

Trilipix (ACCORD) Advisory Committee Meeting

**Endocrinologic and Metabolic Drugs
Advisory Committee**

19 May 2011

Trilipix (ACCORD) Advisory Committee Meeting

**James Stolzenbach, PhD
Dyslipidemia Divisional Vice President
Global Pharmaceutical R&D
Abbott**

Sponsor Assessment of the Data

- ◆ **Patients receiving statins are still at risk for cardiovascular events**
 - Risk is associated with TG and HDL-C values
- ◆ **Outcomes trials including ACCORD Lipid demonstrate that fibrates reduce CV risk in patients with high TG and low HDL-C**
- ◆ **Safety profile of fenofibrate/fenofibric acid is well defined, predictable, and consistent with current prescribing information**
- ◆ **The Trilipix coadministration indication is appropriate**

Agenda

Overview

James Stolzenbach, PhD

*Dyslipidemia Divisional Vice President
Abbott*

Clinical Presentation

Maureen Kelly, MD

*Dyslipidemia Project Director
Abbott*

Clinician Perspective

Peter Jones, MD

Baylor College of Medicine

Closing Remarks

James Stolzenbach, PhD

Consultants Available to the Committee

- ◆ **Anthony Keech, MD**
Professor of Medicine, University of Sydney
Principal Investigator, FIELD Study
- ◆ **Gary Koch, PhD**
Professor of Biostatistics, University of North Carolina
Statistical Consultant
- ◆ **Cheryl Enger, PhD**
Senior Scientist, Innovus (formerly i3)
Epidemiology Consultant
- ◆ **Jaap Mandema, PhD**
President and CEO, Quantitative Solutions, Inc.
Meta-analysis Consultant

Fibrate Drug Class

Bezafibrate

Ciprofibrate

Clofibrate

Fenofibrate **US approved**

Fenofibric acid **US approved**

Gemfibrozil **US approved**

} **Share same
active moiety**

Fibrates are agonists of PPAR α (peroxisome proliferator-activated receptor alpha)

Fenofibrate Cardiovascular Outcomes Studies in General Diabetic Population

ACCORD Lipid

(Action to Control Cardiovascular Risk in Diabetes)

Fenofibrate + simvastatin vs simvastatin + placebo

5518 patients

31% female

Modest degree of dyslipidemia

FIELD

(Fenofibrate Intervention and Event Lowering in Diabetes)

Fenofibrate monotherapy vs placebo

9795 patients

37% female

Modest degree of dyslipidemia

Fenofibrate/Fenofibric Acid History

Fenofibrate first marketed (France)

Fenofibrate first marketed (US)

15 Dec 2008
Trilipix NDA approval (US)



Sep 1997
FIELD recruitment begins

Nov 2005
FIELD presented

Jan 2001
ACCORD recruitment begins

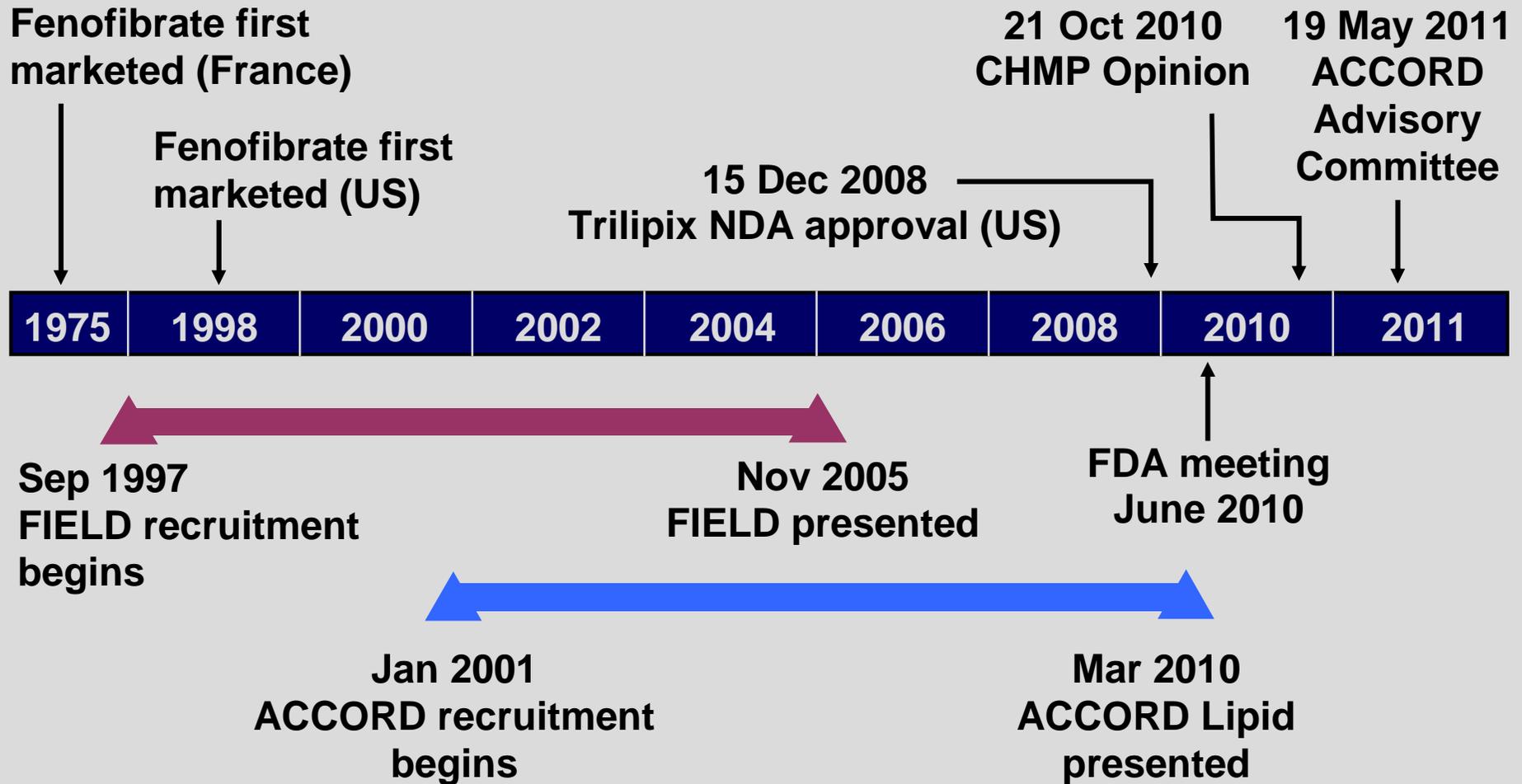
Mar 2010
ACCORD Lipid presented

Trilipix (Fenofibric Acid)

Approved Coadministration Indication

- ◆ **Trilipix was approved by FDA 15 Dec 2008 with the following coadministration indication:**
 - **An adjunct to diet in combination with a statin to reduce TG and increase HDL-C in patients with mixed dyslipidemia and CHD or a CHD risk equivalent who are on optimal statin therapy to achieve their LDL-C goal**

Fenofibrate/Fenofibric Acid History



Coadministration Indication for Fenofibrate in EU

- ◆ **October 2010** - Abbott met with the European Committee for Human Medicinal Products (CHMP) regarding EU-wide referral procedure for fibrates
 - Based on ACCORD Lipid and other data, CHMP revised the indication to allow for fenofibrate coadministration with a statin
 - Consistent with approved US Trilipix coadministration indication

Sources of Information

- ◆ **ACCORD Lipid and other fibrate outcomes trials**
 - Including Abbott-conducted analyses
- ◆ **Trilipix clinical program**
- ◆ **Meta-analyses of fibrate and statin trials**
- ◆ **Postmarketing safety and prescription use data reporting**

Totality of Data Supports Coadministration Therapy in Patients with Elevated TG and/or Low HDL-C

- ◆ **Patients receiving statins are still at risk for cardiovascular events**
 - Risk is associated with TG and HDL-C values
- ◆ **Outcomes trials including ACCORD Lipid demonstrate that fibrates reduce CV risk in patients with high TG and low HDL-C**
- ◆ **Safety profile of fenofibrate/fenofibric acid is well defined, predictable, and consistent with current prescribing information**
- ◆ **The Trilipix coadministration indication is appropriate**
 - Abbott proposes addition of ACCORD Lipid data to the label to guide prescribers

Clinical Presentation

Maureen Kelly, MD
Dyslipidemia Project Director
Global Pharmaceutical R&D
Abbott

Outline of Clinical Presentation

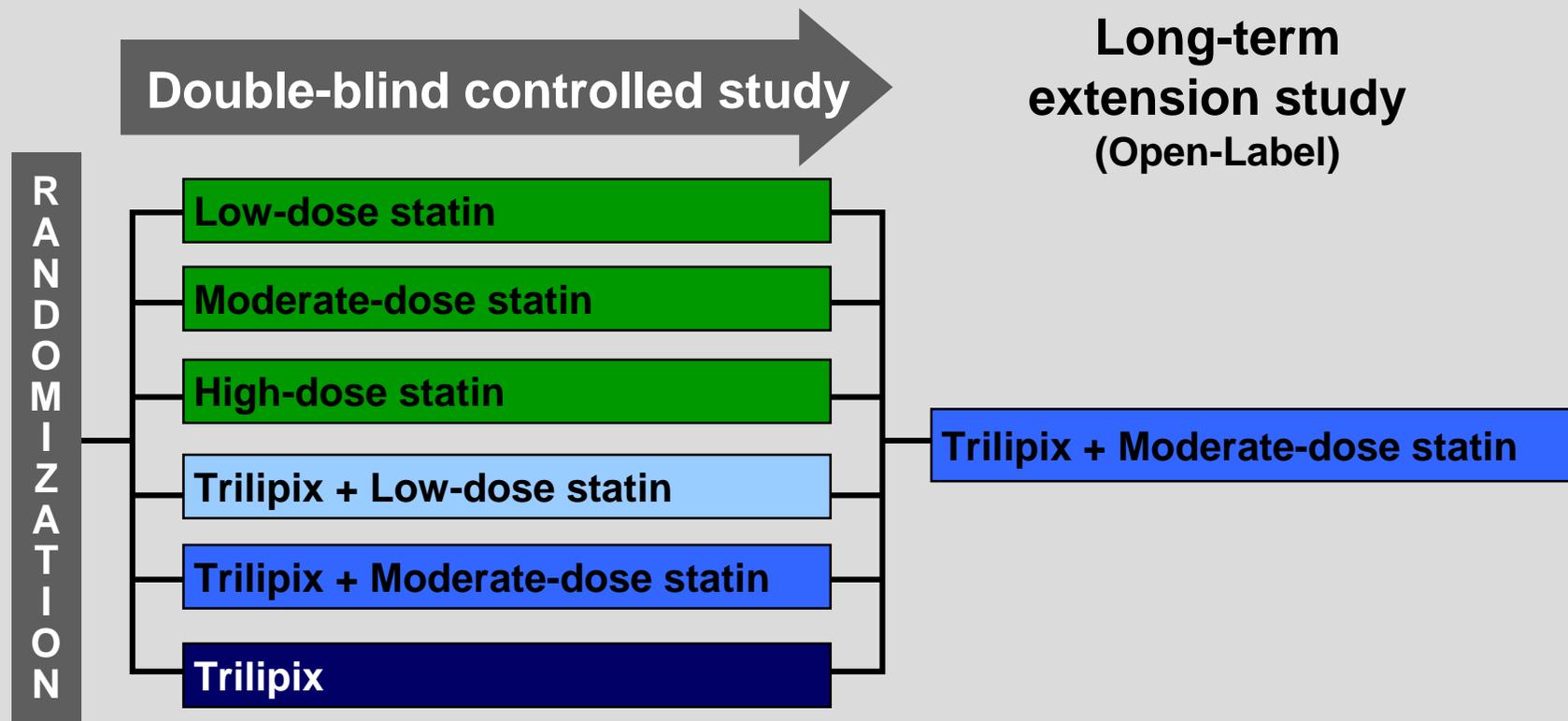
- ◆ **Trilipix clinical program**
- ◆ **CV outcomes trials with fibrates**
- ◆ **Abbott analyses of ACCORD Lipid**
- ◆ **Additional data to support coadministration therapy**
- ◆ **Safety of fenofibrate/fenofibric acid**

Trilipix Clinical Program Overview

- ◆ Three phase 3 double-blind, randomized controlled studies (N = 2698)
- ◆ One long-term open-label extension study (N = 1911)

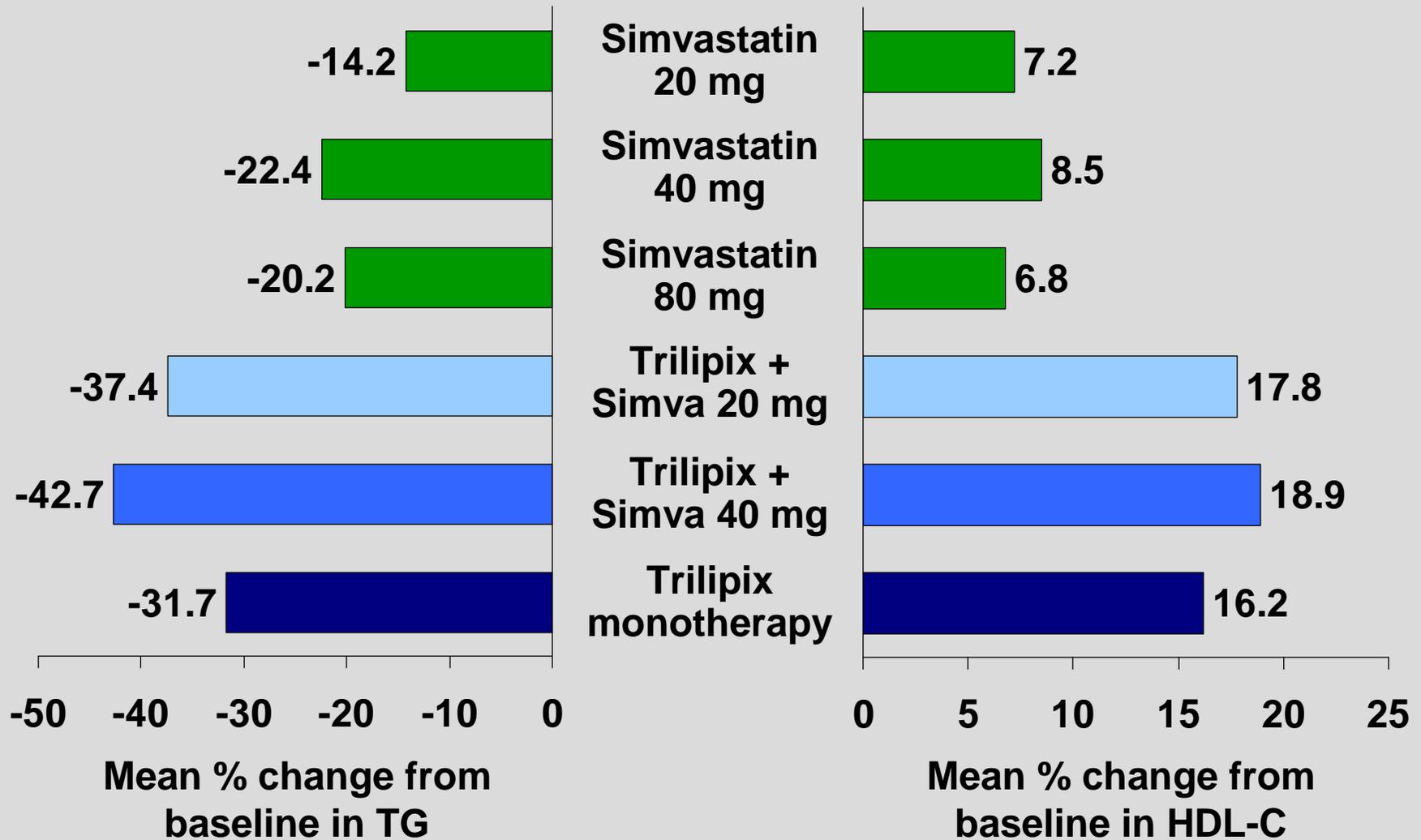
Lipid parameter	Lipid entry criteria (mg/dL)	Mean baseline lipid value (mg/dL)
LDL-C	≥ 130	157
TG	≥ 150	282
HDL-C	< 40 (males)	35
	< 50 (females)	41

Trilipix Phase 3 Study Design



Statins Evaluated: Rosuvastatin, Simvastatin, Atorvastatin

Changes in TG and HDL-C in the Trilipix Clinical Program – Simvastatin Study



Fibrate CV Outcomes Trials

Key Fibrate Outcomes Trials Prior to ACCORD Lipid

Trial	Drug	N	Population
HHS¹	Gemfibrozil	4081	Men, primary prevention
VA-HIT²	Gemfibrozil	2531	Men, secondary prevention
BIP³	Bezafibrate	3090	Men and women, secondary prevention
FIELD⁴	Fenofibrate	9795	Men and women with DM

1 *N Engl J Med.* 1987;317:1237-1245.

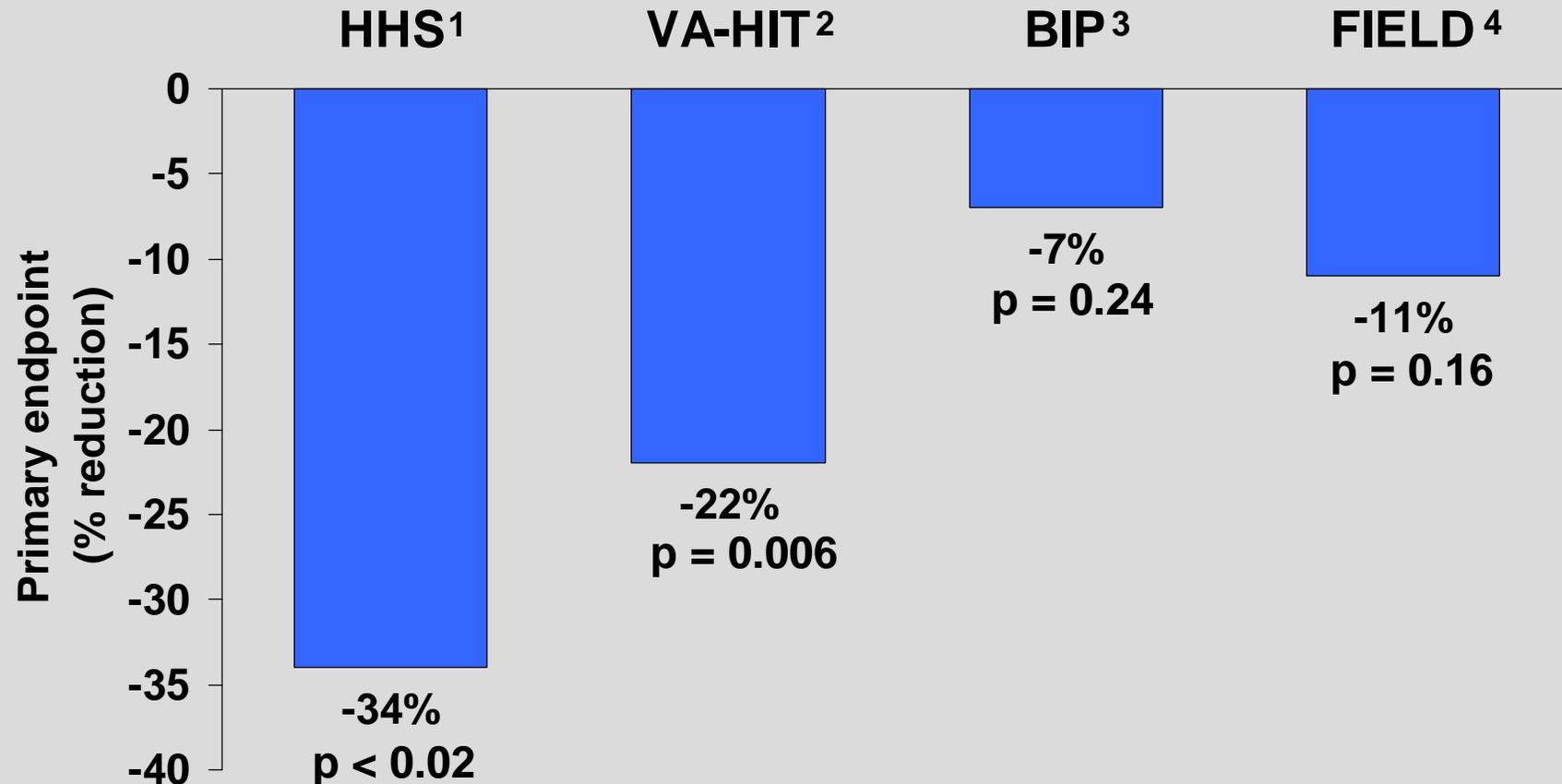
2 *N Engl J Med.* 1999;341:410-418.

3 *Circulation.* 2000;102:21-27.

4 *Lancet.* 2005;366:1849-1861.

Key Fibrate Outcomes Trials Prior to ACCORD

Lipid - Primary Endpoint Results for All Patients



1 *N Engl J Med.* 1987;317:1237-1245.

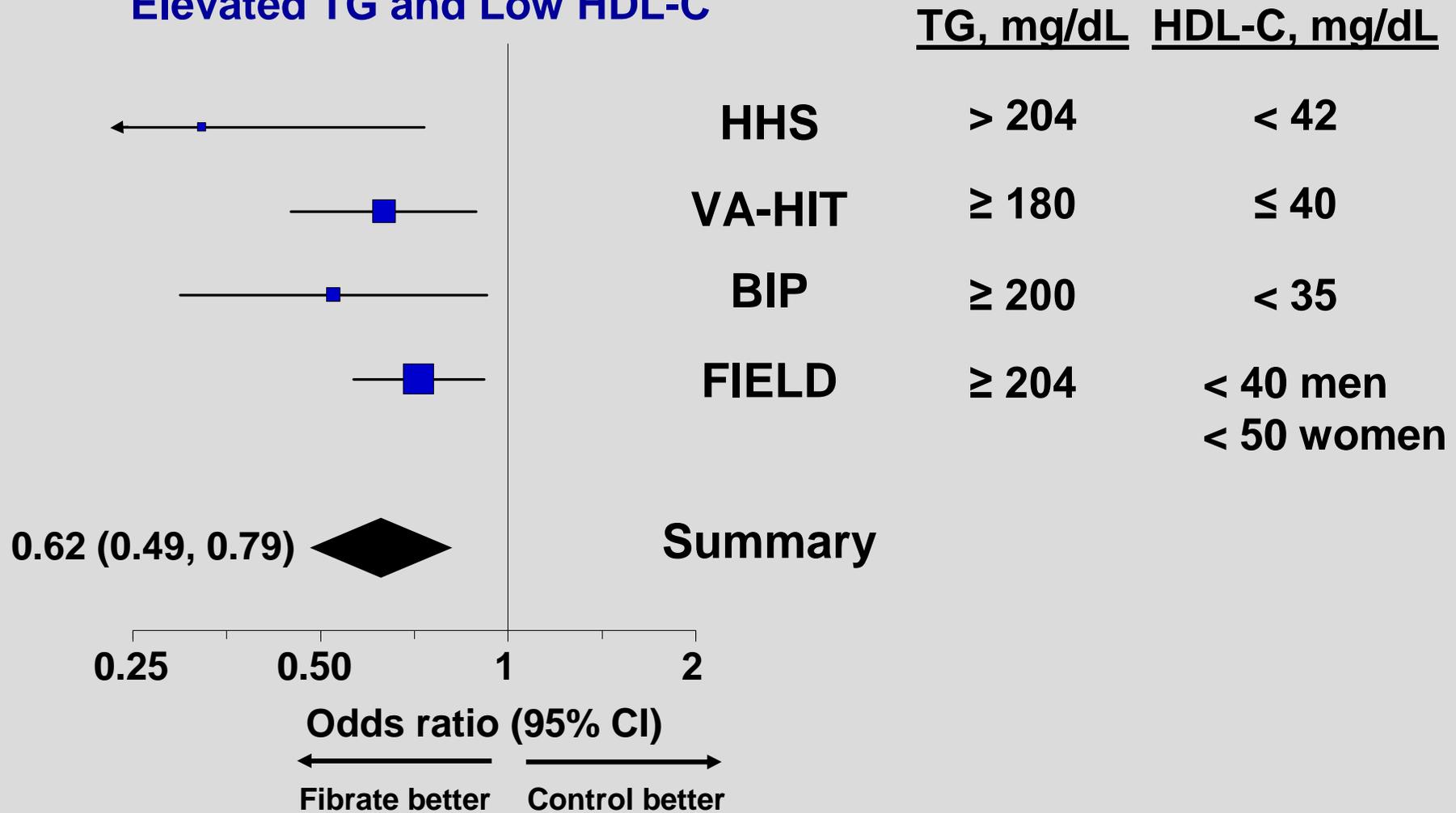
2 *N Engl J Med.* 1999;341:410-418.

3 *Circulation.* 2000;102:21-27.

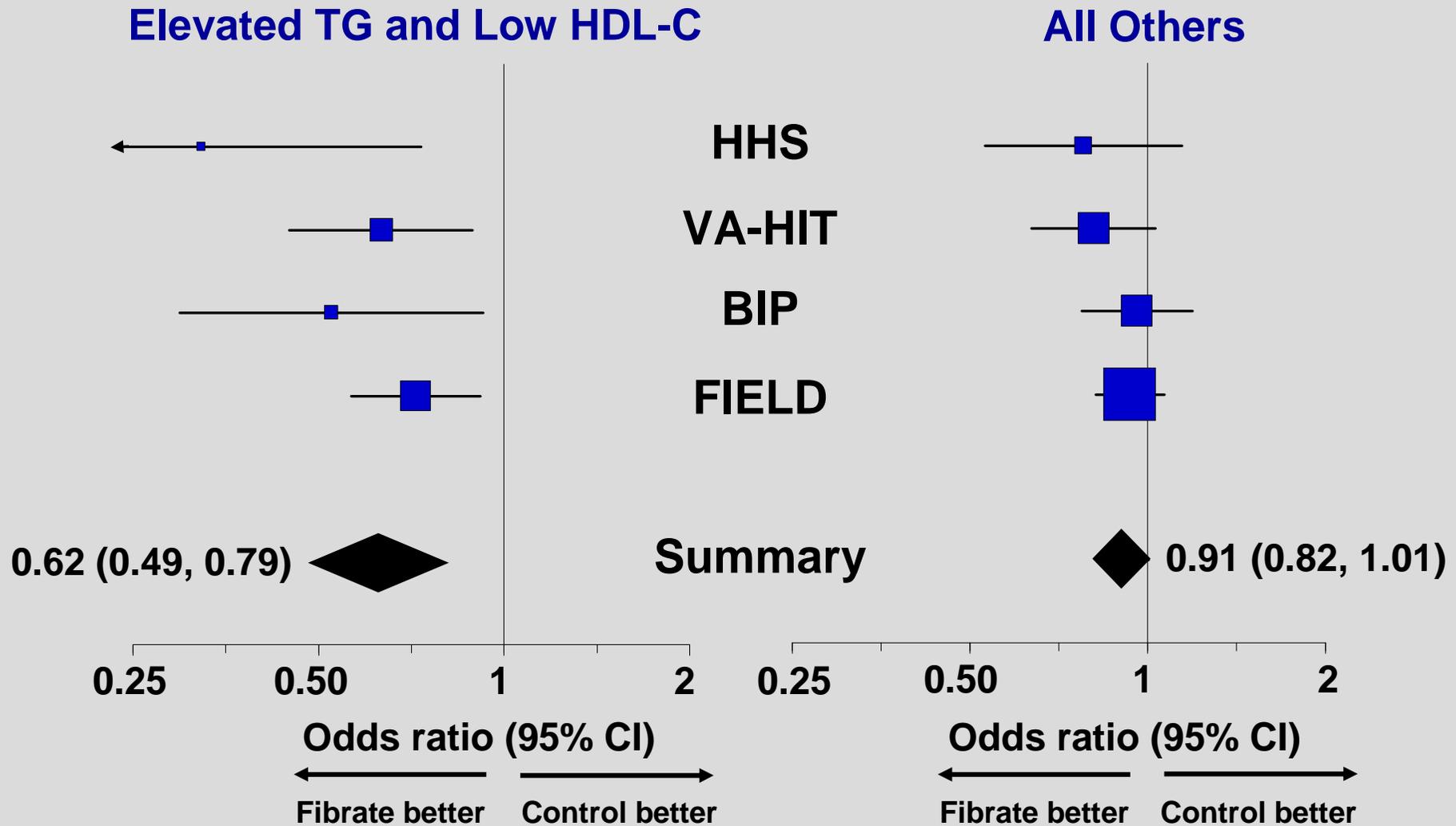
4 *Lancet.* 2005;366:1849-1861.

CV Benefit of Fibrates in Patients with Elevated TG and Low HDL-C

Elevated TG and Low HDL-C



CV Benefit of Fibrates Concentrated in Patients with Elevated TG and Low HDL-C



Summary of Key Fibrate Outcomes Trials

- ◆ **Data available prior to publication of ACCORD Lipid supported 2 conclusions:**
 - **Fibrates reduce risk of CV events in patients with elevated TG and low HDL-C**
 - **Fibrates do not provide a meaningful reduction of CV risk in patients without elevated TG and low HDL-C**

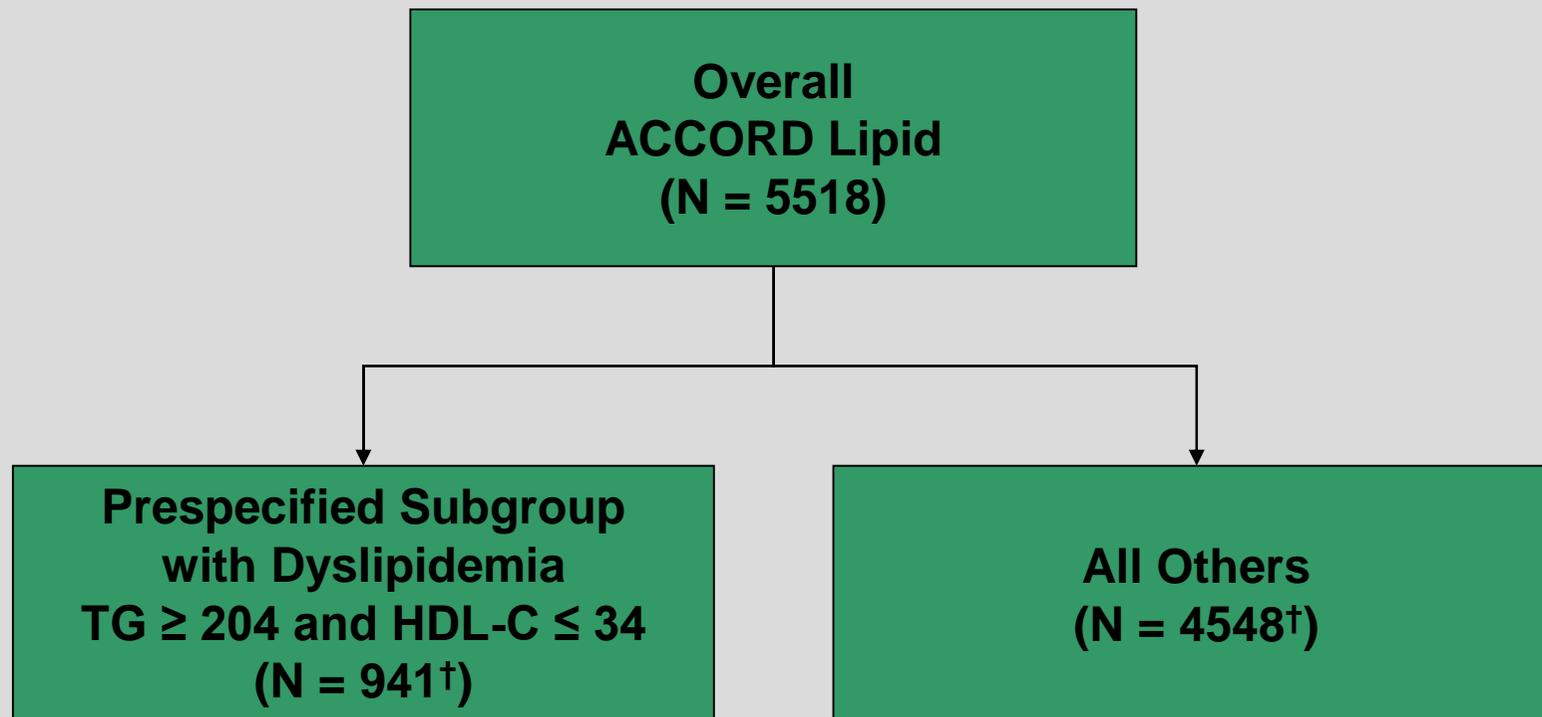
ACCORD Lipid Study Design

	Simvastatin + Placebo	Simvastatin + Fenofibrate
Intensive glycemia (HbA _{1c} < 6%)	1,383	1,374
Standard glycemia (HbA _{1c} 7 - 7.9%)	1,370	1,391
	2,753	2,765

Select Entry Criteria

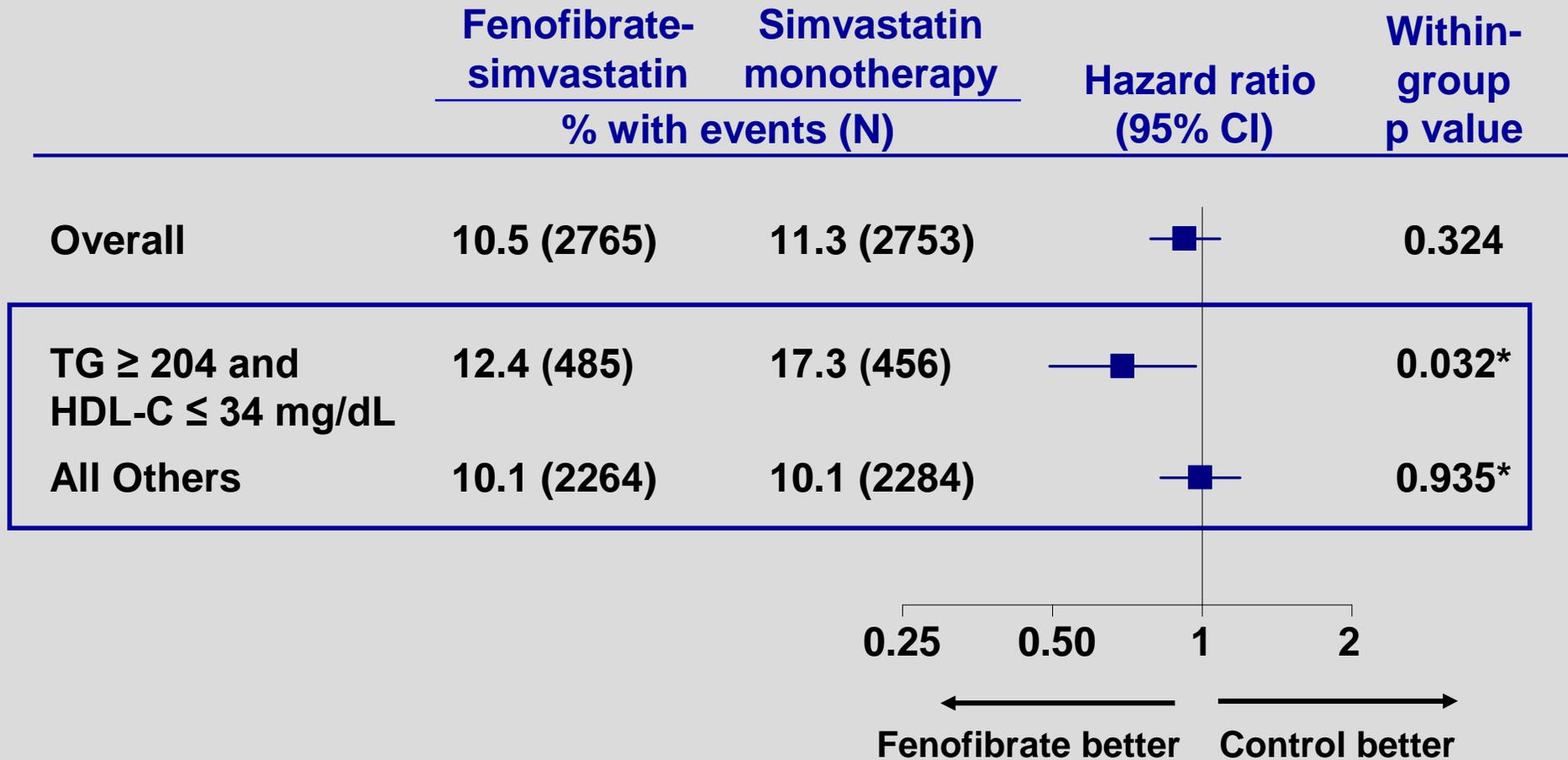
- LDL-C 60 - 180 not receiving lipid medications
- HDL-C < 55 (female or black) or < 50 (others)
- TG < 750 on no meds or < 400 on meds (no minimum TG threshold)
- Patients allowed but not required to be receiving a statin at study entry

ACCORD Lipid Prespecified Subgroup with Dyslipidemia



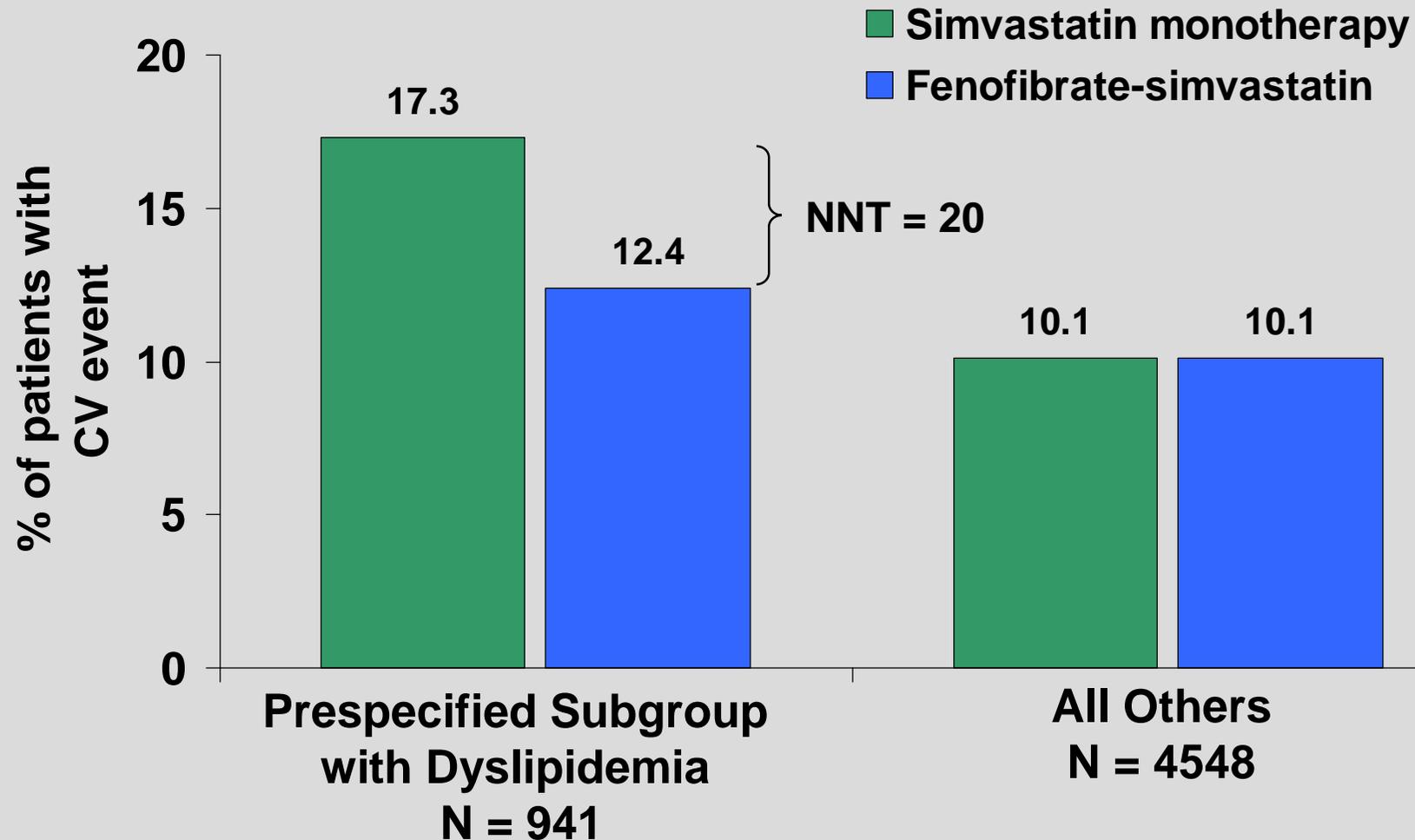
† Excludes 29 patients overall who did not have baseline lipid values.

ACCORD Lipid Prespecified Subgroup with Dyslipidemia

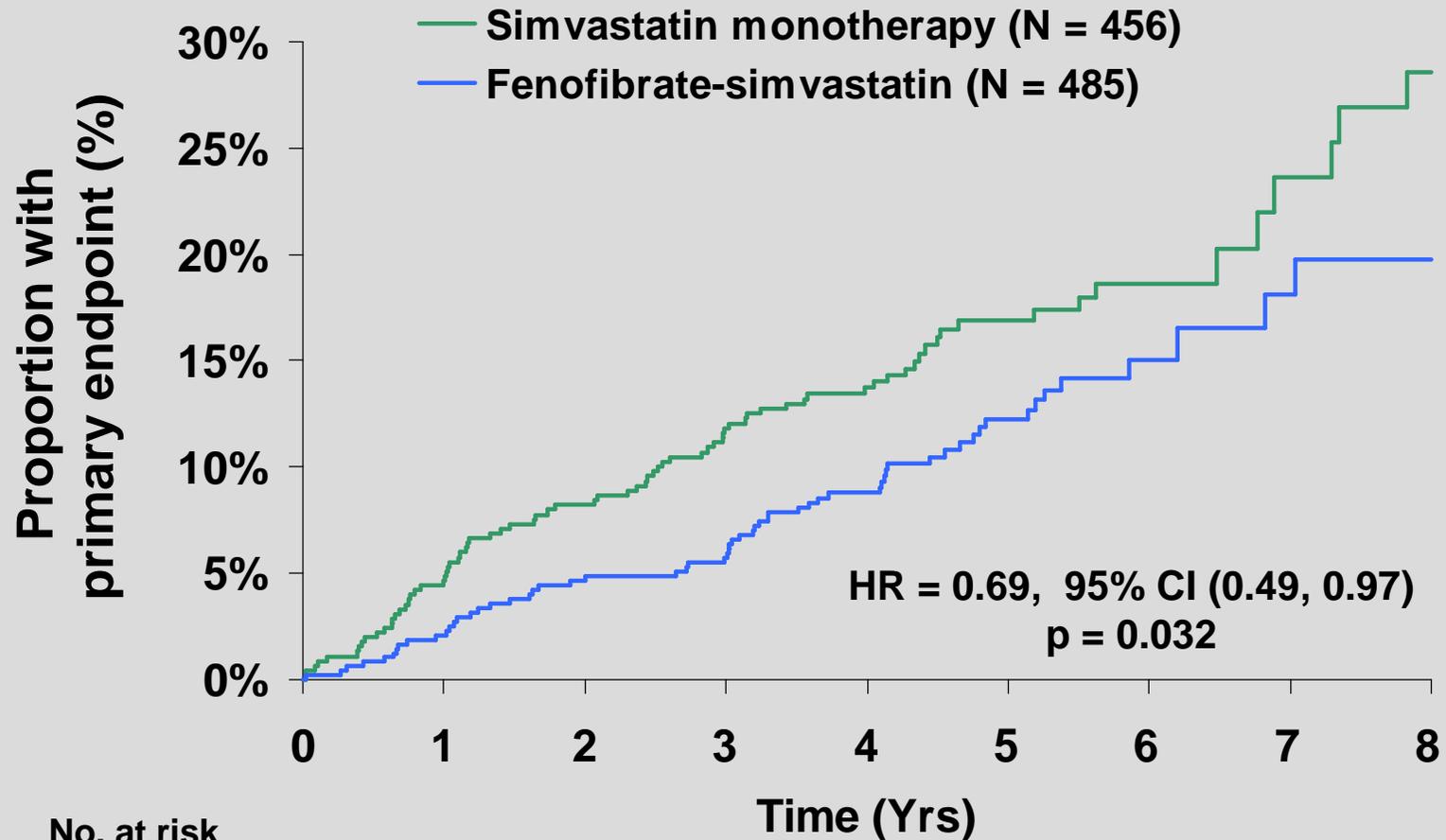


*Treatment-by-subgroup interaction, $p = 0.057$

Reduced Risk of CV Events in ACCORD Lipid Prespecified Subgroup with Dyslipidemia

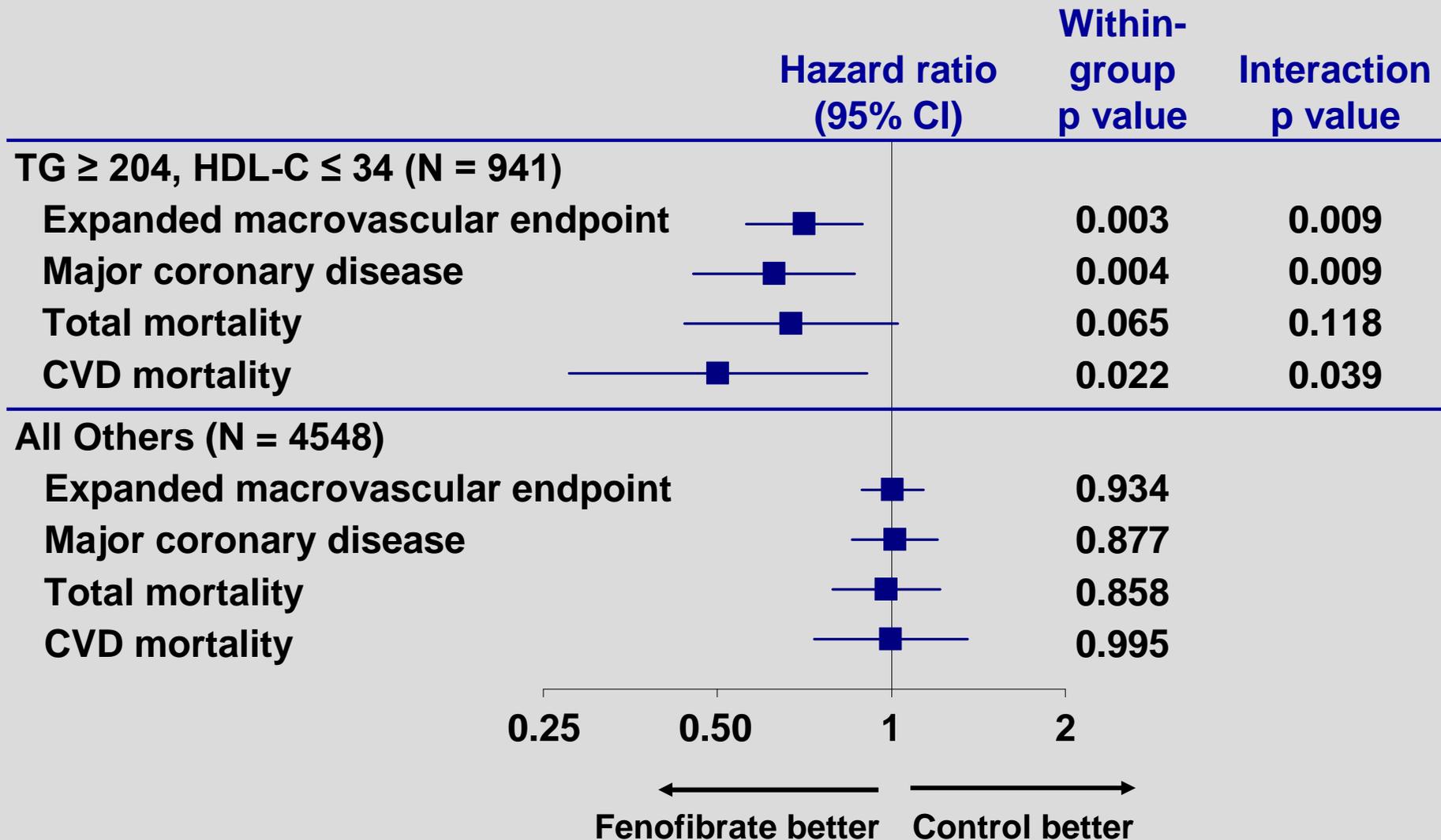


Coadministration Therapy Reduces CV Risk in Prespecified Subgroup with Dyslipidemia



	No. at risk				
Simvastatin monotherapy	456	410	313	76	25
Fenofibrate-simvastatin	485	449	350	81	29

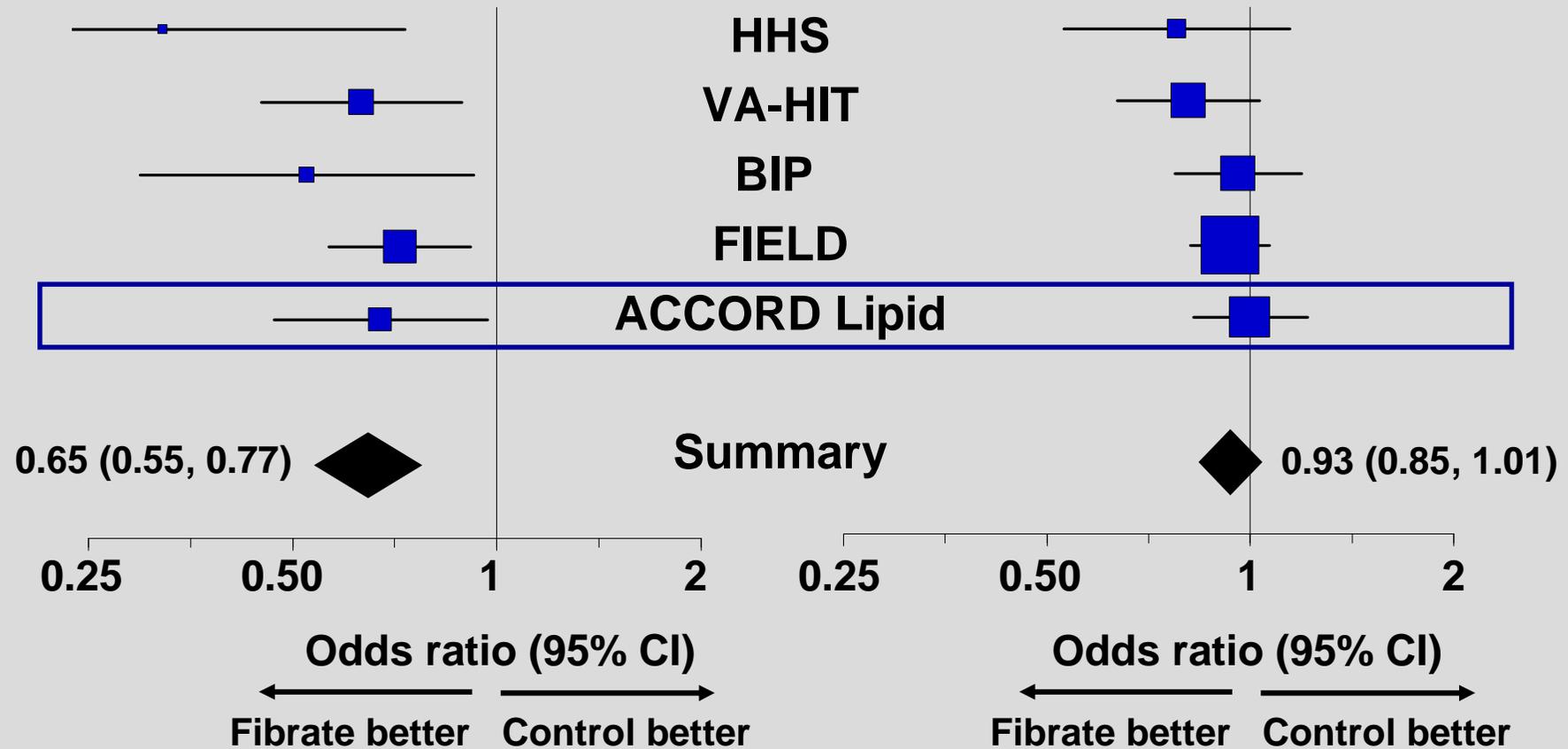
Secondary Endpoints in ACCORD Lipid Prespecified Subgroup with Dyslipidemia



ACCORD Lipid Confirms Earlier Fibrate CV Outcomes Trials

Elevated TG and Low HDL-C

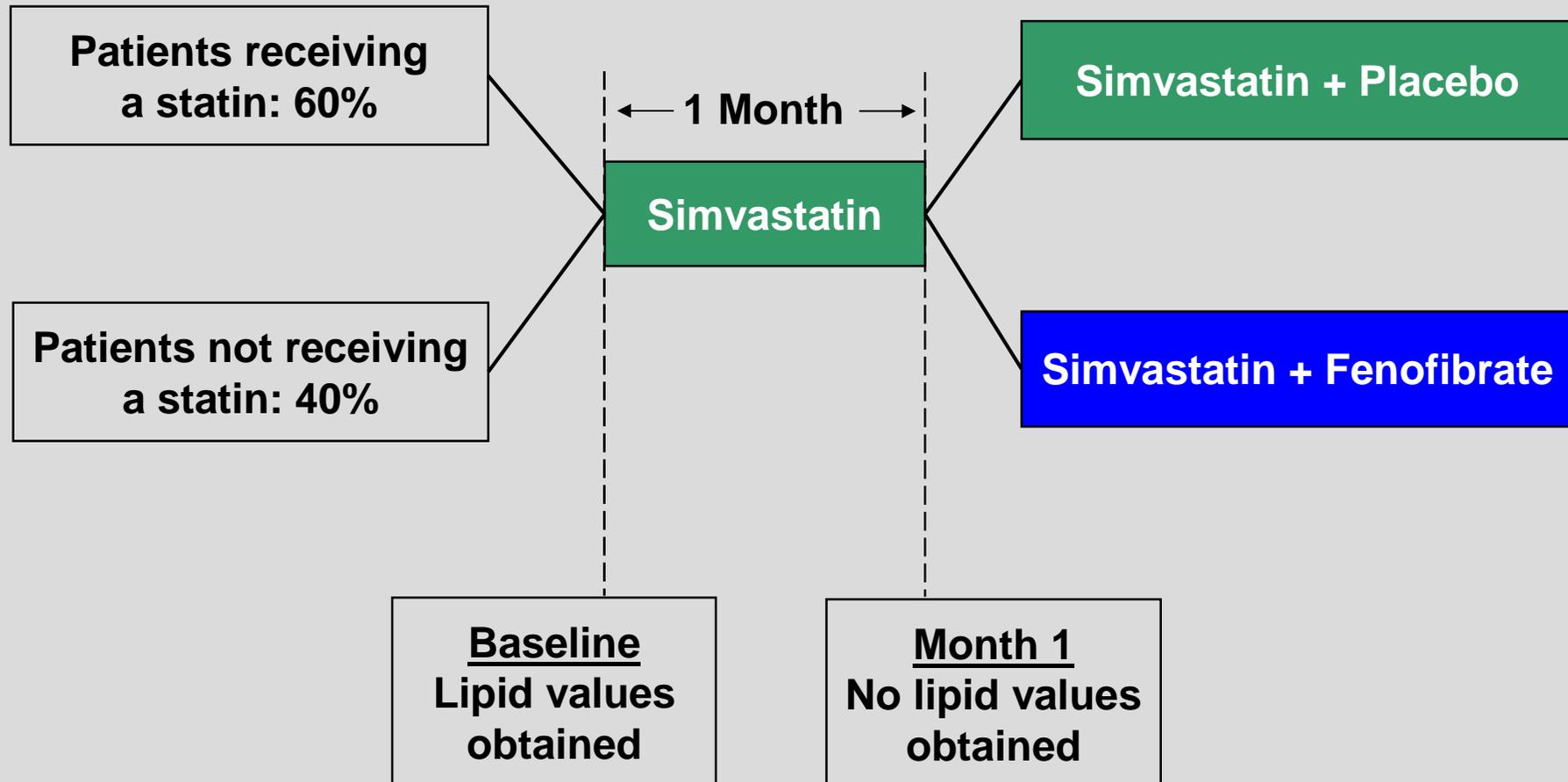
All Others



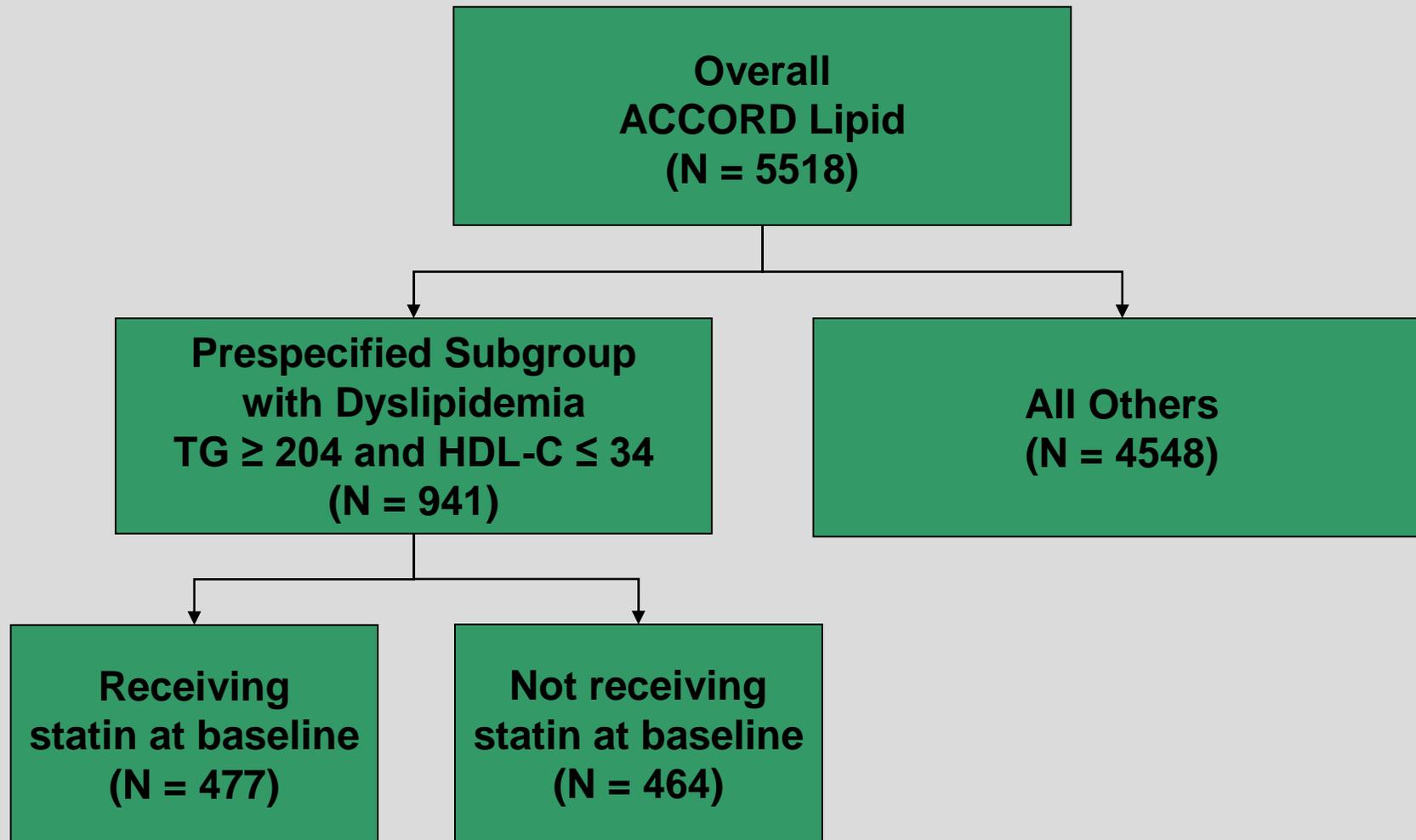
ACCORD Lipid Confirms Earlier Fibrate CV Outcomes Trials

- ◆ Fibrates reduce risk of CV events in patients with elevated TG and low HDL-C
 - With or without concomitant statin therapy
- ◆ Fibrates do not provide a meaningful reduction of CV risk in patients without elevated TG and low HDL-C

ACCORD Lipid Study Design



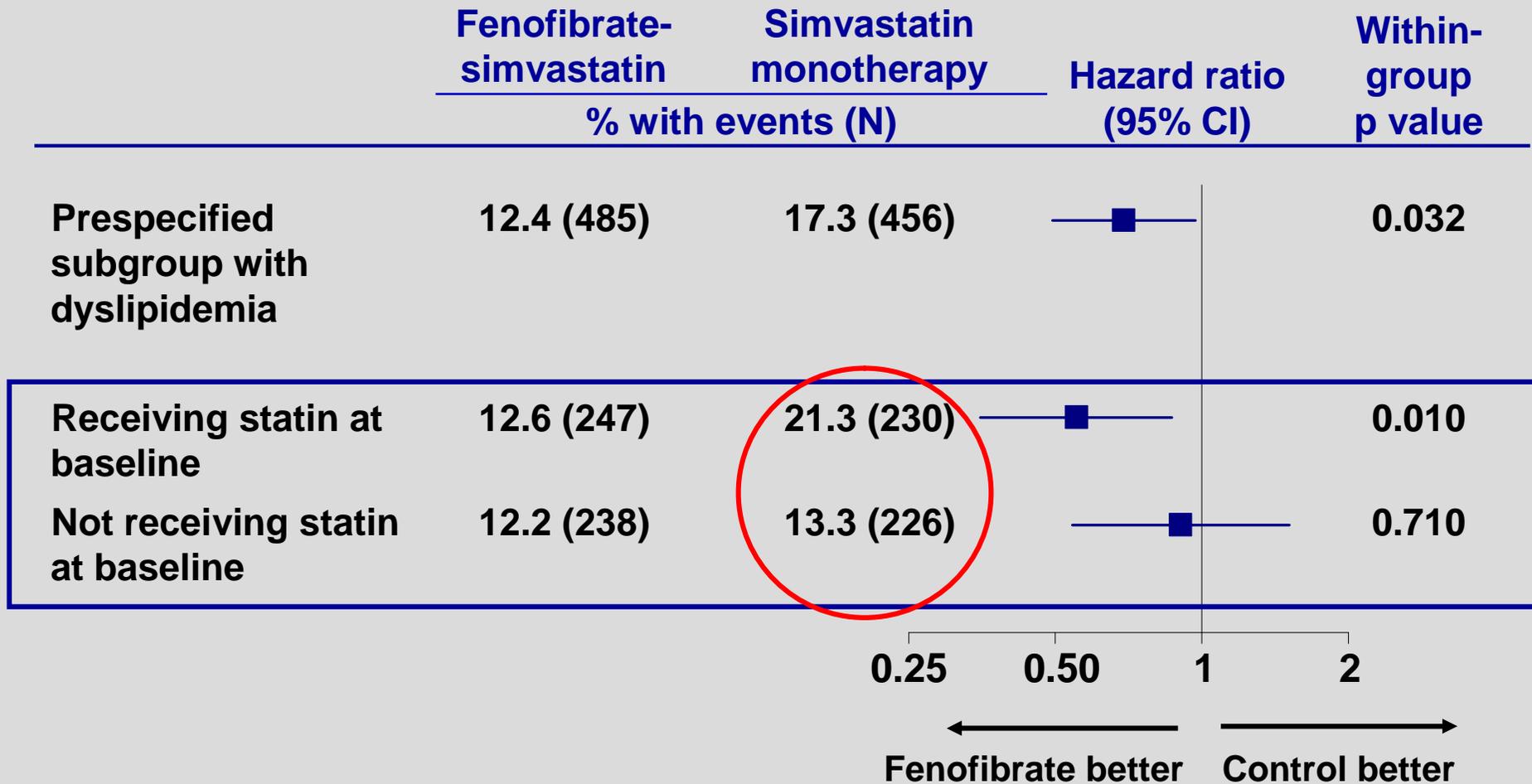
ACCORD Lipid Prespecified Subgroup with Dyslipidemia by Baseline Statin Use



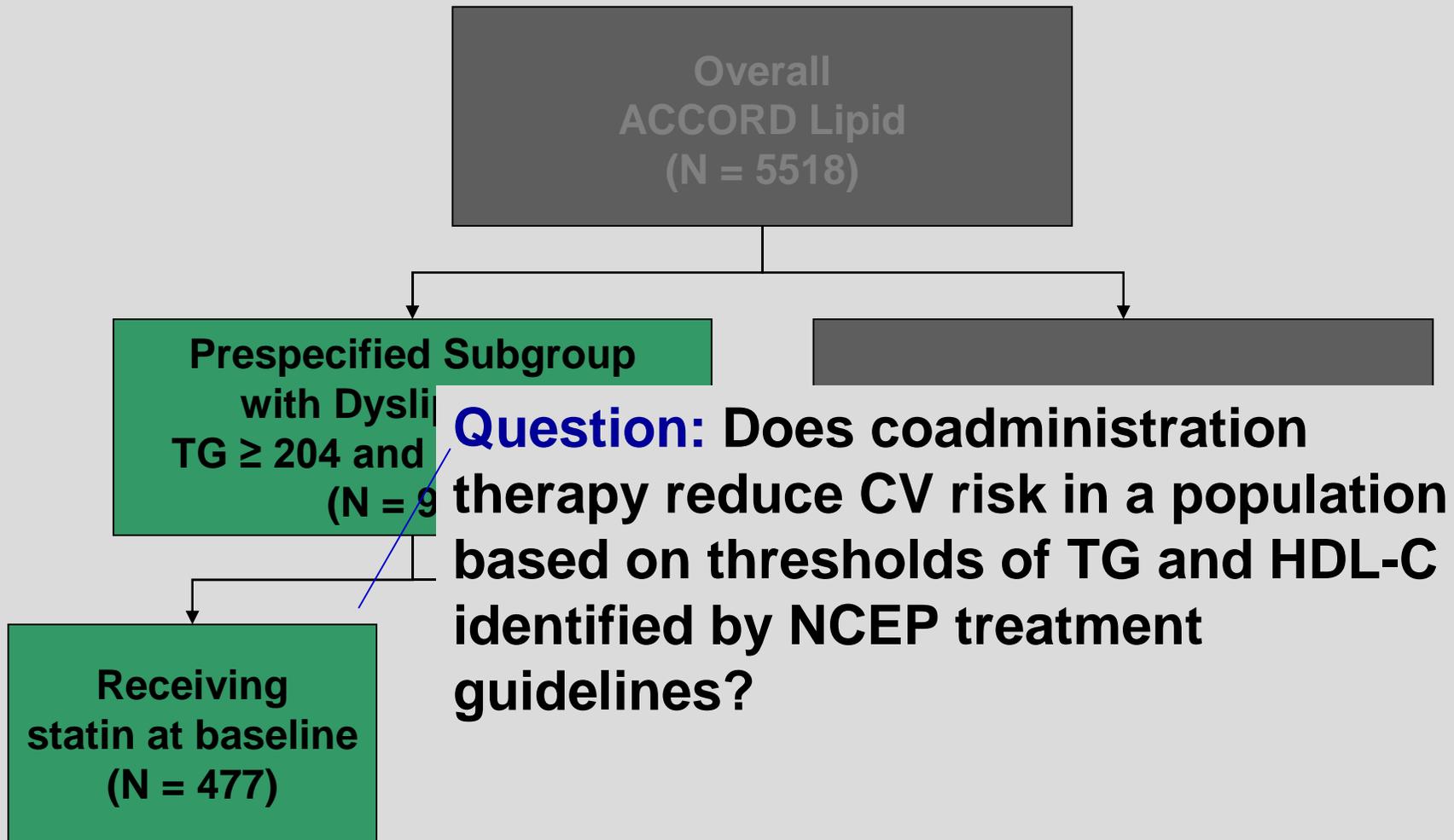
Rationale for Sensitivity Analysis of Patients Receiving a Statin at Baseline

- ◆ **Trilipix coadministration indication is limited to patients already receiving statin therapy**
- ◆ **Treatment guidelines recommend coadministration therapy only if TG and/or HDL-C abnormalities persist after LDL-C-lowering treatment**

ACCORD Lipid Prespecified Subgroup with Dyslipidemia by Statin Use at Baseline



ACCORD Lipid Prespecified Subgroup with Dyslipidemia by Baseline Statin Use



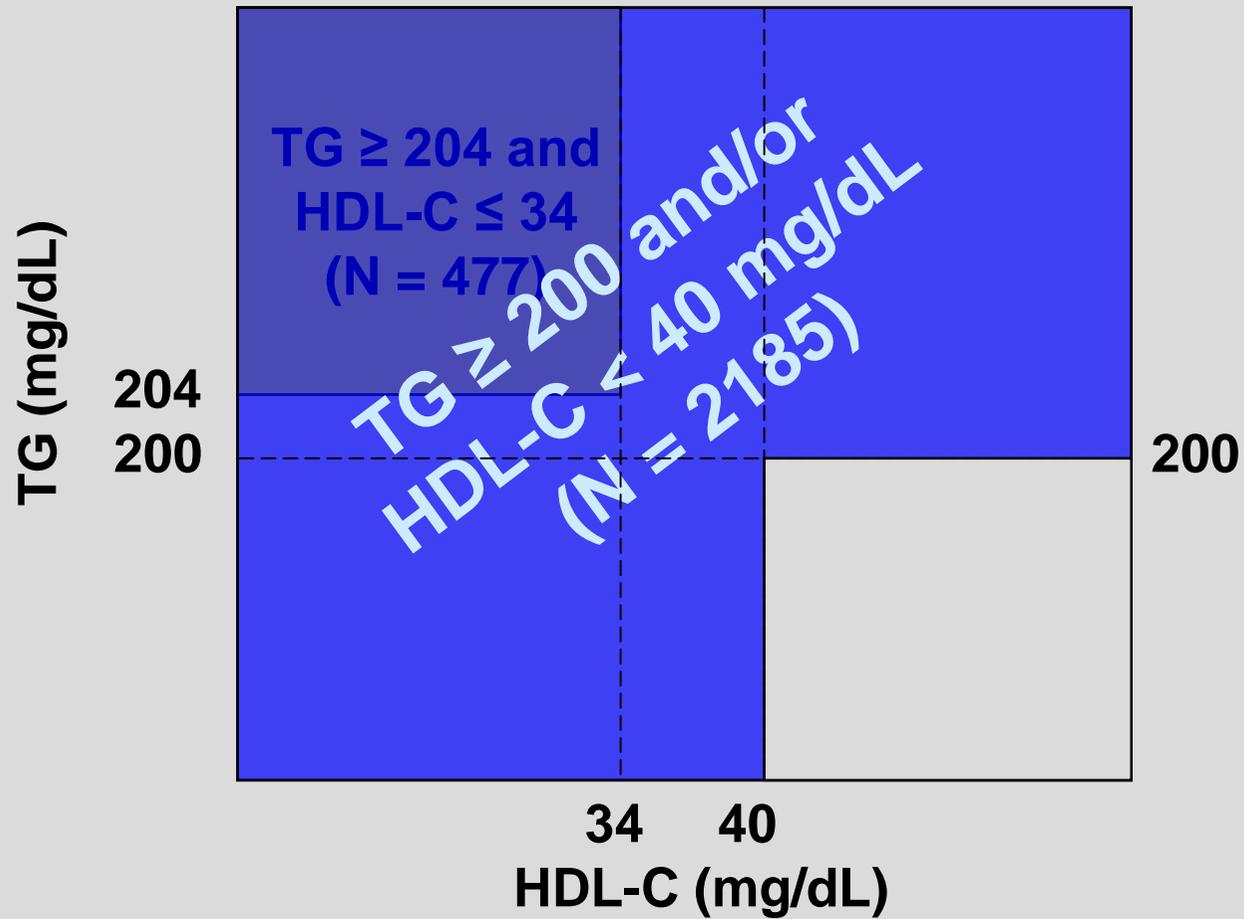
Sensitivity Analysis - Alternative TG and HDL-C Thresholds

◆ NCEP treatment guidelines

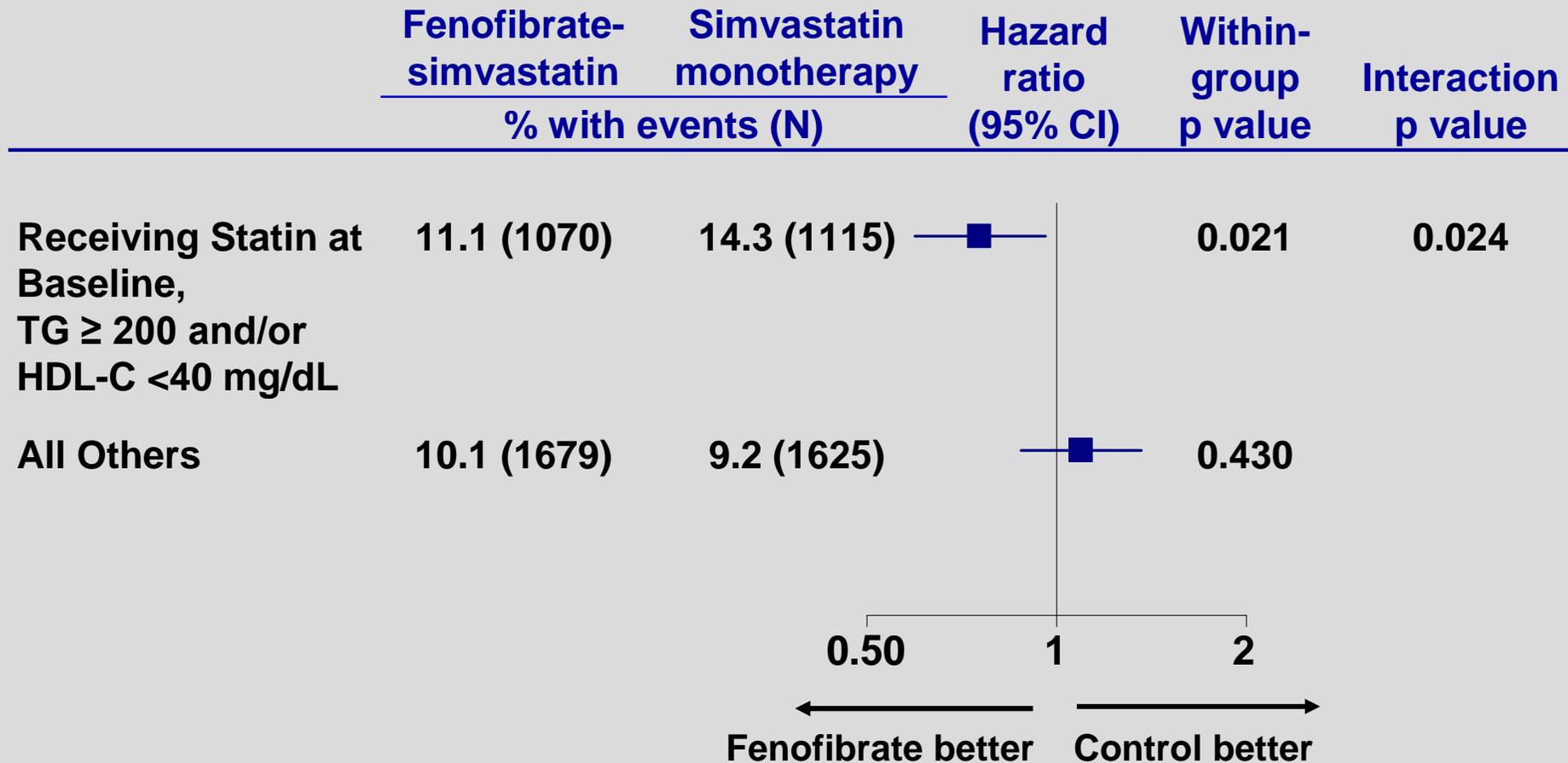
- **TG \geq 200 mg/dL: treatment beyond LDL-C lowering is recommended**
 - **non-HDL-C is the target of therapy**
- **HDL-C $<$ 40 mg/dL: categorically identified as low**
- **For high risk patients with elevated TG or low HDL-C levels, coadministration therapy can be considered**

Alternative TG and HDL-C Thresholds for Patients Receiving a Statin at Baseline

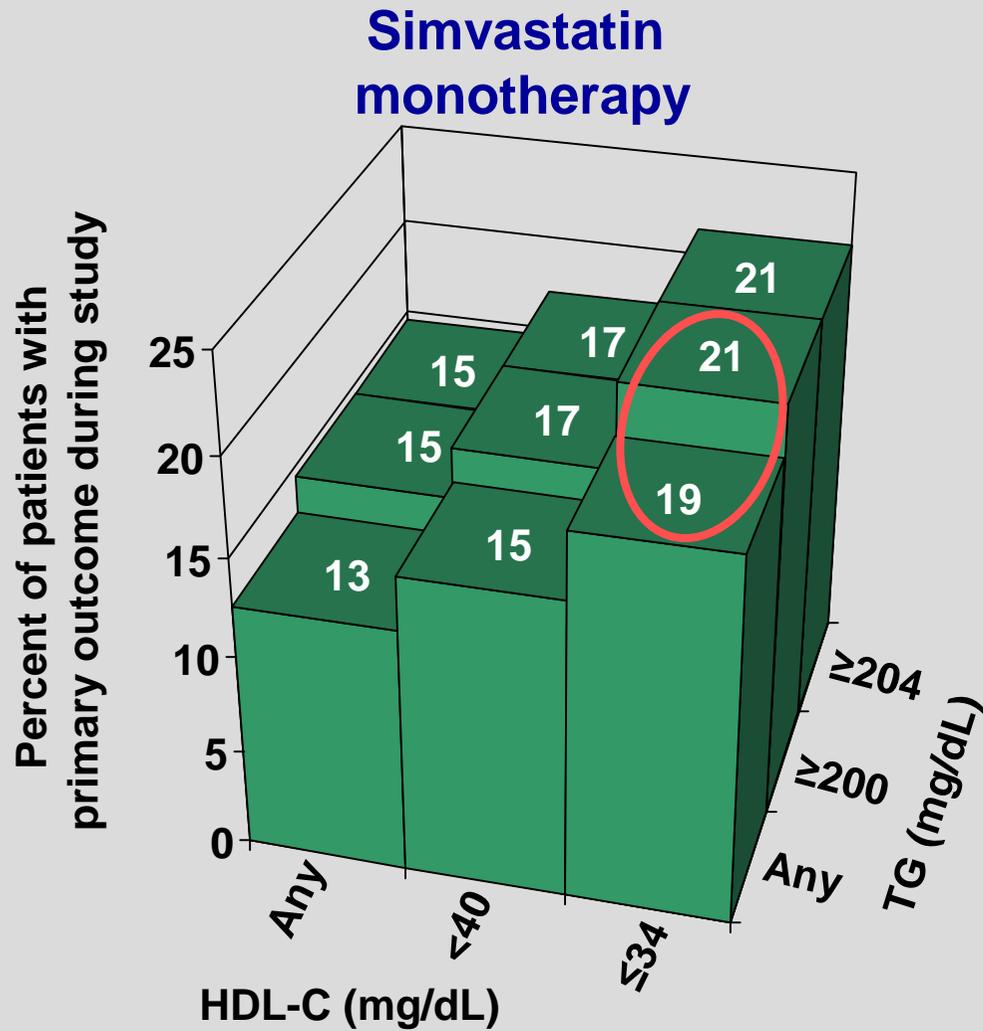
ACCORD Lipid patients receiving a statin at baseline (N = 3280)



ACCORD Lipid Patients Receiving a Statin at Baseline with TG \geq 200 and/or HDL-C $<$ 40 mg/dL

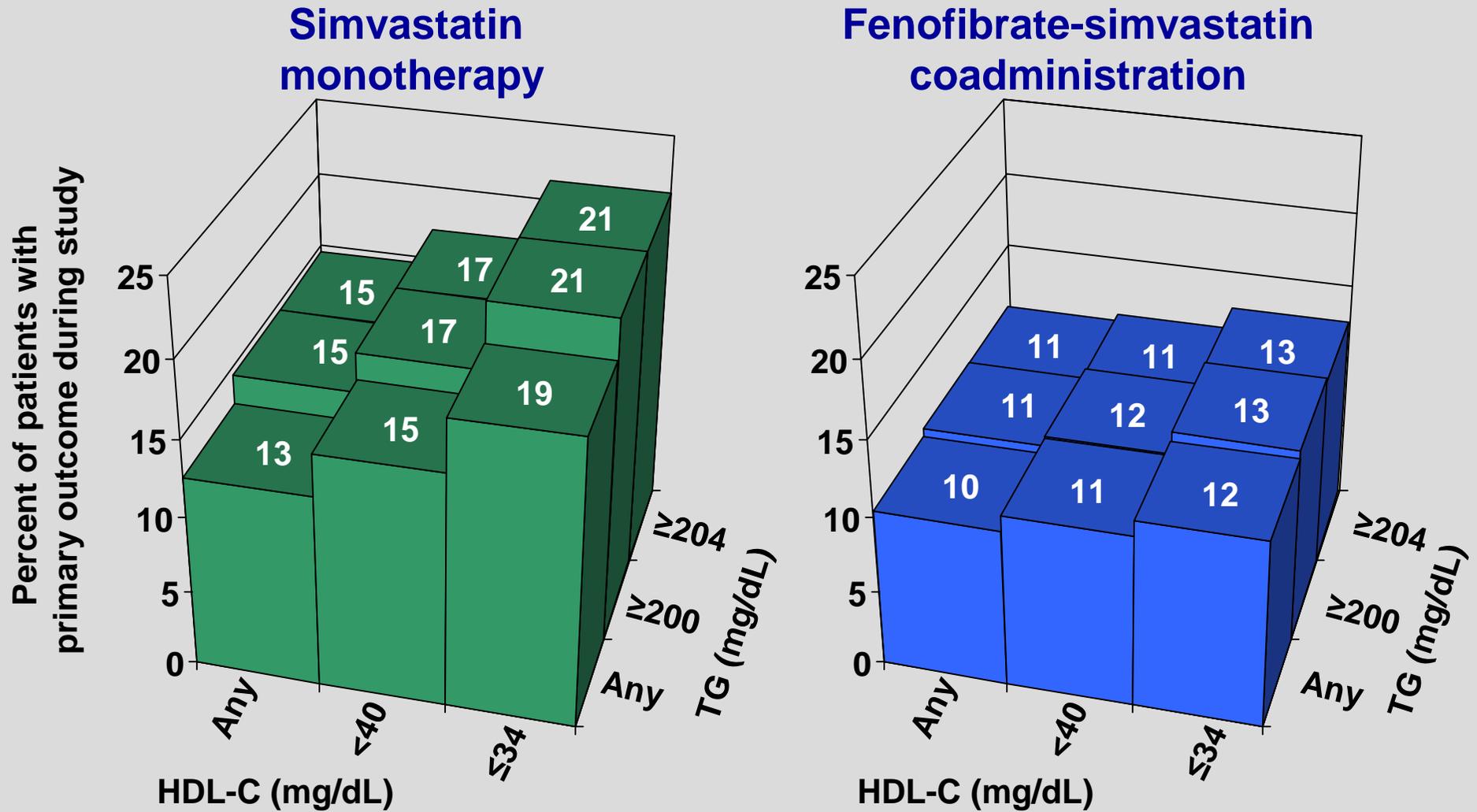


CV Risk Increases with Worsening TG and HDL-C in Patients Treated with Simvastatin Monotherapy



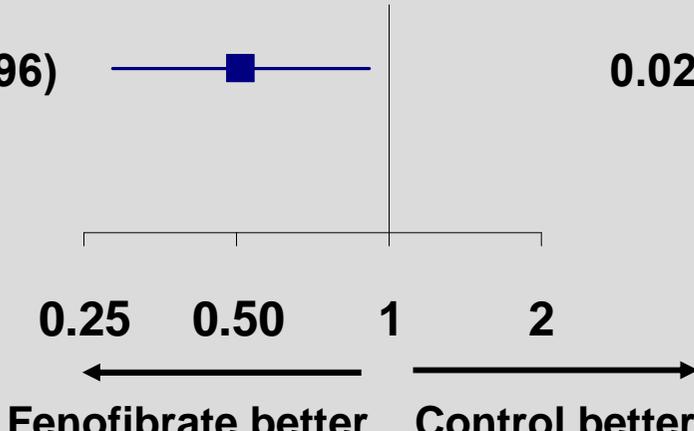
Patients receiving statin at baseline

Addition of Fenofibrate to Simvastatin Reduces Incremental CV Risk



Patients receiving statin at baseline

CV Risk Reduction by Baseline non-HDL-C in ACCORD Lipid Patients Receiving a Statin at Baseline

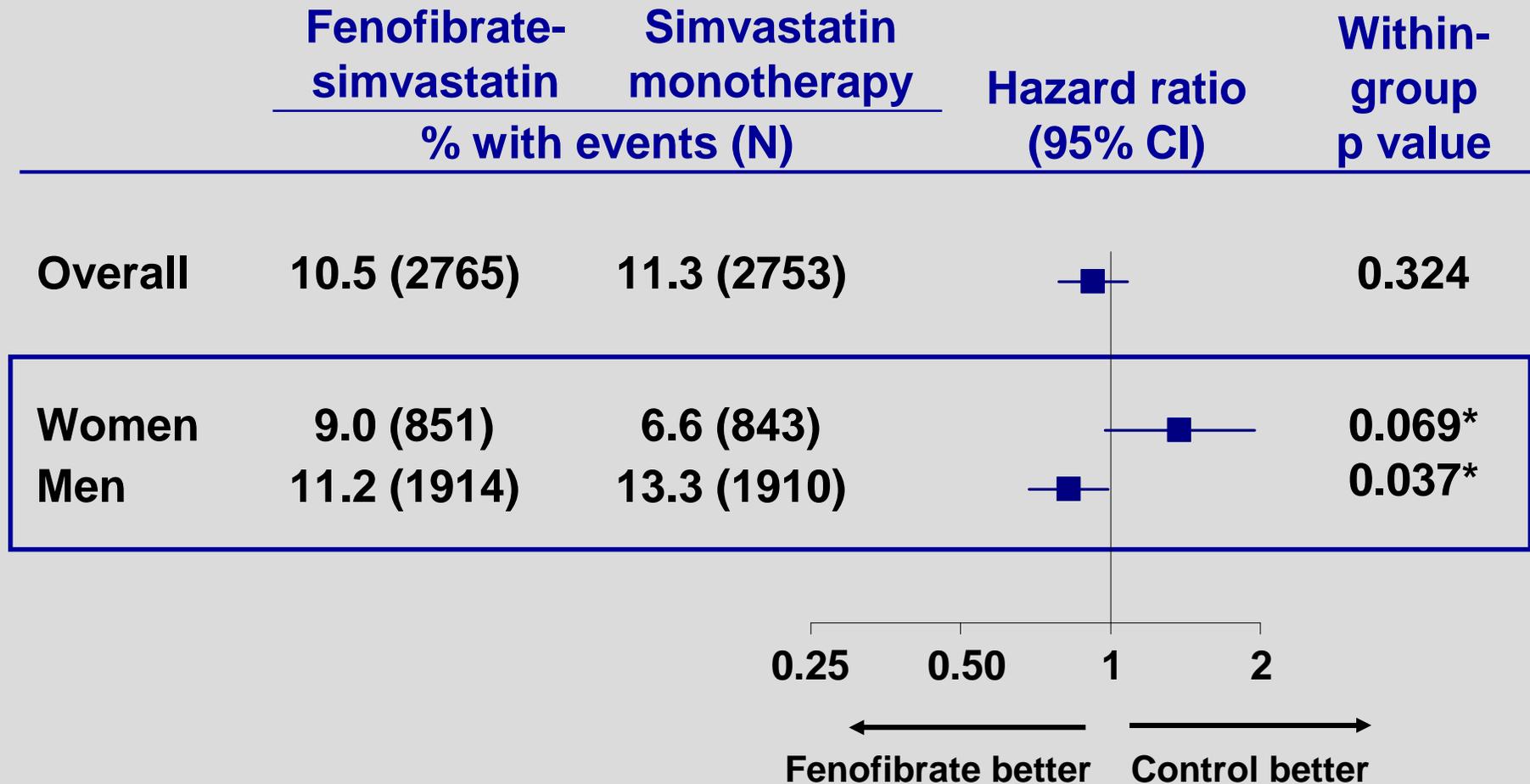
Baseline Non-HDL-C and LDL-C	Fenofibrate- simvastatin % with events (N)	Simvastatin monotherapy % with events (N)	Hazard ratio (95% CI)	Within- group p value
Non-HDL-C \geq 130 mg/dL and LDL-C < 100 mg/dL	8.8 (217)	16.3 (196)		0.023

ACCORD Lipid Efficacy Conclusions

- ◆ **Coadministration therapy reduced CV risk in patients with elevated TG and/or low HDL-C**
 - **Benefit concentrated in patients receiving a statin at baseline**
 - **Benefit present across a range of abnormal TG and HDL-C levels**
- ◆ **Results of ACCORD Lipid were consistent with known epidemiological relationship between TG and HDL-C and CV risk**

ACCORD Lipid Results in Women

ACCORD Lipid Primary Outcome by Gender

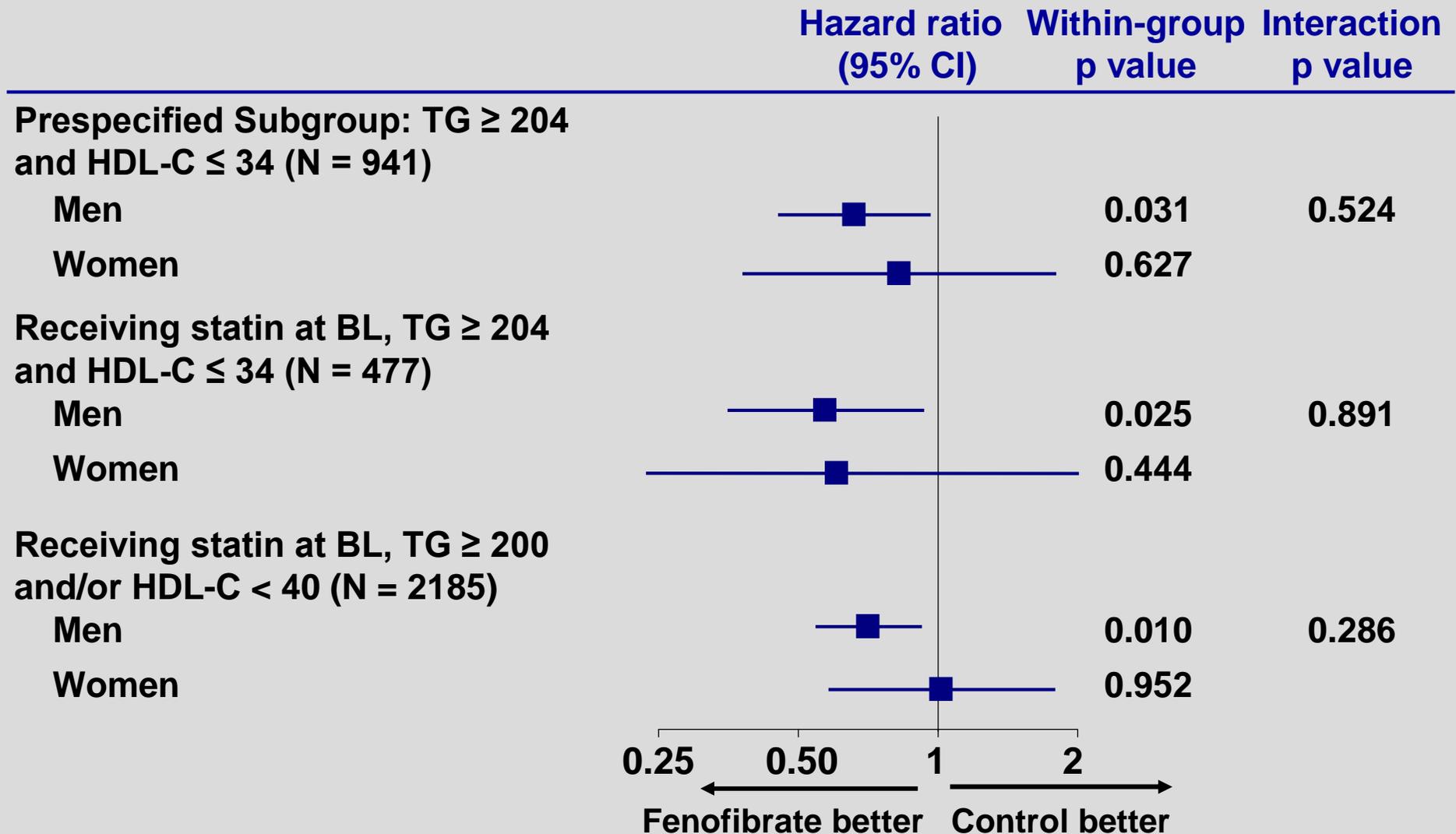


*Treatment-by-gender interaction, $p = 0.011$

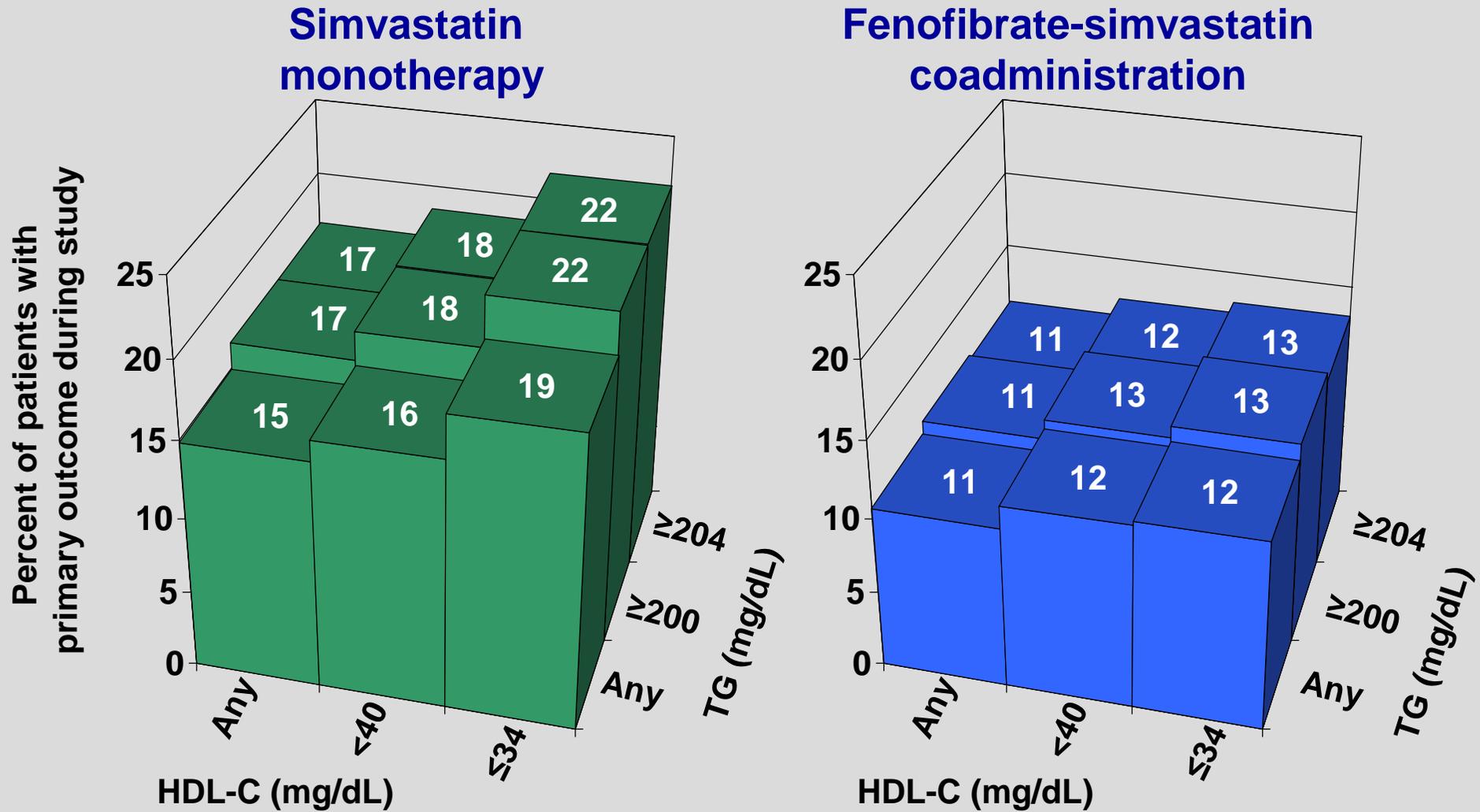
Analyses of Women in ACCORD Lipid

- ◆ **Abbott investigated the findings in women by evaluating:**
 - **Outcomes by gender in patients with dyslipidemia**
 - **Potential explanations**
 - **Baseline imbalances**
 - **Lipid changes**
 - **Other laboratory changes**
 - **Pharmacokinetic interaction**

No Treatment-by-Gender Interaction in Prespecified Subgroup with Dyslipidemia and Sensitivity Analyses

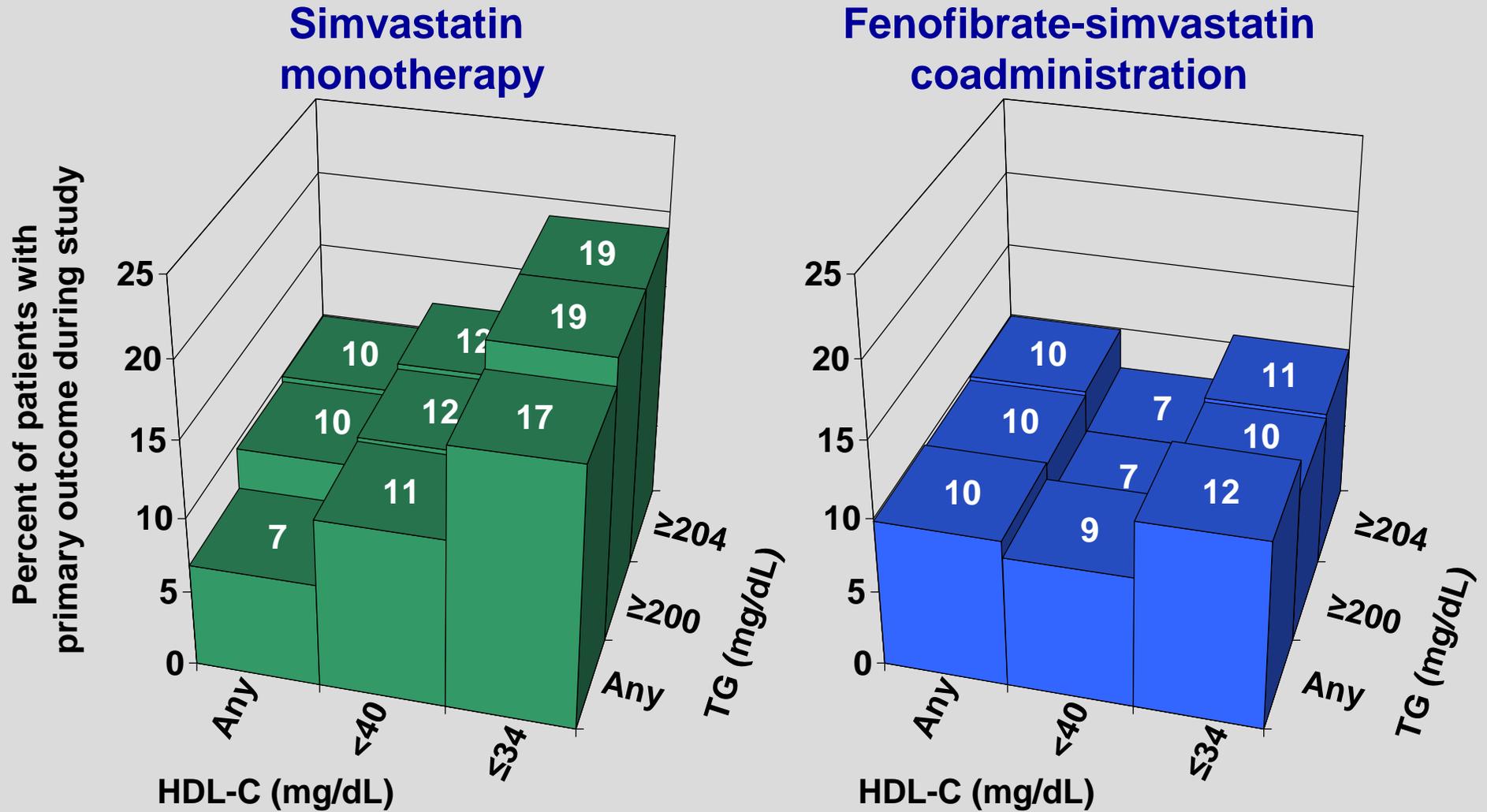


Coadministration of Fenofibrate and Simvastatin Reduces Incremental Risk in Dyslipidemic Men



Men receiving statin at baseline

Coadministration of Fenofibrate and Simvastatin in Dyslipidemic Women Shows a Similar Pattern to Men



Women receiving statin at baseline

Assessment of Potential Explanations for the Findings in Non-dyslipidemic Women

- ◆ **Fenofibrate-statin PK interactions not different between males and females**
- ◆ **In ACCORD Lipid**
 - **No important imbalances in baseline characteristics in women**
 - **Multivariate analysis did not change treatment effect in women**
 - **Lipid changes with coadministration therapy in women similar or better than those in men**

Treatment-by-subgroup Interactions in ACCORD Lipid

- ◆ No clear etiology for treatment-by-gender interaction identified
- ◆ Treatment-by-gender interaction in ACCORD Lipid inconsistent with other trials
- ◆ Treatment-by-gender interaction not present in subgroup with dyslipidemia
- ◆ In contrast, treatment-by-dyslipidemia subgroup interaction consistent with mechanism of action and prior fibrate trials

ACCORD Lipid Safety

Overall Safety Profile in ACCORD Lipid Reassuring

	Fenofibrate-simvastatin, N (%)	Simvastatin monotherapy, N (%)
Blinded study drug discontinuation	628 (23)	516 (19)
CK > 10× ULN	10 (0.4)	9 (0.3)
ALT > 3× ULN	52 (1.9)	40 (1.5)
Hepatitis	3 (0.1)	0
Pancreatitis [†]	5 (0.2)	4 (0.1)
Hemodialysis and ESRD	75 (2.7)	77 (2.8)

† Per Abbott investigation of the ACCORD Lipid database.

Additional Data to Support Coadministration Therapy

Outline of Additional Data to Support Coadministration Therapy

- ◆ **Abbott meta-analysis of 71 lipid studies with CV outcomes**
- ◆ **Published fibrate meta-analysis**
- ◆ **Microvascular benefits of fenofibrate therapy**

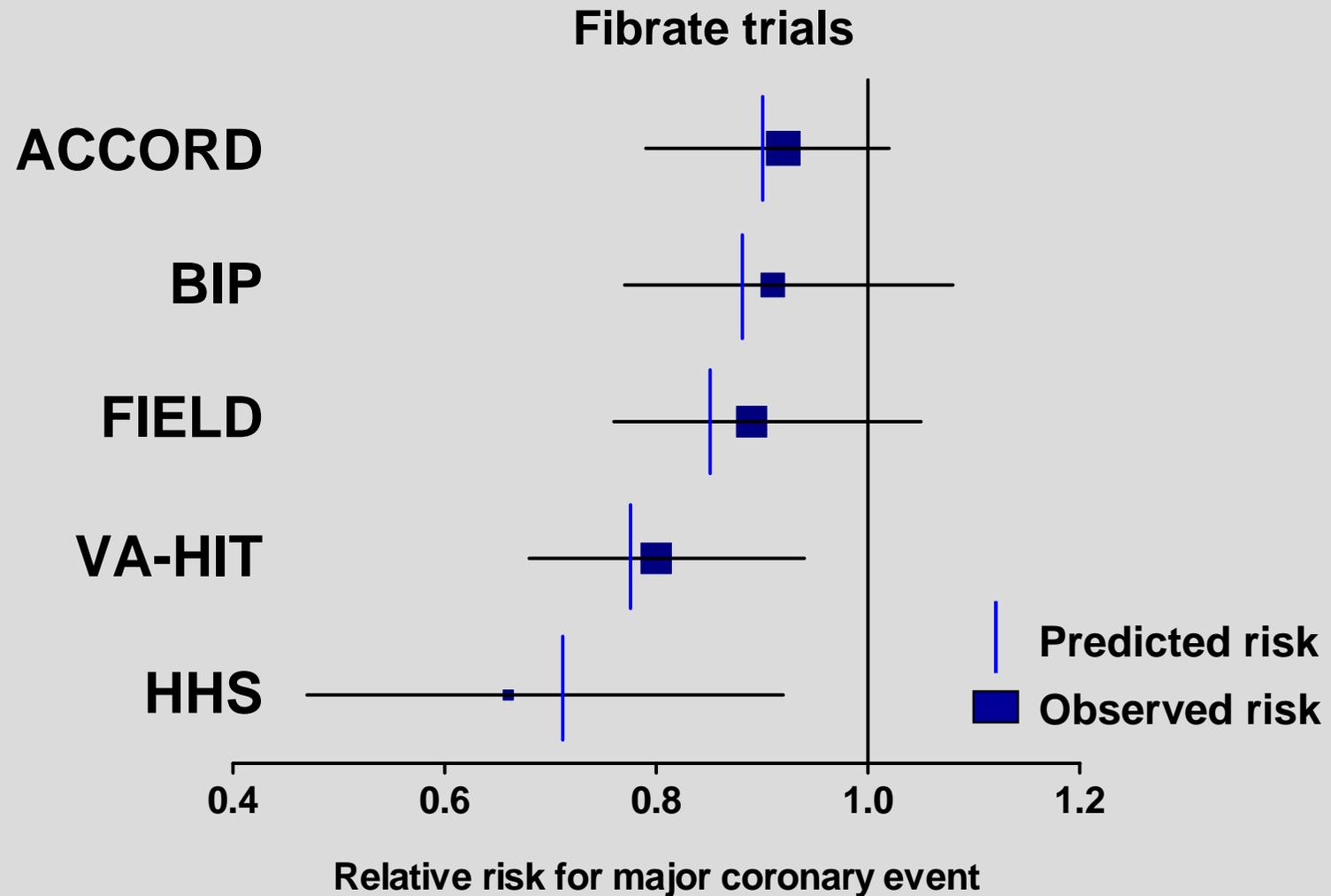
Abbott Meta-analysis Demonstrates Outcomes Are Associated with Changes in LDL-C and TG

- ◆ **71 trials with data on coronary and/or major CV events, including over 215,000 patients**
 - **Multivariate meta-analysis related lipid changes to clinical outcomes**
- ◆ **Coronary/CV outcomes were associated with**
 - **Absolute on treatment changes in both LDL-C and TG**
 - **Significant impact of TG lowering for fibrates as well as statins when estimated independently**
 - **Treatment duration**
 - **Baseline HDL-C**

ACCORD Lipid Results Are Predicted by Abbott Meta-analysis

- ◆ Based on observed TG and LDL-C effects in ACCORD Lipid, meta-analysis predicts HRs of
0.90 [95% CI: 0.85, 0.94] (CV)
0.91 [95% CI: 0.87, 0.95] (coronary)
- ◆ Nearly identical to HR of 0.92 observed overall in ACCORD Lipid
- ◆ Risk reduction in ACCORD Lipid is explained by low median baseline TG

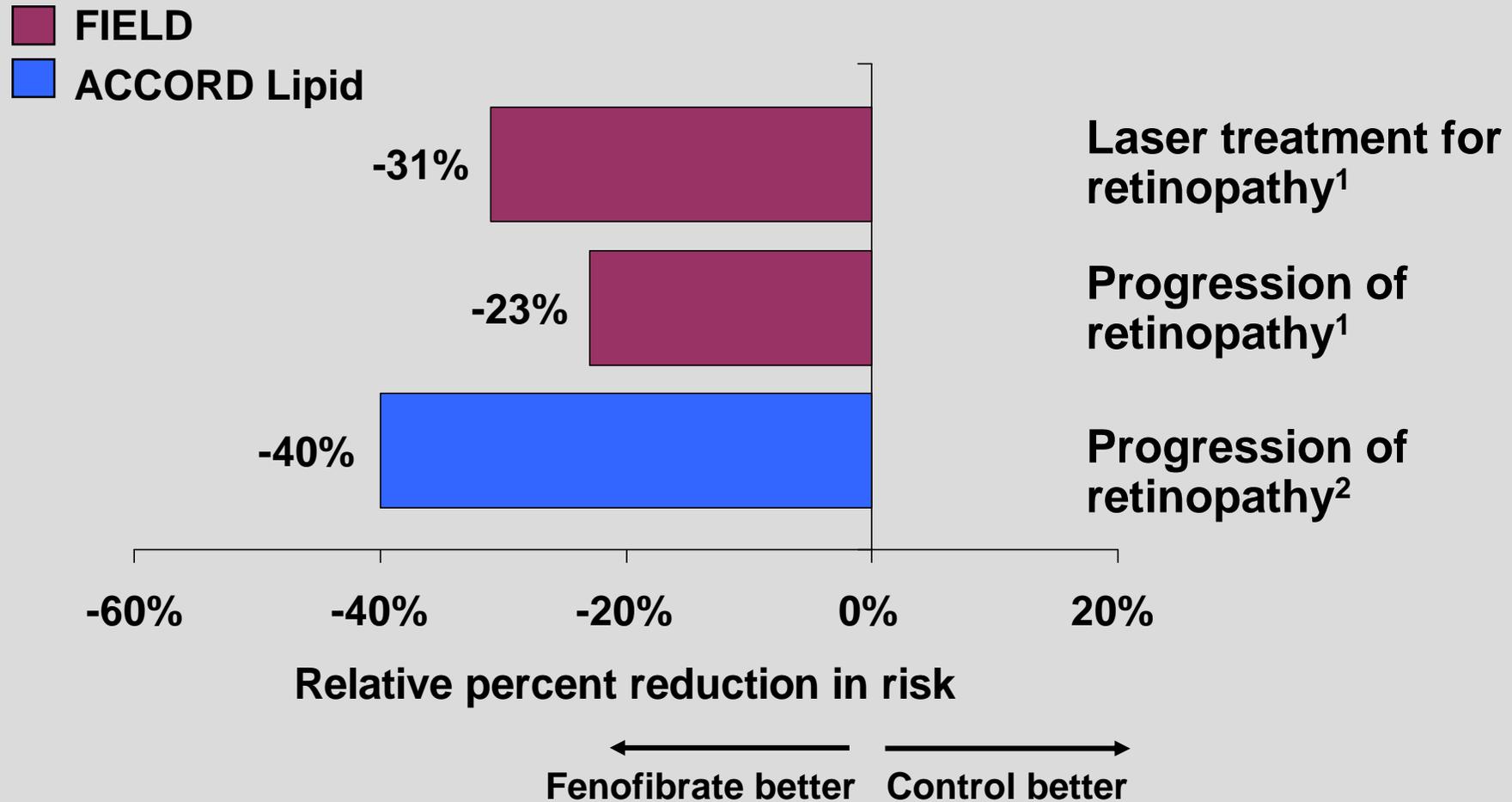
ACCORD Lipid Results Are Predicted by Abbott Meta-analysis



Published Fibrate Meta-analysis Demonstrates Significant Reduction in CV Events

- ◆ Evaluated 18 fibrate trials including over 45,000 patients (including FIELD and ACCORD Lipid)
 - 10% risk reduction in major CVD events ($p = 0.048$)
 - 13% reduction for coronary events ($p < 0.0001$)
- ◆ Larger effect noted in trials with higher baseline TG levels and greater absolute TG reductions
- ◆ No significant increase in risk of serious drug-related AEs
- ◆ Increase in creatinine observed in fibrate-treated patients
- ◆ Fibrate therapy reduced risk of progression of albuminuria

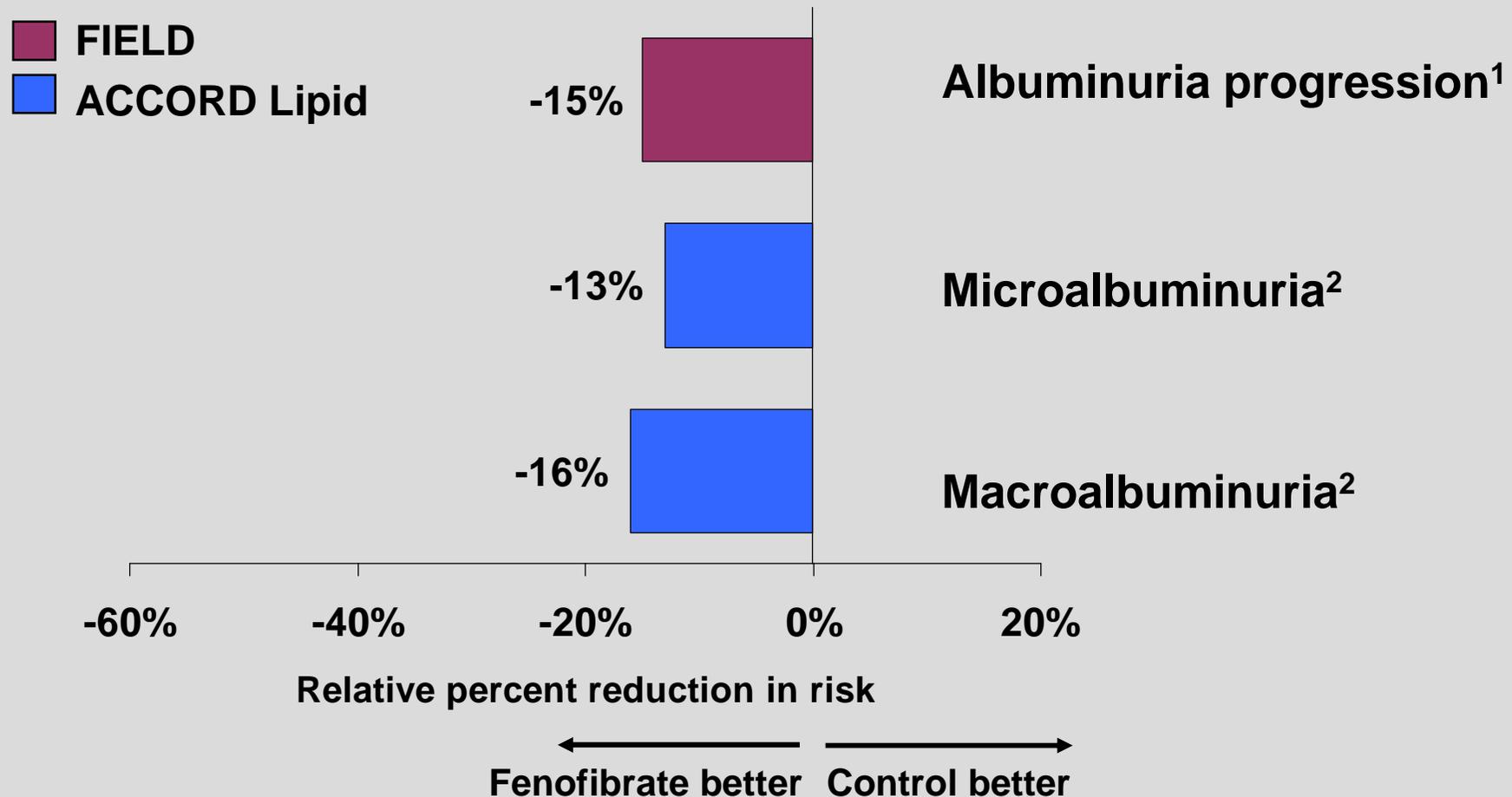
Microvascular Benefits of Fenofibrate - Retinopathy



1 *Lancet*. 2007;370:1687-1697.

2 *N Engl J Med*.2010;363:233-244.

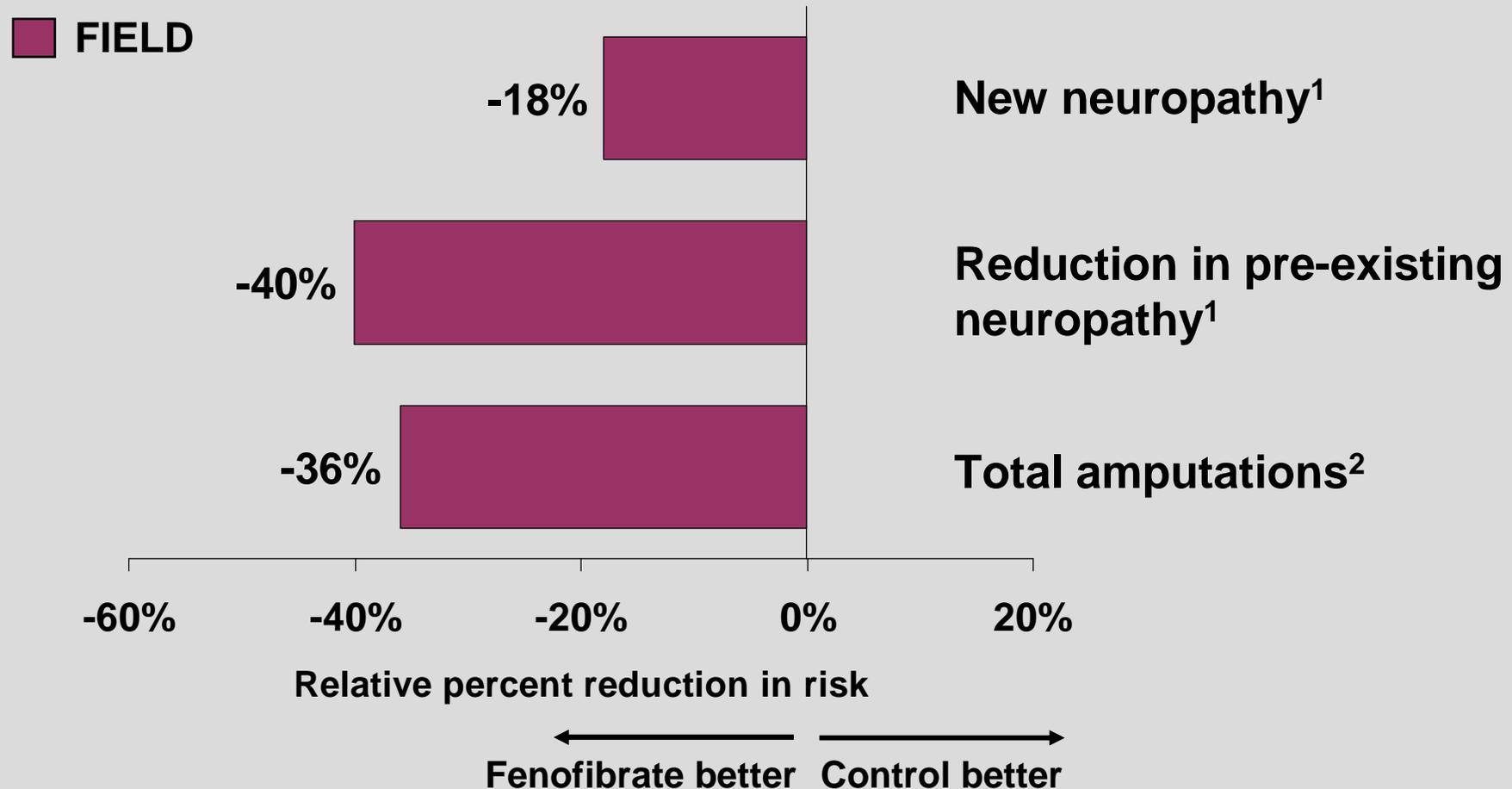
Microvascular Benefits of Fenofibrate - Renal



1. *Lancet*. 2005;366:1849-1861.

2. *N Engl J Med*. 2010;363:233-244.

Additional Microvascular Benefits of Fenofibrate



1. [EAS abstract MS546]. *Atherosclerosis*. 2010;2:109-222.

2. *Lancet*. 2009;373:1780-1788.

Fenofibrate/Fenofibric Acid Safety

Safety of Fenofibrate/Fenofibric Acid - Outline

- ◆ **Current Utilization**
- ◆ **Rhabdomyolysis**
- ◆ **Other Safety Events**

Current Utilization of Coadministration Therapy

Overview of GE Database

- ◆ **Patient-level clinical data from Centricity Physician Office[®] Electronic Medical Records (EMR) July 1, 2000 - October 31, 2010**
 - **30,000 EMR systems in 49 states**
 - **2.3 million patients with dyslipidemia**
 - **Data elements include vital signs, laboratory data, observations, complaints, medication data, and demographics**

Lipid Values of Statin-treated Patients Who Were Prescribed Fenofibrate/Fenofibric Acid

Group	N	Median (mean) TG, mg/dL	Median (mean) HDL-C, mg/dL	Proportion with TG \geq 200 and/or HDL-C $<$ 40 mg/dL
Overall	13,401	303 (370)	38 (39)	89%
Men	7,411	312 (387)	35 (36)	92%
Women	5,990	293 (349)	42 (43)	85%

Source: GE Centricity EMR

Summary of Safety Data for Rhabdomyolysis

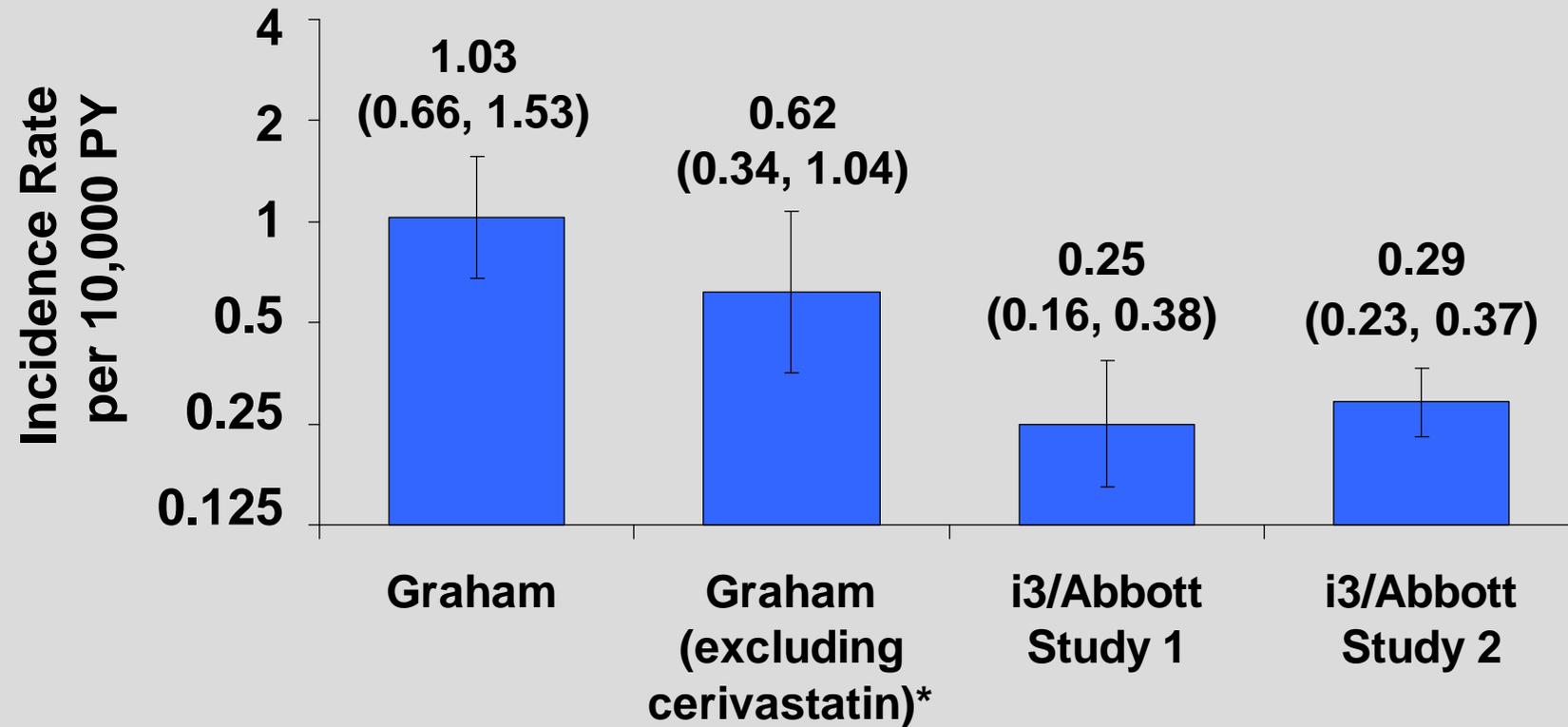
Observational Studies of Hospitalized Rhabdomyolysis

	Graham	i3/Abbott Study 1	i3/Abbott Study 2
Source population	HMO (1998 - 2001)	HMO (2004 - 2007)	HMO (1998 - 2008)
Study completed	2004	2009	2010
Rhabdomyolysis events	24 cases (10 cerivastatin)	22 cases (no cerivastatin)	70 cases (no cerivastatin)
Patients, N	252,460	584,784	1,116,805
PTY (avg duration of follow-up)	232,940 (~0.9 yr)	885,580 (~1.5 yr)	2,389,466 (~2.1 yr)

JAMA. 2004;292:2585-2590.

Am J Cardiol. 2010;106:1594-1601.

Hospitalized Rhabdomyolysis with Lipid-modifying Therapy Is Rare



*Abbott analysis.

JAMA. 2004;292:2585-2590.

Am J Cardiol. 2010;106:1594-1601.

Relative Risk of Hospitalized Rhabdomyolysis for Statin-Fenofibrate Coadministration vs Statin Monotherapy

Source of data	Unadjusted analysis	Adjusted analysis	
	Relative risk (95% CI)	Relative risk (95% CI)	NNH
i3/Abbott Study 1	4.55 (1.51, 13.71)	3.75 (1.23, 11.4)	11,019
i3/Abbott Study 2	5.03 (2.20, 11.51)	3.26 (1.21, 8.8)	17,987

Rhabdomyolysis Summary

- ◆ Rhabdomyolysis during fenofibrate therapy is rare
- ◆ In ACCORD Lipid, no increase in the rate of muscle events in the coadministration group
- ◆ i3/Abbott Study 2 of hospitalized rhabdomyolysis is largest conducted
 - Increase in risk of rhabdomyolysis with coadministration therapy
 - Number needed to harm (NNH): 11,000 - 18,000
- ◆ Available safety data are consistent with the Warnings and Precautions section of the US prescribing information

Other Safety Events of Interest - Renal, Pancreatitis, and Hepatic Events

Renal Events

◆ ACCORD Lipid

- Serum creatinine increases in the coadministration group were reversible
- ESRD and hemodialysis for coadministration group (N = 75) and simvastatin monotherapy group (N = 77)

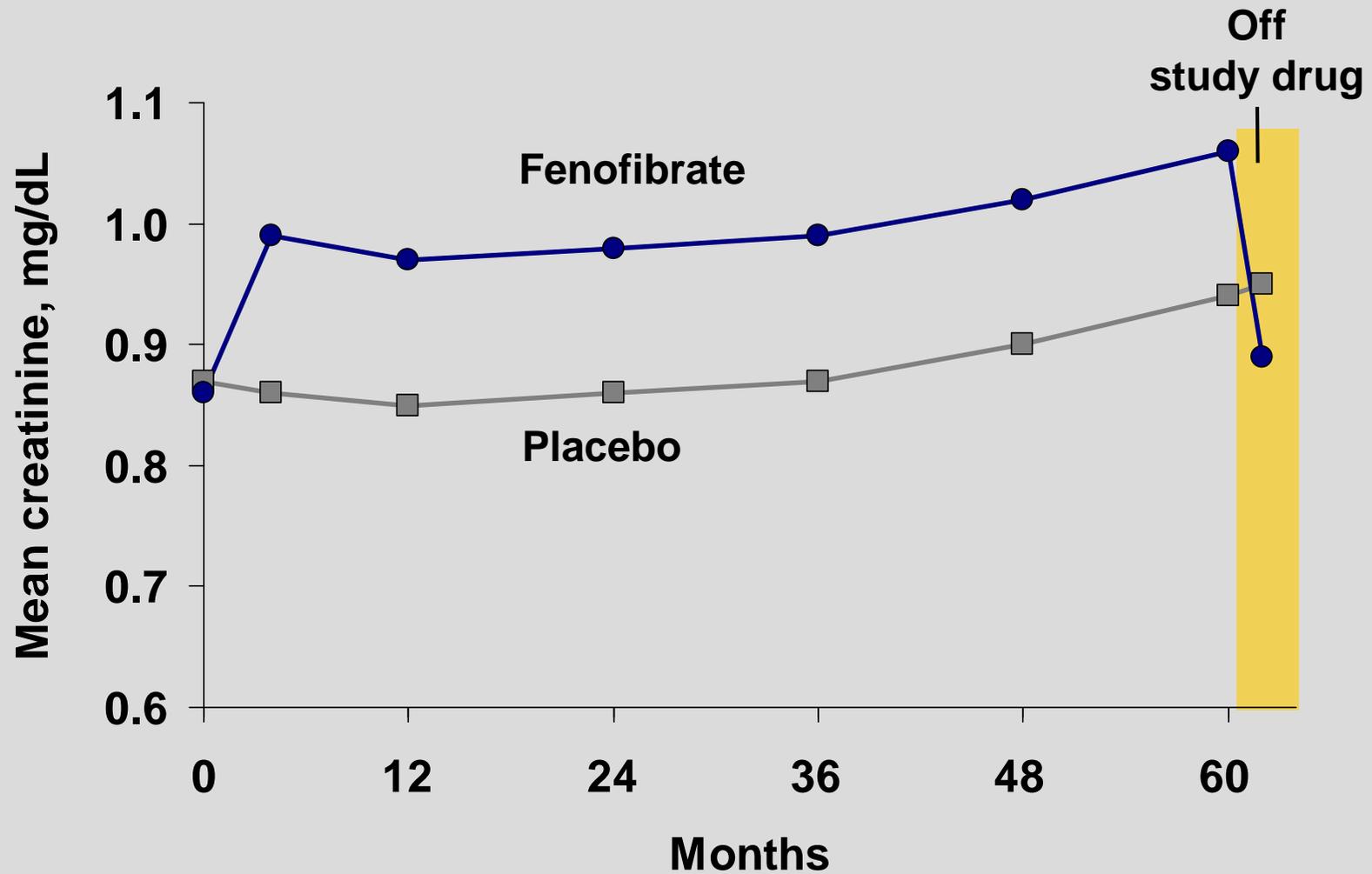
◆ FIELD Study

- Serum creatinine increases in the fenofibrate group reversible
- Renal disease needing dialysis for fenofibrate group (N = 16) and placebo group (N = 21)

◆ i3/Abbott Study 1

- Renal impairment: 1.5-fold increase consistent with previously described transient reversible increases in creatinine

FIELD Renal Substudy



Adapted from Diabetologia. 2011;54(2):280-290.

Pancreatitis

◆ ACCORD Lipid

- 5 (0.2%) serious reports in the coadministration group and 4 (0.1%) serious reports in the simvastatin monotherapy group

◆ FIELD Study

- 40 (0.8%) reports in the fenofibrate group and 23 (0.5%) reports in the placebo group

◆ i3/Abbott Study 1

- Monotherapy: incidence rate ratio ~2.7 with reference to statin monotherapy
- Coadministration therapy: No incremental risk for pancreatitis beyond fenofibrate monotherapy

Hepatic Events

◆ ACCORD Lipid

- ALT > 3× ULN 1.9% for coadministration therapy and 1.5% for simvastatin monotherapy
- Reported event of hepatitis 3 (0.1%) for coadministration therapy and 0 (0%) for simvastatin monotherapy

◆ FIELD Study

- ALT 3× ULN 0.5% for fenofibrate monotherapy and 0.8% for placebo

◆ i3/Abbott Study 1

- No evidence for any difference in risk demonstrated between exposure groups

Summary of Fenofibrate/Fenofibric Acid Safety

- ◆ **Extensive safety experience**
- ◆ **Renal, pancreatic, and hepatic events are well defined and appropriately labeled**
- ◆ **Observational studies of hospitalized rhabdomyolysis confirm incidence is rare with fenofibrate therapy**
 - **Trilipix prescribing information and Medication Guide appropriately describe muscle-related events**

Clinical Presentation Conclusions

Conclusion of Clinical Presentation

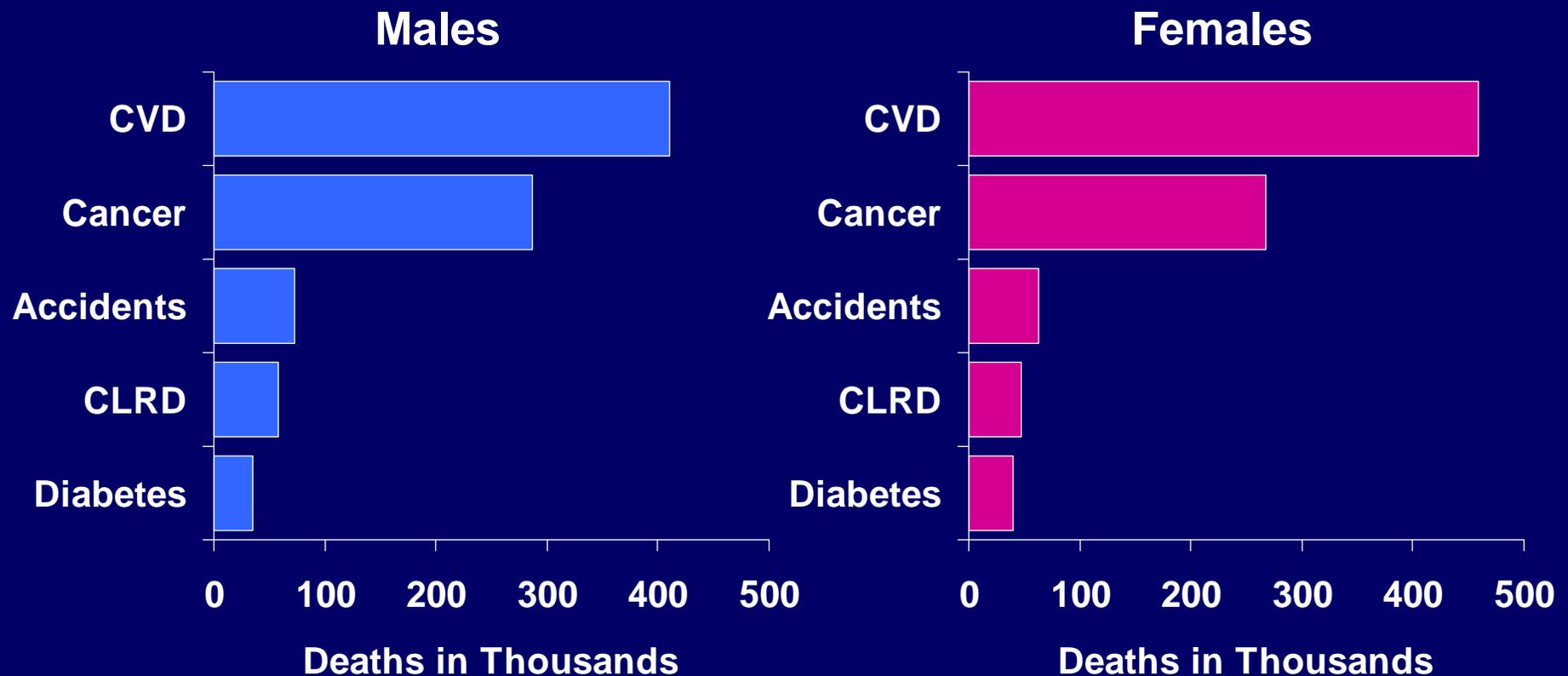
- ◆ ACCORD Lipid demonstrates that coadministration therapy reduces CV risk in patients with elevated TG and/or low HDL-C
 - No treatment-by-gender interaction in prespecified subgroup with dyslipidemia
- ◆ Usage data demonstrate that patients who add fenofibrate/fenofibric acid to existing statin therapy have elevated TG and/or low HDL-C
- ◆ Fenofibrate confers microvascular benefits
- ◆ Safety profile of fenofibrate/fenofibric acid is well characterized and risks are appropriately described in prescribing information

Clinician Perspective

Peter Jones, M.D.
Baylor College of Medicine

Cardiovascular Disease is the Leading Cause of Death in the US

- CVD accounts for ~36% of all deaths in the US



CLRD = chronic lower respiratory disease.

Adapted from *Circulation*. 2008;117:e25-e146.

Dyslipidemia Prevalence in US

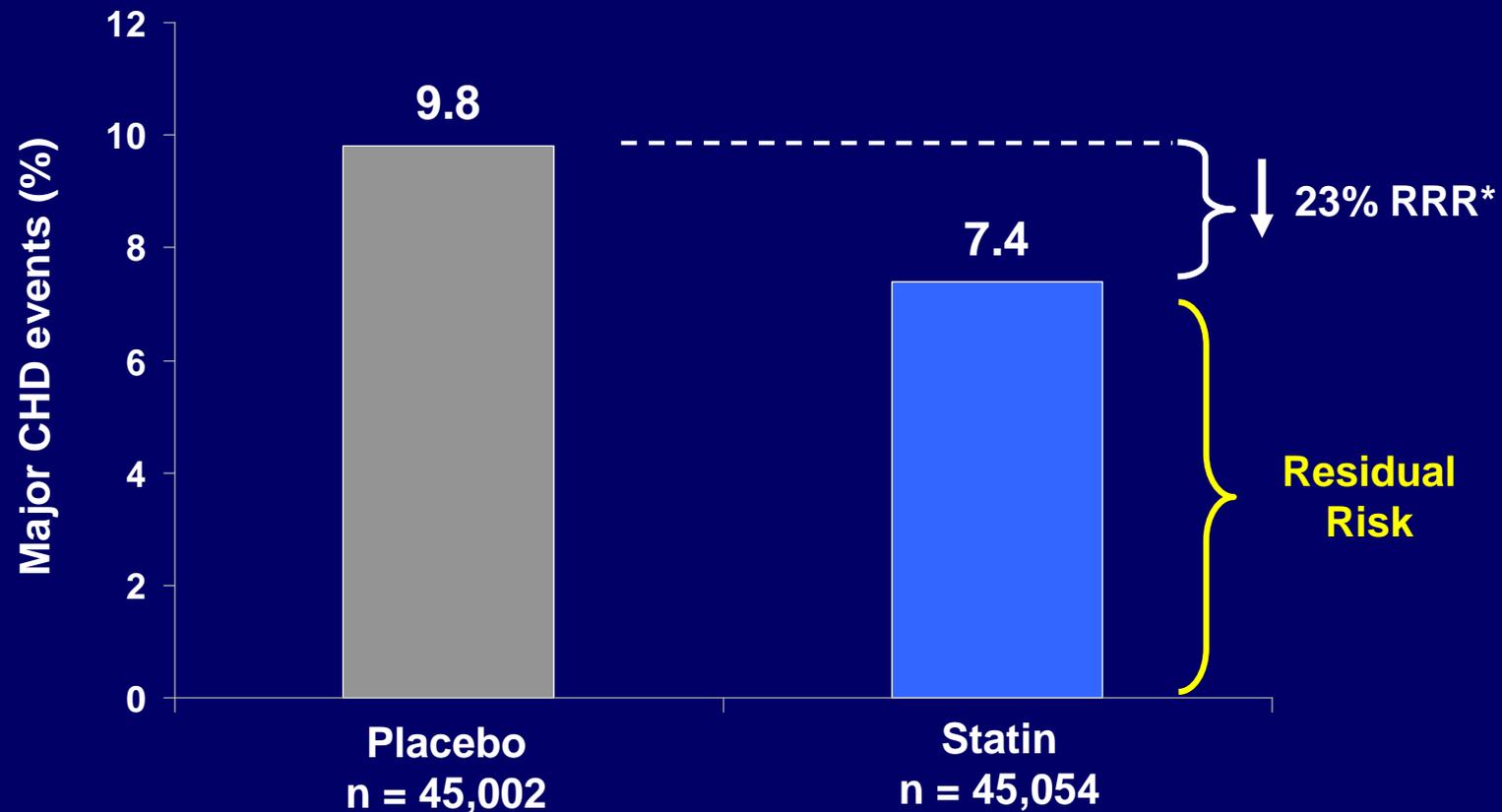
- **NHANES data estimate 100 million people with dyslipidemia**
 - **60 million with high LDL-C**
 - **55 million with low HDL-C**
 - **28 million with high TG**

Lipid disorder definitions: LDL-C \geq 100 for high risk, LDL-C \geq 130 for moderately high risk, LDL-C \geq 130 for moderate risk, LDL-C \geq 160 for low risk; TG \geq 200; Males: HDL-C $<$ 40; Females: HDL-C $<$ 50.

Am Heart J. 2008;156:112-119.

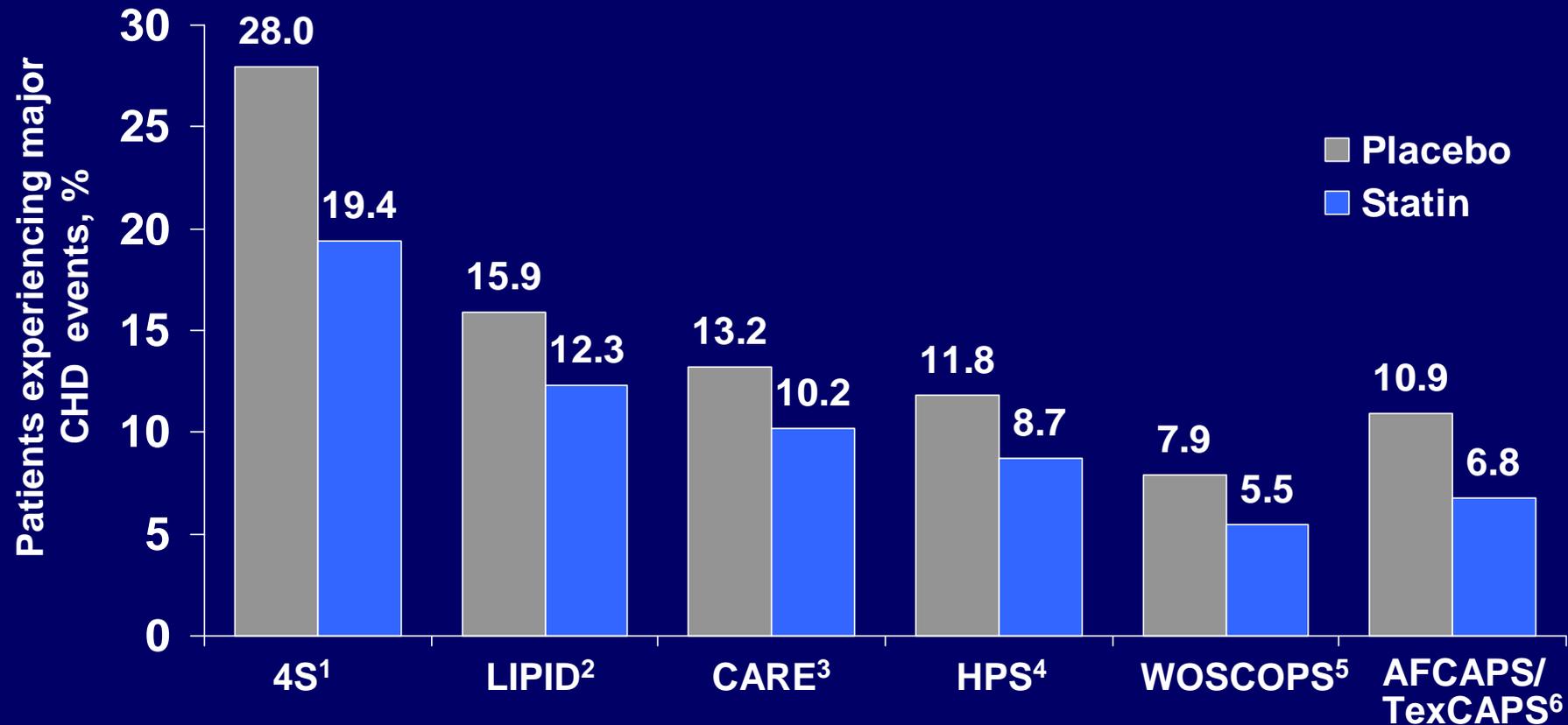
Residual CV Risk After Statin Use

CV Risk Reduction With Statins: Meta-analysis of 14 Statin Primary and Secondary Prevention Trials



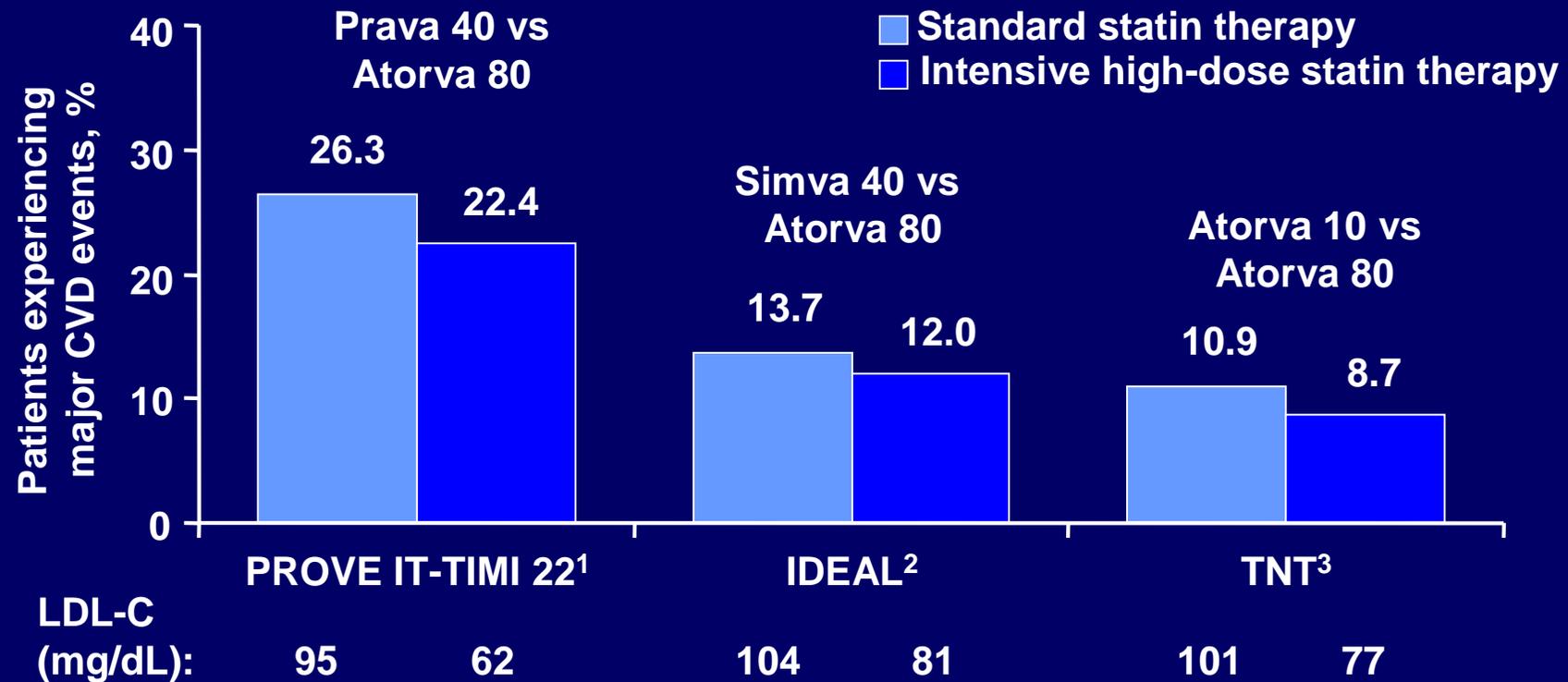
* In the incidence of major CHD events per 1 mmol/L LDL-C reduction.

Residual CV Risk in Major Statin Trials



1 *Lancet*. 1994;344:1383-1389. 2 *N Engl J Med*. 1998;339:1349-1357. 3 *N Engl J Med*. 1996;335:1001-1009.
4 *Lancet*. 2002;360:7-22. 5 *N Engl J Med*. 1995;333:1301-1307. 6 *JAMA*. 1998;279:1615-1622.

Residual CV Risk in Patients Treated With Intensive Statin Therapy

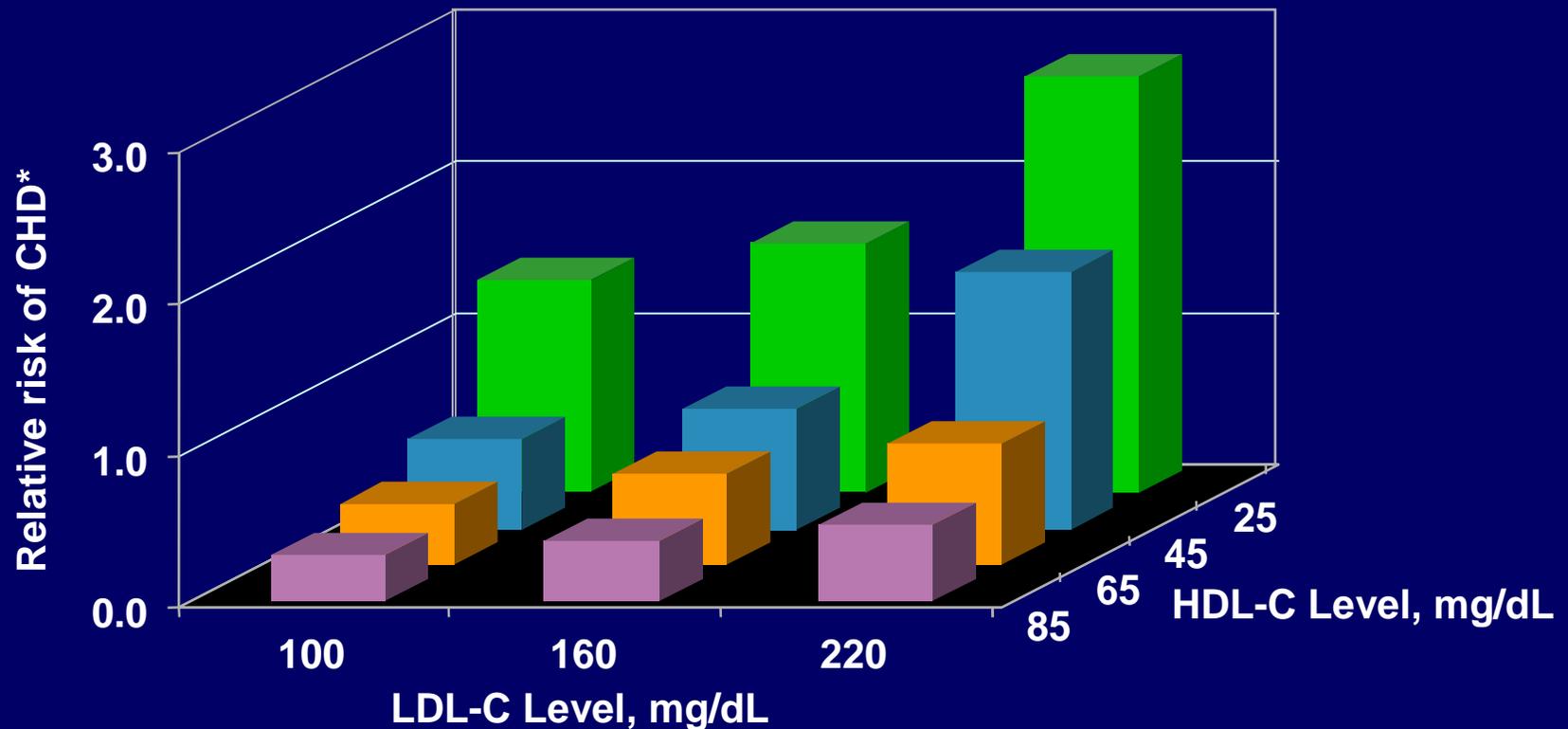


1 *N Engl J Med.* 2004;350:1495-1504. 2 *JAMA.* 2005;294:2437-2445.

3 *N Engl J Med.* 2005;352:1425-1435.

Relationship Between HDL-C and CV Risk

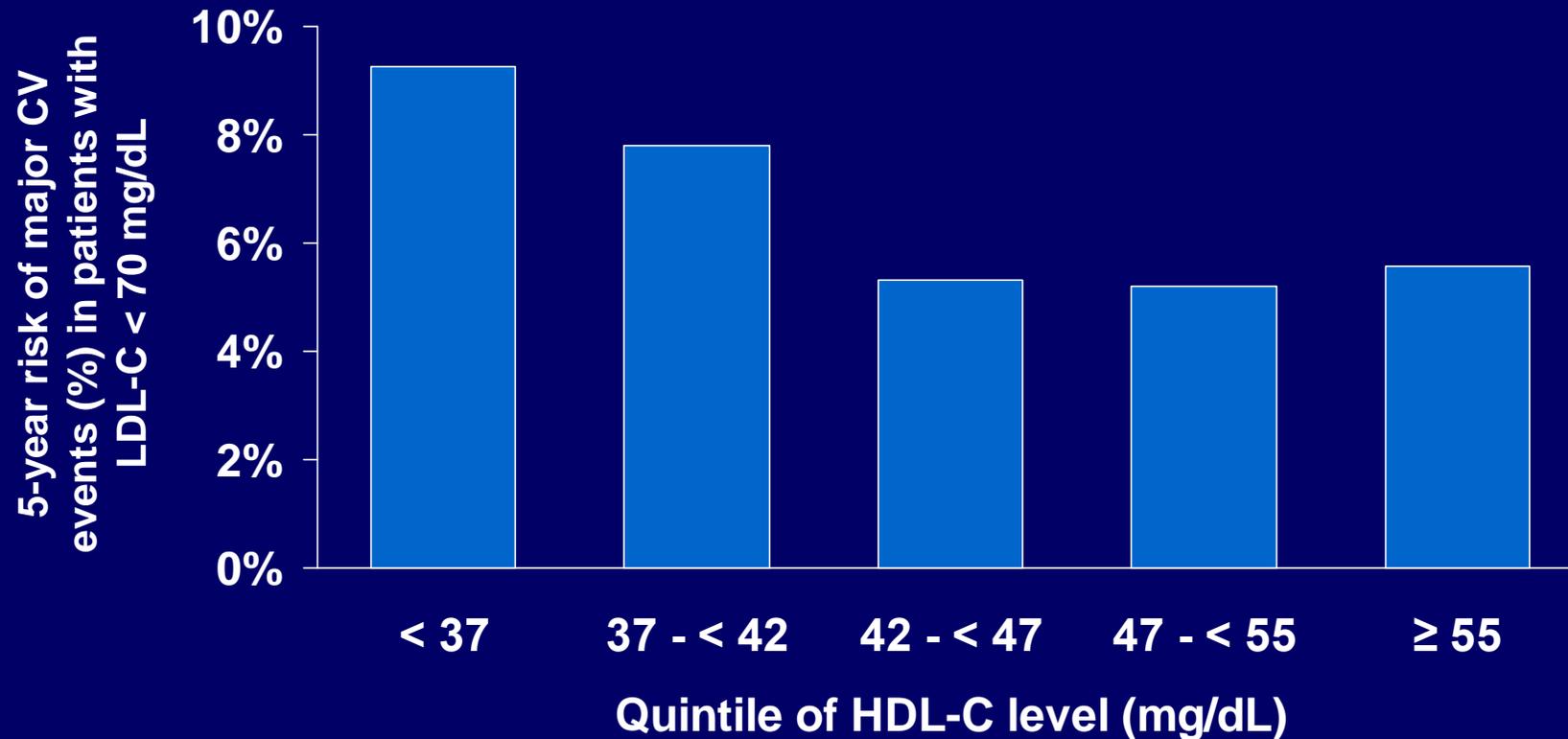
Relative Risk of CAD Related to HDL-C and LDL-C from The Framingham Heart Study



* Risk of coronary artery disease in men aged 50 to 70 years according to HDL-C and LDL-C levels over 4 years of follow-up in the Framingham Heart Study

Can J Cardiol. 1988;4:5A-10A.

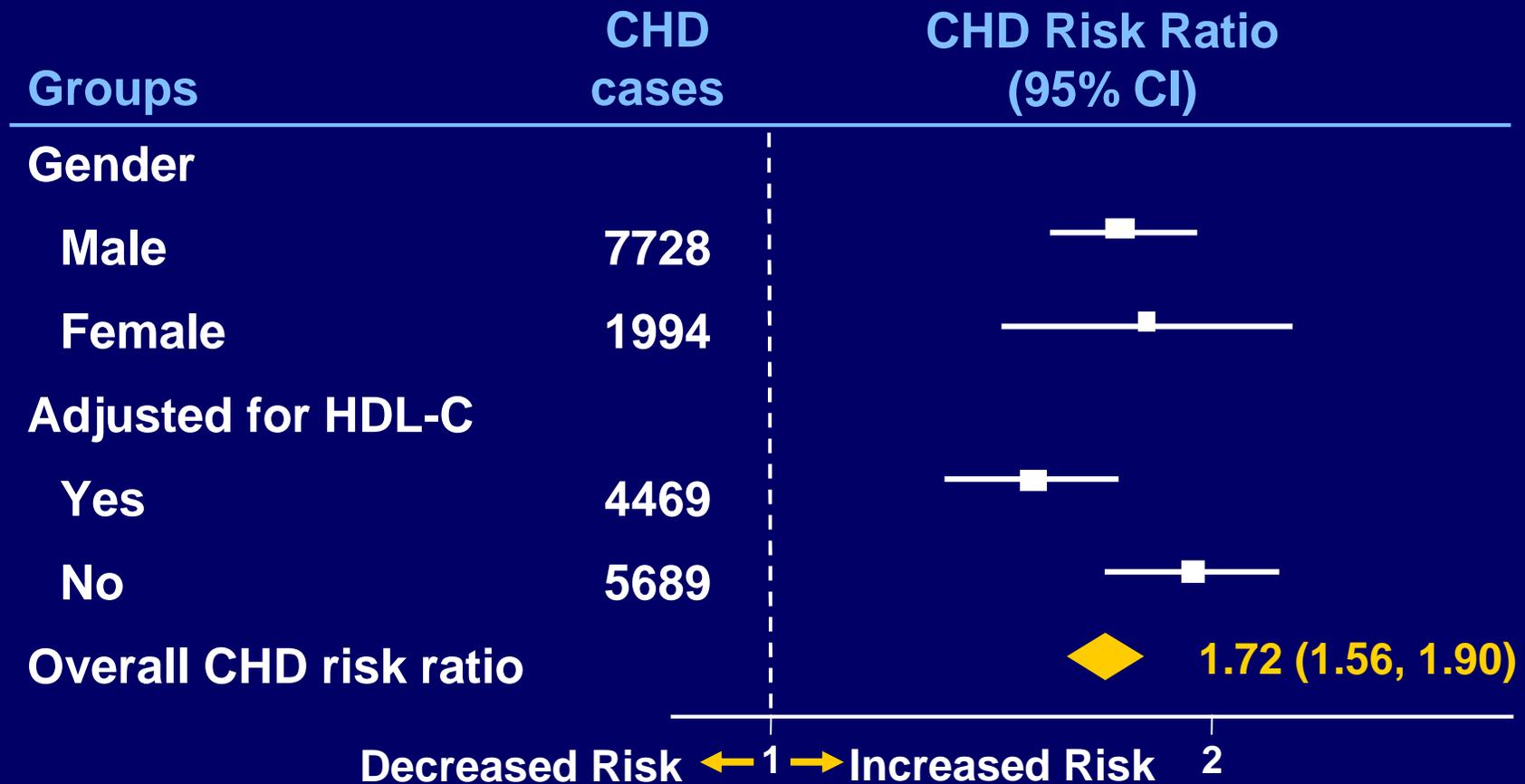
Relationship Between HDL-C and Risk of CV Events for Patients with LDL-C <70 mg/dL in TNT Study



	Q1	Q2	Q3	Q4	Q5
No. of events	57	50	34	34	35
No. of patients	473	525	550	569	544

Relationship Between TG and CV Risk

Higher TG Is Associated with CVD Risk - Meta-analysis of 29 Studies

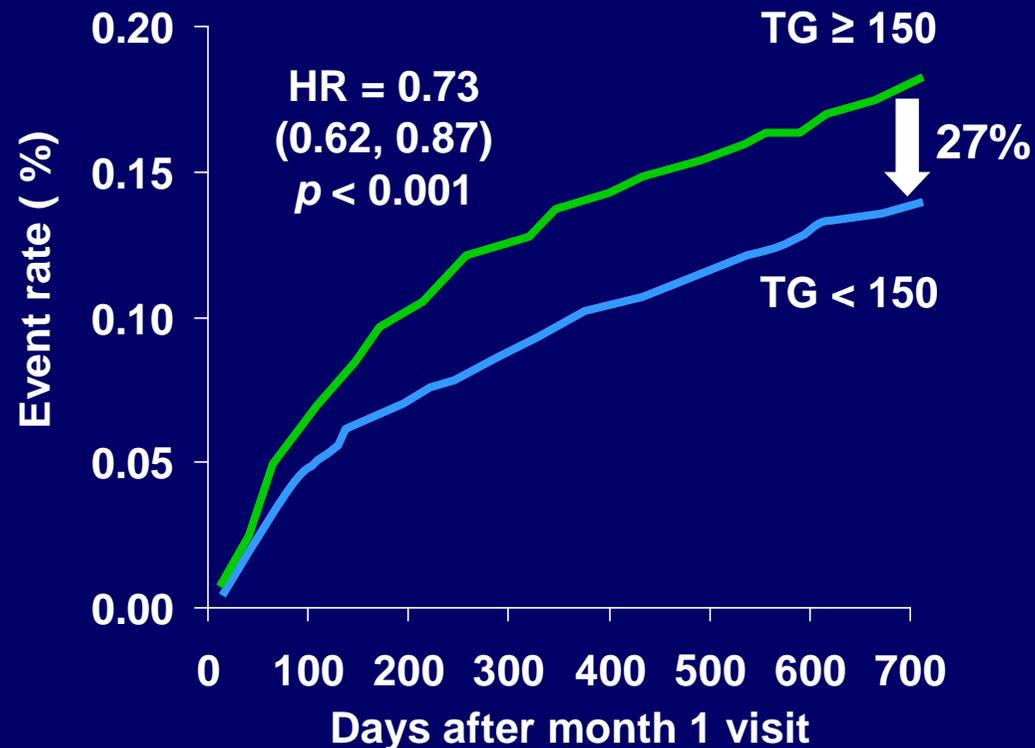


† Individuals in top vs bottom third of usual log-triglyceride values, adjusted for at least age, sex, smoking status, lipid concentrations, and blood pressure (most).

Adapted from Sarwar N, et al. *Circulation*. 2007;115(4):450-458.

Higher On-treatment TG Correlates with Greater CV Risk in PROVE IT-TIMI 22 Trial

Estimates of death, MI, and recurrent ACS
Between 30 days and 2 years of follow-up
According to achieved TG < 150 mg/dL



Guideline Recommendations for the Treatment of Dyslipidemia

National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III

Goals	For patients with CHD or CHD risk equivalents	For patients with 2+ risk factors	For patients with 0 - 1 risk factors
LDL-C	< 100 mg/dL	< 130 mg/dL	< 160 mg/dL
Non-HDL-C*	< 130 mg/dL	< 160 mg/dL	< 190 mg/dL
HDL-C	Low†	High	
	< 40 mg/dL	> 60 mg/dL	
TG	< 150 mg/dL defined as normal		

CHD risk equivalents: Diabetes, peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid artery disease and multiple risk factors that confer a 10-year risk for CHD > 20%

* Non-HDL-C goal is 30 points higher than the LDL-C goal.

† According to the AHA, < 40 mg/dL is low for men; < 50 mg/dL is low for women

JAMA. 2001;285:2486-2497.

Circulation. 2002;106:388-391.

NCEP ATP III: Triglyceride and HDL-C Treatment Recommendations

Lipid parameter (mg/dL)	Therapy
TG \geq 500 (TG primary goal)	Fibrates or nicotinic acid
TG 200-499 (non-HDL-C secondary target of therapy)	Intensify therapy with an LDL-C-lowering drug; second, consider adding a fibrate or nicotinic acid
HDL-C $<$ 40 or TG 150-199 (baseline LDL-C 100-129 in high-risk patients)	Intensify LDL-C-lowering drug, add fibrates or nicotinic acid, or intensify control of other risk factors

2004 update: For high risk patients who have elevated TG or low HDL-C levels, addition of a fibrate or niacin to LDL-C-lowering therapy can be considered

Treatments Targeting TG and HDL-C

- **Fish Oil (polyunsaturated omega-3 fatty acids)**
- **Niacin**
- **Fibrates**

Fish Oil and Niacin

- **Fish Oil**
 - FDA approved indication for severe hypertriglyceridemia (≥ 500 mg/dL)
 - Clinical outcomes data are limited (JELIS Study)
- **Niacin**
 - Clinical outcomes data are limited (Coronary Drug Project)
 - Tolerance/compliance is an issue
 - Adverse effects on glucose and uric acid a consideration

Fibrates

- **CV outcomes benefit demonstrated with gemfibrozil monotherapy (HHS, VA-HIT)**
- **CV outcomes benefit demonstrated in patients with elevated TG and low HDL-C with fenofibrate (FIELD and ACCORD Lipid)**
- **Fibrates considered preferable in patients with glucose management issues or elevated uric acid**

ACCORD Lipid

- **Baseline lipid parameters for overall population:**
 - Mean LDL-C 101 mg/dL
 - Mean HDL-C 38 mg/dL
 - Median TG 162 mg/dL

The ACCORD Lipid population overall would not be considered appropriate for the addition of fibrate or niacin to statin therapy by NCEP ATP III Guidelines

CV Risk in Women with Diabetes

- **CV risk for women with mixed dyslipidemia (especially those with diabetes) is substantial**
- **Benefit of combination therapy with fenofibrate and simvastatin seen in women with elevated TG and low HDL-C in ACCORD Lipid**
- **Lack of similar data for other available therapies (niacin and fish oil)**

Additional Benefits of Fenofibrate Therapy - Renal

- **Proteinuria is a marker of CV risk as well as renal impairment**
- **Reduction in proteinuria seen in patients treated with fenofibrate in ACCORD Lipid was in addition to ACE inhibitor therapy and good glycemic control**
- **Reduction in proteinuria with fenofibrate also demonstrated in FIELD**

Additional Benefits of Fenofibrate Therapy - Eye

- **Diabetic retinopathy is a leading cause of blindness in US adults**
- **Fenofibrate has been shown to slow progression of retinopathy and reduce need for laser therapy in patients with diabetes**
- **Fenofibrate is the only treatment demonstrated to have this effect**
- **Effect consistent in both FIELD and ACCORD Lipid**

Mixed Dyslipidemia in Clinical Practice

- **Clinicians in lipid clinics treat high risk patients with persistent mixed dyslipidemia after statin monotherapy**
- **Many patients are overweight/obese with insulin resistance (prediabetes or diabetes)**

Clinical Scenario (1)

- **Patient Description: 55 yr-old woman with type 2 diabetes mellitus and hypertension**
- **Pertinent Vital Signs: 5 feet, 150 lb, BP 122/82 mmHg**
- **Current Medications: metformin, lisinopril and atorvastatin**
- **Pertinent Laboratory Values:**
 - HbA_{1c} 6.8%
 - eGFR within normal range, elevated microalbumin
 - Lipid Profile: Total-C 180 mg/dL, TG 250 mg/dL, HDL-C 40 mg/dL, LDL-C 90 mg/dL [Calculated non-HDL-C = 140 mg/dL]

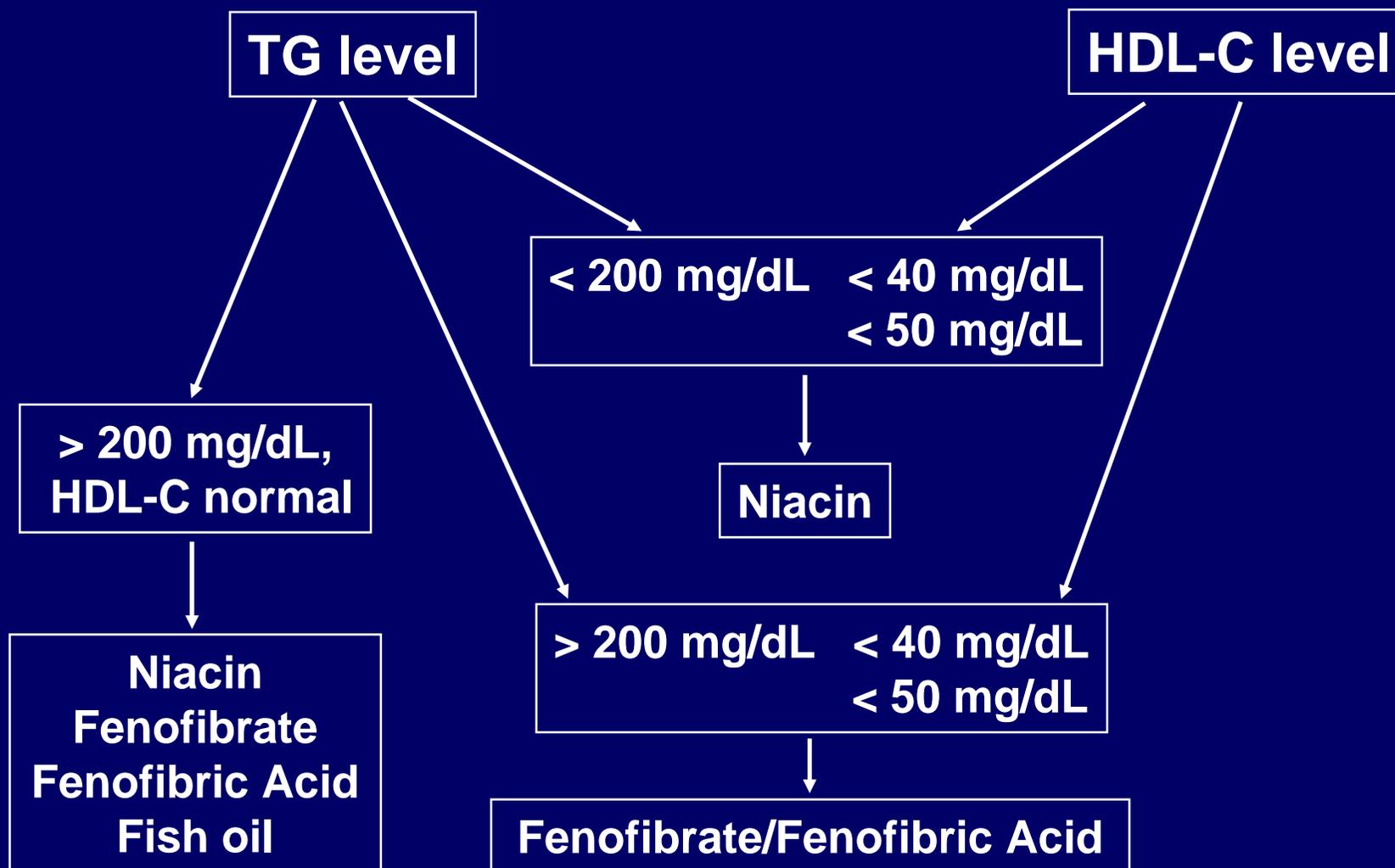
Clinical Scenario (2)

- Patient at BP, HbA_{1c} and LDL-C goals
- Non-HDL-C not at goal (< 130 mg/dL)
- Treatment options to achieve non-HDL-C goal
 - Fish oil
 - Niacin
 - Fibrate (fenofibrate/fenofibric acid)

Clinical Scenario (3)

- **Given the following considerations**
 - **TG and HDL-C are persistently abnormal**
 - **Ongoing statin therapy**
 - **Presence of diabetes (with evidence of microvascular complications)**
- **Fenofibric acid is appropriate additional treatment**

Approach to High-risk Patients With Mixed Dyslipidemia at LDL-C Goal on Statin Therapy



What ACCORD Lipid Adds to Our Understanding

- **Confirms that fenofibrate decreases CV events in men and women with diabetes and elevated TG and low HDL-C who are receiving background statin therapy**
- **This benefit would be expected across the spectrum of insulin resistance**

Conclusions

- Overall, fenofibrate/fenofibric acid is an important therapeutic option for the practicing clinician to treat patients with persistent mixed dyslipidemia after statin therapy
- The additional microvascular benefits in patients with diabetes are an important consideration

Closing Remarks

James Stolzenbach, PhD
Dyslipidemia Divisional Vice President

Risks of Fenofibrate/Fenofibric Acid

- ◆ **Hepatic, pancreatic, and renal events have been observed and are appropriately labeled**
- ◆ **Rhabdomyolysis has been reported with fibrate monotherapy, statin monotherapy, and coadministration therapy**
 - **Increase in risk with coadministration therapy compared with statin monotherapy**
 - **NNH: 11,000 - 18,000 patients for 1 yr**
 - **Muscle-related events are appropriately described in the prescribing information and Medication Guide**

Benefits of Fenofibrate/Fenofibric Acid

- ◆ **Coadministration therapy significantly reduced CV risk in patients with elevated TG and/or low HDL-C in ACCORD Lipid**
 - **Consistent with CV benefit of fibrate therapy in prior trials**
 - **NNT: 20 patients for 4.7 yrs in prespecified subgroup with dyslipidemia**
 - **No treatment-by-gender interaction in prespecified subgroup with dyslipidemia**
- ◆ **Fenofibrate also confers microvascular benefits**

Proposed Changes to Trilipix Prescribing Information

- ◆ **Clarification of coadministration indication**
- ◆ **Addition of ACCORD Lipid information**
 - **Basic study design**
 - **Primary outcome results**
 - **Results by gender**
 - **Results in the prespecified subgroup with dyslipidemia**

FDA Voting Question to the Committee

6A. Taking into account all relevant data and levels of evidence:

Should FDA require the conduct of a clinical trial designed to test the hypothesis that, in high-risk men and women at LDL-C goal on a statin with residually high TG and low HDL-C, add-on therapy with Trilipix vs placebo significantly lowers the risk for MACE?

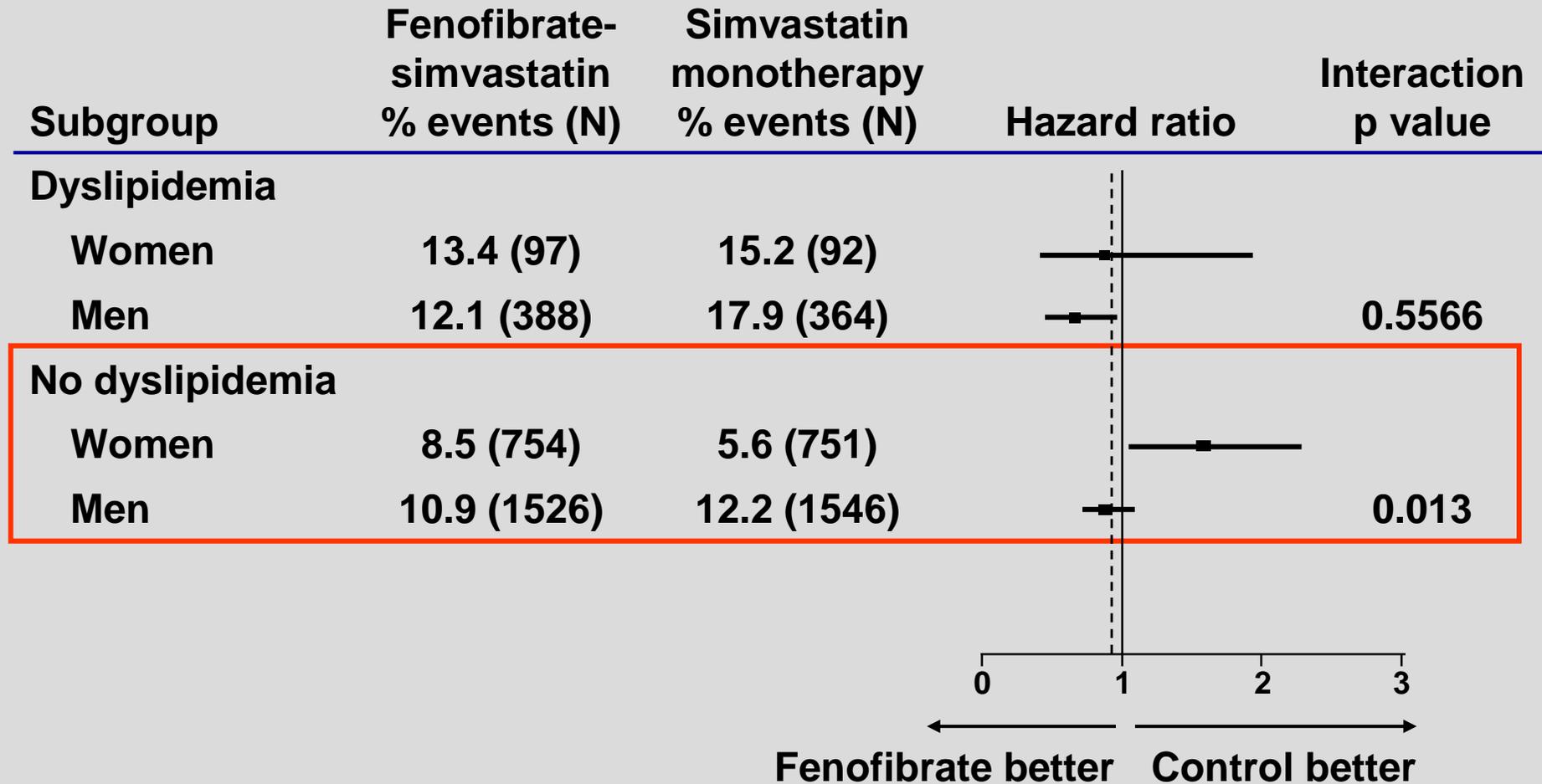
Overall Conclusions

- ◆ Overall benefit-risk profile of fenofibrate/fenofibric acid is positive in appropriate patients
- ◆ Usage data demonstrate that statin-treated patients who were prescribed fenofibrate/fenofibric acid had elevated TG and/or low HDL-C
- ◆ Trilipix prescribing information
 - Identifies the patients who derive CV benefit
 - Appropriately represents safety profile

Trilipix (ACCORD) Advisory Committee Meeting

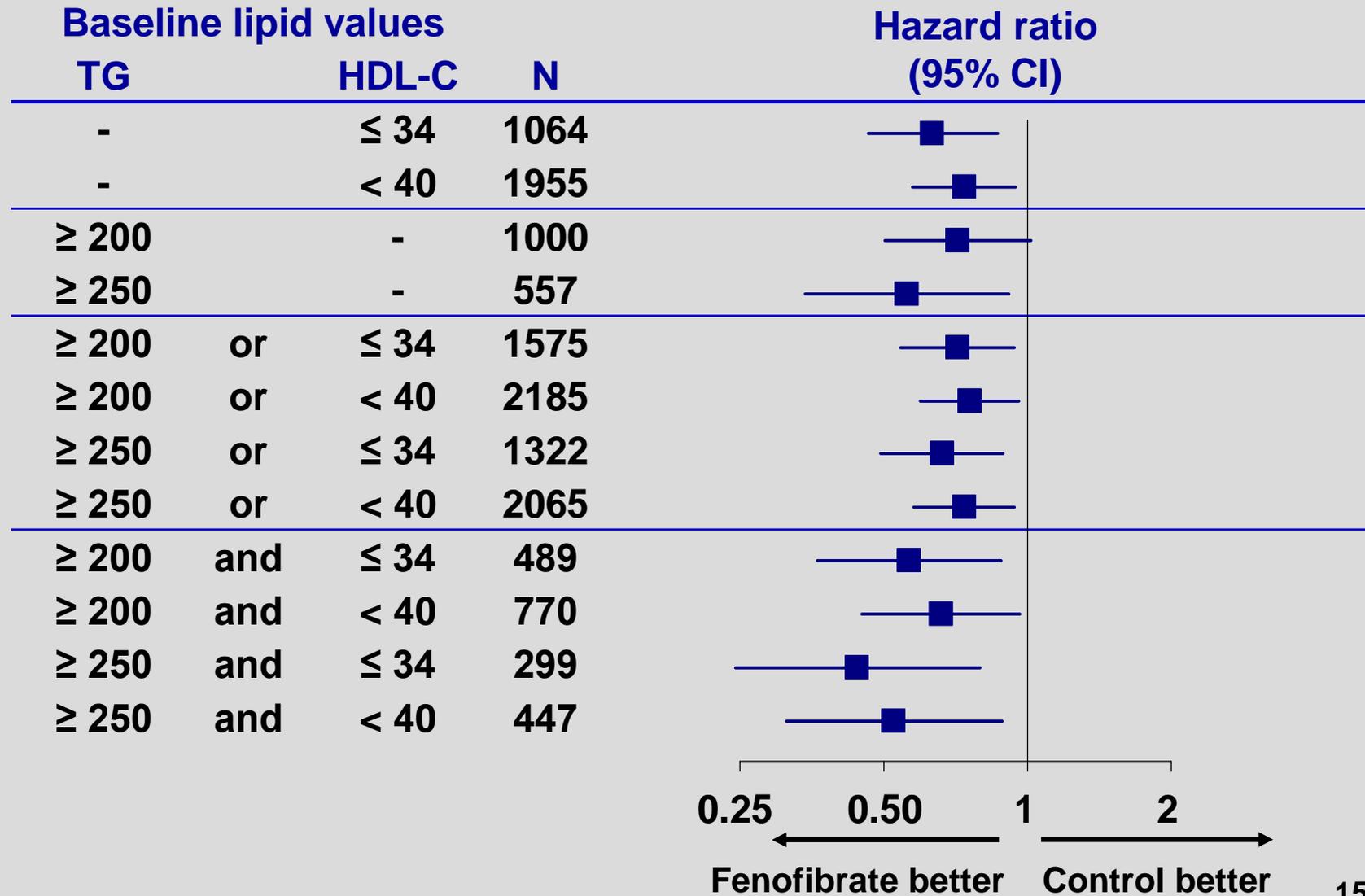
Supporting Slides

Gender Outcomes in Dyslipidemic Group and All Others



Circulation. 2010;122: A20114.

CV Risk Reduction in Patients Receiving a Statin at Baseline in ACCORD Lipid



ACCORD EYE Results

Treatment	Progression of DR (%)	Adjusted OR* (95% CI)	p value	Moderate vision loss	Adjusted HR (95% CI)	p value
Fenofibrate + simvastatin	6.5	0.60 (0.42, 0.87)	0.006	16	1.04 (0.83, 1.32)	0.73
Simvastatin	10.2			15.2		

- ◆ At 4 yrs, the rates of progression of diabetic retinopathy were:
 - 6.5% with fenofibrate + simvastatin vs 10.2% with simvastatin monotherapy (adjusted OR, 0.60; $p = 0.006$)
- ◆ No significant change in moderate vision loss observed in any treatment group

The Accord study group *N Engl J Med* .2010;363.

*Odds ratio for every parameter was adjusted for the other two parameters.