

BACKGROUND: Question and Answers about the SHARP trial

What is chronic kidney disease (CKD)?

Chronic kidney disease occurs when the kidneys are permanently damaged by certain diseases, such as diabetes or high blood pressure, and in some people they may fail progressively. If the kidneys fail completely then the body's waste products have to be removed either by using a kidney machine (haemodialysis) or by flushing the abdomen with fluid (peritoneal dialysis). In some patients kidney function can be restored with a kidney transplant, making dialysis unnecessary.

Why is cardiovascular disease a problem for kidney patients?

Chronic kidney disease can cause other health problems, and one of the most important of these is cardiovascular disease. Indeed for many people with kidney disease, the risk of cardiovascular disease is much greater than the risk of needing dialysis or a kidney transplant. This disease may be present in the heart (for example, causing a heart attack), the brain (causing a stroke) or in arteries in the leg (which may cause poor blood circulation to that limb).

Why do kidney patients develop cardiovascular disease?

The reasons why kidney patients develop cardiovascular disease are not well understood, but some conditions that are common in kidney patients (e.g. high blood pressure and diabetes mellitus) are also causes of cardiovascular disease. Kidney patients are at increased risk of cardiovascular disease due both to atherosclerosis (i.e. build-up of fatty deposits in the arteries) and to stiff arteries and enlarged hearts leading to heart failure.

Why might reducing blood cholesterol be helpful in kidney patients?

Raised blood levels of cholesterol are a known cause of heart attacks and strokes, and reducing cholesterol in patients with normal kidney function has been shown to reduce the risk of these. Consequently, it was thought that lowering cholesterol might prevent at least some of the cardiovascular disease that develops in kidney disease. Previous trials have not, however, been able to demonstrate benefit in patients with kidney disease, but they may have involved too few patients.

What is the SHARP trial?

SHARP is the short name for a randomized controlled trial called the Study of Heart and Renal Protection. It involved more than 9,000 volunteers aged 40 or over with chronic kidney disease who were 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 surgery to unblock their heart arteries. SHARP is much bigger than any previous trial in kidney disease patients

What was the treatment in SHARP?

Volunteers in the SHARP double-blind placebo-controlled trial were randomly allocated either to take cholesterol-lowering therapy with a tablet containing ezetimibe 10mg daily and simvastatin 20mg daily or to take matching dummy "placebo" tablets. Study treatment and follow-up continued for about 5 years.

What is a randomized controlled trial?

In a randomized trial volunteers are selected at random (using a process similar to tossing a coin) to receive either an active (i.e. real) treatment or a control (dummy) treatment.

SHARP is an example of a “double-blind” trial in which neither the trial volunteers nor their doctors knew whether they had been allocated real or dummy treatment. The volunteers in both treatment groups received all other treatments that were thought to be needed.

What are the main aims of SHARP?

SHARP aims to assess whether reducing blood cholesterol levels in people with kidney disease can safely prevent “major atherosclerotic events”. These “events” are defined as heart attacks, “ischaemic” strokes (i.e. strokes caused by blockage of a brain artery), and operations to unblock arteries. The SHARP trial also aims to find out whether lowering blood cholesterol can help patients with chronic kidney disease avoid needing dialysis or kidney transplant.

Weren’t the original aims different?

SHARP originally set out to assess the effects of lowering cholesterol on the risk of “major vascular events”, defined as “major atherosclerotic events” plus other cardiac causes of death and strokes due to bleeding (“haemorrhagic strokes”). But, whilst the trial was ongoing, new information became available from other completed studies that suggested that lowering cholesterol might have little effect on these additional “events”. Before breaking the trial’s code, therefore, the independent Steering Committee decided that analyses of “major atherosclerotic events” would provide the most valuable information to patients and doctors. This change was described in a paper that was published in a leading medical journal before the trial’s code was broken.

How was the trial organised?

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, United Kingdom. The trial was guided by an independent Steering Committee that included many of the world’s most eminent kidney specialists. Regional coordinating centres were based in Australia, Canada, China, Germany, Scandinavia, the USA and the UK. Volunteers joined the study from 18 countries (numbers of patients and numbers of hospitals given in brackets):

Australia	(1043, 36)	Finland	(93, 5)	Norway	(194, 11)
Austria	(111, 5)	France	(264, 16)	Poland	(160, 11)
Canada	(505, 26)	Germany	(1678, 83)	Sweden	(219, 17)
China	(994, 16)	Malaysia	(701, 14)	Thailand	(253, 6)
Czech Republic	(191, 12)	Netherlands	(108, 9)	UK	(1987, 65)
Denmark	(258, 9)	New Zealand	(285, 8)	USA	(394, 31)

How was the study funded?

The SHARP trial was supported by the pharmaceutical companies Merck & Co. and Schering Plough (who merged in 2009), 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).