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ANALYSIS OF 170,000 PATIENTS SHOWS MORE INTENSIVE STATIN TREATMENT CAN SAFELY LEAD TO A FURTHER REDUCTION IN THE RISK OF HEART ATTACK, STROKE AND REVASCULARISATION

Two studies published Online First by *The Lancet* show that more intensive statin treatment to lower levels of bad (LDL) cholesterol in the blood safely lead to even greater reductions in the risk of major cardiovascular events than can regular statin doses. The benefit achieved is directly proportional to the reduction in bad cholesterol, even in patients with already low levels.

In the first study, a meta-analysis from the Cholesterol Treatment Trialists' (CTT) Collaboration, which was jointly coordinated by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) at the University of Oxford and the NHMRC Clinical Trials Centre at the University of Sydney, data from some 170,000 people from 26 randomised trials were analysed. Of these, five trials (around 40,000 people) compared intensive statin treatment with regular statin treatment, and the other 21 studies (130,000 patients) compared statin treatment with control. The study was led by Professor Colin Baigent, a Medical Research Council Scientist at the CTSU.

In the trials of more versus less intensive statin therapy, the further reduction in LDL cholesterol at 1 year was 0·51 mmol/L. Compared with less intensive regimens, more intensive statin treatment produced a highly significant 15% further reduction in major vascular events, consisting of separately significant reductions of 13% in coronary-related death or non-fatal heart attack, of 19% in coronary revascularisation interventions, and of 16% in ischaemic stroke.

Per 1·0 mmol/L reduction in LDL cholesterol, these further reductions in risk were similar to the proportional reductions in the trials of statin versus control. When both types of trial were combined, there was a proportional reduction in major vascular events of 22% per 1·0 mmol/L LDL cholesterol reduction, with similar reductions in all types of patient studied—including those with starting levels of LDL cholesterol lower than 2 mmol/L.

Taking all 26 trials together, all-cause mortality was reduced by 10% per 1·0 mmol/L LDL reduction (largely reflecting significant reductions of 20% in deaths due to coronary heart disease and 11% in other cardiac causes of death), with no significant effect on deaths due to stroke or other vascular causes. No significant effects were observed on deaths due to cancer or other non-vascular causes, and nor was there evidence of any excess risk of incident cancer, even at low LDL cholesterol concentrations.

They conclude: "Further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1·0 mmol/L lowering reducing the annual rate of these major vascular events by just over

a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2–3 mmol/L would reduce risk by about 40–50%."

The second study published today is a randomized trial called the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), which assessed intensive statin therapy with 80 mg vs 20 mg simvastatin in some 12,000 heart attack survivors; this large study, data from which were included in the meta-analysis above, was the largest of the 5 trials comparing more versus less intensive statin therapy. The trial was led by Professor Jane Armitage, also an MRC Scientist at the CTSU in Oxford.

During a mean follow-up of 6·7 (SD 1·5) years, allocation to 80 mg simvastatin produced an average 0·35 mmol/L greater reduction in LDL cholesterol as compared with allocation to 20 mg. This reduction in LDL cholesterol produced a 6% further reduction in major vascular events which, although not statistically significant on its own, was entirely consistent with the benefit that, based on the results of the above meta-analysis, would be anticipated to result from an LDL cholesterol reduction of this size.

Compared with two (0·03%) cases of myopathy (muscle weakness) in patients taking 20 mg simvastatin daily, there were 53 (0·9%) cases in the 80 mg group, including 7 cases of more serious muscle damage (rhabdomyolysis). Dr Louise Bowman, a senior research fellow at CTSU and clinical coordinator of SEARCH explained: "Myopathy is a rare side-effect of statins. It occurs in only about 1 in 10,000 patients per year with standard daily doses of 20-40mg simvastatin but in SEARCH we saw that myopathy is more common with 80mg simvastatin daily. So, it may be safer to lower cholesterol using low doses of more potent statins rather than by increasing the dose of simvastatin – the most commonly used statin. In light of these new findings, the current NICE guidelines for statins may need to be re-examined."

In a linked Comment, Professor Bernard M Y Cheung and Professor Karen S L Lam, University of Hong Kong, Pokfulam, Hong Kong, say: "People with substantial cardiovascular risk should have intensive lipid-lowering therapy. A low baseline LDL concentration is not a reason to withhold statin therapy if the patient is at a definite risk of cardiovascular events (eg, secondary prevention or diabetes). In this setting, the absolute risk reduction, number needed to treat, risk–benefit and cost–benefit ratios are favourable. These numbers will be less persuasive for people at low cardiovascular risk, such as young people with no risk factors. At the population level, statins are underused, so the urgent priority is to identify people who would benefit most from statin therapy and to lower their LDL cholesterol aggressively, with the more potent statins if necessary."

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For both Articles and Comment, see: LINK TO BE ADDED

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