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Association of Lipoproteins, Insulin Resistance, and Rosuvastatin With Incident Type 2 Diabetes Mellitus Secondary Analysis of a Randomized Clinical Trial

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Abstract

Importance—Statins decrease low-density lipoproteins, triglycerides, and cardiovascular events, but increase the risk of being diagnosed with diabetes. The risk factors associated with incident diabetes are incompletely characterized.

Objective—To investigate the association of lipoprotein subclasses and size, and a novel lipoprotein insulin resistance (LPIR) score (a composite of six lipoprotein measures), with incident diabetes among individuals randomized to high-intensity statin or placebo.

Design—JUPITER was an international, randomized, double-blind, placebo-controlled trial. A prespecified secondary aim was to assess the effect of rosuvastatin on diabetes, and incident diabetes was monitored for a median of 2.0 years.

Setting—The study was conducted at 1315 sites in 26 countries.

Participants—JUPITER comprised 17802 men ≥50 years and women ≥60 years with LDL cholesterol <130 mg/dL, hsCRP ≥2 mg/L, and triglycerides <500mg/dL. Those with diabetes were excluded.

Intervention—Rosuvastatin, 20mg daily, or placebo.

Main Outcomes and Measures—Among 11918 participants in JUPITER, we measured baseline size and concentration of lipids, apolipoproteins, and lipoproteins and, in 9180 of these, at 12 months after randomization to rosuvastatin or placebo. LPIR score, a correlate of insulin resistance, was calculated as a weighted combination of size and concentration of LDL, very low-density lipoprotein(VLDL), and high-density lipoprotein(HDL) particles.

Results—Rosuvastatin lowered LDL particles(−49%), VLDL particles(−20%), and triglycerides(−15%), and shifted the lipoprotein subclass distribution towards smaller LDL

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size(−2%), larger VLDL size(3%), and lower LPIR score(−3%). In analyses adjusted for age, sex, race/ethnic origin, exercise, education, family history, and smoking, the hazard ratio for diabetes per standard deviation of LPIR score was 1.99 (1.64–2.42) in placebo and 2.06 (1.74–2.43) in rosuvastatin-allocated individuals. After additional adjustment for systolic blood pressure, body-mass index, hsCRP, glycated hemoglobin, HDL-cholesterol, LDL-cholesterol, and triglycerides, LPIR score remained associated with diabetes in placebo- (1.35[1.03–1.76]) and rosuvastatin-allocated individuals (1.60[1.27–2.03]). Similar trends were seen at 12 months. LPIR score improved the model likelihood ratio (chi-squared = 18.23, p<0.001) and categorical net reclassification index (0.039[0.003, 0.072]; non-events[0.036]; events[0.002]). The c-statistic and integrated discrimination improvement index did not improve.

Conclusions and Relevance—In apparently healthy people, LPIR score, a measure of lipoprotein insulin resistance, was positively associated with incident diabetes including during rosuvastatin therapy.

Statins substantially reduce cardiovascular events[1–3], but are associated with an increased risk of being diagnosed with type 2 diabetes[2–7]. Statin users who develop diabetes very often have evidence of prior impaired fasting glucose, features of insulin resistance, or the metabolic syndrome[8,9], factors that also predispose to the development of diabetes in statin-naïve individuals[10]. Identifying statin users at risk for diabetes has gained greater significance as recent cholesterol guidelines[11] could increase the global prescription of statins.

Both insulin resistance and diabetes are associated with lipoprotein profile changes[12–16] that precede the appearance of overt hyperglycemia. Lipoprotein particles are categorized according to density into low-density lipoproteins (LDL), high-density lipoproteins (HDL), and very low-density lipoproteins (VLDL), and these are further categorized on the basis of particle size and concentration (or, number). Non-randomized observational studies focusing predominantly on statin-naïve populations have reported positive associations of diabetes with higher particle concentrations of small LDL, small HDL, and large VLDL, and inverse associations of diabetes with large LDL and large HDL[12–18], underscoring the complex and incompletely characterized association of lipoproteins with insulin resistance and diabetes. To date, there are no studies examining the various lipoprotein characteristics that precede the onset of diabetes among individuals randomly allocated to statin therapy versus placebo.

In order to address these issues, we used nuclear magnetic resonance (NMR) spectroscopy, immunoassay-measured apolipoproteins, and standard lipid measurements to comprehensively characterize the lipoprotein profiles at baseline and 12 months after randomization to rosuvastatin 20 mg daily or placebo in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study. JUPITER is a primary prevention trial of individuals without prior cardiovascular disease or diabetes but with elevated high-sensitivity C-reactive protein (hsCRP) and low LDL cholesterol who were followed prospectively for incident cardiovascular events[2]. A prespecified secondary aim of the JUPITER trial was to assess the effect of rosuvastatin on incident diabetes[9]. After the trial was completed but before obtaining NMR measurements, we prespecified the hypothesis that lipoprotein insulin resistance (LPIR) score, which

reflects lipoprotein derangements of insulin resistance, would be associated with incident diabetes in placebo- and rosuvastatin-allocated individuals. LPIR score combines six measures of LDL, VLDL, and HDL particle size and concentration, and incorporates lipoprotein characteristics that previously have been individually associated with diabetes and/or insulin resistance[12–16,18]. LPIR score is more strongly correlated with diabetes[19] and insulin resistance (measured by the homeostasis model assessment of insulin resistance [HOMA-IR]) than each of its six subclasses individually, and has been proposed to better reflect the complex biology and regulation of lipoproteins[20]. Here, we describe the prospective association of individual lipoprotein measures and LPIR score with incident diabetes according to randomized treatment allocation.

RESEARCH DESIGN AND METHODS

Study Design

JUPITER was a randomized, double-blind, placebo-controlled, trial conducted at 1315 sites in 26 countries[2,21]. The study protocol was approved by the institutional review board at Brigham and Women's Hospital, Boston, USA, and at participating centers. The effect of rosuvastatin on incident diabetes was a prespecified secondary aim of JUPITER. We used a randomized study design to elucidate possible unique associations between baseline lipoproteins and incident diabetes before and after randomization to rosuvastatin versus placebo.

Study Population

JUPITER was a primary prevention trial of 17802 apparently healthy men and women, who were eligible if they had LDL cholesterol <130 mg/dL, hsCRP ≥2 mg/L, and triglycerides <500 mg/dL. As incident diabetes was a prespecified secondary aim of JUPITER, exclusion criteria of the trial included pre-existing diabetes, defined as fasting glucose of 126 mg/dL or higher at screening visit two or by the use of insulin and/or an oral hypoglycemic agent. Other trial requirements included a willingness to participate for the duration of the study and the ability to provide written consent.[2] There were 8901 subjects each in the placebo and rosuvastatin arms. Study participants were requested to provide a blood sample at baseline and 12 months after randomization; a total of 11918 samples had plasma to obtain complete NMR lipoprotein measurements at baseline, and of these, 9180 samples had plasma for 12 month measurements. Incident diabetes cases were tracked throughout the study period (see Statistical Analysis, below) and were physician reported, as described[2,9].

Laboratory Measurements

We measured plasma lipids, lipoproteins, apolipoproteins, hsCRP, and glycated hemoglobin as described[2,22,23]. LDL cholesterol was calculated using the Friedewald equation (for serum triglyceride <400 mg/dL) or measured by ultracentrifugation (for serum triglyceride ≥ 400 mg/dL)[23,24]. Lipoprotein particle concentration and average particle size of LDL, HDL, and VLDL particles were determined by NMR spectroscopy at LipoScience (now LabCorp)[13,25]. LPIR score is a weighted combination of six lipoprotein subclass measures and reflects the concentrations of large VLDL, large HDL, and small LDL particles, and

average size of VLDL, LDL, and HDL particles. LPIR score ranges from 0 (most insulin sensitive) to 100 (most insulin resistant).

Calculation of Lipoprotein Insulin Resistance (LPIR) Score

The LPIR score was developed as described[20] and in eMethod 1. Briefly, using HOMA-IR measurements for guidance, the six NMR-measured lipoprotein parameters, known to be associated with insulin resistance, were combined to produce a multiplex LPIR score that ranges from 0 (most insulin sensitive) to 100 (most insulin resistant). The algorithm used to generate LPIR divides the six lipoprotein parameters into several particle concentration or size categories, assigns each a numerical weighting score, and sums these to produce the LPIR score. The weighting scores were chosen empirically to reflect the strength and independence of each parameter's association with HOMA-IR in the MESA study population[20]. Accordingly, average VLDL particle size and concentration of large VLDL particles were assigned the greatest weighting scores (32 and 22, respectively) followed by average HDL particle size (20), concentration of large HDL particles (12), concentration of small LDL particles (8) and average LDL particle size (6). This combination of six lipoprotein parameters was more strongly related to insulin resistance than any of the individual parameters or the triglyceride to HDL cholesterol ratio.

Statistical Analysis

Analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC). Spearman coefficients were used to quantify correlations. Diabetes incidence rates were calculated per 100-person years, and exposure time was calculated as the time from randomization to occurrence of the endpoint, or to a participant's last blinded follow-up visit, a process that concluded in August 2008, six months after the primary JUPITER trial was ended by the Data and Safety Monitoring Board[9]. Cox proportional-hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) to compare the risk of diabetes according to tertiles and per one standard deviation of lipoprotein measures using separate models for each measure. To allow for comparison across groups, HRs were calculated using the standard deviation (SD) of baseline levels among all participants. Cox-proportional-hazard models were adjusted for age, sex, self-reported race or ethnic origin, education, exercise, family history of diabetes, and self-reported smoking in the prior month (Model 1). Race or ethnic origin was assessed to explain possible heterogeneity in the risk of developing diabetes. To account for lipoprotein correlations with each other and with metabolic variables, Model 1 was further adjusted for systolic blood pressure, BMI, glycated hemoglobin, LDL-cholesterol and HDL-cholesterol, log-transformed triglycerides, and log-transformed hsCRP (Model 2). Metabolic syndrome was defined according to consensus criteria of the American Heart Association and the National Heart, Lung, and Blood Institute[2]. The probability value for linear trend was obtained by using the median value for each tertile. Statistical tests for interaction between categorical LPIR score and treatment allocation in relation to outcomes were obtained by use of likelihood ratio tests. Statistical significance was established at two-tailed $p<0.05$. The contribution of LPIR score to the prediction of diabetes in models with traditional risk factors was evaluated by likelihood ratio chi-squares, discrimination (Harrell's C-statistic)[26], relative integrated discrimination improvement index (IDI) [27], and net reclassification index (NRI) [28] (eMethod 2).

Conversion Factors

To convert values for LDL, IDL, VLDL, HDL, total cholesterol, and non-HDL cholesterol [calculated as the difference between total cholesterol and HDL cholesterol] from mg/dL to mmol/l, multiply by 0.02586. To convert values for triglycerides from mg/dL to mmol/l, multiply by 0.01129. To convert values for glucose from mg/dL to mmol/l, multiply by 0.05551.

RESULTS

Baseline Characteristics

In this study, a total of 370 (3.1%) individuals were diagnosed with diabetes during a median follow-up period of 2.0 years (IQR 1.6–2.5). There were 158 and 212 cases in the placebo and rosuvastatin arms, respectively. The incidence rate was higher among individuals allocated to rosuvastatin (1.64 per 100 person-years; 95% confidence interval [CI], 1.43–1.87) versus placebo (1.17 per 100 person-years; 95% CI 1.00–1.36). Compared with the overall study population and with those excluded from this study, the current study population had a higher proportion of Caucasians, while other characteristics were generally similar (eTable 1A, Supplement). Increasing tertiles of LPIR score (i.e., higher insulin resistance) were associated with a higher prevalence of clinical risk factors including metabolic syndrome, triglycerides, hypertension, and lower HDL cholesterol, although LDL cholesterol was similar (Table 1; eTable 1B, Supplement). Compared with those who did not develop diabetes, individuals who developed diabetes had a higher prevalence of clinical risk factors including impaired fasting glucose, elevated glycated hemoglobin, family history of diabetes, metabolic syndrome, body-mass index, higher LDL particles, VLDL particles and triglycerides, and LPIR scores (eTable 1C and 1D, Supplement).

Effect of Rosuvastatin Associated with Lipoprotein Measures

Rosuvastatin lowered LDL cholesterol (49%), triglycerides (15%), non-HDL cholesterol (43%), apolipoprotein B (39%), and LPIR score (3%), and raised HDL cholesterol (6%) (Table 2). In addition, rosuvastatin lowered the concentrations of LDL and VLDL particles, and increased HDL particles; these effects differed by particle subclasses, resulting in overall smaller average size for LDL particles and larger size for VLDL and HDL particles ($p<0.001$ for all comparisons) (Table 2). The Spearman coefficients of LPIR score with lipoprotein particle subclasses were generally similar at baseline and after 12 months of rosuvastatin therapy (eTable 2, Supplement).

Lipoprotein Measures, LPIR Score, and Incident Diabetes

Among placebo- and rosuvastatin-allocated individuals, incident diabetes was inversely associated with baseline concentrations of LDL and HDL cholesterol, and positively associated with triglycerides, apolipoprotein B, and LPIR score (Figure 1A; eTable 3A, Supplement). In analyses adjusted for age, sex, race/ethnic origin, education, exercise, family history, and smoking (Model 1), the HR per SD of LPIR score was 1.99 (1.64–2.42; $p<0.001$) in placebo and 2.06 (1.74–2.43; $p<0.001$) in rosuvastatin-allocated individuals (Figure 1A; eTable 3A, Supplement). Substituting fasting glucose for glycated hemoglobin

somewhat attenuated the association between LPIR score and diabetes in placebo (1.55 [1.27–1.90; p<0.001]) and rosuvastatin-allocated individuals (1.63 [1.38–1.93; p<0.001]). Additionally adjusting for systolic blood pressure, BMI, hsCRP, glycated hemoglobin, HDL and LDL cholesterol, and triglycerides (Model 2) attenuated the HRs among placebo (1.35[1.03-1.76]; p=0.027) and rosuvastatin-allocated individuals (1.60 [1.27–2.03]; p<0.001). Similar trends were obtained when assessed across increasing tertiles of LPIR score (Table 3). Tests of interaction between randomized treatment and LPIR tertiles in relation to diabetes in Models 1 and 2 were $P_{interaction}$=0.99 and 0.79, respectively.

Overall (Model 1), placebo- and rosuvastatin-allocated individuals showed generally similar associations for baseline lipoprotein subclass characteristics and incident diabetes (Figure 1A; eTable 3A, Supplement). However, after additionally adjusting for blood pressure, BMI, hsCRP, glycated hemoglobin, and lipids (Model 2), there were some notable differences. In particular, in rosuvastatin-allocated individuals, baseline (but not 12 months) small LDL particles, large VLDL particles, and medium VLDL particles, were positively associated, while small VLDL particles were inversely associated with incident diabetes. These associations were not seen in placebo-allocated individuals (eTables 4A and 4B).

Similar analyses were done at 12 months, and Model 1 associations seen at baseline were generally preserved (Figure 1B). The HR per SD of LPIR score was 2.03 (1.65–2.49; p<0.001) in placebo and 2.03 (1.68–2.45; p<0.001) in rosuvastatin-allocated individuals (Figure 1B). Substituting fasting glucose for glycated hemoglobin attenuated the association of LPIR in placebo (1.62 [1.32–1.99; p<0.001]) and rosuvastatin-allocated individuals (1. 63 [1.35–1.98; p<0.001]). Additional adjustment for Model 2 variables also slightly attenuated the association between LPIR score with diabetes in placebo (1.51 [1.15-1.96]; p=0.0026) and rosuvastatin-allocated individuals (1.58 [1.23–2.01]; p<0.001). Similar trends were obtained across increasing tertiles of LPIR score (Table 4; eTable 5, Supplement). The test of interaction between randomized treatment and LPIR tertiles in relation to diabetes in Models 1 and 2 were $P_{interaction}$=0.98 and 0.86, respectively.

In addition to LPIR score, baseline and 12 month levels of apolipoprotein B were positively associated with diabetes. In mutually adjusted models, LPIR score remained associated with diabetes, while the association between apolipoprotein B and diabetes was completely abrogated (Tables 3 and 4). Likewise, LPIR score and the triglyceride/HDL cholesterol ratio were both significantly associated with diabetes (Tables 3 and 4), but in mutually adjusted models, LPIR score remained significant in both arms, whereas the triglyceride/HDL cholesterol ratio was no longer significant in the rosuvastatin arm.

Model Performance with the LPIR Score

To investigate if LPIR score would improve risk prediction metrics, we used Model 2 and a modified model (Model 2A) that included fasting glucose instead of glycated hemoglobin (eTable 6). The likelihood ratio chi-squares were significantly improved when LPIR score was added to Model 2 (chi-squared = 18.23, p<0.001) and Model 2A (chi-squared = 12.26, p<0.001). The c-statistic of Model 2 (0.827 [0.804 to 0.851]) was unchanged after adding LPIR score (0.827 [0.804 to 0.851]). Similarly, the c-statistic of Model 2A (0.853 [0.832 to 0.873]) was unchanged after adding LPIR score (0.855 [0.835 to 0.873]). Further, the

relative IDI did not improve significantly after addition of the LPIR score to Model 2 (0.038 [−0.009 to 0.076]) and Model 2A 0.0239 [−0.0025 to 0.0504]). However, the categorical NRI was improved after adding LPIR score to Model 2 (0.039 [0.003 to 0.072]) driven mainly by re-classification of non-events (0.036) and events (0.002). The categorical NRI of Model 2A after adding LPIR score was 0.012 (−0.008 to 0.0184).While the improvement in Model 2 NRI was statistically significant, the gain in the model's predictive ability was modest.

DISCUSSION

Results from this study support the following conclusions: first, rosuvastatin was associated with differential effects on the size and concentration of LDL, HDL, and VLDL particles; second, rosuvastatin substantially reduced LDL cholesterol and triglycerides, but only slightly reduced LPIR score, shifting the LDL and VLDL lipoprotein subclass distribution towards a smaller average size for LDL and a larger average size for VLDL particles; third, LPIR score, a lipoprotein correlate of insulin resistance, was positively associated with incident diabetes in both placebo- and rosuvastatin-allocated individuals and finally, LPIR score was significantly associated with incident diabetes after adjusting for traditional risk factors including family history of diabetes, exercise, body-mass index, glycated hemoglobin, HDL cholesterol, non-HDL cholesterol, triglycerides, and apolipoprotein B. This study, nested within a randomized placebo-controlled trial, is the first to characterize the association between LPIR score and diabetes among individuals randomly allocated to placebo or high-intensity statin therapy, and our results suggest that LPIR score may identify additional individuals at risk of developing diabetes, including when on rosuvastatin.

Recently, a similar positive association between LPIR score and incident diabetes was described in a multi-ethnic cohort, in which a small proportion of participants were on cholesterol-lowering medications[19]. Statin users at risk of developing diabetes very often have pre-existing impairments in fasting glucose and features of the metabolic syndrome[8,9], factors that also predispose to diabetes in statin-naïve individuals[10]. To identify other risk factors that might predispose to the development of diabetes, we focused on lipoprotein characteristics, given reports of differing associations between diabetes and size/concentration of LDL, HDL, and VLDL particles[12–16,18]. Here, LPIR score remained associated with diabetes after adjusting for clinical risk factors that were recently shown to be independent predictors of developing diabetes when on a statin[8]. Interestingly, even though rosuvastatin substantially reduced LDL cholesterol and triglycerides, it only slightly reduced LPIR score (by 3%; Table 2), as rosuvastatin altered the LDL and VLDL lipoprotein subclass distribution, resulting in smaller average size for LDL and larger average size for VLDL.

While statins are associated with a higher incidence of diabetes, the underlying mechanisms are not well understood[29] and may involve inhibition of on-target 3-hydroxy-3-methylglutaryl-CoA reductase[30] and effects on glucose tolerance, insulin sensitivity and insulin secretion[31], and circulating levels of adipokines[32]. Animal models have shown that statins alter the expression levels of glucose transporter 4[33] through isoprenoid synthesis[34], the main insulin-responsive glucose transporter that facilitates glucose uptake in muscle and

adipose tissue. Conceivably, lipoproteins that constitute the LPIR score could be involved in these and/or additional pathways[34].

Our study has several strengths including that it was nested within a randomized, prospective trial, its large sample size and number of events, excellent follow-up, robust information on risk factors that could modify or confound our interpretation, and pre-specification of incident diabetes as a secondary endpoint of interest. Our study has potential limitations. JUPITER was stopped early by the independent data and safety monitoring board after a median follow up 1.9 years for cardiovascular and mortality efficacy, and the long-term effect of statins on incident diabetes could not be determined. The JUPITER study included individuals with elevated levels of hsCRP (which is also associated with incident diabetes) and excluded those with serum triglyceride ≥500 mg/dL. This study evaluated a fixed dose of one statin (rosuvastatin 20 mg), and the association of LPIR score and diabetes with other statins or among individuals who do not meet the current study's inclusion or exclusion criteria requires further evaluation. Future studies should also examine whether modifying or adding additional metabolic predictors (e.g. branched chain amino acids) to the LPIR score could result in improved diabetes risk prediction. In conclusion, among placebo- and rosuvastatin-allocated individuals in JUPITER, LPIR score is positively associated with incident diabetes after adjusting for traditional risk factors. LPIR score has the potential to serve as part of a broader clinical approach to identify additional cases at risk for diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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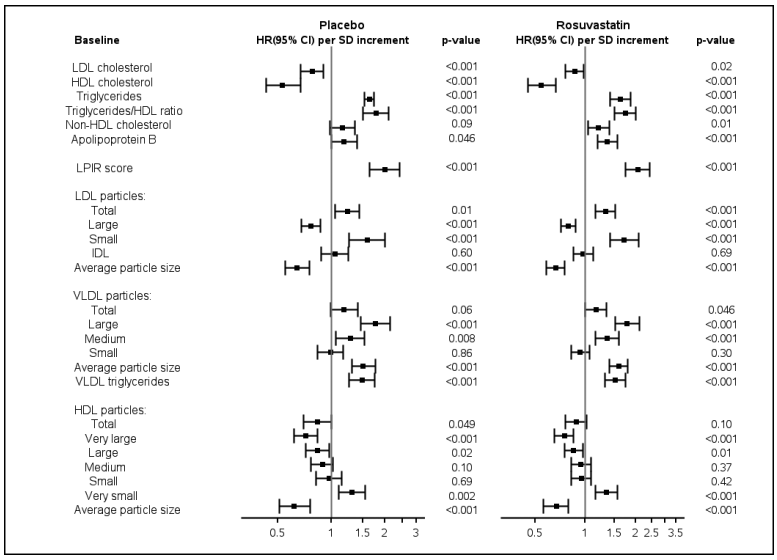

Figure 0001

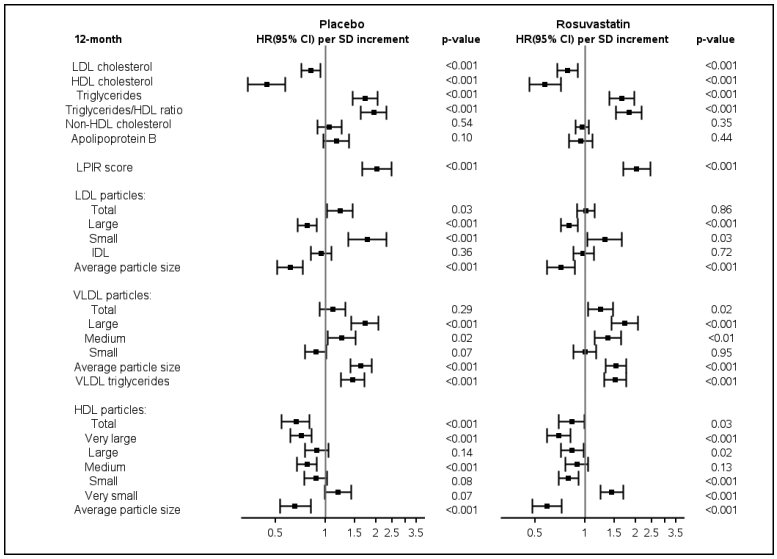

Figure 0002

Figure 1.

A. Baseline Lipoprotein Measures per SD Increments in Relation to Incident Diabetes.

B. 12-month Lipoprotein Measures per SD Increments in Relation to Incident Diabetes.

Cox proportional hazards ratios (per SD increment) were adjusted for Model 1 variables: age, sex, ethnic origin, education, exercise, family history of diabetes, and smoking.

LPIR score ranges from 0 (most insulin sensitive) to 100 (most insulin resistant).

LDL low-density lipoprotein; HDL high-density lipoprotein; IDL intermediate-density lipoprotein; VLDL very low-density lipoprotein; HR, hazard ratio; CI confidence interval; SD standard deviation.

Table 1

Baseline Characteristics of Current Study Participants, According to LPIR Score

	Lower Tertile (n=4002)	Middle Tertile (n=4076)	Upper Tertile (n=3840)
Age (years)	68 (63–73)	66 (60–71)	64 (58–69)
Women	2012 (50.3)	1558 (38.2)	764 (19.9)
Rosuvastatin	2019 (50.5)	1985 (48.7)	1905 (49.6)
Ethnic Origin			
White	3217 (80.4)	3219 (80.7)	3342 (87.1)
Black	411 (10.3)	252 (6.2)	79 (2.1)
Asian	61 (1.5)	67 (1.6)	49 (1.3)
Hispanic	267 (6.7)	432 (10.6)	361 (9.4)
Other	45 (1.1)	34 (0.8)	8 (0.2)
Current smoker	593 (14.8)	594 (14.6)	566 (14.8)
Hypertension	2145 (53.6)	2268 (55.7)	2264 (59.0)
Metabolic syndrome	698 (17.6)	1609 (39.8)	2578 (67.5)
BMI (kg/m^2)	26.7 (23.8–30.1)	28.6 (25.9–32.1)	30.0 (27.3–33.3)
Family history of diabetes	886 (23.5)	984 (25.6)	998 (27.3)
Highest level of education			
Up to high school	2335 (58.4)	2330 (57.2)	1932 (50.3)
Some college	735 (18.4)	777 (19.1)	866 (22.6)
College graduate	589 (14.7)	610 (15.0)	614 (16.0)
Post graduate	341 (8.5)	355 (8.7)	426 (11.1)
Exercise			
Rare or never	1988 (49.7)	2029 (49.8)	1865 (48.6)
Once or less per week	480 (12.0)	493 (12.1)	544 (14.2)
Two to three times per week	742 (18.6)	730 (17.9)	732 (19.1)
Four to seven times per week	790 (19.8)	822 (20.1)	698 (18.2)
Fasting glucose (mg/dL)	92 (86–99)	95 (89–102)	97 (90–105)
Glycated hemoglobin (%)	5.6 (5.4–5.9)	5.7 (5.4–5.9)	5.7 (5.4–5.9)
hsCRP (mg/L)	4.1 (2.7–7.0)	4.2 (2.8–7.0)	4.0 (2.8–6.3)
LDL cholesterol (mg/dL)	109 (95–119)	110 (96–120)	109 (95–119)
HDL cholesterol (mg/dL)	61 (57–71)	49 (42–57)	41 (36–47)
Triglycerides (mg/dL)	87 (69–111)	119 (93–157)	173 (130–237)
Triglyceride/HDL cholesterol ratio	1.45 (1.05–1.98)	2.40 (1.77–3.38)	4.24 (2.96–6.18)
Non-HDL cholesterol (mg/dL)	127 (113–139)	135 (120–146)	144 (130–157)
Apolipoprotein B (mg/dL)	102 (91–112)	109 (97–121)	118 (106–130)

Data are median (IQR) or n (%). Percentages may not add up because of rounding off. BMI body-mass index; hsCRP high sensitivity C-reactive protein; LDL low-density lipoprotein; HDL high-density lipoprotein.

$p<0.001$ with exception of rosuvastatin ($p=0.29$), current smoker ($p=0.95$), exercise ($p=0.082$), hsCRP ($p=0.002$), and LDL cholesterol ($p=0.18$), from Wilcoxon rank sum test for quantitative variables and χ^2 tests for qualitative variables.

LPIR tertiles as follows: lower tertile (score of 40 or lower); middle tertile (41-62); upper tertile (score of 62 or higher).

Table 2

Lipid and Lipoprotein Measures at Baseline and at 12 Months, According to Randomized Treatment Arm*

		Baseline	12 months[a]	Change[b]	Percent Change
LDL cholesterol–mg/dL	Placebo	110 (96, 119)	111 (96, 125)	3 (–8, 15)	2.7 (–7.4, 14.4)
	Rosuvastatin	109 (96, 120)	55 (44, 71)	–51 (–64, –31)	–49.0 (–58.2, –32.7)
HDL cholesterol–mg/dL	Placebo	49 (41, 60)	50 (42, 61)	1 (–3, 5)	1.7 (–6.7, 10.8)
	Rosuvastatin	49 (41, 59)	52 (43, 64)	3 (–1, 8)	6 (–3, 17)
Triglycerides–mg/dL	Placebo	119 (87, 168)	119 (89, 166)	2 (–24, 25)	1.2 (–18.4, 24.7)
	Rosuvastatin	120 (88, 171)	102 (77, 139)	–17 (–48, 5)	–15.4 (–32.8, 5.3)
Triglyceride/HDL cholesterol ratio	Placebo	2.4 (1.5, 3.9)	2.4 (1.6, 3.7)	–0.01 (–0.6, 0.5)	–0.3 (–22.6, 28.1)
	Rosuvastatin	2.4 (1.6, 3.9)	1.9 (1.3, 3.0)	–0.4 (–1.2, 0.1)	–21.0 (–39.4, 3.0)
Non-HDL cholesterol–mg/dL	Placebo	135 (121, 147)	138 (121, 154)	3 (–9, 16)	2.4 (–6.3, 12.0)
	Rosuvastatin	135 (121, 148)	77 (65, 96)	–56 (–71, –34)	–42.7 (–51.0, –27.6)
Apolipoprotein B–mg/dL	Placebo	110 (97, 122)	106 (93, 119)	–3 (–13, 7)	–2.9 (–11.6, 6.3)
	Rosuvastatin	110 (97, 123)	66 (57, 81)	–42 (–54, –27)	–39.4 (–47.6, –26.7)
LPIR score	Placebo	51 (35, 67)	53 (35, 69)	1 (–8, 10)	2.8 (–15.1, 23.9)
	Rosuvastatin	52 (35, 68)	49 (34, 65)	–2 (–11, 7)	–3.2 (–20.6, 16.9)
Total LDL particles–nmol/l	Placebo	1281 (1089, 1476)	1224 (1044, 1427)	–52 (–197, 95)	–4.2 (–14.6, 8.2)
	Rosuvastatin	1274 (1101, 1484)	771 (633, 964)	–487 (–674, –283)	–39.6 (–49.4, –24.6)
Large	Placebo	457 (306, 602)	438 (276, 586)	–20 (–143, 103)	–5.3 (–31.1, 27.3)
	Rosuvastatin	462 (304, 600)	175 (93, 306)	–238 (–392, –70)	–57.5 (–77.3, –24.2)
Small	Placebo	611 (448, 841)	596 (440, 828)	–14 (–159, 127)	–2.6 (–22.9, 23.2)
	Rosuvastatin	608 (446, 848)	494 (374, 625)	–127 (–318, 19)	–22.0 (–42.8, 4.7)
IDL	Placebo	151 (96, 220)	139 (85, 201)	–14 (–83, 56)	–10.6 (–45.4, 49.1)
	Rosuvastatin	157 (99, 225)	83 (52, 124)	–68 (–138, –4)	–46.0 (–69.4, –4.5)
LDL particle average size–nm	Placebo	21.0 (20.5, 21.4)	21.0 (20.5, 21.3)	0 (–0.3, 0.3)	0 (–1.5, 1.4)
	Rosuvastatin	21.0 (20.5, 21.4)	20.6 (20.2, 21.0)	–0.3 (–0.8, 0.1)	–1.5 (–3.7, 0.5)
Total VLDL particles–nmol/l	Placebo	43.8 (30.1, 58.5)	44.0 (31.0, 60.8)	1.2 (–10.0, 13.0)	3.5 (–21.8, 35.4)
	Rosuvastatin	43.3 (29.9, 58.8)	33.8 (23.5, 46.7)	–8.5 (–20.4, 3.2)	–19.6 (–40.6, 10.3)

		Baseline	12 months[a]	Change[b]	Percent Change
Large	Placebo	2.8 (1.3, 4.9)	2.9 (1.3, 5.6)	0.2 (–1.0, 1.6)	8.0 (–35.7, 76.5)
	Rosuvastatin	2.8 (1.4, 5.0)	2.2 (1.1, 4.2)	–0.3 (–1.7, 0.7)	–15.4 (–50.0, 40.0)
Medium	Placebo	11.8 (6.8, 18.6)	13.6 (7.6, 22.4)	1.9 (–3.2, 8.0)	16.6 (–26.6, 86.8)
	Rosuvastatin	11.6 (6.8, 18.6)	10.9 (6.5, 17.1)	–0.7 (–6.0, 4.4)	–7.0 (–43.0, 52.2)
Small	Placebo	27.1 (17.3, 38.1)	25.0 (16.3, 36.4)	–1.4 (–12.0, 9.2)	–6.1 (–37.6, 43.2)
	Rosuvastatin	26.6 (17.0, 38.5)	19.4 (12.4, 28.0)	–6.9 (–17.4, 3.0)	–26.7 (–53.2, 16.4)
VLDL particle average size–nm	Placebo	49.0 (44.2, 53.7)	49.3 (44.6, 54.9)	0.6 (–3.7, 5.0)	1.3 (–7.3, 10.9)
	Rosuvastatin	49.0 (44.3, 54.1)	50.2 (46.1, 55.1)	1.4 (–3.0, 5.9)	2.8 (–5.8, 12.7)
VLDL triglycerides–mg/dL	Placebo	62.3 (42.7, 87.7)	64.0 (44.2, 94.0)	3.1 (–12.1, 20.2)	5.6 (–18.8, 35.8)
	Rosuvastatin	62.3 (43.5, 88.3)	51.6 (36.5, 74.5)	–9.0 (–26.0, 5.5)	–15.2 (–35.9, 11.3)
HDL particles–µmol/l	Placebo	32.3 (28.5, 36.7)	31.6 (27.8, 35.6)	–0.9 (–3.4, 1.7)	–3.0 (–10.1, 5.4)
	Rosuvastatin	32.4 (28.5, 36.5)	33.7 (29.8, 38.0)	1.3 (–1.5, 4.3)	4.1 (–4.5, 13.9)
Very large	Placebo	2.0 (1.1, 3.5)	1.9 (1.0, 3.5)	–0.1 (0.7, 0.6)	–2.3 (–31.3, 33.3)
	Rosuvastatin	2.0 (1.1, 3.4)	2.5 (1.4, 4.2)	0.5 (–0.3, 1.3)	22.9 (–12.4, 74.1)
Large	Placebo	5.6 (4.2, 7.5)	5.4 (4.0, 7.2)	–0.2 (–1.7, 1.1)	–4.5 (–26.6, 23.7)
	Rosuvastatin	5.7 (4.1, 7.5)	5.7 (4.3, 7.5)	0.1 (–1.5, 1.6)	1.1 (–23.2, 33.2)
Medium	Placebo	4.8 (3.0, 7.0)	4.6 (2.7, 6.8)	–0.3 (–2.4, 1.9)	–8.6 (–42.1, 50.6)
	Rosuvastatin	4.8 (3.0, 7.0)	5.5 (3.4, 7.9)	0.6 (–1.7, 3.0)	12.5 (–30.6, 79.2)
Small	Placebo	5.0 (3.0, 7.7)	5.8 (3.3, 8.7)	0.6 (–1.8, 3.1)	10.9 (–32.8, 80.1)
	Rosuvastatin	4.9 (2.9, 7.5)	6.5 (3.8, 9.8)	1.3 (–1.2, 4.3)	28.6 (–22.4, 112.4)
Very small	Placebo	13.2 (10.5, 16.0)	12.2 (9.5, 14.9)	–1.0 (–3.3, 1.2)	–7.6 (–23.1, 10.0)
	Rosuvastatin	13.3 (10.5, 15.9)	11.7 (8.6, 14.7)	–1.5 (–4.0, 0.9)	–11.4 (–29.0, 7.1)
HDL particle average size–nm	Placebo	9.0 (8.6, 9.3)	9.0 (8.6, 9.3)	0 (–0.2, 0.2)	0 (–2.2, 2.2)
	Rosuvastatin	9.0 (8.6, 9.3)	9.1 (8.7, 9.5)	0.1 (–0.1, 0.3)	1.2 (–1.0, 3.6)

[*] To convert values for LDL (low-density lipoprotein), IDL (intermediate-density lipoprotein), VLDL (very low-density lipoprotein), HDL (high-density lipoprotein), and non-HDL cholesterol [calculated as the difference between total cholesterol and HDL cholesterol] to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

[a] P values from the Wilcoxon signed rank test comparing baseline and 12 months values were statistically different (P<0.001), with the exception of triglycerides (P=0.17), triglyceride/HDL cholesterol ratio (P=0.74), very large HDL particles (P=0.002), and HDL particle average size (P=0.99) in the placebo group; and, among very large HDL particles (P=0.05) in the rosuvastatin group.

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[b] P values from Wilcoxon rank sum test comparing change among the rosuvastatin group with change among the placebo group were p<0.001 for all. Values obtained from individuals with baseline and 12-month measurements (N=9,180).

Table 3

Baseline Lipoprotein Measures in Relation to Incident Diabetes, According to Randomized Treatment Arm

	Lower Tertile	Middle Tertile	Upper Tertile	$P_{linear\ trend}$
Placebo				
LDL cholesterol (mg/dL)	≤ 100	101–116	> 116	
Incidence rate per 100 p-y[*]	1.40 (1.09–1.79)	1.21 (0.94–1.57)	0.89 (0.65–1.21)	
Model 1, HR (95% CI)[a]	1.00	0.85 (0.59–1.23)	0.57 (0.38–0.87)	0.01
[c]Model 2, HR (95% CI)[b]	1.00	0.93 (0.64–1.34)	0.54 (0.35–0.83)	0.009
HDL cholesterol (mg/dL)	≤ 43	44–56	> 56	
Incidence rate per 100 p-y	1.81 (1.47–2.25)	1.09 (0.83–1.42)	0.54 (0.36–0.82)	
Model 1, HR (95% CI)	1.00	0.54 (0.37–0.78)	0.28 (0.17–0.45)	<0.001
[d]Model 2, HR (95% CI)	1.00	0.73 (0.49–1.09)	0.55 (0.32–0.94)	0.03
Triglycerides (mg/dL)	≤ 96	97–149	> 149	
Incidence rate per 100 p-y	0.54 (0.36–0.80)	1.16 (0.89–1.52)	1.79 (1.44–2.22)	
Model 1, HR (95% CI)	1.00	2.04 (1.25–3.32)	3.07 (1.93–4.88)	<0.001
[e]Model 2, HR (95% CI)	1.00	1.45 (0.86–2.44)	1.87 (1.10–3.18)	0.02
Triglyceride/HDL cholesterol ratio	≤1.78	1.79–3.27	>3.27	
Incidence rate per 100 p-y	0.48 (0.30–0.71)	1.08 (0.81–1.42)	1.92 (1.55–2.36)	
Model 1, HR (95% CI)	1.00	2.14 (1.27–3.58)	3.91 (2.40–6.37)	<0.001
[f]Model 2, HR (95% CI)	1.00	1.67 (0.98–2.86)	3.24 (1.97–5.33)	<0.001
Non-HDL cholesterol (mg/dL)	≤ 125	126–143	> 143	
Incidence rate per 100 p-y	1.09 (0.82–1.45)	0.96 (0.72–1.28)	1.46 (1.15–1.86)	
Model 1, HR (95% CI)	1.00	0.86 (0.57–1.29)	1.19 (0.81–1.76)	0.37
[g]Model 2, HR (95% CI)	1.00	0.83 (0.54–1.25)	0.79 (0.53–1.18)	0.25
Apolipoprotein B (mg/dL)	≤ 101	102–117	> 117	
Incidence rate per 100 p-y	0.79 (0.57–1.10)	1.35 (1.05–1.72)	1.36 (1.05–1.75)	
Model 1, HR (95% CI)	1.00	1.76 (1.16–2.67)	1.76 (1.14–2.70)	0.01
Model 2, HR (95% CI)	1.00	2.11 (1.28–3.46)	1.83 (1.02–3.28)	0.09
[h]Model 3, HR (95% CI)	1.00	1.33 (0.86–2.06)	1.05 (0.66–1.66)	0.99
LPIR score[j] (range)	≤ 40	41–62	>62	
Incidence rate per 100 p-y	0.53 (0.35–0.79)	0.75 (0.54–1.04)	2.21 (1.82–2.68)	
Model 1, HR (95% CI)	1.00	1.37 (0.80–2.34)	4.08 (2.53–6.57)	<0.001
Model 2, HR (95% CI)	1.00	0.73 (0.41–1.33)	1.49 (0.80–2.78)	0.03
[i]Model 3, HR (95% CI)	1.00	0.86 (0.48–1.54)	2.00 (1.11–3.60)	<0.001
Rosuvastatin				
LDL cholesterol (mg/dL)	≤ 100	101–116	> 116	

	Lower Tertile	Middle Tertile	Upper Tertile	$P_{linear\ trend}$
Incidence rate per 100 p-y[*]	1.92 (1.55–2.39)	1.52 (1.20–1.93)	1.47 (1.15–1.88)	
Model 1, HR (95% CI)[a]	1.00	0.72 (0.52–1.01)	0.73 (0.52–1.03)	0.047
[c]Model 2, HR (95% CI)[b]	1.00	0.71 (0.50–1.00)	0.66 (0.46–0.93)	0.01
HDL cholesterol (mg/dL)	≤ 43	44–56	> 56	
Incidence rate per 100 p-y	2.53 (2.10–3.05)	1.61 (1.28–2.02)	0.73 (0.51–1.04)	
Model 1, HR (95% CI)	1.00	0.61 (0.44–0.83)	0.28 (0.18–0.43)	<0.001
[d]Model 2, HR (95% CI)	1.00	0.72 (0.51–1.02)	0.49 (0.30–0.79)	0.003
Triglycerides (mg/dL)	≤ 96	97–149	> 149	
Incidence rate per 100 p-y	0.88 (0.61–1.21)	1.26 (0.97–1.63)	2.78 (2.32–3.31)	
Model 1, HR (95% CI)	1.00	1.37 (0.89–2.12)	2.97 (2.02–4.37)	<0.001
[e]Model 2, HR (95% CI)	1.00	0.85 (0.54–1.33)	1.43 (0.93–2.20)	0.009
Triglyceride/HDL cholesterol ratio	≤1.78	1.79–3.27	>3.27	
Incidence rate per 100 p-y	0.73 (0.50–1.02)	1.43 (1.11–1.82)	2.75 (2.28–3.28)	
Model 1, HR (95% CI)	1.00	1.78 (1.14–2.77)	3.53 (2.34–5.32)	<0.001
[f]Model 2, HR (95% CI)	1.00	1.29 (0.82–2.03)	2.29 (1.51–3.49)	<0.001
Non-HDL cholesterol (mg/dL)	≤ 125	126–143	> 143	
Incidence rate per 100 p-y	1.24 (0.95–1.61)	1.63 (1.30–2.05)	2.05 (1.67–2.53)	
Model 1, HR (95% CI)	1.00	1.20 (0.84–1.73)	1.49 (1.05–2.12)	0.03
[g]Model 2, HR (95% CI)	1.00	0.98 (0.68–1.42)	0.92 (0.64–1.33)	0.65
Apolipoprotein B (mg/dL)	≤ 101	102–117	> 117	
Incidence rate per 100 p-y	1.02 (0.77–1.37)	1.77 (1.41–2.21)	2.16 (1.76–2.64)	
Model 1, HR (95% CI)	1.00	1.80 (1.23–2.64)	2.22 (1.53–3.22)	<0.001
Model 2, HR (95% CI)	1.00	1.82 (1.17–2.83)	2.31 (1.41–3.78)	0.001
[h]Model 3, HR (95% CI)	1.00	1.22 (0.82–1.80)	1.25 (0.85–1.86)	0.28
LPIR score[j] (range)	≤ 40	41–62	>62	
Incidence rate per 100 p-y	0.60 (0.41–0.88)	1.41 (1.10–1.81)	2.90 (2.44–3.44)	
Model 1, HR (95% CI)	1.00	2.24 (1.39–3.60)	4.97 (3.16–7.82)	<0.001
Model 2, HR (95% CI)	1.00	1.22 (0.72–2.06)	2.10 (1.20–3.66)	0.002
[i]Model 3, HR (95% CI)	1.00	1.23 (0.73–2.07)	2.23 (1.30–3.82)	<0.001

Number of incident diabetes cases among placebo- and rosuvastatin-allocated individuals were 158/6009 and 212/5909, respectively.

[*] Incidence rate per 100 p-y (person-years); HR, hazard ratio; CI, confidence interval. LDL low-density lipoprotein; HDL high-density lipoprotein.

[a] Model 1: Cox proportional hazards ratios were adjusted for age, sex, ethnic origin, education, exercise, family history of diabetes, and smoking

[b] Model 2: Cox proportional hazards ratios were adjusted for Model 1 variables + systolic blood pressure, body-mass index, log transformed hsCRP, glycated hemoglobin, HDL cholesterol, LDL cholesterol, and log transformed triglycerides.

[c] Model 2 excludes LDL cholesterol

[d] Model 2 excludes HDL cholesterol

[e] Model 2 excludes log transformed triglycerides

[f] Model 2 excludes HDL cholesterol and log transformed triglycerides

[g] Model 2 excludes LDL cholesterol and log transformed triglycerides

[h] Model 3 excludes LDL cholesterol and log transformed triglycerides, but includes LPIR score

[i] Model 3 excludes LDL cholesterol and log transformed triglycerides, but includes Apolipoprotein B

[j] LPIR score ranges from 0 (most insulin sensitive) to 100 (most insulin resistant).

Table 4

12-month Lipoprotein Measures in Relation to Incident Diabetes in the Rosuvastatin Arm

	Lower Tertile	Middle Tertile	Upper Tertile	$P_{linear\ trend}$
LDL cholesterol (mg/dL)	≤ 63	64–108	> 108	
Incidence rate per 100 p-y[*]	1.91 (1.61–2.26)	1.08 (0.74–1.57)	1.07 (0.56–2.05)	
Model 1, HR (95% CI)[a]	1.00	0.59 (0.39–0.90)	0.49 (0.23–1.05)	0.02
[c]Model 2, HR (95% CI)[b]	1.00	0.69 (0.44–1.06)	0.35 (0.15–0.84)	0.07
HDL cholesterol (mg/dL)	≤ 45	46–58	> 58	
Incidence rate per 100 p-y	2.65 (2.15–3.26)	1.48 (1.12–1.95)	0.85 (0.59–1.21)	
Model 1, HR (95% CI)	1.00	0.54 (0.38–0.79)	0.31 (0.19–0.50)	<0.001
[d]Model 2, HR (95% CI)	1.00	0.70 (0.47–1.05)	0.67 (0.40–1.13)	0.10
Triglycerides (mg/dL)	≤ 91	92–136	> 136	
Incidence rate per 100 p-y	0.95 (0.69–1.30)	1.43 (1.08–1.88)	2.90 (2.34–3.61)	
Model 1, HR (95% CI)	1.00	1.41 (0.91–2.20)	2.85 (1.91–4.26)	<0.001
[e]Model 2, HR (95% CI)	1.00	1.22 (0.77–1.93)	2.21 (1.41–3.45)	0.001
Triglyceride/HDL cholesterol ratio	≤1.63	1.64–2.88	>2.88	
Incidence rate per 100 p-y	0.80 (0.55–1.12)	1.56 (1.18–2.01)	2.88 (2.30–3.56)	
Model 1, HR (95% CI)	1.00	2.01 (1.27–3.18)	3.36 (2.16–5.25)	<0.001
[f]Model 2, HR (95% CI)	1.00	1.32 (0.82–2.12)	2.36 (1.47–3.67)	<0.001
Non-HDL cholesterol (mg/dL)	≤ 86	87–134	> 134	
Incidence rate per 100 p-y	1.63 (1.36–1.97)	1.73 (1.29–2.31)	1.40 (0.80–2.45)	
Model 1, HR (95% CI)	1.00	1.08 (0.75–1.55)	0.78 (0.41–1.50)	0.79
[g]Model 2, HR (95% CI)	1.00	1.14 (0.79–1.65)	0.65 (0.32–1.32)	0.69
Apolipoprotein B (mg/dL)	≤ 73	74–104	> 104	
Incidence rate per 100 p-y	1.56 (1.29–1.89)	2.00 (1.53–2.60)	1.12 (0.61–2.09)	
Model 1, HR (95% CI)	1.00	1.34 (0.95–1.88)	0.65 (0.31–1.33)	0.90
Model 2, HR (95% CI)	1.00	2.28 (1.38–3.77)	2.33 (0.69–7.85)	0.004
[h]Model 3, HR (95% CI)	1.00	1.27 (0.89–1.81)	0.52 (0.24–1.10)	0.60
LPIR score[j] (range)	≤ 40	41–62	> 62	
Incidence rate per 100 p-y	0.75 (0.51–1.10)	1.27 (0.96–1.68)	3.16 (2.59–3.86)	
Model 1, HR (95% CI)	1.00	1.81 (1.09–3.01)	4.41 (2.73–7.13)	<0.001
Model 2, HR (95% CI)	1.00	1.35 (0.78–2.32)	2.55 (1.38–4.72)	0.001
[i]Model 3, HR (95% CI)	1.00	1.49 (0.87–2.54)	3.33 (1.90–5.81)	<0.001

Number of cases of incident diabetes among rosuvastatin-allocated individuals were 167/4419.

[*]Incidence rate per 100 p-y (person-years); HR, hazard ratio; CI, confidence interval. LDL low-density lipoprotein; HDL high-density lipoprotein.

[a]Model 1: Cox proportional hazards ratios were adjusted for age, sex, ethnic origin, education, exercise, family history of diabetes, and smoking

[b] Model 2: Cox proportional hazards ratios were adjusted for Model 1 variables + systolic blood pressure, body-mass index, log transformed hsCRP, glycated hemoglobin, HDL cholesterol, LDL cholesterol, and log transformed triglycerides.

[c] Model 2 excludes LDL cholesterol

[d] Model 2 excludes HDL cholesterol

[e] Model 2 excludes log transformed triglycerides

[f] Model 2 excludes HDL cholesterol and log transformed triglycerides

[g] Model 2 excludes LDL cholesterol and log transformed triglycerides

[h] Model 3 excludes LDL cholesterol and log transformed triglycerides, but includes LPIR score

[i] Model 3 excludes LDL cholesterol and log transformed triglycerides, but includes Apolipoprotein B

[j] LPIR score ranges from 0 (most insulin sensitive) to 100 (most insulin resistant).