The combined contribution of albuminuria and glomerular filtration rate to the prediction of cardiovascular mortality in elderly men

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Abstract

Background. Cardiovascular risk prediction is particularly important in the primary prevention of cardiovascular disease (CVD). Yet, data on whether the combined addition of albuminuria and estimated glomerular filtration rate (eGFR) improves cardiovascular risk prediction in individuals without CVD in the community is scarce.

Methods. We investigated associations between urinary albumin excretion rate (UAER), cystatin C-based eGFR and cardiovascular mortality in a community-based cohort of elderly men (ULSAM study; n = 1113, mean age 71 years, 208 cardiovascular deaths, median follow-up 12.9 years) with prespecified analyses in participants without CVD at baseline [subsample without CVD: UAER; hazard ratio (HR) per 1 SD 1.26, 95% confidence interval (CI) 1.05–1.51, P = 0.01; eGFR: HR per 1 SD 0.74, 95% CI 0.59–0.92, P = 0.007]. Analyses of model discrimination, calibration, reclassification and global fit suggested that UAER and eGFR add relevant prognostic information beyond established cardiovascular risk factors in participants without prevalent CVD. Interestingly, established cutoffs used to diagnose microalbuminuria (UAER > 20 μg/min) and chronic kidney disease Stage 3 (eGFR < 60 mL/min/1.73m²), appeared less suitable for cardiovascular risk prediction [integrated discrimination improvement (IDI) 0.006, P = 0.11], while cutoffs UAER > 6 μg/min and eGFR < 45 mL/min/1.73m² significantly improved IDI (0.047, P < 0.001).

Conclusions. UAER and eGFR improved cardiovascular risk prediction beyond established cardiovascular risk factors, suggesting that these kidney biomarkers may be useful in predicting cardiovascular death in elderly men.

Keywords: cardiovascular diseases; epidemiology; kidney; prognosis; risk factors

Introduction

International guidelines recommend screening for albuminuria and estimated glomerular filtration rate (eGFR) in patients with hypertension or diabetes in order to identify individuals with an increased cardiovascular risk [1, 2]. It is less studied, however, whether screening for albuminuria and eGFR would substantially improve cardiovascular risk prediction in the general population.

Prior community-based studies report that the combined assessment of albuminuria and eGFR provides additional and independent prognostic information for future cardiovascular events [3–10]. However, several of these prior investigations were limited by lack of data on model discrimination, calibration and reclassification [3, 4, 6–10], use of creatinine-based eGFR equations rather than cystatin C-based eGFR equations [4–10] and inclusion of participants with prevalent cardiovascular disease (CVD) in the study sample [3–8, 10]. Additionally, all these reports used cutoffs for albuminuria and eGFR that are used to diagnose and stage albuminuria and chronic kidney disease in clinical practice in the statistical analyses and none explored optimal cutoff points for the prediction of cardiovascular events. Thus, there is a need for studies that thoroughly evaluates whether the addition of these markers of kidney damage improve the risk stratification of the individual in the primary preventive setting.

We hypothesized that the combined addition of albuminuria and eGFR to a model with established cardiovascular risk factors would improve the risk prediction for
cardiovascular death in the community and specifically in individuals free from CVD. Accordingly, we aimed to investigate whether the addition of urinary albumin excretion rate (UAER) and eGFR (evaluating, both creatinine-based and cystatin C-based glomerular filtration rate (GFR) equations), improved model discrimination, calibration and reclassification for the risk of cardiovascular mortality in a community-based sample of Swedish elderly men. As the clinical relevance of an improved cardiovascular risk prediction is highest in the primary preventive setting, we performed prespecified analyses in participants without prevalent CVD at baseline. Moreover, we aimed to identify optimal cutoffs for eGFR and UAER based on maximal improvement in model discrimination.

Materials and methods

Study sample

The design and selection criteria of the Uppsala Longitudinal Study of Adult Men (ULSAM) have been described previously [11] and on the Internet (http://www.pubcare.uu.se/ULSAM/). At the third examination cycle (1991–95), 1221 men (mean age 71 years) were investigated. Of these, 1113 had valid measurements of serum cystatin C, UAER and all covariates needed for the present study. We also examined a subgroup of 649 men who did not have prevalent CVD at baseline, as previously described [12]. All participants gave written informed consent and the Ethics Committee of Uppsala University approved the study protocol.

Clinical and biochemical evaluation at baseline

Serum cystatin C was measured by latex enhanced reagent (N Latex Cystatin C; Siemens, Deerfield, IL) using a BN ProSpec analyser (Siemens). Serum creatinine was measured with spectrophotometry using Jaffe’s reaction (Roche Diagnostics, Mannheim, Germany) using a Hitachi 717 or 911 (Roche Diagnostics). Our original Jaffe-based creatinine values were recalibrated to provide isotope dilution mass spectrometry traceable values. eGFR was calculated from creatinine by using Modification of Diet in Renal Disease (eGFRMDRD) [13] and Chronic Kidney Disease Epidemiology Collaboration (eGFRCKD-EPI) [14]. eGFR was also calculated from serum cystatin C (eGFRcys), results in milliliter per minute/1.73m² by the formula $\gamma = 77.24e^{-1.263(\text{cr})}$, and have been shown to be closely correlated with iohexol clearance [15]. UAER was calculated as the amount of albumin excreted in the urine per minute during the night. All samples during the night and the first sample of urine after rising were collected and used for the analysis (Albumin RIA 100; Pharmacia, Uppsala, Sweden).

Established cardiovascular risk factors [diabetes, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, use of lipid-lowering treatment, presence or absence of diabetes, smoking status and BMI] were used to calculate hazard ratios (HRs) for cardiovascular mortality. In these models, eGFR and UAER were modelled as continuous variables (expressed as 1 SD increases) or categorical variables (see below for description of cut-offs). In secondary analyses, we also investigated the association between eGFR, UAER and non-cardiovascular mortality.

Proportional hazards assumptions were confirmed by Schoenfeld’s tests. We also performed likelihood-ratio tests to evaluate whether the global model fit improved after the addition of kidney markers.

Methods

The increased discriminative value of the biomarkers was further examined with net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [19]. The IDI was used to identify cutoff points of eGFR and UAER to achieve optimal discrimination as previously described [12, 20]. We also analysed whether UAER and eGFR improved IDI beyond a combination of established risk factors and more recently described risk markers [NT-proBNP, Troponin I and C-reactive protein (CRP)] that previously have been shown to improve cardiovascular risk prediction in the present cohort [12].

To assess the calibration of the Cox models, we used the Gromneshy and Borgan calibration test [21], which compare the number of events that are observed with those that are expected on the basis of estimation from the models, within five risk score groups. A non-significant P-value indicates adequate calibration.

We investigated biological interaction, between eGFRcyst and UAER, by calculating the relative excess risk due to interaction (RERI) by using the methods outlined by Andersson et al. [22] In these analyses, we calculated the separate contributions to the risk of cardiovascular death from the GFRcyst category and UAER category and the interaction between the two. In the absence of the biological interaction between GFRcyst and UAER, the relative excess risk will be 0. All analyses were also performed among the participants who did not have prevalent CVD at baseline.

A two-sided P-value <0.05 was regarded as significant in all analyses. The statistical software packages STATA 10.0 (StataCorp, College Station, TX) and SAS 9.1 for Windows (SAS Institute, Cary, NC) were used.

Results

Baseline characteristics

Baseline characteristics of the whole sample and of the participants without previous CVD are presented in Table 1. During follow-up (median 12.9 years; range 0.7–15.4 years), 208 participants died from CVD (mortality rate 1.6 per 100 person-years at risk) and 261 participants died from non-cardiovascular causes (mortality rate 2.0 per 100 person-years at risk). In participants without prevalent CVD at baseline, 86 died from CVD (rate 1.1 per 100 person-years at risk).

Cox regression (continuous analyses)

In the whole cohort, higher UAER was associated with higher risk of death from CVD after adjustment for established cardiovascular risk factors and eGFR regardless of whether eGFRcyst, eGFRMDRD or eGFRCKD-EPI was included in the model (Table 2). Moreover, higher eGFRcyst, eGFRMDRD and eGFRCKD-EPI were also associated with lower risk of death from CVD independently of established risk factors and UAER (Table 2). In secondary analyses, higher eGFRcyst was associated with lower risk of non-cardiovascular mortality (multivariable HR for 1 SD increase of eGFRcyst 0.85, 95% CI 0.75–0.97, P = 0.01), while UAER, eGFRMDRD or eGFRCKD-EPI did not predict non-cardiovascular mortality (Supplementary Table 1).

In the subsample without CVD at baseline, higher UAER was associated with higher risk of cardiovascular death after adjustment for established risk factors and all eGFR equations. However, in this subsample, only eGFRcyst was significantly associated with cardiovascular mortality after adjustment for established cardiovascular risk factors and UAER (Table 2).
Reclassification after the addition of UAER and eGFR\textsubscript{cyst} to the model with the established risk factors in participants without CVD at baseline is presented in Table 4. In 12 participants who died from cardiovascular causes, reclassification was more accurate when the model with both kidney markers was used, and for seven participants, it became less accurate. Among those subjects who did not die, 62 were reclassified in a lower risk category and 33 in a higher risk category. The NRI was estimated at 0.11 (P = 0.04).

### C-statistics

In the whole cohort, the C-statistic increased significantly for the prediction of cardiovascular mortality when UAER and eGFR were incorporated into a model with the established risk factors (Table 5). In participants without CVD at baseline, the increment in the C-statistic was of similar magnitude but with wider CIs, rendering the association non-significant (P = 0.15, Table 5).

### Calibration

The P-values for the Grønnesby and Borgan statistics indicate adequate calibration for the model with UAER and eGFR, in the whole cohort (P = 0.06) and in the group of participants without prevalent CVD at baseline (P = 0.88).

### Identification of optimal cutoffs

We used eGFR\textsubscript{cyst} in the identification of optimal cutoffs for eGFR, as it was more strongly associated with cardiovascular mortality as compared to creatinine-based eGFR (Table 2).

As seen in Supplementary Figure 1, the highest levels of improved IDI were seen at eGFR\textsubscript{cyst} levels in the range of 40–50 mL/min/1.73m\(^2\). The cutoffs that achieved maximal IDI in the whole sample was eGFR 46 mL/min/1.73m\(^2\) (IDI 0.021, P < 0.001) and in participants without CVD, 45 mL/min/1.73m\(^2\) (IDI 0.036, P = 0.002; Supplementary Figure 1). For UAER, cutoffs across different ranges seemed to improve IDI and there appeared to be no single UAER range that stood out as the only suitable cutoff level (Supplementary Figures 2). In the whole sample, UAER 6 µg/min achieved maximal IDI (0.012, P = 0.001), while UAER 47 µg/min achieved maximal IDI in participants without CVD (0.017, P = 0.035). The second-best cutoff for UAER in participants without CVD (6 µg/min) had an IDI estimate of similar magnitude as the optimal cutoff (0.015, P = 0.002). As it was identical to the optimal cutoff for UAER in the whole sample, we used this cutoff in the RERI-analyses below. When both UAER and eGFR\textsubscript{cyst} were incorporated to the model with established risk factors (using the cutoffs UAER > 6 µg/min and eGFR\textsubscript{cyst} < 45 mL/min/1.73m\(^2\), respectively), the increase in IDI was 0.047 (P < 0.001).

Interestingly, the established cutoffs for eGFR and UAER used to diagnose chronic kidney disease Stage 3 and microalbuminuria (eGFR < 60 mL/min/1.73m\(^2\) and UAER > 20 µg/min, respectively) did not significantly improve IDI in participants free from CVD at baseline (IDI for the separate addition of eGFR\textsubscript{cyst} < 60 mL/min/1.73m\(^2\): 0.003, P = 0.24, for the separate addition of UAER > 20 µg/min: 0.005.

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#### Table 1. Baseline characteristics of the whole study population and in the subsample of participants without CVD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole sample (n = 1113)</th>
<th>Participants without CVD (n = 649)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>71.0 ± 6.1</td>
<td>71.0 ± 0.58</td>
</tr>
<tr>
<td>Urinary albumin excretion rate (µg/min)</td>
<td>25.3 ± 93.1</td>
<td>22.4 ± 98.7</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>1.24 ± 0.27</td>
<td>1.22 ± 0.24</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>94 ± 15</td>
<td>92 ± 14</td>
</tr>
<tr>
<td>eGFR\textsubscript{cyst} (mL/min/1.73m(^2))</td>
<td>62 ± 14</td>
<td>63 ± 13</td>
</tr>
<tr>
<td>eGFR\textsubscript{MDRD} (mL/min/1.73m(^2))</td>
<td>77 ± 11</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>eGFR\textsubscript{K-D} (mL/min/1.73m(^2))</td>
<td>75 ± 12</td>
<td>76 ± 13</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>5.8 ± 1.5</td>
<td>5.7 ± 1.3</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>147 ± 19</td>
<td>147 ± 18</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>84 ± 9</td>
<td>84 ± 9</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>26.3 ± 3.4</td>
<td>26.0 ± 3.1</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.8 ± 1.0</td>
<td>5.8 ± 1.0</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.3 ± 0.3</td>
<td>1.3 ± 0.35</td>
</tr>
<tr>
<td>Diabetes mellitus, no. (%)</td>
<td>117 (10.5)</td>
<td>55 (8.5)</td>
</tr>
<tr>
<td>Diabetes medication, no. (%)</td>
<td>61 (5.5)</td>
<td>23 (3.5)</td>
</tr>
<tr>
<td>Smoking, no. (%)</td>
<td>222 (20.0)</td>
<td>132 (20.3)</td>
</tr>
<tr>
<td>Dyslipidemia, no. (%)</td>
<td>970 (87.1)</td>
<td>563 (86.8)</td>
</tr>
<tr>
<td>Lipid-lowering treatment, no. (%)</td>
<td>100 (9.0)</td>
<td>43 (6.6)</td>
</tr>
<tr>
<td>CVD, no. (%)</td>
<td>464 (42)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Antihypertension treatment, no. (%)</td>
<td>830 (74.6)</td>
<td>460 (70.9)</td>
</tr>
<tr>
<td>Antihypertension treatment, no. (%)</td>
<td>374 (33.6)</td>
<td>142 (21.2)</td>
</tr>
</tbody>
</table>

*Date are mean ± SD for continuous variables and n (%) for dichotomous variables. HDL, high density lipoprotein.

Models that included UAER and eGFR\textsubscript{cyst} showed better global fit than models with only the established risk factors (P < 0.001).

**Integrated discrimination improvement and net reclassification improvement**

In the whole cohort, IDI estimates suggested that the combined or separate addition of UAER and eGFR to the model with establish risk factors improved the discrimination property of the model for the prediction of risk, regardless of which eGFR equation was used. In the subsample without CVD at baseline, the separate and combined addition of UAER and eGFR\textsubscript{cyst} to the model with established risk factors improved IDI beyond the established risk factors (Table 3). Furthermore, the combined addition of UAER and GFR\textsubscript{cyst} to a model with both established cardiovascular risk factors and recently described risk markers (CRP, N-terminal pro-brain natriuretic peptide and troponin I), significantly improved IDI (P < 0.02; see Supplementary Table 2 for details).
Table 2. The association between UAER, eGFR and cardiovascular mortality: multivariable Cox regression (continuous analyses)\(^a\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole sample (n = 1113)</th>
<th></th>
<th></th>
<th>Participants without CVD at baseline (n = 649)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR for 1 SD increase CI (95%)</td>
<td>P-value</td>
<td>HR for 1 SD increase CI (95%)</td>
<td>P-value</td>
</tr>
</tbody>
</table>

- Urinary albumin excretion rate (UAER)
  - Adjusted for cardiovascular risk factors: 1.25 (1.11–1.42) < 0.001 1.29 (1.07–1.56) 0.006
  - Adjusted for cardiovascular risk factors + eGFR\(_{\text{cyst}}\): 1.23 (1.09–1.39) < 0.001 1.26 (1.05–1.51) 0.01

- eGFR\(_{\text{cyst}}\)
  - Adjusted for cardiovascular risk factors: 0.72 (0.62–0.84) < 0.001 0.72 (0.58–0.90) 0.004
  - Adjusted for cardiovascular risk factors + UAER: 0.74 (0.64–0.85) < 0.001 0.74 (0.59–0.92) 0.007

- eGFR\(_{\text{MDRD}}\)
  - Adjusted for cardiovascular risk factors: 0.79 (0.68–0.91) 0.002 0.82 (0.65–1.03) 0.09
  - Adjusted for cardiovascular risk factors + UAER: 0.80 (0.69–0.93) 0.003 0.84 (0.67–1.06) 0.14

- eGFR\(_{\text{CKD-EPI}}\)
  - Adjusted for cardiovascular risk factors: 0.79 (0.69–0.89) < 0.001 0.83 (0.69–1.04) 0.10
  - Adjusted for cardiovascular risk factors + UAER: 0.80 (0.71–0.91) < 0.001 0.86 (0.69–1.07) 0.17

- eGFR\(_{\text{cyst}}\) vs. eGFR\(_{\text{MDRD}}\)
  - Adjusted for cardiovascular risk factors: 0.017 0.005 0.015 0.02
  - Adjusted for cardiovascular risk factors + UAER: 0.011 0.005 0.003 0.36

- eGFR\(_{\text{cyst}}\) vs. eGFR\(_{\text{CKD-EPI}}\)
  - Adjusted for cardiovascular risk factors: 0.011 0.005 0.003 0.25
  - Adjusted for cardiovascular risk factors + UAER: 0.015 0.002 0.002 0.17

- eGFR\(_{\text{MDRD}}\) vs. eGFR\(_{\text{CKD-EPI}}\)
  - Adjusted for cardiovascular risk factors: 0.015 0.002 0.001 0.42
  - Adjusted for cardiovascular risk factors + UAER: 0.023 < 0.001 0.023 < 0.001

\(\text{HR} = 0.20,\) and for the combined addition of eGFR\(_{\text{cyst}} < 60 \text{ mL/min/1.73m}^2\) and UAER > 20 \(\mu\)g/min: IDI 0.006, \(P = 0.11\).

**Discussion**

**Principal findings**

In this community-based sample of elderly men, UAER and eGFR (both creatinine- and cystatin C-based GFR equations) predicted cardiovascular mortality independently of established cardiovascular risk factors and of each other. In men free from CVD at baseline, only UAER and eGFR\(_{\text{cyst}}\) remained significantly associated with cardiovascular mortality. Importantly, the combined addition of UAER and eGFR\(_{\text{cyst}}\) improved model discrimination, calibration and reclassification beyond established cardiovascular risk factors suggesting that these kidney biomarkers may be useful in the prediction of cardiovascular events in...
Comparison with the literature

Our findings that albuminuria and impaired GFR provide additional and independent associations with higher risk for cardiovascular mortality are in accordance with previous community-based studies [3–10]. In a recent report from the HUNT II-study, the combination of eGFR and albuminuria improved the individual risk stratification particularly in subjects >70 years as evaluated by measures of discrimination and reclassification [5]. However, in the HUNT II-study, creatinine-based eGFR was used and the study sample included participants with prevalent CVD. We are aware of only one previous study that has reported these associations in individuals free from CVD [9]. In the study by Cirillo et al., only relative risks were reported, and no analyses of model discrimination, calibration or reclassification were presented. These statistical measures have been suggested to be highly relevant to properly evaluate the clinical utility of a potential risk factor [23].

In the present study, UAER > 6 µg/min and eGFRcyst < 45 mL/min/1.73m² were identified as suitable cutoffs in order to improve model discrimination, while the cutoffs used in clinical practice to diagnose microalbuminuria and chronic kidney disease Stage 3 (UAER > 20 µg/min and eGFR < 60 mL/min/1.73m², respectively) appeared less appropriate. However, given the variability in different cystatin C-assays, the different formulas to estimate GFR, differences between timed samples and spot samples for estimating albuminuria, as well as the high variability of eGFR with age, sex and ethnicity, the suggested optimal cutoffs in the present study should not be directly extrapolated to other study populations. This is further supported by a recent report of the present study population when participants were 50 years old, and the optimal eGFR cutoff (Cockroft-Gault) was substantially higher as compared to present analyses [20]. Before eGFR and UAER should be considered as prognostic markers in the general population, further studies are needed to validate our findings and to explore how optimal cutoff varies with different ages, ethnicities, by sex and with different ways of estimating GFR and albuminuria.

the elderly. The current established cutoffs for microalbuminuria (20 µg/min) and chronic kidney disease Stage 3 (<60 mL/min/1.73m²) used in clinical practice appeared less suitable for cardiovascular risk prediction in our elderly sample. The association between UAER, eGFR and non-cardiovascular mortality seemed weaker as compared to the association with cardiovascular mortality.

<table>
<thead>
<tr>
<th>Model with established risk factors</th>
<th>Model with established risk factors and UAER and eGFRcyst</th>
<th>C-statistic for Cox regression models predicting death from cardiovascular causes in the whole sample and participants without CVD at baseline</th>
<th>C-statistics for death from cardiovascular causes</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants who died from CVD</td>
<td>&lt;5% risk, n (%)</td>
<td>5–20% risk, n (%)</td>
<td>&gt;20% risk, n (%)</td>
<td>Total no., n (%)</td>
</tr>
<tr>
<td>&lt;5% risk</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>5–20% risk</td>
<td>3 (5.0)</td>
<td>45 (75.0)</td>
<td>12 (20.0)</td>
<td>60</td>
</tr>
<tr>
<td>&gt;20% risk</td>
<td>0 (0)</td>
<td>4 (16.0)</td>
<td>21 (84.0)</td>
<td>25</td>
</tr>
<tr>
<td>Total no.</td>
<td>4</td>
<td>49</td>
<td>33</td>
<td>86</td>
</tr>
<tr>
<td>Participants who did not die</td>
<td>&lt;5% risk, n (%)</td>
<td>5–20% risk, n (%)</td>
<td>&gt;20% risk, n (%)</td>
<td>Total no., n (%)</td>
</tr>
<tr>
<td>&lt;5% risk</td>
<td>27 (81.8)</td>
<td>6 (18.2)</td>
<td>0 (0)</td>
<td>33</td>
</tr>
<tr>
<td>5–20% risk</td>
<td>33 (7.2)</td>
<td>399 (86.9)</td>
<td>27 (5.9)</td>
<td>459</td>
</tr>
<tr>
<td>&gt;20% risk</td>
<td>0 (0)</td>
<td>29 (40.8)</td>
<td>42 (59.1)</td>
<td>71</td>
</tr>
<tr>
<td>Total no.</td>
<td>60</td>
<td>434</td>
<td>69</td>
<td>563</td>
</tr>
</tbody>
</table>

*aEstablished risk factors included age, CVD, systolic blood pressure, antihypertensive treatment, total cholesterol, HDL-cholesterol, lipid-lowering treatment, diabetes, smoking and BMI. UAER and eGFRcyst were modelled as continuous variables. The net reclassification improvement was estimated at 0.11 (P = 0.04).

Table 5. C-statistic for Cox regression models predicting death from cardiovascular causes in the whole sample and participants without CVD at baseline.

Table 4. Reclassification of participants without CVD at baseline who died from cardiovascular causes or who did not die, when adding UAER and eGFRcyst to a model with established risk factorsa
Possible mechanisms for observed associations

The present data suggest that albuminuria and impaired GFR reflect divergent aspects of cardiovascular pathology leading to overt CVD. Albuminuria has been suggested to be caused by glomerular basal membrane damage [24] as well as tubular dysfunction [25] and to be a marker of not only kidney damage but also systemic vascular damage [26]. Moreover, albuminuria has been associated with increased inflammation, coagulation defects, insulin resistance, hyperglycaemia and hypertension which may also explain the link with the development of CVD [27]. The effect of low eGFR on CVD may be mediated by loss of nephrons and parenchymal fibrosis leading to CVD through accumulation of uraemic toxins, impaired volume and blood pressure regulation and multiple metabolic abnormities, including anaemia disturbances in calcium-phosphate homeostasis, increased sympathetic nervous activity, oxidative stress and inflammation, all which are associated with accelerated atherosclerosis [28].

The seemingly large RERI-estimate for UAER and eGFRcyst in participants without CVD at baseline (Figure 1b) seem to suggest that there may exist a biological interaction, although it did not reach statistical significance in the present study. In a recent larger study with higher statistical power, a significant biological interaction between cystatin C levels and albuminuria levels was found [3]. Whether the increased risk in participants with both high albuminuria and low eGFR is mediated by unique pathologic pathways leading to CVD as compared to the separate contributions of high albuminuria and low GFR remains to be established.

Clinical implications

Even though preventive treatment is increasingly offered to people >70 years, current cardiovascular risk prediction models were not specifically designed for the elderly. Cardiovascular risk prediction models have generally been derived from younger study populations [29] and the established cardiovascular risk factors have been shown to perform worse in the elderly [30]. To date, the clinical relevance of cardiovascular risk prediction in the elderly is yet to be firmly proven but it is likely to become more important given the growing elderly population. It is noteworthy that despite the addition of both UAER and eGFRcyst to the model with established risk factors, the accuracy of the model to correctly classify the risk of the participants is far from perfect. Thus, there is a need for further studies to investigate novel risk markers in the quest for optimized cardiovascular risk prediction.

Several prior studies suggest that the risk for cardiovascular events in patients with low GFR and/or microalbuminuria may be lowered with antihypertensive treatment (in particular inhibition of the renin-angiotensin-aldosterone system) [31–34] and statin treatment [35, 36]. Some prior studies suggest that a multifactorial intervention is particularly effective [37]. Moreover, several studies have shown that a reduction in albuminuria translates to a reduction of cardiovascular events in patients with diabetes, hypertension and/or CKD [38–43]. Yet, this issue is less studied in the community-based setting. Further studies are needed in order to evaluate whether an improvement in GFR or albuminuria corresponds to a better prognosis in the primary prevention of CVD in the general population.

Strengths and limitations

Strengths of our investigation include the homogenous, community-based study sample with detailed characterization of glucometabolic variables, cardiovascular risk factors and lifestyle factors, the long-term follow-up for cardiovascular mortality, the use of several different eGFR equations and that urinary albumin excretion was assessed in timed urine samples rather than in spot samples.

Some limitations of our study need to be acknowledged. As we only examined men of the same age with a similar ethnic background, the generalizability to women or to other age and ethnic groups is unknown. This may be particularly important for the estimation of GFR [44] and albuminuria [45]. Moreover, we did not use the golden standard method to measure GFR (clearance measurements with exogenous substances) nor did we use three...
consecutive measurements of albuminuria to diagnose microalbuminuria. Yet, any potential bias by variations in UAER and GFR levels would most likely conservatively bias our risk estimates.

Summary

In summary, the combined addition of eGFR and UAER significantly improved model discrimination, calibration and reclassification beyond established cardiovascular risk factors for the prediction of cardiovascular mortality in a community-based sample of elderly men free from CVD. Cutoffs for eGFR and UAER used in clinical practice to diagnose and stage chronic kidney disease and microalbuminuria did not improve model discrimination in this study population.

Supplementary data

Supplementary data is available online at http://ndt.oxfordjournals.org.

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