Kidney function in the very elderly
with hypertension: data from the hypertension
in the very elderly (HYVET) trial

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Abstract

Background: numerous reports have linked impaired kidney function to a higher risk of cardiovascular events and mortality. There are relatively few data relating to kidney function in the very elderly.

Methods: the Hypertension in the Very Elderly Trial (HYVET) was a randomised placebo-controlled trial of indapamide slow release 1.5mg ± perindopril 2–4 mg in those aged ≥80 years with sitting systolic blood pressures of ≥160 mmHg and diastolic pressures of <110 mmHg. Kidney function was a secondary outcome.

Results: HYVET recruited 3,845 participants. The mean baseline estimated glomerular filtration rate (eGFR) was 61.7 ml/min/1.73 m². When categories of the eGFR were examined, there was a possible U-shaped relationship between eGFR, total mortality, cardiovascular mortality and events. The nadir of the U was the eGFR category ≥60 and <75 ml/min/1.73 m². Using this as a comparator, the U shape was clearest for cardiovascular mortality with the eGFR <45 ml/min/1.73 m² and ≥75 ml/min/1.73 m² showing hazard ratios of 1.88 (95% CI: 1.2–2.96) and 1.36 (0.94–1.98) by comparison. Proteinuria at baseline was also associated with an increased risk of later heart failure events and mortality.

Conclusions: although these results should be interpreted with caution, it may be that in very elderly individuals with hypertension both low and high eGFR indicate increased risk.

Keywords: aged, antihypertensive, hypertension, kidney function, mortality, older people
**Introduction**

Impaired kidney function has been shown to be a predictor of death and negative cardiovascular outcomes [1–4]. Numerous reports have linked impaired kidney function, a lower estimated glomerular filtration rate (eGFR), to a higher risk of cardiovascular events and mortality [5–7]. Albuminuria, in the absence of urinary tract infection, may also be a marker for subclinical cardiovascular damage and has been associated with an increased risk of heart failure, cardiovascular events and mortality [8–11].

Hypertension too has an additional deleterious effect on kidney function [1, 12–14]. Those aged 80 and over are the fastest growing sector of the global population in whom low eGFR and hypertension are prevalent [15]. Low eGFR in those aged 75 and over has been also associated with an increased risk of hospitalisation and mortality independent of known cardiovascular co-morbidity at baseline [15, 16].

The Hypertension in the Very Elderly Trial (HYVET) was a double blind placebo-controlled trial designed to investigate the use of antihypertensive treatment in the very elderly [17]. One of the further objectives of the HYVET trial was to assess kidney function [18]. This paper reports the results of the analyses relating to kidney function focusing on the eGFR and its relationship with later cardiovascular events and mortality.

**Subjects and methods**

The HYVET trial recruited patients aged 80 and over. To enter, a baseline creatinine value of <150 µmol/l, sitting systolic blood pressures of ≥160 mmHg, a diastolic pressure of <110 mmHg and a standing systolic pressure of ≥140 mmHg were required. Full details of the protocol have been published elsewhere [18]. In brief, patients were randomised to receive indapamide slow release 1.5 mg or matching placebo to which could be added perindopril 2–4 mg or matching placebos to achieve a goal blood pressure of less than 150/80 mmHg.

Proteinuria was recorded as present or absent at baseline via dipstick with present including a trace. Trial endpoints were collected throughout the trial and validated by independent committee. The eGFR was calculated using the ‘CKD-EPI’ formula (this requires calibrated creatinine values so the available uncalibrated values were multiplied by 0.95) (personal communication, [19]). Analyses were repeated using the MDRD and Lund Malmo equations. The latter have been reported as more accurate in the elderly [5, 19, 20].

Categories of the eGFR (<45, 45–59, 60–74, 75 + ml/min/1.73 m²) were calculated following a previous report that successfully used the ‘CKD-EPI’equation in those aged ≥75 and found a ‘U’-shaped relationship between eGFR and subsequent hospitalisation. The same comparator category of 60–74 ml/min/1.73 m² was used [16]. The <30 and 30–44 categories were pooled because of small numbers. Baseline measures potentially be related to kidney function (urea, uric acid, haemoglobin, glucose, creatinine, serum sodium and potassium) were examined by quintile and Cox proportional hazard regression models employed to determine associations between baseline variables and incident total and cardiovascular mortality, cardiovascular events and heart failure. Residuals were examined to assess a model fit.

All analyses were performed on an intention to treat basis using SAS software version 9.1. The trial is registered with ClinicalTrials.gov number NCT00122811.

HYVET was funded by grants from the British Heart Foundation and Servier International. The trial was co-ordinated by the Department of Care of the Elderly, Imperial College London. Imperial was the sponsor of the trial. The analysis, the interpretation of the data, generation of the manuscript and decision to submit for publication were carried out independently of the funding bodies. All ethical and regulatory approvals were obtained.

**Results**

HYVET recruited 3,845 very elderly hypertensive participants and followed them for a mean of 2.1 years (median 1.8) (for details, see Supplementary data online, Appendix 1). The baseline characteristics shown by categories of the eGFR (calculated using the CKD-EPI equation [19]) are shown in Table 1.

Table 2 shows the adjusted hazard ratio (HR) point estimates and 95% confidence intervals (CIs) for the relationship between baseline eGFR (CKD-EPI) categories and later mortality and cardiovascular events. The point estimates suggest a possible ‘reverse J’-shaped relationship for total and cardiovascular mortality and cardiovascular event outcomes and no clear relationship with heart failure. When using the standard CKD-EPI formula adjusted for Chinese ethnicity as appropriate [21], the most striking findings were for cardiovascular events where there was a suggestion that a high baseline eGFR (≥75 ml/min/1.73 m²) may be associated with an increased risk of later cardiovascular event (HR: 1.46 (95% CI: 1.09–1.96). Also for mortality where a low eGFR (<45 ml/min/1.73 m²) showed a potential link with total (HR: 1.55; 95% CI: 1.13–2.14) and cardiovascular (HR: 1.88; 95% CI: 1.20–2.96) mortality. Repeating the analyses using eGFR calculated in accordance with the MDRD and Lund Malmo equations resulted in similar ‘U’-shaped relationships. Analyses were adjusted for age, sex and previous cardiovascular disease, further adjustment for the trial treatment group and proteinuria did not materially change the results. Re-running the analyses using the eGFR as a continuous variable and including a quadratic term confirmed the presence of a ‘U’ shape for both total and cardiovascular mortality (with nadirs of 68 and 71 ml/min/1.73 m², respectively) although not for cardiovascular events or heart failure.
Kidney function in the very elderly

Table 1. Baseline characteristics of participants with differing degrees of kidney impairment

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>eGFR &lt;45</th>
<th>eGFR 45–59</th>
<th>eGFR 60–74</th>
<th>eGFR ≥75</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%) or mean (standard deviation)</td>
<td>410 (10.7%)</td>
<td>1,194 (31.1%)</td>
<td>1,108 (28.8%)</td>
<td>1,133 (29.5%)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>84.5 (3.7)</td>
<td>83.8 (3.3)</td>
<td>83.5 (3.1)</td>
<td>83.0 (2.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>377 (92%)</td>
<td>824 (69%)</td>
<td>620 (56%)</td>
<td>505 (44.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sitting systolic blood pressure, mmHg</td>
<td>174.2 (9.0)</td>
<td>173.7 (8.9)</td>
<td>173 (9.2)</td>
<td>173.0 (19.8)</td>
<td>0.303</td>
</tr>
<tr>
<td>Creatinine µmol/l</td>
<td>120 (11.8)</td>
<td>101 (12.8)</td>
<td>85.6 (11.2)</td>
<td>68.3 (12.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urea mmol/l</td>
<td>7.0 (2.2)</td>
<td>6.6 (1.7)</td>
<td>6.3 (1.6)</td>
<td>5.8 (1.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Uric acid µmol/l</td>
<td>297 (87.9)</td>
<td>287.3 (79)</td>
<td>282.1 (79.1)</td>
<td>263.1 (77)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Haemoglobin gm/dl</td>
<td>12.5 (1.7)</td>
<td>13.1 (1.6)</td>
<td>13.3 (1.6)</td>
<td>13.4 (1.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose mmol/l</td>
<td>5.5 (1.4)</td>
<td>5.5 (1.6)</td>
<td>5.4 (1.4)</td>
<td>5.3 (1.5)</td>
<td>0.168</td>
</tr>
<tr>
<td>Diabetesb</td>
<td>38 (9.3)</td>
<td>120 (10.1)</td>
<td>107 (9.7)</td>
<td>114 (10.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25 (3.7)</td>
<td>25 (3.8)</td>
<td>25 (3.8)</td>
<td>25.9 (3.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Presence of proteinuria</td>
<td>61 (14.9%)</td>
<td>198 (16.6%)</td>
<td>116 (10.5%)</td>
<td>114 (10.1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mini-Mental State Exam</td>
<td>24.8 (3.9)</td>
<td>25.7 (3.7)</td>
<td>25.4 (4.0)</td>
<td>24.7 (4.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2. Baseline category of the eGFR and later mortality and cardiovascular events

<table>
<thead>
<tr>
<th>Category of eGFR [14] and outcome</th>
<th>&lt;45 ml/min/1.73 m² (HR, 95% CI)</th>
<th>45–59 ml/min/1.73 m² (HR, 95% CI)</th>
<th>60–74 ml/min/1.73 m², reference category (based on previous data in the elderly [11])</th>
<th>≥75 ml/min/1.73 m² (HR, 95% CI)</th>
<th>Overall significance for Cox proportional hazard regression P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortalityb</td>
<td>1.55 (1.13–2.14)</td>
<td>1.20 (0.93–1.55)</td>
<td>1</td>
<td>1.26 (0.97–1.64)</td>
<td>0.0529</td>
</tr>
<tr>
<td>CV mortalityb</td>
<td>1.88 (1.20–2.96)</td>
<td>1.37 (0.96–1.97)</td>
<td>1</td>
<td>1.36 (0.94–1.98)</td>
<td>0.0507</td>
</tr>
<tr>
<td>CVEb,b</td>
<td>1.35 (0.92–1.99)</td>
<td>1.20 (0.90–1.61)</td>
<td>1</td>
<td>1.46 (1.09–1.96)</td>
<td>0.0768</td>
</tr>
<tr>
<td>Heart failureb</td>
<td>0.93 (0.41–2.09)</td>
<td>1.06 (0.59–1.89)</td>
<td>1</td>
<td>1.42 (0.78–2.57)</td>
<td>0.6305</td>
</tr>
</tbody>
</table>

Other baseline measures creatinine, uric acid, haemoglobin, glucose, serum sodium and potassium demonstrated no relationships with these outcomes. Urea demonstrated a U-shaped relationship with cardiovascular mortality such that the highest quintile (mean 8.9 µmol/l, SD 1.5, range 7.7–19.8) was associated with a significantly higher risk of cardiovascular mortality (HR: 1.71; 95% CI: 1.16–2.54) when compared with the third quintile (mean 6.3 µmol/l, SD 0.2, range 5.9–6.7) adjusted for age, sex and the presence of cardiovascular disease at baseline. The presence of proteinuria at baseline was associated with an increased risk of later mortality (HR: 1.37; 1.05–1.78; P = 0.02 and heart failure; HR: 2.03; 1.15–3.59; P = 0.01 adjusted for age, sex and the presence of cardiovascular disease at baseline).

Discussion

Although participants with a baseline creatinine of >150 µmol/l were excluded, the calculation of the CKD-EPI eGFR adjusted for ethnicity revealed that over 10% of the participants had an eGFR <45 ml/min/1.73 m² (CKD stage 3B and above according to UK-based National Institute for Health and Clinical Excellence chronic kidney disease guidelines). In keeping with the earlier paper of Nitsch et al. [16], the HYVET data showed a ‘U’-shaped relationship with the lowest risk at eGFR category 60–74 ml/min/1.73 m² (CKD-EPI). Although not reaching conventional levels of significance, our findings suggest that high as well as low eGFR may be a marker of risk in the very elderly. The reasons for this are not clear. In very elderly individuals lower creatinine may be associated with reduced muscle mass and frailty and therefore also with an increased likelihood of later events. Participants with high serum creatinine concentrations may have been those who were maintaining their muscle mass and functioning better than those with lower creatinine values. Since the eGFR equations have not been robustly validated in the very elderly it is difficult to know whether actual GFR would have a similar relationship with events. Given the need for creatinine to be used in the equations for the eGFR this may make such equations potentially less applicable in such populations.

The trial was not designed to investigate eGFR or creatinine levels and there were few individuals particularly males at lower levels of eGFR. The truncation of creatinine values at trial entry may also explain some of the differences seen in comparison with earlier studies that included participants with wider ranges of creatinine values. Causality also cannot be determined, however, data in this age group are few and these results are in agreement with other emerging data regarding the existence of a ‘U’ shape in the elderly [16].
Further examination of the baseline variables found a relationship between proteinuria and risk of mortality and heart failure confirming findings of previous studies [2, 9–12]. Even the relatively blunt assessment of proteinuria using a dipstick may be sufficient to identify those at risk. With regard to the findings for serum urea, these may have been influenced by dehydration or an increase in catabolism. If this reflects a failure to maintain adequate hydration, or an underlying disease such as infection or cancer these data may tentatively suggest that urea may be a useful addition to the eGFR, particularly in a very elderly hypertensive population with creatinine concentrations \( \leq 150 \) \( \mu \)mol/l.

The endpoints used in the HYVET trial were validated by an independent blinded endpoints committee. Because of the age of the participants, it was not always possible to obtain a detailed cause of death and there is the possibility that some deaths from cardiovascular causes were not classified as such due to lack of sufficient information to allow the endpoint committee to be confident in allocating cause. The follow-up was also fairly short due to a significant reduction in total mortality and stroke with active treatment and the stopping of the trial at the second interim analysis. The nature of the population recruited to the trial means that these findings may not be applicable in those with dementia or requiring nursing care. Despite this the population studied here are likely to be representative of the growing healthy elderly population worldwide.

In this very elderly hypertensive population both low and high eGFR and proteinuria may be useful risk markers.

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**Key points**

- There are relatively few data available with regard to kidney function in the very elderly hypertensive population.
- These data showed a possible ‘U’ shaped relationship between cardiovascular events, mortality and baseline eGFR.
- The presence of proteinuria measured by dipstick was associated with an increased risk of mortality and heart failure.
- Both low and high eGFR may be useful risk markers in similar populations.

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The HYVET trial is registered with ClinicalTrials.gov number NCT00122811 http://clinicaltrials.gov/

The committee members and investigators for HYVET were as follows: Co-ordinating Centre: C.J.B. (lead investigator), A.E.F. (co-investigator), N.S.B. (trial coordinator), R.P. (deputy trial coordinator), HYVET coordinating team at Imperial College London (1999–2008);


Investigators: (*National co-ordinators)

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Conflicts of interest

The trial was co-ordinated by the Department of Care of the Elderly, Imperial College London. Imperial College London was the sponsor of the trial. The analysis, interpretation of the data, generation of the manuscript and decision to submit for publication were carried out independently of the funding bodies. All ethical and regulatory approvals were obtained.

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Supplementary data

Supplementary data mentioned in the text is available to subscribers in Age and Ageing online.

References

Red cell distribution width is an independent predictor of mortality in hip fracture

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Abstract

Background: the red cell distribution width (RDW), an automated measure of variability in the red blood cell size on full blood count (FBC) is an independent predictor of mortality in several disease states and in healthy older people.

Objective: we wanted to determine the prognostic value of RDW in patients following a hip fracture—a condition associated with high mortality.

Design: we examined the relationship between admission RDW and mortality in 698 consecutive patients admitted with hip fracture.

Method: regression analysis was used to examine admission RDW and subsequent mortality, adjusting for admission haemoglobin, mean corpuscular volume, age, gender, pre-morbid residence and independence level, Charlson co-morbidity index and post-operative complications.

Results: the mean age was 78 ± 13 years. Unadjusted 1-year mortality was 12, 15, 29 and 36% across quartiles of increasing RDW. Along with age and post-operative complications, RDW remained significantly associated with in-hospital, 120-day and 1-year mortality [adjusted hazard ratios: HR: 1.119, 95% CI: (1.000–1.253), P = 0.05, 1.134 (1.047–1.227), P = 0.004 and 1.131 (1.067–1.199), P < 0.001, respectively]. These relationships remained significant at all three time points on repeat analysis in non-anaemic patients (n = 548).

Conclusion: RDW, a widely available parameter on FBC, is independently associated with an increased risk of short- and long-term mortality following hip fracture.

Keywords: RDW, hip fracture, mortality, older people

Introduction

The red cell distribution width (RDW) is an automated index of red blood cell (RBC) heterogeneity performed routinely on a full blood count. High RDW indicates greater variation in the cell size. It reflects increased RBC destruction or deficient erythropoiesis resulting in the premature release of RBCs from the bone marrow. Its traditional value has been to advise on the differential diagnosis of microcytosis. Elevated RDW reflects nutritional deficiencies as well as various pathological processes including bone marrow dysfunction, systemic inflammation and oxidative stress [1–3]. Possibly through these mechanisms, RDW has become of increasing interest following its link with mortality in various