Annals of Internal Medicine | Review

Meta-Analysis: The Effect of Statins on Albuminuria

Kevin Douglas, MD; Patrick G. O'Malley, MD, MPH; and Jeffrey L. Jackson, MD, MPH

Background: Albuminuria is an independent risk factor for cardiovascular and renal disease with limited therapeutic options. Data on the effects of statins on albuminuria are conflicting.

Purpose: To determine whether and to what degree statins affect albuminuria.

Data Sources: English-language and non–English-language studies found in PubMed, MEDLINE, EMBASE, BIOSIS, SciSearch, PASCAL, and International Pharmaceutical Abstracts (IPA) databases and the Cochrane Central Register of Controlled Trials that were published between January 1974 and November 2005.

Study Selection: Randomized, placebo-controlled trials of statins reporting baseline and follow-up measurements of albuminuria or proteinuria measured by 24-hour urine collection or the urinary albumin-to-creatinine ratio.

Data Extraction: Two investigators independently abstracted study quality, characteristics, and outcomes.

Data Synthesis: Fifteen studies involving a total of 1384 patients and averaging 24 weeks in duration were included. Meta-analysis of the proportional reduction in proteinuria showed that statins reduced albuminuria (11 studies) and proteinuria (4 studies) in 13 of 15 studies. The reduction in excretion was greater among studies with greater baseline albuminuria or proteinuria: change of 2% (95% CI, −32% to 35%) for those with excretion less than 30 mg/d, −48% (CI, −71% to −25%) for those with excretion of 30 to 300 mg/d, and −47% (CI, −67% to −26%) for those with excretion more than 300 mg/d. Statistical heterogeneity was evident only in the group with excretion greater than 300 mg/d (excretion $<$ 30 mg/d, $I^2 = 23\%$ [$P = 0.27$]; excretion of 30 to 299 mg/d, $I^2 = 0\%$ [$P = 0.64$]; excretion $\geq$ 300 mg/d, $I^2 = 63\%$ [$P = 0.020$]).

Limitations: Published studies were not of high quality on average and varied markedly in effect size, as well as in characteristics of the cohorts. Unpublished studies showing no effect could impact these results.

Conclusion: Statins may have a beneficial effect on pathologic albuminuria. The validity of this finding, and whether this effect translates into reduction of cardiovascular or end-stage renal disease, requires larger studies.

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For author affiliations, see end of text.

A marker of endothelial dysfunction, albuminuria has long been recognized as a risk factor for progression to end-stage renal disease. More recently, however, albuminuria has been recognized as an independent risk factor for cardiovascular morbidity and mortality (1–4). Beyond angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker therapies, therapeutic options to affect the progression of albuminuria are limited.

One therapeutic option may be 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). The beneficial effects of statins on cardiovascular morbidity and mortality cannot be explained solely by their effect on low-density lipoprotein (LDL) cholesterol levels (5–7) and may involve an independent effect on endothelial dysfunction. Some investigators have noted that the effects of statins exceed those expected from simply lowering LDL cholesterol levels and occur too early in treatment to be due to the lowering of LDL cholesterol levels (8). The nonlipid mechanisms that may be involved are called pleiotropic effects, such as lipid-independent plaque stabilization, reduced inflammation, decreased thrombogenicity, increased arterial compliance, and improved endothelial function (7, 9–12).

We systematically reviewed the literature to determine whether and to what degree statins affect albuminuria or proteinuria.

Methods

Literature Search

We searched the PubMed, MEDLINE, EMBASE, BIOSIS, SciSearch, PASCAL, and International Pharmaceutical Abstracts (IPA) databases, as well as the Cochrane Central Register of Controlled Trials, for all relevant articles published in any language between January 1974 and November 2005. We used the following Medical Subject Headings (MeSH) and text words: *proteinuria*, *urinary protein excretion*, *albuminuria*, *urinary albumin excretion*, *pitavastatin*, *mevastatin*, *fluvastatin*, *pravastatin*, *simvastatin*, *atorvastatin*, *cerivastatin*, *lovastatin*, and *rosuvastatin*. We limited our searches to randomized, placebo-controlled trials in adults (age >18 years).

Study Selection

Two investigators independently screened the titles and abstracts of potentially relevant studies before retrieving the full-text articles. When investigators doubted a

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Context

Albuminuria is a marker of endothelial dysfunction and is a risk factor for cardiovascular disease. We do not know whether or to what degree statins affect albuminuria.

Contribution

This meta-analysis of 15 randomized, placebo-controlled trials found that statins reduced albuminuria and proteinuria. Studies with greater baseline albuminuria showed greater reductions.

Cautions

Studies were small, showed heterogeneous effects, and were often of poor quality.

Implications

Statins might reduce albuminuria. We need larger, better studies to confirm these findings and to determine whether reducing albuminuria affects the incidence of end-stage renal disease or cardiovascular disease.

—The Editors

study's eligibility for inclusion, they obtained the full-text article. We included randomized, controlled trials that studied adults and had both a statin group and a placebo group. We considered the end point to be appropriate if proteinuria or albuminuria was measured either by timed urine collections to measure 24-hour excretion or by untimed specimens to calculate albumin-to-creatinine ratios. We complemented the database searches by reviewing the a priori end points of major lipid-lowering trials and the reference lists from original research articles, review articles, and previous meta-analyses. We focused exclusively on published data and did not contact authors of trials that met selection criteria but did not have data on albuminuria or proteinuria.

Validity Assessment

Two reviewers independently assessed study quality by using the Jadad rating instrument (13), complemented by an assessment of the intention-to-treat analysis, loss to follow-up, and industry sponsorship. Jadad scores are based on the description of randomization, blinding, inclusion and exclusion criteria, withdrawals, and method to assess adverse events. Scores can range from 0 to 8, and higher scores indicate better methodologic quality. We calculated interrater agreement, and we resolved differences by consensus.

Data Extraction

We extracted characteristics of the study (author, year, country, design, duration, statin and dosage, and sample size) and the participants (age, sex, presence and type of renal disease, proportion with diabetes, proportion with hypertension, baseline and follow-up cholesterol levels, baseline and follow-up urinary albumin and protein excretion rates, angiotensin-converting enzyme inhibitor use, angiotensin II receptor blocker use, and calcium-channel blocker use). If data could not be extracted or calculated from the manuscript with confidence, no data were entered. Two reviewers independently extracted data, and we resolved disagreements by consensus.

Quantitative Data Synthesis

The principal measure of effect was the weighted mean difference in the proportional change from baseline to follow-up albuminuria (or proteinuria) between the statin and placebo groups. We pooled the results by using a random-effects model to obtain the summary weighted mean difference with confidence interval. To avoid bias from carryover effects, we used data from only the first phase of crossover studies for the analysis when possible. We replaced missing means with the reported medians for calculating the weighted mean difference. We imputed missing SDs on the basis of reported *P* values, if available. We performed these imputations conservatively to err on the side of underestimating the statistical significance of positive studies. Specifically, we approximated imputed values to just reach statistical significance (for example, if the reported *P* value was less than 0.050, we imputed a value that would yield a *P* value of 0.049). When *P* values were not available, we imputed the SDs by using the mean proportional SD of the other studies. Both baseline and follow-up SDs were weighted by sample size and were averaged before inclusion in the random-effects model. We conducted sensitivity analyses for the imputed values.

We assessed heterogeneity by using the I^2 statistic (14). The I^2 statistic is an estimate of the amount of variance due to heterogeneity rather than chance and is based on the traditional measure of variance, the Cochran Q statistic. We assessed the sources of heterogeneity by performing stratified analyses (15). We considered a *P* value less than 0.050 to indicate statistically significant heterogeneity.

We performed 2 subgroup analyses for the variables that we deemed most likely to be the potential sources of statistical heterogeneity and for which data were complete. These variables included the baseline level of urinary excretion (calculated as the weighted average of statin and placebo group data and reflecting the presence and severity of disease and the likelihood of benefit from therapy) and loss to follow-up (the quality measure exhibiting the most variation across studies).

The cut-points used for urinary excretion level were less than 30 mg/d ($n = 3$), corresponding to nonpathologic levels; 30 to 299 mg/d ($n = 6$), corresponding to microalbuminuric levels; and 300 mg/d or greater ($n = 6$), corresponding to macroalbuminuric levels. For losses to follow-up, we used cut-points of more than 20% ($n = 3$) and 5% or less ($n = 12$), which may represent excessive and minimal bias, respectively.

Publication Bias

We assessed publication bias by using the Begg method with funnel plot analysis (16).

Sensitivity Analyses

To exclude the possibility that any one study was exerting excessive influence on the results, we conducted a sensitivity analysis by systematically excluding each study and then reanalyzing the data to assess the change in effect size. In addition, because gross proteinuria might reflect tubular dysfunction rather than endothelial glomerular dysfunction, we conducted a sensitivity analysis by excluding the 4 studies that measured only gross proteinuria.

We performed all analyses with Stata software, version 8.2 (Stata Corp., College Station, Texas). We considered P values less than 0.050 to be statistically significant. We used the Quality of Reports of Meta-analyses (QUOROM) statement to guide both our reporting and our discussion of the results of our meta-analysis (17).

Role of the Funding Source

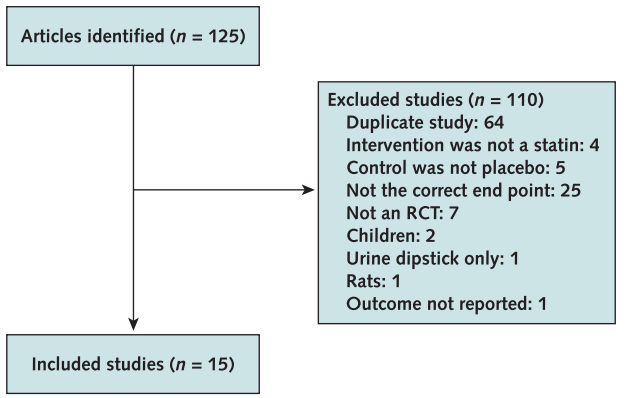
No funding was received in support of our study.

RESULTS

Literature Search

Figure 1 shows the literature search and selection flow chart.

Figure 1. **Study flow diagram.**



RCT = randomized, controlled trial.

Study and Patient Characteristics

Our final pool of eligible studies included 15 randomized, placebo-controlled trials involving 1384 participants (18–32). Studies originated from 10 different countries. Most studies were performed in Europe (53%), and only 1 study was performed in the United States. All studies measured the outcome by using a 24-hour urine collection. Three studies enrolled participants with normal albumin excretion (<30 mg/d), 6 studies enrolled participants with microalbuminuria (30 to 299 mg/d), and 6 studies enrolled participants with gross albuminuria ($n = 2$) or proteinuria ($n = 4$) (≥300 mg/d). The median number of participants in each study was 36 (range, 18 to 864 participants). Statins were (in order of decreasing frequency) simvastatin (5 studies), pravastatin (4 studies), fluvastatin and cerivastatin (2 studies each), and atorvastatin and lovastatin (1 study each). The median reduction in LDL cholesterol level was 26% (range, 10% to 51%). Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were used concurrently in 7 studies and were prohibited in 4 studies. We could not determine their use for the remaining 4 studies. Except for 1 study (26), which measured albuminuria as a potential adverse event, all studies measured either albuminuria ($n = 10$) or proteinuria ($n = 4$) as an a priori efficacy outcome. The median duration of follow-up was 6 months (range, 3 to 46 months). The mean age of participants in a study was 50 years, and 64% of participants were men. A mean of 57% of study participants had diabetes, and 23% had primary renal disease. The median Jadad score was 3 (range, 2 to 7), with acceptable interrater agreement of 91% ($\kappa = 0.76$; $z = 3.30$; $P < 0.001$). **Tables 1** and **2** show detailed information from individual studies.

Quantitative Data Synthesis

Overall Effect

Our analysis of the reduction in albumin excretion among participants treated with statins was too heterogeneous to permit a pooled analysis ($I^2 = 83\%$ [$P < 0.001$]). Therefore, we focused on quantitatively pooling data on the basis of stratified levels of albuminuria (<30 mg/d, 30 to 299 mg/d, and ≥300 mg/d).

Subgroup Analyses

When stratified by baseline urinary albumin excretion, the weighted mean difference in change from baseline was 2% (95% CI, −32% to 35%; $I^2 = 23\%$ [$P = 0.27$]) for those with excretion less than 30 mg/d; −48% (CI, −71% to −25%; $I^2 = 0\%$ [$P = 0.64$]) for those with excretion of 30 to 299 mg/d; and −47% (CI, −67% to −26%; $I^2 = 63\%$ [$P = 0.020$]) for those with excretion of 300 mg/d or greater (**Figure 2**).

Stratification by percentage loss to follow-up reduced statistical heterogeneity within subgroups. For percentage loss to follow-up greater than 20% ($n = 3$), the weighted mean difference in change from baseline was 12% (CI, 0% to 24%; $I^2 = 0\%$ [$P = 0.89$]), whereas for the studies with less than 5% loss to follow-up ($n = 12$), the weighted mean difference was −56% (CI, −65% to −47%; $I^2 = 0\%$ [$P = 0.73$]).

Publication Bias

An evaluation using the Begg method suggested no evidence of publication bias either visually or statistically ($z = 1.24$; $P = 0.22$).

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Table 1. **Fifteen Randomized, Placebo-Controlled Trials Assessing the Effect of Statins on Albuminuria or Proteinuria***

Author, Year (Reference)	Country	Funding Source	Patients Enrolled (Statin/Placebo), *n/n*	Loss to Follow-Up, *%*	Mean Age, *y*
Asselbergs et al., 2004 (18)	The Netherlands	Bristol-Myers Squibb	433/431	25	51
Buemi et al., 2000 (19)	Italy	NR	8/13	0	37
Dalla Nora et al., 2003 (20)	Italy	NR	12/13	0	64
Fried et al., 2001 (21)	United States	Merck & Co.	19/20	56	32
Hommel et al., 1992 (22)	Denmark	Merck & Co.	12/9	0	36
Lam et al., 1995 (23)†	China	NR	18/18	6	24
Lee et al., 2002 (25)†	Taiwan	Daiichi Sankyo	33/33	5	49
Lee et al., 2005 (24)†	Taiwan	Daiichi Sankyo	42/40	0	49
Lintott et al., 1995 (26)	New Zealand	Sandoz	32/10	0	58
Nakamura et al., 2001 (28)	Japan	None	30/30	0	57
Nakamura et al., 2002 (27)	Japan	None	20/20	0	41
Nielsen et al., 1993 (29)	Denmark	None	8/10	0	65
Thomas et al., 1993 (30)†	United Kingdom	Merck & Co.	15/15	23	51
Tonolo et al., 1997 (31)	Italy	None	10/10	5	60
Zhang et al., 1995 (32)	Belgium	NR	10/10	0	43

* ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; CGN = chronic glomerulonephritis; DM = diabetes mellitus; FSGS = focal segmental glomerulosclerosis; MGN = membranous glomerulonephritis; MPGN = mesangial proliferative glomerulonephritis; PCKD = polycystic kidney disease; NR = not reported.
† Proteinuria, not albuminuria, measured.

Table 2. **Fifteen Randomized, Placebo-Controlled Trials Assessing the Effect of Statins on Albuminuria or Proteinuria, Continued***

Author, Year (Reference)	Intervention	Follow-Up, *mo*	Baseline LDL Cholesterol Level, *mmol/L (mg/dL)*	LDL Cholesterol Level Change, *%*	Baseline HDL Cholesterol Level, *mmol/L (mg/dL)*
Asselbergs et al., 2004 (18)†‡	Pravastatin, 40 mg	46	4.12 (159)	–25	1.01 (39)
	Placebo		4.01 (155)	–3	1.01 (39)
Buemi et al., 2000 (19)†§	Fluvastatin, 40 mg	6	NR	NR	NR
	Placebo		NR	NR	NR
Dalla Nora et al., 2003 (20)‡	Atorvastatin, 10 mg	12	3.86 (149)	–28	1.42 (55)
	Placebo		3.16 (122)	6	1.27 (49)
Fried et al., 2001 (21)†‡	Simvastatin, 10 mg	18	3.26 (126)	–23	1.32 (51)
	Placebo		3.29 (127)	–2	1.24 (48)
Hommel et al., 1992 (22)	Simvastatin, 10 mg	3	4.20 (162)	–38	1.50 (58)
	Placebo		4.61 (178)	2	1.30 (50)
Lam et al., 1995(23)‖	Lovastatin, 60 mg	24	4.30 (166)	–30	1.11 (43)
	Placebo		4.12 (159)	–8	1.11 (43)
Lee et al., 2002 (25)‖	Pravastatin, 10 mg	6	3.24 (125)	–18	0.93 (36)
	Placebo		3.19 (123)	–6	0.96 (37)
Lee et al., 2005 (24)‖	Pravastatin, 10 mg	6	3.13 (121)	–16	0.98 (38)
	Placebo		3.19 (123)	–6	0.98 (38)
Lintott et al., 1995 (26)	Fluvastatin, 40 mg	3	NR	–21	NR
	Placebo		NR	–5	NR
Nakamura et al., 2001 (28)†§	Cerivastatin, 0.15 mg	6	5.39 (208)	–30	0.57 (22)
	Placebo		5.44 (210)	3	0.62 (24)
Nakamura et al., 2002 (27)	Cerivastatin, 0.15 mg	6	5.44 (210)	–33	0.65 (25)
	Placebo		5.57 (215)	0	0.67 (26)
Nielsen et al., 1993 (29)	Simvastatin, 20 mg	9	4.40 (170)	–34	1.27 (49)
	Placebo		4.61 (178)	2	1.45 (56)
Thomas et al., 1993 (30)‖	Simvastatin, 40 mg	6	5.91 (228)	–49	NR
	Placebo		5.91 (228)	2	NR
Tonolo et al., 1997 (31)†‡	Simvastatin, 20 mg	12	4.71 (182)	–29	1.30 (50)
	Placebo		4.71 (189)	2	1.19 (46)
Zhang et al., 1995 (32)	Pravastatin, 20 mg	3	3.19 (123)	–19	1.61 (62)
	Placebo		3.19 (123)	3	1.61 (62)

* HDL = high-density lipoprotein; LDL = low-density lipoprotein; NR = not reported.
† Median urinary albumin or protein excretion substituted for mean.
‡ Variances imputed by using average proportional SD method.
§ Variances imputed by using *P* values provided in study.
‖ Proteinuria, not albuminuria, measured.

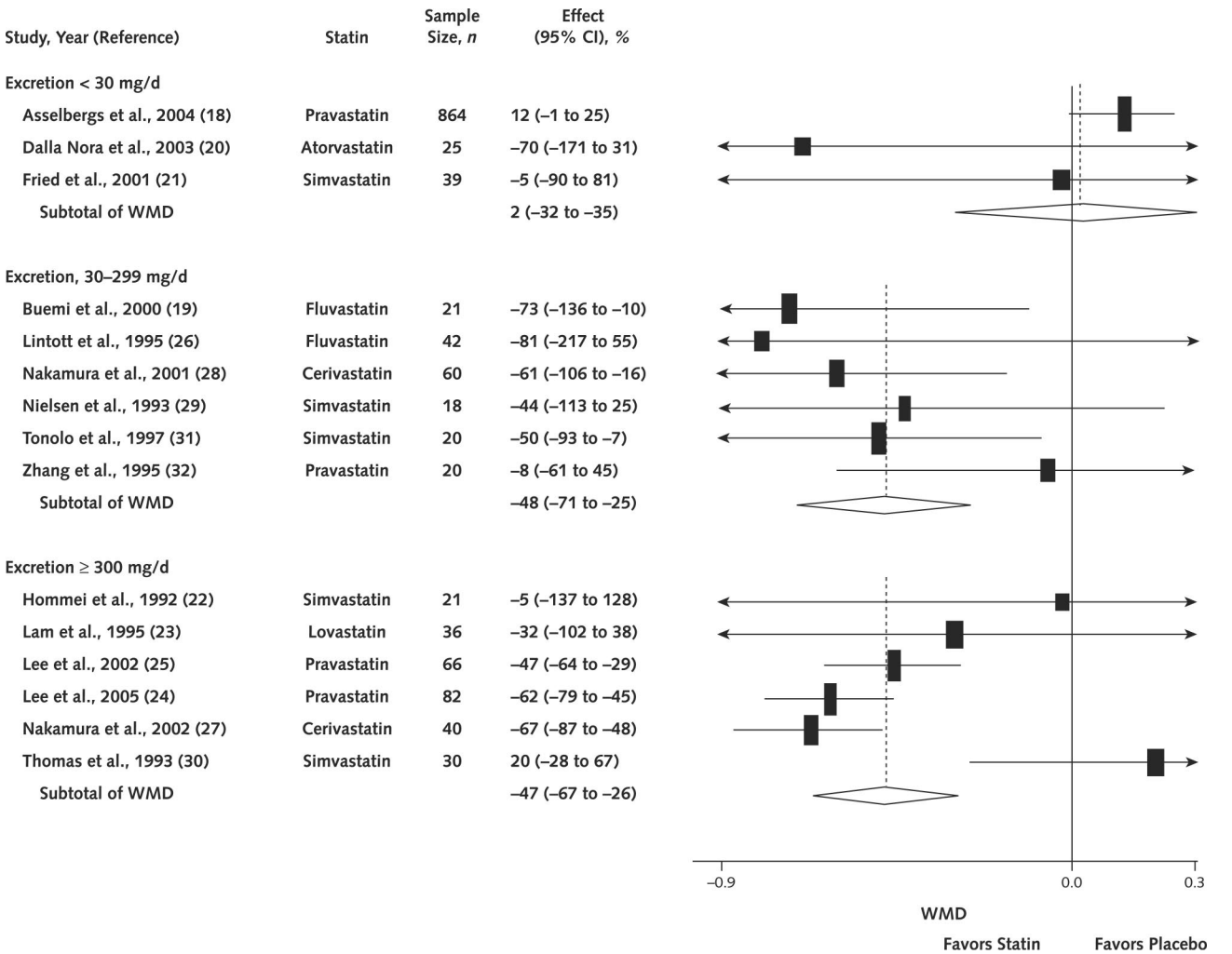
Table 1—Continued

Cause of Albuminuria	Concurrent Use of ACE Inhibitor or ARB, %	Design	Double-Blinded?	Clear Eligibility Criteria	Intention to Treat	Adverse Events Assessment Method Described?
DM (2.45%)	50	Parallel	Yes	Yes	Yes	Yes
IgA nephropathy	0	Parallel	No	Yes	Yes	No
Type 2 DM (100%)	0	Parallel	Yes	Yes	Yes	No
Type 1 DM (100%)	10	Parallel	Yes	Yes	Yes	Yes
Type 1 DM (100%)	76	Parallel	Yes	Yes	Yes	No
Type 2 DM (100%)	15	Parallel	No	No	Yes	No
NR	63	Parallel	Yes	Yes	Yes	Yes
Hypertension	100	Parallel	Yes	Yes	Yes	No
IgA nephropathy or MGN (14%); PCKD (2%); CGN (12%); NR (72%)	NR	Parallel	Yes	Yes	Yes	Yes
Type 2 DM (100%)	NR	Parallel	Yes	Yes	Yes	No
IgA nephropathy (68%); MPGN (32%)	0	Parallel	Yes	Yes	Yes	No
Type 2 DM (100%)	NR	Parallel	Yes	Yes	Yes	No
MGN (50%), FSGS (27%); other (17%); none (6%)	22	Parallel	Yes	Yes	Yes	No
Type 2 DM (100%)	0	Crossover	Yes	Yes	Yes	Yes
Type 1 DM (100%)	NR	Crossover	Yes	Yes	Yes	No

Table 2—Continued

HDL Cholesterol Level Change, %	Baseline Triglyceride Level, *mmol/L (mg/dL)*	Triglyceride Level Change, %	Mean (SD) Baseline Urinary Albumin or Protein Excretion, *mg/d*	Mean (SD) Final Urinary Albumin or Protein Excretion, *mg/d*	Urinary Albumin or Protein Excretion Change, %
NR	1.40 (124)	NR	22 (17)	22 (22)	0
NR	1.30 (115)	NR	24 (16)	20 (15)	–17
NR	1.28 (113)	0	296 (115)	173 (115)	–42
NR	1.20 (106)	13	293 (250)	385 (250)	31
2	1.83 (162)	–20	6 (4)	9 (9)	50
–2	1.55 (137)	14	7 (5)	16 (12)	129
4	0.86 (76)	–13	11 (8)	11 (11)	0
1	0.88 (78)	–12	15 (10)	15 (12)	0
2	1.37 (121)	9	698 (1313)	531 (897)	–24
3	1.86 (165)	11	755 (1290)	610 (968)	–19
–2	2.20 (195)	–9	810 (680)	1130 (1000)	40
–11	2.90 (257)	28	1140 (1273)	1950 (1130)	71
–19	2.72 (241)	–17	1234 (490)	560 (274)	–55
3	2.55 (226)	2	1193 (507)	1096 (456)	–8
8	2.81 (249)	–18	1323 (592)	559 (251)	–58
0	2.68 (237)	1	1207 (531)	1262 (557)	5
NR	NR	–7	200 (537)	145 (387)	–28
NR	NR	24	297 (403)	455 (649)	53
73	2.28 (202)	–21	141 (110)	52 (160)	–63
4	2.24 (198)	3	135 (110)	133 (110)	–1
32	2.32 (205)	32	1800 (600)	800 (400)	–56
–4	2.37 (210)	0	1700 (600)	1900 (600)	12
–1	2.32 (205)	–10	28 (18)	24 (12)	–14
–1	1.62 (143)	10	49 (40)	64 (51)	31
–2	3.11 (275)	–25	5920 (3490)	6400 (3900)	8
2	2.77 (245)	–11	4400 (2680)	3900 (2000)	–11
10	1.60 (142)	–19	73 (34)	48 (34)	–34
9	1.50 (133)	0	70 (34)	81 (34)	16
2	1.19 (105)	–11	94 (53)	71 (95)	–24
0	1.19 (105)	14	94 (53)	78 (92)	–17

Figure 2. **Individual and pooled results of 15 randomized, placebo-controlled trials examining the effect of statins on albuminuria or proteinuria, stratified by baseline excretion.**



Residual statistical heterogeneity: $I^2 = 23\%$ ($P = 0.27$) for excretion < 30 mg/d; $I^2 = 0\%$ ($P = 0.64$) for excretion of 30 to 299 mg/d; and $I^2 = 63\%$ ($P = 0.020$) for excretion ≥ 300 mg/d. WMD = weighted mean difference in the proportional change from baseline to follow-up albuminuria (or proteinuria) between statin and placebo groups.

Sensitivity Analyses

Sensitivity analyses demonstrated that the pooled weighted mean differences were robust to the omission of any one study, as well as to the exclusion of the 4 studies that measured only gross proteinuria. Because we had to impute some means and variances, we also checked to see how sensitive our analyses were to these values. The analyses were insensitive to varying the medians used to impute means ($n = 5$) (by 2-fold) and the estimates of SDs ($n = 6$) (by as much as 70%) without changing the pooled effects of the statins on albuminuria (or proteinuria). Finally, the pooled effects were robust to exclusion of all studies using imputed SDs.

DISCUSSION

In our meta-analysis of randomized, placebo-controlled trials in adults, statins were associated with statistically significant reductions in pathologic but not nonpathologic levels of albuminuria and proteinuria. These effects may have been due to the ability of statins to improve endothelial dysfunction, supported by other biological evidence of such an effect. Most studies have shown that the vasoconstriction associated with endothelial dysfunction can be attenuated or abolished with statin therapy (33–35). This improvement in endothelial function can be seen within 6 weeks (36) and partly results from an increase in endothelial nitric oxide activity by activation of nitric oxide release and concurrent inactivation of superoxide (37). A reduction in serum oxidized LDL cholesterol level may contribute to improvements in endothelial function since oxidized LDL cholesterol downregulates endothelial nitric oxide synthase activity (38).

Another meta-analysis attempted to determine whether a reduction in albuminuria occurs as a manifestation of this process (39). That meta-analysis included fewer ($n = 9$) randomized, controlled trials that were all published before July 1999, finding a trend toward benefit ($P = 0.077$). Similar to our results, that meta-analysis found substantial statistical heterogeneity, which the authors could not explain. Our meta-analysis extends this work by including trials published since 1999 and more thoroughly exploring the sources of heterogeneity.

While we could isolate much of the statistical heterogeneity by stratifying according to baseline urinary albumin (or protein) excretion, residual statistical heterogeneity persisted within the macroalbuminuric (≥300 mg/d) stratum. This statistical heterogeneity was matched by marked clinical heterogeneity. Indeed, the 6 studies within this stratum reported several different causes of nephropathy, including hypertension (1 study [24]), diabetes (2 studies [22, 23]), and several primary renal diseases (2 studies [27, 30]), while 1 study did not report any cause at all (25). In contrast, the pathologic causes of the trials in the lower 2 tiers of urinary excretion exhibited much greater uniformity, with only 2 of the trials (both in the microalbuminuric stratum) citing a cause other than diabetes (19, 26).

Our findings have several limitations. First, we included only published data. In 1 study, meta-analyses limited to published trials, compared with those that included both published and unpublished literature, overestimated the treatment effect by an average of 12% (40). While an attenuation of this magnitude would not substantially alter the conclusions of our meta-analysis, the potential bias is notable. Although we did not find evidence of publication bias either graphically or statistically by using the Begg method, evaluation for publication bias by the Begg method lacks sensitivity. Therefore, while we are fairly confident that substantial publication bias does not exist, we cannot rule it out entirely. Indeed, all positive studies in our review were relatively small. Smaller trials may have inadequate randomization, leading to confounded results that, if positive, may be more likely to be published than those of small negative trials. Our literature search identified 25 studies that met our initial inclusion criteria except for reporting the end point of interest. Investigators of those trials should publish data on albuminuria if such data were collected.

Second, findings of the smaller studies contrasted with those of the much larger study by Asselbergs and colleagues (18). Their study enrolled participants with mean baseline levels of albuminuria that were, at most, only borderline pathologic (<30 mg/d). Therefore, any effect on such an early stage of disease may not be evident without longer follow-up or may not exist. Concurrent use of the angiotensin-converting enzyme inhibitor fosinopril in one half of participants may have further limited the ability of pravastatin to demonstrate benefit. Finally, the study's 25% loss to follow-up may have affected its results. The loss to follow-up may have simply been a general marker for poor adherence among the study participants, and this poor adherence would have tended to limit any apparent benefit within the statin group.

Third, the internal validity of a meta-analysis can only be as good as the quality of the studies reviewed. Although all studies were randomized, only 4 studies actually described the method used for randomization. Although all of the studies were blinded, not all were double-blinded, and only 5 studies described any protocol for assessing adverse effects of therapy. Therefore, while the studies were all randomized, placebo-controlled trials, they were of only mediocre quality overall, as reflected in the median Jadad score of 3.

Fourth, our meta-analysis involved relatively few trials, and consequently, the statistical power available was limited, thereby restricting our ability to run additional subgroup analyses and suggesting that clinically meaningful associations were missed. Indeed, it would be interesting to assess whether variability in response differs among the types of statin and to address whether this is a class effect or is unique to individual statins. With the important caveat that, because we used group data for our analyses, any associations or lack of associations we found could have been the result of within-group confounding leading to the "ecologic fallacy," we find these results provocative nonetheless and worthy of note to guide future study.

In summary, we found that the cumulative trial evidence involving statin therapy among participants with albuminuria and proteinuria suggests that statins may moderately reduce pathologic excretion within a median of 6 months after initiation of therapy. Our findings, while provocative, should be confirmed by larger, high-quality studies that, unlike the study by Asselbergs and colleagues (18), enroll participants with pathologic levels of albuminuria and ensure complete follow-up. Whether our findings of possible benefit may be associated with reduction in cardiovascular disease or end-stage renal disease will require an examination of how proportional changes in albuminuria correlate with changes in actual cardiovascular and renal outcomes.

From Walter Reed Army Medical Center, Washington, DC, and Uniformed Services University of the Health Sciences, Bethesda, Maryland.

Disclaimer: The views expressed herein are those of the authors and do not necessarily reflect those of the U.S. Army or the U.S. Department of Defense.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Kevin Douglas, MD, Walter Reed Army Medical Center, 6900 Georgia Avenue, NW, Washington, DC 20307.

Current author addresses are available at www.annals.org.

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Current Author Addresses: Drs. Douglas, O'Malley, and Jackson: Walter Reed Army Medical Center, 6900 Georgia Avenue, NW, Washington, DC 20307.