What's New in Lipid Management? Cardiovascular Risk Reduction in Chronic Kidney Disease

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Henry's Case

Henry is a 66-year-old, asymptomatic, non-diabetic, non-smoker with no family history of coronary heart disease (CHD) or stoke. Following a recent diagnosis of hypertension, he was taking metoprolol 50 mg o.d. and hydrochlorothiazide 25 mg o.d. His blood pressure was 110/84 mm Hg. His total, LDL and HDL cholesterol and triglyceride (TG) levels were 5.20, 3.46, 0.93, and 1.55 mmol/L respectively. Urinalysis was normal. Serum creatinine level (repeated twice) was 126 µmol/L (normal 60 to 110 µmol/L), giving an estimated glomerular filtration rate (eGFR) of 53 mL/min/1.73m^2, which is consistent with stage 3 or moderate CKD (see Table 1). He was at high CVD risk by the Framingham algorithm, with a target LDL cholesterol < 2 mmol/L. He was started on simvastatin 20 mg daily.

Chronic Kidney Disease (CKD) and Cardiovascular Disease (CVD) Morbidity and Mortality

Chronic kidney disease (CKD) predicts adverse CVD outcomes: for instance, CVD is the main cause of mortality during dialysis and after renal transplantation, with death rates among the highest for any patient group.[1] However, the main CVD end points experienced by CKD patients differ from those seen in the general population. For instance, in CKD most CVD deaths are due to arrhythmia and cardiac arrest, while in the general population, most are due to atherosclerosis-related events, such as myocardial infarction (MI) and stroke. Similarly, cardiovascular pathology in CKD is unique: there is more arterial calcification and cardiomyopathy than in the general population. Long before the onset of end-stage renal disease, patients with mild to moderate renal failure are at increased CVD risk compared to the general population.

Lipid Lowering Therapy for Renal Dyslipidemia

Because complex metabolic changes, including dyslipidemia, accompany declining renal function, CVD risk factor control is logical in CKD.[2] CKD patients are more likely to have elevated triglycerides and decreased HDL-cholesterol, often with minimally increased LDL cholesterol compared to individuals without CKD.[2] Because of the benefit of LDL-lowering therapy — statins mainly — across virtually all high-risk patient groups, two prospective, randomized, placebo-controlled trials of statin monotherapy were undertaken in hemodialysis

patients. One, called 4D, evaluated atorvastatin 20 mg versus placebo, and the other study, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), evaluated rosuvastatin 10 mg versus placebo.[3,4] Unfortunately, both trials were negative; neither showed any difference in major CVD outcomes.[3,4]

These results raised several questions. Because of the distinct lipid profile in CKD, should medications other than statins be evaluated? Because so much CVD in end-stage renal disease is nonatherosclerotic, how much influence can LDL-lowering really have? By the time CKD patients need dialysis, is CVD simply too advanced? Is it by then too late to expect that LDL-lowering therapy will reduce CVD risk?

The SHARP Study

A recently published study has brought some clarity to these issues. The Study of Heart and Renal Protection (SHARP) examined the combination of simvastatin 20 mg plus ezetimibe 10 mg versus placebo in patients at various stages of CKD.[5] Participants either had elevated serum creatinine levels, with eGFR < 60 mL/min/1.73m^2 (pre-dialysis group, N = 6247) or were already receiving dialysis (N = 3023). Participants were age 40 years and older and had no history of MI or coronary revascularization. Non-dialysis patients had an average eGFR of 27 mL/min/1.73m^2. The overall average baseline LDL cholesterol was ~2.7 mmol/L and active treatment reduced it to ~1.8 mmol/L.

The study findings were strongly positive. Over a five year period, ezetimibe plus simvastatin significantly reduced the incidence of major atherosclerotic events (risk ratio [RR]: 0.83; 95% confidence interval [CI] 0.74 to 0.94) and virtually every individual class of event, such as ischemic stroke (RR: 0.72; 95% CI 0.57 to 0.92) and coronary revascularization procedures (RR: 0.73; 95% CI 0.59 – 0.90). However, renal outcomes — such as progression to end-stage renal disease or doubling of creatinine levels — were not statistically different from placebo.[5]

Safety

The authors intentionally chose the active treatment to include a low and well-tolerated dose of

Table 1
Stages of Chronic Kidney Disease

Stage	Glomerular Filtration Rate (mL/min/1.73 m^2)	Description
1	≥ 90	Slightly diminished function; kidney damage* with normal or relatively high GFR
2	60–89	Mild reduction in GFR with kidney damage
3	30–59	Moderate reduction in GFR
4	15–29	Severe reduction in GFR; preparation for renal replacement therapy
5	< 15	Established kidney failure; end stage renal disease or permanent renal replacement therapy

*Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies

an older statin (simvastatin 20 mg/day) in combination with a well-tolerated cholesterol absorption inhibitor (ezetimibe 10 mg/day). As expected, the observed rate of adverse events was low, with essentially no increase in myopathy, liver or gastrointestinal disorders, or cancer with combination treatment over placebo.[5]

Clinical Issues Arising from SHARP

A key pre-specified subgroup analysis showed that pre-dialysis patients had significantly reduced risks of major atherosclerotic events with therapy (RR: 0.78; 95% CI 0.67 to 0.91), while patients on dialysis did not (RR: 0.90; 95% CI 0.75 to 1.08). A test of statistical heterogeneity found that there was no significant difference in the risk reduction between these two subgroups. But from another perspective, the negative result in the dialysis subgroup is in line with the main results of the 4D and AURORA studies. The overall strong significance of SHARP could be seen as being driven by the clearly significant CVD risk reduction in the pre-dialysis patients.

Back to Henry

Henry's eGFR was still 57 mL/min/1.73m^2 after three months. On simvastatin 20 mg, his total, LDL and HDL cholesterol and triglyceride (TG) levels were 4.50, 2.61, 1.14, and 1.05 mmol/L, respectively, with normal CK and ALT. Options now included: 1) titrating simvastatin up to 40 mg daily; 2) switching to a more potent statin, such as rosuvastatin 10 mg; or 3) adding ezetimibe 10 mg. In light of SHARP, option 3 was chosen.

Efforts are underway to combine individual level data from dialysis patients in 4D, AURORA, and now SHARP, using meta-analysis to detect an overall positive result. Perhaps the key may lie with earlier initiation of LDL-lowering treatment, such as in patients with moderate CKD. In any event, SHARP strongly suggests that LDL-lowering with ezetimibe plus simvastatin is safe and effective in patients with early CKD, and possibly in dialysis patients as well.

Table 2

Questions & Answers

1. **When should I initiate a renal patient on lipid-lowering therapy?**
   Early: CVD risk increases from the earliest stages of CKD. But many nephrologists consider that it is never too late for lipid-lowering therapy — even for patients on dialysis.

2. **What is the recommended treatment?**
   Reducing LDL cholesterol < 2.0 mmol/L is most often accomplished with statin monotherapy. CKD patients benefited from the ezetimibe plus simvastatin combination.

3. **What can I do for my statin-intolerant patients (*e.g.*, muscle pain or elevated CK levels)?**
   Several things.[6] First, try rechallenging with another statin: fluvastatin and pravastatin are better tolerated. Non-daily rosuvastatin (*e.g.*, 10 mg every other day) works relatively well but lacks clinical trial evidence of CVD reduction.

4. **Is there anything else I can suggest if the above doesn't work?**
   Switch to another class: *e.g.,* ezetimibe, niacin-based therapy, bile acid sequestrants, or fibrates. Coenzyme Q10 (60 to 120 mg daily) helps anecdotally, but minimal clinical trial evidence supports its use.

Summary

Recent evidence supports LDL-lowering to reduce major atherosclerotic events in CKD patients. The observed CVD event rate reduction of the ezetimibe plus simvastatin combination was consistent with the expected effect given the extent of LDL cholesterol reduction. The SHARP study also showed that the ezetimibe plus simvastatin combination was safe with no increase in myopathy, liver problems, cancer, or nonvascular mortality. Dx

References

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Take-home Messages

- CVD is the main cause of mortality during dialysis and after renal transplantation; although, it is often non-atherosclerotic
- The SHARP study showed that LDL-lowering with ezetimibe plus simvastatin reduced major atherosclerotic events in the CKD population
- Ezetimibe plus simvastatin showed no excess risk of most important side-effects including cancer, and no excess non-vascular death compared to placebo

Resource

1. 2009 Canadian Cardiovascular Society Guidelines for the Treatment of Dyslipidemia. http://www.ccs.ca/download/consensus_conference/consensus_conference_archives/2009_Dyslipidemia-Guidelines.pdf

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