Strategies to halt the progression of CKD G4+: Evidence from Randomized Trials

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Disclosures

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Outline

• Evidence gap in CKD G4+

• Available evidence for the following interventions
  • Bicarbonate
  • Uric Acid Reduction
  • ACE/ARB
  • Phosphate Binders
Evidence Gap

• Patients with CKD Stages G4-5 are often excluded from randomized trials in the general population

• Very few positive trials exist in patients with kidney failure

• Difficult to extrapolate findings from CKD Stage G1-G3A and from patients on dialysis
Bicarbonate – Treatment of Met Acidosis

• Metabolic acidosis is common in patients with advanced CKD

• Patients with diabetes may be at additional risk

• Prolonged metabolic acidosis can lead to bone loss and impaired muscle function

• Clinical practice guidelines recommend bicarbonate supplementation at levels < 22 mEq/l

Susantitaphong et al. AJN 2012
Evidence for Alkali Therapy in CKD

Fig. 1. Study selection flow diagram.
Evidence for Alkali Therapy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Net change (95% CI)</th>
<th>Bicarbonate, n</th>
<th>Control, n</th>
<th>Baseline GFR ml/min</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-term studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Husted</td>
<td>-0.60 (-4.13, 2.93)</td>
<td>6</td>
<td>6</td>
<td>13</td>
<td>4 days</td>
</tr>
<tr>
<td>Passfall</td>
<td>3.10 (-3.02, 9.22)</td>
<td>11</td>
<td>11</td>
<td>13</td>
<td>7 days</td>
</tr>
<tr>
<td>Subtotal (I² = 5%, p = 0.31)</td>
<td>0.37 (-2.82, 3.56)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Long-term studies</strong></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>De Brito-Ashurst</td>
<td>3.68 (1.72, 5.64)</td>
<td>67</td>
<td>67</td>
<td>20</td>
<td>24 months</td>
</tr>
<tr>
<td>Mahajan</td>
<td>2.70 (0.02, 5.38)</td>
<td>37</td>
<td>36</td>
<td>76</td>
<td>60 months</td>
</tr>
<tr>
<td>Disthabanchon</td>
<td>1.30 (-3.64, 6.24)</td>
<td>21</td>
<td>20</td>
<td>19</td>
<td>2-3 months</td>
</tr>
<tr>
<td>Subtotal (I² = 0%, p = 0.63)</td>
<td>3.75 (1.64, 4.66)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Overall (I² = 13%, p = 0.33)</strong></td>
<td>2.47 (0.95, 4.00)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Fig. 2. Forest plot displaying the effect of bicarbonate therapy in patients with CKD on change in GFR (ml/min or ml/min/1.73 m²).
Evidence for Alkali Therapy

• Largest trial – Debrito-Ashurst et al.

• Mean eGFR 20 ml/min, mean HCO3 – 20 mEq/l

• Bicarbonate dose – 22 +/- 10 mEq/day

• Pooled Estimates
  • Slight increase in DBP 2.8 mm Hg
  • Increase in sodium excretion (24 mEq/day)
  • Decrease in serum potassium (0.7 mEq/L)
Uric Acid Reduction

• Uric acid levels are strongly and consistently associated with CKD and CVD in observational studies

• Uric acid reduction in patients with normal kidney function may lead to improvements in blood pressure control

• Randomized controlled trial evidence in patients with advanced CKD remains scarce

Kanji et al. BMC Nephrology 2015
Evidence for Uric Acid Reduction

Figure 1 Flow diagram.
Evidence for Uric Acid Reduction

<table>
<thead>
<tr>
<th>First author (Ref No.)</th>
<th>Year of publication</th>
<th>Journal</th>
<th>Location of trial</th>
<th>Study design</th>
<th>Duration of follow-up</th>
<th>Sample size</th>
<th>Treatment</th>
<th>Control</th>
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</thead>
<tbody>
<tr>
<td>Perez-Ruiz [56]</td>
<td>1999</td>
<td>Journal of Clinical Rheumatology</td>
<td>País Vasco, Spain</td>
<td>Parallel Group RCT</td>
<td>9-12 months</td>
<td>36</td>
<td>Benzbromarone</td>
<td>Alopurinol</td>
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<tr>
<td>Kamper [50]</td>
<td>2001</td>
<td>Clinical Transplantation</td>
<td>Herlev, Denmark</td>
<td>Cross-over RCT</td>
<td>2 weeks</td>
<td>26</td>
<td>Losartan</td>
<td>No treatment</td>
</tr>
<tr>
<td>Schmidt [53]</td>
<td>2001</td>
<td>Nephrology &amp; Dialysis Transplantation</td>
<td>Vienna, Austria</td>
<td>Cross-over RCT</td>
<td>3 weeks</td>
<td>13</td>
<td>Losartan</td>
<td>Enalapril</td>
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<tr>
<td>Chanard [54]</td>
<td>2003</td>
<td>Nephrology &amp; Dialysis Transplantation</td>
<td>Three centres in France</td>
<td>Parallel Group RCT</td>
<td>4 weeks</td>
<td>48</td>
<td>Amlodipine</td>
<td>Tertialol</td>
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<tr>
<td>Siu [48]</td>
<td>2006</td>
<td>American Journal of Kidney Diseases</td>
<td>Hong Kong, China</td>
<td>Parallel Group RCT</td>
<td>12 months</td>
<td>54</td>
<td>Alopurinol</td>
<td>No treatment</td>
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<tr>
<td>Liu [36]</td>
<td>2007</td>
<td>China Pharmacy</td>
<td>Guangzhou and Luzhou, China</td>
<td>Parallel Group RCT</td>
<td>12 months</td>
<td>47</td>
<td>Alopurinol</td>
<td>No treatment</td>
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<tr>
<td>Saris [34]</td>
<td>2007</td>
<td>Nephrology &amp; Dialysis Transplantation</td>
<td>Athens, Greece</td>
<td>Parallel Group RCT</td>
<td>12 months</td>
<td>36</td>
<td>Alopurinol</td>
<td>No treatment</td>
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<tr>
<td>Lei [40]</td>
<td>2009</td>
<td>Shandong Medical Journal</td>
<td>Jinan, China</td>
<td>Parallel Group RCT</td>
<td>12 months</td>
<td>57</td>
<td>Alopurinol</td>
<td>No treatment</td>
</tr>
<tr>
<td>Malagona [35]</td>
<td>2009</td>
<td>Expert Opinion Pharmacotherapy</td>
<td>Catania, Italy</td>
<td>Parallel Group RCT</td>
<td>2 months</td>
<td>38</td>
<td>Rasburicase</td>
<td>Placebo</td>
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<tr>
<td>Nouri-Majlani [52]</td>
<td>2009</td>
<td>Vascular Health, and Risk Management</td>
<td>Yazd, Iran</td>
<td>Parallel Group RCT</td>
<td>5 days</td>
<td>60</td>
<td>Alopurinol</td>
<td>Placebo</td>
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<tr>
<td>Deng [37]</td>
<td>2010</td>
<td>Journal of Practical Medicine</td>
<td>Beijing, China</td>
<td>Parallel Group RCT</td>
<td>12 months</td>
<td>68</td>
<td>Alopurinol</td>
<td>No treatment</td>
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<tr>
<td>Momeni [46]</td>
<td>2010</td>
<td>Iranian Journal of Kidney Disease</td>
<td>Isfahan, Iran</td>
<td>Parallel Group RCT</td>
<td>4 months</td>
<td>44</td>
<td>Alopurinol</td>
<td>Placebo</td>
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<tr>
<td>Shen [38]</td>
<td>2010</td>
<td>China Foreign Medical Treatment</td>
<td>Chengdu, China</td>
<td>Parallel Group RCT</td>
<td>12 months</td>
<td>52</td>
<td>Alopurinol</td>
<td>No treatment</td>
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<td>Tan [39]</td>
<td>2011</td>
<td>Modern Hospital</td>
<td>Guangzhou, China</td>
<td>Parallel Group RCT</td>
<td>24 months</td>
<td>140</td>
<td>Alopurinol</td>
<td>No treatment</td>
</tr>
<tr>
<td>Shi [47]</td>
<td>2012</td>
<td>Kidney and Blood Pressure Research</td>
<td>Guangzhou, China</td>
<td>Parallel Group RCT</td>
<td>6 months</td>
<td>40</td>
<td>Alopurinol</td>
<td>No treatment</td>
</tr>
</tbody>
</table>
Evidence for Uric Acid Reduction

For eGFR – A change of 3 ml/min over follow up was detected
ACE/ARB in advanced CKD

• Mainstay of treatment to prevent CKD progression

• Landmark studies enrolled patients with earlier stages of CKD

• Efficacy may be modified by presence of proteinuria

• Safety may be modified by age
Landmark Trials

• RENAAL
  • Mean eGFR 38 ml/min, Patients with Cr > 3.0 mg/dl excluded

• IDNT
  • Mean eGFR 43 ml/min, Patients with Cr > 3.0 mg/dl excluded

• REIN study
  • Nondiabetic kidney disease, CrCl 20-70, mean eGFR 45 ml/min
  • Baseline proteinuria > 3 g/day
Landmark Trials

Jafar et al. JASN 2007
STOP ACEI Trial

• Motivated by recent findings from ONTARGET and TRANSCEND

• Aims to enroll 410 patients with CKD Stages G4-G5 from 15 UK based Pre Dialysis Clinics

• 3 years of follow up

• Stratified enrollment to ensure balance in proteinuria and CKD Stage

• Measurement of appropriate clinical and surrogate endpoints
Phosphate Binders

• Hyperphosphatemia is associated with early mortality in the general population and in patients on dialysis

• High phosphorous and low calcium levels are associated with progression to kidney failure

• Phosphate loads in the presence of reduced kidney function can lead to FGF23 expression, which may have downstream CV effects
Evidence for phosphate binders

• Two recent meta analyses suggesting non-calcium binders may be associated with improved survival

• Evidence is largely from dialysis trials

• Smaller trials with surrogate outcomes have been performed in the CKD population
Evidence for phosphate binders

• Block et al. – JASN 2012 – Calcium and non-calcium binders vs Placebo
  • N=148
  • No effect on FGF23, slight increase in CAC with binders

• Independent Study – De Iorio et al. CJASN 2013 – Sevelamer vs Calcium Carbonate
  • N=212
  • 50 % Relative risk reduction in death or dialysis

• Two small recent studies on ferric citrate – short follow up (<12 weeks)
Summary

• Limited high quality evidence exists for medical interventions to halt the progression of CKD Stage 4+

• Most randomized trials from the general population do not include these patients

• Dedicated large simple randomized trials should be performed to confirm these preliminary findings