Long-term results from statin trials: answers but more unresolved questions

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This commentary refers to ‘The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the UK’, by P.S. Sever et al., on page 2525

The benefits of statin treatment in both primary and secondary prevention of cardiovascular disease (CVD) have been well established in multiple randomized controlled trials (RCTs). In general the safety profile of statins is good. However, most of the statin trials have an average duration that is fairly short to study the long-term effects and safety of drugs that should be taken lifelong. Therefore, longer follow-up of participants from statin trials is advocated.

The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) is a multicentre trial involving two treatment comparisons in a factorial design. Two antihypertensive regimens [ASCOT blood pressure-lowering arm (ASCOT-BPLA)] are compared and in the lipid-lowering arm (ASCOT-LLA) the effects of atorvastatin 10 mg/day are examined using a double-blind placebo-controlled design; the ASCOT-LLA trial involved 10 305 patients with arterial hypertension, a cholesterol level of ≤ 6.5 mmol/L, and at least three other cardiovascular (CV) risk factors.

The ASCOT-LLA trial was stopped prematurely by the Data Safety Monitoring Board (DSMB) after a mean follow-up of 3.3 years due to a significantly lower incidence of the primary endpoint (non-fatal acute myocardial infarction and fatal coronary heart disease) in the atorvastatin group. The relative risk reduction (RRR) was –35% [95% confidence interval (CI) –17 to –49%, P = 0.0006].

This premature discontinuation has led to some unresolved issues due to reduced power in secondary endpoints and in prespecified subgroup analyses. After the ASCOT-LLA was discontinued, trial physicians were invited to offer atorvastatin 10 mg/day to all LLA patients until the end of ASCOT-BPLA, which was also stopped by the DSMB in early 2005, 2.2 years after the discontinuation of ASCOT-LLA.

At the time of the discontinuation of ASCOT-LLA, 13% of the patients originally assigned to placebo were on any statin, but this had increased to 63% at 5.5 years; their total cholesterol level was reduced, reaching 4.36 mmol/L; it was predicted that this should have accounted for an RRR in primary endpoint of 19% from the end of ASCOT-LLA to the end of ASCOT-BPLA; the observed RRR was 37%.

Among those originally assigned to atorvastatin, 84% of the patients were still taking any statin at 3 years, but this was reduced to 67% at 5.5 years; the total cholesterol level had risen slightly to 4.31 mmol/L. If in this group there was no carry-over benefit from atorvastatin in those who had stopped active treatment at the end of ASCOT-LLA one might have expected a modest rise in event rates. In reality event rates continued to decline, suggesting an important carry-over effect.

At the end of ASCOT-BPLA, the RRR in the primary endpoint among those originally assigned to atorvastatin remained unchanged at 36%; all-cause mortality (showing a non-significant –13% difference at the premature termination of ASCOT-LLA) showed a significant 15% reduction after the extension. These results are consistent with post-trial follow-up observations over short-term periods of up to 2 years from the Scandinavian Simvastatin Survival Study (4S), the LIPID study, and the ALERT trial. During these short-term periods they all observed ongoing benefits in terms of reduced deaths from coronary heart disease (CHD) in the group originally assigned to statin therapy. However, it might be predicted that in long-term follow-up, and assuming treatment rates equalize in those originally assigned placebo and statin, that CV event rates would converge.

Results from long-term follow-up have been reported by the 4S and by the West of Scotland coronary prevention study (WOSCOPS), an RCT in middle-aged men without a history of myocardial infarction. At the 5 years completion of the trial, the combined outcome of coronary death or non-fatal myocardial infarction was significantly reduced in the pravastatin group. An extended follow-up was organized covering ~ 10 years of observations after the end of the trial. The percentages of participants being treated with a statin among those assigned to the original pravastatin and placebo groups were 38.7% and 35.2%, respectively, at 5 years after the end of the trial. There was evidence of
an ongoing reduction in the risk of major coronary events among subjects treated with pravastatin during the trial period; the authors consider it as an ongoing carry-over effect related to a slowing of the progression of the disease and/or a stabilization of existing plaques.

The authors of the 4S study reported on an extended 5 year follow-up of deaths and incident cancers. During the 5 year extension >80% of patients in both groups were treated with lipid-lowering drugs. They found that the survival benefit of patients originally assigned to simvastatin compared with the placebo group persisted during follow-up; the absolute differences in all-cause, CV, and coronary mortality achieved during the double-blind trial changed little during the 5 year extension of the follow-up; the reduction in the relative risk between the two original treatment groups was ascribed to the open-label treatment with lipid-lowering drugs of most of the patients in both groups when the trial ended; there was no evidence of a difference in incident cancers.

Results have now been presented from a 11 year mortality follow-up of the participants recruited in ASCOT-LLA in the UK, representing 45% of the whole ASCOT-LLA study population; comparisons with previous reports from ASCOT-LLA are difficult: the baseline characteristics of the UK participants are different in various respects compared with those of the whole ASCOT-LLA groups; only results on mortality follow-up are given; therefore, only two out of the eight primary and secondary endpoints of ASCOT-LLA can be examined. For the interpretation of the results, one would like to know the proportions of participants on continuous lipid-lowering drug treatment throughout the extension period, but this is not available.

In the whole ASCOT-LLA trial, CV mortality was not significantly different between the atorvastatin and the placebo groups at the premature closure of the trial (−14%; 95% CI –37 to +32). In the UK cohort, CV mortality was non-significantly reduced by −17% (95% CI −49 to +35) at the end of the LLA trial and this became −11% (95% CI −29 to +11) after 11 years. These results are in line with what was observed in the long-term follow-up of the 4S study.

More surprising are the results of total mortality. Similarly to what was seen in the whole ASCOT-LLA, total mortality was not significantly different at the end of the LLA trial between the atorvastatin and the placebo group in the UK subgroup; the difference became significant at the closure of ASCOT-BPLA at 5 years, and in the UK group the difference remained significant at the end of the 11 years of follow-up. Since CV mortality went in the opposite direction, one expects a trend in favour of the group originally assigned to atorvastatin in non-CV mortality, and this was the case. The large majority of non-CV mortality is due to cancer deaths (66 and 60%, respectively, of all non-CV deaths in the groups originally assigned to atorvastatin and to placebo). The difference in cancer mortality rates was not different between the two groups at any point in time, and this is reassuring and confirms observations in WOSCOPS and 4S.

Post-hoc analysis of other non-CV mortality causes of death revealed significant differences in deaths due to infections/respiratory disease during the extension period, resulting in a hazard ratio of 0.64 (95% CI 0.42–0.97) for the total 11 year period. An explanation for these long-term benefits on non-CV deaths is not available, but results from observational studies are congruent and suggest that statins may have a therapeutic role through pleiotropic effects in the management of pneumonia and sepsis, although an explanation for a long-term carry-over effect has not been established. Different unintended benefits and adverse effects of statins have been suggested; this needs further studies, preferably in RCTs, but also re-emphasizes the need for long-term pharmaco-surveillance.

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References