Statins have revolutionised modern cardiovascular treatment by producing a striking reduction in coronary risk. In 2005, the Cholesterol Treatment Trialists’ (CTT) collaboration reported a meta-analysis of 14 randomised trials (including about 90 000 patients) of statin versus placebo that recorded a 20% relative risk reduction in major vascular events (comprising coronary death, non-fatal myocardial infarction, coronary revascularisation, or stroke) per 1 mmol/L decrease in LDL cholesterol.\(^1\)

Findings of other studies subsequently showed the additional benefit of intensive-dose over standard-dose statin treatment.\(^2\)

Although the benefit of statins in these trials was overwhelmingly positive, data for long-term efficacy and tolerability were typically restricted to 5 years, and the safety of prolonged treatment with these HMG-CoA reductase inhibitors, especially in elderly patients, was questioned. Findings of observational studies (not randomised and, thus, subject to confounding) suggest diminished rates of prostate cancer associated with statin use,\(^3\) yet a 50% higher risk of colorectal cancer with more than 5 years of statin treatment.\(^4\) Furthermore, conflicting findings indicate an association between very low total or LDL cholesterol concentrations and higher rates of cancers and non-vascular mortality and morbidity.\(^5\) For this reason, data from randomised trials of statin treatment with extended follow-up of patients were examined to address these concerns and investigate the therapeutic and safety implications of prolonged statin therapy.

In a meta-analysis of 26 randomised controlled trials (21 trials of statin vs placebo and five of high-dose vs standard-dose statin), consisting of more than 160 000 participants, researchers investigated safety and long-term efficacy of statins.\(^5\) With median follow-up of 4.8–5.1 years, intensive statin regimens (compared with placebo) reduced LDL by 0.51 mmol/L at 1 year and produced an additional highly significant 15% risk reduction in major first vascular events, comprising coronary death or non-fatal myocardial infarction (relative risk reduction 13%), coronary revascularisation (19%), and ischaemic stroke (16%). All-cause mortality was reduced by 10% per 1·0 mmol/L reduction in LDL cholesterol and was attributable largely to reductions in coronary death. Despite the low LDL concentrations achieved, deaths due to cancer or non-vascular causes (relative risk 0·97) or cancer incidence (1·00) did not differ.\(^7\)

Nonetheless, critics continue to suggest that statins could increase risk for cancers that take longer than 5 years to emerge clinically.\(^8\) This idea prompted additional studies with extended post-trial follow-up. The West of Scotland Coronary Prevention Study (WOSCOPS), in which 6595 men with hypercholesterolaemia without a history of myocardial infarction were randomly allocated 40 mg daily of pravastatin or placebo from 1989 to 1991, was a 5-year study. Survivors were followed up for about 10 additional years after the trial, for a total follow-up period of about 15 years. The results of the original

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trial indicated a significant decrease in risk of coronary events in the pravastatin group; extended follow-up revealed an ongoing reduction in coronary events in patients originally treated with pravastatin versus placebo (post-trial period 10% vs 8.6%, p=0.02; entire follow-up period 15% vs 11.8%, p<0.001). Similar to data from the CTT Collaboration, no excess risk of non-cardiovascular deaths or fatal or incident cancers was noted.

The Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA), in which patients with hypertension were randomly assigned atorvastatin 10 mg or placebo for primary prevention, was stopped early because of overwhelming benefit. In an extended follow-up study (3.3 years follow-up within the trial and roughly an additional 8 years at the end), results confirmed no increased risk of incident cancer, infections, or respiratory illness. Efficacy data continued to suggest benefit from statin treatment with respect to all-cause mortality, which was decreased by 14%, and non-cardiovascular deaths, which fell by 15%.

In The Lancet, the Heart Protection Study Collaborative Group now report safety and efficacy outcomes of a large cohort of 20 536 patients in the Heart Protection Study (HPS), who were randomly allocated 40 mg simvastatin daily or placebo and were followed up for a mean total period of 11.0 years (including 5.3 years of in-trial follow-up). The in-trial period yielded a reduction of 23% in major vascular events per 1 mmol/L reduction in LDL cholesterol, beginning at year one from randomisation, consistent with previous findings. After this period, there was further divergence for 1 year or more, and the beneficial effect of treatment persisted for the duration of the entire follow-up period, without additional risk reduction in vascular or non-vascular mortality during the post-trial period. These results suggest that the early benefit of statins is likely to be followed by a prolonged legacy period, with benefit maintained over time. Despite noting many cancers during the full follow-up period (n=3493), incident cancer did not differ between the statin and placebo groups at all sites (risk ratio 0.98, 95% CI 0.92–1.05) or at any particular site. There was also no difference in cancer mortality (1.01, 0.92–1.11), or in mortality related to non-vascular causes (0.96, 0.89–1.03), even among elderly patients (aged ≥70 years) or those with below-average pretreatment total cholesterol concentrations (<5 mmol/L).

These results provide contemporary and confirmatory evidence that extended use of statins is safe with respect to possible risk of cancer and non-vascular mortality, even among elderly patients. The original concerns about statin safety were from observational data, which were probably heavily confounded. We now have strong evidence from HPS and several other randomised controlled trials that prolonged treatment with statins is indeed efficacious, safe, and has long-lasting beneficial effects, even after discontinuation of therapy. For this reason, concerns should be put to rest and doctors should feel reassured about the long-term safety of this life-saving treatment for patients at increased cardiovascular risk.

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13 Heart Protection Study Collaborative Group. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20 536 high-risk individuals: a randomised controlled trial. Lancet 2011; published online Nov 23. DOI:10.1016/S0140-6736(11)61125-2.