Clinical Perspectives from Recent CKD Trials

Failure of hard outcome renal CKD progression trials
New avenues?

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Disclosure:
Consultant to AbbVie, Astellas, AstraZeneca, Chemocentryx, Fresenius, Hemocue, Janssen, Novartis, Pfizer, Reata, Takeda;
honoraria paid to Institution
Recent failed trials in CKD protection

- Recently failed CKD progression trials:
  - ON-TARGET (dual RAAS)
  - SUN (sulodexide)
  - TREAT (EPO; darbepoetin)
  - ALTITUDE (dual RAAS; DRI)
  - VA-NEPHRON-D (dual RAAS)
  - BEACON (inflammation; bardoxolone)
  - ASCEND (endothelin antagonist; avosentan)
Reason for trial failure

- the new therapies are developed on the assumption that the intervention is providing additive renal (CV) protection
- Indeed, many of the failed trials conclude that the investigational drug was failing because of the characteristics of the drug itself or because of the wrong target/surrogate

*I submit the hypothesis that it is not the wrong drug but the wrong trial design that might explain the trial failures*
Trial failure; design issues?

• Recently failed CKD progression trials:
  ▪ ON-TARGET (dual RAAS)
  ▪ SUN (sulodexide)
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  ▪ VA-NEPHRON-D (dual RAAS)
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• Design issues:
  ▪ Too low-risk population
  ▪ No effect on surrogate
  ▪ Too high dose
  ▪ Wrong endpoints
  ▪ Too many side effects
ONTARGET: CV and renal outcome during ACEi (ramipril) vs ACEi (ramipril) + AIIA (telmisartan) in high-risk patients


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Microalbuminuria was present in 13.1% of all participants
  - 29.7% of those with diabetes
  - 9.2% of those without known diabetes

Macroalbuminuria was seen in 4.0% of all participants
  - 12.2% of those with diabetes
  - 1.4% of those without known diabetes.
ONTARGET: Incidence of primary and secondary renal outcomes and of its components

<table>
<thead>
<tr>
<th></th>
<th>Ramipril N</th>
<th>Telmisartan N</th>
<th>Ramipril + telmisartan N</th>
<th>Telmisartan Vs Ramipril HR</th>
<th>p</th>
<th>Ram +Telm Vs ramipril HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All dialysis, doubling, death</td>
<td>1150</td>
<td>1147</td>
<td>1233</td>
<td>1·00</td>
<td>0·968</td>
<td>1·09</td>
<td>0·037</td>
</tr>
<tr>
<td>All dialysis and doubling</td>
<td>174</td>
<td>189</td>
<td>212</td>
<td>1·09</td>
<td>0·420</td>
<td>1·24</td>
<td>0·038</td>
</tr>
<tr>
<td>All dialysis</td>
<td>48</td>
<td>51</td>
<td>63</td>
<td>1·07</td>
<td>0·747</td>
<td>1·33</td>
<td>0·133</td>
</tr>
<tr>
<td>All death</td>
<td>1014</td>
<td>989</td>
<td>1065</td>
<td>0·98</td>
<td>0·641</td>
<td>1·07</td>
<td>0·144</td>
</tr>
<tr>
<td>Doubling</td>
<td>140</td>
<td>155</td>
<td>166</td>
<td>1·11</td>
<td>0·378</td>
<td>1·20</td>
<td>0·110</td>
</tr>
<tr>
<td>Acute dialysis</td>
<td>13</td>
<td>20</td>
<td>28</td>
<td>1·55</td>
<td>0·221</td>
<td>2·19</td>
<td>0·020</td>
</tr>
<tr>
<td>Chronic dialysis</td>
<td>33</td>
<td>31</td>
<td>34</td>
<td>0·94</td>
<td>0·817</td>
<td>1·05</td>
<td>0·854</td>
</tr>
</tbody>
</table>

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ONTARGET: Effect of treatment on serum potassium

![Graph showing serum potassium levels over time for dual therapy and mono therapy.](image)

- **Dual therapy**
  - Initial level: 4.45 mmol/L
  - End level: 4.50 mmol/L

- **Mono therapy**
  - Initial level: 4.45 mmol/L
  - End level: 4.45 mmol/L

Serum potassium (mmol/L) vs. Time (years)

Lambers Heerspink et al; EJPC 2014
ONTARGET: Relationship on-treatment serum potassium and cardiovascular outcome

Adjusted risk: Age, gender, diabetes, eGFR, UACR, systolic blood pressure, diuretics

Lambers Heerspink et al; EJPC 2014
ONTARGET: Relation week-6 serum potassium and renal outcome

Adjusted risk: Age, gender, diabetes, eGFR, UACR, systolic blood pressure, diuretics

Lambers Heerspink et al; EJPC 2014
Trial failure; design issues?

• Recently failed CKD progression trials:
  - ON-TARGET (dual RAAS)
  - SUN (sulodexide)
  - TREAT (EPO; darbepoetin)
  - ALTITUDE (dual RAAS; DRI)
  - VA-NEPHRON-D (dual RAAS)
  - BEACON (inflammation; bardoxolone)
  - ASCEND (endothelin antagonist; avosentan)

• Design issues:
  - Too low-risk population
    YES; eGFR >70; Macroalb 4%
  - No effect on surrogate
  - Too high dose
  - Wrong endpoints
    YES; Acute dialysis
  - Too many side effects
    YES; Potassium increase
SUN-Overt; effect of Sulodexide on renal outcome in type 2 diabetes with nephropathy


Dick de Zeeuw June 2014
SUN-Micro; effect of Sulodexide on albuminuria in type 2 diabetes with microalbuminuria

Lewis et al AJKD 2011

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Trial failure; design issues?

- Recently failed CKD progression trials:
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- Design issues:
  - Too low-risk population
  - No effect on surrogate
  - Too high dose
  - Wrong endpoints
  - Too many side effects
TREAT; CV (Death, MI, Myocardial Ischemia, HF, Stroke) and Renal (Death or ESRD) Composite

HR: 1.05 (0.94–1.17)  
P = 0.41

Patients with CV events (%)

Darbepoetin alfa 632 (31.4%)
Placebo 602 (29.7%)

HR: 1.06 (0.95–1.19)  
P = 0.29

Patients with renal events (%)

Darbepoetin alfa 652 (32.4%)
Placebo 618 (30.5%)

TREAT; post-hoc analysis; difference in CV outcome (Death, MI, Stroke, HF) for Hb non-responders vs responders

Trial failure; design issues?

- Recently failed CKD progression trials:
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  - BEACON (inflammation; bardoxolone)
  - ASCEND (endothelin antagonist; avosentan)

- Design issues:
  - Too low-risk population
  - No effect on surrogate: YES (with high dosing)
  - Too high dose: YES
  - Wrong endpoints
  - Too many side effects: ?
ALTITUDE: CV and renal secondary composite endpoint

Cardiovascular composite outcome (%)

Hazard ratio, 1.11 (95% CI, 0.99–1.25); p=0.09

Renal composite outcome (%)

Hazard ratio, 1.03 (95% CI, 0.87–1.23); p=0.74


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ALTITUDE; more blood pressure and albuminuria lowering during Aliskiren

Parving et al; NEJM 2012

Dick de Zeeuw June 2014
Relationship between short-term decrease in albuminuria and long-term renal risk reduction: different randomized clinical trials in different populations


Dick de Zeeuw June 2014
ALTITUDE; effect of Aliskiren on serum potassium course

Trial failure; design issues?

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- Design issues:
  - Too low-risk population
  - No effect on surrogate: YES
  - Too high dose
  - Wrong endpoints
  - Too many side effects: YES
VA-NEPHRON-D: ACEi + ARB no renal protection in diabetes with nephropathy (n=1148)


Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Losartan + placebo</th>
<th>Losartan + lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan + placebo</td>
<td>724</td>
<td>724</td>
</tr>
<tr>
<td>Losartan + lisinopril</td>
<td>724</td>
<td>724</td>
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</tbody>
</table>

Percentage of patients (95% CI)

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<tr>
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<th>Losartan + lisinopril</th>
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</thead>
<tbody>
<tr>
<td>Losartan + placebo</td>
<td>5.7 (4.1–7.8)</td>
<td>5.3 (3.8–7.3)</td>
</tr>
<tr>
<td>Losartan + lisinopril</td>
<td>18.7 (15.6–22.3)</td>
<td>15.2 (12.3–18.6)</td>
</tr>
</tbody>
</table>

Months since randomization

<table>
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<td>724</td>
</tr>
<tr>
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<td>724</td>
<td>724</td>
</tr>
</tbody>
</table>

Primary endpoint (% of patients)

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</tr>
</tbody>
</table>

p=0.30
VA-NEPHRON-D: Acute Kidney Injury

Acute Kidney Injury

Percentage of patients (95% CI)

<table>
<thead>
<tr>
<th>Months since randomization</th>
<th>Losartan + placebo</th>
<th>Losartan + lisinopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.2 (3.8–7.2)</td>
<td>9.2 (7.3–11.7)</td>
</tr>
<tr>
<td>10</td>
<td>11.2 (8.8–14.1)</td>
<td>16.6 (13.8–20.0)</td>
</tr>
<tr>
<td>20</td>
<td>15.4 (12.4–19.1)</td>
<td>23.7 (20.0–28.0)</td>
</tr>
<tr>
<td>30</td>
<td>18.3 (14.2–23.3)</td>
<td>40.8 (28.2–56.4)</td>
</tr>
</tbody>
</table>

Losartan + placebo

Losartan + lisinopril

p<0.001

Number at risk

<table>
<thead>
<tr>
<th>Losartan + placebo</th>
<th>724</th>
<th>638</th>
<th>548</th>
<th>470</th>
<th>355</th>
<th>260</th>
<th>170</th>
<th>89</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan + lisinopril</td>
<td>724</td>
<td>630</td>
<td>528</td>
<td>453</td>
<td>341</td>
<td>251</td>
<td>156</td>
<td>78</td>
<td>7</td>
</tr>
</tbody>
</table>


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VA-NEPHRON-D: Hyperkalemia


Number at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Losartan + placebo</td>
<td></td>
<td>724</td>
<td>648</td>
<td>563</td>
<td>487</td>
<td>379</td>
<td>271</td>
<td>174</td>
<td>90</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Losartan + lisinopril</td>
<td></td>
<td>724</td>
<td>631</td>
<td>535</td>
<td>458</td>
<td>347</td>
<td>258</td>
<td>154</td>
<td>71</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Hyperkalemia (% of patients) (95% CI)

- Losartan + placebo: 2.4 (1.5–3.9), 4.0 (2.7–5.9), 5.1 (3.4–7.5)
- Losartan + lisinopril: 6.5 (4.8–8.6), 9.9 (7.8–12.7), 13.4 (10.4–17.0)

p<0.001
Trial failure; design issues?

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  - Too many side effects

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BEACON; Primary outcome (*ESRD or CV death*) and Secondary outcome (*heart failure*)

Weeks since randomization

Estimated proportion of patients hospitalized for/died of HF by SDT

Estimated proportion of patients with ESRD or CV death by SDT

De Zeeuw et al; NEJM 2013
Trial failure; design issues?

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ASCEND; Effect of endothelin-antagonist Avosentan on primary renal outcome (doubling of serum creatinine, ESRD or death) in patients with type 2 diabetes and nephropathy (n = 1392)

ASCEND; cumulative incidence of CHF by avosentan and placebo treatment arm

Hoekman et al; CJASN 2014; 9: 490-498

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Recently failed CKD progression trials:

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Trial failure; design issues?

- Design issues:
  - Too low risk population
  - No effect on surrogate
  - Too high dose
  - Wrong Endpoints
  - Too much side effects

  Enrichment for risk
  Select responders
  Dose to optimal effect
  Correct endpoint definition
  Select “good” responders

What would have happened if previous trials would have looked at:
  - The responders
  - the good responders

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ONTARGET/TRANSCEND; Post hoc; Changes in albuminuria predict outcome in vascular disease or high risk diabetes

Schmieder et al; JASN 2011

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ONTARGET/TRANSCEND; Post hoc; Changes in albuminuria is best(?) predictor of outcome in patients with vascular disease or high risk diabetes

Schmieder et al; Diabetologia 2014
ALTITUDE; Post hoc; Adjusted renal/CV hazard by 6 month albuminuria change (8561 type 2 diabetes with CKD and/or CV disease)

Adjusted for the baseline covariates including age, gender, log-transformed UACR, eGFR, systolic blood pressure, diastolic blood pressure, HemoglobinA1c, body mass index, HDL cholesterol, LDL-cholesterol, log-transformed triglycerides, hemoglobin, history of cardiovascular disease, serum potassium current smoking, current drinking and randomized active treatment, and the change of covariates for 6 months including eGFR, systolic blood pressure, diastolic blood pressure and serum potassium.

Renal events

Cardiovascular events

Hazard ratio (95% CI)

<table>
<thead>
<tr>
<th>UACR change</th>
<th>N=2738</th>
<th>N=1548</th>
<th>N=1251</th>
<th>N=2514</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;-30</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>-30&lt;-0</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
</tr>
<tr>
<td>0-30</td>
<td>0.6</td>
<td>0.8</td>
<td>1.0</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>0.8</td>
<td>1.0</td>
<td>1.2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

p for trend <0.001

N=2738
N=1548
N=1251
N=2514

KDIGO

Lambers Heerspink et al. ASN 2013

Dick de Zeeuw June 2014
### BEACON; Post hoc analysis; Endpoints after excluding patients with BNP>200 pg/ml

<table>
<thead>
<tr>
<th>Event</th>
<th>All Patients</th>
<th>BNP ≤ 200, No Prior HF Hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO (n = 1097)</td>
<td>BARD (n = 1088)</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PBO (n = 1097)</td>
<td>69 (6)</td>
<td>69 (6)</td>
</tr>
<tr>
<td>BARD (n = 1088)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Composite</td>
<td>69 (6)</td>
<td>69 (6)</td>
</tr>
<tr>
<td>ESRD</td>
<td>51 (5)</td>
<td>43 (4)</td>
</tr>
<tr>
<td>Any Cardiovascular Death</td>
<td>19 (2)</td>
<td>27 (2)</td>
</tr>
<tr>
<td>Secondary Composite</td>
<td>86 (8)</td>
<td>139 (13)</td>
</tr>
<tr>
<td>Heart Failure</td>
<td>55 (5)</td>
<td>96 (9)</td>
</tr>
<tr>
<td>Fatal or Non-fatal Myocardial Infarction</td>
<td>16 (1)</td>
<td>19 (2)</td>
</tr>
<tr>
<td>Fatal or Non-fatal Stroke</td>
<td>11 (1)</td>
<td>14 (1)</td>
</tr>
<tr>
<td>All-Cause Death</td>
<td>31 (3)</td>
<td>44 (4)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>1 (&lt;1)</td>
<td>4 (&lt;1)</td>
</tr>
<tr>
<td>Surgical and medical procedures</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>18 (2)</td>
<td>20 (2)</td>
</tr>
</tbody>
</table>
From trial to practice

• We are carrying out hard end point trials for registration reasons:
  - The trials require to be representative of the patients to be treated with that indication in real life practice

• In trial design:
  - Usually fixed dose
  - If no effect, drug is continued and patient stays in trial
  - Side effects are part of outcome of trial

• In real life drug treatment:
  - Dose is titrated to a target
  - If no effect, drug is stopped
  - If side effect:
    - Side effect is managed
    - if side effect persists, drug is stopped
Future

- Do a trial in which we:
  - Enrich for risk
  - Enrich for good response
  - Enrich to take out bad response
SONAR; Protocol scheme

Run-in Period
- 2 weeks if receiving MTLD of RAS inhibitor
- 4–12 weeks if not receiving max tolerated labeled dose of RAS inhibitor

6-week Enrichment Period
- Atrasentan 0.75 mg QD

Double-Blind Treatment Period

- >30% UACR reduction
  - Atrasentan 0.75 mg QD (n=3148)
  - Placebo QD
- <30% UACR reduction
  - Atrasentan 0.75 mg QD (n=1000)
  - Placebo QD

Follow-up Period (45 days)

Primary endpoint
Time to first occurrence of composite renal endpoint: doubling of serum creatinine or onset of ESRD (needing chronic dialysis or renal transplantation or renal death)

Study completion
425 distinct primary renal events have occurred (adjudicated) in the responder population

De Zeeuw D, et al. Manuscript in preparation; ClinicalTrials.gov NCT01858532
Dick de Zeeuw June 2014
CONCLUSIONS

• Treatment of CKD progression (particularly in diabetes) leaves a large proportion of residual risk

• Recent efforts to slow progression with new medications on top of single RAASi have been unsuccessful

• These failures appear to be largely due to design failures