# HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis

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## ABSTRACT

BACKGROUND: Cardiovascular disease (CVD) is the most frequent cause of death in people with early stages of chronic kidney disease (CKD), for whom the absolute risk of cardiovascular events is similar to people who have existing coronary artery disease. This is an update of a review published in 2009, and includes evidence from 27 new studies (25,068 participants) in addition to the 26 studies (20,324 participants) assessed previously; and excludes three previously included studies (107 participants). This updated review includes 50 studies (45,285 participants); of these 38 (37,274 participants) were meta-analysed.

OBJECTIVES: To evaluate the benefits (such as reductions in all-cause and cardiovascular mortality, major cardiovascular events, MI and stroke; and slow progression of CKD to end-stage kidney disease (ESKD)) and harms (muscle and liver dysfunction, withdrawal, and cancer) of statins compared with placebo, no treatment, standard care or another statin in adults with CKD who were not on dialysis.

METHODS:

*Search methods:* We searched the Cochrane Renal Group's Specialised Register to 5 June 2012 through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

*Selection criteria:* Randomised controlled trials (RCTs) and quasi-RCTs that compared the effects of statins with placebo, no treatment, standard care, or other statins, on mortality, cardiovascular events, kidney function, toxicity, and lipid levels in adults with CKD not on dialysis were the focus of our literature searches.

*Data collection and analysis:* Two or more authors independently extracted data and assessed study risk of bias. Treatment effects were expressed as mean difference (MD) for continuous outcomes (lipids, creatinine clearance and proteinuria) and risk ratio (RR) for dichotomous outcomes (major cardiovascular events, all-cause mortality, cardiovascular mortality, fatal or non-fatal myocardial infarction (MI), fatal or non-fatal stroke, ESKD, elevated liver enzymes, rhabdomyolysis, cancer and withdrawal rates) with 95% confidence intervals (CI).

MAIN RESULTS: We included 50 studies (45,285 participants): 47 studies (39,820 participants) compared statins with placebo or no treatment and three studies (5547 participants) compared two different statin regimens in adults with CKD who were not yet on dialysis. We were able to meta-analyse 38 studies (37,274 participants).

The risk of bias in the included studies was high. Seven studies comparing statins with placebo or no treatment had lower risk of bias overall; and were conducted according to published protocols, outcomes were adjudicated by a committee, specified outcomes were reported, and analyses were conducted using intention-to-treat methods. In placebo or no treatment controlled studies, adverse events were reported in 32 studies (68%) and systematically evaluated in 16 studies (34%).

Compared with placebo, statin therapy consistently prevented major cardiovascular events (13 studies, 36,033 participants; RR 0.72, 95% CI 0.66 to 0.79), all-cause mortality (10 studies, 28,276 participants; RR 0.79, 95% CI 0.69 to 0.91), cardiovascular death (7 studies, 19,059 participants; RR 0.77, 95% CI 0.69 to 0.87) and MI (8 studies, 9018 participants; RR 0.55, 95% CI 0.42 to 0.72). Statins had uncertain effects on stroke (5 studies, 8658 participants; RR 0.62, 95% CI 0.35 to 1.12).

Potential harms from statin therapy were limited by lack of systematic reporting and were uncertain in analyses that had few events: elevated creatine kinase (7 studies, 4514 participants; RR 0.84, 95% CI 0.20 to 3.48), liver function abnormalities (7 studies, RR 0.76, 95% CI 0.39 to 1.50), withdrawal due to adverse events (13 studies, 4219 participants; RR 1.16, 95% CI 0.84 to 1.60), and cancer (2 studies, 5581 participants; RR 1.03, 95% CI 0.82 to 130).

Statins had uncertain effects on progression of CKD. Data for relative effects of intensive cholesterol lowering in people with early stages of kidney disease were sparse. Statins clearly reduced risks of death, major cardiovascular events, and MI in people with CKD who did not have CVD at baseline (primary prevention).

AUTHORS' CONCLUSIONS: Statins consistently lower death and major cardiovascular events by 20% in people with CKD not requiring dialysis. Statin-related effects on stroke and kidney function were found to be uncertain and adverse effects of treatment are incompletely understood. Statins have an important role in primary prevention of cardiovascular events and mortality in people who have CKD.

This abstract is available free of charge from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD007784.pub2/abstract.

## REFERENCE

1. Palmer SC, Navaneethan SD, Craig JC, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev. 2014;(5):CD007784.

## COMMENTS

The association between abnormalities of lipid metabolism and cardiovascular risk has been well documented by numerous studies. Treatment of dyslipidemia with statins can significantly reduce the cardiovascular risk in individuals with abnormalities of the lipid profile.[1] On the other hand, cardiovascular disease remains the leading cause of death among patients with chronic kidney disease (CKD).[2] The role of dyslipidemia as a cardiovascular risk factor and the effects of its treatment with statins in this population remain a matter of debate. Most of the evidence relating to the effect of using statins on cardiovascular disease in non-dialysis CKD individuals comes from post-hoc analyses or assessments on subgroups of large population-based studies.

The authors of the systematic review evaluated 50 studies, including 38 meta-analyses, with 45,285 patients. They demonstrated that the use of statins has been able to reduce cardiovascular events and overall and cardiovascular mortality, but that there has been no evidence of prevention of stroke or effectiveness in delaying the progression of kidney disease. Kidney failure increases the risk of toxicity associated with use of statins, particularly due to the possibility of rhabdomyolysis.[3] The authors point out the lack of conclusive clinical data regarding the adverse effects of statins on non-dialysis CKD patients.

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In relation to the analysis on the effects of statins on the progression of kidney disease, recent findings have been controversial. The study by Palmer et al. did not demonstrate any improvement in this outcome through use of statins, which confirms the findings of the SHARP trial.[4] However, other systematic reviews found slight trends towards smaller declines in glomerular filtration rate (GFR) through use of this medication.[5]

The results from this review are in agreement with the "Kidney Diseases: improving global outcomes" (KDIGO) 2013 guidelines,[6] which recommend statin treatment for dyslipidemia among non-dialysis CKD patients ≥ 50 years of age who present estimated GFR below 60 ml/min per 1.73 $m^2$. For patients aged between 18 and 49 years, KDIGO recommends statins if they have had coronary disease, diabetes or prior history of ischemic stroke, or if there is a risk of myocardial infarction greater than 10% within 10 years.

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