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NASH Resolution is Associated with Improvements in HDL and Triglyceride Levels But Not Improvement in LDL or Non-HDL-C Levels

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Abstract

Background—Nonalcoholic steatohepatitis (NASH) is associated with dyslipidemia and cardiovascular disease (CVD).

Aim—To determine the relationship between resolution of NASH and dyslipidemia.

Methods—Individuals in the Pioglitazone versus Vitamin E versus Placebo for the Treatment of Nondiabetic Patients with Nonalcoholic Steatohepatitis (PIVENS) trial with paired liver biopsies and fasting lipid levels were included (N=222). In the PIVENS trial individuals were randomized to pioglitazone 30mg, vitamin E 800IU or placebo for 96 weeks. Change in lipid levels at 96 weeks was compared between those with and without NASH resolution.

Results—Dyslipidemia at baseline was frequent, with low high-density lipoprotein (HDL) (<40mg/dL in men or <50 mg/dL in women) in 63%, hypertriglyceridemia (≥150 mg/dL) in 46%, hypercholesterolemia (≥200 mg/dL) in 47%, and triglycerides (TG)/HDL>5.0 in 25%. Low-density lipoprotein (LD) ≥ 160 mg/dL was found in 16% and elevated non-HDL cholesterol (non-HDL-C) (≥130 mg/dL) in 73%. HDL increased with NASH resolution but decreased in those without resolution (2.9mg/dL vs. −2.5mg/dL, P<0.001). NASH resolution was associated with significant decreases in TG and TG/HDL ratio compared to those without resolution (TG: −21.1 vs. −2.3mg/dL, P=0.03 and TG/HDL: −0.7 vs 0.1, P=0.003). Non-HDL-C, LDL and cholesterol

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decreased over 96 weeks in both groups but there was no significant difference between groups. Treatment group did not impact lipids.

Conclusions—NASH resolution is associated with improvements in TG and HDL but not in other CVD risk factors including LDL and non-HDL-C levels. Individuals with resolution of NASH may still be at increased risk of CVD. ClinicalTrials.gov identifier: NCT00063622

Keywords

nonalcoholic fatty liver disease; nonalcoholic steatohepatitis; lipids; vitamin E; metformin; non-high density lipoprotein cholesterol; cardiovascular disease risk

Introduction

Cardiovascular disease (CVD) is the leading cause of death among American adults. Dyslipidemia is an important risk factor for the development of CVD, CVD-related and all-cause mortality. Improvements in dyslipidemia can significantly decrease the risk of CVD development and CVD-related death.

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States and, its progressive form, nonalcoholic steatohepatitis (NASH) can evolve to end-stage liver disease. In addition to the liver-related morbidity and mortality associated with NAFLD, NAFLD confers an increased risk of CVD and CVD-related death in part driven by the high prevalence of concurrent dyslipidemia.[1–4]

Dyslipidemia, defined as increased low density lipoprotein, triglyceride and total cholesterol levels and/or decreased high-density lipoprotein levels, is highly prevalent among the general population and particularly common in individuals with NAFLD. Nearly a quarter of all American adults have dyslipidemia, and between 20–81% of those with NAFLD have dyslipidemia.[5]

The dyslipidemia of NAFLD is characterized by increased low-density lipoprotein (LDL) levels and decreased LDL particle size, both of which are established risk factors for CVD.[6–8] Elevated triglyceride (TG) levels and low high-density lipoprotein (HDL) levels are also characteristic of the dyslipidemia of NAFLD and can confer increased risk of CVD. An elevated TG/HDL ratio is linked to an increase in small dense LDL (sdLDL) and an increased LDL particle number both of which are risk factors for atherosclerotic disease.[9–11] In addition, observational studies have shown that elevated TG/HDL ratio is predictive of CVD development.[12–15]

NASH is also associated with increased non-HDL-cholesterol (non-HDL-C), a measure of all apolipoprotein-B containing lipoproteins including very low-density lipoproteins (VLDL), intermediate density lipoproteins (IDL), LDL, chylomicrons and lipoprotein (a), which is also a risk factor for CVD.[1617]

While NAFLD and NASH are both associated with an independent risk of CVD as well as an increased risk driven by dyslipidemia, it is unknown whether NASH resolution is accompanied by an improvement in dyslipidemia or whether the associated dyslipidemia

persists and continues to confer an increased CVD risk. The current study is an evaluation of the relationship between the resolution of NASH and dyslipidemia in participants from the Pioglitazone versus vitamin E versus placebo for the treatment of nondiabetic patients with nonalcoholic steatohepatitis (PIVENS) trial.

Materials and Methods

Study Design

Data for this study were obtained from participants in the PIVENS Trial.[18] PIVENS was a NASH treatment trial conducted by the Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN). The PIVENS trial study design has been previously described and the ClinicalTrials.gov identifier is NCT00063622. Briefly, the PIVENS trial evaluated the efficacy of vitamin E 800 units daily, pioglitazone 30mg daily or placebo in individuals without diabetes mellitus with biopsy-proven NASH over a 96 week period. Vitamin E use was associated with a significantly higher rate of improvement in NASH compared to placebo (43% vs. 19%, P=0.001). No difference was seen in the rate of NASH improvement in the pioglitazone arm compared to placebo (34% vs. 19%, P=NS). Both vitamin E and pioglitazone were associated with significant improvement in steatosis and lobular inflammation but neither was associated with an improvement in fibrosis stage. Pioglitazone use was associated with significant weight gain compared to placebo and vitamin E.

Liver Histology

Participants underwent liver biopsies within 6 months of study randomization and at 96 weeks. All biopsies were centrally evaluated by a panel of NASH CRN pathologists. Liver biopsies were assessed using the NAFLD Activity Score (NAS). The NAS is a composite score ranging from 0 to 8 points composed of steatosis (0–3), hepatocyte ballooning (0–2) and lobular inflammation scores (0–3).[19] Fibrosis stage was scored on a scale of 0–4. The presence of NASH was categorized as definite, possible/borderline or absent. Inclusion criteria for PIVENS: 1.) histological evidence of NASH as defined by a NAFLD activity score of 5 or greater (score must be 1 or greater for steatosis, ballooning, and lobular inflammation) and a finding of possible or definite steatohepatitis as judged by the local NASH CRN pathologist or 2.) a NAFLD activity score of 4 (score must be 1 or greater for steatosis, ballooning, and lobular inflammation) as judged by the local NASH CRN pathologist and a finding of definite NASH as judged by the majority of the local pathologist and two additional NASH CRN pathologists. Resolution of NASH was defined as a diagnosis of no steatohepatitis at 96 weeks among those with possible or definite NASH at baseline.

Laboratory Analyses

Fasting serum total cholesterol, HDL, triglyceride and LDL levels were measured locally at baseline and week 96. LDL was measured indirectly. From these measurements, non-HDL-C (Non-HDL-C=total cholesterol – HDL) and combined dyslipidemia of obesity (triglycerides/HDL) were calculated.

Statistical Analysis

This study was designed to determine the prevalence of dyslipidemia in adults with NASH, differences in dyslipidemia by liver histology and the impact of NASH resolution on dyslipidemia.

Mean lipid levels and lipid level elevations are presented as means (95% confidence intervals) or numbers (percents). Simple and multiple linear regression was used to assess the association between resolution of NASH and mean baseline and 96 week lipid levels. In addition, simple and multiple logistic regression analysis was used to assess the association between resolution of NASH and a binary categorization of dyslipidemia (triglycerides>150 mg/dL vs. ≤150 mg/dL; total cholesterol>200 mg/dL vs. ≤200 mg/dL; HDL<40 mg/dL for males or <50 mg/dL for females vs. ≥40 mg/dL for males or ≥50 mg/dL for females; LDL>130 mg/dL vs. ≤130 mg/dL; non-HDL-C≥130 mg/dL vs. <130 mg/dL; and TG/HDL>5.0 vs. ≤ 5.0). Treatment group (Pioglitazone, Vitamin E) versus placebo, baseline body mass index (BMI), ethnicity, age, gender and statin use at baseline and/or at any point during 96 weeks of follow-up were included in the multivariable model. For the comparison of the mean change in lipid levels between groups, P values were derived in the same manner with the addition of baseline value of the lipid measure to the multivariable model. To test whether the association between resolution of NASH and change in lipid levels differed depending on treatment group, an interaction term for treatment group and resolution of NASH was tested for each lipid measure. The Framingham Risk Score (FRS) was calculated for each individual at baseline and week 96. The FRS is a validated score that estimates an individual's 10-year cardiovascular disease risk and includes age, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure and smoking status.[20] The FRS has been validated in individuals with NAFLD.[21] All analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC) and Stata 13.1 (Stata Corp., College Station, TX). Nominal, two-sided *P* values were used and were considered statistically significant if $P<0.05$.

Results

Baseline Characteristics

All individuals in this study have been described in a previous publication.[18] Baseline demographics, anthropometrics, laboratory data and liver histologic characteristics were evenly distributed across treatment groups.

Baseline Lipid Levels

Dyslipidemia was frequent in this cohort at baseline (Table 1). Mean triglyceride level was 164.6mg/dL (95% CI 153.0–176.2) and 46.2% of individuals had triglycerides ≥ 150mg/dL. Mean HDL level was 43.9mg/dL (95% CI 42.4–45.4) with low HDL (defined as <40mg/dL for men or <50mg/dL for women) found in 63.2%. TG/HDL >5.0 was found in 25.1% of subjects. Total cholesterol ≥ 200mg/dL was found in 47.4% of individuals with a mean total cholesterol level of 196.3 mg/dL. Mean LDL level was 121.5mg/dL. While elevated LDL levels were less frequent in this group, with LDL>160mg/dL in 15.8% and LDL>190mg/dL in 5.7% of individuals, elevated non-HDL-C were found in the majority of individuals.

Mean non-HDL-C level was 152.5mg/dL with 72.5% of individuals found to have a non-HDL-C level ≥ 130mg/dL. This suggests that in these individuals with NAFLD, apolipoprotein-B containing lipoproteins including VLDL, IDL, Lp(a) and chylomicrons were frequently elevated.

Lipid Levels and Resolution of NASH

Resolution of NASH was associated with significant improvements in several lipid types (Table 2). Triglyceride levels decreased significantly in those who experienced resolution of NASH compared to those without resolution of NASH (−21.1mg/dL vs. −2.3mg/dL, P=0.03). HDL increased significantly in those with NASH resolution while HDL decreased in those without resolution of NASH (2.9mg/dL vs. −2.5mg/dL, P<0.0001). TG/HDL ratio also improved significantly in those with NASH resolution compared to those without resolution of NASH (−0.7mg/dL vs. 0.1 mg/dL, p=0.003). Individuals with and without NASH resolution had no significant differences in changes in LDL, total cholesterol or non-HDL-C. The proportion of patients with high triglycerides (≥150 mg/dL) decreased significantly in those with NASH resolution compared to those without resolution (45.5% to 31.2% and 49.7% vs. 47.9% respectively, P=0.03. In addition, the proportion of patients with low HDL (<40mg/dL in men or <50 mg/dL in women) was significantly less common in those with NASH resolution than those without resolution of NASH (59.7% to 49.4% vs. 66.2% to 71.8%, respectively, P=0.009).

To determine whether weight change or change in insulin resistance was related to the changes in lipid levels, correlations of these variables were performed (Supplementary Figures 1 and 2). There was no correlation between change in insulin resistance as assessed by homeostatic model of insulin resistance (HOMA-IR) and any lipid type. In addition, no correlation was seen between change in weight over the study duration and change in lipid levels.

Resolution of NASH and Cardiovascular Disease Risk

To determine the impact of NASH resolution on CVD risk, the Framingham Risk Score (FRS) was determine for all individuals at baseline and at 96 weeks. The FRS predicts an individual's 10 year CVD risk and has been validated in individuals with NAFLD.

NASH resolution was associated with a significant decrease in FRS and predicted CVD risk from baseline to 96 weeks when compared to those without resolution of NASH (−0.21 [−0.79, 0.37] vs. 0.72 [0.19, 1.25], P=0.01).

Change in Lipid Levels by Treatment Group

Pioglitazone use has a favorable impact on several lipid types and results in decreases in triglyceride and small dense LDL levels and increases in HDL levels and LDL particle size. In contrast, pioglitazone has a negative impact on LDL level and cholesterol levels, resulting in increases in both.[22, 23] Vitamin E may impact the oxidation of lipoproteins but there is no evidence that vitamin E impacts serum lipid levels. We analyzed the impact of each treatment (vitamin E, pioglitazone and placebo) on lipid levels over the study duration. There was no significant difference in lipids at baseline or change in lipids at 96 weeks

between treatment groups. (Supplementary Table 1). HDL increased in individuals receiving pioglitazone over the study duration but this was not significantly different from those receiving placebo or vitamin E.

Discussion

The present study demonstrates that dyslipidemia, characterized predominantly by elevated non-HDL-C and low HDL levels, is frequent in individuals with NASH. This study also shows that the resolution of NASH is associated with improvements in triglycerides, HDL and TG/HDL ratio. However, no improvements were seen in non-HDL-C, the most frequent form of dyslipidemia in NASH, LDL or total cholesterol levels. Thus, while NASH resolution is associated with improvements in some aspects of dyslipidemia, several important CVD lipid risk markers remain elevated.

The dyslipidemia of NAFLD and NASH has previously been characterized by hypertriglyceridemia, elevated LDL, elevated total cholesterol and low HDL. Our study confirms these findings and demonstrates that in addition to these parameters, non-HDL-C is the most common lipid abnormality seen in patients with NASH in the PIVENS trial. In fact, the present study found that while LDL was less frequently elevated in those with NASH, elevated non-HDL-C levels were found in the majority of individuals with NASH. Non-HDL-C is a powerful marker of CVD risk and can account for otherwise unmeasured apolipoprotein-B containing lipoproteins including LDL particles, VLDL, IDL and chylomicrons. As non-HDL-C is a marker of CVD and a secondary target of lipid lowering therapy, further study is needed to determine the value of this as a target for lipid lowering therapy in individuals in NASH.[17]

In this study the resolution of NASH was associated with significant improvement in HDL. HDL particles remove excess cholesterol from peripheral tissues including the endothelium via the reverse cholesterol transport pathway which may offer protection against the development of atherosclerosis. In addition, HDL has anti-inflammatory properties that decrease atherosclerotic plaque development and instability. Epidemiologically, high HDL levels are associated with decreased CVD risk while low HDL levels are associated with increased CVD risk and increased all-cause mortality.[15,24,25] In fact, a 1 mg/dL increase in HDL is predicted to result in a 2–3% decreased risk of CVD.[26] The improvement in HDL seen in individuals in the PIVENS trial with resolution of NASH may represent an important improvement in CVD risk.

Resolution of NASH was also associated with decreased triglyceride levels and TG/HDL ratio. Triglycerides, in the form of triglyceride-rich lipoproteins (TRL), also play an important role in atherogenesis, contributing to the development of foam cells in atherosclerotic plaques and promoting the expression of pro-inflammatory genes.[9] TRLs may also inhibit the anti-inflammatory properties of HDL.[9] Both triglyceride levels and TG/HDL are directly correlated with CVD risk and CVD-related mortality.[12,13,15,27,28] Improvements in TG and TG/HDL may be associated with decreased CVD risk in this high risk population. This is supported by the decrease in Framingham Risk Score seen in those

with NASH resolution compared to a mean increase in FRS seen in the group without resolution of NASH.

Our data indicate that while TG and HDL improve with resolution of NASH no significant improvement occurs in LDL, total cholesterol or non-HDL-C. These lipid levels are potent predictors of CVD risk and suggest that despite NASH resolution and decreased FRS, these individuals may remain at increased CVD risk and should be targeted for appropriate risk management and lipid lowering therapy. Physicians treating patients with NASH should be aware that ongoing dyslipidemia management may be needed even after NASH resolution.

The impact of the treatments for NASH in this study on lipid levels is an important consideration. Pioglitazone is a member of the thiazolidinedione class of oral hypoglycemics that act to reduce peripheral insulin resistance and hepatic glucose production via activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ). PPAR-γ activation also alters the transcription of genes involved in lipid metabolism.[29] Pioglitazone use is associated with a decline in triglyceride and small dense LDL levels, as well as an increase in HDL levels and LDL particle size. However, total LDL level and total cholesterol also increased with pioglitazone use. [22, 23] In the present study individuals with NASH resolution did experience decreased triglyceride levels and increased HDL which could be explained by pioglitazone use. However, individuals with NASH resolution who received placebo or vitamin E also experienced these decreases suggesting that the improvements in these lipids was independent of pioglitazone use.

This study has several important limitations. In the present study, the chronology of events is unknown: does an improvement in NASH histology lead to an improvement in HDL and triglyceride levels or do improvements in lipids contribute to NASH resolution? This study describes an association with NASH resolution and improvement in lipids but cannot evaluate causality. However, we hypothesize that resolution of NASH is the driver of improved lipid levels based on treatment trials of NASH using lipid lowering agents. Fibrates, which lower triglycerides and increasing HDL levels, have been evaluated for the treatment of NASH. Fenofibrate given for 48 weeks to individuals with biopsy-proven NAFLD significantly decreased triglyceride levels.[30] However, there was no improvement in hepatic steatosis, NAS, lobular inflammation or fibrosis. Further, a second trial of clofibrate for NASH, again improved triglyceride levels but did not demonstrate any histologic improvement.[31] This could suggest that decreasing triglyceride levels does not result in the resolution of NASH. The interplay between lipid metabolism is complex and the treatments in this study may increase fatty acid oxidation and reduce oxidative stress thus leading to an improvement in NASH and improvements in triglyceride levels. Further prospective study is needed to delineate the mechanisms associated with NASH resolution.

In addition, our study is limited by the use of surrogate markers, lipids levels, for CVD. Long term follow-up is needed to determine the impact of resolution of NASH on CVD events and CVD-related mortality. Finally, the present study could only determine whether individuals were currently on statin therapy and data was not available on previous statin use or duration of use which may impact current lipid levels.

In summary, we have demonstrated that dyslipidemia, most frequently elevated non-HDL-C, is common in individuals with NASH. We have also shown that resolution of NASH is associated with improvement in TG, HDL and TG/HDL ratio but not in non-HDL-C, total cholesterol and LDL levels suggesting that NASH resolution may improve some degree of CVD risk but that residual lipid risk factors remain. Further studies will be needed utilizing direct measurement of apolipoprotein levels, lipoprotein subfractions and proteins involved in lipid metabolism to determine the exact lipid species and metabolic changes driving the high levels of non-HDL-C at baseline and to understand why TG and HDL improve while LDL, total cholesterol and non-HDL-C remain high after resolution of NASH. Understanding the mechanism by which resolution of NASH is associated with improvement in HDL and triglyceride levels will provide new insights into possible treatments for both NASH and its associated dyslipidemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix

The following members of the Nonalcoholic Steatohepatitis Clinical Research Network were instrumental in the design and conduct of PIVENS trial.

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Table 1

Baseline lipid levels and proportion of individuals with dyslipidemia among adults in the PIVENS Trial (N=247)

Lipid type and cutoff for dyslipidemia	Baseline
Total cholesterol (mg/dl)	
Mean (95% CI)	196.3 (191.4–201.2)
≥200 mg/dL, N (%)	117 (47.4%)
Triglycerides (mg/dL)	
Mean (95% CI)	164.6 (153.0–176.2)
≥150 mg/dL, N (%)	114 (46.2%)
HDL (mg/dL)	
Mean (95% CI)	43.9 (42.4–45.4)
<40 mg/dL (males)/<50 mg/dL (females), N (%)	156 (63.2%)
LDL (mg/dL)	
Mean (95% CI)	121.5 (117.2–125.8)
>130 mg/dL, N (%)	104 (42.1%)
Non-HDL-C (mg/dL)	
Mean (95% CI)	152.4 (147.6–157.1)
≥130 mg/dL, N(%)	179 (72.5%)
Triglycerides/HDL	
Mean (95% CI)	4.2 (3.8–4.6)
>5.0, N (%)	62 (25.1%)

Table 2

Changes in lipid levels in individuals with and without resolution of NASH (N=222)

Lipid type and cutoff for dyslipidemia	Resolution of NASH at 96 weeks		P*	Adjusted P†
	Resolved (N=77)	Not resolved (N=145)		
Total cholesterol (mg/dL)				
Mean (95% CI)				
Baseline	192.0 (182.4, 201.5)	200.9 (194.8, 207.0)	0.10	0.17
96 weeks	185.7 (176.1, 195.4)	186.9 (180.7, 193.1)	0.83	0.98
Change from baseline	−6.2 (−14.7, 2.2)	−14.3 (−20.2, −8.4)	0.12	0.31
N (%) >200 mg/dL				
Baseline	36 (46.8%)	72 (49.7%)	0.68	0.96
96 weeks	26 (33.8%)	50 (35.2%)	0.83	0.77
Change from baseline among dyslipidemics (N=107)			0.74	0.94
High at BL/High at 96 wks	21 (58.3%)	39 (54.9%)		
High at BL/Normal at 96 wks	15 (41.7%)	32 (45.1%)		
Triglycerides (mg/dL)				
Mean (95% CI)				
Baseline	158.9 (136.3, 181.4)	174.3 (159.4, 189.3)	0.25	0.29
96 weeks	137.8 (121.9, 153.7)	172.1 (155.8, 188.3)	**0.007**	**0.02**
Change from baseline	−21.1 (−37.1, −5.1)	−2.3 (−13.8, 9.2)	0.06	**0.03**
N (%) ≥150 mg/dL				
Baseline	35 (45.5%)	72 (49.7%)	0.56	0.79
96 weeks	24 (31.2%)	68 (47.9%)	**0.02**	**0.02**
Change from baseline among dyslipidemics (N=104)			**0.046**	0.07
High at BL/High at 96 wks	19 (54.3%)	51 (73.9%)		
High at BL/Normal at 96 wks	16 (45.7%)	18 (26.1%)		
HDL (mg/dL)				
Mean (95% CI)				
Baseline	44.4 (41.7, 47.2)	43.2 (41.4, 45.1)	0.46	0.41
96 weeks	47.4 (43.6, 51.1)	40.7 (39.1, 42.4)	**<0.001**	**<0.001**
Change from baseline	2.9 (0.4, 5.5)	−2.5 (−3.8, −1.2)	**<0.001**	**<0.0001**
N (%) <40 mg/dL (<50 fem.)				
Baseline	46 (59.7%)	96 (66.2%)	0.34	0.83
96 weeks	38 (49.4%)	102 (71.8%)	**0.001**	**0.009**
Change from baseline among dyslipidemics (N=140)			**0.005**	**0.009**
Low at BL/Low at 96 wks	32 (69.6%)	84 (89.4%)		
Low at BL/Normal at 96 wks	14 (30.4%)	10 (10.6%)		
LDL (mg/dL)				
Mean (95% CI)				
Baseline	117.1 (109.0, 125.2)	125.3 (119.8, 130.8)	0.09	0.15
96 weeks	112.0 (103.9, 120.1)	115.2 (109.7, 120.8)	0.50	0.73

Lipid type and cutoff for dyslipidemia	Resolution of NASH at 96 weeks		P*	Adjusted P†
	Resolved (N=77)	Not resolved (N=145)		
Change from baseline	−4.9 (−12.3, 2.6)	−10.7 (−16.3, −5.1)	0.22	0.45
N (%) >130 mg/dL				
Baseline	29 (37.7%)	66 (45.5%)	0.26	0.39
96 weeks	19 (24.7%)	43 (30.3%)	0.38	0.49
Change from baseline among dyslipidemics (N=95)			0.77	0.42
High at BL/High at 96 wks	15 (51.7%)	32 (48.5%)		
High at BL/Normal at 96 wks	14 (48.3%)	34 (51.5%)		
Non HDL-C (mg/dL)				
Mean (95% CI)				
Baseline	147.5 (138.1,157.0)	157.7 (151.9,163.5)	0.06	0.10
96 weeks	138.4 (129.0,147.7)	146.2 (140.3,152.1)	0.14	0.25
Change from baseline	−9.2 (−17.1, −1.3)	−11.8 (−17.5, −6.2)	0.58	0.89
N (%) ≥130 mg/dL				
Baseline	54 (70.1%)	112 (77.2%)	0.25	0.24
96 weeks	44 (57.1%)	98 (69.0%)	0.08	0.10
Change from baseline among dyslipidemics (N=164)			0.39	0.73
High at BL/High at 96 wks	40 (74.1%)	88 (80.0%)		
High at BL/Normal at 96 wks	14 (25.9%)	22 (20.0%)		
Triglycerides/HDL				
Mean (95% CI)				
Baseline	4.1 (3.3, 4.8)	4.4 (4.0, 4.9)	0.40	0.36
96 weeks	3.4 (2.8, 3.9)	4.6 (4.1, 5.1)	**0.003**	**0.004**
Change from baseline	−0.7 (−1.2, −0.2)	0.1 (−0.2, 0.5)	**0.009**	**0.003**
N (%) >5.0				
Baseline	20 (26.0%)	39 (26.9%)	0.88	0.58
96 weeks	17 (22.1%)	42 (29.6%)	0.23	0.25
Change from baseline among dyslipidemics (N=58)			0.40	0.41
High at BL/High at 96 wks	12 (60.0%)	27 (71.1%)		
High at BL/Normal at 96 wks	8 (40.0%)	11 (29.0%)		

*P-values derived from simple linear or logistic regression models.

†Adjusted p-values derived from multiple linear or logistic regression models and included treatment group, age at biopsy (years), gender, baseline BMI, ethnicity, statin use at baseline and/or during follow-up, and for change measures, the baseline value of the lipid measure.