Haptoglobin Phenotype Modifies the Effect of Fenofibrate on Risk of Coronary Event: ACCORD Lipid Trial

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OBJECTIVE

The haptoglobin (Hp)2-2 phenotype (~35–40% of people) is associated with increased oxidation and dysfunctional HDL in hyperglycemia and may explain why drugs designed to pharmacologically raise HDL cholesterol and lower triglycerides have not reliably prevented cardiovascular disease in diabetes. We aimed to determine whether the effect of adding fenofibrate versus placebo to simvastatin on the risk of coronary artery disease (CAD) events depends on Hp phenotype in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial.

RESEARCH DESIGN AND METHODS

Cox proportional hazards regression models quantified the relationship between fenofibrate therapy and CAD events in the ACCORD lipid trial in participants with the Hp2-2 phenotype (n = 1,795) separately from those without (n = 3,201).

RESULTS

Fenofibrate therapy successfully lowered the risk of CAD events in participants without the Hp2-2 phenotype (multivariable adjusted hazard ratio 0.74 [95% CI 0.60–0.90] compared with no fenofibrate therapy) but not in participants with the Hp2-2 phenotype (1.16 [0.87–1.56]; P interaction = 0.009). Subgroup analyses revealed that this protective effect of fenofibrate against CAD events among the non–Hp2-2 phenotype group was pronounced in participants with severe dyslipidemia (P interaction = 0.01) and in males (P interaction = 0.02) with an increased CAD risk from fenofibrate treatment observed in females with the Hp2-2 phenotype (P interaction = 0.002).

CONCLUSIONS

The effect of fenofibrate added to simvastatin on risk of CAD events depends on Hp phenotype in the ACCORD lipid trial.

Despite the well-established association between cardiovascular disease (CVD) and atherogenic dyslipidemia, large clinical trials have failed to provide evidence to support an added benefit from HDL-cholesterol–raising and triglyceride-lowering therapy in addition to optimal statin therapy (1–3). The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial (ClinicalTrials.gov number NCT00000620) was a large multicenter study that concluded that the combination of fenofibrate and simvastatin did not reduce the risk of major CVD events compared

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with simvastatin alone, although a potential benefit was observed in a prespecified subgroup analysis of men and in patients with both triglycerides in the highest third and HDL-cholesterol in the lowest third at baseline (1). Similarly, two other large trials observed no benefit from niacin and statin combination therapy compared with statin monotherapy (2,3). An explanation for the inability of HDL-cholesterol–raising and triglyceride-lowering therapies to prevent CVD events in these clinical trials has not been confirmed, but may be due to differences in unmeasured characteristics between study participants that affect lipid or lipoprotein function.

A common variation in the gene that codes for the abundant plasma protein haptoglobin (Hp) has identified individuals who may be at increased risk of coronary artery disease (CAD) events, such as myocardial infarction (MI), from hyperglycemia and altered HDL function (4–10). Specifically, in patients with the Hp2-2 genotype (who thus produce the Hp2-2 protein and have the Hp2-2 phenotype) and hyperglycemia (often defined as glycated hemoglobin [Hb] $\geq$6.5% [48 mmol/mol]), HDL has been shown to be dysfunctional and proatherogenic with the potential to increase susceptibility to atherosclerosis, deterioration of cardiac function, and, ultimately, CAD (5,10,11). The effect of drugs designed to raise HDL-cholesterol and lower triglycerides in people with the Hp2-2 phenotype ($\sim$35–40% of people worldwide) and hyperglycemia on risk of CAD events is currently unknown but may not have a beneficial effect due to the dysfunctional nature of HDL in these individuals. In contrast, drugs designed to raise HDL-cholesterol and lower triglycerides may be favorable in people without the Hp2-2 phenotype (who thus have the Hp1-1 or Hp2-1 phenotype) in whom the functions of Hp and HDL are better preserved.

The primary objective of the current study was to determine whether the Hp2-2 phenotype influenced the effect of the ACCORD lipid trial (which tested adding fenofibrate therapy vs. placebo to simvastatin) on the risk of CAD events. In the original ACCORD lipid trial, sex as well as baseline combined triglyceride–HDL-cholesterol levels appeared to influence the effect of fenofibrate (1). Additionally, secondary prevention patients have a higher risk of CVD events compared with primary prevention patients (12). Thus, as a secondary objective, we decided a priori to perform stratifications by sex, previous CVD at baseline, and baseline triglyceride and HDL-cholesterol concentrations.

RESEARCH DESIGN AND METHODS

The current study was a hypothesis-driven reanalysis of data from the ACCORD lipid trial with the addition of Hp phenotype measurement to assess the effect of fenofibrate therapy on CAD events among two separate groups: participants with the Hp2-2 phenotype and participants without the Hp2-2 phenotype. The design, methods, and original findings of the ACCORD trial (Clinical Trials.gov identifier NCT00000620) have been reported previously (1,13). Briefly, the ACCORD trial was a large-scale multicenter (77 clinical sites in Canada and the U.S.) double-blind 2 × 2 factorial design randomized control trial in patients with type 2 diabetes at high risk of a CVD event. At baseline, all ACCORD participants had a glycated Hb level $\geq$7.5% (58 mmol/mol) and were aged between 40 and 79 years if they had evidence of clinical CVD or between 55 and 79 years if there was anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for CVD. In the lipid arm of the ACCORD trial, all 5,518 patients had a baseline LDL-cholesterol level of 60–180 mg/dL (1.55–4.65 mmol/L), HDL-cholesterol of $<$55 mg/dL (1.42 mmol/L) for females and Black participants or $<$50 mg/dL for all others, and a serum triglyceride level of $<$750 mg/dL (8.5 mmol/L) if not on a lipid medication or $<$400 mg/dL (4.5 mmol/L) if on a lipid medication. Participants were randomized to receive either fenofibrate or placebo (began 1 month after randomization) in addition to open-label background simvastatin (began at randomization) over a mean follow-up of 4.7 years. Randomization was performed centrally on the study website using permutated blocks to conceal study-group assignment. A fasting plasma lipid profile was measured at 4, 8, and 12 months after randomization and annually thereafter at the ACCORD central laboratory. Safety profiles were determined at 1, 4, 8, and 12 months after randomization and annually thereafter (1,13–15). The dose of simvastatin was modified over time to reflect changing guidelines, and, beginning in 2004, due to a rise in serum creatine levels in some patients, the dose of fenofibrate was modified according to glomerular filtration rate with the use of the abbreviated MDRD equation (1,16–18).

The ACCORD study was completed in 2009, and all collected specimens and data have since become available to non-ACCORD researchers through the National Institutes of Health's Open Biologic Specimen and Data Repository Information Coordinating Center. The ACCORD study protocol was approved by institutional review boards at all participating institutions, and all participants provided written informed consent, including consent for future research.

Hp Phenotyping

The Hp phenotype of patients in ACCORD was determined using a previously validated high-throughput ELISA with a sensitivity and specificity of 99% and 98.1%, respectively (19). Hp phenotype does not change over time, and therefore, a blood sample from either baseline or a follow-up visit was used for each participant. Of the 5,518 ACCORD lipid participants, Hp phenotype was determined for 4,996 (90.5%). The exclusion of the other 522 participants occurred because serum samples from these participants had previously been depleted by the measurement of other biomarkers.

CAD Event Outcome

We report the outcome of CAD events, according to the original ACCORD lipid trial prespecified diagnosis criteria and definition (1) of "major CAD events," which is defined as the first occurrence of a fatal coronary event, a nonfatal MI, or unstable angina. All reported cardiovascular outcomes in the ACCORD trial were adjudicated by a blinded panel using predefined adjudication criteria (1).

Although the mechanism is not well understood, stroke is an end point that has been associated with the Hp1-1 phenotype rather than the Hp2-2 phenotype (20,21), suggesting that CAD and stroke should be separated from a composite CVD outcome for analyses by Hp phenotype. Previous studies suggest that protection against stroke conferred by the Hp2-2 phenotype may be connected to the role of Hp phenotype in angiogenesis, whereas protection against

CAD has been linked to the function of Hp as an Hb scavenger and antioxidant (22,23). For this biological reason, the present analysis studied the outcome of CAD events rather than the original ACCORD lipid trial primary outcome of major CVD events (nonfatal MI, nonfatal stroke, or death from cardiovascular causes, excluding unstable angina).

Statistical Analysis

All statistical analyses were conducted using Stata/IC software version 15.1 (StataCorp, College Station, TX) at a two-tailed α level of 0.05. Participants with the Hp2-1 or Hp1-1 phenotypes (those without the Hp2-2 phenotype) were combined to form a group, which is a common approach when studying the Hp phenotype because of the low frequency of the Hp1-1 phenotype ($\sim$15%) and because the structure and function of the Hp2-1 and Hp1-1 proteins are similar in relation to the Hp2-2 protein (7,8, 24,25).

Participants were grouped based on a combination of their treatment assignment and Hp phenotype, and baseline characteristics were compared using *t* tests, one-way ANOVA, or Kruskal-Wallis tests for continuous variables and χ^2 tests for categorical variables. Less than 3% of data were missing for any of the baseline variables. The analysis was kept similar to the ACCORD lipid trial (1) with stratification by Hp phenotype. As such, the relationship between fenofibrate therapy and the risk of CAD events was determined using Cox proportional hazards regression according to the intention-to-treat principle. The occurrence of events between treatment groups was compared using adjusted hazard ratios (HRs) and 95% CIs for participants with the non–Hp2-2 and Hp2-2 phenotype groups separately. Multivariable Cox regression models were adjusted for the same covariates that were included in the original ACCORD lipid analyses, including: the seven clinical networks; assignment to intensive glycemic control; and a history of CVD at baseline. Additional adjustment was made for age, sex, ethnicity, and three variables that differed between treatment groups: baseline triglycerides, baseline angiotensin receptor blocker use, and baseline aspirin use. Further stratification was performed by sex, previous CVD at baseline, and baseline triglyceride and HDL-cholesterol concentrations. Interactions were tested between fenofibrate assignment and Hp phenotype using an interaction term in the model. There was no significant interaction effect between intensive glycemic control and fenofibrate for CAD events in either phenotype group (data not shown), so the analysis was not stratified by assignment to glycemic control group. Follow-up time was defined as the time from randomization to date of documented outcome (CAD) or until they were censored at 7 years after randomization if no event occurred.

RESULTS

The distribution of Hp phenotype frequencies was 17.9% for Hp1-1, 46.2% for Hp2-1, and 35.9% for Hp2-2. The median follow-up was 4.7 years in each of the Hp phenotype groups. Among those without the Hp2-2 phenotype (n = 3,201), 1,595 were randomized to receive fenofibrate and 1,606 to placebo in combination with simvastatin (Table 1). The mean age was 62.7 ± 6.5, 33.5% were female, and 34.6% had a history of CVD at baseline. Among those who had the Hp2-2 phenotype (n = 1,795), 919 were in the fenofibrate group and 876 were in the placebo group, the mean age was 62.8 ± 6.4, 31.2% were female, and 35.9% had a history of CVD at baseline. Non–Hp2-2 and Hp2-2 treatment groups differed in baseline triglycerides (median of 159 mg/dL among participants without the Hp2-2 phenotype and 169 mg/dL among those with the Hp2-2 phenotype) (Table 1). Among patients with the Hp2-2 phenotype, the treatment groups had different baseline angiotensin receptor blocker (14.0% of the fenofibrate group and 17.7% of the placebo group) and aspirin (58.5% of the fenofibrate group and 53.7% of the placebo group) use. Changes in average total cholesterol, LDL-cholesterol, and HDL-cholesterol as well as changes in median triglycerides for each treatment group stratified by haptoglobin phenotype can be found in Supplementary Fig. 1.

In multivariable adjusted Cox models (Table 2, Figure 1), participants who were allocated to receive fenofibrate compared with placebo had a 26% lower risk of CAD events (HR 0.74 [95% CI 0.60–0.90]) in participants without the Hp2-2 phenotype, but not in participants with the Hp2-2 phenotype (1.16 [0.87–1.56]), with a significant interaction between Hp phenotype and lipid treatment for CAD events (P = 0.009).

When participants without the Hp2-2 phenotype were stratified by sex (P value for sex interaction = 0.02) (Table 3), men who were assigned to receive fenofibrate treatment had a 36% lower risk of CAD events (0.64 [0.50–0.81]) compared with placebo, while there was no significant difference in the risks in females receiving fenofibrate versus those receiving placebo. Secondary prevention patients without the Hp2-2 phenotype who were randomized to fenofibrate had a 30% lower risk of CAD events (0.70 [0.53–0.91]), while there was no significant effect in primary prevention patients, although the interaction was not significant. The protective effect of fenofibrate against CAD among those without the Hp2-2 phenotype was pronounced in participants with both baseline triglycerides in the upper tertile (>204 mg/dL) and HDL cholesterol in the lowest tertile (<34 mg/dL) (0.41 [0.26–0.65]; P interaction = 0.01).

For the Hp2-2 phenotype group, there was no significant difference in CAD risk between treatment groups in males; however, an increased risk of CAD events (2.55 [1.27–5.12]) was observed in females allocated to receive fenofibrate (P value for interaction = 0.002). There was no significant difference in risk of CAD events between treatment groups in primary or secondary prevention patients with the Hp2–2 phenotype. When stratified by baseline lipids, there was no significant difference in the risk of CAD events among patients with the Hp2-2 phenotype who had both baseline triglycerides <204 mg/dL (<2.3 mmol/L) and HDL cholesterol >34 mg/dL (>0.88 mmol/L) or in those with both baseline triglycerides ≥204 mg/dL (≥2.3 mmol/L) and HDL cholesterol ≤34 mg/dL (≤0.88 mmol/L).

CONCLUSIONS

The current study is the first to investigate whether the effect of fenofibrate–simvastatin combination therapy on CAD events in type 2 diabetes depends

Table 1—Baseline characteristics of the ACCORD lipid trial in participants with and without the Hp2-2 phenotype separately

	Non–Hp2-2 phenotype				Hp2-2 phenotype				
Characteristic	All (n = 3,201)	Fenofibrate (n = 1,595)	Placebo (n = 1,606)	P value	All (n = 1,795)	Fenofibrate (n = 919)	Placebo (n = 876)	P value	Overall P value
Age (years)	62.7 ± 6.5	62.6 ± 6.4	62.9 ± 6.5	0.37	62.8 ± 6.4	62.7 ± 6.4	62.8 ± 6.4	0.87	0.84
Female sex	1,073 (33.5)	529 (33.2)	544 (33.9)	0.67	560 (31.2)	288 (31.3)	272 (31.1)	0.90	0.40
Race or ethnic group				0.97				0.16	<0.001
White	2,093 (65.4)	1,044 (65.5)	1,049 (65.3)		1,198 (66.7)	616 (67.0)	582 (66.4)		
Black	549 (17.2)	269 (16.9)	280 (17.4)		181 (10.1)	80 (8.7)	101 (11.5)		
Hispanic	252 (7.9)	128 (8.0)	124 (7.7)		105 (5.9)	60 (6.5)	45 (5.1)		
Other	307 (9.6)	154 (9.7)	153 (9.5)		311 (17.3)	163 (17.7)	148 (16.9)		
Education				0.40				0.79	0.10
Less than high school	450 (14.1)	233 (14.6)	217 (13.5)		213 (11.9)	111 (12.1)	102 (11.6)		
High school or GED	840 (26.2)	418 (26.2)	422 (26.3)		467 (26.0)	234 (25.5)	233 (26.6)		
Some college	1,063 (33.2)	509 (31.9)	544 (34.5)		573 (31.9)	288 (31.3)	285 (32.5)		
College degree or higher	845 (26.4)	433 (27.2)	412 (25.7)		542 (30.2)	286 (31.1)	256 (29.2)		
Previous cardiovascular event	1,108 (34.6)	550 (34.5)	558 (34.7)	0.88	644 (35.9)	335 (36.5)	309 (35.3)	0.60	0.78
Previous congestive heart failure	184 (5.6)	99 (6.2)	85 (5.3)	0.27	76 (4.2)	38 (4.1)	38 (4.3)	0.83	0.08
Smoking status				0.23				0.79	0.49
Current	394 (12.3)	208 (13.0)	186 (11.6)		201 (11.2)	107 (11.6)	94 (10.7)		
Former	1,466 (45.8)	740 (46.4)	726 (45.2)		852 (47.5)	437 (47.6)	415 (47.4)		
Never	1,341 (41.9)	647 (40.6)	694 (43.2)		742 (41.3)	375 (40.8)	367 (41.9)		
Weight (kg)	94.9 ± 18.2	94.7 ± 17.7	95.2 ± 18.6	0.45	94.3 ± 18.7	93.8 ± 18.9	94.9 ± 18.4	0.21	0.34
BMI (kg/m^2)	32.4 ± 5.3	32.4 ± 5.2	32.5 ± 5.4	0.52	32.3 ± 5.4	32.1 ± 5.5	32.5 ± 5.3	0.12	0.31
Blood pressure (mmHg)									
Systolic	134.2 ± 17.9	134.4 ± 17.8	134.1 ± 17.9	0.73	133.5 ± 17.9	132.9 ± 17.7	134.1 ± 18.1	0.16	0.25
Diastolic	74.1 ± 10.7	74.0 ± 10.5	74.1 ± 10.9	0.94	74.0 ± 10.9	73.8 ± 10.8	74.2 ± 10.9	0.42	0.88
Medications									
Insulin	1,108 (34.7)	562 (35.4)	546 (34.1)	0.45	586 (32.8)	295 (32.2)	291 (33.4)	0.61	0.43
Metformin	2,091 (65.3)	1,035 (64.9)	1,056 (65.8)	0.61	1,191 (66.4)	609 (66.3)	582 (66.4)	0.97	0.84
Any sulfonylurea	1,744 (54.5)	872 (54.7)	872 (54.3)	0.83	1,004 (55.9)	509 (55.4)	495 (56.5)	0.65	0.74
Any thiazolidinedione	649 (20.3)	309 (19.4)	340 (21.2)	0.21	364 (20.3)	193 (21.0)	171 (19.5)	0.43	0.53
ACE inhibitor	1,678 (52.4)	826 (51.8)	852 (53.1)	0.49	943 (52.5)	477 (51.9)	466 (53.2)	0.61	0.86
Angiotensin receptor blocker	501 (15.7)	245 (15.4)	256 (15.9)	0.67	284 (15.8)	129 (14.0)	155 (17.7)	0.04	0.20
Aspirin	1,816 (56.7)	913 (57.2)	902 (56.2)	0.55	1,008 (56.2)	538 (58.5)	470 (53.7)	0.03	0.16
β-Blocker	1,041 (32.5)	527 (33.0)	514 (32.0)	0.52	572 (31.9)	294 (32.00)	278 (31.7)	0.88	0.88
Any thiazide diuretic	868 (27.1)	449 (28.2)	419 (26.1)	0.19	481 (26.8)	233 (25.4)	248 (28.3)	0.17	0.29
Any antihypertensive agent	2,593 (81.0)	1,289 (80.8)	1,304 (81.2)	0.81	1,448 (80.7)	729 (79.3)	719 (82.1)	0.16	0.54
Statin	1,950 (60.9)	964 (60.4)	986 (61.4)	0.58	1,126 (62.7)	576 (62.7)	550 (62.8)	0.98	0.59
Any lipid-lowering agent	2,109 (65.9)	1,051 (65.9)	1,058 (65.9)	0.99	1,196 (66.6)	607 (66.1)	589 (67.2)	0.64	0.92

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Table 1—Continued

Characteristic	Non–Hp2-2 phenotype				Hp2-2 phenotype				Overall *P* value
	All (*n* = 3,201)	Fenofibrate (*n* = 1,595)	Placebo (*n* = 1,606)	*P* value	All (*n* = 1,795)	Fenofibrate (*n* = 919)	Placebo (*n* = 876)	*P* value	
Duration of diabetes (years)				0.81				0.77	0.90
Median	10	10	9		9	9	9.5		
IQR	5–15	5–15	5–15		5–15	5–15	5–15		
Glycated Hb (%)				0.15				0.59	0.50
Mean	8.3 ± 1.0	8.3 ± 1.0	8.2 ± 1.0		8.3 ± 1.0	8.3 ± 1.1	8.3 ± 1.0		
Median	8.1	8.1	8		8.1	8.1	8.1		
IQR	7.6–0.8	7.6–8.9	7.5–8.8		7.5–8.8	7.5–8.8	7.5–8.8		
Plasma cholesterol (mg/dL)									
Total	175.2 ± 37.2	174.8 ± 37.2	175.7 ± 37.2	0.50	177.2 ± 38.0	176.0 ± 37.1	178.4 ± 38.9	0.19	0.15
LDL	100.8 ± 30.8	100.2 ± 30.7	101.5 ± 30.8	0.21	101.2 ± 30.9	100.2 ± 30.2	102.1 ± 31.6	0.19	0.34
HDL				0.11					
Mean	38.3 ± 7.9	38.0 ± 8.1	38.5 ± 7.7		38.0 ± 7.5	38.1 ± 7.2	38.1 ± 7.9	0.89	0.37
Median	38	37	38		37	38	37		
IQR	33–43	32–43	33–43		33–43	33–43	33–43		
Plasma triglycerides (mg/dL)				0.07				0.76	<0.001
Median	159	162	157		169	170.5	168		
IQR	111–227	113–231	109–224		120–241	119–241.5	121–241		
Triglycerides ≥204 mg/dL and HDL ≤34 mg/dL, *n* (%)	531 (16.6)	282 (17.7)	249 (15.5)	0.10	326 (18.2)	160 (17.4)	166 (18.9)	0.40	0.14

Data are means ± SD or *n* (%) unless otherwise noted. Percentages may not total 100 because of rounding. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for glycated Hb to millimoles per mole, subtract 2.152 and divide by 0.09148. GED, general equivalency diploma; IQR, interquartile range.

Table 2—Annual rates and unadjusted and multivariable adjusted hazard ratios (HRs) for CAD events‡ if given fenofibrate therapy compared with placebo for the two separate Hp phenotype groups

	Fenofibrate			Placebo			HR			
	N	No. of events	Rate/year	*N*	No. of events	Rate/year	uHR*	95% CI	aHR**	95% CI
Non–Hp2-2 phenotype	1,595	169	2.3	1,606	219	2.9	0.76	0.62–0.93	0.74	0.60–0.90
Hp2-2 phenotype	919	104	2.4	876	83	2.0	1.21	0.91–1.61	1.16	0.87–1.56

The *P* value for the test of interaction between fenofibrate treatment and Hp phenotype is 0.009. aHR, adjusted HR; uHR, unadjusted HR. *uHR compare fenofibrate therapy to reference group of participants who received placebo in unadjusted models. **aHR compares fenofibrate therapy to the reference group of participants who received placebo. Models are adjusted for age, sex, the seven clinical center networks, assignment to intensive glycemic control, history of CVD at baseline, ethnicity, baseline triglycerides, baseline use of angiotensin receptor blockers, and baseline use of aspirin. ‡The CAD event outcome is defined as the first occurrence of a major coronary event: a fatal coronary event, a nonfatal MI, or unstable angina.

on Hp phenotype, and we observed significantly different results in participants with the Hp2-2 phenotype than in those without. Fenofibrate with background simvastatin, compared with simvastatin alone, reduced the risk of CAD events in those without the Hp2-2 phenotype but not in those with the Hp2-2 phenotype. The protective effect of the fenofibrate intervention was especially pronounced in participants without the Hp2-2 phenotype who were male, had previous CVD, and had a combination of high baseline triglycerides and low baseline HDL. We also observed that the intervention was associated with a significantly increased risk of CAD events among females with the Hp2-2 phenotype.

The original ACCORD lipid trial analysis did not reveal that fenofibrate and simvastatin combination therapy reduced the risk of incident CAD (0.92 [0.79–1.07]) compared with simvastatin alone (1). However, our present results suggest that had the original study been conducted in only participants without the Hp2-2 phenotype, fenofibrate and simvastatin would have been reported to reduce the risk of CAD compared with simvastatin alone. Therefore, results of the current study suggest that the effect of adding fenofibrate to simvastatin on

Table 3—Annual rates and multivariable adjusted hazard ratios (HRs) for incident CAD† if given fenofibrate therapy compared with placebo in subgroups by Hp2-2 phenotype

	Fenofibrate			Placebo					
	N	No. of events	Rate/year	*N*	No. of events	Rate/year	aHR*	95% CI	*P* interaction**
Non–Hp2-2 phenotype									
Sex									0.02
Male	1,066	117	2.4	1,062	166	3.4	0.64	0.50–0.81	
Female	529	52	2.1	544	53	2.1	1.11	0.75–1.65	
Previous CVD									0.39
Yes	550	96	3.8	558	132	5.1	0.70	0.53–0.91	
No	1,045	73	1.5	1,048	87	1.8	0.82	0.60–1.12	
Baseline lipids									0.01
TG ≥204 mg/dL and HDL ≤34 mg/dL	282	30	2.4	249	53	4.8	0.41	0.26–0.65	
TG <204 mg/dL and HDL >34 mg/dL	1,313	139	2.3	1,357	166	2.6	0.85	0.67–1.06	
Hp2-2 phenotype									
Sex									0.002
Male	631	69	2.2	604	71	2.4	0.90	0.65–1.27	
Female	288	35	2.6	272	12	0.9	2.55	1.27–5.12	
Previous CVD									0.71
Yes	335	62	4.0	309	49	3.4	1.07	0.73–1.56	
No	584	42	1.5	567	34	1.3	1.24	0.78–1.98	
Baseline lipids									0.03
TG ≥204 mg/dL and HDL ≤34 mg/dL	160	22	2.8	166	27	3.3	0.80	0.44–1.44	
TG <204 mg/dL and HDL >34 mg/dL	759	82	2.3	710	56	1.7	1.28	0.91–1.82	

To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiple by 0.01129. aHR, adjusted HR; TG, triglyceride. *aHRs compare fenofibrate therapy to the reference group of participants who received placebo. Models were adjusted for age, sex, the seven clinical center networks, assignment to intensive glycemic control, history of CVD at baseline, ethnicity, baseline triglycerides, baseline use of angiotensin receptor blockers, and baseline use of aspirin. **P values for interaction between fenofibrate treatment and sex, previous CVD, or baseline lipids. †The CAD event outcome is defined as the first occurrence of a major coronary event: a fatal coronary event, a nonfatal MI, or unstable angina.

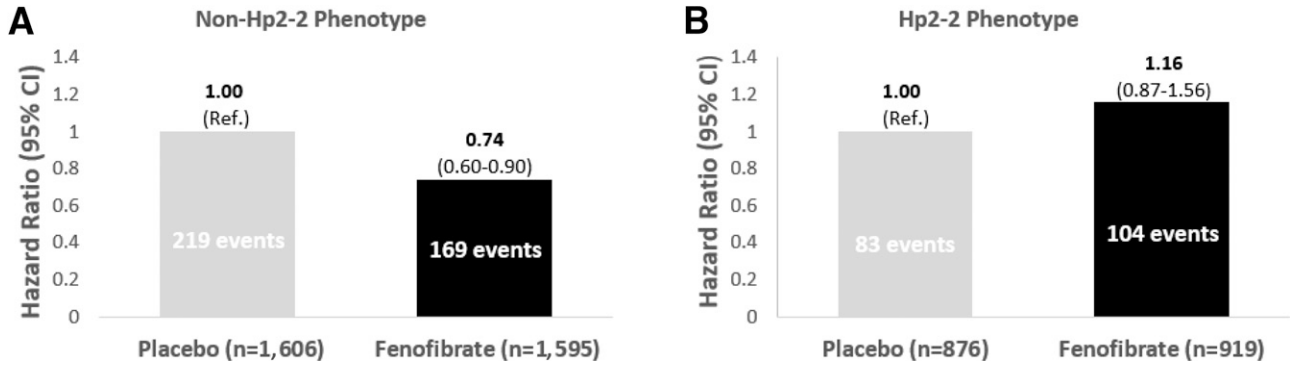

Figure 1—Multivariable adjusted hazard ratios (HRs) for incident CAD events if given fenofibrate compared with placebo in ACCORD lipid participants with the non–Hp2-2 (*A*) and Hp2-2 phenotypes (*B*). The analysis was adjusted for age, sex, the seven clinical center networks, assignment to intensive glycemic control, history of CVD at baseline, ethnicity, baseline triglycerides, baseline use of angiotensin receptor blockers, and baseline use of aspirin.

cardiovascular outcomes may have been confounded by Hp phenotype in the original trial and that Hp phenotype should be considered in the design of future related studies and also potentially in clinical practice.

The findings of this study are supported by previous research on the role of Hp phenotype in HDL-cholesterol dysfunction and CAD risk in hyperglycemia (10,11,26–29). In a subset of participants in the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study who had diabetes, Asleh et al. (29) found that there was a higher proportion of participants with dysfunctional pro-oxidant HDL in the Hp2-2 phenotype compared with the Hp1-1 phenotype at baseline, and, although HDL-cholesterol levels did not change drastically throughout the study, niacin improved HDL-cholesterol antioxidant function in individuals with Hp1-1 but worsened HDL-cholesterol antioxidant function in individuals with the Hp2-2 phenotype. In several in vitro and in vivo studies, individuals with the Hp2-2 phenotype show reduced ability to protect against Hb-mediated oxidative damage, resulting in increased inflammation, oxidative stress, and dysfunctional HDL-cholesterol (11,26–28). Taken together with the results of the current study, it appears that a pronounced risk of CAD in the Hp2-2 phenotype with hyperglycemia may be due, at least in part, to dysfunctional HDL.

The biological mechanism linking HDL dysfunction in the Hp2-2 phenotype to risk of CAD events in hyperglycemia is well supported by scientific literature demonstrating that the Hp2-2 protein is structurally and functionally different than other Hp (non–Hp2-2) proteins. The Hp2-2 protein is substantially larger and more cyclic than other Hp proteins, and thus, the Hp2-2 protein is less functional at preventing oxidative damage by free Hb, which is the primary function of Hp (26–28). In hyperglycemic conditions, the function of Hp2-2 is further impaired, resulting in increased oxidative stress and oxidative modification of HDL cholesterol (Hp can bind to HDL and thereby tether Hb to HDL), which paradoxically turns HDL cholesterol into a proatherogenic, prothrombotic molecule in people with the Hp2-2 phenotype (5,10,11). Therefore, drugs designed to increase HDL-cholesterol may not be beneficial for CAD risk reduction in people with hyperglycemia and the Hp2-2 phenotype. However, they may be beneficial in people with hyperglycemia who do not have the Hp2-2 phenotype because Hp and HDL function are better preserved. Interestingly, vitamin E supplementation has led to improvements in HDL function among people with the Hp2-2 phenotype with diabetes, but not the non–Hp2-2 phenotype (5,25). Further, vitamin E treatment has been associated with CAD risk reduction among the Hp2-2 phenotype with diabetes (30,31), suggesting that the antioxidant vitamin E may help to mitigate the Hp2-2–associated CAD risk. Further research is needed to determine if the effect of fenofibrate on CAD risk in the Hp2-2 phenotype could be modified through vitamin E.

It is plausible that there is also an increased amount of triglyceride–fatty acid oxidation among the Hp2-2 phenotype compared with the non–Hp2-2 phenotype, which could have affected our results; however, this mechanism has not been investigated. Further, the independent role of hypertriglyceridemia in CVD has been debated in the literature for decades (32), and the effect that oxidized triglycerides–fatty acids have on CAD risk in diabetes remains underresearched and would be valuable to measure in future trials of fenofibrates.

Due to the biological rationale linking Hp phenotype, HDL function, and risk of CAD in hyperglycemia and the less well understood association between Hp1-1 and stroke (20,21), the primary outcome of interest for the present analysis was CAD (fatal coronary event, a nonfatal MI, or unstable angina) rather than the ACCORD lipid primary outcome of major CVD events (nonfatal MI, nonfatal stroke, or death from cardiovascular causes, excluding unstable angina) (1). We were underpowered to investigate stroke as an outcome in isolated analyses; however, in a sensitivity analysis in which we investigated the ACCORD major CVD outcome, there was a nonsignificant trend toward benefit from fenofibrate in participants with the non–Hp2-2 phenotype (0.82 [0.66–1.03]; data not shown) and a null effect in the Hp2-2 phenotype (1.02 [0.75–1.37]; data not shown).

Females and males are different biologically, and the roles of endogenous sex hormones and gender on lipid metabolism and cardiometabolic disease are not yet well understood (33,34). A potential explanation for our findings in females could be that postmenopausal metabolic changes may trigger chronic inflammation over time that could alter the quality

of HDL (35,36). In the Multi-Ethnic Study of Atherosclerosis (MESA), Khoudary et al. (35) found a positive association between HDL-cholesterol and plaque formation in postmenopausal women. Given the older age of the ACCORD lipid cohort, HDL dysfunction due to menopausal metabolic changes may explain the neutral effect of fenofibrate among females with the non–Hp2-2 phenotype and the increased risk of CAD events observed among females with the Hp2-2 phenotype who took fenofibrate. However, specific menopausal status information was not collected in the ACCORD lipid trial, and we can only hypothesize that menopausal-related metabolic changes could have influenced the results. In a sensitivity analysis, we removed women who were taking hormone replacement therapy at baseline from the analysis (10.2% of women), and our results did not materially change (data not shown). Females also have naturally higher levels of HDL-cholesterol than males, which may potentially explain why fenofibrate therapy significantly reduced the risk of CAD events in males with the non–Hp2-2 phenotype but not in females of the same phenotype group, as HDL-cholesterol levels may already have been high enough to offer CAD protection from functional HDL in females but not males (37,38). Additionally, higher HDL levels in females may explain our observation of an increased risk of CAD events in females with the Hp2-2 phenotype who received fibrates, as these females would have theoretically had the highest concentrations of oxidatively modified HDL cholesterol of the subgroups.

The finding that the risk of CAD was lower in the Hp2-2 phenotype control group compared with the non–Hp2-2 phenotype control group (0.64 [0.50–0.83]; data not shown) was unexpected and inconsistent with our previous research that reported a higher risk of CAD events in the Hp2–2 phenotype compared with the non–Hp2-2 phenotype group in hyperglycemia (7,8). A potential explanation for this finding could be that the glycemic control treatment differently influenced the risk in the different phenotype groups, since we have previously reported that intensive glycemic control in the ACCORD glycemic control trial was effective at preventing CAD events in the Hp2-2 phenotype but not in the non–Hp2-2 phenotypes (9). However, a test for interaction between fenofibrate treatment and intensive glycemic control was not significant (data not shown). Hp phenotype frequency distribution is also linked to ethnicity/race, with a higher frequency of the Hp1 allele in Black populations, and it is possible that ethnicity/race could have influenced the results (6). However, in a sensitivity analysis in which we restricted the analysis to non-Hispanic White participants only, our results were materially unchanged (data not shown).

Similar to our study, Morieri et al. (39) have also recently observed that the cardiovascular benefits of fibrates are heterogeneous and depend on the presence of atherogenic dyslipidemia. Morieri et al. (39) found a significant interaction effect between the common variant at the PPARA locus (rs6008845, C/T), which codes for peroxisome proliferator-activated receptor-α (PPAR-α), and fenofibrates that reduced major cardiovascular events in T/T homozygotes who received fenofibrates but not in participants without the T/T genotype. The study by Morieri et al. (39) included stroke in the outcome and may, therefore, be the result of a different mechanistic pathway than the current study's results. However, both Hp and PPAR-α are involved in inflammation and lipid metabolism, and future studies are required to determine whether a combined biological mechanism could be at play and to what extent the combination of these two common polymorphisms predicts the response of a patient with type 2 diabetes to fibrates.

This study has several limitations that should be noted. Participants were all middle-aged and elderly individuals at a high risk for CVD who were mostly non-Hispanic White, and it remains unknown whether these results are generalizable to other populations. Furthermore, fenofibrate not only affects HDL, but also lowers triglycerides, increases the size of LDL particles, and has several other nonlipid effects, including a reduction in systemic inflammation (40–42). Therefore, at present, it can only be hypothesized that our findings may be due to prominent HDL dysfunction in patients with the Hp2-2 phenotype and hyperglycemia, and follow-up studies that assess HDL-cholesterol levels and function in the different Hp phenotype groups are warranted to confirm the biological mechanism. We were not able to measure oxidative modification of HDL in the current study, which would be important to consider in future work. Another limitation of our study is that we were underpowered to analyze Hp1-1 participants separately from Hp2-1 participants or analyze stroke as an isolated outcome, and so our study cannot meaningfully contribute knowledge about the relationship between Hp1-1 phenotype and stroke risk or whether the effect of fenofibrate on stroke risk is dependent on Hp phenotype in diabetes. Further targeted studies are needed to address this. Our present work must also be expanded to include a greater representation in participant demographics (sex, ethnicity, and diabetes duration), treatment definitions (medications, doses, and lifestyle, such as diet and physical activity), and study design (such as a trial that incorporates Hp phenotype into treatment planning at baseline) to determine whether Hp phenotype can reliably differentiate susceptible individuals who would most benefit from fenofibrate therapy. Investigations to determine if the effect of simvastatin on CAD in hyperglycemia is dependent on Hp phenotype are also warranted.

Conclusion

In conclusion, the results of the current study suggest that in hyperglycemia fenofibrate–simvastatin combination therapy may only be beneficial for CAD prevention in people who do not have the Hp2-2 phenotype, particularly in males and patients with significant dyslipidemia, and may be harmful for females with the Hp2-2 phenotype. These findings provide an explanation for the failure of randomized clinical trials of HDL-cholesterol–raising and triglyceride-lowering therapies previously reported and, if replicated in future studies, suggest a precision medicine approach to prescribe fenofibrate optimally by which Hp phenotype would serve as a biomarker to help distinguish patients who would receive a cardiovascular benefit from fenofibrate from those who would not.

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Duality of Interest. A.P.L. is the author of a patent owned by his university regarding use of haptoglobin genotype to predict susceptibility to cardiovascular disease in individuals with diabetes. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. R.A.W. and L.E.C. conceived the study idea and design with E.B.R. A.P.L. determined the haptoglobin phenotype in his laboratory while blinded to participant ID and outcome. R.A.W. performed the statistical analyses with guidance from P.A. and with A.S.C. rerunning all analyses in duplicate to confirm all findings. R.A.W. and L.E.C. drafted the manuscript with H.N.G. All authors contributed to additional drafts of the manuscript and approved the submitted version, and each author satisfies the authorship criteria of the International Committee of Medical Journal Editors. L.E.C. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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