Effect of High-Dose Atorvastatin on Renal Function in Subjects With Stroke or Transient Ischemic Attack in the SPARCL Trial

Pierre Amarenco, MD; Alfred Callahan III, MD; Vito M. Campese, MD; Larry B. Goldstein, MD; Michael G. Hennerici, MD, PhD; Michael Messig, PhD; Henrik Sillesen, MD, DMSc; K. Michael A. Welch, MB, ChB; Daniel J. Wilson, MD; Justin A. Zivin, MD, PhD*

Background and Purpose—Higher low-density lipoprotein cholesterol is associated with more rapid chronic kidney disease progression; reduction in cholesterol with statins, in conjunction with statins’ pleiotropic effects, such as decreasing inflammation, may be renoprotective. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial assessed the effect of statin treatment on the risk of nonfatal and fatal stroke in subjects with a noncardioembolic stroke or transient ischemic attack, no known coronary heart disease, and low-density lipoprotein cholesterol between 2.6 and 4.9 mmol/L (100–190 mg/dL).

Methods—We explored the effect of randomization to atorvastatin 80 mg/d or placebo on the change in estimated glomerular filtration rate (eGFR; using the 4-component Modification of Diet in Renal Disease Study equation) in SPARCL subjects (n=4731) with (eGFR, <60 mL/min per 1.73 m²; n=3119) and without (eGFR, ≥60 mL/min per 1.73 m²; n=1600) chronic kidney disease overall and by glycemic status at baseline.

Results—Mean baseline eGFR was similar between treatment groups (65.5±0.26 versus 65.6±0.26 mL/min per 1.73 m² atorvastatin versus placebo; 33% versus 34% had chronic kidney disease, respectively; P=0.55). After 60 months, eGFR increased 3.46±0.33 mL/min per 1.73 m² in those randomized to atorvastatin versus 1.42±0.34 mL/min per 1.73 m² in those randomized to placebo (P<0.001) independent of baseline renal function. In the subgroup with diabetes mellitus at randomization, eGFR increased 1.12±0.92 mL/min per 1.73 m² in the atorvastatin group and decreased 1.69±0.92 mL/min per 1.73 m² in placebo group during a period of 60 months (P=0.016).

Conclusions—This post hoc analysis suggests that atorvastatin treatment may improve renal function in patients with prior stroke or transient ischemic attack with and without chronic kidney disease, and that atorvastatin treatment may prevent eGFR decline in patients with stroke and diabetes mellitus.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00147602.

Key Words: atorvastatin ■ glomerular filtration rate ■ ischemic attack, transient ■ kidney diseases ■ renal insufficiency, chronic ■ stroke

Chronic kidney disease (CKD) is a worldwide public health problem associated with an increased risk of all-cause mortality, cardiovascular events, hospitalization,1,4 reduced quality of life, and higher healthcare costs.5,6 CKD is defined on the basis of pathologic abnormalities, proteinuria or hematuria, and either with or without an estimated glomerular filtration rate (eGFR) <60 mL/min per 1.73 m². CKD has many risk factors in common with cardiovascular disease, including nontraditional risk factors such as oxidative stress and inflammation.5,7,8 Aggressive treatment of comorbid conditions such as diabetes mellitus, hypertension, and dyslipidemia are recommended to reduce cardiovascular disease risk and prevent progressive impairment of renal function.5,7,8 Prior reports indicate that higher low-density lipoprotein cholesterol (LDL-C) levels are associated with a more rapid decrease in eGFR10,11 and that lowering LDL-C with statins in subjects with cardiovascular diseases may be renoprotective.12,13

Received April 23, 2014; final revision received July 16, 2014; accepted July 21, 2014.
Department of Neurology and Stroke Center, Paris-Diderot Sorbonne University, Paris, France (P.A.); Department of Neurology, Vanderbilt University, Nashville, TN (A.C.); Division of Nephrology and Hypertension Center, USC/Keck School of Medicine, Los Angeles, CA (V.M.C.); Department of Neurology, Duke University Medical Center, Durham, NC (L.B.G.); Department of Neurology, Universitat Heidelberg, Mannheim, Germany (M.G.H.; Pfizer Inc, New York, NY (M.M., D.J.W.); Department of Vascular Surgery, University of Copenhagen, Copenhagen, Denmark (H.S.); Office of the President, Rosalind Franklin University, Chicago, IL (K.M.A.W.); and Department of Neurology, University of California, San Diego (J.A.Z.).

*Prepared by the writing committee (listed in alphabetic order) for the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. Guest Editor for this article was Jeffrey L. Saver, MD.

Correspondence to Pierre Amarenco, MD, Department of Neurology and Stroke Center, Bichat University Hospital, Paris-Diderot University, 46, rue Henri Husach, F-75018 Paris, France. E-mail pierre.amarenco@bch.aphp.fr

© 2014 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.114.005832
Post hoc analyses of cardiovascular outcome trials evaluating statins in the treatment of patients with dyslipidemia and coronary heart disease (CHD) or diabetes mellitus suggest renal benefit in addition to marked reductions in major cardiovascular events.\textsuperscript{14–18} Several trials show slowing of time-dependent falls in eGFR, whereas others found a clinically significant improvement of eGFR with statin treatment in subjects with or without CKD.\textsuperscript{14–18} For example, in the Collaborative Atorvastatin Diabetes Study (CARDS) trial, subjects with no history of vascular event and normal LDL-C randomized to 10 mg atorvastatin daily had a modest improvement in annual change in eGFR (net 0.18 mL/min per 1.73 m\textsuperscript{2}; \(P=0.01\)) that was most apparent in those with albuminuria.\textsuperscript{19} Furthermore, the renal benefits of statins have also been examined in systematic reviews and meta-analyses.\textsuperscript{20–23}

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial randomized patients with recent noncardioembolic stroke or transient ischemic attack (TIA) without known CHD to atorvastatin 80 mg/d versus placebo. Treatment was associated with a 16% reduction in the hazard ratio for recurrent stroke (the primary end point), as well as a 35% reduction in major coronary events (a secondary end point).\textsuperscript{24} This post hoc analysis of SPARCL trial data explores the effect of atorvastatin 80 mg/d versus placebo on changes in renal function from baseline as measured by eGFR during the course of the trial in those with and without CKD at baseline. In a secondary analysis, the SPARCL subjects were further stratified based on baseline glycemic status. The safety of atorvastatin therapy in subjects with and without CKD was also assessed.

Methods

Study Design and Patient Population

The design of the SPARCL trial has been described in detail.\textsuperscript{24,25} The study was conducted in compliance with the Declaration of Helsinki and was approved by the local research ethics committee or institutional review board at each center. All participants gave written informed consent. Eligible patients were men and women aged \(\geq\)18 years who had an ischemic or hemorrhagic stroke or a TIA without cardiomebolic cause (diagnosed by a neurologist within 30 days after event) \(\geq\)6 months before randomization, no known CHD, and a screening LDL-C between 2.6 and 4.9 mmol/L (100 and 190 mg/dL). Subjects were randomized to double-blind treatment with atorvastatin 80 mg/d versus placebo on changes in renal function from baseline as measured by eGFR during the course of the trial in those with and without CKD at baseline. In a secondary analysis, the SPARCL subjects were further stratified based on baseline glycemic status. The safety of atorvastatin therapy in subjects with and without CKD was also assessed.

Renal Analyses

Serum creatinine (Scr) measurements were obtained at baseline and 12, 24, 36, 48, and 60 months after randomization. Scr was analyzed by the alkaline picrate method (Jaffe reaction) at a central laboratory by technicians who were unaware of the participant’s treatment assignment. The Roche enzymatic method and Beckman CX3 auto analyzer were used for these determinations. Creatinine measurements were calibrated and adjusted using College of American Pathologists standards, using National Institute of Standards and Technology traceability, with assigned values traceable to isotope dilution mass spectrometry, a calibration panel prepared by the Cleveland Clinic Research Laboratory, and frozen samples from the Modification of Diet in Renal Disease (MDRD) Study. eGFR was calculated using the abbreviated, 4-component, MDRD equation.\textsuperscript{26} Subjects were categorized using a modification of the National Kidney Foundation classification for renal disease using the baseline MDRD eGFR. Those with eGFR \(\leq\)60 mL/min per 1.73 m\textsuperscript{2} were defined as having CKD, whereas those with eGFR \(>60\) mL/min per 1.73 m\textsuperscript{2} were defined as not having CKD.

Given that metabolic and glycemic status may affect renal function, data were further analyzed by baseline glycemic and metabolic status of the subjects in the following 3 groups: normoglycemic subjects without metabolic syndrome or type 2 diabetes mellitus; subjects with metabolic syndrome but without type 2 diabetes mellitus; and subjects with type 2 diabetes mellitus, with or without metabolic syndrome. The definition of metabolic syndrome was based on the National Cholesterol Education Program Adult Treatment Panel III guidelines with body mass index \(\geq\)30 kg/m\textsuperscript{2} substituted for waist circumference.\textsuperscript{27,28}

Statistical Analyses

Mean changes from baseline eGFR during the course of the study were compared between the atorvastatin and placebo treatment groups using a repeated measures ANCOVA model with terms for treatment, time point, race, and age. Initial models tested for treatment by time interactions. Separate ANCOVA models were used to analyze renal function in the groups of subjects with eGFR \(<60\) mL/min per 1.73 m\textsuperscript{2} and eGFR \(\geq 60\) mL/min per 1.73 m\textsuperscript{2}. End of study eGFR values were assigned using the last observation carried forward and were compared between treatment groups using ANCOVA. The Fisher exact test was used to compare the proportions of subjects who had a decline or improvement of renal function between treatment groups. Lipid parameters were compared between treatment groups in intention-to-treat analysis using an ANCOVA model with the baseline lipid parameter as a continuous covariate. Two-sided \(P\) values \(<0.05\) were considered significant.

Results

Subjects

A total of 4731 subjects were enrolled in the SPARCL trial. The cohort for the present analysis included the 4719 SPARCL participants who had a baseline measurement of Scr (Figure 1). Subject demographics and disposition for the renal cohort were similar to those previously published for the overall SPARCL population. Complete renal data, defined as a baseline Scr with \(\geq 2\) follow-up determination, were available for 4393 participants: 2186 of whom were assigned to atorvastatin and 2207 to placebo. A total of 326 participants in the renal cohort (170 in the atorvastatin group and 156 in the placebo group) were excluded from analysis.

Statistical Analyses

Mean changes from baseline eGFR during the course of the study were compared between the atorvastatin and placebo treatment groups using a repeated measures ANCOVA model with terms for treatment, time point, race, and age. Initial models tested for treatment by time interactions. Separate ANCOVA models were used to analyze renal function in the groups of subjects with eGFR \(<60\) mL/min per 1.73 m\textsuperscript{2} and eGFR \(\geq 60\) mL/min per 1.73 m\textsuperscript{2}. End of study eGFR values were assigned using the last observation carried forward and were compared between treatment groups using ANCOVA. The Fisher exact test was used to compare the proportions of subjects who had a decline or improvement of renal function between treatment groups. Lipid parameters were compared between treatment groups in intention-to-treat analysis using an ANCOVA model with the baseline lipid parameter as a continuous covariate. Two-sided \(P\) values \(<0.05\) were considered significant.

Results

Subjects

A total of 4731 subjects were enrolled in the SPARCL trial. The cohort for the present analysis included the 4719 SPARCL participants who had a baseline measurement of Scr (Figure 1). Subject demographics and disposition for the renal cohort were similar to those previously published for the overall SPARCL population.\textsuperscript{24} Complete renal data, defined as a baseline Scr with \(\geq 2\) follow-up determination, were available for 4393 participants: 2186 of whom were assigned to atorvastatin and 2207 to placebo. A total of 326 participants in the renal cohort (170 in the atorvastatin group and 156 in the placebo group) were excluded from analysis.

Statistical Analyses

Mean changes from baseline eGFR during the course of the study were compared between the atorvastatin and placebo treatment groups using a repeated measures ANCOVA model with terms for treatment, time point, race, and age. Initial models tested for treatment by time interactions. Separate ANCOVA models were used to analyze renal function in the groups of subjects with eGFR \(<60\) mL/min per 1.73 m\textsuperscript{2} and eGFR \(\geq 60\) mL/min per 1.73 m\textsuperscript{2}. End of study eGFR values were assigned using the last observation carried forward and were compared between treatment groups using ANCOVA. The Fisher exact test was used to compare the proportions of subjects who had a decline or improvement of renal function between treatment groups. Lipid parameters were compared between treatment groups in intention-to-treat analysis using an ANCOVA model with the baseline lipid parameter as a continuous covariate. Two-sided \(P\) values \(<0.05\) were considered significant.

Results

Subjects

A total of 4731 subjects were enrolled in the SPARCL trial. The cohort for the present analysis included the 4719 SPARCL participants who had a baseline measurement of Scr (Figure 1). Subject demographics and disposition for the renal cohort were similar to those previously published for the overall SPARCL population.\textsuperscript{24} Complete renal data, defined as a baseline Scr with \(\geq 2\) follow-up determination, were available for 4393 participants: 2186 of whom were assigned to atorvastatin and 2207 to placebo. A total of 326 participants in the renal cohort (170 in the atorvastatin group and 156 in the placebo group) were excluded from analysis.

Statistical Analyses

Mean changes from baseline eGFR during the course of the study were compared between the atorvastatin and placebo treatment groups using a repeated measures ANCOVA model with terms for treatment, time point, race, and age. Initial models tested for treatment by time interactions. Separate ANCOVA models were used to analyze renal function in the groups of subjects with eGFR \(<60\) mL/min per 1.73 m\textsuperscript{2} and eGFR \(\geq 60\) mL/min per 1.73 m\textsuperscript{2}. End of study eGFR values were assigned using the last observation carried forward and were compared between treatment groups using ANCOVA. The Fisher exact test was used to compare the proportions of subjects who had a decline or improvement of renal function between treatment groups. Lipid parameters were compared between treatment groups in intention-to-treat analysis using an ANCOVA model with the baseline lipid parameter as a continuous covariate. Two-sided \(P\) values \(<0.05\) were considered significant.

Results

Subjects

A total of 4731 subjects were enrolled in the SPARCL trial. The cohort for the present analysis included the 4719 SPARCL participants who had a baseline measurement of Scr (Figure 1). Subject demographics and disposition for the renal cohort were similar to those previously published for the overall SPARCL population.\textsuperscript{24} Complete renal data, defined as a baseline Scr with \(\geq 2\) follow-up determination, were available for 4393 participants: 2186 of whom were assigned to atorvastatin and 2207 to placebo. A total of 326 participants in the renal cohort (170 in the atorvastatin group and 156 in the placebo group) were excluded from analysis.
group) were excluded from the follow-up analysis because of the absence of a follow-up SCr measurement. There were no differences in baseline characteristics among subjects included in the study and those excluded. Baseline and follow-up eGFR were calculated for the identified population with complete renal data at yearly intervals or until a study primary end point.

### Table 1. Baseline Demographics and Clinical Characteristics of Stroke Prevention by Aggressive Reduction in Cholesterol Levels

<table>
<thead>
<tr>
<th></th>
<th>eGFR &lt;60 mL/min per 1.73 m²</th>
<th>eGFR ≥60 mL/min per 1.73 m²</th>
<th>PValue*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atv 80 mg (n=789)</td>
<td>Placebo (n=811)</td>
<td>All (n=1600)</td>
</tr>
<tr>
<td>MDRD eGFR, mL/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>per 1.73 m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin II blockers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of antihypertensive medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entry events</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values given are number of subjects (%) or mean±SD. ACE indicates angiotensin-converting enzyme; Atv, atorvastatin; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, the Modification of Diet in Renal Disease study; and TIA, transient ischemic attack.

*P* values are between subjects with CKD vs without CKD.
Baseline demographics and clinical characteristics of the renal cohort are given in Table 1. A total of 3119 (66%) of the 4719 participants were classified as having normal or near normal renal function (eGFR, ≥60 mL/min per 1.73 m²) and 1600 (34%) had CKD. The majority of the CKD group had stage 3a CKD (1391 participants [87%]; eGFR, 45–59 mL/min per 1.73 m²) or stage 3b CKD (189 participants [12%]; eGFR, 30–44 mL/min per 1.73 m²). A similar proportion of those randomized to atorvastatin versus placebo had CKD at baseline (789/2356, 33% versus 811/2363, 34%; χ², P=0.546).

The statin drop in (initiating open-label, nonstudy statin therapy) rate for participants assigned to placebo was 7.9% for those with CKD and 7.3% for those without CKD. The discontinuation rate of atorvastatin was 15.8% in participants with CKD and 15.1% in those without CKD. Drop in and discontinuation rates were calculated as percentage of follow-up time for the primary end point.

Subjects with CKD had a baseline eGFR of 52.3±7.0 mL/min per 1.73 m² compared with an eGFR of 72.3±8.9 mL/min per 1.73 m² in those without CKD (P<0.001). Those with CKD were older, more likely to be women, and less frequently smoked cigarettes than those without CKD (P<0.001). Participants with CKD more frequently had hypertension and had higher mean systolic blood pressure (SBP) than participants without CKD (P<0.001). Overall study entry events (stroke or TIA) were different for subjects with versus those without CKD (P=0.006); however, the time to study entry was similar (P=0.639) regardless of CKD status.

**Serum Lipid Levels**

At baseline, total cholesterol, LDL-C, and high-density lipoprotein cholesterol were similar in subjects with or without CKD assigned to atorvastatin or placebo (Table 2). Serum triglyceride levels were higher in both atorvastatin and placebo participants with CKD compared with those without CKD. At the end of study, mean total cholesterol, LDL-C, and triglyceride levels were lower in the atorvastatin versus placebo group, irrespective of CKD status.

**Blood Pressure**

There were modest increases in SBP between baseline and the last visit in atorvastatin- and placebo-treated subjects without CKD. In contrast, there were small decreases in SBP in subjects with CKD, irrespective of therapy (Table 3). The baseline difference in SBP between CKD and non-CKD subjects persisted throughout the trial. SBP control was similar between the atorvastatin- and placebo-treated subjects with and without CKD. Diastolic blood pressure control was marginally better in the atorvastatin versus placebo groups for subjects with and without CKD. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers were used more frequently in those with CKD; however, there were no differences in the use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers between the atorvastatin-treated group and the placebo group (Table 1).

**Renal Outcomes by Treatment Group and Baseline CKD Status**

Mean (±SD) baseline SCr was 1.3±0.3 mg/dL in the CKD population and 1.0±0.1 mg/dL in those without CKD. At baseline, eGFR (mean±SE) was similar between participants randomized to atorvastatin or placebo (65.5±0.26 versus 65.6±0.26 mL/min per 1.73 m²; P=0.382). During follow-up, there was an

![Table 2. Baseline and Follow-Up Changes in Lipid Parameters by Kidney Function](image)

![Table 3. Baseline and Follow-Up Changes in Blood Pressure by Kidney Function](image)
Figure 2. Least squares mean change from baseline in estimated glomerular filtration rate (eGFR) during the course of the study and at final visit after treatment with atorvastatin or placebo. Baseline values are mean values. Final represents the final eGFR and atorvastatin-assigned patient without CKD.

Safety
Persistent elevations in hepatic transaminase levels (2 consecutive elevations >3× the upper limit of normal) were more frequent in atorvastatin-treated subjects versus placebo, but rates were generally low and similar between those with (2.4%) and without CKD (2.0%; Table 4). Persistent elevations in creatine phosphokinase levels (2 consecutive elevations >10× the upper limit of normal) were also similar between participants with and without CKD. The incidence of musculoskeletal adverse events was low and similar between study groups. There were 5 cases of investigator-determined rhabdomyolysis: 2 in placebo-assigned participants with CKD, 2 in atorvastatin-treated participants without CKD, and 1 in a placebo-assigned patient without CKD.

Discussion
This post hoc analysis of the SPARCL trial suggests an improvement in eGFR with atorvastatin 80 mg/d versus placebo in a population of subjects with prior stroke or TIA. In subjects randomized with diabetes mellitus, as expected, there was an overall decline in renal function during the trial, but this decline was almost halted in subjects randomized on atorvastatin. The renoprotective effect occurred within 1 year and was maintained for 60 months of observation and was observed in subjects with and without CKD at baseline.

The renal benefit occurred in association with a 40% reduction in LDL-C (to 80 mg/dL [2.07 mmol/L]) in participants with CKD and 37% reduction (to 80 mg/dL [2.07 mmol/L]) in those without CKD. Importantly, these improvements occurred in a population of subjects who received multiple antihypertensive medications with overall good blood pressure control in both the atorvastatin and placebo groups.

Two observations warrant additional comment. First, except in the diabetic subgroup, we did not find the expected time-dependent fall in eGFR in participants assigned to placebo and usual care. A minimal fall in eGFR was, however, found in the placebo-treated population using a last observation carried...
Drop-in statin therapy, which increased toward the end of the trial, may have minimized the anticipated fall in eGFR in surviving subjects. After randomization, 7.5% of participants assigned to placebo and usual care took a nonstudy statin, most frequently atorvastatin. In addition, study participation with its frequent medical assessments with optimization of risk factor control may have contributed to the better than expected renal outcomes in the placebo group.

Subjects with diabetes mellitus randomized to the placebo group had a time-dependent fall in eGFR during the 5 years of the trial with a significant difference with baseline eGFR. This difference was not observed in diabetic subjects randomized to atorvastatin, suggesting a renoprotective effect of atorvastatin. Interestingly, a similar effect, although more modest, was observed in the primary prevention CARDS trial, which randomized only patients with diabetes mellitus, as well as in the atorvastatin arm of the Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease (PLANET-1) trial. Our data, together with earlier observations from the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) trial and those of CARDS and PLANET-1 trials, suggest that atorvastatin could be renoprotective.

The effect of statin therapy on renal function in patient populations at high risk for cardiovascular disease, or with preexisting CHD, has varied in different trials, possibly because of the populations studied, intensity of treatment, and the specific statin used. In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), using pravastatin 40 mg in hypertensive subjects with moderate dyslipidemia for a mean of 4.8 years, LDL-C decreased by 20.7% in the pravastatin group versus 11.2% in a usual care group. Furthermore, participants had a 6 mL/min per 1.73 m² reduction in eGFR at 4 years and an 8 to 9 mL/min per 1.73 m² decrease at 6 years with no differences between treatment groups for the rate of decline in eGFR or for the development of end-stage renal disease.

In a subgroup of hyperlipidemic CKD subjects with prior myocardial infarction from the Cholesterol and Recurrent Events (CARE) trial, treatment with pravastatin 40 mg did not
result in renal benefit compared with placebo.\textsuperscript{14} The anticipated decrease in eGFR, however, was significantly slower among those in the pravastatin group with a baseline eGFR <40 mL/min per 1.73 m\textsuperscript{2} (2.5 mL/min per 1.73 m\textsuperscript{2} per year slower fall versus placebo; \textit{P}<0.0001). A post hoc subgroup analysis from the Scandinavian Simvastatin Survival Study (4S), which compared 20 to 40 mg simvastatin versus placebo in men and women with CHD found that the annual decline in renal function was lower with simvastatin versus placebo (0.34 versus 0.41 mL/min per 1.73 m\textsuperscript{2} per year; \textit{P}<0.02).\textsuperscript{31} A subanalysis of the Heart Protection Study found that simvastatin 40 mg blunted the overall decline in eGFR in subjects with type 2 diabetes mellitus during a 4.6-year follow-up (–5.9±0.1 versus –6.7±0.1 mL/min per 1.73 m\textsuperscript{2}; \textit{P}=0.0003).\textsuperscript{32} In contrast, in the Study of Heart and Renal Protection (SHARP) trial performed in 9270 patients with moderate to severe CKD,\textsuperscript{33} simvastatin plus ezetimibe reduced the incidence of major atherosclerotic events, but there was no significant reduction in any of the prespecified measures of renal disease progression in the 6247 patients not on dialysis. Further analysis of the SHARP study showed that among the participants who were not on dialysis at randomization, compared with placebo, treatment with simvastatin plus ezetimibe led to a 3% nonsignificant reduction in the incidence of end-stage renal disease and a nonsignificant slowing of the annual rate of change in eGFR by 0.17 mL/min per 1.73 m\textsuperscript{2}.\textsuperscript{34} Noticeably, 63% of the SHARP participants who were not on dialysis at randomization had stage 4 or 5 CKD.\textsuperscript{34} In addition to having more participants with advanced kidney disease at randomization, this SHARP cohort (the participants who were not on dialysis at randomization) differed significantly from that studied in SPARCL. Although the SPARCL study excluded subjects with severe renal dysfunction or nephrotic syndrome;\textsuperscript{25} the SHARP study actively recruited subjects with glomerulonephritis, cystic renal disease, pyelonephritis, as well as subjects with either or both diabetic and hypertensive nephropathy.\textsuperscript{34} Thus, the renoprotective effects of statins may also be limited by the source and severity of kidney disease.

The GREACE study randomized participants with dyslipidemia after myocardial infarction to a titration of atorvastatin 10 to 80 mg to the National Cholesterol Education Program goals versus usual care (ie, lifestyle changes and lipid-lowering agents, including various statins).\textsuperscript{16} At the end of study, creatinine clearance increased by 12% (\textit{P}<0.0001) in the atorvastatin group and by 4.9% (\textit{P}=0.003) in the usual care participants who were given statins, whereas renal function had declined by 5.2% (\textit{P}<0.0001) in participants from both groups who had either stopped or never received statins. This increase was dependent on baseline GFR levels with the greatest benefit (\textit{P}<0.0001) occurring in subjects with baseline GFR <77 mL/min. Renal benefit was also found in the Aggressive Lipid Lowering to Alleviate New Cardiovascular Endpoints (ALLIANCE) trial, a prospective, randomized open-label clinical trial comparing the effects of atorvastatin 10 to 80 mg to usual care with other available lipid-lowering medications including statins, in a cohort of subjects with known coronary artery disease. A post hoc analysis found a modest improvement in eGFR in atorvastatin-treated subjects (0.80±82 mL/min per 1.73 m\textsuperscript{2}) versus a mean decline of 1.36±0.92 mL/min per 1.73 m\textsuperscript{2} in the usual care group (\textit{P}=0.008), after a median follow-up of 54.3 months.\textsuperscript{18} Subjects with CKD at baseline had a 2.31±1.67 mL/min per 1.73 m\textsuperscript{2} increase in eGFR with atorvastatin versus a 0.20±1.75 mL/min per 1.73 m\textsuperscript{2} improvement with usual care (\textit{P}=0.1). A subanalysis of the Treating to New Targets (TNT) study investigated the effect of lipid lowering on renal function with atorvastatin 80 mg versus atorvastatin 10 mg in subjects with known CHD.\textsuperscript{37} After 5-year follow-up, mean change in eGFR increased 3.5±0.14 mL/min per 1.73 m\textsuperscript{2} with atorvastatin 10 mg and 5.2±0.14 mL/min per 1.73 m\textsuperscript{2} with atorvastatin 80 mg (\textit{P}<0.0001).

Improvement in renal function, however, was not found in the Justification for the Use of Statins in Prevention and Intervention Trial Evaluating Rosuvastatin (JUPITER) study, in which rosuvastatin 20 mg was used to treat a low-risk population with elevated high-sensitivity C-reactive protein.\textsuperscript{35} In JUPITER, baseline eGFR was 73.3 mL/min per 1.73 m\textsuperscript{2} in the rosuvastatin group versus 73.6 mL/min per 1.73 m\textsuperscript{2} in the placebo group. Median eGFR declined (\textit{P}=0.02) at 12 months to 66.8 (59.1–76.5) and 66.6 (58.8–76.2) mL/min per 1.73 m\textsuperscript{2} in the rosuvastatin and placebo groups, respectively.

In addition to these findings from individual trials, various meta-analyses have been conducted to investigate effects of statin therapy on renal function.\textsuperscript{20–23} In an early meta-analysis including 13 trials with ≥400 participants, Fried et al\textsuperscript{29} showed that the rate of decline in GFR was lower with treatment with antilipemic agents compared with controls. This finding was later confirmed by Sandhu et al\textsuperscript{31} in a meta-analysis of 27 eligible studies with 39704 participants; the authors found that the weighted mean difference for yearly fall in eGFR was slower (1.22 mL/min per year) in statin recipients compared with control subjects given placebo (95% confidence interval, 0.44–2.00). A significantly slower decrease in eGFR was also observed in a subpopulation of statin-treated patients with cardiovascular disease (0.93 mL/min per year; 95% confidence interval, 0.10–1.76 compared with placebo); however, this benefit of statin therapy did not extend to patients who had diabetic or hypertensive kidney disease or glomerulonephritis.\textsuperscript{21} Although not every meta-analysis has demonstrated renoprotective effects of statins potentially due to insufficient

### Table 4. Incidence of Elevated Laboratory Values and Adverse Events

<table>
<thead>
<tr>
<th>Condition</th>
<th>Atorvastatin (n=1567)</th>
<th>Placebo (n=1552)</th>
<th>Atorvastatin (n=789)</th>
<th>Placebo (n=811)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated AST or ALT*</td>
<td>19 (2.41)</td>
<td>1 (0.12)</td>
<td>32 (2.04)</td>
<td>10 (0.64)</td>
</tr>
<tr>
<td>Elevated CPK†</td>
<td>1 (0.13)</td>
<td>0</td>
<td>1 (0.06)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>43 (5.45)</td>
<td>52 (6.41)</td>
<td>86 (5.49)</td>
<td>88 (5.67)</td>
</tr>
<tr>
<td>Myopathy</td>
<td>1 (0.13)</td>
<td>3 (0.37)</td>
<td>6 (0.38)</td>
<td>4 (0.26)</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>0</td>
<td>2 (0.25)</td>
<td>2 (0.13)</td>
<td>1 (0.06)</td>
</tr>
</tbody>
</table>

Values given are number of subjects (%). ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; eGFR, estimated glomerular filtration rate; and ULN, upper limit of normal.

* \textit{>3× ULN at 2 consecutive measurements.}
† \textit{>10× ULN at 2 consecutive measurements.}
data and the possibility of outcomes reporting bias, it has been noted that significant renoprotective effects of statins in CKD patients may depend on treatment duration. The current SPARCL renal analysis is consistent with previous studies that have suggested renoprotection and improvement in renal function with atorvastatin in high-risk patient populations with vascular disease.

**Limitations**

This was a post hoc analysis, using estimates of renal function and needs to be considered exploratory and hypothesis generating. Estimation of GFR on the basis of serum creatinine also has several limitations. Because serum creatinine is a function of production, it is possible that statins might interfere with creatinine production without affecting GFR. To address this issue, effects of statins on true GFR need to be determined. We did not systematically collect proteinuria and albuminuria and therefore could not utilize proteinuria in the classification of CKD.

Generalizations and comparisons to other populations with CKD should be made with caution because the causes of renal disease in this population are unknown. Given the small proportion of subjects with stage 4 or 5 CKD, our findings may not apply to patients with more severe renal insufficiency (ie, eGFR <30 mL/min per 1.73 m²). Within-treatment comparisons between subjects with eGFR ≥60 mL/min per 1.73 m² and eGFR 60 mL/min per 1.73 m² are not valid as separate ANCOVA models were used to analyze these groups.

The treatment differences observed for changes in renal function may be underestimated because of drop-in statin use in the placebo group, as well as discontinuations in the atorvastatin group. The influence of other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory medications could not be assessed because the study was not designed to monitor actively the use of these drugs. There is however no reason to expect that the percentage of participants who were prescribed such drugs would have been similar between the treatment groups.

**Conclusions**

This exploratory analysis suggests that atorvastatin treatment might be renoprotective in a population of patients with prior stroke or TIA with and without CKD.

**Acknowledgments**

Assistant in preparing the figures and formatting the article for submission was provided by Shuang Li, PhD, at Engage Scientific Solutions and was funded by Pfizer Inc. The full list of participants in the SPARCL Study has been published previously.

**Sources of Funding**

This study was funded by Pfizer, Inc.

**Disclosures**

Dr Amarenco has received consulting fees from AstraZeneca, Bristol-Myers Squibb, Daiichi, Eli Lilly, GlaxoSmithKline, Guebert, Negma, Novartis, Pfizer, Sanofi, Sanofi-Aventis, and Servier; lecture fees from AstraZeneca Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Merck, Otsuka Pharmaceutical, Pfizer, Sanofi-Aventis, and Servier; and grant support from Boehringer-Ingelheim, Bristol-Myers Squibb, Eisai, Pfizer, and Sanofi-Aventis. Dr Campese is a member of the Speaker’s Bureau for Pfizer, Inc. Dr Callahan has received research grant support from Pfizer and honoraria from Pfizer, Sanofi-Aventis, and Bristol-Myers Squibb. Dr Goldstein has received consultancy fees and honoraria from Pfizer. Dr Hennerici has received research grant support from Pfizer. Drs Messig and Wilson are full time employees of Pfizer. Dr Sillesen has received honoraria and research support from Cardoz, Norvatis, and Philips Ultrasound. The other authors report no conflicts.

**References**


Effect of High-Dose Atorvastatin on Renal Function in Subjects With Stroke or Transient Ischemic Attack in the SPARCL Trial


Stroke. 2014;45:2974-2982; originally published online August 21, 2014;
doi: 10.1161/STROKEAHA.114.005832
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/45/10/2974

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/04/06/STROKEAHA.114.005832.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/
Progressive Renal Disease (PLANET-1) trial.29 Our data, together with earlier observations from the Greek Atorvastatin forward analysis, suggests that atorvastatin could be renoprotective. Interestingly, a similar effect, although more pronounced, was observed in diabetic patients from the Prospective Evaluation of Brushstrokes Trial, which randomized only patients with diabetes mellitus,19 suggesting a renoprotective effect of atorvastatin. However, the better than expected renal outcomes in the placebo group were also observed in diabetic patients from the Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack (ALLHAT) trial, where treatment with pravastatin 40 mg did not change renal function.27

The effect of statin therapy on renal function in patients with stroke or transient ischemic attack has varied in different trials, possibly because of the populations studied, intensity of treatment, and the specific statin used.14,16–18,30–32 In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial, treatment with pravastatin 40 mg did not change renal function.27

**Abstract 4**

**Effect of High-Dose Atorvastatin on Renal Function in Subjects With Stroke or Transient Ischemic Attack in the SPARCL Trial**

Pierre Amarenco, MD; Alfred Callahan III, MD; Vito M. Campese, MD; Larry B. Goldstein, MD; Michael G. Hennerici, MD, PhD; Michael Messig, PhD; Henrik Sillesen, MD, DMSc; K. Michael A. Welch, MB, ChB; Daniel J. Wilson, MD; Justin A. Zivin, MD, PhD

(Stroke. 2014;45:2974-2982.)

**Key Words:** atorvastatin • glomerular filtration rate • ischemic attack, transient • kidney diseases • renal insufficiency, chronic • stroke

**Figure 3.** Least squares mean change from baseline in estimated glomerular filtration rate (eGFR) during the course of the study and at final visit after treatment with atorvastatin or placebo in participants with (A) chronic kidney disease (CKD), (B) normal eGFR, or (C) diabetes mellitus. Baseline values are mean values. Final represents the final eGFR available for each participant (last observation carried forward analysis). Subjects without follow-up serum creatinine measurements were excluded.