Apolipoprotein B, Triglyceride-Rich Lipoproteins, and Risk of Cardiovascular Events in Persons with CKD

Julio Alejandro Lamprea-Montealegre,[1,2] Natalie Staplin,[3,4] William G. Herrington,[3,4] Richard Haynes,[3,4] Jonathan Emberson,[3,4] Colin Baigent,[3,4] and Ian H. de Boer,[1,5] on behalf of the SHARP Collaborative Group

Abstract

Background and objectives Triglyceride-rich lipoproteins may contribute to the high cardiovascular risk of patients with CKD. This study evaluated associations of apo-B and markers of triglyceride-rich lipoproteins with cardiovascular events in people with CKD.

Design, setting, participants, & measurements Analyses were conducted in 9270 participants with CKD in the Study of Heart and Renal Protection (SHARP): 6245 not on dialysis (mean eGFR 26.5 ml/min per 1.73 m^2), and 3025 on dialysis when recruited. Cox regression methods were used to evaluate associations of lipids with incident atherosclerotic and nonatherosclerotic vascular events, adjusting for demographics and clinical characteristics. Hazard ratios (HRs) were calculated per 1 SD higher level for apo-B, HDL cholesterol, LDL cholesterol, triglyceride-rich lipoprotein cholesterol (*i.e.*, total cholesterol minus LDL cholesterol minus HDL cholesterol), non-HDL cholesterol, log triglyceride, and log ratio of triglyceride to HDL cholesterol.

Results During a median follow-up of 4.9 years (interquartile range, 4.0–5.5 years), 1406 participants experienced at least one atherosclerotic vascular event. In multivariable adjusted models, positive associations with atherosclerotic vascular events were observed for apo-B (HR per 1 SD, 1.19; 95% confidence interval, 1.12 to 1.27), triglycerides (1.06; 1.00 to 1.13), the ratio of triglyceride to HDL cholesterol (1.10; 1.03 to 1.18), and triglyceride-rich lipoprotein cholesterol (1.14; 1.05 to 1.25). By contrast, inverse associations with nonatherosclerotic vascular events were observed for each of these lipid markers: apo-B (HR per 1 SD, 0.92; 0.85 to 0.98), triglycerides (0.86; 0.81 to 0.92), the ratio of triglyceride to HDL cholesterol (0.88; 0.82 to 0.94), and triglyceride-rich lipoprotein cholesterol (0.85; 0.77 to 0.94).

Conclusions Higher apo-B, triglycerides, ratio of triglyceride to HDL cholesterol, and triglyceride-rich lipoprotein cholesterol concentrations were associated with increased risk of atherosclerotic vascular events in CKD. Reducing triglyceride-rich lipoproteins using novel therapeutic agents could potentially lower the risk of atherosclerotic cardiovascular disease risk in the CKD population.

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[1]Kidney Research Institute, [2]Division of Cardiology, Department of Medicine, and [5]Division of Nephrology, Department of Medicine, University of Washington, Seattle, Washington; [3]Medical Research Council Population Health Research Unit and [4]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom

Correspondence: Dr. Julio Alejandro Lamprea-Montealegre, Cardiology Department, University of Washington School of Medicine, Box 356422, 1959 NE Pacific Street, Seattle, WA 98195. Email: julio.lampreamontealegre@ucsf.edu

Introduction

Persons with CKD have a high burden of atherosclerotic and nonatherosclerotic cardiovascular disease (1). The risk of cardiovascular disease remains high even after reduction of well established causal cardiovascular risk factors, including BP and LDL cholesterol (2–3). Persons with CKD have a high prevalence of hypertriglyceridemia owing to decreased clearance of triglyceride-rich lipoproteins (4), and it has been suggested that in the general population hypertriglyceridemia may be a cause of atherosclerotic cardiovascular disease (5). Evidence that the association between raised triglycerides and cardiovascular disease may be causal is provided by genetic studies of triglyceride mediated pathways, and by meta-analyses of clinical trials of fibrates, which lower triglycerides (6,7). The beneficial effects of triglyceride lowering agents, such as fibrates, appear to be larger among individuals with high baseline triglyceride concentrations (8).

The mechanisms leading to accelerated atherosclerosis in hypertriglyceridemic states are complex and involve multiple lipoproteins. For instance, the direct causal determinants of atherosclerosis in hypertriglyceridemia are not triglycerides *per se*, but triglyceride-rich lipoproteins, which include VLDLs, chylomicrons, and their remnants (small VLDLs or intermediate density lipoprotein particles whose triglyceride has been hydrolyzed by lipoprotein lipase) (9). These lipoproteins are capable of entering the subintimal space and promote atherosclerosis through deposition of their cholesterol content in the atherosclerotic lesion (10). Consistent with a possible causal effect of triglyceride-rich lipoproteins on atherosclerosis, genetic studies of triglyceride-lowering lipoprotein lipase variants have shown that the association between lower triglyceride level and cardiovascular disease risk is proportional to the absolute difference in concentration of apo-B, the main structural protein

of triglyceride-rich lipoproteins (11), that results from different lipoprotein lipase variants.

In this secondary analysis of the Study of Heart and Renal Protection (SHARP), we sought to evaluate the association of apo-B and other markers of triglyceride-rich lipoproteins (triglycerides, the ratio of triglyceride to HDL cholesterol, and triglyceride-rich lipoprotein cholesterol) with atherosclerotic vascular events, nonatherosclerotic vascular events, and nonvascular events in patients with CKD, including participants treated with dialysis. In addition, using the randomized design of SHARP, we assessed the effect of allocation to simvastatin plus ezetimibe on the concentrations of apo-B and other lipid markers, and determined whether the associations of these lipids with atherosclerotic vascular events and nonatherosclerotic vascular events were modified by treatment with simvastatin plus ezetimibe.

Materials and Methods

Study Design and Population

Details of the SHARP trial objectives, design, and methods have been reported previously (12). Briefly, adult patients aged 40 years and older were eligible to participate if they were receiving maintenance dialysis (n=3025) or, if not, had CKD (n=6245) with a measured serum creatinine concentration of at least 1.7 mg/dl for men or 1.5 mg/dl for women. Participants with a history of prior myocardial infarction or coronary revascularization were excluded. After 6 weeks of placebo run-in phase, eligible participants were randomized in a 4:4:1 allocation ratio to receive simvastatin 20 mg plus 10 mg of ezetimibe, placebo, or simvastatin 20 mg alone. After 1 year, patients allocated to simvastatin alone (n=1054) were rerandomized to the combination simvastatin plus ezetimibe or placebo.

In SHARP, all individuals provided written informed consent and ethical approval was obtained from all study sites before enrolment.

Baseline Assessments

In the current analyses, "baseline information" refers to information that was recorded at randomization to simvastatin plus ezetimibe versus placebo (or at screening 6 weeks before). Baseline information included sociodemographic characteristics (including age, sex, ethnicity, and highest attained educational achievement), anthropometric measurements, self-reported medical history, current medication (including antihypertensive treatments), and lifestyle behaviors (including alcohol consumption and smoking).

Nonfasting blood was collected at baseline and 2.5 years (1.5 years for those initially randomized to simvastatin) for central analysis. Apo-B was measured by turbidimetry. The concentrations of total cholesterol and triglycerides were measured using standardized enzymatic methods. LDL cholesterol and HDL cholesterol concentrations were directly measured using BioStat N-geneous reagents (Genzyme Diagnostics) (13). Non-HDL cholesterol concentrations were calculated by the difference between total cholesterol and HDL cholesterol. We also calculated the ratio of triglyceride to HDL cholesterol. Following previous published methods, triglyceride-rich lipoprotein cholesterol (defined as plasma cholesterol that is not carried in LDL or HDL particles, which gives an approximate measurement of the cholesterol content in triglyceride-rich lipoproteins and their remnants) was calculated as nonfasting total cholesterol minus HDL cholesterol minus LDL cholesterol (5,10,14). Troponin I was measured by chemiluminescence immunoassay on an ACCESS2 analyzer using AccuTnI reagent and calibrator (Beckman Coulter Inc.) and Liquichek Cardiac Markers Plus Controls (Bio-Rad Laboratories Ltd.). Assay linearity and functional sensitivity was verified down to at least 0.01 ng/ml.

The Modification of Diet in Renal Disease equation was used to calculate eGFR from serum creatinine. Proteinuria was assessed with the urinary albumin-to-creatinine ratio (uACR).

SHARP Follow-Up Procedures and Study Outcomes

Ascertainment of events in SHARP occurred during scheduled study visits at 2 and 6 months and then at 6-month intervals for at least 4 years. Adjudication of events was made by trained clinicians in a central coordinating center who were blinded to treatment allocation. An atherosclerotic vascular event was defined as the composite end point of new onset of nonfatal myocardial infarction or coronary artery disease death, unstable angina, heart failure due to coronary artery disease, transient ischemic attack, ischemic stroke, or any arterial revascularization procedure excluding dialysis access procedures. A nonatherosclerotic vascular event was defined as the new onset of noncoronary cardiac death, nonischemic heart failure, cardiac arrhythmias, pericardial or valvular heart disease, hemorrhagic stroke, or subarachnoid hemorrhage. These outcomes were prespecified for use in epidemiologic analyses and are expanded versions of major atherosclerotic events and major vascular event end points used in randomized comparisons.

Statistical Analyses

Mean changes in lipid concentrations between the baseline and 2.5 year visit (or 1.5 year visit for those initially allocated simvastatin only) were calculated separately for those allocated simvastatin plus ezetimibe and those allocated placebo, with the absolute difference between these two estimates then presented as a percentage of the mean baseline level (to help facilitate comparability of effects across different lipid markers).

The relevance of baseline lipid and lipoprotein levels to incident atherosclerotic vascular and nonatherosclerotic vascular events was assessed using Cox proportional hazards regression (with the proportional hazard assumption tested through examination of the Schoenfeld residuals). However, the combined effects of measurement error and natural within-person variability mean that such analyses tend to underestimate the importance of long-term average ("usual") levels to risk (15). We therefore corrected for this "regression dilution bias" by dividing the log hazard ratios (HRs) associated with the baseline values (and their SEMs) by an estimate of the regression dilution ratio. Such adjustment allows the relevance of usual lipid and lipoprotein levels to risk to be quantified, but does not affect the assessment of the statistical significance of the associations. Regression dilution ratios were calculated from the 2.5 year (1.5 year for those initially allocated to simvastatin) repeat measurements (Supplemental Table 1), using the Rosner parametric method (16).

The HR estimates derived from Cox models were calculated assuming a log-linear relationship for apo-B, HDL

cholesterol, LDL cholesterol, triglyceride-rich lipoprotein cholesterol, and non-HDL cholesterol, and presented as average HRs per one usual SD (where the usual SD is calculated from the baseline SD by multiplying it by the square root of the regression dilution ratio). However, because of the skewed distribution of triglycerides, estimates of triglycerides and the ratio of triglyceride to HDL cholesterol assumed a log-log linear relationship, and are presented as average HRs per 1.5 and 1.9 times higher lipid levels, respectively (which correspond to about 1 SD difference in usual log lipid levels).

On the basis of explicit assumptions (causal diagram in Supplemental Figure 1) about the relationship between lipids and lipoproteins and vascular events, all Cox analyses were adjusted for age, sex, ethnicity, treatment allocation, prior diabetes, prior vascular disease, smoking status, body mass index, eGFR, and albuminuria. For the primary analyses, no adjustment for other lipids or lipoproteins was made. This was particularly relevant for triglyceride analyses, where other correlated lipoproteins (*e.g.*, HDL) were not considered to be confounders of the association between triglycerides and atherosclerotic vascular events (Supplemental Figure 1). However, given the correlations between different lipids and lipoproteins (Supplemental Figure 2), sensitivity analyses adjusting for other lipids and lipoproteins were also conducted.

In figures, each HR (including the HR for the reference group with HR=1) is presented with a group-specific confidence interval that can be thought of as reflecting the amount of data only in that one group, and allowing appropriate statistical comparisons to be made between any two groups (17).

For each end point (atherosclerotic vascular event, nonatherosclerotic vascular event or nonvascular event), likelihood ratio tests were used to test for effect modification by treatment allocation, baseline GFR (eGFR≥30 ml/min per 1.73 m^2, eGFR<30 ml/min per 1.73 m^2, and on dialysis), baseline albuminuria (uACR≤300 mg/g and uACR>300 mg/g), and by median levels of C-reactive protein (CRP; 3 mg/L), albumin (40 g/L), and troponin I (0.01 ng/ml) at baseline. These markers were chosen to assess for the possibility of reverse causality, in particular for analyses of nonatherosclerotic vascular events and nonvascular events. To further explore the possibility of reverse causality we conducted sensitivity analyses excluding participants in the bottom of each lipid category.

Finally, the effect of allocation to simvastatin plus ezetimibe on major atherosclerotic events (nonfatal myocardial infarction or coronary death, nonhemorrhagic stroke, or arterial revascularization) by baseline lipid and lipoprotein levels was estimated using log-rank methods with standard tests for trend across categories.

Results

Among 9270 participants randomized to simvastatin plus ezetimibe versus placebo, the median baseline triglyceride concentration was 169 mg/dl (Table 1) and was similar among the 6245 participants with CKD not on dialysis (mean eGFR 26.5 ml/min per 1.73 m^2) and the 3025 participants on dialysis at baseline (Supplemental Table 2). The sex composition of the study population was similar across triglyceride concentrations (Table 1). Participants with higher triglyceride concentrations were more likely to be white, more likely to have a history prior vascular disease, diabetes, and to have a higher body mass index. Higher triglyceride concentrations were associated with higher mean LDL cholesterol, non-HDL cholesterol, triglyceride-rich lipoprotein cholesterol, the ratio of triglyceride to HDL cholesterol, and apo-B concentration, and with lower concentrations of HDL cholesterol and apo-A1. The concentration of CRP was higher among participants with higher triglyceride concentrations. Among participants with CKD not on dialysis, higher triglyceride concentrations were observed in participants with higher baseline eGFR (Supplemental Table 2).

Effect of Simvastatin Plus Ezetimibe on Lipids and Lipoproteins

Analyses included 7706 SHARP (n=2398 on dialysis) participants (83% of the initial cohort) with available lipid measurements at 2.5 years from randomization to simvastatin plus ezetimibe versus placebo (or 1.5 years for those initially allocated to simvastatin). There were significant mean reductions of 23% and 22% in the concentration of apo-B and triglyceride-rich lipoprotein cholesterol in participants assigned to treatment with simvastatin plus ezetimibe compared with placebo (Table 2). These reductions were larger among participants with CKD not on dialysis than among those on dialysis. In contrast, triglyceride concentrations and the ratio of triglyceride to HDL cholesterol were only minimally decreased by allocation to simvastatin plus ezetimibe, with a mean reduction of 12% and 8%, respectively, compared with placebo, but the larger reductions were still observed for participants with CKD not on dialysis than for those on dialysis.

Atherosclerotic Vascular Events

During a median follow up of 4.9 years (interquartile range, 4.0–5.5 years), 1406 participants experienced at least one atherosclerotic vascular event. Each 17 mg/dl (1 SD) higher apo-B concentration was associated with a significant 19% higher risk of an atherosclerotic vascular event (Figure 1). Similarly, each 1 SD (0.5) higher log triglyceride (*i.e.*, 50% higher usual triglyceride concentration) was associated with a 6% increased risk of an atherosclerotic vascular event (HR, 1.06; 95% confidence interval [95% CI], 1.00 to 1.13). Similar associations were observed for each 1 SD (90%) higher ratio of triglyceride to HDL cholesterol (HR, 1.10; 95% CI, 1.03 to 1.18) and 1 SD (0.4 mmol/L) higher triglyceride-rich lipoprotein cholesterol (HR, 1.14; 95% CI, 1.05 to 1.25).

There was no evidence of effect modification by baseline eGFR or albuminuria for apo-B or any of the other evaluated lipids and lipoproteins (Tables 3 and 4). Allocation to simvastatin plus ezetimibe did not modify the associations of triglycerides, ratio of triglyceride to HDL cholesterol, or triglyceride-rich lipoprotein cholesterol with atherosclerotic vascular events (Supplemental Table 3). Similarly, there was no evidence of effect modification in the association of lipids and lipoproteins with atherosclerotic vascular events by plasma CRP, troponin I, or albumin concentrations (Supplemental Tables 4–6).

After excluding participants in the bottom lipid/lipoprotein category, the associations between 1 SD higher usual apo-B, LDL cholesterol, and non-HDL cholesterol and the risk of atherosclerotic vascular events were greatly strengthened, but

Table 1. Baseline characteristics by triglyceride group among all 9270 SHARP participants

Characteristic	All Participants	Triglycerides (mg/dl)		
		<132.8 (*n*=2929)	≥132.8 to <212.4 (*n*=2917)	≥212.4 (*n*=3045)
Triglycerides, mg/dl	169 (118–247)	100 (81–118)	167 (150–188)	288 (244–376)
LDL cholesterol, mg/dl	107 (34)	96 (31)	110 (33)	115 (35)
Non-HDL cholesterol, mg/dl	146 (43)	122 (35)	146 (37)	168 (43)
HDL cholesterol, mg/dl	43 (13)	49 (14)	43 (12)	37 (10)
TRL cholesterol, mg/dl	38 (18)	26 (9)	35 (11)	53 (21)
TG/HDLc ratio	1.77 (1.11–2.92)	0.91 (0.67–1.19)	1.75 (1.43–2.16)	3.57 (2.70–5.00)
Apo-A1, mg/dl	134 (29)	139 (31)	135 (28)	128 (26)
Apo-B, mg/dl	96 (26)	84 (22)	98 (23)	107 (26)
Age at randomization, yr	62 (12)	62 (12)	62 (12)	61 (11)
Men	5800 (63%)	1830 (62%)	1751 (60%)	1965 (65%)
Prior vascular disease	1393 (15%)	378 (13%)	492 (17%)	475 (16%)
Diabetes	2094 (23%)	569 (19%)	631 (22%)	812 (27%)
Current smoker	1234 (13%)	377 (13%)	385 (13%)	422 (14%)
Diastolic BP, mm Hg	79 (13)	79 (13)	79 (13)	79 (13)
Systolic BP, mm Hg	139 (22)	139 (22)	139 (22)	138 (22)
Body mass index, kg/m^2	27.1 (5.6)	25.6 (5.3)	27.0 (5.6)	28.5 (5.5)
Albumin, g/l	40.1 (3.7)	39.6 (3.8)	40.0 (3.8)	40.7 (3.6)
C-reactive protein, mg/l	3.0 (1.2–7.1)	2.6 (0.9–6.8)	3.0 (1.2–7.2)	3.4 (1.5–7.1)
Troponin I, ng/ml	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.01 (0.01–0.02)
Ethnicity				
White	6646 (72%)	2034 (69%)	2122 (73%)	2228 (73%)
Black	264 (3%)	130 (4%)	62 (2%)	43 (1%)
Asian	2086 (23%)	678 (23%)	652 (22%)	685 (22%)
Other/not specified	274 (3%)	87 (3%)	81 (3%)	89 (3%)
Comedication				
Antiplatelet therapy	2105 (23%)	654 (22%)	682 (23%)	690 (23%)
ACE inhibitor or ARB	5030 (54%)	1492 (51%)	1624 (56%)	1746 (57%)
β-Blocker	3514 (38%)	938 (32%)	1186 (41%)	1261 (41%)
Calcium channel blocker	3840 (41%)	1218 (42%)	1268 (43%)	1225 (40%)
Kidney status				
Not on dialysis	6245 (67%)	1957 (67%)	1977 (68%)	2092 (69%)
On dialysis	3025 (33%)	972 (33%)	940 (32%)	953 (31%)
MDRD eGFR, ml/min per 1.73 m^2[a,b]				
Mean (SD)	26.6 (13.0)	25.9 (13.2)	26.3 (12.8)	27.5 (13.0)
≥60	88 (1%)	27 (1%)	24 (1%)	37 (2%)
≥30 to <60	2155 (36%)	679 (35%)	703 (36%)	773 (37%)
≥15 to <30	2565 (43%)	773 (39%)	847 (43%)	945 (45%)
<15	1219 (20%)	478 (24%)	403 (20%)	337 (16%)
Not available	218	0	0	0
Urinary albumin-to-creatinine ratio, mg/g[a,b]				
Median (IQR)	206 (44–762)	180 (38–696)	198 (45–695)	242 (48–916)
<30	1107 (20%)	384 (21%)	361 (20%)	358 (19%)
≥30 to ≤300	2108 (38%)	703 (39%)	698 (38%)	696 (36%)
>300	2357 (42%)	715 (40%)	757 (42%)	879 (45%)
Not available	673	155	161	159

Data are *n* (%), mean (SD), or median (IQR). SHARP, Study of Heart and Renal Protection; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDL cholesterol minus HDL cholesterol; TG/HDLc, triglyceride to HDL cholesterol ratio; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MDRD, Modification of Diet in Renal Disease equation; IQR, interquartile range.
[a]Among patients not on dialysis.
[b]Percentages exclude participants for whom data were not available for that category.

the strengths of the associations for triglycerides, triglyceride-rich lipoprotein cholesterol, and the ratio of triglyceride to HDL cholesterol were only modestly increased (Supplemental Table 7).

The association between triglycerides and atherosclerotic vascular events was significantly attenuated when adjusting for HDL and LDL cholesterol but the associations for other lipids and lipoproteins were not attenuated when adjusting for the relevant correlated lipids/lipoproteins (Supplemental Figure 3). The observed associations of apo-B with atherosclerotic vascular events were similar when adjusting for triglyceride levels (Supplemental Figure 3).

Effect of Allocation to Simvastatin Plus Ezetimibe on Major Atherosclerotic Events by Baseline Lipids and Lipoproteins

There was no consistent evidence that the effect of allocation to simvastatin plus ezetimibe on major atherosclerotic events varied by level of baseline lipids and lipoproteins after weighting risk ratios per 20 mg/dl reduction in apo-B (Figure 2).

Table 2. Effect of allocation to simvastatin plus ezetimibe on changes in lipid concentrations between baseline and study midpoint (2.5 years), overall and by baseline eGFR

Lipid	*N*	Mean Baseline Value[a]	Mean Absolute Change (SEM) at 2.5 yr[b]		Relative Difference in Percentage Changes (95% CI)	*P* Value[c]
			Simvastatin Plus Ezetimibe	Placebo		
Triglycerides, mg/dl						
eGFR≥30 ml/min per 1.73 m^2	2043	215.6	−52.0 (3.6)	−24.2 (4.7)	−13% (−18% to −8%)	0.17
eGFR<30 ml/min per 1.73 m^2	3265	200.3	−47.7 (3.1)	−19.7 (2.6)	−14% (−18% to −10%)	
On dialysis	2398	205.3	−37.1 (4.9)	−22.9 (3.9)	−7% (−13% to −0.9%)	
All participants	7706	205.7	−45.5 (2.2)	−21.9 (2.0)	−12% (−14% to −9%)	
HDL cholesterol, mg/dl						
eGFR≥30 ml/min per 1.73 m^2	2043	43.9	0.60 (0.25)	0.26 (0.29)	0.8% (−0.9% to 3%)	0.73
eGFR<30 ml/min per 1.73 m^2	3264	43.7	0.69 (0.23)	0.30 (0.23)	0.9% (−0.6% to 2%)	
On dialysis	2398	41.7	0.61 (0.32)	0.52 (0.31)	0.2% (−2% to 2%)	
All participants	7705	43.1	0.64 (0.16)	0.36 (0.16)	0.7% (−0.4% to 1.7%)	
LDL cholesterol, mg/dl						
eGFR≥30 ml/min per 1.73 m^2	2043	112.4	−43.2 (1.1)	−5.10 (0.86)	−34% (−36% to −31%)	<0.001
eGFR<30 ml/min per 1.73 m^2	3265	109.8	−42.8 (0.9)	−6.12 (0.71)	−33% (−36% to −31%)	
On dialysis	2400	99.6	−29.0 (1.1)	−5.99 (0.85)	−23% (−26% to −20%)	
All participants	7708	107.1	−38.6 (0.6)	−5.81 (0.46)	−31% (−32% to −29%)	
Non-HDL cholesterol, mg/dl						
eGFR≥30 ml/min per 1.73 m^2	2043	151.0	−54.6 (1.4)	−7.16 (1.06)	−31% (−34% to −29%)	<0.001
eGFR<30 ml/min per 1.73 m^2	3264	149.0	−54.7 (1.2)	−8.15 (0.87)	−31% (−33% to −29%)	
On dialysis	2398	136.9	−37.2 (1.4)	−7.71 (1.09)	−22% (−24% to −19%)	
All participants	7705	145.5	−49.2 (0.8)	−7.75 (0.57)	−28% (−30% to −27%)	
Apo-B, mg/dl						
eGFR≥30 ml/min per 1.73 m^2	2040	99.4	−29.3 (0.8)	−3.16 (0.61)	−26% (−28% to −24%)	<0.001
eGFR<30 ml/min per 1.73 m^2	3258	97.9	−29.2 (0.7)	−3.93 (0.52)	−26% (−28% to −24%)	
On dialysis	2402	91.8	−20.4 (0.8)	−4.21 (0.65)	−18% (−20% to −15%)	
All participants	7702	96.3	−26.4 (0.4)	−3.81 (0.34)	−23% (−25% to −22%)	
TRL cholesterol, mg/dl						
eGFR≥30 ml/min per 1.73 m^2	2043	38.5	−11.3 (0.5)	−2.07 (0.49)	−24% (−27% to −21%)	0.01
eGFR<30 ml/min per 1.73 m^2	3264	39.2	−11.9 (0.4)	−2.03 (0.36)	−25% (−28% to −22%)	
On dialysis	2398	37.3	−8.18 (0.51)	−1.72 (0.47)	−17% (−21% to −14%)	
All participants	7705	38.4	−10.6 (0.3)	−1.94 (0.25)	−22% (−24% to −21%)	
TG/HDLc ratio						
eGFR≥30 ml/min per 1.73 m^2	2043	2.66	−0.68 (0.07)	−0.56 (0.21)	−5% (−21% to 12%)	0.64
eGFR<30 ml/min per 1.73 m^2	3264	2.35	−0.54 (0.07)	−0.20 (0.05)	−14% (−22% to −7%)	
On dialysis	2396	2.67	−0.44 (0.13)	−0.34 (0.10)	−4% (−16% to 8%)	
All participants	7703	2.53	−0.55 (0.06)	−0.34 (0.07)	−8% (−15% to −2%)	

Average adherence to allocated treatment was about 65% in those not on dialysis at randomization (irrespective of baseline eGFR) and about 55% in those on dialysis at randomization. 95% CI, 95% confidence interval; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDL cholesterol minus HDL cholesterol; TG/HDLc, triglyceride to HDL cholesterol ratio.
[a]Simvastatin plus ezetimibe and placebo arms combined.
[b]In patients initially allocated to simvastatin, samples scheduled for collection at 2.5 yr were collected at 1.5 yr after rerandomization.
[c]Test for trend across categories of eGFR.

Nonatherosclerotic Vascular Events

Consistent inverse associations between all lipids and lipoproteins (with the exception of HDL cholesterol) and the risk of nonatherosclerotic vascular events were observed (Figure 3). Each 50% higher triglyceride concentration was associated with 14% lower risk of nonatherosclerotic vascular events (HR, 0.86; 95% CI, 0.81 to 0.92). Similarly, for each 90% higher ratio of triglyceride to HDL cholesterol, there was a 12% lower risk of nonatherosclerotic vascular events (HR, 0.88; 95% CI, 0.82 to 0.94) (Supplemental Figure 4).

The observed inverse associations of apo-B, triglycerides, non-HDL cholesterol, triglyceride-rich lipoprotein cholesterol, and the ratio of triglyceride to HDL cholesterol were stronger among participants with higher levels of CRP (Figure 4, Supplemental Table 4). Similar patterns (albeit less pronounced and nonstatistically significant) were observed in analyses stratifying by troponin I, but not for serum albumin concentrations (Supplemental Tables 5 and 6). Excluding participants in the bottom category of lipids and lipoproteins, attenuated the observed inverse associations with nonatherosclerotic vascular events (Supplemental Table 7).

Nonvascular Events

We found no evidence of significant associations between lipids and lipoproteins with nonvascular events, before or after adjustment for other lipids and lipoproteins (Supplemental Figures 5 and 6). There was also no evidence of effect modification by eGFR (Table 3), baseline albuminuria (Table 4), or treatment allocation to simvastatin plus ezetimibe (Supplemental Table 3).

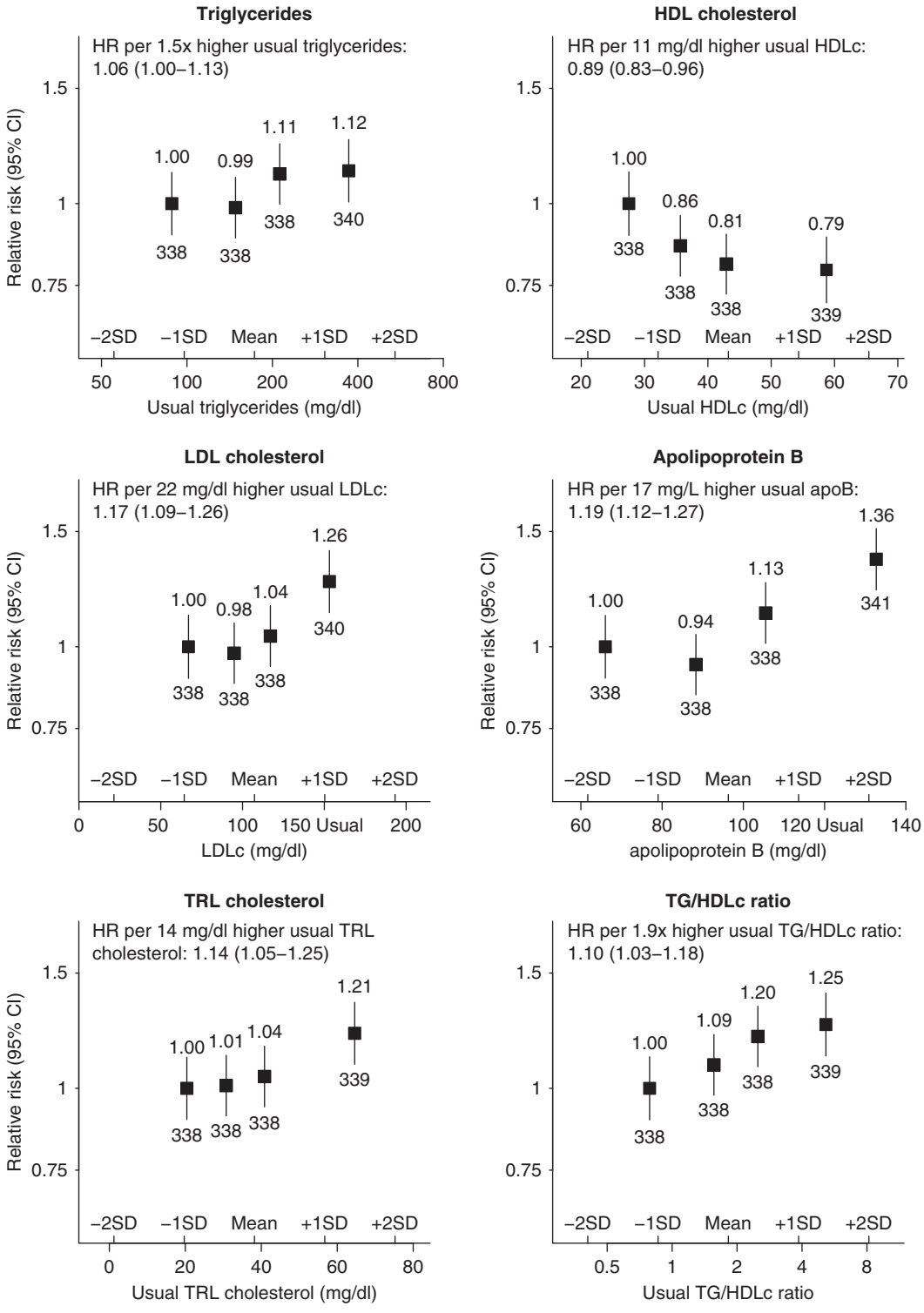

Figure 1. | **Association between usual lipid values and the risk of atherosclerotic vascular events**. HRs adjusted for age, sex, ethnicity, treatment allocation, prior diabetes, prior vascular disease, smoking, body mass index, eGFR, and albuminuria are quoted (above squares) with numbers of events (below). Average HR (95% CI) throughout the range of values studied (*i.e.*, assuming a log-log-linear relationship for triglycerides and triglyceride to HDLc ratio, and log-linear relationships for all other lipids), corresponding to about 1 SD differences in usual lipid values. 95% CI, 95% confidence interval; HDLc, HDL cholesterol; HR, hazard ratio; LDLc, LDL cholesterol; TG, triglyceride; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDLc minus HDLc.

Table 3. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events and nonvascular events, overall and by eGFR

Lipid	Atherosclerotic Vascular Events			Nonatherosclerotic Vascular Events			Nonvascular Events		
	No. of Events	HR (95% CI)	*P* Value[a]	No. of Events	HR (95% CI)	*P* Value[a]	No. of Events	HR (95% CI)	*P* Value[a]
Triglycerides, per 1.5 times higher usual level			0.99			0.23			0.05
eGFR≥30 ml/min per 1.73 m^2	249	1.06 (0.93 to 1.21)		217	0.94 (0.81 to 1.09)		1283	0.93 (0.87 to 0.98)	
eGFR<30 ml/min per 1.73 m^2	538	1.06 (0.96 to 1.17)		546	0.81 (0.73 to 0.89)		3051	0.95 (0.91 to 0.99)	
On dialysis	567	1.05 (0.96 to 1.15)		527	0.86 (0.78 to 0.95)		2464	1.00 (0.96 to 1.05)	
All participants	1354	1.06 (1.00 to 1.13)		1290	0.86 (0.81 to 0.92)		6798	0.98 (0.96 to 1.01)	
HDL cholesterol, per 11 mg/dl higher usual level			0.44			0.07			0.88
eGFR≥30 ml/min per 1.73 m^2	249	0.84 (0.71 to 0.98)		217	0.96 (0.82 to 1.13)		1283	0.96 (0.90 to 1.02)	
eGFR<30 ml/min per 1.73 m^2	538	0.87 (0.78 to 0.97)		546	1.09 (0.99 to 1.20)		3050	0.96 (0.92 to 1.00)	
On dialysis	566	0.93 (0.84 to 1.03)		526	0.93 (0.84 to 1.03)		2462	0.98 (0.93 to 1.02)	
All participants	1353	0.89 (0.83 to 0.96)		1289	1.00 (0.94 to 1.08)		6795	0.98 (0.95 to 1.01)	
LDL cholesterol, per 22 mg/dl higher usual level			0.69			0.05			0.76
eGFR≥30 ml/min per 1.73 m^2	249	1.23 (1.05 to 1.45)		217	0.79 (0.65 to 0.95)		1283	0.92 (0.85 to 0.99)	
eGFR<30 ml/min per 1.73 m^2	538	1.13 (1.01 to 1.27)		546	0.99 (0.88 to 1.10)		3051	0.91 (0.87 to 0.96)	
On dialysis	567	1.17 (1.05 to 1.30)		527	0.84 (0.74 to 0.94)		2464	0.94 (0.89 to 0.99)	
All participants	1354	1.17 (1.09 to 1.26)		1290	0.90 (0.83 to 0.97)		6798	0.95 (0.92 to 0.98)	
Non-HDL cholesterol, per 28 mg/dl higher usual level			0.66			0.16			0.67
eGFR≥30 ml/min per 1.73 m^2	249	1.23 (1.06 to 1.42)		217	0.83 (0.69 to 0.99)		1283	0.91 (0.85 to 0.98)	
eGFR<30 ml/min per 1.73 m^2	538	1.16 (1.05 to 1.28)		546	0.94 (0.85 to 1.05)		3050	0.94 (0.89 to 0.98)	
On dialysis	566	1.13 (1.03 to 1.25)		526	0.82 (0.74 to 0.92)		2462	0.95 (0.91 to 1.00)	
All participants	1353	1.17 (1.09 to 1.24)		1289	0.88 (0.82 to 0.95)		6795	0.96 (0.93 to 0.99)	
Apo-B, per 17 mg/dl higher usual level			0.78			0.09			0.95
eGFR≥30 ml/min per 1.73 m^2	249	1.23 (1.06 to 1.43)		217	0.82 (0.69 to 0.98)		1283	0.95 (0.89 to 1.02)	
eGFR<30 ml/min per 1.73 m^2	538	1.16 (1.04 to 1.28)		546	0.99 (0.89 to 1.10)		3050	0.95 (0.91 to 0.99)	
On dialysis	568	1.19 (1.08 to 1.31)		527	0.86 (0.77 to 0.96)		2474	0.96 (0.91 to 1.00)	
All participants	1355	1.19 (1.12 to 1.27)		1290	0.92 (0.85 to 0.98)		6808	0.98 (0.95 to 1.01)	
TRL cholesterol, per 14 mg/dl higher usual level			0.50			0.40			0.41
eGFR≥30 ml/min per 1.73 m^2	249	1.15 (0.97 to 1.37)		217	0.96 (0.77 to 1.19)		1283	0.93 (0.84 to 1.02)	
eGFR<30 ml/min per 1.73 m^2	538	1.20 (1.05 to 1.38)		546	0.85 (0.73 to 0.99)		3050	1.00 (0.94 to 1.07)	
On dialysis	566	1.08 (0.94 to 1.23)		526	0.79 (0.67 to 0.93)		2462	0.98 (0.91 to 1.05)	
All participants	1353	1.14 (1.05 to 1.25)		1289	0.85 (0.77 to 0.94)		6795	1.00 (0.95 to 1.04)	
TG/HDLc ratio, per 1.9 times higher usual level			0.79			0.16			0.25
eGFR≥30 ml/min per 1.73 m^2	249	1.13 (0.97 to 1.31)		217	0.97 (0.82 to 1.14)		1283	0.95 (0.89 to 1.02)	
eGFR<30 ml/min per 1.73 m^2	538	1.12 (1.00 to 1.25)		546	0.81 (0.72 to 0.91)		3050	0.98 (0.93 to 1.02)	
On dialysis	566	1.07 (0.97 to 1.18)		526	0.90 (0.81 to 1.00)		2462	1.02 (0.97 to 1.07)	
All participants	1353	1.10 (1.03 to 1.18)		1289	0.88 (0.82 to 0.94)		6795	1.00 (0.96 to 1.03)	

HRs adjusted for age, sex, ethnicity, treatment allocation, prior diabetes, prior vascular disease, smoking, body mass index, eGFR, and albuminuria. Average HR (95% CI) throughout the range of values studied (*i.e.*, assuming a log-log-linear relationship for triglycerides and TG/HDLc ratio, and log-linear relationships for all other lipids), corresponding to about 1 SD differences in usual lipid values. HR, hazard ratio; 95% CI, 95% confidence interval; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDL cholesterol minus HDL cholesterol; TG/HDLc, triglyceride to HDL cholesterol ratio.

[a]Test for effect modification by eGFR.

Table 4. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events and nonvascular events, overall and by level of albuminuria

Lipid	Atherosclerotic Vascular Events			Nonatherosclerotic Vascular Events			Nonvascular Events		
	No. of Events	HR (95% CI)	*P* Value[a]	No. of Events	HR (95% CI)	*P* Value[a]	No. of Events	HR (95% CI)	*P* Value[a]
Triglycerides, per 1.5 times higher usual level			0.81			0.66			0.32
uACR≤300 mg/g	379	1.10 (0.98 to 1.23)		339	0.87 (0.77 to 0.99)		2132	0.99 (0.94 to 1.04)	
uACR>300 mg/g	344	1.08 (0.96 to 1.21)		359	0.84 (0.75 to 0.94)		1887	0.95 (0.91 to 1.00)	
All participants not on dialysis	787	1.09 (1.01 to 1.18)		763	0.87 (0.80 to 0.94)		4342	0.98 (0.94 to 1.01)	
HDL cholesterol, per 11 mg/dl higher usual level			0.02			0.81			0.03
uACR≤300 mg/g	379	0.78 (0.68 to 0.89)		339	1.06 (0.93 to 1.20)		2132	0.95 (0.91 to 1.00)	
uACR>300 mg/g	344	0.95 (0.84 to 1.08)		359	1.08 (0.96 to 1.21)		1887	1.03 (0.98 to 1.09)	
All participants not on dialysis	787	0.87 (0.80 to 0.96)		763	1.08 (1.00 to 1.18)		4341	1.00 (0.97 to 1.04)	
LDL cholesterol, per 22 mg/dl higher usual level			0.71			0.06			0.11
uACR≤300 mg/g	379	1.15 (1.00 to 1.32)		339	0.88 (0.75 to 1.02)		2132	0.94 (0.89 to 1.00)	
uACR>300 mg/g	344	1.19 (1.04 to 1.36)		359	1.06 (0.93 to 1.21)		1887	1.01 (0.95 to 1.07)	
All participants not on dialysis	787	1.19 (1.09 to 1.31)		763	0.96 (0.87 to 1.06)		4342	0.98 (0.94 to 1.02)	
Non-HDL cholesterol, per 28 mg/dl higher usual level			0.64			0.05			0.05
uACR≤300 mg/g	379	1.18 (1.04 to 1.33)		339	0.85 (0.74 to 0.98)		2132	0.94 (0.89 to 0.99)	
uACR>300 mg/g	344	1.23 (1.09 to 1.38)		359	1.01 (0.90 to 1.14)		1887	1.01 (0.96 to 1.07)	
All participants not on dialysis	787	1.22 (1.12 to 1.32)		763	0.94 (0.86 to 1.03)		4341	0.99 (0.95 to 1.03)	
Apo-B, per 17 mg/dl higher usual level			0.87			0.02			0.05
uACR≤300 mg/g	379	1.19 (1.05 to 1.35)		339	0.86 (0.75 to 0.99)		2132	0.96 (0.91 to 1.01)	
uACR>300 mg/g	344	1.21 (1.07 to 1.36)		359	1.07 (0.95 to 1.20)		1886	1.04 (0.98 to 1.09)	
All participants not on dialysis	787	1.22 (1.12 to 1.33)		763	0.98 (0.89 to 1.07)		4342	1.01 (0.97 to 1.05)	
TRL cholesterol, per 14 mg/dl higher usual level			0.78			0.28			0.14
uACR≤300 mg/g	379	1.20 (1.03 to 1.40)		339	0.81 (0.66 to 0.99)		2132	0.95 (0.87 to 1.02)	
uACR>300 mg/g	344	1.24 (1.08 to 1.42)		359	0.93 (0.79 to 1.09)		1887	1.02 (0.95 to 1.10)	
All participants not on dialysis	787	1.22 (1.10 to 1.35)		763	0.90 (0.80 to 1.02)		4341	1.01 (0.96 to 1.06)	
TG/HDLc ratio, per 1.9 times higher usual level			0.25			0.53			0.09
uACR≤300 mg/g	379	1.20 (1.06 to 1.37)		339	0.88 (0.77 to 1.02)		2132	1.02 (0.96 to 1.07)	
uACR>300 mg/g	344	1.08 (0.95 to 1.23)		359	0.83 (0.73 to 0.95)		1887	0.95 (0.90 to 1.01)	
All participants not on dialysis	787	1.14 (1.04 to 1.25)		763	0.86 (0.79 to 0.95)		4341	0.98 (0.94 to 1.02)	

HRs adjusted for age, sex, ethnicity, treatment allocation, prior diabetes, prior vascular disease, smoking, body mass index, eGFR, and albuminuria. Average HR (95% CI) throughout the range of values studied (*i.e.*, assuming a log-log-linear relationship for triglycerides and TG/HDLc ratio, and log-linear relationships for all other lipids), corresponding to about 1 SD differences in usual lipid values. HR, hazard ratio; 95% CI, 95% confidence interval; uACR, urinary albumin-to-creatinine ratio; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDL cholesterol minus HDL cholesterol; TG/HDLc, triglyceride to HDL cholesterol ratio.

[a]Test for effect modification by level of albuminuria.

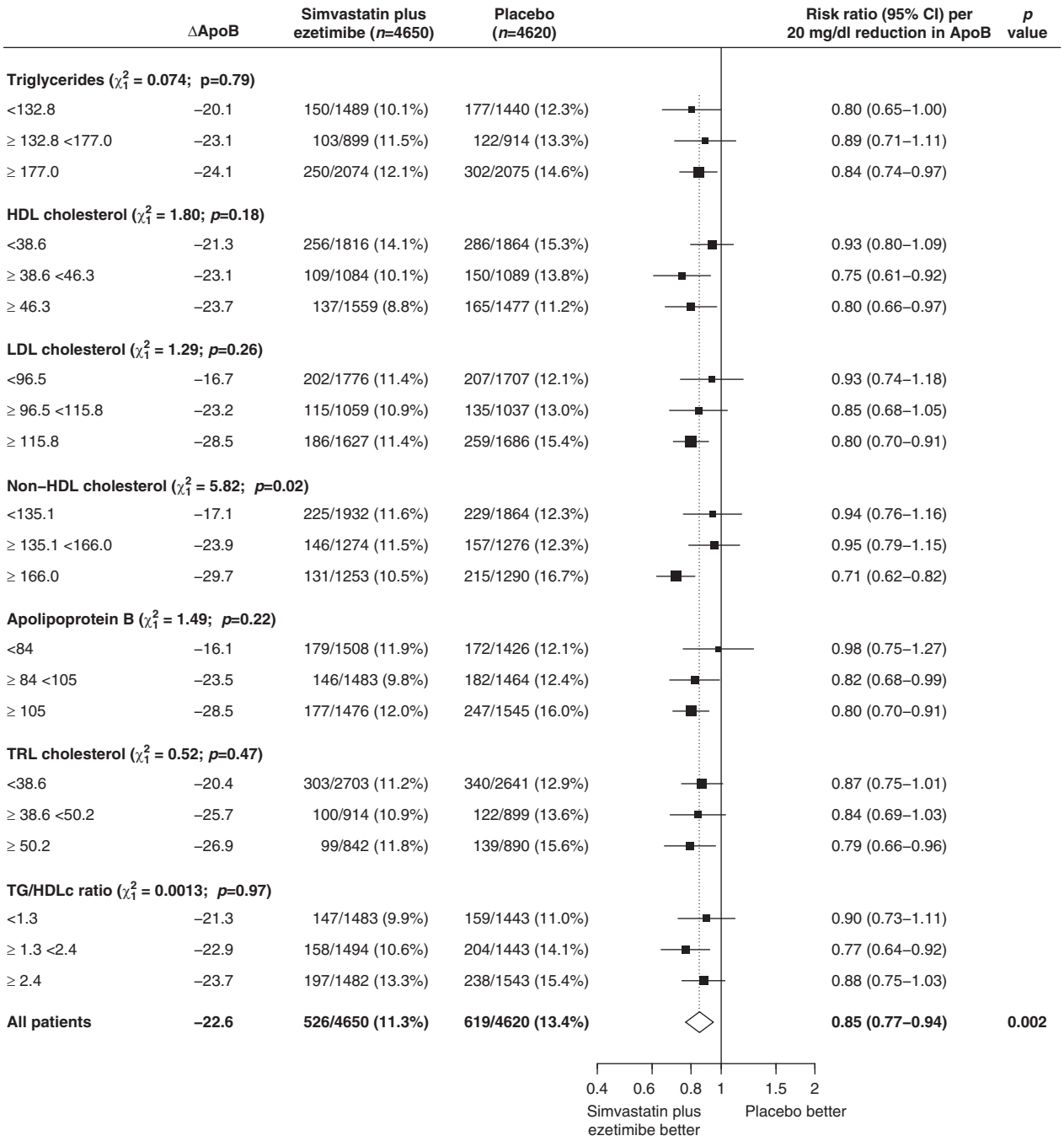

Figure 2. | **Effect of allocation to simvastatin plus ezetimibe on major atherosclerotic events, by level of baseline lipids.** Participants with missing baseline values of lipids are excluded from the subgroup analyses, but are included in the overall result. TG, triglyceride; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDL cholesterol minus HDL cholesterol.

Discussion

In this large cohort of people with moderate to advanced CKD, inclusive of patients on dialysis, we observed that increased levels of apo-B, triglycerides, ratio of triglyceride to HDL cholesterol, LDL cholesterol, and triglyceride-rich lipoprotein cholesterol were associated with increased risk of atherosclerotic vascular events. These associations were not modified by treatment allocation to simvastatin plus ezetimibe, or baseline eGFR or albuminuria. In addition, we observed inverse associations of all evaluated lipids and lipoproteins with nonatherosclerotic vascular events that were largely restricted to participants with high levels of CRP used as a marker of systemic inflammation.

Recently published work in the Chronic Renal Insufficiency Cohort (CRIC) study showed significant associations between higher apo-B and higher VLDL cholesterol concentrations and increased atherosclerotic cardiovascular disease risk in participants with CKD (18). Generally, the associations between lipids and lipoproteins and atherosclerotic vascular event risk in CRIC were weaker than in this

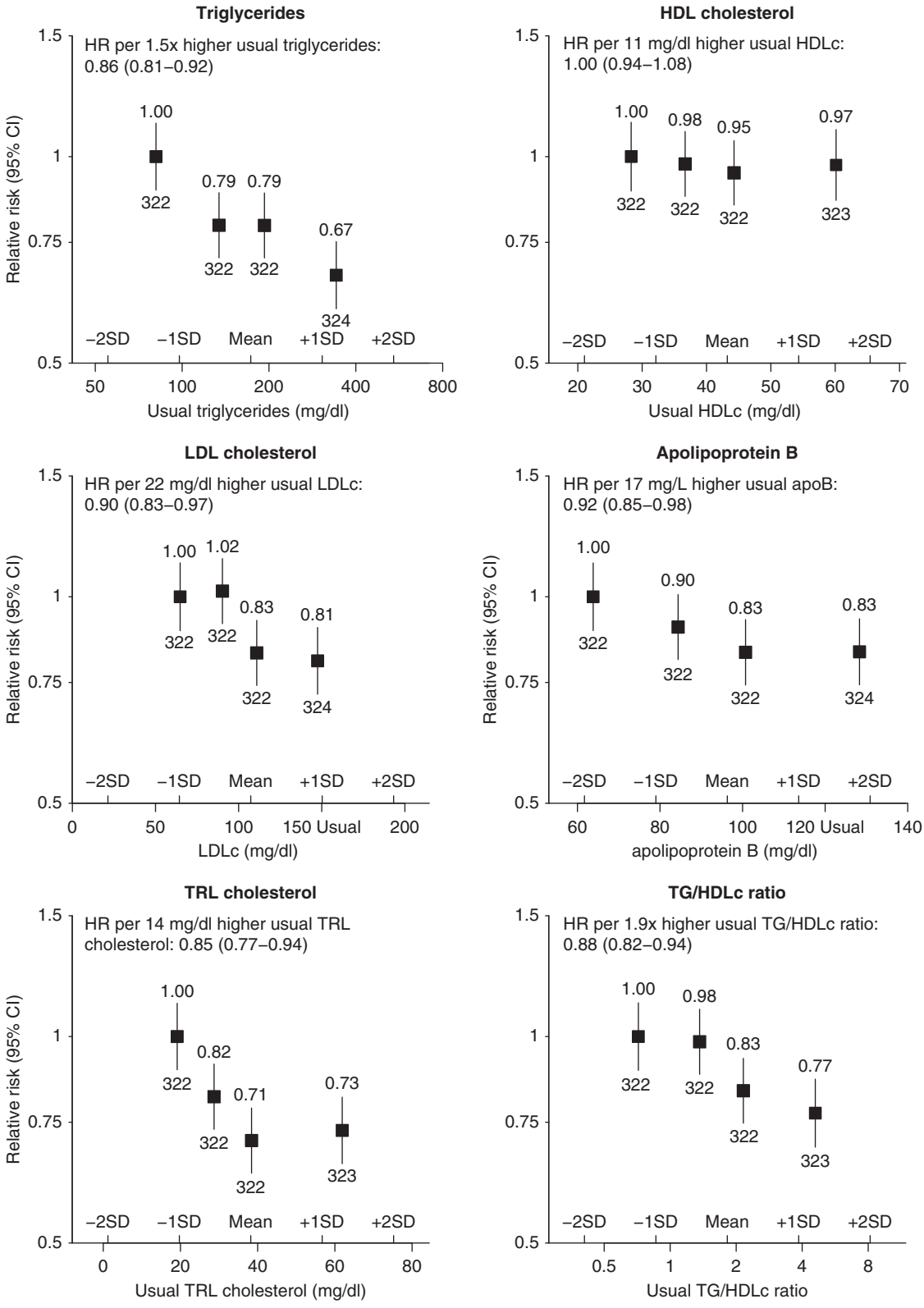

Figure 3. | **Association between usual lipid values and the risk of nonatherosclerotic vascular events.** HRs adjusted for age, sex, ethnicity, treatment allocation, prior diabetes, prior vascular disease, smoking, body mass index, eGFR, and albuminuria are quoted (above squares) with numbers of events (below). Average HR (95% CI) throughout the range of values studied (*i.e.*, assuming a log-log-linear relationship for triglycerides and triglyceride to HDLc ratio, and log-linear relationships for all other lipids), corresponding to about 1 SD differences in usual lipid values. HDLc, HDL cholesterol; LDLc, LDL cholesterol; TG, triglyceride; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDLc minus HDLc.

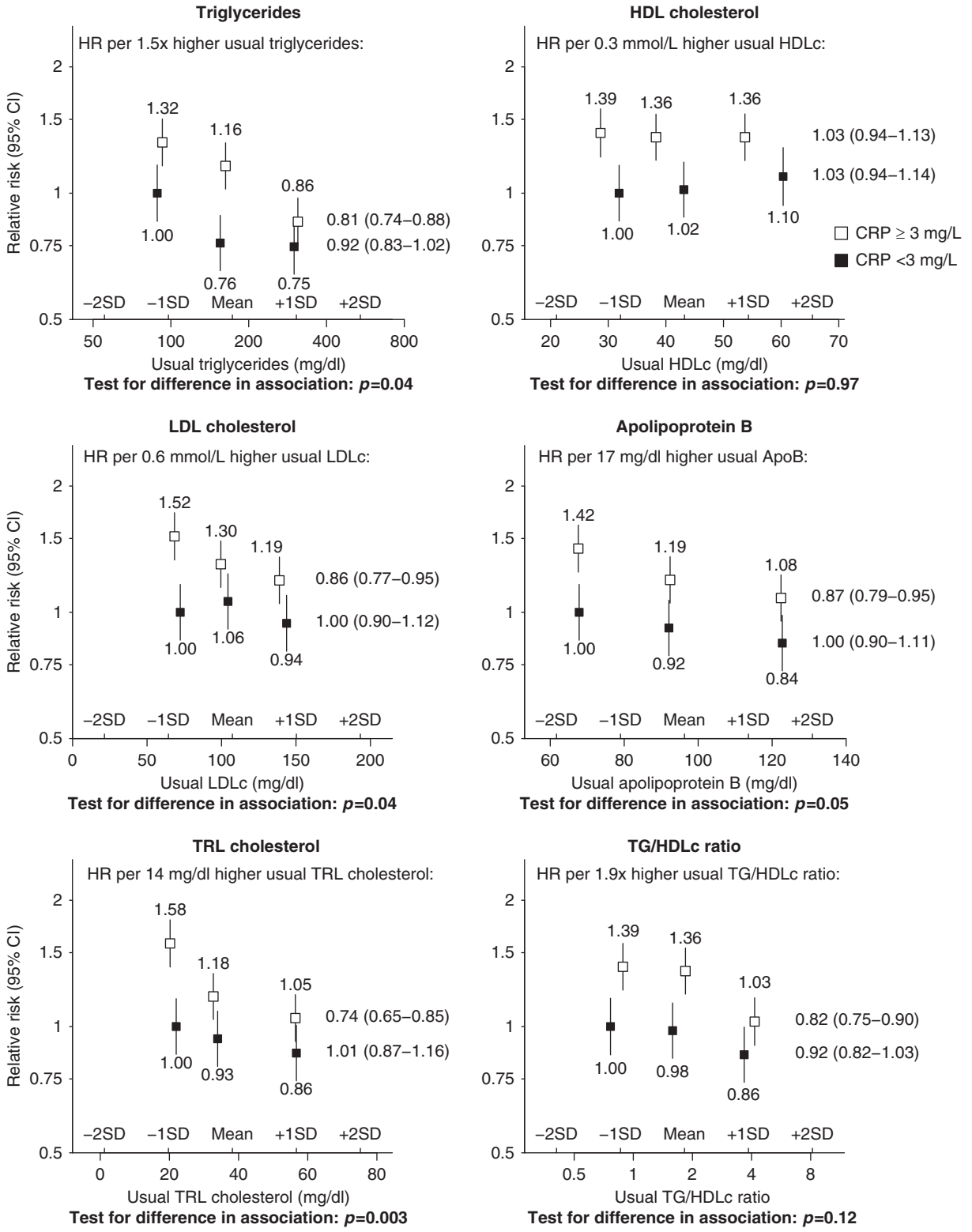

Figure 4. | **Association between usual lipid values and the risk of nonatherosclerotic vascular events, stratified by levels of CRP.** HRs adjusted for age, sex, ethnicity, treatment allocation, prior diabetes, prior vascular disease, smoking, body mass index, eGFR, and albuminuria are quoted (above squares) with numbers of events (below). Average HR (95% CI) throughout the range of values studied (*i.e.*, assuming a log-log-linear relationship for triglycerides and triglyceride to HDLc ratio, and log-linear relationships for all other lipids), corresponding to about 1 SD differences in usual lipid values. CRP, C-reactive protein; HDLc, HDL cholesterol; LDLc, LDL cholesterol; TG, triglyceride; TRL, triglyceride-rich lipoprotein; TRL cholesterol, total cholesterol minus LDLc minus HDLc.

study, perhaps as a result of reverse causality because of the inclusion in CRIC of participants with a history of atherosclerotic cardiovascular disease at baseline. The CRIC analyses also suggested that apo-B is only associated with atherosclerotic vascular event risk in earlier stages of CKD. This is in contrast to our results, which showed no evidence of effect modification of the association between apo-B and atherosclerotic vascular event risk by baseline eGFR.

Although SHARP excluded participants with a history of myocardial infarction or coronary revascularization at baseline, there is still the possibility that the associations between lipids and atherosclerotic vascular events may be subject to reverse causality due to preclinical disease that affects the usual lipid values. In sensitivity analyses excluding participants in the bottom lipid category, the observed associations were strengthened, suggesting that this study may underestimate the true strength of associations between usual lipid/lipoprotein values and atherosclerotic vascular event risk.

Individuals with CKD have a high prevalence of hypertriglyceridemia (19). In our study, for instance, median triglyceride concentration was 168 mg/dl, compared with a median triglyceride concentration of 106 mg/dl in the general adult United States population (20). The hypertriglyceridemia of CKD is a consequence of increased production and diminished clearance of triglyceride-rich lipoproteins (4). In particular, CKD is associated with altered metabolism of apo-CIII (21), resulting in diminished activity of lipoprotein lipase and inhibited removal of triglyceride-rich lipoproteins from plasma (by blocking apos from engaging with their hepatic receptors) (22), and consequently, higher triglyceride-rich lipoprotein concentrations. In contrast, LDL cholesterol concentrations are generally not raised in CKD (19). Several novel triglyceride-rich lipoprotein–lowering therapies have been developed that can reduce triglyceride levels by up to 70%, such as evinacumab, an angiopoietin-like protein 3 antibody (23), and volanesorsen, an antisense oligonucleotide targeting apo-CIII mRNA (24). Given that persons with CKD have increased levels of non-LDL apo-B–containing particles, which are hypothesized to be causally related to cardiovascular disease risk (11), our results suggest they might derive a significant benefit from these new therapies beyond treatment with statins or ezetimibe.

Prior studies have shown inverse associations between triglycerides or the ratio of triglyceride to HDL cholesterol and all-cause or cardiovascular mortality in patients with CKD and ESKD (25,26). In this study, we demonstrated inverse associations only for nonatherosclerotic vascular disease, chiefly in participants with high levels of systemic inflammation. We believe that these results of prior studies are therefore likely to be explained by reverse causality rather than by truly protective mechanisms. Consistent with this, the observed inverse associations were largely eliminated in analyses that excluded the bottom category of apo-B and lipids with nonatherosclerotic vascular events. In CKD, systemic inflammation is associated with hypertriglyceridemia through increased hepatic production and decreased clearance of VLDL particles (secondary to inhibition of lipoprotein lipase) (27). Our results suggest that triglyceride-rich lipoproteins and other lipids may be noncausal markers of increased risk of nonatherosclerotic vascular conditions associated with systemic inflammation and/or other unknown mechanisms.

We defined "triglyceride-rich lipoprotein cholesterol" as that part of plasma cholesterol that is not carried in LDL or HDL particles. As defined, this could include cholesterol carried in VLDL particles synthesized by the liver and cholesterol within remnant particles (*i.e.*, VLDL and intermediate density lipoprotein particles depleted of triglyceride content by lipoprotein lipase) (5,10). There is, however, substantial debate on the definition and measurement of remnant particles and their source (22,28–30). Remnant cholesterol has been hypothesized to be the proximal causal determinant of the association between triglyceride-rich lipoproteins and cardiovascular disease (10,14), but we were not able to address this hypothesis directly in our study because the profile of lipoprotein particles in this population was not characterized in detail.

Assignment to treatment to simvastatin plus ezetimibe compared with placebo reduced the concentrations of apo-B and triglyceride-rich lipoprotein cholesterol, with larger reductions among participants with CKD not on dialysis than among those on dialysis. However, the smaller reductions observed among those on dialysis are likely a result of the lower average use of simvastatin plus ezetimibe or nonstudy statin among those on dialysis compared with participants with CKD not on dialysis (54% versus 65%). Because the magnitude of the protective effect of simvastatin plus ezetimibe is consistent with the absolute reduction in LDL cholesterol, we were unable to evaluate the effect of reducing triglyceride-rich lipoproteins on the risk of cardiovascular events. This is an important limitation given that triglycerides may exert their effects because they are a component of potentially atherogenic lipoproteins (*e.g.*, apo-B–containing lipoproteins such as VLDL) that were not measured directly (31). A further limitation is that we cannot exclude the possibility of underestimation of associations as the result of index event bias, which could have been introduced by the requirement for SHARP participants to have CKD (32).

In conclusion, we found that higher levels of apo-B, triglycerides, the ratio of triglyceride to HDL cholesterol, LDL cholesterol, and triglyceride-rich lipoprotein cholesterol are associated with increased risk of atherosclerotic vascular events in people with moderate to advanced CKD. These observations suggest that triglyceride-rich lipoproteins may be implicated in the substantial residual atherosclerotic cardiovascular disease risk experienced by patients with CKD after statin treatment, and that this population may potentially benefit from novel therapies that lower these lipoproteins substantially.

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Disclosures

Dr. Baigent reports receiving grants from Merck & Co., Inc., Novartis, and Pfizer outside of the submitted work. Dr. de Boer

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Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.07320619/-/DCSupplemental.

Supplemental Table 1. Regression dilution ratios for each lipid.

Supplemental Table 2. (A) Baseline characteristics by triglycerides group among 6245 SHARP participants not on dialysis at baseline. (B) Baseline characteristics by triglycerides group among 3025 SHARP participants on dialysis at baseline.

Supplemental Table 3. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events, and nonvascular events, overall and by treatment allocation.

Supplemental Table 4. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events, and nonvascular events, overall and by level of C-reactive protein.

Supplemental Table 5. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events, and nonvascular events, overall and by level of troponin I.

Supplemental Table 6. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events, and nonvascular events, overall and by level of albumin.

Supplemental Table 7. Association between usual lipid values and the risk of atherosclerotic vascular events, nonatherosclerotic vascular events, and nonvascular events, excluding participants in the bottom lipid category.

Supplemental Figure 1. Causal diagram showing assumed associations between triglycerides, HDL cholesterol, LDL cholesterol, and apo-B, atherosclerotic vascular events, and other characteristics.

Supplemental Figure 2. Correlation between different lipid measures.

Supplemental Figure 3. Association between usual lipid values and the risk of atherosclerotic vascular events, adjusted for other lipid fractions.

Supplemental Figure 4. Association between usual lipid values and the risk of nonatherosclerotic vascular events, adjusted for other lipid fractions.

Supplemental Figure 5. Association between usual lipid values and the risk of nonvascular events.

Supplemental Figure 6. Association between usual lipid values and the risk of nonvascular events, adjusted for other lipid fractions.

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