
Study of Heart and Renal Protection (SHARP)

Final Protocol (Version 5: 12th July 2005)

DOES LOWERING CHOLESTEROL PREVENT MAJOR VASCULAR EVENTS IN PATIENTS WITH CHRONIC KIDNEY DISEASE?

Among patients with pre-existing coronary heart disease, large-scale randomized trials have demonstrated that lowering LDL-cholesterol concentration by about 1 mmol/l for 4-5 years reduces the risk of coronary events and of strokes by about 25%. Patients with established chronic kidney disease (CKD) are at high risk of vascular disease, so the benefits of cholesterol-lowering therapy might be expected to be substantial in this population. But, patients with CKD have generally been excluded from previous trials, and there is currently no reliable randomized evidence that lowering LDL-cholesterol would be beneficial among them.

There are several reasons why the demonstrated benefits of lowering blood cholesterol in other populations might not translate to patients with CKD. First, observational studies among dialysis patients have reported a negative association between blood total cholesterol and mortality. Secondly, only about one quarter of cardiac mortality in such patients appears to be definitely attributable to acute myocardial infarction, and so potentially avoidable with cholesterol-lowering, while the other common causes (e.g. cardiac arrest, arrhythmia, and heart failure) may not be as dependent on cholesterol levels. Finally, the long-term safety of cholesterol reduction among patients with CKD remains unclear. Hence, there is an important need for reliable direct evidence on whether lowering cholesterol prevents a worthwhile proportion of vascular events, without unacceptable toxicity, among patients with chronic kidney disease.

DOES LOWERING CHOLESTEROL DELAY LOSS OF RENAL FUNCTION?

Animal studies have suggested that glomerulosclerosis (a major mechanism leading to loss of renal function) shares many similarities with atherosclerosis, and may be promoted by certain blood lipid abnormalities. A meta-analysis of small-scale randomized trials among CKD patients has suggested that lowering LDL-cholesterol might reduce the rate of nephron loss among patients with progressive renal dysfunction. But, in order to confirm or refute this hypothesis properly, a large-scale trial of cholesterol-lowering therapy in such patients is now needed.

SHARP: A STREAMLINED INTERNATIONAL TRIAL

The Study of Heart and Renal Protection (SHARP) aims to assess the effects of cholesterol-lowering therapy with a combination of simvastatin and the cholesterol-absorption inhibitor ezetimibe among around 9,000 patients with CKD (around 6,000 of whom will be pre-dialysis and 3,000 on dialysis). Such large-scale recruitment will allow reliable assessment of the effects of lowering blood LDL-cholesterol on the risk of major vascular events and on the rate of loss of renal function in patients with various degrees of renal impairment. An international collaboration between nephrologists and clinical trialists, with an International Coordinating Centre and around 6 Regional Coordinating Centres, will conduct the trial in over 200 hospitals in about 10 countries. SHARP is "streamlined": extra work for collaborating doctors and hospitals has been kept to a minimum, and essential data only will be collected electronically to help research staff record accurate information about participants.



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1 INTRODUCTION

1.1 HIGH RISK OF CARDIOVASCULAR DISEASE AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD)*

Patients with end-stage renal disease are at high risk for developing premature cardiovascular disease. In the US, for example, cardiac mortality among dialysis patients younger than 45 years is about 100 times greater than in the general population (see Figure 1).¹ This large proportional increase in risk implies that the absolute risk of cardiac death in young dialysis patients is comparable to that observed in elderly individuals without renal disease. In the general population, most cardiac mortality results from atheromatous coronary heart disease (CHD), but in dialysis patients much cardiac mortality is arrhythmic or due to congestive heart failure.² Such differences may arise, at least in part, because cardiomyopathy is a prominent pathological feature in uraemia, with left ventricular hypertrophy found in about three-quarters of patients upon starting dialysis treatment.³

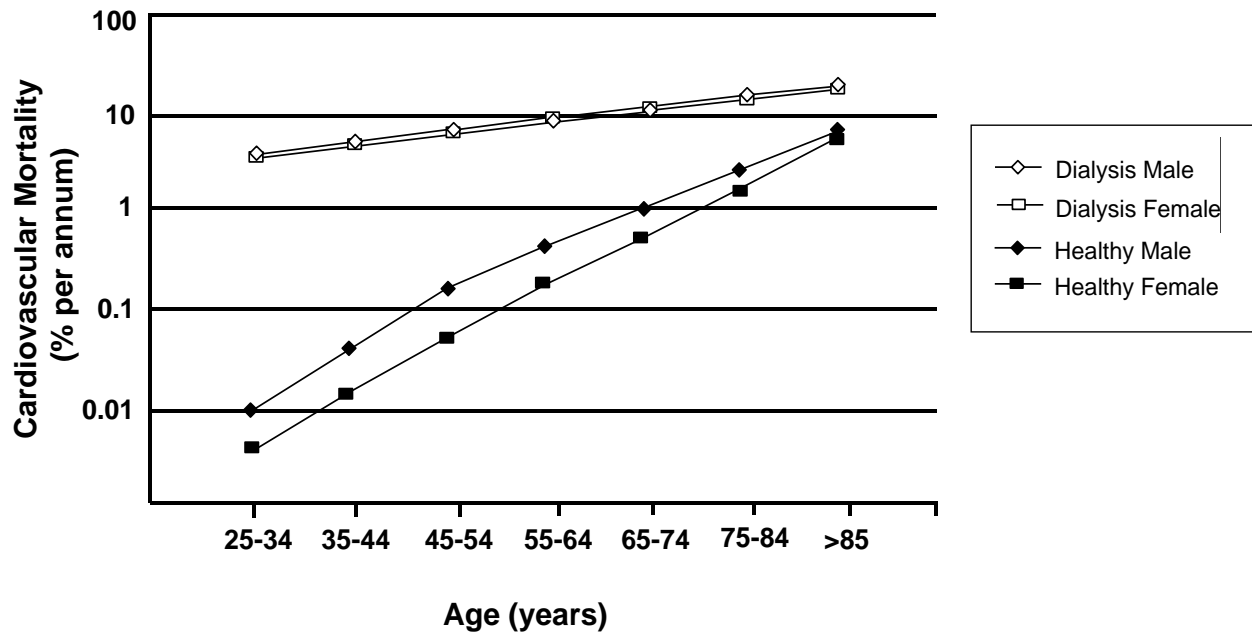


Figure 1: Cardiovascular mortality (death due to arrhythmia, cardiac arrest, myocardial infarction, atherosclerotic disease and pulmonary oedema) in US dialysis patients¹

* Chronic Kidney Disease (CKD) is a term introduced by the National Kidney Foundation K/DOQI Work Group⁴ in order to describe conditions that affect the kidney with potential for progressive loss of kidney function or for complications resulting from decreased kidney function. Chronic Kidney Disease is divided into 5 stages, as shown in Appendix 1. The majority of patients included in the SHARP study will have Stage 2-5 CKD.

At least some of the excess risk of cardiovascular disease appears to develop before end-stage renal failure occurs, since clinical manifestations of congestive heart failure are already present in about a third of new dialysis patients, angina in about a quarter and a history of myocardial infarction in about 10%.⁵ Indeed, the available evidence suggests that such disease is present very early in the natural history of chronic renal failure.² In prospective observational studies among pre-dialysis patients, for example, about one-third of those with moderate reduction in glomerular filtration rate (GFR) equivalent to CKD Stage 3 or higher (GFR < 60 ml/min/1.73m²) have been found to have a history of overt cardiovascular disease.^{6,7}

1.2 EFFECTS OF REDUCING BLOOD CHOLESTEROL AMONG PATIENTS WITH CHRONIC KIDNEY DISEASE

1.2.1 Effects of lowering cholesterol on cardiovascular outcomes

Among patients with CHD but without evidence of chronic kidney disease (CKD), large-scale randomized trials have demonstrated that lowering LDL-cholesterol concentration by about 1 mmol/l (about 40 mg/dl) for 4-5 years reduces the risk of a coronary event by about 25% and the risk of ischaemic stroke by a similar amount.⁸⁻¹² But, patients with established CKD (e.g. GFR <60 ml/min/1.73m²) have generally been excluded from such trials, and it remains substantially uncertain whether such patients would benefit when CHD is clinically absent. Currently, the only source of evidence about the effects of lowering cholesterol in CKD patients comes from analyses of small subgroups within previous trials. These analyses are of limited value because few patients with significant renal dysfunction had been included and most already had CHD. For example, it was observed in the Cholesterol And Recurrent Events (CARE) study that pravastatin 40 mg daily was beneficial among around 1700 patients with very mild renal impairment (mean calculated creatinine clearance 61 ml/min), all of whom had CHD.¹³ Similarly, in the Heart Protection Study (HPS) simvastatin 40 mg daily appeared beneficial among patients with slightly raised blood creatinine (plasma creatinine 130-200 µmol/l in men or 110-200 µmol/l in women).¹¹ But, if patients with CHD are excluded, HPS included only 128 patients with more substantial renal impairment (i.e. creatinine 150-200 µmol/l in men, or 130-200 µmol/l in women), and so does not provide direct evidence about the effects of cholesterol-lowering therapy in CKD patients with no prior CHD.

Moreover, although the benefits of cholesterol-lowering therapy might be expected to be substantial in patients with CKD because they are at high risk of vascular disease, there are several reasons why this might not be the case:¹⁴

(i) No clear association between cholesterol and cardiac outcomes in epidemiological studies of dialysis patients

Observational studies among apparently healthy individuals have shown that there is a roughly linear relationship between risk of death from cardiovascular disease (plotted on a doubling scale) and blood cholesterol.¹⁵ Similarly positive log-linear associations are observed among certain high-risk populations, such as patients with diabetes (Figure 2)¹⁶ or patients with pre-existing cardiovascular disease.¹⁷ Randomized trials of cholesterol-

lowering treatments, such as HMG-CoA reductase inhibitors (“statins”), have established that reducing cholesterol among such high-risk patients reduces the risk of CHD.⁸⁻¹¹ Among patients with CKD, however, the relevance of blood cholesterol to cardiovascular disease is less well understood. One small study among dialysis patients reported a negative association between blood total cholesterol and cardiovascular mortality¹⁸, whilst a much larger study reported a negative association at very low cholesterol levels (which are common in dialysis patients), and a flat relationship at cholesterol levels within the “normal” range (Figure 3).¹⁹ Among dialysis patients with very low cholesterol a negative association between cholesterol and mortality may well be due to “reverse causality”, with malnutrition and other chronic disease both lowering blood cholesterol and, independently, increasing the risk of death^{2,14}. Such a phenomenon is, however, less likely to explain the absence of an association among those with “average” cholesterol levels in Figure 3.

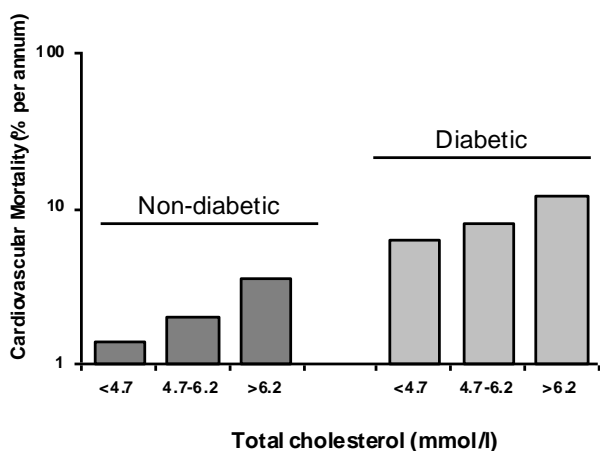


Figure 2: Associations between blood cholesterol and cardiovascular mortality, plotted on a logarithmic scale, among screenees in the Multiple Risk Factor Intervention Trial (MRFIT) with diabetes (n=5,000) or without diabetes (n=340,000)¹⁶

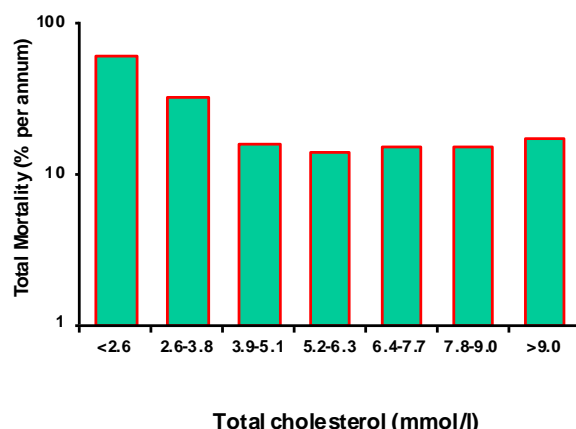


Figure 3: Associations between blood total cholesterol and all-cause mortality, plotted on a logarithmic scale, among 12,000 haemodialysis patients followed for one year.¹⁹

(ii) High proportion of cardiac mortality may be unrelated to CHD

One plausible reason for the lack of a clear association between blood cholesterol and cardiovascular outcomes among dialysis patients is that only about one quarter of cardiac deaths in such individuals are attributed to acute myocardial infarction.⁵ The role of coronary heart disease in the majority of cardiac deaths (i.e. those due to cardiac arrest, arrhythmia, heart failure, or some other cardiac cause) among such patients is less certain, and so cardiac deaths as a whole may not be strongly associated with cholesterol levels in this population.^{2,14} Among dialysis patients there is a very high prevalence of structural cardiac disease (that is, left ventricular hypertrophy, dilatation and fibrosis), which could account for the observation that a high proportion of cardiac mortality among dialysis patients is not directly attributable to CHD.³

(iii) Safety of cholesterol reduction in CKD patients is uncertain

Although there was no specific evidence that cerivastatin was toxic in patients with CKD, its withdrawal from the market due to an excess risk of rhabdomyolysis²⁰ does emphasise the need for careful evaluation of the safety of any cholesterol-lowering regimen directly in patients with CKD. Such patients may be particularly vulnerable to the adverse effects of treatment, and this may be exacerbated by interactions with the many other types of treatments that they typically receive. Despite this, the impact of statins (or other cholesterol-lowering drugs) on myopathy and other potential hazards in patients with CKD is unknown because few were included in previous large-scale randomized trials.

1.2.2 Effects of lowering cholesterol on the progression of renal disease

An additional rationale for a large-scale study in patients with CKD is that it would help to define the role of cholesterol in determining the rate of progression of renal disease. Experimental studies have suggested that glomerulosclerosis (a scarring process associated with loss of renal function) shares many similarities with atherosclerosis, and may likewise be modulated by blood lipids.²¹ Hence, lowering LDL-cholesterol might reduce the rate of nephron loss among patients with progressive renal dysfunction,^{21,22} as suggested by a meta-analysis of small-scale randomized trials.²³ But, a reliable demonstration of this will require a large-scale randomized trial of cholesterol-lowering therapy among patients with CKD.

1.3 HEART AND RENAL PROTECTION (HARP) PILOT STUDIES

1.3.1 Experience in the first HARP pilot study of simvastatin (UK-HARP-I)

The initial stage in developing the present large-scale randomized trial among patients with CKD was to conduct a pilot study. The main aims of this first pilot study (UK-Heart and Renal Protection [UK-HARP-I]) were: (i) to estimate compliance with simvastatin 20 mg daily, and its effects on lipid profile, in this particular group of patients; (ii) to establish that this regimen did not produce an unexpectedly large risk of myopathy or hepatotoxicity; and (iii) to develop efficient methods that might facilitate a large-scale study. A total of 448 patients with chronic kidney disease were randomized to simvastatin 20 mg daily* versus matching placebo (and, in a factorial design, aspirin 100 mg daily versus matching placebo) with treatment continued for 1 year.²⁴ At baseline, a total of 242 patients were pre-dialysis with plasma creatinine ≥ 150 $\mu\text{mol/l}$, 73 were receiving maintenance haemodialysis or peritoneal dialysis, and 133 patients had a functioning renal transplant. Compliance with study treatment was around 80% at 12 months, with no significant differences in compliance between treatment arms. Among patients allocated to simvastatin there was no significant excess of muscle pain or weakness, of abnormal liver function tests or of elevated creatine kinase. In particular, there were no cases of serious myopathy (defined as muscle pain with creatine kinase >10 times the upper limit of normal), although this pilot study was too small to exclude any moderate increase in the frequency of this rare, but serious, adverse event that might exist. Overall, simvastatin 20 mg daily produced a mean

* In patients who were transplanted during the scheduled follow-up period, simvastatin 20 mg was given on alternate days until the end of the study.

proportional reduction in LDL-cholesterol concentration of 26% ($P < 0.0001$) from a baseline mean of 3.2 mmol/l,²⁴ which is similar to the LDL-cholesterol reduction among patients without CKD.²⁵ Thus, simvastatin 20 mg once daily was well-tolerated and effective at lowering LDL-cholesterol in patients with CKD, and was not associated with substantially increased rates of clinical or biochemical adverse effects. The UK-HARP-I study also demonstrated the potential feasibility of conducting a large-scale “mega-trial” of lipid-lowering therapy among patients with CKD.

1.3.2 Additional reductions in LDL-cholesterol by adding ezetimibe, a cholesterol-absorption inhibitor, to simvastatin

Patients with CKD generally have average or below-average LDL-cholesterol levels,^{6,21} yet are at high risk of cardiovascular events.^{1,2,5} In other high-risk settings (such as among patients with diabetes; see Figure 2), there is a roughly log-linear relationship between the risk of CHD and blood cholesterol. This suggests that the proportional reduction in CHD risk associated with a particular prolonged absolute difference in LDL-cholesterol is similar throughout the range observed in Western populations (i.e. above about 3 mmol/l).¹¹ The nature of any true relationship between blood cholesterol and risk of CHD among patients with CKD cannot be determined reliably from existing observational studies.² But, if it is a positive log-linear relationship similar to that observed in other high-risk populations, then several key points follow. First, the absolute size of the reduction in CHD produced by lowering cholesterol may be determined more by an individual’s overall risk than by just their initial cholesterol level. In which case, kidney patients at high-risk of CHD would benefit substantially even if they have “average” or “below-average” blood LDL-cholesterol. Secondly, the proportional reduction (and hence absolute reduction) in the risk of CHD would depend upon the size of the absolute reduction in LDL-cholesterol. As coronary atheroma may cause a somewhat smaller proportion of cardiac events in patients with CKD than in other high-risk settings², it may be important to maximise any reduction in LDL-cholesterol if a worthwhile reduction in cardiac events is to be achieved.

One possible approach would be to use a higher dose of simvastatin than the dose (20 mg daily) that was tested in the first HARP pilot study. Studies among individuals without kidney disease show that there is a linear log-dose response relationship between dose of simvastatin and reductions in cholesterol. In one short-term study, for example, simvastatin at doses of 40 mg, 80 mg and 160 mg daily lowered LDL-cholesterol by 41%, 47% and 53% respectively.²⁶ However, there also appears to be a dose-related increase in the risks of myopathy associated with statin use, and patients with kidney disease may be particularly vulnerable to such adverse effects. An alternative strategy would be to combine a moderate dose of a statin with another cholesterol-lowering drug. Currently licensed cholesterol-lowering agents such as high-dose nicotinic acid and fibrates are associated with some increase in the risk of myopathy when combined with a statin, particularly in patients with reduced renal function.²⁷ The cholesterol absorption inhibitor ezetimibe, which selectively inhibits the passage of dietary and biliary cholesterol across the intestinal wall, may circumvent these difficulties.²⁸⁻³⁰ In one study, the addition of ezetimibe 10 mg daily to simvastatin (in daily doses of 10-80 mg) reduced the mean LDL-cholesterol by 24% as compared to simvastatin alone (i.e. relative to the on-statin LDL-cholesterol).³¹ Overall, compared to placebo, the combination of ezetimibe and simvastatin

reduced LDL-cholesterol by 44%-57%. Indeed, the combination of simvastatin 20 mg and ezetimibe 10 mg daily produced a greater LDL-reduction than simvastatin 80 mg (the maximum licensed dose). In a separate study, among 226 patients who were already taking simvastatin (in a range of doses), the addition of ezetimibe 10 mg daily also produced an incremental reduction of about 24% in LDL-cholesterol as compared to continuation of simvastatin alone at the same dose.³²

Ezetimibe is readily absorbed and undergoes rapid first pass metabolism in the intestine to the phenolic glucuronide, which is at least as active as the parent drug.²⁹ It undergoes extensive entero-hepatic recirculation, leading to an effective half-life of about 24 hours. It is highly protein-bound (and thus unlikely to be eliminated by dialysis) and its distribution is largely confined to the gastro-intestinal tract, which is the major route of elimination (with only about 10-15% excreted in the urine). Ezetimibe does not accumulate significantly in the blood among patients with renal dysfunction.³³ Ezetimibe has no significant effect on the activity of either the cytochrome P450 system or the N-acetyltransferase system,³⁴ indicating that ezetimibe has minimal potential for drug interactions via these mechanisms. (The co-administration of ezetimibe with ciclosporin is the subject of an ongoing pharmacokinetic study, as it is currently unknown whether there are clinically important increases in their blood levels when these drugs are given together.) Ezetimibe does not affect absorption of bile acids,³⁵ triglycerides, fatty acids, or fat soluble vitamins,³⁶ and has not been associated with any excess of clinical adverse effects.^{37,38} As has been observed for other lipid-lowering agents,³⁹ ezetimibe can be associated with minor, reversible increases in liver transaminases, but there is no evidence that ezetimibe causes clinical hepatotoxicity.^{31,32}

1.3.3 The second HARP pilot study of simvastatin and ezetimibe (UK-HARP-II)

In previous studies among patients without renal impairment, the combination of simvastatin and ezetimibe was well tolerated,^{31,32} but the effects of adding ezetimibe to simvastatin among patients with CKD were unknown. The second HARP pilot study (UK-HARP-II) was therefore designed to compare the combination of simvastatin 20 mg plus ezetimibe (10 mg daily) versus simvastatin (20 mg daily) among patients with CKD. The principal aims were to assess the effects of co-administration of ezetimibe in such patients on: tolerability (e.g. unexplained muscle symptoms); markers of safety (differences in alanine transaminase, creatine kinase, creatinine, calcium, phosphate, and lipid-soluble vitamins); and biochemical efficacy (differences in lipid profile). The UK-HARP-II study was completed in February 2003, and preliminary results are now available. Among 203 CKD patients (152 pre-dialysis with creatinine $\geq 150\mu\text{mol/l}$, 18 peritoneal dialysis, 33 haemodialysis; mean baseline LDL-cholesterol 3.07 mmol/l) compliance was 90% at 6 months, and similar in both groups. As compared to simvastatin alone, the co-administration of ezetimibe and simvastatin reduced LDL-cholesterol by 14%, (equivalent to a reduction of 0.43 mmol/l) at 6 months, and total cholesterol and triglycerides were also significantly reduced. Co-administration of ezetimibe with simvastatin was not associated with an excess of abnormal liver function tests or of elevated creatine kinase. There were no serious adverse events due to study treatment.

2 PLAN OF INVESTIGATION

2.1 STUDY AIMS

The primary aim of SHARP is to assess the effects of lowering LDL-cholesterol with combined simvastatin 20 mg and ezetimibe 10 mg daily (denoted “ezetimibe/simvastatin”) versus placebo on the time to a first “major vascular event” (defined as non-fatal myocardial infarction or cardiac death, non-fatal or fatal stroke, or revascularisation). The study will include about 9000 patients with CKD, of whom around 6000 are intended to be pre-dialysis and 3000 on dialysis at randomization.

Secondary aims of the study include an assessment of the effects of ezetimibe/simvastatin on: progression to end-stage renal disease (among pre-dialysis patients); various causes of death; major cardiac events (defined as non-fatal MI or cardiac death); stroke; and hospitalisation for angina. The effects on major vascular events will also be examined among particular subgroups of patients. Tertiary objectives include assessment of the effects of ezetimibe/simvastatin on: hospital admission for heart failure; site-specific cancers; revision of vascular access for dialysis; and various other reasons for hospital admission.

SHARP also aims to extend the information provided by the second HARP pilot (see Section 1.3.3) on the safety of adding ezetimibe to simvastatin among patients with CKD. This will be achieved by comparing ezetimibe/simvastatin with simvastatin alone after one year of treatment (see Section 2.2.2).

2.2 TREATMENT COMPARISONS

2.2.1 Run-in period prior to randomization

Prior to randomization, potentially eligible patients (see Section 3.1) will enter a Run-in period during which they will receive placebo tablets for around 6 weeks. The Run-in period prior to randomization is to help ensure that only those likely to continue taking study treatment for an extended period are randomized. During Run-in, details of each patient’s lipid profile will be provided to their own doctor(s), so that they may decide whether it is appropriate for their patient to be randomized (see Section 3.3). Patients will be randomized only if, at the end of the Run-in period, they seem likely to comply with the study protocol for several years. By this process, many potential drop-outs should be excluded before becoming part of the randomized comparison, with a consequent improvement in statistical sensitivity of the “intention-to-treat” analyses.⁴⁰

2.2.2 Main and subsidiary randomizations

Study medication takes the form of two tablets (with a “double-dummy” technique used to preserve blinding):

- Combination tablet containing ezetimibe 10 mg and simvastatin 20 mg (“ezetimibe/simvastatin”) or matching placebo combination
- Simvastatin 20 mg tablet or matching placebo

During the Run-in period, all patients will take one placebo-combination tablet and one placebo-simvastatin tablet daily. During the first year after randomization, all patients will take two tablets (Figure 4): placebo-combination and placebo-simvastatin (Arm 1); ezetimibe/simvastatin and placebo-simvastatin (Arm 2); or placebo-combination and simvastatin (Arm 3). At the end of the first year, patients in Arm 3 will be randomized to placebo-combination (Arm 3a) or ezetimibe/simvastatin (Arm 3b), and patients in Arms 1 and 2 will discontinue placebo-simvastatin. Thus, from the start of the second year all patients will be taking one tablet daily: placebo-combination (in Arms 1 and 3a) or ezetimibe/simvastatin (in Arms 2 and 3b).

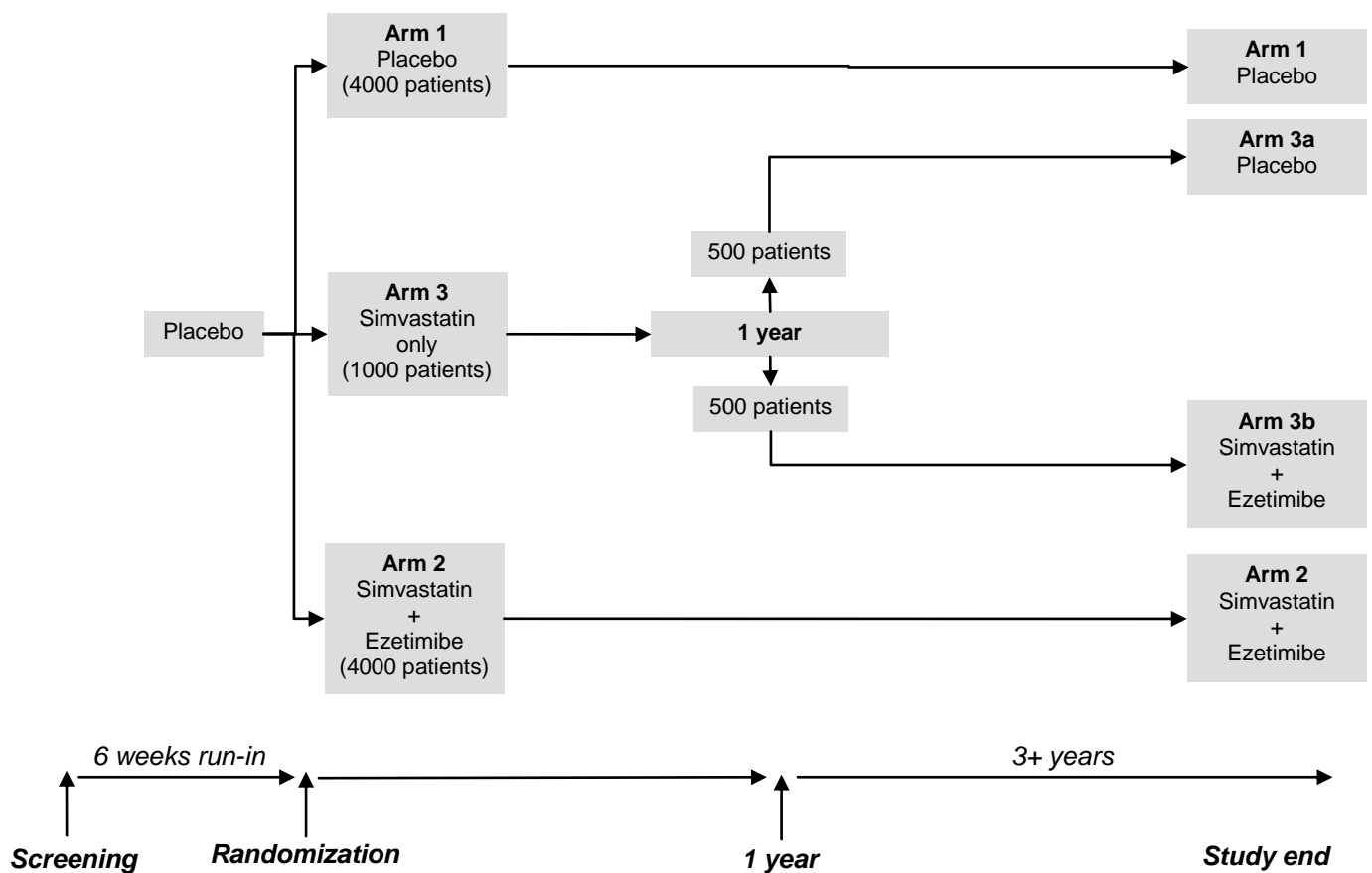


Figure 4: SHARP randomization scheme and timeline

2.3 ASSESSMENT OF OUTCOMES

Two separate Data Analysis Plans will be agreed by the Steering Committee. The first of these will describe detailed methods for the safety (and biochemical efficacy) analyses that are to be carried out on patients in each of the 3 arms who have completed one year of follow-up (see Section 2.3.1 below), and will be approved by the Steering Committee before safety data are unblinded. The second Data Analysis Plan will describe the detailed methods for the main and subsidiary efficacy analyses to be conducted at the end of the trial, and will be approved by the Steering Committee before these data are unblinded.

2.3.1 Safety and biochemical efficacy assessments at 1 year

The one-year safety of adding ezetimibe 10 mg daily to simvastatin 20 mg daily will be assessed among the 4000 patients allocated to ezetimibe/simvastatin (Arm 2) versus the 1000 patients allocated simvastatin alone (Arm 3). Subsidiary comparisons of safety will also be made between ezetimibe/simvastatin (Arm 2) versus placebo (Arm 1), and between simvastatin alone (Arm 3) versus placebo (Arm 1). Safety outcomes include:

- muscle pain or weakness
- elevation of creatine kinase (CK: 5-10 x upper limit of normal [ULN]*; >10 x ULN)
- myopathy (muscle symptoms with CK >10 x ULN and ≤40 x ULN)
- rhabdomyolysis (CK >40 x ULN)
- complications of gall-stones (including cholecystectomy)
- persistent elevation of liver transaminase (alanine transaminase [ALT] >3 x ULN, or, if ALT not available at the Local Clinical Centre, aspartate transaminase [AST] >3 x ULN)

Biochemical efficacy at 1 year will also be assessed (see Section 2.3.5).

2.3.2 Primary assessment at the end of the study

The primary comparison will involve an “intention-to-treat” analysis using the “logrank” test^{40,41} of **major vascular events** during the scheduled treatment period of at least 4 years among ~ 4000 patients allocated active ezetimibe/simvastatin (Arm 2) versus ~4000 allocated placebo (Arm 1). A major vascular event is defined (Appendix 2) as the composite of:

- non-fatal myocardial infarction or cardiac death;
- non-fatal or fatal stroke; or
- revascularisation, including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis).

(Note: Patients allocated to Arm 3 will not be included in the primary comparison, but see Section 2.3.3.)

* The upper limit of normal is the upper limit of the reference range as defined by the laboratory in which the particular blood test was analysed.

2.3.3 Secondary assessments at the end of the study

Unless otherwise indicated, all secondary assessments will be conducted using the “logrank” test among the entire study population (i.e. ~4500 patients allocated active ezetimibe/simvastatin [Arms 2 and 3b] versus ~4500 allocated placebo [Arms 1 and 3a]) during the scheduled treatment period, and will be of the effects of allocation to ezetimibe/simvastatin versus placebo on:

- (i) various vascular events and renal disease progression:
 - major vascular events
 - major cardiac events (non-fatal MI or cardiac death)
 - stroke (fatal or non-fatal);
 - coronary or non-coronary revascularisation;
 - mortality, both overall and within particular categories of causes of death: coronary heart disease; other cardiac; stroke; other vascular; neoplastic; renal; other causes;
 - hospital admission for angina (symptoms suggestive of cardiac chest pain and no other cause identified);
 - end-stage renal disease (need for long-term dialysis or transplantation) [among pre-dialysis patients in Arms 1 and 2 only]; and
 - end-stage renal disease or death from any cause [among pre-dialysis patients in Arms 1 and 2 only];
- (ii) major vascular events in the following different circumstances:
 - (a) patients with or without evidence of a disease that is associated with an increased risk of coronary heart disease, including:
 - peripheral arterial disease;
 - cerebrovascular disease;
 - diabetes mellitus, or
 - at least one of these 3 associated diseases;
 - (b) various other categories of patient determined at randomization:
 - men and women;
 - age 40-59; 50-59; 60-69; ≥70;
 - pre-dialysis and dialysis;
 - smokers and non-smokers;
 - blood creatinine ≤200; 201-400; >400 μmol/l [pre-dialysis patients only];
 - tertiles of blood cystatin C [pre-dialysis patients only];
 - tertiles of Cockcroft-Gault-estimated creatinine clearance⁴² [pre-dialysis patients only];
 - tertiles of Modification of Diet in Renal Disease [MDRD]-estimated glomerular filtration rate⁴³ [pre-dialysis patients only];
 - haemodialysis and peritoneal dialysis [dialysis patients only];
 - diastolic blood pressure <80; 80-89; 90-99; ≥100 mm Hg;
 - systolic blood pressure <140; 140-159; 160-179; ≥180 mm Hg;
 - tertiles of total cholesterol;
 - tertiles of LDL-cholesterol;
 - tertiles of HDL-cholesterol;
 - tertiles of non-HDL cholesterol;

- tertiles of triglycerides;
 - tertiles of apolipoprotein B;
 - tertiles of apolipoprotein A₁;
 - tertiles of body mass index;
 - tertiles of waist circumference;
 - tertiles of haemoglobin;
 - tertiles of blood creatinine (surrogate for nutritional status) [among dialysis patients only];
 - tertiles of plasma albumin;
 - tertiles of calcium-phosphate product (calcium x phosphate);
 - tertiles of proteinuria (as measured by albumin:creatinine ratios);
- (c) the presence or absence of particular non-study treatments at randomization
- aspirin;
 - angiotensin-converting-enzyme [ACE] inhibitors;
 - angiotensin-receptor blockers [ARBs];
 - diuretics;
 - calcium-channel blockers [CCBs];
 - beta-blockers;
 - erythropoietin
 - sevelamer

2.3.4 Tertiary assessments at the end of the study

Additional exploratory analyses will be performed among 9000 patients randomized to ezetimibe/simvastatin versus placebo of the effects on: hospital admission for heart failure; site-specific cancers; development of diabetes among patients without diabetes at baseline; revision of vascular access for dialysis; coronary revascularisation; non-coronary revascularisation procedures (excluding vascular access revisions); and haemorrhagic strokes. The possible adverse effects of combination treatment during the whole of the scheduled treatment period will also be examined, and will supplement the information available from the separate pre-specified assessment of safety outcomes at one year (see Section 2.3.1).

2.3.5 Assessment of biochemical efficacy for the whole study period

Biochemical efficacy will be assessed in 10% random subsamples of patients at 1 year and 4 years, and in all patients at 2.5 years (the anticipated midpoint of the study). The main analyses will be of the effects of ezetimibe/simvastatin versus placebo on:

- total cholesterol
- LDL-cholesterol
- HDL-cholesterol
- non-HDL-cholesterol
- triglycerides
- apolipoprotein-B
- apolipoprotein-A₁
- proteinuria (albumin:creatinine ratio)
- creatinine

- cystatin C

2.4 SAMPLE SIZE AND PREDICTED NUMBER OF EVENTS

2.4.1 Statistical power

After allowance for a “healthy volunteer effect” and the exclusion of patients with a prior history of CHD, extrapolation from observational studies^{6,7} in populations of pre-dialysis patients attending nephrology clinics implies a primary outcome rate (i.e. of “major vascular events”) of around 3% per annum. Among dialysis patients, extrapolation from event rates in registry-based observational studies (again after allowance for patient selection) suggests an event rate of around 5% per annum. Hence, assuming that about two-thirds (~6000) of randomized patients are pre-dialysis and about one-third (~3000) are on dialysis, the average annual event rate would be expected to be about 3.7%. After allowance for some loss of compliance, allocation to ezetimibe/simvastatin versus placebo might be expected to produce an average reduction in LDL-cholesterol over the whole study of at least 1 mmol/l. If it is further assumed that 20% of non-CHD cardiac events among SHARP patients are not influenced by cholesterol-lowering, then allocation to ezetimibe/simvastatin might be expected to produce a 20% reduction in major vascular events during the study. SHARP is, therefore, scheduled to continue until all patients have been followed for at least 4 years and at least 1100 major vascular events have occurred in order to have approximately 90% power to detect a 20% proportional reduction in major vascular events at $P < 0.01$ (2-sided). Based on review of the blinded rate for major vascular events during follow-up, and the unblinded differences in blood lipids observed between the treatment groups, the Steering Committee may modify recruitment or the follow-up duration. Moreover, the Steering Committee can decide to stop the study early in the light of recommendations made by the independent Data Monitoring Committee (see Section 2.5).

SHARP will also have excellent power to assess whether lowering LDL-cholesterol delays progression to end-stage renal disease (need for long-term dialysis or transplantation) among patients with CKD prior to the need for dialysis. Based on the UK-HARP-I pilot study²⁴ and the RENAAL study,⁴⁴ the cumulative incidence of end-stage renal disease in the placebo arm of SHARP is expected to be around 20% by the end of scheduled follow-up. SHARP would, therefore, have over 95% power to detect a 20% proportional reduction in the risk of end-stage renal disease at $2P < 0.01$.

2.5 DATA AND SAFETY MONITORING

2.5.1 Interim analyses: role of the Data Monitoring Committee

During the period of the study, interim analyses of serious adverse events, particularly those believed to be due to study treatment, will be supplied regularly (every 3 months during the first year of the study and 6-monthly thereafter) in strict confidence to the Chairman of the independent Data Monitoring Committee. In the light of these analyses

and the results of any other relevant trials, the Data Monitoring Committee will advise the Steering Committee if, in their view, the randomized comparisons in SHARP have provided **both** (i) “proof beyond reasonable doubt”^{*} that for all, or some specific types, of patient, prolonged use of ezetimibe/simvastatin is clearly indicated or clearly contraindicated in terms of a net difference in time to death; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the main results of any other trials. The Steering Committee can then decide whether to modify the study, or to seek additional data. Unless this happens, the Steering Committee, the collaborators, the study participants, representatives of Merck and Schering-Plough, and all study staff (except those who provide the confidential analyses to the Data Monitoring Committee) will remain blind to the study results.

2.5.2 Monitoring of adverse events

(i) Serious adverse events (SAEs)

Information about the occurrence of study outcomes and all other serious adverse events (SAEs) will be sought at all scheduled visits. Serious adverse events are defined as those adverse events that:

- result in death;
- are life-threatening;
- require in-patient hospitalisation or prolongation of existing hospitalisation;
- result in persistent or significant disability or incapacity;
- result in congenital anomaly or birth defect;
- are important medical events in the opinion of the responsible investigator (i.e. any event that is not immediately life-threatening and does not result in death or hospitalisation but which may jeopardise the participant or may require intervention to prevent one or the other outcomes listed above). Examples of particular relevance to this study include:
 - cancers
 - myopathy (CK >10 x ULN and ≤40 x ULN associated with unexplained muscle pain or weakness)
 - rhabdomyolysis (creatinine kinase [CK] >40 x ULN)
 - cholecystectomy or complications of gallstones
 - hepatitis

(ii) Serious adverse events (SAEs) thought likely to be due to study treatment

Any adverse event that is both serious and, in the opinion of the reporting party^{**}, believed with a reasonable probability to be due to one of the study treatments (i.e. a Serious Adverse Reaction; SAR), is to be reported immediately to a Regional Coordinating Centre [RCC]/International Coordinating Centre [ICC] Clinician. The RCC/ICC Clinician will then record standard information including patient study number, the identity of the person

^{*} Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but in general a difference of at least 3 standard deviations in an interim analysis of total mortality would be needed to justify halting, or modifying, the study prematurely. This criterion has the practical advantage that the exact number of interim analyses is of little importance.⁴¹

^{**} eg the Local Clinical Centre [LCC] Research Nurse or LCC Lead Investigator

reporting the event, a description of the event and their reasons for possible attribution of the event to study treatment. All such reports will be reviewed urgently by the Clinical Coordinator (or his deputy) who will seek any necessary additional information, and review the adverse event's seriousness and relatedness, preferably in discussion with the reporting party*. The Clinical Coordinator (or his deputy) will assess the potential expectedness of each SAR using the Merck Schering-Plough (MSP) Core Data Sheet for ezetimibe/simvastatin and the Merck Core Data Sheet for simvastatin. For confirmed SAR reports, the Clinical Coordinator will then unblind the treatment allocation. All valid reports of Serious Adverse Reactions will be reported to the appropriate concerned parties as outlined in section 3.6.1.

Serious adverse events that are not thought to be due to study treatment will be recorded at each follow-up visit as in Section 2.5.2(i), and will be provided to Merck (on behalf of MSP), blind to treatment allocation, as a monthly line-listing for regulatory purposes.

(iii) Non-serious adverse events

At each Follow-up or Early Recall visit, patients will be asked specifically whether they have developed unexplained muscle pain or muscle weakness. Other adverse events that are not considered serious (according to the definition above) will not be recorded.

2.6 CENTRAL AND REGIONAL COORDINATION OF LOCAL CLINICAL CENTRES (HOSPITAL CLINICS)

2.6.1 Overview of study organisation

SHARP will be coordinated by the International Coordinating Centre (ICC) based at the Clinical Trial Service Unit of Oxford University, working with about 6 Regional Coordinating Centres (RCCs). Each RCC will be responsible for the administrative support of Local Clinical Centres (LCCs) within their own region. In countries where there is no RCC, a National Coordinator (who will be a member of the Steering Committee) will be responsible for liaison with the relevant Regulatory Authority and for helping the RCC to manage the trial in their country. At each LCC, a Lead Investigator (a senior nephrologist or physician) and a LCC Research Nurse (or, in some circumstances, medically qualified research fellow) will be responsible for the identification, recruitment, and follow-up of study patients (see Appendix 3).

2.6.2 Training and monitoring

SHARP will be conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Research Practice (ICH-GCP) and with relevant local, national and international regulations. Prior to initiation of the study at any LCC, the LCC Research Nurse will be trained in the methods of the study and the LCC will be visited by a representative of the RCC and/or ICC to ensure that the site has adequate facilities and resources to carry out the study. In addition, LCC Lead Investigators and LCC

* a report's seriousness and/or relatedness cannot be down-graded without agreement from the relevant reporting parties.

Research Nurses will be provided with materials detailing relevant study procedures for LCCs (“Manual for Local Clinical Centre Procedures”).

During the study, representatives of the relevant RCC and/or the ICC will arrange visits to all study centres on at least 2 occasions in the first year and about once each year thereafter. The purpose of these visits will be to help LCC staff to resolve any local problems with the study, to ensure that the study is conducted according to the protocol, and to review study records, data quality and the completeness of follow-up. A report of each visit will be prepared by the monitor and reviewed by the relevant RCC staff.

2.6.3 Supply of study materials

Study treatments will be manufactured, packaged, labelled and delivered to each LCC by Merck Schering-Plough Pharmaceuticals. An inventory of study drug supplies will be maintained on the SHARP web-based IT system (see Section 2.6.4) and will be monitored at the ICC. The LCC Lead Investigator will be responsible for making appropriate arrangements for the storage and dispensing of study treatments, and for the appropriate documented disposal of unused study drug.

2.6.4 Data management

The SHARP Information Technology (IT) system will include two linked parts: the **LaptopSystem** and the **WebBasedSystem**. The LaptopSystem will comprise a custom-written database application running on centrally-supplied laptop computers of a uniform specification (but appropriately modified for local requirements), with the data being synchronised at regular intervals with the WebBasedSystem located at the ICC. The LaptopSystem will be used by the LCC Research Nurses for particular tasks (e.g. entering new patient details; generating invitation letters and scheduling appointments; entering data for screening, randomization, and follow-up visits; accessing laboratory and other data). The WebBasedSystem will be accessible to RCC and ICC staff using a standard web browser, and will allow messaging (electronic communication between study staff), tracking of serious adverse events, and requesting and tracking of blood samples. All data transfers will be anonymised and cryptographically secured, and all data will be stored securely. All access will require a username/password combination (i.e. “electronic signature”) and will be audited, with study staff only having access to data appropriate to their role in the study.

2.6.5 Laboratory measurement of samples and sample storage

LCC laboratories will be responsible for carrying out CK, liver transaminase and blood creatinine assays during the study (which should provide rapid safety monitoring) and for the lipid profile at screening. All other blood assays, including lipids at randomization, will be conducted at the ICC laboratory. Dedicated sample collection kits supplied to the LCCs will contain all the necessary materials for the collection and processing of blood and urine samples for central analysis.

Blood will be collected into vacuum tubes and centrifuged at the LCC, with plasma then pipetted into the bar-coded cryovials provided, and the remaining cells kept for subsequent extraction of DNA (consenting individuals only). Urine will be collected for measurement of albuminuria (pre-dialysis patients only) into a universal container and then pipetted into a

bar-coded cryovial. Plasma, urine and cells will be stored below -40°C (and preferably below -70°C) at the LCC for up to about 6 months prior to transfer in batches for storage below -70°C at the RCC. At appropriate intervals, the RCC will arrange transfer of samples to the central laboratory.

The central laboratory (at the ICC) will conduct analyses of plasma and urine as specified in Section 2.3.5 of the Protocol. Samples (plasma, DNA or urine) for which permission to store in liquid nitrogen has been declined will then be discarded. All other samples will be stored indefinitely in liquid nitrogen tanks at a secure location, with samples identified only by a barcode.

2.6.6 Source documents and archiving

The clinic visit records (including blood and urine assay results) held on the SHARP LaptopSystem and WebBasedSystem, the additional information obtained on reported outcome measures and other relevant events, death certificates, blood and urine assay results and drug supply records constitute the “source documents” for the study. These will be retained for at least 15 years from the completion of the study. Merck Schering-Plough and regulatory agencies will have the right, in accordance with ICH-GCP, to commission a confidential audit of such records kept in the ICC, RCCs, and LCCs, as long as this does not result in unblinding of the interim results while the study is in progress.

2.6.7 Funding

This study has been initiated and designed by the SHARP Steering Committee, and the data will be collected, analysed and published independently of the source of funding. Merck Schering-Plough will provide an unrestricted grant to the University of Oxford, and the University of Oxford will act as the Sponsor of this study. This grant will support the central and regional administration of the study, meetings and travel, the transport and analysis of blood samples and study materials, the necessary LCC Research Nurse time, and all associated local costs.

2.6.8 Indemnity

Merck Schering-Plough will at all times indemnify the study investigators and their staff from claims that may be made against them for any injury sustained by a study participant as a consequence of effects of the drugs used in accordance with this protocol. The indemnity will be outlined in detail in the agreements between the ICC and the RCCs, and between the RCCs and the relevant LCCs, and/or in a separate letter provided to the LCC by Merck Schering-Plough.

2.6.9 Publications, reports and substudies

Draft copies of any manuscripts will be provided to all collaborators for review prior to their submission for publication. Papers will be written in the name of the SHARP Collaboration, with each individual investigator named personally at the end of the report (or to comply with medical journal requirements, in web-based material posted with the report). Draft copies of any publications will also be provided to Merck Schering-Plough for comments prior to submission of the manuscripts for publication, but responsibility for all study publications will rest entirely with the SHARP Steering Committee.

Proposals for substudies on patients randomized into SHARP will be welcomed, but must be approved by the Steering Committee before they begin. In considering such proposals, the Steering Committee will need to be satisfied that the proposed substudy is of a high quality, and that it will not compromise the main study in any way (for example by reducing the recruitment rate or compliance with study treatment).

3 SUMMARY OF PRACTICAL PROCEDURES (SEE STUDY MANUAL FOR DETAILS)

STUDY SUMMARY

POTENTIALLY ELIGIBLE



- Pre-dialysis (most recent serum or plasma creatinine $\geq 150 \mu\text{mol/l}$ [$\geq 1.7 \text{ mg/dl}$] for men, $\geq 130 \mu\text{mol/l}$ [$\geq 1.5 \text{ mg/dl}$] for women) **OR** on maintenance dialysis (peritoneal or haemodialysis)
- Age ≥ 40 years
- No prior myocardial infarction or coronary revascularisation, or contraindication to study treatments

IDENTIFICATION AND INVITATION



- Seek physicians' consent for access to medical records
- Potentially eligible patients identified from medical records
- Patient sent the Participant Information Sheet and invited to attend screening clinic appointment

SCREENING CLINIC VISIT (-6 WEEKS)



- Written informed consent sought from eligible and willing individuals
- Medical history, height, weight, waist circumference, blood pressure, and eligibility factors recorded (including concurrent medication)
- Non-fasting blood sample for local laboratory analysis of CK, liver transaminase (ALT or AST), creatinine and lipid profile
- Run-in treatment bottles (placebo) given to eligible and consenting patients
- Randomization appointment made for ~6 weeks later
- Patient given Supplementary Participant Information Sheet
- Responsible physician informed of patient's lipid profile and clinical details, and of entry into Run-in

RANDOMIZATION VISIT (0 MONTHS)



- Non-study treatment, serious adverse events during 'Run-in' and blood pressure recorded
- Final check of compliance and eligibility
- Supplementary consent sought for long-term storage of samples (blood, DNA, urine)
- Non-fasting blood samples for local laboratory analysis of CK, ALT/AST and creatinine
- Non-fasting blood sample for central laboratory analysis of lipid profile (and frozen storage if appropriate consent given)
- Urine sample (pre-dialysis patients only) for central laboratory analysis of albumin:creatinine ratio (and frozen storage if appropriate consent given)
- Randomization via a program on LCC Research Nurse's laptop computer
- Allocated Randomization treatment bottles given to patients:
 - Arm 1: Placebo, OR
 - Arm 2: Ezetimibe 10 mg + simvastatin 20 mg daily, OR
 - Arm 3: Simvastatin 20 mg daily (1 year only of treatment with simvastatin, then re-randomization of Arm 3 patients to placebo [Arm 3a] or ezetimibe + simvastatin [Arm 3b])
- Follow-up appointment scheduled for 2 months time
- Inform patient's nephrologist and primary care physician of randomization

FOLLOW-UP VISITS AT 2, 6 MONTHS, THEN 6-MONTHLY



- Non-study medication, compliance, serious adverse events and blood pressure recorded
- Non-fasting blood samples for local laboratory analysis of CK, ALT/AST and creatinine
- Non-fasting blood sample for central laboratory analysis of lipid profile on random subsample of ~10% patients at median follow-up of 1 and 4 years, and all patients at 2.5 years (and frozen storage if appropriate consent given)
- Urine sample taken from pre-dialysis patients at median follow-up of 2.5 years for central assay of albumin:creatinine ratio (and frozen storage if appropriate consent given)
- Follow-up treatment bottle(s) given to patients every 6 months and next Follow-up visit scheduled

MONITORING OF SAFETY AND EFFICACY



- Central monitoring of blood results and serious adverse events by International and RCCs, using web-based monitoring system (with Early Recall visits arranged to monitor any special problems)
- Further details on relevant outcomes from hospital records sought by LCC Research Nurse
- Relevant events confirmed and reviewed by central Outcomes Adjudication Panel

3.1 ELIGIBILITY FOR SHARP

Patients are eligible for randomization into SHARP if: (a) their nephrologist does not believe that there is a definite indication for, or contraindication to, an HMG-CoA reductase inhibitor (“statin”) or ezetimibe; and (b) all inclusion criteria are satisfied whilst no exclusion criterion applies.

3.1.1 Inclusion criteria

- History of CKD
 - pre-dialysis (plasma or serum creatinine $\geq 150 \mu\text{mol/l}$ [$\geq 1.7 \text{ mg/dl}$] in men, or $\geq 130 \mu\text{mol/l}$ [$\geq 1.5 \text{ mg/dl}$] in women, as measured at the most recent routine clinic visit and at the SHARP Screening Visit)
 - dialysis (haemodialysis or peritoneal dialysis)
- Men or women aged ≥ 40 years

3.1.2 Exclusion criteria

- Definite history of myocardial infarction or coronary revascularisation procedure
- Functioning renal transplant, or living donor-related transplant planned
- Less than 2 months since presentation as an acute uraemic emergency (but may be entered later, if appropriate);
- Definite history of chronic liver disease, or abnormal liver function (i.e. ALT $> 1.5 \times$ ULN or, if ALT not available at the LCC, AST $> 1.5 \times$ ULN). (Note: Patients with a history of hepatitis are eligible provided these limits are not exceeded);
- Evidence of active inflammatory muscle disease (e.g. dermatomyositis, polymyositis), or CK $> 3 \times$ ULN;
- Definite previous adverse reaction to a statin or to ezetimibe
- Concurrent treatment with a contraindicated drug (Note: Patients who are temporarily taking such drugs may be re-screened when they discontinue them, if appropriate.)
 - HMG-CoA reductase inhibitor (“statin”)
 - fibric acid derivative (“fibrate”)
 - nicotinic acid
 - macrolide antibiotic (erythromycin, clarithromycin)
 - systemic use of imidazole or triazole antifungals (e.g. itraconazole, ketoconazole)
 - protease-inhibitors (e.g. antiretroviral drugs for HIV infection)
 - nefazodone
 - ciclosporin
 - ezetimibe
- Child-bearing potential (i.e. premenopausal woman who is not using a reliable method of contraception.)
- Known to be poorly compliant with clinic visits or prescribed medication
- Medical history that might limit the individual’s ability to take trial treatments for the duration of the study (e.g. severe respiratory disease, history of cancer other than non-melanoma skin cancer, or recent history of alcohol or substance misuse)

Since the association between blood LDL-cholesterol and risk of cardiovascular disease in CKD is not clearly positive (and may even be negative),^{18,19} the absolute risk of a vascular event among CKD patients is not reliably predicted by higher blood cholesterol concentration. Hence, SHARP does not pre-specify any blood lipid thresholds in order to determine eligibility. Instead, the decision about whether a particular patient is potentially eligible for SHARP is to be made by the patient's doctor(s). Prior to taking this decision, the patient's doctors will be able to give due consideration to the blood lipid profile from the Screening visit, so that no patient whose doctor wishes to start statin treatment should be entered into SHARP. All participating doctors will be provided with updated information about any relevant trial results that emerge. The Steering Committee will also review such information, and can consider the need for lipid thresholds should any relevant information become available during the course of SHARP.

3.2 SCREENING VISIT (-6 WEEKS)

3.2.1 Assessment of relevant medical history and eligibility

Potentially eligible participants will be sent an invitation letter to attend a Screening Visit, together with a Participant Information Sheet. At the Screening Visit, any relevant past medical history and factors relevant to eligibility will be recorded directly onto the Screening Form on the SHARP LaptopSystem. The LCC Research Nurse will check inclusion and exclusion criteria. Any potential problems identified at Screening that might require further investigation or treatment may be brought to the attention of the patient's own doctor(s) by the study staff.

3.2.2 Invitation to participate in the randomized study and patient consent

Those patients who appear to be eligible will have the study explained to them by the study staff, using the Participant Information Sheet as a basis for discussion. Patients will have an opportunity to initiate discussion, and have time to think about their participation in the study, perhaps after discussing it first with their family, primary care physician, or a particular local nephrologist. (Eligible patients who choose to do this will be asked to attend a "Consent-Pending Visit" within about a month.) Patients will be discouraged from participating if it is thought unlikely that they would be willing and able to continue attending Follow-up visits for at least 4 years.

3.2.3 Blood sampling and dispensing of pre-randomization Run-in treatment

Eligible patients who agree to participate will be asked to provide their written informed consent to enter the study. Although this consent procedure will cover the initial analyses of blood and urine both at the local hospital laboratory and at the central laboratory at the ICC, it does not provide for long-term storage of blood or urine samples for future medical research (see below). The LCC Research Nurse will record height, weight, waist circumference, and blood pressure. A non-fasting blood sample will be taken at the Screening Visit (or, for those who defer their decision, at the subsequent Consent-Pending Visit) from all patients who agree to participate in the trial for measurement of CK, liver transaminase, creatinine and lipid profile in the local laboratory. The LCC Research Nurse will then dispense or arrange for the dispensing of "Run-in" treatment bottles containing 8 weeks' supply of placebo study tablets (one tablet to be taken from each bottle in the evening) and arrange an appointment for around 6 weeks later. Such pre-randomization periods can help to identify (and exclude before randomization) those patients who would be unlikely to comply with long-term study treatment and follow-up.

The Run-in period also allows relevant blood results and clinical information on the screened patient to be reviewed before deciding on randomization. Patients are only eligible for randomization if serum or plasma creatinine at the Screening Visit is $\geq 150 \mu\text{mol/l}$ (or $\geq 1.7 \text{ mg/dl}$) in men or $\geq 130 \mu\text{mol/l}$ ($\geq 1.5 \text{ mg/dl}$) in women. Blood results and clinical information will also be sent to the doctor(s) managing that patient, thus allowing time for these doctors to decide whether the blood results or some other clinical feature make the patient unsuitable for entry into the randomized phase of the study.

Patients entering Run-in will be provided with a Supplementary Participant Information Sheet explaining the rationale for long-term storage of patient blood, urine and DNA samples (at the University of Oxford) for use in future medical research. Patients will be asked to read this before the next (Randomization) visit.

3.3 RANDOMIZATION VISIT (0 MONTHS)

3.3.1 Final check of eligibility and compliance before randomization

Patients who attend their Randomization Clinic appointment will be asked if they have experienced myocardial infarction, arterial revascularisation (coronary or non-coronary, but excluding vascular access revision procedures), stroke or any other significant problems during the Run-in period. Details will be recorded directly onto the Randomization Form on the SHARP LaptopSystem, and compliance with Run-in treatment checked (at least 90% of scheduled study treatment should have been taken). Details of non-study treatment will be recorded, and blood pressure will be recorded. Compliant patients who have not experienced a vascular event or other significant problem during Run-in, and are not on a contraindicated drug, will be asked if they are still willing to take study treatment for at least 4 years. If they are, non-fasting blood samples, and a urine sample for pre-dialysis patients, will be collected and processed (see Section 2.6.5). Patients will be asked if they are willing to give consent for long-term storage of plasma, DNA or urine, and asked to indicate on a Supplementary Participant Consent Form which, if any, of these samples may be stored.

3.3.2 Random allocation of study treatment

Eligible and consenting individuals will then be randomized to study treatments by the LCC Research Nurse using a randomization program on the SHARP LaptopSystem. The randomization procedure will use minimized randomization in order to ensure that treatment groups are balanced with respect to prognostically important variables.⁴⁵ Patients will be allocated numbered Treatment bottles containing a 6 month supply of medication. The tablets in the two bottles allocated will correspond to one of the following treatment regimens (see Section 2.2.2):

- Arm 1: Placebo (i.e. placebo-combination and placebo-simvastatin tablets);
- Arm 2: Ezetimibe 10 mg + simvastatin 20 mg daily (i.e. ezetimibe/simvastatin and placebo-simvastatin tablets); or
- Arm 3: Simvastatin 20 mg daily (i.e. placebo-combination and simvastatin tablets)

The numbered treatment bottles will then be dispensed to the patient, either by the LCC Research Nurse, or by the local pharmacy, and patients will be asked to take one tablet

from each bottle in the evening. An appointment for the first post-randomization clinic visit will then be allocated by the study staff, with guidance from the LaptopSystem. The patient's doctor(s) will then be notified that the patient has been randomized into SHARP.

3.4 POST-RANDOMIZATION FOLLOW-UP (2 MONTHS, 6 MONTHS AND THEN 6-MONTHLY)

3.4.1 Recording adverse events and compliance

Following randomization patients are scheduled to attend follow-up visits at 2 months, 6 months, and 6-monthly thereafter, with each patient followed for at least 4 years. At each appointment, details of all hospital admissions, other serious adverse events, and unexplained muscle pain or weakness (see Section 2.5.2) will be recorded directly onto a Follow-up form on the SHARP LaptopSystem. Non-study treatment and blood pressure will be recorded, and compliance with treatment checked. For patients who discontinue study treatment, the reasons for doing so will be recorded.

3.4.2 Blood and urine sampling, and dispensing of study treatment

At each Follow-up visit, a non-fasting blood sample will be taken for local laboratory assay of CK, liver transaminase, and creatinine. Prompted by the LaptopSystem, the LCC Research Nurse will arrange for additional non-fasting blood samples to be collected in a random 10% sample of patients at 1 and 4 years of median follow-up, and on all patients when median follow-up is 2.5 years, with subsequent transfer to the central laboratory for analysis (see Section 2.6.5). Urine will be collected (from patients not receiving dialysis) at a median follow-up of 2.5 years for central laboratory analysis. At each 6-monthly visit each patient will return any unused treatment and, if continued treatment is appropriate, will be given a further 6-month supply of their allocated study treatment. An appointment will then be made for the patient's next scheduled study visit.

3.4.3 Follow-up for randomized patients not attending study clinics

All study patients, irrespective of whether they continue to take study treatment, will be encouraged to attend routine Follow-up clinic visits. If, however, a patient becomes unwilling or unable to attend, then the LCC Research Nurse will telephone the patient at the time of each of their scheduled Follow-up clinics and complete the necessary Follow-up form on the LaptopSystem. If this is not possible, then RCC or LCC staff will attempt to check a patient's progress by direct correspondence with the patient's own doctors. Patients who stop attending study visits will be asked to discontinue study treatment, as study monitoring of safety bloods will no longer be possible.

3.5 EARLY RECALL VISITS AND MODIFYING STUDY TREATMENT

3.5.1 Monitoring significant biochemical abnormalities or other problems

An Early Recall Visit may be arranged for any participant who requires review outside of their planned visit schedule. Examples of circumstances where this may be necessary include the assessment of abnormal values in safety bloods from routine Follow-up visits, and review of symptoms believed by the participant to be related to study treatment. As at routine study visits, the results of blood tests performed at Early Recall Visits will be

entered into the LaptopSystem by staff at the LCCs and these will be monitored by the clinical staff at the ICC and RCCs (see Section 3.8).

3.5.2 Modifying study treatment

Study treatment may be permanently or temporarily discontinued for a particular patient if a significant elevation of liver transaminase or creatine kinase develops (see Section 3.8). In addition to this, the following events are considered sufficient reason to discontinue study treatment permanently:

- serious adverse event (SAE) thought likely to be due to study treatment (see Section 3.6.1)
- conditions or procedures requiring the use of agents that may be contraindicated in patients receiving simvastatin or ezetimibe (e.g. fibrate or high-dose nicotinic acid). Note: Pending the final results of a pharmacokinetic study, ezetimibe is considered to be contraindicated among patients treated with ciclosporin. Consequently, patients who commence treatment with ciclosporin after randomization will be required to discontinue study treatment.
- clear indication for a statin or ezetimibe in the view of the patient's own doctors. (Note: Patients commencing other cholesterol-lowering drugs [e.g. resins] or diets may remain on study treatment, unless such agents are believed to be clearly contraindicated by their own doctors.)
- pregnancy or any other situation where continuing study treatment is not considered to be in the patient's best interests by their own doctors or the SHARP clinical team; or
- at the patient's request, or at the request of their own doctors.

3.5.3 Additional monitoring for patients receiving oral anticoagulants

Anticoagulant control may be disturbed when patients start or stop study treatment (which may contain simvastatin). At the Randomization Visit and each subsequent Visit, patients will be asked about non-study medication. If a patient states that they are taking an oral anticoagulant the LaptopSystem will automatically prompt the nurse to check whether the patient might need to arrange additional monitoring of anticoagulant control (INR), and if so to inform the patient.

3.6 REPORTING OF SERIOUS ADVERSE EVENTS

3.6.1 Immediate reporting of any serious adverse events believed to be due to study treatment

All SAEs considered likely to be due to study treatment (ie Serious Adverse Reactions: SARs) are to be reported immediately to a RCC/ICC Clinician, and will be assessed promptly by the Clinical Coordinator (or his deputy), as described in section 2.5.2 (ii). The Clinical Coordinator will provide an unblinded report of all SARs (both expected and unexpected, and regardless of treatment allocation), to the Chairman of the Data Monitoring Committee. For those SARs that are both unexpected and on active treatment, the ICC will provide an unblinded report to all relevant Institutional Review Boards and Independent Ethics Committees, Investigators and, via Merck Schering-Plough Pharmaceuticals (MSP), to all relevant drug regulatory authorities to comply with expedited reporting requirements for Suspected Unexpected Serious Adverse Reactions

(SUSARs)*. Events associated with placebo will not usually satisfy the criteria for a Serious Adverse drug Reaction and therefore for expedited reporting.

3.6.2 Reporting of other serious adverse events

All reports of SAEs will be entered onto the SHARP IT system (either via the Laptop System or WebBasedSystem) and those that are potential study endpoints will be reviewed, verified and coded (see Section 3.7). SAEs that are not considered due to study treatment will be processed in a manner that allows the ICC to provide information on such events to MSP on a monthly basis for regulatory purposes.

3.6.3 Unblinding

There are 2 main situations in which unblinding of the treatment allocation for an individual participant may be warranted:

- When dealing with SARs as outlined in sections 2.5.2 (ii) and 3.6.1 above
- In a situation where knowledge of the treatment allocation for a patient could influence their immediate management (eg after overdose)

An unblinding facility is accessible via a 24-hour telephone on-call service at the Clinical Trial Service Unit (CTSU). Appropriate requests for unblinding will be reviewed urgently and authorized by the ICC Clinician on-call.

3.7 CONFIRMATION AND VERIFICATION OF STUDY OUTCOMES

3.7.1 Confirmation of all deaths and relevant non-fatal serious adverse events

The LCC Research Nurse will seek additional information from the hospital records and other appropriate sources about serious adverse events that are of particular interest. Such serious adverse events include those reported as myocardial infarction, angina, heart failure, stroke, transient ischaemic attack, revascularisation procedure (excluding dialysis access procedures), angiography, amputation, initiation of dialysis, kidney transplantation, cancer, rhabdomyolysis, hepatitis, or gallbladder disease. The LCC Lead Investigator will be responsible for the review and confirmation of these events, using the SHARP WebBasedSystem, in accordance with the SHARP SOPs, with further review of particular adverse events by a Central Adjudication Panel where appropriate (see Section 3.7.2). The RCC will also seek, from national registries and other relevant sources, the certified cause of death for all patients randomized into the study. For each death reported, the LCC Research Nurse will seek additional information from the hospital records and other appropriate sources. LCC Lead Investigators will be responsible for the review and confirmation of all deaths, using the SHARP WebBasedSystem, in accordance with the SHARP SOPs.

3.7.2 Central verification of study outcomes

A central Outcomes Adjudication Panel will review, blind to treatment allocation, the specified causes of all deaths and all serious adverse events that have been confirmed as: myocardial infarction, angina, stroke, revascularisation procedure (excluding dialysis access procedures), amputation, initiation of dialysis, kidney transplantation, cancer,

* Such as stipulated in the European Clinical Trial Directive (Article 18 of Directive 2001/20/EC) and the FDA Code of Federal Regulations (Title 21 §312)

rhabdomyolysis, hepatitis or gallbladder disease (i.e. cholecystectomy or complications of gall-stones).

3.8 MEASUREMENT OF SAFETY BLOODS

Creatine kinase, liver transaminase (ALT, or, if this is not available, AST) and creatinine will be measured in the LCC laboratory at each study visit during the first year of the study. When average follow-up is about 1 year, the Steering Committee will review the need for routine measurement of these safety bloods. Irrespective of this decision, safety bloods will continue to be carried out whenever a patient complains of unexplained muscle pain; at any Early Recall appointment; and immediately before, and about 3-4 weeks after, restarting study treatment.

The LCC Research Nurse will be responsible for the prompt entry of safety blood results onto the LaptopSystem following each clinic visit. For abnormalities of particular concern (e.g. creatine kinase $>10 \times \text{ULN}$), the LaptopSystem will provide guidance to the LCC Research Nurse in order to facilitate appropriately prompt action. All significantly abnormal safety blood results will also be reviewed by a member of the clinical team at the ICC.

3.8.1 Monitoring of elevated creatine kinase

The management of abnormal creatine kinase (CK) results will be as follows:

- (i) CK $>10 \times \text{ULN}$: Patients with CK $>10 \times \text{ULN}$ and unexplained muscle pain will be instructed to stop study medication immediately. Patients with CK $>10 \times \text{ULN}$ but without unexplained muscle pain will be instructed to return for repeat safety bloods within 1 week.
- (ii) CK $>5 \times \text{ULN}$ but $\leq 10 \times \text{ULN}$: Safety bloods will be repeated within 1 week, and study medication will be stopped if the CK is persistently $>5 \times \text{ULN}$ and is associated with unexplained muscle pain.

3.8.2 Monitoring of liver transaminases

In the event of persistent elevation of ALT (or, if not locally available, AST) $> 3 \times \text{ULN}$, the LCC Lead Investigator will be informed of the abnormality and will be responsible for arranging any further investigations or treatment considered appropriate, including a search for pathological and pharmacological causes of liver dysfunction. Study treatment will be stopped temporarily but may be restarted at the discretion of the LCC Lead Investigator if liver transaminases are subsequently stable at $< 3 \times \text{ULN}$. Persistent elevation of ALT (or of AST) of $>3 \times \text{ULN}$ will be reported as a safety outcome (see Section 2.3.1 and 2.3.4).

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APPENDICES

4.1 APPENDIX 1: CLASSIFICATION OF CHRONIC KIDNEY DISEASE (CKD)

Stage	Description	GFR (ml/min/1.73m ²)
1	Kidney damage with normal or ↑GFR	>90
2	Mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 or dialysis

Abbreviations

GFR: Glomerular filtration rate

(see reference 4)

4.2 APPENDIX 2: DEFINITIONS OF OUTCOMES

1. Major vascular event: the composite outcome of non-fatal myocardial infarction or cardiac death; non-fatal or fatal stroke; or revascularisation, including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis).
2. Myocardial infarction: either (i) the presence of two or more of the following: (a) typical ischaemic chest pain, pulmonary oedema, syncope or shock; (b) development of pathological Q-waves and/or appearance or disappearance of localised ST-elevation followed by T-wave inversion in two or more of twelve standard electrocardiograph leads; and (c) raised concentrations of serum markers consistent with myocardial damage (e.g. rise and fall of CK >2 x ULN, elevated CK-MB, elevated troponin); or (ii) necropsy findings of MI of an age corresponding to time of onset of symptoms. "Silent" myocardial infarctions are not to be included.
3. Cardiac death: death due to hypertensive heart disease, coronary heart disease, other heart disease
4. Stroke: rapid (or uncertain) onset of focal or global neurological deficit lasting more than 24 hours or leading to death. For any stroke reported, information will be sought for review of the likely aetiology (i.e. haemorrhagic or not). **Note:** Traumatic subdural haematoma, transient ischaemic attacks and related syndromes are to be excluded.
5. Revascularisation: Coronary or non-coronary artery grafting or angioplasty (with or without endovascular stenting).
6. End-stage renal disease: need for long-term dialysis or transplantation.

4.3 APPENDIX 3: ORGANISATIONAL STRUCTURE AND RESPONSIBILITIES

Principal Investigators

The Principal Investigators have overall responsibility for:

- The design and conduct of SHARP
- Preparation of the Protocol and subsequent revisions
- Preparation of Standard Operating Procedures
- Design, testing and documentation of all computer systems
- Managing the ICC
- Organising meetings of the SHARP Steering Committee
- Publication of study reports

Steering Committee

The Steering Committee is responsible for:

- Agreement of the final Protocol
- Planning the recruitment of study participants in each of the collaborating countries, in liaison with the Principal Investigators
- Reviewing progress of the study and, if necessary, agreeing changes to the protocol and/or Standard Operating Procedures to facilitate the success of the study
- Reviewing new studies that may be of relevance to SHARP

Data Monitoring Committee

The independent Data Monitoring Committee is responsible for:

- reviewing unblinded interim data from SHARP according to the schedule set out in the Protocol
- advising the Steering Committee if, in their view, the randomized comparisons in SHARP have provided **both** (i) “proof beyond reasonable doubt” that for all, or some specific types, of patient, prolonged use of ezetimibe/simvastatin is clearly indicated or clearly contraindicated in terms of a net difference in time to death; **and** (ii) evidence that might reasonably be expected to influence materially the patient management of many clinicians who are already aware of the main results of any other trials.

International Coordinating Centre

The ICC is responsible for the overall coordination of SHARP. Its functions include:

- Study planning, organisation of Steering Committee meetings
- Contractual issues with RCCs and budget administration
- Recruitment of RCCs and initial training for RCC staff
- Design and maintenance of the SHARP IT system, including the WebBasedSystem for administration and the LaptopSystem for direct data entry
- Provision of laptops and IT support to RCCs
- Provision of study materials
- Assistance with Institutional Review Board / Independent Ethics Committee applications
- Auditing and monitoring of RCCs and of overall progress of the study

- Monitoring of drug supply (in liaison with MSP, who will be responsible for drug distribution to each LCC)
- Monitoring Early Recall appointments arranged by RCCs, and any relevant blood results
- Responding to technical, medical and administrative queries from the RCCs
- Liaison with the Data Monitoring Committee and MSP, and (where appropriate) with regulatory authorities and other outside agencies
- Central laboratory assay of blood lipids and measures of renal function at randomization and at 2.5 years in all participants, and on ~10% participants at 1 and 4 years
- Long-term frozen storage of blood and urine samples

Regional Coordinating Centres

The responsibilities of the RCC, under the direction of the Regional Coordinator, will include:

- Contractual issues with LCCs and regional budget administration
- Recruitment and set-up of approximately 40-50 LCCs within the Region (possibly in a number of different countries)
- Assisting LCCs with Institutional Review Board / Independent Ethics Committee applications
- Liaison with regulatory authorities as appropriate
- Training of LCC Research Nurses
- Assisting LCC's with identifying suitable patients
- Ensuring that the SHARP IT system software is configured in accordance with local requirements, and installation on to study laptops
- Distribution of study laptop computers and other study materials to LCCs
- Responding to simple queries from LCCs about the SHARP IT system
- Monitoring of LCC's through visits (by the study monitor) and by responding to regular or occasional reports on regional progress prepared by the ICC
- Monitoring blood results (CK, ALT/AST, creatinine) measured in local laboratories and instigating Early Recall appointments, where appropriate.
- Responding to technical, medical and administrative queries from the LCCs
- Collection of blood and urine samples for central analysis, and transport to the ICC
- Responding to medical and administrative queries within the Region
- Organisation of meetings of collaborators within the region

National Coordinators

National Coordinators are members of the Steering Committee with responsibility for:

- facilitating approval of the study by the relevant Regulatory Authority in their own country
- providing assistance and advice on national issues to the relevant RCC

Local Clinical Centres

The responsibilities of the LCC Lead Investigator (consultant nephrologist or physician) and LCC Research Nurse will include:

- Obtaining Institutional Review Board / Independent Ethics Committee approval (aided by the RCC)

- Provision of adequate clinic space and access to appropriate hospital computer systems for the LCC Research Nurse
- Liaising with consultant colleagues
- Identification and invitation of patients
- Allocating appropriate appointments
- Conducting clinic procedures; managing and distributing study drugs (in conjunction with the hospital pharmacy), and maintaining the laptop computer, in accordance with the study protocol and standard operating procedures
- Dealing with routine enquiries from patients and their families, in close collaboration with the RCC
- Obtaining appropriate information to confirm potential primary and secondary study endpoints

4.4 APPENDIX 4: STUDY INVESTIGATORS

STEERING COMMITTEE (Major organisational and policy decisions)

Study coordinator	C Baigent*
Clinical coordinator (and UK Regional coordinator)	M Landray*
Chairman of the Steering Committee	R Collins*
Regional coordinators	H Holdaas (Nordic countries) L Jiang (China) B Kasiske (USA) A Levin (Canada) B Neal (Australasia) C Wanner (Central Europe)
National coordinators	ALM de Francisco (Spain) B Feldt-Rasmussen (Denmark) B Fellström (Sweden) D Grobbee (Netherlands) C Grönhagen-Riska (Finland) M Haas (Austria) LS Hooi (Malaysia) Z Massy (France) V Ophascharoensuk (Thailand) V Tesar (Czech Republic) R Walker (New Zealand) D Wheeler (UK) A Wiecek (Poland)
Other members	L Agodoa, J Armitage, A Cass, Z Chen, J Craig, M Gaziano, R Grimm, V Krane, X Li, M Mafham, T Pedersen, P Sleight, J Tobert, C Tomson, D de Zeeuw
Lay member	D Simpson
Statistician	S Parish
Computing	A Baxter, A Young
International Nurse Coordinator	C Knott
Laboratory coordinator	K Kourellias
Administrative coordinators	C Bray, C Leaper
MSP representatives (non-voting)	J Strony, T Musliner

*Principal Investigators

DATA MONITORING COMMITTEE (Interim analyses and response to specific concerns)

Chairman	P Sandercock
Members	C Hill, A Keech, P Whelton, S Yusuf
Statistician to the DMC (non-voting)	R Peto

INTERNATIONAL COORDINATING CENTRE, CLINICAL TRIAL SERVICE UNIT, OXFORD (Overall coordination of SHARP)

Administrative coordinators	C Bray, C Leaper
Clinical staff	M Landray, M Mafham, C Reith
International Nurse Coordinator	C Knott
Laboratory coordinator	K Kourellias
Statistician	J Emberson
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