Annals of Internal Medicine | Review

Benefits and Harms of Statin Therapy for Persons With Chronic Kidney Disease

A Systematic Review and Meta-analysis

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Background: Statins have uncertain benefits in persons with chronic kidney disease (CKD) because 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 stage of kidney disease.

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

Study Selection: Randomized trials comparing the 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 comprising 51 099 participants compared statin with placebo or no treatment. Treatment effects varied with stage of CKD. Moderate- to high-quality evidence indicated that statins reduced all-cause mortality (relative risk [RR], 0.81 [95% CI, 0.74 to 0.88]), cardiovascular mortality (RR, 0.78 [CI, 0.68 to 0.89]), and cardiovascular events (RR, 0.76 [CI, 0.73 to 0.80]) in persons not receiving dialysis. Moderate- to high-quality evidence indicated that statins had little or no effect on all-cause mortality (RR, 0.96 [CI, 0.88 to 1.04]), cardiovascular mortality (RR, 0.94 [CI, 0.82 to 1.07]), or cardiovascular events (RR, 0.95 [CI, 0.87 to 1.03]) in persons receiving dialysis. 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 the trials.

Limitation: There was a reliance on post hoc subgroup data for earlier stages of CKD.

Conclusion: Statins decrease mortality and cardiovascular events in persons with early stages of CKD, have little or no effect in persons receiving dialysis, and have uncertain effects in kidney transplant recipients.

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Persons with early stages of chronic kidney disease (CKD) who are not receiving dialysis have an absolute risk for cardiovascular events similar to that of persons with established coronary artery disease (1), whereas those receiving dialysis have a risk that is 40 to 50 times greater than that of the general population (2). Although 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 patients with CKD because atherosclerosis is a less frequent cause of cardiovascular events than sudden death, arrhythmia, and heart failure (9, 10). The evidence that statins may have less efficacy in patients with CKD was suggested by 2 large trials (4D [Deutsche Diabetes Dialyse Studie] [7] and AURORA [A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events] [8]) that studied persons receiving hemodialysis and found no benefit of statins on mortality or cardiovascular events. Fewer trial data were available to evaluate treatment efficacy in patients with milder CKD who are not receiving dialysis.

Although an earlier meta-analysis found no differences in treatment effects based on severity of CKD (11), additional trials have since been reported, including SHARP (Study of Heart and Renal Protection) (12), trials reporting data for persons with CKD who were not receiving dialysis (4, 6, 13–15), and the AURORA trial (8). On the basis of the data from SHARP, an advisory panel to the U.S. Food and Drug Administration recently voted to recommend simvastatin and ezetimibe for patients in earlier stages of CKD but not for those receiving dialysis, citing insufficient evidence for prevention of major vascular events in the latter population (16). The U.S. Food and Drug Administration subsequently did not include CKD 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

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whether treatment effects differ depending on stage of CKD.

METHODS

For this meta-analysis, we used 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 that compared statins with placebo, no treatment, standard care, or another statin and reported data for adults with CKD (any stage). We identified trials from a meta-analysis published in 2008 (11), and we searched EMBASE, CENTRAL (Cochrane Central Register of Controlled Trials), and the Cochrane 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. Chronic kidney disease was defined according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative criteria (21) (**Appendix Table 1**, available at www.annals.org) (4–8, 13–15, 22–102). We excluded studies with less than 8 weeks of follow-up because 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, nonrandomized cointerventions, 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 urinary protein excretion rate in patients not requiring dialysis, myalgia, elevated creatine kinase level, 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 by using 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 (RRs) and 95% CIs. For continuous outcomes, we calculated mean differences with 95% CIs. We then summarized effect estimates by using the DerSimonian and Laird random-effects model (105). Data for trials comparing 2 statin regimens could not be summarized because of insufficient extractable data. We assessed heterogeneity by using the Cochran Q chi-square test and the I^2 test. A P value less than 0.10 indicated significant heterogeneity. We considered I^2 values less than 25% to represent low heterogeneity, values between 25% and 50% to represent moderate heterogeneity, and values of 50% or greater to represent high heterogeneity. We performed additional prespecified subgroup analyses to explore potential sources of heterogeneity. We analyzed data for all outcomes within subgroups for CKD by including separate categories for persons not receiving dialysis, persons receiving dialysis, and kidney transplant recipients, and we provided an overall summary estimate of treatment effect when formal tests of interaction indicated no statistically significant difference between subgroups. We used the standard continuity correction of 0.05 when estimating summary effects for trials in which no events were reported in 1 group. To assess potential bias from small study effects, we constructed funnel plots for the log risk ratio in individual studies against the SE of the risk ratio and formally assessed for plot asymmetry by using the Egger regression test (106). We conducted analyses by using Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey), and macro routines in SAS, version 9.1 (SAS Institute, Cary, North Carolina) (107). Details of the SAS macro routines are available from the authors by request.

We summarized the quality of the evidence together with absolute treatment effects based on estimated baseline risks by using the Grading of Recommendations Assessment, Development, and Evaluation guidelines (108). To estimate the absolute number of persons with CKD who had cardiovascular or adverse events avoided or incurred with statin therapy, we used 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 level, together with the absolute population risk for persons with each stage of CKD (not receiving dialysis, receiving dialysis, or transplant recipient) derived from previously published observational cohort studies (109–115).

Role of the Funding Source

This study received no specific external funding.

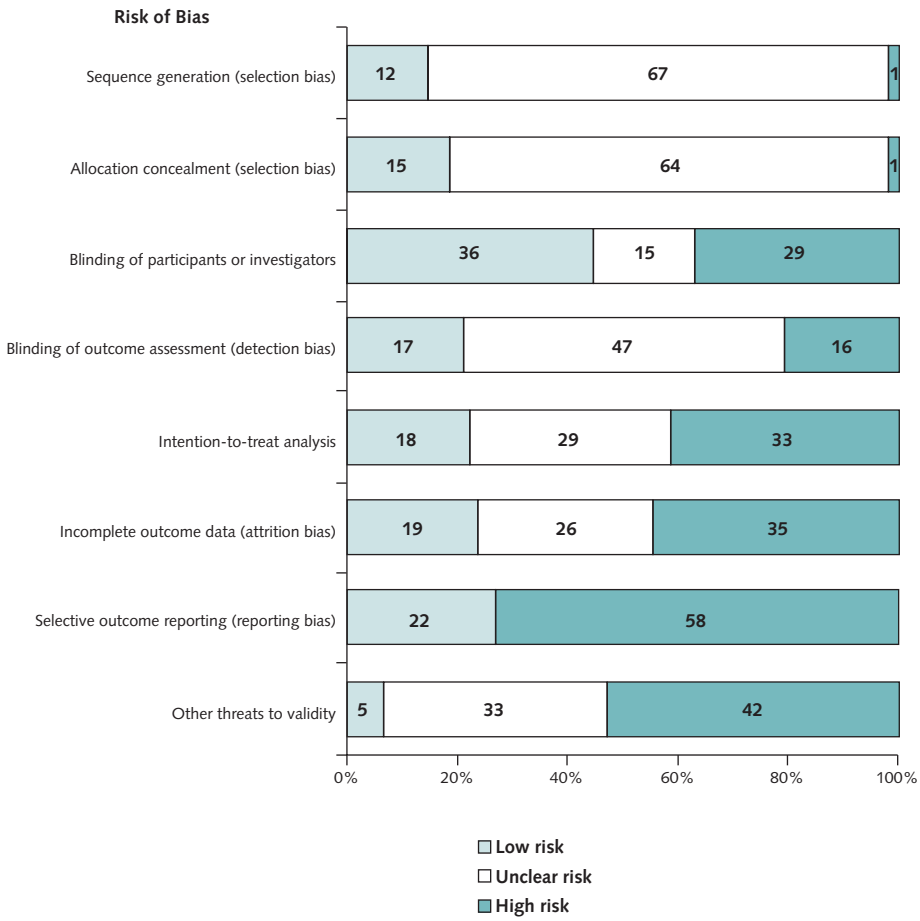
RESULTS

Description of Trials

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

Twelve trials provided data for 36 325 persons with CKD not receiving dialysis (4–6, 13–15, 60, 62, 70, 91,

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



100, 101). We included published data from SHARP for subgroups of persons receiving dialysis and those not receiving dialysis separately for analyses of major cardiovascular events (12, 16). Seven trials or subgroups of trials were available only as conference proceedings (38, 75, 76, 83, 91, 95, 96), and 3 studies were published only as letters (22, 84, 97).

Eighty trials (86 comparisons) compared statin therapy with placebo or no treatment in 51 099 persons (**Supplement 1**, available at www.annals.org). Of these, 48 comparisons included 39 820 persons not receiving dialysis (4–6, 13–15, 22–24, 26–28, 30–32, 34, 37, 40, 42, 43, 52, 55, 57, 59, 60, 62, 63, 65, 66, 69–74, 77–81, 83, 87–91, 93), 21 comparisons included 7982 persons receiving dialysis (7, 8, 36, 38, 50, 53, 54, 56, 61, 64, 67, 68, 73–76, 84, 85, 92, 93), and 17 comparisons included 3297 kidney transplant recipients (25, 29, 33, 35, 39, 41, 44–49, 51, 58, 74, 82, 86). Ten studies provided post hoc data for 30 897 persons not receiving dialysis (4–6, 13–15, 60, 62, 70, 91). Three studies enrolled 3203 persons with established acute (70) or stable (4, 13) coronary artery disease who also had CKD. Most trials (60 comparisons [70%]) evaluated statin doses equivalent to simvastatin, 20 mg, or less. Median follow-up was 6 months (range, 2 months to 5.5 years). Forty-five comparisons (52%; 49 035 persons) reported industry funding. Overall, 9 trials compared statin therapy with the same statin or another statin among 5758 persons with CKD (**Supplement 1**) (94–102). A high proportion of these active comparator studies enrolled kidney transplant recipients (183 persons), and 3 reported funding from industry (100–102).

Risk of Bias in Individual Trials

Risk of bias in trials comparing statin with placebo or no treatment 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. Forty-two trials (53%) reported 1 or more additional risks of bias, including post hoc 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 of follow-up, early termination, alteration of intervention after interim analyses, or allocation of 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 of the risks we assessed (7, 93). In the 9 trials comparing a statin with the same or a different statin, allocation concealment was unclear in all but 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, evidence indicated statistically significantly different treatment effects on mortality according to the stage of CKD ($P = 0.009$) (**Figure 2** and **Table**) (109–115). Moderate- to high-quality evidence indicated that statin treatment reduced all-cause mortality in persons not receiving dialysis (RR, 0.81 [95% CI, 0.74 to 0.88]) but had little or no effect in persons receiving dialysis (RR, 0.96 [CI, 0.88 to 1.04]). We found generally low-quality evidence that treatment effects for mortality were uncertain in kidney transplant recipients (RR, 1.05 [CI, 0.84 to 1.31]). Data for cardiovascular mortality were available in 27 comparisons among 35 417 persons. Moderate- to high-quality evidence indicated that statin therapy reduced cardiovascular mortality in persons not receiving dialysis (RR, 0.78 [CI, 0.68 to 0.89]) but had little or no effect in persons receiving dialysis (RR, 0.94 [CI, 0.82 to 1.07]). The risk estimate in kidney transplant recipients suggested benefit, although the analysis included few events and CIs were wide (RR, 0.68 [CI, 0.45 to 1.02]). The formal test of interaction indicated no statistically significant difference between treatment estimates from the subgroups based on stage of CKD ($P = 0.082$); however, because separate data on persons not receiving dialysis and those receiving dialysis were not available from SHARP (12) or the trial by Stegmayr and colleagues (73), we were unable to include these data in analyses of all-cause or cardiovascular mortality.

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 **Supplement 2** (available at www.annals.org). We used data for the primary outcome of SHARP (major atherosclerotic events) (12) in this meta-analysis. When we analyzed treatment effects according to stage of CKD, we found strong evidence that the treatment effects for statin therapy were statistically significantly different between the subgroups ($P < 0.001$) (**Figure 2**). Moderate- to high-quality evidence indicated that statin therapy prevented major cardiovascular events in persons with CKD who were not receiving dialysis (RR, 0.76 [CI, 0.73 to 0.80]) but had little or no effect in persons receiving dialysis (RR, 0.95 [CI, 0.87 to 1.03]). We found low-quality evidence that the effects of statin treatment in kidney transplant recipients were uncertain (RR, 0.84 [CI, 0.66 to 1.06]).

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 ($P = 0.028$) (**Figure 2**). Overall, statin therapy reduced myocardial infarction in persons not receiving dialysis (RR, 0.55 [CI, 0.42 to 0.72]), but treatment effects were uncertain in persons receiving dialysis (RR, 0.87 [CI, 0.71 to 1.07]) and in kidney transplant recipients (RR, 0.70 [CI, 0.48 to 1.01]). We found no statistically significant difference in treatment effects for stroke between stages of CKD ($P = 0.069$), due in part to imprecise effect estimates for persons receiving dialysis and kidney transplant recipients (**Figure 2**). Statins reduced stroke in persons not receiving dialysis (RR, 0.61 [CI, 0.38 to 0.98]) but had uncertain effects in persons receiving dialysis (RR, 1.30 [CI, 0.79 to 2.11]) and kidney transplant recipients (RR, 1.18 [CI, 0.62 to 2.24]). In all stages of CKD, effects of statin therapy on stroke were uncertain (RR, 0.86 [CI, 0.62 to 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 conferred little or no risk for adverse events, including cancer (RR, 0.96 [CI, 0.89 to 1.04]), myalgia (RR, 0.99 [CI, 0.94 to 1.04]), elevated creatine kinase level (RR, 1.11 [CI, 0.80 to 1.56]), abnormal liver function (RR, 0.99 [CI, 0.70 to 1.40]), or withdrawal from treatment (RR, 1.07 [CI, 0.91 to 1.26]), and had no statistically significant heterogeneity in the analyses.

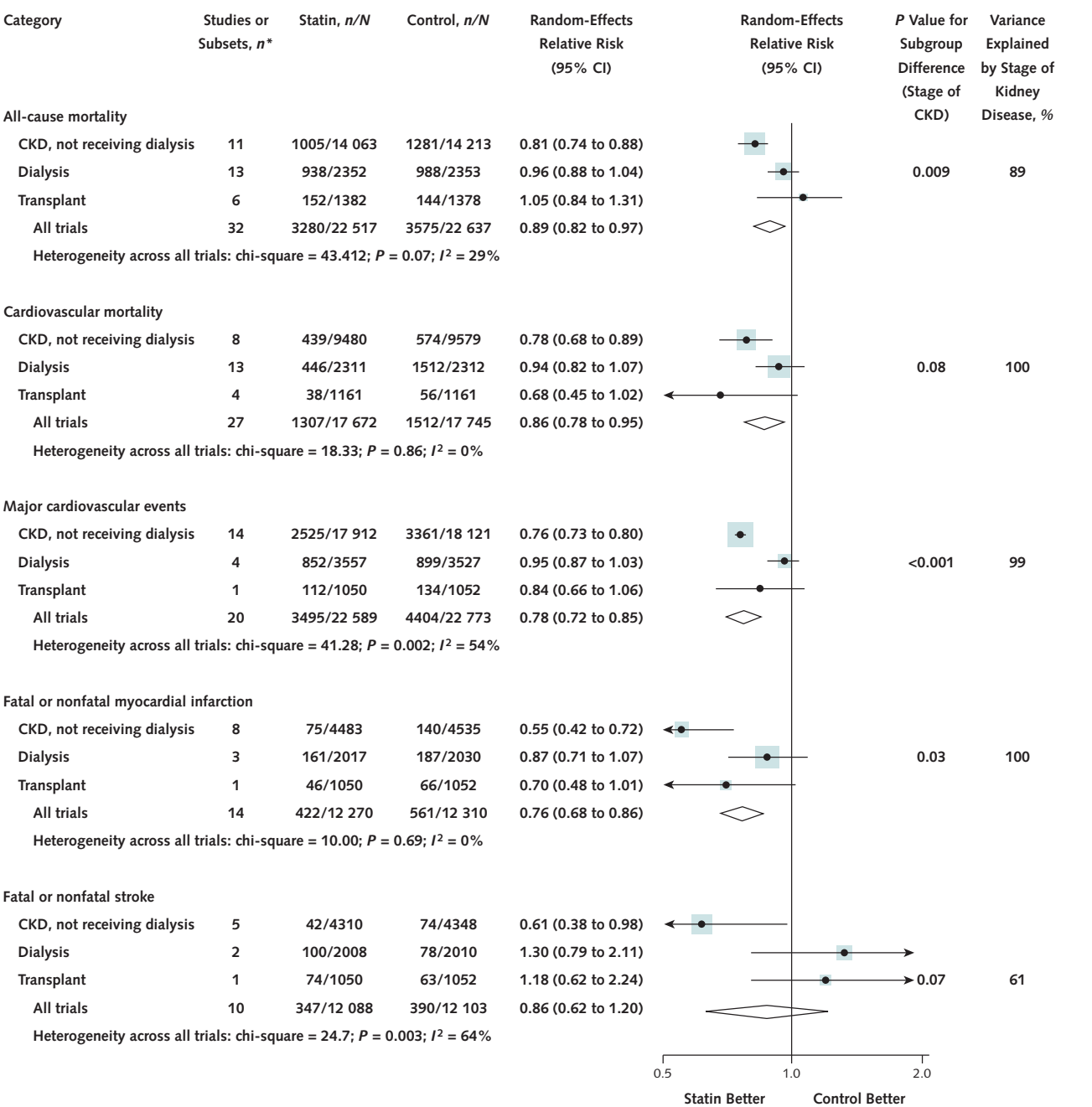
Lipid Levels

Statin therapy decreased serum total cholesterol, low-density lipoprotein cholesterol, and serum triglyceride concentrations but not high-density lipoprotein cholesterol concentrations (**Appendix Table 3**, 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 per 1.73 m^2) were uncertain, with statistically significant heterogeneity

Figure 2. **Effect of statin therapy versus placebo or no treatment on total and cardiovascular mortality and major cardiovascular events, by stage of CKD.**



CKD = chronic kidney disease.
* "Subsets" refers to the presence of data from subgroups of patients with CKD not receiving dialysis or cohorts receiving various types of dialysis (peritoneal dialysis or hemodialysis) within broader trials.

in the analysis (**Appendix Table 3**). Statin treatment reduced proteinuria with statistically significant heterogeneity in the analysis (**Appendix Table 3**).

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 89% of the variation in treatment estimates between trials, as well as statin type (78%), estimated glomerular filtration rate (100%), baseline serum cholesterol level (66%), and proportion of persons with

Table. **GRADE Evidence Profile for Effects of Statin Treatment Versus Placebo or No Treatment From Meta-analyses of Randomized, Controlled Trials in Persons With CKD***

Stage of CKD	Outcome	Comparisons/ Participants, *n/N*	Quality Assessment				
			Study Limitations (Decrease in Quality Score)	Consistency (Decrease in Quality Score); I^2; *P* Value	Directness	Precision (Decrease in Quality Score)	Publication Bias (Decrease in Quality Score)
CKD, not receiving 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 post hoc analysis: 8 trials	No important inconsistency; 32%; 0.143	Direct	No important imprecision	No important publication bias
	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 post hoc analysis: 5 trials	No inconsistency; 0%; 0.95	Direct	No important imprecision	No important publication bias
	Major cardiovascular events	14/36 033	Some limitations; allocation concealment: 6 trials; outcome assessment: 3 trials; ITT analysis: 3 trials; incomplete follow-up: 6 trials; subgroup post hoc analysis: 10 trials	No important inconsistency; 30%; 0.135	Direct	No important imprecision	Potential publication bias (−1)
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 post hoc analysis: 0 trials	No inconsistency; 0%; 0.95	Direct	No important imprecision	No important publication bias
	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 post hoc analysis: 0 trials	No inconsistency; 0%; 0.56	Direct	No important imprecision	No important publication bias
	Major cardiovascular events	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; 0%; 0.72	Direct	No important imprecision	No important publication bias
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; 31%; 0.054	Direct	Imprecise (−1)	No important publication bias
	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; 0%; 0.56	Direct	Imprecise (−1)	No important publication bias
	Major cardiovascular events	1/246	Some limitations; single low-risk trial	Consistency not estimable (−1)	Direct	Imprecise (−1)	Single available trial
Overall	Elevated creatine kinase level (risk for 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; 0%; 0.52	Direct	Imprecise (−1)	No important publication bias

CKD = chronic kidney disease; GRADE = Grading of Recommendations Assessment, Development, and Evaluation; ITT = intention-to-treat.
* Data from reference 108.
† Approximate absolute event rates of outcomes per year were derived from previously published observational cohort studies. Absolute numbers of persons who had CKD with cardiovascular or mortality events avoided or elevated creatine kinase level caused per 1000 treated were calculated from the risk estimate for the outcome (and associated 95% CI) 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).
‡ "High" indicates that further research is very unlikely to change our confidence in the estimate of effect. "Moderate" indicates that further research is likely to have an important effect on our confidence in the estimate of effect and may change the estimate. "Low" indicates that further research is very likely to have an important effect on our confidence in the estimate of effect and is likely to change the estimate.

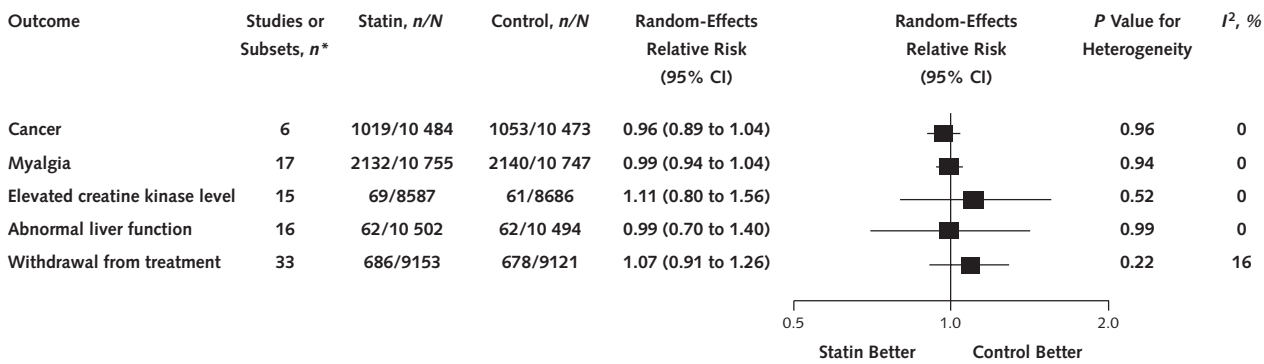
Table— Continued

Summary of Findings				
Relative Effect by Using a Random-Effects Model (95% CI)	Best Estimate of Control Group Risk, %	Median Treatment Duration, *y*	Absolute Effect per Year of Treatment per 1000 Treated (95% CI)†	Quality of Evidence‡
0.81 (0.74–0.88)	2.5	3.9	5 fewer (3 to 7 fewer)	High
0.78 (0.68–0.89)	1.5	4.2	3 fewer (1 to 5 fewer)	High
0.76 (0.73–0.80)	2.0	4.5	5 fewer (4 to 6 fewer)	Moderate
0.96 (0.88–1.04)	20.0	0.5	8 fewer (24 fewer to 8 more)	Moderate
0.94 (0.82–1.07)	10.0	0.5	6 fewer (18 fewer to 7 more)	Moderate
0.95 (0.87–1.03)	15.0	3.6	7 fewer (18 fewer to 5 more)	High
1.05 (0.84–1.31)	2.0	0.5	1 more (3 fewer to 6 more)	Low
0.68 (0.45–1.02)	0.5	0.5	1 fewer (3 to 0 fewer)	Low
0.84 (0.66–1.06)	1.0	5.0	1 fewer (3 fewer to 0.5 more)	Low
1.11 (0.80–1.56)	1.0	6.0	1 more (2 fewer to 5 more)	Low

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, no important residual heterogeneity between trials was observed in treatment estimates for total or cardiovascular mortality, major cardiovascular events, myocardial infarction, or stroke (**Table**). Univariate meta-regression found that statin dose (13.0%), baseline cholesterol level (26.9%), and allocation concealment (9.5%) were responsible for heterogeneity in treatment effects on total cholesterol, and stage of CKD was not (**Appendix Table 4**, 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 an analysis

Figure 3. **Summary of adverse effects for statins versus placebo or no treatment in persons with CKD (any stage).**



CKD = chronic kidney disease.
* "Subsets" refers to subgroups of persons with differing stages of CKD within a single trial for which disaggregated outcome data could be included in the analyses.

for major cardiovascular events after excluding SHARP and found similar differential treatment effects for persons not receiving dialysis (RR, 0.74 [CI, 0.69 to 0.79]) and those receiving dialysis (RR, 0.96 [CI, 0.85 to 1.08]) ($P < 0.001$). When we used major vascular events (nonfatal myocardial infarction or any cardiac death, any stroke, or any arterial revascularization, excluding dialysis procedures) (16) rather than major atherosclerotic events (major vascular event minus noncoronary cardiac death and hemorrhagic stroke) from SHARP in the meta-analysis for major cardiovascular events, the overall risks were similar for persons not receiving dialysis (RR, 0.77 [CI, 0.73 to 0.80]), those receiving dialysis (RR, 0.96 [CI, 0.89 to 1.02]), and kidney transplant recipients (RR, 0.84 [CI, 0.66 to 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 for mortality and cardiovascular outcomes differ depending on stage of CKD. Moderate- to high-quality evidence indicates that statins (generally at doses equivalent to simvastatin, 20 mg) reduce all-cause and cardiovascular mortality and major cardiovascular events in persons not receiving dialysis by about one fifth to one quarter during approximately 5 years of treatment. In absolute terms, 1000 persons with CKD not receiving dialysis would need to receive statin treatment to prevent approximately 5 deaths each year. In persons not receiving dialysis, occlusive vascular events (fatal or nonfatal stroke or myocardial infarction) are proportionally reduced with statin therapy by 40% to 50%. In contrast, moderate- to high-quality evidence indicates that statins have little or no effect on all-cause mortality, cardiovascular mortality, and major cardiovascular events (including myocardial infarction and stroke) in persons receiving dialysis, despite decreases in serum cholesterol levels (1.0 mmol/L [40 mg/dL]). 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. We found low-quality evidence that statins have little or no effect on cancer incidence, myalgia, elevated creatine kinase level, abnormal liver function, or treatment withdrawal compared with placebo; however, the evidence was hampered by lack of systematic reporting of adverse events in more than half of the trials. Insufficient direct comparisons were available to draw conclusions on the efficacy of higher versus lower doses of an individual statin or of one statin versus another. Treatment effects for statins alone are similar to those of combined therapy with statin plus ezetimibe.

Such interventions as statins, angiotensin-converting enzyme inhibitors, and β-blockers clearly prevent adverse cardiovascular events in general populations but have not been proven to improve cardiovascular or mortality outcomes in persons with advanced CKD (116). Persons with CKD are often systematically excluded from randomized trials that evaluate cardioprotective drugs, 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 rate (10). Benefits of statins in other populations (primary care, hypertension, diabetes, or existing cardiovascular disease) may not be generalizable to persons who have CKD because the pathobiology of cardiovascular disease is dominated by vascular calcification, cardiac hypertrophy, and arterial stiffening (118). Consistent with this hypothesis, results of trials of statin therapy in persons receiving dialysis have been negative (7, 8), although the relative overall paucity of statin trials in persons in earlier stages of CKD has led to combining outcomes for persons with different stages of CKD (dialysis

and not receiving 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 persons receiving dialysis has also been questioned because of concerns that such trials may have had insufficient statistical power due to lower-than-expected event rates and primary composite outcomes that include nonatherosclerotic 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 policymakers, this meta-analysis incorporated recently published trial data for statin therapy in more than 50 000 individuals to allow sufficient power to quantify treatment effects for statins based on stage of CKD.

The proportional decreases in major cardiovascular and mortality outcomes and serum cholesterol level 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 for disease is accounted for, statin therapy over 5 years prevents approximately 25 persons with CKD per 1000 treated from having a major cardiovascular event, which is similar to the benefit observed in broader populations with existing coronary heart disease (3).

That statin therapy does not clearly reduce major cardiovascular events in persons receiving dialysis seems to contradict the findings of SHARP, the recent and much-anticipated large trial of combined simvastatin and ezetimibe in more than 9000 persons with a broad range of kidney function, including those receiving dialysis. SHARP investigators concluded that, after nearly 5 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, the primary end point (major atherosclerotic events defined as coronary death, myocardial infarction, ischemic stroke, or any revascularization procedure) in dialysis and nondialysis patients was analyzed separately, and a test for interaction did not indicate that proportional treatment effects statistically differed between the 2 populations, although it was acknowledged that the trial was underpowered for such an analysis (16). Although no statistical difference ($P < 0.05$) was observed for treatment effects in each population, 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 modifies treatment efficacy. The present data are also consistent with earlier trials (4D [7] and AURORA [8]) that found no treatment benefit for composite cardiovascular outcomes in the dialysis population and that treatment benefits of statins for patients receiving dialysis are probably small at best. Notably, our sensitivity analysis that excluded SHARP from summary estimates for major cardiovascular events showed similar differences in treatment efficacy based on category of kidney disease, suggesting that even without the SHARP data, our findings are robust.

The choice of end point has been previously mooted as a potential reason for negative trials in persons receiving dialysis (119) because 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 nonfatal atherosclerotic events (stroke or myocardial infarction) and more than half were revascularization procedures. Although this is plausible, our analysis suggests otherwise. Even outcomes that are clearly related to atherosclerotic occlusion (myocardial infarction and stroke) were not clearly reduced by statin therapy in patients receiving dialysis. However, fewer of these events were available in our meta-analysis, which may have reduced its power to find a difference between treatment groups based on stage of CKD.

Our meta-analysis reminds us again that modification of a surrogate marker (in this case, cholesterol level) in persons with advanced CKD does not necessarily reduce disease burden (120, 121). In the dialysis population, decreasing serum cholesterol levels by proportions equivalent to those achieved in trials in the general population and in persons with earlier stages of CKD has little or no effect on cardiovascular outcomes. Notably, in the 4 trials in patients receiving dialysis that reported major cardiovascular events, baseline serum cholesterol level was generally lower (4.6 mmol/L [178 mg/dL]), although meta-regression could not be done in these trials to evaluate whether serum cholesterol level modified the treatment effects of statins in this population. Nevertheless, in a large trial of rosuvastatin in apparently healthy men and women with low-density lipoprotein cholesterol levels less than 3.4 mmol/L (<130 mg/dL) (122), statin treatment nearly halved the risk for major cardiovascular events, suggesting that lower baseline cholesterol levels in persons receiving dialysis do not explain the reduced benefit from statins in the dialysis population.

Our study has limitations. First, data for treatment effects in persons with earlier stages of CKD who were not receiving dialysis were frequently obtained from reported post hoc analyses of larger trials, which may be less reliable (123). Second, meta-regression analyses to determine the effects of baseline cholesterol level on treatment effects in trials in persons receiving dialysis were not possible because of insufficient trial-level data. Third, we were not able to analyze the relationship between serum cholesterol lowering and treatment effects (to report risk reduction per unit change in serum cholesterol level) because trials that reported the change in serum cholesterol level with treatment did not report clinical outcome data and vice versa.

In conclusion, persons with early stages of CKD have an estimated 10-year risk for cardiovascular disease of at least 20% and experience absolute benefits from statin therapy approximately equivalent to those in persons with

existing coronary artery disease. Statin therapy has little or no effect in persons receiving dialysis. Although it is unclear whether statins should be discontinued in patients initiating dialysis, the benefits in this population are probably small at best. Evidence for statin therapy in kidney transplant recipients is sparse and uncertain.

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Appendix Table 1. Definitions of CKD in Included Trials

Study, Year (Reference)*	Definition of CKD
Statin versus placebo	
Scanferla et al, 1991 (22)	Estimated glomerular filtration rate, 24 to 55 mL/min
Hommel et al, 1992 (23)	Albuminuria >300 mg/d
Mori and Tsuruoka, 1992 (24)	Normal serum creatinine level with increased urinary albumin
Martinez Hernandez et al, 1993 (25)	Kidney transplant
Nielsen et al, 1993 (26)	Persistent microalbuminuria
Thomas et al, 1993 (27)	Proteinuria >1 g/d
Aranda Arcas et al, 1994 (28)	Proteinuria >2 g/d
Arnadottir et al, 1994 (29)	Kidney transplant
Lam et al, 1995 (30)	Proteinuria >0.15 g/d
Lintott et al, 1995 (31)	Estimated glomerular filtration rate, 30 to 60 mL/min
Zhang et al, 1995 (32)	Microalbuminuria (20 to 200 μg/min)
Katznelson et al, 1996 (33)	Kidney transplant
Rayner et al, 1996 (34)	Biopsy-proven idiopathic membranous nephropathy with serum creatinine level >1.7 mg/dL
Paczek et al, 1997 (35)	Kidney transplant (serum creatinine level <1.8 mg/dL)
PERFECT, 1997 (36)	Dialysis
Tonolo et al, 1997 (37)	Albuminuria between 30 and 150 mg/d on 3 occasions during 6 mo before enrollment
Veličković-Radovanović et al, 1997 (38)	Dialysis
Melchor and Gracida, 1998 (39)	Kidney transplant
Imai et al, 1999 (40)	Serum creatinine level ≥1.2 mg/dL and <2.5 mg/dL by the Jaffe method or ≥0.9 mg/dL and <2.2 mg/dL by the enzymatic method
Lepre et al, 1999 (41)	Kidney transplant (serum creatinine level ≤2.8 mg/dL)
Buemi et al, 2000 (42)	IgA nephropathy on light microscopy with stable kidney function
Fried et al, 2001 (43)	Albumin excretion rate <200 μg/min
Hausberg et al, 2001 (44)	Kidney transplant (serum creatinine level <2.5 mg/dL)
Kasiske et al, 2001 (45)	Kidney transplant
Renders et al, 2001 (46)	Kidney transplant (serum creatinine level <3 mg/dL)
Sahu et al, 2001 (47)	Kidney transplant
Santos et al, 2001 (48)	Kidney transplant (creatinine clearance >20 mL/min)
SOLAR, 2001 (49)	Kidney transplant
Chang et al, 2002 (50)	Dialysis
Cofan et al, 2002 (51)	Kidney transplant
Gheith et al, 2002 (52)	Nephrotic syndrome
Harris et al, 2002 (53)	Dialysis
Ichihara et al, 2002 (54)	Dialysis
Nakamura et al, 2002 (55)	Histologic evidence of IgA nephropathy or diffuse mesangial proliferative glomerulonephritis
Saltissi et al, 2002 (56)	Dialysis
Samuelsson et al, 2002 (57)	Moderate to severe chronic renal insufficiency
ALERT, 2003 (58)	Renal or combined renal and pancreas transplant
Bianchi et al, 2003 (59)	Mild to moderate kidney disease with idiopathic glomerulonephritis
HPS, 2003 (60)	Elevated creatinine level, defined as ≥1.2 mg/dL for women and 1.5 mg/dL for men but <2.3 mg/dL for both
Lins et al, 2004 (61)	Dialysis
PPP, 2004 (62)	Moderate chronic kidney disease: estimated glomerular filtration rate, 30 to 59.99 mL/min per 1.73 m^2 Mild chronic kidney disease: estimated glomerular filtration rate, 60 to 89.99 mL/min per 1.73 m^2
PREVEND IT, 2004 (63)	Persistent microalbuminuria
Vernaglione et al, 2004 (64)	Dialysis
Yasuda et al, 2004 (65)	Creatinine clearance, 20 to 70 mL/min per 1.73 m^2; protein excretion, 0.5 to 3.0 g/d
4D, 2005 (7)	Dialysis
Di Lullo et al, 2005 (66)	Creatinine clearance, 45 to 55 mL/min on 24-h collection
Diepeveen et al, 2005 (67)	Dialysis
Dornbrook-Lavender et al, 2005 (68)	Dialysis
Lee et al, 2005 (69)	Urinary protein excretion >300 mg/d
LIPS, 2005 (70)	Creatinine clearance <55.9 mL/min
Nakamura et al, 2005 (71)	Microalbuminuria (20 to 200 μg/min)
Verma et al, 2005 (72)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
Stegmayr et al, 2005 (73)	Estimated glomerular filtration rate <30 mL/min per 1.73 m^2 or dialysis
UK-HARP-I, 2005 (74)	Creatinine level ≥1.7 mg/dL or dialysis or functioning transplant (with any creatinine level)
Vareesangthip et al, 2005 (75)	Dialysis
Ahmadi et al, 2006 (76)	Dialysis
Goicoechea et al, 2006 (77)	Estimated glomerular filtration rate, 15 to 90 mL/min per 1.73 m^2
Nakamura et al, 2006 (78)	Stage 1 chronic kidney disease with renal biopsy or clinical history
Panichi et al, 2006 (79)	Chronic renal failure (not otherwise defined)
4S, 2007 (4)	Estimated glomerular filtration rate <75 mL/min per 1.73 m^2
Dummer et al, 2008 (80)	Stage 3 or 4 chronic kidney disease
Sawara et al, 2008 (81)	Estimated glomerular filtration rate between 15 and 90 mL/min per 1.73 m^2
Serón et al, 2008 (82)	Kidney transplant
Tokunaga et al, 2008 (83)	Albuminuria (not otherwise specified)

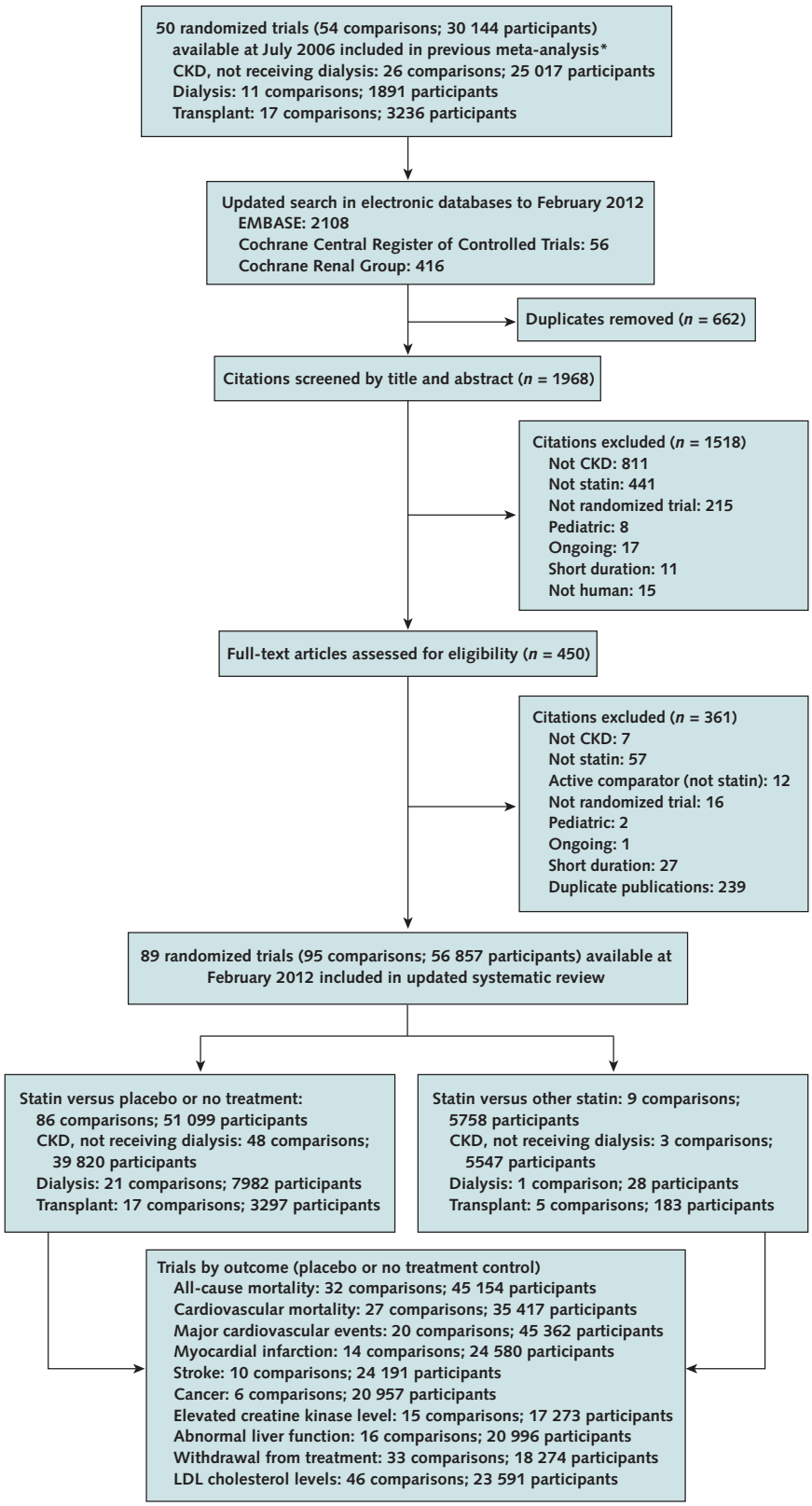
Continued on following page

Appendix Table 1—**Continued**

Study, Year (Reference)*	Definition of CKD
Tse et al, 2008 (84)	Dialysis
ALLIANCE, 2009 (13)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
AURORA, 2009 (8)	Dialysis
Burmeister et al, 2009 (85)	Dialysis
CARDS, 2009 (14)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
MEGA, 2009 (15)	Estimated glomerular filtration rate, 30 to 60 mL/min per 1.73 m^2
Sharif et al, 2009 (86)	Kidney transplant
AFCAPS/TexCAPS, 2010 (5)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
ESPLANADE, 2010 (87)	Proteinuria >0.5 g/d
Fassett et al, 2010 (88)	Autosomal dominant polycystic kidney disease
JUPITER, 2010 (6)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
LORD, 2010 (89)	Serum creatinine level >1.5 mg/dL
Renke et al, 2010 (90)	Estimated glomerular filtration rate >45 mL/min and proteinuria >300 mg/24 h
ASCOT-LLA, 2011 (91)	Estimated glomerular filtration rate, 30 to 60 mL/min per 1.73 m^2
Han et al, 2011 (92)	Dialysis
SHARP, 2011 (12)	CKD (plasma creatinine level ≥1.7 mg/dL) or dialysis
Statin versus other statin	
Castelao et al, 1993 (94)	Kidney transplant
Raiola et al, 1998 (95)	Kidney transplant
Vergoulas et al, 1999 (96)	Kidney transplant
Celik et al, 2000 (97)	Kidney transplant
Tuncer et al, 2000 (98)	Kidney transplant
van den Akker et al, 2003 (99)	Dialysis
IDEAL, 2005 (100)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
TNT, 2008 (101)	Estimated glomerular filtration rate <60 mL/min per 1.73 m^2
PANDA, 2011 (102)	Urinary albumin–creatinine ratio >5 mg/mmol

CKD = chronic kidney disease.
* Year refers to the date of publication of subgroup data for people with CKD. **Appendix Table 2** provides definitions of trial acronyms.

Appendix Figure 1. **Summary of evidence search and selection.**



CKD = chronic kidney disease; LDL = low-density lipoprotein.
* Data from reference 11.

Appendix Table 2. Definitions of Trial Acronyms

Trial Name	Definition
4D	Deutsche Diabetes Dialyse Studie (German Diabetes and Dialysis Study)
4S	Scandinavian Simvastatin Survival Study
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ALERT	Assessment of Lescol in Renal Transplantation
ALLIANCE	Aggressive Lipid-Lowering Initiation Abates New Cardiac Events
ASCOT-LLA	Anglo-Scandinavian Cardiac Outcomes
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
CARDS	Collaborative Atorvastatin Diabetes Study
ESPLANADE	European Study for Preventing by Lipid-Lowering Agents and ACE (angiotensin-converting enzyme)-Inhibition Dialysis Endpoints
HPS	MRC/BHF (Medical Research Council/British Heart Foundation) Heart Protection Study
IDEAL	Incremental Decrease in End Points Through Aggressive Lipid Lowering
JUPITER	Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin
LIPS	Lescol Intervention Prevention Study
LORD	Lipid Lowering and Onset of Renal Disease
MEGA	Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese
PANDA	Protection Against Nephropathy in Diabetes with Atorvastatin
PERFECT	Patients with Endstage Renal Failure: An Evaluation of Cardiovascular Treatments
PPP	Pravastatin Pooling Project
PREVEND IT	Prevention of Renal and Vascular Endstage Disease Intervention Trial
SHARP	Study of Heart and Renal Protection
SOLAR	Study of Lescol [fluvastatin] in Acute Rejection
TNT	Treating to New Targets
UK-HARP-I	First United Kingdom Heart and Renal Protection

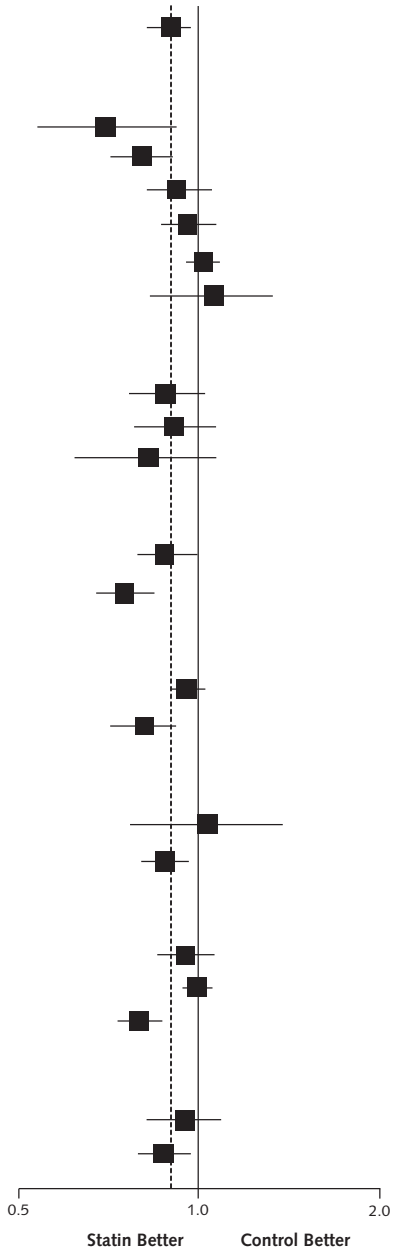
Appendix Table 3. Effects of Statin Therapy on Lipid Concentrations, Proteinuria, and Kidney Function in Persons With CKD

Outcome	Comparisons/Participants, *n/N*	Random-Effects Mean Difference (95% CI)	I^2, %
Total cholesterol	50/6938	–1.2 mmol/L (−1.4 to −1.0 mmol/L) –47.5 mg/dL (−54.7 to −40.3 mg/dL)	94
LDL cholesterol	46/23 591	−1.1 mmol/L (−1.3 to −1.0 mmol/L) −43.1 mg/dL (−49.5 to −36.7 mg/dL)	91
HDL cholesterol	45/22 804	0.02 mmol/L (−0.04 to 0.08 mmol/L) 0.60 mg/dL (−1.7 to 2.9 mg/dL)	86
Triglycerides	43/22 548	−0.2 mmol/L (−0.4 to −0.1 mmol/L) −21.9 mg/dL (−31.3 to −12.5 mg/dL)	86
Glomerular filtration rate	16/3867	2.89 mL/min (−0.58 to 6.36 mL/min)	78
Urinary protein excretion	9/492	−0.32 g/24 h (−0.61 to −0.03 g/24 h)	85

CKD = chronic kidney disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Appendix Figure 2. **Subgroup analysis of potential sources of heterogeneity on effects of statin treatment versus placebo or no treatment for all-cause mortality.**

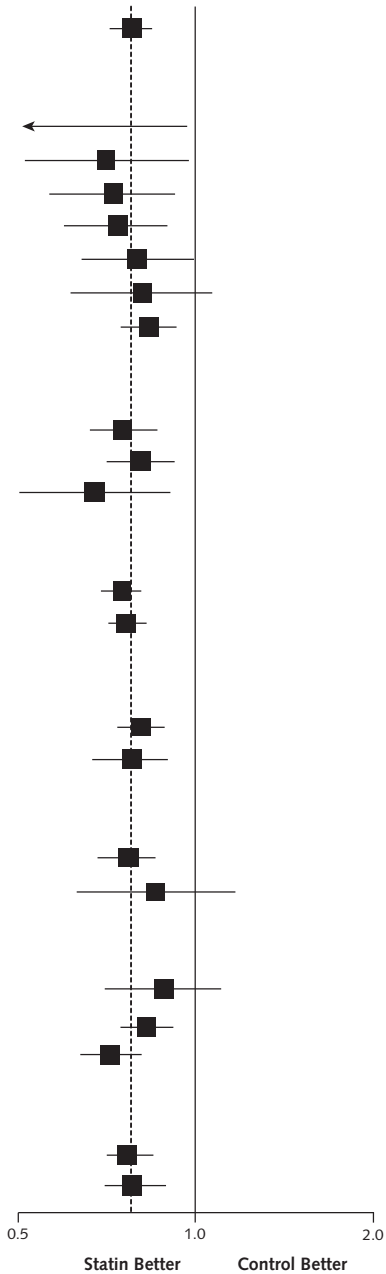
Covariate	Studies or Subsets, *n*	Participants, *n*	Random-Effects Relative Risk (95% CI)	*P* Value for Subgroup Interaction	Explained Variance, %*
None	32	45 154	0.89 (0.82 to 0.97)	NA	0
Statin					
Simvastatin	8	2787	0.70 (0.54 to 0.91)		
Pravastatin	5	20 714	0.80 (0.71 to 0.90)		
Rosuvastatin	5	6304	0.92 (0.81 to 1.04)	0.01	
Atorvastatin	8	3207	0.96 (0.86 to 1.07)		78
Simvastatin plus ezetimibe	1	9270	1.01 (0.95 to 1.09)		
Fluvastatin	5	2872	1.05 (0.83 to 1.33)		
Dose (simvastatin equivalent)					
0–20 mg/d	17	31 896	0.88 (0.77 to 1.01)		
20–40 mg/d	10	9171	0.91 (0.78 to 1.06)	0.77	
40–80 mg/d	5	4087	0.82 (0.62 to 1.07)		0
Estimated glomerular filtration rate					
<60 mL/min per 1.73 m^2	5	9109	0.88 (0.79 to 0.98)	0.04	
≥60 mL/min per 1.73 m^2	3	14 726	0.75 (0.67 to 0.84)		100
Baseline cholesterol level					
<6.0 mmol/L (230 mg/dL)	19	24 696	0.95 (0.89 to 1.01)	0.02	
≥6.0 mmol/L (230 mg/dL)	10	17 301	0.81 (0.71 to 0.92)		66
Age					
>55 y	12	41 140	1.03 (0.77 to 1.37)	0.29	
≤55 y	20	4014	0.88 (0.80 to 0.96)		0
Proportion with diabetes					
>50%	3	2247	0.95 (0.85 to 1.06)		
20%–50%	9	15 094	0.99 (0.94 to 1.04)	<0.001	
<20%	11	24 033	0.79 (0.73 to 0.86)		100
Allocation concealment					
Adequate	10	34 380	0.93 (0.81 to 1.08)	0.41	
Inadequate or unclear	22	10 774	0.87 (0.78 to 0.96)		0



NA = not available.
* "Explained variance" refers to the proportion of variance in the overall treatment effect estimate explained by stage of chronic kidney disease.

Appendix Figure 3. **Subgroup analysis of potential sources of heterogeneity on effects of statin treatment versus placebo or no treatment for major cardiovascular events.**

Covariate	Studies or Subsets, *n*	Participants, *n*	Random-Effects Relative Risk (95% CI)	*P* Value for Subgroup Interaction	Explained Variance, %*
Overall	20	45 362	0.78 (0.71 to 0.84)	NA	0
Statin					
Lovastatin	1	304	0.42 (0.18 to 0.97)		
Fluvastatin	2	2412	0.71 (0.52 to 0.98)		
Simvastatin	3	3652	0.73 (0.57 to 0.92)	0.73	0
Pravastatin	4	20 666	0.74 (0.60 to 0.89)		
Atorvastatin	5	2980	0.80 (0.64 to 1.00)		
Rosuvastatin	3	6078	0.82 (0.62 to 1.07)		
Simvastatin plus ezetimibe	2	9270	0.84 (0.75 to 0.94)		
Dose (simvastatin equivalent)					
0–20 mg/d	11	31 424	0.76 (0.67 to 0.86)		
20–40 mg/d	7	10 092	0.81 (0.71 to 0.92)	0.47	0
40–80 mg/d	2	3846	0.68 (0.51 to 0.90)		
Estimated glomerular filtration rate					
<60 mL/min per 1.73 m^2	7	15 607	0.76 (0.70 to 0.82)	0.77	0
≥60 mL/min per 1.73 m^2	3	14 656	0.77 (0.72 to 0.83)		
Baseline cholesterol level					
<6.0 mmol/L (230 mg/dL)	14	24 297	0.81 (0.74 to 0.89)	0.64	0
≥6.0 mmol/L (230 mg/dL)	4	16 758	0.78 (0.67 to 0.90)		
Age					
>55 y	16	41 050	0.77 (0.69 to 0.85)	0.48	0
≤55 y	3	2983	0.86 (0.63 to 1.17)		
Proportion with diabetes					
>50%	2	2225	0.88 (0.71 to 1.10)		
20%–50%	7	16 196	0.83 (0.75 to 0.92)	0.11	18.1
<20%	7	23 586	0.72 (0.64 to 0.81)		
Allocation concealment					
Adequate	9	35 275	0.73 (0.62 to 0.86)	0.42	0
Inadequate or unclear	11	10 087	0.79 (0.71 to 0.88)		



NA = not available.
* "Explained variance" refers to the proportion of variance in the overall treatment effect estimate explained by stage of chronic kidney disease.

Appendix Table 4. **Subgroup Analysis of Potential Sources of Heterogeneity on Effect of Statins Versus Placebo or No Treatment on Total and LDL Cholesterol Levels at End of Trial**

Covariate	Classification	Total Cholesterol Level at End of Treatment				LDL Cholesterol Level at End of Treatment			
		Comparisons/ Participants, *n/N*	Mean Difference (95% CI), *mg/dL**	P Value for Interaction†	Heterogeneity Explained, %	Comparisons/ Participants, *n/N*	Mean Difference (95% CI), *mg/dL**	*P* Value for Interaction†	Heterogeneity Explained, %
None	Intercept	50/6938	−47.5 (−54.7 to −40.3)	–	0.0	46/23 591	−43.2 (−49.4 to −37.1)	–	0.0
Stage of CKD	Not receiving dialysis	25/2105	−50.6 (−61.0 to −40.3)	0.66	0.0	24/18 879	−44.0 (−52.3 to −35.4)	0.95	0.0
	Dialysis	13/1763	−46.1 (−60.8 to −31.5)			11/1707	−41.3 (−54.4 to −28.3)		
	Transplant	12/3070	−42.7 (−57.2 to −28.2)			11/3005	−43.5 (−56.6 to −30.4)		
Type of statin	Lovastatin	2/99	−48.1 (−81.0 to −15.3)	0.165	4.9	1/34	−38.6 (−80.1 to 2.94)	0.114	7.8
	Simvastatin	16/952	−54.0 (−66.8 to −41.2)			16/982	−48.2 (−58.5 to −37.8)		
	Rosuvastatin	4/291	−39.6 (−63.9 to −15.4)			4/291	−29.5 (−48.8 to −10.3)		
	Atorvastatin	9/1504	−55.8 (−73.0 to −38.4)			8/1471	−51.1 (−65.7 to −36.5)		
	Fluvastatin	8/2984	−42.7 (−59.7 to −25.8)			7/2962	−39.4 (−54.1 to −24.7)		
	Pravastatin	7/994	−30.7 (−50.6 to −10.8)			9/17 811	−34.2 (−47.3 to −21.1)		
	Cerivastatin	1/40	−96.0 (−149.0 to −43.0)			1/40	−86.0 (−126.3 to −45.7)		
	Pitavastatin	2/50	−23.4 (−58.6 to 11.8)			–	–		
Statin dose‡	0–20 mg/d	38/2951	−42.9 (−50.8 to −34.9)	0.028	13.0	34/19 573	−43.1 (−50.1 to −36.2)	0.037	12.1
	20–40 mg/d	9/3866	−54.7 (−69.8 to −39.7)			9/3842	−35.6 (−47.9 to −23.2)		
	40–80 mg/d	3/121	−79.1 (−107.6 to −50.7)			3/121	−69.9 (−93.2 to −46.5)		
Glomerular filtration rate	<60 mL/min per 1.73 m^2	8/609	−52.6 (−70.7 to −34.6)	0.93	0.0	9/5086	−44.6 (−59.0 to −30.0)	0.69	0.0
	≥60 mL/min per 1.73 m^2	8/306	−51.6 (−70.5 to −32.6)			8/12 581	−49.0 (−65.8 to 32.1)		
Age	<55 y	24/4524	−42.2 (−52.5 to −31.8)	0.108	5.0	21/4238	−41.6 (−51.1 to −32.1)	0.43	0.0
	≥55 y	22/2225	−54.8 (−66.2 to −43.2)			22/18 905	−46.9 (−56.3 to −37.6)		
Diabetes	<20%	14/1889	−49.2 (−64.4 to −34.1)	0.49	0.0	15/18 710	−43.9 (−56.2 to −31.5)	0.95	0.0
	20%–50%	6/2442	−59.9 (−83.8 to −35.8)			6/2442	−40.4 (−60.7 to −20.1)		
	>50%	9/1407	−41.3 (−61.8 to −20.8)			7/1635	−44.8 (−64.7 to −24.9)		
Baseline cholesterol level§	<6.0 mmol/L (<230 mg/dL)	26/3793	−36.2 (−45.0 to −27.5)	<0.001	26.9	22/8141	−31.8 (−38.8 to −24.9)	<0.001	41.0
	≥6.0 mmol/L (≥230 mg/dL)	21/2942	−62.5 (−72.9 to −52.0)			22/15 271	−56.3 (−64.0 to −48.7)		
Allocation concealment	Inadequate or unclear	40/4047	−51.5 (−59.3 to −43.7)	0.032	9.5	36/3930	−45.6 (−52.6 to −38.5)	0.186	2.2
	Adequate	10/2891	−33.1 (−48.2 to −17.9)			10/19 661	−36.1 (−48.6 to −23.4)		

CKD = chronic kidney disease; LDL = low-density lipoprotein.

* Values less than 0 indicate that statin therapy is favored, whereas values greater than 0 indicate that placebo is favored. To convert values to mmol/L, multiply by 0.0259.

† Analysis-of-variance *P* value for difference across subgroups.

‡ Statin dose expressed as simvastatin equivalent in all trials.

§ Mean baseline serum cholesterol level in trial; data for treatment group shown if overall baseline cholesterol level was not provided.