Generalisability of cardiovascular RCTs to patients with chronic kidney disease in clinical practice: a comparison between RCTs and real-world data

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Background and Aims: Randomised controlled trials (RCTs) often apply stringent eligibility criteria, which could limit the external applicability of RCTs to patients in routine clinical practice. This is specifically troublesome in the setting of chronic kidney disease (CKD) given that kidney disease is commonly used as an eligibility criterion in RCTs. In this pilot study we estimated the eligibility of patients with CKD in routine clinical practice in five major cardiovascular outcome trials - CREDENCE, DAPA-CKD, CIBIS II, CIBIS III, and AUGUSTUS - and described reasons for ineligibility.

Method: We included patients with CKD (defined as an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² or an urinary albumin creatinine ratio (UACR) >3 mg/mmol present for >3 months) from the Utrecht Patient Oriented Database (UPOD) who visited a cardiovascular outpatient clinic in the University Medical Centre Utrecht between 2012 and 2019. The eligibility criteria were extracted from the selected RCTs and consequently modelled on the patients from UPOD. The percentage of eligible patients and reasons for ineligibility were described descriptively. The percentage of eligible patients for CIBIS II and CIBIS III were only calculated for patients with heart failure, and for the AUGUSTUS trial for patients with coronary artery disease as patients with these conditions were targeted. Patients could not fulfill multiple inclusion criteria and or meet multiple exclusion criteria or both.

Results: In total, 9005 UPOD patients with CKD were included. Patients had a mean age of 65 ± 14 years, 42% was female, mean eGFR was 49 ± 17, 1741 (19%) had a history of atherosclerotic cardiovascular disease, and 765 (8%) of heart failure. Overall, 0.05% of patients would be eligible for the DAPA-CKD trial and 0% for the CREDENCE trial. Of included patients with heart failure, 2% would have been eligible for CIBIS II and 3% for CIBIS III. Of included patients with coronary artery disease, 2% would have been eligible for the AUGUSTUS trial.

Main reasons for ineligibility for DAPA-CKD were not fulfilling the inclusion criteria for eGFR (52%), eGFR (20%), or the prescription of RAAS-inhibitors (arb) (9%) or meeting the exclusion criteria for primary kidney disease (PRD, 6%), or a kidney transplant (15%), or other comorbidities. Similarly, patients were often ineligible for the CREDENCE trial because they did not fulfill the inclusion criteria for UACR (48%), eGFR (18%), HbA1c (35%), or prescription of a RAAS-inhibitor (43%) or met one of the exclusion criteria for PRD (29%), cardiovascular disease (23%), or prescription of a mineralocorticoid receptor antagonist (10%). For CIBIS II, main reasons for ineligibility were not fulfilling the inclusion criteria for left-ventricular ejection fraction (LVEF, 50%) or prescription of an ace-inhibitor (42%) or diuretic (33%) or meeting the exclusion criteria of coronary artery disease (17%) or prescription of a calcium-channel blocker (16%). For CIBIS III, patients were also ineligible because they were not fulfilling the inclusion criteria for age (46%), LVEF (46%), or prescription of diuretics (31%) or met the exclusion criteria for serum creatinine (9%) or prescription of an angiotension receptor blocker (14%). Lastly, for the AUGUSTUS trial, patients were mainly ineligible due to not fulfilling the inclusion criteria of atrial fibrillation (79%) or percutaneous coronary interventions (PCI, 91%) or meeting the eGFR exclusion criteria (14%).

Conclusion: Based on this pilot study, less than 3% of patients with CKD in routine clinical practice would be eligible to participate in cardiovascular RCTs. Patients were often ineligible because they did not fulfill the inclusion criteria and a substantial number of patients was ineligible due to kidney disease. The low eligibility rate of patients with CKD in cardiovascular trials could limit the generalisability of results to patients with CKD treated in practice. To improve generalisability, RCTs in patients with CKD should aim to include more patients who reflect the patients with CKD treated in practice.
A minority of patients with CKD in routine clinical practice would be eligible to participate in cardiovascular RCTs. This could limit the generalisability of results to patients with CKD treated in practice.

Methods

eGFR < 60 ml/min/1.73 m² or UACR > 3 mg/mmol
Real-world data from UMCU:UPOD

Eligibility criteria extracted from elected RCTs and modelled on UPOD

Trials included: CREDENCE, DAPA-CKD, CIBIS II, CIBIS III, AUGUSTUS

Results

UPOD: 9005 patients with CKD included

<table>
<thead>
<tr>
<th>Variable</th>
<th>N (%) / mean (SD)</th>
<th>Eligibility (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (14)</td>
<td>0.05</td>
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<tr>
<td>Female</td>
<td>3805 (42%)</td>
<td>0</td>
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<tr>
<td>Mean eGFR (ml/min/1.73 m²)</td>
<td>49 (17) ml/min/1.73 m²</td>
<td>4 [IQR 2–16] mg/mmol</td>
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<tr>
<td>Median UACR (mg/mmol)</td>
<td>1471 (19%)</td>
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<tr>
<td>History of cardiovascular disease</td>
<td>765 (8%)</td>
<td>2215 (24%)</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>2215 (24%)</td>
<td>0.05</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>0</td>
<td>0.05</td>
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</table>

Main reasons for ineligibility

<table>
<thead>
<tr>
<th>RCT</th>
<th>Eligibility (%)</th>
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<tbody>
<tr>
<td>DAPA-CKD</td>
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<tr>
<td>CREDENCE</td>
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<tr>
<td>CIBIS II</td>
<td>2</td>
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<tr>
<td>CIBIS III</td>
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</tr>
<tr>
<td>AUGUSTUS</td>
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Colombijn, J. et al. NDT (2024) @NDTSocial