

The ACCORD Lipid Trial

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Ginsberg Potential Conflict of Interest

Research funds, consulting, honoraria

- Abbott
- AstraZeneca
- Bristol Myers Squibb
- GlaxoSmithKline
- Isis/Genzyme
- Merck
- Novartis
- Regeneron-SanofiAventis
- Roche
- Takeda

Ginsberg Potential Conflict of Interest

Particularly Relevant to ACCORD

- **Abbott**
 - provided fenofibrate for the trial
 - past consulting
 - provided a grant to fund the renal study
- **Merck**
 - provided simvastatin for the trial
 - present consulting
 - present research grant to study anacetrapib

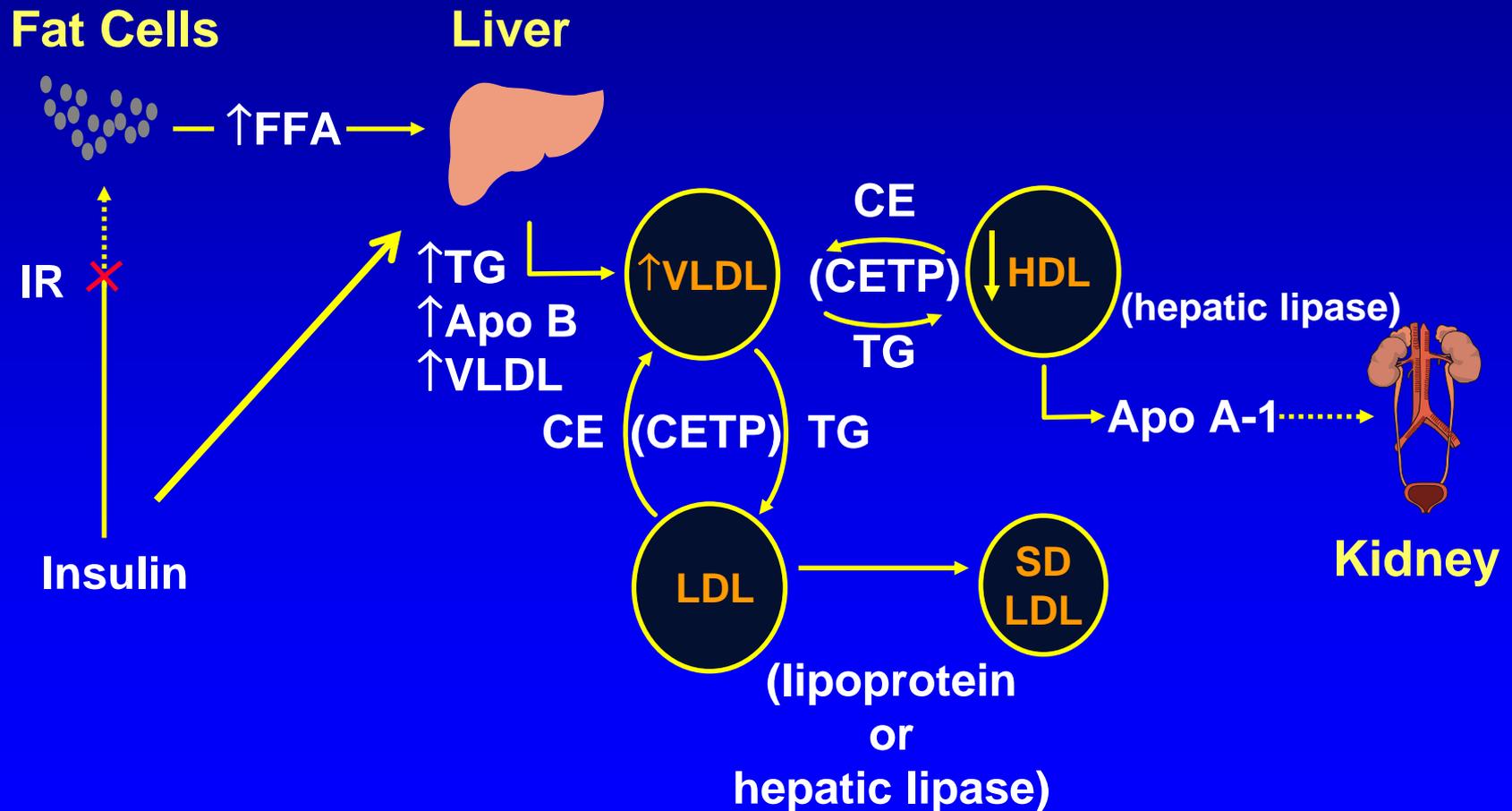
Ginsberg clarifications related to presentation

- All data I will present have been provided by the ACCORD Coordinating Center
- Most of the data I will present have been published or presented at AHA
- Limited unpublished/unpresented data will be shown with the approval of the ACCORD Steering Committee
- I am presenting these data as an expert in lipid metabolism and treatment and as an ACCORD investigator
- I am NOT presenting these data as an official representative of the ACCORD investigators
- Interpretations and conclusions drawn from these data will be mine.

Our patient....

- 60 yr old man
- Post-MI x 3 yrs
- Hypertension- treated
- BMI 29
- HbA1c 7.0%
- TC 225
- LDL 140 (Goal 70)
- TG 250
- HDL 35
- Non HDL 190 (Goal 100)
- 40 mg generic statin
- **HbA1c 7.0%**
- **TC 155**
- **LDL 80 [2.0]**
- **TG 200 [2.3]**
- **HDL 35 [0.9]**
- **Non HDL 120 [3.0]**

Mechanisms Relating Insulin Resistance and Dyslipidemia



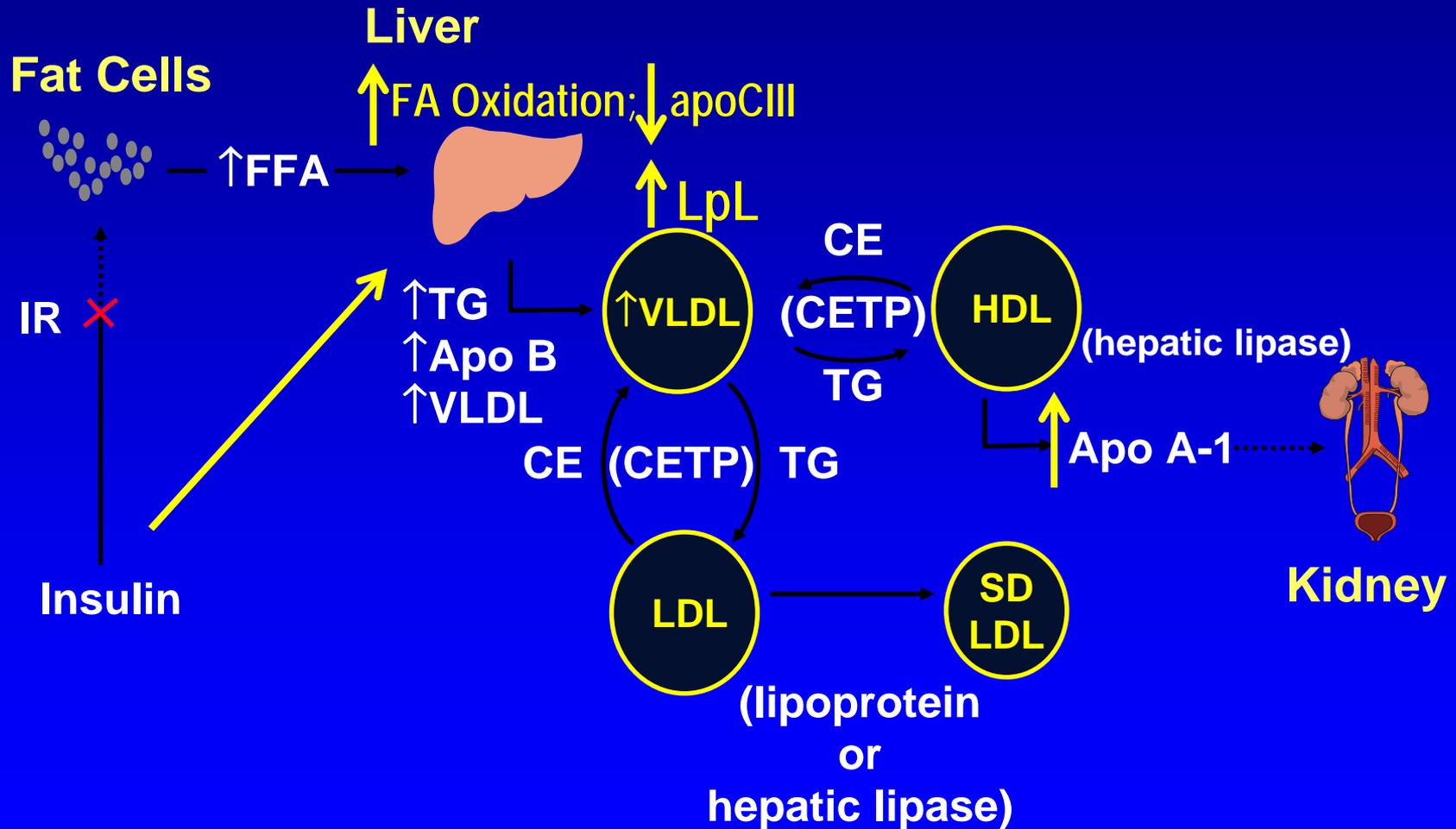
What Should the Next Lipid Target Be for Pharmacologic Therapy?

- LDL-C
- HDL-C
- TG
- LDL size

What Therapy Options are There?

- LDL-C
- HDL-C
- TG
- LDL size
- Fibrates/PPARalpha agonists
- Niacin
- Omega-3 fatty acids
- TZDs/PPARgamma agonists

Diabetic Dyslipidemia: Actions of fibrates



Efficacy of Fibrates in Small Trials

- Triglycerides reduced 35-50%
- HDL increased 10-20%
- LDLC may go down, stay unchanged or rise
- LDL size increases

Statin plus fibrate

- 60-year-old man
- Post-MI x 3 yrs
- Hypertension-treated
- BMI 29
- HbA1c 7.0%
- TC 155
- LDL 80
- TG 200
- HDL 35
- Non HDL 120
- 20 mg generic statin
- Plus fenofibrate
- **HbA1c 7.0%**
- **TC 150**
- **LDL 80 [2.0]**
- **TG 150 [1.7]**
- **HDL 40 [1.0]**
- **Non-HDL 110 [2.75]**

Do Fibrates Reduce Cardiovascular
Events in People with Type 2
Diabetes Mellitus?

Fibrate monotherapy studies

TRIAL	Year Reported	Drug	CHD Risk Reduction (primary endpoint)
Coronary Drug Project (CDP)	1975	Clofibrate	9% (NS)
World Health Organization	1978	Clofibrate	20% (P<0.05)
Helsinki Heart Study (HHS)	1987	Gemfibrozil	34% (P <0.02)
VA-HDL Intervention Trial (VA-HIT)	1999	Gemfibrozil	22% (P <0.006)
Bezafibrate Infarction Prevention (BIP)	2000	Bezafibrate	7.3% (P =0.26)
Fenofibrate Diabetes (FIELD)	2005	Fenofibrate	11% (P=0.16)

Effects of Combination Lipid Therapy on Cardiovascular Events in Type 2 Diabetes Mellitus: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Lipid Trial

Action to Control Cardiovascular Risk in Diabetes

ACCORD

The logo for the ACCORD trial features the word "ACCORD" in a serif font. The letters "A", "C", "C", and "R" are in black. The letter "O" is replaced by a stylized heart shape formed by two overlapping loops, one in green and one in red. The letter "D" is in black. The logo is set against a blue background with a subtle grid pattern.

ACCORD Study Design

- Designed to independently test three medical strategies to reduce cardiovascular disease in diabetic patients
 - **Lipid Trial question:** whether combination therapy with a statin plus a fibrate would reduce cardiovascular disease compared to statin monotherapy in people with type 2 diabetes mellitus at high risk for cardiovascular disease.
- Randomized, placebo-controlled, double-blind clinical trial conducted in 77 clinical sites in the U.S. and Canada

ACCORD Study Design

- Overall ACCORD Glycemia Trial: 10,251 participants
 - **Lipid Trial:** 5,518 participants
 - 2765 randomized to fenofibrate
 - 2753 randomized to placebo
- Primary Outcome: First occurrence of a major cardiovascular event (nonfatal MI, nonfatal stroke, cardiovascular death)
- 87% power to detect a 20% reduction in event rate, assuming placebo rate of 2.4%/yr and 5.6 yrs follow-up in participants without events.

ACCORD Lipid Trial Eligibility

- Stable Type 2 Diabetes >3 months
- HbA1c 7.5% to 11%
- High risk of CVD events = clinical or subclinical disease or 2+ risk factors
- Age
 - ≥ 40 yrs with history of clinical CVD (secondary prevention)
 - ≥ 55 yrs otherwise
- Lipids
 - $60 \leq \text{LDL-C} \leq 180$ mg/dl
 - HDL-C < 55 mg/dl for women/Blacks; < 50 mg/dl otherwise
 - Triglycerides < 750 mg/dl if on no therapy; < 400 mg/dl otherwise
- No contraindication to either fenofibrate or simvastatin

ACCORD Lipid Protocol

- ▶ All participants on open-labeled simvastatin, 20 to 40 mg/day
 - Simvastatin dose complied with lipid guidelines
- ▶ Patients randomized to double-blind placebo or fenofibrate, 54 to 160mg/day
 - Dosing based upon eGFR level
- ▶ Only blinded ACCORD trial
- ▶ Observed Follow-up: 4 to 8 years (mean 4.7 years)

Section 7. Titration of Masked Medication According to Renal Function (Details from ACCORD Protocol, found on www.accordtrial.org)

Participants with a baseline eGFR ≥ 50 mL/min/1.73m² received 160 mg/day of fenofibrate or matched placebo. Those with a baseline eGFR between 30 and <50 received 54 mg/day fenofibrate or placebo.

Serum creatinine levels were measured thereafter every four months. If a participant's eGFR fell to between 30 and <50, the dose of fenofibrate or masked placebo was reduced to 54 mg/day. If an eGFR fell below 30, fenofibrate or masked placebo (but not simvastatin) was permanently discontinued.

	Fenofibrate (N=2765)	Placebo (N=2753)
<u>Masked Medication</u>		
Number (%) of randomized participants prescribed masked medication at most recent visit	2137 (77.3%)	2237 (81.3%)
# (%) on full dose of masked medication	1697 (61.4%)	2043 (74.2%)
# (%) on Reduced dose of masked med	440 (15.9%)	194 (7.1%)
# (%) not on masked medication	628 (22.7%)	516 (18.7%)
# not on masked meds for non-protocol reasons	541	460
# not on masked meds for protocol reasons	87	56
Protocol-specified reasons for Not being on Masked Medication (#):		
Low GFR/Elevated creatinine	66	30
Elevated LDL-C	12	7
Elevated Triglycerides	2	17
Elevated CPK	7	0
Pancreatitis	0	2

Baseline Characteristics

Characteristic	Mean or %	Characteristic	Mean or %
Age (yrs)	62	Total Cholesterol (mg/dl)	175
Women %	31	LDL-C (mg/dl)	101
Race / Ethnicity		HDL-C (mg/dl)	38
White %	68	Triglyceride (mg/dl)*	162
Black %	15	Blood pressure (mm Hg)	134/74
Hispanic %	7	Serum creatinine (mg/dl)	0.9
Secondary prevent %	37	Current smoking %	15
DM duration (yrs)*	9	On a statin %	60
A1c (%) *	8.3	On another LLA %	8
BMI (kg/m ²)	32		

* Median values

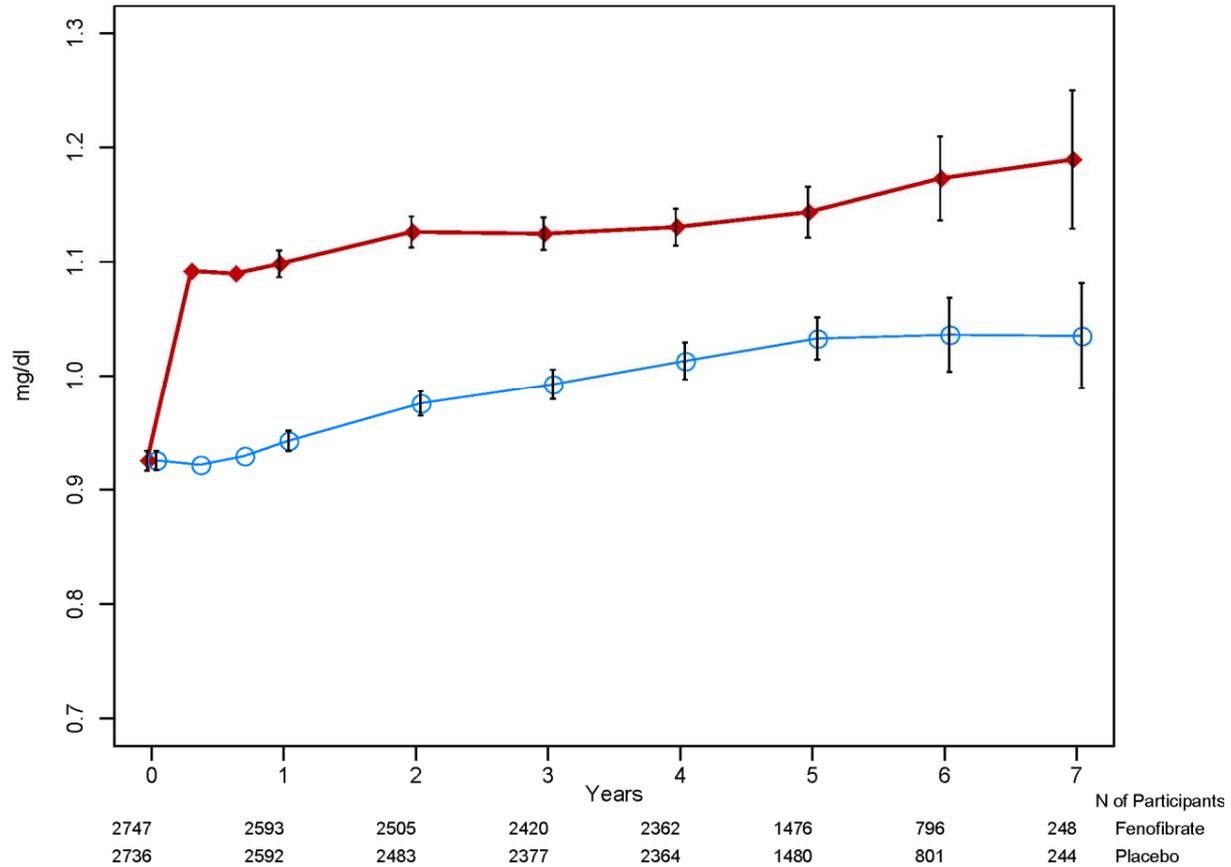
Adverse Experiences During Follow-up

<u>Adverse events (no. (%))</u>	<u>Fenofibrate (N=2765)</u>	<u>Placebo (N=2753)</u>	<u>P value</u>
Out of the ordinary severe muscle aches/pains:			
regardless of CK	1110 (40.1%)	1115 (40.5%)	0.81
plus CK > 5 X ULN	7 (0.3%)	8 (0.3%)	0.79
plus CK > 10 X ULN	1 (0.04%)	2 (0.07%)	0.56
Any nonhypoglycemic SAE	54 (2.0%)	43 (1.6%)	0.27
Any Myopathy/Myositis/ Rhabdomyolysis SAE	4 (0.1%)	4 (0.1%)	1.00
Any Hepatitis SAE	3 (0.1%)	0 (0.0%)	0.18
Any SAE attributed to lipid meds	27 (1.0%)	19 (0.7%)	0.24

Lab Measures During Follow-up

<u>Laboratory Measures (no. (%))</u>	<u>Fenofibrate (N=2765)</u>	<u>Placebo (N=2753)</u>	<u>P value</u>
ALT ever > 3X ULN	52 (1.9%)	40 (1.5%)	0.21
ALT ever > 5X ULN	16 (0.6%)	6 (0.2%)	0.03
CK ever > 5X ULN	51 (1.9%)	59 (2.2%)	0.43
CK ever > 10X ULN	10 (0.4%)	9 (0.3%)	0.83
Serum creatinine elevation			
Women ever > 1.3 mg/dl	235 (27.9%)	157 (18.7%)	<0.001
Men ever > 1.5 mg/dl	698 (36.7%)	350 (18.5%)	<0.001
Post-randomization incidence of microalbuminuria (≥ 30 to < 300 mg/g*)	1050 (38.2%)	1137 (41.6%)	0.01
Post-randomization incidence of macroalbuminuria (≥ 300 mg/g*)	289 (10.5%)	337 (12.3%)	0.03

Serum Creatinine over course of study



Time course of primary renal outcomes for the 3 study groups in ACCORD Lipid Trial and Renal Ancillary Study

Adjusted eGFR, ml/min/1.73m ² , mean (SE)	Fenofibrate Cases (N=321)	Fenofibrate Controls (N=175)	Placebo Controls (N=565)	P-value Fenofibrat e case versus fenofibrate controls	P-value Fenofibrate case versus placebo controls	P-value Fenofibrate controls versus placebo controls
Trial Baseline	96.8 (1.7)	88.6 (2.3)	93.4 (1.3)	0.004	0.1	0.07
Trial Month 4 visit	67.5 (1.1)	89.9 (1.5)	90.2 (0.8)	<0.0001	<0.0001	0.8
Trial Close out visit	72.2 (1.3)	80.0 (1.7)	83.3 (1.0)	0.0003	<0.0001	0.1
Post-close out visit*	83.5 (1.3)	90.0 (1.8)	81.6 (1.0)	0.004	0.3	<0.0001
Mean change, Trial Baseline- to-4 month Visit	-29.3 (1.3)	1.3 (1.8)	-3.1 (1.0)	<0.0001	<0.0001	0.03
Mean change, Trial Close out to Post-close out visit	10.9 (0.7)	9.1 (1.0)	-1.9 (0.5)	0.1	<0.0001	<0.0001

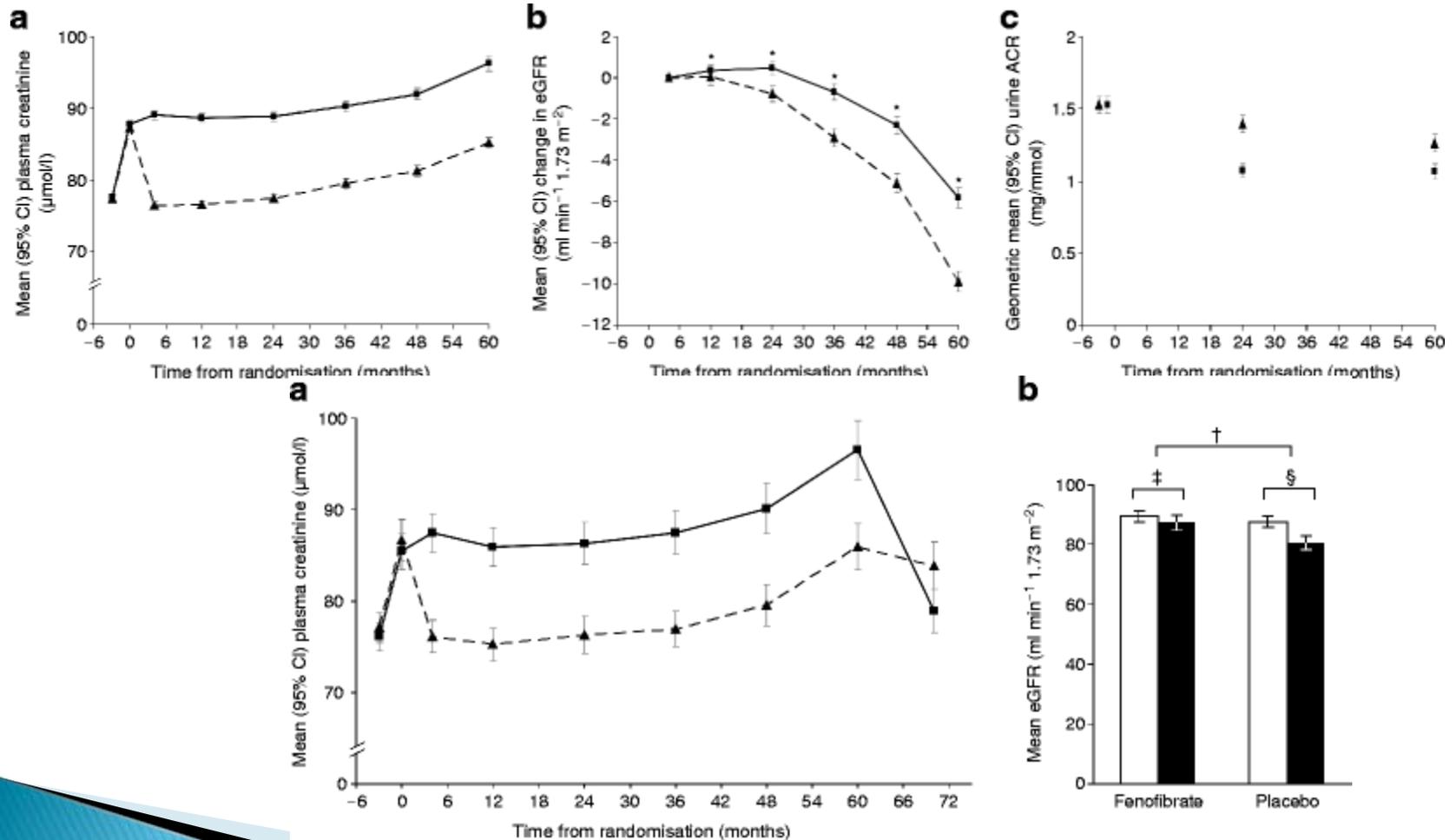
*Post-close out visit: visit for ancillary study participant only that occurred 6-8 weeks post Lipid Trial close out visit. Participants were off masked study medication at the visit.

a.Means were adjusted for age, diabetes duration, gender, non-white race, insulin use, SBP, DBP.

Means of differences were also adjusted for individual time interval between visits

Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes

(FIELD) Study. Diabetologia. 2011 Feb;54(2):280-290.



Relationships between fenofibrate associated creatinine increase >20% (FACI) at month 4 of the study, incident renal disease and primary study outcome.

*Hazard ratio from proportion hazards regression model of time to event.

Outcome	FACI		No FACI		HR* (95% CI)	P valu e
	N	Num (%) or Mean (SD)	N	Num (%) or Mean (SD)		
Microalbuminuria	776	163 (21.0)	890	208 (23.4)	0.92 (0.75-1.14)	0.5
Macroalbuminuria	1051	55 (5.2)	1170	69 (5.9)	1.01 (0.70-1.44)	0.9
End stage renal disease	1212	39 (3.2)	1311	35 (2.7)	1.34 (0.85-2.13)	0.2
Change in urine albumin to creatinine ratio (mg/g) Mean, SD	1027	62 (6.9)	1049	84 (7.9)	---	0.4
Primary study outcome (follow-up fatal/nonfatal CVD events)	1212	117 (9.7)	1311	143 (10.9)	0.94 (0.74, 1.21)	0.6

Changes in HDLC and TG on fenofibrate and placebo

Plasma HDL-C (mg/dl)	Baseline		
	Month 4	4.6%	7.9%
	Year 1	2.5%	6.3%
	Year 2	1.3%	6.1%
	Year 3	1.3%	5.5%
	Year 4†	0.7%	6.3%
	Year 5†	0.7%	6.1%
	Year 6†	1.2%	7.4%
	Year 7†	1.8%	6.8%
	Exit Visit (2009)	1.7%	8.4%

Plasma Triglyceride (mg/dl)	Baseline		
	Month 4	-21.9%	-23.7%
	Year 1	-19.2%	-21.2%
	Year 2	-17.3%	-21.6%
	Year 3	-17.5%	-23.4%
	Year 4†	-15.1%	-23.1%
	Year 5†	-15.7%	-25.0%
	Year 6†	-10.9%	-22.8%
	Year 7†	-15.3%	-29.6%
	Exit Visit (2009)	-13.5%	-22.2%

Primary Outcome

	Fenofibrate (N=2765)		Placebo (N=2753)		HR (95% CI)	P Value
	N of Events	Rate (%/yr)	N of Events	Rate (%/yr)		
<u>Primary Outcome:</u> Major Fatal or Nonfatal Cardiovascular Event	291	2.24	310	2.41	0.92 (0.79 - 1.08)	0.32

Prespecified Secondary Outcomes

Outcome	Fenofibrate (N=2765)		Placebo (N=2753)		HR (95% CI)	P Value
	<u>N of Events</u>	<u>Rate (%/yr)</u>	<u>N of Events</u>	<u>Rate (%/yr)</u>		
Primary + Revasc + hospitalized CHF	641	5.35	667	5.64	0.94 (0.85-1.05)	0.30
Major Coronary Event	332	2.58	353	2.79	0.92 (0.79-1.07)	0.26
Nonfatal MI	173	1.32	186	1.44	0.91 (0.74 - 1.12)	0.39
Total Stroke	51	0.38	48	0.36	1.05 (0.71 - 1.56)	0.80
Nonfatal Stroke	47	0.35	40	0.30	1.17 (0.76 - 1.78)	0.48
Total Mortality	203	1.47	221	1.61	0.91 (0.75 - 1.10)	0.33
Cardiovascular Death	99	0.72	114	0.83	0.86 (0.66 - 1.12)	0.26
Fatal/Nonfatal CHF	120	0.90	143	1.09	0.82 (0.65 - 1.05)	0.10

Section 9. The Pre-Specified Subgroups in which to Examine the Treatment Group Differences in the Primary Outcome in the ACCORD Lipid Trial

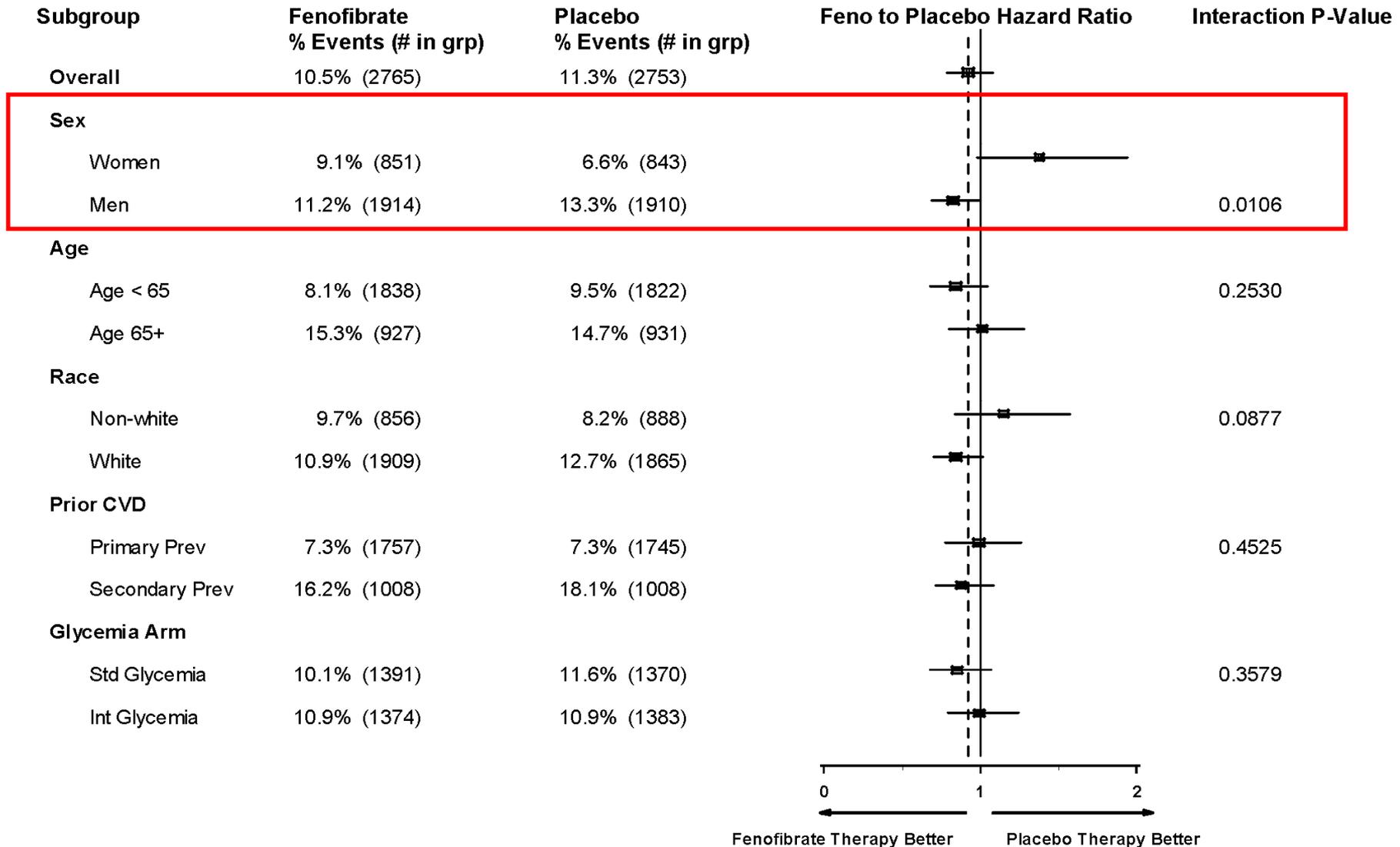
Before the ACCORD Trial Results were shown and reviewed by the ACCORD Steering Committee members, the following subgroups of ten baseline characteristics were specified.

- Gender (female, male)
- Age (< 65, \geq 65 yrs)
- Race (Nonwhite, White)
- Presence of clinical CVD (primary, secondary prevention)
- Glycemia Trial treatment assignment (Intensive, Standard)
- LDL-C (tertiles)
- HDL-C (tertiles)
- Triglyceride (tertiles)
- 'High TG + Low HDL-C' (upper tertile TG + lower tertile HDL-C) vs 'all Others'
- Hba1c (\leq , > median)

Primary Outcome By Treatment Group and Baseline Subgroups:

Women had 56 events on placebo and 77 events on fenofibrate

Men had 254 events on placebo and 214 events on fenofibrate



Secondary Outcomes By Gender (HRs)

Characteristic	Men (N=3824)	Women (N=1694)	Overall
Primary Outcome	0.82	1.38	
Cardiovascular Death	0.84	0.98	
Non-fatal MI	0.79	1.43	
Non-fatal Stroke	1.15	1.20	
Any Stroke	1.05	1.06	
Death from any Cause	0.91	0.89	

* Median values

Why did women in ACCORD have more non-fatal MIs?

Baseline Characteristics By Gender

Characteristic	Men (N=3824)	Women (N=1694)	Overall
Age (years)	62	62	
Sex (%)	69	31	
White/Black/Hispanic (%)	71/14/6	60/19/11	68/15/7
Prior CVD	41.2	26.0	37.0
BMI (Kg/M ²)	32	34	
Diabetes (years)*	10	9	
HbA1c (%)*	8.3	8.3	
Microalbuminuria (%)	33	26	
Macroalbuminuria (%)	7.1	6.9	

* Median values

Baseline Characteristics By Gender

Characteristic	Men (N=3824)	Women (N=1694)	Overall
Laser or Vitrectomy	8.8	8.7	
Peripheral Neuropathy	48	40	
Heart Failure	5.3	5.3	
Amputations	2.3	1.3	
Creatinine mg/dl	1.0	0.8	
TZD use	18.3	16.1	
Beta blockers	33.6	30.3	
ACEI	55.5	49.8	
Calcium channel blockers	18.6	19.5	

* Median values

Baseline Lipid Values By Gender

Lipid Measurement (mg/dl)	Men (N=3824)	Women (N=1694)
Cholesterol	171	185
Triglyceride*	158	171
LDL-Cholesterol	98	106
HDL-Cholesterol	36.6	41.4

Data are means

* Median value

Lipid Response (baseline to 48 mos) to Fenofibrate/Placebo By Gender

Lipid Measurement (mg/dl)	Men (N=2480)	Women (N=1099)
Triglyceride	-43.1/-16.6	-45.9/-14.8
LDL-Cholesterol	-16.3/-20.6	-22.6/-21.4
HDL-Cholesterol	+2.0/+1.6	+2.3/+2.3

Data are means

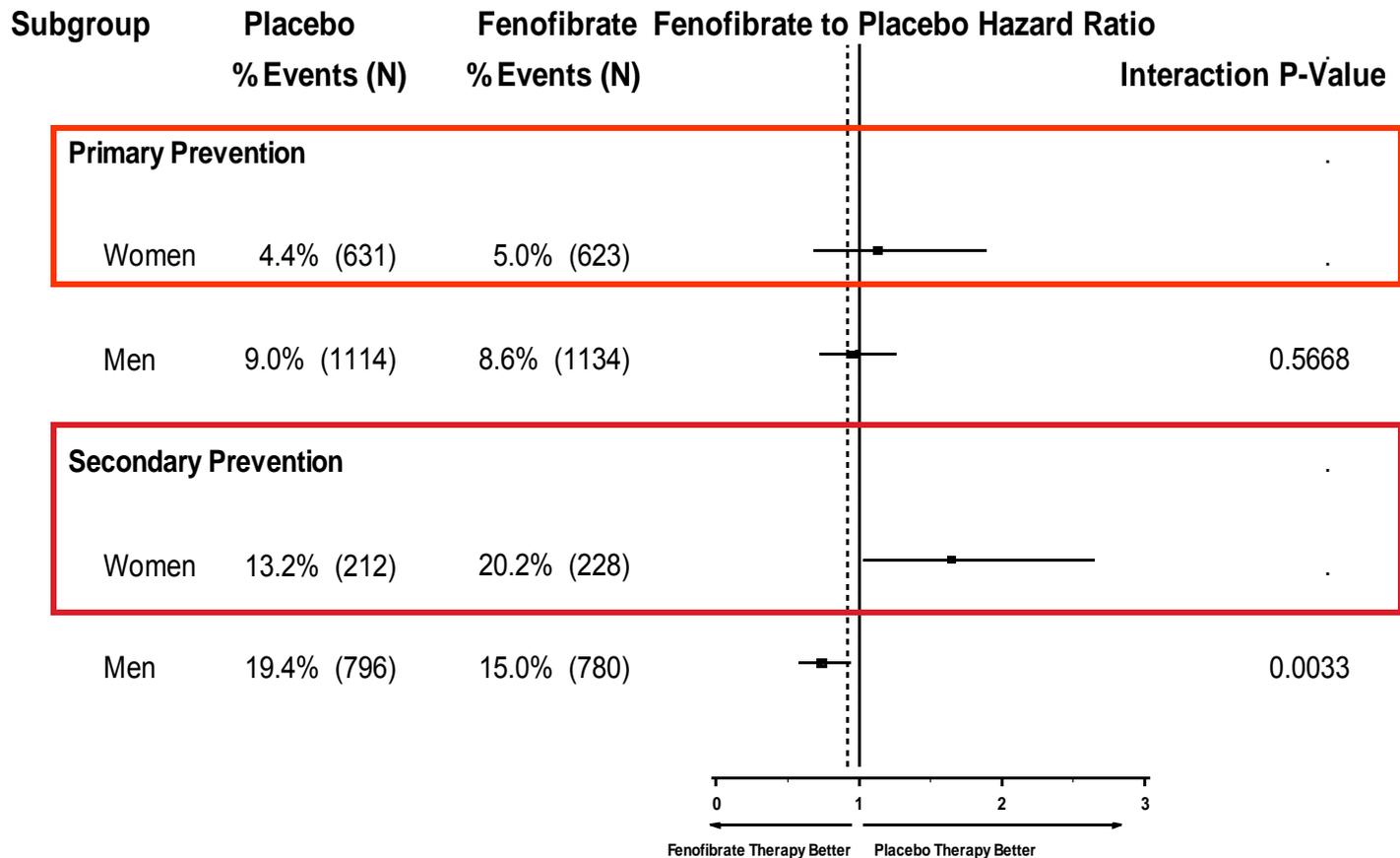
Why did women in ACCORD have more non-fatal MIs?

- I don't know
- They were at lower risk at baseline
- They had lower event rates during the study
- Their baseline lipids were similar to men except for higher HDLC levels
- Their response to fenofibrate was similar to men

Primary Outcome in Primary and Secondary Prevention in Women:

PP: 28 on placebo – 31 in feno

SP: 28 on placebo – 46 in feno



Secondary Outcomes By Primary or Secondary Prevention Status in Women

Characteristic	Primary (Feno=623) (Placebo =631)	Secondary (Feno=228) (Placebo=212)	
Primary Outcome	Feno = 31 Placebo =28	Feno=46 Placebo=28	
Cardiovascular Death	6/6	9/8	
Non-fatal MI	19/16	33/19	
Non-fatal Stroke	6/6	4/1	
CHF	15/18	17/21	

**Why did women in ACCORD
with secondary prevention
status have more non-fatal MIs?**

Baseline Characteristics Women By CVD Status

Characteristic	Women Secondary (N=440)	Women Primary (N=1254)	Overall
Age (years)	61.2	61.8	
Sex (%)			
White/Black/Hispanic (%)	58/21/12	61/18/10	60/19/11
Prior CVD	100	0	37.0
BMI (Kg/M ²)	33.7	33.5	
Diabetes (years)*	11	8	
HbA1c (%)*	8.3	8.1	
Microalbuminuria (%)	37.5	22.0	
Macroalbuminuria (%)	11.2	5.4	

Baseline Characteristics Women By CVD Status

Characteristic	Women Secondary (N=440)	Women Primary (N=1254)	Overall
Laser or Vitrectomy	14.9	6.6	
Peripheral Neuropathy	44	38	
Heart Failure	13.2	2.6	
Amputations	2.3	1.0	
Creatinine mg/dl	0.8	0.8	
TZD use	12	17.5	
Beta blockers	55.5	21.5	
ACEI	55	48	
Calcium channel blockers	25.7	17.4	
Statin Use	69	49	

* Median values

Baseline Lipids by Gender and Primary vs Secondary Status

Lipid Measurement (mg/dl)	Men (Primary N=2236) (Secondary N=1566)	Women (Primary N=1247) (Secondary N=434)
Triglyceride* Primary	157	171
Triglyceride* Secondary	159	169
HDL-C Primary	37	41.7
HDL-C Secondary	36	40.5
LDL-C Primary	102	107
LDL-C Secondary	93	100

*Medians

Lipid Response (baseline to 48 mos) to Fenofibrate/Placebo by Gender and Primary vs Secondary Status

Lipid Measurement (mg/dl)	Men (Primary N=731/730) (Secondary N=511/506)	Women (Primary N=404/410) (Secondary N=145/140)
Triglyceride* Primary	-35/-14	-39/-17
Triglyceride* Secondary	-32/-8	-28/-10
HDL-C Primary	+2.1/+1.8	+3.3/+2.6
HDL-C Secondary	+2.0/+1.4	-0.2/+1.2
LDL-C Primary	-20/-23	-24/-24
LDL-C Secondary	-12/-17	-19/-15

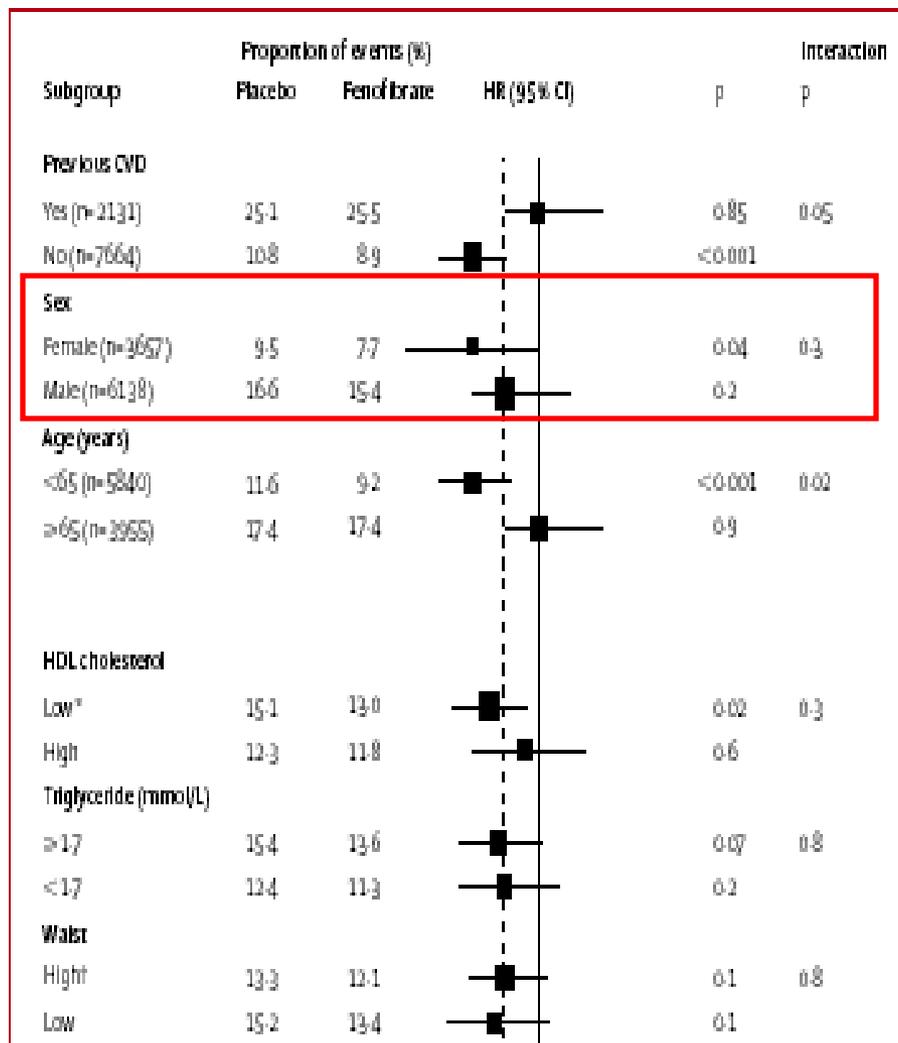
*Medians

Why did women in ACCORD with secondary prevention status have more non-fatal MIs?

- I don't know
- They were at much higher risk at baseline
- They had the highest event rate of any subgroup
- Their baseline lipids were the same as the primary prevention group
- They may not have responded as well to fenofibrate
- This finding may have been by chance

Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial

Lancet. 2005 Nov 26;366(9500):



**Why did dyslipidemic participants
in ACCORD have fewer events?**

Baseline Characteristics By Lipid Subgroup

Characteristic	HTG/Low HDLC (N=940)	All Others (N=4578)	
Age (years)	61.2	62.5	
Male Sex (%)	80.0	67.1	
White/Black/Hispanic (%)	80/6.2/5.4	65/17/7.8	68/15/7
Prior CVD	40.5	35.7	37
BMI (Kg/M ²)	33.0	32.1	
Diabetes (years)*	8.0	10.0	
HbA1c (%)*	8.2	8.1	
Microalbuminuria (%)	36.8	29.2	
Macroalbuminuria (%)	7.7	6.9	

* Median values

Baseline Characteristics By Lipid Subgroup

Characteristic	HTG/Low HDLC (N=940)	All Others (N=4578)	
Laser or Vitrectomy	8.6	8.8	
Peripheral Neuropathy	49	45	
Heart Failure	7.7	4.8	
Amputations	2.2	1.2	
Creatinine mg/dl	1.0	0.9	
TZD use	16	18	
Beta blockers	37	32	
ACEI	55	54	
Calcium channel blockers	17	19	

* Median values

Baseline Lipid Values By Subgroup in ACCORD-Lipid

Lipid Measurement (mg/dl)	HTG/Low HDL-C (N=941)	All Others (N= 4548)
Cholesterol	187.9 ± 40.3	172.5 ± 36.1
Triglyceride*	285	144
LDL-Cholesterol	97.3 ± 32.4	101.2 ± 36.1
HDL-Cholesterol (Men)	29.2 ± 3.8	38.5 ± 6.7
HDL-Cholesterol (Women)	30.8 ± 3.1	42.7 ± 7.1

Data are mean ± sd)

* Median value

Lipid Response (baseline to 48 mos) to Fenofibrate/Placebo by Dyslipidemic Status

Lipid Measurement (mg/dl)	Dyslipidemic (F 316/P 287)	Others (F 1465/P 1495)
Triglyceride	-127/-84	-26/-3
HDL-C	+4.5/+3.3	1.6/1.5
LDL-C	-11/-20	-20/-21
Means		

Data are means

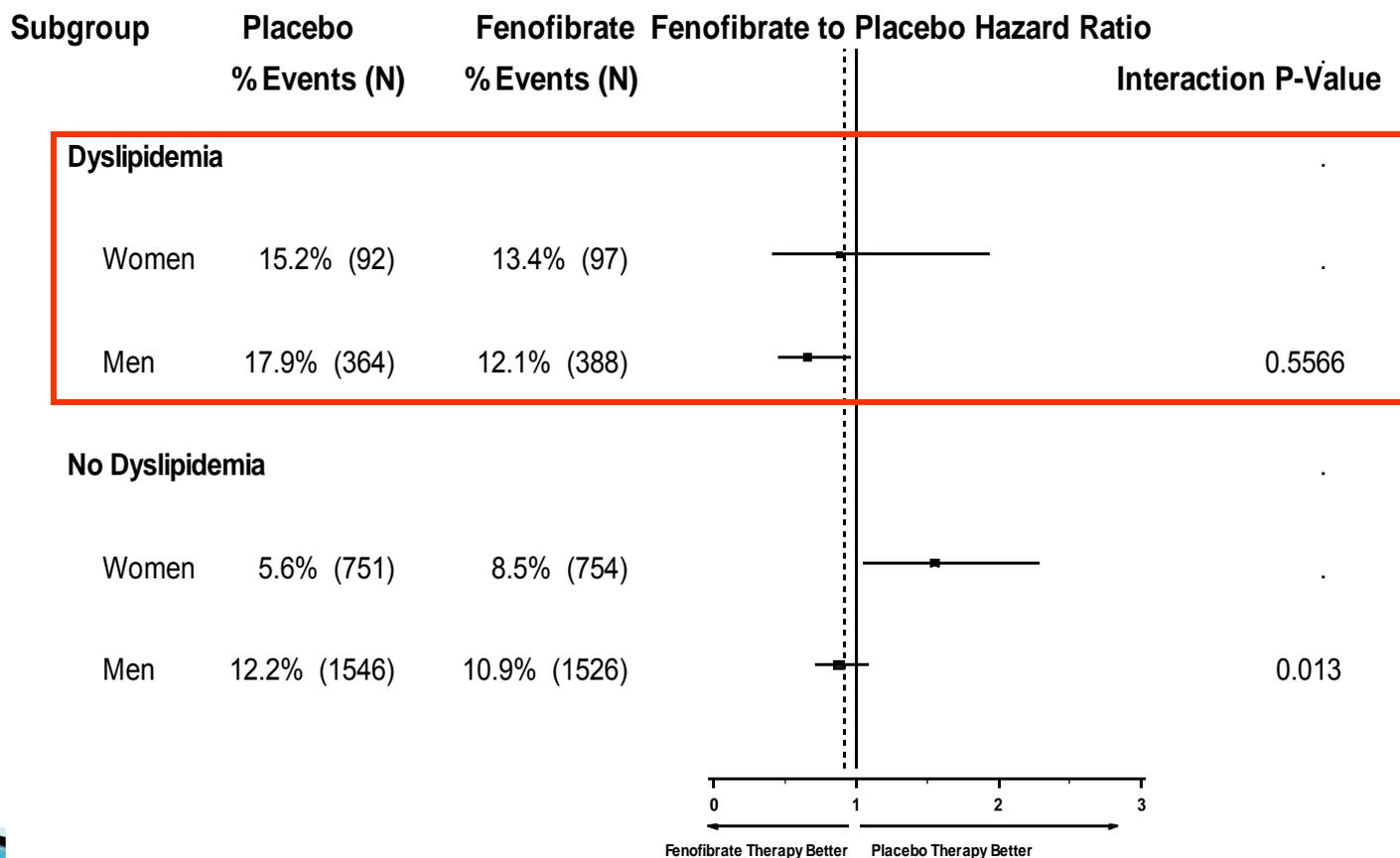
Why did dyslipidemic participants in ACCORD have fewer events?

- I can speculate
- They had slightly higher risk at baseline but much higher event rates during the trial
- They had, by definition, much higher TG and much lower HDLC levels than all others
- They had better TG and HDLC responses to fenofibrate than all others
- On the other hand, this finding could be by chance; however

Comparison of ACCORD subgroup results with those from prior fibrate studies

Trial (Drug)	Primary Endpoint: Entire Cohort (P-value)	Lipid Subgroup Criterion	Primary Endpoint: Subgroup
HHS (Gemfibrozil)	-34% (0.02)	TG > 200 mg/dl LDL-C/HDL-C > 5.0	-71% (0.005)
BIP (Bezafibrate)	-7.3% (0.24)	TG ≥ 200 mg/dl	-39.5% (0.02)
FIELD (Fenofibrate)	-11% (0.16)	TG ≥ 204 mg/dl HDL-C < 42 mg/dl	-27% (0.005)
ACCORD (Fenofibrate)	-8% (0.32)	TG ≥ 204 mg/dl HDL-C ≤ 34 mg/dl	-31%

Loss of Gender Difference in Primary Outcome in the Presence of Dyslipidemia:



Baseline Lipids by Gender and Dyslipidemic Status

Lipid Measurement (mg/dl)	Men (Dyslipids N=751) (Other N=3050)	Women (Dyslipids N=188) (Other N=1493)
Triglyceride* Dyslipidemic	282	305
Triglyceride* Other	137	159
HDL-C Dyslipidemic	29	31
HDL-C Other	39	43
LDL-C Dyslipidemic	96	104
LDL-C Other	99	106

*Medians

Lipid Response (baseline to 48 mos) to Fenofibrate/Placebo by Gender and Dyslipidemic Status

Lipid Measurement (mg/dl)	Men (Dyslipids N=259/236) (Other N=974/1000)	Women (Dyslipids N=57/51) (Other N=491/495)
Triglyceride* Dyslipidemic	-126/-91	-129/-53
Triglyceride* Other	-20/+1	-37/-10
HDL-C Dyslipidemic	+4.4/+3.2	+4.8/+3.8
HDL-C Other	+1.4/+1.3	+2.1/+2.1
LDL-C Dyslipidemic	-10/-20	-14/-22
LDL-C Other	-18/-21	-24/-22

*Medians

Why did dyslipidemic participants in ACCORD have fewer events?

- I can speculate
- They had slightly higher risk at baseline but much higher event rates during the trial
- They had, by definition, much higher TG and much lower HDLC levels than all others
- They had better TG and HDLC responses to fenofibrate than all others
- They did not demonstrate significant gender differences in baseline lipids, response to fenofibrate, or reductions in events on fenofibrate

ACCORD Eye Study Results

Emily Y. Chew, MD

National Eye Institute/National Institutes of Health

& the ACCORD Study and ACCORD Eye Study Research Groups

ACCORD Eye Study Design

▶ **Baseline and Year 4 comprehensive eye exams** including:

- Visual acuity measurements
- Fundus photography of 7 standard stereoscopic fields
- Central grading of the fundus photographs using the Early Treatment Diabetic Retinopathy Study (ETDRS) Classification of diabetic retinopathy

Proportion of Participants with Diabetic Retinopathy Progression at 4 years

	Blood Pressure		Lipid		N=2856 Total
Glycemia	Intensive	Standard	Fenofibrate & Simvastatin	Placebo & Simvastatin	TOTALS
Intensive	9.2% (29/315)	8.1% (25/308)	5.3% (21/400)	7.1% (29/406)	7.5% (104/1429)
Standard	11.4% (38/332)	9.4% (29/308)	7.6% (31/406)	13.4% (51/381)	10.4% (149/1427)
TOTALS	10.4% (67/647)	8.8% (54/616)	6.5% (52/806)	10.2% (80/787)	8.9% (253/2856)

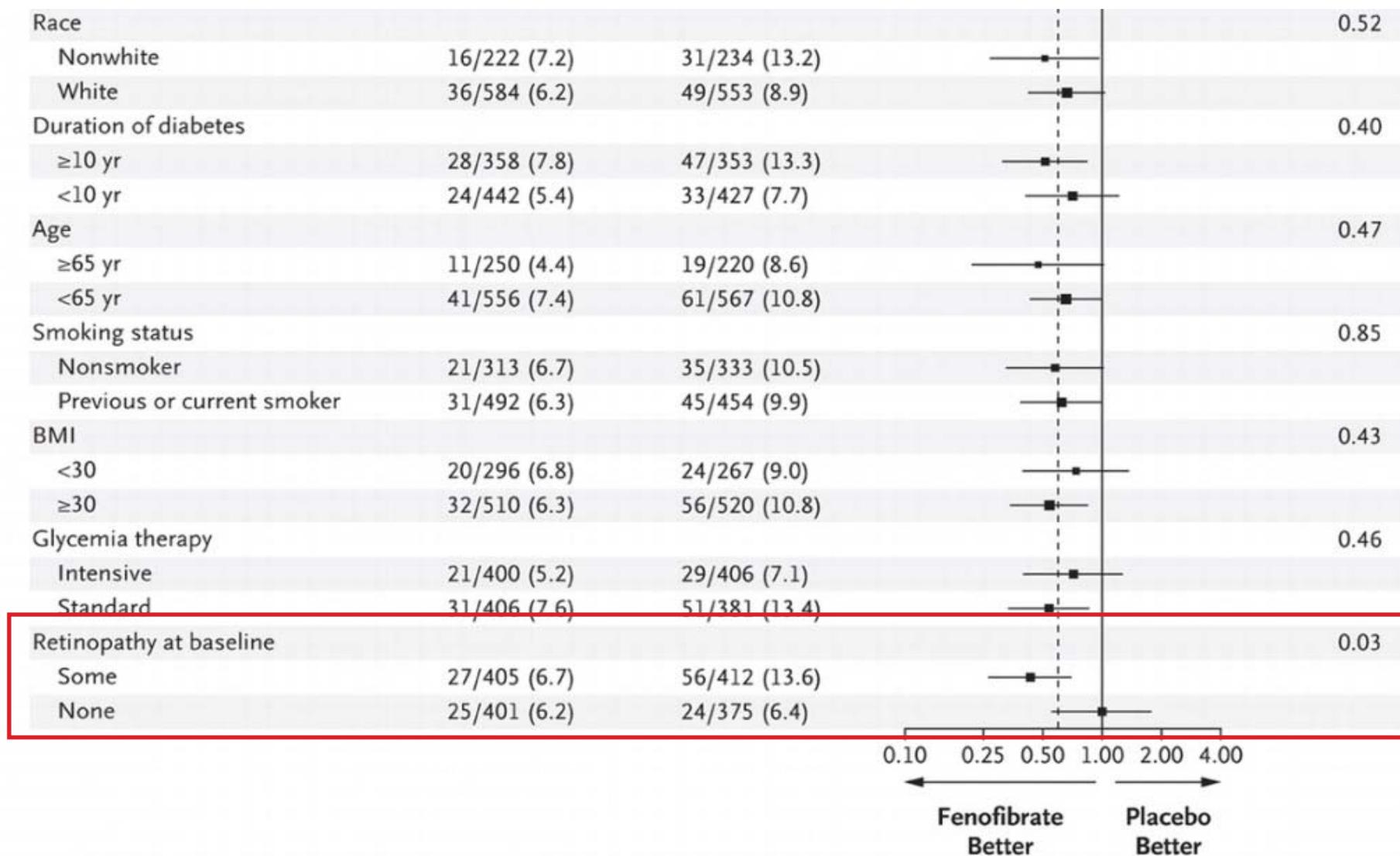
Proportion of Participants with Diabetic Retinopathy Progression at 4 years

N Engl J Med. 2010 Jul 15;363(3):233-44.

Subgroup	Fenofibrate <i>no. with retinopathy progression/total no. (%)</i>	Placebo <i>no. with retinopathy progression/total no. (%)</i>	Odds Ratio (95% CI)	P Value for Interaction
Overall	52/806 (6.5)	80/787 (10.2)		
LDL cholesterol				0.04
14–84 mg/dl	23/315 (7.3)	19/303 (6.3)		
85–111 mg/dl	12/268 (4.5)	29/257 (11.3)		
>112 mg/dl	16/220 (7.3)	32/225 (14.2)		
HDL cholesterol				0.89
5–34 mg/dl	16/251 (6.4)	23/247 (9.3)		
35–40 mg/dl	16/262 (6.1)	25/240 (10.4)		
≥41 mg/dl	19/290 (6.6)	32/298 (10.7)		
Triglycerides				0.10
17–128 mg/dl	18/252 (7.1)	29/256 (11.3)		
129–203 mg/dl	9/277 (3.2)	27/281 (9.6)		
≥204 mg/dl	24/274 (8.8)	24/248 (9.7)		
Triglyceride level ≥204 mg/dl and HDL cholesterol level ≤34 mg/dl				0.07
Yes	10/119 (8.4)	7/116 (6.0)		
No	41/684 (6.0)	73/669 (10.9)		
Sex				0.11
Female	21/247 (8.5)	24/254 (9.4)		
Male	31/559 (5.5)	56/533 (10.5)		
History of cardiovascular disease				0.38
No	31/543 (5.7)	54/532 (10.2)		
Yes	21/263 (8.0)	26/255 (10.2)		

Proportion of Participants with Diabetic Retinopathy Progression at 4 years

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IS IT WORTH ADDING ONE MORE LIPID LOWERING DRUG (FIBRATE) IN YOUR ALREADY STATIN/MULTIDRUG TREATED PATIENT?

(Henry N. Ginsberg, MD *NOT SPEAKING FOR ACCORD*)

Yes if they have significant dyslipidemia with a TG>200 and an HDL<35-40 mg/dl. This is probably about 10% of a Caucasian diabetic population

Maybe if they have retinopathy regardless of lipid levels