



Chronic Kidney Disease

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Mr. Hales

- 57 yr old logger
- Known HTN, but infrequent GP visits; 'non-compliant' with prescribed Tx
- BP 180/110
- eGFR 30 mL/min; ACR 80 mg/mmol
- Smoker – 40 pk-yrs
- Lipids: LDL 3.26; HDL 0.90; TG 3.20
- FBG 5.0 (not diabetic)



Which of the following statements are TRUE?

- A. All studies in CKD pts demonstrate a positive correlation between lipid levels and mortality.
- B. CKD pts demonstrate pronounced abnormalities in lipid metabolism, which likely contribute to accelerated atherosclerosis.
- C. Recommendations to lower lipids in CKD pts are based on Grade A evidence.
- D. Statins clearly improve survival in pts with CKD.
- E. Statins carry an unacceptably high risk of rhabdomyolysis in CKD pts.



Dyslipidemia may injure the kidney by which of the following mechanisms?

- A. Lipoproteins enhance the inflammatory/fibrotic activity of mesangial cells.
- B. Oxidized LDL actively initiates synthesis of ROS in glomeruli and the tubulointerstitium.
- C. Oxidized LDL is taken up by macrophages in the walls of blood vessels (foam cell formation).
- D. All of the above.



OUTLINE

- Pathophysiology of the 'Accelerated Atherosclerosis' of CKD
- Hyperlipidemia and CKD Progression
- Review of Clinical Trial Data
- Back to Mr. Hales: Guidelines for Management



Pathophysiology of Accelerated Atherosclerosis in CKD Patients

- 'Typical' lipid profile in CKD pt:
 - **High TG; Low HDL.... +/- High LDL**
- CKD → oxidative stress → oxidized LDL, which has lower affinity for LDL receptors → decreased removal by liver → greater foam cell formation
- HDL → less of it, and less effective in binding macrophages to extract lipid; fails to reverse LDL oxidation, may even become a pro-oxidant
- HDL is less effective in reducing adhesion of monocytes to endothelial cell surfaces



Does Hyperlipidemia Injure the Kidney?

- Virchow (1858) – ‘fatty metamorphosis of renal parenchyma’
- Animal models:
 - Dyslipidemia induces a proliferative/pro-inflammatory response in glomeruli (PDGF, MCSF, ICAM1)
 - Also observed:
 - Infiltration of monocytes/macrophages
 - Increase in extracellular matrix(ECM)
 - Loss of glomerular permselectivity
 - Degeneration of podocytes



Does Hyperlipidemia Injure the Kidney?

- Mechanisms of injury:
 - Uptake of lipoproteins into mesangial cells → increase synthesis of cytokines/chemokines and ECM proteins
 - Lipids actively initiate synthesis of reactive oxygen species in glomeruli and tubulointerstitium
 - Transcriptional response of tubular epithelium to oxidized lipoproteins → increase in expression of genes encoding fibrogenic and inflammatory cytokines



Review of Clinical Trial Data

Two Meta-Analyses:

1. **Holdass H** *et al.*(2007) The effect of fluvastatin on cardiac outcomes in patients with moderate to severe renal insufficiency: pooled analysis of double-blind, randomized trials. *Int J Cardiol* **117**:64-74
2. **Strippoli G** *et al.*(2008) Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomized controlled trials. *BMJ* **336**:645-651



Fluvastatin for reduction of cardiovascular risk in patients with moderate to severe renal insufficiency

- 30 trials included (11,815 pts); 24 placebo-controlled
 - 1,569 pts had moderate to severe CKD (CrCl < 50 mL/min)
 - 9,914 pts had normal renal fn or mild CKD
 - 80 mg fluvastatin reduced LDL-cholesterol by approx. 30-35% in all pts
 - 5 studies (n=5,402) included in analysis of clinical end points
 - Compared with placebo, fluvastatin significantly reduced combined incidence of cardiac death and nonfatal MI in pts with mod-severe CKD (-41%; p=0.007) and in pts with normal renal fn or mild CKD (-30%; p=0.009)



Fluvastatin for reduction of cardiovascular risk in patients with moderate to severe renal insufficiency

- Reduction in risk of major cardiac events with fluvastatin vs placebo was **not** significant in the mod-severe CKD group (-17%; $p=0.18$); **no significant effect on all-cause mortality or coronary interventions in either renal fn group**
- No significant excess of liver enzyme abnormalities or myopathy in treatment groups, regardless of degree of renal impairment
- **Critical Question:** Does clinical efficacy in pts with $\text{CrCl} < 50$ ml/min differ from that in pts with milder renal impairment?
 - **This meta-analysis did not include many pts with advanced CKD**



Effects of statins in patients with chronic kidney disease

- 50 trials that compared statin Tx with placebo in pts with CKD (n=30,144)
 - Statins safely reduced lipids in all groups (included pre-dialysis, dialysis, and transplant pts)
 - Risk of CV events (MI, stroke, sudden death, or composite) was significantly reduced
 - **No** significant effect on all-cause mortality
 - 'Uncertain' renoprotective effect
- **Major limitation:**
 - Large degree of heterogeneity among pts (a hemodialysis pt is very different from a pt with mild proteinuria, normal GFR)



Can statin therapy improve renal function?

- Multiple post hoc analyses demonstrate that statins slow decline in GFR and reduce proteinuria
 - Heart Protection Study, TNT Study
- **Sandhu *et al.* (2006) JASN (Meta-analysis)**
 - 22 trials (38,867 pts)
 - 76% reduction in rate of GFR decrease (absolute difference of 1.2 mL/min/yr)
 - **BUT**, effect only significant in pts with CVD, not in pts with diabetic/hypertensive kidney disease, or glomerulonephritis



Can statin therapy improve renal function?

- Prospective Pravastatin Pooling Project
 - 3400 pts with moderate CKD (GFR 30-59 mL/min)
 - Overall rate of decline of GFR was 0.7 mL/min/yr
 - Pravastatin reduced rate of decline by 34% (absolute difference of 0.2 mL/min/yr)
 - No significant effect of pravastatin in pts with better renal fn



Summary of Clinical Data: Conclusions

- Patients at all stages of CKD have a significantly elevated risk of all-cause and CV mortality
- CKD may impart a CV risk equivalent to diabetes
- A decrease in CV events and CV mortality has been found in studies of predialysis pts treated with statins
 - data more robust for pts with mild CKD
- Statins may slow the rate of decline in renal fn and reduce proteinuria
- Good side effect profiles with statins reported in pts with CKD



K/DOQI GUIDELINES: Grade 2B*

Recommendation

“We suggest that pts with CKD be treated with the lowest dose of statin that reduces the LDL-C to < 2.6 mmol/L”

- * Grade 2 recommendation is weak; it means “this is our suggestion, but you may want to think about it”
 - Benefits and risks may be finely balanced, or uncertain

Grade B evidence means that best estimates of benefits and risks come from randomized, controlled trials with important limitations (inconsistent results, methodologic flaws, extrapolation from a different population)



Back to Mr. Hales: How to manage?

- Summary of his CV risk profile:
 - Smoker
 - CKD
 - GFR 30 mL/min
 - Albuminuria
 - Hypertension
 - Dyslipidemia

His risk of a CV event is very high!!!



Back to Mr. Hales: How to manage?

- First challenge is to 'engage' him (convince him that intervention can improve his outcome)
- Lifestyle modification:
 - Smoking cessation
 - Dietary Na restriction, reduced fat intake
 - Exercise, weight loss
- Optimal BP control will have greatest impact on slowing progression to ESRD; angiotensin blockade indicated



Back to Mr. Hales: How to manage?

- Lipid-lowering therapy:
 - Suggest lowest dose statin to achieve LDL-C < 2.6
 - Monitor CK, liver chemistry, eGFR every 3 months
 - If he has a CV event → aim for LDL-C < 2.0

Note: Even if he survives long enough to receive a renal transplant → he's likely to die of a CV event, with a functioning graft!