Oregon Heart & Vascular INSTITUTE

Atherosclerosis – A Spectrum of Disease: February 13, 2014

Richard Cameron Padgett, MD
Oregon Cardiology, PC, Director OHVI

Pt RB

Age 38

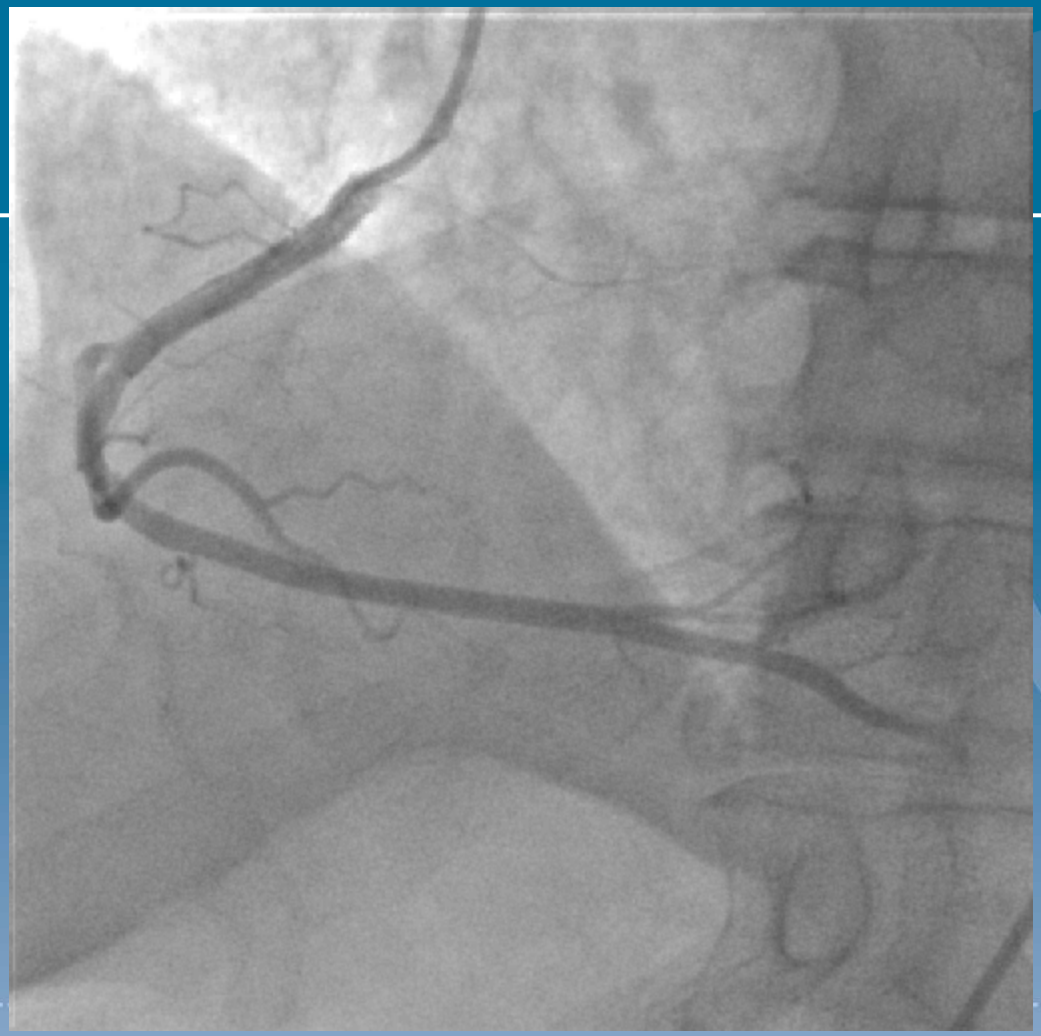
1ppd Smoker

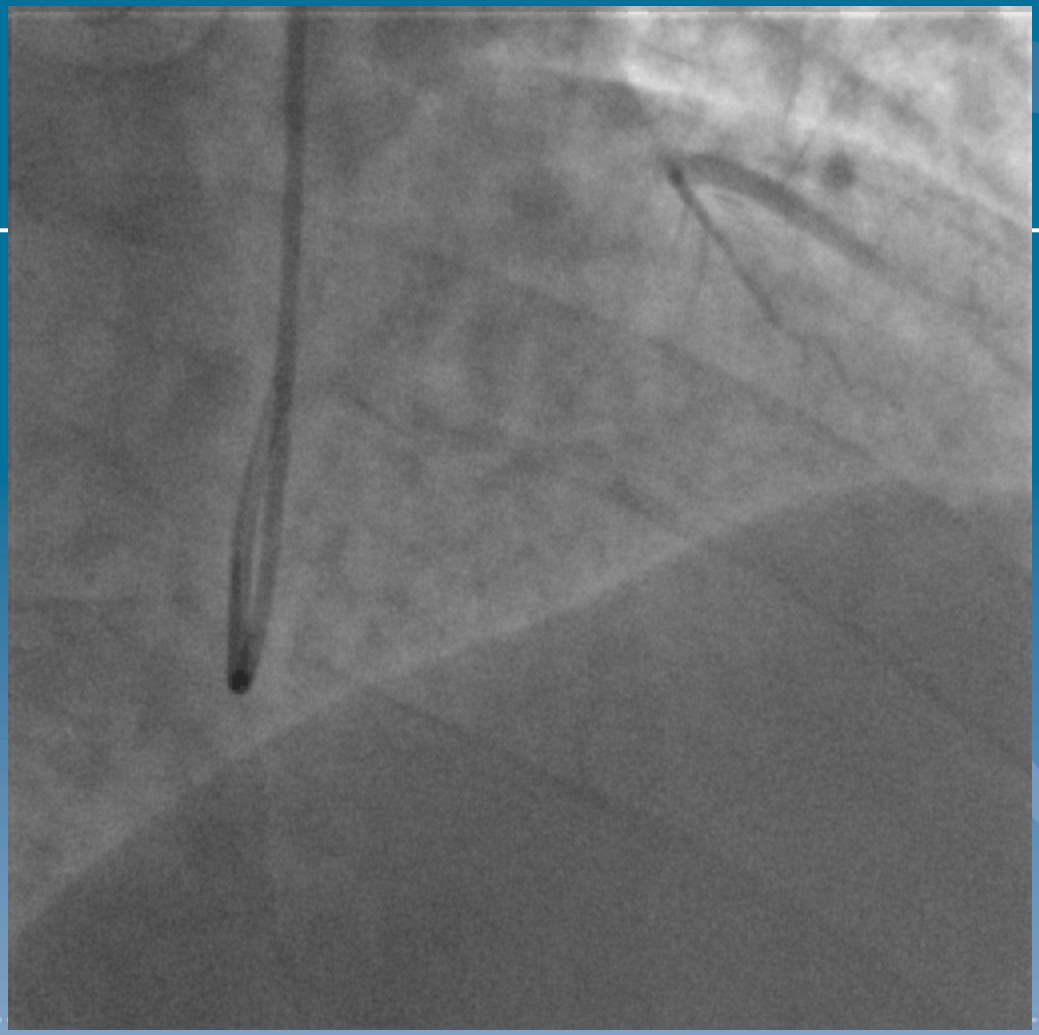
Father had MI @ Age 46

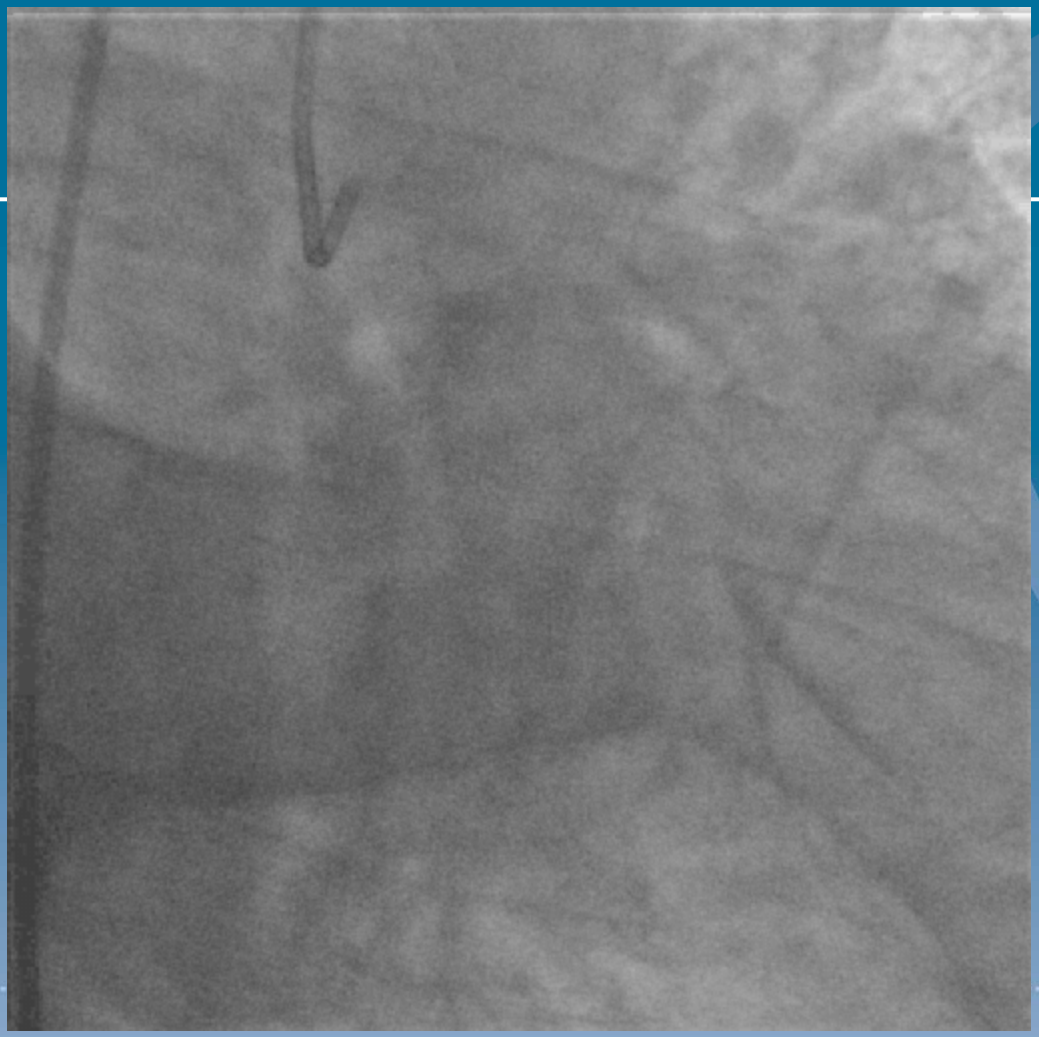
Total Chol 189

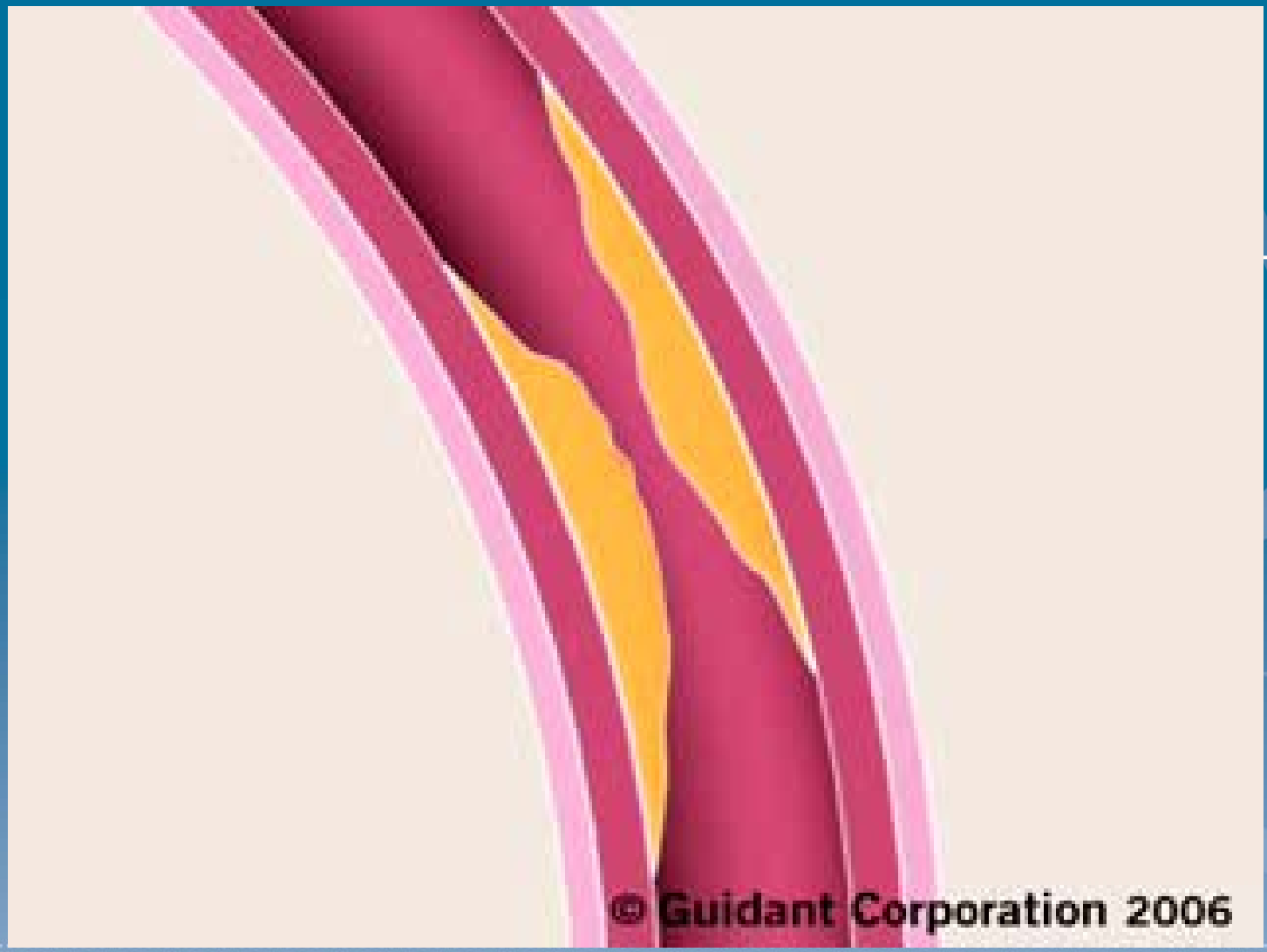
LDL 138

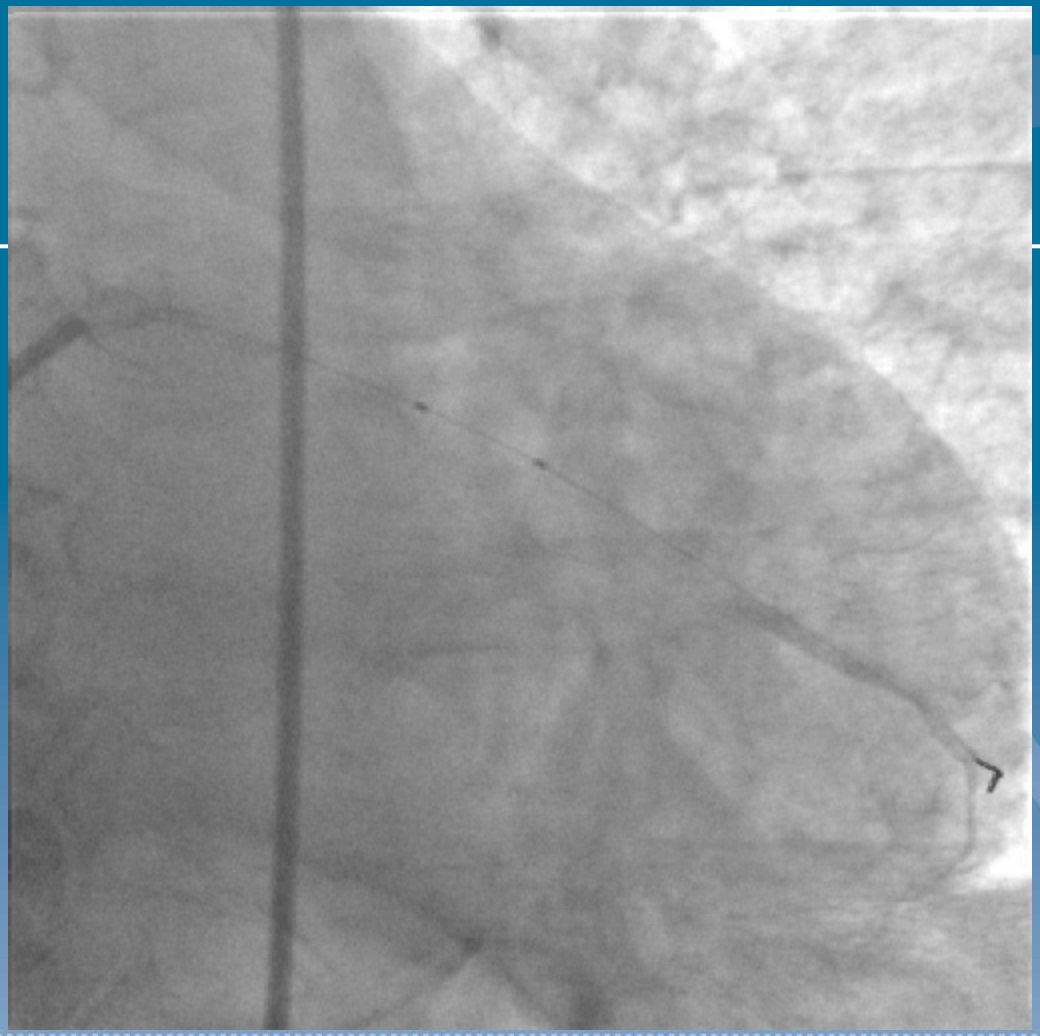
HDL 25

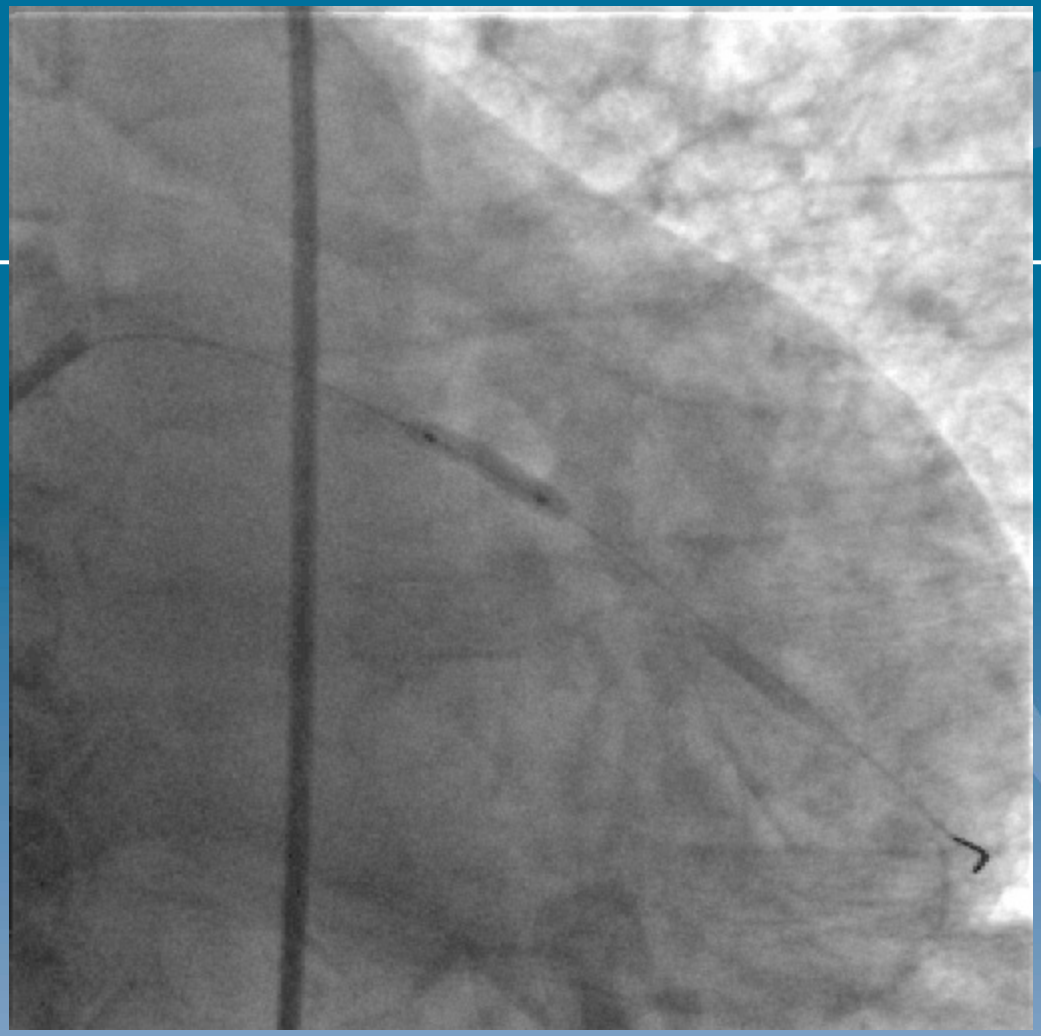


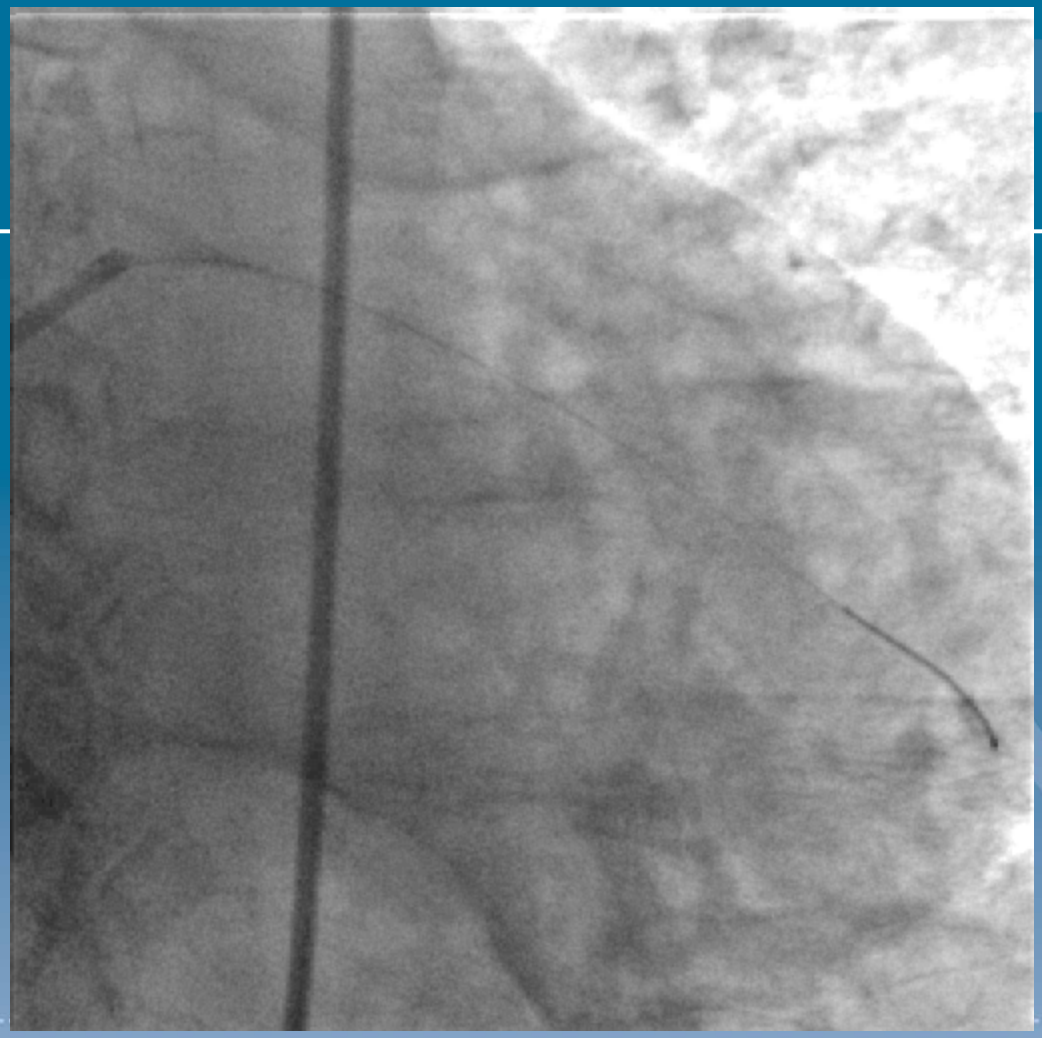


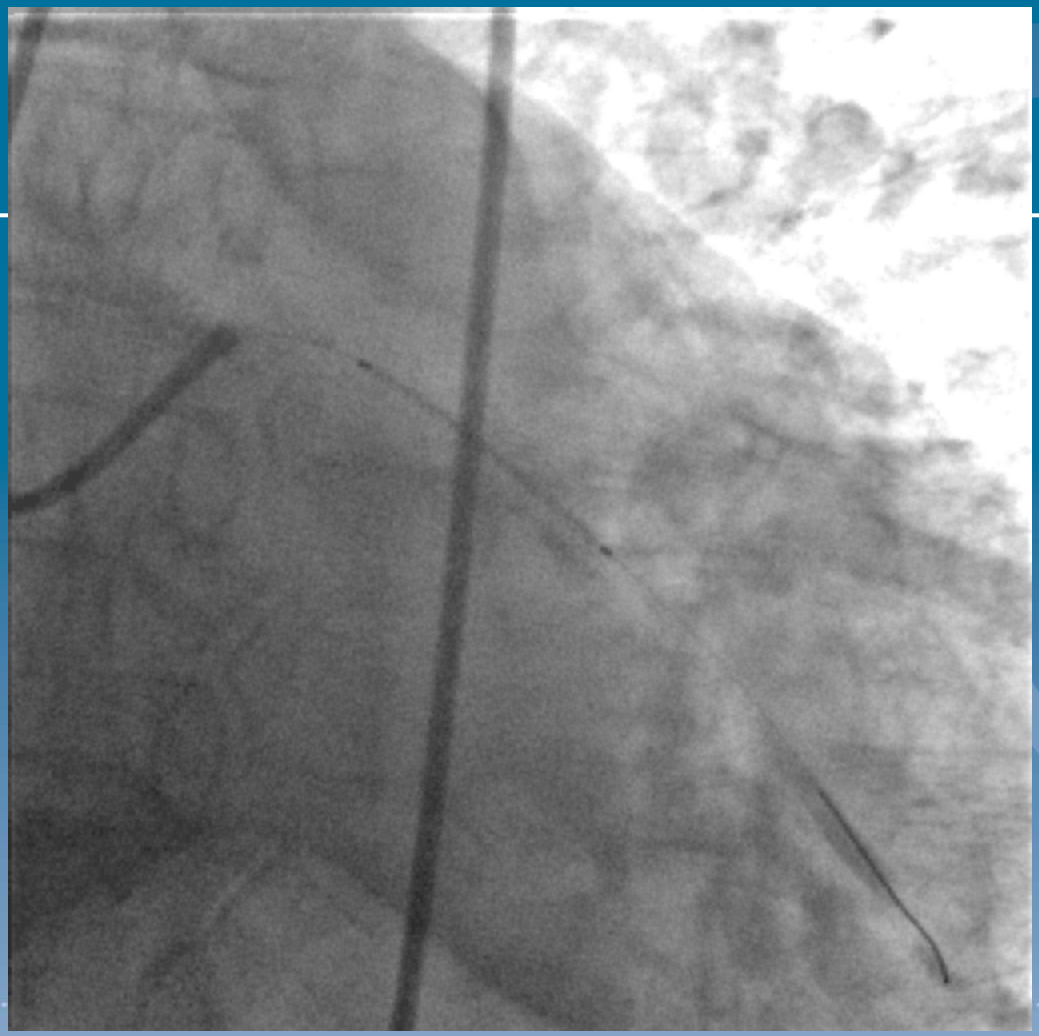


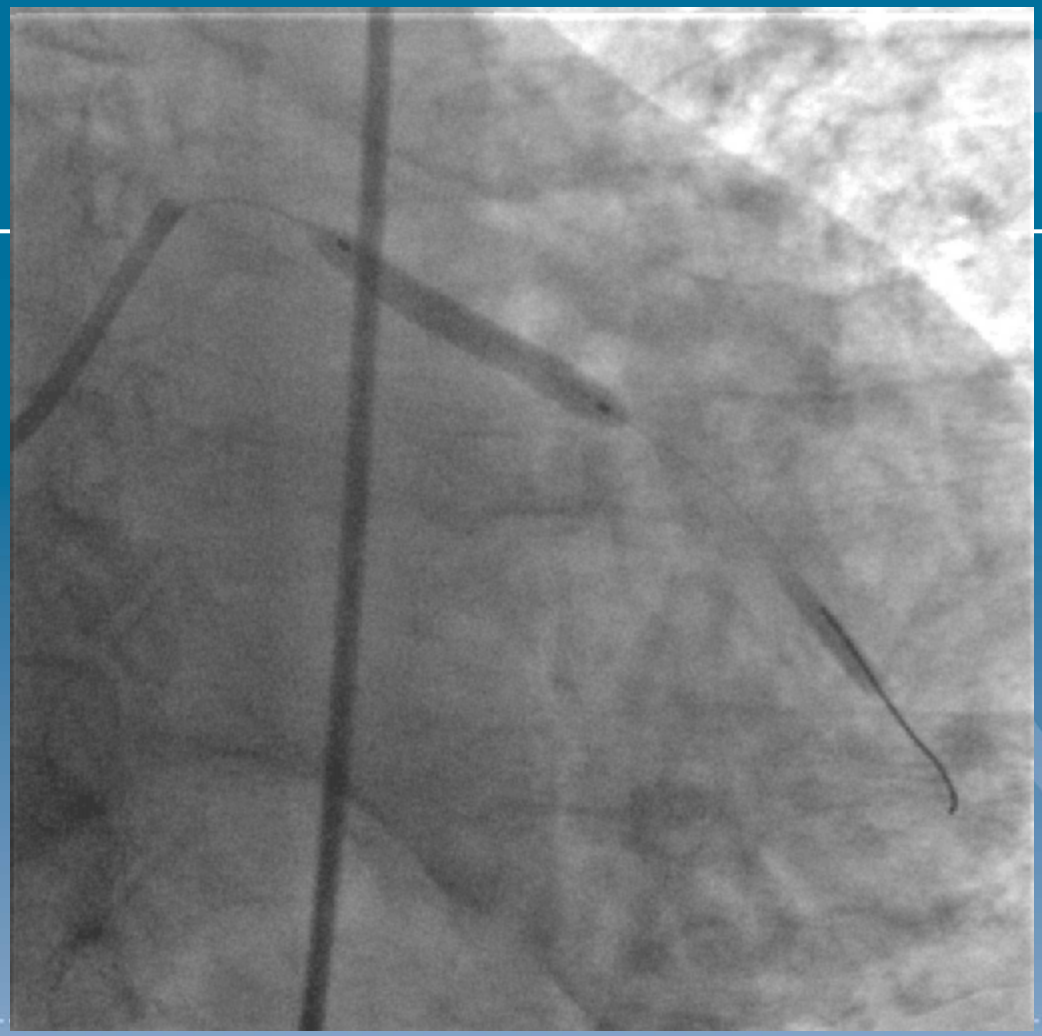

© Guidant Corporation 2006

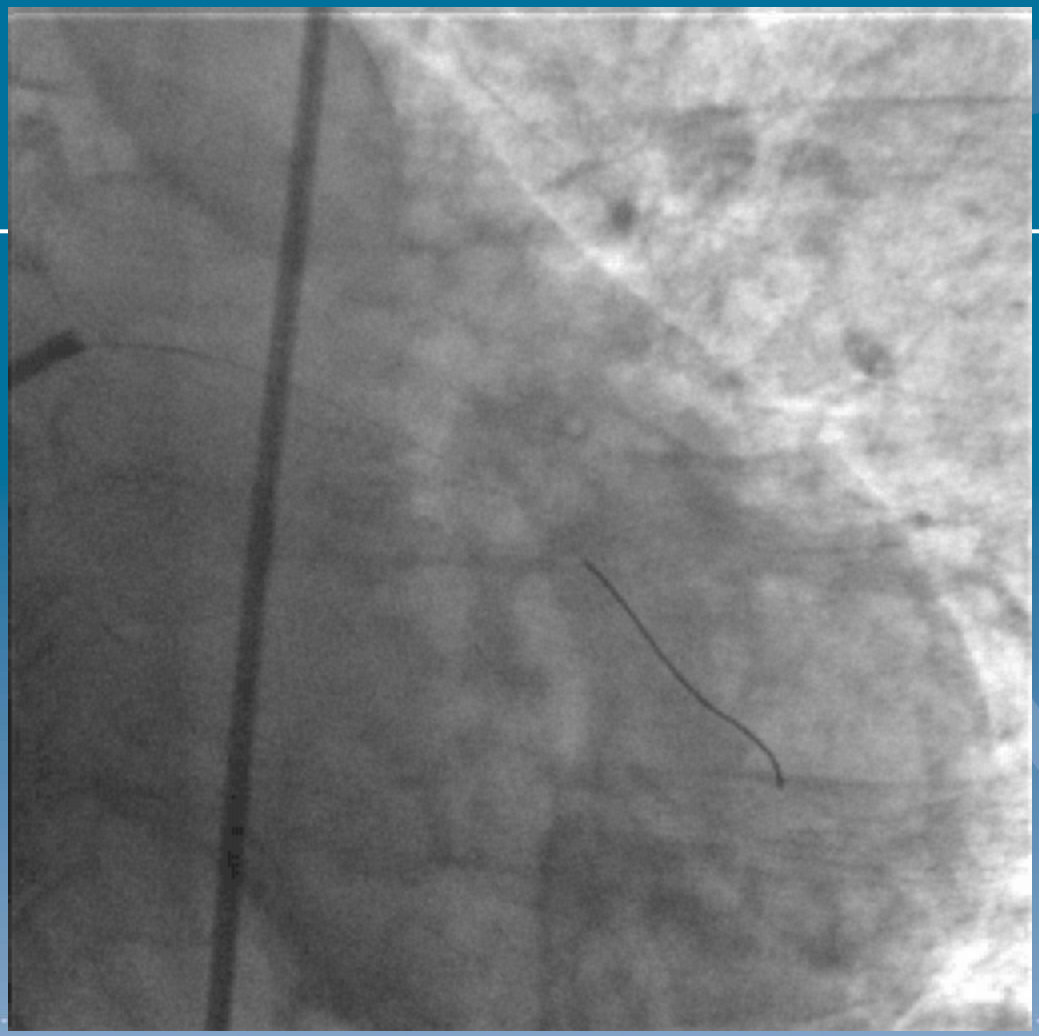












Death is Chasing Them (video)

Current Concepts in Atherosclerosis

Richard C. Padgett, MD

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

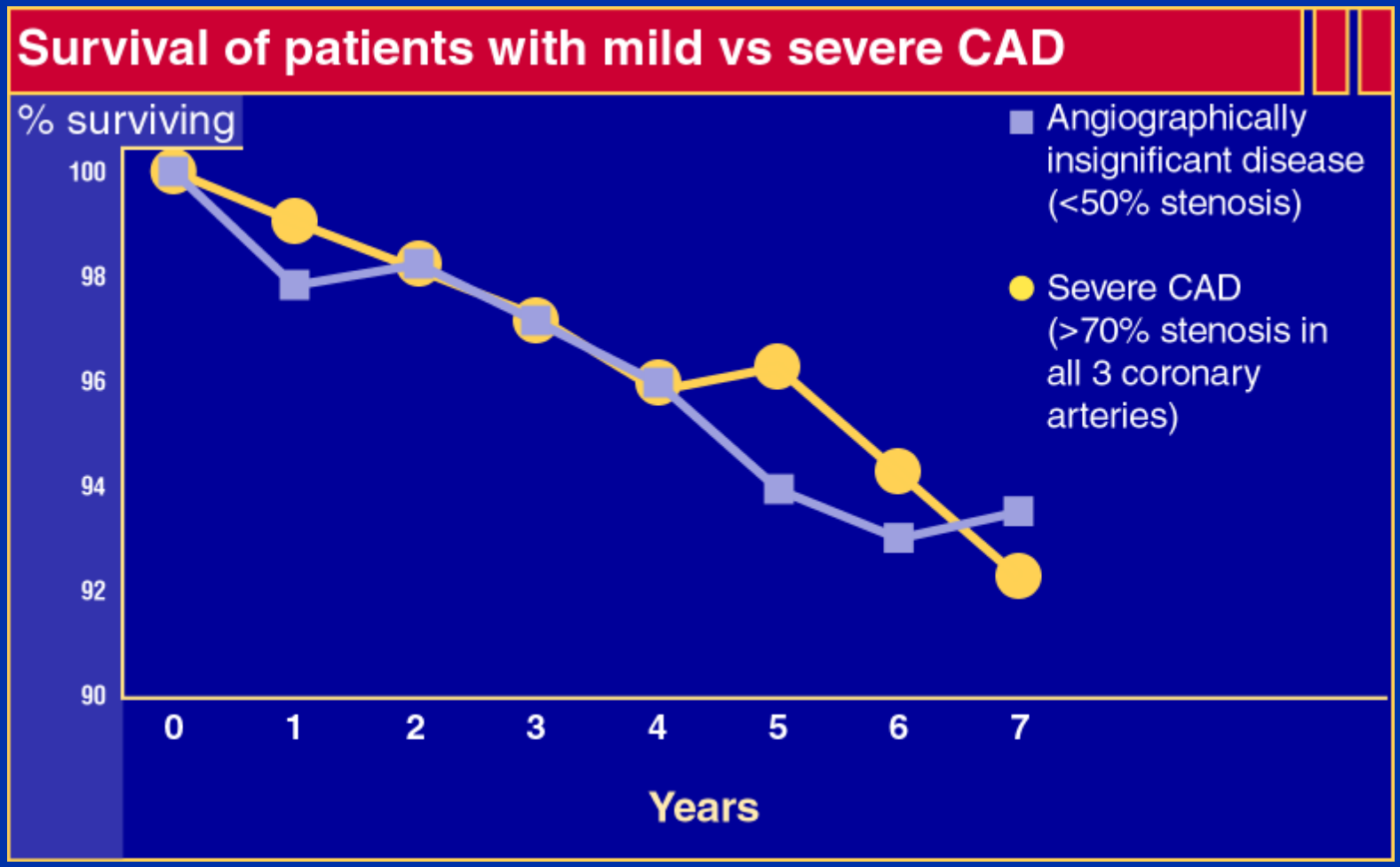
Which Patient needs Treatment

- 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.

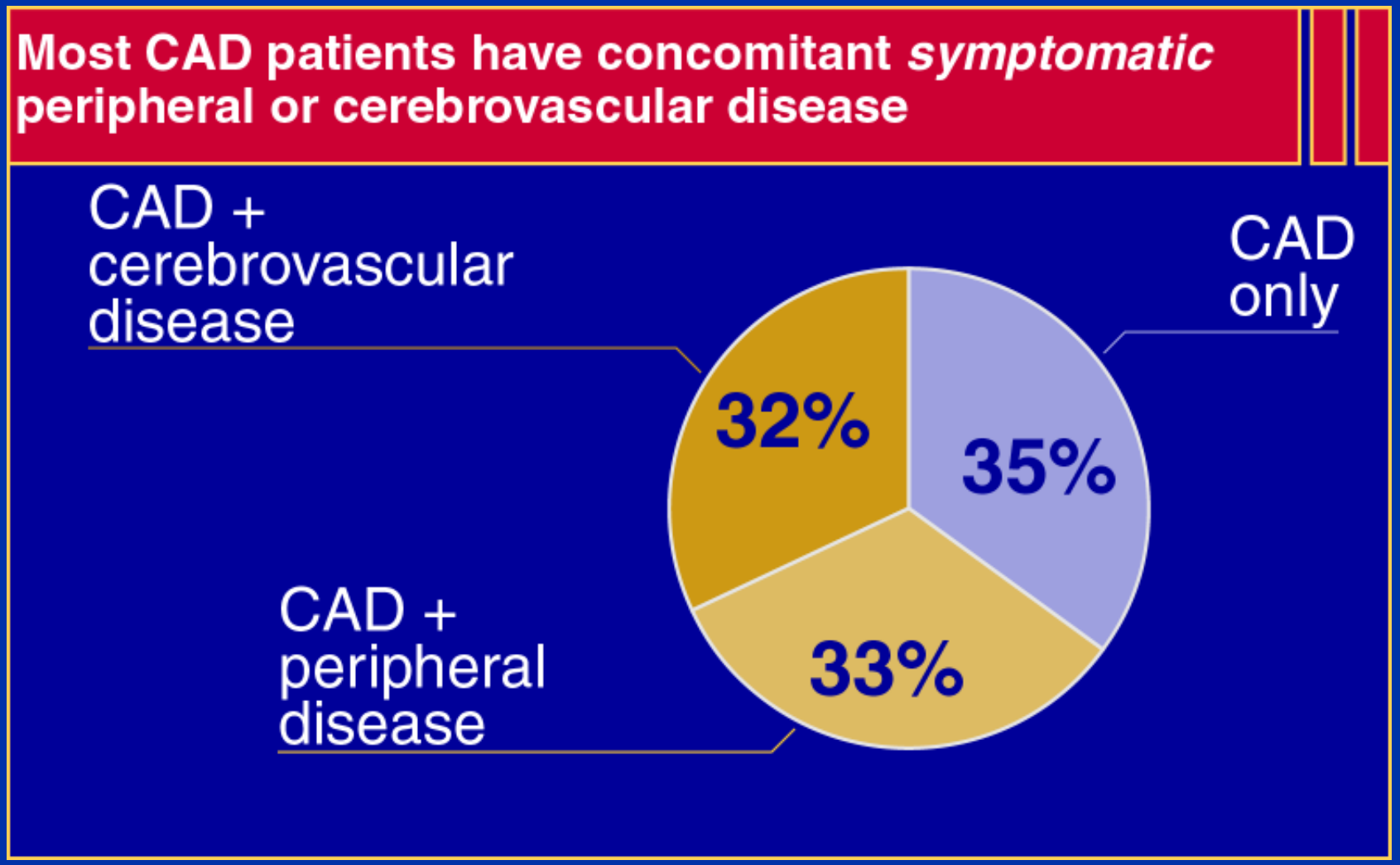
Vascular Disease: Scope of the Problem

- 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

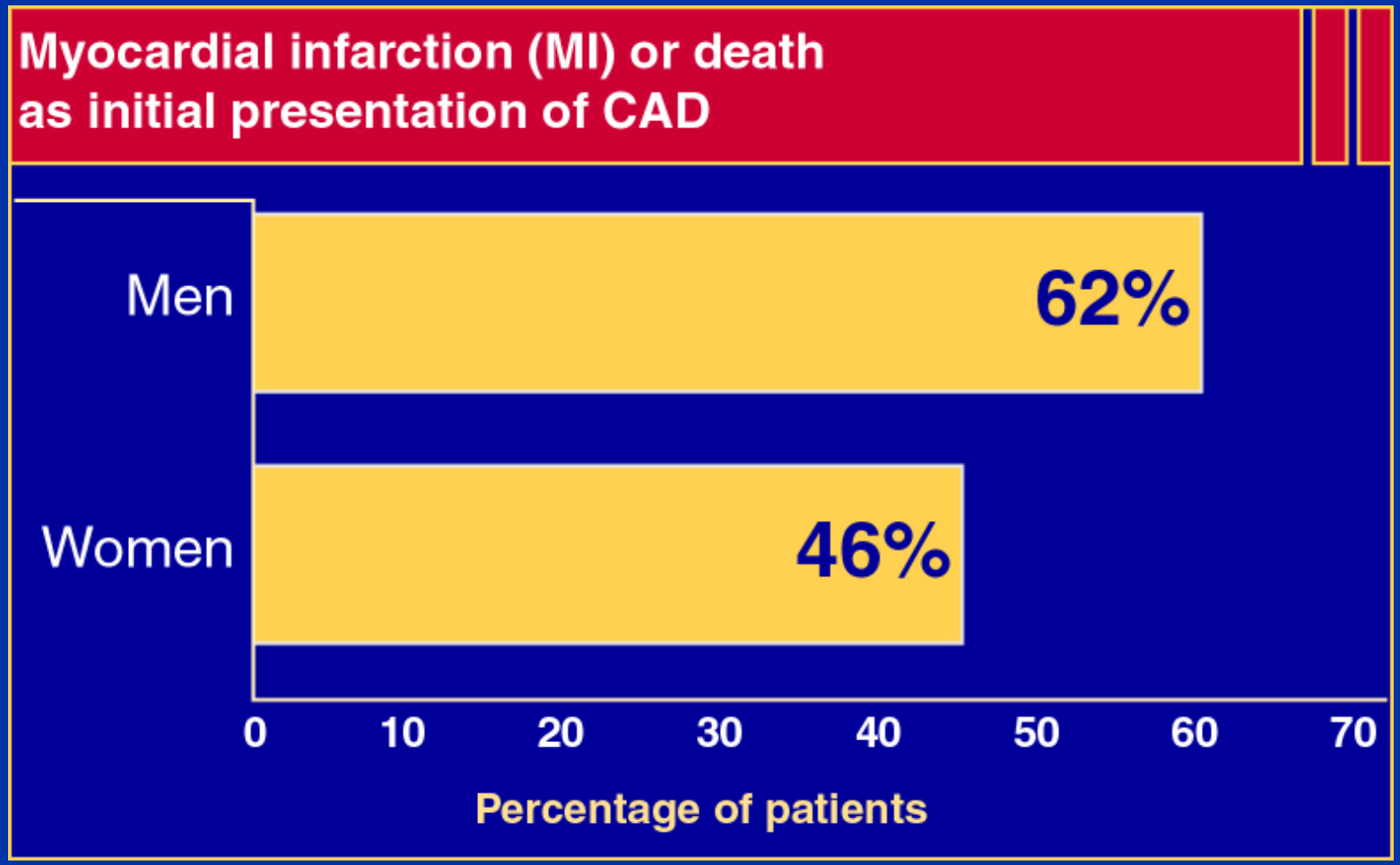
Most CAD patients have concomitant *symptomatic* peripheral or cerebrovascular disease



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

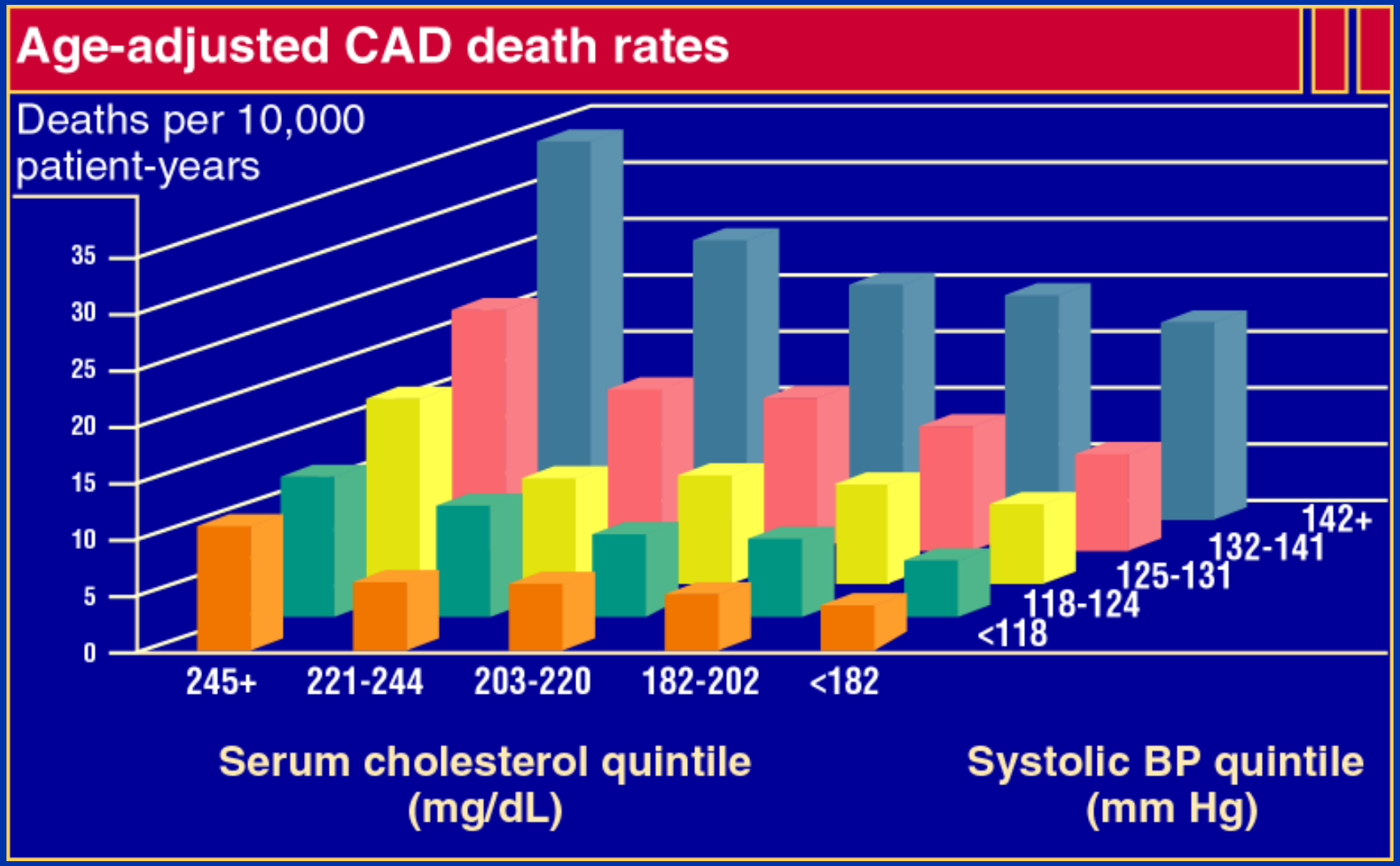
- Family history
- Age
- Gender

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

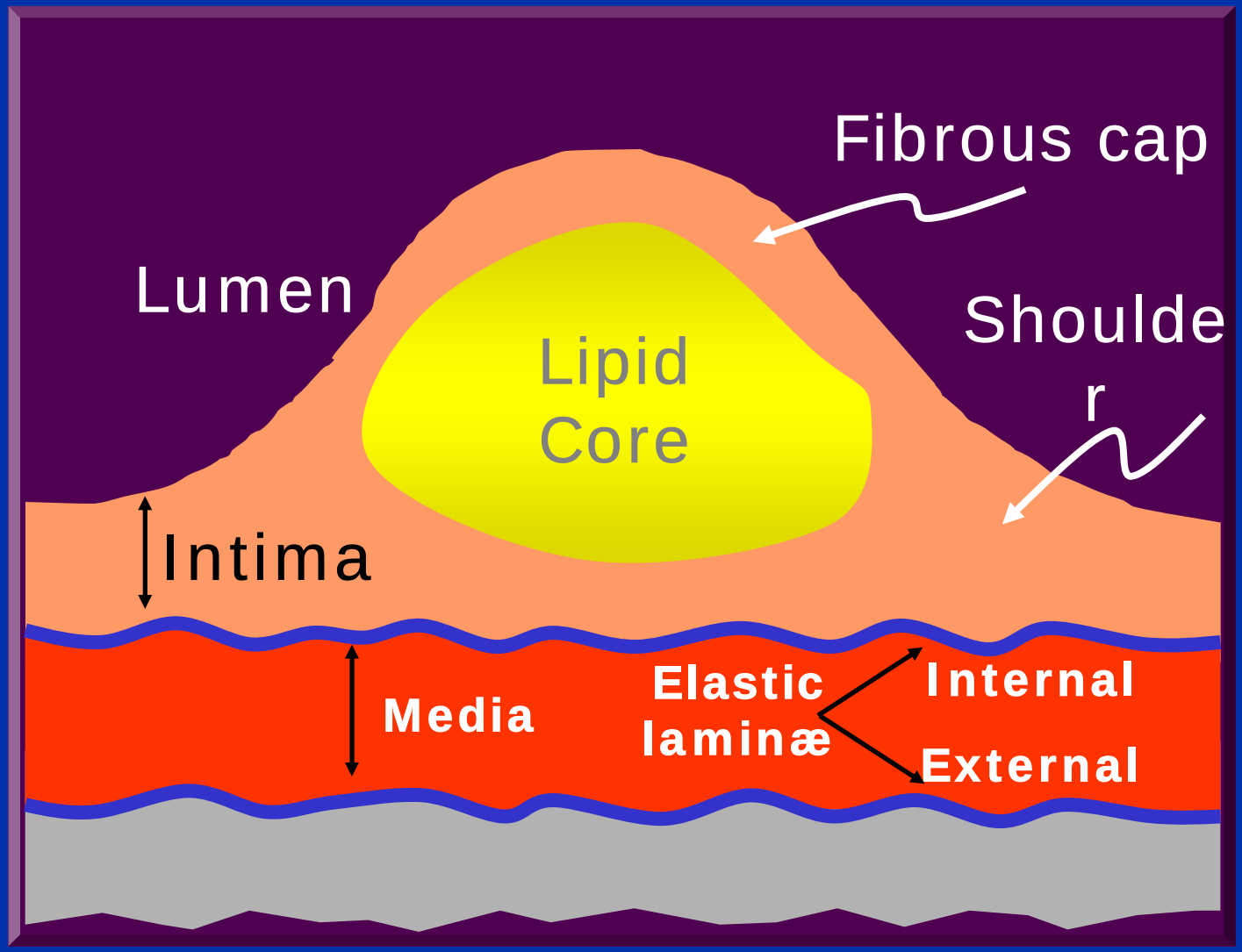
CAD Risk Is Incremental



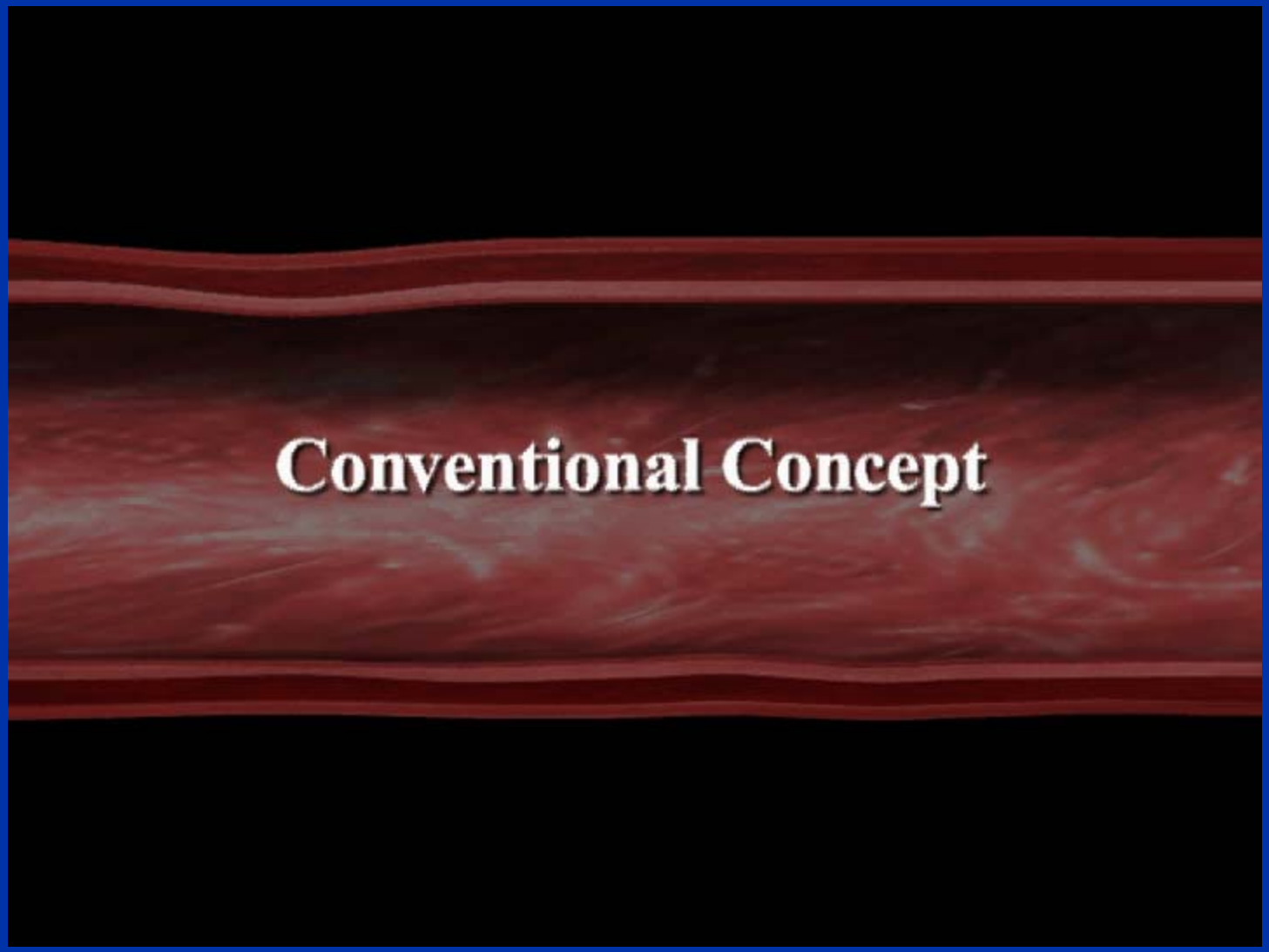
(Adapted from Neaton et al.)

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

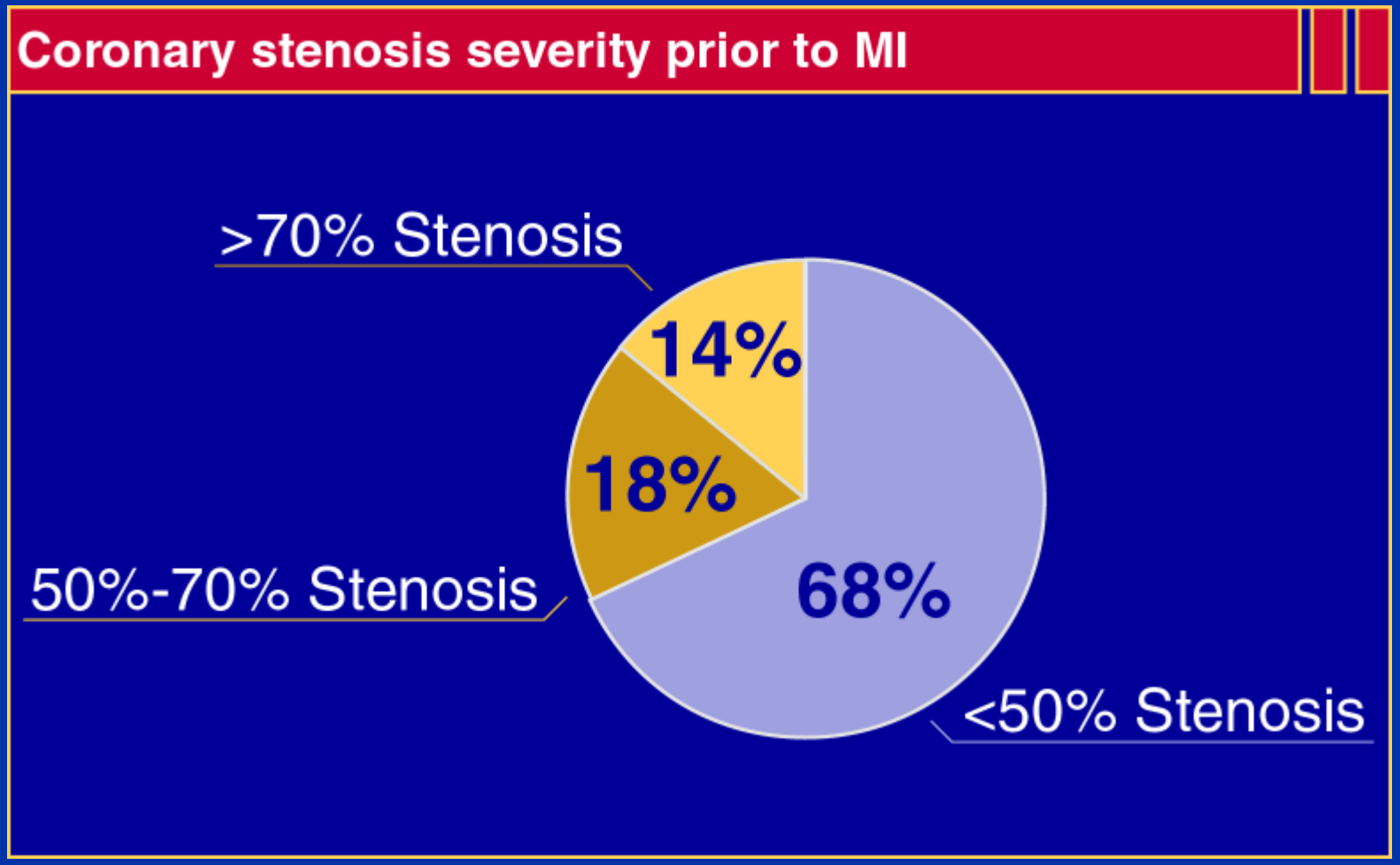
Anatomy of the Atherosclerotic Plaque




Development of Atherosclerotic Plaque


Conventional Concept

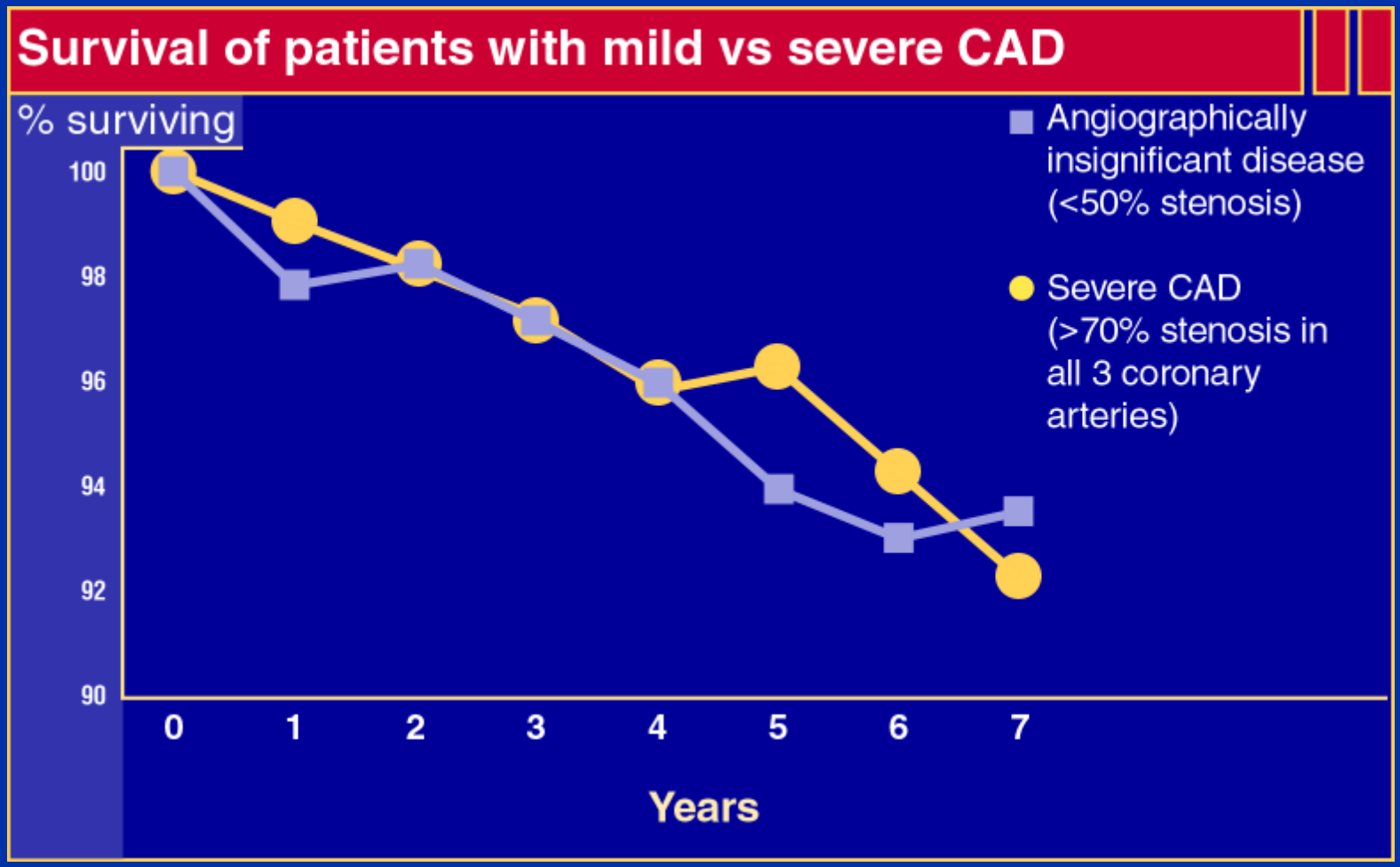
Most Myocardial Infarctions Are Caused by Low-Grade Stenoses



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.

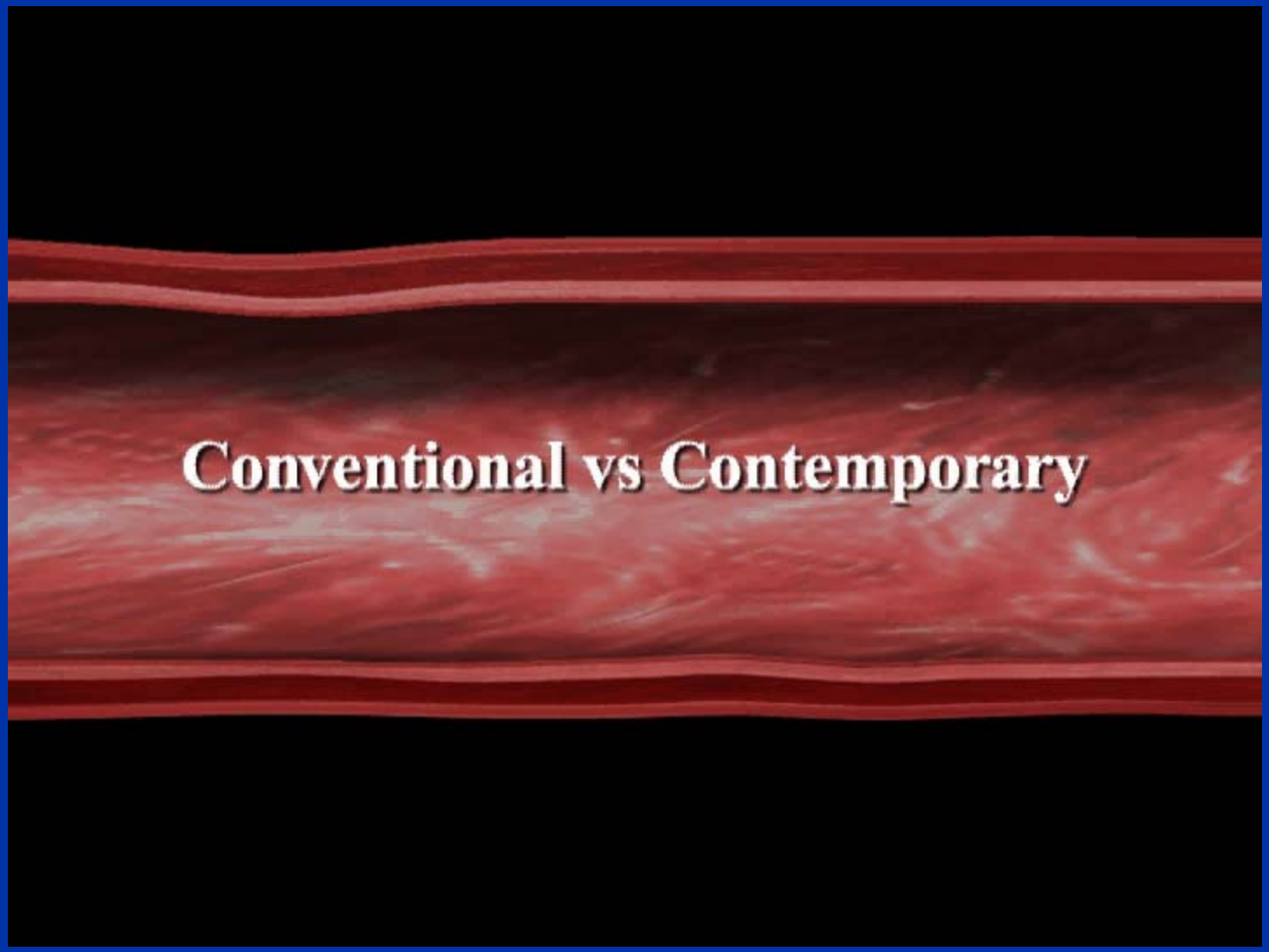
Lesion Severity: A Poor Predictor of Survival

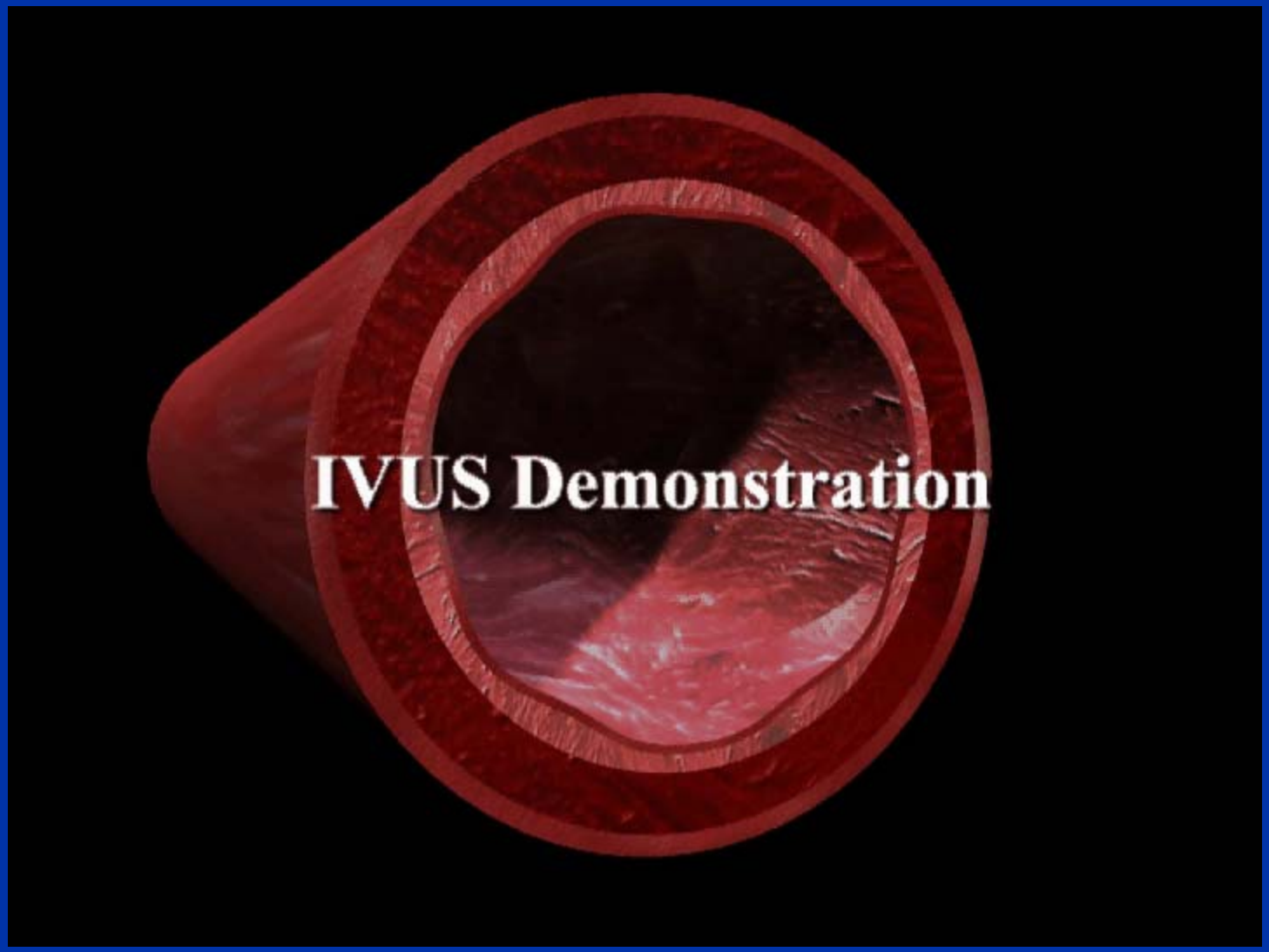


From the Coronary Artery Surgery Study (CASS) as reported by Little et al.

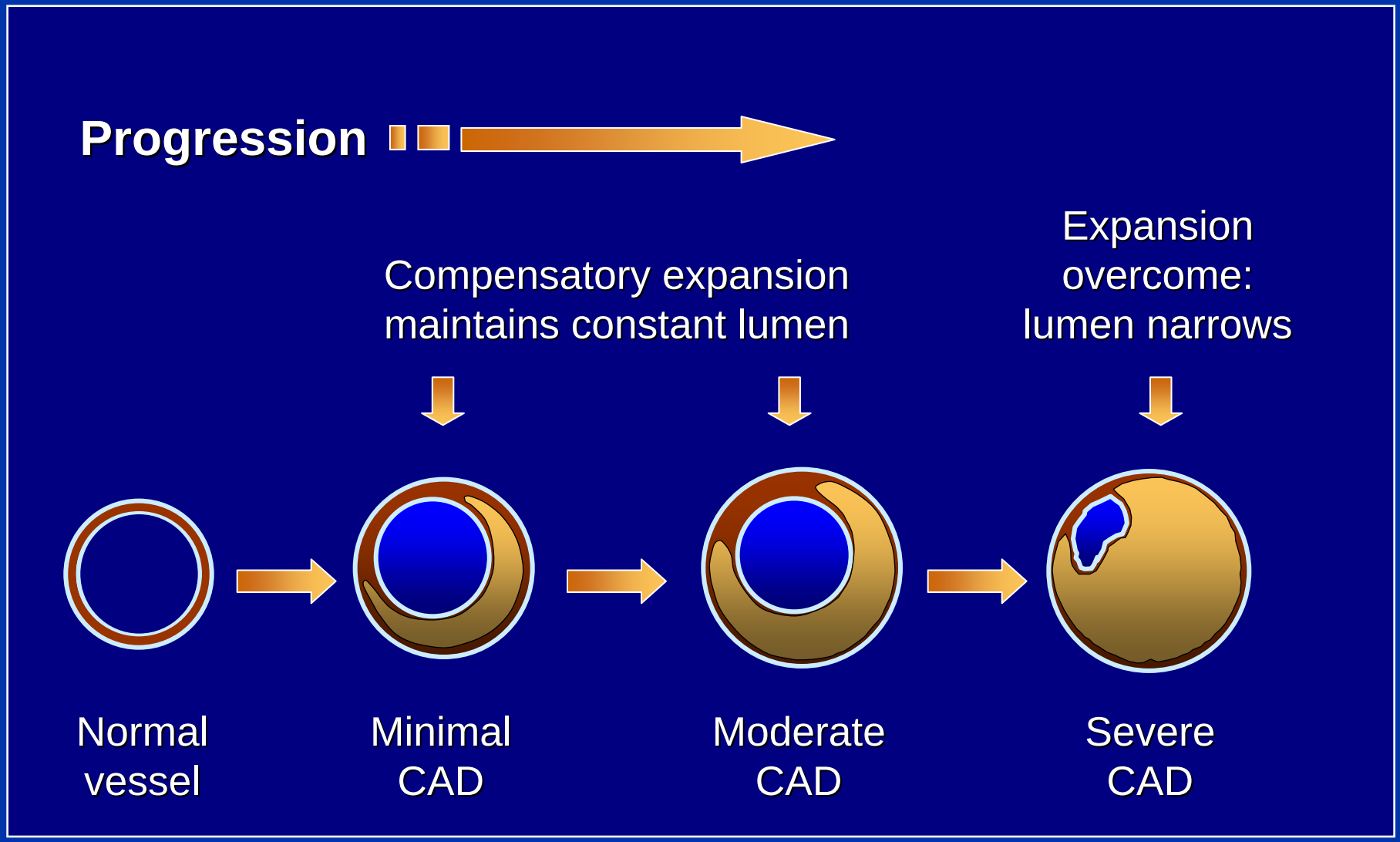
Little WC et al, *Clin Cardiol*, 1991.


Glagov's Model


Conventional vs Contemporary


IVUS Demonstration

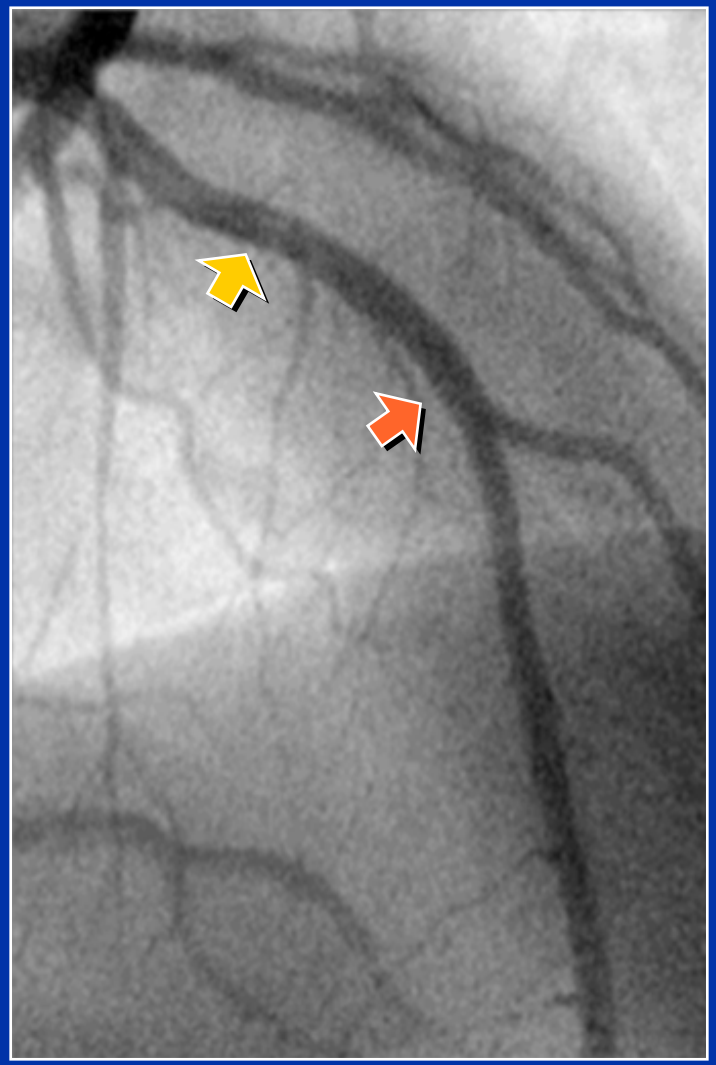
Coronary Remodeling

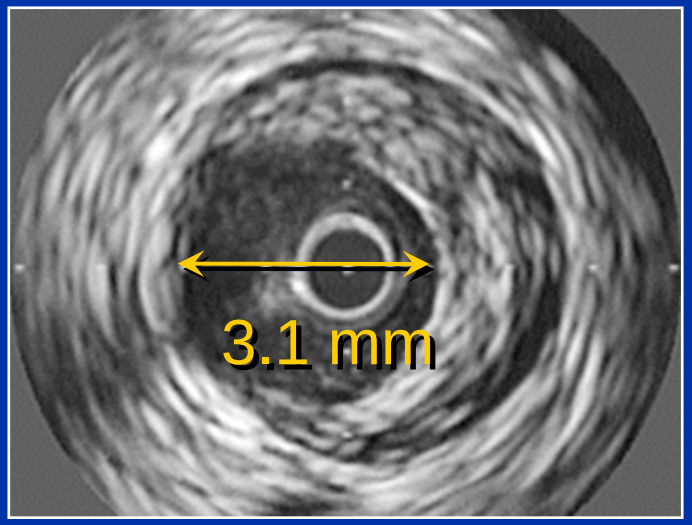


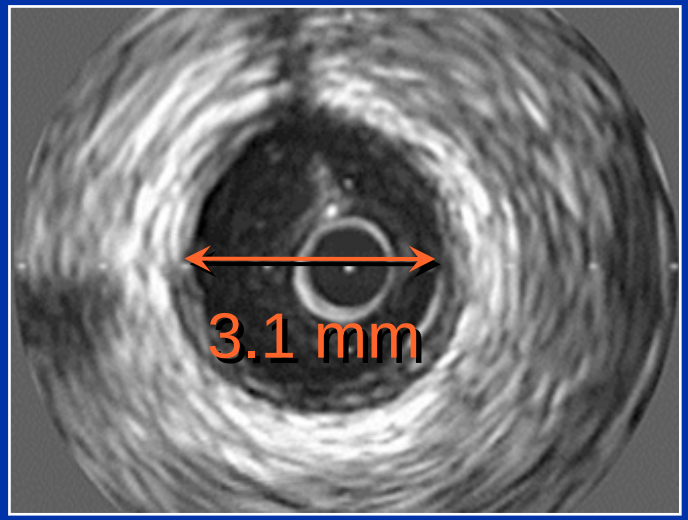
(Adapted from Glagov et al.)

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

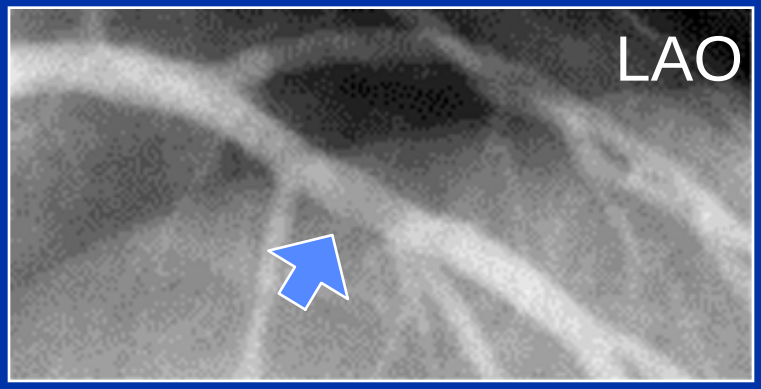
Angiography Cannot Account for Coronary Remodeling

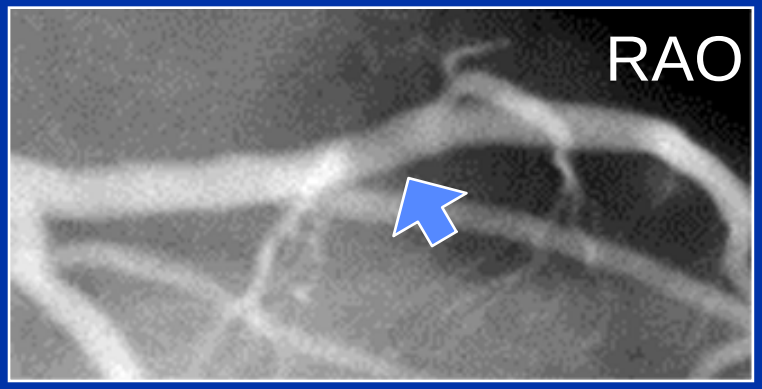


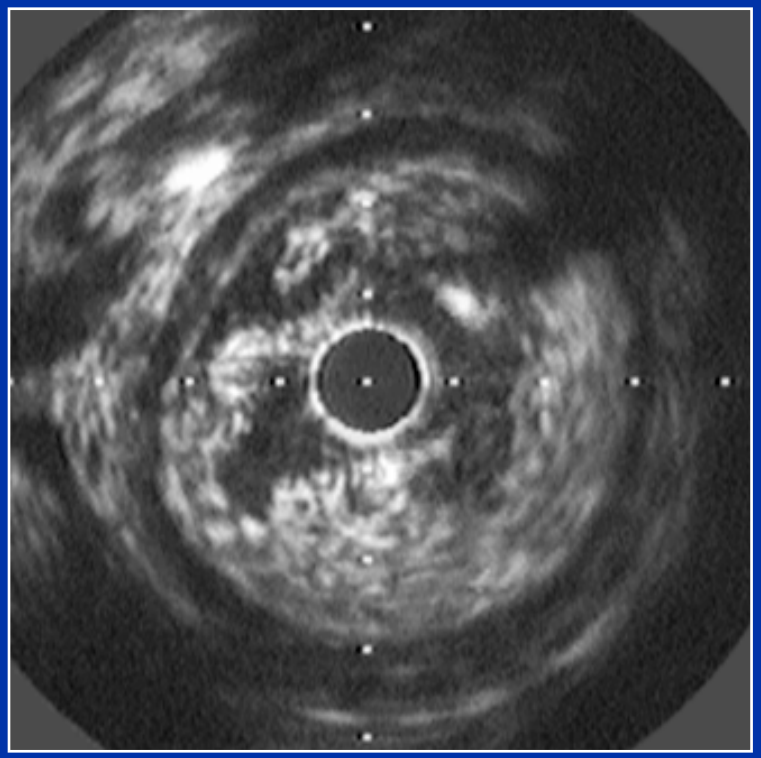


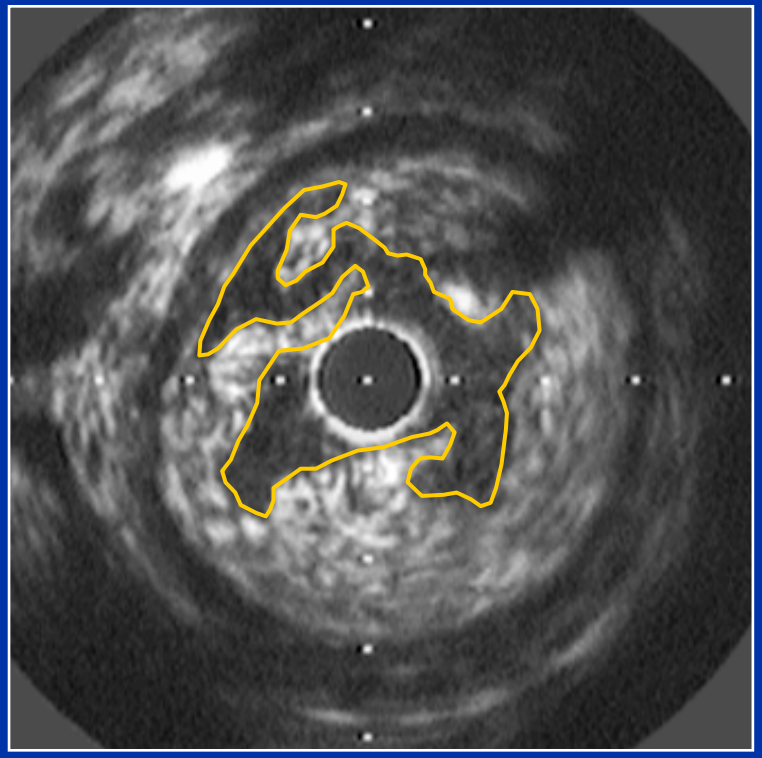


Angiography Masks Complicated Lesions

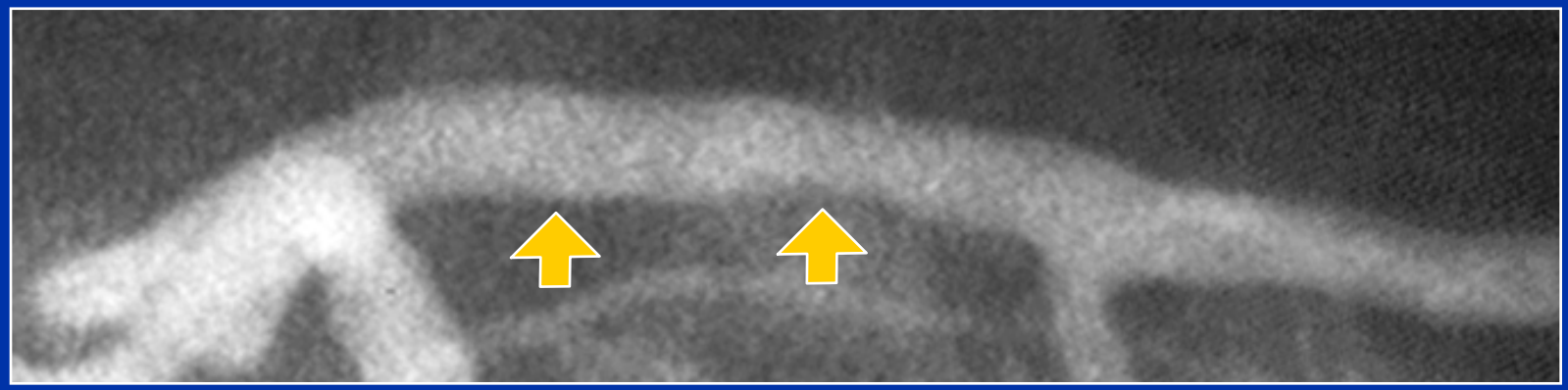


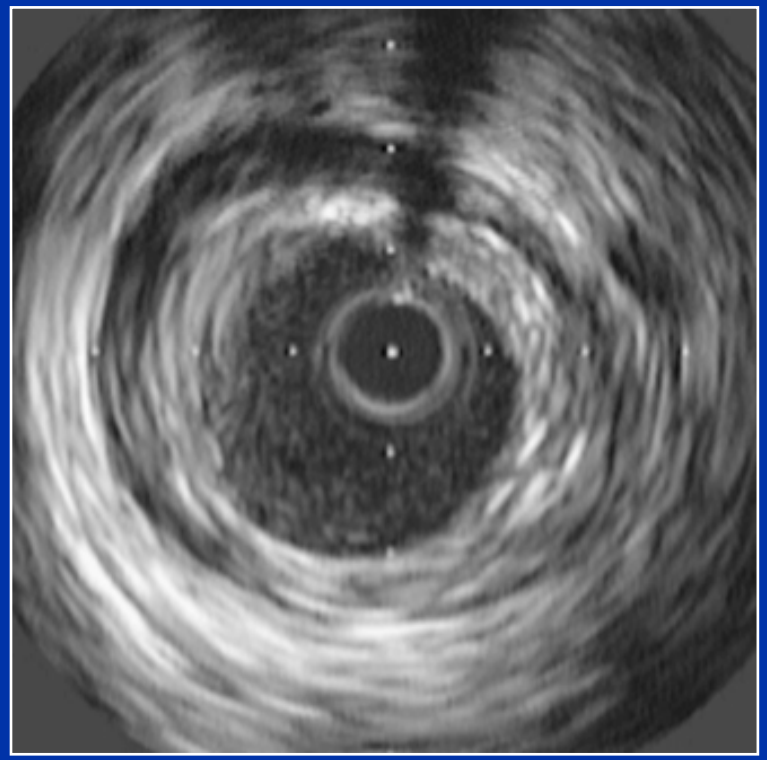


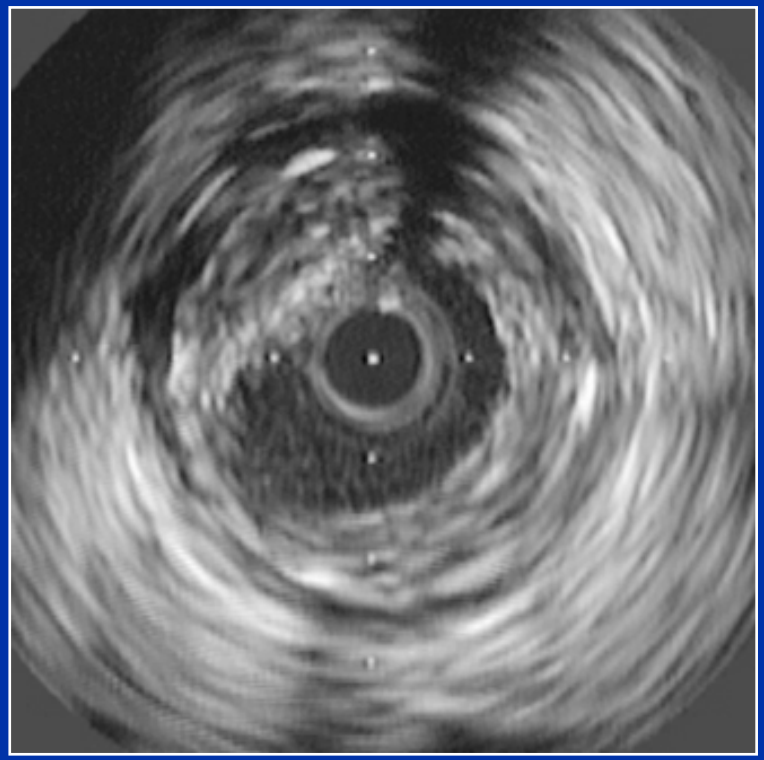


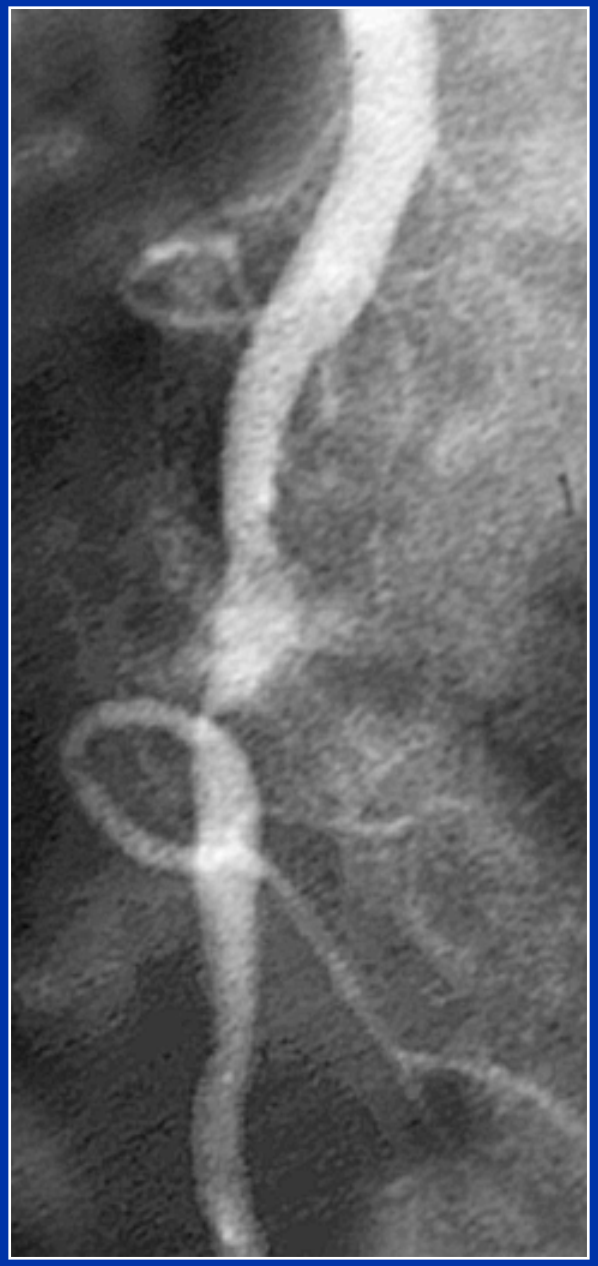


Angiography Underestimates Diffuse Disease









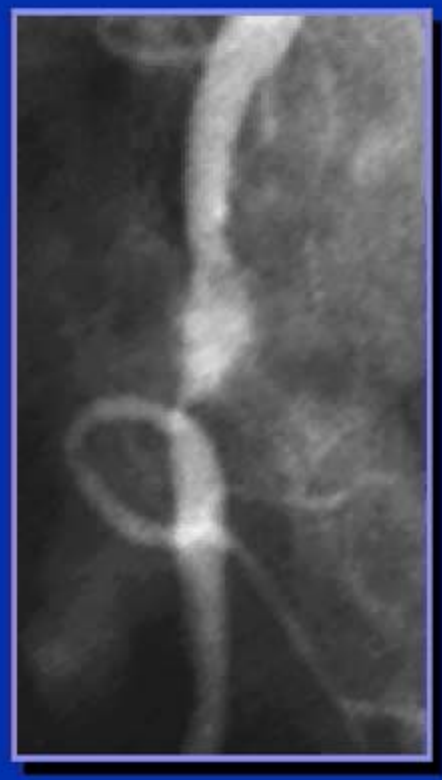
What Is the Culprit Lesion?

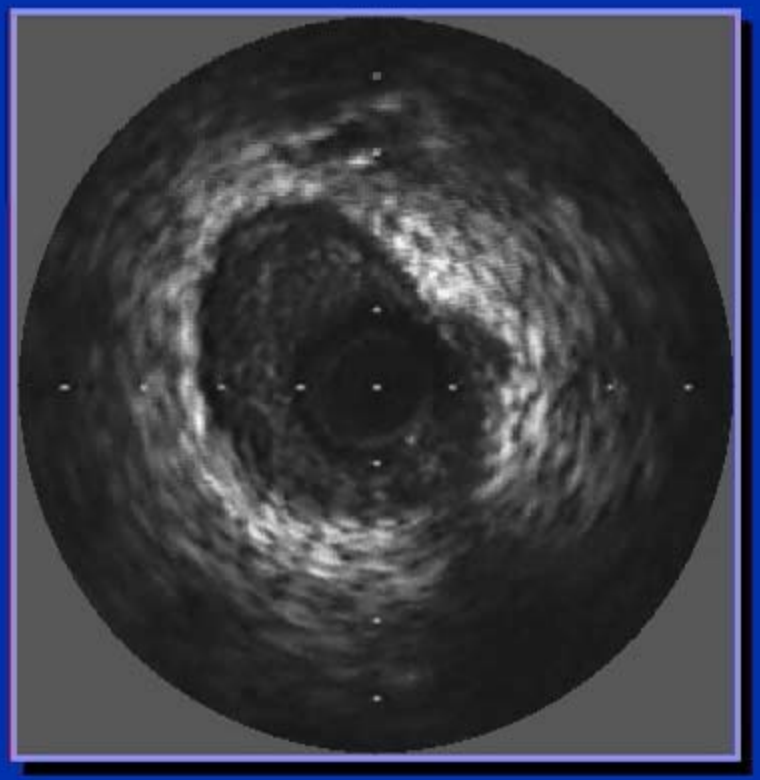
- 58-year-old male with chronic stable angina
- Positive stress test with small reversible ischemic defect on nuclear scintigraphy

Medical Rx, but 6 weeks later…

- 3-day history of unstable angina, including 30 minutes of rest pain
- Medically “cooled off” followed by angiography

Case provided by the McLaren Heart and Vascular Center, Flint, Michigan; used with permission.





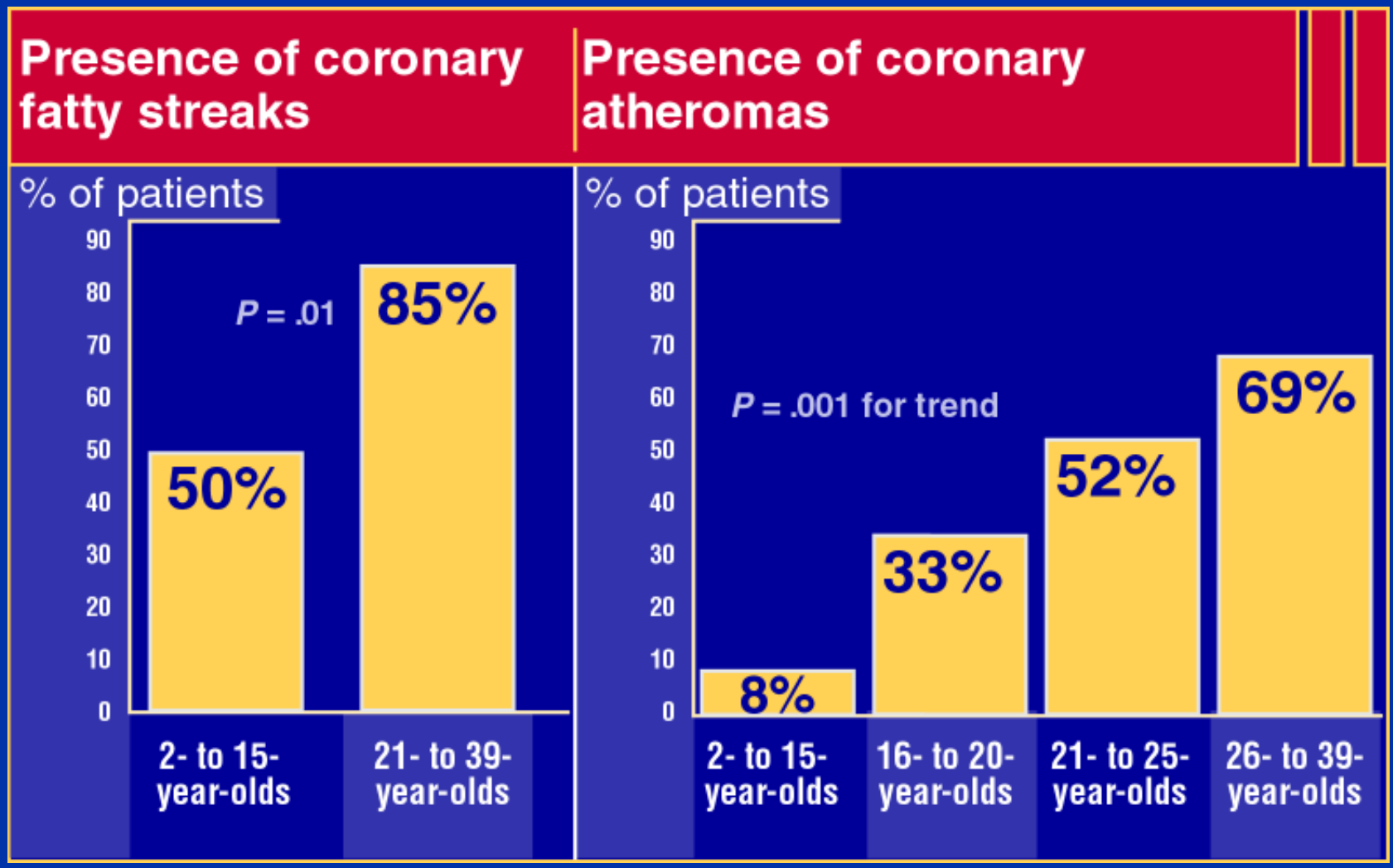
Absence of Correlation Between Angiographic Results and Clinical Outcomes

(Adapted from Brown et al.)

Brown BG et al, *Circulation*, 1993.


Transition to Acute Coronary Syndrome

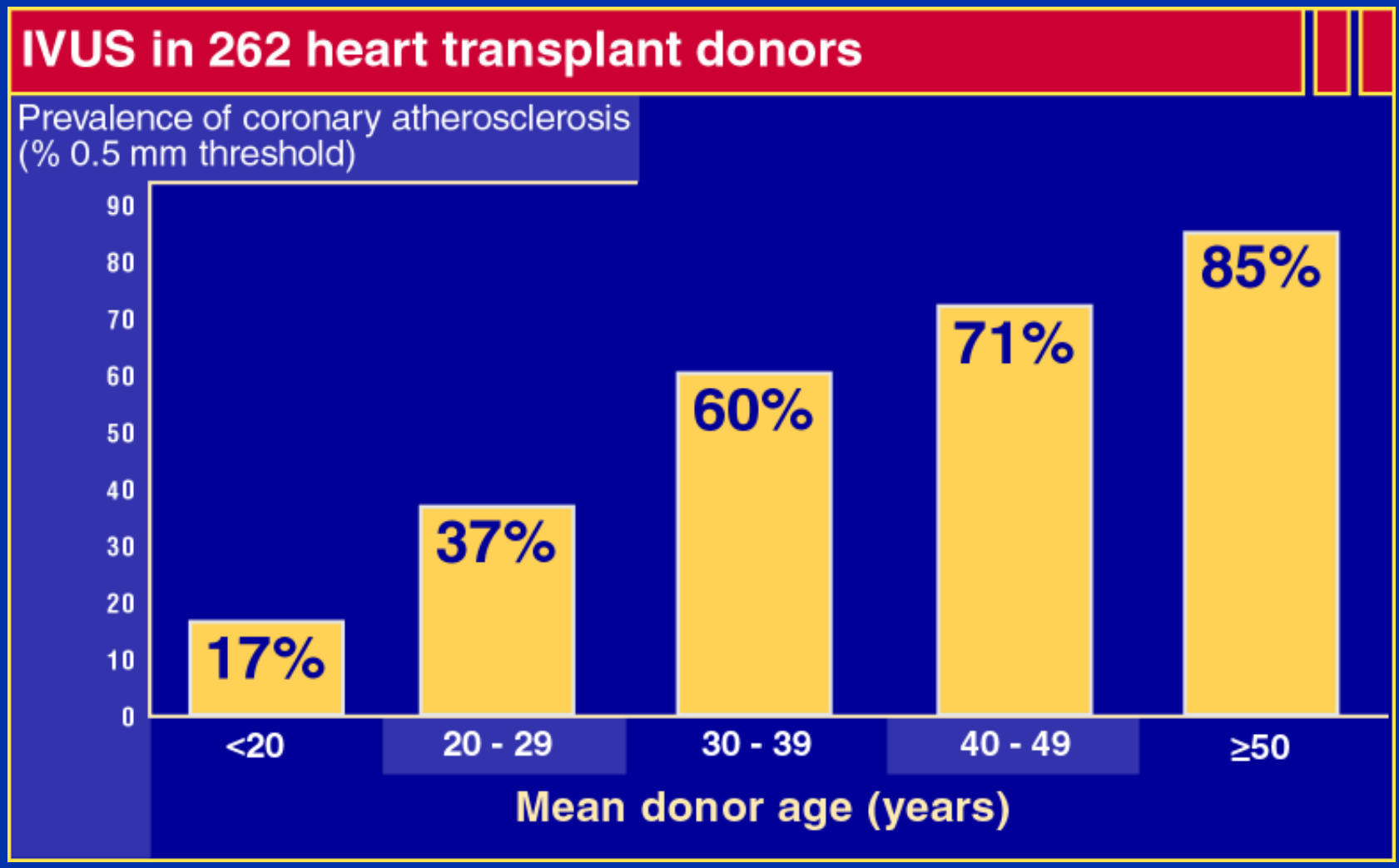
Atherosclerosis Begins in Childhood



(Adapted from Berenson et al.)

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

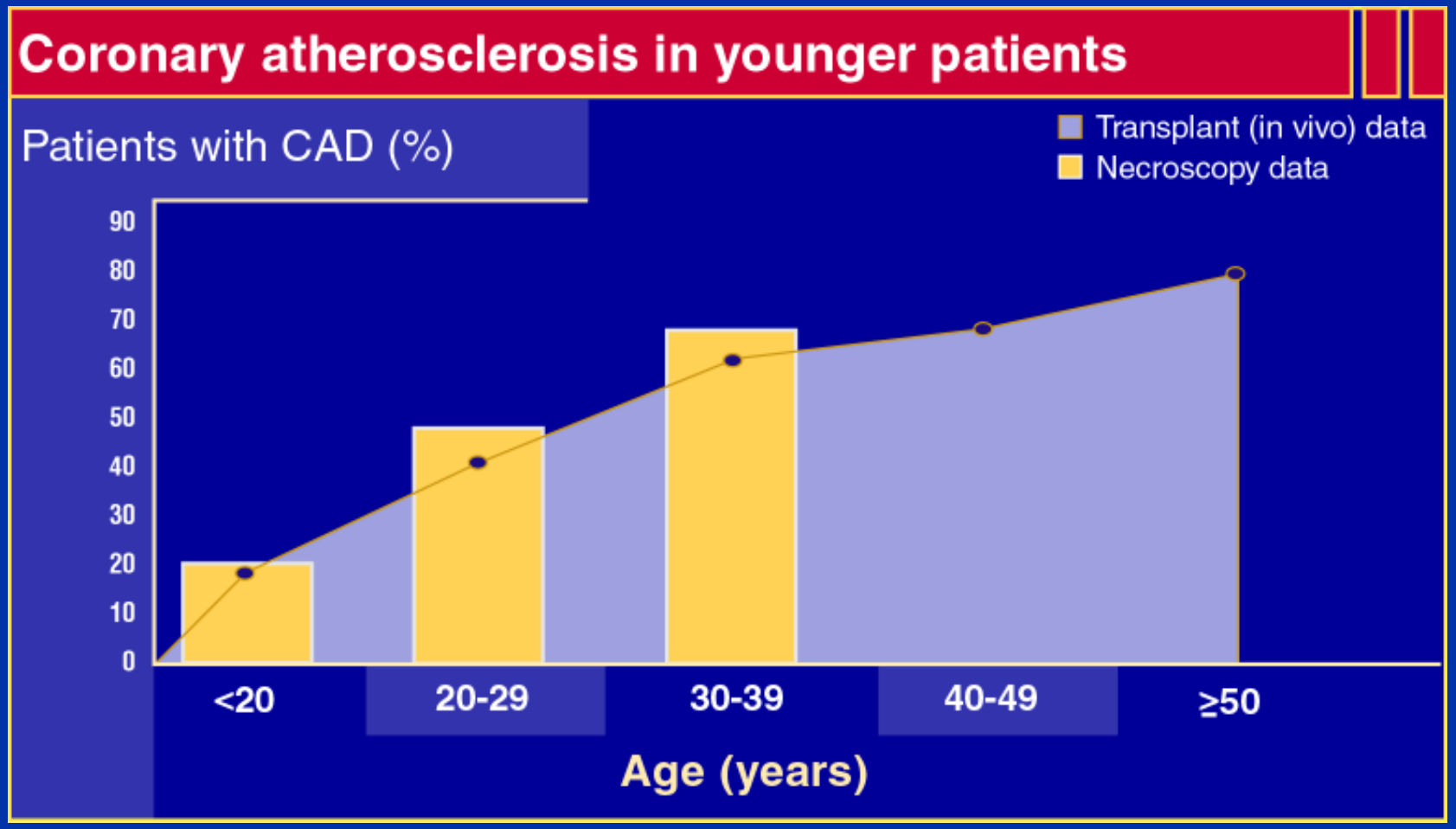
One in Six Teenagers Has Atheromas



(Adapted from Tuzcu et al.)

Tuzcu EM et al, in press.

Consistent Evidence of Early Atherosclerosis



(Adapted from Berenson et al and Tuzcu et al.)

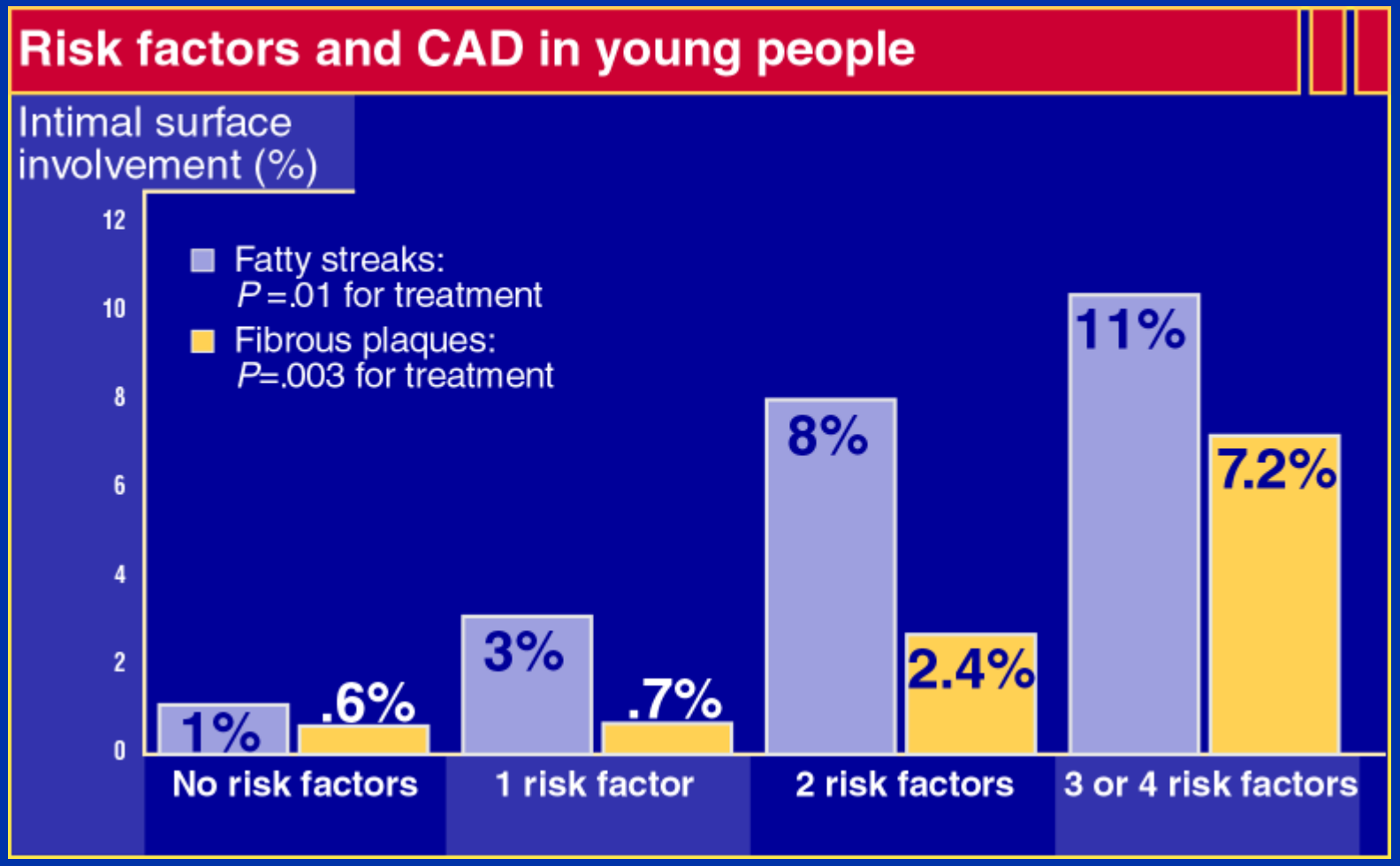
Berenson GS et al, *N Engl J Med*, 1998; Tuzcu EM et al, in press.

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.

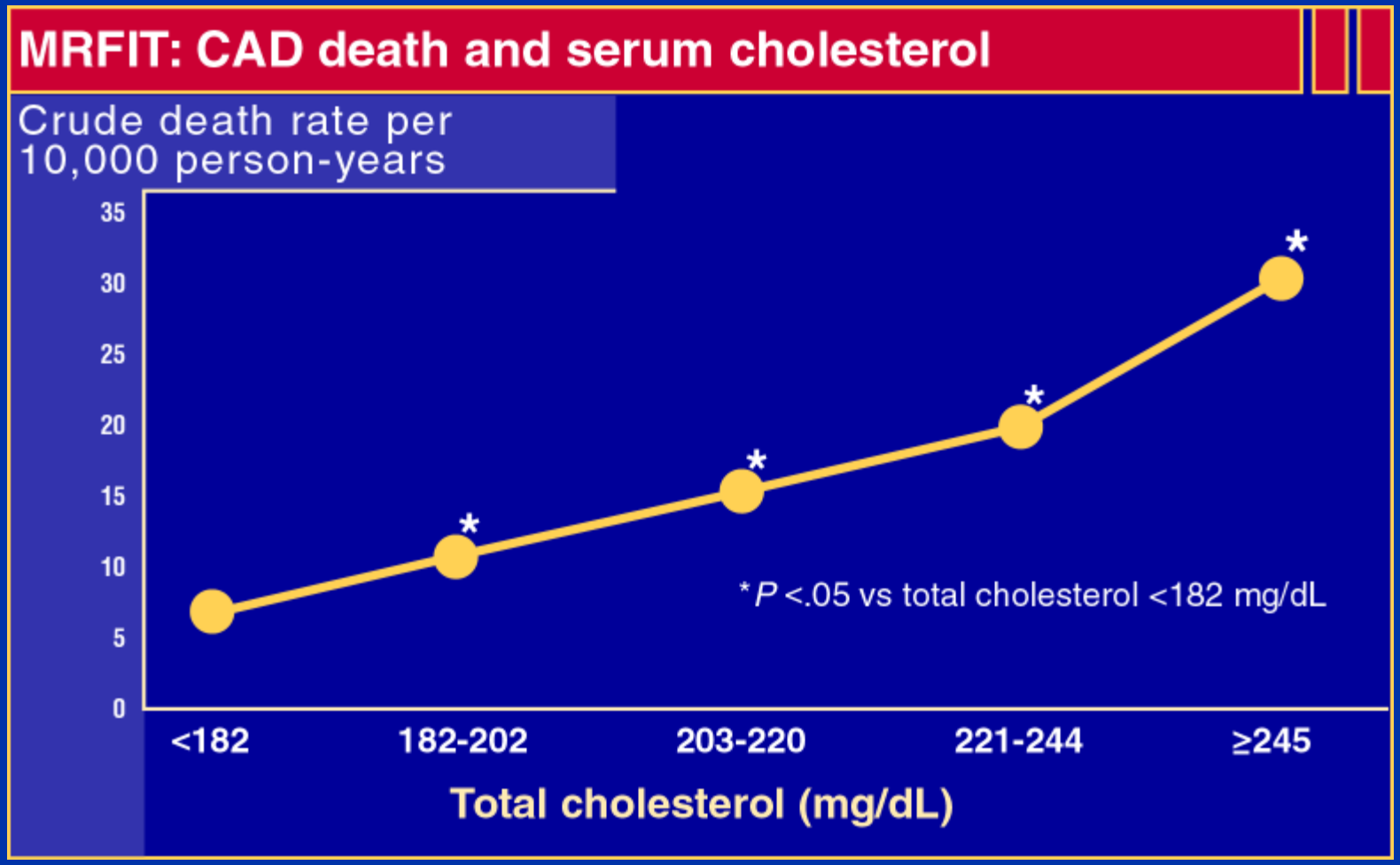
The Correlation Between Atherosclerosis and Risk Factors Begins Early



(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

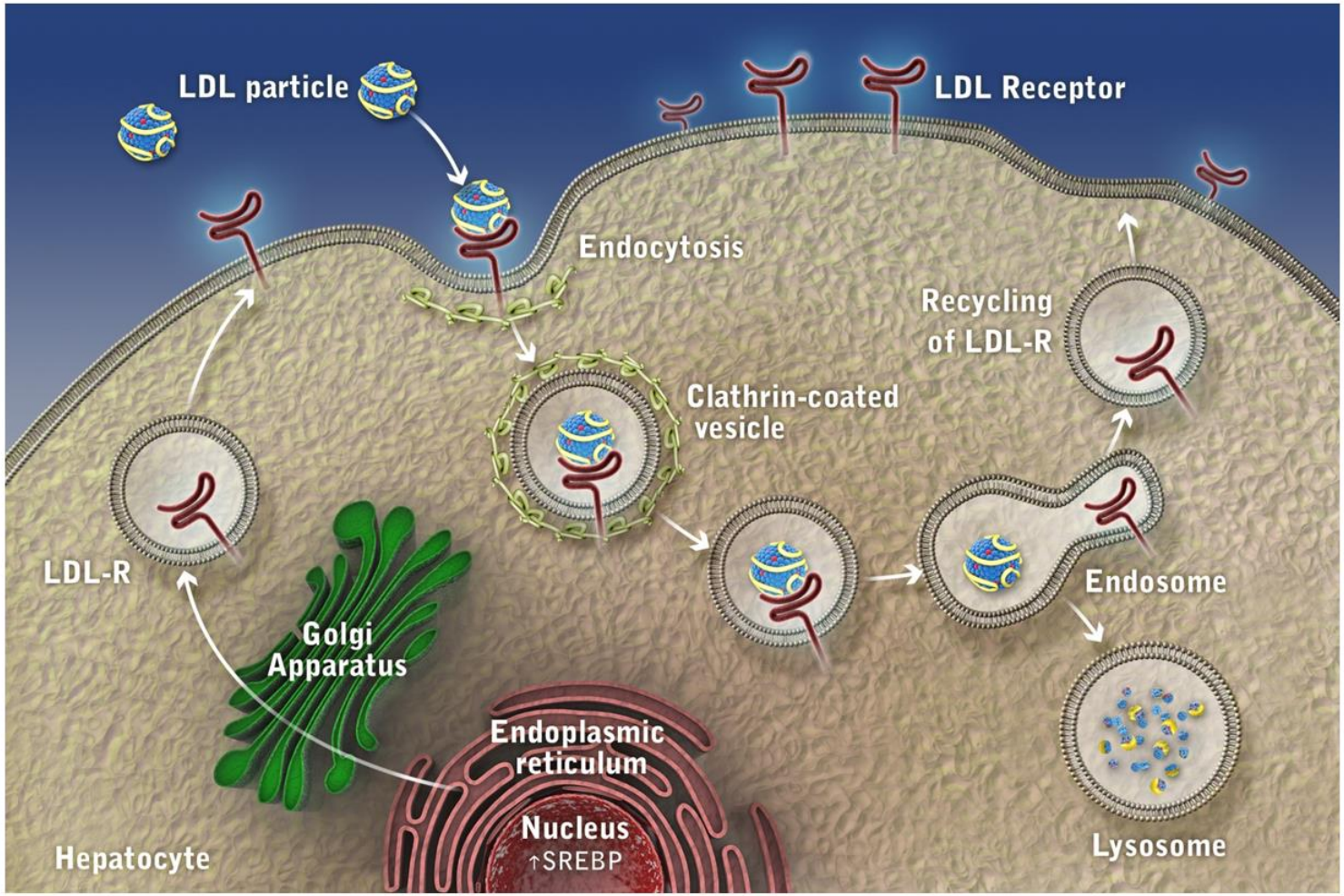
- CAD is a ubiquitous, systemic disease that requires a systemic solution
- Most patients progress to MI or sudden death before a diagnosis of CAD is ever considered
- IVUS demonstrates that remodeling causes angiography to underestimate the extent of disease
- Extraluminal, angiographically silent atheromas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

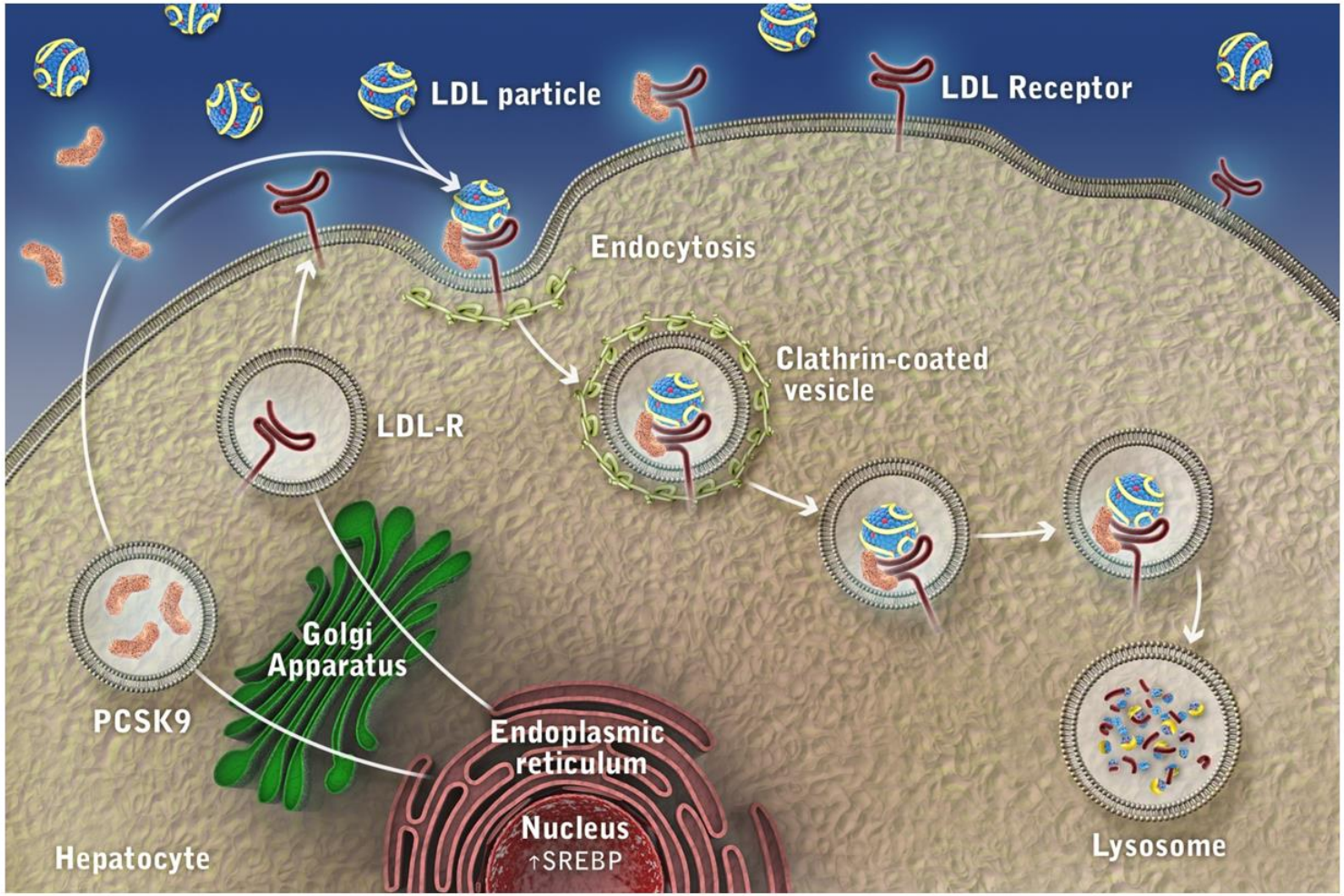
Learning Objectives

- Describe the mechanism of action of PCSK9 in regulation of cholesterol homeostasis
- Discuss the use of PCSK9 monoclonal antibodies for regulating atherogenic lipoprotein metabolism
- Review efficacy and safety data for the various PCSK9 inhibitors for FH as well as severe hypercholesterolemia

LDLR Function and Life Cycle



The Role of PCSK9 in the Regulation of LDLR Expression



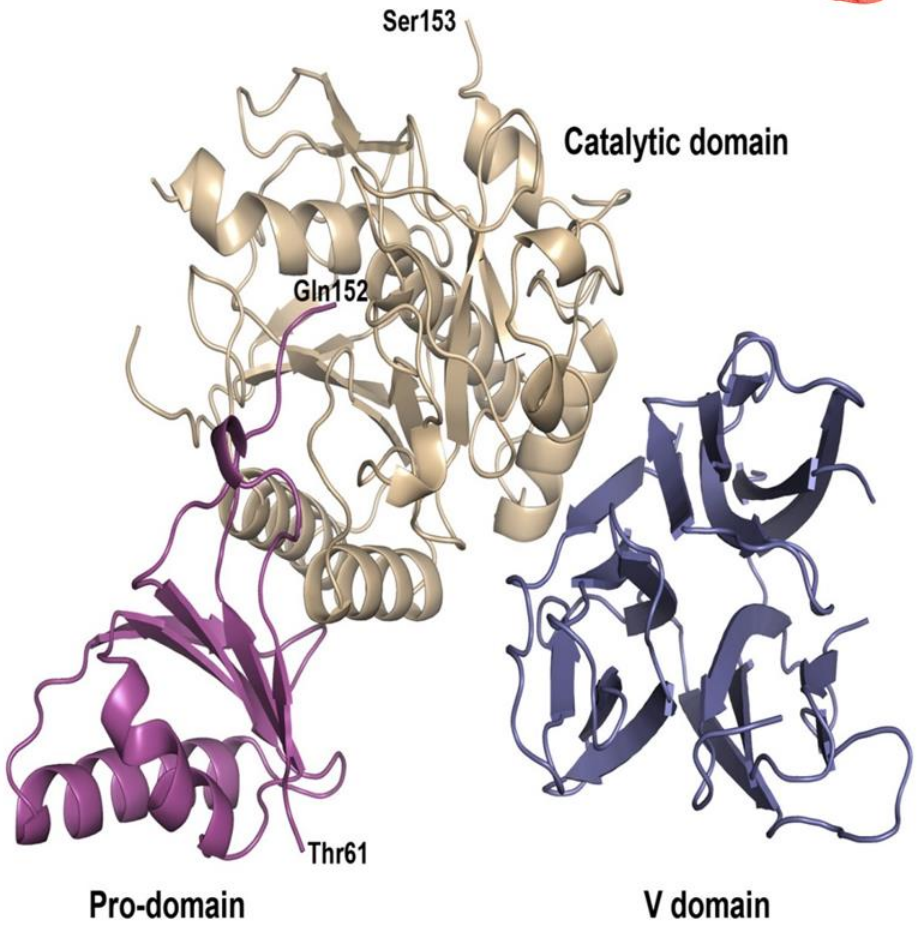
PCSK9

- 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 Structure

- Synthesized primarily by the liver as a 692-amino acid precursor of about 75 kDa (pro-PCSK9)
- Contains signal sequence (aa 1-30), prodomain (aa 31-152), catalytic domain (aa 153-425), and C-terminal domain (aa 426-692)
- Cleavage of prodomain is required for PCSK9 maturation and secretion



Piper DE, et al. *Structure*. 2007;15:545-552.[5]

PCSK9 Synthesis

- Mainly expressed in the liver, its transcription is driven by intracellular cholesterol concentrations (SREBP).
- Autocatalytic processing in the endoplasmic reticulum cleaves the prodomain and produces the mature protein that is then transported to the Golgi apparatus and secreted.
- The prodomain remains noncovalently attached to the catalytic domain, thus covering the catalytic pocket of PCSK9.
- Therefore, PCSK9 capacity to promote LDLR degradation is independent of its catalytic activity.

PCSK9 In and Out of the Cell

- PCSK9 binds the EGF-A domain of LDLR and promotes the degradation of the receptor in the lysosome.
- Since PCSK9 regulates LDLR levels and uses LDLR for its own clearance, it should be expected that LDLR regulates PCSK9 levels.
- PCSK9 may also interact with other members of the LDLR family, such as VLDLR and ApoER2.[a]
- LDLR and PCSK9 can also interact in the secretory pathway.

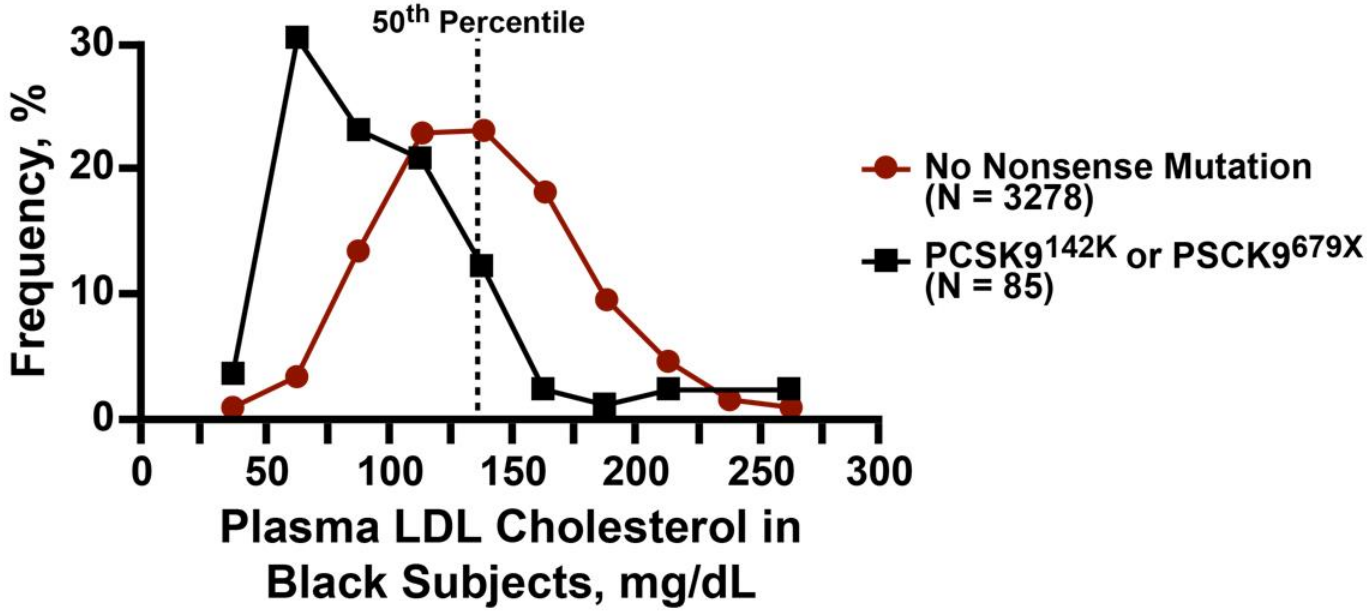
a. Poirier S, et al. *J Biol Chem*. 2008;83:2363-2372.[6]

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]

The PCSK9 Lead

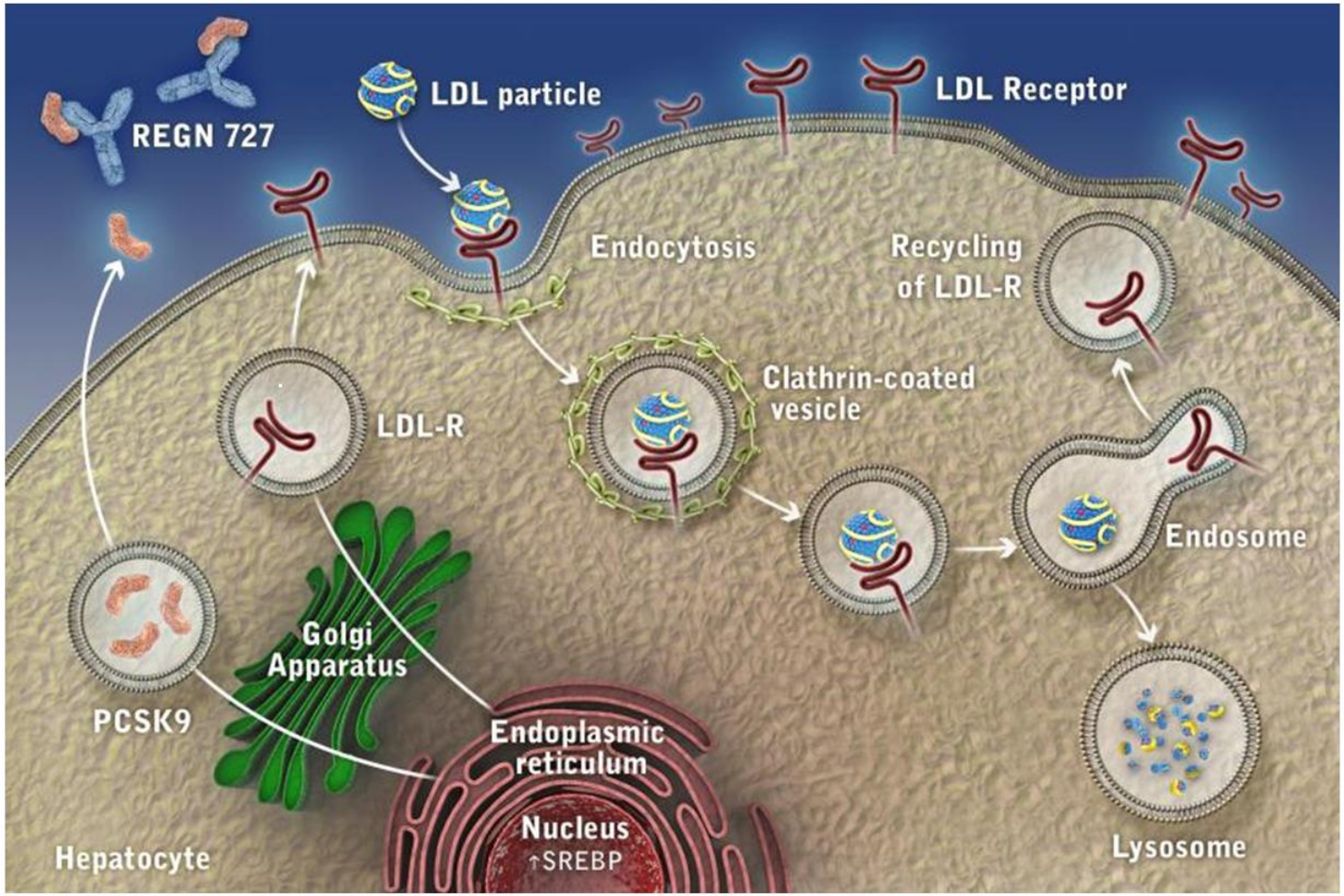


Incidence of CHD Among Black Patients With or Without PCSK9^{142X} or PCSK9^{679X} Allele

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]

Impact of a PCSK9 mAb on LDLR Expression



Mechanism of Action

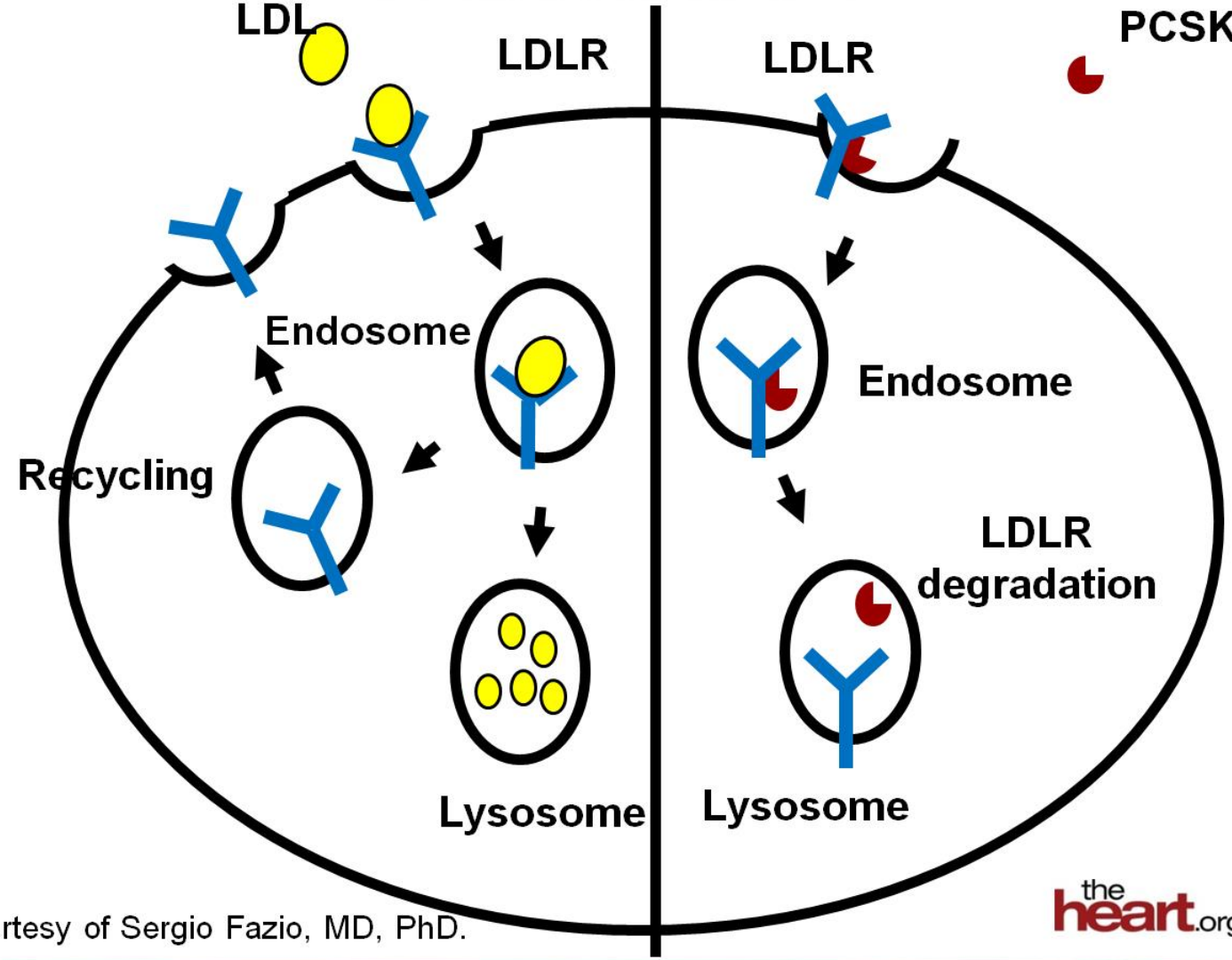


Image courtesy of Sergio Fazio, MD, PhD.

Mechanism of Action (cont)

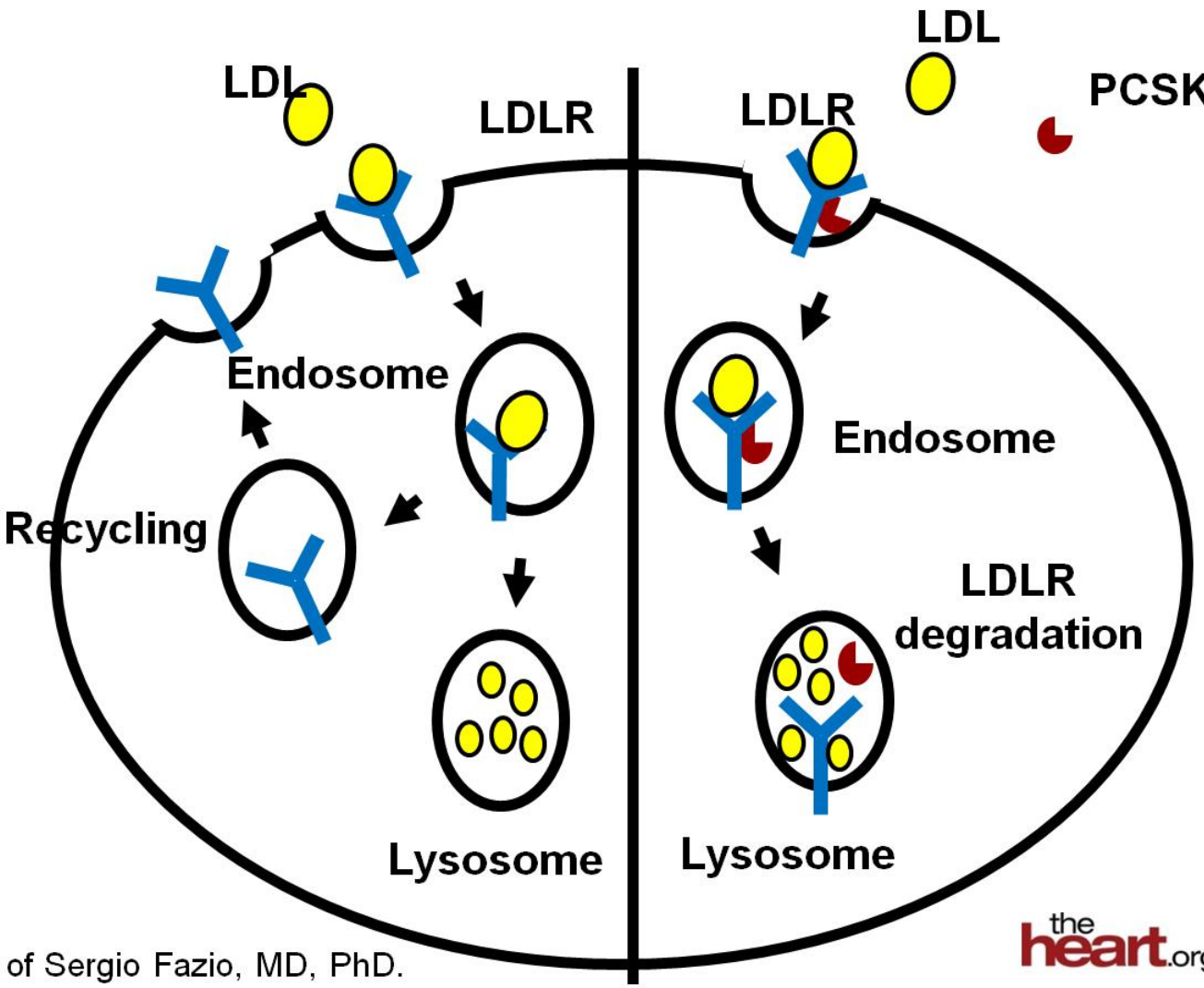
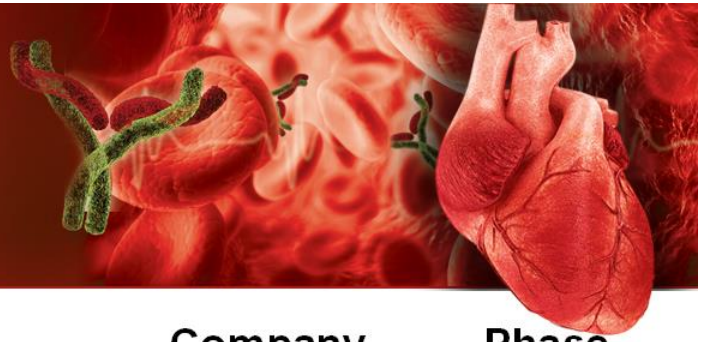


Image courtesy of Sergio Fazio, MD, PhD.

Summary

- PCSK9 regulates LDLR and is regulated by SREBP
- Absence of PCSK9 action causes extremely low LDL-C
- PCSK9 increases ApoB levels in the absence of LDLR
- PCSK9 on serum LDL-C may control peripheral regulation of LDLR expression
- Partner proteins may interfere with PCSK9 action
- Therapeutic avenues are available beyond the blockade of PCSK9/LDLR interactions

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

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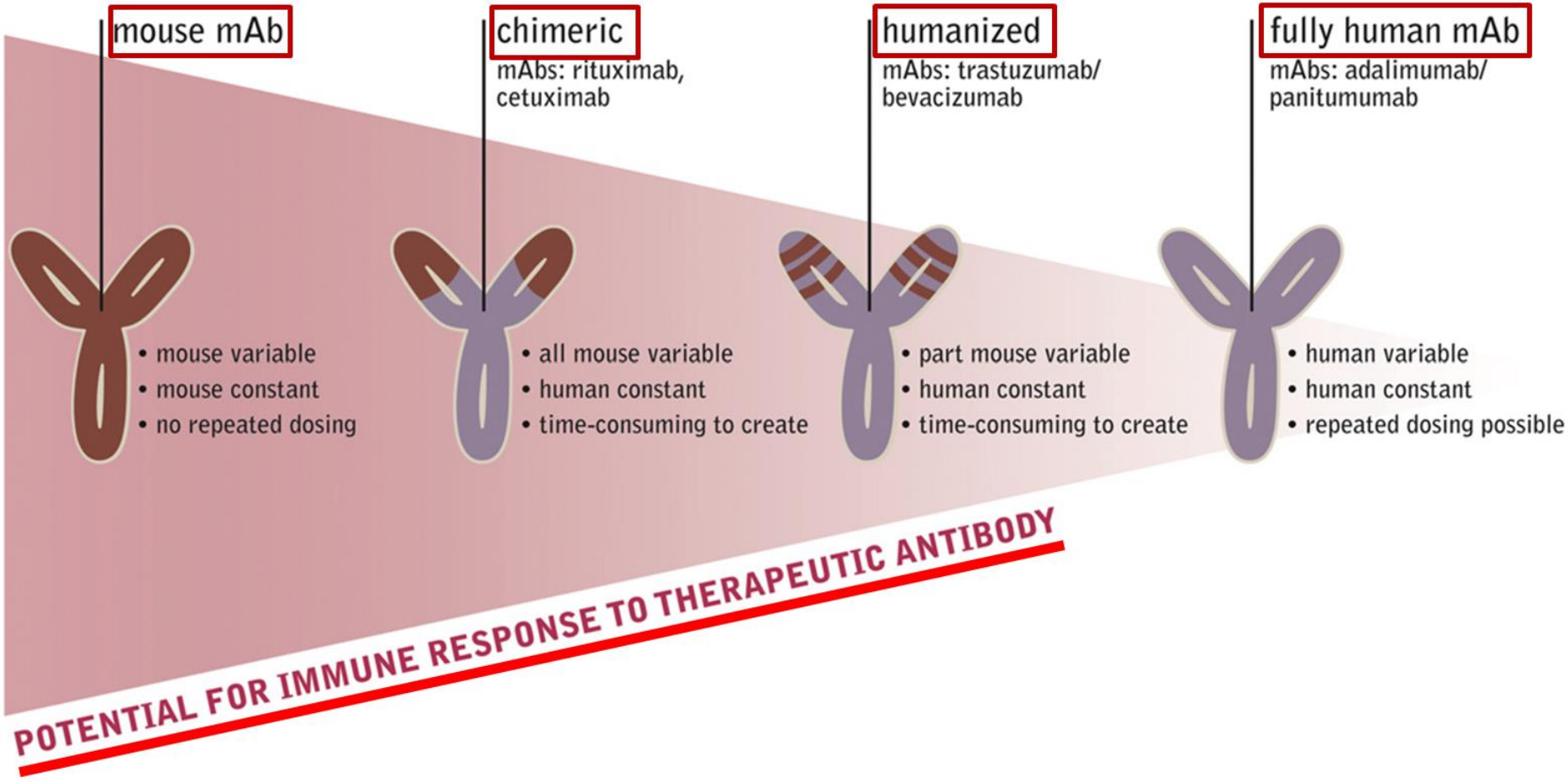
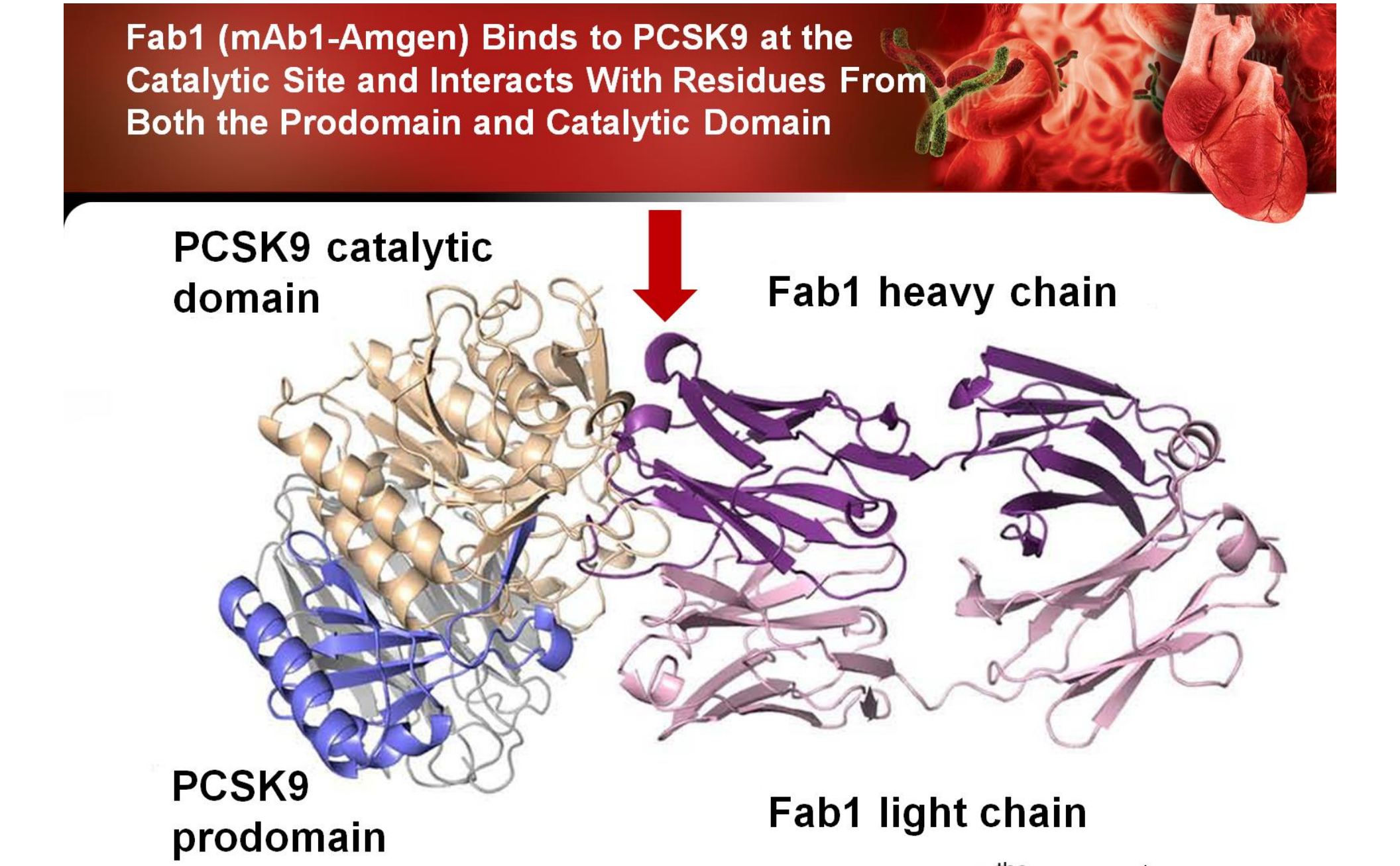
SPC-5001 (antisense) and BMS-844421 (antisense) clinical development have been terminated

Evolution of Therapeutic Monoclonal Antibodies



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

Fab1 (mAb1-Amgen) Binds to PCSK9 at the Catalytic Site and Interacts With Residues From Both the Prodomain and Catalytic Domain



Chan JC, et al. *Proc Natl Acad Sci U S A.* 2009;106:9820-9825.[15]

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

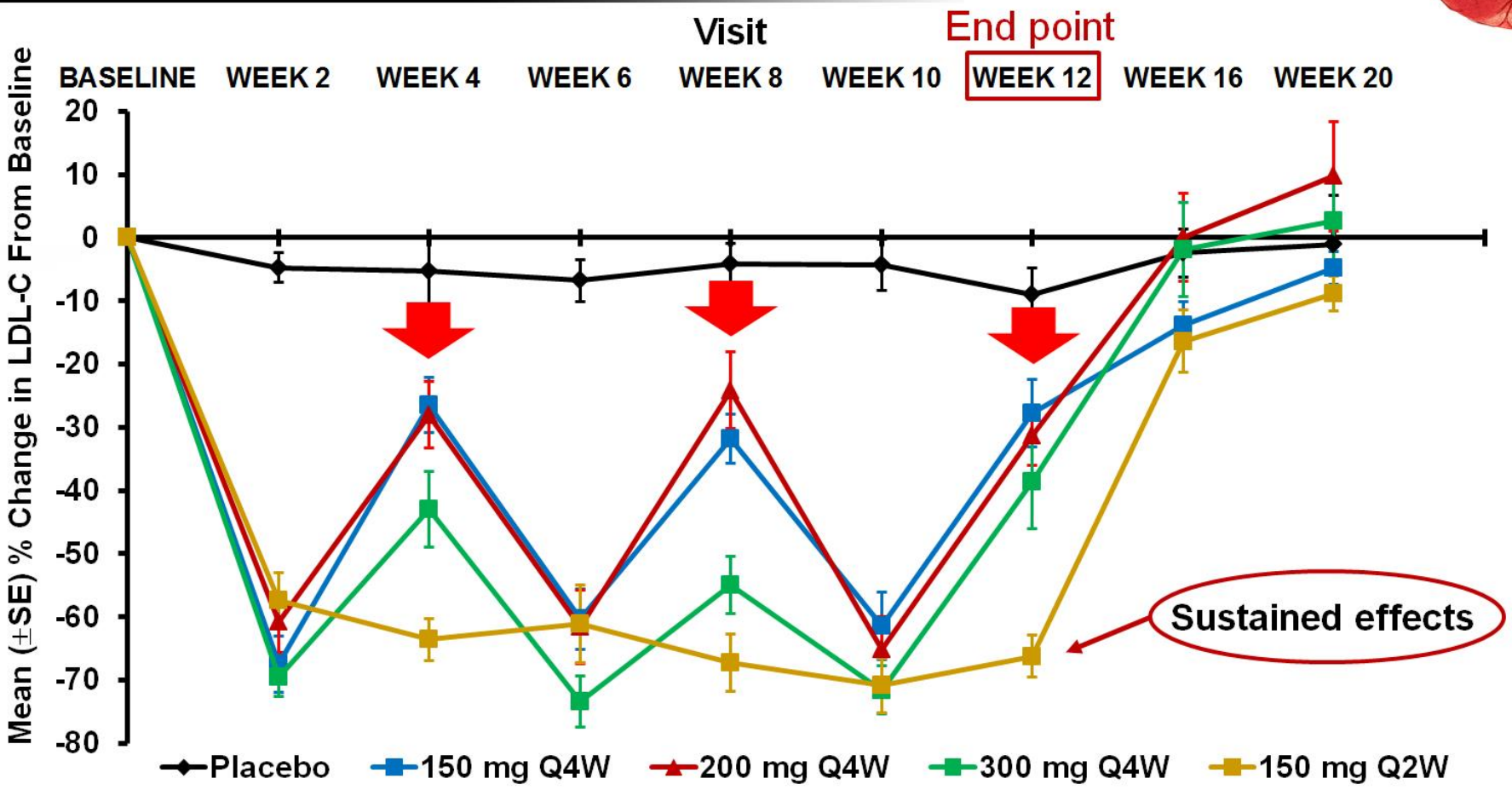
Phase 2: Randomized Trial of REGN727/SAR236553 (n = 62) or Placebo (n = 15) in Patients With HeFH on Stable Statin Doses ± ezetimibe

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]

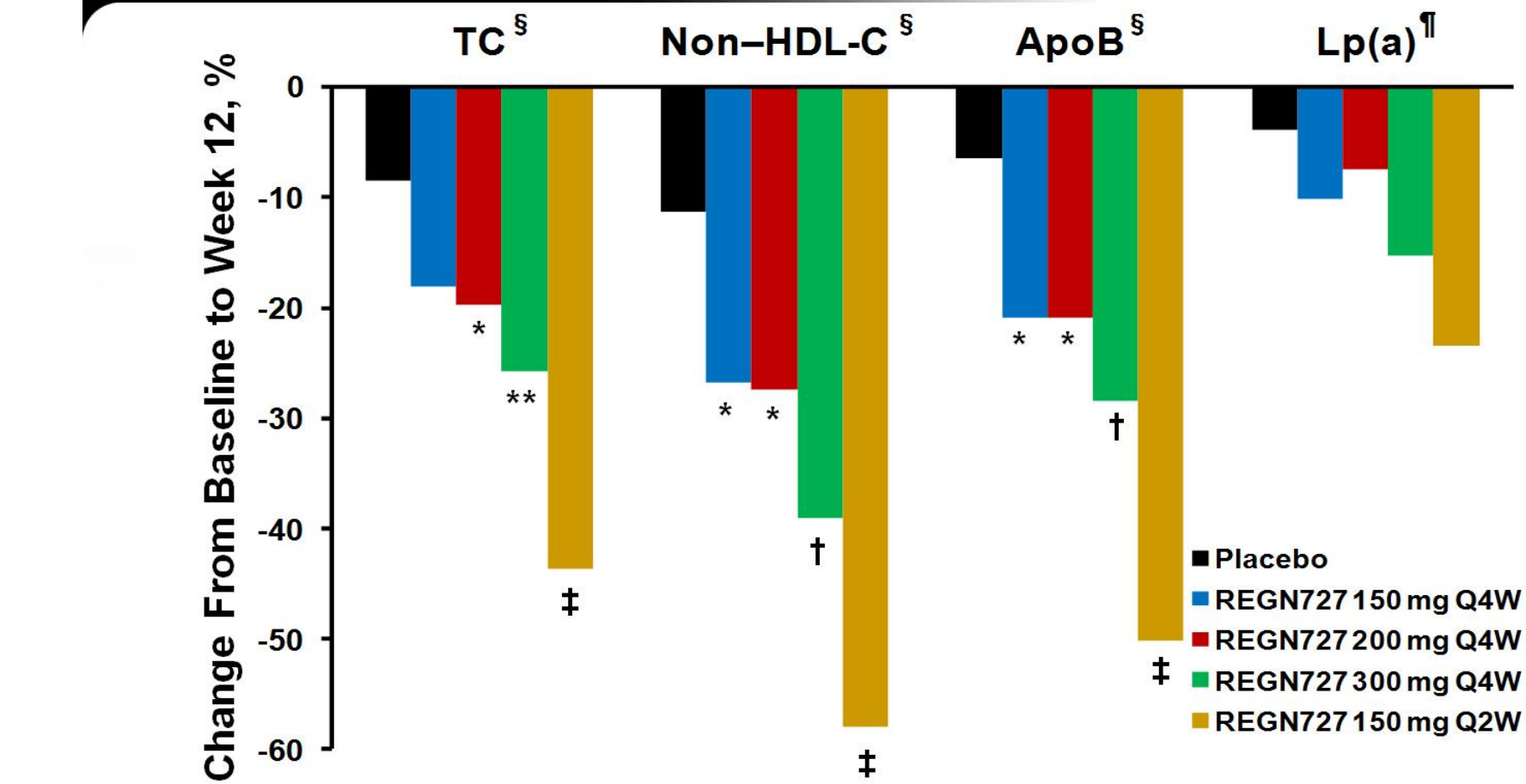
Change in Calculated LDL-C at 2 Weekly Intervals From Baseline to Week 20



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]

Effects of AMG 145 on LDL-C Levels Study Design

Phase 1b: AMG 145 (n = 43) or Placebo (n = 14), Multiple Ascending SC Doses in Subjects With Hypercholesterolemia

Dose-escalation cohorts, subjects on low- to moderate-dose statins
- *simvastatin 20-80 mg/d,*
- *atorvastatin 10-40 mg/d, or*
- *rosuvastatin 5-20 mg/d)*

AMG 145 14 mg SC or Placebo QW 6 doses

AMG 145 35 mg SC or Placebo QW 6 doses

AMG 145 140 mg SC or Placebo Q2W 3 doses

AMG 145 280 mg SC or Placebo Q2W 3 doses

AMG 145 420 mg SC or Placebo Q2W 3 doses

Dose-matched

Subjects on high-dose statins (atorvastatin 80 mg/d or rosuvastatin 40 mg/d)

AMG 145 140 mg SC or Placebo Q2W 3 doses

Subjects with HeFH

AMG 145 140 mg SC or Placebo Q2W 3 doses

Screening
5-35 days

R

Multiple-dose Treatment
6 weeks (QW and Q2W cohorts)
or 8 weeks (Q4W cohorts)

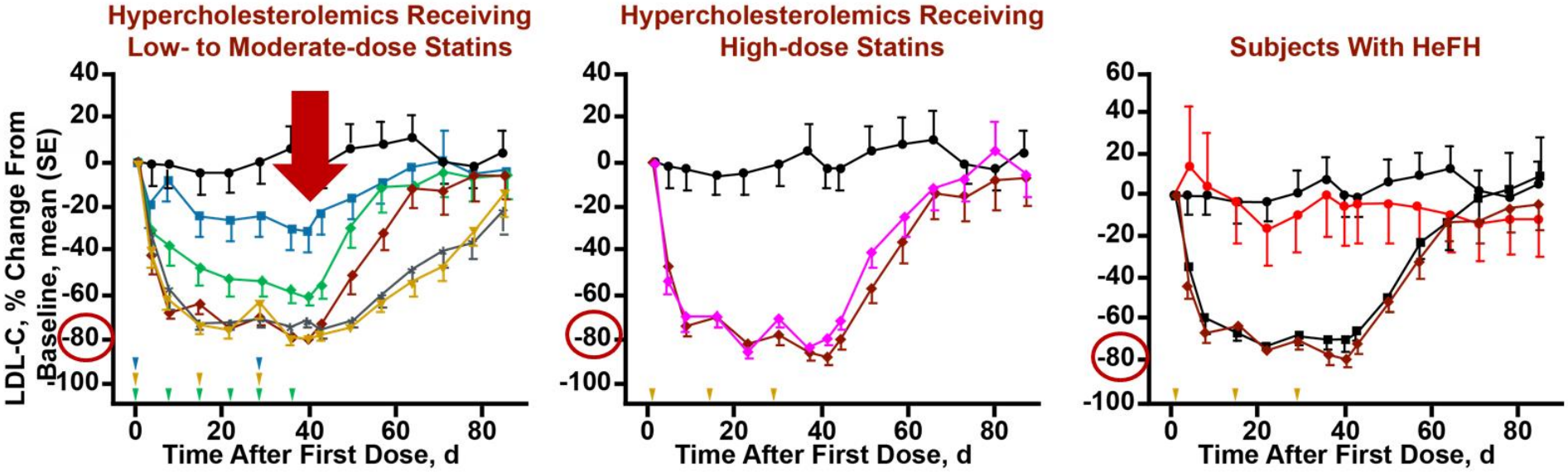
End of Treatment Interval

Follow-up
6 weeks (QW and Q2W)
or 8 weeks (Q4W)

Dias CS, et al. *J Am Coll Cardiol*. 2012;60:1888-1898.[18]

AMG 145: Mean Percentage Change From Baseline in LDL-C

Phase 1b: AMG 145 (n = 43) or Placebo (n = 14), Multiple Ascending Doses in Subjects With Hypercholesterolemia



Dias CS, et al. *J Am Coll Cardiol*. 2012;60:1888-1898.[18]

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.

References

1. Goldstein JL, Hobbs HH, Brown MS. Familial hypercholesterolemia. In Scriver CR, ed: *The Metabolic and Molecular Bases of Inherited Disease*. New York, NY: McGraw-Hill; 2001:2863.

2. Cameron J, Holla ØL, Bergeet KE, al. Investigations on the evolutionary conservation of PCSK9 reveal a functionally important protrusion. *FEBS J*. 2008;275:4121-4133.

3. Abifadel M, Varret M, J Rabès JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. *Nat Genet*. 2003;34:154-156.

4. Cohen J, Pertsemlidis A, Kotowski IK, Graham R, Garcia CK, Hobbs HH. Low LDL cholesterol in individuals of African descent resulting from frequent nonsense mutations in PCSK9. *Nat Genet*. 2005;37:161-165.

5. Piper DE, Jackson S,Liu Q, et al. The Crystal Structure of PCSK9: A Regulator of Plasma LDL-Cholesterol *Structure*. 2007;15:545-552.

6. Poirier S, Mayer G, Benjannet S, et al. The Proprotein Convertase PCSK9 Induces the Degradation of Low Density Lipoprotein Receptor (LDLR) and Its Closest Family Members VLDLR and ApoER2. *J Biol Chem*. 2008;83:2363-2372.

References (cont)

7. Canuel M, Sun X, Asselin MC, Paramithiotis E, Prat A, Seidah NG. Proprotein convertase subtilisin/kexin type 9 (PCSK9) can mediate degradation of the low density lipoprotein receptor-related protein 1 (LRP-1). *Plos ONE*. 2012;7:41865.

8. Melone M, Wilsie L, Palyha O, Strack A, Rashid S. Discovery of a new role of human resistin in hepatocyte low-density lipoprotein receptor suppression mediated in part by proprotein convertase subtilisin/kexin type 9. *J Am Coll Cardiol*. 2012; 52:1697-1705.

9. Sun H, Samarghandi A, Zhang N, et al. Proprotein convertase subtilisin/kexin type 9 interacts with apolipoprotein B and prevents its intracellular degradation, irrespective of the low-density lipoprotein receptor. *Arterioscler Thromb Vasc Biol*. 2012;32:1585-1595.

10. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL and protection against coronary heart disease. *N Engl J Med*. 2006;354:1264-1272.

11. Zhao Z, Tuakli-Wosornu Y, Lagace TA, et al. Molecular characterization of loss-of-function mutations in PCSK9 and identification of a compound heterozygote. *Am J Hum Genet*. 2006;79:514-523.

References (cont)

12. Tavori H, Fan D, Blakemore JL, et al. Serum proprotein convertase subtilisin/kexin type 9 and cell surface low-density lipoprotein receptor: evidence for a reciprocal regulation. *Circulation*. 2013;127:2403-2413.

13. Raal F, Panz V, Immelman A, Pilcher G. Elevated PCSK9 levels in untreated patients with heterozygous or homozygous familial hypercholesterolemia and the response to high-dose statin therapy. *J Am Heart Assoc*. 2013;2:e000028.

14. Catapano AL, Papadopoulos N. The safety of therapeutic monoclonal antibodies: implications for cardiovascular disease and targeting the PCSK9 pathway. *Atherosclerosis*. 2013;228:18-28.

15. Chan JC, Piper DE, Cao Q, et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. *Proc Natl Acad Sci U S A*. 2009;106:9820-9825.

16. Lambert G, Sjouke B , Choque B, Kastelein JJ, Hovingh GK. The PCSK9 decade. *J Lipid Res*. 2012;53:2515-2524.

References (cont)

17. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolaemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. *Lancet*. 2012;380:29-36.

18. Dias CS, Shaywitz AJ, Wasserman SM, et al. Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins. *J Am Coll Cardiol*. 2012;60:1888-1898.

19. Koren MJ, Scott R, Kim JB, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2012;380:1995-2006.

20. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. *J Am Coll Cardiol*. 2012;59:2344-2353.

References (cont)

21. Roth EM, McKenney JM, Hanotin C, et al. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. *N Engl J Med*. 2012;367:1891-1900

22. Giugliano RP, Desai NR, Kohli P, et al; LAPLACE-TIMI 57 Investigators. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): a randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet*. 2012;380:2007-2017.

23. ClinicalTrials.gov. A Multiple Dose Study of PF-04950615 (RN316) in Subjects on High Doses of Statins. NCT01342211. http://www.clinicaltrials.gov/ct2/show/NCT01342211 Accessed July 1, 2013.

24. ClinicalTrials.gov. A Multiple Dose Study Of PF-04950615 (RN316) In Subjects On Maximum Doses Of Statins. NCT01350141. http://www.clinicaltrials.gov/ct2/show/NCT01350141 Accessed July 1, 2013.

References (cont)

25. Gumbiner B. Effects of 12 weeks of treatment with RN316 (PF-04950615), a humanized IgG2Δa monoclonal antibody binding proprotein convertase subtillisin kexin type 9, in hypercholesterolemic subjects on high and maximal dose statins. Paper presented at: AHA Scientific Sessions; 2012; Los Angeles, CA.

26. Sullivan D, Olsson AG, Scott R, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: the GAUSS randomized trial. *JAMA*. 2012;308:2497-2506.

27. Raal F, Scott R, Somaratne R, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation*. 2012;126:2408-2417

References (cont)

28. Clinical Trials.gov. Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER). NCT01764633. http://www.clinicaltrials.gov/ct2/show/NCT01764633 Accessed July 1, 2013.

29. Clinical Trials.gov. Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab SAR236553 (REGN727) (ODYSSEY Outcomes). NCT01663402. http://clinicaltrials.gov/ct2/show/NCT01663402 Accessed July 1, 2013.