Prognostic value of cardiac biomarkers for death in a non-dialysis chronic kidney disease population

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Abstract

**Background.** Excess mortality in patients with chronic kidney disease (CKD) is predominantly due to cardiovascular disease. We explored the prognostic value of biomarkers of cardiac overload [B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)] and inflammation [high-sensitivity C-reactive protein (hsCRP)] for all-cause mortality in patients with CKD.

**Methods.** Plasma BNP (Siemens Medical Solutions Diagnostics, Frimley, Surrey, UK) and NT-proBNP (Roche Diagnostics PLC, East Sussex, UK), and hsCRP (Siemens Medical Solutions Diagnostics) were measured at study entry. Echocardiograms were undertaken, and left ventricular mass index (LVMI) was calculated. CKD patients \((n = 213)\) were followed for up to 53 months. Kaplan–Meier survival analysis with log-rank testing and hazards ratios (HRs) were calculated for each cardiac biomarker, stratified by respective median values, as a predictor of death to assess outcome.

**Results.** Fifty-four deaths occurred. NT-proBNP concentration \(\geq 89\, \text{pmol/L} (HR\ 5.6, P < 0.0001)\), BNP concentration \(\geq 14\, \text{pmol/L} (HR\ 3.5, P < 0.001)\), NT-proBNP/BNP ratio \(\geq 6\, \text{pmol/pmol} (HR\ 2.6, P < 0.01)\) and hsCRP concentration \(\geq 4.7\, \text{mg/L} (HR\ 2.4, P < 0.01)\) were unadjusted predictors of death. Only NT-proBNP \(\geq 89\, \text{pmol/L} (HR\ 2.5, P < 0.05)\) and hsCRP \(\geq 4.7\, \text{mg/L} (HR\ 1.9, P < 0.05)\) were independent predictors of death when the HRs were adjusted for significant clinical variables (age, estimated glomerular filtration rate, LVMI and vascular disease).

**Conclusion.** NT-proBNP and hsCRP can independently predict all-cause mortality in a non-dialysis CKD population and may have a useful role in risk stratification.

**Keywords:** B-type natriuretic peptides; chronic kidney disease; high-sensitivity CRP

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**Introduction**

Cardiovascular disease is prevalent and the leading cause of death in patients with end-stage renal disease (ESRD) [1–3]. The most common manifestation of cardiovascular disease in CKD patients is left ventricular hypertrophy (LVH), predominantly as a result of hypertension and anaemia. LVH is a powerful independent predictor of cardiovascular disease in CKD patients. However, identifying which patients will suffer cardiovascular events is challenging and requires early identification and treatment. The ability to detect significant cardiovascular dysfunction at an early stage could facilitate more aggressive and focused treatment of those at increased risk.

B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are co-secreted in equimolar amounts from the heart in response to left ventricular overload. Diagnostically they are used as rule-out tests to exclude heart failure in patients presenting with shortness of breath. The natriuretic peptides have been shown to predict survival in patients with congestive heart failure [4–6]. Elevated concentrations of BNP and NT-proBNP are found in both ESRD and non-dialysis CKD patients [7–11].

Systemic inflammation plays a major role in the development of atherosclerosis leading to coronary heart disease. C-reactive protein (CRP), an acute phase protein, is the hepatic product of cytokine activation and may act as a marker of inflammatory mediators involved in atherogenic plaque progression and stability. CRP concentrations, when measured using highly sensitive assays (hsCRP), may predict future coronary events [12]. It is generally agreed that a hsCRP concentration \(> 3\, \text{mg/L}\) is a strong risk factor for a coronary event [13].

Cardiac biomarkers have been used in the risk stratification of death for ESRD patients [5,11,14,15]. However, there is little data on the outcome of patients with earlier stages of CKD. We have explored the prognostic value of biomarkers of cardiac overload (BNP and NT-proBNP) and inflammation (hsCRP) for all-cause mortality in patients...
with CKD who have yet to commence renal replacement therapy.

Methods

Patients

Two hundred and twenty-nine patients with CKD, not receiving renal replacement therapy at entry to the study, attending nephrology out-patient clinics were recruited to this single centre study between June 2003 and June 2004 during times when the investigators were available. Excluded from the study were patients with acute renal failure or a functioning renal transplant, those receiving dialysis and patients with a recent (<1 month) cardiac event. In 16 patients, insufficient plasma for analysis of BNP and NT-proBNP was obtained. A final cohort of 213 patients was analysed. The patients were followed for up to 53 months. All patients gave informed consent and the study had ethical approval from the Kent and Medway Strategic Health Authority Research Ethics Committee (REC no EK050/3/03).

Information on patient age, gender, body mass index (BMI), mean arterial blood pressure (MABP), drug history and presence or absence of diabetes mellitus, cardiovascular disease and arteriopathic disease was collated. MABP was calculated from mean diastolic and systolic blood pressure using the formula: diastolic pressure ÷ 1/3 (systolic pressure – diastolic pressure). Vascular disease was considered present if there was a history of myocardial infarction, angina, arrhythmia, valvular disease, congestive cardiac failure or a requirement for coronary intervention (angioplasty, coronary artery bypass graft or pacemaker), cerebrovascular or peripheral vascular disease.

CKD staging was based on the estimated glomerular filtration rate (eGFR) calculated using the simplified Modification of Diet in Renal Disease (MDRD) study formula [16]. Patients were stratified into stage 3 (moderate; eGFR 30–59 mL/min/1.73 m²), stage 4 (severe; eGFR 15–29 mL/min/1.73 m²) and stage 5 (failure; eGFR <15 mL/min/1.73 m²) CKD.

Analytical methods

Blood was collected in the non-fasting state. For routine analyses blood was allowed to clot at room temperature and, following centrifugation, the serum concentrations were determined within 4 h of venesection. For plasma BNP, NT-proBNP, parathyroid hormone (PTH) and blood haemoglobin measurement, blood was collected into plastic tubes containing potassium EDTA (1.8 mg/mL of blood). Aliquots of plasma and serum were frozen in plastic tubes within 3–4 h of collection at −80°C (for natriuretic peptide and hsCRP measurements, respectively) and at −20°C (for PTH measurements). PTH and natriuretic peptide analyses were undertaken within 1 month and 1 year of collection, respectively, and hsCRP was measured within 3 years of collection. Serum creatinine was measured using a compensated rate Jaffe method on an Integra 800 analyser (Roche Diagnostics Ltd, East Sussex, UK). PTH was measured using an immunochemiluminometric assay on an ADVIA Centaur analyser (Siemens Medical Solutions Diagnostics, Frimley, Surrey, UK); the reference range for this assay is 14–72 ng/L. All patients also had blood haemoglobin, serum albumin, cholesterol, calcium and phosphate measured using standard laboratory methods.

Plasma BNP concentration was determined using the ADVIA Centaur® BNP immunoassay on the ADVIA Centaur analyser (Siemens Medical Solutions Diagnostics, Frimley, Surrey, UK). Between-day imprecision (n = 10) was 7.8%, 6.7% and 5.3% at BNP concentrations of 14 pmol/L, 133 pmol/L and 488 pmol/L, respectively. The manufacturer’s proposed decision threshold for excluding heart failure, in patients without renal insufficiency, is 29 pmol/L (100 ng/L).

Plasma NT-proBNP concentration was determined using the Roche proBNP electrochemiluminescence immunoassay on the Elecsys 1010 analyser (Roche Diagnostics PLC, East Sussex, UK). Between-day imprecision (n = 11) was 2.8% and 3.7% at NT-proBNP concentrations of 23 pmol/L and 513 pmol/L, respectively. The manufacturer’s proposed decision threshold for excluding heart failure, in patients without renal insufficiency, is 10 pmol/L (84 ng/L) in males and 18 pmol/L (155 ng/L) in females for patients ≤50 years and 23 pmol/L (194 ng/L) in males and 26 pmol/L (222 ng/L) in females for patients >50 years.

Serum hsCRP concentration was determined using the Dade Behring CardioPhase hsCRP particle-enhanced immunonephelometric assay on the BN ProSpec® analyser (Siemens Medical Solutions Diagnostics). Between-day imprecision (n = 6) was 3.6% and 1.3% at hsCRP concentrations of 1.6 mg/L and 13.3 mg/L, respectively. The manufacturer’s proposed thresholds for cardiovascular risk prediction are ≤1.0 mg/L, low risk; 1.0–3.0 mg/L, average risk; and >3.0 mg/L, high risk.

Patients underwent two-dimensional targeted M-mode echocardiography, and left ventricular mass index (LVMI) (n = 201) was calculated as previously described [10].

Data analysis

Data were analysed using Analyse-it™ (Analyse-it Software Ltd, Yorkshire, UK), InStat™ (GraphPad.com), StatsDirect (Cheshire, UK) and SAS version 8.01 (SAS Institute Inc., Cary, USA). A P-value <0.05 was considered significant.

None of the data, with the exception of haemoglobin, followed a normal distribution; therefore, concentrations were compared between stage 3, 4 and 5 CKD using the Kruskal–Wallis test [non-parametric analysis of variance (ANOVA)]. Categorical variables were compared between stage 3, 4 and 5 CKD using the chi-squared test. Receiver–operator curve (ROC) analysis for NT-proBNP, BNP, NT-proBNP/BNP ratio and hsCRP as a predictor of death was undertaken to enable comparison of areas under the curve and to determine cut-off points at which the sum of sensitivity and specificity was maximized.

Survival analyses

Patients were prospectively followed for up to 53 months [median (IQR) = 40(13–47) months]. All cause mortality
was recorded. Exposure was computed from the date of blood draw until the date of death with censoring for renal replacement therapy (n = 49 patients) or renal transplantation (n = 11 patients). Differences in survival rates were compared between patients with BNP, NT-proBNP, NT-proBNP/BNP ratio or hsCRP concentrations above or below their respective median values for the cohort. Survival curves were determined using the Kaplan–Meier calculation and the significance between the curves tested using the log-rank test. Unadjusted and adjusted hazard ratios (HRs) for death were calculated using Cox’s proportional HR method. Unadjusted HRs were calculated for age, gender, BMI, MABP, eGFR, haemoglobin, parathyroid hormone, calcium × phosphate product, cholesterol, albumin, LVMl, vascular disease and diabetes mellitus. Those variables that had a significant (P < 0.05) HR were included in the Cox’s proportional HR model, and manual backward elimination was used to remove any variables that had become non-significant (P ≥ 0.05). Each cardiac biomarker was then separately entered into the model to provide adjusted HRs. The final adjusted model met the constant proportional hazards assumption. No interactions between eGFR, age and LVMl were found, and no multicollinearity was detected in the final model. The overall fit of the model was highly significant (chi-square likelihood = 44, P < 0.0001). Likelihood ratios were calculated to enable comparison of pre- and post-test probabilities of death with the biomarker assays.

### Results

Patient characteristics for the whole study population and by CKD stage are given in Table 1 and have been described in more detail previously [17]. Over the follow-up period 54 deaths occurred. Survival was decreased amongst those patients with plasma BNP (41% versus 84%, P < 0.0001), plasma NT-proBNP (43% versus 80%, P < 0.0001), plasma NT-proBNP/BNP ratio (55% versus 73%, P = 0.003) and hsCRP (53% versus 76%, P = 0.002) concentrations greater than the median for the cohort (Figure 1).

Unadjusted HRs for death were determined for a range of clinical variables (Table 2). HRs for each of the cardiac biomarkers were then adjusted for those four clinical variables that remained significant in a multiple regression model (i.e. age, eGFR, LVMl and the presence of vascular disease) (Table 3). Significant unadjusted HRs were obtained for plasma BNP (P < 0.001), NT-proBNP (P < 0.0001), NT-proBNP/BNP ratio (P < 0.01) concentrations greater than the median for the cohort (Table 3). When stratified by the accepted 3 mg/L ‘high-risk’ cut-off the unadjusted HR for hsCRP was not significant. However, a significant unadjusted HR for hsCRP was obtained for a concentration greater than the median (HR 2.4, P < 0.01) for the cohort. NT-proBNP (HR 2.5, P < 0.05) and hsCRP (HR 1.9, P < 0.05) concentrations greater than their respective median values were found to be significant independent predictors of death when the HRs were adjusted for all four
significant clinical variables. BNP and NT-proBNP/BNP ratio were not found to be significant independent predictors of death.

The use of biomarkers in combination was also explored, including the previously published cardiac troponin T (cTnT) data from the same cohort [18]. Unadjusted and adjusted HRs were calculated for the following combinations: NT-proBNP concentration ≥ the median with a hsCRP concentration ≥ the median with a cTnT concentration ≥ 0.03 µg/L, hsCRP concentration ≥ the median with a cTnT concentration ≥ 0.03 µg/L and finally NT-proBNP concentration ≥ the median with a hsCRP concentration ≥ the median and a cTnT concentration ≥ 0.03 µg/L. Non-significant unadjusted HRs and subsequently non-significant adjusted HRs were obtained for all combinations of markers (data not shown) and added no further prognostic power than that seen with the individual markers.
The likelihood of death in this population was 25% (i.e. 54 deaths in 213 patients). This likelihood rose to 36% in the presence of an NT-proBNP concentration exceeding 89 pmol/L or hsCRP concentration exceeding 4.7 mg/L (the respective negative likelihoods were 14% and 15%).

ROC analyses showed the optimal cut-off points for this cohort as 128 pmol/L for NT-proBNP, 17.9 pmol/L for BNP, 8.1 pmol/pmol for NT-proBNP/BNP ratio and 8.0 mg/L for hsCRP with areas under the curve of 0.691 [95% confidence interval (CI) 0.611–0.771, \( P < 0.0001 \)], 0.671 (95% CI 0.589–0.752, \( P < 0.0001 \)), 0.620 (95% CI 0.534–0.706, \( P < 0.01 \)) and 0.692 (95% CI 0.608–0.776, \( P < 0.0001 \)), respectively.

**Discussion**

We have compared the prognostic value of several cardiac biomarkers in a large CKD population who have yet to commence renal replacement therapy. We have shown NT-proBNP and hsCRP to be independent predictors of death in this CKD population. Our data are consistent with

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**Fig. 1.** (Continued)
studies in the haemodialysis population, where it has been shown that these same markers are predictors of mortality [15], albeit that the predictive effects we have observed have occurred at much lower NT-proBNP concentrations and higher hsCRP concentrations than those seen in the dialysis patients. A relatively small (n = 83) study of predialysis CKD patients also found NT-proBNP to be an independent predictor of mortality and cardiovascular events, which occurred in 10 patients. The effect was strongest at lower eGFRs, and consistent with our data, pre-existing cardiovascular disease was also an independent predictor of death [19].

Of the cardiac biomarkers we evaluated, NT-proBNP was the strongest significant predictor of death. This is consistent with the findings of deFilippi et al. who found that NT-proBNP, and not BNP, was an independent predictor of death in a heart failure population that had eGFRs <60 mL/min/1.73 m² [20]. BNP and NT-proBNP, upon stimulus, are released in equimolar amounts from the ventricles of the heart, and both natriuretic peptides are used clinically in the diagnosis of heart failure [6]. Why then have we observed differences between the prognostic power of BNP and NT-proBNP in this CKD cohort? Natriuretic peptide concentration is independently increased in response to increasing LVMI, and ultimately L VH, and we have previously shown that this is also true in the CKD population [10]. Natriuretic peptide concentration is also independently increased in CKD patients in response to declining GFR [10]. Almost twice the concentration of NT-proBNP (38%) appears to be retained in the circulation of CKD patients compared to BNP (21%) for every 10 mL/min/1.73 m² reduction in GFR [10]. This observation may be due to the differences in how BNP and NT-proBNP are metabolized. BNP is removed from the circulation by binding to natriuretic peptide receptors A and C and degradation by neutral endopeptidases distributed throughout the endothelium [21,22]. It is not known whether BNP metabolism alters with renal disease. In contrast, NT-proBNP binds to neither natriuretic peptide receptor A nor C and does not act as a substrate for endopeptidases. It is believed to be solely

### Table 2. Unadjusted hazard ratios for death by known clinical variables (n = 213 unless otherwise stated)

<table>
<thead>
<tr>
<th>Clinical Variable</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.08 (1.05–1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female: male (n)</td>
<td>1.07 (0.69–1.90)</td>
<td>0.8</td>
</tr>
<tr>
<td>MABP (mm Hg)</td>
<td>0.99 (0.97–1.02)</td>
<td>0.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.95 (0.90–1.00)</td>
<td>0.1</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>0.97 (0.95–0.99)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>0.76 (0.62–0.94)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Parathyroid hormone (ng/L)</td>
<td>1.00 (0.99–1.00)</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium × phosphate product (mmol²/L²)</td>
<td>1.15 (0.82–1.63)</td>
<td>0.4</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>0.86 (0.67–1.11)</td>
<td>0.2</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>0.89 (0.83–0.96)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVMI (g/m², n = 192)</td>
<td>1.01 (1.00–1.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>2.89 (1.63–5.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (n)</td>
<td>1.33 (0.75–2.37)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

CI, confidence interval; MABP, mean arterial blood pressure; eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index.

All variables included in the model were continuous, with the exception of gender, vascular disease and diabetes mellitus that were dichotomous. The significant unadjusted hazard ratios were included in a Cox’s proportional hazards ratio model where haemoglobin and albumin did not remain significant. Hazard ratios, for each biomarker, were therefore adjusted for age, eGFR, LVMI and presence of vascular disease (Table 3).

For continuous variables, the HRs are expressed as the increased risk associated with an increase (age, MABP, BMI, PTH, calcium × phosphate, cholesterol, LVMI) or decrease (eGFR, haemoglobin, albumin) of one unit (e.g. 1 year for age). For categorical variables, the HRs are expressed as risk if conditions present (vascular disease and diabetes) or if female, rather than male, compared to risk in the absence of conditions.

### Table 3. Unadjusted and adjusted hazard ratios for death by natriuretic peptides and hsCRP

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Patients at risk (n)</th>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>P-value</th>
<th>Adjusted (age, eGFR, LVMI and vascular disease)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP ≥14 pmol/L²</td>
<td>213</td>
<td>3.5 (1.8–6.6)</td>
<td>&lt;0.001</td>
<td>1.2 (0.6–2.5)</td>
<td>0.6</td>
</tr>
<tr>
<td>NT-proBNP ≥89 pmol/L²</td>
<td>213</td>
<td>5.6 (2.8–11.2)</td>
<td>&lt;0.0001</td>
<td>2.5 (1.3–5.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>NT-proBNP/BNP ≥6 pmol/pmol</td>
<td>213</td>
<td>2.6 (1.4–4.8)</td>
<td>&lt;0.01</td>
<td>1.8 (0.9–3.5)</td>
<td>0.1</td>
</tr>
<tr>
<td>hsCRP ≥3 mg/Lb</td>
<td>212</td>
<td>1.7 (0.9–3.4)</td>
<td>0.1</td>
<td>1.5 (0.8–3.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>hsCRP ≥4.7 mg/Lb</td>
<td>212</td>
<td>2.4 (1.4–4.8)</td>
<td>&lt;0.01</td>
<td>1.9 (1.0–3.8)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; CI, confidence interval; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein.

b Respective median value for the cohort.

b High-risk cut-off for hsCRP (3 mg/L).
cleared in the kidney [21], although some studies have suggested equivalent clearance of both natriuretic peptides by the kidney [23,24]. It is also becoming clear that natriuretic peptide assays may have cross reactivity with proBNP and other cleavage products, which may circulate at higher concentrations than previously thought [25]. The relative influence, if any, of these products in the current assays are not known. Whatever the mechanism, BNP concentrations as measured by the present assay are also affected by declining GFR, as described above, although the effect is not as great as that seen with NT-proBNP. In this study, having adjusted for both renal and left ventricular function, we have still observed a difference between the prognostic power of BNP and NT-proBNP.

The NT-proBNP/BNP ratio increases with declining renal function [10]. Intuitively, this has been considered to be consistent with decreased renal clearance of NT-proBNP. However, as discussed above, it could equally reflect upregulated extra-renal BNP metabolism as eGFR falls, or changes in the relative contribution of cross-reacting natriuretic peptide fragments and precursors. The NT-proBNP/BNP ratio was not a significant independent predictor of death, possibly because of its relationship to eGFR.

hsCRP was an independent predictor of death when stratified by the median (4.7 mg/L), but in our hands did not independently predict death at the widely used high-risk concentration of 3 mg/L. We are unaware of other published survival data for hsCRP in the non-dialysis CKD population. Whilst a significant difference was seen in the survival rates of those patients with hsCRP concentrations below and above the median, no significant difference in hsCRP concentration was found between the CKD stages. This is consistent with the findings of Ortega et al. who also found no association between hsCRP concentration and declining renal function in non-dialysis patients [26]. Such observations may, however, be due to survivorship bias. In contrast, some workers have found creatinine clearance to be an independent predictor of hsCRP concentration in non-dialysis CKD populations; however, these studies lacked outcome data to support the role of hsCRP in predicting mortality [27,28].

The outcome data we have presented are at odds with that observed in the dialysed population, where hsCRP was found to be a powerful cardiac biomarker for predicting all cause death at concentrations around 1–3 mg/L [15,29], although the clinical utility of hsCRP to predict death in ESRD is still under debate [30]. A range of factors could account for the differences seen between hsCRP in the pre-dialysis and dialysis populations. Exposure to the dialysis membrane, even modern biocompatible dialysis membranes, and vascular access infections are both associated with cytokine activation and may contribute to a different microinflammatory state to that observed in pre-dialysis patients.

There are several limitations in this study. At inclusion into the study, the patients were at different stages of CKD and cardiac dysfunction. This may have introduced an element of survivorship bias with CKD stage 5 patients, for example, having survived cardiovascular disease that may have killed other patients at an earlier stage of CKD. Nevertheless, this study reflects a reality situation in which patients with varying stages of disease are assessed using similar clinical approaches. As this is one of the first studies to explore the role of these biomarkers in the pre-dialysis CKD population, there is a lack of established cut-off points for each cardiac biomarker. From this population we have derived ROC cut-off points that could be applied to a separate but comparable population. Indeed, a future direction of this work is targeted at validation studies in an attempt to obtain clinically useful cut-off points.

In conclusion, cardiac biomarkers may have a useful role in risk stratification of patients with CKD. Our present work has provided evidence that NT-proBNP and hsCRP can, depending on the cut-off point used, independently predict all-cause mortality in a non-dialysis CKD population. These markers remained significant independent predictors of death even in the presence of a clinical diagnosis of vascular disease. In other words, knowledge of these markers provides additional prognostic information to that supplied by the clinical history alone, including echocardiographic assessment. The clinical challenge is what can be done for these patients to reduce progression of cardiovascular disease. This should include focussing more attention on their conventional cardiovascular risk management (e.g. blockade of the renin–angiotensin–aldosterone system [31] and other anti-hypertensive treatments, management of dyslipidaemia [32] and introducing lifestyle modifications such as smoking cessation, obesity reduction and decreased salt intake) but could extend to more aggressive interventions. There is now a need for the medical community to apply this knowledge in testing and developing interventional strategies to reduce mortality in those at greatest risk.

Acknowledgements. This study was partly funded by East Kent Hospitals NHS Trust. We are grateful to Siemens Medical Solutions Diagnostics for support with reagent costs. We would like to thank the staff of the Institute of Mathematics, Statistics and Actuarial Science, University of Kent for providing expert statistical advice to this study.

Conflict of interest statement. Prof. Price is a former employee of Siemens Medical Solutions Diagnostics. No other conflict of interest is declared.

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