Editorial

Investigating the long-term legacy of statin therapy

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For more than a quarter century, statins have been the predominant pharmacological approach to lowering levels of low-density lipoprotein cholesterol (LDL-C). On the basis of successive clinical trials, their use has expanded, spanning a wide range of cardiovascular risk. Despite their widespread use, there continue to be many unanswered questions with regard to understanding how these agents impact the natural history of atherosclerosis. As the seminal trials of statin therapy were performed more than 20 years ago, there is a unique opportunity to determine the long-term impact of these agents on cardiovascular outcomes in order to investigate potential legacy effects. In particular, such analyses permit evaluation of the long-term effects of relatively finite statin treatment on both cardiovascular outcomes and safety.

The West of Scotland Coronary Prevention Study (WOSCOPS) was the first clinical trial of pravastatin therapy in the primary prevention setting of hypercholesterolaemia. A total of 6,595 males, aged 45 to 64 years, with elevated LDL-C (mean 192 mg/dL) were randomised to treatment with pravastatin 40 mg or placebo. Initial follow-up of almost 5 years revealed a 26% reduction in LDL-C and 31% reduction in the composite of nonfatal myocardial infarction (MI) and death from cardiovascular with pravastatin (1). Subsequent examination of this cohort demonstrated a 12% reduction in all-cause mortality in pravastatin treated patients followed for 10 years (2).

In a recent report, Ford and colleagues (3) now report further on the long-term outcomes of statin use from the WOSCOPS cohort. The initial 5-year period of pravastatin treatment resulted in sustained reductions in all-cause mortality (HR 0.87; 95% CI, 0.80–0.94; P=0.0007), cardiovascular death (HR 0.79; 95% CI, 0.69–0.90; P=0.0004) and coronary heart disease (HR 0.73; 95% CI, 0.62–0.86; P=0.0002) when patients were followed for an additional 15 years after the original treatment period ended. Additional benefits observed more than 20 years after initial randomization to treatment groups included reductions in hospitalisation for heart failure by 35%, MI by 24% and any coronary event by 18%. No impact on non-cardiovascular mortality, hospitalisations or recurrent events from stroke was observed. It is important to note that such long-term benefits were observed despite the fact that statin use beyond the 5-year treatment period of the original study was only 35.2% of placebo and 38.7% of pravastatin treated patients, respectively.

Since the first landmark trial of primary prevention statin use, the Scandinavian Simvastatin Survival Study (4), numerous studies have corroborated the favorable effects of statins on hard cardiovascular outcomes. In parallel, serial plaque imaging studies have demonstrated that statins slow progression of atherosclerosis in a number of vascular territories, with more recent evidence suggesting that high intensity statin therapy can promote plaque regression. While the degree of benefit in these studies associates with the extent of LDL-C lowering, a number of lines of evidence suggest that non-lipid lowering properties of statins may also contribute to their benefit.

Very long-term effects of statin use in the primary prevention setting have previously been reported from

the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA) trial (5). In the original study atorvastatin 10 mg daily given to hypertensive patients produced a 36% reduction in the composite end point of nonfatal MI and fatal coronary events after 3.3 years (6). Extended follow-up of patients to 11 years after randomization demonstrated reductions in both all-cause and non-cardiovascular mortality by 14% and 15% respectively, but unlike the long-term follow-up of WOSCOPS showed no significant persistent difference in the rate of cardiovascular death. The ASCOT-LLA investigators speculated that the legacy effect of low-dose atorvastatin may have been limited to non-cardiovascular deaths, possibly due to its anti-inflammatory, rather than lipid-lowering properties.

The mechanism underlying any potential long-term legacy effect of finite statin treatment on cardiovascular outcomes remains unknown. To what degree changes in plaque burden and composition with statin therapy alter the factors influencing subsequent progression have not been elucidated, given that serial imaging studies have only followed patients to the end of treatment periods in clinical trials. Particular interest has focused on the potential for statin therapy to effect epigenetic changes, which may influence subsequent outcomes. Statins have been proposed to possess pleiotropic activity, with more recent evidence suggesting potential effects on telomere biology (7,8).

Telomeres are located at the terminal end of chromosomes, demonstrated to shorten in length, by 50–200 nucleotides, with each cycle of cell replication. This process ultimately results in an end replication problem, when telomere length reaches a threshold, beyond which cells can no longer replicate, leading to cellular arrest. What ensues is cellular senescence, impaired cellular function and ultimately apoptosis and cell death. The endothelium overlying atherosclerotic plaques commonly display features of senescence (9), with reported associations between shortened leukocyte telomere length (LTL) and cardiovascular risk (10). Reports that patients treated with a statin for at least 3 months have longer LTLs (7), potentially due to increased expression of the telomere repeat-binding factor 2 (TRF2) (8) suggest a possible epigenetic effect.

Previous reports from WOSCOPS have demonstrated that the presence of short LTL at baseline, independently predicts the 5-year risk of coronary heart disease, regardless of treatment allocation during the study (11). Subsequent analyses revealed that pravastatin lowered the risk of cardiovascular events in patients in the two lowest, but not the highest, LTL tertile (11). LTL remained an independent predictor of cardiovascular risk over the next 10 years of follow-up (12). It is therefore possible that favorable effects on LTL with initial, albeit finite, treatment with pravastatin may have contributed to the 20-year legacy impact on cardiovascular outcomes, particularly given that nearly two-thirds of patients were not treated with a statin beyond the end of the original trial. This raises the potential to employ LTL measurements to predict cardiovascular risk and identify patients most likely to benefit from use of statin therapy in primary prevention (11). This mechanism may also underlie the lack of legacy effect for late strokes in WOSCOPS follow up, given that meta-analyses have failed to demonstrate an association between LTL and cerebrovascular disease (10). While of potential importance, the contribution of epigenetic changes to both atherosclerotic plaque and cardiovascular outcomes requires further investigation.

In addition to examination of their impact on cardiovascular outcomes, there continues to be considerable interest in further elucidating the long-term safety profile of statins. The ability to study large cohorts over long follow up provides greater power to more definitively characterize the effect of statins on safety outcomes that occur relatively infrequently in the short term of most clinical outcome trials. In particular, long term follow up enables the ability to investigate reports of potential associations between statin use and incidence of both cancer and diabetes.

While reports of potential associations between statin use and cancer have arisen from individual outcome trials have emerged, extensive investigation has refuted any legitimate sense of such a relationship (13). Earlier analysis of the WOSCOPS population with 15-year follow up reported a greater incidence of prostate cancer in patients originally treated with pravastatin, although no differences in cancer mortality were observed between the groups (2). The current investigation of patients with follow up out to 20 years now demonstrates no difference between the pravastatin and placebo groups with regard to either incidence or mortality attributable to cancer. This finding is consistent with similar reports of no increase in cancer related mortality on long-term follow up of statin treated patients participating in ASCOT-LLA. The ability to follow patients for longer time periods improves the scientific rigor of trying to evaluate cancer related complications of medical interventions. The lack of any such finding, in the longest follow up statin treated patients reported to date, is reassuring of the safety profile of these agents.

The ability to follow up statin treated patients for longer periods is also important in determining the potential outcomes of reports that statins are associated with a greater tendency to progress to type 2 diabetes. Meta-analyses of statin outcome trials have confirmed that statin use, with the exception of pitavastatin, are associated with a greater incidence of new diagnoses of diabetes (14), with evidence that this association is stronger in patients treated with high intensity statin therapy (15). While the mechanism underlying these observations remains uncertain, it is ultimately the clinical implications of such findings that are of greatest importance. The finding that pravastatin treatment in WOSCOPS resulted not only in less cardiovascular events, but also less hospital admissions due to non-cardiovascular complications of diabetes (3) provides reassuring evidence to suggest that such findings do not adversely impact clinical outcomes. The combination of clinical benefits of statin therapy in patients with diabetes and lack of adverse clinical complications of diabetes in these patients supports ongoing use of statins in those at sufficient cardiovascular risk to warrant their use.

The findings of this long-term legacy study are important as they inform the clinician with regard to the balance between safety and efficacy of statin use over time. As with all clinical investigations, there are a number of points requiring consideration with regard to interpreting these results. Limited information is often available in such long term follow up studies. In particular, late stage lipid profiling was not available for all patients, which limits extensive investigation of the association between longer term lipid levels and both safety and efficacy signals. It is also important to reiterate that more than one third of patients in both treatment groups were treated with statin therapy beyond the completion of the original study. The lack of empirical use of statin therapy in the original pravastatin group is likely to be due to the fact that the evidence basis was not yet complete at that time for primary preventive statin use to be applied in clinical practice (2). As evidence continued to accumulate supporting the benefits of statins, their use appeared to be well balanced between the two groups on longer term observation. The lack of data with regard to individual statin use, dose and associated lipid profile, particularly after the 10-year follow up time point further limits the conclusions that can be drawn from these findings. Nevertheless, the findings suggest ongoing clinical benefit, associated with a reassuring safety profile, following statin treated patients for up to 20 years provides important information supporting the potential for relatively short term periods of statin therapy to confer considerable long term benefits for patients at high cardiovascular risk. Whether such benefits imply that statins should be administered for only finite periods or whether they may be observed with emerging approaches to lipid lowering, such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, cannot be concluded from this report. These are interesting and provocative questions that warrant further clinical investigation.

In summary, long term follow up of WOSCOPS patients out to 20 years provides new evidence to support the long term cardiovascular benefits and safety of pravastatin, when used in the primary prevention setting. The ability to demonstrate that these favorable effects are sustained for at least 15 years following completion of the original study supports the concept of a legacy effect of statins, although the true mechanistic rationale for this finding is unknown. Impressively, these favorable effects have now been sustained for at least 15 years after the original study period of randomisation ended, and may speak to a legacy effect of statins that now cost requires further mechanistic elucidation. When combined with cost effectiveness data (16), these findings continue to support the use of statin therapy to treat elevated cholesterol levels in patients at sufficiently high risk of developing cardiovascular events.

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Footnote

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