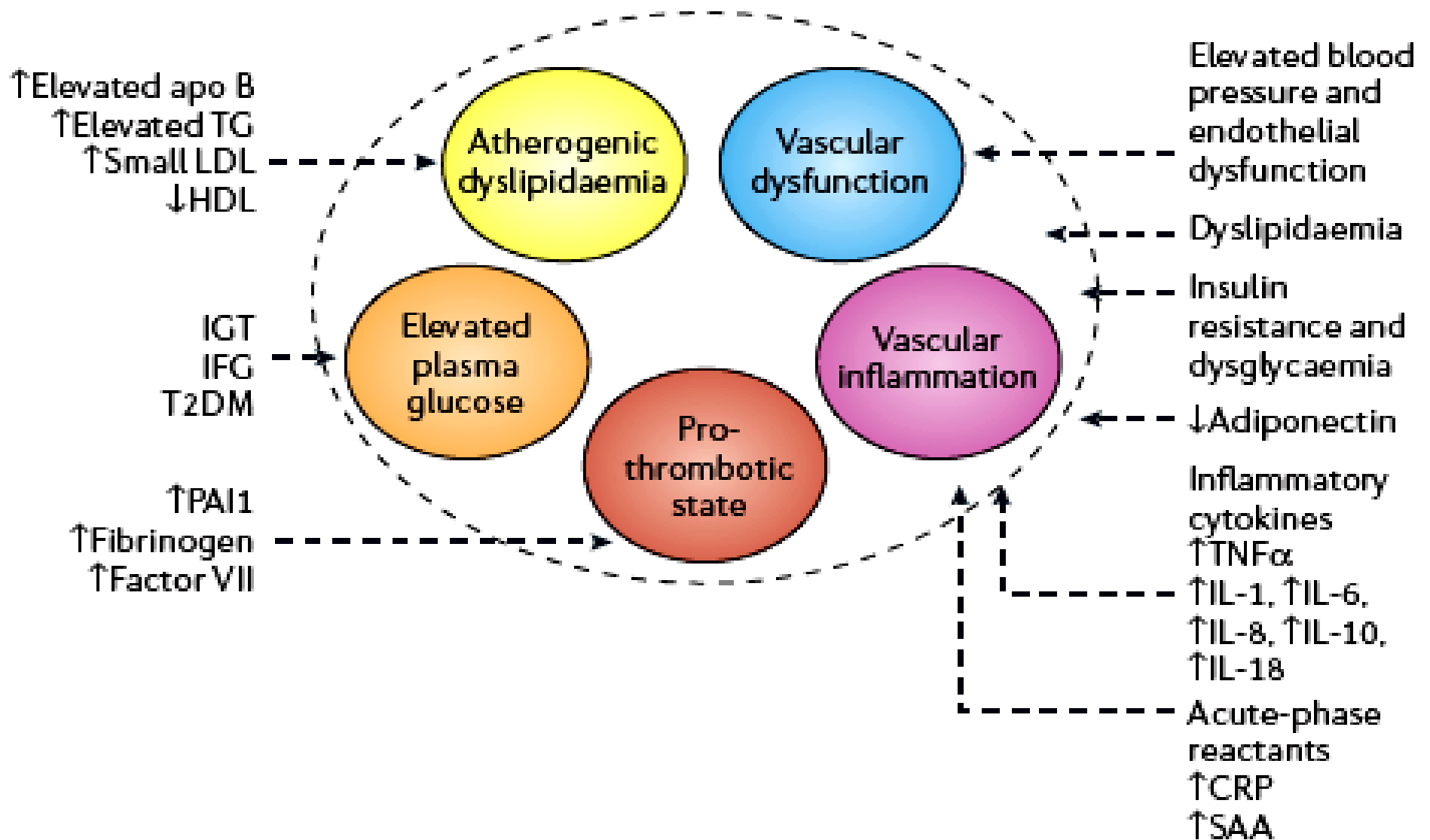


# **Update On Diabetic Dyslipidemia: Who Should Be Treated With A Fibrate After ACCORD-LIPID?**



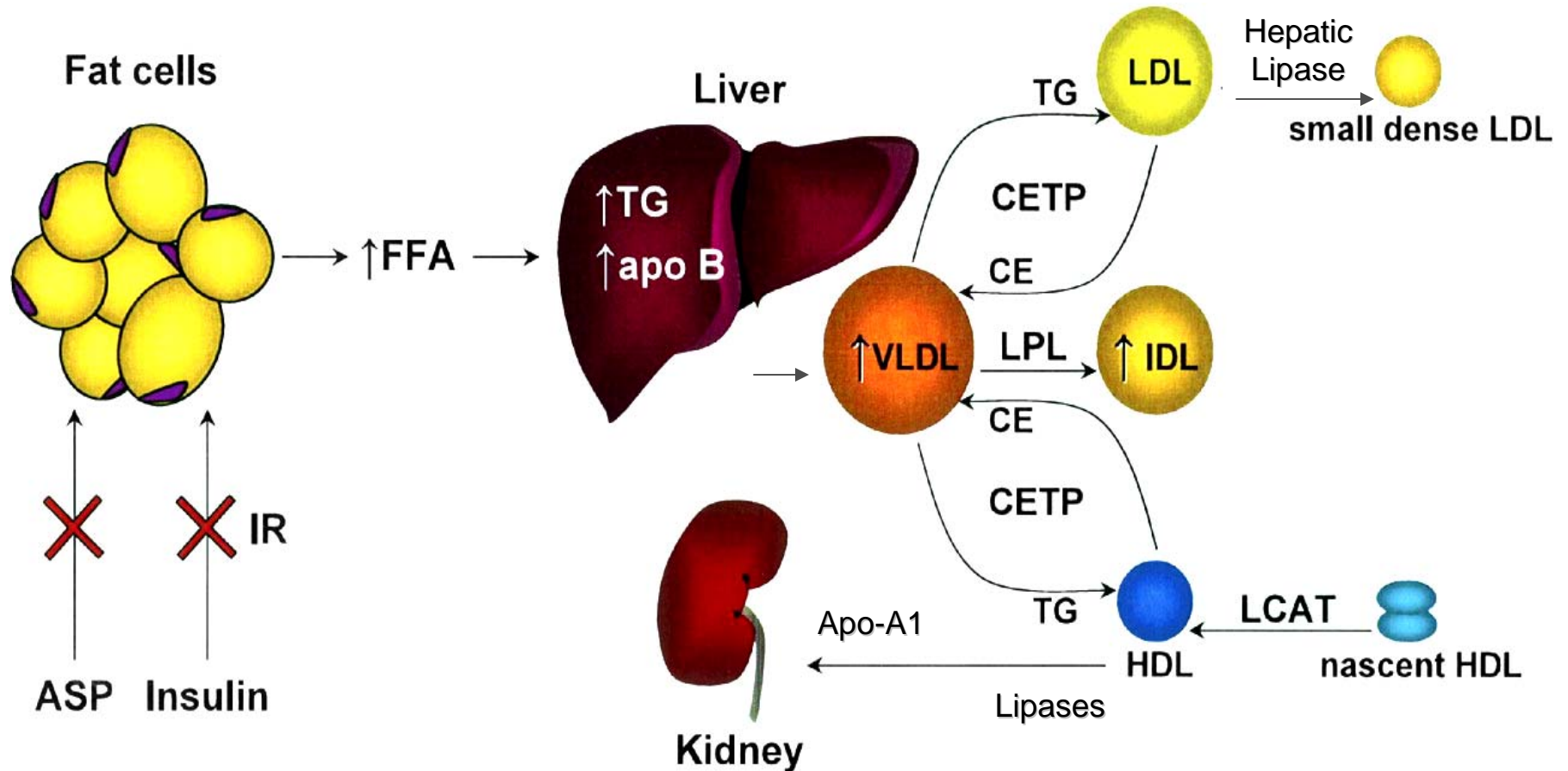
Karen Aspary, MD, MS, ABCL, FACC  
Assistant Clinical Professor of Medicine  
Warren Alpert Medical School of Brown University

# 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

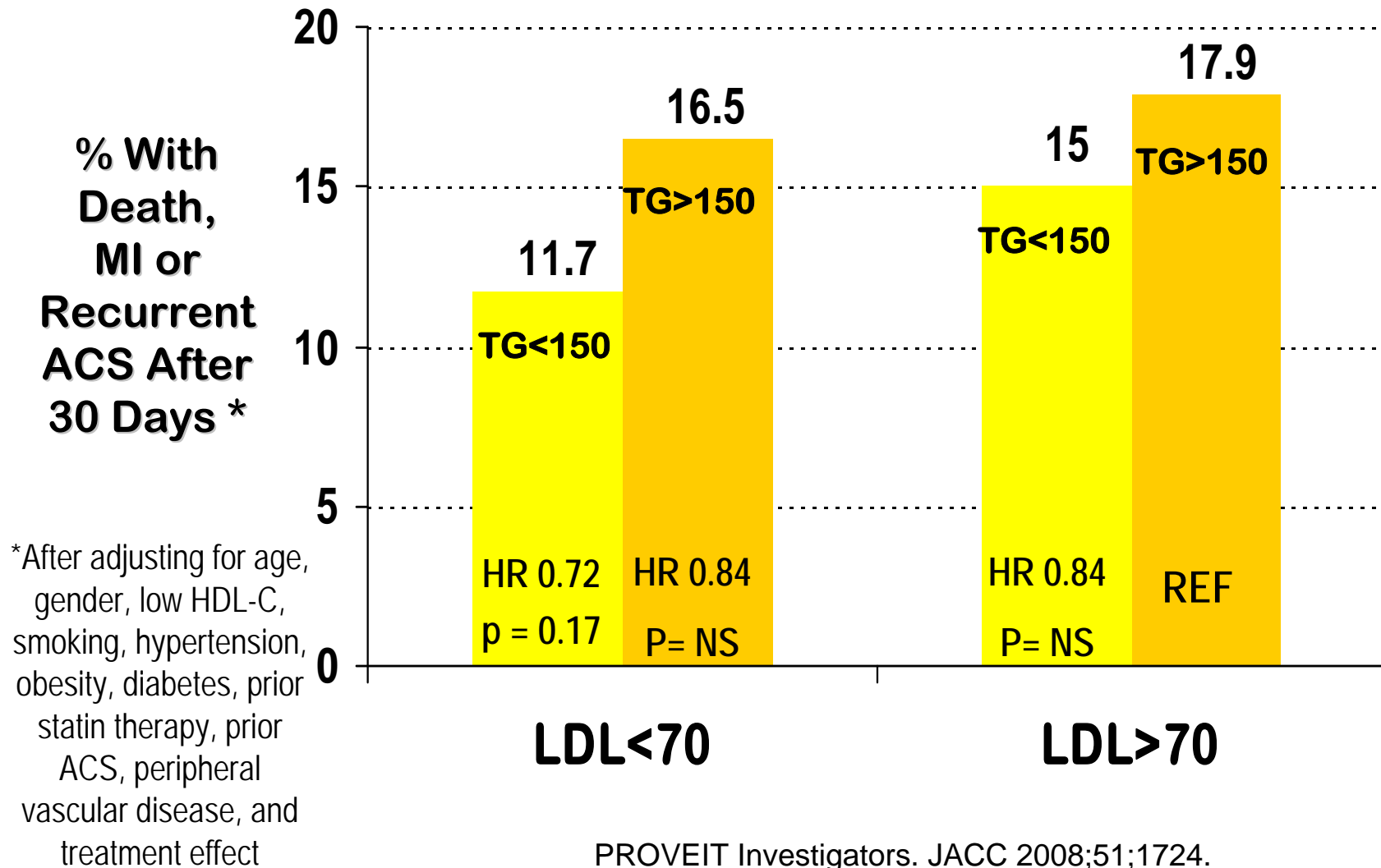


CETP = Cholesterol ester transfer protein

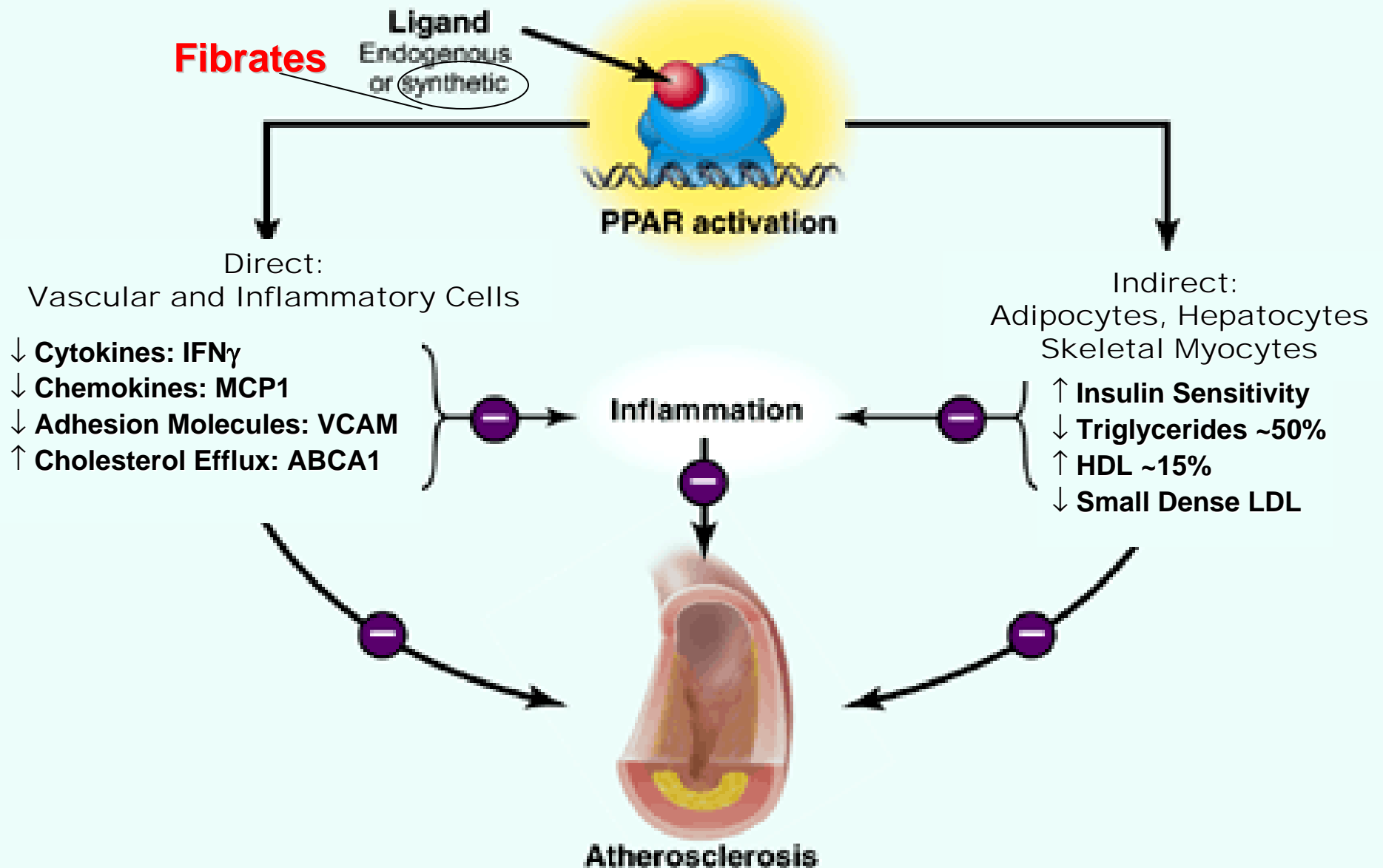


# CHD Risk from Elevated TGs Persists Even When LDL is Lowered to <70 mg/dl

## Sub-Group Analysis from PROVE-IT - 2008



# Fibrates Improve High TGs, Low HDL and Vascular Inflammation via PPAR- $\alpha$ Activation

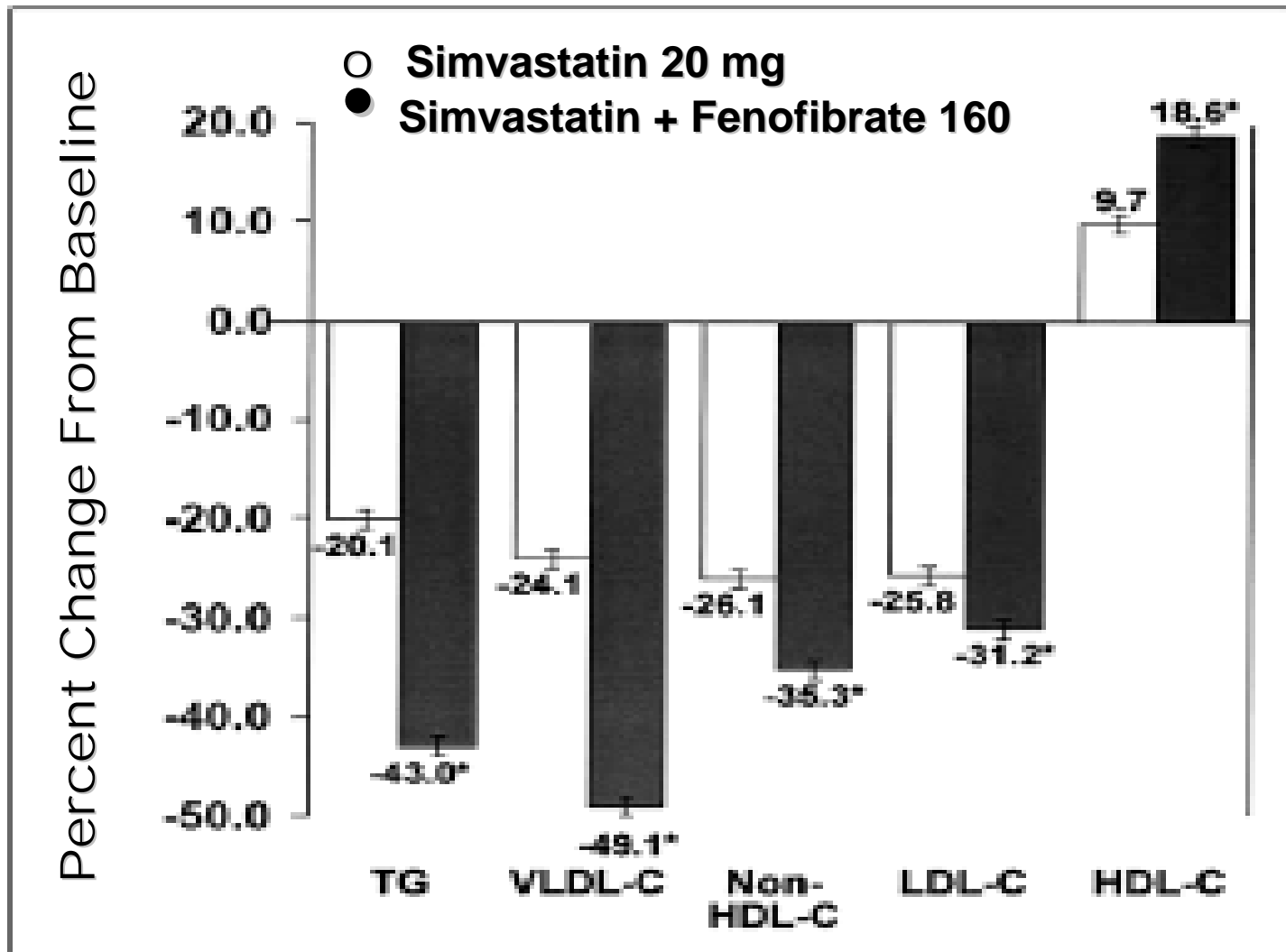


# Lipid Effects of Fibrates

- 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



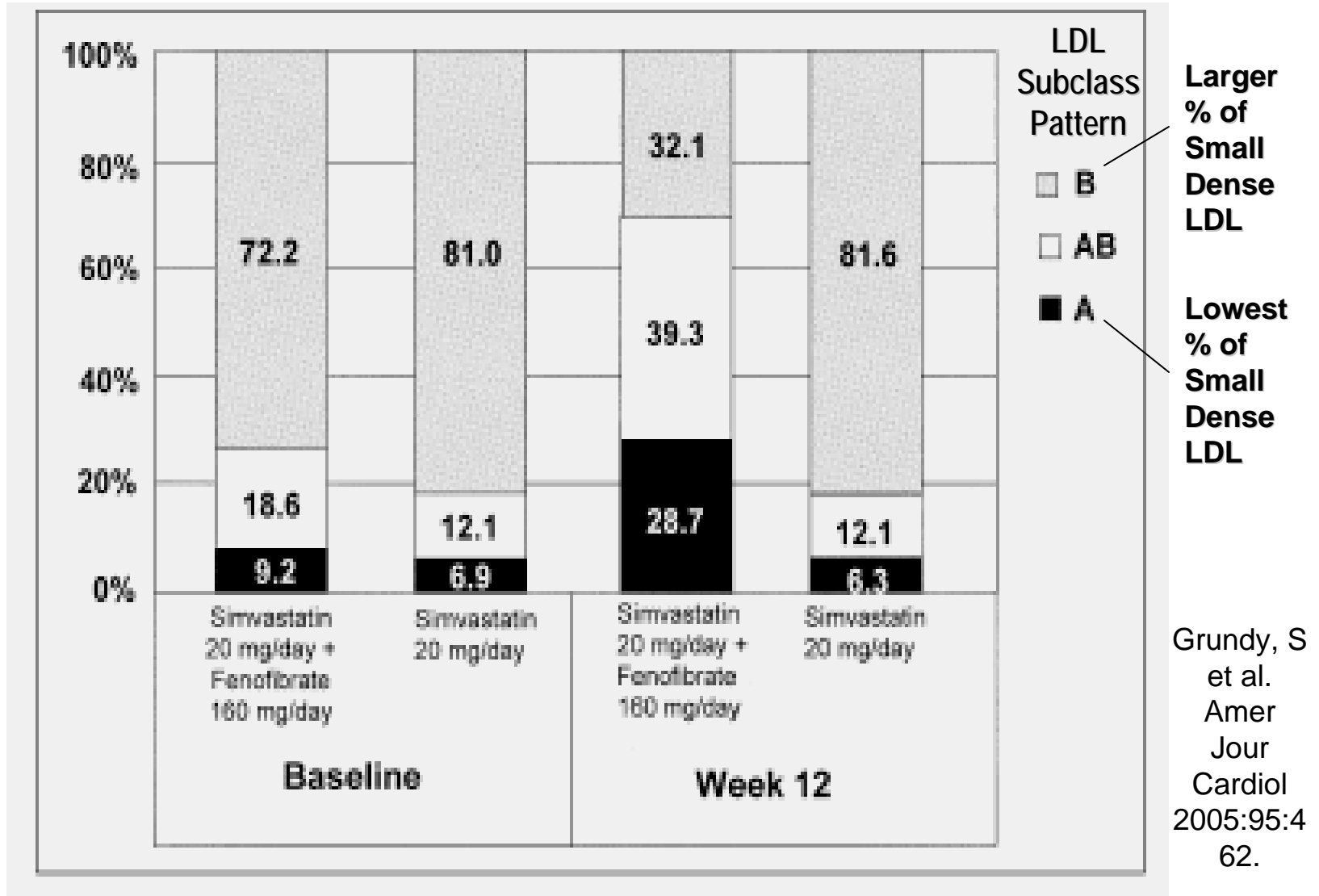
n=618  
\*P=.001

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**

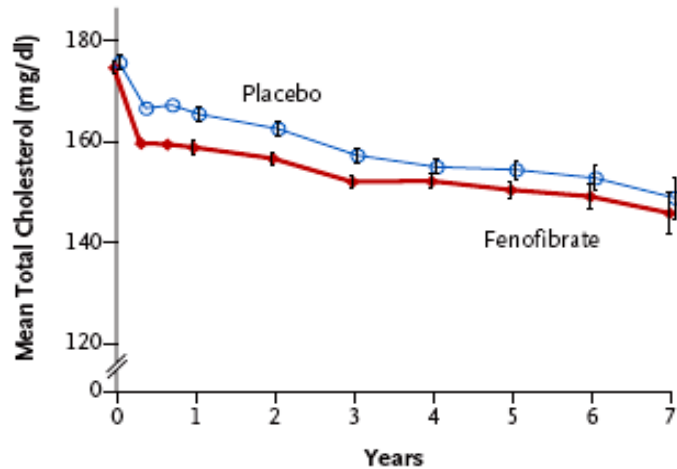
First non-fatal MI, non-fatal CVA or death from CV disease

# 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

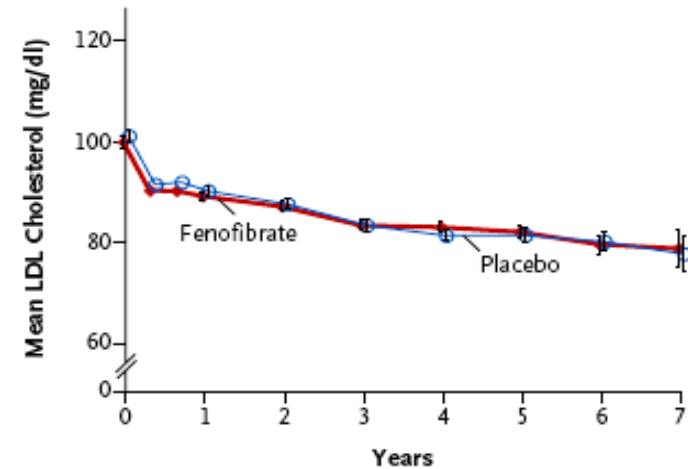
# Lipid Results From ACCORD

## Change in Total Cholesterol



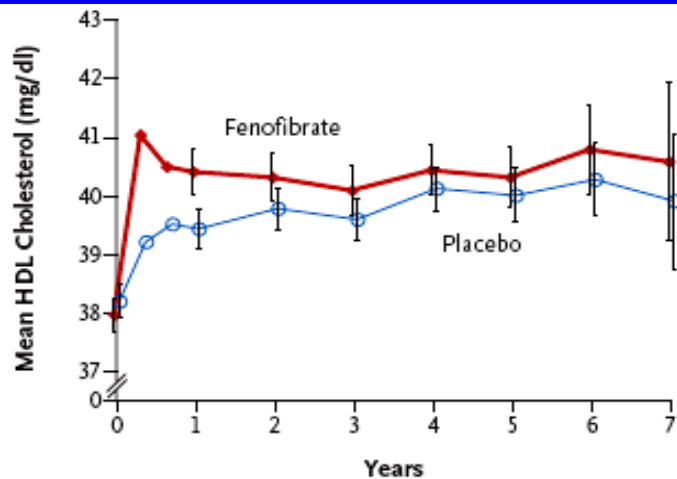
No. of Patients		2747	2593	2505	2417	2361	1478	796	248
Fenofibrate									
Placebo		2735	2591	2484	2375	2364	1480	801	243

## Change in LDL Cholesterol



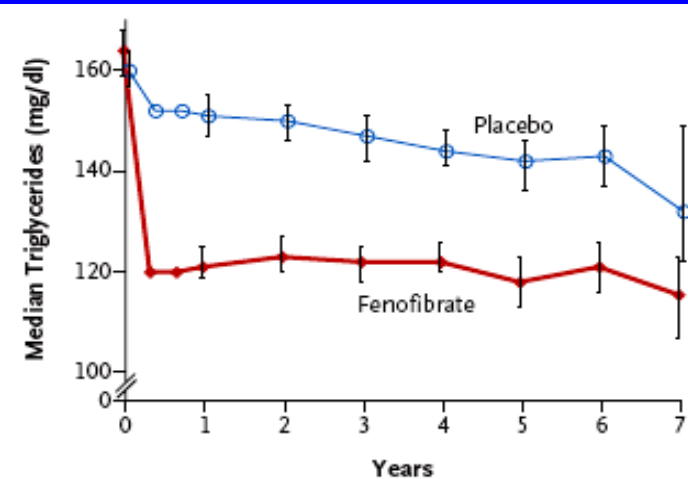
No. of Patients		2747	2593	2505	2417	2361	1477	796	248
Fenofibrate									
Placebo		2735	2591	2484	2375	2364	1480	801	243

## Change in HDL Cholesterol



No. of Patients		2747	2593	2505	2417	2361	1477	796	248
Fenofibrate									
Placebo		2736	2591	2484	2375	2364	1480	801	243

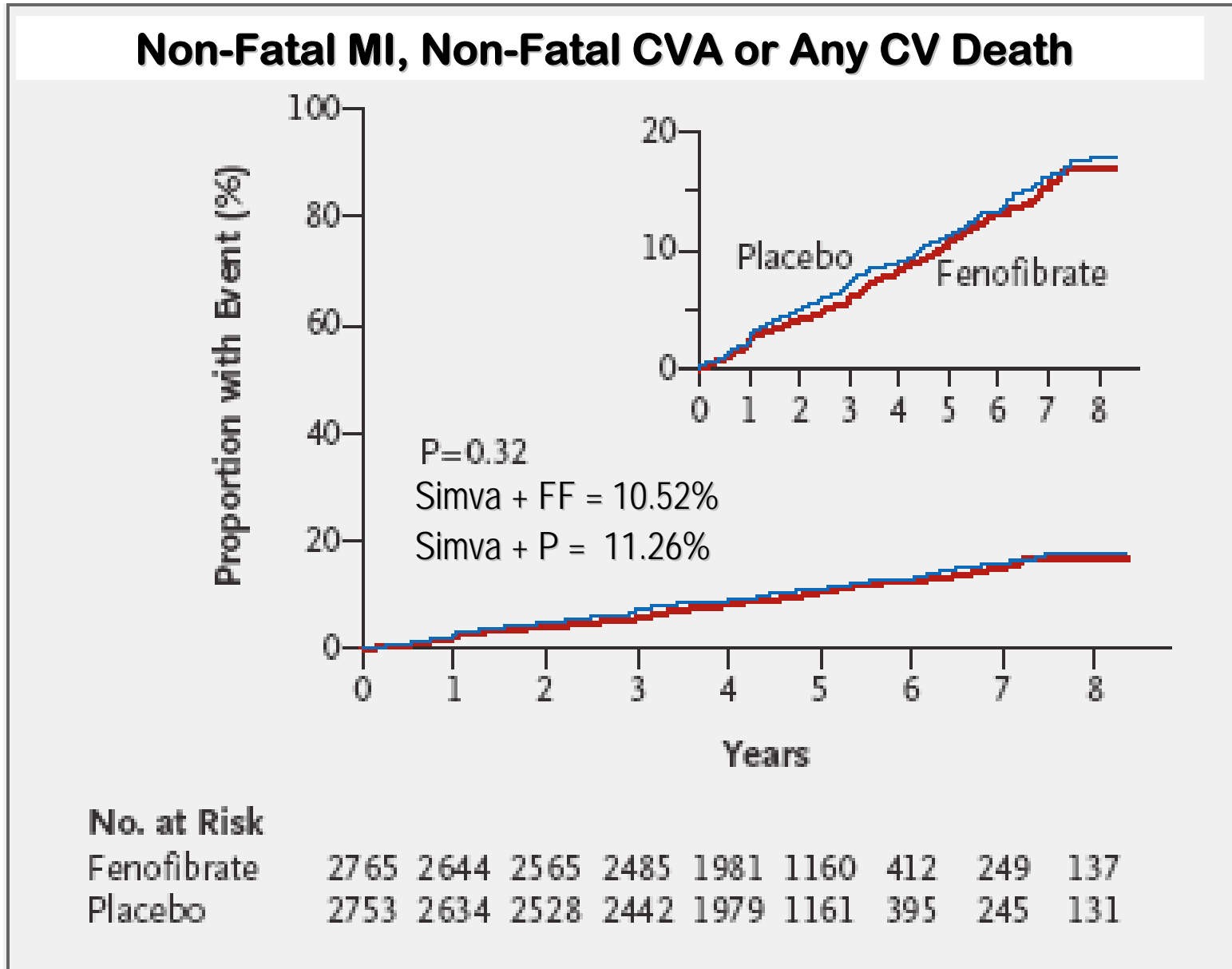
## Change in Triglycerides



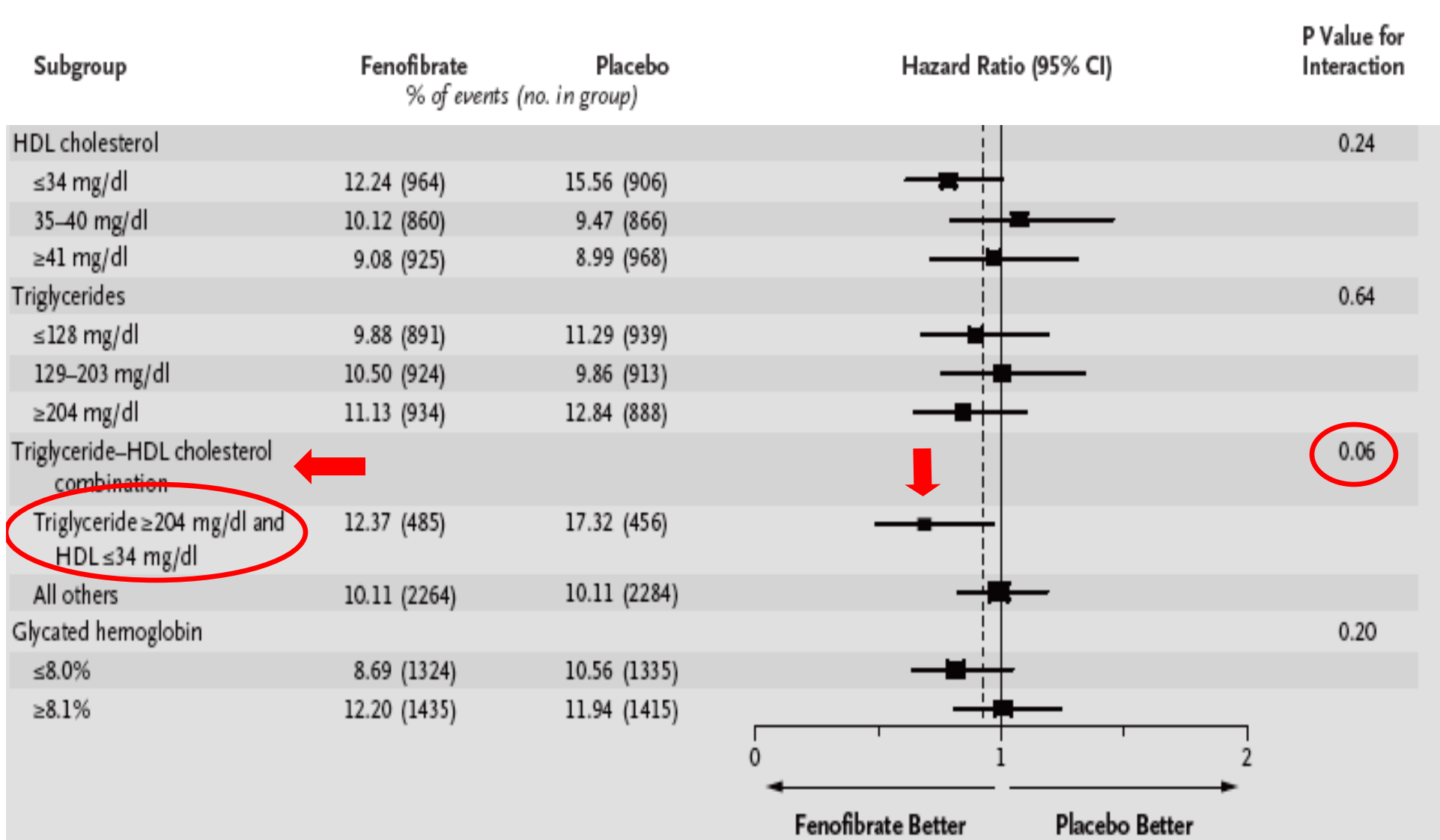
No. of Patients		2747	2593	2505	2417	2361	1478	796	248
Fenofibrate									
Placebo		2735	2591	2484	2375	2364	1480	801	243

Accord Study Group. NEJM 2010; 362: 1563.

# Primary Outcome from ACCORD



# Sub-Group Analysis From ACCORD



# Comparison of ACCORD Sub-Group Results With Previous Fibrate Studies

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