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CV RISK MANAGEMENT IN CKD: What works?

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The management of cholesterol in patients with chronic kidney disease (CKD) has been controversial. Until recently, this debate has been fueled by a lack of supportive studies.

> "Despite the risk of CV events in CKD patients, data supporting lowering cholesterol in this population has been lacking."

Patients reaching dialysis have a high mortality from cardiac causes. Most of these events are not due to atherosclerosis. They are heavily weighted to arrhythmias, cardiac arrest and congestive heart failure. Yet approximately one-quarter of cardiac mortality in CKD patients can be attributed to acute MI and potentially averted with cholesterol lowering.

The Framingham risk score under-predicts cardiac event rates in CKD populations. Patients with CKD suffer all of the traditional CV risk factors (age, diabetes, lipids etc) in addition to others specific to CKD.

Ironically, in Dialysis patients, those with the lowest cholesterol levels actually have the highest risk of mortality. The CHOICE study showed this reverse relationship exists in those CKD patients who have evidence for malnutrition and inflammation. In most other patients, the typical higher cholesterol- higher mortality association remains.

Ultimately, a CKD patient should be seen as having a high future CV risk. In the June 2011 CJASN, prospective data from the VA hospitals confirms CKD as a CV risk equivalent, with a higher risk for CV events in CKD patients than even in those with diabetes without CKD.

Despite the risk of CV events in CKD patients, data supporting lowering cholesterol in this population has been lacking. Major trials of CV outcomes usually excluded patients with ESRD or advanced CKD; consequently there was a gap in data on managing this population. A post-hoc analysis using pooled data from the major pravastatin intervention studies, CARE, LIPID and WOSCOPS found 4491 patients with Stage 3 chronic kidney disease, with an eGFR 30-59.9. These patients had a 25% increased risk of suffering myocardial infarction, cardiac death or need to undergo revascularization. The use of pravastatin significantly reduced this risk by 23%.

Stages of CKD

CKD Stage	eGFRml/min/1.73m^2
Stage 1	>90
Stage 2	60-90
Stage 3	30-59
Stage 4	15-29
Stage 5	<15

*Evidence of chronic kidney damage includes: persistent micro-albuminuria or proteinuria, haematuria, structural adnormalities, biopsy proven glomerulonephritis.

The first prospective RCT of cholesterol lowering in end stage renal disease (ESRD) was published in NEJM in 2005. This trial (4D trial) compared atorvastatin 20 mg daily vs placebo in 1255 diabetic dialysis patients in Germany. Entry LDL was between 2.1-4.9 mmol/L. Despite some use of statin therapy in the placebo arm, the active treatment arm still achieved an average LDL reduction of 1 mmol/l over the 5 years of the trial. However, the primary composite endpoint (cardiovascular death, nonfatal MI, or stroke) was not different between the groups. Stroke rates were in fact higher in the statin arm, even though cardiac events were reduced by 16%, a reduction which had been predicted by the Cholesterol Treatment Trialists. These strokes were both hemorrhagic and non-hemorrhagic, so not all were due to atherosclerosis or preventable by statin therapy.

The AURORA study (NEJM 2009) randomized 2747 ESRD patients to placebo or 10 mg daily of rosuvastatin. Despite an LDL reduction of 43%, an hs-CRP decrease of 11.5% and HDL increase of 2.9%, again there was no difference in the primary outcome (time to CV death, non-fatal myocardial infarction, or non-fatal stroke) over 5 years.

To definitively address the question of LDL lowering in ESRD patients, Dr. Colin Baigent and the University of Oxford Group designed the SHARP trial. They recognized that prior trials of LDL-lowering in ESRD/CKD were inconclusive and may have been influenced by the inclusion of events in the primary composite outcome that were not due to atherosclerosis.

The inclusion criteria included:
age ≥40, no prior history of MI or coronary revascularization, hemodialysis or peritoneal dialysis, if not on dialysis, elevation in creatinine on 2 occasions over 150 umol/L for men and over 130 umol/L for women

In addition, there had to be uncertainty as to whether LDL lowering therapy was indicated or contra-indicated.

> “SHARP is the largest renal trial ever performed”

SHARP is the largest renal trial ever performed. 9438 patients were randomized. For the first year of the trial, 4193 patients received a combination of simvastatin 20 mg and ezetimibe 10 mg, 4191 received placebo and 1054 received simvastatin alone in order to evaluate safety of the statin/ezetimibe combination. After the first year, with no evident safety concerns, the 886 patients in the simvastatin alone group were re-randomized into the placebo and combination arms. Therefore, 4650 patients were treated with combination therapy and 4620 received placebo, with a median follow-up of 4.9 years.

Overall, 80% of patients had micro or macro-albuminuria and the mean eGFR was 27. A total of 3023 patients were on dialysis at the start of the trial, 83.6% of whom were on hemodialysis. Patients with this severity of CKD were not previously randomized into a CV outcomes RCT.

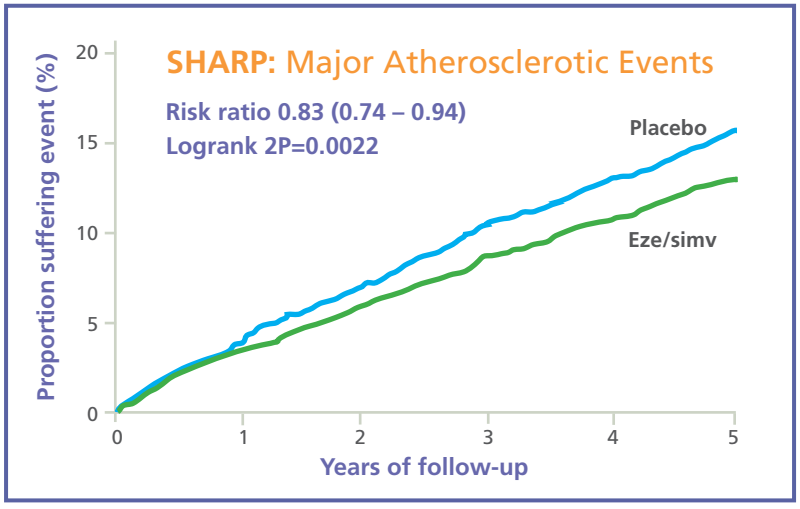
The average baseline LDL was 2.77 mmol/L, 2.57 if on dialysis. Halfway through the trial, 66% of patients were still taking their combination therapy and 64% remained on their placebo.

This drop off in compliance is expected in late stage CKD as the patients grapple with multiple medications and challenging pharmacologic schedules. Also, 6% of the combo arm and 9% of placebo received non-study statin therapy. With 71% compliance at study midpoint, the average LDL reduction was 0.85 mmol/L.

The key outcome was changed part way through the trial, but well before data unblinding. This was to allow the primary endpoint to consist only of events potentially modifiable by lipid lowering therapy, after the lessons learned from 4D and other statin trials.

The primary outcome included major atherosclerotic events (coronary death, MI, non-hemorrhagic stroke, or any revascularization). Subsidiary outcomes consisted of major vascular events (cardiac death, MI, any stroke, or any revascularization) as well as components of major atherosclerotic events. The main renal outcome was progression to ESRD (dialysis or transplant).

When Dr. Baigent presented the 17% reduction in major atherosclerotic events (2P =0.0022), the auditorium of ~8000 nephrologists broke out in spontaneous applause. As nephrologists, we finally had a positive clinical trial that had therapeutic relevance. The reduction in atherosclerotic events was predicted by the Cholesterol Treatment Trialists' Meta-Analysis adding support to the concept that the positive benefits seen in SHARP are directly the result of the LDL lowering.



The Lancet, early on line publication, 9 June 2011 doi:10.1016/S0140-6736(11)60739-3

Even after accounting for hemorrhagic stroke, the trial results remain overwhelmingly positive with the reduction in any major vascular event reduced 15.4% (p=0.0012).

Initially there were 6247 patients not on dialysis, but within one year, almost 2000 progressed to requiring Dialysis. These patients were analyzed with the intention to treat group. Despite this, the reduction in major atherosclerotic events revealed no significant difference between non-dialysis and dialysis patients (p=0.25).

Cause specific mortality was unaffected, not dissimilar to other major trials looking at vascular event reduction (and given the fact the study was not powered to look at this). Nevertheless, disability, the major problem faced by dialysis patients, was impacted positively by therapy.

Although there was a trend toward reduction in the progression to ESRD, it did not reach statistical significance.

Unlike the shorter SEAS trial, there was no increase risk in development of cancer over five years. There was also no difference in muscle or liver biochemistry, or in the incidence of pancreatitis.

> "The largest reduction in events was in those with total cholesterol above **5.5 mmol/L** or an LDL above **3 mmol/L**"

It is interesting to note that the largest reduction in events was in those with total cholesterol above 5.5 mmol/L or an LDL above 3 mmol/L. This same post hoc analysis was published for 4D in CJASN this month, also showing more benefit if baseline LDL was higher.

Ultimately, for Clinicians, the SHARP trial is practice-validating and should encourage us to aggressively treat proteinuric/CKD patients to lower LDL. The evidence is now there for combination statin/ezetimibe. There is also now justification to initiate lipid-lowering therapy in dialysis patients.

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SODIUM

ADEQUATE INTAKE OF SODIUM PER DAY:

1500 mg for people 9-50 years of age
1300 mg for people 51-70 years of age
1200 mg for people 70 years of age or older

A diet low in sodium have been proven to improve risk factors such as high blood pressure and improve outcomes such as heart disease and kidney disease.

The Dietary Approaches to Stop Hypertension (DASH) study produced the DASH eating plan, proven to reduce blood pressure. A DASH diet is low in saturated fat, total fat and cholesterol and emphasizes fruits, vegetables, low fat milk products and whole grains and moderate sodium intake.

What does a **DASH diet** look like?

	DAY 1	DAY 2
breakfast	1 cup plain oatmeal 1 small banana 1 cup skim fat milk ½ cup orange juice	2 slice whole grain bread 1 Tbsp peanut butter 1 med apple 1 cup low fat milk
lunch	2 oz canned tuna in water 1 Tbsp light miracle whip, 2 pieces whole wheat bread ½ cup sliced carrots 1 orange ½ cup apple juice	3 oz grilled boneless skinless chicken breast 1 cup cooked whole wheat pasta with 3 Tbsp sweet and sour sauce 1 cup mixed greens 1 cup diced red pepper and tomato, 1 Tbsp sunflower seeds 1 Tbsp vinaigrette dressing 1 plum ½ cup fruit juice
dinner	3 oz roast beef with ¼ cup fat free, low sodium beef gravy 1 small whole wheat roll 1 cup green beans cooked in 1 tsp oil & spices 1 cup skim milk	3 oz salmon with lemon pepper seasoning 1 cup brown rice 1 cup frozen mixed vegetables 1 cup low fat milk 1 medium chocolate chip cookie
snacks	1 cup sliced vegetables 1 Tbsp low fat ranch salad dressing 1 peach 2 kiwis	1 cup low fat yogurt 1 cup strawberries 1/3 cup almonds
sodium	▶ 1497 mg	▶ 1537 mg

How does 1 meal at common fast food restaurants compare?

McDonald's Bacon'n Egg McMuffin®	Subway 6" Turkey Breast Sandwich on 9 grain wheat bread, no cheese	Tim Horton's Ham & Swiss Sandwich	Wendy's Baconator® Single with Medium Fries
740 mg sodium	**800 mg sodium**	**1450 mg sodium**	**1830 mg sodium**

Follow these tips for a LOW sodium diet:

- Avoid pre-packaged and convenience foods
- Drain and rinse canned food products
- Compare brands, choose products with the least amount of sodium
- Avoid using salt during food preparation
- Don't add extra salt to your food
- Review nutrition information at restaurants and make informed choices

For more useful info: **www.sodium101.ca**
Blood Pressure Canada and The Canadian Stroke Network, "Sodium 101"

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