# High-Density Lipoprotein Cholesterol, Size, Particle Number, and Residual Vascular Risk After Potent Statin Therapy

Samia Mora, Robert J. Glynn and Paul M Ridker

*Circulation.* 2013;128:1189-1197; originally published online September 3, 2013;
doi: 10.1161/CIRCULATIONAHA.113.002671
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

# High-Density Lipoprotein Cholesterol, Size, Particle Number, and Residual Vascular Risk After Potent Statin Therapy

Samia Mora, MD, MHS; Robert J. Glynn, ScD; Paul M Ridker, MD, MPH

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

***Methods and Results***—In Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (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/d 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 low-density lipoprotein 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% confidence interval per 1 standard deviation: 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***—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00239681.

**(*Circulation*. 2013;128:1189-1197.)**

**Key Words:** inflammation ■ HMG-CoA ■ lipids ■ lipoproteins ■ prevention & control ■ statins

The high rate of residual cardiovascular disease (CVD) events occurring among individuals treated with statins (approximately 1 in 7 statin-treated patients during a 5-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 attributable to the 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.

**Editorial see p 1175**
**Clinical Perspective on p 1197**

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 Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), where on-treatment low-density lipoprotein cholesterol (LDL-C) 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, whereas 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-C, apolipoprotein

Received March 16, 2013; accepted July 15, 2013.

From the Center for Cardiovascular Disease Prevention, Division of Preventive Medicine (S.M., R.J.G., P.M.R.) and Division of Cardiovascular Medicine (S.M., P.M.R.), Brigham and Women's Hospital, Harvard Medical School, Boston, MA; and Department of Biostatistics, Harvard School of Public Health, Boston, MA (R.J.G.).

Guest Editor for this article was Steven E. Nissen, MD.

**The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.113.002671/-/DC1.**

Correspondence to Samia Mora, MD, Brigham and Women's Hospital, 900 Commonwealth Avenue East, Boston, MA 02215. E-mail smora@partners.org



***Circulation*** **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.113.002671**

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 nuclear magnetic resonance (NMR) HDL measurements, we prespecified the hypothesis that the residual risk of CVD may be better explained by HDL-P in comparison with HDL-C. We aimed to evaluate this in JUPITER, because 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-C levels.

## Methods

### Study Population

The JUPITER trial randomly assigned 17 802 asymptomatic women ≥60 years and men ≥50 years without a previous history of CVD or diabetes mellitus 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 1 year; 11 953 provided samples both at baseline and 1 year, and these were stored in liquid nitrogen. After trial completion, HDL size and HDL-P were measured by proton 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 1-year measurements.

### Laboratory Measurements

Lipid measurements were performed on fasting samples in a central laboratory.[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 end point triglyceride value. LDL-C concentrations were calculated by the Friedewald equation when triglycerides were <400 mg/dL, and measured by ultracentrifugation when triglycerides were ≥400 mg/dL.[16] ApoA-I was measured by immunonephelometry by using a Behring nephelometric 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 HDL size were measured. HDL-P is the sum of the particle concentrations of the HDL subclasses, which were quantified based on particle size by 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 end point of JUPITER was a composite CVD end point, defined as first myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, or cardiovascular death. We also examined the expanded end point 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 end points were adjudicated by an independent end point 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 versus rosuvastatin group was compared with the Wilcoxon rank sum test.

Statistical tests for outcomes were performed according to the treatment to which participants were randomly assigned. The exposure time was calculated as the time from randomization to occurrence of the primary end point 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 hazards 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-C, 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]). To allow for comparison across groups, the HRs were calculated by using the SDs of baseline levels. Tertile cut points were calculated across both treatment arms. The likelihood ratio $\chi^2$ 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. The probability value for linear trend was obtained by using the median value for each tertile. Results were not adjusted for multiple comparisons, and a 2-tailed $P$ value of <0.05 was considered to indicate statistical significance.

## Results

Baseline characteristics for individuals with NMR HDL measurements (available 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-C, 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-C ($r$=0.55), and triglycerides ($r$=0.74).

HDL-P correlated only moderately with HDL-C at baseline ($r$=0.55, $P$<0.0001; Table I in the online-only Data Supplement) and after 1 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 1 year of statin

**Table 1. Baseline Characteristics**

| Characteristic | Current Study n=10 886 | Not in Current Study n=6916 | Overall Study n=17 802 |
|---|---|---|---|
| Age | 66 (60–71) | 66 (61–71) | 66 (60–71) |
| Women | 3917 (36.0) | 2884 (41.7) | 6801 (38.2) |
| Rosuvastatin | 5367 (49.3) | 3534 (51.1) | 8901 (50.0) |
| Race/ethnicity | | | |
| White | 8982 (82.5) | 3701 (53.5) | 12 683 (71.3) |
| Black | 775 (7.1) | 1449 (21.0) | 2224 (12.5) |
| Asian | 151 (1.4) | 132 (1.9) | 283 (1.6) |
| Hispanic | 895 (8.2) | 1366 (19.8) | 2261 (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) | 1200 (17.4) | 2820 (15.9) |
| Family history of premature coronary disease | 1387 (12.8) | 658 (9.6) | 2045 (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) | – | – |

The values stated are median (25th to 75th %ile) or n (%). Percentages may not add up because of rounding off. HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

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 1 year of statin treatment, HDL size showed greater correlation with HDL-C ($r=0.74$) than at baseline, whereas HDL size remained weakly correlated with HDL-P ($r=0.20$).

## Changes With Rosuvastatin

Random allocation to rosuvastatin 20 mg/d decreased LDL-C 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

**Table 2. Median and 25th and 75th Percentile Values of HDL Measures Among Placebo- and Rosuvastatin-Treated Individuals**

| | | Baseline | Year 1* | Change† | % Change |
|---|---|---|---|---|---|
| LDL cholesterol, mg/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). HDL indicates high-density lipoprotein; and LDL, low-density lipoprotein.

*$P$ values from the Wilcoxon signed rank test comparing baseline and year 1 values were statistically significant ($P<0.001$) for all, with the exception of 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 with the change among the placebo group were <0.001 for all.

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 end point 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, whereas 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), whereas 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 $\chi^2$ probability value of 0.01 indicated added predictive value of on-treatment HDL-P to standard risk factors. In fully adjusted models, the

**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 | | | |
| 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 |

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle number; HR, hazard ratio; LDL, low-density lipoprotein; LRT, likelihood-ratio test; and SD, standard deviation.

*Likelihood ratio $\chi^2$ 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.

†Incidence per 100 person-years

‡Cox proportional hazards 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. 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.

**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 | | | |
| Incidence (95% CI) | 0.70 (0.48–1.02) | 0.77 (0.53–1.13) | 0.75 (0.52–1.09) | | | |
| Adjusted HR (95% CI) | 1.00 | 1.15 (0.65–2.04) | 1.13 (0.59–2.14) | 0.72 | 1.05 (0.81–1.35) | 0.73 |
| 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 |

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle number; HR, hazard ratio; LDL, low-density lipoprotein; LRT, likelihood-ratio test; and SD, standard deviation.

*Likelihood ratio $\chi^2$ 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.

†Incidence per 100 person-years

‡Cox proportional hazards 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. 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.

probability 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 end point of CVD and death (330 events, Tables II and III in the online-only Data Supplement) 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 to 0.80, $P$<0.0001, and for apoA-I 0.79, 95% CI 0.65 to 0.97, $P$=0.02 (Table III in the online-only Data Supplement). 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 3664 statin-allocated individuals (50 CVD events) with on-treatment LDL-C ≤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 2 HDL measures at a time, using the likelihood ratio $\chi^2$ statistic and corresponding $P$ value to assess for statistical significance. For incident CVD (Table 5) and the combined end point of CVD and death (Table IV in the online-only Data Supplement),

**Table 5. Combination of 2 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 | | | | |
| Model 1 | | | | |
| 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 |
| Model 2 | | | | |
| 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 |
| Model 3 | | | | |
| 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 | | | | |
| Model 1 | | | | |
| 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 |
| Model 2 | | | | |
| 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 |
| Model 3 | | | | |
| 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 |

CHD indicates coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particle number; HR, hazard ratio; LDL, low-density lipoprotein; LRT, likelihood-ratio test; and SD, standard deviation.

*Cox proportional hazard regression models included 2 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. 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.

†The likelihood ratio $\chi^2$ *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.

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 end point 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 end point of CVD and death (Table IV in the online-only Data Supplement), 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-C 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 end point 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 inhibitors raise HDL-C by increasing HDL size much more than their effect on increasing the number of HDL particles.[24–28]

Although 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]

Previous epidemiological 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 European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study, HDL-P was inversely associated with CVD,[23] whereas 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 previous 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-C has been reduced to contemporary standards with potent statin therapy. This is particularly relevant because the HDL-modifying drugs now under investigation are expected to be used in the clinical setting of individuals with low LDL-C 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. 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-C in the Heart Protection Study was 89 mg/dL,[37] whereas 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, although 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 mellitus, high LDL-C, 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 prespecified protocol for this study, including the hypothesis that the residual risk of CVD may be better explained by HDL-P than by 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-C, 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 a 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-C lowering with statin therapy.

## Sources of Funding

Research reported in this publication was supported by the National Heart, Lung, And Blood Institute of the National Institutes of Health under Award Number R01HL117861 to Dr Mora. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. JUPITER was financially supported by AstraZeneca, who collected trial data and monitored sites but had no role in the design or conduct of the current study, including data analysis or interpretation, drafting or editing this report, or in preparation, review, or the decision to submit the manuscript for publication. LipoScience Inc (Raleigh, NC) absorbed the cost of performing the NMR HDL measurements and performed the NMR HDL measurements in a blinded manner, but otherwise had no role in the management, analysis, and interpretation of the data, and preparation, review, or approval of the manuscript.

## Disclosures

Dr Mora has received research support from AstraZeneca, Merck, and NHLBI, served as a consultant to Pfizer and Quest Diagnostics, received speaker honoraria from AstraZeneca, Abbott, and the National Lipid Association for educational (nonpromotional) activities, and received travel expense reimbursement from Pfizer. Dr Glynn has received research support from AstraZeneca and NIH. Dr Ridker has received research grant support from AstraZeneca, Novartis, Amgen, and NHLBI, and has served as a consultant to Genzyme, Jannsen, Aegerion, ISIS, Vascular Biogenics, BostonHeart, Pfizer, and Merck. Dr Ridker is listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease that have been licensed to AstraZeneca and Siemens.

## References

1. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
2. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet*. 2010;376:1670–1681.
3. Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Waters DD, Shear CL, Revkin JH,

Buhr KA, Fisher MR, Tall AR, Brewer B; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med*. 2007;357:2109–2122.
4. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011;365:2255–2267.
5. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012;367:2089–2099.
6. Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT, Ruzyllo W, Bachinsky WB, Lasala GP, Lasala GP, Tuzcu EM; ILLUSTRATE Investigators. Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med*. 2007;356:1304–1316.
7. Johannsen TH, Kamstrup PR, Andersen RV, Jensen GB, Sillesen H, Tybjaerg-Hansen A, Nordestgaard BG. Hepatic lipase, genetically elevated high-density lipoprotein, and risk of ischemic cardiovascular disease. *J Clin Endocrinol Metab*. 2009;94:1264–1273.
8. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. *Lancet*. 2012;380:572–580.
9. Barter P, Gotto AM, LaRosa JC, Maroni J, Szarek M, Grundy SM, Kastelein JJ, Bittner V, Fruchart JC; Treating to New Targets Investigators. HDL cholesterol, very low levels of LDL cholesterol, and cardiovascular events. *N Engl J Med*. 2007;357:1301–1310.
10. Fruchart JC, Sacks F, Hermans MP, Assmann G, Brown WV, Ceska R, Chapman MJ, Dodson PM, Fioretto P, Ginsberg HN, Kadowaki T, Lablanche JM, Marx N, Plutzky J, Reiner Z, Rosenson RS, Staels B, Stock JK, Sy R, Wanner C, Zambon A, Zimmet P. The Residual Risk Reduction Initiative: a call to action to reduce residual vascular risk in patients with dyslipidemia. *Am J Cardiol*. 2008;102(10 suppl):1K–34K.
11. Ridker PM, Genest J, Boekholdt SM, Libby P, Gotto AM, Nordestgaard BG, Mora S, MacFadyen JG, Glynn RJ, Kastelein JJ; JUPITER Trial Study Group. HDL cholesterol and residual risk of first cardiovascular events after treatment with potent statin therapy: an analysis from the JUPITER trial. *Lancet*. 2010;376:333–339.
12. Mora S, Glynn RJ, Boekholdt SM, Nordestgaard BG, Kastelein JJ, Ridker PM. On-treatment non-high-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy: JUPITER (Justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). *J Am Coll Cardiol*. 2012;59:1521–1528.
13. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, Macfadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet*. 2009;373:1175–1182.
14. Asztalos BF, Tani M, Schaefer EJ. Metabolic and functional relevance of HDL subspecies. *Curr Opin Lipidol*. 2011;22:176–185.
15. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med*. 2008;359:2195–2207.
16. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499–502.
17. Jeyarajah EJ, Cromwell WC, Otvos JD. Lipoprotein particle analysis by nuclear magnetic resonance spectroscopy. *Clin Lab Med*. 2006;26:847–870.
18. Rosenson RS, Brewer HB Jr, Chapman MJ, Fazio S, Hussain MM, Kontush A, Krauss RM, Otvos JD, Remaley AT, Schaefer EJ. HDL measures, particle heterogeneity, proposed nomenclature, and relation to atherosclerotic cardiovascular events. *Clin Chem*. 2011;57:392–410.
19. Mackey RH, Greenland P, Goff DC Jr, Lloyd-Jones D, Sibley CT, Mora S. High-density lipoprotein cholesterol and particle concentrations, carotid atherosclerosis, and coronary events: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol*. 2012;60:508–516.
20. Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, French BC, Phillips JA, Mucksavage ML, Wilensky RL, Mohler ER, Rothblat GH, Rader DJ. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med*. 2011;364:127–135.
21. Vergeer M, Holleboom AG, Kastelein JJ, Kuivenhoven JA. The HDL hypothesis: does high-density lipoprotein protect from atherosclerosis? *J Lipid Res*. 2010;51:2058–2073.
22. Tan HC, Tai ES, Sviridov D, Nestel PJ, Ng C, Chan E, Teo Y, Wai DC. Relationships between cholesterol efflux and high-density lipoprotein particles in patients with type 2 diabetes mellitus. *J Clin Lipidol*. 2011;5:467–473.
23. El Harchaoui K, Arsenault BJ, Franssen R, Després JP, Hovingh GK, Stroes ES, Otvos JD, Wareham NJ, Kastelein JJ, Khaw KT, Boekholdt SM. High-density lipoprotein particle size and concentration and coronary risk. *Ann Intern Med*. 2009;150:84–93.
24. Brousseau ME, Diffenderfer MR, Millar JS, Nartsupha C, Asztalos BF, Welty FK, Wolfe ML, Rudling M, Björkhem I, Angelin B, Mancuso JP, Digenio AG, Rader DJ, Schaefer EJ. Effects of cholesteryl ester transfer protein inhibition on high-density lipoprotein subspecies, apolipoprotein A-I metabolism, and fecal sterol excretion. *Arterioscler Thromb Vasc Biol*. 2005;25:1057–1064.
25. Davidson MH, McKenney JM, Shear CL, Revkin JH. Efficacy and safety of torcetrapib, a novel cholesteryl ester transfer protein inhibitor, in individuals with below-average high-density lipoprotein cholesterol levels. *J Am Coll Cardiol*. 2006;48:1774–1781.
26. Rashedi N, Brennan DM, Kastelein JJ, Nissen SE, Nicholls SJ. Impact of cholesteryl ester transfer protein inhibition on nuclear magnetic resonance derived lipoprotein particle parameters (abstr). *Atherosclerosis Supplements*. 2011;12:48.
27. Ballantyne CM, Miller M, Niesor EJ, Burgess T, Kallend D, Stein EA. Effect of dalcetrapib plus pravastatin on lipoprotein metabolism and high-density lipoprotein composition and function in dyslipidemic patients: results of a phase IIb dose-ranging study. *Am Heart J*. 2012;163:515–521, 521.e1.
28. Krauss RM, Wojnooski K, Orr J, Geaney JC, Pinto CA, Liu Y, Wagner JA, Luk JM, Johnson-Levonas AO, Anderson MS, Dansky HM. Changes in lipoprotein subfraction concentration and composition in healthy individuals treated with the CETP inhibitor anacetrapib. *J Lipid Res*. 2012;53:540–547.
29. Nissen SE, Tsunoda T, Tuzcu EM, Schoenhagen P, Cooper CJ, Yasin M, Eaton GM, Lauer MA, Sheldon WS, Grines CL, Halpern S, Crowe T, Blankenship JC, Kerensky R. Effect of recombinant ApoA-I Milano on coronary atherosclerosis in patients with acute coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:2292–2300.
30. Zheng C, Aikawa M. High-density lipoproteins: from function to therapy. *J Am Coll Cardiol*. 2012;60:2380–2383.
31. deGoma EM, Rader DJ. High-density lipoprotein particle number: a better measure to quantify high-density lipoprotein? *J Am Coll Cardiol*. 2012;60:517–520.
32. van der Steeg WA, Holme I, Boekholdt SM, Larsen ML, Lindahl C, Stroes ES, Tikkanen MJ, Wareham NJ, Faergeman O, Olsson AG, Pedersen TR, Khaw KT, Kastelein JJ. High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies. *J Am Coll Cardiol*. 2008;51:634–642.
33. Mora S, Szklo M, Otvos JD, Greenland P, Psaty BM, Goff DC Jr, O'Leary DH, Saad MF, Tsai MY, Sharrett AR. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211–217.
34. Kuller LH, Grandits G, Cohen JD, Neaton JD, Prineas R; Multiple Risk Factor Intervention Trial Research Group. Lipoprotein particles,

insulin, adiponectin, C-reactive protein and risk of coronary heart disease among men with metabolic syndrome. *Atherosclerosis*. 2007;195:122–128.
35. Mora S, Otvos JD, Rifai N, Rosenson RS, Buring JE, Ridker PM. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. *Circulation*. 2009;119:931–939.
36. Parish S, Offer A, Clarke R, Hopewell JC, Hill MR, Otvos JD, Armitage J, Collins R; Heart Protection Study Collaborative Group. Lipids and lipoproteins and risk of different vascular events in the MRC/BHF Heart Protection Study. *Circulation*. 2012;125:2469–2478.
37. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.

## CLINICAL PERSPECTIVE

Chemically measured high-density lipoprotein cholesterol (HDL-C) may not be the best clinical measure of HDL. Little is known about alternative HDL measures such as HDL size or particle number (HDL-P) as determinants of residual risk after potent statin therapy. 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 or diabetes mellitus before and after random allocation to rosuvastatin 20 mg/d or placebo. Median follow-up was 2 years. At baseline, HDL-P correlated moderately with HDL-C ($r$=0.55) but more strongly with apoA-I (0.69). HDL size showed greater correlation with HDL-C ($r$=0.65) than with apoA-I ($r$=0.56), and much less with HDL-P ($r$=0.22). Among placebo-allocated individuals, on-treatment HDL-C, apoA-I, and HDL-P had similar inverse associations with cardiovascular disease, whereas HDL size was not associated with cardiovascular disease. Among rosuvastatin-allocated individuals in JUPITER, on-treatment HDL-P had a statistically significant and somewhat stronger association with residual vascular risk (adjusted hazard ratio, 0.72; 95% confidence interval, 0.57–0.93; $P$=0.01) than HDL-C (0.82; 95% confidence interval, 0.63–1.08; $P$=0.16) or apoA-I (0.86; 95% confidence interval, 0.67–1.10; $P$=0.22). HDL size was not associated with residual vascular risk or with risk in the absence of statin therapy. This study suggests that HDL-P may be a better clinical marker of residual risk than HDL-C or apoA-I among individuals treated to very low low-density lipoprotein cholesterol levels with potent statin therapy. This has potential implications for evaluating therapeutic interventions targeting HDL in the era of potent low-density lipoprotein cholesterol lowering with statin therapy.