Plasma BNP in patients on maintenance haemodialysis: a guide to management?

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The number of patients requiring long-term haemodialysis is increasing throughout the world. Cardiovascular disease is much more common in these patients than in the general population and accounts for the majority of deaths. New approaches to management are clearly needed to reduce this excessive cardiovascular burden. We propose that circulating levels of the cardiac natriuretic peptides, B-type natriuretic peptide (BNP) in particular, might provide a useful, objective guide to the management of their hydration status and pharmacotherapy. An overview of the literature shows that plasma levels of the cardiac natriuretic peptides are increased in this patient population and reflect cardiac preload and afterload along with cardiac pathology, thereby providing an index of cardiovascular (especially cardiac) stress and distress. Circulating levels of the cardiac peptides change in parallel with cardiac load, especially across haemodialysis. Furthermore, there is robust evidence that natriuretic peptide levels are predictive of cardiovascular outcome in these patients. Accordingly, we hypothesize that management of their haemodialysis, and pharmacotherapy designed specifically to lower plasma BNP levels to, or close to, the normal range, will reduce the excessive burden on the cardiovascular system and thereby ultimately lower the incidence of cardiovascular disease. We outline, in broad terms, how a trial to test this hypothesis might be designed. *J Hypertens* 23:23–28 © 2005 Lippincott Williams & Wilkins.

Journal of Hypertension 2005, **23**:23–28

Keywords: haemodialysis, hypertension, cardiac natriuretic peptides, brain natriuretic peptide, chronic renal failure

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Received 21 May 2004 **Revised** 6 July 2004
Accepted 10 August 2004

Introduction

Individuals with chronic kidney failure are at high risk of cardiovascular disease [1]. This risk is especially striking for those on maintenance haemodialysis, in whom left ventricular (LV) hypertrophy is present in approximately 75% of patients whereas heart failure afflicts around 40%, and ischaemic heart disease 40% of patients [1]. Not surprisingly, then, cardiovascular disease mortality is many times higher in patients on haemodialysis than in the general population [1]. Whereas 'non-traditional' cardiovascular risk factors [such as disturbances in lipoprotein(a) and apolipoprotein(a), inflammation, abnormal calcium/phosphate metabolism and alterations in endothelin and nitric oxide balance] might contribute to this excessive cardiovascular burden, hypertension and volume overload are likely to be dominant [1,2].

In that the biologically active cardiac natriuretic peptides ANP (atrial natriuretic peptide) and BNP (brain, or B-type natriuretic peptide), along with their amino-terminal peptides (NT-ANP and NT-BNP), are released from the heart in proportion to the degree of stretch of the cardiac chambers [3,4], with LV hypertrophy [5,6], and during myocardial ischaemia [7], it is not unreasonable to make three presumptions with regard to these cardiac peptides in patients on haemodialysis. First, their circulating levels should reflect indices of cardiac work and pathology. Secondly, any decrease or increase in cardiac load should result in parallel changes in plasma ANP and BNP levels. Thirdly, plasma levels of the peptides should be predictive of cardiovascular outcome. If the three presumptions are indeed true, one could then hypothesize that management of patients in regard to dialysis and drug therapy as guided by plasma levels of these peptides, might prove effective in reducing their alarming risk of cardiovascular morbidity and mortality.

We will discuss briefly data bearing on the three presumptions, identify a precedent for the resulting hypothesis, and suggest how the hypothesis might be put to the test. Our focus will be mainly, though not exclusively, on BNP and NT-BNP, since they have,

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under various circumstances (including population screening, acute coronary syndromes, post-myocardial infarction and established heart failure), proved equal or superior to ANP or NT-ANP in reflecting haemodynamic and clinical status, and in predicting cardiovascular morbidity and mortality [8–15].

Plasma natriuretic peptides, haemodynamics and cardiac pathology in patients on haemodialysis

From the numerous published studies quoted below, it is clear that circulating levels of the cardiac natriuretic peptides are elevated in patients on haemodialysis; BNP proportionally more than ANP. Furthermore, most reports show statistically significant associations between plasma natriuretic peptides levels, on the one hand, and haemodynamic variables on the other hand. This has included correlations that are positive between cardiac peptide levels and arterial pressure [16,17], LV mass [18–20], pulmonary artery pressure, pulmonary artery wedge pressure or LV diameters [18,21] and plasma volume [22], and correlations that are inverse between peptide levels and indices of LV systolic function [20,21]. In addition, plasma ANP and BNP concentrations are higher in patients on haemodialysis who have coronary artery disease compared with those who do not [18,21]. Whereas a number of these studies can be criticized on grounds of sparse patient numbers, and since other reports have failed to confirm these statistical associations [23], the largest study, involving 246 patients, observed statistically significant correlations between plasma BNP levels and LV mass ($r = 0.53$, $P < 0.0001$) and LV ejection fraction ($r = -0.42$, $P < 0.0001$), and a high negative predictability (96–97%) in ruling out LV systolic dysfunction [24]. Of course, one should not expect plasma ANP and BNP levels to necessarily reflect volume status with great accuracy [23,25], since, as mentioned already, these peptides are released from the myocardium in response to LV hypertrophy and cardiac ischaemia (as well as to a number of hormones and cytokines), in addition to stretch of the chambers of the heart. Furthermore, the modulatory effects on plasma levels of the cardiac peptides of age and gender [26], obesity and diabetes mellitus [27] must be considered. Although additional information is needed, it seems reasonable, in our view, to conclude from the available evidence that plasma levels of ANP and BNP are largely, though not exclusively, a reflection of cardiac burden (volume status plus afterload) and cardiac pathology (left ventricular hypertrophy and myocardial ischaemia) in haemodialysis patients.

Changes in cardiac haemodynamic load versus changes in plasma ANP and BNP

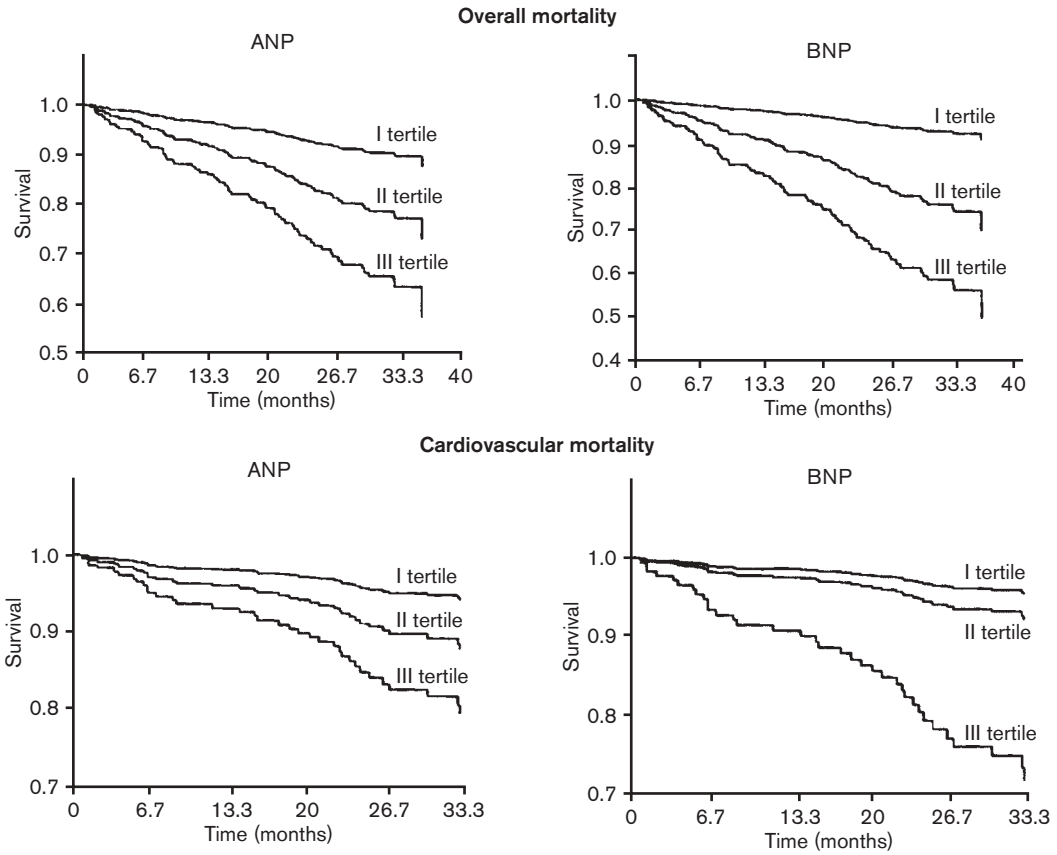
The reduction in fluid volume and arterial pressure across haemodialysis [28] is associated with a pronounced fall in plasma ANP levels and a lesser percentage decline in BNP [29–32]. On the contrary, volume-loading elicits a prompt, vigorous rise in their circulating concentrations [16,33], raising the possibility that cardiac stretch-related release of these peptides is heightened in patients on haemodialysis. Since clearance of the cardiac peptides by haemodialysis is minimal [34,35] and isovolaemic haemodialysis does not change ANP levels in plasma [22], it is evident that, whereas additional factors might be involved [36], alterations in cardiac stretch (preload) and arterial pressure resulting from perturbations in body fluid status account largely for fluctuations in the plasma ANP and BNP concentrations across, and between, dialysis [37–39]. Regarding cardiac afterload, antihypertensive drug treatment in haemodialysis patients is likely to reduce plasma ANP and BNP levels (see below), although there is little published information on this point.

Cardiac natriuretic peptide levels as predictors of cardiovascular outcome

Three separate groups have reported that plasma levels of BNP and/or ANP are robust markers of a heightened risk of cardiovascular events, cardiac death or overall survival [20,40–42]. However, these studies involved small numbers of patients and endpoints were few.

More noteworthy is the report from the Creed Investigators, who studied 246 dialysis patients (212 on haemodialysis) without heart failure over a mean period of 26 months in four dialysis centres in Italy [19]. They noted that baseline plasma ANP and BNP levels were higher ($P < 0.0001$) in those who subsequently suffered a cardiovascular event ($n = 74$) than in event-free patients; were higher ($P < 0.0001$) in patients who died during follow-up ($n = 63$) than in survivors; and for those who succumbed from a cardiovascular cause ($n = 35$), baseline ANP and BNP levels were higher than in survivors ($P < 0.0001$) (Fig. 1). Multivariate analysis revealed both peptides to be significant independent predictors of overall and cardiovascular death [19]. A noteworthy observation in the study by the CREED investigators was that plasma BNP and ANP concentrations were only slightly elevated in patients with a normal LV mass index and normal left ventricular geometry, whereas the levels were most significantly increased in the presence of LV hypertrophy, whether eccentric or concentric. The authors proposed that hypertrophy and remodelling of the left ventricle were major determinants of raised plasma levels of the cardiac natriuretic peptides in patients on chronic dialysis [19]. It is apparent, therefore, that elevated circulating levels of BNP or ANP identify patients who require vigorous treatment to correct abnormalities in LV structure and in volume and blood pressure status.

Fig. 1



Cox proportional hazard survival curves for overall mortality and for cardiovascular mortality in a cohort of 246 patients on dialysis. Patients were stratified in three tertiles according to plasma atrial natriuretic peptide (ANP) and brain (B-type) natriuretic peptide (BNP) concentrations. Tertile I, plasma ANP $<$ 17.9 pmol/l, plasma BNP $<$ 14.3 pmol/l: tertile II, plasma ANP $>$ 17.9 and $<$ 34.8 pmol/l, plasma BNP $>$ 14.3 and $<$ 36.1 pmol/l: tertile III, plasma ANP $>$ 34.8 pmol/l, plasma BNP $>$ 36.1 pmol/l. Data were adjusted for other independent predictors of death. (From Zoccali *et al.* [19], with permission.)

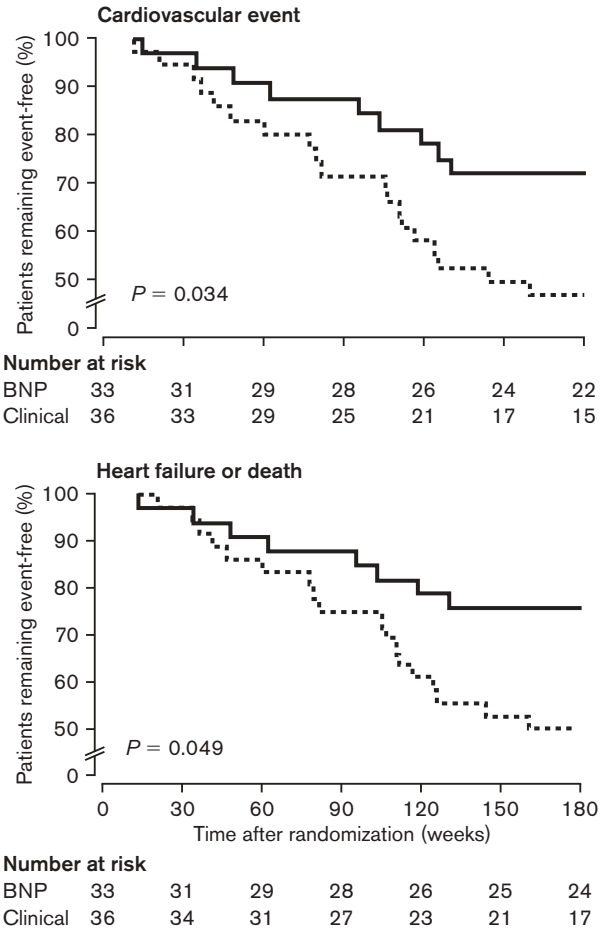
An hypothesis

If, as we suggest, one can accept the validity of the three presumptions discussed above, there is a basis to hypothesize that plasma levels of the cardiac natriuretic peptides will provide a relatively simple, objective guide to the management of patients on long-term haemodialysis. This possibility was raised by the Creed Investigators [19] and by McCullough and Sandberg [43]. The latter authors proposed that a 'BNP reduction ratio', based on plasma BNP levels measured across a 3-h dialysis session, has the potential to guide the management of such patients. Earlier, Andersson *et al.* [44] suggested that plasma ANP levels could possibly be used as 'a marker of proper volume and dry weight' for patients on maintenance dialysis. We propose that such guidance provided by BNP (or its sister peptides) would be directed to normalizing both cardiac preload and afterload and reversing (and preventing) cardiac pathology, LV hypertrophy in particular.

There is a precedent for this hypothesis. Troughton *et al.* [45] showed that for patients ($n = 69$) with chronic heart failure associated with a reduced left ventricular ejection fraction, treatment directed specifically at lowering high circulating levels of BNP reduced cardiovascular events and delayed time to first event, compared with usual, clinically guided therapy (Fig. 2). That study, carried out in a well-staffed outpatient clinic under research conditions, might well have underestimated the potential benefits of this approach to clinical care in the busy primary-care, or typical hospital outpatient clinic. The study of Troughton *et al.* [45] in chronic heart failure could form the basis for a similar investigation in patients on haemodialysis.

In regard to the practicality of testing our hypothesis, availability of sufficient patient numbers requiring chronic haemodialysis and with a high risk of cardiovascular endpoints, will present no problem. Of course,

Fig. 2

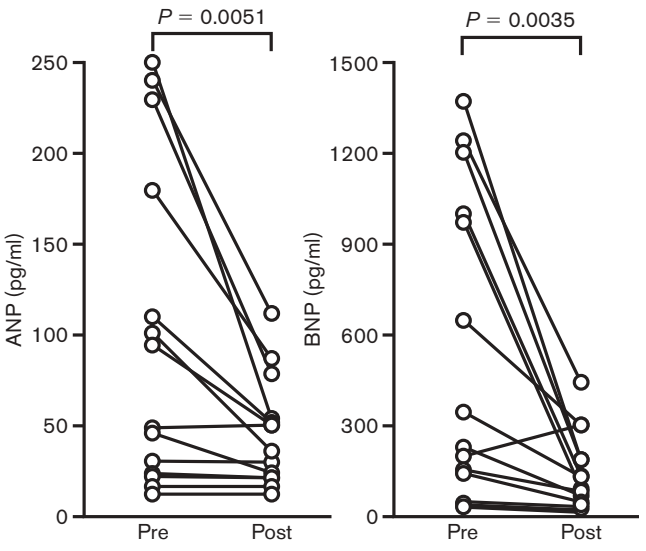


Kaplan–Meier event curves for time to first cardiovascular event in patients with chronic heart failure randomized to 'usual care' (interrupted line) or treatment as determined by plasma levels of brain (B-type) natriuretic peptide (BNP) (continuous line). (From Troughton *et al.* [45], with permission.)

a formal power calculation would be required to determine patient numbers needed and duration of the study. As in the heart failure study of Troughton *et al.* [45], patients on maintenance haemodialysis could be randomized to 'usual care' or care directed to reducing elevated plasma BNP levels to, or close to, normal. The primary endpoint might be fatal and non-fatal cardiovascular events. Reducing natriuretic peptide levels in the hormone-guided group could be achieved by more prolonged, more frequent or more intense haemodialysis and pharmacotherapy, especially with antihypertensive agents. In this regard, there is every reason to think that, as in hypertension and in heart failure [46–49], the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II type I receptor blockers will reduce natriuretic peptide levels in patients on haemodialysis. Certainly, a substantial decline in arterial pressure with ACE inhibition has been shown in patients on chronic haemodialysis [50] and this, together with withdrawal of the direct stimulatory action of angiotensin II on natriuretic peptide secretion, would be expected to result in a fall in plasma levels of BNP and ANP. At least two beta-adrenergic receptor blockers lower both ANP and BNP levels during prolonged administration in cardiac failure [51], and the same applies to metoprolol in patients on haemodialysis [52] (Fig. 3). In the latter study, metoprolol improved left ventricular function in parallel with the fall in natriuretic peptide levels. Current usage of ACE inhibitors and beta-blockers in patients on haemodialysis is stated to be low (less than 25%) [53]. Other drugs which might be utilized to reduce plasma natriuretic peptide levels in the proposed study are nitrates [54] and some calcium-channel blocking agents [55]. As in the heart-failure study of Troughton and colleagues [45], a set sequence of drug treatments (or dose increments) could be planned for both the 'usual care' group of patients and for the group where treatment is guided by plasma BNP levels. Drug dose increments or the addition of a new agent would be dictated by predetermined clinical criteria in the former group and by a predetermined BNP level in the latter group.

The other practical issue for this proposed study is availability of natriuretic peptide assays. A point-of-care assay for BNP (Biosite Triage BNP test), which pro-

Fig. 3



Plasma levels of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) before and after 4 months of treatment with the beta-blocking drug, metoprolol, in 14 patients on haemodialysis. (From Hara *et al.* [52], with permission.)

vides a result in approximately 15 min, has been validated in heart failure (and in patients with suspected heart failure) [56,57], and is now widely available. This, and similar assays under development, would facilitate rapid adjustment of haemodialysis and drug therapy in the proposed study, and also in clinical practice. One caveat here is that whichever assay is utilized, validation specifically for patients on haemodialysis will be necessary. Retained products in chronic renal failure might conceivably cross-react or otherwise interfere in some BNP assays.

Apart from documenting morbidity and mortality in the proposed trial, quality of life measures and cost-effectiveness would need to be compared in the BNP and the 'usual care' groups of patients. Whereas BNP assays are not currently cheap, they are reportedly cost effective, at least in the evaluation and management of patients presenting with acute dyspnoea to an emergency department [58].

Discussion

The number of patients requiring dialysis and renal transplantation worldwide is increasing substantially. In the USA, this number is predicted to surpass 650 000 by 2010 [1]. For patients on haemodialysis, cardiovascular disorders dominate morbidity and mortality. Although the aetiology and pathogenesis of cardiovascular diseases under these circumstances are undoubtedly complex and related in part to non-traditional risk factors [1,59,60], the importance of accepted, traditional risk factors seems undeniable [1,61,62]. Many of these risk factors place a stress on the heart by increasing preload and/or afterload, inducing left ventricular hypertrophy and left atrial dilatation, and promoting coronary atherosclerosis. One response of the heart to increased stress, particularly to stretch of cardiac chambers, is augmented release of the natriuretic peptides, ANP and BNP. Our review of the available literature leads us to conclude that circulating levels of these peptides reflect the level of cardiac stress, distress and pathology – not just body fluid status. Review of these data encourages us to hypothesize that plasma BNP, or a sister peptide, might provide a useful, simple, objective guide to the otherwise complex management of patients who are dependent on haemodialysis. The large and increasing pool of patients on chronic haemodialysis and availability of point-of-care BNP assays makes it feasible to carry out a formal study to address the hypothesis. Should the outcome prove positive, i.e. management directed to normalizing BNP levels is associated with a lower rate of total and cardiovascular endpoints compared to 'usual care', such rapid BNP assays could then be used on a regular basis in clinical practice to guide both dialysis and pharmacotherapy.

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