Diagnostic potential of circulating natriuretic peptides in chronic kidney disease

Patrick B. Mark1,2, Graham A. Stewart2,4, Ron T. Gansevoort2,5, Colin J. Petrie3, Theresa A. McDonagh3,6, Henry J. Dargie2,3, R. Stuart C. Rodger1 and Alan G. Jardine1,2

1Renal Unit, University of Glasgow, 2Division of Cardiovascular and Medical Sciences, 3Department of Cardiology, Western Infirmary, Glasgow, UK, 4Department of Nephrology, Ninewells Hospital, Dundee, UK, 5Clinical Pharmacology, University Medical Center, Groningen, The Netherlands and 6Department of Cardiology, National Heart and Lung Institute, Royal Brompton Hospital, London, UK

Abstract
Background. Measurement of natriuretic peptides, particularly brain natriuretic peptide (BNP) is an established method for the diagnosis of cardiovascular disorders, chiefly left ventricular (LV) dysfunction. The influence of renal function on the diagnostic utility of natriuretic peptides is unclear.
Methods. We performed a cross-sectional study of 296 patients with renal disease but no history of cardiac disease using echocardiography to assess LV mass and function. Circulating levels of atrial natriuretic peptide (ANP) and BNP were also measured.
Results. The incidence of LV hypertrophy increased with progressive renal dysfunction; from 39% in patients with near-normal renal function, to 80% in renal transplant patients. There was a negative correlation between both ANP and BNP, and glomerular filtration rate (GFR) (ANP: \( r = -0.28, P < 0.001 \); BNP: \( r = -0.40, P < 0.001 \)). Serum ANP and BNP had sensitivity and specificity for LV hypertrophy of 39.9%, 87.4% (ANP) and 61.4%, 67.6% (BNP) respectively. Significant confounders in determining serum ANP were haemoglobin, beta blockade and albumin, while serum BNP levels were significantly confounded by GFR, albumin, haemoglobin, beta blockade and age. Conclusions. Across a spectrum of renal dysfunction, GFR is a more important determinant of serum BNP than ventricular function, and several factors are predictors of natriuretic peptide levels. In chronic kidney disease, the use of natriuretic peptides to diagnose LV hypertrophy must be interpreted in light of these other factors. The use of these peptides in renal dysfunction to diagnose LV dysfunction may be of limited value.

Keywords: atrial natriuretic peptide; brain natriuretic peptide; cardiomyopathy; chronic renal failure; left ventricular hypertrophy

Introduction
The measurement of circulating natriuretic peptides has an established role in the diagnosis and management of patients with heart failure [1,2]. Although there is a high prevalence of cardiovascular diseases (CVD), in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [3], the utility of natriuretic peptide measurement is unclear in this population. Early identification of patients with CKD at risk of premature cardiovascular events has become a major public health issue given the emergence of even mild renal dysfunction as an independent risk factor for cardiovascular events [4]. Much of this risk can be explained by a combination of accelerated atherosclerosis [5] and greater prevalence of left ventricular hypertrophy (LVH) [6] with advancing CKD [7].

Circulating levels of natriuretic peptides (atrial natriuretic peptide – ANP, brain natriuretic peptide – BNP) have been associated with structural and functional cardiac abnormalities in patients at different stages of CKD [8,9]. Increased circulating natriuretic peptide levels have also been associated with left ventricular dilatation and dysfunction (abnormalities frequently described as uraemic cardiomyopathy) [10], and shortened survival of patients with ESRD [11]. However, it is difficult to interpret natriuretic peptide measurements in renal disease because of the
relationship between circulating levels and renal function (due to renal metabolism and excretion). This is a particular issue with natriuretic peptides, which are, in part cleared by the kidney, as well as by the endopeptidase system. Thus, levels are inversely related to glomerular filtration rate (GFR). Moreover, the effect of increasing prevalence of LVH with increasing severity of CKD may further compromise the diagnostic utility of natriuretic peptides, particularly as a tool for assessment of left ventricular systolic dysfunction (LVSD).

To investigate the diagnostic utility of natriuretic peptide measurements in CKD, we performed a large, cross-sectional echocardiographic study of uraemic cardiomyopathy at different stages of CKD (including haemodialysis and transplant recipients). The main results of this study have been reported elsewhere [7]. We measured circulating levels of ANP and BNP, in view of the rapidly emerging role for using these peptides for both diagnostic and prognostic use in the management of CVD. In the current analysis, we report the influence of cardiac and renal function on these parameters.

**Patients and methods**

Patients were recruited from the Renal Unit at the Western Infirmary, Glasgow, Scotland in the calendar years 1998 and 1999, as part of the ongoing West of Scotland Kidney Disease Study into cardiovascular complications of renal disease [7]. The study was cross-sectional in design and aimed to recruit approximately 50 patients on haemodialysis, 50 patients with a functioning renal allograft, and 200 patients with proven renal disease (not requiring renal replacement therapy). This latter group was subdivided into quartiles (N = 47) according to the renal function of the participating patients (based on calculated creatinine clearance). The range of renal function in the quartiles was 163–75, 74–44, 43–22, 21–4 ml/min respectively. Within these six groups, patients were contacted randomly, using a published approach to identify a representative, unbiased population. Patients with diabetes mellitus or documented coronary heart disease (i.e. patients with angina, use of nitrates or a history of myocardial infarction) were excluded. The protocol was approved by the hospital Ethics Committee and all patients gave written informed consent.

**Measurements**

Each patient underwent the following investigations: echocardiography, 24 h ambulatory blood pressure measurement (ABPM) and clinic blood pressure measurement, weight and height, 12 lead electrocardiogram (ECG) and 24 h ambulatory ECG. Blood was taken after 30 min rest for routine haematology and biochemistry and plasma samples stored for subsequent analyses. In addition, all patients completed a questionnaire on demographic parameters, medical history and current medication. These investigations were performed on the same day; the patient returned the following day for removal of the ABPM device and ECG recorder. In the haemodialysis patients, echocardiographic measurements and blood samples were performed the morning following haemodialysis on a non-dialysis day.

The detailed echocardiographic methodology has previously been published [7]. Briefly, echocardiography was analysed by a blinded investigator, from two-dimensional guided M-mode images, using American Society of Echocardiography leading edge recommendations [12]. Left ventricular (LV) mass was calculated by the method of Devereux and Reicheck. LV mass index (LVMI) represents LV mass/body surface area; LVH was defined as a LVMI of greater than 131 g/m² (men) and 100 g/m² (women). The characterization of LVH into concentric and eccentric hypertrophy was dependent on measurements of relative wall thickness (RWT = [(2 × PWTd)/LVIDd]; concentric hypertrophy was recorded if the RWT was less than 0.45, or eccentric hypertrophy if the RWT was less than 0.45 (in the presence of LVH). Systolic function was assessed by measuring left-ventricular ejection fraction (EF), from the mean of three measurements in different cardiac cycles using the biplane disc summation method and by calculation of fractional shortening (FS), from the reduction of LV internal diameter during the cardiac cycle. Diastolic function was crudely assessed by measuring the E:A ratio.

Assessment of haematological and biochemical parameters was performed in the routine clinical laboratory. Renal function was estimated using the Cockroft–Gault formula. ANP was measured as previously described [13]; BNP (Shionoria BNP kit, Shionogi, Japan) was measured using commercial assay kits. Samples for natriuretic peptide measurements were made, through indwelling cannulae, after 15 min recumbency, on the same day as the echocardiogram, then centrifuged and the serum stored at −80°C for later analysis.

**Statistical methods**

Data are expressed as mean (SD) for normally distributed variables or as median (inter-quartile range) for non-normally distributed data. Comparisons between groups were made by Student’s t-test or Wilcoxon rank-sum tests, for normally and non-normally distributed data, respectively. Categorical variables were compared using the chi-square test. Data in the various groups of patients with renal disease were compared with data obtained in the group of patients with chronic renal failure and near-normal renal function (i.e. first quartile of renal function) using a one-way ANOVA with Tukey’s pairwise comparison procedure to control for multiple testing. Logarithmic transformation was used for variables with skewed distribution (BNP, ANP and GFR). Correlations between continuous values were assessed using Spearman and Pearson’s correlation coefficient for non-parametric and parametric data respectively. We investigated the determinants of natriuretic peptide levels by multivariate regression analysis, using a stepwise paradigm and the inclusion and exclusion of variables being set at P-values of 0.05 and 0.10 respectively. All other analyses except receiver operator characteristic (ROC) curve analysis were performed using SPSS (V11.5, SPSS Inc., Illinois, USA). ROC curves for independent parameters were drawn and the areas under the curves calculated (MedCalc 8.1, MedCalc Software, Belgium). For a specific parameter (BNP, ANP), the cut-off level that resulted in the highest product of sensitivity and specificity was considered the optimal cut-off for prognostication.
### Results

#### Baseline and echocardiographic characteristics

Echocardiography was performed in 308 patients; 12 were excluded for protocol violations (as described previously [7]) and 296 were included in the analysis. The demographic data are shown in Table 1. Fifty-three patients with a renal allograft entered the study, 55 patients on haemodialysis and 188 patients with renal disease not requiring renal replacement therapy. This latter group of patients was subdivided into quartiles (N = 47) according to their renal function (based on calculated creatinine clearance). The range of renal function in the quartiles was 163–75, 74–44, 43–22, 21–4 ml/min respectively.

The incidence of LVH increased from 39% of patients in the group with near-normal renal function (1st quartile) to 80% in the group of patients with a renal allograft. Left ventricular systolic dysfunction (LVSD) was determined by measurement of ejection fraction. The proportion of patients who fulfilled the criteria for a diagnosis of systolic dysfunction did not show an association between systolic function and renal function. Left ventricular diastolic dysfunction (defined as an E:A ratio of less than 1, at the time of initial analysis) was present in 23–55% of patients and was more common in those with poor renal function (Table 1).

#### Biochemical measurements

The baseline clinical, haematological, biochemical and natriuretic peptide data are shown in Table 1 as well as antihypertensive therapy. Haemoglobin is lower in patients in the presence of reduced renal function, while calcium–phosphate product and parathyroid hormone level are elevated, as expected. There was significantly higher usage of antihypertensive agents, in particular β blockade and calcium channel antagonists with increasing severity of CKD and in renal transplant patients, while there was low use of angiotensin converting enzyme inhibitors in patients on haemodialysis. Figure 1 shows hormone measurements by the subgroups of renal function as described above, demonstrating a trend for ANP and BNP to be higher in patients with advanced renal failure, compared with patients with normal renal function. GFR, calculated by the Cockcroft–Gault formula is likely to be inaccurate in patients established on renal replacement therapy; patients on dialysis were therefore excluded from this analysis. Since ANP, BNP and GFR had a skewed distribution; logarithmic transformation was performed prior to analysis. There was a
significant negative correlation between both ANP and BNP, and GFR (ANP: \( r = -0.28, P < 0.001 \); BNP: \( r = -0.40, P < 0.001 \)). The relationships between ANP and GFR, and BNP and GFR are shown in Figure 2a and b, illustrating the predominant influence of renal function (rather than either systolic dysfunction or LVH) on BNP levels. From these figures it can be seen that a patient with advanced PRD with no evidence of LVSD may have a similar BNP level to that with near normal renal function and systolic dysfunction.

**Diagnostic utility of natriuretic peptides**

To analyse the influence of left ventricular geometry, we looked at the influence of left ventricular hypertrophy, left ventricular dilatation, systolic dysfunction and diastolic dysfunction on serum natriuretic peptides. Figure 3 shows natriuretic peptide measurements according to the presence or absence of structural and functional abnormalities of the heart demonstrating that both ANP is consistently elevated in patients with both concentric and eccentric left ventricular hypertrophy but not significantly in those with evidence of concentric remodelling. BNP was elevated significantly in patients with all types of echocardiographic left ventricular hypertrophy. However, neither natriuretic peptide was statistically significantly elevated in patients with left ventricular systolic dysfunction.

The utility of ANP or BNP levels as a diagnostic test for left ventricular hypertrophy, ventricular dilatation or systolic dysfunction, is demonstrated by area under receiver–operator characteristic (ROC) curves.
These results are shown in Table 2. ANP and BNP have a similar utility for detecting the presence of left ventricular hypertrophy, but neither test is a useful measure of systolic dysfunction in this cohort of patients with varying degrees of progressive renal impairment. The area under the curve (AUC) for the diagnosis of left ventricular hypertrophy for the whole study population using ANP was 0.682 ($P < 0.001$) and 0.686 ($P < 0.001$) with BNP. Using ANP for a diagnosis of left ventricular systolic dysfunction area under the curve for ANP was 0.530 and for BNP was 0.538, with neither result being statistically significant for the diagnosis for LVSD. As we demonstrated a significant relationship between GFR and both ANP we performed ROC curve analysis with patients divided into subgroups of those patients with CKD not on renal replacement therapy, haemodialysis patients and those with a functioning renal transplant. By comparing results across a diverse spectrum of CKD but excluding haemodialysis and renal transplant patients, the diagnostic utility appears reduced for LVH (AUC for ANP = 0.619 ($P = 0.008$); AUC for BNP = 0.642 ($P < 0.001$); Figure 4a and b).

Table 3 gives the sensitivity, specificity, and positive and negative predictive values for BNP concentrations determined by optimum cut-point of the ROC curve for the whole study population, and subdivided into patients with maintained renal function and those on haemodialysis. In the whole study population, the sensitivity of BNP as a test for LVH was 61.4% and specificity was 67.6%. ANP was less sensitive but more specific for LVH with sensitivity of 39.9% and specificity of 87.4%. Overall, although both BNP and ANP were more sensitive for testing for LVSD than for LVH (BNP sensitivity 71.8% for LVSD; ANP sensitivity 77.2% for LVSD), this was less specific. Restriction of the analysis to patients across the spectrum of CKD, not on renal replacement therapy did not substantially improve the diagnostic utility of either natriuretic peptide for the presence of LVH, and although the sensitivity of both BNP (85.2%) and ANP (91.2%) was high for the diagnosis of LVSD, this again was not specific (BNP 29.6%; ANP 18.9%). Both assays performed similarly when analysed for patients on haemodialysis, but interestingly, in the patients whose renal function had been restored by successful renal transplantation, a raised BNP was a less sensitive but more specific test for the diagnosis of both LVH and LVSD.

Analysis of determinants of natriuretic peptide levels

Table 4 shows the results of multivariate linear regression analysis on the determinants of natriuretic peptide levels.
peptides in patients with either native renal function or a renal transplant. Due to the relationship between GFR and natriuretic peptide levels, patients on haemodialysis have been excluded from this analysis. The major, significant determinants of log transformed ANP concentration were haemoglobin, β-blocker therapy, LVMI and albumin. The major determinants of log transformed BNP were GFR, LVMI, albumin, haemoglobin, β-blocker therapy and age. Left ventricular systolic dysfunction was not an independent predictor of either log ANP or log BNP level in this cohort of patients with progressive renal dysfunction. The analysis was repeated using the same multivariate linear regression model for the whole study population including haemodialysis patients. Due to interrelation between renal function and dialysis therapy, GFR was not entered into this model, and instead haemodialysis therapy was used as a categorical variable. The results, demonstrated in Table 5 show that the same variables are independently related to serum natriuretic peptide levels as in the previous model. Haemodialysis (or more plausibly ESRD requiring dialysis therapy) is an independent risk factor for a raised serum BNP.

Discussion

In other populations, measurement of circulating natriuretic peptide levels identifies patients at high risk of cardiac failure for whom further investigations and treatment are warranted [1,2]. Patients with CKD and ESRD have a variety of characteristic forms of uraemic cardiomyopathy – dilated cardiomyopathy,
systolic dysfunction and LVH – that, together with symptomatic left ventricular dysfunction, are associated with an adverse outcome [6]. There is, therefore, considerable interest in the utility of natriuretic peptide measurements in this population. Natriuretic peptides are cleared by the kidney, resulting in increased levels of natriuretic peptides in renal failure. However, the present study suggests that the dependence of natriuretic peptide levels on renal function, haemoglobin, albumin and drug therapy limits their application in the detection and monitoring of cardiac dysfunction in patients with CKD.

Serum BNP has been used to detect and monitor heart disease, and is now an established test for appropriately targeted population-based screening for LVSD. In the general population using serum BNP as a screening test in asymptomatic patients, a BNP concentration of 17.9 pg/ml (5.2 pmol/l) or more gave a sensitivity of 77% and specificity of 87% in all participants for a diagnosis of LVSD, and 92 and 72% in participants aged 55 years or older [2]. In a separate study of symptomatic heart failure patients, newly diagnosed in the primary care setting, a BNP >22.2 pmol/l gave a sensitivity, specificity and positive predictive value for the diagnosis of heart failure of 97, 84 and 70% [1]. Once the diagnosis of cardiac dysfunction has been made, it has been reported that by using serial measurements of natriuretic peptide levels to guide and intensify therapy, prognosis and time to first cardiovascular event can be reduced [14]. Although BNP is known to be dependent on renal function and, both BNP and renal dysfunction [15] are associated with patient survival in a variety of populations at risk of CVD, the influence of renal function on BNP across a spectrum of renal dysfunction requires more detailed study. We studied a population with a wide range of renal function and show, in accord with findings of other studies, that serum BNP is at least dependent on both renal as well as cardiac dysfunction, and is also dependent upon factors associated with progressive renal disease such as hypoalbuminemia, anaemia, advancing age, use of beta blocker therapy and LVH.

BNP is a 32-amino acid polypeptide containing a 17-amino acid ring common to all natriuretic peptides [16]. It is synthesized as high molecular weight preproBNP, in the ventricular myocardium, and enzymatically cleaved to proBNP in response to myocyte stretching. It is subsequently released as hormonally active BNP and inactive N-terminal-proBNP. Therefore, serum levels of both BNP and N-terminal-proBNP are elevated in patients with CHF, associated with left ventricular stretch. However, due to differences in their molecular size and metabolism, there is a variation between the utility of BNP and N-terminal-proBNP in either the diagnosis of ventricular dysfunction or hydration status in patients with either CKD or ESRD. It is secreted by the ventricles in response to myocyte stretch and is therefore believed to be a more sensitive indicator of ventricular structure and function than other natriuretic peptides. Clearance of BNP is by clearance receptors and neuropeptidases, in plasma and in tubular epithelium. Previous studies of the impact of renal clearance on BNP are conflicting [17]. Thus, although 24 h excretion of serum BNP may be increased in renal impairment [18], this observation may reflect increased production in association with left ventricular hypertrophy, and is associated with increased plasma levels. In the extreme example of patients receiving haemodialysis, where endogenous renal function is essentially absent, BNP levels are raised but are also dependent on measured ventricular mass and function. Thus, both ventricular and renal factors contribute to measured levels of BNP. It is well known that left ventricular mass increases with progression of renal disease [7] and that there is a high prevalence of systolic dysfunction in patients with advanced renal failure. The question is whether, or not, these conflicting influences limit the utility of BNP in patients with progressive renal disease or significant chronic renal failure?

We report that serum ANP and BNP increase with deteriorating renal function (Figure 1) and are related to left ventricular mass in patients with renal impairment (including those on haemodialysis). This is in keeping with a recent study showing an increase in N-terminal pro-BNP in association with deteriorating GFR and increasing LVH in asymptomatic CKD patients [8,19]. Some caution may be exerted in interpreting studies using N-terminal pro-BNP in CKD due to the differences in molecular size and mechanisms of clearance, but nonetheless, many of the findings of this study were similar to our own. Although overall, and at any given level of renal function, BNP tends to be higher in those patients with abnormal ventricular function (Figure 2) this does not provide information on the diagnostic utility of BNP against a background of deteriorating renal

### Table 5. Multivariate linear regression analysis assessing determinants of log ANP and log BNP

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio (HR)</th>
<th>Significance (P)</th>
<th>95% CI for HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>log ANP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r² = 0.274</td>
<td>Constant 3.197</td>
<td>0.000</td>
<td>(2.243, 4.152)</td>
</tr>
<tr>
<td></td>
<td>Haemoglobin -0.090</td>
<td>0.000</td>
<td>(-0.128, -0.052)</td>
</tr>
<tr>
<td></td>
<td>β-blockade 0.336</td>
<td>0.000</td>
<td>(0.182, 0.491)</td>
</tr>
<tr>
<td></td>
<td>LVMI 0.002</td>
<td>0.002</td>
<td>(0.001, 0.004)</td>
</tr>
<tr>
<td></td>
<td>Albumin -0.027</td>
<td>0.017</td>
<td>(-0.049, -0.005)</td>
</tr>
<tr>
<td><strong>log BNP</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>r² = 0.475</td>
<td>Constant 2.904</td>
<td>0.000</td>
<td>(1.744, 4.064)</td>
</tr>
<tr>
<td></td>
<td>Haemoglobin -0.115</td>
<td>0.000</td>
<td>(-0.160, -0.071)</td>
</tr>
<tr>
<td></td>
<td>β-blockade 0.556</td>
<td>0.000</td>
<td>(0.378, 0.734)</td>
</tr>
<tr>
<td></td>
<td>Haemodialysis 0.703</td>
<td>0.000</td>
<td>(0.436, 0.970)</td>
</tr>
<tr>
<td></td>
<td>Age 0.013</td>
<td>0.000</td>
<td>(0.007, 0.020)</td>
</tr>
<tr>
<td></td>
<td>Albumin -0.051</td>
<td>0.000</td>
<td>(-0.076, -0.027)</td>
</tr>
<tr>
<td></td>
<td>LVMI 0.002</td>
<td>0.034</td>
<td>(0.000, 0.004)</td>
</tr>
</tbody>
</table>

The same variables were entered in the model as Table 4 bar requirement for haemodialysis was entered instead of GFR, and all patients were included in the analysis.
function. For example, it is clear that a patient with moderate-to-severe renal impairment will have higher levels of BNP than a patient with normal renal function and LVH (Figure 3). This problem is highlighted by the area under a receiver operator characteristic curve (Figure 4) that shows the limitations of using either BNP or ANP to diagnose the presence of LVH in the presence of CKD, and the extremely low specificity for the detection of LVSD in this population.

We also identified factors – other than cardiac dimensions and renal function – that influence serum natriuretic peptide levels. These include haemoglobin, albumin, blood pressure and advancing age. Anaemia is common in CKD due to impaired iron intake and utilization as well as reduced erythropoietin production. Anaemia contributes to both the evolution of LVH in these patients as well as to volume overload and consequent systolic dysfunction. Additionally, haemoglobin has been shown to exhibit an inverse relationship with BNP in studies of patients with LVSD. Moreover, anaemia is also an important prognostic factor in patients with heart failure [20]. Further study is required to assess the influence of correction of haemoglobin in patients at a high risk of cardiovascular events, and to assess the relationship between natriuretic peptide levels, haemoglobin and hydration status. We unfortunately do not have data on erythropoietin use in this cohort of patients, as this is likely to be an important confounder in assessing the relationship between haemoglobin correction, LVH and natriuretic peptide levels. Similarly, hypoalbuminaemia is related to renal impairment due to urinary losses and malnutrition; the effect on ANP and BNP levels is likely to reflect extracellular volume expansion and associated hypervolaemia.

The influence of drug therapy on natriuretic peptide levels in patients with CKD is complex. The majority of patients with PRD have hypertension requiring therapy, frequently with multiple agents. The relationship between β-blocker therapy and raised serum natriuretic peptides may be secondary to LVH and the need for antihypertensive therapy. However, β-blocker therapy may be associated with increased levels of BNP in the early phase of therapy for heart failure, an effect that may contribute to ventricular remodelling mediated by BNP. Additionally, further insights into the complex relationship between ventricular hypertrophy and altered excretion may be inferred from the relative reduction in BNP in the renal transplant patients. In this study, restoration of renal function with a renal allograft was associated with lower BNP levels than dialysis patients compared with the haemodialysis patients and the highest quartile of GFR, despite similar degrees of LVH, adding weight that excretion may have a significant role in determining BNP levels. However, the converse was true for ANP and further study of natriuretic peptide levels pre- and post-renal transplantation is required to explore these findings.

Our study has some limitations. Although our overall population studied is moderately large, the subgroups of CKD we divided our population into are relatively small and may not compare with population based screening studies using natriuretic peptides to assess LVSD. Similarly, the haemodialysis group is smaller than the 212 haemodialysis patients studied by Mallamaci et al. [10] in a similar study. Nonetheless the CKD population is similar in size to other reports [8,19] in this population and natriuretic peptide levels in renal transplant recipients have not previously been studied. Although, by excluding patients with coronary heart disease and diabetic nephropathy, our study population is perhaps healthier than current CKD patients who have a high prevalence of these abnormalities, this ensures that rises in natriuretic peptide levels are less likely to be due to (possibly silent) myocardial ischaemia as has been reported [19]. Excluding these patients makes it unlikely that either ACE inhibitor or β-blocker therapy was prescribed for LVSD, and hence we have pharmacologically normalized ventricular dysfunction in a patient with previous heart failure. Finally, the Cockcroft–Gault equation may not be the most appropriate estimate of renal function in renal transplant recipients, who tend who have subnormal renal function.

Renal dysfunction is now an established, independent risk factor for mortality in patients with CVD. The risk is increased in patients with minor reduction in renal function and is maximal in those patients with ESRD requiring dialysis. There is a clear clinical need for improved tools to diagnose and monitor abnormal LV structure and function in patients with abnormal renal function out with the extremes of renal impairment. It appears that a BNP within the normal range is a reassuring finding, and establishes the patient in a favourable prognostic group. Even patients on haemodialysis may have a normal serum BNP in the presence of normal ventricular geometry. However, we did not find this to be a consistent finding and have shown that renal dysfunction, irrespective of cardiac function is an important confounder. Nonetheless, in keeping with other studies assessing the diagnostic utility of natriuretic peptides in ESRD [10], we have found, despite the low specificity of either ANP or BNP at all stages of renal impairment, these peptides do have a useful negative predictive value for a diagnosis of LVSD of 80.0%, 79.1% in CKD patients, 75.0%, 83.3% in haemodialysis patients and 95.0%, 90.2% in renal transplant patients for ANP and BNP, respectively (Table 3). The role, therefore, of these peptides may be an initial screening test or adding weight to ruling out a diagnosis of heart failure.

The use of natriuretic peptides, specifically BNP, that is proven in other populations is appealing. However, in studies using BNP as a screening tool for CHF, renal function has either not been reported, or has not been assessed across as wide a spectrum of CKD. Moreover, in patients with acute decompensated heart failure, renal function may deteriorate due to hypoperfusion, and there is therefore a complex relationship between serum natriuretic peptides and renal function.
This study highlights the importance of renal dysfunction in determining serum natriuretic peptide levels. Further study will be required in a larger number of patients, both with normal and impaired LV functions across a spectrum of renal dysfunction, to establish a ‘normal’ range of these peptides, corrected for glomerular filtration rate in order to permit the widespread use of BNP in particular in patients with this patient group.

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