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

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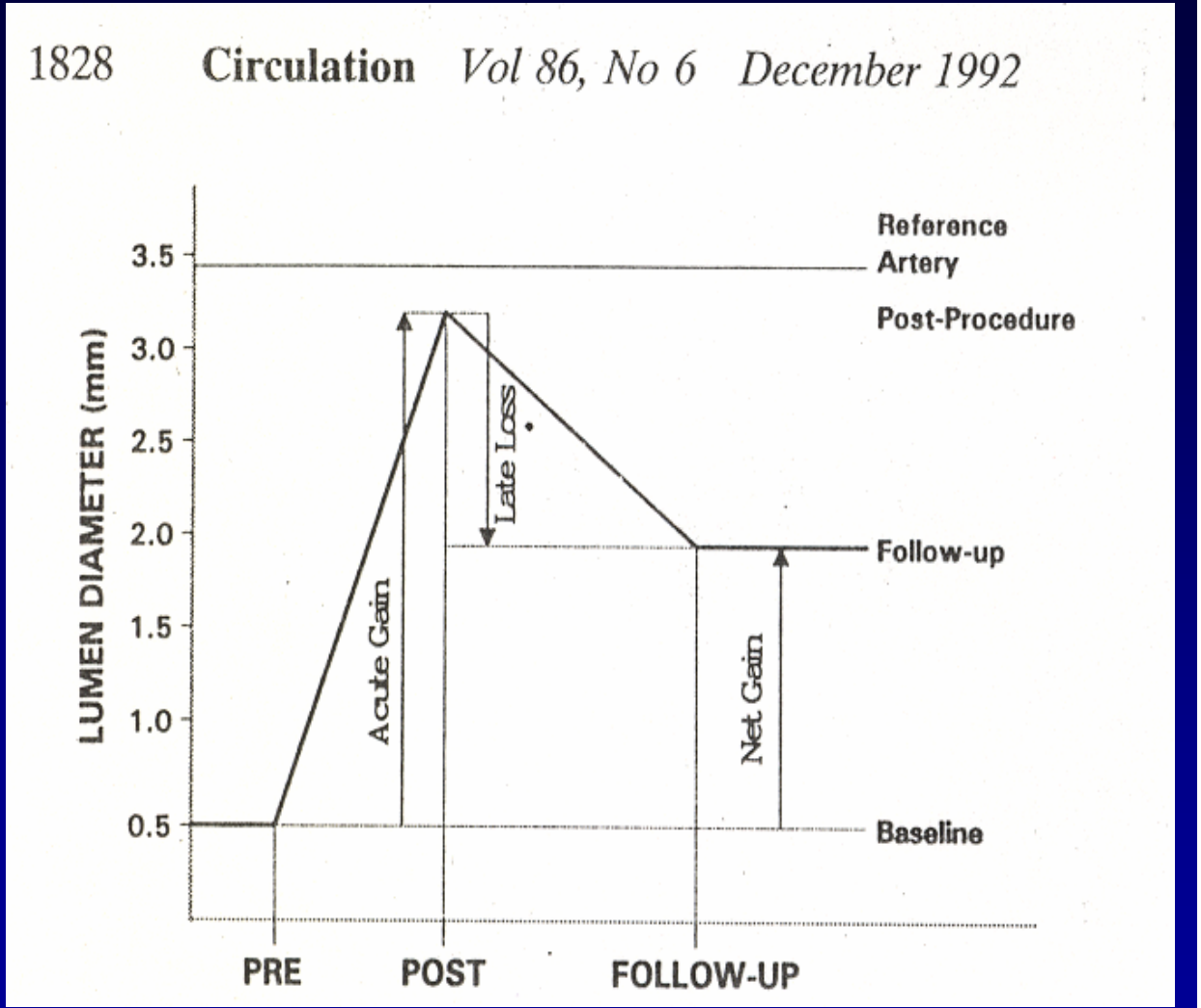
Late Loss and DES

- Brief history of Late Loss
- Restenosis Endpoints
- Late Loss and Clinical Restenosis
- Late Loss Headroom
- Real Data on Late Loss and Clinical Restenosis
- Conclusion

New Restenosis Concepts

Acute Gain
Late Loss
Net Gain



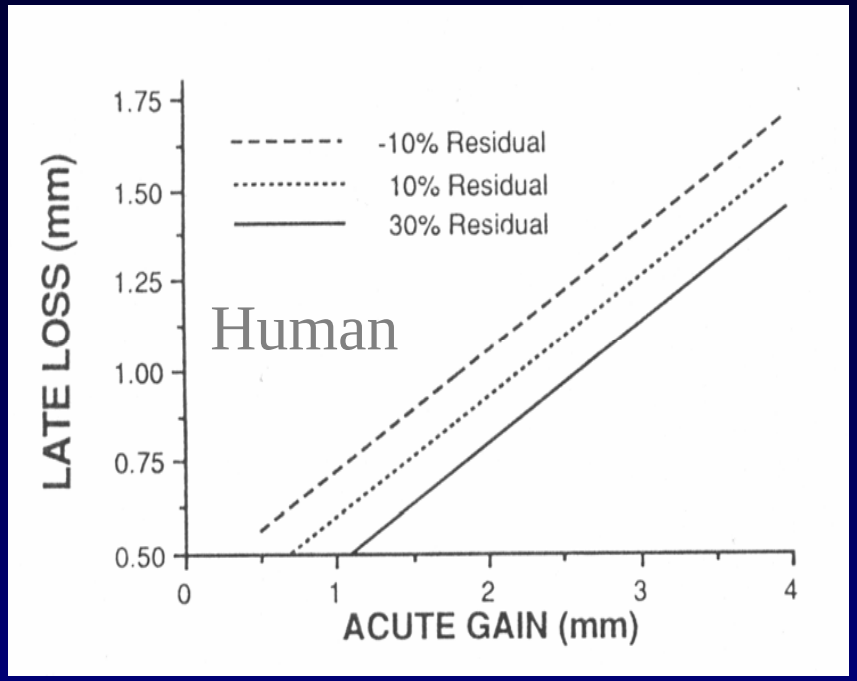
Kuntz, ...Baim
The importance of acute luminal diameter in determining restenosis After coronary atherectomy or stenting. *Circulation* 1992;1827-1835

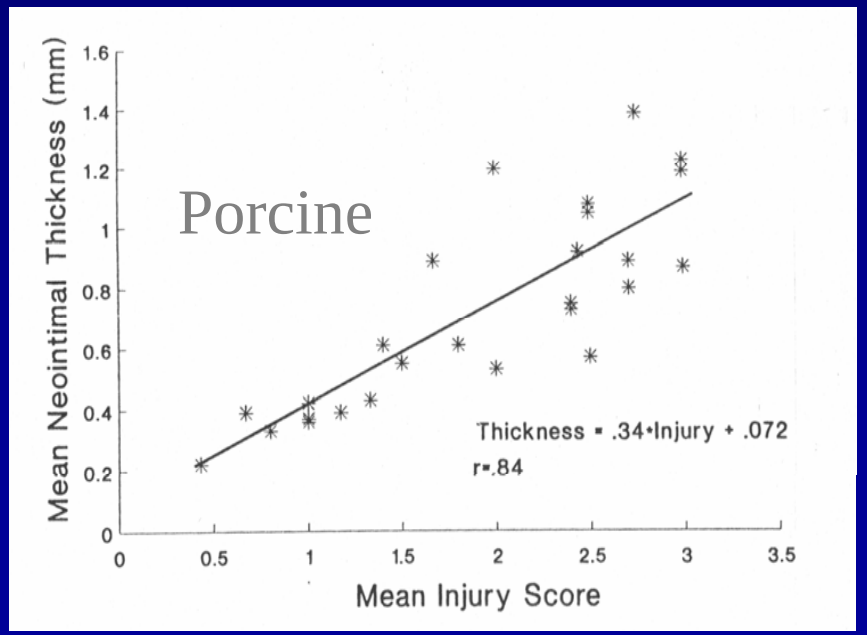
Human Proportional Injury Model

Late loss (neointimal surrogate) is proportional to acute gain (injury surrogate)

Loss Index:
Ratio of Loss-to-Gain

Kuntz, …Baim. Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy.
J Am Coll Cardiol 1993;21:15-25.





Late Loss

- Intuitive measure of coronary obstruction potential
  - Measured at the follow-up MLD
  - Best measurement of the principal physiological flow resistor
    - Flow is reduced by the ***4th order*** of reduction in the radius of the MLD
    - Not described by volume estimators
- It *is* the target of drug therapy
  - *That is, we aim to reduce maximum late loss!*

FIM Sirolimus: Angiographic Results

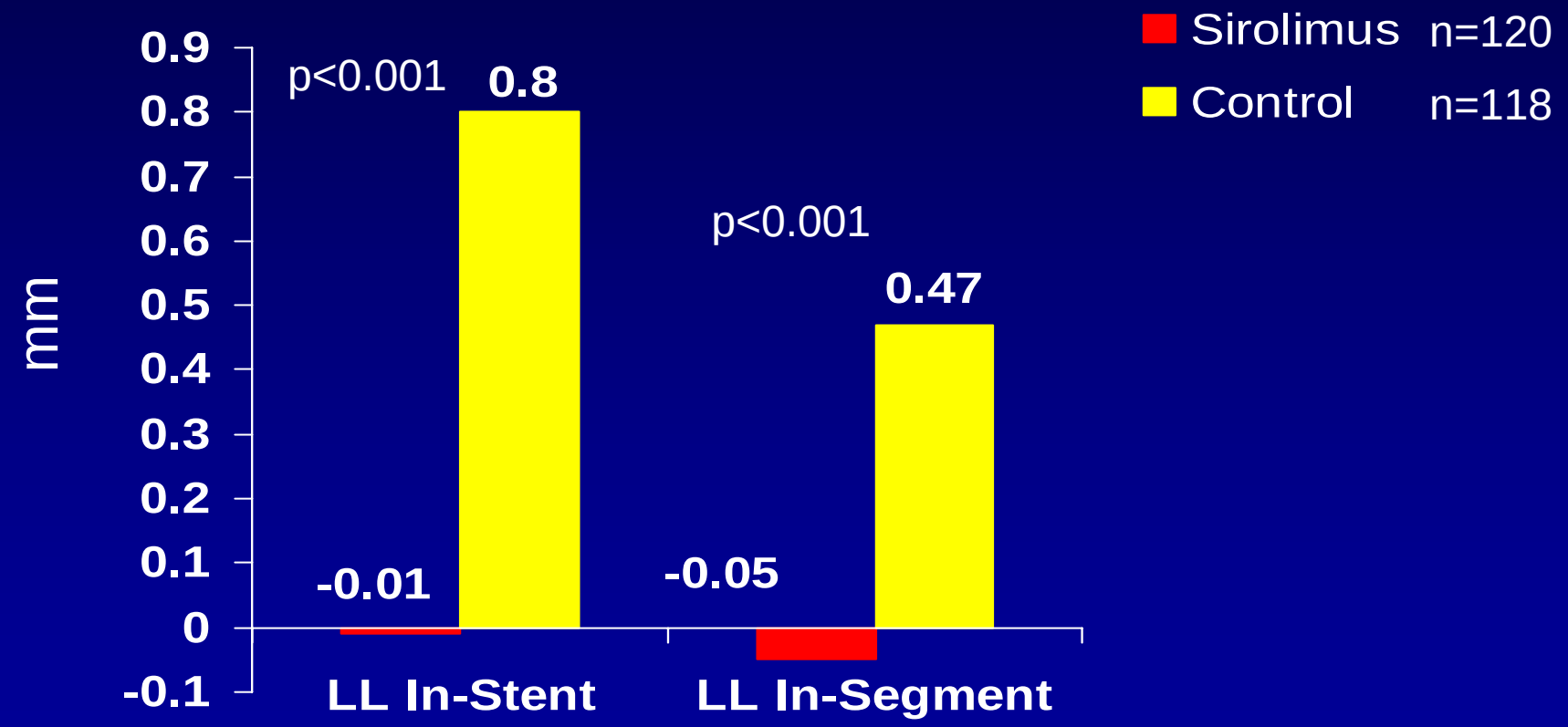
Is This Going to be a Good Stent?

What is the In-stent Late Loss?

Late Loss = 0.11 mm

In-lesion MLD

RAVEL: 6-Month QCA (n=238)
Late Loss

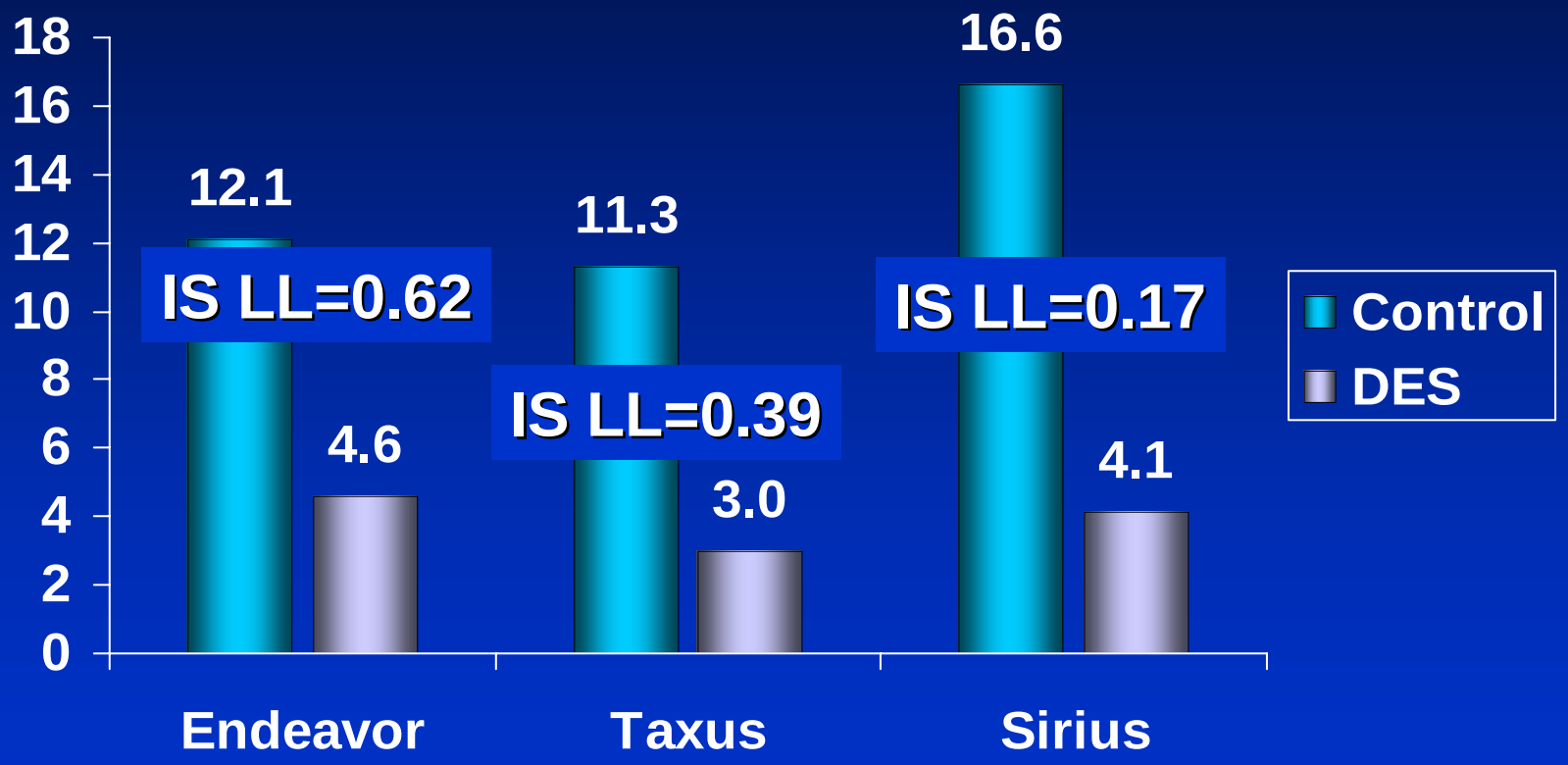


SIRIUS: Clinical Events All Events (To 9 Months)

Events	Sirolimus % n=533	Control % n=525	P-value
Death	0.9 (5)	0.6 (3)	0.726
MI (all)	2.8 (15)	3.2 (17)	0.723
Q-wave	0.8 (4)	0.4 (2)	0.687
Non Q-wave	2.1 (11)	2.9 (15)	0.433
TLR (clinically driven)	**4.1 (22)**	**16.6 (87)**	**<0.001**
TVR (non-TL)	**3.2 (17)**	**4.8 (25)**	**0.210**
MACE	**7.1 (38)**	**18.9 (99)**	**<0.001**
TVF (1st Endpoint)	**8.6 (46)**	**21.0 (110)**	**<0.001**

Pivotal DES Trial Comparisons

TLR to 9 Months



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Restenosis Endponts

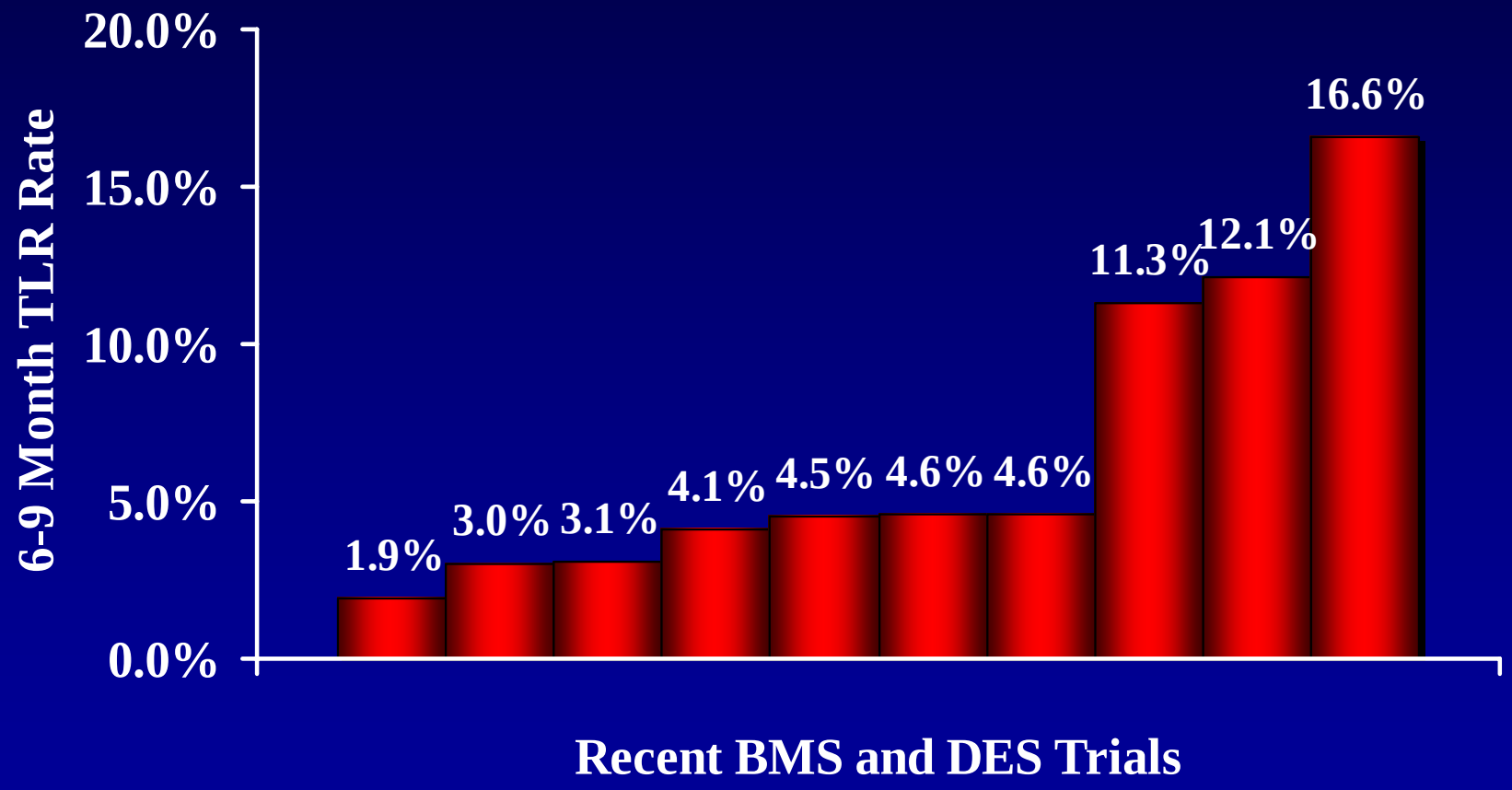
- **Target Lesion Revascularization**
  - Best endpoint in a randomized Trial
  - Needs large sample size for stable Estimation
  - High level of influence by case-mix confounders renders it almost meaningless in comparison across trials.
- **Late Loss (In-stent version only)**
  - Stable and efficient 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

Risk and Restenosis

Some Contemporary Clinical Restenosis Rates



Mauri L, Kuntz R submitted for publication

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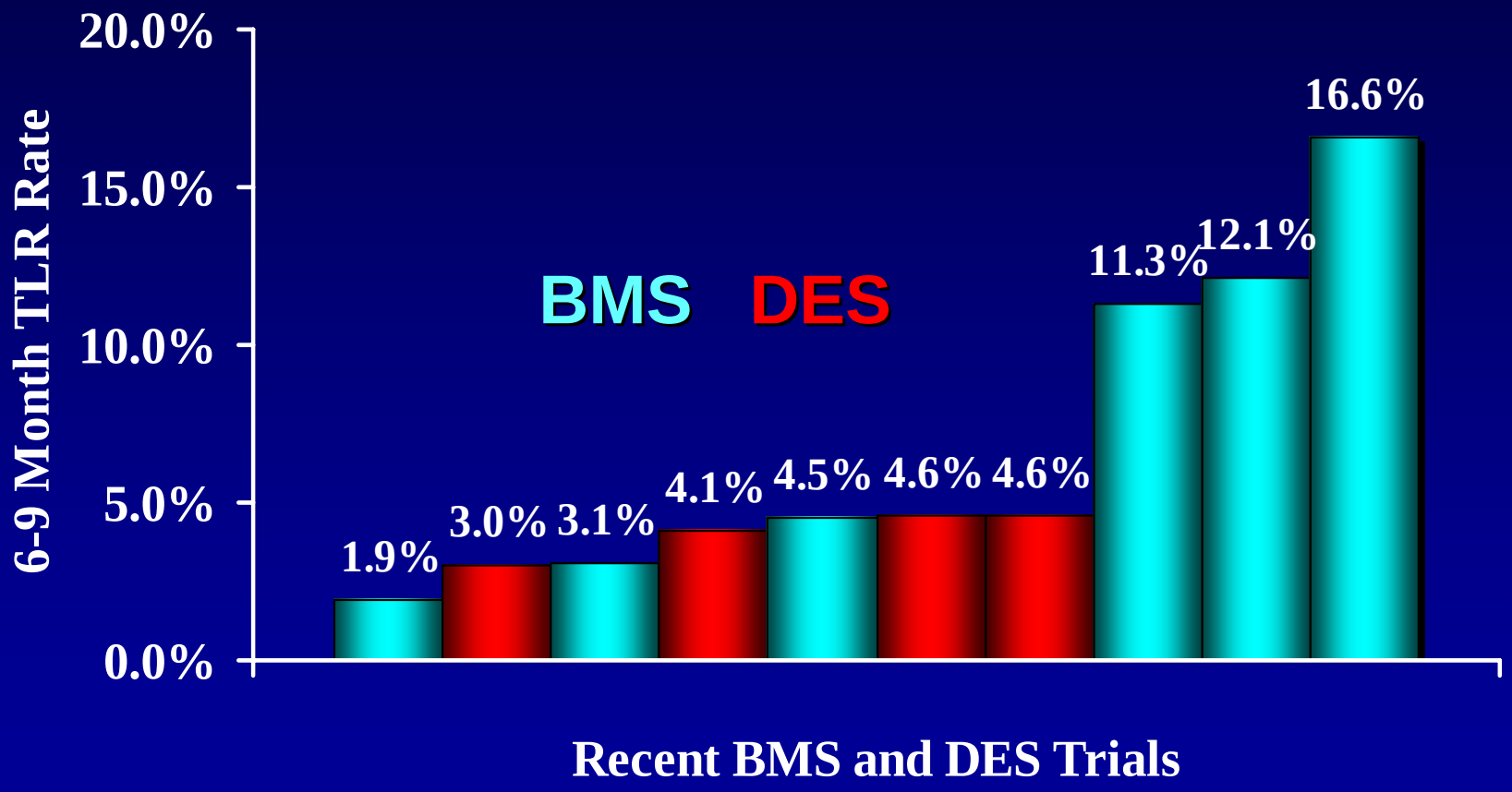

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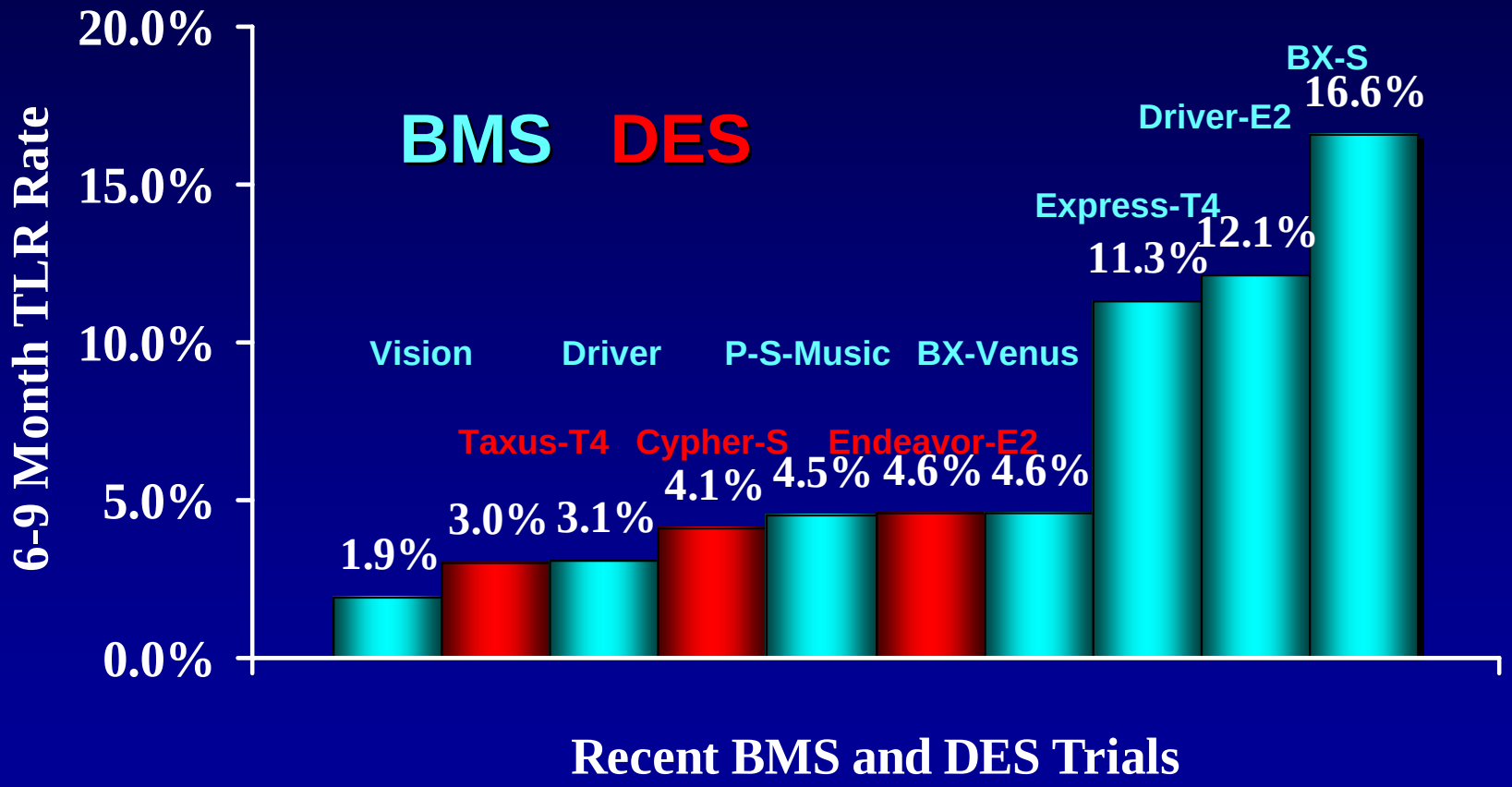

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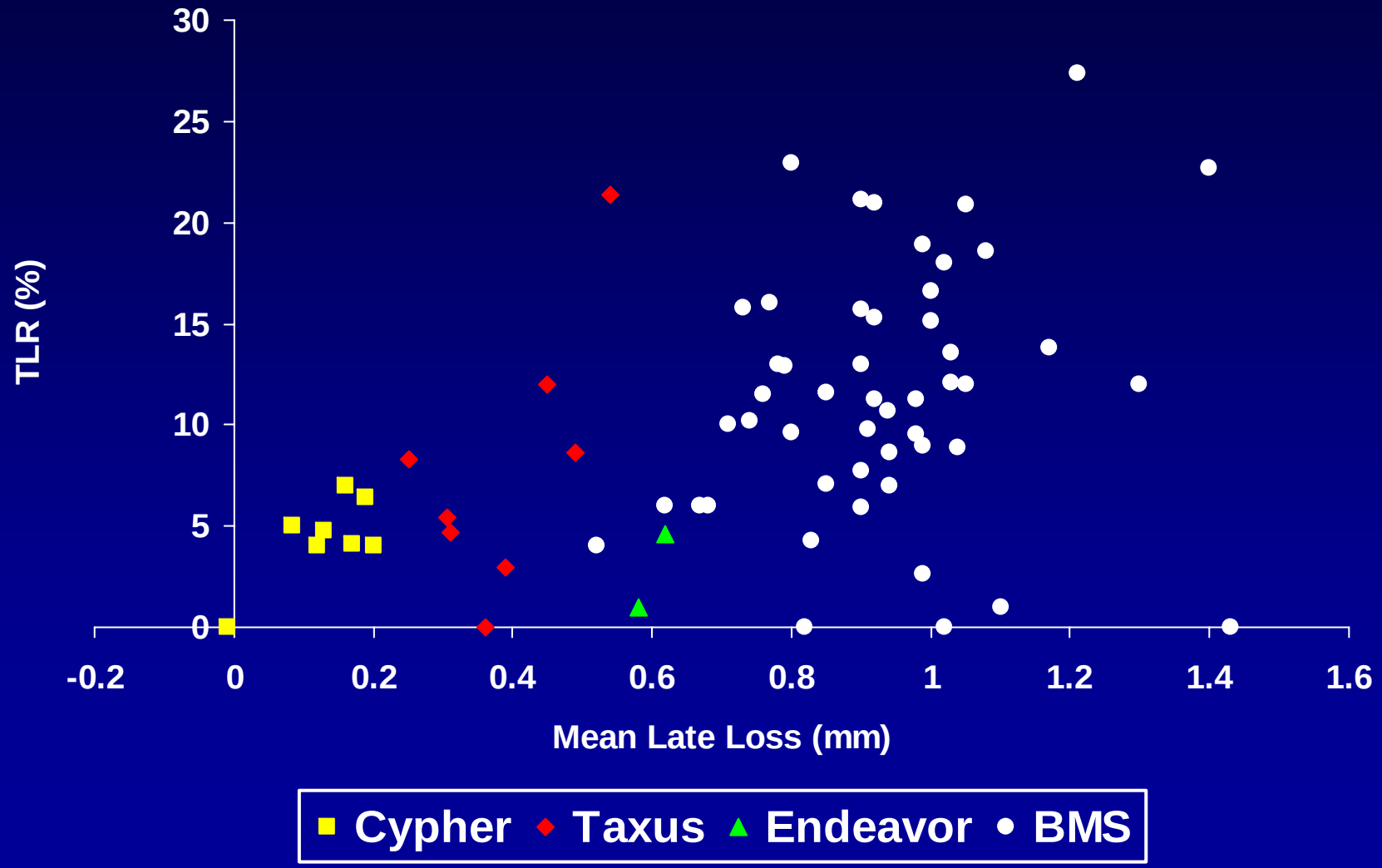
In-Stent Late Loss and TLR

Current DES and BMS Results



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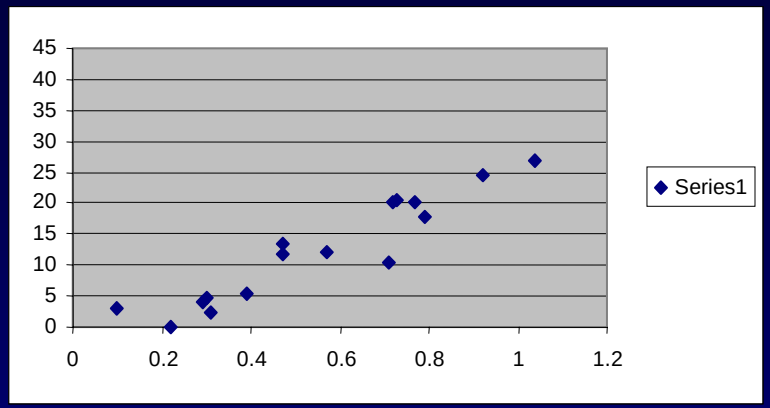
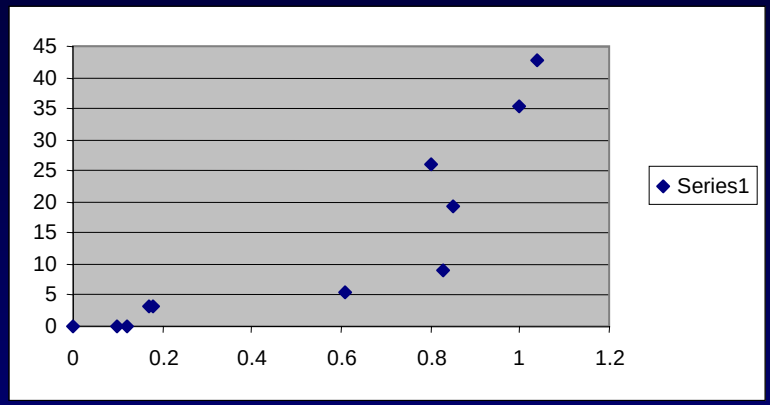
Late Loss Correlates with BAR in DES



Pacl. studies

BAR



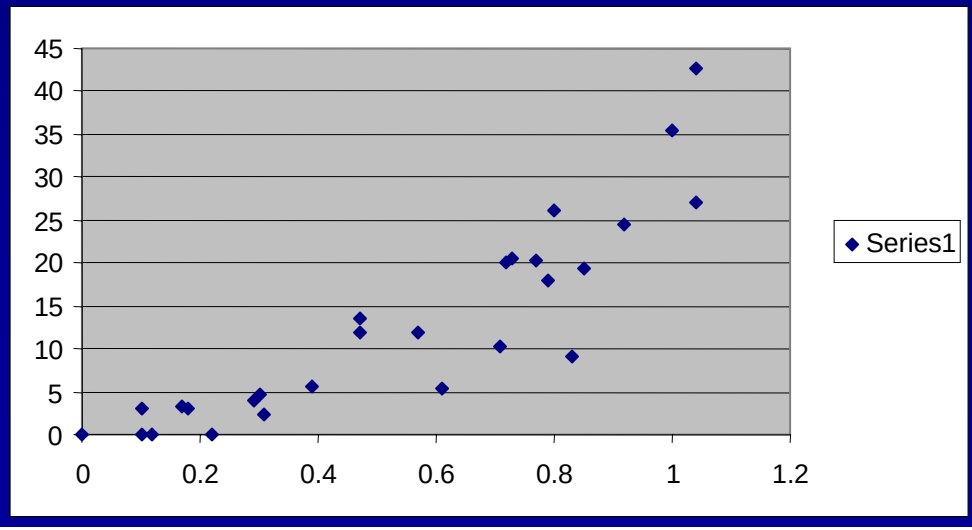
--limus studies

Existing DES Trials

Points are all DES studies with Binary and LL reported (obviously time points etc vary between 6 and 12 months)

All studies

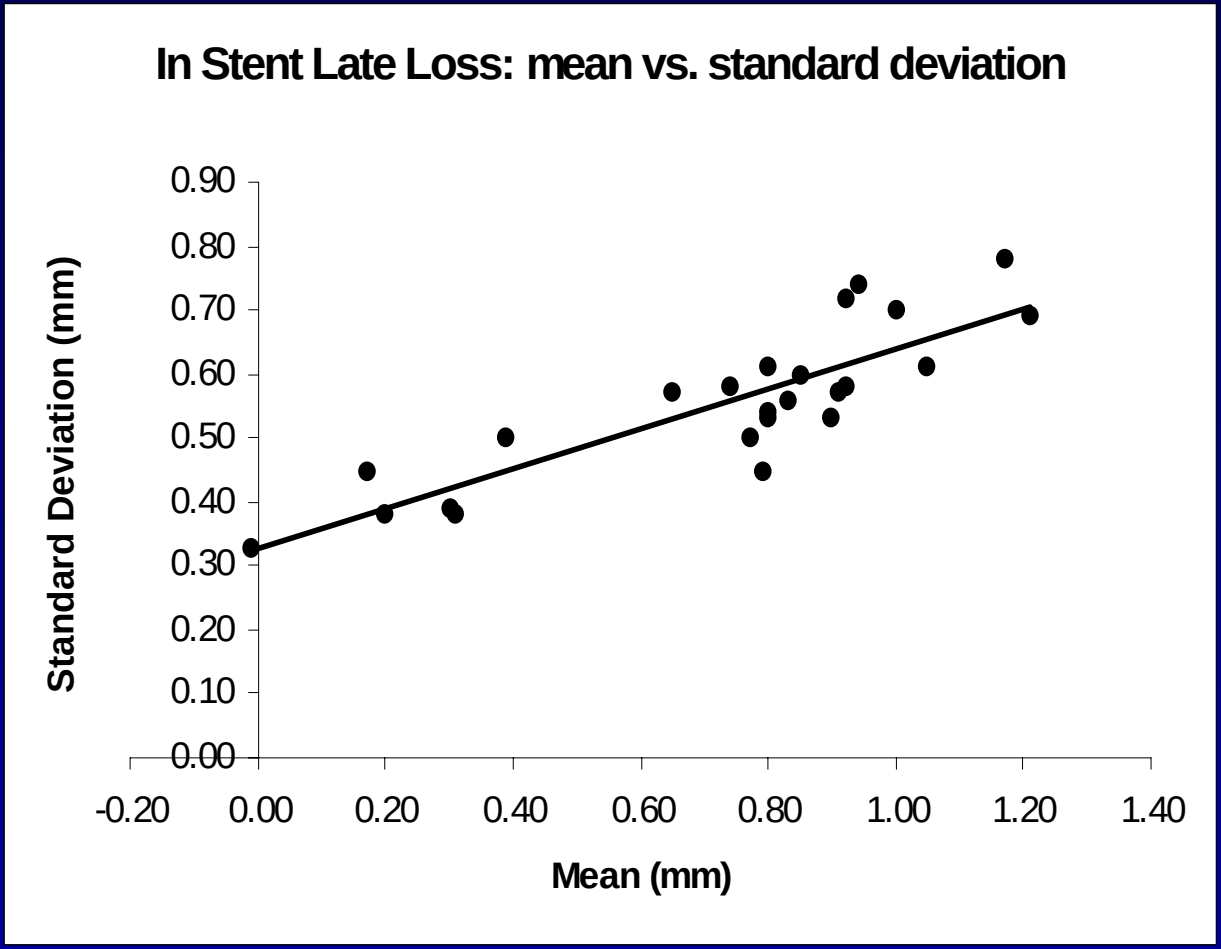
BAR



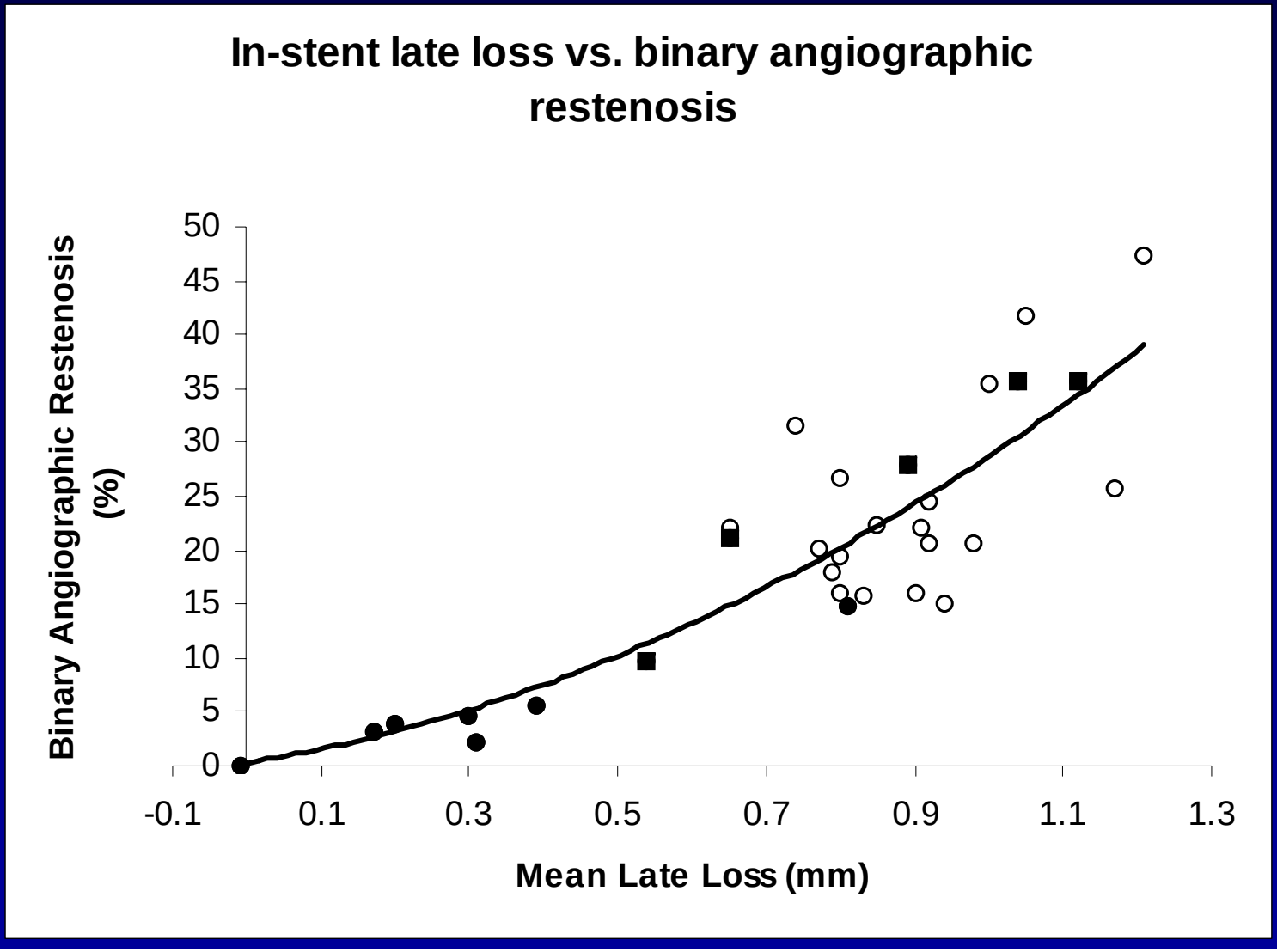
Late Loss is Monotonic (derived from 22 RCTS)

The higher the Late loss, the wider the standard deviation

This means that it is always better to have a lower late loss



In-Stent Late Loss Does Correlate with the Data!
Especially in the DES Late Loss Range
(L Mauri, R Kuntz, *Circulation* in press)



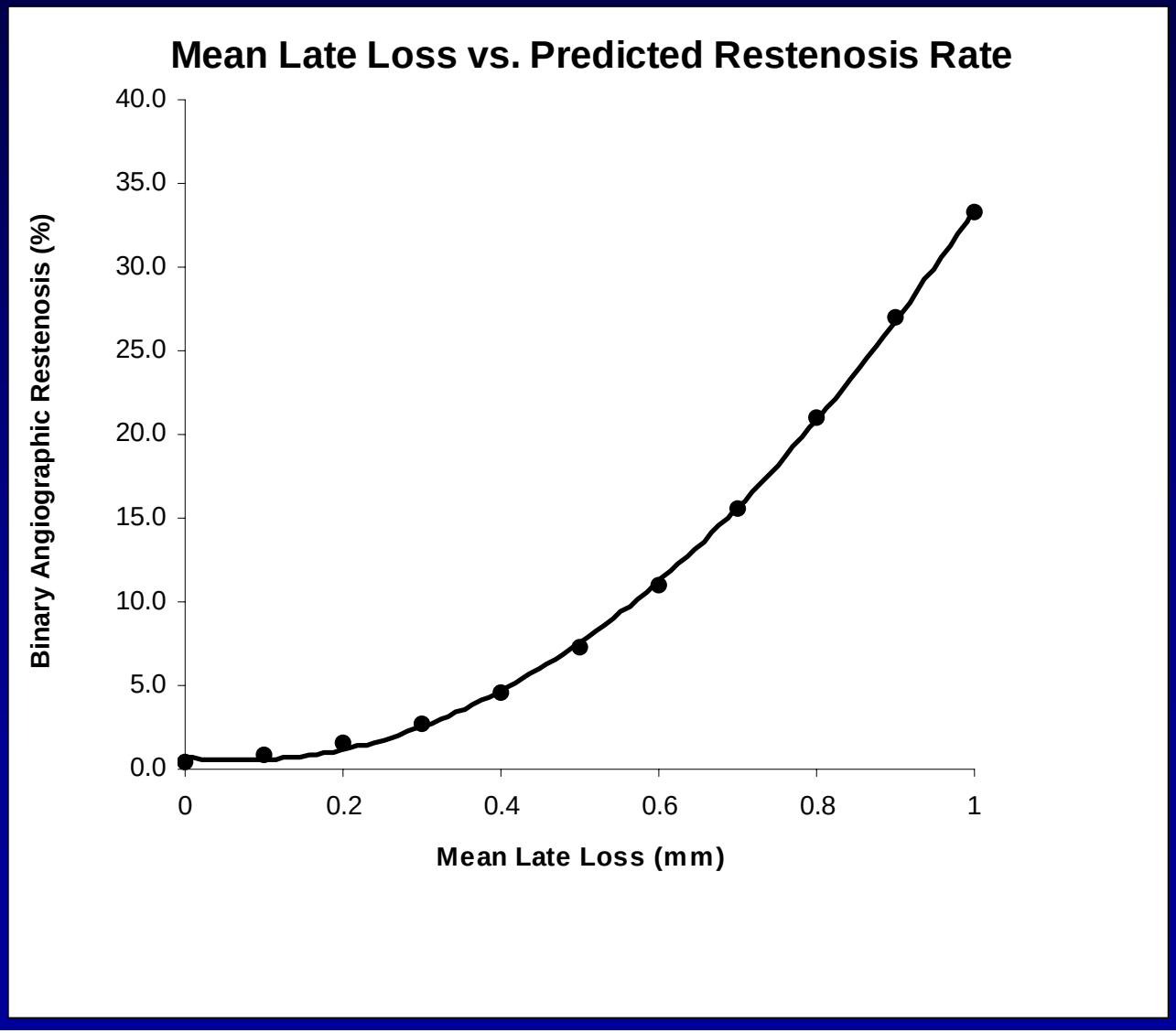
There is no Late Loss Threshold

- Biological effects are continuous
- In our 15 year BMS and DES experience, mean in-stent late loss ranges from 0.1 to 1.2
  - ***The Lower The Better***
- Late Loss is Monotonic
  - There is never an advantage of having a higher late loss
- The real question is: What is the magnitude of the late loss effect on restenosis

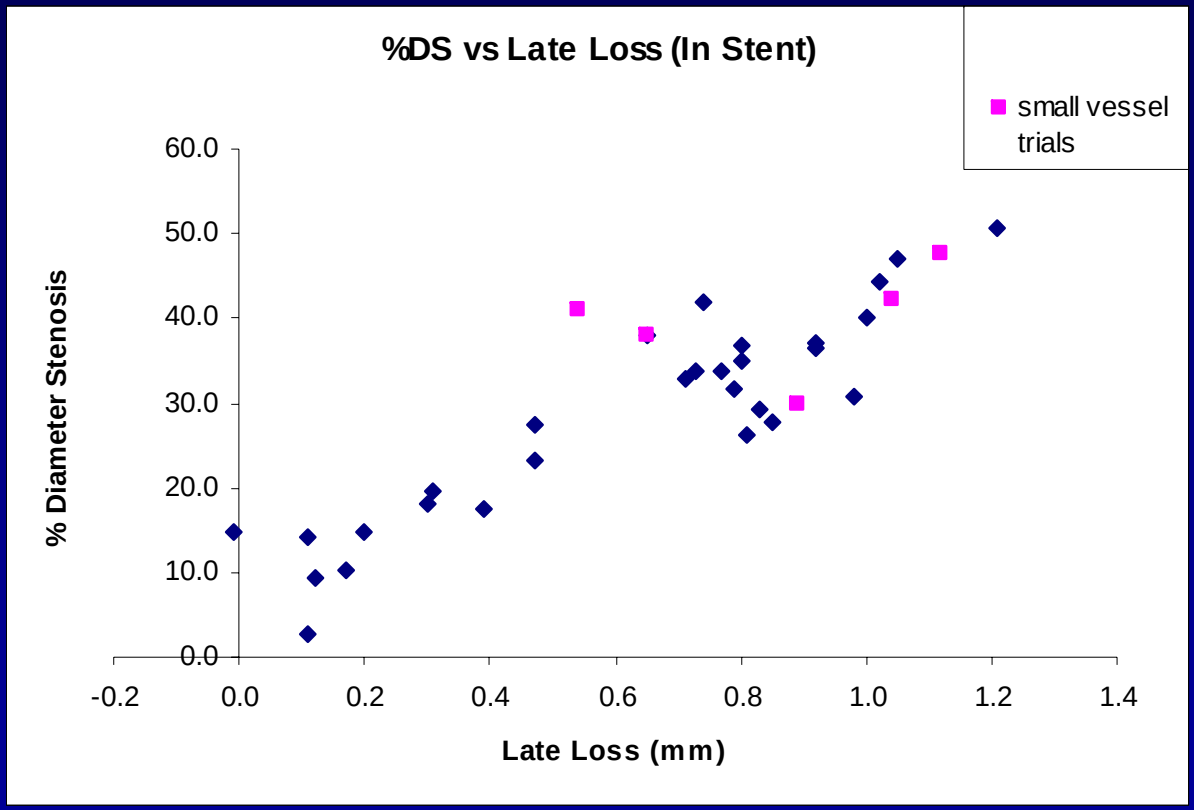
To see the real relationship of late loss and predicted BAR, we need some mathematical treatment

Curvilinear Late Loss BAR Relationship

(L.Mauri, J Orav, R Kuntz *Circulation* in press)



Follow-up Percent Diameter Stenosis
%DS is Correlated with In-Stent Late Loss
(22 Trials L Mauri, R Kuntz)



Risk and Restenosis

Late Loss and Clinical Restenosis

- Factors that put Late Loss into perspective
  - Threshold of late loss that leads to clinical revascularization
    - *Thresholds are different across practices and countries*
    - *Lower for small vessels*
  - Late Loss risk factors: diabetes and long lesions
    - *Shift the late Loss curves to the right*

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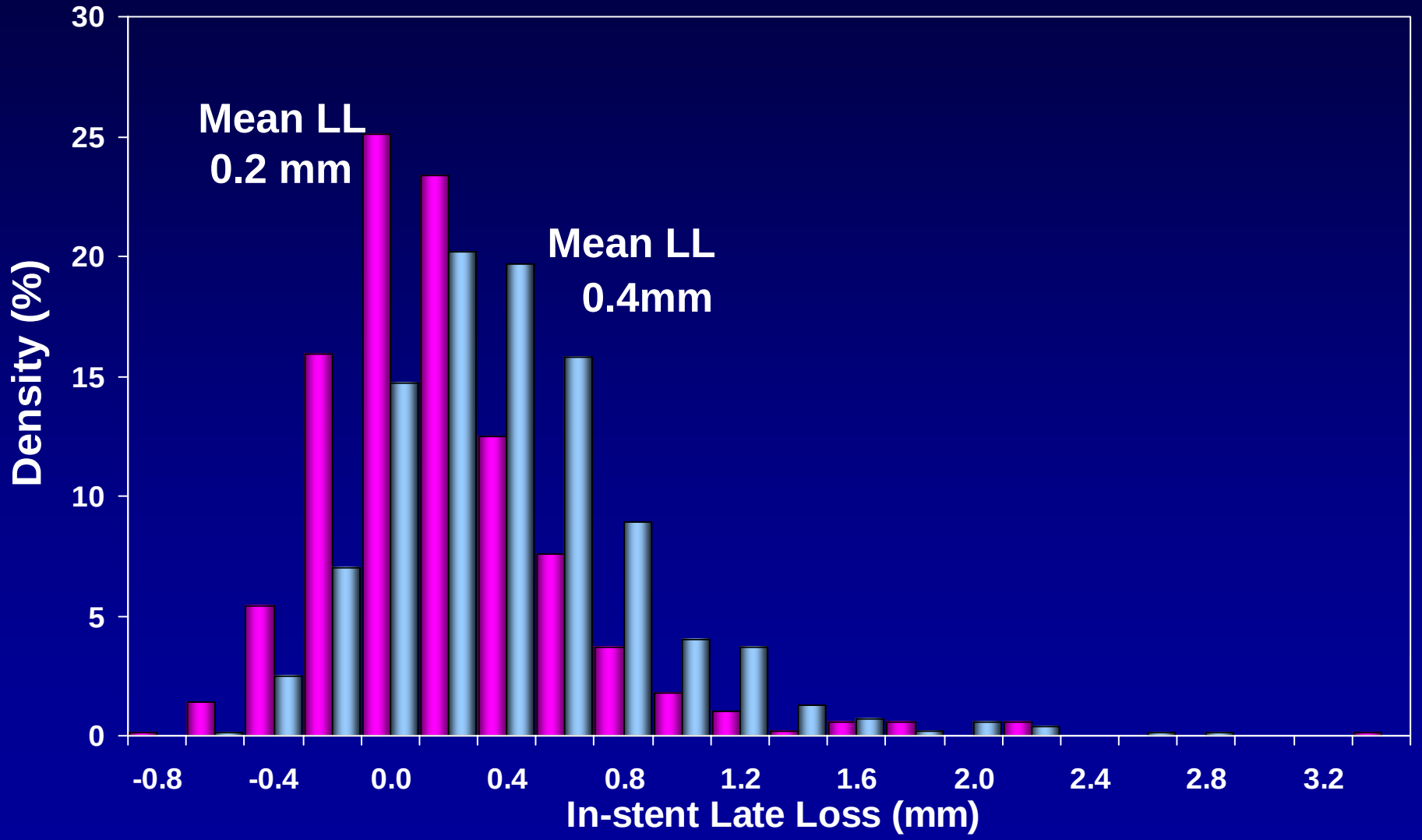
Frequency of Late Loss



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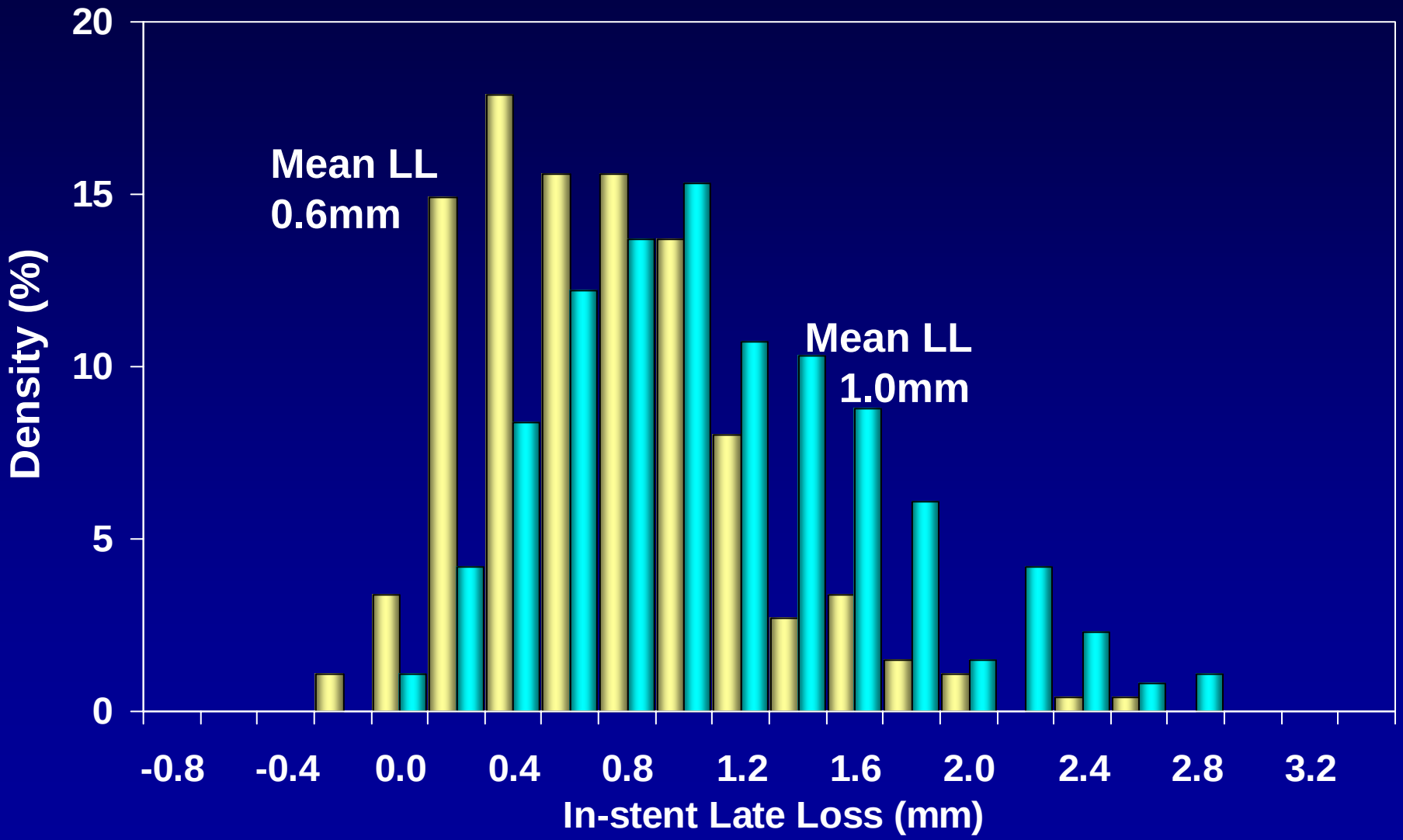

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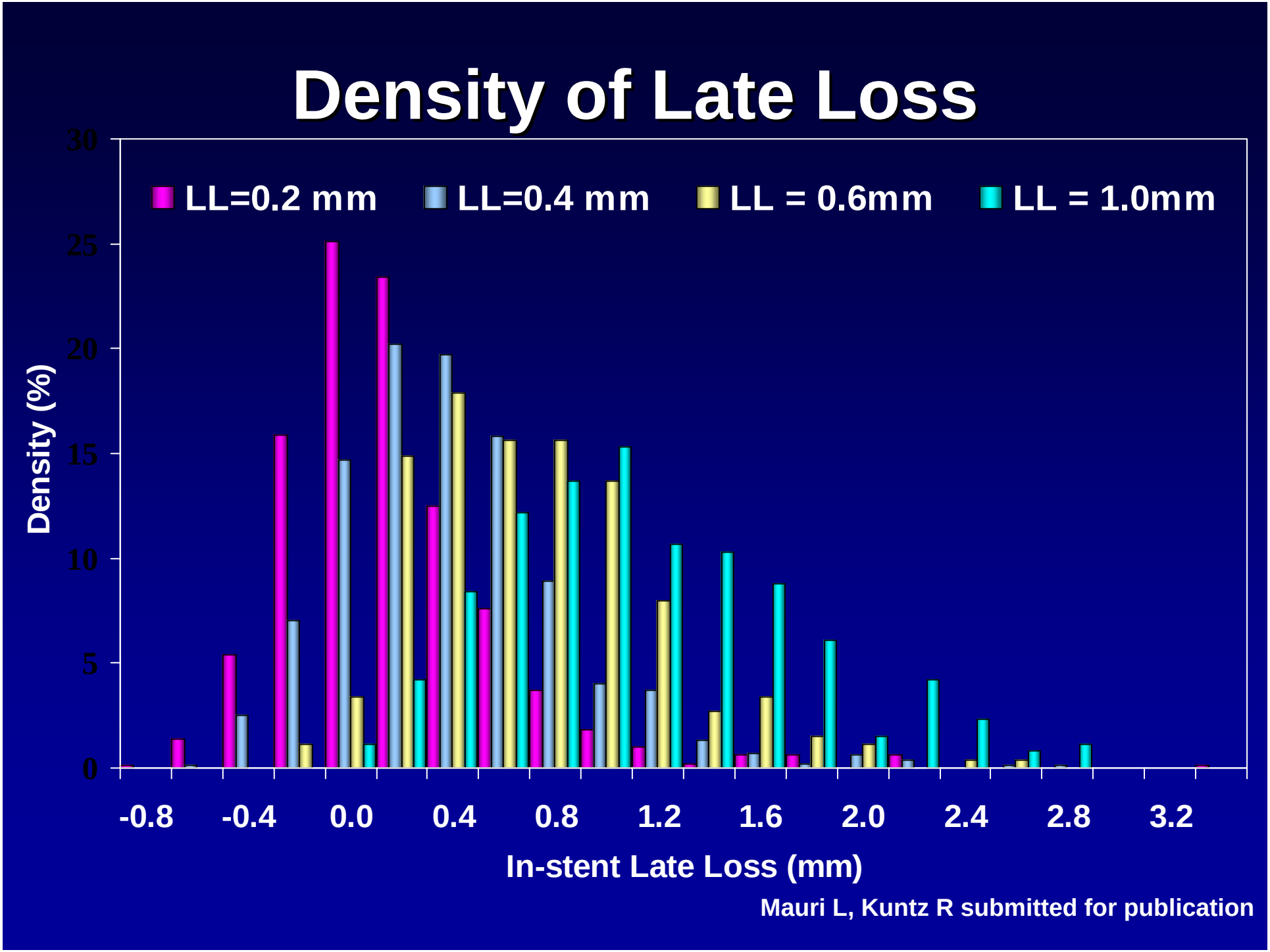
Density of Late Loss



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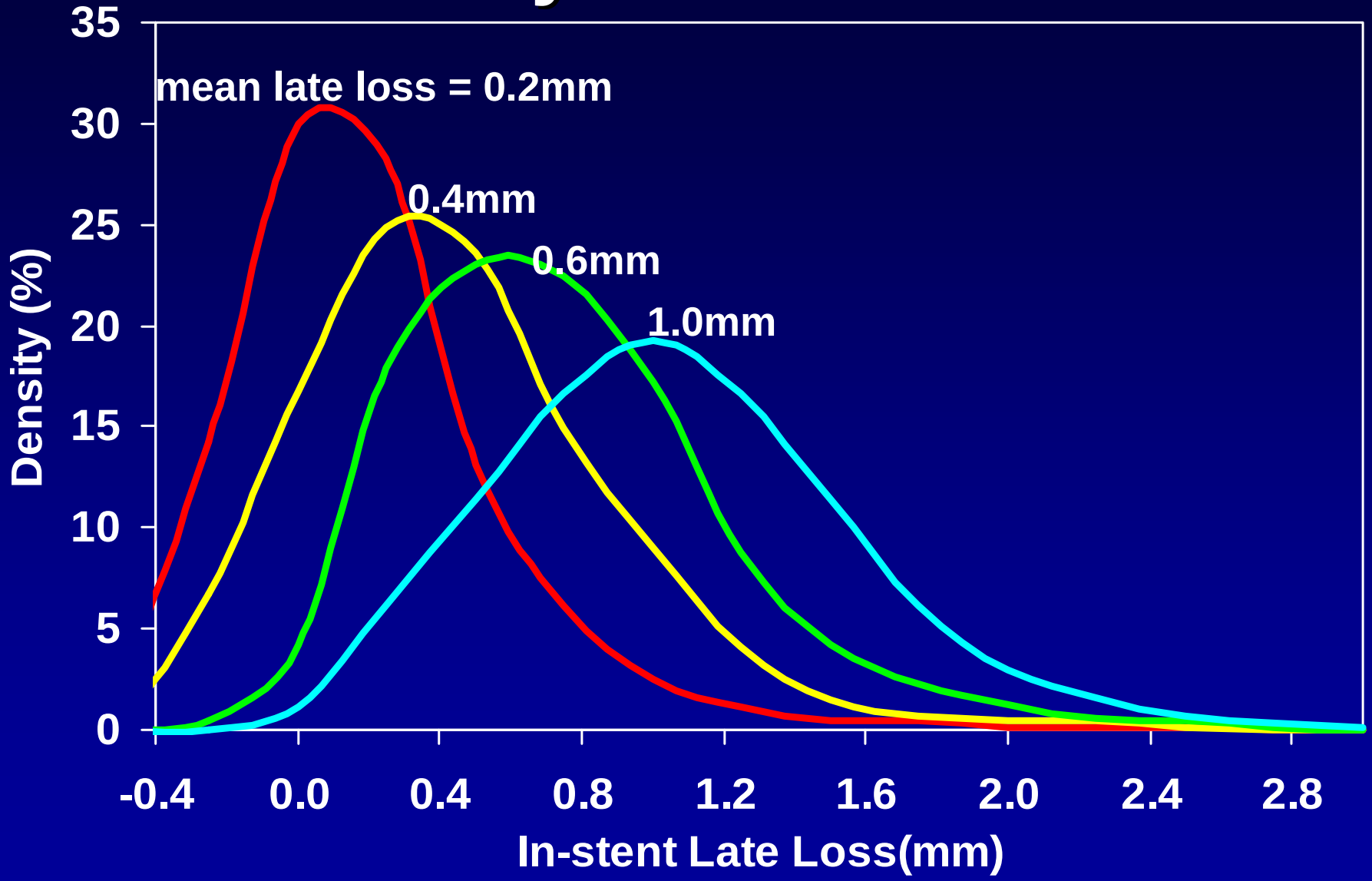

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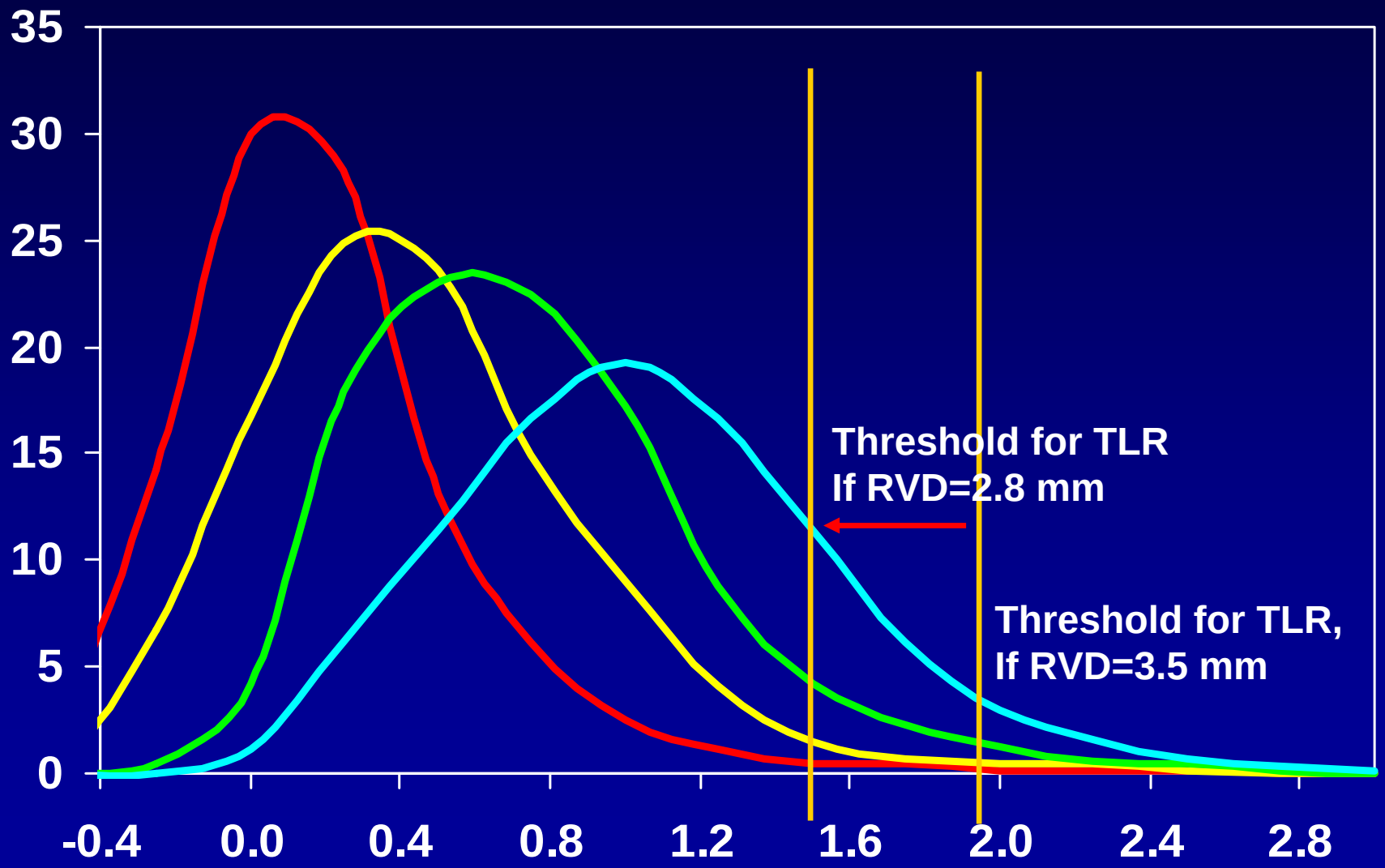
Late Loss and TLR

Effect of mean reference vessel diameter



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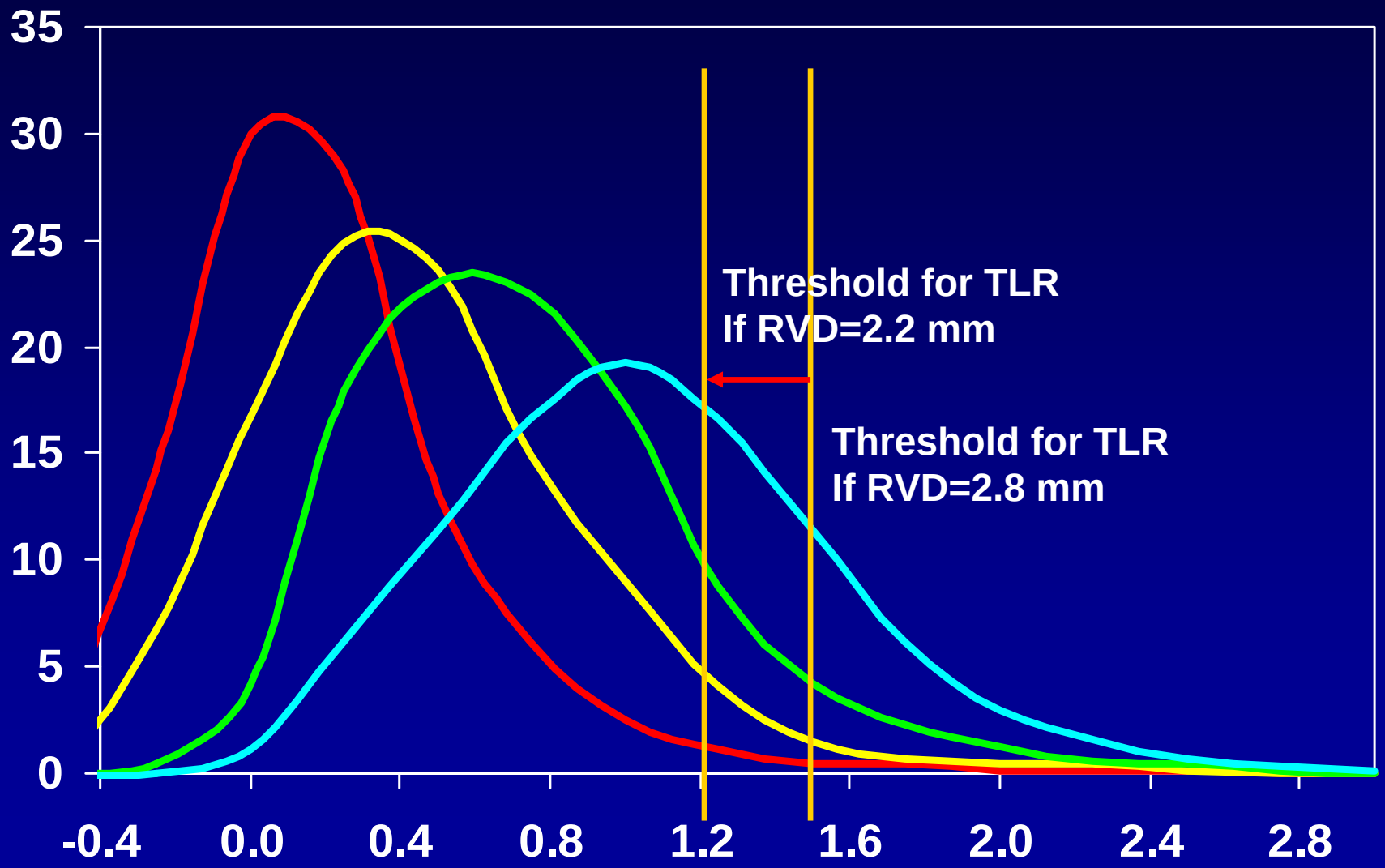
Late Loss and TLR

Effect of small vessel stenting



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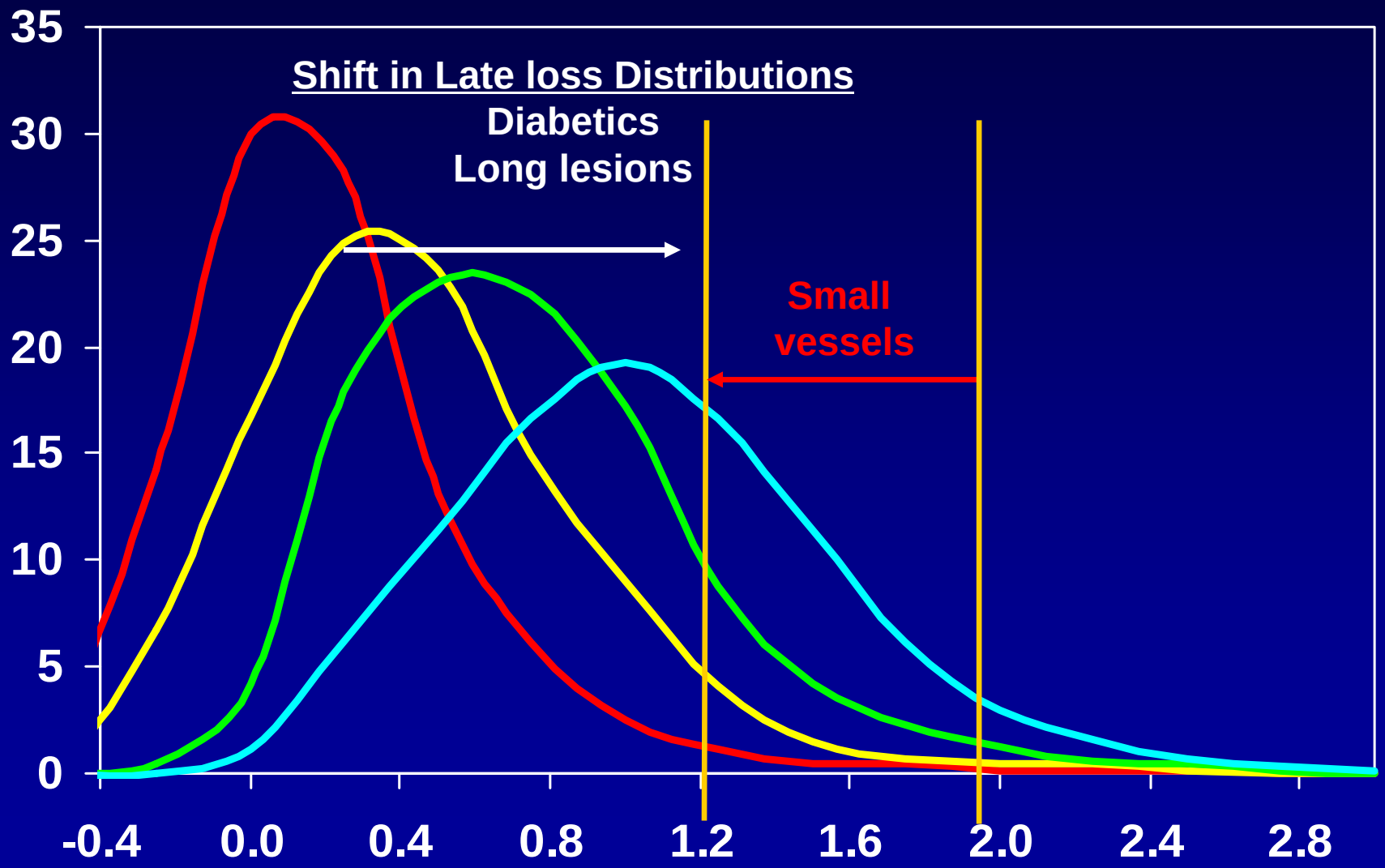
Density of Late Loss



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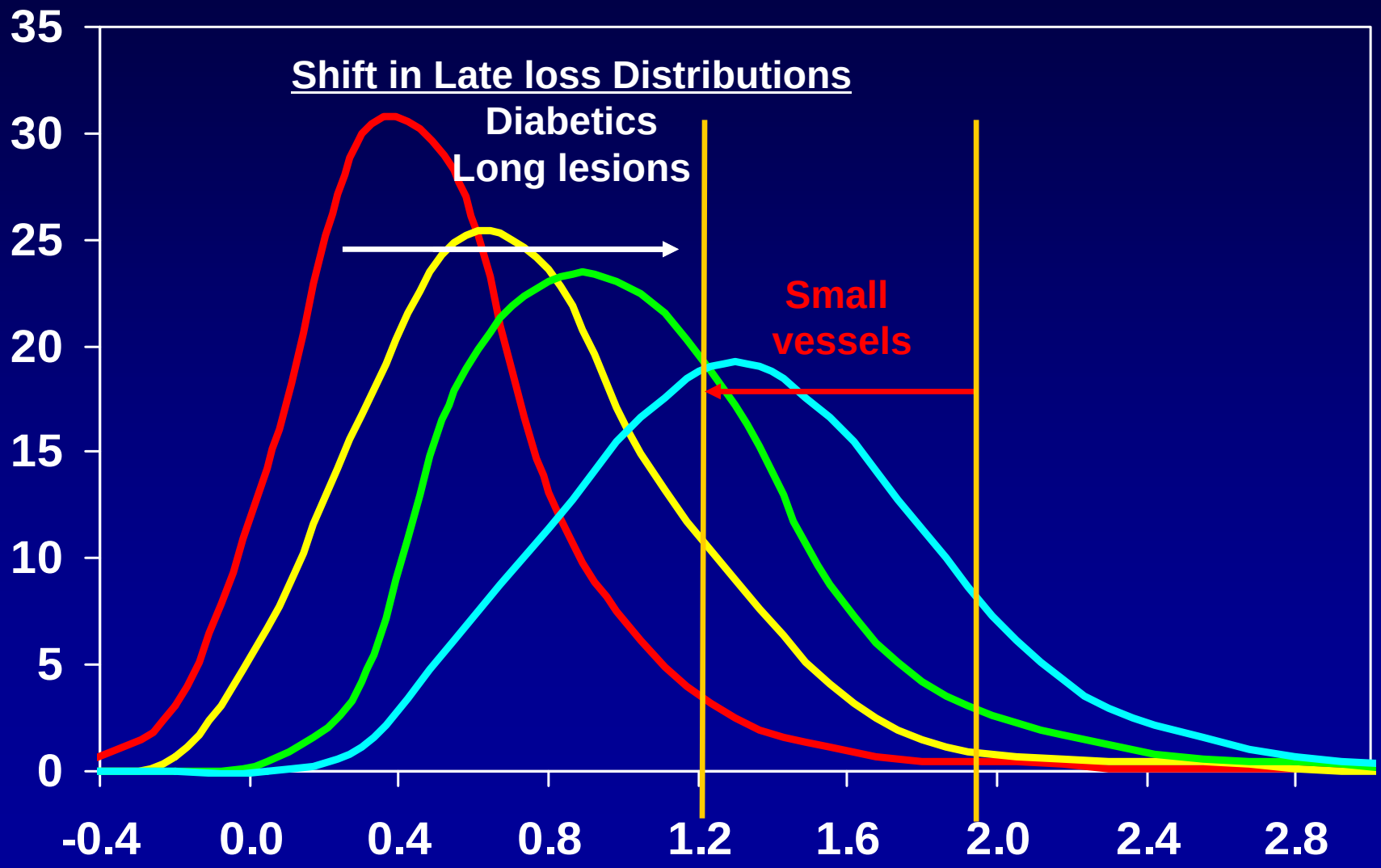
Late Loss and TLR

Effect of High Risk Characteristics



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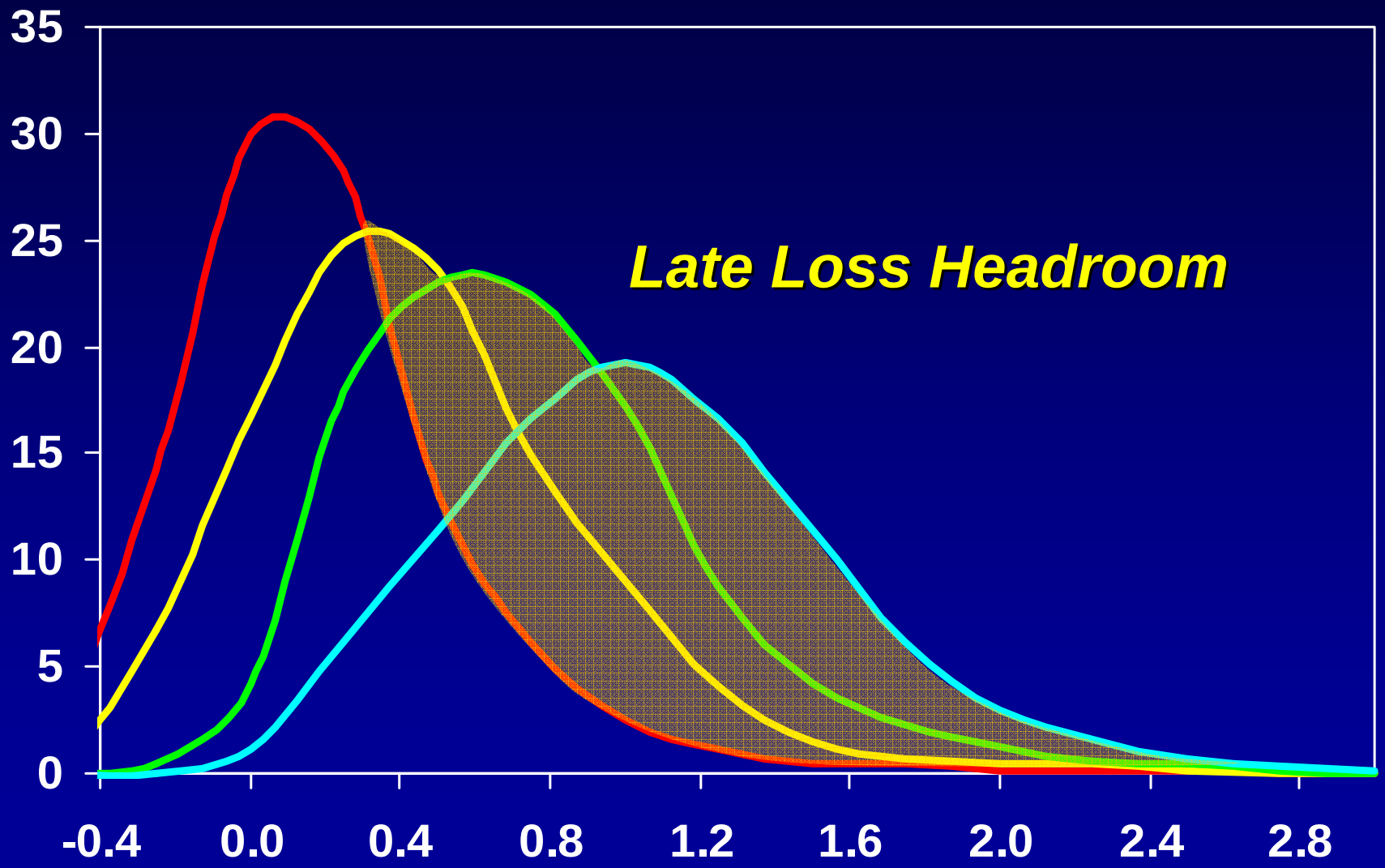
Late Loss Headroom

- 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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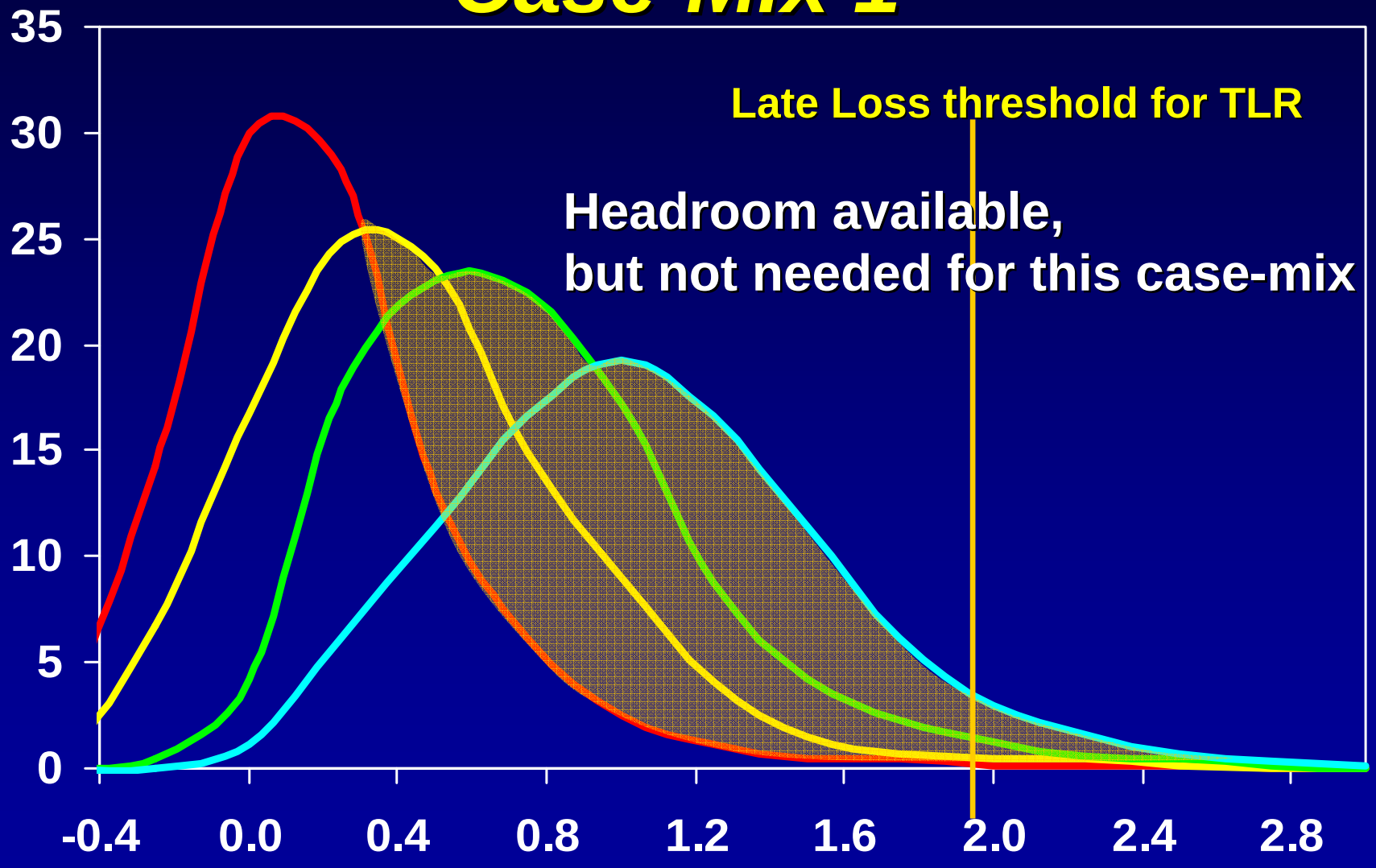
Late Loss Headroom

Case-Mix 1



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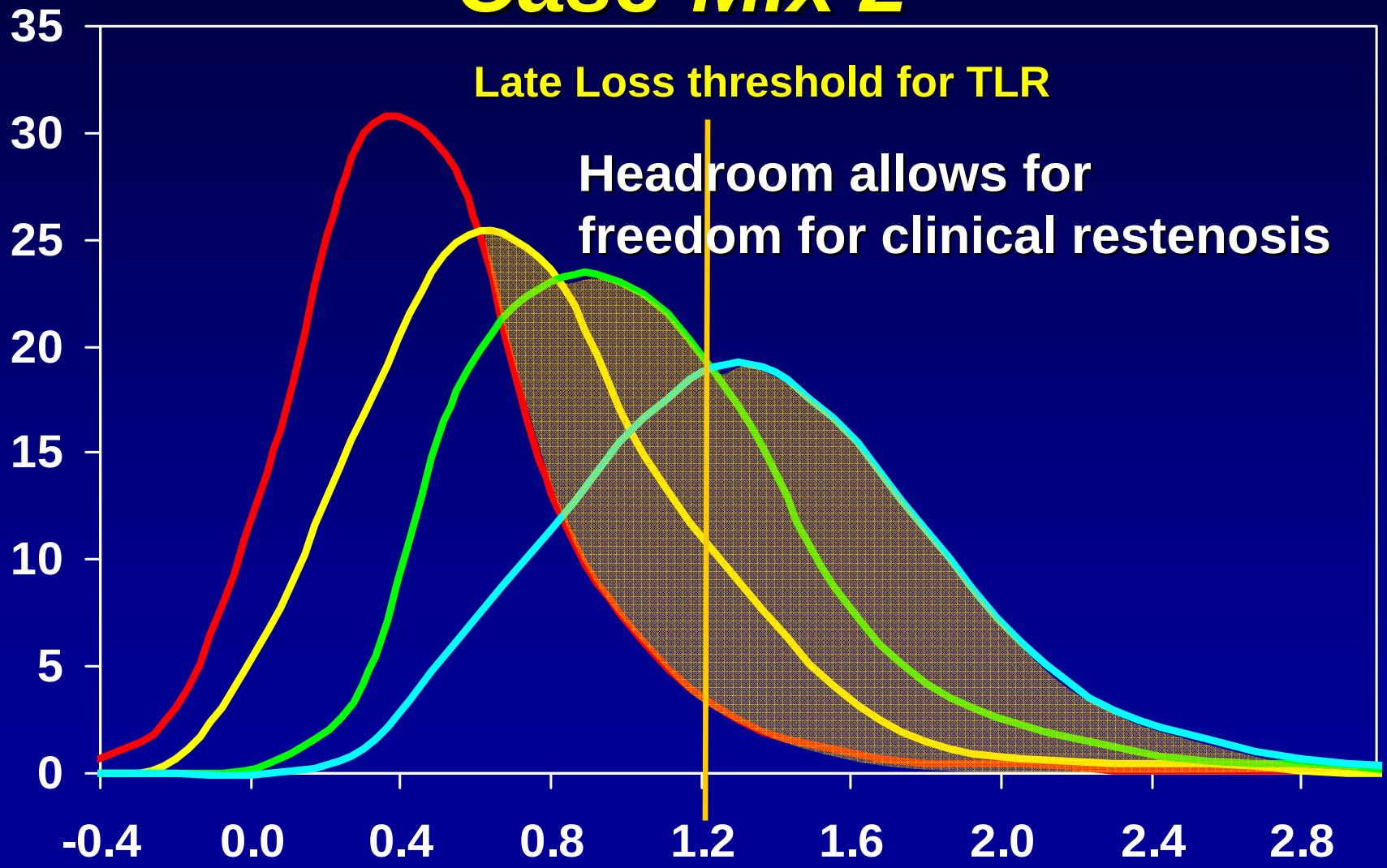
Late Loss Headroom

Case-Mix 2



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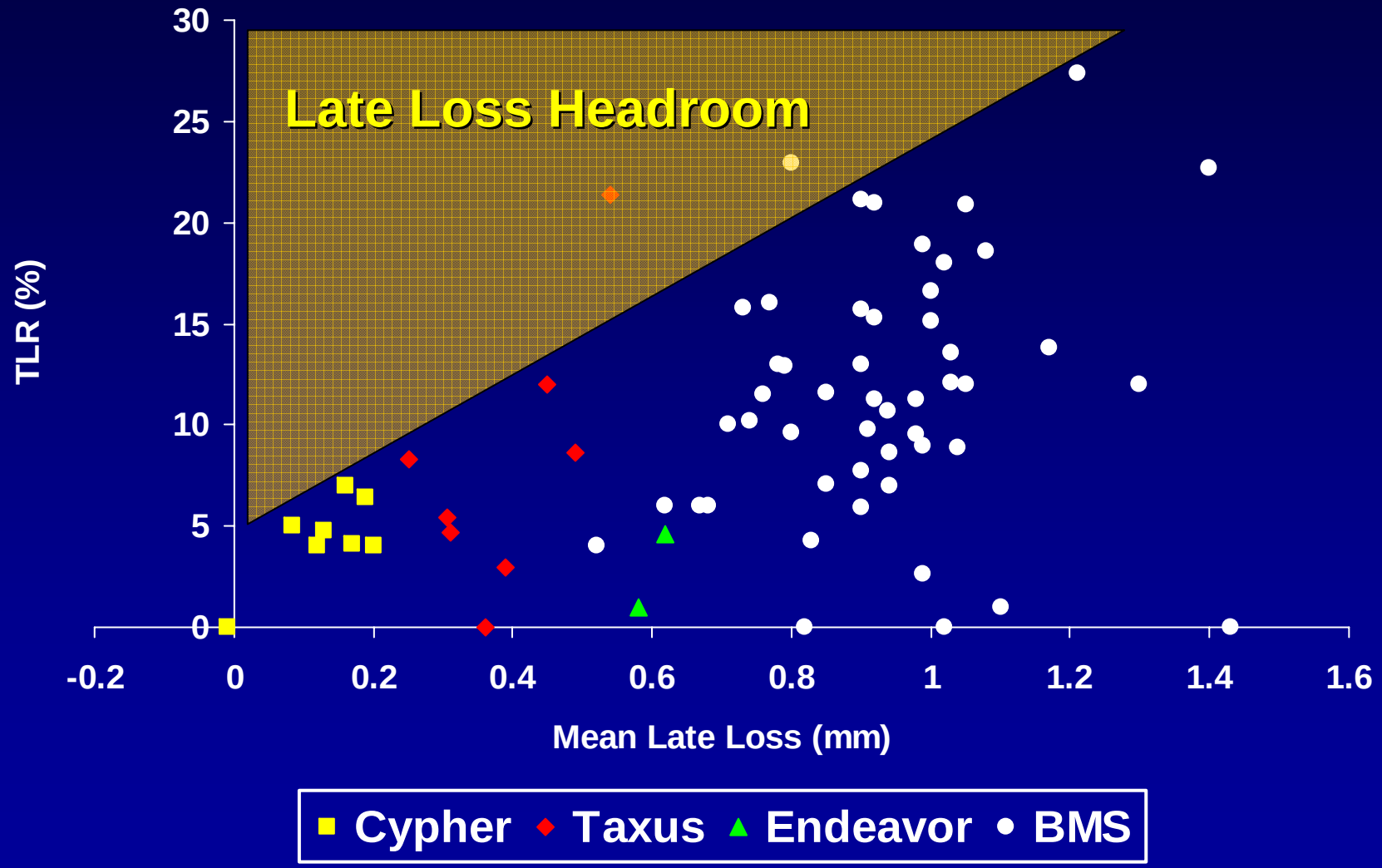
Late Loss Headroom

- 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
- 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



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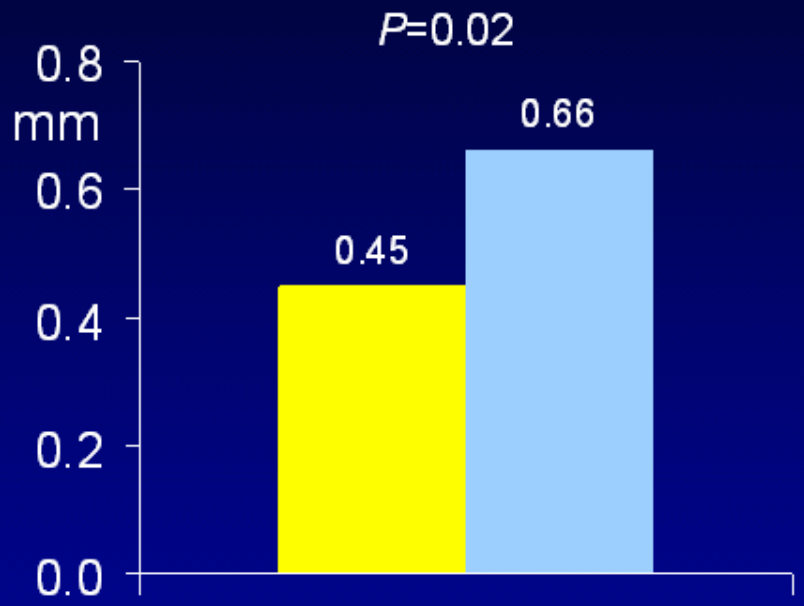
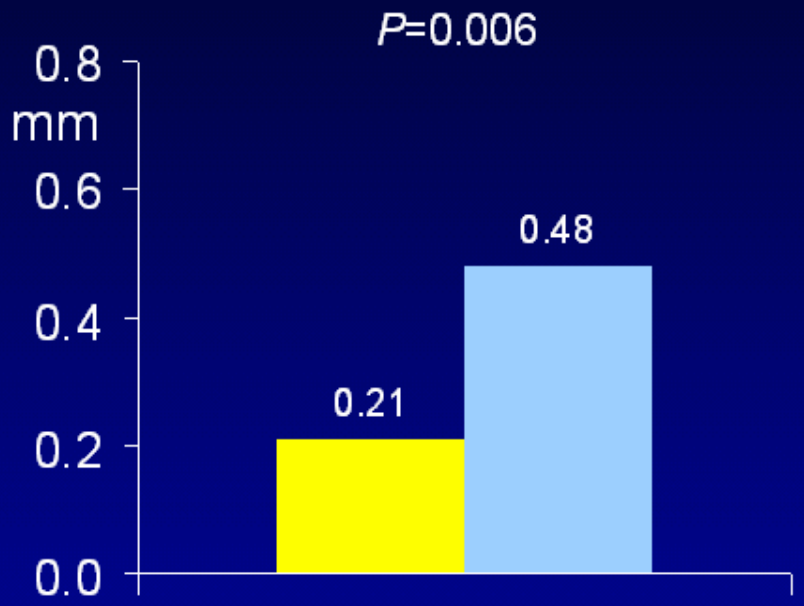
Late Loss and TLR Inter-Relationship in Clinical Trials

- For low risk cohort studies and randomized trials, TLR will be low over a wide range of In-Stent Late Loss values
  - *In such case-mixes, DES stents should be valued on secondary characteristics of safety, deliverability, coverage, etc.*
- For moderate to high risk cohort studies and randomized trials, high in-stent late loss values should predict higher TLR rates

Cypher vs. Taxus I

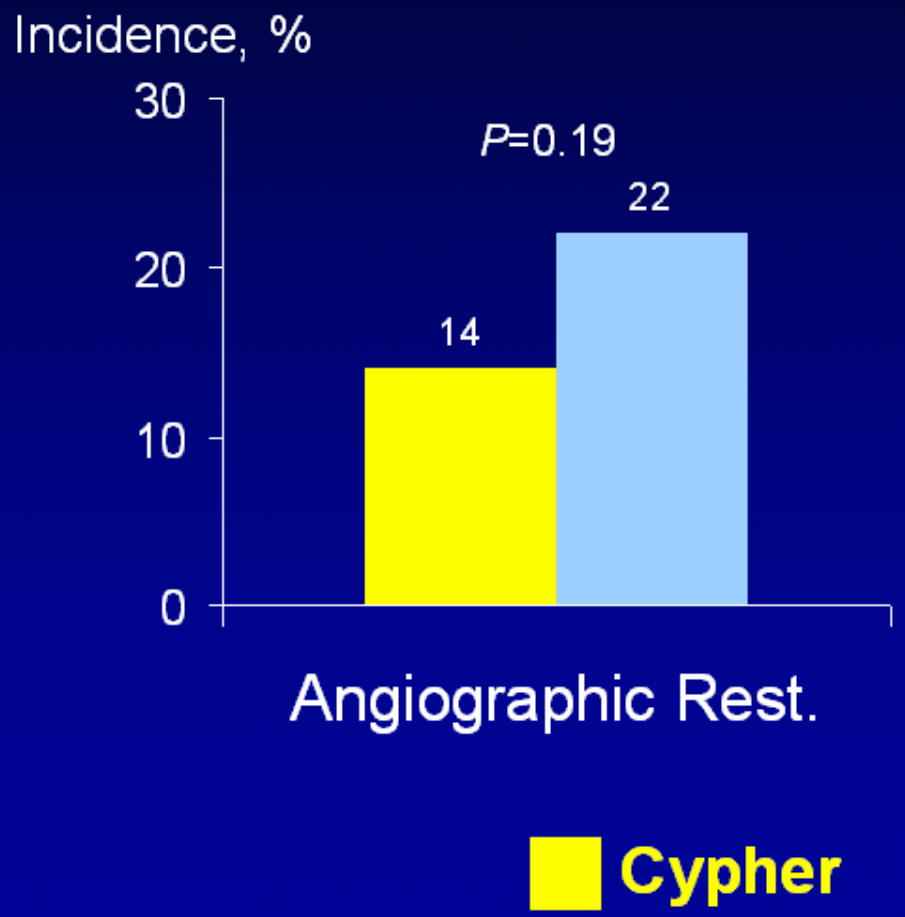


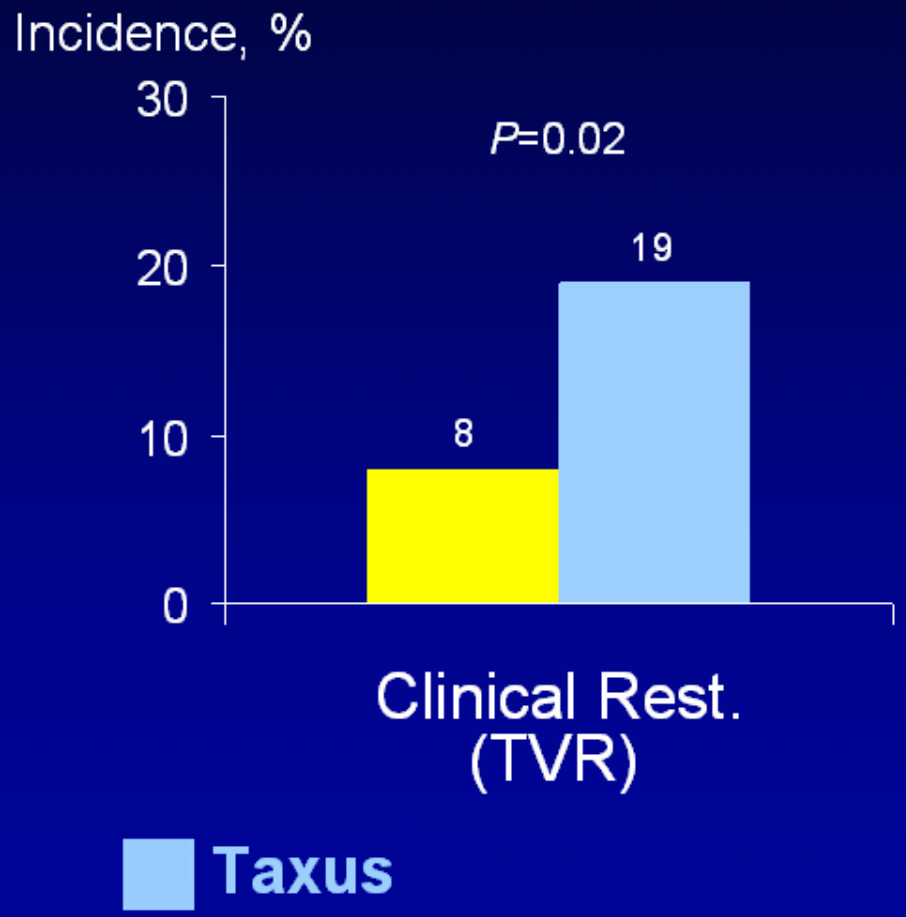


Cypher

Taxus

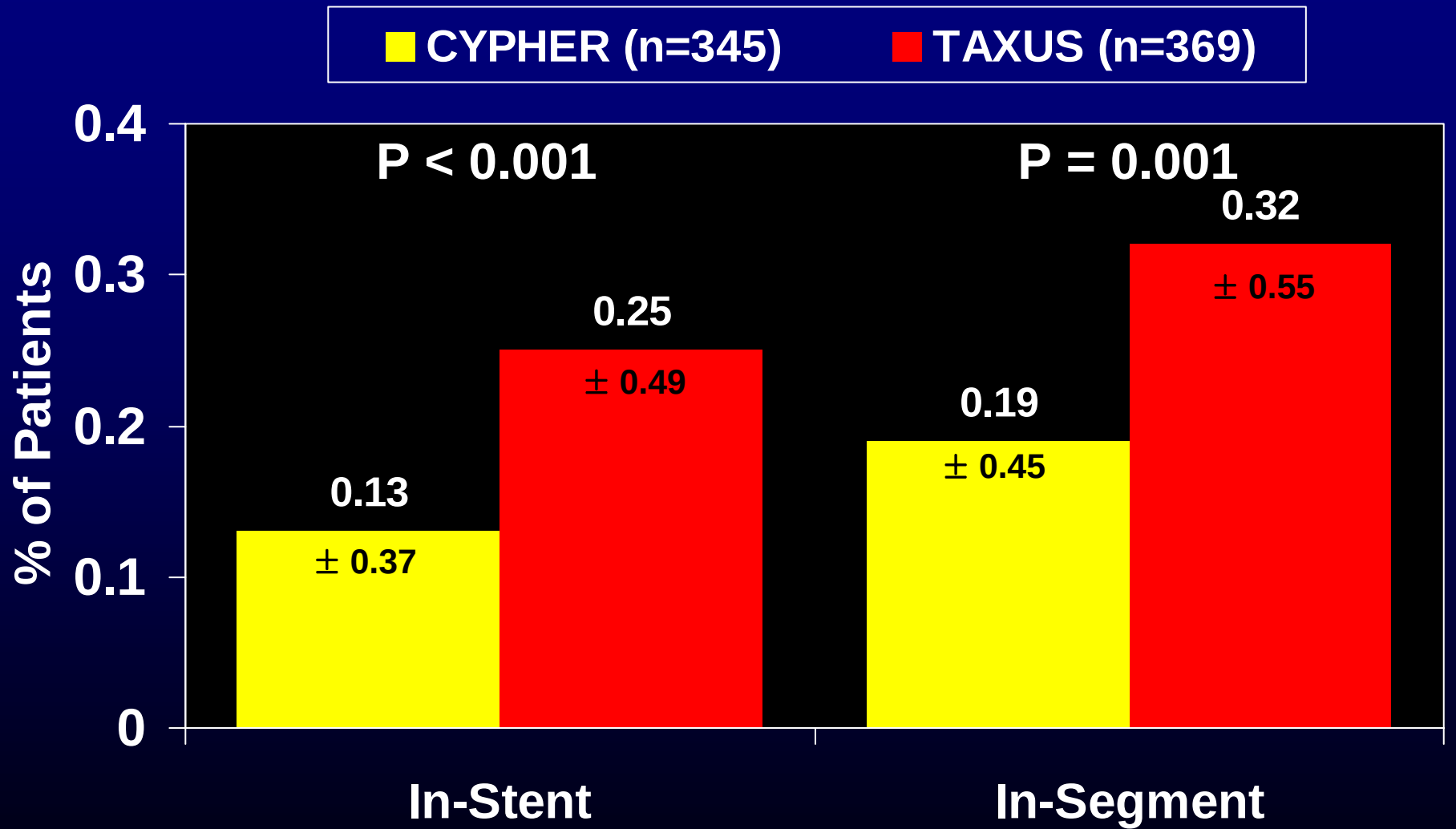
Cypher vs. Taxus II





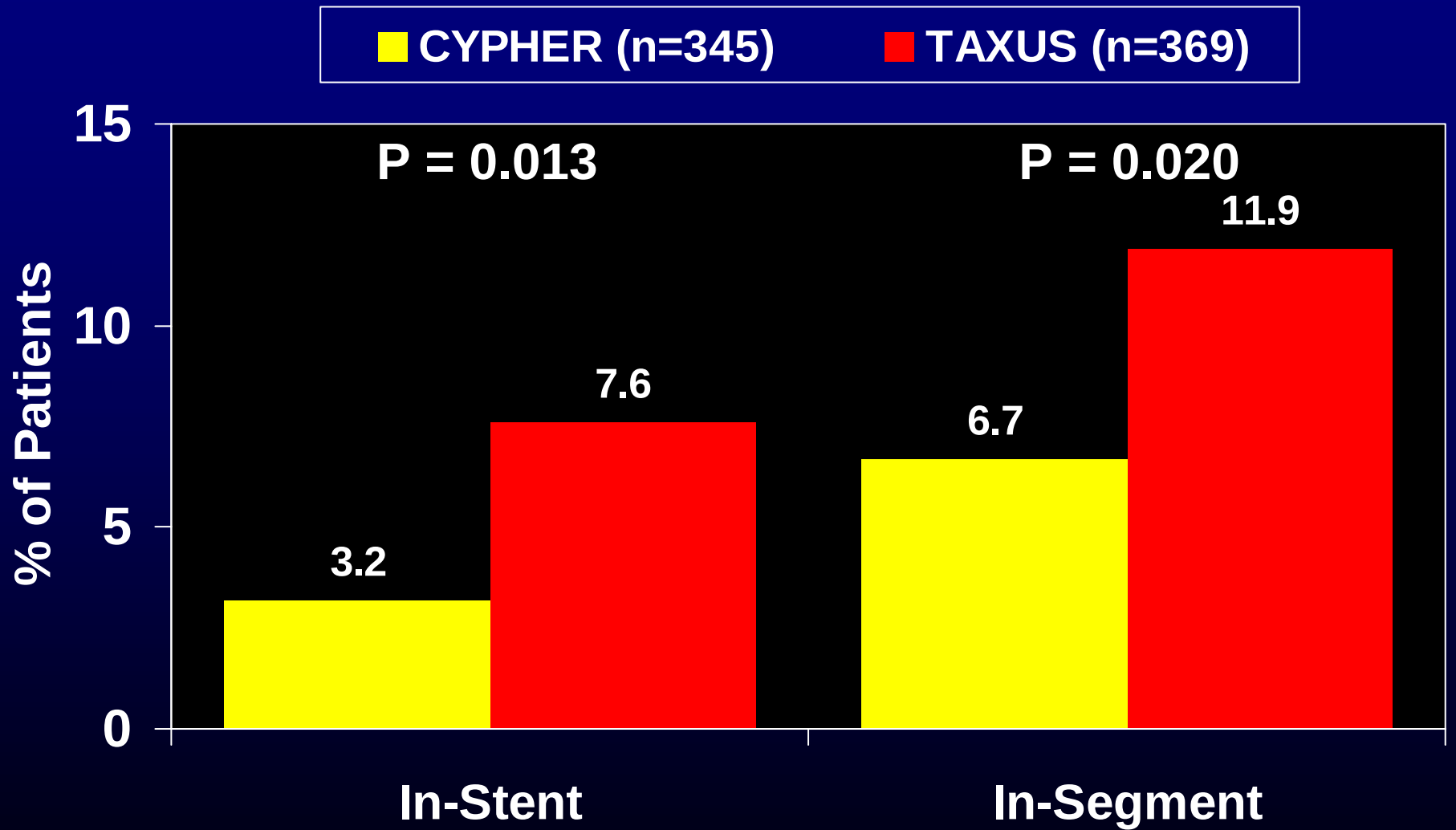
Cypher Taxus

SIRTAX: Late Luminal Loss



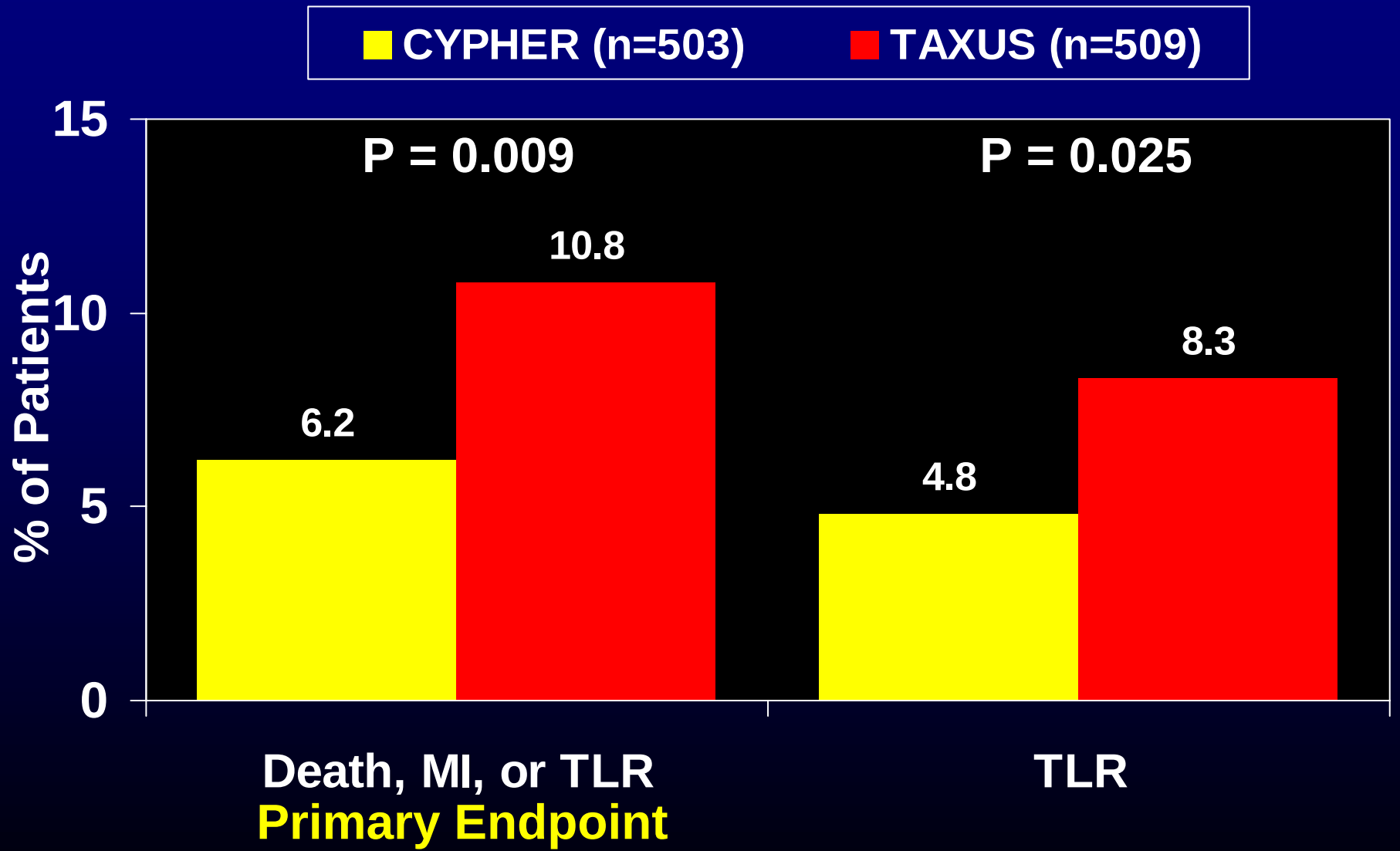
Follow-up Angiography in 527 Patients With 714 Lesions

SIRTAX: Binary Restenosis



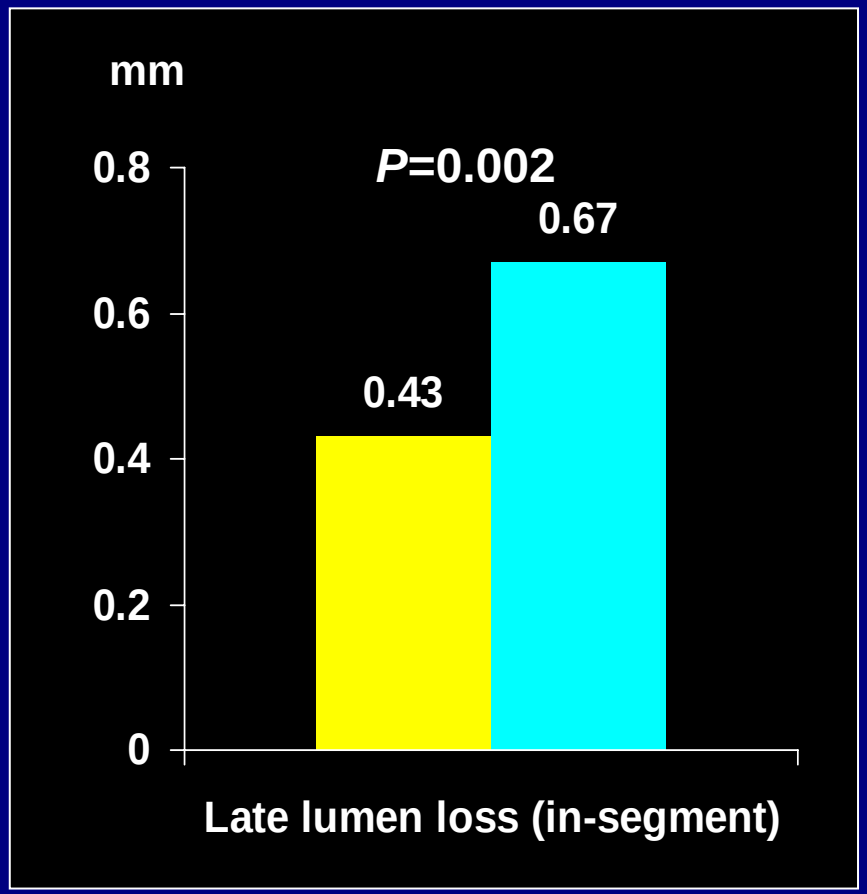
Follow-up Angiography in 527 Patients With 714 Lesions

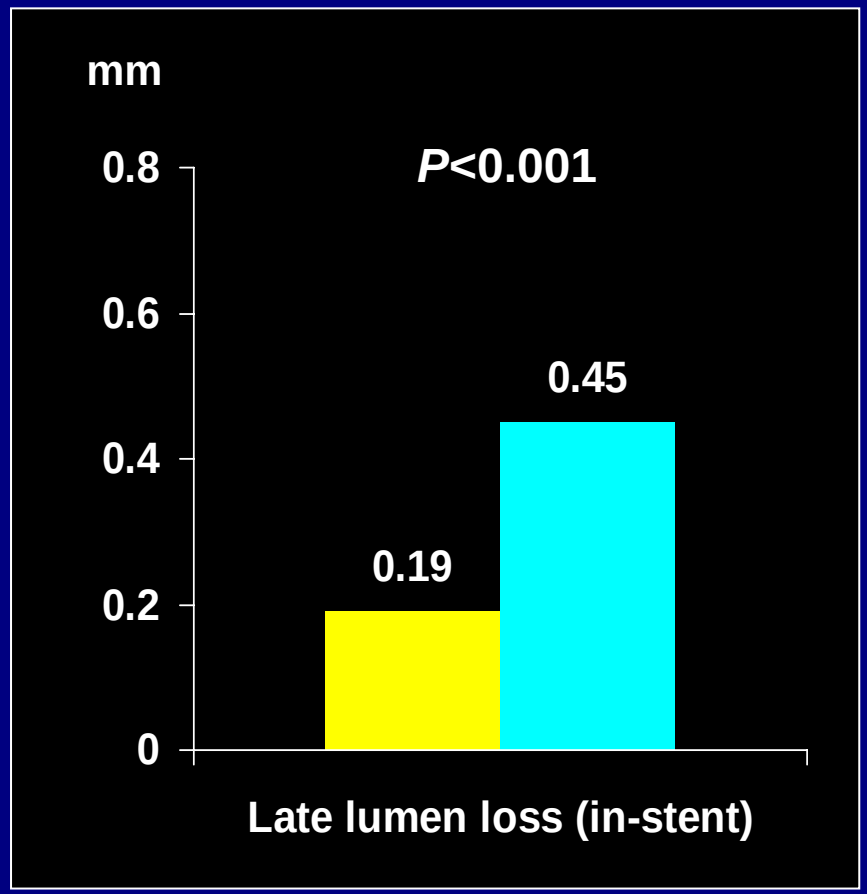
SIRTAX: 9 Month Outcomes



ISAR-DIABETES

Late Lumen Loss





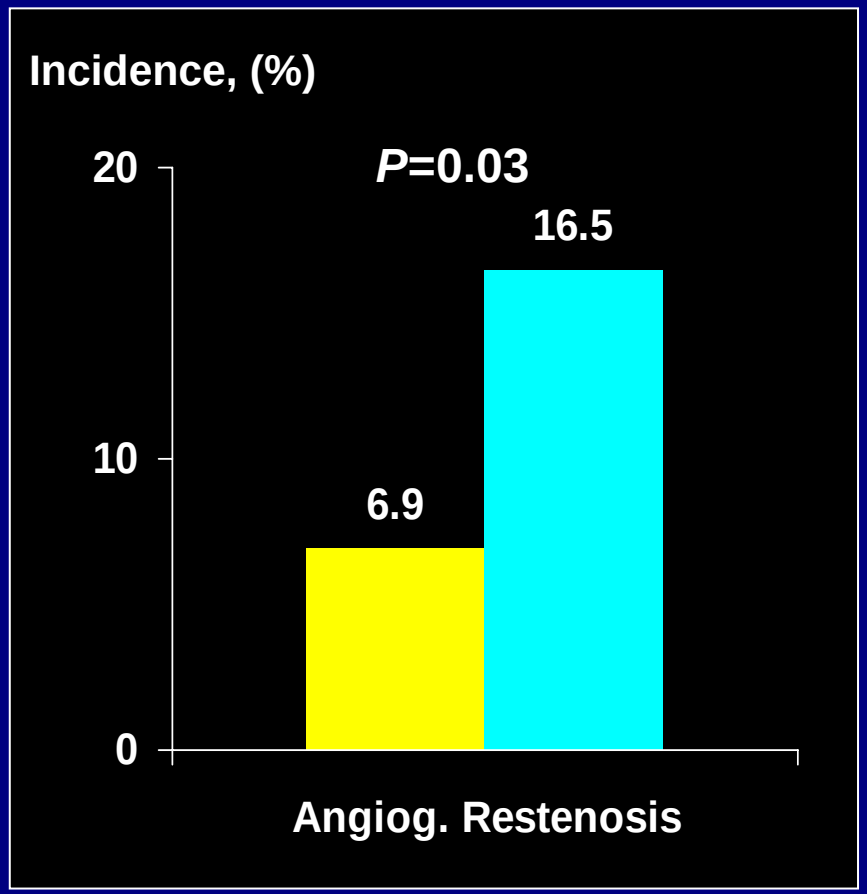
CYPHER

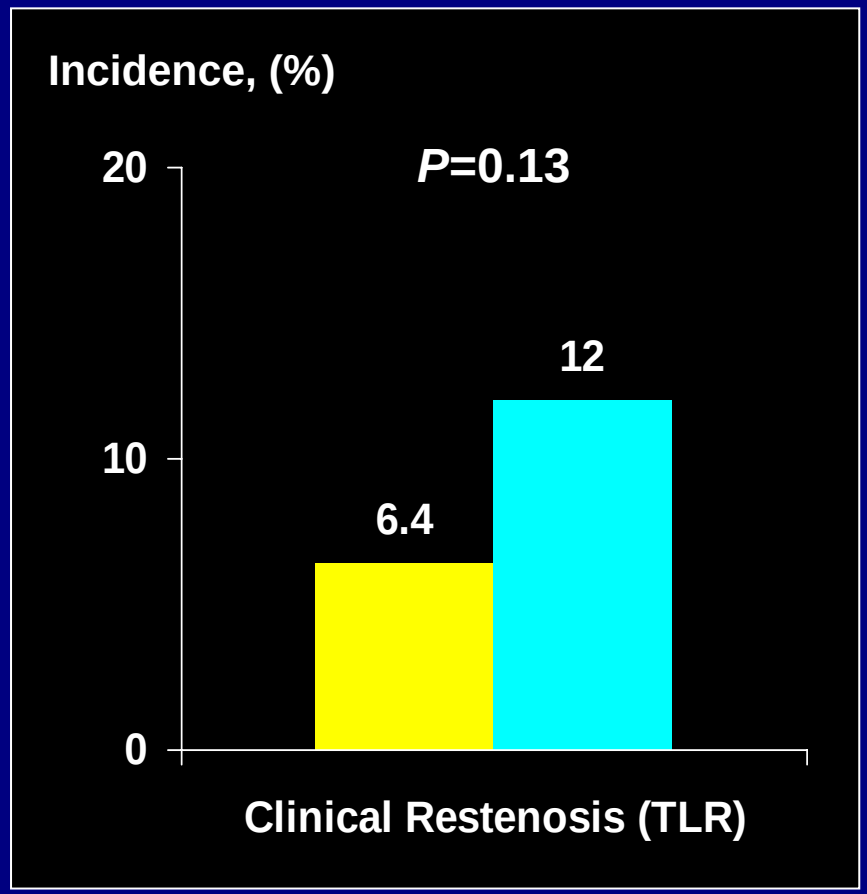
TAXUS

Kastrati, A. ACC 05 LBCT Presentation

ISAR-DIABETES

Restenosis





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Late Loss and Restenosis

TLR and Risk Concepts

- Late Loss is a measure of the propensity for repeat revascularization
- Late Loss "Head Room" is the extra space available for higher risk lesions to provide freedom from repeat revascularization
  - *It's always good to have low late loss*
- Restenosis Risk is important to consider when interpreting the impact of late loss
  - *Some trials have low risk patients, and BMSs do well*
  - *Some trials have high risk patients, and low late loss is needed*

Late Loss and Restenosis

TLR and Risk Concepts

- When given any parameter for a new DES, a low TLR may be reflective of low restenosis risk in the studied cohort, but late loss (in-stent) will give the best estimate of restenosis resistance over the wide range of restenosis risk.