Reducing Residual Cardiovascular Risk In Patients With Atherogenic Dyslipidemia

Program Objectives:

* *Discuss why treating elevated LDL-C alone may not be sufficient*
* *Review current international guidelines on dyslipidemia management*
* *Discuss the role for combination therapy to comprehensively treat mixed dyslipidemia*

Khem L. Khooblall M.D., F.A.C.C.

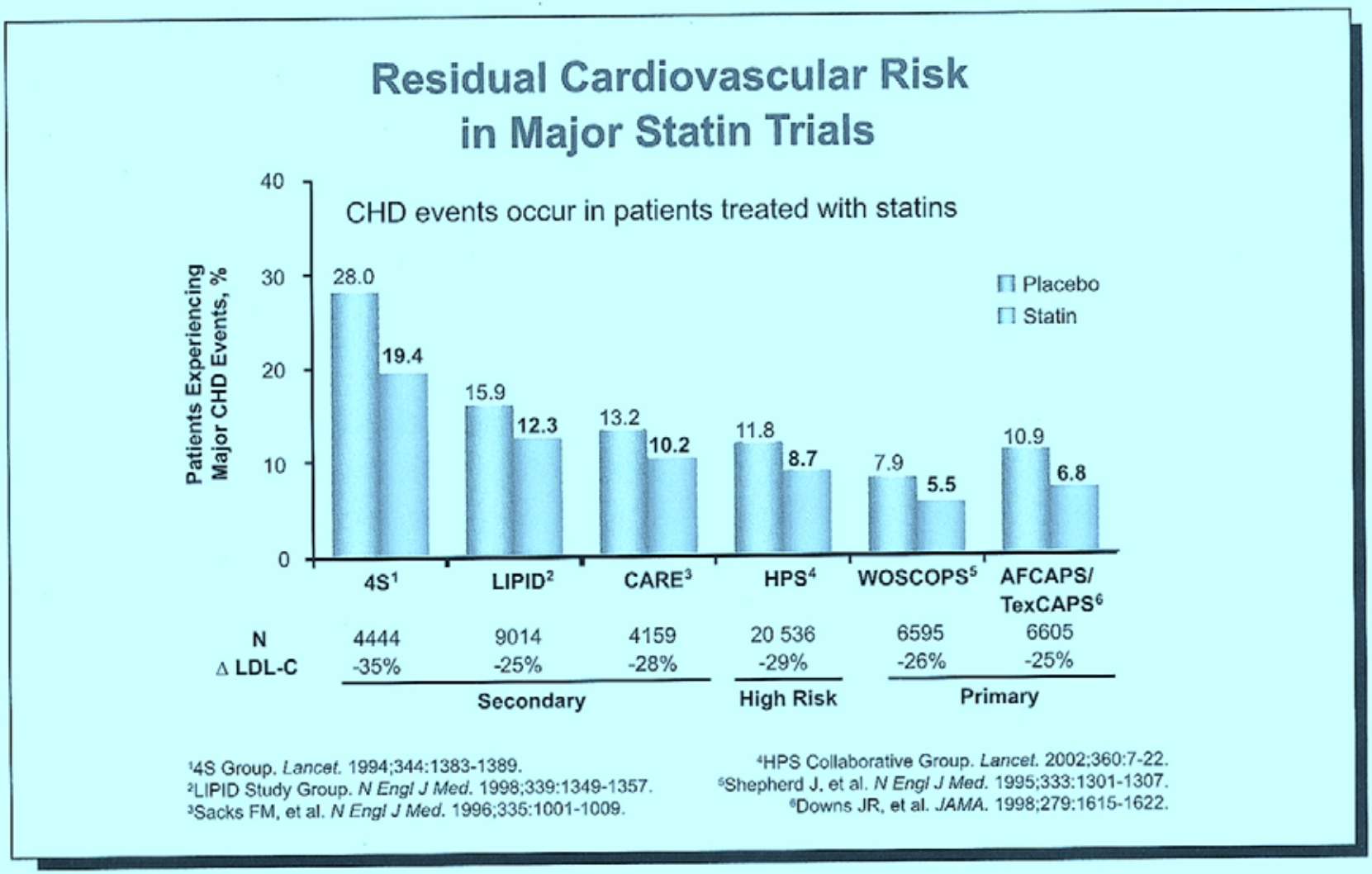


Figure 2. Residual risk: percentage of patients experiencing major coronary events in several large outcome trials.

Despite statin treatment, significant residual risk remained after reducing LDL-cholesterol levels, and two thirds of cardiovascular events still occurred.[17]

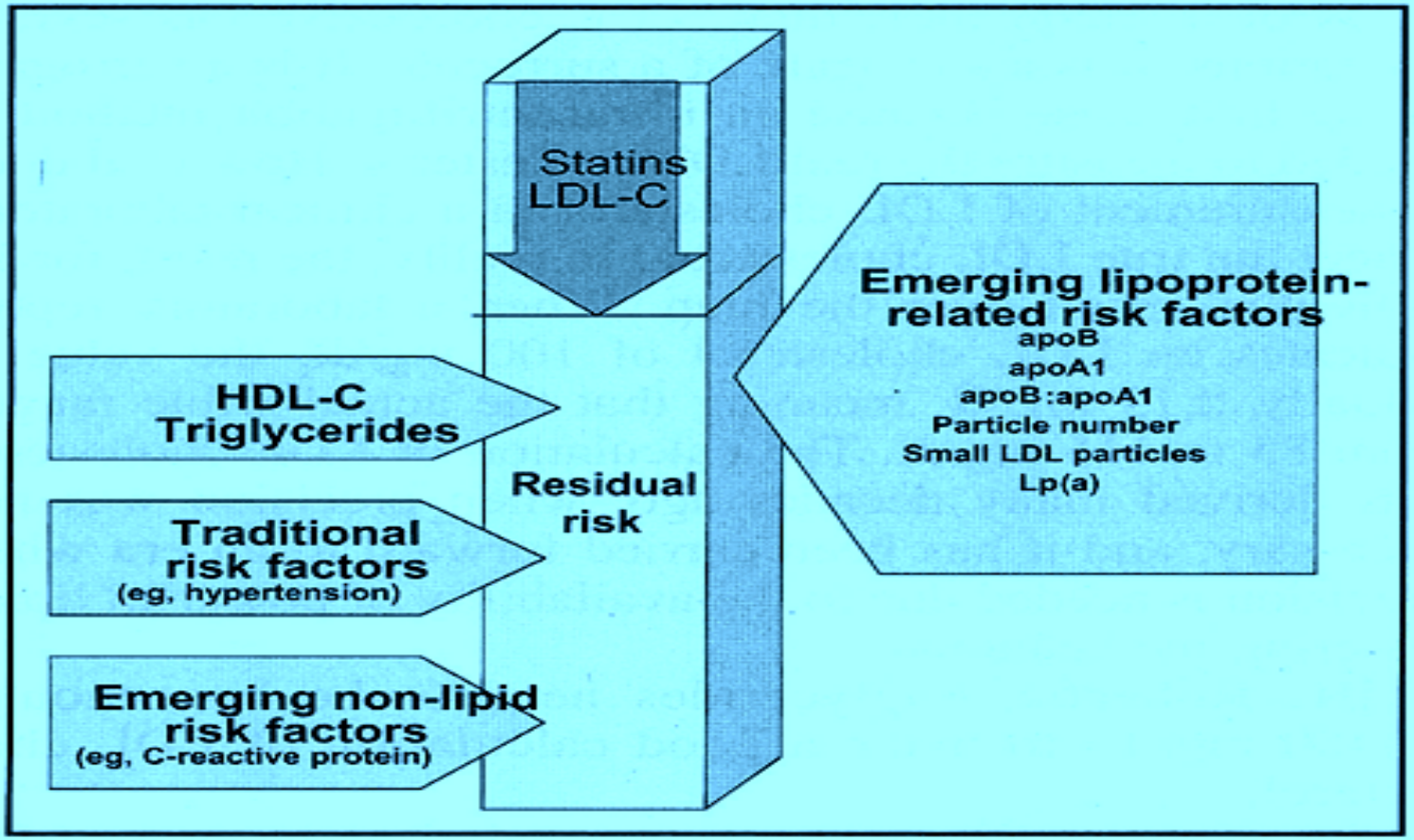


Figure 1. Schematic showing risk factors that may contribute to risk for coronary heart disease. LDL cholesterol may be responsible for approximately 25% to 35% of total risk based on the therapeutic benefit of statin therapy. Other risk factors are responsible for the residual risk. Some emerging lipoprotein-related risk factors may overlap with LDL cholesterol–associated risk and/or contribute to residual risk.

Patients With Diabetes Have Particularly High Residual CVD Risk After Statin Treatment

	Event Rate (No Diabetes)		Event Rate (Diabetes)	
	On Statin	On Placebo	On Statin	On Placebo
HPS[1]* (CHD patients)	19.8%	25.7%	33.4%	37.8%
CARE[2]†	19.4%	24.6%	28.7%	36.8%
LIPID[3]‡	11.7%	15.2%	19.2%	22.8%
PROSPER[4]§	13.1%	16.0%	23.1%	18.4%
ASCOT-LLA[5]‡	4.9%	8.7%	9.6%	11.4%
TNT[6]‖	7.8%	9.7%	13.8%	17.9%

*CHD death, nonfatal MI, stroke, revascularizations
†CHD death, nonfatal MI, CABG, PTCA
‡CHD death and nonfatal MI
§CHD death, nonfatal MI, stroke
‖CHD death, nonfatal MI, resuscitated cardiac arrest, stroke
(80 mg versus 10mg atorvastatin)

[1]HPS Collaborative Group. *Lancet*. 2003;361:2005-2016.
[2]Sacks FM, et al. *N Engl J Med*. 1996;335:1001-1009.
[3]LIPID Study Group. *N Engl J Med*. 1998;339:1349-1357.
[4]Shepherd J, et al. *Lancet*. 2002;360:1623-1630.
[5]Sever PS, et al. *Lancet*. 2003;361:1149-1158.
[6]Shepherd J, et al. *Diabetes Care*. 2006;29:1220-1226.

DYSLIPIDEMIA TYPES

Characterized by Abnormalities in Lipid Levels or the Composition of Lipoprotein

HYPERCHOLESTEROLEMIA: II A: ↑LDL Homogenous Familial, Heterogenous Familial & Non- familial

HYPERTRIGLYCERIDEMIA: [II B] & IV: ↑ TG > 750

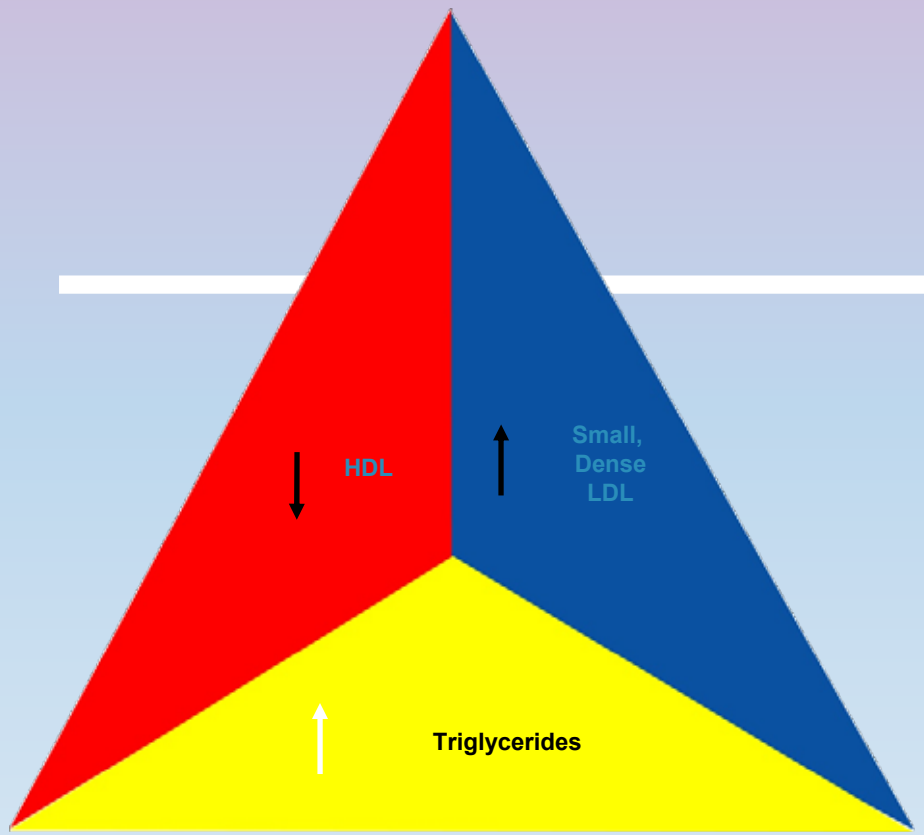
MIXED DYSLIPIDEMIA: II B: ↑ LDL + ↑ TG

ATHEROGENIC DYSLIPIDEMIA: TRIAD: ↑ LDL + ↑ TG + ↓ HDL

NON-DIABETIC
Primary Target: ↓LDL
Secondary Target ↑HDL

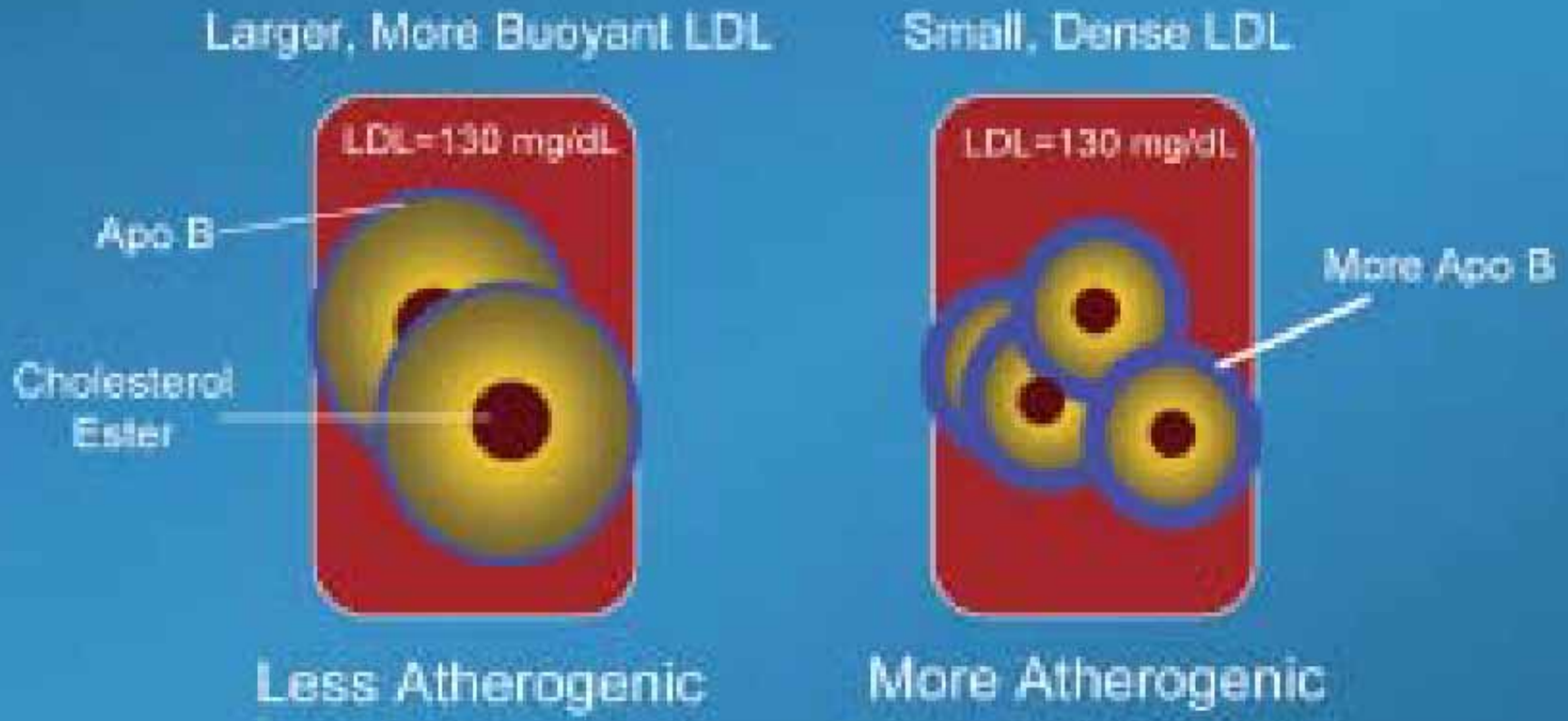
DIABETIC
Primary Target: ↓LDL
Secondary Target: ↑HDL + ↓TG

Reducing the Cardiovascular Disease Risk in Patients With Metabolic Disorders



Lipid Triad

Not all LDL Particles are the Same



Degree of Risk Related to LDL Subtype

Subtype Pattern B: predominance of small, dense LDL particles[1,2]

- Strongly associated with development of CHD; possible mechanisms include:
  - Susceptibility to oxidation[3]
  - Avid binding to the scavenger receptor[4]
  - Promotion of endothelial cell dysfunction[5]
  - Entering the arterial wall more easily[6]

Subtype Pattern A: characterized by large, buoyant LDL particles[1]

- Greater affinity for cholesterol receptors; catabolized rapidly[1]

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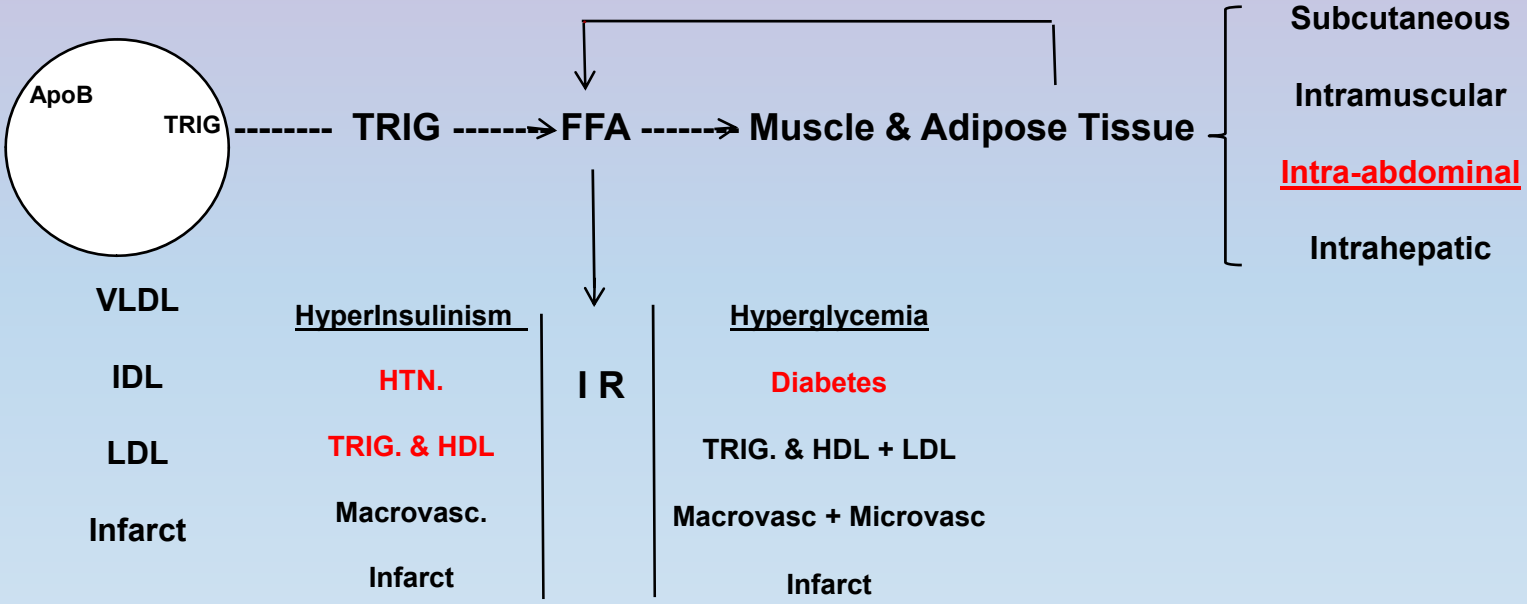
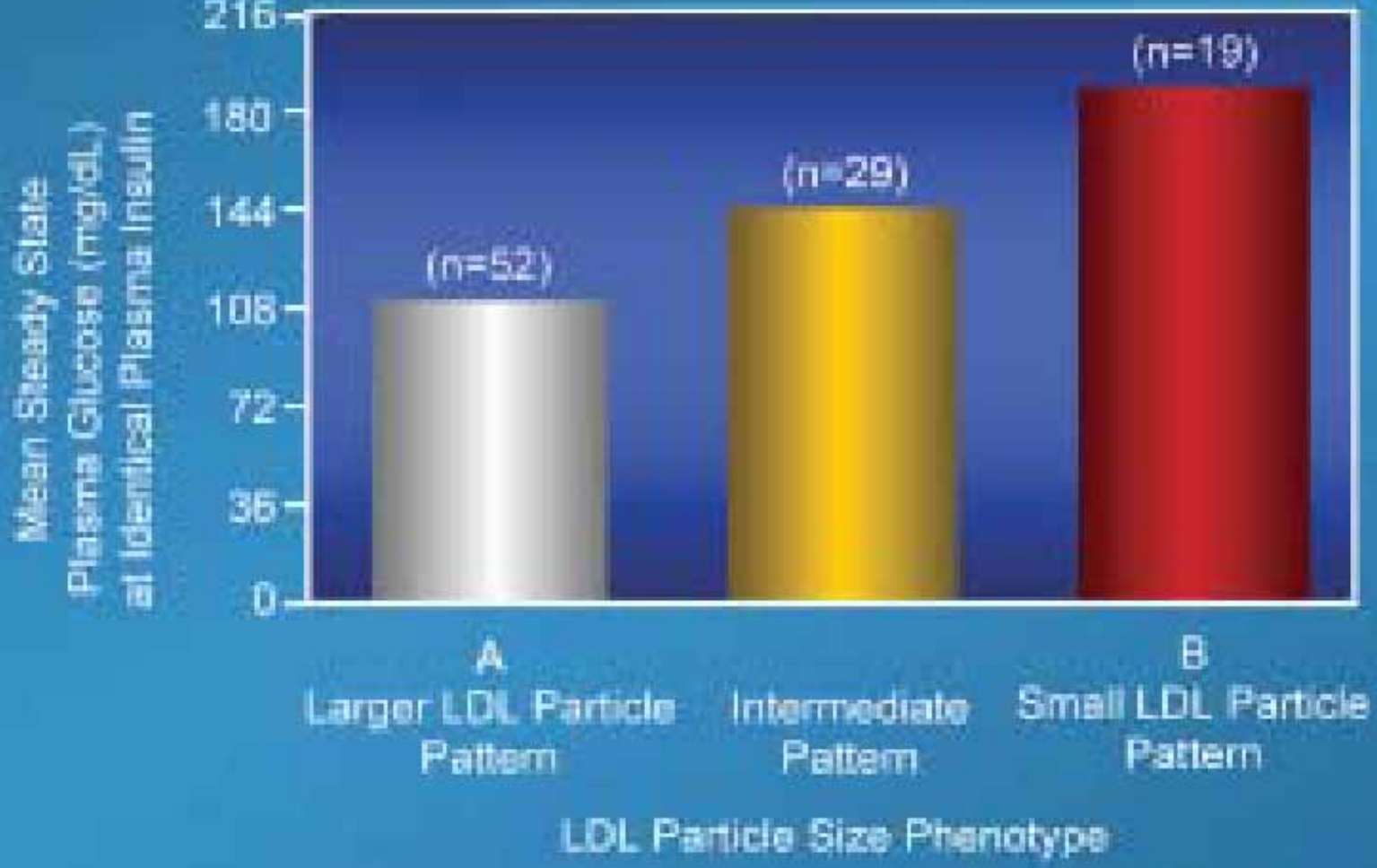
Triglyceride rich VLDL



Association Between Small, Dense LDL Particles and Insulin Resistance



Reaven GM, et al. J Clin Invest. 1993;92:141-146.

Dyslipidemia/Diabetes/CHD Connection

Type 2 diabetes is associated with[1]:

- A 2- to 4-fold increased risk of CVD

Diabetes is associated with:

- Risk for major coronary events similar to that in established CHD[2]

Lipid abnormalities increase risk of CV events in these patients[1]

- Elevated TGs and decreased HDL-C are most common abnormalities

Improved control of lipids may reduce CV event rate by up to 27%[3]

CVD is the major cause of death for people with diabetes[4]

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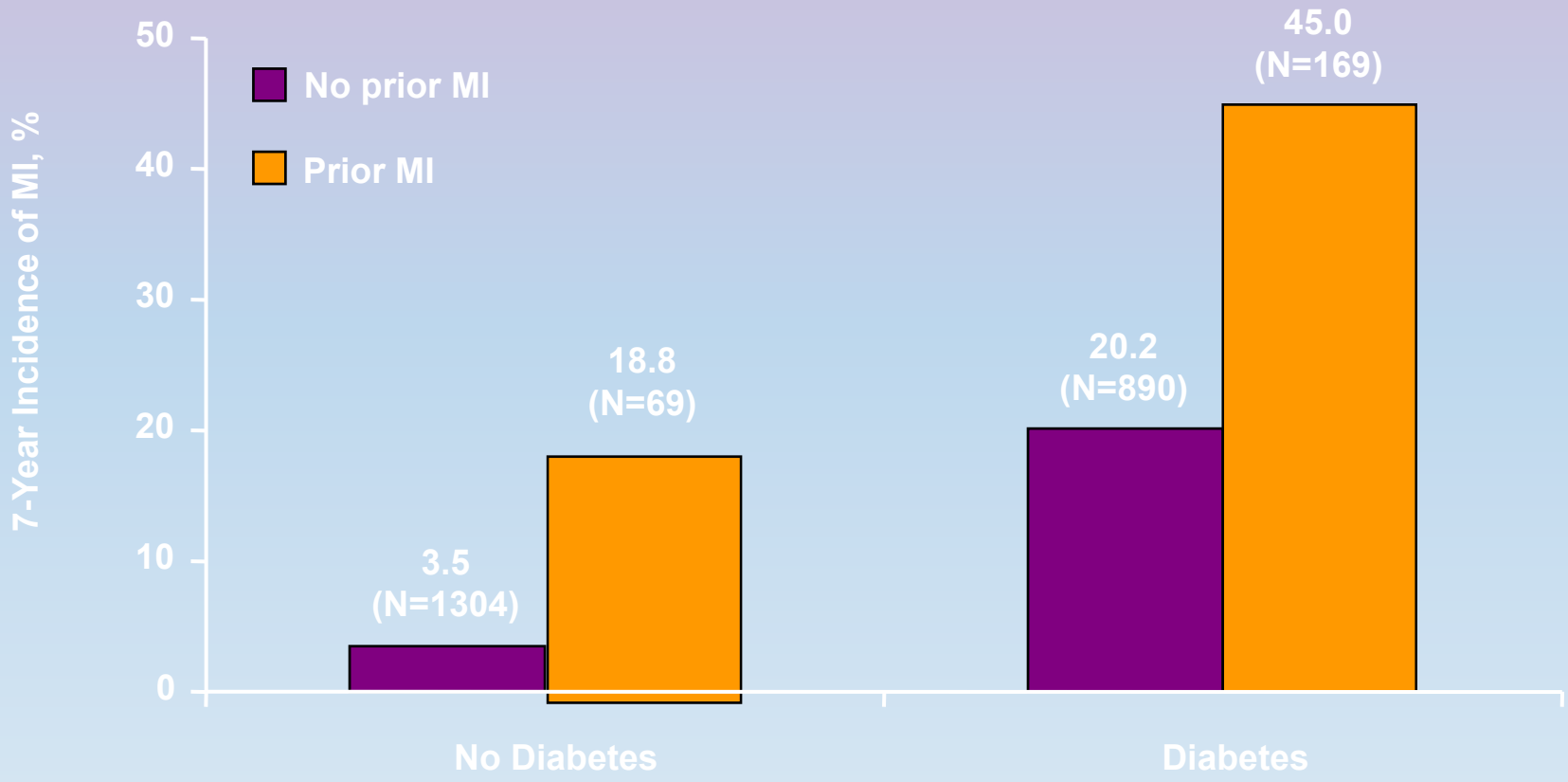
Increased Risk of MI in Patients With Diabetes



Haffner SM et al. *N Engl J Med*. 1998;339:229-234.

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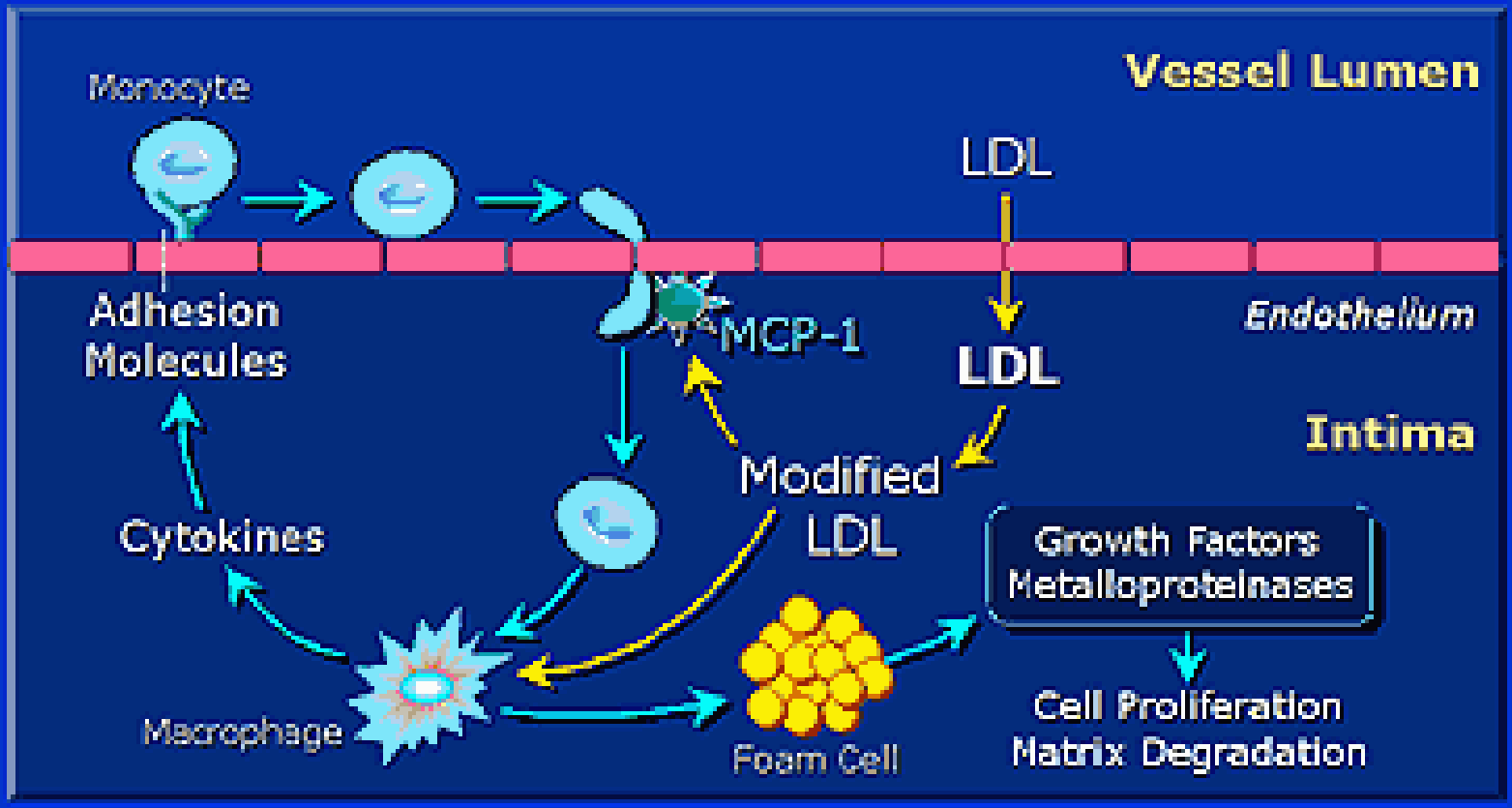
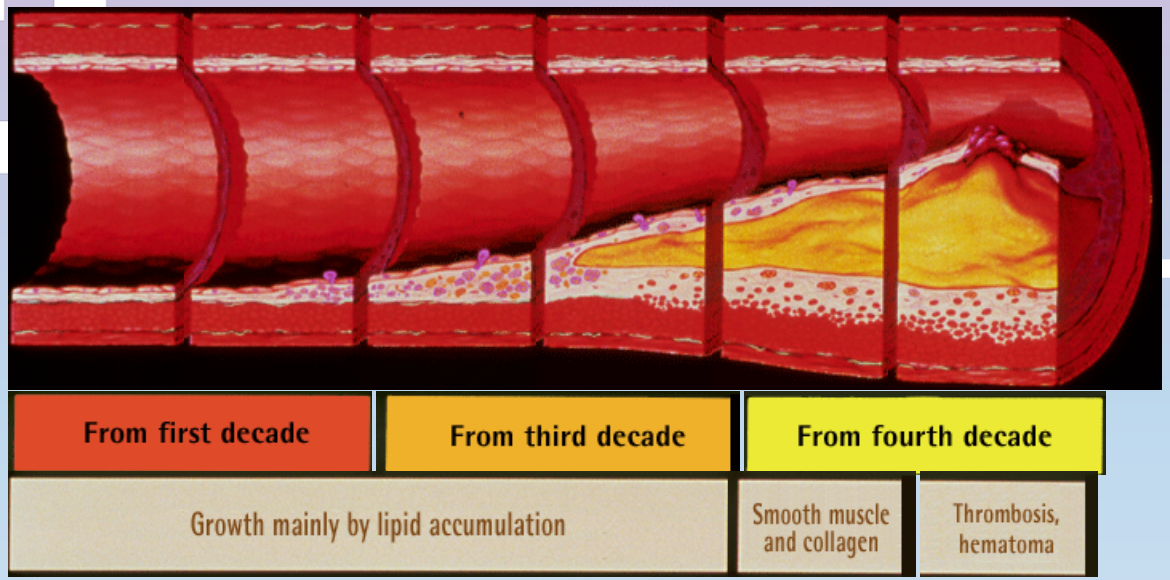
Macrophages and Foam Cells Express Growth Factors and Proteinases

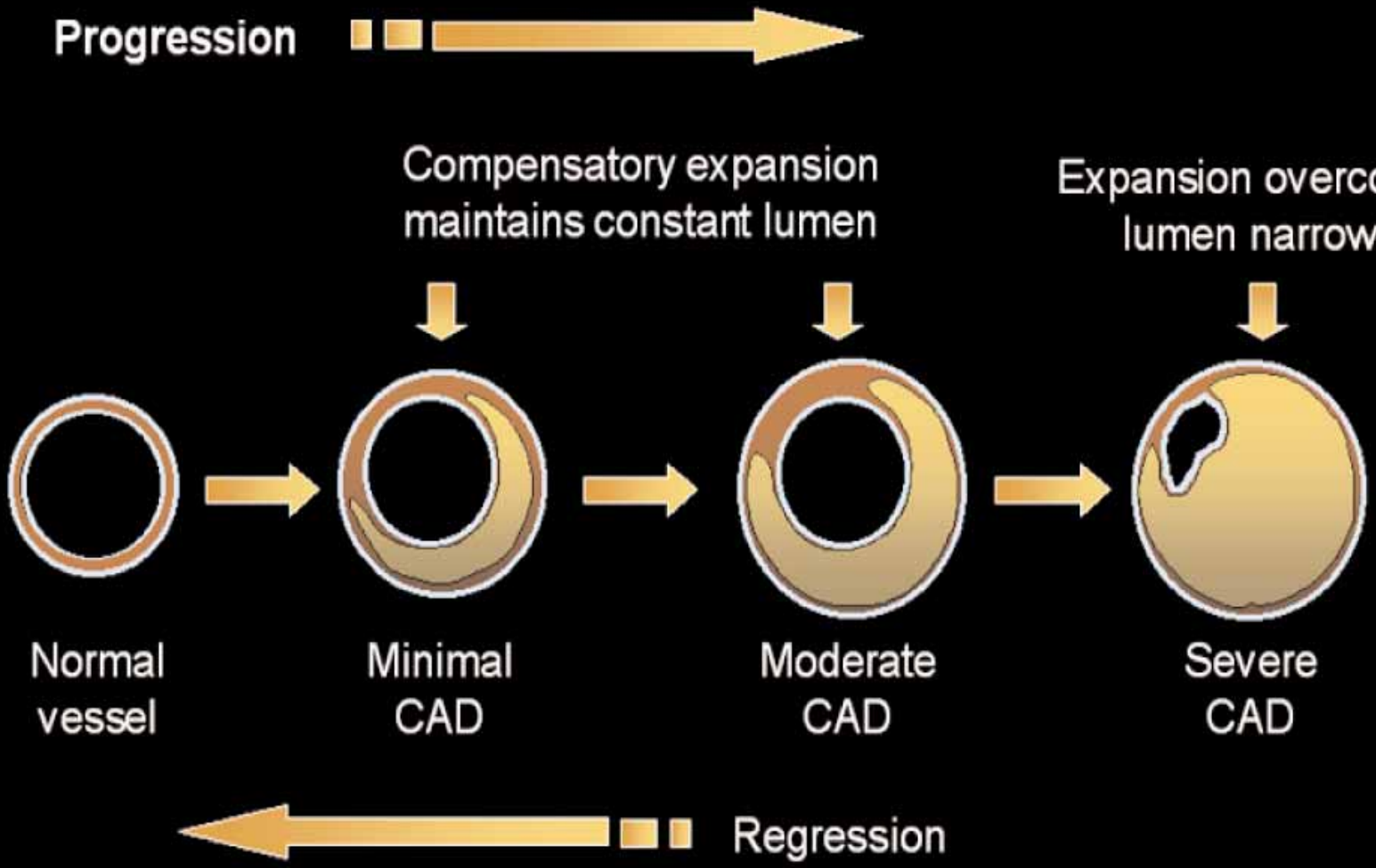


Ross R. *N Engl J Med* 1999;340:115-126.

Timeline of Atherosclerosis

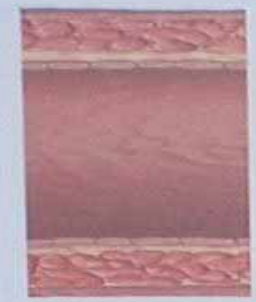


Glagov's coronary remodeling hypothesis: Y2K



Glagov, et al. *N Engl J Med.* 1987;316:1371-1375.

ATHEROSCLEROSIS AND RESULTING COMPLICATIONS



NORMAL

The vessel wall is healthy with intact cellular structure and the artery is free of blockage. Blood can travel easily to and from the heart.

FATTY DEPOSIT

Due to damage to the innermost layer of the artery, fats, cholesterol, platelets, calcium, and other substances build up in the artery wall. This buildup, called plaque, causes narrowing of the artery and can make blood flow difficult.

VULNERABLE

Vulnerable plaques may be susceptible to rupture due to high lipid content, increased inflammation, and a thin fibrous cap.

RUPTURE

Plaque inflammation and increased arterial pressure can trigger plaque rupture. When a plaque ruptures, exposure to blood flow triggers a blood clot, or thrombus.

THROMBUS

A blood clot consisting of platelets and insoluble fibrin forms at the site of injury. Thrombus formation can be very dangerous if the clot breaks free and travels down the blood stream to the heart or brain.

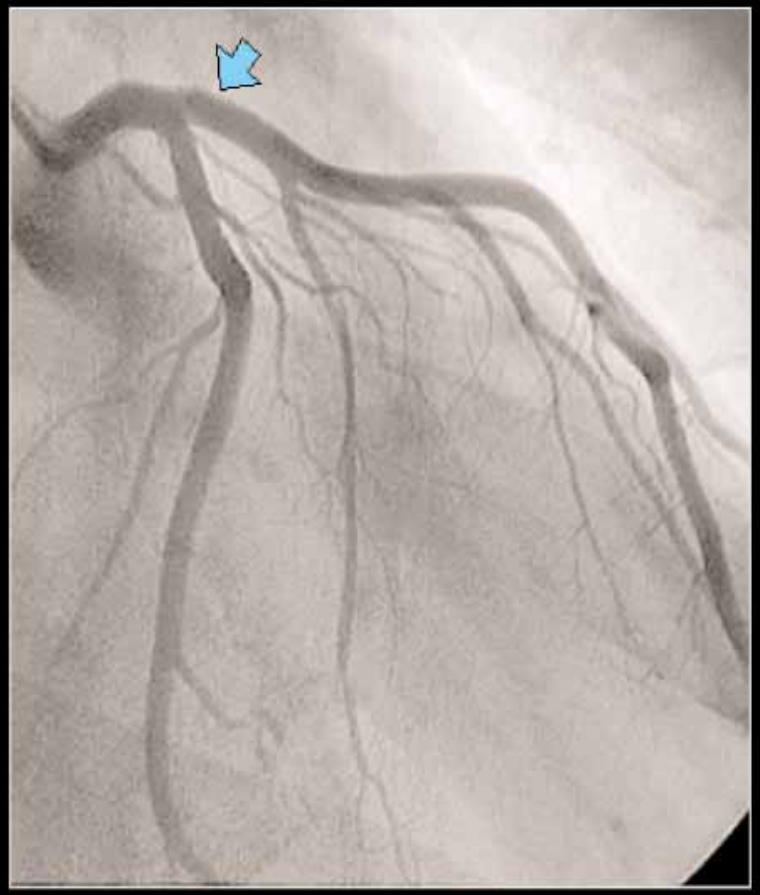
MI

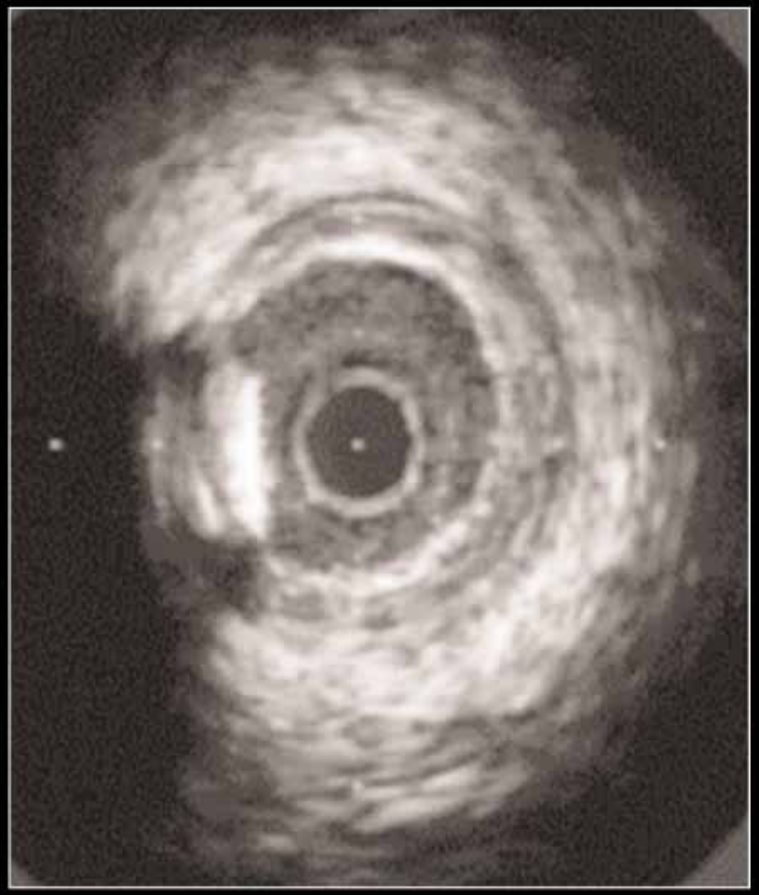
MI or Myocardial Infarction (heart attack) occurs when a clot completely blocks blood flow to an area of the heart. Without the oxygen supplied by blood, heart tissues die.

OBSTRUCTIVE CLOT

Clotting can happen in an area of the artery that has not ruptured. Large buildups of plaque make blockage even more likely to happen. Blood stagnation and coagulation often occurs secondary to reduced blood flow.

Angiographically inapparent coronary atherosclerosis: Diffuse symmetrical disease

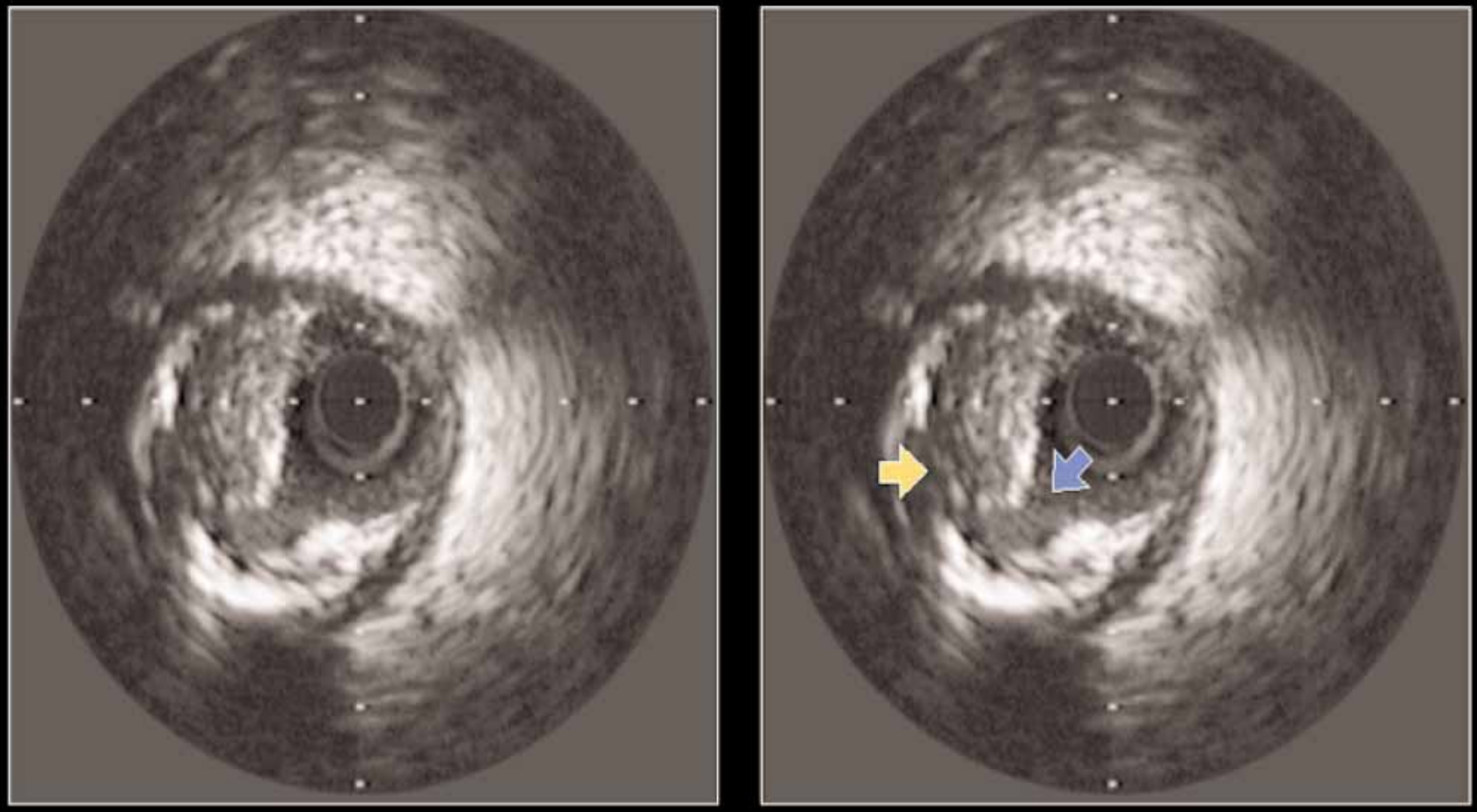




The Cleveland Clinic Intravascular Ultrasound Research Laboratory.

Atheroma rupture: Ultrasound features

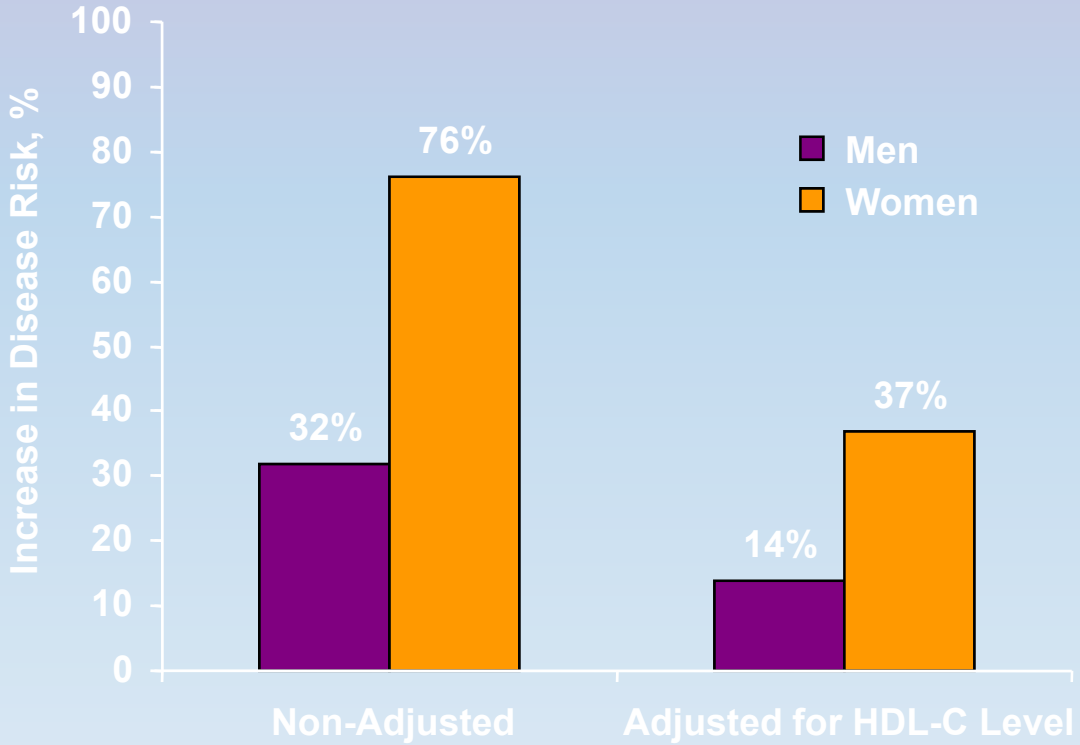
Ulceration with contact between blood and atheroma



The Cleveland Clinic Intravascular Ultrasound Research Laboratory.

Elevated TGs: A Risk Factor for CVD

Increase in relative risk for the association between 89 mg/dL increase in TGs and incident of CVD



Findings from a meta-analysis: 17 of 17 population-based, prospective studies of TGs and CVD.

Austin MA et al. *Am J Cardiol.* 1998;81:7B-12B.

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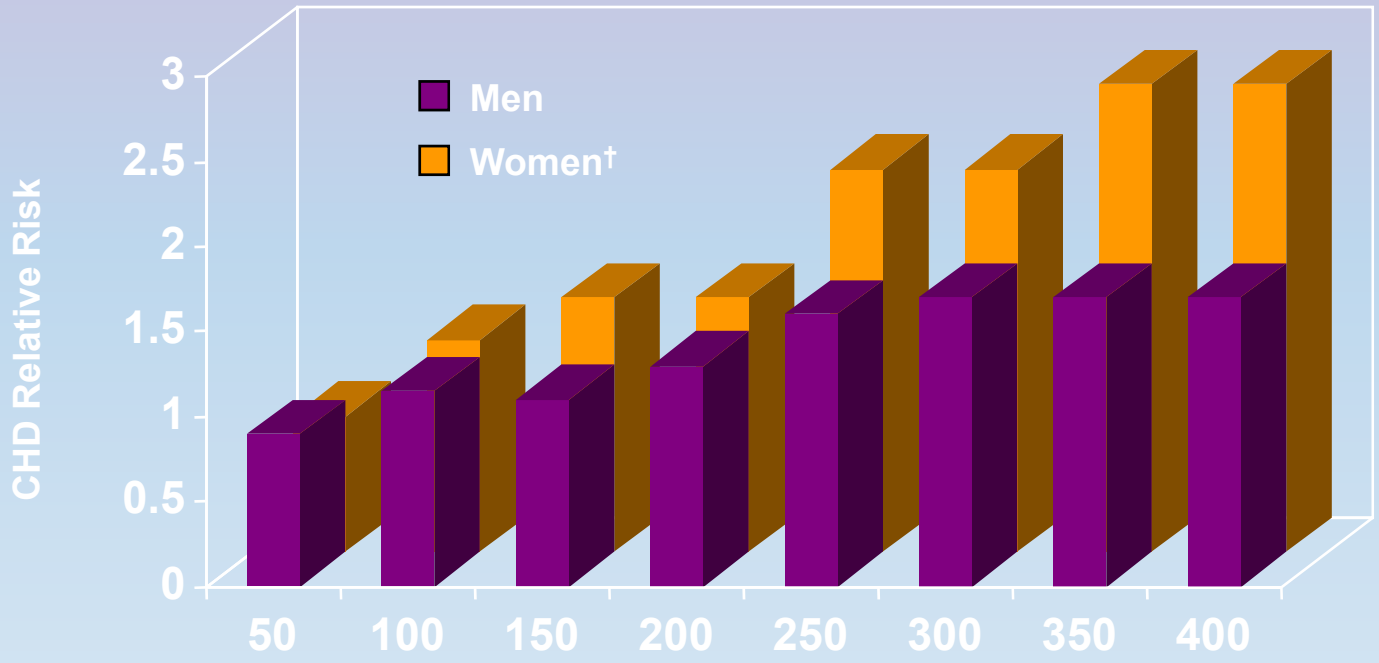
Increasing TG Levels → Increasing CHD Risk

Framingham Heart Study*



*National Heart, Lung and Blood Institute, Boston University School of Medicine.

†Results are statistically significant.

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

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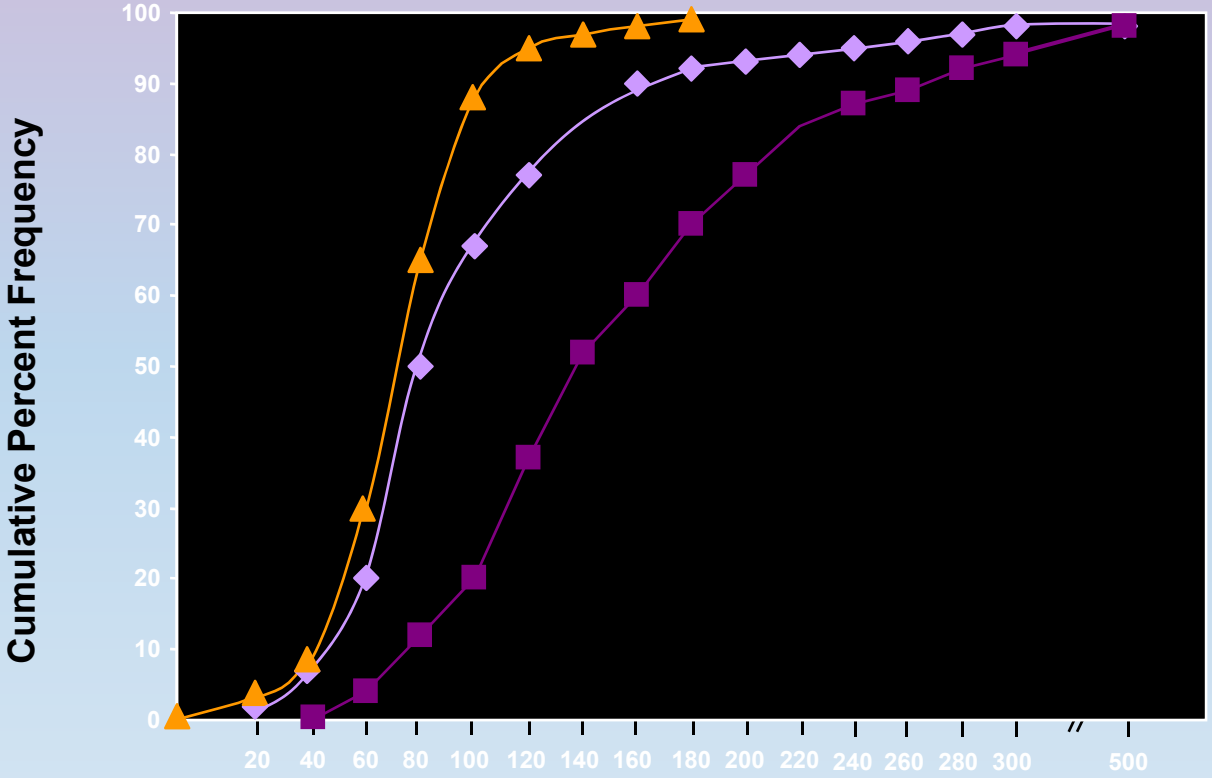
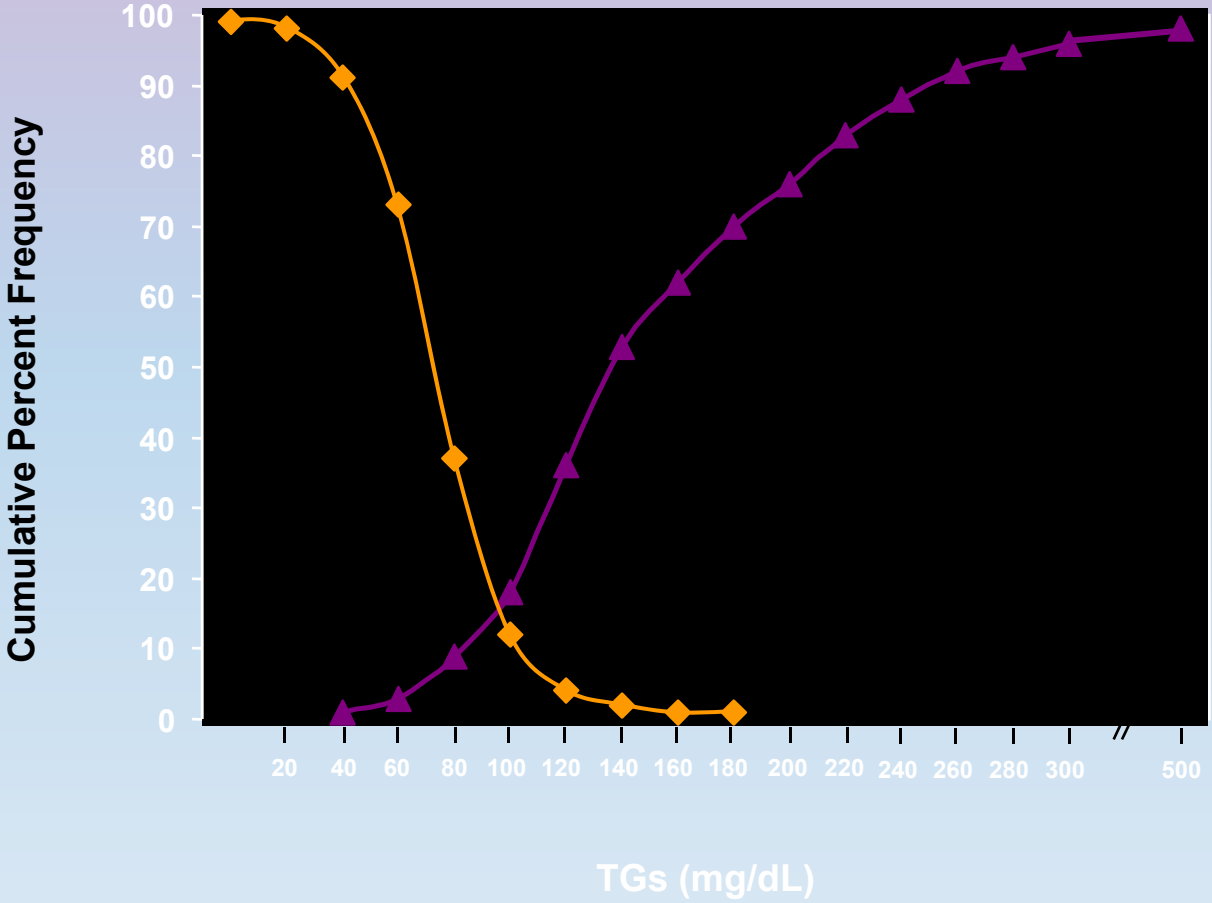
Cumulative Distribution of Adjusted TG Levels by LDL Subtype



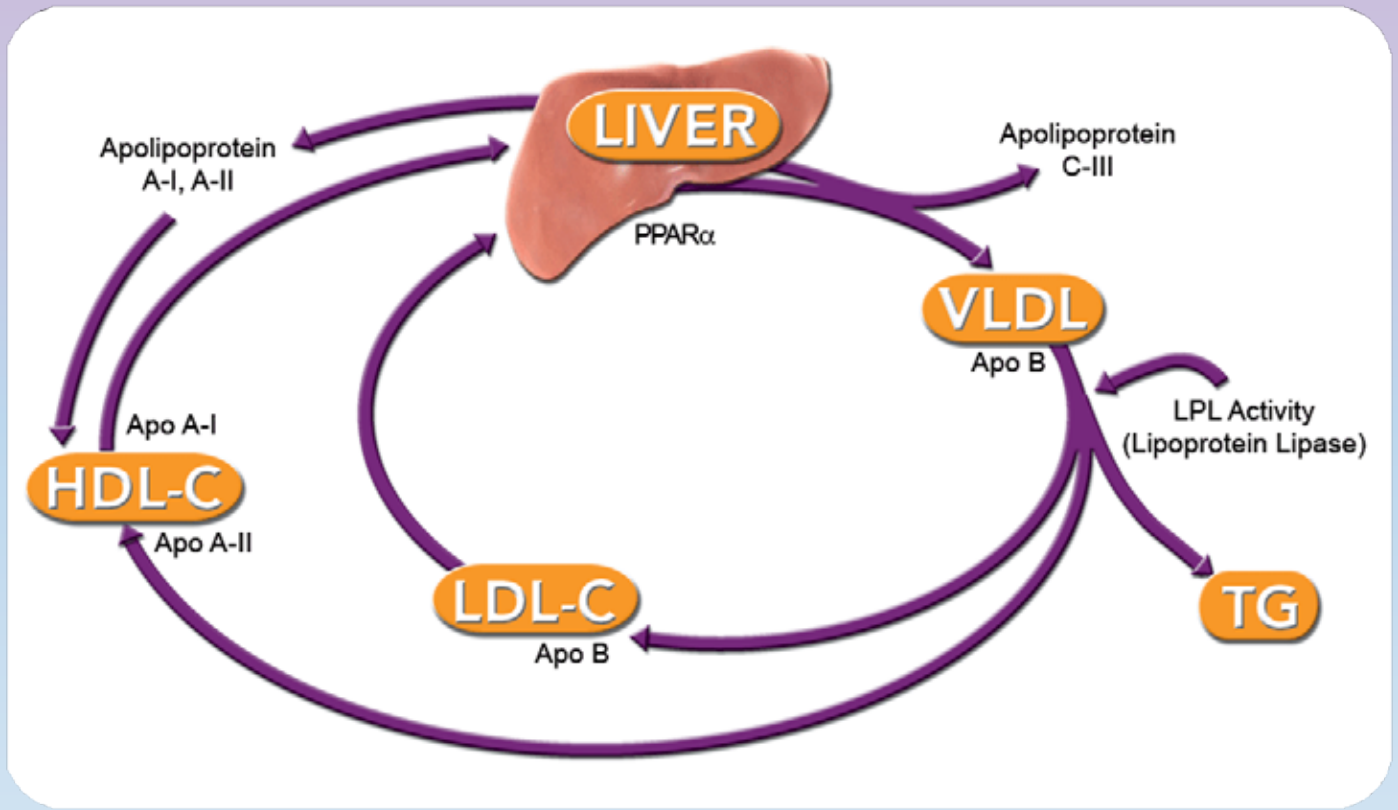
Austin MA et al. *Circulation.* 1990;82:495-506.

Cumulative Distribution of Adjusted TG Levels by LDL Subtype



Austin MA et al. *Circulation.* 1990;82:495-506.

Fenofibrate Mechanism of Action: PPARα Activation[1,2]



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Fenofibrate Mode of Activation

FIBRATES activate → PPARα → Modifies transcription factor in genes

Lipoprotein Lipase can metabolize TRIG.: Energy and Fat storage

1. Once TRIG. Is removed from peripheral circulation

   VLDL & ApoB are reduced

   HDL is increased

   LDL shifts lo large buoyant non-atherogenic particles

   FFA is reduced: improves insulin sensitivity

2. Once TRIG. & FFA removed from liver

   PPARα stimulates production ApoA1 & ApoA2 precursors nascent HDL1

   mature HDL2

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TRILIPIX™ (fenofibric acid) delayed-release capsules: Safety Data Reported Through Week 12 — Other Important Safety Parameters Through Week 12 (N=2698)

Other Important Safety Parameters Through Week 12 (N=2698)[1,2]						
Parameter	TRILIPIX Monotherapy (n=490)	Low-dose Statin Monotherapy (n=493)	TRILIPIX + Low-dose Statin (n=490)	Moderate-dose Statin Monotherapy (n=491)	TRILIPIX + Moderate-dose Statin (n=489)	High-dose Statin Monotherapy (n=245)
Rhabdomyolysis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Creatinine >2 mg/dL	0.8%	0.4%	1.3%	0.0%	1.1%	0.4%
CPK elevation >5x ULN	0.0%	0.4%	1.2%	0.6%	0.2%	1.3%
ALT >3x ULN (2 consecutive)	1.9%	0.0%	1.3%	0.0%	1.3%	0.8%
AST >3x ULN (2 consecutive)	0.2%	0.0%	0.4%	0.0%	0.4%	0.4%

CPK=creatine phosphokinase; ULN=upper limits of normal; ALT=alanine transaminase, AST=aspartate aminotransferase.

TRILIPIX 12 Week Study

Please see Indications and Important Safety Information on slides 39-42.
Full Prescribing Information available from your representative.

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TRILIPIX™ (fenofibric acid) delayed-release capsules: Safety Data Reported up to Week 64 — Other Important Safety Parameters

Other Important Safety Parameters up to Week 64 (N=2201)[1,2]	
Parameter	**Percentage**
Rhabdomyolysis	0.0%
Creatinine >2 mg/dL (n=2166)	1.3%
CPK elevation >5X ULN (n=2168)	1.3%
ALT >3X ULN (n=2166) (2 consecutive)	1.2%
AST >3X ULN (n=2166) (2 consecutive)	0.5%

*All combination therapy (N=2201) included all subjects who received at least 1 dose of TRILIPIX in combination with either a low-dose or moderate-dose statin in 1 of the double-blind controlled studies or in the open-label study. Data collected across the studies during exposure to TRILIPIX in combination with low- or moderate-dose statins were summarized for this analysis set. Subjects who did not enroll in the open-label study were included.

TRILIPIX Long-term Study

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TRILIPIX™ (fenofibric acid) delayed-release capsules: Important Safety Information

- TRILIPIX is contraindicated in patients with severe renal impairment; active liver disease or unexplained persistent liver function abnormalities; preexisting gallbladder disease; in nursing mothers; or in patients with hypersensitivity to fenofibric acid, choline fenofibrate or fenofibrate
- **Fibrate and statin monotherapy increase the risk of myositis or myopathy, and have been associated with rhabdomyolysis. Data from observational studies suggest that the risk for rhabdomyolysis is increased when fibrates are co-administered with a statin. The risk for serious muscle toxicity appears to be increased in elderly patients and in patients with diabetes, renal failure, or hypothyroidism**
- Myopathy should be considered in patients with muscle pain, tenderness, or weakness. If markedly elevated CPK levels occur or myopathy/myositis is diagnosed, TRILIPIX and statin therapy should be discontinued

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Lipid Goals

Parameter	ATP III[1]	AHA Women[2]	ADA Position[3] (for adults with diabetes)
Recommended LDL-C Very High Risk	<100 mg/dL <70 mg/dL (2004 ATP III update)[4]	<100 mg/dL	<100 mg/dL
Recommended TGs	<150 mg/dL	<150 mg/dL	<150 mg/dL
Recommended HDL-C	>40 mg/dL	>50 mg/dL	>40 mg/dL men; >50 mg/dL women
LDL-C Goal for CHD or Equivalents	<100 mg/dL	<100 mg/dL	<70 mg/dL
Non-HDL-C Goal	<130 mg/dL	<130 mg/dL	