Oregon Heart & Vascular INSTITUTE

Atherosclerosis – A Spectrum of Disease: February 14, 2017

Richard Cameron Padgett, MD

Executive Medical Director Oregon Heart & Vascular Institute

Pt RB

Age 38

1ppd Smoker

Father had MI @ Age 46

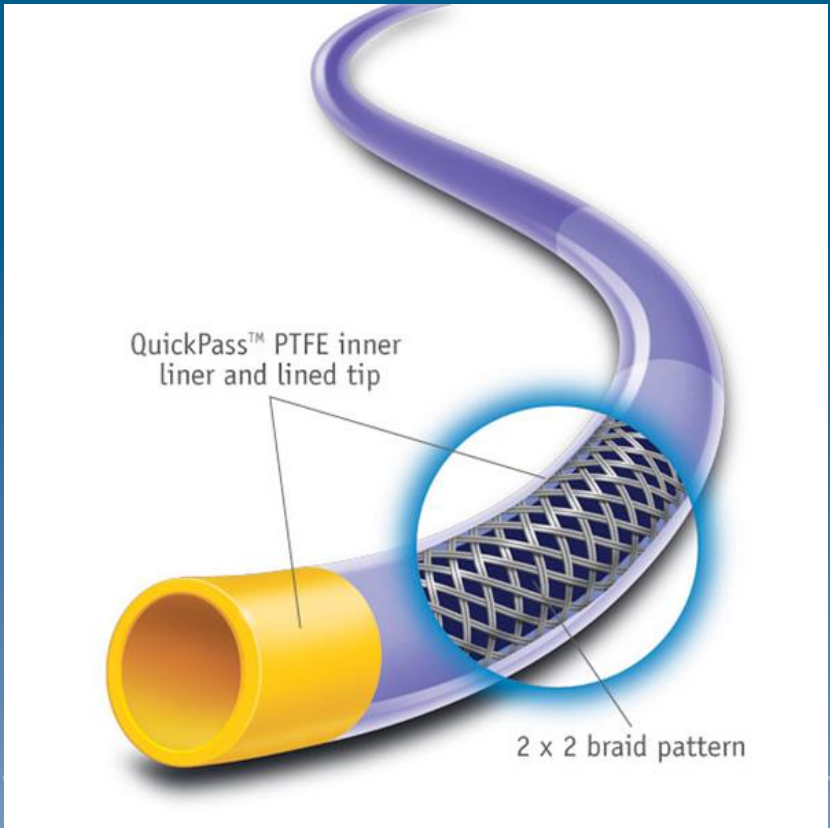
Total Chol 189

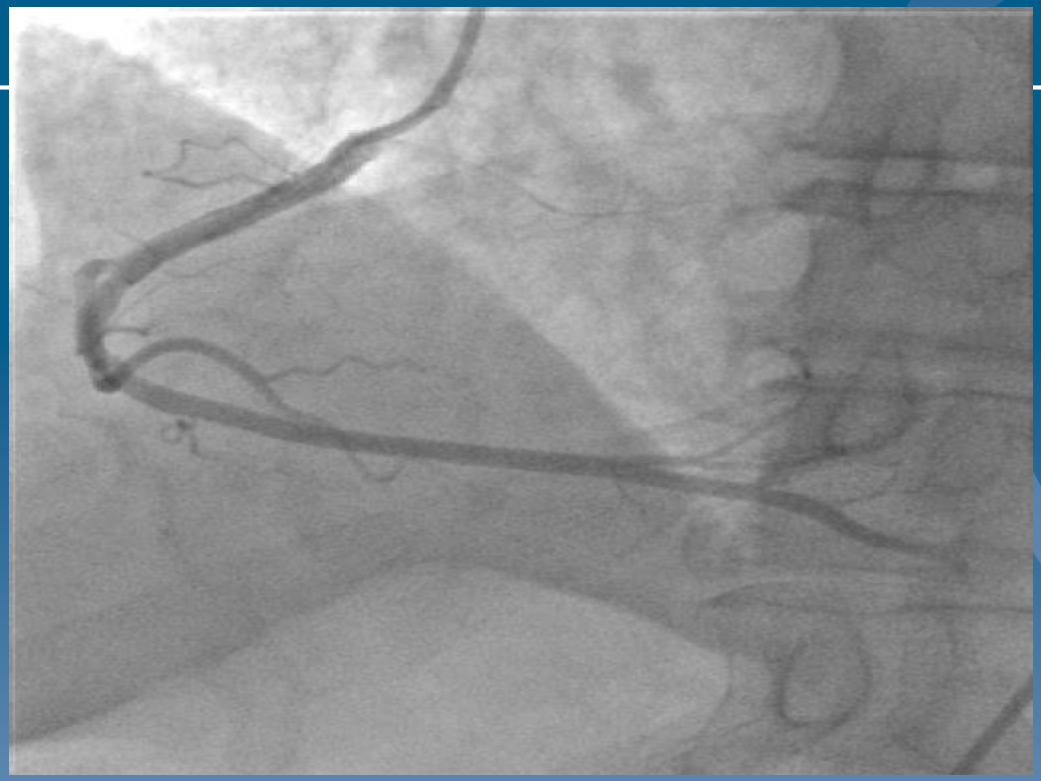
LDL 138

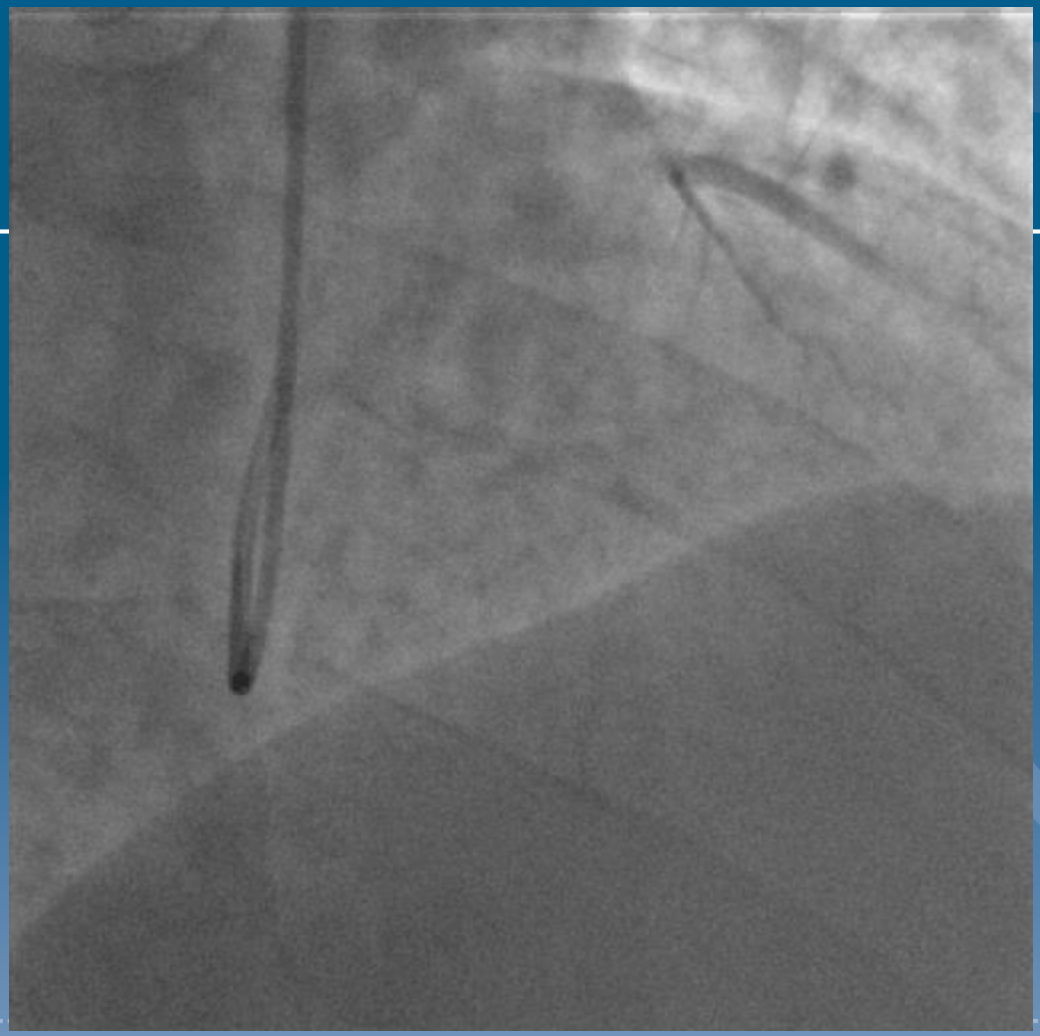
HDL 25

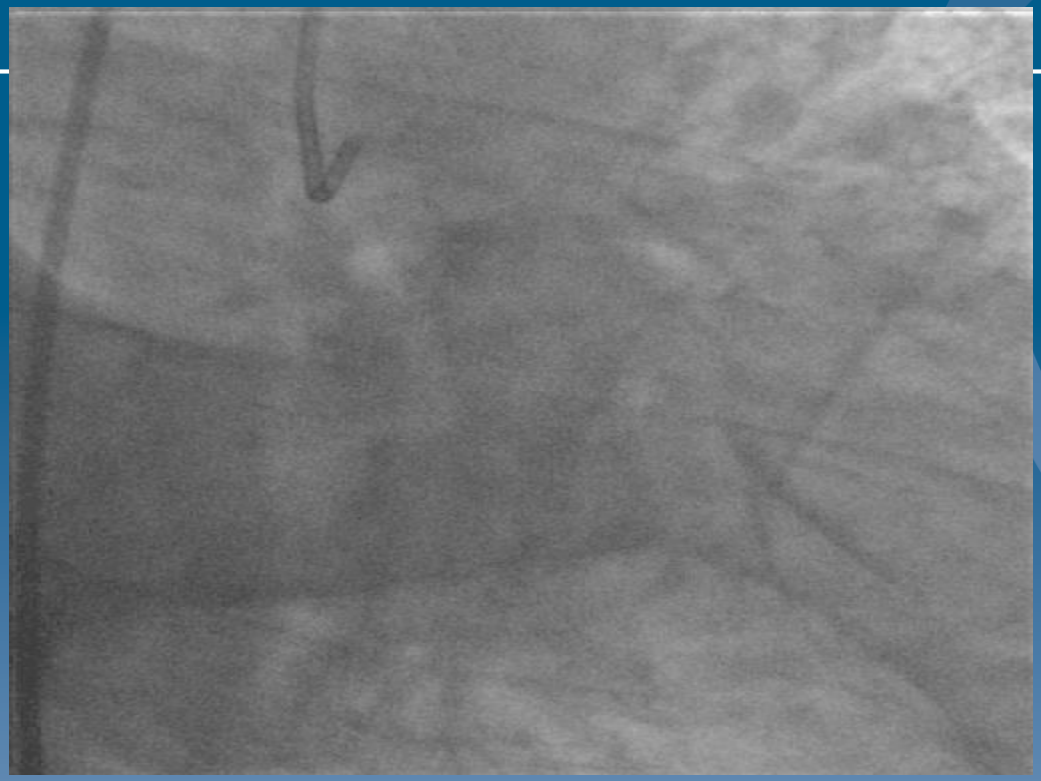
Coronary Angio Suite

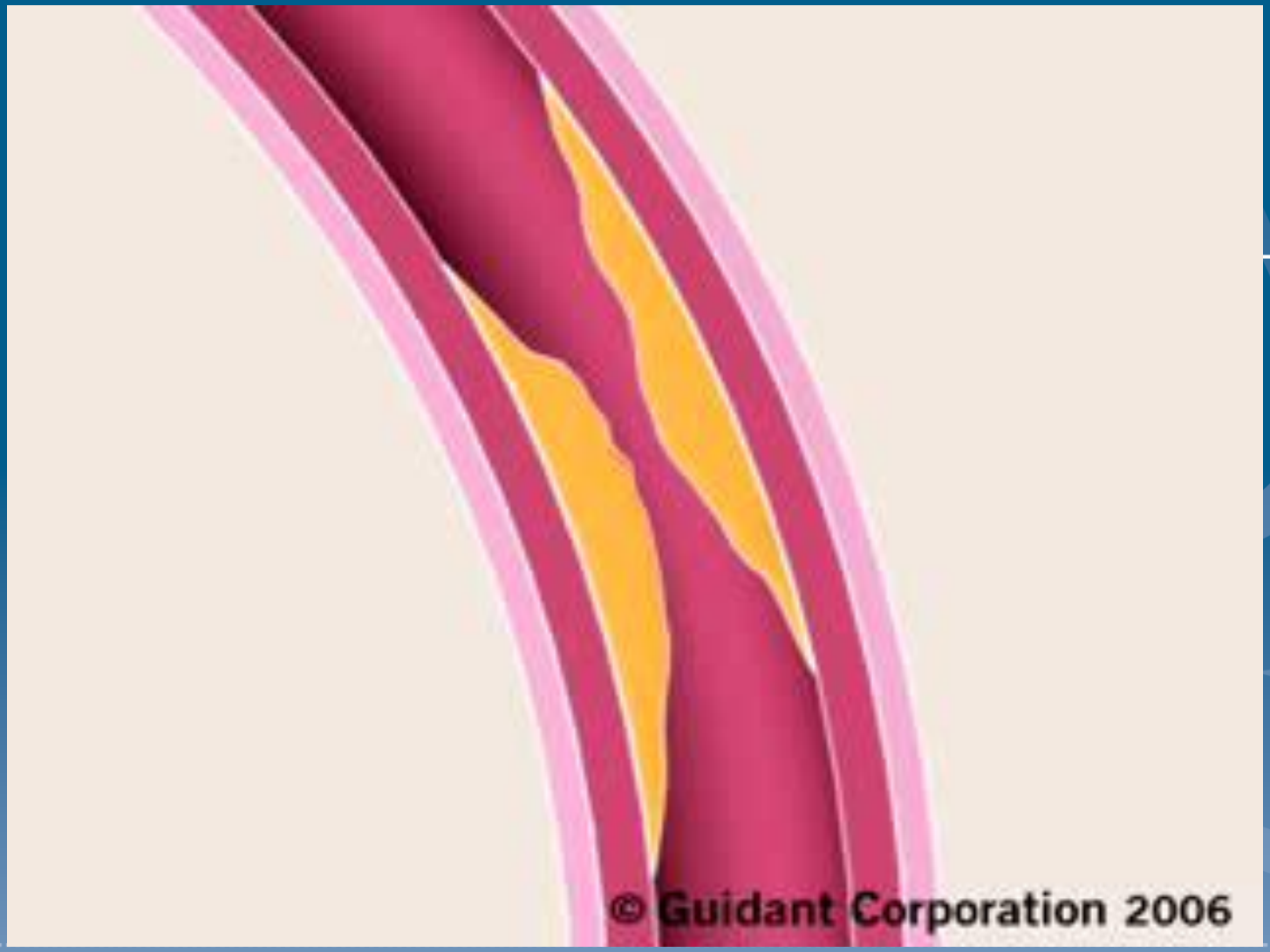
Coronary Catheters

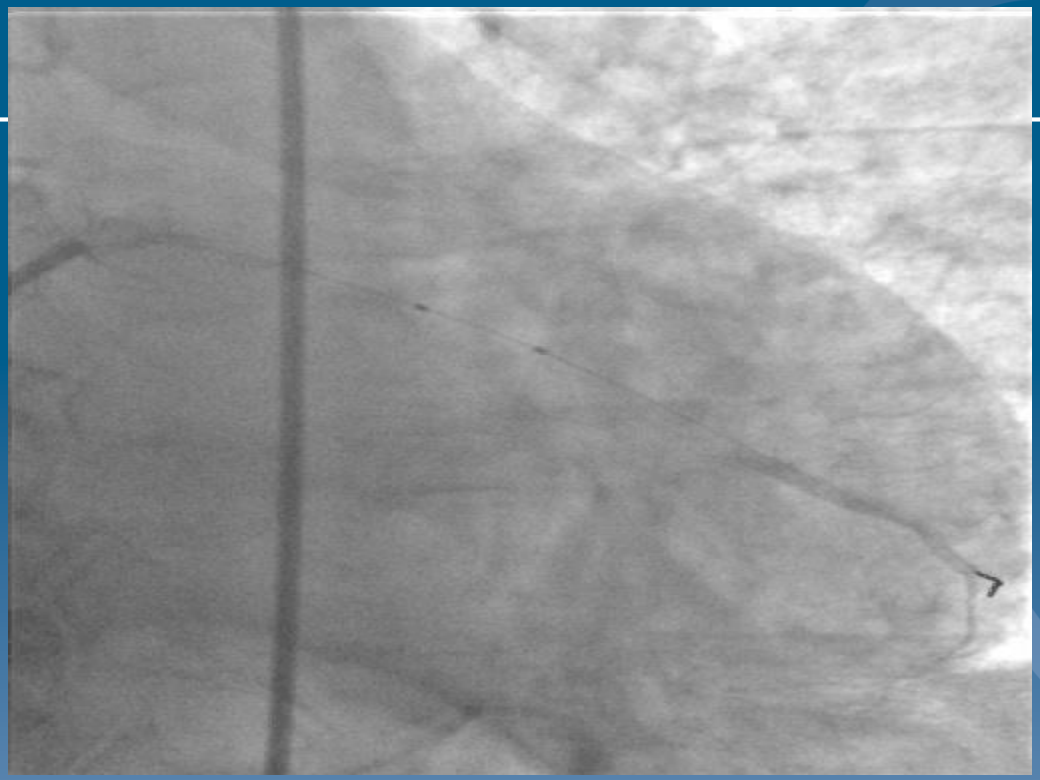


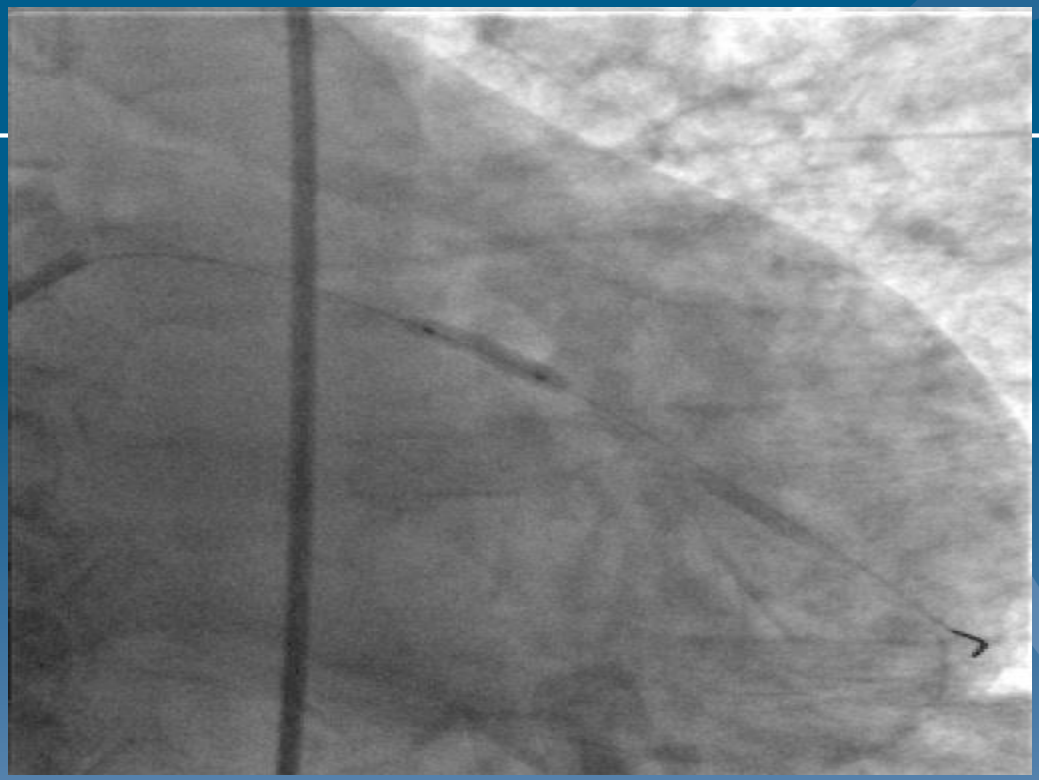


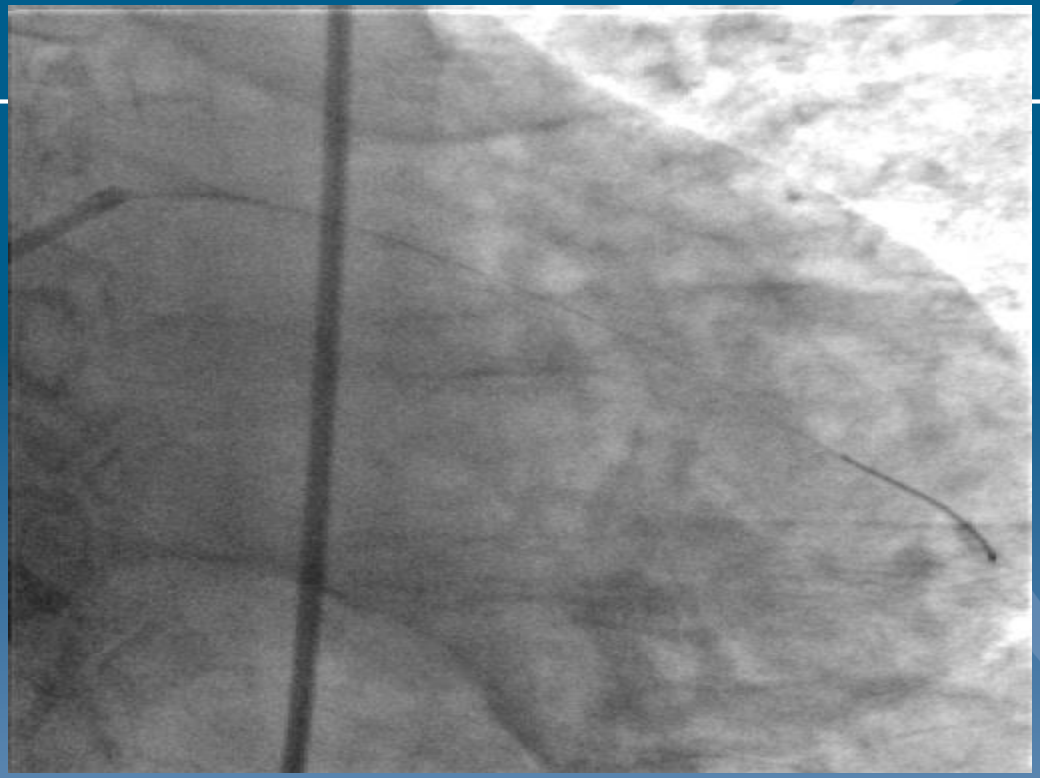


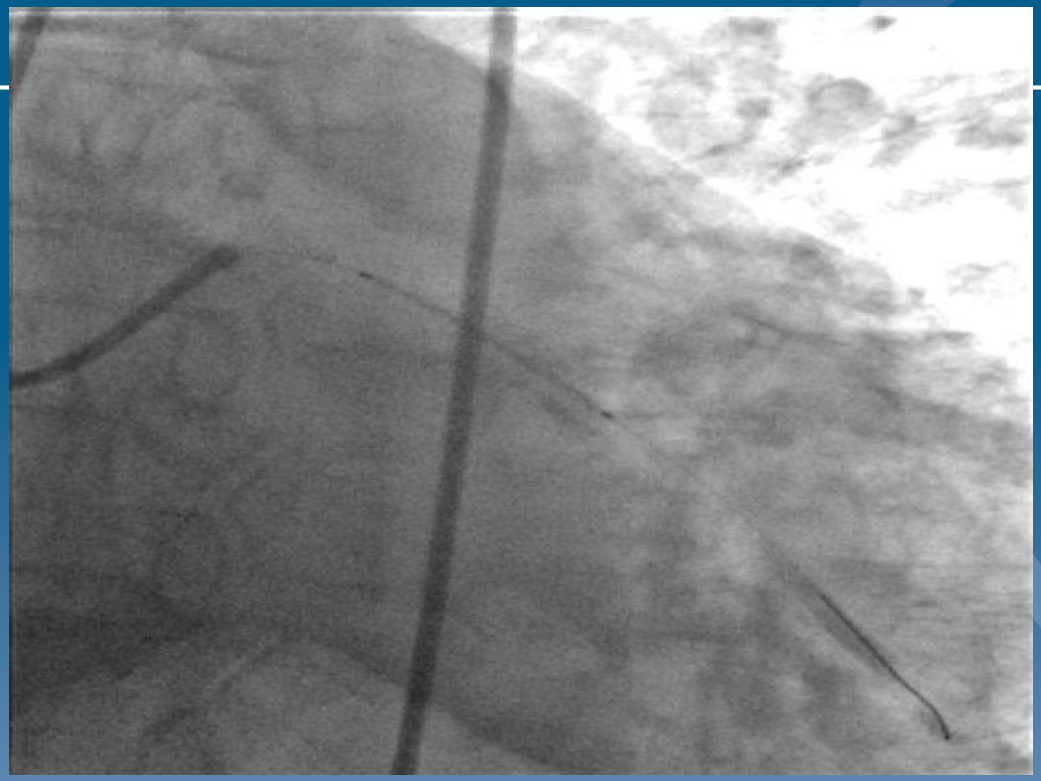


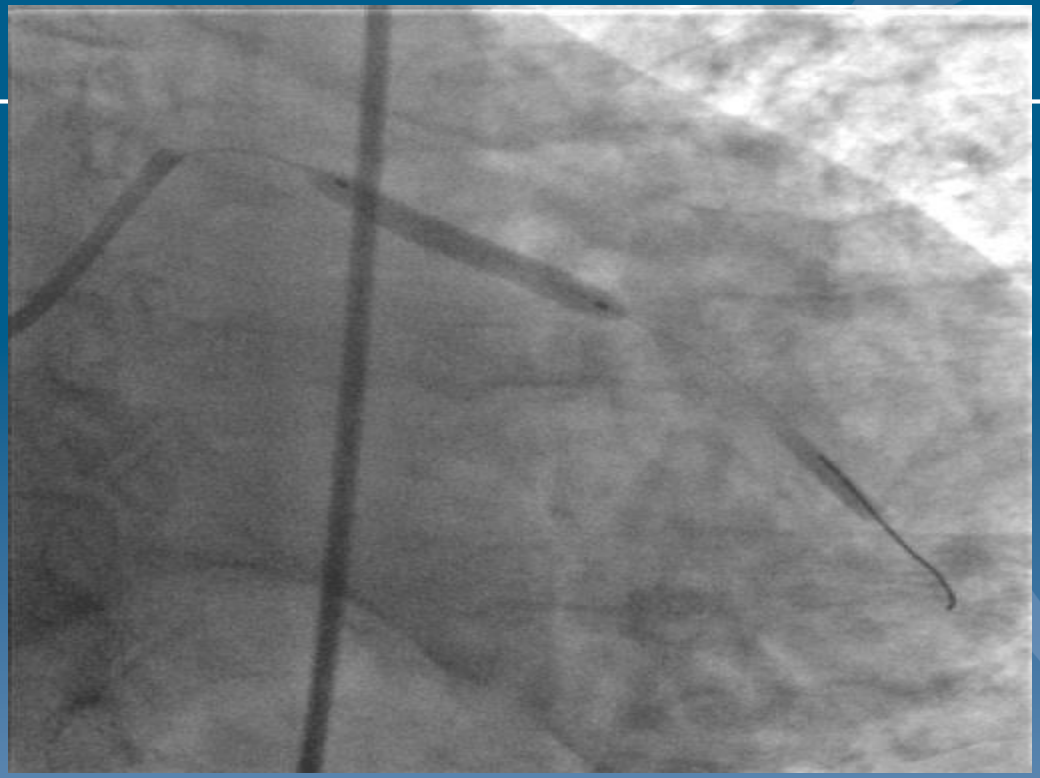

© Guidant Corporation 2006

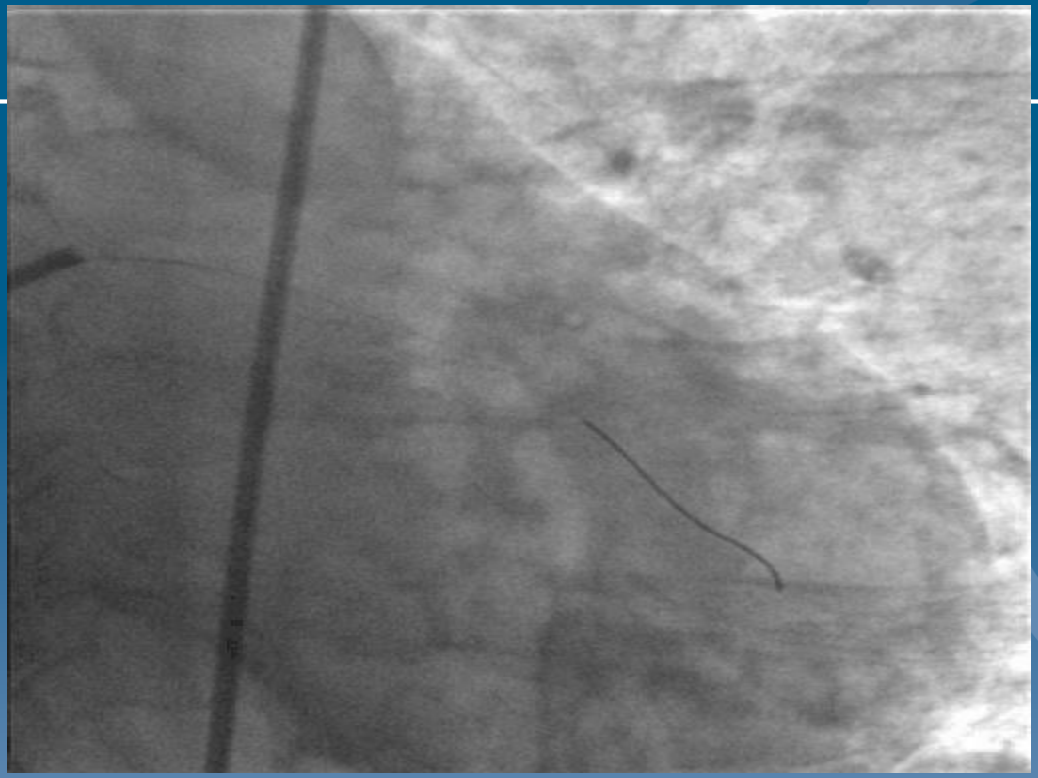




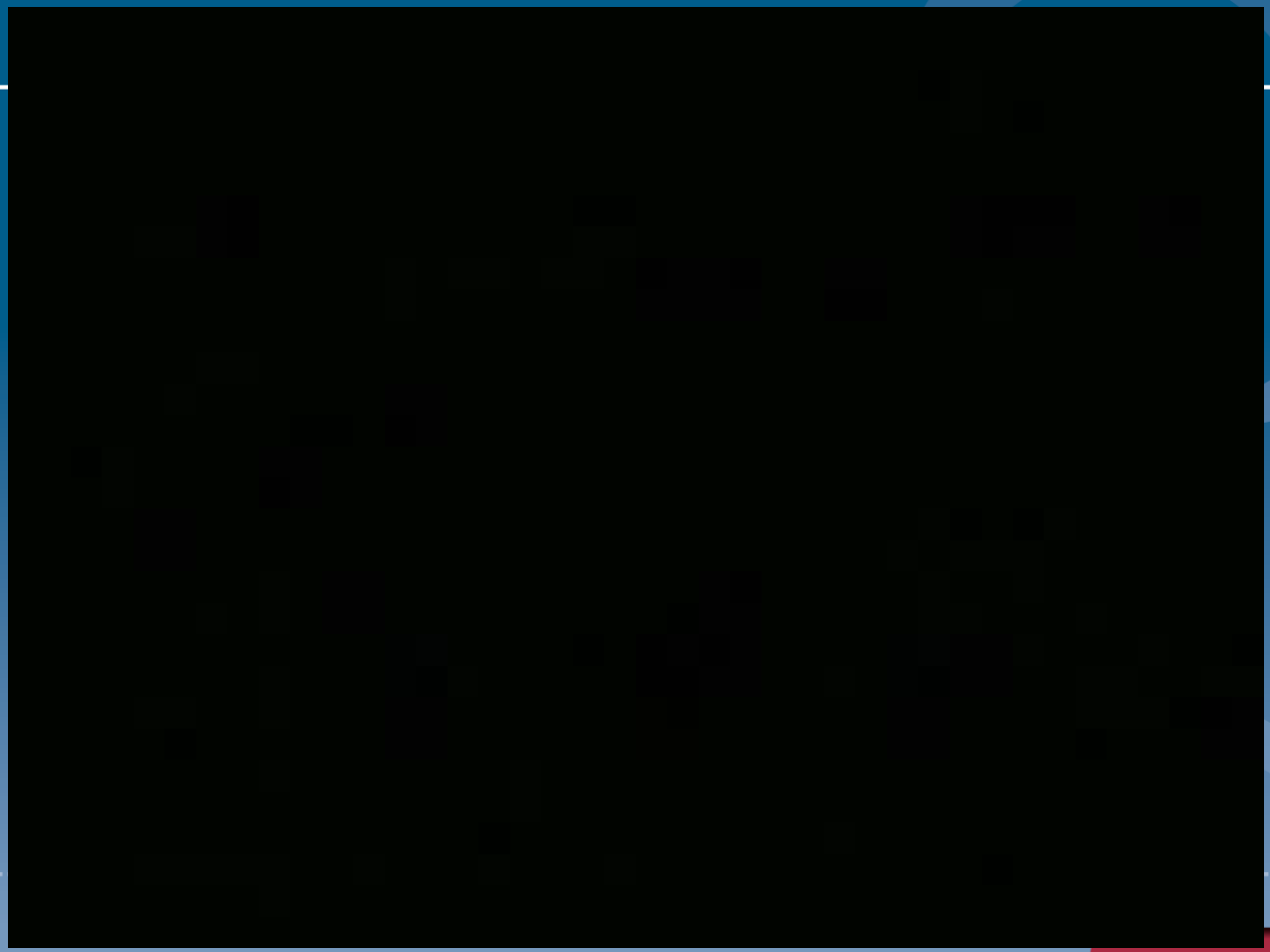








Death is Chasing Them



Current Concepts in Atherosclerosis

Richard C. Padgett, MD

Oregon Heart and Vascular Institute
Oregon Cardiology, PC
Eugene, Springfield, Florence, Reedsport
& Coos Bay

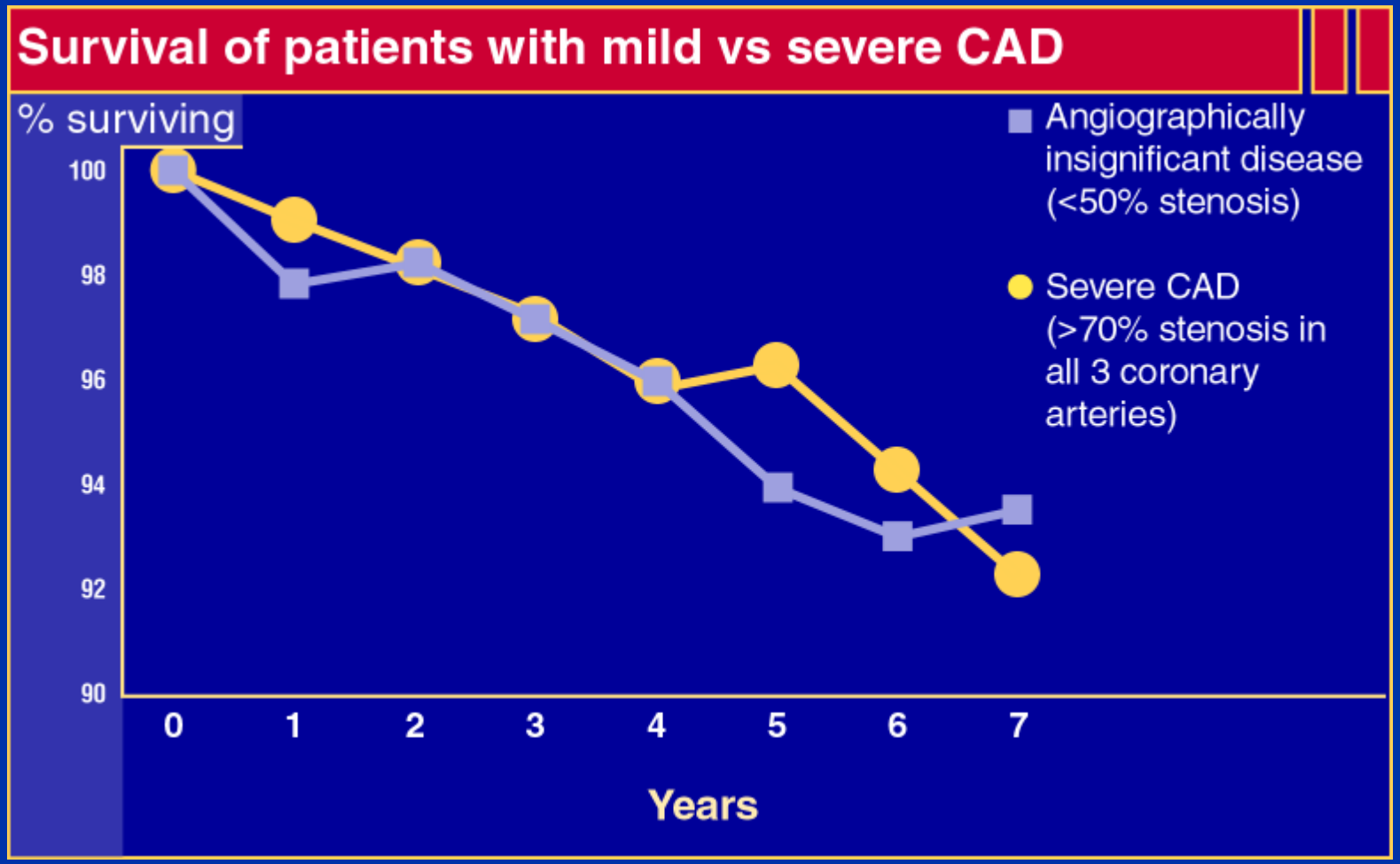
Which Patient needs Treatment

- 60 yo with a 2cm lung mass c/w lung Ca
- 60 yo with a 2cm lung mass and weight loss
- 60 yo with a 2 cm lung mass and Bronchial obstruction

Which Patient needs treatment

- 60 yo with “minor” luminal irregularities
- 60 yo with “mild” coronary artery disease
- 60 yo with “diffuse” coronary artery disease
- 60 yo with 95% stenosis of RCA
- 60 yo with multi-vessel CAD requiring CABG

Lesion Severity: A Poor Predictor of Survival



From the Coronary Artery Surgery Study (CASS) as reported by Little et al.

Little WC et al, *Clin Cardiol*, 1991.

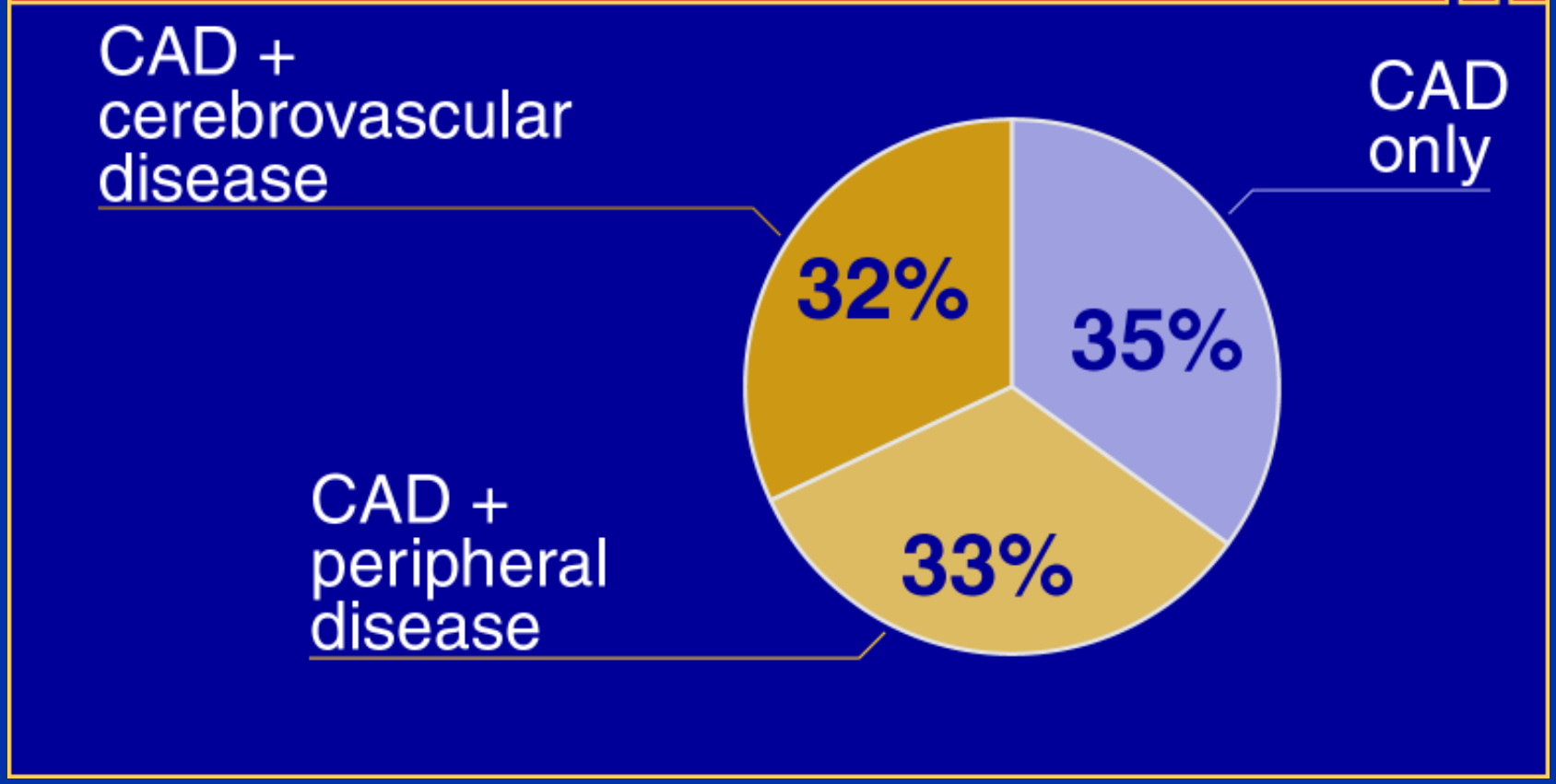
Vascular Disease: Scope of the Problem

- Vascular disease—and CAD in particular—is the leading cause of death in the US and other Western nations
- By 2020, cardiovascular disease will become the most common cause of death worldwide
- Due to the high initial mortality of vascular disease, the target of clinical practice must be aggressive risk factor management

American Heart Association®, *2000 Heart and Stroke Statistical Update*, 1999; Braunwald E, *N Engl J Med*, 1997; Kannel WB in *Atherosclerosis and Coronary Artery Disease*, 1996.

Atherosclerosis: A Systemic Disease

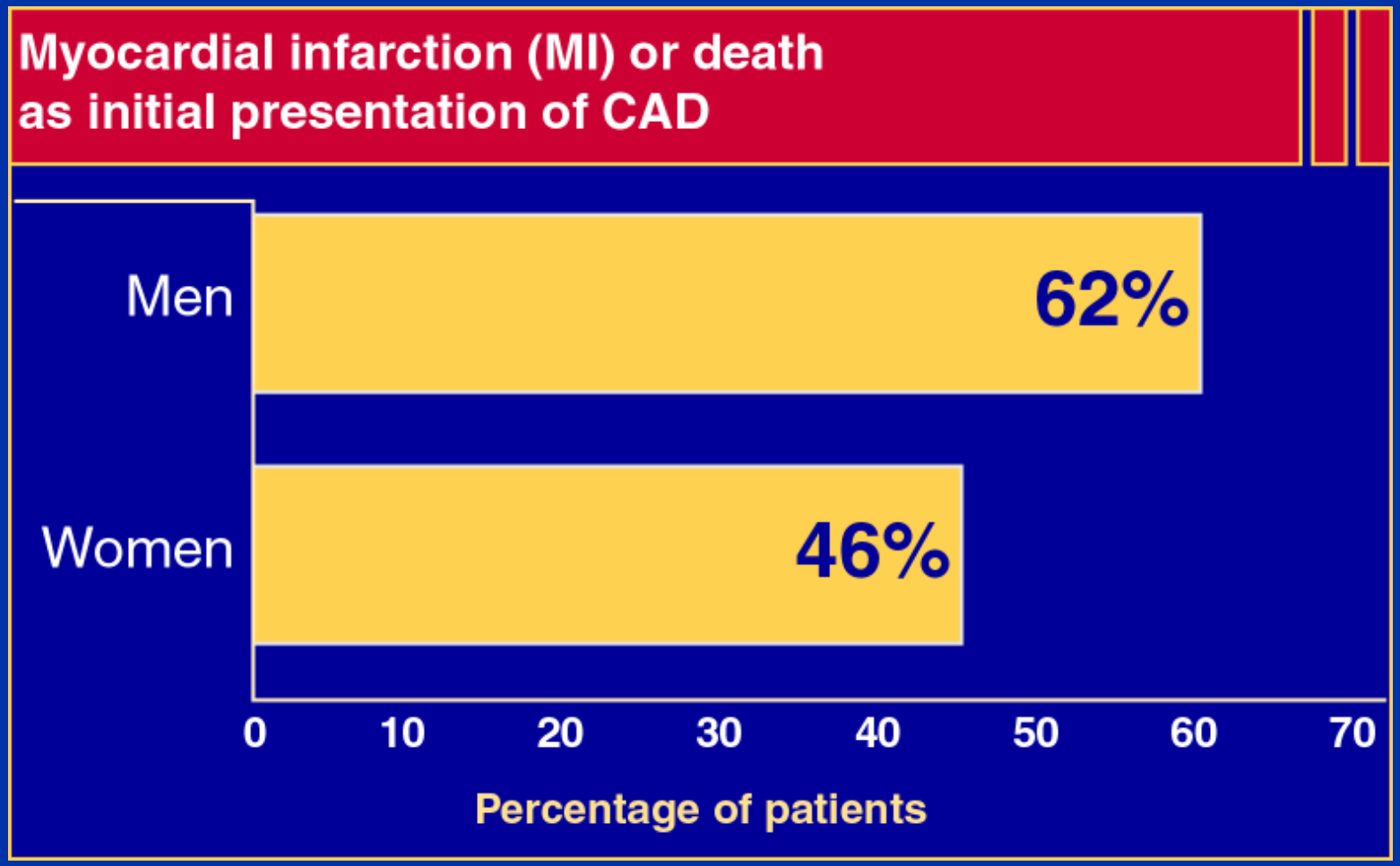
Most CAD patients have concomitant *symptomatic* peripheral or cerebrovascular disease



From a prospective analysis of 1886 patients aged ≥62 years, 810 patients were diagnosed with CAD as defined by a documented clinical history of MI, ECG evidence of Q-wave MI, or typical angina without previous MI. (Adapted from Aronow et al.)

Aronow WS et al, *Am J Cardiol*, 1994.

Coronary Artery Disease (CAD): The Diagnosis Often Comes Too Late



(Adapted from Levy et al.)

Levy D et al in *Textbook of Cardiovascular Medicine*, 1998.

Major Risk Factors for CAD

Modifiable risk factors

- Hypertension
- Dyslipidemia
- Diabetes
- Cigarette smoking
- Obesity
- Physical inactivity

Nonmodifiable risk factors

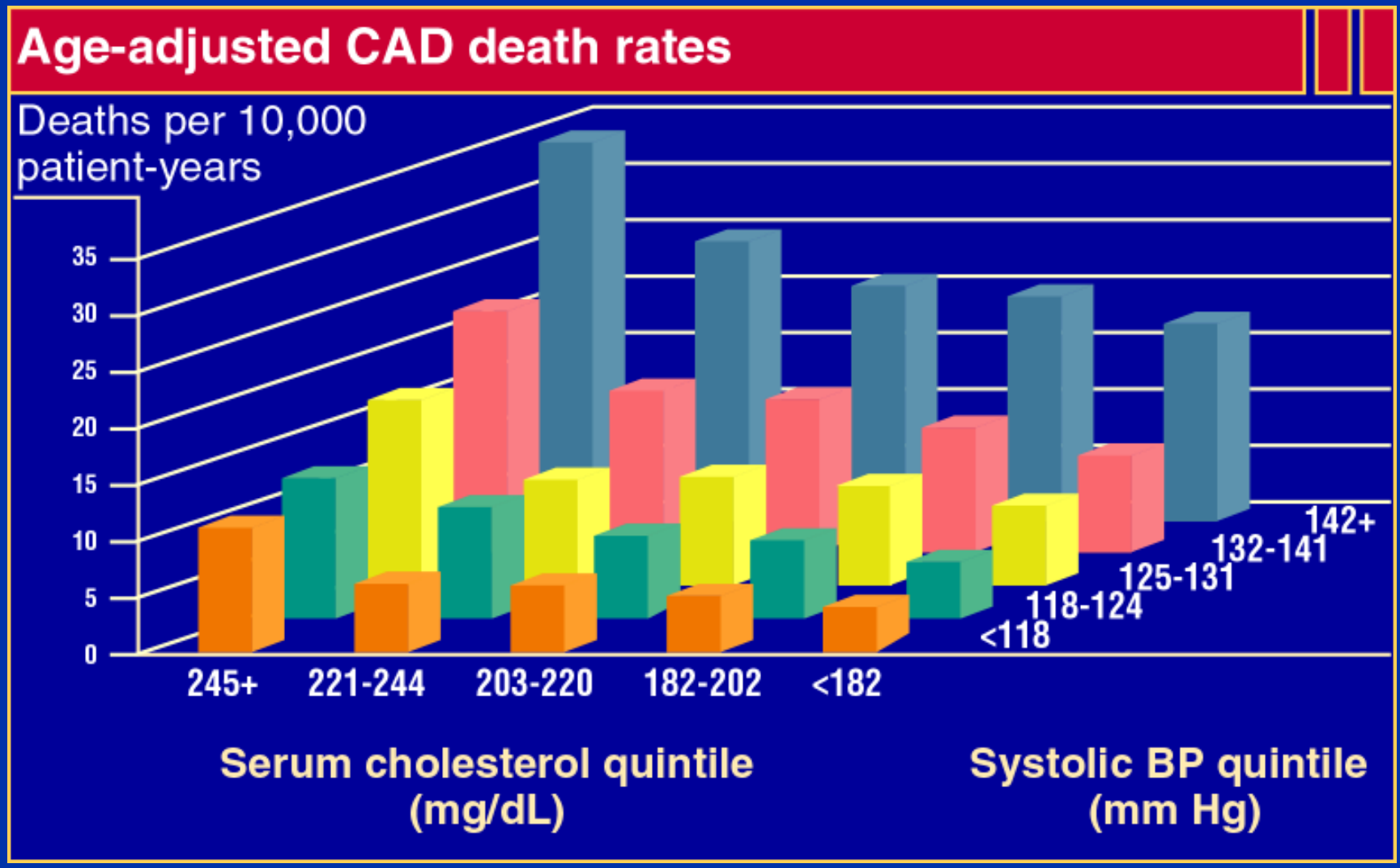
- Family history
- Age
- Gender

Grundy SM et al, *Circulation*, 1998; Grundy SM, *Circulation*, 1999.

New Risk Factors

- Homocysteine
- Lp(a)
- Small dense LDL
- Fibrinogen
- Hs-CRP Risk factor or Disease Identifier
- Coronary Calcium

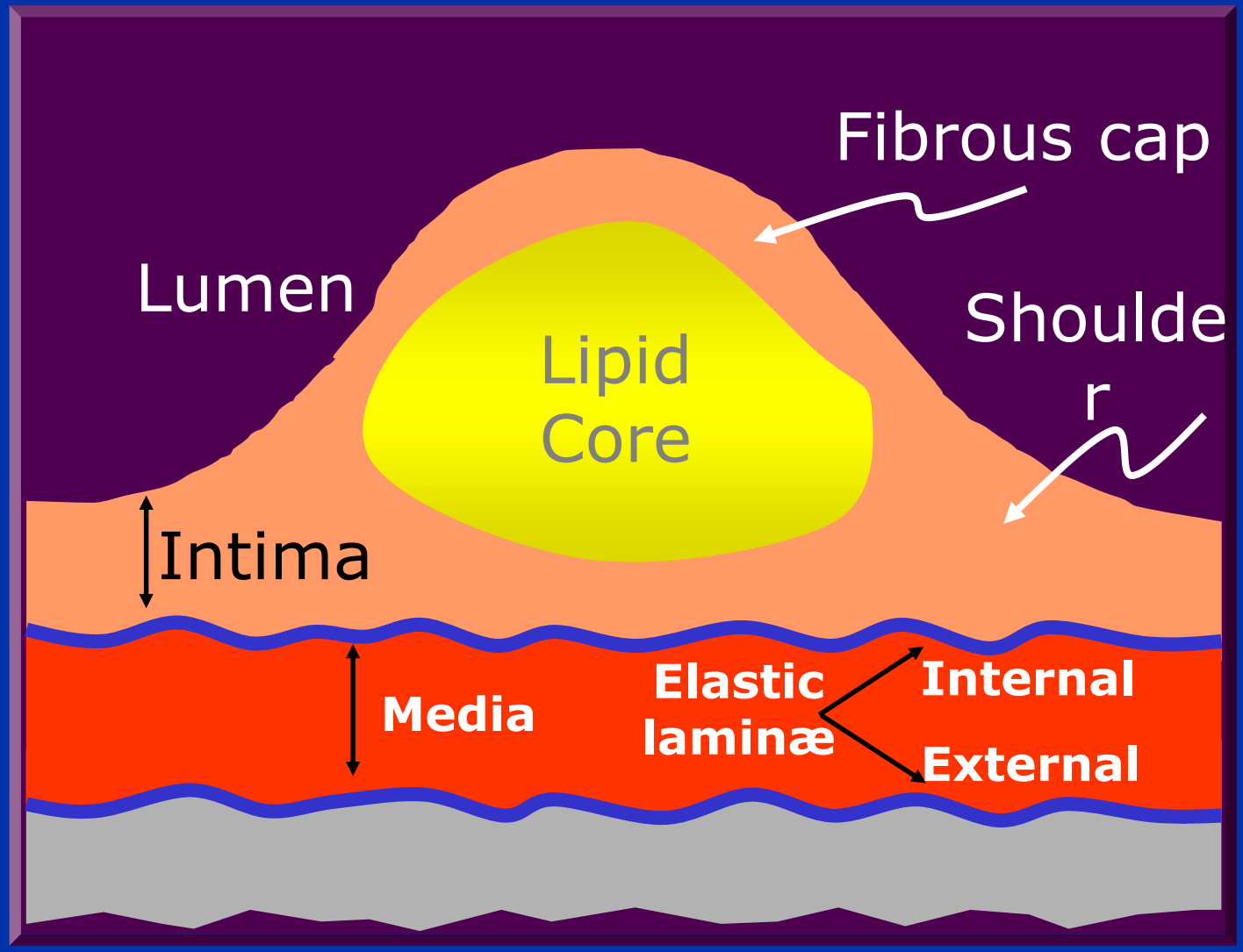
CAD Risk Is Incremental



(Adapted from Neaton et al.)

Neaton JD et al, *Arch Intern Med*, 1992.

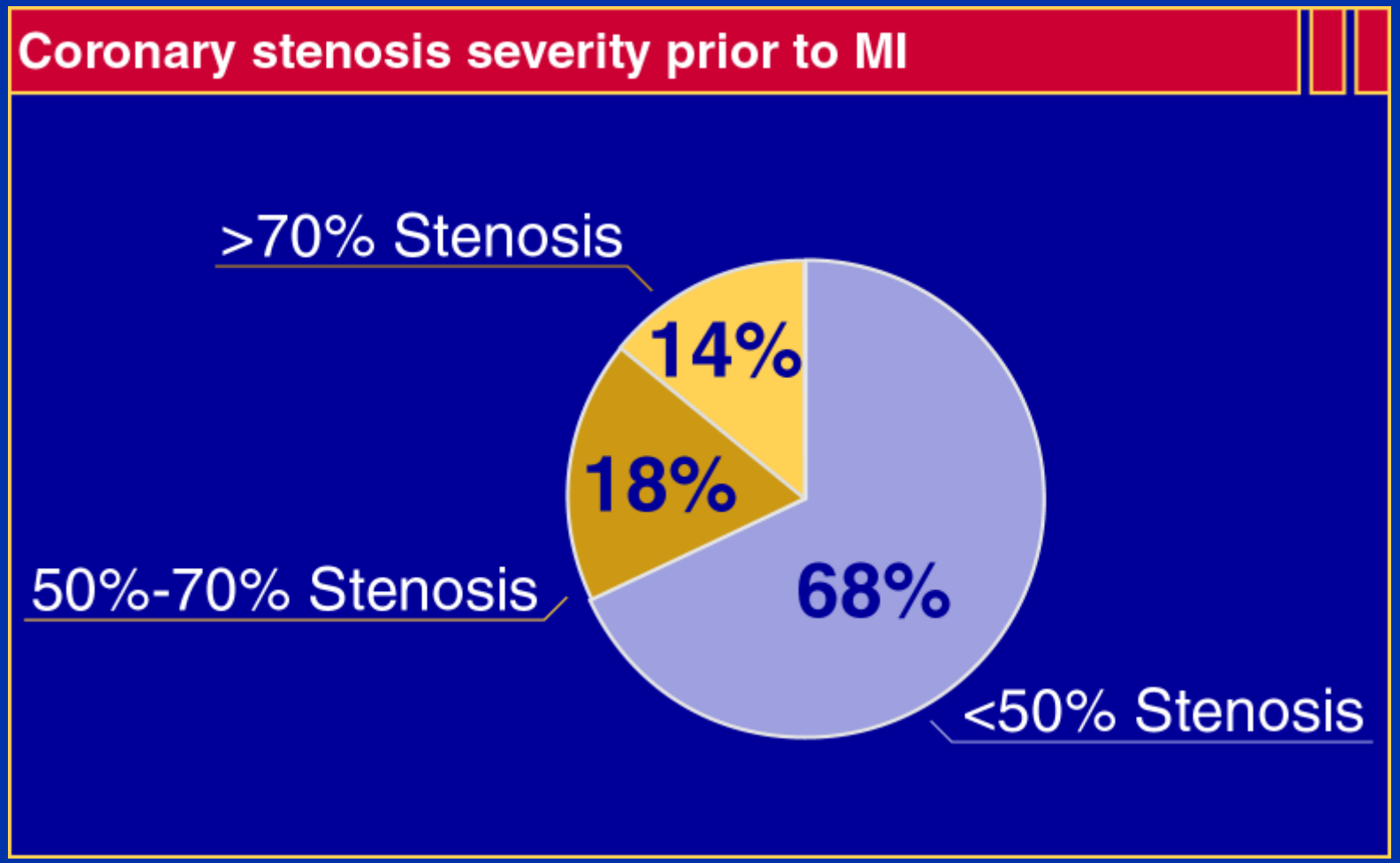
Anatomy of the Atherosclerotic Plaque




Development of Atherosclerotic Plaque

Conventional Concept

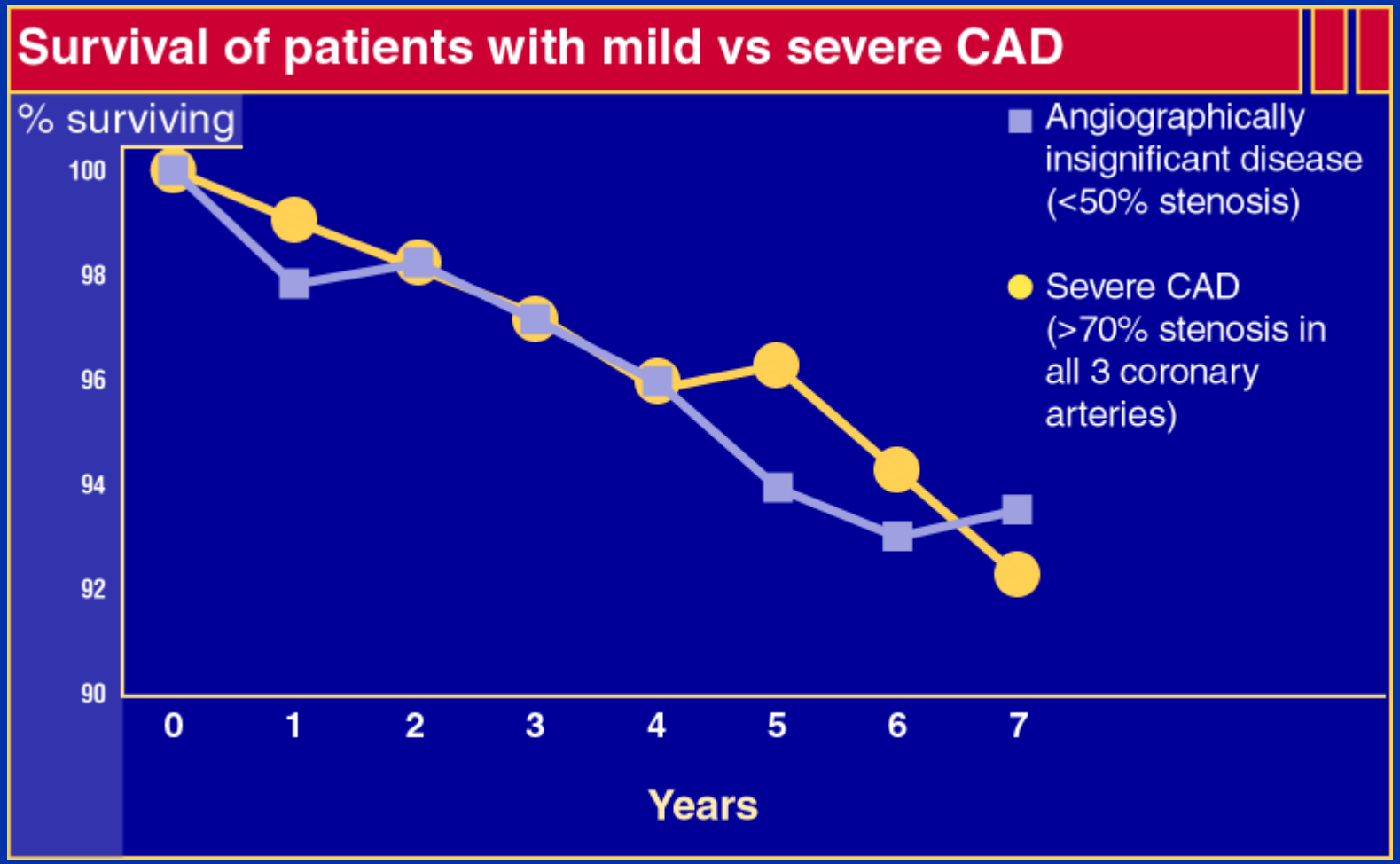
Most Myocardial Infarctions Are Caused by Low-Grade Stenoses



Pooled data from 4 studies: Ambrose et al, 1988; Little et al, 1988; Nobuyoshi et al, 1991; and Giroud et al, 1992.
(Adapted from Falk et al.)

Falk E et al, *Circulation*, 1995.

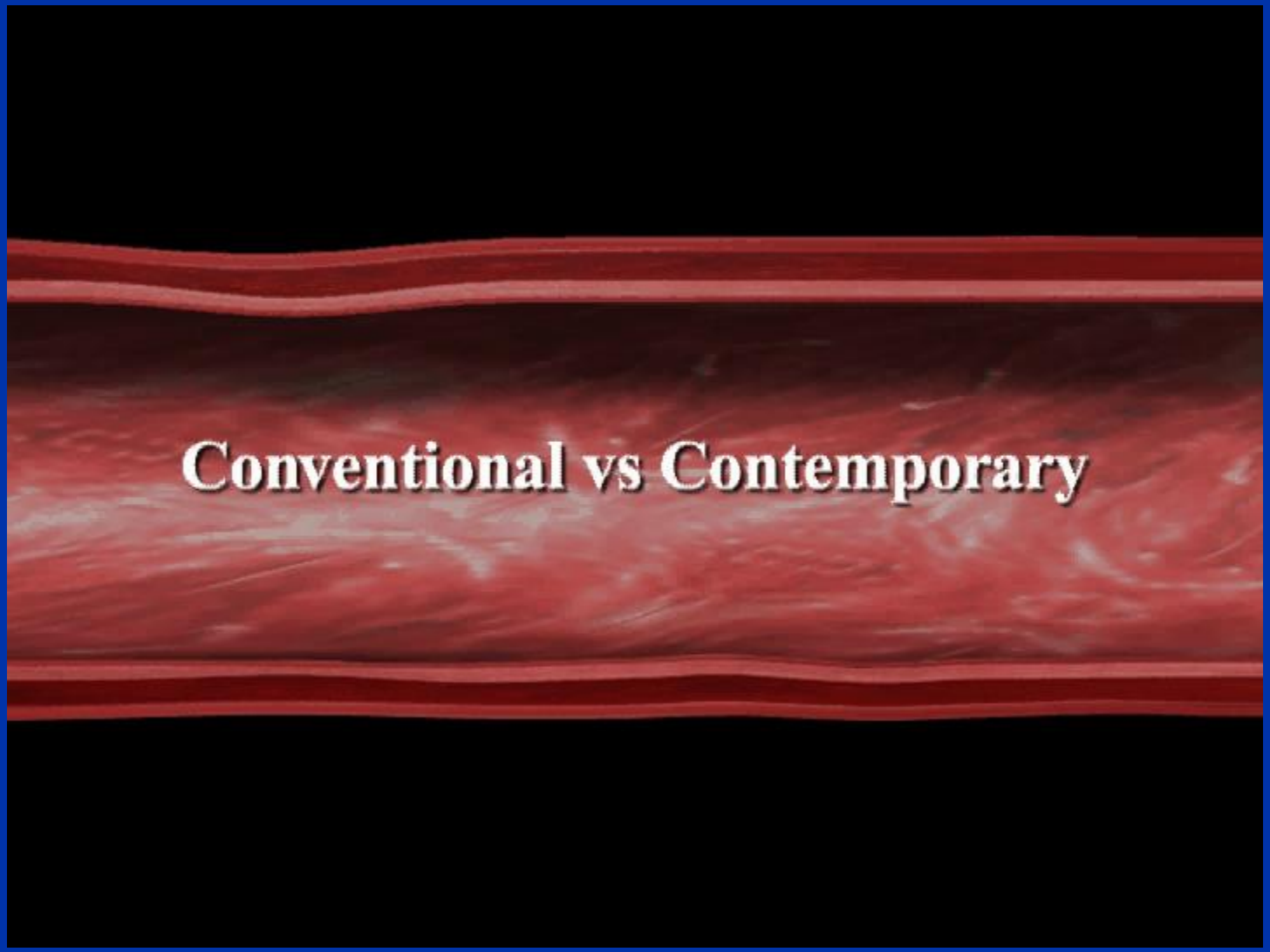
Lesion Severity: A Poor Predictor of Survival



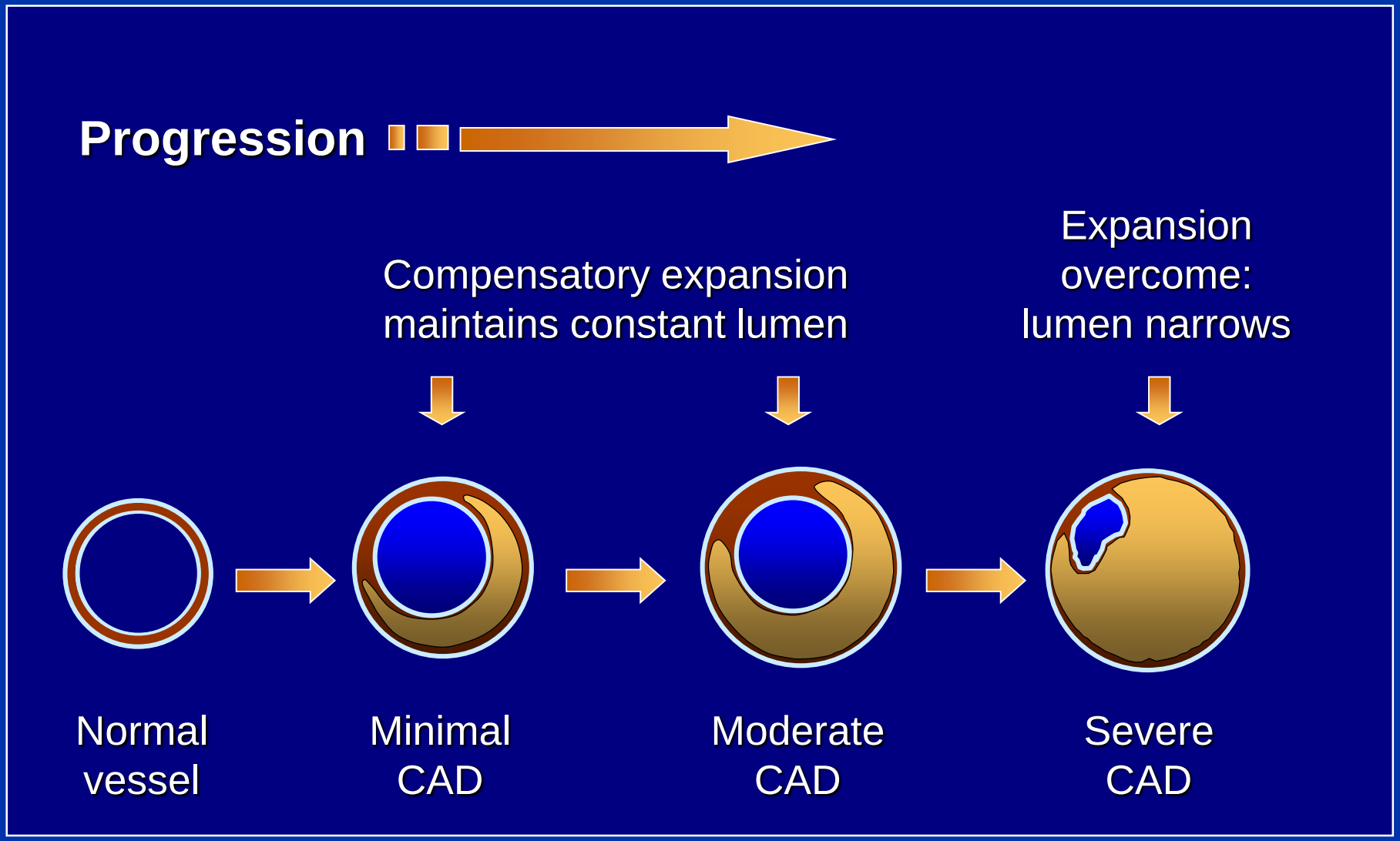
From the Coronary Artery Surgery Study (CASS) as reported by Little et al.

Little WC et al, *Clin Cardiol*, 1991.


Glagov's Model

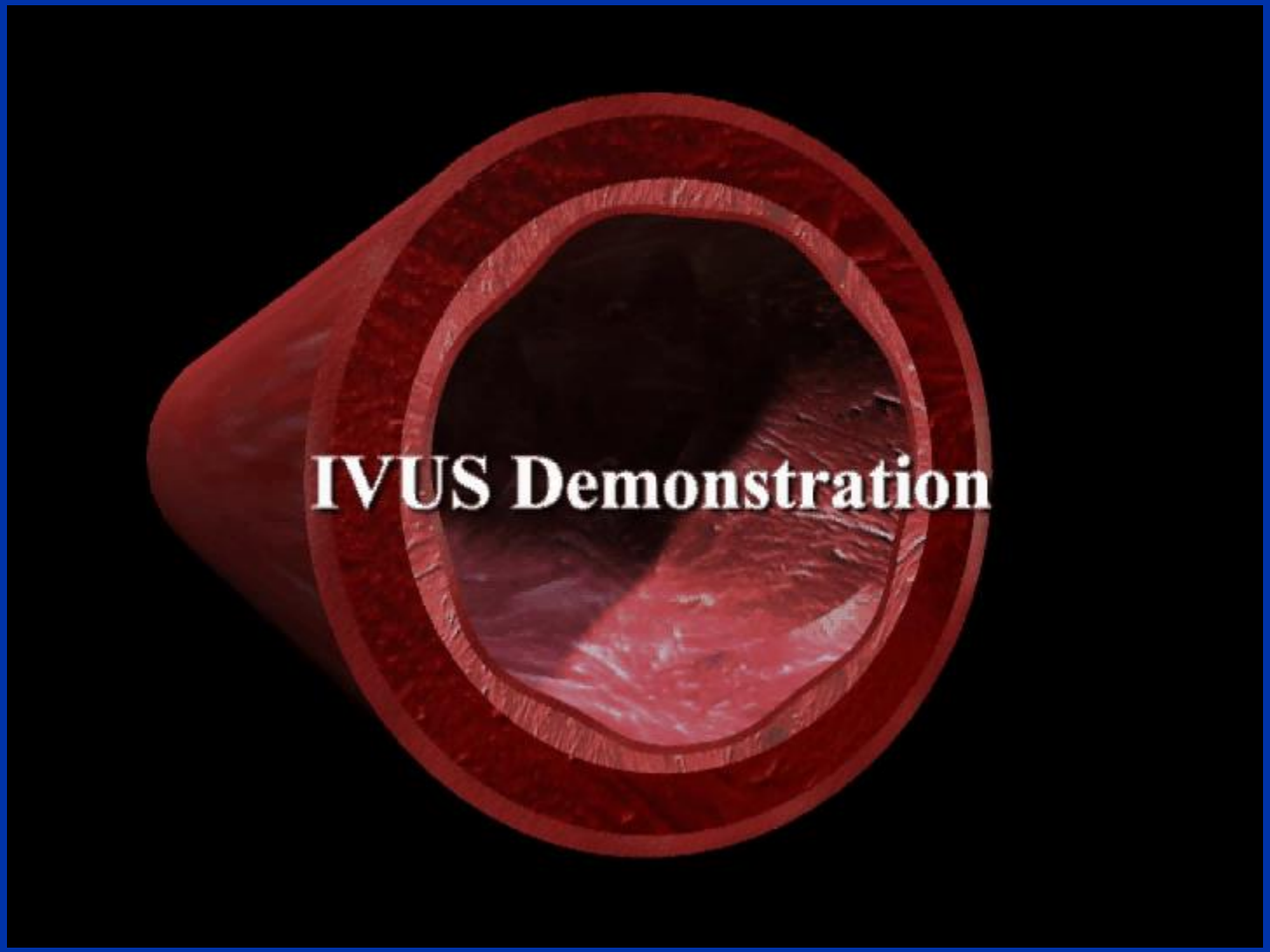

Conventional vs Contemporary

Coronary Remodeling

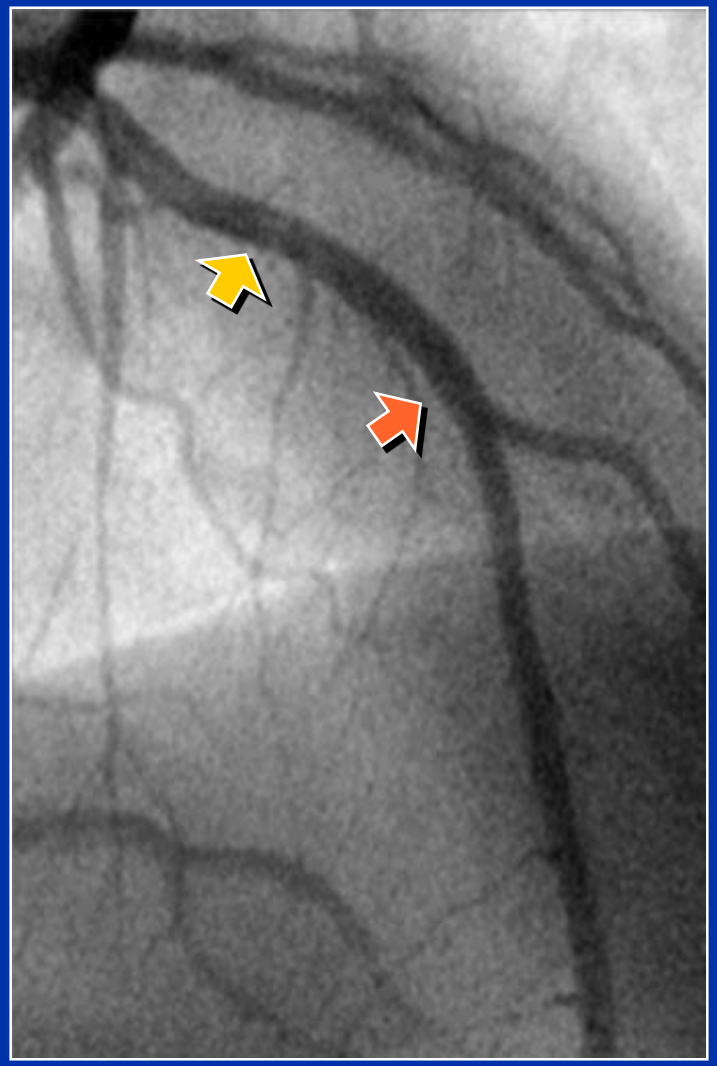


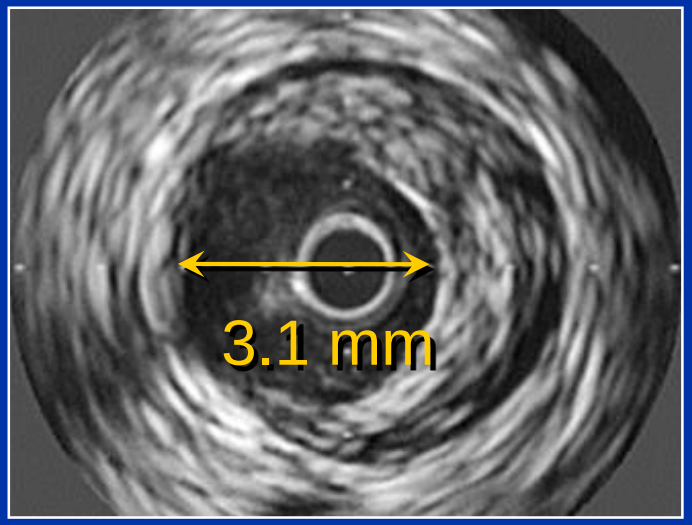
(Adapted from Glagov et al.)

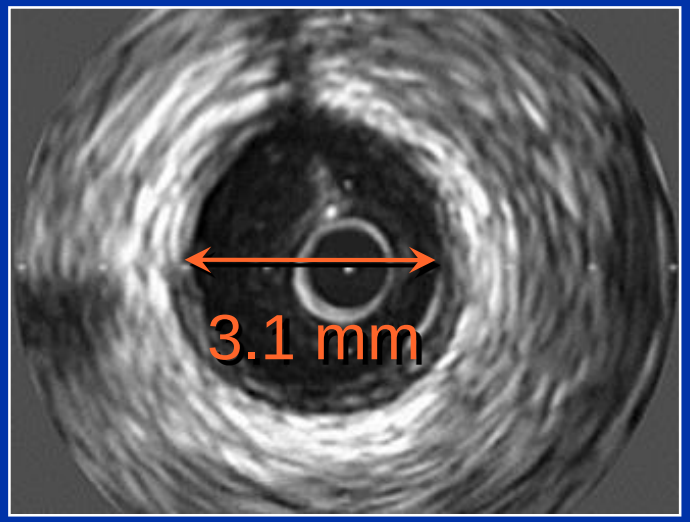
Glagov et al, *N Engl J Med*, 1987.


IVUS Demonstration

Angiography Cannot Account for Coronary Remodeling

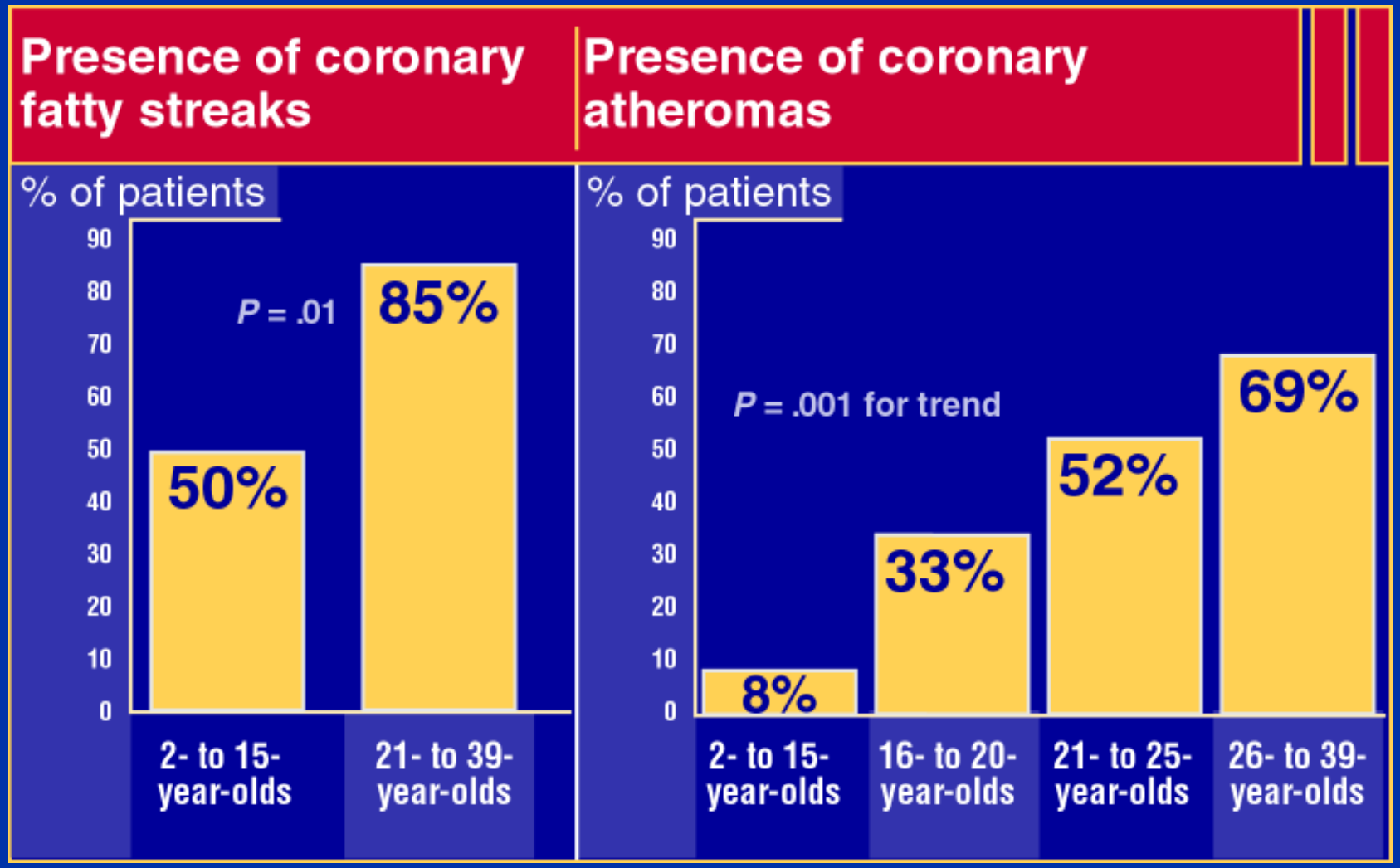







Transition to Acute Coronary Syndrome

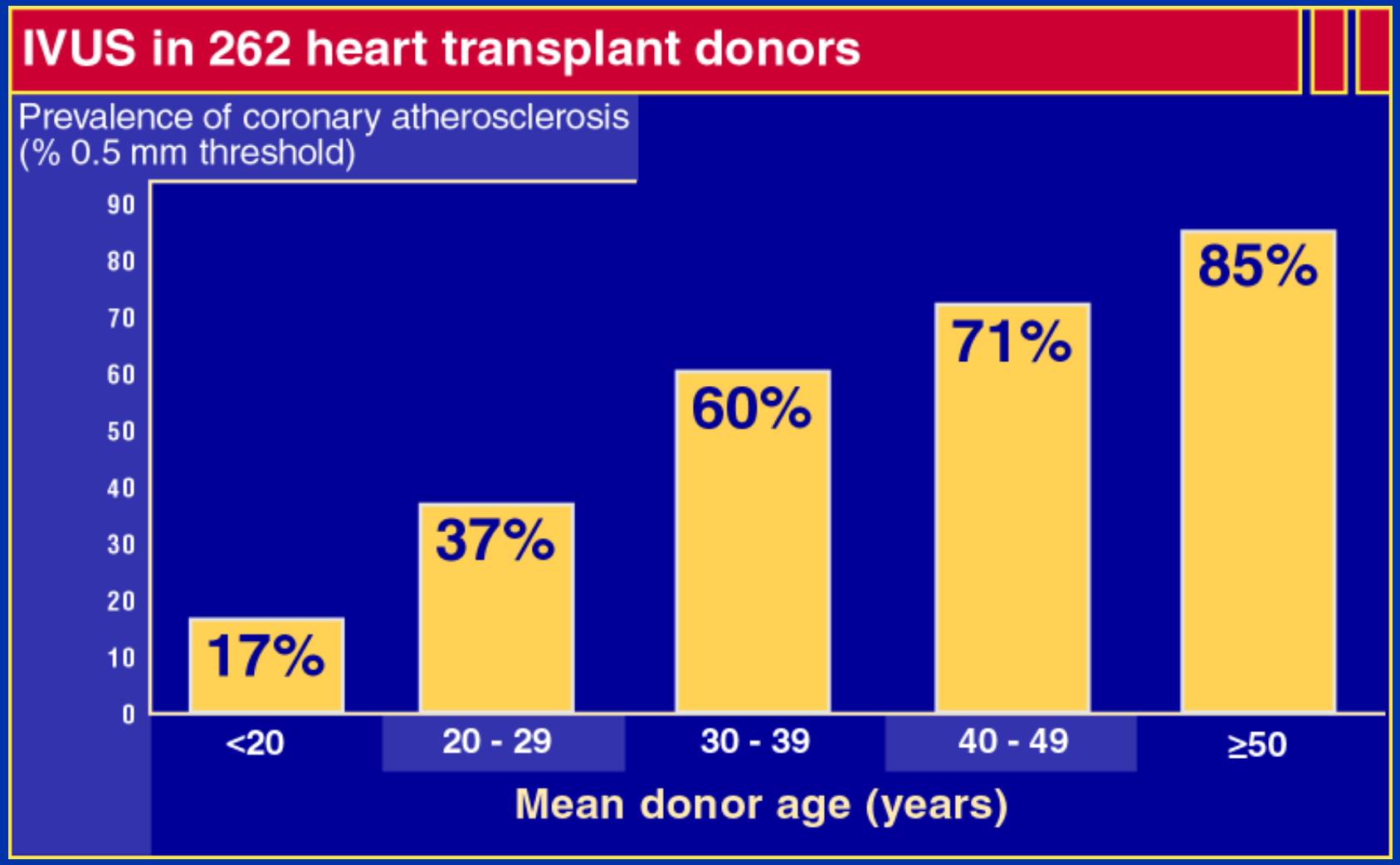
Atherosclerosis Begins in Childhood



(Adapted from Berenson et al.)

Berenson GS et al, *N Engl J Med*, 1998.

One in Six Teenagers Has Atheromas



(Adapted from Tuzcu et al.)

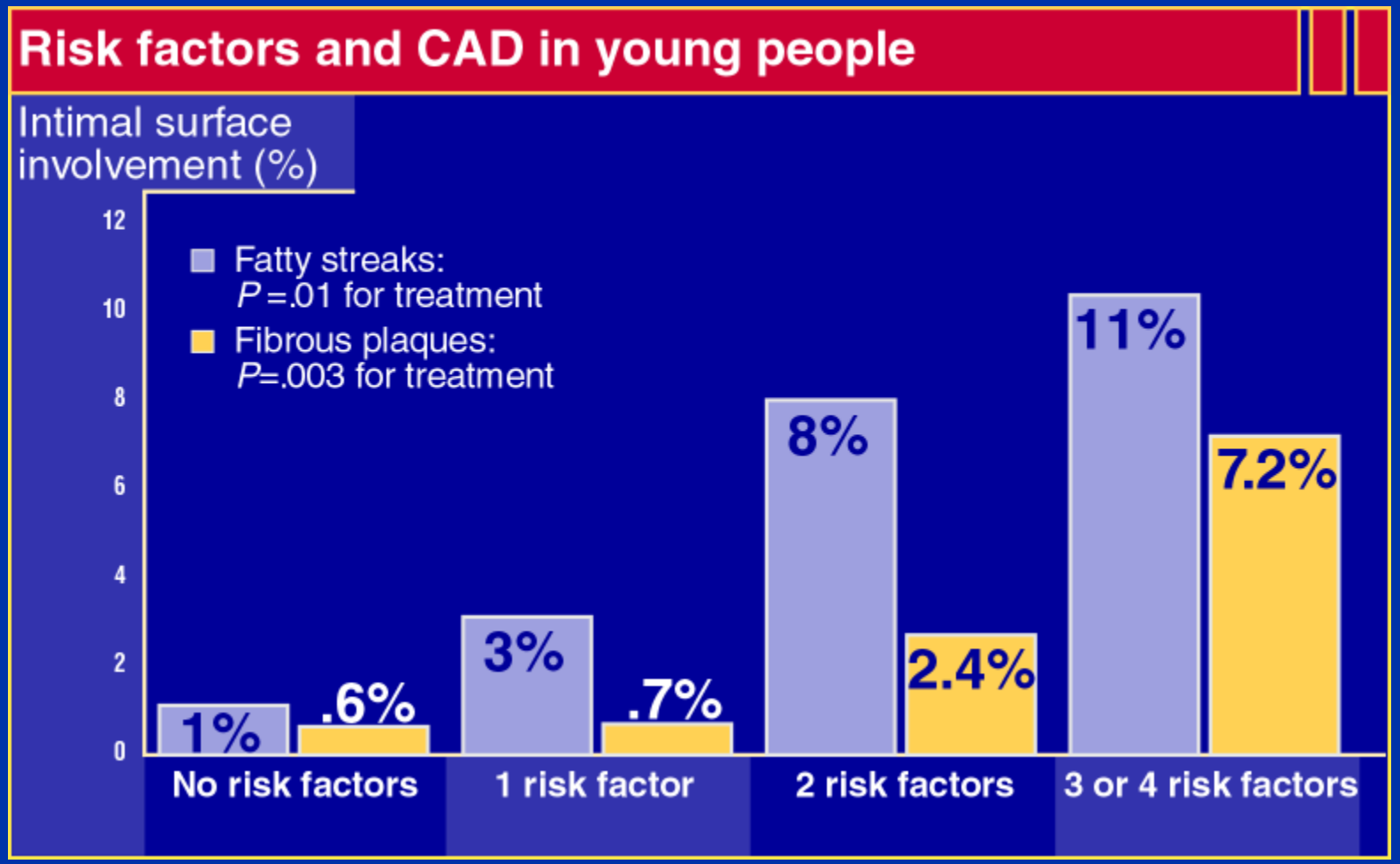
Tuzcu EM et al, in press.

CAD: Silent Disease Necessitates Aggressive Risk Factor Management

- IVUS corroborates necroscopy studies, proving that atherosclerosis begins in youth
- CAD progresses silently; the initial presentation is usually MI or sudden death
- Most atheromas are extraluminal, rendering them angiographically silent
- The only reasonable approach is early and aggressive risk factor management

Berenson GS et al, *N Engl J Med,* 1998; Tuzcu EM et al, in press; Levy D et al in *Textbook of Cardiovascular Medicine*, 1998; Yamashita T et al, *Progress in Cardiovascular Diseases*, 1999; Topol EJ et al, *Circulation*, 1995. Kannel WB in *Atherosclerosis and Coronary Artery Disease*, 1996.

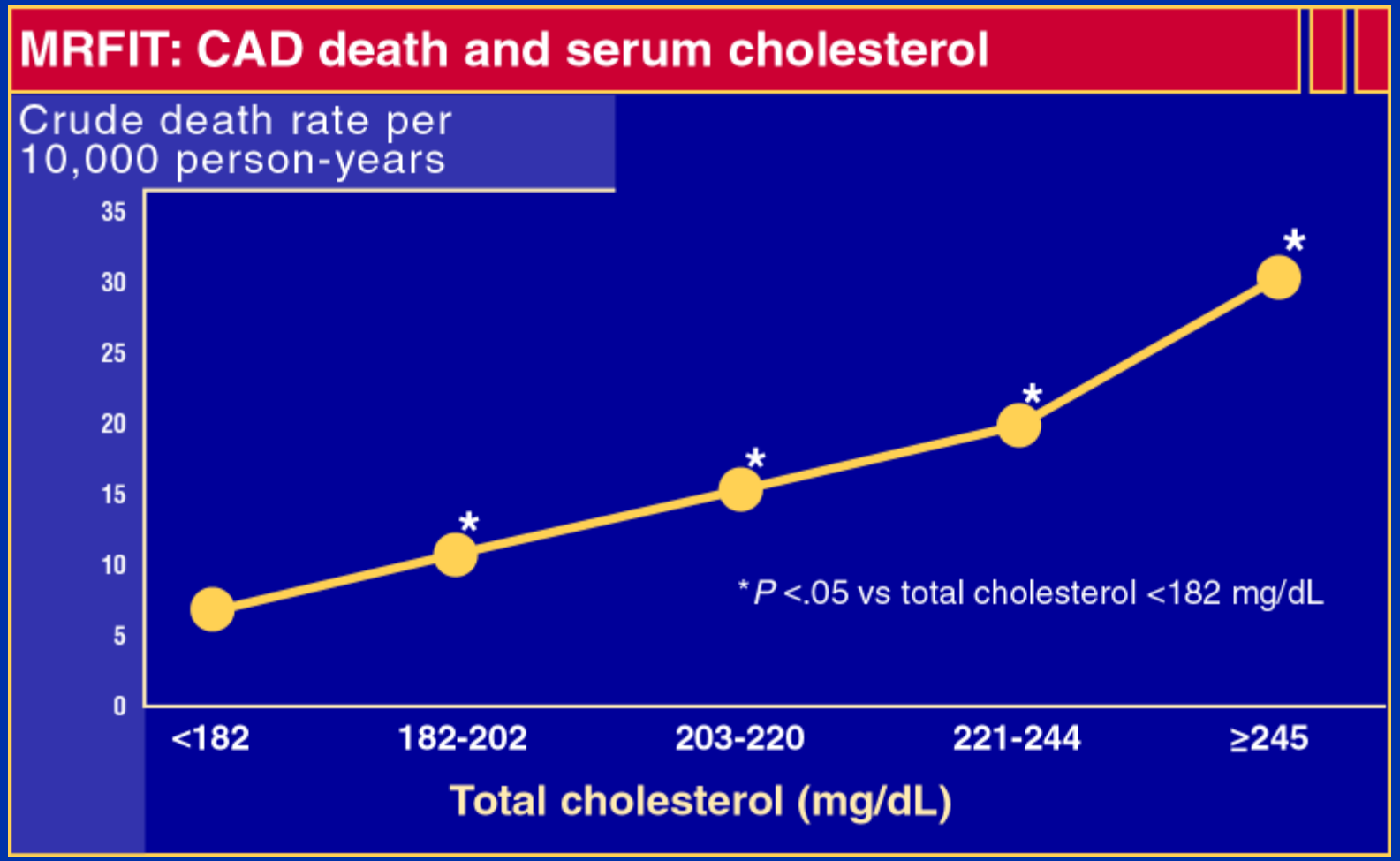
The Correlation Between Atherosclerosis and Risk Factors Begins Early



(Adapted from Berenson et al.)

Berenson GS et al, *N Engl J Med*, 1998.

Small Increases in Cholesterol Lead to Dramatic Increases in CAD Death



(Adapted from Neaton et al.)

Neaton JD et al, *Arch Intern Med*, 1992.

CAD: Not Just a Lipid Disease

- Half of all MIs occur in normolipidemic patients
- Smoking
  Accounts for 200,000 cardiovascular deaths annually
- Diabetes
  Affects 16 million Americans—and is growing
- Hypertension
  Confers as much risk for MI as smoking or dyslipidemia
  - Systolic hypertension is an even greater indicator of CAD risk than diastolic hypertension

Braunwald E, *N Engl J Med,* 1997; Grundy SM et al, *Circulation*, 1998; The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the National High Blood Pressure Education Program Coordinating Committee, *Arch Intern Med*, 1997.

Conclusions: Critical Lessons in Understanding Atherogenesis

- CAD is a ubiquitous, systemic disease that requires a systemic solution
- Most patients progress to MI or sudden death before a diagnosis of CAD is ever considered
- IVUS demonstrates that remodeling causes angiography to underestimate the extent of disease
- Extraluminal, angiographically silent atheromas are responsible for most acute coronary events, including sudden death

Aronow WS et al, *Am J Cardiol,* 1994; Levy D et al in *Textbook of Cardiovascular Medicine,* 1998; Nissen SE et al in *Textbook of Cardiovascular Medicine,* 1998; Falk E et al, *Circulation,* 1995.

"Awaiting overt signs and symptoms of coronary disease before treatment is no longer justified."

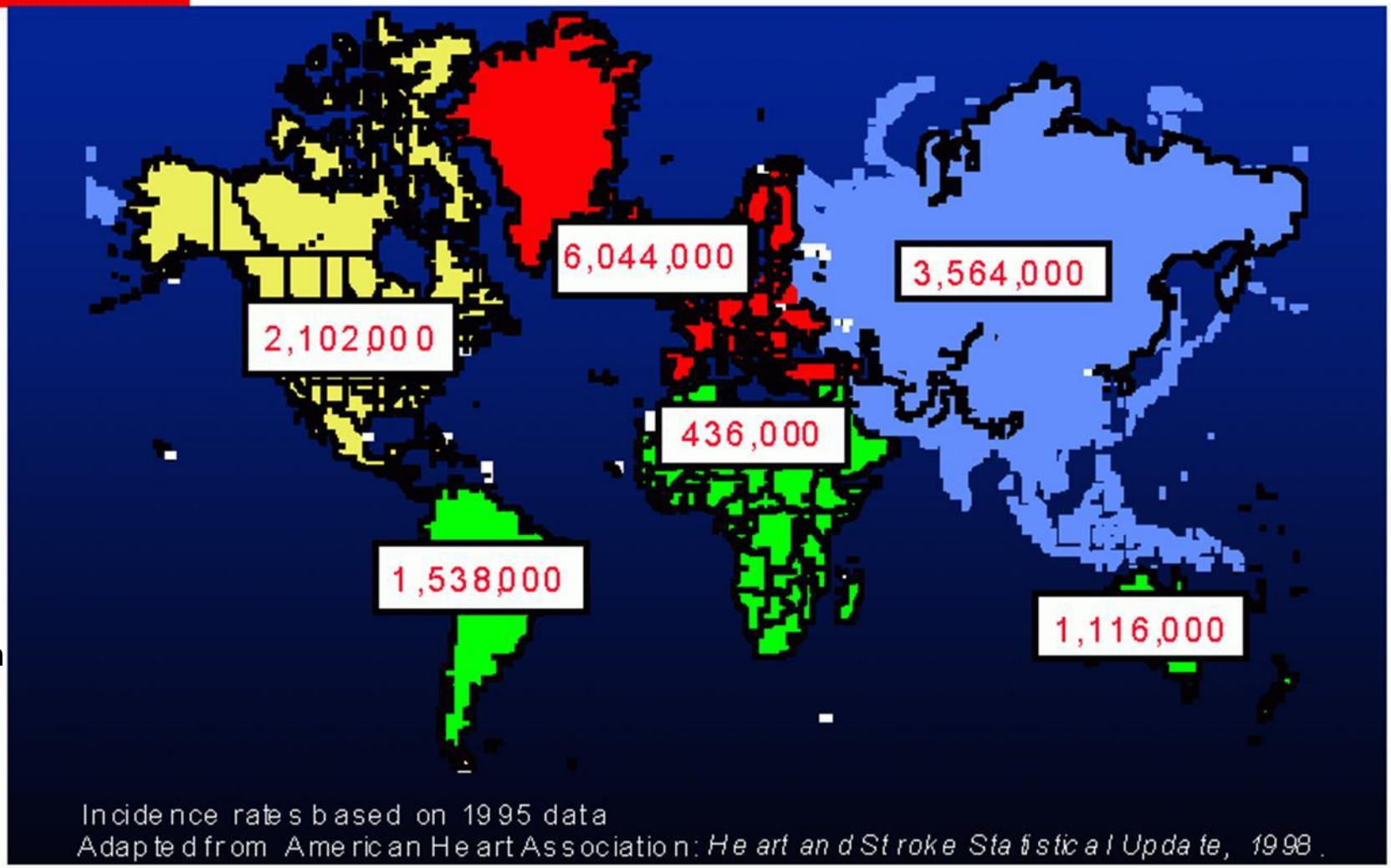
"In some respects, the occurrence of symptoms may be regarded more properly as a medical failure than as the initial indication for treatment."

—William B. Kannel, MD
Department of Medicine
Boston University Medical Center

Kannel WB in *Atherosclerosis and Coronary Artery Disease*, 1996.

The CVD Pandemic: Annual Incidence

> 15 Million Fatal Heart Attacks Each Year



Source:

World Heart Federation

Cardiovascular Disease

- Every 33 seconds, someone dies of a heart attack
- For 60% this is their first sign of Heart Disease
- The number-one killer in the United States since 1900, except during the 1918
- It has killed more Americans than all wars, infectious disease and cancer…Combined

But Who is at Risk?

Jim Fixx, 53 ✝ ♥

- Not Overweight
- Very Fit
- Non-Smoker

Sir Winston Churchill, 91 ✝

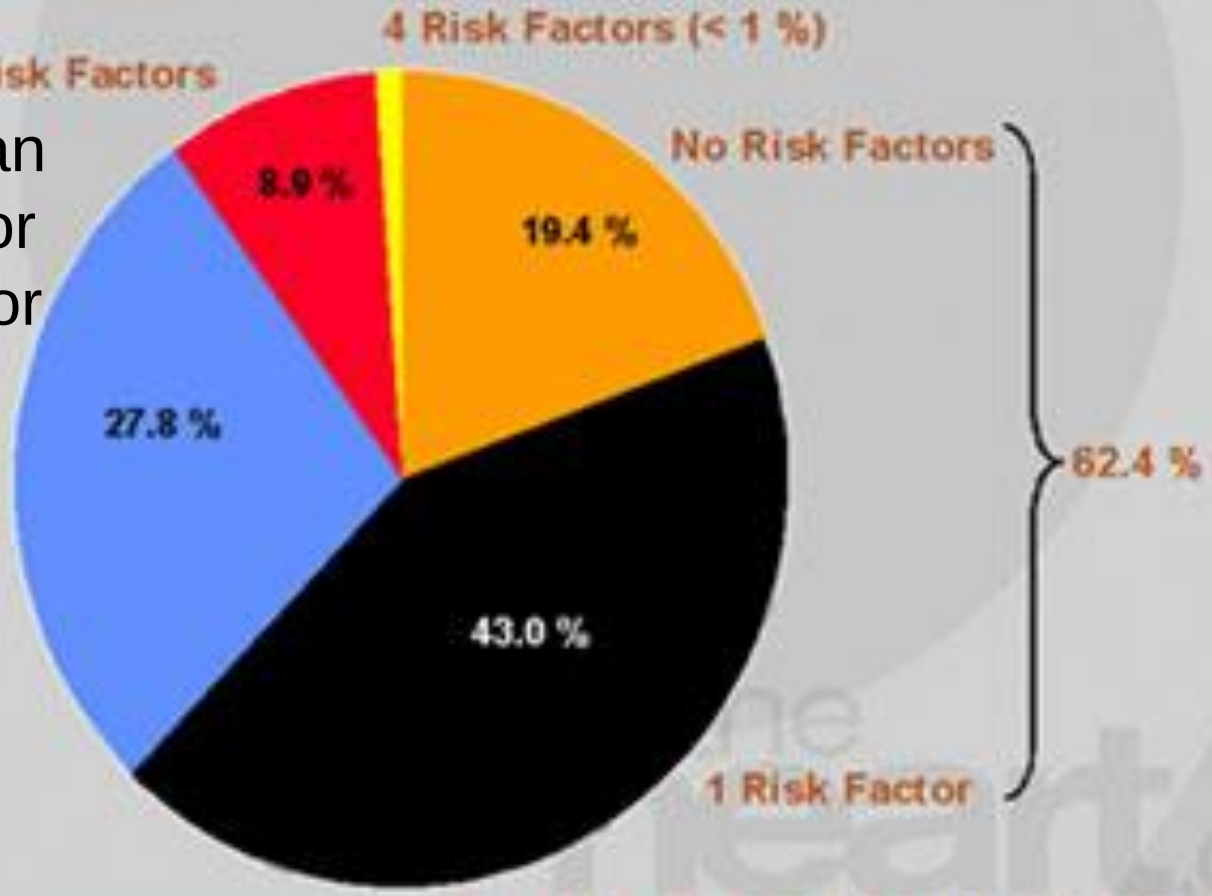
- Overweight
- Not Fit
- Heavy Smoker

Prevalence of Conventional Risk Factors in Patients with Coronary Heart Disease

N = 87,869

Risk factors: Smoking, Hypertension, Cholesterol, Diabetes mellitus

80.6% of American adults have one or more risk factor for heart attack!



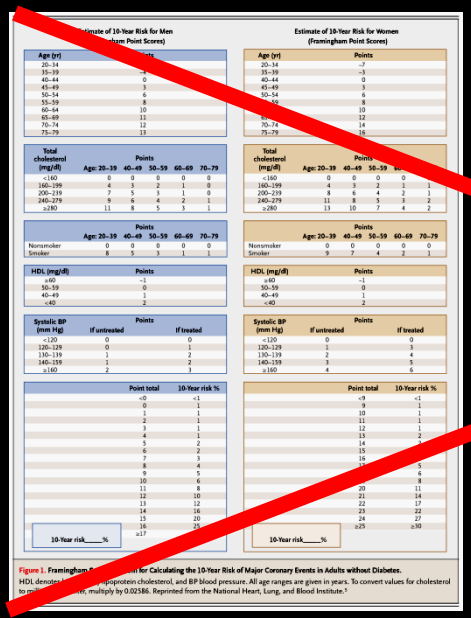
Khot U, et al. *JAMA* 2003;290:898–904.

Eradication of Heart Attack

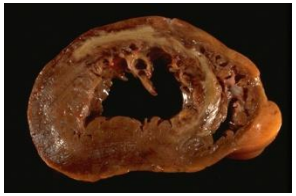
dream or reality?

- Most heart attack is preventable
- Heart attack remains the #1 killer

Traditional approach has failed



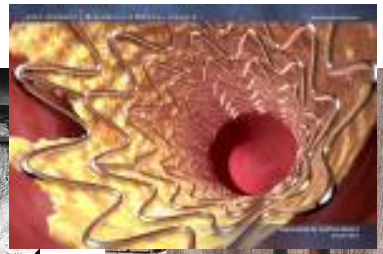
Age	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74		
(Low-risk level)•	(2%)	(3%)	(3%)	(4%)	(5%)	(7%)	(8%)	(10%)	(13%)	Ab[illegible] risk	Absolute Risk‡
Points †										Total CHD‡	Hard CHD¶
0	1.0									2%	2%
[illegible]	1.5	1.0	1.0							3%	2%
2	2.0	1.3	1.3	1.0						4%	3%
3	2.5	1.7	1.7	[illegible]	1.0					5%	4%
4	3.5	2.3	2.3	1.8	1.4	1.0				7%	5%
5	4.0	2.6	2.6	2.0	1.6	1.1	1.0			8%	6%
6	5.0	3.3	3.3	[illegible]	2.0	1.4	1.3	1.0		10%	7%
7	6.5	4.3	4.3	3.3	[illegible]	1.9	1.6	1.3	1.0	13%	9%
8	8.0	5.3	5.3	4.0	3.2	[illegible]	2.0	1.6	1.2	16%	13%
9	10.0	6.7	6.7	5.0	4.0	2.9	[illegible]	2.0	1.5	20%	16%
10	12.5	8.3	8.3	6.3	5.0	3.6	3.1	[illegible]	1.9	25%	20%
11	15.5	10.3	10.3	7.8	6.1	4.4	3.9	3.1	2.3	31%	25%
12	18.5	12.3	12.3	9.3	7.4	5.2	4.6	3.7	[illegible]	37%	30%
13	22.5	15.0	15.0	11.3	9.0	6.4	5.6	4.5	3.5	[illegible]	35%
>14	26.5	>17.7	>17.7	>13.3	>10.6	>7.6	>6.6	>5.3	>4.1	>53%	[illegible]

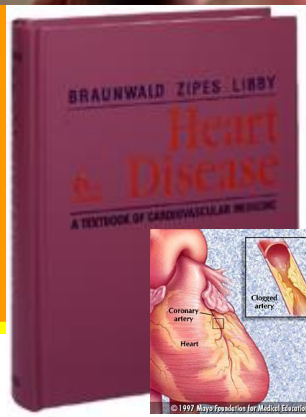


- **Prevention of heart attacks must be the primary goal.**

Treatment should be regarded as “locking the barn door after the horse is stolen”

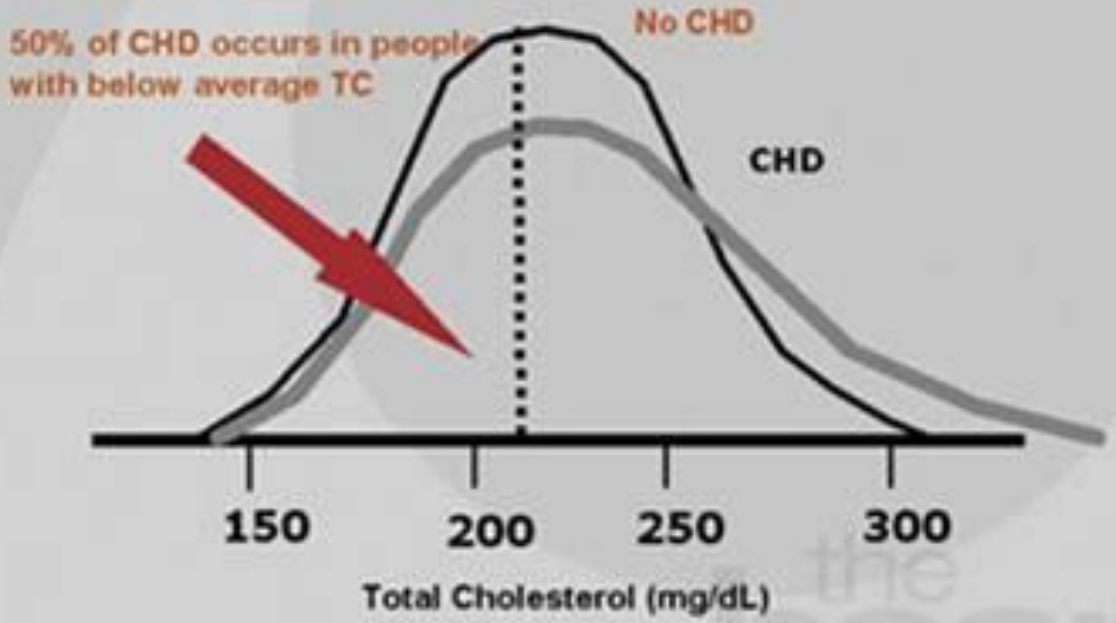
Eugene Braunwald





Total Cholesterol Distribution in CHD vs Non-CHD Population

Framingham Heart Study—26-Year Follow-up



Adapted from Castelli W. *Atherosclerosis* 1996;124(suppl):S1–S9.

140 Million Americans Have Average or High Cholesterol

76.5 Million Americans Have High CRP

Correlates of Elevated C-Reactive Protein Among Adults in the United States: Findings From the 1999-2000 National Health and Nutrition Examination Survey

Analogy of Smoking and Lung Cancer

Of course smoking is a strong risk factor for lung cancer

but

in a town where almost everyone smokes, smoking has no predictive value for lung cancer.

Too many people have risk factors specially when average cholesterol or high CRP is considered as risk factors.

Screening for Atherosclerosis

Risk Factors vs Disease

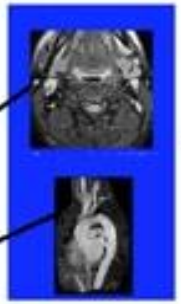
Numerous Risk Factors

- High LDL
- Low HDL
- High BP
- Diabetes
- Smoking
- CRP
- Metabolic Syn
- Lp(a)
- Homocysteine
- Dense LDL
- Lp-PLA2
- ApoB/ApoA
- Family History
- Sedentary Life
- Obesity
- Stress
- ...
- ?

Over 200 risk factors have been reported.

Carotid IMT and Plaque Measured by Ultrasound

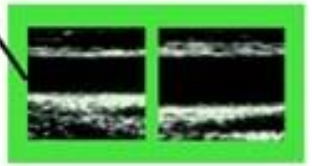
Examples of Arterial Structure Tests



Aortic and Carotid Plaque Detected by MRI

Coronary Calcium Score Measured by CT

Ankle Brachial Index



Brachial Vasoreactivity Measured by Ultrasound

Vascular Compliance Measured by Radial Tonometry

Examples of Arterial Function Tests

Microvascular Reactivity Measured by Fingertip Tonometry

The 1st S.H.A.P.E. Guideline

Towards the National Screening for Heart Attack Prevention and Education (SHAPE) Program

Apparently Healthy Population Men>45y Women>55y[1]

Step 1

- Very Low Risk[3] — Exit
- All >75y receive unconditional treatment[2] — Exit

Atherosclerosis Test

- **Coronary Calcium Score (CCS)**
  or
- **Carotid IMT (CIMT) & Carotid Plaque**[4]

Step 2

Negative Test
- CCS =0
- CIMT <50th percentile

Positive Test
- CCS ≥1
- CIMT ≥50th percentile or Carotid Plaque

Step 3

No Risk Factors[5]	+ Risk Factors	• CCS <100 & <75th% • CIMT <1mm & <75th% & No Carotid Plaque	• CCS 100-399 or >75th% • CIMT ≥1mm or >75th% or <50% Stenotic Plaque	• CCS >100 & >90th% or CCS ≥400 • ≥50% Stenotic Plaque[6]
Lower Risk	**Moderate Risk**	**Moderately High Risk**	**High Risk**	**Very High Risk**

ABI<0.9
CRP>4mg
Optional

LDL Target	**<160 mg/dl**	**<130 mg/dl**	**<130 mg/dl** <100 Optional	**<100 mg/dl** <70 Optional	**<70 mg/dl**
Re-test Interval	5-10 years	5-10 years	Individualized	Individualized	Individualized

- Myocardial IschemiaTest
  - Yes → Angiography → Follow Existing Guidelines
  - No

AEHA

AEHA
The Association for Eradication of Heart Attack

Leading the Way to Eradicate Heart Attacks

The Burden of Sudden Heart Attacks Today

19 million deaths every year

$280 Billion / Year only in the USA

Era of Screening

Regular Screening & Interventions

Get in SHAPE
Screening for Heart Attack Prevention and Education

Era of "Polypill"

Chronic Prophylactic Drug Therapy
Combined Aspirin, Statin, ACE,...

Era of Vaccine

Prevention and Stabilization of Atherosclerosis by Vaccinationa and Immune Modulation Strategies

Learn about the AEHA Vaccine Initiative Mission 2020

AEHA Calls for a Marriage between Fitness and Screening Centers to Proliferate SHAPE Compatible Clinics and Help Fight the Epidemic of Obesity, Diabetes, and Coronary Heart Disease

Shifting Cardiovascular Healthcare to >>>>> Out of Hospital

Produced By: AMERRA, Inc

PCSK9

- Third gene involved in autosomal-dominant hypercholesterolemia
- Found in primates, rats, mice, squirrels, other placental mammals, opossums, chickens, frogs and fish, but not in bovines[a]
- Gain-of-function mutations as cause of ADH in 2 French families[b]
- Loss-of-function mutations as cause of low-plasma LDL-C levels and reduced coronary heart disease risk[c]

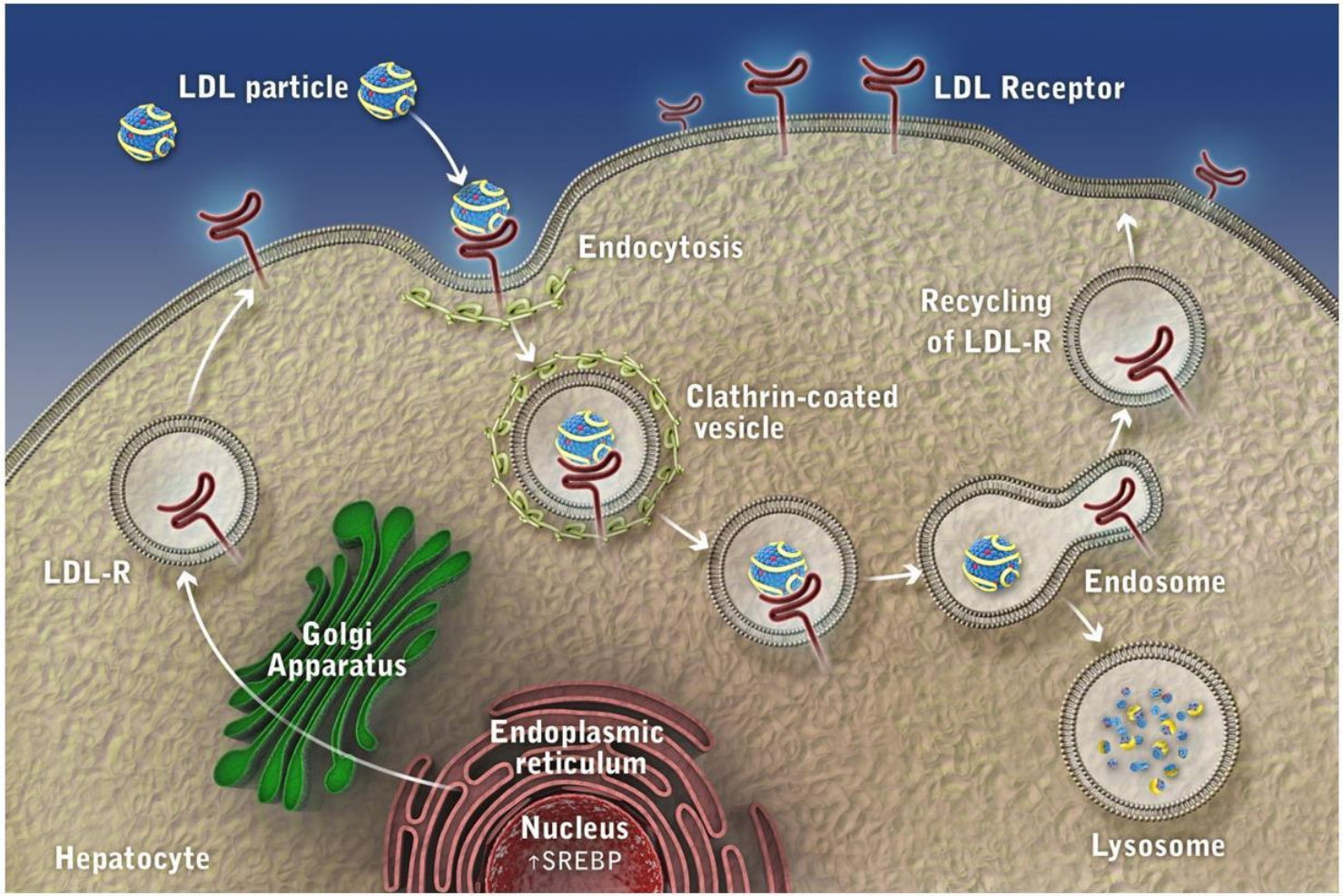
a. Cameron J, et al. *FEBS J*. 2008;275:4121-4133.[2]
b. Abifadel M, et al. *Nat Genet*. 2003;34:154-156.[3]
c. Cohen J, et al. *Nat Genet*. 2005;37:161-165.[4]

PCSK9: The Case for Inhibition as a Therapeutic Strategy

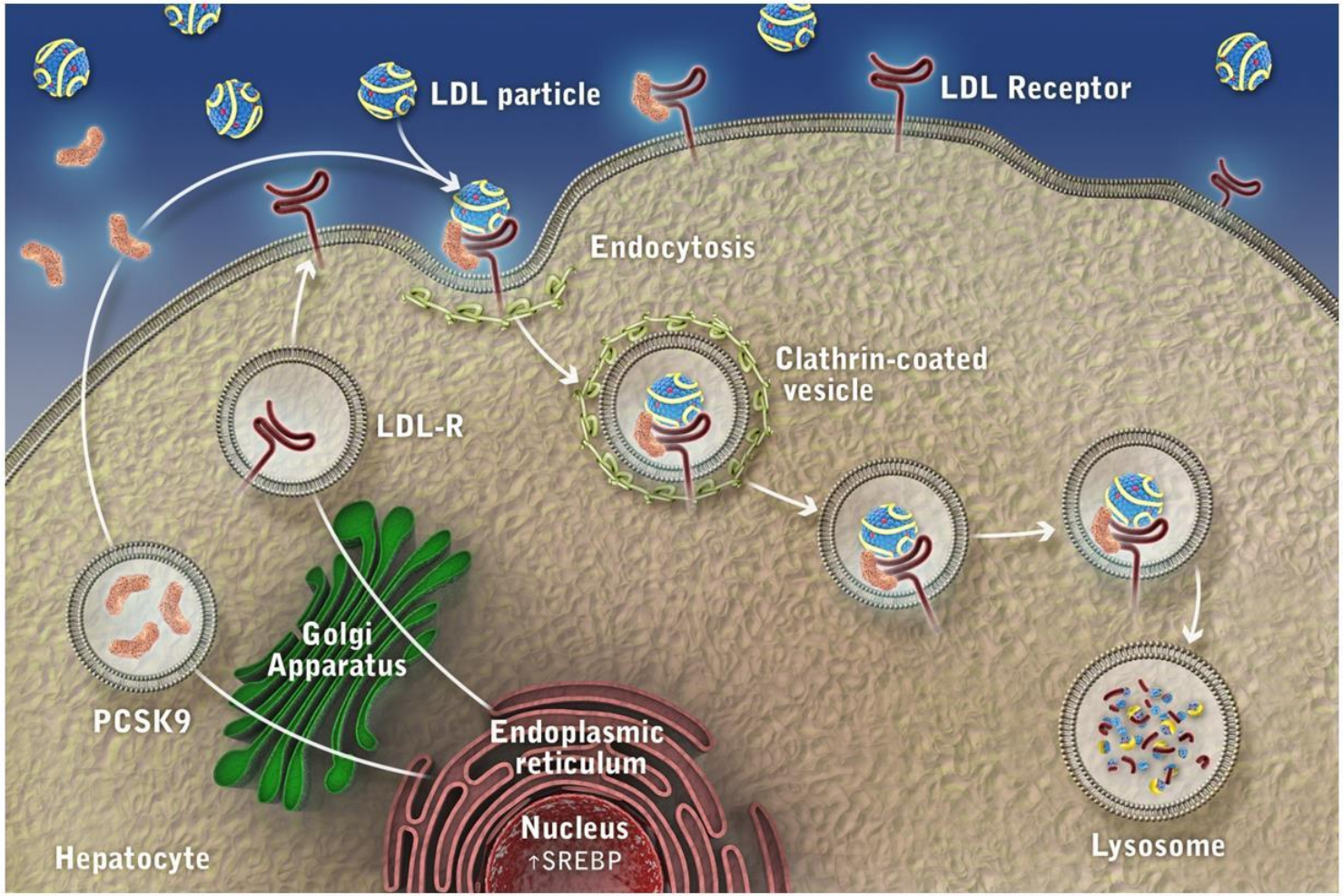
- The Y142X or C679X variants, occurring in 2.6% of the African American population, are associated with a 30% reduction in LDL-C levels and an 88% reduction in rates of coronary heart disease.[a]
- The R46L variant, occurring in 3.2% of whites, is associated with a 15% reduction in LDL-C levels and a 47% reduction in rates of coronary heart disease.[a]
- Two unrelated adult patients with total PCSK9 deficiency have been identified; both had very low plasma levels of LDL-C (14 mg/dL and 16 mg/dL) and no adverse clinical issues.[c]

a. Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272.[10]
b. Zhao Z, et al. *Am J Hum Genet*. 2006;79:514-523.[11]

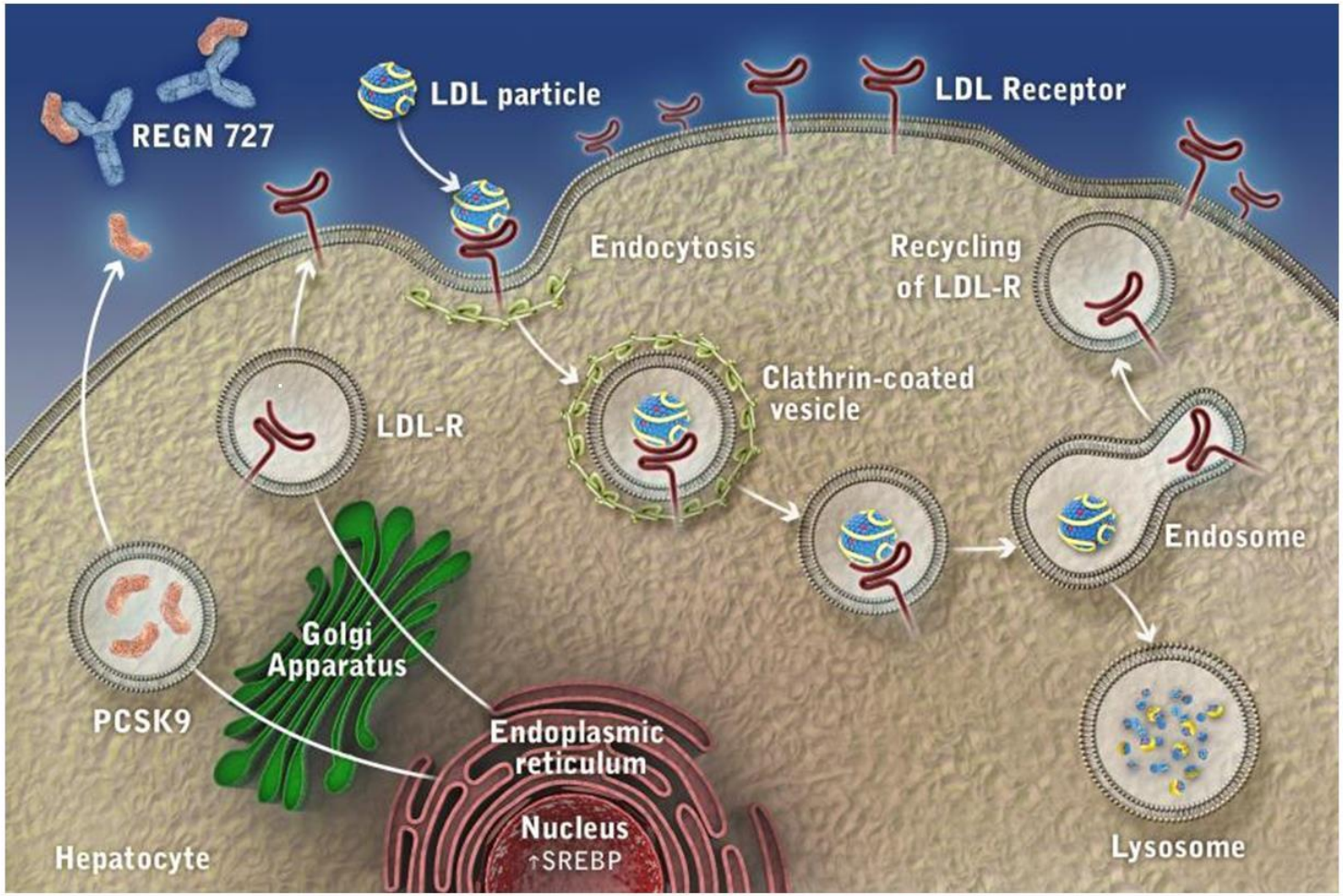
LDLR Function and Life Cycle



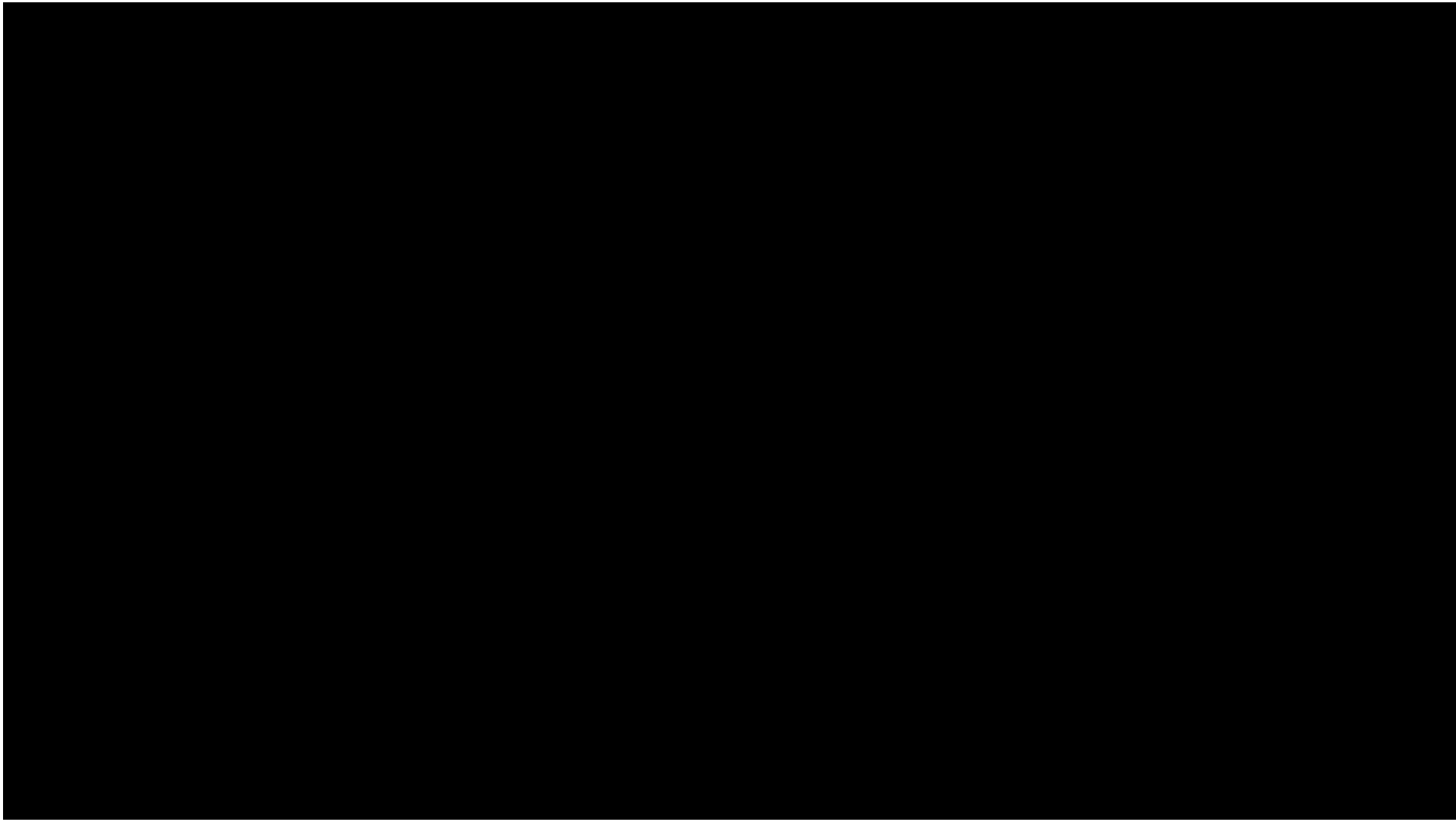
The Role of PCSK9 in the Regulation of LDLR Expression



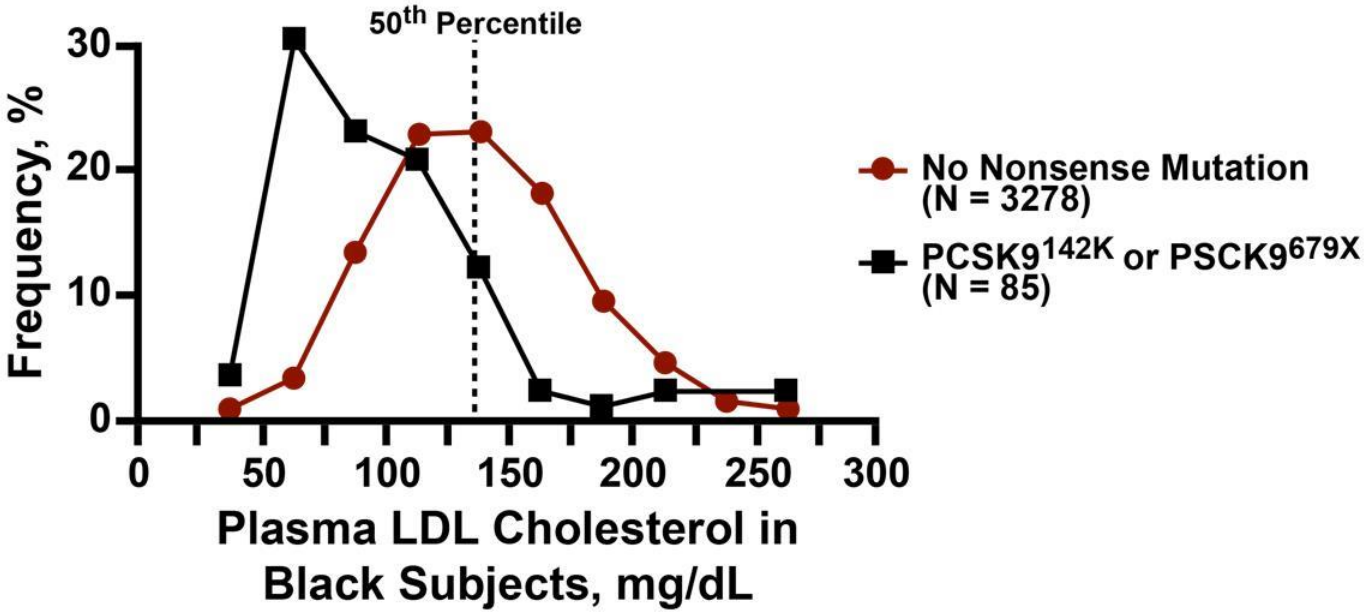
Impact of a PCSK9 mAb on LDLR Expression



LDL Metabolism



The PCSK9 Lead



Incidence of CHD Among Black Patients With or Without PCSK9^{142X} or PCSK9^{679X} Allele

No Nonsense Mutation	Nonsense Mutation	*P* Value
9.7%	1.2%	.008

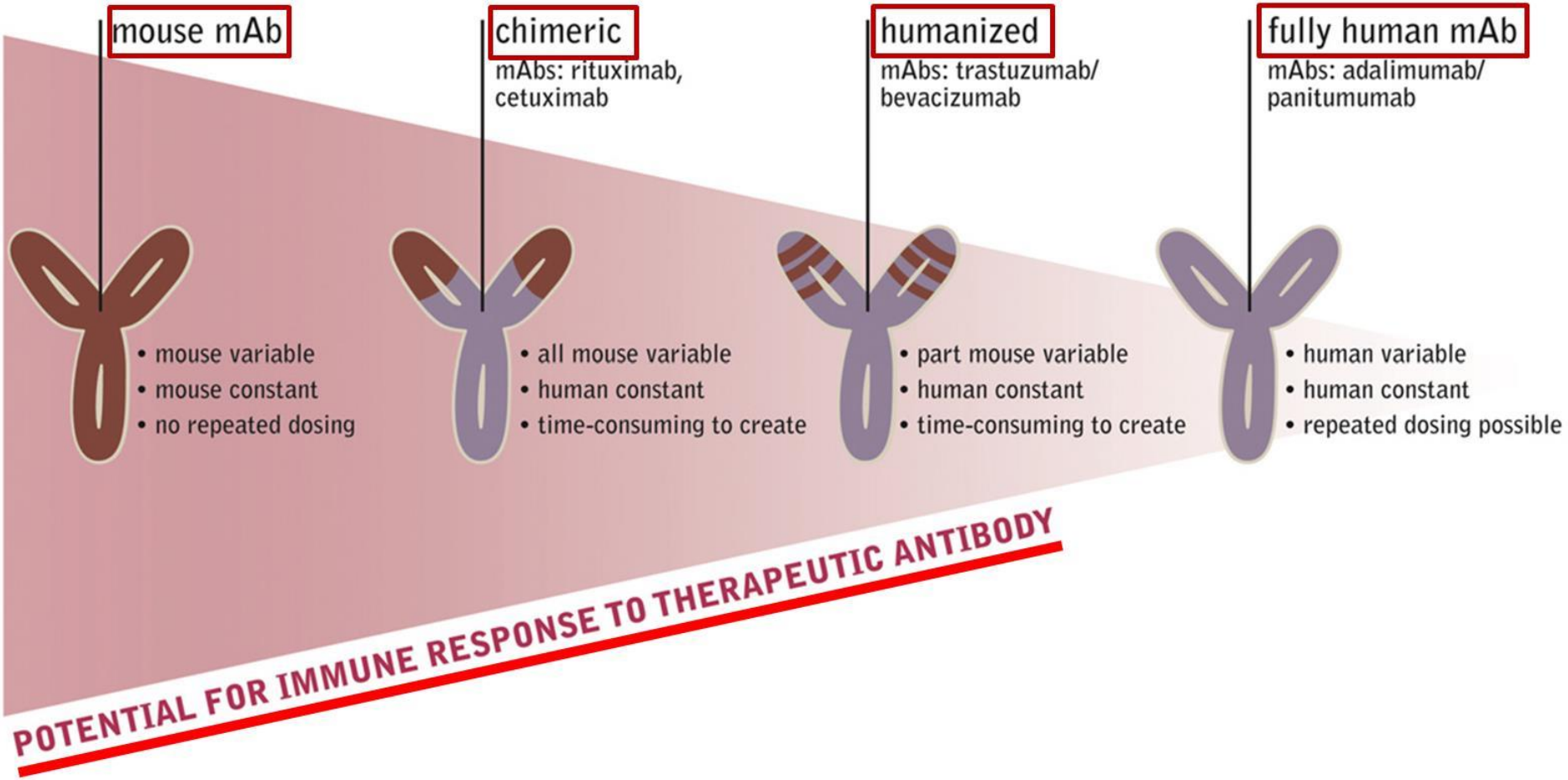
Cohen JC, et al. *N Engl J Med*. 2006;354:1264-1272.[10]

Anti-PCSK9 Agents in Development

Mechanism of action	Class	Agent	Company	Phase
PCSK9 binding	Human monoclonal antibody	REGN727/SAR236553	Regeneron/sanofi	3
	Human monoclonal antibody	AMG145	Amgen	3
	Humanized monoclonal antibody	RN316	Pfizer	2
		LGT209	Novartis	2
		RG7652	Roche/Genentech	2
	Humanized monoclonal antibody	LY3015014	Eli Lilly	1
	Modified binding protein	BMS962476	BMS/Adnexus	1
	Small molecule inhibitor	SX-PCSK9	Serometrix	Preclinical
PCSK9 synthesis	RNA interference	ALN-PCS02	Alnylam	1

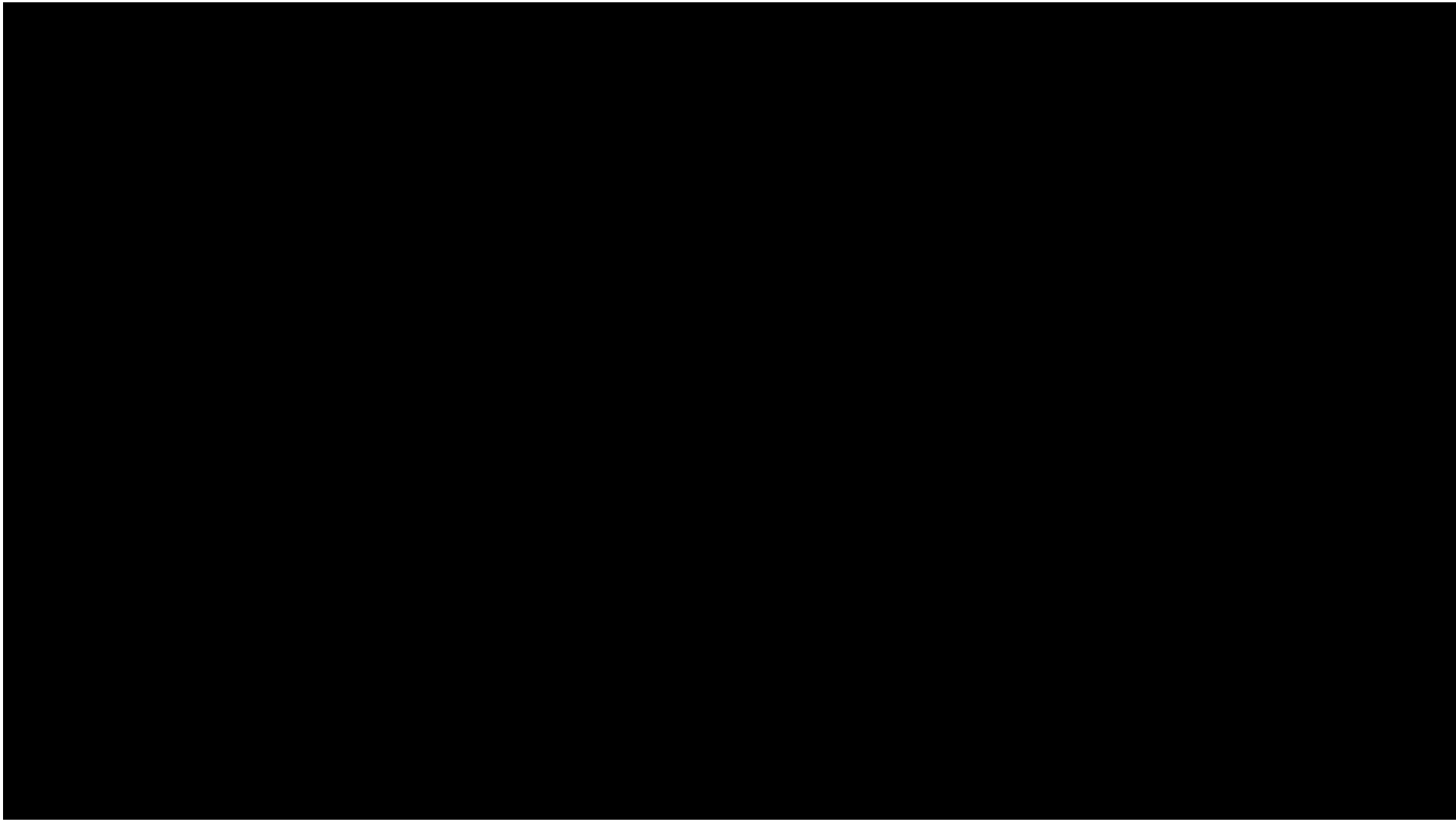
SPC-5001 (antisense) and BMS-844421 (antisense) clinical development have been terminated

Evolution of Therapeutic Monoclonal Antibodies



Catapano AL, et al. *Atherosclerosis*. 2013;228:18-28.[14]

LDL Metabolism



Changes in LDL-C From Baseline to Week 12 by Treatment Group (mITT Population)

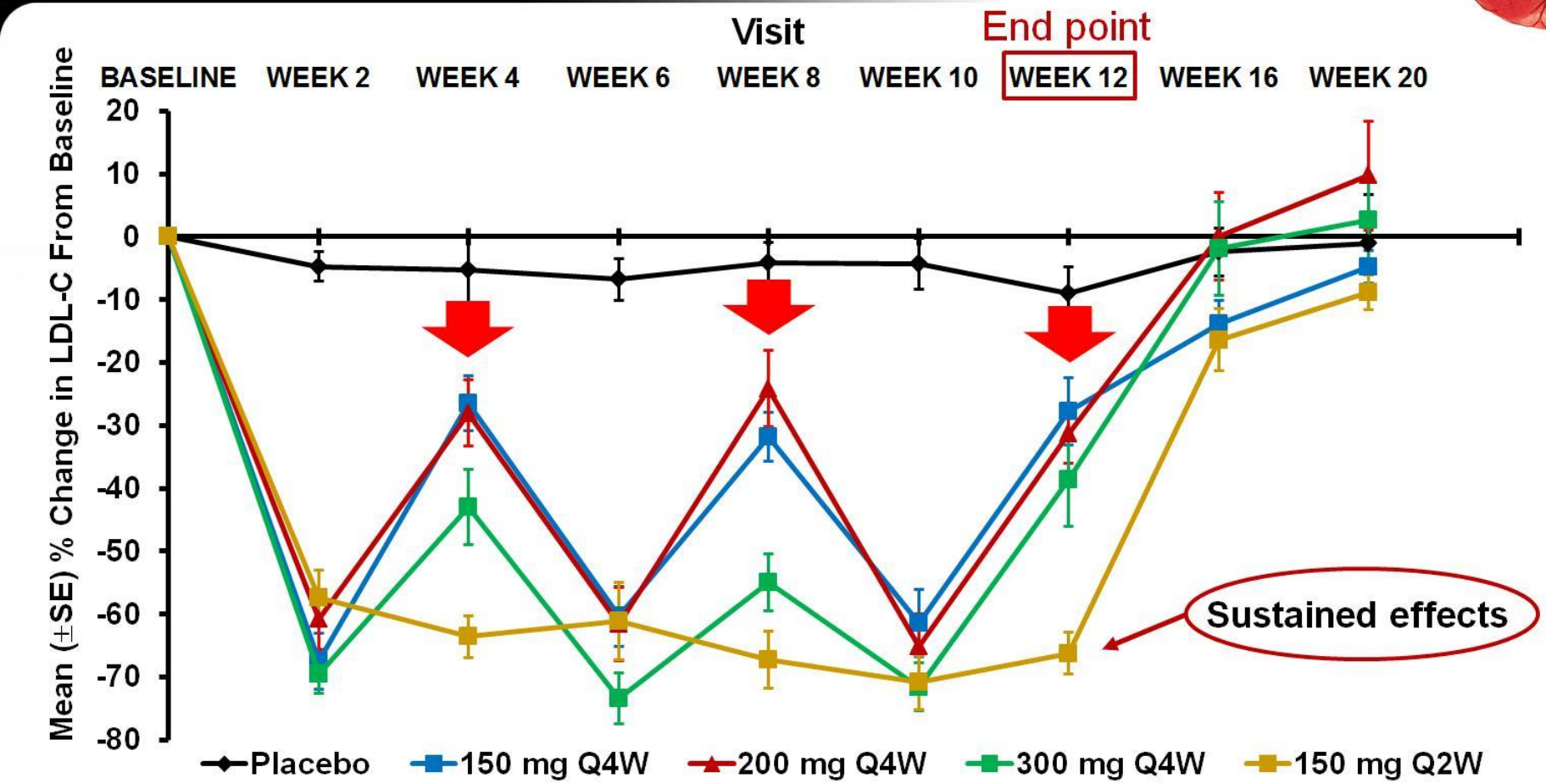
Phase 2: Randomized Trial of REGN727/SAR236553 (n = 62) or Placebo (n = 15) in Patients With HeFH on Stable Statin Doses ± ezetimibe

Intervention	Baseline LDL-C mg/dL (mmol/L)	% Change LDL-C*
Placebo	150.8 (3.9)	–10.7 (5.0)
REGN727 150 mg Q4W	166.7 (4.3)	–28.9 (5.1)†
REGN727 200 mg Q4W	169.8 (4.4)	–31.5 (4.9)†
REGN727 300 mg Q4W	139.6 (3.6)	–42.5 (5.1)†
REGN727 150 mg Q2W	147.2 (3.8)	–67.9 (4.9)†

*LS mean (SE), using LOCF method (12 weeks).
†$P < .001$ for % change REGN727 vs placebo.

Stein EA, et al. *Lancet*. 2012;380:29-36.[17]

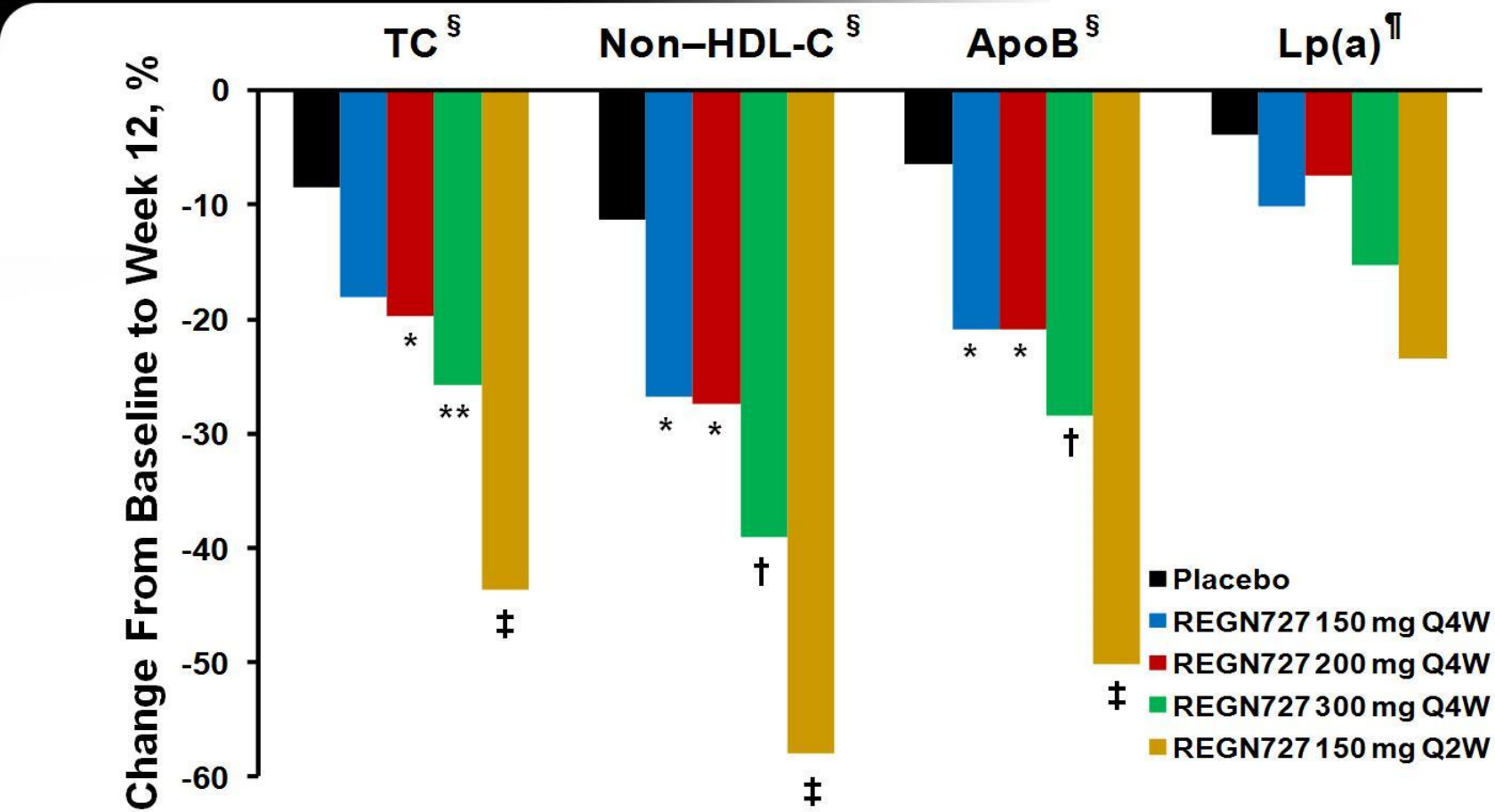
Change in Calculated LDL-C at 2 Weekly Intervals From Baseline to Week 20



Mean percentage change in calculated LDL-C from baseline to weeks 2, 4, 6, 8, 10, 12, 16, and 20 in the mITT population, by treatment group.

Stein EA, et al. *Lancet*. 2012;380:29-36.[17]

Changes in TC, non-HDL-C, ApoB, and Lp(a) From Baseline to Week 12 by Treatment Group (mITT Population)



§ LS mean (SE); ¶median (Q1-Q3).

*P < .05; **P < .01; †P < .001; ‡P < .0001.

Stein EA, et al. *Lancet*. 2012;380:29-36.[17]

Summary

PCSK9 mAbs are clearly leading the way.

PCSK9 mAbs significantly lower TC, LDL-C, ApoB, and Lp(a).

Both the degree and duration of lipid and lipoprotein reductions are dose-dependent.

- Further reductions in LDL-C will not occur once all available PCSK9 in the blood is bound. Higher doses may prolong the duration of action by binding newly released PCSK9.

Every-2-week dosing appears optimal, but every 4 weeks may be reasonable with much higher doses.