Pioglitazone and Rosiglitazone Have Different Effects on
Serum Lipoprotein Particle Concentrations and Sizes in Patients with
Type 2 Diabetes and Dyslipidemia

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Running title: Insulin sensitizers and lipoprotein particles

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ABSTRACT

Objective: Associated with insulin resistance in type 2 diabetes are increased serum triglycerides, decreased HDL-C, and a predominance of large VLDL, small LDL, and small HDL particles. The comparative effects of thiazolidinedione insulin sensitizers on serum lipoprotein particle concentrations and sizes in type 2 diabetes are not known. We studied the effects of pioglitazone (PIO) and rosiglitazone (ROSI) treatments on serum lipoprotein particle concentrations and sizes in type 2 diabetes patients with dyslipidemia.

Research Design and Methods: This is a prospective, randomized, double-blind, multi-center, parallel-group study. After a 4-week placebo washout period, patients randomized to PIO (n=369) were treated with 30 mg qd for 12 weeks followed by 45 mg qd for another 12 weeks, while patients randomized to ROSI (n=366) were treated with 4 mg qd followed by 4 mg bid for the same intervals. Lipoprotein subclass particle concentrations and sizes were determined by proton nuclear magnetic resonance spectroscopy at baseline and endpoint (PIO [n=333] and ROSI [n=325] patients).

Results: PIO-treatment increased total VLDL particle concentration less than ROSI-treatment and decreased VLDL particle size more than ROSI. PIO-treatment reduced total LDL particle concentration whereas ROSI-treatment increased it. Both treatments increased LDL particle size, with PIO-treatment having a greater effect. Whereas PIO-treatment increased total HDL particle concentration and size, ROSI-treatment decreased them; both increased HDL cholesterol levels.

Conclusion: PIO and ROSI treatments have different effects on serum lipoprotein subclass particle concentrations and sizes in patients type 2 diabetes and dyslipidemia. Registered in clinicaltrials.gov as NCT00331487
Two core metabolic defects contribute to the development of type 2 diabetes: insulin resistance and insulin insufficiency. Insulin resistance, present in most of these patients (1), is associated with a cluster of abnormalities that increase the risk for cardiovascular disease (CVD), including dyslipidemia (2,3) characterized by elevated triglycerides (TG), decreased HDL-C, and a predominance of small LDL particles (4-7). A major contributor to this hypertriglyceridemia is hepatic overproduction of TG-rich VLDL and apolipoprotein B (apo B) caused by insulin resistance and increased availability of free fatty acid (FFA) substrate (8,9). Insulin suppresses large VLDL and apo B release in healthy humans (10), but not in patients with type 2 diabetes, resulting in hypertriglyceridemia (11). Decreased lipoprotein lipase (LPL) activity in fat and skeletal muscle contributes to the reduced clearance of TG-rich lipoproteins (10, 11). The exchange of TG in the VLDL particles with the cholesteryl esters in LDL and HDL particles—via the cholesteryl ester transfer protein (CETP) system—leads to accumulation of small LDL and HDL particles, respectively (12). The mean particle size of VLDL increases and the LDL and HDL particle sizes decrease as insulin resistance worsens in non-diabetic subjects and type 2 diabetes patients (7).

By targeting insulin resistance, the thiazolidinedione (TZD) class of oral anti-hyperglycemic medications (OAM) can affect glucose and lipoprotein metabolism. Pioglitazone hydrochloride (PIO; Actos®, Takeda Pharmaceuticals North America, Inc., Lincolnshire, Ill) and rosiglitazone maleate (ROSI; Avandia®, GlaxoSmithKline, Research Triangle Park, NC) are the currently available TZDs for the treatment of type 2 diabetes.

The many reports that suggest that PIO has different effects from ROSI on lipid parameters in type 2 diabetes patients were detailed in our recent report on the first multi-center, prospective, randomized, double-blind, parallel-group comparison of maximally effective monotherapy doses of PIO and ROSI in these patients with dyslipidemia receiving no concomitant glucose-lowering or lipid-altering therapies (13). With the advent of proton nuclear magnetic resonance (NMR) spectroscopy (14), subjects with the same LDL cholesterol (LDL-C) levels have been found to differ in their LDL particle concentration and particle size distribution (15). We now extend our first report of the GLAI Study (13) by describing the effects of PIO and ROSI on the serum lipoprotein subclass particle concentrations and sizes in a sub-group of the parent study.

RESEARCH DESIGN AND METHODS

Subjects

The study design and methods of the GLAI Study have been published (13). Briefly, inclusion criteria included patients 35 years of age or older with a diagnosis of type 2 diabetes, fasting TG levels ≥150 mg/dL and <600 mg/dL, fasting LDL-C levels <130 mg/dL, fasting serum C-peptide levels ≥1 ng/mL, and hemoglobin A1c (A1C) values ≥7% and ≤11% if naïve to previous OAM therapy, or A1C values ≥7% and ≤9.5% if previously treated with OAM monotherapy. Exclusion criteria included treatment with insulin within 60 days of screening, combination OAM therapy, any lipid-altering agent, and any weight loss agent (13). Conducted in accordance with
the Declaration of Helsinki guidelines on good clinical practice, this study was approved by each investigator’s institutional Ethical Review Board and all subjects gave informed consent.

**Study design and methods**

Eligible patients discontinued any current OAM therapy and received oral placebo therapy throughout a 4-week, single-blind, lead-in period. Qualified personnel provided dietary counseling on the American Heart Association weight-maintaining Step I diet. Randomization occurred in a stratified fashion with 4 strata corresponding to previous OAM treatment (previously treated or naïve) and gender (male or female). Patients received either 30 mg PIO qd or 4 mg ROSI qd for the initial 12 weeks. For the final 12 weeks, the doses of PIO and ROSI were increased to the maximally effective doses (for monotherapy) of 45 mg qd or 4 mg bid, respectively. In this sub-study analysis, all patients who had data for baseline and endpoint lipoprotein subclass particle concentrations and sizes were included. The population of subjects pre-specified for the analyses was all subjects randomized. We feel it is important to use this population to be consistent with the pre-planned analyses and to be consistent with the intent-to-treat paradigm.

**Analytical Methods**

The following analyses were performed by Covance Central Laboratory Services, Inc. (Indianapolis, IN): fasting blood samples (after at least 10 hours of fasting) were analyzed (13) for plasma glucose (PG), A1C, serum insulin (SI), serum TG, total cholesterol (TC), HDL-C, and LDL-C. Apolipoproteins B and A-I (Beckman IMMAGE Immunochemistry System, Beckman Instrument, Brea, CA), Lp(a) (SPQ Antibody Reagent of Diasorin, Stillwater, MN), and apo C-III (Wako Chemicals, Richmond, VA) were determined by immunoassay. Lipoprotein subclass particle concentrations and sizes were measured using NMR spectroscopy at LipoScience, Inc. (Raleigh, NC) (14-16). Ten subclass categories were measured in nm: large VLDL (> 60), medium VLDL (35-60), small VLDL (27-35), IDL (23-27), large LDL (21.3-23), medium LDL (19.8-21.2), small LDL (18-19.8), large HDL (8.8-13), medium HDL (8.2-8.8), and small HDL (7.3-8.2). HOMA-IR was determined as a surrogate of insulin resistance (17). The safety assessment has been previously reported (13).

**Statistical methods**

Baseline data are presented as mean ± standard deviation. Differences between treatment groups in demographics and baseline parameters for patients entering active drug therapy were evaluated using Fisher’s Exact test for categorical variables or an independent groups t-test for continuous variables. For the glycemic, lipid, and HOMA-IR variables, analyses of the change from baseline level were conducted on patients for whom a baseline measurement and at least one post-baseline measurement were available. The last observation carried forward (LOCF) change from baseline level was analyzed using a fixed-effects analysis of variance with baseline level of the analyte as a covariate (ANCOVA). The ANCOVA model comprised terms for strata, geographic region in which the investigative site was located, treatment, and baseline value. The LOCF changes from baseline were adjusted for their baseline level using the ANCOVA model and are reported as least-squares
means (LSM) with 95% confidence intervals or with the standard error of the LSM (18,19). Treatments were compared using the LSMs obtained from the ANCOVA model. Spearman correlation coefficients were calculated for selected variables. SAS version 8.2 (SAS Institute, Cary, NC) was used for all analyses. All tests were two-sided and results were considered statistically significant for P<0.05.

RESULTS

The patient flow through the study has been reported (13). In the PIO group 333 (of 369) patients and in the ROSI group 325 (of 366) had baseline and post-baseline lipoprotein NMR data. The distribution of patients among the various withdrawal categories was similar between treatment groups.

Baseline demographics and characteristics

As in the parent study, no statistically significant differences existed between the treatment groups in respect to demographics and baseline characteristics. Data are not repeated here as the majority of the patients from the parent study were included in this sub-study.

Glycemic, lipid, and insulin resistance variables

Baseline levels, change from baseline for fasting TG, TC, LDL-C, HDL-C, FFA, A1C, FPG, FSI, and HOMA-IR for each group, and the comparison of changes in these parameters between groups are similar (Table 1) to those in the parent study (13) with one exception. At baseline all parameters were similar except for fasting TG, which was significantly higher in the PIO group than in the ROSI group in this sub-study. As reported previously (13), TG decreased significantly in the PIO group, whereas it increased (not significantly in this sub-study analysis) in the ROSI group. The change in TG from baseline was significantly different between the two treatments. Both treatments significantly increased TC and LDL-C; however, PIO caused smaller increases. Both treatments significantly increased HDL-C, with PIO resulting in a significantly greater increase. Compared with their respective baseline values, which did not differ between treatment groups, both treatments significantly decreased A1C, fasting plasma FFA, FPG, FSI, and HOMA-IR, resulting in similar endpoint values for both and no significant differences between treatments. Body weight changes from baseline were similar for PIO (2.0 ± 0.2 kg) and ROSI (1.6 ± 0.2 kg).

Particle concentration changes

Table 2 shows the baseline, change from baseline for each group, and a comparison of these changes between them for each sub-fraction particle concentration.

VLDL

Compared with their respective baseline values, PIO-treatment significantly decreased large VLDL particle concentration, but caused no change in total, medium, or small VLDL particles, whereas ROSI-treatment significantly increased the total, large, and medium particle concentrations, but did not change the small VLDL particles. Comparing the two treatments the differences were significant for total, large, and medium VLDL particle concentrations, but not for small VLDL particles.

Intermediate density lipoprotein (IDL)

PIO-treatment significantly decreased IDL particle concentration from baseline, whereas ROSI-treatment
increased it. The between-group difference was statistically significant.

**LDL**

From baseline to endpoint, PIO-treatment significantly decreased total and small, but increased large LDL particle concentrations, whereas ROSI-treatment significantly increased total and large, but caused no change in the small LDL particle concentration. The differences between the treatments were significant for total and small LDL particles, but not for large LDL particles.

**HDL**

Compared with their respective baseline values, PIO-treatment significantly increased total, large, and medium HDL, but decreased small HDL particle concentrations, whereas ROSI-treatment had no effect on total HDL, significantly increased medium HDL, and decreased large and small HDL particle concentrations. The differences between the treatments were significant for total, large, medium, and small HDL particles.

**Particle size changes**

Figure 1 shows the mean baseline and change from baseline for particle size of each lipoprotein class. The baseline mean VLDL particle size was larger in the PIO-treatment than in the ROSI-treatment group (Fig 1a). Both treatments decreased VLDL particle sizes from baseline; however, PIO-treatment decreased the mean VLDL particle size more than ROSI. The mean LDL particle sizes at baseline were comparable in both groups (Fig 1b). PIO and ROSI treatments significantly increased mean LDL particle size; however, PIO-treatment had a greater effect. The mean HDL particle sizes were comparable in both groups at baseline (Fig 1c). There were small but statistically significant changes in mean HDL particle size from baseline for each group and the difference between them was significant.

**Correlation between HOMA-IR and Lipoprotein Particle Size**

There was a negative correlation between HOMA-IR and LDL particle size in the PIO and ROSI groups and in the total study population, (PIO: r = - 0.249; ROSI: r = - 0.267; combined: r = - 0.252; all values p<0.0001). There was also a negative correlation between HOMA-IR and HDL particle size in all 3 groups (PIO: r = - 0.171; p<0.002, ROSI: r = - 0.181; p = 0.001 and combined: r = - 0.165; p<0.0001). There was a positive correlation between HOMA-IR and VLDL particle size in all 3 groups (PIO: r = 0.306; ROSI: r = 0.374; combined: r = 0.339; all values p<0.001).

**Serum apolipoproteins**

PIO-treatment significantly decreased apo C-III (mean ± SD baseline 19.3 ± 7.4 mg/dL; change from baseline - 1.5 [95% CI: -2.1, -1.0] mg/dL) and ROSI increased apo C-III (baseline 18.2 ± 6.7 mg/dL; change from baseline 1.0 (0.4, 1.6) mg/dL). At baseline, PIO-treated subjects had mean apo B levels of 105.0 ± 19.9 mg/dL with a non-significant change of - 0.05 (-2.4, 2.3) mg/dL during treatment. Baseline apo B was 104.0 ± 19.3 mg/dL in the ROSI-treated subjects; with a significant increase of 10.5 (8.1, 12.8) mg/dL during treatment. PIO-treatment had no effect on apo A-I level during treatment (baseline apo A-I 113.8 ± 23.0 mg/dL; change from baseline 1.4 [-0.6, 3.4] mg/dL), whereas ROSI treatment significantly decreased apo A-I (baseline 113.7 ± 22.0 mg/dL; change from baseline - 5.6 (-7.6,-3.6) mg/dL). At baseline, PIO-treated subjects had mean Lp(a) levels of
18.9 ± 22.4 mg/dL with a significant increase of 5.6 (4.3, 6.9) mg/dL during treatment. Baseline Lp(a) was 19.9 ± 23.7 mg/dL in the ROSI-treated subjects; with a significant increase of 2.8 (1.5, 4.1) mg/dL during treatment. Differences between treatments for apo C-III, apo B, apo A-I, and Lp(a) were all significant.

CONCLUSIONS

This study is the first to demonstrate that PIO and ROSI treatments result in significantly different effects on serum lipoprotein subclass particle concentrations and sizes despite similar effects on glycemic control and insulin resistance. These observations were made utilizing NMR spectroscopy—a novel technique that permits evaluation of these important characteristics of lipoproteins, and as such has advanced our understanding of the changes in serum lipoprotein subclass particle concentration and size under normal conditions (16, 20), in specific disease states (7, 21-23), and during treatment with specific drug therapies (24-26).

Garvey et al (7) reported that all three major lipoprotein subclasses differed significantly as a function of insulin sensitivity in insulin-resistant non-diabetic subjects and type 2 diabetes patients. Mean particle size of VLDL increased and the LDL and HDL particle sizes decreased as insulin resistance worsened. The dyslipidemia in type 2 diabetes patients primarily reflected an exacerbation of the changes observed in non-diabetic subjects with insulin resistance. There was a negative correlation between insulin sensitivity and VLDL particle size and a positive correlation between insulin sensitivity and LDL and HDL particle sizes. We corroborated their findings in reporting a positive correlation between HOMA-IR and VLDL particle size and a negative correlation between HOMA-IR and LDL as well as HDL particle size. However, the correlation between insulin resistance and lipoprotein particle sizes, although significant, was modest for VLDL and small for LDL and HDL.

Many studies (13) showed that PIO-treatment decreases fasting TG, whereas ROSI-treatment increases it. One possible explanation for the difference in action of the two treatments may be their effects on VLDL particle concentration and size. Our study demonstrated that PIO-treatment decreased and ROSI-treatment increased large VLDL particle concentration; PIO-treatment resulted in no increase in the medium VLDL particle size and concentration, whereas ROSI-treatment increased them; and PIO-treatment decreased mean VLDL particle size to a greater extent than ROSI-treatment. Additionally, these treatments exerted differential effects on apo C-III, an inhibitor of LPL-mediated lipolysis and remnant clearance (27). In our study, PIO-treatment resulted in a decrease in apo C-III whereas ROSI-treatment caused an increase in apo C-III which is associated with a delay in clearance, especially of smaller VLDL and IDL particles. The greater increase in medium-sized VLDL particle concentration and IDL in the ROSI group may be partially explained by the apo C-III changes. Nagashima et al (28) reported that PIO-treatment reduced TG level, at least in part, by increasing fractional clearance of VLDL and TG from circulation. They attributed the change to increased plasma LPL mass and decreased levels of plasma apo C-III and also suggested that PIO-treatment, by increasing hepatic insulin sensitivity, could reduce expression of the apo C-III gene. A correlation between
insulin resistance and apo C-III production in humans has been reported (29). That the reductions in insulin resistance caused by the two treatments were comparable in our study suggests other mechanisms may contribute to the differences observed in TG changes between PIO and ROSI treatments. Finally, it is possible that PPARα activity in pioglitazone can account for the differences in TG effects. However there is no clear data to indicate pioglitazone has PPARα effects (30).

Previous studies, using methods other than NMR spectroscopy, have reported that PIO-treatment (31, 32, 33) and ROSI-treatment (34) increase LDL particle size. Our study, using NMR spectroscopy, is the first to directly compare the effects of these two treatments on LDL particle size and show they had different effects not only on LDL particle size but also on concentration. The mechanism by which this differential effect on LDL particle size occurred is probably unrelated to the reduction of insulin resistance and glycemic improvement, as both drugs decreased insulin resistance and improved A1C similarly. These independent effects were demonstrated in a study in which metformin and PIO treatment resulted in a reduction in the small LDL sub-fraction, whereas there was no change with a sulfonylurea despite similar improvement in glycemia (33). Florez et al reported that apo C-III correlated inversely with LDL particle size, probably through effects on TG-rich lipoprotein metabolism (35). The increase in total plasma and LDL apo B by ROSI-treatment (34) suggested an increase in LDL particle concentration. We confirmed this with the NMR spectroscopy technique and extended this previous finding by showing that PIO-treatment decreased LDL particle concentration, whereas ROSI-treatment increased it. This may explain the smaller increase in LDL-C occurring with PIO-treatment than with ROSI-treatment. Cromwell and Otvos (36) have reported that LDL particle concentration as measured by NMR spectroscopy was a strong, independent predictor of CHD and was more strongly associated with CHD risk than LDL particle size. Finally, the 2 treatments have divergent effects on IDL and remnants, both independent predictors of cardiovascular disease (37).

Freed et al (34) reported that ROSI-treatment increased HDL-C predominantly by increasing the HDL2 subclass, with minimal change in apo A-I level. We extend these findings by showing that (a) PIO-treatment raised HDL-C more than ROSI-treatment; (b) PIO-treatment had no effect on apo A-I whereas ROSI-treatment decreased it; (c) PIO-treatment increased HDL particle size whereas ROSI-treatment decreased it; and (d) there were significant differences in their treatment effects on HDL particle concentrations. The reason for these differences in the effect between the two treatments on HDL particles, in the presence of similar reductions of insulin resistance, remains to be elucidated. It is possible that PIO-treatment, in causing a decrease in TG and large VLDL, reduced the CETP-mediated exchange of VLDL, TG, and HDL cholesteryl ester, resulting in significant increases in large- and medium-sized HDL particles and a reduction in small particles, leading to a net increase in size. By contrast, the trend toward an increase in TG levels among ROSI-treated patients may explain why there was a decrease in large HDL particles. The increase in HDL-C in the ROSI-treatment group was apparently due to a reduction of smaller-sized and an increase in medium-sized HDL particles by ROSI-treatment,
and a qualitatively similar change was also noted for the PIO-treatment group. These changes could reflect the effect of TZDs on ATP-binding cassette-1 activity, which might be expected to produce these size changes (38). Finally, there are TZD effects that do not appear to result from an improvement of insulin sensitivity. The difference between PIO and ROSI on lipids and lipoproteins may be one of these. Whether these differences are clinically relevant is not known, since evidence for cardiovascular benefit exists for interventions that may increase larger HDL2 particles with nicotinic acid (39) as well as those that appear to increase small HDL particles with fibrates (40).

In summary, our study demonstrates that PIO-treatment and ROSI-treatment differ significantly in their effects not only on serum lipids but also on lipoprotein subclass particle concentrations and particle sizes. These differences were observed despite similar improvements in many non-lipid CVD risk factors associated with insulin resistance and type 2 diabetes. Associations of lipoprotein subclass particle concentration and size have been reported. Whether these differences in lipoprotein subclass particle concentrations and sizes translate into differences for the risk of CVD remain to be established. Further clinical trials are needed to determine if these differences in lipoprotein particle size results in clinically meaningful differences.

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Appendix
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## Table 1—Baseline and change from baseline of lipid, glycemic, and insulin variables

<table>
<thead>
<tr>
<th></th>
<th>PIO (n = 333)</th>
<th></th>
<th>ROSI (n = 325)</th>
<th></th>
<th>Between Groups</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change from Baseline</td>
<td>Baseline</td>
<td>Change from Baseline</td>
<td>LS Mean (95% CI)</td>
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<tr>
<td></td>
<td>Mean ± SD</td>
<td>LS Mean (95% CI)</td>
<td>Mean ± SD</td>
<td>LS Mean (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>[n = 331] 255.3 ± 151.1</td>
<td>−46.7* (−62.5, −31.0)</td>
<td>[n = 324] 230.8 ± 119.8†</td>
<td>12.3 (−3.5, 28.1)</td>
<td>−59.0† (−79.4, −38.7)</td>
</tr>
<tr>
<td>(mg/dL)</td>
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<tr>
<td>Total Chol (mg/dL)</td>
<td>[n = 331] 193.5 ± 31.4</td>
<td>9.6* (5.8, 13.5)</td>
<td>[n = 324] 192.7 ± 32.5</td>
<td>28.5* (24.6, 32.3)</td>
<td>−18.9† (−23.8, −13.9)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>[n = 332] 107.2 ± 25.7</td>
<td>12.5* (9.3, 15.7)</td>
<td>[n = 324] 109.3 ± 25.8</td>
<td>21.4* (18.1, 24.6)</td>
<td>−8.9† (−13.1, −4.7)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>[n = 331] 38.7 ± 9.8</td>
<td>5.2* (4.2, 6.1)</td>
<td>[n = 324] 39.9 ± 10.5</td>
<td>2.3* (1.4, 3.3)</td>
<td>2.9† (1.6, 4.1)</td>
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<td>FFA (mEq/dL)</td>
<td>[n = 331] 0.64 ± 0.28</td>
<td>−0.11* (−0.14, −0.08)</td>
<td>[n = 324] 0.62 ± 0.29</td>
<td>−0.12* (−0.15, −0.09)</td>
<td>0.00 (−0.04, 0.04)</td>
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<td>HbA1c (%)</td>
<td>[n = 330] 7.6 ± 1.2</td>
<td>−0.75* (−0.9, −0.6)</td>
<td>[n = 320] 7.5 ± 1.1</td>
<td>−0.64* (−0.7, −0.5)</td>
<td>−0.12 (−0.3, 0.0)</td>
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<td>FPG (mg/dL)</td>
<td>[n = 332] 179.6 ± 59.9</td>
<td>−33.5* (−38.1, −28.9)</td>
<td>[n = 324] 175.7 ± 55.9</td>
<td>−37.2* (−41.8, −32.6)</td>
<td>3.7 (−2.2, 9.6)</td>
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<tr>
<td>FSI (μ/mL)</td>
<td>[n = 331] 20.0 ± 20.0</td>
<td>−4.8* (−5.8, −3.8)</td>
<td>[n = 324] 18.2 ± 14.9</td>
<td>−4.9* (−5.9, −3.9)</td>
<td>0.06 (−1.2, 1.4)</td>
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<td>HOMA-IR</td>
<td>8.3 ± 6.6</td>
<td>−2.9* (−3.4, −2.5)</td>
<td>7.9 ± 7.5</td>
<td>−3.2* (−3.6, −2.7)</td>
<td>0.22 (−0.3, 0.8)</td>
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</table>

*P value <0.001 for within-group change from baseline. †P value = 0.02 for between-group baseline comparisons. ‡P value < 0.001 for between-group differences.
<table>
<thead>
<tr>
<th>Lipoprotein subclasses particle concentration</th>
<th>PIO (n = 333)</th>
<th>ROSI (n = 325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL Particles nmoles/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>Mean ± SD</td>
<td>LS Mean (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>82.8 ± 27.0</td>
<td>1.7 (–1.6, 5.0)</td>
</tr>
<tr>
<td>Large</td>
<td>10.6 ± 9.8</td>
<td>–2.7* (–3.7, –1.8)</td>
</tr>
<tr>
<td>Medium</td>
<td>35.3 ± 23.8</td>
<td>2.4 (–0.5, 5.2)</td>
</tr>
<tr>
<td>Small</td>
<td>37.0 ± 25.3</td>
<td>2.0 (–0.9, 4.8)</td>
</tr>
<tr>
<td><strong>IDL Particles nmoles/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>36.6 ± 52.2</td>
<td>–6.8* (–13.3, –0.2)</td>
</tr>
<tr>
<td>Small</td>
<td>1175.1 ± 433.8</td>
<td>–200.9* (–256, –146)</td>
</tr>
<tr>
<td><strong>LDL Particles nmoles/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1393.8 ± 360.7</td>
<td>–49.2* (–91.0, –7.4)</td>
</tr>
<tr>
<td>Large</td>
<td>182.6 ± 211.1</td>
<td>161.4* (130.7, 192.1)</td>
</tr>
<tr>
<td>Small</td>
<td>1175.1 ± 433.8</td>
<td>–200.9* (–256, –146)</td>
</tr>
<tr>
<td><strong>HDL umoles/L</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>30.8 ± 6.1</td>
<td>0.8* (0.2, 1.4)</td>
</tr>
</tbody>
</table>

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<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.7 ± 2.2</td>
<td>0.6* (0.4, 0.8)</td>
<td>3.8 ± 2.3</td>
<td>-0.4† (-0.6, -0.2)</td>
</tr>
<tr>
<td>Medium</td>
<td>4.9 ± 3.9</td>
<td>1.7* (1.3, 2.2)</td>
<td>5.2 ± 4.3</td>
<td>4.0* (3.6, 4.5)</td>
</tr>
<tr>
<td>Small</td>
<td>22.2 ± 6.1</td>
<td>-1.6* (–2.3, –0.8)</td>
<td>21.5 ± 5.7</td>
<td>-4.1* (–4.8, –3.3)</td>
</tr>
</tbody>
</table>

*P value < 0.001 for within-group change from baseline. †P value < 0.001 for between-group differences. §P value < 0.05 for within-group change from baseline. ‡P value < 0.05 for between-group differences.
Figure 1. Comparison of least squares mean changes in particle size from baseline for VLDL (panel a), LDL (panel b), and HDL (panel c) for patients treated with PIO and ROSI treatments. Black bars = PIO and white bars = ROSI treatments. Vertical bars represent standard errors. *P value indicates significant difference from baseline within group. †P value indicates significant difference between groups.