Renal dysfunction, as measured by the modification of diet in renal disease equations, and outcome in patients with advanced heart failure

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Aims This study evaluates the prognostic utility of renal dysfunction estimated by the recently validated modification of diet in renal disease (MDRD) equations and compares it with the currently most promising predictor of prognosis in patients with advanced heart failure.

Methods and results We prospectively studied 182 consecutive patients with advanced chronic heart failure (CHF) referred for consideration of cardiac transplantation, with a median follow-up of 642 days. Glomerular filtration rate (GFR) was estimated using the MDRD equations and plasma taken for NT-proBNP analysis. The primary endpoint of all-cause mortality was reached in 40 patients (13.2% crude 1-year mortality), and the combined secondary endpoint of all-cause mortality or urgent CTx was reached in 44 patients. The mean GFR estimated by MDRD-1 was 58 mL/min/1.73 m². The median NT-proBNP concentration was 1505 (517–4014) pg/mL. Although GFR estimated by MDRD-1 was a univariate marker of all-cause mortality, the only predictor of either endpoint independent of other variables was an NT-proBNP concentration above the median.

Conclusion NT-proBNP appears superior to GFR estimated by MDRD in patients with advanced CHF. Moreover, NT-proBNP was able to identify patients with a poor prognosis whose GFR was already low.

KEYWORDS
Natriuretic peptides; Renal dysfunction; Prognosis; Heart failure

Introduction

Chronic heart failure (CHF) is now seen not only as a cardiac disorder but rather a cardio-renal and neurohumoral syndrome.

Renal impairment is often associated with CHF owing to renal hypoperfusion, diuretic treatment, disease-modifying heart failure therapy (ACE-inhibitors, All antagonists, aldosterone antagonists), as well as other concomitant medication and co-morbidities such as diabetes.

Serum creatinine concentration, which is often quoted as a barometer of renal impairment, is actually a poor indicator of renal function. Therefore, estimation of the glomerular filtration rate (GFR) is preferred for the accurate assessment of renal function.1 Until recently, it was not clear how best to estimate renal function in patients with heart failure. However, the modification of diet in renal disease (MDRD) equations2 have recently been validated in patients with severe CHF.3

A GFR < 60 mL/min/1.73 m² is associated with complications of renal disease.1 Moreover, a GFR estimated by creatinine clearance (CrCl) has been shown to be independently predictive of all-cause mortality in asymptomatic4 and symptomatic4–7 left ventricular systolic dysfunction. As patients with advanced heart failure are also likely to have an element of renal dysfunction, it is of interest to know how prognostically relevant this is.

The aim of this study was to evaluate the prognostic utility of renal dysfunction using a GFR estimated by the recently validated MDRD equations and to compare it with NT-proBNP, a powerful independent prognostic marker, in patients with advanced heart failure referred for consideration of cardiac transplantation.

Methods

Patient selection

We recruited 182 consecutive patients with advanced heart failure referred to the Scottish National Advanced Heart Failure Service for cardiac transplant assessment between April 2001 and March
2004. All patients had CHF secondary to left ventricular systolic dysfunction (LVEF < 35% by radionuclide ventriculography—RNVG) and were in New York Heart Association functional class II–IV. This study follows on from our previous research on NT-proBNP as a predictor of mortality in advanced heart failure, with 40 additional patients and a longer period of follow-up.8 No patients declined to take part in this research or fulfilled the exclusion criteria of age <16 years, pregnancy, or known concurrent malignancy. The local research Ethics Committee approved the study protocol and all patients gave written informed consent. The study complies with the Declaration of Helsinki.

At baseline screening, patients had a full medical history taken, clinical examination performed, and NYHA class assigned. All patients had an LVEF measured by RNVG and, where possible, a progressive exercise test to quantify their peak V\textsubscript{O\text{2}}.

Measurement of NT-proBNP
Venous blood samples were collected in ethylenediamine-tetraacetic acid-containing tubes. The samples were centrifuged at 3000 r.p.m. for 10 min at 0 °C and the plasma removed and frozen in aliquots at −70 °C until analysis. NT-proBNP was measured using a chemiluminescent immunoassay kit (Roche Diagnostics) on an Elecsys 2010 analyser. NT-proBNP has a within- and between-assay coefficients of variation of up to a maximum of 6%. The clinicians involved with the patients’ care were blinded to the neurohormone concentrations obtained.

Measurement of renal function
Serum creatinine was measured by using a kinetic alkaline picrate method, and serum albumin by the bromocresol green method. Estimated GFR (eGFR) was obtained by three methods (equations):

- **MDRD-1 equation:**
  \[
  \text{GFR (expressed in mL/min/1.73 m}^2) = 170 \\
  \times (\text{plasma creatinine})^{-0.999} \\
  \times (\text{age})^{-0.176} \\
  \times (0.762 \text{ if patient is female}) \times (1.180 \text{ if patient is black}) \\
  \times (\text{SUN})^{-0.170} \times (\text{albumin})^{0.318}
  \]

- **MDRD-2 (abbreviated) equation:**
  \[
  \text{GFR (expressed in mL/min/1.73 m}^2) = 186 \times (\text{Pcr})^{-1.154} \\
  \times (\text{age})^{-0.203} \times (0.742 \text{ if patient is female}) \\
  \times (1.212 \text{ if patient is black})
  \]

- **Cockcroft-Gault formula normalized to a body surface area of 1.73 m\(^{2}\) (creatinine clearance, expressed in mL/min/1.73 m\(^{2}\)):**
  \[
  \text{GFR (males)} = 1.23 \times \text{weight} (kg) \\
  \times (140 - \text{age})/\text{plasma creatinine (µmol/L)} \\
  \times 1.73/\text{BSA}
  \]
  \[
  \text{GFR (females)} = 1.03 \times \text{weight} (kg) \\
  \times (140 - \text{age})/\text{plasma creatinine (µmol/L)} \times 1.73/\text{BSA},
  \]

where BSA(m\(^{2}\)) = \sqrt{[\text{weight (kg)} \times \text{height (cm)}/3600]}

Follow-up
The primary endpoint was all-cause mortality. The secondary endpoint was all-cause mortality or urgent transplantation. Urgent transplantation is considered in suitable inotrope-dependent patients with end-stage heart failure who have an anticipated life expectancy of <1 week. Patients were followed up until the endpoints were reached or 1 February 2005. The median follow-up was 642 days (range 1–1378). No patients were lost to follow-up.

Data collection and statistical analysis
All patients referred to the Scottish National Advanced Heart Failure Service were assessed and followed up by a dedicated team. In particular, R.S.G. and K.S.C. ensured that data collection for each patient was as complete and accurate as possible, using computerized laboratory results, as well as having each patient’s case-notes kept within the unit for data completeness.

Data analyses were performed using the Statistical Package for Social Sciences (SPSS 13) software (SPSS Inc., Chicago, IL, USA), with assistance from the Robertson Centre for Biostatistics, Glasgow University. Normally distributed, continuous data, unless otherwise stated, are expressed as mean values (±SD). Non-normally distributed continuous data are expressed as medians (25th and 75th percentile).

Cumulative univariate adverse event rates were compared by the use of the log-rank test. Kaplan–Meier survival curves were calculated with the data dichotomized at the median values for each parameter as appropriate. Cox proportional hazards analysis was used and variables achieving \(P < 0.10\) on univariate analysis were then tested in a multiple Cox regression survival model to determine whether parameters of renal function were predictors of both the primary and secondary endpoints, independent from known risk factors (LVEF, peak V\textsubscript{O\text{2}}, NT-proBNP). A \(P < 0.05\) was considered statistically significant.

The ‘log minus log test of proportionality’ in SPSS was used to satisfy the assumption of proportional hazards with each categorical covariate assessed as the strata variable. For continuous variables, the linearity assumption was assessed by the use of transformations of each predictor variable (particularly log transformations).

Results
The baseline clinical and demographic features of the patients are described in Table 1. The population was predominantly male (80.2%). Over 80% of patients were in NYHA classes III and IV, the median LVEF was 13%, and the median peak V\textsubscript{O\text{2}} was 11.3 mL/kg/min. The mean GFR estimated by MDRD-1 was 58 mL/min/1.73 m\(^{2}\). The NT-proBNP values were skewed with a median concentration of 1505 (517–4014) pg/mL. At baseline, 99% of patients were receiving an ACE-inhibitor or angiotensin receptor blocker (mean = 61% of optimal dose), 73% a beta-receptor antagonist, and all patients were on loop diuretics, with a mean furosemide equivalent dose of 119 ± 85 mg.

Of the 182 patients, 40 reached the primary endpoint of death (13.2% crude 1-year mortality) and four were urgently transplanted. The secondary endpoint of death or urgent CTx occurred in 44 patients. A further 29 patients were transplanted during the study, but these subjects were considered survivors.

Figure 1 reveals that 36% of patients had a GFR < 50 mL/min/1.73 m\(^{2}\), 16% a GFR < 40 mL/min/1.73 m\(^{2}\), and 4% a GFR < 30 mL/min/1.73 m\(^{2}\) calculated by MDRD-1. Table 2 shows the univariate and multivariable hazard ratios on Cox regression analysis. Renal dysfunction measured by the MDRD-1 equation (and not MDRD-2 or CG) was predictive of all-cause mortality on univariate analysis, but this was not independent of other known risk factors for death, such as peak V\textsubscript{O\text{2}}, LVEF, and NT-proBNP on multivariable analysis. Indeed, NT-proBNP was the only independent predictor of all-cause mortality [HR = 2.5 (1.0–6.2), \(P = 0.04\)]. For the combined endpoint of all-cause mortality or...
Table 1  General patient characteristics in 182 patients with advanced heart failure

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Patient values (mean ± SD or %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.3 ± 10.5</td>
</tr>
<tr>
<td>Male sex</td>
<td>146 (80.2%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.7 ± 16.5</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173 ± 10</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.6 ± 4.9</td>
</tr>
<tr>
<td>NYHA class (II/III/IV)</td>
<td>36 (19.8%)/115/31 (17%)</td>
</tr>
<tr>
<td>Aetiology (IHD/DCM/other)</td>
<td>45.1%/45.6%/9.3%</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>32 (17.5%)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>13.0 (9.2–19.5)</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>19.8 (13.6–27.9)</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>11.3 ± 3.6</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138 ± 4</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>128 ± 44</td>
</tr>
<tr>
<td>Albumin (g/L)</td>
<td>44 ± 4</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>14.1 ± 1.6</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>1506 (517–4014)</td>
</tr>
<tr>
<td>MDRD-1</td>
<td>58.0 ± 18.3</td>
</tr>
<tr>
<td>MDRD-2</td>
<td>57.2 ± 18.3</td>
</tr>
<tr>
<td>Cockcroft–Gault</td>
<td>64.3 ± 19.5</td>
</tr>
<tr>
<td>Medication (%)</td>
<td></td>
</tr>
<tr>
<td>ACE-inhibitor/ARB</td>
<td>99</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>73</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>62</td>
</tr>
<tr>
<td>Loop diuretic</td>
<td>100</td>
</tr>
<tr>
<td>Thiazide</td>
<td>15</td>
</tr>
<tr>
<td>Digoxin</td>
<td>47</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD or percentage.  
ARB, angiotensin receptor blocker.  
*Non-normally distributed variables are expressed as the median (interquartile range).

Figure 1  Bar graph depicting glomerular filtration rate estimated by the MDRD-1 equation in 182 patients with advanced heart failure.

urgent cardiac transplantation, renal function, whether estimated by MDRD-1, MDRD-2, or CG, was not independently predictive of mortality or need for urgent transplantation in our study. MDRD-1 was a more powerful univariate predictor of cardiovascular mortality (not a pre-specified endpoint, therefore data not shown), but again this did not reach significance in the multivariable model.

Kaplan–Meier survival curves for all-cause mortality are depicted in Figure 2 for NT-proBNP, MDRD-1, MDRD-2, and CG. The only predictor of all-cause mortality was an NT-proBNP above the median value (log-rank statistic = 15.6, P < 0.00001). Kaplan–Meier survival curves for all-cause mortality split into quartiles of NT-proBNP and renal function estimated by MDRD-1 are shown in Figure 3. Again, the only predictor of mortality was NT-proBNP (log-rank statistic = 19.8, P = 0.0002).

A Kaplan–Meier survival curve for the integration of renal function and NT-proBNP is shown in Figure 4. Patients with an NT-proBNP concentration above the median and a GFR estimated by MDRD-1 below its median were at the highest risk of death. Importantly, however, regardless of eGFR, the groups of patients with an NT-proBNP above the median were at the highest risks of death (interaction P = 0.63).

Figure 5 shows the effect of aetiology on eGFR and NT-proBNP as prognostic markers. A low eGFR appeared to be a more discerning of an adverse prognosis in patients with non-ischaemic as opposed to ischaemic heart failure, but this did not reach significance (interaction P = 0.09). A high NT-proBNP concentration identified patients at high risk regardless of aetiology (interaction P = 0.48), although those with ischaemic heart failure and a high NT-proBNP were at the greatest risk of death.

Discussion

This study first of all highlights that advanced heart failure is associated with a poor prognosis: 22% of patients died and 24.2% either did not survive or were urgently transplanted in the median follow-up period of 642 days. The truly advanced nature of the LVSD in this transplant referral population is also highlighted by the fact that the median LVEF was 13% and the median peak VO₂ was 11.3 mL/kg/min, and 80% of patients were either in NYHA class III or IV. However, it is also apparent from this study that patients with advanced heart failure commonly have significant co-existing renal dysfunction—36% of patients had an eGFR < 50 mL/min/1.73 m². This is despite a mean creatinine of only 128 µmol/L.

Chronic renal failure is frequently associated with CHF. Its cause is multi-factorial and includes hypoperfusion, diuretics, ACE-inhibitors, All antagonists, spironolactone, other concomitant medication, and co-morbidities such as diabetes. A reduced GFR has been shown to be an independent predictor of mortality in mild-to-moderate CHF. While this study highlights the very poor prognosis of advanced heart failure in the presence of renal dysfunction, a reduced eGFR was not an independent predictor of an adverse outcome in this cohort with severe HF.

In a retrospective analysis of the SOLVD trial, moderate degrees of renal insufficiency were independently associated with higher all-cause mortality. This was largely due to heart failure progression. However, this study was in less advanced heart failure patients (33.1% NYHA class III/IV in the SOLVD treatment trial compared with 80% in this work) who were not on our current armamentarium of disease-modifying therapy. Also, renal function was estimated by Cockcroft–Gault, which we have demonstrated...
that it over-estimates GFR. It is also of note that patients with a creatinine level of >177 μmol/L were excluded from the SOLV studies.

In a more contemporary population, McAlister et al. demonstrated that renal insufficiency was independently predictive of all-cause mortality. This cohort was older [particularly those with chronic renal failure (CRF)] and had less advanced CHF. It is also of interest that a greater proportion of patients with severe CRF were female compared with those with milder degrees of CRF.

### Table 2

Univariate and multivariable hazard ratios and 95% confidence intervals for all-cause mortality and the combined endpoint of all-cause mortality or urgent transplantation

<table>
<thead>
<tr>
<th></th>
<th>Death</th>
<th>Two-degree endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate HR (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Heart rate</td>
<td>1.3 (0.7–2.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>0.6 (0.3–1.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>0.5 (0.3–1.1)</td>
<td>0.07</td>
</tr>
<tr>
<td>Peak VO₂ (mL/kg/min)</td>
<td>0.5 (0.2–1.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>0.4 (0.2–0.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>2.1 (1.1–4.2)</td>
<td>0.03</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>1.4 (0.8–2.7)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cockcroft-Gault</td>
<td>0.6 (0.3–1.1)</td>
<td>0.11</td>
</tr>
<tr>
<td>MDRD-1</td>
<td>0.5 (0.3–1.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>MDRD-2</td>
<td>0.7 (0.4–1.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>NT-proBNP (pg/mL)</td>
<td>3.2 (1.6–6.3)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

The P values in bold are statistically significant.

HR, hazard ratio; 95% CI, 95% confidence interval.

Figure 2

Kaplan–Meier survival curves for renal function, estimated with the MDRD-1, MDRD-2, and Cockcroft-Gault equations, and NT-proBNP, stratified above (broken line) and below (solid line) the median value, against all-cause mortality in 182 patients with advanced heart failure.
The CHARM study investigators have now reported on the effect of renal dysfunction estimated by the simplified MDRD-2 equation, which we have demonstrated does not predict GFR as accurately as MDRD-1. Nevertheless, the risk for all-cause mortality increased significantly below an eGFR of 60 mL/min/1.73 m² (adjusted hazard ratio 1.50, \( P = 0.006 \) for 45–60 mL/min/1.73 m² and 1.91, \( P < 0.001 \) for <45 mL/min/1.73 m²). To date, however, the CHARM cohorts have yet to report on the prognostic value of the B-type natriuretic peptides.

In a large post-MI cohort from the VALIANT trial, eGFR was a major risk factor for cardiovascular complications (death from cardiovascular causes, re-infarction, congestive heart failure, stroke, or resuscitation after cardiac arrest). This finding was in older and, more frequently, female patients with less severe CRF (mean value of 70 ± 21 mL/min/1.73 m²) than those in our cohort, and not all had LVSD. Smilde et al. demonstrated that GFR estimated by Cockcroft–Gault was a strong predictor of an adverse outcome, particularly in those patients with non-ischaemic heart failure. Similarly, we found that eGFR measured by MDRD-1 was a more discerning marker of mortality in such patients. In contrast, NT-proBNP was shown to predict mortality regardless of aetiology, although patients with ischaemic heart failure and a high NT-proBNP were at the highest risk of death.

Serum sodium was a significant univariate predictor of both endpoints in this study. This is in contrast to the CHARM study, in which serum sodium was not included in their prognostic model. This may simply reflect the advanced nature of our cohort of patients, requiring a more aggressive diuretic regime, as well as more frequent use of aldosterone antagonists—62% in our study compared with 17% in the CHARM study. However, hyponatraemia has previously been shown to be associated with a poor prognosis in other studies.

Transplant programmes often predict such renal impairment by ⁵¹Cr EDTA (⁵¹Chromium ethylenediaminetetraacetic acid). However, the MDRD equations have been shown to provide reasonably precise and accurate estimations of renal function in patients with advanced heart failure. In particular, MDRD-1 predicted GFR with higher accuracy than MDRD-2 or Cockcroft–Gault and had the best performance in predicting a GFR < 60 mL/min/1.73 m², a value below which complications of renal impairment appear.
Indeed, in our study, MDRD-1 was the method of GFR estimation that most significantly predicted mortality, although NT-proBNP appeared a better predictor on multivariable analysis. BNP and its N-terminal fragment (NT-proBNP) are now well established both in the diagnosis and in the assigning of prognosis in all stages of CHF, although further work needs to be carried out to determine suitable cut-points for use in clinical practice. In studies, the B-type natriuretic peptides have been shown to be independent predictors of morbidity and mortality in asymptomatic LVSD and in mild-to-moderate and severe CHF. In addition, BNP has also been demonstrated to be a strong, independent predictor of sudden death in patients with CHF. In this study, NT-proBNP was the only independent predictor of all-cause mortality in patients with advanced heart failure referred for heart transplantation. We have shown for the first time that NT-proBNP appears superior to the assessment of renal function by MDRD, an equation known to accurately predict GFR, in patients referred for heart transplant evaluation. Moreover, NT-proBNP was able to identify patients with a poor prognosis whose GFR is already low for most patients. This study also dispels the common misconception that NT-proBNP loses its predictive ability in patients with renal insufficiency. Indeed, patients with a high NT-proBNP and significant renal impairment were at the highest risk of death in this study. As such, this work adds weight to our previous finding that NT-proBNP appears to be a superior marker of prognosis than traditional markers of outcome in advanced heart failure.

Study limitations
Renal dysfunction is a relative contra-indication to cardiac transplantation and therefore patients with a lower GFR are less likely to be referred for consideration of this procedure. This may have introduced bias, and perhaps a larger number of patients with a wider spread of GFR would have allowed MDRD to have been a significant independent predictor of mortality.

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Conflict of Interest: none declared.

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