Persistent Effects of Intensive Glycemic Control on Retinopathy in Type 2 Diabetes in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Follow-On Study

*The Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Eye Study Group and the Action to Control Cardiovascular Risk in Diabetes Follow-On (ACCORDION) Study Group**

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OBJECTIVES

This study investigated whether the beneficial effects of intensive glycemic control and fenofibrate treatment of dyslipidemia in reducing retinopathy progression demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study persisted beyond the clinical trial.

RESEARCH DESIGN AND METHODS

The ACCORD Study (2003–2009) randomized participants with type 2 diabetes to intensive or standard treatment for glycemia (A1C level at <6.0% [42 mmol/mol] vs. 7.0–7.9% [53–63 mmol/mol]), systolic blood pressure (<120 vs. 140 mmHg), and dyslipidemia (fenofibrate [160 mg] plus simvastatin or placebo plus simvastatin). ACCORD Eye Study participants, who had baseline and year 4 eye examinations and fundus photographs, were reexamined in the ACCORD Follow-On (ACCORDION) Eye Study (2010–2014) 4 years after the ACCORD trial closeout. The outcome measure was diabetic retinopathy progression of three or more steps on the Early Treatment Diabetic Retinopathy Study scale.

RESULTS

Diabetic retinopathy progressed in 5.8% with intensive glycemic treatment versus 12.7% with standard (adjusted odds ratio [aOR] 0.42, 95% CI 0.28–0.63, $P < 0.0001$), 7.5% with intensive blood pressure treatment versus 6.0% for standard (aOR 1.21, 95% CI 0.61–2.40, $P = 0.59$), and 11.8% with fenofibrate versus 10.2% with placebo (aOR 1.13, 95% CI 0.71–1.79, $P = 0.60$) in ACCORDION Eye participants ($n = 1,310$).

CONCLUSIONS

Prior intensive glycemic control continued to reduce diabetic retinopathy progression, despite similar A1C levels, when the ACCORD Study ended. This is the first study in people with type 2 diabetes of 10 years' duration and established cardiovascular disease, unlike the newly diagnosed participants of the UK Prospective Diabetes Study, to demonstrate this effect. The benefit of fenofibrate, however, did not persist. Intensive blood pressure control had no effect.

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The ACCORDION Eye Study Group is listed in Supplementary Appendix 1, Section 1, and the ACCORDION Study Group is listed in Supplementary Appendix 1, Section 2.

The United Kingdom Prospective Diabetes Study (UKPDS) (ISRCTN75451837) demonstrated that intensive glycemic control and intensive blood pressure (BP) control (<150/85 mmHg) slowed the progression of diabetic retinopathy in people with newly diagnosed type 2 diabetes (1,2). The continued beneficial effects of intensive glycemic control for microvascular complications were observed 10 years after the clinical trial (3). Similarly, the Diabetes Control and Complications Trial (DCCT) showed that ~6.5 years of intensive glycemic control was effective in reducing the risk of progression of diabetic retinopathy and that the effect persisted for at least 10 years after the trial ended in people with type 1 diabetes (4). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that fenofibrate reduced retinopathy progression in people with type 2 diabetes and additional risk factors for cardiovascular outcomes (5). For type 1 diabetes, the DCCT showed that ~6.5 years of intensive glycemic control was effective in reducing the risk of progression of diabetic retinopathy and that the effect persisted for at least 10 years after the trial ended (4). Most recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study demonstrated that intensive glycemic control and fenofibrate both reduced retinopathy progression in people with established type 2 diabetes and additional cardiovascular risk factors, whereas lowering of systolic BP (<120 mmHg) did not affect progression compared with <140 mmHg (6).

After the ACCORD trial was completed, surviving participants who were invited for follow-up in the main study and who had fundus photographs at baseline were invited to have additional photographs 8 years after randomization. The effects of a mean of 3.7 years of intensive glycemic control and ~5 years of intensive BP control and/or fenofibrate on the progression of diabetic retinopathy during 8 years of follow-up in the ACCORD Follow-On (ACCORDION) Eye Study are reported here.

RESEARCH DESIGN AND METHODS

ACCORD Study and ACCORD Eye Study

The designs of the original ACCORD Study and the ACCORD Eye Study were previously reported (7,8). Briefly, the ACCORD Study, a randomized trial conducted in the U.S. and Canada, enrolled 10,251 volunteers who had type 2 diabetes with glycosylated hemoglobin of ≥7.5% (58 mmol/mol). All participants were randomized to receive intensive glycemic control (targeting glycated hemoglobin level of <6.0% [42 mmol/mol]) or standard control (target of 7.0–7.9% [53–63 mmol/mol]). The 5,518 participants with dyslipidemia in the lipid trial were given simvastatin to lower the level of LDL cholesterol and were randomly assigned to fenofibrate (160 mg/day), to decrease triglyceride levels and to increase HDL cholesterol levels, or to placebo. The remaining 4,733 participants were randomly assigned intensive BP control (targeting systolic BP of <120 mmHg) or standard treatment (<140 mmHg). The primary outcome was a composite end point of time until the first occurrence of nonfatal stroke, nonfatal myocardial infarction, or death from cardiovascular causes.

The ACCORD Eye Study analyzed a subset of 2,856 participants who had not received laser photocoagulation or vitrectomy for proliferative diabetic retinopathy and who had baseline and year-4 data. These participants had seven-field stereoscopic fundus photographs that were assessed using a standard protocol at the University of Wisconsin-Madison Fundus Photograph Reading Center by trained graders with no knowledge of treatment assignments. The photographs were graded using an abbreviated and modified version of the Early Treatment Diabetic Retinopathy Study (ETDRS) Final Retinopathy Severity Scale for Persons, which accounts for both eyes with 17 steps (from 1, which is no retinopathy in either eye, to 17, which is high-risk proliferative diabetic retinopathy in both eyes) (9).

At each annual ACCORD visit, we asked participants whether they had undergone retinal laser photocoagulation or vitrectomy for proliferative diabetic retinopathy. Visual acuity was measured in the study clinics every 2 years in all ACCORD participants using a standardized visual acuity chart (ETDRS chart) to assess moderate vision loss, defined as worsening in either eye by three or more lines on the visual acuity chart from baseline.

The primary outcome for ACCORD Eye was a composite of progression of retinopathy of three steps or more or vitrectomy or laser photocoagulation for proliferative diabetic retinopathy. The primary goal was to determine whether any of three medical interventions would affect diabetic retinopathy progression. The ACCORD Study demonstrated that both intensive glycemic control and fenofibrate, but not intensive BP control, reduced retinopathy progression (6).

ACCORDION Eye Study

The ACCORDION Eye Study evaluated ACCORD Eye Study participants who had photographs at the ACCORD Eye Study

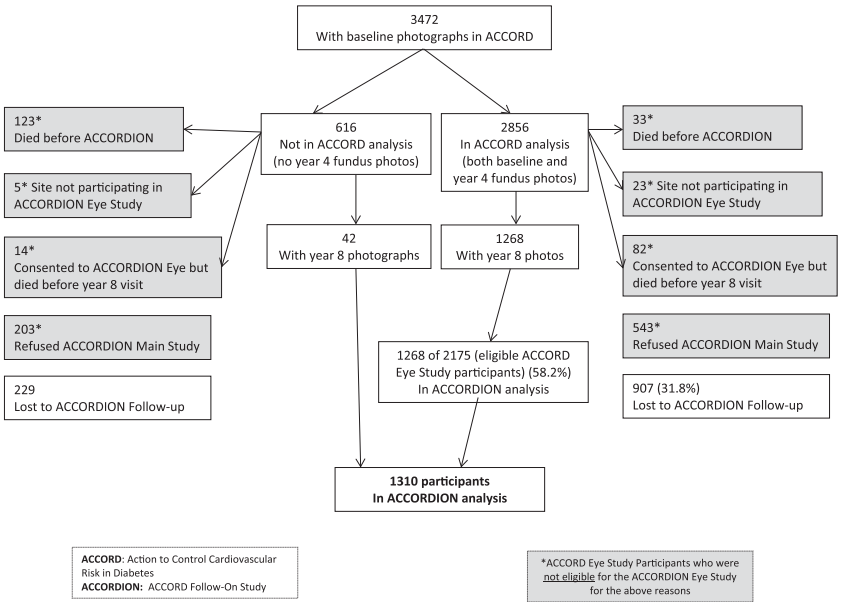

Figure 1—Consolidated Standards of Reporting Trials chart shows ACCORD participants enrolled in the ACCORDION Eye Study. *ACCORD Eye Study participants who were not eligible for the ACCORDION Eye Study for the above reasons.

baseline. The ACCORDION Eye Study examination was ~8 years after randomization and 3 to 5 years after the end of the randomized clinical trial. The 8-year examination included stereoscopic fundus photographs, but no additional clinical data were collected. The primary outcome was progression of diabetic retinopathy by three or more steps on the ETDRS person scale based on fundus photographs at year 8 compared with baseline. Measurement of visual acuity continued every 2 years in all participants at the ACCORDION clinics. A secondary outcome was the effect of the medical therapies on moderate visual loss, defined as in ACCORD Eye, three or more lines of vision loss compared with baseline.

Statistical Analyses

Comparisons of groups were made using a two-sample *t* test, χ^2 test, or trend test (baseline retinopathy). Separate models were used for each of the three primary hypotheses (glycemic control, lipid control, and BP control). In the ACCORDION Eye Study, the main comparisons were made using likelihood-ratio tests from logistic regression models with adjustment for the same factors used in the ACCORDION primary analyses (the trial [lipid vs. BP], the other treatments, prior cardiovascular events, and the network centers that supervised the clinics in each of the local regions). All analyses were based on the intention-to-treat principle. Interval-censored Cox proportional hazards models were used to assess three-step ETDRS progression using data at 0, 4, and 8 years in sensitivity analyses. Similar models were used to test for visual acuity loss in the entire ACCORDION cohort. Finally, models accounting for the competing risk of death were examined (10).

We performed 36 protocol-specified comparisons of subgroups defined on the basis of cutoff points that had been previously chosen (8) or used in the main ACCORD studies (11–13). Tests of interaction of baseline characteristics and other variables with treatment effect were performed by adding the subgroup and the interaction term to the primary models and using a likelihood-ratio test for the interaction. No adjustment for multiple comparisons was made. Multiple imputation was used for sensitivity analyses.

RESULTS

Of 2,856 ACCORD participants with baseline and year 4 eye examinations, 543 refused to enroll in the overall ACCORDION Study, 33 died before ACCORD finished, 82 died in the ACCORDION Study, and 23 were in sites that did not participate in the ACCORDION Study (Fig. 1). This left a potential 2,175 ACCORD Eye Study participants eligible for the ACCORDION Eye Study; of these, 1,268 (58%) had eye examinations at baseline, year 4, and year 8. In addition, 616 ACCORD Eye Study participants had baseline examinations only, and 42 of them returned for the examination at year 8, giving us 1,310 participants for this report. Table 1 compares ACCORD Eye Study participants who were examined in the ACCORDION Eye Study (*n* = 1,310) with those who did not participate in the ACCORDION Eye Study (*n* = 2,162). The ACCORDION Eye Study participants were more likely to be white, with lower levels of glycated hemoglobin, LDL cholesterol, systolic BP, and urinary albumin creatinine ratio, and lower rates of current and past smoking. They had fewer prior cardiovascular events and had less severe diabetic retinopathy than the nonparticipants.

Baseline Characteristics

Of the 1,310 ACCORDION Eye Study participants, 762 were enrolled in the lipid study and 548 in the BP study. The comparisons of the baseline characteristics by treatment group for each of the three studies showed minimal differences (Table 2).

At the beginning of the ACCORD Eye Study in 2003, the baseline glycated hemoglobin was 8.1% (65 mmol/mol) for the intensive glycemia group and 8.2% (66 mmol/mol) for the standard glycemia group (Fig. 2*A*). During the course of the ACCORD Eye Study, the hemoglobin A_{1c} decreased to a mean of 6.4% (46 mmol/mol) in the intensive group and to 7.7% (61 mmol/mol) in the standard

Table 1—Baseline characteristics of ACCORD Eye Study participants who consented and were eligible for the ACCORDION Eye Study

	Not in ACCORDION analysis (*n* = 2,162)	In ACCORDION analysis (*n* = 1,310)	*P* value
Age (years)	61.9 ± 6.9	61.3 ± 5.8	0.0235
Diabetes duration (years)	10.1 ± 7.3	9.9 ± 6.8	0.3652
Female sex	840 (38.9)	493 (37.6)	0.4740
Previous cardiovascular event	762 (35.2)	361 (27.6)	<0.0001
Nonwhite race	733 (33.9)	345 (26.3)	<0.0001
Glycated hemoglobin (%) (mmol/mol)	8.3 ± 1.1 (65 ± 10.9)	8.2 ± 1.0 (67 ± 12.0)	<0.0001
HDL cholesterol (mg/dL)	42.1 ± 11.5	41.7 ± 10.6	0.3365
LDL cholesterol (mg/dL)	103.0 ± 33.4	99.2 ± 32.7	0.0010
Triglycerides (mg/dL)	198.6 ± 163.6	190.6 ± 152.3	0.1506
Systolic BP (mmHg)	135.9 ± 17.3	133.1 ± 16.4	<0.0001
Diastolic BP (mmHg)	75.2 ± 10.8	74.7 ± 10.4	0.1651
Urinary albumin-to-creatinine ratio	94.6 ± 312.1	48.7 ± 164.1	<0.0001
BMI (kg/m^2)	32.6 ± 5.5	32.3 ± 5.4	0.1487
Visual acuity (Snellen equivalent)	74.8 ± 10.7 (20/30)	76.8 ± 9.7 (20/30)	<0.0001
Smoking status			0.0007
Never smoked	842 (38.9)	573 (43.8)	
Previous smoker	987 (45.7)	588 (44.9)	
Current smoker	333 (15.4)	148 (11.3)	
Diabetic retinopathy status			0.0121
None	1,036 (48.8)	687 (52.4)	
Mild	377 (17.8)	251 (19.2)	
Moderate NPDR	675 (31.8)	362 (27.6)	
Severe NPDR	7 (0.3)	3 (0.2)	
PDR	28 (1.3)	7 (0.5)	

Data are presented as mean ± SD or as *n* (%). NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Table 2—Baseline characteristics of the ACCORDION Eye Study participants

	ACCORDION Eye	Glycemia			Lipid			BP		
	Overall (N = 1,310)	Intensive (n = 658)	Standard (n = 652)	P value	Fibrate plus simvastatin (n = 399)	Placebo plus simvastatin (n = 363)	P value	Intensive (n = 280)	Standard (n = 268)	P value
Age (years)	61.3 ± 5.8	61.4 ± 5.9	61.2 ± 5.7	0.51	61.8 ± 5.8	61.1 ± 5.6	0.14	61.3 ± 5.8	61.1 ± 6.1	0.63
Diabetes duration (years)	9.9 ± 6.8	9.6 ± 6.7	10.1 ± 6.9	0.18	9.8 ± 6.5	9.4 ± 6.6	0.37	10.5 ± 6.8	10.1 ± 7.3	0.59
Female sex	493 (37.6)	240 (36.5)	253 (38.8)	0.38	110 (27.6)	134 (36.9)	0.006	127 (45.4)	122 (45.5)	0.97
Previous cardiovascular event	361 (27.6)	187 (28.4)	174 (26.7)	0.48	108 (27.1)	100 (27.5)	0.88	78 (27.9)	75 (28.0)	0.97
Nonwhite race	345 (26.3)	165 (25.1)	180 (27.6)	0.30	105 (26.3)	96 (26.4)	0.97	69 (24.6)	75 (28.0)	0.37
Glycated hemoglobin (%) (mmol/mol)	8.2 ± 1.0 (66 ± 10.9)	8.1 ± 0.9 (65 ± 9.8)	8.2 ± 1.0 (66 ± 10.9)	0.08	8.2 ± 1.0 (66 ± 10.9)	8.1 ± 0.9 (65 ± 9.8)	0.17	8.3 ± 1.0 (67 ± 10.9)	8.2 ± 1.0 (66 ± 10.9)	0.35
HDL cholesterol (mg/dL)	41.7 ± 10.6	41.9 ± 11.0	41.4 ± 10.3	0.44	38.2 ± 7.4	38.9 ± 7.6	0.24	46.2 ± 12.5	45.9 ± 12.8	0.72
LDL cholesterol (mg/dL)	99.2 ± 32.7	97.7 ± 32.7	100.7 ± 32.6	0.10	94.9 ± 30.4	96.4 ± 29.8	0.49	106.1 ± 36.4	102.1 ± 34.4	0.19
Triglycerides (mg/dL)	190.6 ± 152.3	197.3 ± 175.0	183.8 ± 125.1	0.11	186.5 ±101.4	182.8 ± 104.7	0.61	199.1 ± 167.2	198.5 ± 232.7	0.97
Systolic BP (mmHg)	133.1 ± 16.4	132.7 ± 16.1	133.4 ± 16.7	0.47	129.9 ± 15.6	129.4 ± 16.8	0.66	136.8 ± 15.9	138.6 ± 15.0	0.17
Diastolic BP (mmHg)	74.7 ± 10.4	74.7 ± 10.1	74.7 ± 10.6	0.98	73.6 ± 10.0	73.2 ± 10.5	0.54	75.4 ± 10.3	77.4 ± 10.2	0.02
Urinary albumin-to-creatinine ratio	48.7 ± 164.1	44.9 ± 133.5	52.5 ± 190.1	0.41	44.5 ± 126.2	58.7 ± 229.0	0.28	43.9 ± 133.7	46.3 ± 134.6	0.84
BMI (kg/m^2)	32.3 ± 5.4	32.4 ± 5.2	32.3 ± 5.6	0.81	32.0 ± 5.4	32.6 ± 5.3	0.17	32.3 ± 5.6	32.4 ± 5.3	0.83
Visual acuity	76.8 ± 9.7	76.7 ± 9.7	76.9 ± 9.6	0.75	76.8 ± 9.8	77.2 ± 9.6	0.56	76.9 ± 9.2	76.1 ± 10.0	0.33
Smoking status				0.83			0.42			0.98
Never smoked	573 (43.8)	284 (43.2)	289 (44.4)		164 (41.2)	166 (45.7)		123 (43.9)	120 (44.8)	
Previous smoker	588 (44.9)	301 (45.7)	287 (44.1)		183 (46.0)	157 (43.3)		128 (45.7)	120 (44.8)	
Current smoker	148 (11.3)	73 (11.1)	75 (11.5)		51 (12.8)	40 (11.0)		29 (10.4)	28 (10.4)	
Diabetic retinopathy status				0.35			0.32			0.44
None	687 (52.4)	350 (53.2)	337 (51.7)		219 (54.9)	191 (52.6)		143 (51.1)	134 (50.0)	
Mild	251 (19.2)	119 (18.1)	132 (20.2)		75 (18.8)	73 (20.1)		51 (18.2)	52 (19.4)	
Moderate NPDR	362 (27.6)	186 (28.3)	176 (27.0)		103 (25.8)	98 (27.0)		81 (28.9)	80 (29.9)	
Severe NPDR	3 (0.2)	1 (0.2)	2 (0.3)		1 (0.3)	0 (0.0)		1 (0.4)	1 (0.4)	
PDR	7 (0.5)	2 (0.3)	5 (0.8)		1 (0.3)	1 (0.3)		4 (1.4)	1 (0.4)	

NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

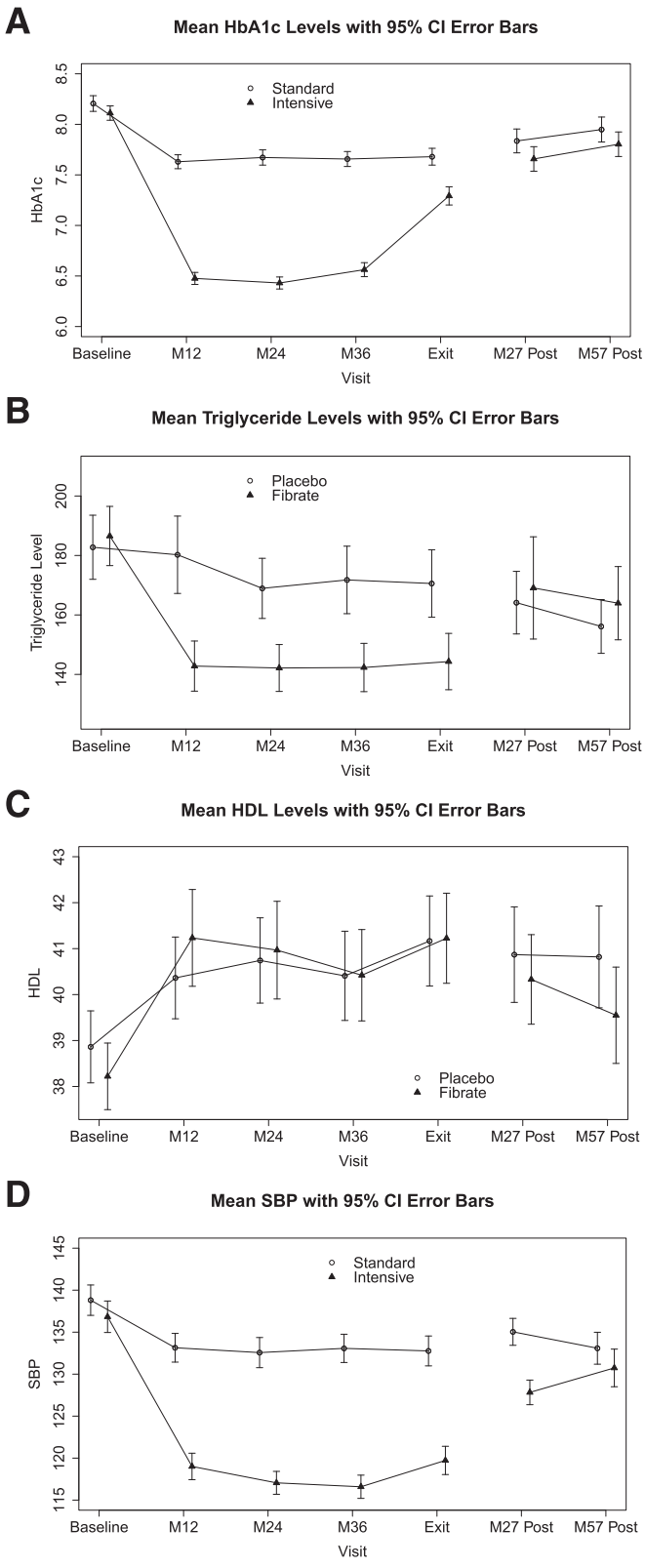

Figure 2—Mean levels for glycosylated hemoglobin A_{1c} (*A*), triglyceride (*B*), HDL cholesterol (*C*), and systolic BP (*D*) through ACCORD and ACCORDION. Exit, end of ACCORD trial; M, month; Post, postend of ACCORD trial.

group. Intensive glycemia management was stopped in February 2008, after a median of 3.7 years (IQR 2.7–4.3) of follow-up due to an increase in all-cause mortality (11). Eye study participants continued in the trial with the standard therapy until the end of the study in June 2009. The glycated hemoglobins were 7.3% (56 mmol/mol) for the intensive glycemia group and 7.7% (61 mmol/mol) for the standard glycemia group at the beginning of the ACCORDION Study. By the end of ACCORDION, the A1C levels were similar: 7.8% (62 mmol/mol) and 7.9% (63 mmol/mol) for the intensive and standard treatment groups, respectively ($P = 0.1$) (Fig. 2*A*).

Similarly, the serum triglyceride levels in both groups of the study were almost identical at baseline at 196 mg/dL and 194 mg/dL, for the fenofibrate plus simvastatin and the placebo plus simvastatin groups, respectively. However, the difference in the serum triglyceride levels achieved during the course of ACCORD in the two treatment groups was eliminated during the ACCORDION Study when fenofibrate was no longer administered (Fig. 2*B*). The difference in the HDL cholesterol achieved during the study also diminished when fenofibrate was stopped (Fig. 2*C*). Intensive BP management also reduced the systolic and diastolic BPs compared with the standard BP treatment during the ACCORD Study. Again, this difference was reduced when the clinical trial was stopped, although some difference remained (Fig. 2*D*).

Progression of Diabetic Retinopathy

Table 3 reports the results of the previously published data on the effects of the medical therapy in ACCORD using the composite primary outcome, which consisted of three or more steps of progression along the ETDRS scale or vitrectomy or laser photocoagulation for diabetic retinopathy. Similar analyses were repeated for the ACCORD data using the ACCORDION primary outcome of progression of three or more steps along the ETDRS scale only. The results for this outcome were not substantially different from the analyses of the composite outcome, confirming the beneficial effects of intensive glycemic control and the management of dyslipidemia with fenofibrate (plus simvastatin) on the progression of diabetic retinopathy, with adjusted odds ratios (ORs) of 0.61 ($P = 0.001$) and 0.54 ($P = 0.002$), respectively (Table 3).

Intensive Versus Standard Glycemic Therapy in ACCORDION

Among the 1,310 participants in the glycemia study, 38 of 658 (5.8%) of the ACCORDION participants randomized to

Table 3—The effects of medical therapies on the progression of diabetic retinopathy in the ACCORD and ACCORDION Studies[a]

	ACCORD[b]			ACCORD (photographic grading data only)[c]			ACCORDION[d]		
	n/N (%)	Adjusted OR (95% CI)	*P* value	*n/N* (%)	Adjusted OR (95% CI)	*P* value	*n/N* (%)	Adjusted OR (95% CI)	*P* value
Glycemia therapy		0.67 (0.51–0.87)	0.003		0.61 (0.46–0.82)	0.001		0.42 (0.28–0.63)	<0.0001
Intensive	104/1,429 (7.3)			81/1,418 (5.7)			38/658 (5.8)		
Standard	149/1,427 (10.4)			126/1,418 (8.9)			83/652 (12.7)		
Dyslipidemia therapy		0.60 (0.42–0.87)	0.006		0.54 (0.36–0.80)	0.002		1.13 (0.71–1.79)	0.60
Simvastatin/fenofibrate	52/806 (6.5)			41/802 (5.1)			47/399 (11.8)		
Simvastatin/placebo	80/787 (10.2)			70/781 (9.0)			37/363 (10.2)		
Antihypertensive therapy		1.23 (0.84–1.79)	0.29		0.97 (0.64–1.47)	0.88		1.21 (0.61–2.40)	0.59
Intensive	67/647 (10.4)			48/640 (7.5)			21/280 (7.5)		
Standard	54/616 (8.8)			48/613 (7.8)			16/268 (6.0)		

[a]Results of likelihood-ratio tests from logistic regression models. [b]Previously reported composite outcome: progression of 3 or more steps on the ETDRS severity scale of diabetic retinopathy, vitrectomy, or photocoagulation for the treatment of proliferative diabetic retinopathy. [c]Outcome consists only of the progression of 3 or more steps on the ETDRS scale for the classification of diabetic retinopathy. [d]At 8 years, photographic grading data only.

intensive glycemic control progressed by three or more steps on the ETDRS scale, and 83 of 652 (12.7%) in the standard treatment group progressed at year 8. The adjusted OR was 0.42 (95% CI 0.28–0.63, $P < 0.0001$) (Table 3). By an interval-censored Cox proportional hazards model with data for years 4 and 8 but including only participants who had data at year 8, the adjusted hazard ratio (HR) was 0.45 (95% CI 0.32–0.64, $P < 0.0001$) (Table 4). Similar analyses including all participants with data at year 4 or year 8 resulted in the adjusted HR of 0.56 (95% CI 0.44–0.71, $P < 0.0001$), again indicating a beneficial effect of intensive glycemic control compared with standard care (Table 4). When adjusted for the competing risk of death, the adjusted HR was 0.58 (95% CI 0.46–0.73, $P < 0.0001$) (Table 4). When the analysis was confined to the follow-up period in ACCORDION only, measuring the change at 8 years from the 4-year visit, the adjusted odds ratio (OR) was 0.67 (95% CI 0.39–1.14, $P = 0.13$).

Fenofibrate Plus Simvastatin Versus Placebo Plus Simvastatin

The rates of diabetic retinopathy progression at year 8 from the beginning of ACCORD were 11.8% (47 of 399) in the fenofibrate group and 10.2% (37 of 363) in the placebo group, with an adjusted OR of 1.13 (95% CI 0.71–1.79, $P = 0.60$) (Table 3). Using the Cox proportional hazards model resulted in an adjusted HR of 0.76 (95% CI 0.57–1.03, $P = 0.08$) (Table 4). When adjusted for the competing risk of death, the adjusted HR was 0.83 (95% CI 0.69–1.00, $P = 0.04$) (Table 4).

Intensive Versus Standard BP Control

The rates of diabetic retinopathy progression were 7.5% (21 of 280) and 6.0% (16 of 268) in the intensive and standard BP groups, respectively, with an adjusted OR of 1.21 (95% CI 0.61–2.40, $P = 0.59$) (Table 3). Using an interval censored Cox proportional hazards model resulted in an adjusted HR of 1.05 (95% CI 0.73–1.51, $P = 0.79$) (Table 4).

Visual Acuity Changes in the ACCORDION Eye Study

Moderate Vision Loss

Visual acuity was measured every 2 years at the clinical site. Moderate vision loss was defined as three or more lines of vision loss on a logarithmic visual acuity

Table 4—The effects of medical therapies in the sensitivity analyses conducted with interval-censored Cox proportional hazards models using both year 4 and year 8 data

	Only participants with year 8 data			All participants (those with years 4 or 8 data)			ACCORDION (death as a competing risk)		
	n/N (%)	Adjusted HR (95% CI)	*P* value	*n/N* (%)	Adjusted HR (95% CI)	*P* value	*n/N* (%)	Adjusted HR (95% CI)	*P* value
Glycemia therapy									
Intensive	49/658 (7.4)	0.45 (0.32–0.64)	<0.0001	106/1,437 (7.4)	0.56 (0.44–0.71)	<0.0001	336/1,541 (21.8)	0.58 (0.46–0.73)	<0.0001
Standard	102/652 (15.6)			183/1,442 (12.7)			428/1,541 (27.8)		
Dyslipidemia therapy									
Simvastatin/fenofibrate	50/399 (12.5)	0.84 (0.57–1.24)	0.38	78/815 (9.6)	0.76 (0.57–1.03)	0.08	219/870 (25.2)	0.83 (0.69–1.00)	0.04
Simvastatin/placebo	50/363 (13.8)			93/796 (11.7)			238/861 (27.6)		
Antihypertensive therapy									
Intensive	29/280 (10.4)	1.23 (0.70–2.14)	0.47	62/650 (9.5)	1.05 (0.73–1.51)	0.79	153/688 (22.2)	0.95 (0.76–1.20)	0.68
Standard	22/268 (8.2)			56/618 (9.1)			154/663 (23.2)		

chart from baseline. The rates of moderate vision loss in the ACCORDION Eye Study at 8 years were 29.6% for the intensive glycemic therapy group and 31.7% for the standard glycemic group, with an adjusted HR of 0.98 (95% CI 0.90–1.07, $P = 0.67$) (Table 5). Rates of moderate vision loss at year 8 were 29.7% and 30.2% in the fenofibrate and placebo groups, respectively, with an adjusted HR of 0.95 (95% CI 0.84–1.08, $P = 0.45$) (Table 5). Such rates of vision loss at year 8 were 32.8% and 30.2% in the intensive BP control and standard groups, respectively, with an adjusted HR of 1.15 (95% CI 1.01–1.31, $P = 0.04$) (Table 5). Table 5 also reports the results from the ACCORD Eye Study for comparison.

Subgroup Analyses

In the ACCORDION Eye Study, similar to the ACCORD Eye Study, we found no significant interactions between treatment and any of the prespecified characteristics in subgroup analyses, with the exception of baseline retinopathy (nominal $P = 0.01$) in the lipid trial and sex (nominal $P = 0.01$) and smoking (nominal $P = 0.02$) in the BP trial (Figs. 3, 4, and 5). With the exception of interaction of sex in the BP trial, there was no interaction between treatment and sex or between sex and race in these analyses.

Sensitivity Analyses

Two sensitivity analyses were done to assess the applicability of these findings from a subset of ACCORDION participants to all ACCORDION participants. First, an analysis was restricted to participants at ACCORDION sites in which 80% or more of the participants were examined in both arms of the glycemia trial at year 8 ($n = 365$). In this subset, the OR for progression of diabetic retinopathy was 0.32 (95% CI 0.06–1.65). Second, the effect of the intervention on a post hoc composite outcome of progression of eye disease or death was estimated as an alternative way of accounting for the competing risk of death. This estimate yielded an OR of 0.71 (95% CI 0.58–0.87).

CONCLUSIONS

Our results showed that intensive glycemic control conferred enduring protection from progression of diabetic retinopathy even though the glycated hemoglobin levels were similar 8 years after randomization and ~4 years after the cessation of the clinical trial. This is the first study in people with type 2 diabetes of ~10 years' duration and established cardiovascular disease, unlike the newly diagnosed participants in the UKPDS, that demonstrated this effect. This phenomenon has been called "metabolic memory" or "legacy effect" in the studies of type 1 diabetes (14). At 10 years after the clinical trial, the UKPDS showed that microvascular complications, which included self-reports of vitreous hemorrhage, retinal photocoagulation, or renal failure, continued to be reduced significantly by 24% in those previously assigned to tight glycemic control (sulfonylurea-insulin group) versus standard glycemic control (relative risk 0.76, 95% CI 0.64–0.89, $P < 0.001$) (3). However, for those randomized to metformin versus standard care in the UKPDS, there was no statistically significant beneficial effect in reducing microvascular risk (relative risk 0.84, 95% CI 0.60–1.17, $P = 0.31$) (3). The first report after the termination of DCCT also showed that after 4 years of follow-up in EDIC, the intensive glycemic treatment group had a 75% ($P < 0.001$) reduction in the risk of progression of diabetic retinopathy compared with the conventional glycemic treatment group (15). This effect was shown to last for 10 years in a subsequent report (14). Their most recent report showed, after a median follow-up of 23 years, a 48% reduction in the risk of ocular procedures in participants originally randomized to the intensive treatment group (16). It has been suggested that it is important to implement intensive glycemic control as early as possible to obtain the maximum effect (14).

The ACCORDION findings demonstrate a similar legacy effect of intensive glycemia control on the progression of retinal disease in people with established type 2 diabetes. Moreover, this effect occurred in response to a median of 3.7 years of intensive glycemic control (17), and was observed in people with type 2 diabetes and additional cardiovascular risk factors, whose mean diabetes duration was 10 years, and whose initial mean HbA_{1c} was 8.2%. These observations suggest that glucose lowering can reduce progression of retinal disease relatively late in the course of diabetes and that the retina responds to relatively short-term changes in glucose levels. Whether

Table 5—The effects of medical therapies in ACCORD and ACCORDION on visual acuity: The results of the proportional hazard modeling for moderate visual loss[a]

	Original ACCORD			ACCORDION[b]		
Treatment	*n*/*N* (%)	Adjusted HR (95% CI)	*P* value	*n*/*N* (%)	Adjusted HR (95% CI)	*P* value
Glycemia therapy		0.88 (0.77–1.01)	0.06		0.98 (0.90–1.07)	0.67
Intensive	409/1,715 (23.8)			508/1,715 (29.6)		
Standard	457/1,737 (26.3)			551/1,737 (31.7)		
Dyslipidemia therapy		0.95 (0.79–1.14)	0.57		0.95 (0.84–1.08)	0.45
Simvastatin and fenofibrate	227/956 (23.7)			284/956 (29.7)		
Simvastatin and placebo	233/950 (24.5)			287/950 (30.2)		
Antihypertensive therapy		1.17 (0.96–1.42)	0.12		1.15 (1.01–1.31)	0.04
Intensive	221/798 (27.7)			262/798 (32.8)		
Standard	185/748 (24.7)			226/748 (30.2)		

[a]Moderate vision loss: three or more lines of visual loss compared with baseline. [b]Participants who were examined in ACCORDION and had visual acuity assessments at their study/medical center.

an even shorter period of glucose lowering could achieve a similar long-term effect on the eyes in either type 2 or type 1 diabetes remains unknown.

Combination therapy with fenofibrate plus simvastatin versus placebo plus simvastatin in the ACCORD Eye Study resulted in beneficial effects. However, when the fenofibrate therapy was discontinued after the ACCORD trial was stopped, the differences in the levels of triglycerides and HDL cholesterol were

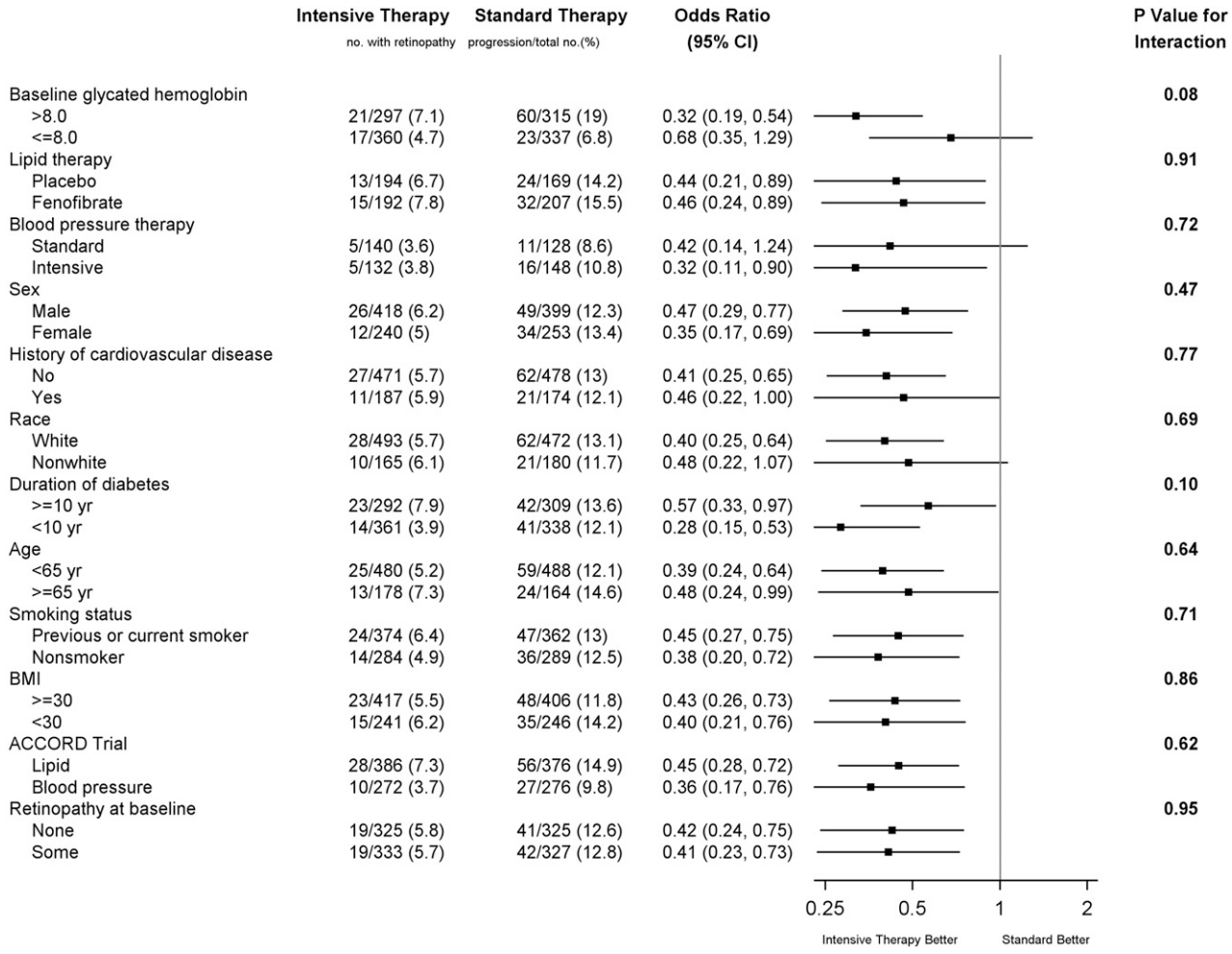

Figure 3—Subgroup effects in the ACCORDION participants previously randomized in the glycemia trial. The estimated ORs for progression of diabetic retinopathy are indicated as squares (with the area proportional to the sample size). The vertical line is the overall treatment effect. Data were missing for some patients in some subgroups. The comparison between the subgroup enrolled in the ACCORDION lipid trial and the subgroup enrolled in the ACCORDION BP trial was not specified within the protocol. Race was self-reported. The BMI is the weight in kilograms divided by the square of the height in meters. A logarithmic scale is used on the *x* axis.

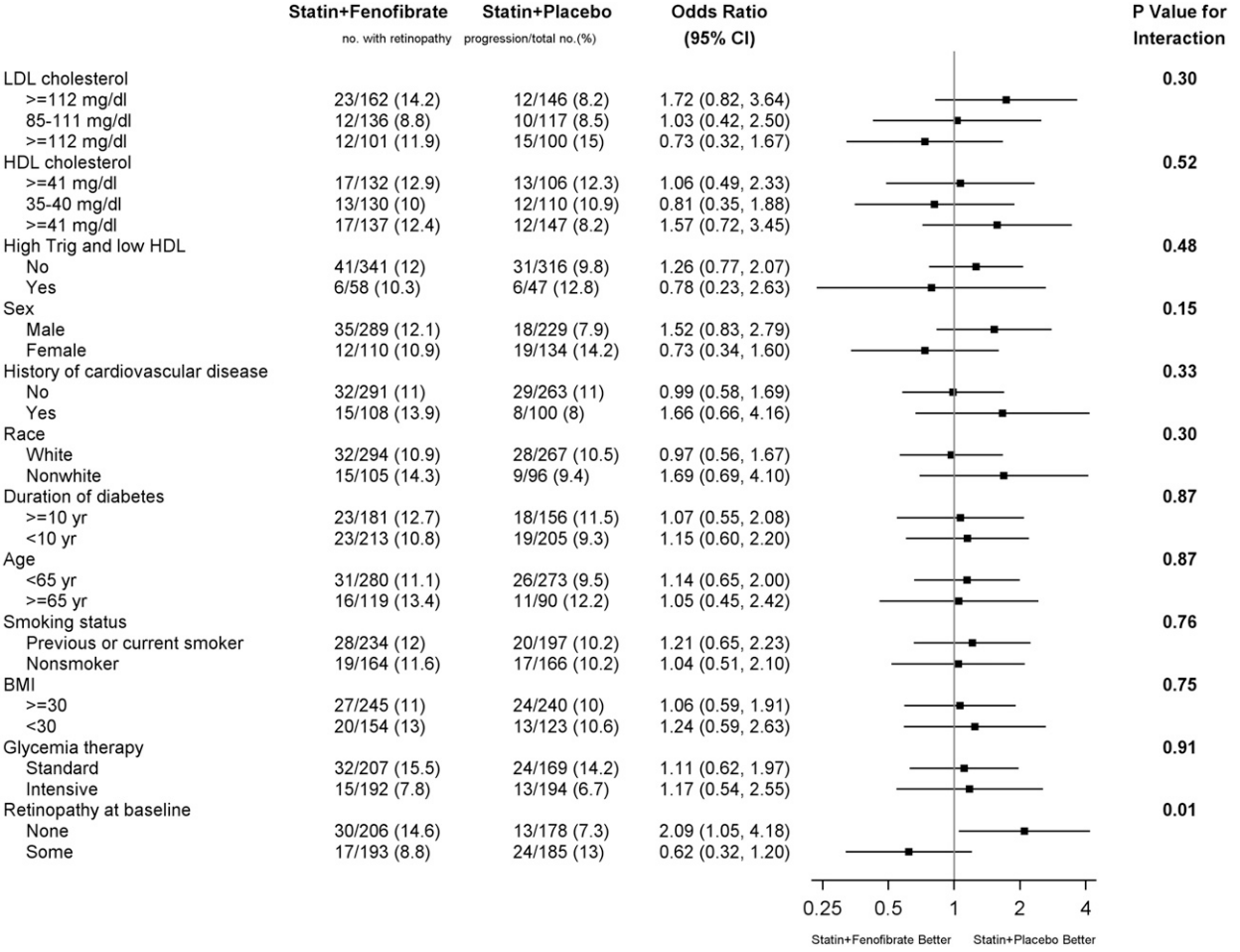

Figure 4—Subgroup effects in the ACCORDION participants previously randomized in the lipid trial. The estimated ORs for progression of diabetic retinopathy are indicated as squares (with the area proportional to the sample size). The vertical line is the overall treatment effect. Data were missing for some patients in some subgroups. Two comparisons were not specified within the protocol: the comparison between the subgroup with triglyceride levels of 204 mg/dL (2.3 mmol/L) or higher and HDL cholesterol levels of 34 mg/dL (0.9 mmol/L) or less and the subgroup with lower triglyceride levels or higher HDL cholesterol levels, and the comparison between the subgroup with some retinopathy and the subgroup with none. Race was self-reported. The BMI is the weight in kilograms divided by the square of the height in meters. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. A logarithmic scale is used on the *x* axis.

lost. The benefit was no longer seen, except in analyses accounting for death as a competing event, and even here, the estimated effect was greatly diminished. This would suggest that the beneficial effect of fenofibrate on the progression of diabetic retinopathy during the trial may be clinically important and that these effects require continued treatment with fenofibrate to be maintained. The subgroup analyses from the ACCORD Eye Study showed that the beneficial effect was most prominent in people who had diabetic retinopathy at baseline (6). Our secondary analyses in the ACCORD Eye Study also showed that in those with baseline mild and moderate diabetic retinopathy, the ORs were 0.27 (95% CI 0.12–0.63, P = 0.0009) and 0.41 (95% CI 0.14–1.18, P = 0.09), respectively (18). These findings confirm the overall FIELD study results, which showed beneficial effects of fenofibrate (200 mg daily) versus placebo in reducing the need for laser photocoagulation (HR 0.69, 95% CI 0.56–0.84, P = 0.0002) (4). In a substudy of participants in the FIELD study with fundus photographs, an exploratory composite end point, which included two-step progression of diabetic retinopathy, the development of macular edema, or the need for laser photocoagulation, was also significantly lower in the fenofibrate group compared with the placebo group (HR 0.66, 95% CI 0.47–0.94, P = 0.02) (4).

The results of these two studies would suggest that fenofibrate may potentially be a therapy for individuals with type 2 diabetes to decrease the progression of diabetic retinopathy, especially in those with preexisting diabetic retinopathy. A number of investigators have evaluated the potential mechanisms of action, including its ability to be a lipid-modifying drug, by decreasing plasma triglyceride, apolipoprotein B, and LDL cholesterol levels and by increasing HDL cholesterol and apolipoprotein A-I (19). However, the beneficial effects of fenofibrate did not correlate with changes in serum lipid levels in the FIELD and ACCORD Eye Study. It is possible that the serum lipids have less of a role, while the regulation of intraretinal lipid transport has been implicated in the pathogenesis of diabetic retinopathy. A number of other nonlipid-related mechanisms have also been proposed, including antiapoptotic, anti-inflammatory,

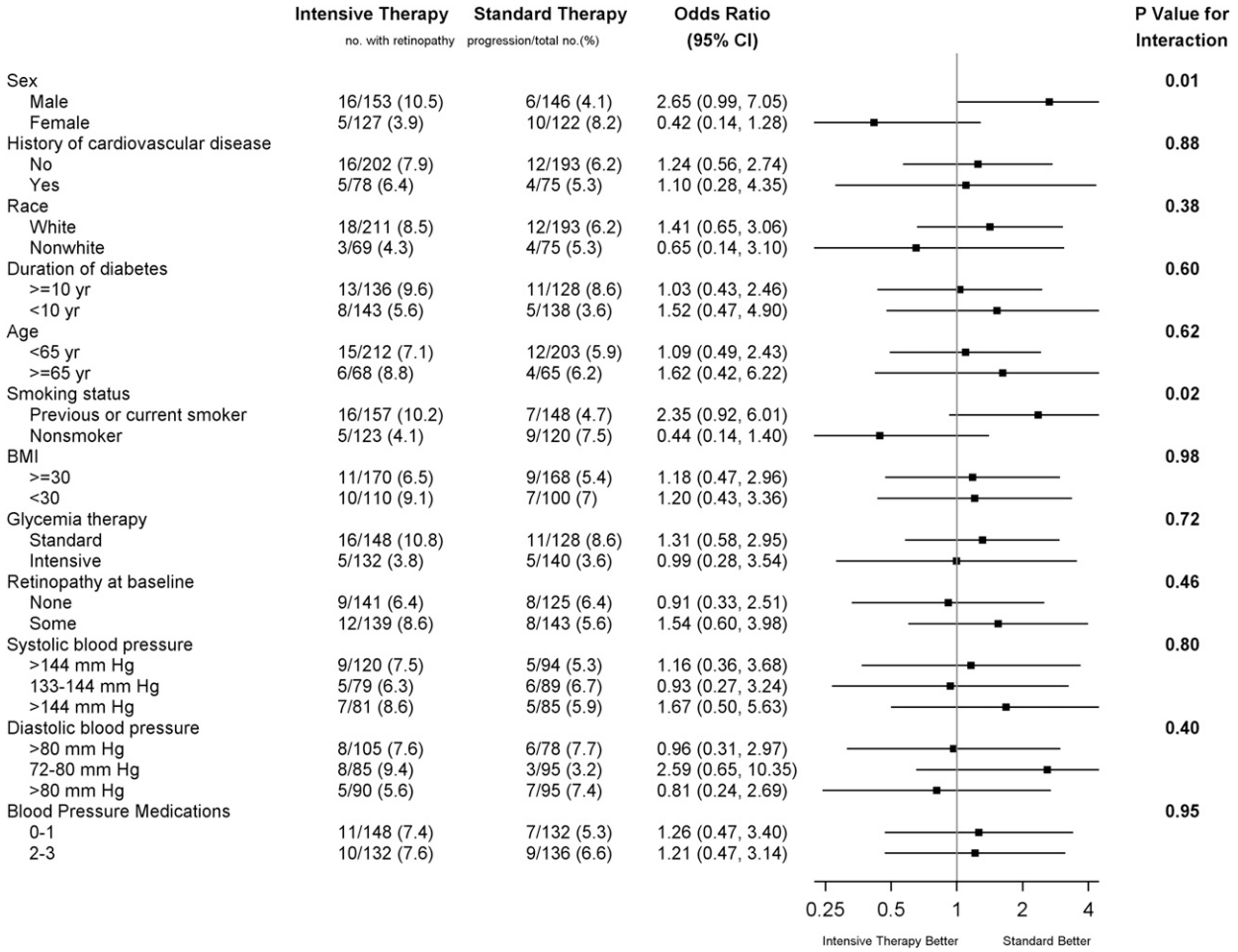

Figure 5—Subgroup effects in the ACCORDION participants previously randomized in the BP trial. The estimated ORs for progression of diabetic retinopathy are indicated as squares (with the area proportional to the sample size). The vertical line is the overall treatment effect. Data were missing for some patients in some subgroups. The last four comparisons shown in the figure were not specified in the protocol. Race was self-reported. The BMI is the weight in kilograms divided by the square of the height in meters. A logarithmic scale is used on the *x* axis.

antioxidant, and antiangiogenic actions. There are also thoughts that fenofibrate, a peroxisome proliferator–activated receptor α agonist, may also impart neuroprotective effects and provide protection from the breakdown of the blood-retinal barrier (20).

Because fenofibrate failed to have an effect on cardiovascular events in ACCORD and FIELD, it is not routinely prescribed for the management of dyslipidemia by medical physicians. Ophthalmologists rarely prescribe medical therapies directed at other organ systems, but in this instance, it is important for both ophthalmologists and medical physicians to collaborate and to reconsider the role of fenofibrate for the treatment of diabetic retinopathy, especially in those who already exhibit some degree of diabetic retinopathy (21).

We did not demonstrate an effect of intensive BP control on the progression of diabetic retinopathy at 4 or 8 years. In contrast, the UKPDS showed that intensive BP control (<150 vs. <180 mmHg) resulted in a significant reduction in the progression of diabetic retinopathy (34.0% vs. 51.3%, $P = 0.004$) and moderate vision loss (10.2% vs. 19.4%, $P = 0.004$) after 7.5 years (2).

That the reduction in the progression of diabetic retinopathy did not affect the rates of moderate visual loss is not surprising. This was also seen in the ACCORD Eye Study. To show a difference in visual acuity, a much larger sample size would be required because the treatments for diabetic retinopathy are highly effective in reducing severe vision loss by as much as 95% (22).

Limitations in the ACCORDION Eye Study include the low recruitment rate of ACCORD Eye participants (nearly 60% of those eligible from the ACCORD Eye cohort) and that the participants in ACCORDION Eye tended to be healthier and younger, with lower baseline glycated hemoglobin, fewer previous cardiovascular events, and less severe diabetic retinopathy. However, our sensitivity analyses showed that the point estimate of 0.32 from the adjusted OR of the participants who were enrolled in clinics, in which 80% of the participants returned for the follow-up study at year 8, was similar to the overall adjusted OR of 0.42. The effect of the intervention on a post hoc composite outcome of progression of eye disease or death was estimated as an alternative way of accounting for the competing risk of death. This estimate yielded an OR of 0.71 (95% CI 0.58–0.87). The point estimates of the clinics with a high yield of return participants in ACCORDION were very similar to the overall results from

ACCORDION Eye, suggesting that these results from the subset of ACCORDION Eye Study participants may indeed be applicable to the ACCORDION Study population.

Another limitation of our study was that data on retinopathy outcomes were collected only once during this follow-up study. Although some studies such as the DCCT collected annual progression rates, it is important to note that progression in diabetic retinopathy was evaluated during 3-year intervals in the UKPDS, a study of individuals with type 2 diabetes. We also found no evidence of significant differences in missing data rates, and the results of the sensitivity analyses supported the results of the primary analyses.

In summary, our study results provide evidence that intensive glycemic control is beneficial for reducing the progression of diabetic retinopathy and that the legacy effect is evident in people with type 2 diabetes. ACCORD previously reported that 3.7 years of intensive glycemic control reduced progression of albuminuria as well as neuropathy during the treatment period and at 1.3 years after cessation of treatment (23). The addition of the ACCORDION retinal results to these prior findings demonstrates a posttreatment benefit of intensive glycemia control on the progression of eye, kidney, and nerve disease. There is also evidence that the beneficial effect of fenofibrate on diabetic retinopathy in the ACCORD Eye Study may be real but requires continued use of this treatment to maintain benefit. Therefore, it may be important to reconsider the use of fenofibrate for the treatment of diabetic retinopathy. Finally, systolic BP control to the levels of 140 mmHg or 120 mmHg had no harmful or beneficial effect in both the ACCORD Eye Study and the ACCORDION Eye Study.

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Author Contributions. E.Y.C., M.D.D., R.P.D., C.M.G., L.H.P., and W.T.A. designed the study, researched the data, wrote the manuscript, contributed to the discussion, and reviewed and edited the manuscript. J.F.L. and W.T.A. conducted the statistical analyses and critically reviewed the manuscript. H.C.G. wrote the manuscript and contributed to the discussion. H.C.G., F.I.-B., C.M.G., W.C.C., M.B.E., J.T.B., and H.N.G. collected the clinical data. F.I.-B., S.G., W.C.C., M.B.E., J.T.B., H.N.G., and D.C.G. reviewed and edited the manuscript. E.Y.C. and W.T.A. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Appendix

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