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COMMENTARY

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Brain natriuretic peptide: microalbuminuria for cardiac disease and diabetes?

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Abbreviations AER: Albumin excretion rate · BNP: Brain natriuretic peptide · NT-pro-BNP: N-terminal pro-BNP

Most people with diabetes will succumb to the cardiovascular complications of their disease. Yet despite this grim statistic some will remain free of macrovascular disease while others spiral inexorably downward through heart failure, stroke or amputation towards an early grave. Early identification of vascular risk is a cornerstone of diabetes management and facilitates tailored intervention at an early stage of disease when a useful response is more likely to be obtained. Screening for microalbuminuria identifies patients with early nephropathy at risk for overt disease and targets them for preventive interventions. Microalbuminuria is also strongly associated with cardiovascular disease, but does not identify its presence or severity. Given the enormous impact of cardiovascular disease, there is an urgent need for an early marker of cardiac disease that will identify end-organ pathology and facilitate its repair, as microalbuminuria does for the kidney.

Recent studies have suggested that serum levels of brain natriuretic peptide (BNP) might be a reliable diagnostic and prognostic marker for cardiac disease [1]. Cardiac BNP is synthesised as a prohormone in response to volume expansion and ventricular wall stress, and is then released into the circulation following cleavage into active BNP and an N-terminal pro-BNP (NT-pro-BNP) fragment [2]. Although these are released in equimolar amounts, NT-pro-BNP is found in higher concentrations in the circulation and has a longer half-life than active BNP, possibly due to differences in its specific degradation. BNP and NT-pro-BNP both correlate with symptoms of heart failure and the severity of systolic and diastolic dysfunction in patients with cardiac disease [3]. Studies in probands without heart failure from the Framingham collective showed that BNP also predicts death, first major cardiovascular events, heart failure and stroke [4]. This issue of *Diabetologia* features two reports that also show plasma NT-pro-BNP to be an independent risk marker for cardiovascular disease in patients with diabetes [5, 6].

The first of these is a prospective observational follow-up study of 198 type 1 diabetic patients with overt nephropathy and a matched control group of 188 patients with long-standing type 1 diabetes and a persistently normal albumin excretion rate (AER) [5]. All were followed for more than 9 years, during which time there were 51 (26%) deaths among patients with diabetic nephropathy and 11 (6%) among those with normal AER. At baseline, plasma NT-pro-BNP was higher in patients with diabetic nephropathy than in patients with normal AER (110 [5-79640] vs 27 [5-455] ng/l). Patients with overt nephropathy and a documented history of myocardial infarction and/or stroke had even higher levels than those with nephropathy and no history of major cardiovascular disease (671 [34-12418] vs 97 [5-79640] ng/l). Nonetheless, and regardless of baseline cardiovascular disease, all patients with elevated plasma NT-pro-BNP had a significantly worse prognosis. Of those with overt nephropathy, 31% with NT-pro-BNP values above the median (110 ng/l) died a cardiovascular death, as against 7% of those with values below the median, whose mortality did not differ significantly from patients without nephropathy (6%). The adjusted hazard

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ratio was 3.81, and the effect remained significant after adjustment for differences in glomerular filtration rate, duration of diabetes and age. This study suggests that a single determination of NT-pro-BNP can divide individuals with overt nephropathy into those at high risk of vascular disease and those at the baseline risk associated with diabetes itself.

The second study featured in this issue of *Diabetologia* examines the utility of NT-pro-BNP in 160 microalbuminuric type 2 diabetic patients enrolled in the Steno-2 Study and followed for an average of 7.8 years [6]. Interestingly, these patients had lower concentrations of NT-pro-BNP (median 33.5 [5-1290] ng/l) than those in the first study. Even so, NT-pro-BNP levels above the median value at baseline were significantly associated with an increased risk for cardiovascular disease, with an unadjusted hazard ratio of 4.4.

Although there is a strong epidemiological link between nephropathy and cardiovascular disease, both studies clearly demonstrate that not all patients with nephropathy share this elevated risk. The finding that some patients remain comparatively free of cardiovascular complications despite persistent microalbuminuria shows that the loss of albumin into the urine is not in itself the vascular equivalent of crossing the Rubicon. Meanwhile, the mechanism (s) that determine plasma concentrations of NT-pro-BNP remain to be established. Many patients with elevated values will have undiagnosed or silent cardiac disease, contributing to the excess of events seen in the group of patients above the median value. Conversely, a low BNP level makes left ventricular dysfunction (both systolic and diastolic) unlikely. It is possible that the risk associated with an elevated BNP is attributable to undiagnosed cardiac dysfunction. However, the Framingham study, in which 10% of patients had diabetes, found that the association between BNP and adverse vascular outcomes remained significant even after adjustment for echocardiographic variables of impaired cardiac function.

Diabetic cardiac disease is associated with a range of morphological changes including myocyte hypertrophy, perivascular fibrosis and the accumulation of amorphous extracellular matrix protein. Over time these processes contribute to the development of left ventricular hypertrophy, coronary heart disease and congestive heart failure, each of which are associated with elevated levels of BNP. Occult cardiomyopathy, characterised by impaired relaxation and a stiff left ventricle, may however precede these overt manifestations in patients with diabetes [7]. Recent surveys demonstrate that up to 60% of patients with diabetes have diastolic dysfunction [8], and that this is an independent risk factor for cardiac death [9]. In other words, and as with microalbuminuria in early nephropathy, stiffening and overload of the diabetic myocardium is a signal that the heart is ‘in trouble’ and means that overt consequences can be expected in the absence of intervention. Even so, occult cardiac disease may not be the only reason why NT-pro-BNP levels are higher in patients with nephropathy as compared to those without. Other factors may include arterial hypertension, renal impairment, elevated extracellular fluid volume and elevated left ventricular mass in the absence of cardiac dysfunction. Since all these may be considered markers of cardiac risk, it is evident that non-specific elevation of BNP may provide a useful global indication of cardiovascular risk in a population setting. Indeed, the observation that BNP encompasses such a wide range of pathogenetic factors may explain why it carries a higher attributable risk than conventional risk factors such as metabolic control and hypertension.

Although NT-pro-BNP proved a good marker of cardiovascular risk in both populations reported in this issue, its value as a screening tool in clinical practice remains uncertain. There is, for example, substantial overlap of NT-pro-BNP values in patients with and without cardiovascular disease. In addition, while both studies showed an increased risk above the median value for NT-pro-BNP, there was a three-fold difference in median values between the studies. This is likely to reflect differences between the groups including age, sex, body mass, severity of renal disease, exercise and drug therapy, all of which may influence BNP levels. Before BNP could, like albuminuria, be considered an effective screening test, the distribution of BNP levels must be clearly established and appropriate cut-off levels defined and agreed. Furthermore, the natural history of diabetic cardiac disease, including progression from latent to declared disease, would have to be clearly understood in relation to BNP. Serial monitoring of this marker might potentially enable the clinician to detect the onset of cardiac dysfunction before echocardiographic changes in an individual with diabetes, but this information is not yet available, and the practical value of the test is limited by the high intra-individual variability associated with conventional BNP assays [10].

Studies in patients with heart failure have demonstrated that interventions that lower BNP levels (exercise, blockade of the renin–angiotensin system, diuresis, etc.) are all associated with improved outcomes. Although NT-pro-BNP is a strong marker of cardiovascular risk in patients with type 2 diabetes, aggressive polypharmacological treatment of patients with type 2 diabetes and microalbuminuria was no more effective than standard treatment in lowering NT-pro-BNP values, despite its added efficacy in improving cardiovascular outcomes. The fact that aggressive therapies can improve cardiovascular outcomes without altering BNP makes the interpretation of risk-reduction impossible with BNP alone. In contrast, reduction of albuminuria in the Steno-2 Study was strongly associated with improved cardiovascular outcomes. Nonetheless, both of these studies suggest that NT-pro-BNP potentially offers information regarding cardiac risk over and above that provided by albuminuria. It is conceivable that NT-pro-BNP therefore represents components of end-organ pathology not specifically managed by polypharmacological interventions, including the accumulation of advanced glycation end products, oxidative stress and vascular calcification.

Unfortunately, BNP is not the ‘microalbuminuria of the heart’ that we need in order to detect and treat cardiovascular disease at an early stage in patients with diabetes. It does, however, identify groups at very high risk of cardiovascular disease, independently of the presence of nephropathy. These findings may be of great value in the design of future intervention studies targeted to reduce the burden of cardiovascular disease in patients with diabetes.

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