Jill Hall, BScPharm & Aleesa Carter, BSP, PharmD Candidates

SHARP: Study of Heart & Renal Protection[1-2]

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? [Death from HF/arrhythmia not MI/stroke]
- **SHARP [1]**: 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] + ezetemibe 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 [EZETROL] **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/1.73m^2 [- 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
1° Major Atherosclerotic Events	11.3%	13.4%	0.83 (0.74-0.94), p=0.0021	2.1%/48
Not on dialysis *	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 *	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	

CKD Staging

Stage	Description	GFR mL/min/1.73m2
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)

* See Appendix 1: Major Atherosclerotic Events by CKD subgroup (benefit ↓'s as CKD progresses towards dialysis)

- 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;
  - o 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** [15 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] ♦ **A Critical Appraisal in 2014 identified several irregularities that could significantly compromise & bias the data.** [i]

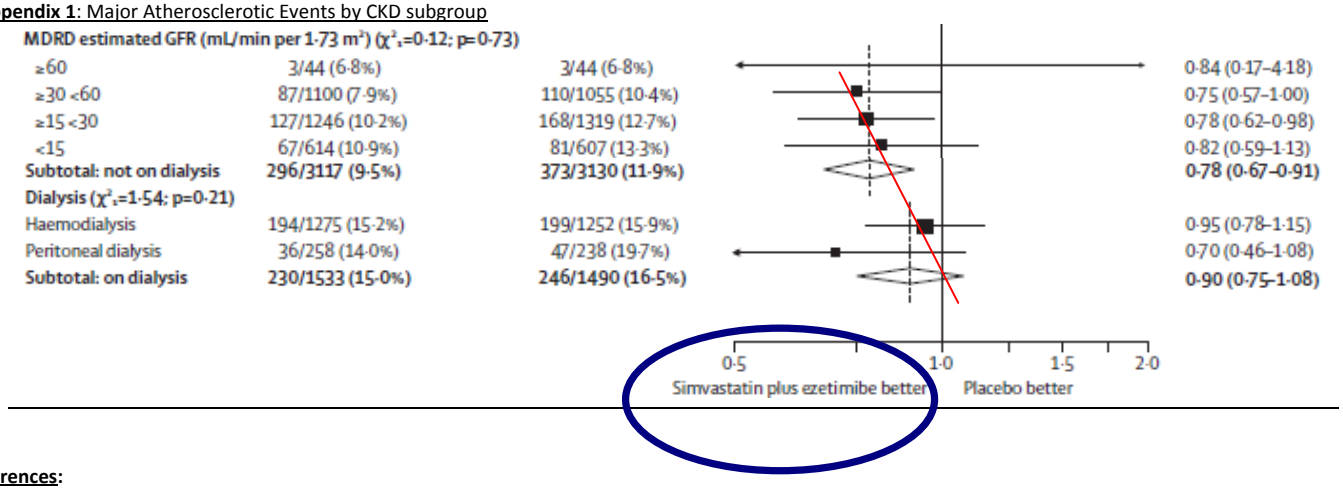
BOTTOM LINE: CKD lipid therapy

- 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 **PO_4**=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 Counsel **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



References:

1. **SHARP** Collaborative Group. SHARP: Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010;160:785-94.
2. Baigent C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection-**SHARP**): a randomized placebo-controlled trial. *Lancet* 2011
3. Cholesterol Treatment Trialists' (**CTT**) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomized trials. Lancet 2010;376:1670–81.
4. Tonelli M, Isles C, Curhan GC et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110:1557-1563.
5. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. (**4D**) *NEJM* 2005; 353:238-248.

März W, Genser B, Drechsler C, et al. German Diabetes and Dialysis Study Investigators (**4D**). Atorvastatin and low-density lipoprotein cholesterol in type 2 diabetes mellitus patients on hemodialysis. Clin J Am Soc Nephrol 2011;6(6):1316-25.

6. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis (**AURORA**). *NEJM* 2009;360:1395-1407.

Holdaas H, Holme I, Schmieder RE, et al. **AURORA** study group. Rosuvastatin in diabetic hemodialysis patients. J Am Soc Nephrol. 2011;22(7):1335-41.

Stippoli GFM, Craig JC. Sunset for statins after AURORA? NEJM 2009;360(14):1455-57.

7. Baigent C et al. First UK heart and renal protection study (**UK HARP I**): Biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis 2005;45:473-84.
8. Landray M et al. The second UK heart and renal protection study (**UK-HARP II**): a randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patients with CKD. Am J Kidney Dis 2006;47(3):385-95.
9. Kastelein JJP, Akdim F et al. Simvastatin with or without Ezetimibe in Familial Hypercholesterolemia. (**ENHANCE**) NEJM 2008:358;14:1431-1443
10. Jander N, Minners J, Holme I et al. Outcome of patients with low-gradient "severe" aortic stenosis (**SEAS**)and preserved ejection fraction. Circulation 2011, 123:887-895.
11. Villines TC, Stanek EJ, Devine PJ et al. The **ARBITER-6HALTS** Trial : Final results and impact of medication adherence, dose, and treatment duration. J Am Coll Cardiol 2010;55:2721–6.
12. Holdaas H, Fellström B, Jardine AG, et al. Assessment of LEscol in Renal Transplantation (**ALERT**) Study Investigators. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Lancet. 2003;361(9374):2024-31.
    Fellström B, Holdaas H, Jardine AG,et al. Assessment of Lescol in Renal Transplantation Study Investigators. Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (**ALERT**) trial. Kidney Int. 2004 Oct;66(4):1549-55.
    Holdaas H, Fellström B, Cole E, et al. Assessment of LEscol in Renal Transplantation (ALERT) Study Investigators. Long-term cardiac outcomes in renal transplant recipients receiving fluvastatin: the **ALERT** extension study. Am J Transplant. 2005 Dec;5(12):2929-36.
13. United States Renal Data System: USRDS 2001 Annual Data Report. Bethesda, MD: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, 2001.
14. Canadian Organ Replacement Register Annual Report: Treatment of End Stage Organ Failure in Canada, 2000-2009. Released January 2011. Available at: https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC1574. (Accessed: July 21, 2011)
15. Baigent C, Landray MJ, Wheeler DC. Misleading associations between cholesterol and vascular outcomes in dialysis patients: the need for randomized trials. Seminars in Dialysis 2007:20(6):498–503

16. Lim SY, Bae EH, Choi JS, et al. other Korea Acute Myocardial Infarction Registry Investigators. Effect on Short- and Long-Term Major Adverse Cardiac Events of Statin Treatment in Patients With Acute Myocardial Infarction and **Renal Dysfunction**. Am J Cardiol. 2012 Feb 20.
17.

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[i] Harbin M, Amadio A, Tejani A. **Critical Appraisal of the SHARP Trial**: The Results May Be Dull. Clin Ther. 2014 Dec 1;36(12):2112-7. doi:10.1016/j.clinthera.2014.10.008. Accessed online 25 Jan, 2014 at: http://www.unboundmedicine.com/medline/citation/25453731/Critical_Appraisal_of_the_SHARP_Trial:_The_Results_May_Be_Dull_