SHARP: Study of Heart & Renal Protection

The Effects of Lowering LDL Cholesterol with Simvastatin plus Ezetimibe in Patients with Chronic Kidney Disease

TRIAL BACKGROUND

- Prevalence of CKD is steadily climbing in Canada. CVD is the leading cause of death in CKD (~10-30 fold higher than general population).
- In late-stage CKD, CVD is incompletely explained by traditional risk factors age, DM, HTN, TLDL/HDL and may be due to novel risk factors anemia, abnormal Ca & PO4 metabolism, eGFR deficiency, chronic inflammation/endothelial dysfunction leading to arterial calcification, LVH, & sympathetic overactivity and death due to arrhythmia or HF. This is in contrast to CKD Stages 1-3 where MI & related atherosclerotic events remain prominent.
- Statins ↓ risk of CV events, MI, ischemic stroke, CV death, revascularization. However, benefit of LDL reduction with statins in patients with Stage 4 CKD was unknown and studies in hemodialysis patients were negative.
- In SHARP (Mc, DB, RT(3)), T2DM on HD n=1255 (Bl: HD 880, CHD 29%, HF 35%, PVD 45%, LDL 3.2mmol/L), atorvastatin 20mg vs. placebo over 4yrs drug exposure 2.3yrs, 1°: major CV events TDM on HD n=2776 (Bl: HD 3.5yrs, DM 26%, CHD 40%, HDL 15%, LDL 2.6mmol/L), rosuvastatin 10mg vs. placebo over 3.8yrs drug exposure 2.2yrs, 1°: major CV events. No patients with advanced CKD but without known CHD.

TRIAL DESIGN

DB, PC, Mc, Country RCT Funded by University of Oxford, Merck (Simvastatin 20mg + Ezetimibe EXELIO, 10mg daily [VYTORIN, combination product not available in Canada]) vs Placebo (Initially randomized 3 ways 4:1:1, Simvastatin/Ezetimibe vs. placebo vs. simvastatin alone to ensure safety of ezetimibe). Inclusion: ≥40 yrs, pre-dialysis: SCR >150µmol/L, HD or PD. Exclusion: MI or coronary revascularization, low compliance during run-in, LFT >2xULN, other lipid drugs, strong CYP3A4 inhibitors, baseline characteristics: Age mean 62, 62% male, dialysis stage 3 to 5, known vascular disease, DM, HTN, HD 129/76mmHg, LDL >2.5mmol/L, meds: diuretics, β-blockers, ACEI, ARB, CCB, BB. Patients randomized to simvastatin group were not randomized to ezetimibe group for safety reasons.

RESULTS (ITT, median follow up 4.9 yrs)

Primary Outcome: Major atherosclerotic events: non-fatal MI or cardiac death, non-hemorrhagic stroke, or any arterial revascularization

Clinical Endpoints

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Combo Simvastatins/Ezetimibe (n=4690)</th>
<th>Placebo (n=4620)</th>
<th>Risk Ratio (95% CI)</th>
<th>ARR/NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Major Atherosclerotic Events</td>
<td>11.3%</td>
<td>13.4%</td>
<td>0.83 (0.74-0.94), p=0.0021</td>
<td>2.1%/48</td>
</tr>
<tr>
<td>Not on dialysis Stage 3 CKD 2155</td>
<td>9.5%</td>
<td>11.9%</td>
<td>0.78 (0.67-0.91),</td>
<td>2.4%/42</td>
</tr>
<tr>
<td>Stage 4 CKD 2565</td>
<td>7.9%</td>
<td>10.4%</td>
<td>0.75 (1.57-1.00),</td>
<td>2.5%/40</td>
</tr>
<tr>
<td>Stage 5 CKD 1221</td>
<td>10.2%</td>
<td>12.7%</td>
<td>0.78 (0.62-0.98),</td>
<td>2.5%/40</td>
</tr>
<tr>
<td>On dialysis Stage 2527</td>
<td>15.0%</td>
<td>16.5%</td>
<td>0.90 (0.75-1.08),</td>
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</tr>
<tr>
<td>Hemodialysis Stage 496</td>
<td>15.2%</td>
<td>15.9%</td>
<td>0.95 (0.78-1.15),</td>
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</tr>
<tr>
<td>Peritoneal Dialysis</td>
<td>14.0%</td>
<td>19.7%</td>
<td>0.70 (0.75-1.08),</td>
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<tr>
<td>2° Major Vascular Event</td>
<td>15.1%</td>
<td>17.6%</td>
<td>0.85 (0.77-0.94),</td>
<td>2.5%/40</td>
</tr>
<tr>
<td>2° Major Coronary Event</td>
<td>4.6%</td>
<td>5.0%</td>
<td>0.92 (0.76-1.11),</td>
<td>--</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>2.9%</td>
<td>3.4%</td>
<td>0.84 (0.66-1.05),</td>
<td>--</td>
</tr>
<tr>
<td>CHD death</td>
<td>2.0%</td>
<td>1.9%</td>
<td>1.01 (0.75-1.35),</td>
<td>--</td>
</tr>
<tr>
<td>2° Non-hemorrhagic stroke</td>
<td>2.8%</td>
<td>3.8%</td>
<td>0.75 (0.60-0.94),</td>
<td>0.9%/112</td>
</tr>
<tr>
<td>Ischemic</td>
<td>2.5%</td>
<td>3.4%</td>
<td>0.72 (0.57-0.92),</td>
<td>--</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.4%</td>
<td>0.4%</td>
<td>0.94 (0.49-1.79),</td>
<td>--</td>
</tr>
<tr>
<td>2° Revascularization</td>
<td>6.1%</td>
<td>7.6%</td>
<td>0.79 (0.68-0.93),</td>
<td>1.5%/67</td>
</tr>
<tr>
<td>Coronary</td>
<td>3.2%</td>
<td>4.7%</td>
<td>1.73 (0.59-0.90),</td>
<td>1.2%/84</td>
</tr>
<tr>
<td>Non-coronary</td>
<td>3.3%</td>
<td>3.7%</td>
<td>1.90 (0.73-1.12),</td>
<td>--</td>
</tr>
<tr>
<td>2° All cause mortality</td>
<td>24.6%</td>
<td>24.1%</td>
<td>1.01 (0.94-1.11),</td>
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<tr>
<td>Change in LDL (mmol/L)</td>
<td>2.77 → 1.93</td>
<td>2.78 → 2.70</td>
<td>~30% reduction</td>
<td></td>
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</tbody>
</table>

Further reading:

- Author’s claim a RR reduction [RR 0.81 (0.70-0.93) per 1mmol/L LDL] is the best estimate of effect in the total population, since attrition ~1/3 in each arm and hence less LDL reduction similar attribution to 40/AURORA, expected 39% LDL, based on ‘lack of heterogeneity’ using χ2 statistic; however, point estimates are not equal between subgroups no benefit seen in Stage 5 CKD or dialysis patients and this statistic has low sensitivity for detecting differences between a small number of groups & assumes similar clinical characteristics known as CKD progresses CVD picture changes.
- 1° outcome driven by pts in CKD stage 3-4, ischemic stroke & revascularization procedures; there was no benefit in nonfatal MI or CHD death.
- Adverse Effects: No difference between groups for muscle pain, CK, LFTs, or cancer. No reduction in pre-specified measures of renal disease progression initiation of maintenance dialysis or transplantation, ESRD or death, ESRD or doubling Scr.
COMMENTS

- Revised 1st outcome is likely the better outcome since it allows determination of benefit from statins by looking at outcomes statins were similar to impact; controversy settled when results between the 2 outcomes were similar and power was adequate for both.
- Cannot conclude if benefit secondary to addition of ezetimibe to statin therapy vs. statin therapy alone; however, lack of clinical benefit despite expected LDL reduction in other trials of combination therapy in a variety of populations.
  - **ENHANCE, SEAS, ARBITER-6 HALT3** suggests ezetimibe did not contribute
    - Uncertainty: clinical effect of simvastatin 20mg or 40mg alone, or any other statin, in this population
    - **Kidney Transplant: ALERT** showed some benefit in cardiac deaths/nonfatal MI but not overall 1st outcome

**Limitations:**
- Change in 1st outcome: risk of bias • multiple analyses: **Risk of Type I error (though did use statistical adjustments)**
- Use of combination simvastatin + ezetimibe: **limits generalizability • heterogeneous population** requires use of sub-group analyses to draw conclusions
- A Critical Appraisal in 2014 identified several irregularities that could significantly compromise & bias the data.

**Strengths:**
- asked an important question yet unamnized in the literature • large, well-designed study • ITT analysis

**BOTTOM LINE: CKD lipid therapy**

- Pattern of CVD changes as CKD progresses: early CKD: cholesterol dependent atheromatous coronary disease; late CKD: vascular calcification, LVH
- Lipid lowering therapy (statin) is indicated to prevent atherosclerotic CVD in patients with CKD including those progressing to ESRD; findings emphasize need to treat early in disease process, however, point at which patients may no longer benefit remains unclear, and there is no evidence to support initiation of statin therapy in dialysis patients.
- Studies confirm that statin therapy is safe in late-stage CKD
- Role of ezetimibe is not clear, but likely to have contributed to clinical outcomes

References: