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COCHRANE COMMENTARY

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Statins for chronic kidney disease not requiring dialysis

WHAT IS THIS REVIEW ABOUT?

This systematic review summarized the evidence from randomized trials evaluating the benefits and harms of statin therapy in adults with chronic kidney disease who were not receiving treatment with dialysis or a transplant. The review assessed the efficacy and safety of statin drugs (atorvastatin, cerivastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin with or without combined ezetimibe therapy) against placebo or another statin. We focus here on the available evidence in placebo-controlled trials for treatment effects on mortality, cardiovascular, adverse event and lipid end-points.

WHAT ARE THE FINDINGS?

Statin therapy reduced major cardiovascular events (13 trials, 36 033 participants; relative risk (RR) 0.72 (confidence interval (CI) 0.66–0.79)), cardiovascular mortality (7 trials, 19 059 participants; RR 0.77 (CI 0.69–0.87)) and all-cause mortality (10 trials, 28 276 participants; RR 0.79 (CI 0.69–0.91)) (Fig. 1). Statin therapy also prevented fatal or nonfatal myocardial infarction (8 trials, 9018 participants; RR 0.55 (CI 0.42–0.72) but had uncertain effects on stroke (5 trials, 8659 participants; RR 0.62 (CI 0.35–1.12). Assuming a 10% 5 year risk, treating 1000 adults with chronic kidney disease for 1 year might be expected to prevent 14 major cardiovascular events (number needed to treat to prevent one event is 71).

Information for potential harmful effects was sparser, with fewer trials contributing data. Statin therapy had uncertain effects on elevation of creatine kinase (7 trials, 4514 participants; RR 0.84 (0.20–3.48)), liver function derangement (7 trials, 7991 participants; RR 0.76 (CI 0.39–1.50)), withdrawal due to adverse events (13 trials, 4219 participants; RR 1.16 (CI 0.84–1.06)) and cancer (2 trials, 5581 participants; RR 1.03 (CI 0.82–1.30)).

Statins significantly lowered serum total cholesterol (25 trials, 2105 participants; mean difference (MD) −1.31 mmol/L (CI −1.72 to −0.91)) and low-density lipoprotein (LDL) cholesterol (22 trials, 2054 participants; MD −1.12 mmol/L (CI −1.39 to −0.87)).

WHAT ARE THE FINDINGS BASED ON?

Forty-seven trials compared statin therapy with placebo involving 39 820 adults with chronic kidney disease. A large proportion of the available data was derived from post-hoc analyses of adults with chronic kidney disease who were enrolled in trials including larger populations including adults without kidney disease (10 trials, 36 325 participants). The trial sample sizes ranged from 14 to 1233 participants, with 8 studies that included more than 1000 participants.

Outcome	No. of trials (participants)	Relative risk (95% confidence interval)
Major cardiovascular event	13 (36,033)	0.72 (0.66 to 0.79)
Cardiovascular mortality	7 (19,059)	0.77 (0.69 to 0.87)
All-cause mortality	10 (28,276)	0.79 (0.69 to 0.91)
Myocardial infarction	8 (9018)	0.55 (0.42 to 0.72)
Stroke	5 (8659)	0.62 (0.35 to 1.12)
Elevated creatine kinase	7 (4514)	0.84 (0.20 to 3.48)
Deranged liver function	7 (7991)	0.76 (0.39 to 1.50)
Withdrawal from treatment	13 (4219)	1.16 (0.84 to 1.06)
Cancer	2 (5581)	1.03 (0.82 to 1.30)

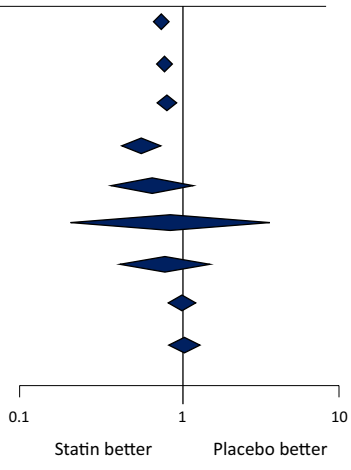

Fig. 1 Effects of statin therapy (all agents) *versus* placebo on clinical outcomes in people who had chronic kidney disease.

The statin dose (equivalent to simvastatin) was 20 mg daily on average, although doses ranged between 5 and 80 mg per day. Participants were generally followed up for 12 months while information for mortality outcomes was based on a median follow-up of 47 months. Three trials enrolled adults with established coronary artery disease while 10 studies excluded participants with cardiovascular disease. The median baseline serum LDL cholesterol was 5.8 mmol/L. Overall, when any limitations in study design, the consistency of results across different trials, the certainty of treatment effects and the chances of missing unpublished results were all considered, there were moderate to high levels of confidence in the available results. This suggested that additional research was unlikely to change the confidence in these results. Results were similar when trials excluding participants with cardiovascular disease were excluded.

IMPLICATIONS FOR PRACTICE

- In adults with chronic kidney disease, statin therapy substantially reduced major cardiovascular events, myocardial infarction and death but had uncertain effects on adverse events including muscle injury, liver enzymes and cancer.
- Benefits of statin therapy are likely to extend to adults with chronic kidney disease without established cardiovascular disease although absolute benefits of treatment will be determined by baseline cardiovascular risk.
- The available evidence for the efficacy of statin therapy in adults with chronic kidney disease is high quality but the balancing of benefits and harms is limited by the lack of toxicity data in available trials.

CLINICAL PERSPECTIVE

Statin therapy is an effective intervention to lower cardiovascular risk in adults with chronic kidney disease. Based on this review, statin treatment proportionally reduces major cardiovascular events and death by 20% to 25%. The absolute benefit of statin therapy in individual patients (equivalent to simvastatin 20 mg daily) can be quantified when considering their baseline cardiovascular risk. In existing trials, the toxicity profile of statin therapy is uncertain and the balance between benefits and harms is incompletely understood.

Palmer SC, Navaneethan SD, Craig JC *et al*. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database of Systematic Reviews* 2014, Issue 5. Art. No.: CD007784. DOI: 10.1002/14651858.CD007784.pub2

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