Title

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Journal

Journal of the American Heart Association, 8(9)

ISSN

2047-9980

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Publication Date

2019-05-07

DOI

10.1161/jaha.118.010827

Peer reviewed

ORIGINAL RESEARCH

Atorvastatin Has a Dose-Dependent Beneficial Effect on Kidney Function and Associated Cardiovascular Outcomes: Post Hoc Analysis of 6 Double-Blind Randomized Controlled Trials

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Background—Kidney function decreases during the lifetime, and this decline is a powerful predictor of both kidney and cardiovascular outcomes. Statins lower cardiovascular risk, which may relate to beneficial effects on kidney function. We studied whether atorvastatin influences kidney function decline and assessed the association between individual kidney function slopes and cardiovascular outcome.

Methods and Results—Data were collected from 6 large atorvastatin cardiovascular outcome trials conducted in patients not selected for having kidney disease. Slopes of serum creatinine reciprocals representing measures of kidney function change ([mg/dL]$^{-1}$/y), were analyzed in 30 621 patients. Based on treatment arms, patients were categorized into 3 groups: placebo (n=10 057), atorvastatin 10 mg daily (n=12 763), and 80 mg daily (n=7801). To assess slopes, mixed-model analyses were performed for each treatment separately, including time in years and adjustment for study. These slopes displayed linear improvement over time in all 3 groups. Slope estimates for patients randomized to placebo or atorvastatin 10 mg and 80 mg were 0.009 (0.0008), 0.011 (0.0006), and 0.014 (0.0006) (mg/dL)$^{-1}$/y, respectively. A head-to-head comparison of atorvastatin 10 and 80 mg based on data from 1 study (TNT [Treating to New Targets]; n=10 001) showed a statistically significant difference in slope between the 2 doses (P=0.0009). From a Cox proportional hazards model using slope as a predictor, a significant (P<0.0001) negative association between kidney function and cardiovascular outcomes was found.

Conclusions—In patients at risk of or with cardiovascular disease, atorvastatin improved kidney function over time in a dose-dependent manner. In the 3 treatment groups, kidney function improvement was strongly associated with lower cardiovascular risk.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00327418; NCT00147602; NCT00327691. **(*J Am Heart Assoc*. 2019;8:e010827. DOI: 10.1161/JAHA.118.010827.)**

Key Words: cardiovascular disease • kidney • lipids • statin therapy

Patients with end-stage renal disease (ESRD) are at increased risk of cardiovascular disease (CVD), and this association between kidney function and cardiovascular outcomes is also observed in patients with relatively normal kidney function.[1] The intricate interaction between the development and progression of chronic kidney disease (CKD) and CVD results from the fact that both share common risk factors such as age, hypertension, diabetes mellitus, and dyslipidemia. Kidney function decline due to these factors usually displays a linear course over the years, and the grade of kidney function decline has recently been demonstrated to be useful as an independent risk factor for mortality, CVD, and/or ESRD in both CKD and non-CKD populations.[2-4] Because of its linearity, the slope visualizing the course of

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Accompanying Tables S1 through S6 and Figure S1 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.010827

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Received October 31, 2018; accepted March 28, 2019.

Clinical Perspective

What Is New?

- In this post hoc analysis of 6 double-blind randomized controlled cardiovascular outcome trials comprising 30 621 patients at risk of or having cardiovascular disease, we demonstrate that atorvastatin treatment improves kidney function over time in a dose-dependent fashion.
- Kidney function improvement, regardless of treatment arm, was associated with lower cardiovascular risk.

What Are the Clinical Implications?

- Our data suggest that both the cardio- and vasculoprotective efficacy of a pharmacological agent, such as atorvastatin, is reflected by the course of kidney function over time, indicating that this kidney-related parameter might represent a surrogate end point for long-term outcomes in cardiovascular risk patients.

kidney function during a given time span—instead of single kidney function measurements—provides additional information. In addition, individual slopes include information about the preceding course of kidney function and may therefore not completely depend on the severity of kidney function impairment at the baseline measurement of a study. Individual slopes over time, therefore, are potentially an important predictor for both CVD and kidney outcomes over the long run.[5] Thus, interventions that beneficially influence slope over time may also reflect cardiovascular and renal protection at an early stage, as has already been demonstrated with other kidney protective agents such as inhibitors of the renin-angiotensin-aldosterone system (RAAS).[6] In patients with CKD, as in other high-risk patients, statins have proven to exert a substantial cardiovascular benefit.[7,8] Whether this effect of statins is partially attributable to an effect on kidney function is unknown.

Current evidence indicates that kidney-protective effects of statins show a heterogeneous picture. Statins reduce, for instance, biomarkers for kidney damage, including albuminuria,[9,10] but not uniformly so.[11] In addition, various controlled trials show that statins are beneficial by inducing a smaller estimated glomerular filtration rate (eGFR) reduction at the end of the study,[12,13] and other studies indicate that eGFR may even improve.[14-16] The heterogeneous effects may depend on both the dose and type of statin used, as also demonstrated by the recent PLANET trials in both diabetic and nondiabetic CKD patients.[11] In PLANET, rosuvastatin negatively influenced kidney function, as expressed by decreased eGFR and increased proteinuria, whereas atorvastatin improved GFR without influencing proteinuria.[11]

We set out to address whether the high-potency statin, atorvastatin, has an effect on age-related kidney function decline during an observation period extending beyond 12 months and whether this effect is dose dependent. Finally, we assessed whether the slopes of individual patients predicted cardiovascular outcome measures.

Methods

Data-Sharing Statement

On request, and subject to certain criteria, conditions, and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines, and medical devices (1) for indications that have been approved in the United States and/or the European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Post hoc evaluation for slopes of kidney function decline was performed using serum creatinine values collected from randomized patients from long-term cardiovascular outcome randomized controlled trials (RCTs) with atorvastatin in which slope analysis was not a predefined outcome (Table 1).[17-25] Studies were eligible for inclusion when they were RCTs with ≥12 months of follow-up; included participants who were older than 18 years; had >2 serum creatinine values measured; and randomly assigned therapy with fixed doses of atorvastatin or placebo. We excluded those studies that were designed to investigate patients with predefined primary kidney disease and/or ESRD. Because plasma creatinine levels were collected only at 2 time points in the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering) trial (in 8888 randomized post–myocardial-infarction patients),[21] and 4D (German Diabetes and Dialysis Study) included type 2 diabetes mellitus patients on dialysis,[24] these studies were excluded from the analysis. ALLIANCE (Aggressive Lipid-Lowering Initiation Abates New Cardiac Events) data were excluded because variable atorvastatin doses were used in the active treatment arm.[25] Three groups were formed, and the data from individual subjects were pooled. To assess the slope in placebo patients, the placebo arms from ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial), CARDS (Collaborative Atorvastatin Diabetes Study), SPARCL (Stroke

Table 1. Overview of Atorvastatin RCTs Included in This Analysis

Study[17-25]	No. of Patients	Clinical Condition	Treatment Arms	FU Duration, y	Time Points of Serum Creatinine Sampling
ASCOT	10 305	Hypertension without CHD	Atorvastatin 10 mg vs placebo	3.1	Baseline, mo 6, y 1, y 2, y 3, y 4
CARDS	2838	Type 2 diabetes mellitus without CHD	Atorvastatin 10 mg vs placebo	3.8	Baseline, y 1, y 2, y 3, y 4
ASPEN	2410	Type 2 diabetes mellitus with/without CHD	Atorvastatin 10 mg vs placebo	4.0	Baseline, y 1, y 2, y 3, y 4
SPARCL	4731	Stroke or transient ischemic attack	Atorvastatin 80 mg vs placebo	4.5	Baseline, y 1, y 2, y 3, y 4, y 5, . . .
TNT	10 001	CHD and LDL-C <130 mg/dL	Atorvastatin 80 mg vs atorvastatin 10 mg	4.9	Baseline, y 1, y 2, y 3, y 4, y 5, . . .
SAGE*	893	Elderly (65-85 y) with documented transient myocardial ischemia	Atorvastatin 80 mg vs pravastatin 40 mg	1.0	Baseline, mo 3, y 1

ASCOT indicates Anglo-Scandinavian Cardiac Outcomes Trial; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; FU, follow-up; LDL-C, plasma LDL cholesterol; RCT, randomized controlled trial; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Levels; SAGE, Study Assessing Goals in the Elderly; TNT, Treating New Targets.
*Only the atorvastatin treatment arm was included in the pooled analysis.

Prevention by Aggressive Reduction in Cholesterol Levels), and ASPEN (Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus) were pooled.[17-19,22] To assess the slope in atorvastatin 80 mg, the 80-mg arms from SPARCL, TNT (Treating New Targets), and SAGE (Study Assessing Goals in the Elderly) were pooled.[17,20,23] Additionally, data derived from the ASCOT, CARDS, and ASPEN trials were pooled, and the slopes within the 10-mg atorvastatin arm from these trials were assessed.[18,19,22] For TNT, which included 10 001 randomized coronary artery disease patients, a formal comparison of the 10-mg dose versus the 80-mg dose was performed.[20]

All participants gave written informed consent before enrollment. All studies were approved by the appropriate local research ethics committee and performed in accordance with the Declaration of Helsinki of the World Medical Association. All data were processed anonymously.

Outcome Measures

The primary outcome was the slope of kidney function as measured by the reciprocal of the serum creatinine level.[2,26] The reciprocal of the serum creatinine level has a linear relationship with the GFR, unlike the serum creatinine level, which has a curvilinear relationship. These values, expressed as $(mg/dL)^{-1}$, approximate GFR values, with which most clinicians are familiar. In addition, equations from the Chronic Kidney Disease Epidemiology Collaboration that are adjusted for ethnic group were used to determine the estimated GFR and eGFR slopes over time. Finally, the proportion of patients who reached an eGFR decline of >30%—a recently advocated surrogate for long-term renal outcomes—was calculated.[4]

Furthermore, the proportion of major cardiovascular events, cardiovascular mortality, and all-cause mortality were assessed. A major cardiovascular event was defined as major coronary event (death from coronary heart disease, nonfatal myocardial infarction, or resuscitation after cardiac arrest), fatal or nonfatal stroke, major cardiovascular event (stroke plus any major coronary event), acute coronary event (major coronary event or unstable angina), any coronary event (acute coronary event, unstable angina, or angina or ischemia requiring emergency hospitalization). Cardiovascular mortality was defined as death from coronary heart disease, fatal myocardial infarction, fatal stroke, or other cardiovascular death.

Statistical Analyses

To determine the slope for the 3 pooled arms, a mixed model was run separately for each treatment pooling with time of assessment as a random effect and with adjustments for study; all per-patient creatinine data were included in the model, starting from baseline. Additionally, homogeneity of slopes in the studies within each pooling was tested by adding study×time of assessment to the mixed model. The slopes were also computed for each of the 3 pooled arms with adjustments for study, age, sex, body mass index, plasma low-density lipoprotein (LDL) cholesterol, systolic blood pressure (BP), diastolic BP, baseline RAAS inhibitor use, baseline aspirin use, diabetes mellitus, smoking, history of CVD, diuretics use, and hypertension. To compare the 10-mg slope to the 80 mg slope, only TNT data were used because in this study subjects were randomized to 10 mg versus 80 mg. This mixed model included treatment, time of assessment, and treatment by time interactions. In additional models, adjustments for (1) number of creatinine measures; (2) age and sex; and (3) change in LDL at month 3 from baseline were made for the slope calculations. Slopes from the mixed model are presented as estimate (standard error [SE]).

To evaluate the impact of individual 1/creatinine slopes on cardiovascular events, a Cox proportional hazards model was

Table 2. Baseline Characteristics (Mean [SD]) of Pooled Treatment Arms

	Placebo (N=10 057)	Atorvastatin 10 mg (N=12 763)	Atorvastatin 80 mg (N=7801)
Sex (% male)	72.5	78.1†	74.1‡‖
Age, y	62.6 (9.2)	61.9 (8.6)†	62.4 (9.8)¶
Ethnicity, %			
Black	3.0	3.2	2.7#
Asian	1.7	1.6	0.8
White	93.1	93.4	94.0§
Other	2.3	1.8	2.5
BMI, kg/m^2	28.4 (4.4)	28.7 (4.5)†	28.1 (4.5)†‖
Systolic BP, mm Hg	151.7 (22.1)	145.9 (23.0)†	133.6 (18.2)†‖
Diastolic BP, mm Hg	88.2 (12.2)	85.4 (12.5)†	79.1 (10.0)†‖
Cholesterol, mg/dL	209 (31)	195 (33)†	189 (33)†‖
HDL-cholesterol, mg/dL	50 (14)	49 (13)†	48 (12)†‖
LDL-cholesterol, mg/dL	129 (28)	115 (29)†	111 (28)†‖
Serum creatinine, mg/dL*	1.1 (0.5-3.3)	1.1 (0.5-3.8)	1.1 (0.6-4.4)†‖
Reciprocal of serum creatinine, (mg/dL)$^{-1}$	0.91 (0.15)	0.89 (0.14)†	0.88 (0.15)†‖
eGFR, mL/(min·1.73 m^2)	66.8 (13.0)	66.5 (12.7)	64.7 (12.9)†‖
CKD (eGFR <60 mL/[min·1.73 m^2]), %	29.8	29.8	35.6†‖
Hypertension, %	82.6	75.6†	57.2†‖
History of cardiovascular event, %	17.3	46.2†	76.4†‖
Diabetes mellitus, %	42.4	36.3†	15.9†‖
Smoking, %	24.7	21.4†	14.7†‖
Comedication, %			
Diuretics	10.6	16.5†	26.5†‖
RAASi	18.7	30.8†	48.2†‖
Aspirin	27.4	45.3†	86.2†‖

BMI indicates body mass index; BP blood pressure; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate (according to the CKD-EPI formula); HDL, high-density lipoprotein; LDL, low-density lipoproteh; RAASi, renin-angiotensin-aldosterone system inhibitor.
*Median (minimum-maximum).
†P<0.0001, ‡P<0.05, §P<0.01 vs placebo.
‖P<0.0001, ¶P<0.001, #P<0.05 vs atorvastatin 10 mg.

used with 1/creatine slope as the predictor in the model. Major cardiovascular events, cardiovascular deaths, and all-cause mortality were assessed. Subjects without the event were censored at their last clinical visit date or the last date they were known to be alive, whichever was later. For major cardiovascular events and cardiovascular death, subjects who had died due to non-cardiovascular causes were censored on the date of death. The Cox model included the slopes with adjustments for each trial. Additionally, an adjusted Cox model was run with adjustments for age, sex, body mass index, plasma LDL, systolic BP, diastolic BP, baseline RAAS inhibitor use, baseline aspirin use, diabetes mellitus, smoking, history of CVD, diuretics use, and hypertension. These analyses were performed for each treatment pooling separately. Additionally, a sensitivity analysis was performed in which slope was included as a quartile in the study-adjusted Cox model.

Results

Patients

In the pooled analysis, individual data of 30 621 patients from 6 RCTs who were randomly assigned to either placebo (10 057), atorvastatin 10 mg (12 763), or atorvastatin 80 mg (7801), were analyzed. Median treatment duration was 3.9 (range: 1-4.9) years. Pooled demographic and baseline characteristics of the 6 RCTs are given in Table 2 (for the demographics of the 6 separate studies included see Tables S1 through S6). Due to differences in disease conditions and

study design, almost all baseline characteristics of the 3 groups, including sex, body mass index, systolic and diastolic BP, reciprocal serum creatinine, plasma total, high-density lipoprotein, and LDL cholesterol, hypertension, history of CVD, and diuretic, RAAS inhibitor, and/or aspirin use, differed significantly. Furthermore, in the atorvastatin 10-mg group, age was significantly lower as compared with the placebo and atorvastatin 80-mg groups. The atorvastin 80-mg group contained a slightly but significantly lower number of subjects from African descent as compared with the atorvastatin 10-mg group and higher numbers of subjects of white descent as compared to placebo. The presence of CKD at baseline was higher and eGFR was lower in the atorvastatin 80-mg group as compared with placebo and the atorvastatin 10-mg groups (Table 2).

Outcomes

Slope of Kidney Function

The average annual change in kidney function (as assessed by the estimate of the reciprocal of the serum creatinine level based on a mean [SD] number of 4.7 [1.4] measurements) from the mixed model, displayed a linear pattern over time, is shown in Figure 1 and Figure S1. Patients randomized to placebo and 10 mg and 80 mg atorvastatin had slopes (estimate [SE]) of 0.009 (0.0008), 0.011 (0.0006), and 0.014 (0.0006) $(mg/dL)^{-1}$/y, respectively ($P<0.0001$ for each group). In the adjusted models with adjustments for (1) number of serum creatinine measures, (2) age and sex, and (3) change in LDL at month 3 from baseline, the slopes did not change. Additionally, slope×study interaction was tested to assess homogeneity of slopes across the studies. The study×slope interactions assessed in each of the 3 pooled groups (atorvastatin 10 mg and 80 mg and placebo) were all statistically significant, indicating differences in slopes among the different studies ($P<0.0005$ in all groups). Overall, the slopes were, however, all in the same direction. The fully adjusted model had minimal impact on the values of the slopes, where slopes (SE) for placebo, atorvastatin 10 mg, and atorvastatin 80 mg were 0.008 (0.0007), 0.011 (0.0005), and 0.014 (0.0006), respectively.

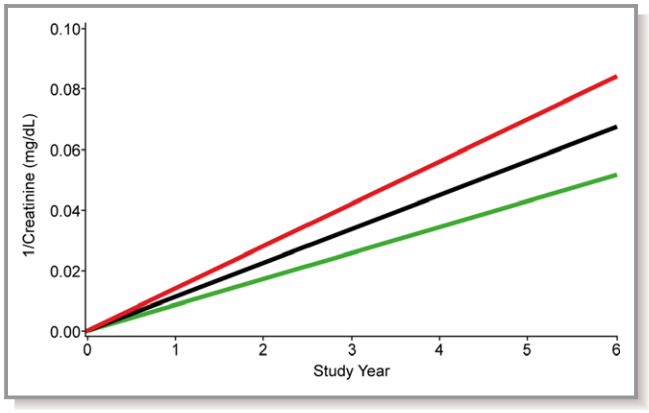

Figure 1. Modeled slopes of reciprocal of serum creatinine across the 3 groups (placebo [green], atorvastatin 10 mg [black], and 80 mg [red]).

In order to perform a formal comparison between the atorvastatin doses, the TNT data set was analyzed and showed a significant dose effect of atorvastatin on average annual change in kidney function. In the patients randomized to atorvastatin 10 mg, the slope was significantly lower (estimate [SE] of 0.012 [0.0007] $(mg/dL)^{-1}$) compared with the slope observed in the 80-mg group (0.015 [0.0007] $(mg/dL)^{-1}$, $P=0.0009$).

The eGFR slopes showed a similar pattern. Placebo and 10 mg and 80 mg atorvastatin had slopes (estimate [SE]) of 0.25 (0.068), 0.51 (0.054), and 0.78 (0.056) mL/(min·1.73 m^2) per year, respectively ($P=0.0002$ for placebo and $P<0.0001$ for atorvastatin 10 mg and atorvastatin 80 mg). Again, the adjusted models affected the slopes negligibly (data not shown). These findings would roughly translate to an eGFR increase of 1.3, 2.6, and 3.9 mL/(min·1.73 m^2) over a 5-year period for placebo, atorvastatin 10 mg, and atorvastatin 80 mg, respectively. In the formal comparison using TNT data, once again a dose effect could be observed (0.58 [0.065] and 0.86 [0.065] mL/(min.1.73 m^2) in the atorvastatin 10- and 80-mg groups, respectively [$P=0.003$]).

To account for the influence of differences in the dropout rate (ie, nonrandom effects) among the treatment arms within the 6 RCTs, a sensitivity analysis was performed including on-treatment creatinine measurements only. This analysis did not influence the results.

Finally, the proportion of patients with a decrease of >30% in eGFR from baseline to the last visit was calculated. The percentage of patients with a decrease >30% were 2.5% (95% CI 2.2% to 2.9%), 2.1% (95% CI 1.9% to 2.4%), and 2.0% (1.7% to 2.4%) for the placebo, atorvastatin 10-mg group, and atorvastatin 80-mg group, respectively.

Effect of Individual Kidney Function Slopes on Cardiovascular Event Rate and Mortality

Figures 2 and 3 report the hazard ratios of the Cox proportional hazard model to assess the effect of average annual change in kidney function on major cardiovascular events, cardiovascular deaths, and all-cause mortality. The model adjusted according to study showed that for these outcomes average annual change in kidney function was a highly significant predictor. In the model with adjustments for age, sex, body mass index, plasma LDL, systolic BP, diastolic BP, baseline RAAS inhibitor use, baseline aspirin use, diabetes mellitus, smoking, history of cardiovascular events at baseline (ie, either a cardiovascular or cerebrovascular event), diuretics

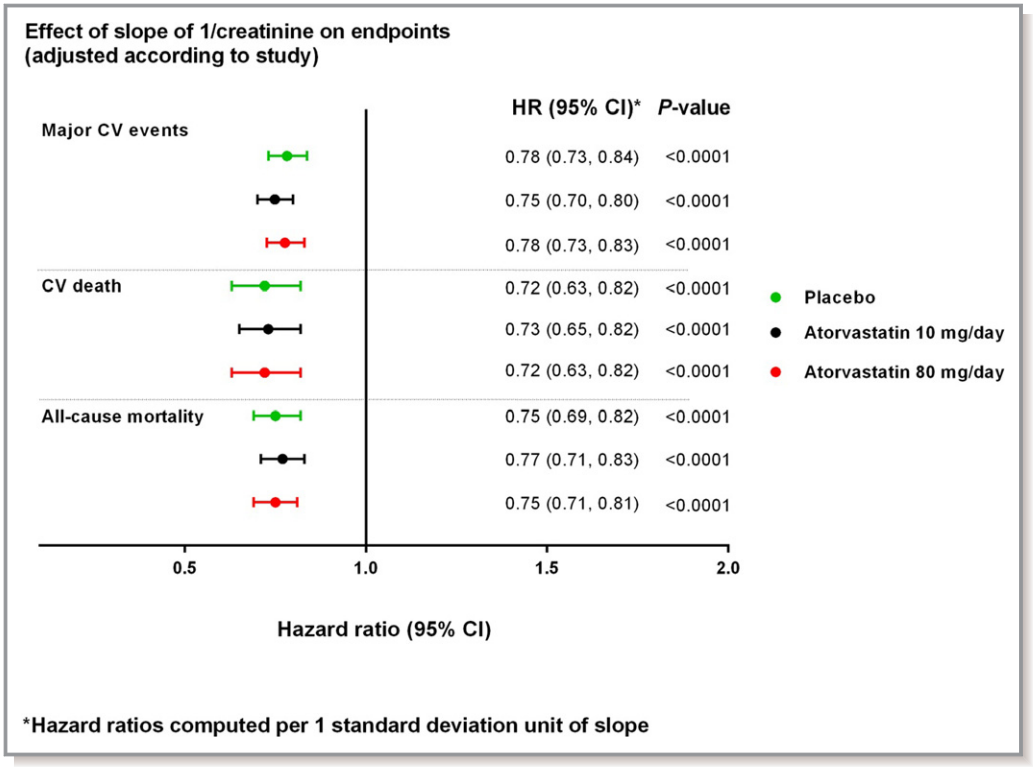

Figure 2. Effect of kidney function slope on cardiovascular (CV) outcomes and all-cause mortality (unadjusted analysis). HR indicates hazard ratio.

use, and hypertension, average annual change in kidney function was a significant predictor within both atorvastatin groups for major cardiovascular events and cardiovascular death. For all-cause mortality, the group treated with atorvastatin 80 mg had the lowest hazard ratio for each SD of kidney function slope. Hazard ratios for major cardiovascular events when the highest quartile was compared with the lowest quartile were 1.82, 2.00, and 1.56 for placebo, atorvastatin 10 mg and atorvastatin 80 mg, respectively ($P<0.0001$). When the slope of eGFR was used similar findings were observed (data not shown).

Discussion

This large-scale post hoc analysis including individual data from 6 long-term cardiovascular outcome trials demonstrates that in patients at risk or with CVD, atorvastatin modestly improves kidney function over time in a dose-dependent manner. In addition, this analysis shows that kidney function improvement is strongly associated with lower cardiovascular risk independent of treatment, whereas a decrease in kidney function is associated with worse cardiovascular outcome. For each SD increment of slope of kidney function, we observed a 13% to 14% reduction in major cardiovascular events and cardiovascular mortality while being treated with atorvastatin (either 10 or 80 mg daily).

Our data therefore indicate that efficacy of cardiovascular protection over the long term obtained with atorvastatin is reflected by effects on the course of kidney function over time. In addition, our results emphasize the bidirectional connection between the cardiovascular system and the kidneys (ie, the cardiorenal axis) in treating cardiovascular disease. This implies that both CVD reduction and renoprotection are achieved by treating patients at risk or with CVD with atorvastatin. Vice versa, a renoprotective strategy, as represented by atorvastatin treatment according to our data, translates into better cardiovascular risk management. In daily clinical practice one may therefore consider incorporating kidney function trajectories as read out for the success of cardiovascular risk management regimens, in addition to control of traditional cardiovascular risk factors such as BP and lipid goals. So far, no adequately powered RCTs have tested the hypothesis that targeting the kidney function change over time may represent a cardiovascular risk factor subject to treatment.

Our results confirm the observations in other cohorts, where kidney function was also found to display a linear relationship over time. Somewhat surprisingly, the slopes in all 3 cohorts had a positive direction. It is known from other cardioprotective agents such as RAAS inhibitors that these drugs protect against kidney function decline, but these agents do not usually improve kidney function.[6] Previous post

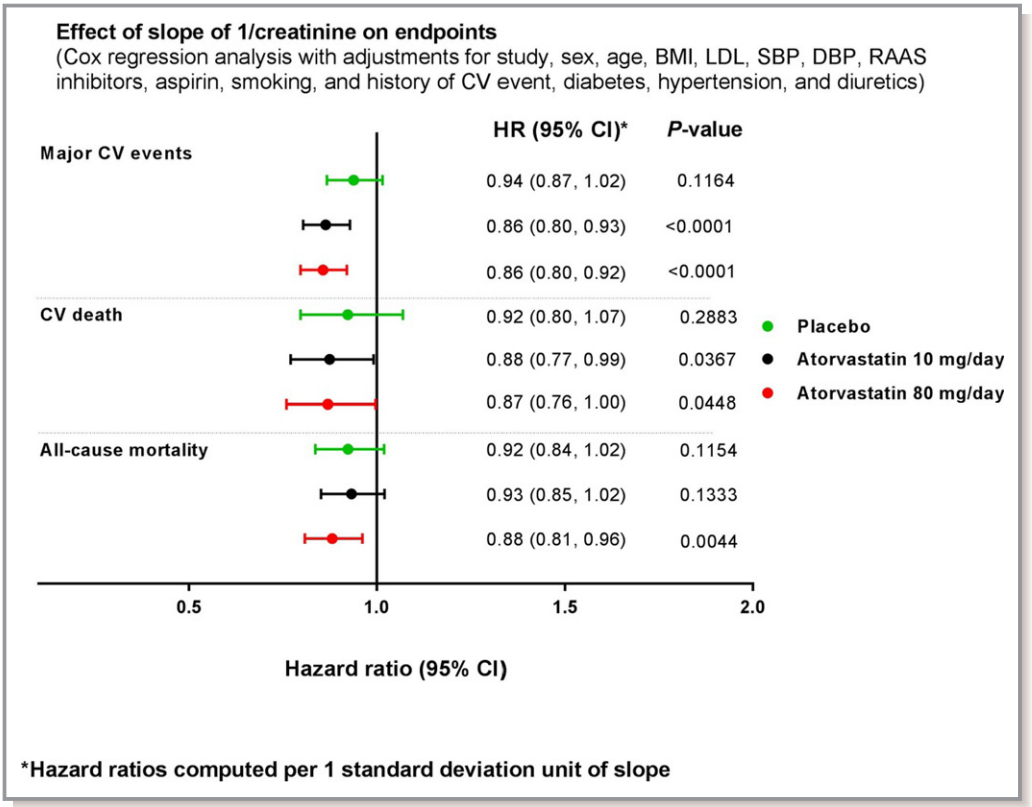

Figure 3. Effect of kidney function slope on cardiovascular (CV) outcomes and all-cause mortality (adjusted analysis). BMI indicates body mass index; DBP, diastolic blood pressure; HR, hazard ratio; LDL, low-density lipoprotein; RAAS, renin-angiotensin-aldosterone system; SBP, systolic blood pressure.

hoc analyses of 2 RCTs (TNT and SPARCL, which were also included in the current analysis) have demonstrated that the average of eGFR increased during follow-up under atorvastatin treatment both in CKD and non-CKD patients.[14,15] A limitation of these 2 analyses was that during follow-up the number of subjects declined, particularly in SPARCL.[14] Therefore, non-random effects might have explained the overall eGFR increase, meaning that only the patients with better outcome—those randomized to the most effective treatment arm—remained in the trial, and those patients with worse eGFR were dropouts. In keeping with this, a closer look at the data from the post hoc analysis of SPARCL revealed that the eGFR change from baseline was less exaggerated when the "last observation carried forward" analysis, including all subjects (ie, a total of 4393 instead of 2169 subjects with complete eGFR data after 60-month follow-up), was performed.[14] According to this analysis, eGFR remained stable in the high-dose atorvastatin arm while eGFR declined in the placebo group.[14] Our study was able to test the robustness of the renal results from the 2 previous post hoc analyses by combining all 6 outcome RCTs in which patients were randomized to atorvastatin or control treatment and by analyzing slopes of kidney function (using both reciprocal serum creatinine and eGFR values) instead of mean eGFR values at follow-up visits. Because of the presumed linearity of slopes when an adequate number of creatinine values are used, the effect of atorvastatin on kidney function decline is subject to differences in follow-up duration and drop-out of patients to a much lesser extent. Yet, in our analysis nonrandom effects related to the protective effect of atorvastatin might have accounted for eGFR improvement. We therefore performed additional sensitivity analyses by including only serum creatinine data while patients were still receiving the study drug, which gave very similar results to the main analysis. The possibility that nonrandom effects may have importantly influenced our results seems therefore unlikely, particularly in regard to comparisons among the 3 groups. Nonrandom effects may, however, have been responsible for the positive slopes observed in the patient group randomized to placebo.

Another explanation for improvement of kidney function over time might relate to changes of muscle mass because serum creatinine and eGFR (calculated by using serum creatinine) depend on muscle mass. Reduction of muscle mass, reflecting protein wasting, will lead to higher reciprocal creatinine values and higher eGFR. Yet, loss of muscle mass is usually associated with worse outcomes, which is in contrast to our observation that positive slopes were associated with a beneficial effect on cardiovascular outcomes.

Finally, the dose-dependent increase of slopes during atorvastatin therapy might relate to increments of creatine kinase activity associated with statin use. High creatine kinase activity may result in lower serum creatinine, higher eGFR, and higher urinary creatinine excretion—parameters that usually reflect increased muscle wasting. However, a recent cohort study in 1801 CKD patients demonstrated that high serum creatine kinase was not associated with more rapid progression to ESRD.[27] In this study high serum creatine kinase was associated with more frequent use of statins, and correction for this potential confounder did influence the results. Therefore, both this study and our finding that a positive slope was also present in the placebo group indicate that muscle wasting does not seem not to be responsible for the unexpected changes in reciprocal serum creatinine slopes.

If changes in creatinine metabolism do not explain our findings, the question arises as to what the slope increment represents? CKD is associated with ventricular and vascular remodeling. The remodeling effects can be reversed by statin use, and that might in turn translate into better kidney function. Progressive kidney function decline has been related to subclinical atherosclerosis as well as to increased arterial inflammation.[28] Atorvastatin has been shown to reverse these vascular alterations that contribute to elevated cardiovascular risk.[29] As a consequence, further decline of kidney function might be prevented. Other possible mediators are oxidative stress and renal microvascular changes, which contribute to renal impairment but are beneficially influenced by statin treatment.[30] Of note, these direct effects, beyond lipid-lowering efficacy, on the vasculature and the kidney might not be present after treatment with all statins. The PLANET studies showed a distinct effect of atorvastatin versus rosuvastatin treatment.[11] Whereas atorvastatin 80 mg induced reduction of albuminuria and stabilization of eGFR, rosuvastatin led to higher albuminuria and decrement of eGFR.

Limitations

A number of limitations of our study need to be addressed. First, ideally the presence of all 3 groups in an RCT would have reduced the large heterogeneity of the baseline characteristics, which was observed in our study due to the use of different sets of studies. Heterogeneous effects across studies on kidney function slope were observed, but the slopes were all in the same direction, indicating that the effect on kidney function was robust. Despite adjustments for baseline characteristics in our analyses, differences in patient characteristics among the trials might still explain to some extent why the size of the effect on slope differed. Second, the studies in this analysis included patients with preserved kidney function and a low risk of development of ESRD. Therefore, the changes in kidney function over time were very small and, thus, of limited value in daily clinical practice. Third, albuminuria is an important risk marker for progressive kidney function decline, but in our analysis we could not evaluate albuminuria effects over time because this was not systemically assessed within the included trials. Finally, for the same reason, we were not able to handle time-varying covariates that influence slopes such as improvement of BP control or the introduction of RAS inhibitors in the follow-up the 6 RCTs.

In conclusion, our analysis shows that atorvastatin improves kidney function over time in a dose-dependent manner (ie, 80-mg versus 10-mg dose). In each of the treatment groups it was shown that kidney function improvement is strongly associated with lower cardiovascular risk. These data support the notion that both the cardio- and vasculoprotective efficacies of a pharmacological agent are reflected by the course of kidney function over time. Although the changes were small, our data also suggest that this kidney-related parameter, and not only LDL-cholesterol lowering, might represent a surrogate end point for long-term outcomes in cardiovascular risk patients.

Acknowledgments

No assistance with content development or writing was provided, but support in preparing the figures was provided by Jon Edwards at Engage Scientific Solutions and was funded by Pfizer. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. None of the academic authors received any compensation for the work on this article.

Sources of Funding

This work including 6 clinical trials (CARDS [ClinicalTrials.gov [NCT00327418]; SPARCL [NCT00147602]; TNT [NCT00327691]; ASCOT; ASPEN; and SAGE) was sponsored by Pfizer.

Disclosures

Drs Fayyad, Laskey, and DeMicco are employees of Pfizer Inc (New York, NY). Dr Waters has received honoraria for lectures and remuneration for participating in clinical trial committees from Merck Schering-Plough (Whitehouse Station, NJ) and Pfizer Inc. The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics (mean (SD)) from ASCOT.

		Placebo	Atorvastatin 10 mg
		N= 5,093	N= 5,121
Sex (% males)		81.4	81.2
Age (yrs)		63.2 (8.6)	63.2 (8.5)
Ethnicity (%)	Black	2.5	2.8
	Asian	1.6	1.5
	Caucasian	94.6	94.6
	Other	1.3	1.2
BMI (kg/m^2)		28.7 (4.6)	28.6 (4.7)
Systolic BP (mmHg)		164.2 (18.0)	164.2 (17.7)
Diastolic BP		95.0 (10.3)	94.9 (10.3)
Cholesterol (mg/dL)		212 (30)	212 (30)
HDL cholesterol (mg/dL)		51 (14)	51 (14)
LDL cholesterol (mg/dL)		133 (28)	133 (28)
Serum creatinine (mg/dL)*		1.1 (0.6-2.5)	1.1 (0.5-3.8)
Reciprocal of serum creatinine $(mg/dL)^{-1}$		0.92 (0.14)	0.92 (0.15)
eGFR ($mL/min/1.73\ m^2$)		68.5 (13.0)	68.6 (13.0)
CKD (eGFR <60 $mL/min/1.73\ m^2$)(%)		24.5	24.4
Hypertension (%)		100	100
History of CV event (%)		13.5	12.5
Diabetes mellitus (%)		24.8	24.5
Smoking (%)		30.5	31.3
Co-medication (%)	Diuretics	1.0	0.8
	RAASi	0.8	0.5
	Aspirin	16.7	16.5

*Median (Minimum-Maximum. BP: blood pressure, eGFR: estimated glomerular filtration rate (according to the CKD-EPI formula), RAASi: RAAS inhibitor.

Table S2. Baseline characteristics (mean (SD)) from ASPEN.

		Placebo	Atorvastatin 10 mg
		N= 1,199	N= 1,211
Sex (% males)		67.0	65.7
Age (yrs)		61.0 (8.2)	61.1 (8.1)
Ethnicity (%)	Black	6.2	6.7
	Asian	2.7	3.1
	Caucasian	84.3	84.1
	Other	6.8	6.2
BMI (kg/m^2)		28.9 (3.8)	28.9 (3.7)
Systolic BP (mmHg)		133.4 (16.5)	133.1 (16.8)
Diastolic BP		79.1 (9.3)	78.7 (9.2)
Cholesterol (mg/dL)		194 (30)	194 (31)
HDL cholesterol (mg/dL)		47 (13)	47 (14)
LDL cholesterol (mg/dL)		114 (26)	113 (25)
Serum creatinine (mg/dL)*		1.1 (0.7-2.6)	1.1 (0.6-3.5)
Reciprocal of serum creatinine $(mg/dL)^{-1}$		0.90 (0.15)	0.91 (0.15)
eGFR ($mL/min/1.73\ m^2$)		66.0 (12.9)	66.2 (12.7)
CKD (eGFR <60 $mL/min/1.73\ m^2$)(%)		31.4	32.0
Hypertension (%)		54.8	55.4
History of CV event (%)		23.8	26.2
Diabetes mellitus (%)		99.8	99.9
Smoking (%)		12.8	12.1
Co-medication (%)	Diuretics	20.7	20.5
	RAASi	35.0	35.2
	Aspirin	3.0	2.5

*Median ((Minimum-Maximum). BP: blood pressure, eGFR: estimated glomerular filtration rate (according to the CKD-EPI formula), RAASi: RAAS inhibitor.

Table S3. Baseline characteristics (mean (SD)) from CARDS.

		Placebo	Atorvastatin 10 mg
		N= 1,406	N= 1,426
Sex (% males)		67.9	68.0
Age (yrs)		61.8 (8.0)	61.5 (8.3)
Ethnicity (%)	Black	2.8	1.8
	Asian	2.6	3.1
	Caucasian	94.0	94.5
	Other	0.6	0.6
BMI (kg/m^2)		28.8 (3.5)	28.7 (3.6)
Systolic BP (mmHg)		144.0 (16.1)	143.9 (15.9)
Diastolic BP		82.8 (8.4)	82.7 (8.5)
Cholesterol (mg/dL)		207 (34)	208 (34)
HDL cholesterol (mg/dL)		55 (14)	54 (13)
LDL cholesterol (mg/dL)		117 (31)	119 (30)
Serum creatinine (mg/dL)*		1.1 (0.7-2.2)	1.1 (0.6-1.9)
Reciprocal of serum creatinine $(mg/dL)^{-1}$		0.89 (0.13)	0.89 (0.13)
eGFR ($mL/min/1.73\ m^2$)		63.8 (11.3)	64.0 (11.2)
CKD (eGFR <60 $mL/min/1.73\ m^2$)(%)		36.8	36.3
Hypertension (%)		79.1	79.8
History of CV event (%)		2.8	3.9
Diabetes mellitus (%)		99.9	99.9
Smoking (%)		22.9	21.5
Co-medication (%)	Diuretics	19.8	18.1
	RAASi	43.7	44.7
	Aspirin	15.0	15.7

*Median ((Minimum-Maximum). BP: blood pressure, eGFR: estimated glomerular filtration rate (according to the CKD-EPI formula), RAASi: RAAS inhibitor.

Table S4. Baseline characteristics (mean (SD)) from SAGE (atorvastatin 80 mg arm only).

		Atorvastatin 80 mg N= 446
Sex (% males)		68.8
Age (yrs)		72.4 (5.1)
Ethnicity (%)	Black	0.5
	Asian	0.2
	Caucasian	97.1
	Other	2.2
BMI (kg/m^2)		27.4 (4.0)
Systolic BP (mmHg)		139.4 (18.6)
Diastolic BP		78.0 (8.9)
Cholesterol (mg/dL)		226 (37)
HDL cholesterol (mg/dL)		45 (12)
LDL cholesterol (mg/dL)		148 (30)
Serum creatinine (mg/dL)*		1.1 (0.7-1.9)
Reciprocal of serum creatinine $(mg/dL)^{-1}$		0.91 (0.16)
eGFR ($mL/min/1.73\ m^2$)		61.5 (13.4)
CKD (eGFR <60 $mL/min/1.73\ m^2$)(%)		46.2
Hypertension (%)		66.4
History of CV event (%)		92.2
Diabetes mellitus (%)		22.4
Smoking (%)		5.4
Co-medication (%)	Diuretics	23.5
	RAASi	47.8
	Aspirin	86.8

*Median ((Minimum-Maximum). BP: blood pressure, eGFR: estimated glomerular filtration rate (according to the CKD-EPI formula), RAASi: RAAS inhibitor.

Table S5. Baseline characteristics (mean (SD)) from SPARCL.

		Placebo	Atorvastatin 80 mg
		N= 2,359	N= 2,360
Sex (% males)		59.1	60.3
Age (yrs)		62.5 (11.3)	63.0 (11.2)
Ethnicity (%)	Black	2.8	3.1
	Asian	0.6	0.6
	Caucasian	93.4	93.3
	Other	3.2	3.0
BMI (kg/m^2)		27.4 (4.5)	27.5 (4.6)
Systolic BP (mmHg)		138.4 (19.3)	138.9 (19.4)
Diastolic BP		81.4 (10.6)	82.0 (10.7)
Cholesterol (mg/dL)		212 (29)	211 (30)
HDL cholesterol (mg/dL)		50 (14)	50 (14)
LDL cholesterol (mg/dL)		134 (24)	133 (24)
Serum creatinine (mg/dL)*		1.1 (0.5-3.3)	1.1 (0.7-4.4)
Reciprocal of serum creatinine $(mg/dL)^{-1}$		0.93 (0.16)	0.92 (0.16)
eGFR ($mL/min/1.73\ m^2$)		65.4 (13.7)	65.1 (13.8)
CKD (eGFR <60 $mL/min/1.73\ m^2$)(%)		36.3	35.4
Hypertension (%)		61.4	62.3
History of CV event (%)		30.9	28.8
Diabetes mellitus (%)		16.9	16.7
Smoking (%)		19.3	19.1
Co-medication (%)	Diuretics	20.7	20.7
	RAASi	34.0	35.7
	Aspirin	70.4	69.9

*Median ((Minimum-Maximum). BP: blood pressure, eGFR: estimated glomerular filtration rate (according to the CKD-EPI formula), RAASi: RAAS inhibitor.

Table S6. Baseline characteristics (mean (SD)) from TNT.

		Atorvastatin 10 mg	Atorvastatin 80 mg
		N= 5,005	N= 4,995
Sex (% males)		80.8	81.2
Age (yrs)		60.9 (8.9)	61.2 (9.0)
Ethnicity (%)	Black	3.1	2.7
	Asian	1.1	1.0
	Caucasian	94.1	94.1
	Other	1.7	2.3
BMI (kg/m^2)		28.6 (4.7)	28.4 (4.5)
Systolic BP (mmHg)		130.9 (16.8)	130.5 (16.8)
Diastolic BP		78.1 (9.5)	77.8 (9.5)
Cholesterol (mg/dL)		175 (24)	175 (24)
HDL cholesterol (mg/dL)		47 (11)	47 (11)
LDL cholesterol (mg/dL)		98 (18)	97 (18)
Serum creatinine (mg/dL)*		1.2 (0.7-3.0)	1.2 (0.6-3.3)
Reciprocal of serum creatinine $(mg/dL)^{-1}$		0.87 (0.13)	0.86 (0.13)
eGFR ($mL/min/1.73\ m^2$)		65.2 (12.5)	64.7 (12.3)
CKD (eGFR <60 $mL/min/1.73\ m^2$)(%)		33.0	34.7
Hypertension (%)		54.4	53.9
History of CV event (%)		97.7	97.5
Diabetes mellitus (%)		15.0	15.0
Smoking (%)		13.4	13.4
Co-medication (%)	Diuretics	31.1	29.5
	RAASi	56.7	54.1
	Aspirin	93.6	93.8

*Median ((Minimum-Maximum). BP: blood pressure, eGFR: estimated glomerular filtration rate (according to the CKD-EPI formula), RAASi: RAAS inhibitor.

Figure S1. Reciprocal of serum creatinine for each individual patient across the 3 groups (placebo (green), atorvastatin 10 mg (black), and 80 mg (red)).