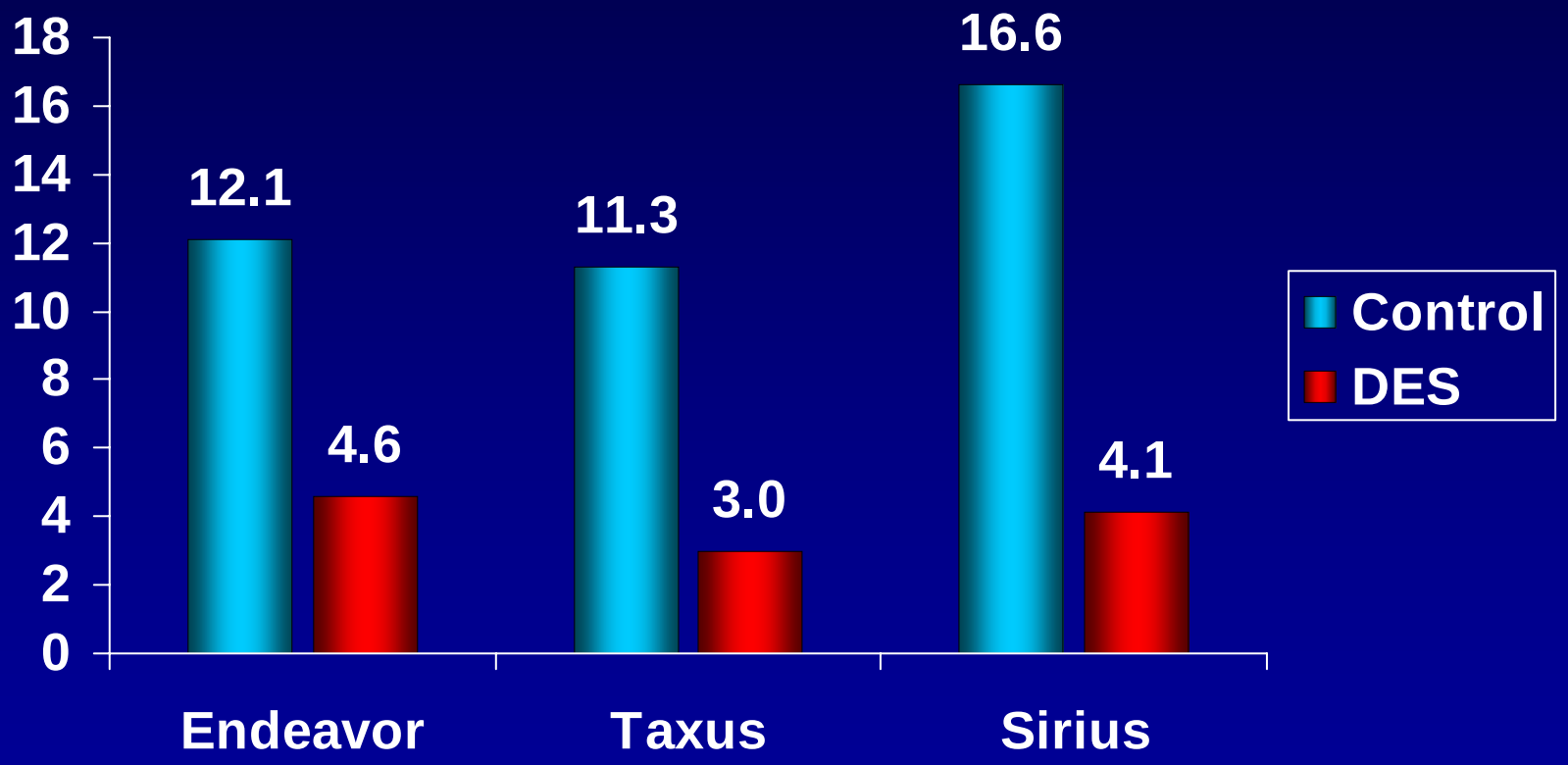
Late Loss Is The Single Best Parameter For Estimating Stent-Based Restenosis Resistance

Richard Kuntz
Brigham and Women's Hospital
Harvard Medical School

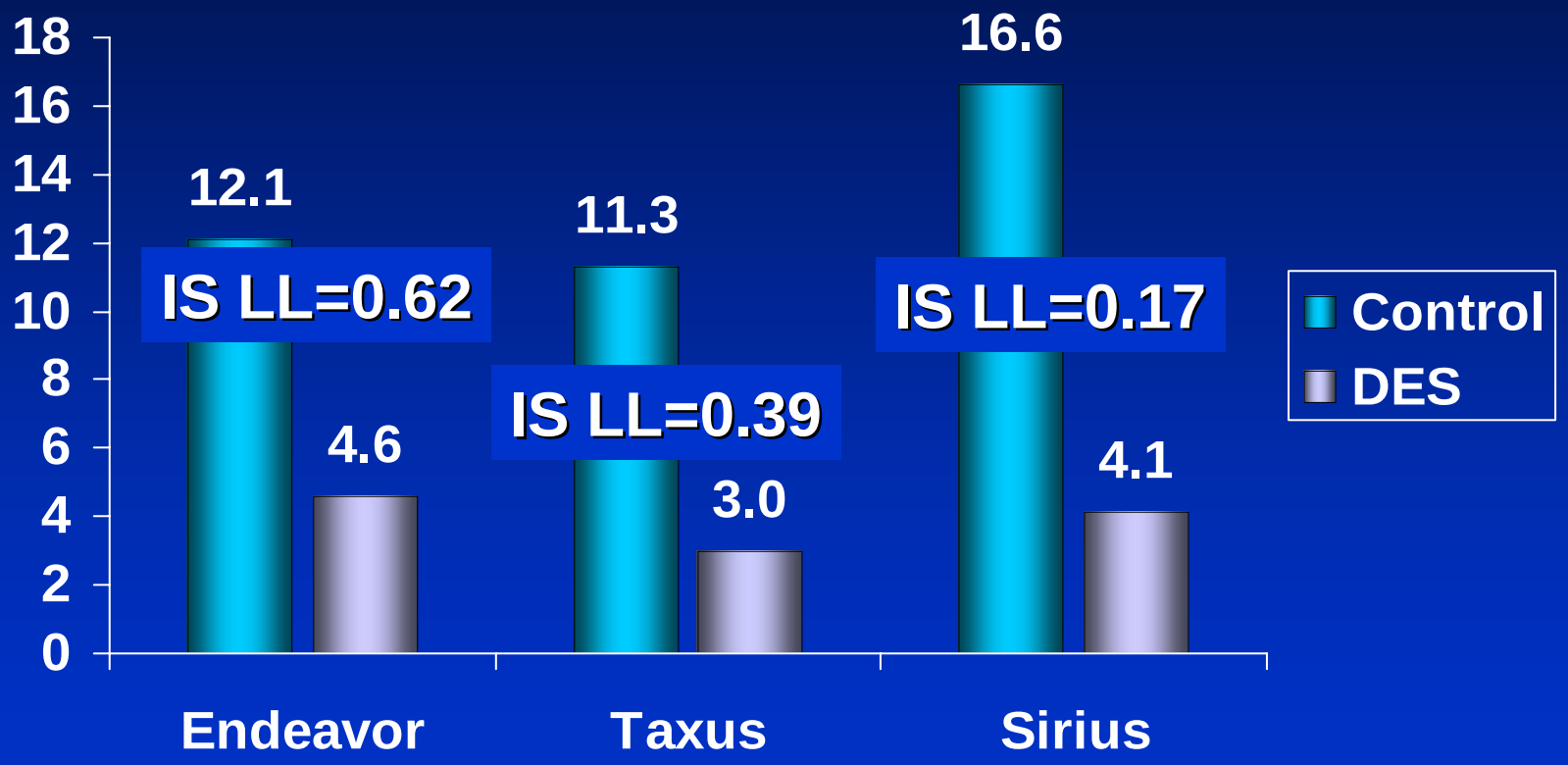
Pivotal Trial Comparisons

TLR to 9 Months



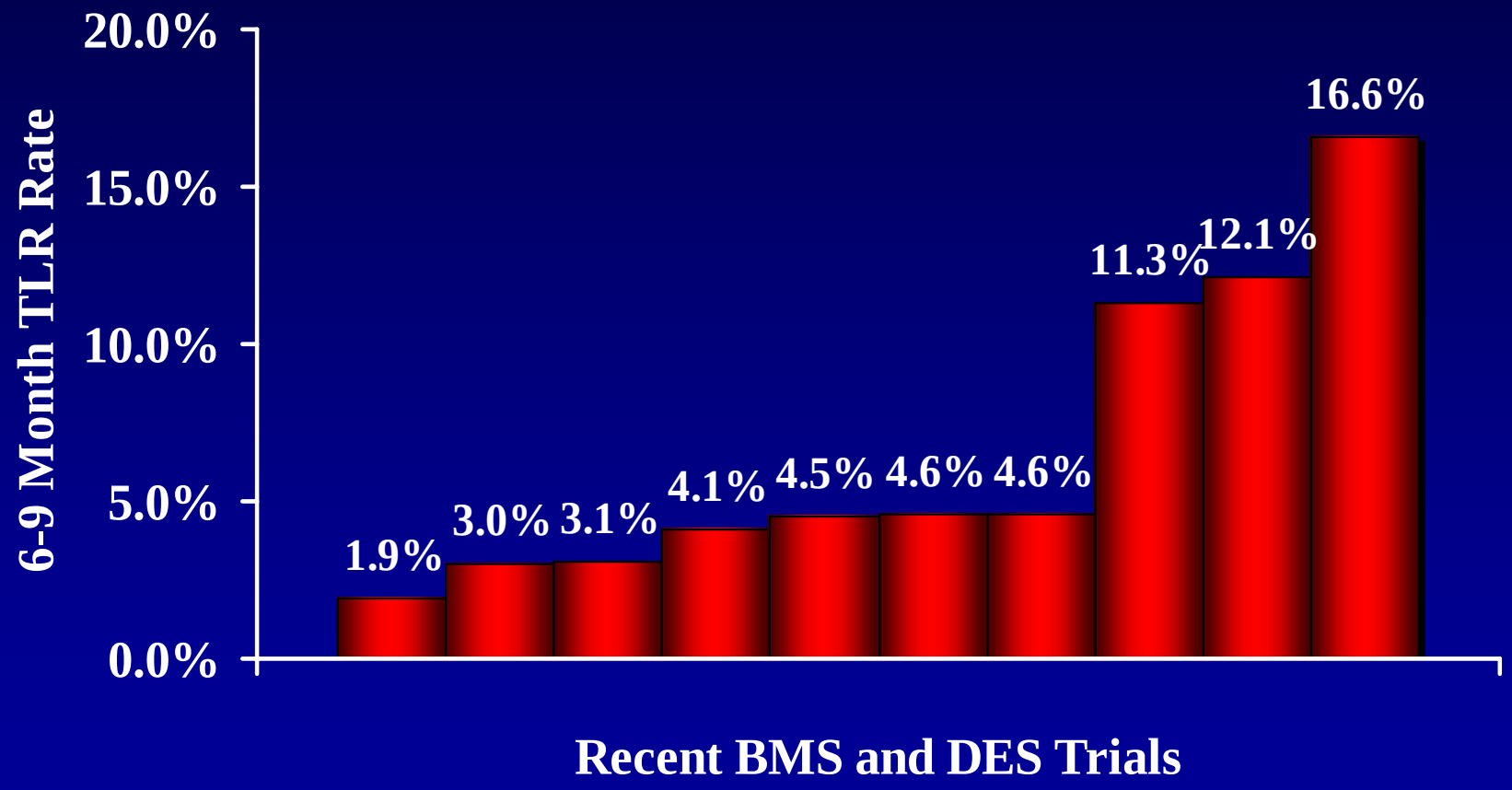
Pivotal DES Trial Comparisons

TLR to 9 Months



Risk and Restenosis

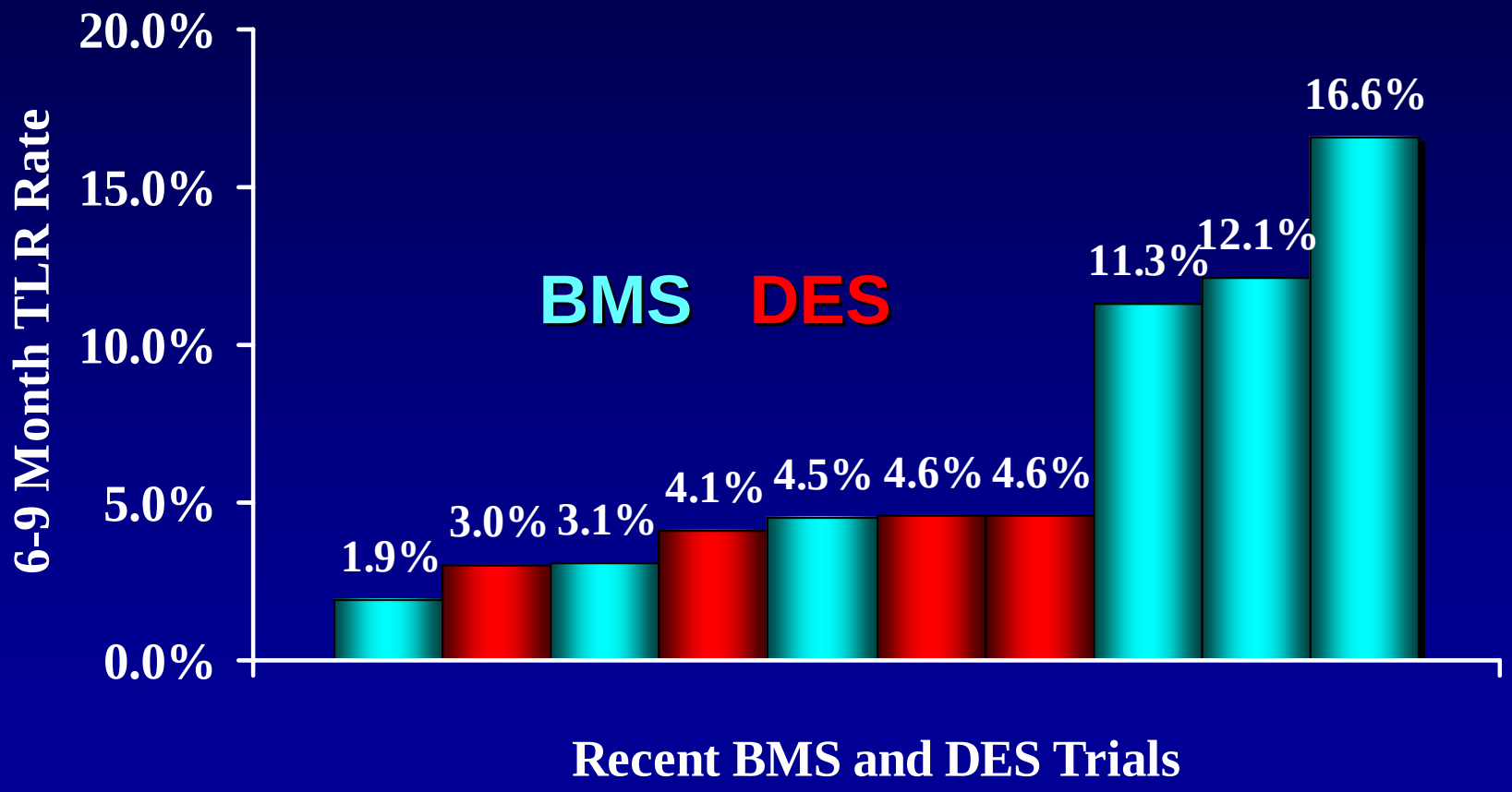
Some Contemporary Clinical Restenosis Rates



Mauri L, Kuntz R submitted for publication

Risk and Restenosis

Some Contemporary Clinical Restenosis Rates



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Risk and Restenosis

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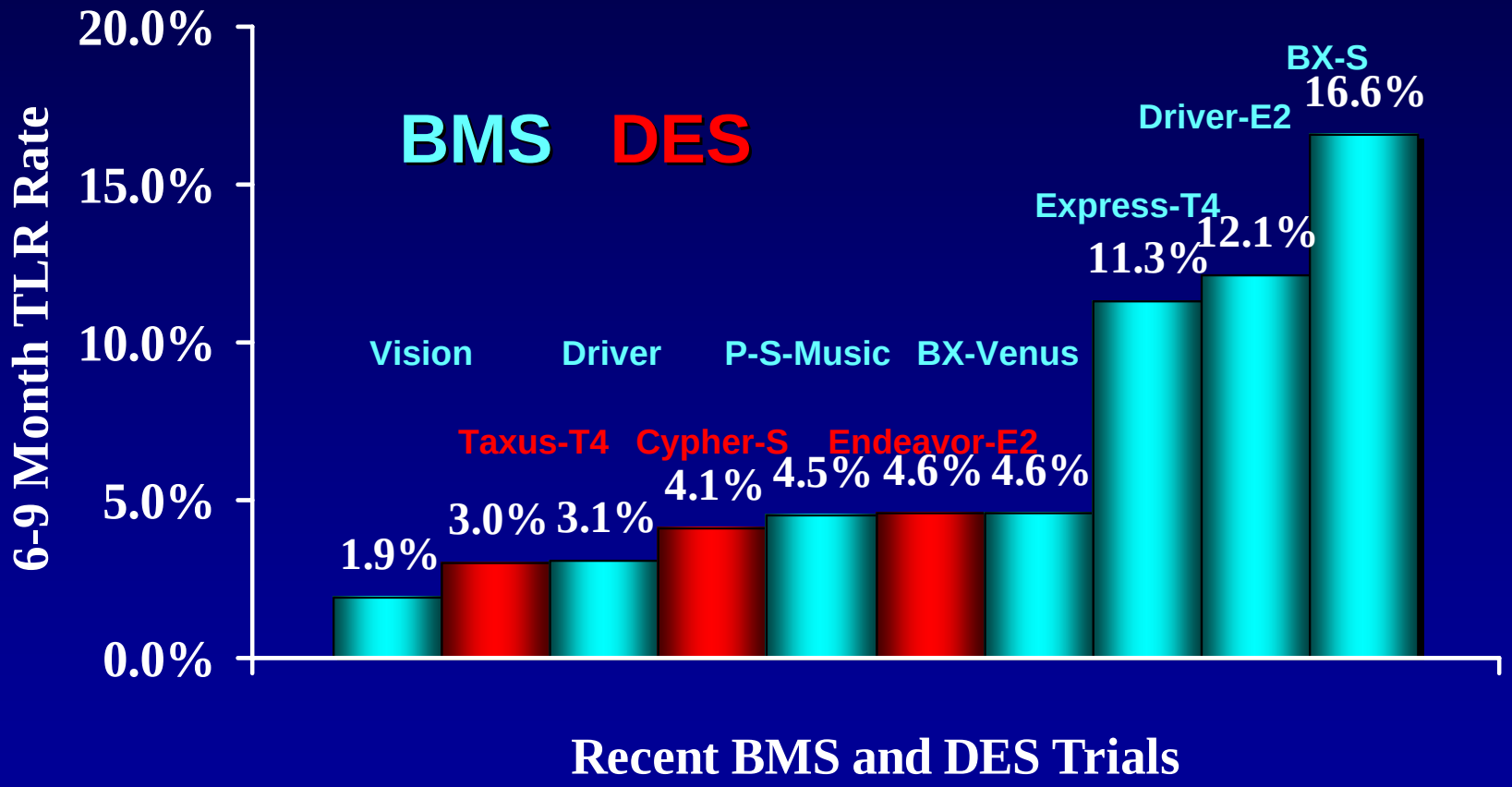

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Restenosis Endponts

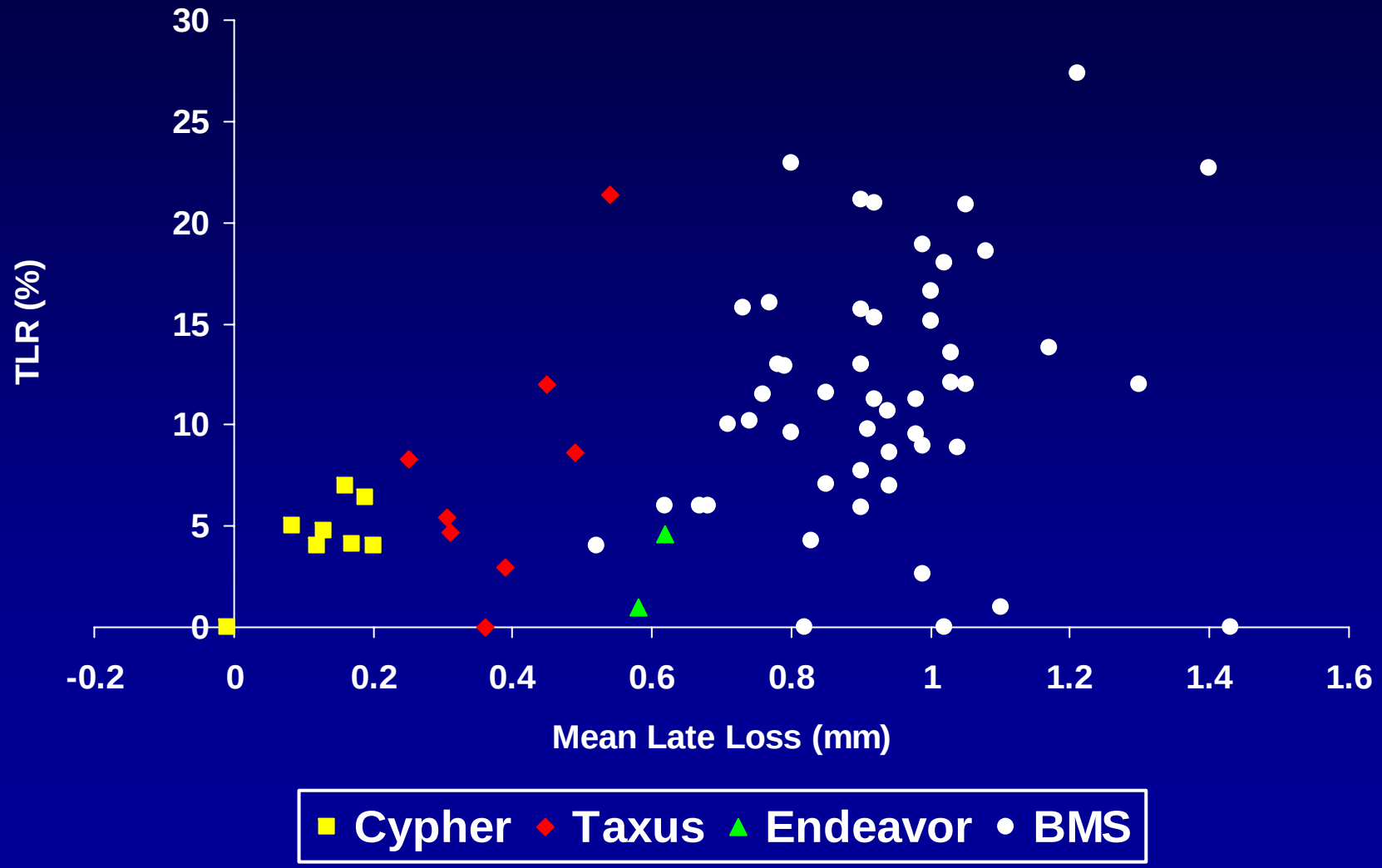
- **Target Lesion Revascularization**
  - Best endpoint in a randomized Trial
  - Needs large sample size for stable Estimation
  - High level of influence by case-mix confounders renders it almost meaningless in comparison across trials.
- **Late Loss (In-stent version only)**
  - Stable and efficient estimate for any stent-type
  - Less influenced by case-mix confounders, and provides a “signature” value for any particular stent.

Restenosis Endponts
The Noise Factor

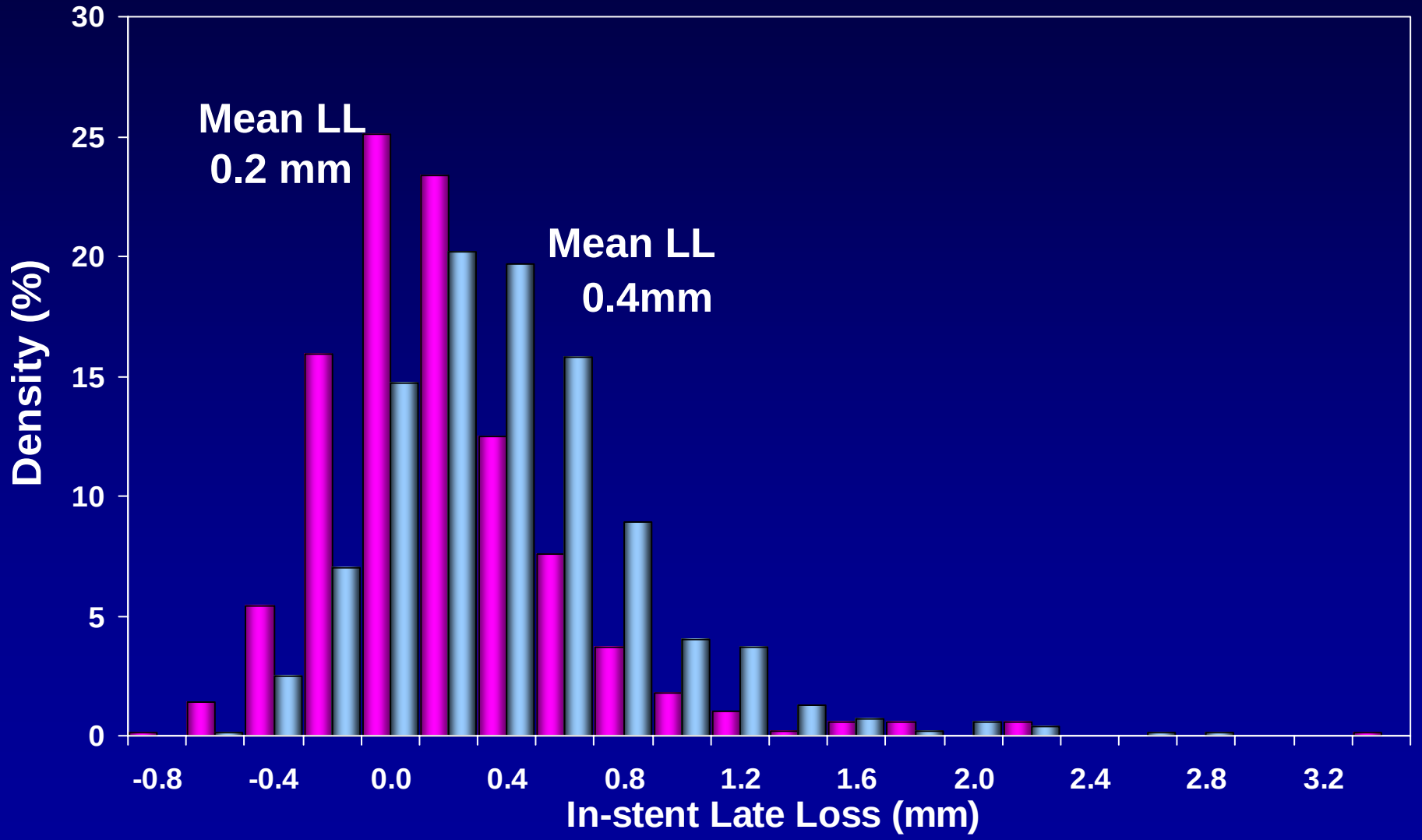
- **Target Lesion Revascularization**
  - Affected by
    - Lesion length
    - Diabetes prevelance
    - Reference vessel size
    - Threshold for revascularization (50-70% renarrowing)
  - Estimates are wide ranging for BMS and DES
- **In-Stent Late Loss**
  - Affected by
    - Diabetes
    - Lesion length
  - Relatively more stable across trials

In-Stent Late Loss and TLR

Current DES and BMS Results



Frequency of Late Loss



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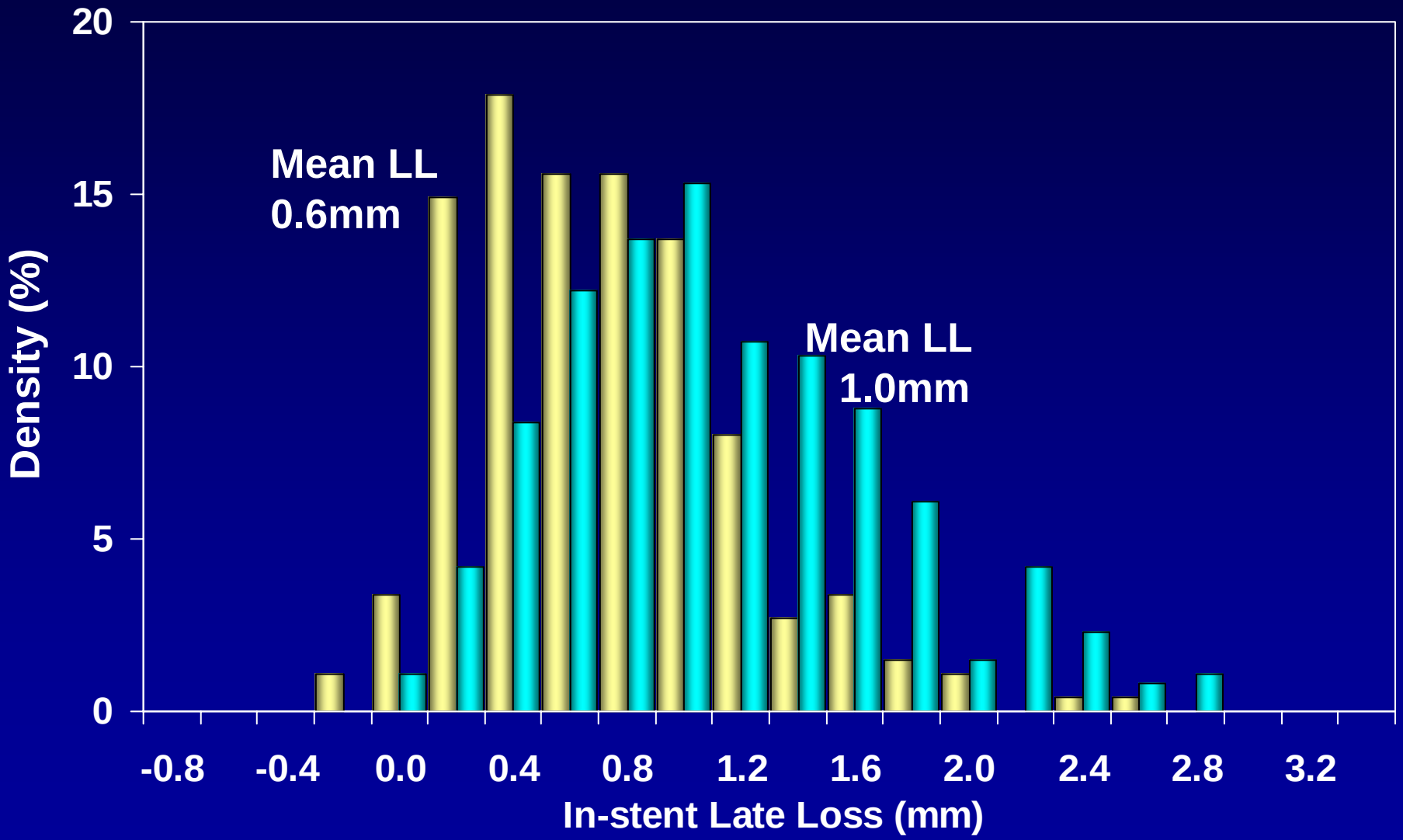
Frequency of Late Loss



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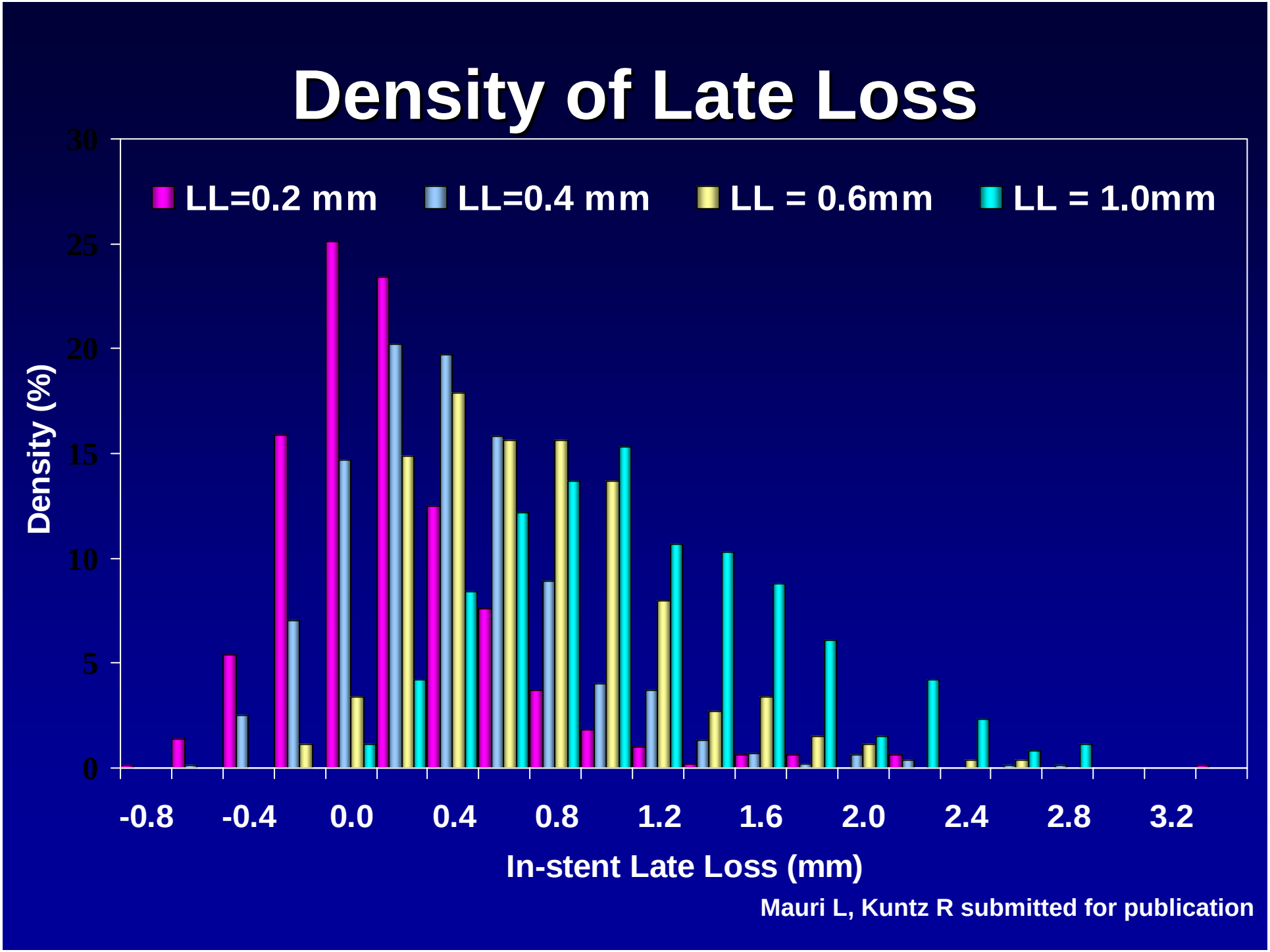
Density of Late Loss



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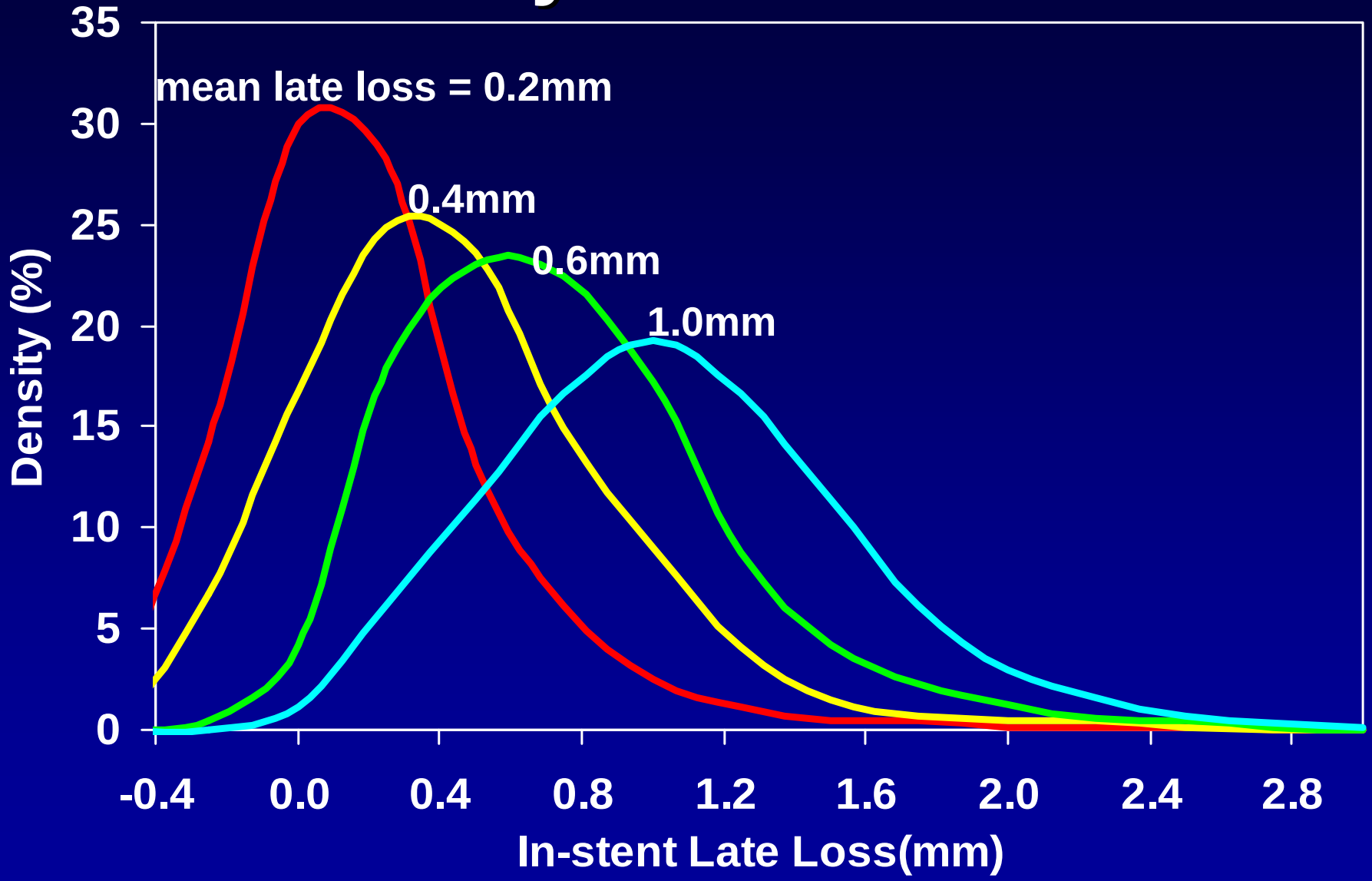

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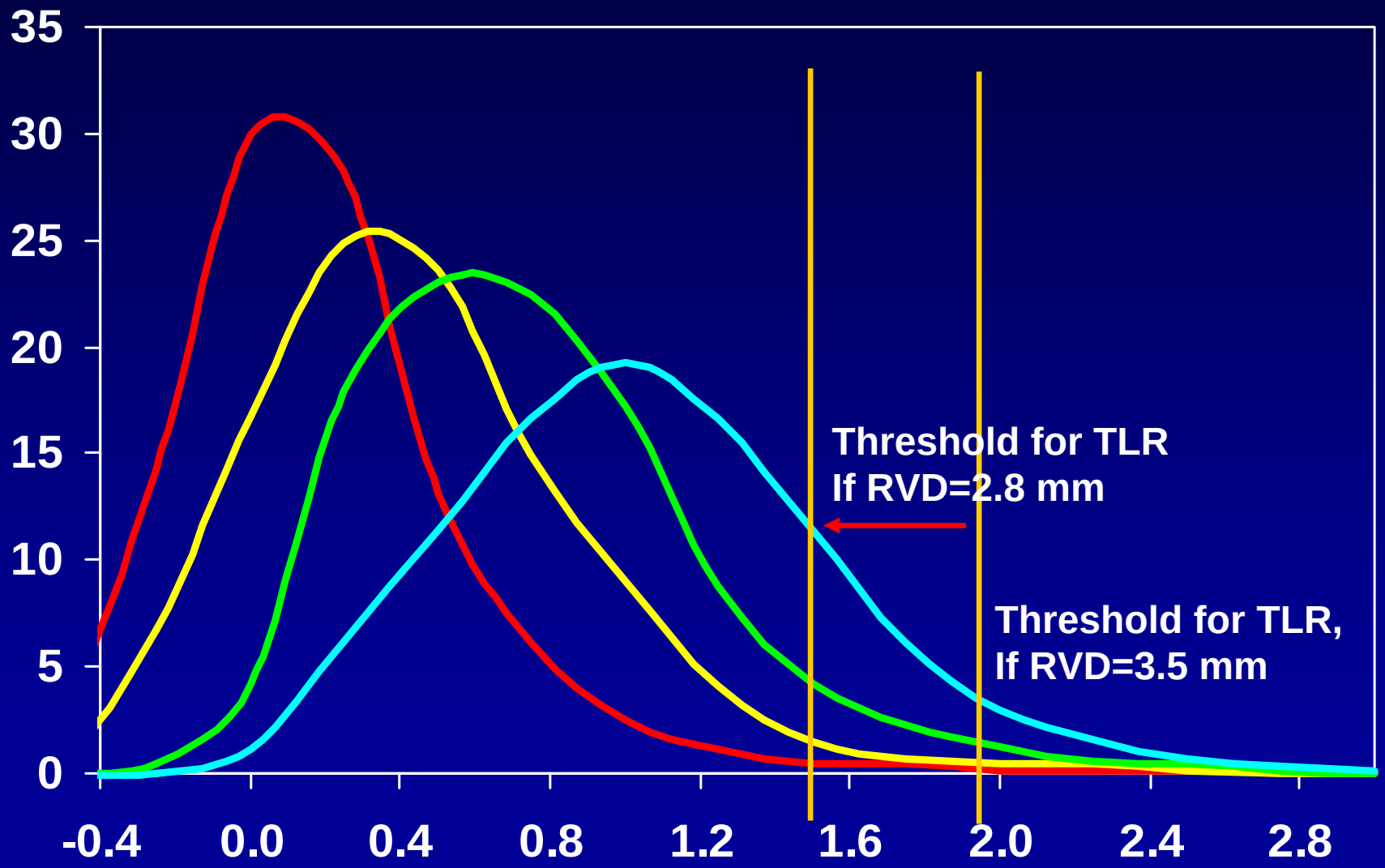
Late Loss and TLR

Effect of mean reference vessel diameter



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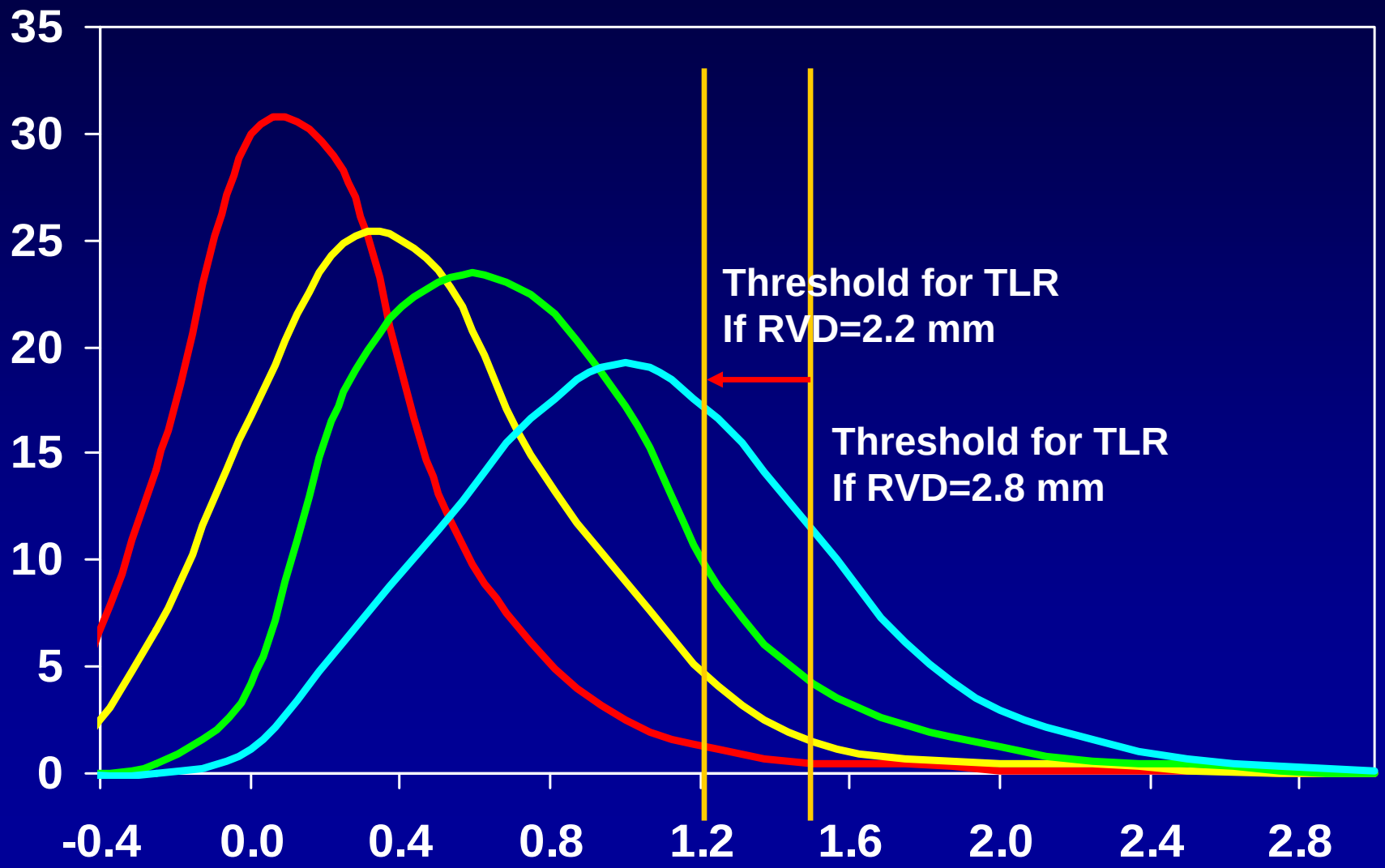
Late Loss and TLR

Effect of small vessel stenting



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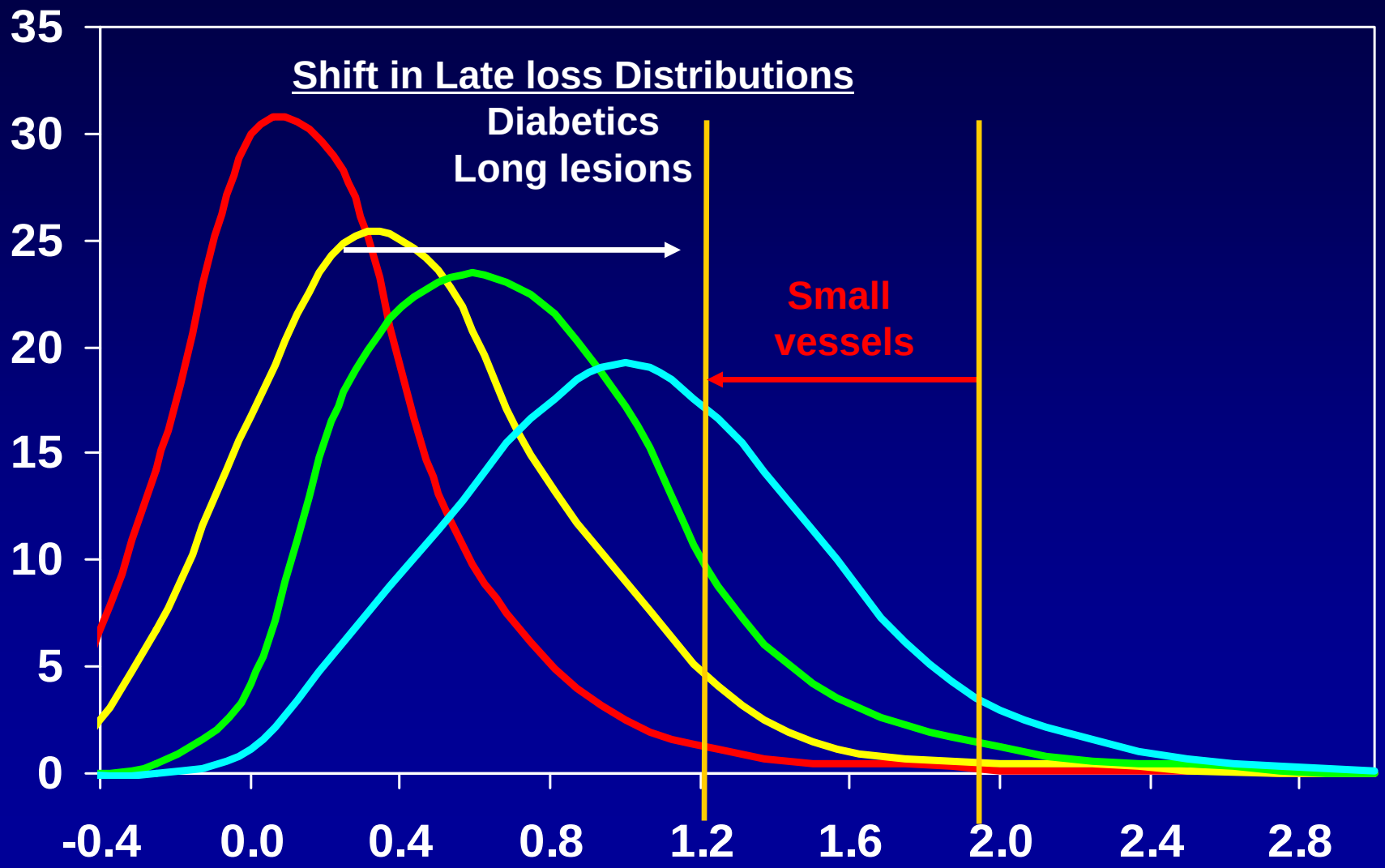
Density of Late Loss



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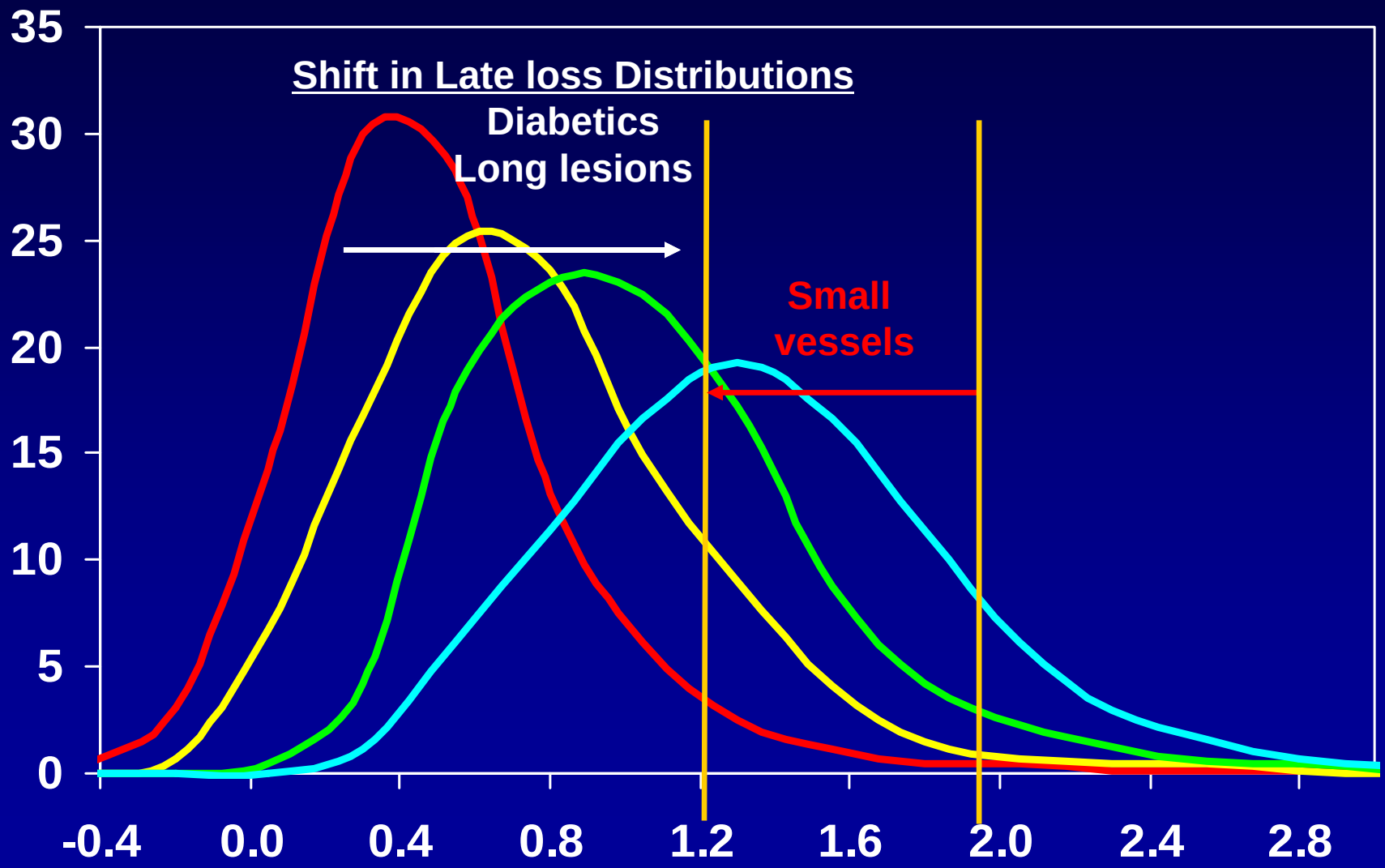
Late Loss and TLR

Effect of High Risk Characteristics



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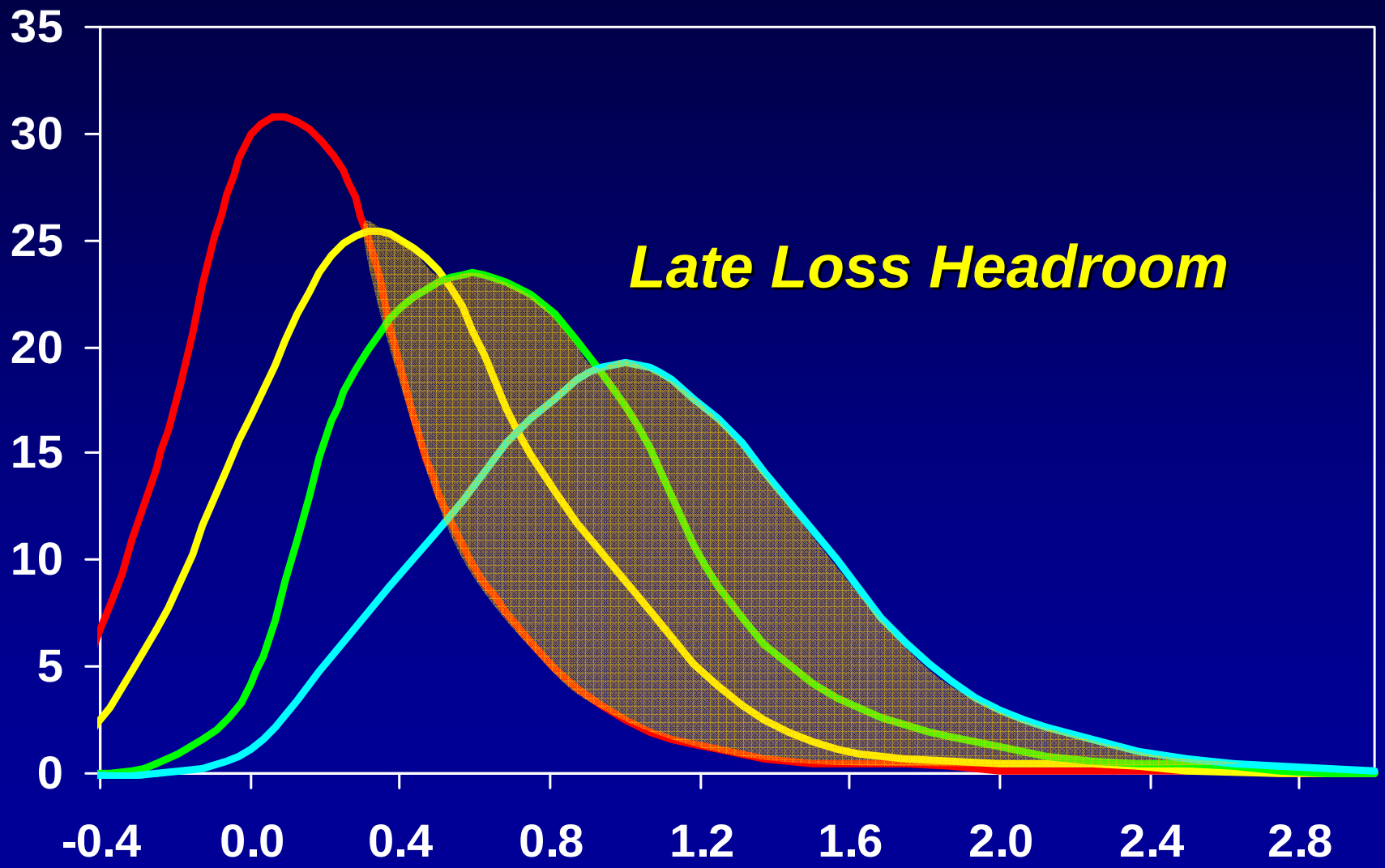
Late Loss Headroom

- Late Loss headroom is the space of extra late loss available for high risk restenosis case-mix cohorts
  - Headroom highest for low in-stent late loss stent systems

Late Loss Headroom



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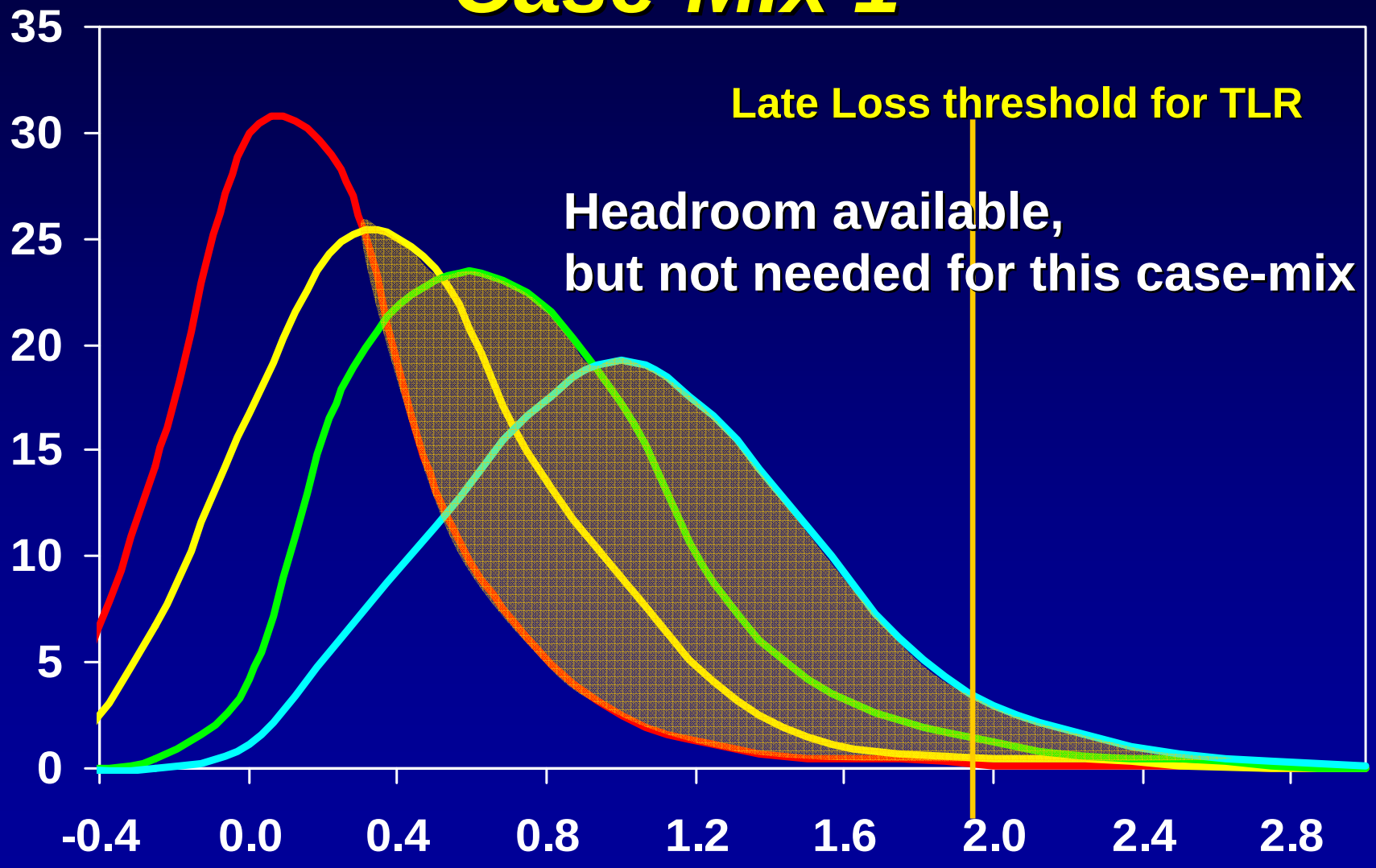
Late Loss Headroom

Case-Mix 1



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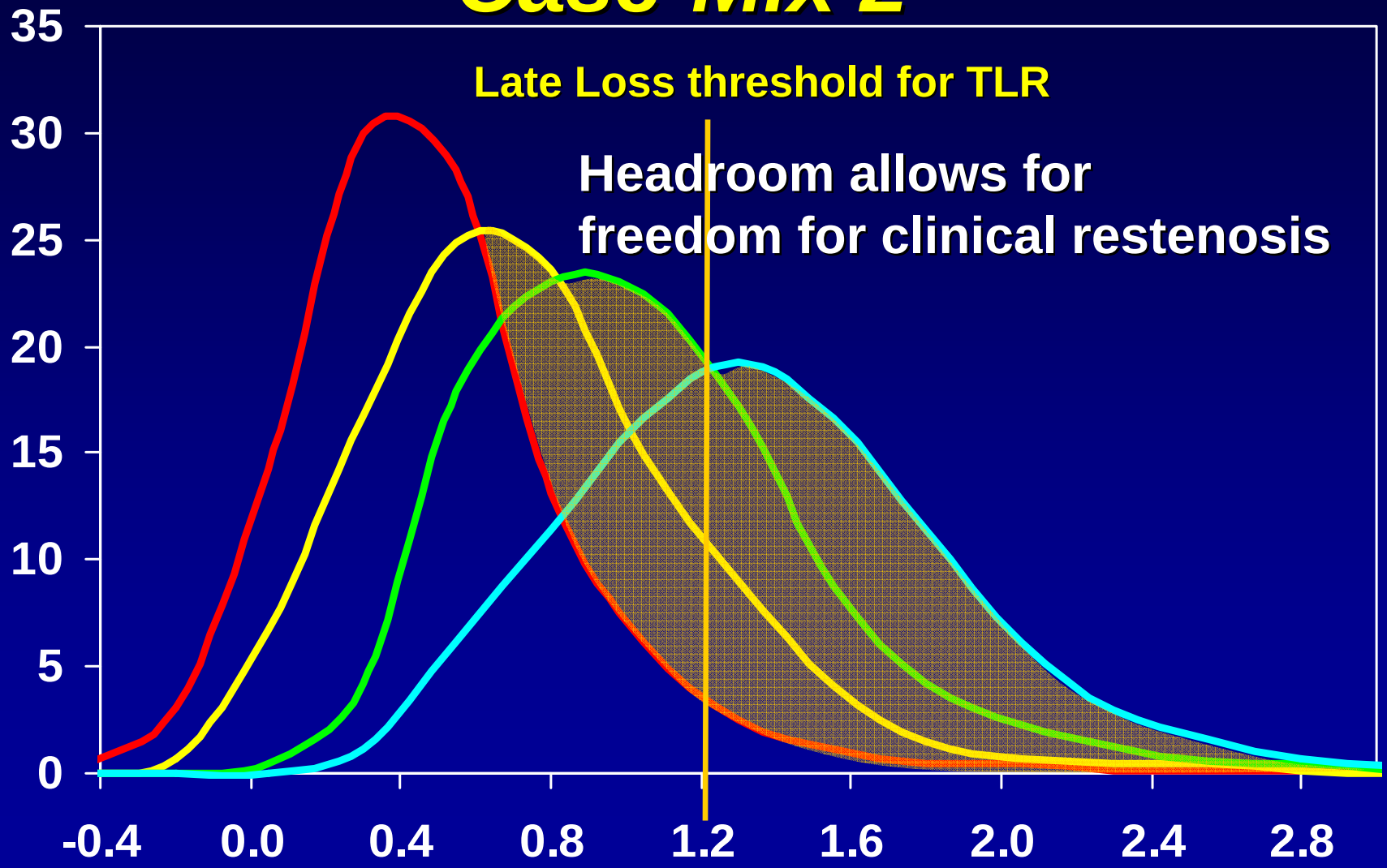
Late Loss Headroom

Case-Mix 2



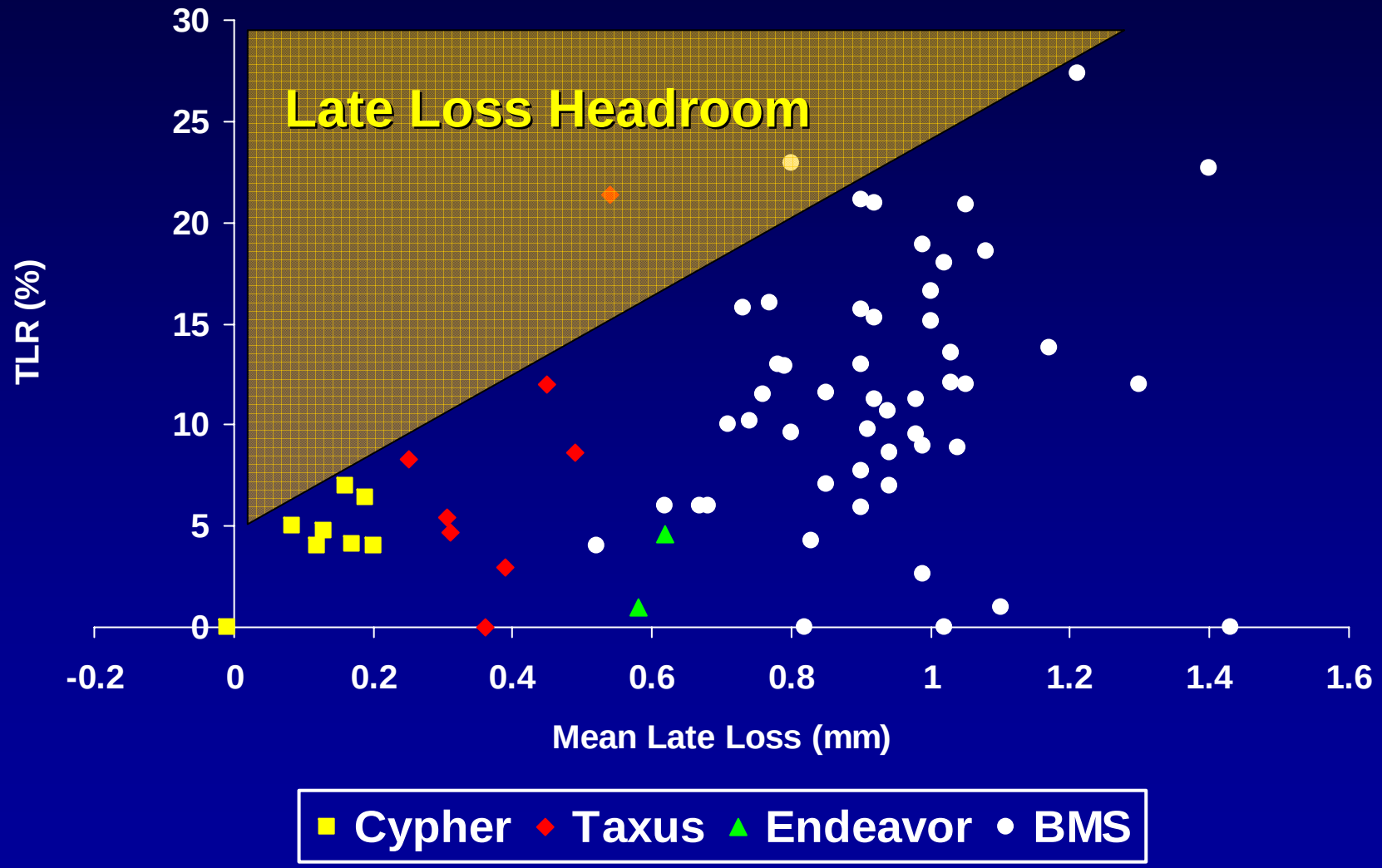
Mauri L, Kuntz R submitted for publication

Late Loss Headroom

- Late Loss headroom is the space of extra late loss available for high risk restenosis case-mix cohorts
  - Headroom highest for low in-stent late loss stent systems
- For low Late Loss stent systems, the headroom concept reduces the chance of high TLR over the wide range of case-mix risk
  - ***Evident in real data from clinical trials***

In-Stent Late Loss and TLR

Late Loss Headroom



L Mauri, J Orav, R Kuntz, submitted

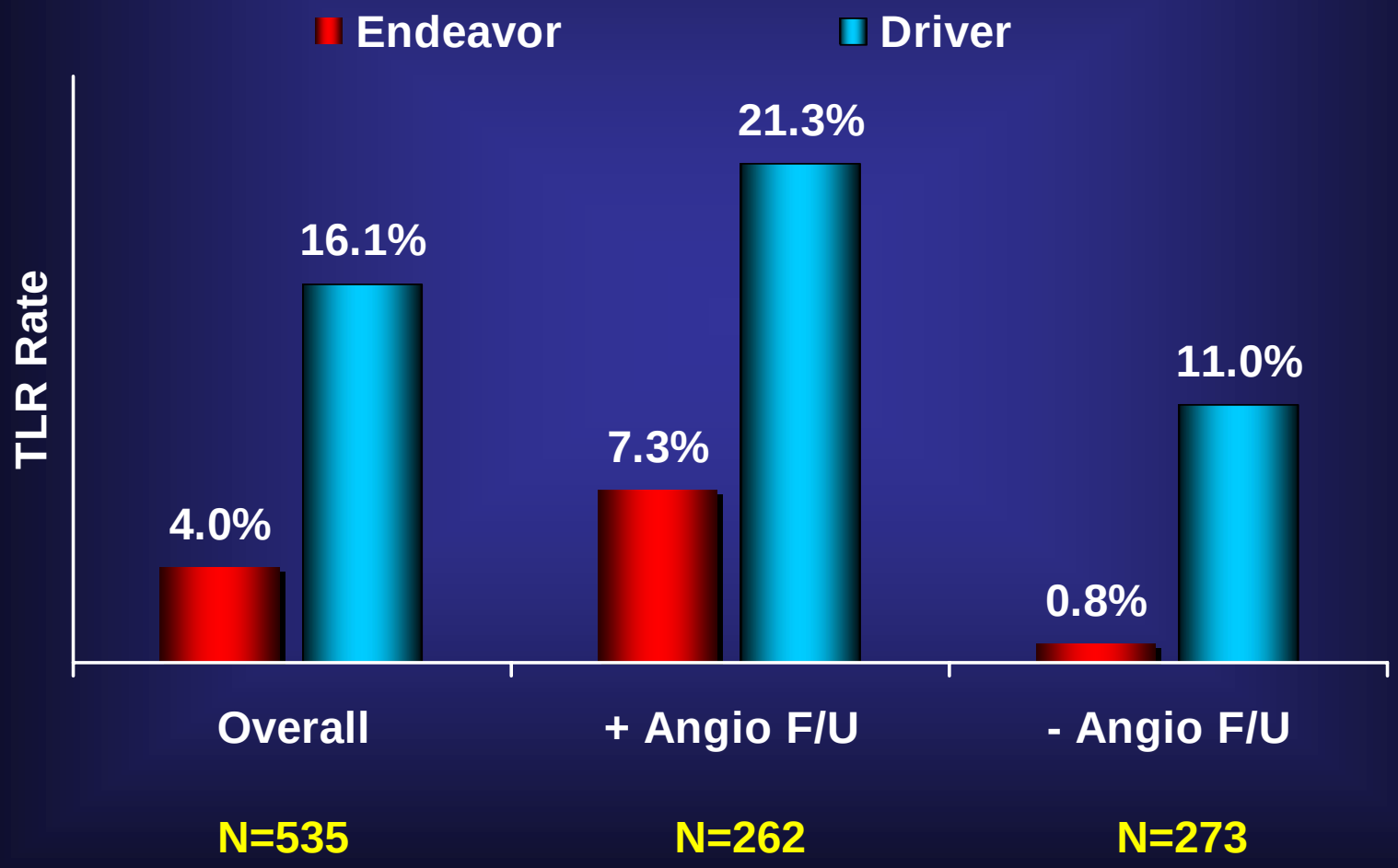
Clinical Results to 9 months

	Endeavor N = 582	Control N = 585	P value
Composite MACE (%)	7.4	14.7	<0.0001
Death	1.2	0.5	ns
Q-Wave MI	0.3	0.9	ns
Non Q-Wave MI	2.4	3.1	ns
CABG	0.0	0.0	ns
TLR	4.6	12.1	<0.0001
CABG	0.3	0.5	ns
PCI	4.3	11.6	<0.0001
TVR (%)	5.7	12.8	<0.0001
TVF (%) (Primary endpoint)	8.1	15.4	<0.0005

Endeavor II

TLR by Angiographic Follow-up

LAD Subset Analysis



ACC Late Breaking Trials, 6 March 2005

Drug Eluting Stent
Late Stent Thrombosis

- EP McFadden, E Stabile, E Regar, et. al. Research Letter, *Lancet* 2004: 364:1519
  - 4 cases of angiographically documented late stent thrombosis, accompanied by acute MI
    - SES (335, 375 days)
    - PES (343, 442 days)
  - All cases occurred soon after clopidogrel cessation

Paclitaxel Stent Thrombosis

Bavry et al, *J Am Coll Cardiol* 2005

- Meta-anlysis of 8 PES/BMS trials

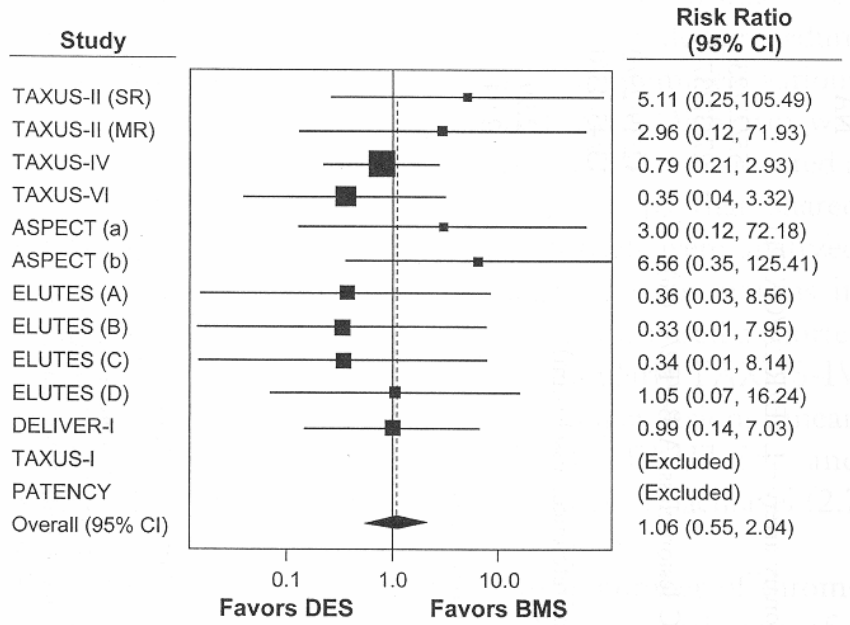


Figure 1. In trials with varying doses of paclitaxel, a = 1.3, b = 3.1, A = 0.2, B = 0.7, C = 1.4, and D = 2.7 μg paclitaxel/mm^2 of stent. BMS = bare-metal stent; CI = confidence interval; DES = drug-eluting stent; MR = moderate-release; SR = slow-release.

PES, SES, and BMS Thrombosis

Moreno et al, *J Am Coll Cardiol* 2005

10 RCT DES studies of 5030 patients pooled

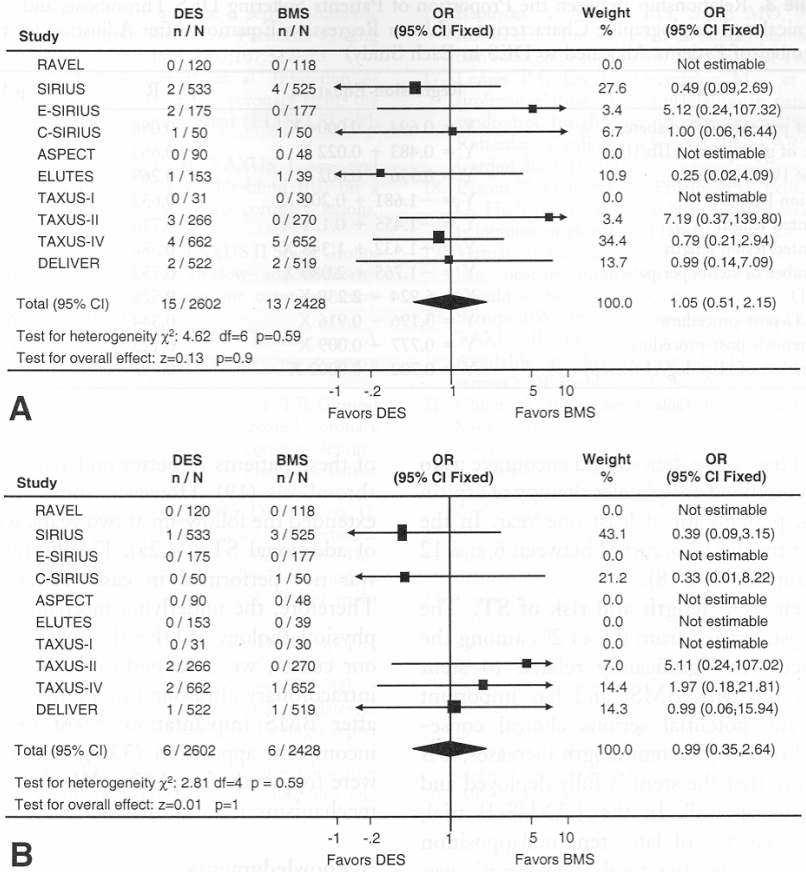
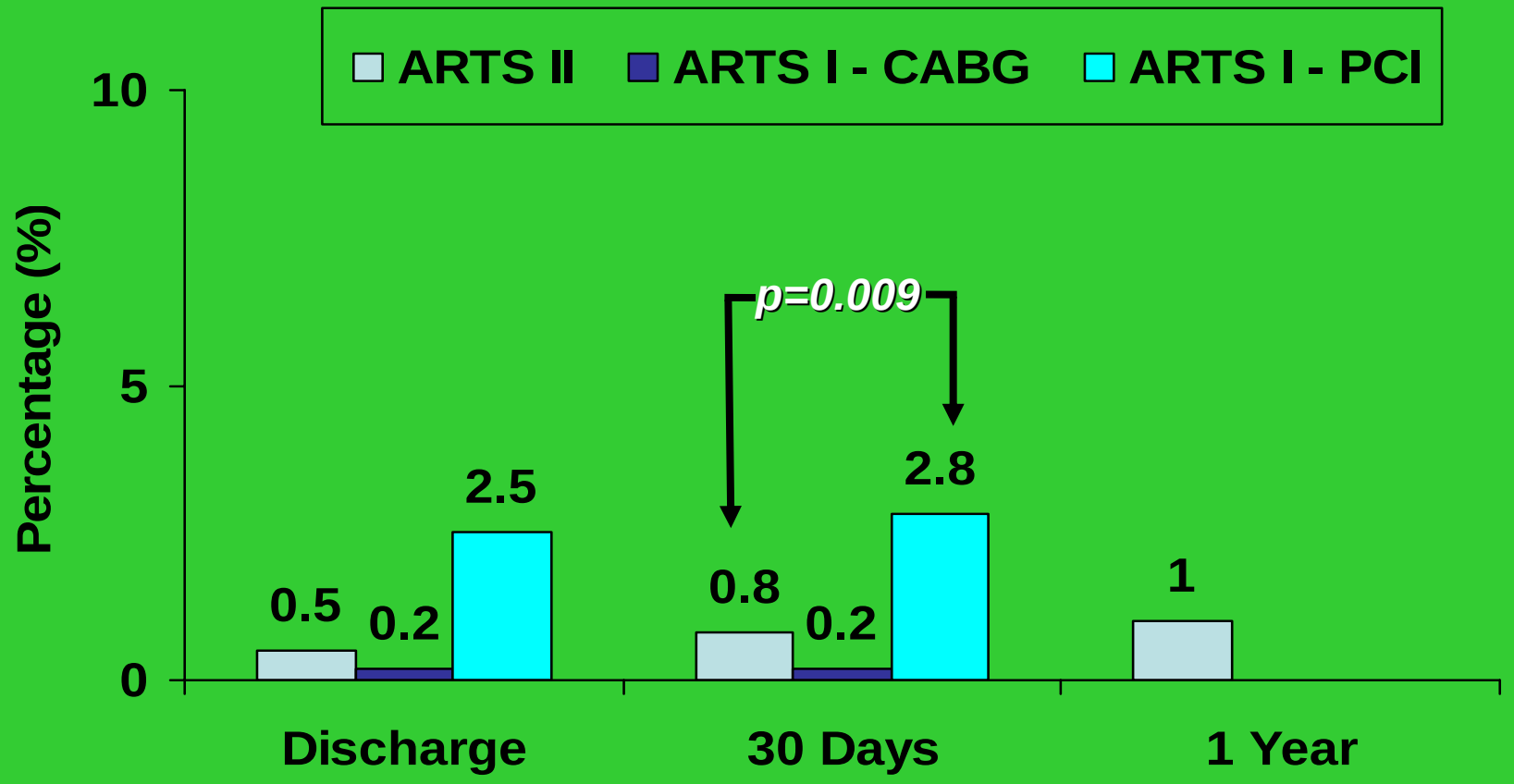


Figure 1. (A) Comparison between the rate of stent thrombosis in patients allocated to drug-eluting stents (DES) or bare-metal stents (BMS) in the randomized studies and in the pooled population. **(B)** Comparison between the rate of late stent thrombosis in patients allocated to DES or BMS in the randomized studies and in the pooled population. CI = confidence interval; OR = odds ratio.

ARTS II

Angiographic Occlusions

*** Definition of thrombotic occlusion: Angiographically proven occlusion (TIMI 0 or 1) or flow limiting thrombus (TIMI 1 or 2)**



ARTS II up to 1 year:
5 TLR (1 Q wave MI, 4 with substantial cardiac enzyme release)

Safety Results

Stent Thrombosis	Endeavor N = 582	Driver N = 585	P value
In-hospital	0.3% (2)	0.3% (2)	
Discharge to 30 days	0.2% (1)	0.9% (5)*	
>30 – 270 days	0	0	
Total at 270 days	0.5% (3)	1.2% (7)	0.34

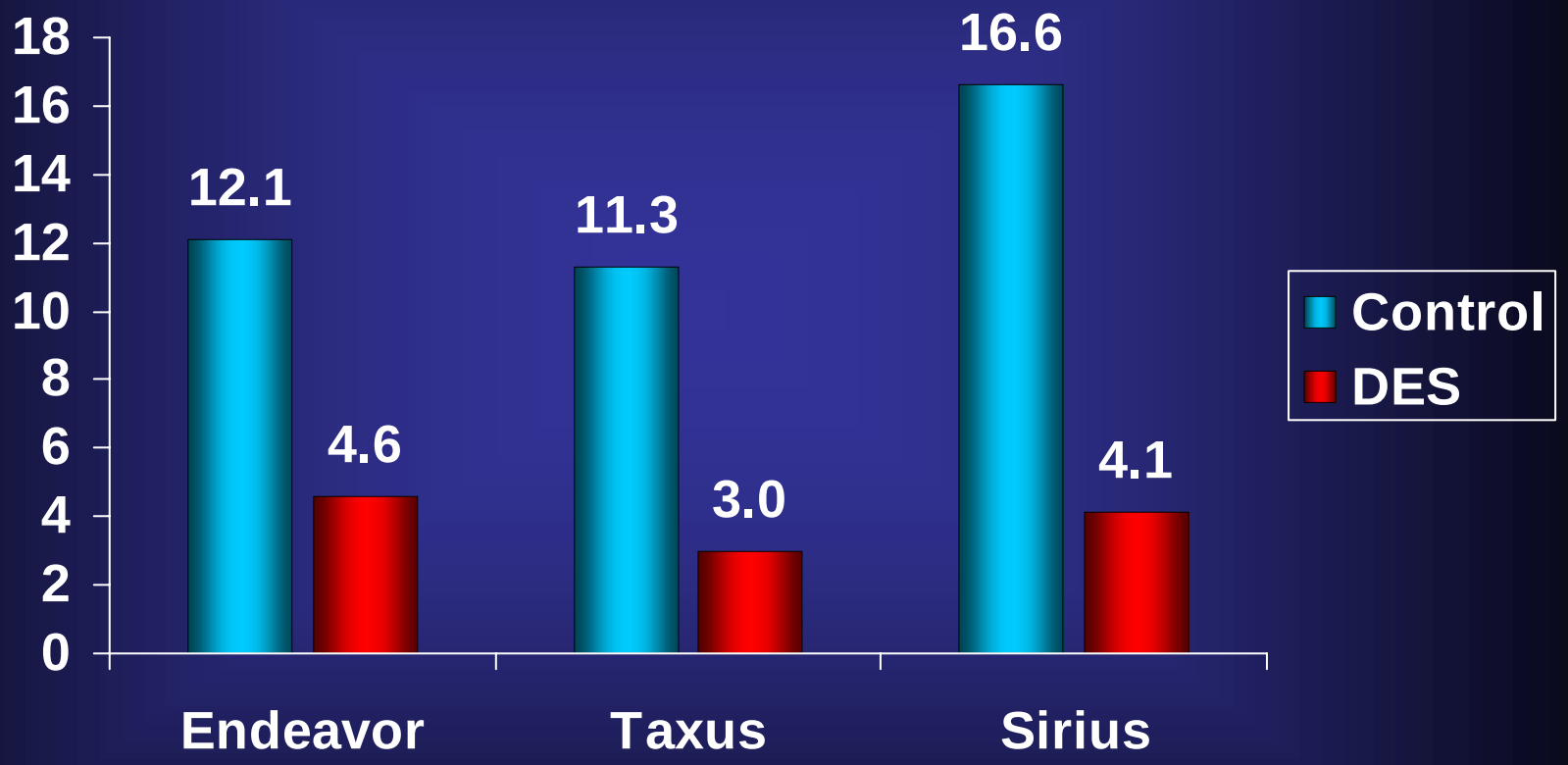
IVUS Results	Endeavor N = 100	Driver N = 83	P value
Late Acquired Stent Malapposition	0%	0%	ns
Late Aneurysm	0%	0%	ns

Stent thrombosis defined as angiographic thrombus or subacute closure in the stented vessel or any death not attributed to a non-cardiac cause within the 1st 30 days

*3/6 post-discharge stent thrombosis cases occurred in Driver arm when Plavix was stopped prematurely

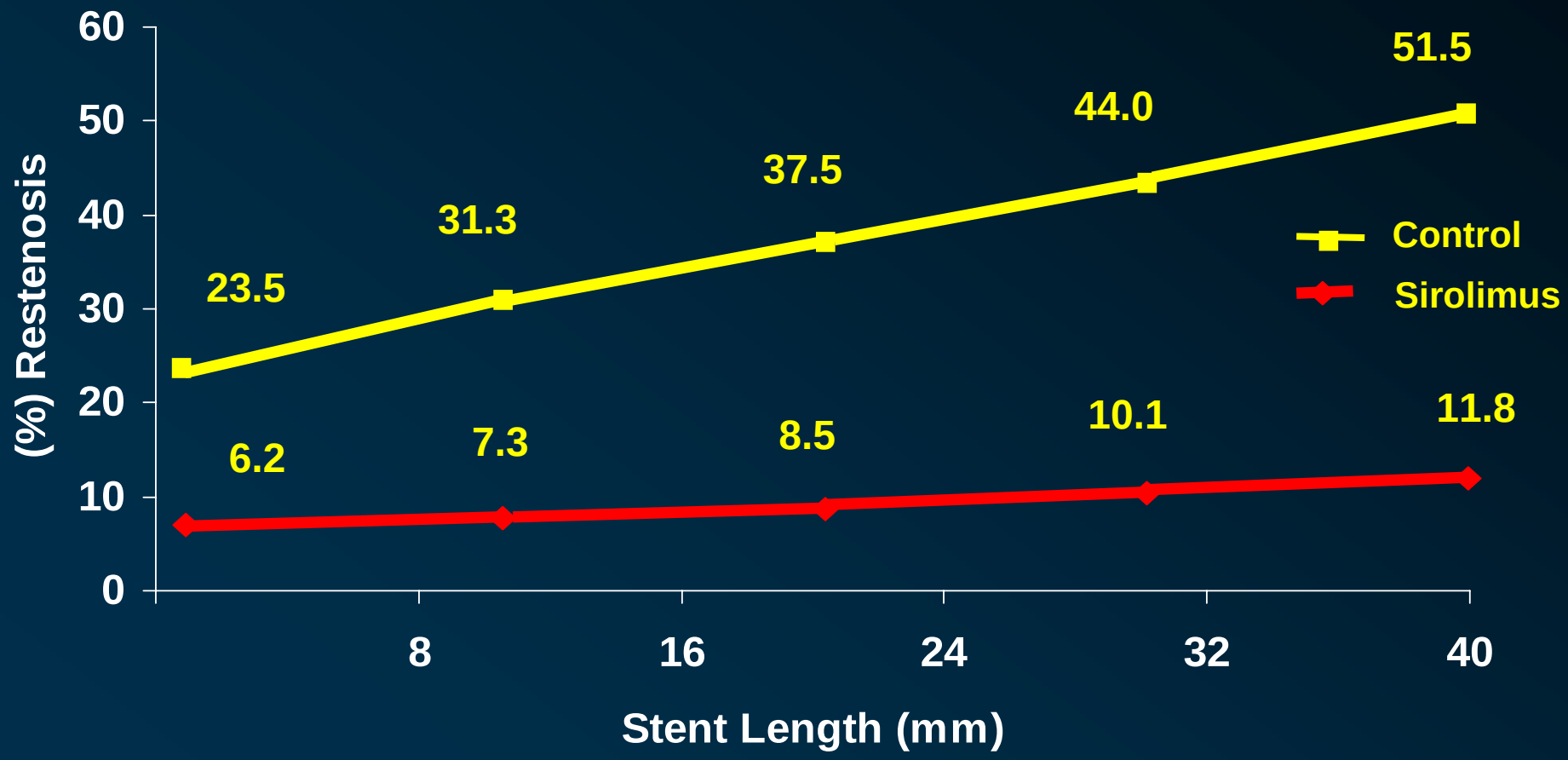
Pivotal Trial Comparisons

TLR to 9 Months



SIRIUS: Restenosis vs. Stent Length

In-Segment



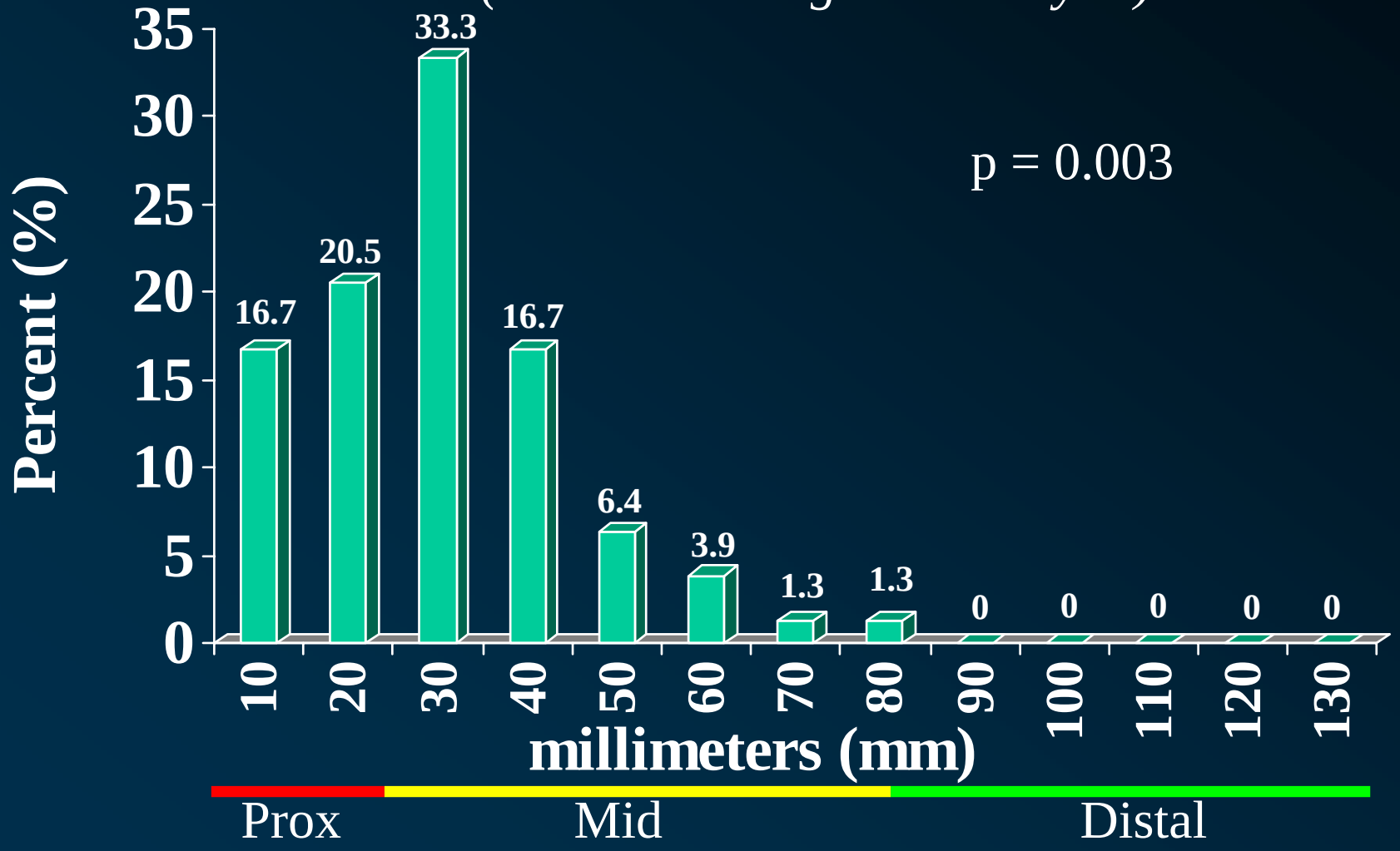
Now That We've Conquered Restenosis Can We Prevent Plaque Rupture?

The Stented Coronary Segement

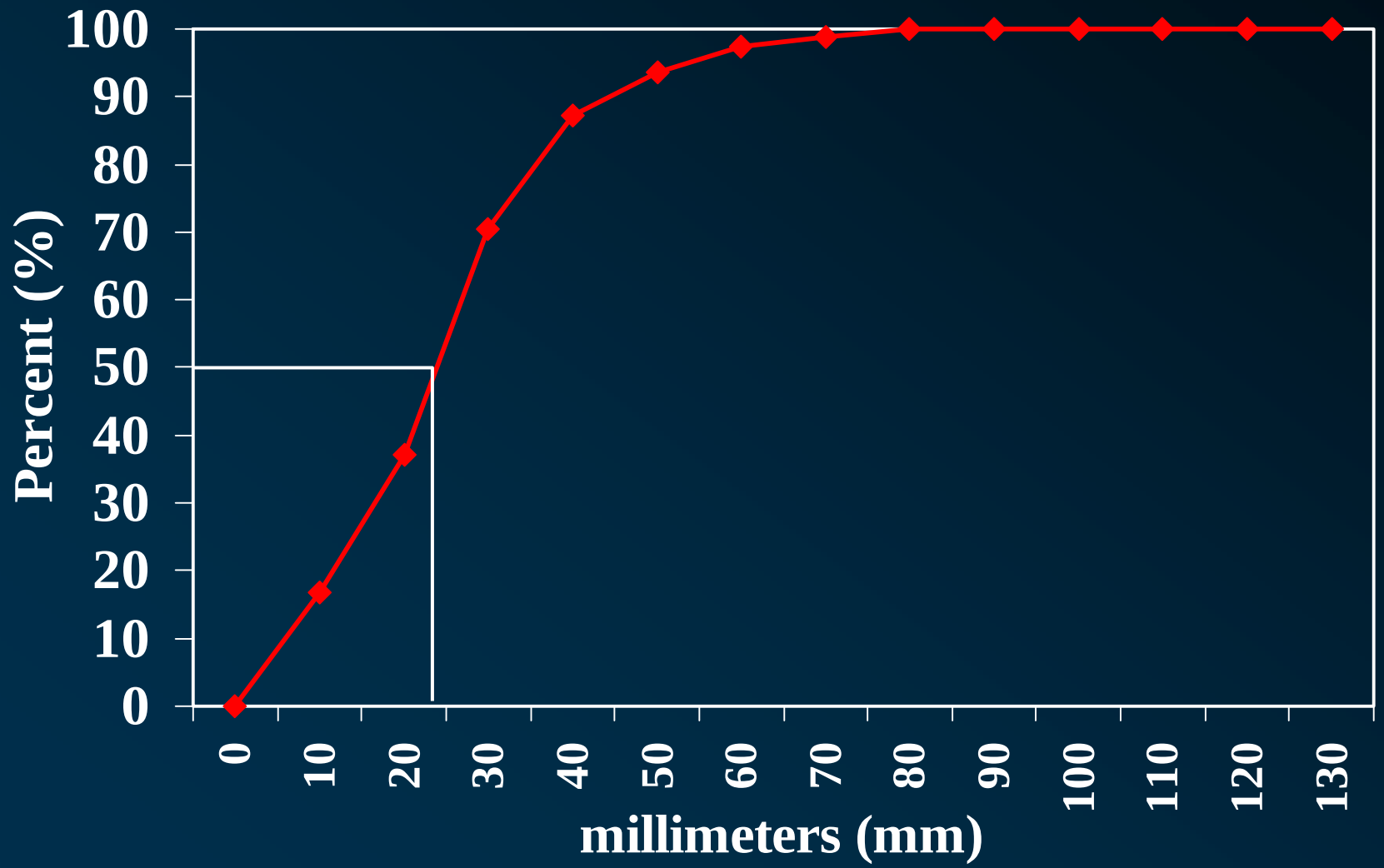
Low incidence of ACS in the segment <0.005 over 4 years

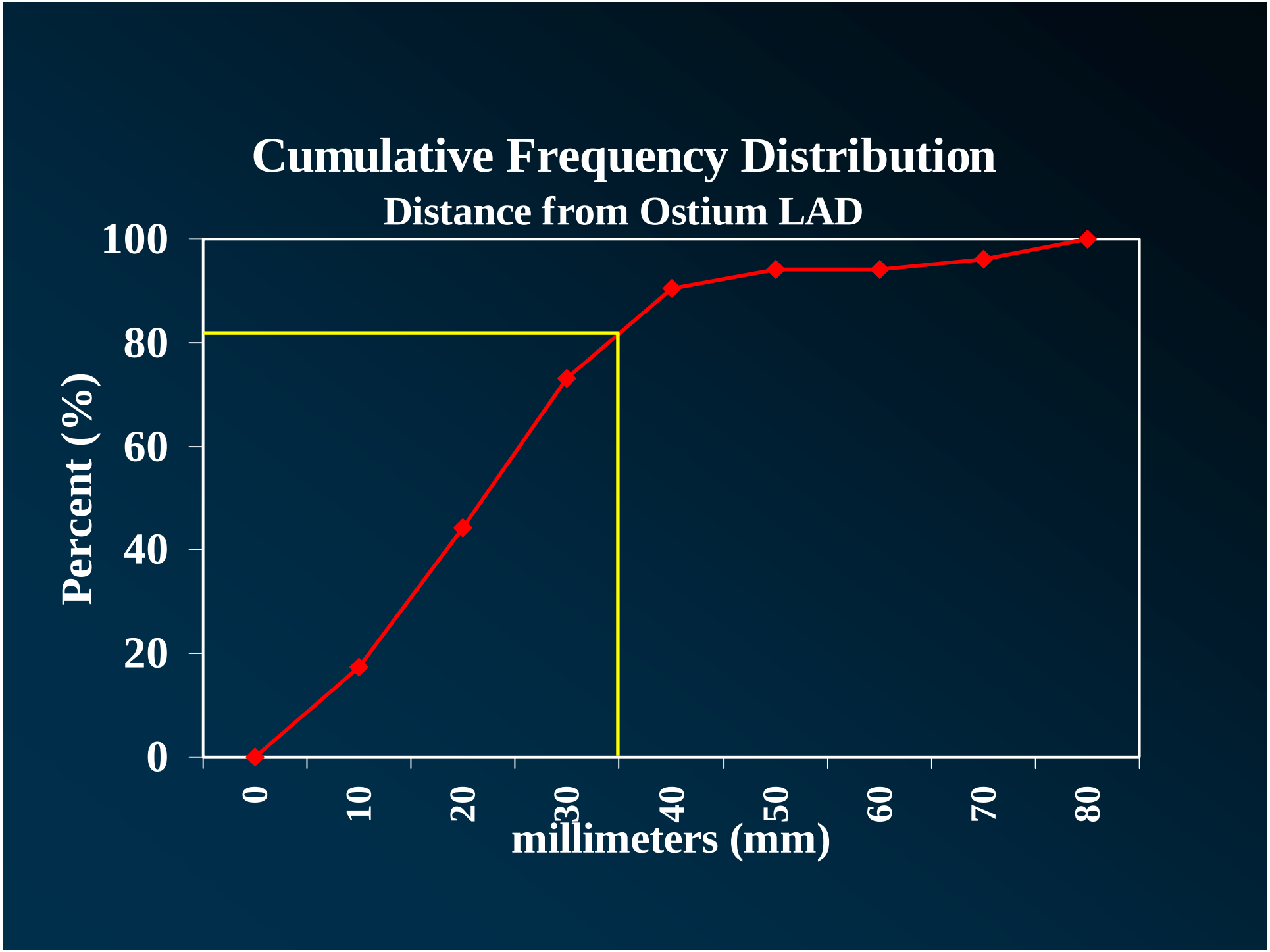
Can't grow atherosclerosis here!

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



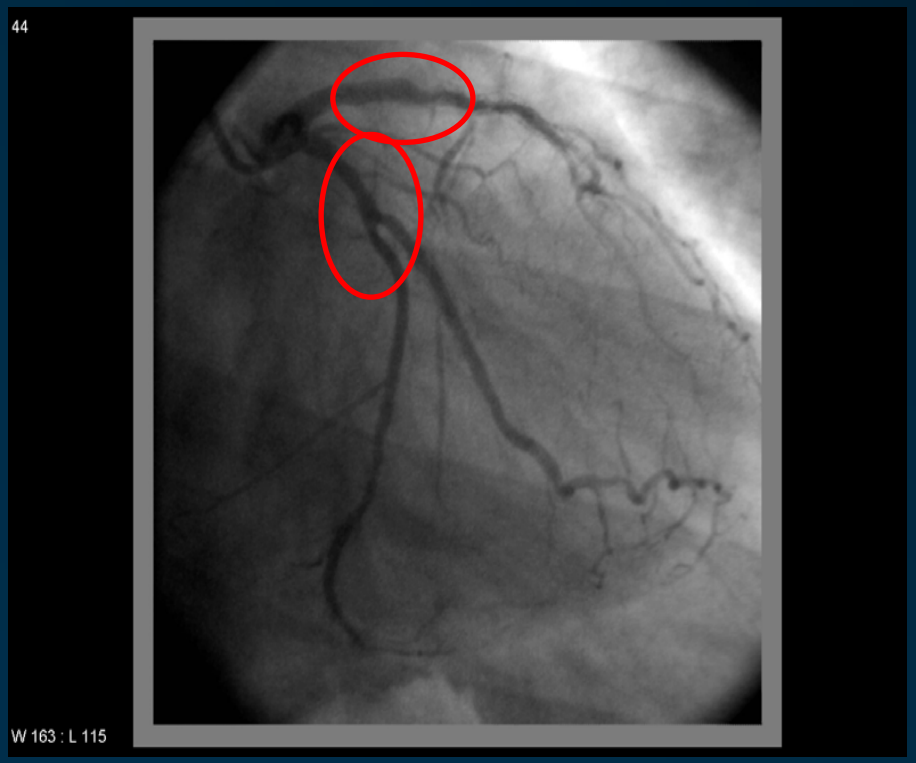
Cumulative Frequency Distribution Curve of Acute Coronary Occlusions by Distance from the Ostium Left Anterior Descending Artery

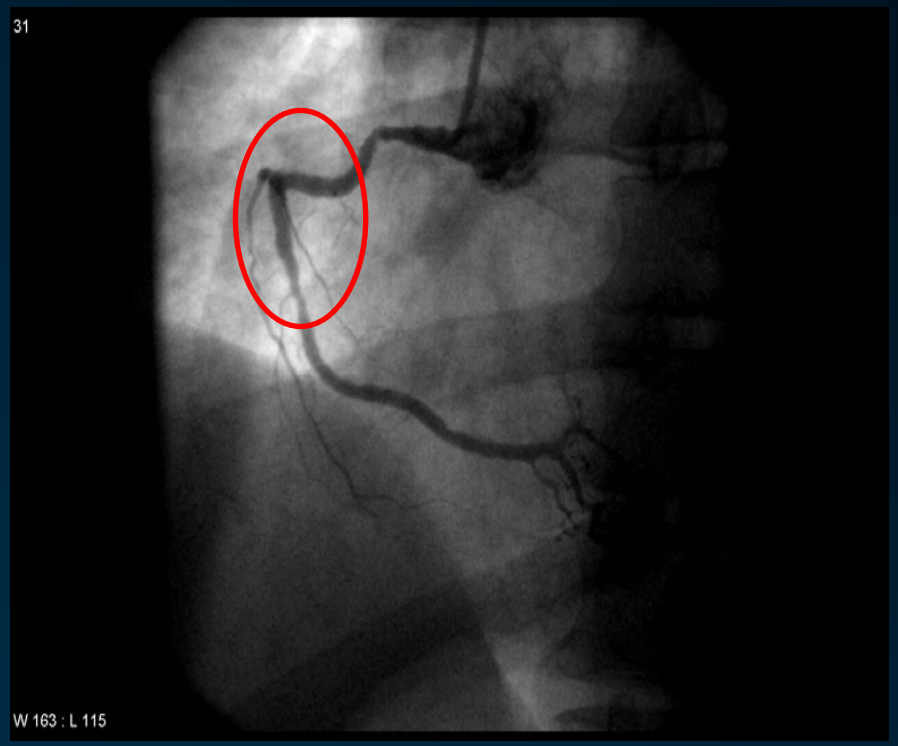



Cumulative Frequency Distribution
Distance from Ostium LAD
Percent (%)
100
80
60
40
20
0
0
10
20
30
40
50
60
70
80
millimeters (mm)

Vulnerable Hot Spots

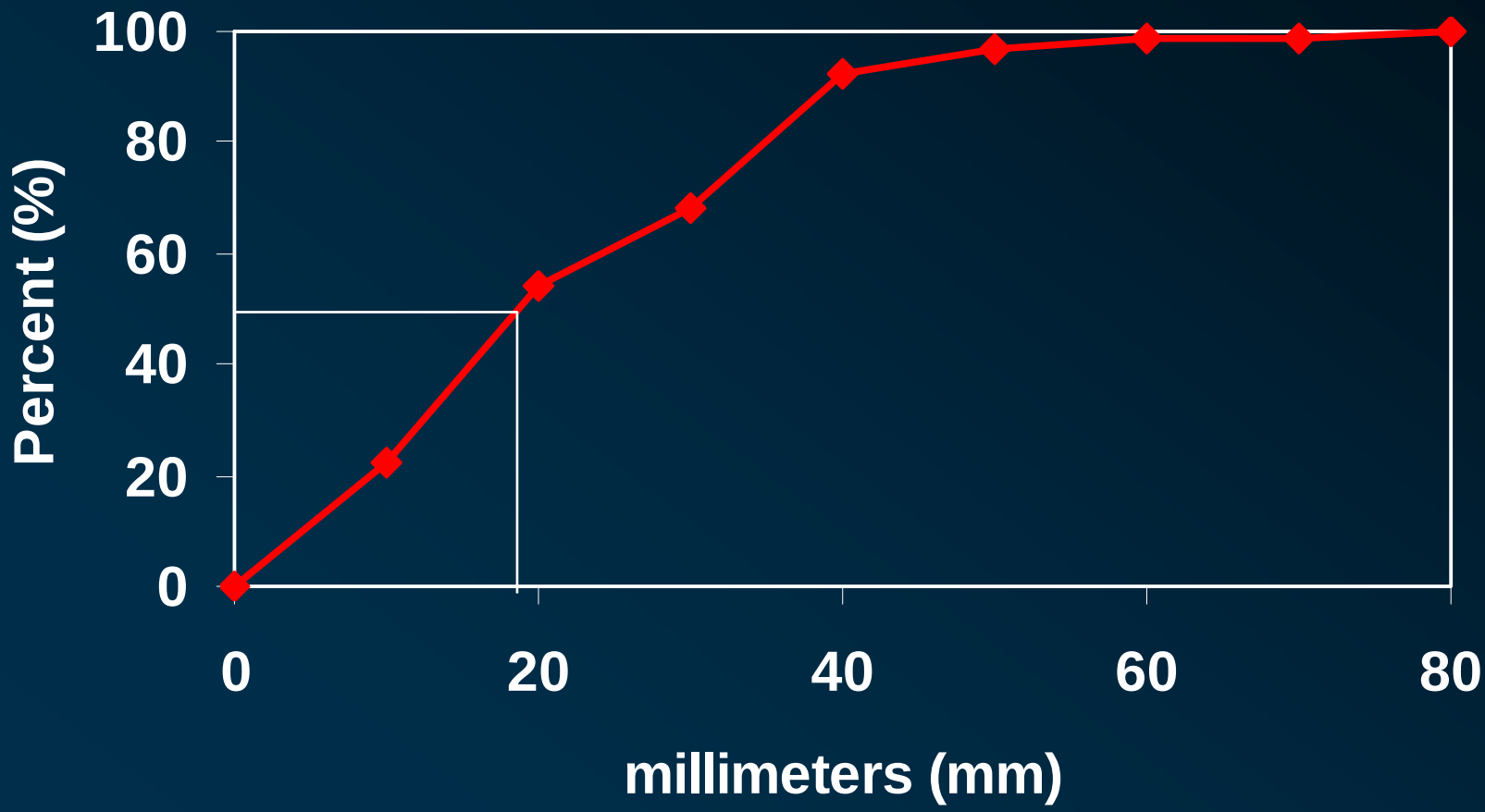
How About A Few DESs



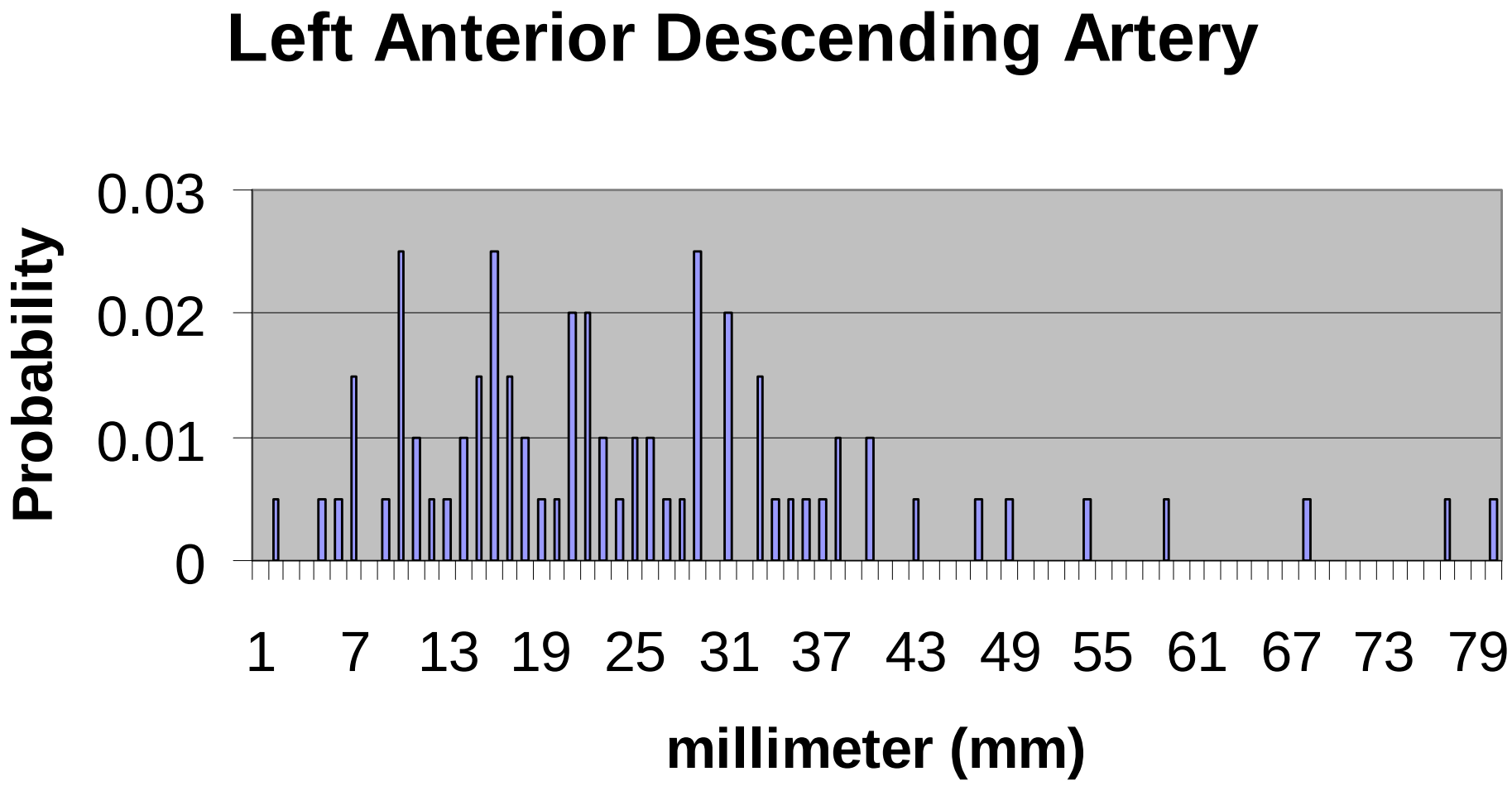


Cumulative Frequency Curve for LAD

Non-Q MI



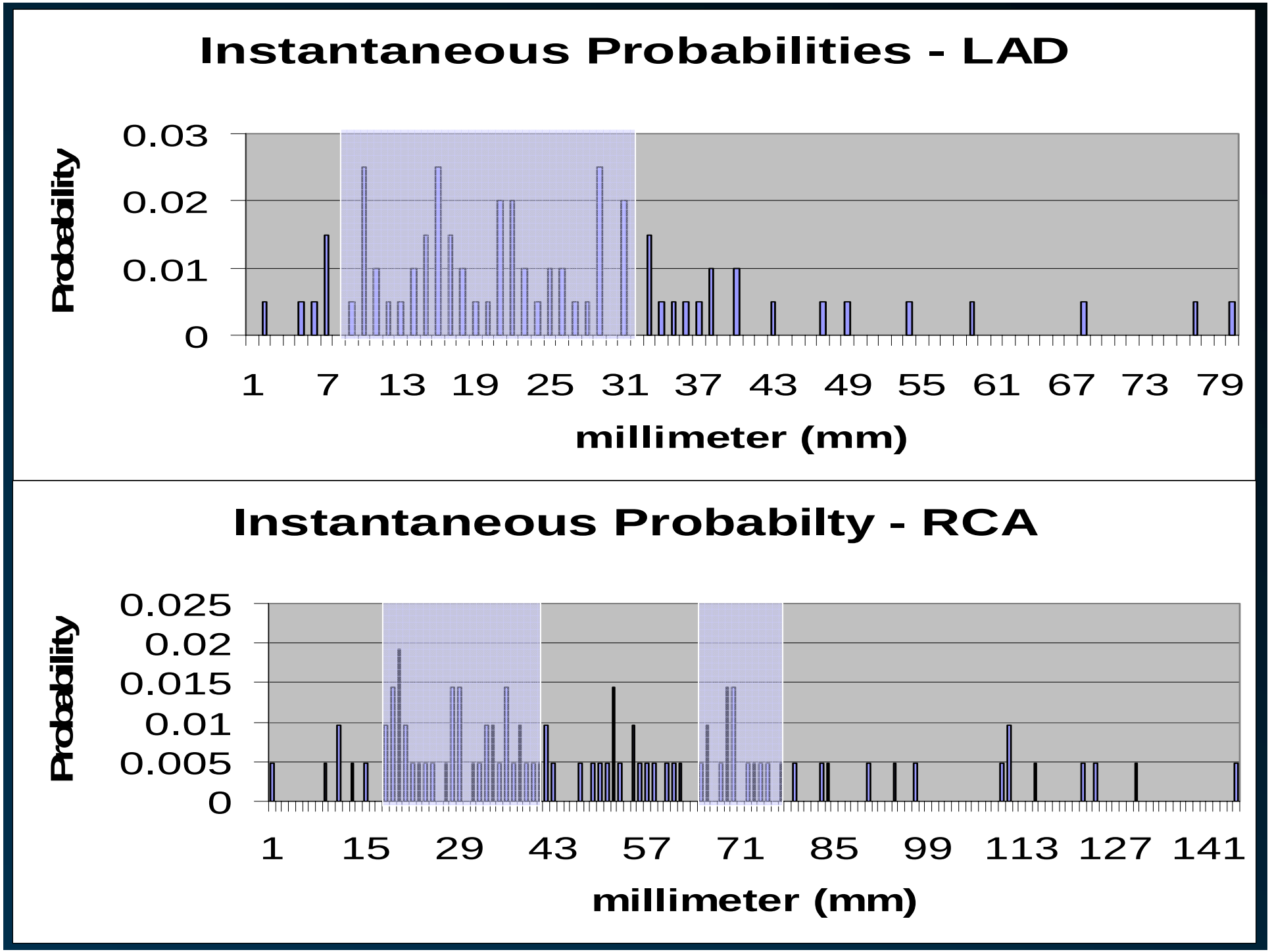
Results: Instantaneous Probabilities of Acute Coronary Occlusion

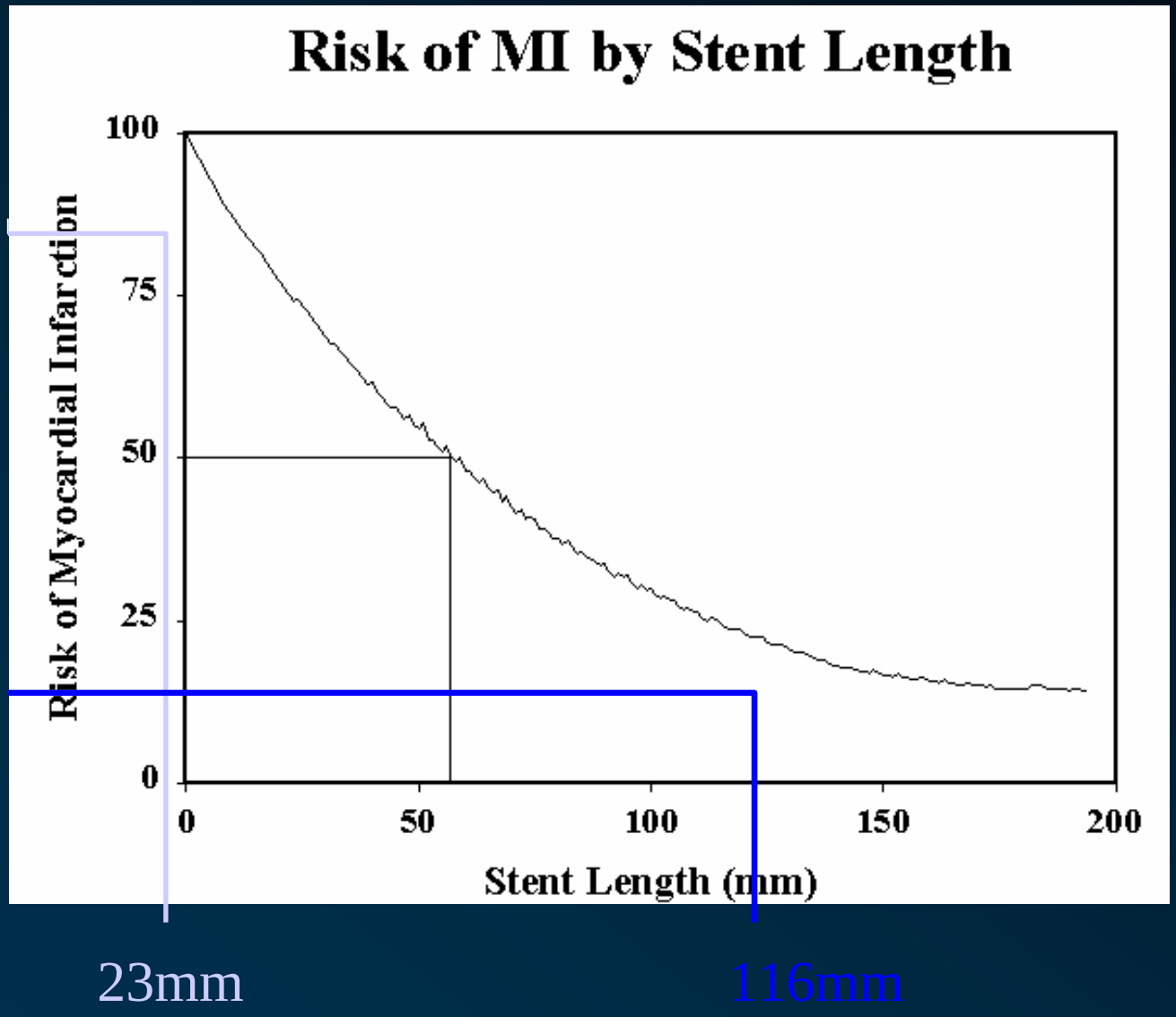


Simulation Optimum Combination

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
50
100
150
200
Stent Length (mm)
23mm
116mm

DES, Late Loss, Preventing MIs

- The introduction of DES has been a remarkable advancement for the Interventional Cardiology community and patients who suffer from coronary disease
  - Already three products have demonstraed breakthrough anti-results in the prevention of restenosis
- Late Loss “Head Room” is the extra space available for higher risk lesions to provide freedom from repeat revascularization
  - *Choice of stent will incorporate patient risk of restenosis and ease-of-use of the stent*

DES, Late Loss, Preventing MIs

- All three DES products appear at lest as safe, in terms of stent thrombosis, as bare metal stents
- The use of stents to prevent MIs may be the first step in prophylactic therapy, but medical therapy must be optimized
  - *The use of geographic spatial maps and imaging techniques will guide placement*
- ***It's good to be an Interventional Cardiologist at this time!***