Therapeutics/Pharmacology

Prevention of cardiovascular morbidity in HD patients: the role of therapeutics versus dialysis technique

Christoph Wanner

Department of Medicine, Division of Nephrology, University Hospital Würzburg

KDIGO Controversies Conference
Novel techniques and innovation in blood purification: How can we improve clinical outcomes in hemodialysis?
Paris, France, 14-15 October, 2011,
**HD Patients: Randomised Trials with Endpoint Cardiovascular Disease**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Year</th>
<th>N</th>
<th>Event</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EPO-Hematocrit</td>
<td>1998</td>
<td>1233</td>
<td>372</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>2000</td>
<td>196</td>
<td>48</td>
<td>P=0.01</td>
</tr>
<tr>
<td>Acetylcysteine</td>
<td>2003</td>
<td>134</td>
<td>51</td>
<td>P=0.03</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>2003</td>
<td>130</td>
<td>71</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Dialysis Dosè x Flux</td>
<td>2004</td>
<td>1800</td>
<td>735</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>2005</td>
<td>1255</td>
<td>469</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>ACE-Inhibitor</td>
<td>2006</td>
<td>450</td>
<td>130</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Folic acid</td>
<td>2007</td>
<td>2056</td>
<td>884</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Rosuvasstatin</td>
<td>2009</td>
<td>2776</td>
<td>804</td>
<td>P&gt;0.05</td>
</tr>
</tbody>
</table>

Why are we not successful identifying therapeutic options / pharmacologic interventions for cardiovascular (cardiac & vascular) protection in renal failure patients?

Did we do something wrong?
How to approach the problem?

Heterogeneity: there are many potent risk factors (non-traditional) but also many outcomes (different from the general population)

The risk factors and outcomes vary in its expression between stages of CKD
Vascular status in stages of CKD

Risk factors:
- Atherosclerosis
- Arteriosclerosis

Kidney disease:
- Mild ↓ Kidney function
- Moderate ↓ Kidney function
- Severe ↓ Kidney function
- Kidney failure

eGFR (ml/min/1.73m²)*

120 90 60 30 15
Statin trials serve as role models: Examples

could not detect a benefit!

was successful!
Secondary prevention
Secondary prevention

AURORA

Cumulative incidence of the primary endpoint (%) vs. Follow-up in Jahren

Placebo
Rosuvastatin

Hazard ratio, 0.96
95% CI 0.84-1.11
p = 0.59
Secondary prevention

AURORA

Primary prevention

SHARP

Risk ratio 0.83 (0.74 - 0.94)
Logrank 2P=0.0022

4D
n=1255  T2DM  20 mg Atorvastatin
66 years, 46% F,
8.5 mo on dialysis

n=2776  10 mg Rosuvastatin
64 years, 38% F, 28% D
3.5 y on dialysis

n=9479
HD  2540
PD  490
CKD  6408
CKD3  2086
CKD4  2552
CKD5  1236
20 mg Simvastatin / 10 mg Ezetimibe
62 years, 37% F, 23% D
eGFR 27 ml/min/1.73m²
About primary endpoints

**4D & AURORA** - cardiovascular:
- death from cardiac *(cardiovascular)* causes,
- nonfatal myocardial infarction
- stroke

**SHARP** - atherosclerotic:
- major coronary event
- non-haemorrhagic stroke
- any revascularization
<table>
<thead>
<tr>
<th>Event</th>
<th>Eze/simv (n=4650)</th>
<th>Placebo (n=4620)</th>
<th>Risk ratio &amp; 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td></td>
</tr>
<tr>
<td>Non-haemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Any revascularization</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</td>
<td></td>
</tr>
<tr>
<td>Major atherosclerotic event</td>
<td>526 (11.3%)</td>
<td>619 (13.4%)</td>
<td>16.5% SE 5.4 reduction (p=0.0022)</td>
</tr>
<tr>
<td>Event</td>
<td>Eze/simv (n=4650)</td>
<td>Placebo (n=4620)</td>
<td>Risk ratio &amp; 95% CI</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------</td>
<td>------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Major coronary event</td>
<td>213 (4.6%)</td>
<td>230 (5.0%)</td>
<td>16.5% SE 5.4 reduction (p=0.0022)</td>
</tr>
<tr>
<td>Non-haemorrhagic stroke</td>
<td>131 (2.8%)</td>
<td>174 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Any revascularization</td>
<td>284 (6.1%)</td>
<td>352 (7.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Major atherosclerotic event</strong></td>
<td><strong>526 (11.3%)</strong></td>
<td><strong>619 (13.4%)</strong></td>
<td></td>
</tr>
<tr>
<td>Other cardiac death</td>
<td>162 (3.5%)</td>
<td>182 (3.9%)</td>
<td>5.4% SE 9.4 reduction (p=0.57)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>45 (1.0%)</td>
<td>37 (0.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Other major vascular events</strong></td>
<td><strong>207 (4.5%)</strong></td>
<td><strong>218 (4.7%)</strong></td>
<td></td>
</tr>
<tr>
<td>Major vascular event</td>
<td>701 (15.1%)</td>
<td>814 (17.6%)</td>
<td>15.3% SE 4.7 reduction (p=0.0012)</td>
</tr>
</tbody>
</table>
Primary composite end point

Relative Risk Reduction 8 % (95 % CI: 0.77-1.10, P=0.37)

Cumulative incidence (%)

Placebo          636             532             383            252             136              51       29
Atorvastatin    619             515             378            252             136              58       19

Median follow-up time of 4 years
Major Atherosclerotic Events
- All cardiovascular events combined -

Cardiac events
Non-fatal MI
Any revascularisation

Secondary endpoint
RRR 18 % (95 % CI: 0.68-0.99, P=0.03)

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Atorvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>636</td>
<td>619</td>
</tr>
<tr>
<td>1</td>
<td>532</td>
<td>515</td>
</tr>
<tr>
<td>2</td>
<td>383</td>
<td>378</td>
</tr>
<tr>
<td>3</td>
<td>252</td>
<td>252</td>
</tr>
<tr>
<td>4</td>
<td>136</td>
<td>136</td>
</tr>
<tr>
<td>5</td>
<td>51</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>29</td>
</tr>
</tbody>
</table>
Vascular active treatments:

- Lipids (statins)
- Phosphate (binders)
- Oxidative stress — acute phase response
- Deficiencies, multiple
- Cinacalcet (EVOLVE Study)
„Antifibrotic“ treatments:

- Aldosterone blockade (spironolactone)
- VDRA (paricalcitol)
- Volume control (diuretics, ultrafiltration)
- ß-Blockade (carvedilol)
- Glycation
- „Anemia“
„Antifibrotic“ treatments:

- Aldosterone blockade (spironolactone)
- VDRA (paricalcitol)
- Volume control (diuretics, ultrafiltration)
  - MiREnDa - Mineralocorticoid Receptor antagonists in End stage renal DiseAse
  - PRIMO - Paricalcitol benefits in Renal failure Induced cardiac MOrbidity
  - Volume control (diuretics, ultrafiltration)
  - BOND – Beta Blocker Outcomes in Nephrological Diseases
  - Glycation
  - „Anemia“
How to solve the problem?

Identify the underlying pathogenesis of the disease and assign potential treatments (athero- vs arteriosclerosis).

Causal relationship of an intervention can only be established by randomization.

Many more trials should be done, all sufficient in size. We have global networks in place!
To be realistic ....

We cannot established effectiveness for all kinds of treatments with outcome trials (feasibility and finances).

We may see more surrogate endpoint marker studies (imaging, histology, biomarker). Do we accept these studies?

How many different treatments / treatment strategies can we establish in a given patient in a specific stage of disease?

Can we bring the magnitude of effect into an order to prioritize the most potent treatments?
Thank you for your attention !