Meta-Analysis of the Effect of Statins on Renal Function

Qiang Geng, PhD, Jingyi Ren, MD, Junxian Song, PhD, Sufang Li, PhD, and Hong Chen, MD*

Statins can significantly improve the lipid profile and reduce cardiovascular events. However, beneficial effects of statins on renal function are still controversial. PubMed, the Cochrane Central Register of Controlled Trials, Web of Knowledge, and ClinicalTrials.gov Web sites were searched for randomized controlled trials. The selected studies reported renal function during treatment with statins and control. Forty-one studies with a total of 88,523 participants were included in this analysis. Compared with statins, placebo group had significantly decreased estimated glomerular filtration rate (eGFR): the standardized mean difference (SMD) of eGFR in change from baseline was 0.15 (95% confidence interval [CI] 0.07 to 0.23, p = 0.0004) in patients with eGFR >60 ml/min and 0.09 (95% CI 0.01 to 0.17, p = 0.02) in patients with eGFR 30 to 60 ml/min. Compared with placebo, statin group had significantly greater reduction of proteinuria: the SMD of proteinuria in change from baseline was −1.12 (95% CI −1.95 to −0.30, p = 0.008) in patients with urinary protein excretion 30 to 300 mg/day and −0.77 (95% CI −1.35 to −0.18, p = 0.01) in patients with urinary protein excretion > 300 mg/day. eGFR was significantly greater with high-intensity statins than with moderate-intensity statins (SMD 0.12, 95% CI 0.08 to 0.16, p = 0.00001). Placebo group had significantly decreased eGFR for 1 to 3 years (SMD 0.05, 95% CI 0.02 to 0.08, p = 0.003) and >3 years (SMD 0.14, 95% CI 0.04 to 0.25, p = 0.007) of statin therapy. The beneficial effect of statins on renal function may be dosage related and duration dependent. In conclusion, statins appear to decrease the rate of reduction of eGFR and slow the progression of pathologic proteinuria moderately. **(Am J Cardiol 2014;114:562−570)**

Statins are the most widely prescribed drugs for the treatment of atherosclerosis, and they substantially reduce cardiovascular disease morbidity and mortality in prevention. However, it has not been established whether statins provide similar beneficial effects on the kidney. There is a growing affirmation that statins may offer renoprotective effects as illustrated in a number of cohort studies, other meta-analyses, and statements by professional organizations.[1−4] In contrast, some studies failed to demonstrate renoprotection from statins.[5] Concerns about these conflicting results make physicians reluctant to prescribe statins in patients with chronic kidney disease (CKD). To assess whether statins had beneficial effects on kidney, we performed this meta-analysis to investigate the effects of statins on estimated glomerular filtration rate (eGFR) and urinary protein excretion between statin and control groups.

Methods

Our meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.[6] We searched the PubMed, the Cochrane Central Register of Controlled Trials, Web of Knowledge, and ClinicalTrials.gov Web sites to identify the published or unpublished randomized controlled trials (RCTs) in any language from 1987 to 2013. The following terms were used: hydroxymethylglutaryl-CoA reductase inhibitors, atorvastatin, simvastatin, rosuvastatin, pravastatin, lovastatin, fluvastatin, pitavastatin, statin, kidney, renal, glomerular filtration rate, nephropathy, albuminuria, and proteinuria.

Two investigators independently identified reports according to the inclusion criteria. Disagreements were resolved by discussion and consensus. Study quality was estimated using the Cochrane classification for assessing the risk of bias (sequence generation, allocation concealment, blinding, selective reporting, and intention-to-treat analysis).[7]

The inclusion criteria were (1) RCTs of statins versus control (placebo, another statin, or usual care); (2) participants aged >18 years; (3) report of baseline and at end of follow-up data on kidney function (eGFR, creatinine clearance, or urinary protein excretion); and (4) report of change from baseline on renal function and damage (eGFR, creatinine clearance, or urinary protein excretion). The exclusion criteria were (1) participants aged <18 years; (2) studies without kidney function; (3) participants with contrast-induced nephropathy or dialysis; and (4) reviews, nonhuman studies, case reports, and abstracts.

The characteristics of the study were extracted from the included studies: author, year, sample size, age, design, follow-up duration, statin and dosage, type of renal disease, eGFR, and urinary protein excretion.

Department of Cardiology, Peking University People's Hospital, Beijing, China. Manuscript received March 27, 2014; revised manuscript received and accepted May 27, 2014.

Drs. Geng and Ren contributed equally to this work.

This work was supported by the National Natural Science Foundation grant 30570712 and 81070179 funded by the national natural science fund committee (China).

See page 570 for disclosure information.

*Corresponding author: Tel: (+86) 10 88325339; fax: (+86) 10 88325339.

E-mail address: chenhongbj@medmail.com.cn (H. Chen).

0002-9149/14/$ - see front matter
http://dx.doi.org/10.1016/j.amjcard.2014.05.033

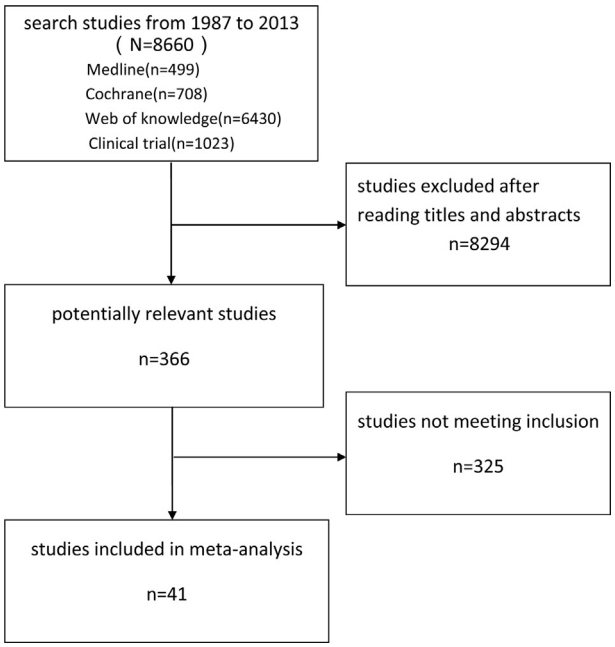

Figure 1. Study selection flow diagram. Initially, 8,660 studies were identified; of these, 8,626 studies failed to meet the inclusion criteria and 41 studies were included in this meta-analysis.

The change from baseline in eGFR in milliliters per minute per year was calculated in this analysis. In our meta-analysis, creatinine clearance is regarded as an eGFR.[8,9] Twenty-five studies (Supplementary References 3,5,6,9,11−14,16−22,24,27,28,30−35,37) enrolled patients with eGFR >60 ml/min/1.73 m^2. Nine studies (Supplementary References 1,4,6,7,10,25,26,29,38) enrolled patients with eGFR <60 ml/min/1.73 m^2.

In our analysis, albuminuria and proteinuria were considered together. Three studies (Supplementary References 2,22,36) enrolled patients with urinary protein (or albumin) excretion <30 mg/day. Six studies (Supplementary References 8,9,15,23,33,35) enrolled patients with urinary protein (or albumin) excretion 30 to 300 mg/day. Thirteen studies (Supplementary References 1,7,9−13,19,20,21,25,32,34) enrolled patients with urinary protein (or albumin) excretion >300 mg/day.

"High-intensity," "moderate-intensity," and "low-intensity" statin therapy definitions were derived from the recent American College of Cardiology/American Heart Association guidelines.[10] We analyzed our data by comparing high-intensity statins versus moderate-intensity statins. We also investigated the effect of high-intensity, moderate-intensity, and low-intensity statins on eGFR and urinary protein excretion. Eight studies (Supplementary References 1,6,27,28,30,39−41) adopted high-intensity statins. Twenty-five studies (Supplementary References 2−5,7,9,11,12,16−18,22−24,26,27,29,31,34,35,37−41) adopted moderate-intensity statins. Twelve studies (Supplementary References 8,10,13−15,19−21,25,32,33,36) adopted low-intensity statins.

Nikolic et al[11] found that the benefit of statins may depend on the duration of treatment. So we investigated the relation between the duration of treatment (<1 year, 1 to 3 years, and >3 years) and the effect of statins on renal function. The duration of statin therapy in 15 studies (Supplementary References 4,8,9,12,15,19−21,26,27,31−34,38) was <1 year. The duration of statin therapy in 11 studies (Supplementary References 1,2,10,13,23,25,28−30,35,36) was from 1 to 3 years. The duration of statin therapy in 12 studies (Supplementary References 3,5,6,7,11,14,16−18,22,24,37) was >3 years.

The I^2 statistic was used to assess heterogeneity. I^2 >50% and p <0.10 indicated statistically significant heterogeneity. A funnel plot was used to assess publication bias. In the present study, 2-sided p <0.05 was considered significant.

The change from baseline in eGFR in milliliters per minute per year and in urinary protein excretion was calculated using the standardized mean difference (SMD). Missing mean was replaced with median. Missing SD was imputed using the width of interquartile ranges divided by 1.35 or on the basis of p values.[7] The meta-analysis was performed using Review Manager software (version 5.0; Cochrane Collaboration, Oxford, United Kingdom).

Results

Initially, 8,660 studies were searched, consisting of 366 potentially relevant studies and 8,294 studies that were removed after reading titles and abstracts. Of 366 potentially relevant studies, 325 failed to match the inclusion criteria. Finally, 41 studies with a total of 88,523 participants were included in this meta-analysis. Flowchart for identification of studies is presented in Figure 1. The baseline characteristics of studies in the meta-analysis are given in Table 1.

AURORA (an assessment of survival and cardiovascular events) and 4D (Deutsche Diabetes Dialyse Studie) studies had evaluated the use of statins in patients on regular hemodialysis. In our meta-analysis, dialysis was one of the exclusion criteria. We could not get the eGFR data of SHARP (study of heart and renal protection) study. We had sent an e-mail to the corresponding author, but the author did not reply to us. So, AURORA, 4D, and SHARP trials were excluded in our meta-analysis.

The risk of bias in the selected studies is presented in Supplementary Table 1. All the studies selected in our meta-analysis were RCTs and had adequate random sequence generation. Twenty-five studies used allocation concealment methods. Twenty-four studies reported that patients were blinded to treatment, and 23 studies reported that the outcome assessors were blinded to the patient groups. Fifteen studies had intention-to-treat analysis. No studies had selective outcome reporting.

To investigate the effects of statins versus placebo on eGFR, 24 studies (Supplementary References 5,6,9,11−14,16−22,24,27,28,30−35,37) enrolled 75,723 participants with eGFR >60 ml/min/1.73 m^2, and 9 studies (Supplementary References 1,4,6,7,10,25,26,29,38) enrolled 2,222 participants with eGFR <60 ml/min/1.73 m^2.

The SMD of eGFR in change from baseline was stratified by baseline eGFR. In patients with eGFR >60 ml/min/1.73 m^2, the SMD of eGFR was 0.15 (95% confidence interval [CI] 0.07 to 0.23, p = 0.0004; Figure 2). In patients