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

Collaborative Atorvastatin Diabetes Study (CARDS)

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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 ≤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.

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.

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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 ≥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).

RESEARCH DESIGN AND METHODS

— Details of the CARDS design, measurements, and end points and a complete list of exclusion criteria have been published previously (4,5). CARDS was a prospective, randomized, double-blind, placebo-controlled trial conducted at 132 centers in the U.K. and Ireland. The study enrolled men and women aged 40–75 years with type 2 diabetes and no prior history of CVD. Other

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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.

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eligibility criteria included LDL cholesterol levels ≤4.14 mmol/l (≤160 mg/dl), triglyceride levels ≤6.78 mmol/l (≤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 ≥2.5 mg · mmol^{-1} · l^{-1}, or an albumin excretion rate on timed collection of ≥20 μg/min and macroalbuminuria as either Albustix or other dipstick evidence of gross proteinuria, an albumin-to-creatinine ratio of ≥25 mg/mmol, or an albumin excretion rate of >200 μg/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 μmol/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 angioplasty 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 ≥65 years (atorvastatin, $n = 572$; placebo, $n = 557$).

The majority of patients in both groups were of white ethnic origin (≥93%), and ~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 ≥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_{1c} ($P = 0.019$), 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 β-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 ≥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	Atorvastatin	Placebo	All	
n	572	557	1,129	856	853	1,709	
Male	396 (69.2)	378 (67.9)	774 (68.6)	576 (67.3)	579 (67.9)	1,155 (67.6)	NS
White ethnic origin	547 (95.6)	539 (96.8)	1,086 (96.2)	803 (93.8)	787 (92.3)	1,590 (93.0)	NS
Age (years)	69 (65–77)	69 (65–76)	69 (65–77)	56 (39–65)	57 (41–65)	57 (39–65)	NS
BMI (kg/m^2)	27.9 ± 3.4	28.2 ± 3.4	28.0 ± 3.4	29.3 ± 3.7	29.3 ± 3.6	29.3 ± 3.6	<0.001
Current smoker	87 (15.2)	89 (16.0)	176 (15.6)	221 (25.8)	234 (27.4)	455 (26.6)	<0.001
Systolic blood pressure (mmHg)	149 ± 16.2	148 ± 16.1	149 ± 16.1	140 ± 14.6	141 ± 15.5	141 ± 15.1	<0.001
Diastolic blood pressure (mmHg)	82 ± 8.6	82 ± 8.3	82 ± 8.4	83 ± 8.4	84 ± 8.4	83 ± 8.4	<0.001
Microalbuminuria	51 (8.9)	50 (9.0)	101 (8.9)	74 (8.6)	76 (8.9)	150 (8.8)	NS
Macroalbuminuria	19 (3.3)	19 (3.4)	38 (3.4)	23 (2.7)	22 (2.6)	45 (2.6)	NS
Retinopathy	177 (30.9)	172 (30.9)	349 (30.9)	249 (29.1)	255 (29.9)	504 (29.5)	NS
Duration diabetes (years)	8.8 ± 6.8	8.4 ± 6.9	8.6 ± 6.8	7.3 ± 6.0	7.4 ± 5.9	7.4 ± 6.0	<0.001
HbA_{1c} (%)	7.8 ± 1.4	7.8 ± 1.3	7.8 ± 1.3	7.9 ± 1.5	7.9 ± 1.5	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	3.00 ± 0.70	3.02 ± 0.71	NS
LDL cholesterol (mg/dl)	118 ± 27.0	118 ± 27.0	118 ± 27.0	117 ± 28.1	116 ± 27.0	117 ± 27.4	NS
HDL cholesterol (mmol/)	1.43 ± 0.33	1.45 ± 0.34	1.44 ± 0.34	1.37 ± 0.31	1.40 ± 0.33	1.38 ± 0.32	NS
HDL cholesterol (mg/dl)	55 ± 12.9	56 ± 13.1	56 ± 13.1	53 ± 11.8	54 ± 12.9	53 ± 12.4	NS
Total cholesterol (mmol/l)	5.28 ± 0.82	5.33 ± 0.80	5.31 ± 0.81	5.40 ± 0.83	5.36 ± 0.82	5.38 ± 0.83	NS
Total cholesterol (mg/dl)	204 ± 31.8	206 ± 31.0	205 ± 31.3	209 ± 31.9	207 ± 31.8	208 ± 32.0	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)	1.73 (1.20–2.53)	1.80 (1.25–2.57)	<0.001
Triglycerides* (mg/dl)	132 (97–180)	139 (100–195)	136 (97–189)	165 (118–230)	153 (106–224)	159 (111–228)	<0.001
Apolipoprotein A1 (mg/l)	1,522 ± 275	1,540 ± 294	1,531 ± 285	1,532 ± 268	1,526 ± 295	1,529 ± 281	NS
Apolipoprotein B (mg/l)	1,137 ± 239	1,138 ± 235	1,138 ± 237	1,188 ± 243	1,158 ± 246	1,173 ± 245	NS
Diabetes treatment							
Diet only	96 (16.8)	97 (17.4)	193 (17.1)	118 (13.8)	131 (15.4)	249 (14.6)	NS
Oral hypoglycemic drugs only	372 (65.0)	361 (64.8)	733 (64.9)	560 (65.4)	555 (65.1)	1,115 (65.2)	NS
Insulin only	84 (14.7)	81 (14.5)	165 (14.6)	126 (14.7)	126 (14.8)	252 (14.7)	NS
Insulin and oral hypoglycemic drugs	20 (3.5)	18 (3.2)	38 (3.4)	52 (6.1)	41 (4.8)	93 (5.4)	NS
Blood pressure–lowering treatment							
α-Blocker	57 (10.0)	50 (9.0)	107 (9.5)	56 (6.5)	54 (6.3)	110 (6.4)	NS
β-Blocker	97 (17.0)	113 (20.3)	210 (18.6)	122 (14.3)	124 (14.5)	246 (14.4)	NS
Calcium antagonist	134 (23.4)	132 (23.7)	266 (23.6)	170 (19.9)	158 (18.5)	328 (19.2)	NS
ACE inhibitor or angiotensin II receptor antagonist	250 (43.7)	233 (41.8)	483 (42.8)	387 (45.2)	382 (44.8)	769 (45.0)	NS
Diuretic	120 (21.0)	149 (26.8)	269 (23.8)	142 (16.6)	133 (15.6)	275 (16.1)	NS

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

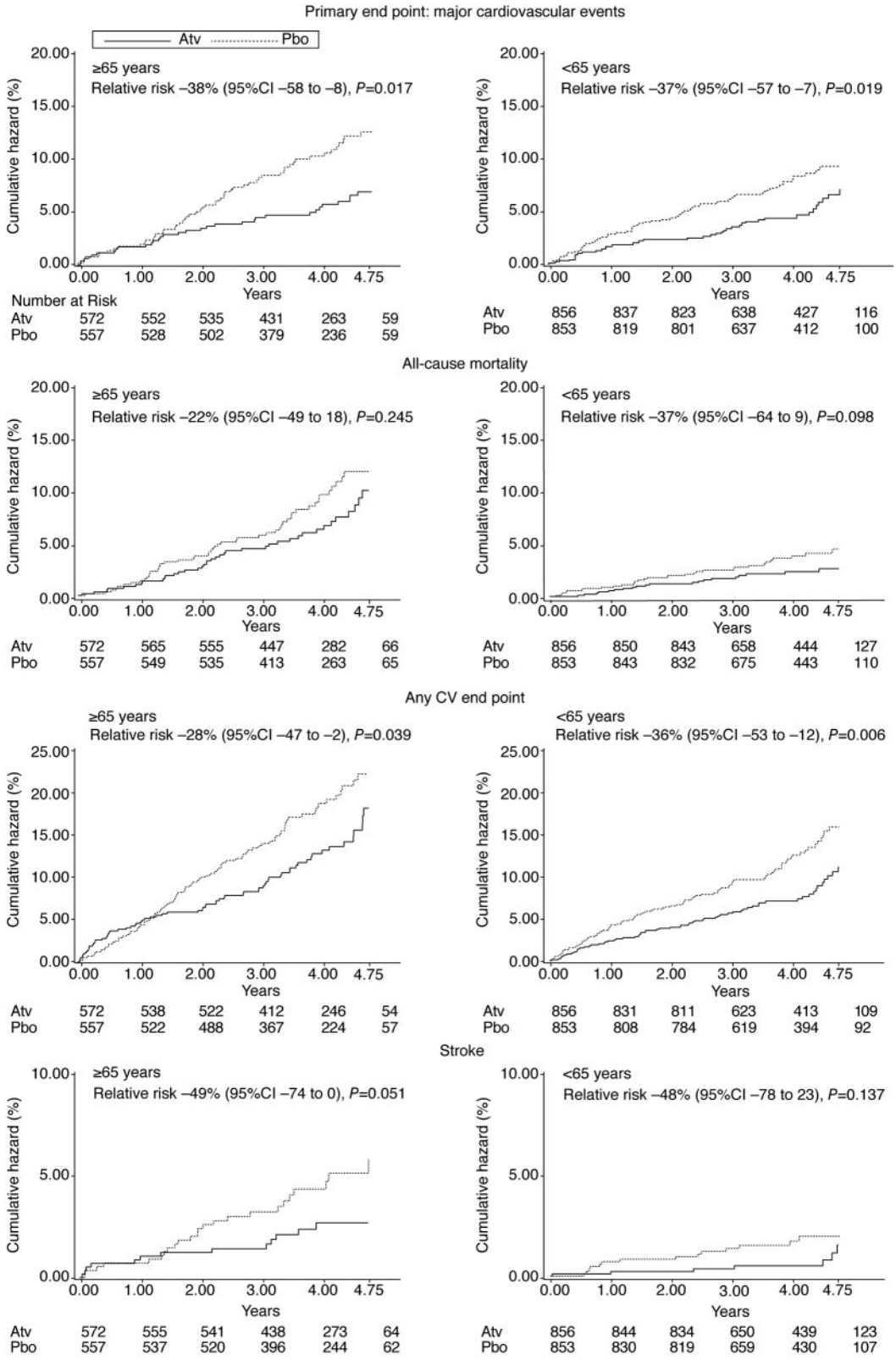

Figure 1—*Cumulative hazard of primary end point, all-cause mortality, any cardiovascular (CV) end point, and stroke. Atv, atorvastatin; Pbo, placebo.*

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

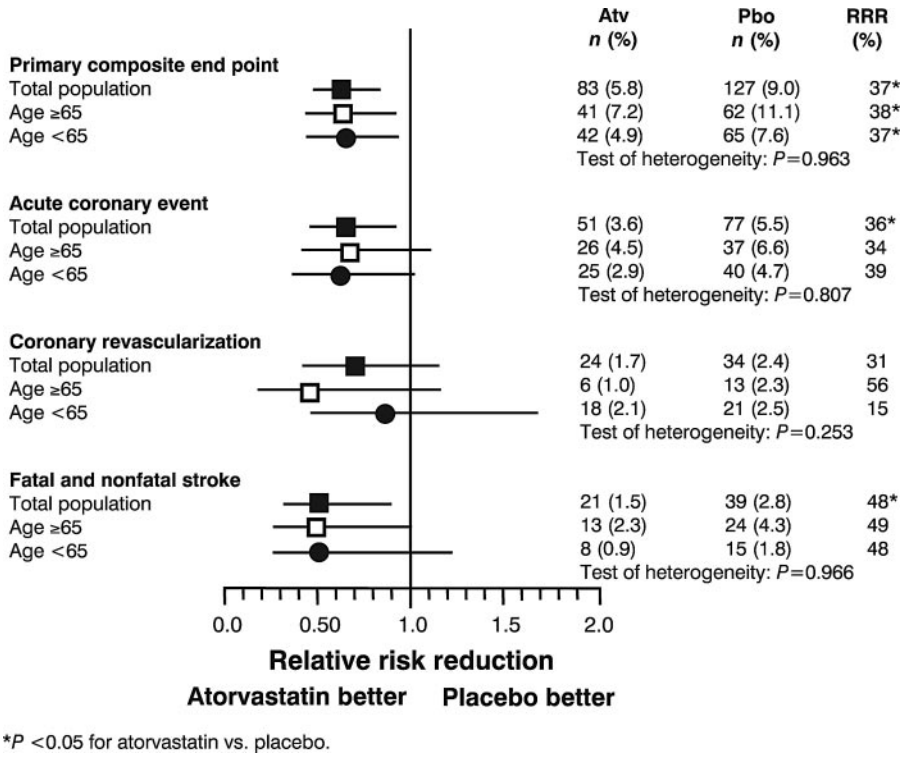

Figure 2—*Composite primary end point and components. The total number of acute coronary events, coronary revascularizations, and strokes (separately) do not equal the total number of primary events shown above because only the first of these events is included in the primary end point. Atv, atorvastatin; 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, compared 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*

	Aged ≥65 years		Aged <65 years	
Type of first event	Atorvastatin	Placebo	Atorvastatin	Placebo
n	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 ≥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 ≥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, uptitration 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 ≥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.

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