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Results from the world's largest trial of the benefits of more intensive cholesterol-lowering and of the safety of folic acid supplementation

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New results announced today (Sunday 9 November 2008) emphasise the importance of lowering cholesterol substantially with statins to produce larger reductions in the risks of heart attacks and strokes.

They also show that folic acid and vitamin B12 supplementation is safe, but it does not protect against heart attacks or strokes. Researchers from Oxford University presented the main results of the 12,000 patient SEARCH¹ clinical trial at the American Heart Association meeting in New Orleans, USA.

Lowering cholesterol with statins has been known for many years to be very effective at preventing heart attacks and strokes. Previous trials have shown that lowering LDL cholesterol by 40mg/dl (about 1 mmol/l) with statin therapy reduces the chances of having a heart attack, stroke or revascularisation procedure by about a quarter. But, it had been uncertain just how intensively to lower LDL cholesterol levels.

SEARCH is the largest randomised trial to assess directly the efficacy and safety of lowering LDL cholesterol more than is typically done. It involved 12,000 men and women who had survived a heart attack. 6,000 were given a higher dose of 80mg simvastatin daily, and 6,000 were given a more standard dose of 20mg simvastatin daily. During an average of 6.7 years of treatment, the 80mg simvastatin regimen lowered LDL cholesterol by an average of 14mg/dl (0.35 mmol/l) more than the 20mg simvastatin regimen. This additional reduction in LDL cholesterol was associated with 6% fewer heart attacks, strokes or revascularisations.

Although not statistically significant on its own, the risk reduction in SEARCH is entirely consistent with the benefit observed in previous statin trials. When it was combined in a meta-analysis with the 4 previous trials that had directly compared more versus less intensive statin regimens, lowering LDL cholesterol further by an average of 20mg/dl was shown to produce highly significant 15% further reductions in heart attacks, strokes and revascularisation procedures.

"A very clear pattern is now emerging that shows the life-saving benefits of statin treatments to reduce LDL cholesterol," said British Heart Foundation Professor of Medicine & Epidemiology, Rory Collins, from Oxford University, who is one of the principal investigators. "Based on the meta-analysis, a 14mg/dl greater reduction in LDL cholesterol would be expected to produce a 6-7 per cent relative reduction in major vascular events, which is exactly what was observed in the SEARCH trial," he said.

"This new work reinforces the fundamental importance of lowering LDL cholesterol as much as we can in our fight against heart disease and strokes.

"All the evidence now points to lower is better as far as LDL cholesterol is concerned, provided that this can be achieved safely. For people who already have evidence of a circulatory problem and are at risk of further problems, doctors should now aim to get their LDL cholesterol as low as possible. We have not found a lower limit of LDL cholesterol below which lowering it further isn't worthwhile and safe."

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SEARCH used 80mg simvastatin daily to achieve more intensive lowering of LDL cholesterol and most of the participants tolerated this dose without any problems. However, 53 of the 6,000 people taking the 80mg simvastatin dose for nearly 7 years (about 1 per 1,000 per year) developed the well-recognised 'myopathy' muscle problem that can occur with statins, compared to just 3 among the 6,000 people taking the standard 20mg simvastatin dose (fewer than 1 per 10,000 per year).

Professor Jane Armitage, another of the SEARCH principal investigators from Oxford University, explained: "Myopathy is a rare side-effect of statins, occurring in only about 1 in 10,000 patients per year with daily doses of 20-40mg simvastatin. SEARCH shows that myopathy is more common with 80mg simvastatin daily. More intensive lowering of LDL cholesterol can, however, be achieved safely with simvastatin by combining a 20-40mg daily dose with other types of drug, such as ezetimibe, that lower LDL effectively. Alternatively, newer statins can be used which have a lower risk of myopathy with doses that are more effective than simvastatin at lowering LDL cholesterol."

Another important finding from the SEARCH randomised trial has conclusively overturned the belief that taking folic acid supplements might protect against vascular disease. In previous studies, higher levels in the blood of the amino acid homocysteine had been linked to higher risks of strokes and heart attacks. Folic acid supplementation, along with vitamin B12, reduces homocysteine levels and it was hoped that this would protect against strokes and heart attacks.

In the SEARCH trial, 6,000 of the patients were given 2mg folic acid and 1mg vitamin B12 daily for an average of 6.7 years and 6,000 were given dummy tablets. About one third of the patients were aged over 70 at the start of the trial. Despite the large numbers of patients studied and the long duration of treatment, no benefits were seen. Importantly, however, long-term supplementation with these vitamins was shown to be safe, with no significant excess of any major adverse events.

Professor Collins said: "Although it is disappointing that these vitamins don't prevent circulatory problems, the SEARCH findings on safety are very reassuring. Certain foods are being fortified with folic acid in some countries, such as the USA, (but not routinely in others, such as Britain), to protect mothers against the possibility of their babies being born with neural tube defects ('spina bifida'). SEARCH has now provided very valuable information that this policy is safe for other people in the population, including older individuals."

Professor Peter Weissberg, Medical Director at the British Heart Foundation, said: "This study is definite proof that whilst no harm is caused by taking folic acid and B vitamins it does not protect against future heart attacks and strokes. Alongside other relevant studies, the research shows that the lower your cholesterol level, the lower your risk of a stroke or heart attack."

He added: "Counter to Britain's current NICE² guidelines, the study suggests that lowering cholesterol may be more safely achieved 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 NICE guidelines for statins may need to be re-examined. Only a small number of people will be taking the high dose of statins associated with an increased risk of side-effects. Anyone who experiences unusual weakness or pain should talk to their GP."

SEARCH was designed, conducted, and analysed independently of the funding source by the CTSU, which is a world-leader in large-scale, international clinical trials. The cost of the trial was provided as a research grant to Oxford University by Merck & Co.

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¹The SEARCH acronym stands for Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine.

²The NICE acronym stands for National Institute for Health and Clinical Excellence (www.nice.org.uk).

For further information contact Andrew Trehearne on (0)1865-743960 or (0)789-404-2600. Journalists wishing to speak with Professor Peter Weissberg should contact the British Heart Foundation duty press officer on 020-7487-7172 or 07764-290381 out of office hours.