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ARTICLE

Lipid lowering in renal disease

SUMMARY

Statins reduce the risk of cardiovascular disease in patients with chronic kidney disease who do not require dialysis. However, this benefit diminishes with progression of kidney disease and in transplant recipients.

Current evidence suggests that statins may not reduce cardiovascular risk in patients with advanced chronic kidney disease requiring dialysis.

Evidence for fibrates is more limited but they appear to reduce lipids and cardiovascular events in patients with mild to moderate chronic kidney disease.

There is little evidence for the benefit of starting statins in patients on haemodialysis.

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Introduction

Chronic kidney disease is characterised by either reduced glomerular filtration rate (GFR) or significant proteinuria. This is associated with increased cardiovascular mortality, which becomes more than 10-fold greater in those on dialysis compared with the general population.[1-3] Renal transplantation lowers this risk, but cardiovascular disease remains the leading cause of death for transplant patients.[4-6]

A characteristic pattern of lipid abnormalities affects those with chronic kidney disease[7,8] and is implicated in the high rates of cardiovascular morbidity and mortality in this population.[9,10] Traditional cardiovascular risk factors such as diabetes and hypertension also contribute. These are prevalent in the chronic kidney disease population along with the proposed cardiovascular risk associated with oxidative stress, inflammation, insulin resistance, anaemia and disturbances of mineral metabolism.

Although statins reduce cardiovascular disease in those at increased risk,[11,12] their effect is less clear in people with chronic kidney disease as most lipid-lowering trials exclude these patients or focus on those receiving haemodialysis.

Dyslipidaemia

Dyslipidaemia contributes to atherosclerosis and is a modifiable risk factor for cardiovascular disease in the general population. Decreasing low-density lipoprotein (LDL) cholesterol by 1 mmol/L reduces major coronary events by approximately 23% in people with intact renal function.[11-19] This is not found in chronic kidney disease. These patients have a different lipid profile – triglycerides are increased, and LDL may also be lower and decreases even further with dialysis.[7] High-density lipoprotein (HDL) may also be lower[5,7,20,21] and is often defective in the removal of cholesterol from macrophages[22] and in nitric oxide production.[23] These changes are likely to exacerbate uraemic endothelial dysfunction.

In patients on haemodialysis, there is a U-shaped relationship between serum cholesterol and mortality with very low and very high concentrations being risk factors for mortality.[24,25] This is related to the effects of survival bias, malnutrition and inflammation.[26] Some studies report higher mortality in dialysis patients with lower serum cholesterols compared to dialysis patients with normal or high serum cholesterol,[27,28] and others show similar results to what is seen in the general population.[29]

In non-dialysis chronic kidney disease there is an unclear relationship between cholesterol and mortality.

Patients with nephrotic-range proteinuria and hypoalbuminaemia have elevated total serum cholesterol,[7] which according to rat models relates to an upregulation of HMG-CoA reductase.[30] Non-diabetic, non-nephrotic patients with chronic kidney disease also show accelerated atherosclerosis, but in the absence of hypercholesterolaemia.[10]

Lipid-lowering treatment in chronic kidney disease

Few studies have looked specifically at lipid-lowering therapy in patients with chronic kidney disease. Most evidence is derived from subgroup or post hoc analyses.

Patients not on dialysis

A meta-analysis of statin efficacy in non-dialysis chronic kidney disease stages 1–5 reported an overall decreased risk for cardiovascular mortality and non-lethal cardiovascular events.[31] Statins resulted in a

RR* of 0.72 (95% CI† 0.66–0.79) for major cardiovascular events, 0.55 (95% CI 0.42–0.72) for myocardial infarction, 0.79 (95% CI 0.69–0.91) for all-cause mortality and an uncertain effect on stroke (RR 0.62, 95% CI 0.35–1.12). Adverse events with statins included elevated creatinine kinase and liver function abnormalities. There was no evidence of an effect on renal function.[31]

The benefit of statins appears to diminish with progression of chronic kidney disease. This probably contributes to the inconsistent relationship in studies between cholesterol-lowering therapy and cardiovascular outcome in chronic kidney disease.[32-40] In a more recent meta-analysis, statin therapy reduced the risk of first major vascular event by 21% (RR 0.79, 95% CI 0.77–0.81) per mmol/L reduction in LDL cholesterol. Smaller relative effects on major vascular events, major coronary events and vascular mortality were observed as GFR declined.[41]

The SHARP trial,[32] which enrolled patients with pre-dialysis chronic kidney disease and those on dialysis, evaluated daily simvastatin 20 mg plus ezetimibe 10 mg or placebo. In the pre-dialysis cohort of 6247 patients (mean GFR of 26.6 mL/min/1.73 m^2), LDL cholesterol fell by 0.85 mmol/L over five years. These patients had a 17% RR reduction in major atherosclerotic events (RR 0.83, 95% CI 0.74–0.94) compared with placebo and the number needed to treat was 48. This compares favourably with numbers needed to treat in primary prevention studies of statins in the general population.[42,43] There was a significant reduction in non-haemorrhagic stroke (RR 0.75, 95% CI 0.60–0.94) and in arterial revascularisation procedures (RR 0.79, 95% CI 0.68–0.93), but no effect on progression of chronic kidney disease.[44]

The rate of adverse events in the SHARP trial was low – myopathy was reported in 0.02% of patients and there was no evidence of increased hepatitis, gallstones, pancreatitis or malignancy in the lipid-lowering group. While this is the largest trial of lipid-lowering drugs in patients with chronic kidney disease to date, it failed to evaluate the role of a statin or ezetimibe alone. Other trials of lipid-lowering therapy in non-dialysis chronic kidney disease show considerable heterogeneity both in study design and impact on cardiovascular end points. For trial details see the Table.[32-39]

Evidence for fibrates in chronic kidney disease is limited. However, a meta-analysis evaluating the evidence for cardiovascular benefit with use of benzafibrate (2 studies), gemfibrozil (2 studies) and fenofibrate (4 studies) reported that fibrates reduced serum lipids, albuminuria and major cardiovascular events (RR 0.70, 95% CI 0.54–0.89) in a subgroup of patients with a GFR 30–59.9 mL/min/1.73 m^2 but had no effect on all-cause mortality.[45] Fibrates were associated with serum creatinine elevations (33 micromol/L, p<0.001) but not an increase in risk of progression to end-stage kidney disease, although the confidence intervals for this outcome were very wide (RR 0.85, 95% CI 0.49–1.49). There was no clear effect of fibrates in patients on dialysis with respect to cardiovascular outcomes or mortality.

Guidelines

Overall evidence suggests that statin therapy in non-dialysis chronic kidney disease reduces the risk of major cardiovascular events similar to the reduction seen in the general population. The greatest benefit for statins and fibrates in chronic kidney disease appears to be in patients with mild to moderate renal impairment (GFR 30–60 mL/min).[31,40,45] However, the Pharmaceutical Benefits Scheme (PBS) does not subsidise statin therapy for chronic kidney disease in the absence of other indications.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[46] recommend statin therapy for all chronic kidney disease patients aged 50 years or older and for younger patients who have additional risk factors for coronary heart disease.

While there is no evidence of more adverse events with higher doses of statins compared to the general population, the KDIGO guidelines recommend reducing the dose in individuals with a GFR of less than 60 mL/min/1.73 m^2. This is based on reduced renal excretion, increased polypharmacy and comorbidity as well as the doses of statin used in chronic kidney disease trials.[46] The guidelines advise against a statin/fibrate combination in patients with chronic kidney disease.

Kidney Health Australia's Caring for Australasians with Renal Impairment (CARI) guidelines are more expansive in their recommendations. They advocate treating all patients with mild–moderate chronic kidney disease with a statin or statin/ezetimibe combination regardless of cardiovascular risk.[47] There are no recommended targets for LDL cholesterol and lipid concentrations based on a diagnosis of chronic kidney disease.[46,47]

Patients on dialysis

In addition to the SHARP trial,[32] there have been two major placebo-controlled randomised trials of statin therapy in haemodialysis patients – 4D[39,48] and AURORA.[38] The 4D study evaluated the effect of 20 mg atorvastatin on cardiovascular disease and death. It included only patients with diabetes and a high cardiovascular disease burden. Despite a profound

* relative risk

† confidence interval

Table **Major lipid-lowering trials in chronic kidney disease and dialysis populations**

Trial	Number of patients	Population	Duration	Statin dose (fixed vs titrated)	Treatment–naïve* or treatment-experienced	Relative hazards for cardiovascular events	Absolute risk reduction in cardiovascular events	Changes in LDL
PREVEND IT 2004[33]	864	CKD (stage 1)	Mean 4 years	Pravastatin 40 mg	Naïve	HR 0.87 (95% CI 0.49–1.57), p=0.647	0.8%	LDL reduction 1.0 mmol/L at 4 years
AFCAPS/ TexCAPS[34]	304	CKD (stages 3 and 4)	Mean 5.3 years	Lovastatin 20 mg dose titrated as per LDL levels at 3 months	Naïve	Adjusted HR 0.31 (95% CI 0.13–0.72), p≤0.01 Unadjusted HR 0.41 (95% CI 0.18–0.91)	7.7%	LDL reduction 1.1 mmol/L at study end
JUPITER 2010[35]	3267	CKD (stages 3 and 4)	Median 1.9 years	Rosuvastatin 20 mg	Naïve	HR 0.55 (95% CI 0.38–0.82), p=0.002	1.9%	LDL reduction 1.4 mmol/L at 4 years
ALLIANCE 2009[36]	579	CKD (stage 3)	Median 4.5 years	Atorvastatin 10 mg titrated to LDL every 4 weeks vs 'usual care', continuation of existing lipid-lowering drugs	Continuation without washout or run-in	HR 0.72 (95% CI 0.54–0.97), p=0.02	8.6%	LDL reduction 1.3 mmol/L at study end
LIPS substudy 2004[37]	310	CKD	Mean 3.8 years	Fluvastatin 40 mg twice a day	Naïve	HR 0.52 (CI not specified), p=0.004	14%	LDL reduction 0.8 mmol/L at 6 weeks
AURORA 2009[38]	2776	Dialysis	Median 3.8 years Mean 3.2 years	Rosuvastatin 10 mg	Naïve	HR 0.96 (95% CI 0.84–1.11), p=0.59	0.3%	LDL reduction 1.1 mmol/L at 3 months
4D 2005[39]	1255	Dialysis	Mean and median of 4 years	Atorvastatin 20 mg	Discontinued† with 4-week run-in	HR 0.92 (95% CI 0.77–1.10), p=0.37	1.4%	LDL reduction 1.3 mmol/L at 4 weeks‡
SHARP 2011[32]	9270	Mixed	Median 4.9 years	Simvastatin 20 mg plus ezetimibe 10 mg	Discontinued† with 6-week run-in	HR 0.83 (95% CI 0.74–0.94), p=0.0021	2.1%	LDL reduction 0.85 mmol/L at study end

CI confidence interval
CKD chronic kidney disease
HR hazard ratio
LDL low-density lipoprotein
* The statin is newly introduced to a patient who has never previously taken a statin.
† Any patient previously taking a statin at randomisation had their statin discontinued over a run-in period.
‡ Note that LDL levels also fell in the placebo group but more slowly.

reduction of LDL cholesterol early in the trial, there was no significant impact on major cardiovascular events or all-cause mortality. A higher rate of haemorrhagic stroke was observed in the atorvastatin group. Post hoc analysis revealed that atorvastatin was beneficial with respect to cardiac events and all-cause mortality in patients with a high baseline LDL.[48]

AURORA investigated the effect of rosuvastatin in haemodialysis patients and likewise found no significant impact on major cardiovascular events.[38] The study also reported an increased incidence of fatal haemorrhagic stroke with rosuvastatin in patients with diabetes, reinforcing the adverse outcomes noted in the 4D study. While the SHARP trial reported a reduction in major atherosclerotic events in the study population overall, a subgroup analysis of those on dialysis revealed no benefit (RR 0.9, 95% CI 0.75–1.08).[32]

A recent meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration indicated there was no benefit in terms of major vascular events, major coronary events or vascular mortality to support statin use in dialysis patients.[41]

Guidelines

Taken together, the available evidence for statin therapy in patients on dialysis suggests minimal to no benefit and possible risk of harm. The KDIGO guidelines conclude that statins cannot be recommended for prevention of cardiovascular events in these patients. They advise against commencing statins with the caveat that patients with recent coronary events and young patients awaiting renal transplantation may derive benefit despite a lack of current data to support this claim.[46] There is no conclusive evidence to guide care for patients already on a statin or statin/ezetimibe who commence dialysis.[5]

After renal transplantation

Recipients of renal transplants suffer the burden of chronic kidney disease due to the legacy effect of chronic uraemia before transplantation, as well as the risk associated with graft dysfunction in the post-transplantation period. Immunosuppression increases their susceptibility to infection and chronic inflammation, and promotes dyslipidaemia, hypertension, obesity and hyperglycaemia. All of these changes are likely to increase their cardiovascular risk.[49-51]

The ALERT[52] study is the largest randomised placebo-controlled trial of statins in a renal transplant population. After 5.1 years of follow-up, the trial failed to show an overall decrease in major cardiovascular events with fluvastatin despite significant reductions in cholesterol. Fewer cardiac deaths and non-fatal myocardial infarctions were seen in the treatment group (RR 0.65, 95% CI 0.48–0.88) compared to placebo but the frequency of coronary revascularisation procedures was not significantly different. A two-year open-label extension of ALERT indicated a significant difference in time to major cardiovascular event (RR 0.79, 95% CI 0.63–0.99) and a 29% reduction in cardiac death or non-fatal myocardial infarction (hazard ratio 0.71, 95% CI 0.55–0.93).[53]

A recent systematic review included several smaller trials of statins after kidney transplantation. It reported no significant cardiovascular or mortality benefits but suggested that statin therapy may increase risk of stroke.[54]

Guidelines

The KDIGO and CARI guidelines recommend statins in kidney transplant recipients but, given the potential for drug interactions, suggest low doses and cautious up-titration particularly when co-administering with ciclosporin.[46,47] When switching from tacrolimus to ciclosporin, statin doses should be reduced.[46]

Conclusion

Statin therapy appears to offer some benefit in patients with renal disease who are not on dialysis and to a more limited extent after transplant. There is no evidence to support commencing statins in those receiving dialysis. Evidence supports the safety of statins in chronic kidney disease but caution is advised with high doses and when there is a potential for drug–drug interactions.

Conflict of interest: none declared

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