

SHARP: Study of Heart & Renal Protection¹⁻²

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 ^{GFR<30} CVD is incompletely explained by traditional risk factors ^{age, DM, HTN, ↑LDL/↓HDL} and may be due to novel risk factors ^{anemia, abnormal Ca & PO4 metabolism, vitD 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} by ~20-25% in the general population ^{CTT MA(3)} & in those with Stage 1-3 CKD ^{PPP(4)}; however benefit of LDL reduction with statins in patients with **Stage 4 CKD was unknown and studies in hemodialysis patients were negative**
 - 4D ^{MC, DB, RCT(5)}: T2DM on HD ^{n=1255 (BL: HD x8mo, CHD 29%, HF 35%, PVD 45%, LDL 3.2mmol/L)}; atorvastatin 20mg ^{vs. placebo} over 4yrs ^{drug exposure 2.3yrs}
 - 1°: major CV events ^{CV death, nonfatal MI, stroke}: 37 vs 38%; RR 0.92 (95% CI 0.77-1.10), NS despite LDL ↓42% ^{to 1.86mmol/L}
 - AURORA ^{MC, DB, RCT(6)}: ESRD on HD ^{n=2776 (BL: HD 3.5yrs, DM 26%, CVD 40%, PVD 15%, LDL 2.6mmol/L)}; rosuvastatin 10mg ^{vs. placebo} over 3.8 yrs ^{drug exposure 2.2yrs}
 - 1°: major CV events ^{CV death, nonfatal MI, stroke}: 28.5 vs 29.4%; RR 0.96 (95% CI 0.84-1.11), NS despite LDL ↓43% ^{to 1.5mmol/L}
- Why were 4D & AURORA negative? Is it possible statins don't work in dialysis patients? Did they study the wrong outcome?
 - SHARP¹: chief aim to determine any vascular benefit of combination simvastatin + ezetimibe ^{in patients with advanced CKD but without known CHD}
 - 2 pilot studies (UK-HARP I+II^{7,8}) demonstrated the safety ^{CK, LFT} & efficacy ^{LDL 20-25%} of simvastatin 20mg ^{chosen as CKD patients at ↑ risk of myopathy} + ezetimibe 10mg in CKD population

TRIAL DESIGN

DB, PC, MC ^{39 countries} RCT ⁿ⁼⁹²⁷⁰ Funded by University of Oxford, Merck ^{Schering-Plough, Australian National HMRC, British Heart Foundation, UK MRC}

(Simvastatin 20mg + Ezetimibe 10mg daily [VYTORIN combination product not available in Canada]) vs Placebo (Initially randomized 3 ways ^{4:4:1}: Simvastatin/Ezetimibe vs. placebo vs. simvastatin alone to ensure safety of ezetimibe ^{simvastatin alone group then re-randomized (n=886)})

Inclusion: ≥40 yrs, pre-dialysis: SCr ⇔ >150umol/L ♂, >130umol/L ♀, OR dialysis ^{HD or PD}

Exclusion: MI or coronary revascularization ^{allowed angina, PVD, CeVD}, low compliance ^{during 6wk run-in}, LFT >2xULN, other lipid drugs, strong CYP3A4 inhibitors

Baseline Characteristics: Age_{mean}=62; 62% ♂; dialysis ^{33%} (HD^{27%}, PD^{6%}), not on dialysis: GFR 27mL/min/1.73m² - Stage 3: 36%, Stage 4: 42%, Stage 5: 20%, known vascular disease ^{15%}, DM ^{23%}, BP ^{139/79mmHg}, LDL ^{2.78mmol/L}, meds ^{differed between dialysis/not}: antiplatelet ^{24%}, ACEi ^{34%}, ARB ^{31%}, CCB ^{40%}, BB ^{38%}

RESULTS (ITT, median follow up 4.9 yrs)

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

Original Primary: Major vascular events: non-fatal MI or cardiac death, any stroke or any arterial revascularization

→ changed to ensure measuring events statins known to impact ^{prevent more numerous non-atherosclerotic events from diluting the benefit on atherosclerotic outcomes}

→ done after randomization complete, near end of follow-up when determined LDL effect less than expected (unblinded) ^{↓0.85 not 1mmol/L} and overall vascular event rate higher than expected in placebo group (blinded) ^{4.3%/yr not 3.7%/yr} and 1/3 of these events were non-coronary cardiac deaths or hemorrhagic strokes ^{thus were inadequately powered to detect a difference}

Clinical Endpoints	Combo ^{Simv+Ezet} (n=4690)	Placebo (n=4620)	Risk Ratio (95% CI)	ARR/NNT	Notes/Comments																		
1° Major Atherosclerotic Events	11.3%	13.4%	0.83 (0.74-0.94), p=0.0021	2.1%/48	CKD Staging <table border="1"> <thead> <tr> <th>Stage</th> <th>Description</th> <th>GFR mL/min/1.73m²</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>Kidney damage with normal or ↑GFR</td> <td>≥90</td> </tr> <tr> <td>2</td> <td>Kidney damage with mild ↓GFR</td> <td>60-89</td> </tr> <tr> <td>3</td> <td>Moderately ↓GFR</td> <td>30-59</td> </tr> <tr> <td>4</td> <td>Severely ↓GFR</td> <td>15-29</td> </tr> <tr> <td>5</td> <td>Kidney failure</td> <td><15 (or dialysis)</td> </tr> </tbody> </table> See Appendix 1: Major Atherosclerotic Events by CKD subgroup (benefit ↓'s as CKD progresses towards dialysis)	Stage	Description	GFR mL/min/1.73m ²	1	Kidney damage with normal or ↑GFR	≥90	2	Kidney damage with mild ↓GFR	60-89	3	Moderately ↓GFR	30-59	4	Severely ↓GFR	15-29	5	Kidney failure	<15 (or dialysis)
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Not on dialysis ⁿ⁼²¹⁵⁵	9.5%	11.9%	0.78 (0.67-0.91)	2.4%/42																			
Stage 3 CKD ⁿ⁼²¹⁵⁵	7.9%	10.4%	0.75 (1.57-1.00)	2.5%/40																			
Stage 4 CKD ⁿ⁼²⁵⁶⁵	10.2%	12.7%	0.78 (0.62-0.98)	2.5%/40																			
Stage 5 CKD ⁿ⁼¹²²¹	10.9%	13.3%	0.82 (0.59-1.13), NS	--																			
On dialysis ⁿ⁼²⁵²⁷	15.0%	16.5%	0.90 (0.75-1.08), NS	--																			
Hemodialysis ⁿ⁼²⁵²⁷	15.2%	15.9%	0.95 (0.78-1.15), NS	--																			
Peritoneal Dialysis ⁿ⁼⁴⁹⁶	14.0%	19.7%	0.70 (0.75-1.08), NS	--																			
2° Major Vascular Event	15.1%	17.6%	0.85 (0.77-0.94)	2.5%/40																			
2° Major Coronary Event	4.6%	5.0%	0.92 (0.76-1.11), NS	--																			
Nonfatal MI	2.9%	3.4%	0.84 (0.66-1.05), NS	--																			
CHD death	2.0%	1.9%	1.01 (0.75-1.35), NS	--																			
2° Non-hemorrhagic stroke	2.8%	3.8%	0.75 (0.60-0.94), NS	--																			
Ischemic	2.5%	3.4%	0.72 (0.57-0.92)	0.9%/112																			
Unknown	0.4%	0.4%	0.94 (0.49-1.79), NS	--																			
2° Revascularization	6.1%	7.6%	0.79 (0.68-0.93)	1.5%/67																			
Coronary	3.2%	4.4%	1.73 (0.59-0.90)	1.2%/84																			
Non-coronary	3.3%	3.7%	1.90 (0.73-1.12), NS	--																			
2° All cause mortality	24.6%	24.1%	1.01 (0.94-1.11), NS	--																			
Change in LDL (mmol/L)	2.77 → 1.93	2.78 → 2.70	~30% reduction																				

- 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 attrition to 4D/AURORA, expected 39% LDL ↓} based on 'lack of heterogeneity' using χ^2 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 ^{dialysis vs not} & assumes similar clinical characteristics ^{know 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 ^{signal from SEAS not confirmed in FDA review of SEAS, IMPROVE-IT, SHARP}
- 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 1° outcome is likely the better outcome since it allows determination of benefit from statins by looking at outcomes statins are known 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-HALTS} suggests ezetimibe did not contribute
 - Uncertainty: clinical effect of simvastatin 20mg or 40mg alone, or any other statin, in this population
- Did not report use of any medications ^{including erythropoietin stimulating agents, phosphate binders, iron therapy} which may also impact long-term CV risk
- Uncertain if benefit across all subgroups of CKD ^{dialysis vs. non-dialysis – underpowered}
 - Kidney Transplant: **ALERT** ⁿ⁼²¹⁰¹ fluvastatin 40mg daily ^{over 5.1yrs} showed some benefit in cardiac deaths/nonfatal MI ^{but not overall 1° outcome}

Strengths: ♦ asked an important question yet unanswered in the literature ♦ large, well-designed study ♦ ITT analysis

Limitations: ♦ change in 1° 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}

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 ^{4D, AURORA, SHARP congruent}
- Studies confirm that statin therapy is **safe** in late-stage CKD
- Role of ezetimibe is not clear, but unlikely to have contributed to clinical outcomes ^{trial of combination vs statin therapy alone unlikely to be done due to huge N required}

ACEi=angiotensin converting enzyme inhibitor ARB=angiotensin receptor blocker ARR=absolute risk reduction BB=beta blocker BL=baseline BP=blood pressure Ca=calcium CCB=calcium channel blocker CeVD=cerebrovascular disease CHD=coronary heart disease CI=confidence interval CK=creatinine kinase CKD=chronic kidney disease CTT MA=Cholesterol Treatment Trialists' MetaAnalysis CV=cardiovascular CVD=cardiovascular disease DB=double blind DM=diabetes ESRD=end-stage renal disease GFR=estimated glomerular filtration rate HD=hemodialysis HDL=high density lipoprotein HF=heart failure HMRC=health medical research council HTN=hypertension ITT=intention to treat LDL=low density lipoprotein LFT=liver function test LVH=left ventricular hypertrophy MC=multicentre MI=myocardial infarction MDRD=Modification of Diet in Renal Disease NNT=number needed to treat NS=non-significant PC=placebo controlled PD=peritoneal dialysis PO₄=phosphate PPP=Pravastatin Pooling Project PVD=peripheral vascular disease RCT=randomized controlled trial RR=relative risk RF=risk factors SCR=serum creatinine T2DM=Type 2 diabetes mellitus UKMRC=United Kingdom Medical Research Council ULN=upper limit of normal ♂=male ♀=female

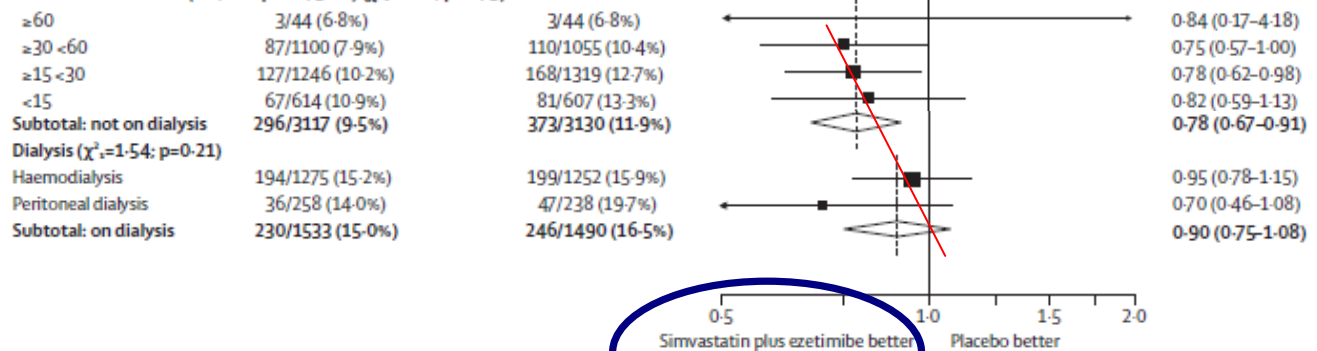
Links to RxFiles:

- Lipid Lowering Chart: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents.pdf>

- Lipid Landmark Trials: <http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-lipid%20agents-major%20trials.pdf>

* Appendix 1: Major Atherosclerotic Events by CKD subgroup

MDRD estimated GFR (mL/min per 1.73 m²) (χ²₁=0.12; p=0.73)



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