

USE OF STATINS IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Cardiovascular disease is the leading cause of mortality in patients with chronic kidney disease (CKD) and dyslipidaemia is an important contributor. The use of statins in this subgroup of patients appears to be beneficial in lowering the cardiovascular (CV) risk from the body of evidence available, although there are some important considerations that need to be taken into account. These include the dose and choice of statin, depending on the stage of the CKD and risk profile of the patient. This review looks at some of the important studies that support the clinical use of statins in patients with CKD and summarises some of the key points that the practising clinician should consider.

Keywords:

Statins ; Chronic Kidney Disease ; Dyslipidaemia ; Cardiovascular Disease

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INTRODUCTION

Patients with chronic kidney disease (CKD) suffer from an increased prevalence of cardiovascular (CV) risk factors, including dyslipidaemia, diabetes and hypertension. Hence, it is not surprising that CV disease is a leading cause of death in patients with CKD and CKD is considered a major independent CV risk factor.^{1,2} CKD is defined as renal impairment > 3 months duration that results in an estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m². CKD is classified into five stages based on the eGFR, Table 1.

The relation between CKD and dyslipidaemia is complicated and not currently fully understood. CKD is associated with dyslipidaemia, in particular elevated triglycerides and reduced HDL-cholesterol levels; levels of LDL-cholesterol are generally not elevated. As CKD progresses the degree of dyslipidaemia often worsens. However the pattern of cardiovascular pathology seen in patients with CKD may be different compared with patients without CKD, with some cohort studies of patients on dialysis showing worse outcomes in those with low LDL-cholesterol levels. CKD leads to a down-regulation of lipoprotein lipase and the LDL-receptor. Increased triglycerides in CKD are due to delayed catabolism of triglyceride-rich lipoproteins, rather than changes in rate of production. It is still unclear however whether dyslipidaemia itself causes kidney disease progression or whether kidney impairment and proteinuria are responsible for both renal disease progression and dyslipidaemia. Limited evidence from experimental models suggests that dyslipidaemia probably increases the likelihood of CKD in the early stages — the

Table 1. Stages of CKD

| CKD stage | GFR (ml/min/1.73 m ²) |
|-------------------|-----------------------------------|
| CKD 1 | ≥90 (with renal damage or injury) |
| CKD 2 (mild) | 60-89 |
| CKD 3 (moderate) | 30-59 |
| CKD 4 (severe) | 15-29 |
| CKD 5 (end-stage) | <15, dialysis, or transplant |

mechanisms may include accelerated intra-renal atherogenesis, cellular impairment in the microvasculature and detrimental effects of lipid deposits on the glomeruli. Therefore, pharmacological agents that can lower the lipid level in patients with CKD are likely to be beneficial.

Statins (inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A, HMG-CoA, reductase) are the most commonly used lipid-lowering medications and have been shown to reduce CV events and/or mortality in most populations of patients studied, including primary and secondary prevention patients and diabetic patients, from numerous major randomised international studies.³⁻⁵ The focus of this article will be on the use of statins in pre-end-stage renal CKD subjects, as this is the group of CKD patients most commonly seen in primary care.

Does the Use of Statins Lower CV Events in Patients with CKD?

Increasing evidence, particularly from meta-analyses, suggest an important role of statins in CV protection in patients with pre-end-stage CKD and post-renal transplant subjects, although at present there is no evidence of benefit in CV outcomes in using statin therapy in dialysis patients.⁶⁻⁹ In the SHARP (Study of Heart and Renal Protection) trial, the use of simvastatin plus ezetimibe versus placebo reduced major atherosclerotic events (coronary death, myocardial infarction, non-haemorrhagic stroke, or any revascularisation) only in the group of patients not on dialysis (risk reduction of 20.2%). In dialysis patients the difference did not reach statistical significance.¹⁰ This observation is consistent with the result of the Prospective Pravastatin Pooling Project that included three large trials involving pravastatin.¹¹ Pravastatin significantly reduced the incidence of myocardial infarction, coronary death, and coronary revascularisation by 23 percent, only in patients with moderate renal insufficiency.

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The Heart Protection Study (HPS) which assessed >20,000 subjects at high CV risk, included a subgroup of 1329 subjects with impaired kidney function. In this subgroup, patients that received simvastatin had a 28-percent proportional risk reduction and an 11-percent absolute risk reduction of a major CV event compared to those randomised to placebo; similar to the effect on the overall cohort.⁴ In another meta-analysis of 38 studies with >37,000 participants with CKD (not on dialysis) there was a consistent reduction in major CV events, all-cause mortality, cardiovascular death and myocardial infarction in patients who received a statin compared with placebo.¹² Similarly, a meta-analysis of 31 randomised controlled trials looking at statin therapy in patients with varying stages of CKD that included at least one CV event (48,429 patients with CKD, including 6690 major cardiovascular events and 6653 deaths) demonstrated that statin therapy produced a 23-percent relative risk (RR) reduction for major CV events, 18-percent RR reduction for coronary events and 9-percent reduction in CV or all-cause deaths, but had no significant effect on stroke.⁹ Adverse events, including hepatic or muscular disorders, were not significantly increased by statins and subgroup analysis revealed that the relative effects of statin therapy in CKD were significantly reduced in those with advanced CKD, although absolute risk reductions were comparable.

Safety of Statins in Patients with CKD

Data on the safety of using statins in patients with CKD has been mixed, with some studies suggesting benefit on renal function, whilst others suggest there may be some detrimental effects. In a recent observational study using administrative databases containing information on >2 million patients, the use of high-potency statins was found to be associated with acute kidney injury, especially within the first 120 days of statin use.¹³ However, in a subsequent analysis of 24 placebo-controlled statin studies and two high- versus low-dose

statin studies, no evidence of renal injury from statin use was found.¹⁴ These discrepancies may be related to the type of analysis used and the quality of data that can be obtained on adverse effects of statins in randomised controlled trials (which may not be powered to look at renal injury). Statins appear to have a nephron-protective role in the prevention of contrast-induced acute kidney injury (CI-AKI). In a randomised study of 2,998 patients with type 2 diabetes and concomitant CKD who were undergoing coronary/peripheral arterial angiography with or without percutaneous intervention, patients that received rosuvastatin 10mg over five days (two days before, and three days after procedure) had a significantly lower incidence of CI-AKI than controls.¹⁵ Similarly, a meta-analysis of 15 trials examining the effect of statin pre-treatment before coronary angiography found a significant reduction in CI-AKI in those treated with high-dose statin compared to controls treated with either placebo or low-dose statin.¹⁶ Thus, the balance of current evidence suggests that statins do not cause any major harm in patients with CKD and their use is therefore not contra-indicated, although some statins require dose restrictions in CKD (Table 2).

High Intensity Statins in Patients with CKD

Most of the studies and meta-analyses conducted to date showing a beneficial effect of statins in patients with CKD have used standard doses of statins. Whether high-intensity statins give greater benefit in patients with CKD is less clear. In a meta-analysis of ten randomised controlled trials involving over 40,000 participants, investigators found that intensive statin therapy (i.e. use of a higher statin dose compared with a clinically common dose) reduced the risk of non-fatal CV events (stroke and non-fatal myocardial infarction) and had a possible role in reducing mortality, although this was not conclusive.¹⁷ In another meta-analysis of six randomised controlled trials (RCTs) involving 10,933 patients with CKD,

Table 2. Statin dosing in patients with CKD

| Statin | Usual dose range (mg/d) | Clearance route | Dose range for CKD stages 1-3 | Dose range for CKD stages 4-5 |
|--------------|-------------------------|-----------------|-------------------------------|-------------------------------|
| Atorvastatin | 10-80 | Liver | 10-80 | 10-80 |
| Fluvastatin | 20-80 | Liver | 20-80 | 20-40 |
| Lovastatin | 10-80 | Liver | 10-80 | 10-20 |
| Pitavastatin | 1-4 | Liver/Kidney | 1-2 | 1-2 |
| Pravastatin | 10-80 | Liver/Kidney | 10-80 | 10-20 |
| Rosuvastatin | 10-40 | Liver/Kidney | 5-40 | 5-10 |
| Simvastatin | 5-40 | Liver | 5-40 | 5-40 |

investigators found that the use of high-intensity statin significantly decreased stroke risk, although the effect on myocardial infarction, heart failure and mortality was less clear.¹⁸ High-intensity statin also lowered LDL-C levels but had no clear effects on renal protection. Contrary to popular belief, there was no evidence from this study that using high-dose statin increased the chances of patients developing rhabdomyolysis or severe liver failure. The incidences of adverse events were very low and pooled results showed no significant difference between the high-dose and normal-dose statin groups (although the investigators noted that good-quality data on all the adverse events from each of the trials was hard to obtain). To further address the question of whether statins, and in particular high-intensity statins, were associated with an increased risk of serious adverse events (SAE) in patients with CKD, investigators studied the results from clinical trials with data from 149,882 patient-years of follow-up.¹⁹ They found no difference in the incidence of renal-related SAEs at 120 days between atorvastatin and placebo in the 24 placebo-controlled trials (10,345 patients on atorvastatin (10 to 80 mg/day) versus 8,945 patients on placebo) or in the high-dose versus low-dose statin trials. In a sub-study of two large RCTs of high-intensity statin therapy in patients post-acute coronary syndrome (ACS) (PROVE IT-TIMI 22 which enrolled 4162 subjects and A-to-Z which enrolled 4497 subjects), investigators found that the incidence of kidney injury-related adverse events was not statistically different for patients on a high-potency versus moderate-potency statin regimen.²⁰ Thus, there is some evidence in support of the clinical benefit of high-intensity statins in patients with CKD, although whether such doses should routinely be used in this group of patients and whether there are any long-term safety issues with using such doses is still unclear and a matter of ongoing debate.

Choice of Statins in Patients with CKD

Since different statins have varying degrees of renal clearance, it is important for the clinician to be aware of the metabolism of the agent of interest and therefore determine whether any dose adjustment is needed in patients with CKD. Most statins are primarily metabolised through the liver, so dose adjustment in patients with early CKD (eGFR > 30 ml/min) are not usually required. With more advanced CKD (eGFR < 30 ml/min or end-stage renal disease) most statins have maximum dose restrictions, although statins should be used with caution in this population (Table 2).

CONCLUSION

CV disease is the leading cause of mortality in patients with CKD and dyslipidaemia is an important contributor, similar to its effect in patients without CKD. Multiple clinical trials and meta-analyses have shown that statins can be safely used in patients with CKD and reduce CV events in individuals with pre-end-stage CKD, or post renal transplant, but not in dialysis patients. Some evidence suggests that high-intensity statin therapy may reduce the risk of stroke in patients with CKD although its effects on all-cause mortality and other CV

endpoints remain unclear. There is no strong evidence that the use of high-intensity statins increase the incidence of serious adverse events in patients with CKD. Some statins need dose adjustment in CKD due to varying routes of clearance and metabolism.

REFERENCES

1. Pinkau T, Hilgers KF, Veelken R, Mann JF. How does minor renal dysfunction influence cardiovascular risk and the management of cardiovascular disease? *J Am Soc Nephrol* 2004;15:517-23.
2. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351:1296–305.
3. No authors listed. Prevention of Cardiovascular Events and Death with Pravastatin in Patients with Coronary Heart Disease and a Broad Range of Initial Cholesterol Levels. *N Engl J Med*. 1998;339(19):1349-57.
4. No authors listed. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002 Jul 6;360:7-22.
5. No authors listed. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–9.
6. Strippoli GF, Navaneethan SD, Johnson DW, Perkovic V, Pellegrini F, Nicolucci A, et al. Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials. *BMJ*. 2008;336:645-51.
7. Palmer SC, Craig JC, Navaneethan SD, Tonelli M, Pellegrini F, Strippoli GF. Benefits and harms of statin therapy for persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:263-75.
8. Upadhyay A, Earley A, Lamont JL, Haynes S, Wanner C, Balk EM. Lipid-lowering therapy in persons with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med*. 2012;157:251-62.
9. Hou W, Lv J, Perkovic V, Yang L, Zhao N, Jardine MJ, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J*. 2013;34:1807-17.
10. Baigent C, Landray M, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377:2181-92.
11. Tonelli M, Isles C, Curhan G, Tonkin A, Pfeffer MA, Shepherd J, et al., Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation*. 2004;110:1557-63.
12. Palmer S, Navaneethan S, Craig JC, Johnson DW, Perkovic V, Hegbrant J, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2014;5:CD007784.
13. Dormut C, Hemmelgarn C, Paterson J, James MT, Teare GF, Raymond CB, et al. Use of high potency statins and rates of admission for acute kidney injury: multicenter, retrospective observational analysis of administrative databases. *BMJ*. 2013;346:f880.
14. Bangalore S, Fayyad R, Hovingh G, Laskey R, Vogt L, DeMicco DA, et al. Statin and the risk of renal-related serious adverse events: Analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and other placebo-controlled trials. *Am J Cardiol*. 2014;113:2018-20.
15. Han Y, Zhu G, Han L, Hou F, Huang W, Liu H, et al. Short-term rosuvastatin therapy for prevention of contrast-induced acute kidney injury in patients with diabetes and chronic kidney disease. *J Am Coll Cardiol*. 2014;63:62-70.
16. Lee J, Park J, Jeon K, Jung JH, Lee SE, Han JK, et al. Efficacy of short-term high-dose statin pretreatment in prevention of contrast-induced acute kidney injury: updated study-level meta-analysis of 13 randomised controlled trials. *PLoS One*.

2014;9:e111397.

17. Mills E, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, et al. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J*. 2011;32:1409-15.

18. Yan Y-L, Qiu B, Wang J, Deng SB, Wu L, Jing XD, et al. High-intensity statin therapy in patients with chronic kidney disease: a systematic review and meta-analysis. *BMJ Open*. 2015;5:e006886.

19. Bangalore S, Fayyad R, Hovingh G, Laskey R, Vogt L, DeMicco DA, et al. Statin and the risk of renal-related serious adverse events: Analysis from the IDEAL, TNT, CARDS, ASPEN, SPARCL, and other placebo-controlled trials. *Am J Cardiol*. 2014;113:2018-20.

20. Sarma A, Cannon C, de Lemos J, Rouleau JL, Lewis EF, Guo J, et al. The incidence of kidney injury for patients treated with a high-potency versus moderate-potency statin regimen after an acute coronary syndrome. *J Am Heart Assoc*. 2014;3:e000784.

LEARNING POINTS

- **Patients with chronic kidney disease (CKD) are at increased risk of cardiovascular disease and CKD is considered an independent risk factor for cardiovascular events**
 - **Statins are effective in reducing the incidence of cardiovascular events in patients with pre-end stage CKD and transplant recipients**
 - **There is currently a lack of strong evidence showing benefit of statins in patients on dialysis**
 - **The use of high intensity statins appears to have some benefit in reducing the incidence of stroke**
 - **The dose of statins may need to be reduced in patients with more severe stages of CKD**
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