Kidney function by creatinine and cystatin c and adverse cardiovascular outcomes in patients with atrial fibrillation


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On behalf of Swiss-AF and Beat-AF investigators

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Background: Atrial fibrillation (AF) patients with chronic kidney disease are at an increased risk for ischemic and bleeding events and all-cause mortality. Accurate kidney function estimation is key for risk assessment. Creatinine is commonly used to calculate the Glomerular Filtration Rate (GFR). However, cystatin c has been described to be more sensitive than creatinine independent of muscle mass, autoimmune disease, inflammation or consuming diseases. Thus, cystatin C might be superior for risk assessment in patients with AF.

Aim: We aimed to investigate the associations between kidney function, assessed by creatinine and cystatin c, and major adverse cardiovascular events (MACE), its individual components, and major bleedings.

Methods: We enrolled 3865 AF patients into two prospective, multicenter cohort studies. Creatinine and cystatin c were measured at baseline and clinical outcome events were assessed yearly. We calculated GFR using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula based on either creatinine (GFRcr), cystatin c (GFRcy) or both (GFRc2). Primary outcome was MACE, defined as a composite of stroke or systemic embolism, myocardial infarction and cardiovascular death. Secondary outcomes were the individual components of MACE and major bleeding. Multivariable adjusted Cox regression analyses were built to investigate the associations between kidney function and adverse outcome events.

Results: Mean age was 71 ± 10 years and 28% were female. Mean creatinine and cystatin levels were 103 ± 32 μmol/l and 1.2 ± 0.4 mg/l, respectively, translating to a GFRc2 of 63.8 ± 21.7 ml/min/1.73 m2. Over a median follow-up of 6 years, the incidence rates for MACE (per 100 person-years) across quartiles (Q1-Q4) of GFRc2 were 22.0, 19.6, 17.4 and 15.9, respectively (Figure). When using multivariable adjusted Cox regression analysis, MACE was significantly associated with GFRcr (per 1 standard deviation: HR 0.87 (95%CI 0.77; 0.97) p=0.01), GFRcy (HR 0.68 (CI 0.58; 0.78), p<0.001) and GFRc2 (HR 0.75 (CI 0.66; 0.86), p<0.001). This association was mainly driven by cardiovascular death (Table). Major bleeding was associated with GFRcy (HR 0.73 (0.60-0.88) p=0.001) and GFRc2 (HR 0.80 (0.67-0.95), p=0.01), but not with GFRcr (HR 0.91 (95% CI 0.78-1.07) p=0.25).

Conclusion: Among AF patients, GFR equations including cystatin c were associated both with MACE and bleeding events, while creatinine based GFR equations were only associated with MACE. Therefore, Cystatin c based GFR equations might offer more comprehensive risk stratification in AF patients.
Figure 1

Multivariate cox regression analysis

<table>
<thead>
<tr>
<th></th>
<th>All patients N=3865</th>
<th>MACE N=687</th>
<th>CV Death N=440</th>
<th>Stroke/SE N=210</th>
<th>MI N=143</th>
<th>Major Bleeding N=336</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GFR (creatinine)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.87 (0.77, 0.97)</td>
<td>0.76</td>
<td>1.17</td>
<td>0.93 (0.73, 1.20)</td>
<td>0.91 (0.78, 1.07)</td>
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<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.01</td>
<td>0.41</td>
<td>0.60 (0.32, 0.99)</td>
<td>0.25</td>
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<tr>
<td><strong>GFR (cystatin c)</strong></td>
<td>(0.58, 0.78)</td>
<td>(0.43, 0.62)</td>
<td>(0.72, 1.20)</td>
<td>(0.62, 1.17)</td>
<td>(0.60, 0.88)</td>
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<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.57</td>
<td>0.32 (0.09, 0.98)</td>
<td>0.001</td>
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<tr>
<td><strong>GFR (combined)</strong></td>
<td>(0.66, 0.86)</td>
<td>(0.52, 0.72)</td>
<td>(0.83, 1.33)</td>
<td>(0.67, 1.19)</td>
<td>(0.67, 0.95)</td>
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<tr>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.69</td>
<td>0.42 (0.19, 0.87)</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

Adjusted for: age, sex, AF-type, diabetes, previous stroke/TIA, systemic arteriosclerosis, heart failure, previous major bleeding, oral anticoagulation or antplatelet, antihypertensive, diuretics. CV = cardiovascular; MACE = major adverse cardiovascular outcome; MI = myocardial infarction; SE = systemic embolism.

Results: HR (95% CI) muper 1 standard deviation increase

Table 1