Reduction in Cardiovascular Events With Atorvastatin in 2,532 Patients With Type 2 Diabetes

Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)

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OBJECTIVE — This study aims to establish the benefits of lowering cholesterol in diabetic patients with well-controlled hypertension and average/below-average cholesterol concentrations, but without established coronary disease.

RESEARCH DESIGN AND METHODS — In the lipid-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA), 10,305 hypertensive patients with no history of coronary heart disease (CHD) but at least three cardiovascular risk factors were randomly assigned to receive 10 mg atorvastatin or placebo. Effects on total cardiovascular outcomes in 2,532 patients who had type 2 diabetes at randomization were compared.

RESULTS — During a median follow-up of 3.3 years, concentrations of total and LDL cholesterol among diabetic participants included in ASCOT-LLA were ~1 mmol/l lower in those allocated atorvastatin compared with placebo. There were 116 (9.2%) major cardiovascular events or procedures in the atorvastatin group and 151 (11.9%) events in the placebo group (hazard ratio 0.77, 95% CI 0.61–0.98; $P = 0.036$). For the individual components of this composite end point, the number of events occurring in the diabetes subgroup was small. Therefore, although fewer coronary events (0.84, 0.55–1.29; $P = 0.14$) and strokes (0.67, 0.41–1.09; $P = 0.66$) were observed among the patients allocated atorvastatin, these reductions were not statistically significant.

CONCLUSIONS — Atorvastatin significantly reduced the risk of major cardiovascular events and procedures among diabetic patients with well-controlled hypertension and without a history of CHD or markedly elevated cholesterol concentrations. The proportional reduction in risk was similar to that among participants who did not have diagnosed diabetes. Allocation to atorvastatin prevented ~9 diabetic participants from suffering a first major cardiovascular event or procedure for every 1,000 treated for 1 year.

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Abbreviations: ALLHAT-LLT, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial—Lipid Lowering Trial; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; CARDS, Collaborative Atorvastatin Diabetes Study; CHD, coronary heart disease; HPS, Heart Protection Study; LLA, lipid-lowering arm.

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

Diabetes is a major cause of cardiovascular morbidity and mortality (1), and patients with diabetes are usually hypertensive (2). Observational data indicate that when risk factors such as raised blood pressure, dyslipidemia, and diabetes coexist, they exert a multiplicative effect on the absolute risk of experiencing cardiovascular events (3), and for any combination of risk factors, cardiovascular risk is higher among diabetic than nondiabetic patients (4). Patients with type 2 diabetes have a dyslipidemia typically characterized by low levels of HDL cholesterol and raised triglyceride levels rather than elevated LDL or total cholesterol levels (5).

Before the recruitment of patients into the Anglo-Scandinavian Cardiac

Outcomes Trial (ASCOT) (6), only small numbers of diabetic patients without vascular disease had been included in trials of lipid-lowering therapy (7,8). More recently, two trials incorporating substantial numbers of diabetic patients have been reported. In the Heart Protection Study (HPS) (9), substantial benefits of lipid lowering were demonstrated in a cohort of 5,963 diabetic subjects, both in the presence (51%) and absence (49%) of established cardiovascular disease (10). In the Collaborative Atorvastatin Diabetes Study (CARDS), 2,838 subjects with type 2 diabetes who did not have established cardiovascular disease were randomly assigned to receive atorvastatin or placebo (11). In CARDS, statin treatment significantly reduced the composite primary end point of major cardiovascular events by 37%.

The relative risk reduction in end points associated with statin use appears independent of the baseline cholesterol concentration (7,12). Hence it is important to evaluate the impact of statin use in patients at relatively high absolute risk, such as diabetic patients with well-controlled blood pressure and average or below-average serum cholesterol concentrations.

ASCOT (6) is a multicenter trial designed to compare two antihypertensive treatment strategies for the prevention of coronary heart disease (CHD) events in 19,342 hypertensive patients who have no history of CHD. In a two-by-two factorial design, ASCOT included a double-blind randomized comparison of the cardiovascular effects of atorvastatin with placebo among 10,305 patients who had total cholesterol concentrations ≤6.5 mmol/l. The main results of the lipid-lowering arm (LLA) of ASCOT have been published (12). This report presents a detailed analysis of the 2,532 diabetic participants whose investigation was a prespecified subsidiary aim of the trial.

RESEARCH DESIGN AND METHODS

The study design, organization, measurements, end points, rationale, power calculations, recruitment rates, and some baseline characteristics of the ASCOT trial have been published previously (6). Patients eligible for inclusion in ASCOT were men and women with hypertension aged 40–79 years at randomization (6). Study participants were required to have at least three of the following risk factors: type 2 diabetes, male sex, age ≥55 years, microalbuminuria or proteinuria, smoking, ratio of plasma total cholesterol to HDL cholesterol ≥6, premature family history of CHD, left ventricular hypertrophy, other specified abnormalities on electrocardiogram, peripheral arterial disease, previous stroke, or transient ischemic attack.

The diagnosis of type 2 diabetes was based on a self-reported history and receiving any treatment including dietary maneuvers, oral hypoglycemic agents, or insulin. Further details are outlined on the ASCOT web page (www.ascotstudy.org). Patients who had not previously been diagnosed as having type 2 diabetes but who were found at baseline to have a fasting glucose >6.0 mmol/l and a 2-h value of ≥11.1mmol/l after a 75-g glucose load were also considered as having type 2 diabetes (13).

Exclusion criteria included previous myocardial infarction, currently treated angina, a cerebrovascular event within the previous 3 months, fasting triglyceride level >4.5 mmol/l, heart failure, uncontrolled arrhythmias, or any clinically important hematological or biochemical abnormality on routine screening. Eligibility for ASCOT-LLA also required a total cholesterol concentration ≤6.5 mmol/l and no current use of a statin or fibrate.

Most patients in ASCOT-LLA were recruited from family practice. The study conformed to good clinical practice guidelines and was undertaken following the guidelines of the Declaration of Helsinki. The protocol and all subsequent amendments were reviewed and ratified by ethics review boards in the U.K., Ireland, and the Nordic countries.

Patients were recruited between February 1998 and May 2000. Eligibility criteria were established and written informed consent was obtained ~4 weeks before randomization. Blood pressure was measured using standard procedures; nonfasting blood samples were collected and 12-lead electrocardiograms were assessed centrally. After the 4-week run-in period, eligible recruits were randomized, and they underwent a physical examination; blood pressure, heart rate, and 12-lead electrocardiogram were again recorded. Fasting blood samples were obtained for total cholesterol, HDL cholesterol, triglyceride, and glucose levels.

Patients with a nonfasting total cholesterol concentration ≤6.5 mmol/l at the initial screening visit, who were untreated with a statin or fibrate, were randomly assigned by computer (using minimization procedures) to receive atorvastatin 10 mg daily or matching placebo. Management of the blood pressure–lowering arm is detailed elsewhere (6). Patients were randomly assigned one of two antihypertensive regimens. At each follow-up visit, antihypertensive drug therapy was titrated to achieve target blood pressures (<140/90 mmHg for nondiabetic patients and <130/80 mmHg for diabetic patients); information was recorded about adverse events and any new cardiovascular event or procedure, including the cause for any hospital admission. Information on potential end points was reviewed by a blinded end point committee.

Statistical methods

Given the observed rate of total cardiovascular events and procedures among diabetic subjects in the placebo arm, a median 3.3-year follow-up, and a two-sided significance level of 5%, the study had 75% power to detect a reduction of 25% in total cardiovascular events and procedures among the 2,532 diabetic patients. Total cardiovascular events and procedures included the following diagnoses: cardiovascular mortality, nonfatal myocardial infarction (symptomatic plus silent), unstable angina, chronic stable angina, life-threatening arrhythmias, nonfatal heart failure, nonfatal stroke, peripheral arterial disease, retinal vascular thrombosis, revascularization procedures, transient ischemic attacks, and reversible ischemic neurological deficits.

We compared the times to first end points in the atorvastatin and placebo groups on an intention-to-treat basis. For the main analyses, we used log-rank procedures and Cox's proportional hazards model to calculate confidence intervals. Cumulative incidence curves were generated by the Kaplan-Meier method for all cardiovascular events and procedures in the active and placebo groups. ASCOT-LLA was stopped prematurely after a median follow-up of 3.3 years on the grounds that atorvastatin had resulted in a highly significant reduction in the primary end point of fatal CHD events and nonfatal myocardial infarction.

Role of the funding source

ASCOT was conceived, designed, and coordinated by an independent investigator-led steering committee. The principal

Table 1—*Baseline characteristics for patients with diabetes in ASCOT-LLA*

	Atorvastatin	Placebo
n	1,258	1,274
Demographics and clinical characteristics		
Female sex	289 (23.0)	311 (24.4)
Age (years)		
≤60	425 (33.8)	391 (30.7)
>60	833 (66.2)	883 (69.3)
Means ± SD	63.6 ± 8.5	64.0 ± 8.2
White	1,131 (89.9)	1,163 (91.3)
Current smoker	257 (20.4)	258 (20.3)
Alcohol consumption (units/week)	6.7 ± 10.3	6.6 ± 10.8)
Systolic blood pressure (mmHg)	165.1 ± 17.6	164.8 ± 17.1
Diastolic blood pressure (mmHg)	92.9 ± 10.3	92.4 ± 10.3
Heart rate (bpm)	73.7 ± 13.2	74.1 ± 13.1
BMI (kg/m^2)	30.3 ± 5.0	30.1 ± 4.7
Total cholesterol (mmol/l)	5.3 ± 0.8	5.3 ± 0.8
LDL cholesterol (mmol/l)	3.3 ± 0.7	3.3 ± 0.8
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.3
Triglycerides (mmol/l)	1.9 ± 1.0	1.9 ± 1.0
Glucose (mmol/l)	8.6 ± 2.8	8.7 ± 2.8
Creatinine (mmol/l)	97.1 ± 15.4	98.7 ± 18.0
Medical history		
Previous stroke /transient ischemic attack	93 (7.4)	98 (7.7)
LVH (according to ECG or ECHO)	119 (9.5)	111 (8.7)
ECG abnormalities other than LVH	180 (14.3)	194 (15.2)
Peripheral vascular disease	70 (5.6)	65 (5.1)
Other significant cardiovascular disease	50 (4.0)	43 (3.4)
Number of risk factors (including diabetes)	4.1 ± 1.0	4.0 ± 1.0
Drug therapy		
Oral hypoglycemics	645 (51.3)	683 (53.6)
Insulin	92 (7.3)	96 (7.5)
Previous antihypertensive treatments		
None	189 (15.0)	209 (16.4)
One	557 (44.3)	555 (43.6)
Two or more	512 (40.7)	510 (40.0)
Lipid-lowering therapy	14 (1.1)	20 (1.6)
Aspirin use	228 (18.1)	208 (16.3)

Data are *n* (%) or means ± SD. ECG, electrocardiogram; ECHO, echocardiogram; LVH, left ventricular hypertrophy.

funding source had two nonvoting members on that committee. The trial database is held independently and this report was prepared independently of the principal funding source.

RESULTS — In ASCOT, 19,342 patients were randomly assigned to one of two antihypertensive regimens. In ASCOT-LLA, 10,305 patients were further randomly assigned atorvastatin 10 mg daily or placebo, of whom 2,532 were classified as having type 2 diabetes. Baseline characteristics of participants in these two randomized groups were well matched (Table 1). Overall, 90% of diabetic participants were white and 76% male, with a mean age of 64 years. The average number of additional risk factors in the diabetic subpopulation was three. Baseline blood pressures and lipid concentrations were almost identical in the two groups. At the end of follow-up of the LLA, complete information was obtained for all except 30 of the diabetic patients originally randomized; vital status was obtained for all but four patients.

Among diabetic participants in the atorvastatin group, total cholesterol and calculated LDL cholesterol levels at year 1 of follow-up were lower than in the placebo group by ~1.3 and 1.2 mmol/l, respectively (Table 2). By the end of the study, these differences were 0.9 and 0.9 mmol/l, respectively. In those allocated atorvastatin compared with placebo, triglyceride levels were lowered by 0.3 mmol/l after 1 year and 0.2 mmol/l at study completion. Changes in HDL cholesterol concentration were minimal in both groups. After 3 years follow-up, 84% of diabetic patients originally assigned atorvastatin were still taking the statin and 14% of those in the placebo group had been prescribed open-label statins.

Blood pressure control throughout the trial was similar in diabetic patients assigned atorvastatin and placebo, with mean values at the end of follow-up of 138.5 mmHg systolic and 77.7 mmHg diastolic and 138.4 mmHg systolic and 77.3 mmHg diastolic, respectively. Body weight, fasting blood glucose, and creatinine were well matched at baseline and were unaltered in either group by the time of close out. At randomization, 52% of the diabetic patients were receiving oral hypoglycemic drugs, and 7% were receiving insulin. By the end of the trial, these proportions had increased to 68 and 14%, respectively.

Compared with placebo, atorvastatin significantly lowered the incidence of total cardiovascular events and procedures among the diabetic group by 23% (hazard ratio [HR] 0.77, 95% CI 0.61–0.98; $P = 0.036$) (Fig. 1). This was similar to the proportional reduction observed among participants without diabetes (Fig. 2). Even excluding 306 diabetic people with some other preexisting cardiovascular disease, there was still a significant reduction in total cardiovascular events and procedures of 25% (95% CI 0.57–0.99; $P = 0.038$) among the remaining 2,226 diabetic patients. A post hoc subgroup analysis of the diabetic patients is shown in Table 3. Small numbers of events in each subgroup limit the validity of statistical comparisons. However, there is no statistical heterogeneity within this population.

The effect of atorvastatin on total cardiovascular events and procedures in the diabetic subgroup was unaffected by baseline cholesterol concentration. The HRs were 0.72 (95% CI 0.44–1.18), 0.74 (0.52–1.05), and 0.84 (0.54–1.31) for those with baseline cholesterol concentrations of <5.0, 5.0 to <6.0, and ≥6.0 mmol/l, respectively.

In the diabetic subgroup there were no statistically significant effects of allocation to atorvastatin for any of the individ-

Table 2—*Plasma lipid concentrations (mmol/l) by visit and treatment (diabetic patients only)*

	Cholesterol		HDL Cholesterol		LDL Cholesterol		Triglycerides	
	Atorvastatin	Placebo	Atorvastatin	Placebo	Atorvastatin	Placebo	Atorvastatin	Placebo
Baseline	5.35 ± 0.83 (1,258)	5.33 ± 0.84 (1,274)	1.24 ± 0.32 (1,258)	1.22 ± 0.33 (1,274)	3.30 ± 0.73 (1,150)	3.29 ± 0.75 (1,147)	1.86 ± 1.05 (1,180)	1.86 ± 1.04 (1,176)
6 month	3.99 ± 0.82 (1,158)	5.31 ± 0.87 (1,170)	1.23 ± 0.32 (1,157)	1.22 ± 0.34 (1,170)	2.08 ± 0.67 (1,086)	3.29 ± 0.78 (1,084)	1.50 ± 0.89 (1,100)	1.89 ± 1.11 (1,118)
1 year	4.01 ± 0.81 (1,134)	5.27 ± 0.87 (1,149)	1.22 ± 0.33 (1,134)	1.20 ± 0.33 (1,149)	2.10 ± 0.66 (1,078)	3.27 ± 0.76 (1,068)	1.54 ± 1.01 (1,094)	1.83 ± 1.09 (1,099)
2 years	3.95 ± 0.81 (1,114)	5.12 ± 0.93 (1,132)	1.21 ± 0.32 (1,114)	1.20 ± 0.33 (1,131)	2.08 ± 0.67 (1,063)	3.14 ± 0.79 (1,053)	1.50 ± 0.88 (1,077)	1.79 ± 1.05 (1,080)
3 years	3.96 ± 0.83 (908)	5.04 ± 0.95 (954)	1.22 ± 0.33 (908)	1.22 ± 0.33 (954)	2.10 ± 0.69 (887)	3.07 ± 0.79 (906)	1.42 ± 0.78 (892)	1.72 ± 1.20 (925)
Lipid closeout	4.02 ± 0.81 (1,080)	4.95 ± 0.92 (1,108)	1.23 ± 0.33 (1,079)	1.23 ± 0.34 (1,108)	2.15 ± 0.68 (1,040)	3.02 ± 0.78 (1,060)	1.44 ± 0.82 (1,050)	1.62 ± 1.00 (1,083)

Data are mean ± SD (*n*).

ual components of the composite end point nor for any of the other predefined secondary end points (Table 4). Numbers of events for each component were small, and estimates of hazard ratios were therefore necessarily unstable. However, risk reductions in the primary end point of the trial (fatal CHD and nonfatal myocardial infarction) did not differ significantly between those with or without diabetes at entry (16 and 44%, respectively; $P = 0.14$). Fatal and nonfatal strokes were similarly reduced among those with or without diabetes (33 and 24%, respectively; $P = 0.66$). The use of atorvastatin in the diabetic population was not associated with any excess risk of adverse reactions, and there were no significant differences in liver enzyme abnormalities between those allocated statin and placebo. No cases of rhabdomyolysis were reported.

CONCLUSIONS — The risk reductions in cardiovascular events and procedures reported here are similar for those patients with and without diabetes. However, given that diabetic patients are at higher absolute risk of a cardiovascular event than those without diabetes (39 vs. 28 per 1,000 patient years, respectively, in the placebo group), the absolute benefit of this lipid-lowering therapy is greater for those hypertensive patients who were also diabetic. These benefits are over and above those likely to have accrued as a result of the extensive blood pressure lowering achieved in ASCOT-LLA (12), which previous trials (14,15) have clearly shown to be associated with major reductions in cardiovascular events in the diabetic population.

These risk reductions in the diabetic population in ASCOT-LLA were associated with an average reduction in total and LDL cholesterol concentrations of ~1 mmol/l. These differences in cholesterol between active and placebo groups were somewhat less at the close of the trial than at the end of the first year because 14% of the patients with diabetes who were originally allocated placebo treatment were subsequently prescribed open-label statins by practitioners, compared with 8% for the nondiabetic population in ASCOT-LLA.

In the total ASCOT-LLA population, the primary end point of nonfatal myocardial infarction and fatal CHD was reduced by 36% ($P = 0.0005$). Among the diabetic subgroup, the observed 16% risk reduction was not statistically significant, but only 84 such first events occurred among these diabetic participants; the proportional reduction was not significantly different from the reduction among the nondiabetic participants. The premature stopping of the trial reduced the anticipated number of coronary events and other end points, and hence the power of any tests to compare effects of statin with placebo in the subgroups.

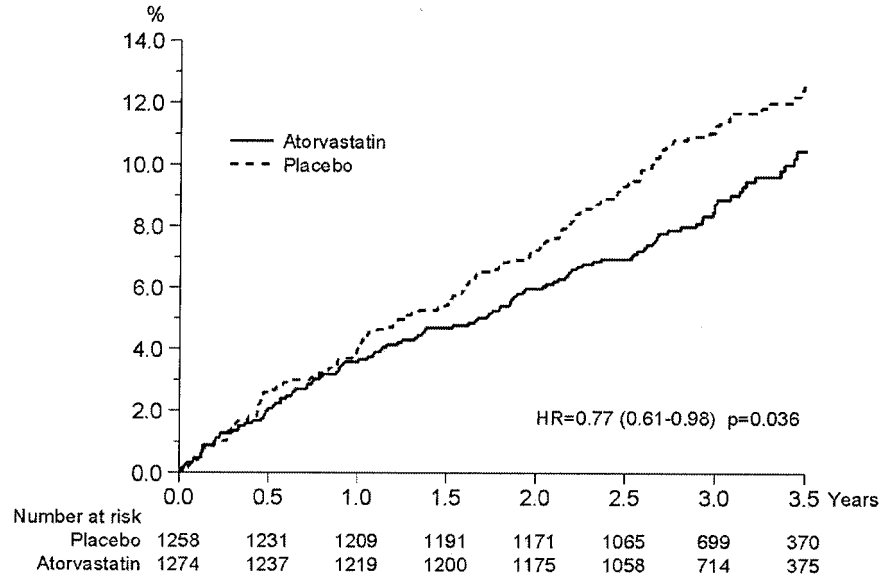

Figure 1—*Cumulative incidence for total cardiovascular events and procedures among diabetic participants in ASCOT-LLA.*

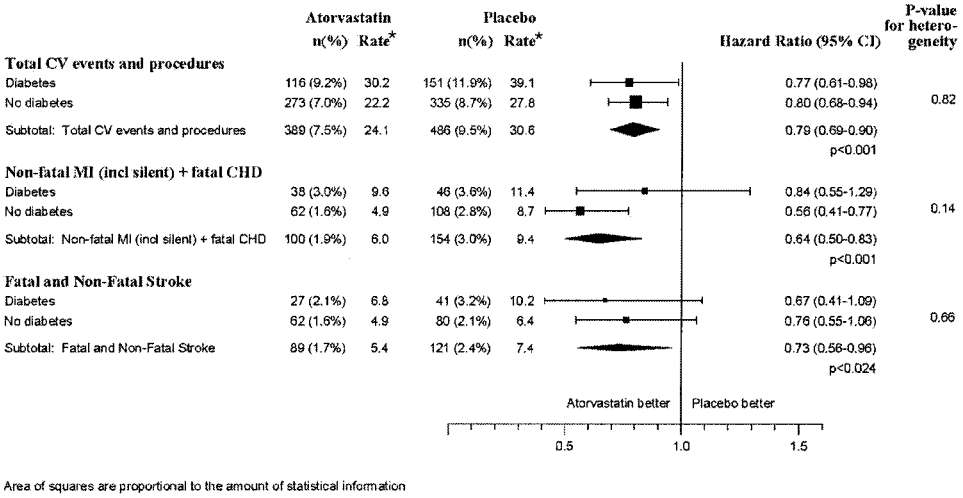

Figure 2—*Effect of atorvastatin and placebo on cardiovascular (CV) and coronary end points by diabetic status in ASCOT-LLA. MI, myocardial infarction. *Per 1,000 patient-years.*

Three other studies have recently reported observations on statin use in diabetic patients. Among 5,963 diabetic participants in the HPS (10), allocation to simvastatin resulted in an average reduction in LDL cholesterol concentration of 1.0 mmol/l and reduced the incidence of major vascular events by 24%, which is a risk reduction similar to that reported in this article. Lipid profiles in diabetic patients in HPS showed some important differences from those in ASCOT-LLA. In HPS, diabetic participants had higher total cholesterol levels (5.7 vs. 5.3 mmol/l) and lower HDL cholesterol levels (1.1 vs. 1.2 mmol/l) than those in ASCOT-LLA. Additionally, the diabetic subgroup in the HPS was at substantially higher absolute cardiovascular risk because of much higher rates of preexisting cardiovascular disease. However, even in the subgroup of 2,912 HPS diabetic patients without known cardiovascular disease, similar and significant risk reductions in cardiovascular end points were reported (10).

In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial–Lipid Lowering Trial (ALLHAT-LLT) (16), 3,638 hypertensive patients with diabetes were randomly assigned to pravastatin (40 mg daily) or "usual care," and followed for an average of 5.2 years. Overall, the ALLHAT-LLT population was older and at higher cardiovascular risk than the ASCOT-LLA participants. Among the diabetic population in ALLHAT-LLT, the use of pravastatin was associated with an 11% nonsignificant reduction in fatal CHD and nonfatal myocardial infarction. However, these data are difficult to interpret because in the whole ALLHAT-LLT population, the differential effect of pravastatin on total and LDL cholesterol (11 and 17%, respectively) was smaller than expected due to extensive statin use in the usual care group. This contrasts with equivalent figures of 24 and 35%, respectively, in the whole ASCOT-LLA population.

In CARDS (11), the reduction in the composite end point of major cardiovascular events for the same dose of atorvastatin was greater than that reported here for total cardiovascular events and procedures among diabetic subjects in ASCOT-LLA (37 vs. 23%). However, the composition of these two end points is different and so the data are not strictly comparable (6,11). Nevertheless, fatal CHD and nonfatal myocardial infarctions were reduced by 33% in CARDS (HR 0.67, 95% CI 0.47–0.97) and only by 16% in ASCOT-LLA (0.84, 0.55–1.29). The percentage reduction in stroke ob-

Table 3—*HR by subgroups (diabetic patients only) for total cardiovascular events and procedures*

	Atorvastatin		Placebo			
	n (%)	Rate*	*n* (%)	Rate*	Unadjusted HR (95% CI)	*P* value
Age ≤60 years	20 (4.7)	14.9	34 (8.7)	28	0.53 (0.31–0.92)	0.022
Age >60 years	96 (11.5)	38.4	117 (13.3)	44.3	0.87 (0.66–1.14)	0.300
Female sex	26 (9.0)	28.8	31 (10.0)	31.9	0.90 (0.53–1.51)	0.686
Male sex	90 (9.3)	30.6	120 (12.5)	41.6	0.74 (0.56–0.97	0.028
LDL <3.46 mmol/l	56 (8.5)	27.5	62 (9.1)	29.3	0.93 (0.65–1.34)	0.708
LDL ≥3.46 mmol/l	53 (10.8)	36.3	72 (15.5)	52.9	0.69 (0.48–0.98)	0.037
HDL <1.3 mmol/l	67 (9.2)	30.6	96 (12.7)	42.7	0.72 (0.52–0.98)	0.036
HDL ≥1.3 mmol/l	49 (9.3)	29.7	55 (10.6)	34.1	0.87 (0.59–1.28)	0.481
Triglycerides <1.4 mmol/l	37 (8.7)	28.2	55 (13.3)	43.8	0.64 (0.42–0.97)	0.036
Triglycerides ≥1.4 mmol/l	72 (9.5)	31.6	81 (10.6)	35.1	0.90 (0.65–1.24)	0.512
Glucose <5.6 mmol/l	5 (6.0)	19.4	8 (10.1)	33.1	0.59 (0.19–1.81)	0.354
Glucose ≥5.6 mmol/l	104 (9.5)	31.2	128 (11.7)	38.6	0.81 (0.62–1.05)	0.105
All diabetic patients	116 (9.2)	30.2	151 (11.9)	39.1	0.77 (0.61–0.98)	0.036

*Rates are per 1,000 patient-years.

Table 4—*HR for end points included in total cardiovascular events and procedures (diabetic patients only)*

	Atorvastatin		Placebo			
	n (%)	Rate	*n* (%)	Rate	Unadjusted HR (95% CI)	*P* value
Fatal CHD	17 (1.4)	4.2	10 (0.8)	2.4	1.72 (0.79–3.76)	0.167
Fatal stroke	5 (0.4)	1.2	10 (0.8)	2.4	0.51 (0.17–1.48)	0.207
Other fatal cardiovascular	4 (0.3)	1	1 (0.1)	0.2	4.07 (0.45–36.41)	0.174
Nonfatal myocardial infarction	22 (1.7)	5.5	36 (2.8)	8.9	0.62 (0.37–1.06)	0.077
Unstable angina	9 (0.7)	2.3	12 (0.9)	2.9	0.76 (0.32–1.81)	0.541
Chronic stable angina	9 (0.7)	2.3	19 (1.5)	4.7	0.48 (0.22–1.06)	0.063
Life-threatening arrhythmias	3 (0.2)	0.7	1 (0.1)	0.2	3.07 (0.32–29.51)	0.306
Nonfatal heart failure	15 (1.2)	3.8	13 (1.0)	3.2	1.18 (0.56–2.49)	0.656
Nonfatal stroke	23 (1.8)	5.8	31 (2.4)	7.7	0.76 (0.44–1.30)	0.308
Peripheral arterial disease	10 (0.8)	2.5	12 (0.9)	3	0.85 (0.37–1.97)	0.706
Retinal vascular thromboses	1 (0.1)	0.2	1 (0.1)	0.2	1.03 (0.06–16.54)	0.981
Coronary revascularization procedures	13 (1.0)	3.3	26 (2.0)	6.4	0.51 (0.26–0.99)	0.044
Other revascularization procedures	2 (0.2)	0.5	9 (0.7)	2.2	0.23 (0.05–1.06)	0.060
Transient ischemic attack	5 (0.4)	1.3	13 (1.0)	3.2	0.39 (0.14–1.10)	0.064
Reverse ischemic neurodeficit	3 (0.2)	0.7	7 (0.5)	1.7	0.44 (0.11–1.69)	0.216

served in the CARDS trial of 48% (0.52, 0.31–0.89) was larger than the 33% reduction seen in ASCOT-LLA (0.67, 0.41–1.09). The latter reduction is larger than observed in most previous statin trials, including the 24% reduction experienced among the diabetic population in HPS (10). These apparent disparities may be the result of chance (e.g., only 84 and 108 fatal CHD and nonfatal myocardial infarction events occurred in ASCOT-LLA and CARDS, respectively). In addition, the greater impact of atorvastatin on LDL cholesterol and triglyceride levels relative to placebo seen in CARDS (at least in part reflecting more drop-in and drop-out to/from therapy in ASCOT-LLA), may have contributed to the greater impact seen in CARDS.

It is also possible that other factors could have influenced the benefits of atorvastatin in ASCOT-LLA. For example, β-blockers and diuretics that were allocated to 50% of ASCOT-LLA patients may have adversely affected lipid profiles more among those taking a statin than placebo and thereby have reduced the relative benefits of statins.

Thus, findings among the large subgroup of patients with type 2 diabetes in the ASCOT-LLA support those arising from analyses of the diabetic subgroups of earlier statin trials (10,17) and from CARDS (11). These data also extend the database specifically in relation to patients with hypertension and no history of CHD. Hence the findings reinforce recent guidelines that advocate a more aggressive approach to lipid-lowering therapy for patients with diabetes (18–20). It now therefore seems reasonable to recommend that all patients with type 2 diabetes and hypertension (at least all those >50 years of age and/or having diabetes for ≥10 years) should be routinely considered for statin therapy.

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