

# What Are the Proper End Points for DES Trials?

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# *The Perception*



“drug”eluting

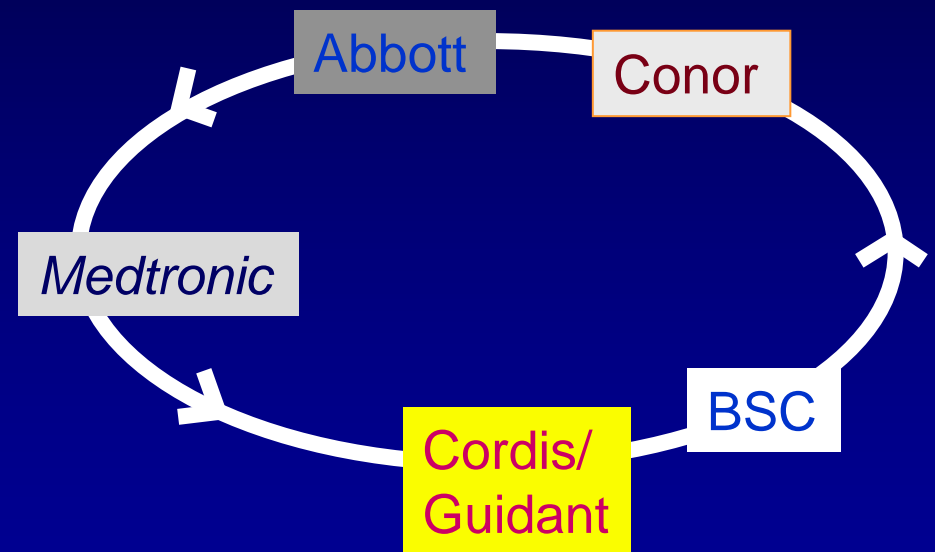


“just” bare metal

# Feeding Frenzy



# Who's ahead?



**Drug Eluting Stents**



**Clinical Results**

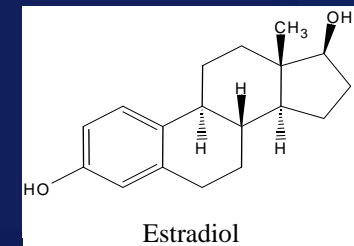
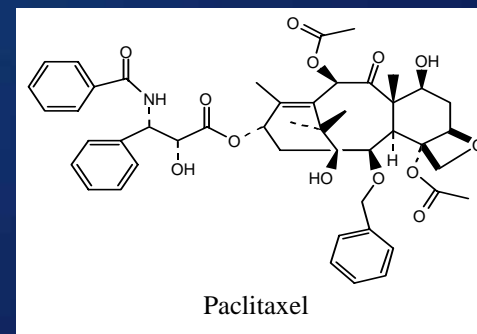
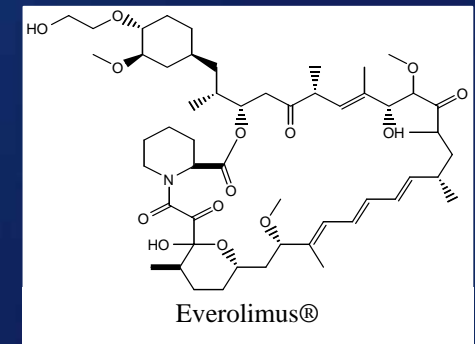
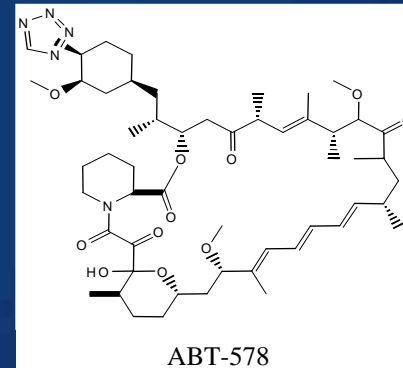
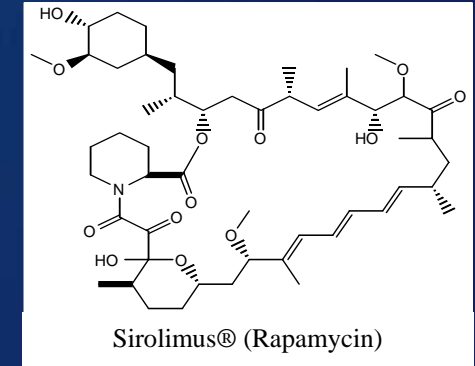
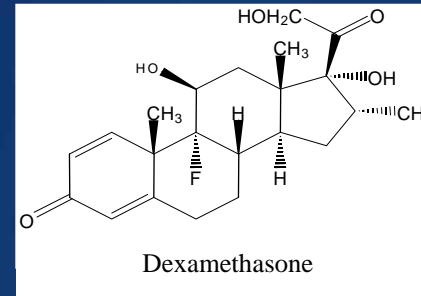
**Drug Eluting Stents**



**Clinical Results**

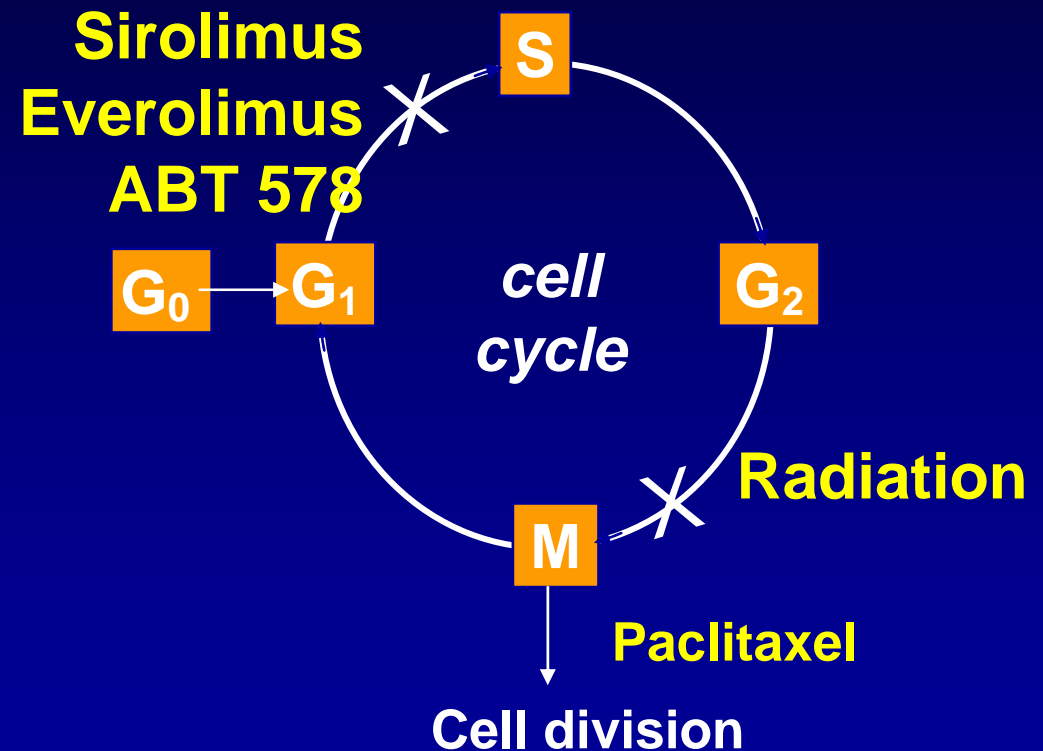
# In Search of Drugs to treat Restenosis

Drug Development	
Mechanism of action	✓
Cytostatic or cytotoxic	✓
Physiochemical properties	✓
Drug dosage	✓
Lipophilic and lipophobic	
Drug elution profile	✓
Tissue uptake	✓
Vascular toxicity	✓
Longitudinal and circumferential distribution	✓
Drug retention	✓
Polymer interaction	✓
Therapeutic window	✓

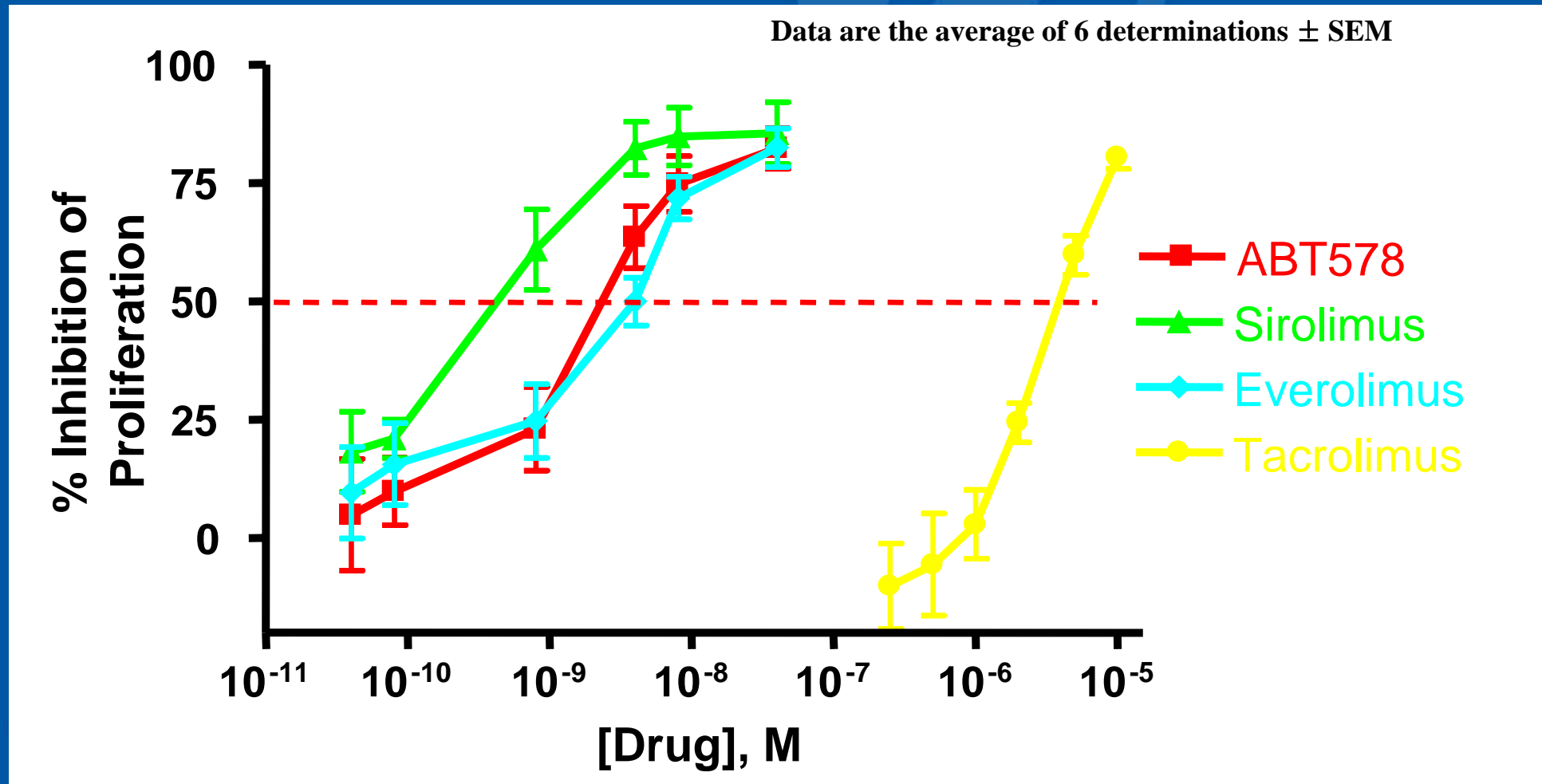


# Drugs that Inhibit Restenosis

- Drugs used in DES
  - Induce cell-cycle arrest in late G<sub>1</sub> phase
  - Decrease TGF  $\beta$
  - Elevate p53 levels
  - Inhibit microtubular assembly
  - Inhibit CDK/cyclin complexes



# Effect of 'rolimus Drugs on Proliferation of Human Coronary Artery Smooth Muscle Cells

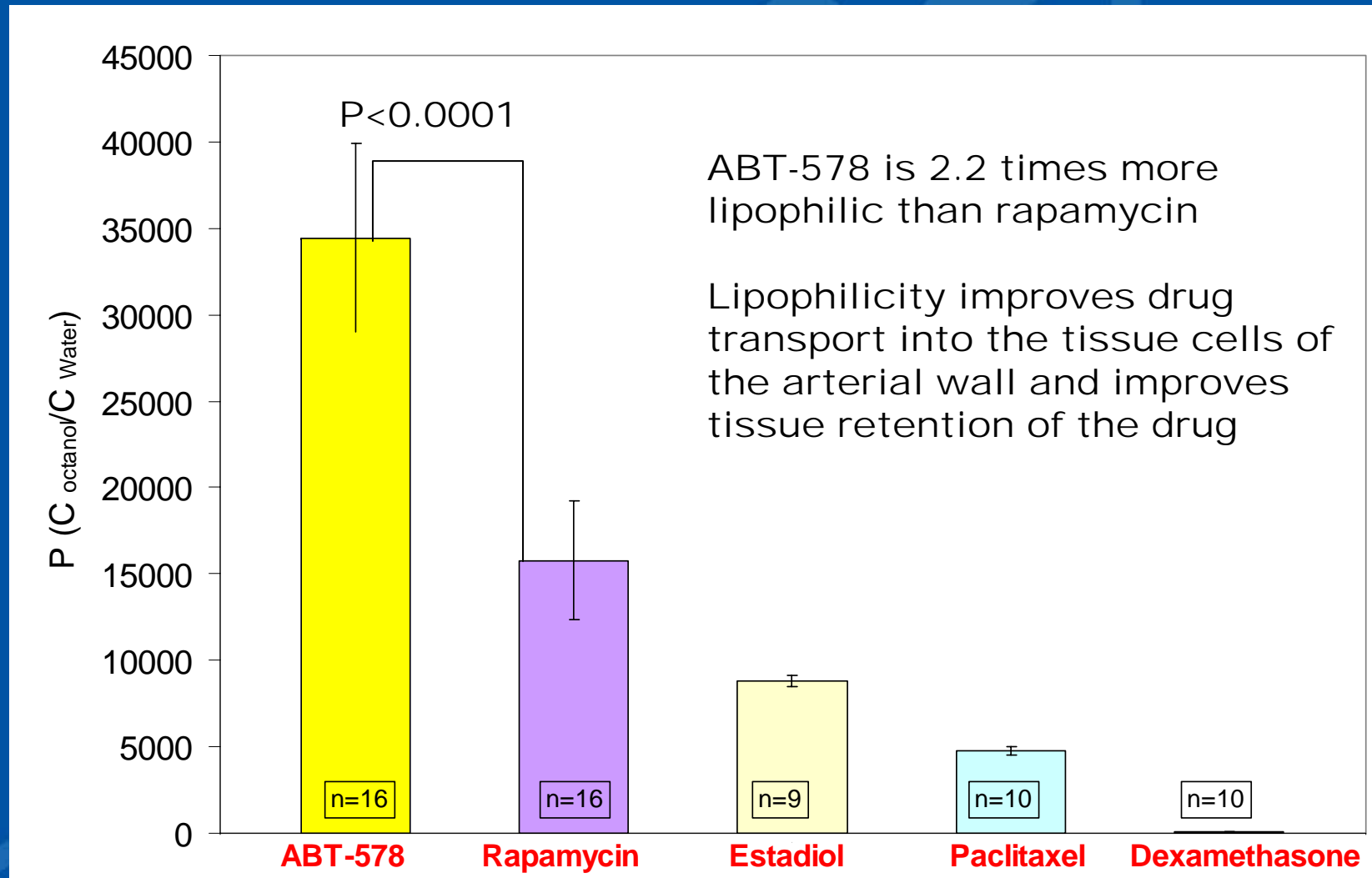


Chen Y-C, Burke SE, Toner J. Comparative potency of ABT-578, Sirolimus, Everolimus, Tacrolimus, Paclitaxel, and dexamethasone in inhibiting human coronary artery smooth muscle cell proliferation *in vitro*. Abbott Laboratories 5 IR-002-AP-03-RO, 2003.

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# Lipophilicities of Some Clinical DES Agents



Determination of Partition Coefficients for ABT-578, Rapamycin, Paclitaxel, Dexamethasone, and Estradiol at 22 deg C, Abbott Laboratories Report on File, 2004

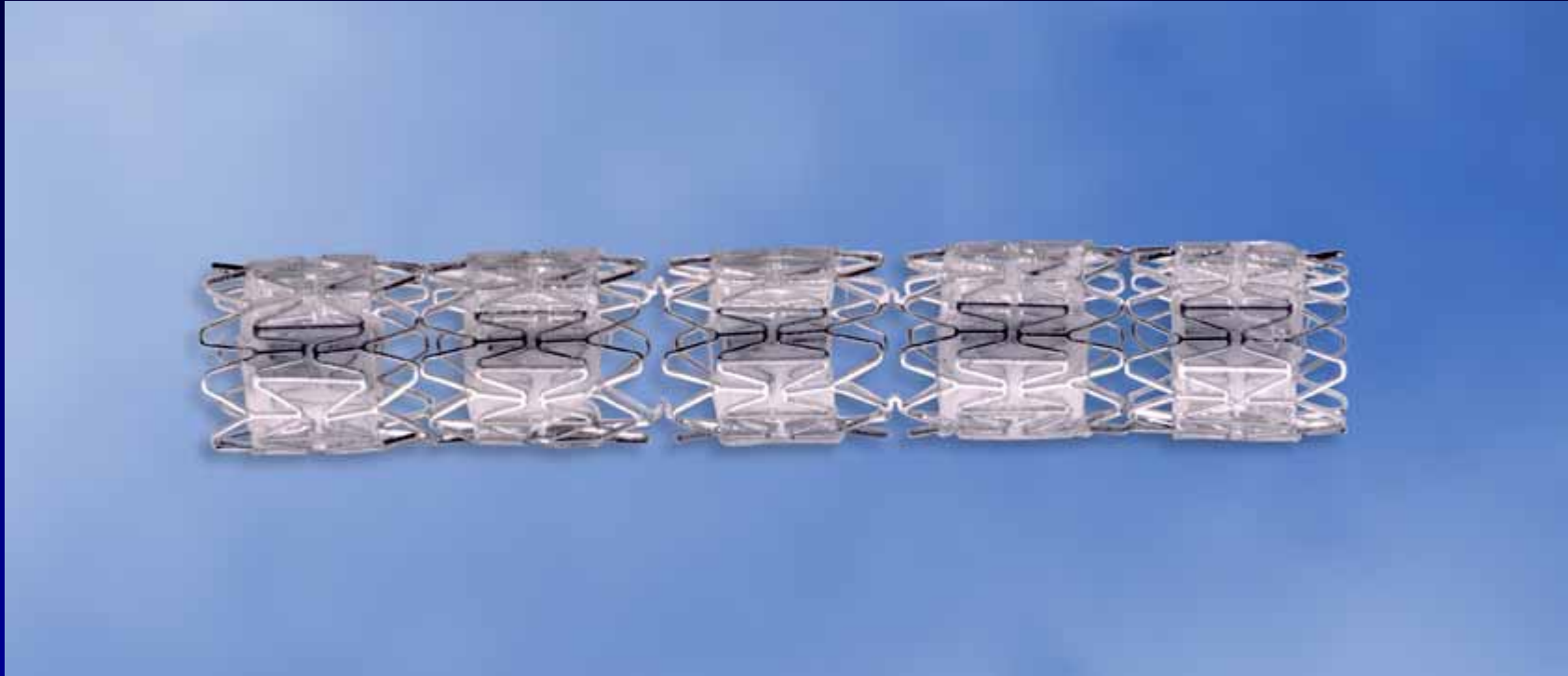
Drug **Eluting** Stents



Clinical Results

# Quanam Drug Eluting Stent

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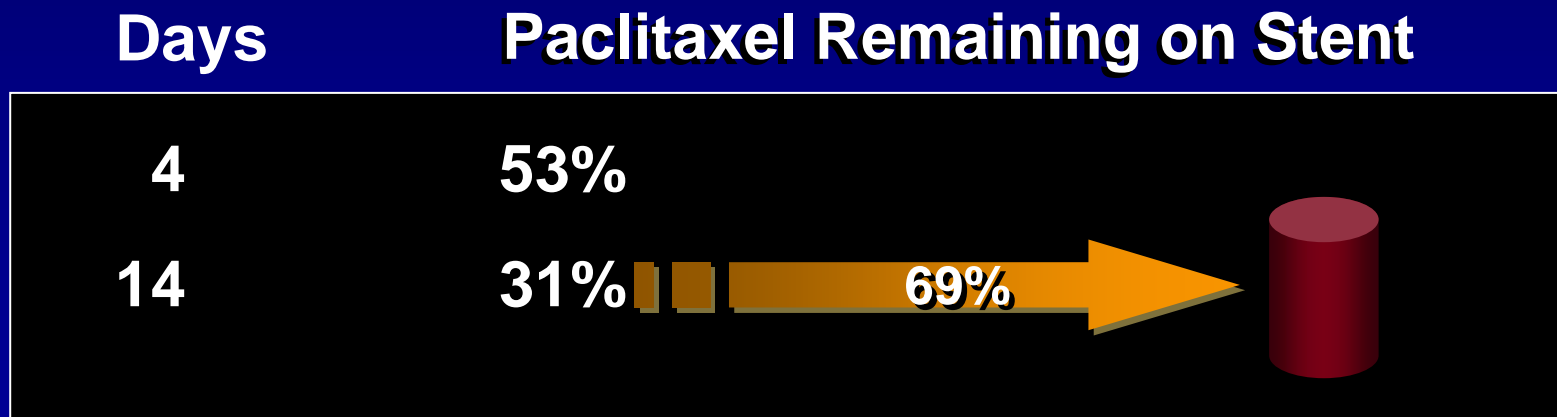


Quanam QuaDS Stent. Quanam polymer sleeves loaded with a microtubular inhibitor. Polymere sleeves are tightly stretched over dedicated metal stents .

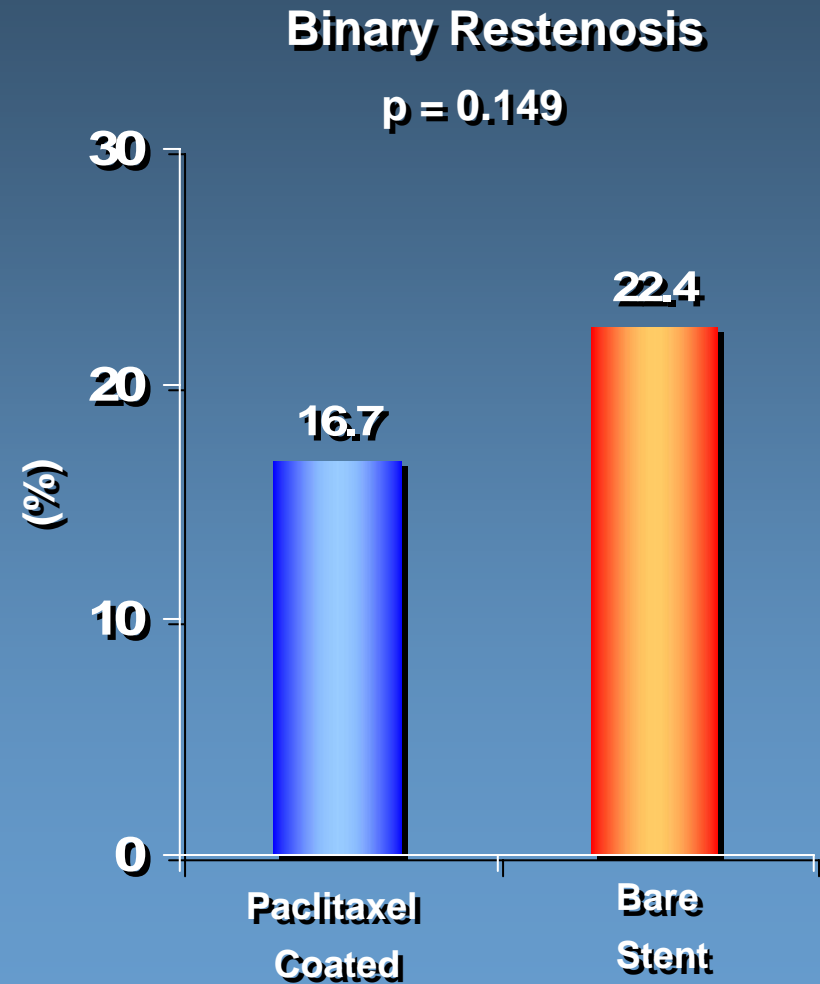
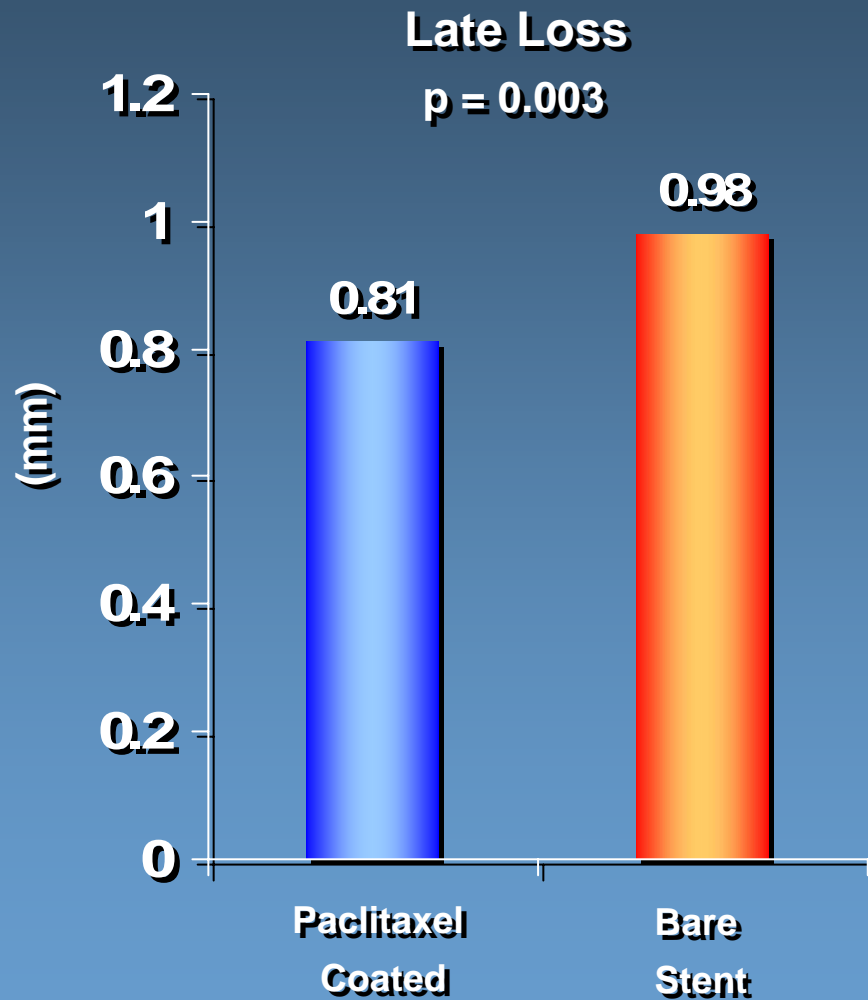
# *In vivo Pharmacokinetic Study*

## *What happens to a stent bound drug?*

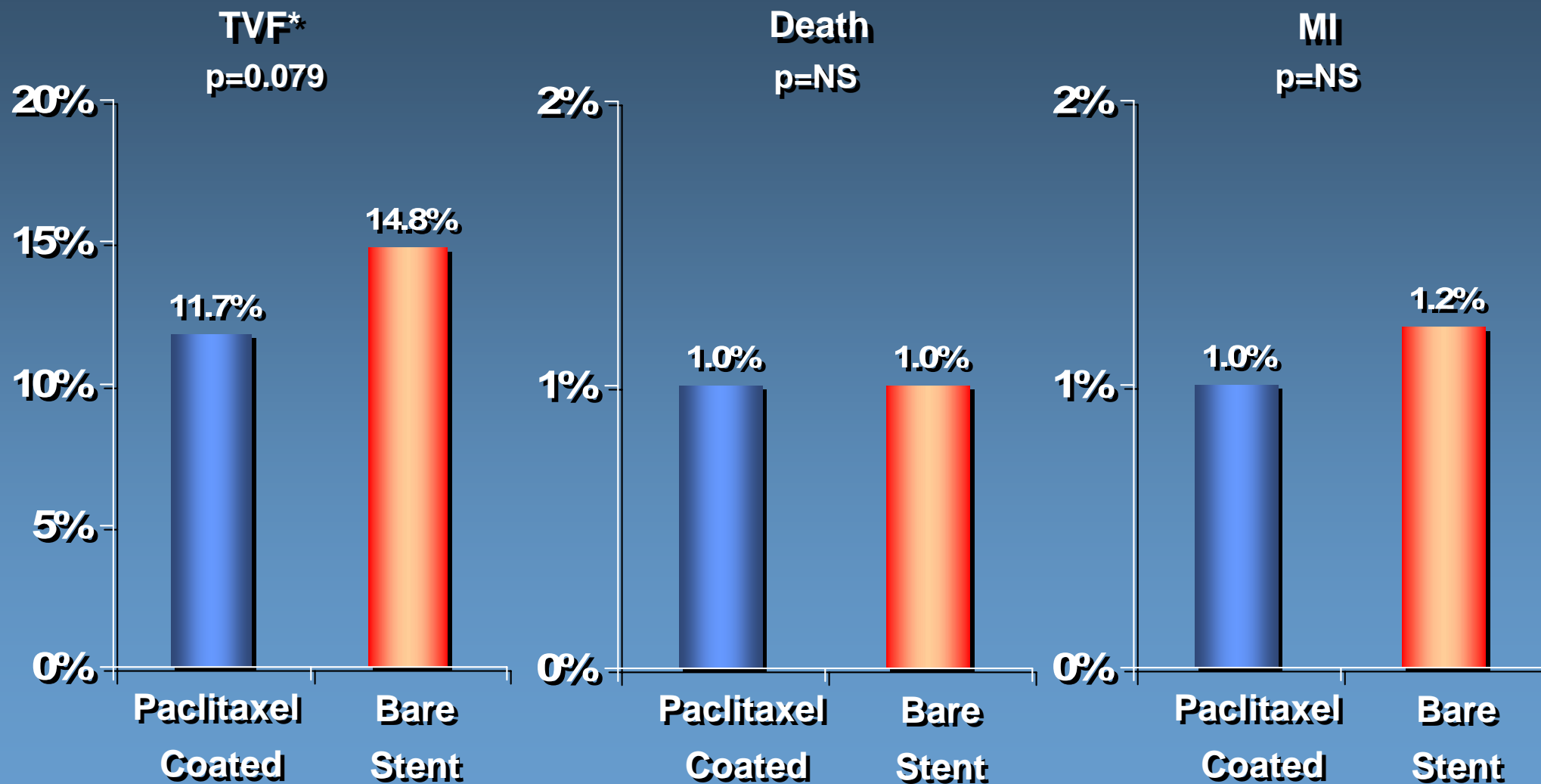
- **Stent Platform: V-Flex Plus™ (Cook Inc.)**



# DELIVER- Non-Polymeric Paclitaxel Stent 8 Month In-stent Angiographic Results

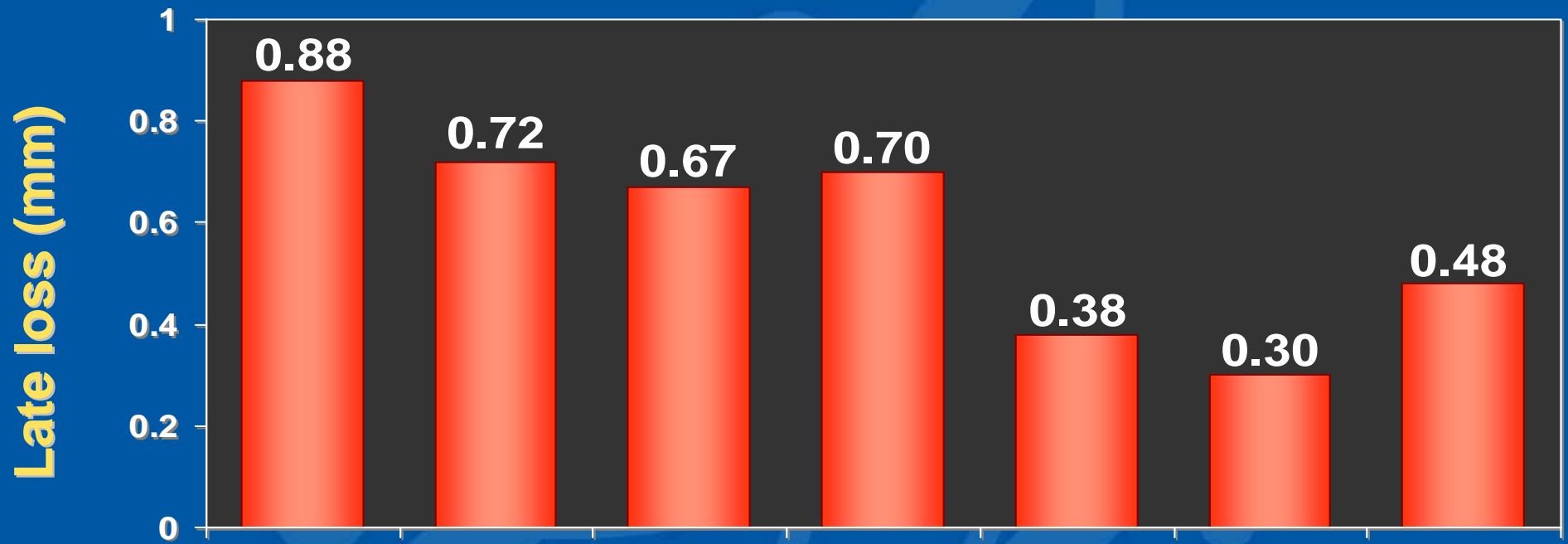


# DELIVER: 9 Month Clinical Event Results



\* TVF = Death/MI/TLR

# PISCES (n=221): QCA at 4 Months



	D0	D1	D2	D3	D4	D5	D6
N	43	29	28	28	38	26	29
Dose (ug)	-	10	10	10	10	30	30
Release (d)	-	5	10	10	30	30	10

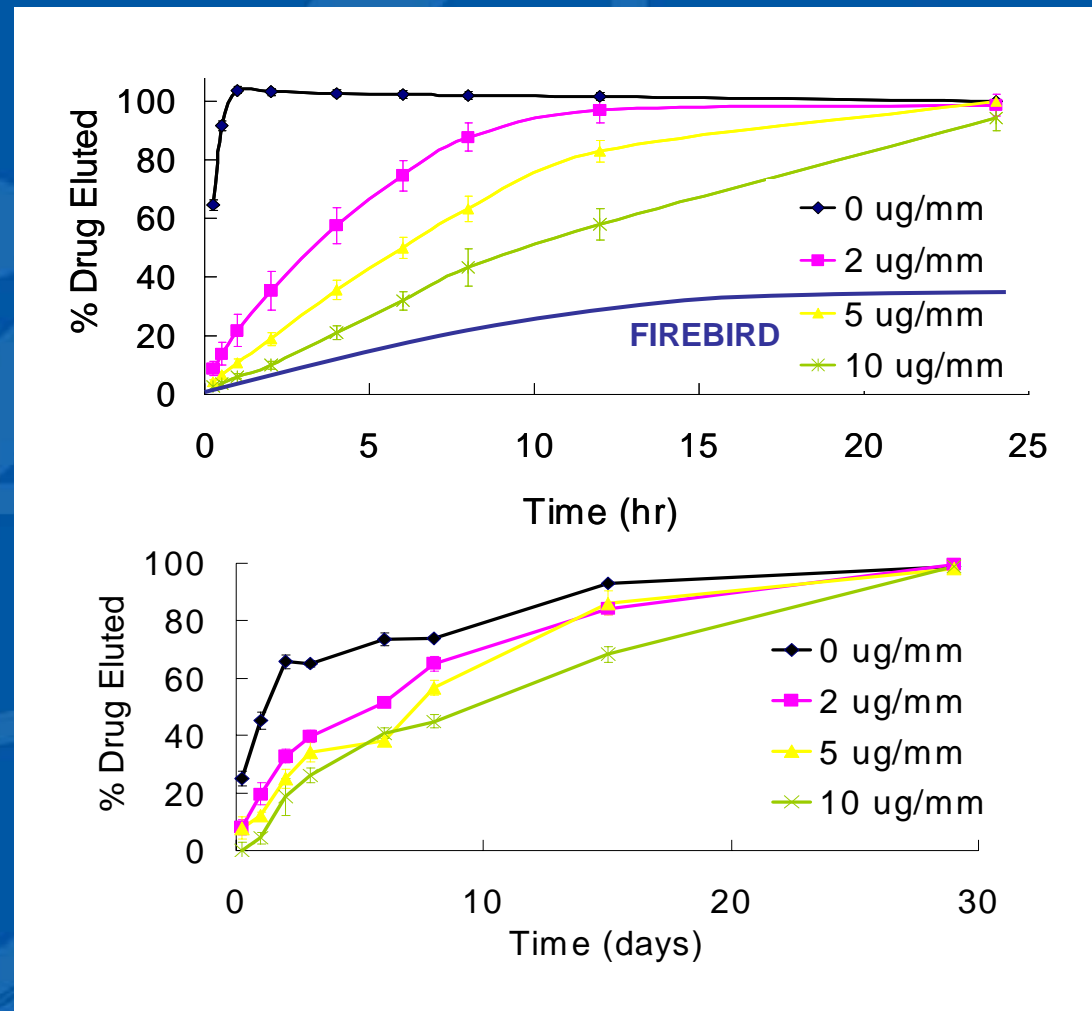


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# The Effect of Adding a Polymer Topcoat on the Elution Rate from Drug-Eluting Stents

For *in vitro* testing, stents (n=12 per group) were placed in a 1% solution of solutol in acetate buffer, and aliquots removed at designated time points and assayed for ABT-578 via HPLC.

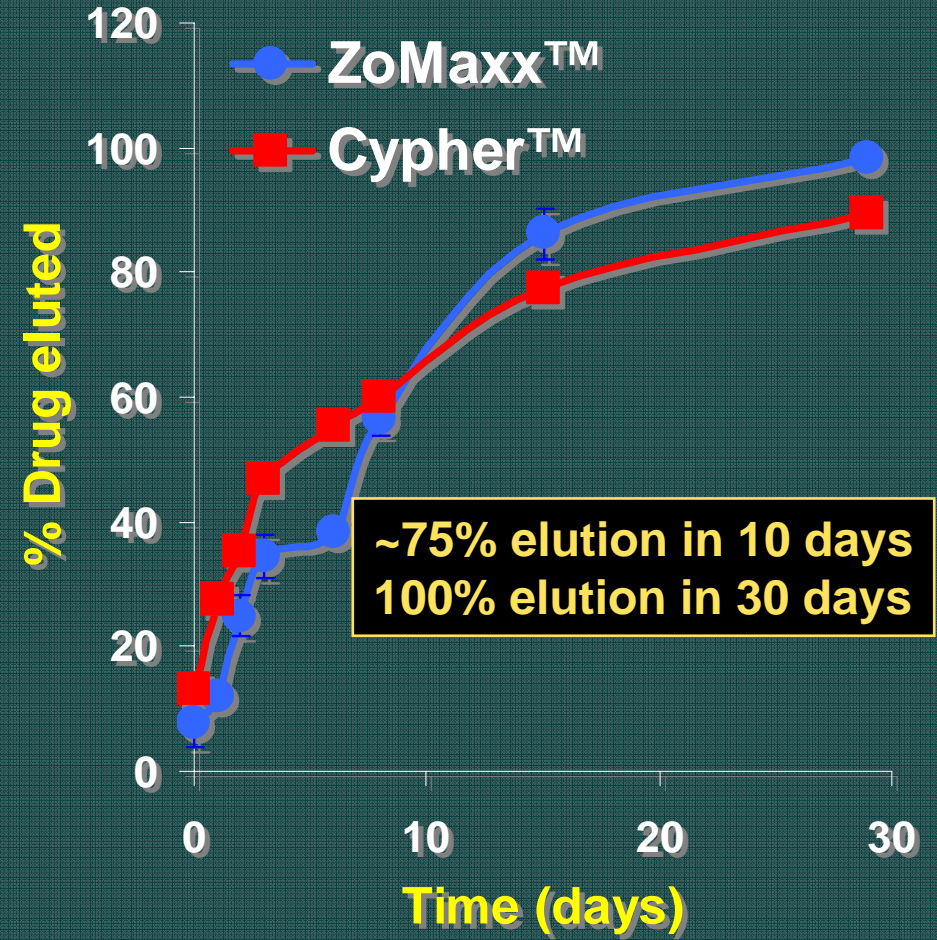
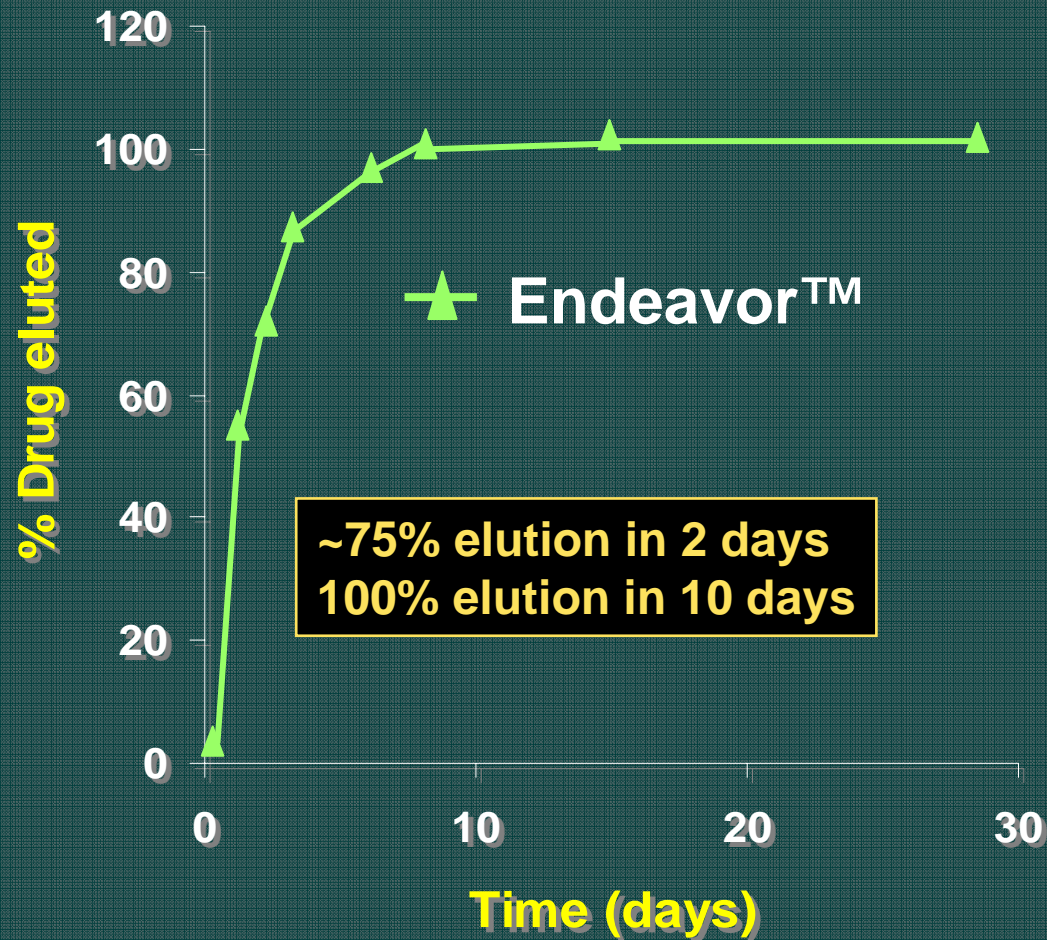
For *in vivo* testing, 128 stents (32 per group) were implanted in the common iliac arteries of New Zealand White rabbits and expanded to a 1:1.1 balloon-to-artery ratio. At set time (4 stents per group per time point), animals were euthanized, stents explanted, and the amount of ABT-578 remaining on the explanted stent was measured using HPLC.





# Comparison of *in vivo* Elution Rates

## Rabbit iliac models



ZoMaxx and Cypher data from B. Chevalier, EuroPCR 2004  
Endeavor data from G. Laarman, EuroPCR 2004

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**Drug Eluting Stents**



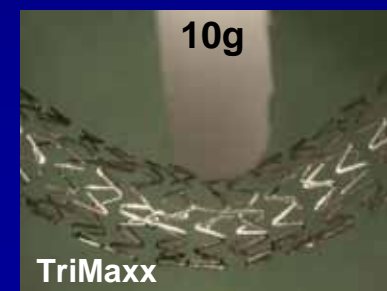
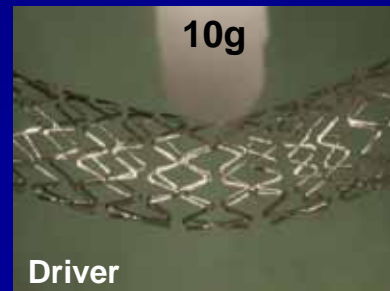
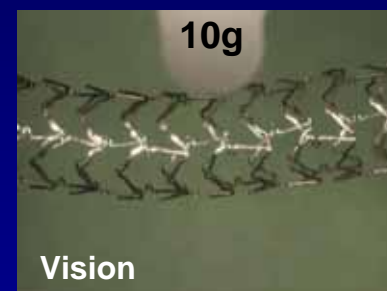
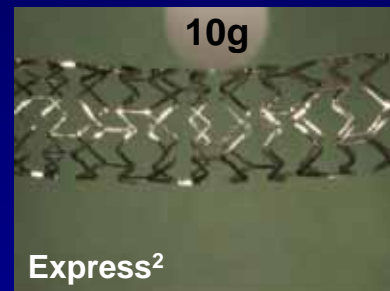
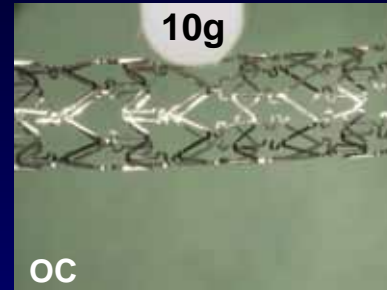
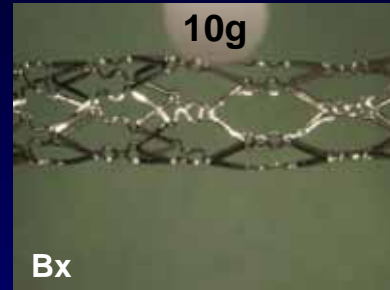
**Clinical Results**

**DELIVERABILITY !**

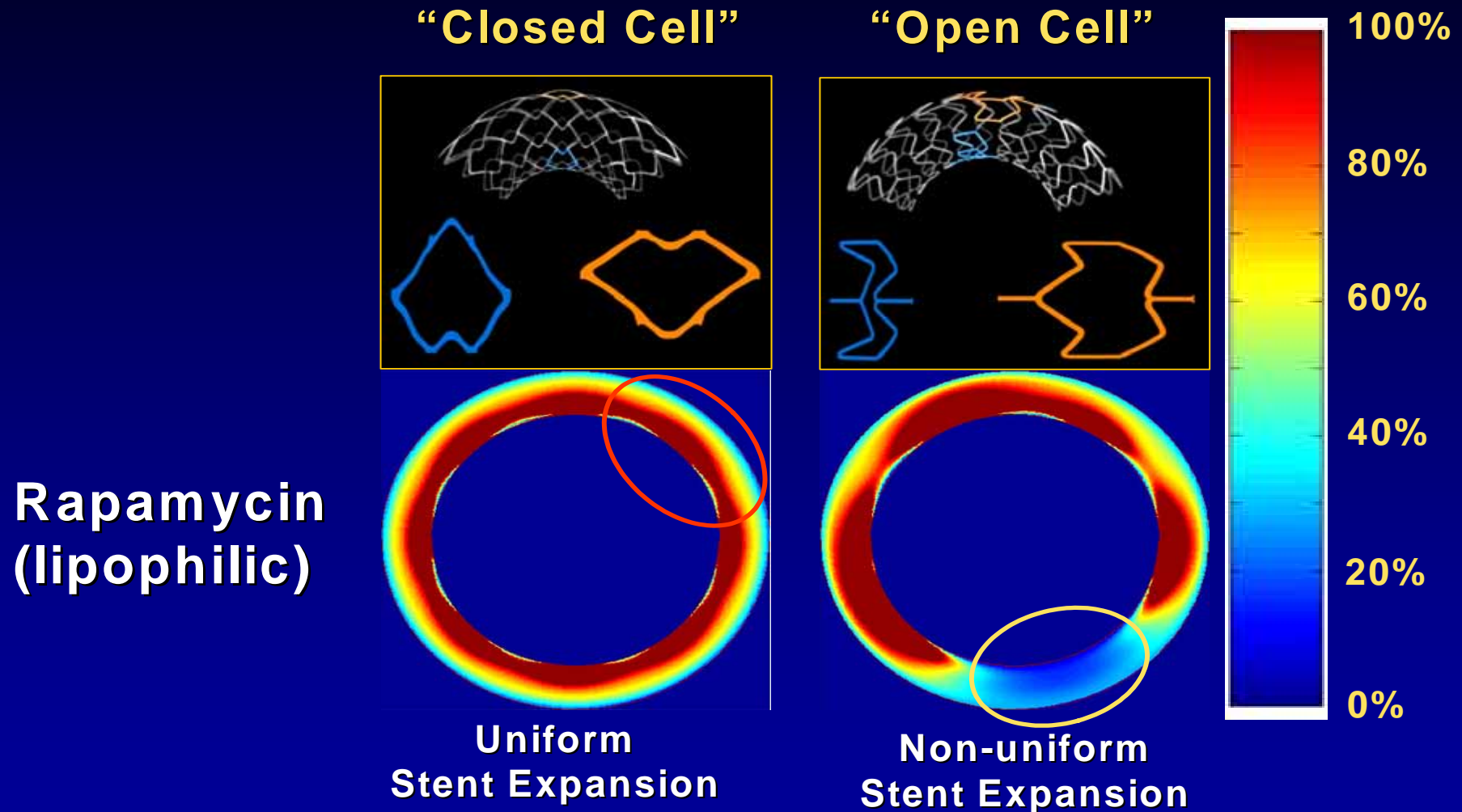
**DELIVERABILITY !**

**DELIVERABILITY !**

# Stent Flexibility



# Drug – Stent Interactions



*Hwang, Wu & Edelman, Circ 2001*

# Angiographic Measures

Pre-Procedure	<b>CYPHER<sup>®</sup></b> ( 684 patients; 970 lesions)	<b>TAXUS<sup>™</sup></b> ( 669 patients; 941 lesions)	<b>P-Value</b>
Reference Vessel Diameter (mm)	2.40 ± 0.48	2.40 ± 0.48	<b>P=NS</b>
% Diameter Stenosis	61.21 ± 12.26	61.43 ± 11.75	<b>P=NS</b>
Lesion Length (mm)	16.96 ± 10.04	17.31 ± 10.09	<b>P=NS</b>
<b>Post-procedure</b>			
In-stent Minimum Luminal Diameter (mm)	2.08 ± 0.35	2.16 ± 0.37	<b>P&lt;0.001</b>
In-stent % Diameter Stenosis	15.96 ± 6.91	15.00 ± 7.49	<b>P=0.004</b>
Absolute Gain In-stent (mm)	1.17	1.25	<b>P&lt;0.001</b>

# Angiographic Outcomes

## 8 Month Post-Procedure

	CYPHER®	TAXUS™	P-Value
In-stent MLD (mm)	2.00 ± 0.54	1.85 ± 0.52	<0.001
In-lesion MLD (mm)	1.79 ± 0.51	1.71 ± 0.49	<0.001
In-stent %DS	23.11 ± 16.59	26.70 ± 15.84	<0.001
In-lesion %DS	29.11 ± 15.81	31.06 ± 15.36	0.009
In-stent Late-loss (mm)	0.09 ± 0.43	0.31 ± 0.44	<0.001
In-lesion Late-loss (mm)	0.04 ± 0.38	0.16 ± 0.40	<0.001
In-stent Net Gain (mm)	1.08 ± 0.54	0.94 ± 0.55	<0.001
In-lesion Net Gain (mm)	0.88 ± 0.50	0.79 ± 0.52	<0.001

**Drug Eluting Stents**



**Clinical Results**

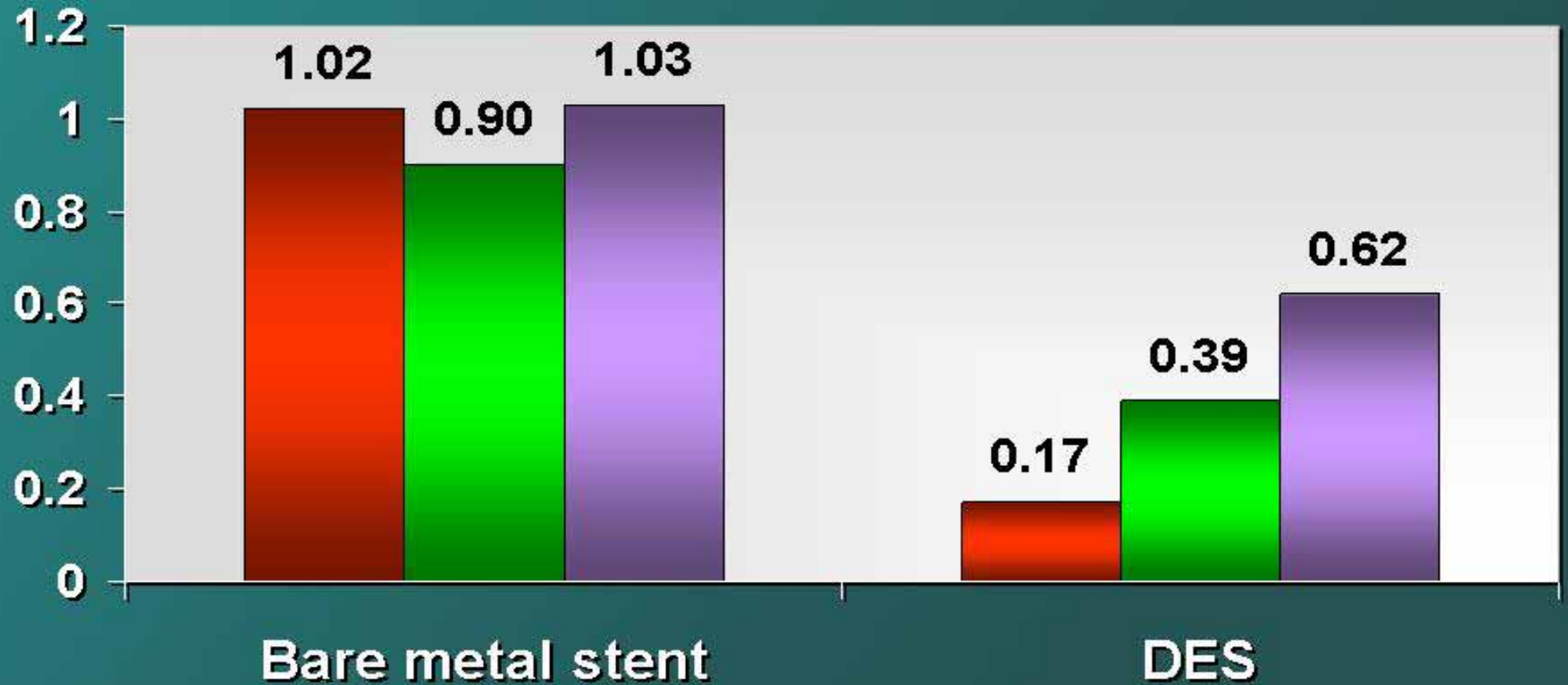


ARE ALL DES THE SAME ?

## Late loss (in-stent)

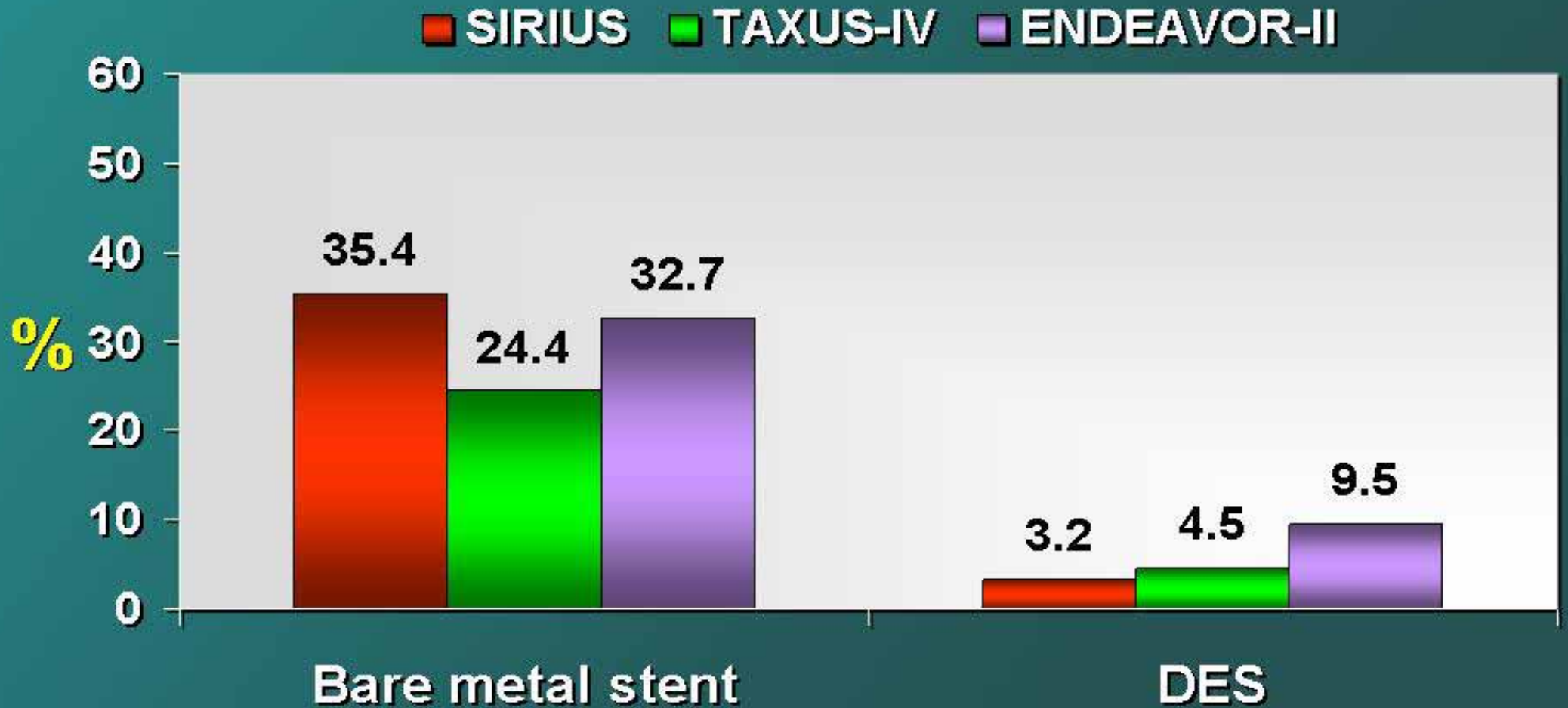
mm

■ SIRIUS ■ TAXUS-IV ■ ENDEAVOR-II



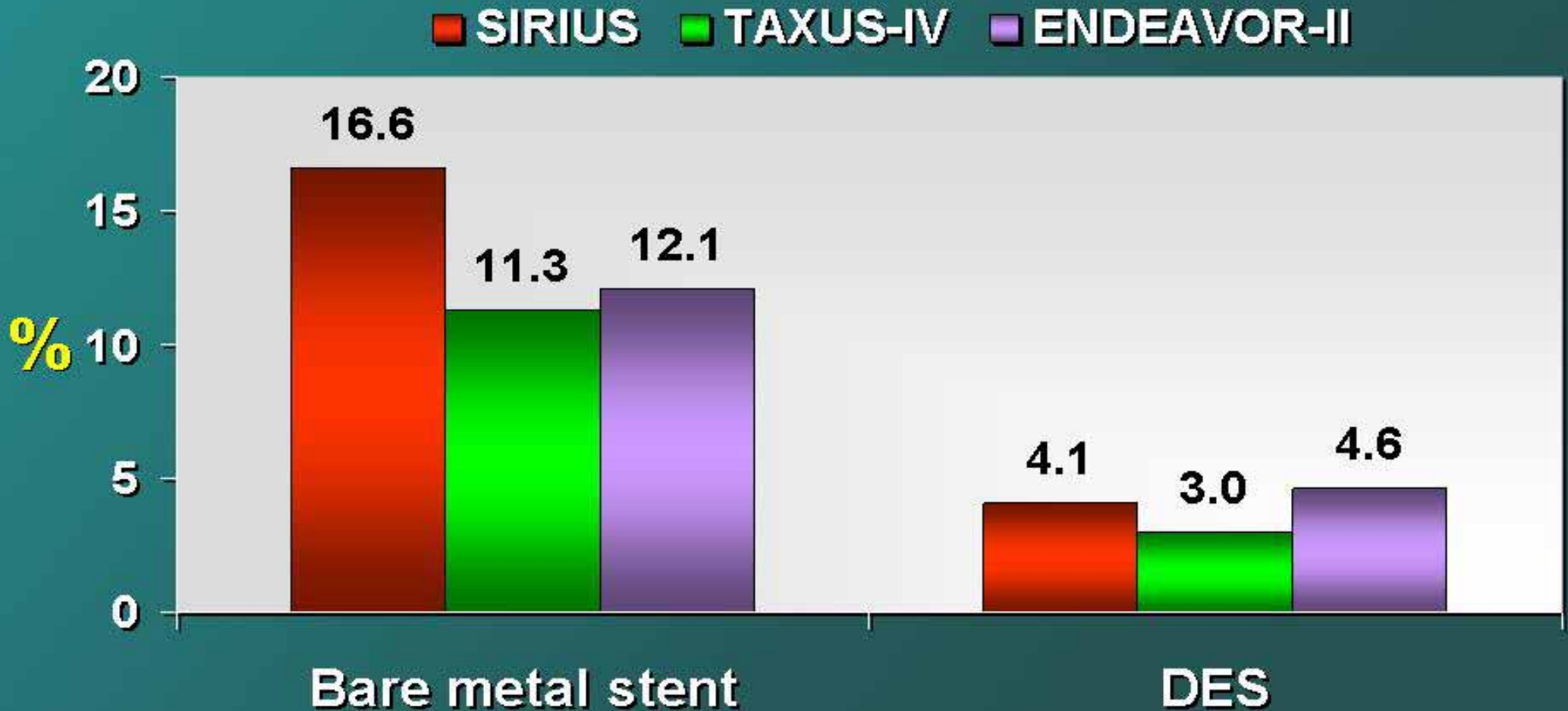
ARE ALL DES THE SAME ?

# Binary restenosis (in-stent)



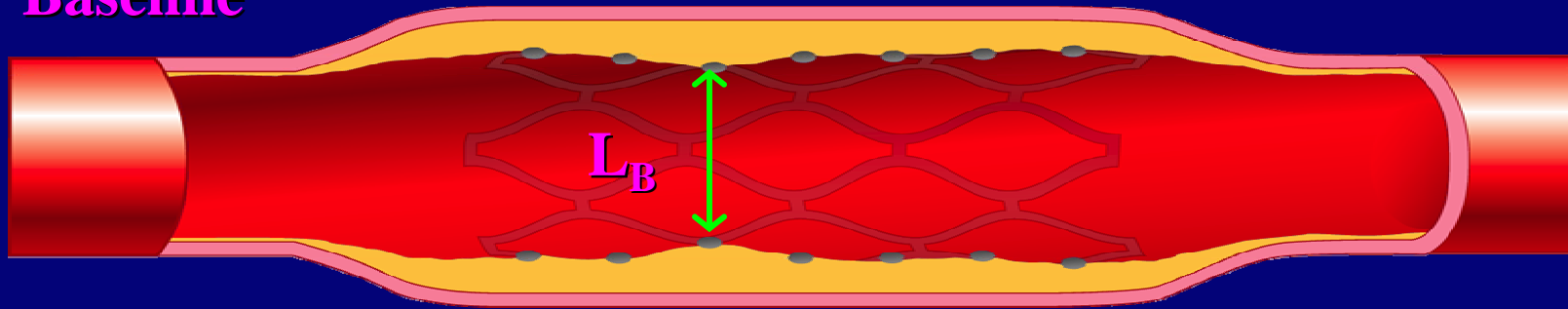
*ARE ALL DES THE SAME ?*

**Target lesion revascularization at 9 mos**

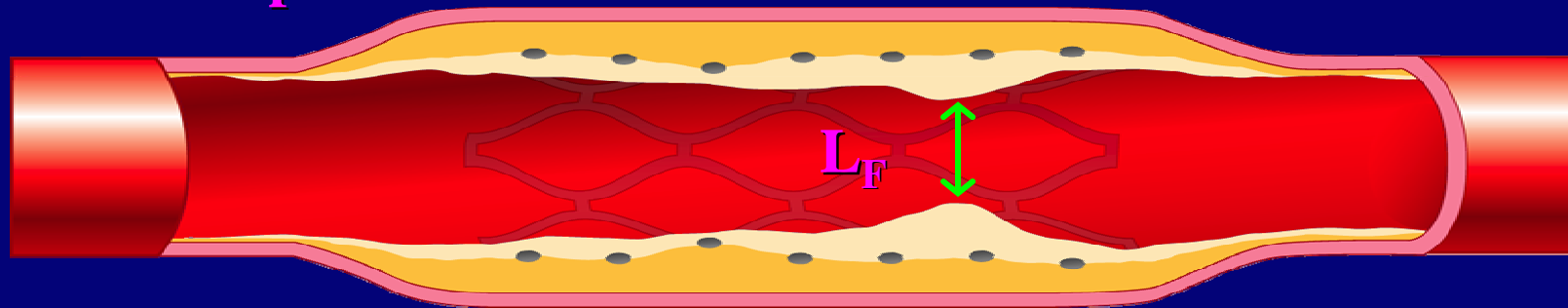


# Angiographic Late Lumen Loss

Baseline



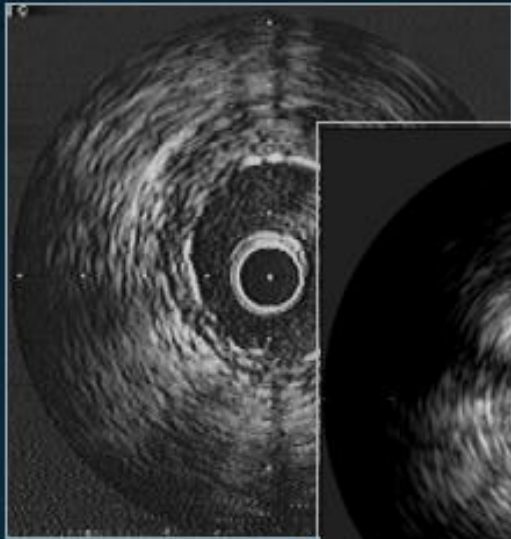
Follow-up



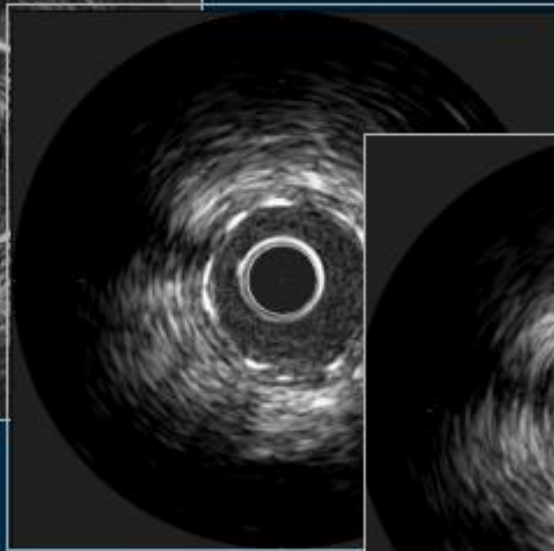
$$\text{Late Lumen Loss} = L_B - L_F$$

# Visual significance of late loss

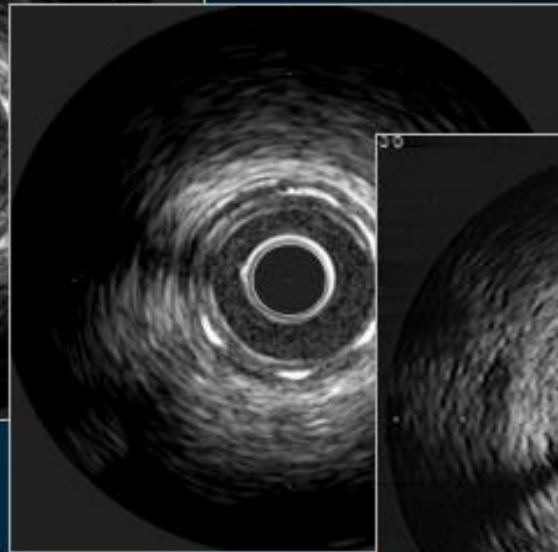
late loss 0.01 mm



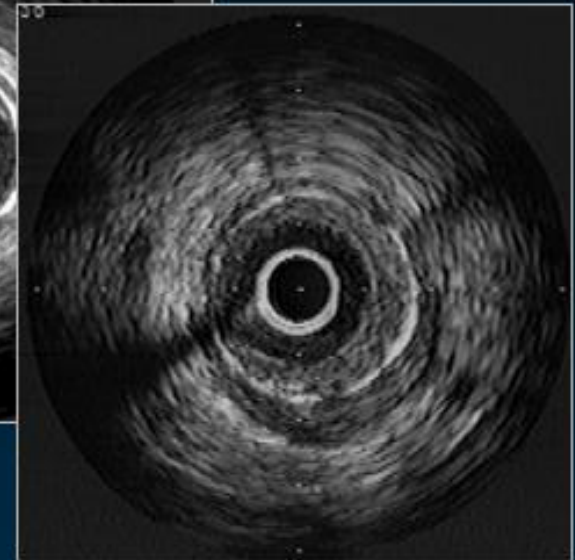
0.32 mm



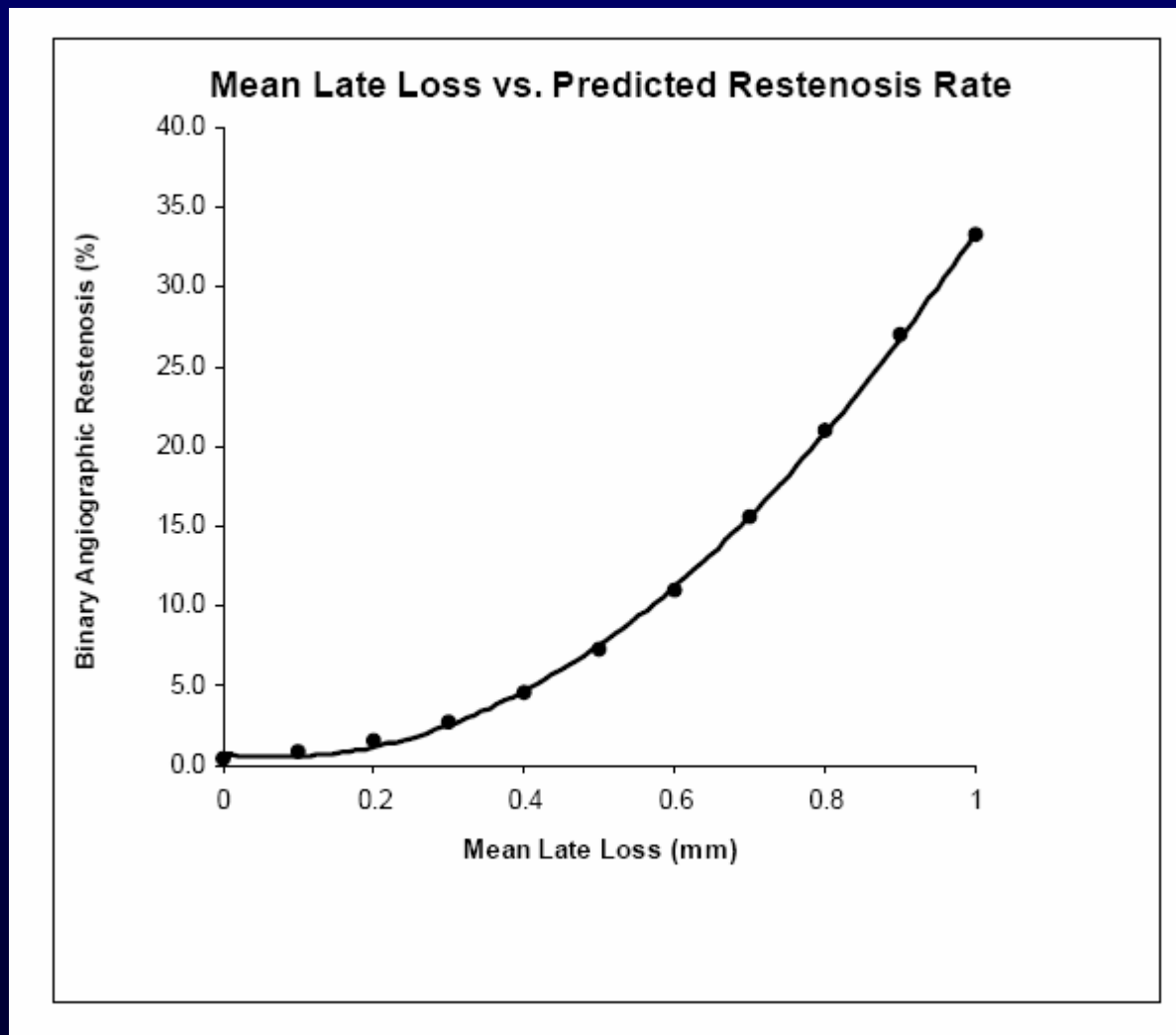
0.61 mm



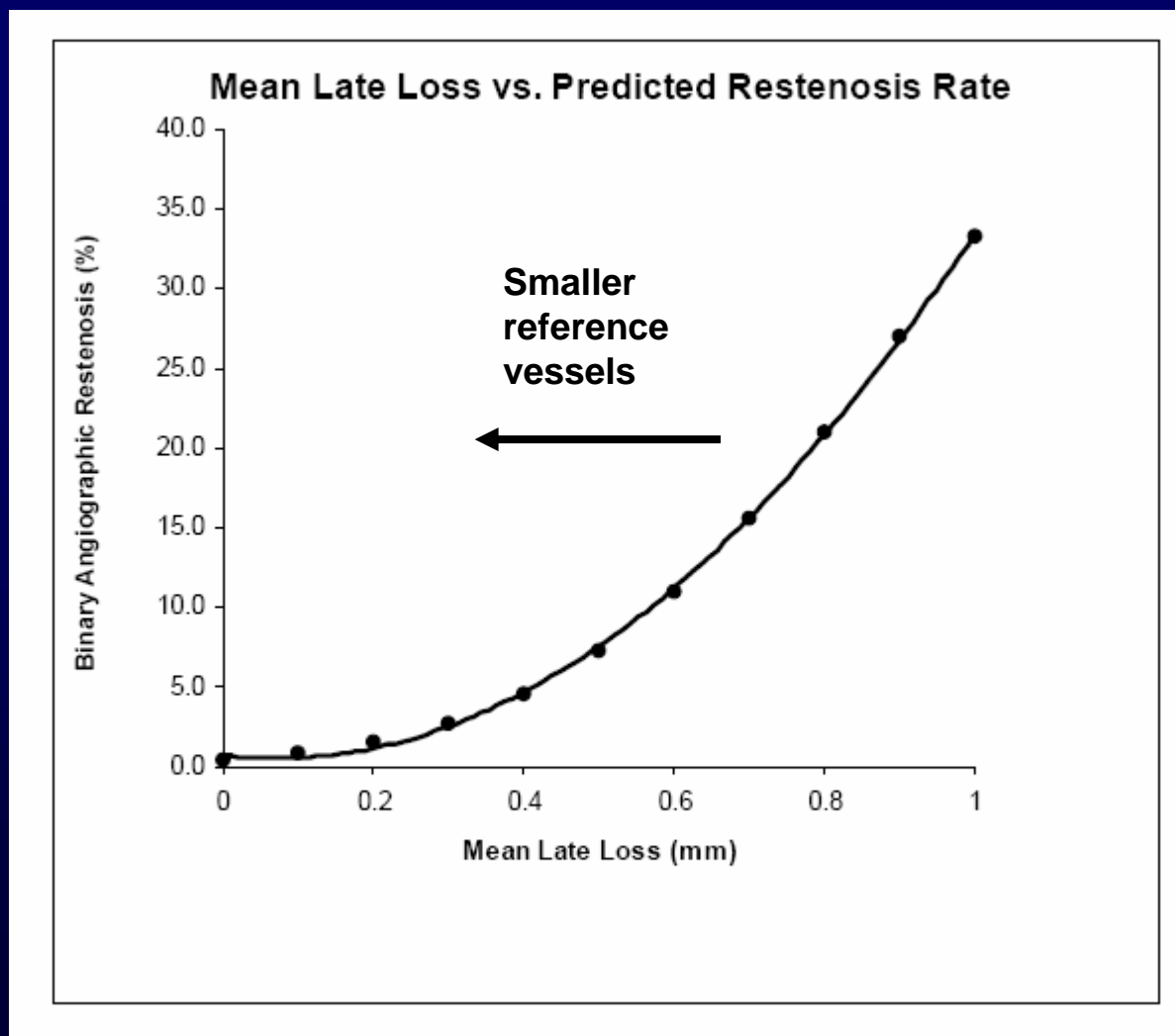
0.9 mm



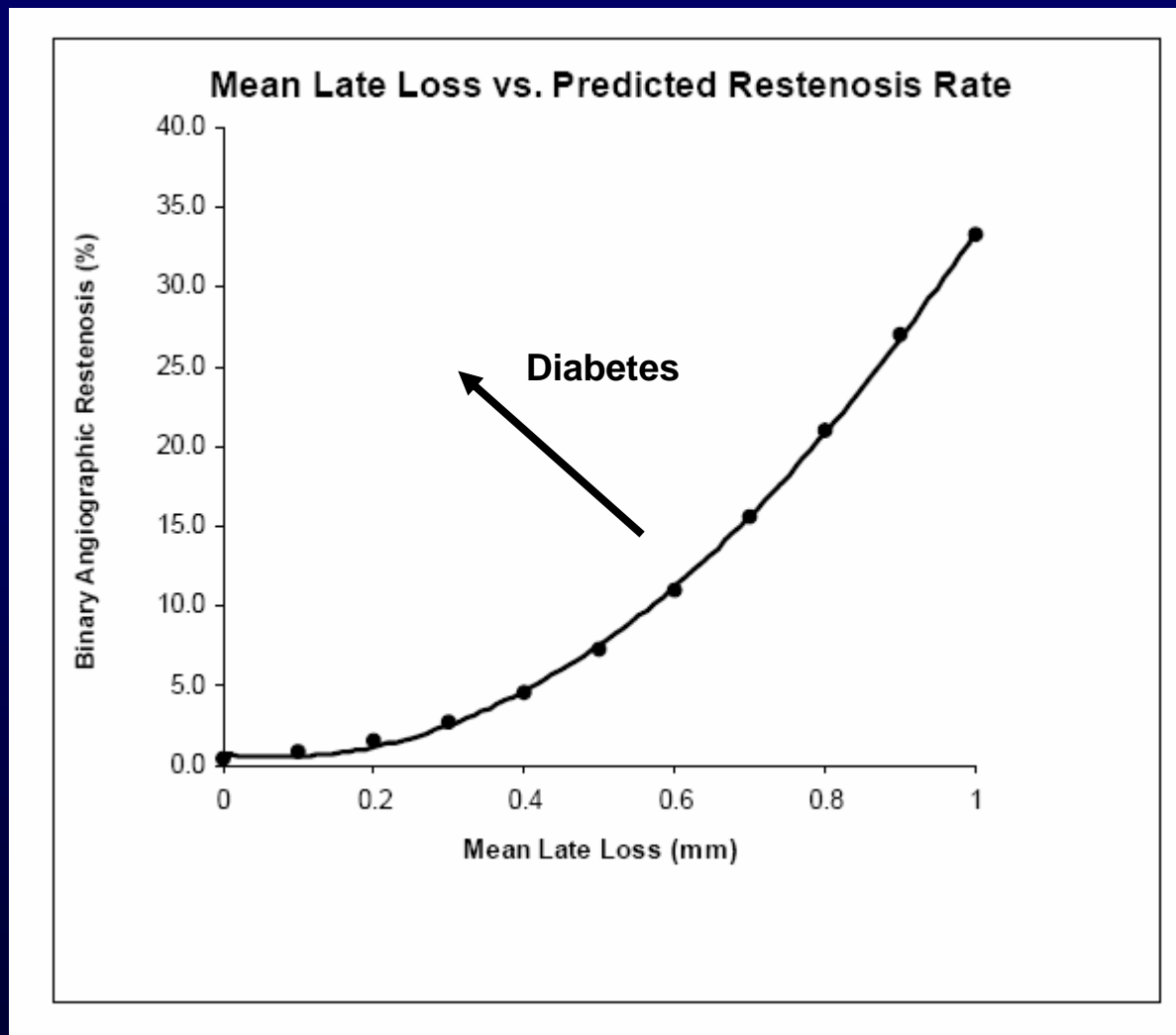
**Mean late loss vs. predicted restenosis rate** Predicted restenosis rates for a reference population of mean RVD 2.79 mm and mean post-stent MLD 2.67 mm.



**Mean late loss vs. predicted restenosis rate** Predicted restenosis rates for a reference population of mean RVD 2.79 mm and mean post-stent MLD 2.67 mm.

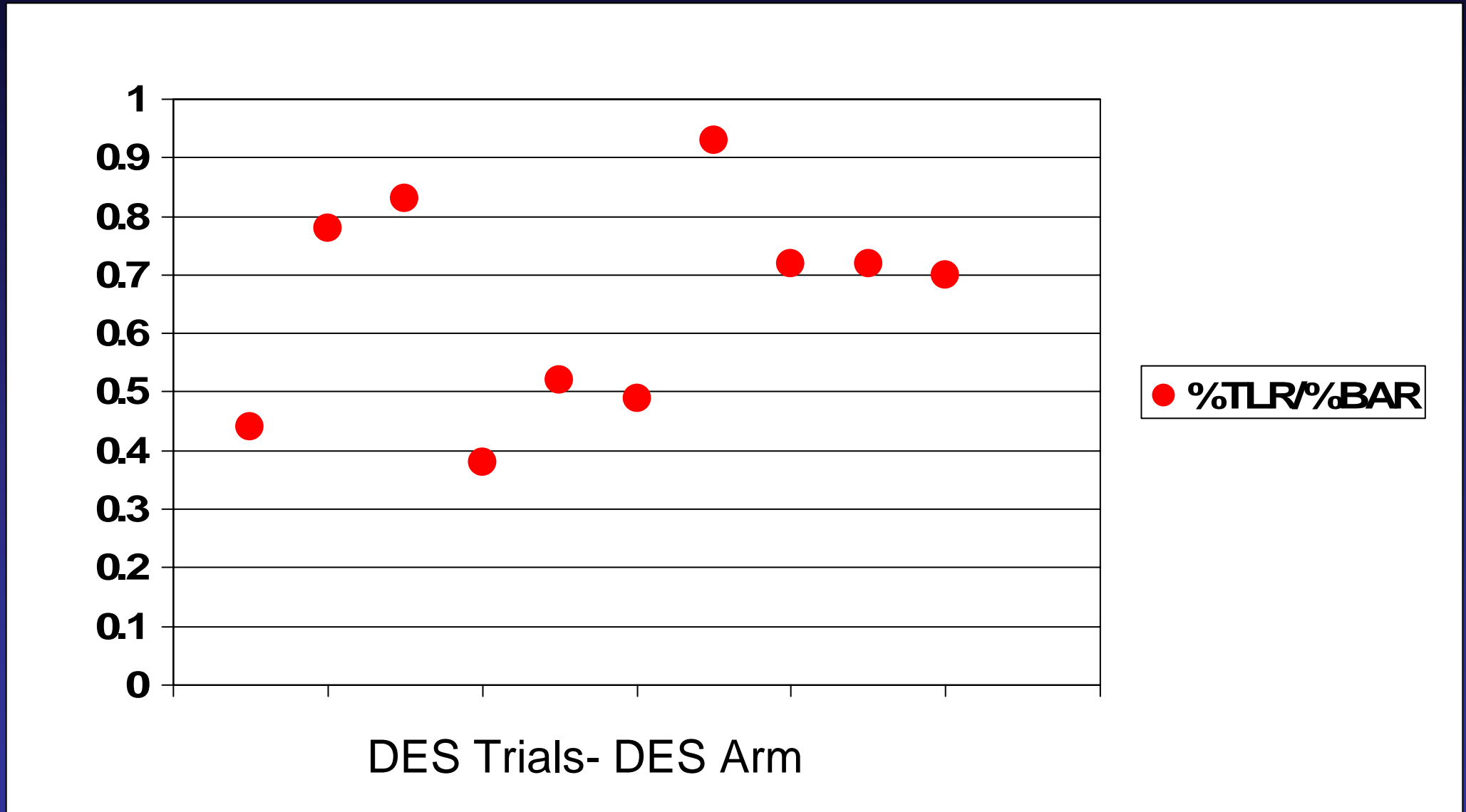


**Mean late loss vs. predicted restenosis rate** Predicted restenosis rates for a reference population of mean RVD 2.79 mm and mean post-stent MLD 2.67 mm.





## Relation between Binary Restenosis Rate (in-segment) vs %TLR



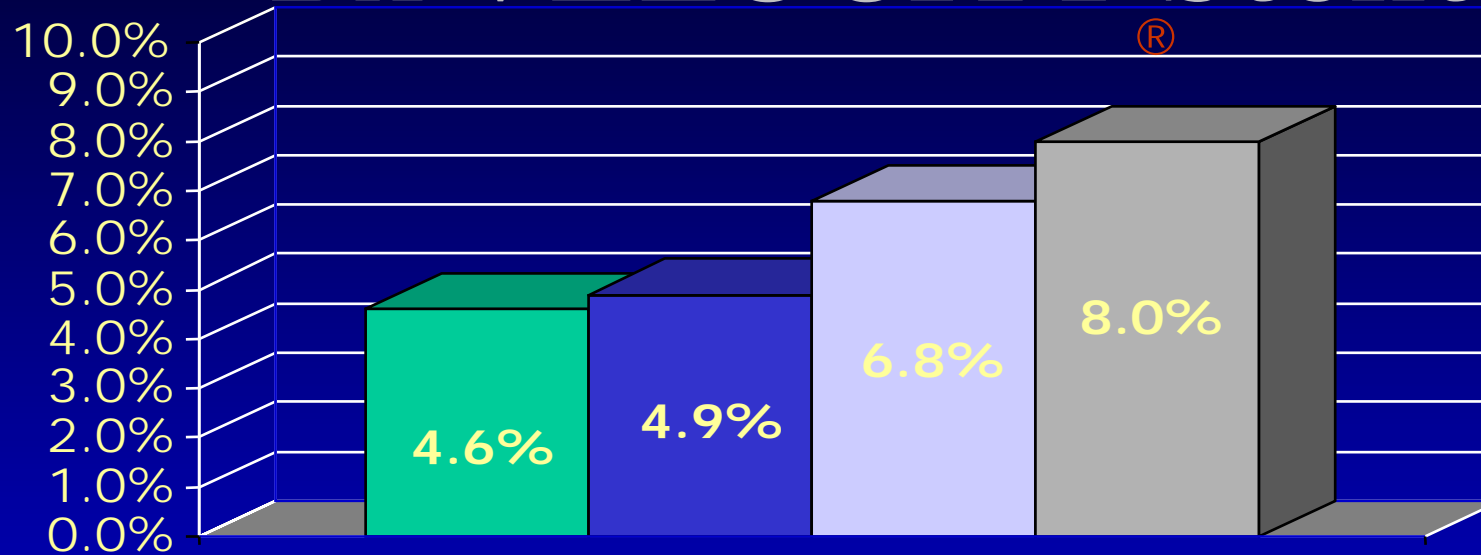
## When does BAR becomes TLR?

- Baseline vessel size
- Restenosis length
- Presence of disease elsewhere in the vessel
- Presence of symptoms
- Viability of the myocardium
- Method of QCA in the core lab
- Physician judgement
- Angiographic follow-up at or before clinical follow-up

# Trial Design Drives Outcomes

*TLR Is also Influenced by Trial Design*

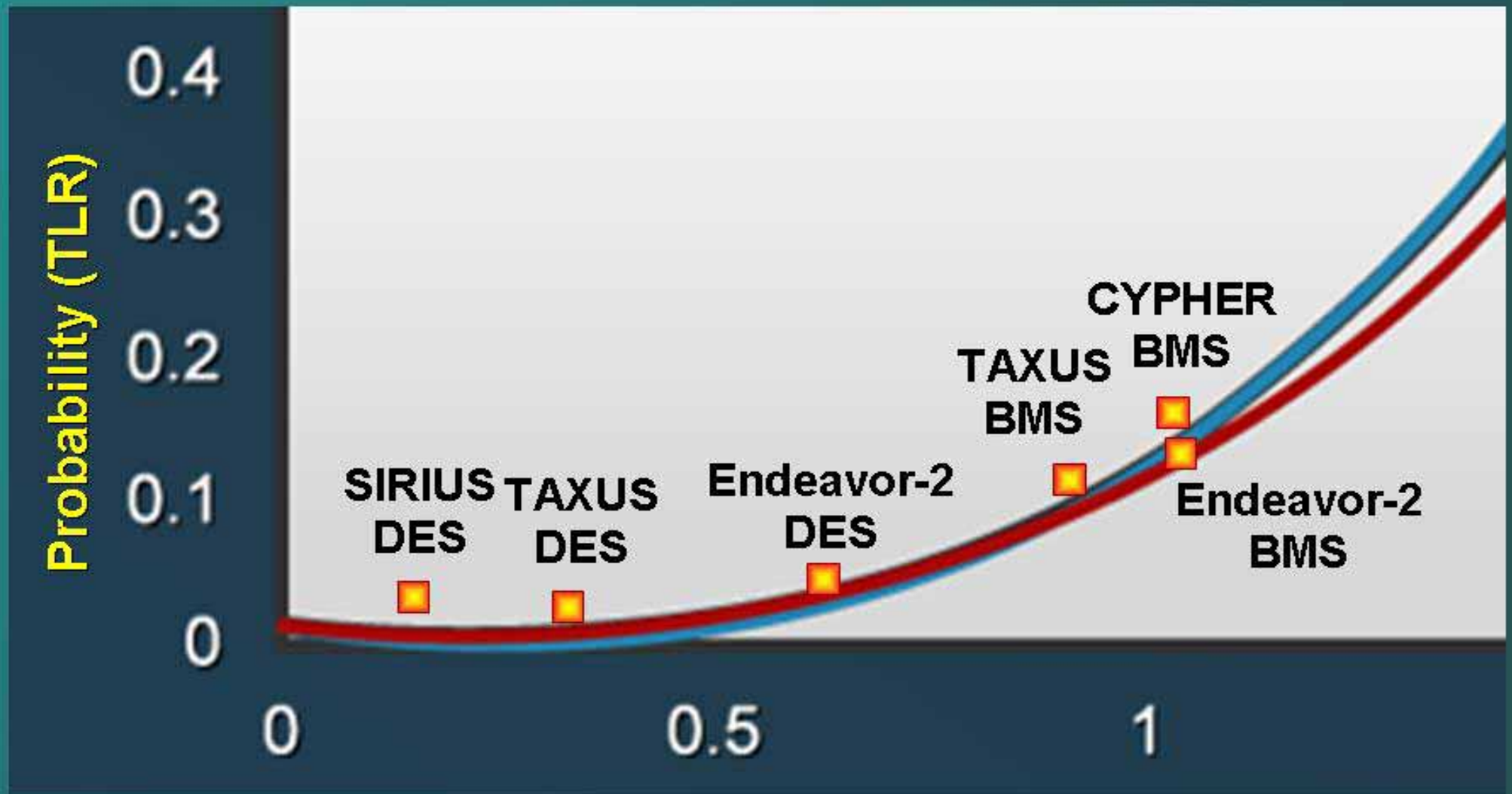
## Bx VELOCITY Stent



**Six-Mos. Target Lesion  
Revascularization (TLR)**

	Diabetics	MLD-post	Stented Length	Diabetics	MLD-post	Stented Length	Diabetics	MLD-post	Stented Length
<b>Diabetics</b>	23.4%	10.7%	21.2%	28.2%					
<b>MLD-post</b>	2.90 mm	2.55 mm	2.41 mm	2.68 mm					
<b>Stented Length</b>	16.3 mm	18.0 mm	18.0 mm	21.2 mm					

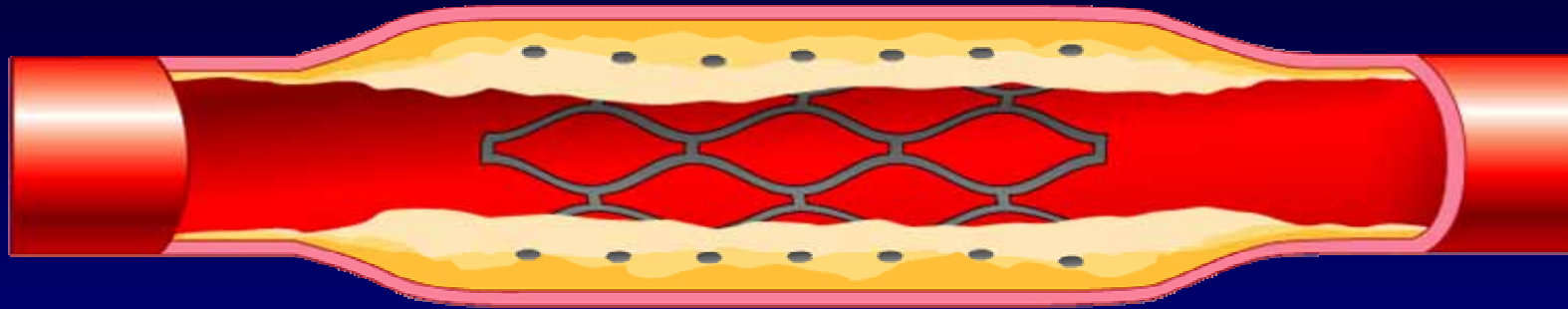
# De Novo "Pivotal" RCTs



**In-Stent Late Lumen Loss**

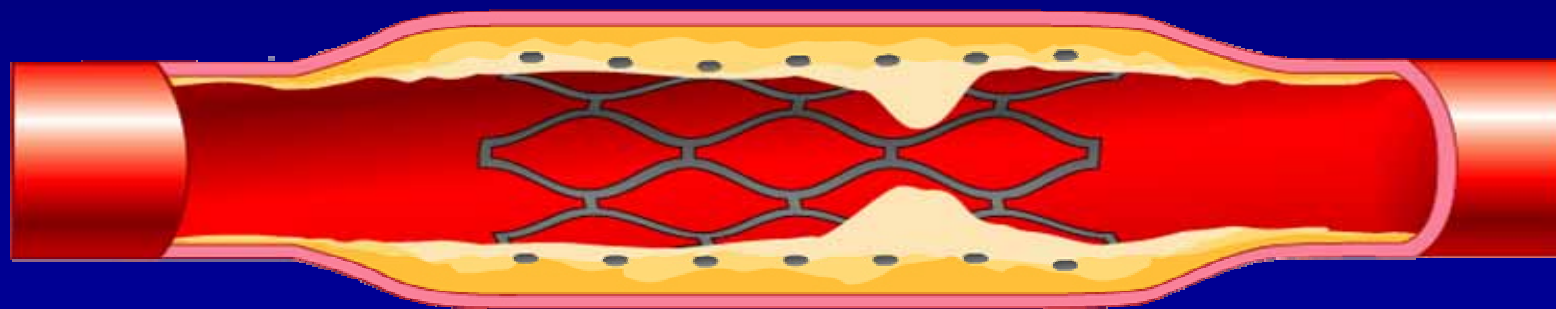
# 3D-IVUS: Diffuse vs Focal Neointima

Diffuse NIH



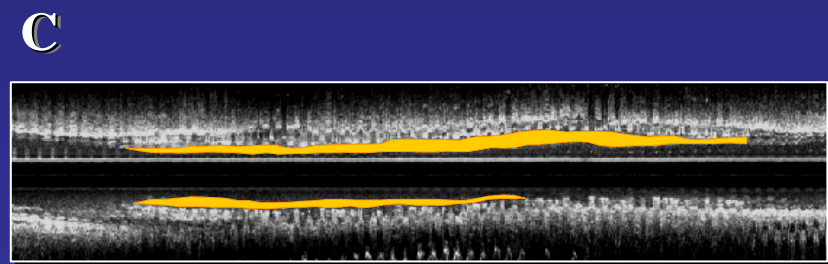
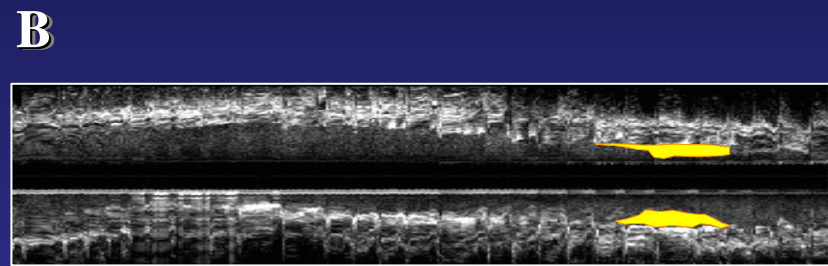
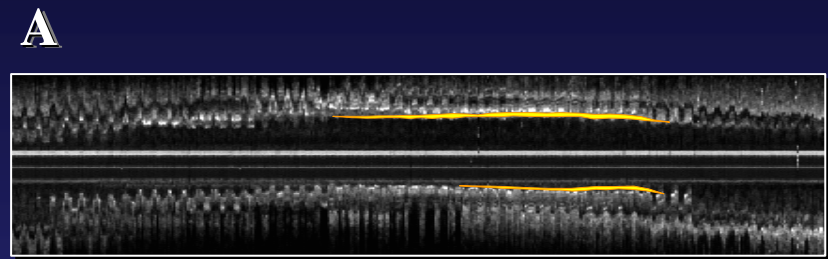
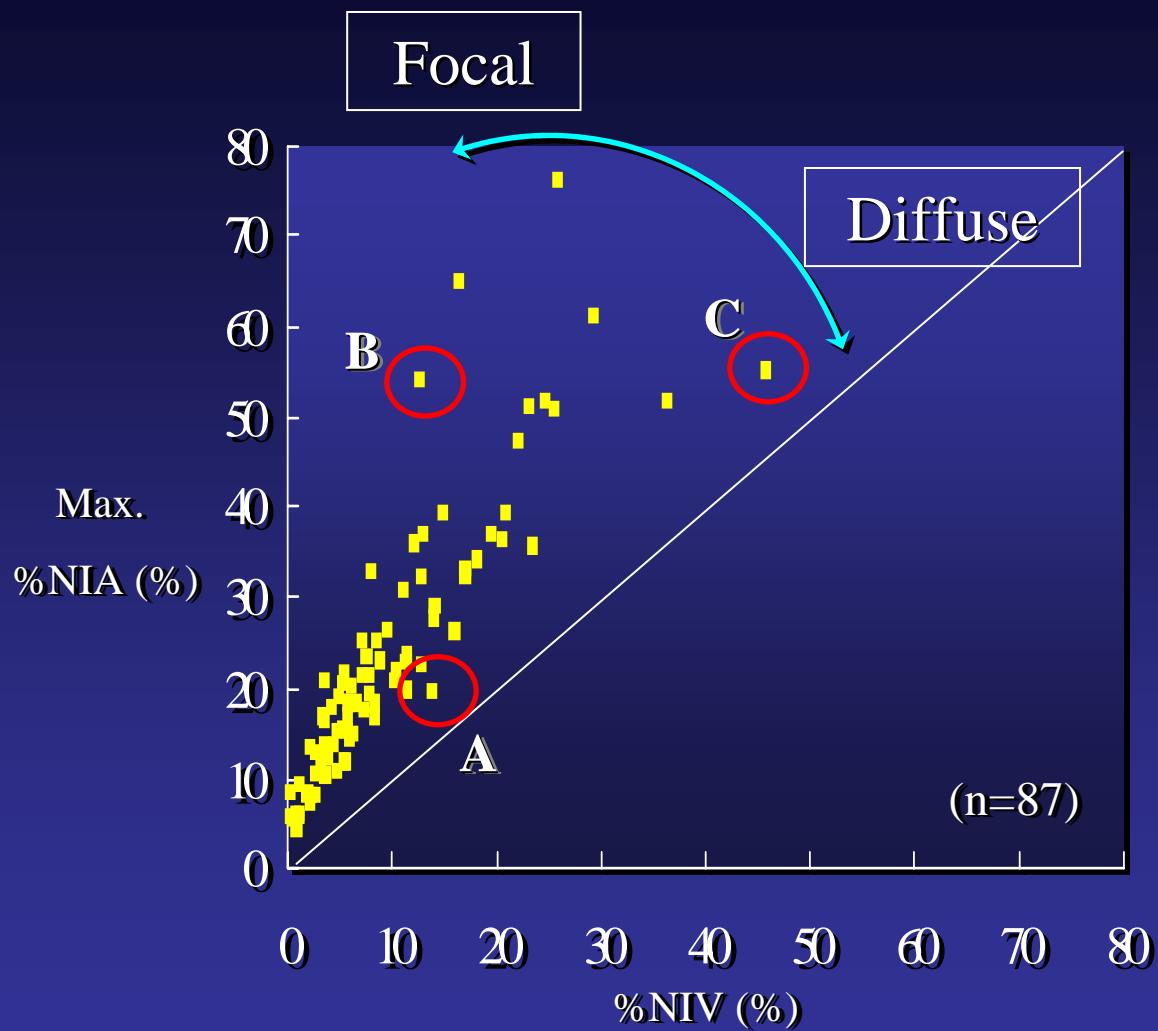
*%NI Volume = 10%*

Focal NIH



*%NI Volume = 10%*

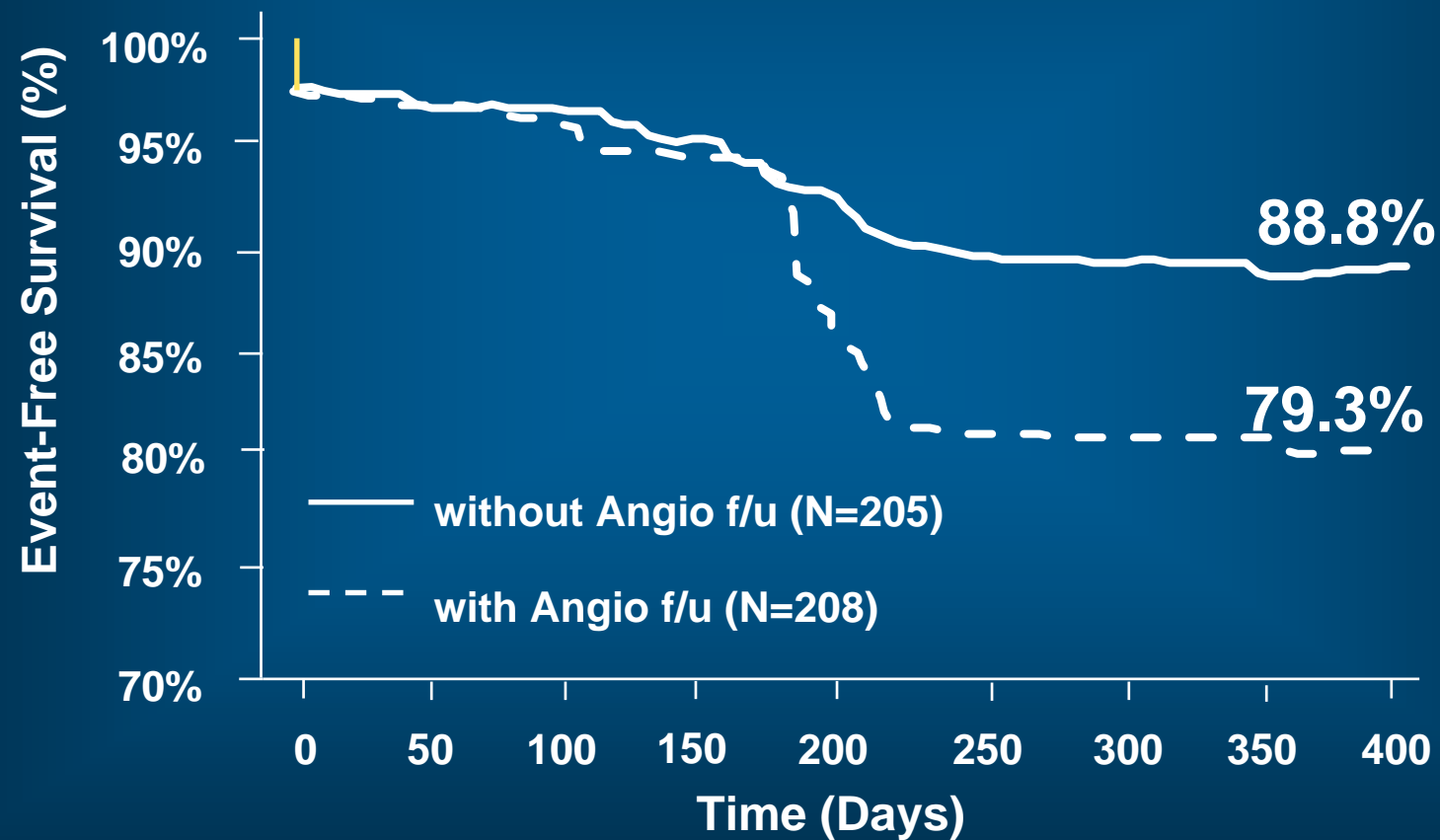
# Relationship between Volume and Area Obstruction



# Impact of angiographic follow-up: Benestent II

## Benestent II Clinical Results:

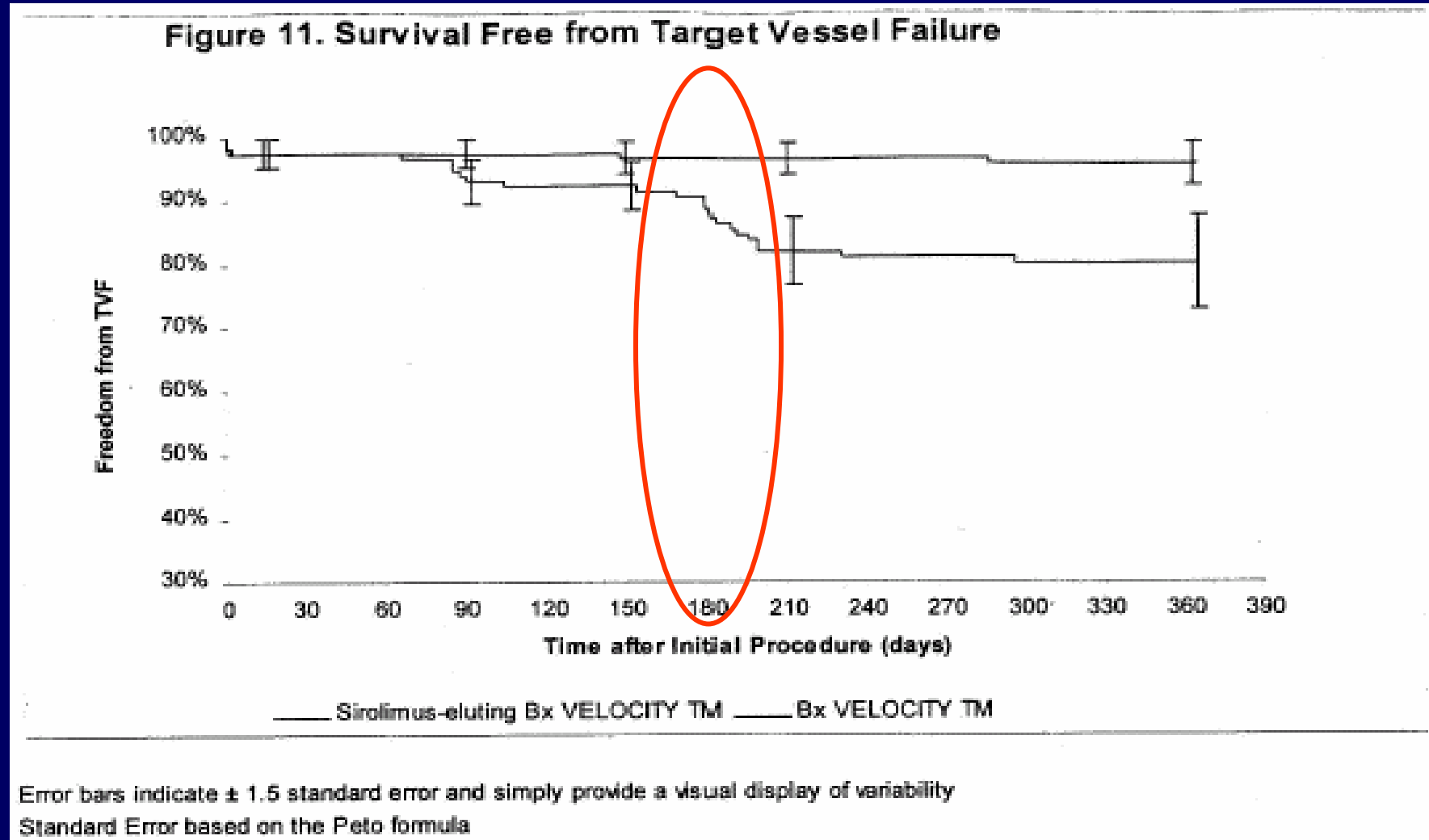
### Event-Free Survival at One Year with and without angio follow-up



*P.W. Serruys, MD, ThoraxCenter, Rotterdam, Netherlands  
European Society of Cardiology, August, 1997*

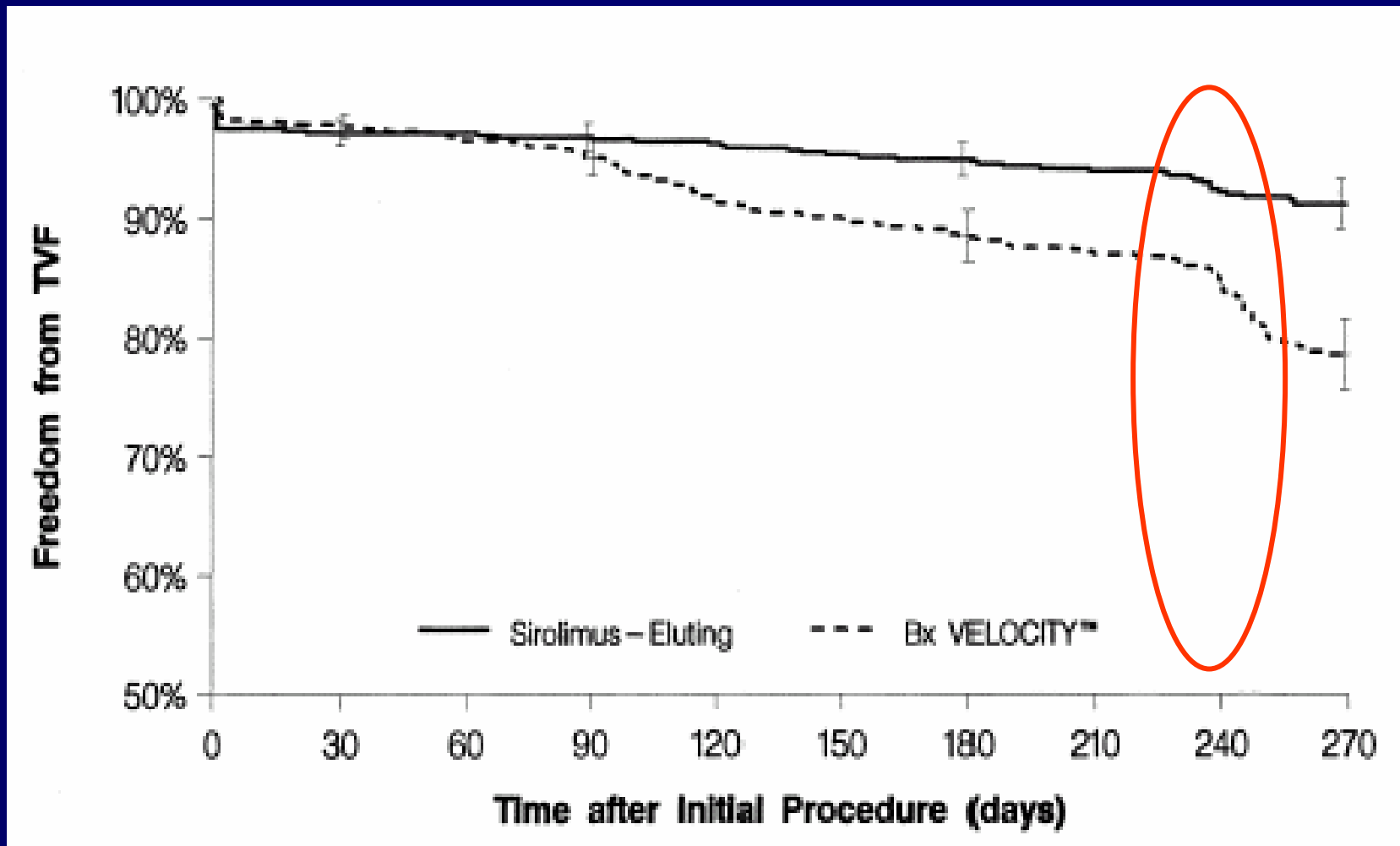
**Ranking Scale**

# Influence of Angiography RAVEL



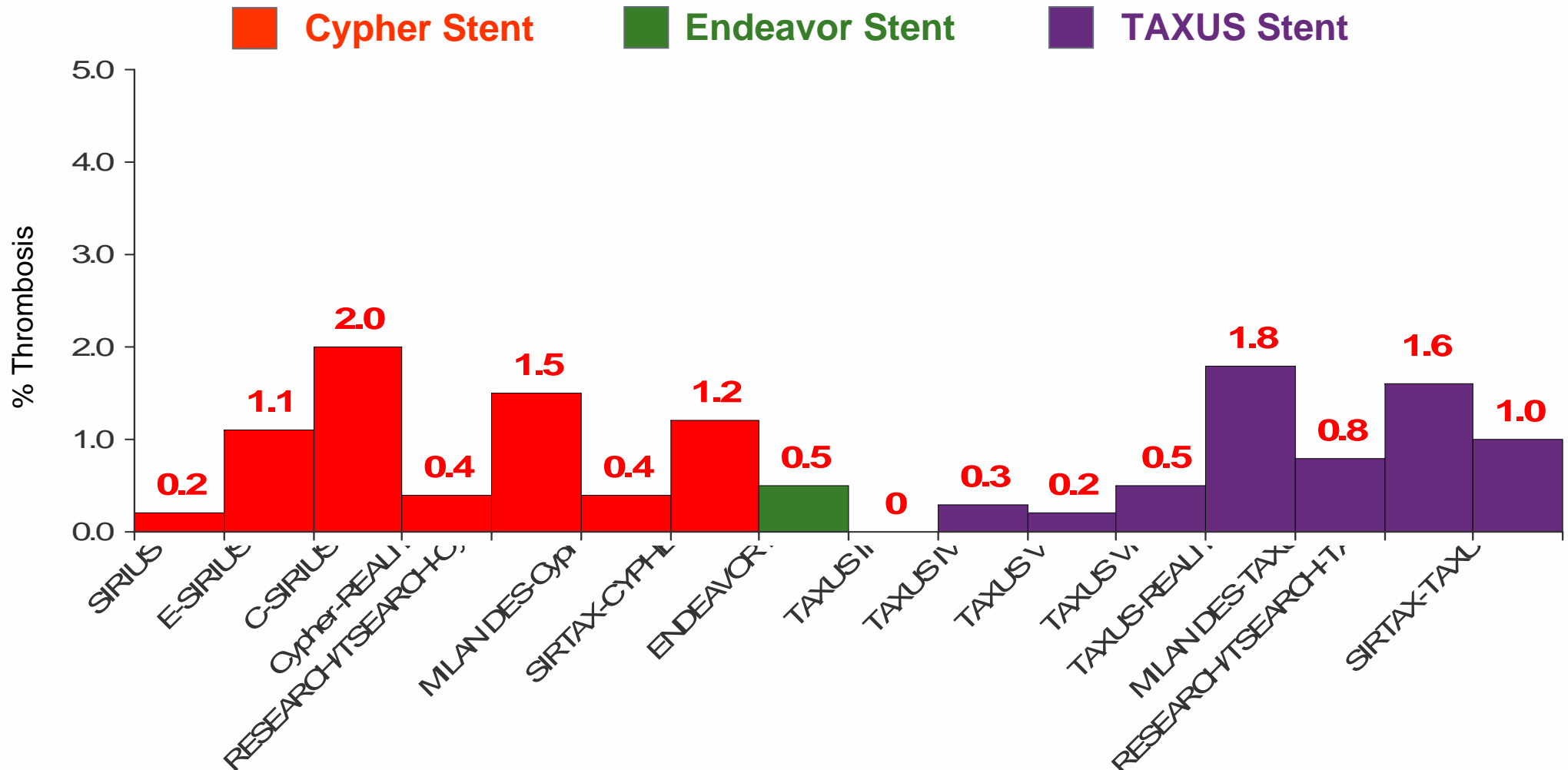


# Influence of Angiography SIRIUS



# SAT Rates Across Trials

*Out of Hospital to 30 Days*



Data sources available on file.

TAXUS Stent = TAXUS® Express<sup>2™</sup> Stent; Cypher is a trademark of Cordis Corp. ENDEAVOR is a trademark of Medtronic.

## Conclusions:

1. All three components of a DES is important and affects the angiographic and clinical outcomes
2. The angiographic (also IVUS) outcomes (late loss, %neointimal within the stent) can provide efficacy and failure evaluation
3. The clinical outcomes depends on trial design (patient populations, % angiographic follow-up)
4. DES systems are different, performance will likely be the same in same subsets while different in others