Epidemiologic Stent-Based Approach to Vulnerable Plaque Stabilization Based on Statistical Modeling of Plaque Rupture and Death

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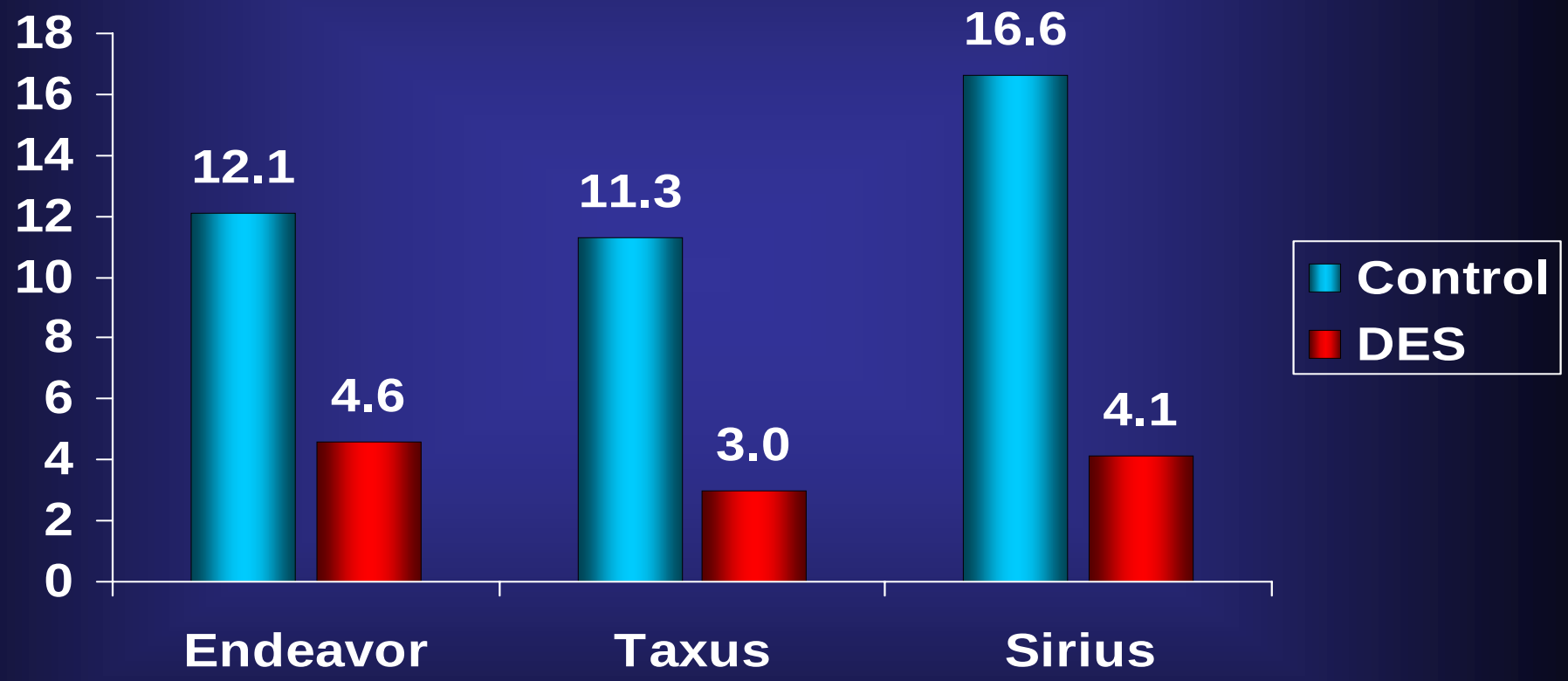
Pivotal Trial Comparisons

TLR to 9 Months



Now That We've Conquered Restenosis Can We Prevent Plaque Rupture?

MI and Plaque Facts

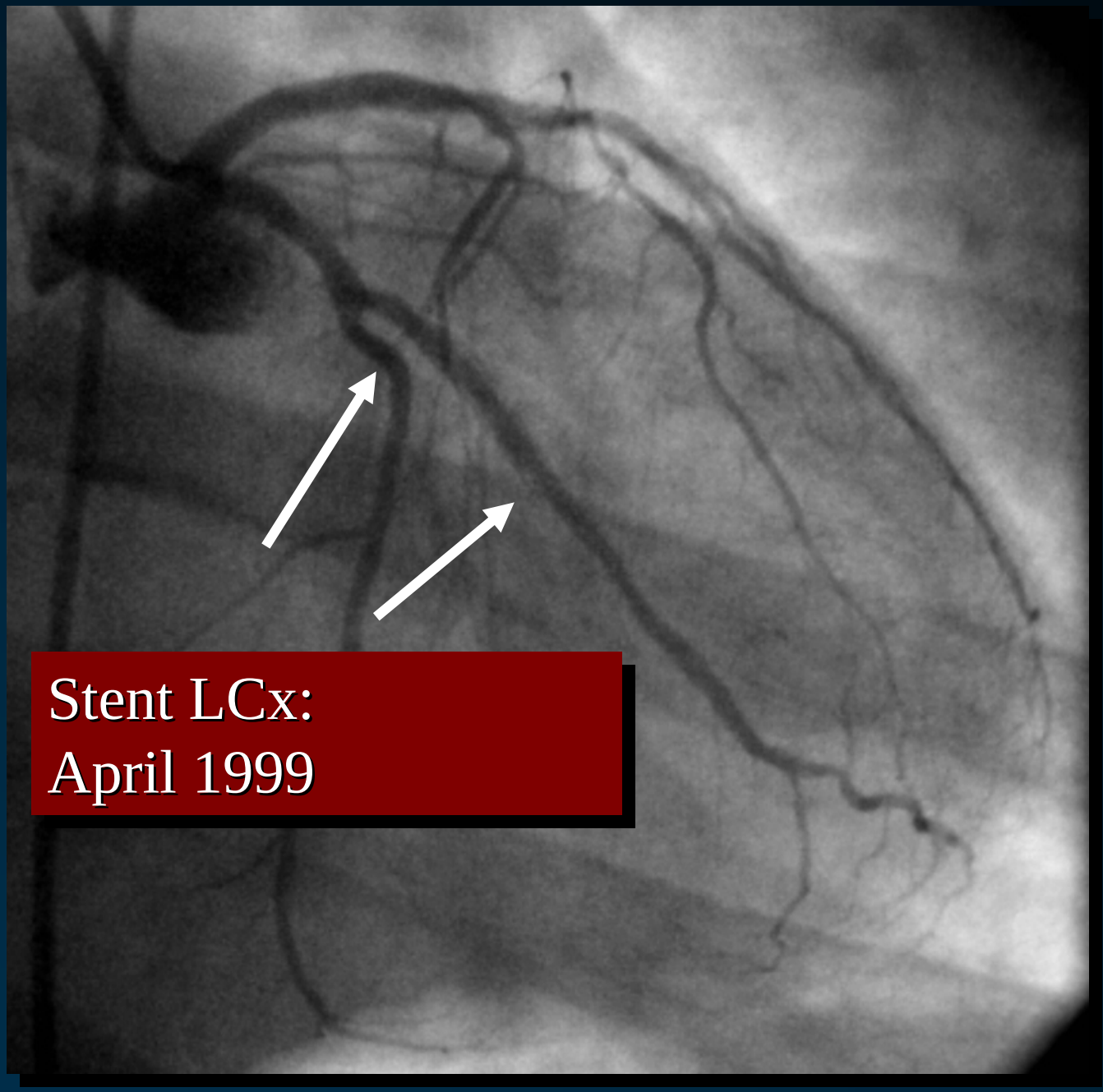
- 700,000 fatal MI's/year (US)
- Incidence of spontaneous MI ~0.3-0.5%/year
- 30-40% of acute rupture (ACS) occur in patients unaware they have heart disease
- In asymptomatic "healthy" people
  - 9% carry previously ruptured plaques
  - 22% for diabetics and hypertensive patients

Preventing Vulnerable Plaque may be like finding a needle in the hay stack

The Natural History of Plaque Rupture

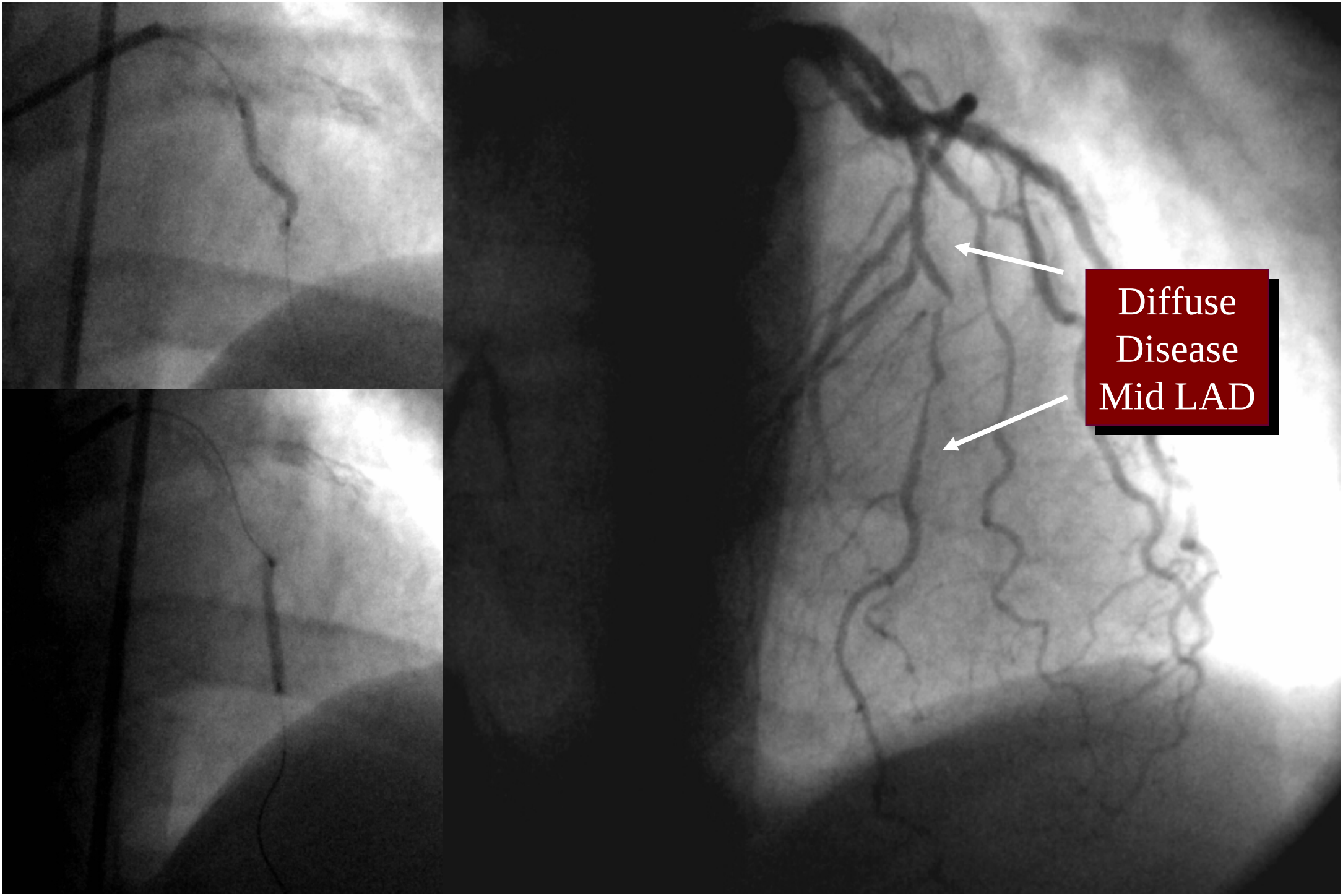
- 46 year old diabetic man presents in April 1999
  - ACS with 3-vessel moderate obstructive CAD
  - Wanted to avoid CABG despite mortality benefit
  - Tight left circumflex lesion was felt to be the culprit lesion, and this was successfully stented

- Received aspirin, unfractionated heparin, and eptifibate

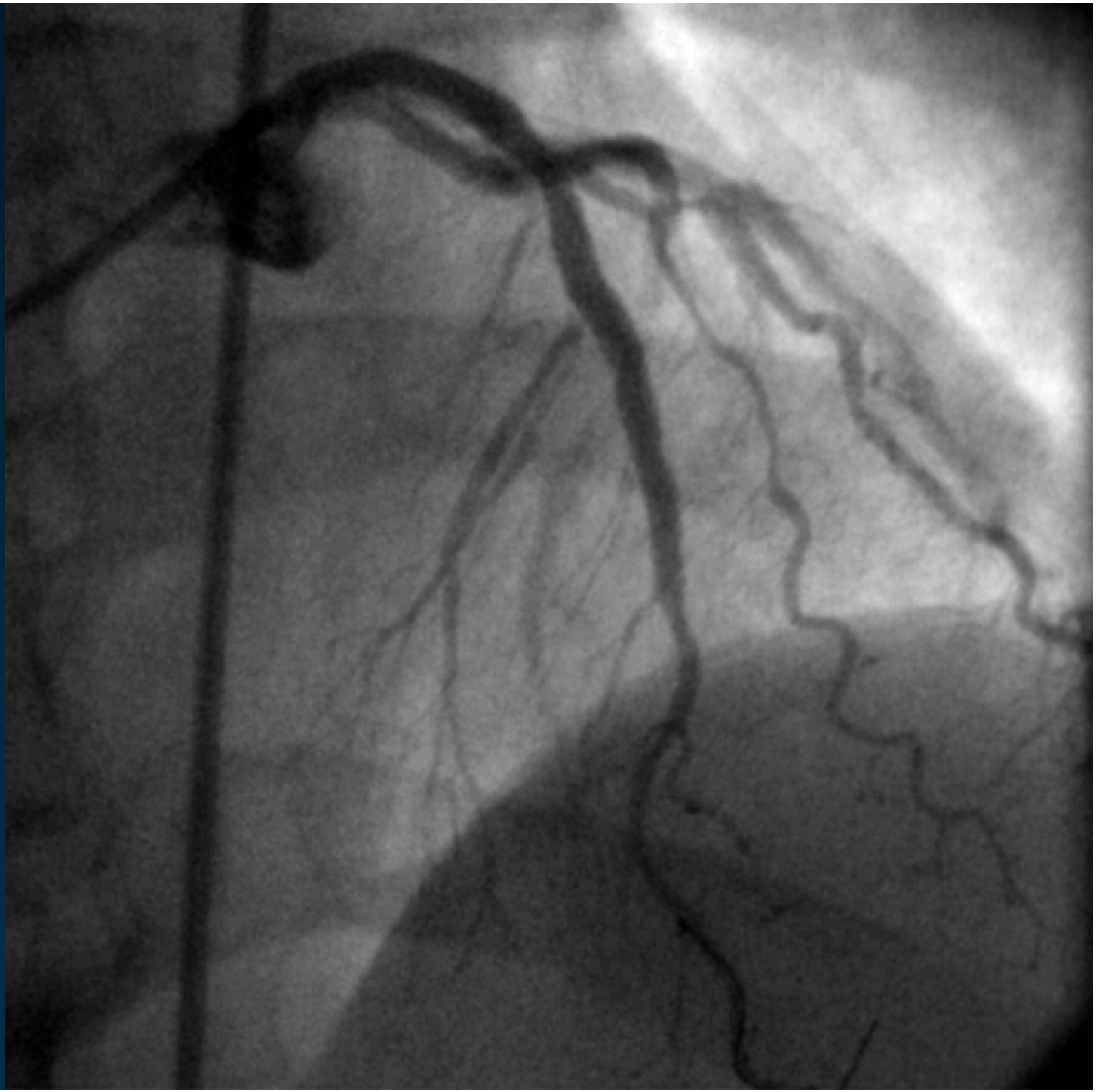


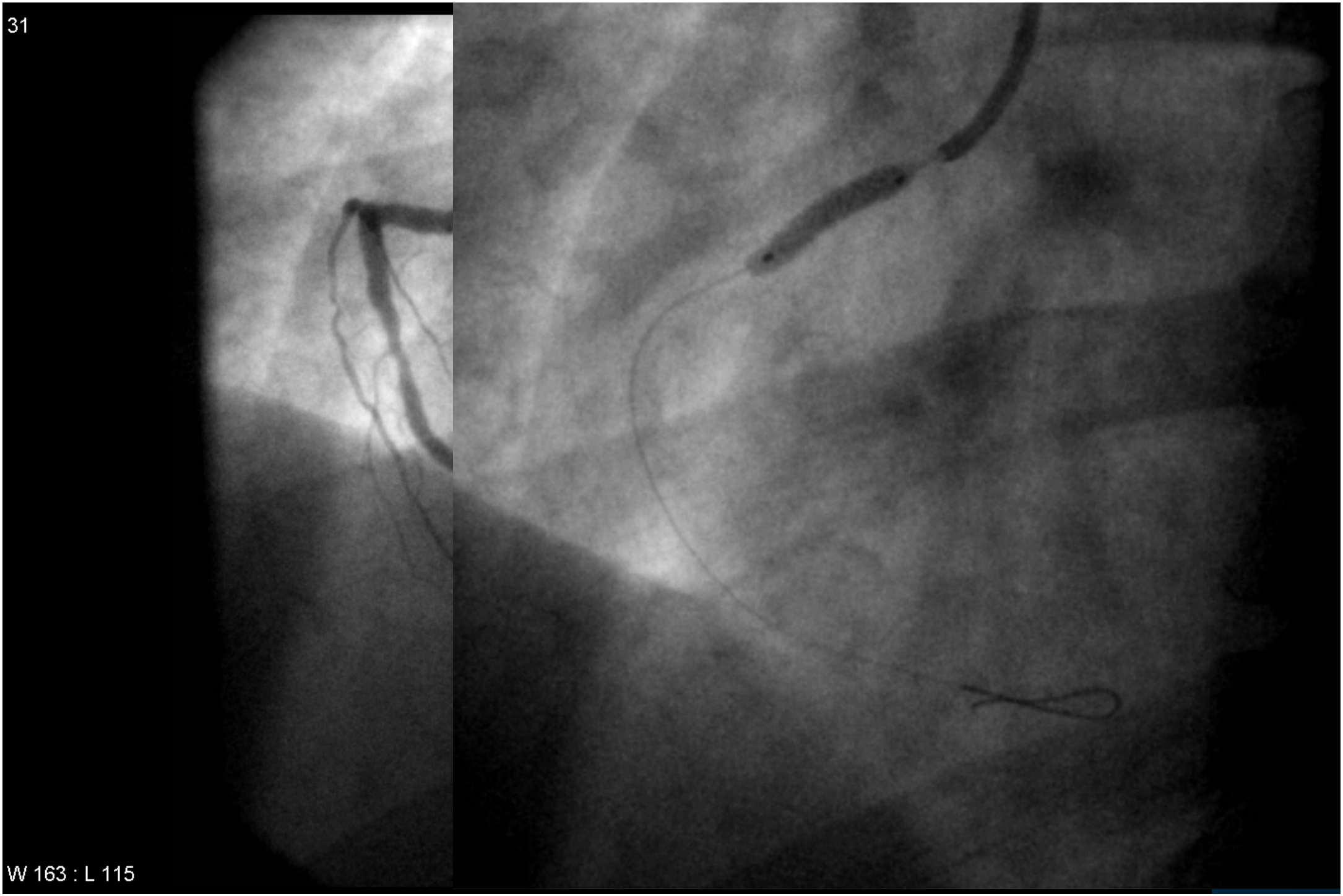
The Natural History of Plaque Rupture

- Re-presentation in March 2001 with ACS and anterior wall ischemia

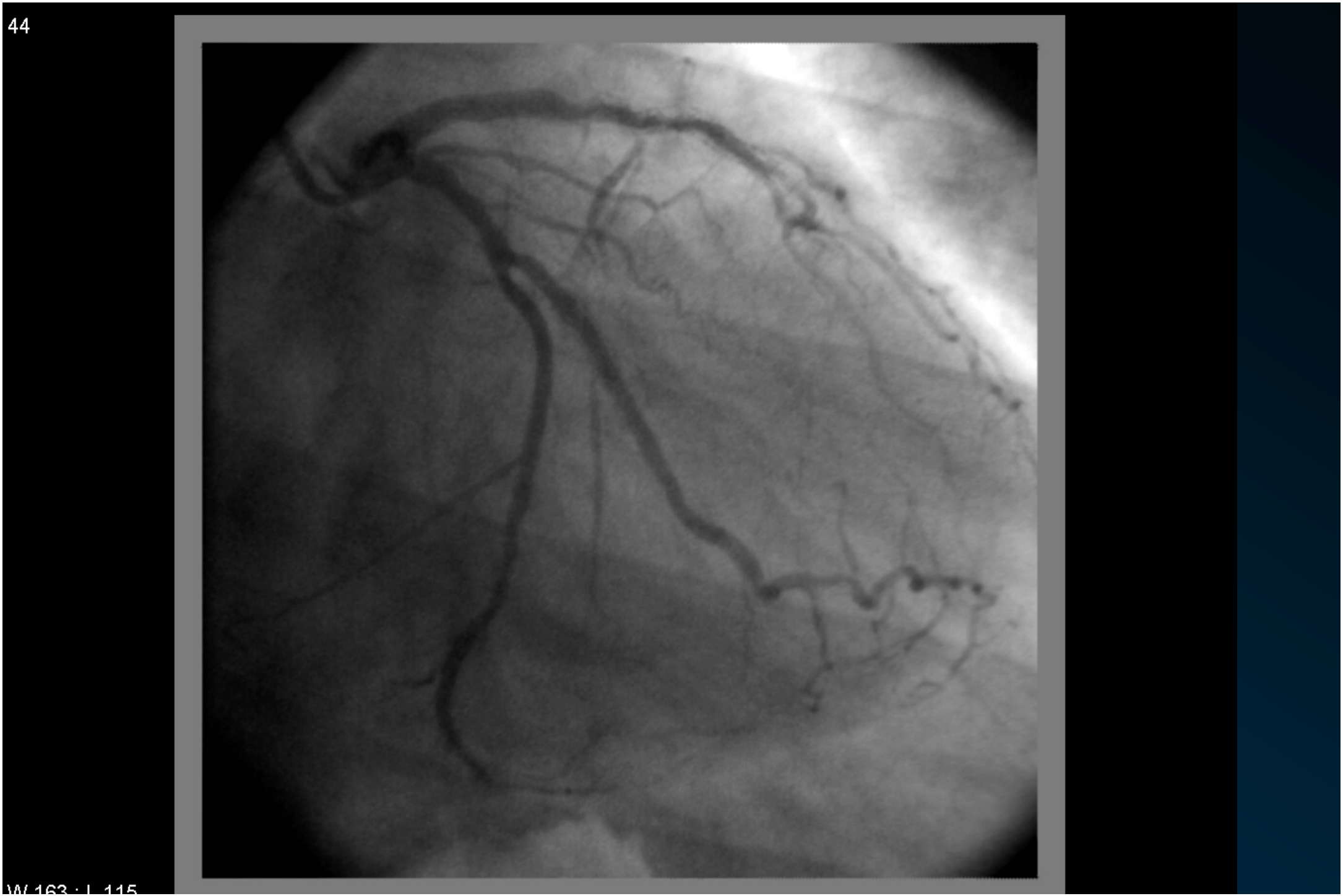

Diffuse
Disease
Mid LAD

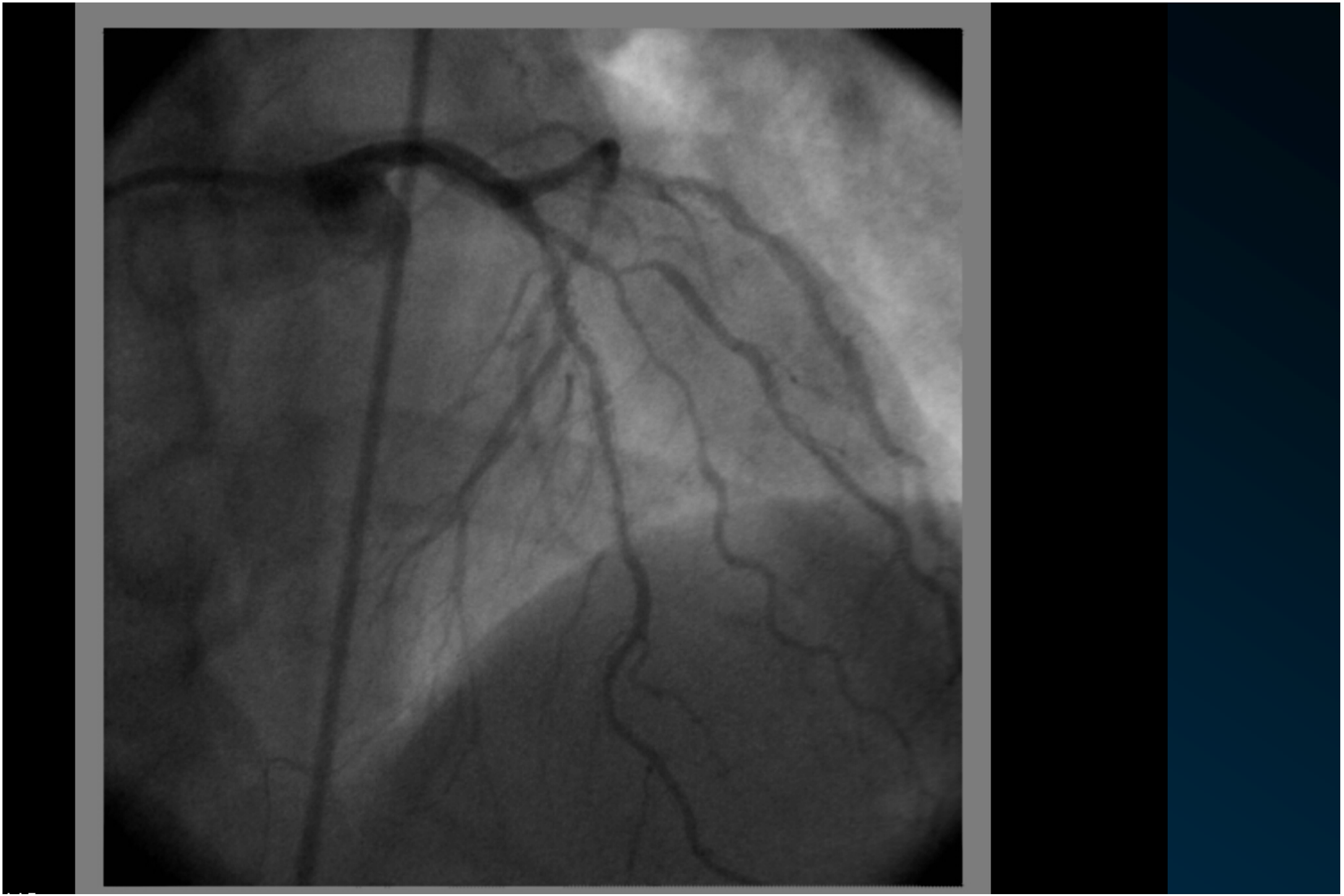
- As the patient continued to strongly wish to avoid CABG, complete revascularization of the coronary vasculature bed was pursued

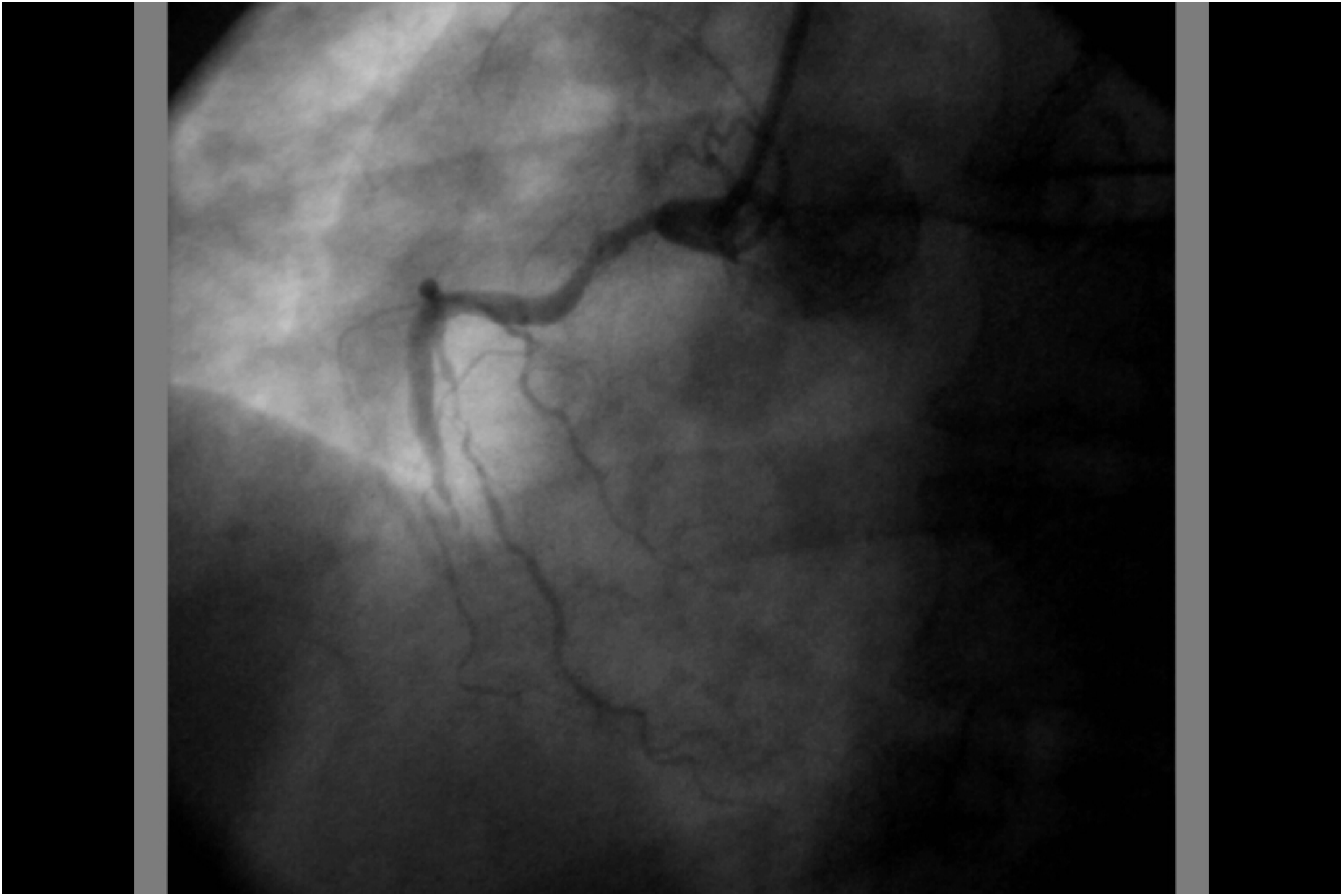



31
W 163 : L 115

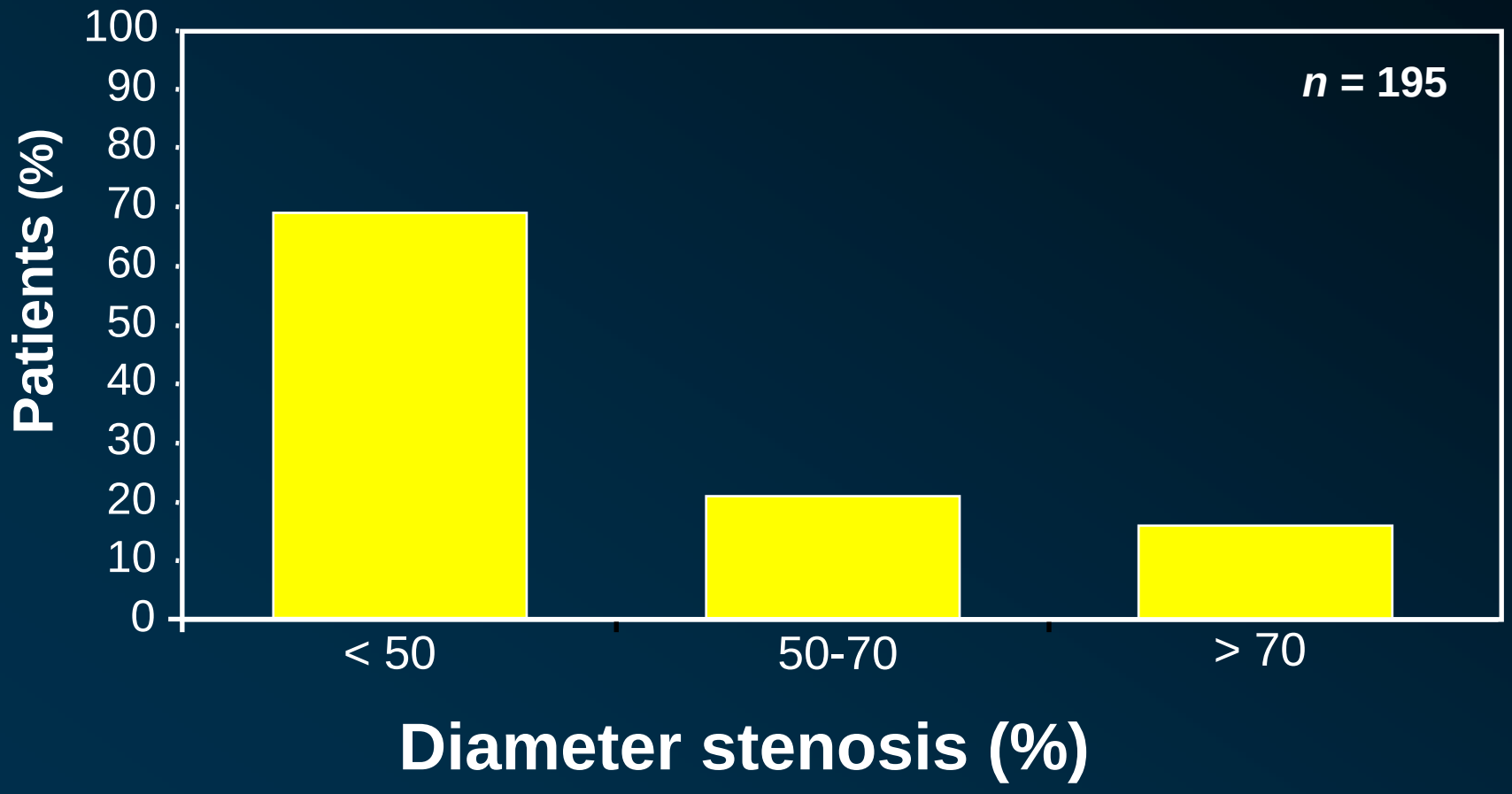
- No peri-procedural complications
- Patient discharged on aspirin, clopidogrel, ACE inhibitor, lipid lowering therapy, and insulin-sensitizing agent
- Angina is relieved and patient returns to work unrestricted
- Moderate LDL control (LDL 98 mg/dl)
- Represents 4 months later with an acute myocardial infarction


44
W 163 · L 115





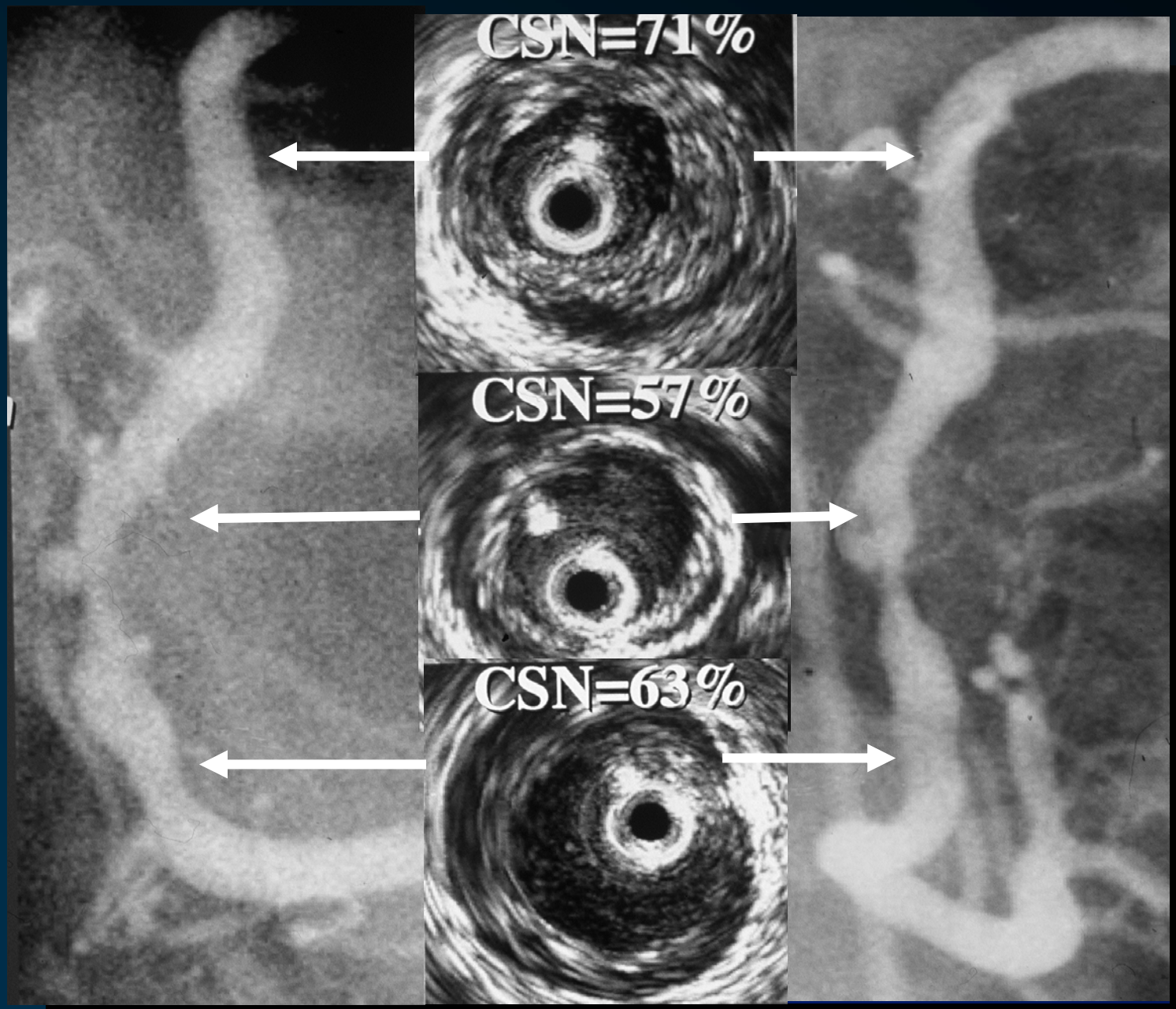
Severity of coronary artery stenosis before acute MI



Data from four studies. *Smith SC. Circulation 1996*

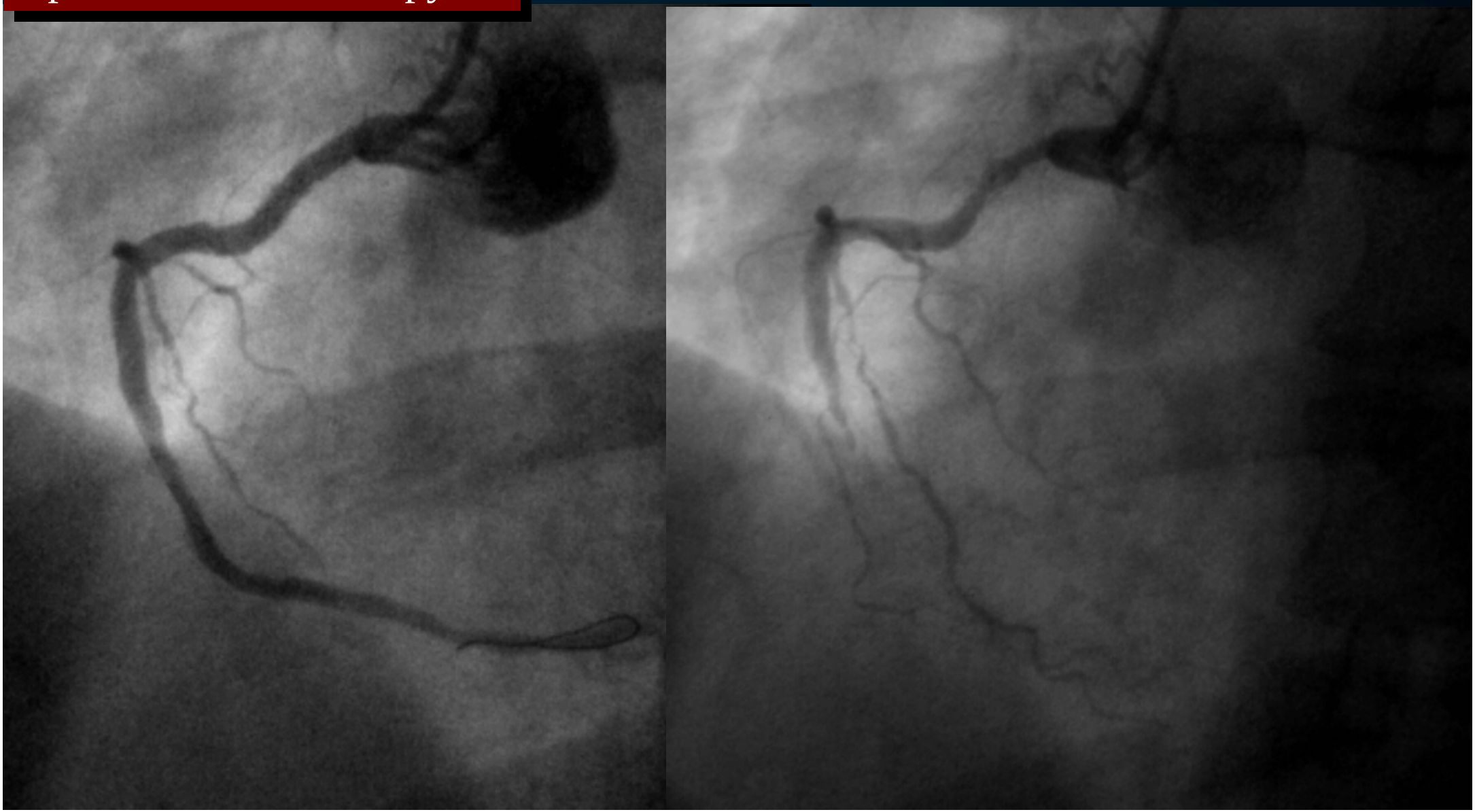
> 90% of "Normal" Arteries Have Significant Plaque Burden by IVUS

Gary Mintz



March 2001
Complete Revascularization
Optimal medical therapy

July 2001
Acute Inferior Wall MI



The Stents as a Prophylactic Device to Prevent Myocardial Infarctions

- PCI with and with or without stents have been proposed to re-injure arterial segments and leave a primitive scar behind that is not capable of "growing" atherosclerosis
  - B. Meier has proposed this with PTCA
  - We have observed this with our large FDA stent databases (HCRI)

The Stented Coronary Segement

Low incidence of ACS in the segment <0.005 over 4 years

Can't grow atherosclerosis here!

In Patients with STEMI

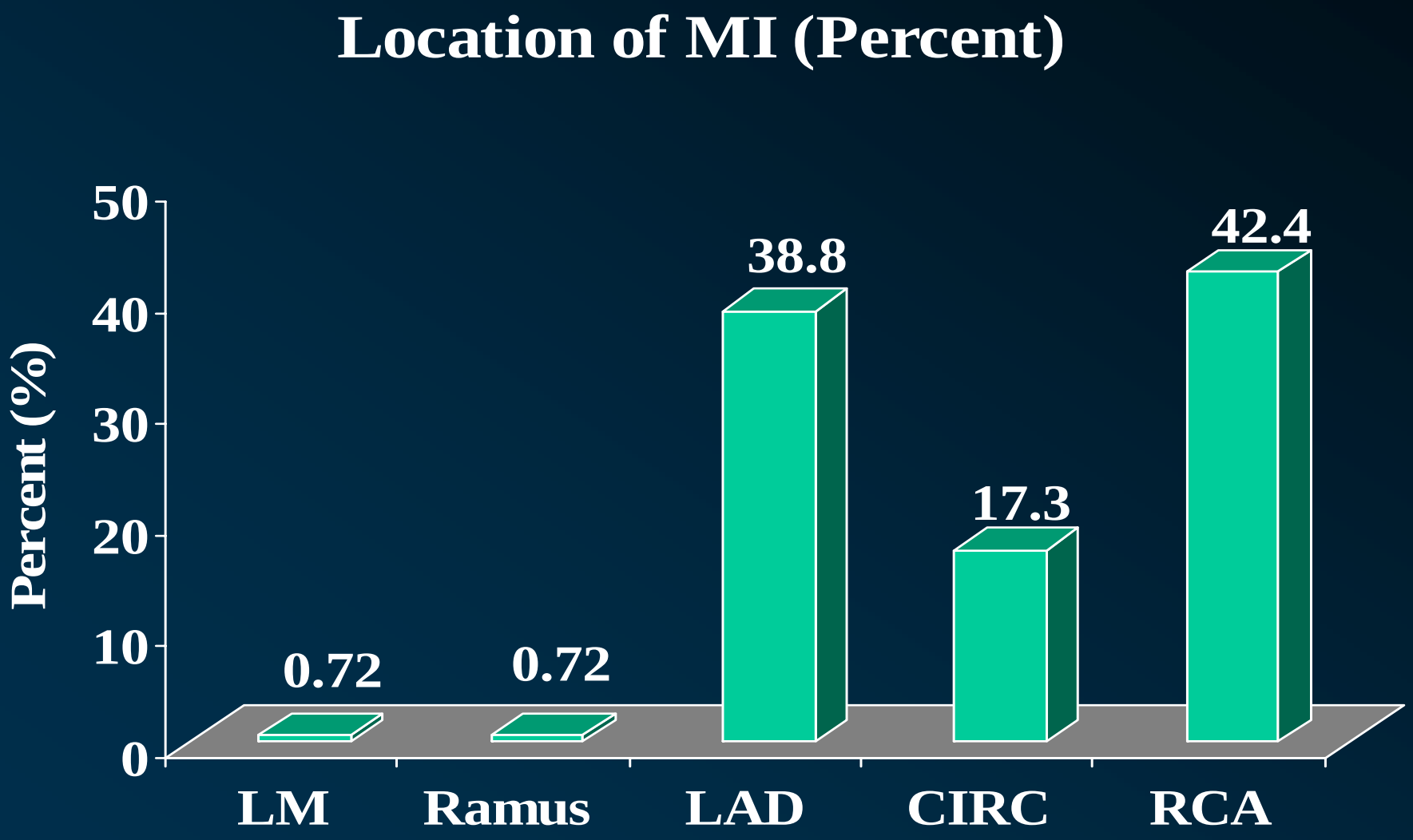
Spatial distribution of coronary thromboses are clustered

Wang J, Kuntz, R, *Circulation* 2004;110:278-84.

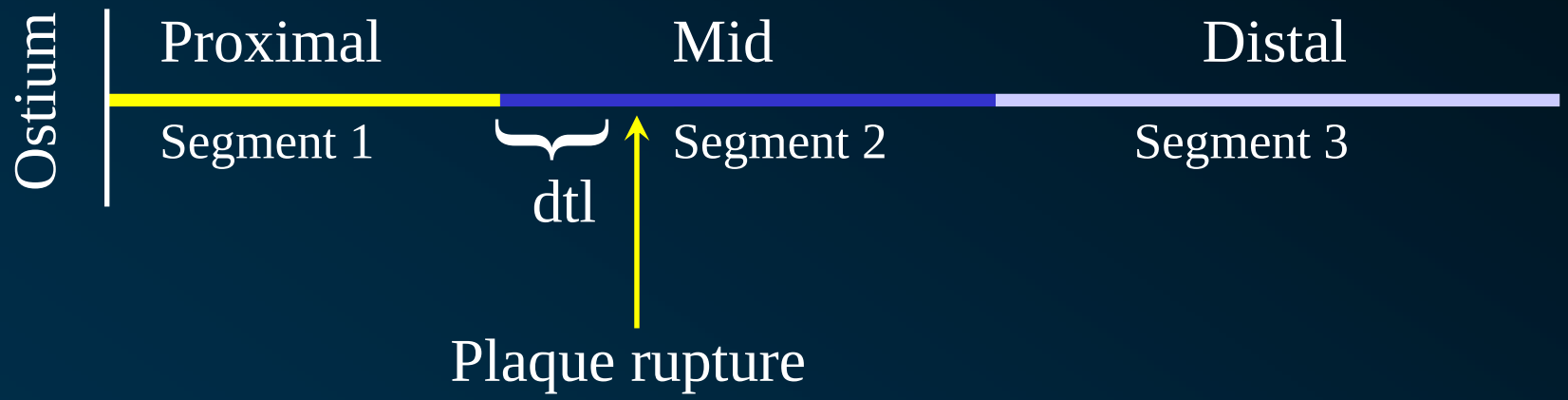
Spatial Distribution of Acute Thromboses

- Datasets (600 patients):
  - 200 consecutive patients at the BWH with acute STEMI
  - 400 patients in the multicenter COOL MI STEMI-Radiant cooling trial

Consecutive Acute MIs at BWH (n=200)



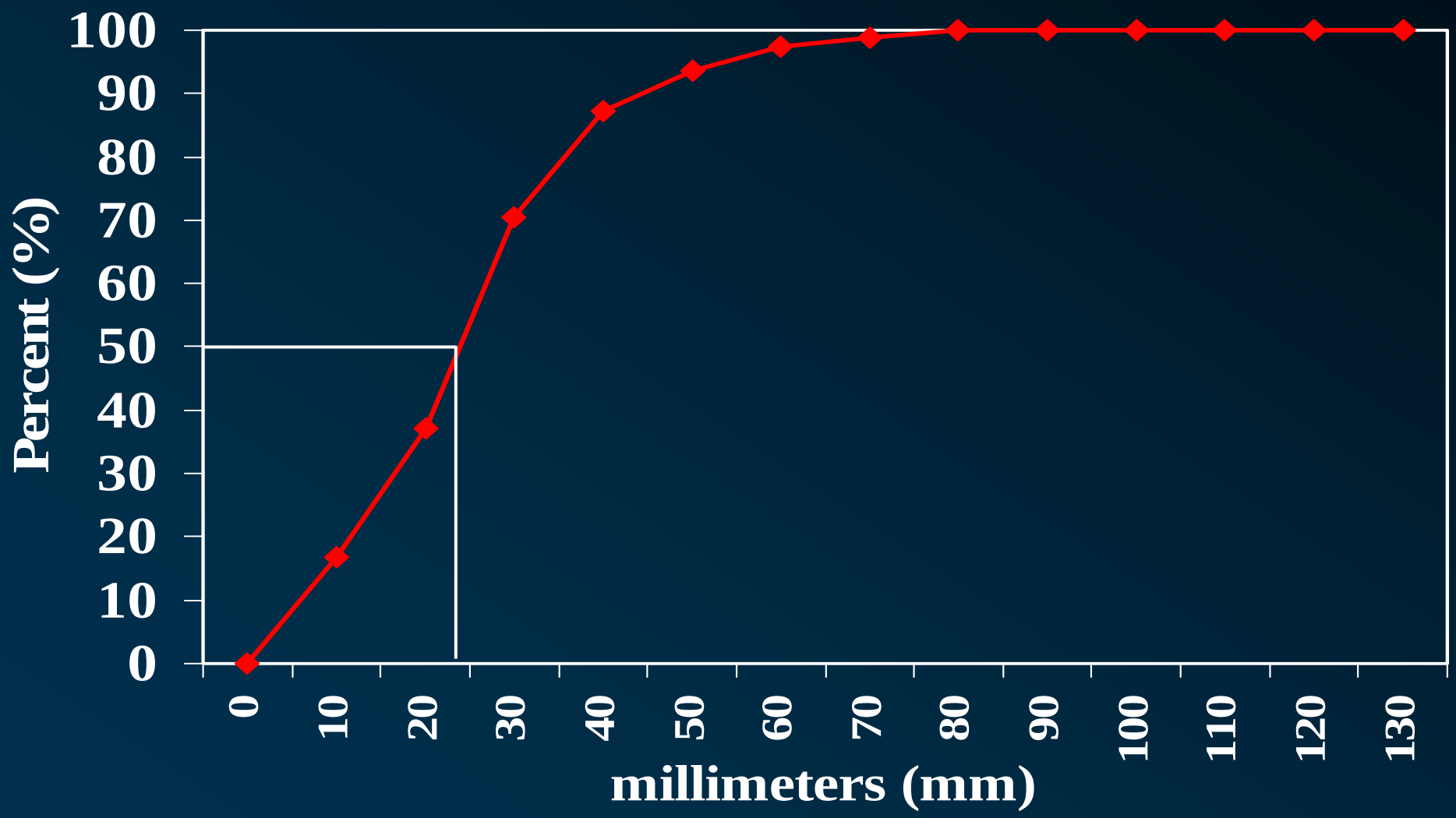
2. Normalized Length Analysis

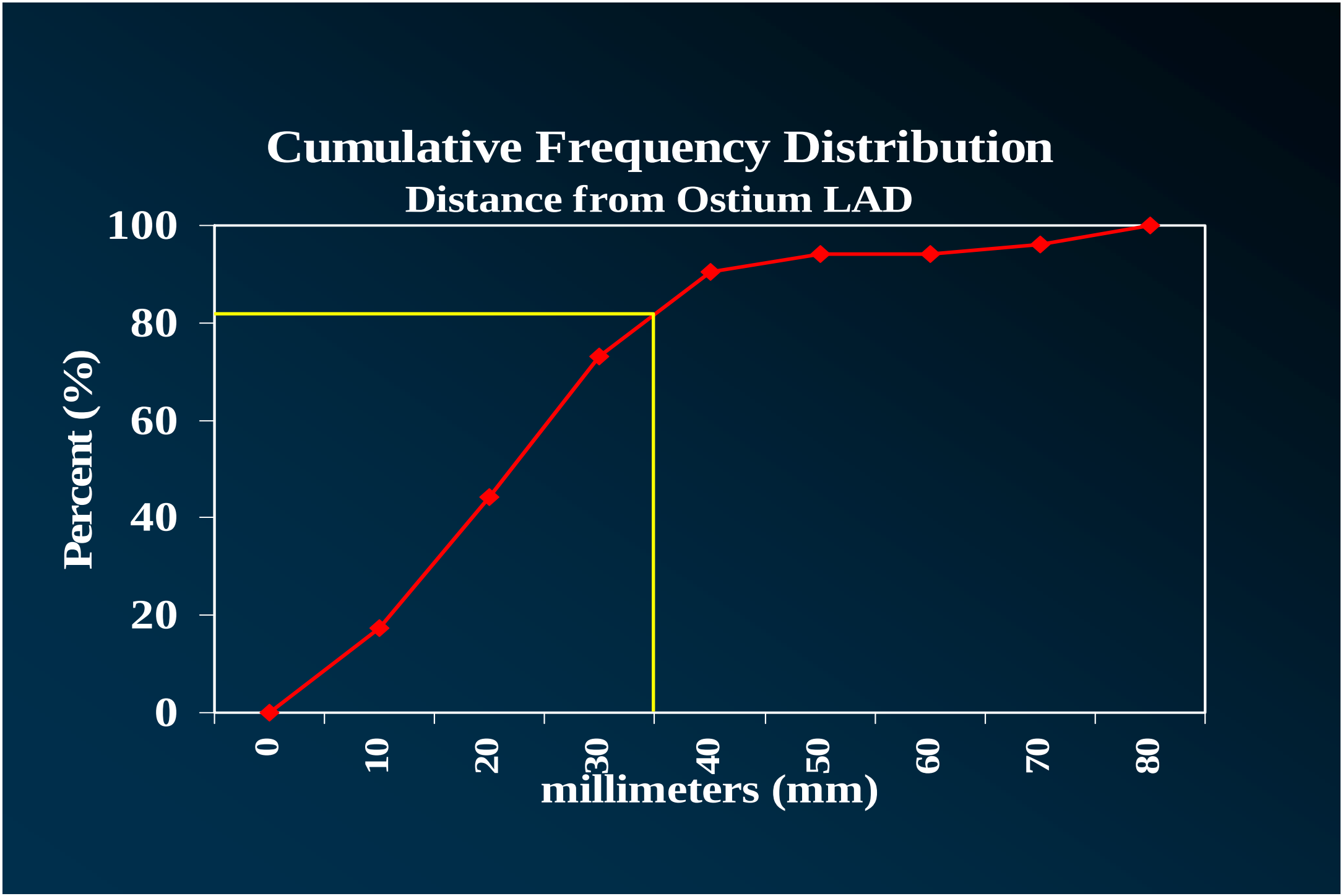


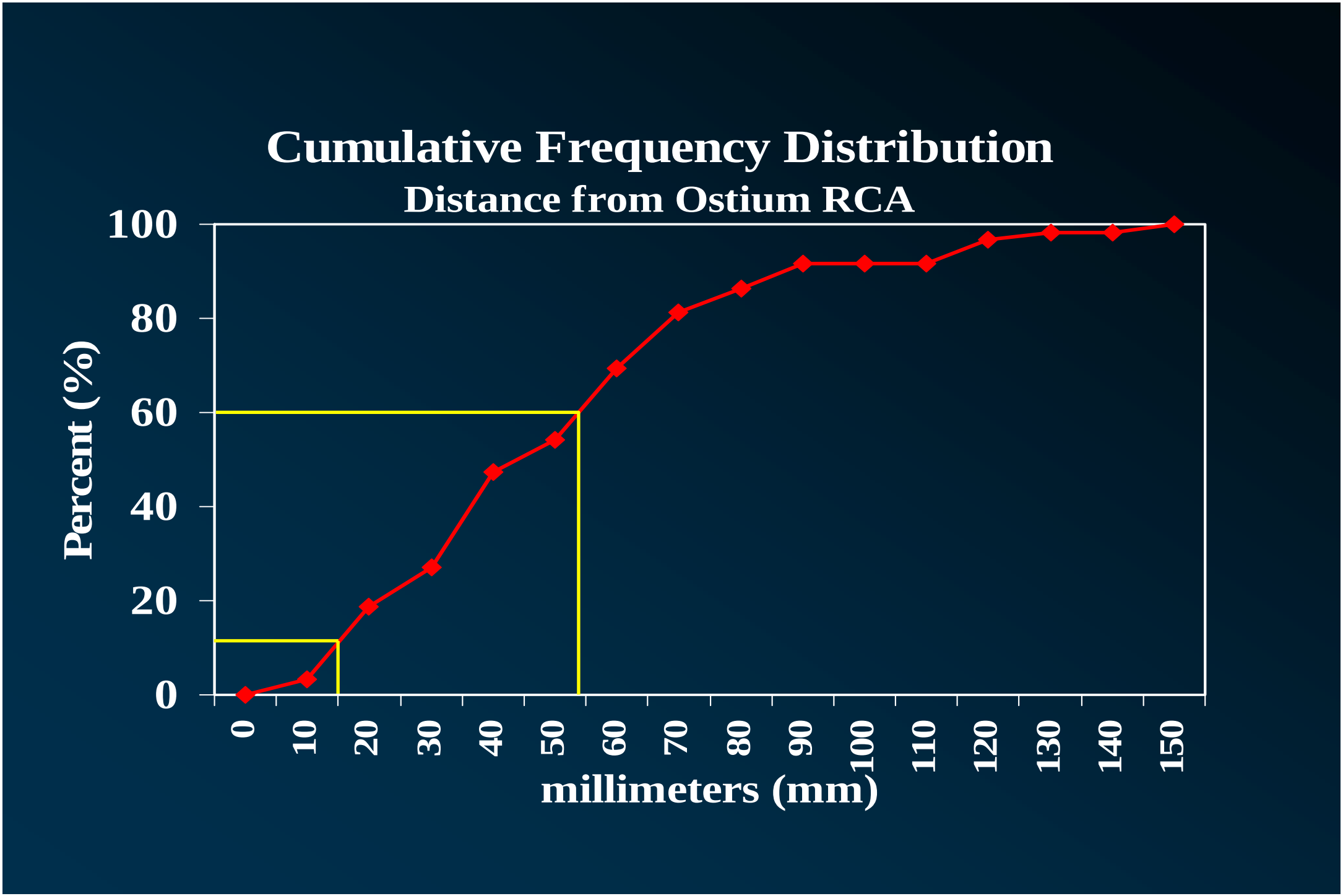
Length analysis = (Seg 1 + dtl) / (Seg 1 + Seg 2 + Seg 3)

Distribution of Acute Coronary Occlusions
Left Anterior Descending Artery
(Normalized Segment Analysis)

Cumulative Frequency Distribution Curve of Acute Coronary Occlusions by Distance from the Ostium Left Anterior Descending Artery




Cumulative Frequency Distribution
Distance from Ostium LAD
Percent (%)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
millimeters (mm)


Cumulative Frequency Distribution
Distance from Ostium RCA
Percent (%)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
millimeters (mm)

In Patients with non-STEMI

Spatial distribution of coronary thromboses

L Mauri, Wang J, Kuntz, R, submitted

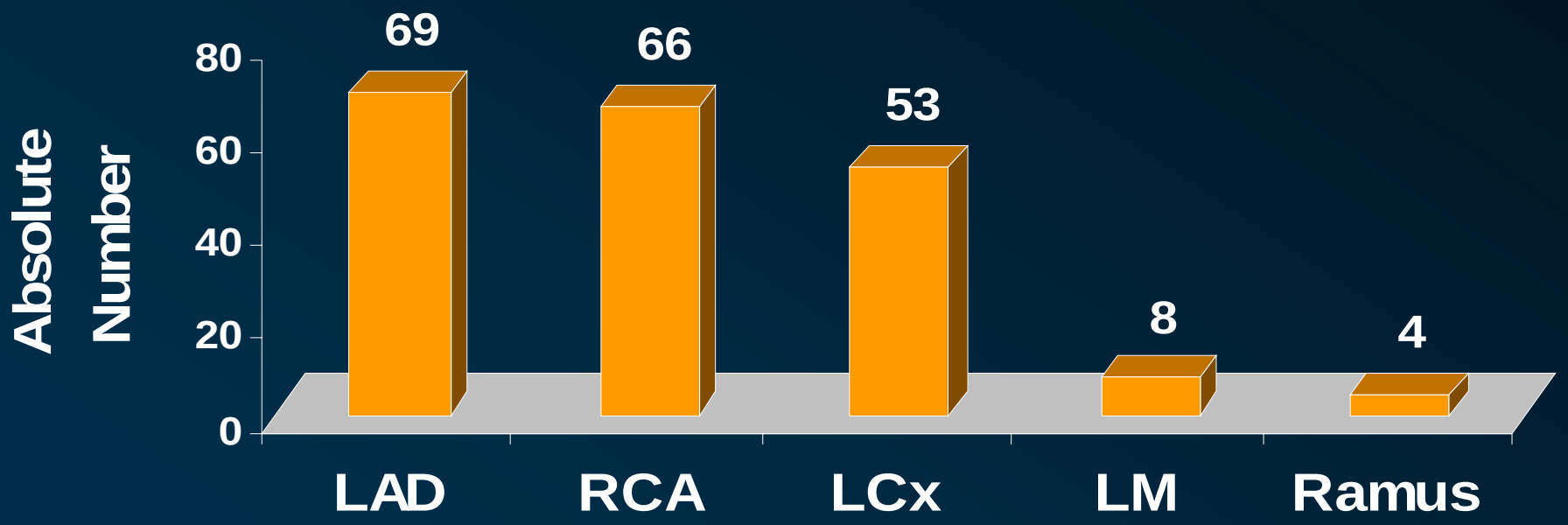
Screening

Number screened	391
Number excluded	191
STEMI	56
Prior CABG	69
No clear culprit	38
R/O MI	6
Pt appears twice	7
Recent Intervention	5
Prior Transplant	1
Other	9

Number accepted	200
Pts w/mult lesions	68
Total lesions	274
RCA	81
LAD	87
Diag	12
LCx	40
OM	38
LM	11
Ramus	5

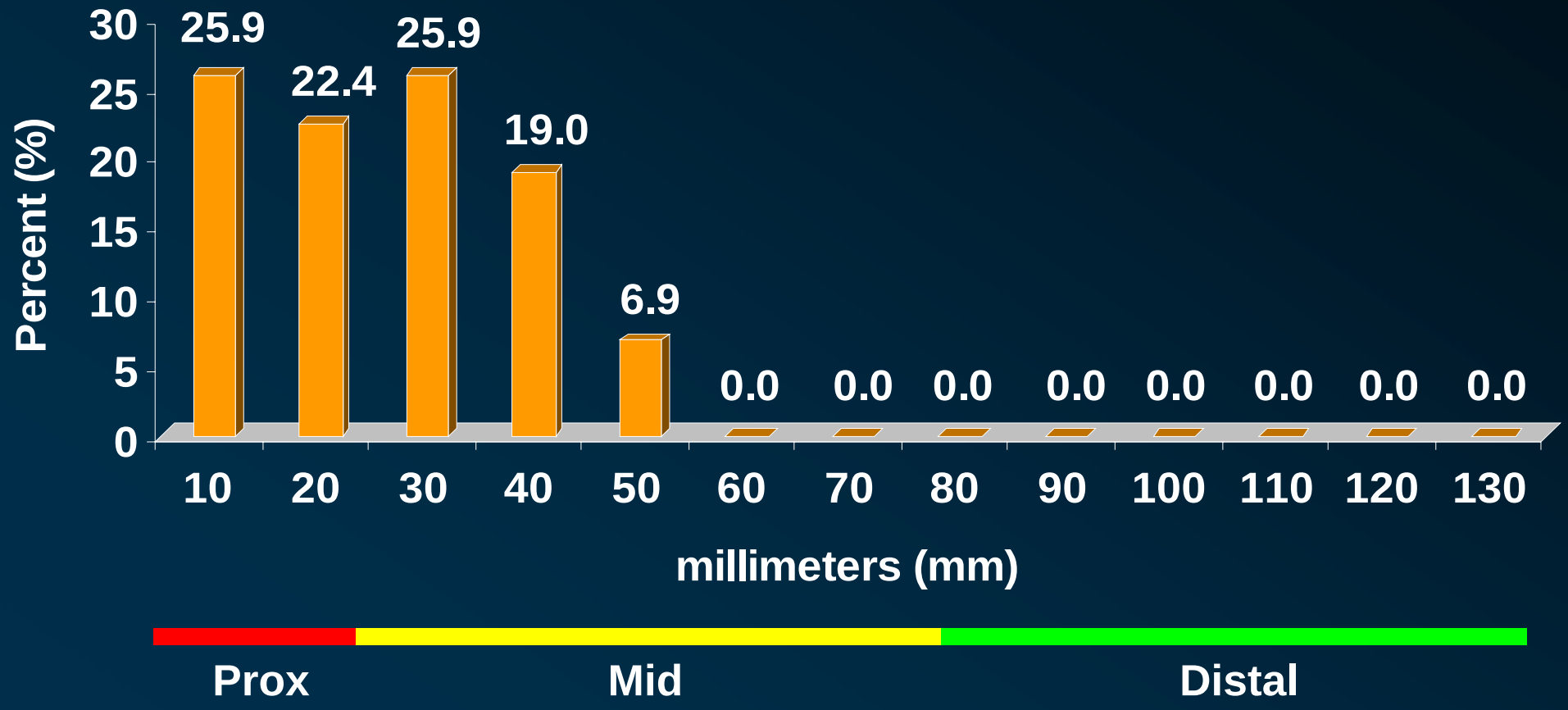
Location of MI

200 lesions



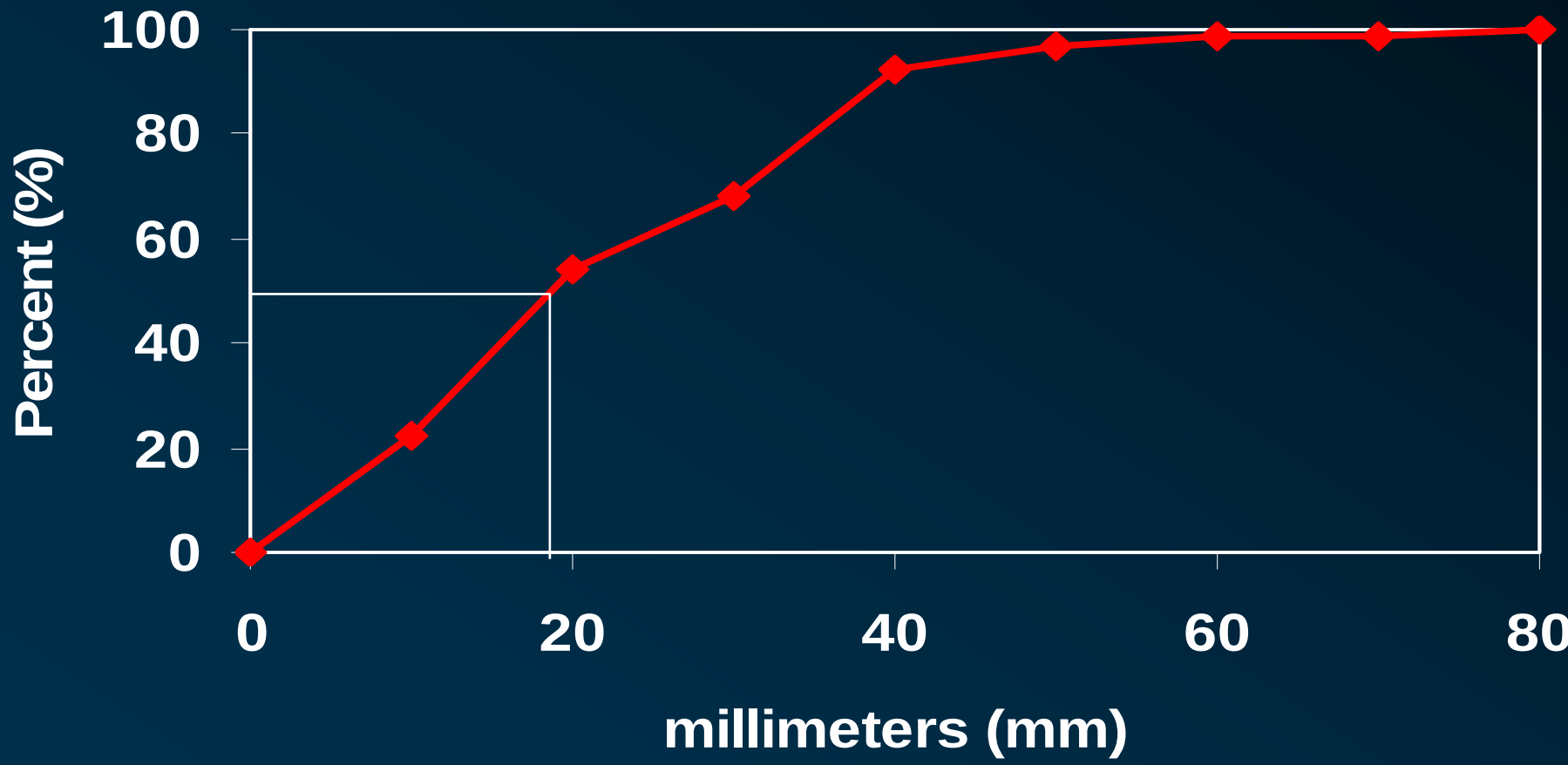
Distribution of MI in LAD

Normalized Segment Analysis

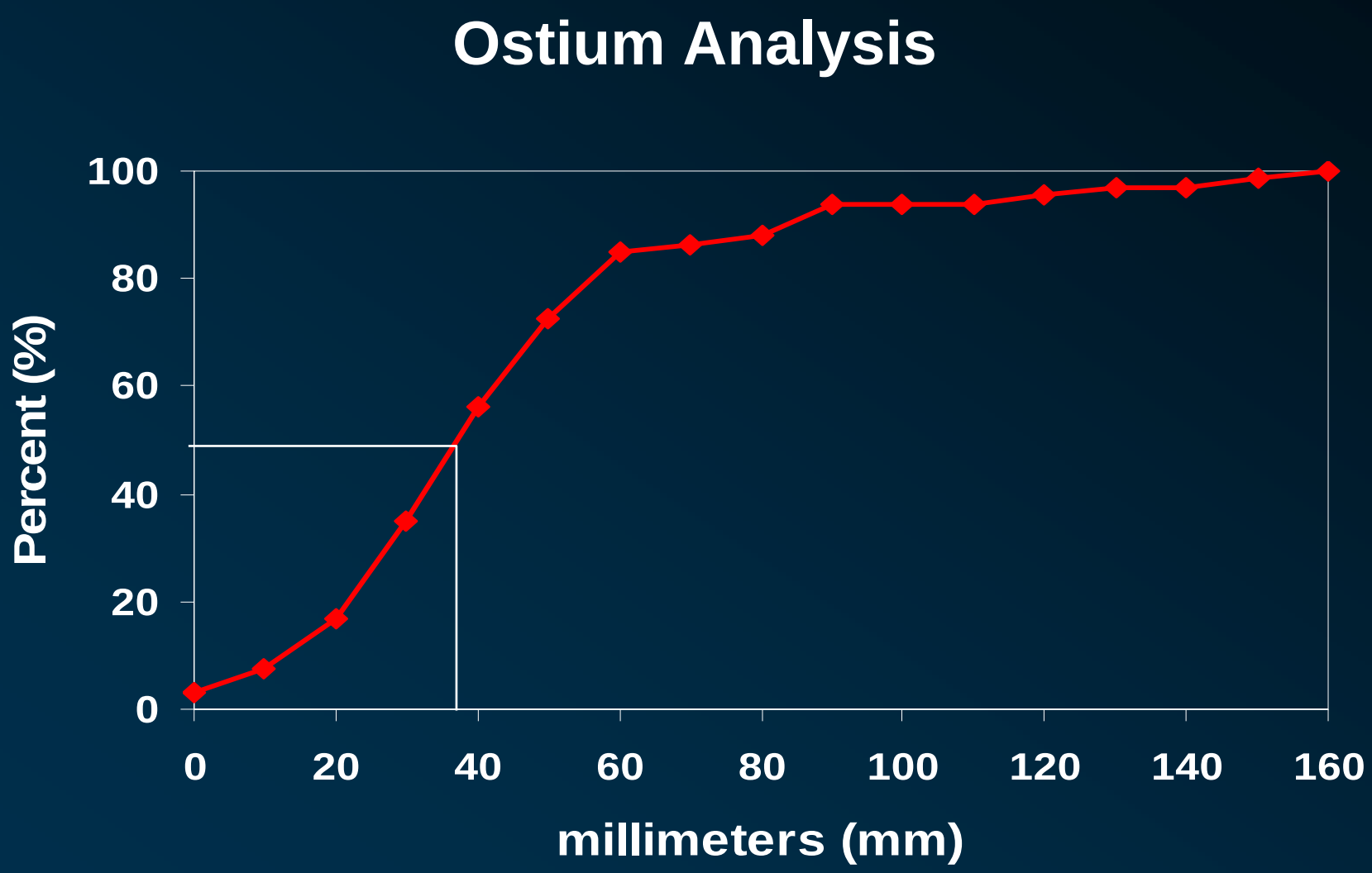


Cumulative Frequency Curve for LAD

Ostium Analysis

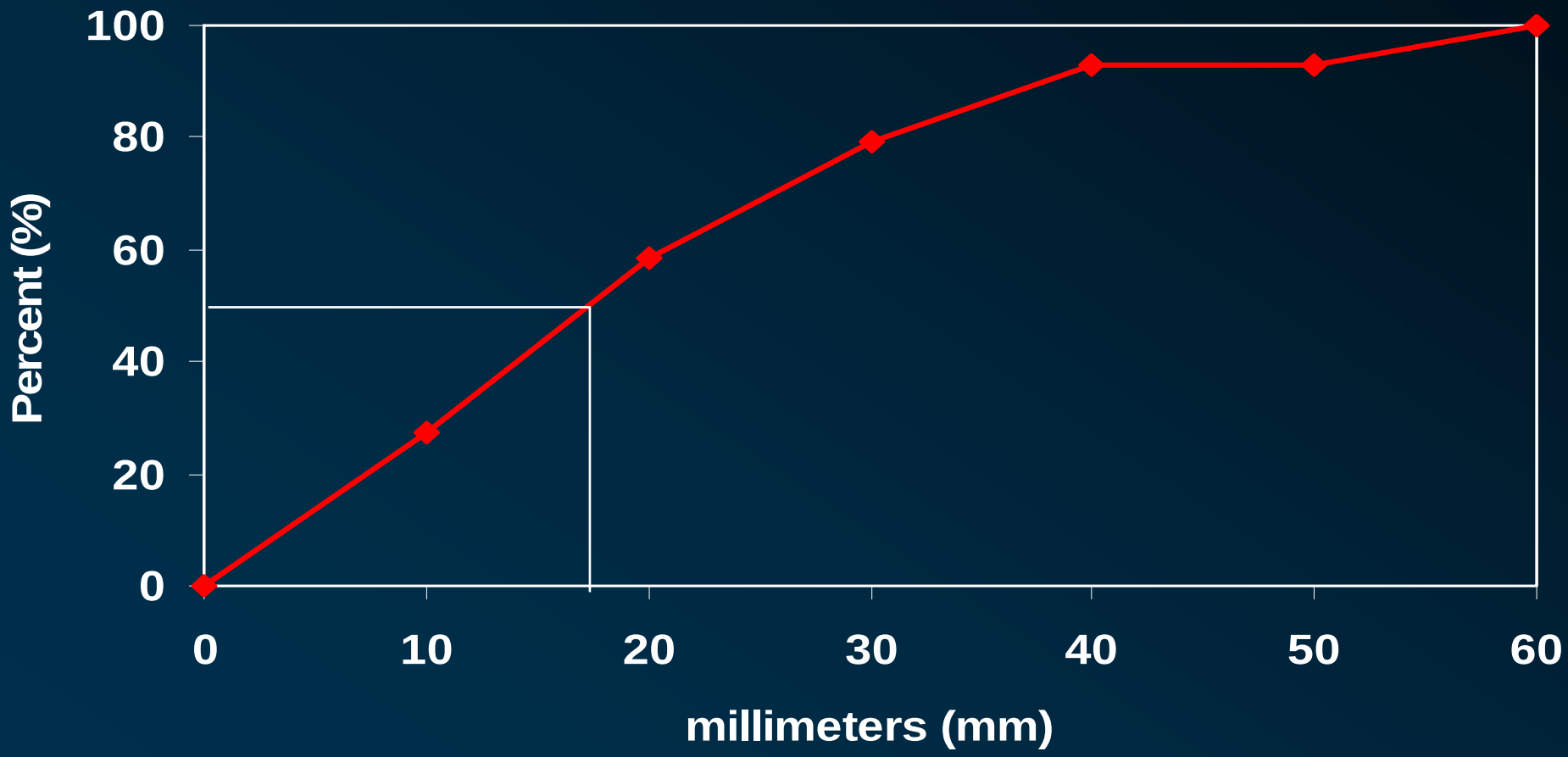


Cumulative Frequency Curve for RCA



Cumulative Frequency Curve for LCx

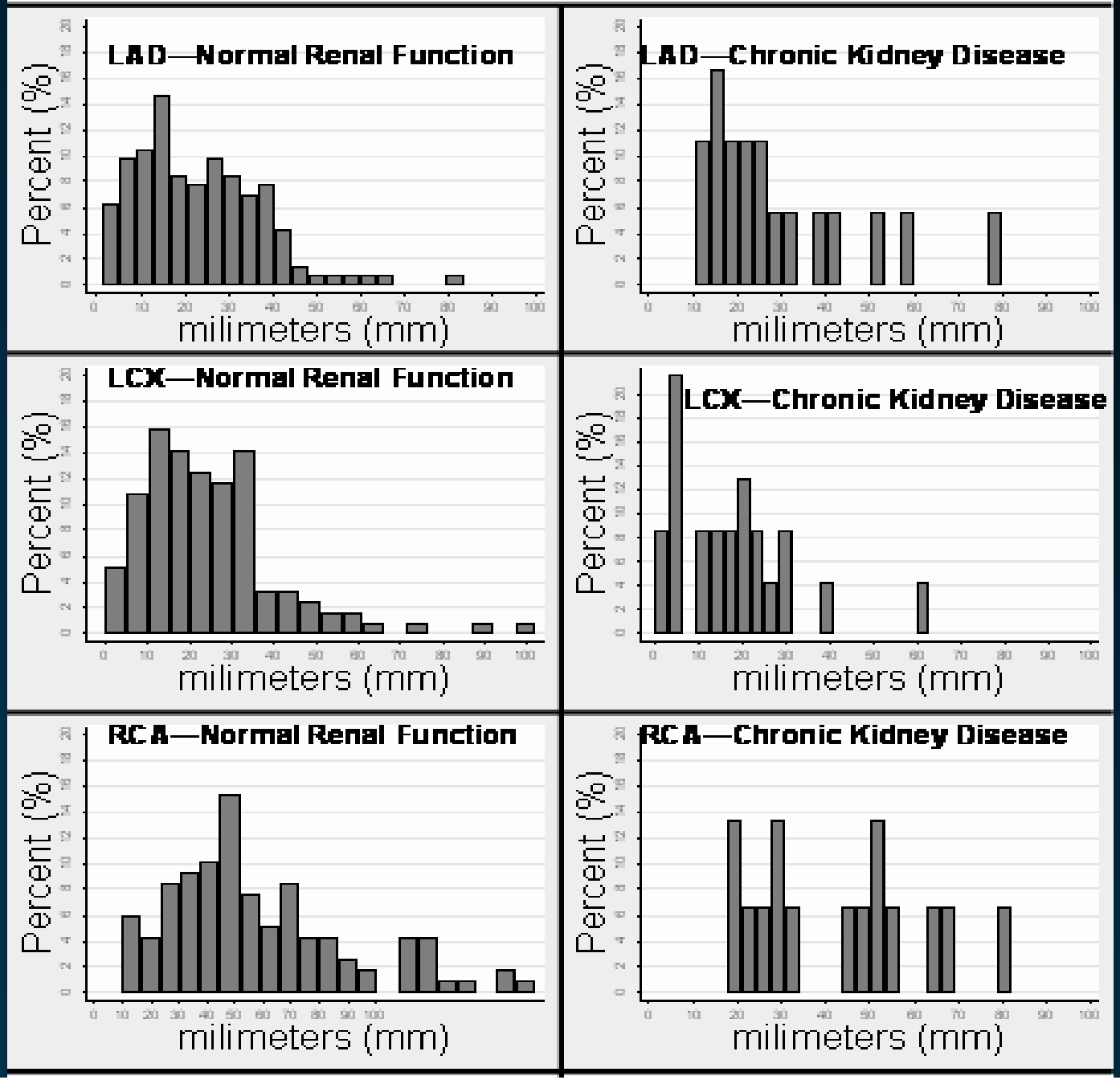
Ostium Analysis



Renal Disease and Spatial Distribution

D Charytan, L Mauri, Wang J, Kuntz, R, submitted

Figure 2. Distribution of Coronary Thrombosis



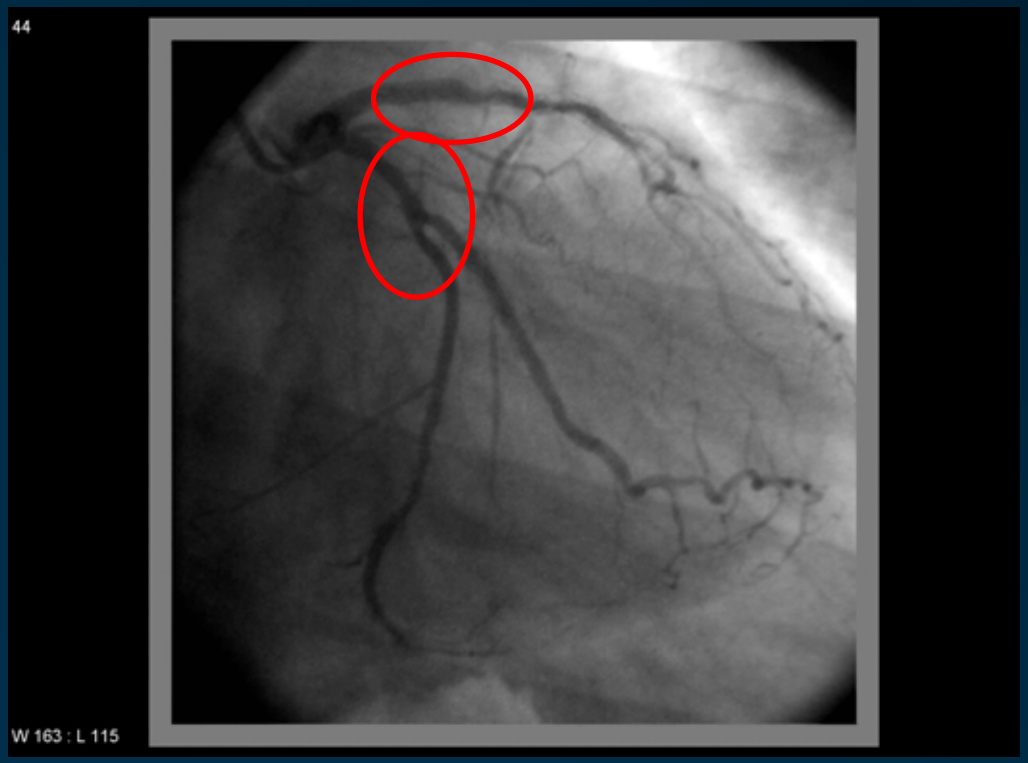
Renal Function	Median DTL (mm)	P Value* Vs. Normal Renal Function
Normal Renal Function (n=390)	28.67	--
CKD, Non-dialysis (n=58)	21.96	0.08
Dialysis Dependant (n-20)	24.375	0.41

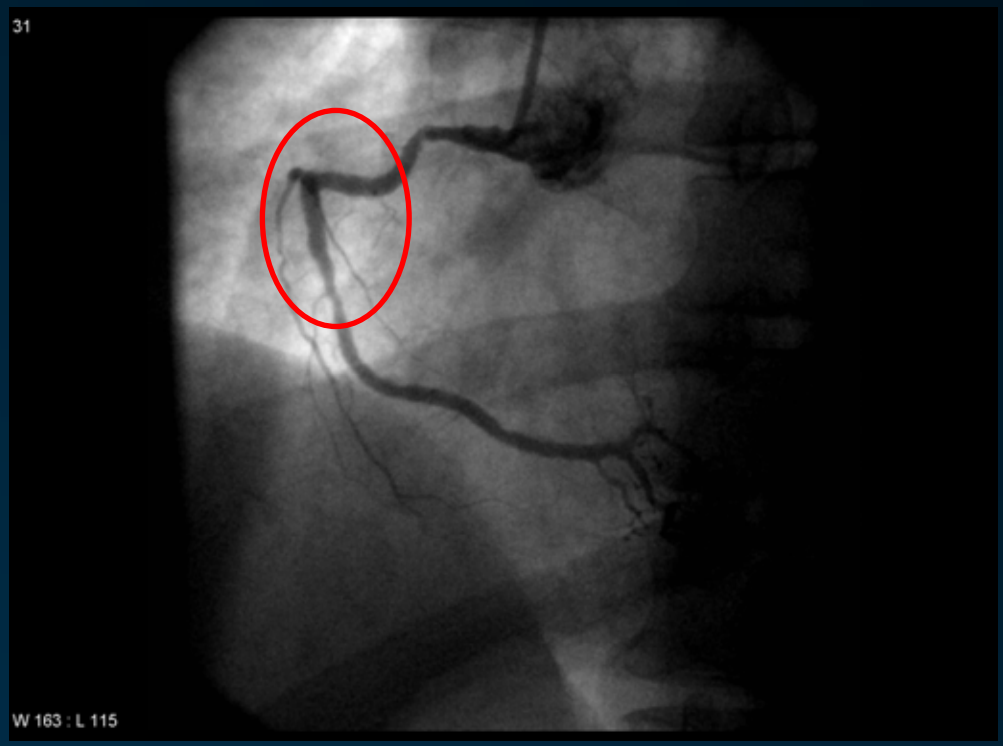
What Can Be Used To Prevent MIs?

- Drugs
- Stents

Vulnerable Hot Spots

How About A Few DESs





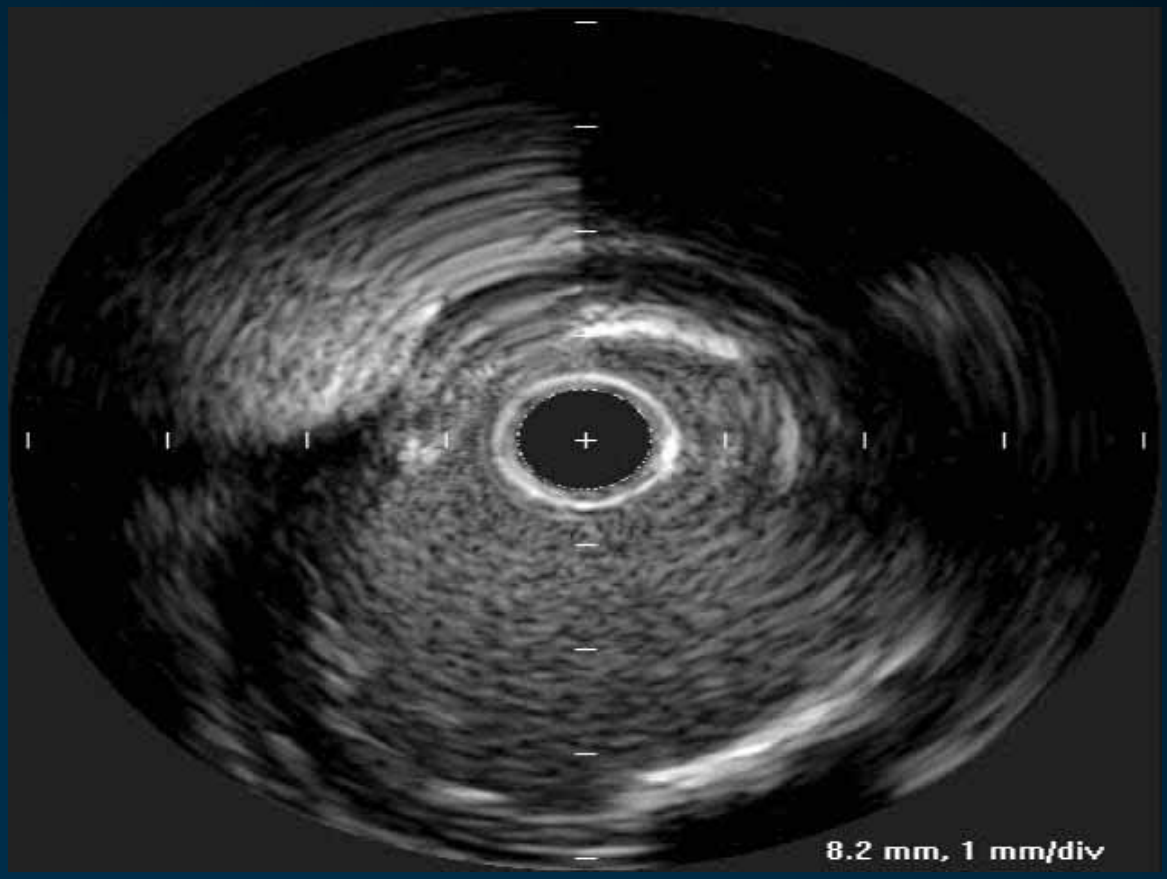
Non-Obstructive Plaque Stenting

- 86 y.o. mman with new chest discomfort and SOB
- Risk factors: Dyslipidemia, family history of CAD, remote smoking
- ECG: Normal
- Troponin 0.26 ng/ml (ULN: 10)
  - CK, CK-MB: WNL
- Cath indication: persistent chest pain and elevated troponin

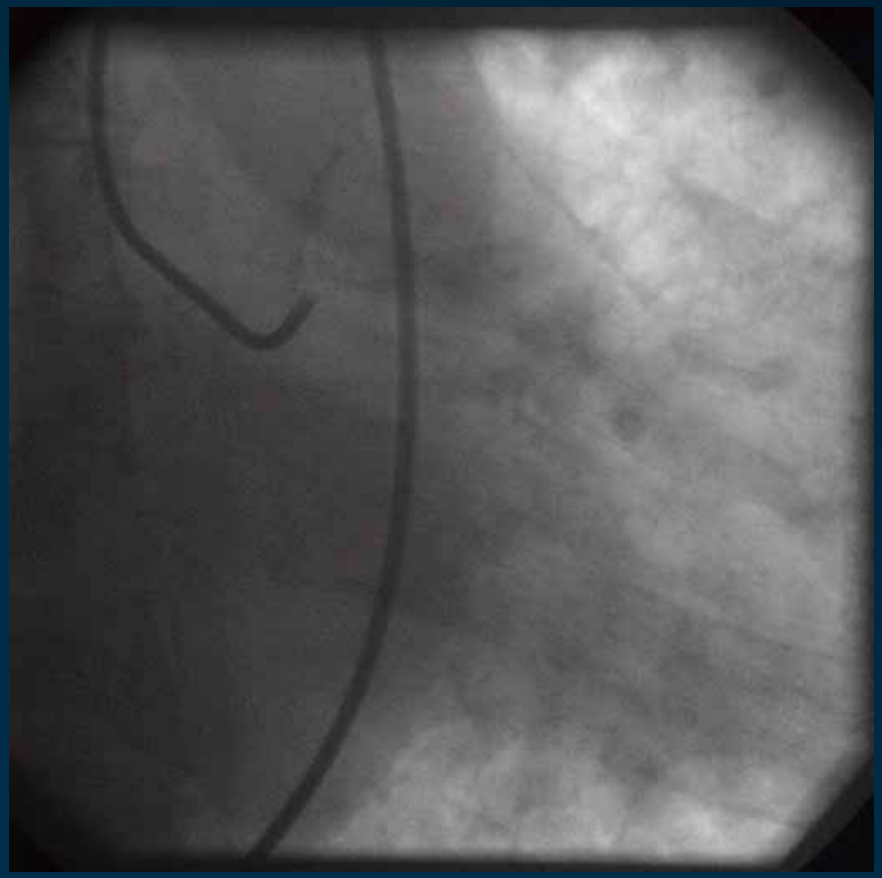
Non-Obstructive Plaque Stenting

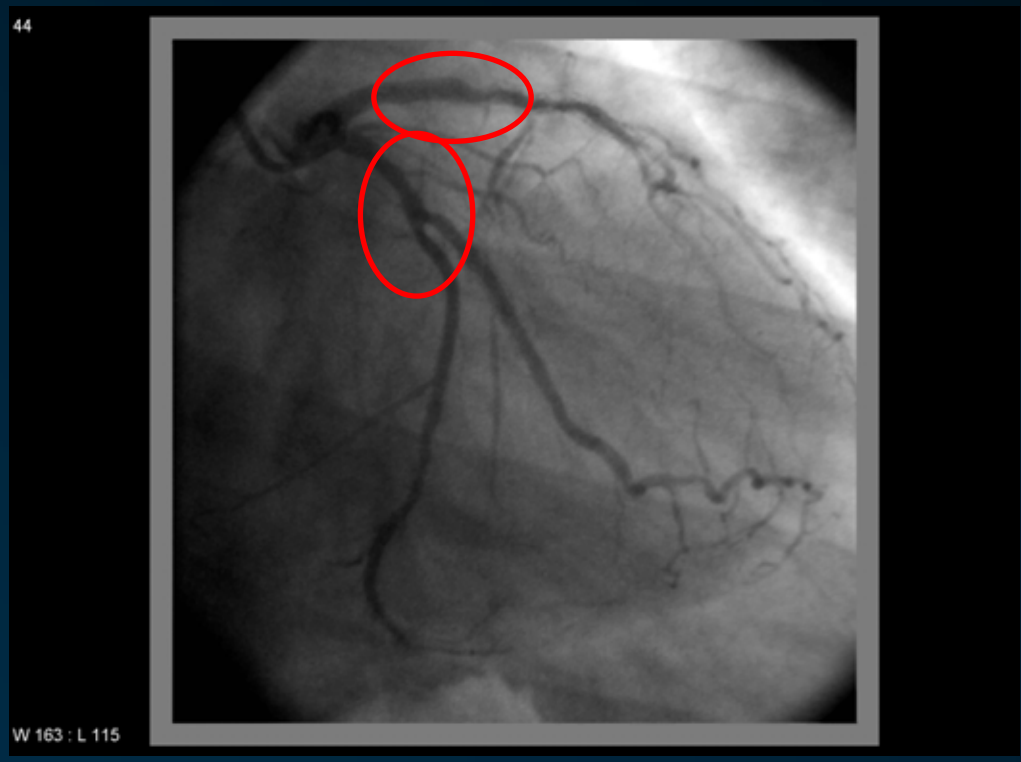
Non-Obstructive Plaque Stenting

Non-Obstructive Plaque Stenting

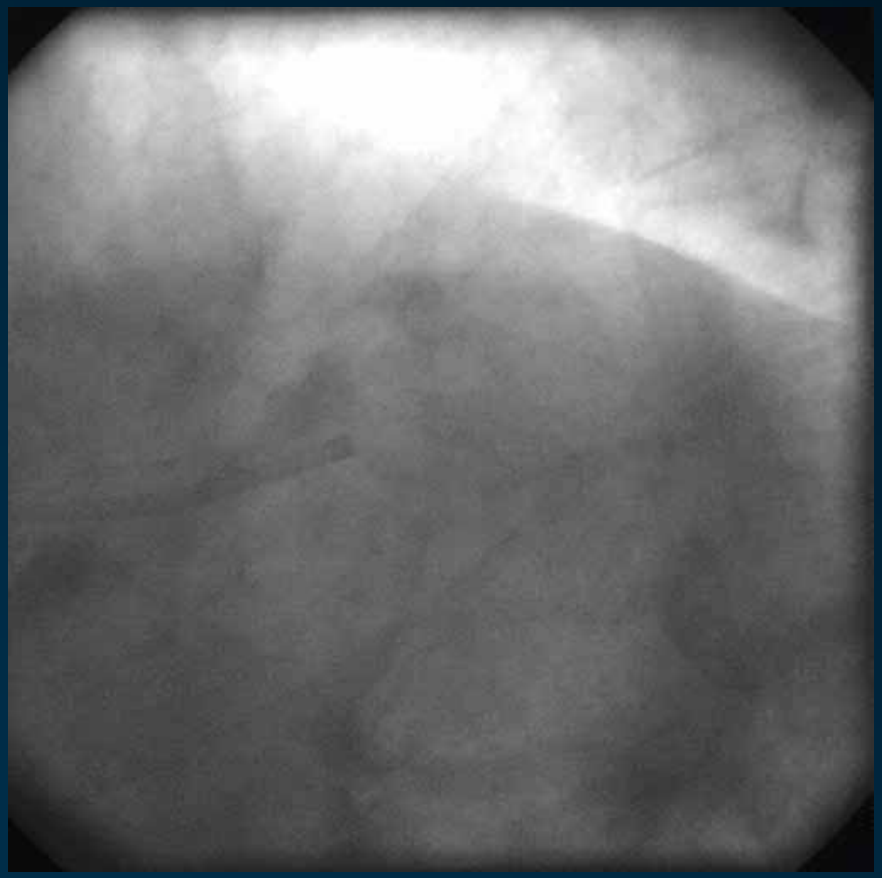


Non-Obstructive Plaque Stenting





Non-Obstructive Plaque Stenting



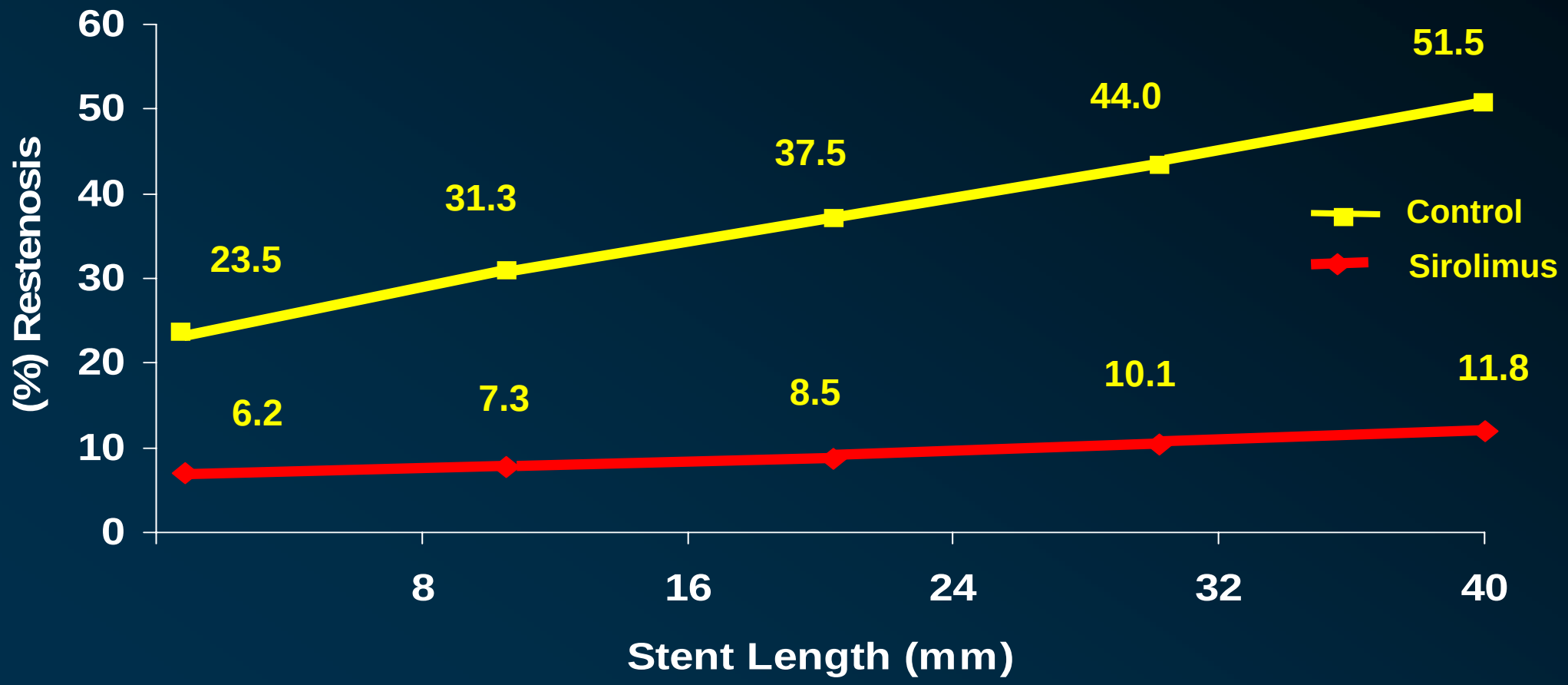
SIRIUS

Stent Thrombosis (1080 days)

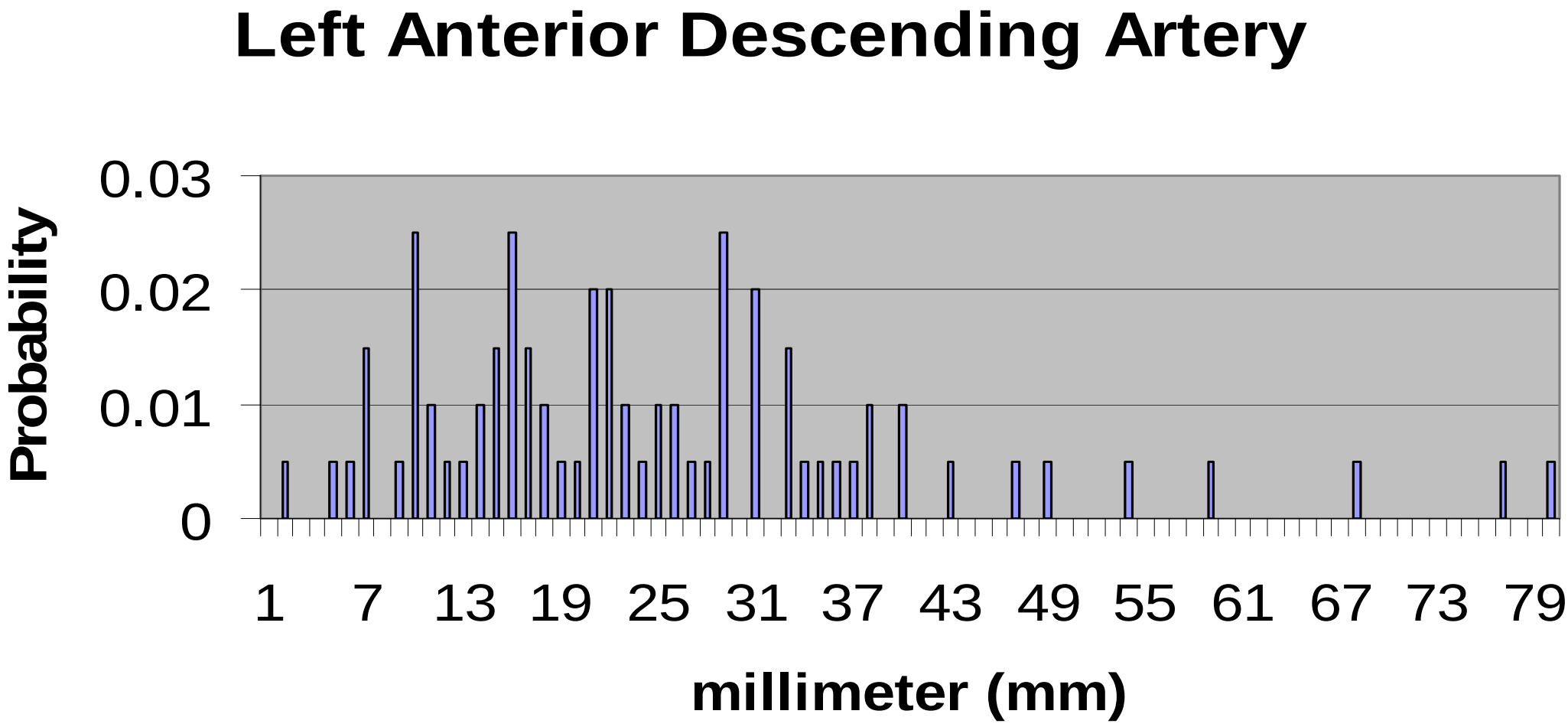
	Sirolimus (%) (n=533)	Control (%) (n=525)
Acute (≤ 24 hours)	0	0
Subacute (1-30 days)	0.2% (1)	0.2% (1)
Late (31-270 days)	0.2% (1)	0.6% (3)
Late (271-720 days)	0.2% (1)	0
Late (721-1080 days)	0.2% (1)	0
Total	***0.8% (4)***	***0.8% (4)***

SIRIUS: Restenosis vs. Stent Length

In-Segment



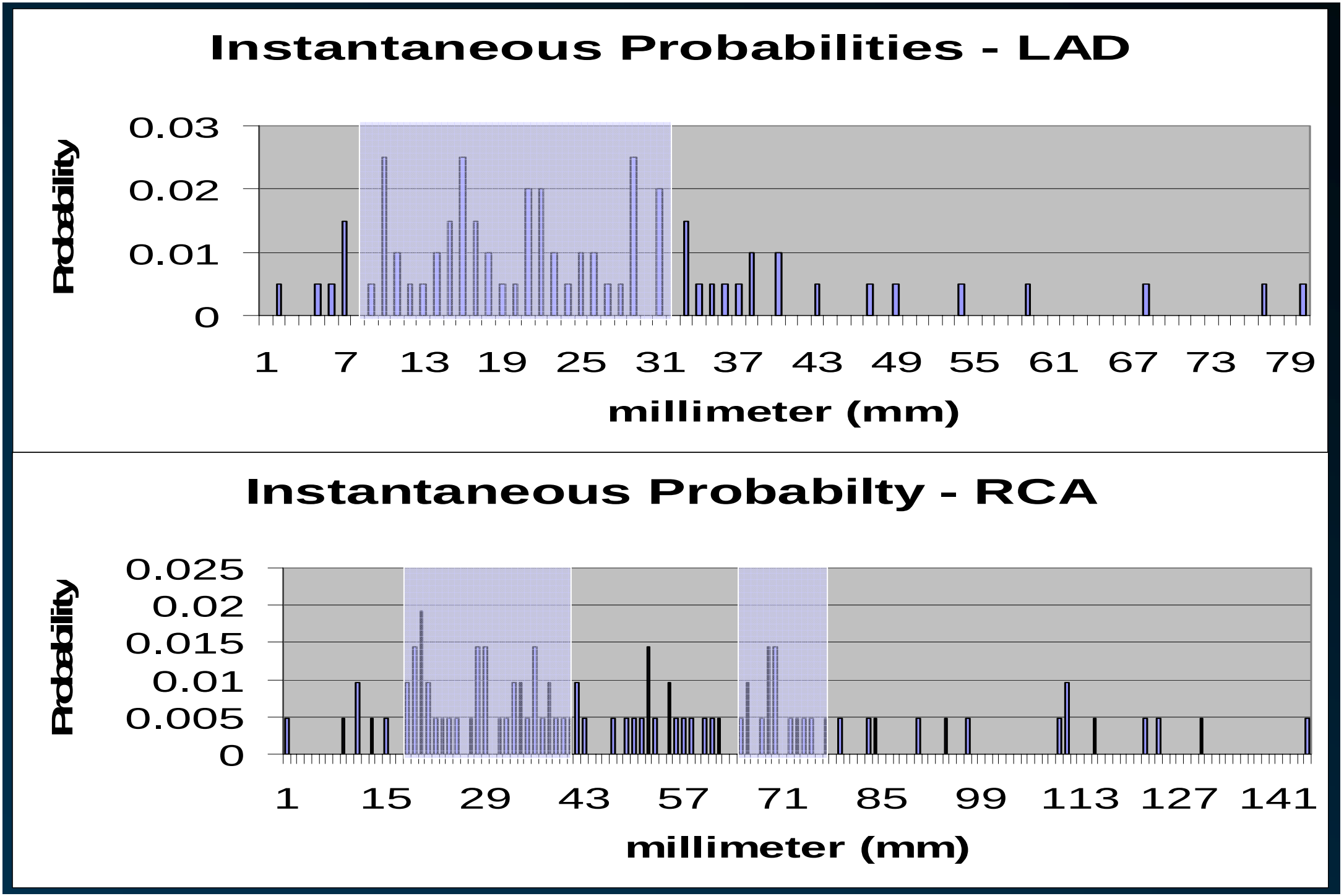
Results: Instantaneous Probabilities of Acute Coronary Occlusion

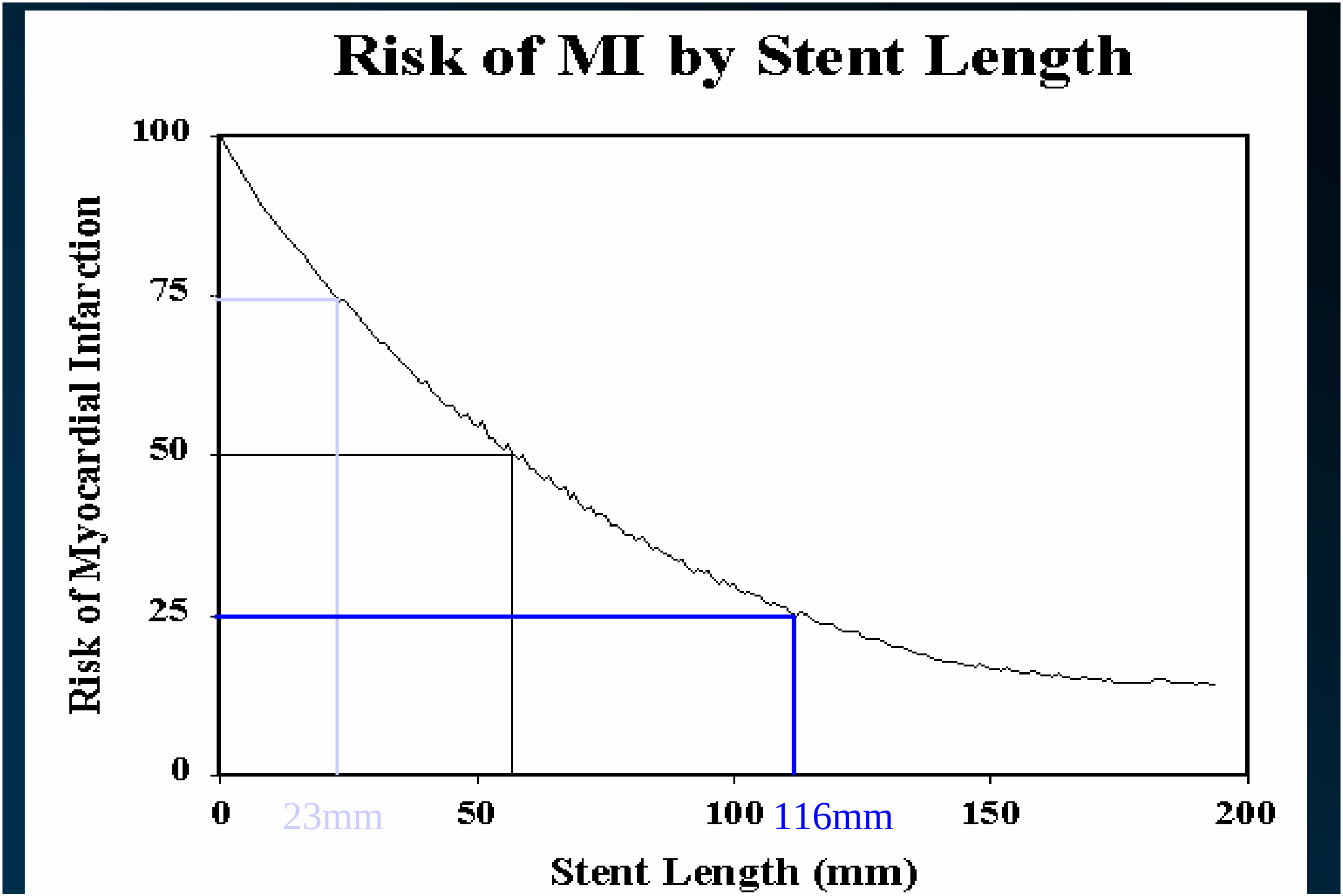


Simulation Optimum Combination

Vessel	Stent Length	Starting Location*
LAD	23mm	9mm
RCA	23mm	18mm
RCA	13mm	65mm

* Absolute distance from ostium


Instantaneous Probabilities - LAD
Probability
0.03
0.02
0.01
0
1
7
13
19
25
31
37
43
49
55
61
67
73
79
millimeter (mm)
Instantaneous Probabilty - RCA
Probability
0.025
0.02
0.015
0.01
0.005
0
1
15
29
43
57
71
85
99
113
127
141
millimeter (mm)


Risk of MI by Stent Length
Risk of Myocardial Infarction
100
75
50
25
0
0
23mm
50
100
116mm
150
200
Stent Length (mm)

Clinical Implications

- *Estimation of the absolute risk of myocardial infarction is critical to the application of this model*

Patient Prototype	5yr Risk of MI	Risk Reduction 25% (23mm)	50% (59mm)	75% (116mm)
HCRI - FDA Trials Single vessel stent	9.5%	7.1%	4.8%	2.4%
BARI – Diabetics Multivessel Disease	66%	49.5%	33%	16.5%

DES Stent Trial to Prevent Death and MI

- Hypothesis:
  - Prohylactic DES placement prevents MI
- Reference population
  - Patients with known obstructive CAD
    - Problem with inference to patients with non-obstructive CAD
- Eligible Study Patients
  - Need for ischemic-driven PCI revascularization
  - Risk of MI >5-8% per year (diabetics with 2-3 vessel disease etc)

DES Stent Trial to Prevent Death and MI

- Randomized Intervention
  - After obstructive lesion treated, prophylactic stenting of some “vulnerable” hot spots
- Intervention Goals
  - Intervention aimed at reducing MI risk by >50%
  - Proximal hot spots preferred
- Trade-offs
  - Risk of SAT and restenosis from DES

Conclusions

- The New Target
  - The non-obstructive plaque may be more important than the obstructive plaque, in terms of mortality and morbidity
- If we assume:
  - DES causes near negligible acute and late complications
  - Stented segments have low risk of future atherosclerosis pathology (VP potential removed)
  - We can identify patients with approximately >3-8% risk of MI/year

Conclusions (2)

- Is it reasonable to test:
  - "Hot spot" stenting in high risk (MI) patients who are otherwise undergoing obstructive coronary treatment
- Studies/Information needed
  - Better discrimination of patient risk of MI
    - Currently we have only crude measures
  - Safety studies of non-obstructive coronary segment stenting
  - RCT of prohylactic stenting plus obstructive lesion stenting vs. obstructive lesion stenting alone.