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# Kidney Diseases 2017: 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 Published or unpublished randomized, controlled trials or crossover trials of statins that reported assessment of kidney function or proteinuria were included, and studies of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.

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 suggest-

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ed 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 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.

**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.