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On-Treatment Non-HDL Cholesterol, Apolipoprotein B, Triglycerides, and Lipid Ratios in Relation to Residual Vascular Risk after Treatment with Potent Statin Therapy: The JUPITER Trial

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Abstract

Objectives—To determine whether residual risk after high-dose statin therapy for primary prevention individuals with low LDL cholesterol (LDL-C) is related to on-treatment apolipoprotein B, non-HDL cholesterol (non-HDL-C), or lipid ratios, and how they compare with on-treatment LDL cholesterol (LDL-C).

Background—Guidelines focus on LDL-C as the primary target of therapy, yet residual risk for cardiovascular disease (CVD) among statin-treated individuals remains high and not fully explained.

Methods—Participants in the randomized placebo-controlled JUPITER trial were adults without diabetes or CVD, with baseline LDL-C<130 mg/dL, high-sensitivity C-reactive protein ≥2 mg/L, and triglycerides <500 mg/dL. Individuals allocated to rosuvastatin 20 mg daily with baseline and on-treatment lipids and lipoproteins were examined in relation to the primary endpoint of incident

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CVD (non-fatal myocardial infarction or stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death).

Results—Using separate multivariate Cox models, statistically significant associations of a similar magnitude with residual risk of CVD were found for on-treatment LDL-C, non-HDL-C, apolipoprotein B, total/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-1. The respective adjusted standardized hazard ratios (95% confidence intervals) for each of these measures were 1.31 (1.09–1.56), 1.25 (1.04–1.50), 1.27 (1.06–1.53), 1.22 (1.03–1.44), 1.29 (1.09–1.52), and 1.27 (1.09–1.49). The overall residual risk and the risk associated with these measures decreased among participants achieving on-treatment LDL-C ≤70 mg/dL, on-treatment non-HDL-C ≤100 mg/dL, or on-treatment apolipoprotein B ≤80 mg/dL. By contrast, on-treatment triglycerides showed no association with CVD.

Conclusions—In this primary prevention trial of non-diabetic individuals with low LDL-C, on-treatment LDL-C was as valuable as non-HDL-C, apolipoprotein B, or ratios in predicting residual risk.

Keywords

apolipoproteins; lipids; lipoproteins; primary prevention; trials

Introduction

Statins are the most widely used lipid-lowering agents and the standard of care for individuals with dyslipidemia, prior cardiovascular disease (CVD), or at high-risk for CVD.[1,2] Current guidelines focus on LDL cholesterol (LDL-C) lowering as the primary target of therapy, tailoring the level of optimal LDL-C reduction to the individual's level of cardiovascular risk.[1,2] Nonetheless, the risk among statin-treated individuals remains high and has been termed "residual risk". The 5-year incidence rate of a major CVD event occurring among statin-treated patients in randomized clinical trials is one in five (22%) for individuals with prior CVD, and one in ten (10%) for individuals with no prior CVD.[3,4]

Residual risk after statin treatment may be related to the on-treatment concentrations of lipids, apolipoproteins, or other biomarkers beyond LDL-C.[5] In a recent analysis from the Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, on-treatment concentrations of high-sensitivity C-reactive protein (hsCRP) were predictive of residual risk among primary prevention individuals treated with potent statin therapy,[6] but on-treatment HDL cholesterol (HDL-C) and apolipoprotein A-1 were not.[7] It is possible that other lipid or apolipoprotein measures, such as the LDL-C/HDL-C ratio or apolipoprotein B/A-1 ratio may provide better risk information than HDL-C or apolipoprotein A-1 alone.[8]

Further, apolipoprotein B has been proposed as a therapeutic target for lipid-lowering.[9,10] Apolipoprotein B reflects the number of potentially atherogenic lipoprotein particles, since each very-low-density lipoprotein and LDL particle carries on its surface one apolipoprotein B molecule.[11] On-treatment apolipoprotein B has been compared with LDL-C in asymptomatic individuals for the primary prevention of CVD among statin-treated individuals with low HDL-C in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[12] and amongdiabetic patients in the Collaborative Atorvastatin Diabetes Study (CARDS).[13] In AFCAPS/TexCAPS, on-treatment apolipoprotein B was a better predictor of events compared with LDL-C, but comparison with non-HDL-C was not reported.[9,12] By contrast, among statin-treated patients in CARDS, none of the on-treatment lipids or apolipoproteins were statistically significantly associated with events.[13]

Among patients with stable coronary disease treated with potent statin therapy, apolipoprotein B and non-HDL-C were comparable as predictors of residual risk.[14] But it is uncertain if apolipoprotein B or non-HDL-C are better targets of therapy compared with LDL-C for the primary prevention of CVD among non-diabetic individuals with low LDL-C treated with potent statin therapy.

This analysis of the JUPITER trial cohort addressed, in a primary prevention setting of non-diabetic individuals with baseline low LDL-C but elevated hsCRP, whether residual risk after high-dose statin therapy was related to on-treatment levels of apolipoprotein B, non-HDL-C, or lipid ratios, and how they compared with on-treatment LDL-C. A secondary aim was to explore residual risk associations of these measures among the subgroup of individuals who achieved very low cholesterol targets on statin therapy.

Methods

Study population

The JUPITER design has been previously published.[15–17] Asymptomatic individuals (women ≥ 60 years, men ≥ 50 years) without prior history of coronary disease, stroke or diabetes and who had LDL-C <130 mg/dL, hsCRP ≥2.0 mg/L, and triglycerides <500 mg/dL were randomized. Drugs that were exclusion criteria included current use of hormone therapy, previous or current use of lipid-lowering therapy, or immunosuppressant agents. Family history of premature atherosclerosis was defined as coronary disease in a first-degree relative, male <55 or female <65 years old. Of the 8901 individuals randomized to rosuvastatin therapy, we included individuals who had both baseline and on-treatment one-year measures for all the lipid and lipoprotein variables examined, resulting in a sample size of 7832.

Laboratory measurements

Measurements were performed in a central laboratory on fasting (at least 8 hours) blood samples.[18] Concentrations of apolipoproteins B and A-1 were measured by immunonephelometry using a Behring nephelometeric assay (Marburg, Germany). Assessment for total cholesterol used an enzymatic procedure (cholesterol esterase) with a colorimetric endpoint. Triglycerides were measured with an enzymatic hydrolysis procedure to obtain a colorimetric endpoint triglyceride value. HDL-C was measured in the resulting supernatant after heparin–manganese precipitation of apolipoprotein B–containing proteins. LDL-C concentrations were calculated by the Friedewald equation when triglycerides were <400 mg/dL,[19] and measured by ultracentrifugation when triglycerides were ≥400 mg/dL. A high-sensitivity assay (Behring Nephelometer) was used for measurement of hsCRP.

Outcomes

The trial was expected to last approximately five years, but on March 30, 2008, the Independent Data and Safety Monitoring Board terminated the trial early upon determination that the accumulated evidence from the trial and other sources constituted proof beyond a reasonable doubt that rosuvastatin was indicated for a specified group of participants (after 1.9 year median follow-up, maximal follow-up 5.0 years). Follow-up included structured interviews assessing outcomes. The primary endpoint of the JUPITER trial was a composite endpoint (CVD), defined as the combined endpoint of myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. For this analysis, we also examined the expanded secondary endpoint of CVD or death. Myocardial infarction, stroke, and CVD death were confirmed according to standard criteria. Unstable angina was ischemic chest pain at rest or with minimal exertion occurring within the preceding 48 hours, requiring hospitalization and presence of

objective evidence of ischemia. Arterial revascularization was coronary artery bypass graft surgery, bypass grafting of any peripheral artery or carotid artery, or the performance of at least one percutaneous transluminal intervention. All reported primary endpoints that occurred through March 30, 2008 were adjudicated by an independent endpoint committee blinded to randomized treatment assignment.

Statistical Analyses

Statistical analyses were performed with SAS software, version 9.1 (SAS Institute Inc, Cary, NC). Medians, 25th, and 75th percentiles were calculated for continuous variables. Statistical comparisons were made with the Sign tests for comparing the change from baseline to on-treatment values.

Statistical tests for outcomes were performed according to intention-to-treat. The exposure time was calculated as the time from randomization to occurrence of the primary endpoint or the date of death, last study visit, withdrawal, loss to follow-up, or March 30, 2008, whichever came first. Absolute event rates were calculated per 100-person years. Cox proportional hazard models were used to calculate the hazard ratios and 95% confidence intervals (CIs). All regression analyses were adjusted for age, sex, smoking status, family history of premature atherosclerosis, body-mass index, systolic blood pressure, and fasting glucose. Each lipid measure was examined in tertiles and as continuous variables (per one standard deviation). P value for linear trend was obtained using the median value for each tertile. All P-values were two-tailed. The likelihood ratio χ^2 statistic was also used to evaluate the significance of individual lipid measures.

We conducted two additional exploratory analyses to evaluate 1) whether any measure of on-treatment lipids was significantly related to residual risk after control for on-treatment LDL-C, and 2) whether on-treatment lipid measures remained associated with risk among individuals who achieved clinically accepted guideline recommended cut-points for each of LDL-C (<100 or <70 mg/dL), non-HDL-C (<130 or <100 mg/dL), or apolipoprotein B (<90 or <80 mg/dL).

Results

The baseline characteristics for individuals randomly allocated to receive rosuvastatin and who had on-treatment lipid and lipoprotein measurements available for analysis at baseline and one-year were similar to the overall JUPITER study population.[17,20] The JUPITER patients were selected to have an LDL-C <130 mg/dL and triglycerides <500 mg/dL, and hence the total cholesterol, LDL-C, and non-HDL cholesterol were all low (respective median baseline concentrations of 186, 108, and 134 mg/dL). The apolipoprotein B levels were not low (median baseline concentration 109 mg/dL). Random allocation to rosuvastatin in the JUPITER trial decreased median on-treatment concentrations of total, LDL, and non-HDL-C to a similar extent on a mass concentration scale (−50 mg/dL, −50 mg/dL, and −54 mg/dL, respectively) and reduced apolipoprotein B by 41 mg/dL (Table 1). There was greater proportional LDL-C lowering (46.2%) compared with non-HDL-C (40.3%) or apolipoprotein B (37.6%) with rosuvastatin therapy. Triglycerides were also reduced, but to a lesser extent.

The primary endpoint was reduced with rosuvastatin by 44% (P<0.001).[17] Table 2 shows CVD incidence rates and associations for each of the on-treatment lipids, apolipoproteins, and ratios (examined in tertiles) with incident events obtained from separate Cox regression models that adjusted for non-lipid risk factors. Generally similar and significant associations were obtained for on-treatment concentrations of LDL-C, non-HDL-C, and apolipoprotein B with CVD. By contrast, on-treatment triglycerides, HDL-C, and apolipoprotein A-1 showed

no associations with CVD risk. Similar results were noted for the expanded secondary endpoint of CVD or death, except that apolipoprotein A-1 now became statistically significant and the apolipoprotein B/A-1 ratio now had a greater magnitude of association (2.12, 95 % CI 1.44–3.12).

When lipids, apolipoproteins, and ratios were examined as standardized continuous variables, results were generally similar for LDL-C, non-HDL-C, apolipoprotein B, and the ratios (Table 3), as were the goodness-of-fit likelihood ratio χ^2 statistics that added each of these variables to a model with only non-lipid risk factors. Specifically, for on-treatment LDL-C, non-HDL-C, apolipoprotein B, and the ratios, total/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-1, the respective adjusted standardized hazard ratios (95% CIs) were 1.31 (1.09–1.56), 1.25 (1.04–1.50), 1.27 (1.06–1.53), 1.22 (1.03–1.44), 1.29 (1.09–1.52), and 1.27 (1.09–1.49).

We then conducted two exploratory analyses. First, we assessed whether any of the measures non-HDL-C, apolipoprotein B, total/HDL-C, LDL-C/HDL-C, or apolipoprotein B/A-1 was significantly related to residual risk after controlling for on-treatment LDL-C. In models that included on-treatment LDL-C, none of the other lipid measures remained statistically significant.

Subsequently, we compared associations with residual risk among the subgroups of individuals who achieved the clinical recommendations for LDL-C targets, or the alternative recommended targets for non-HDL-C or apolipoprotein B. As shown in Table 4, among the subgroups of individuals achieving the lower clinical targets (LDL-C ≤70 mg/dL, non-HDL-C ≤100 mg/dL, or apolipoprotein B ≤80 mg/dL), the magnitude of residual risk was small and the residual risk associated with these measures became attenuated and mostly no longer statistically significant. Apolipoprotein B/A-1 retained its association with the expanded secondary endpoint of CVD or death, but this was also attenuated in the subgroup of individuals who achieved apolipoprotein B ≤80 mg/dL on therapy.

Discussion

In the JUPITER trial of primary prevention non-diabetic individuals with low LDL-C, measuring on-treatment LDL-C was as valuable as measuring non-HDL-C or apolipoprotein B, or the ratios (total/HDL-C, LDL-C/HDL-C, and apolipoprotein B/A-1) in relation to residual risk of CVD. The magnitude of the overall residual risk and the risk associated with these measures decreased after achieving on-treatment concentrations of LDL-C ≤70 mg/dL, non-HDL-C ≤100 mg/dL, or apolipoprotein B ≤80 mg/dL. Furthermore, the current findings do not support the hypothesis that on-treatment triglycerides are related to residual risk among non-diabetic primary prevention individuals with baseline triglycerides <500 mg/dL and elevated hsCRP who are treated with potent statin therapy; however, median on-treatment triglycerides was low at 118 mg/dL.

Optimal targets of statin therapy

It has been a matter of controversy whether measuring non-HDL-C or apolipoprotein B concentrations are useful among primary prevention individuals treated with statin therapy, and whether either measure, or both, should be used as alternative or in addition to LDL-C. Among primary prevention populations, only 2 prior trials (AFCAPS/TexCAPS and CARDS) evaluated this question. On-treatment apolipoprotein B was better as a predictor of events compared with LDL-C in asymptomatic individuals with low HDL-C in AFCAPS/TexCAPS, although non-HDL-C was not evaluated in that study,[12] while among diabetic patients in CARDS none of the on-treatments lipids or apolipoproteins were statistically significantly associated with risk in the statin-allocated arm (although LDL-C and LDL-C/

HDL-C ratio were borderline significant).[9,13] The present JUPITER analysis, which was conducted among primary prevention individuals who were non-diabetic and without dyslipidemia, adds to the prior literature in finding that measuring LDL-C alone was as valuable as measuring non-HDL-C or apolipoprotein B, or the ratios (total/HDL-C, LDL-C/HDL-C, apolipoprotein B/A-1), in relation to residual risk.

Data from secondary prevention trials that evaluated the predictive value of LDL-C, non-HDL-C, and apolipoprotein B in relation to recurrent events also has been mixed and inconclusive.[14,21,22] In the Scandinavian Simvastatin Survival Study (4S)[21], on-treatment LDL-C was comparable with non-HDL-C or the total/HDL-C ratio, while apolipoprotein B had weaker association with recurrent events. In the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial,[22] on-treatment apolipoprotein B was better than LDL-C, although non-HDL-C was not reported. In the combined analysis from the Treating to New Targets (TNT) and Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) which compared potent versus less intensive statin therapy for the secondary prevention of cardiovascular disease,[14] non-HDL-C and apolipoprotein B were comparable in relation to risk. Compared with TNT/IDEAL, the JUPITER on-statin arm achieved lower levels of lipids and apolipoproteins, but had magnitude of associations with CVD that were generally similar to TNT/IDEAL (online appendix Table). Among acute coronary syndrome patients in the PROVE IT-TIMI 22 trial, on-treatment apolipoprotein B was equivalent to LDL-C or non-HDL-C.[23]

An unresolved important question relates to the optimal treatment targets of statin therapy for primary prevention. Subgroup analyses from the current study suggest that the magnitude of overall residual risk is small, and that most of the associations with CVD were attenuated below levels of LDL-C, non-HDL-C, or apolipoprotein B that corresponded to established targets previously derived from secondary prevention trials (LDL-C ≤70, non-HDL-C ≤100 mg/dL, or apolipoprotein B ≤80 mg/dL). The current data also do not support obtaining more than one of these measures in addition to LDL-C for assessing residual risk. These results, however, should be considered exploratory since they were derived from subgroup analysis and remain to be tested in a prospective clinical trial in the primary prevention setting.

Triglycerides and residual risk

Another area of recent controversy has been whether triglycerides contribute to risk among statin-treated individuals as compared with untreated individuals. The lack of association for on-treatment triglycerides with residual risk in JUPITER is supported by most prior statin trials which also found no significant associations for on-treatment triglycerides,[12,21, 24, 25] as well as data from a meta-analysis.[26] Importantly, however, in the present JUPITER trial as well as in former statin trials, those with the highest triglycerides were excluded and most included individuals had relatively low on-treatment triglycerides. Therefore, we cannot exclude that higher on-treatment triglycerides may be important for predicting residual risk.

Study limitations

The present study has potential limitations. Median duration of follow-up in JUPITER was 1.9 years (maximum 5.0 years) due to early termination of the trial for benefit, and data for events occurring long term could not be assessed. JUPITER excluded individuals with known CVD, diabetes or high triglycerides who met entry criteria for LDL-C and hsCRP, and it is unclear if our results would be applicable to other individuals from primary or secondary prevention who were excluded from the trial. JUPITER was a randomized clinical trial that tested a fixed dose of a potent statin and did not test the efficacy of different doses of statins nor did it test a strategy based on achieving different lipid targets. Finally, while

standardized regression coefficients provide some ability to compare effect sizes across biomarkers, they are dependent on the study-specific variability of these biomarkers which is influenced by the trial eligibility criteria.

Study Strengths

Strengths of the present study are the large number of individuals with baseline and on-treatment lipid and lipoprotein measures as well as detailed information on cardiovascular risk factors. Finally, few previous studies have examined individuals from primary prevention who had baseline low or average LDL-C and who attained even lower LDL-C concentrations with potent therapy.

Conclusions

In this large randomized primary prevention trial of non-diabetic individuals, on-treatment LDL-C was as valuable as non-HDL-C, apolipoprotein B, and several ratios in the prediction of residual risk. Among participants achieving on-treatment concentrations of LDL-C ≤70 mg/dL, non-HDL-C ≤100 mg/dL, or apolipoprotein B ≤80 mg/dL, the overall magnitude of residual risk was small and the risk associated with these measures decreased and was no longer statistically significant. Finally, the present study does not support the routine measurement of triglycerides among non-diabetic individuals without significant dyslipidemia who are treated with potent statin therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations

CVD	cardiovascular disease
LDL-C	LDL cholesterol
JUPITER	Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
hsCRP	high-sensitivity C-reactive protein (hsCRP)
HDL-C	HDL cholesterol
Non-HDL-C	non-HDL-cholesterol

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Table 1

Median, 25th, and 75th percentile values for lipids, apolipoproteins, and ratios among 7,832 rosuvastatin-treated individuals with baseline and 1-year measures of all lipid variables examined

	Baseline	Year 1	Change	*P value*
Lipids, mg/dL				
Total cholesterol	186 (169, 200)	133 (116,155)	−50 (−67, −27)	<0.0001
LDL cholesterol	108 (94,119)	55 (44,71)	−50 (−63, −29)	<0.0001
Non-HDL cholesterol	134 (118,147)	76 (64,96)	−54 (−70, −31)	<0.0001
Triglycerides	118 (85, 169)	99 (74, 137)	−17 (−48, 5)	<0.0001
HDL cholesterol	49 (40,60)	52 (43,64)	3 (−2,8)	<0.0001
Apolipoproteins, mg/dL				
Apolipoprotein A-I	163 (144,185)	165 (145,188)	2 (−12,16)	<0.0001
Apolipoprotein B	109 (95,122)	66 (56,81)	−41 (−54, −24)	<0.0001
Ratios				
Total/HDL cholesterol	3.67 (3.06,4.41)	2.50 (2.10,3.05)	−1.11 (−1.65, −0.61)	<0.0001
LDL/HDL cholesterol	2.14 (1.69,2.64)	1.05 (0.78,1.46)	−1.02 (−1.44, −0.57)	<0.0001
Apolipoprotein B/A-I	0.66 (0.55,0.80)	0.40 (0.32,0.52)	−0.25 (−0.35, −0.14)	<0.0001

Table 2

Risk of first CVD event or death for on-treatment lipids, apolipoproteins, and ratios by tertiles

	Tertile 1	Tertile 2	Tertile 3	*P* for linear trend
Lipids				
Total cholesterol, mg/dL	<123	123–145	>145	
No. CVD/No. CVD or death/Total N	37/60/2726	22/36/2498	42/69/2608	
CVD Incidence Rate	0.60	0.40	0.78	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.75 (0.44–1.28)	1.53 (0.96–2.45)	0.04
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.72 (0.47–1.09)	1.47 (1.02–2.11)	0.02
LDL cholesterol, mg/dL	<48	48–64	>64	
No. CVD/No. CVD or death/Total N	30/53/2628	23/40/2618	48/72/2586	
CVD Incidence Rate	0.51	0.39	0.91	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.83 (0.48–1.43)	1.99 (1.25–3.19)	0.0007
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.78 (0.52–1.18)	1.63 (1.13–2.34)	0.002
Non-HDL cholesterol, mg/dL	<69	69–88	>88	
No. CVD/No. CVD or death/Total N	31/52/2713	31/46/2595	39/67/2524	
CVD Incidence Rate	0.52	0.53	0.75	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.11 (0.67–1.84)	1.64 (1.01–2.66)	0.03
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.98 (0.66–1.46)	1.72 (1.19–2.48)	0.001
Triglycerides, mg/dL	<83	83–121	>121	
No. CVD/No. CVD or death/Total N	35/53/2663	30/52/2581	36/60/2588	
CVD Incidence Rate	0.61	0.54	0.62	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.94 (0.58–1.55)	1.06 (0.65–1.73)	0.76
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.12 (0.76–1.66)	1.31 (0.89–1.93)	0.16
HDL cholesterol, mg/dL	<47	47–59	>59	
No. CVD/No. CVD or death/Total N	41/67/2770	27/48/2522	33/50/2540	
CVD Incidence Rate	0.66	0.50	0.60	
CVD $HR_{adjusted}$ (95% CI)	1.00	0.80 (0.48–1.33)	1.04 (0.63–1.71)	0.84
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.85 (0.56–1.24)	0.83 (0.56–1.23)	0.36
Apolipoproteins				
Apolipoprotein A-1, mg/dL	<152	152–179	>179	
No. CVD/No. CVD or death/Total N	36/64/2612	40/62/2649	25/39/2571	
CVD Incidence Rate	0.64	0.69	0.44	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.06 (0.66–1.68)	0.76 (0.44–1.30)	0.33
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.92 (0.64–1.31)	0.59 (0.39–0.90)	0.01
Apolipoprotein B, mg/dL	<60	60–75	>75	
No. CVD/No. CVD or death/Total N	29/48/2660	30/46/2628	42/71/2544	
CVD Incidence Rate	0.50	0.50	0.78	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.01 (0.60–1.68)	1.60 (0.98–2.59)	0.04
CVD/death $HR_{adjusted}$ (95% CI)	1.00	0.91 (0.61–1.37)	1.64 (1.13–2.38)	0.003
Ratios				

	Tertile 1	Tertile 2	Tertile 3	*P* for linear trend
Total/HDL cholesterol	<2.23	2.23–2.83	>2.83	
No. CVD/No. CVD or death/Total N	31/48/2613	32/49/2613	38/68/2606	
CVD Incidence Rate	0.54	0.55	0.68	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.04 (0.63–1.73)	1.27 (0.77–2.10)	0.31
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.10 (0.73–1.65)	1.63 (1.11–2.39)	0.008
LDL/HDL cholesterol	<0.87	0.87–1.29	>1.29	
No. CVD/No. CVD or death/Total N	25/45/2611	33/54/2611	43/66/2610	
CVD Incidence Rate	0.43	0.56	0.79	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.20 (0.70–2.03)	1.82 (1.10–3.02)	0.01
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.15 (0.77–1.73)	1.64 (1.11–2.42)	0.008
Apolipoprotein B/A-1	<0.35	0.35–0.47	>0.47	
No. CVD/No. CVD or death/Total N	25/42/2611	29/42/2611	47/81/2610	
CVD Incidence Rate	0.43	0.49	0.86	
CVD $HR_{adjusted}$ (95% CI)	1.00	1.15 (0.66–1.98)	1.96 (1.18–3.25)	0.004
CVD/death $HR_{adjusted}$ (95% CI)	1.00	1.02 (0.66–1.57)	2.12 (1.44–3.12)	<0.0001

Incidence rates are per 100 person-years. Hazard ratios were adjusted for sex, age, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose.

Table 3

Risk of first CVD event or death for standardized on-treatment lipids, apolipoproteins, and ratios

	SD	Standardized $HR_{adjusted}$ (95% CI)	*P value*	Likelihood Ratio χ^{2*} (*P value*)
Lipids				
Total cholesterol, mg/dL	33.1			
CVD		1.19 (0.98–1.45)	0.08	2.84 (0.09)
CVD/death		1.21 (1.04–1.41)	0.02	5.45 (0.02)
LDL cholesterol, mg/dL	27.4			
CVD		1.31 (1.09–1.56)	0.004	7.64 (0.006)
CVD/death		1.29 (1.12–1.49)	0.0004	11.44 (0.0007)
Non-HDL cholesterol, mg/dL	30.8			
CVD		1.25 (1.04–1.50)	0.02	5.18 (0.02)
CVD/death		1.28 (1.11–1.47)	0.0005	10.69 (0.001)
Triglycerides, mg/dL	62.7			
CVD		0.93 (0.74–1.17)	0.56	0.36 (0.55)
CVD/death		1.04 (0.90–1.21)	0.57	0.30 (0.58)
HDL cholesterol, mg/dL	16.3			
CVD		0.89 (0.70–1.12)	0.29	1.15 (0.28)
CVD/death		0.86 (0.72–1.03)	0.10	2.90 (0.09)
Apolipoproteins				
Apolipoprotein A-1, mg/dL	32.4			
CVD		0.81 (0.65–1.01)	0.06	3.50 (0.06)
CVD/death		0.77 (0.65–0.92)	0.003	9.15 (0.002)
Apolipoprotein B, mg/dL	22.1			
CVD		1.27 (1.06–1.53)	0.009	6.13 (0.01)
CVD/death		1.30 (1.13–1.49)	0.0003	12.05 (0.0005)
Ratios				
Total/HDL cholesterol	0.86			
CVD		1.22 (1.03–1.44)	0.02	4.59 (0.03)
CVD/death		1.24 (1.09–1.41)	0.0009	9.41 (0.002)
LDL/HDL cholesterol	0.65			
CVD		1.29 (1.09–1.52)	0.002	7.85 (0.005)
CVD/death		1.29 (1.14–1.46)	<0.0001	13.11 (0.0003)
Apolipoprotein B/A-1	0.17			
CVD		1.27 (1.09–1.49)	0.003	7.37 (0.007)
CVD/death		1.30 (1.16–1.46)	<0.0001	15.85 (<0.0001)

Standardized hazard ratios were adjusted for sex, age, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose.

*Likelihood ratio χ^2 and p values obtained from the Cox proportional hazards regression comparing models that added the lipid variable to a referent model (non-lipid covariates only). A higher χ^2 value indicates a better model fit.

Table 4

Risk of first CVD event or death for standardized on-treatment lipids, apolipoproteins, and ratios by subgroups

	CVD		CVD/death	
	Standardized $HR_{adjusted}$ (95% CI)	***P value***	**Standardized $HR_{adjusted}$ (95% CI)**	***P value***
LDL cholesterol < 100 mg/dL (No. CVD/No. CVD or death/Total N: 86/140/6970)				
LDL cholesterol	1.70 (1.22–2.36)	0.002	1.47 (1.13–1.91)	0.004
Non-HDL cholesterol	1.31 (0.97–1.79)	0.08	1.34 (1.05–1.71)	0.02
Apolipoprotein B	1.40 (1.05–1.86)	0.02	1.35 (1.08–1.70)	0.009
Total/HDL cholesterol	1.15 (0.90–1.48)	0.26	1.18 (0.97–1.42)	0.10
LDL/HDL cholesterol	1.43 (1.09–1.88)	0.01	1.34 (1.07–1.67)	0.01
Apolipoprotein B/A-I	1.31 (1.07–1.61)	0.009	1.30 (1.12–1.51)	0.001
LDL cholesterol < 70 mg/dL (No. CVD/No. CVD or death/Total N: 61/103/5793)				
LDL cholesterol	0.96 (0.56–1.73)	0.96	0.88 (0.58–1.36)	0.57
Non-HDL cholesterol	0.66 (0.39–1.12)	0.13	0.85 (0.57–1.28)	0.44
Apolipoprotein B	0.88 (0.56–1.37)	0.56	1.00 (0.71–1.40)	0.96
Total/HDL cholesterol	0.92 (0.61–1.37)	0.67	1.05 (0.79–1.40)	0.73
LDL/HDL cholesterol	1.17 (0.72–1.89)	0.52	1.15 (0.80–1.66)	0.46
Apolipoprotein B/A-I	1.18 (0.86–1.62)	0.31	1.24 (1.01–1.53)	0.04
Non-HDL cholesterol < 130 mg/dL (No. CVD/No. CVD or death/Total N: 87/141/7035)				
LDL cholesterol	1.58 (1.18–2.13)	0.002	1.37 (1.08–1.74)	0.01
Non-HDL cholesterol	1.36 (0.99–1.88)	0.06	1.36 (1.06–1.76)	0.02
Apolipoprotein B	1.40 (1.04–1.87)	0.03	1.35 (1.07–1.70)	0.01
Total/HDL cholesterol	1.15 (0.87–1.53)	0.33	1.20 (0.97–1.49)	0.10
LDL/HDL cholesterol	1.41 (1.07–1.86)	0.02	1.32 (1.05–1.65)	0.02
Apolipoprotein B/A-I	1.29 (1.05–1.60)	0.02	1.29 (1.11–1.51)	0.001
Non-HDL cholesterol < 100 mg/dL (No. CVD/No. CVD or death/Total N: 70/114/6108)				
LDL cholesterol	1.26 (0.79–2.01)	0.33	1.11 (0.77–1.59)	0.58
Non-HDL cholesterol	0.98 (0.59–1.62)	0.93	1.05 (0.71–1.57)	0.79
Apolipoprotein B	1.14 (0.74–1.73)	0.56	1.10 (0.79–1.53)	0.58
Total/HDL cholesterol	1.05 (0.71–1.56)	0.79	1.12 (0.83–1.50)	0.45
LDL/HDL cholesterol	1.29 (0.85–1.97)	0.24	1.22 (0.88–1.70)	0.24
Apolipoprotein B/A-I	1.23 (0.93–1.63)	0.14	1.26 (1.03–1.52)	0.02
Apolipoprotein B < 90 mg/dL (No. CVD/No. CVD or death/Total N: 76/125/6511)				
LDL cholesterol	1.44 (0.98–2.11)	0.06	1.25 (0.92–1.69)	0.15
Non-HDL cholesterol	1.12 (0.74–1.69)	0.60	1.23 (0.89–1.68)	0.21
Apolipoprotein B	1.29 (0.86–1.91)	0.22	1.30 (0.96–1.78)	0.09
Total/HDL cholesterol	1.03 (0.73–1.47)	0.86	1.14 (0.88–1.48)	0.34
LDL/HDL cholesterol	1.31 (0.90–1.89)	0.16	1.24 (0.93–1.66)	0.14
Apolipoprotein B/A-I	1.23 (0.94–1.60)	0.12	1.28 (1.06–1.53)	0.009
Apolipoprotein B < 80 mg/dL (No. CVD/No. CVD or death/Total N: 66/107/5798)				
LDL cholesterol	1.38 (0.86–2.23)	0.18	1.15 (0.80–1.67)	0.45
Non-HDL cholesterol	1.05 (0.62–1.76)	0.86	1.08 (0.72–1.62)	0.72

	CVD		CVD/death	
	Standardized $HR_{adjusted}$ (95% CI)	***P value***	**Standardized $HR_{adjusted}$ (95% CI)**	***P value***
Apolipoprotein B	1.27 (0.77–2.09)	0.36	1.18 (0.80–1.75)	0.41
Total/HDL cholesterol	0.96 (0.62–1.47)	0.84	1.05 (0.76–1.44)	0.78
LDL/HDL cholesterol	1.20 (0.76–1.92)	0.44	1.15 (0.80–1.65)	0.45
Apolipoprotein B/A-I	1.18 (0.85–1.63)	0.32	1.22 (0.98–1.51)	0.08

Standardized hazard ratios were adjusted for sex, age, smoking status, family history of premature atherosclerosis, body mass index, systolic blood pressure, and fasting glucose.