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REVIEW

Cumulative clinical trial data on atorvastatin for reducing cardiovascular events: the clinical impact of atorvastatin

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Key words: **Atorvastatin – Coronary heart disease – Lipid lowering therapy – Statins**

ABSTRACT

Background: Since the 1990s a multitude of statin trials have definitively demonstrated the ability of statin therapy to reduce the risk of adverse coronary heart disease (CHD) events. Among these, the Atorvastatin Landmarks program – a group of 32 major atorvastatin trials – has assessed the efficacy and safety of atorvastatin across its full dose range and has helped illustrate its effectiveness in treatment of cardiovascular disease and its related disorders and also in non-cardiovascular outcomes.

Scope: This paper will review the major atorvastatin clinical trials and report the important findings and their clinical significance.

Findings: Clinical trials with atorvastatin have established significant reductions in cardiovascular events in patients with and without CHD. Studies show that high-dose atorvastatin will reduce LDL to ≈ 70 mg/dL in many patients and improve cardiac outcomes. Current evidence suggests that high-dose atorvastatin can halt and, in some cases, reverse atherosclerotic progression. A study of diabetic patients showed atorvastatin decreased the occurrence of acute CHD events, coronary revascularizations, and stroke. Atorvastatin has been found to be effective for reducing nonfatal myocardial infarctions and fatal CHD in hypertensive patients with three or more additional risk factors. High-dose atorvastatin was found to be effective in reducing risk of recurrent stroke in patients with prior cerebrovascular events, has been shown to benefit patients suffering a recent acute coronary syndrome, and to slow cognitive decline in preliminary studies of patients with Alzheimer's disease. Atorvastatin has been associated with reduced progression of mild chronic kidney disease; however, in a randomized trial of patients with end stage renal disease on hemodialysis, atorvastatin showed no statistically significant benefit. Limitations of this review include lack of generalizablity of the atorvastatin trial data to other statins, lack of head to head outcome trials involving the newer more potent statins, and the relatively short study durations (none exceeded 5 years) when atherosclerosis is typically a decades-long disease.

Conclusion: A compelling body of evidence documents that atorvastatin reduces major cardiovascular events in both secondary and primary prevention of CHD and in a broad range of patients and disease conditions. Furthermore, throughout its dose range, atorvastatin is safe and well tolerated.

Introduction

In the 1990s, numerous statin trials demonstrated unequivocally that reducing serum cholesterol levels with statin treatment could significantly and safely reduce the risk of coronary heart disease (CHD) events in patients with and without clinically apparent coronary artery disease. Nevertheless, many clinical questions remained unanswered, such as whether benefits associated with statin therapy extended to other patient populations (patients with recent acute coronary syndromes, patients with diabetes, patients with stroke but no overt CHD, etc.), the effects of statins on intermediate or surrogate clinical end points

for atherosclerotic disease (e.g., carotid intima media thickness, endothelial function, coronary calcification), and whether there are clinically important noncardiovascular and possibly non-lipid-lowering benefits of statins.

To date, 32 major trials have extensively (Table 1) assessed the efficacy and safety of atorvastatin across its full dose range and have helped elucidate optimal treatment strategies in the management of cardiovascular disease and its related disorders. During the 10 years since atorvastatin's release many large randomized trials have been completed, providing a considerable body of data about the safety and efficacy of this agent. This manuscript will review key outcomes-related data that have provided a greater insight into the complex relationship between elevated cholesterol levels, atherosclerosis and other cardiovascular and noncardiovascular outcomes.

Overview of atorvastatin trials

Prior to the development of statins, epidemiologic evidence had long demonstrated the association between high levels of both total cholesterol and low-density lipoprotein cholesterol (LDL-C) and increased risk of CHD[1,2]. However, meta-analyses of pre-statin clinical trials were unable to show a clear causal link between lowering LDL-C and reducing risk of CHD events[3,4], possibly in-part due to the insufficient LDL-C-lowering capacity of non-statin lipid lowering medications. With the development of first-generation statins, such as lovastatin, pravastatin, and simvastatin, which lowered LDL-C more than earlier non-statin therapies, it became possible to definitively establish that lowering LDL-C with statin therapy reduces cardiovascular morbidity and mortality[5–8]. The advent of atorvastatin and later rosuvastatin, heralded the more potent second generation of statins.

Clinical trials with atorvastatin have demonstrated significant reductions in cardiovascular events in patients with[9–13] and without CHD[14–16]. The greater lipid-lowering efficacy of atorvastatin versus first-generation statins allowed greater insight into the effect of statins on atherosclerotic progression and the benefits of intensive versus more moderate lipid-lowering therapy.

Data accrued over many years have also allowed extensive analysis of safety and efficacy of atorvastatin across a large range of patient populations, and across a dosage range from 10 to 80 mg/day. This review presents the data accumulated over the past decade on atorvastatin's lipid-lowering efficacy, its effects on cardiovascular end points, surrogate clinical end points, and noncardiovascular end points (Figure 1).

Lipid-lowering studies

Initial lipid-lowering studies of atorvastatin established the superior LDL-C-lowering efficacy of atorvastatin versus first-generation statins in a range of dyslipidemic patients[17–20]. Atorvastatin 10–20 mg/day was well-tolerated and efficacious in young patients (aged 10–17 years of age) with severe or familial hypercholesterolemia[21]. Several clinical studies, including trials with a treat-to-target design, showed that the majority of hypercholesterolemic patients, even those with or at high risk of CHD, could achieve LDL-C treatment targets with atorvastatin 10–80 mg/day[18–20,22,23]. Mean baseline LDL-C levels were 172–181 mg/dL in these studies; after 6–8 weeks of atorvastatin therapy these levels were reduced to approximately 113 mg/dL (≈ 37% reduction) and 83 mg/dL (≈ 53% reduction) with 10 and 80 mg/day doses, respectively. Furthermore, it was established that, by appropriately adjusting the starting dose of atorvastatin according to baseline LDL-C levels and CHD risk category, the majority of patients could achieve their LDL-C treatment goal without dose titration[22].

Surrogate end-point studies

Although epidemiologic studies demonstrated a clear correlation between cholesterol levels and risk of CHD[2,24], it was initially unknown whether statins could affect atherosclerotic progression. Early, randomized, placebo-controlled quantitative coronary angiography trials initially demonstrated that lovastatin and pravastatin significantly slowed atherosclerosis progression, as measured by the decrease in coronary artery lumen diameter[25,26].

Atorvastatin was first shown to favorably alter the atherosclerotic process in hypercholesterolemic patients through its effect on carotid intimal thickness. Two atorvastatin trials demonstrated that atorvastatin 80 mg/day reduced carotid intima-media thickness, as measured by carotid B-mode ultrasound, to a greater extent than either simvastatin or pravastatin. The Effects of Atorvastatin Versus Simvastatin on Atherosclerosis Progression (ASAP) study was conducted in patients with heterozygous familial hypercholesterolemia[27]. Atorvastatin 40–80 mg/day was associated with significant regression of the mean carotid intima-media thickness, whereas mean progression was observed with

Table 1. *Overview of atorvastatin trials*

Study	Design	Subjects	Atorvastatin dose (mg)	Mean treated LDL-C (mg/dL)	Mean follow-up
ACOT-LLA	Multi, pros, rand, 2 × 2 factorial	19 257	10	89	3.3 years
CARDS	Multi, rand, DB, placebo-control	2838	10	82	3.9 years
SPARCL	Multi, rand, DB, placebo-control	4731	80	73	4.9 years
IDEAL	Multi, open-label, stratified rand	8888	80	81	4.8 years
TNT	Multi, rand, DB, parallel-control	10 001	10	101	4.9 years
			80	77	
PROVE IT-TIMI 22	Multi, rand, DB, parallel-control	4162	80	62	2 years
ACCESS	Multi, rand, open-label, parallel-group	3916	10–80 titrated	104	54 weeks
ASSET	Multi, rand, open-label, parallel-group, Rx to target	1424	10–80 titrated	114	54 weeks
ATGOAL	Multi, open-label, parallel-arm, single-step titration	1295	Mean dose = 11.6	114	8 weeks
			Mean dose = 14.4	111	
			Mean dose = 41.9	104	
CHALLENGE	Multi, rand, open-label, parallel-group	1732	10	113	6 weeks
			80	83	
CURVES	Multi, rand, open-label, parallel-group, comparative	534	10	132	8 weeks
			20	115	
			40	101	
			80	98	
NASDAC	Multi, rand, DB, parallel-arm	919	10	110	8 weeks
			20	97	
			40	88	
			80	85	
PEDIATRICS	Multi, rand, DB, open-label	187	10–20	131	12 months
ALLIANCE	Multi, rand, population-based, open-label	2442	10–80 titrated (mean 40.5)	95	4 years
ASPEN	Multi, rand, DB, parallel-group, placebo-controlled	2410	10	79	4 years
AVERT	Multi, rand, open-label	341	80	77	18 months
4D	Multi, rand, DB, placebo-control, parallel-group	1255	20	72 (at 4 weeks)	4 years
GREACE	Single, rand, open-label	1600	10–80 titrated	97	3 years
MIRACL	Multi, rand, DB, placebo-controlled	3086	80	72	16 weeks
ARBITER	Single, rand, open-label, parallel-group	161	80	76	12 months
ASAP	Multi, rand, DB, parallel-group	325	80	150	2 years
BELLES	Multi, rand, DB, parallel-group	614	80	92	12 months
REVERSAL	Multi, rand, DB, parallel-group	654	80	79	18 months
SAGE	Multi, rand, DB, parallel-group	893	80	66	12 months
TREADMILL	Multi, rand, DB, placebo-controlled	364	10	≈ 75	12 months
			80	≈ 60	
Vascular Basis Study	Multi, rand, DB, parallel-group, placebo-controlled	300	10–80 titrated	85.1	12 months
			With vitamin C and E	84.6	

simvastatin 20–40 mg/day (Figure 2). The ENHANCE study using a similar patient population and trial design showed no difference in carotid intima-media thickness progression in patients treated with combination simvastatin/ezetimibe versus simvastatin alone despite greater differences in on-treatment LDL reductions in the ENHANCE study (–41% with simvastatin, vs. –58% with simvastatin/ezetimibe) compared to the ASAP study (–41% with simvastatin, vs. –51% with atorvastatin)[28]. Similar effects were found in The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) study, which again

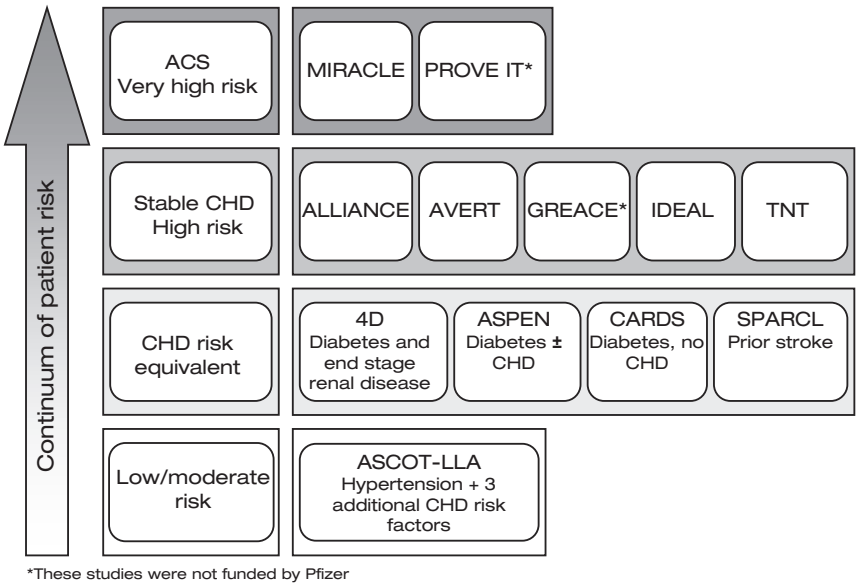


Figure 1. *Atorvastatin landmarks – major trials by category*

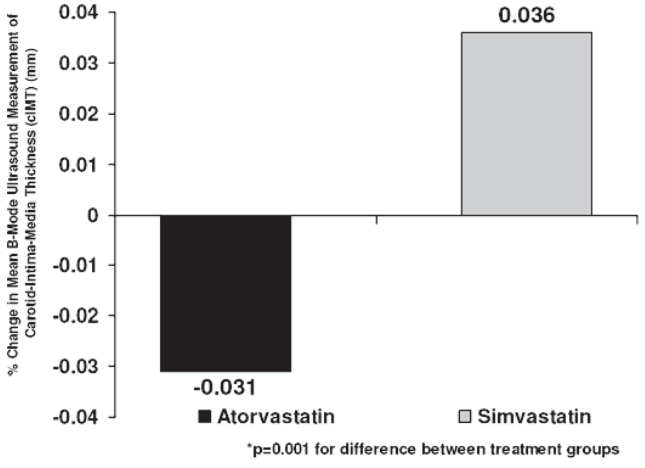


Figure 2. *ASAP: Atorvastatin resulted in regression of carotid intima-media thickness (cIMT) over 2 years (from Smilde* et al.[27]*)*

demonstrated significant regression in carotid intima-media thickness in hypercholesterolemic patients randomized to atorvastatin 80 mg/day versus no change in patients randomized to pravastatin 40 mg/day ($p = 0.03$)[29].

Coronary plaque volume increases with atherosclerotic progression and can be accurately measured by using intravascular ultrasound. Three trials have examined the percent change in coronary plaque volume with atorvastatin versus usual care or more moderate statin therapy and provided evidence that atorvastatin therapy can halt atherosclerotic progression. In the German Atorvastatin Intravascular Ultrasound Study (GAIN), conducted in 131 patients who had undergone coronary intervention, absolute plaque volume increased less in those who received atorvastatin 20–80 mg/day (1.2 mm^3) than in those who received usual care (9.6 mm^3), although the difference between the two groups did not reach statistical significance ($p = 0.191$)[30]. This was supported by the Early Statin Treatment in Patients with Acute Coronary Syndrome Study (ESTABLISH), in which 70 patients who had received percutaneous coronary intervention and were randomized to atorvastatin 20 mg/day experienced a significant reduction in plaque volume, whereas plaque volume significantly increased in patients who received usual care ($p < 0.0001$)[31]. The largest of the intracoronary ultrasound atherosclerotic progression studies, The Reversal of Atherosclerosis with Aggressive Lipid Lowering Study (REVERSAL), enrolled 654 patients with CHD who presented for diagnostic coronary angiography or interventional percutaneous coronary procedures. Patients randomized to atorvastatin 80 mg/day experienced no increase in plaque volume from baseline (–0.4%), whereas plaque volume significantly increased (2.7%) in patients randomized to pravastatin 40 mg/day ($p = 0.02$)[32].

Other atorvastatin trials have assessed the use of other surrogate end points, adding novel data to the body of scientific knowledge of statins. The Treatment of Peripheral Arterial Disease with Moderate or Intensive Lipid Lowering Study (TREADMILL) assessed whether atorvastatin could reduce the symptoms of peripheral arterial disease in 354 patients. Although maximal walking time did not change significantly after 12 months of treatment, atorvastatin 80 mg/day was associated with a significant increase in pain-free walking time versus placebo ($p = 0.025$)[33]. The Beyond Endorsed Lipid Lowering with Electron-beam computed tomography (EBCT) Scanning Trial

(BELLES) was a prospective study in postmenopausal, hypercholesterolemic women with a total coronary calcium volume score of ≥30. EBCT was used to measure percent change from baseline in total coronary calcium volume score, a measure of coronary artery calcified plaque burden. There was no change in median percent change from baseline in total calcium volume score between those randomized to atorvastatin 80 mg/day and those randomized to pravastatin 40 mg/day[34].

Evidence is emerging from the most recent atorvastatin trials that more intensive lipid-lowering therapy may be required to reduce clinical events than is required to reduce ischemia. The Vascular Basis Study demonstrated that, in patients aged 21–85 years with stable CHD, 12-months' treatment with atorvastatin 10–80 mg/day (baseline LDL-C: 149 mg/dL; post-treatment LDL-C: 85.1 mg/dL), atorvastatin 10–80 mg/day plus vitamins C and E (baseline LDL-C: 141 md/dL; post-treatment LDL-C: 84.6 mg/dL), and diet plus low-dose lovastatin (baseline LDL-C: 151 mg/dL; post-treatment LDL-C: 123 md/dL) each reduced ischemic episodes from baseline as measured by 48-hour ambulatory electrocardiogram (−1.6, −1.2, and −3.1 events, respectively, all $p \leq 0.005$) with no difference in efficacy between the three treatment groups ($p = 0.15$)[35]. This result was confirmed in the Study Assessing Goals in the Elderly (SAGE), which observed significant differences from baseline in mean total duration of ischemic events as measured by 48-hour ambulatory electrocardiogram in patients aged 65–85 years randomized to atorvastatin 80 mg/day (−47.6 minutes; baseline LDL-C: 148 mg/dL; post-treatment LDL-C: 66 mg/dL) or to pravastatin 40 mg/day (−46.1 minutes; baseline LDL-C:144 mg/dL; post-treament LDL-C: 97 mg/dL) (both $p < 0.001$). However, there was no significant difference in effect between the two statin-treatment groups ($p = 0.88$)[36]. Nonetheless, in SAGE, mortality was reduced by 67% (2.7% absolute reduction) with atorvastatin relative to pravastatin ($p = 0.014$) and there was also a trend for a greater reduction in major acute cardiovascular events with atorvastatin (3.1% absolute reduction, 29% relative reduction, $p = 0.114$).

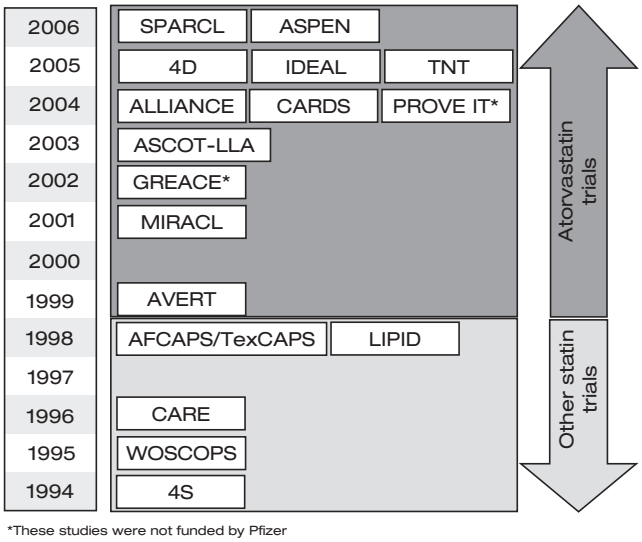
Clinical end-point studies

The benefits of atorvastatin observed in surrogate clinical end-point trials, which indicated that atorvastatin slows and may halt atherosclerotic progression has been further supported by clinical outcome trials, which demonstrate that atorvastatin therapy reduces hard cardiovascular events. These trials built upon the initial evidence provided in earlier statin trials (Figure 3). The clinical benefits of atorvastatin have been assessed in a broad range of patients, from those who were only at moderate risk of CHD to those who were at highest risk (Figure 4).

Patients at moderate CHD risk

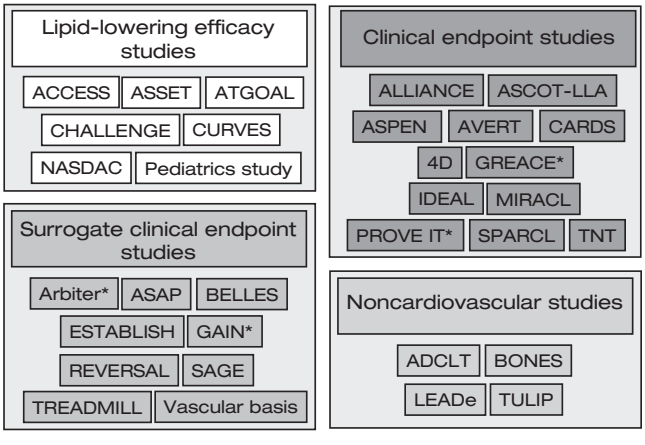
Early large placebo-controlled trials established that statin therapy can significantly reduce coronary end points in patients without established CHD.

The Anglo-Scandinavian Cardiac Outcomes Trial Lipid-Lowering Arm (ASCOT–LLA) randomized 10305 hypertensive patients with ≥3 additional CHD risk factors, but without overt CHD, to atorvastatin 10 mg/day or placebo. ASCOT–LLA achieved a significant 36% reduction in the composite end



*These studies were not funded by Pfizer

Figure 3. *Atorvastatin trials which built upon the initial evidence provided by trials of earlier statins*



*These studies were not funded by Pfizer

Figure 4. *Atorvastatin clinical end-point studies which have been conducted across the CHD risk continuum*

point of nonfatal myocardial ischemia (MI) and fatal CHD (HR = 0.64, 95% CI: 0.50–0.83, $p = 0.0005$) and was terminated early for benefit after a median of only 3.3 years (see Figure 5). Baseline LDL-C for the patients treated with atorvastatin 10 mg/day was 131 mg/dL and fell to 89 mg/dL with atorvastatin treatment. Importantly, those randomized to atorvastatin experienced a statistically significant reduction in cardiovascular end points by just 90 days after randomization.

Patients with a CHD risk equivalent

Atorvastatin trials have prospectively assessed the effects of atorvastatin therapy throughout the range of CHD risk equivalents including peripheral artery disease, abdominal aortic aneurysm, symptomatic carotid artery disease, diabetes, or multiple risk factors that confer a >20% 10-year CHD risk[37].

Diabetes

The Collaborative Atorvastatin Diabetes Study (CARDS) prospectively randomized 2838 patients with diabetes and no CHD to atorvastatin 10 mg/day or placebo[15]. CARDS was terminated early after a median of 3.9 years because atorvastatin reduced the risk of the combined primary end point of acute CHD events, coronary revascularization, or stroke by 37% versus placebo (HR = 0.63, 95% CI: 0.48–0.83, $p = 0.001$) (see Figure 6).

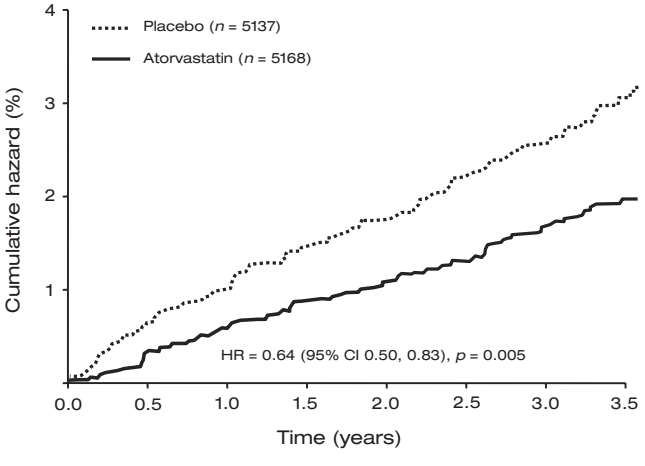


Figure 5. *ASCOT–LLA: Cumulative hazard for the primary end point of nonfatal myocardial infarction and fatal coronary heart disease with atorvastatin 10 mg/day versus placebo in patients with hypertension and at least three other CV risk factors (from Sever* et al.[16]*)*

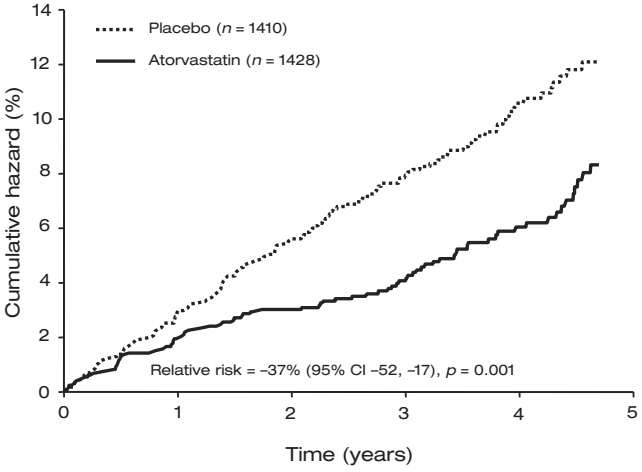


Figure 6. *CARDS: Cumulative hazard for the primary end point of major cardiovascular events with atorvastatin 10 mg/day versus placebo in diabetic patients without a prior history of CHD (from Colhoun* et al.[15]*)*

The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in non-insulin-dependent diabetes mellitus (NIDDM) (ASPEN) prospectively randomized 2410 patients with diabetes, with or without prior myocardial infarction (MI), to atorvastatin 10 mg/day or placebo[38]. After 4 years, atorvastatin reduced cardiovascular events by 10% versus placebo, although the difference between the two groups did not reach significance (HR = 0.90, 95% CI: 0.73–1.12, $p = 0.34$), possibly due to the high drop-in rate of statin therapy within the placebo group during the trial, caused by increased awareness of the need for statin treatment of patients with diabetes during the study period. Benefit in patients with diabetes and CHD was similar to the benefits observed in prior statin secondary prevention CHD trials.

End-stage renal disease

The Determination of Cardiovascular Endpoints in NIDDM Dialysis Patients Study (4D) assessed the effects of atorvastatin 20 mg/day in 1255 patients with diabetes and end-stage renal failure[39]. After 4 years, atorvastatin-treated patients experienced an 8% reduction in the composite primary end point (death from cardiac causes, fatal or nonfatal stroke, or nonfatal MI) compared with placebo-treated patients, but the difference was not significant (HR = 0.92, 95% CI: 0.77–1.10, $p = 0.37$). It was speculated that the very high risk profile of these patients may mean that treatment is better initiated in patients with milder renal insufficiency, for whom statin therapy is recommended, before they reach the final stages of kidney disease.

Prior stroke

Patients who have experienced stroke of atherosclerotic origin are at high CHD risk and prior stroke is now considered a CHD risk equivalent. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (SPARCL) was the first large-scale prospective trial to assess the effect of statin therapy on a primary end point of stroke in patients with recent stroke or transient ischemic attack, but no clinical manifestations of CHD[14]. A total of 4731 patients were randomized to atorvastatin 80 mg/day or placebo and were followed for a median of 4.9 years. Those randomized to atorvastatin 80 mg/day experienced a 16% risk reduction in stroke compared with placebo (HR = 0.84, 95% CI: 0.71–0.99, p = 0.03) (see Figure 7). There was an overall reduction in the incidence of stroke in the atorvastatin treated patients despite the increase in hemorrhagic strokes (HR = 1.66, 95% CI: 1.08–2.55)[14].

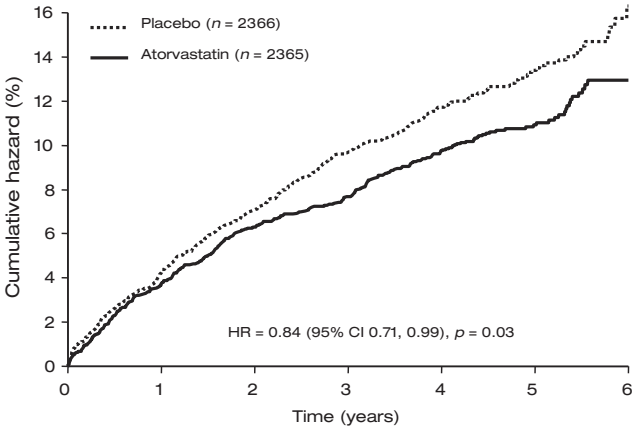


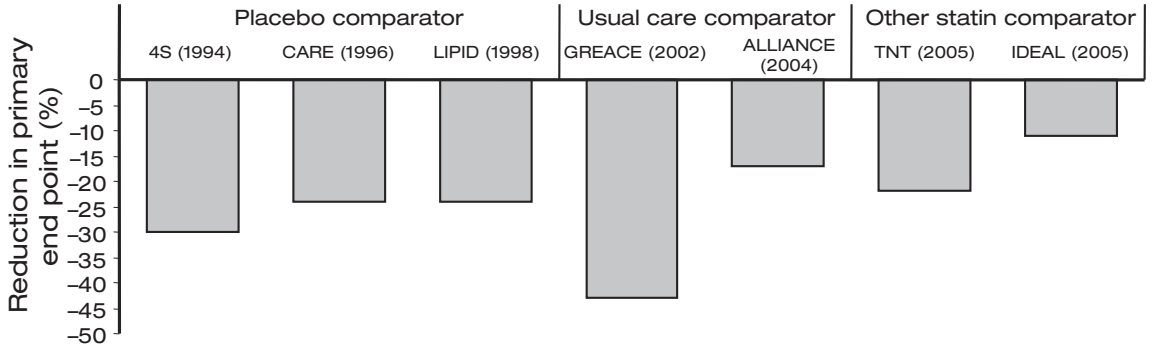
Figure 7. *SPARCL: Cumulative hazard for the primary end point of fatal or nonfatal stroke with atorvastatin 80 mg/day versus placebo (from Amarenco* et al.*[14])*

Patients with CHD

Patients with known CHD are at high risk of future CV events. Early statin trials in these high-risk patients, such as the Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE) trial, and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study, observed significant reductions in mortality[8,40] and cardiovascular end points[6] with statin therapy versus placebo over long follow-up durations of ≥ 5 years (Figure 8).

With the development of atorvastatin and its superior lipid-lowering capacity, clinical trials were able to demonstrate, in studies of ≤ 4 years' duration, the significant cardiovascular benefits of focused atorvastatin therapy versus usual care in a managed care setting in the Aggressive Lipid Lowering Initiation Abates New Cardiac Events (ALLIANCE) study (a multicenter randomized trial involving 2442 subjects with atorvastatin doses titrated up to 80 mg/day to achieve NCEP ATP III guidelines versus usual care)[13] and versus usual care in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study (Figure 8) (a single center randomized trial involving 1600 subjects treated with atorvastatin titrated up to 80 mg/day for target LDL-C of < 100 mg/dL versus usual care)[41].

The Atorvastatin Versus Revascularization Treatments Study (AVERT) assessed the benefits of atorvastatin 80 mg/day versus angioplasty on a background of usual care in patients with stable CHD[42]. Atorvastatin reduced the incidence of ischemic CHD events (p = 0.045) and time to first ischemic event was significantly longer in patients who received atorvastatin compared with those who underwent coronary angiography and percutaneous coronary intervention as warranted (p = 0.03).



GREACE: atorvastatin 10–80 mg/day to an LDL-C goal of < 100 mg/dL vs. usual care in Greece
ALLIANCE: atorvastatin 10–80 mg/day to an LDL-C goal of < 80 mg/dL vs. usual care in US managed healthcare organizations
TNT: atorvastatin 80 mg/day vs. atorvastatin 10 mg/day
IDEAL: atorvastatin 80 mg/day vs. simvastatin 20–40 mg/day

Figure 8. *Reductions in the primary end point in large, randomized clinical trials in patients with CHD*

Two atorvastatin trials of approximately 5 years' duration each assessed whether intensive statin therapy to lower LDL-C below earlier recommended treatment goals would provide greater cardiovascular benefit than more moderate LDL-C lowering in patients with stable coronary artery disease (Figure 4). In the Treating to New Targets Trial (TNT) involving 10 001 patients, lipid lowering with atorvastatin 80 mg/day to a mean LDL-C of 77 mg/dL produced a 22% relative risk reduction in the primary end point of major cardiovascular events versus LDL-C lowering with atorvastatin 10 mg/day to a mean LDL-C level of 101 mg/dL (HR = 0.78, 95% CI 0.69–0.89, $p < 0.001$)[10] (see Figure 9). There were no significant differences in all-cause mortality between the two groups, although the study was not powered to assess this end point and rates of coronary death were very low in the trial compared with previous secondary prevention statin trials.

The results of the Incremental Decrease in End Points through Aggressive Lipid Lowering Trial (IDEAL), demonstrated an 11% reduction in the primary end point (time to major coronary event, i.e. CHD death, nonfatal MI, resuscitated cardiac arrest) with atorvastatin 80 mg/day versus simvastatin 20–40 mg/day, but the difference did not reach statistical significance (HR = 0.89, 95% CI: 0.78–1.01, $p = 0.07$)[9]. However, reductions in secondary end points did reach significance, including nonfatal MI (17%), coronary revascularization (23%), and peripheral arterial disease (24%) ($p \leq 0.02$).

Compared with more moderate statin therapy, atorvastatin 80 mg/day yielded significant relative risk reductions in major cardiovascular events (22 and 13%), all coronary events (21 and 16%) and all cardiovascular events (19 and 16%), in both TNT and IDEAL, respectively.

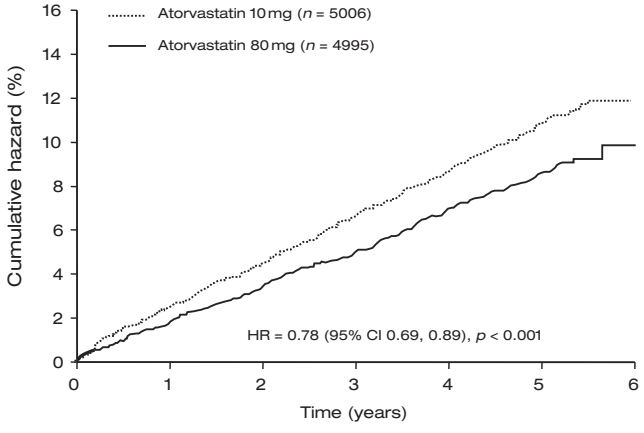


Figure 9. *TNT: Cumulative hazard for the primary end point of first major cardiovascular event with atorvastatin 80 mg/day versus 10 mg/day in patients with stable CHD (from LaRosa* et al.*[10])*

Patients with ACS

Patients with acute coronary syndrome (ACS) are at very high risk of recurrent CHD events, including sudden death and stroke. Clinical trials of atorvastatin have demonstrated early and significant cardiovascular benefits in this patient population (Figure 4).

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study (MIRACL) assessed the effects of early, rapid, and intensive reduction in serum lipids in patients hospitalized for ACS[11]. Prior to this trial, the benefits of statin therapy started earlier than 6 months following an ACS were uncertain as these patients were excluded from prior statin trials. Within 16 weeks, patients randomized to atorvastatin 80 mg/day within 96 hours of hospitalization for an ACS experienced a significant 16% reduction in recurrent ischemic events versus patients randomized to placebo (HR = 0.84, 95% CI: 0.70–1.00, $p = 0.048$). The Pravastatin or Atorvastatin Evaluation and Infection Therapy – Thrombolysis in Myocardial Infarction 22 Study (PROVE IT–TIMI 22) compared the effects of intensive LDL-C lowering with atorvastatin 80 mg/day in patients hospitalized with ACS with the effects of more moderate LDL-C lowering with pravastatin 40 mg/day[12]. Over the mean 2-year follow-up, treatment with atorvastatin 80 mg/day within 10 days of hospitalization resulted in a significant 16% relative risk reduction in cardiovascular end points (all-cause mortality, MI, re-hospitalization for unstable angina, revascularization, stroke) versus pravastatin 40 mg/day (HR = 0.84, 95% CI: 0.74–0.95, $p = 0.005$).

Noncardiovascular end points

In addition to the clarification and expansion of our knowledge of the cardiovascular benefits of statin therapy, atorvastatin trials have also evaluated potential noncardiovascular benefits of atorvastatin. Among the most promising of these potential benefits is that for patients with Alzheimer's disease (AD). The Alzheimer's Disease Cholesterol-Lowering Treatment (ADCLT) Trial, a pilot study with 67 patients with probable or possible AD, showed that patients randomized to atorvastatin 80 mg/day (baseline LDL-C of 124 mg/dL to 56 mg/dL post-treatment) experienced significantly less cognitive decline as measured by the Alzheimer's Disease Assessment Scale – Cognitive Subscale compared with patients receiving placebo ($p = 0.003$). In the ADCLT trial all but six patients were also receiving therapy with cholinesterase inhibitors. The Lipitor's Effect in Alzheimer's Dementia Study (LEADe) is a larger study designed to confirm this finding and is due to report out in 2008. Some case

reports have suggested an association of atorvastatin and memory loss or decline in cognitive function. However, large prospective studies are needed to confirm this possible adverse effect of statin therapy[43].

Other trials have also been conducted to assess the effect of atorvastatin on bone mineral density in postmenopausal women at risk of osteoporosis and on benign prostatic hyperplasia in men aged ≥ 50 years[44]. No effect was found on bone mineral density in 626 dyslipidemic postmenopausal women aged 40–75 years at risk of osteoporosis randomized to atorvastatin 10–80 mg/day versus placebo[45] (baseline LDL-C of 159.1 for placebo, 154.8, 158.0, 155.4, 155.6 for atorvastatin 10–80 mg, respectively). Both the atorvastatin and placebo groups received 500 mg of calcium and 200 IU of vitamin D.

Many other trials are under way to evaluate potential benefits of statins in various disorders, including polycystic ovary syndrome[46], lupus[47], sepsis[48], rheumatoid arthritis[49,50] multiple sclerosis[51–54], and leukemia[55].

Early benefit

Data suggest that acute coronary syndrome patients who receive atorvastatin achieve clinical benefits within a short time after initiation of therapy. In PROVE IT–TIMI 22, the benefits of atorvastatin 80 mg/day versus pravastatin 40 mg/day in reducing a composite end point of death, MI, and recurrent ACS were observed as early as 30 days[56]. In patients without prior CHD, atorvastatin 10 mg/day versus placebo significantly reduced CHD events after 90 days in ASCOT–LLA[57] and major cardiovascular events after 18 months in CARDS[58]. The atorvastatin and placebo Kaplan–Meier curves depicting the primary end points (nonfatal MI and fatal CHD) for ASCOT–LLA, (Figure 5) and (acute CHD, coronary revascularization, or stroke) for CARDS (Figure 6) showed significant early separation that prompted premature termination of both studies for atorvastatin related benefits.

Age

There has been uncertainty about the benefit of statins in older patients. However, subanalyses of atorvastatin data yield strong evidence that the benefits of statins are not confined to patients aged < 65 years. The benefits of atorvastatin on the primary end point in CARDS were found to be consistent across patients aged ≥ 65 years (1129 patients) and < 65 years (1709 patients) with no heterogeneity of effect[59]. Similarly, in MIRACL, treatment-by-age heterogeneity tests indicated no difference in treatment effect by age for any of its primary or secondary end points[60]. Relative risk reductions in the primary end point with atorvastatin versus placebo were similar in 849 patients ≥ 65 years and 689 patients < 65 years. No difference in treatment effect was observed for 314 patients aged ≥ 80 years and < 80 years ($p = 0.19$)[60].

Data from ALLIANCE demonstrated that patients aged ≥ 65 years receiving focused care with atorvastatin 10–80 mg/day experienced significantly greater risk reductions in the primary end point compared with those receiving usual care; rates of serious adverse events were similar between atorvastatin and usual care (HR = 0.83, 95% CI; 0.71–0.97, $p = 0.026$)[61]. Analysis of the PROVE IT–TIMI 22 data revealed that patients aged ≥ 70 years who achieved LDL-C < 70 mg/dL within 30 days experienced a 40% reduction in the composite end point of death, MI, or unstable angina compared with their counterparts with LDL-C ≥ 70 mg/dL[62]. For patients aged < 70 years who achieved LDL-C levels < 70 mg/dL within 30 days, the reduction was 26% versus their counterparts with higher LDL-C levels. Data from TNT revealed that the use of high-dose atorvastatin in patients aged ≥ 65 years to lower LDL-C levels < 100 mg/dL reduced absolute risk of a first major cardiac event, nonfatal non-procedure-related MI, resuscitated cardiac arrest or nonfatal stroke by 2.3% and the relative risk by 19%[63]. Together these data demonstrate that the benefits of statins are apparent throughout the adult age range.

Metabolic syndrome or diabetes

In the TNT trial, atorvastatin 80 mg/day reduced the risk of major cardiovascular events among 5584 CHD patients with the metabolic syndrome by 29% compared with atorvastatin 10 mg/day (HR = 0.71, 95% CI: 0.61–0.84, $p < 0.0001$)[64]. Similarly, in the MIRACL study, clinical benefits observed with atorvastatin 80 mg/day compared with placebo were similar among patients with and without metabolic syndrome[65].

In addition to the data from prospective trials such as CARDS, subgroup analyses have demonstrated significant cardiovascular benefits of atorvastatin versus placebo or more moderate statin therapy in a broad range of patients with diabetes. These benefits have been observed in diabetic patients without overt CHD in ASCOT-LLA[66], in diabetic patients with CHD in GREACE[67] and TNT[68], and in very high-risk diabetic patients with ACS in PROVE IT–TIMI 22[69]. These data support recommendations by the American Diabetes Association that almost all diabetes patients

over the age of 40 years will benefit from statin therapy[70].

Renal function

The increased risk of cardiovascular mortality and morbidity in patients with advanced chronic kidney disease (CKD) is well-established, and recent data have shown that renal function is an important independent predictor of cardiovascular disease, even in patients with mild renal insufficiency[71]. Accordingly, renal insufficiency is now considered to be a CHD risk equivalent, as is the case with diabetes. Data from TNT indicate that the decline in renal function that would have been expected during the 5-year study (up to 6.7 ml/min per 1.73 m^2 illustrated in controls of other cardiovascular treatment trials) was not observed in either atorvastatin treatment group[72]. Furthermore, there was a greater improvement in renal function with high-dose (GFR increase of 5.2 ± 0.14 ml/min per 1.73 m^2) compared with low-dose atorvastatin (GFR increase of 3.5 ± 0.14 ml/min per 1.73 m^2; $p < 0.0001$), suggesting that the benefits of an aggressive atorvastatin treatment strategy extend to significant improvement in renal function. These data are consistent with two previous atorvastatin studies (ALLIANCE[73] and GREACE[74]), which have shown significant renal benefits over a regimen of usual care in patients with established CHD. Although the mechanisms responsible for renoprotection with statins have yet to be determined, lowering LDL-C levels to well below 100 mg/dL with high-dose atorvastatin would appear to maximize renal benefits in high-risk patients with CHD.

Stroke

Epidemiologic evidence does not demonstrate a clear relationship between serum cholesterol and stroke[75–77]. Nevertheless, data from early placebo-controlled statin trials demonstrated reductions in risk of first stroke in patients with CHD[6,8,40]. Atorvastatin trials demonstrated that intensive atorvastatin therapy (80 mg/day) yielded further reductions in risk of stroke versus less intensive atorvastatin (10 mg/day) in patients with CHD (HR = 0.77, 95% CI: 0.64–0.93, $p = 0.007$) and also in high risk patients with ACS treated with atorvastatin 80 mg/day versus placebo (HR = 0.40, 95% CI: 0.19–0.88, $p = 0.02$)[10,11]. CARDS[78] and ASCOT–LLA[16] demonstrated risk reductions of 48 and 27%, respectively, for first stroke with atorvastatin 10 mg/day versus placebo in patients without CHD. The cumulative hazard estimate for time to stroke from the CARDS study is shown in Figure 10. However, other trials using simvastatin and pravastatin have failed to show significant reductions in recurrent stroke[79,80].

SPARCL was the first large-scale, randomized, prospective trial with stroke reduction as the primary end point. This study showed a 16% reduction in recurrent stroke with atorvastatin (80 mg/day) versus placebo in patients with recent stroke but without CHD (HR = 0.84, 95% CI: 0.71–0.99, $p = 0.03$)[14] (see Figure 7). Together, these results indicate that atorvastatin therapy may help to protect brain health in some individuals.

A 600-patient study evaluating atorvastatin for preventing progressive cognitive impairment in patients with mild-to-moderate Alzheimer's dementia at baseline has been fully enrolled and is scheduled to be completed within the next year. To our knowledge this is the only ongoing major randomized placebo-controlled trial trial using atorvastatin[81].

Safety in clinical studies

A wealth of data has been analyzed to assess the safety of atorvastatin across the dose range. An analysis of 49 completed trials showed that the incidence of treatment-associated musculoskeletal adverse events for atorvastatin 80 mg/day was similar to that for atorvastatin 10 mg/day and placebo[82]. In a pooled analysis of 44 atorvastatin trials, including a number of studies that initiated treatment at the 80 mg/day dose level, the incidence of treatment-associated myalgia was low in the atorvastatin (1.9%), placebo (0.8%), and other statin (2.0%) groups[83]. Musculoskeletal side-effects of atorvastatin have been found not to be dose-dependent, a finding not true for other statin medications. Transaminase elevations are dose-

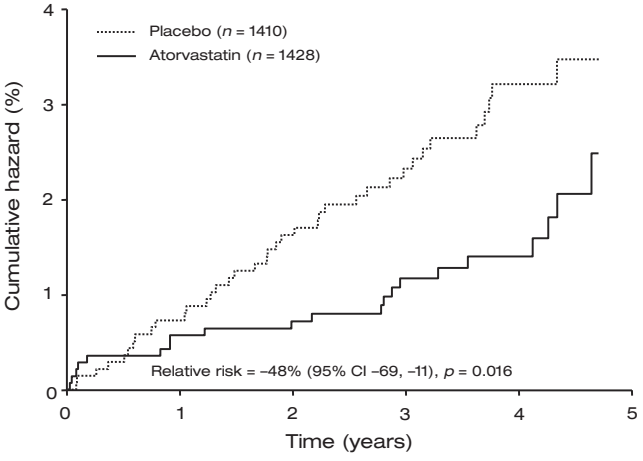


Figure 10. *CARDS: Cumulative hazard for fatal and nonfatal stroke with atorvastatin 10 mg/day versus placebo in diabetic patients without a prior history of CHD or stroke (from Hitman* et al.[78]*)*

dependent with atorvastatin, but the incidence is still acceptably small even at the 80 mg/day dose (≈1.0% risk of aspartate minotransferase/alanine aminotransferase [AST/ALT] elevation ≥3× upper limit of normal). No cases of hepatic failure or lasting liver damage have been documented in the cumulative experience from the 32 major trials of atorvastatin encompassing a total of more than 67 000 patients.

Concern has been raised that lowering LDL-C too much may have adverse consequences. However, an analysis of the PROVE IT–TIMI 22 trial ascertained that patients with the lowest achieved LDL-C levels (< 40 mg/dL) showed greater reductions in the primary end point compared with those with higher LDL-C levels[56]. There was no relationship between adverse events and achieved LDL-C levels. Similar results were obtained in an analysis of data from the TNT trial[84].

The risk of rhabdomyolysis, the only potentially life-threatening adverse effect of atorvastatin, is seen in approximately one in 22 727 patients treated with atorvastatin[85]. No fatal cases of rhabdomyolysis were seen in more than 67 000 patients enrolled in the major atorvastatin trials.

Limitations

Although this review has encompassed most of the important trials involving atorvastatin, limitations of this review include lack of generalizability of the atorvastatin trial data to other statins, lack of head to head outcome trials involving the newer more potent statins, and the relatively short study durations (none exceeded 5 years) when atherosclerosis is typically a decades-long disease.

Conclusion

A clinical trial database larger than that for any other statin documents that atorvastatin reduces major cardiovascular events in both the secondary and primary prevention of CHD and in a broad range of patients and disease conditions. Furthermore, throughout its dose range from 10 to 80 mg/day, atorvastatin has been found to be safe and generally well-tolerated.

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