Published in final edited form as:

Ann Intern Med. 2012 August 21; 157(4): 263–275. doi:10.7326/0003-4819-157-4-201208210-00007.

Benefits and harms of statin therapy for persons with chronic kidney disease: A systematic review and meta-analysis

Suetonia C Palmer, MBChB, PhD^{1,2}, Jonathan C Craig, MBChB, MM, MPH, PhD^{2,3}, Sankar D Navaneethan, MD, MPH^{2,4}, Marcello Tonelli, MD PhD^{2,5}, Fabio Pellegrini, MSc^{6,7}, and Giovanni FM Strippoli, MD, MM, MPH, PhD^{2,3,6,8,9}

¹Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand

²Cochrane Renal Group, Sydney, Australia ³School of Public Health, University of Sydney, Sydney, Australia ⁴Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, USA ⁵Division of Nephrology and Immunology, University of Alberta, Edmonton, Canada ⁶Consorzio Mario Negri Sud, S. Maria Imbaro, Italy ⁷Scientific Institute Casa Sollievo della Sofferenza, Italy ⁸Diavrum Scientific Medical Office, Lund, Sweden ⁹Department of Emergency and Organ Transplantation, University of Bari, Italy

Abstract

Background—Statins have uncertain benefits in chronic kidney disease (CKD) as individual trials may have insufficient power to determine whether treatment effects differ with severity of CKD.

Purpose—To summarize the benefits and harms of statin therapy for adults with CKD and examine whether effects of statins vary by kidney disease stage.

Data Sources—Cochrane and EMBASE databases (inception to February 2012).

Study Selection—Randomized trials comparing effects of statins with placebo, no treatment or another statin on mortality and cardiovascular outcomes.

Data Extraction—Two independent reviewers extracted data and assessed risk of bias.

Data Synthesis—Eighty trials ($n=51,099$) compared statin with placebo or no treatment. Treatment effects varied with stage of CKD. In persons not on dialysis, statins reduced all-cause (relative risk, 0.81, 95% confidence interval, 0.74-0.88) and cardiovascular (0.78, 0.68-0.89) mortality and cardiovascular events (0.76, 0.73-0.80) in moderate-high quality evidence. For persons on dialysis, statins had little or no effect on all-cause (0.96, 0.88-1.04) or cardiovascular (0.94, 0.82-1.07) mortality or cardiovascular events (0.95, 0.87-1.03) in moderate-high quality evidence. Effects of statins in kidney transplant recipients were uncertain. Statins had little or no effect on cancer, myalgia, liver function, or withdrawal from treatment, although adverse events were evaluated systematically in fewer than half of trials.

Corresponding author: Giovanni FM Strippoli, Department of Clinical Pharmacology and Epidemiology, Consorzio Mario Negri Sud, Via Nazionale 8/a, 66030, S Maria Imbaro, Italy (strippoli@negrisud.it and rs01@diavrum.com).

Authors' contributions:

Study concept and design: Palmer, Craig, Strippoli

Acquisition of data: Palmer, Craig, Navaneethan, Strippoli

Analysis and interpretation of the data: Palmer, Craig, Navaneethan, Tonelli, Pellegrini, Strippoli

Primary drafting of the manuscript: Palmer, Craig, Strippoli

Critical revision of the manuscript and redrafting for important intellectual content: Palmer, Craig, Navaneethan, Tonelli, Pellegrini, Strippoli

Statistical analysis: Palmer, Craig, Pellegrini, Strippoli

Limitations—Reliance on post hoc subgroup data for earlier stages of CKD and lack of data for primary and secondary prevention.

Conclusions—Statins lower mortality and cardiovascular events in persons with early stages of CKD, have little or no effect in persons on dialysis, and have uncertain effects in kidney transplant recipients.

Introduction

For persons with early stages of chronic kidney disease (CKD) not on dialysis, the absolute risk of cardiovascular events is similar to that of persons with established coronary artery disease(1), and for persons on dialysis the risk is 40-50 times higher than the general population(2). While statin therapy consistently reduces coronary events in the general population(3), the clinical benefits of lipid-lowering in persons with CKD are less certain(4-8). The benefits of statins are potentially greater in persons with CKD because of the substantially higher incidence of occlusive vascular disease. Conversely, statins may be less effective in CKD because atherosclerosis is a less frequent cause of cardiovascular events compared with sudden death, arrhythmia and heart failure(9, 10). The evidence that statins may have lower treatment efficacy in CKD was suggested by two large trials (4D and AURORA) in persons on hemodialysis that found no benefit of statins on mortality or cardiovascular events(7, 8). Fewer trial data have been available to evaluate treatment efficacy in people with milder CKD who are not on dialysis.

While an earlier meta-analysis found no differences in treatment effects based on severity of CKD(11), additional trials have since been reported, including the Study of Heart and Renal Protection (SHARP) (12), trials reporting data for persons with CKD not on dialysis (4, 6, 13-15), and the AURORA study in persons on dialysis(8). Considering the SHARP data, an advisory panel to the Food and Drug Administration (FDA) recently voted to recommend simvastatin and ezetimibe in earlier stages of CKD, but not in people on dialysis, citing insufficient evidence for prevention of major vascular events in the latter population(16); the FDA has subsequently not included chronic kidney disease as a specific indication for the drug (17).

In light of the recent availability of new data and high-profile treatment and policy uncertainty, we have conducted a systematic review of the benefits and harms of statin therapy in persons with CKD, specifically to address whether treatment effects differ depending on stage of CKD.

Methods

The present meta-analysis utilizes methods and definitions from an earlier meta-analysis(11) and followed published, peer-reviewed protocols(18-20).

Data Sources and Searches

We considered randomized trials in which statins were compared to placebo, no treatment, standard care, or another statin in which data for adults with CKD (any stage) were reported. We identified trials from an earlier meta-analysis published in 2008(11) and searched EMBASE and the Cochrane's Central Register of Controlled Trials (CENTRAL) and Renal Group's Specialized Register from inception to February 2012 without language restriction. Details of the search strategies are available from the authors by request.

Study Selection

Two reviewers independently screened the database search by title and abstract, then full text, to identify potentially eligible trials that fulfilled inclusion criteria. CKD was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) criteria(21) (**Appendix Table 1**; available at www.annals.org). We excluded studies with follow up less than eight weeks' duration as such studies would not permit detection of mortality or cardiovascular outcomes related to statin treatment(103).

Data Extraction and Quality Assessment

We extracted data for population characteristics, interventions, non-randomized co-interventions, and risk of bias according to standard criteria(104). We extracted data on the following outcomes: all-cause and cardiovascular mortality, major cardiovascular events, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, end-stage kidney disease, cancer, end of study estimated glomerular filtration rate and urine protein excretion rate in individuals not requiring dialysis, myalgia, elevated creatine kinase, abnormal liver function, withdrawal from treatment, and end of study serum lipid concentrations. Two or more authors independently evaluated the following risk of bias items based on standardized methods: sequence generation; allocation concealment; blinding; intention-to-treat analysis; completeness of outcome data; selective outcome reporting; and other threats to validity(104).

Data Synthesis and Statistical Analysis

For dichotomous outcomes, we calculated relative risks (RR) and 95% confidence intervals (CI). For continuous outcomes, we calculated mean differences (MD) with 95% CI. We then summarized effect estimates using the DerSimonian and Laird random effects model(105). Data for trials comparing two differing statin regimens could not be summarized due to insufficient extractable data. We assessed heterogeneity using the χ^2 (Cochran Q) statistic and the I^2 test. $P < 0.10$ indicated significant heterogeneity. Values of $I^2 < 25\%$, 25% to 50%, and 50% were considered to represent low, moderate, and large heterogeneity, respectively. We performed additional pre-specified subgroup analyses to explore potential sources of heterogeneity. We analyzed data for all outcomes within subgroups for CKD including separate categories for persons not on dialysis, persons on dialysis and kidney transplant recipients separately, and provided an overall summary treatment effect estimate when formal tests of interaction indicated no significant difference between subgroups. We used the standard continuity correction of 0.5 to cells when estimating summary effects for trials in which no events were reported in one arm. To assess potential bias from small study effects, we constructed funnel plots for the log risk ratio in individual studies against the standard error of the risk ratio and formally assessed for plot asymmetry using the Egger regression test(106). We conducted analyses using Comprehensive Meta-Analysis (Version 2, Biostat, Englewood, NJ, 2005) and macro routines in SAS language(107) (SAS Institute Inc., Cary, NC; Release 9.1, 2002-2003). Details of the SAS macro routine are available from the authors by request.

We summarized the quality of the evidence together with absolute treatment effects based on estimated baseline risks using Grading of Recommendations Assessment Development and Evaluation (GRADE) guidelines(108). We estimated 134 the absolute numbers of persons with CKD who had cardiovascular or adverse events avoided or incurred with statin therapy using the risk estimate (and 95% CI) obtained from the corresponding meta-analysis for the outcomes of all-cause and cardiovascular mortality, major cardiovascular events, and elevated creatine kinase together with the absolute population risk for persons with each stage of CKD (not on dialysis, on dialysis, transplant recipient) derived from previously published observational cohort studies(109-115).

Role of the funding source

No specific external funding source contributed to this work. The authors had full responsibility for data collection, data interpretation, and writing of the report. The first and last authors had full access to all the data and had the final responsibility to submit the paper for publication.

Results

Description of trials

We included 50 randomized trials that were reported in an earlier meta-analysis to July 2006(11). Electronic searches conducted in February 2012 identified 2580 additional citations (**Appendix Figure 1**; available at www.annals.org). Of these, we included 89 unique trials (95 comparisons) in 56,857 persons with CKD. **Appendix Table 2** (available at www.annals.org) provides full details of included trial acronyms.

Twelve trials provided data for 36,325 persons with CKD not on dialysis(4-6, 13-15, 60, 62, 70, 91, 100, 101). We included published data from SHARP for subgroups of persons on dialysis and persons not on dialysis separately for analyses of major cardiovascular events(12, 16). Seven trials or subgroups of trials were only available as conference proceedings(38, 75, 76, 83, 91, 95, 96), and three studies were only published as letters(22, 84, 97).

80 trials (86 comparisons) compared statin therapy against placebo or no treatment in 51,099 persons (**Appendix Table 3**; available at www.annals.org). Of these, 48 comparisons included 39,820 persons not on dialysis, 21 comparisons included 7982 persons on dialysis and 17 comparisons included 3297 kidney transplant recipients. Ten studies provided posthoc data for 30,897 persons not on dialysis(4-6, 13-15, 60, 62, 70, 91). Three studies enrolled 3203 persons with established acute(70) or stable coronary artery disease(4, 13) and who had CKD. Most trials (60 comparisons [70%]) evaluated statin doses equivalent to simvastatin 20 mg or less. Median follow up was six months (range 2 months to 5.5 years). Forty-five (52%; 49,035 persons) comparisons reported industry funding. Overall, nine trials evaluated statin therapy against the same statin or another statin among 5758 persons with CKD (**Appendix Table 3**; available at www.annals.org (94-102). A high proportion of these active comparator studies enrolled kidney transplant recipients (183 persons) and three reported funding from industry (100-102).

Risk of bias in individual trials

Risk of bias in trials comparing statin to placebo or no treatment control is summarized in **Figure 1**. Less than one-third of placebo or no treatment-controlled studies reported adequate sequence generation, allocation concealment, blinding of outcome assessment or completeness of outcome reporting, or provided analyses by intention-to-treat methods. 42 trials (53%) reported one or more other additional risks of bias including posthoc subgroup analysis, imbalance in participant characteristics at baseline, publication only in conference proceedings or letter format, insufficient extractable data (not included in meta-analyses), participant refusal for follow up, early termination, altering intervention after interim analyses, or allocating participants to treatment without a washout period for statin or related intervention. Two trials (SHARP and 4D) were at low risk of reporting bias for all the risks we assessed(7, 93). In the 9 trials comparing a statin versus statin, allocation concealment was unclear in all except 1 study(100), participants and investigators were blinded in 2 trials(101, 102), outcome assessment was blinded in 4 trials(98, 100-102), analyses were by intention to treat in 2 trials(100, 101), and completeness to follow up was adequate in 2 trials(100, 101).

Outcomes

Statin versus placebo or no treatment

All-cause and cardiovascular mortality: Among 32 comparisons in 45,154 persons, there was evidence of significantly different treatment effects on mortality according to the stage of CKD ($P = 0.009$) (**Figure 2; Table 1**) (109-115). In moderate-high quality evidence, statin treatment reduced all-cause mortality in persons not on dialysis (RR 0.81 [CI 0.74–0.88]), but had little or no effect in persons on dialysis (RR, 0.96 [CI 0.88–1.04]). Treatment effects for mortality were uncertain in kidney transplant recipients (RR 1.05 [CI 0.84–1.31]) in generally lower-quality evidence. Data for cardiovascular mortality were available in 27 comparisons among 35,417 persons. Statin therapy reduced cardiovascular mortality in persons not on dialysis (RR 0.78 [CI 0.68–0.89]), while having little or no effect in persons on dialysis (RR 0.94 [CI 0.82–1.07]) in moderate-quality evidence. The risk estimate in kidney transplant recipients suggested benefit, although the analysis included few events and confidence intervals were wide (0.68 [CI 0.45–1.02]). The formal test of interaction indicated no significant difference between treatment estimates from the subgroups based on stage of CKD ($P = 0.08$), although we were not able to include the data from SHARP(12) or the trial by Stegmayr *et al*(73) for persons not dialysis and those on dialysis separately in analyses of all-cause or cardiovascular mortality, as these data were not available.

Major cardiovascular events: Data for 7899 major cardiovascular events were available among 45,362 persons. Definitions of major cardiovascular events included in the analyses are described in **Appendix Table 4**(available at www.annals.org). We used data for the primary outcome of SHARP (major atherosclerotic events) in this meta-analysis (12). When we analyzed treatment effects according to stage of CKD, there was strong evidence that the treatment effects for statin therapy differed significantly between the subgroups ($P < 0.0001$) (**Figure 2**). Statin therapy prevented major cardiovascular events in persons with CKD not on dialysis (RR 0.76 [CI 0.73–0.80]) but had little or no effect in persons on dialysis (RR 0.95 [CI 0.87–1.03]) in moderate-high quality evidence. The effects of statin treatment in kidney transplant recipients were uncertain (RR 0.84 [CI 0.66–1.06]) in lower-quality evidence.

Myocardial infarction and stroke: Information was available for 983 fatal or nonfatal myocardial infarctions among 24,580 persons and 737 fatal or nonfatal strokes among 24,191 persons. Effect estimates for myocardial infarction were modified by stage of CKD ($P = 0.03$) (**Figure 2**). Overall, statin therapy reduced myocardial infarction in persons not on dialysis (RR 0.55 [CI 0.42–0.72]) but treatment effects were uncertain in persons on dialysis (RR 0.87 [CI 0.71–1.07]) and in kidney transplant recipients (RR 0.70 [CI 0.48–1.01]). There was no significant difference in treatment effects for stroke between stages of CKD ($P = 0.07$), due in part to imprecise effect estimates for persons on dialysis or after kidney transplantation (**Figure 2**). Statin reduced stroke in persons not on dialysis (RR 0.61 [CI 0.38–0.98]) but were uncertain in persons on dialysis (RR 1.30 [CI 0.79–2.11]) and kidney transplant recipients (RR 1.18 [0.62–2.24]). Overall, in all stages of CKD effects of statin therapy on stroke were uncertain (RR 0.86 [CI 0.62–1.20]).

Adverse events: Adverse events were evaluated and reported systematically in fewer than half of the comparisons (33 comparisons; 45,568 persons) (**Figure 3**)(4-8, 13, 15, 29, 39, 43, 46, 48, 53, 56, 58, 60-63, 66, 68, 70, 72, 74, 80, 82, 85, 93). Statins had little or no risks of adverse events including cancer (RR 0.96, CI 0.89–1.04), myalgia (RR 0.99, CI 0.94–1.04), elevated creatine kinase (RR 1.11, CI 0.80–1.56), abnormal liver function (RR 0.99, CI 0.70–1.40), or withdrawal from treatment (RR 1.07, CI 0.91–1.26) without significant heterogeneity in the analyses.

Lipid levels: Statin therapy lowered serum total cholesterol concentrations, low density lipoprotein concentrations, and serum triglycerides but not high-density lipoprotein cholesterol (**Appendix Table 5**; available at www.annals.org).

Proteinuria and glomerular filtration rate: Effects of statin therapy on creatinine clearance or glomerular filtration rate (in ml/min or ml/min/1.73 m²) were uncertain with significant heterogeneity in the analysis (**Appendix Table 5**; available at www.annals.org). Statin treatment reduced proteinuria with significant heterogeneity in the analysis (**Appendix Table 5**; available at www.annals.org).

Exploration of heterogeneity and Sensitivity Analyses: We explored potential sources of the heterogeneity observed in treatment effects for all-cause mortality, major cardiovascular events and serum cholesterol levels. In univariate meta-regression for all-cause mortality, stage of CKD explained 88% of the variation in treatment estimates between trials, as well as statin type (78%), estimated glomerular filtration rate (100%), baseline serum cholesterol (66%), and proportion of persons with diabetes (100%) (**Appendix Figure 2**; available at www.annals.org). For major cardiovascular events, stage of CKD explained 100% of the heterogeneity observed (**Appendix Figure 3**; available at www.annals.org). In subgroup analyses, when summary treatment estimates were calculated separately by stage of CKD, there was no important residual heterogeneity observed in treatment estimates for total or cardiovascular mortality, major cardiovascular events, myocardial infarction or stroke between trials (**Table 1**). On univariate metaregression, statin dose (13.0%), baseline cholesterol (26.9%) and allocation concealment (9.51%), but not stage of CKD, were responsible for heterogeneity in treatment effects on total cholesterol (**Appendix Table 6**; available at www.annals.org).

When we limited analyses to comparisons with follow up of 12 months or longer we observed similar treatment effects (data not shown). Given that SHARP evaluated the effect of combined simvastatin-ezetimibe therapy, rather than statin alone, we conducted analysis for major cardiovascular events with SHARP excluded and found similar differential treatment effects for persons not on dialysis (RR 0.74, CI 0.69–0.79) and dialysis (RR 0.96, CI 0.85–1.08) ($P < 0.001$). When we used major vascular event (16) (nonfatal myocardial infarction or any cardiac death, any stroke, or any arterial revascularization excluding dialysis procedures) rather than major atherosclerotic event (major vascular event minus non-coronary cardiac death and hemorrhagic stroke) from SHARP in the meta-analysis for major cardiovascular event, the overall risks were similar (not on dialysis; RR 0.77, CI 0.73–0.80, dialysis; RR 0.96, CI 0.89–1.02, kidney transplant recipients; RR 0.84, CI 0.66–1.06). Stage of CKD remained an effect modifier explaining 100% of the variance observed.

Discussion

Our results show that the benefits of statin therapy differ significantly depending on stage of CKD for mortality and cardiovascular outcomes. Statins (generally at doses equivalent to simvastatin 20mg) reduce all-cause and cardiovascular mortality and major cardiovascular events in persons not on dialysis by approximately one-fifth to one-quarter during approximately five years of treatment in moderate-high quality evidence. In absolute terms, 1000 persons with CKD not on dialysis need to receive statin treatment to prevent approximately 5 deaths each year. In persons not on dialysis, occlusive vascular events (fatal or nonfatal stroke or myocardial infarction) are proportionally reduced with statin therapy by 40-50%. By contrast, for people on dialysis statins have little or no effect on all-cause mortality, cardiovascular mortality, and major cardiovascular events (including myocardial infarction and stroke) in moderate-high quality evidence, despite lowering of serum cholesterol levels (40 mg/dl [1.0 mmol/l]). Evidence for statin treatment in kidney transplant

recipients is sparse and uncertain. Overall, differences in treatment effects of statins on mortality and major cardiovascular events in individual trials are largely or entirely explained by stage of CKD. Overall, statins have little or no effect on cancer incidence, myalgia, elevated creatine kinase, or abnormal liver function or treatment withdrawal compared to placebo in lower-quality evidence hampered by lack of systematic reporting of adverse events in over half of trials. Insufficient direct comparisons were available to draw conclusions on the efficacy of different higher versus lower doses of an individual statin, or of one statin versus another. Treatment effects for statins alone are similar to combined therapy with statin plus ezetimibe.

Interventions including statins, angiotensin-converting enzyme inhibitors, and beta blockers, which clearly prevent adverse cardiovascular events in general populations, have not been proven to improve cardiovascular or mortality outcomes in persons with advanced CKD(116). Few randomized trials evaluate cardioprotective drugs in persons with CKD (who are often systematically excluded), and the quality and coverage of evidence on which to guide decision-making in this population is suboptimal(117) despite a persistently high annual mortality(10). Benefits of statins in other populations (primary care, hypertension, diabetes, or existing cardiovascular disease) may not be generalizable to persons who have CKD as the pathobiology of cardiovascular disease is dominated by vascular calcification, cardiac hypertrophy, and arterial stiffening(118). Consistent with this hypothesis, trials of statin therapy in dialysis have been negative(7, 8), although the relative overall paucity of statin trials in earlier stages of CKD has led to combining outcomes for persons with different stages of CKD (dialysis and not on dialysis) to provide summary estimates of effect(11, 12). This approach may be unreliable for both groups. The validity of negative findings in statin trials in dialysis has also been questioned based on concerns that such trials may have had insufficient statistical power, due to lower than expected event rates and primary composite outcomes that include non-atherosclerotic events which are potentially unmodified by statin treatment(119). To address the persistent uncertainties about statin effects across the spectrum of CKD for patients, clinicians and policy-makers, this meta-analysis incorporates recent published trial data for statin therapy in over 50,000 individuals to allow sufficient power to quantify treatment effects for statins based on stage of CKD.

The proportional reductions in major cardiovascular and mortality outcomes and serum cholesterol in trials of CKD (predialysis) with statin treatment are similar to or larger than those observed in trials in other at-risk populations(3). When baseline risk of disease is accounted for, statin therapy over 5 years prevents approximately 25 individuals with CKD experiencing a major cardiovascular event per 1000 treated, which is similar to the benefit observed in broader populations with existing coronary heart disease(3).

The finding that statin therapy does not clearly reduce major cardiovascular events in people on dialysis appears to contradict the findings of SHARP, the recent and much-anticipated large trial of combined simvastatin and ezetimibe in over 9000 individuals with a broad range of kidney function including those on dialysis. SHARP investigators concluded that, after nearly five years of treatment, major atherosclerotic events are safely reduced in a wide range of patients with advanced CKD including persons requiring dialysis at baseline. In SHARP, analyses of the primary endpoint (major atherosclerotic events, defined as coronary death, myocardial infarction, ischemic stroke, or any revascularization procedure) were conducted separately in dialysis and non-dialysis patients, and a test for interaction did not indicate that proportional treatment effects were statistically different between the two different populations although it was acknowledged that the trial was underpowered for such an analysis(16). While no statistical difference (at the $P<0.05$ level) was observed for treatment effects in each population (dialysis or not), point estimates for major cardiovascular events for the predialysis and dialysis populations in SHARP were

statistically similar to summary effects observed in the present meta-analysis, which finds (with more events) that stage of CKD significantly modifies treatment efficacy. The present data are also consistent with earlier trials (4D(7) and AURORA(8)) finding no treatment benefit for composite cardiovascular outcomes in the dialysis population and that treatment benefits of statins for dialysis patients are likely to be small at best. Notably, our sensitivity analysis excluding SHARP from summary estimates for major cardiovascular events demonstrated similar and significant differences in treatment efficacy based on category of kidney disease, suggesting that even without SHARP data, the present findings are robust.

The choice of endpoint has been previously mooted as a potential reason for negative trials in dialysis(119), as primary outcome events in the 4D(7) and AURORA(8) trials may have included a smaller proportion of modifiable vascular events (dominated by vascular deaths) whereas SHARP events were predominantly non-fatal atherosclerotic events (stroke or myocardial infarction), and over half were revascularization procedures. Although this is plausible, the current analysis suggests otherwise. Even outcomes that are clearly related to atherosclerotic occlusion (myocardial infarction and stroke) were not clearly reduced by statin therapy in dialysis patients. However, relatively fewer of these events were available in the current meta-analysis, which may have reduced the power of the analyses to find a difference between treatment groups based on stage of CKD.

The present meta-analyses reminds us again that modification of a surrogate marker, in this case cholesterol, in people with advanced CKD does not necessarily reduce disease burden(120, 121). In the dialysis population, lowering serum cholesterol by proportions equivalent to that achieved in trials in the general population and in people with earlier stages of CKD has little or no effect on cardiovascular outcomes, as might be hoped. Notably, in the four trials in dialysis that reported major cardiovascular events, baseline serum cholesterol was generally lower (178 mg/dl [4.6 mmol/l]), although meta-regression could not be performed in these trials to evaluate whether serum cholesterol modified treatment effects of statins in this population. Nevertheless, in a large trial of rosuvastatin (JUPITER) in apparently healthy men and women with LDL cholesterol levels below 130 mg/dl [3.4 mmol/l](122), statin treatment nearly halved the risk of major cardiovascular events, suggesting that relatively lower baseline cholesterol levels in people on dialysis does not explain the reduced benefit from statins in the dialysis population.

Our study does have potential limitations. First, data for treatment effects in people with earlier stages of CKD not on dialysis were frequently sourced from reported posthoc analyses of larger trials, which may be less reliable(123). Second, 354 meta-regression analyses to determine the effects of baseline cholesterol on treatment effects in trials in dialysis were not possible due to insufficient trial-level data. Third, we were not able to analyse the relationship between serum cholesterol lowering and treatment effects (to report risk reduction per unit change in serum cholesterol), as trials that general reported the change in serum cholesterol with treatment did not report clinical outcome data and *vice versa*. Finally, we could not analyze the relative benefits of statin therapy in the primary prevention of cardiovascular disease as compared to secondary prevention as too few trials provided sufficient data in these specific populations.

In conclusion, persons with early stages of CKD have an estimated 10-year risk of cardiovascular disease of 20% or more and experience absolute benefits from statin therapy approximately equivalent to persons with existing coronary artery disease. Statin therapy has little or no effect in people on dialysis. Although it is unclear whether statins should be discontinued in patients initiating dialysis, the benefits in this population are likely to be small at best. Evidence for statin therapy in kidney transplant recipients is sparse and uncertain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Potential conflicts of interest:

No specific external funding was received for this project. Dr Palmer received support from an unrestricted Amgen Dompé Consorzio Mario Negri Fellowship. Professor Craig was a member of the steering committee for the Study of Heart and Renal Protection (SHARP)

Funding

None

References

1. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998; 32(5 Suppl 3):S112–9. [PubMed: 9820470]
2. de Zager DJ, Grootendorst DC, Jager KJ, van Dijk PC, Tomas LM, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA.* 2009; 302(16):1782–9. [PubMed: 19861670]
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005; 366(9493):1267–78. [PubMed: 16214597]
4. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. *Am J Kidney Dis.* 2007; 49(3):373–82. [PubMed: 17336698]
5. Kendrick J, Shlipak MG, Targher G, Cook T, Lindenfeld J, Chonchol M. Effect of lovastatin on primary prevention of cardiovascular events in mild CKD and kidney function loss: a post hoc analysis of the Air Force/Texas Coronary Atherosclerosis Prevention Study. *Am J Kidney Dis.* 2010; 55(1):42–9. [PubMed: 19932541]
6. Ridker PM, MacFadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention-an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol.* 2010; 55(12):1266–73. [PubMed: 20206456]
7. Wanner C, Krane V, März W, Olschewski M, Mann JF, Ruf G, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *New Engl J Med.* 2005; 353(3):238–48. [PubMed: 16034009]
8. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *New Engl J Med.* 2009; 360(14):1395–407. [PubMed: 19332456]
9. Green D, Roberts PR, New DI, Kalra PA. Sudden cardiac death in hemodialysis patients: an in-depth review. *Am J Kidney Dis.* 2011; 57(6):921–9. [PubMed: 21496983]
10. Greene DS, Barbhuiya RH. Clinical pharmacokinetics of nefazodone. *Clinical Pharmacokinetics.* 1997; 33(4):260–75. [Review] [51 refs]. [PubMed: 9342502]
11. 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(7645):645–51. [PubMed: 18299289]
12. Baigent C, Landray M, Reith C, Emberson J, Wheeler DC, Tomson CR, 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(9784):2181–92. [PubMed: 21663949]

13. Koren MJ, Davidson MH, Wilson DJ, Fayyad RS, Zuckerman A, Reed DP, et al. Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. *Am J Kidney Dis.* 2009; 53(5):741–50. [PubMed: 19216014]
14. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis.* 2009; 54(5):810–9. [PubMed: 19540640]
15. Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y, et al. Pravastatin and cardiovascular risk in moderate chronic kidney disease. *Atherosclerosis.* 2009; 206(2):512–7. [PubMed: 19423108]
16. Alpert JE, Uebelacker LA, McLean NE, Nierenberg AA, Pava JA, Worthington JJ III, et al. Social phobia, avoidant personality disorder and atypical depression: co-occurrence and clinical implications. *Psychological Medicine.* 1997; 27(3):627–33. [PubMed: 9153683]
17. Toyoda K, Matsui H, Shoda T, Uneyama C, Takada K, Takahashi M. Assessment of the carcinogenicity of stevioside in F344 rats. *Food & Chemical Toxicology.* 1997; 35(6):597–603. [PubMed: 9225018]
18. Navaneethan SD, Nigwekar SU, Perkovic V, Johnson DW, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for dialysis patients. *Cochrane Database Syst Rev.* 2009; (3):CD004289.
19. Navaneethan SD, Pansini F, Perkovic V, Manno C, Pellegrini F, Johnson DW, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev.* 2009; (2):CD007784. [PubMed: 19370693]
20. Navaneethan SD, Perkovic V, Johnson DW, Nigwekar SU, Craig JC, Strippoli GF. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. *Cochrane Database Syst Rev.* 2009; (2):CD005019. [PubMed: 19370615]
21. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002; 39(2 Suppl 1):S1–266. [PubMed: 11904577]
22. Scanferla F, Toffoletto PP, Roncali D, Bazzato G. Associated effect of hepatic hydroxymethylglutaryl coenzyme A reductase + angiotensin converting enzyme inhibitors on the progression of renal failure in hypertensive subjects. *Am J Hypertens.* 1991; 4(10 (Pt 1)):868–74. [PubMed: 1747221]
23. Hommel E, Andersen P, Gall MA, Nielsen F, Jensen B, Rossing P, et al. Plasma lipoproteins and renal function during simvastatin treatment in diabetic nephropathy. *Diabetologia.* 1992; 35(5):447–51. [PubMed: 1521727]
24. Mori Y, Tsuruoka A. Effect of pravastatin on microalbuminuria in patients with non-insulin-dependent diabetes mellitus. *Journal of the Japan Diabetes Society.* 1992; 35(3):265–8.
25. Martinez Hernandez BE, Persaud JW, Varghese Z, Moorhead JF. Low-dose simvastatin is safe in hyperlipidaemic renal transplant patients. *Nephrol Dial Transplant.* 1993; 8(7):637–41. [PubMed: 8396749]
26. Nielsen S, Schmitz O, Moller N, Porsken N, Klausen IC, Alberti KG, et al. Renal function and insulin sensitivity during simvastatin treatment in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia.* 1993; 36(10):1079–86. [PubMed: 8243858]
27. Thomas ME, Harris KP, Ramaswamy C, Hattersley JM, Wheeler DC, Varghese Z, et al. Simvastatin therapy for hypercholesterolemic patients with nephrotic syndrome or significant proteinuria. *Kidney Int.* 1993; 44(5):1124–9. [PubMed: 8264145]
28. Aranda Arcas JL, Sanchez R, Guijarro C, Araque A, Pulido F, Praga M, et al. [Effect of pravastatin on hypercholesterolemia associated with proteinuria]. [Spanish]. *Anales de Medicina Interna.* 1994; 11(11):523–7. [PubMed: 7654898]
29. Arnadottir M, Eriksson LO, Germershausen JJ, Thysell H. Low-dose simvastatin is a well-tolerated and efficacious cholesterol-lowering agent in ciclosporin-treated kidney transplant recipients: double-blind, randomized, placebo-controlled study in 40 patients. *Nephron.* 1994; 68(1):57–62. [PubMed: 7991041]
30. Lam KS, Cheng IK, Janus ED, Pang RW. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. *Diabetologia.* 1995; 38(5):604–9. [PubMed: 7489845]

31. Lintott CJ, Scott RS, Bremer JM, Shand BI. Fluvastatin for dyslipoproteinemia, with or without concomitant chronic renal insufficiency. *Am J Cardiol.* 1995; 76(2):97A–101A. [PubMed: 7793418]
32. Zhang A, Vertommen J, Van Gaal L, De Leeuw I. Effects of pravastatin on lipid levels, in vitro oxidizability of non-HDL lipoproteins and microalbuminuria in IDDM patients. *Diabetes Res Clin Pract.* 1995; 29(3):189–94. [PubMed: 8591712]
33. Katznelson S, Wilkinson AH, Kobashigawa JA, Wang XM, Chia D, Ozawa M, et al. The effect of pravastatin on acute rejection after kidney transplantation--a pilot study. *Transplantation.* 1996; 61(10):1469–74. [PubMed: 8633373]
34. Rayner BL, Byrne MJ, van Zyl-Smit R. A prospective clinical trial comparing the treatment of idiopathic membranous nephropathy and nephrotic syndrome with simvastatin and diet, versus diet alone. *Clin Nephrol.* 1996; 46(4):219–24. [PubMed: 8905205]
35. Paczek L, Bill M, Wyzgal J, Gaciong Z, Gradowska L, Juskowa J, et al. The effect of hypolipidemia treatment on the function of kidney transplanted from cadavers. *Polskie Archiwum Medycyny Wewnetznej.* 1997; 97(2):144–56.
36. Walker RJ, Sutherland WH, Walker HL, MaMahon S, Robson RA. Effect of treatment with simvastatin on serum cholesteryl ester transfer in patients on dialysis. PERFECT Study Collaborative Group. *Nephrol Dial Transplant.* 1997; 12(1):87–92. [PubMed: 9027779]
37. Tonolo G, Ciccarese M, Brizzi P, Puddu L, Secchi G, Calvia P, et al. Reduction of albumin excretion rate in normotensive microalbuminuric type 2 diabetic patients during long-term simvastatin treatment. *Diabetes Care.* 1997; 20(12):1891–5. [PubMed: 9405913]
38. Velickovic-Radovanovic R, Avramovic M, Malobabic Z, Djordjevic V, Kostic S, Mitic B. Therapeutic effects of simvastatin on hyperlipidemia in uraemic patients on CAPD [abstract]. *Nephrol Dial Transplant.* 1997; 12(9):A187.
39. Melchor JL, Gracida C. Treatment of hypercholesterolemia with fluvastatin in kidney transplant patients. *Transplant Proceed.* 1998; 30(5):2054.
40. Imai Y, Suzuki H, Saito T, Tsuji I, Abe K, Saruta T. The effect of pravastatin on renal function and lipid metabolism in patients with renal dysfunction with hypertension and hyperlipidemia. Pravastatin and Renal Function Research Group. *Clin Exp Hypertens.* 1999; 21(8):1345–55. [PubMed: 10574417]
41. Lepre F, Rigby R, Hawley C, Saltissi D, Brown A, Walsh Z. A double-blind placebo controlled trial of simvastatin for the treatment of dyslipidaemia in renal allograft recipients. *Clin Transplant.* 1999; 13(6):520–5. [PubMed: 10617243]
42. Buemi M, Allegra A, Corica F, Aloisi C, Giacobbe M, Pettinato G, et al. Effect of fluvastatin on proteinuria in patients with immunoglobulin A nephropathy. *Clin Pharmacol Ther.* 2000; 67(4):427–31. [PubMed: 10801253]
43. Fried LF, Forrest KY, Ellis D, Chang Y, Silvers N, Orchard TJ. Lipid modulation in insulin-dependent diabetes mellitus: effect on microvascular outcomes. *J Diabetes Complications.* 2001; 15(3):113–9. [PubMed: 11358679]
44. Hausberg M, Kosch M, Stam F, Heidenreich S, Kisters K, Rahn KH, et al. Effect of fluvastatin on endothelium-dependent brachial artery vasodilation in patients after renal transplantation. *Kidney Int.* 2001; 59(4):1473–9. [PubMed: 11260410]
45. Kasiske BL, Heim-Duthoy KL, Singer GG, Watschinger B, Germain MJ, Bastani B. The effects of lipid-lowering agents on acute renal allograft rejection. *Transplantation.* 2001; 72(2):223–7. [PubMed: 11477342]
46. Renders L, Mayer-Kadner I, Koch C. Efficacy and drug interactions of the new HMG-CoA reductase inhibitors cerivastatin and atorvastatin in CsA-treated renal transplant recipients. *Nephrol Dial Transplant.* 2001; 16(1):141–6. [PubMed: 11209008]
47. Sahu K, Sharma R, Gupta A. Effect of lovastatin, an HMG CoA reductase inhibitor, on acute renal allograft rejection. *Clin Transplant.* 2001; 15(3):173–5. [PubMed: 11389707]
48. Santos AF, Keitel E, Bittar AE, Neumann J, Fuchs FD, Goldani JC, et al. Safety and efficacy of simvastatin for hyperlipidemia in renal transplant recipients: a double-blind, randomized, placebo-controlled study. *Transplant Proceed.* 2001; 33(1-2):1194–5.

49. Holdaas H, Jardine AG, Wheeler DC, Brekke IB, Conlon PJ, Fellstrom B, et al. Effect of fluvastatin on acute renal allograft rejection: a randomized multicenter trial. *Kidney Int.* 2001; 60:1990–7. [PubMed: 11703619]
50. Chang JW, Yang WS, Min WK, Lee SK, Park JS, Kim SB. Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients. *Am J Kidney Dis.* 2002; 39(6):1213–7. [PubMed: 12046033]
51. Cofan F, Zambon D, Laguna JC, Casals E, Ros E, Cofan M, et al. Pravastatin improves low-density lipoprotein oxidation in renal transplantation. *Transplant Proceed.* 2002; 34(1):389–91.
52. Gheith OA, Sobh MA, Mohamed KE, El Baz M, El Hussein F, Gazarin SS, et al. Impact of treatment of dyslipidemia on renal function, fat deposits and scarring in patients with persistent nephrotic syndrome. *Nephron.* 2002; 91(4):612–9. [PubMed: 12138263]
53. Harris KP, Wheeler DC, Chong CC. Atorvastatin in CAPD Study Investigators. Continuous ambulatory peritoneal dialysis. A placebo controlled trial examining atorvastatin in dyslipidemic patients undergoing CAPD. *Kidney Int.* 2002; 61(4):1469–74. [PubMed: 11918754]
54. Ichihara A, Hayashi M, Ryuzaki M, Handa M, Furukawa T, Saruta T. Fluvastatin prevents development of arterial stiffness in haemodialysis patients with type 2 diabetes mellitus. *Nephrol Dial Transplant.* 2002; 17(8):1513–7. [PubMed: 12147804]
55. Nakamura T, Ushiyama C, Hirokawa K, Osada S, Inoue T, Shimada N, et al. Effect of cerivastatin on proteinuria and urinary podocytes in patients with chronic glomerulonephritis. *Nephrol Dial Transplant.* 2002; 17(5):798–802. [PubMed: 11981066]
56. Saltissi D, Morgan C, Rigby RJ, Westhuyzen J. Safety and efficacy of simvastatin in hypercholesterolemic patients undergoing chronic renal dialysis. *Am J Kidney Dis.* 2002; 39(2):283–90. [PubMed: 11840368]
57. Samuelsson O, Attman PO, Knight-Gibson C, Mulec H, Weiss L, Alaupovic P. Fluvastatin improves lipid abnormalities in patients with moderate to advanced chronic renal insufficiency. *Am J Kidney Dis.* 2002; 39(1):67–75. [PubMed: 11774104]
58. Holdaas H, Fellstrom B, Jardine AG, Holme I, Nyberg G, Fauchald P, et al. Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. *Lancet.* 2003; 361(9374):2024–31. [PubMed: 12814712]
59. Bianchi S, Bigazzi R, Caiazza A, Campese VM. A controlled, prospective study of the effects of atorvastatin on proteinuria and progression of kidney disease. *Am J Kidney Dis.* 2003; 41(3):565–70. [PubMed: 12612979]
60. Collins R, Armitage J, Parish S, Sleight P, Peto R. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet.* 2003; 361(9374):2005–16. [PubMed: 12814710]
61. Lins RL, Matthys KE, Billiouw JM, Dratwa M, Dupont P, Lameire Nh, et al. Lipid and apoprotein changes during atorvastatin up-titration in hemodialysis patients with hypercholesterolemia: a placebo-controlled study. *Clin Nephrol.* 2004; 62(4):287–94. [PubMed: 15524059]
62. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. *Circulation.* 2004; 110(12):1557–63. [PubMed: 15364796]
63. Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation.* 2004; 110(18):2809–16. [PubMed: 15492322]
64. Vernaglion L, Cristofano C, Muscogiuri P, Chimienti S. Does atorvastatin influence serum C-reactive protein levels in patients on long-term hemodialysis? *Am J Kidney Dis.* 2004; 43(3):471–8. [PubMed: 14981605]
65. Yasuda G, Kuji T, Hasegawa K, Ogawa N, Shimura G, Ando D, et al. Safety and efficacy of fluvastatin in hyperlipidemic patients with chronic renal disease. *Ren Fail.* 2004; 26(4):411–8. [PubMed: 15462110]
66. Di Lullo L, Addesse R, Comegna C, Firmi G, Galderisi C, Iannacci GR, et al. Effects of fluvastatin treatment on lipid profile, C-reactive protein trend, and renal function in dyslipidemic patients with chronic renal failure. *Adv Ther.* 2005; 22(6):601–12. [PubMed: 16510377]

67. Diepeveen SH, Verhoeven GH, van der Palen J, Dikkeschei LD, Denmacker PN, Kolsters G, et al. Effects of atorvastatin and vitamin E on lipoproteins and oxidative stress in dialysis patients: a randomised-controlled trial. *J Intern Med.* 2005; 257(4):438–45. [PubMed: 15836660]
68. Dornbrook-Lavender KA, Joy MS, Denu-Ciocca CJ, Chin H, Hogan SL, Pieper JA. Effects of atorvastatin on low-density lipoprotein cholesterol phenotype and C-reactive protein levels in patients undergoing long-term dialysis. *Pharmacotherapy.* 2005; 25(3):335–44. [PubMed: 15843280]
69. Lee TM, Lin MS, Tsai CH, Chang NC. Add-on and withdrawal effect of pravastatin on proteinuria in hypertensive patients treated with AT1 receptor blockers. *Kidney Int.* 2005; 68:779–87. [PubMed: 16014056]
70. Lemos PA, Serruys PW, de Feyter P, Mercado NF, Goedhart D, Saia F, et al. Long-term fluvastatin reduces the hazardous effect of renal impairment on four-year atherosclerotic outcomes (a LIPS substudy). *Am J Cardiol.* 2005; 95(4):445–51. [PubMed: 15695126]
71. Nakamura T, Sugaya T, Kawagoe Y, Ueda Y, Osada S, Koide H. Effect of pitavastatin on urinary liver-type fatty acid-binding protein levels in patients with early diabetic nephropathy. *Diabetes Care.* 2005; 28(11):2728–32. [PubMed: 16249547]
72. Verma A, Ranganna KM, Reddy RS, Verma M, Gordon NF. Effect of rosuvastatin on C-reactive protein and renal function in patients with chronic kidney disease. *Am J Cardiol.* 2005; 96(9): 1290–2. [PubMed: 16253600]
73. Stegmayr BG, Brännström M, Bucht S, Crougneau V, Dimeny E, Ekspong A, et al. Low-dose atorvastatin in severe chronic kidney disease patients: a randomized, controlled endpoint study. *Scand J Urol Nephrol.* 2005; 39(6):489–97. [PubMed: 18161210]
74. Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *Am J Kidney Dis.* 2005; 45(3):473–84. [PubMed: 15754269]
75. Vareesangthip K, Laouthaiwattana P, Hanlakorn P, Suwannaton L, Larprakitachorn R, Chuawattana D, et al. Effects of simvastatin on the kinetics of erythrocyte sodium lithium countertransport and C-reactive protein in hemodialysis patients [abstract no: TH-PO726]. *J Am Soc Nephrol.* 2005; 16:276A.
76. Ahmadi FI, Eslami K, Maziar S, Lessan-Pezeshki M, Khatami MR, Mahdavi-mazdeh M, et al. Effect of lovastatin on high-sensitivity C-reactive protein and hemoglobin in hemodialysis patients [abstract no: SP637]. *Nephrol Dial Transplant.* 2006; 21(Suppl 4):iv229.
77. Goicoechea M, De Vinuesa SG, Lahera V, Cachofeiro V, Gomez-Campdera F, Vega A, et al. Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease. *J Am Soc Nephrol.* 2006; 17(Suppl 3):S231–S5. [PubMed: 17130267]
78. Nakamura T, Sugaya T, Kawagoe Y, Suzuki T, Inoue T, Node K. Effect of pitavastatin on urinary liver-type fatty-acid-binding protein in patients with nondiabetic mild chronic kidney disease. *Am J Nephrol.* 2006; 26(1):82–6. [PubMed: 16534182]
79. Panichi V, Paoletti S, Mantuano E, Manca-Rizza G, Filippi C, Santi S, et al. In vivo and in vitro effects of simvastatin on inflammatory markers in pre-dialysis patients. *Nephrol Dial Transplant.* 2006; 21(2):337–44. [PubMed: 16249194]
80. Dummer CD, Thome FS, Zingano B, Lindoso A, Veronese FV. Acute effect of simvastatin on inflammation and oxidative stress in chronic kidney disease. *J Nephrol.* 2008; 21(6):900–8. [PubMed: 19034875]
81. Sawara Y, Takei T, Uchida K, Ogawa T, Yoshida T, Tsuchiya K, et al. Effects of lipid-lowering therapy with rosuvastatin on atherosclerotic burden in patients with chronic kidney disease. *Intern Med.* 2008; 47(17):1505–10. [PubMed: 18758125]
82. Seron D, Oppenheimer F, Pallardo LM, Lauzurica R, Errasti P, Gomez-Huertas E, et al. Fluvastatin in the prevention of renal transplant vasculopathy: results of a prospective, randomized, double-blind, placebo-controlled trial. *Transplantation.* 2008; 86(1):82–7. [PubMed: 18622282]
83. Tokunaga M, Tamura M, Kabashima N, Serino R, Shibata T, Matsumoto M, et al. Beneficial effects of pitavastatin on albuminuria and renal function in essential hypertensive patients with

- chronic kidney disease [abstract no: TH-PO875]. *J Am Soc Nephrol*. 2008; 19 (Abstracts Issue): 307A.
84. Tse KC, Yung S, Tang CS, Tam S, Lai KN, Chan TM. Atorvastatin at conventional dose did not reduce C-reactive protein in patients on peritoneal dialysis. *J Nephrol*. 2008; 21(3):283. [PubMed: 18587714]
 85. Burmeister JE, Miltersteiner DR, Campos BM. Rosuvastatin in hemodialysis: short-term effects on lipids and C-reactive protein. *J Nephrol*. 2009; 22(1):83–9. [PubMed: 19229822]
 86. Sharif A, Ravindran V, Moore R, Dunseath G, Luzio S, Owens D, et al. The effect of rosuvastatin on insulin sensitivity and pancreatic beta-cell function in nondiabetic renal transplant recipients. *Am J Transplant*. 2009; 9(6):1439–45. [PubMed: 19459810]
 87. Ruggenti P, Perna A, Tonelli M, Loriga G, Motterlini N, Rubis N, et al. Effects of add-on fluvastatin therapy in patients with chronic proteinuric nephropathy on dual renin- angiotensin system blockade: The ESPLANADE trial. *Clin J Am Soc Nephrol*. 2010; 5(11):1928–38. [PubMed: 20671225]
 88. Fassett RG, Coombes JS, Packham D, Fairley KF, Kincaid-Smith P. Effect of pravastatin on kidney function and urinary protein excretion in autosomal dominant polycystic kidney disease. *Scand J Urol Nephrol*. 2010; 44(1):56–61. [PubMed: 20034362]
 89. Fassett RG, Robertson IK, Ball MJ, Geraghty DP, Coombes JS. Effect of atorvastatin on kidney function in chronic kidney disease: A randomised double-blind placebo-controlled trial. *Atherosclerosis*. 2010; 213(1):218–24. [PubMed: 20810109]
 90. Renke M, Tylicki L, Rutkowski P, Neuwelt A, Larczynski W, Zietkiewicz M, et al. Atorvastatin improves tubular status in non-diabetic patients with chronic kidney disease - placebo controlled, randomized, cross-over study. *Acta Biochimica Polonica*. 2010; 57(4):547–52. [PubMed: 21079818]
 91. Gupta AK, Chang CL, Dahlof B, Poulter NR, Sever PS. Cardiovascular and all-cause mortality outcomes among hypertensive patients with moderate renal dysfunction in the ASCOT-LLA, and its extended follow-up. *J Hum Hypertens*. 2011; 25(10):633–4.
 92. Han SH, Kang EW, Yoon SJ, Yoon HS, Lee HC, Yoo TH, et al. Combined vascular effects of HMG-CoA reductase inhibitor and angiotensin receptor blocker in non-diabetic patients undergoing peritoneal dialysis. *Nephrol Dial Transplant*. 2011; 26(11):3722–8. [PubMed: 21385862]
 93. Baigent C, Landray MJ, 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(9784):2181–92. [PubMed: 21663949]
 94. Castela AM, Grino JM, Andres E, Gilvernet S, Seron D, Castineiras MJ, et al. HMGCoA reductase inhibitors lovastatin and simvastatin in the treatment of hypercholesterolemia after renal transplantation. *Transplant Proceed*. 1993; 25(1 Pt 2):1043–6.
 95. Raiola P, Manzo M, Saggese A. Comparison of atorvastatin(ATV) with fluvastatin(FLV) in renal transplant patients with dyslipoproteinemia [abstract]. *J Am Soc Nephrol*. 1998; 9:693A. Program & Abstracts.
 96. Vergoulas G, Miserlis G, Gakis D, Imvrios G, Papagiannis A, Papanikolaou V, et al. Lovastatin (l) versus fluvastatin (f) in the treatment of hypercholesterolemic (hch) renal transplant recipients (rtr) [abstract]. *Nephrol Dial Transplant*. 1999; 14(9):A312.
 97. Celik A, Unsal A, Mutaf I, Habif S, Ok E, Bayindir O. Which dosage of simvastatin in renal transplant patients? *Nephron*. 2000; 84(1):81–2. [PubMed: 10644914]
 98. Tuncer M, Suleymanlar G, Ersoy FF, Yakupoglu G. Comparison of the effects of simvastatin and pravastatin on acute rejection episodes in renal transplant patients. *Transplant Proceed*. 2000; 32(3):622–5.
 99. van den Akker JM, Bredie SJ, Diepenveen SH, van Tits LJ, Stalenhoef AF, van Leusen R. Atorvastatin and simvastatin in patients on hemodialysis: effects on lipoproteins, C-reactive protein and in vivo oxidized LDL. *J Nephrol*. 2003; 16(2):238–44. [PubMed: 12768071]
 100. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the

- IDEAL study: a randomized controlled trial. *JAMA*. 2005; 294(19):2437–45. [PubMed: 16287954]
101. Shepherd J, Kastelein JJ, Bittner V, Deedwania P, Breazna A, Dobson S, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. *J Am Coll Cardiol*. 2008; 51(15):1448–54. [PubMed: 18402899]
 102. Rutter MK, Prais HR, Charlton-Menys V, Gittins M, Roberts C, Davies RR, et al. Protection Against Nephropathy in Diabetes with Atorvastatin (PANDA): A randomized double-blind placebo-controlled trial of high- vs. low-dose atorvastatin. *Diabet Med*. 2011; 28(1):100–8. [PubMed: 21166851]
 103. Briel M, Schwartz GG, Thompson PL, de Lemos JA, Blazing MA, van Es GA, et al. Effects of early treatment with statins on short-term clinical outcomes in acute coronary syndromes: a meta-analysis of randomized controlled trials. *JAMA*. 2006; 295(17):2046–56. [PubMed: 16670413]
 104. Furr LA. Psycho-social aspects of serious renal disease and dialysis: a review of the literature. *Social Work in Health Care*. 1998; 27(3):97–118. [Review] [30 refs]. [PubMed: 9654617]
 105. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986; 7(3):177–88. [PubMed: 3802833]
 106. Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Stat Med*. 2006; 25(20):3443–57. [PubMed: 16345038]
 107. van Houwelingen HC, Arends LR, Stijnen T. Advanced methods in meta-analysis: multivariate approach and meta-regression. *Stat Med*. 2002; 21(4):589–624. [PubMed: 11836738]
 108. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008; 336(7650):924–6. [PubMed: 18436948]
 109. Anavekar NS, McMurray JJ, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *The New England journal of medicine*. 2004; 351(13):1285–95. [PubMed: 15385655]
 110. Chan J, Hui RL, Levin E. Differential association between statin exposure and elevated levels of creatine kinase. *Ann Pharmacother*. 2005; 39(10):1611–6. [PubMed: 16160000]
 111. Di Angelantonio E, Chowdhury R, Sarwar N, Aspelund T, Danesh J, Gudnason V. Chronic kidney disease and risk of major cardiovascular disease and non-vascular mortality: prospective population based cohort study. *BMJ*. 2010; 341:c4986. [PubMed: 20884698]
 112. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med*. 1998; 339(12):799–805. [PubMed: 9738087]
 113. Kasiske BL, Maclean JR, Snyder JJ. Acute myocardial infarction and kidney transplantation. *J Am Soc Nephrol*. 2006; 17(3):900–7. [PubMed: 16481414]
 114. Trivedi H, Xiang Q, Klein JP. Risk factors for non-fatal myocardial infarction and cardiac death in incident dialysis patients. *Nephrol Dial Transplant*. 2009; 24(1):258–66. [PubMed: 18682489]
 115. Weiner DE, Tabatabai S, Tighiouart H, Elsayed E, Bansal N, Griffith J, et al. Cardiovascular outcomes and all-cause mortality: exploring the interaction between CKD and cardiovascular disease. *Am J Kidney Dis*. 2006; 48(3):392–401. [PubMed: 16931212]
 116. Wetmore JB, Shireman TI. The ABCs of cardioprotection in dialysis patients: a systematic review. *Am J Kidney Dis*. 2009; 53(3):457–66. [PubMed: 19022545]
 117. Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. *J Am Soc Nephrol*. 2004; 15(2):411–9. [PubMed: 14747388]
 118. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet*. 2000; 356(9224):147–52. [PubMed: 10963260]
 119. Stevens KK, Jardine AG. SHARP: a stab in the right direction in chronic kidney disease. *Lancet*. 2011; 377(9784):2153–4. [PubMed: 21663950]
 120. Palmer SC, Hayen A, Macaskill P, Pellegrini F, Craig JC, Elder GJ, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. *JAMA*. 2011; 305(11):1119–27. [PubMed: 21406649]

121. Phrommintikul A, Haas SJ, Elvik M, Krum H. Mortality and target haemoglobin concentrations in anaemic patients with chronic kidney disease treated with erythropoietin: a meta-analysis. *Lancet*. 2007; 369(9559):381–8. [PubMed: 17276778]
122. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *New Engl J Med*. 2008; 359(21):2195–207. [PubMed: 18997196]
123. Boutron I, Dutton S, Ravaud P, Altman DG. Reporting and interpretation of randomized controlled trials with statistically nonsignificant results for primary outcomes. *JAMA*. 2010; 303(20):2058–64. [PubMed: 20501928]

Figure 1.
Risk of bias in trials comparing statin regimens with placebo or no treatment

Figure 2.

Effect of statin therapy versus placebo or no treatment control on total and cardiovascular mortality and major cardiovascular events, grouped by stage of chronic kidney disease. 95% CI, 95% confidence interval; CKD, chronic kidney disease. *Subsets of trials refers to presence of data from subgroups with chronic kidney disease not on dialysis or cohorts on various types of dialysis (peritoneal dialysis or hemodialysis) within broader trials

Figure 3.

Summary of adverse effects for statins versus placebo or no treatment control in people with chronic kidney disease (any stage). 95% CI, 95% confidence interval; CKD, chronic kidney disease

GRADE evidence profile for effects of statin treatment versus placebo or no treatment from meta-analyses of randomised controlled trials in people with chronic kidney disease*

Table 1

Quality assessment				Summary of findings					Quality of evidence [‡]	
No. of comparisons (No. of participants)	Study limitations (Decrease in Quality Score)	Consistency; I ² (Decrease in Quality Score)	Directness	Precision (Decrease in Quality Score)	Publication bias (Decrease in Quality Score)	Relative Effect by using a Random-Effects Model (95% CI)	Best estimate of control group risk, %	Median treatment duration (years)		Absolute effect (95% CI) of treatment per 1000 treated [†]
Chronic kidney disease not on dialysis										
All-cause mortality										
11 (28 276)	Some limitations; Allocation concealment 5 trials; outcome assessment blinding 3 trials; ITT analysis 3 trials; incomplete follow up 5 trials; subgroup trials; post hoc analysis 8 trials	No important inconsistency I ² = 32%, P = 0.14	Direct	No important imprecision	No important publication bias	0.81 (0.74 - 0.88)	2.5	3.9	5 fewer; 3 - 7 fewer	High
Cardiovascular mortality										
8 (21 832)	Some limitations; Allocation concealment 4 trials; outcome assessment 3 trials; ITT analysis 3 trials; incomplete follow up 5 trials; subgroup trials; post hoc analysis 5 trials	No inconsistency I ² = 0%, P = 0.95	Direct	No important imprecision	No important publication bias	0.78 (0.68 - 0.89)	1.5	4.2	3 fewer; 1 - 5 fewer	High
Major cardiovascular events:										
14 (36 033)	Some limitations; Allocation concealment 6	No important inconsistency I ² = 30%, P = 0.13	Direct	No important imprecision	Potential publication bias (-1)	0.76 (0.73 - 0.80)	2	4.5	5 fewer; 4 - 6 fewer	Moderate

Quality assessment			Summary of findings							
No. of comparisons (No. of participants)	Study limitations (Decrease in Quality Score)	Consistency; I ² (Decrease in Quality Score)	Directness	Precision (Decrease in Quality Score)	Publication bias (Decrease in Quality Score)	Relative Effect by using a Random-Effects Model (95% CI)	Best estimate of control group risk, %	Median treatment duration (years)	Absolute effect (95% CI) of treatment per 1000 treated [†]	Quality of evidence [‡]
Dialysis										
All-cause mortality										
13 (4705)	Serious limitations (-1); Allocation concealment 12 trials; outcome assessment blinding 11 trials; not ITT analysis 9 trials; incomplete follow up 10 trials; subgroup trials; post hoc analysis 0 trials	No inconsistency I ² = 0%, P = 0.95	Direct	No important imprecision	No important publication bias	0.96 (0.88 - 1.04)	20	0.5	8 fewer; 24 fewer - 8 more	Moderate
Cardiovascular mortality										
13 (1850)	Serious limitations (-1); Allocation concealment 12 trials; outcome assessment 11 trials; not ITT analysis 9 trials; incomplete follow up 9 trials; subgroup trials; post hoc analysis 0 trials	No inconsistency I ² = 0%, P = 0.56	Direct	No important imprecision	No important publication bias	0.94 (0.82 - 1.07)	10	0.5	6 fewer; 18 fewer - 7 more	Moderate

Major cardiovascular events:

Quality assessment				Summary of findings						
No. of comparisons (No. of participants)	Study limitations (Decrease in Quality Score)	Consistency; I ² (Decrease in Quality Score)	Directness	Precision (Decrease in Quality Score)	Publication bias (Decrease in Quality Score)	Relative Effect by using a Random-Effects Model (95% CI)	Best estimate of control group risk, %	Median treatment duration (years)	Absolute effect (95% CI) per year of treatment per 1000 treated [†]	Quality of evidence [‡]
4 (7084)	Some limitations; Allocation concealment 1 trial; outcome assessment 1 trial; ITT analysis 1 trial; incomplete follow up 0 trials; subgroup post hoc analysis 0 trials	No inconsistency I ² = 0%, P = 0.72	Direct	No important imprecision	No important publication bias	0.95 (0.87 - 1.03)	15	3.6	7 fewer; 18 more	High
Kidney transplant										
All-cause mortality										
6 (2760)	Serious limitations (-1); Allocation concealment 5 trials; outcome assessment 3 trials; ITT analysis 4 trials; incomplete follow up 4 trials; subgroup post hoc analysis 0 trials	Some inconsistency I ² = 31%, P = 0.05	Direct	Imprecise (-1)	No important publication bias	1.05 (0.84 - 1.31)	2	0.5	1 more; 3 fewer - 6 more	Low
Cardiovascular mortality										
4 (2322)	Serious limitations (-1); Allocation concealment 4 trials; outcome assessment 3 trials; ITT analysis 3 trials; incomplete follow up 3 trials; subgroup post hoc analysis 0 trials	No inconsistency I ² = 0%, P = 0.56	Direct	Imprecise (-1)	No important publication bias	0.68 (0.45 - 1.02)	0.5	0.5	1 fewer; 3 - 0 fewer	Low

Quality assessment				Summary of findings				
No. of comparisons (No. of participants)	Study limitations (Decrease in Quality Score)	Consistency; I ² (Decrease in Quality Score)	Directness	Precision (Decrease in Quality Score)	Publication bias (Decrease in Quality Score)	Relative Effect by using a Random-Effects Model (95% CI)	Best estimate of control group risk, %	Median treatment duration (years)
Major cardiovascular events:								
1 (246)	Some limitations; single low risk trial	Consistency not estimable (–1)	Direct	Imprecise (–1)	Single available trial	0.84 (0.66 – 1.06)	1	5
Overall: elevated creatine kinase (risk of rhabdomyolysis)								
15 (17 273)	Serious limitations (–1); Unclear allocation concealment 78%; outcome assessment not blinded 75%; not ITT analysis 72%; incomplete follow up 78%	No inconsistency I ² = 0%, P = 0.52	Direct	Imprecise (–1)	No important publication bias	1.11 (0.80 – 1.56)	1	6

95% CI, 95% confidence interval. GRADE = Grading of Recommendations Assessment, Development and Evaluation

* Data obtained from reference 108.

[†] Approximate absolute event rates of outcomes per year are derived from previously published observational cohort studies. Absolute numbers of people who had chronic kidney disease with cardiovascular or mortality events avoided or elevated creatine kinase caused per 1000 treated were calculated from the risk estimate for the outcome (and associated 95% confidence interval) obtained from meta-analysis of placebo-controlled trials together with the absolute population risk estimated from the previously published observational cohort studies across the median duration of the available trials(109-115).

[‡] Definitions of evidence quality are: High quality – Further research is very unlikely to change our confidence in the estimate of effect; Moderate quality – Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; Low quality – Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; Very low quality – Any estimate of effect is very uncertain.