AJKD

Original Investigation

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

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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.

Am J Kidney Dis. ■(■):■-■. © *2016 by the National Kidney Foundation, Inc.*

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

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Received June 24, 2015. Accepted in revised form January 11, 2016.

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0272-6386

http://dx.doi.org/10.1053/j.ajkd.2016.01.016

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

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