Statin therapy for prevention of coronary artery disease. The earlier the better or the longer the better?

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The current study of Sever et al. reports the outcomes of subjects who were originally assigned to either atorvastatin or placebo in ASCOT-LLA and followed to the end of ASCOT-BPLA (5.5 years). At the end of ASCOT-BPLA, despite extensive cross-over to and from statin usage, the relative risk reduction in primary events among those originally assigned to atorvastatin remained unchanged from the core trial, at 36%. Although a secondary endpoint, and commented upon cautiously by the authors, the extension trial showed a significant 15% reduction in all-cause mortality among patients assigned to atorvastatin (P = 0.02), in contrast to the non-significant 13% reduction observed at the end of the core study. This is an important message to the medical community.

There may be some limitations to the study. First, there was incomplete clinical information on 230 patients at the end of the ASCOT-LLA extension (110 in the atorvastatin arm and 120 in the placebo arm). However, based on the overall incidence rate, the number of missed events is unlikely to have affected the main conclusion of the paper. Secondly, the use of statins during the extension phase was surprisingly low given the accumulating evidence for the benefits of statin treatment: only ~60% of the patients in either arm were taking atorvastatin or another statin. In the 2-year extensions of the 4S, LIPID, and ALERT trials, open-label statin use was between 80% and 90%.

These minor points should not, however, detract from the study’s important conclusion that the effect of statin therapy is durable over the long term. What is the main message? Early initiation of statin treatment and sustained use during the core trial might have provided a carryover effect to those originally assigned atorvastatin but who discontinued the drug. This could account for the unchanged relative risk reduction. Mitigation of the atherosclerotic process might be a possible mechanism and, although speculative, there is support for such a hypothesis from other extension studies in which patients were offered open-label statin treatment at the end of the core study. The recently published WOSCOPS extension demonstrated that during an extended post-study follow-up period of ~10 years, there was evidence of the lower the better for the optimal intensity of lipid-lowering therapy has been the focus of recent clinical trials, with growing support in the cardiovascular community for the concept of 'the lower the better' for LDL-cholesterol. As a result, the target for LDL-cholesterol has also been strongly recommended.1 Sever and colleagues have presented the results of a 2-year extension of the Anglo-Scandinavian Cardiac Outcomes Trial lipid-lowering arm (ASCOT-LLA Extension).3

In the initial ASCOT trial, the blood pressure-lowering arm (ASCOT-BPLA) compared the effect of two different antihypertensive regimens on cardiovascular outcomes. ASCOT-LLA was a double-blind, placebo-controlled trial of atorvastatin 10 mg/day in patients enrolled in ASCOT-BPLA who had total cholesterol ≤6.5 mmol/L.

The core ASCOT-LLA trial was discontinued prematurely after a median follow-up of 3.3 years due to a significant difference in the primary end-point, non-fatal myocardial infarction and fatal coronary heart disease. By the time the trial was stopped, only 100 primary events had occurred in the atorvastatin group compared with 154 events in the placebo group [hazard ratio 0.64, 95% confidence interval (CI) 0.50–0.83, P = 0.005].4 After the core LLA study was discontinued, trial physicians were invited to offer atorvastatin 10 mg/day to all LLA patients until the end of ASCOT-BPLA.
an ongoing reduction in coronary events among study participants initially allocated to statin treatment. The authors attributed this effect to stabilization of existing plaque and to slower progression of coronary artery disease. The LIPID study group also reported results from a 2-year extension, during which there were ongoing benefits in terms of reduced deaths from coronary causes or from any cause. The results of the 2-year extension of the 4S study and the ALERT trial also support the findings of the study by Sever et al.

This important study supports the premise that early initiation and sustained administration of statin treatment is important for maximizing long-term outcomes. Prolonged use of statins is an important message to the medical community, and is a key adjunct to discussions of LDL-cholesterol targets for the concept of ‘the lower the better’.

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References