

Effects of statins in patients with chronic kidney disease: meta-analysis and meta-regression of randomised controlled trials

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EDITORIAL by Clase

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ABSTRACT

Objective To analyse the benefits and harms of statins in patients with chronic kidney disease (pre-dialysis, dialysis, and transplant populations).

Design Meta-analysis.

Data sources Cochrane Central Register of Controlled Trials, Medline, Embase, and Renal Health Library (July 2006).

Study selection Randomised and quasi-randomised controlled trials of statins compared with placebo or other statins in chronic kidney disease.

Data extraction and analysis Two reviewers independently assessed trials for inclusion, extracted data, and assessed trial quality. Differences were resolved by consensus. Treatment effects were summarised as relative risks or weighted mean differences with 95% confidence intervals by using a random effects model.

Results Fifty trials (30 144 patients) were included. Compared with placebo, statins significantly reduced total cholesterol (42 studies, 6390 patients; weighted mean difference -42.28 mg/dl (1.10 mmol/l), 95% confidence interval -47.25 to -37.32), low density lipoprotein cholesterol (39 studies, 6216 patients; -43.12 mg/dl (1.12 mmol/l), -47.85 to -38.40), and proteinuria (g/24 hours) (6 trials, 311 patients; -0.73 g/24 hour, -0.95 to -0.52) but did not improve glomerular filtration rate (11 studies, 548 patients; 1.48 ml/min (0.02 ml/s), -2.32 to 5.28). Fatal cardiovascular events (43 studies, 23 266 patients; relative risk 0.81, 0.73 to 0.90) and non-fatal cardiovascular events (8 studies, 22 863 patients; 0.78, 0.73 to 0.84) were reduced with statins, but statins had no significant effect on all cause mortality (44 studies, 23 665 patients; 0.92, 0.82 to 1.03). Meta-regression analysis showed that treatment effects did not vary significantly with stage of chronic kidney disease. The side effect profile of statins was similar to that of placebo. Most of the available studies were small and of suboptimal quality; mortality data were provided by a few large trials only.

Conclusion Statins significantly reduce lipid concentrations and cardiovascular end points in patients with chronic kidney disease, irrespective of stage of disease, but no

benefit on all cause mortality or the role of statins in primary prevention has been established. Reno-protective effects of statins are uncertain because of relatively sparse data and possible outcomes reporting bias.

INTRODUCTION

Cardiovascular disease accounts for the largest proportion of fatalities in people with chronic kidney disease.¹ Dyslipidaemia is one of several factors that have been implicated in the increased cardiovascular risk associated with chronic kidney disease and also in the progression of renal damage.²⁻⁴ Optimal management of dyslipidaemia, particularly reduction of low density lipoprotein cholesterol, should lead to both cardiovascular and renal benefits.

Clinical trials in the general population and in people with established cardiovascular disease have found a strong association between reducing lipid concentrations and the risk of all cause mortality and cardiovascular mortality.^{5,6} Data in people with chronic kidney disease have been conflicting; some observational studies in dialysis patients have shown a clear, linear relation between low density lipoprotein cholesterol and cardiovascular end points, whereas others have not.^{7,8} Few randomised trials have been done in patients with chronic kidney disease.

In a recent meta-analysis, Douglas et al reported the beneficial effects of statins in patients with overt proteinuria but not in those with microalbuminuria or normoalbuminuria.⁹ Similarly, Sandhu et al reported a slowing of the decline in glomerular filtration rate in patients with chronic kidney disease and concomitant cardiovascular disease, along with improvement in proteinuria.¹⁰ The aim of our study was to evaluate the efficacy and safety of statins for renal and cardiovascular outcomes in all stages of chronic kidney disease.

METHODS

Inclusion criteria

We included all randomised controlled trials and quasi-randomised controlled trials of any statin against placebo, no treatment, or another statin in adult patients with chronic kidney disease. We defined

patients with chronic kidney disease as those who were having maintenance dialysis treatment, had had renal transplantation, had an elevated baseline mean serum creatinine, or had an impairment of the glomerular filtration rate along with other markers of kidney damage such as proteinuria.¹¹

Data sources and searches

We searched Medline, Embase, the Cochrane Central Register, and the Renal Health Library of the Cochrane Renal Group. Search terms covered chronic kidney disease, dialysis, renal transplantation, hypercholesterolaemia, hyperlipidaemia, dyslipidaemia, and statins. We considered randomised controlled trials without language restriction. We searched the reference lists of identified trials and review articles for additional trials. We sought information about unpublished and ongoing randomised controlled trials.

Data collection and analysis

Two authors independently reviewed literature searches to identify relevant trials. We extracted data on study sample, population characteristics, interventions, co-interventions, and methodological quality. We extracted data on the following outcomes: all cause mortality, fatal cardiovascular and cerebrovascular events, non-fatal cardiovascular and cerebrovascular events separately, end stage renal disease, doubling of serum creatinine concentration, lipid concentrations at the end of treatment, creatinine clearance and 24 hour urinary protein excretion, acute allograft rejection rates, and adverse events.

We used relative risk to analyse dichotomous data. We pooled risk estimates from individual trials.¹² Where continuous measurements of outcomes were used, we calculated the weighted mean difference by using the values of the outcome at the end of treatment.

We analysed heterogeneity across included trials.¹³ We did subgroup analysis and meta-regression where possible to explore the role of potential sources of heterogeneity related to the participants, the agent used, and trial quality on the effect of the interventions. We analysed trials done in pre-dialysis, dialysis, and transplant populations separately and pooled the results when formal tests of interaction indicated no significant difference between the estimates from the separate groups.

Quality assessment

At least two authors independently assessed the methodological quality of included randomised controlled trials by using standard domains: allocation concealment; blinding of investigators, participants, and outcome assessors; use of intention to treat analysis; completeness of follow-up.

RESULTS

Search results

The search identified 869 articles, of which we excluded 801 trials. Full text assessment of the remaining 68 articles resulted in identification of 50

eligible randomised controlled trials with 54 comparisons of statins versus placebo or no treatment (comparisons: pre-dialysis, n=26; dialysis, n=11; transplant, n=17), which included 30 144 patients.^{14w1-w49}

Trial characteristics

All trials studied the effect of statins on lipid concentrations and safety. The 26 randomised controlled trials in pre-dialysis chronic kidney disease enrolled participants with diabetic nephropathy (n=6), hypertensive nephropathy (n=2), or various forms of nephrotic and non-nephrotic glomerulonephritis. One trial (n=20 patients) was done in patients with polycystic kidney disease.^{w12} Fifteen of these randomised controlled trials evaluated the potential renoprotective effect of statins. Five randomised controlled trials in renal transplant recipients reported biopsy proved acute allograft rejection rates, but no trial reported the effects on chronic allograft nephropathy.^{w35-w39} Liver function tests and creatinine phosphokinase concentrations were the only safety parameters reported consistently in all trials. Follow-up ranged from two months to 60 months in all trials, and several different statins were used.

Trial quality

The methodological quality of many trials was sub-optimal. Concealment of allocation was adequate in 11 (22%) randomised controlled trials, clearly inadequate in 9 (18%), and unclear in the remainder. Participants, investigators, and outcome assessors were blinded in only 10 (20%) randomised controlled trials, and only 10 (20%) randomised controlled trials were analysed on an intention to treat basis. The dropout rate was less than 10% in 43 (86%) randomised controlled trials.

Effect of statins on surrogate end points in chronic kidney disease

Total cholesterol

Total cholesterol concentrations were significantly lower with statins than with placebo (42 comparisons, 6390 patients; weighted mean difference -42.28 mg/dl (-1.10 mmol/l), 95% confidence interval -47.25 to -37.32). We found significant heterogeneity for this outcome (heterogeneity $\chi^2=804.09$, $I^2=94.9\%$), which was largely explained by the type of statin (38.42% of heterogeneity) and the baseline cholesterol concentration (60.73% of heterogeneity; greater differences in patients with higher baseline values). Stage of chronic kidney disease was not an effect modifier.

Low density lipoprotein cholesterol

Low density lipoprotein cholesterol concentrations were significantly lower with statins than with placebo (39 comparisons, 6216 patients; weighted mean difference -43.12 mg/dl (-1.12 mmol/l), -47.85 to -38.40). We found significant evidence of heterogeneity between agents. The type of statin explained 38.42% of existing heterogeneity in the effect of statins on total cholesterol concentrations at the end of treatment and

10.99% of that on low density lipoprotein cholesterol (see *bmj.com*).

High density lipoprotein cholesterol

Statins had no significant effect compared with placebo on the concentration of high density lipoprotein cholesterol in chronic kidney disease (40 comparisons, 5621 patients; weighted mean difference 0.41 mg/dl (0.01 mmol/l), 0.78 to 1.60). We found considerable heterogeneity (heterogeneity $\chi^2=693.78$, $I^2=94.4\%$), but this was not explained by stage of chronic kidney disease.

Triglycerides

We found a significant reduction in triglyceride concentrations with statins in comparison with placebo

(39 comparisons, 5569 patients; weighted mean difference -23.71 mg/dl (-0.23 mmol/l), -33.52 to -13.90) overall and separately in pre-dialysis patients (15 comparisons, 836 patients; -28.71 mg/dl (-0.28 mmol/l), -48.55 to -8.87) and transplant patients (11 comparisons, 2955 patients; -25.24 mg/dl (-0.25 mmol/l), -33.49 to -16.99) but not in dialysis patients (13 comparisons, 1778 patients; -22.67 mg/dl (-0.22 mmol/l), -46.80 to 1.46).

Proteinuria and creatinine clearance

We found a significant reduction in 24 hour urinary protein excretion (g/24 h) in chronic kidney disease (pre-dialysis) patients receiving statins compared with placebo (6 randomised controlled trials, 311 patients;

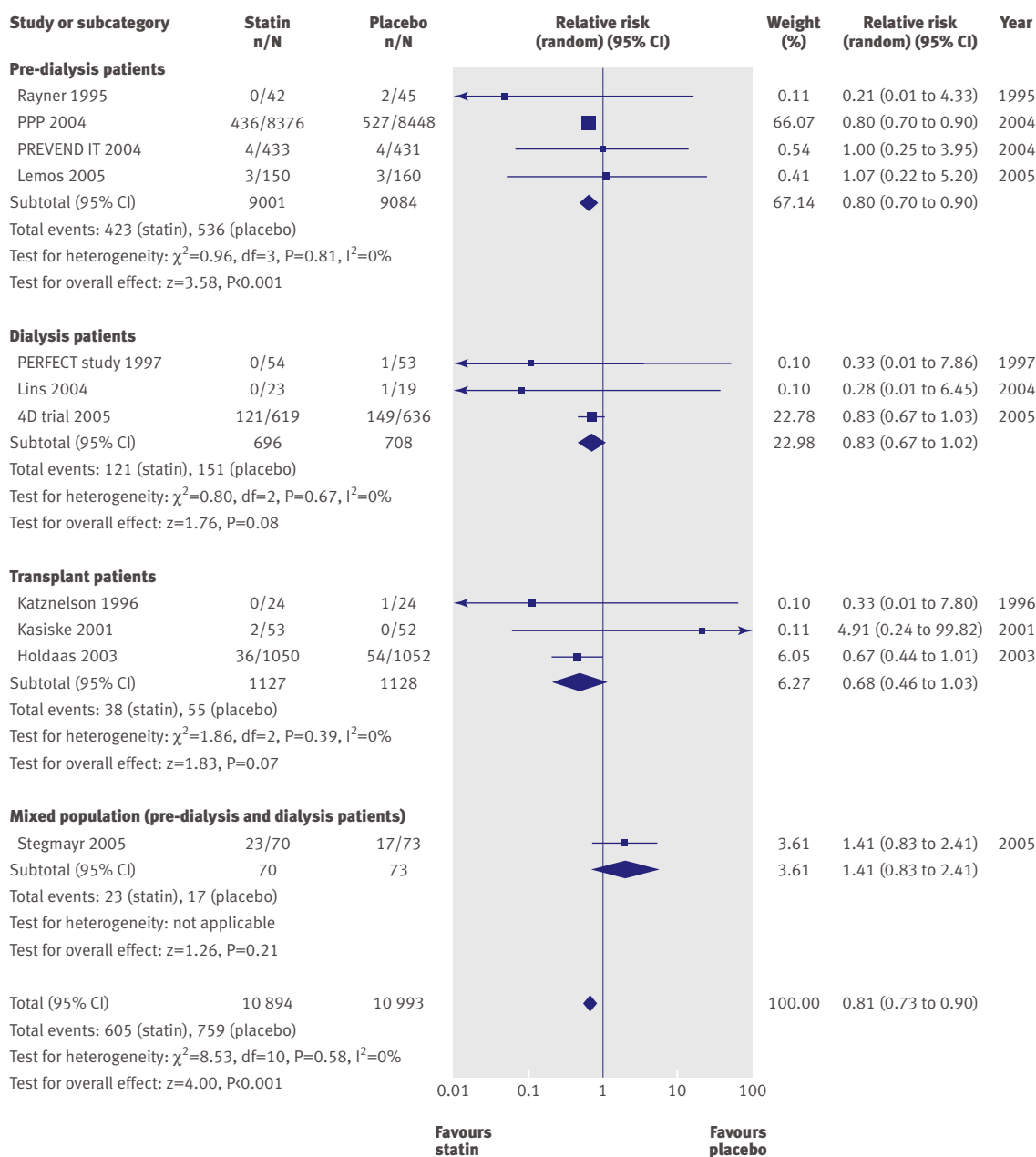


Fig 1 Effect of statins compared with placebo or no treatment on cardiovascular mortality in pre-dialysis, dialysis, and transplant patients. Only studies with at least one event are included in the plot

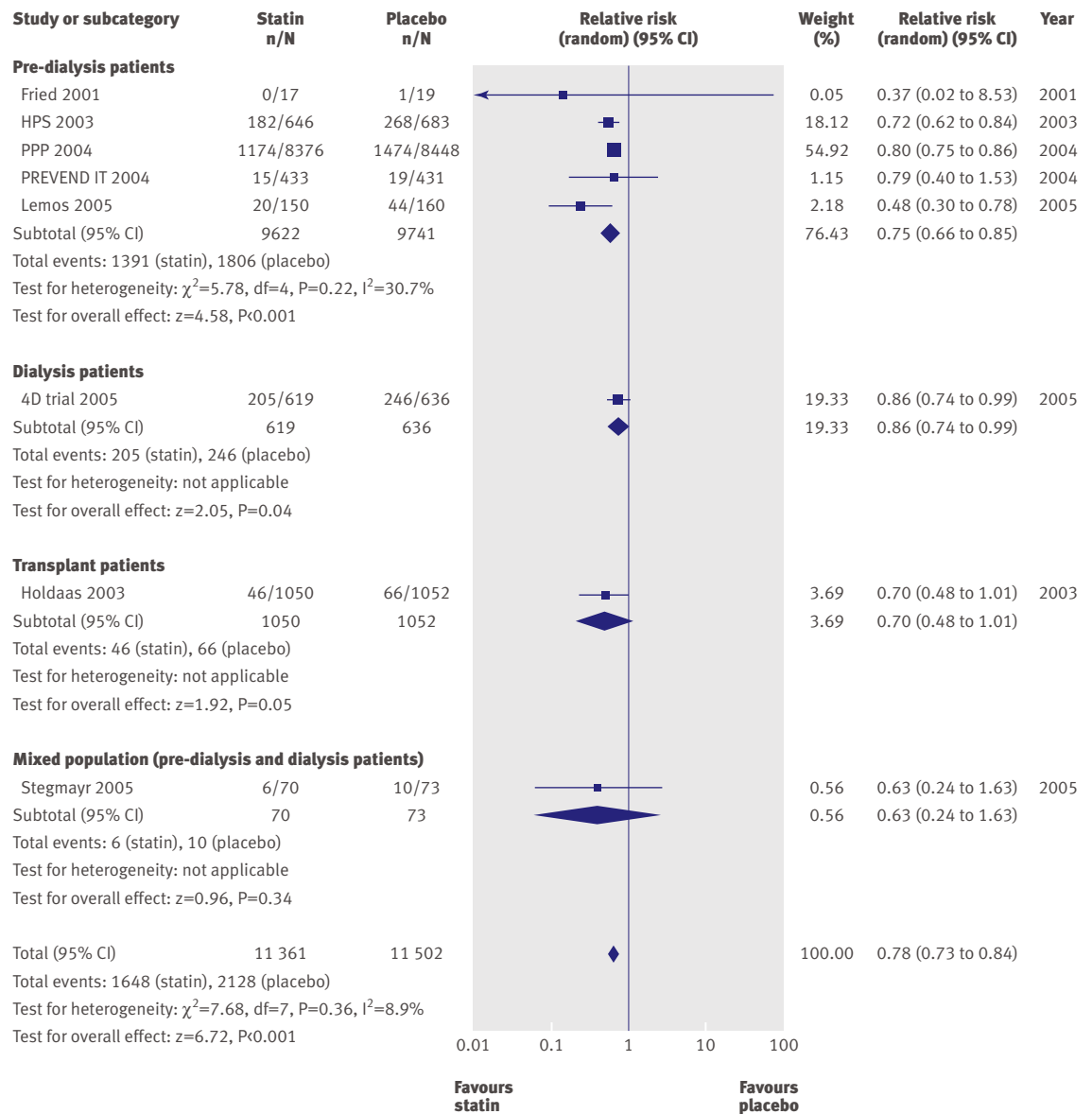


Fig 2 | Effect of statins compared with placebo or no treatment on cardiovascular events in pre-dialysis, dialysis, and transplant patients. Only studies with at least one event are included in the plot

weighted mean difference -0.73 g/24 hour, -0.95 to -0.52), with significant heterogeneity in this analysis (heterogeneity $\chi^2=12.07$, $I^2=58.6\%$). Creatinine clearance (either in ml/min or ml/min/1.73 m²) did not change with statins in comparison with placebo (11 randomised controlled trials, 548 patients; weighted mean difference 1.48 ml/min (0.024 ml/s), -2.32 to 5.28).

Effect of statins on patient level end points in chronic kidney disease

All cause and cardiovascular mortality and non-fatal cardiovascular events

We found no significant reduction in the risk of all cause mortality with statins in chronic kidney disease overall (44 trials, 23 665 patients; relative risk 0.92 , 95% confidence interval 0.82 to 1.03). A significant

(approximately 20%) reduction in risk occurred in pre-dialysis patients (21 trials, 18 781 patients; relative risk 0.81 , 0.74 to 0.89), largely driven by the pravastatin pooling project, but we found no statistically significant interaction between the separate groups of pre-dialysis, dialysis, and transplant patients (heterogeneity $\chi^2=16.05$, $I^2=25.2\%$, $P=0.12$ for interaction), suggesting that stage of chronic kidney disease is not a proved effect modifier, which makes the overall estimate of effect the most robust.

We found a significant (approximately 20%) reduction in the risk of cardiovascular mortality (43 trials, 23 266 patients; relative risk 0.81 , 0.73 to 0.90), with no statistically significant heterogeneity (heterogeneity $\chi^2=8.45$, $I^2=0\%$, $P=0.23$ for interaction) (fig 1) and no apparent difference in treatment effect across pre-dialysis, dialysis, and transplant populations.

Compared with placebo, statins also significantly decreased the risk of non-fatal cardiovascular events by 20% (8 trials, 22 863 patients, relative risk 0.78, 0.73 to 0.84), with no significant heterogeneity among the studies (heterogeneity $\chi^2=7.68$, $I^2=8.9\%$) (fig 2). This effect was consistent across pre-dialysis and dialysis patients, with no significant interaction ($P=0.18$ for interaction).

End stage renal disease and allograft rejection

We found no trials reporting end stage renal disease or doubling of creatinine as an outcome. No significant reduction occurred in the risk of acute allograft rejection with statins used for three months in the immediate post-transplant period compared with placebo (5 trials, 639 patients; relative risk 0.73, 0.49 to 1.10). We found a significant heterogeneity among these trials (heterogeneity $\chi^2=8.97$, $I^2=55.4\%$), which could be explained by the different sample sizes in the included studies, the different subsets of patients included, and the different immunosuppressive regimens used.

Adverse effects

We found no significant increase in the risk of abnormalities in liver function tests (26 trials, 6726 patients) or raised creatinine phosphokinase concentrations (risk of rhabdomyolysis) (29 trials, 6829 patients; relative risk 1.50, 0.86 to 2.59; heterogeneity $\chi^2=7.73$, $I^2=0\%$) for statins compared with placebo. We also found no significant difference in the risk of withdrawal from the study owing to adverse events for statins compared with placebo (20 trials, 4887 patients; relative risk 1.03, 0.84 to 1.25; heterogeneity $\chi^2=17.79$, $I^2=10\%$).

Analysis of heterogeneity

Meta-regression of heterogeneity was possible only for the outcome of total cholesterol and low density lipoprotein cholesterol at end of treatment. On univariate meta-regression, the type of statin (38.42%), baseline cholesterol concentrations (60.73%), and allocation concealment (13.80%) seemed to be responsible for most of the heterogeneity in the effect of statins on total cholesterol concentrations; statin type (10.99%), age (19.39%), baseline cholesterol concentrations (34.43%), and allocation concealment (20.05%) were the major causes of heterogeneity in the analysis of effect of statins on low density lipoprotein cholesterol concentrations. The observed significant heterogeneity by type of statin may be largely explained by the single trial of cerivastatin.^{w5} When we excluded this trial from the analyses, heterogeneity became non-significant.

For both total cholesterol and low density lipoprotein cholesterol concentrations at the end of treatment, the multivariate meta-regression model including the type of statin, dose of statin, age of participants, allocation concealment, and baseline cholesterol concentrations explained most of the identified heterogeneity in the effect of statins versus placebo. The effect of statins on

total cholesterol and low density lipoprotein cholesterol was dose dependent (see bmj.com).

DISCUSSION

Key findings

Our meta-analysis found that statins are associated with lipid lowering, cardiovascular, and antiproteinuric benefits in chronic kidney disease. They seem to be safe in chronic kidney disease, with respect to the risk of rhabdomyolysis and hepatotoxicity and because limited withdrawals occurred in the treatment group. The risk of cardiovascular events and cardiovascular mortality is reduced by statin treatment in people at different stages of chronic kidney disease, and the magnitude of cardiovascular benefit achieved seems broadly similar in these groups and approximates that of statin treatment in other populations.¹⁵ Although statins have been conclusively shown to reduce cardiovascular mortality and all cause mortality in the general population,¹⁶⁻¹⁸ considerable uncertainty has surrounded the generalisability of the findings of these trials to people with chronic kidney disease.

Our findings support suggestions that the inverse relations identified between lipid abnormalities and cardiovascular outcomes in the observational studies can be explained by reverse causality, whereby ill health and poor nutrition separately caused both lower cholesterol concentrations and a higher risk of death. The results support the use of statins in people with chronic kidney disease who have established occlusive coronary disease or cerebrovascular disease or are at particularly high risk of these cardiovascular events. Controversy arises when patients have established (stages 3-5) chronic kidney disease and have not yet had a vascular event.

In our systematic review, data on major clinical end points were available from relatively few studies. The small number of participating studies with substantial numbers of these end points meant that statistical power to detect such differences was suboptimal. That important differences exist in the effects of statins among people with different degrees of chronic kidney disease remains possible. A substantial proportion of the participants in the studies included in this meta-analysis had established occlusive arterial disease and may therefore benefit more than people without such disease (primary prevention). This review did not show a significant beneficial effect on all cause mortality. This may be due to a type II statistical error or it may reflect the fact that typical occlusive atherosclerotic diseases are responsible for a minority of deaths in people with chronic kidney disease.¹⁹

The type and magnitude of the effect of statins on lipid profiles in patients with chronic kidney disease in this review were similar to those described in previous meta-analyses of lipid lowering trials in chronic kidney disease and dialysis patients,^{20,21} as well as in patients without chronic kidney disease. This finding is not unexpected, as dosing of statins in chronic kidney disease and the general population is similar.^{22,23}

WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients with chronic kidney disease are at increased risk of cardiovascular disease
 Statins reduce cardiovascular mortality and all cause mortality in the general population
 The role of statins in chronic kidney disease is controversial

WHAT THIS STUDY ADDS

Statins reduce cardiovascular deaths in patients with chronic kidney disease by a similar rate to that seen in the general population
 The efficacy of statins in reducing all cause mortality in kidney disease patients and their role in primary prevention need to be established in ongoing trials
 Statins are safe as regards major side effects such as hepatotoxicity, rhabdomyolysis, and treatment withdrawal

The multivariate meta-regression model that explained most of the heterogeneity in the effect of statins compared with placebo was one that included the type of statin (largely explained by a single trial of cerivastatin), dose of statin, patient's age, baseline cholesterol concentration, and allocation concealment.

Comparison with other studies

We could not clearly confirm evidence of a renoprotective effect of statins in patients with pre-dialysis chronic kidney disease, as indicated by significantly lower values of 24 hour urinary protein excretion and no difference in creatinine clearance in the statin treated groups. Earlier reviews analysed the proportional reduction in proteinuria, but we analysed the end of treatment values of both treatment and placebo groups. We also identified a trend towards a protective effect of statins on acute renal allograft rejection, but this may have been limited by insufficient statistical power. Outcome reporting bias is a potential problem; less than a quarter of trials reported creatinine data and proteinuria. None of the available trials reported end stage renal disease or doubling of serum creatinine as study end points.

The beneficial effect of statins on cardiovascular end points and some evidence of renal benefit seen in our systematic review may be potentially explained by cholesterol dependent effects, cholesterol independent effects, or both. Statins may modulate cardiovascular risk by decreasing inflammation, enhancing endothelial function, inhibiting smooth muscle proliferation, exerting direct antithrombotic effects, and stabilising pre-existing atherosclerotic plaque.²⁴⁻²⁶ Statins have also recently been shown to ameliorate vascular calcification, which is an important problem in patients with chronic kidney disease.

Concerns have been expressed about an increased risk of side effects of statins in patients with chronic kidney disease.²⁷ In this analysis of more than 6500 such patients, we did not find statins to be associated with an increased incidence of abnormalities in liver function tests or raised serum creatinine phosphokinase concentrations compared with placebo.

Strengths and weaknesses

A strength of this study is that it is the first to assess cardiovascular, renal, and toxicity outcomes, providing a comprehensive systematic review of the benefits and harms of statins on the basis of a pre-specified detailed published protocol. Two independent investigators extracted and analysed data and assessed methodological quality. The possibility of publication bias was minimised by inclusion of both published and unpublished trials.

The main weakness of this study was the relative paucity of high quality randomised controlled trials. The vast majority of studies evaluated failed to specify whether randomisation allocation was concealed, outcome assessors were blinded, or data were analysed on an intention to treat basis. Many studies were small and often short in duration, and the results of our review were dominated by the results of three major trials.^{14w10 w42} Moreover, we found evidence of trial heterogeneity in some analyses. However, we have not been able to show any significant interaction in any analysis in which cumulative estimates were provided, and strong agreement exists between point estimates for individual outcomes in the separate subgroups of pre-dialysis, dialysis, and transplant patients.

Future research and ongoing trials

Our analysis confirmed the role of statins in secondary prevention in patients with chronic kidney disease. Trials of primary prevention with statins are ongoing in people with greater degrees of chronic kidney disease and lower levels of cardiovascular risk.^{19,28} Their combined results will help to resolve the question of whether higher concentrations of low density lipoprotein cholesterol are a cause of vascular disease in patients with chronic kidney disease.

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- Foley RN, Collins AJ. End-stage renal disease in the United States: an update from the United States renal data system. *J Am Soc Nephrol* 2007;18:2644-8.
- Ganesh S, Stack A, Levin N. Association of elevated serum PO(4), Ca x PO(4), and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 2001;12:2131-8.
- Mallamaci F, Zoccali C, Tripepi G, Fermo I, Benedetto FA, Cataliotti A, et al. Hyperhomocysteinemia predicts cardiovascular outcomes in hemodialysis patients. *Kidney Int* 2002;61:609-14.
- Jungers P, Massy ZA, Khoa TN, Fumeron C, Labrunie M, Lacour B, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. *Nephrol Dial Transplant* 1997;12:2597-602.

- 5 Rossouw JE, Lewis B, Rifkin BM. The value of lowering cholesterol after myocardial infarction. *N Engl J Med* 1990;323:1112-9.
- 6 Law MR, Wald NJ, Thompson SG. By how much and how quickly does reduction in serum cholesterol concentration lower risk of ischaemic heart disease? *BMJ* 1994;308:367-72.
- 7 Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD. Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 2003;63:793-808.
- 8 Seliger SL, Weiss NS, Gillen DL, Kestenbaum B, Ball A, Sherrard DJ, et al. HMG-CoA reductase inhibitors are associated with reduced mortality in end stage renal disease patients. *Kidney Int* 2002;61:297-304.
- 9 Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med* 2006;145:117-24.
- 10 Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol* 2006;17:2006-16.
- 11 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation classification, and stratification. 2000. www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm.
- 12 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials* 1986;7:177-88.
- 13 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-60.
- 14 Wanner C, Krane V, Marz W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med* 2005;353:238-48.
- 15 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian simvastatin survival study (4S). *Lancet* 1994;344:1383-9.
- 16 Kong SX, Crawford SY, Gandhi SK, Seeger JD, Schumock GT, Lam NP, et al. Efficacy of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors in the treatment of patients with hypercholesterolemia: a meta-analysis of clinical trials. *Clin Ther* 1997;19:778-97.
- 17 Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality: an overview of randomized trials. *JAMA* 1997;278:313-21.
- 18 Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 2003;326:1423.
- 19 United States Renal Data System. Mortality and cause of death. 2007. www.usrds.org/2007/ref/H_morte_07.pdf.
- 20 Massy ZA, Ma JZ, Louis TA, Kasiske BL. Lipid-lowering therapy in patients with renal disease. *Kidney Int* 1995;48:188-98.
- 21 Navaneethan SD, Shrivastava R. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev* 2004;(4):CD004289.
- 22 Stern RH, Yang BB, Horton M, Moore S, Abel RB, Olson SC. Renal dysfunction does not alter the pharmacokinetics or LDL-cholesterol reduction of atorvastatin. *J Clin Pharmacol* 1997;37:816-9.
- 23 Halstenson CE, Triscari J, DeVault A, Shapiro B, Keane W, Pan H. Single-dose pharmacokinetics of pravastatin and metabolites in patients with renal impairment. *J Clin Pharmacol* 1992;32:124-32.
- 24 Sotiriou CG, Cheng JW. Beneficial effects of statins in coronary artery disease—beyond lowering cholesterol. *Ann Pharmacother* 2000;34:1432-9.
- 25 Robinson JG, Smith B, Maheshwari N, Schrott H. Pleiotropic effects of statins: benefit beyond cholesterol reduction? A meta-regression analysis. *J Am Coll Cardiol* 2005;46:1855-62.
- 26 Kinlay S, Selwyn AP. Effects of statins on inflammation in patients with acute and chronic coronary syndromes. *Am J Cardiol* 2003;91:9-13B.
- 27 Sica DA, Gehr TW. 3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors and rhabdomyolysis: considerations in the renal failure patient. *Curr Opin Nephrol Hypertens* 2002;11:123-33.
- 28 Baigent C, Landry M. Study of heart and renal protection (SHARP). *Kidney Int* 2003;84:S207-10.

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Helicobacter pylori test and treat versus proton pump inhibitor in initial management of dyspepsia in primary care: multicentre randomised controlled trial (MRC-CUBE trial)

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ABSTRACT

Objective To determine the cost effectiveness of *Helicobacter pylori* “test and treat” compared with empirical acid suppression in the initial management of patients with dyspepsia in primary care.

Design Randomised controlled trial.

Setting 80 general practices in the United Kingdom.

Participants 699 patients aged 18-65 who presented to their general practitioner with epigastric pain, heartburn, or both without “alarm symptoms” for malignancy.

Intervention *H pylori* ¹³C urea breath test plus one week of eradication treatment if positive or proton pump inhibitor alone; subsequent management at general practitioner's discretion.

Main outcome measures Cost effectiveness in cost per quality adjusted life year (QALY) (EQ-5D) and effect on dyspeptic symptoms at one year measured with short form Leeds dyspepsia questionnaire.

Results 343 patients were randomised to testing for *H pylori*, and 100 were positive. The successful eradication rate was 78%. 356 patients received proton pump inhibitor for 28 days. At 12 months no significant

differences existed between the two groups in QALYs, costs, or dyspeptic symptoms. Minor reductions in costly resource use over the year in the test and treat group “paid back” the initial cost of the intervention.

Conclusions Test and treat and acid suppression are equally cost effective in the initial management of dyspepsia. Empirical acid suppression is an appropriate initial strategy. As costs are similar overall, general practitioners should discuss with patients at which point to consider *H pylori* testing.

Trial registration Current Controlled Trials ISRCTN87644265.

INTRODUCTION

The cost effectiveness of strategies for managing dyspepsia have been studied in several randomised controlled trials and summarised in a Cochrane review.¹ An economic model has suggested that testing for and treating *Helicobacter pylori* (“test and treat”) is cost effective, with an incremental cost effectiveness ratio of £63 (€83; \$124) per month free of symptoms over five years, compared with