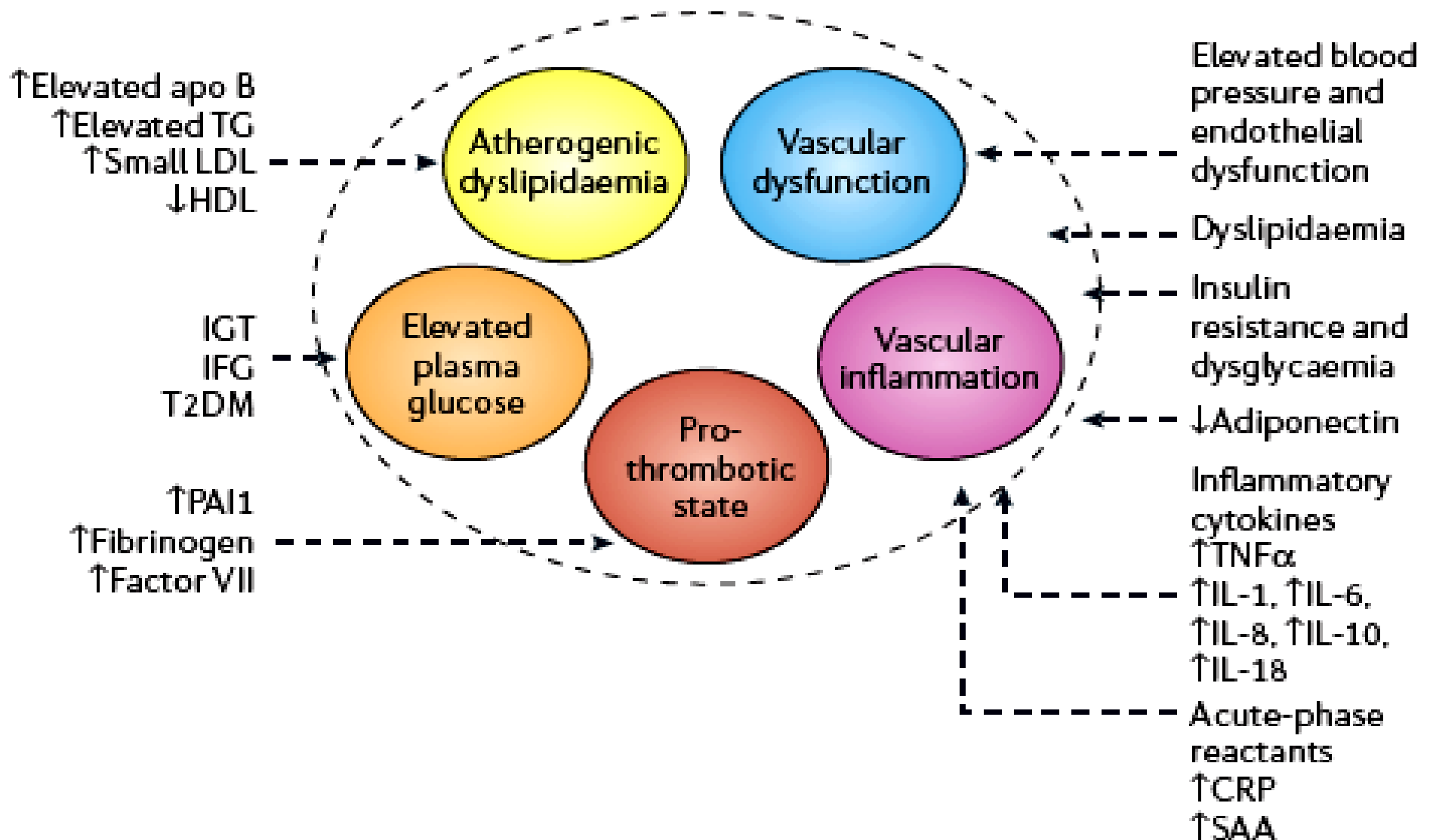


Update On Diabetic Dyslipidemia: Who Should Be Treated With A Fibrate After ACCORD-LIPID?



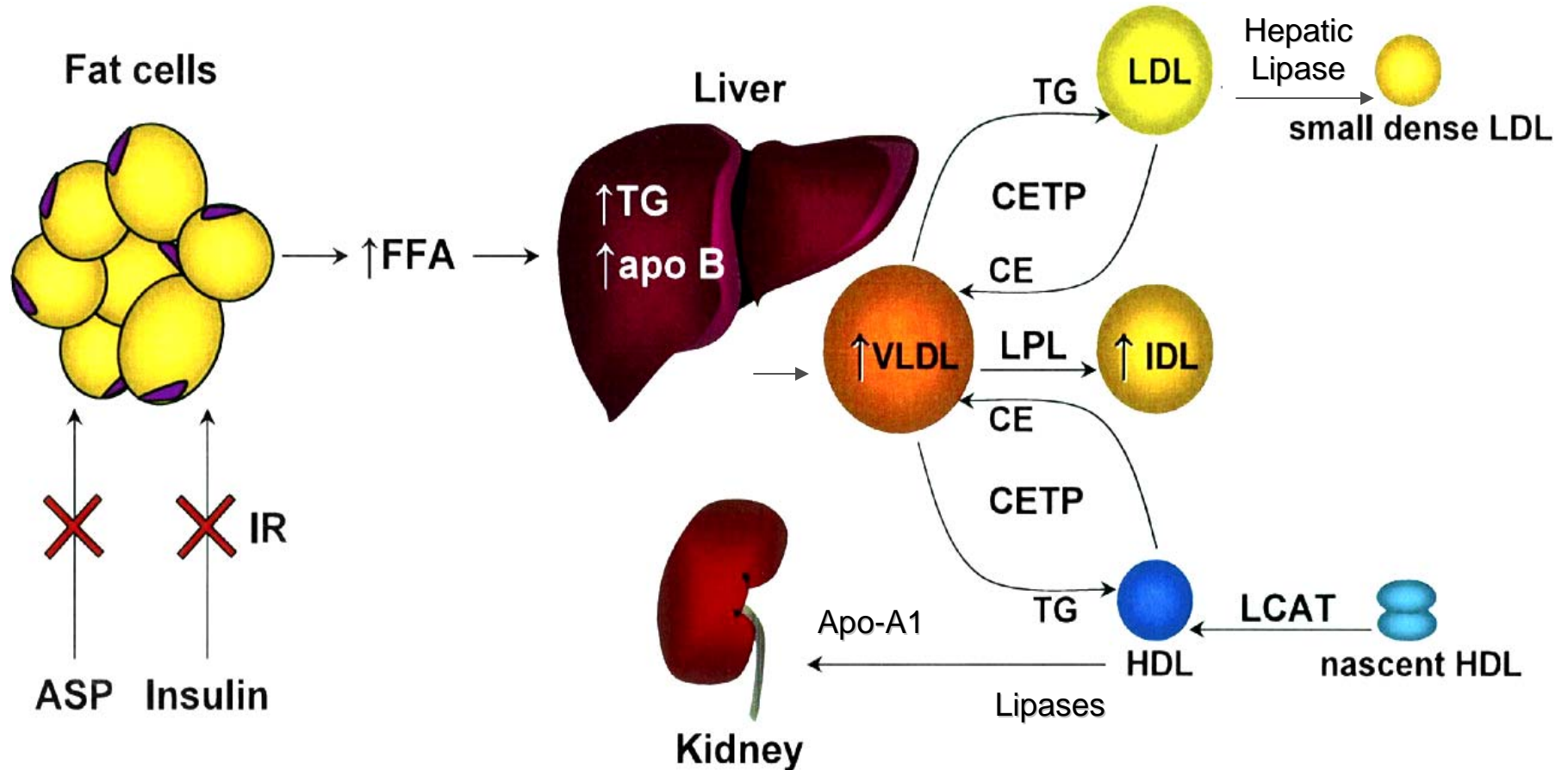
Karen Aspary, MD, MS, ABCL, FACC
Assistant Clinical Professor of Medicine
Warren Alpert Medical School of Brown University

Insulin Resistance Creates A Dyslipidemic, Inflammatory, and Pro-Thrombotic State



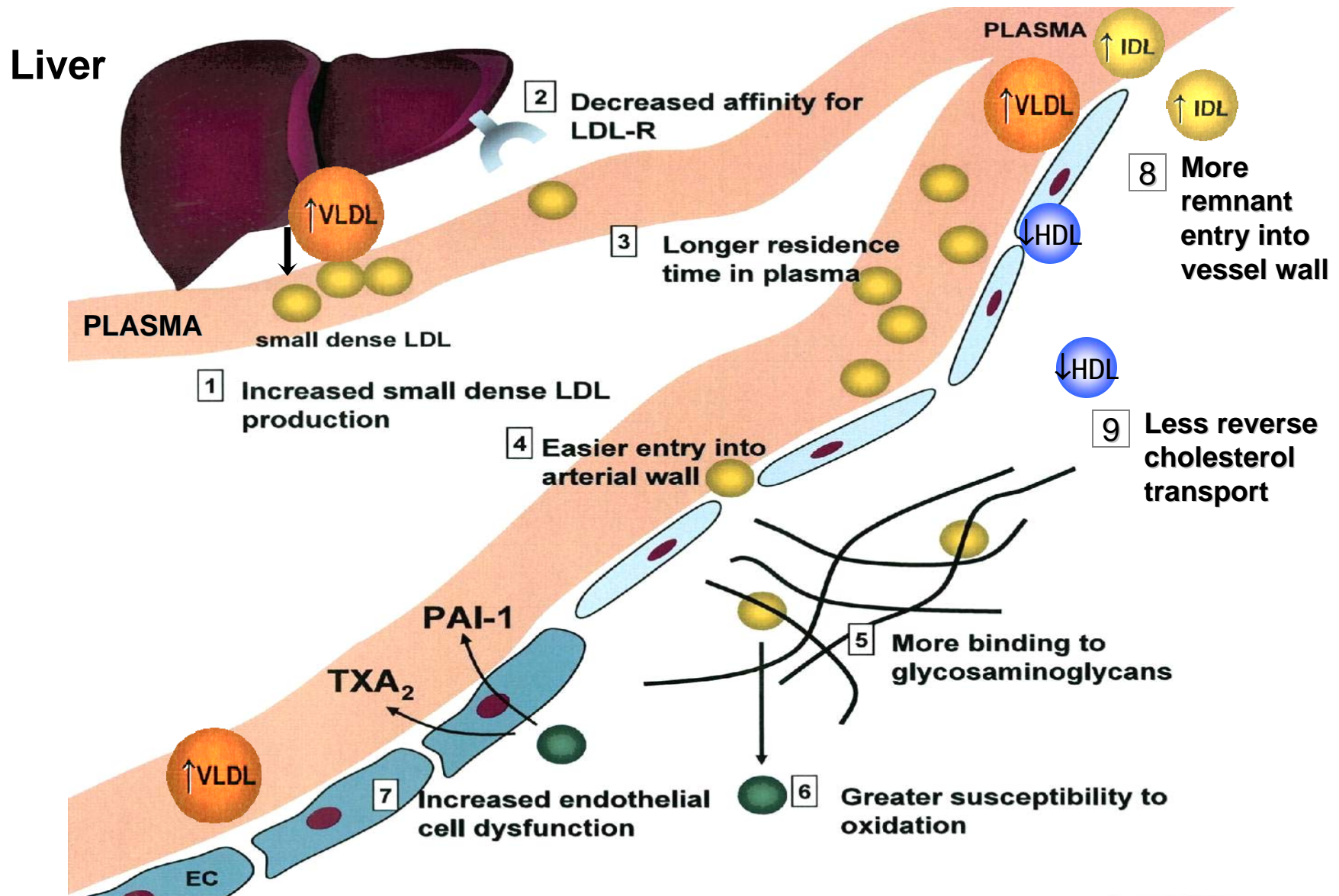
From Grundy, S. Nature Reviews 2006;5:295-309.

The Atherogenic Dyslipidemia of Insulin Resistance is a “Lipid Triad” of High TGs, Small Dense LDL and Low HDL



CETP = Cholesterol ester transfer protein

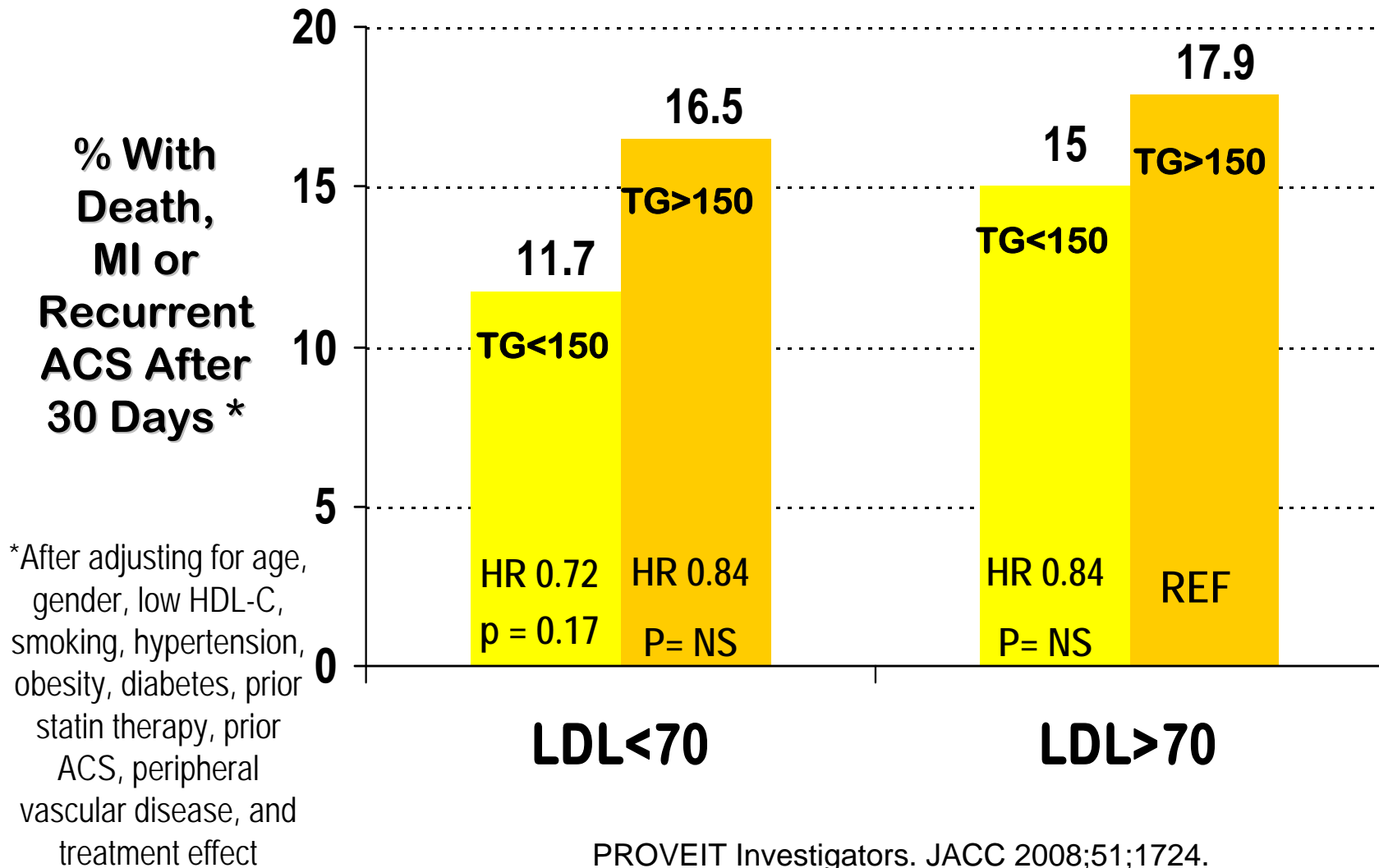
The Lipid Triad Accelerates Atherosclerosis via Multiple Mechanisms



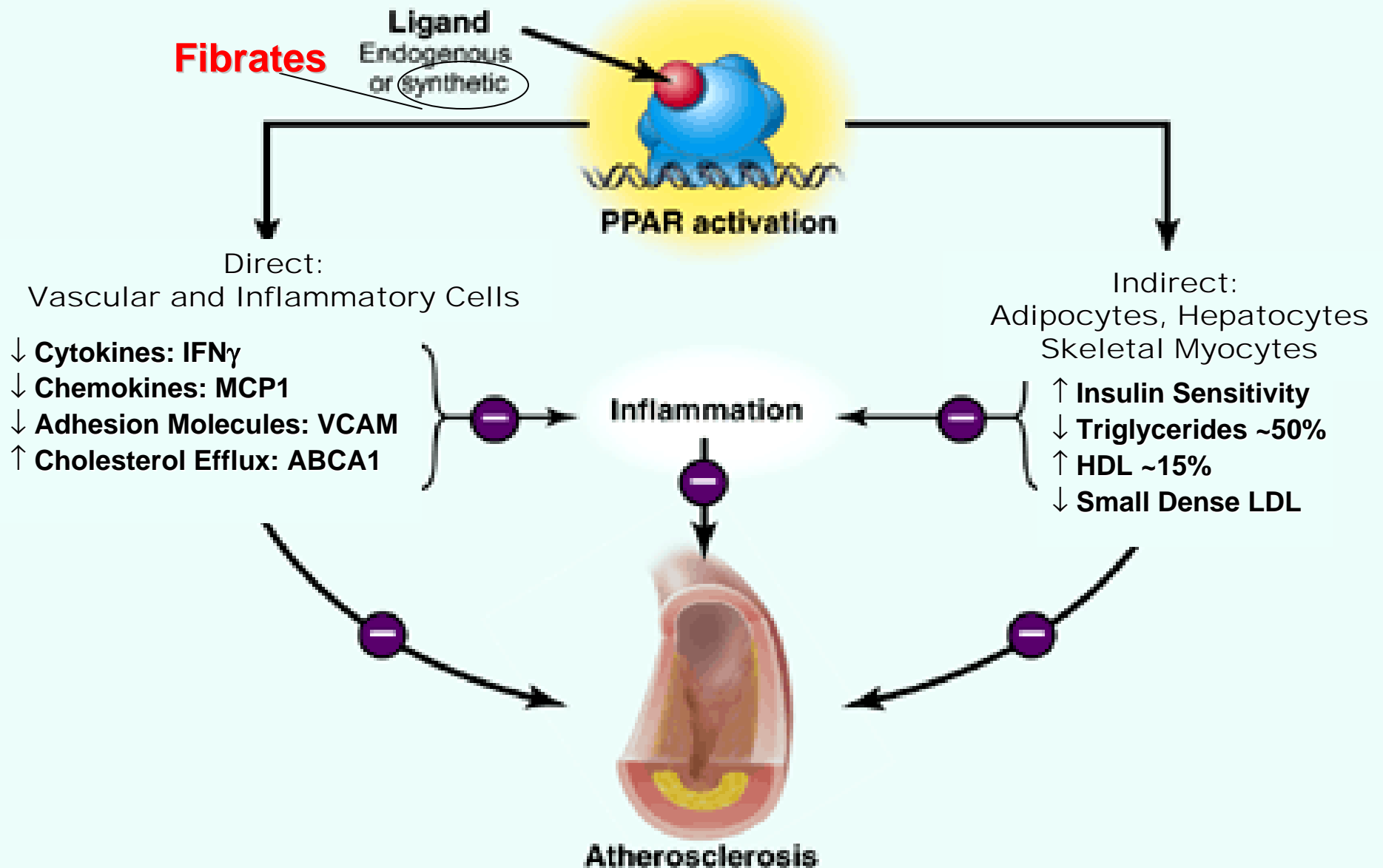
Modified from: Mudd, J. O. et al. JACC 2007;50:1735-1741

CHD Risk from Elevated TGs Persists Even When LDL is Lowered to <70 mg/dl

Sub-Group Analysis from PROVE-IT - 2008



Fibrates Improve High TGs, Low HDL and Vascular Inflammation via PPAR- α Activation

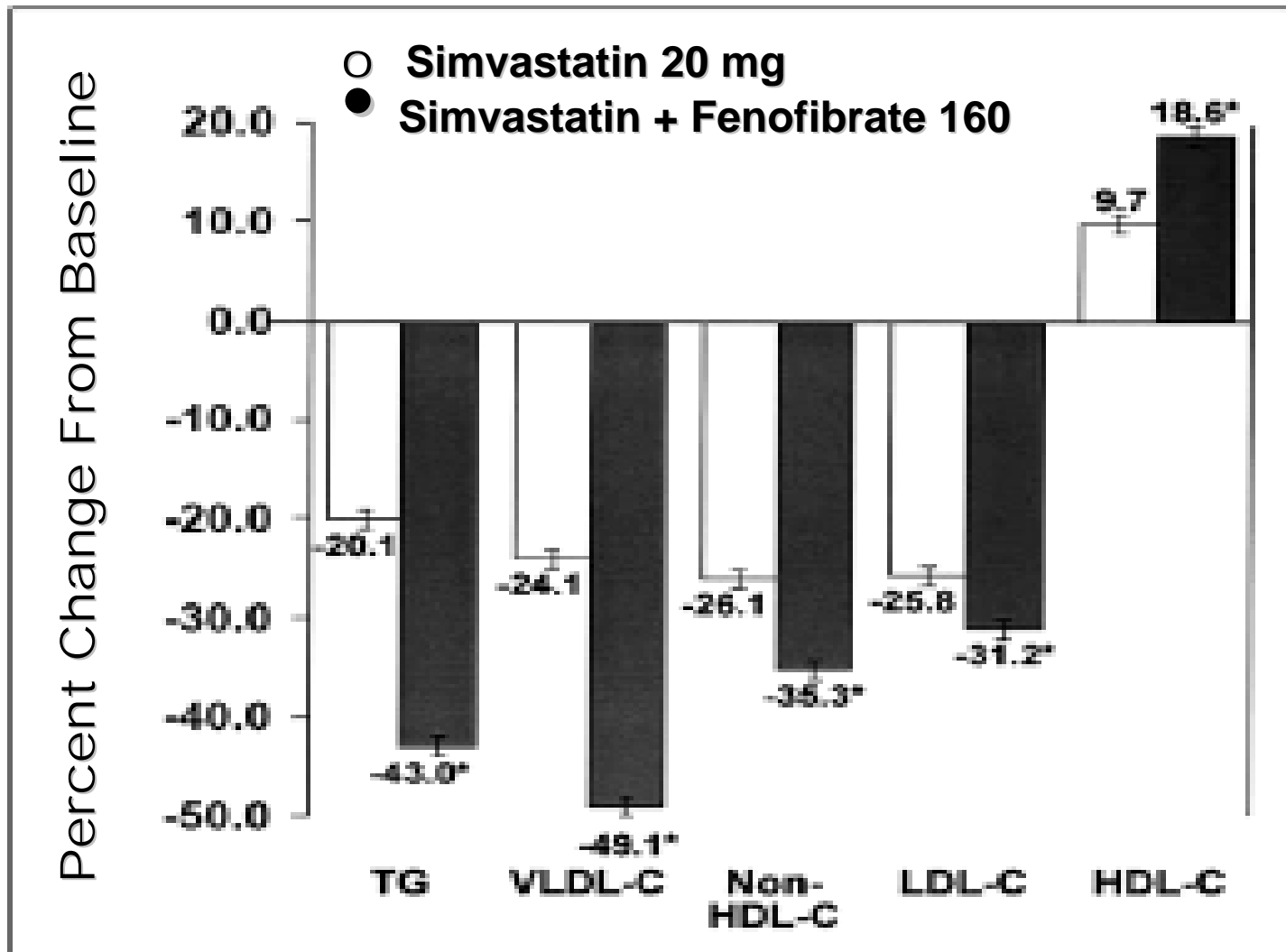


Lipid Effects of Fibrates

- **Decrease in TGs of ~ 50%**
- **Increase in HDL-C of ~ 15%**
- **Decrease in Apoprotein-B**
- **Increase in LDL particle size**
- **Decrease in LDL particle number**

Fenofibrate Added to Simvastatin Significantly Improves Dyslipidemia

Results From the SAFARI Trial - 2005

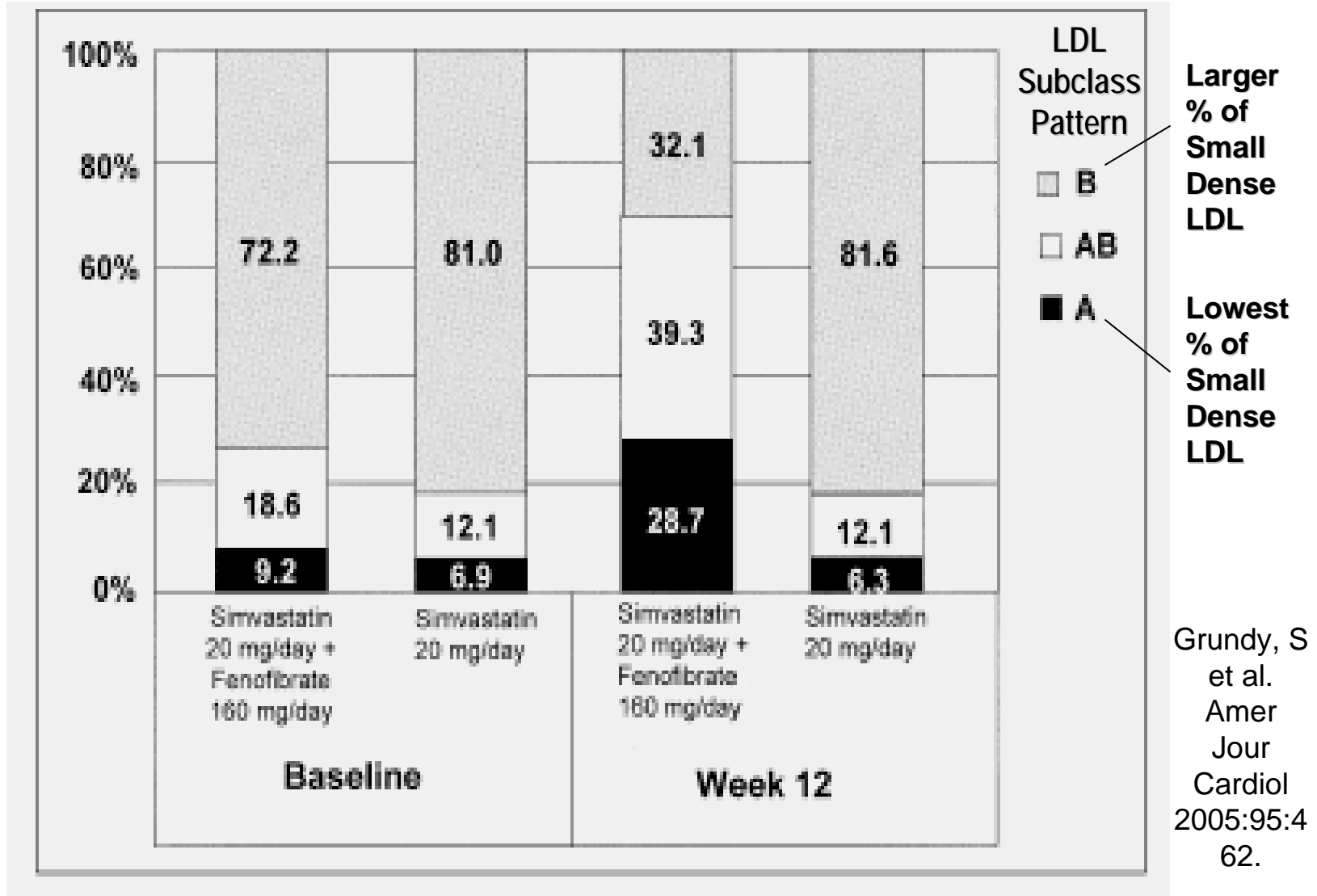


n=618
*P=.001

Grundy, S
et al.
Amer
Jour
Cardiol
2005;95:4
62.

Fenofibrate Added to Simvastatin Favorably Shifts LDL Subclass Pattern

Results From the SAFARI Trial - 2005



Design of the ACCORD-Lipid Study

Hypothesis

Statin-fibrate therapy is superior to statin monotherapy for reducing CV events in patients with DM 2

Patients

5,518 Men + Women with DM 2 and HgA1C $\geq 7.5\%$

Design

Simvastatin 20mg + Fenofibrate 160mg
vs. Simvastatin 20mg + Placebo

Follow Up

4.7 Years

Primary Endpoint

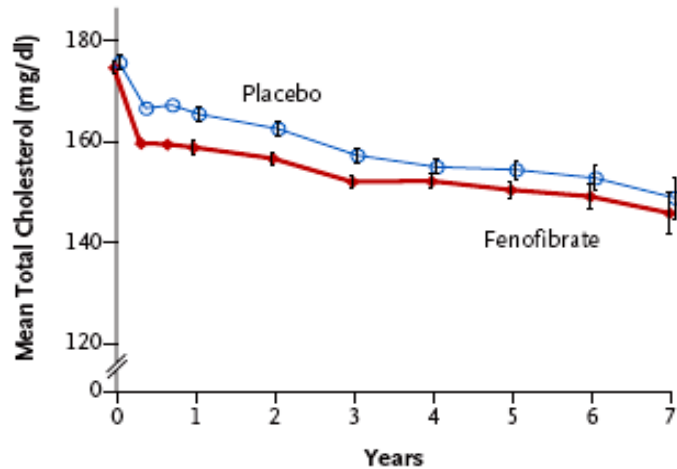
First non-fatal MI, non-fatal CVA or death from CV disease

Baseline Characteristics of ACCORD Subjects

Characteristic	All Patients
Age, mean	62.3 yrs
BMI	32.3
Duration of DM, yrs, median	9
HgA1c, mean	8.3%
FBS, mg/dl, mean	175.8
GFR>50ml/min/BSA	97%
Total Chol, mg/dl	175
LDL, mg/dl	100.6
HDL, mg/dl	38
TG, median	162

Lipid Results From ACCORD

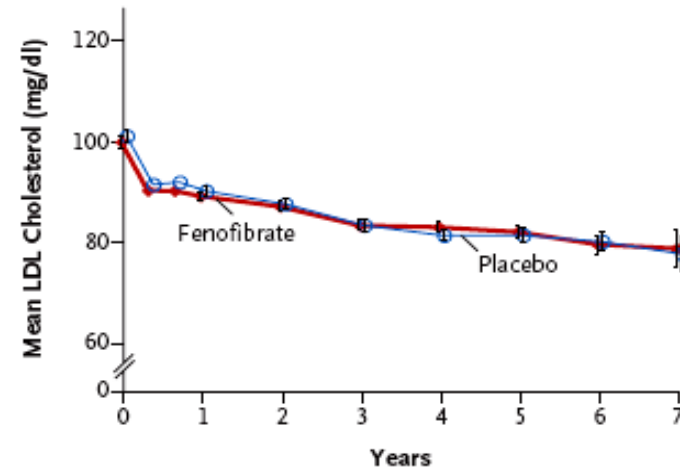
Change in Total Cholesterol



No. of Patients

Fenofibrate	2747	2593	2505	2417	2361	1478	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

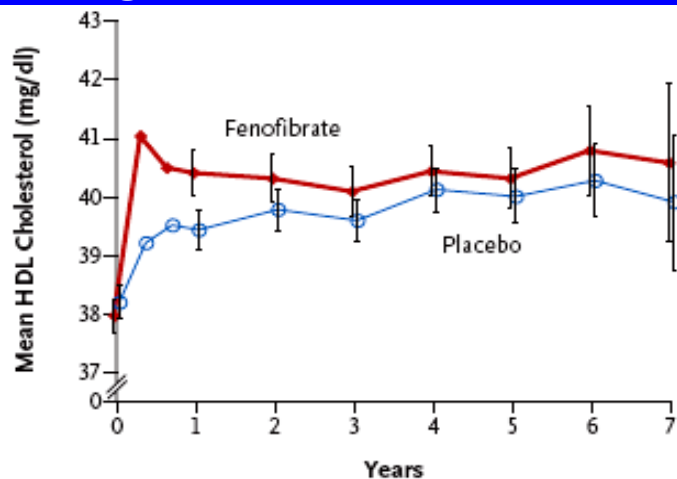
Change in LDL Cholesterol



No. of Patients

Fenofibrate	2747	2593	2505	2417	2361	1477	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

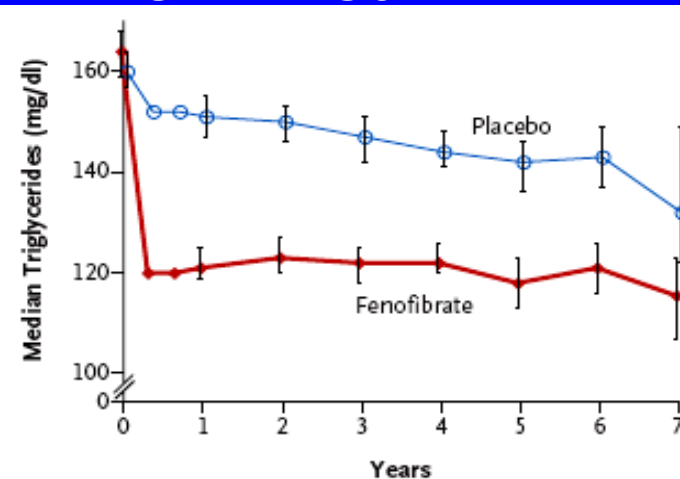
Change in HDL Cholesterol



No. of Patients

Fenofibrate	2747	2593	2505	2417	2361	1477	796	248
Placebo	2736	2591	2484	2375	2364	1480	801	243

Change in Triglycerides

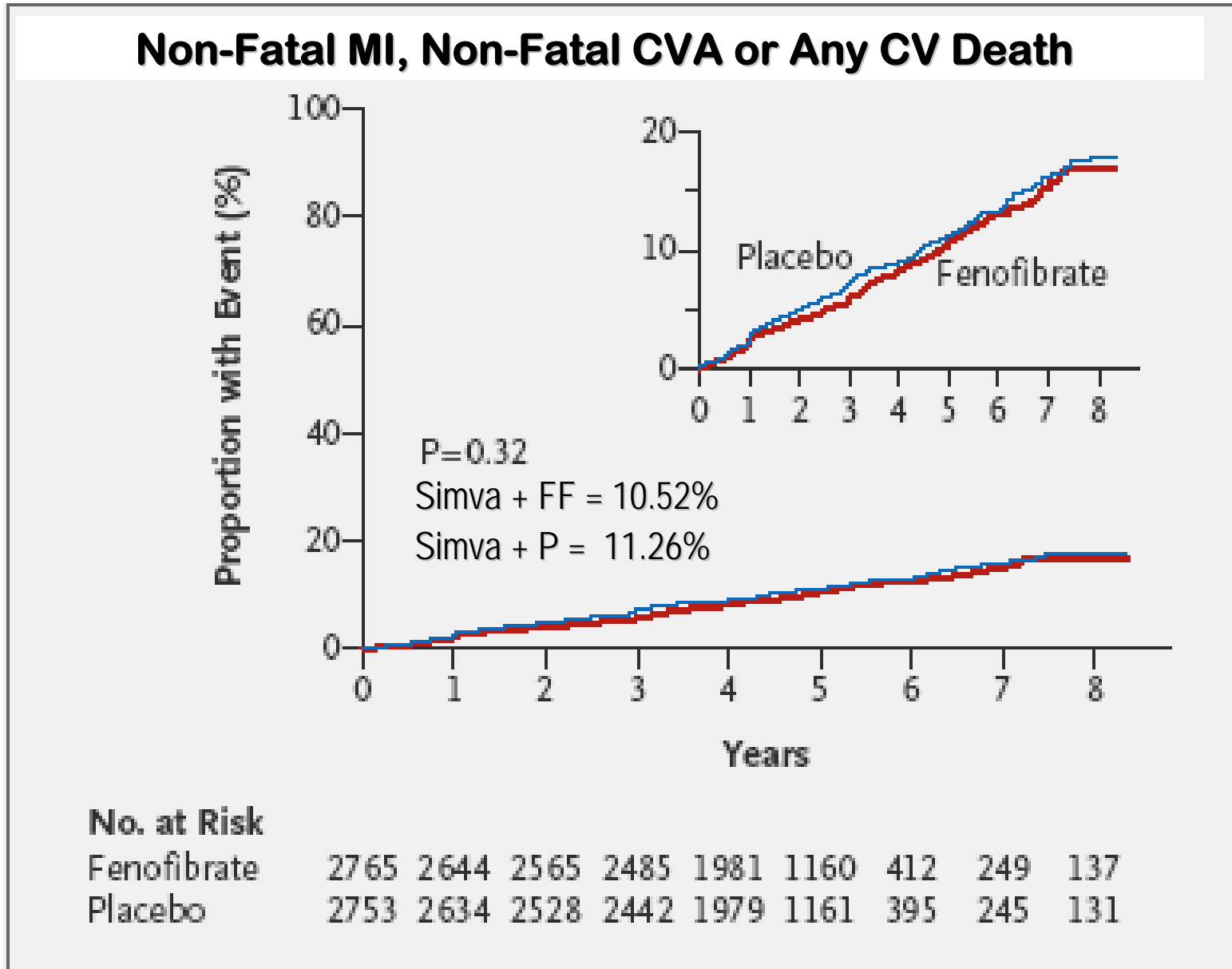


No. of Patients

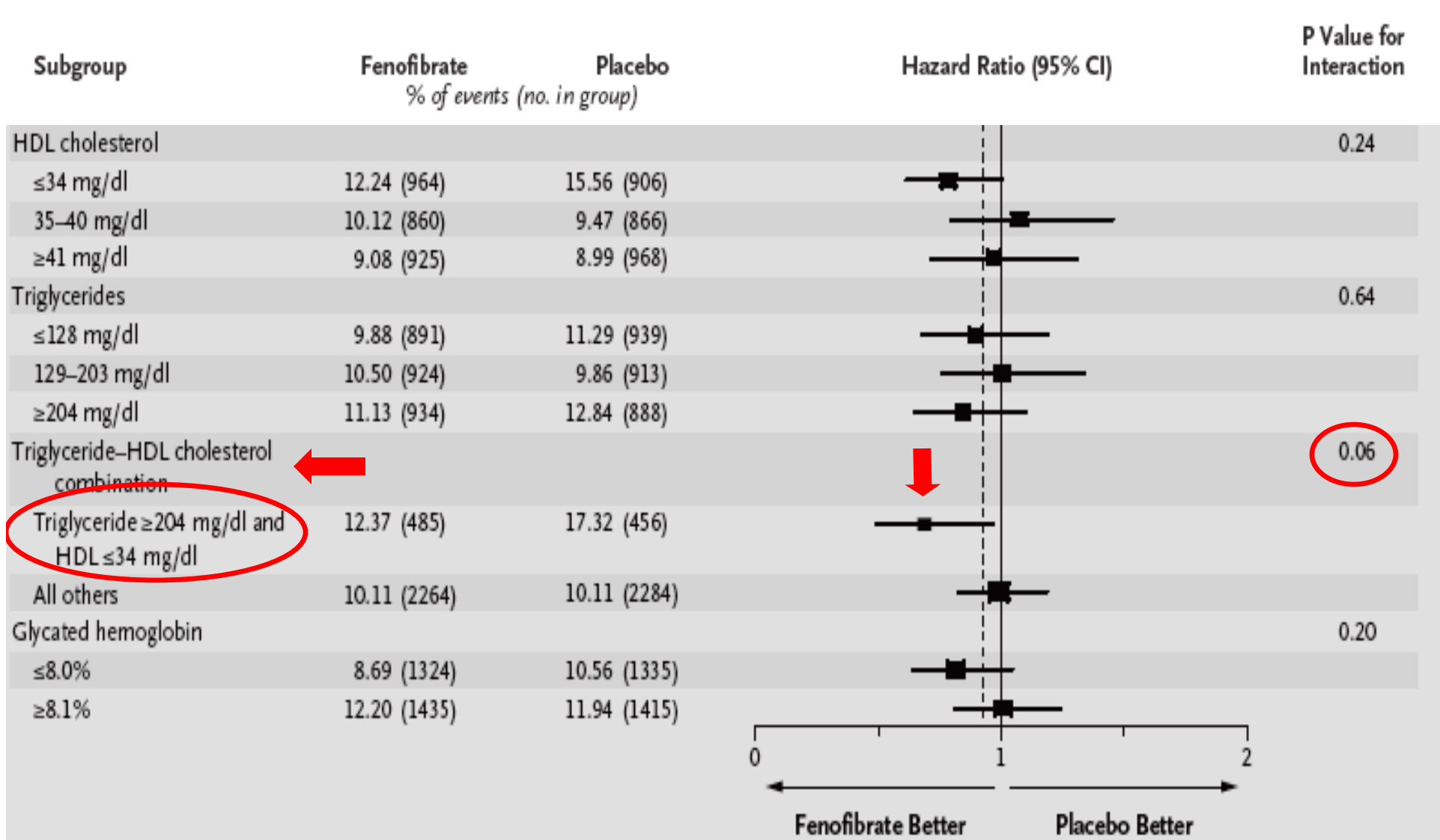
Fenofibrate	2747	2593	2505	2417	2361	1478	796	248
Placebo	2735	2591	2484	2375	2364	1480	801	243

Accord Study Group. NEJM 2010; 362: 1563.

Primary Outcome from ACCORD



Sub-Group Analysis From ACCORD



Accord Study Group. NEJM 2010;362:1563-74.

Comparison of ACCORD Sub-Group Results With Previous Fibrate Studies

Trial, Year	All Pts Relative RR (p value)	↑ TG Sub-Group Relative RR (p value)
Helsinki Heart Gemfibrozil, 1987	- 34% (p=0.02)	TG>200, LDL/HDL>5: * - 71% (p<0.005)
VA-HIT Gemfibrozil, 1999	- 22% (p=0.0006)	Diabetics: * - 32% (p=0.004)
BIP Benafibrate, 2000	- 7.3% (p=0.24)	TG>200, HDL <35: * - 42% (p=0.02)
FIELD Fenofibrate, 2005	- 11% (p=0.16)	TG>204 HDL<42: * - 27% (p<0.005)
ACCORD Fenofibrate, 2010	- 8% (p=0.32)	TG>204 HDL <35: * - 31% (p=0.057)

Modified From: Ginsberg, HN ACC Scientific Sessions, March 2010

Algorithm for Treating Diabetic Dyslipidemia in Practice

Diet and Lifestyle Measures for Treating High TGs-Low HDL

- 1. Restrict alcohol**
- 2. Restrict excess calories**
- 3. Restrict excess carbohydrate,
especially refined CHO**
- 4. Increase intake of fish oils**
- 5. Increase daily exercise**

Summary

- Insulin resistance creates the “lipid triad” of TG-rich VLDL, small-dense LDL and reduced HDL, along with an inflammatory and pro-thrombotic state, all of which increase vascular risk
- Fibrates affect multiple genes involved in lipid metabolism, glucose homeostasis and inflammation via activation of the PPAR family of transcription factors
- Fenofibrate added to low dose statins has favorable effects on TGs, HDL, and small dense LDL, and is generally safe
- CV events are significantly reduced by statin-fibrate therapy in insulin resistant patients, but the benefits are confined to those with combined \uparrow TGs \gg 200 mg/dl and \downarrow HDL < 40 mg/dl
- Diet change, exercise and glycemic control remain the cornerstones of TG-lowering in all insulin resistant patients