Different Time Course for Prevention of Coronary and Stroke Events by Atorvastatin in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA)

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The lipid-lowering properties of statins reduce rates of coronary artery disease (CAD) events and strokes. Findings of recently conducted, longitudinal intervention studies suggest that these benefits occur early and may be, in part, independent of the lipid-lowering properties of statin therapy. We analyzed data from the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) to determine the timing of cardiovascular risk reduction. Relative risk reductions in CAD events were large compared with placebo, becoming apparent at 30 days and significant within 3 months, but they tended to decrease with time. Risk reductions in stroke were also apparent at 30 days but remained constant throughout the trial. Significant differences in hazard ratio between atorvastatin and placebo occurred at 2-year follow-up. Such apparently differential effects on CAD and stroke events suggest that mechanisms of action for CAD and stroke prevention may be different. These observations support the hypothesis that non–lipid-lowering actions of atorvastatin may have contributed to early protection against CAD in ASCOT-LLA. **(Am J Cardiol 2005;96[suppl]:39F–44F)**

Observational studies have demonstrated strong associations between increasing levels of serum cholesterol and coronary artery disease (CAD) events and outcome.[1] Despite a broadly similar atherosclerotic disease process being accountable for ischemic stroke, the association is less clear for serum cholesterol and stroke, being present (albeit less strongly) in some studies but not in others.[2] The full impact of exposure to higher levels of serum cholesterol—which is largely the result of dietary intake of saturated fat—on CAD incidence would appear, from a variety of sources of data, to become evident over a period of years.[1]

Conversely, when serum cholesterol is reduced by diet and/or other nonpharmacologic methods, accompanying reductions in CAD events are seen over a similar period of 4 to 5 years.[3] The introduction of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor class of drugs (statins) ushered in a new era in the treatment of dyslipidemia and in the primary and secondary prevention of cardiac and cerebrovascular events. Results from large-scale, multicenter intervention trials have consistently shown reductions in CAD incidence during statin therapy. In many but not all studies, reductions in CAD incidence were accompanied by reductions in stroke events.[4–12] However, compared with the observational data, reductions in CAD event rates during statin therapy appear much sooner than might be predicted. Indeed, reductions in CAD event rates are evident in some studies within the first year or earlier of active treatment.[8,13–15] Along with evidence from experimental studies, these observations have led to the suggestion that certain benefits associated with statins may be independent of their lipid-lowering properties.[16]

Moreover, there has been considerable speculation about whether there are differences between individual statins in non–lipid-lowering properties and hence a potential difference in the magnitude and time course of benefit in the prevention of CAD and other cardiovascular events.[17–20] In the context of early onset of effect with statin therapy, we have conducted a post hoc analysis of data from the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA) with the objective of determining the timing of cardiovascular risk reduction.

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The Anglo-Scandinavian Cardiac Outcomes Trial was conceived, designed, and coordinated by an independent investigator-led Steering Committee, members of which represented all the countries where the trial was undertaken. The principal funding source had 2 nonvoting members on that committee. The trial database is held, and this report was prepared, independently of the principal funding source.

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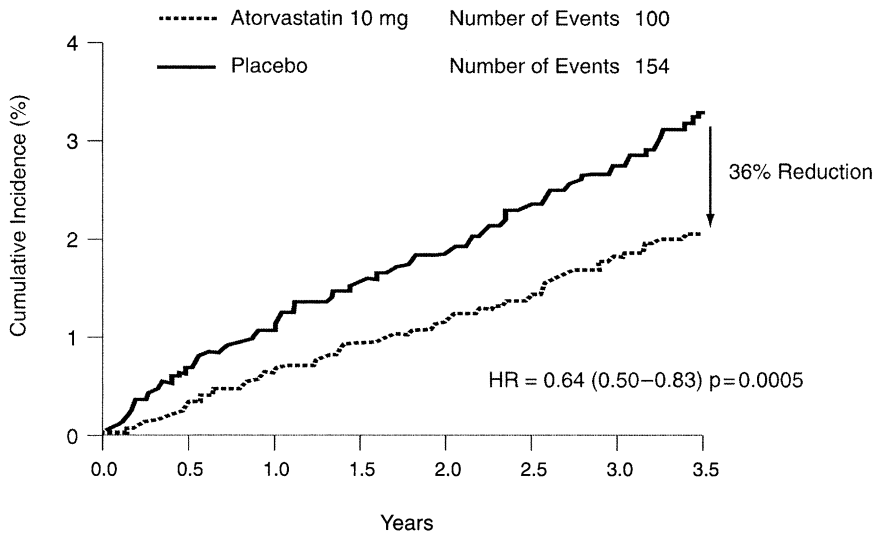

Figure 1. Cumulative incidence for primary end point of nonfatal myocardial infarction and fatal coronary artery disease in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). HR = hazard ratio. (Adapted with permission from *Lancet*.[14])

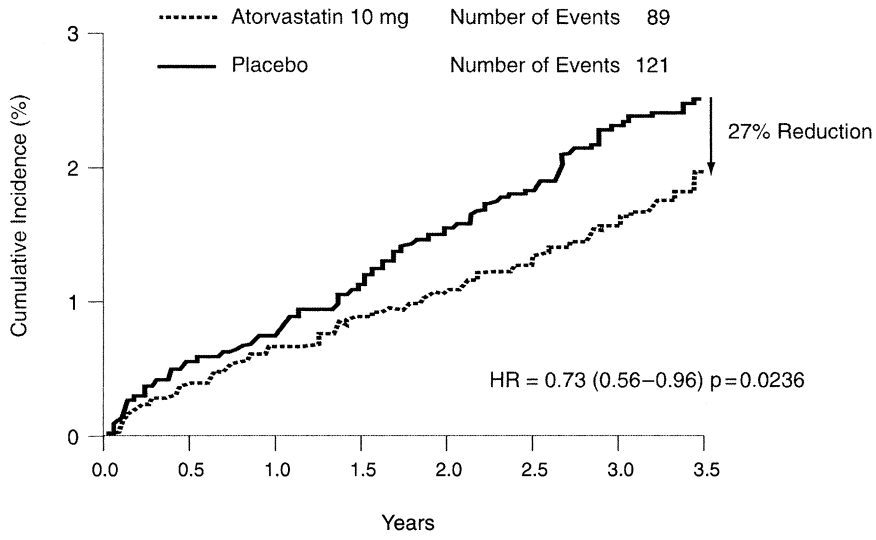

Figure 2. Cumulative incidence for the secondary end point of fatal and nonfatal stroke in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). HR = hazard ratio. (Adapted with permission from *Lancet*.[14])

Post Hoc Analysis of Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm

The main results of ASCOT-LLA have been previously reported.[14] In brief, 10,305 adult outpatients with well-controlled hypertension and ≥3 additional cardiovascular risk factors were randomized to placebo or to a 10-mg/day dose of atorvastatin. The primary end point was nonfatal myocardial infarction (MI) and fatal CAD. Baseline total cholesterol concentrations were ≤6.5 mmol/L. The trial was halted early after a follow-up period of 3.3 years because CAD events in the atorvastatin treatment arm were reduced by 36% compared with placebo ($p = 0.0005$). In addition, the reduction in CAD events was accompanied by a 27% reduction in stroke events ($p = 0.02$).

The time to first primary end point event in the atorvastatin and placebo groups was compared on an intention-to-treat basis. All analyses excluded end points deemed invalid by the end point committee, with statistical censoring enforced at the end of the study on October 1, 2002, or death before that date. The date used to indicate a silent MI was taken as the mean time between the dates of 2 electrocardiography procedures, the first of which showed no MI and the second of which did. For the main analyses, the log-rank procedure and the Cox proportional hazards model were used to calculate confidence interval. Cumulative incidence curves were generated by the Kaplan-Meier method for all major end points in the active and placebo groups.

Life-table analyses suggested that for CAD events, Kaplan-Meier curves for atorvastatin and placebo separated very early

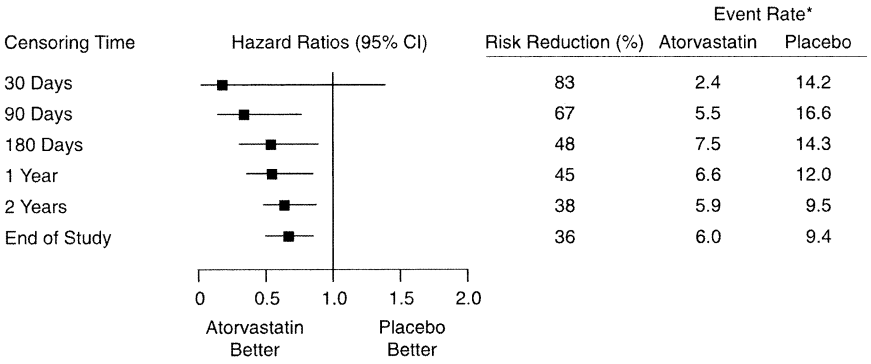

Figure 3. Forest plot of hazard ratios and 95% confidence intervals (CI) for coronary artery disease events at differing censoring times throughout the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). *Per 1,000 patient-years.

Table 1
Rates and hazard ratios at various time points*

Time Point	Atorvastatin N (%)	Rate*	Placebo N (%)	Rate*	HR (95% CI)	p Value
Primary end point						
30 days	1 (0.02)	2.4	6 (0.12)	14.2	0.17 (0.02–1.38)	0.058
90 days	7 (0.14)	5.5	21 (0.41)	16.6	0.33 (0.14–0.78)	0.008
180 days	19 (0.37)	7.5	36 (0.70)	14.3	0.52 (0.30–0.91)	0.020
1 year	34 (0.66)	6.6	61 (1.19)	12.0	0.55 (0.36–0.84)	0.005
2 years	60 (1.16)	5.9	96 (1.87)	9.5	0.62 (0.45–0.85)	0.003
End of study	100 (1.93)	6.0	154 (3.00)	9.4	0.64 (0.50–0.83)	0.001
Heterogeneity test					p = 0.60	
Stroke						
30 days	4 (0.08)	9.4	6 (0.12)	14.3	0.66 (0.19–2.35)	0.52
90 days	13 (0.25)	10.2	16 (0.31)	12.7	0.81 (0.39–1.68)	0.57
180 days	20 (0.39)	7.9	29 (0.56)	11.5	0.69 (0.39–1.21)	0.19
1 year	34 (0.66)	6.6	38 (0.74)	7.5	0.89 (0.56–1.41)	0.61
2 years	56 (1.08)	5.5	78 (1.52)	7.7	0.71 (0.51–1.00)	0.05
End of study	89 (1.72)	5.4	121 (2.36)	7.4	0.73 (0.56–0.96)	0.02
Heterogeneity test					p = 0.97	

CI = confidence interval; HR = hazard ratio.
* Per 1,000 patient years.

in the course of treatment (Figure 1). Similar, albeit less marked, differences were observed with stroke (Figure 2). Thus, additional analyses were undertaken to shed further light on the time interval to benefit for both CAD and stroke.

Time course for reduction in CAD event rates: Relative risk reductions for CAD were greatest within the first few months of treatment with atorvastatin and stabilized thereafter (Figure 3; Table 1). It is evident that there was a trend for benefit from atorvastatin as early as 30 days after randomization (1 vs 6 events, p = 0.058). Significant benefits were observed at 90 days (7 vs 21 events, p = 0.008), 180 days (19 vs 36 events, p = 0.020), 1 year (34 vs 61 events, p = 0.005), and 2 years (60 vs 96 events, p = 0.003). Risk reductions in CAD were maintained through the termination of the trial (100 vs 154 events, p = 0.001). However, a trend analysis failed to achieve statistical significance (p = 0.12).

Time course for reduction in stroke event rates: In contrast to the observation of an early beneficial effect of atorvastatin therapy on CAD event rates, no similar trend was observed for stroke outcome (Figure 2; Table 1). Relative risk reductions for stroke were constant throughout the trial (Figure 4). Significant benefits compared with placebo were evident at 2-year follow-up (56 vs 78 events, p = 0.05) and at the closeout of the trial (89 vs 121 events, p = 0.02).

Interpretation of data: Treatment groups were well matched at baseline for systolic and diastolic blood pressure, which decreased progressively throughout the trial in both groups. The higher event rates in the placebo arm of the study and the gradual reduction with time, for both CAD events and stroke, may be explained by improvements in blood pressure control. However, ASCOT-LLA was not designed to assess the effects of antihypertensive therapy on reductions in cardiovascular and cerebrovascular risk that are associated with statins. Thus, the findings of improved blood pressure in this cohort likely confound the ability to identify differences between atorvastatin and placebo.[14] These results confirm and extend previous reports, suggesting that benefits from treatment

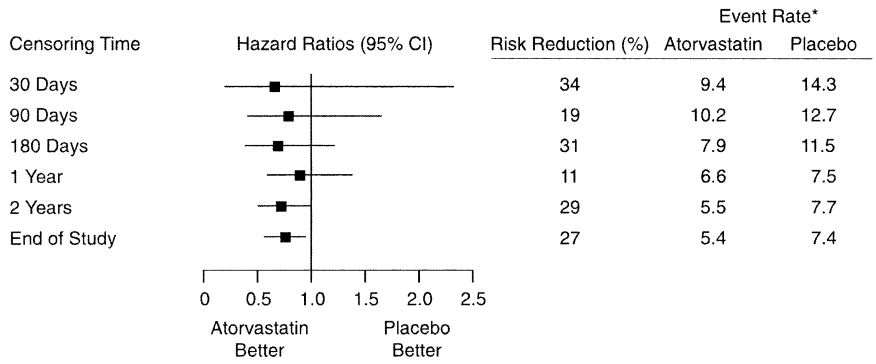

Figure 4. Forest plot of hazard ratios and 95% confidence intervals (CI) for stroke events at differing censoring times throughout the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA). *Per 1,000 patient-years.

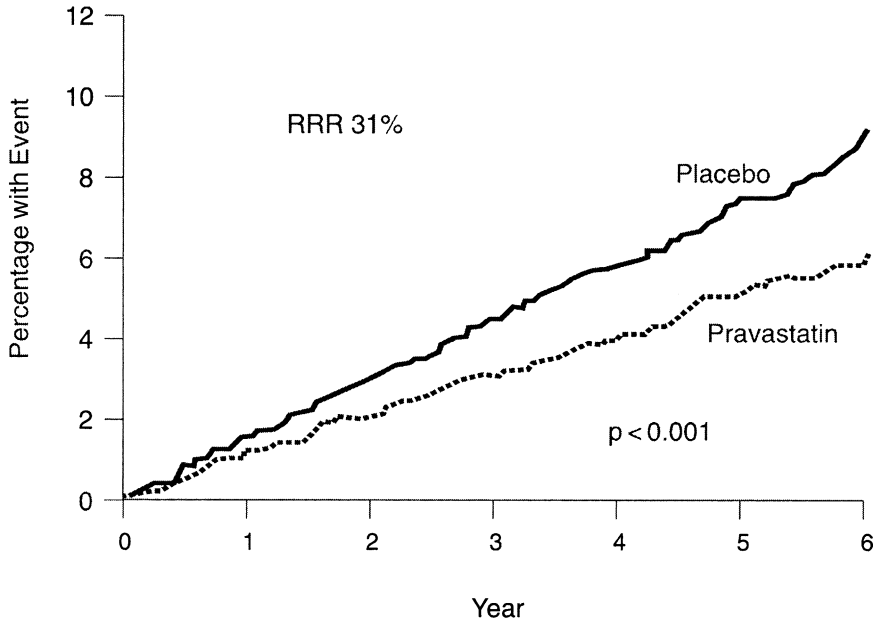

Figure 5. Cumulative incidence for primary end point of fatal and nonfatal coronary artery disease in the West of Scotland Coronary Prevention Study (WOSCOPS). RRR = relative risk reduction. (Adapted with permission from *N Engl J Med*.[22])

with atorvastatin and possibly other statins rapidly reduce CAD events.[13]

Mechanism Underlying Early Coronary Artery Disease Risk Reduction

Observations reported in ASCOT-LLA do not provide insight into possible mechanisms underlying the early risk reduction in CAD events.[14] However, it is unlikely that these beneficial effects are solely related to rapid reductions in the lipid content of plaque in the coronary circulation. More likely explanations may be derived from a more complete understanding of the so-called pleiotropic actions of statins, some of which may be independent of lowering low-density lipoprotein (LDL) cholesterol,[16] and include early stabilization of vulnerable plaques, improvement in endothelial function, possibly relating to induction of nitric oxide synthase, together with reductions in oxidative stress, and plasminogen activator inhibitor inhibition. Anti-inflammatory effects of atorvastatin are supported by observations on reductions in C-reactive protein.[21]

In view of the small number of events early in ASCOT-LLA, some caution needs to be expressed about the conclusions from observations on the time course of protection against stroke and CAD events.[14] Any differences in early protection against stroke and CAD events may be explained by the fact that although atherosclerotic disease underlies the pathogenesis of most strokes, the variable mechanisms, including atherothrombosis, emboli from carotid and endomyocardial thrombus, and intracerebral hemorrhage contributing to the totality of stroke events, may be less critically dependent on lowering of LDL cholesterol or indeed any, or some, of the putative pleiotropic mechanisms described above. Nonetheless, the findings of ASCOT-LLA

suggest that statins may exert different effects on the coronary versus cerebral vasculature, which underscores the need for further studies.

Observations from Other Trials

It is noteworthy that findings from other trials demonstrate an early benefit of statin therapy. The Collaborative Atorvastatin Diabetes Study (CARDS) was stopped prematurely, again suggesting early benefits of treatment. The objective of CARDS, which enrolled nearly 3,000 patients with type 2 diabetes mellitus, was to assess the efficacy of lipid-lowering therapy with atorvastatin (10 mg) as primary prevention of CAD in patients with no history of CAD.[15] The primary end point, which was time to onset of acute coronary events, stroke, or coronary revascularization, was met and the trial was terminated 2 years before its expected conclusion. Treatment with atorvastatin in this high-risk population reduced acute CAD by 36%, stroke by 48%, coronary revascularizations by 31%, and death rates by 27%.

The West of Scotland Coronary Prevention Study (WOSCOPS) was a primary prevention trial that also demonstrated an early separation of statin therapy from placebo.[22,23] In this trial, 6,595 men with moderate hypercholesterolemia were randomized to long-term treatment with placebo or pravastatin 40 mg. The primary end point was fatal and nonfatal MI, other cardiovascular death, or first coronary artery bypass graft surgery or percutaneous transluminal coronary angioplasty. The survival curve for patients with an end point event demonstrates an earlier protective effect for pravastatin compared with placebo (Figure 5). However, the onset of between-group differences in end point events did not appear as early as in the atorvastatin trials (Figure 1). Cardiovascular risk reduction in WOSCOPS was independent of reductions in LDL cholesterol, which suggests that the benefits of pravastatin in this population were not solely caused by cholesterol-lowering properties.

The findings of a study of high-risk patients also demonstrate early reduction in CAD risk.[13] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial, 4,162 patients who were hospitalized for an acute coronary syndrome were randomized to a 2-year course of low-intensity (pravastatin 40 mg) or high-intensity (atorvastatin 80 mg) treatment. The primary end point was a composite of events, including death from any cause, nonfatal acute MI, rehospitalization for unstable angina, stroke, and coronary revascularization. At 2-year follow-up, rates of the composite primary end point were 26.3% for low-intensity (pravastatin 40 mg) and 22.4% for high-intensity (atorvastatin 80 mg) treatment ($p = 0.005$). Statistically significant between-group differences were observed at 6 months. In this study, a head-to-head comparison of 2 statins demonstrated that greater reductions in LDL cholesterol concentrations were associated with significantly greater CAD risk reduction. Although this may have resulted from greater potency of one statin over another in terms of LDL cholesterol reduction, differential pleiotropic effects of statins may have also contributed.

Conclusion

Analyses described in this article provide further evidence that CAD risk factor reduction may be an early benefit of statin treatment. These risk reductions are not predictable by extrapolation from observational studies and should stimulate further research on the underlying mechanisms at the molecular and tissue levels.

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