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Original Investigation

Effect of Statins on Kidney Disease Outcomes: A Systematic Review and Meta-analysis

Xiaole Su, MD,[1,2] Lu Zhang, MD,[1,3] Jicheng Lv, MD, PhD,[1] Jinwei Wang, PhD,[1] Wanyin Hou, MD,[1] Xinfang Xie, MD,[1] and Hong Zhang, MD, PhD[1]

Background: The effects of statin administration on kidney disease outcomes remain controversial. We undertook a systematic review and meta-analysis to assess the efficacy of statins on kidney outcomes.

Study Design: We conducted a meta-analysis of randomized controlled trials (RCTs) using MEDLINE (1946 to August 31, 2015), EMBASE (1966 to August 31, 2015), and the Cochrane Library database (no date restriction).

Setting & Population: Adults who were not receiving dialysis, for whom kidney disease outcomes were reported.

Selection Criteria for Studies: RCTs in which statins were given for at least 6 months and kidney outcomes were measured.

Intervention: Statins versus control, including placebo, usual care, and different types or doses of statins.

Outcomes: Kidney failure events, rate of change in estimated glomerular filtration rate (eGFR) per year, change in proteinuria or albuminuria, and, in patients with chronic kidney disease, major cardiovascular events.

Results: 57 eligible studies with 143,888 participants were included. Statin treatment did not produce an apparent beneficial effect for kidney failure events (OR, 0.98; 95% CI, 0.87-1.10; $P = 0.7$) or end-stage renal disease events (OR, 0.98; 95% CI, 0.90-1.07; $P = 0.7$). However, mean difference for rate of decline in eGFR (0.41 [95% CI, 0.11-0.70] mL/min/1.73 m^2 per year slower in statin recipients) and standardized mean difference for change in proteinuria or albuminuria (-0.65 [95% CI, -0.94 to -0.37] standard deviation units, statin recipients vs controls) were statistically significant. In addition, statin therapy significantly reduced the risk for cardiovascular events (OR, 0.69; 95% CI, 0.61-0.79; $P < 0.001$) in patients with chronic kidney disease.

Limitations: Inclusion of several post hoc analyses from large RCTs and substantial heterogeneity in secondary outcome analyses.

Conclusions: Statin therapy does not reduce the risk for kidney failure events in adults not receiving dialysis for whom kidney disease outcomes were reported, but may modestly reduce proteinuria and rate of eGFR decline.

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INDEX WORDS: Chronic kidney disease (CKD); kidney disease outcomes; kidney failure; statins; hydroxymethylglutaryl-CoA reductase inhibitor; lipid lowering; dyslipidemia; atorvastatin; rosuvastatin; simvastatin; pravastatin; estimated glomerular filtration rate (eGFR); proteinuria; albuminuria; cardiovascular events; systematic review.

Chronic kidney disease (CKD) is a major health problem and is associated with increased risk for all-cause mortality, cardiovascular disease, and end-stage renal disease (ESRD).[1-5] Abnormal lipid metabolism is common in patients with kidney disease.[6] Experimental studies have shown that dyslipidemia is causally associated with glomerular injury, resulting in glomerulosclerosis.[7,8] Post hoc analyses of several large trials have demonstrated that dyslipidemia is significantly associated with increased risk for developing reduced kidney function or faster estimated glomerular filtration rate (eGFR) decline in a general population without kidney disease.[9,10]

The effects of statins on kidney disease progression remain controversial. Several trials have evaluated the effects of statins on kidney disease outcomes. Although some trials have shown benefits of statins,[11-13] others have shown no effect.[14-16] Thus, there is uncertainty about the presence and magnitude of their renal protective effects. Furthermore, most published articles were based on post hoc analyses of cardiovascular benefits of statin treatment. A previous overview of trials using patients with or without kidney disease found that statin therapy decreased proteinuria and led to a slight decrease in the rate of kidney function loss, mainly in a population of patients with early kidney

From the [1]Renal Division, Peking University First Hospital; Peking University Institute of Nephrology; Key Laboratory of Renal Disease, Ministry of Health of China; Key Laboratory of Chronic Kidney Disease Prevention and Treatment (Peking University), Ministry of Education, Beijing; [2]Renal Division, Shanxi Medical University Second Hospital, Shanxi Kidney Disease Institute, Taiyuan; and [3]Renal Division, Jiangsu Province Hospital of Chinese Medicine, Nanjing, China.

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Address correspondence to Jicheng Lv, MD, PhD, Renal Division, Peking University First Hospital, Institute of Nephrology, Peking University, No. 8, Xishiku Street, Xicheng District, Beijing, China. E-mail: jichenglv75@gmail.com

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disease.[17] However, the large Study of Heart and Renal Protection (SHARP) included 6,245 participants with advanced CKD and found that statin administration did not reduce the risk for kidney failure or rate of change in eGFR.[14] Prior systematic reviews have provided strong evidence to suggest that statin therapy reduced the risk for major vascular events, as well as death, in patients with kidney disease across a wide range of kidney function.[18-20]

With this systematic review, our aim was to synthesize all available clinical trial information for statin administration in people with or without kidney disease and evaluate the efficacy of statins on kidney outcomes.

METHODS

Data Sources and Search Strategy

We performed this systematic review according to a prespecified protocol (Item S1, available as online supplementary material) and reporting was done in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.[21] Relevant studies were identified by searching the following data sources: MEDLINE by Ovid (from 1946 to August 31, 2015), EMBASE (from 1966 to August 31, 2015), and the Cochrane Library database (Cochrane Central Register of Controlled Trials; no date restriction), with relevant text words and medical subject headings that included all spellings of "kidney," "kidney function tests," "glomerular filtration rate," "proteinuria," "hydroxymethylglutaryl-CoA reductase inhibitor," "simvastatin," "atorvastatin," "rosuvastatin," and "pravastatin" (Item S1). Trials were considered without language restriction. To ensure a comprehensive literature search, we examined reference lists from included articles. The ClinicalTrials.gov website was also searched for randomized trials that were registered as completed but not yet published.

Study Selection and Outcome Estimation

We included data from randomized controlled trials (RCTs) in which a statin was given for at least 6 months to adults who were not receiving dialysis, irrespective of whether participants had CKD at baseline, and for which kidney outcomes, including kidney failure events, eGFR, or proteinuria data, were reported.

The primary outcome was kidney failure events, including >25% or 50% decrease in eGFR, doubling of serum creatinine level, or ESRD as defined by the authors of each study during the follow-up period. If more than one of the methods for defining kidney failure event was provided by a study, we used that reporting more events for increased study power. Secondary outcomes included the following.

1. Rate of change in eGFR per year. We pooled eGFR data calculated by the MDRD (Modification of Diet in Renal Disease) Study formula, CKD-EPI (CKD Epidemiology Collaboration) or Cockcroft-Gault equation, and creatinine clearance (milliliters per minute or milliliters per minute per 1.73 m^2). Positive differences in the rate of change in eGFR represent a slower decline in the statin group than in the control group.
2. Change in proteinuria or albuminuria from baseline to end of follow-up. Results from urinary protein excretion or urinary albumin excretion were converted to grams per 24 hours. Results from protein-creatinine ratio (PCR) or albumin-creatinine ratio (ACR) were converted to milligrams per gram of creatinine. Negative differences in change in proteinuria represent a greater decrease in the statin group than in the control group.
3. Effect of statin administration on major cardiovascular events in a subgroup of patients with CKD (defined as a composite including fatal or nonfatal myocardial infarction, fatal or nonfatal stroke, revascularization procedures, cardiovascular death, and heart failure or comparable definitions used by individual authors).

Data Extraction and Quality Assessment

Published reports were obtained for each eligible trial, and relevant information was extracted into a spreadsheet. The data sought included study characteristics (design, method of randomization, and withdrawals/dropouts); baseline patient characteristics (age, sex, cause of kidney disease, mean proteinuria or albuminuria, eGFR, fasting serum low-density lipoprotein cholesterol [LDL-C] concentration); type of statin used; dose of drug; follow-up duration; change in eGFR, proteinuria or albuminuria, and LDL-C concentrations; and outcome events. When the required quantitative data were not provided in relevant articles, we used g3 data software (www.frantz.fi/software/g3data.php) to extract exact numbers from published figures.[18]

We evaluated all potentially relevant sources of bias using the Cochrane Collaboration risk of bias tool,[22,23] including assessment of financial conflicts of interest as has been recommended.[24] We developed operational definitions for high, low, and unclear risk of bias for each of the 7 domains (Item S2). We summarized both individual (Fig S1) and aggregate (Fig S2) risk of bias data for the included studies. The literature search, study selection, data extraction, and quality assessment were undertaken independently by 2 authors (X.S. and L.Z.) using a standardized approach according to the predefined protocol (Item S1). Disagreement was resolved by consensus or by discussion with a third author (J.L.).

Data Synthesis and Analysis

Individual patient data were not available from the studies in this analysis, so tabular data were used. If odds ratios (ORs) were unavailable in the original article, individual study ORs and 95% confidence intervals (CIs) were calculated from event numbers and the total population at risk extracted from each trial before data pooling. In consideration of potential heterogeneity among the included studies, which cannot be avoided, the random-effects model was applied using the empirical Bayes procedure[25] with Knapp-Hartung modification based on *t* distribution[26] to analyze all outcomes. Simultaneously, DerSimonian-Laird[27] and restricted maximum likelihood[28] estimators with CIs contructed by normal distribution[23,27] or Knapp-Hartung approach[26] were also performed as sensitivity analysis. For a binary outcome, a fully Bayesian method assuming a binomial likelihood on the log-odds scale rather than normal approximation was implemented by WinBUGS (Medical Research Council Biostatistics Unit).[29,30] We used noninformative priors with vague normal (mean, 0; variance, 100,000) and uniform (0-1) prior distributions for parameters. Three Markov chain Monte Carlo chains of 55,000 iterations each were used to compute the posterior distributions, after 5,000 burn-in iterations (see codes in Item S3). We used the Brooks-Gelman-Rubin statistic and inspection of trace plots to check for convergence of Markov chain Monte Carlo chains.[31] Mean differences were used to pool rates of change in eGFRs, which were defined as difference from baseline in eGFR divided by number of years between creatinine measurements. Standardized mean differences were used to pool results from all studies that reported changes in proteinuria or albuminuria (including urinary albumin excretion, urinary protein excretion, ACR, or PCR). When data for change from baseline were available in the included trials, we directly extracted them from the literature. When the change-from-baseline standard deviation was missing, we calculated it using correlations that were estimated from other included studies that had a similar follow-up period and reported in considerable detail according to the imputed formulation and its related interpretations in Cochrane Handbook.[23] We replaced missing mean data with median data.[32] Missing standard deviation

data were imputed using interquartile range (dividing by 1.35 only when large sample size),[23] full range (dividing the range by values from the table of critical values for Pearson table),[33,34] or reported *P* value.[23] Summary estimates of mean differences and standardized mean differences were also obtained using a random-effects model.

The percentage of variability across studies attributable to heterogeneity beyond chance was estimated using the I^2 statistic. We explored potential heterogeneity by comparing summary results obtained from subsets of studies grouped by number of patients, mean age, type and doses of statin, follow-up duration, baseline mean LDL-C concentrations and their differences in changes, baseline mean eGFR, baseline mean proteinuria or albuminuria, and different participants by classifying them in CKD (either proteinuria or GFR $\leq$ 60 mL/min/1.73 m^2) and non-CKD groups, as well as cardiovascular disease and non–cardiovascular disease groups. Between-subgroup heterogeneity was assessed by χ^2 test and metaregression.[35] A 2-sided $P < 0.05$ was considered statistically significant, and statistical analyses were performed using Metafor packages from R software, version 3.1.1 (R Foundation for Statistical Computing); WinBUGS, version 1.4.3; RevMan, version 5.0.16 (The Nordic Cochrane Centre, Cochrane Collaboration); and STATA, version 12.0 (StataCorp LP).

RESULTS

Search Results and Characteristics of Included Studies

The literature search yielded 4,192 articles, of which 176 were reviewed in full text (Fig 1). As shown in Table 1 and Table S1, a total of 57 eligible trials reported in 67 publications[11-18,36-94] with a total of

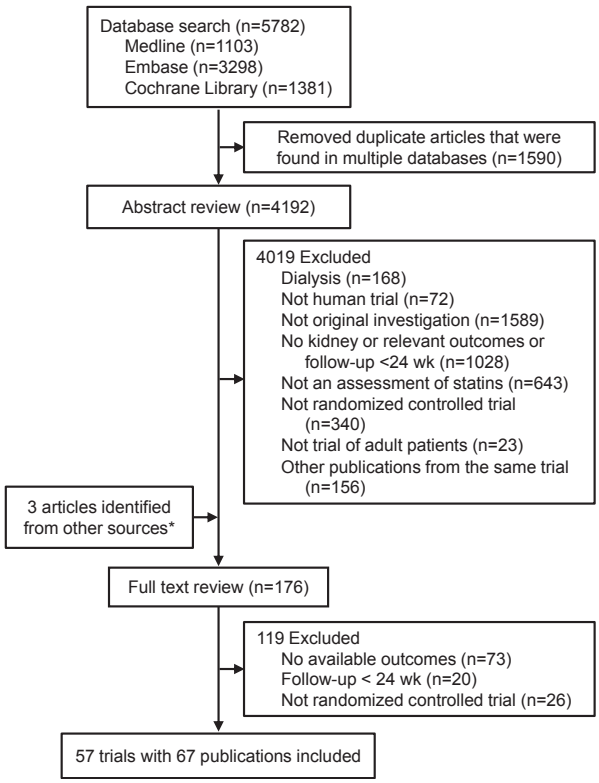

Figure 1. Identification process for eligible studies. *Searching on ClinicalTtrials.gov and references.

Table 1. Summary of Characteristics of Included Trials and Patients

Type of Statin	No. of Studies (No. of Patients)	Sample Size	Follow-up, y	Male Sex	Age, y	Baseline Proteinuria, g/dL	Baseline eGFR, mL/min	Baseline LDL-C, mmol/L
Pravastatin[a]	12 (37,289)	441 (33-10,355)	2.9 (0.5-6.0)	61.2%	55 (48-67)	0.76 (0.02-1.3)	71.0 (33.3-88.0)	3.8 (2.9-5.3)
Simvastatin[a]	10 (26,035)	47 (18-15,696)	1.0 (0.5-5.5)	65.2%	58 (32-65)	0.07 (0.02-5.20)	70.8 (36.0-96.9)	4.5 (2.9-7.2)
Atorvastatin[a]	10 (21,603)	862 (25-10,305)	2.9 (0.5-5.0)	69.0%	63 (57-82)	1.30 (0.01-2.20)	64.4 (30.5-76.5)	3.5 (2.5-5.1)
Fluvastatin[a]	5 (2,479)	80 (43-2,102)	1.0 (0.5-5.1)	57.7%	50 (23-58)	1.13 (0.45-10.5)	61.8 (59.5-107.0)	4.3 (3.6-7.7)
Rosuvastatin[a]	5 (23,102)	147 (38-17,802)	1.0 (0.5-2.3)	61.9%	65 (46-73)	0.14 (0.14-0.14)	69.8 (53.5-100.0)	3.3 (2.5-3.6)
Lovastatin[a]	2 (5,028)	2,014 (34-4,994)	3.7 (2.0-5.3)	70.4%	57 (57-58)	0.98 (0.98-0.98)	85.5 (83.6-87.3)	4.0 (3.9-4.2)
Pitavastatin[a]	2 (50)	25 (20-30)	0.8 (0.5-1.0)	60.0%	45 (40-50)	0.93 (0.15-1.70)	NA	NA
Cerivastatin[a]	2 (100)	50 (40-60)	0.5 (0.5-0.5)	60.0%	49 (41-57)	0.97 (0.14-1.8)	103.0 (103.0-103.0)	5.6 (5.4-5.8)
Different statin compared	6 (14,016)	598 (120-8,836)	1 (1.5-4.8)	65.4%	60 (54-62)	NA	73.3 (68.2-85.0)	3.9 (2.7-5.3)
High vs low dose compared	3 (14,186)	4,181 (349-9,656)	3.5 (2.0-5.0)	67.4%	60 (57-61)	NA	60.2 (68.2-85.0)	2.9 (2.5-4.4)
All	57 (143,888)	120 (18-15,696)	1.0 (0.5-6.0)	64.5%	58 (23-82)	0.81 (0.01-10.50)	69.8 (33.3-107.0)	3.8 (2.5-7.7)

Note: Unless otherwise indicated, values are given as median (range).
Abbreviations: eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NA, not available.
[a]Versus placebo or usual care.

143,888 participants were included in this review. Overall, 8 different statins were studied, and follow-up duration ranged from approximately 6 months to 6 years. Thirty-four trials were placebo controlled and 14 trials were usual-care controlled. Six trials compared different statins, and 3 trials compared intensive lipid-lowering therapy and conventional or low-dose therapy with the same statin. Twenty-one trials reported post hoc analysis of the subgroup with all patients.

The reported trial quality varied substantially (Figs S1 and S2). In the meta-analysis for primary outcome, data were obtained from studies that generally had lower risk of bias than other included studies: random sequence generation was assessed as low risk in 57%, allocation concealment was low risk in 50%, participants and personnel were blinded in 93%, outcome assessors were blinded in 79%, and attrition and reporting bias were low risk in 86%. However, in meta-analyses for secondary outcome, data were obtained from studies with higher risk of bias (Fig S1). In all included studies, biases of conflicts of interest from pharmaceutical industry study funding and author-industry financial relationships were high risk in 40% and 42%, respectively (Figs S1 and S2). In order to investigate reporting/published bias, we searched and found that 27 studies reported their protocols in 176 full-text peer-reviewed articles. In studies in which no outcomes of interest for this systematic review were reported, we did not find any preplanned kidney outcome.

Effect of Statins on Designated Outcomes

Effect on Kidney Function

Data for effects of statin treatment on kidney failure events were available from 13 publications[11-16,36-42] concerning 16 trials, which included 81,487 participants and 8,498 events, and on ESRD events, from 4 trials,[12,14,16,41] which included 18,776 participants and 2,543 events. As shown in Fig 2, when compared with placebo or usual-care control groups, statin treatment did not produce an apparent beneficial effect for kidney failure events in general (OR, 0.98; 95% CI, 0.87-1.10; $P = 0.7$) or for ESRD events specifically (OR, 0.98; 95% CI, 0.90-1.07, $P = 0.7$); there was no evidence of heterogeneity in the magnitude of effect across included studies ($I^2 = 50\%$ [95% CI, 0%-75%]; $I^2 = 0\%$ [95% CI, 0%-80%]). Three trials reported in 2 publications[36,40] with 10,905 patients and 158 kidney failure events compared effects of a high-dose statin to a low-dose statin. Intensive lipid lowering reduced the risk for kidney failure (OR, 0.69; 95% CI, 0.50-0.96; Fig S3). This effect was mainly dominated by the TNT (Treating to New Targets) Study.[36] There was no statistical heterogeneity in all subgroup analyses apart from the borderline significance for effects of different types of statins ($P = 0.07$; Table S2).

The effect of statin administration on rate of change in eGFR was available in 47 trials of 128,601 participants.[11-16,36-39,43-76] When considering studies that

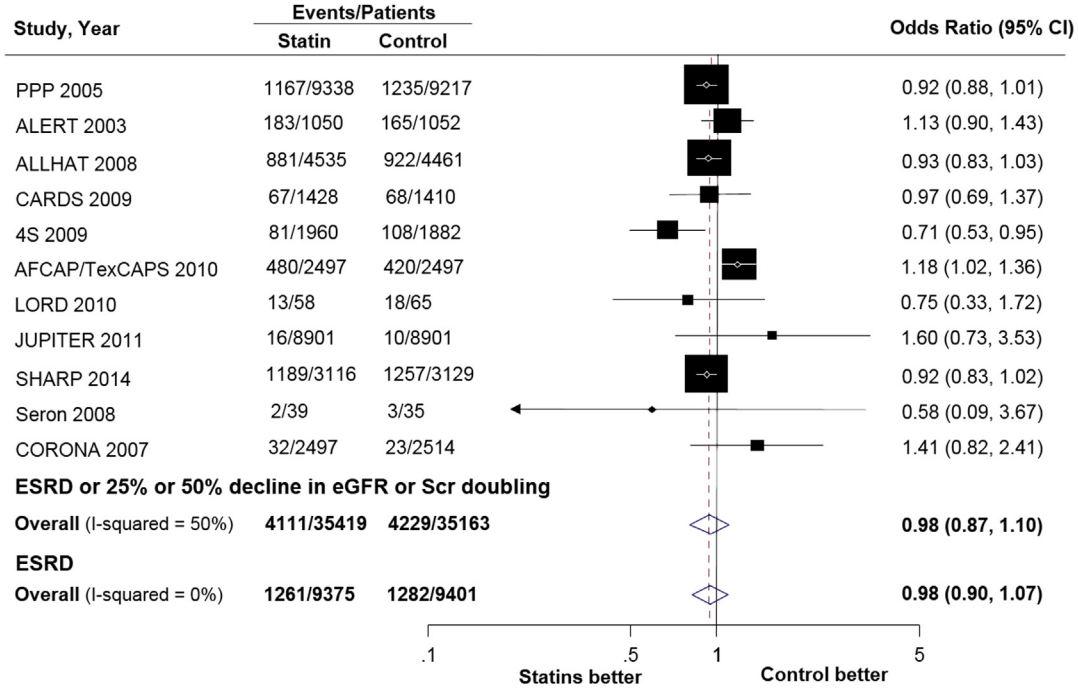

Figure 2. Forest plot for kidney failure events. Abbreviations and definitions: CI, confidence interval; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PPP, Pravastatin Pooling Project (PPP) Study, including CARE, LIPID, and WOSCOPS studies, is a subgroup analysis of patients in the 3 studies; Scr, serum creatinine.

were placebo or usual-care controlled, statin therapy slowed the rate of eGFR decline by 0.41 mL/min/1.73 m^2 per year (95% CI, 0.11-0.70; Fig 3). There was evidence of significant heterogeneity for effects across included studies ($I^2 = 90\%$; 95% CI, 87%-92%). Intensive lipid lowering reduced the rate of eGFR decline by 0.35 (95% CI, 0.27-0.42) mL/min/1.73 m^2 per year (Fig S4). Compared to rosuvastatin or simvastatin, atorvastatin significantly slowed the rate of eGFR decline in direct comparison trials (mean differences of 2.45 and 0.33, respectively; Fig S5). Subgroup analysis showed that there was heterogeneity for the effects of different types of statins ($P < 0.001$; Table 2).

Effect on Proteinuria and Albuminuria

Twenty-nine trials with 4,968 participants reported data regarding the effects of statins on changes in proteinuria or albuminuria. Of these, 11 studies with a total of 2,833 participants provided data for urinary protein excretion[12,38,46-49,51,58,62,67,73]; 12 studies with 1,227 participants, urinary albumin excretion[43-45,52,54,55,63,77-81]; 5 studies with 788 participants, ACR[60,71,76,82]; and 1 study with 120 participants, PCR.[69] The standardized mean difference in change in proteinuria or albuminuria was statistically significant at −0.65 (95% CI, −0.94 to −0.37) compared with the placebo or usual-care control groups, with substantial

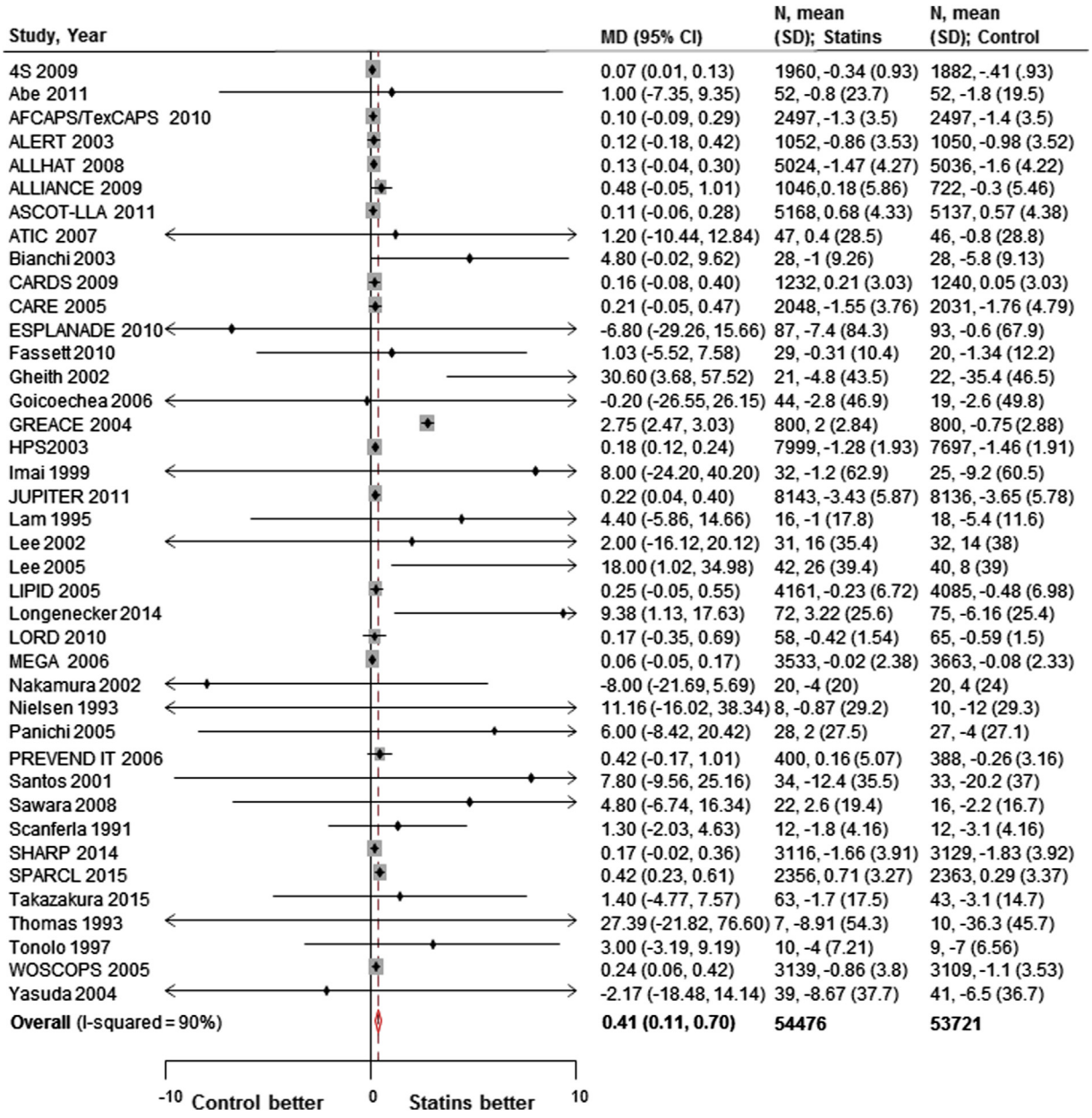

Figure 3. Forest plot for rate of change in estimated glomerular filtration rate (eGFR). Positive values in difference of change represent slower decline for eGFR in statin group than in control group. Abbreviations: CI, confidence interval; MD, mean difference; SD, standard deviation.

Table 2. Subgroup Analysis of Kidney Function by Outcome

Subgroup	No. of Trials	N	WMD/SMD (95% CI)	Mean LDL-C Difference, mmol/L	*P* for WMD/SMD	I^2	*P* for Heterogeneity Test[a]
Rate of Change in eGFR							
Statin type							
Atorvastatin	9	21,212	0.78 (0.02 to 1.55)	1.1	<0.001	97%	<0.001
Pravastatin	11	36,961	0.13 (0.06 to 0.21)	0.8	<0.001	0%	
Rosuvastatin	4	16,568	2.19 (−1.60 to 5.99)	1.1	0.1	37%	
Simvastatin	9	25,983	0.13 (0.07 to 0.19)	1.4	<0.001	12%	
Cerivastatin	1	40	−8.00 (−21.69 to 5.69)	1.9	0.3	—	
Lovastatin	2	5,028	0.10 (−0.09 to 0.30)	1.0	0.3	0%	
Fluvastatin	4	2,405	3.01 (−10.79 to 16.82)	1.2	0.7	70%	
Atorvastatin vs other statins	5	10,399	0.94 (−0.68 to 2.56)	0.4	0.1	37%	
High vs low dose	2	10,005	0.35 (0.27 to 0.42)	0.4	0.4	0%	
Clinical characteristics of participants							
CVD	8	57,758	0.54 (0.21 to 0.86)	1.0	0.001	97%	0.06
Non-CVD	32	50,448	0.17 (0.07 to 0.26)	1.1	<0.001	22%	
CKD	27	17,230	0.15 (0.08 to 0.22)	1.0	<0.001	0%	0.3
Non-CKD	11	52,348	0.55 (0.16 to 0.94)	0.9	0.003	97%	
Baseline eGFR							
<60 mL/min/1.73 m^2	12	7,039	0.19 (0.01 to 0.37)	1.0	0.04	0%	0.4
≥60 mL/min/1.73 m^2	26	85,365	0.41 (0.02 to 0.80)	0.9	0.04	98%	
Baseline proteinuria or albuminuria							
<1 g/d	13	12,009	0.17 (0.04 to 0.30)	1.0	0.01	0%	0.8
≥1 g/d	9	670	4.08 (−2.79 to 10.96)	1.3	0.2	73%	
Difference of LDL-C decline[b]							
≥1.4 mmol/L	9	24,023	0.94 (0.04 to 1.85)	1.8	0.03	97%	0.9
1.0-<1.4 mmol/L	10	29,956	0.18 (0.12 to 0.23)	1.1	0.009	36%	
0.6-<1.0 mmol/L	9	29,903	0.17 (0.07 to 0.28)	0.9	0.001	0%	
<0.6 mmol/L	10	38,995	0.16 (−0.06 to 0.38)	0.4	0.2	86%	
Change of Proteinuria or Albuminuria							
Statin type							
Atorvastatin	4	310	−0.71 (−1.44 to 0.02)	1.8	0.06	80%	<0.001
Pravastatin	6	1,089	−0.60 (−1.11 to −0.08)	0.9	0.02	89%	
Rosuvastatin	2	142	−0.59 (−1.03 to −0.15)	1.0	0.009	32%	
Simvastatin	5	173	−0.21 (−0.73 to 0.30)	1.4	0.4	60%	
Cerivastatin	2	100	−1.75 (−2.22 to −1.29)	1.8	<0.001	0%	
Lovastatin	1	34	−0.48 (−1.16 to 0.21)	1.0	0.2	-	
Fluvastatin	4	2,405	−0.10 (−0.49 to 0.28)	1.5	0.6	84%	
Pitavastatin	2	50	−1.52 (−2.66 to −0.38)	NA	0.009	67%	
Atorvastatin vs rosuvastatin[c]	3	665	−0.23 (−0.39 to −0.07)	0.2	0.005	0%	
Clinical characteristics of participants							
CVD	2	139	−0.87 (−2.17 to 0.42)	0.9	0.1	92%	0.1
Non-CVD	22	4,449	−0.57 (0.80 to −0.34)	1.1	<0.001	89%	
CKD	20	2,801	−0.62 (−1.10 to −0.17)	1.1	0.02	85%	0.2
Non-CKD	5	930	−0.52 (−1.21 to 0.17)	1.2	0.1	88%	
Baseline eGFR							
<60 mL/min/1.73 m^2	7	505	−0.51 (−0.85 to −0.18)	1.1	0.003	69%	0.1
≥60 mL/min/1.73 m^2	21	4,366	−0.47 (−0.71 to −0.24)	1.3	<0.001	89%	
Baseline proteinuria or albuminuria							
<30 mg/d	5	930	−0.52 (−1.21 to 0.17)	1.2	0.1	88%	0.1
30-300 mg/d	6	2,308	−0.60 (−1.10 to −0.10)	1.1	0.02	84%	
>300 mg/d	12	831	−0.66 (−1.10 to −0.21)	1.5	0.004	89%	

(Continued)

Table 2 (Cont'd). Subgroup Analysis of Kidney Function by Outcome

Subgroup	No. of Trials	N	WMD/SMD (95% CI)	Mean LDL-C Difference, mmol/L	*P* for WMD/SMD	I^2	*P* for Heterogeneity Test[a]
Difference of LDL-C decline[b]							
≥1.7 mmol/L	5	266	−1.20 (−1.97 to 0.44)	2.0	0.002	87%	0.7
1.2-<1.7 mmol/L	6	2,348	−0.54 (−1.03 to −0.06)	1.4	0.03	85%	
0.8-<1.2 mmol/L	5	1,197	−0.32 (−0.77 to 0.13)	1.0	0.2	89%	
<0.8 mmol/L	6	303	−0.20 (−0.59 to 0.19)	0.6	0.3	62%	

Note: Positive values in difference of change represent slower decline in eGFR in statin group than in control group. Negative values in difference of change represent greater decreases for proteinuria or albuminuria in statin group than in control group.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein cholesterol; NA, not available; SMD, standardized mean difference; WMD, weighted mean difference.

[a]*P* value calculated by χ^2 statistics was shown. Statistical significance of results from meta regression was consistent.

[b]Between treatment and control groups.

[c]Trials comparing other statins were not found.

heterogeneity (I^2 = 89%; 95% CI, 86%-92%; Fig 4). Compared to rosuvastatin, atorvastatin significantly reduced ACR/PCR in direct comparison trials (standardized mean difference, −0.23; 95% CI, −0.39 to −0.07; Fig S6). Similar to results seen with rate of change in eGFR, subgroup analysis showed that there was heterogeneity for the effects of different types of statins ($P < 0.001$; Table 2).

Effect on Major Cardiovascular Events in CKD Patients

Data regarding effects of statin administration on major cardiovascular events in patients with CKD were available from 13 publications[13,15,12,57,37,39,38,56,11,52,14,55,50] comprising 15 trials, including 34,853 participants and 5,491 events. Overall, statin therapy significantly reduced the risk for cardiovascular events (OR, 0.69; 95% CI, 0.61-0.79; $P < 0.001$) without evidence of heterogeneity in results of individual trials (I^2 = 33%; 95% CI, 0%-66%; Fig S7).

Sensitivity Analysis

Results did not vary using different random-effects estimation methods (Fig S8; Table S3).

DISCUSSION

There is epidemiologic and clinical evidence supporting the idea that dyslipidemia is a risk factor for CKD initiation or progression.[9,10,95] Effects of statin administration on kidney disease outcomes remain controversial. This large quantitative review, including 57 trials, more than 140,000 participants, and 8,498 kidney failure events, suggests that statin therapy produces a mild reduction in proteinuria and rate of decline in eGFR of 0.41 mL/min/1/73 m^2 per year. However, these effects did not translate into a risk reduction of kidney failure events. Similar to our prior study,[18] this study showed that statin therapy induced a 30% risk reduction in major cardiovascular events in patients with CKD. Although this study did not show clear renal benefits, the lack of evidence for an adverse effect of statin on kidney outcomes is important, particularly in light of the clear cardiovascular benefits of statins.

The large volume of data available was beneficial for this meta-analysis. To our knowledge, the current study represents the largest systematic review of statin administration on kidney disease progression and the first meta-analysis that evaluates the effect of statin treatment on kidney failure events. Several prior overviews have evaluated effects of statins on kidney disease outcomes in patients with cardiovascular risk or CKD. Meta-analyses that included 26 trials with 39,704 participants reported significant benefits of statins, with differences in eGFR decline of 1.22 (95% CI, 0.44-2.00) mL/min per year.[17] A recent review that included 41 studies with a total of 88,523 patients found that statin therapy reduced the slope of eGFR decline.[96] However, both studies focused on effects of proteinuria reduction or eGFR decline and not on clinically relevant renal benefits, such as kidney failure events. Additionally, these studies cannot exclude the possibility that statin administration increases creatinine excretion and influences serum creatinine level. The findings of these studies therefore have limited application in clinical practice. Our study, which examined nearly double the number of participants in prior reviews, found a nonsignificant beneficial effect in composite kidney failure events and ESRD. This finding aligns with SHARP, a large trial.[14]

However, this study might not be the final answer for the question of lowering LDL-C levels and progression of kidney disease. First, the study cannot exclude that intensive LDL-C lowering would have an effect on reducing the risk for kidney disease progression. We observed that an intensive strategy reduced the risk for kidney failure by 31% compared to the usual dose

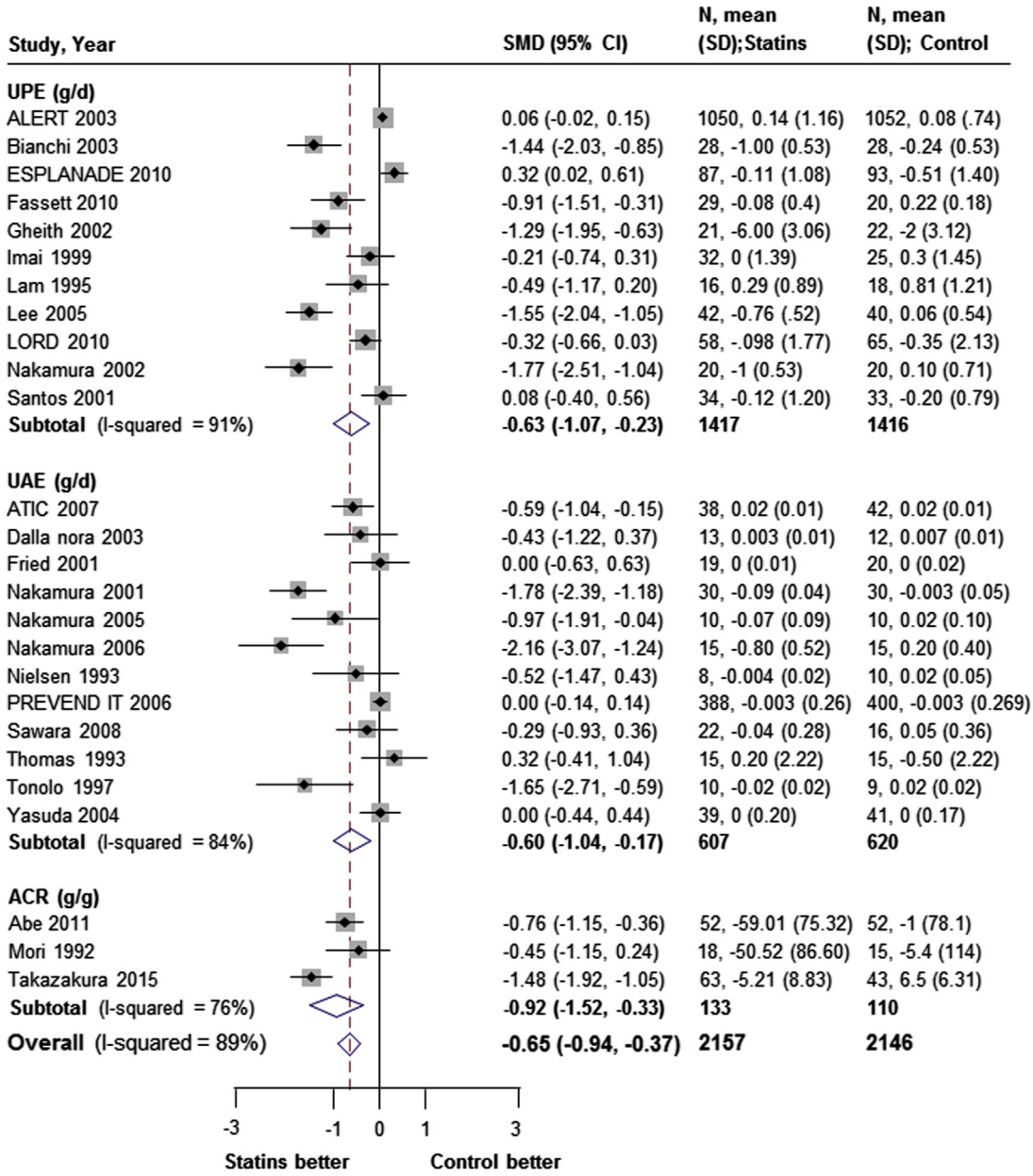

Figure 4. Forest plot for change in proteinuria or albuminuria. Negative values in difference of change represent greater decreases for proteinuria or albuminuria in statin group than in control group. Abbreviations: ACR, albumin-creatinine ratio; CI, confidence interval; PCR, protein-creatinine ratio; SD, standard deviation; SMD, standard mean difference; UAE, urinary albumin excretion; UPE, urinary protein excretion.

of statin (mainly dominated by the TNT Study[36]). Second, there is heterogeneity in terms of the effects of kidney protection among different types of statins. In direct comparison trials, atorvastatin was reported to confer the greatest renal benefit. Furthermore, atorvastatin, pravastatin, and simvastatin showed a trend in reducing the risk for kidney failure, with the pooled risk reduction for kidney failure of 6% (95% CI, 1%-12%), whereas other statins did not show the same effect. The current study cannot exclude the possibility of a more moderate kidney protective effect of some statins. Despite its large size, even SHARP did not reach sufficient statistical power to detect such a modest proportional risk reduction, in which the relative risk reduction for kidney failure or doubling of serum creatinine level was 7% (95% CI, −1% to 14%; $P = 0.09$).[14] A population of nearly 20,000 patients will be required for a future study to have sufficient power to demonstrate an absolute risk reduction in patients with high risk for kidney disease progression and whether such a risk reduction is clinically relevant. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), which had 18,144 participants, has provided an example of a 6%

relative cardiovascular risk reduction with ezetimibe therapy, which translates into a worthwhile absolute risk reduction in patients with coronary disease.[97,98] Statin administration for kidney protection remains to be debated. Regardless, statins also should be used for patients with kidney disease and high-risk cardiovascular disease when considering atherosclerotic disease according to the KDIGO (Kidney Disease: Improving Global Outcomes) lipid guidelines and European lipid guidelines.

The study has some potential limitations. First, post hoc analyses from large RCTs accounted for a considerable proportion of the study's included trials (21 of 57 trials). Most large RCTs of statins were principally designed to evaluate cardiovascular outcomes in persons presenting with cardiac disease. They were not specifically designed to test kidney function. In secondary outcome analyses, the relative paucity of high-quality RCTs limited the conclusions able to be drawn about eGFR and proteinuria, although the quality of the studies included in the primary outcome was considered good. Second, we found evidence of substantial heterogeneity in secondary outcome analyses, although we tried to address this by using random-effects models. We acknowledge the possibility that this heterogeneity had an impact on our results. Third, findings related to changes in proteinuria are based on a much smaller number of patients (n = 4,977) compared with the other analyses. Fourth, as discussed, a potential effect on creatinine generation and/or tubular secretion from statin treatment has not been removed.[99] Large prospective randomized trials including measured (not estimated) GFR are needed to definitively prove a positive effect of statins on kidney function progression. Fifth, we included only published studies in this analysis, and reporting bias could not be excluded because not all studies reported each outcome. In particular, kidney outcomes were not primary end points in most included trials and thus it is likely that some were not reported because they were not significant. Because we did not find an overall benefit of statins on kidney failure, this effect may be limited. However, this may produce much bias in comparison of a high versus low dose of statin for which a renal benefit was shown in 3 high-dose statin therapy trials. Finally, there were 21 missing standard deviations of change in eGFR and proteinuria, and we used the imputation of correlation referred to in the Cochrane Handbook.[23] We concede that doing so may produce uncertainty and underestimate the width of CIs, although most of these missing standard deviations were from trials with relatively small sample sizes.

In conclusion, this review suggests that statin therapy does not reduce the risk for kidney disease progression in adults not receiving dialysis in whom kidney disease outcomes were reported. However, statin therapy seems to modestly reduce proteinuria and rate of eGFR decline. The effects of kidney protection may differ according to the type of statin. The clinical significance of the results requires confirmation with further studies.

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Contributions: Research idea and study design: JL, HZ; data acquisition: XS, LZ; data analysis/interpretation: XS, LZ, JL, WH; statistical analysis: XS, XX, JW; supervision or mentorship: JL, HZ. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. JL takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Characteristics of included trials and patients.
Table S2: Subgroup analysis of kidney failure events.
Table S3: Statistical analysis of different statistical estimators.
Figure S1: Risk of bias graph.
Figure S2: Risk of bias summary.
Figure S3: Forest plot for kidney failure events, low- vs high-dose statins.
Figure S4: Forest plot for rate of change in eGFR, low- vs high-dose statins.
Figure S5: Forest plot for rate of change in eGFR in different statins.
Figure S6: Forest plot for change of ACR or PCR in different statins.
Figure S7: Forest plot for major CV events in CKD patients.
Figure S8: Forest plot for sensitivity analysis of different statistical estimators.
Item S1: Study protocol.
Item S2: Risk of bias for the outcome.
Item S3: WinBUGS codes for full Bayes method.
Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2016.01.016) is available at www.ajkd.org

REFERENCES

1. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80(1):17-28.

2. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-2081.

3. van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. *Kidney Int*. 2011;79(12):1341-1352.

4. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80(1):93-104.

5. Astor BC, Matsushita K, Gansevoort RT, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with mortality and end-stage renal disease. A collaborative meta-analysis of kidney disease population cohorts. *Kidney Int*. 2011;79(12):1331-1340.

6. Parikh NI, Hwang SJ, Larson MG, Meigs JB, Levy D, Fox CS. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. *Arch Intern Med*. 2006;166(17):1884-1891.

7. Bussolati B, Deregibus MC, Fonsato V, et al. Statins prevent oxidized LDL-induced injury of glomerular podocytes by activating the phosphatidylinositol 3-kinase/AKT-signaling pathway. *J Am Soc Nephrol*. 2005;16(7):1936-1947.

8. Guijarro C, Egido J. Transcription factor-kappa B (NF-kappa B) and renal disease. *Kidney Int*. 2001;59(2):415-424.

9. Schaeffner ES, Kurth T, Curhan GC, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. *J Am Soc Nephrol*. 2003;14(8):2084-2091.

10. Muntner P, Coresh J, Smith JC, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the Atherosclerosis Risk in Communities Study. *Kidney Int*. 2000;58(1):293-301.

11. Tonelli M, Isles C, Craven T, et al. Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. *Circulation*. 2005;112(2):171-178.

12. Fellstrom B, Holdaas H, Jardine AG, et al. Effect of fluvastatin on renal end points in the Assessment of Lescol in Renal Transplant (ALERT) trial. *Kidney Int*. 2004;66(4):1549-1555.

13. Huskey J, Lindenfeld J, Cook T, et al. Effect of simvastatin on kidney function loss in patients with coronary heart disease: findings from the Scandinavian Simvastatin Survival Study (4S). *Atherosclerosis*. 2009;205(1):202-206.

14. Haynes R, Lewis D, Emberson J, et al. Effects of lowering LDL cholesterol on progression of kidney disease. *J Am Soc Nephrol*. 2014;25(8):1825-1833.

15. 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):42-49.

16. Rahman M, Baimbridge C, Davis BR, et al. Progression of kidney disease in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Am J Kidney Dis*. 2008;52(3):412-424.

17. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. *J Am Soc Nephrol*. 2006;17(7):2006-2016.

18. Hou W, Lv J, Perkovic V, et al. Effect of statin therapy on cardiovascular and renal outcomes in patients with chronic kidney disease: a systematic review and meta-analysis. *Eur Heart J*. 2013;34(24):1807-1817.

19. Zhang X, Xiang C, Zhou YH, Jiang A, Qin YY, He J. Effect of statins on cardiovascular events in patients with mild to moderate chronic kidney disease: a systematic review and meta-analysis of randomized clinical trials. *BMC Cardiovasc Disord*. 2014;14:19.

20. Baigent C, Keech A, Kearney PM, 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):1267-1278.

21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6(7):e1000097.

22. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.

23. Higgins JP, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.0.1 (updated March 2011). The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

24. Roseman M, Milette K, Bero LA, et al. Reporting of conflicts of interest in meta-analyses of trials of pharmacological treatments. *JAMA*. 2011;305(10):1008-1017.

25. Morris CN. Parametric empirical Bayes inference: theory and applications. *J Am Stat Assoc*. 1983;78(381):47-55.

26. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. *Stat Med*. 2003;22(17):2693-2710.

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.

28. Harville DA. Maximum likelihood approaches to variance component estimation and to related problems. *J Am Stat Assoc*. 1977;72(358):320-338.

29. Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Stat Med*. 2002;21(11):1601-1623.

30. Cornell JE, Mulrow CD, Localio R, et al. Random-effects meta-analysis of inconsistent effects: a time for change. *Ann Intern Med*. 2014;160(4):267-270.

31. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. *J Comput Graph Stat*. 1998;7(4):434-455.

32. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.

33. Wiebe N, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. *J Clin Epidemiol*. 2006;59(4):342-353.

34. Egon SP. The percentage limits for the distribution of range in samples from a normal population (n $\leq$ 100.). *Biometrika*. 1932;24(3/4):404-417.

35. Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, eds. *Systematic Reviews in Health Care: Meta-analysis in Context*. 2nd ed. London: BMJ Books; 2001:285-312.

36. Shepherd J, Kastelein JJ, Bittner V, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. *Clin J Am Soc Nephrol*. 2007;2(6):1131-1139.

37. Colhoun HM, Betteridge DJ, Durrington PN, 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):810-819.

38. 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):218-224.

39. Vidt DG, Ridker PM, Monyak JT, Schreiber MJ, Cressman MD. Longitudinal assessment of estimated glomerular filtration rate in apparently healthy adults: a post hoc analysis from the JUPITER study (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin). *Clin Ther*. 2011;33(6):717-725.

40. Sarma A, Cannon CP, de Lemos J, et al. The incidence of kidney injury for patients treated with a high-potency versus moderate-potency statin regimen after an acute coronary syndrome. *J Am Heart Assoc*. 2014;3(3):e000784.

41. Seron D, Oppenheimer F, Pallardo LM, et al. Fluvastatin in the prevention of renal transplant vasculopathy: results of a prospective, randomized, double-blind, placebo-controlled trial. *Transplantation*. 2008;86(1):82-87.

42. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357(22):2248-2261.

43. Thomas ME, Harris KP, Ramaswamy C, et al. Simvastatin therapy for hypercholesterolemic patients with nephrotic syndrome or significant proteinuria. *Kidney Int*. 1993;44(5):1124-1129.

44. Nielsen S, Schmitz O, Moller N, et al. Renal function and insulin sensitivity during simvastatin treatment in type 2 (non-insulin-dependent) diabetic patients with microalbuminuria. *Diabetologia*. 1993;36(10):1079-1086.

45. Tonolo G, Ciccarese M, Brizzi 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):1891-1895.

46. 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):1345-1355.

47. Gheith OA, Sobh MA, Mohamed Kel S, et al. Impact of treatment of dyslipidemia on renal function, fat deposits and scarring in patients with persistent nephrotic syndrome. *Nephron*. 2002;91(4):612-619.

48. Lee TM, Lin MS, Tsai CH, Chang NC. Add-on and withdrawal effect of pravastatin on proteinuria in hypertensive patients treated with AT receptor blockers. *Kidney Int*. 2005;68(2):779-787.

49. Nakamura T, Ushiyama C, Hirokawa K, et al. Effect of cerivastatin on proteinuria and urinary podocytes in patients with chronic glomerulonephritis. *Nephrol Dial Transplant*. 2002;17(5):798-802.

50. Collins R, Armitage J, Parish S, Sleigh 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):2005-2016.

51. 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):565-570.

52. Atthobari J, Brantsma AH, Gansevoort RT, et al. The effect of statins on urinary albumin excretion and glomerular filtration rate: results from both a randomized clinical trial and an observational cohort study. *Nephrol Dial Transplant*. 2006;21(11):3106-3114.

53. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study. *J Clin Pathol*. 2004;57(7):728-734.

54. Nanayakkara PW, van Guldener C, ter Wee PM, et al. Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on carotid intima-media thickness, endothelial function, and renal function in patients with mild to moderate chronic kidney disease: results from the Anti-Oxidant Therapy in Chronic Renal Insufficiency (ATIC) Study. *Arch Intern Med*. 2007;167(12):1262-1270.

55. Sawara Y, Takei T, Uchida K, et al. Effects of lipid-lowering therapy with rosuvastatin on atherosclerotic burden in patients with chronic kidney disease. *Intern Med*. 2008;47(17):1505-1510.

56. Nakamura H, Mizuno K, Ohashi Y, Yoshida T, Hirao K, Uchida Y. Pravastatin and cardiovascular risk in moderate chronic kidney disease. *Atherosclerosis*. 2009;206(2):512-517.

57. Koren MJ, Davidson MH, Wilson DJ, et al. Focused atorvastatin therapy in managed-care patients with coronary heart disease and CKD. *Am J Kidney Dis*. 2009;53(5):741-750.

58. 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.

59. Athyros VG, Karagiannis A, Ganotakis ES, et al. Association between the changes in renal function and serum uric acid levels during multifactorial intervention and clinical outcome in patients with metabolic syndrome. A post hoc analysis of the ATTEMPT study. *Curr Med Res Opin*. 2011;27(8):1659-1668.

60. Abe M, Maruyama N, Okada K, Matsumoto S, Matsumoto K, Soma M. Effects of lipid-lowering therapy with rosuvastatin on kidney function and oxidative stress in patients with diabetic nephropathy. *J Atheroscler Thromb*. 2011;18(11):1018-1028.

61. Gupta A, Chang CL, Collier D, Dahlof B, Poulter NR, Sever PS. The relationship between statin therapy and progression of renal damage among 10305 hypertensive patients randomised in the ASCOT-Lipid-Lowering Arm (LLA). *Atherosclerosis*. 2011;12(suppl 1):158-159.

62. Santos AF, Keitel E, Bittar AE, et al. Safety and efficacy of simvastatin for hyperlipidemia in renal transplant recipients: a double-blind, randomized, placebo-controlled study. *Transplant Proc*. 2001;33(1-2):1194-1195.

63. Yasuda G, Kuji T, Hasegawa K, et al. Safety and efficacy of fluvastatin in hyperlipidemic patients with chronic renal disease. *Ren Fail*. 2004;26(4):411-418.

64. Panichi V, Paoletti S, Mantuano E, et al. In vivo and in vitro effects of simvastatin on inflammatory markers in pre-dialysis patients. *Nephrol Dial Transplant*. 2005;21(2):337-344.

65. Goicoechea M, de Vinuesa SG, Lahera V, et al. Effects of atorvastatin on inflammatory and fibrinolytic parameters in patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17(12)(suppl 3):S231-S235.

66. Holme I, Fayyad R, Faergeman O, et al. Cardiovascular outcomes and their relationships to lipoprotein components in patients with and without chronic kidney disease: results from the IDEAL trial. *J Intern Med*. 2010;267(6):567-575.

67. Ruggenenti P, Perna A, Tonelli M, 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):1928-1938.

68. 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.

69. Milionis HJ, Rizos E, Kostapanos M, et al. Treating to target patients with primary hyperlipidaemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). *Curr Med Res Opin*. 2006;22(6):1123-1131.

70. Leiter LA, Rosenson RS, Stein E, et al. Efficacy and safety of rosuvastatin 40 mg versus atorvastatin 80 mg in high-risk patients with hypercholesterolemia: results of the POLARIS study. *Atherosclerosis*. 2007;194(2):e154-e164.

71. Zeeuw D, Anzalone DA, Cain VA, et al. Renal effects of atorvastatin and rosuvastatin in patients with diabetes who have progressive renal disease (PLANET I): a randomised clinical trial. *Lancet Diabetes Endocrinol*. 2015;3(3):181-190.

72. Lee TM, Su SF, Tsai CH. Effect of pravastatin on proteinuria in patients with well-controlled hypertension. *Hypertension*. 2002;40(1):67-73.

73. Lam KS, Cheng IK, Janus ED, Pang RW. Cholesterol-lowering therapy may retard the progression of diabetic nephropathy. *Diabetologia*. 1995;38(5):604-609.

74. Amarenco P, Callahan A, Campese VM, et al. Effect of high-dose atorvastatin on renal function in subjects with stroke or transient ischemic attack in the SPARCL trial. *Stroke*. 2014;45(10):2974-2982.

75. Longenecker CT, Hileman CO, Funderburg NT, McComsey GA. Rosuvastatin preserves renal function and lowers cystatin C in HIV-infected subjects on antiretroviral therapy: the SATURN-HIV trial. *Clin Infect Dis*. 2014;59(8):1148-1156.

76. Takazakura A, Sakurai M, Bando Y, et al. Renoprotective effects of atorvastatin compared with pravastatin on progression of early diabetic nephropathy. *J Diabetes Investig*. 2015;6(3):346-353.

77. Nakamura T, Ushiyama C, Hirokawa K, Osada S, Shimada N, Koide H. Effect of cerivastatin on urinary albumin excretion and plasma endothelin-1 concentrations in type 2 diabetes patients with microalbuminuria and dyslipidemia. *Am J Nephrol*. 2001;21(6):449-454.

78. 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):2728-2732.

79. 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):82-86.

80. 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):113-119.

81. Dalla Nora E, Passaro A, Zamboni PF, Calzoni F, Fellin R, Solini A. Atorvastatin improves metabolic control and endothelial function in type 2 diabetic patients: a placebo-controlled study. *J Endocrinol Invest*. 2003;26(1):73-78.

82. Mori Y, Yokoyama J, Tsuruoka A, Ikeda Y. Effect of pravastatin on microalbuminuria in patients with non-insulin-dependent diabetes mellitus - a randomized control study. *Jikeikai Med J*. 1992;39:341-348.

83. Abe M, Maruyama N, Yoshida Y, Ito M, Okada K, Soma M. Efficacy analysis of the lipid-lowering and renoprotective effects of rosuvastatin in patients with chronic kidney disease. *Endocr J*. 2011;58(8):663-674.

84. Douglas K, O'Malley PG, Jackson JL. Meta-analysis: the effect of statins on albuminuria. *Ann Intern Med*. 2006;145(2):117-124.

85. Blazing MA, De Lemos JA, Dyke CK, Califf RM, Bilheimer D, Braunwald E. The A-to-Z Trial: methods and rationale for a single trial investigating combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and defining the efficacy of early aggressive simvastatin therapy. *Am Heart J*. 2001;142(2):211-217.

86. Nazer B, Ray KK, Murphy SA, Gibson CM, Cannon CP. Urinary albumin concentration and long-term cardiovascular risk in acute coronary syndrome patients: a PROVE IT-TIMI 22 substudy. *J Thromb Thrombolysis*. 2013;36(3):233-239.

87. Rahman M, Ford CE, Cutler JA, et al. Long-term renal and cardiovascular outcomes in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol*. 2012;7(6):989-1002.

88. Stein EA, Vidt DG, Shepherd J, Cain VA, Anzalone D, Cressman MD. Renal safety of intensive cholesterol-lowering treatment with rosuvastatin: a retrospective analysis of renal adverse events among 40,600 participants in the rosuvastatin clinical development program. *Atherosclerosis*. 2012;221(2):471-477.

89. 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):373-382.

90. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359(21):2195-2207.

91. Tonelli M, Moye L, Sacks FM, Cole T, Curhan GC. Effect of pravastatin on loss of renal function in people with moderate chronic renal insufficiency and cardiovascular disease. *J Am Soc Nephrol*. 2003;14(6):1605-1613.

92. Tonelli M, Jose P, Curhan G, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ*. 2006;332(7555):1426.

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

94. SHARP Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J*. 2010;160(5):785-794.

95. Manttari M, Tiula E, Alikoski T, Manninen V. Effects of hypertension and dyslipidemia on the decline in renal function. *Hypertension*. 1995;26(4):670-675.

96. Geng Q, Ren J, Song J, Li S, Chen H. Meta-analysis of the effect of statins on renal function. *Am J Cardiol*. 2014;114(4):562-570.

97. Blazing MA, Giugliano RP, Cannon CP, et al. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18,144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. *Am Heart J*. 2014;168(2):205-212.e201.

98. Laufs U, Descamps OS, Catapano AL, Packard CJ. Understanding IMPROVE-IT and the cardinal role of LDL-C lowering in CVD prevention. *Eur Heart J*. 2014;35(30):1996-2000.

99. Campese VM, Park J. HMG-CoA reductase inhibitors and renal function. *Clin J Am Soc Nephrol*. 2007;2(6):1100-1103.