Natriuretic peptides, novel biomarkers, and the prediction of future events

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This editorial refers to ‘N-terminal pro-B-type natriuretic peptide and the prediction of primary cardiovascular events: results from 15-year follow-up of WOSCOPS’, by P. Welsh et al., on page 443

Background

Since their establishment as pillars of heart failure (HF) diagnosis, the role of natriuretic peptides (NPs) in clinical medicine has been growing impressively. This remarkable family of proteins includes B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP), and atrial natriuretic peptide (ANP). NPs are released by the ventricular myocardium in response to wall stress, and function as protective hormones that antagonize the pathophysiology of HF. Their functions include increasing the glomerular filtration rate, up-regulating sodium and water excretion, increasing vasodilation, preventing cardiac hypertrophy, and inhibiting the renin–aldosterone system.1

While Sudoh et al. first isolated BNP in 1988, its role as a HF biomarker was not fully recognized until 2002 by the multicentre Breathing Not Properly trial. This study set BNP’s accuracy of HF diagnosis at 100 pg/mL to be 83.4%, with a negative predictive value of 96% at a cut-off of 50 pg/mL.2 Years later, Januzzi et al. solidified NT-proBNP in the acute setting in the PRIDE study.3 Since then, the repertoire of these biomarkers has expanded into areas of risk stratification and treatment guidance. The potential to risk stratify those with clinically evident cardiovascular disease (CVD) and perhaps even those who have yet to develop it is certainly an important task. Indeed, in the current phase of their clinical evolution, NPs are being actively researched as possible screening tools for asymptomatic people in the outpatient setting. If validated, these markers, perhaps in the company of other novel biomarkers, could allow those at risk for CVD without classic risk factors such as hypertension, diabetes mellitus, and hyperlipidaemia to be identified and treated before the appearance of full-on CVD.

There should be no surprise that NPs are being actively researched as a means for screening for subclinical CVD and to predict future events, for a variety of reasons.4 First, NP levels are often elevated early on in CVD processes, which could allow the early identification of those who may be developing pathology.5 Secondly, the myriad of illnesses that cause elevations of NPs, such as heart failure, valvular disease, and left ventricular (LV) dysfunction, are prevalent and result in considerable disability and cost. Catching these conditions early could lead to early intervention that may curb this morbidity. Lastly, detecting these oncoming diseases quickly and efficiently in those at high risk could result in a means of cost-effective screening.

In recent years, the Framingham Offspring Study has examined the prospective utility of NPs. The investigators measured levels of BNP in 3346 asymptomatic people and found that it was independently predictive of HF, stroke, atrial fibrillation, and death that persisted even after adjustment for classic risk factors.6 Furthermore, those with BNP values > 20 pg/mL (80th percentile) had a 76% risk increase for first major CV event and a 62% risk increase of death.6 Hence, there is reason to believe that NPs may be a means to identify those at risk of developing CVD despite lacking symptoms or classic risk factors.

The understanding that CVD risk is not always tied to possessing these risk factors is an important one. The third NHANES (National Health and Nutrition Examination Survey) study demonstrated that 99% of those aged between 35 and 74 years have at least one suboptimal risk factor for CVD.7 As many of these people will never develop clinical CVD, there is a need for additional tools to allow the identification and classification of those at risk of developing clinical disease ideally even before risk factors can manifest.

Limitations of current cardiovascular disease risk assessment tools

The current utilities used to assess risk of CVD are based upon risk factors and often result in focusing on those of high risk for disease. In
doing so, the studies and the clinicians they influence may be missing the bulk of those who will eventually develop CVD. These contemporary risk stratification methods also tend to focus on coronary artery disease rather than all CVD, have fewer data on risk in minorities, and a general underestimation of risk over a person’s lifetime. Furthermore, classic risk factors for CVD suffer from low specificity and lackluster predictive values, especially when it comes to identification of those that may have subclinical CVD. Early treatment of this cohort could greatly reduce future morbidity as well as avoiding the costlier treatments of advanced disease.

The WOSCOPS follow-up

In their follow-up of the West of Scotland Coronary Prevention Study (WOSCOPS), Welsh et al. has continued the solid foundation of NPs in the realm of risk stratification. In a cohort of 4801 middle-aged men with moderate hypercholesterolaemia (serum triglycerides < 6.0 mmol/L and LDL 4.5–6.0 mmol/L), they found that NT-proBNP was significantly associated with risk increase for CVD with a hazard ratio (HR) of 1.17 [95% confidence interval (CI) 1.11–1.23, P < 0.001] per standard deviation (SD) increase in log NT-proBNP after adjustment for risk factors and C-reactive protein.9

They also found variations in the predictive strength of NPs. NT-proBNP performed better in predicting the risk of fatal CVD (HR = 1.34, 95% CI 1.19–1.52) as opposed to non-fatal CVD (HR = 1.17, 95% CI 1.10–1.24) (P = 0.022). Also, importantly, adding NT-proBNP to classic CVD risk factors led to improvement of the C-statistic (+0.013; P < 0.001).

Interestingly, the authors pointed out that NT-proBNP values were greater in those in lower socio-economic groups, suggesting broader commentary regarding health maintenance and subclinical disease. This cohort could greatly benefit from screening and early therapeutic intervention before they progress to overt clinical disease and require costlier treatments and follow-ups.

The authors astutely point out that due to the well researched properties of NPs such as being elevated in conditions such as HF and both clinical and subclinical ischaemia, the results of their study should not be a shock. NT-proBNP, and other NPs, can provide a hint at underlying pathology that has not yet manifested as visible disease.

Of course, the WOSCOPS cohort is not the ideal study population as it is limited to middle-aged men: specifically those with a certain range of hypercholesterolaemia. Although this makes it more difficult to generalize to the population as a whole, Welsh et al. provide valuable evidence for the case of NPs in risk stratification for death and CVD. Looking ahead, NPs could be combined with other biomarkers to strengthen their predictive abilities and clinical utilities. In fact, several studies have already looked into this intriguing possibility.

A multimarker approach

The idea of using multiple biomarkers in tandem to strengthen their clinical utility is not a new one, but the incorporation of NPs and other markers to identify risk in those who have yet to develop CVD is still in its early stages. Wang et al. examined the role of multiple biomarkers within the Framingham Heart Study cohort including C-reactive protein, BNP, aldosterone, renin, D-dimer, homocysteine, NT-proANP, fibrinogen, and several others. They found BNP to predict mortality risk best, with a HR of 1.4.10 Moreover, BNP, with an adjusted HR of 1.25 per 1 SD increment, was also the strongest in predicting a first major cardiovascular events such as myocardial infarction, coronary insufficiency, stroke, and HF.10 Those in the highest quintile of multimarker scores had an adjusted HR of 4.08 (P < 0.001) to predict mortality when compared with those in the lowest quintile. Unfortunately, this effect was only modest when conventional risk factors of CVD were included in the analysis.10 Although disappointing, this may be a reflection of the markers chosen for the analysis. Some of the biomarkers chosen have never had strong evidence behind them as a means of assessing risk of death or future events. As research continues, novel markers may emerge to combine with NPs to form powerful multimarker panels.

Despite modest increases in HRs when added to traditional risk factors (C-statistic 0.80 with sex, age, and traditional risk factors as predictors vs. 0.82 when biomarkers are added to those),10 the markers in the study of Wang et al. (as well as novel markers currently in development) could have their largest impact in those that lack risk factors. It can be argued that those of moderate to low risk would benefit the most from early and aggressive therapy to avoid developing overt clinical disease or even fully manifested risk factors. As new markers are discovered and developed, the power of such multimarker panels will surely increase.

Novel biomarkers in cardiovascular disease risk assessment: ST2 and galectin-3

Several novel biomarkers are waiting in the wings to join NPs in the risk assessment, prognostic determination, and treatment guidance of CVD (Figure 1). One of these with promising evidence thus far is ST2, a member of the interleukin-1 (IL-1) family of proteins. Released by cardiomyocytes and fibroblasts in response to cardiac strain, there are two different forms: a soluble form (sST2) and a transmembrane form (ST2L).11 ST2L’s ligand, IL-33, has been implicated in protection against fibrosis and LV hypertrophy in the setting of increased cardiac pressures.11 Unfortunately, it seems as if circulating levels of sST2 can bind IL-33 and neutralize this advantageous effect. Recent studies have shown that measuring sST2 can predict mortality in subjects with myocardial infarction12 as well as acute and chronic HF.13,14

ST2 has also been examined in the outpatient setting. In a study of 588 outpatients referred for echocardiogram, those with high sST2 levels had a higher risk of mortality (adjusted HR = 2.5, P = 0.02) and, when working in tandem with BNP, the biomarkers combined for an adjusted HR of 4.3 (P = 0.01).11 In fact, those with both BNP and sST2 elevated in this study had a 2.6 times higher risk of death within 1 year than those with only one of the markers elevated.11

Galectin-3 (Gal-3) is another novel biomarker that may play a role in risk stratification of CVD and predicting mortality in the coming years. It is released from macrophages and alters a variety of physiological and pathological cascades, including fibrosis and inflammation.15 In rat models, high levels of Gal-3 have been
associated with LV dysfunction, and there is even evidence that it could be responsible for cardiac fibrogenesis by activating myofibroblasts.\(^{16}\) If this is the case, Gal-3 could be not only a biomarker of poor prognosis, but also a possible target of therapy.

Gal-3 was also examined in the Framingham Offspring cohort, where the investigators found that it was associated with a risk of incident HF with a HR of 1.28 (per 1 SD increase in log Gal-3; 95% CI 1.14–1.43; \(P < 0.0001\)). This significance was maintained after adjustment for BNP and clinical variables (HR 1.23; 95% CI 1.04–1.47; \(P = 0.02\)). Moreover, Gal-3 was also associated with all-cause mortality risk (adjusted HR = 1.15; 95% CI 1.04–1.28; \(P = 0.01\)).\(^{17}\) While further research is required to understand this new marker fully, the early results are quite promising.

Studies such as Welsh et al.’s WOSCOPS follow-up have helped lay the ground work for NPs being utilized in predicting risk of CVD in asymptomatic individuals. Information such as this could lead to a considerable decrease in the morbidity and mortality of CVD in the general population as well as providing a cost-effective means of avoiding overt disease, all through early detection of subclinical pathology. Now with markers such as ST2 and Gal-3 being discovered, researched, and tested, NPs may not have to go it alone for much longer.

**Conflict of interest:** A.M. is a speaker and consultant for Alere and a consultant for both BG Medicine and Critical Diagnostics. A.F. has no conflicts of interest to declare.

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