

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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### Section 3. Description of ETDRS grading scale.

Table 1. Abbreviated Summary of ETDRS Final Retinopathy Severity Scale for Individual Eyes

Level	Severity
10	DR absent
20	Microaneurysms only
35	Mild NPDR (HE, SE and/or mild H)
43	Moderate NPDR (mild IRMA or moderate H)
47	Moderately severe NPDR (mild VB, moderate IRMA or severe H)
53	Severe or very severe NPDR (moderate/severe VB, severe IRMA and/or very severe H)
60	Scars of photocoagulation for PDR or severe NPDR (SPC)
61	Mild PDR
65	Moderate PDR
71, 75	High risk PDR

H- Hemorrhage, HE – hard exudates, SE – soft exudates, IRMA – intraretinal microvascular abnormalities, VB –venous beading, DR- diabetic retinopathy, NPDR – Non proliferative diabetic retinopathy, PDR – proliferative diabetic retinopathy. Levels 35-53 require presence of microaneurysms in addition to specified abnormalities. The definition for each level assumes that the definition for any higher level is not met. Severities of abnormalities are defined in References 2 and 6.

Table 2. Abbreviated Summary of ETDRS Final Retinopathy Severity Scale for Persons

Level	Description	Scale step
10/10	No DR	1
20/<20	Microaneurysms only, one eye	2
20/20	Microaneurysms only, both eyes	3
35/<35	Mild NPDR, one eye	4
35/35	Mild NPDR, both eyes	5
43/<43	Moderate NPDR, one eye	6
43/43	Moderate NPDR, both eyes	7
47/<47	Moderately severe NPDR, one eye	8
47/43	Moderately severe NPDR, both eyes	9
53/<53	Severe or very severe NPDR, one eye	10
53/53	Severe or very severe NPDR, both eyes	11
60 or 61/<60	Mild PDR and/or SPC, one eye	12
60 or 61/60 or 61	Mild PDR and/orSPC, both eyes	13
65/<65	Moderate PDR, one eye	14
65/65	Moderate PDR, both eyes	15
71+/<71	High risk PDR, one eye	16
71+/71+	High risk PDR, both eyes	17+

Table 1 presents an abbreviated and slightly modified version of the Early Treatment Diabetic Retinopathy Study (ETDRS) Final Diabetic Retinopathy Severity Scale for individual eyes. The underlying scale had 6 steps, designated 1-6, which are retained here as the first digits of levels 10-65.<sup>1</sup> The second digit of each level, where different from 0, represents the final of several alternative definitions that were considered during development of the ETDRS scale and has no numerical meaning.<sup>2</sup> Level 60 was added after publication of the scale to prevent eyes in which few or none of the abnormalities graded remained following photocoagulation from being categorized as having mild or no retinopathy. When progression along the scale is assessed levels 60 and 61 are pooled as a single category (the 7<sup>th</sup> step on the Eye Scale). Levels 71 and 75 are usually considered separate steps. The scale is ordinal, but one of the goals in designing

it was that the steps divide the retinopathy severity spectrum into similar, clinically reasonable intervals.

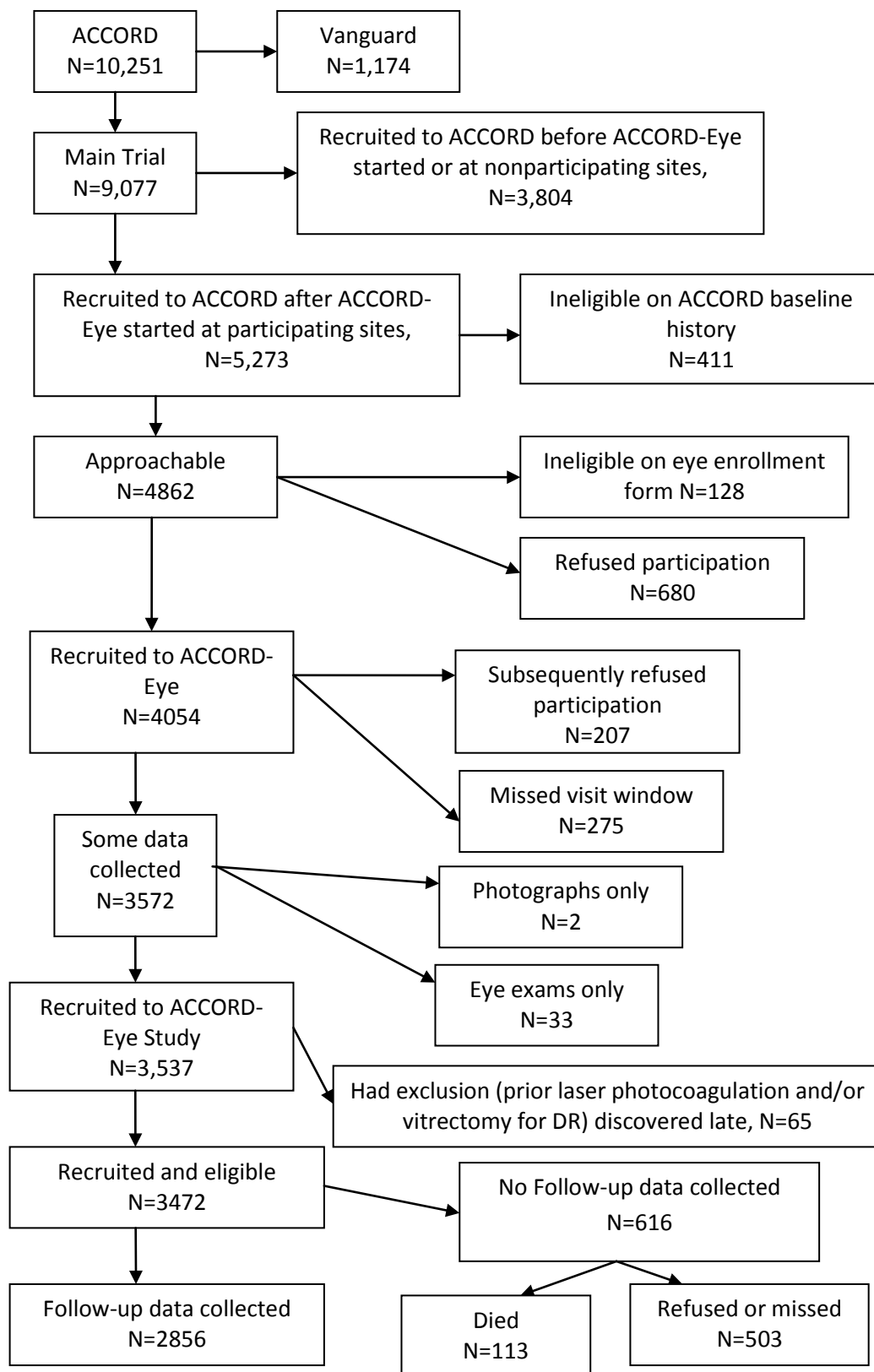
In Table 2 the eye levels defined in Table 1 are combined for persons in what has been called the “worse eye emphasized” method; persons are first categorized by maximum severity level in either eye and then by severity level in the second eye, either the same level as the first eye (e.g., 35/35) or any lesser level (e.g., 35/<35).

In the Diabetes Control and Complications Trial (DCCT) progression (worsening) by 3 or more steps on the person scale was chosen as the principal retinopathy outcome measure, in part because it was considered to be a clinically important change and in part to compensate for grading variability. In quality control exercises conducted throughout the trial exact agreement between replicate gradings was reported as ranging from 53.3% to 67.6%, agreement within 1 step from 84.3% to 95.0% and agreement within 2 steps from 96.2% to 98.3%.<sup>3</sup> Other outcomes frequently used are progression by 2 or more steps on the eye scale, which is similar to 3 or more steps on the patient scale, and 2 or more steps on the person scale, which increases the number of outcomes but may reduce precision.<sup>4,5</sup>

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2. Early Treatment Diabetic Retinopathy Study Research Group. Fundus photographic risk factors for progression of diabetic retinopathy. ETDRS Report Number 12. *Ophthalmology* 1991;98:823-833
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## Section 4. ACCORD Eye CONSORT diagram



## Section 5. Baseline characteristics of ACCORD Eye participants with and without follow-up and rest of ACCORD main trial

Baseline characteristics of participants enrolled in ACCORD Eye Study (with and without follow-up) with that of participants enrolled in the remainder of the ACCORD main trial. Reported values are either the means (SDs) or N (percentages).

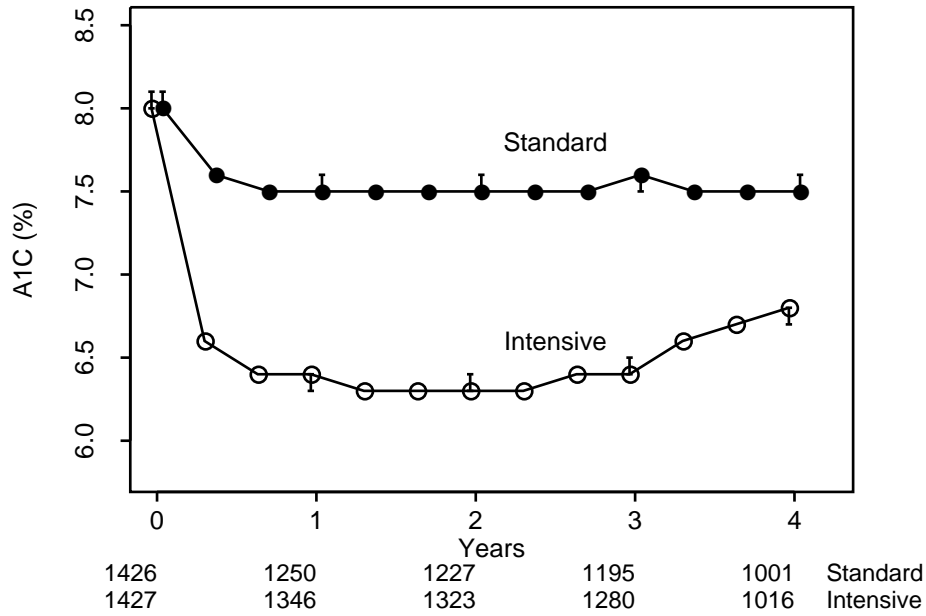
Variable	ACCORD Eye Study Participants with Follow-up	ACCORD Eye Study Participants without Follow-up	Remaining ACCORD Main Trial Participants	
	N=2856	N=616	N=5605	
Age (yr)	61.6 (6.3)	62.1 (7.1)	62.3 (6.9)	
Diabetes Duration (yr)	10.0 (7.1)	10.3 (7.0)	11.2 (8.1)	
Female	1090 (38.2%)	243 (39.4%)	2152 (38.4%)	
Previous cardiovascular event	895 (31.3%)	228 (37.0%)	2079 (37.1%)	
Nonwhite	860 (30.1%)	218 (35.4%)	2088 (37.3%)	
HbA1c (%)	8.2 (1.0)	8.4 (1.1)	8.2 (1.0)	
HDL (mg/dL)	41.9 (11.3)	41.7 (10.9)	41.8 (11.7)	
LDL (mg/dL)	100.7 (32.7)	105.3 (35.0)	105.0 (34.3)	
Triglycerides (mg/dL)	195.1 (162.6)	198.2 (144.2)	189.6 (148.7)	
Systolic BP (mm Hg)	134.5 (17.0)	136.4 (17.2)	136.5 (17.1)	
Diastolic BP (mm Hg)	74.9 (10.5)	75.3 (11.3)	74.7 (10.7)	
Urinary Albumin/Creatinine (mg/mg)	71.8 (253.1)	102.7 (322.4)	102.7 (382.9)	
BMI (kg/m <sup>2</sup> )	32.4 (5.5)	32.7 (5.5)	32.2 (5.5)	
Visual Acuity (mean of both eyes)*	75.9 (10.2)*	73.7 (10.9)*	72.8 (12.7)*	
Smoking	Never	1188 (41.6%)	227 (36.9%)	2351 (42.0%)
	Former	1280 (44.8%)	295 (47.9%)	2428 (43.4%)
	Current	387 (13.6%)	94 (15.3%)	814 (14.6%)

\*Approximate Snellen Visual Acuity (74 to 78 letter = 20/30, 69 to 73 letters = 20/40)

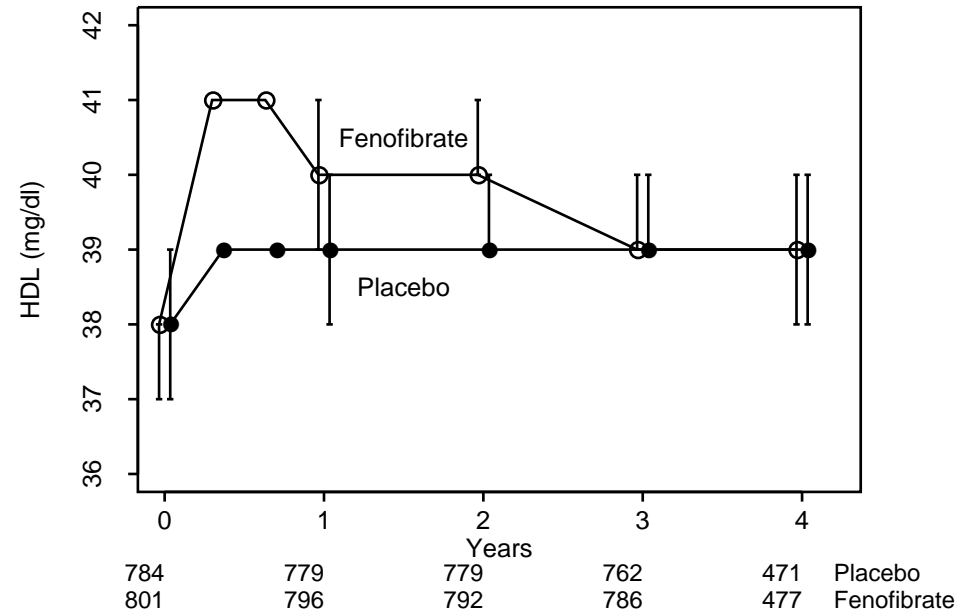
## **Section 6. Longitudinal plots of A1c, HDL, triglycerides, and systolic BP**

Figure. Median A1c (a), HDL (b), triglycerides (c), and systolic blood pressure (d) by treatment assignment with 95% confidence intervals.

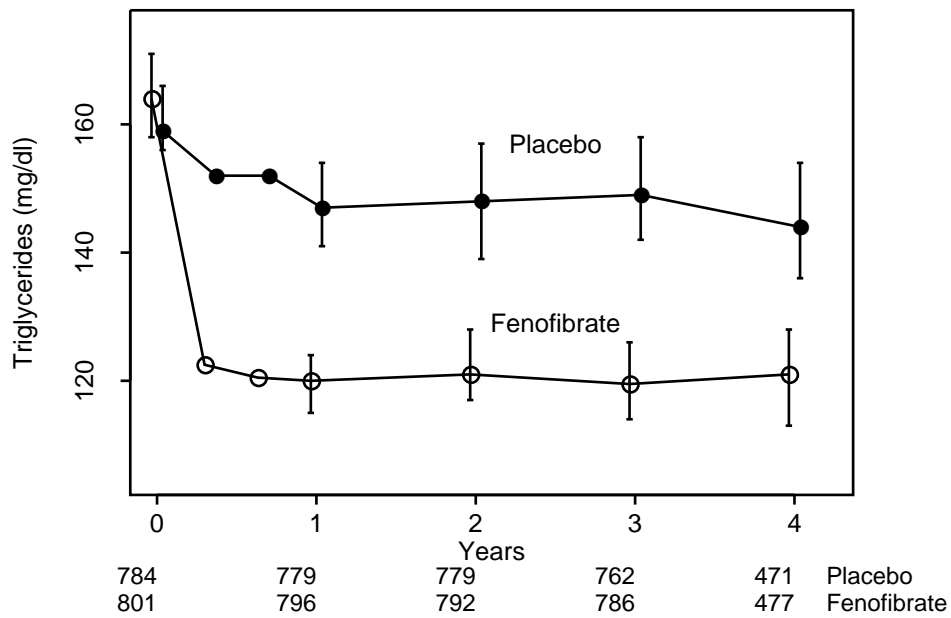
(a) A1C



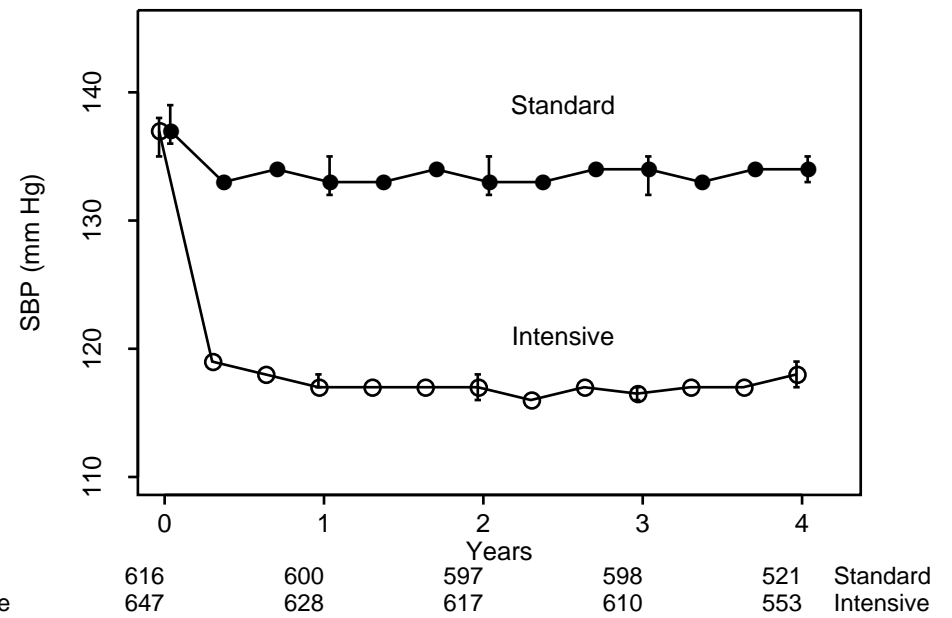
(b) HDL



(c) Triglycerides



(d) SBP



## Section 7. Additional ACCORD Eye analyses

Table 1. Percentages with DR progression (the ACCORD Eye primary outcome). Note: This expands the paper's Table 3 to provide rates for all treatment combinations.

	Blood Pressure		Lipid		
<b>Glycemia</b>	Intensive	Standard	Fenofibrate	Placebo	<b>Totals</b>
Intensive	9.2% (29/315)	8.1% (25/308)	5.3% (21/400)	7.1% (29/406)	7.3% (104/1429)
Standard	11.4% (38/332)	9.4% (29/308)	7.6% (31/406)	13.4% (51/381)	10.4% (149/1427)
<b>Totals</b>	10.4% (67/647)	8.8% (54/616)	6.5% (52/806)	10.2% (80/787)	8.9% (253/2856)

Table 2. Unadjusted and model adjusted proportions and confidence intervals. All confidence intervals are for the less intensive intervention minus the more intensive intervention.

		Unadjusted		Model Adjusted	
<b>Comparison</b>	<b>Trial Arm</b>	<b>Proportion with DR Progression</b>	<b>95% Confidence Interval For Difference*</b>	<b>Proportion with DR Progression</b>	<b>95% Confidence Interval For Difference**</b>
Glycemia	Intensive	0.0728	(0.0108, 0.0527)	0.0701	(0.0110, 0.0516)
	Standard	0.1044		0.1014	
Lipids	Fenofibrate	0.0645	(0.0101, 0.0649)	0.0599	(0.0104, 0.0621)
	Placebo	0.1017		0.0962	
Blood Pressure	Intensive	0.1036	(-0.0488, 0.0169)	0.1012	(-0.0487, 0.0146)
	Standard	0.0877		0.0842	

\*Uses the Agresti and Min exact confidence interval (Agresti A, MinY. (2001). On small-sample confidence intervals for parameters in discrete distributions. Biometrics 57: 963-971) as implemented in StatXact 8 PROCs (<http://www.cytel.com/>).

\*\*Approximate confidence intervals for model-adjusted proportions using the delta method approximation.

Table 3. Percentage of participants missing the primary outcome.

	Blood Pressure		Lipid		
<b>Glycemia</b>	Intensive	Standard	Fenofibrate	Placebo	<b>Totals</b>
Intensive	19.2% (75/390)	19.4% (74/382)	13.8% (64/464)	17.6% (87/493)	17.4% (300/1729)
Standard	19.4% (80/412)	16.8% (62/370)	18.0% (89/495)	18.2% (85/466)	18.1% (316/1743)
<b>Totals</b>	19.3% (155/802)	18.1% (136/752)	16.0% (153/959)	17.9% (172/959)	17.7% (616/3472)

Table 4. Assessment of differential missingness. (This compares the proportions in Table 3 using a two-sample chi-square test (unadjusted p-values) and using the primary logistic regression model.)

Treatment	Unadjusted P-value	Adjusted (Primary Model) P-value
Glycemia	0.55	0.49
Lipid	0.25	0.23
Blood Pressure	0.53	0.48

Table 5. Sensitivity analyses comparing the primary analysis to the multiple imputation analyses.

Analysis	Effect	OR	95% CI	P-value
Primary	Glycemia	0.67	(0.51,0.87)	0.0025
	Lipid	0.60	(0.42,0.87)	0.0056
	Blood Pressure	1.23	(0.84,1.79)	0.29
Multiple imputation, separate imputation models by treatment group	Glycemia	0.68	(0.51,0.91)	0.0092
	Lipid	0.61	(0.43,0.87)	0.0058
	Blood Pressure	1.20	(0.79,1.81)	0.39
Multiple imputation, one imputation model	Glycemia	0.67	(0.51,0.87)	0.0029
	Lipid	0.58	(0.40,0.84)	0.0043
	Blood Pressure	1.25	(0.82,1.90)	0.29

## Section 8. ACCORD design and details of allocation to blood pressure and lipid Trials (Details from ACCORD Protocol, found on [www.accordtrial.org](http://www.accordtrial.org))

ACCORD was designed as a double 2X2 factorial trial of 10,000 eligible participants. The factors employed in the design were: intensive versus standard glycemic control, intensive versus standard blood pressure control, and, in the presence of LDL-C lowering, fibrate versus placebo. As shown in the figure below, all 10,000 required participants were to be randomized to one or the other glycemic treatment groups, and to either blood pressure or lipid trial treatment groups in two non-overlapping 2 X 2 layouts. Specifically, and based upon the sample size requirements for the separate blood pressure and lipid trials, it was planned that 4200 blood pressure-eligible participants would be assigned to and randomized within the blood pressure trial and 5800 lipid participants would be assigned to and randomized within the lipid trial.

Glycemia Trial	Blood Pressure Trial		Lipid Trial		
	SBP < 120 mm Hg	SBP < 140 mm Hg	Fibrate	Placebo	
A1c < 6.0%	1050	1050	1450	1450	5000
7.0% < A1c < 7.9%	1050	1050	1450	1450	5000
	2100	2100	2900	2900	
	4200		5800		10000

All 10,000 participants had to be eligible for the overarching glycemia trial and for either the blood pressure and/or lipid trial. Participants eligible for the lipid trial but not the blood pressure trial were randomized to one of the four cells in the lipid and glycemic control 2 X 2 layout; similarly for those eligible for the blood pressure intervention but not the lipid intervention. Participants eligible for both the lipid and the blood pressure interventions were randomly assigned to one or the other trial using probabilistic weights designed to ensure that the 4200 BP/5800 Lipid split was efficiently achieved. Because progress towards the BP goal of 4200 subjects was more rapid than progress towards the Lipid goal of 5800, the vast majority of participants eligible for both trials were allocated to the Lipid trial (see consort diagram in the online supplements for the BP and Lipid trials). Furthermore, the BP trial was allowed to over-recruit in order to efficiently meet the goal of 10,000 subjects enrolled for the glycemia trial. Overall, 10,251 participants were recruited for the glycemia trial, with 4733 also enrolled in the BP trial and the remaining 5518 enrolled in the Lipid trial.

## **Section 9. ACCORD Eye Study design and details of eligibility criteria**

(Details from ACCORD Eye Study Protocol, found on [www.accordanc.org](http://www.accordanc.org))

The ACCORD Eye Study consisted of 2 eye exams with fundus photography of 7 stereoscopic fields, at baseline and year 4 of follow-up. The length of follow-up for subjects in the diabetic retinopathy study ranged from 4 to 6 years. Patients who had a history of laser photocoagulation or vitrectomy for diabetic retinopathy in either eye at baseline were excluded from the Eye Study. All ACCORD participants without an exclusion criterion were eligible for ACCORD Eye.

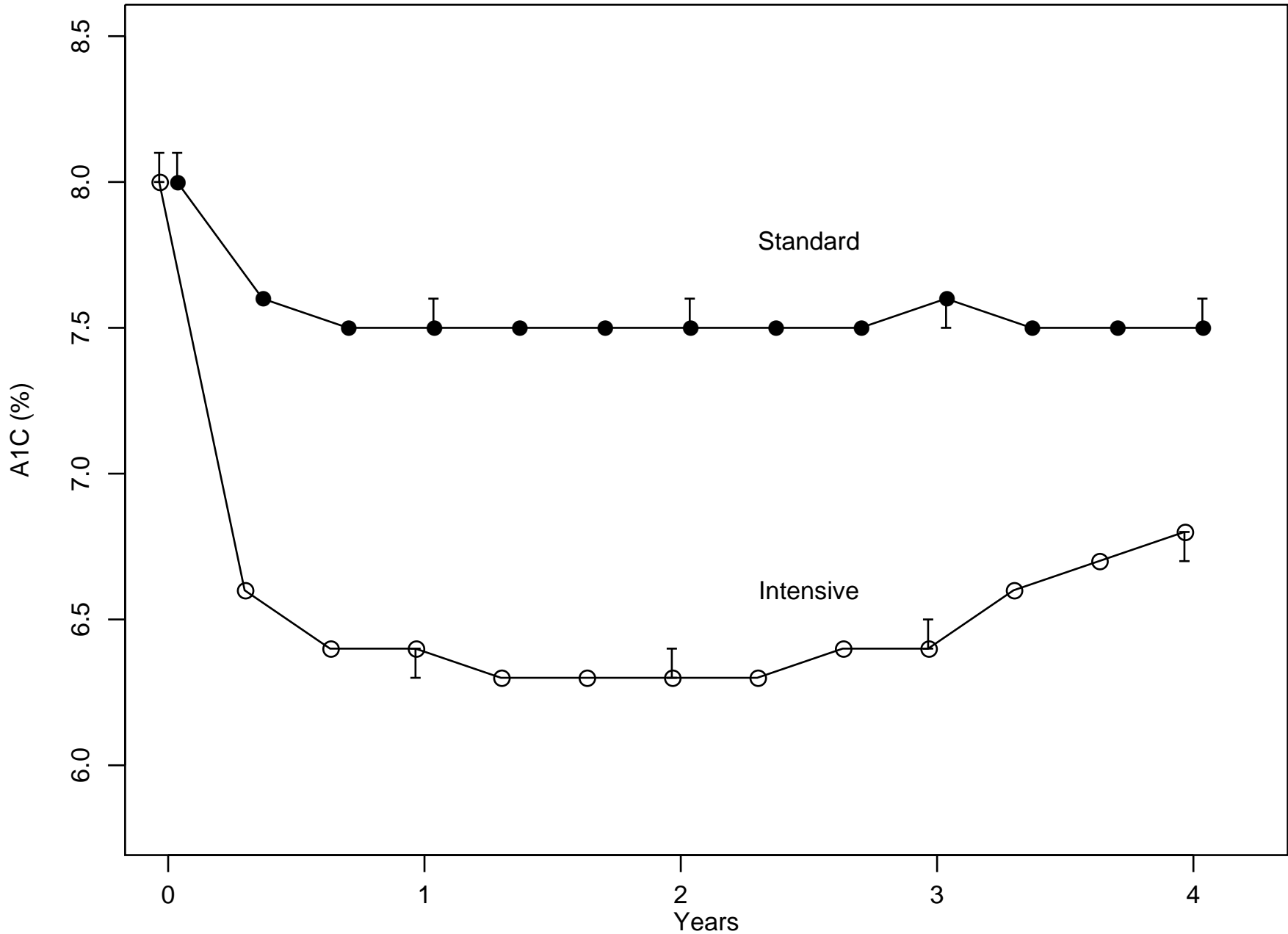
The main ACCORD Trial, which followed the Vanguard Phase, recruited and randomized patients from February 2003 through October 2005. The Eye Study recruited patients from October 2003 through February 2006.

The patients enrolled in the Vanguard Phase did not participate in the Eye Study because baseline fundus photographs were not collected. All clinical centers from all clinical networks were encouraged to participate in the Eye Study; however, only 68 of the 77 clinics recruited patients into the ACCORD Eye Study. Due to the lag between the start of recruitment for the main trial and for the Eye Study, participants who were randomized for the main trial in February 2003 through June 2003 (later at some clinical sites due to later IRB approval) were not eligible for recruitment into the Eye Study because baseline fundus photographs could not be obtained within four months of randomization.

## **Section 10. Longitudinal plots of A1c, HDL, triglycerides, and systolic BP**

Note: These plots are presented in Section 6. They are reproduced here in a larger format to allow greater clarity.

# Median A1C and 95% CIs



1426  
1427

1250  
1346

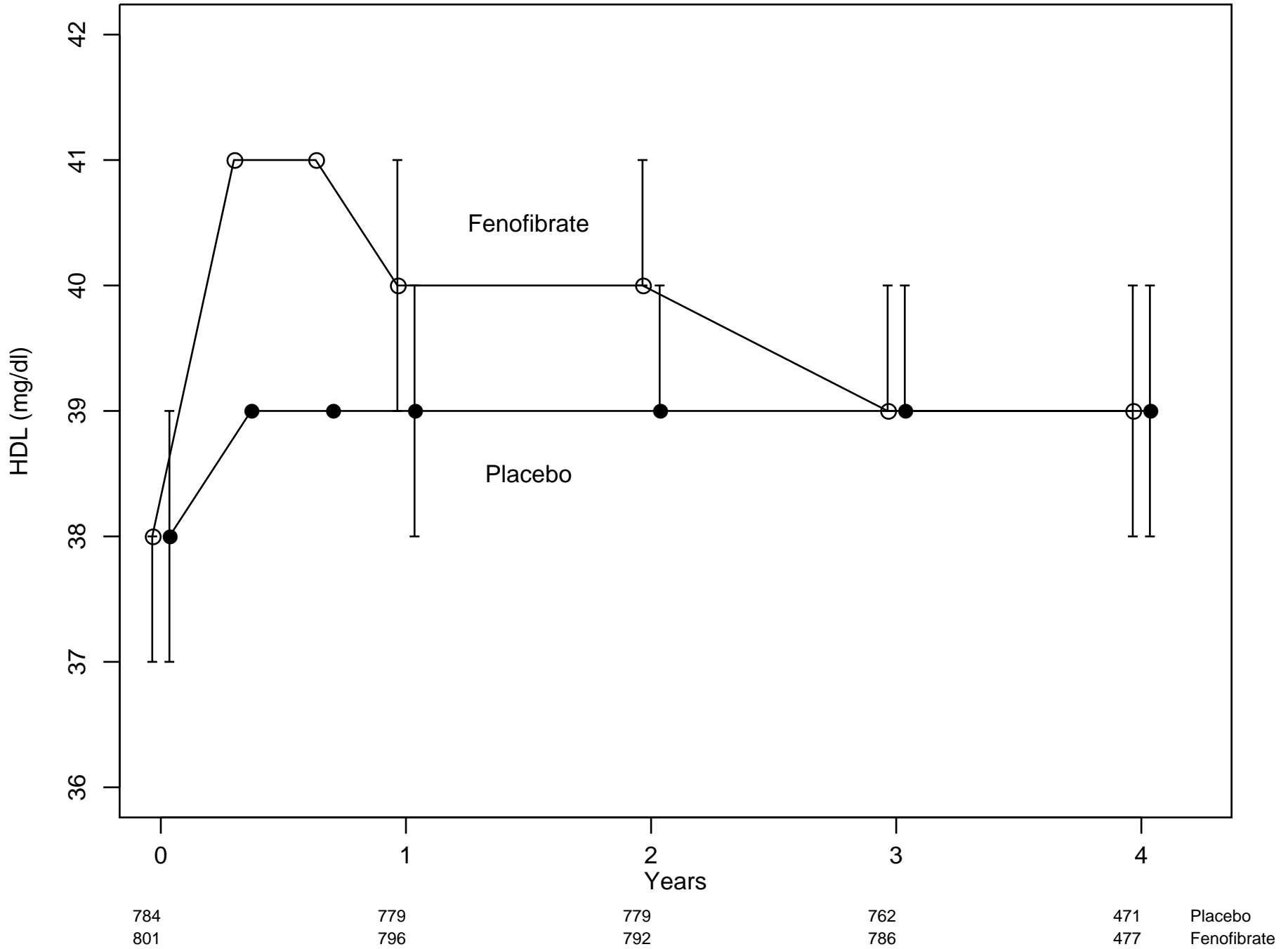
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1323

1195  
1280

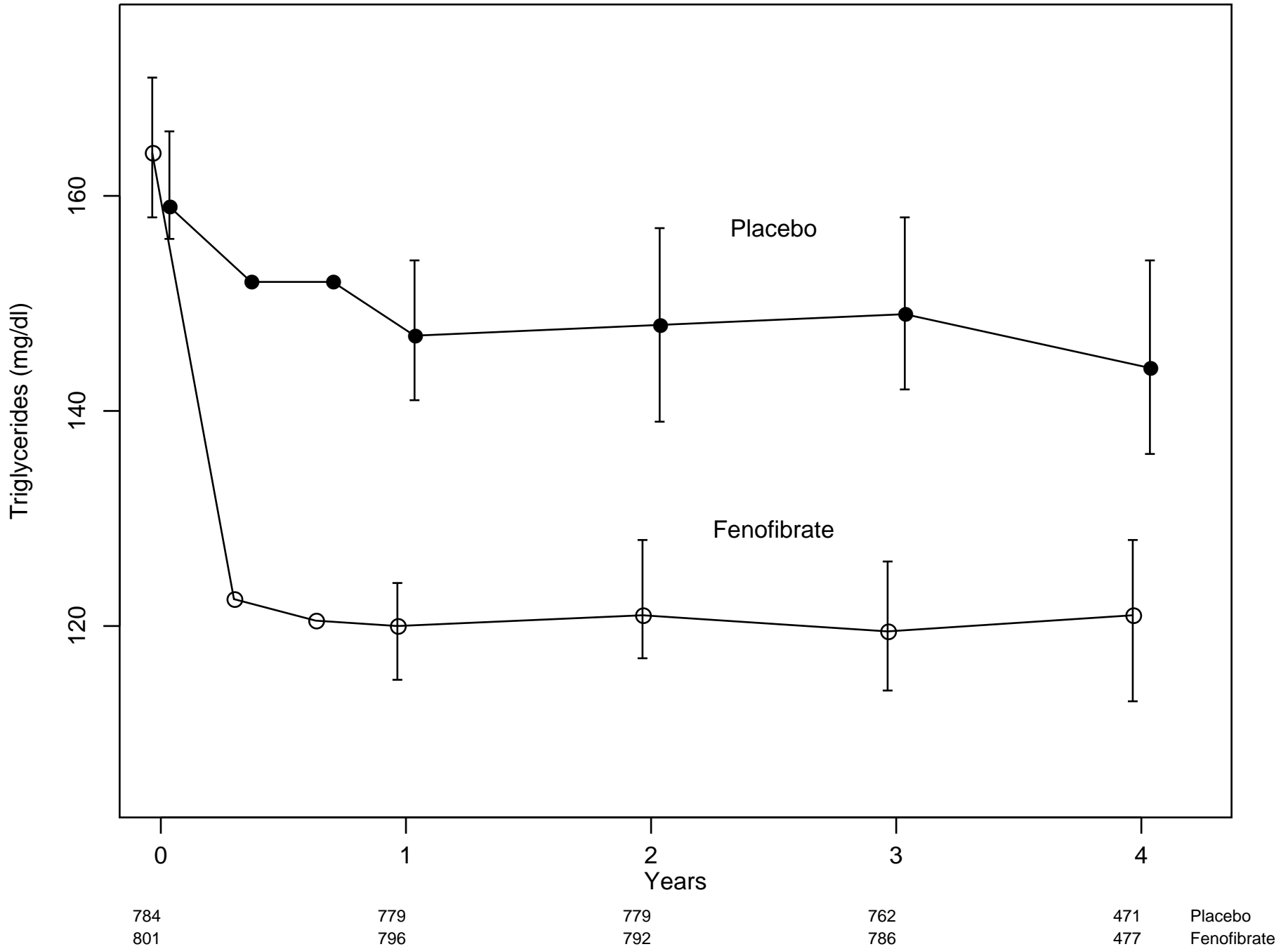
1001  
1016

Standard  
Intensive

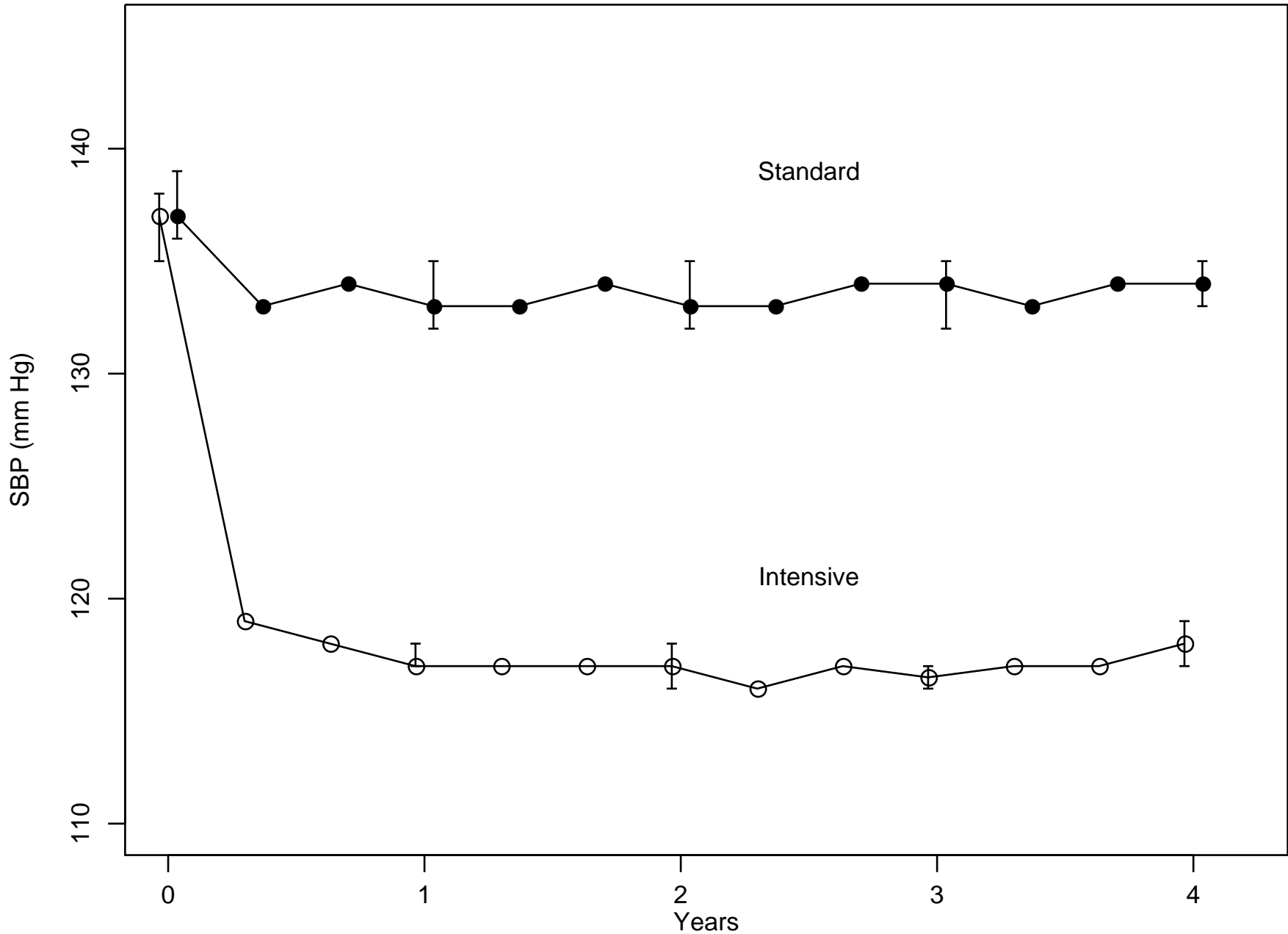
# Median HDL and 95% CIs



# Median Triglycerides and 95% CIs



# Median SBP and 95% CIs



616  
647

600  
628

597  
617

598  
610

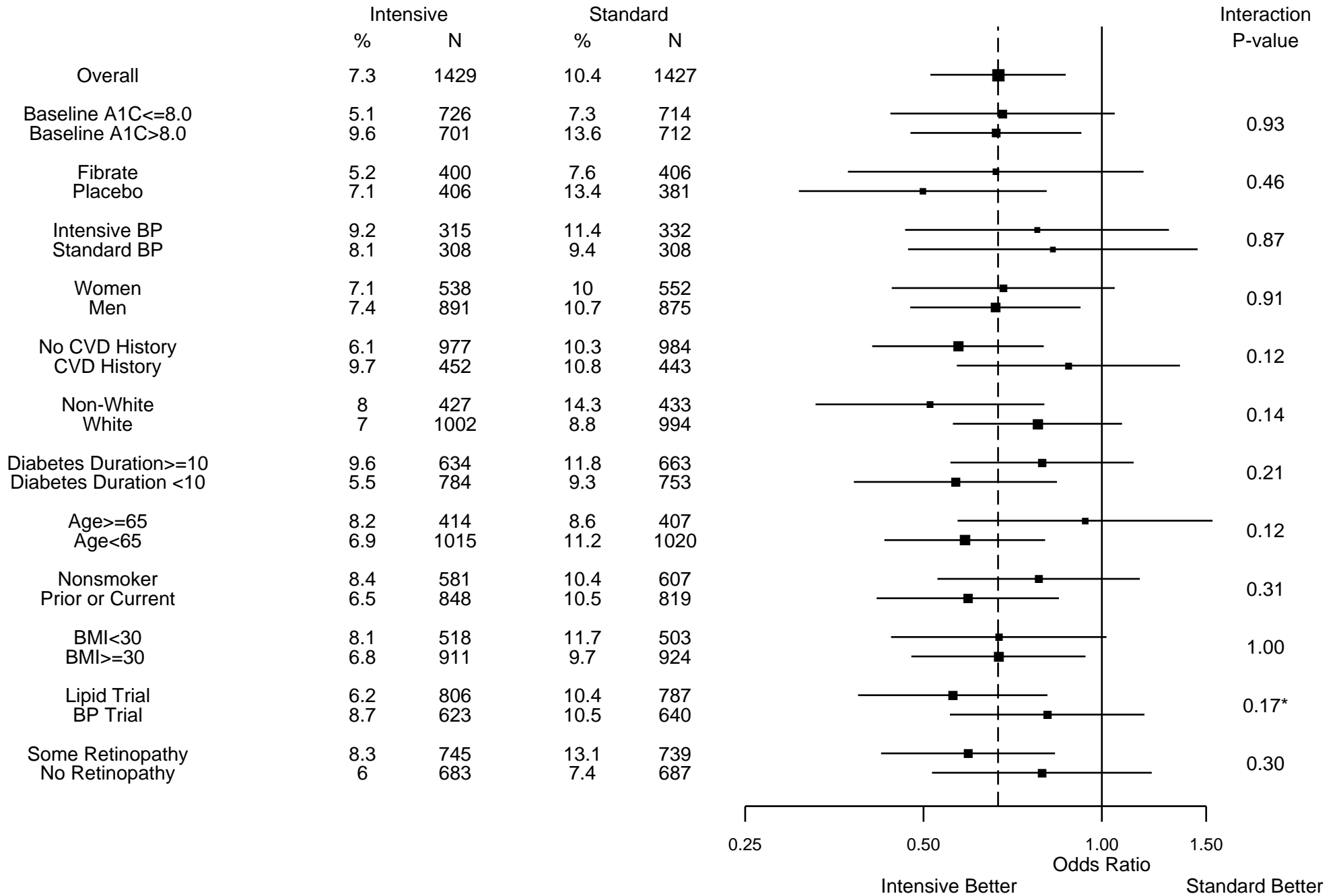
521  
553

Standard  
Intensive

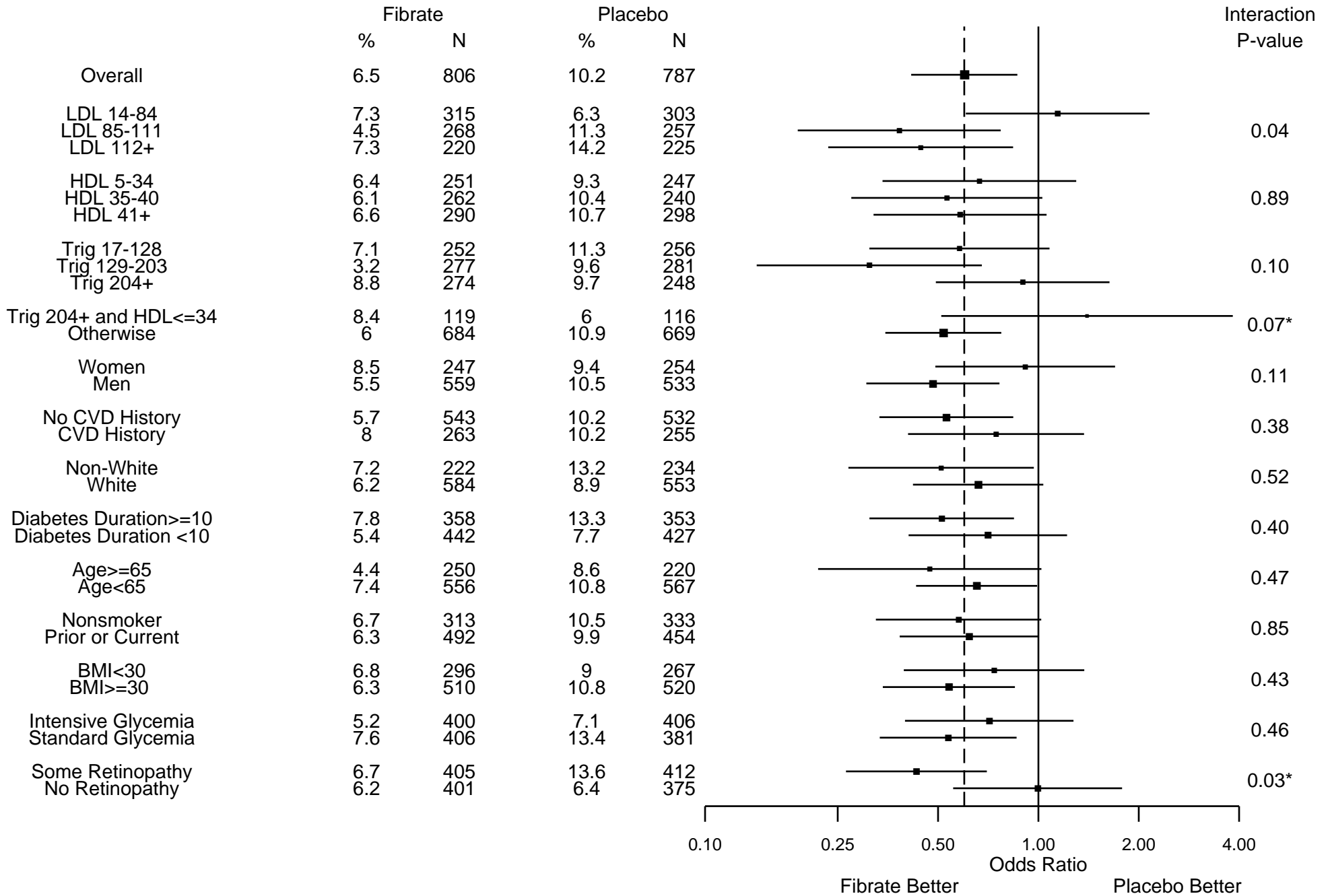
## **Section 11. Subgroup Analyses (Forest Plots)**

Note: These plots are presented in Figures 1-3 of the paper. They are reproduced here in a larger format to allow greater clarity.

# Glycemia Subgroups



# Lipid Subgroups



# Blood Pressure Subgroups

