CTSU Clinical Trial Service Unit & Epidemiological Studies Unit

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Good news for kidney patients: World's largest kidney disease trial shows big benefits from reducing cholesterol

Denver: Around a quarter of all heart attacks, strokes, and operations to open blocked arteries could be avoided in people with chronic kidney disease by using the combination of ezetimibe and simvastatin to lower blood cholesterol levels. That's the conclusion from the world's largest ever randomized trial in kidney disease.

Unveiling the key findings today (Saturday 20 November) at the American Society of Nephrology, the trial's principal investigator Professor Colin Baigent said: "This is excellent news for patients who have kidney disease. It was already known that cholesterol-lowering could reduce the risk of heart attacks, strokes and the need for surgery to unblock arteries in people with normal kidney function. But, this trial now shows that cholesterol-lowering has similar effects in people with chronic kidney disease, irrespective of the severity of their illness. Taking ezetimibe plus simvastatin long-term would avoid around one quarter of heart attacks, strokes and operations to unblock arteries, leading to their prevention in at least 250,000 people with kidney disease worldwide each year."

The Study of Heart and Renal Protection (SHARP) involved almost 9,500 volunteers aged 40 or over with chronic kidney disease recruited from 380 hospitals in 18 countries. Patients included in the trial had lost at least 50% of their normal kidney function, with a third of them requiring dialysis treatment. None had had a previous heart attack or needed bypass surgery or "stents" to unblock their heart arteries. Volunteers in this double-blind placebo-controlled trial were randomly allocated to take either cholesterol-lowering therapy with a tablet containing ezetimibe 10mg daily and simvastatin 20mg daily, or matching dummy "placebo" tablets. Study treatment and follow-up continued for an average of 5 years.

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CANCER RESEARCH UK
British Heart Foundation
MRC Medical Research Council

SHARP was designed, conducted and analysed independently of all funding sources by the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU) of Oxford University, with guidance by an independent Steering Committee that included many of the world's leading kidney specialists. The study was supported by Merck (known as MSD outside of the US and Canada), who also supplied the study treatments, with additional support from the Australian National Health and Medical Research Council (NHMRC), the British Heart Foundation (BHF) and the UK Medical Research Council (MRC). Planning began in the mid-1990s, with two pilot studies followed by a main study that started in 2003 and ended in September of this year.

Summary of major findings

- The patients allocated to take ezetimibe plus simvastatin had one-sixth fewer heart attacks, strokes or operations to unblock arteries ("major atherosclerotic events"), with similar reductions observed in all types of patient studied.
- During this long trial, the proportion of patients who stopped taking their allocated treatment was about one third, but this was not generally due to side-effects and was the same for both real and dummy treatments. If taken without interruption, however, ezetimibe plus simvastatin could have even larger effects than were seen in SHARP, potentially reducing risk by about one quarter.
- Adding 10mg daily of ezetimibe to 20mg daily of simvastatin produced a large reduction in LDL ("bad") cholesterol safely. This combination treatment may be particularly good for kidney patients, as it avoids the possibility of side-effects with high statin doses.
- There was no support for previous concerns with ezetimibe about possible adverse effects on cancer, and no evidence of an increased risk of muscle or liver problems.

Professor Baigent said: "We knew from previous trials that statins reduce the risk of heart attacks and strokes in people with normal kidney function. But it had been widely believed that raised cholesterol was not an important cause of heart disease or stroke in people with chronic kidney disease, so that lowering cholesterol might not be beneficial for them. SHARP now provides the first direct evidence that cholesterol-lowering is indeed effective in kidney patients, and that the benefits are substantial."

SHARP co-principal investigator, Dr Martin Landray said that SHARP provides reassuring evidence about the safety of the ezetimibe and simvastatin combination: "There was no evidence of any serious adverse effects and, in particular, no support for earlier concerns that ezetimibe might cause cancer. SHARP shows clearly that the large cholesterol reduction produced with this treatment is safe, and provides similar benefits to those seen in people with normal kidney function."

The SHARP results are also relevant to people who don't have chronic kidney disease. The combination of ezetimibe and a statin produced similar benefits to those resulting from the same LDL cholesterol reduction achieved with a high dose of a statin. Since the lower the cholesterol the bigger the risk reduction, these results suggest that patients who remain at high risk of major atherosclerotic events despite maximal statin therapy may benefit further from adding ezetimibe to their current statin regimen.

Chronic kidney disease affects about one in 10 people worldwide. People with chronic kidney disease tend to have a very high risk of developing heart disease or experiencing a stroke. Until now, it has not been known how to prevent these conditions in such patients. Consequently, it is likely that the SHARP results will result in cholesterol-lowering treatment being used widely in this large group of high-risk people who were previously not being given such treatment.

Weblink: www.sharpinfo.org

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Please note that I will be in Denver from late afternoon, Wednesday 17 November- Sunday 21 November.