KDIGO CLINICAL PRACTICE GUIDELINE
FOR THE MANAGEMENT OF BLOOD PRESSURE
IN CHRONIC KIDNEY DISEASE

Supplementary Tables
December 2012
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<tr>
<th>Abbreviation</th>
<th>Description</th>
<th>Definition</th>
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<tbody>
<tr>
<td>∆</td>
<td>Change</td>
<td>KDOQI Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>↓</td>
<td>Decrease</td>
<td>kg Kilogram</td>
</tr>
<tr>
<td>↑</td>
<td>Increase</td>
<td>L Liter</td>
</tr>
<tr>
<td>ACEI</td>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>LOCF Last observation carried forward</td>
</tr>
<tr>
<td>ACR</td>
<td>Albumin-creatinine ratio</td>
<td>LV Left ventricular</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blockers</td>
<td>μ Micro-</td>
</tr>
<tr>
<td>β</td>
<td>Beta</td>
<td>MAP Mean arterial pressure</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
<td>mg Milligram</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
<td>MI Myocardial infarction</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
<td>min Minute</td>
</tr>
<tr>
<td>CCB</td>
<td>Calcium channel blockers</td>
<td>mL Milliliter</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
<td>mmHg Millimeters of Mercury</td>
</tr>
<tr>
<td>CHF</td>
<td>Chronic heart failure</td>
<td>mmol Millimole</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
<td>mo Month</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
<td>mol Mole</td>
</tr>
<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
<td>nd Not documented</td>
</tr>
<tr>
<td>CV</td>
<td>Cardiovascular</td>
<td>NS Not significant</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebrovascular accident</td>
<td>NNT Number needed to treat</td>
</tr>
<tr>
<td>d</td>
<td>day</td>
<td>OR Odds ratio</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
<td>PCR Protein-creatinine ratio</td>
</tr>
<tr>
<td>dL</td>
<td>Declitrit</td>
<td>PKD Polycystic kidney disease</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
<td>pts Patients</td>
</tr>
<tr>
<td>DRI</td>
<td>Direct rennin inhibitor</td>
<td>RCT Randomized controlled trial</td>
</tr>
<tr>
<td>eCrCl</td>
<td>Estimated creatinine clearance</td>
<td>RR Relative risk</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
<td>RRT Renal replacement therapy</td>
</tr>
<tr>
<td>ERT</td>
<td>Evidence review team</td>
<td>SBP Systolic blood pressure</td>
</tr>
<tr>
<td>ESRD</td>
<td>End stage renal disease</td>
<td>SCCR Serum creatinine</td>
</tr>
<tr>
<td>ESRF</td>
<td>End stage renal failure</td>
<td>SD Standard deviation</td>
</tr>
<tr>
<td>EU</td>
<td>European union</td>
<td>UACR Urinary albumin-creatinine ratio</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
<td>UAE Urinary albumin excretion</td>
</tr>
<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
<td>UAER Urinary albumin excretion rate</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
<td>UK United Kingdom</td>
</tr>
<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
<td>UPCR Urinary protein-creatinine ratio</td>
</tr>
<tr>
<td>HR</td>
<td>Hazards ratio</td>
<td>UPE Urinary protein excretion</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
<td>US United States</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
<td>y year</td>
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Supplemental Table 1. General population RCTs comparing BP targets in CKD subgroups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Country</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Pahor 1998</td>
<td>5 y</td>
<td>US[72]</td>
<td>Placebo [No BP target]</td>
<td>216 (216) 177 (177)</td>
<td>Scr 119.4-212.2 μmol/L nd</td>
<td>172/77 (172/77) 140/70 (154/75) 37 (17%) [26 (15%)] HR 1.18 (0.72; 1.95) NS</td>
</tr>
<tr>
<td>CV Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any CV event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>36 (17%) [47 (27%)] HR 0.59 (0.38; 0.91) nd</td>
</tr>
<tr>
<td>Stroke</td>
<td>Pahor 1998</td>
<td>5 y</td>
<td>US[72]</td>
<td>Placebo [No BP target]</td>
<td>216 (216) 177 (177)</td>
<td>Scr 119.4-212.2 μmol/L nd</td>
<td>172/77 (172/77) 140/70 (154/75) 14 (7%) [22 (12%)] HR 0.51 (0.26; 1.00) nd</td>
</tr>
<tr>
<td>Any coronary event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>16 (7%) [21 (12%)] HR 0.62 (0.32; 1.19) NS</td>
</tr>
</tbody>
</table>

1 Primary outcome
### Supplemental Table 2. Evidence profile of RCTs examining the effect of blood pressure target in patients with CKD without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>2 RCTs [1° in 1 RCT] (High)</td>
<td>1934 (972)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>No difference³</td>
<td>Critical</td>
</tr>
<tr>
<td>Mortality</td>
<td>3 RCTs (High)</td>
<td>1929 (980)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Imprecision (-1)</td>
<td>Low</td>
<td>Insufficient evidence</td>
<td>Critical</td>
</tr>
<tr>
<td>CV mortality</td>
<td>2 RCTs (High)</td>
<td>1429 (708)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Imprecision (-1)</td>
<td>Moderate</td>
<td>Insufficient evidence</td>
<td>Critical</td>
</tr>
<tr>
<td>CV events</td>
<td>1 RCT (High)</td>
<td>1094 (540)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Insufficient evidence</td>
<td>Critical</td>
</tr>
<tr>
<td>ESRD</td>
<td>2 RCTs (High)</td>
<td>1927 (980)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Possible benefit for lower target</td>
<td>Critical</td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>0 RCT</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>High</td>
</tr>
<tr>
<td>Kidney function (continuous)</td>
<td>3 RCTs [1° in 1 RCT] (High)</td>
<td>1674 (833)</td>
<td>No limitation (0)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>No difference⁶</td>
<td>Moderate</td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>0 RCT</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Benefit for low target</td>
<td>High</td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>1 RCT (High)</td>
<td>754 (380)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Hyperkalemia: 0% for low BP target and 1% for usual BP target (from 1 RCT)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adverse events</td>
<td>1 RCT</td>
<td>1094 (540)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Hyperkalemia: 0% for low BP target and 1% for usual BP target (from 1 RCT)</td>
<td>Moderate</td>
</tr>
<tr>
<td>Total</td>
<td>3 RCTs</td>
<td>2269 (1140)</td>
<td>--</td>
<td>--</td>
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</tr>
</tbody>
</table>

**Balance of potential benefits and harms**

- Possible benefit from lower target for kidney outcomes
- Possibly greater benefit from lower target for kidney outcomes in higher proteinuria subgroups
- Insufficient evidence for CV outcomes

**Quality of overall evidence**

- Moderate for kidney outcomes
- Moderate for CV outcomes

---

² Trial period results were not significant. Follow up of AASK was not significant. Follow-up of MDRD showed benefit of lower target.
³ Possible benefit for individuals with proteinuria (UPCR >0.22g/g) in AASK Follow up
⁴ MDRD follow-up study was considered to be “fair” quality
⁵ Trial period results were not significant. Long-term follow-up of MDRD showed benefit of lower target.
⁶ Benefit for proteinuria subgroups in MDRD Study 1 and 2.
Supplemental Table 3. RCTs examining the effect of blood pressure targets in patients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/ 1.73 m², ESRD or death during the trial</td>
<td>AASK 2002 2006 2010&lt;sup&gt;8&lt;/sup&gt;</td>
<td>4 y</td>
<td>Lower BP [Target MAP 92] Usual BP [Target MAP 102-107]</td>
<td>380 (540) 374 (554)</td>
<td>GFR 46 mL/min/1.73 m² Mean Male 0.61g/24h Female 0.36 g/24h</td>
<td></td>
<td></td>
<td>nd</td>
<td>Risk reduction 2% (-22; 21)&lt;sup&gt;9&lt;/sup&gt;</td>
<td>NS</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/ 1.73 m² or ESRD during the trial</td>
<td>US[11;70;99 ]</td>
<td>(4 y)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nd</td>
<td>Risk reduction 2% (-31; 20)&lt;sup&gt;10&lt;/sup&gt;</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>ESRD or death during the trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>nd</td>
<td>Risk reduction 12% (-13; 32)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>First CV hospitalization and death during the trial [from post-trial follow up]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>71 (13%) [78 (14%)]</td>
<td>HR 0.84&lt;sup&gt;12&lt;/sup&gt; (0.61; 1.16)</td>
<td>NS</td>
<td>Fair&lt;sup&gt;13&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>7</sup> Shaded studies were included in previous KDOQI guideline  
<sup>8</sup> Study only included African American patients  
<sup>9</sup> Adjusted  
<sup>10</sup> Adjusted  
<sup>11</sup> Adjusted  
<sup>12</sup> Adjusted  
<sup>13</sup> From post-trial follow-up data
<table>
<thead>
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<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Outcome</th>
<th>No analyzed / Enrolled</th>
<th>Blood Pressure</th>
<th>Results</th>
</tr>
</thead>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Baseline Proteinuria</td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>eGFR 48 mL/min/1.73 m²</td>
<td>Median UPCR 0.08</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention</td>
</tr>
<tr>
<td><strong>First CV hospitalization or ESRD during the trial [from post-trial follow up]</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Doubling of Scr, ESRD, or death both phases [from post-trial follow up]</td>
<td></td>
<td></td>
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<tr>
<td>Doubling of Scr or ESRD during both phases [from post-trial follow up]</td>
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<td></td>
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<tr>
<td>ESRD or death during both phases [from post-trial follow up]</td>
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<td>Doubling of Scr, ESRD, or death in UPCR ≤0.22 [from post-trial follow up]</td>
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<sup>14</sup> Adjusted
<sup>15</sup> From post-trial follow up data
<sup>16</sup> From post-trial follow up data
<sup>17</sup> From post-trial follow up data
<sup>18</sup> From post-trial follow up data
<sup>19</sup> From post-trial follow up data
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<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Event Results</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
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<td>Doubling of Scr or ESRD in UPCR ≤0.22 [from post-trial follow up]</td>
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<td>(Baseline</td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
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<tr>
<td>ESRD or death in UPCR ≤0.22 [from post-trial follow up]</td>
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<tr>
<td>Doubling of Scr, ESRD, or death in UPCR &gt;0.22 [from post-trial follow up]</td>
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<td>(Baseline</td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
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<tr>
<td>Doubling of Scr or ESRD in UPCR &gt;0.22 [from post-trial follow up]</td>
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<td>ESRD, or death in UPCR &gt;0.22 [from post-trial follow up]</td>
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<table>
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<tr>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
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<th>P value</th>
<th>Quality</th>
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<tr>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
<td>Events No (%)</td>
<td>Intervention</td>
</tr>
<tr>
<td>181 (540)</td>
<td>176 (554)</td>
<td>eGFR 41 mL/min/1.73 m²</td>
<td>Median UPCR 0.58</td>
<td>98 (27%)</td>
<td>83 (22%)</td>
<td>HR 1.39 (1.04; 1.87)</td>
<td>0.03</td>
</tr>
<tr>
<td>119 (33%)</td>
<td>112 (30%)</td>
<td>HR 1.12 (0.87; 1.45)</td>
<td>NS</td>
<td>Fair²¹</td>
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</tr>
<tr>
<td>136 (75%)</td>
<td>149 (85%)</td>
<td>HR 0.73 (0.58; 0.93)</td>
<td>0.01</td>
<td>Fair²²</td>
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<tr>
<td>118 (65%)</td>
<td>143 (81%)</td>
<td>HR 0.67 (0.52; 0.87)</td>
<td>0.002</td>
<td>Fair²⁴</td>
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</tbody>
</table>

²⁰ From post-trial follow up data  
²¹ From post-trial follow up data  
²² From post-trial follow up data  
²³ From post-trial follow up data  
²⁴ From post-trial follow-up data
<table>
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<th>Study Year</th>
<th>Duration</th>
<th>Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESRD or death</td>
<td>MDRD Study 2 1994[46;79]</td>
<td>3 y (2 y)</td>
<td>Lower BP [MAP ≤92 mmHg]25 Usual BP [MAP ≤107 mmHg]26</td>
<td>Glomerular filtration rate (GFR) or serum creatinine (Scr) Baseline 2.0 mg/dL GFR 19 mL/min/1.73 m²</td>
<td>132 (132) 123 (123)</td>
<td>Baseline 133/81 (133/82) Achieved MAP 90 [126/77]27 (MAP 94 [134/81])</td>
<td>Events No (%) Intervention Control</td>
<td>--</td>
<td>RR 0.85 (0.60; 1.22)</td>
<td>nd</td>
</tr>
<tr>
<td>Kidney failure or all-cause mortality during the trial [from post-trial follow up]</td>
<td>MDRD 2005 US[86]</td>
<td>4 y (2 y)</td>
<td>Lower BP [Target MAP &lt;92 (&lt;125/75) or &lt;98] Usual BP [Target MAP &lt;107 (&lt;140/90) or &lt;113]</td>
<td>GFR 33 mL/min/1.73 m²</td>
<td>0.39 g/d</td>
<td>130/80 (131/80) 126/77 (134/81)</td>
<td>--</td>
<td>146 total</td>
<td>HR 0.7730 (0.54; 1.11)</td>
<td>NS</td>
</tr>
<tr>
<td>Kidney failure or all-cause mortality [from post-trial follow up]</td>
<td>AASK 2002[87] US[99]</td>
<td>6 y (2 y)</td>
<td>Lower BP [Target MAP 92] Usual BP [Target MAP 102-107]</td>
<td>GFR 46 mL/min/1.73 m²</td>
<td>Male 0.61g/24h Female 0.36 g/24h</td>
<td>380 (540) 374 (554) 152/96 (149/95) 128/78 (141/85)</td>
<td>2%</td>
<td>32</td>
<td>HR 0.7733 (0.65; 0.91)</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

**Mortality**

| All cause mortality | AASK 2002[87] US[99] | 4 y (4 y) | Lower BP [Target MAP 92] Usual BP [Target MAP 102-107] | GFR 46 mL/min/1.73 m² | Male 0.61g/24h Female 0.36 g/24h | 380 (540) 374 (554) 152/96 (149/95) 128/78 (141/85) | 2% | 32 | HR 0.7733 (0.65; 0.91) | 0.0024 | Fair34 |

---

25 For patients ≥61 y, target was ≤98 mmHg
26 For patients ≥61 y, target was ≤113 mmHg
27 The actual mean follow-up systolic and diastolic BP in the usual group were 132.7/80.2 mmHg and in the low BP group were 125.6/76.7 mmHg (Tom Greene, PhD, personal communication, October 2009)
28 Primary outcome
29 Adjusted
30 Adjusted
31 From post-trial follow up data
32 Primary outcome
33 Adjusted
34 From post-trial follow up data
35 Study only included African American patients
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR or Scr</td>
<td></td>
<td></td>
<td>RR/OR/HR</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline Proteinuria</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention (Control)</td>
<td>(95% CI)</td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
<td>(Control)</td>
<td></td>
</tr>
<tr>
<td>Death [from post-trial follow up]</td>
<td>MDRD 2005 US[86]</td>
<td>6 y (2 y)</td>
<td>Lower BP [Target MAP (&lt;92 (&lt;125/75) or &lt;98)]</td>
<td>432 (432)</td>
<td>408 (408)</td>
<td>130/80 (131/80)</td>
<td>126/77 (134/81)</td>
<td>10% [6%]</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Usual BP [Target MAP (&lt;107 (&lt;140/90) or &lt;113)]</td>
<td>36 Success</td>
<td>36 Failure</td>
<td>26/108 (26/108)</td>
<td>36/111 (36/111)</td>
<td>9% [3%]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR 33 mL/min/1.73 m²</td>
<td>0.39 g/d</td>
<td></td>
<td>1.06 [0.76; 1.49]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UPE 2.9 g/d</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Death</td>
<td>REIN 2 2005 Italy[85]</td>
<td>Median 19 mo (36 y)</td>
<td>Conventional BP [DBP (&lt;90)]</td>
<td>168 (169)</td>
<td>167 (169)</td>
<td>136/84 (137/84)</td>
<td>134/82 (130/80)</td>
<td>3 [2%]</td>
<td>RR 1.49 [0.25; 8.81]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensified BP [(&lt;130/80)]</td>
<td>36 Success</td>
<td>36 Failure</td>
<td>3 [2%]</td>
<td>RR 1.49 [0.25; 8.81]</td>
<td>nd</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Scc 2.7 μmol/L</td>
<td>GFR 34 mL/min/1.73 m²</td>
<td>UPE 2.9 g/d</td>
<td></td>
<td>1.49 [0.25; 8.81]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Male 0.61g/24h</td>
<td>Female 0.36 g/24h</td>
<td></td>
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<tr>
<td>CV mortality</td>
<td>AASK 2002 2006 US[70;99]</td>
<td>6 y (4 y)</td>
<td>Lower BP [Target MAP 92]</td>
<td>380 (540)</td>
<td>374 (554)</td>
<td>152/96 (149/95)</td>
<td>128/78 (141/85)</td>
<td>1% [1%]</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Usual BP [Target MAP 102-107]</td>
<td>540 (540)</td>
<td>554 (554)</td>
<td>16 (3%)</td>
<td>HR 0.98 [0.48; 2.01]</td>
<td>NS</td>
</tr>
<tr>
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<td></td>
<td>GFR 46 mL/min/1.73 m²</td>
<td>Male 0.61g/24h</td>
<td>Female 0.36 g/24h</td>
<td>1% [1%]</td>
<td>nd</td>
</tr>
<tr>
<td>CV death</td>
<td>REIN 2 2005 Italy[85]</td>
<td>Median 19 mo (36 y)</td>
<td>Conventional BP [DBP (&lt;90)]</td>
<td>168 (169)</td>
<td>167 (169)</td>
<td>136/84 (137/84)</td>
<td>134/82 (130/80)</td>
<td>1% [1%]</td>
<td>RR 0.99 [0.06; 15.76]</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Intensified BP [(&lt;130/80)]</td>
<td>36 Success</td>
<td>36 Failure</td>
<td>1% [1%]</td>
<td>RR 0.99 [0.06; 15.76]</td>
<td>nd</td>
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<tr>
<td></td>
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<td></td>
<td>Scc 2.7 μmol/L</td>
<td>GFR 34 mL/min/1.73 m²</td>
<td>UPE 2.9 g/d</td>
<td></td>
<td>0.99 [0.06; 15.76]</td>
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<td>Male 0.61g/24h</td>
<td>Female 0.36 g/24h</td>
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<tr>
<td>CV events (composite)</td>
<td>AASK 2002 2006 US[70;99]</td>
<td>4 y (4 y)</td>
<td>Lower BP [Target MAP 92]</td>
<td>380 (540)</td>
<td>374 (554)</td>
<td>152/96 (149/95)</td>
<td>128/78 (141/85)</td>
<td>2% [3%]</td>
<td>nd</td>
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<tr>
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<td>Usual BP [Target MAP 102-107]</td>
<td>540 (540)</td>
<td>554 (554)</td>
<td>108 (20%)</td>
<td>HR 1.06 [0.76; 1.49]</td>
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<td>CV events</td>
<td>Stroke events</td>
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<td>Lower BP [Target MAP 92]</td>
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<td>374 (554)</td>
<td>152/96 (149/95)</td>
<td>128/78 (141/85)</td>
<td>2% [3%]</td>
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<td>Usual BP [Target MAP 102-107]</td>
<td>540 (540)</td>
<td>554 (554)</td>
<td>108 (20%)</td>
<td>HR 1.06 [0.76; 1.49]</td>
<td>NS</td>
</tr>
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<td></td>
<td>GFR 46 mL/min/1.73 m²</td>
<td>Male 0.61g/24h</td>
<td>Female 0.36 g/24h</td>
<td>2% [3%]</td>
<td>nd</td>
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<td>UPE 2.9 g/d</td>
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<td></td>
<td></td>
<td></td>
<td>Male 0.61g/24h</td>
<td>Female 0.36 g/24h</td>
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<td>Scc 2.7 μmol/L</td>
<td>GFR 34 mL/min/1.73 m²</td>
<td>UPE 2.9 g/d</td>
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<td>1.06 [0.76; 1.49]</td>
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<td></td>
<td>Male 0.61g/24h</td>
<td>Female 0.36 g/24h</td>
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36 Noted as statistically significant in letter to Annals by Good, 2005
37 From post-trial follow up data
38 Calculated by ERT
39 Study only included African American patients
40 Adjusted
41 Calculated by ERT
42 Study only included African American patients
43 Adjusted
44 Calculated by ERT
45 Calculated by ERT
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<th>Study Year</th>
<th>Year</th>
<th>Country (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>CAD events</td>
<td>2002 US[99]</td>
<td>4 y (4 y)</td>
<td>Lower BP [Target MAP 92]</td>
<td>Male</td>
<td>GFR 46 mL/min/1.73 m²</td>
<td>0.61 g/24h</td>
<td>nd</td>
<td>19 (4%)</td>
<td>18 (4%)</td>
<td>0.85 (0.47; 1.54)</td>
<td>nd</td>
<td>Good</td>
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<tr>
<td>ESRD during trial</td>
<td>2005 US[86]</td>
<td>4 y (2 y)</td>
<td>Low BP [Target MAP &lt;92 (&lt;125/75) or &lt;98]</td>
<td>nd</td>
<td>GFR 33 mL/min/1.73 m²</td>
<td>0.39 g/d</td>
<td>nd</td>
<td>127 total</td>
<td>HR 0.76 (0.52; 1.10)</td>
<td>NS</td>
<td>Fair 49</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD from post-trial follow up</td>
<td>2005 Italy[85]</td>
<td>6 y (2 y)</td>
<td>Conventiona l BP [DBP &lt;90]</td>
<td>nd</td>
<td>Scr 2.7 μmol/L</td>
<td>GFR 34 mL/min/1.73 m²</td>
<td>UPE 2.9 g/d</td>
<td>34 (20%)</td>
<td>RR 0.89 (0.59; 1.34)</td>
<td>NS</td>
<td>Good</td>
<td></td>
<td></td>
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<tr>
<td>ESRD in pts with proteinuria &lt;3g/24h</td>
<td>2005 Italy[85]</td>
<td>Median 19 mo (36 mo)</td>
<td>Intensified BP [DBP &lt;90]</td>
<td>nd</td>
<td>Scr 2.7 μmol/L</td>
<td>GFR 36 mL/min/1.73 m²</td>
<td>UPE 1.8 g/d</td>
<td>--</td>
<td>HR 0.94 (0.45; 1.96)</td>
<td>NS</td>
<td>Fair</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD in pts with proteinuria ≥3g/24h</td>
<td>2005 Italy[85]</td>
<td>62 (169)</td>
<td>Scr 2.7 μmol/L</td>
<td>GFR 31 mL/min/1.73 m²</td>
<td>UPE 4.9 g/d</td>
<td>--</td>
<td>HR 0.92 (0.45; 1.81)</td>
<td>NS</td>
<td>Fair</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

46 Calculated by ERT
47 Study only included African American patients
48 Adjusted
49 From post-trial follow-up data
50 Adjusted
51 From post-trial follow-up data
52 Calculated by ERT
### Supplemental Table 4. RCTs examining the effect of blood pressure targets in patients with CKD without DM [continuous outcomes] 53

<table>
<thead>
<tr>
<th>Outcome (Units)</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or ( \text{Scr} )</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>( \Delta )</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Acute slope. ( \Delta )GFR in first 3 mo, mL/min/1.73 m²/y</td>
<td>AASK 2002US[54]</td>
<td>4 y (4 y)</td>
<td>Lower BP [Target MAP 92]</td>
<td>380 (540)</td>
<td>374 (554)</td>
<td>Male 0.61g/24h Female 0.36 g/24h</td>
<td>152/96 (149/95)</td>
<td>128/78 (141/85)</td>
<td>4655 (45)</td>
<td>-2.11 (-2.32)</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic slope: ( \Delta )GFR after first 3 mo, mL/min/1.73 m²/y</td>
<td></td>
<td></td>
<td>Usual BP [Target MAP 102-107]</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Total slope56: ( \Delta )GFR over 4 y, mL/min/1.73 m²/y</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>Mean difference (lower vs. usual)</td>
<td>-1.82</td>
<td>&lt;0.001</td>
<td>Good</td>
</tr>
<tr>
<td>**Acute slope, ( \downarrow ) GFR in patients with GFR 25-55 mL/min/1.73 m², mL/min/4 mo</td>
<td>MDRD Study 1 1994 1995 US[46;79]</td>
<td>4 mo (2 y)</td>
<td>Low BP [MAP ≤92 mmHg][57]</td>
<td>285 (285)</td>
<td>300 (300)</td>
<td>( \text{Scr} ) 2.0 mg/dL GFR 38 mL/min/1.73 m²</td>
<td>132/81 (132/82)</td>
<td>126/77[59] (MAP 94 [134/81])</td>
<td>38 (39)</td>
<td>-3.4 (-1.9)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

53 Shaded studies were included in previous KDOQI guideline
54 Study only included African American patients
55 Primary outcome
56 The results of the blood pressure comparison differed significantly depending on the level of baseline proteinuria for the acute slope (P=0.008) and total slopes (P=0.004) but not for the chronic slope (P=0.16).
57 For patients ≥61, target was ≤98 mmHg
58 For patients ≥61, target was ≤113 mmHg
59 The actual mean follow-up systolic and diastolic BP in the usual group were 132.7/80.2 mmHg and in the low BP group were 125.6/76.7 mmHg (Tom Greene, PhD, personal communication, October 2009)
<table>
<thead>
<tr>
<th>Outcome (Units)</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr.</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic slope, ↓GFR in patients with GFR 25-55 mL/min/1.73 m², mL/min/3y</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
<td>4 mo-3y (2 y)</td>
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<tr>
<td>Total slope, ↓GFR in patients with GFR 25-55 mL/min/1.73 m², mL/min/3y</td>
<td>3 y (2 y)</td>
<td>3 y (2 y)</td>
<td>3 y (2 y)</td>
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<td>3 y (2 y)</td>
</tr>
<tr>
<td>Total slope, ↓GFR in subgroup of patients with GFR 25-55 and proteinuria &gt;0.25 g/d</td>
<td>132 (132)</td>
<td>123 (123)</td>
<td>132 (132)</td>
<td>123 (123)</td>
<td>132/81 (132/81)</td>
<td>123/81 (123/82)</td>
<td>132/81 (132/81)</td>
<td>123/81 (123/82)</td>
</tr>
<tr>
<td>Total slope, ↓GFR in subgroup of patients with GFR 13-24 mL/min/1.73 m², mL/min/3y</td>
<td>3 y (2 y)</td>
<td>3 y (2 y)</td>
<td>3 y (2 y)</td>
<td>3 y (2 y)</td>
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</table>

60 By interaction analysis
61 The actual mean follow-up systolic and diastolic BP in the usual group were 132.7/80.2 mmHg and in the low BP group were 125.6/76.7 mmHg (Tom Greene, PhD, personal communication, October 2009)
62 By interaction analysis
<table>
<thead>
<tr>
<th>Outcome (Units)</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or $S_Cr$</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tr>
<td>Median rate of ↓GFR, mL/min/1.73 m²/mo</td>
<td>REIN 2 2005 Italy[85]</td>
<td>Median 19 mo (36 y)</td>
<td>Conventional BP [DBP &lt;90]</td>
<td>Intensified BP [&lt;130/80]</td>
<td>$S_Cr$ 2.7 μmol/L GFR 34 mL/min/1.73 m²</td>
<td>UPE 2.9 g/d</td>
<td>168 (169)</td>
<td>167 (169)</td>
<td>0.24 (IQR 0.0001; 0.56)</td>
<td>[0.22 (IQR 0.06; 0.55)]</td>
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<tr>
<td>Median rate of ↓CrCl, mL/min/1.73 m²/mo</td>
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<tr>
<td>Rate of ↓GFR in pts with proteinuria &lt;3g/24h, mL/min/1.73 m²/mo</td>
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<tr>
<td>Rate of ↓GFR in pts with proteinuria ≥3g/24h, mL/min/1.73 m²/mo</td>
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</table>

Proteinuria

| %ΔProteinuria (geometric mean UPCR) | AASK 2002[83] US[99] | 4 y (4 y) | Lower BP [Target MAP 92] | Usual BP [Target MAP 102-107] | GFR 46 mL/min/1.73 m² | Male 0.61g/24h Female 0.36 g/24h | Male 0.61; Female 0.36 (Male 0.61; Female 0.46) | -17% (+7%) | <0.001 | Good |

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63 Study only included African American patients
### Supplemental Table 5. General population RCTs comparing ARB vs. CCB in CKD subgroups with and without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Country</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td>Baseline GFR or Scr (Treatment)</td>
<td>Baseline Proteinuria</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events (%) Intervention [Control]</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
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<td></td>
<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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<tr>
<td>Sudden death</td>
<td>CASE-J</td>
<td>3 y (3 y)</td>
<td>Japan[87]</td>
<td>Candesartan Amlodipine</td>
<td>1376 (1376) 1344 (1344) nd nd</td>
<td>163/92 (163/92) 136/77 (135/77)</td>
<td>8 (1%) [12 (1%)]</td>
<td>RR 0.6564 (0.27; 1.59)</td>
</tr>
<tr>
<td><strong>CV Events</strong></td>
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<td></td>
<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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<tr>
<td>Cerebrovascular events⁶⁵</td>
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<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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<tr>
<td>CV events</td>
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<td></td>
<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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<tr>
<td>Cardiac events⁶⁷</td>
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<td></td>
<td></td>
<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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</tr>
<tr>
<td>Cerebrovascular events⁶⁹ in patients with CKD Stage 3</td>
<td>CASE-J</td>
<td>3 y (3 y)</td>
<td>Japan[87]</td>
<td>Candesartan Amlodipine</td>
<td>1140 (1140) 1125 (1125) nd nd</td>
<td>163/92 (163/92) 136/77 (135/77)</td>
<td>72 (6%) [71 (6%)]</td>
<td>RR 1.00⁶⁷ (0.73; 1.37)</td>
</tr>
<tr>
<td>CV events in patients with CKD Stage 3</td>
<td>CASE-J</td>
<td>3 y (3 y)</td>
<td>Japan[87]</td>
<td>Candesartan Amlodipine</td>
<td>1140 (1140) 1125 (1125) nd nd</td>
<td>163/92 (163/92) 136/77 (135/77)</td>
<td>72 (6%) [71 (6%)]</td>
<td>RR 1.00⁶⁷ (0.73; 1.37)</td>
</tr>
<tr>
<td>Cardiac events⁶⁷ in patients with CKD Stage 3</td>
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<td></td>
<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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<tr>
<td>Cerebrovascular events⁷⁴ in patients with CKD Stage 4</td>
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<td></td>
<td>Baseline Intervention Control</td>
<td>Achieved Intervention Control</td>
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</tbody>
</table>

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⁶⁴ Calculated by ERT  
⁶⁵ New occurrence or reoccurrence of a stroke or transient ischemic attack  
⁶⁶ Calculated by ERT  
⁶⁷ New occurrence, aggravation, or reoccurrence of heart failure, angina pectoris, or acute MI  
⁶⁸ Calculated by ERT  
⁶⁹ New occurrence or reoccurrence of a stroke or transient ischemic attack  
⁷⁰ Calculated by ERT  
⁷¹ Calculated by ERT  
⁷² New occurrence, aggravation, or reoccurrence of heart failure, angina pectoris, or acute MI  
⁷³ Calculated by ERT  
⁷⁴ New occurrence or reoccurrence of a stroke or transient ischemic attack  
⁷⁵ Calculated by ERT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>Intervention</th>
<th>Control</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV events in patients with CKD Stage 4</td>
<td></td>
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<td></td>
<td>9 (14%) [18 (30%)] RR 0.48</td>
<td>(0.23; 0.98)</td>
<td>nd</td>
</tr>
<tr>
<td>Cardiac events in patients with CKD Stage 4</td>
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<td></td>
<td>3 (5%) [1 (2%)] RR 2.86</td>
<td>(0.31; 26.75)</td>
<td>NS</td>
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<tr>
<td>Kidney Function</td>
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<tr>
<td>Renal events in patients with CKD Stage 3</td>
<td>CASE-J 2009</td>
<td>3 y</td>
<td>Candesartan Amlodipine</td>
<td>1140 (1140)</td>
<td>1125 (1125)</td>
<td>nd</td>
<td>nd</td>
<td>163/92 (163/92) 136/77 (135/77)</td>
<td>14 (1%) [9 (1%)] RR 1.54</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Renal events in patients with CKD Stage 4</td>
<td>Japan[87]</td>
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<td></td>
<td>3 (5%) [14 (23%)] RR 0.20</td>
<td>(0.06; 0.68)</td>
<td>nd</td>
</tr>
</tbody>
</table>

76 Calculated by ERT
77 New occurrence, aggravation, or reoccurrence of heart failure, angina pectoris, or acute MI
78 Calculated by ERT
79 SCr ≥ 4.0 mg/dL, end stage renal disease, doubling of SCr
80 Calculated by ERT
81 SCr ≥ 4.0 mg/dL, end stage renal disease, doubling of SCr
82 Calculated by ERT
83 SCr ≥ 4.0 mg/dL, end stage renal disease, doubling of SCr
84 Calculated by ERT
### Supplemental Table 6. General population RCTs comparing ACEI or ARB vs. control (active or placebo) in CKD subgroups with and without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>intervened [Control]</td>
<td>Achieved [Control]</td>
</tr>
<tr>
<td><strong>Composite outcome</strong></td>
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<td>nd</td>
<td>nd</td>
<td>nd</td>
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<tr>
<td>Kidney failure or halving of GFR &lt;60 mL/min/1.73 m²</td>
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<td>nd</td>
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<tr>
<td>ALLHAT 2006 Multi[50]</td>
<td></td>
<td>5 y (5 y)</td>
<td>Lisinopril Chlorthalidone</td>
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<td>nd</td>
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<tr>
<td>Kidney failure or halving of GFR &lt;60 mL/min/1.73 m²</td>
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<td>nd</td>
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<tr>
<td>CV death, MI or stroke in patients with Scr ≥1.4 mg/dL</td>
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<td></td>
<td></td>
<td>nd</td>
<td>UACR 0.73 mg/mmol</td>
<td>139/79 (141/79)</td>
<td>nd</td>
</tr>
<tr>
<td>HOPE 2001 Multi [58]</td>
<td></td>
<td>4 y (4 y)</td>
<td>Ramipril Placebo</td>
<td></td>
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<td>nd</td>
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<tr>
<td>CV death, MI or stroke in patients CrCl ≤65 mL/min</td>
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<tr>
<td>CV mortality, MI or revascularization in patients with eGFR &lt;45 mL/min/1.73 m²</td>
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<tr>
<td>PEACE 2006 2007 Multi[89;90]</td>
<td></td>
<td>5 y (5 y)</td>
<td>Trandolapril Placebo</td>
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<tr>
<td>CV mortality, MI or revascularization in patients with eGFR 45-59.9 mL/min/1.73 m²</td>
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<tr>
<td>Outcome Description</td>
<td>Study Year Country</td>
<td>Duration Outcome (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Blood pressure</td>
<td>Results</td>
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<tr>
<td><strong>Composite of CV death, nonfatal MI, and coronary revascularization in patients with low-medium microalbuminuria</strong></td>
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<tr>
<td><strong>Composite of CV death, nonfatal MI, and coronary revascularization in patients with high microalbuminuria-macroalbuminuria</strong></td>
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<tr>
<td><strong>Dialysis, or doubling of Scr in patients with UACR ≥3.4 mg/mmol</strong></td>
<td>TRANSCEEND, 2009 Multi[62]</td>
<td>5 y (5 y) Telmisartan Placebo</td>
<td></td>
<td>nd nd nd nd nd nd</td>
<td>RR 0.557 (0.2; 1.2) NS</td>
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<tr>
<td><strong>Dialysis, or doubling of Scr in patients with eGFR &lt;60 mL/min/1.73 m²</strong></td>
<td>Val-HeFT 2009 Multi[10]</td>
<td>2 y (2 y) Valsartan Placebo</td>
<td></td>
<td>2890 (2890) GFR 47 mL/min/m² Serum albumin 4.0 g/dL</td>
<td>nd nd 499 (34%) [549 (38%)] HR 0.86 (0.74; 0.99) nd</td>
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<td><strong>First morbid event with eGFR &lt;60 mL/min/m²</strong></td>
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<td><strong>Mortality</strong></td>
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<tr>
<td>All death in patients with Scr ≥1.4 mg/dL</td>
<td>HOPE 2001 Multi [58]</td>
<td>4 y (4 y) Ramipril Placebo</td>
<td></td>
<td>509 (509) 471 (471) UACR 0.73 mg/mmol</td>
<td>139/79 nd nd 13% [23%] HR 0.59 (0.42; 0.83) nd</td>
<td></td>
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<tr>
<td>All death in patients CrCl ≤65 mL/min</td>
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</tbody>
</table>

85 Calculated by ERT  
86 Calculated by ERT  
87 Estimated from figure  
88 Estimated from figure  
89 Death sudden death with resuscitation, hospitalization for HF, administration of IV inotropic or vasodilator drugs for ≥4 h without hospitalization
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality in patients with eGFR &lt;45 mL/min/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[Control]</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interven(157)</td>
<td>138/76</td>
<td>13 (17%)</td>
<td>(0.54; 1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Placebo</td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Total mortality in patients with eGFR 45-59.9 mL/min/m²</td>
<td></td>
<td></td>
<td></td>
<td>Interven(1198)</td>
<td>135/77</td>
<td>56 (9%)</td>
<td>(72; 12%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Placebo</td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Total mortality in patients with eGFR&lt;60 mL/min/m²</td>
<td>PEACE 2006 2007</td>
<td>Median 5 y (5 y)</td>
<td>Trandapril</td>
<td></td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td>1355 (1355)</td>
<td>eGFR&lt;60</td>
<td>69 (92)</td>
<td>HR 0.73</td>
</tr>
<tr>
<td>All-cause mortality in patients with low-medium microalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td>Interven(332/1498)</td>
<td>139/79</td>
<td>37 (39)</td>
<td>(0.58; 1.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Placebo</td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>All-cause mortality in patients with high microalbuminuria-macroalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td>Interven(73/1498)</td>
<td>147/82</td>
<td>8 (13)</td>
<td>(0.28; 1.44)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Placebo</td>
<td></td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Death in patients with eGFR &lt;60 mL/min/m²</td>
<td>Val-HeFT 2009</td>
<td>2 y (2 y)</td>
<td>Valsartan</td>
<td>2890 (2890)</td>
<td>Serum albumin 4.0 g/dL</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>Multi[10]</td>
<td></td>
<td>Placebo</td>
<td></td>
<td>nd</td>
<td>362 (341)</td>
<td>(0.85; 1.20)</td>
</tr>
<tr>
<td>CV Mortality</td>
<td></td>
<td></td>
<td></td>
<td>Interven(509/3394)</td>
<td>UACR 0.73 mg/mmol</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>CV death in patients with Scr ≥1.4 mg/dL</td>
<td>HOPE 2001</td>
<td>4 y (4 y)</td>
<td>Ramipril</td>
<td>471 (471)</td>
<td>139/79</td>
<td>9%</td>
<td>(0.39; 0.91)</td>
</tr>
<tr>
<td></td>
<td>Multi [58]</td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td>9%</td>
<td>[15%]</td>
</tr>
<tr>
<td>CV death in patients CrCl ≤65 mL/min</td>
<td></td>
<td></td>
<td></td>
<td>Interven(3394)</td>
<td>141/79</td>
<td>8%</td>
<td>(0.53; 0.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control Placebo</td>
<td></td>
<td>8%</td>
<td>[11%]</td>
</tr>
<tr>
<td>CV mortality in patients with eGFR &lt;45 mL/min/m²</td>
<td>PEACE 2006 2007</td>
<td>Median 5 y (5 y)</td>
<td>Trandapril</td>
<td>157 (157)</td>
<td>Scr 1.6 mg/dL</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td></td>
<td>Multi[89;90]</td>
<td></td>
<td>Placebo</td>
<td></td>
<td>nd</td>
<td>11 (14%)</td>
<td>(14; 8%)</td>
</tr>
</tbody>
</table>

90 Adjusted
91 Calculated by ERT
92 Calculated by ERT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality in patients with eGFR 45-59.9 mL/min/m²</td>
<td></td>
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<tr>
<td>CV death in patients with low-medium microalbuminuria</td>
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<tr>
<td>CV death in patients with high microalbuminuria-macroalbuminuria</td>
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<tr>
<td>CV Events</td>
<td></td>
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</tr>
</tbody>
</table>

### CHD in entire subgroup with GFR <60 mL/min/1.73 m²

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD in entire subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
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</tr>
<tr>
<td>CHD in DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi [50]</td>
<td>5 y (5 y)</td>
<td>Lisinopril</td>
<td>1533 (1533)</td>
<td>2613 (2613)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>nd nd nd</td>
<td>184 (12%) [318 (12%)]</td>
<td>RR 1.00 (0.84; 1.20)</td>
</tr>
<tr>
<td>CHD in non-DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
<td></td>
<td>Lisinopril</td>
<td>1032 (1032)</td>
<td>1732 (1732)</td>
<td>GFR 49 mL/min/1.73 m²</td>
<td>nd nd nd</td>
<td>108 (11%) [186 (11%)]</td>
<td>RR 1.00 (0.79; 1.26)</td>
</tr>
<tr>
<td>MI in patients with Scr ≥1.4 mg/dL</td>
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<tr>
<td>MI in patients</td>
<td></td>
<td></td>
<td></td>
<td>509 (509)</td>
<td>471 (471)</td>
<td></td>
<td></td>
<td>14% [19%]</td>
<td>HR 0.78 (0.54; 1.11)</td>
</tr>
<tr>
<td>CrCl ≤65 mL/min</td>
<td>HOPE 2001 Multi [58]</td>
<td>4 y (4 y)</td>
<td>Ramipril</td>
<td>509 (509)</td>
<td>471 (471)</td>
<td>UACR 0.73 mg/mmol</td>
<td>139/79 nd</td>
<td>11% [14%]</td>
<td>HR 0.74 (0.61; 0.91)</td>
</tr>
<tr>
<td>Stroke in patients with Scr ≥1.4 mg/dL</td>
<td></td>
<td></td>
<td>Placebo</td>
<td>509 (509)</td>
<td>471 (471)</td>
<td></td>
<td></td>
<td>4% [6%]</td>
<td>RR 0.83 (0.44; 1.56)</td>
</tr>
<tr>
<td>Stroke in patients</td>
<td></td>
<td></td>
<td></td>
<td>3394 (3394)</td>
<td></td>
<td></td>
<td></td>
<td>4% [6%]</td>
<td>HR 0.69 (0.49; 0.91)</td>
</tr>
</tbody>
</table>

93 Calculated by ERT
94 Calculated by ERT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Baseline GFR or Scr</td>
<td>Baseline Proteinuria</td>
</tr>
<tr>
<td>CV mortality or MI in patients with eGFR &lt;45 mL/min/m²</td>
<td>PEACE 2006 2007 Multi[89;90]</td>
<td>Median 5 y (5 y)</td>
<td>Trandolapril</td>
<td>Placebo</td>
<td>157 (157)</td>
<td>nd</td>
</tr>
<tr>
<td>CV mortality or MI in patients with eGFR 45-59.9 mL/min/m²</td>
<td>PREVEND IT 2004 Netherlands [12]</td>
<td>4 y (4 y)</td>
<td>Fosinopril</td>
<td>Placebo</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
<td>Lisinopril</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Kidney failure in entire subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi[50]</td>
<td>5 y (5 y)</td>
<td>Lisinopril</td>
<td>Chlorthalidone</td>
<td>501 (501)</td>
<td>881 (881)</td>
</tr>
<tr>
<td>Kidney failure in DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi[50]</td>
<td>5 y (5 y)</td>
<td>Lisinopril</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Kidney failure in non-DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>HOPE 2003 Multi[59]</td>
<td>5 y (5 y)</td>
<td>Ramipril</td>
<td>Placebo</td>
<td>333 (333)</td>
<td>SCr 1.578 mg/dL</td>
</tr>
<tr>
<td>Dialysis</td>
<td></td>
<td></td>
<td>Ramipril</td>
<td>Placebo</td>
<td>333 (333)</td>
<td>SCr 1.578 mg/dL</td>
</tr>
<tr>
<td>Kidney failure</td>
<td></td>
<td></td>
<td>Ramipril</td>
<td>Placebo</td>
<td>333 (333)</td>
<td>SCr 1.578 mg/dL</td>
</tr>
</tbody>
</table>

Newly developed renal insufficiency defined as SCr ≥1.4 mg/dL

Doubling of Scr

Dialysis

ESRD

Kidney failure in entire subgroup with GFR <60 mL/min/1.73 m²

Kidney failure in DM subgroup with GFR <60 mL/min/1.73 m²

Kidney failure in non-DM subgroup with GFR <60 mL/min/1.73 m²

Dialysis

HOPE 2003 Multi[59]
Supplemental Table 7. Evidence profile of RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>4 RCTs [1° in 2 RCTs] (High)</td>
<td>1069 (539)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>Benefit for ACEI</td>
<td>Critical</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 RCTs (High)</td>
<td>1148 (582)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Imprecision (-1)</td>
<td>Moderate</td>
<td>Insufficient evidence for ACEI or ARB</td>
<td>Critical</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>CV events</td>
<td>4 RCTs (High)</td>
<td>1148 (582)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Imprecision (-1)</td>
<td>Moderate</td>
<td>Insufficient evidence for ACEI or ARB</td>
<td>Critical</td>
</tr>
<tr>
<td>ESRD</td>
<td>3 RCTs (High)</td>
<td>483 (243)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Possible benefit for ACEI or ARB</td>
<td>Critical</td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>1 RCT (High)</td>
<td>131 (66)</td>
<td>Some limitations (-1)</td>
<td>N/A</td>
<td>Direct (0)</td>
<td>Sparse (-1) Imprecision (-1)</td>
<td>Very low</td>
<td>Insufficient evidence for ACEI or ARB</td>
<td>Critical</td>
</tr>
<tr>
<td>ΔKidney function (continuous)</td>
<td>5 RCTs [1° in 1 RCT] (High)</td>
<td>803 (404)</td>
<td>No limitations (0)</td>
<td>Important inconsistencies (-1)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Low</td>
<td>Possible benefit for ACEI</td>
<td>Moderate</td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>1 RCTs (High)</td>
<td>179 (92)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit for ACEI</td>
<td>High</td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>4 RCTs (High)</td>
<td>1069 (539)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Benefit for ACEI and ARB</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adverse events</td>
<td>6 RCTs</td>
<td>1458 (746)</td>
<td>Drug discontinuation: 1-17% for ACEI or ARB and 1-14% for placebo (from 5 RCTs) Hyperkalemia: 0-2% for ACEI or ARB and 0-1% for Placebo (from 5 RCTs) Early rise in creatinine: 0-6% in ACEI and ARB and 0-4% in Placebo (from 4 RCTs)</td>
<td>Drug discontinuation: 1-17% for ACEI or ARB and 1-14% for placebo (from 5 RCTs) Hyperkalemia: 0-2% for ACEI or ARB and 0-1% for Placebo (from 5 RCTs) Early rise in creatinine: 0-6% in ACEI and ARB and 0-4% in Placebo (from 4 RCTs)</td>
<td>Moderate</td>
<td></td>
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</tr>
</tbody>
</table>

Balance of potential benefits and harms
No benefit in individuals with no or little proteinuria from the lower target.
Possible benefit from lower target in individuals with proteinuria above 0.3-1 g/d.
Insufficient evidence for CV outcomes

Quality of overall evidence
High for no proteinuria
Moderate for proteinuria 0.3-1 g/d
Moderate for CV outcomes
Supplemental Table 8. RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD without DM [categorical outcomes] 97

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>Intervention</th>
<th>Control</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events No (%)</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
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</tr>
<tr>
<td>Doubling of Scr, or the need for dialysis</td>
<td>Maschio 1996 Multi[66]</td>
<td>3 y (3 y)</td>
<td>Benazpril</td>
<td>Placebo</td>
<td>300 (300)</td>
<td>283 (283)</td>
<td>Scr 2.1 mg/dL</td>
<td>UPE 1.8 g/d</td>
<td>142/87 (144/88)</td>
<td>137/85 (145/87)</td>
<td>31 (10%)</td>
<td>[57 (20%)]</td>
<td>RR 0.51&lt;sup&gt;100&lt;/sup&gt; (0.34; 0.77)</td>
<td>&lt;0.001</td>
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<tr>
<td>Doubling of Scr, ESRD, or death</td>
<td>Hou 2006&lt;sup&gt;101&lt;/sup&gt; China[43]</td>
<td>3 y (3 y)</td>
<td>Benazepril (Scr 3.0-5 mg/dL)</td>
<td>Placebo</td>
<td>112 (112)</td>
<td>112 (112)</td>
<td>GFR 26 ml/min/1.73 m²</td>
<td>Scr 4.0 mg/dL</td>
<td>UPE 1.6 g/d</td>
<td>153/87 (152/85)</td>
<td>126/75&lt;sup&gt;102&lt;/sup&gt; (126/75)</td>
<td>44 (41%)&lt;sup&gt;103&lt;/sup&gt; [65 (60%)]</td>
<td>RR 0.68&lt;sup&gt;104&lt;/sup&gt; (0.51; 0.89)</td>
<td>0.004</td>
</tr>
<tr>
<td>Doubling of Scr or ESRD</td>
<td>GISEN 1997 Italy[2]</td>
<td>3 y (3 y)</td>
<td>Ramipril</td>
<td>Placebo</td>
<td>78 (78)</td>
<td>88 (88)</td>
<td>GFR 40 ml/min/1.73 m²</td>
<td>UPE 5.6 g/24h</td>
<td>150/92 (150/91)</td>
<td>144/88 (145/90)</td>
<td>18 (23%)</td>
<td>[40 (45%)]</td>
<td>RR 0.51&lt;sup&gt;105&lt;/sup&gt; (0.32; 0.81)</td>
<td>0.004</td>
</tr>
<tr>
<td>ESRD &amp; doubling Scr</td>
<td>HVKIN 2006&lt;sup&gt;106&lt;/sup&gt; Hong Kong[53]</td>
<td>2 y (2 y)</td>
<td>Valsartan</td>
<td>Placebo</td>
<td>49 (54)</td>
<td>47 (55)</td>
<td>GFR 78 ml/min/1.73 m²</td>
<td>MAP 92.7 (100.9)</td>
<td>137/83 (136/81)</td>
<td>1 (2%)&lt;sup&gt;107&lt;/sup&gt; [4 (8%)]</td>
<td>RR 0.24&lt;sup&gt;108&lt;/sup&gt; (0.03; 2.07)</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mortality

| Death | Maschio 1996 Multi[66] | 3 y (3 y) | Benazpril | Placebo | 300 (300) | 283 (283) | Scr 2.1 mg/dL | UPE 1.8 g/d | 142/87 (144/88) | 137/85 (145/87) | 8 (3%) | [1 (0.4%)] | RR 7.55<sup>110</sup> (0.95; 59.96) | nd<sup>111</sup> | Good |

97 Shaded studies were included in previous KDOQI guideline
98 Estimated from graph
99 Benefit of ramipril only statistically significant in people with 24 hour urine protein excretion ≥3g
100 Calculated by ERT
101 All Chinese patients
102 Estimated from graph
103 Primary outcome
104 Calculated by ERT
105 Calculated by ERT
106 All Chinese patients
107 Primary outcome
108 Calculated by ERT
109 Estimated from graph
110 Calculated by ERT
111 The death rates in the benazepril group and placebo groups were 1 death per 93 patient-years and 1 per 656 patient-years, respectively (P=0.04)."
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>Hou 2006[^112] China[^43]</td>
<td>3 y (3 y)</td>
<td>Benazepril (Sc 3.0-5 mg/dL)</td>
<td>Placebo 112 (112)</td>
<td>GFR 26 mL/min/1.73 m²</td>
<td>UPE 1.6 g/d</td>
<td>153/87 (152/85)</td>
<td>126/75[^113] (126/75)</td>
<td>1 (1%) [0 (0%)]</td>
<td>--</td>
<td>nd</td>
<td>Good</td>
</tr>
<tr>
<td>Death</td>
<td>Ruggenenti 1999 Italy[^84]</td>
<td>2.5 y (2.5 y)</td>
<td>Ramipril</td>
<td>Placebo 92 (99)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>UPE 1.7 g/d</td>
<td>142/89 (145/90)</td>
<td>nd</td>
<td>1 (0.01%) [0 (0%)]</td>
<td>--</td>
<td>nd</td>
<td>Good</td>
</tr>
<tr>
<td>Death</td>
<td>GISEN 1997 Italy[^2]</td>
<td>3 y (3 y)</td>
<td>Ramipril</td>
<td>Placebo 78 (78)</td>
<td>GFR 40 mL/min/1.73 m²</td>
<td>UPE 5.6 g/24h</td>
<td>150/92 (150/91)</td>
<td>144/88 (145/90)</td>
<td>2 (3%) [1 (1%)]</td>
<td>RR 2.26[^114] (0.21; 24.41)</td>
<td>nd</td>
<td>Good</td>
</tr>
<tr>
<td>CV events</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Non-fatal CV events</td>
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<tr>
<td>MI</td>
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<tr>
<td>Stroke</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>Maschio 1996 Multi[^66]</td>
<td>3 y (3 y)</td>
<td>Benazpril</td>
<td>Placebo 300 (300)</td>
<td>Sc 2.1 mg/dL</td>
<td>UPE 1.8 g/d</td>
<td>142/87 (144/88)</td>
<td>137/85 (145/87)</td>
<td>1 (0.3%) [1 (0.4%)]</td>
<td>RR 0.94[^119] (0.06; 15.01)</td>
<td>nd</td>
<td>Good</td>
</tr>
<tr>
<td>Angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertensive crisis</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension or dizziness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[^112]: All Chinese patients
[^113]: Estimated from graph
[^114]: Calculated by ERT
[^115]: Estimated from graph
[^116]: Calculated by ERT
[^117]: Calculated by ERT
[^118]: Calculated by ERT
[^119]: Calculated by ERT
[^120]: Calculated by ERT
[^121]: Calculated by ERT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>Hou 2006</td>
<td>China</td>
<td>3 y</td>
<td>Benazepril (SCr 3.0-5 mg/dL)</td>
<td>Placebo 112 (112)</td>
<td>GFR 26 mL/min/1.73 m² SCr 4.0 mg/dL</td>
<td>UPE 1.6 g/d</td>
<td>153/87 (152/85)</td>
<td>126/75 (126/75)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Ruggenenti</td>
<td>Italy</td>
<td>Median 2.5 y</td>
<td>Ramipril</td>
<td>Placebo 92 (99)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>UPE 1.7 g/d</td>
<td>142/89 (145/90)</td>
<td>nd</td>
</tr>
<tr>
<td>Stroke</td>
<td>GISEN 1997</td>
<td>Italy</td>
<td>3 y</td>
<td>Ramipril</td>
<td>Placebo 78 (78)</td>
<td>GFR 40 mL/min/1.73 m²</td>
<td>UPE 5.6 g/24h</td>
<td>150/92 (150/91)</td>
<td>144/88 (145/90)</td>
</tr>
<tr>
<td>Aortic aneurysm</td>
<td>GISEN 1997</td>
<td>Italy</td>
<td>2.5 y</td>
<td>Ramipril</td>
<td>Placebo 99 (99)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>UPE 1.7 g/d</td>
<td>142/89 (145/90)</td>
<td>nd</td>
</tr>
</tbody>
</table>

Note: Calculations and estimates marked with superscript numbers refer to specific methods of calculation:
- 122 All Chinese patients
- 123 Estimated from graph
- 124 Calculated by ERT
- 125 Calculated by ERT
- 126 Calculated by ERT
- 127 Calculated by ERT
- 128 Calculated by ERT
- 129 Calculated by ERT
- 130 Calculated by ERT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>Intervention</th>
<th>Control</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for dialysis</td>
<td>GISEN 1997</td>
<td>3 y (3 y)</td>
<td>Ramipril</td>
<td>Placebo</td>
<td>78 (78)</td>
<td>88 (88)</td>
<td>GFR 40 mL/min/1.73 m²</td>
<td>UPE 5.6 g/24h</td>
<td>150/92 150/91</td>
<td>144/88 145/90</td>
</tr>
<tr>
<td></td>
<td>Cinotti 2001</td>
<td>23 mo (24 mo)</td>
<td>Lisinopril Conventional anti-HTN therapy</td>
<td>66 (66)</td>
<td>65 (65)</td>
<td>GFR 36 mL/min/1.73 m²</td>
<td>UPE 0.35 mg/min</td>
<td>141/85 142/86</td>
<td>139/83 137/82</td>
<td>2 (3%) [5 (8%)]</td>
</tr>
<tr>
<td>Kidney function</td>
<td>Cinotti 2001</td>
<td>23 mo (24 mo)</td>
<td>Lisinopril Conventional anti-HTN therapy</td>
<td>66 (66)</td>
<td>65 (65)</td>
<td>GFR 36 mL/min/1.73 m²</td>
<td>UPE 0.35 mg/min</td>
<td>141/85 142/86</td>
<td>139/83 137/82</td>
<td>3 (5%) [7 (11%)]</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Ruggenenti 1999</td>
<td>Median 2.5 y (2.5 y)</td>
<td>Ramipril</td>
<td>Placebo</td>
<td>92 (99)</td>
<td>87 (87)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>UPE 1.7 g/d</td>
<td>142/89 145/90</td>
<td>nd</td>
</tr>
</tbody>
</table>

131 Calculated by ERT  
132 Estimated from graph  
133 Calculated by ERT  
134 Estimated from graph  
135 Calculated by ERT  
136 Calculated by ERT
## Supplemental Table 9: RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median slope of ↓1/S Cr, dL/mg/dL</td>
<td>Hou 2006 China[43]</td>
<td>3 y (3 y)</td>
<td>Benazepril (S Cr 3.0-5 mg/dL)</td>
<td>Placebo 112 (112)</td>
<td>GFR 26 mL/min/1.73 m² S Cr 4.0 mg/dL</td>
<td>UPE 1.6 g/d</td>
<td>153/87 (152/85)</td>
<td>126/75 (126/75)</td>
<td>4.0 (3.9)</td>
</tr>
<tr>
<td>Median slope of ↓eGFR, mL/min/1.73 m² y</td>
<td>Ruggenenti 1999 Italy[84]</td>
<td>2.5 y (2.5 y)</td>
<td>Ramipril</td>
<td>Placebo 99 (99)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>UPE 1.7 g/d</td>
<td>142/89 (145/90)</td>
<td>nd</td>
<td>50 (43)</td>
</tr>
<tr>
<td>Mean rate of ↓GFR, mL/min/month</td>
<td>GISEN 1997 Italy[2]</td>
<td>3 y (3 y)</td>
<td>Ramipril</td>
<td>Placebo 78 (78)</td>
<td>GFR 40 mL/min/1.73 m²</td>
<td>UPE 5.6 g/24h</td>
<td>150/92 (150/91)</td>
<td>144/88 (145/90)</td>
<td>40 (37)</td>
</tr>
<tr>
<td></td>
<td>Cinotti 2001 Italy[26]</td>
<td>23 mo (24 mo)</td>
<td>Lisinopril</td>
<td>Conventional anti-HTN therapy</td>
<td>GFR 36 mL/min/1.73 m² S Cr 2.27 mg/dL</td>
<td>UPE 0.35 mg/min</td>
<td>141/85 (142/86)</td>
<td>139/83 (137/82)</td>
<td>36 (35)</td>
</tr>
<tr>
<td>Rate of ↓GFR, mL/min/1.73 m²</td>
<td>HVKIN 2006 Hong Kong[53]</td>
<td>2 y (2 y)</td>
<td>Valsartan</td>
<td>Placebo 49 (54)</td>
<td>GFR 78 mL/min/1.73 m²</td>
<td>2.3 g/d</td>
<td>137/83 (136/81)</td>
<td>MAP 92.7 (100.9)</td>
<td>78 (87)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔUPE, g/24h</td>
<td>Maschio 1996 Hong Kong[66]</td>
<td>3 y (3 y)</td>
<td>Benazepril</td>
<td>Placebo 300 (300)</td>
<td>S Cr 2.1 mg/dL</td>
<td>UPE 1.8 g/d</td>
<td>142/87 (144/88)</td>
<td>137/85 (145/87)</td>
<td>1.8 (1.8)</td>
</tr>
</tbody>
</table>

---

137 Shaded studies were included in previous KDOQI guideline
138 All Chinese patients
139 Estimated from graph
140 Estimated from graph
141 Primary outcome
142 All Chinese patients
143 Estimated from graph
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of ↓ UPE</td>
<td>Hou 2006 China[43]</td>
<td>3 y (3 y)</td>
<td>Benazepril (Scr 3.0-5 mg/dL)</td>
<td>Intervention 112 Placebo 112</td>
<td>GFR 26 mL/min/1.73 m²</td>
<td>UPE 1.6 g/d</td>
<td>153/87 (152/85)</td>
<td>126/75</td>
</tr>
<tr>
<td>UPE, g/24h</td>
<td>GISEN 1997 Italy[2]</td>
<td>3 y (3 y)</td>
<td>Ramipril</td>
<td>Placebo 78 88</td>
<td>GFR 40 mL/min/1.73 m²</td>
<td>UPE 5.6 g/24h</td>
<td>150/92 (150/91)</td>
<td>144/88</td>
</tr>
<tr>
<td>ΔProteinuria, g/d</td>
<td>HVKIN 2006 Hong Kong[53]</td>
<td>2 y (2 y)</td>
<td>Valsartan</td>
<td>Placebo 49 47</td>
<td>GFR 78 mL/min/1.73 m²</td>
<td>2.3 g/d</td>
<td>137/83 (136/81)</td>
<td>MAP 92.7 (100.9)</td>
</tr>
<tr>
<td>%ΔProteinuria, g/d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

144 All Chinese patients  
145 Estimated from graph  
146 Placebo value not provided but stated as not being significantly different than baseline  
147 All Chinese patients
## Supplemental Table 10. Evidence profile of RCTs examining the effect of ACEI or ARB vs. CCB in patients with CKD without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
</table>
| Composite kidney outcomes    | 3 RCTs[143]  
[1° in 1 RCT]  
(High) | 1059 (646) | No limitations (0) | No important inconsistencies (0) | Direct (0) | None (0) |  | High | Benefit for ACEI | Critical |
| Mortality                    | 3 RCTs (High) | 908 (569) | No limitations (0) | No important inconsistencies (0) | Direct (0) | Imprecision (-1) |  | Moderate | Insufficient evidence for ACEI vs. CCB | Critical |
| CV mortality                 | 2 RCTs (High) | 801 (516) | Some limitations (-1) | No important inconsistencies (0) | Direct (0) | Imprecision (-1) |  | Low | Insufficient evidence for ACEI vs. CCB | Critical |
| CV events                    | 2 RCTs (High) | 801 (516) | No limitations (0) | NA | Direct (0) | Sparse (-1)  
Imprecision (-1) |  | Low | Insufficient evidence for ACEI vs. CCB | Critical |
| ESRD                         | 1 RCT (High) | 653 (436) | No limitations (0) | NA | Direct (0) | Sparse (-1)  |  | Moderate | Benefit for ACEI | Critical |
| Kidney function (categorical)| 1 RCT (High) | 454 (309) | No limitations (0) | NA | Direct (0) | Sparse (-1)  |  | Moderate | Benefit for ACEI | High |
| Kidney function (continuous) | 6 RCTs  
[1° in 2 RCTs]  
(High) | 1356 (798) | Some limitations (-1) | No important inconsistencies (0) | Uncertainty about directness (-1) | None (0) |  | Low | No benefit for ACEI in overall slope. Possible benefit after 3 months with ACEI[149] | Moderate |
| Proteinuria (categorical)    | 0 RCTs | -- | -- | -- | -- | -- |  | -- | -- | High |
| Proteinuria (continuous)     | 7 RCTs (High) | 1463 (851) | Some limitations (-1) | No important inconsistencies (0) | Uncertainty about directness (-1) | None (0) |  | Low | Benefit for ACEI or ARB | Moderate |
| Adverse events               | 6 RCTs | 1343 (790) | Drug discontinuation: 16-38% for ACEI or ARB and 9-40% for CCB (from 4 RCTs)  
Hyperkalemia: 2-5% for ACEI or ARB and 0-6% for CCB (from 3 RCTs) |  |  |  |  |  |  |  |
| Total                        | 7 RCTs (High) | 1463 (851) | Balance of potential benefits and harms  
Benefit for ACEI for kidney outcomes  
Insufficient evidence for CV outcomes |  |  |  |  |  |  |  |  |
| Balance of potential benefits and harms | Benefit for ACEI for kidney outcomes  
Insufficient evidence for CV outcomes |

---

143 AASK study includes death in composite outcome.

149 Decision on chronic slope primarily based on AASK results.
### Supplemental Table 11. RCTs examining the effect of ACEI or ARB vs. CCB in patients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year County</th>
<th>Duration</th>
<th>Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/1.73 m², ESRD or death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/1.73 m² or ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD or death</td>
<td>AASK 2001 2006 (^{150}) US[7;70]</td>
<td>4 y (≥3y)</td>
<td>Ramipril Amlodipine</td>
<td>GFR 46 mL/min/1.73 m² UPCR Male 0.34 Female 0.32</td>
<td>151/96 (150/96) 135/82 (133/81)</td>
<td>Blood pressure</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
<td>Quality</td>
</tr>
<tr>
<td>First CV hospitalization and death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First CV hospitalization or ESRD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/1.73 m², ESRD or death in sub-group with UPCR&gt;0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration</th>
<th>Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
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</table>

\(^{150}\) Study only included African American patients
\(^{151}\) Adjusted
\(^{152}\) Adjusted
\(^{153}\) Adjusted
<table>
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<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Intervention</th>
<th>Control</th>
<th>Baseline GFR or S&lt;sub&gt;Cr&lt;/sub&gt;</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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</thead>
<tbody>
<tr>
<td>RRT, D/C due to renal function, ≤50% GFR, doubling of S&lt;sub&gt;Cr&lt;/sub&gt;, or hospitalization on for transient renal failure</td>
<td>AVER 2008 EU[35]</td>
<td>Aver</td>
<td>3 y (3 y)</td>
<td>Enalapril</td>
<td>Amlodipine</td>
<td>130 (131)</td>
<td>128 (132)</td>
<td>2.05 mg/dL</td>
<td>GFR 45 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>UPE 1249 mg/24h</td>
<td>165/103 (165/102)</td>
</tr>
<tr>
<td>Doubling S&lt;sub&gt;Cr&lt;/sub&gt; and/or dialysis</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>Spain</td>
<td>3 y (3 y)</td>
<td>Fosinipril</td>
<td>Nifedipine GITS</td>
<td>80 (129)</td>
<td>68 (112)</td>
<td>2.8 mg/dL</td>
<td>0.34 g/dL</td>
<td>1.7 g/24h</td>
<td>155/96 (158/96)</td>
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<tr>
<td>Mortality</td>
<td>AASK 2001[155] US[7]</td>
<td>AASK 2006[158] US[70]</td>
<td>4 y (≥3y)</td>
<td>Ramipril</td>
<td>Amlodipine</td>
<td>436 (436)</td>
<td>217 (217)</td>
<td>GFR 46 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.34 g/dL</td>
<td>1.7 g/24h</td>
<td>151/96 (150/96)</td>
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<tr>
<td>All cause mortality</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>Spain</td>
<td>3 y (3 y)</td>
<td>Fosinipril</td>
<td>Nifedipine GITS</td>
<td>80 (129)</td>
<td>68 (112)</td>
<td>2.8 mg/dL</td>
<td>0.34 g/dL</td>
<td>1.7 g/24h</td>
<td>155/96 (158/96)</td>
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<tr>
<td>Death</td>
<td>Nephros 2001 Multi[41]</td>
<td>Multi</td>
<td>2 y (nd)</td>
<td>Ramipril</td>
<td>Felodipine</td>
<td>53 (53)</td>
<td>54 (54)</td>
<td>GFR 44 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>149 μmol/L</td>
<td>UA 506 mg/24h</td>
<td>154/99 (159/100)</td>
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<tr>
<td>CV mortality</td>
<td>AASK 2006[158] US[70]</td>
<td>AASK 2006[158] US[70]</td>
<td>4 y (≥3y)</td>
<td>Ramipril</td>
<td>Amlodipine</td>
<td>436 (436)</td>
<td>217 (217)</td>
<td>GFR 46 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.34 g/dL</td>
<td>1.7 g/24h</td>
<td>151/96 (150/96)</td>
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<tr>
<td>CV mortality</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>Spain</td>
<td>3 y (3 y)</td>
<td>Fosinipril</td>
<td>Nifedipine GITS</td>
<td>80 (129)</td>
<td>68 (112)</td>
<td>2.8 mg/dL</td>
<td>0.34 g/dL</td>
<td>1.7 g/24h</td>
<td>155/96 (158/96)</td>
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154 Primary outcome
155 Study only included African American patients
156 Adjusted
157 Calculated by ERT
158 Study only included African American patients
159 Calculated by ERT
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year (Country)</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<td></td>
<td>Baseline SBP/DBP</td>
<td>Achieved SBP/DBP</td>
<td>Events No (%)</td>
<td>RR/OR/HR (95% CI)</td>
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<td>Intervention (Control)</td>
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</tbody>
</table>

**CV events**

| Stroke events | AASK 2006[160] US[70] | 4 y (≥3y) | Ramipril | Amlodipine | 436 (436) | 217 (217) | GFR 46 mL/min/1.73 m² | UPCR Male 0.34 Female 0.32 | 151/96 (150/96) | 135/82 (133/81) | 89 (20%) [28 (13%)] | HR 1.49 (0.90; 2.45) | NS | Good |
| CHF events | ESPIRAL 2001 Spain[64] | 3 y (3 y) | Fosinipril | Nifedipine | 80 (129) | 68 (112) | Scr 2.8 mg/dL | 1.7 g/24h | 155/96 (158/96) | 135/83 (144/81) | 1 (1%) [0 (0%)] | -- | nd | Poor |
| CAD events | ESRD AASK 2001[164] US[7] | 4 y (≥3y) | Ramipril | Amlodipine | 436 (436) | 217 (217) | GFR 46 mL/min/1.73 m² | UPCR Male 0.34 Female 0.32 | 151/96 (150/96) | 135/82 (133/81) | 47 (15%) [32 (21%)] | Risk reduction 44% (13; 65) | 0.01 | Good |

**ESRD**

| Kidney function | AASK 2001[166] US[7] | 4 y (≥3y) | Ramipril | Amlodipine | 309 (436) | 145 (217) | GFR 46 mL/min/1.73 m² | UPCR Male 0.34 Female 0.32 | 151/96 (150/96) | 135/82 (133/81) | 44 (14%) [29 (18%)] | Risk reduction 41% (5; 63) | 0.03 | Good |

---

160 Study only included African American patients
161 Calculated by ERT
162 Calculated by ERT
163 Calculated by ERT
164 Study only included African American patients
165 Adjusted
166 Study only included African American patients
167 Adjusted
### Supplemental Table 12. RCTs examining the effect of ACEI or ARB vs. CCB in patients with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR 46 ml/min/1.73 m²</td>
<td>UPCR Male 0.34, Female 0.32</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Acute slope – ΔGFR in first 3 mo, mL/min/1.73 m²/y</td>
<td>4 y (≥3 y)</td>
<td>436 (436)</td>
<td>217 (217)</td>
<td>GFR 46 ml/min/1.73 m²</td>
<td>UPCR Male 0.34, Female 0.32</td>
<td>151/96 (150/96)</td>
<td>135/82 (133/81)</td>
</tr>
<tr>
<td>Chronic slope – ΔGFR after first 3 mo, mL/min/1.73 m²/y in sub-group with UPCR ≤0.22</td>
<td>3 y (3 y)</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Chronic slope – ΔGFR after first 3 mo, mL/min/1.73 m²/y in sub-group with UPCR &gt;0.22</td>
<td>3 y (3 y)</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
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</tbody>
</table>

168 Study only included African American patients
169 Primary outcome
170 Significant interactions of the treatment regimen with baseline proteinuria (P=0.001) and baseline GFR (P=0.006). Acute rise in GFR with amlodipine confined to people with UPCR ≤0.22.
171 Significant interactions of the treatment regimen with baseline proteinuria (P<0.001) and baseline GFR (P=0.003). Higher proteinuria = More beneficial effect of ramipril.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or SCr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mean slope over 3y in subgroup with UPCR≤ 0.22</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>3 y (3 y)</td>
<td>Enalapril Amlodipine</td>
<td>70 (70) nd nd nd nd nd nd</td>
<td>-13.54 (-4.25)</td>
<td>0.04 Poor</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Total mean slope over 3y in subgroup with UPCR&gt; 0.22</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>3 y (3 y)</td>
<td>Fosinipril Nifedipine GITS</td>
<td>70 (70) nd nd nd nd nd</td>
<td>+0.75 (+1.25)</td>
<td>0.03 Fair</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆GFR, mL/min/1.73 m²</td>
<td>AVER 2008 EU[35]</td>
<td>3 y (3 y)</td>
<td>Enalapril Amlodipine</td>
<td>70 (70) nd nd nd nd nd nd</td>
<td>-12.41 (-6.62)</td>
<td>NS Poor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆GFR, mL/min/1.73 m² (LOCF)</td>
<td>AVER 2008 EU[35]</td>
<td>3 y (3 y)</td>
<td>Enalapril Amlodipine</td>
<td>70 (70) nd nd nd nd nd nd</td>
<td>-12.41 (-6.62)</td>
<td>NS Poor</td>
<td></td>
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</tr>
<tr>
<td>∆SCr, mg/dL</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>3 y (3 y)</td>
<td>Fosinipril Nifedipine GITS</td>
<td>70 (70) nd nd nd nd nd nd</td>
<td>-13.54 (-4.25)</td>
<td>0.04 Poor</td>
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</table>

172 Primary outcome
173 ERT estimated from graph
<table>
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<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔGFR in patients with proteinuria between 1-3g/24h, mL/min/1.73 m²</td>
<td>Peng 2009174 China[76]</td>
<td>1 y (1 y)</td>
<td>Valsartan Benidipine</td>
<td></td>
<td>61 (61) 59 (59)</td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>1.98 g/24h</td>
<td>150/95 (151/95)</td>
<td>126/76 (126/77)</td>
</tr>
<tr>
<td>ΔGFR in patients with proteinuria &gt;1g/24h, mL/min/1.73 m²</td>
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<td></td>
<td></td>
<td></td>
<td>57 (57) 59 (59)</td>
<td>GFR 52 mL/min/1.73 m²</td>
<td>0.61 g/24h</td>
<td>150/97 (157/96)</td>
<td>128/78 (127/78)</td>
</tr>
<tr>
<td>ΔScr, mg/dL</td>
<td>JLIGHT 2004175 Japan[44]</td>
<td>12 mo (12 mo)</td>
<td>Losartan Amlodipine</td>
<td>47 (58) 40 (59)</td>
<td>Scr 2.04 mg/dL</td>
<td>2.85 g/d</td>
<td>156/94 (155/93)</td>
<td>140/83 (134/80)</td>
<td>2.04 (1.97)</td>
</tr>
<tr>
<td>ΔCrCl, mL/min</td>
<td>Del Vecchio 2004 Italy[30]</td>
<td>48 wks (48 wks)</td>
<td>Enalapril Manidipine</td>
<td>44 (69) 46 (67)</td>
<td>Scr 1.86 mg/dL CrCl 46 mL/min</td>
<td>1.37 g/24h</td>
<td>157/100 (155/100)</td>
<td>134/85 (138/86)</td>
<td>1.064 (0.720)</td>
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<td>ΔScr, mg/dL</td>
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<tr>
<td>Slope of 1/Scr</td>
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<td>1.86 (2.00)</td>
<td>+0.13 (+0.09)</td>
<td>NS Poor</td>
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<tr>
<td>ΔCrCl, mL/min</td>
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<td>1.064 (0.720)</td>
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<td>NS Poor</td>
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<tr>
<td>Slope of CrCl</td>
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<td>-0.003 (-0.005)</td>
<td>--</td>
<td>NS Poor</td>
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**Proteinuria**

<table>
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<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tbody>
<tr>
<td>ΔUPCR, (%)</td>
<td>AASK 2001178 US[7]</td>
<td>4 y (≥3y)</td>
<td>Ramipril Amlodipine</td>
<td>436 (436) 217 (217)</td>
<td>GFR 46 mL/min/1.73 m² UPCR Male 0.34 Female 0.32</td>
<td>151/96 (150/96)</td>
<td>135/82 (133/81)</td>
<td>Male 34; Female 0.32 Male 0.30; Female 0.30</td>
<td>-20% (+0.58%)</td>
</tr>
<tr>
<td>ΔUPE, mg/24h</td>
<td>AVER 2008 EU[35]</td>
<td>3 y (3 y)</td>
<td>Enalapril Amlodipine</td>
<td>130 (131) 128 (132)</td>
<td>Scr 2.05 mg/dL GFR 45 mL/min/1.73 m² UPE 1249 mg/24h</td>
<td>165/103 (165/102)</td>
<td>138/85 (138/84)</td>
<td>UPE 1249 (1296)</td>
<td>-246 (-149)</td>
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174 All Chinese patients
175 All Japanese patients
176 ERT estimated from graph
177 ERT estimated from graph
178 Study only included African American patients
<table>
<thead>
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<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>Blood pressure</th>
<th>Results</th>
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<tbody>
<tr>
<td>ΔProteinuria, g/24h</td>
<td>ESPIRAL 2001 Spain[64]</td>
<td>3 y (3 y)</td>
<td>Fosinipril Nifedipine GITS</td>
<td>Baseline GFR or Scr</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
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<tr>
<td>ΔProteinuria in patients with proteinuria between 1-3g/24h, g/24h</td>
<td>Peng 2009 China[76]</td>
<td>1 y (1 y)</td>
<td>Valsartan Benidipine</td>
<td>Baseline GFR</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
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<td>UAE (statistical analysis of transformed values)</td>
<td>Nephros 2001 Multi [41]</td>
<td>2 y (nd)</td>
<td>Ramipril Felodipine</td>
<td>Baseline GFR</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
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<tr>
<td>ΔProteinuria, g/24h</td>
<td>Del Vecchio 2004 Italy[30]</td>
<td>48 wks (48 wks)</td>
<td>Enalapril Manidipine</td>
<td>Baseline GFR</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
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<tr>
<td>%ΔProteinuria, g/d</td>
<td>JUGHT 2004 Japan[44]</td>
<td>12 mo (12 mo)</td>
<td>Losartan Amlodipine</td>
<td>Baseline GFR</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
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179 ERT estimated from graph
180 All Chinese patients
181 All Japanese patients
182 ERT estimated from graph
<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>1 RCT [1° in 1 RCT] (High)</td>
<td>343 (168)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
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<tr>
<td>Mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
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<tr>
<td>CV mortality</td>
<td>0 RCTs</td>
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<td>--</td>
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<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>CV events</td>
<td>1 RCT (High)</td>
<td>343 (168)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>1 RCT (High)</td>
<td>207 (101)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>Kidney function (continuous)</td>
<td>1 RCT (High)</td>
<td>207 (101)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>No difference</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Insufficient evidence</td>
<td>Critical</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>3 RCTs [1° in 1 RCT] (High)</td>
<td>632 (309)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>No difference</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>3 RCTs</td>
<td>632 (309)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Early rise in creatinine: 2-3% in ACEI and 3% in ARB (from 1 RCT)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 RCTs</td>
<td>632 (309)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Summary of findings**

- **Quality of overall evidence**
  - Low for kidney outcomes
  - Low for CV outcomes

**Balance of potential benefits and harms**

- Insufficient evidence for kidney and CV outcomes
### Supplemental Table 14. RCTs examining the effect of ACEI vs. ARB in patient with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events No (%)</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention/Control</td>
<td>(Treatment)</td>
<td>(Control)</td>
<td>Intervention</td>
<td>(Control)</td>
<td>(Control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention/Control</td>
<td>(Treatment)</td>
<td>(Control)</td>
<td>Intervention</td>
<td>(Control)</td>
<td>(Control)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite kidney outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benazepril [40 mg/d titrated]</td>
<td>Losartan [200 mg/d titrated]</td>
<td>84 (84)</td>
<td>87 (87)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>UPE 2.1 g/d</td>
<td>150/86</td>
<td>124/76</td>
</tr>
<tr>
<td>Doubling of Sc, ESRD, or death</td>
<td>Hou 2007</td>
<td>China[42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [10 mg/d fixed]</td>
<td>Losartan [50 mg/d fixed]</td>
<td>84 (84)</td>
<td>88 (88)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>UPE 1.4 g/d</td>
<td>151/86</td>
<td>124/76</td>
<td>26 (31%)</td>
</tr>
<tr>
<td>CV events</td>
<td>Hou 2007</td>
<td>China[42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated]</td>
<td>Losartan [200 mg/d titrated]</td>
<td>84 (84)</td>
<td>87 (87)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>UPE 2.1 g/d</td>
<td>150/86</td>
<td>124/76</td>
<td>10 (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benazepril [10 mg/d fixed]</td>
<td>Losartan [50 mg/d fixed]</td>
<td>84 (84)</td>
<td>88 (88)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>UPE 1.4 g/d</td>
<td>151/86</td>
<td>124/76</td>
</tr>
<tr>
<td>ESRD</td>
<td>Woo 2009</td>
<td>Singapore[88]</td>
<td>6 y (6 y)</td>
<td>Enalapril 20mg/d</td>
<td>Losartan 200mg/d</td>
<td>61 (69)</td>
<td>63 (67)</td>
<td>eGFR 62 mL/min/y</td>
<td>UPE 2.2 g/d</td>
<td>134/83</td>
<td>129/83</td>
<td>19 (31%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 10mg/d</td>
<td>Losartan 200mg/d</td>
<td>40 (45)</td>
<td>46 (45)</td>
<td>eGFR 61 mL/min/y</td>
<td>UPE 2.3 g/d</td>
<td>132/86</td>
<td>130/84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 20mg/d</td>
<td>Losartan 100mg/d</td>
<td>61 (69)</td>
<td>43 (45)</td>
<td>eGFR 62 mL/min/y</td>
<td>UPE 2.2 g/d</td>
<td>134/83</td>
<td>129/83</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 10mg/d</td>
<td>Losartan 100mg/d</td>
<td>40 (45)</td>
<td>43 (45)</td>
<td>eGFR 61 mL/min/y</td>
<td>UPE 2.3 g/d</td>
<td>132/86</td>
<td>130/84</td>
</tr>
</tbody>
</table>

183 All Chinese patients
184 Estimated from graph
185 Primary outcome
186 Calculated by ERT
187 Estimated from graph
188 Primary outcome
189 Calculated by ERT
190 All Chinese patients
191 Estimated from graph
192 Calculated by ERT
193 Estimated from graph
194 Calculated by ERT
195 Calculated by ERT
196 Calculated by ERT
197 Calculated by ERT
198 Calculated by ERT
## Supplemental Table 15. RCTs examining the effect of ACEI vs. ARB in patient with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>Baseline GFR or S(_C)r</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>(\Delta) Intervention [Control]</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔeGFR, mL/min/y</td>
<td>Woo 2009</td>
<td>Singapore [98]</td>
<td>6 y (6 y)</td>
<td>Enalapril 20mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.2 g/d (134/83)</td>
<td>129/83</td>
<td>62</td>
<td>-3.5 (-0.7)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 10mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.3 g/d (132/84)</td>
<td>128/83</td>
<td>61</td>
<td>-3.2 (-0.7)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 20mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.2 g/d (134/83)</td>
<td>129/83</td>
<td>62</td>
<td>-3.5 (-0.7)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 10mg/d</td>
<td>Losartan 100mg/d</td>
<td>UPE 2.3 g/d (132/84)</td>
<td>128/83</td>
<td>61</td>
<td>-3.2 (-0.7)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%ΔProteinuria, g/d</td>
<td>Hou 2007</td>
<td>China [42]</td>
<td>3 y (3 y)</td>
<td>Benazepril 40 mg/d [titrated]</td>
<td>Losartan 200 mg/d [titrated]</td>
<td>UPE 2.1 g/d (150/86)</td>
<td>124/76</td>
<td>2.1</td>
<td>50% (53%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Benazepril 10 mg/d [fixed]</td>
<td>Losartan 50 mg/d [fixed]</td>
<td>UPE 1.4 g/d (151/86)</td>
<td>124/76</td>
<td>1.4</td>
<td>38% (41%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>ΔUPE, g/d</td>
<td>Woo 2009</td>
<td>Singapore [98]</td>
<td>6 y (6 y)</td>
<td>Enalapril 20mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.2 g/d (134/83)</td>
<td>129/83</td>
<td>2.2</td>
<td>-0.5 (-1)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 10mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.3 g/d (132/84)</td>
<td>128/83</td>
<td>2.3</td>
<td>-0.6 (-1)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 20mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.2 g/d (134/83)</td>
<td>129/83</td>
<td>2.2</td>
<td>-0.5 (-1)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Enalapril 10mg/d</td>
<td>Losartan 200mg/d</td>
<td>UPE 2.3 g/d (132/84)</td>
<td>128/83</td>
<td>2.3</td>
<td>-0.6 (-1)</td>
<td>nd</td>
<td>Fair</td>
</tr>
<tr>
<td>†UACR, mg/mmol</td>
<td>Menne 2008</td>
<td>Multi[67]</td>
<td>30 wks (30 wks)</td>
<td>Lisinopril</td>
<td>Valsartan</td>
<td>CrCl 105 mg/mL</td>
<td>UACR 9.6 mg/mmol</td>
<td>153/91 (137/81)</td>
<td>9.6 (-1) (-51%)</td>
<td>Geometric mean</td>
<td>NS</td>
</tr>
</tbody>
</table>

---

199 All Chinese patients
200 Estimated from graph
201 Estimated from graph
202 Primary outcome
<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>1 RCT [1 in 1 RCT] (High)</td>
<td>168 (84)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit for high doses of ACEI</td>
<td>Critical</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV events</td>
<td>1 RCT (High)</td>
<td>168 (84)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence</td>
<td>Critical</td>
</tr>
<tr>
<td>ESRD</td>
<td>2 RCTs (High)</td>
<td>269 (145)</td>
<td>No limitations (0)</td>
<td>Important inconsistencies (-1)</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Possible benefit</td>
<td>Critical</td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>1 RCT (High)</td>
<td>168 (84)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit for higher doses of ACEI</td>
<td>High</td>
</tr>
<tr>
<td>Kidney function (continuous)</td>
<td>2 RCTs (High)</td>
<td>269 (145)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Very low</td>
<td>Possible benefit for higher dose ACEI</td>
<td>Moderate</td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>2 RCTs (High)</td>
<td>269 (145)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Very low</td>
<td>Possible benefit for higher dose ACEI</td>
<td>Moderate</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 RCTs</td>
<td>269 (145)</td>
<td>Drug discontinuation: 6-7% vs. 4% for ACEI</td>
<td></td>
<td>Drug discontinuation: 6-7% vs. 4% for ACEI</td>
<td></td>
<td>Moderate</td>
<td>Drug discontinuation: 6-7% vs. 4% for ACEI</td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
<td>Hyperkalemia: 4% vs. 0% for ACEI</td>
<td></td>
<td>Hyperkalemia: 4% vs. 0% for ACEI</td>
<td></td>
<td></td>
<td>Hyperkalemia: 4% vs. 0% for ACEI</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2 RCTs</td>
<td>269 (145)</td>
<td>Early rise in creatinine: 3% vs. 2% in ACEI</td>
<td></td>
<td>Early rise in creatinine: 3% vs. 2% in ACEI</td>
<td></td>
<td></td>
<td>Early rise in creatinine: 3% vs. 2% in ACEI</td>
<td></td>
</tr>
</tbody>
</table>

Balance of potential benefits and harms
Possible benefit for kidney outcomes in higher dose ACEI
Insufficient evidence for CV outcomes

Quality of overall evidence
Low for kidney outcomes
Low for CV outcomes
### Supplemental Table 17. RCTs examining the effect of high dose ACEI vs. low dose ACEI in patient with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Study Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doubling of Scr, ESRD, or death</td>
<td>Hou 2007[203]</td>
<td>China[42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated]</td>
<td>84 (84)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>149/86 (151/86)</td>
<td>RR 1.38 (0.70; 2.75)</td>
<td>0.04 Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV events</td>
<td>Hou 2007[206]</td>
<td>China[42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated]</td>
<td>84 (84)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>149/86 (151/86)</td>
<td>RR 1.25 (0.52; 3.01) nd Good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD</td>
<td>Hou 2007[209]</td>
<td>China[42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated]</td>
<td>84 (84)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>149/86 (151/86)</td>
<td>RR 1.38 (0.70; 2.75) NS Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESRD (CKD Stage 5, eGFR &lt;15 mL/min)</td>
<td>Woo 2009[211]</td>
<td>Singapore[98]</td>
<td>6 y (6 y)</td>
<td>Enalapril [20 mg/d]</td>
<td>61 (69)</td>
<td>eGFR 62 mL/min</td>
<td>134/83 (132/86)</td>
<td>RR 1.38 (0.70; 2.75) NS Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney function</td>
<td>Hou 2007[213]</td>
<td>China[42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated]</td>
<td>84 (84)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>149/86 (151/86)</td>
<td>RR 1.38 (0.70; 2.75) NS Fair</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

203 All Chinese patients
204 Estimated from graph
205 Primary outcome
206 All Chinese patients
207 Estimated from graph
208 Calculated by ERT
209 All Chinese patients
210 Estimated from graph
211 Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
212 Calculated by ERT
213 All Chinese patients
214 Estimated from graph
### Supplemental Table 18. RCTs examining the effect of high dose ACEI vs. low dose ACEI in patient with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>p value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%↓CrCl</td>
<td>Hou 2007²¹⁵</td>
<td>China [42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated] Benazepril [10 mg/d fixed]</td>
<td>84 (84) 84 (84)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>UPE 2.1 g/d</td>
<td>Baseline SBP/DBP</td>
<td>149/86  (151/86)</td>
<td>124/76 (124/76)²¹⁶</td>
<td>35 (34)</td>
</tr>
<tr>
<td>ΔeGFR, mL/min</td>
<td>Woo 2009²¹⁷</td>
<td>Singapore [98]</td>
<td>6 y (6 y)</td>
<td>Enalapril [20 mg/d] Enalapril [10 mg/d]</td>
<td>61 (69) 40 (43)</td>
<td>eGFR 62 mL/min</td>
<td>UPE 2.2 g/d</td>
<td>Achieved SBP/DBP</td>
<td>134/83 (132/86)</td>
<td>129/83 (130/84)</td>
<td>62 (61)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>%ΔProteinuria</td>
<td>Hou 2007²¹⁸</td>
<td>China [42]</td>
<td>3 y (3 y)</td>
<td>Benazepril [40 mg/d titrated] Benazepril [10 mg/d fixed]</td>
<td>84 (84) 84 (84)</td>
<td>eGFR 31 mL/min/1.73 m²</td>
<td>UPE 2.1 g/d</td>
<td>Baseline SBP/DBP</td>
<td>149/86 (151/86)</td>
<td>124/76 (124/76)²¹⁹</td>
<td>2.1 (1.4)</td>
</tr>
<tr>
<td>ΔUPE, g/d</td>
<td>Woo 2009²²⁰</td>
<td>Singapore [98]</td>
<td>6 y (6 y)</td>
<td>Enalapril [20 mg/d] Enalapril [10 mg/d]</td>
<td>61 (69) 40 (43)</td>
<td>eGFR 62 mL/min</td>
<td>UPE 2.2 g/d</td>
<td>Achieved SBP/DBP</td>
<td>134/83 (132/86)</td>
<td>129/83 (130/84)</td>
<td>2.2 (2.3)</td>
</tr>
</tbody>
</table>

²¹⁵ All Chinese patients  
²¹⁶ Estimated from graph  
²¹⁷ Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)  
²¹⁸ All Chinese patients  
²¹⁹ Estimated from graph  
²²⁰ Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
**Table 19. Evidence profile of RCTs examining the effect of high vs. low dose ARB in patients with CKD without DM**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td>1 RCT [1’ in 1 RCT] (High)</td>
<td>175 (87)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit in high doses of ARB</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>CV mortality</strong></td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>CV events</strong></td>
<td>1 RCT (High)</td>
<td>175 (87)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>ESRD</strong></td>
<td>2 RCTs (High)</td>
<td>281 (150)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Possible benefit in high doses of ARB</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Kidney function (categorical)</strong></td>
<td>1 RCT (High)</td>
<td>175 (87)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit in high doses of ARB</td>
<td>High</td>
</tr>
<tr>
<td><strong>∆Kidney function (continuous)</strong></td>
<td>3 RCTs (High)</td>
<td>608 (317)</td>
<td>No limitations (0)</td>
<td>Important inconsistencies (0)</td>
<td>Uncertainty about directness (0)</td>
<td>None (0)</td>
<td>Low</td>
<td>Possible benefit for higher dose ARB</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Proteinuria (categorical)</strong></td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria (continuous)</strong></td>
<td>3 RCTs [1’ in 1 RCT] (High)</td>
<td>608 (317)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (0)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Benefit for higher dose ARB</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>3 RCTs</td>
<td>608 (317)</td>
<td>Drug discontinuation: 3-11% vs. 3-15% for ARB (from 3 RCTs) Hyperkalemia: 6% vs. 3% for ARB (from 1 RCT) Early rise in creatinine: 3% vs. 3% for ARB (from 1 RCT)</td>
<td>Drug discontinuation: 3-11% vs. 3-15% for ARB (from 3 RCTs) Hyperkalemia: 6% vs. 3% for ARB (from 1 RCT) Early rise in creatinine: 3% vs. 3% for ARB (from 1 RCT)</td>
<td>Drug discontinuation: 3-11% vs. 3-15% for ARB (from 3 RCTs) Hyperkalemia: 6% vs. 3% for ARB (from 1 RCT) Early rise in creatinine: 3% vs. 3% for ARB (from 1 RCT)</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3 RCTs</td>
<td>608 (317)</td>
<td>Balance of potential benefits and harms Possible benefit for kidney outcomes with higher dose ARB arm Insufficient evidence for CV outcomes</td>
<td>Quality of overall evidence Moderate for kidney outcomes Low for CV outcomes</td>
<td>Moderate</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
## Supplemental Table 20. RCTs examining the effect of high dose ARB vs. low dose ARB in patient with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>RR/OR/HR (95% CI)</th>
<th>p value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td>Hou 2007221 China[42]</td>
<td>3 y (3 y)</td>
<td>Losartan [200 mg/d titrated]</td>
<td>Losartan [50 mg/d fixed]</td>
<td>87 (87)</td>
<td>88 (88)</td>
<td>eGFR 30 mL/min/1.73 m²</td>
<td>UPE 2.0 g/d</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention [Control]</td>
</tr>
<tr>
<td>CV events</td>
<td>Hou 2007224 China[42]</td>
<td>3 y (3 y)</td>
<td>Losartan [200 mg/d titrated]</td>
<td>Losartan [50 mg/d fixed]</td>
<td>87 (87)</td>
<td>88 (88)</td>
<td>eGFR 30 mL/min/1.73 m²</td>
<td>UPE 2.0 g/d</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention [Control]</td>
</tr>
<tr>
<td><strong>ESRD</strong></td>
<td>Hou 2007227 China[42]</td>
<td>3 y (3 y)</td>
<td>Losartan [200 mg/d titrated]</td>
<td>Losartan [50 mg/d fixed]</td>
<td>87 (87)</td>
<td>88 (88)</td>
<td>eGFR 30 mL/min/1.73 m²</td>
<td>UPE 2.0 g/d</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention [Control]</td>
</tr>
<tr>
<td>ESRD</td>
<td>Woo 2009229 Singapore[98]</td>
<td>6 y (6 y)</td>
<td>Losartan [200 mg/d]</td>
<td>Losartan [100 mg/d]</td>
<td>63 (67)</td>
<td>43 (45)</td>
<td>eGFR 64 mL/min</td>
<td>UPE 2.2 g/d</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention [Control]</td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
<td>Hou 2007231 China[42]</td>
<td>3 y (3 y)</td>
<td>Losartan [200 mg/d titrated]</td>
<td>Losartan [50 mg/d fixed]</td>
<td>87 (87)</td>
<td>88 (88)</td>
<td>eGFR 30 mL/min/1.73 m²</td>
<td>UPE 2.0 g/d</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Events No (%) Intervention [Control]</td>
</tr>
</tbody>
</table>

---

221 All Chinese patients  
222 Estimated from graph  
223 Primary outcome  
224 All Chinese patients  
225 Estimated from graph  
226 Calculated by ERT  
227 All Chinese patients  
228 Estimated from graph  
229 Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)  
229a Calculated by ERT  
229b All Chinese patients  
229c Estimated from graph
**Supplemental Table 21. RCTs examining the effect of high dose ARB vs. low dose ARB in patient with CKD without DM [continuous outcomes]**

| Outcome | Study Year | Duration (Treatment) | Country | Description | No analyzed / Enrolled | Baseline GFR or $\text{SCr}$ | Baseline Proteinuria | Blood pressure | Results | $\Delta$ | Intervention [Control] | $\Delta$ | Intervention [Control] | $\Delta$ | Intervention [Control] | $\Delta$ | Intervention [Control] | $\Delta$ | Intervention [Control] | $\Delta$ | Intervention [Control] | $\Delta$ |
|---------|------------|----------------------|---------|-------------|------------------------|-------------------------------|--------------------------------|-----------------|---------|---------|------------------------|--------|------------------------|--------|------------------------|--------|------------------------|--------|------------------------|--------|
| **Kidney function** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| $\% \downarrow \text{CrCl}$ | Hou 2007<sup>233</sup> [234] China[42] | 3 y (3 y) | | Losartan [200 mg/d titrated] | 87 (87) | 88 (88) | eGFR 30 mL/min/1.73 m² | UPE 2.0 g/d | 152/86 (149/86) | 124/76 (124/76)<sup>234</sup> | 34 (34) 55% reduction in intervention group compared to control group | 0.04 | Fair |
| $\% \Delta \text{eGFR}, \text{mL/min/1.73 m²}$ | SMART 2009 Canada[22] | 30 wk (30 wk) | | Candesartan [64 mg] | 84 (90) | 72 (90) | eGFR 55 mL/min/1.73 m² | 24h urinary protein 2.83 g/d | 132/77 (133/77) | 130/76 (133/75) | 49 (52) -10 (-9) NS Good |
| | | | | Candesartan [128 mg] | 75 (89) | 72 (90) | eGFR 49 mL/min/1.73 m² | 24h urinary protein 2.85 g/d | 132/77 (133/77) | 130/76 (133/75) | 49 (52) -8 (-9) NS Good |
| | | | | Candesartan [64 mg] | 83 (89) | 88 (90) | eGFR 49 mL/min/1.73 m² | 24h urinary protein 2.85 g/d | 132/77 (133/77) | 130/76 (133/75) | 49 (55) -8 (-10) nd Fair |
| | | | | Candesartan [128 mg] | 84 (90) | 72 (90) | eGFR 55 mL/min/1.73 m² | 24h urinary protein 2.83 g/d | 132/77 (133/77) | 130/76 (133/75) | 119 (127) +9 (+8) NS Good |
| | | | | Candesartan [128 mg] | 75 (89) | 72 (90) | eGFR 49 mL/min/1.73 m² | 24h urinary protein 2.85 g/d | 132/77 (133/77) | 130/76 (133/75) | 135 (127) +7 (+8) NS Good |
| | | | | Candesartan [64 mg] | 83 (89) | 88 (90) | eGFR 49 mL/min/1.73 m² | 24h urinary protein 2.85 g/d | 132/77 (133/77) | 130/76 (133/75) | 135 (119) +7 (+9) nd Fair |
| **Proteinuria** | | | | | | | | | | | | | | | | | | | | | | | | | | |
| $\Delta \text{eGFR}, \text{mL/min/y}$ | Woo 2009<sup>235</sup> Singapore [98] | 6 y (6 y) | | Losartan [200 mg/d] | 63 (67) | 43 (45) | eGFR 64 mL/min | UPE 2.2 g/d | 132/84 (132/85) | 128/83 (128/84) | 64 (61) -0.7 (-3.5) nd Fair |

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<sup>233</sup> All Chinese patients  
<sup>234</sup> Estimated from graph  
<sup>235</sup> Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Outcome)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or S\textsubscript{Cr}</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>%ΔProteinuria, g/d</td>
<td>Hou 2007[236] China[42]</td>
<td>3 y (3 y)</td>
<td>Losartan [200 mg/d titrated]</td>
<td>87 (87)</td>
<td>eGFR 30 mL/min/1.73 m\textsuperscript{2} UPE 2.0 g/d</td>
<td></td>
<td>152/86 (149/86)</td>
<td>124/76 [237]**</td>
<td>2.0 (1.6)</td>
<td>53% (41%)</td>
</tr>
<tr>
<td>24h urine protein, g/d</td>
<td>SMART 2009 Canada[22]</td>
<td>30 wk (30 wk)</td>
<td>Candesartan [64 mg]</td>
<td>84 (90)</td>
<td>eGFR 55 mL/min/1.73 m\textsuperscript{2} 24h urinary protein 2.63 g/d</td>
<td>133/79 (133/77)</td>
<td>132/77 (133/75)</td>
<td>2.83 [238]**</td>
<td>-22.23</td>
<td>0.0492</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Candesartan [16 mg]</td>
<td>72 (90)</td>
<td>eGFR 49 mL/min/1.73 m\textsuperscript{2} 24h urine protein 2.85 g/d</td>
<td>132/77 (133/77)</td>
<td>130/76 (133/75)</td>
<td>2.85 [239]**</td>
<td>-36.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Candesartan [128 mg]</td>
<td>83 (89)</td>
<td>eGFR 49 mL/min/1.73 m\textsuperscript{2} 24h urine protein 2.85 g/d</td>
<td>132/77 (133/79)</td>
<td>130/76 (132/77)</td>
<td>2.85 [240]**</td>
<td>-36.95</td>
<td>nd</td>
</tr>
<tr>
<td>ΔUPE, g/d</td>
<td>Woo 2009[241] Singapore [98]</td>
<td>6 y (6 y)</td>
<td>Losartan [200 mg/d]</td>
<td>63 (67)</td>
<td>eGFR 64 mL/min UPE 2.2 g/d</td>
<td></td>
<td>132/84 (132/85)</td>
<td>128/83 (128/84)</td>
<td>2.2 (2.0)</td>
<td>nd</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Outcome)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or S\textsubscript{Cr}</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>%ΔProteinuria, g/d</td>
<td>Hou 2007[236] China[42]</td>
<td>3 y (3 y)</td>
<td>Losartan [200 mg/d titrated]</td>
<td>87 (87)</td>
<td>eGFR 30 mL/min/1.73 m\textsuperscript{2} UPE 2.0 g/d</td>
<td></td>
<td>152/86 (149/86)</td>
<td>124/76 [237]**</td>
<td>2.0 (1.6)</td>
<td>53% (41%)</td>
</tr>
<tr>
<td>24h urine protein, g/d</td>
<td>SMART 2009 Canada[22]</td>
<td>30 wk (30 wk)</td>
<td>Candesartan [64 mg]</td>
<td>84 (90)</td>
<td>eGFR 55 mL/min/1.73 m\textsuperscript{2} 24h urinary protein 2.63 g/d</td>
<td>133/79 (133/77)</td>
<td>132/77 (133/75)</td>
<td>2.83 [238]**</td>
<td>-22.23</td>
<td>0.0492</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Candesartan [16 mg]</td>
<td>72 (90)</td>
<td>eGFR 49 mL/min/1.73 m\textsuperscript{2} 24h urine protein 2.85 g/d</td>
<td>132/77 (133/77)</td>
<td>130/76 (133/75)</td>
<td>2.85 [239]**</td>
<td>-36.95</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Candesartan [128 mg]</td>
<td>83 (89)</td>
<td>eGFR 49 mL/min/1.73 m\textsuperscript{2} 24h urine protein 2.85 g/d</td>
<td>132/77 (133/79)</td>
<td>130/76 (132/77)</td>
<td>2.85 [240]**</td>
<td>-36.95</td>
<td>nd</td>
</tr>
<tr>
<td>ΔUPE, g/d</td>
<td>Woo 2009[241] Singapore [98]</td>
<td>6 y (6 y)</td>
<td>Losartan [200 mg/d]</td>
<td>63 (67)</td>
<td>eGFR 64 mL/min UPE 2.2 g/d</td>
<td></td>
<td>132/84 (132/85)</td>
<td>128/83 (128/84)</td>
<td>2.2 (2.0)</td>
<td>nd</td>
</tr>
</tbody>
</table>

\[236\] All Chinese patients
\[237\] Estimated from graph
\[238\] Primary outcome
\[239\] Primary outcome
\[240\] Primary outcome
\[241\] Patients with IgA nephropathy and moderate grade proteinuria (mean 2.2g/d)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/1.73 m², ESRD or death</td>
<td>AASK 2002/2006</td>
<td>4 y (≥3 y)</td>
<td>Ramipril Metoprolol</td>
<td>309 (436) 300 (441)</td>
<td>GFR 45 mL/min/1.73 m², Male 0.61 g/24h, Female 0.41 g/24h</td>
<td>151/96 (150/96) 135/82 (133/81)</td>
<td></td>
<td>Risk reduction 22% (-2; 41)</td>
<td>0.04</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>↓ GFR 50% or 25 mL/min/1.73 m² or ESRD</td>
<td>AASK 2002 US[70;99]</td>
<td>4 y</td>
<td>Ramipril Metoprolol</td>
<td>309 (436) 300 (441)</td>
<td>GFR 45 mL/min/1.73 m², Male 0.61 g/24h, Female 0.41 g/24h</td>
<td>151/96 (150/96) 135/82 (133/81)</td>
<td></td>
<td>Risk reduction 22% (-2; 41)</td>
<td>NS</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>ESRD or death</td>
<td></td>
<td></td>
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<tr>
<td>First CV hospitalization and death</td>
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</tr>
<tr>
<td>First CV hospitalization or ESRD</td>
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<tr>
<td><strong>Mortality</strong></td>
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<tr>
<td>All cause mortality</td>
<td>AASK 2002 US[99]</td>
<td>4 y (≥3 y)</td>
<td>Ramipril Metoprolol</td>
<td>309 (436) 300 (441)</td>
<td>GFR 45 mL/min/1.73 m², Male 0.61 g/24h, Female 0.41 g/24h</td>
<td>151/96 (150/96) 135/82 (133/81)</td>
<td></td>
<td>Risk reduction 21% (-5; 40)</td>
<td>NS</td>
<td>Good</td>
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<tr>
<td>CV mortality</td>
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242 Study only included African American patients
243 Adjusted
244 Adjusted
245 Adjusted
246 Adjusted
247 Adjusted
248 Study only included African American patients
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or $\text{Scr}^*$</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure Results</th>
<th>Events No (%) Intervention</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td>AASK 2002 2006$^{249}$ US[70;99]</td>
<td>4 y (≥3 y)</td>
<td>Ramipril Metoprolol</td>
<td>309 (436) 300 (441)</td>
<td>GFR 45 mL/min/1.73 m²</td>
<td>Male 0.61 g/24h Female 0.41 g/24h</td>
<td>151/96 (150/96) 135/82 (135/81)</td>
<td>1% (1%)</td>
<td>nd</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>CV death</td>
<td>2006 $^{249}$ US[70;99]</td>
<td>4 y (≥3 y)</td>
<td>Ramipril Metoprolol</td>
<td>436 (436) 441 (441)</td>
<td>GFR 45 mL/min/1.73 m²</td>
<td>Male 0.61 g/24h Female 0.41 g/24h</td>
<td>12 (3%)</td>
<td>HR 1.06$^{250}$ (0.47; 2.39)</td>
<td>NS</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>CV events (composite)</td>
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<td></td>
<td>309 (436) 300 (441)</td>
<td>GFR 45 mL/min/1.73 m²</td>
<td>Male 0.61 g/24h Female 0.41 g/24h</td>
<td>3% (3%)</td>
<td>nd</td>
<td>NS</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Stroke events</td>
<td>AASK 2002 2006$^{251}$ US[70;99]</td>
<td>4 y (≥3 y)</td>
<td>Ramipril Metoprolol</td>
<td>436 (436) 441 (441)</td>
<td>GFR 45 mL/min/1.73 m²</td>
<td>Male 0.61 g/24h Female 0.41 g/24h</td>
<td>23 (5%)</td>
<td>RR 1.01$^{252}$ (0.58; 1.78)</td>
<td>nd</td>
<td>Good</td>
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<tr>
<td>CHF events</td>
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<td></td>
<td></td>
<td>20 (5%)</td>
<td>RR 0.92$^{253}$ (0.51; 1.66)</td>
<td>nd</td>
<td>Good</td>
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<tr>
<td>CAD events</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>19 (4%)</td>
<td>RR 1.07$^{254}$ (0.57; 2.01)</td>
<td>nd</td>
<td>Good</td>
</tr>
<tr>
<td>ESRD</td>
<td>AASK 2002$^{255}$ US[99]</td>
<td>4 y (≥3 y)</td>
<td>Ramipril Metoprolol</td>
<td>309 (436) 300 (441)</td>
<td>GFR 45 mL/min/1.73 m²</td>
<td>Male 0.61 g/24h Female 0.41 g/24h</td>
<td>151/96 (150/96) 135/82 (135/81)</td>
<td>nd</td>
<td>Risk reduction 22% (-10; 45)$^{256}$</td>
<td>NS</td>
<td>Good</td>
</tr>
</tbody>
</table>

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$^{249}$ Study only included African American patients
$^{250}$ Adjusted
$^{251}$ Study only included African American patients
$^{252}$ Calculated by ERT
$^{253}$ Calculated by ERT
$^{254}$ Calculated by ERT
$^{255}$ Study only included African American patients
$^{256}$ Adjusted
Supplemental Table 23. RCTs examining the effect of ACEI vs. β-blocker in patients with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention Control Intervention Control</td>
<td>Male 0.61 g/24h Female 0.41 g/24h</td>
<td>151/96 (150/96) 135/82 (135/81) 46258 (46)</td>
<td>-1.87 (-2.12)</td>
<td>NS</td>
<td>Good</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td>Baseline SBP/DBP Intervention (Control) Achieved SBP/DBP Intervention (Control) Baseline Intervention (Control) Δ Intervention [Control]</td>
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<td></td>
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<td>0.007</td>
<td>Good</td>
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<td>Kidney function</td>
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<tr>
<td>Acute slope –ΔGFR in first 3 months, mL/min/1.73 m²/y</td>
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<tr>
<td>Chronic slope –ΔGFR after first 3 months, mL/min/1.73 m²/y</td>
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<tr>
<td>Total slope –ΔGFR over 4 y, mL/min/1.73 m²/y</td>
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</table>

257 Study only included African American patients
258 Primary outcome
Supplemental Table 24. RCTs examining the effect of ACEI + CCB vs. ACEI in patients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR 43 mL/min/1.73 m² Scr 147 mol/L</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Nephros 2001 Multi[41]</td>
<td>2 y (nd)</td>
<td>Ramipril + felodipine Ramipril</td>
<td>51 (51) 53 (53)</td>
<td>UAE 530 mg/24h</td>
<td>154/99 (159/100)</td>
<td>134/85 (139/88)</td>
<td>0 (0%) [0 (0%)]</td>
<td>--</td>
<td>nd</td>
<td>Fair</td>
</tr>
</tbody>
</table>

**Kidney function**

Regression coefficients for overall effect calculated from baseline GFR (mL/min/y)

-3.2 (-6.8; 0.4) $^{259}$ [-4.7 (-8.8; -1.5)]

Regression coefficients for 1/SCr (1/μmol/L/y) × 10⁻³

-2.4 $^{260}$ [-3.8]

Regression coefficients for long-term effect calculated from 3 month GFR (mL/min/y)

-3.8 (-6.8; 0.9) $^{261}$ [-5.8 (-8.7; 0.3)]

$^{259}$ Primary outcome

$^{260}$ Primary outcome

$^{261}$ Primary outcome
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
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<tr>
<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
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<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
<td>Quality</td>
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<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
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<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
<td>Quality</td>
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<tr>
<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
<td>Quality</td>
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<tr>
<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
<td>Quality</td>
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<tr>
<td>Outcome</td>
<td>Study Year</td>
<td>Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or Scr</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Events</td>
<td>RR/OR/HR (95% CI)</td>
<td>P value</td>
<td>Quality</td>
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</table>

Regression coefficients for $1/\text{Scr}$ (1/μmol/L/y) $\times 10^{-3}$

262 Primary outcome
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Year</th>
<th>Duration</th>
<th>Country</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
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<td>Proteinuria</td>
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<tr>
<td>UAE (statistical analysis of transformed values)</td>
<td>Nephros 2001 Multi[41]</td>
<td>2 y</td>
<td>Ramipril + felodipine</td>
<td>Ramipril</td>
<td>GFR 43 mL/min/1.73 m², Scr 147 mol/L</td>
<td>UAE 530 mg/24h</td>
<td>SBP 154/99 (159/100)</td>
<td>DBP 134/85 (139/88)</td>
<td>SBP/DBP 530 (506)</td>
</tr>
</tbody>
</table>

Supplemental Table 25. RCTs examining the effect of ACEI + CCB vs. ACEI in patients with CKD without DM [continuous outcomes]
### Supplemental Table 26. RCTs examining the effect of ACEI + CCB vs. CCB in patients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
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</tr>
<tr>
<td>Death</td>
<td>Nephros 2001 Multi[41]</td>
<td>2 y</td>
<td>Ramipril + felodipine</td>
<td>51 (51)</td>
<td>54 (54)</td>
<td>GFR 43 mL/min/1.73 m² Scr 147 mol/L</td>
<td>UAE 530 mg/24h</td>
<td>154/99 (159/100)</td>
<td>134/85 (139/86)</td>
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<tr>
<td><strong>Kidney function</strong></td>
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</tr>
<tr>
<td>Regression coefficients for overall effect calculated from baseline GFR (mL/min/y)</td>
<td>Nephros 2001 Multi[41]</td>
<td>2 y</td>
<td>Ramipril + felodipine</td>
<td>51 (51)</td>
<td>54 (54)</td>
<td>GFR 43 mL/min/1.73 m² Scr 147 mol/L</td>
<td>UAE 530 mg/24h</td>
<td>154/99 (159/100)</td>
<td>134/85 (139/86)</td>
</tr>
<tr>
<td>Regression coefficients for 1/Scr (1/μmol/L/y) X 10⁻³</td>
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<tr>
<td>Regression coefficients for long-term effect calculated from 3 month GFR (mL/min/y)</td>
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263 Primary outcome  
264 Primary outcome  
265 Primary outcome
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<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
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</tbody>
</table>

Regression coefficients for 1/Scr (1/μmol/L/y) X 10^{-3}

-2.8^266 [-9.0] -- NS Good

266 Primary outcome
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteinuria</td>
<td>Nephros 2001 Multi[41]</td>
<td>Multi</td>
<td>2 y (nd)</td>
<td>Ramipril + felodipine</td>
<td>Intervention 51 (51) Control 54 (54)</td>
<td>GFR 43 mL/min/1.73 m²</td>
<td>Scr 147 mol/L</td>
<td>UAE 530 mg/24h</td>
<td>Baseline SBP/DBP Intervention (Control) 154/99 (159/100)</td>
<td>Achieved SBP/DBP Intervention (Control) 134/85 (139/88)</td>
<td>Baseline Intervention (Control) 530 (365)</td>
</tr>
</tbody>
</table>

Supplemental Table 27. RCTs examining the effect of ACE + CCB vs. CCB in patients with CKD without DM [continuous outcomes]
### Supplemental Table 28. RCTs examining the effect of CCB vs. CCB in patients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td>All-cause mortality</td>
<td>CARTER 2007</td>
<td>Japan[36]</td>
<td>12 mo (12 mo)</td>
<td>Cilnidipine</td>
<td>147 (179)</td>
<td>130 (160)</td>
<td>Scr 1.27 mg/dL</td>
<td>UPCR 1921 mg/g</td>
<td>152/87 (152/88)</td>
<td>133/76 (135/78)</td>
<td>2 (1%)</td>
<td>[3 (2%)]</td>
</tr>
<tr>
<td>CV mortality</td>
<td>CARTER 2007</td>
<td>Japan[36]</td>
<td>12 mo (12 mo)</td>
<td>Cilnidipine</td>
<td>147 (179)</td>
<td>130 (160)</td>
<td>Scr 1.27 mg/dL</td>
<td>UPCR 1921 mg/g</td>
<td>152/87 (152/88)</td>
<td>133/76 (135/78)</td>
<td>0 (0%)</td>
<td>[2 (2%)]</td>
</tr>
<tr>
<td><strong>CV events</strong></td>
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<td>CVD events-all</td>
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<tr>
<td>Angina pectoris</td>
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<tr>
<td>MI</td>
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<tr>
<td>Abdominal aortic rupture</td>
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</tr>
<tr>
<td>Sudden death</td>
<td>CARTER 2007</td>
<td>Japan[36]</td>
<td>12 mo (12 mo)</td>
<td>Cilnidipine</td>
<td>147 (179)</td>
<td>130 (160)</td>
<td>Scr 1.27 mg/dL</td>
<td>UPCR 1921 mg/g</td>
<td>152/87 (152/88)</td>
<td>133/76 (135/78)</td>
<td>0 (0%)</td>
<td>[1 (1%)]</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
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<tr>
<td>Stroke-cerebral infarction</td>
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<tr>
<td>Stroke-transient ischemic attack</td>
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</table>

<sup>267</sup> Calculated by ERT
<sup>268</sup> Calculated by ERT
<sup>269</sup> Calculated by ERT
<sup>270</sup> Calculated by ERT
## Supplemental Table 29. RCTs examining the effect of CCB vs. CCB in patients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>ΔScr, mg/dL</td>
<td>CARTER 2007 Japan[36]</td>
<td>12 mo (12 mo)</td>
<td>Cilnidipine</td>
<td>Intervention</td>
<td>147 (179)</td>
<td>130 (160)</td>
<td>1.27 mg/dL</td>
<td>UPCR 1921 (152/88)</td>
<td>Intervention (Control)</td>
<td>152/87 (152/88)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔUPCR, mg/g</td>
<td>CARTER 2007 Japan[36]</td>
<td>12 mo (12 mo)</td>
<td>Cilnidipine</td>
<td>Intervention</td>
<td>147 (179)</td>
<td>130 (160)</td>
<td>1.27 mg/dL</td>
<td>UPCR 1921 (152/88)</td>
<td>Intervention (Control)</td>
<td>152/87 (152/88)</td>
</tr>
</tbody>
</table>

271 Primary outcome
**Supplemental Table 30. RCTs examining the effect of β-blocker vs. CCB in patients with CKD without DM [categorical outcomes]**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>↓GFR 50% or 25 mL/min/1.73 m², ESRD or death</td>
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<tr>
<td>↓GFR 50% or 25 mL/min/1.73 m² or ESRD or death</td>
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</tr>
<tr>
<td>AASK 2002</td>
<td>2006[272] US[70;99]</td>
<td>4 y (≥3 y)</td>
<td>Metoprolol Amlodipine</td>
<td>300 (441) 145 (217)</td>
<td>46 mL/min/1.73 m² Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96) 135/81 (133/81)</td>
<td>nd</td>
<td>Risk reduction 20% (-10; 41) [273]</td>
<td>NS Good</td>
<td></td>
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<tr>
<td>ESRD or death</td>
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<tr>
<td>First CV hospitalization and death</td>
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<tr>
<td>First CV hospitalization or ESRD</td>
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<tr>
<td><strong>Mortality</strong></td>
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</tr>
<tr>
<td>All cause mortality</td>
<td>AASK 2002[273]</td>
<td>4 y (≥3 y)</td>
<td>Metoprolol Amlodipine</td>
<td>300 (441) 145 (217)</td>
<td>46 mL/min/1.73 m² Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96) 135/81 (133/81)</td>
<td>2% [2%]</td>
<td>nd</td>
<td>NS Good</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CV mortality</td>
<td>AASK 2002</td>
<td>2006[274]</td>
<td>4 y</td>
<td>Metoprolol Amlodipine</td>
<td>300 (441) 145 (217)</td>
<td>46 mL/min/1.73 m² Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96) 135/81 (133/81)</td>
<td>1% [1%]</td>
<td>nd</td>
<td>NS Good</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

272 Study only included African American patients  
273 Adjusted  
274 Adjusted  
275 Adjusted  
276 Adjusted  
277 Adjusted  
278 Study only included African American patients  
279 Study only included African American patients
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or ( S_{Cr} )</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>p value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>US[70;99]</td>
<td>(≥3 y)</td>
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</tr>
<tr>
<td>Stroke events</td>
<td>AASK 2002 2006</td>
<td>4 y (≥3 y)</td>
<td>Metoprolol Amlodipine</td>
<td>46 mL/min/1.73 m²</td>
<td>Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96) 135/81 (133/81) 3% [2%] nd NS Good</td>
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<td>CHF events</td>
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<tr>
<td>CAD events</td>
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</tr>
<tr>
<td>ESRD</td>
<td>AASK 2002 2006</td>
<td>4 y (≥3 y)</td>
<td>Metoprolol Amlodipine</td>
<td>46 mL/min/1.73 m²</td>
<td>Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96) 135/81 (133/81) nd Risk reduction 59% (36; 74%) &lt;0.001 Good</td>
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</tr>
</tbody>
</table>

280 Adjusted  
281 Study only included African American patients  
282 Adjusted  
283 Calculated by ERT  
284 Calculated by ERT  
285 Calculated by ERT  
286 Study only included African American patients  
287 Adjusted
Supplemental Table 31. RCTs examining the effect of β-blocker vs. CCB in patients with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention Control</td>
<td>Baseline</td>
<td>Blood pressure</td>
<td>Results</td>
<td>Intervention [Control]</td>
<td>Achieved Intervention (Control)</td>
<td>Baseline Intervention (Control)</td>
<td>∆ Intervention [Control]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention Control</td>
<td>Male 0.63g/24h Female 0.44 g/24h</td>
<td>SBP/DBP</td>
<td>Intervention</td>
<td>Control</td>
<td>Control</td>
<td>Achieved</td>
<td>Intervention</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Acute slope – ∆GFR in first 3 months, mL/min/1.73 m²/y</td>
<td>AASK 2002288 US[99]</td>
<td>4 y (≥3 y)</td>
<td>Metoprolol Amlodipine</td>
<td>300 (441)</td>
<td>145 (217)</td>
<td>46 mL/min/1.73 m²</td>
<td>Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96)</td>
<td>135/81 (133/81)</td>
<td>46289 (46)</td>
</tr>
<tr>
<td>Chronic slope – ∆GFR after first 3 months, mL/min/1.73 m²/y</td>
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<tr>
<td>Total slope – ∆GFR over 4 y, mL/min/1.73 m²/y</td>
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<tr>
<td>Proteinuria</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>%∆Proteinuria (geometric mean UPCR)</td>
<td>AASK 2002290 US[99]</td>
<td>6 mo (6 mo)</td>
<td>Metoprolol Amlodipine</td>
<td>300 (441)</td>
<td>145 (217)</td>
<td>46 mL/min/1.73 m²</td>
<td>Male 0.63g/24h Female 0.44 g/24h</td>
<td>150/95 (150/96)</td>
<td>135/81 (133/81)</td>
<td>Male 0.61; Female 0.41 (Male 0.63; Female 0.44)</td>
</tr>
</tbody>
</table>

288 Study only included African American patients
289 Primary outcome
290 Study only included African American patients
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Baseline GFR or Scr</td>
<td>Baseline Proteinuria</td>
<td>Achieved SBP/DBP Intervention (Control)</td>
<td>Baseline SBP/DBP Intervention (Control)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Vonend 2003 Germany &amp; Hungary [96]</td>
<td>24 wk (22 wk)</td>
<td>Moxonidine Nitrendipine</td>
<td>89 (89) 82 (82)</td>
<td>SCR 285 µmol/L</td>
<td>Albuminuria 1.3 g/24h</td>
<td>149/90 (150/90)</td>
<td>141/86 [91] (137/80)</td>
</tr>
</tbody>
</table>

[91] Estimated from graph
### Supplemental Table 33. General population RCTs comparing ACEI + diuretic vs. placebo in CKD with DM subgroups [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention Control</td>
<td>Intervention Control</td>
<td></td>
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</tr>
<tr>
<td>Composite kidney outcome</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>New-onset microalbuminuria(^{292}), new onset nephropathy(^{293}), doubling of Scr, or doubling of Scr to &gt;200 μmol/L or ESRD in eGFR&lt;60 mL/min/1.73 m²</td>
<td>ADVANCE 2009 Multi[29]</td>
<td>4 y (4 y)</td>
<td>Perindopril-Indapamide Placebo</td>
<td>1063 (1063)</td>
<td>1094 (1094)</td>
<td>nd nd</td>
<td>nd nd</td>
</tr>
<tr>
<td>Composite CV outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite of major macrovascular events(^{294}) in patients with CKD 1 or 2</td>
<td></td>
<td>2482</td>
<td>eGFR 87 mL/min/1.73 m²</td>
<td>UACR ≥30</td>
<td>148/82</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Composite of major macrovascular events(^{296}) in patients with CKD 3</td>
<td></td>
<td>2033</td>
<td>eGFR 51 mL/min/1.73 m²</td>
<td>UACR 30-150 mg/g</td>
<td>nd</td>
<td>147/80</td>
<td>nd</td>
</tr>
<tr>
<td>Composite of major macrovascular events(^{296}) in patients with UACR 30-150</td>
<td>ADVANCE 2010 Multi[40]</td>
<td>4 y (4 y)</td>
<td>Perindopril-Indapamide Placebo</td>
<td>nd</td>
<td>UACR ≥150 mg/g</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Composite of major macrovascular events(^{297}) in patients with UACR ≥150</td>
<td></td>
<td>nd</td>
<td>nd</td>
<td>UACR ≥150 mg/g</td>
<td>nd</td>
<td>nd</td>
<td>61 (14%) [77 (18%)]</td>
</tr>
<tr>
<td>Composite of major macrovascular events(^{298}) in patients with eGFR ≤60</td>
<td></td>
<td>nd</td>
<td>nd</td>
<td>UACR ≥2 mg/mmol</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>Relative risk reduction of MI, stroke or CV death</td>
<td>MICRO-HOPE 2000 Multi[4]</td>
<td>4 y (4 y)</td>
<td>Ramipril Placebo</td>
<td>814</td>
<td>326</td>
<td>nd</td>
<td>UACR ≥2 mg/mmol</td>
</tr>
</tbody>
</table>

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\(^{292}\) UACR 30-300 μg/mg  
\(^{293}\) New onset macroalbuminuria defined as UACR >300μg/mg, which required confirmation by a 2nd sample  
\(^{294}\) CV death, non-fatal MI, or non-fatal stroke  
\(^{296}\) CV death, non-fatal MI, or non-fatal stroke  
\(^{297}\) CV death, non-fatal MI, or non-fatal stroke  
\(^{298}\) CV death, non-fatal MI, or non-fatal stroke  
\(^{299}\) Estimated from figure
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<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Country</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or SCR</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
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<tr>
<td>Composite of cardiovascular death, non-fatal MI and resuscitative cardiac arrest</td>
<td>EUROPA 2007 Multi[19]</td>
<td>4 y (4 y)</td>
<td>Perindopril Placebo</td>
<td>6295</td>
<td>GFR &lt;75 mL/min/1.73 m²</td>
<td>nd</td>
<td>140/81</td>
<td>nd</td>
<td>nd</td>
<td>HR 0.84 (0.72; 0.98)</td>
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<td>All-cause mortality in patients with CKD 1 or 2</td>
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<td></td>
<td></td>
<td>2482</td>
<td>eGFR 87 mL/min/1.73 m²</td>
<td>UACR ≥30</td>
<td>148/82</td>
<td>nd</td>
<td>114 (9%) [126 (10%)]</td>
<td>HR 0.90 (0.70; 1.10)</td>
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<td>All-cause mortality in patients with CKD 3</td>
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<td></td>
<td>2033</td>
<td>eGFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>147/80</td>
<td>nd</td>
<td>117 (12%) [135 (13%)]</td>
<td>HR 0.87 (0.67; 1.10)</td>
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<td>All-cause mortality in patients with UACR 30-150</td>
<td>ADVANCE 2010 Multi[40]</td>
<td>4 y (4 y)</td>
<td>Perindopril-Indapamide Placebo</td>
<td>nd</td>
<td>nd</td>
<td>UACR ≥150 mg/g</td>
<td>nd</td>
<td>64 (12%) [69 (14%)]</td>
<td>HR 0.87 (0.62; 1.22)</td>
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<td>All-cause mortality in patients with UACR ≥150</td>
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<td>1757</td>
<td>Sc 102 μmol/L CrCl 50 mL/min</td>
<td>nd</td>
<td>149/84</td>
<td>nd</td>
<td>153 [138]</td>
<td>Risk reduction -4% (-31; 17)</td>
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<tr>
<td>Total death in CKD patients</td>
<td>PROGRESS 2007 2008 Multi[69;77]</td>
<td>4 y (4 y)</td>
<td>Perindopril-Indapamide Placebo</td>
<td>1757</td>
<td>eGFR ≤60 mL/min/1.73 m²</td>
<td>nd</td>
<td>149/84</td>
<td>nd</td>
<td>153 [138]</td>
<td>Risk reduction -4% (-31; 17)</td>
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<td>CV mortality</td>
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<td>148/82</td>
<td>nd</td>
<td>61 (5%) [79 (6%)]</td>
<td>HR 0.77 (0.55; 1.07)</td>
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<td>CV death in patients with CKD 3</td>
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<td>2033</td>
<td>eGFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>147/80</td>
<td>nd</td>
<td>66 (7%) [82 (8%)]</td>
<td>HR 0.80 (0.58; 1.11)</td>
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<td>CV death in patients with UACR 30-150</td>
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<td>nd</td>
<td>UACR ≥150 mg/g</td>
<td>nd</td>
<td>62 (5%) [78 (7%)]</td>
<td>HR 0.79 (0.57; 1.10)</td>
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<td>Sc 102 μmol/L CrCl 50 mL/min</td>
<td>nd</td>
<td>149/84</td>
<td>nd</td>
<td>153 [138]</td>
<td>Risk reduction -4% (-31; 17)</td>
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<td>68 (6%) [94 (9%)]</td>
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<td>Study Year Country</td>
<td>Duration Outcome (Treatment)</td>
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<td>Baseline Description</td>
<td>Baseline Proteinuria</td>
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<td>Achieved Blood Pressure</td>
<td>Events (%) Intervention [Control]</td>
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<td>Placebo</td>
<td>1757</td>
<td>GFR or Scr &gt; 102 μmol/L CrCl 50 mL/min</td>
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<td>85 [86]</td>
<td>Risk reduction 7% (-24; 32)</td>
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<td>Major cerebrovascular events in patients with CKD 1 or 2</td>
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<td>148/82</td>
<td>nd</td>
<td>69 (6%) [77 (6%)]</td>
<td>HR 0.89 (0.64; 1.23)</td>
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<td>56 (5%) [63 (5%)]</td>
<td>HR 0.88 (0.61; 1.26)</td>
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<td>75 (6%) [82 (7%)]</td>
<td>HR 0.90 (0.66; 1.24)</td>
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<td>147/80</td>
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<td>74 (7%) [86 (8%)]</td>
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<td>51 (5%) [60 (5%)]</td>
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<td>39 (9%) [38 (9%)]</td>
<td>HR 0.95 (0.61; 1.49)</td>
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<td>21 (5%) [36 (9%)]</td>
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<td>Major cerebrovascular events in patients with eGFR ≤60</td>
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<td>77 (7%) [98 (9%)]</td>
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<td>PROGRESS 2007 2008 Multi[69;77]</td>
<td>4 y (4 y)</td>
<td>Perindopril-Indapamide</td>
<td>Placebo</td>
<td>1757</td>
<td>GFR or Scr &gt; 102 μmol/L CrCl 50 mL/min</td>
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<td>149/84</td>
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<td>178 [222]</td>
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<td>Major vascular event in patients with CKD (per 100 person-y)</td>
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<td>Relative risk reduction of major vascular event in patients with CKD</td>
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<td>Major vascular event in patients with CKD over 5 y</td>
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<td>Incidence rate of stroke in patients with CKD (per 100 person-y)</td>
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<td>Relative risk reduction of stroke in patients with CKD</td>
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<td>Absolute risk reduction of stroke in patients with CKD over 5 y</td>
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<td>Kidney Function</td>
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<td>Blood pressure</td>
<td>Results</td>
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<td>Progression of nephropathy in patient with microalbuminuria</td>
<td>ADVANCE 2009 Multi[29]</td>
<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
<td>1441 (1441) 1421 (1421)</td>
<td>nd nd nd nd</td>
<td>89 (6%) [128 (9%)]</td>
<td>HR 0.69 (0.52; 0.91)</td>
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<td>Regression of nephropathy in patients with microalbuminuria</td>
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<td>Perindopril-Indapamide Placebo</td>
<td>197 (197) 204 (204)</td>
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<td>797 (55%) [698 (49%)]</td>
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<td>Regression of nephropathy in patients with macroalbuminuria</td>
<td>ADVANCE 2010 Multi[40]</td>
<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
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<td>51 (26%) [47 (23%)]</td>
<td>HR 1.08 (0.72; 1.60)</td>
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<td>New or worsening nephropathy in patients with CKD 1 or 2</td>
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<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
<td>2482</td>
<td>eGFR 87 mL/min/1.73m² UACR ≥30 148/82 nd</td>
<td>75 (6%) [105 (9%)]</td>
<td>HR 0.69 (0.51; 0.93)</td>
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<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
<td>2033</td>
<td>eGFR 51 mL/min/1.73m² UACR ≥30 147/80 nd</td>
<td>64 (6%) [68 (7%)]</td>
<td>HR 0.93 (0.66; 1.31)</td>
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<td>New or worsening nephropathy in patients with UACR 30-150</td>
<td>ADVANCE 2010 Multi[40]</td>
<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
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<td>74 (6%) [97 (8%)]</td>
<td>HR 0.75 (0.55; 1.01)</td>
<td>NS</td>
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<td>New or worsening nephropathy in patients with UACR ≥150</td>
<td>ADVANCE 2010 Multi[40]</td>
<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
<td>nd nd UACR ≥150 mg/g</td>
<td>53 (12) [64 (15%)]</td>
<td>HR 0.76 (0.53; 1.09)</td>
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<td>New or worsening nephropathy in patients with eGFR ≤60</td>
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<td>4 y</td>
<td>Perindopril-Indapamide Placebo</td>
<td>nd nd UACR ≥150 mg/g</td>
<td>72 (7%) [76 (7%)]</td>
<td>HR 0.95 (0.69; 1.32)</td>
<td>NS</td>
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300 Worsening of at least one albuminuria stage (from normoalbuminuria or either micro- or macroalbuminuria or from micro- to macroalbuminuria)
301 Improvement of at least one albuminuria stage.
302 Improvement of at least one albuminuria stage.
303 Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
304 Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
305 Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
306 Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
307 Development of macroalbuminuria, doubling of serum creatinine to a level of at least 2.26 mg/dL, need for RRT or death due to renal disease
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<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
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<td>Control</td>
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<td>ΔeGFR in patients with microalbuminuria, mL/min</td>
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<td>4 y (4 y)</td>
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<td>Placebo</td>
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<td>1421 (1421)</td>
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<td>ΔeGFR in patients with macroalbuminuria, mL/min</td>
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</tbody>
</table>
### Supplemental Table 35. General population RCTs comparing ARB or (ACE + ARB) vs. ACE in CKD subgroups with and without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>Intervention</th>
<th>Control</th>
<th>Intervention</th>
<th>Control</th>
<th>Baseline GFR or S&lt;sub&gt;Cr&lt;/sub&gt;</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcomes</td>
<td></td>
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<tr>
<td>Dialysis, doubling of S&lt;sub&gt;Cr&lt;/sub&gt; or death in patients with microalbuminuria or macroalbuminuria</td>
<td></td>
<td></td>
<td>4 y (4 y)</td>
<td>Telmisartan</td>
<td>2673 (2673)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ramipril + Telmisartan</td>
<td>Ramipril</td>
<td>2648 (2648)</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td></td>
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</tr>
<tr>
<td>Dialysis, doubling of S&lt;sub&gt;Cr&lt;/sub&gt; or death in patients with eGFR &lt;60 mL/min/1.73 m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ONTARGET 2008 Multi[63]</td>
<td></td>
<td></td>
<td>Telmisartan</td>
<td>4046 (4046)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ramipril + Telmisartan</td>
<td>Ramipril</td>
<td>3988 (3988)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

308 Estimated from figure 309 Estimated from figure 310 Estimated from figure 311 Estimated from figure
Supplemental Table 36. General population RCTs comparing CCB vs. active control in CKD subgroups with and without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study, Year, Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure Results</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite outcome</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney failure or halving of GFR in entire subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi[50]</td>
<td>5 y (5y)</td>
<td>Amlodipine</td>
<td>1516 (1516)</td>
<td>2613 (2613)</td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>90 (6%) [180 (7%)]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chlorthalidone</td>
<td>506 (506)</td>
<td>881 (881)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>56 (11%) [96% (11%)]</td>
</tr>
<tr>
<td>Kidney failure or halving of GFR in DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi[50]</td>
<td>5 y (5y)</td>
<td>Amlodipine</td>
<td>1010 (1010)</td>
<td>1732 (1732)</td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>34 (3%) [84% (5%)]</td>
</tr>
<tr>
<td>All-cause mortality and progression of CKD³¹² in patients with diabetic nephropathy</td>
<td>ACCOMPLI SH 2010 Multi[15]</td>
<td>3 y (3 y)</td>
<td>Benazepril + amlodipine</td>
<td>335 (561)</td>
<td>309 (532)</td>
<td>In all CKD pts: Scr &gt; 130 mol/L eGFR 45 mL/min/1.73 m²</td>
<td>In all CKD pts: UACR &gt; 28.8 mg/mmol</td>
<td>In all CKD patients: 145/78</td>
<td>nd</td>
<td>28 (8%) [30 (10%)]</td>
</tr>
<tr>
<td>CV Events</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD in entire subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi[50]</td>
<td>5 y (5y)</td>
<td>Amlodipine</td>
<td>1516 (1516)</td>
<td>2613 (2613)</td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>194 (13%) [318 (12%)]</td>
</tr>
<tr>
<td>CHD in DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>506 (506)</td>
<td>881 (881)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>83 (16%) [132 (15%)]</td>
</tr>
</tbody>
</table>

³¹² Time to first event of doubling of serum creatinine concentration or end-stage renal disease, defined as eGFR less than 15 mL/min/1·73 m² or need for chronic dialysis.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study, Year, Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD in non-DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td>ALLHAT 2006 Multi[50]</td>
<td>5 y (5 y)</td>
<td>Amlodipine</td>
<td></td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>111 (11%)</td>
<td>RR 1.05 (0.83; 1.33)</td>
</tr>
<tr>
<td>ESRD</td>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>1516 (1516)</td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>65 (4%)</td>
<td>RR 0.92 (0.68; 1.24)</td>
</tr>
<tr>
<td>Kidney failure in entire subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
<td></td>
<td>Amlodipine + Chlorthalidone</td>
<td>506 (506)</td>
<td>GFR 50 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>44 (9%)</td>
<td>RR 1.11 (0.77; 1.63)</td>
</tr>
<tr>
<td>Kidney failure in DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>1010 (1010)</td>
<td>GFR 51 mL/min/1.73 m²</td>
<td>nd</td>
<td>nd</td>
<td>21 (2%)</td>
<td>RR 0.66 (0.40; 1.09)</td>
</tr>
<tr>
<td>Kidney failure in non-DM subgroup with GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
<td></td>
<td>Amlodipine</td>
<td>1732 (1732)</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>16 (5%)</td>
<td>HR 0.78 (0.38; 1.56)</td>
</tr>
<tr>
<td>Progression of CKD313 in patients with diabetic nephropathy314</td>
<td>ACCOMPLISH 2010 Multi[15]</td>
<td>3 y (3 y)</td>
<td>Benazepril + amlodipine</td>
<td>335 (561)</td>
<td>In all CKD pts: S&lt;sub&gt;c&lt;/sub&gt; 140 mol/L</td>
<td>In all CKD pts: UACR 28.8 mg/mmol</td>
<td>In all CKD patients: 145/78</td>
<td>nd</td>
<td>16 (5%)</td>
</tr>
</tbody>
</table>

313 Time to first event of doubling of serum creatinine concentration or end-stage renal disease, defined as eGFR less than 15 mL/min/1·73 m² or need for chronic dialysis.

314 In all CKD patients, the progression of kidney disease (doubling of S<sub>c</sub> or ESRD) was slower in the benazepril + amlodipine group (1.6 mL/min/1.73m²) vs. the benazepril + hydrochlorothiazide group (-2.3 mL/min/1.73m²) [p=0.001].
Supplemental Table 37. Evidence profile of RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence</th>
<th>Generalizability/ applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>DM2</td>
<td>2 RCTs (High)</td>
<td>2661 (1330)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>Benefit for ACEI or ARB</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>[1˚ in 2 RCTs]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>DM2</td>
<td>3 RCTs (High)</td>
<td>3251 (1719)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>No difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DM1</td>
<td>1 RCT (High)</td>
<td>405 (206)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence</td>
<td></td>
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</tr>
<tr>
<td>Mortality</td>
<td>DM2</td>
<td>3 RCTs (High)</td>
<td>7564 (3768)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>No difference</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>DM1</td>
<td>1 RCT (High)</td>
<td>405 (206)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence</td>
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</tr>
<tr>
<td>CV mortality315</td>
<td>DM2</td>
<td>3 RCTs (High)</td>
<td>8365 (4265)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>No difference</td>
<td>Critical</td>
</tr>
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</tr>
<tr>
<td>CV events</td>
<td>DM2</td>
<td>6 RCTs (High)</td>
<td>3251 (1719)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>No difference</td>
<td>Critical</td>
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<tr>
<td>ESRD</td>
<td>DM2</td>
<td>3 RCTs (High)</td>
<td>5773 (3773)</td>
<td>No limitations (0)</td>
<td>Important inconsistencies (-1)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Possible benefit</td>
<td>Critical</td>
</tr>
<tr>
<td></td>
<td>DM1</td>
<td>1 RCT (High)</td>
<td>405 (206)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Possible benefit</td>
<td></td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>DM2</td>
<td>3 RCTs (High)</td>
<td>5773 (3773)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>Benefit of ACEI or ARB vs. Placebo</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>DM1</td>
<td>1 RCT (High)</td>
<td>405 (206)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit of ACEI or ARB vs. Placebo</td>
<td></td>
</tr>
<tr>
<td>∆Kidney function (continuous)</td>
<td>DM2</td>
<td>3 RCTs (High)</td>
<td>2193 (1188)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Possible benefit</td>
<td>Moderate</td>
</tr>
<tr>
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</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>DM2</td>
<td>2 RCTs (High)</td>
<td>1104 (729)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Benefit of ACEI or ARB vs. Placebo</td>
<td>High</td>
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</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>DM2</td>
<td>6 RCTs (High)</td>
<td>3176 (1772)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Low</td>
<td>Benefit</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>DM1</td>
<td>1 RCT (High)</td>
<td>137 (67)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Benefit</td>
<td></td>
</tr>
</tbody>
</table>

315 Includes 1 study (Brenner 2001) with a composite outcome for CVD mortality and morbidity

316 The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.
<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Summary of findings</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>6 RCTs</td>
<td>8069 (4196)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Drug discontinuation: 8-17% for ACEI or ARB and 1-22% for placebo (from 4 RCTs) Hyperkalemia: 1-2% for ACEI or ARB and 0.5-1% for placebo (from 2 RCTs) Early rise in creatinine: 0.2-2% in ACEI and ARB and 0-2% in Placebo (from 2 RCTs)</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>DM2 7 RCTs</td>
<td>9240 (4795)</td>
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<tr>
<td></td>
<td>DM1 2 RCTs</td>
<td>542 (273)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Balance of potential benefits and harms</td>
<td>Possible benefit for preventing ESRD, slowing loss of kidney function and reducing proteinuria. No difference for CV outcomes³¹⁷</td>
<td>Quality of overall evidence</td>
<td>Moderate for kidney outcomes</td>
<td>High for CV outcomes</td>
<td></td>
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</tr>
</tbody>
</table>

³¹⁷ The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.
### Supplemental Table 38. RCTs examining the effect of ACEI or ARB vs. placebo in patients with CKD and DM [categorical outcomes] 318

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR(95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Type 2 DM</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Overt albuminuria</td>
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<td></td>
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</tr>
<tr>
<td>Composite of doubling of Scr, ESRD or death</td>
<td>RENAAL 2001 Multi[20]</td>
<td>41 mo (41 mo)</td>
<td>Losartan Placebo</td>
<td>751 (751) 762 (762)</td>
<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
<td>152/82 (153/82)</td>
<td>140/74 (142/74)</td>
<td>327 (44%)319 [359 (47%)]</td>
<td>Risk reduction 16% (2%; 28%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Overt albuminuria</td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
<td>RENAAL 2001 Multi[20]</td>
<td>41 mo (41 mo)</td>
<td>Losartan Placebo</td>
<td>751 (751) 762 (762)</td>
<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
<td>152/82 (153/82)</td>
<td>140/74 (142/74)</td>
<td>158 (21%) [155 (20%)]</td>
<td>Risk reduction -2% (-27%; 19%)</td>
<td>NS</td>
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<td>Mortality</td>
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<tr>
<td>Death</td>
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<td>32 mo (≥24 mo)</td>
<td>Irbesartan Placebo</td>
<td>579 (579) 569 (569)</td>
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<td>UAE 2900 mg/24h</td>
<td>160/87 (158/87)</td>
<td>140/77 (144/80)</td>
<td>189 (33%)320 [222 (39%)]</td>
<td>RR 0.81 (0.67; 0.99)321</td>
<td>0.03</td>
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<td>Microalbuminuria</td>
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<td>All-cause mortality</td>
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<td>24 mo (24 mo)</td>
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<td>UAE 53.4 μg/min</td>
<td>153/91 (153/90)</td>
<td>141/83 (144/83)</td>
<td>3 (2%) [1 (1%)]</td>
<td>RR 3.11323 (0.33; 29.63)</td>
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<td>Death</td>
<td>Lewis 1993 US[51]</td>
<td>36 mo (36 mo)</td>
<td>Captopril Placebo</td>
<td>206 (207) 199 (202)</td>
<td>CrCl 84 mL/min</td>
<td>Scr 1.3 mg/dL</td>
<td>UPE 2500 mg/24h</td>
<td>137/85 (140/86)</td>
<td>MAP 96 (100)</td>
<td>8 (4%) [14 (7%)]</td>
<td>RR 0.55325 (0.24; 1.29)</td>
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</table>

318 Shaded studies were included in previous KDOQI guideline
319 Primary outcome
320 Primary outcome
321 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
322 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
323 Calculated by ERT
324 Calculated by ERT
325 Calculated by ERT
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<th>Duration Outcome (Treatment)</th>
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<th>Baseline</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
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<td>CV-mortality</td>
<td>DIABHYC R 2004 Multi[65]</td>
<td>47mo (47mo)</td>
<td>Ramipril Placebo</td>
<td>2443 (2443)</td>
<td>2469 (2469)</td>
<td>Scr 89.2 µmol/L</td>
<td>145/82 (145/82)</td>
<td>142/80 (142/80)</td>
<td>141 (6%) [133 (5%)]</td>
<td>RR 1.07 (0.85; 1.35)</td>
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<td>41 mo (41 mo)</td>
<td>Losartan Placebo</td>
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<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
<td>152/82 (153/82)</td>
<td>140/74 (142/74)</td>
<td>158 (21%) [155 (20%)]</td>
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<td>CV-mortality</td>
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<td>565 (569)</td>
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<td>UPE 2.9 g/d</td>
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<td>140/77 (144/80)</td>
<td>37 (7%) [46 (8%)]</td>
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<td>MI RENAAL 2001 Multi[20]</td>
<td>41 mo (41 mo)</td>
<td>Losartan Placebo</td>
<td>751 (751)</td>
<td>762 (762)</td>
<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
<td>152/82 (153/82)</td>
<td>140/74 (142/74)</td>
<td>50 (7%) [86 (9%)]</td>
<td>Risk reduction 28%</td>
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<td>First hospitalization for CHF</td>
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<td>CHF IDNT 2001 2003 Multi[18;52]</td>
<td>32 mo (≥24 mo)</td>
<td>Irbesartan Placebo</td>
<td>579 (579)</td>
<td>569 (569)</td>
<td>Scr 1.7 mg/dL</td>
<td>UPE 2.9 g/d</td>
<td>160/87 (158/87)</td>
<td>140/77 (144/80)</td>
<td>138 (24%) [144 (25%)]</td>
<td>RR 0.91 (0.72; 1.14)</td>
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<td>Myocardial infarction</td>
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326 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
<table>
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<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac revascularization</td>
<td>IRMA 2 2001 Multi[74]</td>
<td>24 mo (24 mo)</td>
<td>Irbesartan 300mg</td>
<td>194 (194) 201</td>
<td>1.05 mg/dL</td>
<td>UAE 53.4 μg/min</td>
<td>153/91 (153/90) 141/83 (144/83)</td>
<td>31 (5%) of patients [39 (6%) of patients]</td>
<td>HR 0.80 (0.49; 1.30)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>Cardiac revascularization</td>
<td>IRMA 2 2001 Multi[74]</td>
<td>24 mo (24 mo)</td>
<td>Irbesartan 150mg</td>
<td>195 (195)</td>
<td>1.0 mg/dL</td>
<td>UAE 58.3 μg/min</td>
<td>153/90 (153/90) 143/83 (144/83)</td>
<td>9 (5%) [18 (9%)]</td>
<td>RR 0.52 (0.24; 1.12)</td>
<td>NS</td>
<td>Fair</td>
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<tr>
<td>Composite CV events</td>
<td>DIABHYCA R 2004 Multi[65]</td>
<td>47 mo (47mo)</td>
<td>Ramipril</td>
<td>2443 (2443) 2469 (2469)</td>
<td>89.2 μmol/L</td>
<td>nd</td>
<td>145/82 (145/82) 142/80 (142/80)</td>
<td>362 (15%)° 327 [377 (15%)]</td>
<td>RR 0.97 (0.85; 1.11)</td>
<td>NS</td>
<td>Good</td>
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<tr>
<td>MI</td>
<td>Trevisan 1995 Italy[92]</td>
<td>6 mo (6 mo)</td>
<td>Ramipril</td>
<td>54 (60) 54 (62)</td>
<td>1.0 mg/dL</td>
<td>UPE 89.3 mg/24h</td>
<td>147/90 (151/91) 142/87 (149/87)</td>
<td>1 (2%) [1 (2%)]</td>
<td>RR 1.00 (0.06; 15.58)</td>
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<td>Good</td>
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<tr>
<td>Normoalbuminuria</td>
<td>Ravid 1993 Israel[82]</td>
<td>84 mo (64 mo)</td>
<td>Enalapril</td>
<td>49 (nd) 45 (nd)</td>
<td>106.5 μmol/L</td>
<td>UAE 11.6 mg/24h</td>
<td>MAP 98 (nd) MAP 100 (102)</td>
<td>0 (0%) [1 (2%)]</td>
<td>RR 0.31° 328 (0.01; 7.33)</td>
<td>nd</td>
<td>Good</td>
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<tr>
<td>ESRD</td>
<td>RENAAL 2001 2004 Multi[20;83]</td>
<td>48 mo (48 mo)</td>
<td>Losartan</td>
<td>751 (751) 762 (762)</td>
<td>1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
<td>152/82 (153/82) 140/74 (142/74)</td>
<td>147 (20%) [194 (26%)]</td>
<td>Risk reduction 28% (11%; 42%)</td>
<td>0.002</td>
<td>Good</td>
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<tr>
<td>ESRD in highest Scr tertile (2.1-3.6 mg/dL)</td>
<td>RENAAL 2001 2004 Multi[20;83]</td>
<td>41 mo (41 mo)</td>
<td>Losartan</td>
<td>248 (248) 263 (263)</td>
<td>2.1-3.6 mg/dL</td>
<td>CrCl 28.9 mL/min</td>
<td>UACR 1737</td>
<td>89° 329 (36%) [118 (45%)]</td>
<td>RR 0.80° 330 (0.65; 0.99)</td>
<td>&lt;0.05</td>
<td>Fair</td>
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<tr>
<td>ESRD in middle Scr tertile (1.6-2.0 mg/dL)</td>
<td>RENAAL 2001 2004 Multi[20;83]</td>
<td>264 (264) 244 (244)</td>
<td>Losartan</td>
<td>264 (264) 244 (244)</td>
<td>1.6-2.0 mg/dL</td>
<td>CrCl 39.1 mL/min</td>
<td>UACR 1045</td>
<td>45° 331 (17%) [54 (22%)]</td>
<td>RR 0.77° 332 (0.54; 1.10)</td>
<td>NS</td>
<td>Fair</td>
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</tbody>
</table>

° Primary outcome
°° Calculated by ERT
°°° No of events calculated by ERT
°°°° Calculated by ERT
°°°°° No of events calculated by ERT
°°°°°° Calculated by ERT
<table>
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<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Country</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tr>
<td>ESRD in lowest Sc(0.9-1.6 mg/dL)</td>
<td>IDNT 2001 Multi[52]</td>
<td>32 mo (≥24 mo)</td>
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<td>239 (239)</td>
<td>149/82 (149/83)</td>
<td>14 (6%)</td>
<td>RR 0.75 &lt;i&gt;0.39; 1.44&lt;/i&gt;</td>
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<td>ESRD in CKD2</td>
<td>DIABHYCA R 2004 Multi[65]</td>
<td>47 mo (47 mo)</td>
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<tr>
<td>ESRD in CKD3</td>
<td>Lewis 1993 US[51]</td>
<td>36 mo (36 mo)</td>
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<td>1030</td>
<td>152/82 (153/82)</td>
<td>64 (12%)</td>
<td>RR 0.40 &lt;i&gt;0.13; 1.30&lt;/i&gt;</td>
<td>Good</td>
</tr>
<tr>
<td>ESRD in CKD4</td>
<td>Lewis 1993 US[51]</td>
<td>36 mo (36 mo)</td>
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**Microalbuminuria**

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<th>Description</th>
<th>No of events calculated by ERT</th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
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<tr>
<td>ESRD</td>
<td>IDNT 2001 Multi[52]</td>
<td>32 mo (≥24 mo)</td>
<td></td>
<td>579 (579)</td>
<td>160/87 (158/87)</td>
<td>82 (14%)</td>
<td>RR 0.83 &lt;i&gt;0.62; 1.11&lt;/i&gt;</td>
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<tr>
<td>ESRD</td>
<td>DIABHYCA R 2004 Multi[65]</td>
<td>47 mo (47 mo)</td>
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<td>2443 (2443)</td>
<td>145/82 (145/82)</td>
<td>4 (0.2%)</td>
<td>RR 0.40 &lt;i&gt;0.13; 1.30&lt;/i&gt;</td>
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**Type 1 DM**

**Overt albuminuria**

| Dialysis or transplantation | Lewis 1993 US[51] | 36 mo (36 mo) | | | 206 (207) | | | | |

**Kidney Function**

**Type 2 DM**

**Overt albuminuria**

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*333* No of events calculated by ERT
*334* Calculated by ERT
*335* No of events calculated by ERT
*336* No of events calculated by ERT
*337* No of events calculated by ERT
*338* Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
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**Outcome**: Study, Year, Country, Duration (Treatment), Intervention, Control, No analyzed / Enrolled, Baseline Description, No analyzed / Enrolled, Baseline GFR or Scr, Baseline Proteinuria, Blood pressure Results, P value, Quality.

**Microalbuminuria**

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**Type 1 DM**

**Overt albuminuria**

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**Proteinuria**

**Type 2 DM**

**Microalbuminuria**

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339 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.

340 Primary outcome

341 Adjustments for differences in mean arterial pressure

342 Primary outcome

343 Primary outcome

344 Calculated by ERT

345 Calculated by ERT

346 Calculated by ERT

347 Calculated by ERT
<table>
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<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country (Treatment)</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or $Sc_r$</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events (%)</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
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**Notes:**
- Calculated by ERT
- Calculated by ERT
- Calculated by ERT
- Calculated by ERT
- Calculated by ERT

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348 Calculated by ERT
349 Calculated by ERT
350 Calculated by ERT
351 Calculated by ERT
352 Calculated by ERT
## Supplemental Table 39. RCTs examining the effect of ACEI or ARB vs. placebo in patient with CKD and DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Country</th>
<th>Description</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tr>
<td><strong>Overt albuminuria</strong></td>
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</tr>
<tr>
<td>Median rate of ↓GFR /CrCl, ml/min/1.73 m²</td>
<td>RENAA 2001 Multi[20]</td>
<td>41 mo (41 mo)</td>
<td>Losartan</td>
<td>Placebo</td>
<td>751 (751)</td>
<td>762 (762)</td>
<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
</tr>
<tr>
<td>Change in slope of 1/Scr, dL/mg/L</td>
<td>RENAA 2001 Multi[20]</td>
<td>41 mo (41 mo)</td>
<td>Losartan</td>
<td>Placebo</td>
<td>751 (751)</td>
<td>762 (762)</td>
<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
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<tr>
<td><strong>Microalbuminuria</strong></td>
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<tr>
<td>ΔGFR /CrCl, ml/min/1.73 m²</td>
<td>IRMA 2001 Multi[74]</td>
<td>24 mo (24 mo)</td>
<td>Irbesartan 300 mg</td>
<td>Placebo</td>
<td>194 (194)</td>
<td>201 (201)</td>
<td>Scr 1.05 mg/dL</td>
<td>UACR 53.4 mg/g</td>
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<td></td>
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<td></td>
<td>Irbesartan 150 mg</td>
<td>Placebo</td>
<td>195 (195)</td>
<td>201 (201)</td>
<td>Scr 1.0 mg/dL</td>
<td>UACR 58.3 mg/g</td>
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<tr>
<td>ΔScr, μmol/L</td>
<td>Ravid 1993 Israel[82]</td>
<td>60 mo (60 mo)</td>
<td>Enalapril</td>
<td>Placebo</td>
<td>48 (nd)</td>
<td>42 (nd)</td>
<td>Scr 10.65 μmol/L</td>
<td>UAE 142.7 mg/24h</td>
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<tr>
<td>%ΔUACR</td>
<td>RENAA 2001 Multi[20]</td>
<td>41 mo (41 mo)</td>
<td>Losartan</td>
<td>Placebo</td>
<td>751 (751)</td>
<td>762 (762)</td>
<td>Scr 1.9 mg/dL</td>
<td>UACR 1237 mg/g</td>
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<tr>
<td>%ΔProteinuria, μg/min</td>
<td>IRMA 2001 Multi[74]</td>
<td>24 mo (24 mo)</td>
<td>Irbesartan 300 mg</td>
<td>Placebo</td>
<td>194 (194)</td>
<td>201 (201)</td>
<td>Scr 1.0 mg/dL</td>
<td>UAE 53.4 μg/min</td>
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<td>Irbesartan 150 mg</td>
<td>Placebo</td>
<td>195 (195)</td>
<td>201 (201)</td>
<td>Scr 1.0 mg/dL</td>
<td>UAE 58.3 μg/min</td>
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<tr>
<td>ΔUACR, mg/dL</td>
<td>Agha 2009 Pakistan[6]</td>
<td>6mo (6mo)</td>
<td>Losartan</td>
<td>Placebo</td>
<td>190 (193)</td>
<td>171 (190)</td>
<td>Scr 1.2 mg/dL</td>
<td>UAE 102 mg/dL</td>
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<td>ΔProteinuria, μg/min</td>
<td>Trevisan 1995 Italy[92]</td>
<td>6 mo (6 mo)</td>
<td>Ramipril</td>
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<td>54 (60)</td>
<td>54 (62)</td>
<td>Scr 1.0 mg/dL</td>
<td>62 μg/min</td>
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353 Shaded studies were included in previous KDOQI guideline
354 Calculated by ERT from graph
355 Calculated by ERT from graph
356 Primary outcome
357 Calculated by ERT from graph
358 Estimated from graph
359 Estimated from graph
360 Primary outcome
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<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Blood pressure</th>
<th>Results</th>
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<td>(Control)</td>
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<td>ΔAlbuminuria, mg/24h</td>
<td>Ravid 1993 Israel[82]</td>
<td>60 mo (60 mo)</td>
<td>Enalapril</td>
<td>Placebo</td>
<td>MAP 98 (nd)</td>
<td>142.7 (123.1)</td>
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<td>ΔUACR after adjustment for SBP, mg/g</td>
<td>INNOVATION 2007 Japan[55]</td>
<td>16mo (≥12mo)</td>
<td>Telmisartan</td>
<td>Placebo</td>
<td>UACR 171 mg/g</td>
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<td>Microalbuminuria</td>
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<td>Captopril</td>
<td>Placebo</td>
<td>UPE 89.3 mg/24h</td>
<td>62 (62)</td>
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<td>Laffel 1995 US[49]</td>
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**Notes:**
- Estimated from graph
- Primary outcome
- Primary outcome
## Supplemental Table 40. Evidence profile of RCTs examining the effect of ACEI or ARB vs. Dihydropyridine CCB in patients with CKD and Type 2 DM

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<th>Outcome</th>
<th># of studies and study design</th>
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<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
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<td>Composite kidney outcomes</td>
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<td>1146 (579)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
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<td>Moderate</td>
<td>Benefit ACEI or ARB vs. CCB</td>
<td>Critical</td>
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<td>[1 in 1 RCT]</td>
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<tr>
<td>Mortality</td>
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<td>NA</td>
<td>Direct (0)</td>
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<td>Moderate</td>
<td>No difference for ACEI or ARB vs. CCB</td>
<td>Critical</td>
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<td>CV mortality</td>
<td>2 RCTs (High)</td>
<td>1229 (623)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>Imprecision (-1)</td>
<td>Moderate</td>
<td>Insufficient evidence for ACEI or ARB vs. CCB</td>
<td>Critical</td>
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<td>CV events</td>
<td>3 RCTs (High)</td>
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<td>No important inconsistencies (0)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>High</td>
<td>No difference for ACEI or ARB vs. CCB</td>
<td>Critical</td>
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<td>ESRD</td>
<td>1 RCT (High)</td>
<td>1146 (579)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Possible benefit for ACEI or ARB vs. CCB</td>
<td>Critical</td>
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<tr>
<td>Kidney function (categorical)</td>
<td>1 RCT (High)</td>
<td>1146 (579)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>Benefit for ACEI or ARB vs. CCB</td>
<td>High</td>
</tr>
<tr>
<td>ΔKidney function (continuous)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>1 RCT (High)</td>
<td>117 (53)</td>
<td>Serious limitations (-2)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Very low</td>
<td>Insufficient evidence for ACEI or ARB vs. CCB</td>
<td>High</td>
</tr>
<tr>
<td>[1 in 1 RCT]</td>
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</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>4 RCTs (High)</td>
<td>888 (449)</td>
<td>No limitations (0)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Benefit for ACEI or ARB vs. CCB</td>
<td>Moderate</td>
</tr>
<tr>
<td>[1 in 4 RCTs]</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>3 RCTs</td>
<td>1978 (985)</td>
<td>Drug discontinuation: 7-13% for ACEI (from 3 RCTs) and 6-9% in CCB (from 2 RCTs) Hyperkalemia: 2% for ACEI or ARB and 0.5% for CCB (from 1 RCT) Early rise in creatinine: 0.2% in ACEI and 0% in CCB (from 1 RCT)</td>
<td>Drug discontinuation: 7-13% for ACEI (from 3 RCTs) and 6-9% in CCB (from 2 RCTs) Hyperkalemia: 2% for ACEI or ARB and 0.5% for CCB (from 1 RCT) Early rise in creatinine: 0.2% in ACEI and 0% in CCB (from 1 RCT)</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7 RCTs</td>
<td>3466 (1739)</td>
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</tr>
</tbody>
</table>

### Balance of potential benefits and harms
Possible benefit for ACEI or ARB in preventing ESRD, slowing loss of kidney function and reducing proteinuria
No difference for CV Events

### Quality of overall evidence
Moderate for kidney outcomes
Moderate for cardiovascular outcomes

---

364 The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.
365 The data is consistent with the use of ACEI or ARB in preventing congestive heart failure.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
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<tr>
<td>Overt albuminuria</td>
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<tr>
<td>Composite of doubling of Scr, ESRD or death</td>
<td>IDNT 2001 Multi[52]</td>
<td>32 mo (≥24 mo)</td>
<td>Irbesartan Amlodipine</td>
<td>579 (579) 567 (567)</td>
<td>Scr 1.7 mg/dL UAE 2900 mg/24h</td>
<td>160/87 (159/87)</td>
<td>140/77 (141/77)</td>
<td>189 (33%)[367] [233 (41%)]</td>
<td>RR 0.76 (0.63; 0.92)</td>
<td>0.005</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
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<tr>
<td>Overt albuminuria</td>
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</tr>
<tr>
<td>Death</td>
<td>IDNT 2001 Multi[52]</td>
<td>32 mo (≥24 mo)</td>
<td>Irbesartan Amlodipine</td>
<td>579 (579) 567 (567)</td>
<td>Scr 1.7 mg/dL UAE 2900 mg/24h</td>
<td>160/87 (159/87)</td>
<td>140/77 (141/77)</td>
<td>87 (15%) [83 (15%)]</td>
<td>RR 1.05 (0.76; 1.42)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td><strong>CV mortality</strong></td>
<td></td>
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<td>Overt albuminuria</td>
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</tr>
<tr>
<td>CV mortality</td>
<td>IDNT 2003 Multi[18]</td>
<td>32 mo (≥24 mo)</td>
<td>Irbesartan Amlodipine</td>
<td>574 (579) 565 (567)</td>
<td>Scr 1.67 mg/dL UPE 2.9 g/d</td>
<td>160/87 (159/87)</td>
<td>140/77 (141/77)</td>
<td>52 (9%) [37 (7%)]</td>
<td>HR 1.36 (0.89; 2.07)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Microalbuminuria</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Death from MI</td>
<td>Chan 1992 Hong Kong[24]</td>
<td>12 mo (12 mo)</td>
<td>Enalapril Nifedipine</td>
<td>49 (52) 41 (50)</td>
<td>CrCl 66 mL/min UAE 64.7 mg/24h MAP 120 (117)</td>
<td>MAP 99 (97)</td>
<td>1 (2%) [0 (0%)]</td>
<td>RR 2.52 (0.11; 61.12)</td>
<td>nd</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td><strong>CV events</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Overt albuminuria</td>
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<tr>
<td>Composite of CVD</td>
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<td></td>
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</tr>
<tr>
<td>Composite CV events</td>
<td>IDNT 2001 Multi[18;52]</td>
<td>32 mo (≥24 mo)</td>
<td>Irbesartan Amlodipine</td>
<td>579 (579) 567 (567)</td>
<td>Scr 1.7 mg/dL UPE 2.9 g/d</td>
<td>160/87 (159/87)</td>
<td>140/77 (141/77)</td>
<td>259 in 30% of patients [278 in 28% of patients]</td>
<td>HR 0.90 (0.74; 1.10)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>CHF</td>
<td></td>
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</tr>
</tbody>
</table>

---

366 Shaded studies were included in previous KDOQI guideline
367 Primary outcome
368 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
369 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
370 All patients were Chinese
371 Calculated by ERT
372 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Events (%) Intervention [Control]</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.54</td>
<td>(0.97; 2.45)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>CVA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 1.55</td>
<td>(0.84; 2.87)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>Cardiac revascularization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 0.93</td>
<td>(0.55; 1.55)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 1.82</td>
<td>(0.61; 5.44)</td>
<td>NS</td>
<td>Poor</td>
</tr>
<tr>
<td>Composite of CV events</td>
<td>DIAL 2004 Italy[28]</td>
<td>12 mo (12 mo)</td>
<td>Ramipril Lercanidipine</td>
<td>66 (89) 64 (91)</td>
<td>Scr 79.6 µmol/L UAE 86.5 µg/min</td>
<td>156/93 (155/92) 140/80 (140/80)</td>
<td>2 (3%) [5 (8%)]</td>
<td>RR 0.39</td>
<td>(0.08; 1.93)</td>
<td>nd</td>
<td>Fair</td>
<td></td>
</tr>
<tr>
<td>ESRD Overt albuminuria</td>
<td>ESRD IDNT 2001 Multi[52]</td>
<td>32 mo (≥24 mo)</td>
<td>Irbesartan Amlodipine</td>
<td>579 (579) 567 (567)</td>
<td>Scr 1.7 mg/dL UAE 2900 mg/24h</td>
<td>160/87 (159/87) 140/77 (141/77)</td>
<td>82 (14%) [104 (16%)]</td>
<td>RR 0.76</td>
<td>(0.57; 1.02)</td>
<td>NS</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Kidney function</td>
<td>Overt albuminuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>RR 0.61</td>
<td>(0.48; 0.79)</td>
<td>&lt;0.001</td>
<td>Good</td>
</tr>
<tr>
<td>Proteinuria Microalbuminuria</td>
<td></td>
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</tr>
</tbody>
</table>

373 The J-MIND contains both micro- and normo-albuminuric patients
374 Estimated from graph
375 Calculated by ERT
376 Calculated by ERT
377 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
378 Adjustment for base-line covariates was performed with the use of Cox proportional-hazards models with terms for the treatment assignment and the base-line covariates.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline</th>
<th>Baseline</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>J-MIND</td>
<td>2001</td>
<td>Japan</td>
<td>24 mo</td>
<td>Enalapril retard</td>
<td>Intervention (24 mo)</td>
<td>Control (nd)</td>
<td>Intervention (nd)</td>
<td>Control (CrCl 102 mL/min UAE 42 mg/dL)</td>
<td>Intervention (Baseline 161/90 (162/90) Achieved 145/82 (143/82))</td>
<td>Events (% Intervention [Control]) 6% (6%) RR 0.91 (0.21; 3.87)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>64</td>
<td>102</td>
<td>42</td>
<td>161/90</td>
<td>145/82</td>
<td>6%</td>
</tr>
</tbody>
</table>

379 The J-MIND contains both micro- and normo-albuminuric patients
380 Baseline UAE is reported for all patients enrolled some of whom are normoalbuminuric.
381 Estimated from graph
382 Primary outcome
383 Calculated by ERT
## Supplemental Table 42. RCTs examining the effect of ACEI or ARB vs. dihydropyridine CCB in patients with CKD and Type 2 DM [continuous outcomes] 384

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline</th>
<th>Baseline</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>GFR or Scr</td>
<td>Proteinuria</td>
<td>SBP/DBP Intervention (Control)</td>
<td>Intervention (Control)</td>
<td>Δ Intervention (Control)</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ΔMedian UAE</td>
<td>Agardh 1996 UK[5]</td>
<td>12 mo (12 mo)</td>
<td>Lisinopril</td>
<td>Nifedipine</td>
<td>168 (168)</td>
<td>167 (167)</td>
<td>CrCl 101.58 mL/min</td>
<td>UAE 94.3 mg/24h</td>
<td>163/99 (161/97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UAER 94.3 µg/min</td>
<td>147/85 (148/86)</td>
<td>135/78 (136/79)</td>
</tr>
<tr>
<td>ΔUAER</td>
<td>MARVAL 2002 UK[95]</td>
<td>3 mo (6 mo)</td>
<td>Valsartan</td>
<td>Amlodipine</td>
<td>142 (169)</td>
<td>136 (163)</td>
<td>Sc&gt; 97.3 µmol/L</td>
<td>UAER 57.9 µg/min</td>
<td>147/85 (148/86)</td>
</tr>
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<tr>
<td></td>
<td></td>
<td>5 mo (6 mo)</td>
<td></td>
<td></td>
<td>142 (169)</td>
<td>136 (163)</td>
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<td></td>
<td>6 mo (6 mo)</td>
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<td></td>
<td>163 (169)</td>
<td>158 (163)</td>
<td>LOCF [</td>
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</tr>
<tr>
<td>%ΔUAER</td>
<td>Chan 2000 Hong Kong[25]</td>
<td>60 mo (60 mo)</td>
<td>Ramipril</td>
<td>Lercanidipine</td>
<td>66 (89)</td>
<td>64 (91)</td>
<td>Sc&gt; 79.6 µmol/L</td>
<td>UAER 86.5 µg/min</td>
<td>156/93 (155/92)</td>
</tr>
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</tr>
<tr>
<td>Mean albuminuria value during treatment period, mL/min</td>
<td>Chan 2000 Hong Kong[25]</td>
<td>60 mo (60 mo)</td>
<td>Enalapril</td>
<td>Nifedipine</td>
<td>52 (52)</td>
<td>50 (50)</td>
<td>CrCl 73.7 mL/min</td>
<td>UAE 73.4 mg/24h</td>
<td>172/83 (169/93)</td>
</tr>
</tbody>
</table>

384 Shaded studies were included in previous KDOQI guideline 385 Primary outcome 386 Primary outcome 387 Primary outcome 388 All patients were Chinese 389 Primary outcome
### Supplemental Table 43. Evidence profile of RCTs examining the effect of ACEI vs. ARB in patients with Type 2 DKD

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 RCT (High)</td>
<td>250 (130)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (1) Imprecision (-1)</td>
<td>Very low</td>
<td>Insufficient evidence for ACEI and ARB.</td>
<td>Critical</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>CV events</td>
<td>1 RCT (High)</td>
<td>250 (130)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (1) Imprecision (-1)</td>
<td>Very low</td>
<td>Insufficient evidence for ACEI and ARB.</td>
<td>Critical</td>
</tr>
<tr>
<td>ESRD</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>High</td>
</tr>
<tr>
<td>ΔKidney function (continuous)</td>
<td>2 RCTs ([1 in 1 RCT])</td>
<td>348 (179)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Very low</td>
<td>Insufficient evidence for ACEI and ARB.</td>
<td>Moderate</td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>High</td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>3 RCTs ([1 in 1 RCT])</td>
<td>567 (289)</td>
<td>Serious limitations (-2)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Very low</td>
<td>Insufficient evidence for ACEI and ARB.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
| Adverse events                         | 1 RCT                        | 250 (130)           |                                             |                            |                                                          |                      | Drug discontinuation: 14% for ACEI and 18% in CCB
Early rise in creatinine: 0.02% in ACEI and 0.02% in CCB | Moderate            |
| Total                                  | 3 RCTs                       | 567 (289)           |                                             |                            |                                                          |                      | Quality of overall evidence
Insufficient evidence for CV outcomes
Insufficient evidence for kidney outcomes | Very low for CV outcomes
Very low for kidney outcomes |
### Supplemental Table 44. RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration (Treatmen)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
<td></td>
<td>Baseline SBP/DBP (Control)</td>
<td>Achieved SBP/DBP (Control)</td>
<td>Events (%) Intervention (Control)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
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</tr>
<tr>
<td>Death</td>
<td>Barnett 2004 Multi[16]</td>
<td>60 mo (60 mo)</td>
<td>Enalapril</td>
<td>Telmisartan</td>
<td>130 (130)</td>
<td>120 (120)</td>
<td></td>
<td>152/86 (153/85)</td>
<td>149/79 (146/80)</td>
<td>6 (5%) [6 (5%)]</td>
</tr>
<tr>
<td>CV events</td>
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<tr>
<td>CHF/Non-fatal MI</td>
<td>Barnett 2004 Multi[16]</td>
<td>60 mo (60 mo)</td>
<td>Enalapril</td>
<td>Telmisartan</td>
<td>130 (130)</td>
<td>120 (120)</td>
<td></td>
<td>152/86 (153/85)</td>
<td>149/79 (146/80)</td>
<td>13 (10%) [18 (15%)]</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
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</tr>
</tbody>
</table>

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390 Estimated from figure
391 Estimated from figure
392 Calculated by ERT
393 Estimated from figure
394 Calculated by ERT
395 Calculated by ERT
Supplemental Table 45. RCTs examining the effect of ACEI vs. ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or S(_C)</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
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<tr>
<td>Kidney function</td>
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<tr>
<td>ΔGFR, ml/min/1.73 m(^2)</td>
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</tr>
<tr>
<td>Barnett 2004 Multi[16]</td>
<td></td>
<td>60 mo (60 mo) Enalapril Telmisartan 130 (130) 120 (120)</td>
<td>GFR 94.3 ml/min/1.73 m(^2) S(_C) 0.99 mg/dL Median UAE 60 µg/min</td>
<td>152/86 (153/85) 149/79(^{396}) (146/80)</td>
<td>94.3(^{397}) (91.4)</td>
<td>3.0 (+7.6; -1.6)(^{398})</td>
<td>nd Fair</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Difference in ΔGFR, ml/min/1.73 m(^2)</td>
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<tr>
<td>Barnett 2004 Multi[16]</td>
<td></td>
<td>60 mo (60 mo) Enalapril Telmisartan 130 (130) 120 (120)</td>
<td>GFR 94.3 ml/min/1.73 m(^2) S(_C) 0.99 mg/dL Median UAE 60 µg/min</td>
<td>152/86 (153/85) 149/79(^{396}) (146/80)</td>
<td>94.3(^{397}) (91.4)</td>
<td>3.0 (+7.6; -1.6)(^{398})</td>
<td>nd Fair</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Difference in ΔSCr, mg/dL</td>
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<tr>
<td>Barnett 2004 Multi[16]</td>
<td></td>
<td>60 mo (60 mo) Enalapril Telmisartan 130 (130) 120 (120)</td>
<td>GFR 94.3 ml/min/1.73 m(^2) S(_C) 0.99 mg/dL Median UAE 60 µg/min</td>
<td>152/86 (153/85) 149/79(^{396}) (146/80)</td>
<td>94.3(^{397}) (91.4)</td>
<td>3.0 (+7.6; -1.6)(^{398})</td>
<td>nd Fair</td>
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<tr>
<td>Geometric means of GFR, ml/min</td>
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<tr>
<td>Lacourciere 2000 Canada[48]</td>
<td></td>
<td>12 wk (52 wk) Enalapril Losartan 49 (52) 49 (51)</td>
<td>GFR 95 mL/min UAE 73.9 µg/min</td>
<td>154/88 (158/90) 138/79 (144/82)</td>
<td>95 (97) -2(^{399}) (-6)</td>
<td>nd Fair</td>
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<tr>
<td>Difference in ΔSCr, mg/dL</td>
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<tr>
<td>Barnett 2004 Multi[16]</td>
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<td>60 mo (60 mo) Enalapril Telmisartan 130 (130) 120 (120)</td>
<td>GFR 94.3 ml/min/1.73 m(^2) S(_C) 0.99 mg/dL Median UAE 60 µg/min</td>
<td>152/86 (153/85) 149/79(^{396}) (146/80)</td>
<td>94.3(^{397}) (91.4)</td>
<td>3.0 (+7.6; -1.6)(^{398})</td>
<td>nd Fair</td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>ΔUAE rate</td>
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<tr>
<td>Barnett 2004 Multi[16]</td>
<td></td>
<td>5 y (5 y) Enalapril Telmisartan 130 (130) 120 (120)</td>
<td>GFR 94.3 ml/min/1.73 m(^2) S(_C) 0.99 mg/dL Median UAE 60 µg/min</td>
<td>152/86 (153/85) 149/79(^{402}) (146/80)</td>
<td>60 (46) 0.99 (1.03)</td>
<td>nd Fair</td>
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<tr>
<td>Adjusted reduction in AER, mg/24h</td>
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<tr>
<td>Sengul 2006 Turkey[88]</td>
<td></td>
<td>24 wk (24 wk) Lisinopril Telmisartan 110 (110) 109 (119)</td>
<td>GFR 92.4 ml/min/1.73 m(^2) S(_C) 85.4 mmol/L Median UAE 60 µg/min</td>
<td>151/88 (150/90) 140/82 (140/85)</td>
<td>264(^{403}) (256) -98 (-80)(^{404}) NS Poor</td>
<td></td>
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</tr>
</tbody>
</table>

\(^{396}\) Estimated from figure

\(^{397}\) Primary outcome

\(^{398}\) Since upper level of 95% CI of the difference between the enalapril and telmisartan groups was greater than +10ml/min/1.73m\(^2\), in favor of enalapril, telmisartan is not inferior to enalapril.

\(^{399}\) Estimated from figure

\(^{400}\) Estimated from figure

\(^{401}\) Estimated from figure

\(^{402}\) Estimated from figure

\(^{403}\) Primary outcome

\(^{404}\) Adjusted mean difference 18 (95% CI 0; 37), Adjusted for treatment, baseline value, weight and change in DBP. Adjusted mean difference 18, (0; 37.0) p=0.12
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔSCr, mmol/L</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Geometric means of albuminuria, μg/min</td>
<td>Lacourciere 2000 Canada[48]</td>
<td>12 wk (52 wk)</td>
<td>Enalapril Losartan</td>
<td>49 (52) 49 (51)</td>
<td>GFR 95 mL/min UAE 73.9 μg/min</td>
<td>154/88 (158/90) 138/79 (144/82)</td>
<td>73.9 (64.1) 73.9 (64.1)</td>
<td>73.9 (64.1) 73.9 (64.1)</td>
<td>-23.2 (-9.0) -34.5 (-27.3)</td>
<td>NS NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>28 wk (52 wk)</td>
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<tr>
<td></td>
<td></td>
<td>52 wk (52 wk)</td>
<td></td>
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</tr>
</tbody>
</table>

405 There was no significant difference between groups with respect to the change from baseline in log UAE after 12 and 28 weeks of treatment. At week 52, analyses showed a significant quantitative treatment-by-center interaction characterized by a variation in the magnitude of treatment differences from center to center. The difference between groups with respect to the change from baseline in log UAE is not significant when the interaction is taken into account and significant (P = 0.026) otherwise.
**Supplemental Table 46. Evidence profile of RCTs examining the effect of ARB vs. ARB in patients with CKD and DM**

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td>2 RCTs (High)</td>
<td>1684 (835)</td>
<td>No limitations (0)</td>
<td>Important inconsistency(^{106}) (-1)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>No difference</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>2 RCTs (High)</td>
<td>1684 (835)</td>
<td>No limitations (0)</td>
<td>Important inconsistency (-1)</td>
<td>Direct (0)</td>
<td>Imprecision (-1)</td>
<td>Low</td>
<td>Possible benefit for Telmisartan</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>CV mortality and morbidity</strong></td>
<td>2 RCTs (High)</td>
<td>1684 (835)</td>
<td>No limitations (0)</td>
<td>Important inconsistency (-1)</td>
<td>Direct (0)</td>
<td>None (0)</td>
<td>Moderate</td>
<td>Possible benefit for Telmisartan</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>ESRD</strong></td>
<td>1 RCT (High)</td>
<td>857 (428)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence for Telmisartan</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Kidney function (categorical)</strong></td>
<td>1 RCT (High)</td>
<td>857 (428)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence for Telmisartan</td>
<td>Critical</td>
</tr>
<tr>
<td><strong>Kidney function (continuous)</strong></td>
<td>1 RCT (High)</td>
<td>857 (428)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Possible benefit for Valsartan on measured CrCl (but not for Scr or eGFR).</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Proteinuria (categorical)</strong></td>
<td>1 RCT (High)</td>
<td>340 (168)</td>
<td>No limitations (0)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Moderate</td>
<td>No difference</td>
<td>High</td>
</tr>
<tr>
<td><strong>Proteinuria (continuous)</strong></td>
<td>3 RCTs (High) ([^1]* in 2 RCTs)</td>
<td>2024 (1003)</td>
<td>No limitations (0)</td>
<td>Important inconsistency (-1)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Low</td>
<td>Possible benefit for Telmisartan</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>3 RCTs</td>
<td>2024 (1003)</td>
<td>Drug discontinuation: 1.4-2% for ARB and 1.4-3% in ARB (from 2 RCTs) Hyperkalemia: 2% for ARB and 3% for ARB (from 1 RCT)</td>
<td></td>
<td></td>
<td></td>
<td>Quality of overall evidence</td>
<td>Moderate for CV outcomes</td>
<td>Low for kidney outcomes</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3 RCTs</td>
<td>2024 (1003)</td>
<td></td>
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</tr>
</tbody>
</table>

**Balance of potential benefits and harms**
Possible benefit for telmisartan vs. losartan for CV outcomes but no difference between telmisartan vs. valsartan.
Insufficient evidence for kidney outcomes

\(^{106}\) For mortality, the AMADEO study showed statistically significant benefit and Galle study was not statistically significant
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
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</tr>
<tr>
<td>Composite of doubling of Scr, ESRD or all-cause death</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/62 (149/63) 142/79 (142/78)</td>
<td>22 (5%) [16 (4%)]</td>
<td>RR 1.23</td>
<td>NS</td>
</tr>
<tr>
<td>Composite of doubling of Scr, ESRD and death</td>
<td>AMADEO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 ml/min/1.73 m² Scr 1.54 mg/dL</td>
<td>UPCR 1971 mg/g</td>
<td>144/80 (143/80) 135/77 (136/77)</td>
<td>3% [8%]</td>
<td>RR 0.5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
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<tr>
<td>All cause death</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/62 (149/63) 142/79 (142/78)</td>
<td>15 (4%) [8 (2%)]</td>
<td>RR 1.88</td>
<td>NS</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>AMADEO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 ml/min/1.73 m² Scr 1.54 mg/dL</td>
<td>UPCR 1971 mg/g</td>
<td>144/80 (143/80) 135/77 (136/77)</td>
<td>2 (0.5%) [13 (3%)]</td>
<td>RR 0.16</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>CV mortality</strong></td>
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<tr>
<td>Death from cardiovascular cause</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/62 (149/62) 142/79 (142/78)</td>
<td>8 (2%) [6 (1%)]</td>
<td>RR 1.34</td>
<td>nd</td>
</tr>
<tr>
<td><strong>CV mortality and morbidity</strong></td>
<td></td>
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</tr>
<tr>
<td>Composite CV morbidity and mortality</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/62 (149/62) 142/79 (142/78)</td>
<td>31 (7%) [33 (8%)]</td>
<td>RR 0.94</td>
<td>NS</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<tr>
<td>Stroke</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/62 (149/62) 142/79 (142/78)</td>
<td>4 (1%) [11 (3%)]</td>
<td>RR 0.36</td>
<td>nd</td>
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407 Calculated by ERT
408 Calculated by ERT
409 Calculated by ERT
410 Calculated by ERT
411 Calculated by ERT
412 Calculated by ERT
413 Calculated by ERT
414 Calculated by ERT
<table>
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<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or $\text{SCr}$</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tbody>
<tr>
<td>Cardiovascular morbidity and mortality</td>
<td>AMADEO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 mL/min/1.73 m² $\text{SCr}$ 1.54 mg/dL</td>
<td>UPCR 1971 mg/g</td>
<td>Baseline SBP/DBP Intervention (Control) Achieved SBP/DBP Intervention (Control)</td>
<td>Events (%) Intervention [Control]</td>
<td>RR/OR/HR (95% CI)</td>
<td>0.04</td>
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<td>ESRD</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 mL/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>Baseline SBP/DBP Intervention (Control) Achieved SBP/DBP Intervention (Control)</td>
<td>Events (%) Intervention [Control]</td>
<td>RR/OR/HR (95% CI)</td>
<td>NS</td>
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<tr>
<td>Kidney function</td>
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<tr>
<td>Doubling of $\text{SCr}$</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 mL/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>Baseline SBP/DBP Intervention (Control) Achieved SBP/DBP Intervention (Control)</td>
<td>Events (%) Intervention [Control]</td>
<td>RR/OR/HR (95% CI)</td>
<td>NS</td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>Transition rates from incipient to overt nephropathy (UACR &gt;300 mg/g and $\geq$30%)</td>
<td>INNOVATIO N 2007 Japan[55]</td>
<td>16mo (≥12mo)</td>
<td>Telmisartan 80mg Telmisartan 40mg</td>
<td>168 (nd) 172 (nd)</td>
<td>$\text{SCr}$ 0.8 mg/dL</td>
<td>UACR 172 mg/g</td>
<td>Baseline SBP/DBP Intervention (Control) Achieved SBP/DBP Intervention (Control)</td>
<td>Events (%) Intervention [Control]</td>
<td>RR/OR/HR (95% CI)</td>
<td>nd</td>
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<tr>
<td>Transition rate in normotensive patients</td>
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<tr>
<td>Micacroalbuminuria remission</td>
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415 Calculated by ERT
416 Calculated by ERT
417 Calculated by ERT
418 Calculated by ERT
419 Calculated by ERT
420 Calculated by ERT
## Supplemental Table 48. RCTs examining the effect of ARB vs. ARB in overtly albuminuric patients with CKD and Type 2 DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Results</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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</thead>
<tbody>
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<tr>
<td><strong>Kidney function</strong></td>
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</tr>
<tr>
<td>%ΔeGFR, ml/min/1.73 m²</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/82 (149/82) 142/79 (142/78)</td>
<td>48.4 (48.6)</td>
<td>-6% (-5%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>%ΔCrCl, ml/min/1.73 m²</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/82 (149/82) 142/79 (142/78)</td>
<td>57.8 (59.0)</td>
<td>-21% (-14%)</td>
<td>0.001</td>
<td>Good</td>
</tr>
<tr>
<td>%ΔSCr, mg/24h</td>
<td>VIVALDI 2008 Multi[37]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Valsartan</td>
<td>428 (443) 429 (442)</td>
<td>eGFR 56.7 ml/min/1.73 m²</td>
<td>UPER 2.7 g/d</td>
<td>148/82 (149/82) 142/79 (142/78)</td>
<td>2750 (2890)</td>
<td>14% (12%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
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</tr>
<tr>
<td>%ΔUPER, mg/24h</td>
<td>AMADEO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 ml/min/1.73 m²</td>
<td>UPCR 1971 mg/L</td>
<td>144/80 (143/80) 135/77 (136/77)</td>
<td>2750 (2890)</td>
<td>33% (-33%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>%ΔUAE, mg/24h</td>
<td>AMADEO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 ml/min/1.73 m²</td>
<td>UPCR 1971 mg/L</td>
<td>144/80 (143/80) 135/77 (136/77)</td>
<td>2750 (2890)</td>
<td>33% (-33%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>UPCR</td>
<td>AMADEO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 ml/min/1.73 m²</td>
<td>UPCR 1971 mg/L</td>
<td>144/80 (143/80) 135/77 (136/77)</td>
<td>2750 (2890)</td>
<td>33% (-33%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>UACR</td>
<td>AMMARO 2008 Multi[14]</td>
<td>12 mo (12 mo)</td>
<td>Telmisartan Losartan</td>
<td>407 (419) 420 (441)</td>
<td>eGFR 49.5 ml/min/1.73 m²</td>
<td>UPCR 1971 mg/L</td>
<td>144/80 (143/80) 135/77 (136/77)</td>
<td>2750 (2890)</td>
<td>33% (-33%)</td>
<td>NS</td>
<td>Good</td>
</tr>
<tr>
<td>ΔUACR after adjustment for SBP, mg/g</td>
<td>INNOVATION N 2007 Japan[55]</td>
<td>16mo (≥12mo) Telmisartan 80mg Telmisartan 40mg</td>
<td>168 (nd) 172 (nd) 168 (nd) 172 (nd)</td>
<td>Scr 0.8 mg/dL UACR 172 mg/g</td>
<td>138/78 (137/78) 128/74 (132/74)</td>
<td>172 (173)</td>
<td>172 (173)</td>
<td>58.8 (-37.9)</td>
<td>nd</td>
<td>Good</td>
<td></td>
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</tbody>
</table>

421 Primary outcome
422 Adjustment made for an analysis of covariance that included treatment and pooled center as class effects, with baseline as a covariate, was performed on the log-transformed data
423 Primary outcome
**Supplemental Table 49. RCTs examining the effect of DRI + ARB vs. placebo+ ARB in microalbuminuric patients with CKD and Type 2 DM [continuous outcomes]**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or ( \text{Scr} )</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Δ Intervention (Control)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Baseline SBP/DBP (Control)</td>
<td>Achieved SBP/DBP (Control)</td>
<td>Baseline SBP/DBP (Control)</td>
<td>Achieved SBP/DBP (Control)</td>
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<td>Intervention</td>
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<td>Kidney function</td>
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<tr>
<td>↓( \text{eGFR, ml/min/1.73 m}^2 )</td>
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<tr>
<td></td>
<td>AVOID 2008 2010 Mult[75,78]</td>
<td>6 mo (6 mo)</td>
<td>Aliskiren + Losartan</td>
<td>Placebo + Losartan</td>
<td>259 (301) 265 (298)</td>
<td>eGFR 68.5 mL/min/1.73 m^2</td>
<td>UACR 513 mg/g</td>
<td>135/78 (134/77)</td>
<td>133/78 (135/79)</td>
<td>68.5 (66.8)</td>
<td>2.4 (1.1; 3.7)</td>
</tr>
<tr>
<td>Δ ( \text{eGFR in patients with GFR＜60 ml/min/1.73 m}^2 )</td>
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<td></td>
<td>AVOID 2008 2010 Mult[75,78]</td>
<td>6 mo (6 mo)</td>
<td>Aliskiren + Losartan</td>
<td>Placebo + Losartan</td>
<td>129 (129) 119 (119)</td>
<td>eGFR 47.1 mL/min/1.73 m^2</td>
<td>UACR 628 mg/g</td>
<td>136/77 (135/75)</td>
<td>133/76 (139/75)</td>
<td>47.1 (44.7)</td>
<td>-1.7 (+0.25)</td>
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<tr>
<td>Δ ( \text{eGFR in patients with GFR 60-90 ml/min/1.73 m}^2 )</td>
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<td></td>
<td>AVOID 2008 2010 Mult[75,78]</td>
<td>6 mo (6 mo)</td>
<td>Aliskiren + Losartan</td>
<td>Placebo + Losartan</td>
<td>104 (104) 122 (122)</td>
<td>eGFR 73.6 mL/min/1.73 m^2</td>
<td>UACR 410 mg/g</td>
<td>134/78 (133/76)</td>
<td>136/78 (135/80)</td>
<td>73.6 (72.4)</td>
<td>-2.7 (-4.8)</td>
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<tr>
<td>Δ ( \text{eGFR in patients with GFR＞90 ml/min/1.73 m}^2 )</td>
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<tr>
<td></td>
<td>AVOID 2008 2010 Mult[75,78]</td>
<td>6 mo (6 mo)</td>
<td>Aliskiren + Losartan</td>
<td>Placebo + Losartan</td>
<td>64 (64) 51 (51)</td>
<td>eGFR 102.5 mL/min/1.73 m^2</td>
<td>UACR 530 mg/g</td>
<td>135/80 (133/78)</td>
<td>134/79 (134/79)</td>
<td>102.5 (100.4)</td>
<td>-5.6 (-9.5)</td>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>Difference in %</td>
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<tr>
<td>%( \text{UACR, mg/g} )</td>
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<td></td>
<td>AVOID 2008 2010 Mult[75,78]</td>
<td>6 mo (6 mo)</td>
<td>Aliskiren + Losartan</td>
<td>Placebo + Losartan</td>
<td>259 (301) 265 (298)</td>
<td>eGFR 68.5 mL/min/1.73 m^2</td>
<td>UACR 513 mg/g</td>
<td>135/78 (134/77)</td>
<td>133/78 (135/79)</td>
<td>513^426 (553)</td>
<td>18% (7; 28)</td>
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<td>Difference in %</td>
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<tr>
<td>%( \text{overnight UAE rate (geometric mean)} )</td>
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<td>AVOID 2008 2010 Mult[75,78]</td>
<td>6 mo (6 mo)</td>
<td>Aliskiren + Losartan</td>
<td>Placebo + Losartan</td>
<td>129 (129) 119 (119)</td>
<td>eGFR 47.1 mL/min/1.73 m^2</td>
<td>UACR 628 mg/g</td>
<td>136/77 (135/75)</td>
<td>133/76 (139/75)</td>
<td>628 (670)</td>
<td>-9 (+13)</td>
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</table>

^424 Estimated from graph
^425 Estimated from graph
^426 Primary outcome
^427 Adjustment for the change from baseline in systolic blood pressure
^428 Adjustment for the change from baseline in systolic blood pressure
<table>
<thead>
<tr>
<th></th>
<th>GFR &gt;60-90 ml/min/1.73 m², mg/g</th>
<th>GFR &gt;90 ml/min/1.73 m², mg/g</th>
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<td>ΔUACR at 24 wks (%)</td>
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<tr>
<td>in patients with GFR</td>
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<td>≥50 (%) in patients</td>
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<tr>
<td>with GFR &lt;60</td>
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<tr>
<td>ml/min/1.73 m², mg/g</td>
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<tr>
<td>UACR reduction ≥50 (%)</td>
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<tr>
<td>in patients with GFR</td>
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<tr>
<td>&gt;60 ml/min/1.73</td>
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<td>m², mg/g</td>
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<tr>
<td>eGFR</td>
<td>73.6 mL/min/1.73 m²</td>
<td>102.5 mL/min/1.73 m²</td>
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<td>UACR</td>
<td>410 mg/g</td>
<td>530 mg/g</td>
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<td>134/78</td>
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<td>410</td>
<td>-23 (-1)</td>
<td>27 (-11)</td>
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<td>Good</td>
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<td>UACR reduction ≥50 (%)</td>
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<tr>
<td>in patients with GFR</td>
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<tr>
<td>&gt;60 ml/min/1.73</td>
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<td>m², mg/g</td>
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<tr>
<td>eGFR</td>
<td>47.1 mL/min/1.73 m²</td>
<td>530 mL/min/1.73 m²</td>
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<tr>
<td>UACR</td>
<td>628 mg/g</td>
<td>628 mg/g</td>
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<tr>
<td>136/77</td>
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<td>136/78</td>
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<tr>
<td>133/76</td>
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<td>133/76</td>
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<tr>
<td>628</td>
<td>25/122 (11/115)</td>
<td>General consent was granted</td>
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<td>0.019</td>
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<td>UACR reduction ≥50 (%)</td>
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<tr>
<td>in patients with GFR</td>
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<tr>
<td>&gt;60 ml/min/1.73</td>
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<td>m², mg/g</td>
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<td>eGFR</td>
<td>73.6 mL/min/1.73 m²</td>
<td>102.5 mL/min/1.73 m²</td>
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<td>UACR</td>
<td>410 mg/g</td>
<td>530 mg/g</td>
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<td>410</td>
<td>-23 (-1)</td>
<td>27 (-11)</td>
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<td>0.012</td>
<td>Good</td>
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<tr>
<td>UACR reduction ≥50 (%)</td>
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<tr>
<td>in patients with GFR</td>
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<tr>
<td>&gt;90 ml/min/1.73</td>
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<tr>
<td>m², mg/g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR</td>
<td>102.5 mL/min/1.73 m²</td>
<td>530 mL/min/1.73 m²</td>
</tr>
<tr>
<td>UACR</td>
<td>530 mg/g</td>
<td>628 mg/g</td>
</tr>
<tr>
<td>136/78</td>
<td></td>
<td>136/78</td>
</tr>
<tr>
<td>134/79</td>
<td></td>
<td>134/79</td>
</tr>
<tr>
<td>530</td>
<td>18/62 (8/50)</td>
<td>NS Good</td>
</tr>
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</table>

429 Primary outcome
430 Primary outcome
431 Primary outcome
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events (%)</th>
<th>RR/OR/HR (95% CI)</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV mortality</td>
<td>IDNT 2003 Multi[18]</td>
<td>30 mo (≥24 mo)</td>
<td>Amlodipine Control</td>
<td>565 (567)</td>
<td>565 (569)</td>
<td>Scr 1.65 mg/dL</td>
<td>UPE 2.9 g/d</td>
<td>159/87 (158/87)</td>
<td>141/77 (144/80)</td>
<td>37 (7%)</td>
<td>HR 0.79 (0.51; 1.22)</td>
</tr>
<tr>
<td>CV events</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Composite CV events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>IDNT 2003 Multi[18]</td>
<td>30 mo (≥24 mo)</td>
<td>Amlodipine Control</td>
<td>565 (567)</td>
<td>565 (569)</td>
<td>Scr 1.65 mg/dL</td>
<td>UPE 2.9 g/d</td>
<td>159/87 (158/87)</td>
<td>141/77 (144/80)</td>
<td>29 (in 5% of patients)</td>
<td>HR 0.58 (0.37; 0.92)</td>
</tr>
<tr>
<td>CVA</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Cardiac revascularization</td>
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</table>

432 Primary outcome
433 Primary outcome
434 Primary outcome
435 Primary outcome
436 Primary outcome
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<tr>
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<tr>
<td>Proteinuria</td>
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<tr>
<td>Overt albuminuria</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%↓UACR</td>
<td>Epstein 2006 Multi[33]</td>
<td>3 mo (3 mo)</td>
<td>Eplerenone 50 + Enalapril</td>
<td>Placebo + Enalapril</td>
<td>83 (91)</td>
<td>80 (91)</td>
<td>GFR 73 mL/min Scr 80µmol/L</td>
<td>UACR 422 mg/g</td>
<td>140/83 (146/88)</td>
<td>nd</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>%↓UACR</td>
<td>Epstein 2006 Multi[33]</td>
<td>3 mo (3 mo)</td>
<td>Eplerenone 100 + Enalapril</td>
<td>Placebo + Enalapril</td>
<td>77 (86)</td>
<td>80 (91)</td>
<td>GFR 75 mL/min Scr 80µmol/L</td>
<td>UACR 240 mg/g</td>
<td>140/85 (146/88)</td>
<td>nd</td>
</tr>
</tbody>
</table>

437 Primary outcome
438 Primary outcome
### Supplemental Table 52. RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome Description</th>
<th>Study Year Country</th>
<th>Duration (Treatment)</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Events</th>
<th>RR/OR/HR (95% CI)</th>
<th>p value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Composite kidney outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, ESRD and doubling of Scr</td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m²</td>
<td>Median ACR 160.9 mg/mmol</td>
<td>137/78 (137/78)</td>
<td>131/74 (131/73)</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m²</td>
<td>Median ACR 160.9 mg/mmol</td>
<td>137/78 (137/78)</td>
<td>131/74 (131/73)</td>
</tr>
<tr>
<td><strong>CV events</strong></td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m²</td>
<td>Median ACR 160.9 mg/mmol</td>
<td>137/78 (137/78)</td>
<td>131/74 (131/73)</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m²</td>
<td>Median ACR 160.9 mg/mmol</td>
<td>137/78 (137/78)</td>
<td>131/74 (131/73)</td>
</tr>
<tr>
<td><strong>ESRD</strong></td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m²</td>
<td>Median ACR 160.9 mg/mmol</td>
<td>137/78 (137/78)</td>
<td>131/74 (131/73)</td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m²</td>
<td>Median ACR 160.9 mg/mmol</td>
<td>137/78 (137/78)</td>
<td>131/74 (131/73)</td>
</tr>
</tbody>
</table>

439 Calculated by ERT
440 Calculated by ERT
441 Calculated by ERT
442 Calculated by ERT
443 Calculated by ERT
444 Calculated by ERT
### Supplemental Table 53. RCTs examining the effect of endothelin antagonist vs. endothelin antagonist in patients with CKD with Type 2 DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>Baseline GFR or $S_\text{Cr}$</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔeGFR, ml/min/1.73 m$^2$</td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m$^2$</td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median %ΔACR, mg/mmol</td>
<td>ASCEND 2010 Multi[60]</td>
<td>5 mo (4 mo)</td>
<td>Avosentan 25 mg/d</td>
<td>Avosentan 50 mg/d</td>
<td>455 (455)</td>
<td>478 (478)</td>
<td>eGFR 34 mL/min/1.73 m$^2$</td>
</tr>
<tr>
<td>Outcome</td>
<td># of studies and study design</td>
<td>Total N (Treatment)</td>
<td>Methodological quality of studies per outcome</td>
<td>Consistency across studies</td>
<td>Directness of the evidence generalizability/applicability</td>
<td>Other considerations</td>
<td>Quality of evidence for outcome</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------</td>
<td>---------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------</td>
<td>--------------------------------------------------------</td>
<td>---------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Composite kidney outcomes</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 RCT (High)</td>
<td>154 (76)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1) Imprecision (-1)</td>
<td>Very low</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV events</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>ESRD</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>1 RCT (High)</td>
<td>154 (76)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1) Imprecision (-1)</td>
<td>Very low</td>
</tr>
<tr>
<td>∆Kidney function (continuous)</td>
<td>2 RCTs [1° in 1 RCT] (High)</td>
<td>256 (130)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Very low</td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>2 RCTs (High)</td>
<td>256 (130)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>Sparse (-1)</td>
<td>Very low</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 RCTs</td>
<td>256 (130)</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td>2 RCTs</td>
<td>256 (130)</td>
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</tr>
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</table>

**Balance of potential benefits and harms**

Possible benefit for increase in eGFR but insufficient evidence for clinically relevant outcomes

**Quality of overall evidence**

Very low for kidney outcomes
### Supplemental Table 55. RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM [categorical outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention Control</td>
<td>Intervention Control</td>
<td>76 (76) 78 (78)</td>
<td>146 μmol/L GFR 43 mL/min</td>
<td>UPE 129 mg/L</td>
<td>170/104 (169/104)</td>
<td>nd</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>Midtvedt 2001 Norway[68]</td>
<td>1 y (1 y)</td>
<td>Lisinopril Nifedipine</td>
<td>76 (76) 78 (78)</td>
<td>146 μmol/L GFR 43 mL/min</td>
<td>UPE 129 mg/L</td>
<td>170/104 (169/104)</td>
<td>nd</td>
<td>2 (3%) [0 (0%)]</td>
</tr>
<tr>
<td>Kidney function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑GFR &gt;5 mL/min</td>
<td>Midtvedt 2001 Norway[68]</td>
<td>1 y (1 y)</td>
<td>Lisinopril Nifedipine</td>
<td>76 (76) 78 (78)</td>
<td>146 μmol/L GFR 43 mL/min</td>
<td>UPE 129 mg/L</td>
<td>170/104 (169/104)</td>
<td>nd</td>
<td>18 (23%) [49 (64%)]</td>
</tr>
<tr>
<td>↓GFR &gt;5 mL/min</td>
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</tr>
</tbody>
</table>

445 Calculated by ERT
446 Calculated by ERT
Supplemental Table 56. RCTs examining the effect of ACE or ARB vs. CCB in transplant recipients with CKD without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration Outcome measurement (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
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</tr>
<tr>
<td>Kidney function</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆GFR, mL/min</td>
<td>Midtvedt 2001</td>
<td>Norway[68]</td>
<td>1 y (1 y)</td>
<td>Lisinopril Nifedipine</td>
<td>76 (76) 78 (78)</td>
<td>UPE 129 mg/L</td>
<td>170/104 (169/104)</td>
<td>nd</td>
<td>43‡ (46)</td>
<td>+1 (+10)</td>
</tr>
<tr>
<td>∆Scr, μmol/L</td>
<td>Midtvedt 2001</td>
<td>Norway[68]</td>
<td>1 y (1 y) 2 y (1 y)</td>
<td>Lisinopril Nifedipine</td>
<td>76 (76) 78 (78)</td>
<td>UPE 129 mg/L</td>
<td>170/104 (169/104)</td>
<td>nd</td>
<td>146 (137)</td>
<td>-2 (-12)</td>
</tr>
<tr>
<td>∆Scr, mg/dL</td>
<td>El-Agroudy 2003</td>
<td>Egypt[32]</td>
<td>12 mo (12 mo)</td>
<td>Losartan Amlodipine</td>
<td>54 (54) 48 (54)</td>
<td>UPE 129 mg/L</td>
<td>170/104 (169/104)</td>
<td>nd</td>
<td>-24 (+76)</td>
<td>NS (0.06)</td>
</tr>
<tr>
<td>∆Proteinuria, g/d</td>
<td>Midtvedt 2001</td>
<td>Norway[68]</td>
<td>1 y (1 y) 2 y (1 y)</td>
<td>Losartan Amlodipine</td>
<td>54 (54) 48 (54)</td>
<td>MAP 108 (108)</td>
<td>108 (108)</td>
<td>nd</td>
<td>-49 (+136)</td>
<td>NS (0.06)</td>
</tr>
<tr>
<td>∆Proteinuria, g/d</td>
<td>El-Agroudy 2003</td>
<td>Egypt[32]</td>
<td>12 mo (12 mo)</td>
<td>Losartan Amlodipine</td>
<td>54 (54) 48 (54)</td>
<td>MAP 108 (108)</td>
<td>108 (108)</td>
<td>nd</td>
<td>-0.4 (+0.2)</td>
<td>nd (0.6)</td>
</tr>
<tr>
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</tr>
</tbody>
</table>
Table 57. Evidence profile of RCTs examining the effect of CCB vs. placebo in transplant recipients without DM

<table>
<thead>
<tr>
<th>Outcome</th>
<th># of studies and study design</th>
<th>Total N (Treatment)</th>
<th>Methodological quality of studies per outcome</th>
<th>Consistency across studies</th>
<th>Directness of the evidence generalizability/applicability</th>
<th>Other considerations</th>
<th>Summary of findings</th>
<th>Quality of evidence for outcome</th>
<th>Qualitative and quantitative description of effect</th>
<th>Importance of outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite kidney outcomes</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
<td>Critical</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
<td>Critical</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>CV mortality</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
<td>Critical</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>CV events</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
<td>Critical</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>ESRD</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Critical</td>
<td>Critical</td>
<td>--</td>
<td>Critical</td>
</tr>
<tr>
<td>Kidney function (categorical)</td>
<td>1 RCT (High)</td>
<td>253 (130)</td>
<td>Some limitations (-1)</td>
<td>NA</td>
<td>Direct (0)</td>
<td>Sparse (-1)</td>
<td>Low</td>
<td>Insufficient evidence</td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>∆Kidney function (continuous)</td>
<td>3 RCTs (High)</td>
<td>581 (287)</td>
<td>Some limitations (-1)</td>
<td>No important inconsistencies (0)</td>
<td>Uncertainty about directness (-1)</td>
<td>None (0)</td>
<td>Low</td>
<td>Benefit for CCB</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (categorical)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>High</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria (continuous)</td>
<td>0 RCTs</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Moderate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td>2 RCTs</td>
<td>463 (228)</td>
<td></td>
<td></td>
<td>Drug discontinuation: 5% for CCB and 1-2% for placebo (from 2 RCTs)</td>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 RCTs</td>
<td>581 (287)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Quality of overall evidence: Low for kidney outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Balance of potential benefits and harms:
Possible benefit for kidney function outcomes
Table 58. RCTs examining the effect of CCB vs. placebo in transplant recipients [categorical outcome] 447

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or S\textsubscript{cr}</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney function</td>
<td>Rahn 1999 Germany</td>
<td>24 mo</td>
<td>Nitrendipine Placebo</td>
<td>130 (130) 123 (123)</td>
<td>S\textsubscript{cr} 146.7 μmol/L</td>
<td>nd</td>
<td>141/88 (143/88) 138/86 (143/90)</td>
<td>26 (20%) [40 (33%)]</td>
<td>RR 0.62\textsuperscript{448} (0.40; 0.94)</td>
</tr>
</tbody>
</table>

\[\text{\textsuperscript{447}}\text{Shaded studies were included in previous KDOQI guideline}\]

\[\text{\textsuperscript{448}}\text{Calculated by ERT}\]
**Supplemental Table 59. RCTs examining the effect of CCB vs. placebo in transplant recipients without DM [continuous outcome]**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Country</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or SCr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>↑SCr, μmol/L</td>
<td>Rahn 1999 Germany[81]</td>
<td>24 mo (24 mo)</td>
<td>Nitrendipine Placebo</td>
<td>130 (130) 123 (123)</td>
<td>SCr 146.7 μmol/L nd</td>
<td>nd</td>
<td>141/88 (143/88) 138/86 (143/90)</td>
<td>146.7 (137.0) [Control] +1.8 (+23.4) [Treatment]</td>
<td>0.025</td>
<td>Good</td>
</tr>
<tr>
<td>∆CrCl, mL/min</td>
<td>van Riemsdijk 2000 Netherlands[94]</td>
<td>3 mo (12 mo)</td>
<td>Isradipine Placebo</td>
<td>98 (98) 112 (112) nd nd nd nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>Final Scr, μmol/L</td>
<td>van Riemsdijk 2000 Netherlands[94]</td>
<td>3 mo (12 mo)</td>
<td>Isradipine Placebo</td>
<td>98 (98) 112 (112) nd nd nd nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Final CrCl, mL/min</td>
<td>van Riemsdijk 2000 Netherlands[94]</td>
<td>3 mo (12 mo)</td>
<td>Isradipine Placebo</td>
<td>98 (98) 112 (112) nd nd nd nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Graft function [SCr, mg/dL]</td>
<td>Kuypers 2004 Multi[47]</td>
<td>24 mo (24 mo)</td>
<td>Lacidipine Placebo</td>
<td>59 (66) 59 (65)</td>
<td>SCr 1.8 mg/dL eGFR 52 mL/min Calculate d GFR 61 mL/min nd</td>
<td>150/90 (150/90)[450] 138/82 (144/84)[451]</td>
<td>1.8 (2.0) -0.28 (-0.24)</td>
<td>0.005</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Graft function [eCrCl, mL/min]</td>
<td>Kuypers 2004 Multi[47]</td>
<td>24 mo (24 mo)</td>
<td>Lacidipine Placebo</td>
<td>59 (66) 59 (65)</td>
<td>SCr 1.8 mg/dL eGFR 52 mL/min Calculate d GFR 61 mL/min nd</td>
<td>150/90 (150/90)[450] 138/82 (144/84)[451]</td>
<td>52 (47) +11.1 (+6.4) NS (0.09)</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft function [calculated CrCl, mL/min]</td>
<td>Kuypers 2004 Multi[47]</td>
<td>24 mo (24 mo)</td>
<td>Lacidipine Placebo</td>
<td>59 (66) 59 (65)</td>
<td>SCr 1.8 mg/dL eGFR 52 mL/min Calculate d GFR 61 mL/min nd</td>
<td>150/90 (150/90)[450] 138/82 (144/84)[451]</td>
<td>61 (51) +11.0 (+2.5) 0.03</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graft function [mGFR, mL/min]</td>
<td>Kuypers 2004 Multi[47]</td>
<td>24 mo (24 mo)</td>
<td>Lacidipine Placebo</td>
<td>59 (66) 59 (65)</td>
<td>SCr 1.8 mg/dL eGFR 52 mL/min Calculate d GFR 61 mL/min nd</td>
<td>150/90 (150/90)[450] 138/82 (144/84)[451]</td>
<td>50 (47) -0.1 (-4.7) &lt;0.05</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

449 Shaded studies were included in previous KDOQI guideline
450 Estimated from graph
451 Estimated from graph
Supplemental Table 60. RCTs examining the effect of ACE vs. ARB in hypertensive transplant recipients without DM [continuous outcomes]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or S_c</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Kidney function</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔS_c, mg/dL</td>
<td>el-Agroudy 2003 Egypt[32]</td>
<td>12 mo (12 mo)</td>
<td>Captopril Losartan</td>
<td>54 (54) 54 (54) S_c 1.5 mg/dL 0.9 g/d</td>
<td>106 (108) 94 (95) 1.5 (1.5)</td>
<td>0.0 (0.0)</td>
<td>nd</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Proteinuria</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔProteinuria, g/d</td>
<td>el-Agroudy 2003 Egypt[32]</td>
<td>12 mo (12 mo)</td>
<td>Captopril Losartan</td>
<td>54 (54) 54 (54) S_c 1.5 mg/dL 0.9 g/d</td>
<td>106 (108) 94 (95) 0.8 (0.9)</td>
<td>-0.4 (-0.4)</td>
<td>nd</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcome</td>
<td>Study Year Country</td>
<td>Duration (Treatment)</td>
<td>Description</td>
<td>No analyzed / Enrolled</td>
<td>Baseline GFR or ( S_{Cr} )</td>
<td>Baseline Proteinuria</td>
<td>Blood pressure</td>
<td>Results</td>
<td>P value</td>
<td>Quality</td>
</tr>
<tr>
<td>---------</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
<td>Baseline SBP/DBP (Control)</td>
<td>Achieved SBP/DBP (Control)</td>
<td>Events No (%) Intervention [Control]</td>
<td>RR/OR/HR (95% CI)</td>
</tr>
<tr>
<td>Composite of kidney and CV outcomes</td>
<td></td>
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</tr>
<tr>
<td>Composite of all-cause mortality, CV morbidity and all-cause graft failure (CrCl&lt;15mL/min or dialysis)</td>
<td>SECRET452</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.11 g/L</td>
<td>138/84 (138/85)</td>
<td>131/80 (137/83)</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>SECRET455</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.11 g/L</td>
<td>138/84 (138/85)</td>
<td>131/80 (137/83)</td>
</tr>
<tr>
<td>CV mortality</td>
<td>SECRET457</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.11 g/L</td>
<td>138/84 (138/85)</td>
<td>131/80 (137/83)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Nephrotic syndrome (proteinuria &gt;3.5g/24h)</td>
<td>SECRET459</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.11 g/L</td>
<td>138/84 (138/85)</td>
<td>131/80 (137/83)</td>
</tr>
</tbody>
</table>

452 A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.

453 Primary outcome

454 Calculated by ERT

455 A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.

456 Calculated by ERT

457 A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.

458 Calculated by ERT

459 A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.

460 Calculated by ERT
Supplemental Table 62. RCTs examining the effect of ARB vs. placebo in transplant recipients without DM [continuous outcome]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year Country</th>
<th>Duration Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>∆Albumin concentration, mg/L</td>
<td>SECRET 461</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.11 g/L</td>
<td>138/84 (138/85)</td>
<td>16.40</td>
<td>0.0001</td>
</tr>
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<td></td>
<td></td>
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<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>131/80 (137/83)</td>
<td>-1.80</td>
<td>(+1.05)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>SECRET 461</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.11 g/L</td>
<td>138/84 (138/85)</td>
<td>0.11</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>131/80 (137/83)</td>
<td>-0.01</td>
<td>(0.00)</td>
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<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>SECRET 461</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.12 g/L</td>
<td>0.14 (0.14)</td>
<td>0.12</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
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<td>Placebo</td>
<td></td>
<td></td>
<td></td>
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<td>-0.01</td>
<td>(+0.03)</td>
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<td></td>
</tr>
<tr>
<td>Proteinuria</td>
<td>SECRET 461</td>
<td>20 mo (37 mo)</td>
<td>Candesartan</td>
<td>255 (255)</td>
<td>247 (247)</td>
<td>nd</td>
<td>0.01 g/L</td>
<td>0.02 (0.02)</td>
<td>0.01</td>
<td>0.0003</td>
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<tr>
<td></td>
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<td>Placebo</td>
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<td>-15.0</td>
<td>(+23.5)</td>
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</tr>
</tbody>
</table>

*SECRET 461 A predefined interim analysis showed that there would be too few events to permit any conclusions about the effect of treatment on the primary efficacy variable within the planned time course of the study. The trial was therefore terminated, and each patient made a final visit at the next scheduled time point.*
Supplemental Table 63. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [categorical outcome]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Outcome (Treatment)</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Duration</th>
<th>Baseline GFR or SCr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Intensified BP control (Target MAP &lt;50th percentile)</td>
<td>Conventional BP control (Target MAP 50th-95th percentile)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite kidney outcome</td>
<td>ESCAPE 2009 EU[34]</td>
<td>5 y (5 y)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>↓50% GFR or progression to ESRD</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>ESCAPE 2009 EU[34]</td>
<td>5 y (5 y)</td>
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<td>ESRD</td>
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<td>5 y (5 y)</td>
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462 50% decline in the glomerular filtration rate or progression to end-stage renal disease
### Supplemental Table 64. RCTs examining the effect of intensified vs. conventional BP control on children with CKD without DM [continuous outcome]

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study Year</th>
<th>Duration</th>
<th>Country</th>
<th>Description</th>
<th>No analyzed / Enrolled</th>
<th>Baseline GFR or Scr</th>
<th>Baseline Proteinuria</th>
<th>Blood pressure</th>
<th>Results</th>
<th>P value</th>
<th>Quality</th>
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<td><strong>Kidney function</strong></td>
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<td>Annual ↓GFR rate, mL/min/1.73 m²</td>
<td>ESCAPE 2009 EU[34]</td>
<td>5 y (5 y)</td>
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<td>Intensified BP control (Target MAP &lt;50th percentile)</td>
<td>182 (189)</td>
<td>190 (196)</td>
<td>GFR 46 mL/min/1.73 m²</td>
<td>UPCR 1.4</td>
<td>90 (90)</td>
<td>Total cohort 82</td>
<td>46 (45)</td>
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<td>Proteinuria</td>
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<td>Conventional BP control (Target MAP 50th-95th percentile)</td>
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<td>Median UPE, g/g</td>
<td>ESCAPE 2009 EU[34]</td>
<td>6 mo (5 y)</td>
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<td>Intensified BP control (Target MAP &lt;50th percentile)</td>
<td>372 (385)</td>
<td></td>
<td>GFR 46 mL/min/1.73 m²</td>
<td>UPCR 1.4</td>
<td>90 (90)</td>
<td>Total cohort 82</td>
<td>0.82 (IQR 0.27; 1.74)</td>
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<td>Inclusion Criteria</td>
<td>Arm 1 (mean age ± SD)</td>
<td>Arm 2 (mean age ± SD)</td>
<td>Arm 3 (mean age ± SD)</td>
<td>Arm 4 (mean age ± SD)</td>
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<td>Agha 2009[6]</td>
<td>nd</td>
<td>Losartan (53.9 ± 11.1)</td>
<td>Control (54.7 ± 10.9)</td>
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<td>Nifedipine (60.2 ± 8.9)</td>
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<td>AMADEO 2008[14]</td>
<td>21-80 y</td>
<td>Telmisartan (60.0 ± 9.2) 66.8% &lt;65 y Losartan (60.5 ± 9.4) 62.1% &lt;65 y</td>
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<td>Barnett 2004[16]</td>
<td>35-80 y</td>
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<td>Telmisartan (60.0 ± 9.1)</td>
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<td>IDNT 2003[18]</td>
<td>30-70 y</td>
<td>Irbesartan (59.3 ± 7.1)</td>
<td>Amlodipine (59.1 ± 7.9)</td>
<td>Placebo (58.3 ± 8.2)</td>
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<td>31-70 y</td>
<td>Losartan (60 ± 7)</td>
<td>Placebo (60 ± 7)</td>
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<td>Chan 1992[24]</td>
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<td>Enalapril (60.1 ± 9.2)</td>
<td>Nifedipine (56.1 ± 9.9)</td>
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<td>Nifedipine (56.2 ± 9.9)</td>
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<td>Ramipril (60 ± 7)</td>
<td>Lercanidipine (58 ± 7)</td>
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<td>Epstein 2006[33]</td>
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<td>Eplerenone 100 mg [Median (25th-75th percentile)] [58 (53; 66)]</td>
<td>Eplerenone 50 mg [Median (25th-75th percentile)] [58 (52; 66)]</td>
<td>Placebo [Median (25th-75th percentile)] [60 (53; 66)]</td>
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<td>Valsartan (61.4 ± 9.1)</td>
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<td>Lacourciere 2000[48]</td>
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<td>Losartan [59.2 (9.2)]</td>
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<td>Captopril (35 ± 7)</td>
<td>Placebo (34 ± 8)</td>
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<td>Amlodipine (59.1 ± 7.9)</td>
<td>Placebo (58.3 ± 8.2)</td>
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<td>DIABHYCAR 2004[65]</td>
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<td>Placebo (65.0 ± 8.3)</td>
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<td>Arm 1 (mean age ± SD)</td>
<td>Arm 2 (mean age ± SD)</td>
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<td>Placebo (58.3 ± 8.7)</td>
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<td>AVOID 2008[75]</td>
<td>18-85 y</td>
<td>Aliskiren (58.9 ± 9.6)</td>
<td>Placebo (61.8 ± 9.6)</td>
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<td>&gt;30 y</td>
<td>Lowest Tertile Losartan (59.6 ± 7.4)</td>
<td>Lowest Tertile Placebo (60.2 ± 7.5)</td>
<td>Middle Tertile Losartan (60.7 ± 7.2)</td>
<td>Middle Tertile Placebo (60.3 ± 7.6)</td>
<td>Highest Tertile Losartan (59.6 ± 7.4)</td>
<td>Highest Tertile Placebo (60.5 ± 7.4)</td>
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<td>Telmisartan (56.5 ± 8.2)</td>
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<td>18-65 y</td>
<td>Ramipril (56 ± 7)</td>
<td>Placebo (58 ± 7)</td>
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<td>Amlodipine (57 [range 35; 75])</td>
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<td>AASK 2001[7]</td>
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<td>Amlodipine (54.4 ± 10.7)</td>
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<td>Candesartan 16mg (56.5 ± 12.2)</td>
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<td>Candesartan 128mg (54.6 ± 12.6)</td>
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<td>Cinotti 2001[26]</td>
<td>18-70 y</td>
<td>Lisinopril (49.6 ± 10.8)</td>
<td>Control (52.1 ± 11.0)</td>
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<td>Mandipine (56.4 ± 10.0)</td>
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<td>3-18 y</td>
<td>Intensified BP Control (11.5 ± 4.1)</td>
<td>Conventional BP Control (11.5 ± 4.0)</td>
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<td>Amlodipine (57.5 ± 12.9)</td>
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<td>CARTER 2007[36]</td>
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<td>Cilnidipine (59.9 ± 13.3)</td>
<td>Amlodipine (59.3 ± 12.9)</td>
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<td>Nephros 2001[41]</td>
<td>18-74 y</td>
<td>Ramipril+Felodipine (Median [25th-75th percentile]) [52 (45; 60)]</td>
<td>Ramipril (Median [25th-75th percentile]) [53 (43; 61)]</td>
<td>Felodipine (Median [25th-75th percentile]) [54 (49; 62)]</td>
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<td>Hou 2006[43]</td>
<td>18-70 y</td>
<td>Benazepril (SCR 1.5-3.0 mg/dL) (45.1 ± 13.0)</td>
<td>Benazepril (SCR 3.1-5.0 mg/dL) (44.4 ± 16.8)</td>
<td>Placebo (45.0 ± 14.1)</td>
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<td>Hou 2007[42]</td>
<td>18-70</td>
<td>Benazepril (10 mg/d) (59.1 ± 12.6)</td>
<td>Benazepril (40 mg/d) (49.1 ± 14.3)</td>
<td>Losartan (50 mg/d) (51.5 ± 13.3)</td>
<td>Losartan (200 mg/d) (51.0 ± 13.5)</td>
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<td>Losartan (55.7 ± 13.6)</td>
<td>Amlodipine (57.5 ± 11.9)</td>
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<td>≥18 y</td>
<td>Valsartan (41 ± 9)</td>
<td>Placebo (40 ± 10)</td>
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<td>Fosinopril (53 ± 14)</td>
<td>Nifedipine GTS (56 ± 14)</td>
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<td>Benazepril (51 ± 13)</td>
<td>Placebo (51 ± 12)</td>
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<td>VALERIA 2008[67]</td>
<td>18-75 y</td>
<td>Valsartan (57.0 ± 11.4)</td>
<td>Lisinopril (59.7 ± 9.5)</td>
<td>Valsartan+Lisinopril (59.2 ± 11.4)</td>
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<td>18-70 y</td>
<td>Ramipril or Amlodipine or Metroprolol (55 ± 11)</td>
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<td>Benidipine or Valsartan (43.2 ± 9.5)</td>
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<td>MDRD 1995[79]</td>
<td>18-70 y</td>
<td>Low BP goal or Usual BP goal (325 pts &lt;55y; 260 pts ≥55y)</td>
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<td>Ruggenenti 1999[84]</td>
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<td>Ramipril (49.1 ± 1.3)</td>
<td>Control (50.3 ± 1.5)</td>
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<tr>
<td>REIN 2005[85]</td>
<td>18-70 y</td>
<td>Intensified BP Control (54.6 ± 14.7)</td>
<td>Conventional BP Control (53.1 ± 15.8)</td>
<td></td>
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<tr>
<td>MDRD 2005[86]</td>
<td>18-70 y</td>
<td>Low Target BP (51.5 ± 12.6)</td>
<td>Usual Target BP (52.0 ± 12.2)</td>
<td></td>
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<tr>
<td>Vonend 2003[96]</td>
<td>≥18 y</td>
<td>Monoxidine (55.7 ± 14.0)</td>
<td>Nifedipine (53.3 ± 13.4)</td>
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<tr>
<td>Woo 2009[98]</td>
<td>nd</td>
<td>Normal dose ACE (34 ± 10)</td>
<td>Low dose ACE (32 ± 12)</td>
<td>Normal dose ARB (33 ± 10)</td>
<td>Low dose ARB (33 ± 10)</td>
<td></td>
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<tr>
<td>AASK 2002[99]</td>
<td>18-70 y</td>
<td>Ramipril (54.4 ± 10.9)</td>
<td>Amlodipine (54.5 ± 10.7)</td>
<td>Metoprolol (54.9 ± 10.4)</td>
<td>Low BP target (54.5 ± 10.9)</td>
<td>High BP target (54.7 ± 10.4)</td>
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<tr>
<td>Txp</td>
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<tr>
<td>el-Agroudy 2003[32]</td>
<td>≥18 y</td>
<td>Losartan (29.9 ± 8)</td>
<td>Captopril (31.4 ± 8)</td>
<td>Amlodipine (28.6 ± 7)</td>
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<tr>
<td>Kuypers 2004[47]</td>
<td>18-65 y</td>
<td>Lacidipine (46.5 ± 12.6)</td>
<td>Placebo (48.3 ± 12.6)</td>
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<tr>
<td>Midvedt 2001[68]</td>
<td>≥18 y</td>
<td>Nifedipine (45.2 ± 8.4)</td>
<td>Lisinopril (43.5 ± 13.1)</td>
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<tr>
<td>Philipp 2010[80]</td>
<td>30-69 y</td>
<td>Candesartan (50.0 ± 11.6)</td>
<td>Placebo (49.7 ± 10.9)</td>
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<tr>
<td>Rahn 1999[81]</td>
<td>18-60 y</td>
<td>Nifedipine (43 ± 1)</td>
<td>Placebo (42 ± 1)</td>
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<tr>
<td>Study, Year</td>
<td>Inclusion Criteria</td>
<td>Arm 1 (mean age ± SD)</td>
<td>Arm 2 (mean age ± SD)</td>
<td>Arm 3 (mean age ± SD)</td>
<td>Arm 4 (mean age ± SD)</td>
<td>Arm 5 (mean age ± SD)</td>
<td>Arm 6 (mean age ± SD)</td>
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<tr>
<td>van Riemdijk 2000[94]</td>
<td>18-70 y</td>
<td>Isradipine (45)</td>
<td>Placebo (46)</td>
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<td>General Population</td>
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<tr>
<td>ACCOMPLISH[15]</td>
<td>≥55 y</td>
<td>Benazepril + Amlodipine (≥65: 77.2%; ≥75: 35.7%)</td>
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<tr>
<td>ADVANCE[29;40]</td>
<td>≥55 y</td>
<td>CKD Stage 1/ 2 (65.0 ± 6.4)</td>
<td>CKD Stage 3 (68.3 ± 6.4)</td>
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<tr>
<td>ALLHAT[50]</td>
<td>≥55 y</td>
<td>No ages given for CKD subgroup</td>
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<tr>
<td>CASE-J[87]</td>
<td>20-85 y</td>
<td>No ages given</td>
<td></td>
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<tr>
<td>EUROPA[19]</td>
<td>≥18 y</td>
<td>eGFR &lt;75 (65.2)</td>
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<tr>
<td>HOPE[57]</td>
<td>≥55 y</td>
<td>Candesartan (65.6 ± 10.3)</td>
<td>Amlodipine (65.3 ± 10.6)</td>
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<tr>
<td>MICRO-HOPE[4]</td>
<td>≥55 y</td>
<td>No ages given for CKD subgroup</td>
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<tr>
<td>ONTARGET[63]</td>
<td>≥55 y</td>
<td>No ages given</td>
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<tr>
<td>Pahor[72]</td>
<td>≥60 y</td>
<td>Active treatment (73.9 ± 6.7)</td>
<td>Control (74.1 ± 7.0)</td>
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<tr>
<td>PEACE[89;90]</td>
<td>≥50 y</td>
<td>eGFR &lt;45: (70.2 ± 7.9)</td>
<td>eGFR 45.0-59.9: (68.0 ± 7.7)</td>
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<tr>
<td>PREVEND IT[12]</td>
<td>28-95 y</td>
<td>Active Fosinopril (51.1 ± 12.2)</td>
<td>Placebo (51.5 ± 12.2)</td>
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<tr>
<td>PROGRESS[69]</td>
<td>nd</td>
<td>CKD Subgroup (70 ± 8)</td>
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<tr>
<td>TRANSCEND[61]</td>
<td>≥55 y</td>
<td>No ages given for CKD subgroup</td>
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<tr>
<td>Val-HeFT[10]</td>
<td>nd</td>
<td>CKD, No Proteinuria (66 ± 9)</td>
<td>CKD, Proteinuria (65 ± 10)</td>
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</table>
## Supplemental Table 66. PICO criteria for blood pressure targets in elderly studies

<table>
<thead>
<tr>
<th>Study Author Year</th>
<th>Population</th>
<th>Duration</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Achieved BP mmHg Intervention (Comparator)</th>
<th>Baseline GFR or SCr Intervention (Control)</th>
<th>Baseline Proteinuria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>VALISH[71] Ogihara 2010 UI20530299</td>
<td>70-85 years, stable seated SBP of ≥160 to 199 mm Hg N=3260</td>
<td>Median 3 y</td>
<td>Strict treatment group (SBP&lt;140 mm Hg)</td>
<td>Moderate treatment group (SBP maintained at ≥140 mm Hg and &lt;150 mm Hg)</td>
<td>137/75 (142/77)</td>
<td>S&lt;sub&gt;C&lt;/sub&gt; ≤2.0 (≤2.0) mg/dL (based on exclusion criteria)</td>
<td>nd</td>
<td>Primary outcome: Composite of cardiovascular events: sudden death, fatal or non-fatal stroke, fatal or non-fatal MI, death due to heart failure, other cardiovascular death, hospitalization, and renal disorder HR 0.9 (0.6 to 1.34)</td>
</tr>
<tr>
<td>JATOS[45] Ishii 2008 UI19139601</td>
<td>Elderly (65-85) HTN patients SBP &gt;160 mm Hg N=4508</td>
<td>2 y</td>
<td>Strict treatment group (SBP&lt;140 mm Hg)</td>
<td>Moderate treatment group (SBP maintained at ≥140 mm Hg and &lt;150 mm Hg)</td>
<td>136/75 (146/78)</td>
<td>S&lt;sub&gt;C&lt;/sub&gt; &lt;1.5 (&lt;1.5) mg/dL (based on exclusion criteria)</td>
<td>nd</td>
<td>Primary outcome: Combined incidence of cerebrovascular disease, cardiac and vascular disease and renal failure P=0.99 (P value between the 2 treatment groups did not differ significantly)</td>
</tr>
<tr>
<td>HYVET[17] Beckett 2008 UI18378519</td>
<td>80+years, SBP ≥160 mm Hg and &lt;200 mm Hg sitting and ≥140 mm Hg standing with a sitting DBP of &lt;110 mm Hg N=3845</td>
<td>Median 2 y</td>
<td>Indapamide (slow release 1.5 mg) Perindopril if needed (SBP &lt;150 mm Hg DBP &lt;80 mm Hg)</td>
<td>Placebo</td>
<td>145/79 (159/83)</td>
<td>S&lt;sub&gt;C&lt;/sub&gt; 88.6 (89.2) µmol/L (Excluded S&lt;sub&gt;C&lt;/sub&gt; &gt;150 µmol/L or 1.7 mg/dL)</td>
<td>nd</td>
<td>Primary outcome: Fatal and non fatal stroke and death 51 events occurred in the active treatment group as compared with 69 events in the placebo group. RR of fatal and non fatal stroke of 30% (-1 to 51; P=0.06) RR of death from any cause of 21% (4 to 35; P=0.02)</td>
</tr>
<tr>
<td>STONE[38] Gong 1996 UI8906524</td>
<td>Patients 60-90 years, SBP=160 mm Hg or DBP ≥96 mm Hg N=1632</td>
<td>30 mo</td>
<td>Nifedipine (SBP 140-159 mm Hg and DBP 90 mm Hg)</td>
<td>Placebo (Safety level SBP ≥200 mm Hg or DBP ≥110 mm Hg)</td>
<td>147/85 (156/92)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Clinical events and risk modification. 77 events occurred in the placebo and 32 in the Nifedipine group. Significant reduction in relative risk was observed for strokes and severe arrhythmia with an overall decrease from 1.0 to 0.41 (CI 0.27 to 0.61). There was a significant decrease in RR in stages 2 and 3 HTN, which corresponded to 28.8 and 16.1% with placebo and Nifedipine.</td>
</tr>
<tr>
<td>Trial</td>
<td>Year</td>
<td>N</td>
<td>Follow up (y)</td>
<td>Entry age (y)</td>
<td>Mean age (y)</td>
<td>Entry SBP (mm Hg)</td>
<td>Entry DBP (mm Hg)</td>
<td>Target SBP (mm Hg)</td>
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<tr>
<td>ALLHAT Old[73]</td>
<td>2003</td>
<td>5700</td>
<td>4.9</td>
<td>&gt;75</td>
<td>NA</td>
<td>≤180</td>
<td>≤110</td>
<td>&lt;140</td>
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<tr>
<td>ANBP2[31]</td>
<td>2003</td>
<td>6083</td>
<td>4.1</td>
<td>65-84</td>
<td>71.9</td>
<td>≥160</td>
<td>≥90</td>
<td>&lt;160 and &lt;140 if tolerated</td>
</tr>
<tr>
<td>CASTE[23]</td>
<td>1994</td>
<td>655</td>
<td>7.0</td>
<td>≥65</td>
<td>73.7</td>
<td>≥160</td>
<td>≥95</td>
<td>NS</td>
</tr>
<tr>
<td>HEP[9]</td>
<td>1986</td>
<td>884</td>
<td>4.4</td>
<td>60-79</td>
<td>68.8</td>
<td>≥170</td>
<td>≥105</td>
<td>NS</td>
</tr>
<tr>
<td>HYVET pilot[21]</td>
<td>2003</td>
<td>1283</td>
<td>1.1</td>
<td>≥80</td>
<td>83.8</td>
<td>170-219 and SBP≥140</td>
<td>95-119</td>
<td>&lt;150</td>
</tr>
<tr>
<td>HYVET[17]</td>
<td>2003</td>
<td>3845</td>
<td>1.8</td>
<td>≥80</td>
<td>83.6</td>
<td>≥160 -199 and ≥140 standing</td>
<td>90-110</td>
<td>&lt;150</td>
</tr>
<tr>
<td>JATOS[45]</td>
<td>2008</td>
<td>4418</td>
<td>2.0</td>
<td>65-85</td>
<td>NA</td>
<td>≥160</td>
<td>NS</td>
<td>&lt;140 (strict) or &lt;160 but, at or &gt;140 (mild)</td>
</tr>
<tr>
<td>MRC Older[93]</td>
<td>1992</td>
<td>4396</td>
<td>5.8</td>
<td>65-74</td>
<td>70.3</td>
<td>160-209</td>
<td>&lt;114</td>
<td>If ≥180, then ≤150</td>
</tr>
<tr>
<td>SCOPE[54]</td>
<td>2003</td>
<td>4969</td>
<td>3.7</td>
<td>70-89</td>
<td>76.4</td>
<td>160-179</td>
<td>90-99</td>
<td>&lt;160</td>
</tr>
<tr>
<td>SHELL[56]</td>
<td>2003</td>
<td>1882</td>
<td>2.7</td>
<td>≥60</td>
<td>72.4</td>
<td>≥160</td>
<td>≤95</td>
<td>≤160 and ≥20; If&gt;180, then &lt;160; if 160-180, then ≤20</td>
</tr>
<tr>
<td>SHEP[1]</td>
<td>1991</td>
<td>4736</td>
<td>4.5</td>
<td>≥60</td>
<td>71.6</td>
<td>160-219</td>
<td>&lt;90</td>
<td>NA</td>
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<tr>
<td>STONE[38]</td>
<td>1996</td>
<td>1632</td>
<td>3.0</td>
<td>60-79</td>
<td>66.4</td>
<td>≥160</td>
<td>&gt;95</td>
<td>140-159</td>
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<td>STOP[27]</td>
<td>1991</td>
<td>1627</td>
<td>2.1</td>
<td>70-84</td>
<td>75.7</td>
<td>180-230 and DBP≥90</td>
<td>105-120</td>
<td>&lt;160</td>
</tr>
<tr>
<td>STOP 2[39]</td>
<td>1999</td>
<td>6614</td>
<td>5.0</td>
<td>70-84</td>
<td>76</td>
<td>≥180</td>
<td>≥105</td>
<td>&lt;160</td>
</tr>
<tr>
<td>SYST China[97]</td>
<td>1998</td>
<td>2394</td>
<td>3.0</td>
<td>≥60</td>
<td>66.5</td>
<td>160-219</td>
<td>&lt;95</td>
<td>&lt;150 and ≥20</td>
</tr>
<tr>
<td>SYST Eur[91]</td>
<td>1997</td>
<td>4695</td>
<td>2.0</td>
<td>≥60</td>
<td>70.3</td>
<td>160-219 and SBP≥140</td>
<td>&lt;95</td>
<td>&lt;150 and ≥20</td>
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<tr>
<td>VALISH[71]</td>
<td>2010</td>
<td>3079</td>
<td>3.07</td>
<td>70-84</td>
<td>76.1</td>
<td>SBP 160-199</td>
<td>NS</td>
<td>Strict SBP&lt;140 and moderate ≥140 to &lt;150</td>
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</table>
## Supplemental Table 68. PICO criteria for blood pressure agents in elderly studies

<table>
<thead>
<tr>
<th>Study Author Year</th>
<th>Population</th>
<th>Duration</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Achieved BP mmHg Intervention (Comparator)</th>
<th>Baseline GFR or SCR Intervention (Control)</th>
<th>Baseline Proteinuria</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EWPHE[8] Amery 1958 U12856778</td>
<td>60 years old +, SBP between 160 and 239 mmHg and between 90 and 119 mm Hg DBP sitting, consent N=840</td>
<td>12 y</td>
<td>HCTZ 25mg or Triamterene 50mg (titrated)</td>
<td>Placebo</td>
<td>148/85 (167/90)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Morbidity and mortality Total cardiovascular mortality rate was significantly reduced (-38%, P=0.023) Non-fatal morbid cardiovascular study-terminating events occurred at a rate of 20/1000 patients-years in the placebo group and 8/1000 patient-years in the actively treated group. This reduction (-60%, P=0.0064) was mainly accounted for by a 63% reduction in severe CHF.</td>
</tr>
<tr>
<td>MRC[93] Tuomilehto 1992 U11352716</td>
<td>Patients age 65-74, mean SBP 160-209 mm Hg and mean DBP &lt;115 mm Hg N=4396</td>
<td>6 y</td>
<td>Diuretic Beta-blocker</td>
<td>Placebo</td>
<td>156/77 153/75 165/84 nd</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Strokes, coronary events, and death from all causes Then number of strokes (fatal and non-fatal) was significantly reduced in people randomized to receive active treatment (101 v 134 placebo, P=0.04) with RR 25% (CI 3% to 42%). Coronary events were less common in those allocated to active treatment (128 events) than in those receiving placebo (159; P=0.08) with RR of 19% (-2% to 36%). All cause mortality was similar in the treated and placebo groups (23.9 v 24.7 per patient-years).</td>
</tr>
<tr>
<td>SCOPE[54] Lithell 2003 U12714861</td>
<td>Patients 70-89 years, SBP 160-179 mm Hg, DBP 90-99 mm Hg, mini mental state examination test score ≥24 N=4964</td>
<td>4 y</td>
<td>Candesartan</td>
<td>Placebo</td>
<td>145/80 (149/82) S&lt;sub&gt;G&lt;/sub&gt; 88.0 μmol/L (89.0 μmol/L) (Excluded SCr &gt;180 μmol/L in men and &gt;140 μmol/L in women)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Major cardiovascular events, a composite of cardiovascular death, non-fatal stroke and non-fatal MI. A first major cardiovascular event occurred in 242 candesartan patients and in 268 placebo patients: RR with candesartan was 10.9% (-6.0 to 25.1, P=0.19). Candesartan treatment reduced non-fatal stroke by 27.8% (1.3 to 47.2, P=0.04) and all stroke by 23.6% (-0.7 to 42.1, P=0.056). There were no significant differences in MI and cardiovascular mortality.</td>
</tr>
<tr>
<td>SHELL[56] Malacoo 2003 U112875478</td>
<td>Patients ≥60 years, sitting SBP ≥160 mm Hg with a DBP ≥95 mm Hg N=1882</td>
<td>3 y</td>
<td>Prospective study with open design</td>
<td>Lacidipine Chlorthalidone</td>
<td>142/79 (143/80) S&lt;sub&gt;G&lt;/sub&gt; &gt;2.0 (&gt;2.0) mg/dL (based on exclusion criteria)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Composite of cardiovascular and cerebrovascular events. Overall incidence of the primary endpoint was 9.3% with no significant between-group difference. Total mortality was also similar between groups.</td>
</tr>
<tr>
<td>Study Author Year</td>
<td>Population</td>
<td>Duration</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Achieved BP mmHg Intervention (Comparator)</td>
<td>Baseline GFR or Scr Intervention (Control)</td>
<td>Baseline Proteinuria</td>
<td>Outcomes</td>
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<tr>
<td>SHEP[1] SHEP Cooperative Research Group 1991 UI2046107</td>
<td>60+ years old, SBP from 160-219 mm Hg and DBP ≤90 mm Hg N=4736</td>
<td>5 y</td>
<td>Chlorthalidone (step 1) Atenolol (step 2)</td>
<td>Placebo</td>
<td>144/68 (155/71)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Non fatal and fatal stroke. The 5 year incidence of total stroke was 5.2 per 100 participants for active treatment and 8.2 per 100 for placebo. RR by proportional hazards regression analysis was 0.64 (P=.0003)</td>
</tr>
<tr>
<td>STONE[38] Gong 1996 UI8906524</td>
<td>Patients 60-90 years, SBP≥160 mm Hg or DBP ≥96 mm Hg N=1632</td>
<td>3 y</td>
<td>Nifedipine (SBP 140-159 mmHg and DBP 90 mm Hg)</td>
<td>Placebo (Safety level SBP ≥200 mmHg or DBP ≥110 mm Hg)</td>
<td>147/85 (156/92)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Clinical events and risk modification. 77 events occurred in the placebo and 32 in the Nifedipine group. Significant reduction in relative risk was observed for strokes and severe arrhythmia with an overall decrease from 1.0 to 0.41 (CI 0.27 to 0.61). There was a significant decrease in RR in stages 2 and 3 HTN, which corresponded to 28.8 and 16.1% with placebo and Nifedipine.</td>
</tr>
<tr>
<td>STOP[27] Dahlof 1991 UI1682683</td>
<td>Patients 70-84 years, SBP between 180-230 mm Hg and DBP of at least 90 mm Hg or DBP between 105 and 120 mm Hg irrespective of the SBP. N=1627</td>
<td>5 y</td>
<td>Atenolol, HCTZ plus Amiloride, or Prindolol</td>
<td>Placebo</td>
<td>166/85 (193/95)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: Fatal and non fatal stroke and MI and other cardiovascular death. Active treatment significantly reduced the number of primary endpoints (94 v 88; P=0.0031) and stroke morbidity and mortality (53 v 29; P=0.0081). There was also a significant reduced number of deaths in the active treatment group (63 v 36; P=0.0079)</td>
</tr>
<tr>
<td>STOP 2[39] Hansson 1999 UI10577635</td>
<td>Patients 70-84 years, SBP between 180-230 mm Hg and DBP of at least 90 mmHg or DBP between 105 and 120 mm Hg irrespective of the SBP. N=6617</td>
<td>5 y</td>
<td>Conventional drugs: Atenolol, HCTZ plus Amiloride, Prindolol or Metoprolol (&lt;160/95 mmHg) Enalapril or Lisinopril (&lt;160/95 mmHg) Felodipine or Isradipine (&lt;160/95 mmHg)</td>
<td>Placebo</td>
<td>158/81 159/81 159/80</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: The composite of fatal and non fatal stroke and MI and other cardiovascular disease. The primary combined endpoint occurred in 221 of 2213 patients in the conventional drugs group (19.8 events per 1000 patient-years) and in 438 of 4401 in the newer drugs group (19.8 per 1000; relative risk 0.99 (CI 0.84 to 1.16), P=0.89). The combined endpoint of fatal and non stroke and MI and other cardiovascular mortality occurred in 460 patients taking conventional drugs and in 887 taking newer drugs (CI 0.96 (0.80 to 1.08), P=0.49)</td>
</tr>
<tr>
<td>Study Author Year</td>
<td>Population</td>
<td>Duration</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Achieved BP mmHg Intervention (Comparator)</td>
<td>Baseline GFR or SCR Intervention (Control)</td>
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<tr>
<td>SYST China[97] Wang 2000 UI10647760</td>
<td>Patients 60+ years, sitting SBP 160-219 mm Hg and DBP &lt;95 mm Hg N=1253</td>
<td>3 y</td>
<td>Nitrendipine</td>
<td>Placebo</td>
<td>↓20/5 (↓11/2)</td>
<td>SCr &gt;2.0 mg/dL (SCr &gt;2.0 mg/dL) (based on exclusion criteria)</td>
<td>nd</td>
<td>Primary outcome: Cardiovascular mortality, fatal and nonfatal cardiovascular events and strokes. In the placebo group diabetes raised the risk of all end points 2-to 2-fold (P≤0.05). However, active treatment reduced the excess risk associated with diabetes to a non significant level (P values ranging from .12 to 86) except for cardiovascular mortality (P=0.04). Active treatment had reduced the incidence of total mortality (P&lt;0.01), fatal and nonfatal stroke (P&lt;0.05), and all cardiovascular end points (P&lt;0.01). In single and multiple regression, all end points with the exception of fatal and nonfatal stroke were positively correlated with SBP.</td>
</tr>
<tr>
<td>SYST Eur[91] Staessen 1997 UI9297994</td>
<td>Patients 60+years old, sitting SBP 160-219 mm Hg and DBP &lt;95 mm Hg N=4695</td>
<td>2 y</td>
<td>Nitrendipine</td>
<td>Placebo</td>
<td>151/79 (161/84)</td>
<td>SCr &gt;2.0 mg/dL (SCr &gt;2.0 mg/dL) (based on exclusion criteria)</td>
<td>nd</td>
<td>Primary outcome: Fatal and non fatal stroke. Active treatment reduced the total rate of stroke from 13.7 to 7.9 endpoints per 1000 patients-years (42% reduction; P=0.007). In the active treatment group, all fatal and non-fatal cardiac endpoints, including sudden death, declined by 26% (P=0.03). Non-fatal cardiac endpoints decreased by 33% (P=0.03) and all fatal and non fatal cardiovascular endpoints by 31% (P&lt;0.001). Cardiovascular mortality was slightly lower on active treatment (-27%, P=0.07), but all cause mortality was not influenced (-14%; P=0.22).</td>
</tr>
<tr>
<td>ANBP2[31] Doggrell 2003 UI12740004</td>
<td>65-84 years old, SBP &gt;160 mm Hg or an average DBP of &gt;90 mm Hg N=6083</td>
<td>4 y</td>
<td>ACEI</td>
<td>Diuretic</td>
<td>141/79 (142/79)</td>
<td>nd</td>
<td>nd</td>
<td>Primary outcome: All CV events or death from any cause. The HR for all CV events or death from any cause among subjects in the ACEI group as compared with that of the Diuretic group was 0.89 (95% CI, 0.79 to 1.00; P=0.05).</td>
</tr>
</tbody>
</table>

The table provides a summary of studies comparing different interventions for patients with high blood pressure, focusing on achieved blood pressure reductions, baseline GFR or SCr, and outcomes like cardiovascular mortality, fatal and nonfatal strokes, and total mortality. The studies also assess the impact of diabetes on end points and the reduction in risk associated with active treatment compared to placebo.
References


63. Mann JF, Schmieder RE, McQueen M et al.: Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 372(9638):547-53, 2008


