ORIGINAL ARTICLE

Atorvastatin in Patients with Type 2 Diabetes Mellitus Undergoing Hemodialysis

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ABSTRACT

BACKGROUND

Statins reduce the incidence of cardiovascular events in persons with type 2 diabetes mellitus. However, the benefit of statins in such patients receiving hemodialysis, who are at high risk for cardiovascular disease and death, has not been examined.

METHODS

We conducted a multicenter, randomized, double-blind, prospective study of 1255 subjects with type 2 diabetes mellitus receiving maintenance hemodialysis who were randomly assigned to receive 20 mg of atorvastatin per day or matching placebo. The primary end point was a composite of death from cardiac causes, nonfatal myocardial infarction, and stroke. Secondary end points included death from all causes and all cardiac and cerebrovascular events combined.

RESULTS

After four weeks of treatment, the median level of low-density lipoprotein cholesterol was reduced by 42 percent among patients receiving atorvastatin, and among those receiving placebo it was reduced by 1.3 percent. During a median follow-up period of four years, 469 patients (37 percent) reached the primary end point, of whom 226 were assigned to atorvastatin and 243 to placebo (relative risk, 0.92; 95 percent confidence interval, 0.77 to 1.10; P=0.37). Atorvastatin had no significant effect on the individual components of the primary end point, except that the relative risk of fatal stroke among those receiving the drug was 2.03 (95 percent confidence interval, 1.05 to 3.93; P=0.04). Atorvastatin reduced the rate of all cardiac events combined (relative risk, 0.82; 95 percent confidence interval, 0.68 to 0.99; P=0.03, nominally significant) but not all cerebrovascular events combined (relative risk, 1.12; 95 percent confidence interval, 0.81 to 1.55; P=0.49) or total mortality (relative risk, 0.93; 95 percent confidence interval, 0.79 to 1.08; P=0.33).

CONCLUSIONS

Atorvastatin had no statistically significant effect on the composite primary end point of cardiovascular death, nonfatal myocardial infarction, and stroke in patients with diabetes receiving hemodialysis.

Primary and secondary prevention trials, including those involving persons with diabetes mellitus, have documented substantial cardiovascular benefit from the administration of statins.[1,2] The recent Collaborative Atorvastatin Diabetes Study (CARDS) reported a decrease in deaths from cardiovascular causes among persons with type 2 diabetes mellitus in the absence of marked renal insufficiency.[3] There are no prospective data on the effects of statins in patients with end-stage renal disease with type 2 diabetes mellitus who are receiving hemodialysis, although type 2 diabetes is the most common diagnosis among patients at excessive risk of cardiovascular events[4] whose condition requires hemodialysis in both Germany[5] and the United States.[6] Abnormalities in serum lipid levels that are associated with renal disease rank high among the factors implicated in accelerated atherosclerosis.[7] However, not all the observational data on patients receiving hemodialysis link dyslipidemia with reduced rates of survival; indeed, opposite trends have been noted.[8] An observational retrospective analysis of patients receiving hemodialysis, the U.S. Renal Data System Morbidity and Mortality Study, Wave 2,[9] reported that the risk of death from cardiovascular causes was decreased by 36 percent among patients receiving statins, as compared with those who did not receive statins. There has been concern about the side effects of statins in patients receiving hemodialysis,[10] but data from small cohorts appeared to be reassuring.[11] The present investigator-initiated, prospective, randomized, placebo-controlled study of patients with type 2 diabetes mellitus receiving hemodialysis was designed to answer these questions.

METHODS

STUDY DESIGN

Subjects with type 2 diabetes mellitus 18 to 80 years of age who had been receiving maintenance hemodialysis for less than two years were enrolled at 178 centers in Germany. Exclusion criteria included levels of fasting serum low-density lipoprotein (LDL) cholesterol of less than 80 mg per deciliter (2.1 mmol per liter) or more than 190 mg per deciliter (4.9 mmol per liter), triglyceride levels greater than 1000 mg per deciliter (11.3 mmol per liter); liver-function values more than three times the upper limit of normal or equal to those in patients with symptomatic hepatobiliary cholestatic disease; hematopoietic disease or systemic disease unrelated to end-stage renal disease; vascular intervention, congestive heart failure, or myocardial infarction within the three months preceding the period of enrollment; unsuccessful kidney transplantation; and hypertension resistant to therapy (i.e., systolic blood pressure continuously greater than 200 mm Hg or diastolic blood pressure greater than 110 mm Hg). On enrollment, lipid-lowering medications were discontinued, and patients received placebo during the four-week run-in phase of the study. Thereafter, eligible patients were randomly assigned to double-blind treatment with either atorvastatin at a dose of 20 mg once daily or matching placebo. Data were recorded at four weeks and then every six months. The protocol was approved by the ethics committee at the coordinating center and the 29 regional institutional review boards. Specifically, the ethical implications of the inclusion of a placebo group — that is, of not providing lipid-lowering medications to those randomly assigned to the control group — were taken into account and considered acceptable. Written informed consent was obtained from all patients.

Academic investigators led, managed, and coordinated the study. The principal investigators wrote the protocol and prepared the manuscript. The data were monitored and collected by two contract research organizations supported by Pfizer, one of which (Datamap) holds the data. A university-based, independent statistician performed the statistical analyses. The plan for the statistical analysis was completed before the database was locked and unblinded.

A computer-generated randomization code was prepared by a central Pfizer unit that was independent of local study personnel. Medication was prepackaged on the basis of a block size of four subjects at each center. Each consecutive subject was given the next consecutive randomization number, and eligible patients were assigned in a 1:1 ratio to receive the study drug or placebo. Lipid levels measured after randomization were not released to the clinical sites. If LDL cholesterol levels fell below 50 mg per deciliter (1.3 mmol per liter), the dose of atorvastatin was reduced to 10 mg per day. To maintain blinding, a randomly selected subject from the placebo group received an identical dose reduction. One person in the central laboratory who had access to the randomization code controlled the changes in dose. After a patient reached a primary end point, the study drug could be replaced by treatment with

an active statin. Details of the study design have been described previously.[12,13]

END POINTS

The study end points and serious adverse events were continuously monitored and reported to the contract research organization. Every end point was adjudicated by three members of the end-point committee, on the basis of predefined criteria that are part of the study protocol. All analyses of primary and secondary end points were based on the classification by the end-point committee that was agreed on by consensus or majority vote. All committee members were blinded to the treatment assignments until August 13, 2004. The primary end point was a composite of death from cardiac causes, fatal stroke, nonfatal myocardial infarction, or nonfatal stroke, whichever occurred first. Only one event per subject was included in the analysis. Myocardial infarction was diagnosed when two of the following three criteria were met: typical symptoms; elevated levels of cardiac enzymes (i.e., a level of creatine kinase MB above 5 percent of the total level of creatine kinase, a level of lactic dehydrogenase 1.5 times the upper limit of normal, or a level of troponin T greater than 2 ng per milliliter); or diagnostic changes on the electrocardiogram. A resting electrocardiogram was recorded every six months and evaluated by independent cardiologists from the electrocardiographic monitoring board, according to the Minnesota classification system for the electrocardiogram (codes 1-1-1 through 9-2 for QRS-complex, ST-segment, or T-wave changes). An electrocardiogram that documented silent myocardial infarction was considered evidence of a primary end point.

Stroke was defined as a neurologic deficit lasting longer than 24 hours. Computed tomographic or magnetic resonance imaging of the brain was recommended and available in all but 16 cases. Death from cardiac causes comprised fatal myocardial infarction (death within 28 days after a myocardial infarction), sudden death, death due to congestive heart failure, death due to coronary heart disease during or within 28 days after an intervention, and all other deaths ascribed to coronary heart disease. Patients who died unexpectedly and did not present with a potassium level greater than 7.5 mmol per liter before the start of the three most recent sessions of hemodialysis were considered to have had sudden death from cardiac causes.

Secondary end points included death from all causes, all cardiac events combined, and all cerebrovascular events combined. Death from any cause other than cardiac disease or cerebrovascular disease was treated as a competing risk.

A central laboratory performed all the analyses. LDL cholesterol was measured directly by agarose-gel electrophoresis with subsequent enzymatic staining for cholesterol with the use of the rapid electrophoresis system (Helena Diagnostika). This method produces more accurate measurements of LDL cholesterol than ultracentrifugation and precipitation combined in samples with elevated triglyceride concentrations.[14]

STATISTICAL ANALYSIS

The study was designed to have 90 percent power to detect a 27 percent reduction in the incidence of the composite primary end point at an alpha level of 0.05 in a two-sided test, adjusted for one preplanned interim analysis according to an alpha-spending function based on the O'Brien–Fleming method, yielding a nominal level of significance for the final analysis of 0.045.[15] The alpha-spending function would have allowed for additional interim analyses, if necessary. For the study to have this level of power, at least 424 primary end points had to occur (event-driven analysis), requiring the randomization of at least 1200 patients. This calculation was based on observational studies.[16,17] The results were assessed in an intention-to-treat analysis. The primary end points were evaluated according to time-to-event analysis. Death from other causes was treated as a competing event, and for patients who died from other causes, follow-up was censored as of the date of death.[18] Times to an event for patients without a primary end point or competing event were treated as censored and were calculated as the time from randomization to the date of the last contact.

Cumulative incidence and Kaplan–Meier curves were used only to show the survival curves within the treatment groups and to calculate the corresponding survival probabilities. The Cox proportional-hazards model was used to estimate the multivariate relative risks of the primary and secondary end points with corresponding 95 percent confidence intervals. Adjustments were made for sex, age, and baseline status with respect to coronary heart disease. Unless otherwise stated, the baseline lipid and safety laboratory value was defined as the last value measured during the run-in period. The baseline

data were analyzed with the use of standard descriptive statistics.

RESULTS

PATIENTS

A total of 1255 subjects were randomly assigned to double-blind treatment with either atorvastatin (619) or placebo (636) between March 1998 and October 2002 and were followed until their final visit in March 2004 (Fig. 1). The two groups of patients were well matched with respect to baseline characteristics and concomitant therapy (Table 1). Nineteen percent of the patients had taken statins before entering the study. The mean length of follow-up was 3.96 years in the atorvastatin group and 3.91 years in the placebo group (median, 4.0 and 4.08 years, respectively).

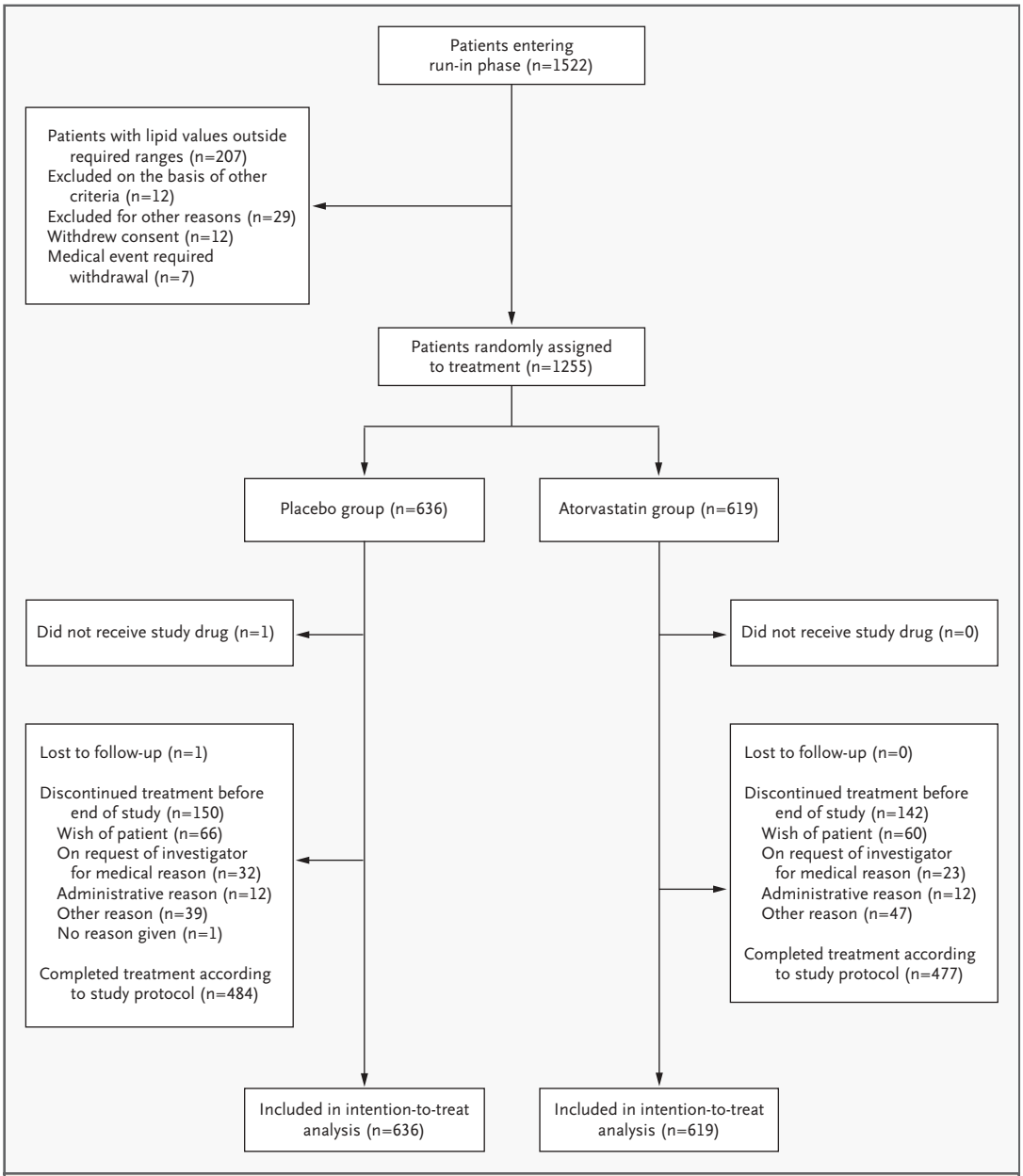

Figure 1. Numbers of Patients Who Entered the Study, Were Assigned to a Study Group, and Completed the Protocol.

Table 1. Baseline Characteristics of Patients in the Placebo and Atorvastatin Groups.*

Characteristic	Placebo Group (N=636)	Atorvastatin Group (N=619)
Age — yr	65.7±8.3	65.7±8.3
Female sex — no. (%)	292 (45.9)	286 (46.2)
Known duration of diabetes — yr	18.7±8.8	17.5±8.7
Time receiving dialysis — mo	8.4±6.9	8.2±6.9
Blood pressure — mm Hg		
Systolic	145±22	146±22
Diastolic	76±11	76±11
Current smoker — no. (%)	58 (9.1)	50 (8.1)
Former smoker — no. (%)	188 (29.6)	211 (34.1)
History of cardiovascular disease and intervention (%)†		
Myocardial infarction	17.3	17.9
Myocardial infarction, either CABG or PTCA, or coronary heart disease‡	28.1	30.7
Myocardial infarction or either CABG or PTCA	22.5	23.7
CABG or PTCA	11.8	14.2
Congestive heart failure§	34.9	35.9
Cardiac-valve disorder	7.7	7.3
Peripheral vascular disease	43.6	45.7
Stroke or TIA	18.2	17.4
Body-mass index¶	27.5±5.0	27.6±4.6
Hemoglobin — g/dl	10.9±1.4	10.9±1.3
Glycosylated hemoglobin — %	6.8±1.3	6.7±1.2
Albumin — g/liter	3.8±0.3	3.8±0.3
Calcium — mg/dl	9.2±0.8	9.2±0.8
Phosphate — mg/dl	6.1±1.6	6.0±1.6

LIPID LEVELS

At randomization, the median level of LDL cholesterol was 121 mg per deciliter (3.13 mmol per liter) in the atorvastatin group and 125 mg per deciliter (3.23 mmol per liter) in the placebo group. After four weeks, in the atorvastatin group, the median level of LDL cholesterol was 72 mg per deciliter (1.86 mmol per liter; median change from baseline, −42 percent). In the placebo group, the level of LDL cholesterol remained essentially unchanged (120 mg per deciliter [3.10 mmol per liter]; median change from baseline, −1.3 percent) (Fig. 2).

PRIMARY OUTCOMES

The cumulative incidence of the primary end point was 12.6 percent at one year and 31.9 percent at three years in the atorvastatin group, as compared with 11.2 percent and 30.5 percent, respectively, in the placebo group (Fig. 3). The relative risk reduction afforded by active treatment, as compared with placebo, was 8 percent (hazard ratio, 0.92; 95 percent confidence interval, 0.77 to 1.10; P=0.37). A similar number of patients died from cardiac causes in the two groups (20 percent in the atorvastatin group and 23 percent in the placebo group; relative risk, 0.81; 95 percent confidence interval, 0.64 to 1.03; P=0.08). Eleven percent (70) of the patients in the atorvastatin group had a nonfatal myocardial infarction, as compared with 12 percent (79) of those in the placebo group (relative risk, 0.88; 95 percent confidence interval, 0.64 to 1.21; P=0.42). More patients (27) died of stroke in the

Table 1. (Continued.)

Characteristic	Placebo Group (N=636)	Atorvastatin Group (N=619)
Lipid values — mg/dl		
Total cholesterol	220±42	218±43
LDL cholesterol	127±30	125±29
HDL cholesterol	36±14	36±13
Triglycerides	267±168	261±165
LDL cholesterol levels — no. (%)		
<100	120 (18.9)	122 (19.7)
100–129	241 (37.9)	252 (40.7)
130–159	186 (29.2)	169 (27.3)
≥160	89 (14.0)	76 (12.3)
Antihypertensive medication — %		
ACE inhibitors	47	49
Angiotensin II–receptor antagonists	12	12
Beta-blockers	38	37
Calcium antagonists	40	41
Antiplatelet therapy	50	54
Use of erythropoietin — %	81	81
Dose per wk — IU	6.225	6.202

* Plus–minus values are means ±SD. To convert hemoglobin values to millimoles per liter, multiply by 0.6206. To convert values for calcium to millimoles per liter, multiply by 0.250. To convert values for phosphate to millimoles per liter, multiply by 0.3229. To convert values for total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. CABG denotes coronary-artery bypass grafting, PTCA percutaneous transluminal coronary angioplasty, TIA transient ischemic attack, and ACE angiotensin-converting enzyme.
† Types of disease and intervention are not mutually exclusive.
‡ Disease was documented by coronary angiography.
§ Most of the patients had New York Heart Association class II heart failure.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.

atorvastatin group than in the placebo group (13; relative risk, 2.03; 95 percent confidence interval, 1.05 to 3.93; P=0.04). Nonfatal stroke was distributed equally in the two groups (33 patients in the atorvastatin group and 32 patients in the placebo group; relative risk, 1.04; 95 percent confidence interval, 0.64 to 1.69; P=0.89) (Table 2).

SECONDARY OUTCOMES

Death from all causes was similar in the two groups (48 percent in the atorvastatin group, as compared with 50 percent in the placebo group; relative risk, 0.93; 95 percent confidence interval, 0.79 to 1.08; P=0.33). Of nominal significance, the risk of all cardiac events combined was reduced by 18 percent in the atorvastatin group, with a total event rate of 33 percent, as compared with 39 percent in the placebo group (relative risk, 0.82; 95 percent confidence interval, 0.68 to 0.99; P=0.03) (Table 2). This result was driven mainly by differences in the rates of coronary-artery bypass grafting and percutaneous transluminal coronary angioplasty. The incidence of all cerebrovascular events combined in the atorvastatin group was not different from that in the placebo group (relative risk, 1.12; 95 percent confidence interval, 0.81 to 1.55; P=0.49) (Table 2).

ADHERENCE, TOLERABILITY, AND ADVERSE EVENTS

The mean (±SD) duration of exposure to placebo was 27.2±17.9 months (range, 0.03 to 70.2), and to atorvastatin, 28.5±18.6 months (range, 0.07 to

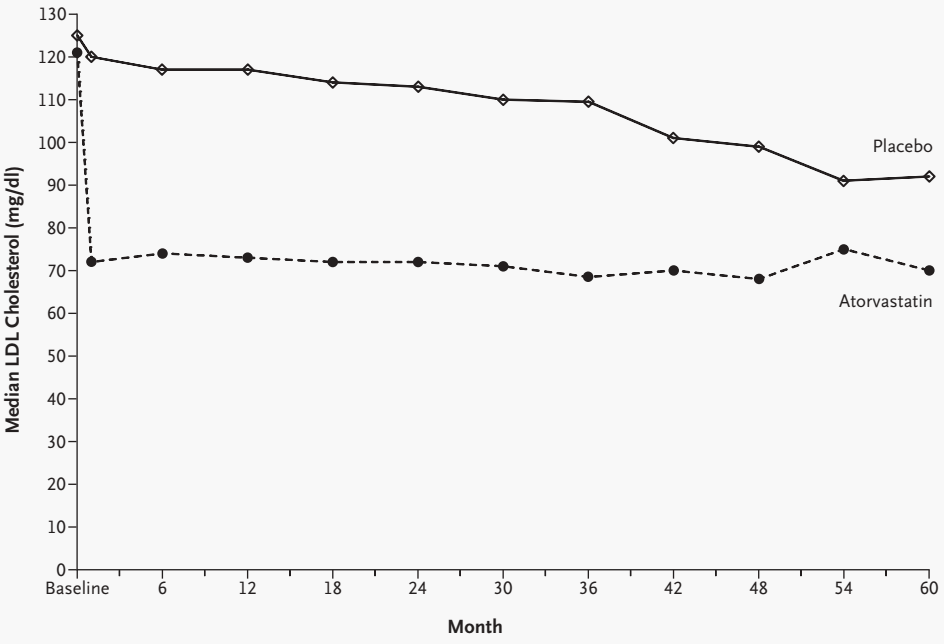

Figure 2. Median Level of Low-Density Lipoprotein (LDL) Cholesterol from Baseline to the End of the Study.
To convert values for LDL cholesterol to millimoles per liter, multiply by 0.02586.

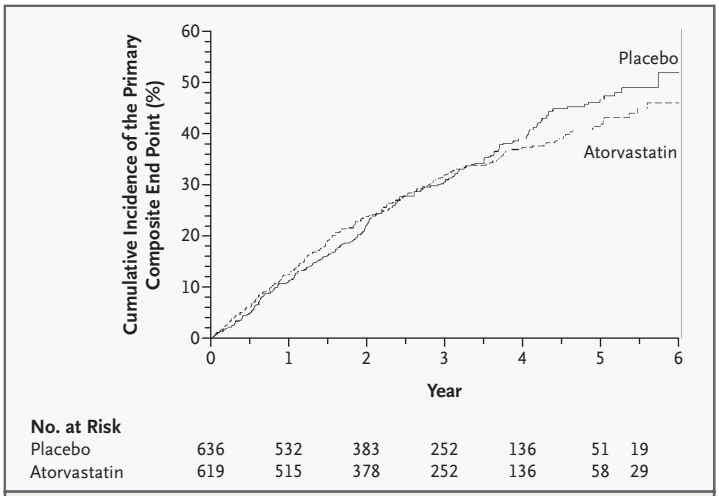

Figure 3. Estimated Cumulative Incidence of the Composite Primary End Point.

69.9). In the placebo group, 82 percent of patients took the study medication without interruption, and in the atorvastatin group, 80 percent of patients did so. The average number of days that treatment was interrupted was 12±36 in the placebo group and 13±40 in the atorvastatin group. During treatment, the dose of atorvastatin or matching placebo was halved when administered to 190 patients (15 percent). During the study, 98 patients in the placebo group (15 percent) began nonstudy statins, as compared with 10 percent of those in the atorvastatin group. The proportion of patients who continued to receive the study drug at one and two years, expressed as a percentage of those who remained alive and free of a primary event, was 74 percent (459 patients) and 51 percent (317 patients), respectively, in the atorvastatin group and 74 percent (469 patients) and 48 percent (303 patients), respectively, in the placebo group.

Table 2. Rates of Primary and Secondary End Points.*

End Point	Placebo Group (N=636)	Atorvastatin Group (N=619)	RR (95% CI)	P Value
	no. (%)			
Primary	243 (38)	226 (37)	0.92 (0.77–1.10)	0.37
Death from cardiac causes	149 (23)	121 (20)	0.81 (0.64–1.03)	0.08
Sudden death	83 (13)	77 (12)		
Fatal myocardial infarction	33 (5)	23 (4)		
Death due to congestive heart failure	24 (4)	17 (3)		
Death after interventions to treat coronary heart disease	4 (0.6)	3 (0.5)		
Other death due to coronary heart disease	5 (0.8)	1 (0.2)		
Nonfatal myocardial infarction	79 (12)	70 (11)	0.88 (0.64–1.21)	0.42
Silent	50 (8)	41 (7)		
Nonsilent	35 (6)	33 (5)		
Fatal stroke	13 (2)	27 (4)	2.03 (1.05–3.93)	0.04
Ischemic	7 (1)	18 (3)		
Hemorrhagic	5 (0.8)	3 (0.5)		
Other (not classified)	1 (0.2)	6 (1)		
Nonfatal stroke	32 (5)	33 (5)	1.04 (0.64–1.69)	0.89
Secondary				
All cardiac events combined	246 (39)	205 (33)	0.82 (0.68–0.99)	0.03
Death from cardiac causes	149 (23)	121 (20)		
Nonfatal myocardial infarction	79 (12)	70 (11)		
PTCA	45 (7)	34 (5)		
CABG	30 (5)	24 (4)		
Other interventions to treat coronary heart disease	0	1 (0.2)		
All cerebrovascular events combined	70 (11)	79 (13)	1.12 (0.81–1.55)	0.49
Stroke	44 (7)	59 (10)	1.33 (0.90–1.97)	0.15
Ischemic	33 (5)	47 (8)		
Hemorrhagic	8 (1)	5 (1)		
Other (not classified)	6 (1)	10 (2)		
TIA or PRIND	31 (5)	26 (4)		
Death from all causes	320 (50)	297 (48)	0.93 (0.79–1.08)	0.33
Death from causes other than cardiovascular or cerebrovascular disease	158 (25)	149 (24)	0.95 (0.76–1.18)	0.62
Fatal infection	68 (11)	60 (10)		
Fatal cancer	19 (3)	17 (3)		
Other	71 (11)	72 (12)		

* The total number of patients reaching the primary end point does not equal the sum of the numbers for each component of the primary end point, because only the first event per patient is included in the primary end point. Thus, a patient who had a stroke and a myocardial infarction was counted once in the primary end point, but appears in the separate totals for stroke and myocardial infarction. RR denotes relative risk, CI confidence interval, CABG coronary-artery bypass grafting, TIA transient ischemic attack, and PRIND prolonged reversible ischemic neurologic deficit.

Patients receiving hemodialysis generally have many adverse and serious adverse events (Table 3), but no cases of rhabdomyolysis or severe liver disease were detected in either group. The study medication was discontinued by the investigators in one patient receiving placebo because of a report of myalgia in combination with elevated creatine kinase levels.

DISCUSSION

We examined the value of lowering the level of LDL cholesterol in patients receiving hemodialysis who have type 2 diabetes mellitus, among whom the average annual incidence of myocardial infarction or death from coronary heart disease is 8.2 percent. This incidence rate exceeds the average annual rates of major coronary events that were reported in the placebo group of the Scandinavian Simvastatin Survival Study (6.6 percent) and is the highest rate of cardiovascular events in a long-term prospective trial of statin therapy.[19] Atorvastatin (20 mg daily) lowered LDL cholesterol levels by 42 percent, to 72 mg per deciliter, which is close to the target value of 70 mg per deciliter (1.81 mmol per liter) recommended by the Third Adult Treatment Panel of the National Cholesterol Education Program for persons at very high risk of cardiovascular disease. Despite the high rate of cardiovascular events and the pronounced LDL cholesterol–lowering activity of atorvastatin, a significant reduction in the incidence of the composite primary end point was not achieved.

Of nominal significance, more cases of fatal stroke occurred in the atorvastatin group (27) than in the placebo group (13). This finding is unexplained and could be a chance finding, particularly in view of the data from CARDS, which indicate that atorvastatin lowers the incidence of stroke.[3] That study reported a relative risk for stroke of 0.52 (95 percent confidence interval, 0.31 to 0.89) in persons with type 2 diabetes mellitus who were taking atorvastatin. The rate of fatal and nonfatal stroke decreased from 2.8 to 1.5 percent (39 vs. 21 patients), whereas in the present study, it increased from 7.0 to 9.7 percent (44 vs. 59 patients).

The complete absence of a stroke benefit and the increase in fatal strokes contribute considerably to the finding that the treatment effect on the primary end point was less than predicted. A possible reason for the unexpected results with regard to the primary end point might be related to the LDL cholesterol concentration at baseline. In general, the absolute risk reduction attained by lowering LDL cholesterol by a given percentage is less when pretreatment concentrations are low than when they are high.[20] The baseline levels of LDL cholesterol among patients in our study were, on average, above the target (126 mg per deciliter [3.25 mmol per liter]). Given the log-linear relation between LDL cholesterol and coronary heart disease, reducing levels of LDL cholesterol by 40 percent from a starting level of 125 mg per deciliter would result in an approximate relative risk reduction of 30 percent or more.[20] This estimate is empirically supported by the results of CARDS[3] and the British Heart Protection Study[21] and is very close to our initial assumption of a risk reduction of 27 percent.

Since we did not fully achieve this benefit, we speculate that the pathogenesis of vascular events in patients with diabetes mellitus who are receiving hemodialysis may, at least in part, be different from that in patients without end-stage renal disease. Subgroup analyses showed no difference in outcome for any LDL cholesterol level or patients with and patients without cardiovascular disease. Interestingly, there was a continuous decrease in LDL

Table 3. Adverse Events.*

Event	Placebo Group	Atorvastatin Group
	no. of events	
Total	2255	2276
Serious events	1060	1073
Events requiring hospitalization	942	949
Events requiring discontinuation of study drug	52	73
Drug-related serious events	1	1
Diagnosis of cancer	44	39
Severe hyperkalemia	9	3
Severe hypoglycemia	4	6
Ventricular fibrillation or tachycardia	13	7
Myalgia or myopathy	5	7
Creatine kinase level		
3 to 5 times the upper limit of normal	3	11
>5 to 10 times the upper limit of normal	1	1
Alanine aminotransferase level >4 times the upper limit of normal	1	5

* Some patients had more than one event.

cholesterol levels over time among patients in both groups. Some malnutrition cannot be ruled out during the course of the study, although there was no decrease in the body-mass index.

The extremely high rate of death from cardiovascular causes among patients receiving dialysis[22] is explained by more than the traditional coronary risk factors. Apart from the presence of many aggravating coexisting factors, such as inappropriate left ventricular hypertrophy, cardiac fibrosis, cardiac microvessel disease,[23] and sympathetic overactivity, among others, there are also indications that atherosclerosis itself is promoted by risk factors other than the traditional cardiovascular risk factors.[24,25] The most plausible explanation for the absence of a significant effect on mortality from cardiac causes and cardiac end points in this study is the presence of additional pathogenetic pathways in cardiovascular disease. The dose of atorvastatin in the present study was 20 mg, which is lower than the high dose used in a recent study by LaRosa et al.[26] in which intensive lipid-lowering therapy with atorvastatin at a dose of 80 mg per day was more effective than a dose of 10 mg per day in patients with stable coronary heart disease. However, whether such an advantage would accrue if patients with type 2 diabetes who were receiving dialysis were given a higher dose of atorvastatin is unknown.

Several important conclusions can be drawn from this study. First, we showed that it is difficult to rely on uncontrolled observational studies that show substantial advantages of statins in the treatment of patients receiving hemodialysis.[9,27] Second, and more important, is the conclusion that the benefit of atorvastatin is limited when intervention with statins is postponed until patients have reached end-stage renal disease. Subgroup analyses of major statin-intervention trials documented a cardiovascular benefit in patients with chronic kidney disease (stages 1, 2, and 3 according to the classification of the National Kidney Foundation).[28,29] According to CARDS, lowering LDL cholesterol levels early during the clinical course of type 2 diabetes mellitus is of benefit.[3] Third, there was no excess of serious adverse events; specifically, no cases of rhabdomyolysis occurred, but we found a nominally significant increase in fatal stroke.

We conclude that in persons with type 2 diabetes mellitus who are receiving maintenance hemodialysis and have LDL cholesterol values between 80 and 190 mg per deciliter, routine treatment with a statin to reduce the primary composite end point of death from cardiac causes, myocardial infarction, and stroke is not warranted. The initiation of lipid-lowering therapy in patients with type 2 diabetes mellitus who already have end-stage renal disease may come too late to translate into consistent improvement of the cardiovascular outcome.

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Dr. Wanner reports having received consulting fees and lecture fees from Genzyme; Dr. März, consulting fees, lecture fees, a research grant and stock options from Pfizer; and Dr. Mann, lecture fees from Aventis, Roche, and Janssen Cilag. Dr. Ritz is a member of the safety board of a trial sponsored by AstraZeneca and reports having received consulting fees from the company.

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APPENDIX

The following investigators and research coordinators participated in the study known as the 4D Study (a complete list is available at www.uni-wuerzburg.de/ nephrologie): *Steering committee:* C. Wanner, E. Ritz. *Clinical coordinator:* V. Krane. *Medical end-point monitors:* Z. Ülger, F. Swoboda. *Data and safety monitoring committee:* M. Wehling (chair), E. Keller (deceased), M. Schumacher, T. Eschenhagen. *Event committee:* J. Mann (chair), J. Bommer, P. Schanzenbächer, P. Schollmeyer, M. Schartl. *Electrocardiography monitoring board:* F. Heinrich, H. Mörl. *Biometric and statistical analysis:* University of Freiburg, M. Olschewski. *Central laboratory (lipid and safety core laboratory):* University of Freiburg, W. März. *Contract research organization:* Kendle, Munich, S. Reichmuth (*Project manager*); Datamap, Freiburg, J. Lilienthal. *Sponsor:* Pfizer, Karlsruhe, G. Ruf, B. Rauer (*Project manager*).

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