

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

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Lancet 2004; 364: 685–96

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Summary

Background Type 2 diabetes is associated with a substantially increased risk of cardiovascular disease, but the role of lipid-lowering therapy with statins for the primary prevention of cardiovascular disease in diabetes is inadequately defined. We aimed to assess the effectiveness of atorvastatin 10 mg daily for primary prevention of major cardiovascular events in patients with type 2 diabetes without high concentrations of LDL-cholesterol.

Methods 2838 patients aged 40–75 years in 132 centres in the UK and Ireland were randomised to placebo (n=1410) or atorvastatin 10 mg daily (n=1428). Study entrants had no documented previous history of cardiovascular disease, an LDL-cholesterol concentration of 4·14 mmol/L or lower, a fasting triglyceride amount of 6·78 mmol/L or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. The primary endpoint was time to first occurrence of the following: acute coronary heart disease events, coronary revascularisation, or stroke. Analysis was by intention to treat.

Findings The trial was terminated 2 years earlier than expected because the prespecified early stopping rule for efficacy had been met. Median duration of follow-up was 3·9 years (IQR 3·0–4·7). 127 patients allocated placebo (2·46 per 100 person-years at risk) and 83 allocated atorvastatin (1·54 per 100 person-years at risk) had at least one major cardiovascular event (rate reduction 37% [95% CI –52 to –17], $p=0\cdot001$). Treatment would be expected to prevent at least 37 major vascular events per 1000 such people treated for 4 years. Assessed separately, acute coronary heart disease events were reduced by 36% (–55 to –9), coronary revascularisations by 31% (–59 to 16), and rate of stroke by 48% (–69 to –11). Atorvastatin reduced the death rate by 27% (–48 to 1, $p=0\cdot059$). No excess of adverse events was noted in the atorvastatin group.

Interpretation Atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes without high LDL-cholesterol. No justification is available for having a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statins. The debate about whether all people with this disorder warrant statin treatment should now focus on whether any patients are at sufficiently low risk for this treatment to be withheld.

Introduction

Type 2 diabetes is associated with a two to fourfold increased risk of both coronary heart disease and stroke.^{1–3} Case-fatality rates for myocardial infarction and stroke are also raised,^{4–6} emphasising the need for primary prevention. Findings of observational studies¹ suggest that lipid lowering should have an important place in the primary prevention of cardiovascular disease in people with diabetes. Although LDL-cholesterol is not usually greatly increased in such individuals, it is at least as strong a predictor of coronary heart disease risk as in the general population.¹ In the UK Prospective Diabetes Study,^{7,8} a 1·57-fold increased risk of coronary heart disease was reported for every 1 mmol/L increment in LDL-cholesterol. LDL-cholesterol also predicts stroke risk in patients with type 2 diabetes.⁹

Trials that included participants with diabetes and coronary heart disease have shown that cholesterol

lowering with statins substantially reduces risk of subsequent cardiovascular events.^{10–13} The benefit of lipid lowering for primary prevention of cardiovascular disease is based on evidence showing a significant 33% reduction of this disorder in 2912 patients with diabetes but no previous occlusive vascular disease in the Heart Protection Study (HPS)¹⁴ and a non-significant 16% reduction in coronary heart disease in 2532 hypertensive patients with diabetes without previous occurrence of coronary heart disease in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA).¹⁵

Current prescription rates for lipid lowering in patients with diabetes remain low, even in those with existing cardiovascular disease.^{16,17} Researchers on the international AUDIT study¹⁸ reported that most diabetes specialists were not convinced of the need for lipid lowering down to current guideline targets for primary prevention of cardiovascular disease in type 2 diabetes.

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Furthermore, these guidelines are not consistent with respect to which patients with diabetes warrant lipid-lowering therapy.^{19–21} Thus, further evidence from clinical trials is needed to show the benefits of statin treatment for primary prevention of cardiovascular disease in type 2 diabetes more convincingly and to quantify the benefit more precisely.

The aim of the Collaborative Atorvastatin Diabetes Study (CARDS) was to assess the effectiveness of 10 mg of atorvastatin daily versus placebo in the primary prevention of cardiovascular disease in patients with type 2 diabetes. The trial was stopped 2 years earlier than planned because of significant benefit at the second interim analysis.

Patients and methods

The CARDS protocol has been described in detail elsewhere.²² The study was undertaken in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice. Every centre obtained local research ethics committee approval after approval from the multicentre research ethics committee. All patients gave fully informed written consent.

Patients

Investigators in 132 clinical centres around the UK and Ireland identified potentially eligible individuals by reviewing computerised registers of patients and by opportunistic assessment of people attending diabetes clinics. Men and women aged 40–75 years with type 2 diabetes mellitus (defined with 1985 WHO criteria) diagnosed at least 6 months before study entry were considered for inclusion provided they had at least one or more of the following: a history of hypertension, defined as receiving antihypertensive treatment or having systolic blood pressure of 140 mm Hg or greater or diastolic blood pressure of 90 mm Hg or greater on at least two successive occasions; retinopathy—ie, any retinopathy, maculopathy, or previous photocoagulation; microalbuminuria or macroalbuminuria, defined as a positive Micral or other strip test, an albumin creatinine ratio of 2.5 mg/mmol or greater, or an albumin excretion rate on timed collection of 20 µg/min or more, all on at least two successive occasions; or currently smoking (no minimum number of cigarettes per day was required). All patients reporting current smoking were counselled to quit.

Patients were ineligible if they had any past history of myocardial infarction, angina, coronary vascular surgery, cerebrovascular accident, or severe peripheral vascular disease (defined as warranting surgery). We checked eligibility against the patient's clinical notes and their own recall and assessed lipid eligibility criteria by blood testing at one screening and four pretreatment visits over a 10-week period. We asked patients to attend these visits after a 12 h fast. Mean serum LDL-cholesterol concentration during baseline visits had to be 4.14 mmol/L or lower and serum triglycerides 6.78 mmol/L or less. We excluded patients if they

had a plasma creatinine concentration greater than 150 µmol/L, glycated haemoglobin (HbA1c) of more than 12%, or if during the baseline phase they had less than 80% compliance with placebo. We randomised patients between November, 1997, and June, 2001.

Procedures

Within every centre, the local investigator sequentially randomly assigned eligible patients to study treatment (either placebo or atorvastatin 10 mg daily) from a block of drugs that had been prepackaged for every centre by Pfizer, according to a computer-generated randomisation code. Investigators, pharmacists, study administrators, and patients were unaware of the randomisation code throughout the study.

We saw patients monthly for the first 3 months, then at 6 months, and thereafter 6-monthly. At these visits, we checked safety variables, recorded any adverse events and endpoints, and measured blood pressure and weight. Participating clinics used their usual method for measuring blood pressure. A resting electrocardiogram was recorded annually and Minnesota coded. At every follow-up visit we assessed patient's compliance: they were deemed compliant if they had taken at least 80% of the study drug.

We asked all patients about adverse clinical events at every follow-up visit. Events that needed admission, were life-threatening or fatal, or that caused persistent or significant incapacity were reported as serious adverse events. We discontinued study treatment if amounts of liver transaminase rose to three or more times the upper limit of normal or if creatine phosphokinase concentrations increased to ten or more times the upper limit of normal and if the abnormality persisted on a repeat sample.

To be eligible as endpoints, cardiovascular events had to be acute and hospital-verified. An independent endpoint committee reviewed all reported cardiovascular events and deaths and classified them according to criteria specified in the endpoint protocol. Sudden deaths ascribable to coronary heart disease, but for which an acute myocardial infarction could not be confirmed, were classified as acute coronary heart disease deaths. In addition to clinical events, annual electrocardiograms were Minnesota coded centrally for detection of Q-wave silent myocardial infarction that had not presented clinically.

We gave patients either a fixed dose of placebo or atorvastatin 10 mg daily. If lipid-lowering therapy had to be started for any clinical indication during the study period the investigator could prescribe additional treatment on top of study drug while remaining unaware of treatment allocation. The drugs and doses that were allowed as additional therapy were: atorvastatin 10 mg, simvastatin (up to) 40 mg, pravastatin (up to) 40 mg, fluvastatin (up to) 80 mg, and cerivastatin 0.3 mg (before its withdrawal). If LDL-cholesterol concentrations rose to more than 4.65 mmol/L or triglyceride amounts to more

than 9.0 mmol/L, and these levels persisted 4 weeks later despite attempts to improve glycaemic control, dietary compliance, or both, then the study drug was withdrawn but the patient continued to be followed up. In October, 2002 (ie, for the last 8 months of the study), a protocol change was made that allowed add-in treatment (the same drugs and doses listed above) rather than withdrawal of study drug when these lipid concentrations were exceeded. Participants remained on study drug irrespective of how low their LDL-cholesterol fell.

We measured serum cholesterol and triglyceride concentrations by an automated enzymatic method.²³ Serum apolipoprotein A1 and B concentrations were ascertained by immunonephelometry using a Cobas Mira (Roche, Basel, Switzerland), with reagents and standards supplied by the manufacturer. For samples not needing ultracentrifugation (ie, serum triglyceride \leq 4 mmol/L), we did heparin-manganese precipitation of apolipoprotein-B-containing lipoproteins on whole serum and measured HDL-cholesterol remaining in the supernatant by an enzymatic method. LDL-cholesterol was then calculated with the Friedewald formula.²⁴ If serum triglycerides exceeded 4.0 mmol/L, VLDL was removed by ultracentrifugation. We measured the cholesterol content (LDL and HDL) of a sample of the infranatant. In a second sample, heparin-manganese precipitation of the remaining apolipoprotein-B-containing lipoproteins was done and the supernatant cholesterol (HDL) was measured. We then calculated LDL-cholesterol as the ultracentrifuge infranatant cholesterol ((LDL+HDL)-HDL).

The laboratory participated in the appropriate national quality-control schemes for all analytes. Serum HDL-cholesterol was calibrated against a Centre for Disease Control and Prevention registered laboratory, which also uses the heparin-manganese method, with the regression equation from 86 comparisons between 1999 and 2003.²⁵ By comparison of the heparin-manganese method against a direct HDL procedure (ABX HDL-C Direct method ABX, Shefford, UK) we noted the direct method read on average 10% lower.

We did haematology analyses on whole blood containing potassium EDTA with a Sysmex SE 9500 autoanalyser (Sysmex, Kobi, Japan). We measured HbA1c in whole blood containing fluoride oxalate with a Biorad Diamat high-pressure liquid chromatography analyser (Biorad, Hercules, CA, USA), with standards and controls supplied by the manufacturer. The upper limit of normal for the laboratory was 6.5%. Glucose was measured in plasma containing fluoride oxalate, whereas all other analytes were quantified in heparinised plasma. All other analytes were assessed with an Hitachi 747 autoanalyser (Hitachi, Tokyo, Japan), with standards and controls as recommended by the manufacturer. Creatinine and albumin concentrations were measured annually in single urine samples that stick testing had confirmed were free of infection. Microalbuminuria was defined as an albumin

creatinine ratio greater than 2.5 mg/mmol and macroalbuminuria as a ratio greater than 25 mg/mmol.

Statistical analysis

The study was designed to have 90% power to detect a reduction of a third in the primary endpoint in the atorvastatin 10 mg daily group at a significance level of $p < 0.05$. We judged $p < 0.049$ to be significant for the primary endpoint analyses because this value allowed for the interim analysis effects on the type 1 error rate. To achieve the specified statistical power, assuming a cumulative annual incidence of 2.35% for the primary endpoint in the placebo group, a total of 304 primary endpoints needed to accrue.

The primary endpoint consisted of the first of the following: acute coronary heart disease event (myocardial infarction including silent infarction, unstable angina, acute coronary heart disease death, resuscitated cardiac arrest), coronary revascularisation procedures, or stroke. Prespecified secondary efficacy outcomes were effect of treatment on total mortality and effect of atorvastatin on any acute, hospital-verified cardiovascular endpoint. All analyses were by intention to treat and were specified in an analysis plan before unmasking. All patients who were randomised and took at least one dose of study drug were included in the analyses. The main analysis was a Cox regression survival analysis, comparing the hazard rates for the primary endpoint in the two treatment groups, yielding the hazard ratio as a measure of effect size with its significance level. We confirmed that further stratification by centre did not appreciably alter the hazard ratio. The same statistical approach was used to compare mortality rates and time to the first of any acute cardiovascular endpoint between the treatment arms. The validity of the proportional-hazards assumption was confirmed by a test for interaction of the hazard ratio with time.

Prespecified tests of heterogeneity were used to assess whether the effects in particular subgroups (age, sex, and baseline lipids) differed between groups and we prespecified that we would report the treatment effect for acute coronary heart disease events, coronary revascularisations, and stroke separately. The power to detect small differences in treatment effect between subgroups or to detect significance of treatment effect within subgroups is limited, particularly since the trial terminated early.

We assessed the effect of atorvastatin on lipid concentrations with a linear mixed model using all data for every patient. These models included a test of interaction between the treatment effect and time. A conservative approach of imputing missing lipid values from pretreatment concentrations was used for any patients with no post-treatment values. We calculated numbers needed to treat as the reciprocal of the absolute risk reduction for the primary endpoint for a treatment duration of 4 years (the median follow-up time) in 1000 patients.

The protocol specified that the independent data and safety monitoring board would undertake an interim analysis when 25%, 50%, and 75% of the total anticipated primary endpoints had accrued. The interim analyses used an asymmetric (Peto-Haybittle) type rule²⁶ and we prespecified that the board might advise termination if a significant difference emerged in favour of atorvastatin (at $p < 0.0005$ one-sided, $p < 0.001$ two-sided at any analysis) or in favour of placebo (at $p < 0.005$, 0.1, and 0.2 one-sided, for the three interim analyses, respectively). At the second interim analysis a significant difference was reported in favour of atorvastatin at $p < 0.001$ (two-sided) and so the data and safety monitoring board recommended termination. The CARDS steering committee accepted their recommendation and trial termination was announced on June 12, 2003, 2 years earlier than the anticipated date.

Role of the funding source

CARDS was designed by the coprincipal investigators (HC, DJB, PND, GAH, AWN, JHF) and was funded by the UK Department of Health, Diabetes UK, and Pfizer. All three funding sources had a voting member on the executive and steering committees. Site monitoring, data collection, and data entry was done by staff at Pfizer UK, but data and site monitoring quality-control specification was undertaken in conjunction with the CARDS coordinating Centre at University College London (UCL). Data analysis and its prespecification were done

independently by the CARDS coordinating centre at UCL. This report was prepared by the authors independently of the funding sources, and although the sponsors were allowed to comment on the manuscript they had no right of veto over any of its contents.

Results

Of 4053 individuals initially screened, 3249 (80%) entered the baseline phase (figure 1). Failure to meet the randomisation criteria was the most typical reason for not

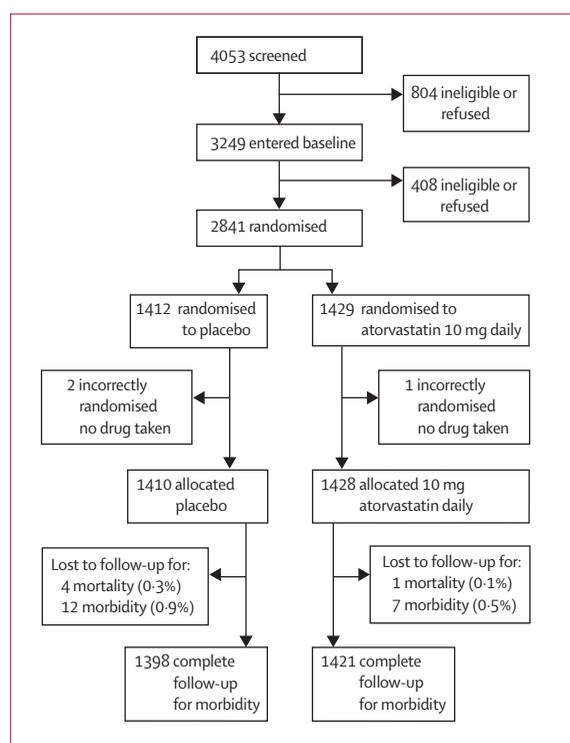


Figure 1: Trial profile

	Placebo (n=1410)	Atorvastatin (n=1428)
Demographics		
Age (years)	61.8 (8.0)	61.5 (8.3)
Age <60 years	529 (38%)	558 (39%)
Age 60–70 years	708 (50%)	703 (49%)
Age >70 years	173 (12%)	167 (12%)
Women	453 (32%)	456 (32%)
White ethnic origin	1326 (94%)	1350 (95%)
Diabetes duration (years)	7.8 (6.33)	7.9 (6.36)
Lipids		
Total cholesterol (mmol/L)	5.35 (0.82)	5.36 (0.83)
LDL-cholesterol (mmol/L)	3.02 (0.70)	3.04 (0.72)
HDL-cholesterol (mmol/L)	1.42 (0.34)	1.39 (0.32)
Median (IQR) triglyceride (mmol/L)	1.67 (1.17–2.40)	1.70 (1.20–2.40)
Non-HDL cholesterol	3.93 (0.82)	3.96 (0.82)
Apolipoprotein A1 (mg/L)	1530 (294)	1530 (271)
Apolipoprotein B (mg/L)	1150 (241)	1170 (243)
Diabetes treatment		
Diet only	228 (16%)	214 (15%)
Oral hypoglycaemic drug only	916 (65%)	932 (65%)
Insulin only	207 (15%)	210 (15%)
Insulin and oral hypoglycaemic drug	59 (4%)	72 (5%)
Retinopathy	427 (30%)	426 (30%)
Body-mass index (kg/m ²)	28.8 (3.52)	28.7 (3.61)
Obese (body-mass index >30 kg/m ²)	537 (38%)	515 (36%)
Albuminuria*		
Micro	153 (15%)	148 (15%)
Macro	17 (2%)	24 (2%)
Median (IQR) urinary albumin creatinine ratio	1.08 (0.57–2.82)	1.15 (0.63–2.78)
Smoking		
Never	485 (34%)	498 (35%)
Ex-smoker	601 (43%)	622 (44%)
Current	323 (23%)	308 (22%)
Hypertension	1184 (84%)	1193 (84%)
Blood pressure		
Systolic (mm Hg)	144 (16.1)	144 (15.9)
Diastolic (mm Hg)	83 (8.4)	83 (8.5)
Blood-pressure lowering drugs		
α blocker	104 (7%)	113 (8%)
β blocker	237 (17%)	219 (15%)
Calcium antagonist	290 (21%)	304 (21%)
Angiotensin-converting enzyme inhibitor or angiotensin II receptor antagonist	615 (44%)	637 (45%)
Diuretic	282 (20%)	262 (18%)
Aspirin or other antiplatelet drug	207 (15%)	221 (15%)
Plasma creatinine (μmol/L)	102 (15.0)	102 (14.7)
HbA1c (%)	7.81 (1.39)	7.87 (1.42)
Fasting plasma glucose (mmol/L)	9.84 (3.21)	10.01 (3.27)

Data are number of patients (%) or mean (SD), unless otherwise indicated. To convert from mmol/L to mg/dL for cholesterol multiply by 38.7; for triglycerides by 88.5. *Albuminuria was identified on the basis of two raised sequential pretreatment readings; denominators are 1013 for placebo and 1006 for atorvastatin.

Table 1: Baseline characteristics

Timepoint	Number of patients (%) ^a taking at least one lipid-lowering drug, including study statin	
	Placebo	Atorvastatin
1 year	32/1349 (2%)	1252/1391 (90%)
2 years	90/1305 (7%)	1184/1360 (87%)
3 years	121/1018 (12%)	918/1071 (86%)
4 years	96/650 (15%)	542/692 (78%)
Average	9%	85%

^aDenominator is patients not known to be dead who have not yet had a primary endpoint. Non-compliance is assumed when data are missing.

Table 2: On-study drug compliance and non-study lipid-lowering drug use

entering this phase (n=647; 81%); of the remaining patients, most simply no longer wanted, or were able, to take part. Of those entering the baseline phase, 2838 were randomised and took at least one dose of study drug. Three patients were randomised but took no drug because we realised they did not meet the entry criteria before they actually took their first dose. Reasons for exclusion at baseline included failure to meet the randomisation criteria (248; 60%) or illness (47; 11%). Only 14 (3%) patients were not randomised because of poor compliance

during the baseline period; the main reason for exclusion in the remainder was that they no longer wanted to take part.

Participants were mainly of white ethnic origin (n=2676; 94%), men (1929; 68%), and had a mean age of 62 years (SD 8). The two treatment groups were well balanced in terms of age, sex, baseline cardiovascular disease risk factors, and diabetes-specific factors (table 1). At entry, 1795 (63%) had one, 859 (30%) had two, 168 (6%) had three, and 16 (1%) had four of the additional entry criteria risk factors (albuminuria, retinopathy, hypertension, current smoking) reported by the local investigator, and these proportions were the same in each group.

Before randomisation, 116 (4%) patients had a concentration of LDL-cholesterol greater than 4.14 mmol/L and 418 (15%) had total cholesterol of more than 6.2 mmol/L. 18% of each group (268 atorvastatin, 249 placebo) were on metformin only at baseline, 28% were on metformin and a sulfonyleurea (404 atorvastatin, 392 placebo), and 23% of each group were on a sulfonyleurea only (326 atorvastatin, 329 placebo). Five participants in each group were incorrectly randomised with previous cardiovascular disease. Three patients were entered who had type 1 diabetes (two placebo, one atorvastatin group).

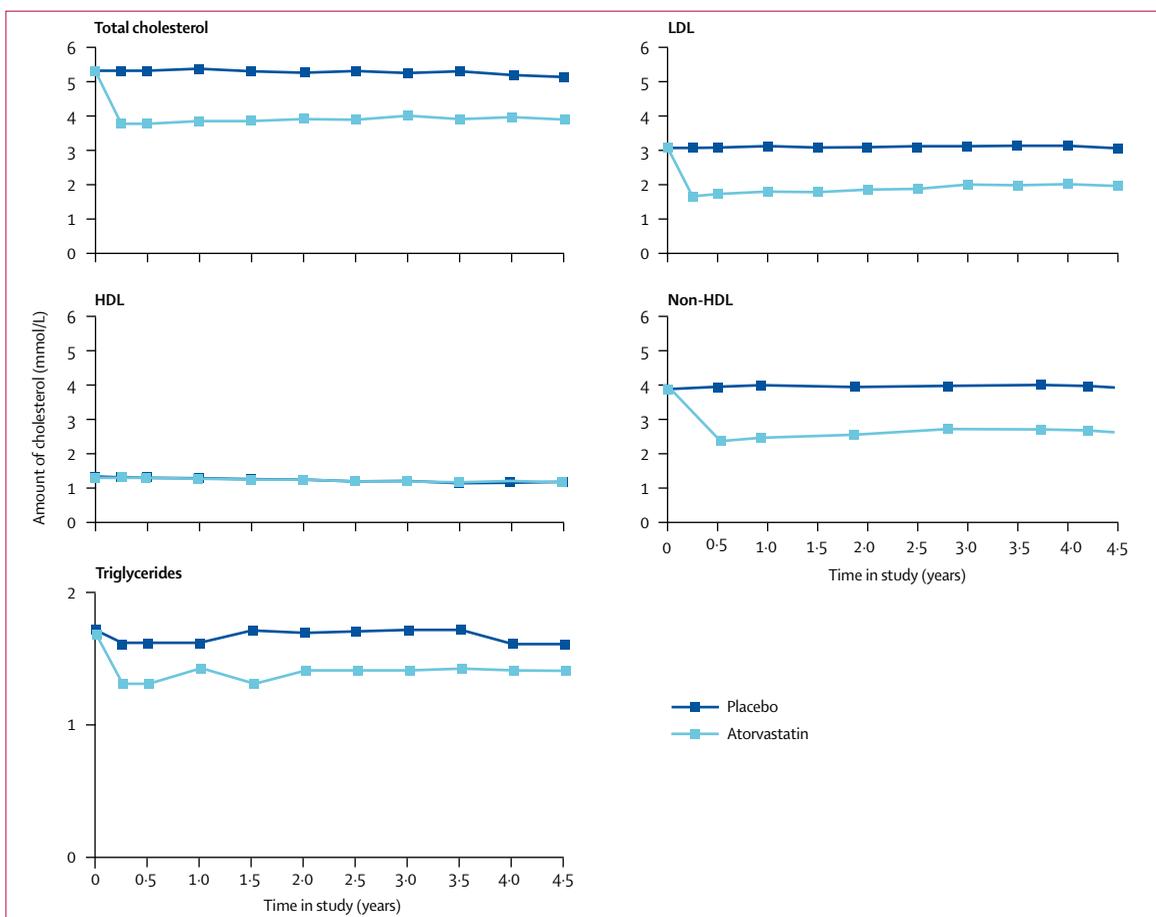


Figure 2: Median lipid concentrations

	Mean (SD) concentration						Average treatment effect across the study		
	Baseline	6 months	1 year	2 years	3 years	4 years	Absolute units (95% CI)	Percentage effect* (95% CI)	p
Number of patients†									
Placebo	1409	1306	1290	1258	977	609
Atorvastatin	1428	1346	1322	1279	1014	632
LDL-cholesterol (mmol/L)									
Placebo	3.02 (0.70)	3.07 (0.79)	3.10 (0.80)	3.04 (0.82)	3.04 (0.82)	3.12 (0.80)	-1.20 (-1.23 to -1.17)	-40% (-41 to -39)	<0.0001
Atorvastatin	3.04 (0.72)	1.75 (0.63)	1.86 (0.69)	1.94 (0.73)	2.07 (0.71)	2.11 (0.70)
Total cholesterol (mmol/L)									
Placebo	5.35 (0.82)	5.40 (0.89)	5.42 (0.90)	5.34 (0.93)	5.31 (0.90)	5.28 (0.91)	-1.40 (-1.43 to -1.37)	-26% (-27 to -26)	<0.0001
Atorvastatin	5.36 (0.83)	3.87 (0.76)	3.97 (0.81)	4.03 (0.83)	4.14 (0.87)	4.12 (0.84)
HDL-cholesterol (mmol/L)									
Placebo	1.42 (0.34)	1.39 (0.36)	1.37 (0.37)	1.33 (0.36)	1.29 (0.33)	1.23 (0.30)	0.02 (0.01 to 0.03)	1% (0.7 to 2)	0.0002
Atorvastatin	1.39 (0.32)	1.41 (0.35)	1.37 (0.33)	1.35 (0.35)	1.30 (0.32)	1.26 (0.30)
Non-HDL-cholesterol (mmol/L)									
Placebo	3.93 (0.82)	4.01 (0.89)	4.05 (0.91)	4.00 (0.92)	4.02 (0.91)	4.05 (0.90)	-1.42 (-1.45 to -1.39)	-36% (-37 to -35)	<0.0001
Atorvastatin	3.96 (0.82)	2.47 (0.74)	2.60 (0.80)	2.68 (0.83)	2.85 (0.86)	2.86 (0.82)
Triglyceride (mmol/L)									
Placebo	1.93 (1.09)	1.97 (1.22)	1.96 (1.23)	1.98 (1.24)	1.94 (1.21)	1.90 (1.10)	-0.39 (-0.42 to -0.36)	-19% (-20 to -17)	<0.0001
Atorvastatin	1.95 (1.08)	1.53 (0.93)	1.58 (0.88)	1.61 (0.93)	1.66 (0.98)	1.61 (0.93)
Apolipoprotein A1 (mg/L)									
Placebo	1530 (290)	1410 (260)	1460 (300)	1390 (270)	1330 (260)	1310 (230)	-0.16 (-1.4 to 1.1)	-0.1% (-0.9 to 0.7)	0.80
Atorvastatin	1530 (270)	1470 (250)	1470 (290)	1400 (270)	1320 (270)	1320 (230)
Apolipoprotein B (mg/L)									
Placebo	1150 (240)	1150 (280)	1100 (230)	1070 (220)	1060 (220)	1050 (210)	-27 (-28 to -26)	-23% (-24 to -22)	<0.0001
Atorvastatin	1170 (240)	960 (300)	800 (200)	790 (200)	810 (200)	800 (190)

*Treatment effect on within-person change in lipid or lipoprotein across all study points as percentage of placebo mean. †Numbers of patients at every timepoint are given for LDL-cholesterol only, some of the other analytes may have slightly different numbers of patients.

Table 3: Effect of treatment on lipids and lipoproteins

2819 (99%) of those randomised were fully assessable for mortality and morbidity at study termination (figure 1). The median period of observation for the primary endpoint was 4.0 years (IQR 3.0–4.7) in the atorvastatin group and 3.9 years (2.9–4.6) in the placebo group: altogether, 5384 person-years of observation were

available for the primary endpoint in the atorvastatin group and 5166 person-years for the placebo group.

Table 2 shows the proportion of patients allocated placebo and atorvastatin 10 mg daily who were taking atorvastatin, a non-study statin, or both at various timepoints during the study. On average, for 4 years of follow-up, assuming non-compliance in patients missing follow-up and considering only those who did not yet have a primary endpoint, 9% of the placebo group were taking a statin and 85% of those allocated atorvastatin were either taking it, another statin, or both. The net difference in statin use is therefore about 75% rather than 100% if all patients had remained fully compliant with the study drug to which they had been allocated and no add in had occurred.

Figure 2 shows the group median, and table 3 the mean, lipid and lipoprotein concentrations, summarising the treatment effect throughout the study. Allocation to atorvastatin was associated with a net reduction in LDL-cholesterol and triglycerides, and a negligible increase in HDL-cholesterol (table 3). During the treatment phase, median LDL-cholesterol in the atorvastatin group was typically around 2.0 mmol/L (figure 2), and throughout the study at least 75% of patients allocated atorvastatin had a concentration of LDL-cholesterol less than 2.47 mmol/L and at least 25% had a concentration lower than 1.66 mmol/L.

Allocation to atorvastatin was associated with a 37% reduction in incidence of major cardiovascular events (p=0.001; figures 3 and 4). Adjustment for baseline age

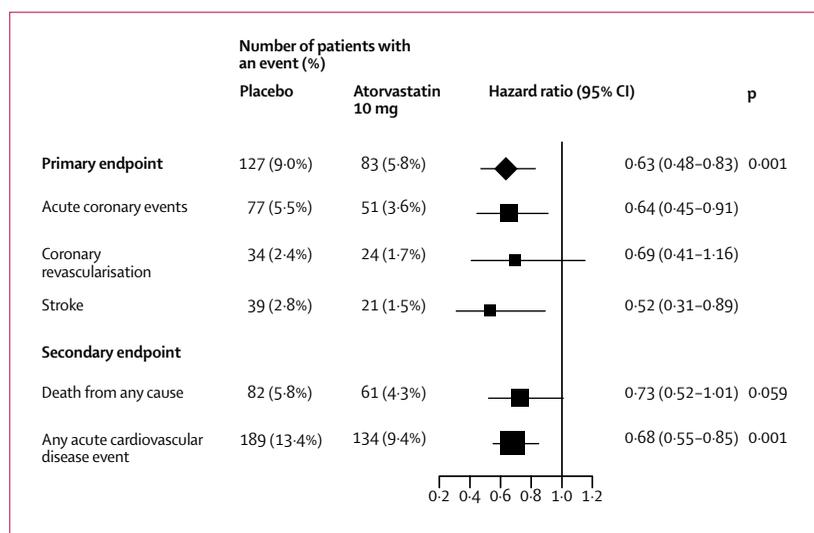


Figure 3: Effect of treatment on primary and secondary endpoints

Total number of acute coronary events, coronary revascularisations, and strokes separately do not equal the total number of primary events shown above, because only the first of these events is included in the primary endpoint. Thus, an individual who has had a stroke and a revascularisation will be counted only once in the primary endpoint but will appear in both separate totals for revascularisation and stroke. Symbol size is proportional to amount of statistical information.

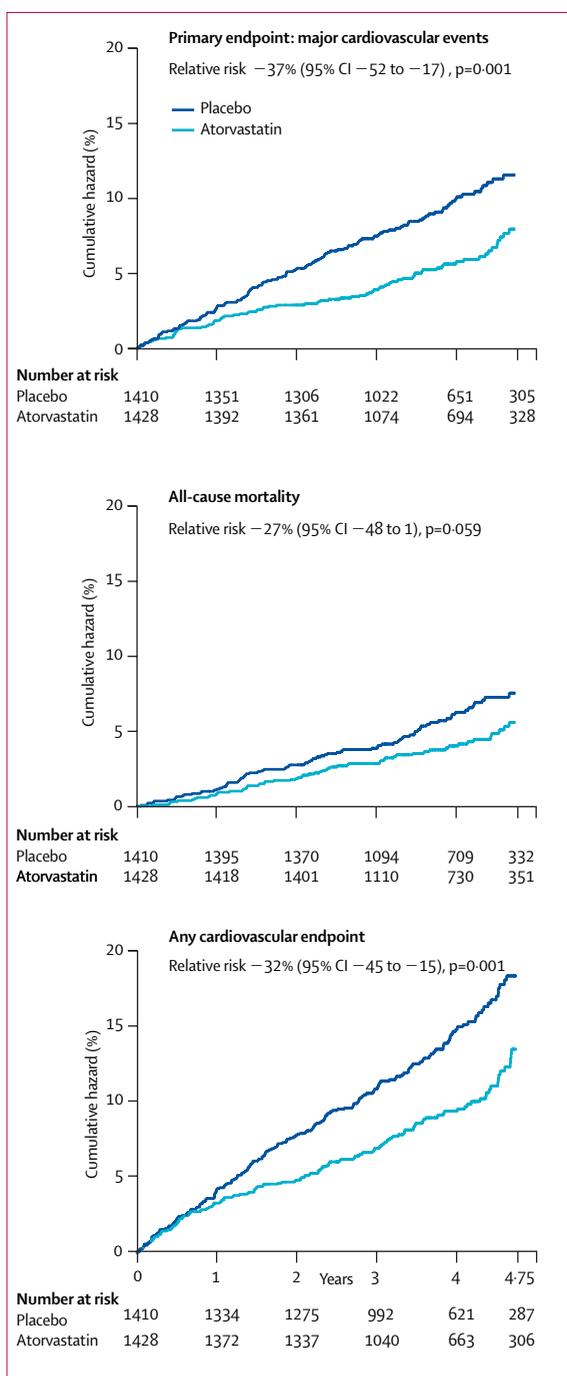


Figure 4: Cumulative hazard of primary endpoint, all-cause mortality, and any cardiovascular endpoint
*p for heterogeneity.

and sex and stratification by centre made no difference to the estimate of the treatment effect (36% risk reduction, p=0.002). There was no violation of the proportional-hazards assumption in the model (p=0.93 for the test for interaction of the hazard ratio with time). Table 4 shows the composition of the primary endpoint in each group.

	Placebo (n=1410)	Atorvastatin (n=1428)
Type of first event		
Fatal myocardial infarction	20	8
Other acute coronary heart disease death	4	10
Non-fatal myocardial infarction*	41	25
Unstable angina	9	7
Resuscitated cardiac arrest	0	0
Coronary revascularisation	18	12
Fatal stroke	5	1
Non-fatal stroke	30	20
Total	127	83

*Five silent myocardial infarctions included in each group.

Table 4: Breakdown of primary endpoint by treatment group

We observed a reduction of 36% in acute coronary events, 31% in coronary revascularisation events, and 48% in stroke, when assessed separately (figure 3). Incidence of acute coronary heart disease events was 1.47 per 100 person-years at risk for patients allocated placebo and 0.94 per 100 person-years at risk for those allocated atorvastatin. If unstable angina was excluded from the definition of non-surgical acute coronary events (to allow comparison with other major clinical trials), incidence was 1.31 per 100 person-years at risk for placebo and 0.88 per 100 person-years at risk for atorvastatin (relative risk reduction 33% [95% CI -53 to -3]). For acute coronary heart disease events plus revascularisations, incidence was 1.93 per 100 person-years at risk for placebo and 1.18 per 100 person-years at risk for atorvastatin.

Prespecified tests for evidence of heterogeneity of effect were not significant for sex (p=0.59) or median age at entry (p=0.58). Patients with lipid concentrations above and below the baseline median had similar treatment effects (figure 5). No evidence of heterogeneity was recorded for baseline systolic blood pressure (p=0.2), retinopathy (p=0.7), albuminuria (p=0.34), smoking status (p=0.7), or HbA1c (p=0.7).

Incidence of major cardiovascular disease events was 24.6 per 1000 person-years at risk in the placebo group and 15.4 per 1000 person-years at risk in the atorvastatin group. Therefore, allocation of 1000 patients to atorvastatin 10 mg daily would avoid 37 first major cardiovascular disease events over a 4-year follow-up period. 27 patients would need to be treated for 4 years to prevent one event. However, incidence of first or subsequent major cardiovascular disease events was 31.8 per 1000 person-years at risk in the placebo group and 19.5 per 1000 person-years at risk in the atorvastatin group. Therefore, allocation of 1000 such patients to atorvastatin 10 mg daily would be expected to be associated with 50 fewer first or subsequent major cardiovascular disease events over a 4-year period of follow-up.

82 people in the placebo group (6% of those randomised; 1.51 per 100 person-years at risk) and

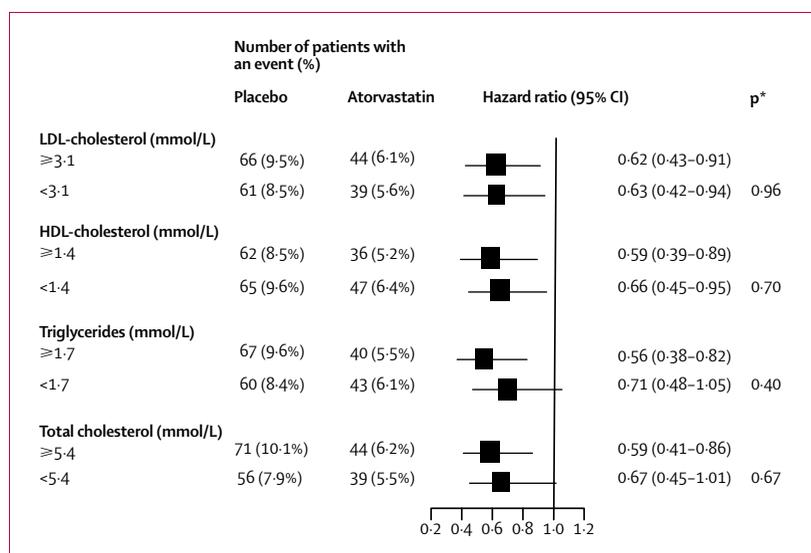


Figure 5: Effect of treatment on the primary endpoint by median lipid level at baseline. Symbol size is proportional to amount of statistical information. p values are for test of heterogeneity.

61 who were allocated atorvastatin (4% of those randomised, 1.10 per 100 person-years at risk) died, a 27% reduction in total mortality (figures 3 and 4). Allocation to atorvastatin was associated with a 32% reduction in the rate of acute cardiovascular endpoints.

Overall frequency of adverse events or serious adverse events did not differ between treatments. In each group, 1.1% of patients randomised (19 atorvastatin, 20 placebo) had one or more serious adverse events judged by the attending clinician to be possibly associated with study drug. A similar proportion reported that they discontinued study drug at some point during the trial because of an adverse event (145 [10%] placebo, 122 [9%] atorvastatin). 30 people in the placebo group and 20 in the atorvastatin group died from cancer ($p=0.14$). Overall, 45 non-cardiovascular deaths happened in the placebo group (3.2% of those randomised) and 36 in the atorvastatin group (2.5%). When we excluded patients allocated placebo who had ever taken additional statin treatment, there remained no difference in the overall frequency of adverse events or serious adverse events between the treatment groups.

No occurrences of rhabdomyolysis were reported. One case of myopathy was seen in each of the placebo and atorvastatin groups and myalgia was noted in 72 patients allocated placebo and 61 allocated atorvastatin. Ten individuals in the placebo group (0.7% of those randomised) and two (0.1%) in the atorvastatin group had at least one rise in creatinine phosphokinase of ten or more times the upper limit of normal on routine safety screening. In six of these ten placebo patients and in both atorvastatin patients, pretreatment creatinine phosphokinase concentrations were also above the upper limit of normal. Only one of these ten people in the placebo group reported any statin use at any point in

the study. Nine patients allocated placebo and seven in the atorvastatin group discontinued from study drug because of muscle-related events. 14 (1%) individuals allocated placebo and 17 (1%) atorvastatin had at least one increase of alanine transaminase of three or more times the upper limit of normal. At least one rise in aspartate transaminase of three or more times the upper limit of normal was reported in four (0.3%) patients in the placebo group and six (0.4%) in the atorvastatin group. Of those allocated placebo with transaminase rises, three with increased alanine transaminase and one with raised aspartate transaminase had received additional statin treatment.

At randomisation, two-thirds of patients in both treatment groups reported use of blood-pressure lowering drugs (table 1); at 4 years, 595 (84%) allocated placebo and 605 (83%) allocated atorvastatin were taking these drugs. Mean systolic and diastolic blood pressure at this timepoint was 144 (SD 17) and 79 (10) mm Hg in the placebo group and 143 (17) and 80 (10) mm Hg in the atorvastatin group. Mean body-mass index at 4 years was 29.4 kg/m² (SD 4) in patients allocated placebo and 29.2 kg/m² (4) in those allocated atorvastatin, and at 4 years follow-up, mean HbA1c was 8.1% (1.5) in the placebo group and 8.3% (1.5) in the atorvastatin group. At 4 years, use of insulin alone and the combination of insulin and oral hypoglycaemic drugs had risen; insulin alone was taken by 139 (20%) individuals allocated placebo and 156 (21%) allocated atorvastatin and the combination by 118 (17%) placebo and 137 (19%) atorvastatin patients. Use of oral hypoglycaemic drugs alone had fallen since randomisation, and 403 (57%) in the placebo group and 397 (54%) in the atorvastatin group were taking these drugs.

Discussion

The results of CARDS show that atorvastatin 10 mg daily leads to a substantial reduction (37%) in major cardiovascular events in patients with type 2 diabetes with no history of cardiovascular disease and without high LDL-cholesterol concentrations; this drug also reduced the risk of stroke (48%). The treatment effect did not vary by pretreatment cholesterol amount. On-treatment LDL-cholesterol concentrations were substantially lower than current target amounts in most treatment guidelines, and no safety concerns were raised.^{19–21} Adverse event rates were similar in the treated and placebo groups, and no cases of rhabdomyolysis were noted. The large treatment effect reported led to termination of the trial 2 years earlier than expected.

We recorded a 27% fall in all-cause mortality in patients allocated atorvastatin. The early termination of the trial meant that fewer deaths were observed than originally envisaged, reducing the power of the trial to show a significant reduction in all-cause mortality. A reasonable interpretation of these data is, however, that treatment resulted in a substantial reduction in

mortality, although the exact magnitude of this effect remains imprecise.

These data extend and strengthen the evidence for more widespread use of statins for primary prevention in type 2 diabetes and show that such treatment is safe. This evidence emphasises the pivotal role that lipid lowering has in the primary prevention of cardiovascular disease in type 2 diabetes and should result in lipids receiving at least the same attention as glycaemic and blood-pressure control in the management of such patients.

The CARDS findings are robust. The absence of any active treatment run-in period means that the safety data are representative of use in clinical practice. Evaluability for morbidity and mortality was almost complete at the termination of the trial. All analyses were prespecified before unmasking of data, and the data analysis team was independent of the study sponsors.

The average difference in statin use across the study between patients allocated placebo and those allocated atorvastatin was 75% rather than 100% if all patients had remained on the treatment to which they had been allocated. Thus, the recorded 37% risk reduction in the primary endpoint of major cardiovascular disease events is a conservative estimate, and we could argue that with perfect compliance and no add-in treatment a risk reduction of up to 49% in this endpoint might be expected.

The risk reduction in major cardiovascular disease events in CARDS is larger than the point estimates seen in HPS and ASCOT-LLA,^{14,15} but accords with the findings of those studies. HPS included 2912 patients with diabetes and no previous occlusive vascular disease. Over about 5 years of follow-up, 13.5% of the placebo group had a major vascular event compared with 9.3% of those allocated simvastatin 40 mg daily, a relative risk reduction of 33% ($p=0.0003$).¹⁴ The average difference in LDL-cholesterol between treatment groups was 0.9 mmol/L compared with 1.20 mmol/L in CARDS. In the lipid-lowering group of ASCOT-LLA,¹⁵ patients with hypertension without coronary heart disease or a recent cerebrovascular event had a significant 36% reduction ($p=0.0005$) in non-fatal myocardial infarction and fatal coronary heart disease with the same dose of atorvastatin 10 mg daily as in CARDS. However, in the 2532 patients with hypertension and diabetes in ASCOT-LLA, non-fatal myocardial infarction and fatal coronary heart disease (the primary endpoint) were reduced by 16%. This reduction in coronary heart disease was not significant ($p=0.43$) but neither was it significantly different from the treatment effect in the overall trial population—ie, no heterogeneity of effect.¹⁵ The lower estimate of treatment effect in patients with diabetes in ASCOT-LLA compared with CARDS and HPS is most probably attributable to chance, especially since only 84 coronary heart disease events arose in people with diabetes. Other possible explanations raised by the ASCOT-LLA investigators were the greater add-in treatment in the placebo arm in patients with

diabetes compared with those without this disorder. Together, the CARDS, HPS, and ASCOT-LLA studies provide evidence that statin treatment is effective for the primary prevention of cardiovascular disease in type 2 diabetes.

The large reduction in acute coronary events in CARDS was consistent with the noted average difference in LDL-cholesterol between the treatment groups of 1.20 mmol/L. However, the relation between LDL-cholesterol and stroke risk is less clear in observational studies^{27,28} and so the effect on stroke was not predictable. Large-scale meta-analyses have not shown any relation with all strokes combined or have reported positive associations with ischaemic stroke and inverse associations with haemorrhagic stroke.^{27,28} This inconsistency in the strength of relation between LDL-cholesterol and stroke in epidemiological studies could partly indicate the absence of distinction between haemorrhagic and ischaemic strokes in some studies. In a meta-analysis of statin trials, a 21% reduction in stroke risk was reported for every 1 mmol/L LDL-cholesterol reduction.²⁹ Thus, a decrease of about 1.2 mmol/L should lead to a reduction in stroke of about 25%. The effect seen in CARDS is almost double this value at 48%, although the 95% CI includes a 25% effect.

How soon after starting treatment does benefit accrue? The proportional-hazards assumption was not violated and is consistent with achievement of the relative risk reduction from quite early after treatment initiation. Indeed, post-hoc analysis shows that the relative risk reduction in the primary endpoint at 1 year was 33% and at 2 years was 45% ($p=0.002$ at 2 years).

To what proportion of patients with type 2 diabetes can the data on benefits and safety of atorvastatin be generalised? Although the inclusion criteria required that for individuals to be eligible for randomisation one or more additional risk factors for cardiovascular disease should be present, we think that in fact most patients with type 2 diabetes probably have at least one risk factor anyway. For example, in patients with this disorder and no previous cardiovascular disease in the population-based Tayside study,³⁰ 70% had at least one of hypertension, current smoking, or retinopathy (data for our other entry risk factor, albuminuria, were not available; personal communication, Peter James and Andrew Morris, University of Dundee, UK). This finding suggests that the CARDS results are directly applicable to most patients with type 2 diabetes. Analysis of the data available from NHANES III (<http://www.cdc.gov/nchs>) in the USA shows that 82% of patients with diabetes have at least one of the CARDS entry criteria risk factors, but no previous coronary heart disease. Furthermore, in CARDS, no evidence was recorded of heterogeneity in the treatment effect by baseline risk factors, suggesting that the relative risk reduction of more than a third that was noted is likely to extend to patients with type 2 diabetes without any of these risk factors. A primary prevention trial of lipid

lowering that focuses on patients with type 2 diabetes and no additional risk factors will probably never be undertaken. This fact, and the good safety profile we reported, suggests that it is justifiable to infer that the relative risk reduction reported would probably be generalisable to all patients with type 2 diabetes without previous cardiovascular disease.

Selection of patients warranting treatment should be based on the absolute risk reduction and not just the relative risk reduction. In CARDS, the risk of major cardiovascular disease events over the median follow-up of 4 years in the placebo group was 10%, so that even with the most conservative assumptions—ie, assuming a constant hazard rather than one increasing with age—CARDS patients typically had a 10-year risk of a major cardiovascular disease event of about 25%. Treatment with atorvastatin 10 mg daily for 4 years in 1000 such patients would prevent 37 first major cardiovascular events and 50 first or subsequent such events. One major first cardiovascular event would be avoided for every 27 patients treated for 4 years. We have expressed these measures of absolute benefit at our median duration of follow-up of 4 years. The absolute risk of cardiovascular disease in patients with diabetes and no previous occlusive disease in HPS was very similar to CARDS at 13.5% over 5 years in the placebo group. The HPS investigators estimated that 5 years of simvastatin treatment would prevent 30 major cardiovascular disease events in patients with diabetes and no previous occlusive vascular disease. Extrapolation of the CARDS results to 5 years gives an estimate of 46 events avoided for 5 years of treatment with atorvastatin.

Current guidelines on lipid-lowering treatment for primary prevention of cardiovascular disease in type 2 diabetes vary. The American Diabetes Association, the Joint European Societies, and the National Cholesterol Education Programme (NCEP) panel are now consistent in recommending lipid-lowering treatment for the primary prevention of cardiovascular disease in patients with diabetes whose LDL-cholesterol is 3.35 mmol/L or greater.^{19–21} For those with an LDL-cholesterol of 2.6–3.35 mmol/L these guidelines differ, with the Joint European Societies recommending treatment, the NCEP recommending treatment in most patients with diabetes except when there is low risk, eg, because of young age, and the American Diabetes Association refraining from unequivocally recommending drug treatment for LDL-cholesterol in this range. The targets for patients on treatment are 2.5–2.6 mmol/L in all three guidelines.^{19–21}

With respect to these guidelines, some key aspects of CARDS included that at study entry, two-thirds of patients had LDL-cholesterol at or below the American Diabetes Association treatment threshold level of 3.35 mmol/L. Indeed, at entry a quarter of individuals already had LDL-cholesterol at or below the current American Diabetes Association and Joint European Societies guideline target level. During the treatment phase, 75% of patients

allocated to atorvastatin 10 mg achieved a concentration at or below the current European target of 2.5 mmol/L. The median LDL-cholesterol on atorvastatin was just 2 mmol/L and 25% had a concentration less than 1.7 mmol/L. Thus, much of the efficacy and safety profile reported in CARDS relates to levels of starting and achieved LDL-cholesterol below those specified in the European Societies and American Diabetes Association guidelines.

In July, 2004, the NCEP made a revision of the ATP III guidelines recommending optional target concentrations of LDL-cholesterol of 1.8 mmol/L in patients with diabetes who have previous cardiovascular disease.²¹ They refrained from making this recommendation in individuals with diabetes without previous cardiovascular disease or from clearly recommending treatment initiation at an LDL-cholesterol less than 2.6 mmol/L in such patients. One of the reasons given for the differing recommendations for primary and secondary prevention was that in HPS, in patients with diabetes without previous cardiovascular disease, whose baseline LDL-cholesterol was less than 3 mmol/L, the 30% reduction of major vascular events was of marginal significance.¹⁴ We contend that the issue here is not significance of effects but consistency of the size of treatment effect across such subgroups in HPS and other trials. However, in response to the NCEP concern about the marginal significance level in HPS for patients with a starting LDL-cholesterol less than 3 mmol/L, we note that in CARDS the risk reduction in such patients was significant at $p=0.025$. Since only 743 patients in CARDS (26%) had a baseline LDL-cholesterol concentration less than 2.6 mmol/L, we would not expect a significant result, but in a post-hoc analysis in this small subgroup in CARDS the treatment effect is a 26% reduction in major cardiovascular events.

The data safety monitoring board paid particular attention to data for patients with LDL-cholesterol less than 1 mmol/L and did not note any concerns about safety. Meta-analyses from the Cholesterol Treatment Trialists' Collaboration³¹ will include CARDS data and will be important in showing unequivocally the safety of achieving very low concentrations of LDL-cholesterol, because analyses of efficacy and safety in subgroups of individual trials are based on few patients at such LDL-cholesterol concentrations. Other analyses that might be considered in meta-analyses include the treatment effect in the context of concurrent treatments such as metformin. One of the important issues that CARDS cannot address is whether a higher dose of atorvastatin or addition of other drugs such as a fibrate or a selective cholesterol absorption inhibitor, eg, ezetimibe, would have achieved an even greater relative risk reduction. The ACCORD trial (<http://www.accordtrial.org>) will assess the potential additional benefit of combination statin-fibrate treatment but will not report for several years. Future

analyses of CARDS will include a cost-effectiveness analysis.

In conclusion, CARDS shows that atorvastatin 10 mg daily is safe and efficacious in reducing the risk of first cardiovascular disease events, including stroke, in patients with type 2 diabetes at the lower end of the cholesterol distribution. The data challenge the use of a particular threshold level of LDL-cholesterol as the sole arbiter of which patients with type 2 diabetes should receive statin treatment, as is the case in most of the current guidelines. The absolute risk, determined by other risk factors in addition to LDL-cholesterol, should drive the treatment threshold considerations and safety considerations only should drive target levels. The data suggest that the target level of 2.5–2.6 mmol/L in current guidelines could be lowered. The debate about whether all patients with type 2 diabetes warrant statin treatment should now focus on whether any patients can reliably be identified as being at sufficiently low risk for this safe and efficacious treatment to be withheld.

Contributors

D J Betteridge, H M Colhoun, P N Durrington, J H Fuller, G A Hitman, and H A W Neil were coprincipal investigators and led the design and overall implementation of the trial. M I Mackness and V Charlton-Menys were responsible for laboratory analyses. S J Livingstone did statistical analyses. M J Thomason coordinated data collection. H M Colhoun wrote the initial draft of the paper in consultation with the coprincipal investigators. All authors contributed to interpretation of data and revision of the manuscript and have seen and approved the final version.

Conflict of interest statement

DJB and HMC have served as consultants to, and received travel expenses and payments for speaking at meetings from, Pfizer. PND has received travel expenses, payment for speaking at meetings, and funding for research from Pfizer. JHF has served as consultant to and received travel expenses, payment for speaking at meetings, or funding for research from pharmaceutical companies marketing lipid-lowering drugs, including AstraZeneca and Pfizer. GAH has served as consultant to and received travel expenses, payment for speaking at meetings, or funding for research from pharmaceutical companies marketing lipid-lowering drugs, including AstraZeneca and Pfizer. HAWN has served as consultant to and received travel expenses, payment for speaking at meetings, or funding for research from pharmaceutical companies marketing lipid-lowering drugs, including AstraZeneca, Merck Sharp and Dohme, and Pfizer. The UCL coordinating centre was partly funded by a grant from Pfizer UK and Pfizer Inc to UCL. SJL, MJT, MIM, and VC-M have no conflicts of interest to declare.

Acknowledgments

We thank all patients for their participation in CARDS, staff of the Central Manchester and Manchester Children's University Hospitals NHS Trust Clinical Laboratories, and the doctors, nurses, and administrative staff in hospitals, general practices, and site-managed organisations that assisted with the study. The study was funded by Diabetes UK, the UK Department of Health, Pfizer UK, and Pfizer Inc (manufacturers of atorvastatin).

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- References**
- 1 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993; **16**: 434–44.
 - 2 Ho JE, Paultre F, Mosca L. Is diabetes mellitus a cardiovascular disease risk equivalent for fatal stroke in women? Data from the Women's Pooling Project. *Stroke* 2003; **34**: 2812–16.
 - 3 McCarron P, Greenwood R, Elwood P, et al. The incidence and aetiology of stroke in the Caerphilly and Speedwell Collaborative Studies II: risk factors for ischaemic stroke. *Public Health* 2001; **115**: 12–20.
 - 4 Chun BY, Dobson AJ, Heller RF. The impact of diabetes on survival among patients with first myocardial infarction. *Diabetes Care* 1997; **20**: 704–08.
 - 5 Wannamethee G, Whincup PH, Shaper AG, Walker M, MacFarlane PW. Factors determining case fatality in myocardial infarction "who dies in a heart attack"? *Br Heart J* 1995; **74**: 324–31.
 - 6 de Jong G, van Raak L, Kessels F, Lodder J. Stroke subtype and mortality a follow-up study in 998 patients with a first cerebral infarct. *J Clin Epidemiol* 2003; **56**: 262–68.
 - 7 Turner RC, Millns H, Neil HA, et al. Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). *BMJ* 1998; **316**: 823–28.
 - 8 Stevens RJ, Kothari V, Adler AI, Stratton IM. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). *Clin Sci (Lond)* 2001; **101**: 671–79.
 - 9 Kothari V, Stevens RJ, Adler AI, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK Prospective Diabetes Study risk engine. *Stroke* 2002; **33**: 1776–81.
 - 10 Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). *Diabetes Care* 1997; **20**: 614–20.
 - 11 The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998; **339**: 1349–57.
 - 12 Goldberg RB, Mellies MJ, Sacks FM, et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. *Circulation* 1998; **98**: 2513–19.
 - 13 Heart Protection Study Collaborative Group. 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.
 - 14 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 2003; **361**: 2005–16.
 - 15 Sever PS, Dahlöf B, Poulter NR, 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**: 1149–58.
 - 16 Saydah SH, Fradkin J, Cowie CC. Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA* 2004; **291**: 335–42.
 - 17 Osborne CA, Philbin M. Application of evidence-based criteria of appropriate aspirin and appropriate lipid-lowering therapy in diabetic inpatients. *Int J Pharmacy Practice* 2003; **11**: R73.
 - 18 Leiter LA, Betteridge DJ, and AUDIT Investigators. The AUDIT Study: a worldwide survey of physicians attitudes about diabetic dyslipidaemia. *Diabetes* 2004; **53** (suppl 2): A285.
 - 19 Haffner SM. Dyslipidemia management in adults with diabetes. *Diabetes Care* 2004; **27** (suppl 1): S68–71.
 - 20 De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2003; **10**: S1–10.
 - 21 Grundy SM, Cleeman JI, Bairy NM, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004; **109**: 3112–21.
 - 22 Colhoun HM, Thomason MJ, Mackness MI, et al. Design of the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med* 2002; **19**: 201–11.
 - 23 Mackness MI, Durrington PN. Lipoprotein separation and analysis for clinical studies. In: Converse CA, Skinner ER, eds. *Lipoprotein analysis: a practical approach*. Oxford: Oxford University Press, 1992.
 - 24 Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18**: 499–502.
 - 25 Nauck M, Wiebe D, Warnick GR. Measurement of high-density lipoprotein cholesterol. In: Rifai N, Warnick GR, Dominiczak MH, eds. *Handbook of lipoprotein testing*. Washington: AACC Press, 2000: 221–44.
 - 26 Peto R. Clinical trial methodology. *Biomedicine*. 1978; **28**: 24–36.
 - 27 Eastern Stroke and Coronary Heart Disease Collaborative Research Group. Blood pressure, cholesterol, and stroke in eastern Asia. *Lancet* 1998; **352**: 1801–07.
 - 28 Zhang X, Patel A, Horibe H, et al. Cholesterol, coronary heart disease, and stroke in the Asia Pacific region. *Int J Epidemiol* 2003; **32**: 563–72.
 - 29 Heart Protection Study Collaborative Group. 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**: 757–67.
 - 30 Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. *BMJ* 2002; **324**: 939–42.
 - 31 Cholesterol Treatment Trialists' (CTT) Collaboration. Protocol for a prospective collaborative overview of all current and planned randomized trials of cholesterol treatment regimens. *Am J Cardiol* 1995; **75**: 1130–34.