Evidence- and Guideline-Based Management of Hypertriglyceridemia

Michael B. Bottorff, PharmD, FCCP, FNLA, CLS, *Chair*

Michael B. Bottorff, PharmD, FCCP, FNLA, CLS, *Chair*

Professor and Chair
Department of Pharmacy Practice
School of Pharmacy
South College
Knoxville, TN

Disclosures

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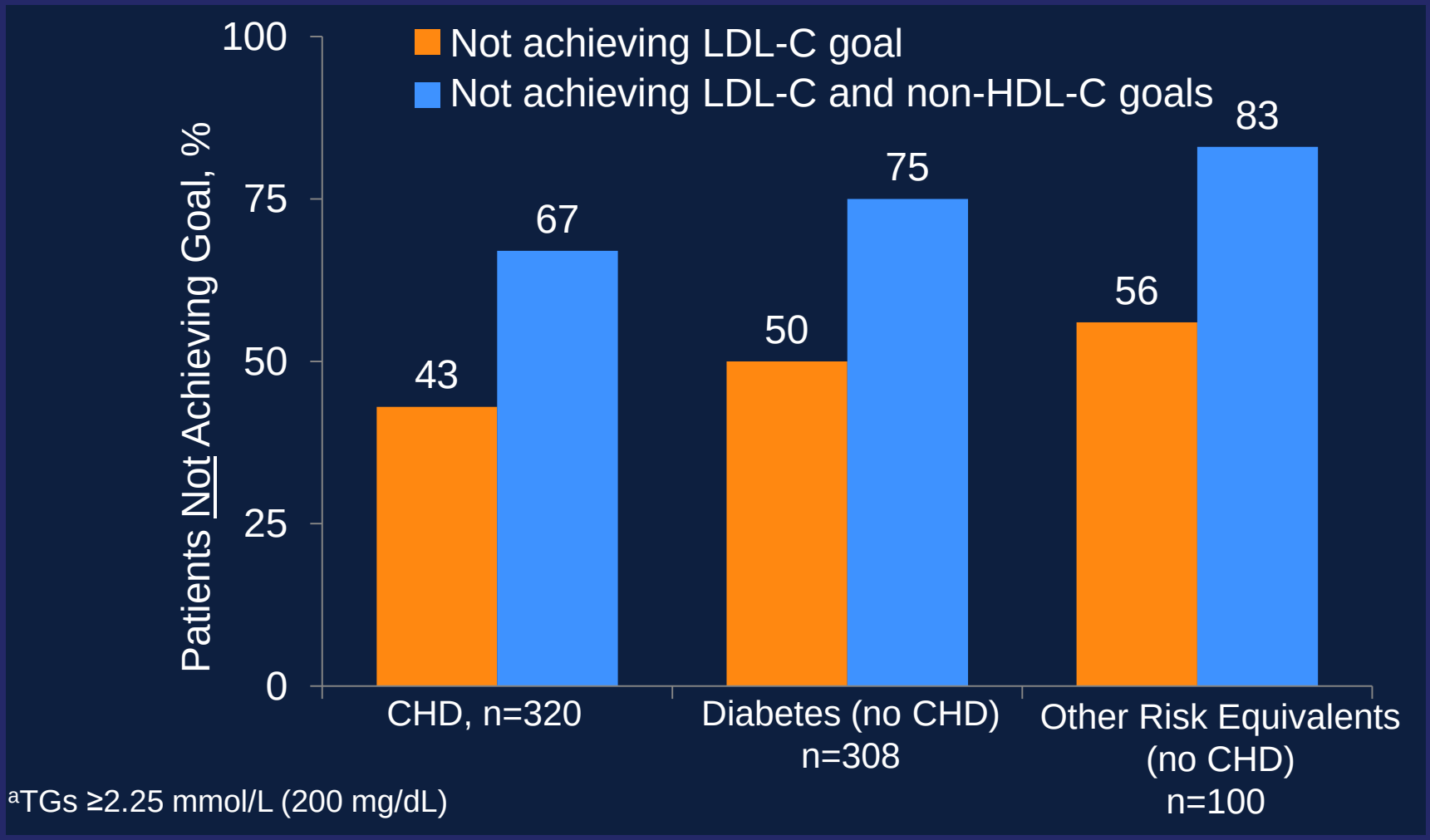
ATP III Treatment Recommendations for Elevated TG

TG (mg/dL)	ATP III Classification	Primary Target of Therapy	Treatment Recommendations
150–199	Borderline high	LDL-C goal	**↓Weight and ↑Physical activity**
200–499	High	LDL-C goal	**↓Weight and ↑Physical activity** Consider non-HDL-C goal: ↓LDL-C with statin or ↓VLDL-C with niacin or fibrate ↓Sugar and carbs*
≥500	Very high	↓TG to prevent acute pancreatitis	**Very low fat diet** (fat ≤15% total calories) **↓Weight and ↑Physical activity** **Add niacin or fibrates** (+OM-3 as per FDA indication*)

*Not in ATP III statement. ATP=Adult Treatment Panel; carbs=carbohydrates; FDA=US Food and Drug Administration; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; OM=omega; TG=triglyceride(s); VLDL-C=very-low-density lipoprotein cholesterol. NCEP ATP III. *Circulation* 2002;106:3143-421.

Hypertriglyceridemic Patients[a] Not Achieving Combined LDL-C and Non-HDL-C Goals

NEPTUNE II: Patients with CHD and CHD Risk Equivalents



[a]TGs ≥2.25 mmol/L (200 mg/dL)

CHD=coronary heart disease; NEPTUNE= National Cholesterol Education Program (NCEP) Evaluation Project Utilizing Novel E-Technology. Davidson MH et al. *Am J Cardiol.* 2005;96:556-63.

T2DM Patients Attaining Lipid Goals While on Statins

Lipid parameter	Number (n / N)	% of those using statin
TC <4 mmol/L (<155 mg/dL)	4284 / 9052	47.3
LDL-C <2.0 mmol/L (<77 mg/dL)	3445 / 8201	42.0
HDL-C >1.0 mmol/L (>39 mg/dL) (male)	3096 / 5307	58.3
HDL-C >1.2 mmol/L (>46 mg/dL) (female)	2252 / 4132	54.5
Fasting TG <1.7 mmol/L (<150 mg/dL)	4916 / 9161	53.7

T2DM=type 2 diabetes mellitus; TC=total cholesterol. Feher M et al. *Diabetes Metab Syndr Obes*. 2013;6:11-5.

Basic Principles of CVD Risk Management

1. Systematically quantify CVD risk
2. Look for 2° causes of dyslipidemia and HTN
3. Treat contributory metabolic disorders
4. Try diet and lifestyle change in everyone
5. Risk category determines LDL-C / non-HDL-C goals
6. Use statins and statin adjuncts to achieve goals
7. Consider possibility of TG / HDL-C medications (fibrates, niacin, and OM-3)

CVD=cardiovascular (CV) disease; HTN=hypertension.

Treatment of Mixed Hyperlipidemia

High LDL-C and TGs

Therapeutic Lifestyle Change

Drug Therapy

STEP 1

Achieve the LDL-C goal

STEP 2

Achieve the non-HDL-C goal
Increase LDL-C lowering or
Add a fibrate, niacin or fish oils

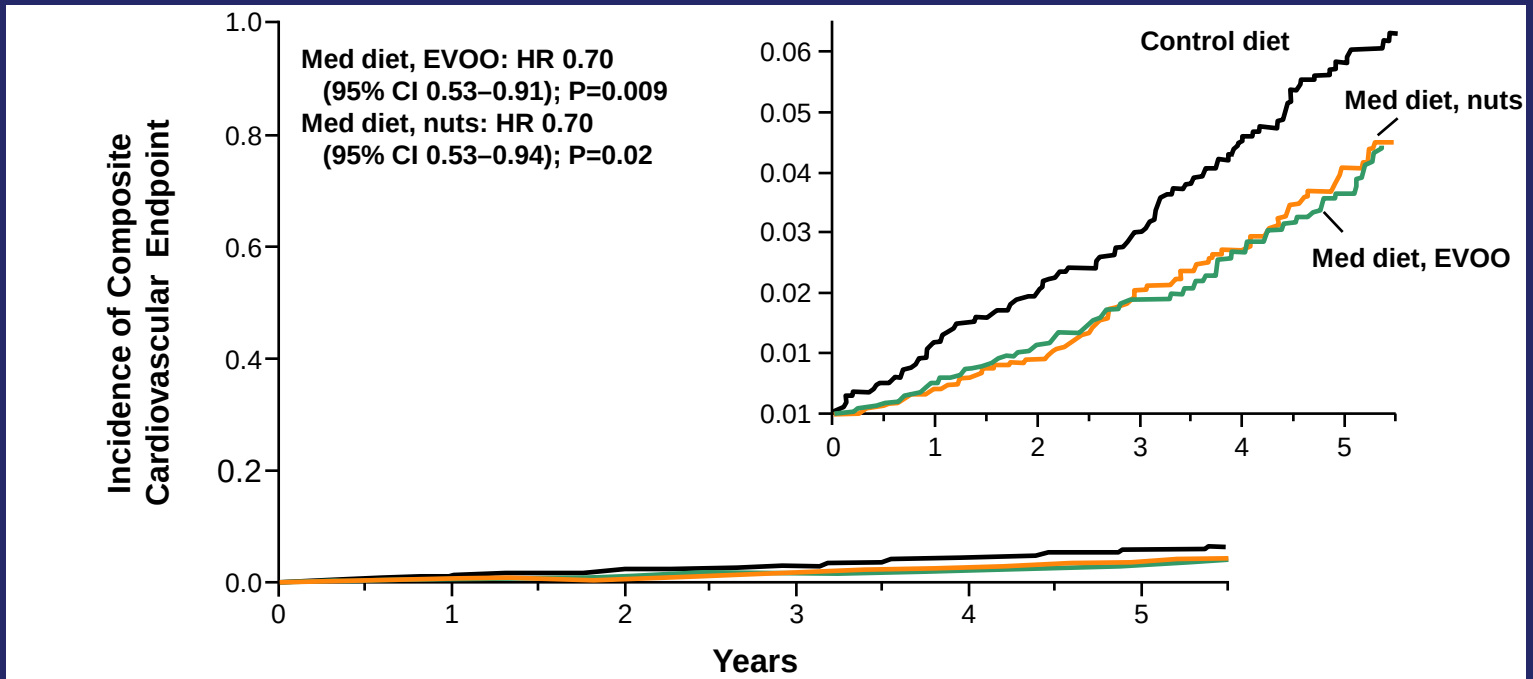
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. *JAMA* 2001;285:2486-97.

Lifestyle and Diet Can Improve Dyslipidemia

Diet / Lifestyle Change	Lipid Profile Change
Smoking cessation	↑HDL-C 4 mg/dL[1]
Weight loss (5%–10%)	↓TG 20%, ↓LDL-C 15%, ↑HDL-C 10%[2]
Diet ↑Fruits, vegetables & low-fat dairy; ↓Sugar ↓Total carb; ↓Fat (to 33%–50% of calories)	↓LDL-C, ↑HDL-C[1] ↓TG 9 mg/dL[2]
Brisk 30-min walk, 3x/wk	↓LDL-C, ↑HDL-C 5%–10%[1]

[1]Sampson UK et al. *Curr Atheroscler Rep.* 2012;14:1-10. [2]Miller M et al. *J Am Coll Cardiol.* 2008;51:724-30.
min=minute; wk=week.

Effect of Mediterranean Diet on MI, Stroke, or Death from CVD



No. at risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031

N=7447 persons, age range 55 to 80 years at high CV risk, but no CVD, were enrolled to: 1. Control diet (advice to ↓dietary fat); 2. Med diet supplemented with EVOO; or 3. Med diet supplemented with mixed nuts. Both Med diets were rich in beans, fish, fruits and vegetables, and even drinking wine with meals.

CI=confidence interval; EVOO=extra virgin olive oil; HR=hazard ratio; Med=Mediterranean; MI=myocardial infarction.

Estruch R et al. *N Engl J Med*. 2013;368:1279-90.

Effects of Nutrition Practices on TG Lowering

Nutrition Practice	TG-Lowering Response
Weight loss (5%–10% of body weight)	20%
Mediterranean-style diet vs low-fat diet	10% – 15%
Add marine-derived EPA / DHA (per gram)	5% – 10%
Decrease carbohydrates (1% energy replacement with MUFA / PUFA)	1% – 2%
Eliminate trans fats (1% energy replacement with MUFA / PUFA)	1%

DHA=docosahexaenoic acid; EPA=eicosapentaenoic acid; MUFA=monounsaturated fatty acid (FA); PUFA=polyunsaturated FA.

Miller M et al. *Circulation.* 2011;123:2292-333.

AHA Scientific Statement: Treatment Effect by Drug Class for Lowering TG Levels

Drug	% TG Reduction
Fibrates	30–50
Immediate-release niacin	20–50
OM-3	20–50
Extended-release niacin	10–30
Statins	10–30
Ezetimibe	5–10

TG reduction values are not always corrected for baseline TG levels. As the greatest reduction in TG levels occur in those with the highest TG levels at baseline, this may not be a fair assessment of the TG-lowering effect of lipid-altering drugs in patients with HTG.

AHA=American Heart Association; HTG=hypertriglyceridemia. Miller M et al. *Circulation*. 2011;123:2292-333.

Properties Considered when Selecting Lipid-Altering Drugs

- Effects can be additive, synergistic, unhelpful, and adverse
- Impact on
  - Hard outcomes
  - Other lipid parameters
  - Other measures of known CV risk
  - Drug-drug interactions
  - Safety and adverse effects
  - Inflammation and other biomarkers
  - Patient preference and compliance

Pharmacologic Therapy for Very High TG Levels

Drug Class	Very High TG Indications*		Select Adverse Effects (AEs) (Common causes are shown in yellow)
	TG >500 mg/dL	Type IV Hyper-lipidemia	
Fenofibrate[a]	☑	☑	**Dyspepsia, various upper gastrointestinal complaints, cholesterol, gallstones, myopathy** Gemfibrozil should not be combined with statins, and has limited use in current practice.
Extended-release Niacin (ERN)[b]	☑	☑	**Flushing, pruritus, diarrhea, vomiting, hyperglycemia, hyperuricemia or gout, dyspepsia and exacerbation of peptic ulcer, hepatotoxicity** HPS2-THRIVE study of ERN / LRPT did not achieve 1° endpoint & showed significant ↑ in nonfatal serious AEs in ERN / LRPT group

*Data from individual product labeling for each drug in patients with very ↑TG. [a]145 mg per day. [b]2 grams per day.
HPS2-THRIVE=Heart Protection Study 2-Treatment of HDL to Reduce the Incidence of Vascular Events; LRPT= laropiprant.
Fredrickson DS et al. *Ann Intern Med*. 1975;82:150-7. Miller M et al. *Circulation*. 2011;123:2292-333.

Pharmacologic Therapy for Very High TG Levels

Drug Class	Very High TG Indications*			Select Adverse Effects
	TG >500 mg/dL	Type III Hyper-lipidemia	Type IV Hyper-lipidemia	
OM-3 FA (EPA / DHA)[a]	☑			Eructation, dyspepsia, taste perversion
OM-3 FA (EPA only)[a]	☑			Arthralgia
Statins		☑[b]	☑[c]	Myalgia, myopathy (rare), rhabdomyolysis (very rare), ↑A1c, cognitive impairment

*Data from individual product labeling for each drug in patients with very ↑TG. [a]4 grams per day. [b]Atorvastatin, rosuvastatin, and simvastatin. [c]Atorvastatin and simvastatin. A1c=glycated hemoglobin.

Fredrickson DS et al. *Ann Intern Med*. 1975;82:150-7. Miller M et al. *Circulation*. 2011;123:2292-333.

Lipid Effects of Drug Classes in Subjects with Primary Hyperlipidemia / Mixed Dyslipidemia and Isolated HTG

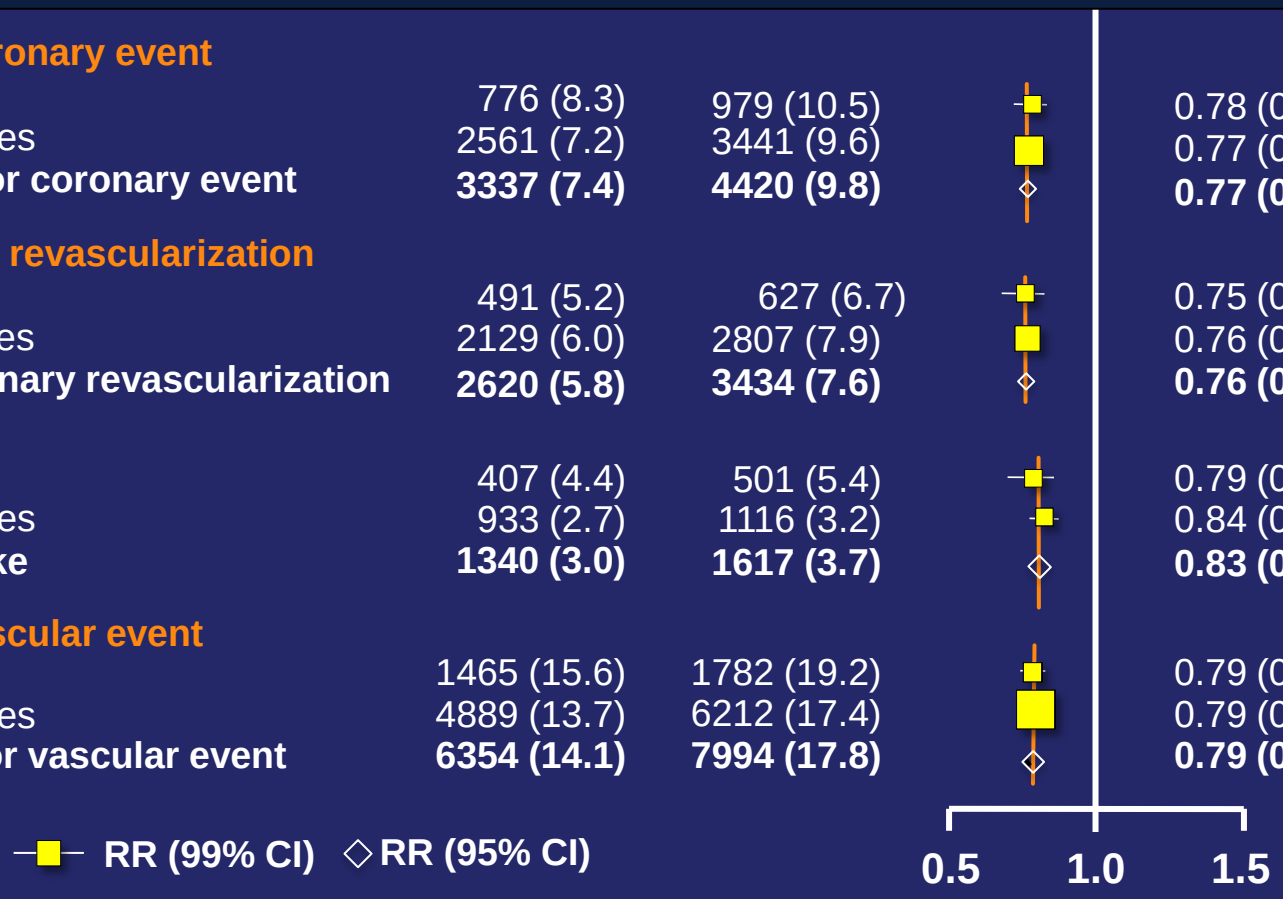
Type of dyslipidemia / medication	TG*	LDL-C*	HDL-C*	Non-HDL-C*
Mixed dyslipidemia				
• Statins	–10 to –37	–26 to –63	+5 to +16	–44 to –60
• OM-3 fatty acids	–19 to –44	–6 to +25	–5 to +7	–1 to –7
• Fenofibrate, fenofibric acid and gemfibrozil	–24 to –36	–5 to –31	+10 to +16	–17
• Niacin	–5 to –38	–3 to –17	+10 to +26	NR
Isolated HTG				
• Statins	–21 to –52	–27 to –45	+3 to +22	–29 to –52
• OM-3 fatty acids	–26 to –52	+17 to +49	+9 to +14	–10 to –14
• Fenofibrate, fenofibric acid and gemfibrozil	–46 to –62	+3 to +47	+18 to +23	NR

*Range, %.

NR=not reported. Maki KC et al. *J Clin Lipidol*. 2012;6:413-26.

Meta-analysis: Effects of Cholesterol Lowering on Major Vascular Events Among Patients with Diabetes in 14 Randomized Trials of Statins: A Meta-Analysis

Major vascular event and prior diabetes	Events (%) Treatment	Events (%) Control	RR (CI)
Major coronary event			
Diabetes	776 (8.3)	979 (10.5)	0.78 (0.69 - 0.87)
No diabetes	2561 (7.2)	3441 (9.6)	0.77 (0.73 - 0.81)
Any major coronary event	**3337 (7.4)**	**4420 (9.8)**	**0.77 (0.74 - 0.80)**
Coronary revascularization			
Diabetes	491 (5.2)	627 (6.7)	0.75 (0.64 - 0.88)
No diabetes	2129 (6.0)	2807 (7.9)	0.76 (0.72 - 0.81)
Any coronary revascularization	**2620 (5.8)**	**3434 (7.6)**	**0.76 (0.73 - 0.80)**
Stroke			
Diabetes	407 (4.4)	501 (5.4)	0.79 (0.67 - 0.93)
No diabetes	933 (2.7)	1116 (3.2)	0.84 (0.76 - 0.93)
Any stroke	**1340 (3.0)**	**1617 (3.7)**	**0.83 (0.77 - 0.88)**
Major vascular event			
Diabetes	1465 (15.6)	1782 (19.2)	0.79 (0.72 - 0.86)
No diabetes	4889 (13.7)	6212 (17.4)	0.79 (0.76 - 0.82)
Any major vascular event	**6354 (14.1)**	**7994 (17.8)**	**0.79 (0.77 - 0.81)**



RR=relative risk. Kearney PM et al. *Lancet*. 2008;371:117–125.

Statins Reduce CVD Events in HTG Patients (HTG Subgroup Data)

Statin Trial (Subgroup)	Drug	Risk difference vs placebo	P-value
WOSCOPS (↑TG)	Pravastatin	–31% (–32%)	<0.001 (0.003)
CARE (↑TG)	Pravastatin	–24% (–15%)	0.003 (0.07)
PPP Project (Highest TG tertile)	Pravastatin	–23% (–15%)	<0.001 (0.029)
4S (Dyslipidemia)	Simvastatin	–34% (–52%)	<0.001 (<0.001)
JUPITER (Older subjects with ↑TG)	Rosuvastatin	–44% (–21%)	<0.001 (NS)
CTT (Highest TG tertile)	Various statins	–21% (–24%)	<0.001 (<0.001)

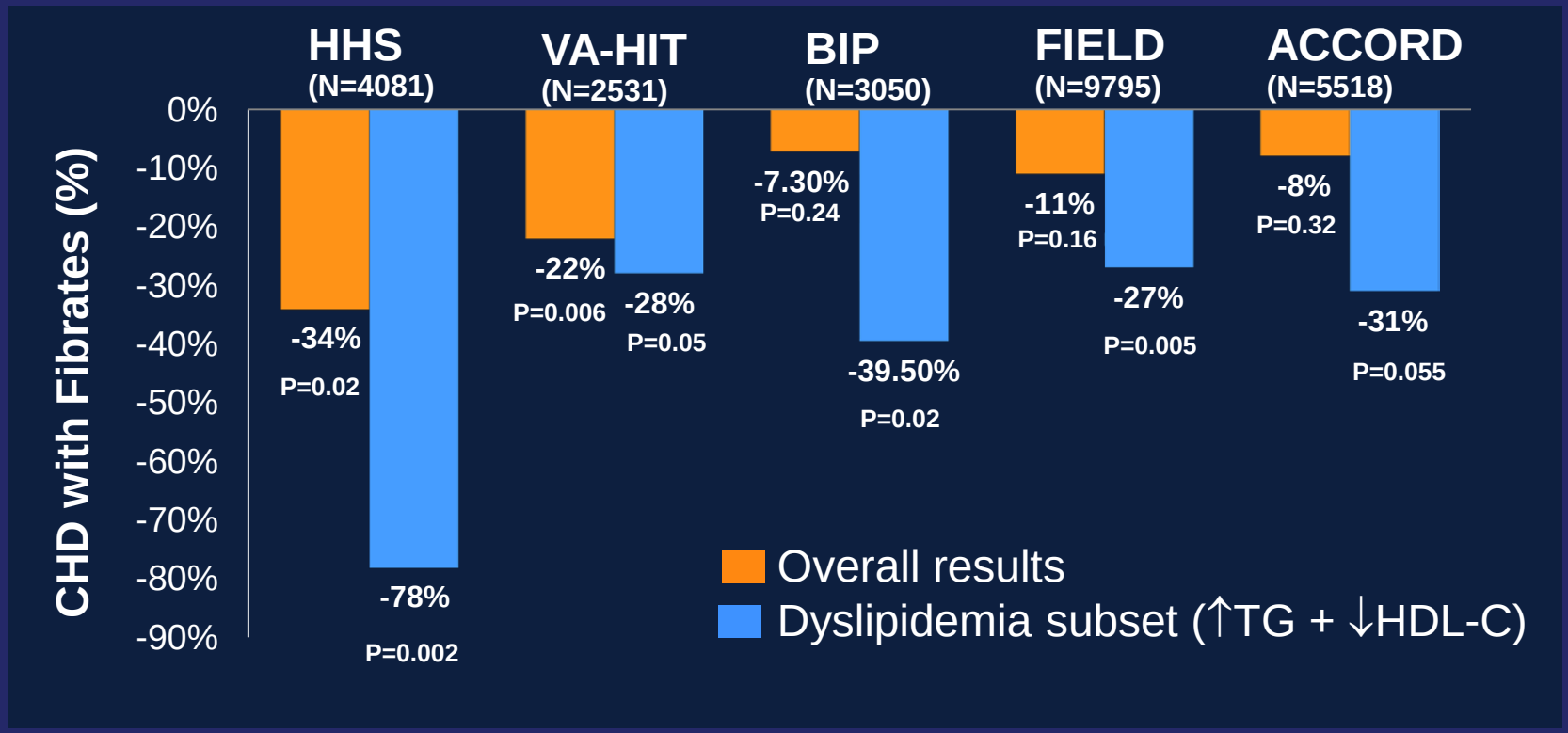
4S=Scandinavian Simvastatin Survival Study; CARE=Cholesterol and Recurrent Events; CTT=Cholesterol Treatment Trialists; JUPITER=Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; PPP=Prospective Pravastatin Pooling; NS=not significant; WOSCOPS=West of Scotland Coronary Prevention Study. Maki KC et al. *J Clin Lipidol*. 2012;6:413-26.

Median follow-up: ≥5 yrs.

Fibrate Efficacy Overview: CHD Risk Reduced 27%–78% in Patients with Dyslipidemia

Overview of fibrate efficacy in clinical trials

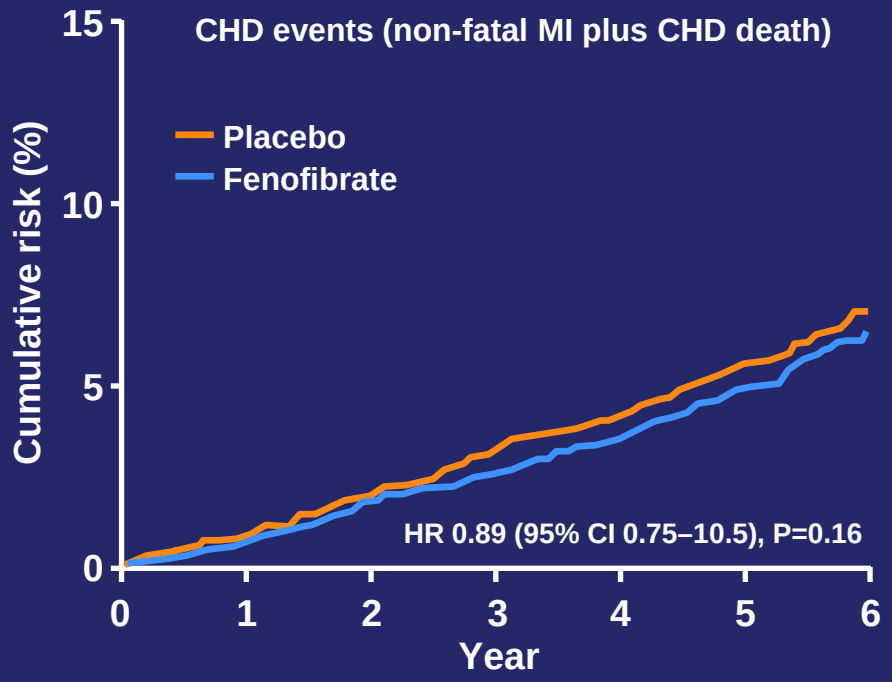
CHD events significantly reduced in patients with dyslipidemia



ACCORD=Action to Control Cardiovascular Risk in Diabetes; BIP=Bezafibrate Infarction Prevention; FIELD=Fenofibrate Intervention and Event Lowering in Diabetes; HHS=Helsinki Heart Study; VA-HIT=Veterans Affairs High-Density Lipoprotein Intervention Trial. Elam M et al. *Curr Opin Lipidol.* 2011;22:55-61. Guyton JR et al. Paper presented at: AHA SS; Nov. 6, 2012; Los Angeles, CA. Maki KC et al. *J Clin Lipidol*. 2012;6:413-26. Rosenblit PD. *Curr Cardiol Rep*. 2012;14:112-24. Saito Y et al. *Atherosclerosis*. 2008;200;135-40. Elam JC. *Curr Opin Lipidol*. 2011;22:55-61

FIELD Trial

- 9795 patients with diabetes mellitus (DM) not on a statin
- TC 3–6.5 mmol/L (116–251 mg/dL) + *either* TC/HDL-C ratio ≥4 *or* TGs 1–5 mmol/L (89–443 mg/dL)
- Fenofibrate 200 mg/day vs placebo
- Lipid effects at 4 months: TG ↓28.6%, HDL-C ↑5.1%, LDL-C ↓12%

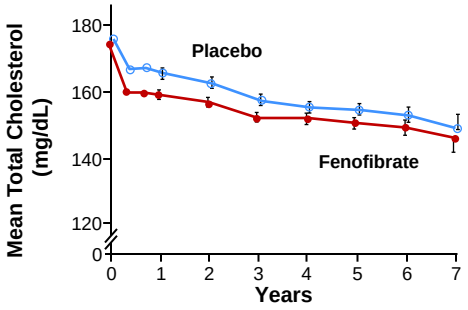


- More “drop in” of statin therapy in placebo arm (17% vs 8%)
- 11% ↓ in total coronary events (ie, including stroke and revascularization)

Keech A et al. *Lancet.* 2005;366:1849-61.

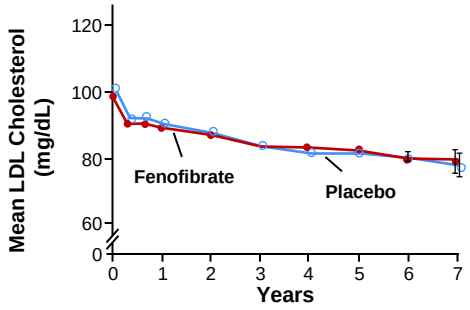
ACCORD: Overall Outcomes

A. Total Cholesterol



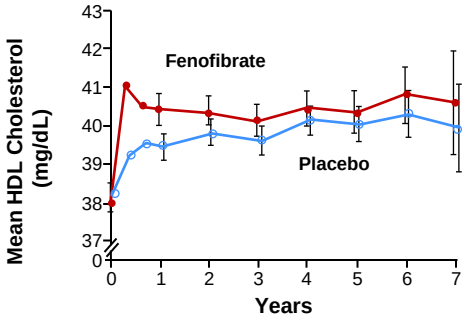
No. of Patients								
Fenofibrate	2747	2593	2505	2417	2361	1478	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

B. LDL Cholesterol



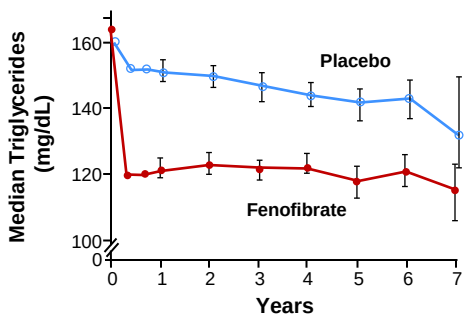
No. of Patients								
Fenofibrate	2747	2593	2505	2417	2361	1477	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

C. HDL Cholesterol



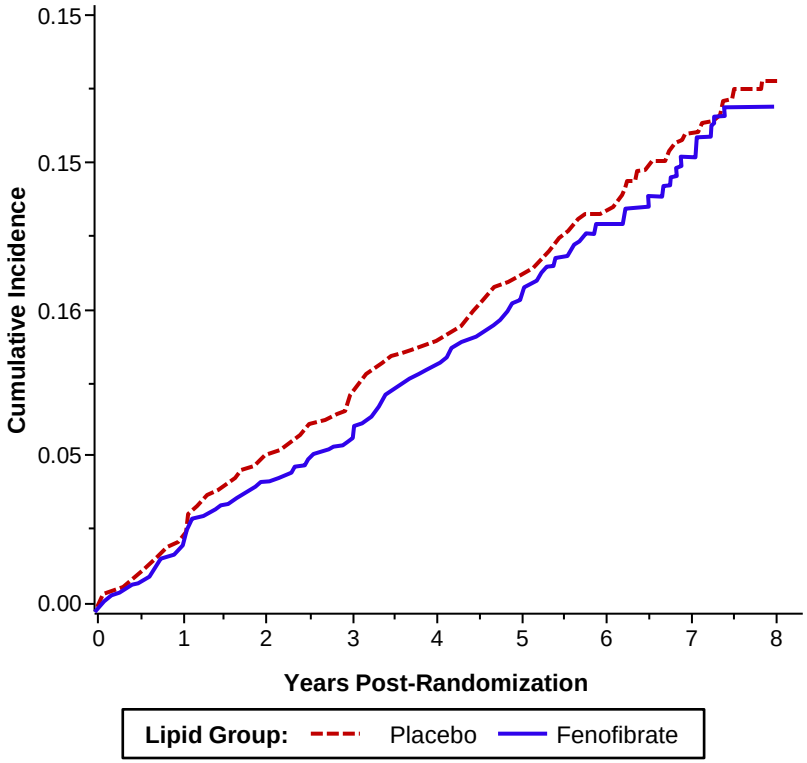
No. of Patients								
Fenofibrate	2747	2593	2505	2417	2361	1477	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

D. Triglycerides



No. of Patients								
Fenofibrate	2747	2593	2505	2417	2361	1478	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

Kaplan-Maier Estimates of Cumulative Incidence Lipid Trial – Primary Outcome

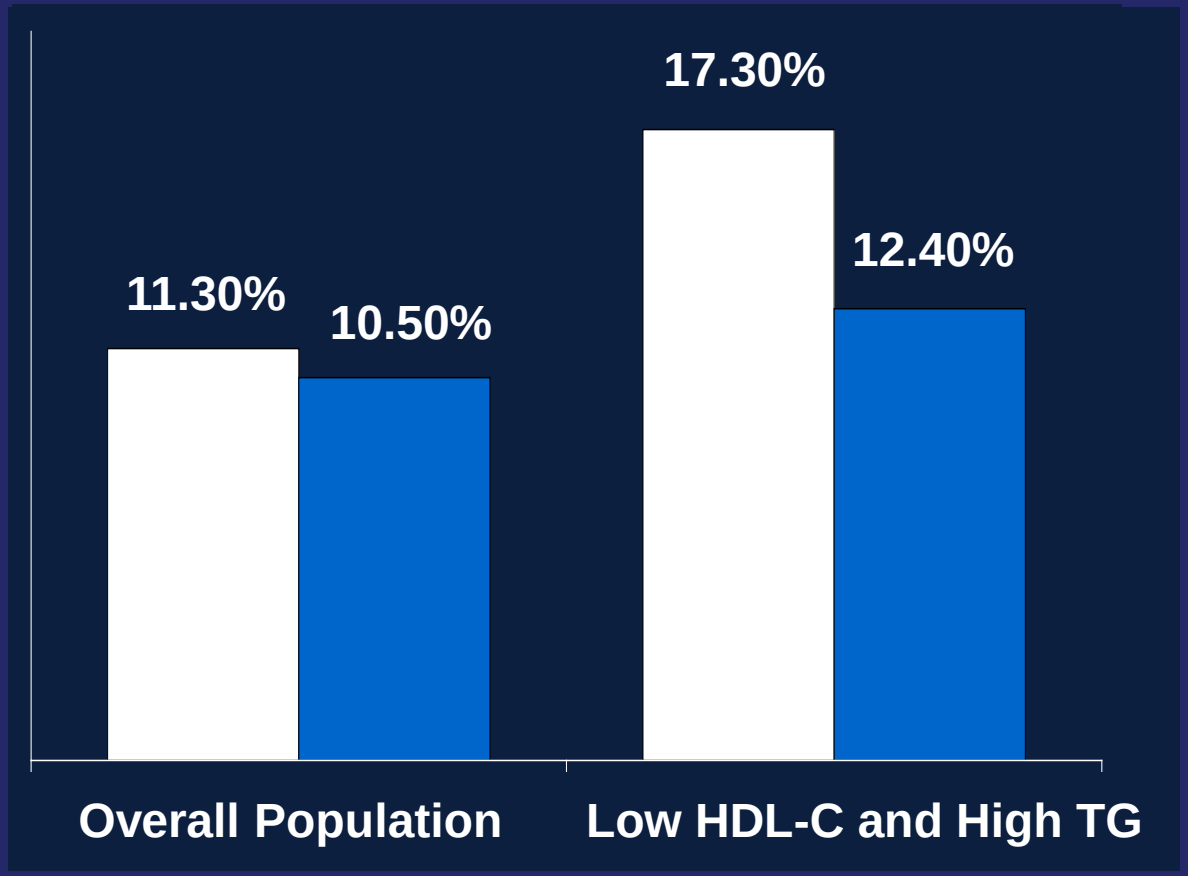


No significant changes in primary endpoint

Ginsberg HN et al. *N Engl J Med*. 2010;36:1563-74.

ACCORD: Efficacy in Patients with Dyslipidemia

Primary outcome reached in those with HDL-C <34 mg/dL and TGs >204 mg/dL

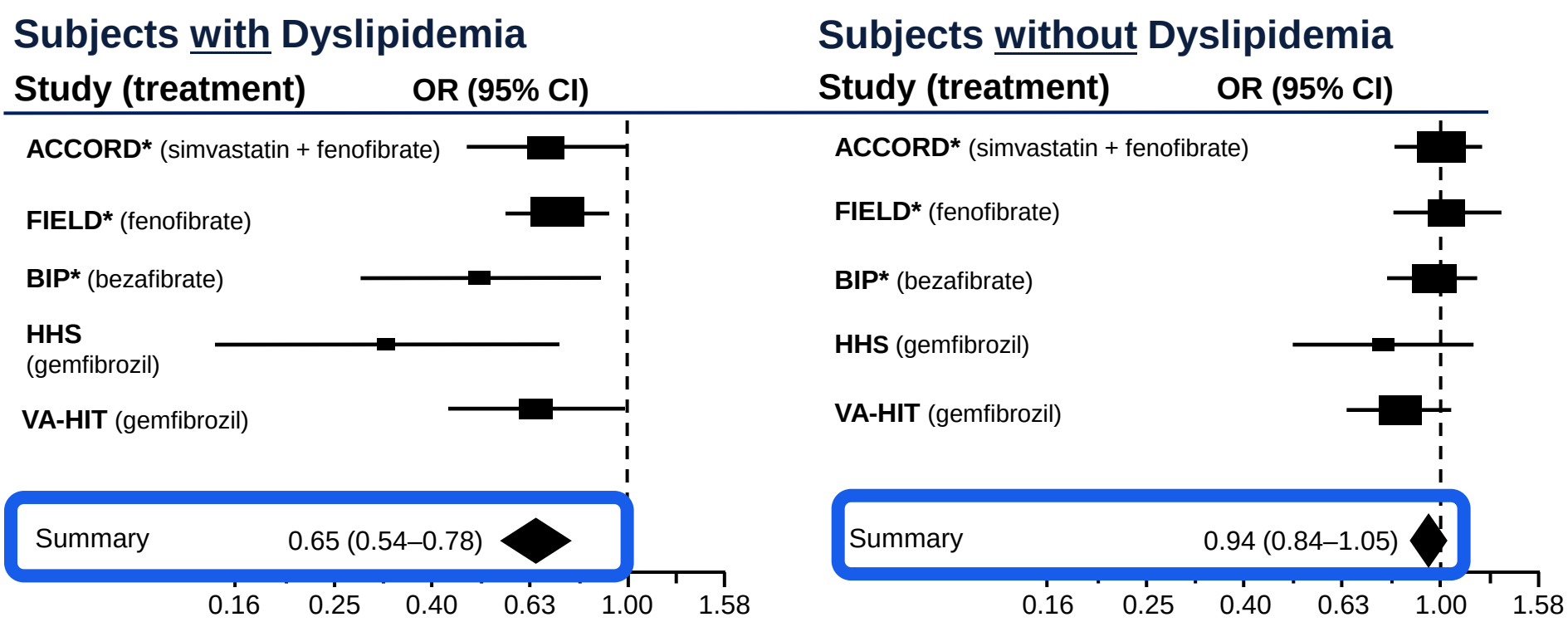


Trend towards fewer CHD events seen in patients with low HDL-C and high TGs at baseline (P=0.06)

- Statin
- Statin + Fibrate

Ginsberg HN et al. *N Engl J Med*. 2010;36:1563-74.

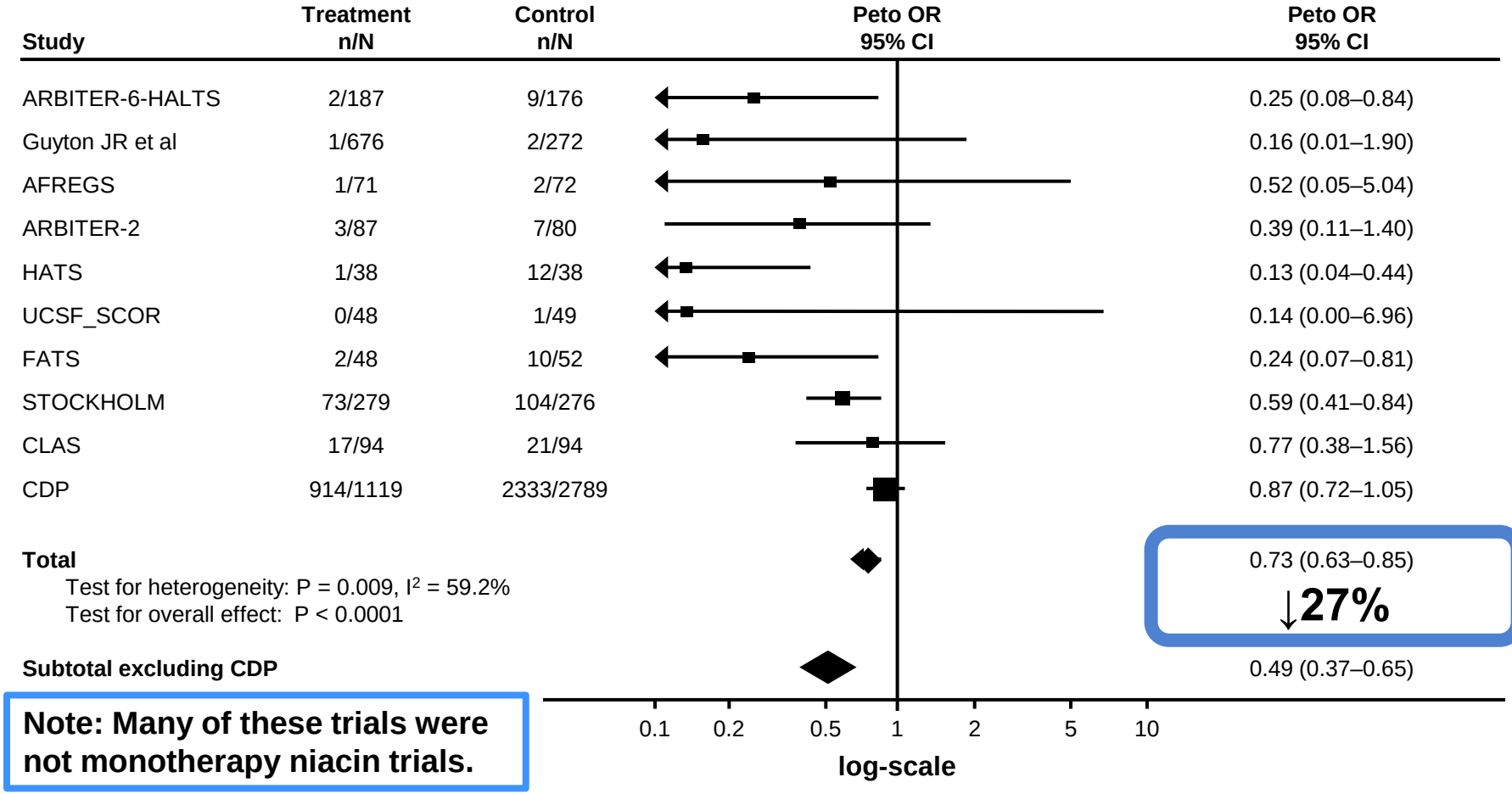
Meta-analysis of Fibrate Randomized Clinical Trials



Dyslipidemia = TG ≥204 mg/dL & HDL-C ≤34mg/dL

*Did not meet primary endpoint. Sacks FM et al. *N Engl J Med.* 2010;363:692-4.

Niacin Reduces Total CVD (CHD + CVA): Pre-AIM-HIGH Trials

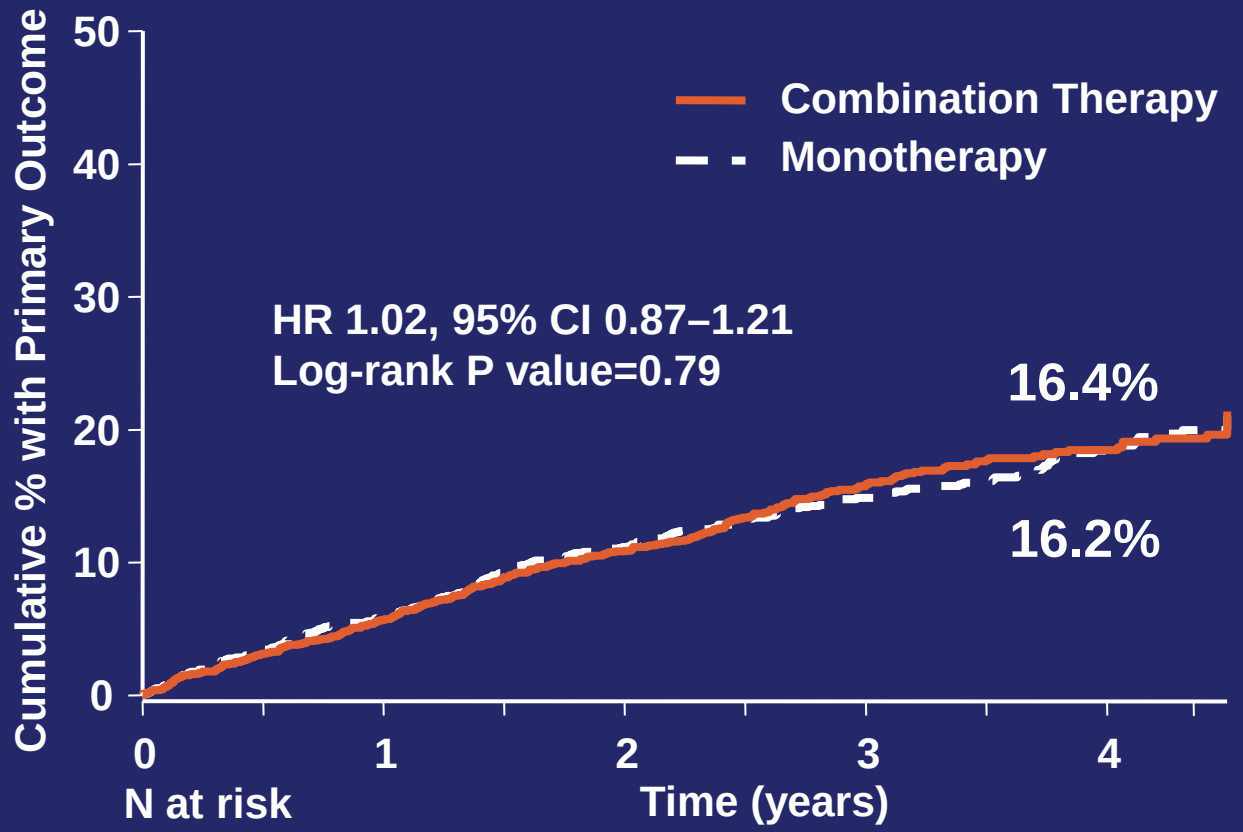


Note: Many of these trials were not monotherapy niacin trials.

AFREGS=Armed Forces Regression Study; AIM-HIGH=Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes; ARBITER=Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol; CDP=Coronary Drug Project; CLAS=Cholesterol-Lowering Atherosclerosis Study; CVA=cerebrovascular accident; FATS=Familial Atherosclerosis Treatment Study; HALTS=HDL and LDL Treatment Strategies in Atherosclerosis; HATS=HDL-Atherosclerosis Treatment Study; OR=odds ratio; STOCKHOLM=Stockholm Ischaemic Heart Disease Secondary Prevention Study; UCSF-SCOR=University of California San Francisco Arteriosclerosis Specialized Center of Research Intervention Trial. Bruckert E et al. *Atherosclerosis*. 2010;210:353-61.

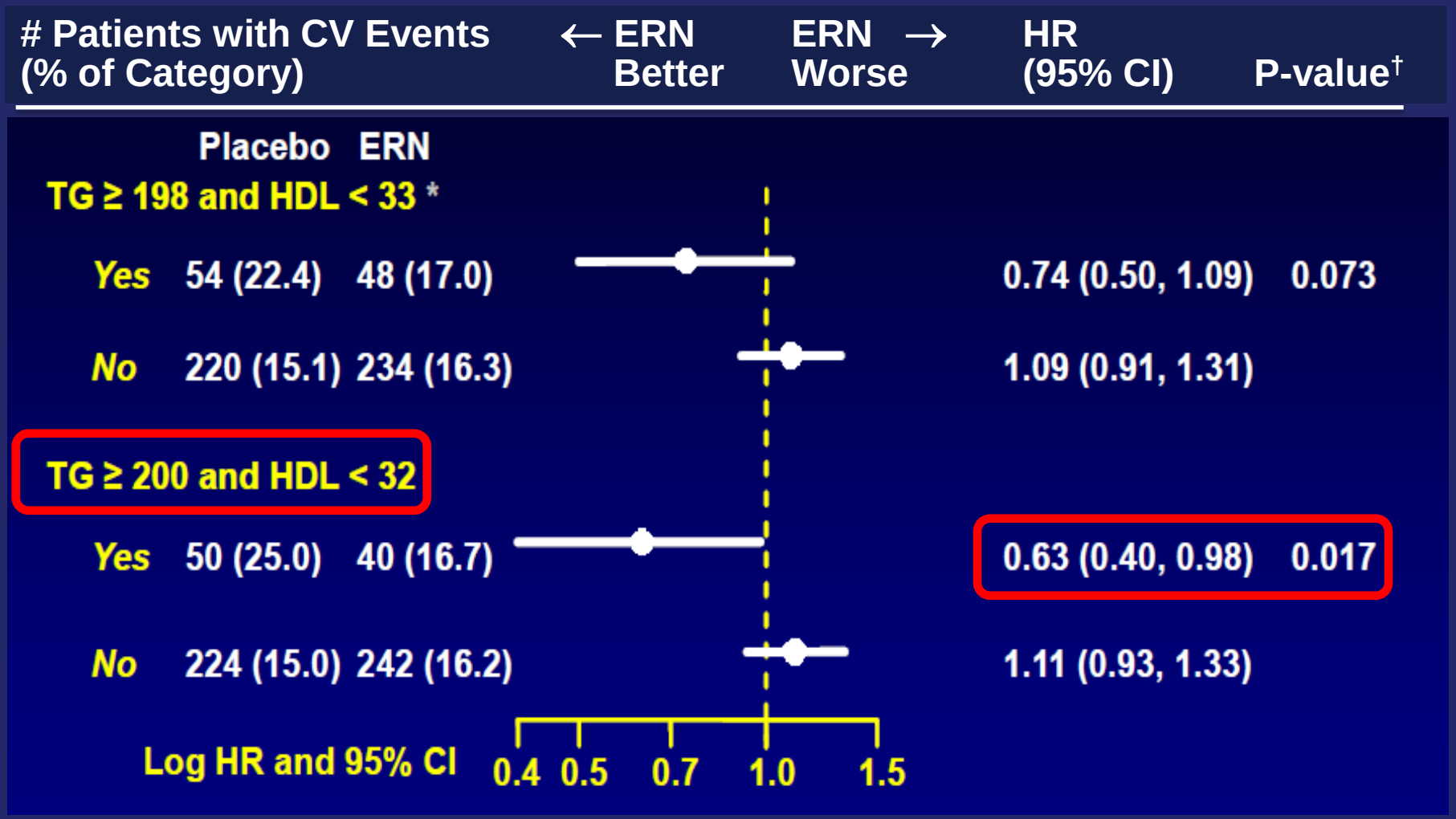
AIM-HIGH Primary Endpoint: CHD Death, Nonfatal MI, Ischemic Stroke, High-risk ACS, Hospitalization for Coronary or Cerebrovascular Revascularization

Baseline Lipid Levels (Monotherapy arm, n=1696)	
Lipid	Mean (SD) or Median, mg/dL
LDL-C	74.0 (22.7)
Non-HDL-C	110.3 (26.0)
HDL-C	34.9 (5.6)
TG	163



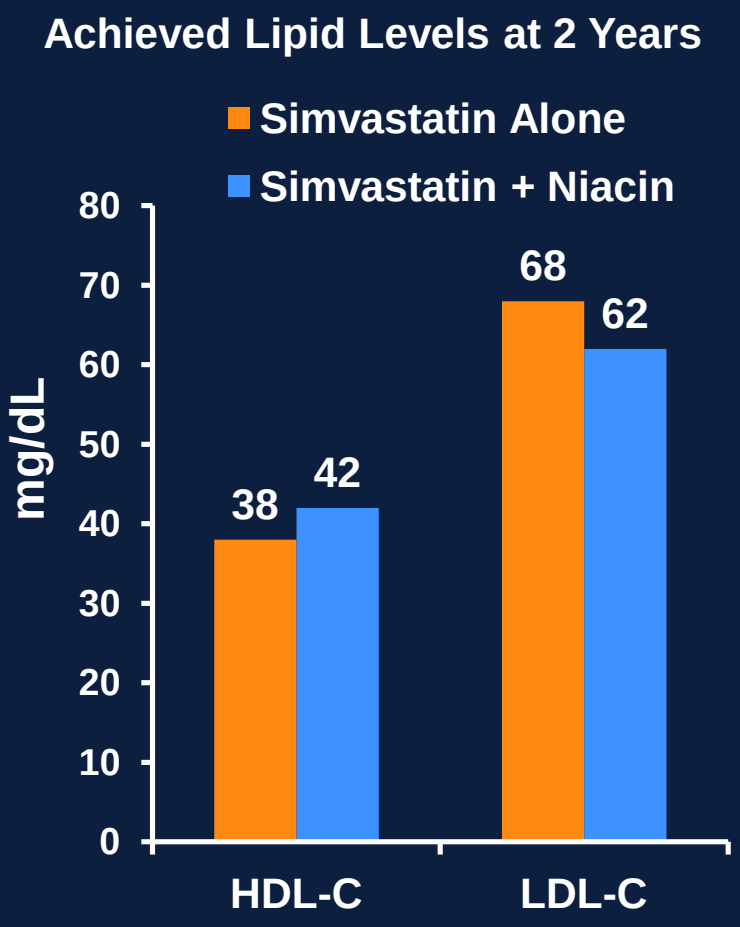
ACS=acute coronary syndrome; SD=standard deviation. AIM-HIGH Investigators. *N Engl J Med.* 2011;365:2255-67.

AIM-HIGH: Extended-Release Niacin in Patients with HTG & Low HDL-C

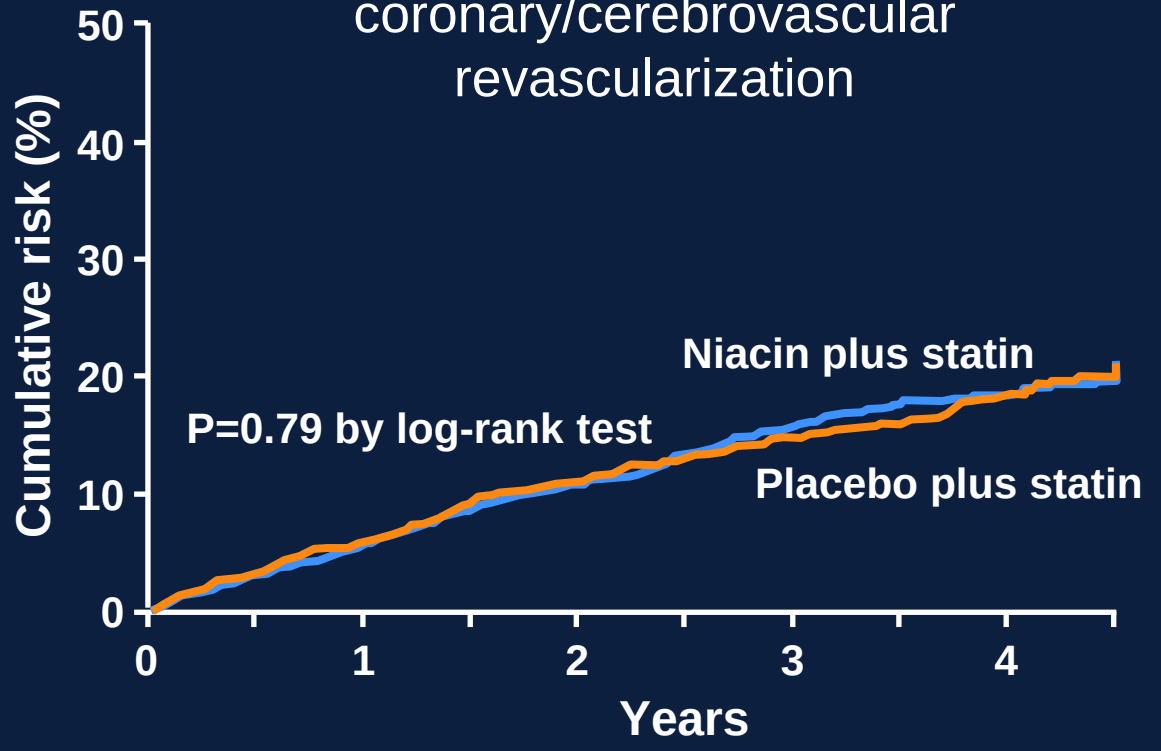


*Highest tertile of TG and lowest tertile of HDL-C. †Heterogeneity by treatment. All measurements in mg/dL.
Guyton JR et al. Paper presented at: AHA SS; Nov. 6, 2012; Los Angeles, CA.

AIM-HIGH Trial: Results



Primary endpoint:
CHD death, MI, stroke, hospitalization for ACS, symptom-driven coronary/cerebrovascular revascularization

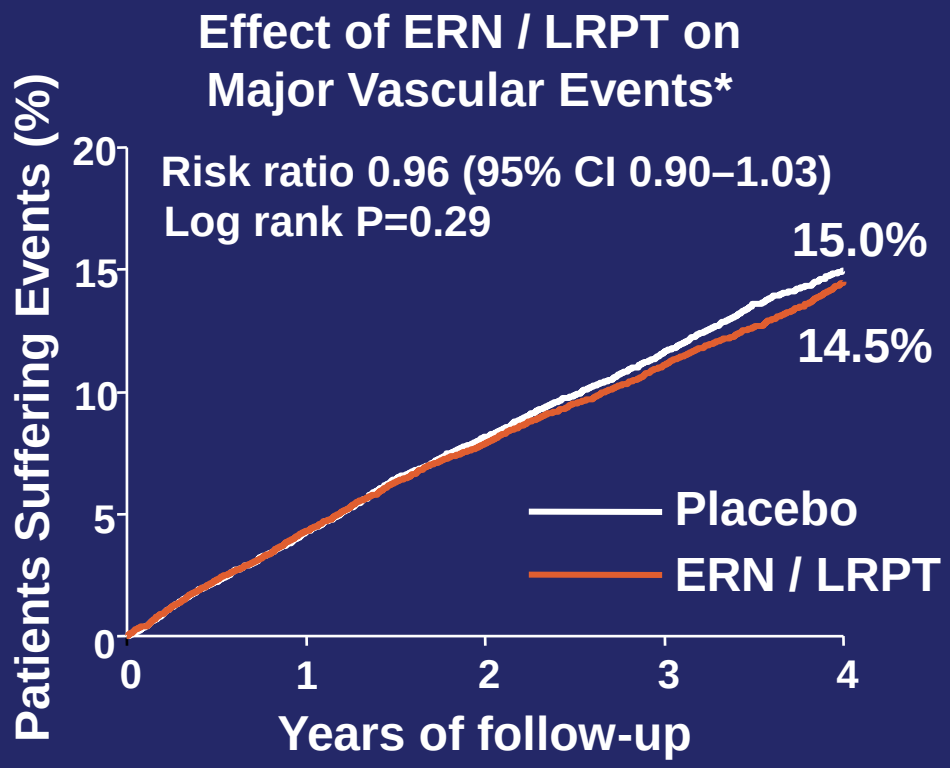


AIM-HIGH Investigators. *N Engl J Med.* 2011;365:2255-67.

HPS2-THRIVE: Randomized Placebo-controlled Trial of ERN and Laropiprant in 25,673 Patients with Pre-existing CVD

Baseline Lipids on Statin-based Rx

Lipid	Mean (SD) at baseline, mg/dL
TC	128 (22)
Direct-LDL	63 (17)
HDL-C	44 (11)
TG	125 (74)

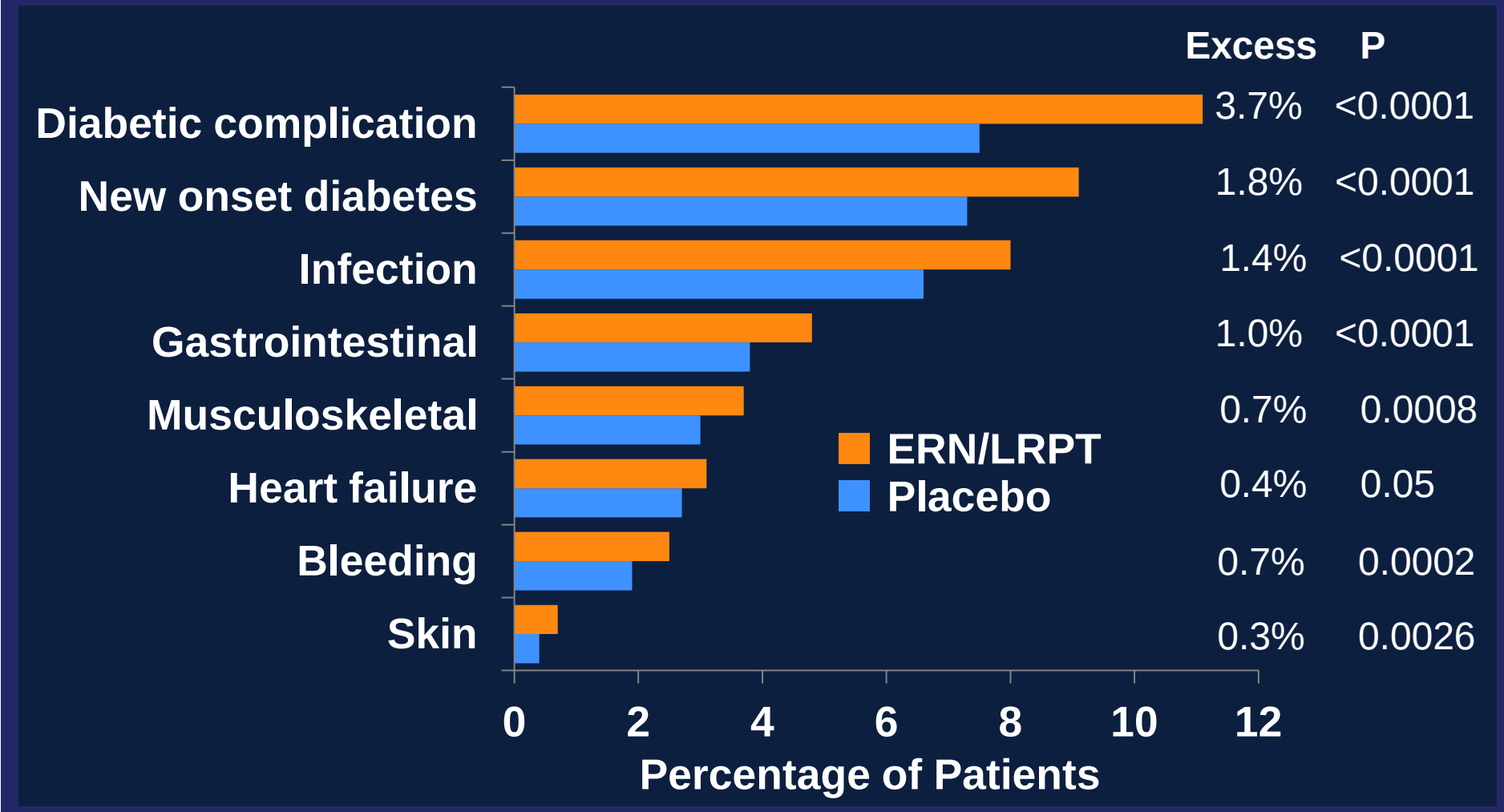


"Significant excesses of serious adverse events (SAEs) due to known and unrecognised side-effects of niacin. Over 4 years, ER niacin/laropiprant caused SAEs in ~30 patients per 1000."

*Non-fatal MI or coronary death, any non-fatal or fatal stroke, coronary or non-coronary artery surgery or angioplasty.

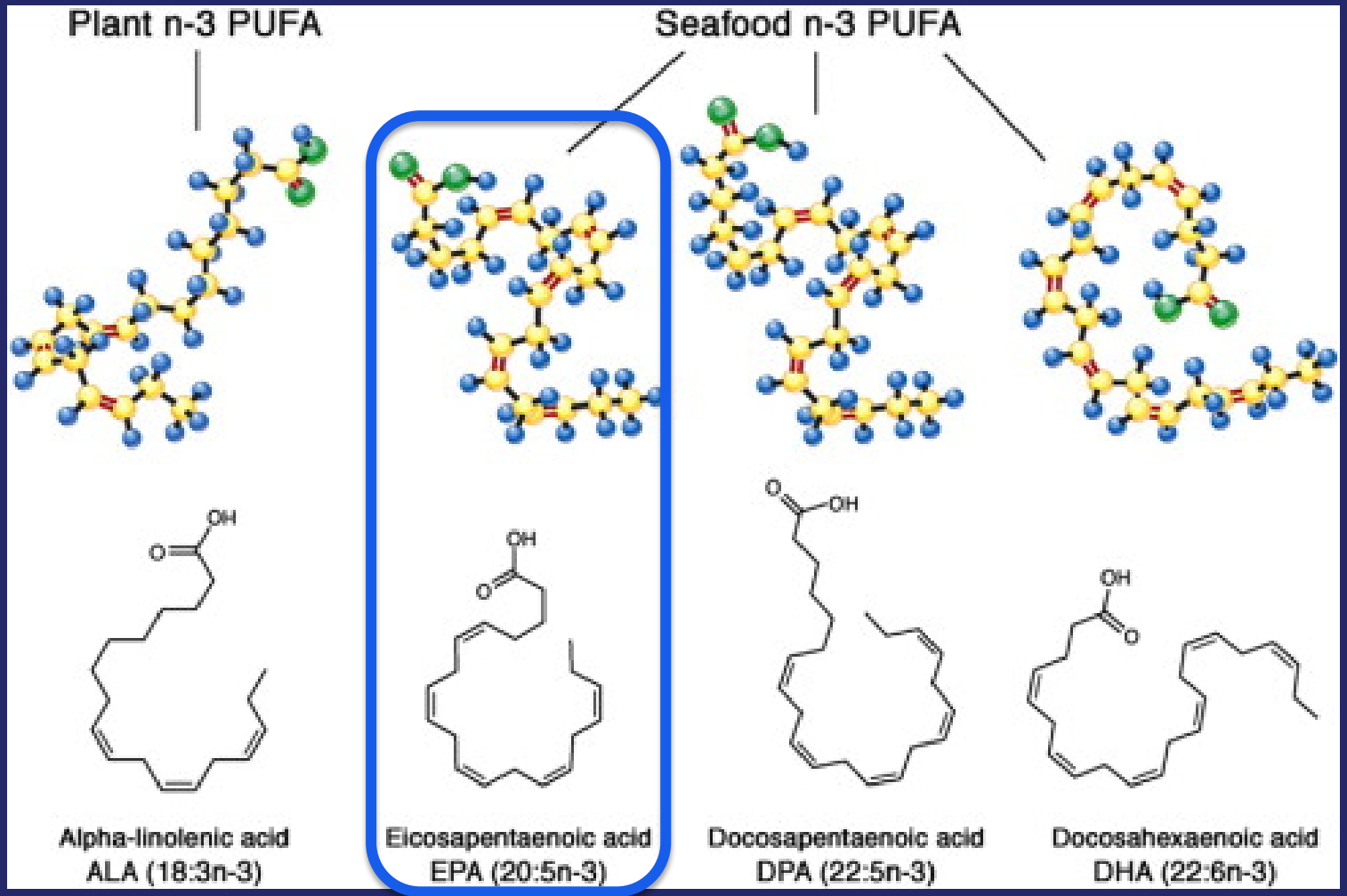
Presented at: ACC.13: American College of Cardiology 62nd Annual Scientific Session. Available at: http://www.thrivestudy.org/

Effect of ERN / LRPT on SERIOUS AEs (Median Follow-up 3.9 yrs)



HPS2-THRIVE
Available at: http://www.thrivestudy.org/

OM-3 FA Molecular Structure



Adapted from Mozafarian D, Wu JH. *J Am Coll Cardiol*. 2011;58:2047-67.

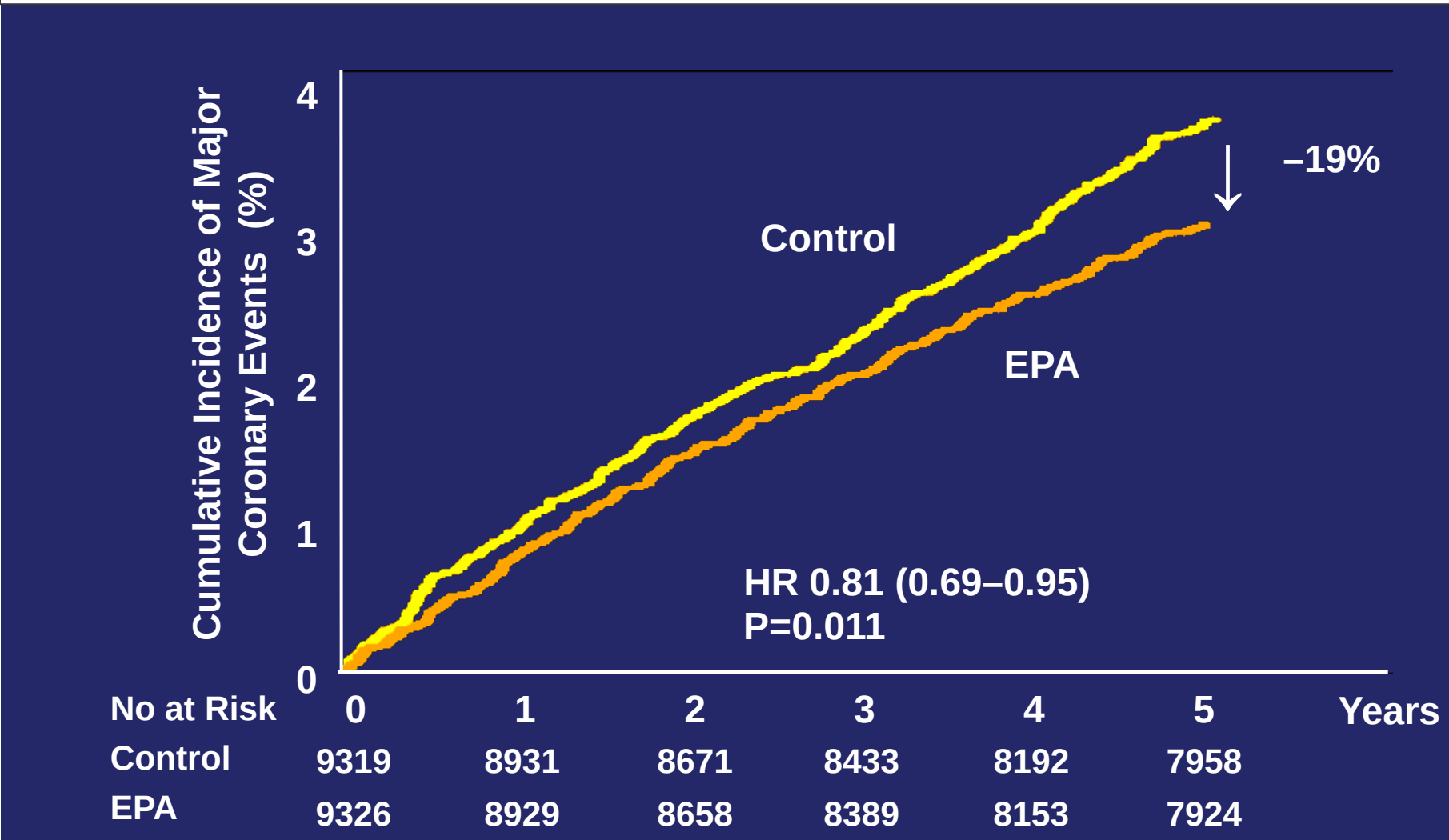
Select OM-3 Outcomes Studies

	GISSI-P[1-2]	ORIGIN[3]	JELIS[4]	REDUCE-IT[5] (Ongoing)
OM-3 Type/dose	**EPA/DHA 1 g/day[2]**	**EPA/DHA 1 g/day**	**EPA 1.8 g/day**	**EPA 4 g/day**
Population	Italian	International	Japanese	International
N	11,324	12,536	18,645	~8,000
Gender	85% male	65% male	31% male	Accrual ongoing
Risk Profile	Recent MI (≤3 mos; median 16 days)	High CV risk, and IFG, IGT, or T2DM	80% 1° prev; TC ≥6.5 mM; excl MI ≤6 mos prior	TG >150 mg/dL +CHD or ↑CHD risk
Follow-up	3.5 years	6.2 years (median)	4.6 years (mean)	4–6 years (planned)
Statin Use	Minimal	53% in n-3 FA arm, 55% in pbo arm	All on statins (simvastatin or pravastatin)	All on background statins (LDL-C goal)
Primary Endpoint	All-cause death, NF MI, NF stroke	Death from CV causes	MACE	MACE
Result	**RRR 10% (P=0.048)/ 15% (P=0.023)**	**HR 0.98 P=0.72**	**RRR 19% (no minimum TG level) P=0.011**	**Powered for 15% RRR**
LDL-C	↑2%–3% >control groups	↓12% both arms	↓25% in both groups	–

The results of these trials should not be compared across these individual studies.

[1]GISSI-Prevenzione Investigators. *Lancet*. 1999;354:447-55. [2]www.trialresultscenter.org/study4440-GISSI-P.htm. [3]ORIGIN Investigators. *N Engl J Med*. 2012;367:309-18. [4]Yokoyama M et al. *Lancet.* 2007;369:1090-8. [5]http://www.clinicaltrials.gov. excl=excluded; GISSI=Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; IFG=impaired fasting glucose; IGT=impaired glucose tolerance; JELIS=Japan EPA Lipid Intervention Study; MACE=major adverse cardiac event; mos=months; NF=non-fatal; ORIGIN=Outcome Reduction with an Initial Glargine Intervention; pbo=placebo; prev=prevention; REDUCE-IT=Reduction of Cardiovascular Events with EPA-Intervention Trial; RRR=relative risk reduction.

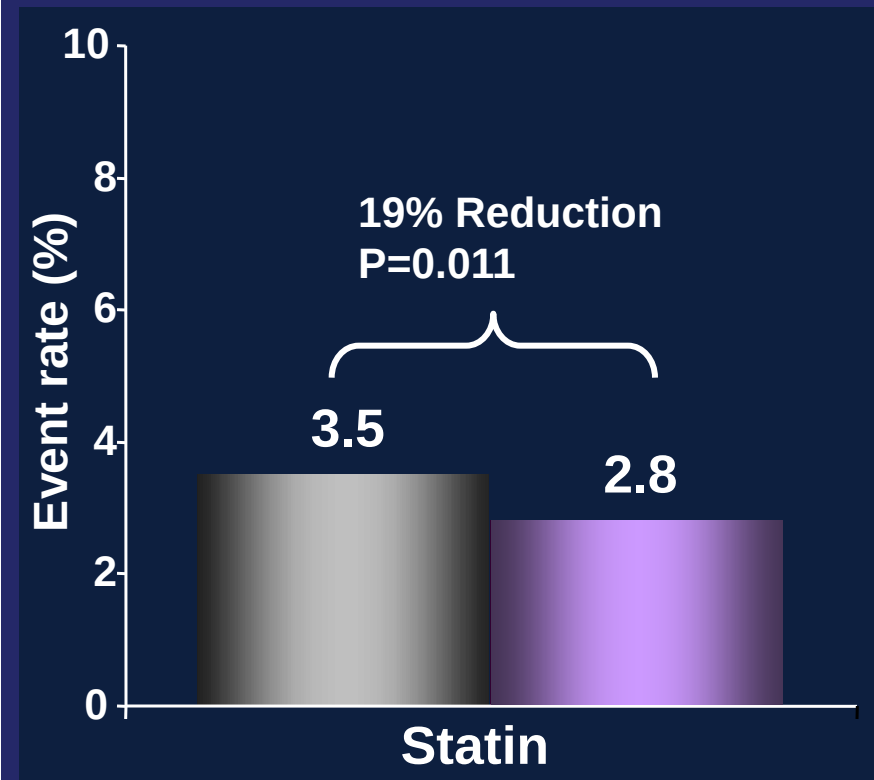
JELIS: Kaplan-Meier Estimates of Major Coronary Events



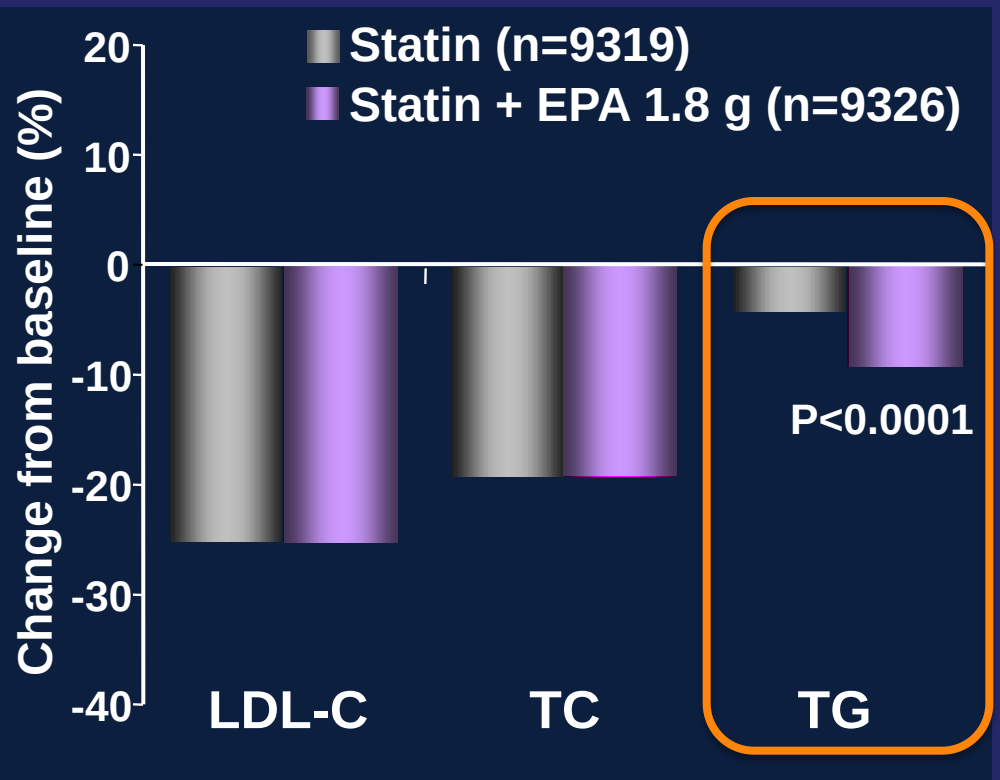
Yokoyama M et al. *Lancet.* 2007;369:1090-8.

Addition of EPA to Statin Therapy in Japanese Patients

Major CHD Events*



Lipid Effects

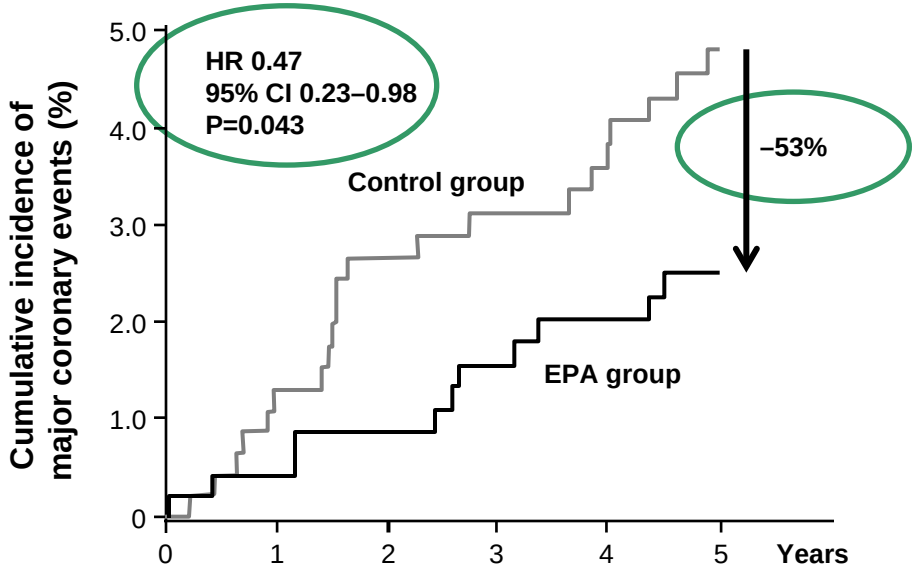


*Sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or coronary artery bypass graft (CABG).

Yokoyama M et al. *Lancet.* 2007;369:1090-8.

Patient Subgroup – TG >150 mg/dL and HDL-C <40 mg/dL: JELIS

Effects of EPA on CAD in HTG patients with multiple RFs: Sub-analysis of primary prevention cases from JELIS



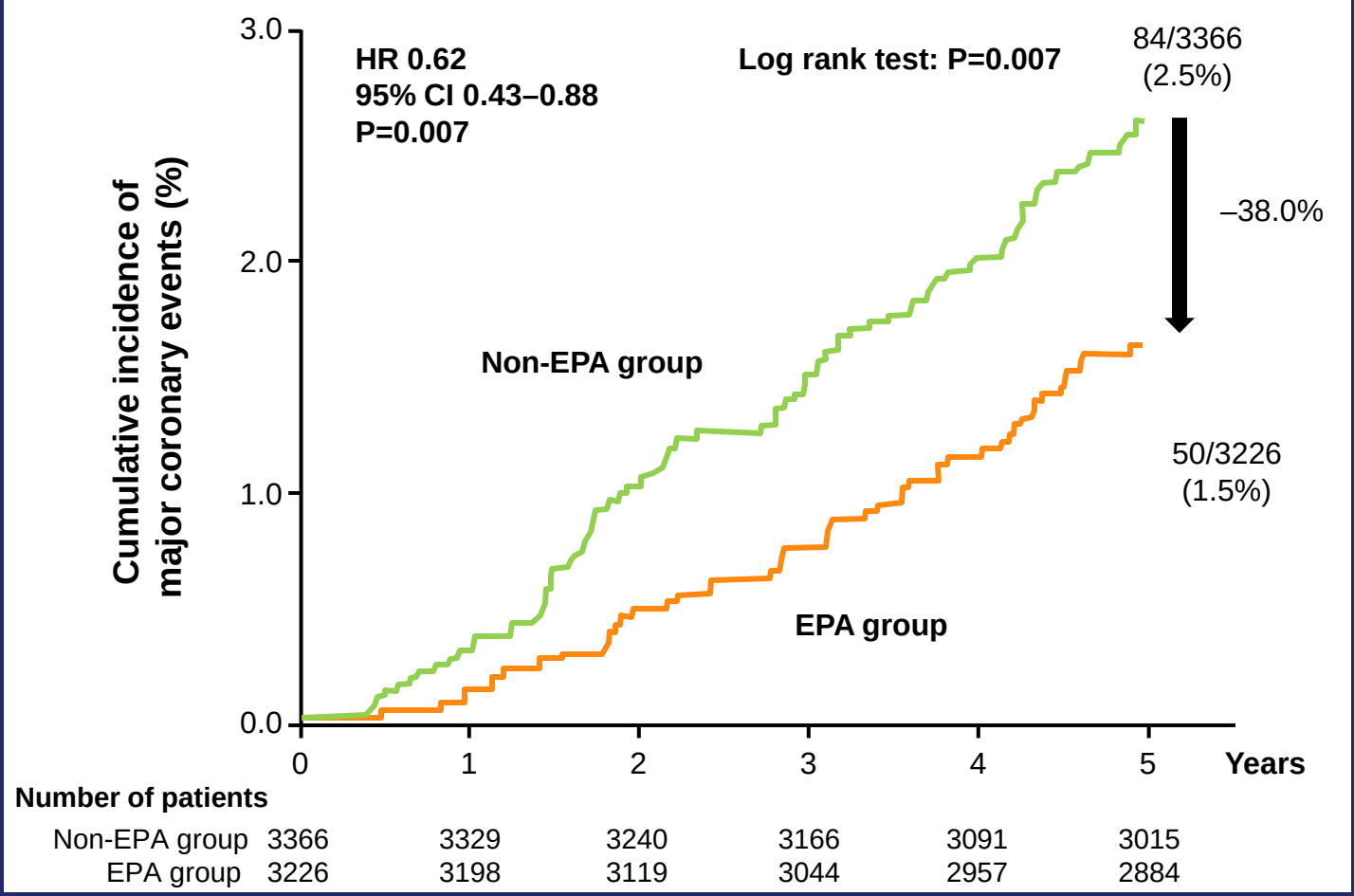
Effects of EPA on incidence of major coronary events for high TG / low HDL-C group

HR and P-value adjusted for age, gender, smoking, diabetes, and HTN

CAD=coronary artery disease; RFs=risk factors. Saito Y et al. *Atherosclerosis*. 2008;200:135-40.

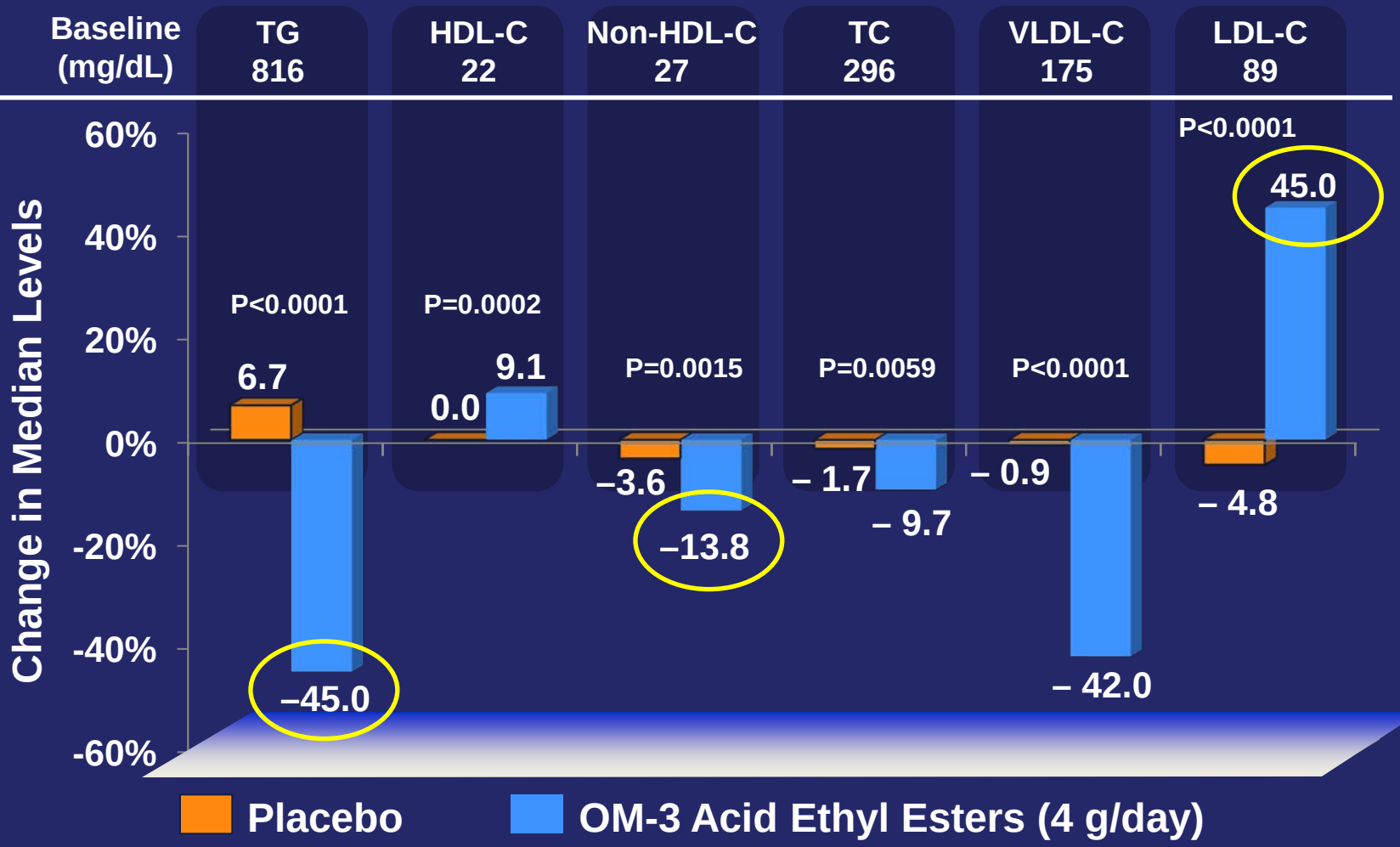
JELIS: Subanalysis

EPA Reduces the Risk of CAD in Patients with High Levels of Non-HDL-C and/or LDL-C



Sasaki J et al. *J Atheroscler Thromb*. 2012;19:194-204.

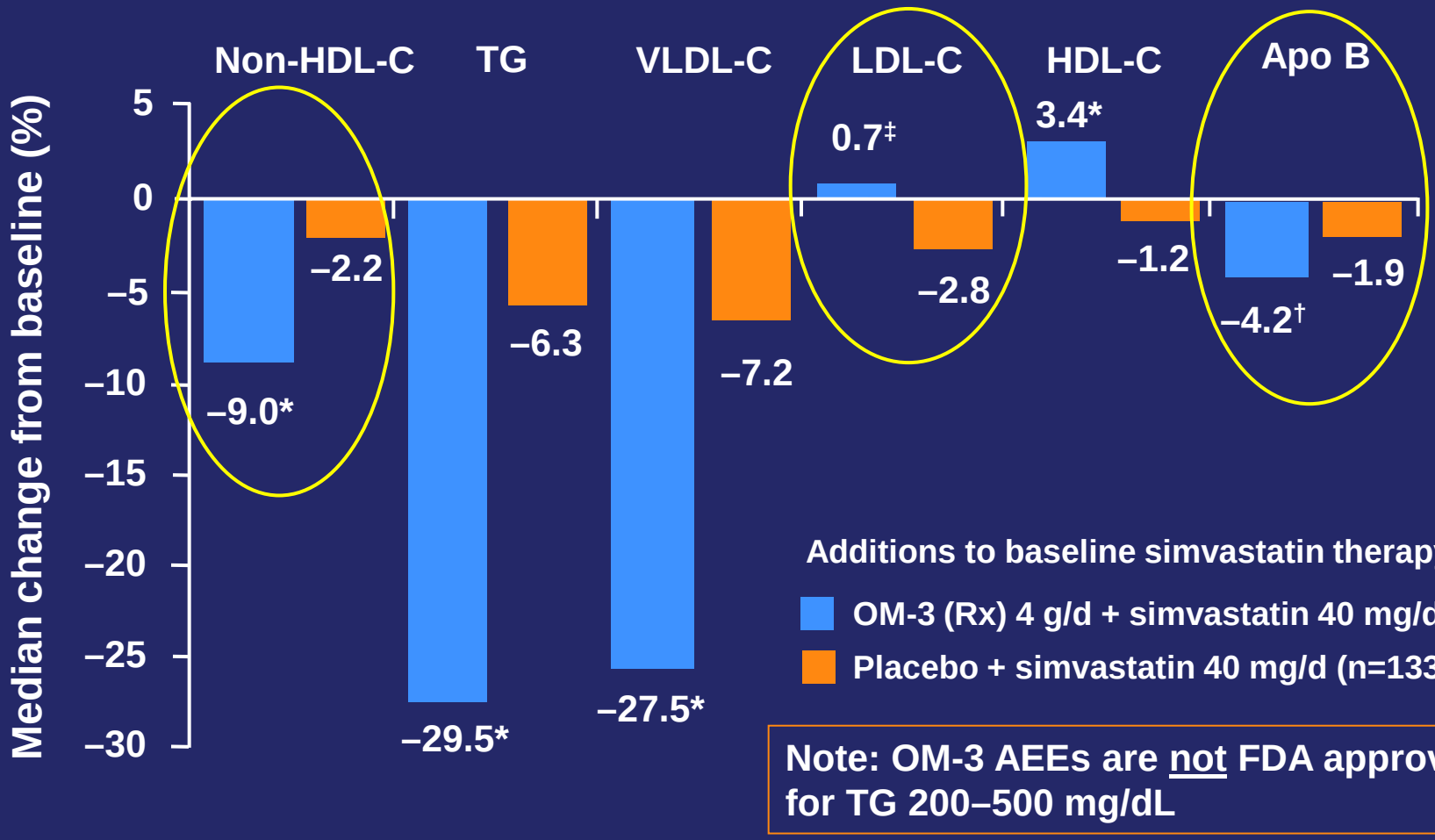
OM-3 Acid EPA+DHA and Lipid Levels in Patients with TG >500 mg/dL



Pooled analysis (N=82).

Harris WS et al. *J Cardiovasc Risk* 1997;4:385-91 and Pownall HJ et al. *Atherosclerosis* 1999;143:285-97.

Statin + EPA+DHA OM-3: COMBOS Primary and Secondary Efficacy Results

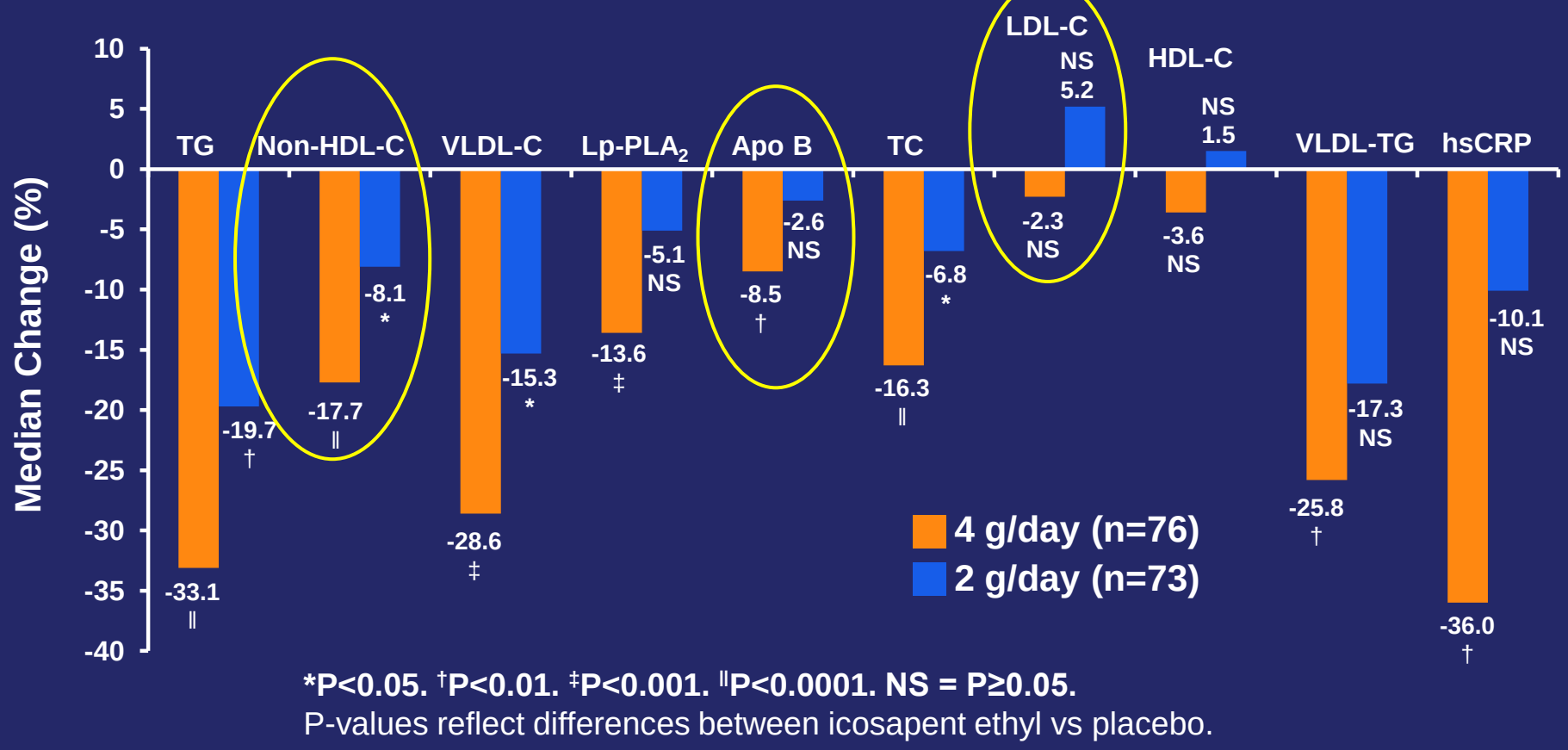


***P<0.0001 between groups. †P=0.0232 between groups. ‡P=0.0522 between groups.**

AEEs=acid ethyl esters; COMBOS=Combination of Prescription Omega-3 with Simvastatin.

Davidson MH et al. *Clin Ther*. 2007;29:1354-67.

MARINE: Icosapent Ethyl (Pure EPA): Median Placebo-Adjusted Change from Baseline for Efficacy Endpoints

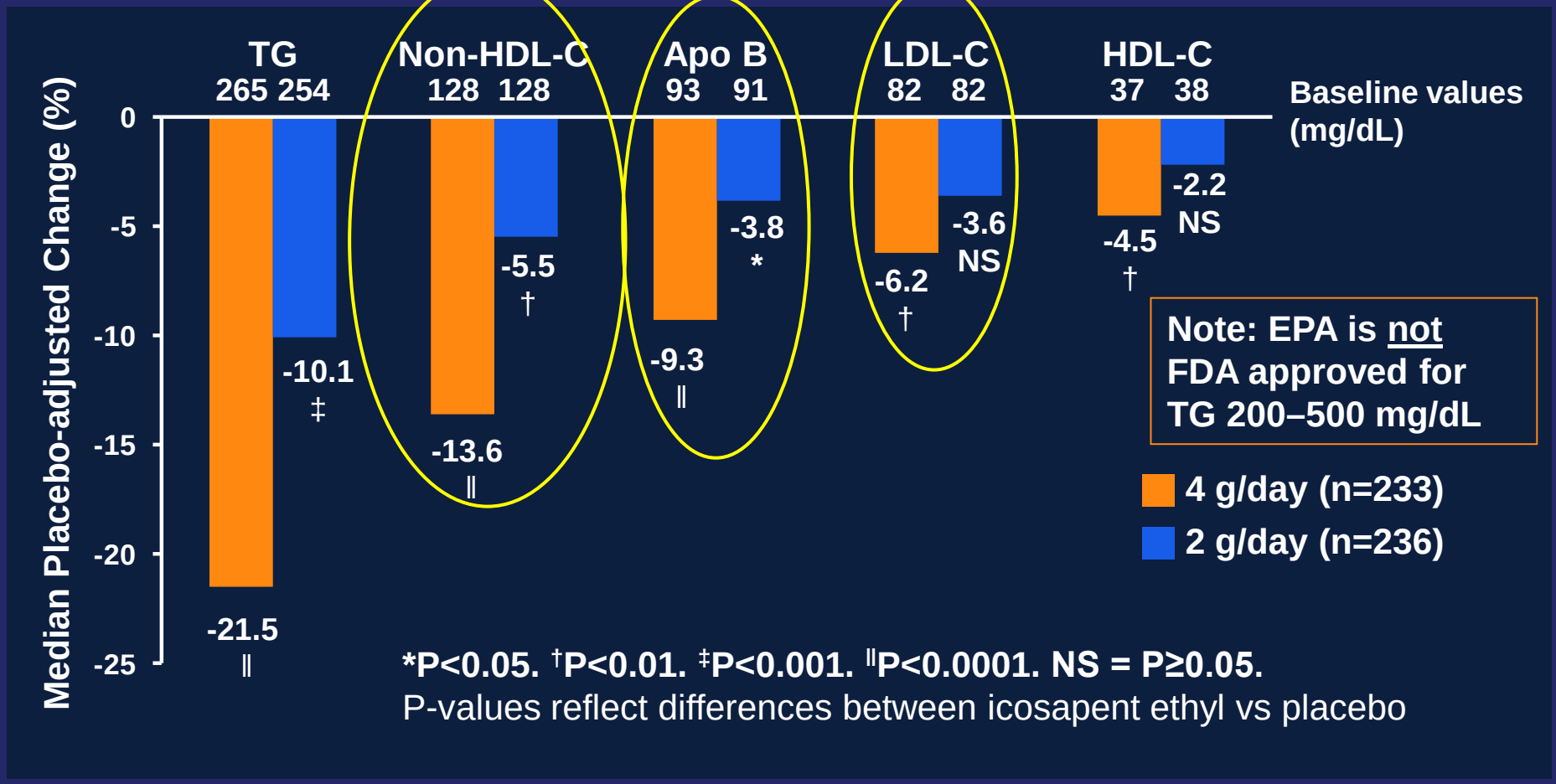


***P<0.05. †P<0.01. ‡P<0.001. ‖P<0.0001. NS = P≥0.05.**
P-values reflect differences between icosapent ethyl vs placebo.

Apo=apolipoprotein; hsCRP=high-sensitivity C-reactive protein; ITT=intention to treat; Lp-PLA=lipoprotein-associated phospholipase A; MARINE=Multi-center, Placebo-controlled, Randomized, Double-blind, 12-week Study with an Open-label Extension. Bays HE et al. *Am J Cardiol*. 2011;108:682-90. Bays HE et al. Paper presented at: European Society of Cardiology (ESC) Congress 2011; August 29, 2011; Paris, France.

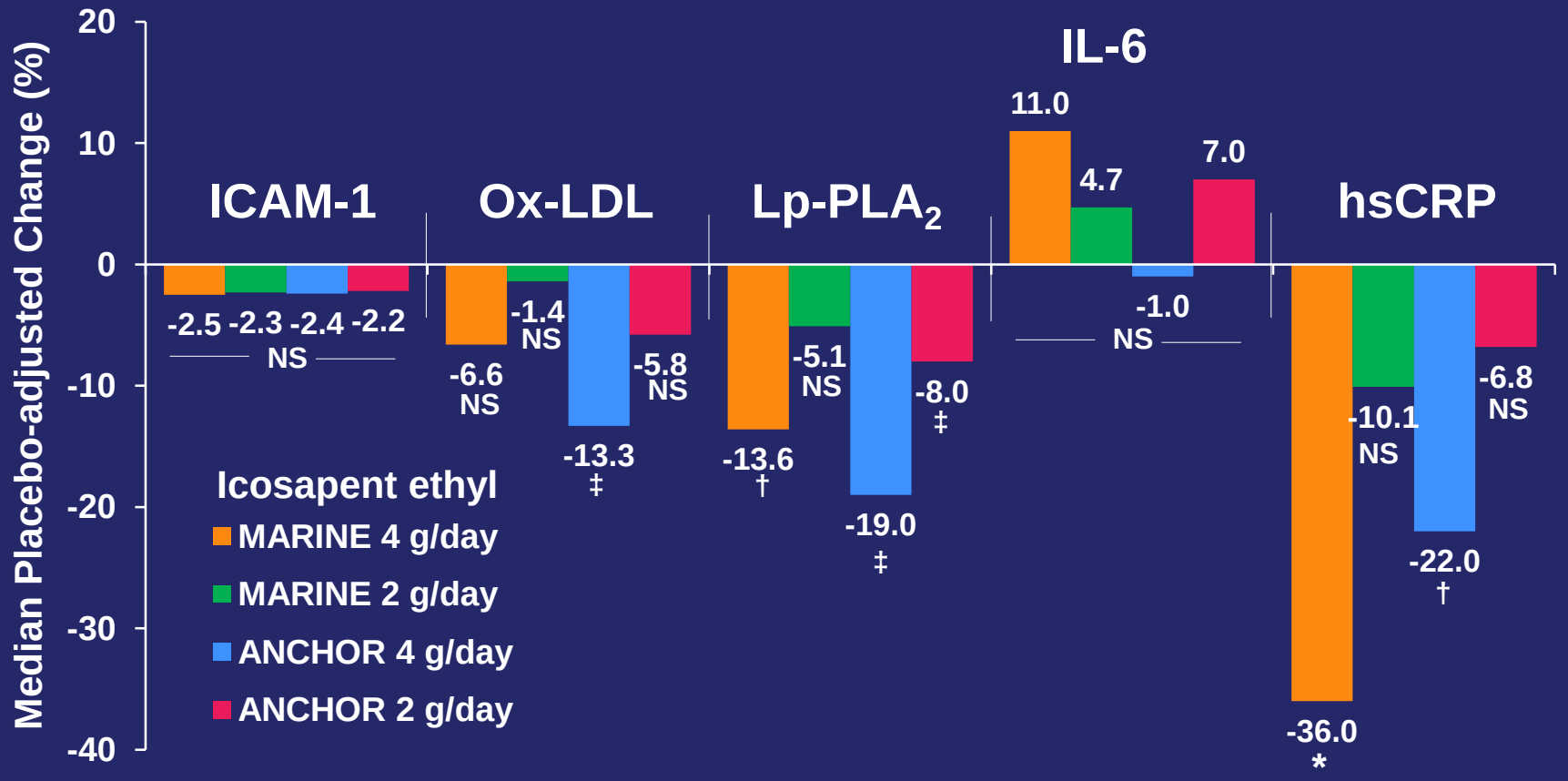
ANCHOR: Icosapent Ethyl (Pure EPA): Median Placebo-Adjusted Change from Baseline for Efficacy Endpoints

The ANCHOR Study: TG ≥200 and <500 mg/dL



12-week trial in high-risk statin-treated patients (N=702) with residually ↑TG levels (≥200 and <500 mg/dL) despite LDL-C control (≥40 and <100 mg/dL). ANCHOR=Effect of AMR101 (Ethyl Icosapentate) on Triglyceride (Tg) Levels in Patients on Statins With High Tg Levels (≥200 and <500 mg/dL). Ballantyne CM et al. *Am J Cardiol*. 2012;110:984-92.

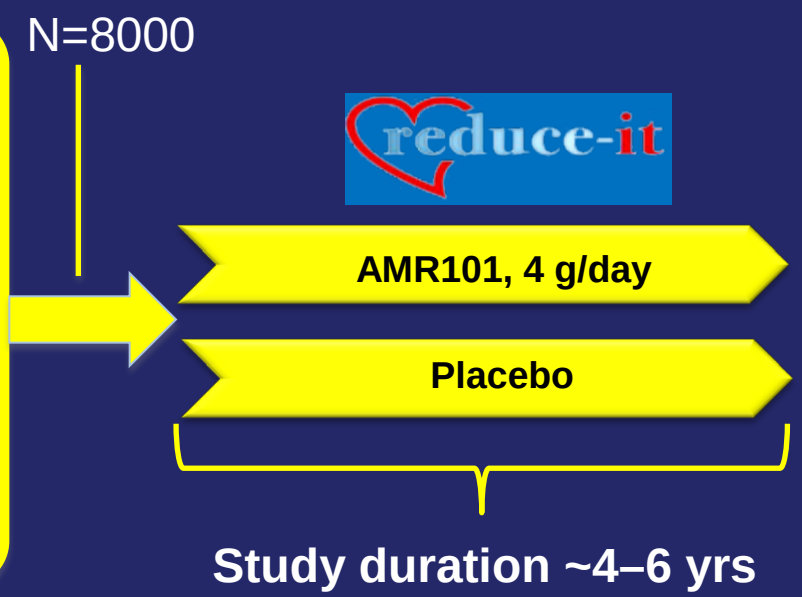
Effect of Icosapent Ethyl on Markers of Inflammation



*P<0.01; †P<0.001; ‡P<0.0001 vs placebo.
ICAM= intercellular adhesion molecule; IL=interleukin; Ox-LDL=oxidized LDL.
Bays HE et al. *Am J Cardiovasc Drugs*. 2013;13:37-40.

Reduction of CV Events with EPA – Intervention Trial

- **Men & women ≥45 yo**
- **Prior CHD (70% patients) or T2DM + ≥1 RF**
- **Atherogenic dyslipidemia:**
  - **Hx of ↑TC (at LDL-C goal on statin)**
  - **TG 150–500 mg/dL**



Primary endpoint: Prevention of 1st major CV event

- Randomized, double-blind, parallel group design
- Secondary outcome measures: Incidence of additional CV events, lipid and lipoprotein levels, subgroup analyses such as diabetes, etc.
- Multinational trial
- Anticipated completion 2016

AMR101=icosapent ethyl

Hx=history; yo=years old.

National Institutes of Health (NIH) website. http://clinicaltrials.gov/ct2/show/NCT01492361?term=REDUCE-IT&rank=1

Approximate Levels of EPA and DHA Through Dietary Intake of Fish

Fish	EPA plus DHA (mg/100 g eaten)
Salmon Atlantic wild	1,840
Salmon Atlantic farmed	2,150
Salmon Chinook	1,740
Salmon Coho wild	1,060
Salmon Coho farmed	1,280
Herring Atlantic	2,000
Herring Pacific	2,130
Mackerel Pacific and jack	1,850
Mackerel Atlantic	1,200
Mackerel king	400
Halibut Atlantic and Pacific	470
Halibut Greenland	1,180
Tuna bluefin	1,500
Tuna yellowfin	280
Tuna skipjack	300
Bluefish	990
Pollock Alaskan	120‡
Cod Atlantic	160
Cod Pacific	280
Sablefish (black cod)†	1,790
Bass sea	760
Bass freshwater	760
Whitefish	1,610
Trout rainbow wild	990
Trout rainbow farmed	1,150

Approximate levels of EPA and DHA in dry-heat cooked fish*

100 g ≈ 3.5 oz, or ~¾ cup of flaked fish

*Cooked fish (dry heat) often has less OM-3 fatty acid content than raw fish: 100 g of fish would be ~4 oz, which would be a bit larger than a deck of playing cards. The amount of OM-3 FAs varies considerably in the same type of fish, depending on the environment and location.

†Sablefish or “black cod” is not part of the codfish family.

‡Alaskan Pollock is the fish used in many fast-food restaurants, where it is usually battered and fried.

Bays HE. *Drugs Today (Barc).* 2008;44:205-46.

Prescription-Only OM-3s vs Dietary Supplement OM-3s

	OM-3 acid ethyl esters	Icosapent ethyl	Dietary Supplements
FDA product classification	Drug	Drug	Food
FDA approval	Yes	Yes	No
Ingredients	DHA + EPA	EPA	Variable amounts of DHA + EPA (may include other PUFAs)
Quantity of OM-3 per capsule	1 g	1 g	Typically 300 mg – 800 mg EPA & DHA Typically 100 – 400 EPA
Capsules/day to achieve 4g OM-3	4	4	Typically 5 – 13 for EPA & DHA Typically 10 – 40 EPA
Recommended dose	4 g/day	4 g/day	In patients with CHD: Consume ~1 g of EPA+DHA per day, preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician. In patients requiring TG lowering: 2–4 grams of EPA+DHA per day provided as capsules under a physician's care When using prescription OM-3 agents to reduce TG levels: 4 grams of OM-3 FAs per day
Tested in clinical trials	Yes	Yes	Not required

New Drugs in Triglyceride Metabolism

- Variety of targets
  - Fish oil – purified EPA
  - DGAT inhibition
  - MTP inhibition
  - PPAR agonists
  - Gene therapy
- Complex pathways, multiple candidates
- Hepatic, gut and periphery
- Efficacy (outcomes) and safety remain under investigation

DGAT=diacylglycerol acyl transferases; MTP=microsomal triglyceride transfer protein;
PPAR= peroxisome proliferator-activated receptor.

Role of Pharmacist: What to Tell Patients

- The vast majority of patients need statin therapy to reduce the risk of CVD
  - LDL elevations
  - Mixed dyslipidemias
- The addition of niacin or fibrate to statin therapy has not demonstrated additional CVD prevention
  - Mixed dyslipidemia subgroup?
- OM-3 fish oil-based fatty acids underutilized as a TG-reducing therapy and show mixed results in reducing CVD events
  - Ongoing REDUCE-IT trial in patients with TG 150–500 mg/dL
  - Prescription OM-3 products have advantages in purity, consistency of content and FDA-required testing