Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease

SHARP Collaborative Group

Background Lowering low-density lipoprotein (LDL) cholesterol with statin therapy has been shown to reduce the incidence of atherosclerotic events in many types of patient, but it remains uncertain whether it is of net benefit among people with chronic kidney disease (CKD).

Methods Patients with advanced CKD (blood creatinine 1.7 mg/dL [150 mol/L] in men or 1.5 mg/dL [130 mol/L] in women) with no known history of myocardial infarction or coronary revascularization were randomized in a ratio of 4:4:1 to ezetimibe 10 mg plus simvastatin 20 mg daily versus matching placebo versus simvastatin 20 mg daily (with the latter arm rerandomized at 1 year to ezetimibe 10 mg plus simvastatin 20 mg daily vs placebo). The key outcome will be major atherosclerotic events, defined as the combination of myocardial infarction, coronary death, ischemic stroke, or any revascularization procedure.

Results A total of 9,438 CKD patients were randomized, of whom 3,056 were on dialysis. Mean age was 61 years, two thirds were male, one fifth had diabetes mellitus, and one sixth had vascular disease. Compared with either placebo or simvastatin alone, allocation to ezetimibe plus simvastatin was not associated with any excess of myopathy, hepatic toxicity, or biliary complications during the first year of follow-up. Compared with placebo, allocation to ezetimibe 10 mg plus simvastatin 20 mg daily yielded average LDL cholesterol differences of 43 mg/dL (1.10 mmol/L) at 1 year and 33 mg/dL (0.85 mmol/L) at 2.5 years. Follow-up is scheduled to continue until August 2010, when all patients will have been followed for at least 4 years.

Conclusions SHARP should provide evidence about the efficacy and safety of lowering LDL cholesterol with the combination of ezetimibe and simvastatin among a wide range of patients with CKD. (Am Heart J 2010;0:1-10.e10.)

Background

Observational studies in unselected populations have shown that there is a continuous positive relationship between coronary heart disease (CHD) risk and blood low-density lipoprotein (LDL) cholesterol that extends well below the range seen in Western populations.[1,2] A meta-analysis of randomized trials has shown that statin therapy reduces the incidence of major coronary events (nonfatal myocardial infarction [MI] or CHD mortality), of ischemic strokes, and of coronary revascularizations by about one fifth for every 1-mmol/L (39-mg/dL) reduction in LDL cholesterol, while producing no benefit on hemorrhagic stroke or on vascular causes of death other than CHD.[3,4] Among people without known chronic kidney disease (CKD), in whom estimated glomerular filtration rate (eGFR) is typically greater than about 60 mL/min/1.73 m^2, the proportional reduction in the risk of a major vascular event (ie, major coronary event, stroke, or coronary revascularization) appears to be independent of renal function.[4]

The etiology of cardiovascular disease among patients with preserved renal function (or only minor renal dysfunction) is typically atherosclerotic, but a quite distinct type of cardiovascular pathology is observed once GFR falls to less than about 30 mL/min/1.73 m^2. Several mechanisms resulting from renal metabolic

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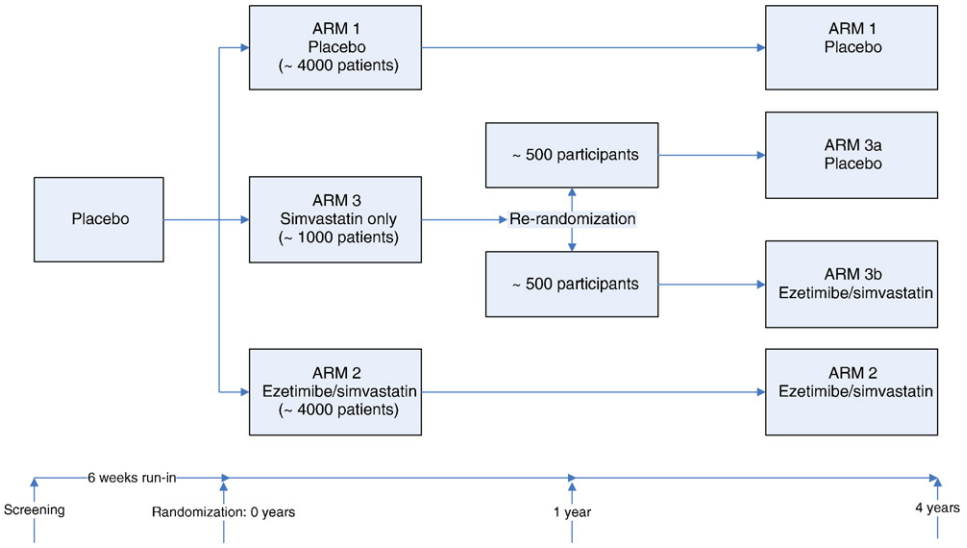
Figure 1



SHARP randomization structure.

Although the chief aim of SHARP is to determine any vascular benefits of LDL lowering among patients with advanced CKD, the trial also provides an opportunity to test the hypothesis that lowering LDL cholesterol might reduce the rate of loss of renal function.[12] Among people without known CKD, meta-analyses of randomized trials have suggested that statin therapy might reduce the rate of loss of eGFR by about one third[13,14]; so a similar proportional effect among patients with advanced CKD, in whom there is rapid loss of renal function, would yield a worthwhile delay in the need for renal replacement therapy (ie, dialysis or transplantation).

In this article, we describe the SHARP trial design, patient characteristics, early safety data, lipid effects, and statistical analysis plan.

Methods

Aims

SHARP aims to assess the efficacy and safety of lowering LDL cholesterol with the combination of ezetimibe 10 mg plus simvastatin 20 mg (ezetimibe/simvastatin 10/20 mg) daily among men or women aged at least 40 years without known CHD (prior MI or coronary revascularization) who had evidence of CKD (determined by screening creatinine ≥1.7 mg/dL [≥150 μmol/L] in men or ≥1.5 mg/dL [≥130 μmol/L] in women; Box). It was intended to recruit about 3,000 CKD patients requiring dialysis and 6,000 not on dialysis. Using a "double-dummy" method to maintain blinding for both patients and physicians, patients were randomized in a ratio of 4:4:1 to ezetimibe/simvastatin 10/20 mg daily versus matching placebo versus simvastatin 20 mg daily (Figure 1). After 1 year, patients initially allocated simvastatin 20 mg daily alone (who formed a comparison group for the assessment of any early adverse effects of ezetimibe) were rerandomized to ezetimibe/simvastatin 10/20 mg daily versus placebo for the remainder of the scheduled study treatment period.

Sample size and predicted number of events

A meta-analysis of statin trials available in 2000 (which was subsequently published[3]) indicated that statin therapy produced a reduction of about one quarter in ***major vascular events*** (defined as cardiac death, nonfatal MI, coronary revascularization, or stroke) per 1-mmol/L LDL cholesterol reduction. Based on the expectation that ezetimibe/simvastatin 10/20 mg would reduce LDL cholesterol by an average of 39 mg/dL (1 mmol/L) in the SHARP trial, together with the assumption that about one fifth of cardiac deaths might be nonatherosclerotic (and, hence, potentially not susceptible to prevention by lowering LDL cholesterol), it was hypothesized that the risk of major vascular events might be reduced by 20%. The annual incidence of major vascular events was projected to be about 5% among CKD patients on dialysis at baseline and about 3% among those who were not, so the average event rate during follow-up was estimated to be 3.7% per annum (based on 1:2 ratio of these groups). Under these assumptions, a study in which all patients were followed for at least 4 years from trial entry, yielding at least 1,100 major vascular events, would have 90% power at $P < .01$ (2-sided).

Based on the UK-HARP-I pilot study[8] and the RENAAL study,[15] the cumulative incidence of ***end-stage renal disease*** (defined as starting long-term dialysis or transplantation) among patients not on dialysis at baseline was expected to be about 20% after 4 years. Consequently, the inclusion of 6,000 such patients in SHARP provides >95% power at $P < .01$ (2-sided) to detect a 20% relative reduction in the risk of end-stage renal disease.

Table I. Baseline demographic characteristics, overall and by renal status at randomization

	Not on dialysis	On dialysis	All patients
Number randomized	6382	3056	9438
Renal diagnosis			
Glomerulonephritis	1063 (17%)	689 (23%)	1752 (19%)
Diabetic nephropathy	916 (15%)	477 (16%)	1393 (15%)
Hypertensive or renovascular disease	1334 (22%)	482 (16%)	1816 (20%)
Cystic kidney disease	690 (11%)	374 (12%)	1064 (12%)
Pyelonephritis/obstructive nephropathy	413 (7%)	202 (7%)	615 (7%)
Other known cause	911 (15%)	373 (12%)	1284 (14%)
Unknown cause	796 (13%)	403 (13%)	1199 (13%)
Unavailable	259	56	315
Age, y			
Mean (SD)	62.3 (11.7)	58.9 (11.8)	61.2 (11.9)
40-49	1099 (17%)	825 (27%)	1924 (20%)
50-59	1516 (24%)	826 (27%)	2342 (25%)
60-69	1794 (28%)	740 (24%)	2534 (27%)
70+	1973 (31%)	665 (22%)	2638 (28%)
Sex			
Men	3954 (62%)	1946 (64%)	5900 (63%)
Women	2428 (38%)	1110 (36%)	3538 (37%)
Physical measurements			
Systolic blood pressure, mm Hg	139 (21)	139 (24)	139 (22)
Diastolic blood pressure, mm Hg	80 (13)	78 (13)	79 (13)
Body mass index, kg/m^2	27.4 (5.5)	26.4 (5.8)	27.1 (5.6)
Waist circumference, cm	96.7 (14.8)	97.0 (15.7)	96.8 (15.1)
Smoking			
Current smoker	791 (12%)	475 (16%)	1266 (13%)
Prior diseases*			
Angina	212 (3%)	77 (3%)	289 (3%)
Peripheral arterial disease	371 (6%)	229 (7%)	600 (6%)
Cerebrovascular disease	464 (7%)	187 (6%)	651 (7%)
Any vascular disease	933 (15%)	437 (14%)	1370 (15%)
Diabetes	1429 (22%)	650 (21%)	2079 (22%)
Ethnic group			
White	4567 (72%)	2206 (72%)	6773 (72%)
Black	130 (2%)	146 (5%)	276 (3%)
Chinese	1031 (16%)	109 (4%)	1140 (12%)
Other Asian	528 (8%)	442 (14%)	970 (10%)
Other/not specified	126 (2%)	153 (5%)	279 (3%)

Mean (SD) or number (percentage) shown.
*Cerebrovascular disease includes stroke and transient ischemic attack. *Any vascular disease* is defined as a history of angina, peripheral arterial disease, or cerebrovascular disease at the screening visit.

Results

Screening clinic visit

SHARP has been conducted in 380 hospitals in 18 countries. Between June 2003 and June 2006, 11,792 potentially eligible CKD patients attended the study screening visits. Medical history and other eligibility criteria were checked (Box), and 11,364 (96%) eligible patients agreed to participate. Among these patients, written informed consent was obtained; blood pressure, height, weight, and waist circumference were measured; nonfasting blood was taken for local laboratory assays (lipid profile, creatine kinase [CK], alanine aminotransferase [ALT] or aspartate aminotransferase [AST], creatinine); and single-blind study placebo tablets were provided. Study data were entered directly into electronic case-report forms on dedicated laptop computers.

Run-in period before randomization

During run-in, the patient's physicians were provided with a summary of the screening data for each of their patients, including the results of local laboratory blood assays on screening blood samples. Randomization could be considered at the end of the run-in period only if the responsible physician (typically the nephrologist) confirmed that this was appropriate and no objection had been raised by any other physician caring for the patient. Patients who were noncompliant (ie, took <90% of run-in treatment) or who were thought likely to have difficulties in attending clinics for any reason were not to be randomized. Hence, in addition to allowing a review by the patient's physicians, the run-in period allowed many potential dropouts to be excluded before being randomized, with a consequent improvement in statistical sensitivity.[16]

Randomization clinic visit

Participating patients returned for a randomization appointment approximately 6 weeks after the screening visit. Those who had not had a serious adverse event rendering them ineligible during the run-in period (eg, MI) and who had not commenced a contraindicated drug (eg, statin) were asked if they were still willing to take study treatment for at least 4 years. A total of 1,926 patients entered run-in but were not randomized. Of these, 1,678 dropped out before the randomization visit, with the reasons given including (>1 reason was possible) the following: patient's request (23%), physician's request (44%), ineligible screening blood result (32%), or some other reason (11%). A further 248 patients attended the randomization visit but were not randomized, generally because of poor compliance during run-in or their reluctance to continue. Patients who agreed to be randomized provided nonfasting blood samples and, if not on dialysis, a urine sample, and were asked for their consent for long-term storage of plasma, DNA, and urine for unspecified future analyses. Samples were cooled, spun, and separated locally, whereupon plasma and whole blood aliquots were stored locally at −40°C before shipment on dry ice to the central laboratory (Wolfson Laboratories, CTSU, University of Oxford, United Kingdom). Patients were allocated their study treatment using a minimized randomization algorithm on the laptop computer (which was synchronized regularly with the central database) to help ensure balance with respect to important prognostic characteristics.[17]

A total of 9,438 CKD patients were randomized, of whom 3,056 were receiving maintenance dialysis (2,556 hemodialysis and 500 peritoneal dialysis) and 6,382 were not (Table I). The most common recorded causes of renal disease were glomerulonephritis (19%), diabetic nephropathy (15%), and hypertensive or renovascular disease (20%). Mean age was 61 years (SD 12), 63% were male, mean blood pressure was 139/79 mm Hg, mean body mass index was 27.1 (SD 5.6) kg/m^2, and 22% had diabetes. Patients who had a prior history of MI or coronary revascularization were not eligible, but 15% had some other vascular disease (eg, angina pectoris, stroke, or peripheral vascular disease). About three quarters of the study population were white, whereas 3% were black, 12% were Chinese, and 10% were other Asian.

Among the 6,382 patients not on dialysis at randomization, the average eGFR, calculated with the Modified Diet and Renal Disease equation[18], was 26.5 (SD 13.0) mL/min/1.73 m^2 (Table II). About two fifths of the patients not on dialysis had Kidney Disease Outcomes Quality Initiative[19] stage 3 disease (eGFR of 30-59 mL/min/1.73 m^2), two fifths had stage 4 disease (eGFR of 15-29 mL/min/1.73 m^2), and one fifth had stage 5 disease (eGFR <15 mL/min/1.73 m^2). Among the 5,681 (89%) nondialysis patients who had a measurement of urinary albumin to creatinine ratio (ACR), about one fifth had values in the reference range (ACR <30 mg/g), two fifths had microalbuminuria (ACR ≥30 and ≤300 mg/g), and two fifths had macroalbuminuria (ACR >300 mg/g). Overall, among the 9,044 patients for whom a blood sample was available at randomization, mean plasma concentrations were 189 (SD 45) mg/dL for total cholesterol, 108 (SD 34) mg/dL for LDL cholesterol, 43 (SD 13) mg/dL for high-density lipoprotein (HDL) cholesterol, and 206 (SD 152, interquartile range 119-249) mg/dL for triglycerides. Mean LDL cholesterol concentration was lower among patients on dialysis than those who were not (100 vs 111 mg/dL, $P < .0001$).

Table II. Laboratory values at randomization, overall and by renal status at randomization

	Not on dialysis	On dialysis	All patients
Number randomized	6382	3056	9438
eGFR, mL/min/1.73 m^2			
Mean (SD)	26.5 (13.0)	–	–
<15	1237 (20%)	–	–
15-29	2628 (43%)	–	–
30-59	2197 (36%)	–	–
60-89	67 (1%)	–	–
≥ 90	21 (0%)	–	–
Missing	232		
Urinary ACR			
Normal	1124 (20%)	–	–
Microalbuminuria	2125 (37%)	–	–
Macroalbuminuria	2432 (43%)	–	–
Missing	701		
Lipids			
Number with baseline LDL cholesterol analyzed	6149 (96%)	2895 (95%)	9044 (96%)
Total cholesterol, mg/dL	194 (45)	179 (45)	189 (45)
LDL cholesterol, mg/dL	111 (33)	100 (33)	108 (34)
HDL cholesterol, mg/dL	44 (13)	42 (13)	43 (13)
Triglycerides, mg/dL	206 (146)	206 (164)	206 (152)
Apolipoprotein B, mg/dL	99 (25)	92 (26)	96 (26)
Apolipoprotein A$_1$, mg/dL	136 (29)	129 (27)	134 (29)
Apolipoprotein B: apolipoprotein A$_1$	0.75 (0.23)	0.74 (0.24)	0.75 (0.24)

Mean (SD) or number (percentage) shown. *Microalbuminuria* is defined as an ACR ≥30 and ≤300 mg/g. *Macroalbuminuria* is defined as ACR ≥300 mg/g. To convert milligrams per deciliter to millimoles per liter, multiply by 0.02586 for cholesterol and by 0.01129 for triglycerides; to convert apolipoprotein A$_1$ and B from milligrams per deciliter to grams per liter, divide by 100.

Aspirin or other antiplatelet therapy was being prescribed at baseline to 22% of randomized patients and an oral anticoagulant to 4% (Table III). As expected in this high-risk CKD population, a high proportion were receiving angiotensin-converting-enzyme (ACE) inhibitors (35% of all patients), angiotensin-receptor blockers (23%), calcium-channel blockers (41%), β-blockers (37%), and diuretics (42%), with many (60%) receiving >1 of these agents.

Postrandomization follow-up visits

Participants were to be seen in the study clinics for routine follow-up at 2 months, at 6 months, and then

Table III. Medication use at randomization, overall and by renal status at randomization

	Not on dialysis	On dialysis	All patients
Number randomized	6382	3056	9438
Antiplatelet therapy	1207 (19%)	871 (29%)	2078 (22%)
Oral anticoagulant	211 (3%)	167 (5%)	378 (4%)
ACE inhibitor	2537 (40%)	813 (27%)	3350 (35%)
Angiotensin II receptor blocker	1657 (26%)	488 (16%)	2145 (23%)
Calcium-channel blocker	2819 (44%)	1087 (36%)	3906 (41%)
β-Blocker	2349 (37%)	1181 (39%)	3530 (37%)
Diuretic	2869 (45%)	1062 (35%)	3931 (42%)
Miscellaneous blood pressure–lowering drug	1201 (19%)	563 (18%)	1764 (19%)
Phosphate binder	1021 (16%)	2479 (81%)	3500 (37%)
Erythropoietin-stimulating agent	779 (12%)	1724 (56%)	2503 (27%)
Iron-containing preparation	845 (13%)	1319 (43%)	2164 (23%)
Vitamin D supplement	1313 (21%)	1539 (50%)	2852 (30%)

every 6 months until the final follow-up visits between March and August 2010 (minimum of 4 years for all patients). It was also possible to arrange an “early recall” visit for any participant who required review outside of his or her planned visit schedule. At each follow-up, compliance with study treatment was reviewed, any unexplained muscle pain and nonstudy treatment recorded, and blood pressure measured. Samples of nonfasting blood were taken for local laboratory assay of CK, liver transaminases (ALT or AST), and creatinine. Information was to be recorded about any suspected MI, stroke, vascular procedure, cancer, or other serious adverse event (together with the reasons for all hospital admissions, including day cases), irrespective of compliance with study treatment. If a participant became unwilling or unable to attend his or her scheduled follow-up visits, information about any serious adverse events was to be obtained from them by telephone or by direct correspondence with their own physicians until the scheduled end of the study. Local study staff aimed to obtain extra information from hospital records and other appropriate sources about all reports of serious adverse events that are of particular interest for the study aims (ie, death, MI, angina, heart failure, stroke, transient ischemic attack, revascularization procedure, angiography, amputation, initiation of dialysis, kidney transplant, cancer, myopathy, rhabdomyolysis, hepatitis, or gallbladder disease). This information has been sent to the International Coordinating Centre for further review and central adjudication in accordance with prespecified definitions by trained clinicians who are blind to treatment allocation.

Effects of study treatment on blood lipids

The protocol specified that central analysis of blood lipid concentrations was to be conducted on blood samples collected from about 10% of participants at their 1- and 4-year follow-up visits and from all participants at their 2.5-year visits, and that unblinded lipid differences were to be periodically reviewed by the Steering Committee to monitor study power. The sampling procedure at 1 and 4 years was designed to ensure that the sample was representative of the whole study population, particularly in regard to the proportions recruited in each country and in the proportions of nondialysis and dialysis patients. The 1- and 4-year samples were each collected during separate calendar periods of approximately 6 months during the trial, with the aim of sampling about 10% of patients from around one third of each country's sites during those periods. Blood samples at randomization and 1 year were available for 787 participants (91% of those alive and selected for sampling) and at randomization and 2.5 years from 6,632 participants (86%), with collection of 4-year samples still in progress at the time of this report. In the case of nonattendance when scheduled to provide a blood sample, a patient's randomization lipid parameters were imputed based on the assumption that the patient was not taking study treatment at that time. Compared with placebo, allocation to ezetimibe/simvastatin yielded mean reductions in LDL cholesterol concentrations of 43 (SE 2.2) mg/dL at 1 year and of 33 (SE 0.8) mg/dL at 2.5 years (Table IV).

Safety of study treatment at 1 year

Because relatively little information was available about the safety of ezetimibe at the time that SHARP was initiated, the protocol included a simvastatin-alone arm and prespecified that unblinded information on a limited number of safety outcomes (but not on study outcomes) was to be reviewed by the Steering Committee after each patient had completed 1 year of follow-up. Compared with the 1,054 patients who were allocated simvastatin alone (as well as with the 4,191 patients allocated placebo), no significant excesses were observed among the 4,193 allocated ezetimibe/simvastatin in any of these safety outcomes (Table V). About 10% of patients reported muscle pain during the first year, but there was no significant excess among the patients allocated ezetimibe/simvastatin. Few elevations in CK to between 5× and 10× the upper limit of normal (ULN) or above 10× ULN were observed and, again, the rates were similar in each randomized group. There were only 7 confirmed cases of ***myopathy*** (defined as CK >10× ULN plus muscle symptoms or evidence of organ damage), 5 of which were in patients allocated placebo, including 1 case of ***rhabdomyolysis*** (defined as myopathy with CK >40× ULN plus evidence of end-organ damage) in a patient

Table IV. Biochemical efficacy at 1 and 2.5 years, by initial randomized treatment allocation

	1 y				2.5 y†		
	Placebo	Simvastatin only	Ezetimibe plus simvastatin	*P**	Placebo	Ezetimibe plus simvastatin	*P*
Total cholesterol, mg/dL	−1 (2)	−36 (4)	−54 (2)	<.0001	−8 (1)	−49 (1)	<.0001
LDL cholesterol, mg/dL	1 (1)	−29 (3)	−42 (2)	<.0001	−6 (0.5)	−39 (0.6)	<.0001
HDL cholesterol, mg/dL	1 (0.5)	1 (0.6)	1 (0.5)	.76	0 (0.2)	1 (0.2)	.21
Triglycerides, mg/dL	−10 (5)	−21 (8)	−37 (4)	<.0001	−21 (1)	−45 (1)	<.0001
Apolipoprotein B, mg/dL	−1 (1)	−22 (2)	−30 (1)	<.0001	−4 (0.4)	−27 (0.5)	<.0001
Apolipoprotein A_1, mg/dL	1 (1)	5 (2)	5 (1)	.01	8 (0.4)	10 (0.4)	.04

Mean (SE) changes in lipids from randomization to 1-year visit in 787 patients (assuming zero change in lipids for 75 nonattendees). Changes in lipids at the 2.5-year visit are among 6632 attendees (assuming zero change in lipids for 1105 nonattendees). For triglycerides, the geometric mean percentage change in each group (and its standard error) is shown applied to the baseline mean value. To convert milligrams per deciliter to millimoles per liter, multiply by 0.02586 for cholesterol and by 0.01129 for triglycerides; to convert apolipoprotein A_1 and B from milligrams per deciliter to grams per liter, divide by 100.

*Test of difference between placebo and ezetimibe/simvastatin combination therapy, ignoring simvastatin-only group.

†Patients initially randomized to simvastatin only were to be rerandomized to ezetimibe/simvastatin combination or placebo after 1 year.

Table V. Safety at 1 year by initial randomized treatment allocation

	Placebo	Simvastatin only	Ezetimibe plus simvastatin	*P**	*P*†
Number randomized	4191	1054	4193		
Muscle pain	393 (9.4%)	103 (9.8%)	430 (10.3%)	.19	.68
CK					
>5× but ≤10 × ULN					
Asymptomatic	11 (0.3%)	5 (0.5%)	16 (0.4%)	.44	.88
Muscle symptoms present	3 (0.1%)	1 (0.1%)	1 (0.0%)	.62	.86
>10× but ≤40 × ULN					
Not on dialysis‡					
No end-organ damage§					
Asymptomatic	0 (0.0%)	1 (0.1%)	0 (0.0%)	–	.46
Muscle symptoms present	0 (0.0%)	0 (0.0%)	0 (0.0%)	–	–
With end-organ damage§	4 (0.1%)	0 (0.0%)	1 (0.0%)	.37	1.0
On dialysis‡					
Asymptomatic	1 (0.0%)	0 (0.0%)	2 (0.0%)	1.0	1.0
Muscle symptoms present	0 (0.0%)	0 (0.0%)	1 (0.0%)	1.0	1.0
>40× ULN					
Not on dialysis‡					
With end-organ damage§	1 (0.0%)	0 (0.0%)	0 (0.0%)	1.0	–
Persistently elevated liver transaminases‖	5 (0.1%)	0 (0.0%)	7 (0.2%)	.77	.39
Hepatitis¶					
Infective	6 (0.1%)	1 (0.1%)	6 (0.1%)	1.0	1.0
Noninfective	1 (0.0%)	0 (0.0%)	2 (0.0%)	1.0	1.0
No cause identified	1 (0.0%)	1 (0.1%)	2 (0.0%)	1.0	1.0
Complications of gallstones					
Acute pancreatitis	5 (0.1%)	0 (0.0%)	4 (0.1%)	1.0	.70
Other complications	19 (0.5%)	3 (0.3%)	17 (0.4%)	.87	.77
Hospitalization with gallstones#	4 (0.1%)	4 (0.4%)	2 (0.0%)	.68	.02
Pancreatitis					
Acute (excluding gallstones)	7 (0.2%)	1 (0.1%)	2 (0.0%)	.18	1.0
Chronic	1 (0.0%)	0 (0.0%)	0 (0.0%)	1.0	–

*Test of difference between ezetimibe/simvastatin combination therapy and placebo.

†Test of difference between ezetimibe/simvastatin combination therapy and simvastatin only.

‡At the time of presentation with raised CK.

§*End-organ damage* is defined as acute initiation of dialysis or a >20% rise in serum creatinine. Among patients already on dialysis, it is not possible to determine if end-organ damage has occurred.

‖At least 2 consecutive ALT or AST >3× ULN without other indication of hepatitis.

¶Infective hepatitis—definite evidence of an infective cause; noninfective hepatitis—definite evidence of a noninfective cause; no cause identified—includes cases with negative viral serology result and those with no viral serology result available.

#With no reported complications.

allocated placebo (who was not taking a nonstudy statin). No excesses were observed of persistent liver transaminase elevations, hepatitis, gallstone complications, or pancreatitis.

Discussion

Statin therapy is now widely recommended for the primary and secondary prevention of vascular disease in a wide range of people,[20-22] but 2 previous trials have failed to show a clear benefit among patients with end-stage renal failure who were undergoing dialysis.[6,7] Consequently, there remains considerable uncertainty as to whether lowering LDL cholesterol is of value among dialysis patients, as well as among those with less severe renal impairment who have not yet commenced dialysis. The SHARP trial, which has recruited >9,000 patients with advanced CKD, 3,000 on dialysis and 6,000 not, can help to address this clinical uncertainty.

In the International Conference on Harmonisation–Good Clinical Practice Statistical Principles for Clinical Trials, it is recommended that checks are made during a trial that its actual performance has not affected statistical power, that assumptions underlying the original design remain plausible, and that the statistical analysis plan remains appropriate in the light of emerging results from other relevant trials.[23] The guidelines indicate that, until the study treatment has been unblinded, it is appropriate to make any changes that might help the trial to provide more reliable information about the effects of treatment. In particular, it is stated that "The primary variable … should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial."[23] The overall incidence rate for major vascular events (4.3% per annum) in SHARP was slightly higher than had been anticipated; but blinded central adjudication showed that about one third of these events were noncoronary cardiac deaths or hemorrhagic strokes, which an updated meta-analysis of statin trials has indicated are not prevented by LDL-lowering therapy.[4] In addition, unblinded review of the lipid assays in SHARP showed that the mean LDL cholesterol reduction at 2.5 years (ie, at about the midpoint of the trial) was 33 mg/dL, rather than the anticipated difference of 39 mg/dL. Based on the larger-than-expected proportion of major vascular events that were nonatherosclerotic (and so not likely to be reduced by LDL-lowering therapy) and the smaller-than-expected reduction in LDL cholesterol, a relative risk reduction of 13% in the original primary outcome of major vascular events may be all that can realistically be expected. Table VI indicates that SHARP would have only 66% power at $P = .01$ (2-sided) to detect such a difference among the ~8400 patients initially randomized to ezetimibe/simvastatin versus placebo (Arm 2 versus Arm 1 in Figure), which is the population specified in the protocol for the primary comparison.

Table VI. Improvement in study power by changing to new primary outcome comparison

Outcome	Anticipated proportional reduction*	n†	Expected result (active vs placebo)‡	Power at $2P = .01$
Original primary	13%	~8400	737 versus 845	66%
	13%	~9400	807 versus 927	72%
New primary	18%	~8400	525 versus 639	84%
	18%	~9400	576 versus 701	88%

*Treatment effects estimated using data from the Cholesterol Treatment Trialists Collaboration.[4]
†Sample size is increased from ~8400 to ~9400 by the inclusion of participants randomized to simvastatin only for the first year and subsequently randomized to ezetimibe/simvastatin versus placebo. For these participants, events are only counted in the primary outcome if they occur after the second randomization.
‡Based on blinded outcome event rates in November 2009.

SHARP is overseen by an independent Steering Committee that includes nephrologists, cardiologists, clinical trialists, and statisticians, with 2 nonvoting observers from the funder. The independent sponsor is the University of Oxford, and the trial is funded by the supplier of the study drugs (Merck & Co). Changes to the study plans in response to a revision of the underlying sample size assumptions are entirely appropriate provided that care is taken to avoid bias by, as in the case of SHARP, remaining blind to the effects of study treatment on the efficacy outcomes.[23,24] Consequently, in October 2009, the Steering Committee decided to change the primary outcome to *major atherosclerotic events*, defined as the combination of MI, coronary death, ischemic stroke, or any revascularization procedure (ie, exclusion of noncoronary cardiac deaths and strokes confirmed to be hemorrhagic from the original major vascular event outcome). A relative risk reduction of 18% in this revised outcome seems realistic, and Table VI shows that SHARP has good statistical power to detect such an effect among the 8,400 patients initially randomized to ezetimibe/simvastatin versus placebo. Moreover, because even better power can be achieved by including those patients who were randomly allocated between ezetimibe/simvastatin versus placebo following allocation to simvastatin for 1 year (ie, arm 3b vs 3a in Figure 1), the Steering Committee decided that the main comparisons should include them. These and other changes are described in the revised statistical analysis plan for SHARP (online Appendix A).

The independent sponsor is required by its contract with the funder to seek its formal agreement to any protocol change, but the funder declined to approve the changes agreed by the Steering Committee. Although it is not possible to revise the protocol accordingly, the Steering Committee is free to change the statistical analysis plan as it considers appropriate while it remains blind to the effects of treatment on efficacy end points.

The present report and related appendices are, therefore, intended to record that the chief emphasis for evaluating the efficacy of study treatment in SHARP will now not be on the primary outcome in the protocol of major vascular events, but will instead be on the new key outcome of major atherosclerotic events. This change of emphasis should help to reduce the risk of a false-negative result (in which a potential beneficial effect on atherosclerotic outcomes is diluted by a lack of benefit on nonatherosclerotic components), a scenario that would have adverse consequences for patients.

During the conduct of SHARP, an unexpected concern was raised by the SEAS placebo-controlled trial of ezetimibe 10 mg plus simvastatin 20 mg daily among 1,873 people with moderate aortic stenosis about an apparent excess risk of cancer (105 on ezetimibe plus simvastatin vs 70 on placebo, $P = .01$).[25] The SHARP investigators received agreement from its Data Monitoring Committee to access unblinded data on incident cancers (but no other clinical events), as did the investigators for IMPROVE-IT, which is comparing simvastatin plus ezetimibe versus simvastatin among 18,000 patients with acute coronary syndrome.[26] When these interim data on cancer were examined together in a meta-analysis,[27] they did not provide support for the hypothesis that ezetimibe might cause cancer; and their Data Monitoring Committees recommended that each trial continue. Completion of SHARP in 2010 (and, subsequently, of IMPROVE-IT in 2013) will provide additional evidence about the effects on cancer and other nonvascular outcomes of adding ezetimibe to simvastatin (which has been shown on its own to be safe in large-scale trials[3,4]).

In conclusion, SHARP has randomized 9,438 patients with CKD to receive LDL-lowering therapy or placebo for an average of about 4.4 years. Final follow-up will be completed by August 2010, and the results will be presented by the end of the year. As described above, the chief emphasis will be on the revised outcome of major atherosclerotic events (and not on the protocol-defined outcome of major vascular events), although results will also be presented for the original primary and other efficacy and safety outcomes.

Acknowledgements

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Disclosures

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Appendix A. Statistical Analysis Plan for SHARP (finalized on August 20, 2010; blind to results by allocated treatment for clinical outcomes)

Introduction

In accordance with the guidance provided by ICH-GCP Statistical Principles for Clinical Trials,[23] checks have been made during the SHARP trial to ensure that statistical power has been maintained and that assumptions underlying the original design remain plausible. Review of the unblinded lipid assays during SHARP showed that the mean LDL cholesterol reduction at 2.5 years (ie, at about the midpoint of the trial) was 33 mg/dL (0.85 mmol/L) rather than the anticipated difference of 39 mg/dL (1 mmol/L), and review of blinded data on clinical outcomes showed that about one third of the original protocol-defined primary outcome of major vascular events (defined as cardiac death, MI, any stroke, or any revascularization procedure)[28] among the CKD patients in SHARP are noncoronary cardiac deaths or hemorrhagic strokes, which have been found in other trials not to be prevented by statin therapy.[4] Consequently, in October 2009, the Steering Committee decided (blind to the effects of study treatment on clinical outcomes) to make a number of changes in the plans for analyses in order to ensure that SHARP remains sensitive to any benefits on atherosclerotic outcomes that may exist.

The main change was to place the chief emphasis on "major atherosclerotic events," defined as the combination of coronary death, MI, ischemic stroke or any revascularization procedure (ie, excluding noncoronary cardiac deaths and strokes confirmed to be hemorrhagic) rather than on major vascular events. Consequently, although an analysis of major vascular events will be provided, the chief emphasis will be on the analyses of major atherosclerotic events among all of the patients randomized to ezetimibe/simvastatin versus placebo at any time point (ie, Arm 2 plus 3b vs Arm 1 plus 3a, see Figure 1 of the main article). This should help to reduce the possibility of a false negative result by ensuring that a potential beneficial effect on atherosclerotic outcomes is not diluted by a lack of benefit on nonatherosclerotic components.

Comparisons of ezetimibe/simvastatin versus placebo. The prespecified comparisons involve "intention-to-treat" analyses among all of patients ever randomized to ezetimibe/simvastatin versus all patients allocated to placebo, with stratification by whether patients were initially allocated simvastatin for 1 year (Arm 3b vs Arm 3a) or not (Arm 2 vs Arm 1).

Key outcome. The chief emphasis will be on the effects of ezetimibe/simvastatin on the overall incidence of first major atherosclerotic event (ie, coronary death, MI, ischemic stroke, or any revascularization procedure).

Subsidiary outcomes. In support of the analyses of major atherosclerotic events, analyses will be conducted of:

- the original protocol-defined primary outcome of major vascular events (ie, cardiac death, MI, any stroke, or any revascularization), which will also be analysed separately (as in the original protocol) for Arm 2 versus Arm 1;
- the separate components of major atherosclerotic events:
  - major coronary events (coronary death or nonfatal MI)
  - ischemic stroke
  - coronary or noncoronary revascularization (excluding dialysis access procedures)

The main renal outcome will be end-stage renal disease, which is defined as commencement of long-term dialysis or transplantation among patients not on dialysis at the time of randomization to ezetimibe/simvastatin versus placebo.

Tertiary outcomes and comparisons. It is not anticipated that SHARP will have good power to explore subgroup effects reliably, but tertiary comparisons will assess whether there is definite evidence of variations in the effects of ezetimibe/simvastatin on major atherosclerotic events in different subgroups, based on characteristics at the time of randomization to ezetimibe/simvastatin versus placebo:

- patients who were receiving dialysis and those who were not
- patients with evidence of pre-existing atherosclerotic disease, including: coronary disease (ie, angina); peripheral arterial disease; cerebrovascular disease; at least one of these 3 conditions; none of them
- diabetes and no diabetes
- men and women
- age: 40 to 49, 50 to 59, 60 to 69, $\geq$70
- smokers and nonsmokers
- diastolic blood pressure: <80, 80 to 89, 90 to 99, $\geq$100 mm Hg
- systolic blood pressure: <140, 140 to 159, 160 to 179, $\geq$180 mm Hg
- approximate tertiles of lipid parameters: total cholesterol, LDL-cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides, apolipoprotein B, apolipoprotein A_1
- approximate tertiles of body mass index, waist circumference, hemoglobin, plasma albumin, plasma phosphate
- use of particular drugs, including antiplatelet therapy, oral anticoagulants, angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker, β-blocker, calcium-channel blocker, diuretic, erythropoietin, sevelamer

Subgroup comparisons of the effects on major atherosclerotic events will also be conducted separately among

patients who, at the time of their randomization to ezetimibe/simvastatin versus placebo, were:

(i) on dialysis, subdivided by:
- hemodialysis and peritoneal dialysis

(ii) not on dialysis, subdivided by:
- GFR estimated from modified diet and renal disease equation:[18] ≥60, 30 to 59, 15 to 29, <15 mL/min/1.73 m^2
- approximate tertiles of cystatin C
- normoalbuminuria; microalbuminuria; macroalbuminuria (based on urinary albumin-creatinine ratio)

In addition, subgroup analyses will assess whether the effects on end-stage renal disease of ezetimibe/simvastatin vary according to baseline renal function. Progression to end-stage renal disease is rapid when GFR is already below 15 mL/min per 1.73 m^2 (ie, Kidney Disease Outcomes Quality Initiative[19] stage 5 CKD), so even a large proportional reduction in the rate of progression might result in only a short delay before commencing dialysis. By contrast, for patients with stage 3 CKD (ie, GFR 30-60 ml/min per 1.73 m^2), a small proportional reduction in the rate of progression might correspond to a delay of some months. Hence, exploratory analyses among patients presenting at different stages of CKD will compare both proportional and absolute effects of allocated treatment on the slope of estimated GFR over time and, separately, on the need for dialysis or transplantation.

Tertiary comparisons will also examine the effects of ezetimibe/simvastatin on:

- mortality, both overall and within particular categories of causes of death: cardiac (coronary, other cardiac), stroke (ischemic, hemorrhagic and unknown type), other vascular, neoplastic, renal, other and unknown causes
- cancers, subdivided by site (in categories previously defined in a published interim analysis of SHARP cancers,[27] with appropriate statistical adjustment for multiplicity), and excluding any recurrences of cancers known to be present prior to randomization to ezetimibe/simvastatin
- stroke, both overall and subtypes (ischemic, hemorrhagic, and unknown)
- transient ischemic attacks
- hospital admission for angina and, separately, for heart failure
- development of diabetes among patients who were not known to have it at the time of randomization to ezetimibe/simvastatin
- revision of vascular access for dialysis
- end-stage renal disease or death from any cause and, separately, doubling of plasma creatinine or end-stage renal disease (among those not on dialysis at the time of randomization to ezetimibe/simvastatin).

Additional safety outcomes. In addition to assessing the effects of allocation to ezetimibe/simvastatin on the efficacy and safety outcomes listed above, assessments will be made on:

- muscle-related outcomes:
  - muscle pain or weakness
  - elevations of creatine kinase: >5 but ≤10 × ULN, >10 and ≤40 × ULN, and > 40 × ULN; subdivided into those: without symptoms, with symptoms but no evidence of end-organ damage, with symptoms and evidence of end-organ damage, with symptoms among dialysis patients (when end-organ damage cannot be assessed)
- Liver-related outcomes:
  - hepatitis, subdivided into: infective (definite evidence of an infective cause), noninfective (definite evidence of a non-infective cause), no cause identified (eg, negative viral serology or no serology available)
  - persistently elevated liver transaminases (at least 2 consecutive alanine or aspartate transaminase >3 × ULN without other indication of hepatitis)
- complications of gallstones: acute pancreatitis with gallstones; cholelithiasis requiring hospital admission; other complications of gallstones
- pancreatitis (without gallstones): acute pancreatitis; chronic pancreatitis.

Details of analyses

Analysis of efficacy and safety outcomes. The analyses will involve comparisons of ezetimibe/simvastatin versus placebo during the period for which patients were scheduled to take study medication, irrespective of compliance (ie, "intention-to-treat" analyses[29,30]). Analyses will be based on the first relevant un-refuted event, that is, an event of a particular type will be included in an analysis provided that it has either been confirmed or has not been refuted during the adjudication process. In particular, outcomes that involve MI will include definite, probable and possible cases.

Time-to-event analyses will use log-rank methods[29,30] to calculate average event rate ratios, confidence intervals, and two-sided *P* values. All analyses will be stratified by whether patients were originally randomized to ezetimibe/simvastatin versus placebo (Arm 2 vs Arm 1) or were re-randomized after about 1 year on allocated simvastatin (Arm 3) to ezetimibe/simvastatin versus placebo (Arm 3b vs Arm 3a). Log-rank observed (O) minus expected (E) values and their variances will be calculated for each of the two strata, and the overall log-rank statistic derived as the sum of the log-rank statistics for the 2 strata. The variance for the overall log-rank statistic is the sum of the variances of the log rank (O-E)

for each stratum. The overall log rank (O-E) and its variance will be used to derive the stratified odds ratio, its confidence interval, and 2-sided *P* value.[29,30]

Tests for heterogeneity of effects. The large number of major atherosclerotic events expected in this study may allow direct assessment of the effects of treatment in some subcategories of patient (eg, baseline levels of LDL cholesterol). However, when a number of different subgroups are considered, chance alone may lead to there being no apparent effect in several small subgroups in which the effect of treatment really is about the same as is observed overall. In such circumstances, "lack of direct evidence of benefit" is not good "evidence of lack of benefit," and clearly significant overall results would provide strong indirect evidence of benefit in some small subgroups where the results, if considered in isolation, are not conventionally significant (or, even, perhaps, adverse).[29–31] Hence, unless the proportional effect in some specific subcategory is clearly different from that observed overall, the effect in that subcategory is likely to be best estimated indirectly by applying the proportional effect observed among all patients in the trial to the absolute risk of the event observed among control patients in that category.[29,30] Tests for heterogeneity of the proportional effect on particular outcomes in specific subgroups will be used (with allowance for multiple comparisons and other differences between subgroups) to determine whether the effects in those subgroups are clearly different from the overall effect.[29,30] If, however, such subgroups can be arranged in some meaningful order (eg, baseline renal function) then assessment of any linear trend in the proportional effects on outcome will be made instead. Baseline status of patients will be as measured at the time of their randomization to ezetimibe/simvastatin versus placebo (so, for patients in arm 3, their baseline characteristics will, wherever possible, be updated to reflect their status when re-randomized).

Allowance for multiplicity of comparisons. The key analysis of major atherosclerotic events and the subsidiary analysis of major vascular events (the original primary outcome) will be performed without adjustment for multiplicity. The subsidiary analyses of the separate components of major atherosclerotic events will be assessed with appropriate adjustment for multiplicity using the Hochberg procedure.[32] For the interpretation of tertiary comparisons, allowance will be made for multiple hypothesis testing,[29,30] taking into account the nature of events (including timing, duration and severity) and evidence from other studies. In addition to the prespecified comparisons, many other analyses will be performed, with due allowance for their exploratory and, perhaps, data-dependent nature. Conventionally, 2-sided *P* values <.05 are described as "significant." However, the larger the number of events on which a comparison is based and the more extreme the *P* value (or, analogously, the further the lower limit of the confidence limit is from the null hypothesis) after allowance has been made for the nature of the particular comparison (ie, primary, secondary or tertiary; prespecified or exploratory), the more reliable the comparison and, hence, the more definite any finding should be considered.

Analyses of biochemical efficacy. Biochemical efficacy samples were scheduled to be taken from 10% of the study population at their 1- and 4-year follow-up visits and from all patients at their 2.5-year visits. Absolute changes in plasma lipids between randomization and follow-up are calculated for each patient, with zero change assigned to anyone selected for blood sampling who was alive at the time of the follow-up assessment but failed to provide a sample for any reason (since such patients are likely to have discontinued treatment). Student's *t* test will be used to compare the mean changes observed in the ezetimibe/simvastatin and placebo groups.

Health economic analyses. For the purposes of within-trial economic analyses and assessment of healthcare resource utilization, a summary of all major vascular events, cardiac events, revascularization procedures (coronary or noncoronary), deaths, onset of end-stage renal disease, hospital admission for angina, and hospital admission for heart failure will be derived. A separate analysis plan for determining the costing of these events, sensitivity analyses, subgroup analyses, variance estimation, and statistical testing for treatment comparisons will be developed. In addition to the within-trial analyses, survival analyses will be used to generate a prediction model for the projection of events beyond the trial treatment period and evaluation of the lifetime cost-effectiveness of ezetimibe/simvastatin.

Appendix B. Trial organization

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