Paradoxical Reduction in HDL-C with Fenofibrate and Thiazolidinedione Therapy
In Type 2 Diabetes: the ACCORD Lipid Trial
(10/28/13 Revision)

Short running title: ACCORD Lipid - Paradoxical Reduction in HDL-C

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Abstract

Objective. To determine the occurrence of extremely low HDL-C among participants in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial and to examine the relationship of this finding with treatment with fenofibrate and thiazolidinedione (TZD).

Research Design and Methods. The ACCORD Lipid Trial was a randomized double blind placebo controlled study conducted in patients with type 2 diabetes at 77 clinical centers across the United States and Canada in a 5,518 patient sub-set of the larger 10,251 ACCORD Glycemia Trial. Patients were enrolled from January 11, 2001 until October 29, 2005 and followed until end of study visits between March 1 and June 30, 2009. Follow-up in ACCORD Lipid was 4 to 8 years (mean 4.7 years). Patients were treated with blinded fenofibrate or placebo on a background of simvastatin therapy. The main outcome measures for these descriptive, post hoc analyses was the occurrence of extremely low HDL-C (defined as < 25 mg/dl [0.647 mmol/L]) during the trial.

Results. Among ACCORD Lipid Trial participants, the occurrence of extremely low HDL-C ever during study follow-up was 106% higher among those randomized to fenofibrate (10.1% fenofibrate vs. 4.9% placebo; P<0.001). The occurrence of low HDL-C was associated with concurrent treatment with fenofibrate and TZD (7.0% for both vs. 2.2% for neither at 48 months post-randomization).

Conclusions. Idiosyncratic and marked reduction in HDL-C can occur in some patients treated with both fenofibrate and TZD. Practitioners should recognize this important potential idiosyncratic reaction and take appropriate corrective action.


Abstract Word Count: 248
The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a National Heart, Lung, and Blood Institute (NHLBI) funded study that evaluated the effect of intensive control of blood glucose, blood pressure and lipoproteins on cardiovascular risk in patients with Type 2 Diabetes (1). Embedded within the overall ACCORD trial was a lipid treatment trial in which study participants were randomized to receive either fenofibrate or placebo administered with background LDL-C lowering therapy with simvastatin. During the trial the new onset of a marked reduction in HDL-C levels among some Lipid Trial participants was noted. Individual cases have been reported in the literature of paradoxical substantial reductions in HDL-C of up to 50% in patients receiving fenofibrate, thiazolidinedione (TZD) or both (2-5). Using data collected in the ACCORD Lipid Trial we examined the relationship between concomitant administration of fenofibrate and TZD, primarily rosiglitazone, and the occurrence of low HDL-C.

Research Design and Methods

The rationale, design, and primary results of the ACCORD Lipid have been previously reported (1,6-8). Overall in ACCORD, 10,251 participants were randomly assigned to receive either intensive glycemic control (targeting an HbA1C value below 6.0% [42 mmol/mol]) or standard therapy (targeting an HbA1C of 7.0 to 7.9% [53 to 63 mmol/mol]) (1). Employing a double 2X2 factorial design, 4,733 of ACCORD participants were also enrolled in the ACCORD
Blood Pressure trial and 5,518 were enrolled in ACCORD Lipid. The hypothesis tested in the Lipid Trial was whether combination treatment with fenofibrate (to both raise HDL-C and lower triglyceride levels) and a statin (to reduce LDL-C) would reduce CVD event rates in high-risk people with type 2 diabetes mellitus compared with treatment with only a statin (1).

After institutional review board approval, participants were recruited from 77 clinical centers across the United States and Canada. All Lipid Trial participants were treated with simvastatin 20-40 mg per day and were then randomly assigned to receive fenofibrate or matching placebo in a double-blind design. Clinic personnel were blinded to lipid measurements throughout the trial. Randomizations occurred from January 11, 2001 until October 29, 2005 using permuted blocks to maintain allocation concealment. End of Study Visits were scheduled between March 1 and June 30, 2009. Follow-up in ACCORD Lipid was 4 to 8 years with a mean of 4.7 years. To be eligible for ACCORD, participants had documented T2DM and a glycated hemoglobin level of 7.5% or more, and either were age 40-79 years with evidence of clinical CVD or age 55-79 years with evidence of subclinical CVD or at least two additional CVD risk factors. Participants were eligible for the embedded ACCORD Lipid Trial if they met the following additional entry criteria using lipid measurements obtained within the previous year: (1) an LDL-C between 60 and 180 mg/dl, inclusive; (2) HDL-C less than 55 mg/dl for women and Blacks, or less than 50 for all other groups; and (3) triglycerides less than 750 mg/dl if not on a lipid medication or less than 400 mg/dl if on a lipid medication. Among the ACCORD Lipid exclusion criteria were the use of a medication known to interact with statins or fibrate; history of pancreatitis, myositis/myopathy, or gallbladder disease; and refusal to discontinue any current lipid-altering treatment.

Open-labeled simvastatin therapy began at the randomization visit and the blinded fenofibrate/placebo medication was initiated one month later. The initial dose of simvastatin complied with current national lipid guidelines at the time the study began and was modified over time in response to changing guidelines (7). The maximum daily dose of simvastatin used was 40 mg (7). At the beginning of the trial, the initial dose of fenofibrate was 160 mg/day. Because of an observed rise in serum creatinine in some participants on fenofibrate, the dose of fenofibrate was reduced to 48 mg/day in individuals with an estimated glomerular filtration rate of, 50 ml/min/m² or less (9). Whereas rosiglitazone was the predominant TZD used in ACCORD, the analyses presented here also represent limited use of pioglitazone (e.g., only 23 participants were on the combination of pioglitazone and fenofibrate at post-randomization month 24, and only 72 were on the combination at month 48).

In the Lipid trial, a blinded fasting plasma lipid profile was measured at the ACCORD Central Laboratory at baseline, 4, 8, 12 months post-randomization, annually thereafter, and at study end. During follow-up, some participants obtained unblinded lipid measurements from their private health care providers and informed ACCORD clinic staff of low HDL-C values, which sometimes occurred after the initiation of a TZD
for the Glycemia Trial. After review of unblinded analyses by the ACCORD Data and Safety Monitoring Board (DSMB), an alert system was put in place for clinic personnel to be notified by the ACCORD Central Laboratory if a participant had an extremely low HDL-C (defined as an HDL-C consistently less than 20 mg/dl [517 mmol/L]) during ACCORD study follow-up.

The pre-specified primary outcome for all ACCORD trials was the first post-randomization occurrence of a major cardiovascular event, specifically nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. All-cause mortality was a pre-specified secondary outcome. Deaths, myocardial infarctions, and strokes were adjudicated by a central committee whose members were unaware of treatment group assignment (1,10).

All analyses were conducted at the Coordinating Center with the use of S-Plus software, version 8.0 (Insightful) or SAS software, version 9.3 (SAS Institute). The post-randomization occurrence and prevalence (at selected visits) of low HDL-C was examined with simple counts and percent of participants by ACCORD trial, treatment group, and (within the Lipid Trial) TZD use. A HDL-C cutoff of < 25 mg/dl (< 0.647 mmol/L) was chosen prior to the initiation of analyses. All analyses were repeated with a cutoff of < 20 mg/dl (< 0.517 mmol/L) to assess the sensitivity of our results. In an exploration of how Lipid Trial participants who ever had a low HDL-C during follow-up differed from all other lipid participants, baseline characteristics were compared using chi-square tests and two-sample t-tests. Two multivariate generalized linear regression models were used to examine the relationship between medication use (fenofibrate and TZDs) and 24- and 48-month post-randomization HDL-C levels, with the interaction term “Lipid Treatment Assignment X TZD use at time of blood draw” as the primary independent variable of interest and controlling for Lipid Trial treatment assignment, current TZD use, and other covariates identified in the baseline comparison analysis: gender, age in years, race (white/non-white), and baseline values of HDL-C, LDL-C, triglycerides, and HbA1c. The analyses presented are for descriptive and exploratory purposes, and are hypothesis generating only. No adjustments were made for multiple testing. Nominal P values are reported throughout as simple guides to possible associations.

Results

Restricting lipid measurements to those obtained at the annual visits (common to all ACCORD participants), 627 (6.1%) of all 10,251 randomized ACCORD participants had an
HDL-C reported by the Central Laboratory as being less than 25 mg/dl (<0.647 mmol/L) at an annual follow-up visit (Table 1). There was no difference in the post-randomization occurrence of low HDL-C between the glyceria treatment groups (6.1% Intensive vs. 6.2% Standard; p=0.83) or between the blood pressure treatment groups (4.8% Intensive vs. 4.2% Standard; p=0.28). However, a greater proportion of Lipid Trial participants had a low HDL-C recorded at a follow-up annual visit compared with Blood Pressure Trial participants (7.5% Lipid vs. 4.5% Blood Pressure; p<0.001). Among Lipid Trial participants, the occurrence of low HDL-C was 106% higher among those randomized to fenofibrate (10.1% fenofibrate vs. 4.9% placebo; P<0.001). Because ACCORD Lipid participants had additional measurements at 4 and 8 months, the occurrence of any follow-up visit low HDL-C was re-examined; 561 of the 5518 ACCORD Lipid participants at an HDL-C < 25 mg/dl at some point during follow-up: 364 (13.2%) in the fenofibrate group and 197 (7.2%) in the placebo group.

Given the prior reports of iatrogenic lowering of HDL-C with concomitant fenofibrate and TZD treatment (2,4,5,11-13), we examined the cross-sectional prevalence of low HDL-C among Lipid Trial participants at baseline (prior to initiation of fenofibrate treatment) and at post-randomization Months 24 and 48, stratified by fenofibrate treatment assignment and TZD use at each time point (Table 2). At baseline there was no difference in the prevalence of low HDL-C between the assigned lipid treatment groups (2.1% for those subsequently assigned to fenofibrate vs. 2.4% assigned placebo) or between those on (1.5%) or not on a TZD (2.4%). However, at both Months 24 and 48, the prevalence of a low HDL-C was generally twice as great for participants randomized to fenofibrate compared to placebo, (5.1% vs 2.5% and 5.1% vs 2.3% at months 24 and 48 post-randomization, respectively), but these higher proportions were due to the increases in low HDL-C in the groups receiving fenofibrate and TZD (e.g., 7.2% for participants on both medications compared to 2.2% for those on only fenofibrate at Month 24 and 7.0% for those on both medications compared to 3.6% for those only on fenofibrate at Month 48). Indeed, the prevalence of HDL-C < 25 mg/dl did not increase significantly in the groups not receiving a TZD (Table 2). To assess the sensitivity of our results, all the above analyses were repeated with a cutoff of <20 mg/dl and the trends were found to be the same.

Because low HDL-C levels were associated with fenofibrate and/or TZD use, the overall effects of these medications on HDL-C were examined in two covariate-adjusted linear regression analyses predicting HDL-C levels at Months 24 and 48, with the interaction term “Lipid Treatment Assignment X TZD use at time of blood draw” as the primary independent variable of interest (Table 3). Examination of the regression coefficients for Month 24 (Model 1) indicated that (1) in the absence of a TZD, fenofibrate was associated with a 1.42 mg/dl (0.037 mmol/L) higher HDL-C, (2) in the absence of fenofibrate, TZD use was associated with a 1.48 mg/dl (0.038 mmol/L) higher HDL-C, and (3) the combination of fenofibrate/TZD use was associated with a 1.53 mg/dl (0.040 mmol/L) higher HDL-C compared to being on neither. At the 48-month visit, the same general trends existed, although there was a suggestion that TZD use alone was associated with a greater increase (2.13 mg/dl [0.055 mmol/L]) in HDL-C than fenofibrate alone (0.72 mg/dl increase [0.019 mmol/L]).

Results of "average" HDL-C levels at various timepoints can be misleading when HDL-C values or changes in HDL-C values are widely distributed in a population. To explore this, we
compared the distribution of HDL-C values at the 24 and 48 month post-randomization visits among participants on placebo/no TZD versus those on fenofibrate alone, TZD alone, or on both (Figure). At both time points and compared with those on placebo/no TZD, there was a shift toward higher HDL-C values in study participants treated with fenofibrate, TZD, or both. However, a greater proportion of participants on the fenofibrate/TZD combination had lower HDL-C levels at both follow-up visits compared to all other participants. For example at month 24 (as shown in the left tails of Figure and in Table 2), 7.1% of the participants on the combination had an HDL-C value of 25 mg/dl or less compared to 2.4% of all other participants. In addition to these observations regarding the actual HDL-C values at these follow-up visits, these patterns remained when the absolute changes in HDL-C from baseline to 24 or 48 months were examined in the four medication groups (Supplement Figure).

To gain further insight into the potential relevance of the observed changes in post-randomization HDL-C levels, we examined in the four medication groups the prevalence of a 30% relative reduction in HDL-C from baseline to the 24 and 48 month follow-up visits, as well as the coincident prevalence of HDL-C <25 mg/dl and a 30% reduction (Supplemental Table). In both analyses, it was clear that the combination of fenofibrate and TZD was associated with about 5-fold increases in the prevalence of these outcomes.

In order to determine if iatrogenic reductions in HDL-C might be associated with increased risk of CVD events, post-randomization analyses examined the effect of fenofibrate and low HDL-C values on all-cause mortality. Consistent with the known inverse relationship between HDL-C and CVD risk, overall with both lipid treatment groups combined, all-cause mortality was 35% higher in the participants who ever had a post-randomization HDL-C < 25 mg/dl compared to those who did not (10.0 deaths/100 participants vs. 7.4/100 respectively). This 35% increase in mortality was true regardless of whether the participants were assigned to the fenofibrate group (9.6% vs. 7.0%) or to the placebo group (10.7% vs. 7.8%).

Conclusions

Treatment of patients with diabetes and other chronic diseases often involves complex medical regimens. We tend to evaluate pharmacological interventions by concentrating on the biological effects of a single agent on the disease process and often fail to recognize drug-drug interactions. Fenofibrate would be expected to ameliorate diabetic dyslipidemia by lowering triglycerides and raising HDL-C. Similarly, modest increases in HDL-C have been reported with TZD use (14, 15). In this descriptive post hoc analysis of the ACCORD Lipid Trial population as a whole, fenofibrate exhibited the expected effect with an increase in mean HDL-C when compared with baseline. TZD use was also associated with a modest overall increase in HDL-C, as was the combination of the two agents (Table 3). Supplementing the observations of these average responses, however, we also observed a dramatically divergent HDL-C response in the tails of the distribution to combined fenofibrate and TZD treatment. As presented in the Figure, a greater proportion of participants on the combination (18.2%) at 24 months had an HDL-C of up to 50 mg/dl (1.293 mmol/L) compared to only 13.8% of all other participants. But, at the other
of the distribution, a greater proportion of the same group of participants (7.1%) also had an HDL-C of 25 mg/dl or less compared to only 4% of all other participants.

Aside from concomitant TZD treatment, low HDL-C at baseline, a history of coronary heart disease, and the baseline prevalence of lower alcohol intake, were factors associated with low HDL-C levels during ACCORD follow-up (data not shown). Because of the approach used to assess the prevalence of low HDL-C in this study favors selection of participants whose baseline HDL-C was low and therefore more likely to fall below 25 mg/dl, it is difficult to attribute these factors as contributing to iatrogenic reduction in HDL-C or as predictors of paradoxical response to fenofibrate. A prior study of 43 patients with fenofibrate related reduction in HDL-C found only low baseline HDL-C as a predictor of fenofibrate response (16), however, this analysis has a similar bias to our own. Thus it appears that paradoxical reduction in HDL-C in a subset of patients treated with concomitant TZD and fenofibrate is truly an idiosyncratic reaction that is difficult to predict.

For simple analytic purposes we defined extremely low HDL-C as a level lower than 25 mg/dl. Although this analysis clearly conveys the prevalence of extremely low HDL-C among study participants it does bias toward selection of participants whose HDL-C was lower at baseline and therefore more likely to fall below the 25 mg/dl threshold at the follow-up visits. Given the similar baseline HDL-C levels of study participants, it is important to note that the occurrence of excess cases of extremely low HDL-C was seen in study participants randomized to fenofibrate either alone or, in particular, in combination with TZD. In all, as compared to those randomized to fenofibrate placebo, the proportion of Lipid Trial participants who ever had an extremely low HDL-C during ACCORD was more than two times greater among those randomized to fenofibrate compared to those randomized to placebo (10.1% vs 4.9%, Table 1). Further analysis indicates that the majority of these cases occurred among those concurrently treated with fenofibrate and a TZD (Table 2). These data suggest that iatrogenic lowering of HDL-C could occur with a frequency of up to 5% or 1 in 20 patients with T2DM who are treated with combined fenofibrate and TZD therapy. This prevalence was supported by alternative analyses that determined the number of ACCORD participants experiencing a significant (30%) decrease in HDL-C from baseline and those experiencing a coincident 30% decrease in HDL-C and a follow-up HDL-C of less than 25 mg/dl (Supplemental Table). These findings are particularly significant in that the number of cases reported here are greater than all previous case reports combined and allows a determination of the prevalence of this idiosyncratic reaction. Also, since this was a randomized controlled trial of fenofibrate therapy, study participants were randomly assigned to fenofibrate treatment regardless of baseline HDL-C levels thereby reducing the potential for selection bias.

Although our analyses cannot exclude the possibility that paradoxical lowering of HDL-C also occurred in some patients treated with either fenofibrate or TZD alone, there was no increase in overall prevalence of low HDL-C in groups not receiving TZD compared to baseline (Table 2), suggesting the risk of such HDL-C lowering was greatest in those receiving both agents. This finding is concordant with the findings of a prior retrospective pharmacoepidemiologic survey of diabetic patients (17). On the other hand, although most case reports of HDL-C lowering involved combined treatment with fibrate and TZDs (5,11-13,16,18),
this effect has also been observed with either TZD or fibrate treatment alone (5,16). Although rosiglitazone was the predominant TZD used in the ACCORD Lipid Trial, paradoxical HDL-C lowering has also been reported with other TZDs, including pioglitazone (5). (As noted above, pioglitazone use in ACCORD was too low to allow us to analyze the effects of each TZD separately.) Similarly, decreased HDL-C has also been reported with other fibrates (ciprofibrate and bezafibrate) with the sole exception being gemfibrozil (5). These case reports have shown that HDL-C returns to baseline levels following discontinuation of either fibrate or TZD (11,18). Notably, HDL-C levels increased above 25 mg/dl in 73.1% of these ACCORD study participants following receipt by the site investigator of a lab alert containing instructions to discontinue TZD and/or fenofibrate.

Although apolipoprotein A-I (ApoA1) levels were not assessed in ACCORD, other case reports have noted concomitant reduction in ApoA1 with reduced HDL-C indicating decreased HDL-C particle number in addition to reduced cholesterol content of HDL-C (12). These findings highlight the biological diversity in response to medical interventions and clearly raise the question of how drug-drug interactions may play a role in clinical responses.

The idiosyncratic occurrence of paradoxical lowering of HDL-C with fibrate and/or TZD suggests that some individuals may be predisposed to this effect, possibly due to polymorphism(s) of one or more genes related to HDL-C metabolism. Fibrates increase ApoA1 production in the human via activation of a PPAR response element (PPRE) in the ApoA1 promoter (19). In contrast, ApoA1 promoters which lack a functional PPRE, either due to species variation or experimental manipulation, are negatively regulated by fibrates (20-22). Accordingly, mutation in the ApoA1 gene or alternatively, the PPARα nuclear receptor itself may underlie genetic susceptibility to paradoxical HDL-C lowering with fibrate treatment. Alternatively, paradoxical lowering of HDL-C could also result from altered expression of genes related to HDL-C catabolism, for example the scavenger receptor B1 (SRB1), Lecithin:Cholesterol acyltransferase (LCAT) or Cholesteryl ester transfer protein (CETP) (23). Relevant to this issue is an interesting study reported a paradoxical, but reproducible decrease of HDL-C in a patient after ciprofibrate treatment which was exclusively due to an increased catabolism (24).

Although gene polymorphisms involving the ApoAI/C3/A4/A5 gene cluster, PPARα, ApoE and Lipoprotein Lipase have been associated with altered lipoprotein response to fenofibrate (25-27), no gene polymorphism has been specifically linked to paradoxical lowering of HDL-C with fibrate. Whereas our findings might implicate the combination of PPARα/γ ligands in paradoxical lowering of HDL-C, it is interesting to note that this effect has not been described among dual PPARα/γ agonists currently in development (28-29).

Epidemiological studies have long shown an increased risk of cardiac events associated with lower HDL-C. In a recent observational cohort study of 30,067 patients with type 2 diabetes mellitus, Nichols et al. used a categorical analysis centered on baseline HDL-C to show that a >6.5 mg /dl decrease in HDL-C was associated with a 11% increase in CVD risk (30). Given the vigilance of ACCORD investigators, the observed fall in HDL-C in select patients was noted early on in the study and then carefully analyzed by the DSMB at each of their meetings. In addition, investigators were notified of participants with extremely low HDL-C values and
advised to discontinue either TZD or fenofibrate/placebo. When examined in crude, post-randomization post hoc analyses, we observed that all-cause mortality was higher in the group of patients who ever had an HDL-C < 25 mg/dl compared with those who did not, which is not entirely unexpected, given the higher prevalence of coronary disease and lower baseline HDL-C in this group. However, this finding was true regardless of whether they were treated with fenofibrate or placebo. Thus we were unable to detect an adverse effect of fenofibrate-related reduction in HDL-C. It is important to note that the study was not designed or powered to evaluate the impact of this unexpected response to treatment on mortality. Nevertheless, these observations should alert practitioners to the potential for paradoxical reduction in HDL-C with fenofibrate treatment, especially when used concomitantly with a TZD. Although the mechanism of iatrogenic reduction in HDL-C with combined fenofibrate and TZD treatment is unknown and there is as yet no definitive proof of lack of harm, if the magnitude of the reduction in HDL-C is significant it may be appropriate to discontinue either fenofibrate or the TZD, and monitor HDL-C levels to confirm return to baseline levels.
Acknowledgments

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Conflict of Interest Disclosures: All authors have completed and submitted to Dr. Byington (in February/March 2013) the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr. Linz reported that he owns common stock from Pfizer, Novartis, Astra-Zeneca, and Roche. Dr. Byington reported that he is a member of a Data Safety Monitoring Board for Eli Lilly. Dr. O’Connor reported that he received (or may receive) funding from NIH and that he and his institution may receive monies, royalties and stocks from Diabetes Decision Support for patent. Dr. Leiter reported that he received consultant fees from Astra-Zeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Novo Nordisk, Sanofi, Servier, Roche, Amgen, Takeda, and GlaxoSmithKline; Dr. Leiter also received (or may receive) payments for grant work for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novartis, Novo Nordisk, Sanofi, GlaxoSmithKline, Roche, and Amgen; Dr. Leiter also received payments for lectures for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi, and Novartis; Dr. Leiter also received payment for the development of educational presentations for AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, and Novartis. Dr. Weiss reported receiving consulting fees from Sanofi-Aventis; Dr. Weiss also received (or will receive) payments for grant work for Mannkind, Bristol-Myers Squibb, Keryx, Eisai, Intekrin Therapeutics, Orexigen Therapeutics, Boehringer Ingelheim, Sanofi-Aventis, Amylin, Novo Nordisk, NephroGenex, Genzyme/Isis, Amarin, Roche, Weight Watchers International, Eli Lilly, Reata Pharmaceuticals; Dr. Weiss has also received payment for lectures for Amarin, GlaxoSmithKline, Bristol-Myers Squibb, AstraZeneca, Takeda, Sanofi Aventis, Eli Lilly, Novo Nordisk, Santarus, and Vivus, and has received payment for developing educational materials for the American Association of Clinical Endocrinologists; Dr. Weiss also owns stock in Bristol-Myers Squibb and Sanofi-Aventis. Dr. Force reported that he has grant funding from Sanofi Aventis, Amylin, and Merck. Dr. Ismail-Beigi reported that he has received payments for consulting for Novo Nordisk, and he has grants with NIH and Novo Nordisk; Dr. Ismail-Beigi also has stock with Thermalin. Dr. Ginsberg reported that he received consultant fees from Merck, Pfizer, AstraZeneca, Bristol-Myers Squibb, Novartis, Boehringer Ingelheim, Sanofi, Regeneron, Amgen, Roche-Genetech; Dr. Ginsberg also had (or will have) grant funding from Merck, Genzyme Sanofi, and Regeneron Sanofi. Dr. Elam reported he received consultant fees from
Abbott and that he received lecture payments from Merck Schering Plough and Abbott-Solvay. Ms. Lovato and Drs. Crouse, Papademetriou, and Simmons reported having no disclosures.

Dr. Byington is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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References


Figure Legend

Figure 1 - Cumulative percent of participants at months 24 (A) and 48 (B) post-randomization follow-up visits with an HDL-C that is equal to or less than the value specified on the X-axis, by lipid treatment group assignment and use of a TZD at time of visit-specific blood draw. 88% (64%) of all randomized Lipid Trial participants were available for this analysis at Month 24 (at Month 48). Abbreviations: TZD, thiazolidinedione; Mn, Mean HDL-C value in group at visit in mg/dl; N, number of participants in group. To convert HDL-C to millimoles per liter, multiply by 0.02586.
Table 1 - Number (%) of ACCORD participants who ever had a post-randomization HDL-C recorded at an annual follow-up visit that was <25 mg/dl (<0.647 mmol/L), by trial and treatment group assignment*

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</tbody>
</table>

*Data are presented as number (%). Denominators are the cell- or marginal-specific numbers of randomized participants. There were 10,251 participants in the Glycemia Trial, 4733 in the Blood Pressure Trial, and 5518 in the Lipid Trial. Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes.
Table 2 - Number (%) of ACCORD Lipid Trial participants who had an HDL-C < 25 mg/dl (<0.647 mmol/L) at baseline and 24 and 48 month post-randomization visits, by treatment group and TZD use at visit-specific blood draws*

<table>
<thead>
<tr>
<th>On TZD at Visit-specific Blood Draw?</th>
<th>At Baseline (Randomization) Visit (N=5480 with HDL-C value and TZD use data)</th>
<th>At 24 Month Post-RZ Visit (N=4852 with HDL-C value and TZD use data)</th>
<th>At 48 Month Post-RZ Visit (N=3531 with HDL-C value and TZD use data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Fenofibrate</strong></td>
<td><strong>Placebo</strong></td>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Yes</td>
<td>6/457 (1.3%)</td>
<td>8/489 (1.6%)</td>
<td>14/946 (1.5%)</td>
</tr>
<tr>
<td>No</td>
<td>52/2288 (2.3%)</td>
<td>59/2246 (2.6%)</td>
<td>111/4534 (2.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>58/2745 (2.1%)</td>
<td>67/2735 (2.4%)</td>
<td>125/5480 (2.3%)</td>
</tr>
</tbody>
</table>

*Data are presented as number (%). Denominators for percents are the cell-specific numbers of lipid trial participants who had an HDL-C measurement at the specified visit and for whom the concomitant use or nonuse of a TZD was recorded on study forms. Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; TZD, thiazolidinedione; RZ, randomization
Table 3 – Covariate adjusted mean differences in post-randomization HDL-C values among Lipid Trial treatment and TZD groups, relative to being on neither. Results from two multiple generalized linear regression models predicting HDL-C levels at 24 and 48 months post-randomization.*

<table>
<thead>
<tr>
<th>On TZD at Visit-specific Blood Draw?</th>
<th><strong>Model 1: Predicted HDL-C differences at 24 month post-randomization visit</strong> (Number of Participants in Model = 4824)</th>
<th><strong>Model 2: Predicted HDL-C differences at 48 month post-randomization visit</strong> (Number of Participants in Model = 3509)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td><strong>Fenofibrate</strong></td>
<td>+1.52 (P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td><strong>Placebo</strong></td>
<td>+1.48 (P&lt;0.001)</td>
</tr>
<tr>
<td>No</td>
<td><strong>Fenofibrate</strong></td>
<td>+1.42 (P&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td><strong>Placebo</strong></td>
<td>0.00 (reference cell)</td>
</tr>
</tbody>
</table>

* Covariates in each model are Lipid Trial Treatment Group Assignment, TZD use at time of visit-specific blood draw, Fenofibrate X TZD Use Interaction, and baseline age, race, HbA1c, LDL-C, Triglyceride, and HDL-C. P-values reflect differences between cell-specific mean HDL-Cs vs the reference cell (i.e., being assigned placebo and not on TZD). Abbreviation: TZD, thiazolidinedione.