Impact of atorvastatin among older and younger patients in the Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm

David J. Collier[a], Neil R. Poulter[b], Björn Dahlöf[c], Peter S. Sever[b], Hans Wedel[d], Jan Buch[e], Mark J. Caulfield[a], on behalf of the ASCOT Investigators

Objective **Older patients experience higher rates of cardiovascular disease than younger patients, but may be undertreated with statins due to doubts about efficacy and safety. The Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial allowed an evaluation of the efficacy and safety of atorvastatin among older (≥65 years) and younger (<65 years) patients with hypertension.**

Methods **A total of 10 305 patients with hypertension, at least three other cardiovascular risk factors, total cholesterol concentrations of 251 mg/dl or less, and no known coronary heart disease (CHD) were randomized to receive atorvastatin 10 mg or placebo. The primary endpoint was a composite of nonfatal myocardial infarction and fatal CHD.**

Results **There were 4445 patients in the older group (mean 71 years) and 5860 patients (mean 57 years) in the younger group. Among those taking placebo, the older group experienced a higher rate of primary endpoints than the younger group (11.7 vs. 7.6 events per 1000 patient years, respectively). After a median follow-up of 3.3 years, the primary endpoint was reduced by a similar proportion in both older and younger patients (37 vs. 33%, respectively). Although older patients reported more serious adverse events than younger patients, there were no significant differences between atorvastatin and placebo within each age group.**

Conclusion **Atorvastatin reduced the risk of major cardiovascular events to a similar relative extent in both older and younger patients with treated hypertension. However, given that event rates were higher in older patients, the absolute benefits of atorvastatin were greater for older than younger patients.** *J Hypertens* **29:592–599**

Journal of Hypertension 2011, **29**:592–599

Keywords: cardiovascular disease prevention, cholesterol, coronary disease mortality, elderly, follow-up studies, hypertension, lipid lowering, randomized controlled trials, statins, treatment outcomes

Abbreviations: ALT, alanine aminotransferase; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm; BP, blood pressure; CARE, Cholesterol and Recurrent Events (CARE) study; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; ECHO, echocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LIPID, Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) study; LVH, left ventricular hypertrophy; MI, myocardial infarction; NHANES, National Health and Nutrition Evaluation Survey; NICE, National Institute of Clinical Excellence; PROSPER, PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial; RCT, randomized controlled trial; SAE, serious adverse event; SE, standard error; TC, total cholesterol; TIA, transient ischemic attack; ULN, upper limit of normal

[a]Barts and The London, Queen Mary's School of Medicine and Dentistry, [b]Imperial College London, London, UK, [c]Sahlgrenska University Hospital/Östra, [d]Nordiska School of Public Health, Göteborg, Sweden and [e]Pfizer Inc., New York, New York, USA

Correspondence to David J. Collier, PhD, Clinical Pharmacology, William Harvey Research Institute, Barts and The London, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK
Tel: +44 20 7882 3415; fax: +44 20 7882 3430; e-mail: d.j.collier@qmul.ac.uk

Received 22 March 2010 **Revised** 5 October 2010
Accepted 17 November 2010

Introduction

Of the 80 million Americans affected by cardiovascular disease (CVD), 47.6% are estimated to be aged 60 years or older [1]. In the United States in 2005, 82% of all coronary heart disease (CHD) deaths [1] and 86% of all stroke deaths occurred in patients aged 65 years or older [2].

Low-density lipoprotein cholesterol (LDL-C) has long been established as an independent risk factor for CVD [3]. Large outcome trials have consistently demonstrated statin-associated reductions in LDL-C and cardiovascular events in both primary and secondary prevention [4–10].

Trials among older adults and subgroup analyses comparing older and younger patients have also demonstrated statin-associated reductions in major cardiovascular events in older populations [4–13]. A meta-analysis of 14 trials demonstrated that a 40 mg/dl (1 mmol/l) reduction in LDL-C associated with statin therapy in patients aged 65 years or older significantly reduced the risk of any coronary or vascular event irrespective of baseline LDL-C levels [9]. More recently, a meta-analysis demonstrated the cardiovascular benefits of statins in patients aged 65 years or older with established CHD [13].

The present work was presented as a poster at the International Stroke Conference, 31st Annual Meeting, at Kissimmee, Florida, USA, 16–18 February 2006 and the abstract was subsequently published in *Stroke* 2006; **37**:695.

0263-6352 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI:10.1097/HJH.0b013e328342c8f7

The evidence regarding the reduction in stroke events with statin treatment in older patients is less consistent. The Cholesterol and Recurrent Events (CARE) study reported that compared with placebo, pravastatin 40 mg significantly reduced stroke events among patients aged 65–75 years [6], a result that was also seen among older participants of the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) study [5,11]. However, compared with placebo, the same pravastatin dose was not associated with a reduction in stroke events among patients aged 70–82 years in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial [8]. Given the particularly high incidence of stroke in the PROSPER population [8] and the short follow-up period, it is possible that this finding occurred by chance. Thus, further investigation into the effects of statins on stroke, among older patients using databases from other large outcome trials, is warranted.

The absolute benefit of cholesterol lowering is potentially greater among older than younger patients, due to their higher cardiovascular risk. Despite this, statin therapy continues to be underutilized in older patients in real-world clinical practice [14–16]. This may reflect recent reports in the literature that have questioned the efficacy and safety of statins in older patients [17], including the apparent absence of benefit on stroke events and an increase in cancer rates reported in the PROSPER trial [8].

The Lipid-Lowering Arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-LLA) was a primary prevention trial in patients with hypertension who were neither hyperlipidemic by contemporary standards nor had a history of CHD [18–20]. Follow-up was planned for an average of 5 years, but this part of the trial was stopped after a median of 3.3 years due to a significant 36% reduction in the risk of nonfatal myocardial infarction (MI) and fatal CHD with 10 mg of atorvastatin compared with placebo [19]. ASCOT-LLA was important in showing that the benefits of statins extend to patients without CHD who are not traditionally thought to be dyslipidemic, but are at moderate risk of CHD and stroke. This post-hoc analysis uses data from ASCOT-LLA to compare the efficacy and safety of atorvastatin 10 mg in patients aged 65 years and older with patients aged less than 65 years.

Methods

ASCOT was a multicenter, international randomized trial that compared two antihypertensive regimens (atenolol ± thiazide diuretic vs. amlodipine ± perindopril) for the prevention of CHD and other vascular events in 19 257 patients with hypertension and at least three additional cardiovascular risk factors, but no history of CHD [18]. In a two-by-two factorial design, the trial included a lipid-lowering arm (ASCOT-LLA) that was a double-blind, randomized comparison of atorvastatin vs. placebo among 10 305 patients who had a nonfasting baseline total cholesterol concentration of 251 mg/dl or less (≤6.5 mmol/l) [18]. The ASCOT-LLA study design, trial management, and main results have been published previously [18–20].

This post-hoc analysis uses data from ASCOT-LLA to compare the effect of atorvastatin in older (aged ≥65 years) vs. younger patients (aged <65 years) with relatively well controlled raised blood pressure (BP). The evaluated endpoints were consistent with the original trial design and included the primary endpoint of nonfatal MI (including silent MI) and fatal CHD. The seven secondary endpoints were nonfatal MI (excluding silent MI) and fatal CHD; total coronary endpoints; total cardiovascular events and procedures; all-cause mortality; cardiovascular mortality; fatal and nonfatal stroke; and fatal and nonfatal heart failure.

Statistical methods

Time to first endpoint was compared between the atorvastatin and placebo groups on an intention-to-treat basis. Log-rank procedures and Cox's proportional hazard models were used to calculate confidence intervals (CIs). Cumulative incidence curves were generated by the Kaplan–Meier method for each endpoint in the atorvastatin and placebo groups. All statistical tests were two-sided.

Results

Among the 10 305 patients randomized in ASCOT-LLA, 4445 patients (43%) were aged 65 years or older and 5860 (57%) were aged less than 65 years. In both age groups, baseline characteristics were well matched between those randomized to atorvastatin and placebo (Table 1). The mean age of the older group was 71 years and the younger group was 57 years. In both age groups, patients were mainly white (96 vs. 94%) and men (80 vs. 82%). Although both groups had a similar number of additional cardiovascular risk factors (3.7 vs. 3.6, respectively), they were distributed very differently. At baseline, patients aged 65 years or older had higher SBP (168 ± 18.5 vs. 161 ± 16.8 mmHg), lower DBP (92 ± 10.4 vs. 97 ± 9.7 mmHg), and hence higher pulse pressure (76 ± 16.3 vs. 64 ± 14.6 mmHg) than those aged less than 65 years. Heart rates were lower among the older patients (70 ± 12.4 vs. 73 ± 12.7 beats/min). Older patients had higher rates of previous stroke or transient ischemic attack [(TIA) 14 vs. 7%], diabetes (27 vs. 23%), electrocardiograph abnormalities other than left ventricular hypertrophy (17 vs. 12%), and peripheral vascular disease (7 vs. 4%) than younger patients, putting the older group at higher absolute cardiovascular risk. Consistent with their medical history and increased cardiovascular risk, a greater proportion of older patients reported taking prophylactic aspirin compared with younger patients (24 vs. 13%). Patients aged less than 65 years were more likely to have untreated hypertension

Table 1 Baseline characteristics

	Patients aged ≥65 years		Patients aged <65 years	
	Atorvastatin ($n=2189$)	Placebo ($n=2256$)	Atorvastatin ($n=2979$)	Placebo ($n=2881$)
Demographic and clinical characteristics				
Men, *n* (%)	1780 (81.3)	1792 (79.4)	2409 (80.9)	2382 (82.7)
Age, years, mean (SD)	71.1 (4.1)	71.1 (4.0)	57.2 (5.6)	57.0 (5.7)
White, *n* (%)	2105 (96.2)	2167 (96.1)	2784 (93.5)	2696 (93.6)
Current smoker, *n* (%)	524 (23.9)	529 (23.4)	1194 (40.1)	1127 (39.1)
Alcohol consumption, mean units/week, (SD)	6.9 (10.4)	6.7 (10.3)	8.8 (11.9)	9.3 (13.1)
SBP, mean mmHg (SD)	168.2 (18.6)	168.2 (18.4)	161.2 (16.5)	161.1 (17.0)
DBP, mean mmHg (SD)	92.3 (10.4)	92.2 (10.3)	97.0 (9.8)	97.2 (9.7)
Heart rate, mean beats/min (SD)	69.8 (12.5)	70.2 (12.4)	72.4 (12.8)	73.1 (12.6)
BMI, mean kg/m^2 (SD)	27.9 (4.4)	28.0 (4.3)	29.2 (4.9)	29.2 (4.7)
TC, mean mg/dl (SD)	210.9 (30.8)	211.8 (30.4)	212.4 (29.9)	211.5 (30.2)
LDL-C, mean mg/dl (SD)	132.8 (28.0)	134.2 (28.2)	133.0 (27.7)	132.1 (27.8)
HDL-C, mean mg/dl (SD)	51.6 (14.4)	51.3 (13.6)	49.9 (13.9)	49.7 (13.8)
Triglycerides, mean mg/dl (SD)	135.9 (68.7)	136.1 (64.9)	154.7 (88.5)	153.2 (85.0)
Glucose, mean mg/dl (SD)	111.7 (37.8)	113.5 (37.8)	111.7 (37.8)	111.7 (37.8)
Creatinine, mean mg/dl (SD)	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
Medical history				
Previous stroke or TIA, *n* (%)	285 (13.0)	319 (14.1)	200 (6.7)	197 (6.8)
Diabetes mellitus, *n* (%)	570 (26.0)	620 (27.5)	688 (23.1)	654 (22.7)
LVH (on ECG or ECHO), *n* (%)	340 (15.5)	314 (13.9)	404 (13.6)	415 (14.4)
ECG abnormalities (not LVH), *n* (%)	383 (17.5)	378 (16.8)	358 (12.0)	351 (12.2)
Peripheral vascular disease, *n* (%)	155 (7.1)	142 (6.3)	106 (3.6)	111 (3.9)
Number of risk factors, mean (SD)	3.7 (0.9)	3.7 (0.9)	3.6 (0.8)	3.6 (0.8)
Drug therapy				
No previous antihypertensive use, *n* (%)	378 (17.3)	387 (17.2)	643 (21.6)	609 (21.1)
Prior lipid-lowering therapy, *n* (%)	20 (0.9)	26 (1.2)	21 (0.7)	26 (0.9)
Aspirin use, *n* (%)	534 (24.4)	542 (24.0)	395 (13.3)	360 (12.5)

CVD, cardiovascular disease; ECHO, echocardiogram; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVH, left ventricular hypertrophy; TC, total cholesterol; TIA, transient ischemic attack.

prior to the study start (21 vs. 17%); higher BMI (29 ± 4.8 vs. 28 ± 4.3 kg/m^2); to be a current smoker (40 vs. 24%); and drink more alcohol (9 ± 12.5 vs. 7 ± 10.3 units/week) than the older group.

Baseline mean total cholesterol, LDL-C, and high-density lipoprotein cholesterol (HDL-C) levels were similar among the older and younger groups (Table 1). However, the older group had lower baseline mean triglycerides compared with the younger group [136 ± 66.8 mg/dl (1.5 ± 0.7 mmol/l) vs. 154 ± 86.8 mg/dl (1.7 ± 0.9 mmol/l)].

In both age groups, BP at the end of follow-up in ASCOT-LLA was similar in those randomized to atorvastatin and placebo. Among older patients, the final mean BP was 140/77 mmHg in both the atorvastatin and placebo groups. Among younger patients, the final mean BP was 137/82 mmHg in those randomized to atorvastatin and 137/83 mmHg in those randomized to placebo.

ASCOT-LLA was stopped prematurely after a median follow-up of 3.3 years on the recommendation of the Data Safety Monitoring Board. Among the older group, complete follow-up information was obtained for all but 42 patients and vital status for all but six patients. Among the younger group, complete follow-up information was obtained for all but 77 patients and vital status for all but 11 patients.

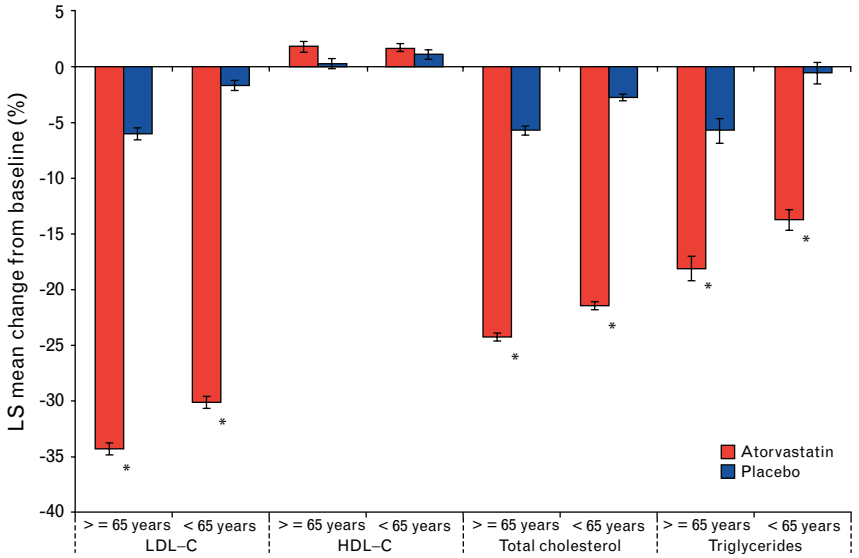
Serum lipid levels

Compared with placebo, atorvastatin had similar effects on plasma lipid levels in both age groups with a slight (nonsignificant) tendency for a greater effect among the older group (Fig. 1).

After the first year of follow-up, compared with placebo, atorvastatin lowered total cholesterol by 24% [51 mg/dl (1.3 mmol/l)] in the older group and by 23% [51 mg/dl (1.3 mmol/l)] in the younger group. Over the same period, calculated LDL-C levels were lowered by 35% [48 mg/dl (1.2 mmol/l)] in the older group and by 34% [46 mg/dl (1.2 mmol/l)] in the younger group and triglycerides were lowered by 17% [24 mg/dl (0.3 mmol/l)] in both the older and younger groups.

At the end of follow-up, the atorvastatin treatment effect in the older group had been reduced to 20% [40 mg/dl (1.0 mmol/l)] for total cholesterol; 31% [38 mg/dl (1.0 mmol/l)] for LDL-C; and 14% [16 mg/dl (0.2 mmol/l)] for triglycerides (Fig. 1). Among younger patients, the treatment effect had been reduced to 19% [39 mg/dl (1.0 mmol/l)], 28% [35 mg/dl (0.9 mmol/l)], and 14% [18 mg/dl (0.2 mmol/l)], respectively (Fig. 1). Changes in HDL-C were minimal in both older and younger patients at both the end of year 1 and at the end of follow-up. As previously reported [19], the reduction in the treatment effect seen between year 1 and the end of follow-up is likely to be related to drop-outs in the atorvastatin arm and drop-ins to statin treatment in the placebo arm. During the study, more patients in the older group dropped out of the atorvastatin arm compared with the younger group (20 vs. 13.5%, respectively; $P < 0.0001$). However, a similar proportion of

Fig. 1



Changes in serum lipid levels between baseline and end of follow-up in patients aged at least 65 years and patients aged less than 65 years. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LS, least squares. *$P<0.0001$ vs. placebo. Error bars represent the standard error.

patients in the placebo arm took open-label statins in both the older and younger groups (12.1 vs. 11.5%, respectively; $P=0.53$).

Cardiovascular outcomes

The primary endpoint of nonfatal MI (including silent MI) and fatal CHD was significantly lower in the atorvastatin group compared with the placebo group in both older (hazard ratio, 0.63; 95% CI 0.44–0.89; $P<0.01$) and younger (hazard ratio 0.67; 95% CI 0.46–0.96; $P=0.03$) patients (Figs 2 and 3).

There were also significant reductions in three of the seven secondary endpoints in both age strata (Fig. 2). Compared with placebo, atorvastatin reduced nonfatal MI (excluding silent MI) and fatal CHD by 38% in the older group (hazard ratio 0.62; 95% CI 0.43–0.91; $P=0.01$) and by 37% (hazard ratio 0.63; 95% CI 0.43–0.93; $P=0.02$) in the younger group; total coronary events were reduced by 30% (hazard ratio 0.70; 95% CI 0.54–0.91; $P<0.01$) in the older group and by 26% (hazard ratio 0.74; 95% CI 0.56–0.98; $P<0.04$) in the younger group; and total cardiovascular events and procedures were reduced by 21% in the older group (hazard ratio 0.79; 95% CI 0.67–0.95; $P<0.01$) and by 20% (hazard ratio 0.80; 95% CI 0.65–0.99; $P=0.04$) in the younger group (Figs 2 and 3).

Compared with placebo, atorvastatin reduced fatal and nonfatal stroke by a nonsignificant 20% in the older group (hazard ratio 0.80; 95% CI 0.58–1.11, $P=0.18$) and by 37% in the younger group (hazard ratio 0.63; 95% CI 0.38–1.03; $P=0.06$; Figs 2 and 3).

There was no significant heterogeneity between the age subgroups for any endpoint (Fig. 2).

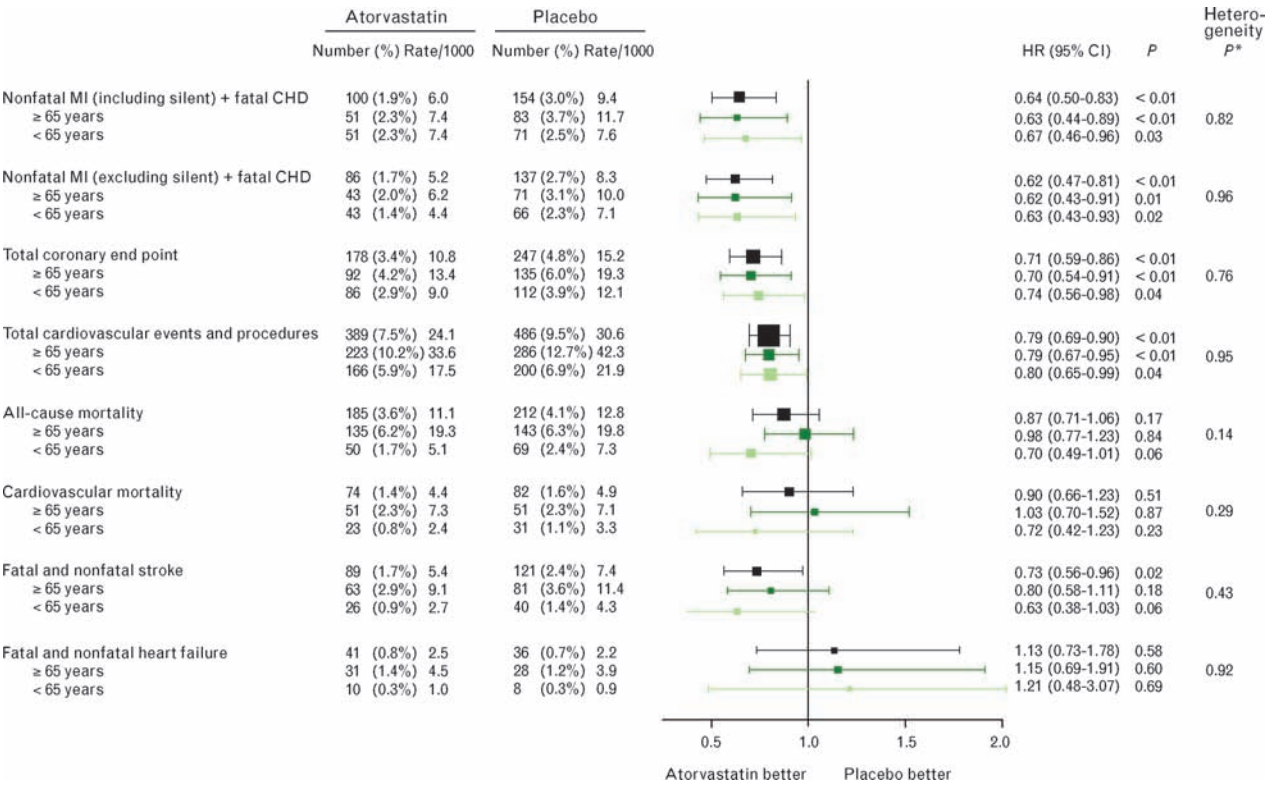
As expected, older patients were at higher absolute coronary risk compared with the younger group (11.7 vs. 7.6 primary endpoints per 1000 patient years, respectively, in the placebo group), and thus the absolute benefits of atorvastatin were greater among older patients with hypertension.

Safety

Safety outcomes are summarized in Table 2. Although older patients reported more serious adverse events (SAEs) than younger patients (27 vs. 20%, respectively), within each age group there was no difference in the proportion of patients reporting SAEs in the atorvastatin and placebo arms. In the older group, 26.3% of those randomized to atorvastatin reported a SAE compared with 27.3% randomized to placebo. In the younger group, 18.4% of those randomized to atorvastatin reported a SAE compared with 20.9% randomized to placebo. Furthermore, in the older group, no patients randomized to atorvastatin discontinued treatment due to a SAE and only nine patients (0.4%) discontinued in the placebo group. Among younger patients, 0.1% discontinued atorvastatin and 0.3% of patients discontinued placebo due to a SAE.

For patients aged 65 years or older, there was no excess of deaths between the atorvastatin and placebo groups from cancer (2.8% of patients in each group) or from all noncardiovascular causes (3.8 and 4.1% of patients, respectively). There were no significant differences

Fig. 2



Hazard ratios for primary and secondary endpoints among all patients, patients aged at least 65 years, and patients aged less than 65 years. CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction. *Per 1000 patient years. †*P* value for heterogeneity between the older and younger groups.

between the atorvastatin and placebo groups in the incidence of alanine aminotransferase elevations (defined as >3 times the upper limit of normal; 0.5 and 0.7% of patients, respectively). There were also no differences between treatment groups in the development of myalgia, diabetes, renal impairment, heart failure, life-threatening arrhythmias, or nonfatal cancer. No cases of rhabdomyolysis were reported among patients aged 65 years and older, and only one case was reported among those aged less than 65 years.

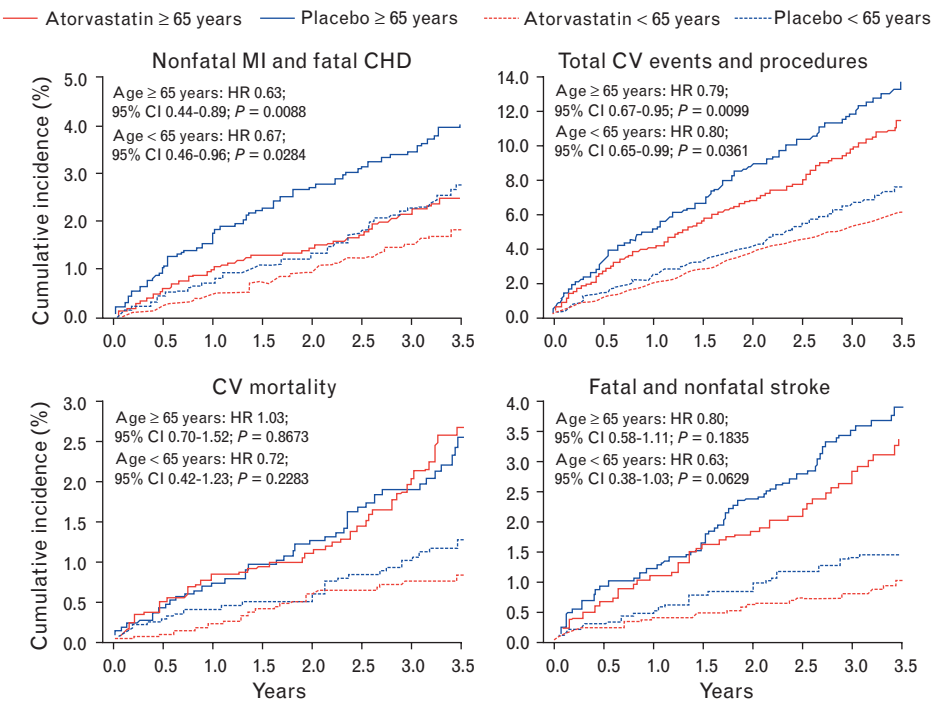
Discussion

Atorvastatin 10 mg significantly reduced the relative risk of the primary endpoint [nonfatal MI (including silent MI) and fatal CHD] to a similar extent (37 and 33%, respectively) in older (aged ≥65 years) and younger patients (aged < 65 years) with relatively well controlled hypertension and without a history of CHD or markedly elevated baseline cholesterol levels. However, because the older group was at higher absolute coronary risk compared with the younger group (11.7 vs. 7.6 primary endpoints per 1000 patient years, respectively, in the placebo group), the absolute benefits of atorvastatin were greater among older patients with hypertension.

In the overall ASCOT-LLA population, compared with placebo, atorvastatin was associated with a significant 27% reduction in fatal and nonfatal stroke [19]. In this post-hoc analysis, there was no significant difference in the reduction in this endpoint between the older and younger groups [20% ($P = 0.18$) vs. 37% ($P = 0.06$), respectively]. However, due to the relatively small number of stroke events in ASCOT-LLA (overall 144 among the older group and 66 among the younger group) and the truncated follow-up, the study had very limited power to detect a significant effect on stroke in these age subgroups. Furthermore, the treatment effect would have been diluted through drops-out from those randomized to atorvastatin (20 vs. 13.5% among the older and younger groups, respectively) and drop-ins among those allocated to placebo (12 vs. 11.5%, respectively). Thus, the observed effect is likely to be an underestimate of the true effect of the drug.

The current evidence concerning the association between total cholesterol and stroke remains the subject of much debate. The Prospective Studies Collaboration combined data from 61 prospective observational studies (900 000 adults aged between 40 and 89 years without

Fig. 3



Cumulative incidence for nonfatal myocardial infarction and fatal coronary heart disease, total cardiovascular events and procedures, cardiovascular mortality, and fatal and nonfatal stroke among patients aged at least 65 years and patients aged less than 65 years. CHD, coronary heart disease; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

previous CVD), but could not explain the absence of an independent positive association between total cholesterol and stroke mortality, particularly at older ages and higher levels of BP [21]. Although these observational data are consistent with the results from PROSPER [8] that demonstrated no benefit from statin therapy on stroke mortality, it conflicts with the findings from many other randomized controlled trials (RCTs) [5,6,9,10]. For example, the Cholesterol Treatment Trialists' Collaboration (to which ASCOT-LLA contributed data) [9] analyzed 90 056 patients participating in 14 RCTs and demonstrated that for a 38.6 mg/dl (1 mmol/l) reduction in total cholesterol, statins reduced stroke by 17% (hazard ratio 0.83; 95% CI 0.78–0.88; $P < 0.0001$). In support of these findings, the recently published Stroke Prevention by Aggressive Reduction in Cholesterol Levels

Table 2 Safety outcomes

	Patients aged ≥65 years		Patients aged <65 years	
	Atorvastatin ($n = 2189$)	Placebo ($n = 2256$)	Atorvastatin ($n = 2979$)	Placebo ($n = 2881$)
SAE (%)				
All reported SAEs	26.3	27.3	18.4	20.9
Discontinuations due to all SAEs	0	0.4	0.1	0.3
AE (%)				
Discontinuations due to all AEs	3.5	3	2	2.2
Discontinuations due to musculoskeletal or connective tissue disorders	0.8	0.7	0.6	0.3
Myalgia (all grades)	2.6	3.3	2.9	2.8
Development of diabetes mellitus	2.8	3.1	4.7	3.8
Development of renal impairment	0.9	0.8	0.4	0.2
ALT elevations ($>3 \times$ ULN)	0.5	0.7	1.1	1.9
Heart failure	1.4	1.2	0.3	0.3
Life-threatening arrhythmias	0.3	0.1	0.1	0
Non-CV deaths	3.8	4.1	0.9	1.3
New nonfatal cancer	6.8	6.7	4	4
Deaths from cancer	2.8	2.8	0.6	0.8

AE, adverse event; ALT, alanine aminotransferase; CV, cardiovascular; SAE, serious adverse event; ULN, upper limit of normal.

(SPARCL) study of 4731 patients (mean age 63 years) with recent stroke or TIA but no known CHD, reported a significant 16% reduction in fatal and nonfatal stroke in patients receiving atorvastatin 80 mg compared with placebo over a median 4.9-year follow-up (hazard ratio 0.84; 95% CI 0.71–0.99; $P = 0.03$) [10]. This significant treatment difference was driven by the smaller number of ischemic strokes in the atorvastatin-treated vs. placebo-treated patients (218 vs. 274, respectively). Hemorrhagic strokes were much less common in both treatment groups. However, there were more hemorrhagic strokes in the atorvastatin-treated than the placebo-treated patients (55 vs. 33, respectively). Unfortunately, the inclusion of patients with brain hemorrhage at the start of the study was thought to preclude any meaningful conclusions on the benefits or potential risks of statins on hemorrhagic strokes in patients with a prior history of strokes and TIA [10]. Nevertheless, the association between low LDL cholesterol and hemorrhagic stroke had been observed in Multiple Risk Factor Intervention Trial (MRFIT) [22] and the Honolulu Heart Program [23] and simvastatin did result in an increase in the rate of hemorrhagic stroke in the Heart Protection Study (HPS) [24], so the overall benefit of statin therapy on stroke appears limited to the prevention of ischemic stroke. As ischemic stroke is more frequent, especially when BP is controlled, as in the ASCOT and HPS cohorts, statins prevent strokes overall. Amarenco *et al.* [10] suggest that the potential risk of hemorrhage should be considered when using statins in patients with prior hemorrhagic strokes and take into account the risk of major coronary events that were so strongly prevented in SPARCL (hazard ratio 0.65; 95% CI 0.49–0.87; $P = 0.003$). Thus, further studies are needed to elucidate the relationship and mechanism of action underpinning statin-associated LDL-C reduction and stroke events in older adults.

Despite the growing evidence that cholesterol lowering with statins gives similar relative and much greater absolute benefits in older patients, treatment in the community is lagging behind [14]. Data from the US National Health and Nutrition Examination Survey (NHANES 2004) demonstrated that among adults aged at least 65 years with dyslipidemia, less than half (43%) reported receiving lipid-lowering treatment [16]. Similarly, data from the nationally representative 2003 Health Survey for England demonstrated that among adults with hypertension and total cholesterol 193 mg/dl (5 mmol/l) or more, only one third (32.7%) reported being prescribed statin therapy [15].

Reasons for the underuse of lipid-lowering therapy, particularly among the elderly, may partly be due to concerns about the predictive value of LDL-C in the elderly [25] and the safety of statins in this age group [8,17]. Recent data from the Whitehall study demonstrated that the associations between ischemic heart disease and total cholesterol to HDL-C ratio and apolipoprotein (Apo)-B to Apo-A1 ratio were not reduced as age increased, even in patients aged 80 years and above [26]. The authors concluded that 'differences in lipid levels that are achievable by statin use were associated with about a one-third lower risk of ischemic heart disease, irrespective of age' [26].

Despite widespread anxiety about the safety of statins in older patients and concerns about the detrimental effects of poly-pharmacy [17], adding atorvastatin to the antihypertensive regimen of patients aged 65 years or older in ASCOT-LLA caused large cardiovascular benefits but very few additional problems. In ASCOT-LLA, compared with placebo, atorvastatin was as well tolerated in patients aged 65 years or older as in those aged less than 65 years. The concerns regarding the increase in cancer rates, as seen in the PROSPER trial [8], were not replicated in ASCOT-LLA in either the older or younger group nor in the Cholesterol-Lowering Treatment Trialists Collaboration [9]. Furthermore, our findings are consistent with a pooled analysis of 50 published and unpublished randomized atorvastatin trials (not including ASCOT-LLA) involving 5924 patients aged 65 years or older, which found that adverse event profiles for patients receiving atorvastatin 10–80 mg were similar to those seen in matched patients receiving placebo [12].

This post-hoc subgroup analysis of the ASCOT-LLA trial contributes to the growing body of evidence from epidemiologic studies of cholesterol in the elderly [26], and RCTs [6–13] that have demonstrated the scientific basis and value of statin therapy in older adults. Indeed, guidelines are already shifting to reflect the improved evidence for treating older patients; the latest guidance from the National Institute of Clinical Excellence (NICE) in the UK advocates treating all patients with statins who have had cardiovascular events, or have more than 20% 10-year absolute risk of a cardiovascular event regardless of their starting level of cholesterol [27]. The National Cholesterol Education Program Treatment Panel III guidelines also highlight that older persons benefit from therapeutic lowering of LDL-C [28].

Thus, the findings from this subanalysis of the ASCOT-LLA data reinforce current guidelines that recommend statin therapy for older patients at moderate cardiovascular risk, even when total cholesterol is not considered to be elevated.

Acknowledgements

A full list of investigators and sponsors of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study is available in the primary publication. This substudy was an independent analysis funded by Pfizer Inc. D.C. had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in the design of the study, the interpretation of the data,

and the development of the article. Editorial support was provided by Dr Richard Hogan and Dr Sarah Partridge of UBC Scientific Solutions and funded by Pfizer Inc., New York, New York, USA.

D.J.C., N.R.P., B.D., P.S.S., H.W., and M.J.C. have served as consultants or received travel expenses, or payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market blood-pressure-lowering or lipid-lowering drugs. D.J.C., M.J.C., N.R.P., and P.S.S. are grateful for support from the NIHR Biomedical Research funding scheme. J.B. was an employee of Pfizer at the time the study was conducted.

References

1 Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, *et al.* Heart Disease and Stroke Statistics 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009; **119**:e21–e181.

2 Kung HC, Hoyert DL, Xu J, Murphy SL. Deaths: final data for 2005. *Natl Vital Stat Rep* 2008; **56**:1–120.

3 Stamler J, Wentworth D, Neaton JD. Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356 222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA* 1986; **256**:2823–2828.

4 Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, *et al.* Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333**:1301–1307.

5 Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998; **339**:1349–1357.

6 Lewis SJ, Moye LA, Sacks FM, Johnstone DE, Timmis G, Mitchell J, *et al.* Effect of pravastatin on cardiovascular events in older patients with myocardial infarction and cholesterol levels in the average range. Results of the Cholesterol and Recurrent Events (CARE) trial. *Ann Intern Med* 1998; **129**:681–689.

7 MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002; **360**:7–22.

8 Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, *et al.* Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER): a randomised controlled trial. *Lancet* 2002; **360**:1623–1630.

9 Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. *Lancet* 2005; **366**:1267–1278.

10 Amarenco P, Bogousslavsky J, Callahan A, Goldstein LB, Hennerici M, Rudolph AE, *et al.* High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; **355**:549–559.

11 Hunt D, Young P, Simes J, Hague W, Mann S, Owensby D, *et al.* Benefits of pravastatin on cardiovascular events and mortality in older patients with coronary heart disease are equal to or exceed those seen in younger patients: results from the LIPID trial. *Ann Intern Med* 2001; **134**:931–940.

12 Hey-Hadavi JH, Kuntze E, Luo D, Silverman P, Pittman D, Lepetri B. Tolerability of atorvastatin in a population aged > or = 65 years: a retrospective pooled analysis of results from fifty randomized clinical trials. *Am J Geriatr Pharmacother* 2006; **4**:112–122.

13 Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJ, Eisenberg MJ. Statins for secondary prevention in elderly patients: a hierarchical bayesian meta-analysis. *J Am Coll Cardiol* 2008; **51**:37–45.

14 Ko DT, Mamdani M, Alter DA. Lipid-lowering therapy with statins in high-risk elderly patients: the treatment-risk paradox. *JAMA* 2004; **291**:1864–1870.

15 Primatesta P, Poulter NR. Levels of dyslipidaemia and improvement in its management in England: results from the Health Survey for England 2003. *Clin Endocrinol (Oxf)* 2006; **64**:292–298.

16 McDonald M, Hertz RP, Unger AN, Lustik MB. Prevalence, awareness, and management of hypertension, dyslipidemia, and diabetes among United States adults aged 65 and older. *J Gerontol A Biol Sci Med Sci* 2009; **64**:256–263.

17 Ali R, Alexander KP. Statins for the primary prevention of cardiovascular events in older adults: a review of the evidence. *Am J Geriatr Pharmacother* 2007; **5**:52–63.

18 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.* Rationale, design, methods and baseline demography of participants of the Anglo-Scandinavian Cardiac Outcomes Trial. ASCOT investigators. *J Hypertens* 2001; **19**:1139–1147.

19 Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, *et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003; **361**:1149–1158.

20 Sever PS, Poulter NR, Dahlof B, Wedel H, Beevers G, Caulfield M, *et al.* The Anglo-Scandinavian Cardiac Outcomes Trial lipid lowering arm: extended observations 2 years after trial closure. *Eur Heart J* 2008; **29**:499–508.

21 Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. *Lancet* 2007; **370**:1829–1839.

22 Iso H, Jacobs DR Jr, Wentworth D, Neaton JD, Cohen JD. Serum cholesterol levels and six-year mortality from stroke in 350 977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989; **320**:904–910.

23 Yano K, Reed DM, MacLean CJ. Serum cholesterol and hemorrhagic stroke in the Honolulu Heart Program. *Stroke* 1989; **20**:1460–1465.

24 Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20 536 people with cerebrovascular disease or other high-risk conditions. *Lancet* 2004; **363**:757–767.

25 Schatz IJ, Masaki K, Yano K, Chen R, Rodriguez BL, Curb JD. Cholesterol and all-cause mortality in elderly people from the Honolulu Heart Program: a cohort study. *Lancet* 2001; **358**:351–355.

26 Clarke R, Emberson JR, Parish S, Palmer A, Shipley M, Linksted P, *et al.* Cholesterol fractions and apolipoproteins as risk factors for heart disease mortality in older men. *Arch Intern Med* 2007; **167**:1373–1378.

27 National Institute for Clinical Excellence. Technology Appraisal 94. Statins for the prevention of cardiovascular events; 2006. www.nice.org.uk/TA094.

28 Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, *et al.* Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **110**:227–239.