

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Fibrates

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Introduction

- What is the role of fibrates in the treatment of dyslipidemia?
- What key studies have demonstrated significant clinical benefit with combination therapy (statins + fibrates)?
- What are the current AACE treatment guidelines regarding the use of fibrates for dyslipidemia management?
- What specific populations benefit from fibrate therapy?

Dyslipidemia Treatment: Pharmacologic Therapy with Fibrates

- Fibrates are recommended to treat severe hypertriglyceridemia (TG >500 mg/dL)
- Fibrates may improve ASCVD outcomes in primary and secondary prevention when TG concentrations are ≥ 200 mg/dL and HDL-C concentrations are <40 mg/dL
- Fibrates are useful in patients with severely elevated TG and increased risk of pancreatitis

ASCVD, atherosclerotic cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Jellinger P, et al. *Endocr Practice*. 2017;23(4):479-497.

Dyslipidemia Treatment: Fibrate Dosing

Agent	Usual recommended starting daily dosage	Dosage range	Method of administration
FIBRATES			
Fenofibrate	48-145 mg	48-145 mg	Oral
Gemfibrozil	1,200 mg	1,200 mg	Oral
Fenofibric acid	45-135 mg	45-135 mg	Oral

Metabolic Effects:

- Primarily ↓ TG 20%-35%, ↑ HDL-C 6%-18% by stimulating lipoprotein lipase activity
- Fenofibrate may ↓ TC and LDL-C 20%-25%
- Lower VLDL-C and LDL-C; reciprocal rise in LDL-C transforms the profile into a less atherogenic form by shifting fewer LDL particles to larger size
- Fenofibrate ↓ fibrinogen level

HDL-C, high-density lipoprotein cholesterol; LDL, low-density lipoprotein, LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; VLDL-C, very low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. 2017;23(4):479-497; Aguilar-Salinas CA, et al. *Metabolism*. 2001;50:729-733; Athyros VG, et al. *Coron Artery Dis*. 1995;6:251-256; Avellone G, et al. *Blood Coagul Fibrinolysis*. 1995;6:543-548; Bröijersen A, et al. *Arterioscler Thromb Vasc Biol*. 1996;16:511-516; Bröijersen A, et al. *Thromb Haemost*. 1996;76:171-176; Davidson MH, et al. *Am J Cardiol*. 2007;99:3C-18C; Farnier M, et al. *Eur Heart J*. 2005;26:897-905; Guyton JR, et al. *Arch Intern Med*. 2000;160:1177-1184; Hottelart C, et al. *Nephron*. 2002;92:536-541; Insua A, et al. *Endocr Pract*. 2002;8:96-101; Kockx M, et al. *Thromb Haemost*. 1997;78:1167-1172; Lopid (gemfibrozil) [PI] 2010; McKenney JM, et al. *J Am Coll Cardiol*. 2006;47:1584-1587; Syväne M, et al. *Atherosclerosis*. 2004;172:267-272; Tricor (fenofibrate) [PI]; 2010; Trilipix (fenofibric acid) [PI]; 2016; Westphal S, et al. *Lancet*. 2001; 358:39-40.

Fibrates: Metabolic Effects and Main Considerations

- Gemfibrozil may ↑LDL-C 10%-15%
- Administered twice daily, before morning and evening meals
- GI symptoms, possible cholelithiasis
- May potentiate effects of orally administered anticoagulants
- Gemfibrozil may ↑ fibrinogen level; gemfibrozil and fenofibrate can ↑ homocysteine independent of vitamin concentrations
- May exacerbate muscle disorders; myopathy/rhabdomyolysis when used with statins
- Fibrates are associated with increased serum creatinine levels, which may not reflect renal dysfunction
- Fenofibrate dose should be cut by $\frac{2}{3}$ and gemfibrozil by $\frac{1}{2}$ when eGFR is 15-60 mL/min/1.73 m²; avoid fibrates when eGFR is <15mL/min/1.73 m²
- Can improve diabetic retinopathy

eGFR, estimated glomerular filtration rate; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. 2017;23(4):479-497.



FIELD Study: Fenofibrate Intervention and Event Lowering in Diabetes

FIELD Study

- **Objective:** Patients with T2D are at increased risk of CVD, which can be amenable to fibrate therapy; the 2005 Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study assessed the effect of fenofibrate on CVD events in these patients
- **Methods:** Multinational, randomized controlled trial; 9,795 participants with T2D and not on statins, received fenofibrate or placebo for ~5 years; the primary outcome was CHD death and nonfatal MI
- **Conclusions:** Fenofibrate did not significantly reduce the risk of coronary events; it did reduce total CV events by 11%, mainly due to fewer non-fatal MIs and revascularizations. The higher rate of starting statin therapy in patients allocated to placebo might have masked a moderately larger treatment benefit

CV, cardiovascular; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes Study; MI, myocardial infarction; T2D, type-2 diabetes.

Keech A, et al. *Lancet*. 2005;366:1849-1861.

FIELD Study: CHD Event Risk

Multinational, 5-year randomized controlled trial (N=9795) of patients with T2D taking statin therapy and assigned to add-on treatment with fenofibrate or placebo

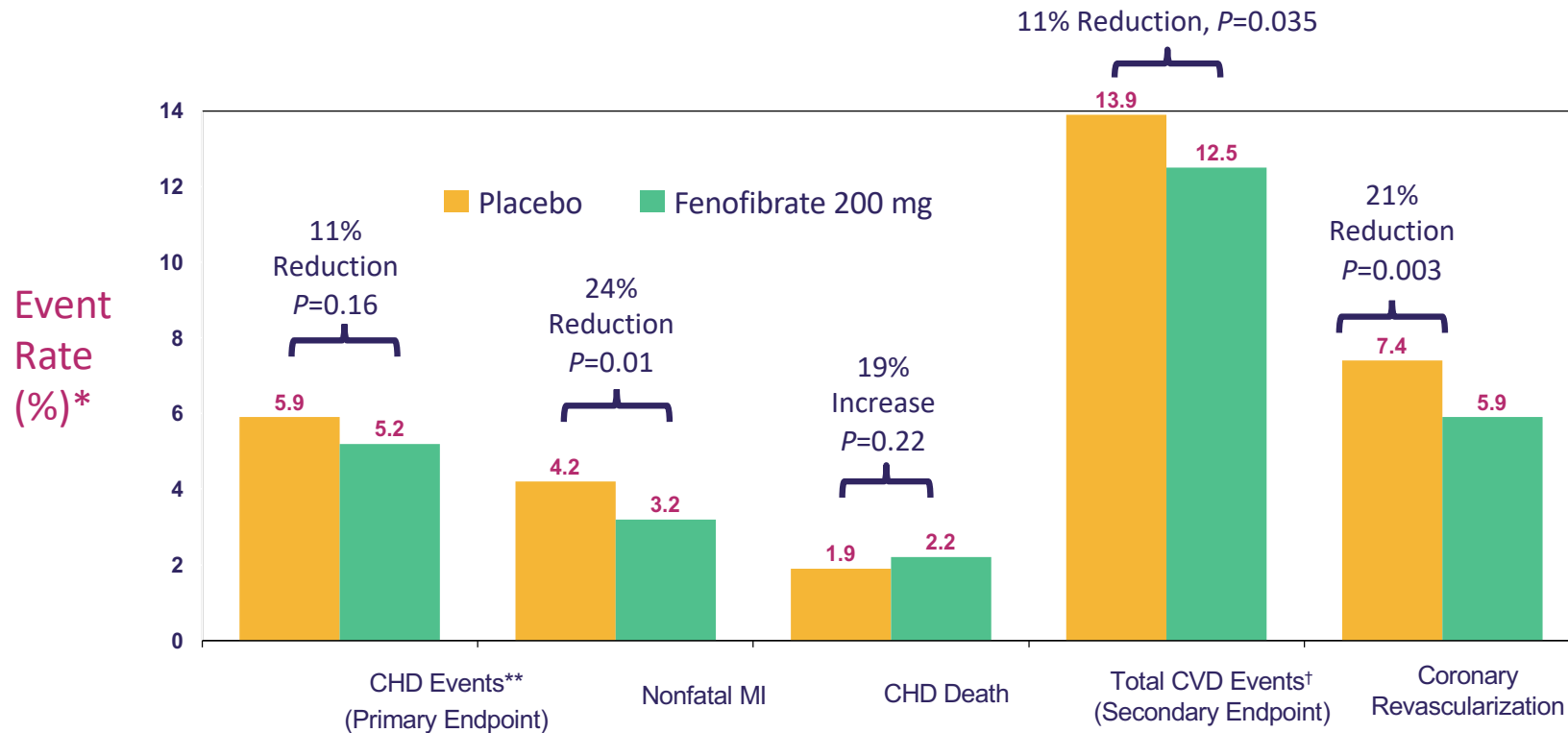
Outcome	Fenofibrate % (n)	Placebo % (n)	HR	95% CI	P-value
Coronary events	5% (256)	6% (288)	0.89	0.75-1.05	0.16
CHD mortality	2% (110)	2% (93)	1.19	0.90-1.57	0.22
Nonfatal MI	3% (158)	4% (207)	0.76	0.62-0.94	0.01

CHD, coronary heart disease; MI, myocardial infarction; T2D, type-2 diabetes.

Keech A, et al. *Lancet*. 2005;366:1849-1861.

FIELD Study: Primary and Secondary Endpoints*

9,795 Patients With T2D; Baseline cholesterol (mg/dL): TC 194; TG 154; HDL-C 42; LDL-C 119; Non-HDL 152



* Not corrected for large placebo-group statin drop-in rate.

** Nonfatal MI and CHD death

† CHD events, stroke, CVD death, revascularizations

CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; T2DM, type-2 diabetes; TC, total cholesterol; TG, triglycerides.
Keech A, et al. *Lancet*. 2005;366:1849-1861.

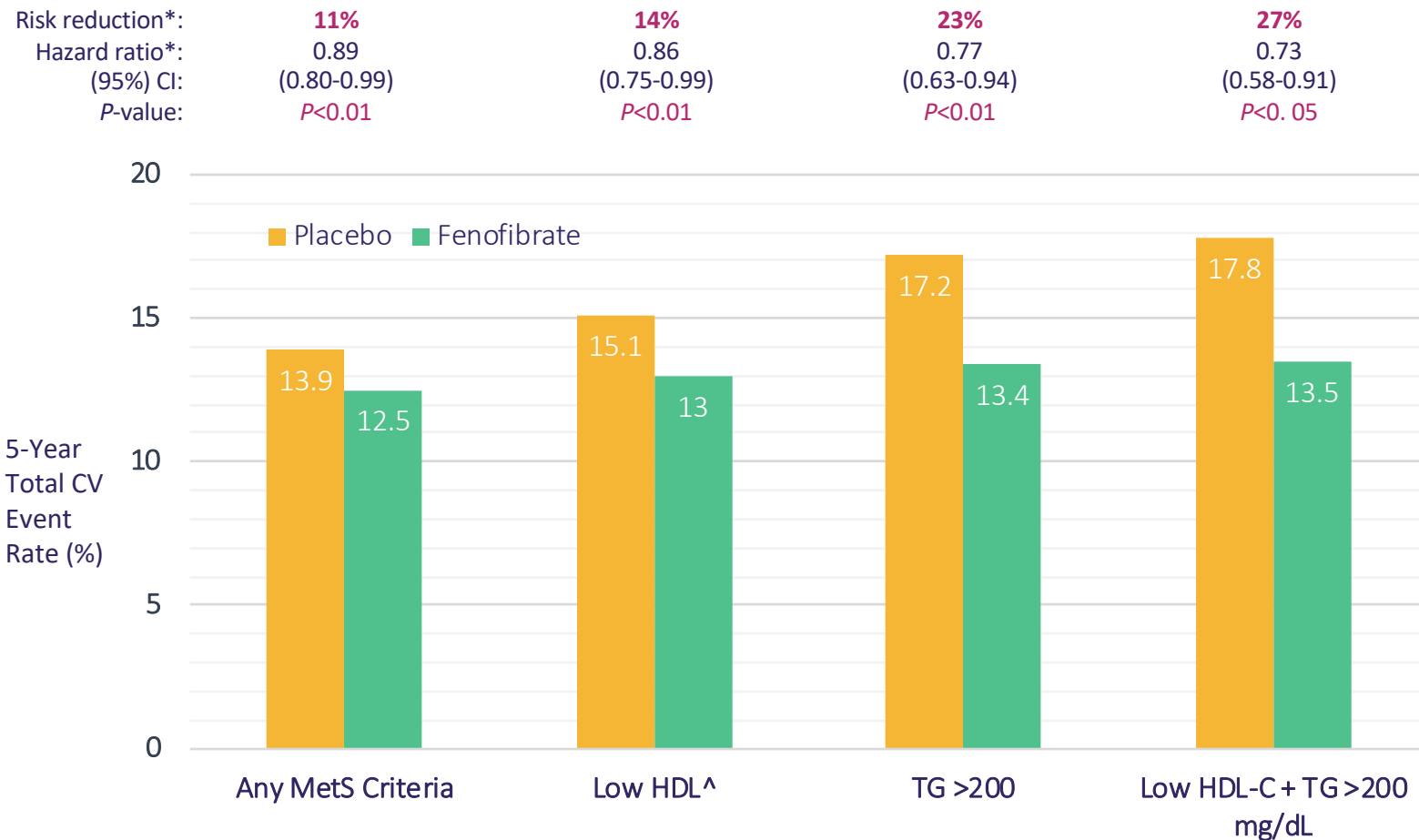
FIELD Study: Effects of Metabolic Syndrome

- **Objective:** This analysis of FIELD study data evaluated whether CVD risk and the effects of fenofibrate differed in patients with and without metabolic syndrome, and according to various metabolic syndrome features, in patients with T2D
- **Methods:** The prevalence of metabolic syndrome and its features was calculated; Cox proportional models—adjusted for age, sex, CVD status, and baseline A1C levels—were used to determine the independent contributions of metabolic syndrome features to total CVD event rates, as well as fenofibrate effects
- **Conclusions:** Metabolic syndrome components identify higher CVD risk in individuals with T2D, so the absolute benefit of fenofibrate is likely to be greater when metabolic syndrome features are present; the greatest benefits of fenofibrate are seen in patients with marked hypertriglyceridemia

A1C, glycated hemoglobin; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes Study; T2D, type-2 diabetes.

Scott R, et al. *Diabetes Care*. 2009;32(3):493-498.

FIELD Study: Highest Therapeutic Benefit of Fenofibrate in Patients with Elevated TG and Low HDL-C

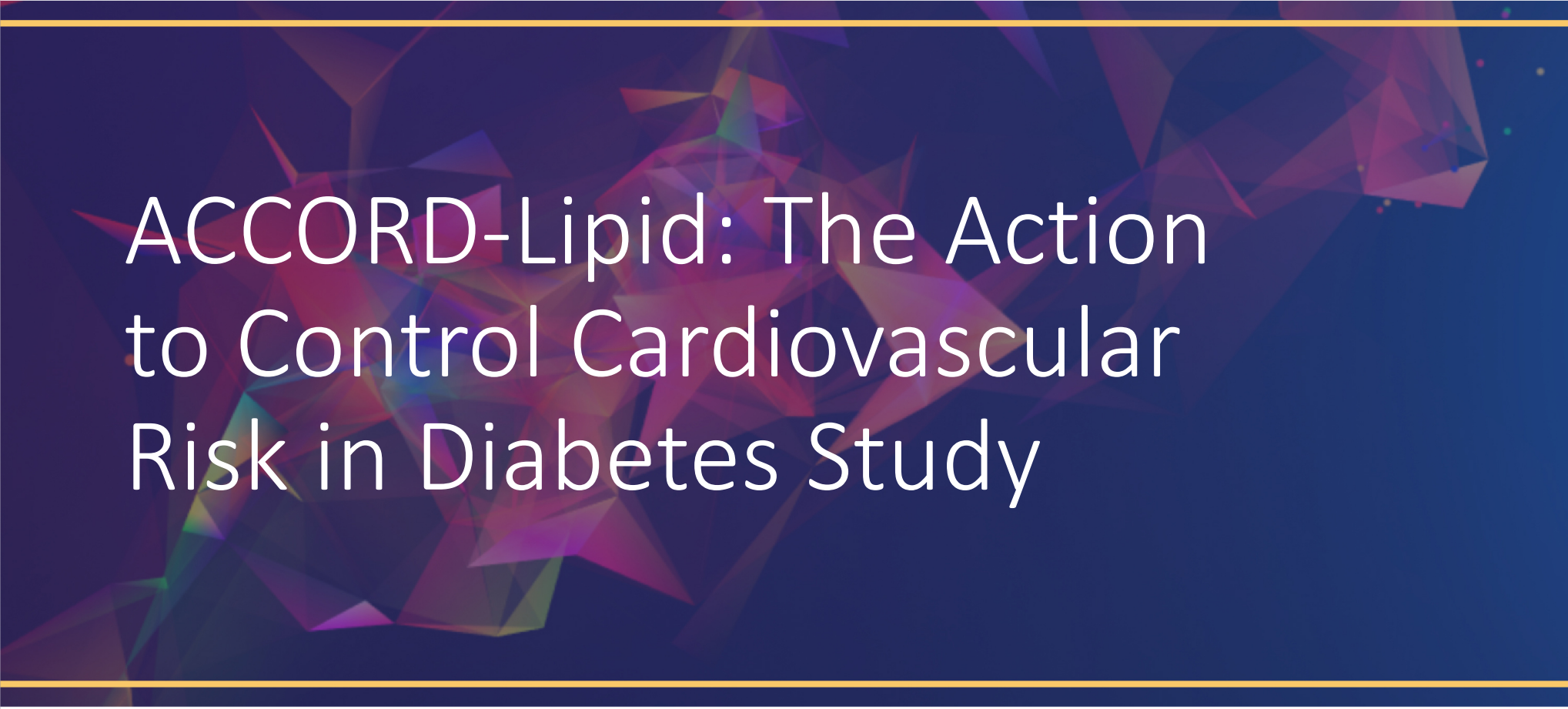


CI, confidence interval;
CV, cerebrovascular;
FIELD, Fenofibrate
Intervention and Event
Lowering in Diabetes trial;
HDL, high-density
lipoprotein; HDL-C, high-
density lipoprotein
cholesterol; MetS,
metabolic syndrome; TG,
triglycerides.

Scott R, et al. *Diabetes Care*
2009;32(3):493-498.

* Not corrected for large placebo group statin drop-in rate

**HDL <40 mg/dL (men) and <50 mg/dL (women)



ACCORD-Lipid: The Action to Control Cardiovascular Risk in Diabetes Study

ACCORD-Lipid Study

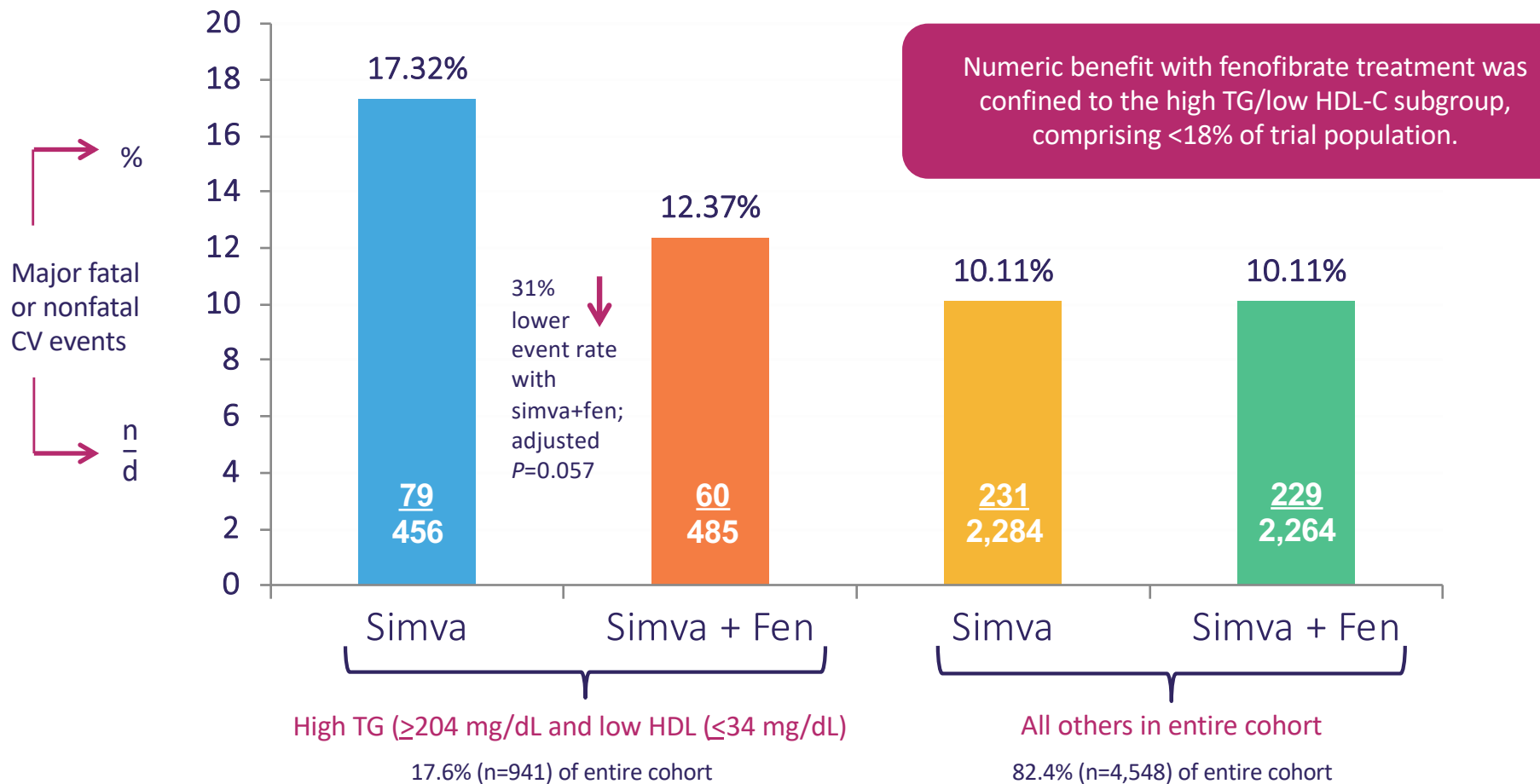
- **Objective:** ACCORD-Lipid investigated whether combination therapy with a statin plus a fibrate, compared with statin monotherapy, reduced CVD risk in patients with T2D at high risk for CVD
- **Methods:** Patients with T2D (N=5518) were randomly assigned to treatment with open-label simvastatin plus masked fenofibrate or placebo; the primary outcome was first occurrence of nonfatal MI, nonfatal stroke, or death from CV causes; mean follow-up was 4.7 years
- **Conclusions:** Compared with simvastatin alone, combination fenofibrate and simvastatin did not reduce the rate of fatal CV events, nonfatal MI, or nonfatal stroke; the greatest benefit for combination therapy was observed in patients with high TG and low HDL-C levels. These results do not support the routine use of fenofibrate and simvastatin to reduce CV risk in the majority of high-risk patients with T2D

ACCORD, Action to Control Cardiovascular Risk in Diabetes; CV, cardiovascular; CVD, cardiovascular; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; T2D, type-2 diabetes; TG, triglycerides

Ginsberg HN, et al. (ACCORD Study Group) *N Engl J Med*. 2010;362(17):1563-1574.

ACCORD-LIPID: Primary Outcomes

High TG/Low HDL-C vs All Others in Full Cohort



ACCORD, Action to Control Cardiovascular Risk in Diabetes; CV, cardiovascular; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Elam M, et al. *Clin Lipidol*. 2011;6(1):9-20; Ginsberg HN, et al. (ACCORD Study Group) *N Engl J Med*. 2010;362(17):1563-1574.



Other Studies/Comparisons

Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial (VA-HIT)

- **Objective:** To address the hypothesis that gemfibrozil therapy aimed at raising HDL-C and lowering TG levels would reduce the incidence of death from CHD and nonfatal MI in men with CHD who had low levels of both HDL-C and LDL-C
- **Methods:** This double-blind trial compared gemfibrozil (1200 mg per day) with placebo in 2531 men with CHD, HDL-C ≤ 40 mg/dL, and LDL-C ≤ 140 mg/dL. The primary study outcome was nonfatal MI or death from coronary causes, and median duration of follow-up was 5.1 years
- **Conclusions:** Gemfibrozil therapy resulted in a significant reduction in the risk of major CV events in patients with CHD whose primary lipid abnormality was low HDL-C; this suggests that the rate of coronary events can be reduced by raising HDL-C and lowering TG without LDL-C-lowering

CHD, coronary heart disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides.

Rubins H, et al. *N Engl J Med*. 1999;341(6):410-418

Helsinki Heart Study (HHS)

- **Objective:** Five-year primary prevention trial to test the hypothesis that gemfibrozil use reduces CHD incidence by lowering LDL-C and increasing HDL-C levels
- **Methods:** Double-blind, placebo-controlled primary prevention trial among 4081 middle-aged men with dyslipidemia. After the 5-year trial, the participants were notified of their treatment group and invited to continue or start gemfibrozil therapy for 5 additional years. Approximately two-thirds of participants in both groups chose gemfibrozil therapy; follow-up has been conducted for 18 years
- **Conclusions:** Significant reductions in CHD mortality, but no difference in all-cause mortality, were observed in patients receiving fenofibrate. The greatest benefit was seen in patients with high baseline TG levels and an elevated LDL-C:HDL-C ratio

CHD, coronary heart disease. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides.

Tenkanen L, et al. *Arch Intern Med.* 2006;166(7):743-748.

Bezafibrate Infarction Prevention (BIP) Trial

- **Objective:** To determine whether bezafibrate, which raises HDL-C and reduces TG, reduces CHD mortality and nonfatal MI in patients with established CAD, HDL-C <45 mg/dL, and moderately elevated cholesterol
- **Methods:** Double-blind randomized trial of 3090 patients with previous MI or stable angina and dyslipidemia who received bezafibrate or placebo and were followed for a mean of 6.2 years; primary endpoint was fatal or nonfatal MI or sudden death
- **Conclusions:** Bezafibrate therapy led to a substantial increase in HDL-C and a reduction in TG levels. In patients with TG ≥ 200 mg/dL, treatment reduced the probability of the primary endpoint by 39.5% ($P=0.002$); reductions in patients with TG <200 mg/dL were not significant

CAD, coronary artery disease; CHD, coronary heart disease; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; TG, triglycerides.

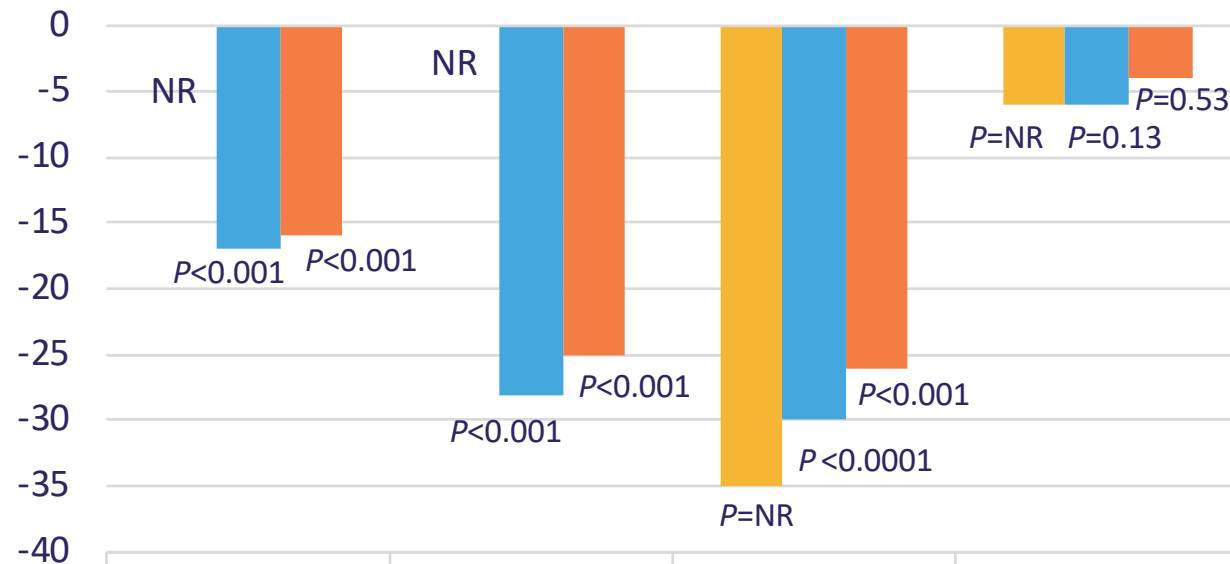
BIP Study Group. *Circulation*. 2000;102:21-27

Independent Meta-Analysis of 5 Major Fibrate Trials In Patients with Moderate Dyslipidemia

HHS, BIP, VA-HIT, FIELD, ACCORD-Lipid

Baseline Moderate Dyslipidemia: TG>200, HDL-C<35-40 mg/dL

CVD Events, RRR



ACCORD, Action to Control Cardiovascular Risk in Diabetes Study Group; BIP, Bezafibrate Infarction Prevention Trial; CVD, cardiovascular disease; FIELD, Fenofibrate Intervention and Event Lowering in Diabetes Trial; HDL, high-density lipoproteins; HDL-C, high-density lipoprotein cholesterol; HHS, Helsinki Heart Study; NR, not reported; RRR, relative risk reduction; TG, triglycerides; VA-HIT, Veterans Affairs High Density Lipoprotein Cholesterol Intervention Trial.

Fibrate groups	Low HDL	High TG	High TG, Low HDL	Neither
■ Sacks et al.	0	0	-35	-6
■ Bruckert et al.	-17	-28	-30	-6
■ Lee et al.	-16	-25	-26	-4

Rosenblit P. *Curr Cardiol Rep.* 2012;14:112-124

Summary and Conclusions

- Treatment with fibrates has been found effective as both monotherapy and combination therapy for lowering TG and raising HDL-C
- Multiple studies show that fibrates are only significantly effective in reducing CVD events in patients with TG >200 mg/dL and HDL-C <40 mg/dL¹
- Treatment of elevated TG (>500 mg/dL) is important to reduce the risk of pancreatitis

CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Jellinger P, et al. *Endocr Practice*. 2017;23(4):479-497.