

# Analysis of Efficacy and Safety in Patients Aged 65–75 Years at Randomization

## Collaborative Atorvastatin Diabetes Study (CARDS)

H. ANDREW W. NEIL, DSC<sup>1</sup>  
DAVID A. DEMICCO, PHARM<sup>2</sup>  
DON LUO, PHD<sup>2</sup>  
D. JOHN BETTERIDGE, PHD<sup>3</sup>  
HELEN M. COLHOUN, MD<sup>4</sup>  
PAUL N. DURRINGTON, MD<sup>5</sup>

SHONA J. LIVINGSTONE, MSc<sup>6</sup>  
JOHN H. FULLER, FRCP<sup>6</sup>  
GRAHAM A. HITMAN, MD<sup>7</sup>  
ON BEHALF OF THE CARDS STUDY  
INVESTIGATORS

**CONCLUSIONS** — Absolute and relative benefits of statin therapy in older patients with type 2 diabetes are substantial, and all patients warrant treatment unless specifically contraindicated.

*Diabetes Care* 29:2378–2384, 2006

**OBJECTIVE** — Rates of cardiovascular disease are highest in the elderly. Lipid-lowering statin therapy reduces the proportional risk as effectively in older patients as in younger individuals; however, limited data are available for elderly patients with type 2 diabetes. We conducted a post hoc analysis to compare the efficacy and safety of atorvastatin among 1,129 patients aged 65–75 years at randomization with 1,709 younger patients in the Collaborative Atorvastatin Diabetes Study (CARDS).

**RESEARCH DESIGN AND METHODS** — CARDS was a randomized placebo-controlled trial of 10 mg/day atorvastatin for primary prevention of cardiovascular disease in patients aged 40–75 years with LDL cholesterol concentrations  $\leq 4.14$  mmol/l followed for a median of 3.9 years. The primary end point was time to first occurrence of acute coronary heart disease events, coronary revascularizations, or stroke.

**RESULTS** — Atorvastatin treatment resulted in a 38% reduction in relative risk ([95% CI –58 to –8],  $P = 0.017$ ) of first major cardiovascular events in older patients and a 37% reduction ([–57 to –7],  $P = 0.019$ ) in younger patients. Corresponding absolute risk reductions were 3.9 and 2.7%, respectively (difference 1.2% [95% CI –2.8 to 5.3],  $P = 0.546$ ); numbers needed to treat for 4 years to avoid one event were 21 and 33, respectively. All-cause mortality was reduced nonsignificantly by 22% ([–49 to 18],  $P = 0.245$ ) and 37% ([–64 to 9],  $P = 0.98$ ), respectively. The overall safety profile of atorvastatin was similar between age-groups.

The incidence of cardiovascular disease (CVD) (1) and its case fatality (2) increase with age. The extent of avoidable CVD morbidity and mortality associated with undertreatment may therefore be greater in older patients than in younger patients. Numerous trials involving various patient populations have conclusively demonstrated the efficacy and safety of statins for the primary and secondary prevention of CVD, and the clinical benefits in the elderly are consistent with those seen in the general population (3). There are, however, few data on cardiovascular outcomes in patients aged  $\geq 65$  years with type 2 diabetes; in this age-group, the number of patients needed to treat (NNT) to prevent one event would be expected to be lowest. We therefore conducted a post hoc analysis comparing the efficacy and safety of atorvastatin treatment among older patients compared with younger individuals in the Collaborative Atorvastatin Diabetes Study (CARDS) (4). CARDS was a randomized, double-blind, placebo-controlled trial designed to evaluate statin therapy for primary prevention of CVD in patients with type 2 diabetes, without elevated LDL cholesterol. The results showed a 37% reduction in the incidence of major cardiovascular end points, including a 48% reduction in the incidence of stroke (4).

From the <sup>1</sup>Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, U.K.; <sup>2</sup>Pfizer, New York, New York; <sup>3</sup>The Middlesex Hospital, University College London, London, U.K.; <sup>4</sup>The Conway Institute, University College Dublin, Dublin, Ireland; the <sup>5</sup>Department of Medicine, Manchester Royal Infirmary, University of Manchester, Manchester, U.K.; the <sup>6</sup>Department of Epidemiology and Public Health, Royal Free and University College Medical School, London, U.K.; and the <sup>7</sup>Centre for Diabetes and Metabolic Medicine, Barts and The London Queen Mary's School of Medicine and Dentistry, London, U.K.

Address correspondence and reprint requests to Professor H.A.W. Neil, Division of Public Health and Primary Health Care, University of Oxford, Old Road Campus, Headington, Oxford OX3 7LF, U.K. E-mail: andrew.neil@wolfson.ox.ac.uk.

Received for publication 19 May 2006 and accepted in revised form 10 August 2006.

H.A.W.N. and D.A.D. contributed equally to this work.

H.A.W.N. and P.N.D. have received research support from and have served as consultants for AstraZeneca, Merck Sharp and Dohme, Schering Plough, Solvay Health Care, and Pfizer. D.J.B. has received honoraria from and has served on an advisory board for Pfizer. H.M.C. has received honoraria from, has served on an advisory board for, and has received research support from Pfizer. J.H.F. has served as a consultant for and has received research funding from AstraZeneca, Fournier, and Pfizer. G.A.H. has received lecture fees from and has served on an advisory board for Pfizer, GlaskoSmithKline, and AstraZeneca.

**Abbreviations:** CARDS, Collaborative Atorvastatin Diabetes Study; CPK, creatinine phosphokinase; CTT, Cholesterol Treatment Trialists'; CVD, cardiovascular disease; NNT, number of patients needed to treat; ULN, upper limit of normal.

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

DOI: 10.2337/dc06-0872. Clinical trial reg. no. NCT00327418, clinicaltrials.gov.

© 2006 by the American Diabetes Association.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

eligibility criteria included LDL cholesterol levels  $\leq 4.14$  mmol/l ( $\leq 160$  mg/dl), triglyceride levels  $\leq 6.78$  mmol/l ( $\leq 600$  mg/dl), and the presence of at least one other CVD risk factor (hypertension, retinopathy, microalbuminuria, macroalbuminuria, or currently smoking). Microalbuminuria was defined as a positive Micral or other test strip, an albumin-to-creatinine ratio of  $\geq 2.5$  mg  $\cdot$  mmol<sup>-1</sup>  $\cdot$  l<sup>-1</sup>, or an albumin excretion rate on timed collection of  $\geq 20$   $\mu$ g/min and macroalbuminuria as either Albustix or other dipstick evidence of gross proteinuria, an albumin-to-creatinine ratio of  $\geq 25$  mg/mmol, or an albumin excretion rate of  $>200$   $\mu$ g/min ( $>300$  mg/24 h), all on at least two successive occasions. A complete list of exclusion criteria has been published previously (5) and includes active liver disease, hepatic dysfunction, alanine aminotransferase/aspartate aminotransferase levels  $>1.5$  times the upper limit of normal (ULN), plasma creatinine  $>150$   $\mu$ mol/l, severe renal dysfunction, nephrotic syndrome, or creatinine phosphokinase (CPK) levels  $>3$  times ULN. The study was conducted in accordance with the Declaration of Helsinki and Guidelines on Good Clinical Practice. Every center obtained local research ethics committee approval after approval from the multicenter research ethics committee. All patients gave fully informed written consent.

Following a 6-week, single-blind, placebo run-in period designed to assess treatment compliance and confirm study eligibility, patients at each center were sequentially randomized to receive 10 mg atorvastatin or placebo daily based on a computer-generated randomization code. Clinic visits were scheduled monthly for the first 3 months, at 6 months, and every 6 months thereafter. All efficacy and safety end points were recorded during these visits. The study was designed to continue until the accrual of the prespecified number of clinical end points. The protocol called for interim analyses when 25, 50, and 75% of the anticipated end points had accrued and permitted study termination if significant differences emerged in favor of atorvastatin or placebo.

The primary study end point was the time to first occurrence of the following: fatal and nonfatal acute myocardial infarction, silent myocardial infarction, acute coronary heart disease death, unstable angina, coronary artery bypass graft, percutaneous transluminal coronary an-

gioplasty and other coronary revascularization procedures, or stroke. Secondary end points included 1) death from all causes and 2) any acute hospital-verified cardiovascular end point, which consisted of the primary end point (major CVD events) plus all other hospital-verified CVD events (i.e., angina, other acute coronary heart disease events, nonfatal transient ischemic attack, and peripheral vascular disease requiring hospitalization or surgery).

### Statistical methods

All the statistical analyses were by intention to treat. The statistical methods have been described in detail previously (4), but, in brief, the main analysis was a Cox regression survival analysis comparing the hazard rates for the primary end point in the active treatment and placebo groups for each of the two age subgroups, yielding the hazard ratio as a measure of effect size with its significance level. The effect of atorvastatin on lipid concentrations was assessed using a linear mixed model as previously described. The NNTs were calculated as the reciprocal of the absolute risk reduction for the primary end point for a treatment duration of 4 years (median follow-up time) per 1,000 patients. The study was terminated in June 2003, 2 years earlier than the anticipated date, following the second planned interim analysis, which revealed a significant difference in favor of atorvastatin ( $P < 0.001$ ; two sided).

**RESULTS** — Participant flow through the trial and patient demographic and baseline characteristics have been described in detail in previous publications (4–6). Of the 4,053 patients initially screened, 3,249 were eligible to enter the single-blind placebo phase. Of these, 2,838 met all study criteria and were randomized to treatment (1,428 to atorvastatin and 1,410 to placebo). More than one-third of these patients were aged  $\geq 65$  years (atorvastatin,  $n = 572$ ; placebo,  $n = 557$ ).

The majority of patients in both groups were of white ethnic origin ( $\geq 93\%$ ), and  $\sim 68\%$  in each group were male (Table 1). The distribution of risk factors within each of the two age subgroups was similar for patients allocated to active treatment or placebo. Patients aged  $\geq 65$  years, compared with younger patients, had a significantly longer mean duration of diabetes ( $P < 0.001$ ) and higher systolic blood pressure ( $P <$

0.001) but had a significantly lower HbA<sub>1c</sub> ( $P = 0.019$ ), diastolic blood pressure ( $P < 0.001$ ), BMI ( $P < 0.001$ ), triglyceride concentration ( $P < 0.001$ ), and prevalence of cigarette smoking ( $P < 0.001$ ). Older patients were also more likely to have been prescribed  $\beta$ -blockers and diuretics, although this difference was not statistically significant. The proportion of patients with one, two, three, and four additional cardiovascular risk factors was 64, 30, 6, and 1% in the older group and 63, 31, 6, and  $<1\%$  in the younger group, respectively. Patients in the atorvastatin and placebo groups were followed for a median of 4.0 (interquartile range 3.0–4.7) and 3.9 (2.9–4.6) years, respectively. Compliance with allocated therapy was similar in older and younger patients. The average study statin use over the duration of the trial in the atorvastatin group was 84.8% in the older patients and 85.6% in younger patients; corresponding figures for nonstudy statin use in the placebo group were 7.5 and 9.9% in the older and younger patients, respectively.

In the total trial population, as previously reported, treatment with 10 mg atorvastatin was associated with a 37% reduction in the primary end point (95% CI  $-52$  to  $-17$ ],  $P = 0.001$ ). Figure 1 shows that consistent results were observed across the subgroups of older patients (relative risk reduction [RRR] 38% [95% CI  $-58$  to  $-8$ ],  $P = 0.017$ ) and younger patients (37% [ $-57$  to  $-7$ ],  $P = 0.019$ ), and there was no evidence of heterogeneity of effect for the primary end point or its components (Fig. 2).

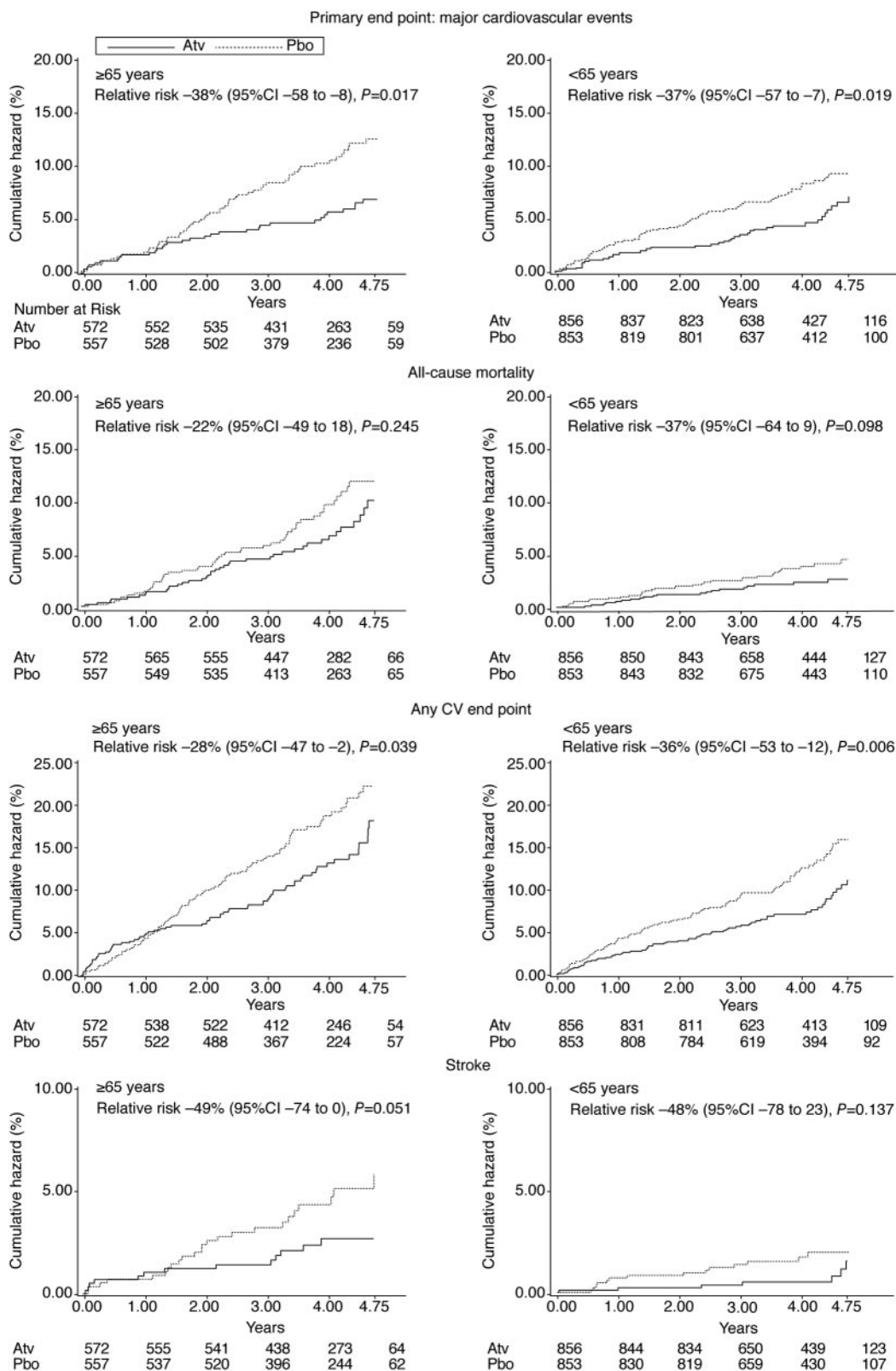
Table 2 shows a further breakdown of the primary and secondary end point components by age-group. A total of 89 patients in the older group (7.0% atorvastatin, 8.8% placebo, RRR 22%,  $P = 0.245$ ) and 54 patients in the younger group (2.5% atorvastatin, 3.9% placebo, RRR 37%,  $P = 0.098$ ) died during the study (Fig. 1).

The incidence of first major cardiovascular events in patients aged  $\geq 65$  years was 31.2 per 1,000 person-years at risk in the placebo group and 19.3 per 1,000 person-years at risk in the atorvastatin group. The corresponding rates in the younger group were 20.4 and 12.9 per 1,000 person-years, respectively. The allocation of 1,000 patients in the older group to atorvastatin would therefore avoid 48 first major cardiovascular events over a 4-year follow-up period and 30 events in the younger group. The inci-

Table 1—Baseline characteristics and medications in patients aged ≥65 years and <65 years

	Aged ≥65 years		Aged <65 years		P value (aged ≥65 vs. <65 years)
	Atorvastatin	Placebo	All	All	
n	572	557	1,129	1,709	
Male	396 (69.2)	378 (67.9)	774 (68.6)	1,155 (67.6)	NS
White ethnic origin	547 (95.6)	539 (96.8)	1,086 (96.2)	1,590 (93.0)	NS
Age (years)	69 (65–77)	69 (65–76)	69 (65–77)	57 (41–65)	NS
BMI (kg/m <sup>2</sup> )	27.9 ± 3.4	28.2 ± 3.4	28.0 ± 3.4	29.3 ± 3.6	<0.001
Current smoker	87 (15.2)	89 (16.0)	176 (15.6)	234 (27.4)	<0.001
Systolic blood pressure (mmHg)	149 ± 16.2	148 ± 16.1	149 ± 16.1	141 ± 15.1	<0.001
Diastolic blood pressure (mmHg)	82 ± 8.6	82 ± 8.3	82 ± 8.4	84 ± 8.4	<0.001
Microalbuminuria	51 (8.9)	50 (9.0)	101 (8.9)	76 (8.9)	NS
Macroalbuminuria	19 (3.3)	19 (3.4)	38 (3.4)	22 (2.6)	NS
Retinopathy	177 (30.9)	172 (30.9)	349 (30.9)	255 (29.9)	NS
Duration diabetes (years)	8.8 ± 6.8	8.4 ± 6.9	8.6 ± 6.8	7.4 ± 5.9	<0.001
HbA <sub>1c</sub> (%)	7.8 ± 1.4	7.8 ± 1.3	7.8 ± 1.3	7.9 ± 1.5	0.019
LDL cholesterol (mmol/l)	3.06 ± 0.70	3.06 ± 0.71	3.06 ± 0.70	3.03 ± 0.73	NS
LDL cholesterol (mg/dl)	118 ± 27.0	118 ± 27.0	118 ± 27.0	116 ± 27.0	NS
HDL cholesterol (mmol/l)	1.43 ± 0.33	1.45 ± 0.34	1.44 ± 0.34	1.40 ± 0.33	NS
HDL cholesterol (mg/dl)	55 ± 12.9	56 ± 13.1	56 ± 13.1	54 ± 12.9	NS
Total cholesterol (mmol/l)	5.28 ± 0.82	5.33 ± 0.80	5.31 ± 0.81	5.40 ± 0.83	NS
Total cholesterol (mg/dl)	204 ± 31.8	206 ± 31.0	205 ± 31.3	207 ± 31.8	NS
Triglycerides* (mmol/l)	1.50 (1.10–2.03)	1.57 (1.13–2.20)	1.53 (1.10–2.13)	1.87 (1.33–2.60)	<0.001
Triglycerides* (mg/dl)	132 (97–180)	139 (100–195)	136 (97–189)	153 (106–224)	<0.001
Apolipoprotein A1 (mg/l)	1,522 ± 275	1,540 ± 294	1,531 ± 285	1,526 ± 295	NS
Apolipoprotein B (mg/l)	1,137 ± 239	1,138 ± 235	1,138 ± 237	1,158 ± 246	NS
Diabetes treatment					
Diet only	96 (16.8)	97 (17.4)	193 (17.1)	131 (15.4)	NS
Oral hypoglycemic drugs only	372 (65.0)	361 (64.8)	733 (64.9)	555 (65.1)	NS
Insulin only	84 (14.7)	81 (14.5)	165 (14.6)	126 (14.8)	NS
Insulin and oral hypoglycemic drugs	20 (3.5)	18 (3.2)	38 (3.4)	41 (4.8)	NS
Blood pressure-lowering treatment					
α-Blocker	57 (10.0)	50 (9.0)	107 (9.5)	54 (6.3)	NS
β-Blocker	97 (17.0)	113 (20.3)	210 (18.6)	124 (14.5)	NS
Calcium antagonist	134 (23.4)	132 (23.7)	266 (23.6)	158 (18.5)	NS
ACE inhibitor or angiotensin II receptor antagonist	250 (43.7)	233 (41.8)	483 (42.8)	382 (44.8)	NS
Diuretic	120 (21.0)	149 (26.8)	269 (23.8)	133 (15.6)	NS

Data are mean (range), n (%), or means ± SD. \* Triglyceride values are presented as median (interquartile range). NS, not significant.

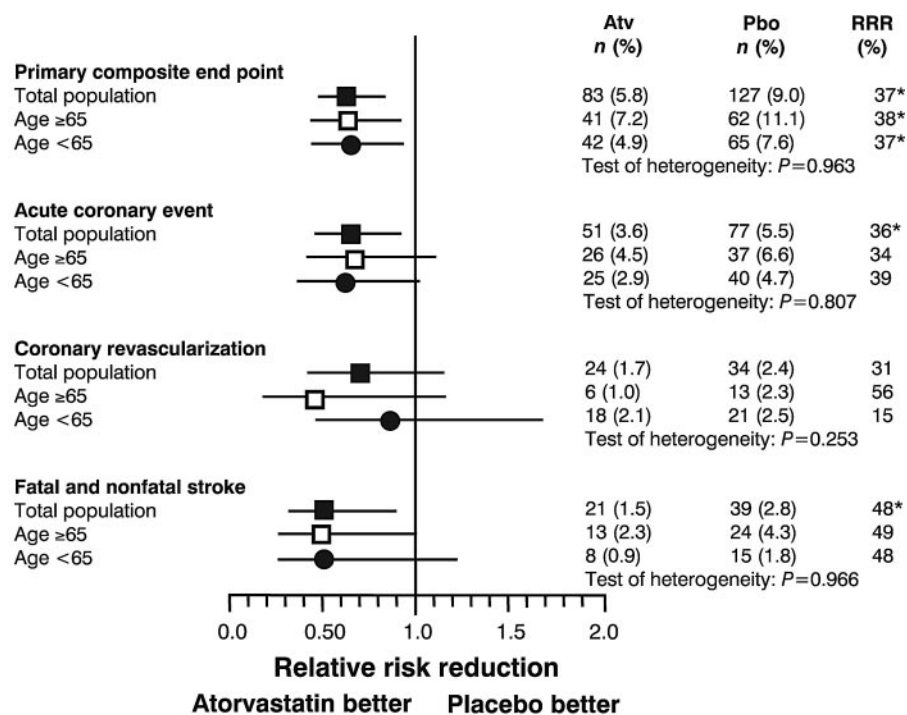


**Figure 1**—Cumulative hazard of primary end point, all-cause mortality, any cardiovascular (CV) end point, and stroke. Atv, atorvastatin; Pbo, placebo.

dence of first and subsequent major cardiovascular events in the older group was 38.1 per 1,000 person-years at risk in the

placebo group and 24.2 in the atorvastatin group. The corresponding rates in the younger group were 25.9 and 15.8 per

1,000 person-years at risk. The NNT to avoid a first major cardiovascular event over 4 years was 21 for patients aged



\**P* <0.05 for atorvastatin vs. placebo.

**Figure 2**—Composite primary end point and components. The total number of acute coronary events, coronary revascularizations, 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 end point. Atv, atorvastatin; Pbo, placebo; RRR, relative risk reduction.

≥65 years and 33 for younger patients. The corresponding NNTs to avoid first and subsequent events were 18 and 25, respectively.

There were no differences in the change in lipid and lipoprotein concentrations over the course of the trial between older and younger patients. Mean LDL cholesterol levels at baseline were 3.02 mmol/l (117 mg/dl) in the younger and 3.06 mmol/l (118 mg/dl) in the older group. By study end, 10 mg atorvastatin decreased LDL cholesterol levels, com-

pared with placebo, by 41% in the older group (*P* < 0.001 vs. placebo) and by 38% in the younger group (*P* < 0.001 vs. placebo); corresponding reductions in total cholesterol were 27% (*P* < 0.001 vs. placebo) and 26% (*P* < 0.001 vs. placebo), respectively. Only modest improvements in HDL cholesterol and triglycerides were observed with the 10-mg dose in both age-groups, with a 2% increase in HDL cholesterol in the older group (*P* = 0.078) and a 1% increase in the younger group (*P* = 0.022)

and a 19% decrease in triglycerides in both groups (*P* < 0.001).

**Adverse events**

For both age-groups, there were no differences between atorvastatin and placebo in the proportion of patients experiencing all-cause adverse events. Treatment-associated adverse events occurred in 25% of atorvastatin-treated patients versus 24% of placebo-treated patients aged ≥65 years and 21% of atorvastatin-treated patients versus 27% of placebo-treated patients in the younger group. Treatment-associated serious adverse events occurred in 1.2% of atorvastatin-treated patients and 1.6% of placebo-treated patients aged ≥65 years. Corresponding figures for the younger group were 0.9 and 0.8%, respectively. Three percent of atorvastatin-treated patients and 3.9% of placebo-treated patients in the older group discontinued treatment as a result of treatment-associated adverse events. Similar discontinuation rates were observed for patients in the younger group (2.8% for atorvastatin-treated patients vs. 3.0% for placebo-treated patients). Myalgia was reported in 3.5% of patients receiving atorvastatin and 4.8% receiving placebo in the older group and 4.3 and 4.7% of patients, respectively, in the younger group. Single elevations in CPK >10 times ULN were only observed in four patients receiving placebo in the younger group, and persistent CPK elevations >10 times ULN were not observed in any patient during the study. No cases of rhabdomyolysis were reported in this study. Persistent alanine aminotransferase elevations more than three times ULN were observed in two atorvastatin-treated patients in the older group and one placebo-treated patient in

**Table 2**—Breakdown of primary end point components by age-group

Type of first event	Aged ≥65 years		Aged <65 years	
	Atorvastatin	Placebo	Atorvastatin	Placebo
<i>n</i>	572	557	856	853
Fatal myocardial infarction	2 (0.3)	12 (2.2)	6 (0.7)	8 (0.9)
Other acute coronary heart disease death	8 (1.4)	1 (0.2)	2 (0.2)	3 (0.4)
Nonfatal myocardial infarction*	11 (1.9)	19 (3.4)	14 (1.6)	22 (2.6)
Unstable angina	5 (0.9)	3 (0.5)	2 (0.2)	6 (0.7)
Resuscitated cardiac arrest	0	0	0	0
Coronary revascularization	2 (0.3)	6 (1.1)	10 (1.2)	12 (1.4)
Fatal stroke	1 (0.2)	4 (0.7)	0	1 (0.1)
Nonfatal stroke	12 (2.1)	17 (3.1)	8 (0.9)	13 (1.5)
Total	41 (7.2)	62 (11.1)	42 (4.9)	65 (7.6)

Data are *n* (%). \*Silent myocardial infarctions included.

the younger group. Persistent aspartate aminotransferase elevations were not observed in any patient.

**CONCLUSIONS**— Patients aged  $\geq 65$  years comprised nearly 40% of the CARDS population. In this subgroup of older patients without elevated LDL cholesterol concentrations, treatment with 10 mg/day atorvastatin produced a substantial 38% reduction in the incidence of first major cardiovascular events, including a 49% reduction in the incidence of stroke. This was similar to the 37% reduction in major events observed in younger patients. There was, however, a greater reduction in the absolute risk of cardiovascular events in older patients (3.9 vs. 2.7%) reflecting their higher absolute risk, and the NNT to avoid one event over 4 years was lower in the older group (21 vs. 33). Treatment was equally well tolerated and safe in older and younger patients and similarly efficacious in reducing total cholesterol, LDL cholesterol, and triglycerides.

The study was a large, rigorously designed and conducted randomized placebo-controlled trial with a high participation rate and almost complete follow-up. Although patients were required to have at least one entry criteria risk factor, the trial population is likely to be representative of older patients in the community with type 2 diabetes (4). The findings are not, however, directly applicable to the very elderly since patients aged  $>75$  years at randomization were excluded. Although this was a post hoc analysis, the results are consistent with other prospective trials that included elderly patients with and without diabetes (3); the findings are therefore unlikely to be attributable to chance. The relatively small numbers of patients in each subgroup was a limitation since it reduced the statistical power of the analysis. Furthermore, because the trial was stopped 2 years earlier than expected, fewer events than anticipated accrued (4). Consequently, although there was a statistically significant 38% reduction in the incidence of first major cardiovascular events in patients aged  $\geq 65$  years, the 49% reduction in the incidence of stroke was of borderline conventional significance ( $P = 0.051$ ) and the reductions in acute coronary events and coronary revascularization were not statistically significant.

The outcomes observed in the trial will have underestimated the true effect of the drug due to crossover of patients onto,

or away from, their allocated therapy. With complete adherence and no add-in lipid-lowering therapy, the risk of a first major cardiovascular event would be expected to be nearly halved. The trial used a fixed dose of 10 mg atorvastatin daily; although in routine clinical practice, up-titration of the dose to achieve individual treatment goals would be expected to further reduce cardiovascular event rates (7–10).

Few trials have assessed the efficacy of statins for the primary or secondary prevention of CVD in patients with type 2 diabetes (3,11–15). Some of these trials found a statistically significant benefit but others did not, probably because the number of patients in the diabetes subgroups were too small (11) or the reduction in LDL cholesterol was inadequate (12). However, individual patient data from all these trials were included in the recently published Cholesterol Treatment Trialists' (CTT) collaborators systematic prospective meta-analysis (3), which reported the efficacy and safety of cholesterol-lowering treatment in 90,056 participants, including 18,686 with diabetes, in 14 randomized trials of statins (including CARDS). Overall, there was a 21% reduction (95% CI 19–23) in major vascular events per 1 mmol/l reduction in LDL cholesterol and no difference in treatment effect between patients with and without diabetes. There were similar proportional reductions in major cardiovascular events in older and younger patients and in those with and without prior CVD. The CTT meta-analysis also reported a significant trend toward greater proportional reductions in major vascular events associated with greater LDL cholesterol reductions. The treatment effect in both age-groups in CARDS was, however, 20–25% greater than would have been predicted by the CTT meta-analysis for the observed LDL cholesterol reduction.

The results of our analysis have a number of implications for clinical practice. Although statins are often underprescribed both in the elderly and in patients with diabetes (16), current clinical guidelines recommend statin treatment for all patients with diabetes aged  $\geq 40$  years and make no distinction between middle-aged and older patients (17,18). Our results extend the evidence base for these recommendations by demonstrating that 10 mg/day atorvastatin produced the same proportional reduction in the incidence of major cardiovascular events in

older as in younger patients. It was equally well tolerated and safe, and treatment adherence was similar despite the extensive use of concomitant drug therapy in older patients. There was a larger reduction in absolute risk of major vascular events in older patients (3.9 vs. 2.7%) reflecting their higher absolute risk, although this difference did not reach statistical significance probably because the number of events was too small. It did however result in a smaller NNT to avoid a first major vascular event over 4 years in older patients compared with younger patients (21 vs. 33, respectively). Given the larger reduction in event rates in older patients, treatment would also be expected to be more cost-effective in older than younger patients (19). In conclusion, the results of our analysis strongly support recently published guidelines recommending statin treatment for all patients aged  $>40$  years with type 2 diabetes, including the elderly, regardless of their baseline LDL cholesterol levels.

**Acknowledgments**— CARDS was funded by Diabetes U.K., the U.K. Department of Health, Pfizer U.K., and Pfizer.

## References

1. British Heart Foundation. *European Cardiovascular Disease Statistics*. 2005 ed. London, British Heart Foundation, 2005
2. Norris RM: Fatality outside hospital from acute coronary events in 3 British health districts 1994–5. *BMJ* 316:1065–1070, 1998
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R, the Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 366:1267–1278, 2005
4. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason SJ, Mackness MI, Charlton-Menys V, Fuller JH, the CARDS Investigators: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364:685–696, 2004
5. Colhoun HM, Thomason MJ, Mackness MI, Maton SM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Fuller JH, the Collaborative Atorvastatin Diabetes Study (CARDS): Design of the Collaborative Atorvastatin Diabetes Study (CARDS) in

- patients with type 2 diabetes. *Diabet Med* 19:201–211, 2002
6. Thomason MJ, Colhoun HM, Livingstone SJ, Mackness MI, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Fuller JH, the CARDS Investigators: Baseline characteristics in the Collaborative Atorvastatin Diabetes Study (CARDS) in patients with type 2 diabetes. *Diabet Med* 21:901–905, 2004
  7. Athyros VG, Papageorgiou AA, Symeonidis AN, Didangelos TP, Pehlivanidis AN, Bouloukos VI, Mikhailidis DP, the GREACE Study Collaborative Group: Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. *Angiology* 54:679–690, 2003
  8. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK, the Treating New Targets (TNT) Investigators: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 352: 1425–1435, 2005
  9. Pedersen TR, Faengeman O, Kastelein JPP, Olsson AG, Tikkanen MJ, Holme I, Larson ML, Bendixen FS, Lindahl C, Szarek M, Tsai J, the Incremental Disease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group: High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. *JAMA* 294: 2437–2445, 2005
  10. Koren MJ, Hunninghake DB, the ALLIANCE Investigators: Clinical outcomes in managed-care patients with coronary heart disease treated aggressively in lipid-lowering disease management clinics: the ALLIANCE study. *J Am Coll Cardiol* 44: 1772–1779, 2004
  11. Downs JR, Clearfield M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Krueyer W, Gotto AM Jr: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/ TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 279:1615–1622, 1998
  12. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group: Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). *JAMA* 288: 2998–3007, 2002
  13. Sever PS, Poulter NR, Dahlof B, Wedel H, Collins R, Beevers G, Caulfield M, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J: Reduction in cardiovascular events with atorvastatin in 2,532 patients with type 2 diabetes: Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). *Diabetes Care* 28: 1151–1157, 2005
  14. Shepherd J, Blauw GJ, Murphy MB, Bollan EL, Buckley BM, Cobbe SM, Ford I, Gaw A, Hyland M, Jukema JW, Kamper AM, Macfarlane PW, Meinders AE, Norrie J, Packard CJ, Perry IJ, Stott PJ, Sweeney BJ, Twomey C, Westendorp RG, the PROSPER Study Group: Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet* 360:1623–1630, 2002
  15. Collins R, Armitage J, Parish S, Sleight P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial: Heart Protection Study Collaborative Group. *Lancet* 361:2005–2016, 2003
  16. DeWilde S, Carey IM, Bremner SA, Richards N, Hilton SR, Cook DG: Evolution of statin prescribing 1994–2001: a case of agism but not sexism? *Heart* 89:417–421, 2003
  17. American Diabetes Association: Standards of medical care in diabetes–2006. *Diabetes Care* 29 (Suppl. 1):S4–S43, 2006
  18. British Cardiac Society, British Hypertension Society, Diabetes UK, HEART UK, Primary Care Cardiovascular Society, Stroke Association: JBS2: Joint British Societies' guidelines on prevention of cardiovascular disease in clinical practice. *Heart* 91 (Suppl. 5):1–52, 2005
  19. Mihaylova B, Briggs A, Armitage J, Parish S, Gray A, Collins R, the Heart Protection Study Collaborative Group: Cost-effectiveness of simvastatin in people at different levels of vascular risk: economic analysis of a randomised trial in 20,536 individuals. *Lancet* 365:1779–1785, 2005