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HDL cholesterol, size, particle number, and residual vascular risk after potent statin therapy

Samia Mora, MD, MHS, **Robert J. Glynn, ScD**, and **Paul M Ridker, MD, MPH**
Center for Cardiovascular Disease Prevention, Division of Preventive Medicine (Mora, Glynn, Ridker) and Division of Cardiovascular Medicine (Mora and Ridker), Brigham and Women's Hospital, Harvard Medical School, and Department of Biostatistics, Harvard School of Public Health (Glynn), Boston, Massachusetts

Abstract

Background—Chemically-measured high-density lipoprotein cholesterol (HDL-C) may not be the best clinical measure of HDL. Little is known about alternative HDL meassures such as HDL size or particle number (HDL-P) as determinants of residual risk after potent statin therapy.

Methods and Results—In JUPITER, HDL size and HDL-P were measured by nuclear magnetic resonance spectroscopy, and HDL-C and apolipoprotein A-I (apoA-I) were chemically assayed in 10,886 participants without cardiovascular disease (CVD) before and after random allocation to rosuvastatin 20 mg/day or placebo. Levels were examined with first CVD (N=234). HDL-P correlated better with apoA-I (Spearman r=0.69, p<0.0001) than with HDL-C (r=0.55, p<0.0001). Rosuvastatin lowered LDL cholesterol (49%) and raised HDL-C (6.1%), apoA-I (2.1%), HDL-P (3.8%) and HDL size (1.2%); all p<0.0001. Among placebo-allocated individuals, on-treatment HDL-C, apoA-I, and HDL-P had similar inverse associations with CVD (risk factor-adjusted hazard ratio and 95% CI per 1-SD: 0.79 [0.63–0.98], 0.75 [0.62–0.92], and 0.81 [0.67–0.97], respectively). Among rosuvastatin-allocated individuals, on-treatment HDL-P had a statistically significant and somewhat stronger association with CVD (0.73, 0.57–0.93, p=0.01) than HDL-C (0.82, 0.63–1.08, p=0.16) or apoA-I (0.86, 0.67–1.10, p=0.22). Among rosuvastatin-allocated individuals, on-treatment HDL-P remained significant (0.72, 0.53–0.97, p=0.03) after additionally adjusting for HDL-C. In risk factor-adjusted models, HDL size showed no significant association with CVD.

Conclusions—In the setting of potent statin therapy, HDL particle number may be a better marker of residual risk than chemically-measured HDL-C or apoA-I. This has potential implications for evaluating novel therapies targeting HDL.

Clinical Trial Registration—ClinicalTrials.gov; NCT00239681

Keywords

inflammation; lipids; lipoproteins; prevention; statins

Corresponding Author: Samia Mora, MD, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215. Telephone: 617-278-0783. Facsimile: 617-264-9194. smora@partners.org.

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The high rate of residual cardiovascular disease (CVD) events occurring among individuals treated with statins (approximately one in seven statin-treated patients during a five-year period)[1, 2] has driven interest in therapeutic interventions targeted at reducing residual risk by modulating high-density lipoprotein (HDL). Major efforts have been directed in translational experimental laboratories and large-scale trials using agents that raise HDL cholesterol (HDL-C). Recent failures of drugs that raised HDL-C without reducing events[3–5] or atherosclerosis[6] may be in part due to limitations of the specific agents tested or the trial designs. This, in addition to recognizing that certain polymorphisms in the hepatic and endothelial lipase genes resulting in low or high HDL-C may not correspond to expected differences in risk,[7, 8] have raised the possibility that HDL-C may not be the best clinical measure of HDL.

Nevertheless, until recently low HDL-C was believed to be an important risk factor for residual risk among statin-treated patients.[9, 10] But an analysis from JUPITER (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), where on-treatment LDL cholesterol was very low (median 54 mg/dL), challenged this hypothesis. In JUPITER, on-treatment HDL-C was not predictive of residual risk among statin-treated individuals, while HDL-C was predictive among those taking placebo.[11] Similarly, on-treatment apolipoprotein A-I (apoA-I, the major protein of HDL particles) and triglycerides were not predictive of residual risk.[12] This contrasted with significant associations for LDL cholesterol, apolipoprotein B, non-HDL-C, and high-sensitivity C-reactive protein (hsCRP).[12, 13]

Chemically-measured HDL-C, which evaluates the cholesterol carried by HDL particles, may not fully capture HDL-related cardioprotection. It has been hypothesized that alternative indices of HDL, such as HDL function, size, or the concentration (number) of HDL particles (HDL-P), may be better clinical markers of HDL. HDL-C is carried within lipoprotein particles that are particularly heterogeneous, varying in size, density, charge, lipid and proteomic composition, apolipoproteins, metabolism, and function.[14] Very little is known about the impact of statin therapy on measures of HDL other than HDL-C.

After the JUPITER trial completion but before obtaining the NMR HDL measurements, we pre-specified the hypothesis that the residual risk of CVD may be better explained by HDL-P compared with HDL-C. We aimed to evaluate this in JUPITER, as the trial provides a unique opportunity to address whether or not residual risk is related to HDL measures after random allocation to potent statin therapy in a primary prevention population that achieved very low LDL cholesterol levels.

Methods

Study population

The JUPITER trial randomized 17,802 asymptomatic women ≥60 years and men ≥50 years without prior history of CVD or diabetes who had LDL-C <130 mg/dL, hsCRP ≥2.0 mg/L, and triglycerides <500 mg/dL, as previously described.[15] Exclusion criteria included previous or current use of lipid-lowering therapy. Study participants were asked to provide a blood sample before randomization and after one year; 11,953 provided samples both at baseline and one year and these were stored in liquid nitrogen. After trial completion, HDL size and HDL-P were measured by proton nuclear magnetic resonance (NMR) spectroscopy on these samples. A total of 10,886 had complete baseline values of the HDL measures, and 10,046 had both baseline and one year measurements.

Laboratory measurements

Lipid measurements were performed in a central laboratory on fasting samples.[12] Chemically-measured HDL-C was assayed in the resulting supernatant after heparin–manganese precipitation of apolipoprotein B–containing proteins. Triglycerides were measured with an enzymatic hydrolysis procedure to obtain a colorimetric endpoint triglyceride value. LDL cholesterol concentrations were calculated by the Friedewald equation when triglycerides were <400 mg/dL, and measured by ultracentrifugation when ≥400 mg/dL.[16] Apo A-I was measured by immunonephelometry using a Behring nephelometeric assay (Marburg, Germany).

Samples for lipoprotein particle analysis by NMR spectroscopy were shipped on dry ice to LipoScience, Inc. (Raleigh, NC) where HDL-P and size were measured. HDL-P is the sum of the particle concentrations of the HDL subclasses, which were quantified based on particle size using the amplitudes of their lipid methyl group NMR signals.[17, 18] Mean HDL size was calculated as the weighted average of the HDL subclasses.

Outcomes

The primary endpoint of JUPITER was a composite CVD endpoint, defined as first myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. We also examined the expanded endpoint of CVD and all-cause death as we had previously done in relation to HDL-C and other lipids.[12] Follow-up included structured interviews assessing outcomes. All reported primary endpoints were adjudicated by an independent endpoint committee blinded to randomized treatment assignment. CVD events were confirmed according to standard criteria.[15]

Statistical analyses

Statistical analyses were performed with STATA software, version 10.1. Medians, 25th, and 75th percentiles were calculated for continuous variables. Spearman correlation coefficients were used as nonparametric measures of association for HDL measures. Change from baseline to on-treatment levels were compared statistically with Wilcoxon signed rank test, and change among the placebo group vs rosuvastatin group was compared with the Wilcoxon rank-sum test.

Statistical tests for outcomes were performed according to the treatment to which participants were randomized. 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 trial completion, whichever came first. Absolute event rates were calculated per 100-person years. Cox proportional hazard models were used to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs). All regression analyses were risk factor-adjusted for age, sex, smoking status, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides (natural log-transformed), and family history of premature atherosclerosis. Each HDL measure was examined in tertiles and as continuous variables (per 1-standard deviation [1-SD]). In order to allow for comparison across groups, the HRs were calculated using the SDs of baseline levels. Tertile cutpoints were calculated across both treatment arms. The likelihood ratio χ^2 statistic and corresponding p-value were used to evaluate the additional predictive value of HDL-P or HDL size over a model with risk factors alone or with HDL-C. P value for linear trend was obtained using the median value for each tertile. Results were not adjusted for multiple comparisons, and a two-tailed P-value <0.05 was considered to indicate statistical significance.

Results

Baseline characteristics for individuals with NMR HDL measurements (cavailable for analysis were generally similar to the overall JUPITER population (Table 1).[15] The current study however had more white participants. Median baseline HDL-C, apoA-I, LDL cholesterol, and hsCRP were 49 mg/dL (1.27 mmol/L), 164 mg/dL, 109 mg/dL (2.82 mmol/L), and 4.1 mg/L, respectively, almost identical to the JUPITER population as a whole,[15] and similar to the individuals who were not in the current study. Median HDL size (9.0 nm) and HDL-P (32.3 μmol/L) were consistent with values seen from other asymptomatic populations.[19]

Reproducibility and correlations

Among the placebo-treated individuals, Spearman self-correlation coefficients showed high agreement over time between baseline and 1-year values for HDL-C, apoA-I, HDL size, and HDL-P (r=0.85, 0.75, 0.80, and 0.73, respectively, all p<0.0001). These compared favorably with coefficients for total cholesterol (r=0.62), LDL cholesterol (r=0.55), and triglycerides (r=0.74).

HDL-P correlated only moderately with HDL-C at baseline (r=0.55, p<0.0001; Supplemental Table 1) and after one year of statin therapy (r=0.63, p<0.0001). HDL-P correlated more strongly with apoA-I at baseline (0.69, p<0.0001) and after one year of statin therapy (0.72, p<0.0001). HDL size showed greater correlation with HDL-C (r=0.65) than with apoA-I (r=0.56), and much less correlation with HDL-P (r=0.22). After one year of statin treatment, HDL size showed greater correlation with HDL-C (r=0.74) than at baseline, while HDL size remained weakly correlated with HDL-P (r=0.20).

Changes with rosuvastatin

Random allocation to rosuvastatin 20 mg/day decreased LDL-cholesterol by 51 mg/dL (49%), and increased HDL-C by 3 mg/dL and apoA-I by 3 mg/dL, similar to the main trial findings (all p<0.0001, Table 2).[15] Further, HDL size was increased by 0.1 nm, and HDL-P by 1.3 μmol/L (p<0.0001 for all). There was a greater proportional HDL-C increase (6.1%) with statin therapy from baseline to 1-year than was seen for apoA-I (2.1%) or HDL-P (3.8%). HDL size also increased with statin therapy, but to a lesser extent (1.2%).

Association with CVD events

During a median follow-up of 2.0 years (maximum 5.0), a total of 234 primary events occurred among the 10,886 individuals. The primary endpoint was reduced with rosuvastatin 20 mg versus placebo by 43% (p<0.001), almost identical to the overall JUPITER results (44%).[15] Table 3 shows crude incidence CVD rates and risk factor-adjusted associations for baseline HDL measures (examined in tertiles and per 1-SD).

Among placebo-allocated individuals, generally similar inverse associations were obtained for baseline HDL-C, apoA-I, and HDL-P with CVD, while baseline HDL size showed no statistically significant association with CVD. Among rosuvastatin-allocated individuals, no statistically significant association was seen with CVD in relation to baseline HDL-C (adjusted HR 0.96, 95% CI 0.72–1.29 per 1-SD of 15.3 mg/dL), apoA-I (0.84, 95% CI 0.65–1.10 per 30.2 mg/dL), or size (1.07, 95% CI 0.82–1.39 per 0.52 nm), while baseline HDL-P had a statistically significant association (0.78, 95% CI 0.61–0.99 per 6.32 μmol/L).

On-placebo (year 1) levels of HDL-C, apoA-I, and HDL-P also had inverse association with CVD (Table 4), which was not seen for HDL size. Among rosuvastatin-allocated individuals, on-treatment HDL-P had a statistically significant and somewhat stronger

association with CVD (0.73, 0.57–0.93, p=0.01) than HDL-C (0.82, 0.63–1.08, p=0.16) or apoA-I (0.86, 0.67–1.10, p=0.22). The likelihood ratio χ^2 p-value of 0.01 indicated added predictive value of on-treatment HDL-P to standard risk factors. In fully-adjusted models, the p-value for trend was also highly statistically significant across HDL-P tertiles (p=0.005).

Additional analyses

Generally stronger associations were obtained for HDL-P and apoA-I when examined in relation to the expanded secondary endpoint of CVD and death (330 events, Supplemental Tables 2 and 3) than with CVD alone. For example, among rosuvastatin-allocated individuals, the adjusted HR per 1-SD of on-treatment HDL-P was 0.66, 95% CI 0.54–0.80, p<0.0001, and for apoA-I 0.79, 95% CI 0.65–0.97, p=0.02 (Supplemental Table 3). There was a suggestion that greater HDL size may be associated with increased risk of CVD or death, although this did not reach statistical significance (p=0.09).

Overall, similar patterns of association were seen for women and men (all p-interaction>0.05). Further adjustment for hsCRP and LDL particle concentration did not alter the association of HDL-P with CVD. On-treatment HDL-P remained significantly associated with CVD among the 3,664 statin-allocated individuals (50 CVD events) with on-treatment LDL cholesterol ≤70 mg/dL (adjusted HR per 1-SD 0.70, 95% CI 0.51–0.95, p=0.02, p-interaction=0.71). Similar results were obtained among the subgroup with on-treatment apolipoprotein B ≤80 mg/dL (0.73, 95% CI 0.55–0.97, p=0.03, p-interaction=0.85).

Analyses combining HDL measures

To further address biological relationships between the HDL measures, we repeated analyses adjusting for risk factors plus two HDL measures at a time, using the likelihood ratio χ^2 statistic and corresponding p-value to assess for statistical significance. For incident CVD (Table 5) and the combined endpoint of CVD and death (Supplemental Table 4), HDL-P was inversely associated with risk and remained significant in almost all the models that included HDL-C or HDL size, in particular among rosuvastatin-allocated individuals.

By contrast, after additionally adjusting for HDL-P, there was no statistically significant association for HDL-C with CVD or the combined endpoint of CVD and death. However, HDL-C was generally inversely associated with risk in models that additionally adjusted for HDL size. Finally, HDL size was not significantly associated with CVD after adjustment for HDL-C or HDL-P. However, for the combined endpoint of CVD and death (Supplemental Table 4), HDL size became positively and statistically significantly associated in most models that adjusted for HDL-C or HDL-P.

Discussion

Among placebo-allocated individuals in JUPITER, on-treatment HDL-C, apoA-I, and HDL-P had similar inverse associations with CVD. Among rosuvastatin-allocated individuals in JUPITER, on-treatment HDL-P had a statistically significant and somewhat stronger association with CVD than HDL-C or apoA-I. This study suggests that HDL-P may be a better marker of residual risk than HDL-C or apoA-I among individuals treated to very low LDL cholesterol levels with potent statin therapy. HDL size was not associated with residual vascular risk or with risk in the absence of statin therapy. However, after additionally adjusting for HDL-C or HDL-P, larger HDL size was associated with increased risk for the combined endpoint of CVD and all-cause death.

Because HDL particles are quite heterogeneous, and because their functions cannot be inferred from the plasma concentration of chemically-measured HDL-C, interest has focused recently on measuring HDL-P, HDL size, and various HDL functions.[14, 20] HDL-C is correlated with other HDL parameters such as size and HDL-P, but the relationships are complex.[21] The association of HDL-C with CVD is influenced by metabolic relationships with insulin resistance, abdominal obesity, inflammation, and atherogenic lipoproteins.[21] By contrast, HDL-P appears to be much less correlated with these factors.[19] Furthermore, HDL-P may reflect greater reverse cholesterol transport capacity,[22] and other functional properties, such as antioxidant capacity, more closely than HDL-C.[23]

Both niacin and cholesteryl ester transfer protein (CETP) inhibitors raise HDL-C by increasing HDL size much more than their effect on increasing the number of HDL particles.[24–27,28] While our study was observational and hypothesis-generating, its findings suggest that the number of HDL particles[29] may matter more than the size of the particle or the level of HDL-C as a determinant of residual risk among statin-treated individuals.[30] Future studies are needed to examine the various functional properties of HDL in relation to HDL-P, HDL size, and other measures of HDL, and how these are impacted by therapies targeting HDL.[31]

Prior epidemiologic studies comparing HDL-P with HDL-C are few in number, have not addressed residual risk on a background of potent statin therapy, and have sometimes provided conflicting results. In the EPIC-Norfolk study, HDL-P was inversely associated with CVD,[23] while HDL-C and HDL size appeared to confer risk at very high values after adjusting for apolipoproteins B and A-I,[32] consistent with our findings. Among multiethnic individuals, we have previously shown that HDL-P was more closely related to subclinical atherosclerosis and coronary events than HDL-C,[19, 33] and that very high HDL-C may confer increased risk after adjusting for HDL-P and risk factors.[19] Inverse associations of HDL-P with coronary death were also seen in a small case-control study among men with the metabolic syndrome.[34] However, in the Women's Health Study, HDL-P was not associated with incident CVD events among healthy low-risk women, in contrast with inverse associations seen for HDL size and HDL-C.[35] None of these prior population-based studies evaluated residual risk on statin therapy.

To our knowledge, this is the first direct comparison of HDL-C, apoA-I, HDL-P, and HDL size in relation to residual risk in a population whose LDL cholesterol has been reduced to contemporary standards with potent statin therapy. This is particularly relevant because HDL-modifying drugs now under investigation are expected to be used in the clinical setting of individuals with low LDL cholesterol levels on potent statins. In this regard, data evaluating residual risk in relation to on-statin HDL-C, HDL-P, and HDL size are limited to a post-hoc investigation of the MRC/BHF Heart Protection Study (HPS). In that secondary prevention setting evaluating simvastatin, both HDL-C and HDL-P were inversely associated with residual risk. [36] HDL size carried increased risk of other cardiac events (mostly heart failure) after adjusting for HDL-P. The average on-statin LDL cholesterol in HPS was 89 mg/dL,[37] while that in JUPITER was substantially lower (54 mg/dL). Finally, in the recent dal-OUTCOMES trial where dalcetrapib was given on a background of statin treatment, baseline HDL-C did not predict risk, though HDL-P and HDL size were not evaluated.[5]

Strengths of this study include the large number of individuals with HDL measures assessed both at baseline and on-treatment, the random allocation of a potent statin versus placebo, and the detailed information on cardiovascular risk factors and outcomes. The present study also has potential limitations. In particular, JUPITER excluded individuals with known CVD, diabetes, high LDL cholesterol, or high triglycerides. Further, the median HDL-C in

JUPITER was 49 mg/dL and the expected increase in HDL-C with rosuvastatin was less than may have been anticipated. Thus, it is uncertain if our data would generalize to individuals who do not meet the current study's inclusion or exclusion criteria. This study was conducted after trial completion, but before obtaining the NMR measurements we had a pre-specified protocol for this study, including the hypothesis that the residual risk of CVD may be better explained by HDL-P compared with HDL-C. This study was limited to HDL measurements obtained by NMR; other technologies were not examined.[14,20,28] Finally, as shown by the significant findings in this study for on-treatment HDL-P, and our previous significant findings for on-treatment LDL cholesterol, non-HDL-C, apolipoprotein B, and hsCRP, we had adequate power to detect true patterns of residual risk in both randomization groups. However, we are unable to rule out possible association for HDL-C and apoA-I with residual risk because of the relatively small number of events in the rosuvastatin arm. Finally, our results should be viewed as hypothesis-generating and will require further evaluation in other studies.

In conclusion, this study provides evidence that the number of HDL particles may be a better marker of residual risk than HDL-C or apoA-I. This has potential implications for evaluating therapeutic interventions targeting HDL in the era of potent LDL cholesterol lowering with statin therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics

	Current Study N=10,886	Not in Current Study N=6,916	Overall Study N=17,802
Characteristic	**Median (25^{th} – 75^{th} %ile) or N (%)**	**Median (25^{th} – 75^{th} %ile) or N (%)**	**Median (25^{th} – 75^{th} %ile) or N (%)**
Age	66 (60 – 71)	66 (61 – 71)	66 (60 – 71)
Women	3,917 (36.0%)	2884 (41.7%)	6801 (38.2%)
Rosuvastatin	5,367 (49.3%)	3,534 (51.1%)	8901 (50.0%)
Race/ethnicity			
White	8,982 (82.5%)	3,701 (53.5%)	12,683 (71.3%)
Black	775 (7.1%)	1,449 (21.0%)	2,224 (12.5%)
Asian	151 (1.4%)	132 (1.9%)	283 (1.6%)
Hispanic	895 (8.2%)	1,366 (19.8%)	2,261 (12.7%)
Other/unknown	83 (0.8%)	266 (3.9%)	349 (2.0%)
Body-mass index, kg/m^2	28.4 (25.5 – 32.0)	28.2 (25.0 – 32.0)	28.4 (25.3 – 32.0)
Systolic blood pressure, mm Hg	134 (124 – 146)	134 (124 – 144)	134 (124 – 145)
Diastolic blood pressure, mm Hg	80 (75 – 86)	80 (75 – 88)	80 (75 – 87)
Current smoker	1620 (14.9%)	1,200 (17.4%)	2,820 (15.9%)
Family history of premature coronary disease	1,387 (12.8%)	658 (9.6%)	2,045 (11.5%)
Glucose, mg/dL	95 (88 –102)	93 (86 – 101)	94 (88 – 102)
High-sensitivity C-reactive protein, mg/L	4.1 (2.8 – 6.8)	4.6 (2.9 – 7.7)	4.3 (2.9 – 7.1)
LDL cholesterol, mg/dL	109 (95 – 119)	107 (92 – 118)	108 (94 – 119)
Total cholesterol, mg/dL	186 (171 – 200)	184 (166 – 199)	185 (169 – 200)
Triglycerides, mg/dL	116 (84 – 166)	121 (88 – 174)	118 (85 – 169)
HDL cholesterol, mg/dL	49 (41 – 60)	48 (39 – 58)	49 (40 – 60)
Apolipoprotein A-I, mg/dL	164 (146 – 185)	159 (141 – 182)	162 (144 – 184)
HDL size, nm	9.0 (8.6–9.4)	---	---
HDL particles, μmol/L	32.2 (28.3–36.5)	---	---

Percentages may not add up due to rounding off

Table 2

Median, 25th, and 75th percentile values of HDL measures among placebo- and rosuvastatin-treated individuals

		Baseline	Year 1*	Change**	% Change
LDL cholesterol, md/dL	Placebo	109 (96, 119)	110 (95,125)	3 (−8, 15)	2.7 (−7.5, 14.4)
	Rosuvastatin	109 (95,119)	54 (43, 71)	−51 (−64, −31)	−48.8 (−58.3, − 33.1)
HDL cholesterol, mg/dL	Placebo	50 (41,60)	50 (42,62)	1 (−3, 5)	1.7 (−6.7, 10.8)
	Rosuvastatin	50 (41,60)	53 (44,65)	3 (−1, 8)	6.1 (−2.6, 16.7)
Apolipoprotein A-I, mg/dL	Placebo	164 (145, 185)	163 (145, 184)	0 (−13, 12)	0 (− 7.9, 7.8)
	Rosuvastatin	164 (146, 186)	167 (147, 190)	3 (−11, 17)	2.1 (−6.3, 10.6)
HDL size, nm	Placebo	9.0 (8.6, 9.4)	9.0 (8.6, 9.4)	0 (−0.2, 0.2)	0 (−2.2, 2.2)
	Rosuvastatin	9.0 (8.6, 9.4)	9.2 (8.7, 9.5)	0.1 (−0.1, 0.3)	1.2 (−1.0, 3.6)
HDL particles, μmol/L	Placebo	32.3 (28.4, 36.6)	31.5 (27.8, 35.6)	−0.9 (−3.4, 1.7)	−3.0 (−10.2, 5.5)
	Rosuvastatin	32.4 (28.4, 36.5)	33.5 (29.6, 37.9)	1.3 (−1.7, 4.3)	3.8 (−4.9, 13.8)

Values obtained from individuals with both baseline and year 1 measurements (N=10,046).

* P values from the Wilcoxon signed rank test comparing baseline and year 1 values were statistically significant (p<0.001) for all except for apolipoprotein A-I and HDL size among the placebo group (p=0.09 and 0.74, respectively).

** P values from the Wilcoxon rank-sum test comparing the change among the rosuvastatin group wwith the change among the placebo group were <0.001 for all.

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Table 3

Baseline HDL measures in relation to incident CVD events, by treatment group

	Tertile One	Tertile Two	Tertile Three	P-trend	HR per 1-SD increase	P_{LRT} #
Placebo (No. events/N: 152/5519)						
HDL cholesterol, mg/dL	≤44	45–56	>56			
Incidence (95% CI) *	1.56 (1.24–1.98)	1.15 (0.87–1.53)	0.87 (0.62–1.22)			
Adjusted HR (95% CI) **	1.00	0.75 (0.51–1.11)	0.55 (0.34–0.90)	0.02	0.88 (0.71–1.09)	0.22
Apolipoprotein A-I, mg/dL	≤152	153–177	>177			
Incidence (95% CI)	1.57 (1.25–1.98)	1.27 (0.96–1.67)	0.71 (0.49–1.04)			
Adjusted HR (95% CI)	1.00	0.89 (0.62–1.29)	0.52 (0.32–0.85)	0.01	0.85 (0.70–1.02)	0.08
HDL size, nm	≤8.7	8.8–9.2	>9.2			
Incidence (95% CI)	1.44 (1.14–1.82)	1.18 (0.89–1.57)	0.95 (0.68–1.33)			
Adjusted HR (95% CI)	1.00	0.83 (0.56–1.23)	0.69 (0.42–1.11)	0.13	0.72 (0.49–1.08)	0.11
HDL particles, μmol/L	≤29.7	29.8–34.9	>34.9			
Incidence (95% CI)	1.65 (1.30–2.09)	1.14 (0.86–1.52)	0.87 (0.63–1.19)			
Adjusted HR (95% CI)	1.00	0.73 (0.50–1.07)	0.60 (0.39–0.90)	0.01	0.79 (0.66–0.94)	0.006
Rosuvastatin (No. events/N: 82/5367)						
HDL cholesterol	≤44	45–56	>56			
Incidence (95% CI)	0.71 (0.50–1.01)	0.71 (0.49–1.04)	0.63 (0.42–0.94)			
Adjusted HR (95% CI)	1.00	1.14 (0.64–2.01)	1.17 (0.61–2.26)	0.65	0.96 (0.72–1.29)	0.80
Apolipoprotein A-I, mg/dL	≤152	153–177	>177			
Incidence (95% CI)	0.88 (0.64–1.21)	0.62 (0.42–0.93)	0.53 (0.34–0.83)			
Adjusted HR (95% CI)	1.00	0.78 (0.45–1.33)	0.77 (0.42–1.43)	0.39	0.84 (0.65–1.10)	0.20
HDL size	≤8.7	8.8–9.2	>9.2			

	Tertile One	Tertile Two	Tertile Three	P-trend	HR per 1-SD increase	P_{LRT} #
Incidence (95% CI)	0.68 (0.48–0.96)	0.69 (0.47–1.01)	0.69 (0.47–1.02)			
Adjusted HR (95% CI)	1.00	1.04 (0.60–1.83)	1.19 (0.64–2.23)	0.58	1.07 (0.82–1.39)	0.64
HDL particles	≤29.7	29.8–34.9	>34.9			
Incidence (95% CI)	0.85 (0.61–1.19)	0.63 (0.42–0.93)	0.58 (0.38–0.87)			
Adjusted HR (95% CI)	1.00	0.71 (0.42–1.20)	0.74 (0.42–1.30)	0.27	0.78 (0.61–0.99)	0.04

*Incidence per 100 person-years

**Cox proportional hazard ratios were adjusted for age, sex, race, smoking, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides, and family history of premature CHD. Standard deviations (SDs) were 15.3 mg/dL for HDL-C, 30.2 mg/dL for apolipoprotein A-I, 0.52 nm for HDL size, and 6.32 μmol/L for HDL-P.

#Likelihood ratio chi2 comparing a model that adds either HDL-C, HDL size, or HDL-P to the basic risk factors of age, sex, race, smoking, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides, and family history of premature CHD.

Table 4

On-treatment HDL measures in relation to incident CVD events, by treatment group

	Tertile One	Tertile Two	Tertile Three	P-trend	HR per 1-SD increase	P_{LRT}#
Placebo (No. events/N: 144/5114)						
HDL cholesterol, mg/dL	≤46	47–58	>58			
Incidence (95% CI)*	1.78 (1.43–2.20)	0.84 (0.59–1.20)	0.90 (0.63–1.28)			
Adjusted HR (95% CI)**	1.00	0.47 (0.30–0.73)	0.50 (0.31–0.81)	0.003	0.79 (0.63–0.98)	0.03
Apolipoprotein A-I, mg/dL	≤ 152	153–178	>178			
Incidence (95% CI)	1.73 (1.37–2.18)	1.10 (0.82–1.48)	0.82 (0.57–1.18)			
Adjusted HR (95% CI)	1.00	0.67 (0.46–0.99)	0.51 (0.32–0.82)	0.004	0.75 (0.62–0.92)	0.004
HDL size	≤8.8	8.9–9.3	>9.3			
Incidence (95% CI)	1.17 (0.91–1.50)	1.44 (1.09–1.90)	1.11 (0.79–1.57)			
Adjusted HR (95% CI)	1.00	1.42 (0.95–2.11)	1.06 (0.65–1.73)	0.62	0.94 (0.77–1.15)	0.54
HDL particles	≤30.0	30.1–35.1	>35.1			
Incidence (95% CI)	1.48 (1.17–1.87)	1.29 (0.98–1.71)	0.81 (0.55–1.19)			
Adjusted HR (95% CI)	1.00	1.00 (0.69–1.45)	0.68 (0.43–1.08)	0.13	0.81 (0.67–0.97)	0.02
Rosuvastatin (No. events/N: 82/4932)						
HDL cholesterol, mg/dL	≤46	47–58	>58			
Incidence (95% CI)	0.94 (0.68–1.31)	0.67 (0.44–1.01)	0.61 (0.41–0.90)			
Adjusted HR (95% CI)	1.00	0.71 (0.40–1.27)	0.71 (0.38–1.30)	0.28	0.82 (0.63–1.08)	0.16
Apolipoprotein A-I, mg/dL	≤152	153–178	>178			
Incidence (95% CI)	0.85 (0.59–1.22)	0.82 (0.57–1.18)	0.54 (0.36–0.82)			
Adjusted HR (95% CI)	1.00	0.93 (0.55–1.59)	0.72 (0.39–1.32)	0.29	0.86 (0.67–1.10)	0.22
HDL size	≤8.8	8.9–9.3	>9.3			

	Tertile One	Tertile Two	Tertile Three	P-trend	HR per 1-SD increase	P_{LRT}#
Incidence (95% CI)	0.68 (0.48–0.96)	0.69 (0.47–1.01)	0.69 (0.47–1.02)			
Adjusted HR (95% CI)	1.00	1.04 (0.60–1.83)	1.19 (0.64–2.23)	0.58	1.07 (0.82–1.39)	0.64
HDL particles	≤30.0	30.1–35.1	>35.1			
Incidence (95% CI)	1.21 (0.88–1.68)	0.71 (0.49–1.05)	0.45 (0.29–0.70)			
Adjusted HR (95% CI)	1.00	0.63 (0.38–1.06)	0.44 (0.25–0.79)	0.005	0.73 (0.57–0.93)	0.01

*Incidence per 100 person-years

**Cox proportional hazard ratios were adjusted for age, sex, race, smoking, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides, and family history of premature CHD. Standard deviations (SDs) were 15.3 mg/dL for HDL-C, 30.2 mg/dL for apolipoprotein A-I, 0.52 nm for HDL size, and 6.32 μmol/L for HDL-P.

#Likelihood ratio chi2 comparing a model that adds either HDL-C, HDL size, or HDL-P to the basic risk factors of age, sex, race, smoking, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides, and family history of premature CHD.

Table 5

Combination of two HDL measures at a time in mutually-adjusted multivariable models for incident CVD

	Baseline		Year 1	
	HR per 1-SD (95% CI)*	P_{LRT}#	HR per 1-SD (95% CI)*	P_{LRT}#
Placebo				
HDL cholesterol	0.95 (0.73–1.24)	0.73	0.74 (0.56–0.96)	0.03
HDL size	0.87 (0.67–1.12)	0.26	1.11 (0.87–1.42)	0.73
HDL cholesterol	1.09 (0.84–1.41)	0.38	0.88 (0.66–1.18)	0.38
HDL particles	0.75 (0.60–0.94)	0.01	0.87 (0.68–1.11)	0.26
HDL size	0.90 (0.73–1.11)	0.31	0.99 (0.81–1.21)	0.89
HDL particles	0.80 (0.67–0.96)	0.02	0.81 (0.67–0.98)	0.03
Rosuvastatin				
HDL cholesterol	0.89 (0.63–1.27)	0.45	0.67 (0.47–0.96)	0.03
HDL size	1.14 (0.82–1.58)	0.52	1.35 (0.97–1.89)	0.08
HDL cholesterol	1.23 (0.88–1.70)	0.24	1.03 (0.75–1.41)	0.88
HDL particles	0.70 (0.52–0.94)	0.02	0.72 (0.53–0.97)	0.03
HDL size	1.13 (0.87–1.48)	0.80	1.10 (0.86–1.40)	0.47
HDL particles	0.76 (0.59–0.97)	0.03	0.72 (0.57–0.92)	0.009

*Cox proportional hazard regression models included two HDL measures together with age, sex, race, smoking, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides, and family history of premature CHD. Standard deviations (SDs) were 15.3 mg/dL for HDL-C, 30.2 mg/dL for apolipoprotein A-I, 0.52 nm for HDL size, and 6.32 μmol/L for HDL-P.

#Likelihood ratio chi2 p-value for adding the corresponding HDL measure to a model with the other HDL measure. All models also adjusted for the basic risk factors of age, sex, race, smoking, systolic blood pressure, body-mass index, fasting glucose, LDL cholesterol, triglycerides, and family history of premature CHD