Rosuvastatin in Diabetic Hemodialysis Patients

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ABSTRACT

A randomized, placebo-controlled trial in diabetic patients receiving hemodialysis showed no effect of atorvastatin on a composite cardiovascular endpoint, but analysis of the component cardiac endpoints suggested that atorvastatin may significantly reduce risk. Because the AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial included patients with and without diabetes, we conducted a *post hoc* analysis to determine whether rosuvastatin might reduce the risk of cardiac events in diabetic patients receiving hemodialysis. Among the 731 participants with diabetes, traditional risk factors such as LDL-C, smoking, and BP did not associate with cardiac events (cardiac death and nonfatal myocardial infarction). At baseline, only age and high-sensitivity C-reactive protein were independent risk factors for cardiac events. Assignment to rosuvastatin associated with a nonsignificant 16.2% reduction in risk for the AURORA trial's composite primary endpoint of cardiac death, nonfatal MI, or fatal or nonfatal stroke (HR 0.84; 95% CI 0.65 to 1.07). There was no difference in overall stroke, but the rosuvastatin group had more hemorrhagic strokes than the placebo group (12 *versus* two strokes, respectively; HR, 5.21; 95% CI 1.17 to 23.27). Rosuvastatin treatment significantly reduced the rates of cardiac events by 32% among patients with diabetes (HR 0.68; 95% CI 0.51 to 0.90). In conclusion, among hemodialysis patients with diabetes mellitus, rosuvastatin might reduce the risk of fatal and nonfatal cardiac events.

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Primary and secondary prevention trials in patients with diabetes mellitus have documented substantial cardiovascular benefit from statin treatment.[1] In patients with diabetes mellitus and impaired renal function, a beneficial effect of statin treatment has also been reported.[2,3] In patients undergoing hemodialysis one observational study, where more than a third of the patients had a diagnosis of diabetes mellitus and another study where more than half of the patients had diabetes, the use of statins was associated with reduced cardiovascular-related deaths and all-cause mortality.[4,5] There are only two published randomized, controlled statin trials in hemodialysis patients. The German Diabetes and Dialysis Study (4D) in type 2 diabetic patients receiving hemodialysis showed that atorvastatin had no statistically significant effect on the composite primary endpoint of cardiovascular events.[6] In addition, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) included both

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diabetic ($n = 731$) and nondiabetic ($n = 1545$) patients, and reported no effect on a composite cardiovascular and cerebrovascular endpoint for the overall trial population.[7]

A protective effect of statin treatment on coronary endpoints has consistently been demonstrated in a variety of populations,[8] but not necessarily for a broader range of cardiovascular endpoints.[9–12] The choice of primary endpoints in prospective outcome trials is, to some extent, arbitrary.[13,14] The design of the 4D study originally included only cardiac (presumed coronary) events as the primary endpoint.[15] A late amendment during the final recruitment period of the trial added stroke as a component of the primary endpoint.[16,17] Separate analysis of cardiac endpoints in the 4D study showed a significant risk reduction of events in the atorvastatin arm as compared with placebo.[16] Based on these findings from the 4D we hypothesized, before unblinding of the AURORA trial, that rosuvastatin might reduce the risk of coronary events in diabetic patients. In this analysis we therefore examined the effect of rosuvastatin on time to first cardiac event (combined endpoint of cardiac death and nonfatal myocardial infarction) in patients with a diagnosis of diabetes mellitus.

RESULTS

Patients

During the recruitment period, from January 2003 through December 2004, a total of 731 out of 2776 (26.3%) patients with diabetes mellitus at inclusion were randomly assigned to double-blind treatment with rosuvastatin (388 patients) at a dose of 10 mg per day, or placebo (343 patients). Randomization was stratified by diabetic status. Of those enrolled, three patients were randomized incorrectly and were not included in the intention-to-treat (ITT) population. The diagnosis of diabetes was based on information from the investigators. The mean length of follow-up was 2.8 years (maximum 5.5 years); no patient was lost to follow-up. During the trial 432 patients died, 219 (56.4%) in the rosuvastatin arm, and 213 (62.1%) in the placebo arm.

The main reasons for premature withdrawal of study drug were death; 238 (117 who were receiving rosuvastatin and 121 who were receiving placebo), renal transplantation; 55 (33 who were receiving rosuvastatin and 22 who were receiving placebo), adverse events; 122 (61 who were receiving rosuvastatin and 61 who were receiving placebo). Whatever the reason for withdrawal (except death) all patients were followed for event until the end of the study, thus no patient was lost to follow-up.

The diabetic patients in the trial allocated to placebo or rosuvastatin were well matched at inclusion. The mean exposure to study medication was 2.4 (median 2.2) years.

Lipids and C-Reactive Protein Levels

Baseline lipid levels are shown in Table 1. After 3 months, low-density lipoprotein-cholesterol (LDL-C) was reduced by a mean of 1.1 ± 0.9 mmol/L (–38.5%, $P < 0.001$), in the rosuvastatin group and no change in the placebo group (Figure 1a). At 3 months, rosuvastatin also reduced total cholesterol by 1.2 mmol/L (–22.50%, $P < 0.0001$). Median high-sensitivity C-reactive protein (hsCRP) was elevated at baseline (Table 1) and decreased in the rosuvastatin group at 3 months by 10.9%; $P < 0.002$ *versus* placebo group (Figure 1d).

Clinical Endpoints

The composite cardiac endpoint (cardiac death or nonfatal MI) occurred in 85 diabetic patients allocated to rosuvastatin (7.8 events per 100 patient-yr) and in 104 diabetic patients

Table 1. Baseline characteristics of the patients

	Rosuvastatin (*n = 388*)	Placebo (*n = 343*)
Female gender, *n* (%)	135 (35)	117 (34)
Mean (SD) age, yr	65 (8.2)	65 (8.5)
Caucasian, *n* (%)	295 (76)	257 (75)
Mean (SD) body mass index, kg/m^2	26.6 (5.0)	26.9 (5.7)
Mean (SD) blood pressure, mmHg		
Systolic	140.3 (23.9)	141.3 (26.6)
Diastolic	75.6 (11.7)	74.4 (13.2)
Mean (SD)		
Calcium, mmol/L	2.3 (0.2)	2.3 (0.2)
Phosphate, mmol/L	1.8 (0.6)	1.8 (0.5)
Albumin, g/L	39.3 (3.5)	39.3 (3.6)
Hemoglobin, g/dl	11.6 (1.6)	11.4 (1.7)
Current smoker, *n* (%)	34 (9)	54 (16)
Mean (SD) years on hemodialysis	2.4 (2.0)	2.4 (2.1)
History of cardiovascular disease, *n* (%)	218 (56)	192 (56)
peripheral artery disease	100 (26)	94 (27)
chronic angina	105 (27)	82 (24)
myocardial infarction	62 (16)	42 (12)
ischemic cerebral vascular accident	55 (14)	38 (11)
coronary revascularization	35 (9)	28 (8)
carotid artery disease	28 (7)	23 (7)
transient ischemic attack	24 (6)	19 (6)
Baseline medication, *n* (%)		
ACE/ARB	169 (44)	153 (45)
Beta-blocker	150 (37)	105 (39)
Mean (SD) Lipid levels, mmol/l		
total cholesterol[a]	4.49 (1.15)	4.35 (1.09)
LDL-C[b]	2.51 (0.89)	2.43 (0.87)
HDL-C[c]	1.11 (0.38)	1.08 (0.38)
triglyceride[d]	1.90 (1.29)	1.85 (1.13)
Median (interquartile range) hsCRP, mg/L	5.02 (1.91–14.25)	5.51 (1.99–15.18)

[a]To convert to mg/dl, divide by 0.02586.
[b]To convert to mg/dl, divide by 0.02586.
[c]To convert to mg/dl, divide by 0.02586.
[d]To convert to mg/dl, divide by 0.01129.
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

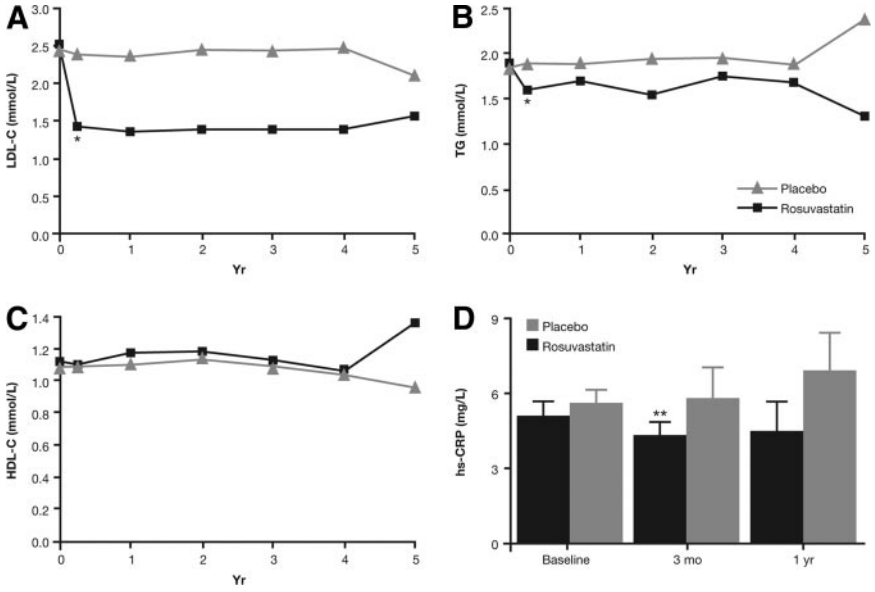

Figure 1. Patients randomized to rosuvastatin show a sustained reduction in LDL-cholesterol, triglycerides, and hsCRP levels. The figure shows mean levels of LDL-C (A), TG (B), HDL_C (C) and median (95% CI) levels of hs CRP (D) in subjects randomized to rosuvastatin or placebo. *$P < 0.0001$; **$P < 0.0002$ for between group comparison of the percentage change between baseline and three months.

allocated to placebo (10.8 events per 100 patient-yr), (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.51 to 0.90; $P = 0.008$), Figure 2. For the chosen *post hoc* composite cardiac endpoint the number needed to treat was 11.9 per 100 treated patients for 2.8 years.

For the primary endpoint chosen in the overall AURORA trial (cardiac death, nonfatal MI, fatal or nonfatal stroke),[7] there was a nonsignificant reduction of 16.2% for rosuvastatin in the diabetes subpopulation, (HR, 0.838; 95% CI, 0.654 to 1.074; $P = 0.163$). There was no difference in overall stroke incidence, 38 in the rosuvastatin group *versus* 20 in the placebo group (HR, 1.65; 95% CI, 0.96 to 2.83; $P = 0.07$) or fatal stroke 18 *versus* 11 (HR, 1.41; 95% CI, 0.67 to 2.99; $P = 0.37$), respectively. Although numerically small numbers, there was an increased incidence of hemorrhagic strokes in the treatment arm compared with placebo arm, 12 *versus* two respectively, (HR, 5.21; 95% CI, 1.17 to 23.27; $P = 0.031$). We also examined the treatment effect adjusted for β-blockers, angiotensin converting enzyme/angiotensin receptor blockers or sevelamer usage and serum calcium and phosphate levels. The treatment effect was unchanged when these covariates were included (data not shown). There were no significant interactions for mortality and primary composite endpoint by diabetic status $P = 0.725$, and $P = 0.155$ respectively, whereas the interaction for cardiac events was highly significant, $P = 0.007$.

There was no significant effect of rosuvastatin on time to death from any cause (HR, 0.86; 95% CI, 0.71 to 1.04.10; $P = 0.108$). The proportion of deaths attributable to cardiac disease was 34.8% in the rosuvastatin arm and 47.1% in the placebo arm. Of all cardiac events, 63.5% were fatal in the rosuvastatin arm and 71.2% in the placebo arm.

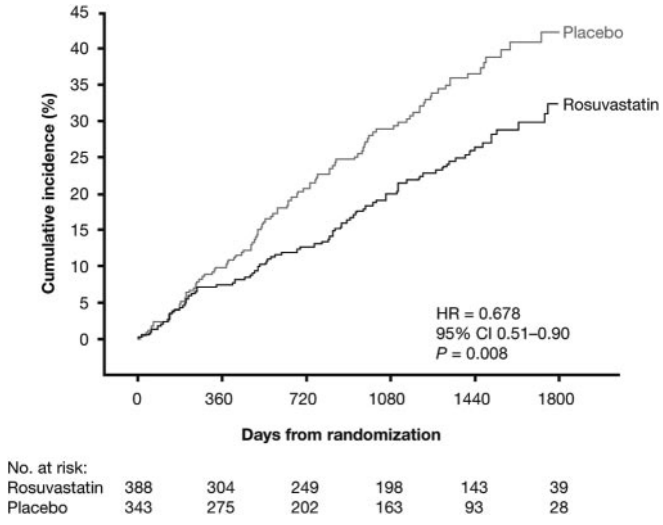

Figure 2. Patients randomized to rosuvastatin have a reduced composite cardiac event rate. The figure shows Kaplan-Meier curved for cardiac events by treatment group.

Adverse Events

As seen in previous studies in patients with end-stage renal disease, there was a high incidence of adverse and serious adverse events.[6,12] Adverse events were reported by 95% and 94% and serious adverse events by 77% and 79% of rosuvastatin- and placebo-treated patients, respectively. Most individuals reported multiple events with no significant difference between treatment groups (Table 2).

Table 2 Side effects

Subjects with adverse events, %	Rosuvastatin	Placebo	*P*-value
Any serious adverse events	77	79	0.69
Event leading to death	41	46	0.17
Event requiring permanent withdrawal	41	48	0.06
Any adverse event	95	94	0.09
Liver related adverse event	4.4	4.7	0.83
ALT >3 × ULN	0.5	0.9	0.66
Muscle-related adverse event	21	21	0.90
Creatine kinase >3 × ULN	0.8	0	1.0
Cancer-related	7.0	5.9	0.67
Renal-related	28	22	0.06
Rhabdomyolysis	0	0.3	1.0

ALT, alanine aminotransferase; ULN, upper limit of normal.

Relationship between Baseline Risk Factors and Cardiac Outcome

There was no significant relationship between baseline LDL-C levels (HR per unit change 1.032; 95% CI 0.869 to 1.225; $P = 0.72$) and the primary composite cardiac endpoint (Table 3). Age (HR 1.023; 95% CI 1.004 to 1.042; $P = 0.018$) and hsCRP, mg/L, (HR 1.190; 95% CI 1.053 to 1.345; $P = 0.005$) were the only significant independent risk factors for time to first cardiac event in diabetic patients (Table 3).

DISCUSSION

In this *post hoc* analysis of the AURORA trial we have shown that treatment with rosuvastatin in diabetic patients undergoing hemodialysis reduced atherosclerotic coronary events by 32%. This finding parallels the cardiac and definite cardiac events results in the 4D trial.[6] Thus, although 4D is interpreted as a negative outcome trial, atorvastatin had a beneficial effect on secondary analysis of cardiac endpoints with a risk reduction of 18% ($P = 0.03$). The reduction of cardiac events in diabetic patients observed both in AURORA and 4D show a similar magnitude of risk reduction to a wide range of statin-treated populations, including patients with diabetes and normal, or mildly impaired, renal function.[1,3,8] In patients reaching end-stage renal failure, and treated with dialysis or transplantation, there are only three randomized controlled statin trials.[6,7,12] Although most papers dealing with these issues state that more randomized trials are needed, it is unlikely that future resources will be allocated to further lipid-lowering trials in these populations.[18] It is, therefore, a necessity that the clinical community aggregate existing knowledge, not only from subgroups of randomized trials, but also from observational and registry data and put findings in context with the general knowledge and experience with lipid lowering by statins.

Although statin treatment failed to show an overall effect on the primary composite cardiovascular endpoint in AURORA and 4D,[6,7] a lack of effects on chosen primary composite endpoints in statin trials have also been demonstrated for other patient populations. In patients with chronic heart failure[9,10] and in patients with aortic stenosis,[11] lipid lowering was without effect. In populations where statins have failed to show a beneficial effect, the primary endpoints were often complex and consisted of different components for cardiovascular events of which a beneficial effect of statin therapy could be questioned. Thus, in both end-stage renal disease and advanced chronic heart failure, sudden death is much more common than nonfatal myocardial infarction. Moreover, whereas in patients with atherosclerotic coronary artery disease (such as 4S) sudden death is likely to be due to occlusive coronary disease, in patients with end-stage renal disease and advanced chronic kidney disease this presumption may not be appropriate. Many "sudden" cardiac deaths may be due to primary arrhythmia or heart failure, and thus may not be remediable to statin therapy. The choice of primary endpoints in outcome studies is—to some extent—arbitrary, and reflects the need to accumulate end points within a reasonable period of time, often by choosing a composite end-point with the implication that all components of the composite end-point share a common pathophysiology that is potentially modifiable by the chosen intervention.[13,19] One example is the inclusion of "coronary arrest with resuscitation" to fatal and nonfatal myocardial infarction as part of the composite endpoint in the Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) trial, contributing to a negative result.[20] In the Assessment of LEscol in Renal Transplantation (ALERT) trial, coronary intervention procedures were added to the original proposed primary endpoint, resulting in a nonsignificant finding for the core study,[12] although an extension of the trial demonstrated a benefit.[21] In the 4D trial, cerebrovascular events were added to the primary composite endpoint very late in the inclusion period,[17] making the primary endpoint nonsignificant. In AURORA, and in the chronic heart failure trials, the proportion of cardiac deaths due to coronary disease may be relatively small, and thus may have contributed to the negative results. The major issue that emerges from both 4D and AURORA, and from the chronic heart failure trials is the pathophysiology of sudden cardiac death, and the extent to which is it is dependent on atherosclerotic coronary disease. Our observation that statin therapy is associated with a reduction in the composite end-point of cardiac death in the diabetic subgroup, but not the whole, study population in AURORA might be taken to suggest that atherosclerotic coronary disease is a more common cause of sudden cardiac death in patients with diabetes compared with nondiabetic patients with end-stage renal disease.

There is a growing awareness of avoiding a too wide inclusion of endpoints in statin trials. The Study of Heart and Renal Protection (SHARP) steering committee narrowed the focus for the primary endpoint of the study by excluding previous endpoints of noncoronary coronary events and hemorrhagic stroke.[22]

Table 3. Risk factors for time to first cardiac event in diabetic patients by cox regression analysis adjusted for each other at baseline

	HR	95% CI		*P*-value
		Lower	Upper	
Age of randomization, years	1.023	1.004	1.042	0.018
Gender, male	1.215	0.869	1.697	0.254
LDL-C at baseline, mmol/L	1.032	0.869	1.225	0.718
Baseline body mass index, kg/m^2	0.998	0.969	1.028	0.883
Current smoker, yes	1.187	0.763	1.847	0.447
hsCRP at baseline, mg/L	1.190	1.053	1.345	0.005
Albumin at baseline, g/L	0.965	0.922	1.009	0.114
Duration of dialysis at baseline, years	0.958	0.887	1.035	0.280
Baseline systolic blood pressure, mmHg	0.997	0.991	1.003	0.312

Statin treatment has also lowered stroke incidence in most, but not all trials.[23] In the 4D study, the number of fatal strokes was significantly increased in the treatment arm compared with placebo arm. Due to a relatively low number of events this could have been a chance finding. In the diabetic populations in AURORA, there was no difference in the total or fatal strokes, but a significant although numerically small increase in hemorrhagic strokes. The yearly incidence of stroke in 4D was 3%, an incidence close to that reported from a United States Renal Data System dialysis population.[24] In the diabetic subpopulation in AURORA the yearly incidence was 2%. At inclusion in the 4D, the patients had a BP of 146/76 mmHg while our patients had 141/75 mmHg. A difference of 5 mmHg in systolic BP might explain why 4D patients had increased occurrence of fatal strokes.[24–26]

Diabetic patients in AURORA had lower levels of atherogenic lipids at inclusion than patients recruited to 4D, LDL-C 2.6 mmol/L (100 mg/dl) *versus* 3.2 mmol/L (126 mg/dl) respectively. Although the LDL-C lowering effect of statin therapy was remarkably similar in AURORA and 4D, 39% *versus* 42% at 3 months respectively, in 4D the LDL-C difference between the arms tended to dissipate at the end of the study; in contrast, there was a sustained LDL-C difference throughout the AURORA trial period. However, we did not see an association between LDL-C at baseline and coronary events. This is well recognized in hemodialysis patients with inflammation and an inverse relation between atherogenic lipids and cardiovascular risk has been described.[27,28] In our trial, rosuvastatin had a robust lowering effect of LDL-C and to a lesser degree an effect on hsCRP. The increased inflammation status in our patients could have masked an association between LDL-C and coronary events.

Hemodialysis is associated with an increased inflammation status.[29,30] hsCRP was elevated at baseline in our patients, the level of 5 mg/L was identical to the level of hsCRP at inclusion of patients into the 4D study.[29] In 4D, treatment with atorvastatin had a minimal effect on hsCRP level and this was modestly lowered by 10.9% in the treatment arm in our study. This contrasts to the CRP lowering effect of 37% by rosuvastatin in apparently healthy subjects with low LDL-C and elevated hsCRP of 4 mg/L at inclusion in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial in which statin treatment resulted in a 42% cardiovascular risk reduction.[31] Although there generally is an association between hsCRP and cardiovascular events,[32] this is apparently not so for genetic-related increases in CRP.[33,34] The CRP associated with the atherosclerotic process *per se* thus might differ from increases due to polymorphism in the CRP gene and the CRP increase associated with hemodialysis treatment. CRP in this population was a marker for coronary endpoints paralleling the findings in renal transplant populations.[35] Although rosuvastatin reduced hsCRP by 10.9%, it is likely that the major impact on cardiac events was due to the lipid-lowering effect of statin therapy.

There is underuse of statin treatment in patients with chronic kidney disease partly due to uncertainty of documented effected and partly due to fear of side effects.[36] In diabetic patients included in the AURORA trial, no excess of side effects in the statin arm was noted. We observed one rhabdomyolosis in the placebo arm and none in the rosuvastatin arm. There were few muscle- and liver-related adverse events, and they appeared equally in placebo and treatment arms. Concerns have been raised about increased risk of cancer in lipid-lowering trials,[11,37] but in the diabetes subpopulation examined, no increase in any type of incident cancer was observed in relation to statin treatment.

LDL-C lowering with statins has consistently decreased the occurrence of cardiovascular events in a broad range of patients.[8] Based on the magnitude of reduction of cardiac endpoints in the 4D trial, the lead authors have argued for administration of statins to diabetic patients receiving hemodialysis.[38] In this *post hoc* analyses of the diabetes subpopulation in the AURORA trial, the reduction of events of the primary endpoint was not statistically significant. Although there was no difference in overall stroke incidence or fatal stroke, there was an increase in hemorrhagic strokes. However, restricting the analysis to cardiac events we observed a significant reduction with rosuvastatin treatment.

CONCISE METHODS

Study Design

The design and methods of the AURORA trial (ClinicalTrials. gov number NCT00240331) have been reported in detail elsewhere.[39,40] Briefly, the AURORA trial was a prospective, randomized, multicenter trial involving 2776 patients, 50 to 80 years of age, who were undergoing maintenance hemodialysis with diverse causes for end-stage renal disease, including diabetes mellitus.

In this study, we analyzed cardiac events in diabetic patients randomized to receive rosuvastatin 10 mg daily or placebo, who were recruited to the trial. Of 731 diabetic patients, 388 were randomly allocated to rosuvastatin and 343 to placebo (Figure 3). Follow-up visits were performed 3 months after randomization and then every 6 months. Assessments included laboratory evaluations once yearly, pill counts, and potential adverse events. Blood samples were analyzed at a central laboratory for levels of lipids and hsCRP. A closeout visit occurred after study termination.

Endpoints

The endpoint in this study was the time to a first cardiac event (nonfatal myocardial infarction (MI) or cardiac death). Cardiac death included death due to myocardial infarction, heart failure and all sudden (presumed cardiac) death where there was no other obvious explanation. This definition is in common with the majority of statin outcome trials but differs from the SHARP study, where sudden death was not attributed to cardiac disease in the absence of evidence to support it. The cardiac events were reviewed and adjudicated by a blinded Clinical Endpoint Committee to ensure consistency of event diagnosis.

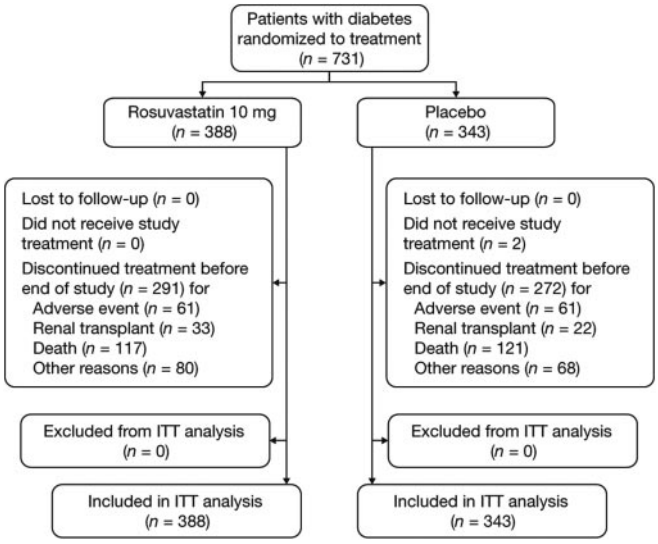

Figure 3. The disposition of patients is similar between randomizations groups.

Statistical Analysis

The *post hoc* analyses performed on the ITT population included all randomized diabetic patients ($n = 731$), and used an unadjusted Cox proportional-hazards model of time to first coronary event to compare study groups and calculate HR (SPSS software, version 16, SPSS Inc., Chicago, IL). Patients who received a transplant were not censored and were included in the analysis. The score test was used to calculate *P*-values. Test of interaction between the diabetic subgroup and treatment was done by testing for significance of the product term between treatment group and grouping by diabetes. A Cox model adjusted for baseline covariates clinically relevant to atherosclerotic coronary endpoints in hemodialysis populations; duration of dialysis, albumin concentration, systolic BP, hsCRP, smoking, body mass index, LDL-C, gender and age, was estimated to investigate their associations with outcomes. No other endpoint than non-CHD death was censored in the analysis of each endpoint.

For lipid and hsCRP data, analysis of covariance (ANCOVA), with baseline values as covariates, was used to test the difference in percentage change from baseline between rosuvastatin and placebo.

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DISCLOSURES

HH reports having served as a consultant to Novartis, AstraZeneca, and Schering-Plough, and having received lecture fees from Novartis and AstraZeneca, as well as having served as national coordinator for the SHARP study at Oxford University's Clinical Trial Service Unit. IH has received Steering committee fees from Merck Sharp & Dohme, Pfizer and Roche. RES reports having served as a consultant to and received lecture fees from AstraZeneca, Novartis, Merck Sharp & Dohme, and Pfizer. AGJ reports having served as a consultant to Novartis, AstraZeneca, and Wyeth, and having received lecture fees from Novartis and Astellas. FZ reports having served as a consultant to Servier, Novartis, ResMed, Daiichi-Sankyo, Pfizer, AstraZeneca, and Merck, and having received lecture fees from Pfizer, Daiichi-Sankyo, Servier, and Medtronic. GN declares no conflict of interest. BF reports having served as a consultant to AstraZeneca, Novartis, Roche, and Wyeth, having been paid lecture fees by Astellas, Novartis, and Roche, and having received grant support from Novartis, Roche, Merck/Schering-Plough, and Wyeth, as well as having served as national co-coordinator for the SHARP study at Oxford University's Clinical Trial Service Unit.

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