the bottom tertile of BNP values was 2.89 (95% CI, 1.91–4.38), which was almost identical to the RR for the extreme tertiles of NTproBNP concentration (2.82; 95% CI, 2.35–3.38). After they excluded studies with <250 events (an attempt to limit inflation of the RR estimate by reporting bias), the authors obtained an adjusted RR for the extreme tertiles of BNP and NTproBNP concentrations of 1.94 (95% CI, 1.57–2.39). Importantly, the risk did not change substantially when the authors excluded from the analysis studies that included congestive heart failure as part of the CVD end point (RR, 2.78; 95% CI, 2.20–3.52), and the risks of cardiovascular events were similar across the 3 populations with different baseline risks. Specifically, after the investigators adjusted for conventional risk factors, the RR among patients in the highest tertile of BNP or NTproBNP concentration, compared with patients in the lowest tertile, was 2.60 (95% CI, 1.99–3.38) for those with preexisting CVD, 3.35 (95% CI, 2.38–4.71) for those with increased risk markers, and 2.68 (95% CI, 2.07–3.47) for those in general populations. In studies that reported separate coronary and cerebrovascular outcomes, the adjusted RR for coronary heart disease (2.03; 95% CI, 1.51–2.66) was similar to that for stroke (1.93; 95% CI, 1.58–2.37), although the authors again observed considerable heterogeneity between studies.

BNPs and CVD Risk Prediction

Improvements in clinical risk stratification are measured in 3 domains: calibration, discrimination, and clinical risk classification. If a prediction model is well calibrated, the model-derived estimates of absolute risk
will agree with the observed risk for a given population. Discrimination is the ability to distinguish cases from noncases and is typically represented by the C statistic, the C index, or the area under the ROC curve. Finally, the ability of a new test to reclassify patients into different clinical categories of risk will often determine whether a new prediction model alters therapeutic decision-making.

The fully adjusted association of BNP and NTproBNP with incident CVD events is strong across a range of baseline risk; however, whether BNP or NTproBNP adds to established predictive models based on conventional risk markers is less clear. Di Angelantonio et al. report the observed changes in discrimination, as measured by the ROC curve, in 14 studies with a total of 2684 CVD events (637 in general populations, 479 in those with increased markers of risk, and 1568 in those with prevalent CVD). In general, adding BNP or NTproBNP to existing risk models leads to modest improvements in the area under the ROC curve, with increases of 0.01–0.10. As the authors note, however, the improvements in the area under the ROC curve tend to be smaller in general populations (range, 0.007–0.03) than in populations with increased risk factors or prevalent CVD (range, 0.02–0.10). Although the shift in the area under these ROC curves suggests BNP or NTproBNP may be a valuable risk marker in patients with existing CVD (and perhaps in the lower-risk populations as well), only 2 studies reported measures of calibration or reclassification. Both of these studies were performed in the general population, and their results were mixed. One study found good calibration and improvements in both the C statistic and clinical reclassification when NTproBNP was used in conjunction with other novel biomarkers (4), whereas the other found an improvement in the C statistic, no change in calibration, and no significant changes in risk classification (5). Whether adding BNP or NTproBNP to existing models improves clinical risk classification in patients with increased risk markers or in patients with existing CVD has not been well studied.

Even a risk-prediction model with improved calibration, discrimination, and substantial clinical risk reclassification ultimately may not alter therapeutic decision-making, however. If the clinical categories into which patients are reclassified are not used in actual decision-making or if the reclassification does not lead to clear alterations in primary or secondary preventive care that have demonstrable benefit, then a new diagnostic test may not have an important impact on public health. In fact, although some evidence supports the use of BNP or NTproBNP to guide the decision to pursue an early invasive strategy in patients with acute coronary syndromes, there are at present no widely accepted therapeutic interventions for increased BNP or NTproBNP concentrations in stable primary- or secondary-prevention patients. Experience from the field of heart failure, in which the use of BNP and NTproBNP as management (rather than diagnostic) tools is associated with both potential benefit and harm, dictates that any interventions proposed for CVD prevention that are guided by BNP or NTproBNP results be tested in a randomized fashion.

The comprehensive study by Di Angelantonio et al. is informative but is unlikely to alter contemporary primary or secondary preventive cardiovascular care. It succinctly summarizes our current understanding of the role of BNPs as markers and predictors of cardiovascular events in populations over a wide range of absolute risk. The authors have highlighted the many gaps in our knowledge, including the need for more prospective studies focused on how BNP and NTproBNP alter calibration and clinical risk reclassification in populations at all levels of absolute risk. If such studies suggest that the use of BNPs may make clinically relevant changes in risk prediction, then randomized trials of therapeutic interventions designed to reduce that risk would be warranted. In the meantime, clinicians can continue to work together with their patients in achieving the well-established goals of primary and secondary preventive care: healthy eating habits, regular exercise, smoking cessation, control of hypertension and hyperlipidemia, and adherence to antiplatelet therapies when indicated.

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