Statins for Improving Renal Outcomes: A Meta-Analysis

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Statins frequently are used to prevent cardiovascular events. Several recent studies suggest that statins also may have renal benefits, although this is controversial. This systematic review and meta-analysis were performed to assess the effect of statins on change in kidney function and urinary protein excretion. Medline, EMBASE, the Cochrane Central Register of Controlled Trials, conference proceedings, and the authors' personal files were searched. Published or unpublished randomized, controlled trials or crossover trials of statins that reported assessment of kidney function or proteinuria were included, and studies of individuals with ESRD were excluded. Data were extracted for study design, subject characteristics, type of statin and dose, baseline/change in cholesterol levels, and outcomes (change in measured or estimated GFR [eGFR] and/or urinary protein excretion). Weighted mean differences were calculated for the change in GFR between statin and control groups using a random-effects model. A random-effects model also was used to calculate the standardized mean difference for the change in urinary protein excretion between groups. Twenty-seven eligible studies with 39,704 participants (21 with data for eGFR and 20 for proteinuria or albuminuria) were identified. Overall, the change in the weighted mean differences for eGFR was statistically significant (1.22 ml/min per yr slower in statin recipients; 95% confidence interval [CI] 0.44 to 2.00). In subgroup analysis, the benefit of statin therapy was statistically significant in studies of participants with cardiovascular disease (0.93 ml/min per yr slower than control subjects; 95% CI 0.10 to 1.76) but was NS for studies of participants with diabetic or hypertensive kidney disease or glomerulonephritis. The standardized mean difference for the reduction in albuminuria or proteinuria as a result of statin therapy was statistically significant (0.58 units of SD greater in statin recipients; 95% CI 0.17 to 0.98). Statin therapy seems to reduce proteinuria modestly and results in a small reduction in the rate of kidney function loss, especially in populations with cardiovascular disease.

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Chronic kidney disease (CKD) is a common condition that is associated with adverse outcomes and high health care costs (1). Risk factors for development and progression of CKD are similar to those implicated in cardiovascular disease (CVD) and include hypertension (HTN), diabetes, and dyslipidemia (2,3). As with cardiovascular outcomes, renal outcomes in CKD are improved by BP reduction (4), tight glycemic control (5), interruption of the renin/angiotensin system (6,7), and possibly smoking cessation (8). Despite these therapies, CKD often is progressive, and additional strategies to preserve kidney function are needed.

Animal models of hyperlipidemia that is produced by cholesterol-rich diets show evidence of renal injury on biopsy (9), and epidemiologic studies suggest that elevated cholesterol and triglyceride levels are associated with more rapid kidney function loss (10–12). Possible mechanisms include accelerated atherosclerosis of arteries within the kidney and damaging effects of lipids on mesangial cells (13). Studies in animal models show that treatment of dyslipidemia reduces renal injury by decreasing urine albumin excretion and reducing histologic damage, such as mesangial matrix expansion and hypercellularity (14–16). A previous systematic review pooled the literature from all human studies that were conducted before 2000 (17) (n = 404 participants) and suggested that pharmacologic lipid modification may slow the progression of CKD. Studies that were included in this review evaluated multiple classes of medications, including statins, fibric acid derivatives, and probucol.

More recently, results from several studies (18–20) addressed the potential renal benefits of statins in particular. Statins inhibit 3-hydroxy-3-methylglutaryl CoA reductase, the rate-limiting enzyme in the production of mevalonic acid, which is essential for cholesterol synthesis. Given the increasing use of statins for prevention of CVD, a summary of their effects on renal function loss would be of interest to clinicians and may help to inform recommendations for management of CKD. We conducted a systematic review and meta-analysis to determine the effect of statins on the rate of kidney function loss and proteinuria.

Materials and Methods

The institutional review board at the University of Alberta approved this study, which was conducted and reported in accordance with published guidelines (21).

Search Strategy

A comprehensive search strategy was formulated to identify all relevant studies regardless of language or publication status, including published, unpublished, in press, and in progress. Two reviewers searched Medline (1969 to March 2005), EMBASE (1988 to March 2005), and the Cochrane

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Central Register of Controlled Trials (CENTRAL) databases. The search strategies are included in the Appendix. The search terms were identified to include all studies that evaluated statin therapy on the effect of renal function or proteinuria. The citations of existing reviews and of trials that were identified by the above methods were reviewed by two reviewers to include pertinent studies. Abstracts from major nephrology conference proceedings (American Society of Nephrology; Canadian Society of Nephrology), the metaRegistry of controlled trials (www.controlled-trials.com/mrct/), and the personal files of the review authors also were searched. Any study that was considered relevant by one or both reviewers was retrieved for further review.

Study Selection

All studies that were identified by the search strategy were screened independently by two reviewers. The full text of the potentially relevant articles subsequently was obtained. Each study was assessed independently by two reviewers for inclusion in the review using predetermined eligibility criteria. Studies were eligible for inclusion when they were randomized, controlled trials or randomized, crossover trials; included participants who were older than 18 yr; measured or estimated kidney function (GFR, creatinine clearance, or proteinuria); and randomly assigned therapy with a statin. We excluded studies that did not have a control group for direct comparison with the statin group and those that included participants with ESRD. Disagreements were resolved by discussion and/or consultation with a third party.

Validity Assessment and Data Extraction

The qualitative details were assessed to evaluate impact on internal validity. A standard data extraction method was used to record the following properties of each trial in a database: Study characteristics (design, method of randomization, and withdrawals/dropouts), participants (age, gender, renal function at the time statin therapy was initiated, fasting serum lipid profile, and cause of renal disease), therapeutic intervention (type of statin, dose of statin, duration of therapy, and co-interventions), outcomes (types of outcome measures, timing of outcomes, and adverse effects), results, whether the studies used an intention-to-treat analysis, and funding source. Study quality was assessed using a previously validated index (22,23). A second reviewer checked the extracted data for accuracy. In cases in which necessary data were missing from the studies, additional information was requested from the authors.

Outcome Measures

The primary outcome was rate of change in estimated GFR (eGFR) in milliliters per minute per year. Although creatinine clearance is conceptually different from GFR, it commonly is used as an estimate of GFR (24); therefore, creatinine clearance was used interchangeably with GFR to assess the primary outcome. Similarly, estimates of GFR and/or creatinine clearance that were normalized to body surface area were pooled with those that were not. Because the focus of this analysis was on change in kidney function and because the index of kidney function was constant for both groups within a particular study, these decisions were considered unlikely to introduce bias. Positive differences in per-year rates of change indicate slower decline in renal function in the statin group, as compared with the placebo group.

As a secondary outcome, we considered change in urinary protein excretion from baseline to end of follow-up. Results from timed urine specimens for proteinuria and albuminuria were converted to grams per 24 h. Results from spot urine specimens (protein to creatinine or albumin to creatinine ratio) were converted to milligrams per gram of creatinine. Negative differences in changes from baseline indicate greater decreases in proteinuria or albuminuria in the statin group as compared with the placebo group.

Clinical Subpopulations

The primary analysis pooled the results from all studies. However, we presented results separately for trials that studied participants who were selected on the basis of CVD, glomerulonephritis (GN), diabetes, or HTN. Because of the large size of the CVD group, we also presented results from the GN, diabetes, and HTN groups combined.

Statistical Analyses

SD were imputed using interquartile ranges (dividing the range by 1.35 [25]) and full ranges (dividing the range by values from Pearson's table [26]). Change-from-baseline SD were calculated using correlations that were estimated from other included studies (27). GFR means and SD were extrapolated to per-year estimates, assuming a linear rate of change and holding the coefficient of variation fixed (28). Standardized mean difference (SMD) was used to pool results from all studies that reported untransformed change in urinary protein excretion (*i.e.*, those that were not reported solely as geometric means or logged values). Weighted mean differences (WMD) were used to pool change-from-baseline per-year GFR estimates. Percentage of prevented loss was calculated using the difference in change-from-baseline GFR means divided by the control change-from-baseline GFR mean. An overall pooled percentage of prevented loss was calculated using the same weights as those used in the WMD calculation. WMD was used to pool results separately for timed collections of urinary protein or albumin.

We used Review Manager 4.2.7 (29) to pool data and calculate mean differences. Because of the differences expected between studies (particularly in clinical populations), we decided *a priori* to combine results using a random-effects model. Statistical heterogeneity was quantified using the I^2 statistic (30). *A priori* we planned to use meta-regression (31) to examine the association between certain variables (mean age, mean total serum cholesterol, baseline mean GFR, baseline mean proteinuria, type of statin, and quality criteria) and the effect of statins on the outcomes. In sensitivity analyses, we assessed the likelihood that our findings were influenced by the assumptions that we made about the SD of the effect sizes. Results were robust to increasing and decreasing this SD by a factor of 1.5, suggesting that these estimates were unlikely to have influenced our findings. Additional sensitivity analyses included only trials with ≥1 yr of follow-up. Publication bias was assessed using weighted regression (32). Statistical significance was set at $P < 0.05$ for all analyses.

Results

Trial Flow and Study Characteristics

Figure 1 shows trial flow among studies that were considered for

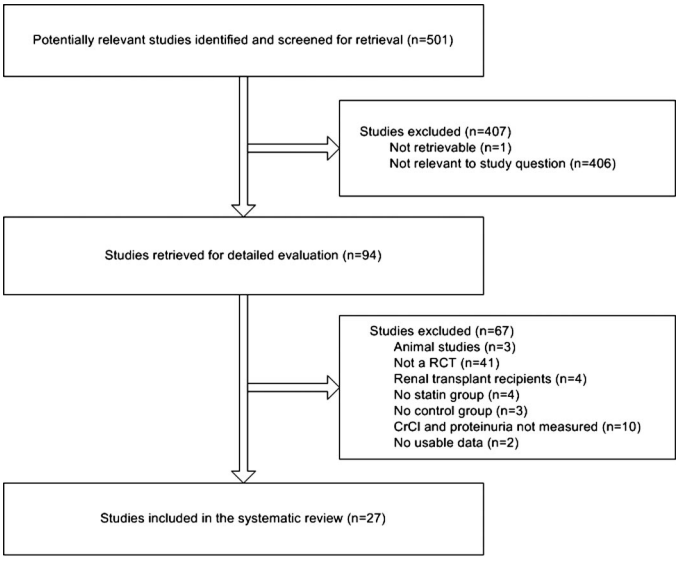


Figure 1. Flow diagram of studies considered for inclusion.

inclusion. Two trials were excluded because they did not report data that permitted calculation of the effect of statin therapy on eGFR or urinary protein excretion (33,34). Twenty-seven eligible studies with a total of 39,704 participants were included in this review (18–20,35–59). Of these, 21 studies provided data on rate of change in eGFR, 10 on change in proteinuria, and 10 on change in albuminuria (results do not add to 27 because some studies evaluated multiple outcomes). Six different statins were studied, and follow-up duration ranged from approximately 3 mo to 6 yr (median 1 yr). Study quality generally was poor; only four (15%) of 27 of studies had a Jadad score of ≥4, and 16 (59%) of 27 had a Jadad score of ≤2. The characteristics of the included studies are shown in Table 1.

Assessment of Publication Bias

There was some asymmetry of the funnel plot, suggesting that a few small negative trials were missing (data not shown). However, the weighted regression test detected no statistical evidence of publication bias (bias = 1.5, $P = 0.24$).

Effect of Statins on Rate of Change in eGFR

The effect of statins on rate of change in eGFR was favorable in 18 of 22 cohorts (38,867 participants). Overall, the change in the WMD for eGFR was statistically significant (1.22 ml/min per yr; 95% confidence interval [CI] 0.44 to 2.00), corresponding to a 76% reduction in the overall rate of loss. There was substantial heterogeneity in the estimate of statin effect on renal function loss ($I^2 = 96\%$; Figure 2A). The benefit of statin therapy was statistically significant in the CVD subpopulation (0.93 ml/min per yr; 95% CI 0.10 to 1.76; $I^2 = 99\%$, six cohorts, 38,311 participants; Figure 2A). The effect of statins was NS in the other individual subpopulations (diabetes: 3.24 ml/min per yr, 95% CI −0.46 to 6.95, $I^2 = 0\%$, five cohorts, 122 participants; GN: 1.4, 95% CI −6.7 to 9.5, $I^2 = 69\%$, seven studies, 222 participants; and HTN: 6.1, 95% CI −2.3 to 14.4, $I^2 = 56\%$, four cohorts, 212 participants). When these three subpopulations were combined, the pooled effect of statins remained nonsignificant (3.1 ml/min per yr; 95% CI −0.2 to 6.4; $I^2 = 46\%$; 16 cohorts, 556 participants).

Results were similar when analyses were limited to trials with ≥1 yr of follow-up. Specifically, the overall benefit of statin therapy was 1.24 ml/min per 1.73 m^2/yr (95% CI 0.47 to 2.02), and substantial heterogeneity remained ($I^2 = 98\%$). Little change was apparent in the diabetes, HTN, and CVD subgroups when trials with <1 yr of follow-up were excluded. However, in the GN subgroup, the overall beneficial effect of statins on GFR increased from 1.40 (95% CI −6.69 to 9.49) to 5.35 ml/min per 1.73 m^2/yr (95% CI 2.19 to 8.51), and the heterogeneity disappeared (from 69% to 0%).

Factors Associated with the Effect of Statins on eGFR

Mean age, mean baseline serum cholesterol, mean change in baseline serum cholesterol in the statin therapy group, mean eGFR at baseline, and clinical population (CVD *versus* non-CVD) were explored in univariable meta-regression. None was found to be significantly associated with the effect of statins on rate of change in eGFR (all $P > 0.1$). However, three trials that used atorvastatin were associated with an additional beneficial effect on kidney function loss ($\beta = 2.5$ ml/min per yr slower; 95% CI 1.8 to 3.2; $P < 0.001$), compared with trials that studied other statins (Figure 2B). Adjustment for atorvastatin (*versus* other statins) reduced I^2 from 96% to 46%, suggesting that this characteristic accounted for a substantial proportion of the observed heterogeneity in the effect of statin therapy. One atorvastatin study (36) was particularly influential; removing this study reduced the pooled rate of change in eGFR to 0.42 ml/min per yr (95% CI 0.13 to 0.71; I^2 reduced to 62%).

Three of six quality items were significantly associated with treatment effect in meta-regression. Open-label trials and trials that reported withdrawals explicitly were associated with larger treatment effects ($\beta = 2.4$ ml/min per yr, 95% CI 1.7 to 3.2, $P < 0.001$, I^2 reduced to 49%; and 2.5 ml/min per yr, 95% CI 1.9 to 3.2, $P < 0.001$, I^2 reduced to 45%). Trials with an industrial sponsor were associated with smaller treatment effects in univariable meta-regression ($\beta = -2.5$ ml/min per yr; 95% CI −3.5 to −1.6; $P < 0.001$; I^2 reduced to 58%). Restricting the meta-analysis to high-quality trials (Jadad score ≥3) maintained the statistical significance of the overall change in GFR but reduced the estimate from 1.22 (95% CI 0.44 to 2.00) to 0.22 ml/min per yr (0.07 to 0.38; $I^2 = 42\%$; nine cohorts, 34,453 participants).

Effect of Statins on Proteinuria and Albuminuria

The point estimate for the effect of statins on rate of change in proteinuria was favorable in seven of nine studies (350 participants) that performed timed urine collections. Overall, the change in proteinuria WMD was statistically NS (reduction of 0.37 g/24 h; 95% CI −0.75 to 0.02) and had large heterogeneity ($I^2 = 83\%$; Figure 3A). One trial assessed proteinuria in terms of urinary protein:creatinine ratio and found a significant reduction as a result of statin therapy (reduction 4400 mg/g; 95% CI 2806 to 5994).

The point estimate for the effect of statins on rate of change in albuminuria was favorable in three of seven studies (904 participants) that performed timed urine collections. Overall, the change in albuminuria WMD was statistically NS (−0.02 g/24 h; 95% CI −0.06 to 0.02), and heterogeneity was large at 92%. Two studies provided albuminuria data only in natural logarithm form, meaning that their results could not be pooled with those of the others. When the logged results from these two studies alone were pooled, the WMD for the effect of statin therapy was statistically NS (−0.22 g/24 h; 95% CI −0.53 to 0.09). One trial assessed albuminuria in terms of urinary albumin:creatinine ratio and found a significant reduction as a result of statin therapy (reduction 56 mg/g; 95% CI 3 to 110).

When reductions in albuminuria and proteinuria were considered together, the number of studies that were available for analysis increased to 18. The SMD for the effect of proteinuria on albuminuria or proteinuria was statistically significant (−0.58 units of SD; 95% CI −0.98 to −0.17; $I^2 = 89\%$; Figure 3B). Results were similar when only trials with at least 1 yr of follow-up were included (−0.47 units of SD; 95% CI −0.90 to −0.05; $I^2 = 76\%$). Meta-regression was repeated using the same list of covariates considered in analyses of eGFR; none was found to be significantly associated with the effect of statins on rate of change in combined albuminuria and proteinuria (all $P > 0.1$). Of note, the effect of statins on proteinuria was not significantly more pronounced in any of the four clinical subpopulations.

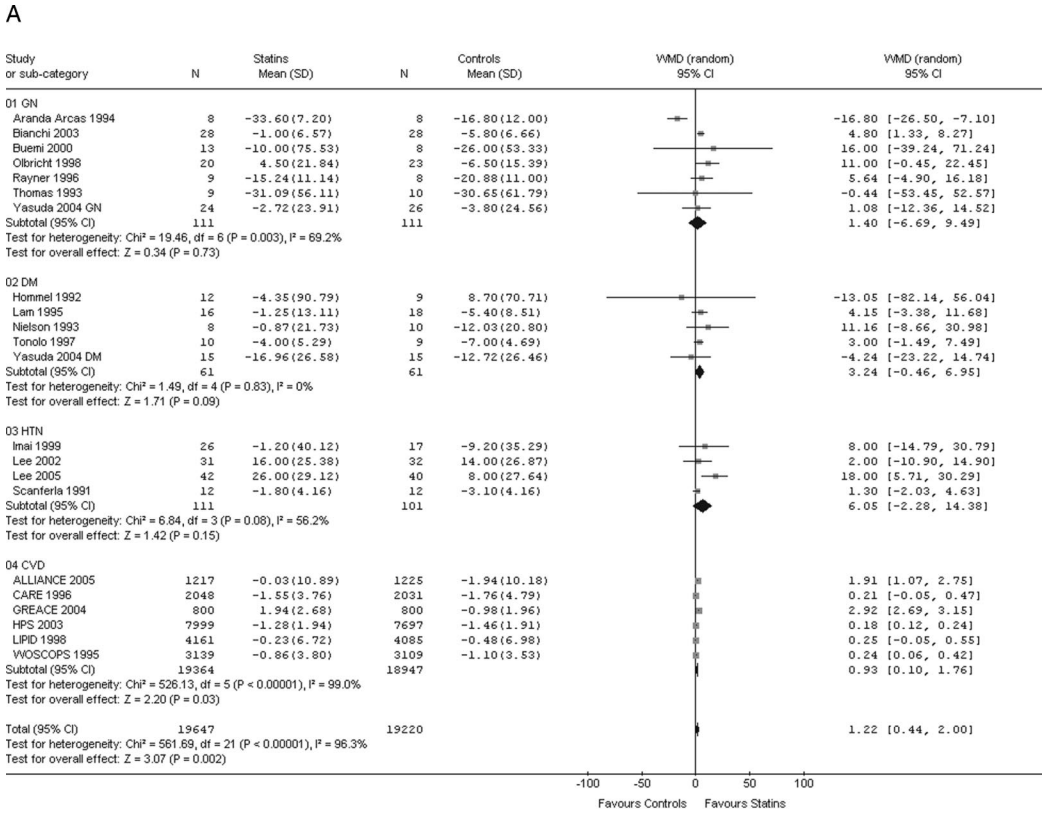
Discussion

We identified 27 randomized, controlled trials that studied the effects of statin therapy on kidney function and proteinuria in a total of nearly 40,000 participants. Overall, statin therapy reduced the rate

Table 1. Characteristics of included studies[a]

Study	Clinical Population	Statin	Dose (mg)	Follow-Up (yr)	Sample Size	Mean Age (yr)	Baseline Mean GFR (ml/min)	Baseline Mean Proteinuria (g/24 h)	Cholesterol (mmol/L)	Change in Cholesterol[b] (mmol/L)	Allocation Concealment	Jadad Score	% Lost to Follow-Up
ALLIANCE 2005 (52,53)	CVD	Atorva	10 to 80	2.0	2442	61	88	—	—	−1.34	Unclear	2	21
Aranda Arcas 1994 (50)	GN	Prava	20 to 40	0.5	16	52	65	4.15	9.95	−3.25	Unclear	1	—
Bianchi 2003 (37)	GN	Atorva	10 to 40	1.0	56	56	50	2.20	8.03	−2.69	Unclear	1	—
Buemi 2000 (47)	GN	Fluva	40	0.5	21	37	90	0.84	5.13	−0.73	Unclear	1	—
CARE 1996 (51)	CVD	Prava	40	5.0	4079	59	71	—	5.40	—	Adequate	3	0
Fried 2001 (18)	Diabetes	Simva	10 to 20	2.0	36	32	—	0.01[c]	4.99	−0.69	Adequate	2	5
GREACE 2004 (36)	CVD	Atorva	10 to 80	4.0	1600	58	77	—	—	−2.38	Unclear	2	1
Hommel 1992 (46)	Diabetes	Simva	10 to 20	0.2	21	38	67	—	6.57	−1.60	Unclear	3	24
HPS 2003 (57)	CVD	Simva	40	4.6	15696	64	—	—	5.84	—	Adequate	5	24
Imai 1999 (38)	HTN	Prava	5 to 10	0.5	43	55	60	1.24	6.45	−0.86	Unclear	1	—
Lam 1995 (48)	Diabetes	Lova	20 to 60	2.0	34	56	84	0.98	6.44	−1.70	Unclear	2	6
Lee 2002 (58)	HTN	Prava	10	0.50	63	48	88	1.21	5.36	−0.75	Adequate	2	5
Lee 2005 (19)	HTN	Prava	10	0.5	82	—	87	1.27	—	−0.78	Adequate	3	13
Lintott 1995 (49)	Hyperlipidemia	Fluva	40	0.2	42	58	—	0.22[c]	—	—	Unclear	4	0
LIPID 1998 (54)	CVD	Prava	40	6.1	8246	62	71	—	5.64	−1.00	Unclear	4	0
Mori 1992 (60)	Diabetes	Prava	10	1.5	26	63	—	—	5.20	−1.03	Unclear	1	—
Nakamura 2001 (35)	Diabetes	Ceriva	0.15	0.5	60	57	—	0.14[c]	6.72	−2.59	Unclear	2	—
Nielson 1993 (43)	Diabetes	Simva	10	0.7	18	65	97	—	6.70	−1.60	Unclear	2	—
Olbricht 1998 (55)	GN	Simva	10 to 40	2.0	43	—	84	6.70	—	—	Unclear	3	23
PREVEND IT 2004 (20)	General	Prava	40	4.0	647	51	—	0.04[c]	5.80	−1.00	Unclear	5	25
Rayner 1996 (44)	GN	Simva	10 to 40	2.0	12	43	79	5.07	10.26	−2.53	Inadequate	1	65
Scanferla 1991 (41)	HTN	Simva/ Prava	10	1.0	24	—	41	—	6.83	−1.42	Unclear	1	—
Thomas 1993 (45)	GN	Simva	10 to 40	0.5	30	51	76	5.16	9.31	—	Unclear	3	23
Tonolo 1997 (39)	Diabetes	Simva	20	1.0	19	61	99	0.07[c]	6.56	−1.20	Unclear	3	5
WOSCOPS 1995 (56)	CVD	Prava	40	4.9	6248	55	77	—	7.03	—	Unclear	3	30
Yasuda 2004 (42)	GN/ diabetes	Fluva	20	0.9	80	58	60	0.75[c]	—	−1.10	Unclear	1	10
Zhang 1995 (40)	Diabetes	Prava	20	0.2	20	43	—	0.09[c]	5.43	−0.65	Unclear	1	—

[a]CVD, cardiovascular disease; GN glomerulonephritis; HTN, hypertension.
[b]In statin group.
[c]Albuminuria.



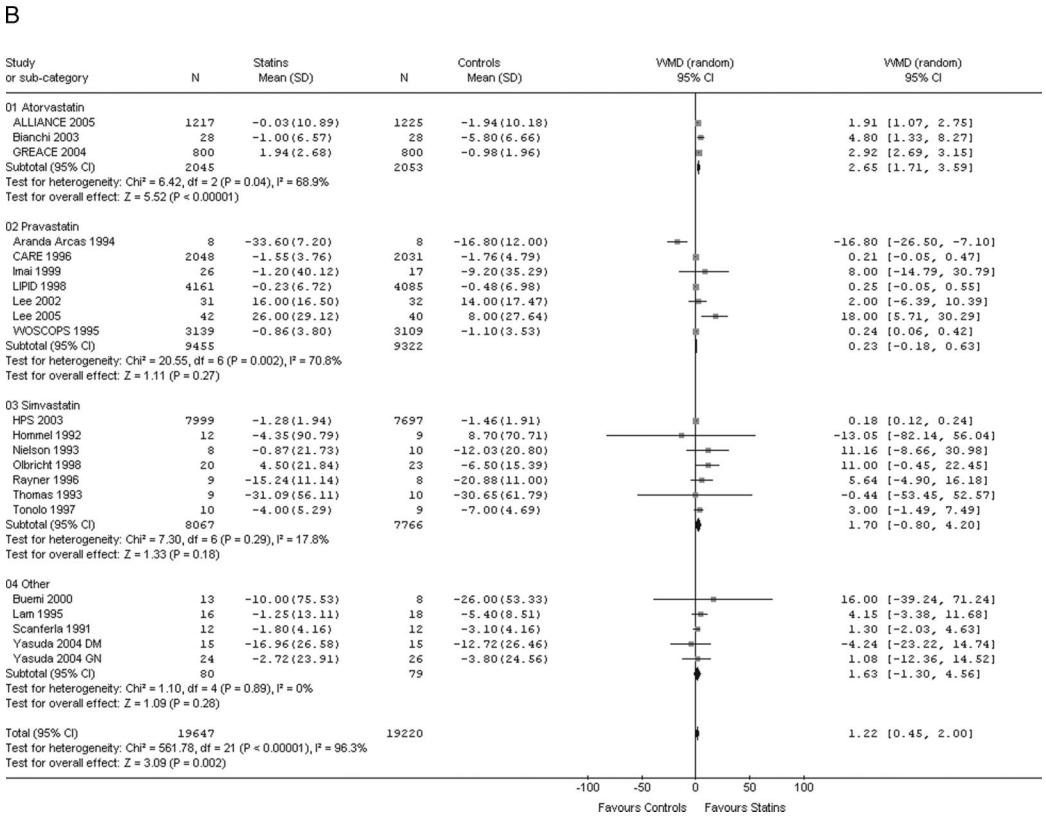


Figure 2. (A) Change in estimated GFR (eGFR; ml/min per yr) for statins *versus* controls by clinical population. GN, glomerulonephritis; DM, diabetes mellitus; HTN, hypertension; CVD, cardiovascular disease. Positive differences in per-year rates of change indicate slower decline in renal function in the statin group, as compared with the placebo group. (B) Change in eGFR (ml/min per yr) for statins *versus* controls by statin. Positive differences in per-year rates of change indicate slower decline in renal function in the statin group, as compared with the placebo group.

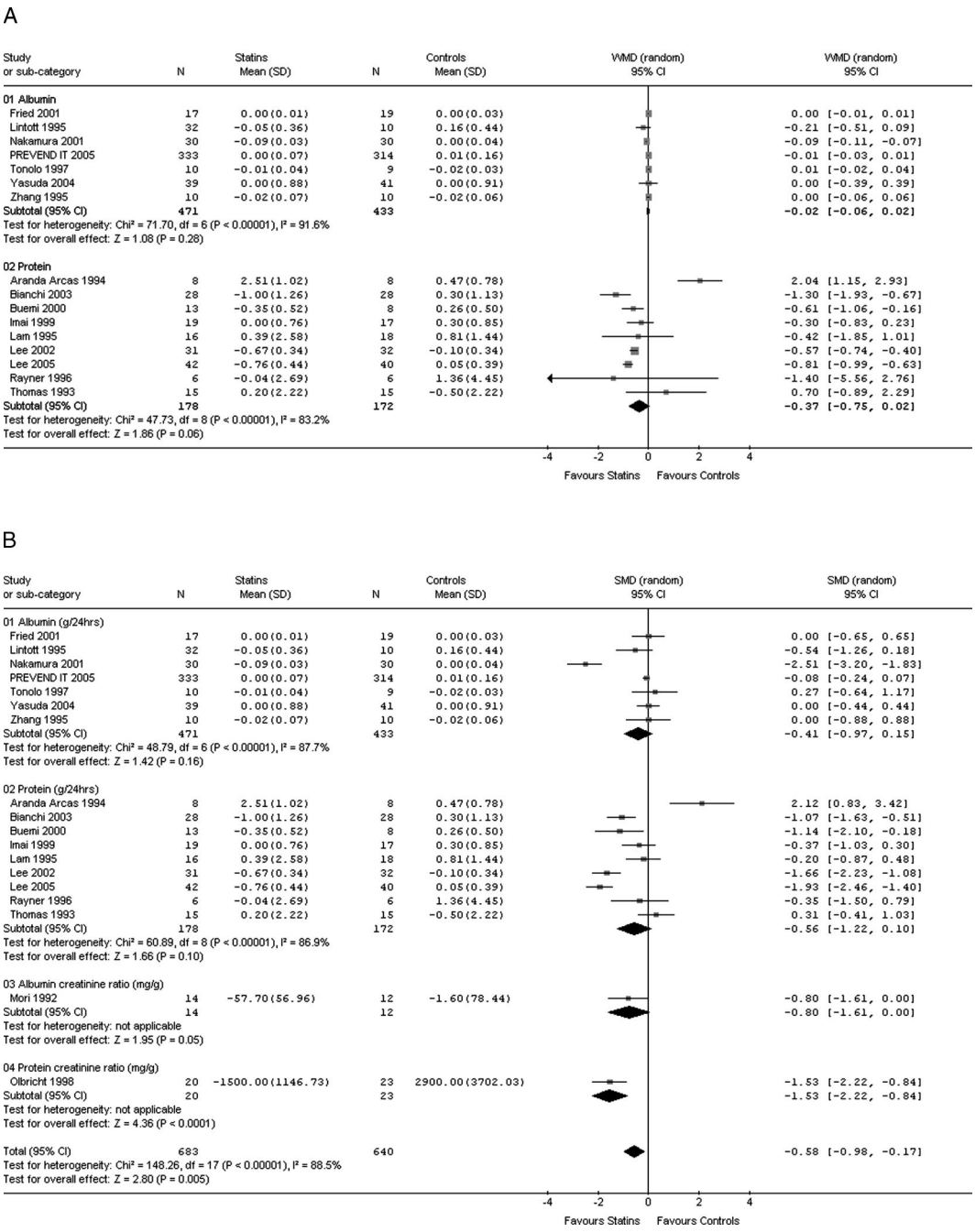


Figure 3. (A) Change in urinary protein excretion (g/24 h) for statins *versus* controls, expressed as weighted mean difference (WMD). (B) Change in urinary protein excretion for statins *versus* controls, expressed as standardized mean difference (SMD). Negative differences in changes from baseline indicate greater decreases in proteinuria or albuminuria in the statin group as compared with the placebo group.

of decline in eGFR (1.22 ml/min per yr slower than placebo; 95% CI 0.44 to 2.00). Although statistically significant, the magnitude of this benefit is relatively modest compared with other interventions, such as tight BP control and the use of angiotensin-converting enzyme inhibitors, which reduce rates of renal loss by approximately 3 to 4 ml/min per yr (60,61). However, this low absolute reduction may be due to a relatively slow rate of progression even in placebo recipients, because statins seemed to reduce the rate of kidney function loss by approximately 76%. In addition, statin treatment seemed to reduce the severity of urinary protein excretion. Significant between-study heterogeneity in the estimated effect of statins was observed for both eGFR and proteinuria.

When specific subgroups of participants were considered, statin treatment did not significantly reduce the rate of kidney function loss in participants with GN, diabetes, or HTN. However, a significant benefit of statin therapy was observed in the much larger subgroup of participants with CVD ($n = 38,311$). Even within this subgroup, we observed statistically significant heterogeneity, which seemed to be

due to the large treatment effect observed in the two trials that studied atorvastatin. Meta-regression found that atorvastatin use was associated with a significantly larger beneficial effect on the rate of kidney function loss than other statins ($P < 0.001$), and excluding the more influential of the two reduced the pooled benefit of statin therapy on eGFR from 1.2 to 0.4 ml/min per yr. Whether the seemingly larger benefit of atorvastatin was due to its relatively more potent lipid-lowering effect as compared with other statins, resulted from pleiotropic (non–lipid-mediated) effects, or was confounded by other between-study differences will require further study. However, the magnitude of cholesterol reduction from baseline was not significantly associated with the seeming renal benefit of statins in meta-regression.

Other study characteristics that were associated with larger treatment effects included open-label design, explicit reporting of loss to follow-up, and lack of industrial sponsorship. We were unable to identify any clinical characteristics that were responsible for significant heterogeneity of effect, which by extension might have suggested populations that would derive particular renal benefit from statins.

Statin treatment also seemed to reduce modestly urinary protein excretion. Studies that reported urinary protein excretion were conducted in participants with GN, diabetes, or HTN and used a variety of indices for protein excretion. The overall estimate pooled data from 18 studies of 1323 participants and indicated that statin therapy reduced protein excretion by 0.6 SD ($P = 0.005$). It is difficult to convert SMD to absolute treatment effects, but Figure 3A suggests that statin therapy reduced 24-h protein excretion by approximately 0.4 g in the populations studied. Although NS, this point estimate may provide some guidance as to the absolute magnitude of the reduction in protein excretion observed when results from all studies were pooled. Whether the absolute magnitude of this seeming reduction would be larger in the presence of heavier proteinuria will require further study.

Hyperlipidemia is associated with more rapid kidney function loss, and individuals with renal impairment are more likely to have hyperlipidemia, although not all patients with elevated lipid levels have kidney disease (62). It has been speculated that hyperlipidemia may exacerbate preexisting renal impairment by direct injury to the glomerular basement membrane (63). A second possibility is that statins improve GFR by improving endothelial function, leading to increased renal perfusion (64). Finally, the putative benefits of statins on kidney function may be attributable to their effects on proteinuria, which is a powerful predictor of kidney function loss. Experimental data suggest that statins reduce proteinuria at least in part by reducing inflammation and fibrosis in the renal interstitium, seemingly through actions on monocyte chemotactic protein-1 and TGF-β (65,66). Like others (58), Zoja *et al.* (65,66) found that the effects of statins were markedly enhanced by concomitant use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Although we were not able to confirm this hypothesis in our study, therapy of progressive renal disease in humans typically includes these agents, especially in the presence of proteinuria.

To our knowledge, this is the largest systematic review to evaluate the renal effects of statins. Our findings generally are consistent with an earlier meta-analysis that identified a total of 13 studies (404 participants) and included multiple classes of lipid-lowering agent (17). Although our analysis was performed and reported as recommended by published guidelines, it has several limitations that should be considered. First, there was considerable variation in study populations, intervention (type and dose of statin), outcomes (estimates of GFR and proteinuria), and duration. Although we attempted to control for some of these differences using stratification and meta-regression, it is likely that these differences contributed to the between-study heterogeneity alluded to above. Second, we acknowledge that pooled analyses potentially are problematic in the face of substantial heterogeneity. Although we attempted to address this through the use of random-effects models, it is possible that this heterogeneity affected our results. Third, 12 (44%) of 27 included studies were <1 yr in duration, and all studied surrogates for the clinically relevant outcome of interest: Progression to ESRD. Whether the modest reduction in the rate of kidney function loss suggested in this review will result in a clinically relevant renal benefit remains unclear. Fourth, although we included unpublished studies when possible, the possibility of publication bias remains. Fifth, although it has been suggested that the renal effects of statins may be most pronounced in individuals with lower levels of kidney function (36,67), most studies did not stratify by baseline kidney function; therefore, we could not confirm this possibility. However, baseline kidney function was not significantly associated with the effect of statins on rate of change in GFR in univariable meta-regression. Finally, although useful for summarizing the current state of knowledge, systematic review and meta-analysis have widely known limitations (68).

Despite our findings, these methodologic limitations (especially those that are attributable to the existing literature on this topic) make it clear that additional large randomized trials will be required to show that statins are associated with renal benefit. Participants should have progressive loss of kidney function, and specific populations of interest would include those with lower GFR at baseline, as well as people with heavy proteinuria. A clinically relevant outcome such as the composite of ESRD, doubling of serum creatinine, or death should be studied, and duration of follow-up should be at least 4 yr and possibly longer. These studies will need to be conducted at multiple centers, because the known cardiovascular benefit of statins in people with mild to moderate CKD will pose an additional ethical challenge to recruitment. The ongoing Study of Heart and Renal Protection (SHARP) (69) is an example of such a trial, but other studies are needed, especially in patients with GN.

Conclusion

Statin therapy seems to reduce proteinuria modestly and results in a small reduction in the rate of kidney function loss, especially in populations with CVD. Further studies are required to confirm the benefit of statins in other populations.

Appendix Table 1. Medline search

Set	Search
1	kidney failure/ or exp kidney failure, chronic/
2	exp Kidney Diseases/dt, th [Drug Therapy, Therapy]
3	exp Glomerular Filtration Rate/de [Drug Effects]
4	Nephrotic Syndrome/dt, th [Drug Therapy, Therapy]
5	exp Diabetic Nephropathies/ or exp Albuminuria/
6	1 or 2 or 3 or 4 or 5
7	exp Antilipemic Agents/ or exp Pravastatin/ or exp Hydroxymethylglutaryl-CoA Reductase Inhibitors/ or exp Lovastatin/ or exp Anticholesteremic Agents/ or exp Hyperlipidemia/ or exp Hypercholesterolemia/
8	exp LIPOPROTEINS, HDL CHOLESTEROL/ or exp CHOLESTEROL/ or exp LIPOPROTEINS, VLDL CHOLESTEROL/ or exp LIPOPROTEINS, LDL CHOLESTEROL
9	7 or 8
10	6 and 9
11	limit 10 to (human and ('therapy (sensitivity)' or 'therapy (specificity)' or 'therapy (optimized)') and 'all adult (19 plus years)' and randomized controlled trial)

Appendix Table 2. EMBASE search

Set	Search
1	exp Kidney Failure/dt [Drug Therapy]
2	exp Chronic Kidney Failure/dt [Drug Therapy]
3	exp Chronic Kidney Disease/dt [Drug Therapy]
4	exp Kidney Disease/dt [Drug Therapy]
5	exp Nephrotic Syndrome/ or exp Diabetic Nephropathy/
6	1 or 2 or 3 or 4 or 5
7	exp STATIN/dt [Drug Therapy]
8	exp DYSLIPIDEMIA/dt [Drug Therapy]
9	exp HYPERLIPIDEMIA/dt [Drug Therapy]
10	exp HIGH DENSITY LIPOPROTEIN CHOLESTEROL/ or exp CHOLESTEROL/ or exp LOW DENSITY LIPOPROTEIN CHOLESTEROL/ or exp VERY LOW DENSITY LIPOPROTEIN CHOLESTEROL/
11	exp Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/ct, dt [Clinical Trial, Drug Therapy]
12	7 or 8 or 9 or 10 or 11
13	6 and 12
14	limit 13 to (human and journal and adult <18 to 64 yr>)
15	Randomized Controlled Trial/
16	exp Randomization/
17	Double Blind Procedure/
18	Single Blind Procedure/
19	or/15-18
20	Clinical Trial/
21	(clin$ adj25 trial$).mp.
22	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).mp.
23	exp Placebo/
24	(placebo$ or random$).mp.
25	exp Methodology/
26	exp Comparative Study/
27	exp Evaluation/
28	exp Follow Up/
29	exp Prospective Study/
30	(control$ or prospectiv$ or volunteer$).mp.
31	or/20–30
32	19 or 31
33	limit 32 to human
34	Nonhuman/
35	33 not 34
36	14 and 35

Appendix Table 3. CENTRAL search

Set	Search
1	renal insufficien$.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
2	chronic renal failure.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
3	chronic kidney disease$.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
4	progressive renal disease$.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
5	nephropath$.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
6	diabetic nephropath$.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
7	1 or 2 or 3 or 4 or 5 or 6
8	statin.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
9	dyslipidemia.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
10	hyperlipidemia.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
11	HMG-CoA reductase inhibitor.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
12	3-hydroxy-3-methylglutaryl coenzyme.mp. [mp = title, original title, abstract, mesh headings, heading words, keyword]
13	8 or 9 or 10 or 11 or 12
14	7 and 13
15	limit 14 to randomized controlled trial

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