

## Cardiovascular Risk Factors

ROB WALKER (*Dunedin, New Zealand*)

### Lipid-lowering therapy in patients with chronic kidney disease

**Date written:** January 2005  
**Final submission:** August 2005  
**Author:** Rob Walker

#### GUIDELINES

**No recommendations possible based on Level I or II evidence.**

#### SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- **There are no randomised clinical trials with clinical endpoints to state that patients with chronic kidney disease (CKD) and/or on renal replacement therapy without evidence of coronary artery disease should be placed on lipid-lowering therapy.**
- **Patients with mild CKD (Stage 1 & 2) with established coronary artery disease may benefit from treatment with a cholesterol-lowering agent, preferably to statin. (level III evidence)**

#### Background

Cardiovascular events are the leading cause of mortality in patients with CKD (ANZDATA 2004). However, the role of cholesterol in the pathogenesis of vascular disease in CKD remains uncertain. A number of observational studies along with reports from Registries confirm the high incidence of cardiovascular disease in patients with CKD. ANZDATA 2004 demonstrated that cardiac events were the cause of death in 42% of dialysis patients and 30% of transplant recipients. Similar data has been reported from the USRDS (Foley et al 1998).

Previous randomised clinical trials of lipid lowering therapy have excluded patients with CKD (K/DOQI Stage 3–5, GFR < 60 mL/min). The guidelines reflect this uncertainty as to the benefits of lipid-lowering therapy as a primary prevention strategy for coronary heart disease in patients with established CKD. In CKD (Stage 1 & 2) patients with documented coronary artery disease, posthoc analysis of trials of lipid-lowering therapy as secondary prevention of coronary artery disease would indicate that statin therapy may be warranted (level III evidence, see below). There

are no randomised controlled trials (RCTs) of lipid-lowering therapy for secondary prevention of coronary artery disease, in patients with CKD (Stage 3–5).

A systematic review on the risk and benefit of different cholesterol-lowering interventions (Bucher et al 1999) included 59 trials involving 85 431 participants in the intervention arm and 87 729 participants in the control arm (Renal disease was not defined). Trials were pooled according to pharmacological intervention. Only statins demonstrated a large and statistically significant reduction in mortality from coronary heart disease (RR: 0.66 95% CI: 0.54–0.79) and from all causes (RR: 0.75; 95% CI: 0.65–0.86). Meta-regression analysis demonstrated that variability in results across trials could be largely explained on the basis of differences in the magnitude of cholesterol reduction.

A meta-analysis of the effects of statins on risk of coronary disease with clinical outcomes, pooled 5 studies with 30 817 patients with a mean duration of treatment of 5.4 yrs. (LaRossa et al 1999). Statin therapy produced a 28% reduction in LDL-C, 20% in cholesterol, 13% reduction in triglycerides. Overall, statins reduced the risk of cardiovascular event by 31% (95% CI: 26%–36%) and 21% all-cause mortality.

## **Search strategy**

**Databases searched:** An extensive search of the literature using the Cochrane library, Medline and Embase using standard search criteria was undertaken by the Cochrane Renal Group. Key MeSH terms: - Kidney failure chronic, renal dialysis, antilipemic agents, lipids, hyperlipidemia, lipoproteins, kidney diseases, peritoneal dialysis, kidney transplantation, were combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – February week 3, 2004). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** March 2004.

## **What is the evidence?**

There have been only two randomised placebo controlled studies investigating lipid-lowering therapy in patients with CKD with cardiovascular outcomes as the end points. These studies utilised two highly selected groups of patients with CKD. The ALERT study recruited patients with a renal transplant. The 4D study recruited patients with diabetes on haemodialysis.

1. The Assessment of Lescol in Renal Transplantation (ALERT) study (Holdass et al 2003) compared fluvastatin 80 mg daily with placebo in 2 102 transplant recipients with a functioning graft over a mean of 5.1 years. The primary end point was the occurrence of a major adverse cardiac event, defined as cardiac death, non-fatal MI or coronary intervention procedure. Secondary endpoints were individual cardiac events, combined cardiac death, or non-fatal MI, cerebrovascular events, non-cardiovascular death, all-cause mortality, and graft loss or doubling of serum creatinine. Analysis was by intention to treat. Fifteen percent of participants had had a previous cardiovascular event. Fluvastatin lowered LDL cholesterol by 32%. Risk reduction with fluvastatin for the primary endpoint was not significant (RR: 0.83, 95%

---

CI: 0.64–1.06 P = 0.139). There were fewer cardiac deaths or non-fatal MI (RR: 0.65, 95% CI: 0.48–0.88] P = 0.05) with fluvastatin. Other secondary end points did not differ significantly between the groups.

2. The 4D (Die Deutsche Diabetes Dialyse) study (Atorvastatin was conducted in patients with type 2 diabetes mellitus undergoing haemodialysis. (Wanner et al 2005). This study assessed the effects of atorvastatin 20 mg daily compared with placebo among 1255 haemodialysis patients with type 2 diabetes mellitus. Entry criteria: Less than 2 years on dialysis, LDL cholesterol > 2.1 mmol/L and < 4.9 mmol/L; triglycerides < 11.8 mmol/L; no cardiovascular events in the previous 3 months prior to enrolment. The primary endpoints were the composite outcome of cardiovascular death, fatal and non-fatal MI and stroke. The study outcome was event driven to achieve 469 primary event endpoints. There was a mean follow up of 4.8 years . At entry, 30% of patients already had had MI or evidence of ischaemic heart disease; 35% had a diagnosis of congestive heart failure and 44% had evidence of peripheral vascular disease. Atorvastatin lowered cholesterol by 30% and LDL cholesterol by 41% at 4 weeks. At completion of the study, atorvastatin reduced the risk of a primary endpoint by 8% (RR: 0.92; 95% CI: 0.77–1.10) which was not significant. There was no difference in all-cause mortality. For all cardiovascular events there was an 18% reduction which just reached significance (RR: 0.82; 95% CI: 0.68–0.99).

There are no reported randomised clinical trials of lipid-lowering therapy as primary prevention of coronary artery disease in patients with CKD or on renal replacement therapy with appropriate clinical end points of cardiovascular morbidity or mortality.

Post hoc secondary analysis of the Cholesterol and Recurrent Events (CARE) study, a secondary prevention trial of patients with coronary artery disease, identified 1711 patients with renal insufficiency defined as a calculated GFR (Cockcroft – Gault equation) of less than or equal to 75 mL/min ( mean  $61.3 \pm 10.1$  mL/min, serum creatinine  $111 \pm 21$   $\mu$ mol/L). Exclusion criteria for this study included patients with 2+ proteinuria or greater on routine dipstick testing or serum creatinine values more than 1.5 times the upper limit of normal (as defined by the central study laboratory). The posthoc analysis demonstrated a lower incidence of the primary endpoint of death from coronary disease or symptomatic non-fatal MI (adjusted hazard ratio 0.72, 95% CI: 0.55–0.95 P = 0.02). Tests for interaction suggested the observed benefit was independent of the presence and severity of renal insufficiency. The incidence of side effects was similar in the pravastatin and placebo groups (Tonelli et al 2003).

Pooling data from 3 large pravastatin (CARE, WOSCOPS & LIPID) trials allowed a posthoc analysis of lipid-lowering therapy on cardiovascular events in patients with moderate CKD. Of 19 700 participants in the 3 trials, 4 491 had moderate CKD (calculated creatinine clearance 30–59mL/min) –44.6% of whom had a serum creatinine level within the normal laboratory range. Pravastatin significantly reduced the incidence of the primary outcome (time to myocardial infarction, coronary death, or percutaneous/surgical coronary revascularisation) (HR: 0.77, 95% CI: 0.68–0.86). (Tonelli et al 2004)

Post hoc secondary analysis from the Veterans' Affairs High Density Lipoprotein Intervention Trial (VA-HIT), a secondary prevention randomised trial of gemfibrozil versus placebo, analysed 1 046 men (of the 2 531 participants) with renal impairment

defined as creatinine clearance  $\leq 75$  mL/min, determined by the Cockcroft-Gault formula). The mean creatinine clearance in both groups was  $61.5 \pm 9.6$  mL/min. Patients with a plasma creatinine greater than 2.0 mg/dl (0.21 mmol/l) were excluded from the trial. The primary outcome (coronary death of non-fatal myocardial infarction) was lower in the gemfibrozil group (HR: 0.73, 95% CI: 0.56–0.96,  $P = 0.02$ ). Gemfibrozil reduced the risk of the combined outcome of coronary death, non-fatal MI or stroke (HR: 0.74, 95% CI: 0.58–0.95,  $P = 0.02$ ) but not the need for coronary revascularisation (HR 0.85, 95% CI: 0.66–1.10) or total mortality (HR: 1.03, 95% CI: 0.78–1.35). Gemfibrozil appears effective for secondary prevention of cardiovascular events in males with mild to moderate CKD (Tonelli et al 2004).

In the Heart Protection Study, 1 329 patients out of 20 536 patients enrolled in the study, had an elevated creatinine (110  $\mu$ mol/L or above for women and 130  $\mu$ mol/L or above for men, but less than 200  $\mu$ mol/L for both). In this group the rate of major cardiovascular events (major CHD events, strokes of any type, coronary and non-coronary revascularisations) was reduced from 39.2%–28.2% over 5 years with simvastatin treatment, compared with a reduction from 24.2%–19.2% in the 19 207 people with normal creatinine levels (Heart protection study collaborative group 2002).

Data is not available from RCTs that equates lowering of cholesterol with improved cardiovascular outcomes in patients with CKD. An earlier systematic review of hyperlipidaemia in patients with CKD conducted by Kasiske (1998) demonstrated that elevated cholesterol or LDL-cholesterol is associated with cardiovascular disease in CKD but was not able to make any conclusion regarding impact of therapy on cardiovascular outcomes. In the same review, statins were shown to be the most effective drug to reduce LDL-cholesterol. Fibrates were also effective but dosage reduction is needed in the presence of renal impairment.

There are a number of uncontrolled studies which have investigated lipid-lowering therapy in patients with CKD. These papers have used cholesterol lowering as the end-point rather than cardiovascular outcomes. They demonstrate the effectiveness of statins in lowering LDL cholesterol and total cholesterol with no substantial increase in side-effects related to statin therapy in patients with CKD. These papers have not been cited here.

## **Summary of the evidence**

To date, there is no evidence that primary prevention with cholesterol-lowering therapy reduces the risk of cardiovascular events in patients with established CKD. Therefore no guideline on the role of lipid-lowering therapy for primary prevention of coronary artery disease can be made until current studies are concluded.

The beneficial effects of lipid-lowering therapy in secondary prevention of cardiovascular events in non-CKD patients, is well established (Heart protection study collaborative group 2002). Current recommendations would suggest that patients with mild CKD and established ischaemic heart disease may benefit from lipid-lowering therapy. However, in a very high risk group of diabetics with end stage kidney disease (ESKD), many of whom had significant cardiovascular disease, lipid-lowering therapy failed to improve clinical outcome (Wanner et al 2005). Clearly,

more studies are required to examine the role of lipid-lowering therapy for primary and secondary prevention of cardiovascular disease in patients with CKD or on renal replacement therapy.

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**British Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** No recommendation.

**INTERNATIONAL GUIDELINES:** No recommendation.

A task force convened by the National Kidney Foundation (USA) concluded that patients with chronic renal failure and/or on renal replacement therapy should be considered in the highest risk group for cardiovascular disease (Lively et al 1998).

In the non-renal failure population, there are very clear guidelines published by a number of Task Force groups including the National Cholesterol Education Program (NCEP), The Second Joint Task Force of European and Other Societies on Coronary Prevention and The National Heart Foundation of Australia for lipid-lowering therapy in at-risk groups.

### **Recommendations:**

- Non-pharmacological therapy including smoking cessation, physical exercise and dietary modification to reduce hyperlipidaemia should be introduced. Assess absolute cardiovascular risk and be most aggressive in lowering lipids in those at highest coronary risk.
- National Heart Foundation of Australia guidelines for those identified as 'highest risk' group, recommend: Drug therapy should be initiated if total cholesterol is greater than 5 mmol/L; LDL cholesterol > 3.0 mmol/L or triglycerides > 2.0 mmol/L. Target levels should be cholesterol < 4.5 mmol/L; LDL cholesterol < 2.5 mmol/L and triglycerides < 2.0 mmol/L.

### **Implementation and audit**

Await evidence from clinical trials, and then assess application of guideline on cardiovascular mortality via ANZDATA.

### **Suggestions for future research**

1. Randomised placebo controlled clinical trials of lipid lowering therapy in CKD are currently underway addressing these concerns. (SHARP and AURORA) In the absence of evidence of ischaemic heart disease, patients with CKD should be enrolled in such studies. The trials are due to be reported in 2008–2009.

## **References**

ANZDATA Registry Report 2004. Australia and New Zealand Dialysis and Transplant Registry, Adelaide South Australia.

Bucher HC, Griffith LE, Guyatt GH. Systematic review on the risk and benefit of different cholesterol-lowering interventions. *Arterioscler Thromb Vasc Biol* 1999; 19: 187–95.

Foley RN, Parfrey PS, Sanak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J kidney Dis* 1998; 32(suppl 3): 112–119.

Nutrition and Metabolism Advisory Committee. Guide for the use of lipid-lowering drugs in adults. Position statement prepared by the nutrition and Metabolism Advisory Committee for the National Heart Foundation of Australia. Melbourne: National Heart Foundation, 1998.

Heart Protection Study Collaborative Group. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20536 high risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002; 360: 7–22.

Holdass H, Fellstrom B, Jardine AG et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre randomised placebo controlled trial. *Lancet* 2003; 361: 2024–31.

Kasiske BL. Hyperlipidemia in patients with chronic renal disease. *Am J Kidney Dis* 1998; 32 (suppl 3): S142–S146

La Rosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: A meta-analysis of randomised controlled trials. *JAMA* 1999; 282: 2340–6.

Levey AS, Beto JA, Coronado BE et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: What do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kidney Dis* 1998; 32: 853–906.

National Cholesterol Education Program Adult Treatment Panel II. Summary of the second report of the national cholesterol education program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *JAMA* 1993; 269: 3015–23.

Second Joint Task Force of European and other Societies on Coronary Prevention. Prevention of coronary heart disease in clinical practice. *Euro. Heart J*. 1998; 19: 1434–503

Tonelli M, Moye L, Sacks FM et al. Pravastatin for secondary prevention of cardiovascular events in persons with mild chronic renal insufficiency. *Ann Intern Med* 2003; 138: 98–104.

Tonelli M, Isles C, Curhan GC et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation* 2004; 110: 1557–63.

Tonelli M, Collins D, Robins S et al. The Veterans' Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) investigators. *Kidney Int* 2004; 66: 1123–30.

Wanner C, Krane V, Marz et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Eng J Med*. 2005; 353: 238–48.