

## ORIGINAL ARTICLE

# Rosuvastatin and Cardiovascular Events in Patients Undergoing Hemodialysis

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## ABSTRACT

**BACKGROUND**

Statins reduce the incidence of cardiovascular events in patients at high cardiovascular risk. However, a benefit of statins in such patients who are undergoing hemodialysis has not been proved.

**METHODS**

We conducted an international, multicenter, randomized, double-blind, prospective trial involving 2776 patients, 50 to 80 years of age, who were undergoing maintenance hemodialysis. We randomly assigned patients to receive rosuvastatin, 10 mg daily, or placebo. The combined primary end point was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary end points included death from all causes and individual cardiac and vascular events.

**RESULTS**

After 3 months, the mean reduction in low-density lipoprotein (LDL) cholesterol levels was 43% in patients receiving rosuvastatin, from a mean baseline level of 100 mg per deciliter (2.6 mmol per liter). During a median follow-up period of 3.8 years, 396 patients in the rosuvastatin group and 408 patients in the placebo group reached the primary end point (9.2 and 9.5 events per 100 patient-years, respectively; hazard ratio for the combined end point in the rosuvastatin group vs. the placebo group, 0.96; 95% confidence interval [CI], 0.84 to 1.11;  $P=0.59$ ). Rosuvastatin had no effect on individual components of the primary end point. There was also no significant effect on all-cause mortality (13.5 vs. 14.0 events per 100 patient-years; hazard ratio, 0.96; 95% CI, 0.86 to 1.07;  $P=0.51$ ).

**CONCLUSIONS**

In patients undergoing hemodialysis, the initiation of treatment with rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. (ClinicalTrials.gov number, NCT00240331.)

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**P**ATIENTS UNDERGOING MAINTENANCE hemodialysis have a greatly increased risk of premature cardiovascular disease.<sup>1,2</sup> However, the pattern of cardiovascular disease in such patients differs from that in the general population, and although the risk of myocardial infarction is increased, other cardiovascular events, such as sudden cardiac death and heart failure, predominate.<sup>1-3</sup> Moreover, the relationship between cardiovascular disease and conventional risk factors is inconsistent, inverse, or U-shaped.<sup>1,2,4</sup> Since low-density lipoprotein (LDL) cholesterol levels may be low or normal in patients with advanced renal disease, there is particular uncertainty regarding the use of lipid-lowering therapy.<sup>1,2,4,5</sup>

Statin therapy has been proved to reduce the incidence of cardiovascular events and mortality in diverse patient populations at increased risk.<sup>3,6-10</sup> Observational studies have suggested that statin therapy is also associated with improved survival among patients undergoing hemodialysis,<sup>11</sup> and statin use is endorsed by clinical guidelines in many countries,<sup>12,13</sup> but a benefit of statin therapy in these patients has not been proved. The only large-scale trial involving this population, Die Deutsche Diabetes Dialyse Studie (the 4D study),<sup>14</sup> showed no significant benefit of statin therapy with regard to a composite cardiovascular end point in patients with type 2 diabetes who were undergoing hemodialysis. Some have attributed the lack of benefit to the very high cardiovascular risk among patients with type 2 diabetes and end-stage renal disease and to the futility of a single intervention.<sup>1,2,15</sup> However, the question of the efficacy of statin therapy for the greater population of recipients of hemodialysis remains unanswered. A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) was therefore designed to investigate the effects of statin therapy in patients undergoing regular hemodialysis treatment.

## METHODS

### STUDY DESIGN

AURORA was a randomized, double-blind, placebo-controlled, multicenter trial.<sup>16,17</sup> The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference of Harmonisation, and local regulatory

requirements; it was approved by ethics committees at all participating centers.

The executive steering committee designed the trial and supervised its conduct in collaboration with the sponsor, AstraZeneca. The sponsor collected the trial data and analyzed them according to a predefined statistical analysis plan. The analyses were verified by Dr. A.H. Zwinderman, an independent statistician at the Department of Clinical Epidemiology, Biostatistics, and Bioinformatics, University of Amsterdam. The manuscript was prepared and submitted for publication by the steering committee; the academic authors had access to the study data and vouch for the accuracy and completeness of the reported analyses.

### PATIENTS

Men and women 50 to 80 years of age who had end-stage renal disease and had been treated with regular hemodialysis or hemofiltration for at least 3 months were recruited from 280 centers in 25 countries. The major exclusion criteria were statin therapy within the previous 6 months, expected kidney transplantation within 1 year, and serious hematologic, neoplastic, gastrointestinal, infectious, or metabolic disease (excluding diabetes) that was predicted to limit life expectancy to less than 1 year. Other exclusion criteria were a history of a malignant condition, active liver disease (indicated by an alanine aminotransferase level that was more than three times the upper limit of the normal range), uncontrolled hypothyroidism, and an unexplained elevation in the creatine kinase level to more than three times the upper limit of the normal range.<sup>16,17</sup>

Eligible patients were randomly assigned (in blocks of four in a 1:1 ratio) to receive either rosvastatin, 10 mg daily, or matching placebo. Follow-up visits were scheduled to occur 3 months after randomization and then every 6 months. Assessments included laboratory evaluations once yearly and, at each visit, pill counts and structured interviews to assess potential adverse events. Blood samples were analyzed at a central laboratory for levels of lipids and high-sensitivity C-reactive protein. A closeout visit occurred after termination of the study.

### END POINTS

The primary end point was the time to a major cardiovascular event, defined as a nonfatal myocardial infarction, nonfatal stroke, or death from

cardiovascular causes. All myocardial infarctions, strokes, and deaths were reviewed and adjudicated by a clinical end-point committee whose members were unaware of the randomized treatment assignments, in order to ensure consistency of the event diagnosis.

Secondary end points included all-cause mortality, cardiovascular event-free survival (i.e., freedom from nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, and death from any other cause), procedures performed for stenosis or thrombosis of the vascular access for long-term hemodialysis (arteriovenous fistulas and grafts only), and coronary or peripheral revascularization, death from cardiovascular causes, and death from noncardiovascular causes.

#### STATISTICAL ANALYSIS

The initial calculation of statistical power was based on an estimated rate of major cardiovascular events in the placebo group of 11% per year. It was estimated that 620 events would be required for the analysis, assuming a 25% benefit of intervention, 90% power, and a two-sided significance level of 0.05. The trial was predicted to last 3.9 years.<sup>16</sup>

In 2005, after the publication of the results of 4D and related trials,<sup>3,14</sup> we reevaluated the underlying assumptions of our trial. In the revised calculation of power, we assumed a neutral (0%) treatment effect on stroke<sup>14</sup> and predicted a 19.5% reduction in the rate of major cardiovascular events with active therapy. With a two-sided significance level of 0.05 and 87% power, we estimated that 805 major cardiovascular events were required for analysis. An interim analysis was performed when 305 patients had reached a primary end point; continuation of the study was recommended by the data and safety monitoring board. The overall significance level was appropriately adjusted for the interim analysis.

In the primary intention-to-treat analyses, which included all patients who underwent randomization, an unadjusted Cox proportional-hazards model was used to compare the study groups and calculate hazard ratios (SAS software, version 8.2). The score test was used to calculate P values. Cox analyses of the primary outcome were performed in prespecified groups; subgroups were defined according to median values or values divided into thirds or according to condition (e.g., diabetes). P values for the interaction between the

subgroup and treatment are reported. A Cox model adjusted for baseline covariates was estimated to investigate the association with outcomes.

For lipid data, analysis of variance with baseline values as covariates was used to test the difference (i.e., the percent change from baseline) between rosuvastatin and placebo. For the level of high-sensitivity C-reactive protein, a two-sample sign test was used. Values of more than 40 mg per liter (the upper limit of the assay for the laboratory) were set at 40 mg per liter.

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## RESULTS

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#### PATIENTS

During the recruitment period, from January 2003 through December 2004, a total of 3021 patients were screened, and 2776 patients were randomly assigned to double-blind treatment with rosuvastatin at a dose of 10 mg (1391 patients) or placebo (1385 patients) (see the flow diagram in the Supplementary Appendix, available with the full text of this article at NEJM.org). A total of 245 patients did not undergo randomization: 19 had an adverse event, 156 did not fulfill screening criteria, and 70 chose not to participate. Of those enrolled, 3 patients were randomly assigned incorrectly and were not included in the intention-to-treat population, leaving a total of 2773 patients. The two groups of patients were well matched with respect to baseline characteristics (age, sex, and race or ethnic group) and concomitant therapy, as well as mean duration of dialysis therapy at baseline (Table 1).

The mean length of follow-up was 3.2 years (maximum, 5.6). No patients were lost to follow-up. During the follow-up period, 1296 patients died. Of the 1164 deaths that were adjudicated, 648 were deaths from cardiovascular causes. Altogether, 804 patients had a major cardiovascular event, and 674 patients (332 who were receiving rosuvastatin and 342 who were receiving placebo) died while receiving the study drug. In addition, 440 patients (207 who were receiving rosuvastatin and 233 who were receiving placebo) discontinued the study medication after an adverse event, including study end points, and 370 patients (197 who were receiving rosuvastatin and 173 who were receiving placebo) discontinued therapy because of renal transplantation. The mean duration of exposure to the study medication was 2.4 years (median, 2.2).

Characteristic	Rosuvastatin (N=1389)	Placebo (N=1384)	P Value†
Age — yr	64.1±8.6	64.3±8.7	0.51
Female sex — no. (%)	538 (38.7)	512 (37.0)	0.35
Race or ethnic group — no. (%)‡			
White	1174 (84.5)	1180 (85.3)	0.60
Black	50 (3.6)	48 (3.5)	0.92
Asian	70 (5.0)	69 (5.0)	1.00
Hispanic	57 (4.1)	56 (4.0)	1.00
Other	38 (2.7)	31 (2.2)	0.46
Body-mass index§	25.4±4.7	25.4±5.1	0.96
Blood pressure — mm Hg			
Systolic	137.1±24.5	136.8±24.5	0.79
Diastolic	75.9±12.8	75.6±12.5	0.45
Current smoker — no. (%)	202 (14.5)	227 (16.4)	0.54
Cholesterol — mg/dl			
Total	176±42	174±43	0.19
LDL	100±35	99±34	0.34
HDL	45±15	45±16	0.85
Triglycerides — mg/dl	157±95	154±97	0.45
High-sensitivity C-reactive protein — mg/liter			0.19
Median	4.8	5.2	
Interquartile range	2.0–13.6	2.1–14.4	
Hemoglobin — g/dl	11.7±1.6	11.7±1.6	0.38
Albumin — g/liter	39.7±3.5	39.7±3.4	0.65
Calcium — mmol/liter	2.3±0.2	2.3±0.2	0.21
Phosphate — mmol/liter	1.8±0.6	1.8±0.5	0.29
Duration of treatment with hemodialysis — yr	3.5±3.9	3.5±3.8	0.59
Duration of dialysis sessions — hr/week	11.9±1.8	11.9±1.8	0.82
Cause of end-stage renal disease — no. (%)			
Nephrosclerosis	273 (19.7)	281 (20.3)	0.70
Glomerulonephritis or vasculitis	250 (18.0)	262 (18.9)	0.56
Diabetes	286 (20.6)	249 (18.0)	0.084
Tubulointerstitial disease	206 (14.8)	193 (13.9)	0.52
Hereditary	171 (12.3)	185 (13.4)	0.43
Other	203 (14.6)	214 (15.5)	0.56
Clinical history — no. (%)			
Diabetes	388 (27.9)	343 (24.8)	0.064
Cardiovascular disease	549 (39.5)	556 (40.2)	0.76
Myocardial infarction	146 (10.5)	136 (9.8)	0.57
Coronary revascularization	82 (5.9)	91 (6.6)	0.48
Peripheral vascular disease	212 (15.3)	210 (15.2)	0.96

**Table 1. (Continued.)**

Characteristic	Rosuvastatin (N=1389)	Placebo (N=1384)	P Value†‡
Drug therapy — no. (%)			
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	497 (35.8)	523 (37.8)	0.29
Calcium-channel blocker	480 (34.6)	501 (36.2)	0.38
Beta-blocker	534 (38.4)	498 (36.0)	0.18
Diuretic	428 (30.8)	422 (30.5)	0.87
Platelet inhibitor	593 (42.7)	571 (41.3)	0.46
Vitamin D	643 (46.3)	659 (47.6)	0.49
Calcium substitution	1032 (74.3)	1027 (74.2)	0.97
Sevelamer	398 (28.7)	366 (26.4)	0.20
Erythropoietin	1204 (86.7)	1225 (88.5)	0.15

\* Plus–minus values are means  $\pm$ SD. To convert values for low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

† P values for mean data were calculated with the use of Student's t-test, for percentages with the use of Fisher's exact test, and for medians with the use of the Wilcoxon rank-sum test.

‡ Race or ethnic group was self-reported.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

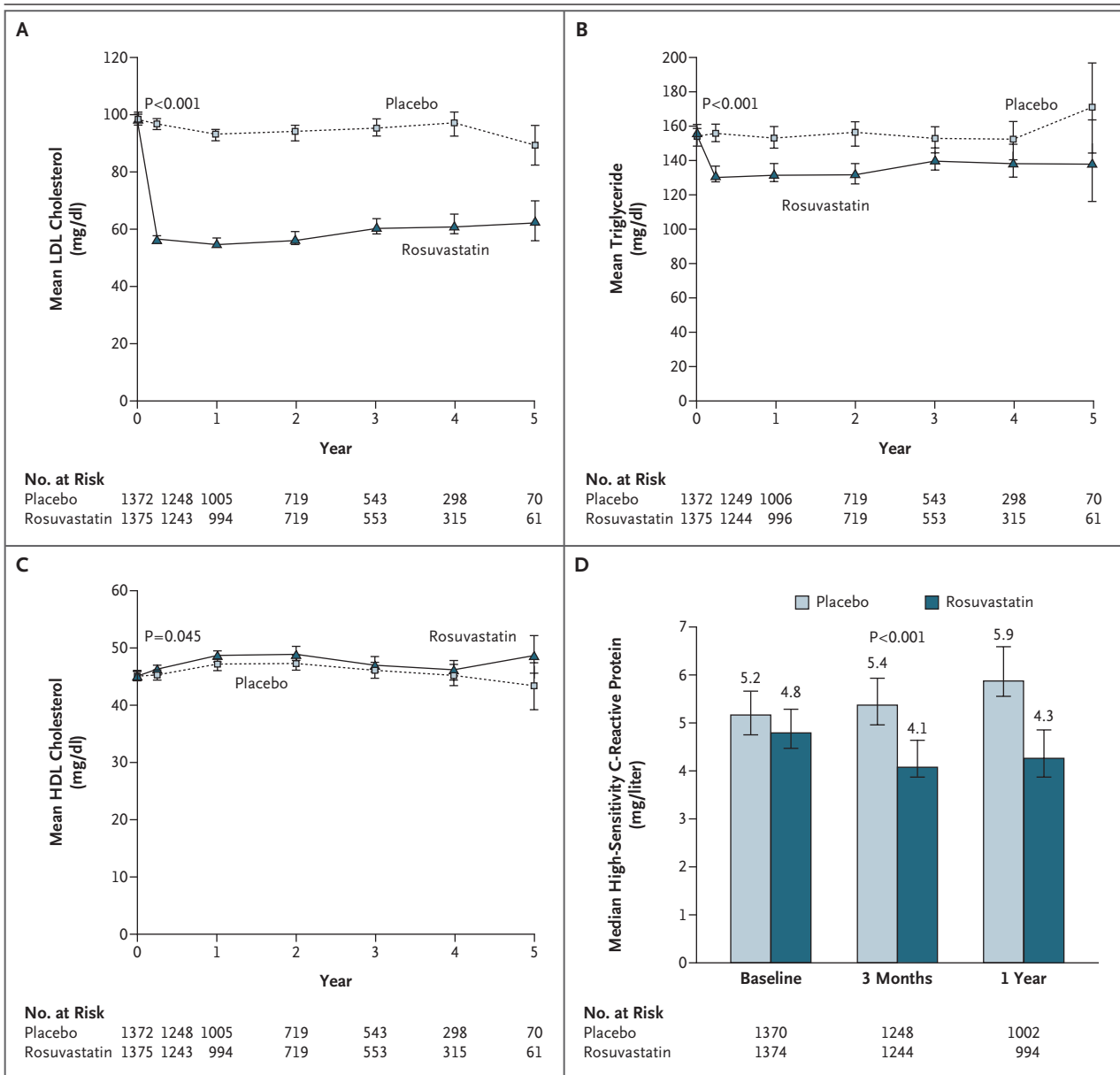
#### LIPID AND C-REACTIVE PROTEIN LEVELS

Baseline lipid levels are shown in Table 1. At 3 months, the LDL cholesterol level in the rosuvastatin group was 42.9% lower than the baseline level (mean  $\pm$ SD) difference,  $42\pm 30$  mg per deciliter [ $1.1\pm 0.8$  mmol per liter], as compared with a 1.9% reduction in the placebo group (mean difference,  $1.9\pm 23$  mg per deciliter [ $0.05\pm 0.59$  mmol per liter];  $P<0.001$  for the between-group comparison) (Fig. 1A). At 3 months, rosuvastatin also reduced the total cholesterol level, by 26.6% (by  $47\pm 35$  mg per deciliter [ $1.2\pm 0.9$  mmol per liter]), as compared with a 0.5% reduction ( $1\pm 27$  mg per deciliter [ $0.03\pm 0.70$  mmol per liter]) in the placebo group ( $P<0.001$ ), and the triglyceride level was reduced by 16.2% (by  $26\pm 71$  mg per deciliter [ $0.29\pm 0.80$  mmol per liter]), as compared with an increase of 0.9% ( $1.8\pm 72$  mg per deciliter [ $0.02\pm 0.81$  mmol per liter]) in the placebo group ( $P<0.001$ ) (Fig. 1B). There was a modest increase of 2.9% in the high-density lipoprotein cholesterol level ( $1.2\pm 10$  mg per deciliter [ $0.03\pm 0.26$  mmol per liter]), as compared with an increase of 0.8% ( $0.4\pm 9.3$  mg per deciliter [ $0.01\pm 0.24$  mmol per liter]) in the placebo group ( $P=0.045$ ) (Fig. 1C). Toward the end of the study, there was a trend toward a convergence of the lipid levels in the active-treatment and placebo groups, probably

reflecting withdrawals from active therapy and “drop-in” therapy with statins in the placebo group. The median high-sensitivity C-reactive protein level was elevated at baseline (Table 1) and decreased by 11.5% in the rosuvastatin group at 3 months (by 0.65 mg per liter, vs. an increase of 0.21 mg per liter in the placebo group;  $P<0.001$ ) (Fig. 1D).

#### PRIMARY OUTCOMES

The primary end point occurred in 396 patients assigned to receive rosuvastatin (9.2 events per 100 patient-years) and in 408 patients assigned to receive placebo (9.5 events per 100 patient-years) (Fig. 2 and Table 2). There was no significant effect of active treatment (hazard ratio for the primary end point in the rosuvastatin group vs. the placebo group, 0.96; 95% confidence interval [CI], 0.84 to 1.11;  $P=0.59$ ). Among the components of the primary end point, we also observed no significant effect of rosuvastatin therapy as compared with placebo. The respective event rates were 7.2 and 7.3 per 100 patient-years for death from cardiovascular causes ( $P=0.97$ ), 2.1 and 2.5 per 100 patient-years for nonfatal myocardial infarction ( $P=0.23$ ), and 1.2 and 1.1 per 100 patient-years for nonfatal stroke ( $P=0.42$ ) (Table 2). A per-protocol analysis of patients who continued to receive active study medication until they reached a study



**Figure 1.** Changes in Levels of Lipids and C-Reactive Protein, According to Study Group.

Panel A shows low-density lipoprotein (LDL) cholesterol levels, Panel B triglyceride levels, Panel C high-density lipoprotein (HDL) cholesterol levels, and Panel D high-sensitivity C-reactive protein levels. P values are for between-group comparisons of the percent change from baseline to 3 months in lipid levels, calculated with the use of analysis of variance with baseline values as covariates, and in C-reactive protein levels, calculated with the use of the two-sample sign test. I bars denote 95% confidence intervals. To convert values for LDL, HDL, and total cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

end point confirmed the lack of an effect of rosuvastatin on the primary composite end point.

**SECONDARY OUTCOMES AND SUBGROUPS**

Death from any cause occurred in 636 patients (13.5 per 100 patient-years) in the rosuvastatin

group and 660 (14.0 per 100 patient-years) in the placebo group. There was no significant effect of rosuvastatin on all-cause mortality (hazard ratio, 0.96; 95% CI, 0.86 to 1.07; P=0.51) or on death from noncardiovascular causes (hazard ratio, 0.92; 95% CI, 0.77 to 1.09; P=0.34). None of the pre-

specified secondary outcomes were influenced by active treatment (Table 2). The lack of an effect of rosuvastatin therapy on the primary end point was consistent in all prespecified subgroups (Fig. 3), including patients with diabetes, preexisting cardiovascular disease, hypertension, a high LDL cholesterol level, or an elevated high-sensitivity C-reactive protein level. Subgroup analyses according to the overall time on hemodialysis therapy or the overall time on renal-replacement therapy also did not influence the response to therapy (data not shown).

#### ADHERENCE TO STUDY THERAPY AND ADVERSE EVENTS

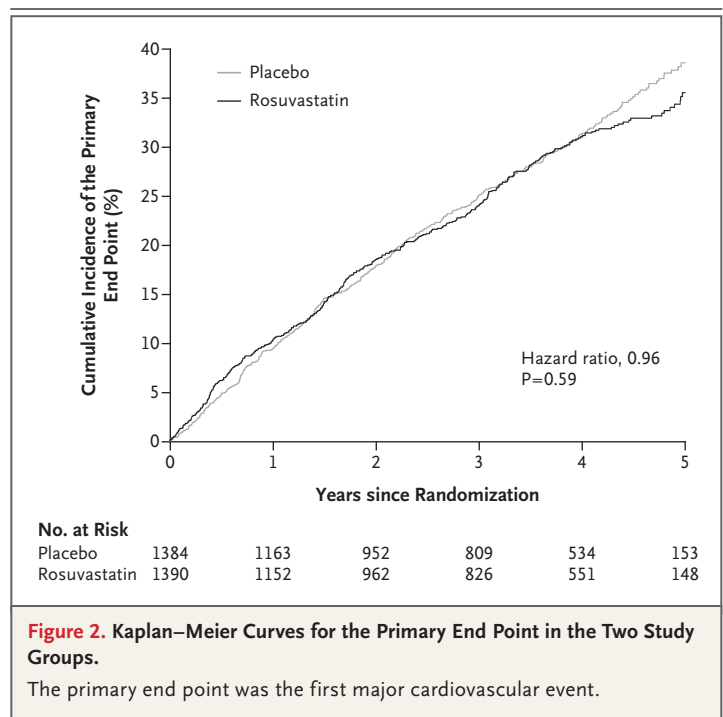
According to tablet counts, 91.7% of rosuvastatin tablets and 89.5% of placebo tablets were taken as intended by patients in the study. Consistent with previous studies in patients with end-stage renal disease, there was a high incidence of adverse and serious adverse events.<sup>3,14</sup> Adverse events were reported in 1338 patients who received rosuvastatin (96.3%) and in 1332 patients who received placebo (96.7%). Serious adverse events were reported in 1140 patients who received rosuvastatin (82.1%) and in 1159 patients who received placebo (84.1%). Most patients reported multiple events; a total of 36,780 adverse events and 9017 serious adverse events were reported during the study, with no significant difference between treatment groups (Table 3).

#### RELATIONSHIP BETWEEN LIPID LEVELS AND OUTCOMES

Given the lack of a treatment effect of rosuvastatin on the primary end point, we examined the relationship between lipid levels and cardiovascular end points within the trial. There was no relationship between the primary cardiovascular end point and either baseline LDL cholesterol levels (hazard ratio per 1 mg per deciliter [0.03 mmol per liter], 1.00; 95% CI, 0.82 to 1.29;  $P=0.83$ ) or LDL cholesterol levels at 3 months (hazard ratio, 0.95; 95% CI, 0.83 to 1.09;  $P=0.48$ ).

#### DISCUSSION

In this trial, we examined the potential benefits of statin therapy with regard to the increased cardiovascular risk associated with maintenance hemodialysis therapy.<sup>1,2,4,16,17</sup> We found no effect of rosuvastatin on the primary end point of nonfatal myocardial infarction, nonfatal stroke, or



**Figure 2.** Kaplan–Meier Curves for the Primary End Point in the Two Study Groups.

The primary end point was the first major cardiovascular event.

death from cardiovascular causes. Analyses of individual components of the primary end point and of several secondary end points were consistent with the main finding. Rosuvastatin had no benefit in any subgroup examined, including patients with diabetes.<sup>16,17</sup>

The lack of a benefit of rosuvastatin was observed despite a mean 43% reduction in the LDL cholesterol level at 3 months and the expected benefits with regard to other lipid levels.<sup>3,6-10,14</sup> As expected in a population of patients undergoing hemodialysis, baseline cholesterol levels were not high. However, in the subgroup analyses (Fig. 3), there was no benefit at any baseline LDL cholesterol level or in groups with preexisting cardiovascular disease, regardless of the lipid level. Previous studies<sup>4</sup> have shown an inconsistent (or inverse) relationship between the LDL cholesterol level and outcomes in patients undergoing hemodialysis.<sup>1,2,4</sup> Our findings suggest that in such patients, a reduction of the LDL cholesterol level with statins does not necessarily reduce cardiovascular risk.

In the 4D study,<sup>14,18</sup> 1225 patients with type 2 diabetes undergoing maintenance hemodialysis received either atorvastatin at a dose of 20 mg or placebo. Although the median LDL cholesterol level was reduced by 42% with atorvastatin, there was no significant reduction in the composite pri-

**Table 2. End Points According to Study Group.\***

Event	Rosuvastatin (N=1389)		Placebo (N=1384)		Hazard Ratio (95% CI)	P Value
	no. of patients	no. of events/ 100 patient-yr	no. of patients	no. of events/ 100 patient-yr		
<b>Primary end point</b>						
Combined outcome (major cardiovascular event)	396	9.2	408	9.5	0.96 (0.84–1.11)	0.59
Death from cardiovascular causes	324	7.2	324	7.3	1.00 (0.85–1.16)	0.97
Nonfatal myocardial infarction	91†	2.1	107	2.5	0.84 (0.64–1.11)	0.23‡
Nonfatal stroke	53†	1.2	45	1.1	1.17 (0.79–1.75)	0.42‡
<b>Secondary end point</b>						
Death						
From any cause	636	13.5	660	14.0	0.96 (0.86–1.07)	0.51
From coronary heart disease (definite)	143	3.2	156	3.5		
From coronary heart disease (suspected)	61	1.4	53	1.2		
From other cardiac cause	36	0.8	30	0.7		
From other vascular cause	44	1.0	48	1.1		
From other cardiovascular cause	0	0.0	1	0.0		
From noncardiovascular cause	248	5.5	268	6.0	0.92 (0.77–1.09)	0.34
From ischemic stroke	14	0.3	17	0.4		
From unclassified stroke	9	0.2	4	0.1		
From primary intracerebral hemorrhage, cerebellar hemorrhage, or both	17	0.4	15	0.3		
Nonfatal myocardial infarction						
Definite	74†	1.7	100	2.3		
Suspected	19†	0.4	7	0.2		
Nonfatal stroke						
Ischemic	43†	1.0	38	0.9		
Not classified	3†	0.1	1	0.0		
Primary intracerebral hemorrhage, cerebellar hemorrhage, or both	8†	0.2	6	0.1		
Major cardiovascular event or cause-specific death	614	14.2	645	15.1	0.94 (0.84–1.05)	0.30
Atherosclerotic cardiac event§	258	5.9	266	6.1	0.96 (0.81–1.14)	0.64
Vascular access procedure¶	390	10.9	360	10.0	1.10 (0.95–1.27)	0.19
Revascularization¶	148	3.5	152	3.6	0.98 (0.78–1.23)	0.88

\* All events were adjudicated by the end-point committee except for some of the deaths from any cause that were reported after the patient had withdrawn from the study assessments, vascular access procedure, and revascularization.

† Patients may have had more than one event.

‡ This comparison was not part of the prespecified statistical analysis plan.

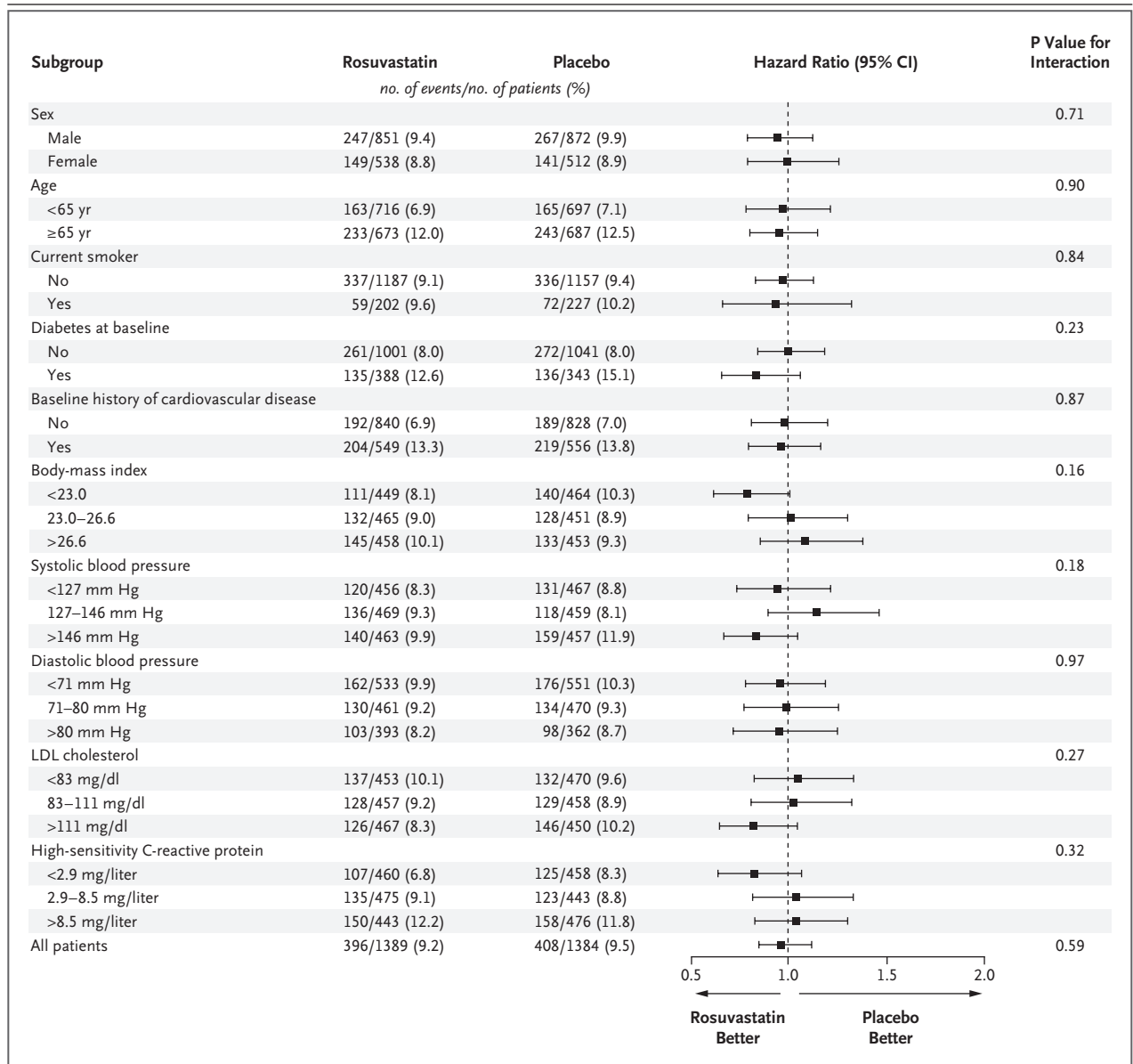
§ Atherosclerotic cardiac event is the combined end point of coronary heart disease and nonfatal myocardial infarction.

¶ These events were adjudicated by the study-team physician.

primary cardiovascular end point. In contrast, previous trials and post hoc analyses have shown benefits of statin therapy in patients with diabetes, including diabetes with less advanced chronic kidney disease.<sup>19–22</sup> The lack of a benefit of statin

therapy in the 4D and AURORA studies suggests that cardiovascular disease in patients undergoing hemodialysis differs from that in other patients.<sup>23,24</sup>

Other trials examining cardiovascular outcomes



**Figure 3. Hazard Ratio for the Primary End Point in Predefined Subgroups.**

In the age category, the two subgroups shown are patients with a baseline age below the median value and those with a baseline age above the median. For categories with three subgroups, patients are divided according to their baseline values. Values for low-density lipoprotein (LDL) cholesterol were calculated with the use of Friedewald's formula; to convert the values to millimoles per liter, multiply by 0.02586.

in patients with chronic kidney disease have been limited to post hoc assessments of patients recruited for cardiovascular prevention trials,<sup>19-21</sup> studies of modest size,<sup>22</sup> and studies involving patients treated by means of renal transplantation.<sup>3,25</sup> In these studies, statin therapy has been shown to reduce the incidence of cardiovascular events.<sup>6-10,26</sup> These results contrast with the lack

of benefit in patients undergoing hemodialysis seen in our trial and raise the questions of whether statin therapy becomes ineffective with worsening renal disease and, if so, at which stage? These questions may be answered by the ongoing Study of Heart and Renal Protection (SHARP) (ClinicalTrials.gov number, NCT00125593),<sup>27</sup> which will evaluate the benefit of simvastatin plus ezeti-

**Table 3. Monitored Adverse Events and Measured Laboratory Values in the Safety-Analysis Population.\***

Variable	Rosuvastatin (N=1389)	Placebo (N=1378)	P Value
	<i>no. of patients (%)</i>		
<b>Monitored adverse events</b>			
Any adverse event	1338 (96.3)	1332 (96.7)	0.56
Serious adverse event			
Any	1140 (82.1)	1159 (84.1)	0.80
Requiring permanent discontinuation of study drug	438 (31.5)	443 (32.1)	0.78
Drug-related†	16 (1.2)	11 (0.8)	0.35
Event leading to death	640 (46.1)	662 (48.0)	0.49
<b>Death</b>			
From cardiovascular causes	324 (23.3)	324 (23.5)	0.92
From noncardiovascular causes	248 (17.9)	267 (19.4)	0.34
Infection	105 (7.6)	100 (7.3)	0.78
Cancer	25 (1.8)	27 (2.0)	0.75
From unspecified causes‡	68 (4.9)	71 (5.2)	0.77
Infection§	976 (70.3)	956 (69.4)	0.16
Gastrointestinal disorder¶	814 (58.6)	788 (57.2)	0.26
Hepatic disorder	66 (4.8)	54 (3.9)	0.28
Musculoskeletal disorder**	310 (22.3)	343 (24.9)	0.21
Rhabdomyolysis††	3 (0.2)	2 (0.1)	0.66
Newly diagnosed cancer	107 (7.7)	118 (8.6)	0.41
New-onset diabetes mellitus	10 (0.7)	14 (1.0)	0.40
<b>Laboratory values</b>			
Alanine aminotransferase >4× ULN	5 (0.4)	6 (0.4)	0.75
Creatine kinase level			
3–5× ULN	7 (0.5)	6 (0.4)	0.79
>5× ULN	3 (0.2)	3 (0.2)	0.99

\* The safety-analysis population consisted of patients who were randomly assigned to receive at least one dose of study medication. Many patients reported multiple adverse events; only the first event of each category is recorded. ULN denotes upper limit of the normal range.

† Drug-related events were evaluated by the investigator.

‡ Five of the deaths from unspecified causes in the rosuvastatin group and four in the placebo group were listed by the investigator but not adjudicated by the clinical end-point committee.

§ Bronchitis, pneumonia, nasopharyngitis, and urinary tract infections were most frequently reported, and the frequency was similar in the two groups.

¶ Diarrhea, nausea, abdominal pain, and constipation were most frequently reported, and the frequency was similar in the two groups.

|| Increased hepatic-enzyme levels were most frequently reported.

\*\* Muscle spasm, pain, and weakness were most frequently reported, and the frequency was similar in the two groups.

†† Five cases of rhabdomyolysis were reported by the investigators. Only one patient with rhabdomyolysis had a creatine kinase level that was more than 10 times the upper limit of the normal range, together with muscle symptoms. Four patients recovered from the event, and one patient, in the placebo group, died.

mibe in patients across the spectrum of renal dysfunction.

There are several caveats to consider with regard to interpretation of our results. First, we excluded patients who were already receiving statins. Although we do not have a registry that

would enable us to examine this excluded group systematically, we estimate that it may account for as many as 35 to 40% of all patients with end-stage renal disease. This group may include patients who had previously had cardiac events or had undergone cardiovascular interventions and

may also include patients for whom statins were initiated at earlier stages of progressive kidney disease. We also observed a lower-than-predicted yearly event rate for the primary end point.<sup>1,2,16,28</sup> Thus, we cannot rule out selection bias or the possibility that investigators excluded patients whom they believed warranted statin therapy.

Another issue is that we recruited patients who were 50 to 80 years of age, even though the increase in cardiovascular risk affects all age groups of patients undergoing hemodialysis therapy<sup>28</sup> and is disproportionately higher among younger patients. Thus, possible benefits in younger patients, most of whom will ultimately receive transplants, were not explored in our trial. Finally, a high proportion of patients discontinued the study medication during the study; this is a reflection of the difficulties in performing clinical trials in this population, with high incidences of adverse events and hospitalization for coexisting illness, as well as the unpredictable availability of renal transplants. The main reasons for discontinuation of therapy were transplantation, adverse events, and study end points. It is possible that the withdrawal rate masks the potential benefit of statin therapy, although the high discontinuation rate is partly a consequence of the high event rate and is consistent with the findings of the 4D study.<sup>14,18</sup>

Increasingly, the benefits of statin therapy are attributed to pleiotropic effects that are independent of a lowering of the LDL cholesterol level, and they include improvements with respect to endothelial function and inflammation<sup>29</sup> and a reduction of the high-sensitivity C-reactive protein level. In the recent Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) (NCT00239681),<sup>10</sup> involving subjects without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels ( $\geq 2.0$  mg per liter), rosuvastatin reduced both the high-sensitivity C-reactive protein level (by 37%) and major cardiovascular events (by 44%). In contrast, in our trial, although high-sensitivity C-reactive protein levels were elevated at baseline (by 5.0 mg per liter) and were decreased by rosuvastatin, there was no reduction in cardiovascular events. This finding may reflect different causes of elevated high-sensitivity C-reactive protein levels in patients undergoing hemodialysis.

AURORA and 4D are not the only studies to show a lack of benefit of statin therapy in specific populations. Patients in the Controlled Ro-

suvastatin Multinational Trial in Heart Failure (CORONA) (NCT00206310)<sup>30</sup> and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure Study (GISSI-HF) (NCT00336336)<sup>31</sup> trial had heart failure and low ejection fractions. Like the patient population in our study, patients in these two trials had advanced disease associated with coexisting conditions and had significant reductions in lipid and high-sensitivity C-reactive protein levels with statin treatment, but no reduction in cardiovascular end points.

Safety concerns have limited the use of statin therapy in patients with renal disease.<sup>1,2</sup> We observed no increase in the incidence of muscle-related adverse events, rhabdomyolysis, or liver disease in the rosuvastatin group as compared with the placebo group. Five cases of rhabdomyolysis were reported during the trial (in two patients receiving placebo and in three patients receiving rosuvastatin). Concern has also been expressed about an excess risk of cancer related to statin therapy,<sup>32,33</sup> but no increase in the number of new cancer diagnoses was seen in our trial. In the 4D study,<sup>14,18</sup> atorvastatin was associated with an increased incidence of stroke, although the numbers were small. We found no significant effect of rosuvastatin on the incidence of stroke, but there was a marginal increase in hemorrhagic strokes in patients with diabetes who received rosuvastatin (12 events, vs. 2 events in patients with diabetes in the placebo group;  $P=0.07$ ), which is consistent with the findings of the 4D study.<sup>14,18</sup> Although concern was expressed about an increase in physician-reported cases of diabetes with rosuvastatin in the JUPITER trial,<sup>10</sup> we did not find an excess of new-onset diabetes.

In conclusion, the AURORA trial evaluated the effect of rosuvastatin on cardiovascular events in a population of patients with end-stage renal disease. Despite significantly reducing the levels of LDL cholesterol and high-sensitivity C-reactive protein, treatment with rosuvastatin was not associated with a reduction in the combined end point of myocardial infarction, stroke, or death from cardiovascular causes.

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#### APPENDIX

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