Efficacy and Safety of Atorvastatin in the Prevention of Cardiovascular End Points in Subjects With Type 2 Diabetes

The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN)

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OBJECTIVE — Cardiovascular disease (CVD) risk is increased in type 2 diabetes. The purpose of this study was to assess the effect of 10 mg of atorvastatin versus placebo on CVD prevention in subjects with type 2 diabetes and LDL cholesterol levels below contemporary guideline targets.

RESEARCH DESIGN AND METHODS — Subjects were randomly assigned to receive 10 mg of atorvastatin or placebo in a 4-year, double-blind, parallel-group study. The composite primary end point comprised cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, recanalization, coronary artery bypass surgery, resuscitated cardiac arrest, and worsening or unstable angina requiring hospitalization.

RESULTS — A total of 2,410 subjects with type 2 diabetes were randomized. Mean LDL cholesterol reduction in the atorvastatin group over 4 years was 29% versus placebo ($P < 0.0001$). When we compared atorvastatin versus placebo, composite primary end point rates were 13.7 and 15.0%, respectively (hazard ratio 0.90 [95% CI 0.73–1.12]). In the subset of 1,905 subjects without prior myocardial infarction or interventional procedure, 10.4% of atorvastatin- and 10.8% of placebo-treated subjects experienced a primary end point (0.97 [0.74–1.28]). In the 505 subjects with prior myocardial infarction or interventional procedure, 26.2% of atorvastatin- and 30.8% of placebo-treated subjects experienced a primary end point (0.82 [0.59–1.15]). Relative risk reductions in fatal and nonfatal myocardial infarction were 27% overall ($P = 0.10$) and 19% ($P = 0.41$) and 36% ($P = 0.11$) for subjects without and with prior myocardial infarction or interventional procedure, respectively.

CONCLUSIONS — Composite end point reductions were not statistically significant. This result may relate to the overall study design, the types of subjects recruited, the nature of the primary end point, and the protocol changes required because of changing treatment guidelines. For these reasons, the results of the Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) did not confirm the benefit of therapy but do not detract from the imperative that the majority of diabetic patients are at risk of coronary heart disease and deserve LDL cholesterol lowering to the currently recommended targets.

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Abbreviations: ALLHAT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ASPEN, Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; CVD, cardiovascular disease; DSMB, Data and Safety Monitoring Board; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes; ITT, intent-to-treat; NCEP, National Cholesterol Education Program.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Individuals with type 2 diabetes without prior myocardial infarction have been shown to have a risk of myocardial infarction as high as that of nondiabetic individuals with previous myocardial infarction in some (1–4) but not all studies (5–8). Differences in the risk of cardiovascular disease (CVD) associated with type 2 diabetes may be related to the severity of associated risk factors, such as abnormal lipoprotein profile, obesity, metabolic syndrome, microvascular inflammation, blood pressure, and impaired renal function (9). Statin treatment reduces the risk of cardiovascular events compared with placebo in type 2 diabetic subjects both with and without vascular disease (10–16).

The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus (ASPEN) investigated the potential cardiovascular benefit of 10 mg of atorvastatin in a cohort consisting entirely of individuals with type 2 diabetes, with and without prior myocardial infarction or interventional procedure, and LDL cholesterol levels below contemporary guideline targets.

RESEARCH DESIGN AND METHODS

— Subjects were recruited between 1996 and 1999 at 70 centers in 14 countries (Australia, Austria, Canada, Finland, France, Germany, Italy, the Netherlands, New Zealand, Norway, South Africa, Spain, Switzerland, and the U.S.). Subjects were instructed in the National Cholesterol Education Program (NCEP) Step 1 or similar diet.

Male and female subjects, aged 40–75 years, were eligible for inclusion if they had type 2 diabetes by the World

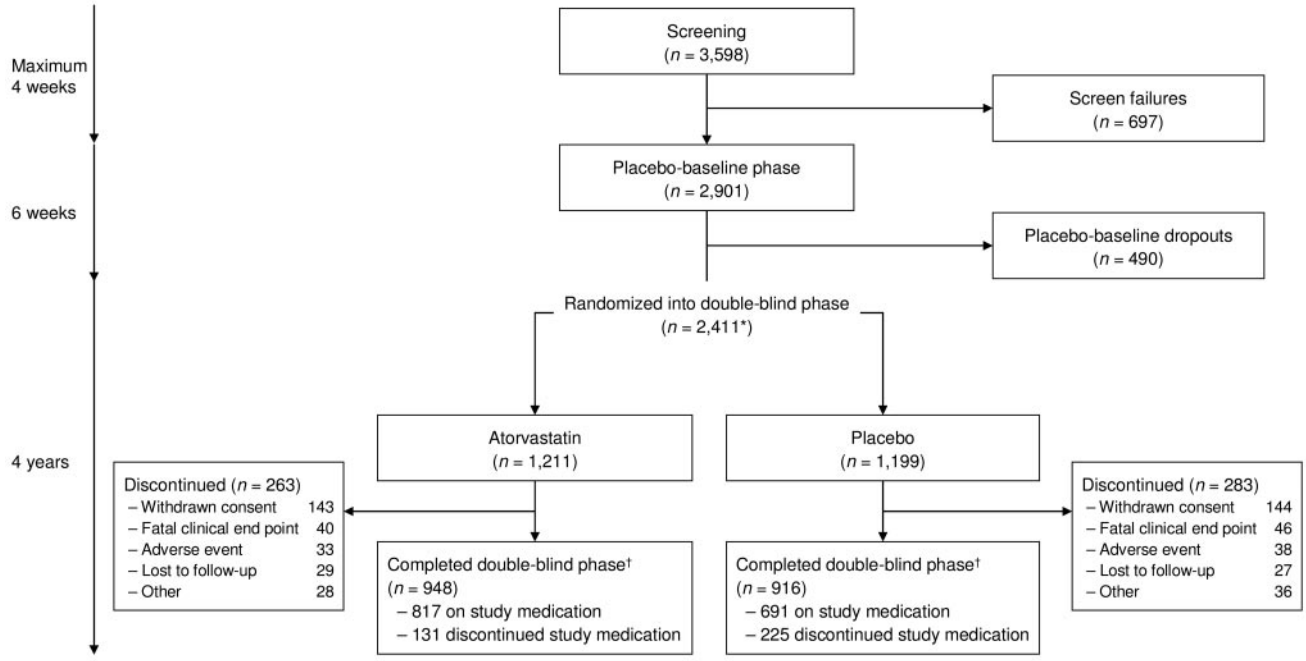

Figure 1—*Study flow chart. *One patient was randomly assigned to receive placebo, but did not receive any study medication. †Some patients who experienced nonfatal clinical end points remained in the study to complete 4 years of follow-up.*

Health Organization definition (17) ≥3 years before screening. LDL cholesterol criteria were *1*) LDL cholesterol ≤140 mg/dl (3.6 mmol/l) if subjects had documented myocardial infarction or an interventional procedure >3 months before screening or 2) LDL cholesterol ≤160 mg/dl (4.1 mmol/l) if not. Triglyceride levels were required to be ≤600 mg/dl (6.8 mmol/l) at all visits.

Exclusions were type 1 diabetes; myocardial infarction, interventional procedure, or episodes of unstable angina ≤3 months before screening; HbA_{1c} (A1C) >10%; active liver disease or hepatic dysfunction (aspartate or alanine aminotransferase levels ≥1.5 × the upper limit of normal); severe renal dysfunction or nephrotic syndrome; congestive heart failure treated with digoxin; creatine phosphokinase ≥3 × the upper limit of normal; blood pressure >160/100 mmHg; BMI >35 kg/m^2; abuse of alcohol and/or drugs; hypersensitivity to the study medication; participation in another clinical study within 30 days of screening; placebo run-in compliance rate <80%; current or planned pregnancy; or use of excluded medications. These medications included immunosuppressive agents, drugs known to interact with the study medications or affect clinical laboratory parameters (e.g., systemic steroids or isotretinoin), and drugs associated with increased risk of rhabdomyolysis with statins (e.g., cyclosporine and macrolide antibiotics). Subjects taking lipid-altering medications, including other statins, were screened after a 4-week washout phase, except in the case of probucol, which was discontinued for at least 6 months before screening.

The study was conducted in compliance with the Declaration of Helsinki and applicable national laws and regulations. The study was approved by the local institutional review board or ethics committee at each participating center. Written informed consent was obtained from all subjects before enrollment, and participants were permitted to withdraw from the study at any time.

ASPEN was a phase IIIB randomized double-blind, placebo-controlled, 4-year study (Fig. 1). Subjects were eligible for the screening visit after initiating an NCEP Step 1 or similar diet and optimizing antidiabetic therapy (in accordance with treatment guidelines at the time of the study). Within 4 weeks of screening, subjects entered the 6-week, single-blind, placebo-baseline period, at the end of which baseline values for vital signs and lipids were obtained and subjects were randomly assigned to double-blind treatment with 10 mg/day of atorvastatin or placebo.

ASPEN was originally designed as a secondary cardiovascular prevention trial in patients with prior myocardial infarction or interventional procedure, but advances in treatment guidelines for individuals with coronary heart disease (CHD) impaired recruitment. The protocol was amended within 2 years of the start of the study to enroll subjects without prior myocardial infarction or interventional procedure. Subsequent treatment guidelines necessitated all secondary prevention subjects and primary prevention subjects with a primary CVD end point to discontinue the study medication and commence active therapy under local guidelines, as mandated by the Data and Safety Monitoring Board (DSMB). An independent, blinded end point committee adjudicated primary and secondary end points reported by study investigators, excluding coronary artery bypass grafting and recanalization procedures.

Efficacy assessments

The primary end point was the time to the first occurrence of a composite clinical end point of cardiovascular death (fatal myocardial infarction, fatal stroke, sudden cardiac death, heart failure, or arrhythmic nonsudden cardiovascular death), nonfatal or silent myocardial infarction, nonfatal stroke, recanalization, coronary artery bypass grafting, resusci-

tated cardiac arrest, or worsening or unstable angina requiring hospitalization. Secondary end points included the time to the first occurrence of individual components of the primary composite end point, noncardiovascular death, transient ischemic attack, worsening or unstable angina not requiring hospitalization, angina or ischemic pain requiring hospitalization, surgery for or new diagnosis of peripheral arterial disease, or acute ischemic heart failure requiring hospitalization. Efficacy analyses were based on the intent-to-treat (ITT) population (randomly assigned subjects receiving at least one dose of the study medication and providing any postrandomization data).

Serum lipid levels (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) were assessed at 0, 12, 24, 36, and 48 study months, after a 12-h fast, and 6–18 h after the previous dose of study medication. LDL cholesterol was calculated according to the Friedewald formula (18). Subjects with triglyceride levels >400 mg/dl had LDL cholesterol levels measured by ultracentrifugation.

Safety assessments

The safety population included all subjects who were randomly assigned to and received at least one dose of study medication. Adverse events and vital signs were recorded at each study visit (months 0, 1, 2, 3, and 6 and every 6 months thereafter). Serious adverse events were to be reported immediately to the sponsor. The DSMB monitored all end point summaries and medically serious adverse events. Physical examinations, electrocardiograms, hematological analysis, and urinalysis were performed at months 12, 24, 36, and 48. Safety clinical laboratory tests were carried out at baseline and at months 1, 2, 3, 6, 18, 30, and 42.

Statistical analyses

A sample size of 1,600 subjects was calculated to have a ~90% power to detect a 32% risk reduction on estimated 4-year event rates of 18% in the placebo group and 12.2% in the atorvastatin group at a two-sided 5% significance level. To allow for a 20% dropout rate, the target enrollment was 2,250 subjects (1,125 per treatment arm). The study was not powered to detect differences in the primary or secondary prevention subgroups alone.

The primary efficacy analysis compared the treatment groups from the time of the first dose of the randomized study medication to the time of the first primary clinical end point using a Cox proportional hazards model, stratified by country and subject type (primary or secondary prevention). The estimated hazard ratio (HR), 95% CI, and *P* value are presented. ANCOVA models were used to compare the treatment groups in terms of absolute and percent changes in total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides from baseline to each study visit, with terms for treatment and baseline lipid value.

RESULTS

Subject disposition

Of 3,598 subjects screened, 2,901 were entered into the placebo run in. Of 490 subjects not randomly assigned, the most common reasons were failure to meet eligibility criteria ($n = 341$), other/administrative reasons ($n = 99$), and lack of compliance ($n = 35$). Of 2,411 subjects randomly assigned, 2,410 received at least one dose of the assigned medication (1,211 atorvastatin and 1,199 placebo) and constituted the ITT population (Fig. 1). The majority of secondary prevention subjects were recruited in the 1st (44%) and 2nd years (32%), whereas the majority of primary prevention subjects were recruited in the 2nd (45%) and 3rd years (38%), reflecting the change in protocol.

Subjects were followed for up to 4.25 years, with a median of 4 years. The double-blind treatment phase was completed by 78.3% of subjects in the atorvastatin group ($n = 948$) and 76.4% of subjects in the placebo group ($n = 916$); 67.5% in the atorvastatin group and 57.6% in the placebo group were taking study medication at study completion.

Baseline subject demographics

Baseline characteristics were similar between treatment groups for the total cohort and the primary and secondary prevention subgroups (Table 1). The secondary prevention population comprised more men than the primary prevention population (81.6 vs. 62.3%) and had a higher proportion of subjects aged ≥65 years (46.1 vs. 33.4%). Mean duration of diabetes, cardiovascular history, and baseline lipid parameters were similar between the treatment groups (Table 1).

Concomitant medications

Classes of concomitant medications used during the study included metabolic and nutritional (98.3% atorvastatin and 98.1% placebo), cardiovascular (78.7 and 84.4%), musculoskeletal (71.9 and 71.8%), anti-infective (57.1 and 55.8%), antihypertensive (55.5 and 59.5%), and central nervous system (53.9 and 52.6%). Similar percentages of subjects in each treatment group took concomitant medications in these classes. More placebo-treated subjects took concomitant antihyperlipidemic agents (26.9%) than in the atorvastatin group (15.4%).

Lipid parameters

Significant mean percent reductions from baseline were observed for LDL cholesterol, total cholesterol, and triglycerides in the atorvastatin group compared with the placebo group for the total ITT cohort and both the primary and secondary prevention populations (Table 1). Increases in HDL cholesterol were greater with atorvastatin than with placebo ($P = 0.0005$). Blood pressure and A1C did not change significantly in either treatment group over the course of the study (Table 1).

Primary efficacy outcome

Fewer primary end points were observed with atorvastatin treatment (13.7%) than with placebo (15.0%) over the 4 years of the study. However, the time to first primary event was not significantly different between the two treatment groups (HR 0.90 [95% CI 0.73–1.12]; $P = 0.34$) (Figs. 2 and 3). A similar number of primary prevention subjects in each group experienced a primary end point (10.4% atorvastatin and 10.8% placebo) (0.97 [0.74–1.28]). Fewer secondary prevention subjects experienced a primary end point with atorvastatin (26.2%) than with placebo (30.8%), also not significant (0.82 [0.59–1.15]).

Secondary efficacy outcomes

Incidence of fatal/nonfatal myocardial infarction was 27% lower with atorvastatin treatment than with placebo ($P = 0.10$) (Fig. 2). The reduction was somewhat more pronounced in the secondary prevention group.

All-cause mortality was similar between the treatment groups during the 4-year treatment phase for the total cohort (5.8% atorvastatin and 5.7% placebo) and for both primary prevention (4.6 and 4.3%) and secondary prevention subjects (10.3 and 10.7%).

Safety

Adverse events occurred with similar frequency in both treatment groups for the

Table 1—*Baseline and on-treatment characteristics of randomized subjects*

	All subjects		Primary prevention		Secondary prevention	
	Atorvastatin	Placebo	Atorvastatin	Placebo	Atorvastatin	Placebo
n	1,211	1,199	959	946	252	253
Age (years)	61.1 ± 8.1	61.0 ± 8.2	60.5 ± 8.3	60.4 ± 8.3	63.1 ± 7.2	63.2 ± 7.4
≥65	448 (37)	422 (35)	332 (35)	305 (32)	116 (46)	117 (46)
Men	796 (66)	803 (67)	593 (62)	594 (63)	203 (81)	209 (83)
Race						
Caucasian	1,018 (84)	1,011 (84)	805 (84)	792 (84)	213 (85)	219 (87)
Black	81 (6.7)	74 (6.2)	73 (7.6)	68 (7.2)	8 (3.2)	6 (2.4)
BMI (kg/m^2)	28.9 ± 3.7	28.8 ± 3.8	28.9 ± 3.7	28.8 ± 3.7	28.9 ± 3.7	28.9 ± 3.8
Current smokers	147 (12)	153 (13)	119 (12)	132 (14)	28 (11)	21 (8)
Median duration of diabetes (years)	8.0	8.0	8.0	8.0	8.0	10.0
Blood pressure (mmHg)						
Systolic	133.1 ± 16.8	133.4 ± 16.4	133.0 ± 17.0	133.0 ± 16.7	133.6 ± 16.0	134.9 ± 15.3
Diastolic	76.9 ± 9.1	76.3 ± 9.0	77.1 ± 8.8	76.7 ± 8.8	76.0 ± 10.0	74.9 ± 9.6
History of hypertension	671 (55)	657 (55)	498 (52)	499 (53)	173 (69)	158 (63)
History of hyperlipidemia	343 (28)	369 (31)	265 (28)	275 (29)	78 (31)	94 (37)
Glomerular filtration rate (ml/min per 1.73 m^2)	65.7 ± 11.5	65.8 ± 11.9	66.1 ± 11.4	66.7 ± 11.8	64.0 ± 11.6	62.6 ± 11.9
CVD history						
Myocardial infarction	208 (17)	187 (16)	0	0	208 (83)	187 (74)
Interventional procedure	145 (12)	170 (14)	0	0	145 (58)	170 (67)
Angina	200 (17)	195 (16)	55 (6)	47 (5)	145 (58)	148 (58)
Peripheral arterial disease	101 (8)	107 (9)	64 (7)	53 (6)	37 (15)	54 (21)
Cerebrovascular disease	61 (5)	62 (5)	38 (4)	32 (3)	23 (9)	30 (12)
Arrhythmia	108 (9)	119 (10)	67 (7)	77 (8)	41 (16)	42 (17)
LDL cholesterol (mg/dl)						
Baseline	113 ± 25	114 ± 26	114 ± 26	114 ± 26	112 ± 24	113 ± 25
End of treatment (% change)	−30.29	−1.09	−30.48	−0.48	−29.65	−3.31
P value (% change)	<0.0001		<0.0001		<0.0001	
Total cholesterol (mg/dl)						
Baseline	194 ± 31	194 ± 31	195 ± 31	195 ± 31	188 ± 26	191 ± 29
End of treatment (% change)	−19.70	−1.41	−19.78	−1.38	−19.47	−1.45
P value (% change)	<0.0001		<0.0001		<0.0001	
HDL cholesterol (mg/dl)						
Baseline	47 ± 14	47 ± 13	48 ± 14	47 ± 13	42 ± 11	44 ± 12
End of treatment (% change)	2.17	−0.18	1.93	−0.33	2.98	0.52
P value (% change)	0.0005		0.002		0.143	
Triglycerides (mg/dl)						
Baseline	147 (101–208)	145 (102–213)	145 (99–205)	144.5 (103–211)	151.5 (104–219)	147 (99–219)
End of treatment (% change)	−3.90	10.01	−4.72	7.24	−0.79	20.44
P value (% change)	<0.0001		<0.0001		0.0005	
A1C (%)	7.6 ± 1.2	7.5 ± 1.3	7.6 ± 1.2	7.6 ± 1.3	7.6 ± 1.3	7.4 ± 1.2
Baseline	7.8 ± 1.4	7.7 ± 1.4	7.8 ± 1.4	7.7 ± 1.4	7.9 ± 1.5	7.8 ± 1.4
End of treatment						

Data are means ± SD, *n* (%), mean, or median (interquartile range). End of treatment lipid changes are from a last-observation-carried-forward analysis. To convert from mg/dl to mmol/l for cholesterol, divide by 38.67; for triglycerides, divide by 88.57.

total, primary prevention, and secondary prevention groups. Serious adverse events were experienced by 37.7% of atorvastatin-treated subjects and 35.4% of placebo-treated subjects. Four atorvastatin-treated subjects experienced serious adverse events that were considered treatment related (headaches, kidney failure, gastrointestinal bleeding, and transami-

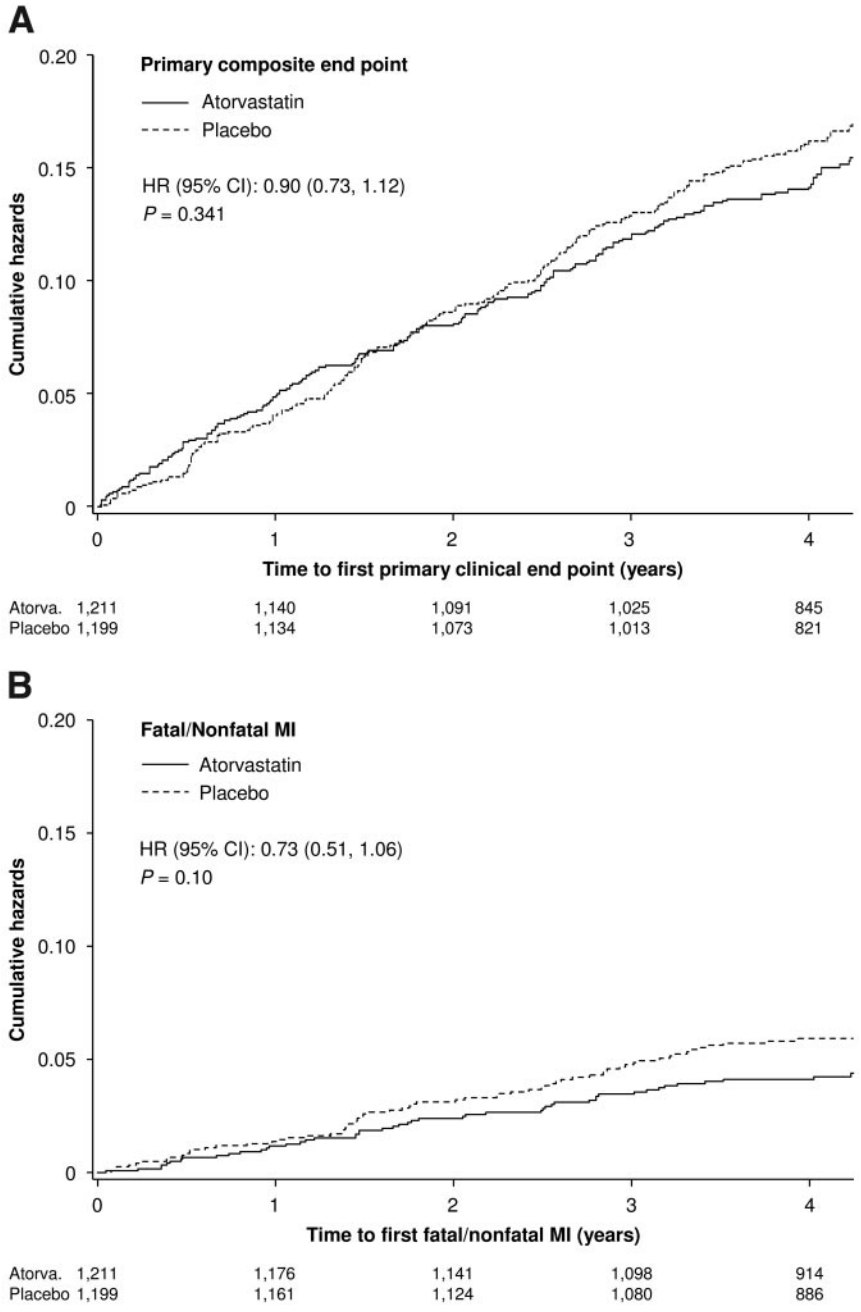

Figure 2—*Cumulative hazards of the primary composite end point* (A) *and fatal/nonfatal myocardial infarction* (B) *for the overall study population.*

nase elevation) versus three placebo-treated subjects (cholestatic jaundice, duodenal ulcer, and vertigo). Results of liver function tests were abnormal in 1.4% in the atorvastatin group and 1.2% in the placebo group. Myalgia rates were 3.0% in the atorvastatin group and 1.6% in the placebo group. Rhabdomyolysis was reported once in each group; neither of which was considered by the investigators to be related to the study treatment.

CONCLUSIONS — The ASPEN did not find a significant reduction in the primary composite end point comparing 10 mg of atorvastatin with placebo (13.7 and 15.0%). However, a 27% reduction in fatal and nonfatal myocardial infarction, although nonsignificant, is comparable to that found in statin cardiovascular end point trials (19). The result for the primary end point differs from the majority of recent studies showing a significant CHD benefit of treating individuals with type 2 diabetes (13–16), with or without prior CHD. The reasons for this result may relate to the overall study design, the types of subjects recruited, the nature of the primary end point, and the protocol changes required because of changing treatment guidelines.

Equivalent CVD rates in diabetic patients without prior CHD and nondiabetic patients with CHD were reported in at least three observational studies (1–4). However, at least four other studies did not report as high a rate of CHD in diabetic patients without CHD (5–8). Therefore, the response to statin therapy in diabetic subjects without CHD appears to be conditioned by the intensity of their risk factors. Factors enhancing CHD rates among diabetic subjects include increasing duration of diabetes. CHD rates in diabetic patients without CHD reach equivalence to those in nondiabetic patients with CHD after 10 years of diabetes in observational studies (3,7). In the ASPEN, the median duration of diabetes was 8 years. Also relevant is the varied risk profile of patients enrolled from different countries in the ASPEN, several of which would have had low background rates of CHD (20).

During the course of the ASPEN, a perception of heightened CVD risk in diabetes evolved (1), and changing lipid treatment guidelines led to the recommendation of lower LDL cholesterol target levels (21). Following the NCEP advisory of 2001 (21), the DSMB recommended that the study medication be discontinued for all secondary prevention subjects and primary prevention subjects with an adjudicated end point and that usual care be provided. Thus, only 67% of atorvastatin- and 58% of placebo-treated patients completed the double-blind phase receiving study medication. Concomitant lipid-lowering treatment in the placebo group was 26.9% compared with 15.4% in the atorvastatin group, leading to an LDL cholesterol reduction of 29% versus placebo. The effect of a high statin drop-in rate had been reported previously in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study (22,23). The use of nonstudy statin therapy in the usual care group of ALLHAT resulted in an LDL cholesterol reduction of only 16.7% with pravastatin versus usual care during 4.8 years' follow-up and 11% in the FIELD study.

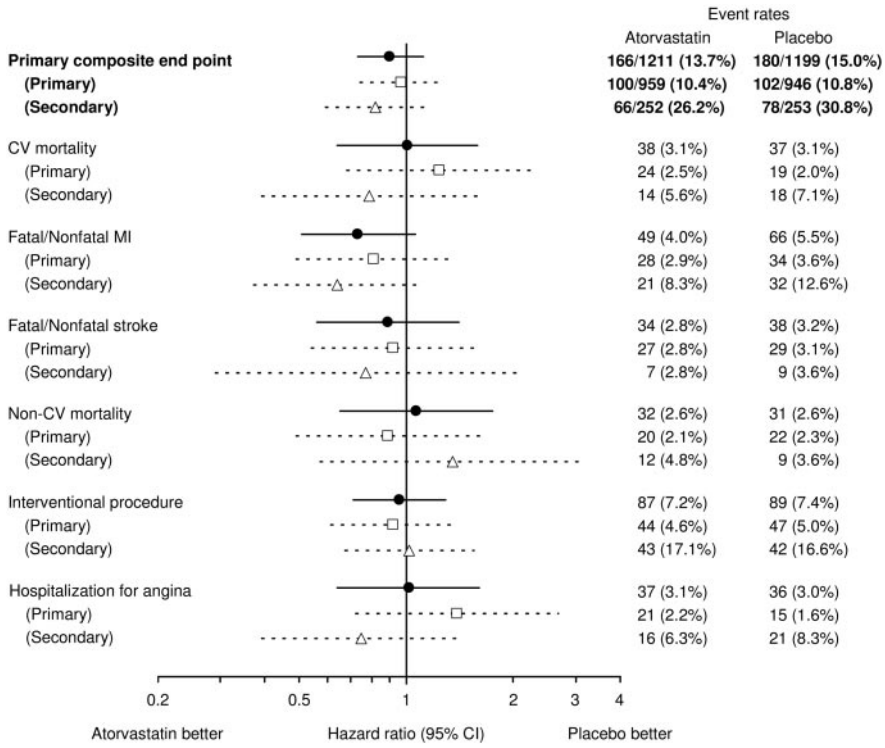

Figure 3—*Cox proportional hazards for the primary composite end point and secondary composite and individual end points for all subjects and the primary and secondary prevention populations. CV, cardiovascular.*

Lower treatment thresholds and heightened CHD risk awareness may have led to the recruitment of a low CVD risk group. A lower risk primary prevention cohort would be expected to show less benefit from statin therapy, an expectation observed in the ASPEN primary prevention group. In fact, ASPEN had the lowest untreated rate of CHD death and nonfatal myocardial infarction of any secondary prevention study so far reported (15.8 vs. 21.0–45.4%) (10–13) and among the lowest for a primary prevention study (4.4 vs. 3.6–6.5%) (13–15).

With respect to the quality of the end point, the 15% event rate in the placebo group may have been inflated by the inclusion of hospitalization for angina pectoris and interventions, both of which were frequently the recorded in the primary composite end point (44 recanalizations and 29 hospitalizations for angina). These end points may have diluted the atorvastatin effect, which is evident in the clinical end points of fatal and nonfatal myocardial infarction (Fig. 3) and the 28% reduction in CHD death and nonfatal myocardial infarction in the secondary prevention cohort, within the range of that for other secondary prevention trials (13–55%) (10–13).

The ASPEN corresponds most closely to the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) and the Collaborative Atorvastatin Diabetes Study (CARDS), both primary prevention studies. In ASCOT, a nonsignificant 16% reduction in CHD death and nonfatal myocardial infarction was observed with 10 mg of atorvastatin in the subcohort of hypertensive subjects with diabetes (24), although a significant benefit was demonstrated when total cardiovascular events and procedures were investigated as a composite end point (15). A significant 37% reduction in risk of cardiovascular events was observed with 10 mg of atorvastatin in CARDS, but the reduction in LDL cholesterol was greater than that in ASPEN. Furthermore, primary prevention patients in both CARDS and ASCOT were older and more hypertensive and included more smokers and men (14,15). Sample size and concomitant risk bear on the outcome of ASCOT and CARDS, as in the ASPEN.

The play of chance may also mitigate against a positive result in the ASPEN, given the low absolute event rates. Unlike previous atorvastatin studies (14,24–27), no divergence was observed until after 1.5 years. Furthermore, 42% of events in the atorvastatin group were experienced by subjects who had discontinued therapy for >1 year previously, potentially reducing the benefit.

The pathophysiology of CVD in diabetes must also be considered. An excess of CHD is reported among diabetic subjects even at the lowest LDL cholesterol levels observed in the Multiple Risk Factor Intervention Trial (MRFIT) (28), meaning that some CHD risk in diabetes may be due to glycemic injury beyond remediation with LDL cholesterol lowering. Triglyceride and HDL cholesterol abnormalities are a further reason for CVD risk in diabetes beyond LDL cholesterol (29).

In summary, the primary end point in the ASPEN did not reach statistical significance in a combined cohort of primary and secondary prevention diabetic subjects recruited during a time of heightened awareness of CHD risk among individuals with diabetes. The point estimate for CVD benefit observed in the secondary prevention cohort for fatal and nonfatal myocardial infarction was similar to that in other trials and supports the rationale for statin therapy for these subjects. For primary prevention subjects, the risk of CHD was low, and the results suggest that subjects with these characteristics are best managed in an individualized way, focusing on all identifiable risk factors, as foreseen by the NCEP panel (30). The present data do not detract from the imperative that the majority of diabetic patients, especially those with existing CHD (10–15), are at risk of CHD and deserve LDL cholesterol lowering to the currently recommended targets (30).

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APPENDIX

ASPEN Study Group members

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