VYTORIN® (ezetimibe/simvastatin) and ZETIA® (ezetimibe)

Supplemental New Drug Applications

SHARP (Study of Heart and Renal Protection)

Endocrinologic and Metabolic Drugs Advisory Committee Briefing Document

02-November-2011

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

List of Tables 4
List of Figures 5
List of Abbreviations and Definitions of Terms 6
Study of Heart and Renal Protection (SHARP) Key Dates 9

1. Introduction with Background on ZETIA® (ezetimibe) and VYTORIN® (ezetimibe/simvastatin), including Proposed Indication Based on SHARP 10
2. Summary 12
3. Background 19
3.1 Epidemiology of Cardiovascular Disease in Patients with Chronic Kidney Disease 19
3.2 Use of Lipid-Lowering Agents in Patients with CKD; U.S. Data 21
3.3 Lipid-Lowering Therapy for the Prevention of CVD in Patients with CKD 21
3.4 Lipid-Lowering for Slowing the Progression of Renal Disease 22
4. Study of Heart and Renal Protection (SHARP) 22
4.1 Introduction 22
4.2 Study Participants 24
4.2.1 Inclusion and Exclusion Criteria 24
4.3 Study Design 25
4.4 Evaluation Criteria 26
4.4.1 Protocol-Specified Primary Outcome 26
4.4.2 Key Outcome Specified in the Statistical Analysis Plan (SAP) 26
4.4.3 Secondary Comparisons 26
4.4.4 Tertiary Comparisons 27
4.4.5 Additional Safety Outcomes 28
4.5 Sample Size and Power 28
4.6 Trial Conduct 29
4.6.1 Method of Assigning Subjects to Treatment Groups 30
4.6.2 Determination and Adjudication of Outcomes 30
4.6.3 Recording of Adverse Events 31
4.7 Statistical Analysis 32
4.8 Disposition of Study Participants 37
4.9 Demographic and Other Patient Characteristics 39
4.10 Efficacy 41
4.10.1 Major Vascular Events (MVE) and Major Atherosclerotic Events (MAE) 41
4.10.2 Components of MVE and MAE 45
4.10.3 Subgroup Analyses 51
4.10.4 Renal Endpoints 55
4.10.5 Compliance 55
4.10.6 Lipids and Apolipoproteins 57
4.10.6.1 Lipid and Apolipoprotein Changes at 12 Months 57

4.10.6.2 Lipids and Apolipoproteins Over the Course of the Study 61
4.10.7 Discussion of Efficacy 66
4.10.7.1 SHARP in the Context of Previous Studies in Patients Predominantly Without CKD 66
4.10.7.2 Cardiovascular Outcomes in SHARP in the Context of Previous Studies with Ezetimibe 66
4.10.7.3 SHARP in the Context of Previous Studies in CKD 68
4.10.7.4 Extrapolating the Outcome Results of SHARP to Clinical Practice 69
4.11 Safety 70
4.11.1 Introduction 70
4.11.2 Adverse Event Summary 72
4.11.3 Specific Adverse Events 76
4.11.3.1 Cancer 76
4.11.3.2 Hemorrhagic Stroke 80
4.11.3.3 Myopathy 80
4.11.3.4 Liver and Gall Bladder 83
4.11.3.5 Diabetes and Pancreas 85
4.11.4 Summary of Safety Data 86
5. Benefit-Risk Analysis for Prevention of Major Vascular Events with Ezetimibe/Simvastatin in Patients with CKD 87
6. References 88

List of Tables

		PAGE
Table 1	Comparison of Main Outcomes	15
Table 2	Cardiovascular Outcomes by Treatment Group in All Patients Randomized to Ezetimibe/Simvastatin 10/20 mg or Placebo	17
Table 3	NKF KDOQI Stages of Chronic Kidney Disease	19
Table 4	Reasons for Stopping Study Treatment Before Scheduled End	39
Table 5	Baseline Characteristics and Laboratory Measurements	40
Table 6	Average Use of Study Simvastatin/Ezetimibe 10/20 mg or Non-Study LDL-C Lowering Drug and Average Change From Baseline in Plasma LDL-C	56
Table 7	Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and One Year in Patients Initially Randomized to Ezetimibe/Simvastatin 10/20 mg, Simvastatin 20 mg or Placebo	58
Table 8	Mean ± SE LDL-Cholesterol (mmol/L) at Baseline and Follow-up Visits	62
Table 9	Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and 2.5 Years of Follow-Up	64
Table 10	Principal Safety Data Categories	71
Table 11	Serious Adverse Reactions Attributed to Study Treatment	73
Table 12	Serious Adverse Events that Resulted in Discontinuation of Study Treatment	74
Table 13	Non-Serious Adverse Events that Resulted in Discontinuation of Study Treatment	75
Table 14	Cancer Incidence and Cancer Mortality By Site	77
Table 15	Number of Patients with Myopathy and Rhabdomyolysis ('On-Treatment' Analysis)	82
Table 16	Etiology of Hepatitis ('On-Treatment' Analysis)	84
Table 17	Gallstones: Number (%) of Patients	85
Table 18	Pancreatitis without Gallstones: Number (%) of Patients	86

List of Figures

		PAGE
Figure 1	SHARP Study Design	13
Figure 2	Summary of Patient Accounting	37
Figure 3	Effect of Ezetimibe/Simvastatin 10/20 mg on the Protocol Primary Endpoint MVE in All Patients Excluding Those Originally Randomized to Simvastatin Alone (N=8,384), on the SAP Key Outcome MAE in All Patients (N=9,270), and on the SAP Subsidiary Outcome MVE in All Patients (N=9,270)	42
Figure 4	Effect of Ezetimibe/Simvastatin 10/20 mg on MVE in All Patients Except Those Originally Allocated to Simvastatin Alone (Arm 2 Versus Arm 1)	43
Figure 5	Effect of Ezetimibe/Simvastatin 10/20 mg Versus Placebo on MAE in All Randomized Patients (Arms 2+3b Versus Arms 1+3a)	44
Figure 6	Effect of Ezetimibe/Simvastatin 10/20 mg on the Components of Major Vascular Events in All Randomized Patients	46
Figure 7	Components of MAE and MVE In All Patients Randomized to Ezetimibe/Simvastatin 10/20 mg Versus Placebo	48
Figure 8	Subcomponents of Major Coronary Events, Non-Hemorrhagic Stroke, and Revascularization Procedures	49
Figure 9	MAE by Baseline Characteristics Other Than Renal Function	52
Figure 10	MAE by Baseline Characteristics Other Than Renal Function, Per mmol/L Reduction in LDL Cholesterol	53
Figure 11	MAE by Baseline Renal Status	54
Figure 12	MAE by Baseline Renal Status Per mmol/L Reduction in LDL Cholesterol	55
Figure 13	Cause-Specific and Overall Mortality	72
Figure 14	Cancer Incidence by Year of Follow-Up	78

List of Abbreviations and Definitions of Terms

Abbreviation	Definition
4D	German Diabetes and Dialysis Study
4S	Scandinavian Simvastatin Survival Study
ACE	Angiotension Converting Enzyme
ACR	Albumin:Creatinine Ratio
ACS	Acute Coronary Syndrome
ALT	Alanine Aminotransferase
Apo	Apolipoprotein
ARB	Angiotension Receptor Blocker
AST	Aspartate Aminotransferase
ASTRONOMER	Aortic Stenosis Progression Observation: Measuring the Effects of Rosuvastatin
AURORA	Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft
CASHMERE	Carotid Atorvastatin Study in Hyperlipidemic Post-Menopausal Women: a Randomized Evaluation of Atorvastatin versus Placebo)
CCB	Calcium Channel Blocker
CHD	Coronary Heart Disease
CHF	Congestive Heart Failure
CI	Confidence Interval
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
CSR	Clinical Summary Report
CTSU	Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Medicine, University of Oxford
CTT	Cholesterol Treatment Trialists'
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
E	Expected
EAS	European Atherosclerosis Society
eGFR	Estimated Glomerular Filtration Rate
ENHANCE	Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression Study
ESC	European Society of Cardiology
ESRD	End Stage Renal Disease
Eze/simv	Ezetimibe/Simvastatin
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
gm	Gram

List of Abbreviations and Definitions of Terms (Cont.)

Abbreviation	Definition
HARP	Heart and Renal Protection Study
HDL-C	High-Density Lipoprotein Cholesterol
Het $\chi 2$	Chi-Squared Heterogeneity Test
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HMG-CoA	Hydroxy-methylglutaryl Coenzyme A
HoFH	Homozygous Familial Hypercholesterolemia
HPS	Heart Protection Study
HR	Hazard Ratio
ICH	International Conference on Harmonization
IMPROVE-IT	IMProved Reduction of Outcomes: Vytorin Efficacy International Trial
IMT	Intima-Media Thickness
INR	International Normalized Ratio
ITT	Intention To Treat
LDL-C	Low-Density Lipoprotein Cholesterol
LVH	Left Ventricular Hypertrophy
MAE	Major Atherosclerotic Events
MDRD	Modified Diet and Renal Disease
Mg	Milligram
Mg/dL	Milligrams Per Deciliter
MI	Myocardial Infarction
mmHG	Millimeters of Mercury
mmol/L	Millimoles Per Liter
MRL	Merck Research Laboratories
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MVE	Major Vascular Events
NHANES	National Health and Nutrition Examination Survey
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NSAE	Non Serious Adverse Event
O-E	Difference Between the Observed and Expected
PAD	Peripheral Arterial Disease
PCI	Percutaneous coronary intervention
PTCA	Percutaneous Transluminal Coronary Angioplasty
P-value	Probability Value
PVD	Peripheral Vascular Disease
RADIANCE	Rating Atherosclerotic Disease Change by Imaging with a New CETP Inhibitor Study
RR	Risk Ratio
SAE	Serious Adverse Event
SALTIRE	Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression Study
SAP	Statistical Analysis Plan
SSAR	Suspected Serious Adverse Reaction

List of Abbreviations and Definitions of Terms (Cont.)

Abbreviation	Definition
SE	Standard Error
SEARCH	Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine
SEAS	Simvastatin and Ezetimibe in Aortic Stenosis
SHARP	Study of Heart and Renal Protection
SPARCL	Stroke Prevention by Aggressive Reduction in Cholesterol Levels
SSAR	Suspected Serious Adverse Reaction
TC	Total Cholesterol
TG	Triglycerides
TIA	Transient Ischemic Attack
UK	United Kingdom
UK-HARP	UK-Heart and Renal Protection Study
ULN	Upper Limit of Normal
Var	Variance

Study of Heart and Renal Protection (SHARP)

Key Dates

Event	Date
First dose of double-blind study medication	20-Aug-2003
Last participant randomized	Aug 2006
Steering Committee's decision on primary endpoint	02-Oct-2009
Baseline/1-year safety paper, including finalized SAP, accepted for publication in the American Heart Journal	10-Aug-2010
Last dose of study medication	18-Aug-2010
Unblinding of individual patient outcome data	07-Oct-2010
First public presentation of results	20-Nov-2010
Final database lock	05-Jan-2011
Publication of main results in the Lancet	25-Jun-2011

1. Introduction with Background on ZETIA® (ezetimibe) and VYTORIN® (ezetimibe/simvastatin), including Proposed Indication Based on SHARP

ZETIA® (ezetimibe) is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. ZETIA® was approved in the USA 25-Oct-2002 and is currently indicated as an adjunct to diet to:

- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with primary hyperlipidemia, alone or in combination with an HMG-CoA reductase inhibitor (statin)
- Reduce elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate
- Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin
- Reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)

The recommended dose of ZETIA® is 10 mg once daily. ZETIA® can be administered with or without food.

VYTORIN® contains ezetimibe and simvastatin, an HMG-CoA reductase inhibitor. VYTORIN® was approved in the USA 23-Jul-2004 and is currently indicated as an adjunct to diet to:

- Reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hyperlipidemia or mixed hyperlipidemia.
- Reduce elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid lowering treatments

In VYTORIN® the dose of ezetimibe is fixed at 10 mg, and the dose of simvastatin is 10-80 mg. The usual dosage range is 10/10 mg/day to 10/40 mg/day. The recommended usual starting dose is 10/10 mg/day or 10/20 mg/day. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 10/80-mg dose of VYTORIN® should be restricted to patients who have been taking VYTORIN® 10/80 mg chronically (e.g., for 12 months or more) without evidence of muscle toxicity.

Merck has submitted supplemental applications to the FDA for the use of VYTORIN® and ZETIA® (the latter when given together with simvastatin) to reduce the risk of major cardiovascular events in patients with chronic kidney disease (CKD).

The applications are based on the SHARP (**S**tudy of **H**eart **a**nd **R**enal **P**rotection) study.

SHARP was designed and implemented by the Clinical Trial Service Unit (CTSU) in the Nuffield Department of Clinical Medicine at the University of Oxford, which has successfully conducted numerous cardiovascular outcome trials over a period of about 25 years. The study was funded by a joint venture of Merck and Schering-Plough (the two companies later merged in November 2009 under the Merck name), but the University of Oxford was the regulatory sponsor. The SHARP data are proprietary to CTSU, and CTSU, guided by the SHARP Steering Committee, was responsible for the data analysis plan and the conduct of all analyses. Merck does not have access to the individual patient data and did not independently conduct any analyses of the SHARP data.

SHARP was a randomized, double-blind, placebo-controlled, parallel group, multicenter study of ezetimibe/simvastatin 10/20 mg per day (combination tablet) versus placebo designed to assess the effect of LDL-C lowering on the time to a first major vascular event in patients with CKD. SHARP is the largest clinical trial of VYTORIN™ completed to date, and enrolled a total of 9,438 patients with CKD, a patient group at very high risk for cardiovascular disease. One third were on dialysis at randomization, and of the pre-dialysis patients mean eGFR was 26.6 ml/min/1.73 m^2.

Although patients with CKD are at high risk for developing premature cardiovascular disease, they have generally been excluded from large-scale outcome studies. Prior to the conduct of the SHARP study, it was unclear if LDL-C lowering therapy would be beneficial for patients with CKD. The SHARP study is the first prospective clinical study in patients with CKD to demonstrate the benefit on major vascular events of lowering LDL-C. Overall, the safety profile of ezetimibe/simvastatin 10/20 mg in the SHARP study was consistent with the profile in the approved labels. The SHARP results have been posted to ClinicalTrials.gov: identifier: NCT00125593 and published [1; 2].

As will be shown, the results of the SHARP study provide good evidence that ezetimibe/simvastatin 10/20 mg reduces the risk of major cardiovascular events in patients with chronic kidney disease. Since there are no approved medications to reduce cardiovascular events in patients with CKD, there is a significant unmet medical need in this population.

Based on the data presented herein, the proposed indication for VYTORIN® and ZETIA® for prevention of major cardiovascular events in CKD is as follows:

- VYTORIN is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease
- The combination of ZETIA and simvastatin is indicated to reduce the risk of major cardiovascular events in patients with chronic kidney disease.

2. Summary

This section is a brief introduction to SHARP and its results. More detail will be found in the sections that follow.

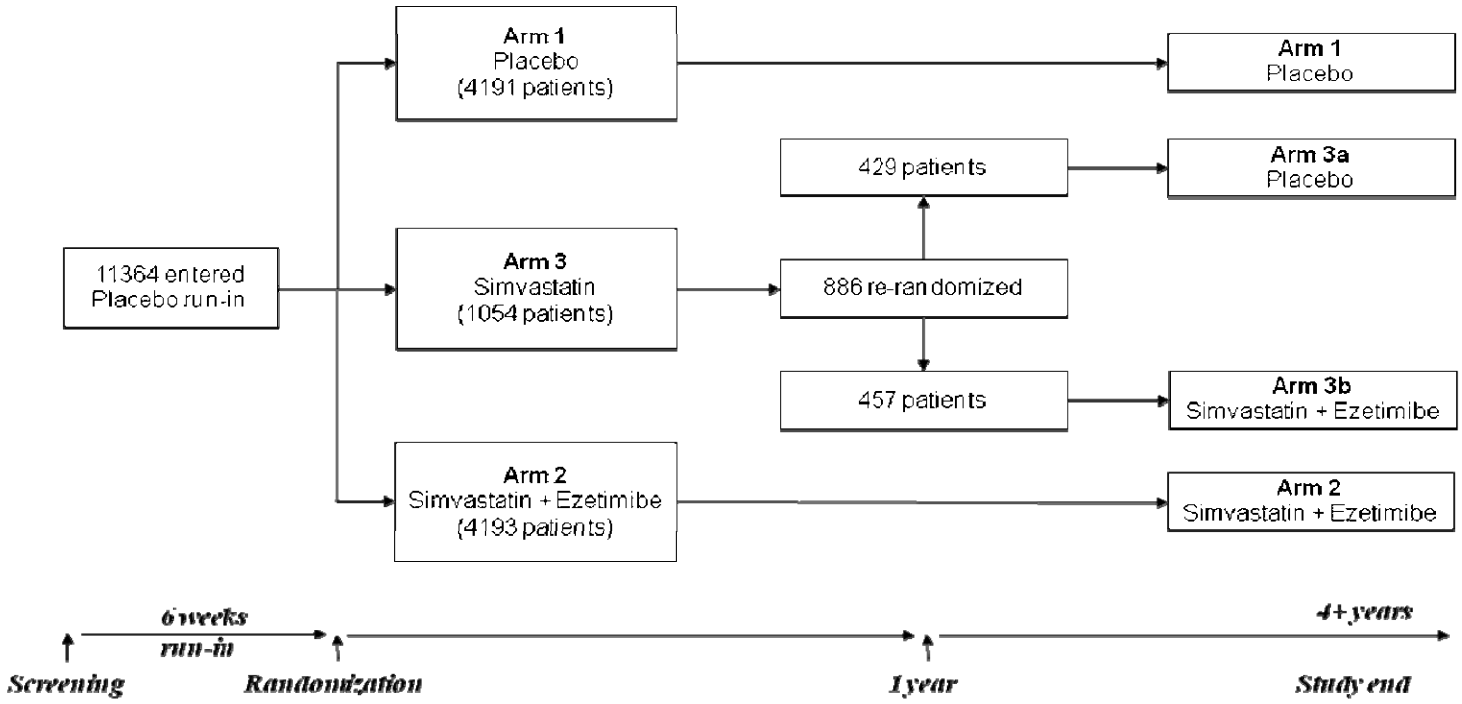
Patients with chronic kidney disease (CKD) are at a greatly increased risk of cardiovascular morbidity and mortality [3; 4; 5; 6], yet have been largely excluded from cardiovascular outcome trials with statins. The rationale for this exclusion includes concerns about reduced elimination of statins and consequently more risk of adverse effects in patients with severely impaired renal function [7], and doubts about the ability of lipid-lowering treatments to affect major components of cardiovascular disease in CKD patients, especially deaths due to arrhythmias or heart failure that may have non-atherosclerotic causes. Therefore, the Study of Heart and Renal Protection (SHARP) was designed to address a clinically important question: can a substantial reduction of low density lipoprotein-cholesterol (LDL-C), achieved with the combination of ezetimibe 10 mg and simvastatin 20 mg, safely reduce cardiovascular risk in patients with CKD?

Study Design:

SHARP was a double-blind, placebo-controlled, multinational, multicenter study in men or women with CKD with no known history of MI or coronary revascularization. Patients were eligible for randomization if (a) the patient's nephrologist did not believe that there was a definite need for, or contraindication to, an HMG-CoA reductase inhibitor ("statin") or ezetimibe; and (b) all eligibility criteria were satisfied. Prior to randomization, potentially eligible patients entered a run-in period during which they received one placebo-ezetimibe/simvastatin tablet and one placebo-simvastatin tablet daily for ~6 weeks. Eligible patients who completed the run-in phase were then randomized to 1 of 3 treatment arms in a 4:4:1 ratio: placebo (Arm 1), ezetimibe/simvastatin 10/20 mg (Arm 2), or simvastatin 20 mg (Arm 3). After 1 year, patients in Arm 3 were re-randomized to 1 of 2 treatment arms in a 1:1 ratio: placebo (Arm 3a) or ezetimibe/simvastatin 10/20 mg (Arm 3b). The main purpose of the 1-year simvastatin alone group was to provide a control group for the assessment of any adverse effects of ezetimibe, should there have been any unexpected adverse effects observed with ezetimibe/simvastatin 10/20 mg. Follow-up visits after randomization were scheduled at 2 and 6 months, and then every 6 months, during a scheduled treatment period of at least 4 years. The study design with actual patient numbers is shown in Figure 1.

Figure 1

SHARP Study Design



Median follow-up (for Simvastatin+Ezetimibe vs Placebo) = 4.9 years

The primary outcome as specified in the protocol was the first major vascular event (MVE) (non-fatal MI or cardiac death, non-fatal or fatal stroke, or revascularization [including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation]) in patients initially randomized to ezetimibe/simvastatin versus placebo. The 'key outcome' (see below and section 4.7) was subsequently pre-specified in the statistical analysis plan (SAP) directed by the SHARP Steering Committee as first major atherosclerotic event (MAE) (non-fatal MI or coronary death, ischemic stroke, or any arterial revascularization procedure). The reasons for this were: first, review of the unblinded lipid measurements at 2.5 years of follow-up showed that the mean LDL-C reduction in the active treatment group relative to the placebo group was 33 mg/dL rather than the anticipated difference of 39 mg/dL, reducing the expected effect on atherosclerotic cardiovascular outcomes; and secondly, review of the blinded data on clinical outcomes found that about one-third of the protocol-defined primary outcome of MVE were non-coronary cardiac deaths or hemorrhagic stroke, neither of which have been found in meta-analyses of trials in patients without CKD to be prevented by statin therapy [8; 9]. Therefore in October 2009, the Steering Committee of SHARP, blind to the effect of study treatment on efficacy endpoints or safety outcomes, recommended changing the protocol-defined primary outcome to exclude non-coronary cardiac death and hemorrhagic stroke. The rationale was to minimize dilution of a potential benefit on atherosclerotic outcomes by a lack of benefit on non-atherosclerotic components. The Steering Committee also agreed to include in the primary analysis all patients allocated to ezetimibe/simvastatin 10/20 mg or placebo at any time point in the study, thus including those who had been randomized to the simvastatin alone arm in the first year.

Merck had a contractual right to decline major changes to the agreed study protocol. The company did not disagree with the scientific arguments for changing the primary endpoint, but after extensive deliberations and consultation with outside experts, declined the Steering Committee's request to modify the primary endpoint in the SHARP protocol (for more detail see 4.7). Therefore the protocol and SAP differ in terms of the composition of the primary endpoint and the number of patients included in the primary analysis, as shown in Table 1. However, as shown below, the risk reductions for MVE and MAE are numerically virtually identical.

Table 1

Comparison of Main Outcomes

	Protocol Primary Outcome	**SAP Key Outcome**
Composite Endpoint	Major vascular events (MVE)	Major atherosclerotic events (MAE)
Endpoint Components	Major *cardiac* events: MI, *cardiac* death	Major *coronary* events: MI, *coronary* death
	Any stroke	*Ischemic* stroke
	Any revascularization procedure*	Any revascularization procedure*
Population Analyzed	All patients randomized to ezetimibe/simvastatin, *excluding* patients initially randomized to simvastatin. Arm 2 vs Arm 1, total N=8,384.	All patients randomized to ezetimibe/simvastatin, *including* 886 patients initially randomized to simvastatin. Arm 2+3b vs Arm 1+3a, total N=9,270.
MVE/MAE Differences	*Includes* non-coronary cardiac death and hemorrhagic stroke, *excludes* patients initially randomized to simvastatin	*Excludes* non-coronary cardiac death and hemorrhagic stroke, *includes* patients initially randomized to simvastatin

*Coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis)

Summary of Results:

Main Efficacy Outcomes

Ezetimibe/simvastatin produced highly significant reductions in both the protocol-specified primary outcome and the SAP key outcome:

Protocol-specified primary outcome, MVE in Arm 2 versus Arm 1 (also a SAP-specified secondary comparison)

Compared to placebo (Arm 1, n=4,191), ezetimibe/simvastatin 10/20 mg (Arm 2, n=4,193) reduced the risk of MVE by 16% (risk ratio 0.84, 95% CI 0.75 - 0.93, p=0.0010).

SAP key outcome, MAE in all patients ever randomized to ezetimibe/simvastatin 10/20 mg versus placebo (Arms 2 + 3b versus Arms 1 + 3a)

Compared to placebo (Arms 1 + 3a, n=4,620), ezetimibe/simvastatin 10/20 mg (Arms 2 + 3b, n=4,650) reduced the risk of MAE in all randomized patients by 17% (risk ratio 0.83, 95% CI 0.74 – 0.94, p=0.0021).

Effects on specific cardiovascular outcomes

The effects of ezetimibe/simvastatin on MVE and MAE and their components and subcomponents are shown in Table 2. The results for MVE shown in this table are marginally different from the protocol-specified primary outcome shown above because all patients randomized are included, as was indicated in the protocol. The protocol stated that this would be done if there was no heterogeneity of the results in those who had or had not been allocated simvastatin prior to randomization to ezetimibe/simvastatin versus placebo, as was the case.

It is important to note that there was insufficient statistical power to reliably detect plausible effects on any of the components and subcomponents, and as expected statistically significant effects were observed on some and not on others. The lack of power is reflected in the wide confidence intervals.

A detailed presentation and discussion of effects on cardiovascular outcomes may be found in Section 4.10.

Table 2

Cardiovascular Outcomes by Treatment Group in All Patients Randomized to Ezetimibe/Simvastatin 10/20 mg or Placebo

Outcome	Eze/Simv 10/20 (N=4650)*	Placebo (N=4620)*	Risk Ratio (95% CI)	P-value
Major Vascular Events (MVE)†	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.0012
Major Atherosclerotic Events (MAE)‖	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.0021
Major Cardiac Events	367 (7.9%)	403 (8.7%)	0.90 (0.78-1.04)	0.16
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Coronary Death	91 (2.0%)	90 (1.9%)	1.01 (0.75-1.35)	0.95
Other Cardiac Death	162 (3.5%)	182 (3.9%)	0.89 (0.72-1.09)	0.26
Major Coronary Events‡	213 (4.6%)	230 (5.0%)	0.92 (0.76-1.11)	0.37
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Ischemic Stroke	114 (2.5%)	157 (3.4%)	0.72 (0.57-0.92)	0.0073
Stroke of Unknown Type	18 (0.4%)	19 (0.4%)	0.94 (0.49-1.79)	0.85
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.0036
Coronary Revascularization	149 (3.2%)	203 (4.4%)	0.73 (0.59-0.90)	0.0027
Non-coronary Revascularization	154 (3.3%)	169 (3.7%)	0.90 (0.73-1.12)	0.36

† MVE are defined as the composite of nonfatal MI, cardiac death, stroke, or any revascularization procedure. Values are slightly different from those shown above under 'Protocol-specified primary outcome' because Arms 3a and 3b are included here.
‡ Major coronary events consist of nonfatal MI and coronary death
‖ MAE are defined as the composite of nonfatal MI, coronary death, ischemic stroke, or any revascularization procedure.
* Eze/simv Arms 2 + 3b; Placebo: Arms 1+3a

Reduction of LDL Cholesterol and the Effect of Non-Compliance

At the midpoint of the study, 2.5 years, which is considered a reasonable surrogate for the average value over the course of the study, the intention to treat (ITT) difference in mean LDL-C between the ezetimibe/simvastatin and placebo groups (Arms 2+3b versus Arms 1+3a) was 0.85 mmol/L (33 mg/dL), representing a 32% difference. In short-term studies, ezetimibe/simvastatin 10/20 mg lowered LDL-C by 52% [10]. In SHARP, the observed effect on LDL-C was reduced by substantial non-compliance (including both participants allocated to ezetimibe/simvastatin who did not take it and participants allocated to placebo who took non-study statin), totaling about one third of the participants at the study midpoint). For this reason, the ITT analysis underestimates the effects on outcomes in patients with CKD taking ezetimibe/simvastatin 10/20 mg daily as prescribed. With full compliance and no non-study statin, the estimated LDL-C reduction would have been about 1.3 mmol/L (50 mg/dL) throughout the study (i.e., 0.85 mmol/L x 3/2). Because the reduction in cardiovascular risk with treatments that lower LDL-C is proportional to the absolute reduction of LDL-C, this suggests that in patients with CKD taking ezetimibe/simvastatin 10/20 mg as prescribed, the expected reduction in the risk of MAE would be about 25% (17% x 3/2).

Safety

Safety parameters were evaluated on an ITT basis, with additional on-treatment evaluations for myopathy, including rhabdomyolysis, and hepatitis.

There were no significant differences between the ezetimibe/simvastatin 10/20 mg and placebo groups on all-cause mortality, or on any specific cause of death.

There were no significant differences in the incidence of cancer overall or at any particular site, or in cancer mortality.

On an on-treatment basis (i.e., in patients compliant with study treatment and not taking non-study statins), the incidence of myopathy (unexplained muscle pain or weakness accompanied by creatine kinase >10xULN) including rhabdomyolysis in the ezetimibe/simvastatin group was 0.17%, compared to 0.065% in the placebo group.

The incidence of consecutive elevations of transaminases >3xULN was 0.65% in the ezetimibe/simvastatin group, compared to 0.56% in the placebo group. There was no suggestion of any increase in non-viral hepatitis or gallstones.

There were no significant effects on the incidence of new onset diabetes, hypoglycemia or other complications of diabetes.

The overall incidence of serious adverse events and adverse events leading to discontinuation of study medication was similar in the two groups. No new adverse effects attributable to ezetimibe/simvastatin were observed in SHARP compared to the well characterized safety profile for this combination drug.

Conclusions

The results of SHARP show that in patients with chronic kidney disease ezetimibe/simvastatin 10/20 mg reduces the risk of major cardiovascular events.

There was no evidence in SHARP for an increase in the risk of cancer, collectively or at any site, or in cancer mortality. There were very few cases of myopathy or rhabdomyolysis in the ezetimibe/simvastatin treatment group, no excess of liver disease, or gallstone complications, and no new adverse effects were found.

Ezetimibe/simvastatin 10/20 mg is thus a well tolerated treatment to reduce the high risk of major cardiovascular events in CKD patients.

3. Background

3.1 Epidemiology of Cardiovascular Disease in Patients with Chronic Kidney Disease

CKD (as defined in Table 3) is associated with increased risk of cardiovascular disease (CVD) morbidity and mortality [11; 12; 6], and the prevalence of CVD is higher in those with lower GFR [6; 13]. A patient with CKD is more likely to have a cardiovascular event and die than to reach end stage renal disease (ESRD) [14]. However, the pathophysiology of CVD in patients with CKD is not completely understood, and CVD in patients with renal impairment is believed to have atherosclerotic and non-atherosclerotic components. In patients with CKD the most common etiology of CVD is congestive heart failure (CHF), especially in older patients [12]. Cardiac arrhythmias are also a common cause of mortality in CKD patients.

Table 3

NKF KDOQI Stages of Chronic Kidney Disease

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

NKF KDOQI = National Kidney Foundation Kidney Disease Outcomes Quality Initiative
GFR = Glomerular filtration rate [15]

In middle-aged patients with ESRD the prevalence of CHF has been estimated to be about 40% and CHF is an independent predictor of death [11]. In a prospective study of 433 patients, mean age 51 years, starting ESRD treatment, 31% had CHF [16]. Other clinical manifestations of CVD in this group of patients at the start of ESRD were coronary artery disease in 14%, angina pectoris in 19%, arrhythmia in 7% and peripheral vascular disease (PVD) in 8%. On echocardiography, 74% had left ventricular hypertrophy (LVH), 32% left ventricular dilatation, and 15% systolic dysfunction. The overall median survival time was about 4 years. Age, diabetes mellitus, CHF, PVD, and systolic dysfunction were independent predictors of mortality.

In patients with end stage renal disease (ESRD, defined as the requirement for maintenance dialysis or a renal transplant) CVD is the single largest cause of mortality. While overall mortality is lower in patients with less severe kidney disease, mortality from CVD is still the principal cause of death, and the absolute risk of death from CVD increases as the severity of renal disease progresses [12]. However, although cardiovascular mortality is mainly due to atherosclerotic coronary heart disease (CHD) in the general population, CHD is not the most common cause of cardiovascular mortality in patients with ESRD [17].

In the United States, in 2006-2008, the unadjusted rate for all cause mortality in patients with ESRD was 155.9 per 1,000 patient years at risk [17]. For all cardiovascular causes of death, the most common cause of death was cardiac arrest (unadjusted rate 34.3) followed by acute MI (rate 8.9), cerebrovascular disease (rate 5.8), cardiac arrhythmia (rate 4.6), congestive heart failure (rate 3.9), cardiomyopathy (rate 3.3), atherosclerotic heart disease (rate 2.5), and other less common causes [17]. It should be noted, however, that the occurrence of new atherosclerotic CHD in advanced CKD can be difficult to determine clinically, mainly because symptoms and signs of myocardial ischemia can occur in the absence of angiographic coronary artery lesions [5], so it is possible that there are misclassification errors in some of the sudden or arrhythmic deaths and that some of these could be due to MI and vice-versa [18].

The increased cardiovascular risk in patients with CKD develops due to increased exposure both to risk factors that result directly from renal damage (e.g. hypertension, proteinuria and dyslipidemia), and, in some patients, from exposures that increase the risk both of CKD and of CVD (e.g. diabetes, cigarette smoking and obesity) [5]. Data from NHANES 1999-2006 show that patients with CKD are 4-5 times more likely to have hypertension than patients without CKD [6]. It is estimated from the NHANES database that about 80% of patients with CKD stages 3-4 have hypertension, but only 20% are aware of having high blood pressure and are receiving adequate treatment [6]. In participants in NHANES 1999-2006 with estimated GFR < 30, 30 to < 45 and 45 to < 60 ml/min/1.73 m^2 , 37, 24, and 17%, respectively, reported having diabetes, compared to 6.1% of those with estimated GFR above 60 [6].

Although the risk of cardiovascular morbidity and mortality is highest in patients with ESRD, CVD develops before end stage renal failure occurs. In two prospective observational studies in adult patients with CKD not on dialysis, mean ages 63 [19] and 56 years [20], approximately one-third of those with moderate reduction in GFR (<60 ml/min/1.73m^2) were found to have a history of CVD (including angina, MI, positive angiography, coronary revascularization, CHF, transient ischemic attack (TIA)/stroke, peripheral arterial disease (PAD) and renovascular disease [19; 20]. The presence of CVD correlated with quicker progression to ESRD [20].

3.2 Use of Lipid-Lowering Agents in Patients with CKD; U.S. Data

Among patients with CKD in the United States, 47-49% were prescribed lipid-lowering agents (predominately statins) in 2008 [14]. Statin use was higher in patients with either diabetes or CVD (57-72%). However, the use of lipid-lowering agents (predominately statins) is lower in patients transitioning to ESRD (31% of patients at 9 months prior to initiation of therapy for ESRD). Furthermore, of CKD patients using lipid-lowering agents before ESRD, approximately two-thirds remain on a lipid-lowering agent 3 months after the onset of therapy for ESRD [21]. This suggests that some patients are taken off lipid-lowering medications after dialysis is started. In patients with ESRD and CVD, statin use is higher. Data from 2007 in patients with ESRD show that statins are prescribed to 55% of patients with acute MI, 61% with PCI, 62% with CABG, 39% with CVA/TIA, and 35% with CHF [22].

3.3 Lipid-Lowering Therapy for the Prevention of CVD in Patients with CKD

Large scale randomized trials in patients with CHD, but without CKD, have shown that lowering LDL-C with a statin reduced the risk of coronary events and ischemic stroke. [23; 24; 25; 26; 27]. Meta-analyses of individual patient data from randomized trials of statin therapy in 90,000 patients, later updated to 170,000, found that lowering cholesterol reduced the incidence of major vascular events (non-fatal MI and fatal CHD, fatal and non-fatal ischemic strokes and coronary revascularization procedures) by about 20% for every 1 mmol/L (39 mg/dL) reduction in LDL-C, irrespective of whether patients had pre-existing CHD [9; 8]. Many of the trials in the meta-analysis excluded patients with moderate or severe GFR reduction (GFR<60 ml/min/1.73m^2), but some evaluated relatively small subgroups with reduced renal function. Most of these patients already had CHD. An analysis was performed of the effect of statins in 26 outcome trials on major vascular events according to eGFR, divided into three categories: <60 mL/min/1.73 m^2, ≥60 to <90 mL/min/1.73 m^2, and ≥90 mL/min/1.73 m^2 [8]. The category <60 mL/min/1.73 m^2 excluded two trials in patients on hemodialysis, 4D [28] and AURORA [29] (which are discussed in Section 4.10.7.3. As expected, event rates in the control groups increased with declining renal function. Patients with reduced renal function experienced proportional benefits similar to those with normal renal function: the risk reduction per mmol/L LDL-C lowering was very similar (22 to 23%) in each of the three categories.

3.4 Lipid-Lowering for Slowing the Progression of Renal Disease

Observational data have suggested that dyslipidemia may be associated with reduced kidney function in the general population and in patients with CKD [30; 31; 32; 33]. Studies in animals have found that high cholesterol diets led to impaired glomerular function, and that treatment with lipid-lowering medication reduced renal injury [34; 35; 36; 37; 38]. Several meta-analyses of randomized trials of statins have found slower deterioration of GFR in statin-treated patients [39; 40; 41]. A review and meta-analysis of 27 randomized controlled trials of statins (with 39,704 participants) that reported assessment of kidney function or proteinuria found a statistically significant slower decline in GFR (a difference of 1.22 ml/min per year; 95% CI 0.44 to 2.00) in patients receiving statins relative to controls [41]. There was also a modest reduction in proteinuria in statin-treated patients that was statistically significant.

4. Study of Heart and Renal Protection (SHARP)

4.1 Introduction

An initial 1-year placebo-controlled pilot study, UK-HARP-I, in 448 patients with CKD [42] showed that simvastatin 20 mg alone could be used safely and effectively in patients with CKD. However, it was recognized [43] that a LDL-lowering regimen that could lower LDL-C substantially more than the 26% observed in that study at one year would provide a better test of the hypothesis that cardiovascular risk in CKD patients could be reduced by prolonged lowering of LDL-C. Increasing the dose of simvastatin was not considered prudent because doubling the dose of any statin produces only an additional mean 6% reduction in LDL-C from the original baseline, while the risk of myopathy in the general population increases slightly with a single doubling of the daily dose to simvastatin 40 mg, and more so with two dose doublings to 80 mg daily [44]. This information was available in prescribing information when SHARP was being designed. Furthermore, post-marketing surveillance has suggested that the risk of myopathy with simvastatin is greater in patients with complicated medical histories [44]. These include patients with CKD, as recently confirmed by the final results of SEARCH, in which the risk of myopathy and "incipient myopathy" combined was 2.5 times greater during treatment with simvastatin 80 mg in patients with an estimated glomerular filtration rate (eGFR)<60 ml/min/1.73 m^2 compared to those with eGFR≥60 ml/min/1.73 m^2 [45]. There is also evidence from a study of lovastatin, which is structurally and pharmacologically closely related to simvastatin, that plasma levels of HMG-Co A reductase inhibitory activity are roughly doubled in patients with CKD [7].

The cholesterol absorption inhibitor ezetimibe was available for prescription in many countries at the time SHARP was designed. This drug was known to be well tolerated with very few adverse effects and no known serious safety issues, and yet would provide an additional mean reduction in LDL-C of approximately 20% when added to therapy with a statin. Using it in a combination product with simvastatin 20 mg was thus an appropriate means to obtaining greater LDL-C reduction than that obtainable with simvastatin alone at any dose, with a high likelihood of a good safety profile during long-term use in renal patients. A second pilot study, UK HARP II [46], was conducted in 203 CKD patients treated for 6 months with ezetimibe/simvastatin 10/20 mg versus

simvastatin 20 mg alone. This study showed that ezetimibe added to simvastatin 20 mg produced an additional 21% reduction of LDL-C from the level achieved with simvastatin monotherapy, with no detectable adverse effects, enabling SHARP to go forward.

The design of SHARP was fully in accordance with current practice. It was designed and implemented by the Clinical Trial Service Unit (CTSU) in the Nuffield Department of Clinical Medicine at the University of Oxford, which has successfully conducted numerous cardiovascular outcome trials over a period of about 25 years. The study was funded by a joint venture of Merck and Schering-Plough (the two companies later merged in November 2009 under the Merck name), but the University of Oxford was the regulatory sponsor. It was fully compliant with Good Clinical Practice Guidelines and applicable regional statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects. An independent data and safety monitoring committee was provided with unblinded analyses at regular intervals.

SHARP was fully double-blind using the double-dummy technique, and most important, with over 9,000 patients in 18 countries and median follow-up in survivors of 4.9 years, it was large and long enough to provide reliable efficacy and safety evidence. The countries participating (and the number of patients randomized) were: Australia (n=1043), Austria (n=111), Canada (n=505), China (n=994), Czech Republic (n=191), Denmark (n=258), Finland (n=93), France (n=264), Germany (n=1678), Malaysia (n=701), Netherlands (n=108), New Zealand (n=285), Norway (n=194), Poland (n=160), Sweden (n=219), Thailand (n=253), United Kingdom (n=1987), and the United States (n=394). One third of the patients were on dialysis at randomization, and of the pre-dialysis patients mean eGFR was 27 ml/min/1.73 m^2, with nearly all having eGFR<60 ml/min/1.73 m^2. The patients in SHARP met the K/DOQI definition of CKD and were at K/DOQI renal insufficiency stages 3-5 [47]. Patients with a definite history of MI and those who had undergone coronary revascularization were excluded because it was thought that the physicians treating such patients might decide to commence LDL-C lowering therapy during the study, which would reduce its power to address the study hypothesis. Consequently, only 15% of randomized patients had any form of clinically apparent atherosclerotic disease at baseline.

4.2 Study Participants

SHARP was designed to evaluate adults with CKD who did not have a history of MI or coronary revascularization.

4.2.1 Inclusion and Exclusion Criteria

Inclusion Criteria

- History of CKD
  - For patients not on dialysis, plasma or serum creatinine ≥150 μmol/L (≥1.7 mg/dL) in men, or ≥130 μmol/L (≥1.5 mg/dL) in women, as measured at the most recent routine clinic visit and at the SHARP screening visit, or
  - Patients on dialysis (hemodialysis or peritoneal dialysis)
- Men or women aged ≥40 years

Exclusion Criteria

- Definite history of MI or coronary revascularization procedure
- Functioning renal transplant, or living donor-related transplant planned
- Less than 2 months since presentation as an acute uremic emergency (but could have been entered later, if appropriate)
- Definite history of chronic liver disease, or abnormal liver function (i.e. ALT>1.5xULN or, if ALT not available, AST>1.5xULN). (Note: Patients with a history of hepatitis were eligible provided these limits were not exceeded.)
- Evidence of active inflammatory muscle disease (e.g. dermatomyositis, polymyositis), or CK>3xULN
- Definite previous adverse reaction to a statin or to ezetimibe
- Concurrent treatment with a contraindicated drug (Note: Patients who were temporarily taking such drugs could be re-screened when they discontinued them, if appropriate.)
  - HMG-CoA reductase inhibitor (“statin”)
  - Ezetimibe
  - 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
  - Cyclosporine

- Child-bearing potential (i.e. premenopausal woman not using a reliable method of contraception.)
- Known to be poorly compliant with clinic visits or prescribed medication
- Medical history that could 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)

4.3 Study Design

For the most part, the design of SHARP was fairly typical of large long-term cardiovascular outcome trials based on the "large simple trial" philosophy, which emphasizes maximizing the number of randomized participants (and thus relevant outcomes) by keeping the measurements to only those needed for adequate assessment, thereby minimizing cost and complexity. The only unusual feature of the design of SHARP was re- randomization after one year of 1 in 9 of the participating subjects who had initially been randomized to simvastatin monotherapy, as previously shown in Figure 1.

The study was a double-blind, placebo-controlled, multicenter study conducted across 18 countries. Patients were eligible for randomization into SHARP if: (a) their nephrologist did not believe that there was a definite need for, or contraindication to, an HMG-CoA reductase inhibitor ("statin") or ezetimibe; and (b) all inclusion criteria were satisfied while no exclusion criterion applied.

Prior to randomization, potentially eligible patients entered a run-in period during which they received one placebo-ezetimibe/simvastatin combination tablet and one placebo-simvastatin tablet daily for about 6 weeks. Eligible patients who completed the run-in phase were initially randomized in a 4:4:1 ratio to placebo (4191 patients, Arm 1) ezetimibe/simvastatin 10/20 mg (4193 patients, Arm 2), or for one year only, simvastatin 20 mg alone (1054 patients, Arm 3). At 1-year after their randomization, 886 patients (those who were willing and without a medical reason to stop) of the 1054 patients initially randomized to simvastatin 20 mg alone were re-randomized to ezetimibe/simvastatin 10/20 mg or placebo. Therefore, of the total of 9,270 patients randomized to these two groups, 886 (9.6%) had previously been randomized to simvastatin 20 mg alone for 1 year. The purpose of including simvastatin 20 mg alone for the first year of the study was primarily to provide a safety control for ezetimibe/simvastatin 10/20 mg, should some unexpected adverse effect of the latter emerge; in that event, the comparison of these 2 arms would provide a randomized comparison of ezetimibe versus placebo on a background of simvastatin. This would facilitate discrimination between a new adverse effect of simvastatin specific to CKD patients and an adverse effect specific to ezetimibe. No unexpected adverse effects were observed, so the simvastatin 20 mg alone arm was a reasonable precaution but in retrospect not needed. However, it did allow assessment of the proportion of LDL-C reduction attributable to the components of ezetimibe/simvastatin in this population, using the baseline and 1-year lipid measurements in the 3 initial treatment arms. There was no intention to compare cardiovascular outcomes in the three arms at 1 year, as such

an analysis would have been futile due to grossly inadequate statistical power and the lag time between starting lipid-lowering treatment and cardiovascular risk reduction.

4.4 Evaluation Criteria

The primary comparison specified in the protocol differs from the key outcome specified in the SAP (written before unblinding) for the reasons noted briefly in Section 2 (Summary) and in more detail below in Section 4.7 (Statistical Analysis). Table 1 in Section 2 shows the differences between these endpoints and comparisons. The study design appears first in Section 2, Figure 1.

4.4.1 Protocol-Specified Primary Outcome

The protocol-specified primary outcome was of the effect of treatment on MVE, (comprising non-fatal MI or cardiac death, non-fatal or fatal stroke, or revascularization procedures including coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis) during the scheduled treatment period of at least 4 years in patients originally allocated to ezetimibe/simvastatin 10/20 mg (Arm 2) versus patients originally allocated to placebo (Arm 1).

4.4.2 Key Outcome Specified in the Statistical Analysis Plan (SAP)

Based on blinded review during the trial, as described in section 4.7, the independent Steering Committee decided that for the SAP the chief emphasis was to be on the effects in <u>all</u> patients randomized to ezetimibe/simvastatin 10/20 mg versus placebo (i.e., Arms 2+3b versus Arms 1+3a) on the overall incidence of first MAE, which is a composite endpoint comprising major coronary events (i.e., coronary death or non-fatal MI), ischemic stroke, or any revascularization procedure. The endpoint corresponds to MVE minus non-coronary cardiac deaths and hemorrhagic stroke.

4.4.3 Secondary Comparisons

- The original protocol-specified primary outcome of MVE in patients initially allocated to ezetimibe/simvastatin (Arm 2) versus placebo (Arm 1), and also MVE in all patients ever randomized to ezetimibe/simvastatin versus placebo (Arms 2+3b versus Arms 1+3a). The separate components of MVE are evaluated in the entire study population as secondary or tertiary outcomes.
- The separate components of MAE (major coronary events [coronary death or non-fatal MI], ischemic stroke, coronary or non-coronary revascularization) in all patients ever randomized to ezetimibe/simvastatin versus placebo.
- End-stage renal disease (ESRD), defined as commencement of long-term dialysis or transplantation in patients not on dialysis at the time of randomization, in all patients ever randomized to ezetimibe/simvastatin versus placebo.

4.4.4 Tertiary Comparisons

It was not anticipated that SHARP would have good power to explore subgroup effects reliably, but tertiary comparisons assessed whether there was definite evidence of variations in the effects of ezetimibe/simvastatin 10/20 mg on MAE 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 or without evidence of pre-existing atherosclerotic disease, including: coronary disease (i.e., angina); PAD; cerebrovascular disease
- Diabetes and no diabetes
- Men and women
- Age: 40-59; 50-59; 60-69; ≥70
- Smokers and non-smokers
- Diastolic BP: <80; 80-89; 90-99; ≥100 mm Hg
- Systolic BP: <140; 140-159; 160-179; ≥180 mm Hg
- Approximate tertiles of lipid parameters: total cholesterol; LDL-C; HDL-C; non-HDL-C; TG; apolipoprotein B; apolipoprotein A1
- Approximate tertiles of: BMI; waist circumference; hemoglobin; plasma albumin; plasma phosphate
- Use of particular drugs, including: antiplatelet therapy; oral anticoagulants; ACE inhibitor or angiotensin-receptor blocker ARB; beta-blocker; calcium channel blocker (CCB); diuretic; erythropoietin; sevelamer
- Patients on dialysis (subdivided by hemodialysis and peritoneal dialysis) versus those not on dialysis (subdivided by GFR estimated from MDRD equation ≥60; 30-59; 15-29; <15 ml/min/1.73m^2 , approximate tertiles of cystatin C, and by normoalbuminuria, microalbuminuria, and macroalbuminuria [based on the urinary albumin: creatinine ratio])
- Baseline renal function (estimated GFR ≥60 , 30-59, 15-29, <15 ml/min/1.73 m^2)

Tertiary comparisons also examined 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;
- Cancer, subdivided by site (in categories previously defined in a published interim analysis [48] of SHARP cancers, excluding any recurrences of cancers known to be present prior to randomization to ezetimibe/simvastatin.

- Stroke, both overall and subtypes (ischemic, hemorrhagic and unknown)
- TIA
- 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
- ESRD or death from any cause and, separately, doubling of plasma creatinine or ESRD (among those not on dialysis at the time of randomization to ezetimibe/simvastatin).

4.4.5 Additional Safety Outcomes

In addition to assessing the effects of allocation to ezetimibe/simvastatin on the efficacy and safety outcomes listed above, the SAP specified that assessments were to be made on:

- Muscle-related outcomes:
  - Muscle pain or weakness
  - Elevations of CK: >5 but ≤10xULN; >10 and ≤40xULN; and >40xULN; 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); non-infective (definite evidence of a non-infective cause); no cause identified (e.g., negative viral serology or no serology available)
  - Persistently elevated liver transaminases (at least 2 consecutive ALT or AST >3xULN 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.

4.5 Sample Size and Power

The sample size of approximately 9000 patients, including 6000 patients not on dialysis and about 3000 patients on dialysis was based upon the estimation of the event rate. The annual event rate for the original primary endpoint (MVE) was estimated to be about 3.7% based on a 3% per annum event rate for pre-dialysis patients and a 5% per annum event rate for dialysis patients. A study with at least 1100 events and all patients followed for at least 4 years was estimated to provide 90% power to detect a 20% proportional reduction with an alpha level of 0.01.

9,438 patients with CKD were initially randomized in a ratio of 4:4:1 to ezetimibe/simvastatin 10/20 mg (Arm 2; n=4193) versus matching placebo (Arm 1; n=4191) versus simvastatin 20 mg daily (Arm 3; n=1054). Of 1,054 patients initially randomized to simvastatin 20 mg (Arm 3), 429 patients were re-randomized at 1 year to placebo (Arm 3a) and 457 patients to ezetimibe/simvastatin 10/20 mg (Arm 3b). Therefore, of the total of 9,270 patients randomized to ezetimibe/simvastatin 10/20 mg (n=4650) versus placebo (n=4620), 886 (9.6%) had previously been randomized to simvastatin 20 mg alone for 1 year. The disposition of patients in the trial is displayed in Figure 2 (Section 4.8).

4.6 Trial Conduct

Potentially eligible patients were identified from medical records and invited to attend a screening clinic appointment at which medical history and eligibility criteria were assessed, written informed consent obtained, and non-fasting blood samples taken for local laboratory assays. Single-blind study placebo tablets were dispensed for a 6-week run-in period to identify patients who were non-compliant and could be excluded prior to randomization, thereby improving statistical power. Ethical approval was obtained from all study sites prior to enrollment. At the end of the run-in period, patients were initially randomized to placebo (Arm 1), ezetimibe 10 mg daily combined with simvastatin 20 mg daily (ezetimibe/simvastatin 10/20mg) (Arm 2), or simvastatin 20 mg daily (Arm 3). After one year, patients initially allocated to simvastatin alone were re-randomized to placebo (Arm 3a) or ezetimibe/simvastatin 10/20 mg (Arm 3b).

Randomization occurred between August 2003 and August 2006. After randomization, participants were evaluated in the study clinics for routine follow-up checks and blood safety monitoring at 2, 6 and 12 months and then every 6 months for at least 4 years. The final follow-up visits occurred between March and August 2010. For participants requiring additional tests or evaluations, early recall visits were arranged. At each follow-up visit, compliance with study treatment was estimated, unexplained muscle pain and non-study treatment recorded, and weight and blood pressure measured. Non-fasting blood samples were taken for local laboratory assay of CK, liver transaminases, and creatinine. Lipid profiles were measured by the central laboratory at randomization in all participants, in about 10% of participants attending study visits at 1 and 4 years after the initial randomization, and in all participants attending the 2.5 year clinic visit. Differences between the treatment groups in average blood lipid concentrations were based on comparisons between all patients allocated ezetimibe/simvastatin 10/20 mg and all allocated placebo irrespective of whether they were still compliant. Missing data were imputed from the initial randomization values, because failure to attend the clinic strongly suggested non-compliance. Urine samples were taken at the randomization visit and at 2.5 years for central laboratory analysis of albumin and creatinine (in patients not on dialysis and in dialysis patients able to pass urine).

At each follow-up visit, information was recorded about any reported myocardial infarction, stroke, vascular procedure, cancer, other reasons for hospitalization, or other serious adverse events. For participants who were unwilling or unable to attend follow-up visits, information about potential serious adverse events was obtained from them or from a relative or care-giver by telephone, or from their own doctors until the scheduled end of the study. Local study staff sought to obtain additional information from hospital records and other sources about all reported serious adverse events that might relate to study outcomes (i.e., death, myocardial infarction, cardiac arrest, angina, heart failure, stroke, transient ischemic attack, revascularization procedures, angiography, amputation, initiation of dialysis, kidney transplant, renal failure, cancer, myopathy, rhabdomyolysis, hepatitis, gallstones, and pancreatitis). This information was sent to the CTSU for central adjudication, by trained clinicians who were blinded to study treatment allocation.

4.6.1 Method of Assigning Subjects to Treatment Groups

At the end of the run-in period, eligible patients who agreed to continue in the trial were allocated to the study treatment (placebo, ezetimibe/simvastatin 10/20 mg, or simvastatin 20 mg) by the local study laptop computer with minimized randomization [49] which balanced for age, sex, ethnic origin, dialysis versus non-dialysis, previous vascular disease, previous diabetes, systolic blood pressure, creatinine, and total cholesterol. A double-dummy method was employed in order to ensure that patients and study staff remained unaware of the treatment allocation. After being in the trial for about one year, all patients discontinued the tablet containing simvastatin or matching placebo; and those patients who were previously in Arm 3 and therefore allocated to simvastatin 20 mg daily alone in the first year were randomized to either ezetimibe/simvastatin or placebo. Since all patients were unaware of their allocated treatment throughout the trial, patients did not know whether they had been allocated to Arm 3 and hence were not alerted to any change of LDL-lowering therapy after one year (and nor were the study staff).

4.6.2 Determination and Adjudication of Outcomes

<u>Confirmation of All Deaths and Relevant Non-Fatal SAEs</u>

The local clinic staff sought additional information from the hospital records and other appropriate sources about all deaths, and non-fatal SAEs that were outcome measures. Copies of supporting documentation for these events were reviewed by physicians trained in SHARP adjudication methods who followed a specific set of procedures. Where possible, the certified cause of death and details about non-fatal cancers were also sought from national registries and other relevant sources.

<u>Central Verification of Study Outcomes</u>

The team responsible for adjudication reviewed, blind to treatment allocation, the specified causes of all deaths and any SAE reported by the local centers that might represent any of the following conditions: MI, acute coronary syndrome (ACS)/hospitalization with angina, heart failure/pulmonary edema/congestive cardiac failure, cardiac arrest, chest pain, ventricular tachycardia, cor pulmonale, any stroke, TIA, amaurosis fugax, subarachnoid hemorrhage, spontaneous subdural hematoma, any revascularization procedure (excluding dialysis access procedures), any angiogram, any

amputation, initiation of dialysis, kidney transplantation, acute on chronic renal failure, any cancer or treatment of cancer, rhabdomyolysis or myopathy, any hepatitis, cirrhosis/chronic liver disease, liver problem, jaundice, or any gallbladder disease (i.e., cholecystectomy or complications of gall-stones), any pancreatitis, and any serious adverse event with insufficient details. The adjudication was done, in accordance with a detailed Standard Operating Procedure for event adjudication in SHARP, by a small group of CTSU-trained physicians working on SHARP, with the help of language translation from collaborators.

Cardiac deaths were comprised of coronary death (death due to MI, and death believed to be due to coronary atherosclerosis even if the criteria for MI were not met) and other cardiac deaths (when the criteria for MI were not met and the cause of cardiac death was not believed to be due to atherosclerotic heart disease). Coronary death included death following admission with ACS/angina, death from ischemic cardiomyopathy, death due to MI, and death from ischemic heart disease that did not meet the definition for acute MI. Other cardiac death included death from non-ischemic cardiomyopathy or HF, and death from heart disease without evidence of underlying coronary atherosclerosis (e.g. sudden cardiac death), death from cardiac arrest, ventricular tachycardia or other arrhythmia with no evidence of underlying coronary disease, and death from other cardiac diseases (e.g., valvular heart disease). Despite the detailed criteria for adjudication, in this CKD population it was not always possible to distinguish cardiac from non-cardiac deaths and coronary deaths from other cardiac deaths. If in doubt, the adjudicators defaulted to ‘non-cardiac’ and ‘other cardiac’.

Stroke was coded when there was a rapid or uncertain onset of a focal or global neurological deficit lasting more than 24 hours or leading to death. Hemorrhagic stroke was diagnosed by evidence from brain imaging or post mortem study of primary intracerebral or intracerebellar hemorrhage. Ischemic stroke was diagnosed when evidence from neuro-imaging or post mortem study excluded primary intracerebral and/or cerebellar hemorrhage or another cause (such as tumor). Evidence of cerebral and/or cerebellar infarction was not required. Evidence of hemorrhagic transformation of an infarct was coded as ischemic stroke. Stroke without data from neuro-imaging or a post-mortem study was classified as unknown stroke.

4.6.3 Recording of Adverse Events

In SHARP, all serious adverse events (SAEs) were recorded. For non-serious AEs, only those that led to discontinuation of study treatment were recorded. Also recorded were adverse events of special interest, which may or may not have been reported as SAEs. These included muscle symptoms, pancreatitis, complications of gallstones, hepatitis, development of diabetes, complications of diabetes, revision of vascular access for dialysis, and CK elevations >10 times ULN. The procedure for confirmation of all deaths and relevant non-fatal SAEs that were collected as study outcomes is described in the preceding section, 4.6.2.

Serious Adverse Events

In the context of SHARP, an adverse event means any unfavorable and unintended change in the structure (signs), function (symptoms), or chemistry (laboratory data) of the body temporally associated with any use of a study treatment (i.e., a study drug), **whether or not considered related to the use of the study treatment and regardless of whether the patient was taking study drug at the time the adverse event occurred**.

A serious adverse event (SAE) is any adverse event or experience occurring at any dose that:

- **results in death**; or
- **is life threatening**; or
- **results in a persistent or significant disability/incapacity**; or
- **requires inpatient hospitalization or prolongation of existing hospitalization**
- **results in a congenital anomaly/birth defect; or**
- **constitutes an 'other important medical event'** in the opinion of the responsible investigator (i.e., any event that is not immediately life-threatening and does not result in death or hospitalization, but which may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above). Examples of particular relevance to the SHARP study include cancers, myopathy, rhabdomyolysis, cholecystectomy or complications of gallstones, and hepatitis.

4.7 Statistical Analysis

Statistical/analytical Methods

The SHARP data are proprietary to CTSU, and by contractual agreement Merck does not have access to the database. All analyses were conducted by CTSU, which has supplied the unblinded data to FDA as part of the regulatory submission.

The statistical techniques used in SHARP are standard for cardiovascular outcome trials. Patients were allocated to treatments based on a minimized randomization method [49], which CTSU has previously used in the Heart Protection Study (HPS) [26] and SEARCH [50]. Data were collected in the clinics using a laptop computer-based case report form system programmed specifically for SHARP and designed to minimize data entry errors, and added to the central database in Oxford by encrypted data transfer to a dedicated, secure computer. Adjudication of endpoints was performed blind to treatment allocation according to detailed standard operating procedures. All analyses of efficacy outcomes and lipid changes were based on the intention-to-treat principle. Analyses were based on the first relevant, un-refuted endpoint event; that is, an event of a particular type that was either established during the adjudication process, or, in the small minority of cases when sufficient information for adjudication could not be obtained, the event as reported by the local research staff. Stratified log-rank method was employed for analyzing time-to-event endpoints to calculate average event rate ratios, confidence intervals and 2-sided p-values [51; 52]. Except where otherwise stated, analyses were of all patients ever randomized to ezetimibe/simvastatin versus placebo, with stratification by whether

patients were originally randomized to ezetimibe/simvastatin versus placebo (Arm 2 versus Arm 1) or were re-randomized after about 1 year on allocated simvastatin to ezetimibe/simvastatin versus placebo (Arm 3b versus 3a). Log-rank observed (O) minus expected (E) values and their variances were calculated for each of the two strata, and the overall log-rank statistic was derived as the ratio of the sum of the (O-E) to the sum of the variances of (O-E) from each stratum. The overall log rank (O-E) and its variance was used to derive the stratified risk ratio, its confidence interval and 2-sided p-value. Events that had occurred in the simvastatin only arm (Arm 3) prior to re-randomization to ezetimibe/simvastatin versus placebo did not contribute to the randomized comparison of ezetimibe/simvastatin versus placebo, but were used to update the baseline status at the time of re-randomization to placebo (Arm 3a) or ezetimibe/simvastatin (3b).

Handling of Missing Data

The trial used an ITT approach in that all randomized patients were to be followed for outcome information until the scheduled final follow-up visit regardless of whether or not they continued on study therapy. Patients who were lost to follow-up were included in outcome analyses by censoring their observation period.

Difference in change in biochemical efficacy parameters (i.e., lipids and apolipoproteins) between ezetimibe/simvastatin and placebo were analyzed using Student's t-test. In the analysis of change in plasma lipids, a change score of zero was imputed for patients missing specific follow-up measurements since such patients were considered likely to have discontinued treatment.

Multiple Comparisons/Multiplicity

Multiplicity adjustment was not employed in the evaluation of the original primary endpoint for MVE or for the key outcome analysis of MAE specified in the SAP. The Hochberg procedure was employed for the evaluation of the separate components of MAE, as outlined in the SAP. For the interpretation of tertiary comparisons, allowance was made for multiple hypotheses testing, taking into account the nature of events (including timing, duration and severity) and evidence from other studies. In addition to the pre-specified comparisons, other analyses were performed, with due qualitative allowance for their exploratory and, perhaps, data-dependent nature.

The Protocol-Specified Primary Endpoint, and the SAP-specified Key Outcome

As briefly explained in Section 2 (Summary), the primary comparison specified in the protocol differs from the key outcome specified in the SAP (written before unblinding). The primary endpoint specified in the protocol was MVE, defined as "the composite of non-fatal MI 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)" during the scheduled treatment period of at least 4 years in patients initially allocated ezetimibe/simvastatin 10/20 mg (Arm 2) versus placebo (Arm 1). SHARP is overseen by an independent Steering Committee which includes nephrologists, cardiologists, clinical trialists and statisticians, with two non-voting observers from Merck. The independent sponsor is the University of Oxford and the trial was funded by a joint venture of Merck and Schering Plough; the two companies merged in November 2009 under the Merck name. In accordance with ICH

guidelines [53], blinded aggregate endpoint event rates (i.e., for both treatment groups combined) and the unblinded effects of treatment on LDL-C were monitored during the trial to ensure that the statistical power was maintained and that the original assumptions underlying the design of the trial remained plausible. (Note, however, that all investigators remained blind to individual patient allocations and to the effects of treatment on clinical outcomes.) The ICH E9 guidelines [53] state that until a trial is unblinded, it is appropriate to make changes to help the trial provide more reliable information about the effects of treatment. The LDL-C reduction at 2.5 years (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) [1], reducing the expected effect on atherosclerotic cardiovascular outcomes. In addition, review of blinded data on clinical outcomes found that about one-third of the original protocol-defined primary outcome of MVE were events adjudicated to be non-coronary cardiac deaths or hemorrhagic stroke [1], which have been found in trials in patients with or without CKD not to be prevented by statin therapy [28; 8; 29].

Based on these considerations, on 02-Oct-2009 (about 11 months before the last patient visit) the Steering Committee of SHARP, blind to the effect of study treatment on efficacy or safety outcomes (other than group level effects on lipids, as indicated above, and the pre-specified 1-year safety assessment), recommended changing the primary outcome from MVE to MAE, defined as the combination of major coronary events (coronary death and MI), ischemic (i.e. non-hemorrhagic) stroke, or any revascularization procedure. Thus the new proposed primary outcome excluded non-coronary cardiac death and hemorrhagic stroke [54]. The rationale was to avoid, as far as possible, dilution of a potential benefit on atherosclerotic outcomes by a lack of benefit on non-atherosclerotic components.

A large majority of the Steering Committee [54] felt that its recommendation to change the primary study endpoint was consistent with ICH guidelines to ensure 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" [53]. The contract between the University of Oxford, and the funding source, Merck, required the consent of Merck for any significant change to the study protocol. Merck did not disagree with the scientific arguments for changing the primary endpoint. However, after extensive deliberations and consultation with outside experts, Merck declined the Oxford request to modify the primary endpoint in the SHARP protocol, given general concerns around late-stage changes to primary endpoints in outcomes studies and the belief that the relevant findings of SHARP could be scientifically communicated without such a change. This decision was communicated to the Oxford investigators in June 2010. Both Merck and the Oxford investigators regarded the issue not as contentious but rather as one on which knowledgeable people could reasonably differ; indeed within the Steering Committee itself there had been a small minority of dissenters at its meeting of 02-Oct-2009 [54].

The investigators were then left to reconcile the decision of their independent Steering Committee to change the protocol-defined primary endpoint with Merck's decision to decline the proposed protocol change. The SHARP protocol specified the production of an analysis plan that "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". In July-August 2010, while still blinded, the Oxford investigators wrote a SAP specifying, as directed by the Steering Committee, that the chief emphasis of the analyses would be the key outcome of MAE, in all patients ever randomized to ezetimibe/simvastatin 10/20 mg versus placebo (Arms 2+3b versus Arms 1+3a), with the primary endpoint as defined in the protocol retained as one of the subsidiary analyses. The decision to include in the key outcome the 886 patients initially randomly allocated to simvastatin 20 mg alone and then re-randomized to ezetimibe/simvastatin (Arm 3b) versus placebo (Arm 3a) after 1 year was made to increase the power of the trial slightly further. These proposed changes to the primary outcome were estimated to reduce the probability of a false negative result from approximately 1 in 3 to 1 in 8 [1]. The protocol-defined primary endpoint and the SAP key outcome have earlier been compared and contrasted in the Summary (Section 2, Table 1); this table is repeated below.

Table 1

Comparison of Main Outcomes

	Protocol Primary Outcome	**SAP Key Outcome**
Composite Endpoint	Major vascular events (MVE)	Major atherosclerotic events (MAE)
Endpoint Components	Major *cardiac* events: MI, *cardiac* death	Major *coronary* events: MI, *coronary* death
	Any stroke	*Ischemic* stroke
	Any revascularization procedure*	Any revascularization procedure*
Population Analyzed	All patients randomized to ezetimibe/simvastatin, *excluding* patients initially randomized to simvastatin. Arm 2 vs Arm 1, total N=8,384.	All patients randomized to ezetimibe/simvastatin, *including* 886 initially randomized to simvastatin. Arm 2+3b vs Arm 1+3a, total N=9,270.
MVE/MAE Differences	*Includes* non-coronary cardiac death and hemorrhagic stroke, *excludes* patients initially randomized to simvastatin	*Excludes* non-coronary cardiac death and hemorrhagic stroke, *includes* patients initially randomized to simvastatin

*Coronary or non-coronary angioplasty or grafting, and non-traumatic amputation (but excluding vascular access surgery for dialysis)

The SHARP SAP was included as an appendix to a paper summarizing the study design, baseline characteristics of the study population, lipid changes, and one year safety data, which was finalized and accepted for publication on 10-Aug-2010. The paper and SAP appeared in print in November 2010 [1], but were available online on 18-Sep-2010, preceding the unblinding of individual patient outcome data, which commenced on 07-Oct-2010 (C. Baigent, personal communication, 27-Jan-2011). As previously noted, group level unblinding was performed by the study statistician for the purpose of tracking between-group lipid differences over the course of the trial, as well as publishing 1-year safety data; however, outcome endpoints remained blinded, and the clinic staff and the Oxford clinicians responsible for adjudicating endpoints remained blinded throughout. The main results of the study were presented to the Steering Committee on 21-Oct-2010 and to the American Society of Nephrology on 20-Nov-2010 [55]. The full study results were published by the investigators and all other members of the Steering Committee in June 2011 [2]. The authors focused on the analyses specified in the SAP, and therefore placed the chief emphasis on the overall incidence of first MAE in all patients ever randomized to ezetimibe/simvastatin 10/20 mg versus all patients allocated to placebo.

The end result is that the protocol and SAP are not completely concordant. However, the Clinical Study Report (CSR) submitted to FDA presented both the primary endpoint as defined in the protocol and the outcome of chief emphasis specified in the SAP, as well as the subsidiary and tertiary outcomes described in the latter. Having declined to agree to the modification of the protocol primary endpoint, Merck considered itself bound to the protocol-specified endpoint for the purpose of proposing modifications to prescribing information.

As discussed in Section 4.10, the effects of ezetimibe/simvastatin on cardiovascular risk in SHARP are very similar numerically regardless of whether the emphasis is on the primary endpoint as defined in the protocol or the key outcome of the SAP, and highly significant in both cases. Therefore, although discordance between the protocol of an outcome study and its SAP is unusual, in this case it does not complicate interpretation of the results (although inevitably the presentation of the data is more complex than usual). Furthermore, the discordance is a clear demonstration of the independence of the Oxford investigators from the funding source, Merck.

The CSR submitted to FDA contains extensive subgroup analyses by baseline characteristics based both on the key outcome of the SAP (MAE) and on the primary endpoint of the protocol (MVE), but as in the published paper [2] this background document limits the analyses of subgroups to the most important baseline characteristics and presents the results only for MAE. This is appropriate as the results of SHARP will be presented to the Advisory Committee by the study sponsor, the University of Oxford, whose investigators are responsible for the SAP. Because the results are so similar whether the subgroup analyses are based on the SAP or the protocol, presenting complete analyses based on both would have added no useful information, while making this document unnecessarily long and cumbersome.

4.8 Disposition of Study Participants

Figure 2

Summary of Patient Accounting

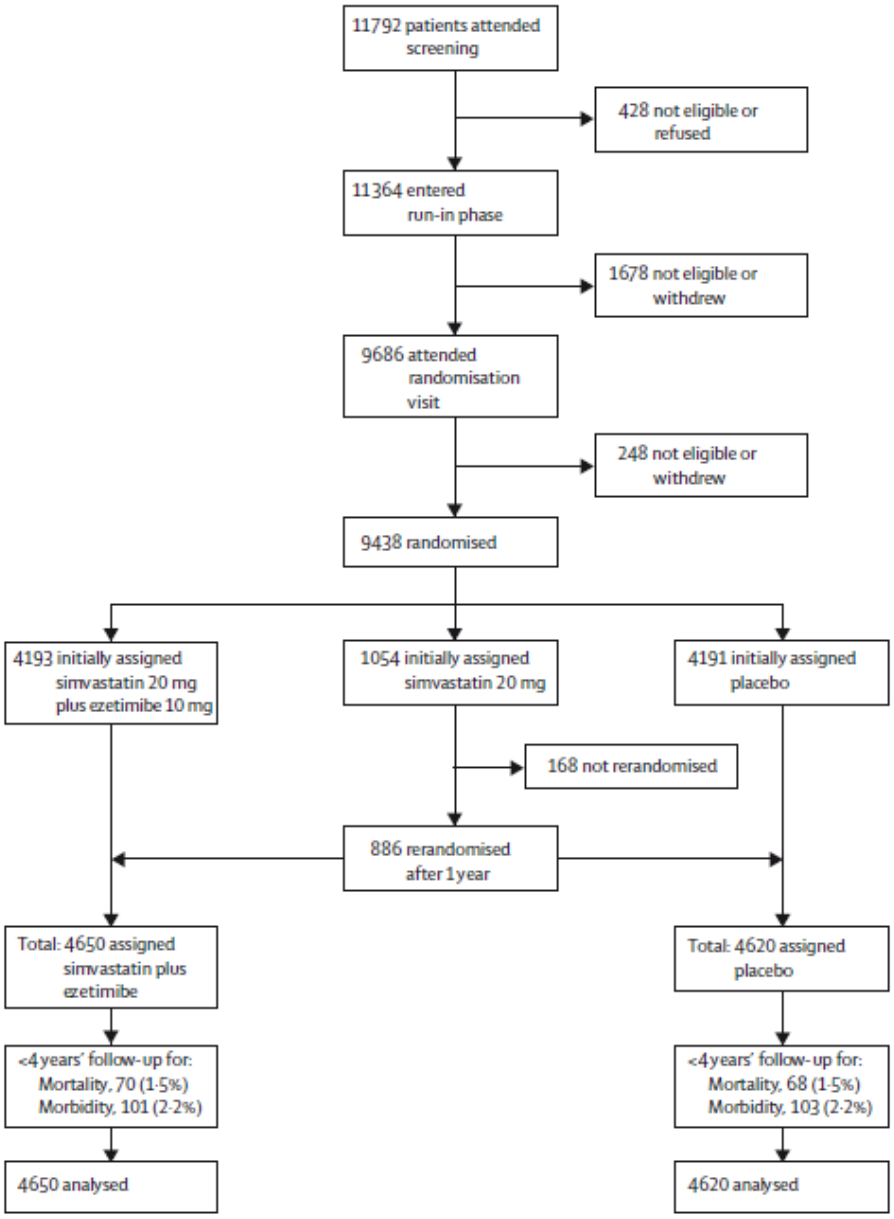


Figure 2 shows the disposition of patients in SHARP from the initial screening visit through complete follow-up. Of 11,792 patients who attended screening, 11,364 eligible patients agreed to participate in the study. These patients signed informed consent and entered the run-in phase. There were 1,678 patients who entered run-in and then dropped out of the run-in phase before the randomization visit. The most common reason given (in 743 patients, 6.5%) was that the patient's physician did not want the patient to continue in the trial. In 149 patients (1.3%), the physician wanted to start lipid-lowering treatment. In 175 (1.5%) patients, elevated ALT, AST, or CK made the patient ineligible for the study.

Of 9,686 patients who completed the run-in phase, 248 patients were not eligible for the study or withdrew from the study. Thus 9,438 patients were randomized to ezetimibe/simvastatin 10/20 mg, placebo, or simvastatin 20 mg in a 4:4:1 ratio. Of 1054 patients initially randomized to simvastatin 20 mg alone, 168 (16%) were not re-randomized to ezetimibe/simvastatin versus placebo for the following reasons: 46 (4%) patients died before re-randomization, 103 (10%) stopped study treatment and 19 (2%) did not attend the randomization visit.

Overall, 9270 patients were randomly assigned to ezetimibe/simvastatin 10/20 mg (4650 patients, 4193 initially plus 457 after one year) versus placebo (4620 patients, 4191 initially plus 429 after one year). The median duration of follow-up was 4.9 years for the surviving patients.

During the treatment period, slightly fewer patients allocated ezetimibe/simvastatin 10/20 mg discontinued study treatment (1522 [32.7%] ezetimibe/simvastatin versus 1658 [35.9%] placebo). This was largely due to the higher use of non-study statins by placebo-allocated patients (337 [9.6%] ezetimibe/simvastatin versus 513 [14.6%] placebo; $p < 0.0001$). The reasons for stopping study treatment are shown in Table 4. In patients allocated to ezetimibe/simvastatin, there were no significant excesses of discontinuations due to suspected serious adverse reactions (that is, serious adverse events believed to be related to study treatment), other serious adverse events, non-serious adverse events, or other reasons.

Table 4

Reasons for Stopping Study Treatment Before Scheduled End

Reason for Stopping	Ezetimibe/simvastatin 10/20 mg (N=4650) n (%)	Placebo (N=4620) n (%)
Suspected Serious Adverse Reaction	17 (0.4%)	12 (0.3%)
Other Serious Adverse Event	303 (6.5%)	310 (6.7%)
Non-Serious Adverse Event	165 (3.5%)	131 (2.8%)
Other Reason	**946 (20.3%)**	**1126 (24.4%)**
Difficulty attending clinic	82 (1.8%)	90 (1.9%)
Awaiting bloods	5 (0.1%)	1 (0.0%)
Difficulty taking tablets	95 (2.0%)	81 (1.8%)
Contraindicated medication	248 (5.3%)	449 (9.7%)
Patient wishes	417 (9.0%)	409 (8.9%)
Other reasons	16 (0.3%)	10 (0.2%)
Reason not specified	83 (1.8%)	86 (1.9%)
None of the Above	**91 (2.0%)**	**79 (1.7%)**
No reason given on form	5 (0.1%)	9 (0.2%)
Stopped attending clinic	86 (1.8%)	70 (1.5%)
Any Reason	**1522 (32.7%)**	**1658 (35.9%)**
Had SSAR but did not stop	3 (0.1%)	1 (0.0%)

More than one reason may apply to a patient.
SSAR = suspected serious adverse reaction

Some of the data in the above table appear in the Lancet publication of the SHARP results [2], and there are slight discrepancies in some of the numbers. However the data in Table 4 are correct and an erratum will appear in the Lancet.

Since the analyses were based on an ITT approach, patients who discontinued study medication were followed for outcomes. At the end of the trial mortality information was available in 98.5% of all patients randomized and full morbidity information in 97.8%.

4.9 Demographic and Other Patient Characteristics

Table 5 shows baseline demographic and other characteristics of all patients randomized to ezetimibe/simvastatin 10/20 mg versus placebo. Selected variables indicated by an asterisk were updated at one year for patients originally randomized to simvastatin 20 mg who were re-randomized to ezetimibe/simvastatin or placebo.

Table 5

Baseline Characteristics and Laboratory Measurements

	Ezetimibe/Simvastatin 10/20 mg (n=4650)		Placebo (n=4620)	
Previous vascular disease*	711	(15%)	682	(15%)
Diabetes*	1054	(23%)	1040	(23%)
Men	2915	(63%)	2885	(62%)
Age at randomization (years)*	62	(12)	62	(12)
Current smoker	626	(13%)	608	(13%)
Diastolic blood pressure (mm Hg)*	79	(13)	79	(13)
Systolic blood pressure (mm Hg)*	139	(22)	139	(22)
Total cholesterol (mmol/L)	4.88	(1.20)	4.90	(1.17)
LDL cholesterol (mmol/L)	2.77	(0.88)	2.78	(0.87)
HDL cholesterol (mmol/L)	1.12	(0.35)	1.11	(0.34)
Triglycerides (mmol/L)	2.31	(1.76)	2.34	(1.68)
Body-mass index (kg/m2)*	27.1	(5.7)	27.1	(5.6)
Renal status*				
On dialysis	1533	(33%)	1490	(32%)
Hemodialysis	1275	(27%)	1252	(27%)
Peritoneal dialysis	258	(6%)	238	(5%)
Not on dialysis†	3117	(67%)	3130	(68%)
MDRD-estimated GFR (mL/min per 1·73 m2)*‡§‖				
Mean (SD)	26.6	(12.9)	26.6	(13.1)
≥60	44	(1%)	44	(1%)
≥30 to <60	1100	(37%)	1055	(35%)
≥15 to <30	1246	(41%)	1319	(44%)
<15	614	(20%)	607	(20%)
Not available	113	---	105	---
Urinary albumin:creatinine ratio (mg/g)‡§#				
Median (IQR)	217	(44–788)	196	(43–748)
<30	545	(20%)	562	(20%)
≥30 to ≤300	1032	(37%)	1076	(39%)
>300	1203	(43%)	1156	(41%)
Not available	337	---	336	---

Data are n (%), mean (SD), or median (IQR). MDRD=Modified Diet in Renal Disease [56].
GFR=glomerular filtration rate.
* Variables updated at 1 year for patients originally allocated simvastatin only who were re-randomized to ezetimibe/simvastatin or placebo.
† Five versus five patients received a transplant before re-randomization.
‡ Percentages exclude participants for whom data were not available for that category.
§ For patients not on dialysis.
‖ MDRD-estimated GFR was evaluated in 3004 patients allocated to ezetimibe/simvastatin and 3025 patients allocated to placebo.
\# Urinary albumin:creatinine ratio was measured in 2780 patients allocated to ezetimibe/simvastatin and 2794 patients allocated to placebo.
Conversion factor for mmol/L to mg/dL for cholesterol is 38.7 and 88.6 for triglycerides.

Baseline characteristics were well balanced between the treatment groups. Mean age at randomization was 62 years, and 5800 (63%) patients were male. Mean blood pressure was 139/79, mean BMI 27 kg/m^2, 13% were current smokers, 23% had diabetes, and 15% had a history of vascular disease (angina, stroke, or peripheral vascular disease). Ethnic origin was white in 6646 (72%) patients, black in 264 (3%), Asian in 2086 (23%), and other or unspecified in 274 (3%). Mean plasma concentrations at baseline for non-fasting lipids in the ezetimibe/simvastatin and placebo groups were: total cholesterol, 189 (SD 46) and 190 (SD 45) mg/dL (4.88; SD 1.20 and 4.90; SD 1.17 mmol/L); LDL-C, 107 (SD 34) and 108 (SD 34) mg/dL (2.77; SD 0.88 and 2.78; SD 0.87 mmol/L); HDL-C, 43 (SD 14) and 43 (SD 13) mg/dL (1.12; SD 0.35 and 1.11; SD 0.34 mmol/L); triglycerides, 205 (SD 156) and 207 (SD 149) mg/dL (2.31; SD 1.76 and 2.34; SD 1.68 mmol/L). Mean hemoglobin was 12.3 g/dL.

At randomization, 3023 (33%) patients were receiving maintenance dialysis, most commonly hemodialysis. Mean LDL-C levels were lower in patients on dialysis compared to patients not on dialysis: 100.6 (SD 35) mg/dL (2.6; SD 0.9 mmol/l) versus 112 (SD 35) mg/dL (2.9; SD 0.9 mmol/L); $p < 0.0001$.

Among 6029 (97%) of 6247 patients not on dialysis with centrally measured creatinine, the average eGFR estimated with the MDRD equation was 26.6 (SD 13.0) ml/min per 1.73 m^2. At randomization, 36% of the patients had K/DOQI stage 3 disease (GFR 30-59 ml/min per 1.73 m^2), 43% stage 4 disease (GFR 15-29 ml/min per 1.73 m^2), and 20% stage 5 disease (GFR <15 ml/min per 1.73 m^2).

In 5574 (89%) of 6247 patients not on dialysis with a centrally measured urinary albumin:creatinine ratio (ACR), 20% had ACR below 30 mg/g, 38% had ACR 30-300 mg/g, and 42% had ACR higher than 300 mg/g.

4.10 Efficacy

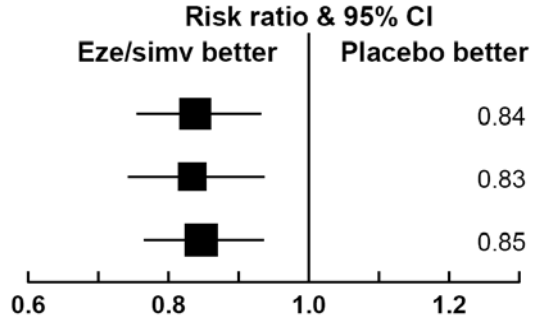
4.10.1 Major Vascular Events (MVE) and Major Atherosclerotic Events (MAE)

The main outcomes defined in the protocol and SAP have been discussed in the preceding sections, and defined and compared in Table 1. The protocol-defined primary comparison is the first occurrence of MVE in Arm 2 versus Arm 1. The key outcome of the SAP is the first occurrence of MAE in Arms 2+3b versus Arms 1+3a. As noted above in Table 1, MAE includes the same endpoints as MVE except for non-coronary cardiac death and hemorrhagic stroke. The effects of ezetimibe/simvastatin 10/20 mg on the main outcomes are shown in Figure 3. This figure also includes as the bottom row MVE in all randomized patients, which was a subsidiary comparison specified in both the SAP and protocol.

Figure 3

Effect of Ezetimibe/Simvastatin 10/20 mg on the Protocol Primary Endpoint MVE in All Patients Excluding Those Originally Randomized to Simvastatin Alone (N=8,384), on the SAP Key Outcome MAE in All Patients (N=9,270), and on the SAP Subsidiary Outcome MVE in All Patients (N=9,270)

Event	Eze/simv	Placebo	O-E	Var	z	Risk ratio & 95% CI	p
MVE (arm 2 vs 1)	639 (15.2%)	749 (17.9%)	-61.2	346.9	-3.28	0.84 (0.75-0.93)	0.0010
MAE (arm 2+3b vs 1+3a)	526 (11.3%)	619 (13.4%)	-51.9	286.2	-3.07	0.83 (0.74-0.94)	0.0021
MVE (arm 2+3b vs 1+3a)	701 (15.1%)	814 (17.6%)	-63.2	378.7	-3.25	0.85 (0.77-0.94)	0.0012

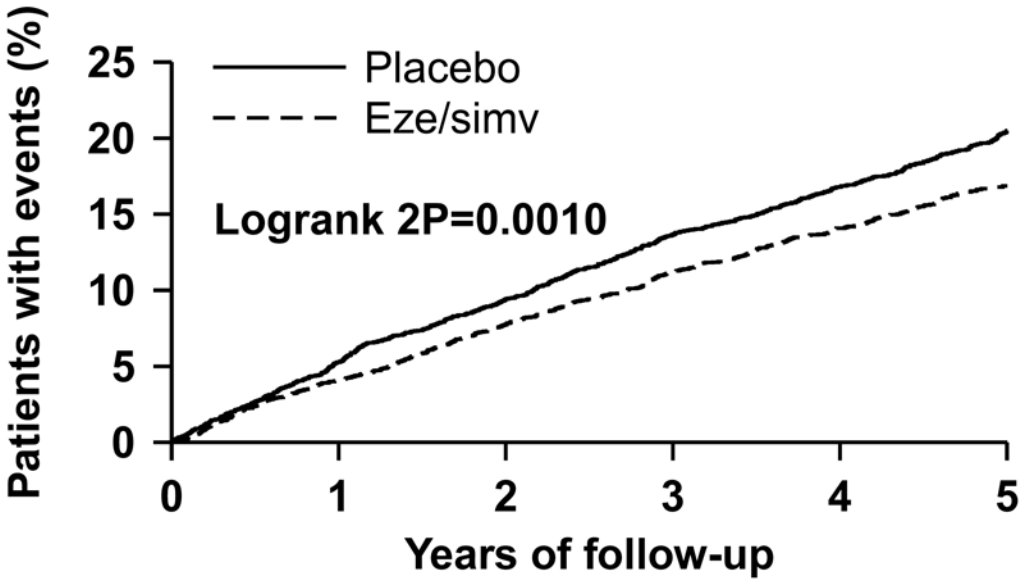


The logrank 'observed minus expected' statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (risk ratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

The effects of treatment with ezetimibe/simvastatin 10/20 mg versus placebo on MVE and MAE are also displayed in the form of Kaplan-Meier plots in Figure 4 and Figure 5.

Figure 4

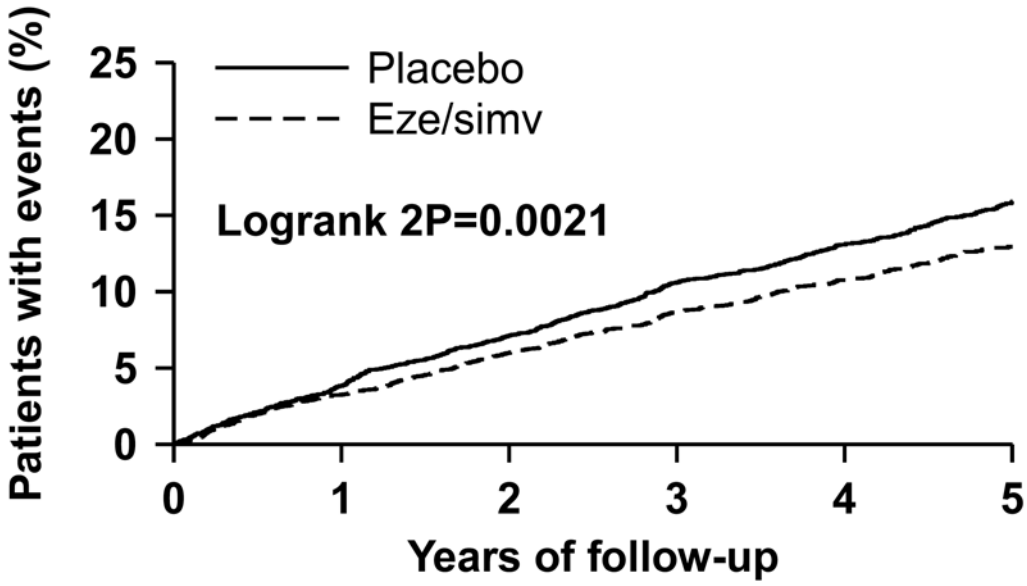
Effect of Ezetimibe/Simvastatin 10/20 mg on MVE in All Patients Except Those Originally Allocated to Simvastatin Alone (Arm 2 Versus Arm 1)



At risk						
Pbo	4191	3807	3495	3177	2419	1239
E/S	4193	3868	3567	3273	2501	1232

Figure 5

Effect of Ezetimibe/Simvastatin 10/20 mg Versus Placebo on MAE in All Randomized Patients (Arms 2+3b Versus Arms 1+3a)



At risk						
Pbo	4620	4204	3849	3469	2566	1269
E/S	4650	4271	3939	3546	2655	1265

The risk reductions for the protocol-defined primary endpoint MVE and the key outcome of the SAP MAE were both highly significant and numerically very similar, 16% and 17% respectively. Therefore, the main efficacy conclusion to be derived from SHARP is not dependent on which of these is regarded as more important, as the null hypothesis is decisively rejected in either case. MVE in all patients randomized is also shown in Figure 3 because both the protocol and the SAP specified that a secondary analysis of MVE and its components would be performed in all patients randomized to ezetimibe/simvastatin or placebo. As would be expected, the inclusion of 886 patients (9.6% of the total of 9,270) who comprised Arms 3a and 3b had a minimal effect on the observed risk reduction.

4.10.2 Components of MVE and MAE

The components of the protocol-defined primary endpoint MVE are presented in Table 2 (previously shown in the Summary, Section 2) and in Figure 6, Figure 7, and Figure 8.

Table 2

Cardiovascular Outcomes by Treatment Group in All Patients Randomized to Ezetimibe/Simvastatin 10/20 mg or Placebo

Outcome	Eze/Simv 10/20 (N=4650)*	Placebo (N=4620)*	Risk Ratio (95% CI)	P-value
Major Vascular Events (MVE)†	701 (15.1%)	814 (17.6%)	0.85 (0.77-0.94)	0.0012
Major Atherosclerotic Events (MAE)‖	526 (11.3%)	619 (13.4%)	0.83 (0.74-0.94)	0.0021
Major Cardiac Events	367 (7.9%)	403 (8.7%)	0.90 (0.78-1.04)	0.16
Nonfatal MI	134 (2.9%)	159 (3.4%)	0.84 (0.66-1.05)	0.12
Cardiac Death	253 (5.4%)	272 (5.9%)	0.93 (0.78-1.10)	0.38
Coronary Death	91 (2.0%)	90 (1.9%)	1.01 (0.75-1.35)	0.95
Other Cardiac Death	162 (3.5%)	182 (3.9%)	0.89 (0.72-1.09)	0.26
Major Coronary Events‡	213 (4.6%)	230 (5.0%)	0.92 (0.76-1.11)	0.37
Any Stroke	171 (3.7%)	210 (4.5%)	0.81 (0.66-0.99)	0.038
Non-hemorrhagic Stroke	131 (2.8%)	174 (3.8%)	0.75 (0.60-0.94)	0.011
Ischemic Stroke	114 (2.5%)	157 (3.4%)	0.72 (0.57-0.92)	0.0073
Stroke of Unknown Type	18 (0.4%)	19 (0.4%)	0.94 (0.49-1.79)	0.85
Hemorrhagic Stroke	45 (1.0%)	37 (0.8%)	1.21 (0.78-1.86)	0.40
Any Revascularization	284 (6.1%)	352 (7.6%)	0.79 (0.68-0.93)	0.0036
Coronary Revascularization	149 (3.2%)	203 (4.4%)	0.73 (0.59-0.90)	0.0027
Non-coronary Revascularization	154 (3.3%)	169 (3.7%)	0.90 (0.73-1.12)	0.36

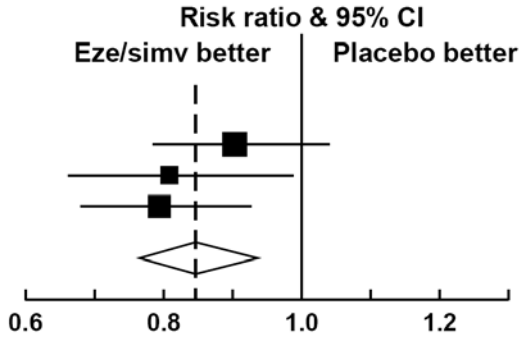
† MVE are defined as the composite of nonfatal MI, cardiac death, stroke, or any revascularization. Values are slightly different from those shown above under 'Protocol-specified primary outcome' because Arms 3a and 3b are included here.
‡ Major coronary events consist of nonfatal MI and coronary death
‖ MAE are defined as the composite of nonfatal MI, coronary death, ischemic stroke, or any revascularization.
* Eze/simv Arms 2 + 3b; Placebo: Arms 1+3a

In Figure 6 cardiac deaths and non-fatal MI are combined as 'major cardiac events'. In the SAP, any revascularization procedure is a subsidiary comparison and non-fatal MI is a subcomponent of the subsidiary comparison 'major coronary events', while total stroke and cardiac deaths are tertiary comparisons. The SAP and protocol specified that these comparisons were to be performed in all patients randomized. Thus, in contrast to the analysis of the protocol-defined primary endpoint, patients in Arms 3a and Arm 3b are included. For this reason, the numbers of patients with major vascular events in Figure 6 match the bottom row in Figure 3.

Figure 6

Effect of Ezetimibe/Simvastatin 10/20 mg on the Components of Major Vascular Events in All Randomized Patients

Event	Eze/simv (n=4650)	Placebo (n=4620)	O-E	Var	z	Risk ratio & 95% CI	p
Major cardiac event	367 (7.9%)	403 (8.7%)	-19.6	192.5	-1.41	0.90 (0.78-1.04)	0.16
Any stroke	171 (3.7%)	210 (4.5%)	-20.3	95.2	-2.08	0.81 (0.66-0.99)	0.04
Any revascularization procedure	284 (6.1%)	352 (7.6%)	-36.7	159.0	-2.91	0.79 (0.68-0.93)	0.0036
Major vascular event	**701(15.1%)**	**814(17.6%)**	**-63.2**	**378.7**	**-3.25**	**0.85 (0.77-0.94)**	**0.0012**



Hetereogeneity between MVE components: $\chi^2_2 = 1.65$ ($p = 0.44$)

The logrank 'observed minus expected' statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (risk ratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

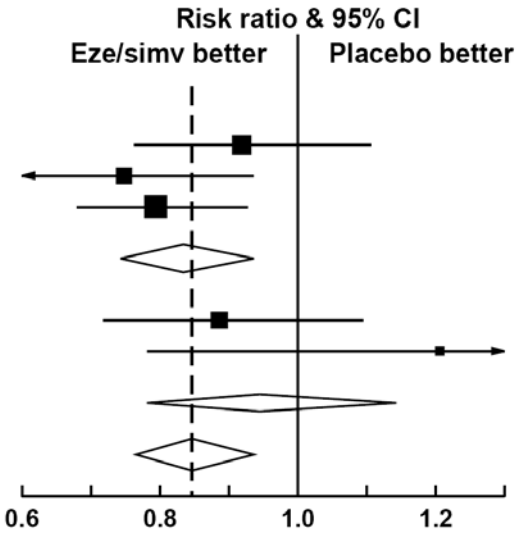
There was no significant heterogeneity between the effects on the components of MVE shown in Figure 6, ($\chi_2^2 = 1.65$, p=0.44), and stroke and revascularization procedures were separately significantly reduced (p=0.038 -- rounded to 0.04 in the figure -- and p=0.0036 respectively).

Figure 7 provides the components of MAE, and also includes those components of MVE which were not included as components of MAE. The components of MAE include coronary death and MI -- these closely related subcomponent endpoints are shown separately in Figure 8 and, as specified in the SAP, combined in Figure 7 as 'major coronary event'. The other components of MAE are non-hemorrhagic stroke and any revascularization procedure. The SAP specified ischemic as opposed to non-hemorrhagic stroke, and was not explicit about the approach to stroke of unknown type, which comprised 9.7% of all patients with stroke, evenly distributed between the two treatment groups, as shown in Figure 8. The Coordinating Centre, blind to the results, decided to combine strokes of unknown type with patients with known ischemic stroke to arrive at the totals for non-hemorrhagic stroke which were included in total MAE shown in Figure 7. Including the patients with stroke of unknown type meant that the observed risk reduction for non-hemorrhagic stroke (25%, p=0.011) was slightly less than for ischemic stroke alone (28%, p=0.0073). Revascularization procedures include coronary and non-coronary procedures. The subcomponents of major coronary events, stroke, and revascularization procedures are shown in Figure 8.

Figure 7

Components of MAE and MVE In All Patients Randomized to Ezetimibe/Simvastatin 10/20 mg Versus Placebo

Event	Eze/simv (n=4650)	Placebo (n=4620)	O-E	Var	z	Risk ratio & 95% CI	p
Major coronary event	213 (4.6%)	230 (5.0%)	-9.4	110.7	-0.89	0.92 (0.76-1.11)	0.37
Non-haemorrhagic stroke	131 (2.8%)	174 (3.8%)	-22.1	76.2	-2.54	0.75 (0.60-0.94)	0.01
Any revascularization procedure	284 (6.1%)	352 (7.6%)	-36.7	159.0	-2.91	0.79 (0.68-0.93)	0.0036
Major atherosclerotic event	**526(11.3%)**	**619(13.4%)**	**-51.9**	**286.2**	**-3.07**	**0.83 (0.74-0.94)**	**0.0021**
Other cardiac death	162 (3.5%)	182 (3.9%)	-10.4	86.0	-1.12	0.89 (0.72-1.09)	0.26
Haemorrhagic stroke	45 (1.0%)	37 (0.8%)	3.8	20.5	0.85	1.21 (0.78-1.86)	0.40
Other major vascular events	**207 (4.5%)**	**218 (4.7%)**	**-6.0**	**106.2**	**-0.58**	**0.94 (0.78-1.14)**	**0.56**
Major vascular event	**701(15.1%)**	**814(17.6%)**	**-63.2**	**378.7**	**-3.25**	**0.85 (0.77-0.94)**	**0.0012**

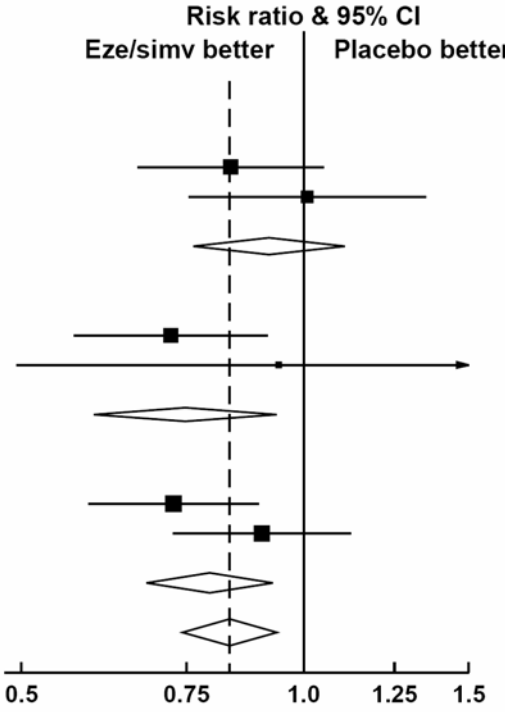


The logrank 'observed minus expected' statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (risk ratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

Figure 8

Subcomponents of Major Coronary Events, Non-Hemorrhagic Stroke, and Revascularization Procedures

Event	Eze/simv (n=4650)		Placebo (n=4620)		Risk ratio & 95% CI	p
Coronary events						
Non-fatal MI	134	(2.9%)	159	(3.4%)	0.84 (0.66-1.05)	0.12
CHD death	91	(2.0%)	90	(1.9%)	1.01 (0.75-1.35)	0.95
Subtotal: Any major coronary event	**213**	**(4.6%)**	**230**	**(5.0%)**	**0.92 (0.76-1.11)**	**0.37**
Non-haemorrhagic stroke						
Ischaemic	114	(2.5%)	157	(3.4%)	0.72 (0.57-0.92)	0.0073
Unknown type	18	(0.4%)	19	(0.4%)	0.94 (0.49-1.79)	0.85
Subtotal: Any non-haemorrhagic	**131**	**(2.8%)**	**174**	**(3.8%)**	**0.75 (0.60-0.94)**	**0.01**
Revascularization procedures						
Coronary	149	(3.2%)	203	(4.4%)	0.73 (0.59-0.90)	0.0027
Non-coronary	154	(3.3%)	169	(3.7%)	0.90 (0.73-1.12)	0.36
Subtotal: Any revascularization	**284**	**(6.1%)**	**352**	**(7.6%)**	**0.79 (0.68-0.93)**	**0.0036**
Total: Any major atherosclerotic event	**526**	**(11.3%)**	**619**	**(13.4%)**	**0.83 (0.74-0.94)**	**0.0021**



There was no significant heterogeneity in effects on the components of MAE (χ_2^2 =2.2, p=0.33). Of these, the risk reductions in non-hemorrhagic stroke and any revascularization procedure were both separately statistically significant, and remain so after applying the Hochberg multiplicity correction to the uncorrected p-values displayed in Figure 7 (corrected p=0.022 and 0.011 respectively). Although this is a conservative approach and not standard practice for the components of a composite endpoint, the SAP called for the application of the Hochberg procedure to the components of MAE specifically.

As previously noted, MVE components not included as components of MAE are other cardiac death (i.e. non-CHD) and hemorrhagic stroke, which are tertiary endpoints. Figure 7 shows that there were fewer other cardiac deaths (162 [3.5%] versus 182 [3.9%]) and more hemorrhagic strokes (45 [1.0%] versus 37 [0.8%]) in patients randomized to ezetimibe/simvastatin, but neither of these differences was statistically significant.

The treatment effect was significant within some but not all of the individual components of MVE and MAE, which is to be expected as SHARP was underpowered for the individual components, as is usually the case for studies with composite endpoints; indeed there would be little point in specifying any composite endpoint if there were sufficient power for all its components. Therefore, the fact that the risk reduction for major coronary events separately was not statistically significant does not constitute evidence that the study treatment was ineffective for this component. The 95% confidence interval for major coronary events alone easily includes the 16-17% reduction in MVE or MAE.

Major coronary events, and coronary revascularization procedures, which are performed to relieve ischemic cardiac pain, are both the result of atherosclerosis in the coronary arteries. There was a very clear effect on coronary revascularization procedures: the 21% reduction in the risk of any revascularization procedure was driven mainly by coronary revascularization procedures. Of 636 patients who had a revascularization procedure, 352 (55%) had a coronary procedure (coronary artery bypass graft or percutaneous coronary intervention), for which the risk reduction was 27% (p=0.0027), compared to 10% for non-coronary revascularization procedures (p=0.36). The clear reduction in the need for coronary revascularization is good evidence that ezetimibe/simvastatin reduced atherosclerotic disease in the coronary arteries and its manifestations.

In addition, in the CTT meta-analysis of 170,000 participants in 26 lipid-lowering outcome trials [8], risk reductions produced by LDL-C lowering treatment were essentially identical for major coronary events (24% per mmol/L reduction in LDL-C) and coronary revascularization procedures (25% per mmol/L reduction in LDL-C), supporting the inference that both these outcomes stem from the same underlying disease process and reductions in their occurrence similarly reflect the anti-atherosclerotic effect of lipid lowering. Thus, coronary revascularization should not be regarded as a "soft" endpoint in this context. For stroke the corresponding risk reduction in the meta-analysis was 15% per mmol/L. Thus there is no evidence from previous studies that the effect of LDL-C lowering treatment on major coronary events is any less than for coronary revascularization procedures or other important outcomes. This supports the inference

that the differences in magnitude and significance levels among the MVE and MAE component risk reductions observed in SHARP are simply a matter of chance.

Approximately 24% of the patients in both groups randomized in SHARP died during the course of the 4.9 year follow-up period of the study, for a total of 2257 deaths and an average annual mortality rate of 4.9% (Figure 13, Section 4.11.2). By comparison, in SEARCH [50], a contemporaneous study in a slightly older (mean age at baseline 64 years) population of patients all of whom had a history of MI, randomized to simvastatin 80 mg or 20 mg, the mortality rate was 16% during 6.7 years of follow-up (annual mortality rate 2.4%). This 2-fold difference indicates the very high risk nature of the SHARP patient population and is consistent with epidemiological studies of CKD patients [3; 4; 5], as well as 4D and AURORA [28; 29]. No significant differences between treatment groups in overall or cause-specific mortality were observed in SHARP. Again, the study was simply not powered to detect differences in mortality. With over 9,000 patients, SHARP was a large trial by any standards, but because only one third of the deaths were vascular and only 181 (8% of all deaths) were due to coronary disease and thus potentially reducible by lipid-lowering therapy, to detect plausible reductions in total or vascular mortality reliably would have required a trial many times larger. Coronary mortality can be included in a composite endpoint as was done in SHARP, but total or vascular mortality is simply not a practical endpoint for outcome studies in CKD patients.

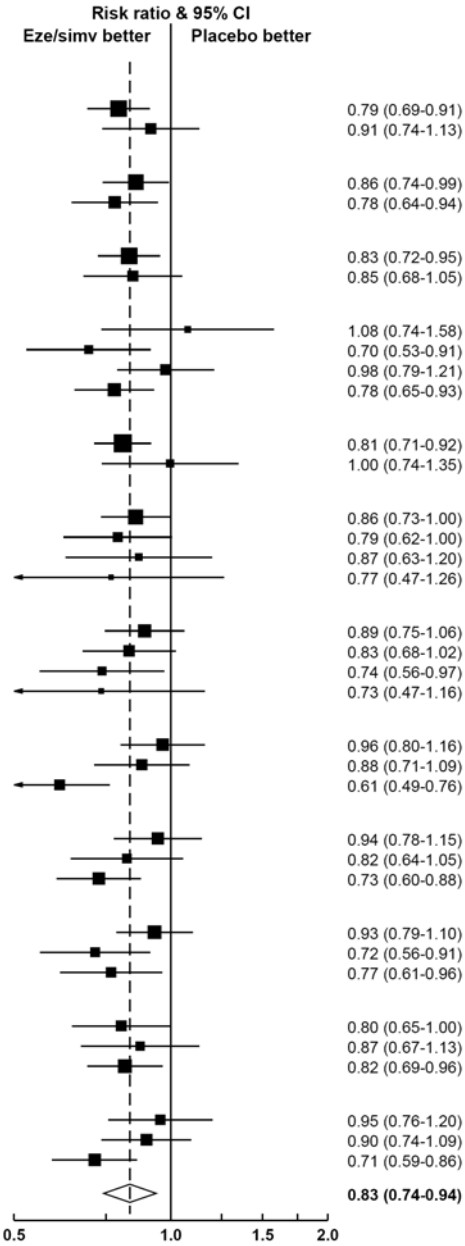
4.10.3 Subgroup Analyses

As shown in Figure 9, without adjusting for multiplicity there was no significant heterogeneity in the effect of treatment on MAE when the study population was divided into subgroups based on numerous demographic factors including age, sex, prior atherosclerotic disease, diabetes, smoking status or blood pressure, with the exception of BMI (p=0.04). Other less important demographic subgroups specified in the SAP were also analyzed, and the results were submitted to FDA but omitted here for the sake of brevity. For blood lipids, without adjusting for multiplicity, there was a significant trend test result indicating a greater reduction in risk in patients with higher baseline total-C. The trend test for LDL-C approached statistical significance, and was significant in the case of the related non-HDL-C and apolipoprotein-B (data not shown). Such trends for lipoproteins rich in apolipoprotein-B are to be expected, because the percentage reduction in LDL-C (and apolipoprotein B) produced by statins or ezetimibe is independent of the baseline value, so absolute reductions in LDL-C will be larger when the baseline value is higher. This was observed in SHARP when patients were divided by approximate tertiles according to their baseline lipid values: at 2.5 years the difference between the mean reduction in LDL-C in patients allocated to ezetimibe/simvastatin and those allocated to placebo was 0.63 mmol/L (32%) in patients with baseline LDL-C<2.5 mmol/L, 0.86 mmol/L (31%) in patients with baseline LDL-C≥2.5 <3.0 mmol/L, and 1.07 mmol/L (29%) in patients with baseline LDL-C≥3.0 mmol/L.

Figure 9

MAE by Baseline Characteristics Other Than Renal Function

Baseline characteristic	Eze/simv (n=4650)	Placebo (n=4620)	Risk ratio & 95% CI
Prior vascular disease (χ^2_1 = 1.21; p = 0.27)			
No	359 /3939 (9.1%)	447 /3938 (11.4%)	0.79 (0.69-0.91)
Yes	167 /711 (23.5%)	172 /682 (25.2%)	0.91 (0.74-1.13)
Diabetes (χ^2_1 = 0.58; p = 0.45)			
No diabetes	333 /3596 (9.3%)	385 /3580 (10.8%)	0.86 (0.74-0.99)
Diabetes	193 /1054 (18.3%)	234 /1040 (22.5%)	0.78 (0.64-0.94)
Gender (χ^2_1 = 0.02; p = 0.90)			
Male	376 /2915 (12.9%)	445 /2885 (15.4%)	0.83 (0.72-0.95)
Female	150 /1735 (8.6%)	174 /1735 (10.0%)	0.85 (0.68-1.05)
Age at randomization (years) (χ^2_1 = 0.60; p = 0.44)			
40-49	56 /968 (5.8%)	50 /908 (5.5%)	1.08 (0.74-1.58)
50-59	85 /1161 (7.3%)	119 /1149 (10.4%)	0.70 (0.53-0.91)
60-69	163 /1226 (13.3%)	171 /1246 (13.7%)	0.98 (0.79-1.21)
70+	222 /1295 (17.1%)	279 /1317 (21.2%)	0.78 (0.65-0.93)
Current smoker (χ^2_1 = 1.57; p = 0.21)			
No	440 /4024 (10.9%)	536 /4012 (13.4%)	0.81 (0.71-0.92)
Yes	86 /626 (13.7%)	83 /608 (13.7%)	1.00 (0.74-1.35)
Diastolic BP (mmHg) (χ^2_1 = 0.11; p = 0.74)			
<80	305 /2279 (13.4%)	360 /2339 (15.4%)	0.86 (0.73-1.00)
≥80 <90	122 /1385 (8.8%)	146 /1309 (11.2%)	0.79 (0.62-1.00)
≥90 <100	69 /710 (9.7%)	78 /701 (11.1%)	0.87 (0.63-1.20)
≥100	28 /267 (10.5%)	34 /256 (13.3%)	0.77 (0.47-1.26)
Systolic BP (mmHg) (χ^2_1 = 1.49; p = 0.22)			
<140	238 /2431 (9.8%)	264 /2414 (10.9%)	0.89 (0.75-1.06)
≥140 <160	167 /1384 (12.1%)	198 /1387 (14.3%)	0.83 (0.68-1.02)
≥160 <180	88 /626 (14.1%)	115 /614 (18.7%)	0.74 (0.56-0.97)
≥180	32 /203 (15.8%)	42 /198 (21.2%)	0.73 (0.47-1.16)
Total cholesterol (mmol/L) (χ^2_1 = 9.01; p = 0.0027)			
<4.5	222 /1754 (12.7%)	222 /1680 (13.2%)	0.96 (0.80-1.16)
≥4.5 <5.5	163 /1523 (10.7%)	184 /1526 (12.1%)	0.88 (0.71-1.09)
≥5.5	118 /1186 (9.9%)	195 /1224 (15.9%)	0.61 (0.49-0.76)
LDL cholesterol (mmol/L) (χ^2_1 = 3.63; p = 0.06)			
<2.5	202 /1776 (11.4%)	207 /1707 (12.1%)	0.94 (0.78-1.15)
≥2.5 <3.0	115 /1059 (10.9%)	135 /1037 (13.0%)	0.82 (0.64-1.05)
≥3.0	186 /1627 (11.4%)	259 /1686 (15.4%)	0.73 (0.60-0.88)
HDL cholesterol (mmol/L) (χ^2_1 = 2.30; p = 0.13)			
<1.0	256 /1816 (14.1%)	286 /1864 (15.3%)	0.93 (0.79-1.10)
≥1.0 <1.2	109 /1084 (10.1%)	150 /1089 (13.8%)	0.72 (0.56-0.91)
≥1.2	137 /1559 (8.8%)	165 /1477 (11.2%)	0.77 (0.61-0.96)
Triglycerides (mmol/L) (χ^2_1 = 0.00; p = 0.95)			
<1.5	150 /1489 (10.1%)	177 /1440 (12.3%)	0.80 (0.65-1.00)
≥1.5 <2.0	103 /899 (11.5%)	122 /914 (13.3%)	0.87 (0.67-1.13)
≥2.0	250 /2074 (12.1%)	302 /2075 (14.6%)	0.82 (0.69-0.96)
Body mass index (kg/m²) (χ^2_1 = 4.04; p = 0.04)			
<24	145 /1385 (10.5%)	144 /1338 (10.8%)	0.95 (0.76-1.20)
≥24 <28	185 /1523 (12.1%)	207 /1533 (13.5%)	0.90 (0.74-1.09)
≥28	183 /1646 (11.1%)	254 /1652 (15.4%)	0.71 (0.59-0.86)
All patients	**526 /4650 (11.3%)**	**619 /4620 (13.4%)**	**0.83 (0.74-0.94)**

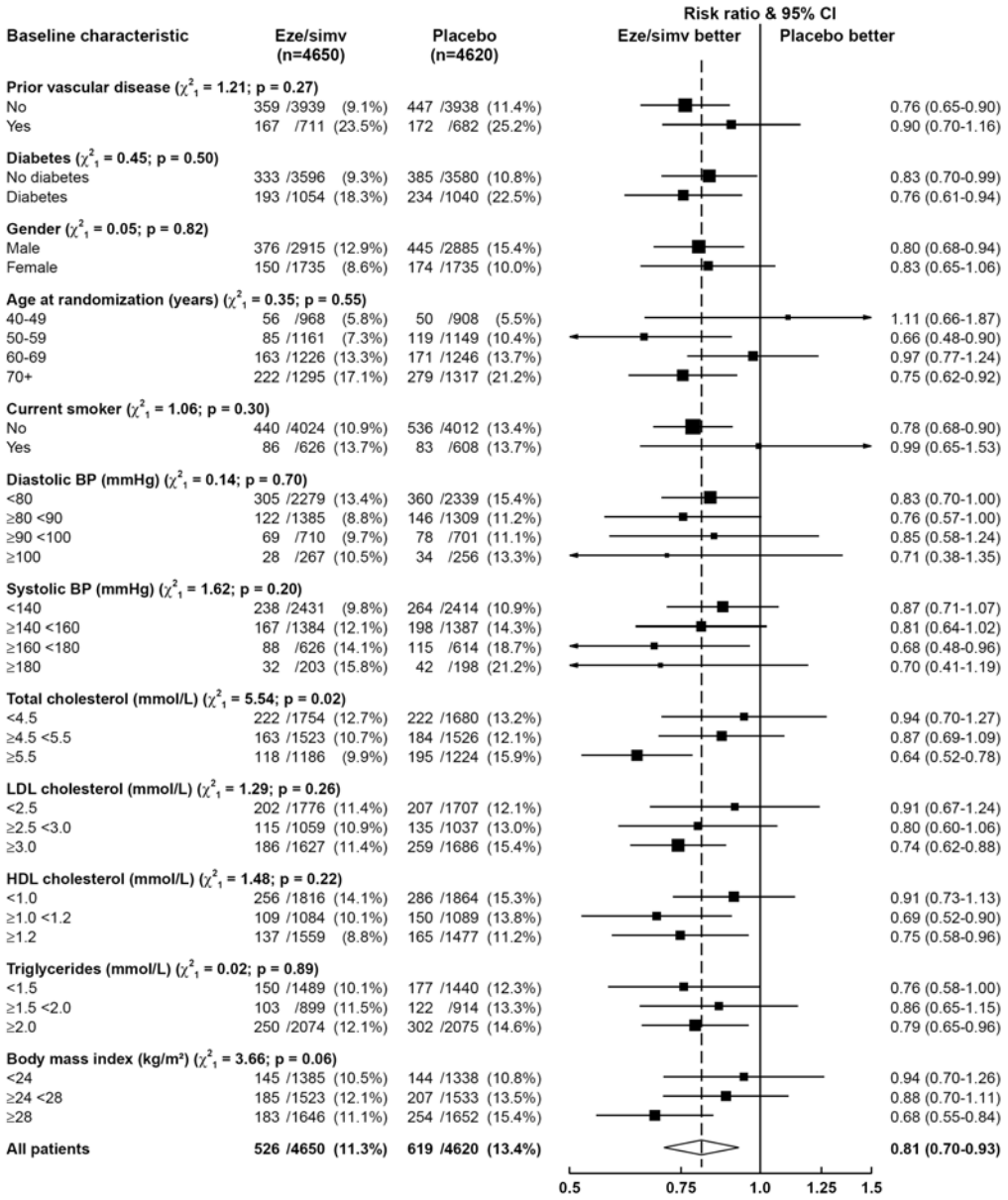


The critical values for χ^2 for one degree of freedom for p-values of 0.05, 0.01 and 0.001 are 3.84, 6.64 and 10.83 respectively before any adjustment for multiple comparisons.

In SHARP, after weighting the MAE risk ratios according to the reductions in LDL-C (Figure 10), the trends were much reduced, and remained conventionally statistically significant (without adjustment for multiplicity) only for total cholesterol (trend p=0.02). Thus, given the number of such subgroup analyses performed, there is no good evidence that any particular subgroup in SHARP obtained greater or lesser clinical benefit, other than that attributable to variations among subgroups in the absolute reduction of LDL-C.

Figure 10

MAE by Baseline Characteristics Other Than Renal Function, Per mmol/L Reduction in LDL Cholesterol



In SHARP there was no trend (with or without weighting for reduction of LDL-C) towards a greater effect of treatment in the 15% of patients with a history of atherosclerotic disease; thus SHARP is a true test of lowering LDL-C in patients with CKD, as opposed to patients with both known CHD and CKD.

Similar results were obtained in subgroup analyses based on MVE (data have been submitted to FDA but for the sake of brevity are not shown here).

In SHARP there was no significant heterogeneity in the effect of ezetimibe/simvastatin on cardiovascular risk between the pre-dialysis patients and the dialysis patients, although the observed MAE risk reduction was smaller in the dialysis patients: 22% and 10% (χ_1^2 =1.3, p=0.25), respectively (Figure 11). For MVE (χ_1^2 =3.0, p=0.08) the risk reductions were 22% and 6% (data not shown). The difference in mean LDL-C between the ezetimibe/simvastatin and placebo groups was also smaller in the dialysis patients compared to the pre-dialysis patients: in pre-dialysis patients, the difference at 2.5 years in mean LDL-C between treatment groups was 0.96 mmol/L (37 mg/dL), compared to 0.60 mmol (23 mg/dL) in patients on dialysis. This difference is attributable to a lower baseline LDL-C and poorer compliance in dialysis patients; the latter is not unexpected given the multiple medications such patients typically take, and their more severe illness. The smaller absolute change in LDL-C would be expected to yield a proportionately smaller cardiovascular risk reduction. Expressing the results as risk reduction per 1 mmol/L lowering of LDL-C (Figure 12) narrows the difference between the pre-dialysis and dialysis patients, because the result for the pre-dialysis patients barely changes (their mean LDL-C difference was almost 1 mmol/L, as noted above), whereas the risk reduction for the dialysis patients increases from 10% to 16% .

Figure 11

MAE by Baseline Renal Status

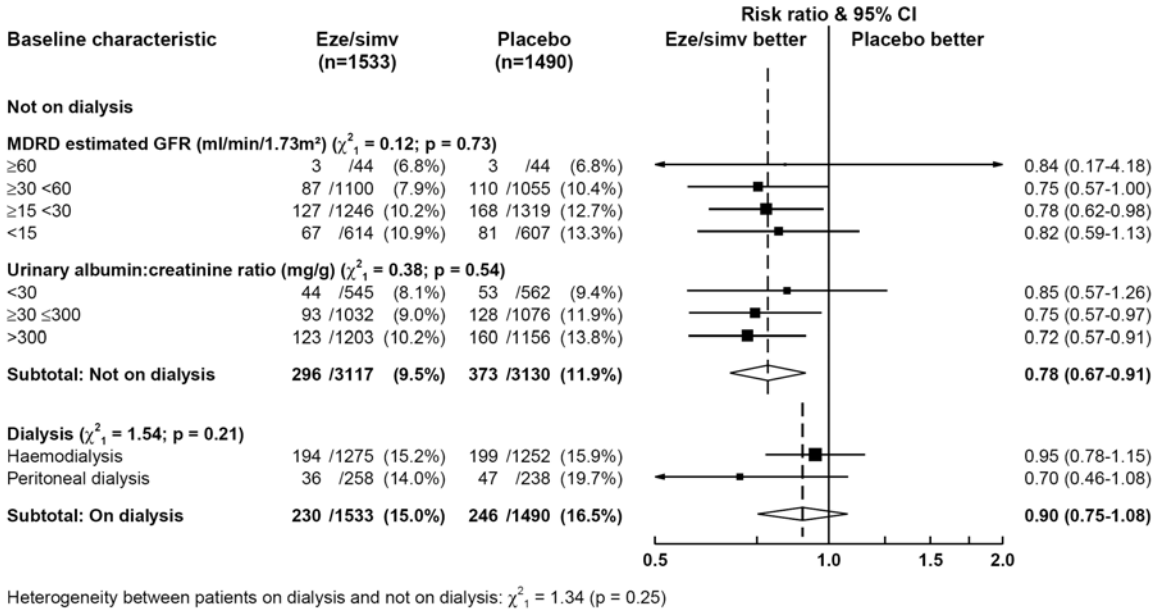
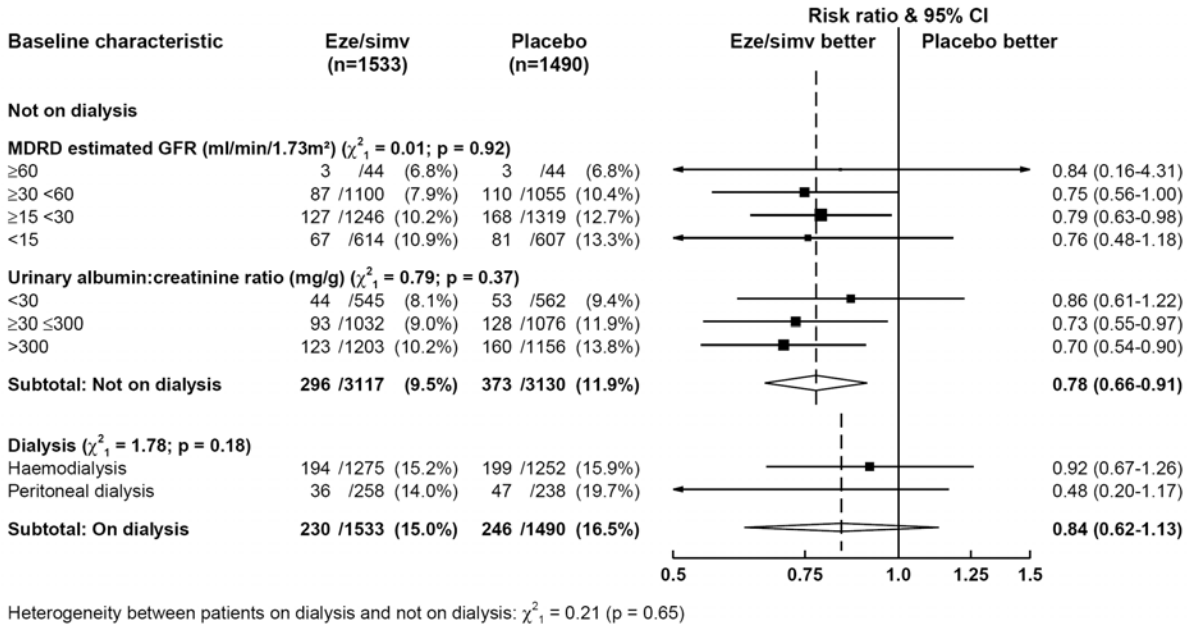


Figure 12

MAE by Baseline Renal Status Per mmol/L Reduction in LDL Cholesterol



4.10.4 Renal Endpoints

The principal renal outcome measure was progression to end-stage renal disease (ESRD, i.e. need for dialysis or kidney transplant) in pre-dialysis patients, one third of whom entered ESRD during the course of the study [2]. The risk ratio was 0.97 (95% confidence interval 0.89-1.05). The composite endpoint ESRD or death occurred in almost half the pre-dialysis study population, and was similarly not affected (risk ratio 0.97, 95% CI 0.90-1.04). There was a trend towards reduction in the tertiary composite endpoint, progression to ESRD or a twofold increase in plasma creatinine: risk ratio 0.93 (95% CI 0.86-1.01, p=0.10). Overall, there is no good evidence for a beneficial effect on the progression of CKD in SHARP, but the small trends towards benefit at least indicate that a harmful effect is unlikely.

4.10.5 Compliance

Compliance with study medication was assessed at the randomization visit and all follow-up visits by questioning participants and by visually estimating remaining tablets in the bottle. A participant was considered to be compliant with allocated study treatment if, since their last visit, he or she took at least 80% of the allocated medication. Of those patients who took less than 80%, a large majority took very little or none of the allocated medication. The denominator for assessing compliance was the number of surviving participants allocated that study treatment and for whom there was information for the

current visit or if no information, were not known to have died by that visit. Patients who did not attend the study visit were assumed to be non-compliant. Patients were also considered to be non-compliant if they had stopped study treatment because of an SAE, NSAE, or for other reasons. If no estimate of compliance was provided, then non-compliance was assumed.

As shown in Table 6, among the participants allocated ezetimibe/simvastatin 10/20mg, 3403 (77%) of 4435 at the end of the first year of follow-up and 2397 (68%) of 3512 at the end of the fourth year either remained compliant with study drug or were taking a non-study statin. At the approximate mid-point of the study (2.5 years) 2864 (71%) of 4058 participants allocated to ezetimibe/simvastatin 10/20 mg were taking study drug or a non-study statin. Use of non-study LDL-C lowering drugs by patients allocated to placebo increased during the trial, from 124 (3%) of 4162 patients at the end of the first year, to 341 (9%) of 3735 patients at 2.5 years, and 447 (14%) of 3278 patients at the end of the fourth year. Therefore, the intention-to-treat comparisons of LDL-C assess the effects of about two-thirds of subjects taking LDL-C lowering treatment, which resulted in an average LDL-C difference at 2.5 years of 0.85 mmol/L [32.9 mg/dL] between the treatment groups (Table 6).

Table 6

Average Use of Study Simvastatin/Ezetimibe 10/20 mg or Non-Study LDL-C Lowering Drug and Average Change From Baseline in Plasma LDL-C

Follow-up* (months)	LDL-Cholesterol Lowering Drug Use		LDL-Cholesterol Difference (mmol/L)		
	Ezetimibe/ simvastatin 10/20 mg	Placebo	Ezetimibe/ simvastatin 10/20 mg	Placebo	Between-Group Difference
12	77%	3%	-1.08	0.02	-1.09 (0.06)
30	71%	9%	-1.00	-0.15	-0.85 (0.02)
48	68%	14%	-0.84	-0.08	-0.77 (0.06)

* In the 9.6% of patients who had been initially allocated to simvastatin, no 12- month sample was included in the analysis as this would have reflected the effect of simvastatin 20 mg alone, while samples collected at 30 and 48 months reflect the effects of treatment 18 and 36 months after re-randomization to ezetimibe/simvastatin or placebo. Patients with missing values at randomization were not included in this analysis. Patients with missing values at the follow-up visit were assigned their value at randomization.

Conversion factor for mmol/L to mg/dL for cholesterol is 38.7.

Compliance was lower in patients on dialysis compared to patients not on dialysis. At 2.5 years of follow-up the average use of ezetimibe/simvastatin 10/20 mg or non-study statin was 65% and 11% (absolute difference 54%) in patients on dialysis allocated to ezetimibe/simvastatin 10/20 mg or placebo, respectively, and 73% and 8%, respectively, (absolute difference 65%) in patients not on dialysis. Poorer compliance, taken together with the lower baseline LDL-C in patients on dialysis (2.6 mmol/l [101 mg/dL] versus 2.9 mmol/L [112 mg/dL]) yielded a smaller average LDL-C reduction in patients on dialysis compared to patients not on dialysis: 0.60 mmol/L (23 mg/dL) versus 0.96 mmol/L (37 mg/dL), as previously noted in Section 4.10.3.

4.10.6 Lipids and Apolipoproteins

Non-fasting blood samples were evaluated for lipids by local laboratories at the screening visit. At the original randomization visit, the lipid profile (total cholesterol, LDL-C, HDL-C, TGs, apoB and apoA1) was assessed in non-fasting samples by the central laboratory at CTSU. LDL-C was measured directly (not calculated by the Friedewald equation as is commonly done). During follow-up, central laboratory analysis of the lipid profile was performed on non-fasting blood samples collected from a random sample of about 10% of participants at their 1 year and 4 year visits, and from all participants at their 2.5 year visits. In the analysis of change in plasma lipids, a change of zero was imputed for patients missing specific follow-up measurements since such patients are likely to have discontinued treatment.

4.10.6.1 Lipid and Apolipoprotein Changes at 12 Months

Mean lipids and apolipoproteins at randomization and at one year of treatment for patients randomized to ezetimibe/simvastatin 10/20 mg, simvastatin 20 mg, or placebo are shown in Table 7. The absolute and percentage differences in this table refer to comparisons between the ezetimibe/simvastatin and placebo groups.

Table 7

Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and One Year in Patients Initially Randomized to Ezetimibe/Simvastatin 10/20 mg, Simvastatin 20 mg or Placebo

Time From Randomization (Months)	Ezetimibe/ simvastatin 10/20 mg	Simvastatin 20 mg	Placebo	Absolute Difference*	Percentage Difference*	p-Value
Total cholesterol (mmol/L)						
0	n=4019 4.89 ± 0.02	n=1013 4.84 ± 0.04	n=4014 4.91 ± 0.02	-0.02 ± 0.03	0%	0.40
12	n=391 3.49 ± 0.05	n=108 3.91 ± 0.11	n=365 4.88 ± 0.06	-1.39 ± 0.08	-29%	<0.0001
LDL cholesterol (mmol/L)						
0	n=4018 2.78 ± 0.01	n=1013 2.76 ± 0.03	n=4014 2.79 ± 0.01	-0.01 ± 0.02	-1%	0.46
12	n=391 1.70 ± 0.04	n=108 2.04 ± 0.08	n=365 2.80 ± 0.05	-1.09 ± 0.06	-39%	<0.0001
HDL cholesterol (mmol/L)						
0	n=4015 1.12 ± 0.01	n=1013 1.10 ± 0.01	n=4014 1.11 ± 0.01	0.01 ± 0.01	1%	0.18
12	n=391 1.14 ± 0.02	n=108 1.17 ± 0.03	n=365 1.12 ± 0.02	0.02 ± 0.03	1%	0.54

Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and One Year in Patients Initially Randomized to Ezetimibe/Simvastatin 10/20 mg, Simvastatin 20 mg or Placebo (Cont.)

Time From Randomization (Months)	Ezetimibe/ simvastatin 10/20 mg	Simvastatin 20 mg	Placebo	Absolute Difference*	Percentage Difference*	p-Value
Non-HDL cholesterol (mmol/L)						
0	n=4015 3.77 ± 0.02	n=1013 3.75 ± 0.03	n=4014 3.80 ± 0.02	-0.03 ± 0.02	-1%	0.19
12	n=391 2.35 ± 0.05	n=108 2.75 ± 0.11	n=365 3.76 ± 0.06	-1.41 ± 0.08	-37%	<0.0001
Triglycerides (mmol/L)						
0	n=4018 2.31 ± 0.03	n=1013 2.33 ± 0.05	n=4013 2.34 ± 0.03	-0.03 ± 0.04	-1%	0.42
12	n=391 1.79 ± 0.06	n=108 1.72 ± 0.11	n=365 2.36 ± 0.13	-0.57 ± 0.14	-24%	<0.0001
Apolipoprotein B (mg/dL)						
0	n=4022 96.20 ± 0.41	n=1015 96.09 ± 0.79	n=4018 96.89 ± 0.40	-0.69 ± 0.57	-1%	0.23
12	n=391 65.94 ± 1.11	n=108 73.33 ± 2.39	n=364 94.05 ± 1.29	-28.11 ±1.70	-30%	<0.0001

Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and One Year in Patients Initially Randomized to Ezetimibe/Simvastatin 10/20 mg, Simvastatin 20 mg or Placebo (Cont.)

Time From Randomization (Months)	Ezetimibe/ simvastatin 10/20 mg	Simvastatin 20 mg	Placebo	Absolute Difference*	Percentage Difference*	p-Value
Apolipoprotein A1 (mg/dL)						
0	n=4026 134.49 ±0.46	n=1015 132.22 ±0.88	n=4019 133.47 ±0.45	1.02 ± 0.64	1%	0.11
12	n=391 139.20 ±1.48	n=108 140.19 ±2.64	n=365 136.05 ±1.48	3.15 ± 2.09	2%	0.13

* Absolute and percentage differences refer to comparisons between the means in the ezetimibe/simvastatin and placebo groups. The numbers of patients given are the number with lipid measurements.
The 0 month value is the value at the first randomization. Patients with missing values at randomization were not included in this analysis. Patients with missing values at the follow-up visit were imputed as a zero change from the previous value.
Conversion factor for mmol/L to mg/dL for cholesterol is 38.7 and 88.6 for triglycerides.

Compared to placebo, ezetimibe/simvastatin 10/20 mg reduced LDL-C by 1.09 mmol/L (42.2 mg/dL) at one year. Compared to simvastatin 20 mg, ezetimibe/simvastatin 10/20 mg produced an additional reduction in LDL-C of 0.34 mmol/L (13.2 mg/dL) at one year of treatment. From these data, it can be estimated that the ezetimibe component of ezetimibe/simvastatin 10/20 mg contributed approximately 31% (0.34/1.09) of the LDL-C reduction observed with the combination.

Ezetimibe/simvastatin reduced non-HDL-C by 1.4 mmol/L (54 mg/dL) and apoB by 28 mg/dL compared to placebo. It also reduced TG by 0.57 mmol/L (50.5 mg/dL) compared to placebo, an effect similar to that produced by simvastatin 20 mg alone. In patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo, HDL-C did not change appreciably. There was a non-significant increase in apoA1 of 3.15 mg/dL. As presented in Section 4.10.5, Table 6, at 12 months of treatment 77% of patients allocated to ezetimibe/simvastatin 10/20 mg and placebo, respectively, demonstrated ≥80% compliance, while 3% of patients in the placebo group took non-study statin.

4.10.6.2 Lipids and Apolipoproteins Over the Course of the Study

Table 8 shows LDL-C levels at the initial randomization visit and at the 12, 18, 30, and 48 month visits in all patients randomized to ezetimibe/simvastatin 10/20 mg versus placebo. In patients initially allocated to simvastatin, no 12 month samples were collected, while samples scheduled for collection at 2.5 and 4 years were collected at 1.5 and 3 years after re-randomization at 1 year.

Table 8

Mean ± SE LDL-Cholesterol (mmol/L) at Baseline and Follow-up Visits

Time From Final Randomization * (Months)	Ezetimibe/ simvastatin 10/20 mg	Placebo	Absolute Difference	Percentage Difference	p-Value
Baseline	n=4462 2.77 ± 0.01	n=4430 2.78 ± 0.01	-0.01 ± 0.02	0%	0.49
12	n=391 1.70 ± 0.04	n=365 2.80 ± 0.05	-1.09 ± 0.06	-39%	<0.0001
18	n=399 1.75 ± 0.04	n=384 2.62 ± 0.05	-0.87 ± 0.06	-33%	<0.0001
30	n=3473 1.80 ± 0.02	n=3452 2.65 ± 0.01	-0.85 ± 0.02	-32%	<0.0001
48	n=385 1.94 ± 0.05	n=407 2.72 ± 0.04	-0.78 ± 0.06	-29%	<0.0001

*Values at baseline represent the LDL-C level before the initial randomization in all patients ever randomized to ezetimibe/simvastatin versus placebo. Values at 12, 30, and 48 months represent LDL-C levels in patients in Arms 1 and 2. Values at 18 months represent LDL-C levels in patients in Arms 3a and 3b taken 18 months after their final randomization to ezetimibe/simvastatin versus placebo. Patients with missing values at randomization were not included in this analysis. Patients with missing values at the follow-up visit were assigned their value at randomization
Conversion factor for mmol/L to mg/dL for cholesterol is 38.7.

As shown in Table 8 the absolute difference in LDL-C between the ezetimibe/simvastatin and placebo treatment groups at one year (when about 75% of patients were taking ≥80% of their allocated treatment) was about 1.1 mmol/L (42 mg/dL) and declined throughout the trial to 0.77 mmol/L (30 mg/dL) at 4 years. The lessening of the absolute and percentage difference in total- and LDL-C as the trial progressed was likely due to a decrease in compliance to the allocated study treatment and an increase in non-study statin use in patients allocated to placebo, as shown in Section 4.10.5 Table 6. At 48 months, compliance with >80% of study treatment had decreased to 60% and 56% in patients allocated to ezetimibe/simvastatin 10/20 mg and placebo, respectively, and non-study statin use had increased to 9% and 14%, respectively. As noted in Section 4.10.5, compliance was lower in patients on dialysis, and this, along with the lower baseline LDL-C level in patients on dialysis, resulted in a smaller average reduction in LDL-C in patients on dialysis compared to those not on dialysis.

Table 9 summarizes the levels of lipids and apolipoproteins at randomization, and at the 2.5 year visit when all patients were scheduled to have lipids measured. The values for LDL-C are also in Table 8 above. In patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo, LDL-C was reduced by 0.85 mmol/L (33 mg/dL), representing a 32% reduction compared to placebo. Non-HDL-C decreased by 1.08 mmol/L (42 mg/dL), a 30% reduction compared to placebo, and TG by 0.28 mmol/L (24.8 mg/dL), a 13% reduction compared to placebo.

Table 9

Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and 2.5 Years of Follow-Up

Time From Initial Randomization (Months)	Ezetimibe/ simvastatin 10/20 mg	Placebo	Absolute Difference	Percentage Difference	p-Value
Total cholesterol (mmol/L)					
0	n=4463 4.88 ± 0.02	n=4430 4.90 ± 0.02	-0.02 ± 0.03	0%	0.42
30	n=3474 3.66 ± 0.02	n=3452 4.73 ± 0.02	-1.07 ± 0.03	-23%	<0.0001
LDL cholesterol (mmol/L)					
0	n=4462 2.77 ± 0.01	n=4430 2.78 ± 0.01	-0.01 ± 0.02	0%	0.49
30	n=3473 1.80 ± 0.02	n=3452 2.65 ± 0.01	-0.85 ± 0.02	-32%	<0.0001
HDL cholesterol (mmol/L)					
0	n=4459 1.12 ± 0.01	n=4430 1.11 ± 0.01	0.01 ± 0.01	1%	0.12
30	n=3470 1.14 ± 0.01	n=3452 1.13 ± 0.01	0.02 ± 0.01	2%	0.03
Non-HDL cholesterol (mmol/L)					
0	n=4459 3.75 ± 0.02	n=4430 3.79 ± 0.02	-0.03 ± 0.02	-1%	0.19
30	n=3470 2.52 ± 0.02	n=3452 3.60 ± 0.02	-1.08 ± 0.03	-30%	<0.0001

Mean ± SE Lipids (mmol/L) and Apolipoproteins (mg/dL) at Randomization and 2.5 Years of Follow-Up (Cont.)

Time From Initial Randomization (Months)	Ezetimibe/ simvastatin 10/20 mg	Placebo	Absolute Difference	Percentage Difference	p-Value
Triglycerides (mmol/L)					
0	n=4462 2.31 ± 0.03	n=4429 2.34 ± 0.03	-0.03 ± 0.04	-1%	0.49
30	n=3473 1.84 ± 0.03	n=3450 2.12 ± 0.03	-0.28 ± 0.04	-13%	<0.0001
Apolipoprotein B (mg/dL)					
0	n=4467 95.91 ± 0.39	n=4435 96.67 ± 0.38	-0.76 ± 0.55	-1%	0.17
30	n=3466 70.32 ± 0.44	n=3451 93.09 ± 0.44	-22.77 ± 0.62	-24%	<0.0001
Apolipoprotein A1 (mg/dL)					
0	n=4471 134.51 ± 0.43	n=4436 133.38 ± 0.43	1.13 ± 0.61	1%	0.06
30	n=3480 144.97 ± 0.52	n=3455 142.84 ± 0.51	2.14 ± 0.73	1%	0.0033

* Values at time 0 (baseline) represent the level before the initial randomization in all patients ever randomized to ezetimibe/simvastatin versus placebo. The 30 month row only includes patients in Arms 1 and 2. Patients with missing values at randomization were not included in this analysis. Patients with missing values at the follow-up visit were assigned their value at randomization
Conversion factor for mmol/L to mg/dL for cholesterol is 38.7

.

4.10.7 Discussion of Efficacy

4.10.7.1 SHARP in the Context of Previous Studies in Patients Predominantly Without CKD

In a recent meta-analysis of treatments to lower LDL-C in 26 outcome trials in 170,000 participants followed over an average of 5 years, a 22% reduction in the risk of major vascular events (a composite endpoint similar but not identical to MVE and MAE as defined in SHARP) per 1.0 mmol/L LDL-C reduction was observed (risk ratio 0.78, 95% confidence interval 0.76-0.80) [8]. For a reduction of 0.85 mmol/L as observed in SHARP, the meta-analysis would predict a percent risk reduction of 22 x 0.85 = 19%, close to the 16%/17% reduction observed for MVE/MAE. Thus the point estimate of the observed result is marginally below that of the meta-analysis, but the confidence interval clearly includes it. Therefore, the relationship between LDL-C and MVE and MAE reduction in SHARP was consistent with previous primary and secondary cardiovascular outcome studies in patients predominantly without CKD.

4.10.7.2 Cardiovascular Outcomes in SHARP in the Context of Previous Studies with Ezetimibe

SHARP is not only the first study to show that lowering LDL-C in CKD patients reduces the risk of major cardiovascular events, but also the first study to show a clear beneficial effect of the combination of ezetimibe and a statin on the primary endpoint in any patient population. There are two previous studies, one an imaging study and the other an outcome study, in which ezetimibe did not demonstrate a significant benefit on the primary endpoint. First, in ENHANCE [57], ezetimibe compared to placebo on a background of simvastatin therapy did not affect carotid intima-media thickness (IMT) in an ultrasound imaging study in 720 patients with familial hypercholesterolemia. Slowing of the progression of carotid atherosclerosis as measured by intima-media thickness has been observed in several studies with statins, and the failure of ezetimibe is probably attributable to the fact that most of these patients had been aggressively treated with statins for many years prior to the study, so that their baseline intima-media thickness was barely above the normal range [58]. In retrospect, this is consistent with the findings of later IMT studies, where treatment with atorvastatin, which has proven outcomes data [8], similarly did not show a reduction in IMT in the RADIANCE I study in 850 patients with familial hypercholesterolemia exposed to prior lipid-lowering therapy [59], as well as in CASHMERE [60] in postmenopausal women, who had baseline IMT close to the normal range.

Second, in SEAS, ezetimibe/ simvastatin 10/40 mg for a median follow-up period of over 4 years in 1,873 patients with aortic stenosis had no effect on aortic valve disease and its complications. In two much smaller and shorter studies, SALTIRE [61], and ASTRONOMER [62], atorvastatin 80 mg and rosuvastatin 40 mg, respectively, were also ineffective against aortic valve disease, as measured by echocardiographic hemodynamic parameters and aortic valve calcium score. Aortic valve disease may simply be a condition that does not respond to lipid-lowering, at least in its more advanced stages. However, the hazard ratio in SEAS for a secondary endpoint of 'ischemic cardiovascular events' was 0.78 (95% CI 0.63-0.97, p=0.02) with ezetimibe/simvastatin, and this

beneficial effect has been more firmly established by a detailed subsequent analysis [63]. The beneficial effect of ezetimibe/simvastatin on ischemic events in patients with aortic stenosis is also supported in the newly issued guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) [64].

In SHARP, at 1 year the difference in LDL-C between patients allocated to ezetimibe/simvastatin 10/20 mg and simvastatin 20 mg alone was -0.34 mmol/L (13 mg/dL), and between ezetimibe/simvastatin 10/20 mg and placebo it was -1.09 mmol/L (42 mg/dL). Therefore ezetimibe contributed 31% and simvastatin contributed 69% of the LDL-C lowering effect of the ezetimibe/simvastatin 10/20 mg combination in the SHARP population, consistent with previous studies designed to evaluate the lipid-lowering effects of these two agents separately and in combination [65].

Although it enabled the calculation above, as previously noted in Section 4.3, the simvastatin-alone arm was included primarily to assist in the evaluation of short-term adverse effects of ezetimibe in this study population, and as such it continued for only the first year of the study. It is therefore not informative with respect to the effect of ezetimibe *per se* on cardiovascular outcomes. SHARP was not intended to address that issue; another study, IMPROVE-IT [66], has been designed specifically for this purpose and is ongoing. As discussed below, the reduction in cardiovascular risk in SHARP is commensurate with the results in previous studies of LDL-lowering treatments, which show on average a 22% reduction in major vascular events per mmol/L reduction in LDL-C. In theory, it is possible that all of the benefit shown in SHARP was due only to simvastatin, which has been proven in numerous studies to reduce cardiovascular risk [23; 26]. Simvastatin 20 mg alone would have produced an estimated reduction in LDL-C at 2.5 years (the study midpoint) of 0.59 mmol/L (the observed 0.85 mmol/L x 69%) in SHARP, and an expected risk reduction in major vascular events of 13% (0.59 x 22%), which is less than that observed.

A variety of drugs, including ezetimibe, statins, and bile acid sequestrants, that reduce LDL-C by different mechanisms have been approved for favorably modifying lipids prior to outcomes data being available; it is well demonstrated that lowering LDL-C will reduce cardiovascular risk, and the magnitude of the risk reduction is clearly proportional to the amount that LDL-C is lowered [8; 67]. For this reason, the effect on CV outcomes seen in SHARP, which, as noted above, is in line with what would be predicted given the observed LDL-C reductions attributable to the combined use of simvastatin and ezetimibe, is consistent with these effects on outcomes reflecting a contribution by the ezetimibe component. Additionally, while there may be remaining uncertainty of the direct effect of ezetimibe in this trial, SHARP clearly demonstrates that the use of the combination product, including the ezetimibe component, is safe in this setting and therefore the combined use of ezetimibe and simvastatin for use of modifying CV risk in renal patients is favorable.

4.10.7.3 SHARP in the Context of Previous Studies in CKD

Two previous studies in patients undergoing hemodialysis have tested the hypothesis that lowering LDL-C would reduce cardiovascular risk in patients with advanced CKD. 4D compared atorvastatin 20 mg versus placebo in 1,255 patients with diabetes undergoing hemodialysis over a follow-up period of four years. The primary endpoint, a composite of non-fatal MI, stroke and cardiac death, occurred in 469 patients. The relative risk of the primary endpoint was 0.92 (95% CI 0.77-1.10, p=0.37). Atorvastatin reduced the rates of all cardiac events combined (risk ratio 0.82, 95% CI 0.68-0.99, p=0.03), but this was offset by a non-significant increase in all cerebrovascular events combined (relative risk 1.12, 95% CI 0.81-1.55, p=0.49).

A second larger study, AURORA, compared rosuvastatin 10 mg against placebo in 2,776 patients undergoing dialysis [29]. The primary endpoint, a composite of non-fatal MI, non-fatal stroke and cardiovascular death, occurred in 804 patients. The risk ratio was 0.96 (95% CI 0.84-1.11, p=0.59), and there were no significant effects on any secondary endpoint.

In addition to including only patients on dialysis, AURORA and 4D used different composite primary endpoints that excluded revascularization procedures. The non-significant results for the primary endpoint of the 4D and AURORA trials might be the result of several factors, most importantly the different composition of their primary endpoints, as well as the high incidence of deaths due to CHF, LVH, and arrhythmias in patients undergoing hemodialysis, and the smaller patient numbers, which all result in reduced statistical power to detect effects on atherosclerotic events likely to be influenced by lowering LDL-C. Further analysis and discussion of the similarities and differences between SHARP and other studies in CKD patients may be found in Figure 6 and associated text of the published paper on SHARP [2]. In brief, the proportional effects of LDL-C lowering in these studies and SHARP were statistically compatible for non-fatal MI, non-fatal non-hemorrhagic stroke, coronary revascularization, and any vascular death (nonsignificant p-values for all heterogeneity tests). Furthermore, the effects on particular vascular outcomes in these trials were compatible with those observed for non-CKD populations evaluated in the CTT meta-analysis [8].

In SHARP there was no significant heterogeneity in the effect of ezetimibe/simvastatin on cardiovascular risk between the pre-dialysis patients and the dialysis patients, although the observed MAE risk reduction was smaller in the dialysis patients; 22% and 10% (χ_1^2 =1.3, p=0.25), respectively. The difference in mean LDL-C between the ezetimibe/simvastatin and placebo groups was also smaller in the dialysis patients compared to the pre-dialysis patients: in pre-dialysis patients, the difference at 2.5 years in mean LDL-C between treatment groups was 0.60 mmol (23 mg/dL) in patients on dialysis, compared to 0.96 mmol/L (37 mg/dL) in pre-dialysis patients. This difference is attributable to a lower baseline LDL-C and poorer compliance in dialysis patients; the latter is not unexpected given the multiple medications such patients typically take and their more severe illness. The smaller absolute change in LDL-C would be expected to yield a proportionately smaller cardiovascular risk reduction. Expressing the risk

reductions per mmol/L reduction in LDL-C, the risk reductions were more similar: 22% in the pre-dialysis patients and 16% in the dialysis patients (Figure 12).

The Cholesterol Treatment Trialists' (CTT) Collaboration [8] performed an analysis of the effect of statins on major vascular events according to eGFR in 26 statin outcome trials, divided into three categories: < 60 mL/min/1.73 m^2, ≥ 60 to < 90 mL/min/1.73 m^2, and ≥ 90 mL/min/1.73 m^2. The category < 60 mL/min excluded 4D and AURORA. As expected, event rates in the control groups increased with declining renal function. The risk reduction per mmol/L LDL-C lowering was very similar (22 to 23%) in each of the three categories, indicating that patients with reduced renal function experience proportional benefits similar to those with normal renal function. These findings are consistent with the results of SHARP.

In pre-dialysis patients, there are no conflicting results from any other study. Among patients with CKD in clinical practice, far more are at the pre-dialysis stage than on dialysis; furthermore, the overwhelming majority of patients on maintenance dialysis were previously pre-dialysis patients. Therefore, whether or not ezetimibe/simvastatin may reduce overall cardiovascular risk somewhat less effectively in dialysis patients is a relatively unimportant clinical question. The treating nephrologist can largely sidestep the issue by starting treatment with ezetimibe/simvastatin early in CKD, and should not wait until a patient requires maintenance dialysis. If a pre-dialysis patient has obtained a worthwhile reduction in LDL-C without significant adverse effects then, in most cases, there will be no good reason to stop treatment with ezetimibe/simvastatin when dialysis is needed because the existing evidence, although not absolutely definitive, strongly suggests there is continued benefit.

4.10.7.4 Extrapolating the Outcome Results of SHARP to Clinical Practice

The analyses of endpoint events in SHARP are based on the standard intention-to-treat approach, which permits an unbiased and rigorous conclusion as to whether a treatment is beneficial or harmful. Using this approach, ezetimibe/simvastatin 10/20 mg clearly reduces cardiovascular risk in CKD. However, in long-term clinical trials such as SHARP where, for a variety of reasons, a substantial number of participants either do not take the allocated treatment or take similar treatments prescribed outside the study, an adjustment needs to be made to the observed magnitude of the benefit in order to better quantify the benefit the treatment can provide. The risk reduction relevant to prescribers and patients is that which an individual taking ezetimibe/simvastatin consistently for 5 years could expect, as opposed to an observed risk reduction diluted by the effects of drop-ins and drop-outs, which together reduced net compliance to only about two thirds of the population at the 2.5 year midpoint. On the basis that approximately one-third of the patients effectively did not contribute to the comparison of the two treatment groups, an unbiased estimate of the effect of taking ezetimibe/simvastatin 10/20 mg consistently is yielded by multiplying the observed risk reductions by 3/2.

The same result is obtained if the adjustment is made on the basis of LDL-C: two thirds net compliance produced two thirds of the reduction in LDL-C that would have occurred had there been neither drop-ins nor drop-outs (that is, there was an observed reduction in LDL-C of 32% at the study midpoint of 2.5 years, which is about two thirds of the 52% LDL-C reduction that has been observed in short-term studies, where compliance is typically high).

The observed reductions in the risk of MVE and MAE were 16% and 17% respectively. After making allowance for net noncompliance as indicated above, risk reductions of about one quarter would be expected in a patient taking most of the ezetimibe/simvastatin 10/20 mg prescribed for 5 years. Evidence is accumulating in subjects without CKD that the earlier lipid-lowering treatment begins, the greater the ultimate benefit [68; 69]. Although not directly addressed by SHARP, it is likely that greater cardiovascular benefit could accrue from starting ezetimibe/simvastatin in patients with renal disease before eGFR falls below 60 mL/min/1.73 m^2.

4.11 Safety

4.11.1 Introduction

With over 9,000 patients followed for a median duration in survivors of 4.9 years, SHARP is much larger than any previous completed study with ezetimibe and simvastatin in combination or ezetimibe alone, and is also the largest study with any lipid-lowering treatment in CKD. Overall, the safety profile of ezetimibe/simvastatin 10/20 mg in SHARP was good, especially considering that CKD patients suffer multiple complications and take numerous concomitant medications. A third of the study population was on dialysis at randomization, a third of the pre-dialysis patients went on to ESRD during the course of the study and a quarter of the randomized patients died during the course of the study. Other than a small excess of myopathy/rhabdomyolysis cases in patients taking ezetimibe/simvastatin 10/20 mg, which was expected and will be discussed below, no important adverse effects were observed. A summary of the main safety data categories is provided in Table 10, and further information follows in Sections 4.11.2 to 4.11.4. Unless otherwise indicated, adverse events were assessed on an ITT basis.

Table 10

Principal Safety Data Categories

	Ezetimibe/simvastatin (N=4650)		Placebo (N=4620)	
	n	(%)	n	(%)
Deaths	1142	(24.6%)	1115	(24.1%)
Cancers	438	(9.4%)	439	(9.5%)
Non-Endpoint† SAEs	3258	(70.1%)	3270	(70.8%)
SAEs Considered Drug-Related‡	20	(0.43%)	13	(0.28%)
Other SAEs Causing Discontinuation	303	(6.5%)	310	(6.7%)
Increased Creatine Kinase				
>5 to ≤ 10 times ULN	50	(1.1%)	47	(1.0%)
> 10 to ≤ 40 times ULN	17	(0.4%)	16	(0.3%)
> 40 times ULN	4	(0.1%)	5	(0.1%)
Myopathy/Rhabdomyolysis (ITT)	9	(0.19%)	5	(0.11%)
Myopathy/Rhabdomyolysis (on-treatment)	8	(0.17%)	3	(0.065%)
Hepatitis: non-infective or cause unknown (ITT)	9	(0.19%)	7	(0.15%)
Hepatitis: non-infective or cause unknown (on-treatment)	7	(0.15%)	6	(0.13%)
Transaminases >3xULN‖	30	(0.65%)	26	(0.56%)

† Excludes deaths, major vascular events, cancer, TIA, hospitalization for angina or heart failure, dialysis access revision, diabetes and hypoglycemia, initiation of dialysis, pancreatitis, hepatitis, gallstone complications/hospitalizations, myopathy and rhabdomyolysis.
‡ Among patients with SAEs considered drug-related, 17 (0.4%) allocated to ezetimibe/simvastatin versus 12 (0.3%) allocated to placebo discontinued study treatment.
‖ On 2 consecutive measurements

Short-term adverse effects were also evaluated during the first year of the trial in 9438 patients randomized to simvastatin 20 mg versus ezetimibe/simvastatin 10/20 mg versus placebo. There were no differences in adverse effects at 1 year between patients allocated simvastatin 20 mg alone compared to ezetimibe/simvastatin 10/20 mg. These data have been published [1]. As with the efficacy data, the safety data presented in this document are from 9270 patients during the whole follow-up period which comprise data from patients initially randomized to ezetimibe/simvastatin 10/20 mg versus placebo (N=8,384), and for the period beyond year 1 in patients initially randomized to simvastatin 20 mg who were re-randomized to ezetimibe/simvastatin 10/20 mg versus placebo (N=886).

4.11.2 Adverse Event Summary

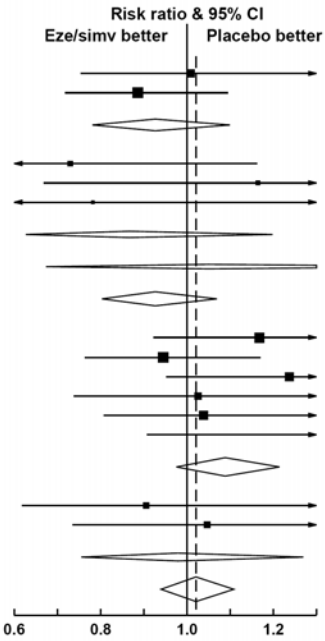
Cause-Specific Mortality

The numbers of deaths overall and of deaths due to non-vascular causes collectively were not significantly different in patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo. There were no significant differences between the ezetimibe/simvastatin and placebo groups in mortality from specific non-CHD or non-vascular causes, including cancer (Figure 13).

Figure 13

Cause-Specific and Overall Mortality

Event	Eze/simv	Placebo	O-E	Var	z	Risk ratio & 95% CI	p
CHD death	91 (2.0%)	90 (1.9%)	0.4	45.2	0.06	1.01 (0.75-1.35)	
Other cardiac death	162 (3.5%)	182 (3.9%)	-10.4	86.0	-1.12	0.89 (0.72-1.09)	
Cardiac death	**253 (5.4%)**	**272 (5.9%)**	**-10.0**	**131.2**	**-0.87**	**0.93 (0.78-1.10)**	**0.38**
Ischaemic stroke	30 (0.6%)	41 (0.9%)	-5.6	17.7	-1.33	0.73 (0.46-1.16)	
Haemorrhagic stroke	27 (0.6%)	23 (0.5%)	1.9	12.5	0.54	1.16 (0.67-2.03)	
Unspecified stroke	11 (0.2%)	14 (0.3%)	-1.5	6.2	-0.61	0.78 (0.36-1.71)	
Stroke (any type)	**68 (1.5%)**	**78 (1.7%)**	**-5.2**	**36.5**	**-0.87**	**0.87 (0.63-1.20)**	**0.39**
Any other vascular death	**40 (0.9%)**	**38 (0.8%)**	**0.9**	**19.5**	**0.21**	**1.05 (0.67-1.64)**	**0.83**
Subtotal: any vascular	**361 (7.8%)**	**388 (8.4%)**	**-14.3**	**187.2**	**-1.04**	**0.93 (0.80-1.07)**	**0.30**
Any cancer (including complications)	150 (3.2%)	128 (2.8%)	10.8	69.5	1.29	1.17 (0.92-1.48)	
Renal death	164 (3.5%)	173 (3.7%)	-4.8	84.2	-0.52	0.95 (0.76-1.17)	
Any respiratory death	124 (2.7%)	100 (2.2%)	11.9	56.0	1.59	1.24 (0.95-1.61)	
Gastrointestinal	72 (1.5%)	70 (1.5%)	0.9	35.5	0.15	1.03 (0.74-1.42)	
Other medical causes	124 (2.7%)	119 (2.6%)	2.3	60.7	0.29	1.04 (0.81-1.34)	
Trauma / fracture	34 (0.7%)	22 (0.5%)	6.0	14.0	1.60	1.53 (0.91-2.59)	
Subtotal: any non-vascular	**668(14.4%)**	**612(13.2%)**	**27.1**	**320.0**	**1.51**	**1.09 (0.98-1.21)**	**0.13**
Sudden death	50 (1.1%)	55 (1.2%)	-2.6	26.2	-0.51	0.91 (0.62-1.33)	
Death (reason unclear)	63 (1.4%)	60 (1.3%)	1.4	30.7	0.25	1.05 (0.74-1.49)	
Subtotal: unknown causes	**113 (2.4%)**	**115 (2.5%)**	**-1.2**	**57.0**	**-0.16**	**0.98 (0.76-1.27)**	**0.87**
Total: all causes	**1142(24.6%)**	**1115(24.1%)**	**11.6**	**564.1**	**0.49**	**1.02 (0.94-1.11)**	**0.63**



The logrank 'observed minus expected' statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (risk ratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

Non-fatal Serious Adverse Events

As specified in the protocol, only adverse events that were serious, or that led to discontinuation of study treatment were recorded. Non-fatal SAEs, regardless of causality and compliance with study medication, and excluding MVEs and other pre-specified outcomes (cancer, TIA, hospitalization for angina or heart failure, dialysis access revision, diabetes and hypoglycemia, initiation of dialysis, renal transplantation, pancreatitis, hepatitis, myopathy, rhabdomyolysis) were reported in 3258 (70%) patients allocated to ezetimibe/simvastatin and 3270 (71%) patients allocated to placebo (p=0.42).

The most common SAEs were renal, affecting 42% of patients. Gastrointestinal (GI) SAEs (not related to the liver, pancreas, or the biliary tract) were present in about 21% of patients in each treatment group. There was no significant imbalance in any particular SAE in patients randomized to ezetimibe/simvastatin versus placebo with the exception of hemodialysis access (excluding revision), which was less frequent in patients allocated to ezetimibe/simvastatin compared to placebo.

"Suspected" Serious Adverse Reactions

Table 11 lists "suspected" serious adverse reactions (SSARs), which are defined as unwanted or harmful reactions considered by the reporting investigator to be both serious and likely to be related to the study treatment.

Table 11

Serious Adverse Reactions Attributed to Study Treatment

Suspected Serious Adverse Reaction	Ezetimibe/ simvastatin 10/20 mg (N=4650)	Placebo (N=4620)
	n	n
CK>10 ≤40xULN, muscle symptoms†	4	3
CK>40xULN, muscle symptoms‡	3	0
CK>40xULN, no muscle symptoms	0	1
Non-infective hepatitis	1	0
Hepatitis, unknown etiology	0	1
Complications of gallstones	1	0
Acute pancreatitis (without gallstones)	3	1#
Chronic pancreatitis	0	2
Gastritis	0	1
GI hemorrhage	1	0
Diarrhea	1	0
Difficulty controlling INR	1	0
Peripheral neuropathy	0	1
Acute interstitial nephritis	1	0
Eczema/dermatitis	2	0
Psoriasis	0	1
Allergic or anaphylactic reaction	2	3
Total	**20 (0.43%)**	**13 (0.28%)**

† These patients meet the criteria for myopathy, defined as CK elevation >10xULN plus unexplained muscle pain or weakness.
‡ These patients meet the criteria for rhabdomyolysis, defined as myopathy with CK elevation >40xULN.
# This patient had both acute and chronic pancreatitis and therefore also appears in the row below.
Note: Suspected serious adverse reaction refers to an unwanted or harmful reaction that is considered by the reporting investigator to be both serious and likely to be directly related to the study treatment based upon information from the patient and/or the patient's physician.

Of 33 patients with suspected serious adverse reactions, 20 (0.4%) patients were allocated to ezetimibe/simvastatin 10/20 mg and 13 (0.3%) patients were allocated to placebo. The most common were CK elevations >10xULN, which were observed in 7 patients allocated to ezetimibe/simvastatin 10/20 mg and 4 patients allocated to placebo. SSARs led to discontinuation of study treatment in 17 (0.4%) patients allocated to ezetimibe/simvastatin 10/20 mg and 12 (0.3%) patients allocated to placebo. Four patients (3 allocated to ezetimibe/simvastatin 10/20 mg and 1 allocated to placebo) had a SSAR but continued taking study medication.

Serious Adverse Events That Resulted in Discontinuation of Study Treatment

Serious adverse events that led to discontinuation of study treatment before the scheduled end of the trial are shown in Table 12. The most common SAE that led to discontinuation of study treatment in patients randomized to ezetimibe/simvastatin 10/20 mg versus placebo was renal transplantation (often because of starting cyclosporine), which occurred in 152 (3.3%) patients allocated to ezetimibe/simvastatin and 148 (3.2%) patients allocated to placebo.

Table 12

Serious Adverse Events that Resulted in Discontinuation of Study Treatment

Reason for stopping	Ezetimibe/ simvastatin 10/20 mg (N=4650)		Placebo (N=4620)	
	n	(%)	n	(%)
Suspected Serious Adverse Reaction	17	(0.4%)	12	(0.3%)
Other serious adverse event				
Cardiac disorder	38	(0.8%)	53	(1.1%)
Stroke	10	(0.2%)	15	(0.3%)
Other vascular disorder	7	(0.2%)	10	(0.2%)
Cancer	30	(0.6%)	20	(0.4%)
Renal transplant	152	(3.3%)	148	(3.2%)
Other renal	8	(0.2%)	13	(0.3%)
Respiratory	2	(0.0%)	5	(0.1%)
Gastrointestinal	13	(0.3%)	21	(0.5%)
Other medical	37	(0.8%)	22	(0.5%)
Non-medical	2	(0.0%)	1	(0.0%)
Unspecified SAE	4	(0.1%)	2	(0.0%)
Subtotal	303	(6.5%)	310	(6.7%)

Non-serious Adverse Events

Non-serious AEs (NSAEs) were not routinely collected in SHARP. NSAE data were only collected when the NSAE was a reason for stopping study treatment. As shown in Table 13, below, there was a greater number of NSAEs that led to study drug discontinuation in patients allocated to ezetimibe/simvastatin 10/20 mg versus placebo. The difference is largely accounted for by the greater number of patients allocated to ezetimibe/simvastatin with muscle pain and with abnormal safety blood results (CK, ALT, and/or AST), which were the most common NSAEs that led to discontinuation of study treatment. There was also an imbalance in the number of patients who reported skin symptoms: 19 versus 8 for ezetimibe/simvastatin 10/20 mg versus placebo.

Table 13

Non-Serious Adverse Events that Resulted in Discontinuation of Study Treatment

	Ezetimibe/ simvastatin 10/20 mg (N=4650)	Placebo (N=4620)
Reason for Stopping	n (%)	n (%)
Non-serious adverse event		
General/miscellaneous	10 (0.2%)	15 (0.3%)
Chest pain/palpitation	2 (0.0%)	5 (0.1%)
Dizziness/blackouts	1 (0.0%)	0 (0.0%)
Respiratory symptoms	1 (0.0%)	2 (0.0%)
Upper GI symptoms	10 (0.2%)	9 (0.2%)
Lower GI symptoms	10 (0.2%)	13 (0.3%)
Abdominal pain/distention	4 (0.1%)	4 (0.1%)
Genitourinary symptoms	0 (0.0%)	1 (0.0%)
Skin symptoms	19 (0.4%)	8 (0.2%)
Bleeding symptoms	0 (0.0%)	1 (0.0%)
Headache	0 (0.0%)	0 (0.0%)
Other neurological symptoms	3 (0.1%)	7 (0.2%)
Psychological symptoms/mood disorders	3 (0.1%)	2 (0.0%)
Joint symptoms	10 (0.2%)	8 (0.2%)
Muscle pain	49 (1.1%)	28 (0.6%)
Abnormal safety blood result	43 (0.9%)	28 (0.6%)
Subtotal	165 (3.5%)	131 (2.8%)

The total number of patients stopping study medication due to any adverse event, whether serious or not, or drug-related or not, was 485 (10.4%) of patients allocated to ezetimibe/simvastatin and 453 (9.8%) of patients allocated to placebo. Patients stopping study medication due to an adverse event accounted for about one-third of the non-compliant patients.

4.11.3 Specific Adverse Events

4.11.3.1 Cancer

A recent safety concern surrounding ezetimibe has been possible effects on the risk of cancer, which was raised by the result of SEAS in 2008 [70]. In that study, the first cardiovascular outcome clinical trial that included ezetimibe, ezetimibe/simvastatin 10/40 mg was compared against placebo in 1873 patients followed for over 4 years. There were 166 patients who developed cancer after randomization, 101 in the ezetimibe/simvastatin group, versus 65 in the placebo group (p=0.006). The excess was due predominantly to a higher incidence of cancers of the prostate and skin in the active treatment group. Because there have been many studies with statins reporting the incidence of cancer, and collectively the numbers are very similar in the active treatment and control groups [8; 67], the concern arising from the SEAS results was centered on ezetimibe, notwithstanding the fact that rodent carcinogenicity studies with ezetimibe were negative and there are no other clinical data suggesting an increase in the risk of cancer.

The hypothesis generated by SEAS, that ezetimibe may increase the risk of cancer, is not supported by the results of SHARP, in which the number of cancers was much larger. There was no significant effect of ezetimibe/simvastatin 10/20 mg on incident cancers or cancer deaths collectively or at any site as shown in Table 14 below. In particular, in contrast to SEAS, the incidence of cancers of the prostate and skin in the ezetimibe/simvastatin group was in both cases *lower* than in the placebo group. There was no evidence that ezetimibe/simvastatin increased the incidence of cancer (438 [9.4%] versus 439 [9.5%], RR 0.99, 95% CI 0.87-1.13, p=0.89).When non-melanoma skin cancers were excluded, there was still no evidence that ezetimibe/simvastatin increased the incidence of cancer (322 [6.9%] versus 307 [6.6%], RR 1.04, 95% CI 0.89-1.22, p=0.60). Furthermore, there was no evidence of an emerging excess of cancer with more prolonged treatment and follow-up, as shown in Figure 14.

Table 14

Cancer Incidence and Cancer Mortality By Site

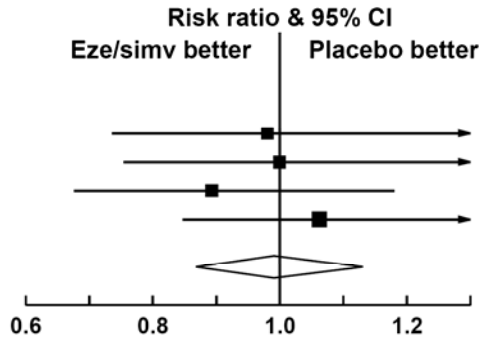
	Cancer Incidence			Cancer Mortality		
	Ezetimibe/ Simvastatin 10/20 mg (n=4650)	**Placebo (n=4620)**	**p value**	**Ezetimibe/ Simvastatin 10/20 mg (n=4650)**	**Placebo (n=4620)**	**p value**
Lip/mouth/pharynx/esophagus	14 (0.3%)	16 (0.3%)	0.84	9 (0.2%)	8 (0.2%)	1.0
Stomach	11 (0.2%)	14 (0.3%)	0.68	10 (0.2%)	11 (0.2%)	1.0
Large bowel or intestine	53 (1.1%)	35 (0.8%)	0.07	20 (0.4%)	15 (0.3%)	0.51
Pancreas	9 (0.2%)	10 (0.2%)	1.0	7 (0.2%)	10 (0.2%)	0.62
Liver/gallbladder/bile ducts	8 (0.2%)	4 (0.1%)	0.39	4 (0.1%)	4 (0.1%)	1.0
Lung	42 (0.9%)	35 (0.8%)	0.51	32 (0.7%)	22 (0.5%)	0.23
Other respiratory	3 (0.1%)	4 (0.1%)	1.0	2 (0.0%)	3 (0.1%)	1.0
Skin	136 (2.9%)	153 (3.3%)	0.32	4 (0.1%)	4 (0.1%)	1.0
Breast	29 (0.6%)	21 (0.5%)	0.33	1 (0.0%)	1 (0.0%)	1.0
Prostate	39 (0.8%)	52 (1.1%)	0.20	6 (0.1%)	2 (0.0%)	0.27
Kidney*	31 (0.7%)	23 (0.5%)	0.35	5 (0.1%)	1 (0.0%)	0.22
Bladder and urinary tract (not kidney)	26 (0.6%)	32 (0.7%)	0.50	8 (0.2%)	7 (0.2%)	1.0
Genital site	12 (0.3%)	14 (0.3%)	0.84	4 (0.1%)	2 (0.0%)	0.69
Hematological	26 (0.6%)	27 (0.6%)	1.0	6 (0.1%)	14 (0.3%)	0.12
Other known site	9 (0.2%)	12 (0.3%)	0.65	3 (0.1%)	5 (0.1%)	0.72
Unspecified cancer	13 (0.3%)	7 (0.2%)	0.27	11 (0.2%)	5 (0.1%)	0.21
Any incident cancer†	**438 (9.4%)**	**439 (9.5%)**	**0.89**	**132 (2.8%)**	**114 (2.5%)**	**0.26**

For the individual sites, multiple continuity corrected p values are reported; any value that is based on data from more than five patients could have yielded a value less than 0.05 by chance. Uncorrected p values that are less than the inverse of the number of such tests were therefore corrected by multiplying by the number of such tests to correct for this multiplicity of comparisons. In all cases, this yielded p values of 1.0.
* Includes two versus one cases and one versus zero deaths due to cancer in a transplanted kidney.
† Excludes 18 (0.4%) versus 14 (0.3%) deaths from cancers diagnosed before randomization.

Figure 14

Cancer Incidence by Year of Follow-Up

Year of follow-up	Eze/simv (n=4650)	Placebo (n=4620)	O-E	Var	z	Risk ratio & 95% CI (Eze/simv better | Placebo better)	p
1	93 /4650 (2.0%)	94 /4620 (2.0%)	-0.9	46.7	-0.14	0.98 (0.74-1.31)	
2	97 /4303 (2.3%)	96 /4257 (2.3%)	-0.0	48.2	-0.00	1.00 (0.75-1.33)	
3	94 /3975 (2.4%)	104 /3925 (2.6%)	-5.6	49.5	-0.80	0.89 (0.68-1.18)	
4+	154 /3569 (4.3%)	145 /3550 (4.1%)	4.5	74.7	0.52	1.06 (0.85-1.33)	
All follow-up	**438 /4650 (9.4%)**	**439 /4620 (9.5%)**	**-2.0**	**219.2**	**-0.14**	**0.99 (0.87-1.13)**	**0.89**



χ^2_1 for trend = 0.12 (p = 0.73)

The logrank "observed minus expected" statistic (O-E) and its variance (Var or V) are calculated using standard methods, stratifying for whether patients were randomized to ezetimibe/simvastatin versus placebo at the first or second randomizations. The log (riskratio [RR]) is calculated as (O-E)/V, and the 95% confidence limits as (O-E)/V ± 1.96/ √V, and the normal variate z, equal to (O-E)/√V, is presented with its 2 sided p-value.

The number of patients with incident cancers in SHARP (877) was five times greater than in SEAS (175), providing more statistical power. This illustrates once again that, in any study, imbalances between treatment groups can easily occur due to chance [48], especially when the numbers in a study are relatively small and multiple comparisons are made of possible adverse events. The final results of SHARP are concordant with the interim analysis by Peto et al. [48] of cancers in SHARP and IMPROVE-IT taken together. IMPROVE-IT [71] is an ongoing study of ezetimibe/simvastatin 10/40 mg versus simvastatin 40 mg alone in about 18,000 patients with acute coronary syndrome. At the time of the interim analysis, the mean duration of follow-up was 2.7 years in SHARP and 1.0 years in IMPROVE-IT, and person-years of follow-up were approximately 25,000 and 12,000, respectively. SHARP thus contributed the majority of the data in the interim analysis, which was performed as a consequence of the results of SEAS and published together with it [48]. Peto et al found that there were fewer incident cancers in the pooled ezetimibe/simvastatin groups compared to the control groups, and therefore concluded that the difference in incident cancers between treatment groups in SEAS was likely due to chance. In the interim analysis, the only site where there was a nominally significant (before appropriate adjustment for multiplicity) difference in incident cancers was the kidney (25 versus 11, unadjusted p = 0.03) [48]. In the final results of SHARP, there were only a few more kidney cancers in the ezetimibe/simvastatin group than in the placebo group (31 versus 23), and the difference is not statistically significant (unadjusted p =0.28). Moreover, fewer cases occurred following the interim analysis among the patients in the ezetimibe/simvastatin group in SHARP (6 versus 12), which does not provide independent support for the earlier trend. Statistical comparisons made at 16 cancer sites, as in Table 14, are likely to observe chance imbalances at one or two sites. At only one site in SHARP was there an imbalance against active treatment that came close to reaching statistical significance (but again, only before adjustment for multiplicity): this was large bowel/intestine (risk ratio 1.50 (95% CI 0.99-2.28). There was no suggestion of any such effect in SEAS (9 in the ezetimibe/simvastatin group versus 8 in the placebo group).

There was a non-significant excess of cancer deaths in the ezetimibe/simvastatin groups in the interim pooled analysis of SHARP and IMPROVE-IT (97 versus 72, p=0.07) [48]. Although an increase in cancer mortality without a corresponding increase in incidence is biologically implausible [48] (and would have to be balanced by an equally implausible decrease in non-fatal cancers), this near-significant interim result had also raised concern [72; 73]. Of the patients with incident cancer in SHARP, 246 died of the disease during the follow-up period, substantially more than in the interim analysis of SHARP and IMPROVE-IT combined (169). There were no significant differences in cancer deaths overall (including pre-randomization cancers, risk ratio 1.17, 95% CI 0.92 -1.48, p=0.20), or at any site. The final results of SHARP are thus consistent with the conclusions of Peto et al. [48] that the near-significant difference in cancer mortality observed previously was a chance effect. In conclusion, the results of SHARP do not indicate an effect of ezetimibe on the incidence or mortality of cancer overall or at any site.

4.11.3.2 Hemorrhagic Stroke

As shown in Figure 7, non-significantly more patients allocated to ezetimibe/simvastatin suffered a hemorrhagic stroke: 45 (1.0%) versus 37 (0.8%) in the placebo group, of which 27 and 23, respectively, were fatal. A significant increase in the risk of hemorrhagic stroke has been reported in SPARCL, a study comparing atorvastatin 80 mg to placebo in patients with a history of stroke or transient ischemic attack [74]. When the data on hemorrhagic stroke in a meta-analysis of statin studies [8] are combined with SPARCL and another study, CORONA [75] -- which like SPARCL was not available for inclusion in the meta-analysis -- there was a 21% increase in the risk of hemorrhagic stroke (p=0.01) [8]. In contrast to the non-significant difference in hemorrhagic stroke seen in SHARP, the beneficial effect on non-hemorrhagic (i.e. ischemic stroke and stroke of undetermined type) was statistically significant (RR 0.75, 95% CI 0.60–0.94) (Figure 8). Because ischemic stroke is much more common than hemorrhagic stroke, especially in Western populations, the overall effect of treatment on stroke taken as a whole was significantly beneficial in SHARP (Figure 6, risk ratio 0.81, 95% CI 0.66-0.99, p=0.038), consistent with several previous studies comparing statins against placebo [26; 74], as well as a meta-analysis of statin studies [8]. Therefore, although the slight adverse trend on hemorrhagic stroke in SHARP possibly reflects a real effect of statins (or lipid-lowering therapy in general), in most patients it will be far outweighed by the beneficial effect on ischemic stroke and other cardiovascular events (as observed in SHARP).

4.11.3.3 Myopathy

Introduction

Myopathy has not been definitely causally associated with ezetimibe, but it is a known adverse effect of simvastatin and other statins. Since myopathy was first described with lovastatin in 1988, Merck has carefully assessed myopathy during treatment with lovastatin and simvastatin both in clinical trials and post-marketing surveillance. The risk of statin-induced myopathy is strongly dose-dependent; in the case of simvastatin, particularly at the 80 mg dose. In SEARCH (also conducted by CTSU) [76], with a follow-up period of 6.7 years, there was one case of myopathy among the 6,033 patients taking simvastatin 20 mg and 52 cases among the 6,031 patients taking simvastatin 80 mg (i.e. incidence rates of 0.017% versus 0.9%). The prescribing information for both simvastatin and ezetimibe/simvastatin has included information about the dose-related risk of myopathy for many years, and a recent update following the results of SEARCH limits the usual dosage range to a maximum of 40 mg of simvastatin, except in patients already tolerating the 80 mg dose chronically.

Definitions of Myopathy and Rhabdomyolysis in SHARP

The traditional definition of myopathy in the context of statins that has been used by Merck, other companies with statins, and academic investigators for more than 20 years is CK elevation >10xULN plus unexplained muscle pain or weakness [77; 78]. That definition is used in the analysis of SHARP. There is no consensus definition of rhabdomyolysis, but two definitions have been used [77]: myopathy with CK>40xULN (which typically is ~10,000 U/L), and more stringently, myopathy with CK>40xULN plus evidence of renal damage. The latter was used in SEARCH and is considered optimal in patients without renal disease, since the magnitude of CK elevation may not be a good indicator of the clinical severity of muscle injury; for example, strenuous exercise can produce very large but asymptomatic increases in CK [79]. However, the substantial efforts of the CTSU physician adjudicators notwithstanding, it was difficult to ascertain acute renal damage secondary to myopathy accurately in the SHARP population. These patients had progressive renal disease and a background study rate of acute deterioration of renal function (acute-on-chronic renal failure) of approximately 1% of participants per year of follow-up, and of course, ascertainment of deterioration of renal function is impossible in patients who are on dialysis. At the very least, the accuracy of ascertainment is a matter of clinical judgment and not a proven fact. Therefore, the definition of rhabdomyolysis used in this document and the published paper is myopathy with CK>40xULN, regardless of renal damage.

Incidence of Myopathy in SHARP

Using these definitions, over the course of the study there were 9 cases of myopathy in patients allocated to ezetimibe/simvastatin and 5 in patients allocated to placebo. One patient allocated to ezetimibe/simvastatin had stopped taking it 3 months before developing myopathy, and 2 patients allocated to placebo were taking non-study statin at the time they developed myopathy, lovastatin (dosage uncertain) in one case (which met the criteria for rhabdomyolysis) and simvastatin 20 mg daily in the other. In the latter, myopathy resolved and CK fell to the normal range within a week of switching from simvastatin to fluvastatin 20 mg, a less potent statin. In these two patients, myopathy was considered to be probably statin-induced and, for this reason, they are not counted in the control group for the on-treatment analysis. The on-treatment analysis is shown in Table 15.

Table 15

Number of Patients with Myopathy and Rhabdomyolysis ('On-Treatment' Analysis)

Event	Ezetimibe/simvastatin 10/20 mg (N=4650)	Placebo (N=4620)
	n (%)	n (%)
Myopathy	8 (0.17%)	3 (0.065%)
Rhabdomyolysis	4 (0.09%)	0 (0.0%)
Not rhabdomyolysis	4 (0.09%)	3 (0.065%)

Myopathy is defined as CK>10xULN plus unexplained muscle symptoms, and includes those patients with rhabdomyolysis. Rhabdomyolysis is defined as patients with myopathy, with CK>40xULN.
One patient allocated to ezetimibe/simvastatin who was not taking study drug, and 2 patients allocated to placebo who were taking non-study statins are excluded from this table.

Four of the 8 patients taking ezetimibe/simvastatin and none of the 3 in the placebo group met the definition of rhabdomyolysis. (As noted above, one additional patient who was allocated to placebo developed rhabdomyolysis, but was taking a non-study statin and so excluded from the on-treatment analysis in Table 15.) All patients with myopathy, including those who developed rhabdomyolysis, recovered after treatment with ezetimibe/simvastatin was stopped. In the intention-to-treat and on-treatment analyses, the incremental incidence of myopathy (including rhabdomyolysis) above the placebo group was 4 and 5 patients respectively among about 4,500 patients allocated to ezetimibe/simvastatin for about 5 years, yielding an annual incremental incidence of approximately 0.1%, or about 1 per 5,000 patients per year.

Although a cross-study comparison of very small numbers and therefore subject to considerable uncertainty, the incremental 0.1% incidence of myopathy (including rhabdomyolysis) above the rate in the placebo group in patients taking ezetimibe/simvastatin in SHARP appears higher than that attributed to simvastatin 20 mg alone in SEARCH (1 of 6,033 patients, 0.017%), [44]). As previously noted in Section 4.1, for pharmacokinetic and patient susceptibility reasons patients with CKD are likely to be more vulnerable to statin-induced myopathy. Consistent with this (although again a cross-study comparison of very small numbers) are the rates of myopathy in the control groups in SHARP and HPS; the rate of myopathy in the placebo group in SHARP was 0.065% (3 of 4620 patients over 4.9 years), which appears higher than the 0.019% rate of myopathy in the placebo group of the Heart Protection Study [26] (2 of 10,267 patients over 5 years, excluding a patient taking cerivastatin). Thus, the higher but still very low observed rate in the ezetimibe/simvastatin 10/20 group in SHARP is not unexpected.

4.11.3.4 Liver and Gall Bladder

Small excesses of liver enzyme elevations have been observed in previous studies with simvastatin and other statins, and where ezetimibe has been added to statin therapy. In SHARP, the incidence of consecutive increases in transaminases >3xULN was slightly, but not significantly, higher in patients allocated to ezetimibe/simvastatin (0.65%) compared to placebo (0.56%). There was no evidence of any excess of clinical liver disease.

The incidence of non-viral hepatitis was similar in the ezetimibe/simvastatin and placebo groups, as has been the case in previous trials with simvastatin and ezetimibe separately or together. In SHARP, hepatitis was classified as infective when the cause was viral; non-infective when there was evidence of a non-infectious cause (such as alcohol, or medications); and no cause identified (unknown etiology) when serology was negative or unavailable and no obvious non-infective cause could be identified. Hepatitis was reported in 21 (0.45%) patients allocated to ezetimibe/simvastatin 10/20 mg and 18 (0.39%) patients allocated to placebo. These cases were adjudicated to be infective hepatitis in 12 (0.26%) patients allocated ezetimibe/simvastatin versus 12 (0.26%) allocated placebo; non-infective hepatitis in 6 (0.13%) versus 4 (0.09%) patients; and hepatitis with no cause identified in 3 (0.06%) versus 3 (0.06%) patients. One patient allocated to placebo appears in both the infective hepatitis and unknown etiology categories. In this patient, initial viral tests were negative, but repeat tests and confirmatory tests were positive for Hepatitis C and radiological imaging showed suspicion of cirrhosis. One patient allocated to ezetimibe/simvastatin who developed non-infective hepatitis had discontinued study treatment at least 1.5 years before the hepatitis event. Another patient allocated to ezetimibe/simvastatin with hepatitis of unknown etiology was noted to have elevated transaminases and hepatitis at the randomization visit before study drug had been taken. An on-treatment analysis is presented in Table 16, which again shows no significant difference between the treatment groups.

Table 16

Etiology of Hepatitis ('On-Treatment' Analysis)

Etiology of Hepatitis	Ezetimibe/simvastatin 10/20 mg (N=4650) n (%)	Placebo (N=4620) n (%)
Infective Hepatitis	12 (0.26%)	12 (0.26%)
Non-Infective Hepatitis	5 (0.11%)	4 (0.09%)
Unknown Etiology	2 (0.04%)	2 (0.04%)
TOTAL	19 (0.41%)	18 (0.39%)

This table does not include hepatitis that occurred in one patient randomized to simvastatin 20 mg alone prior to randomization to ezetimibe/simvastatin or placebo.

Not included in this table are 2 patients allocated to ezetimibe/simvastatin who were not taking study medication at the time of the hepatitis event. One patient was adjudicated as having non-infective hepatitis, but had stopped study medication approximately 1.5 years before the event. The other patient was adjudicated as having hepatitis of unknown etiology but the event occurred at the randomization visit before study medication had been taken.

An additional patient allocated to placebo was originally adjudicated as having hepatitis of unknown etiology, but was later adjudicated to have Hepatitis C. This patient only appears in the infective hepatitis category.

Studies in mice have suggested that ezetimibe decreases biliary saturation and could reduce the risk of gallstones [80; 81]. There was no evidence for such a beneficial effect in SHARP, but also no evidence of any hazard. Cases of gallstones and their complications, including pancreatitis secondary to gallstones, were evenly distributed between the treatment groups (Table 17).

Table 17

Gallstones: Number (%) of Patients

Gallstones	Ezetimibe/simvastatin 10/20 mg (N = 4650) n (%)	Placebo (N = 4620) n (%)	P-value
Complicated*	85 (1.83%)	76 (1.65%)	0.55
Uncomplicated	21 (0.45%)	30 (0.65%)	0.25

* Complications of gallstones included acute pancreatitis, cholecystectomy, gallstones with cholecystitis, bile duct stones with or without cholecystitis, and bile duct stones with cholangitis.

4.11.3.5 Diabetes and Pancreas

Ezetimibe/simvastatin did not significantly increase the risk of new onset diabetes (172 (4.8%) new cases in patients allocated to ezetimibe/simvastatin vs 162 (4.5%) new cases in patients allocated to placebo; risk ratio 1.06, 95% CI 0.85-1.32, p=0.59) or diabetic complications (risk ratio 1.07, 95% CI 0.84-1.37, p=0.56). There was a borderline significant increase in the incidence of hypoglycemia (risk ratio 1.50, 95% CI 0.99-2.28, p=0.06). Hypoglycemia has not previously been a concern with either ezetimibe or statins, and the p-value stated above has not been corrected for the multiple safety comparisons made. Therefore, this apparent difference may well be a chance finding.

Pancreatitis was among the safety endpoints specified in the SAP. This condition is most commonly caused either by gallstones (or fragments thereof) obstructing the common bile duct, or by substantial consumption of alcohol. An uncommon cause is marked hypertriglyceridemia, where the mechanism appears to be the intra-pancreatic production of irritating free fatty acids by pancreatic lipases. In SHARP, as noted above, there was no effect on the incidence of gallstones, and so the observed even distribution of pancreatitis secondary to gallstones (11 (0.24%) cases in patients allocated to ezetimibe/simvastatin versus 12 (0.26%) cases in patients allocated to placebo) is to be expected. Table 18 shows that there were fewer cases of pancreatitis not associated with gallstones in patients allocated to ezetimibe/simvastatin. Most cases were acute pancreatitis.

Table 18

Pancreatitis without Gallstones: Number (%) of Patients

Event	Ezetimibe/ simvastatin 10/20 mg (N = 4650) n (%)	Placebo (N = 4620) n (%)	P-value
Acute pancreatitis	11 (0.24%)	22 (0.48%)	---
Chronic pancreatitis	2 (0.04%)	6 (0.13%)	---
Total: Pancreatitis (without gallstones)	12 (0.26%)	27 (0.58%)	0.02

The limited literature on the subject suggests, based on epidemiological studies, that statins might increase the risk of pancreatitis [82; 83], so the SHARP results were unexpected and led to a review of the incidence of pancreatitis in HPS (simvastatin 40 mg versus placebo in 20,000 patients [84] and SEARCH (simvastatin 80 mg versus 20 mg in 12,000 patients, [76]). In HPS, there were 33 cases (0.3%) and 41 cases (0.4%) in the simvastatin 40 mg and placebo groups respectively; in SEARCH there were 19 cases (0.3%) and 29 cases (0.5%) in the simvastatin 80 mg and 20 mg groups, respectively. The possibility that ezetimibe/simvastatin or the components alone, or lipid-lowering therapy in general, could decrease the risk of pancreatitis may be a hypothesis worth testing in existing clinical trial databases or future large studies.

4.11.4 Summary of Safety Data

There were no significant differences between the ezetimibe/simvastatin 10/20 mg and placebo groups on all-cause mortality, on any specific cause of death, or in the incidence of cancer overall or at any particular site.

The incremental incidence of myopathy (including rhabdomyolysis) with ezetimibe/simvastatin in this population was approximately 0.1%, or about 1 per 5,000 patients per year.

There were no significant differences between the treatment groups in the incidence of consecutive elevations of transaminases >3xULN (0.65% in the ezetimibe/simvastatin group versus 0.56% in the placebo group), of non-viral hepatitis or of gallstones. Excluding cases secondary to gallstones, 12 patients had pancreatitis in the ezetimibe/simvastatin group, compared to 27 in the placebo group.

There were also no significant effects on the incidence of new onset diabetes, hypoglycemia or other complications of diabetes. The overall incidence of serious adverse events and adverse events leading to discontinuation of study medication was similar in the two groups. No new adverse effects of ezetimibe/simvastatin were discovered.

5. Benefit-Risk Analysis for Prevention of Major Vascular Events with Ezetimibe/Simvastatin in Patients with CKD

The results of SHARP show that in patients with CKD, ezetimibe/simvastatin 10/20 mg reduces the risk of major vascular events. (In the proposed labeling, the term 'cardiovascular' is used instead of 'vascular' only because it is a more familiar term for most prescribers.) On an intention-to-treat basis, the risk reductions in MVE and MAE were 16% and 17%, respectively. Taking into account the fact that dropouts and drop-ins together reduced net compliance at the 2.5 year midpoint to only about two thirds of the population, it can be estimated that the reduction in risk of major vascular events in patients who take their prescribed treatment should be about one quarter. In subgroup analysis, the only important heterogeneity of this effect was attributable to greater absolute reductions of LDL-C in the subgroups with high levels of lipoproteins rich in apolipoprotein B at baseline. This heterogeneity was much reduced when the risk reductions were weighted by achieved reductions in LDL-C. There was no significant heterogeneity in subgroups divided by numerous baseline variables including CKD stage, dialysis vs. non-dialysis, the presence of coronary disease or diabetes, or demographic characteristics.

There was no evidence in SHARP for an increase in the risk of cancer incidence or mortality, collectively or at any site. Over a follow-up period of 4.9 years, the incidence of myopathy (including rhabdomyolysis) in the ezetimibe/simvastatin treatment group exceeded that in the placebo group by only 0.1% in absolute terms. All patients with myopathy, including those with rhabdomyolysis, recovered after treatment with ezetimibe/simvastatin was stopped. There was no evidence for adverse effects on the liver or gallbladder, other than a slight and non-significant increase in the incidence of consecutive increases in transaminases >3xULN, as expected. No new adverse effects were identified.

Ezetimibe/simvastatin 10/20 mg is thus a well-tolerated treatment to reduce the very high cardiovascular risk of CKD patients. SHARP is the first study to show that lipid-lowering treatment is beneficial in these patients, and as such represents an important medical advance which warrants a description in labeling, including an indication.

6. References

1. SHARP Collaborative Group. 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. Am Heart J 2010;160(5):785-94.e.10.
2. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The eff ects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181-92.
3. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. N Eng J Med 2004;351(13):1344-6.
4. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-Y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351(13):1296-305.
5. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. Lancet 2000;356:147-52.
6. U.S. Renal Data System. USRDS 2010 Annual Data Report (Chapter 1): Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States, 1.i (CKD in the General Population), National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, www.usrds.org/atlas.htm, 2010.
7. Quérin S, Lambert R, Cusson JR, Grégoire S, Vickers S, Stubbs RJ, et al. Single-dose pharmacokinetics of 14C-lovastatin in chronic renal failure. Clin Pharmacol Ther 1991;50:437-41.
8. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
9. Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.
10. U.S. Product Circular: VYTORIN (ezetimibe/simvastatin) Tablets: 2011.
11. Foley RN, Parfrey PS, Sarnak MJ. Cardiovascular disease in chronic renal disease: clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32(5):S112-S119.
12. U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, http://www.usrds.org/atlas.htm, 2009.
13. Lash JP, Go AS, Appel LJ, He J, Ojo A, Rehman M, et al. Chronic renal insufficiency cohort (CRIC) study: baseline characteristics and associations with kidney function. Clin J Am Soc Nephrol 2009;4:1302-11.
14. U.S. Renal Data System. USRDS 2010 Annual Data Report (Chapter 3): Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States, 3.i (Care of Patients with CKD), National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, www.usrds.org/atlas.htm, 2010.

15. Kidney Disease Outcomes Quality Initiative. Part 4. definition and classification of stages of chronic kidney disease. Am J Kidney Dis 2002;39(Suppl 2):S46-S75.

16. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kid Int 1995;47:186-92.

17. U.S. Renal Data System. USRDS 2010 Annual Data Report (Chapter H): Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States, H.12 (Mortality Rates by Primary Cause of Mortality), National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, www.usrds.org/reference.htm, 2010.

18. Perneger TV, Klag MJ, Whelton PK. Cause of death in patients with end-stage renal disease: death certificates vs registry reports. Am J Public Health 1993;83(12):1735-8.

19. Landray MJ, Thambyrajah J, McGlynn FJ, Jones HJ, Baigent C, Kendall MJ, et al. Epidemiological evaluation of known and suspected cardiovascular risk factors in chronic renal impairment. Am J Kidney Dis 2001;38(3):537-46.

20. Levin A, Djurdjev O, Barrett B, Burgess E, Carlisle E, Ethier J, et al. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. Am J Kidney Dis 2001;38(6):1398-407.

21. U.S. Renal Data System. USRDS 2010 Annual Data Report (Chapter 7): Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States, 7.i (Transition to ESRD), National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, www.usrds.org/atlas.htm, 2010.

22. U.S. Renal Data System. USRDS 2010 Annual Data Report (Chapter 9): Atlas of Chronic Kidney Disease and End Stage Renal Disease in the United States, 9.ii (Special Studies), National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, www.usrds.org/atlas.htm, 2010.

23. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.

24. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996;335(14):1001-9.

25. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Eng J Med 1998;339(19):1349-57.

26. Collins R, Armitage J, Parish S, Sleight P, Peto R. MRC/BHF heart protection study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.

27. White HD, Simes RJ, Andeson N, E., Hankey GJ, Watson JDG, et al. Pravastatin therapy and the risk of stroke. N Engl J Med 2000;343(5):317-26.

28. Wanner C, Krane V, März W, Olschewski M, Mann JFE, Ruf.G., et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. N Engl J Med 2005;353(3):238-48.

29. Fellstrom BC, Jardine AG, Schmieder RE, Holdaas H, Bannister K, Beutler J, et al. Rosuvastatin and cardiovascular eventsin patients undergoing hemodialysis. N Engl J Med 2009;360(14):1395-407.

30. Hunsicker LG, Adler S, Caggiula A, England BK, Green T, Kusek JW, et al. Predictors of the progression of renal disease in the modification of diet in renal disease study. Kid Int 1997;51:1908-19.

31. Manttari M, Tiular E, Alkoski T, Manninen V. Effects of hypertension and dyslipidemia on the decline in renal function. Hypertension 1995;26:670-5.

32. Muntner P, Coresh J, Smith C, Eckfeldt J, Klag MJ. Plasma lipids and risk of developing renal dysfunction: the atherosclerosis risk in communities study. Kid Int 2000;58:293-301.

33. Krolewski AS, Warram JH, Christlieb AR. Hypercholsterolemia-a determinant of renal function loss and deaths in IDDM patients with nephropathy. Kidney Int 1994;45(Suppl 45):S-125-S-131.

34. Kasiske BL, O'Donnell MP, Schmitz PG, Kim Y, Keane WF. Renal injury of diet-induced hypercholesterolemia in rats. Kid Int 1990;37:880-91.

35. Kasiske BL, O'Donnell MP, Cleary MP, Keane WF. Treatment of hyperlipidemia reduces glomerular injury in obese Zucker rats. Kid Int 1988;33:667-72.

36. Kasiske BL, O'Donnell MP, Garvis WJ, Keane WF. Pharmacologic treatment of hyperlipidemia reduces glomerular injury in rat 5/6 nephrectomy model of chronic renal failure. Circ Res 1988;62(2):367-74.

37. Wellmann KF, Volk BW. Renal changes in experimental hypercholesterolemia in normal and in subdiabetic rabbits. Lab Invest 1971;24(2):144-55.

38. Harris KPG, Purkerson ML, Yates J, Klahr S. Lovastatin amerliorates the develoment of glomerulosclerosis and uremia in experimental nephrotic syndrome. Am J Kidney Dis 1990;XV(1):16-23.

39. Fried LF, Orchard TJ, Kasiske BL. Effect of lipid reduction on the progression of renal disease: A meta-analysis. Kid Int 2001;59:260-9.

40. Tonelli M, Isles C, Craven T, Tonkin A, Pfeffer MA, Shepherd J, et al. Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. Circulation 2005;112:171-8.

41. Sandhu S, Wiee N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol 2006;17:2006-16.

42. Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, et al. First United Kingdom Heart and Renal Protection (UK-HARP-I) Study: Biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis 2005;45(3):473-84.

43. Baigent C, Landry M. Study of heart and renal protection (SHARP). Kidney Int 2003;63(Suppl 84):S207-S210.

44. US Product Circular: ZOCOR (simvastatin) Tablets: 2011.

45. SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy - a genomewide study. N Engl J Med 2008;359(8):780-99.

46. Landray M, Baigent C, Leaper C, Adu D, Altmann P, Armitage J, et al. The Second United Kingdom Heart and Renal Protection (UK-HARP-II) Study: A randomized controlled study of the biochemical safety and efficacy of adding ezetimibe to simvastatin as initial therapy among patientsWith CKD. Am J Kidney Dis 2006;47(3):385-95.

47. National Kidney Foundation. Part 4. Definition and classification of stages of chronic kidney disease. Am J Kidney Dis 2002;39(2(Suppl. 1)):S46-S75.

48. Peto R, Emberson J, Landray M, Baigent C, Collins R, Clare R, et al. Analyses of cancer data from three ezetimibe trials. N Engl J Med 2008;359(13):1357-66.

49. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 1975;31:103-15.

50. SEARCH Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12064 survivors of myocardial infarction: a double-blind randomised trial. Lancet 2010;376:1658-69.

51. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: I. Introduction and design. Br J Cancer 1976;34:585-612.

52. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II Analysis and Examples. Br J Cancer 1977;35(1):1-39.

53. ICH harmonised tripartite guideline: statistical principles for clinical trials E9, 05-Feb-1998.

54. SHARP Steering Committee. SHARP Steering Committee Meeting, Danesfield House, Marlow, 02-Oct-2009.

55. Baigent C, Landray M. The results of the Study of Heart and Renal Protection (SHARP), 2010. [Internet] 2010 [accessed 2011], available from: http://www.ctsu.ox.ac.uk/~sharp/slides.htm.

56. Levey AS, Greene T, Kusek JW, Beck GJ. A simplified equation to predict glomerular filtration rate from serum creatinine [Abstract]. J Am Soc Nephrol 2000;11:155A.

57. Kastelein JJP, Akdim F, Stroes ESG, Zwinderman AH, Bots ML, Stalenhoef AFH, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358(14):1431-43.

58. Brown BG, Taylor AJ. Does ENHANCE diminish confidence in lowering LDL or in ezetimibe? N Engl J Med 2008;358(14):1504-7.

59. Kastelein JJP, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, et al. Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Eng J Med 2007;356(16):1620-30.

60. Stein EA. Additional lipid lowering trials using surrogate measurements of atherosclerosis by carotid intima-media thickness: more clarity or confusion? J Am Coll Cardiol 2008;52(25):2206-9.

61. Cowell SJ, Newby DE, Prescott RJ, Bloomfield P, Reid J, Northridge DB, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005;352(23):2389-97.

62. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis - results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010;121:306-14.

63. Holme I, Boman K, Brudi P, Egstrup K, Gohlke-Baerwolf C, Kestäniemi YA, et al. Observed and predicted reduction of ischemic cardiovascular events in the simvastatin and ezetimibe in aortic stenosis trial. Am J Cardiol 2010;105(12):1802-8.

64. Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J 2011;32:1769-818.

65. Bays HE, Ose L, Fraser N, Tribble DL, Quinto K, Reyes R, et al. A multicenter, randomized, double-blind, placebo-controlled, factorial design study to evaluate the lipid-altering efficacy and safety profile of the ezetimibe/simvastatin tablet compared with ezetimibe and simvastatin monotherapy in patients with primary hypercholesterolemia. Clin Ther 2004;26(11):1758-73.

66. Califf RM, Lokhnygina Y, Cannon CP, Stepanavage ME, McCabe CH, Musliner TA, et al. An update on the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) design. Am Heart J 2010;159(5):705-9.

67. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90 056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78.

68. Brown MS, Goldstein JL. Lowering LDL - Not only how low, but how long? Science 2006;311:1721-3.

69. Steinberg D, Witztum JL. Inhibition of PCSK9: a powerful weapon for achieving ideal LDL cholesterol levels. PNAS 2009;106(24):9546-7.

70. Rossebø AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359(13):1343-56.

71. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, et al. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): Comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. Am Heart J 2008;156(5):826-32.

72. Nissen SE. Analyses of cancer data from three ezetimibe trials [Letter]. N Engl J Med 2009;360(1):86-7.

73. Drazen JM, D'Agostino RB, Ware JH, Morrissey S, Curfman GD. Ezetimibe and cancer -- an uncertain association [editorial]. N Engl J Med 2008;359(13):1398-9.

74. Amarenco P, Bogousslavsky J, Callahan A, Goldstein LB, Hennerici M, Rudolph AE, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355(6):549-59.

75. Kjekshus J, Apetrei E, Barrios V, Böhm M, Cleland JGF, Cornel JH, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357(22):2248-61.

76. MRL Clinical Study Report (Synopsis), Multicenter Study: A Randomised Double-Blind Trial of the Effects on Coronary Heart Disease of Standard Versus Larger Blood Cholesterol Reductions with Statin Therapy and of Blood Homocysteine Reductions with Folate-Based Therapy (Protocol 158 MK-0733).

77. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med 2003;163:553-64.

78. Tobert JA. Efficacy and long-term adverse effect pattern of lovastatin. Am J Cardiol 1988;62:28J-34J.

79. Clarkson PM, Kearns AK, Rouzier P, Rubin R, Thompson PD. Serum creatine kinase levels and renal function measures in exertional muscle damage. Med Sci Sports Exerc 2006;38(4):623-7.

80. Wang HH, Portincasa P, Mendez-Sanchez N, Uribe M, Wang DQ. Effect of ezetimibe on the prevention and dissolution of cholesterol gallstones. Gastroenterology 2008;134(7):2101-10.

81. Mathur A, Walker JJ, Al-Azzawi HH, Lu D, Swartz-Basile DA, Nakeeb A, et al. Ezetimibe ameliorates cholecystosteatosis. Surgery 2007;142:228-33.

82. Johnson JL, Loomis IB. A case of simvastatin-associated pancreatitis and review of statin-associated pancreatitis. Pharmacotherapy 2006;26(3):414-22.

83. Singh S, Loke YK. Statins and pancreatitis: a systematic review of observational studies and spontaneous case reports. Drug Safety 2006;29(12):1123-32.

84. MRL Clinical Study Report (Synopsis), Multicenter Study: A Randomized Study of the Effects on Mortality and Morbidity of HMG-CoA Reductase Inhibitors and of Antioxidant Vitamins in a Wide Range of People at High Risk of Coronary Artery Disease (Protocol 102 MK0733).