Are All DES Going to Achieve the Same Clinical Results ?

Alan C. Yeung, MD

Interventional Cardiology Professor of Medicine

Stanford University School of Medicine

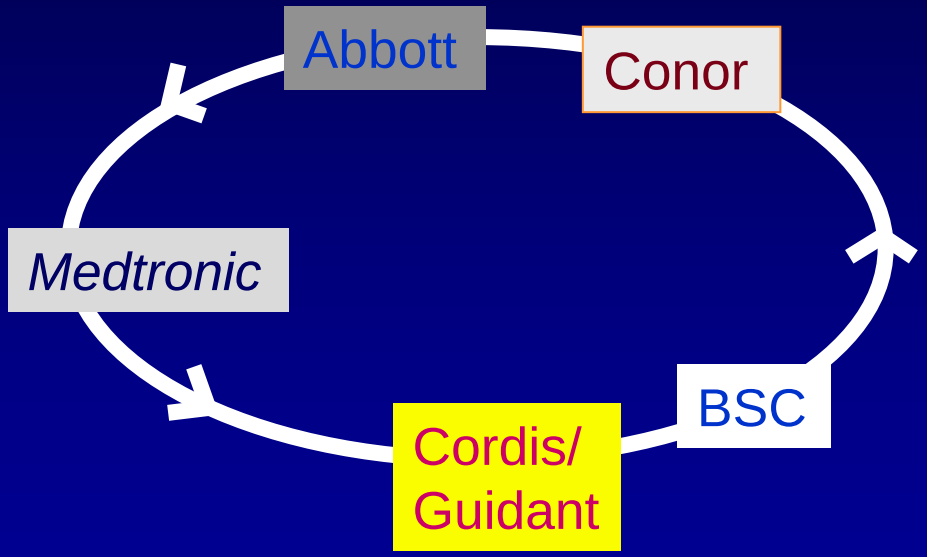
The Perception

“drug”eluting

“just” bare metal

Feeding Frenzy

Who's ahead?



Drug Eluting Stents

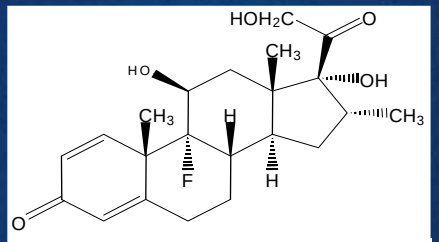
Clinical Results

Drug Eluting Stents

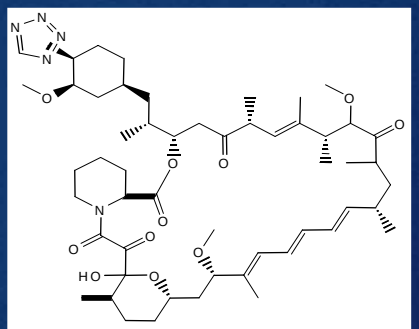
Clinical Results

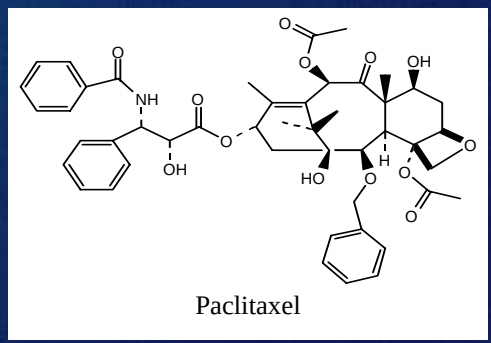
In Search of Drugs to treat Restenosis

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	✓

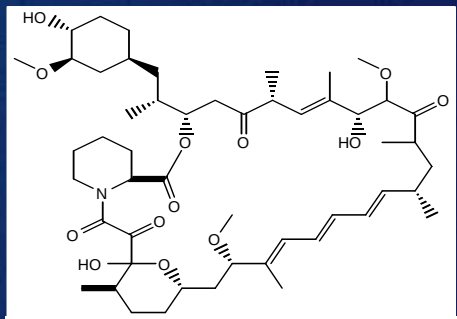


Dexamethasone

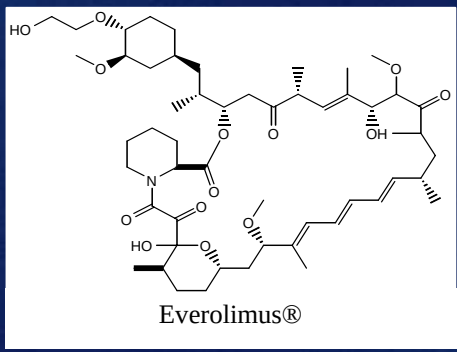

ABT-578



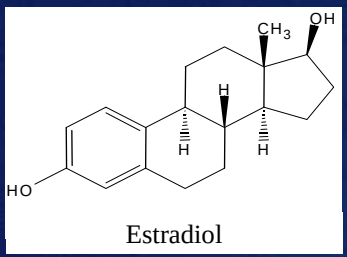
Paclitaxel



Sirolimus® (Rapamycin)



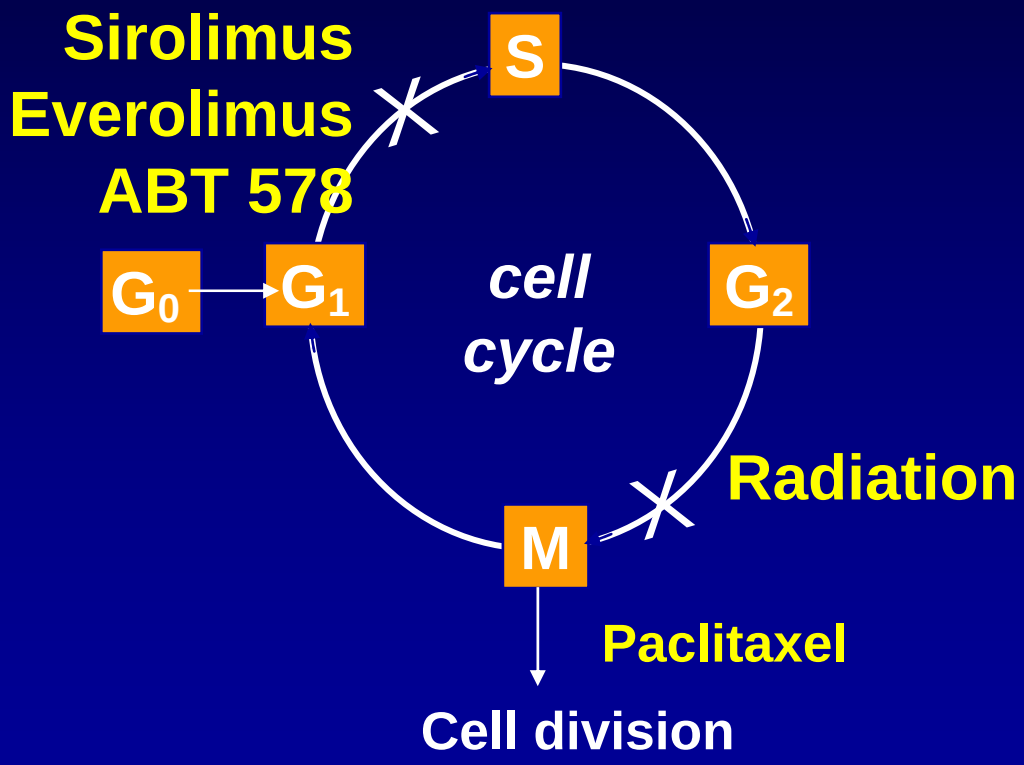
Everolimus®



Estradiol

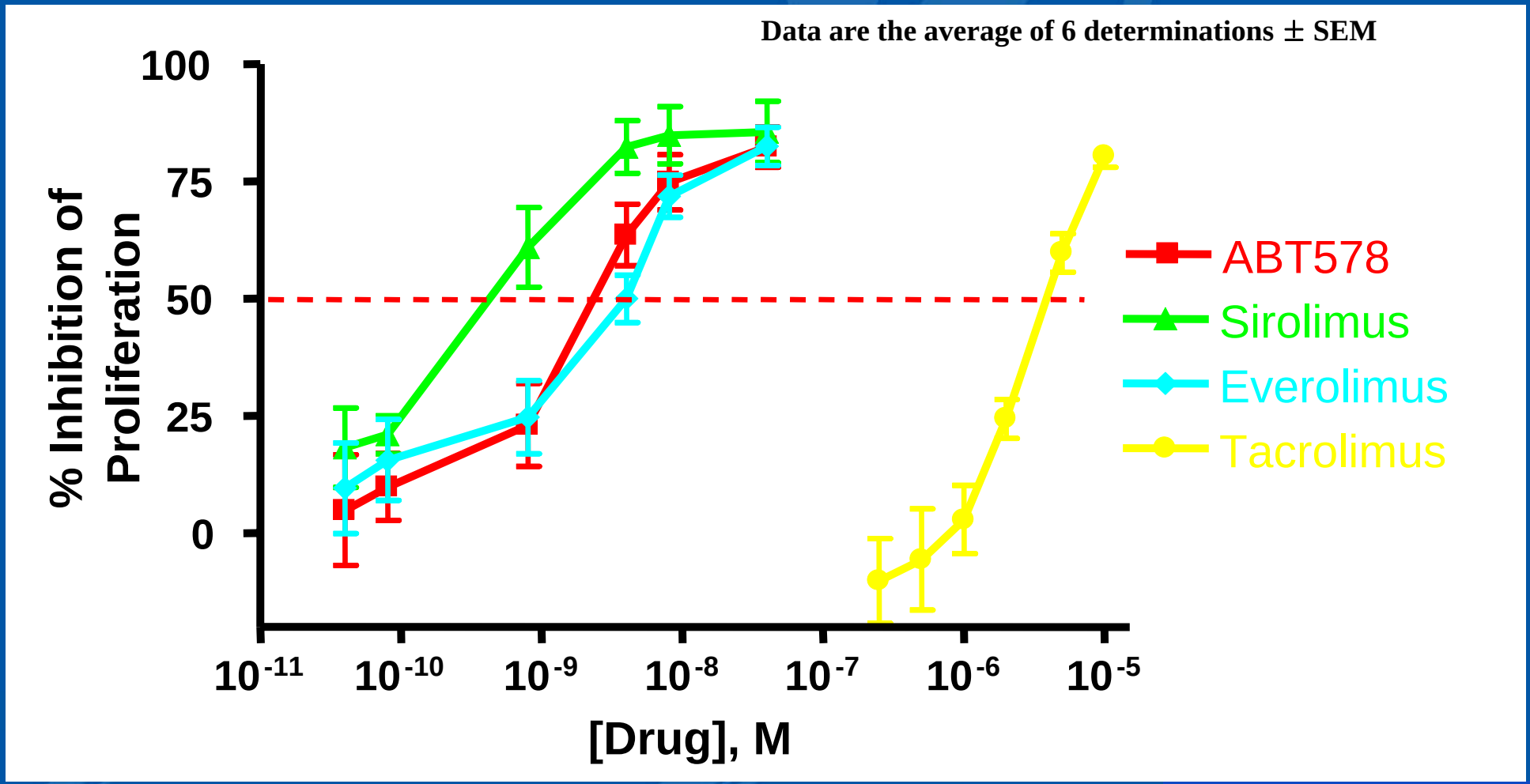
Drugs that Inhibit Restenosis

- Drugs used in DES
  - Induce cell-cycle arrest in late G_1 phase
  - Decrease TGF β
  - Elevate p53 levels
  - Inhibit microtubular assembly
  - Inhibit CDK/cyclin complexes



Slide courtesy of Ron Waksman, MD. Washington Hospital Center Washington, DC

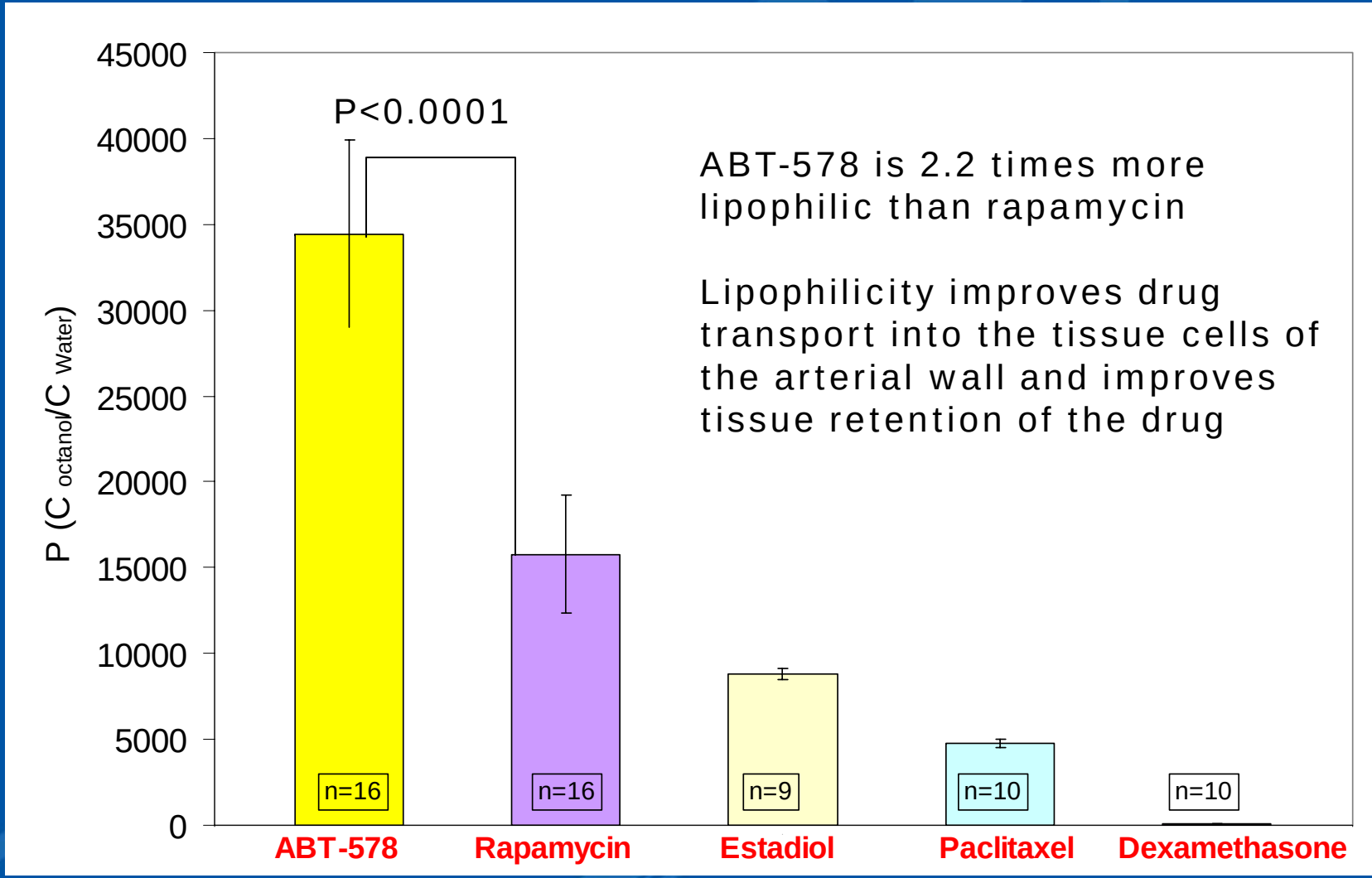
Effect of 'rolimus Drugs on Proliferation of Human Coronary Artery Smooth Muscle Cells



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.

Stanford

Lipophilicities of Some Clinical DES Agents

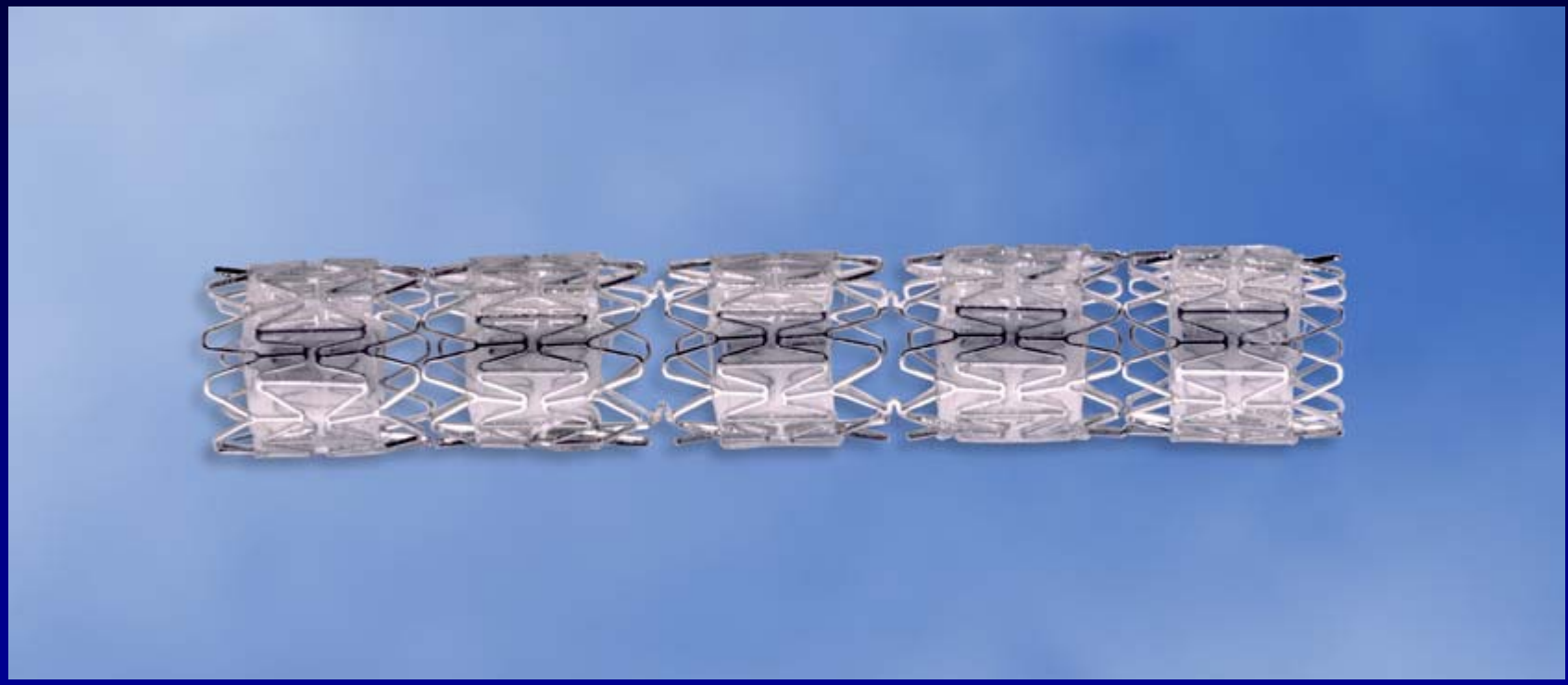


Determination of Partition Coefficients for ABT-578, Rapamycin, Paclitaxel, Dexamethasone, and Estradiol at 22 deg C, Abbott Laboratories Report on File, 2004

Drug Eluting Stents

Clinical Results

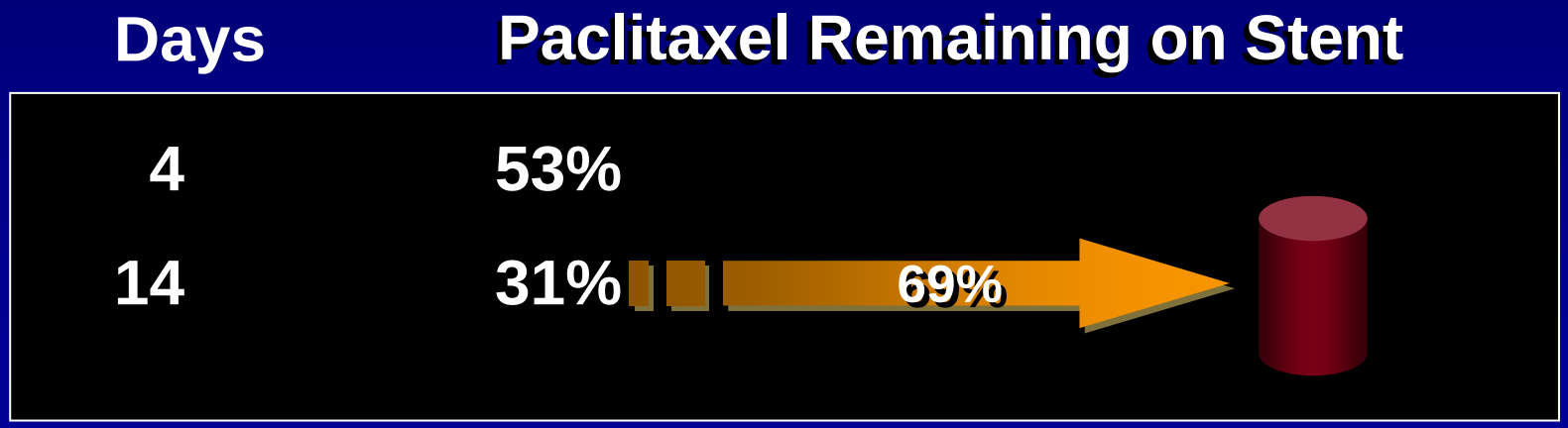
Quanam Drug Eluting Stent



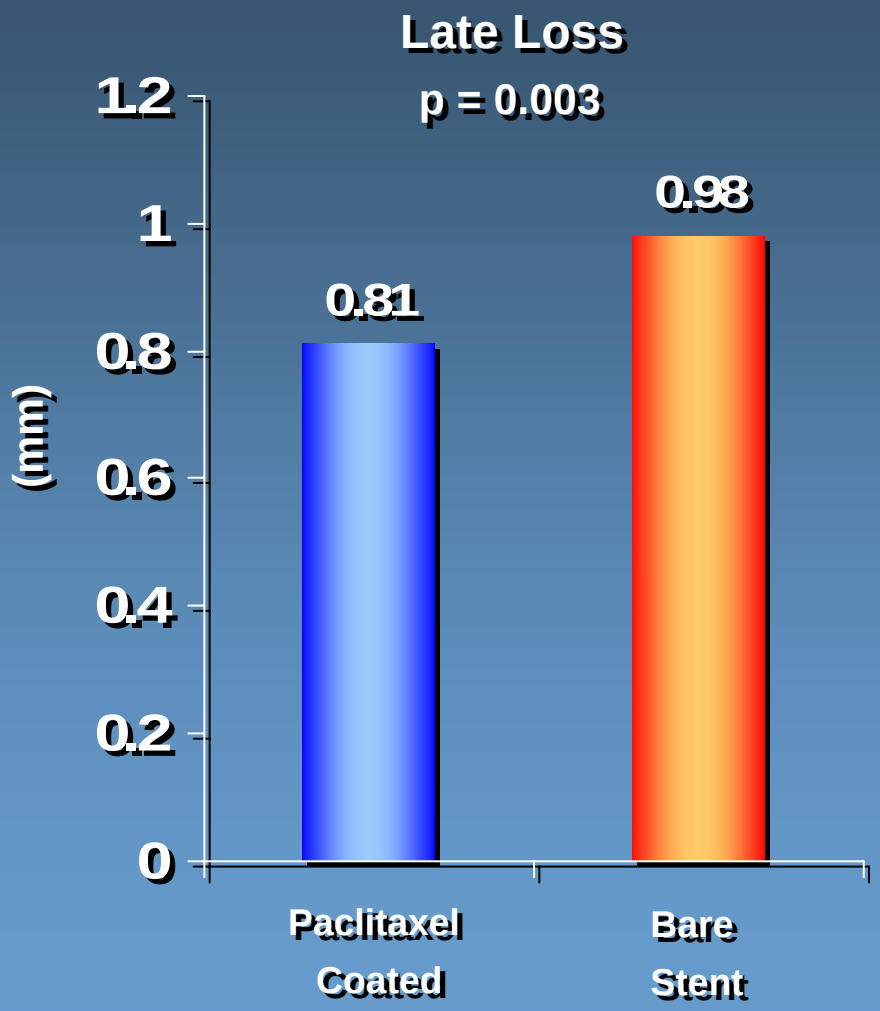
Quanam QuaDS Stent. Quanam polymer sleeves loaded with a microtubular inhibitor. Polymere sleeves are tightly stretched over dedicated metal stents .

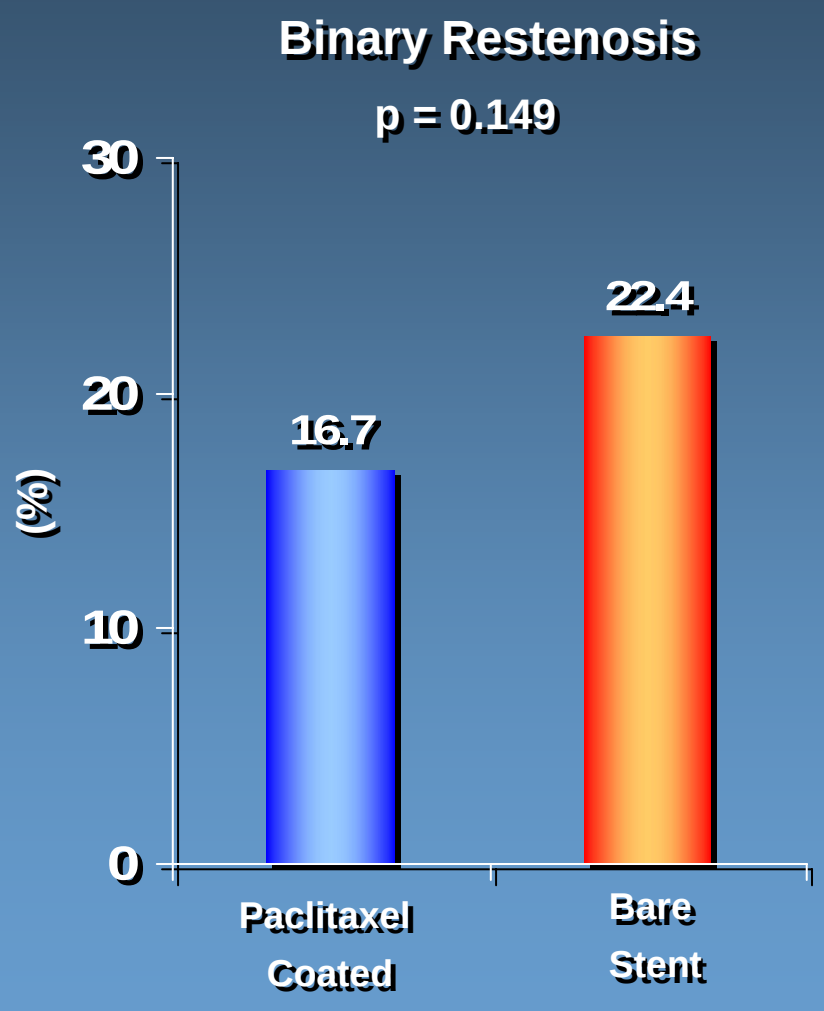
In vivo Pharmacokinetic Study
What happens to a stent bound drug?

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



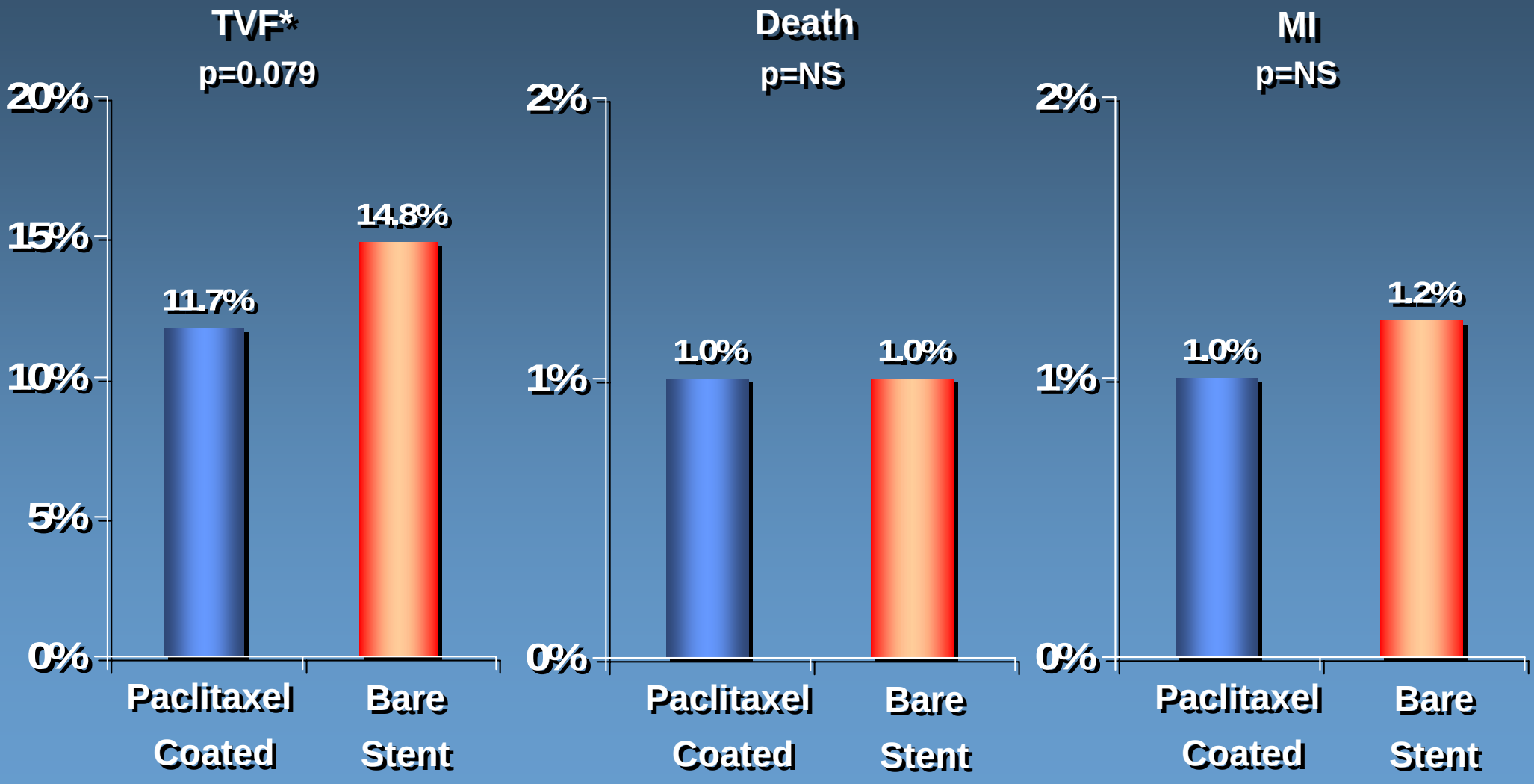
DELIVER- Non-Polymeric Paclitaxel Stent
8 Month In-stent Angiographic Results





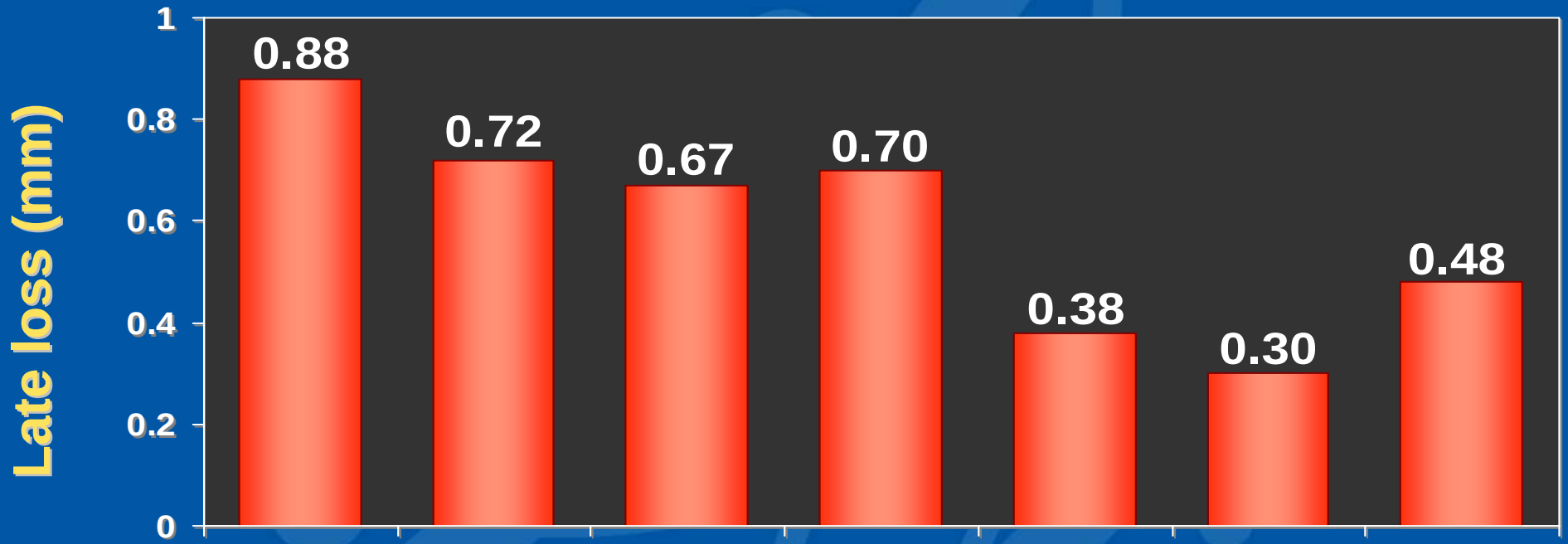
ACC 2003 Late Breaking Trials

DELIVER: 9 Month Clinical Event Results



* TVF = Death/MI/TLR

PISCES (n=221): QCA at 4 Months



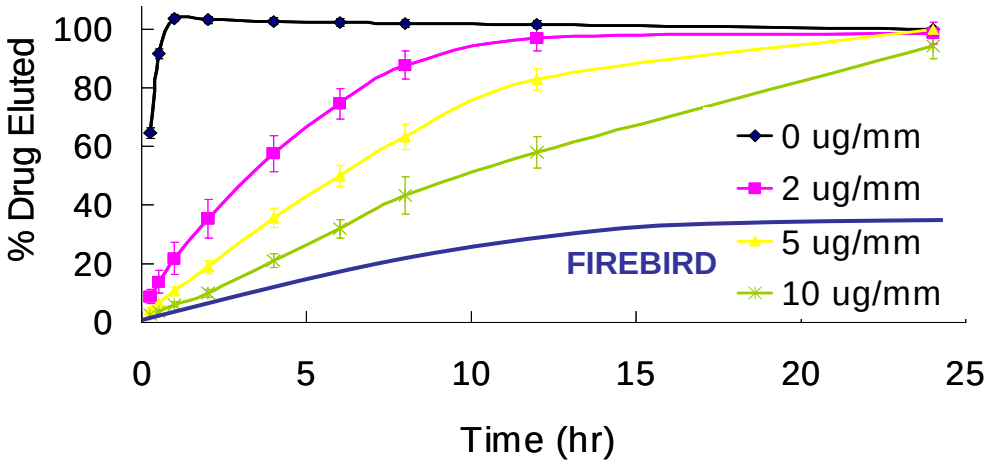
	D0	D1	D2	D3	D4	D5	D6
N	43	29	28	28	38	26	29
Dose (ug)	-	10	10	10	10	30	30
Release (d)	-	5	10	10	30	30	10

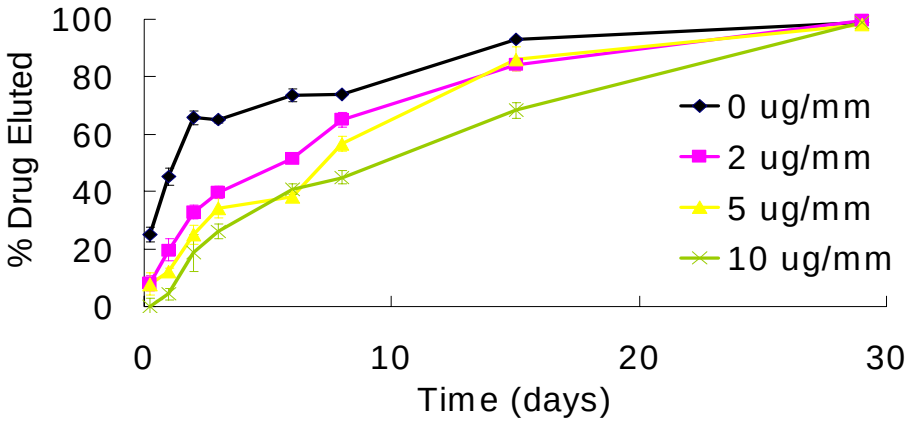
Stanford

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.

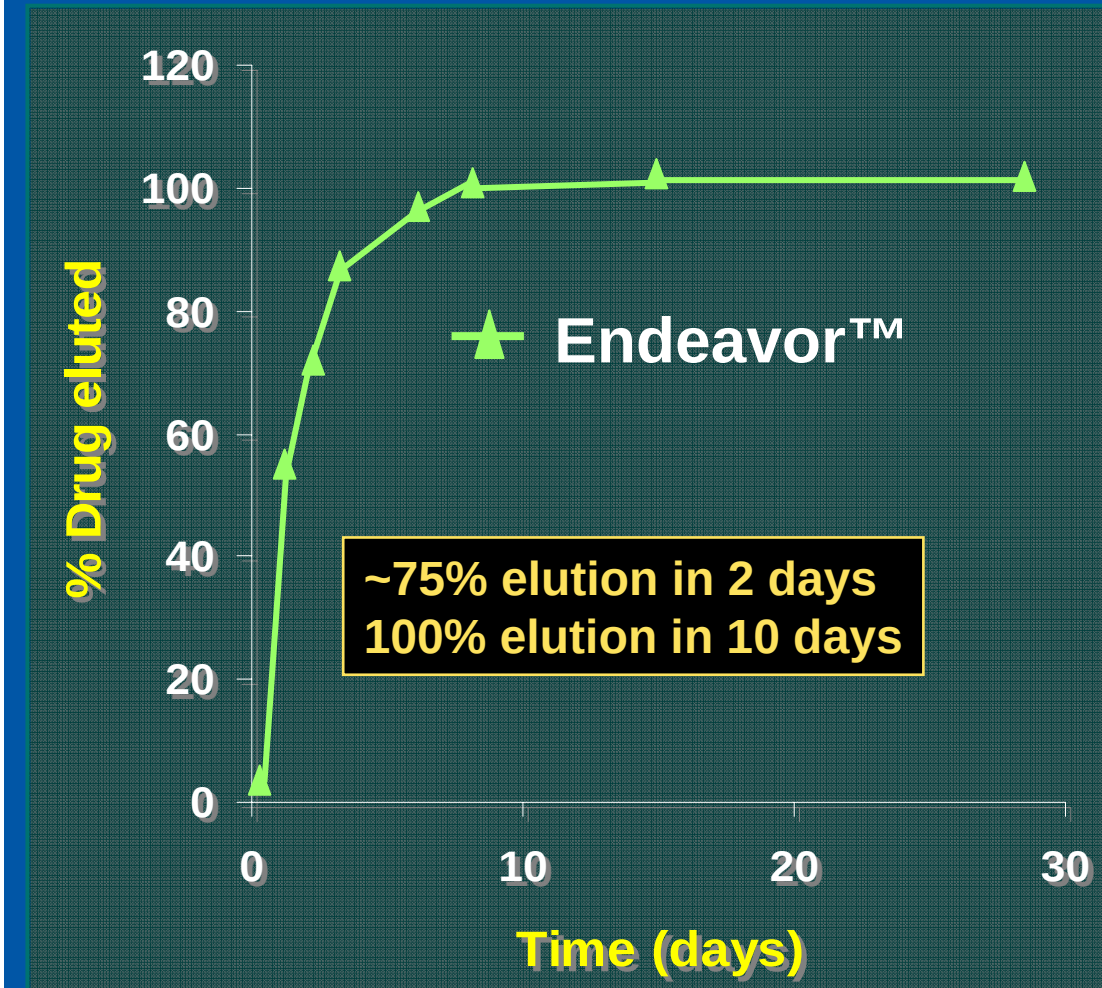
For *in vivo* testing, 128 stents (32 per group) were implanted in the common iliac arteries of New Zealand White rabbits and expanded to a 1:1.1 balloon-to-artery ratio. At set time (4 stents per group per time point), animals were euthanized, stents explanted, and the amount of ABT-578 remaining on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

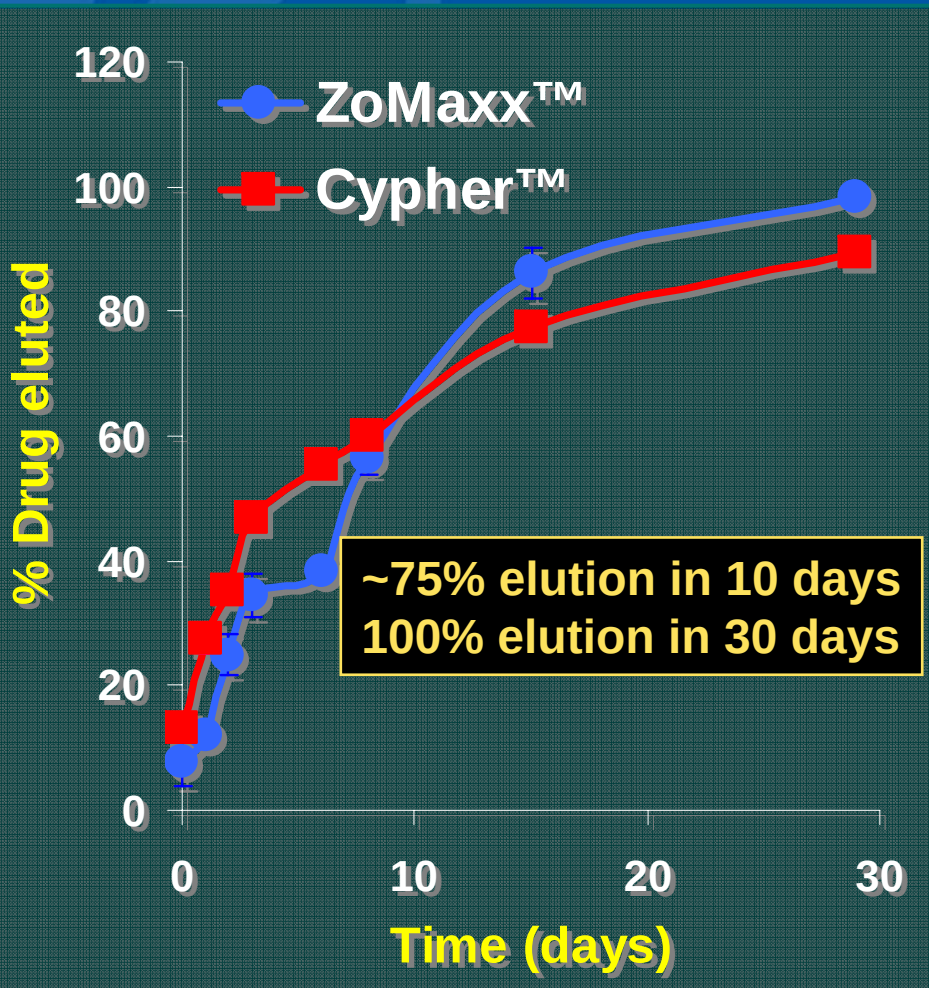




Comparison of *in vivo* Elution Rates

Rabbit iliac models





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

Stanford

Drug Eluting Stents

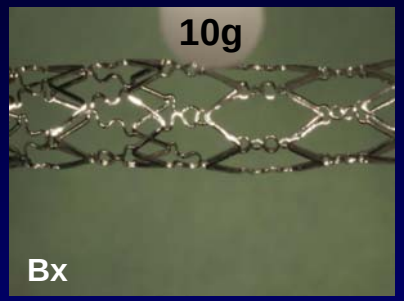
Clinical Results

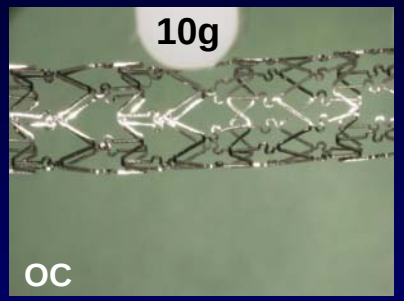
DELIVERABILITY !

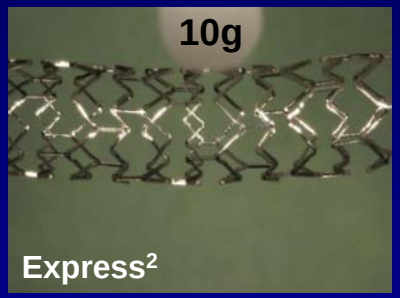
DELIVERABILITY !

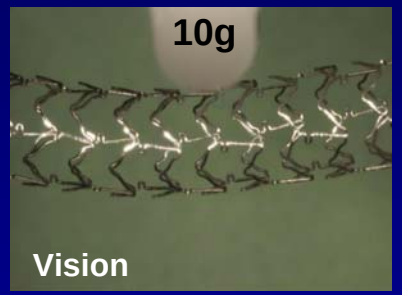
DELIVERABILITY !

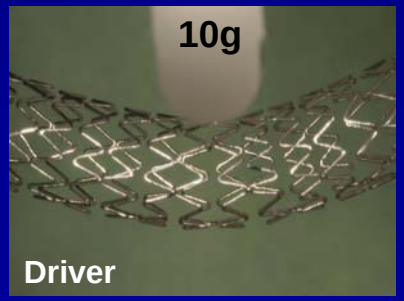
Stent Flexibility



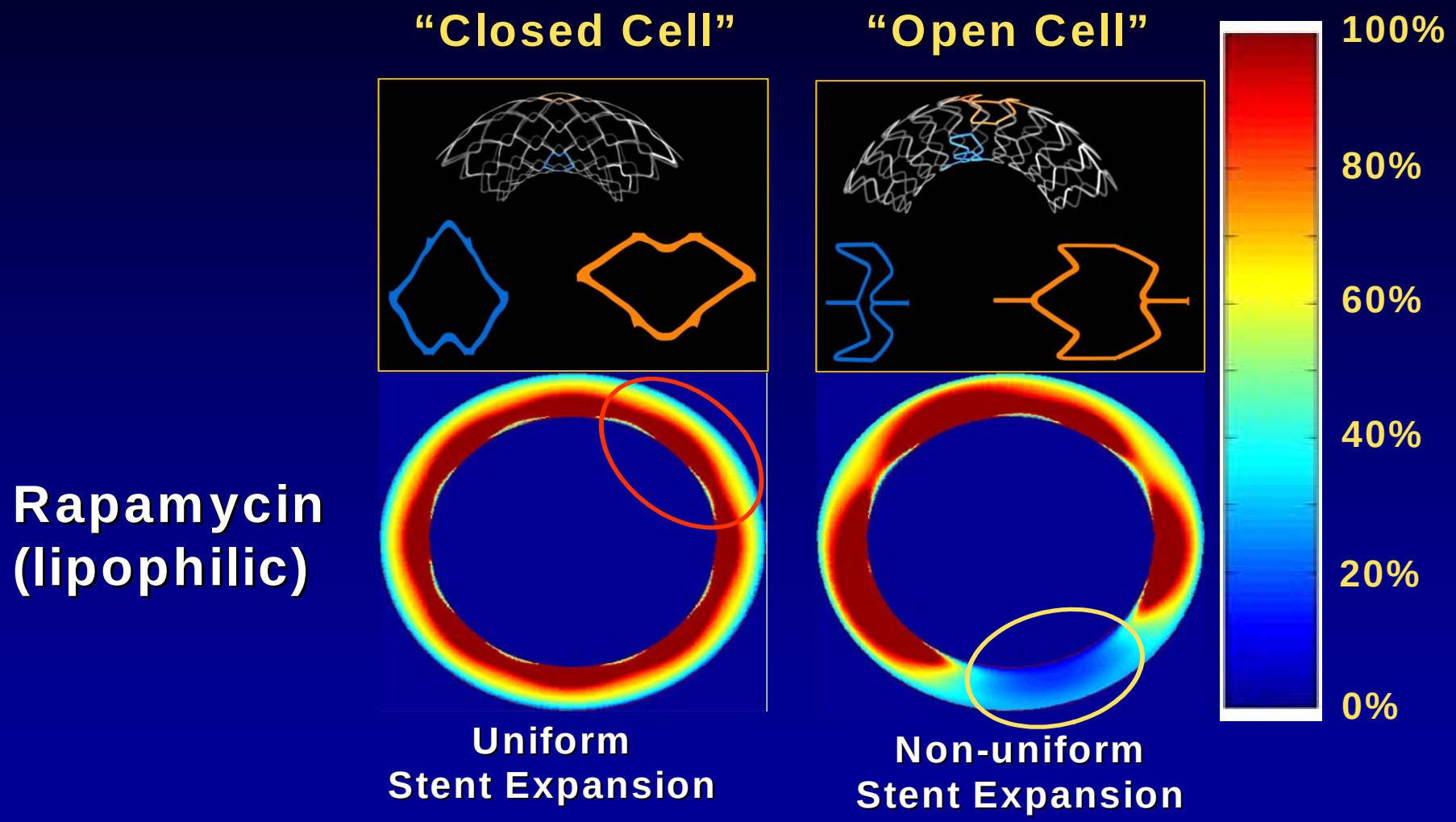








Drug – Stent Interactions



Hwang, Wu & Edelman, Circ 2001

REALITY

Intention-to-Treat Analyses

Angiographic Measures

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

REALITY

Intention-to-Treat Analyses

Angiographic Outcomes

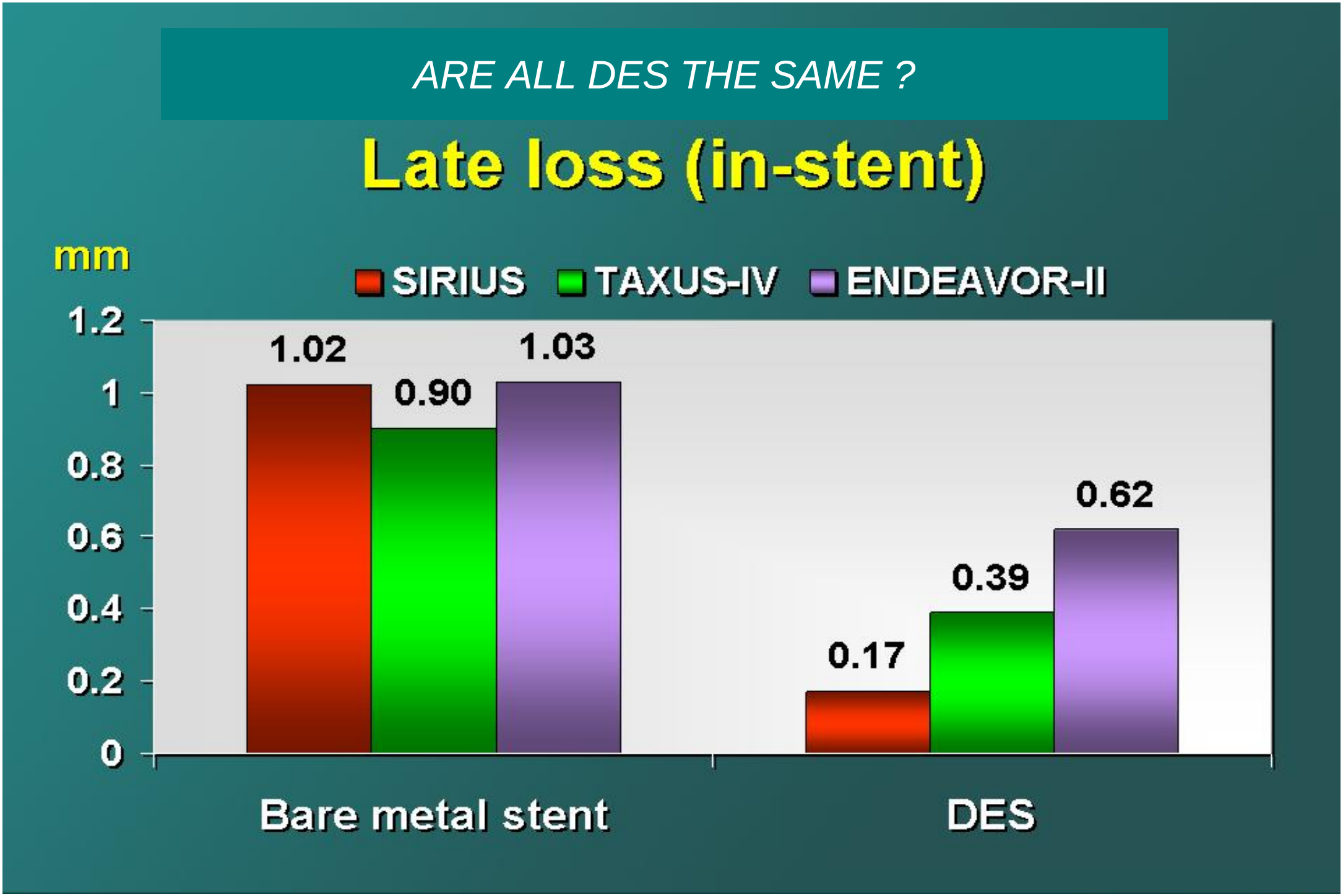
8 Month Post-Procedure

	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

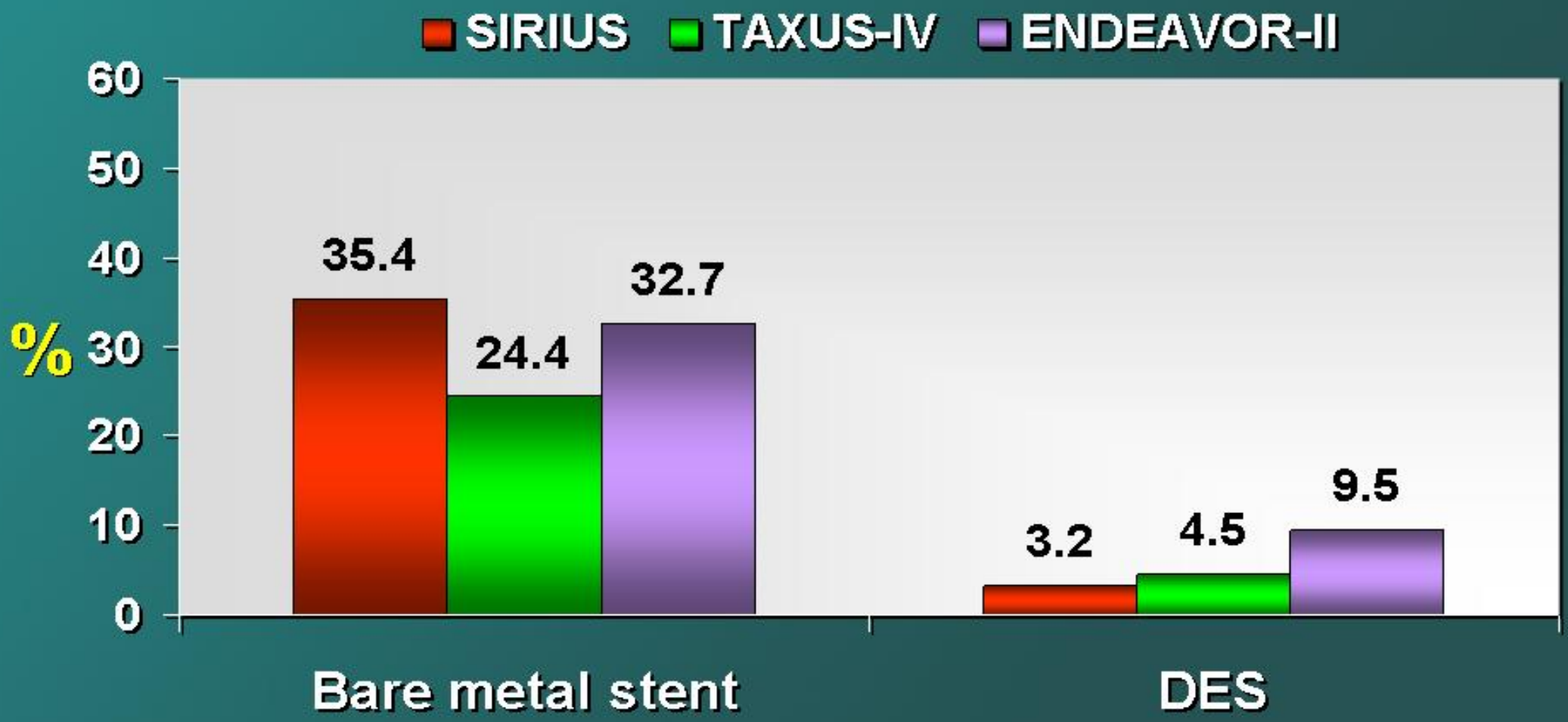
Clinical Results

ARE ALL DES THE SAME ?



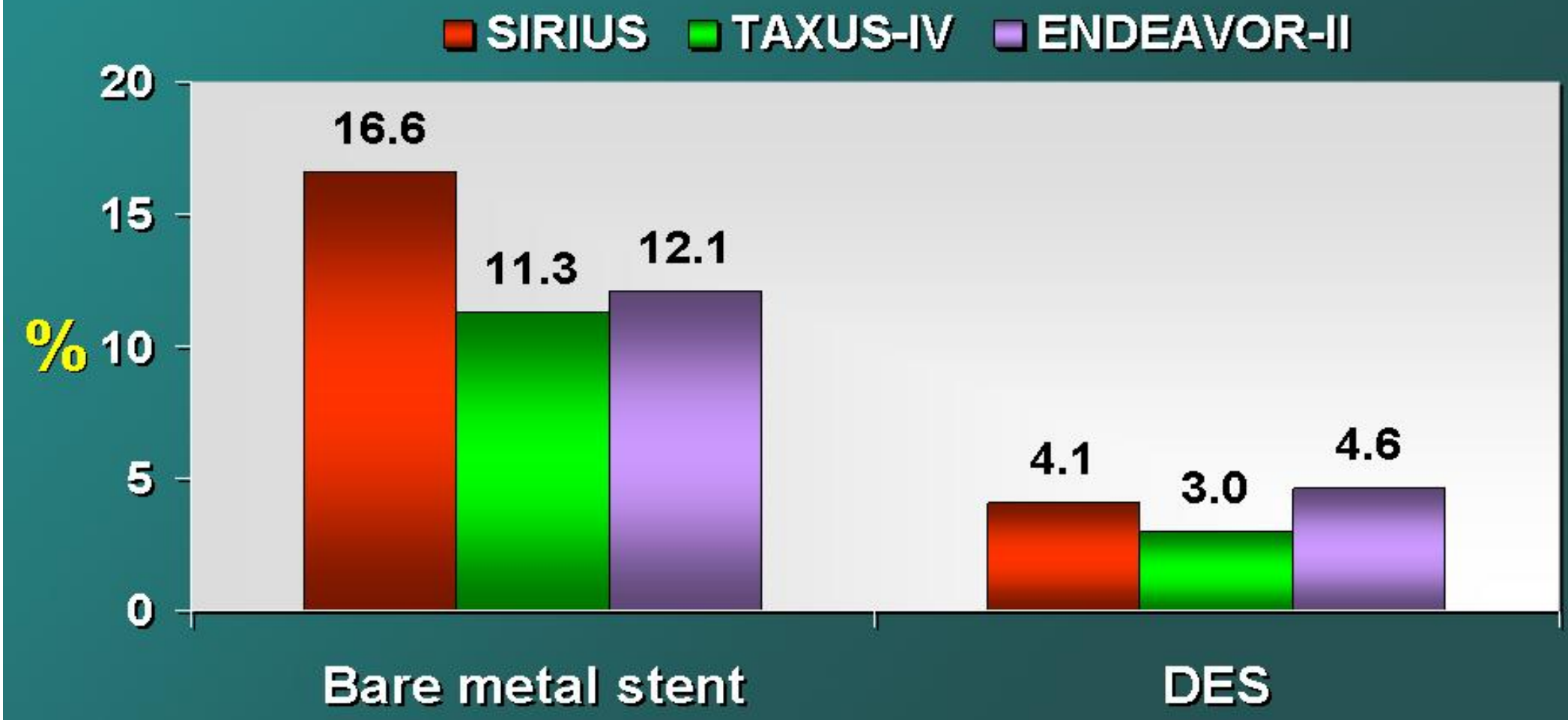
ARE ALL DES THE SAME ?

Binary restenosis (in-stent)



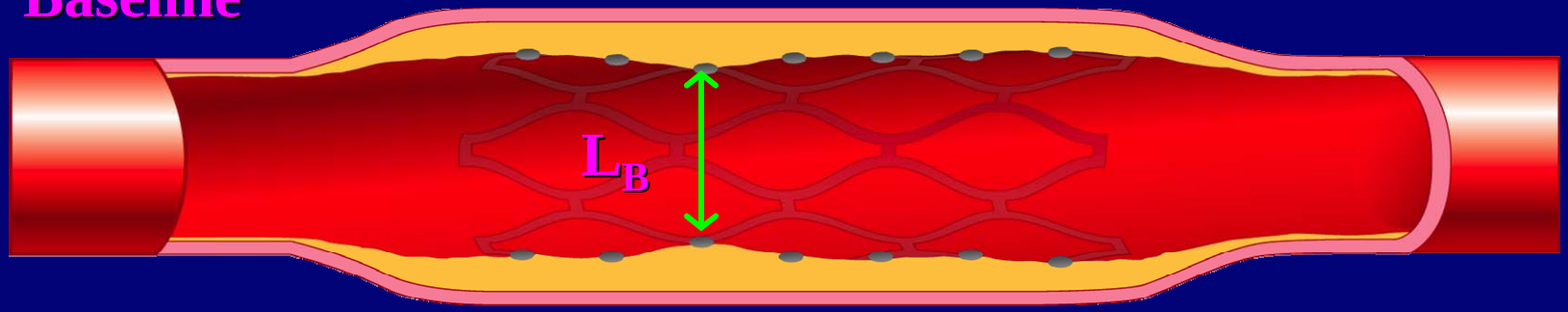
ARE ALL DES THE SAME ?

Target lesion revascularization at 9 mos

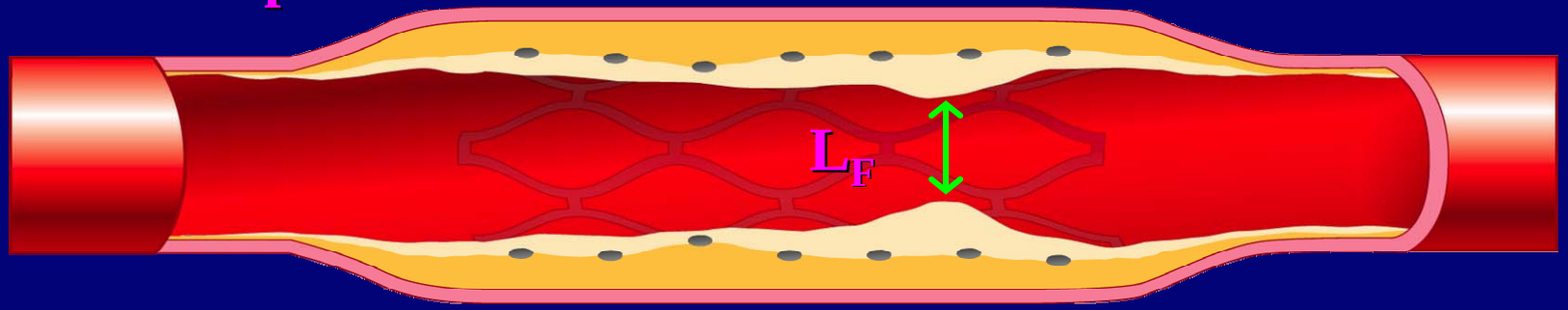


Angiographic Late Lumen Loss

Baseline

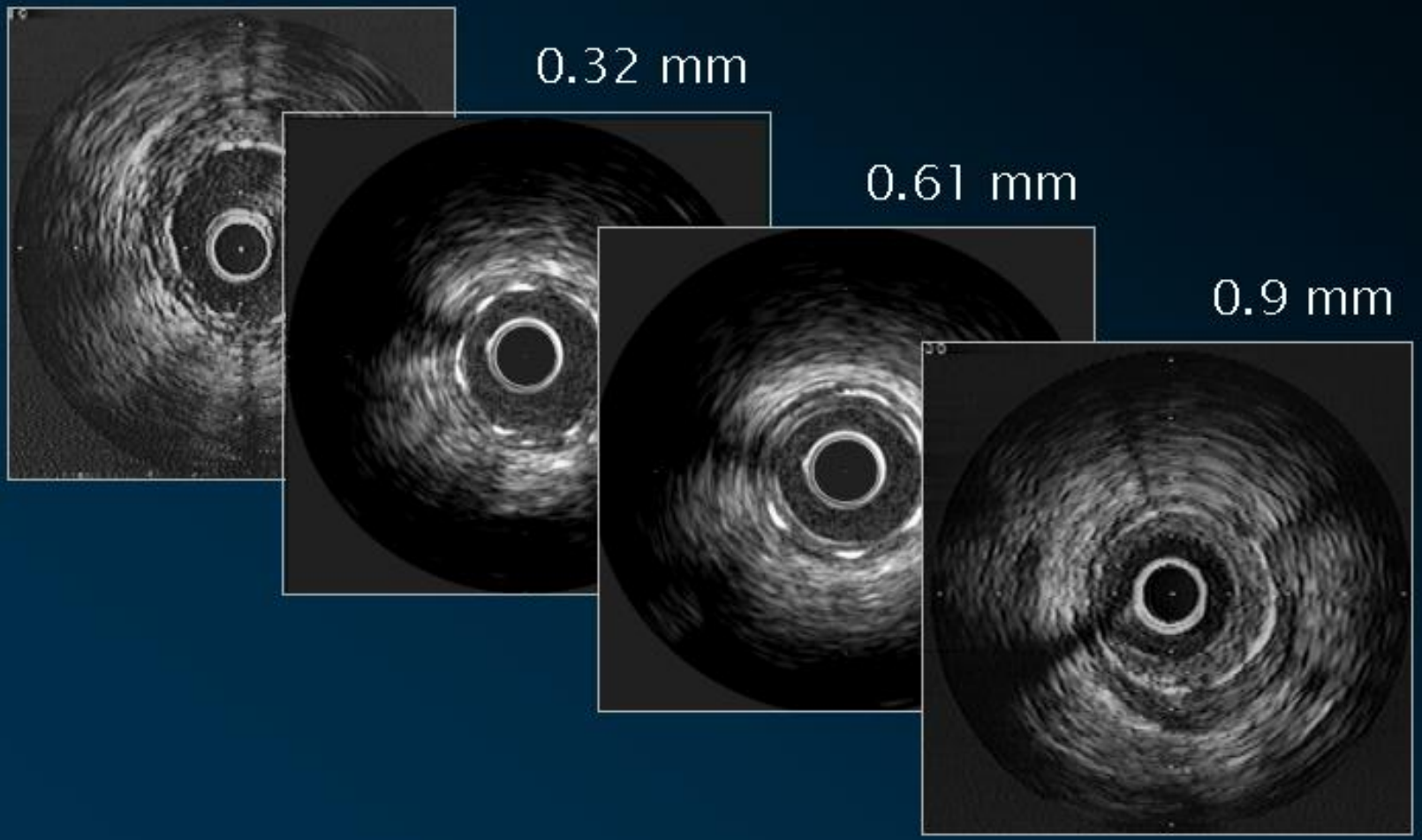


Follow-up

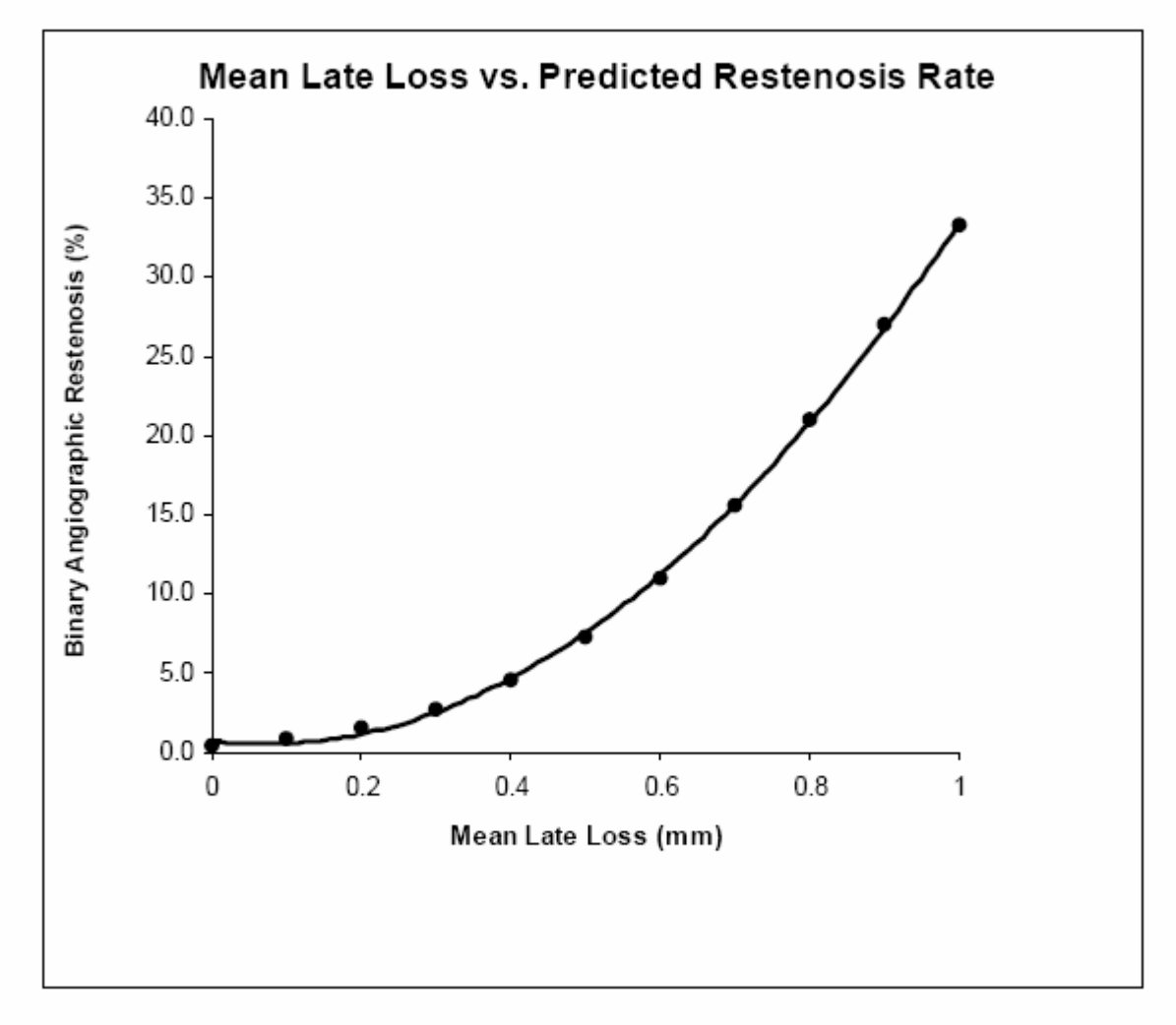


$$\textit{Late Lumen Loss} = L_B - L_F$$

Visual significance of late loss

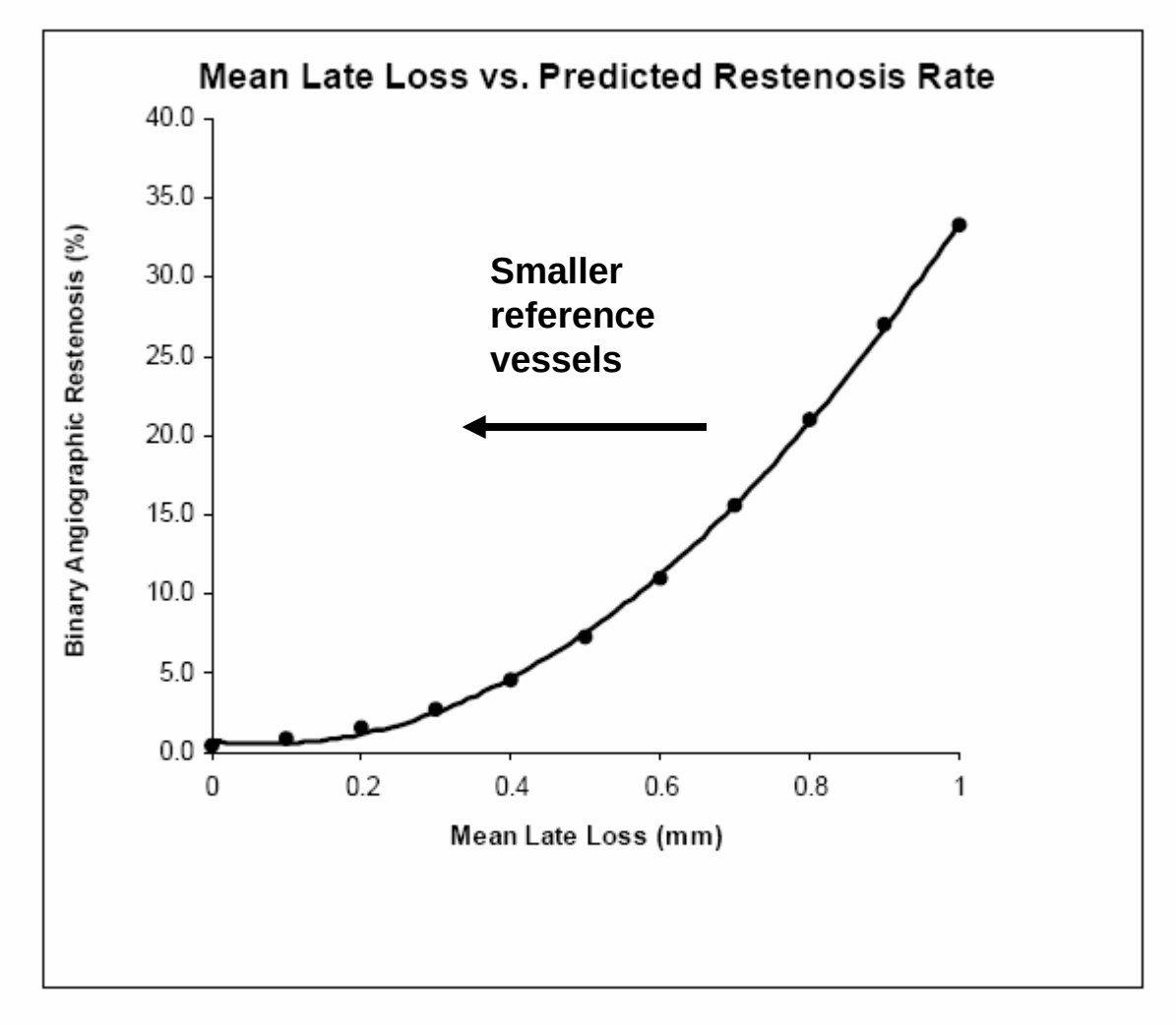


Mean late loss vs. predicted restenosis rate Predicted restenosis rates for a reference population of mean RVD 2.79 mm and mean post-stent MLD 2.67 mm.



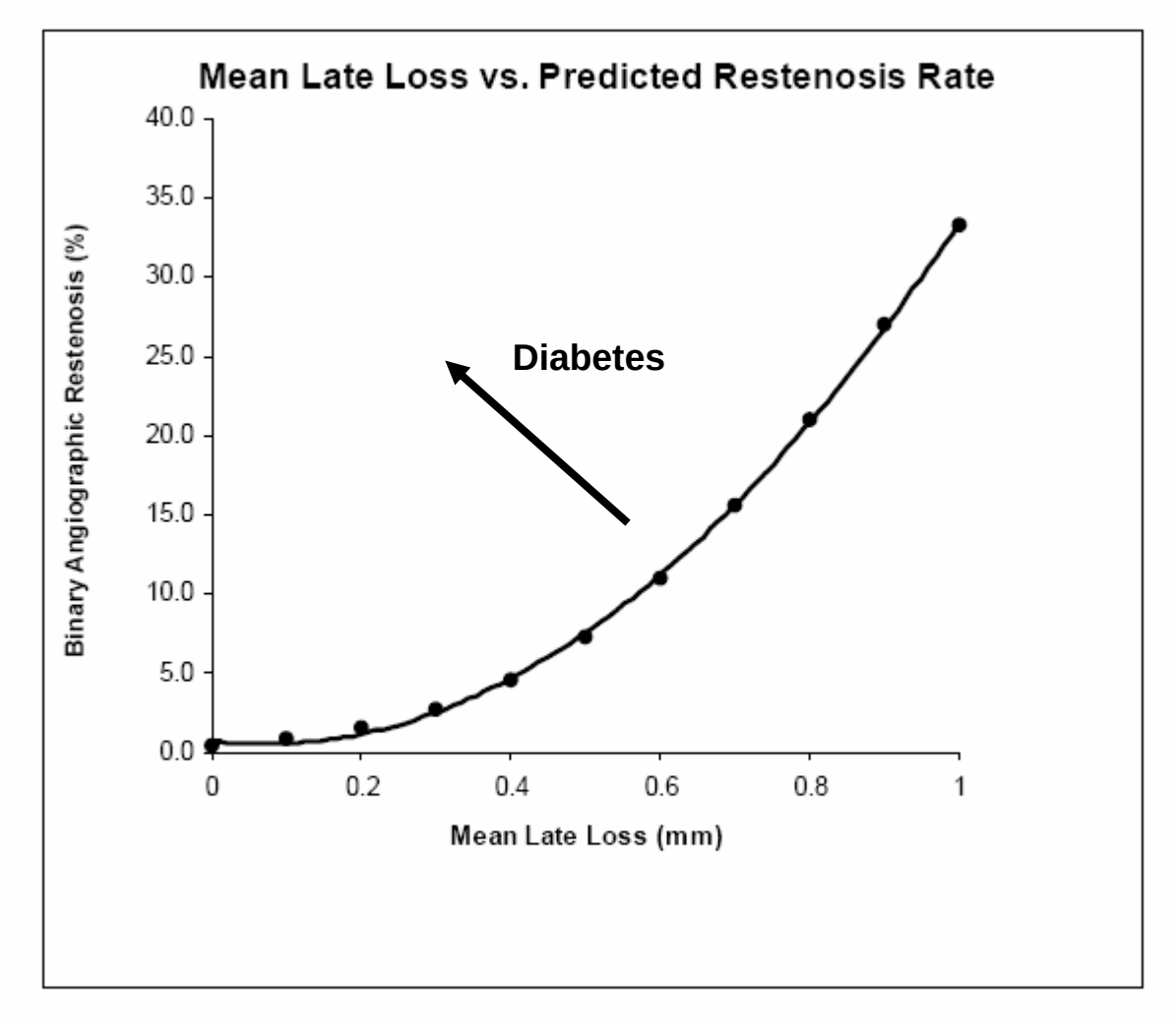
Mauri et al Circulation 2005

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.



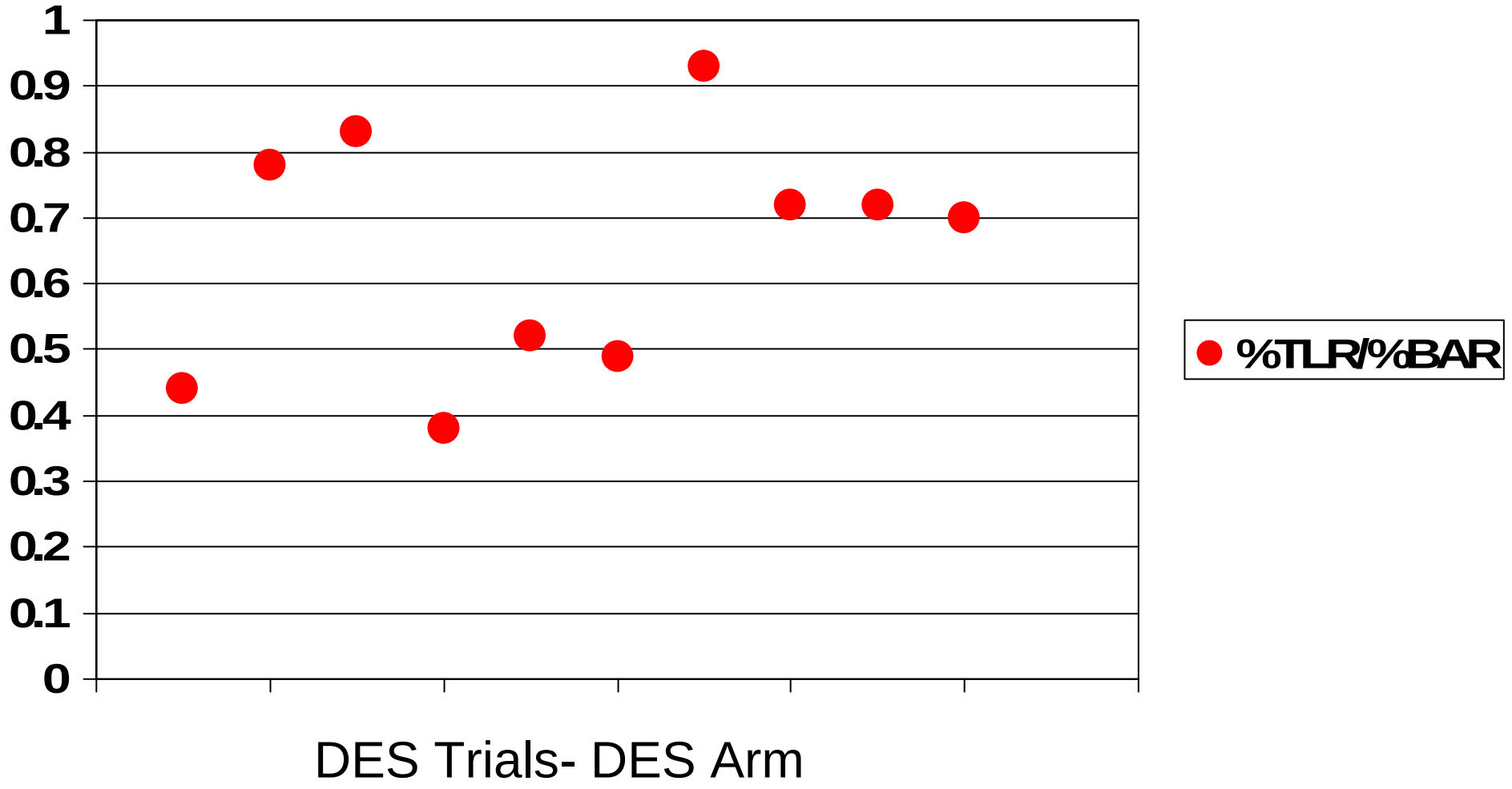
Mauri et al Circulation 2005

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.



Mauri et al Circulation 2005

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

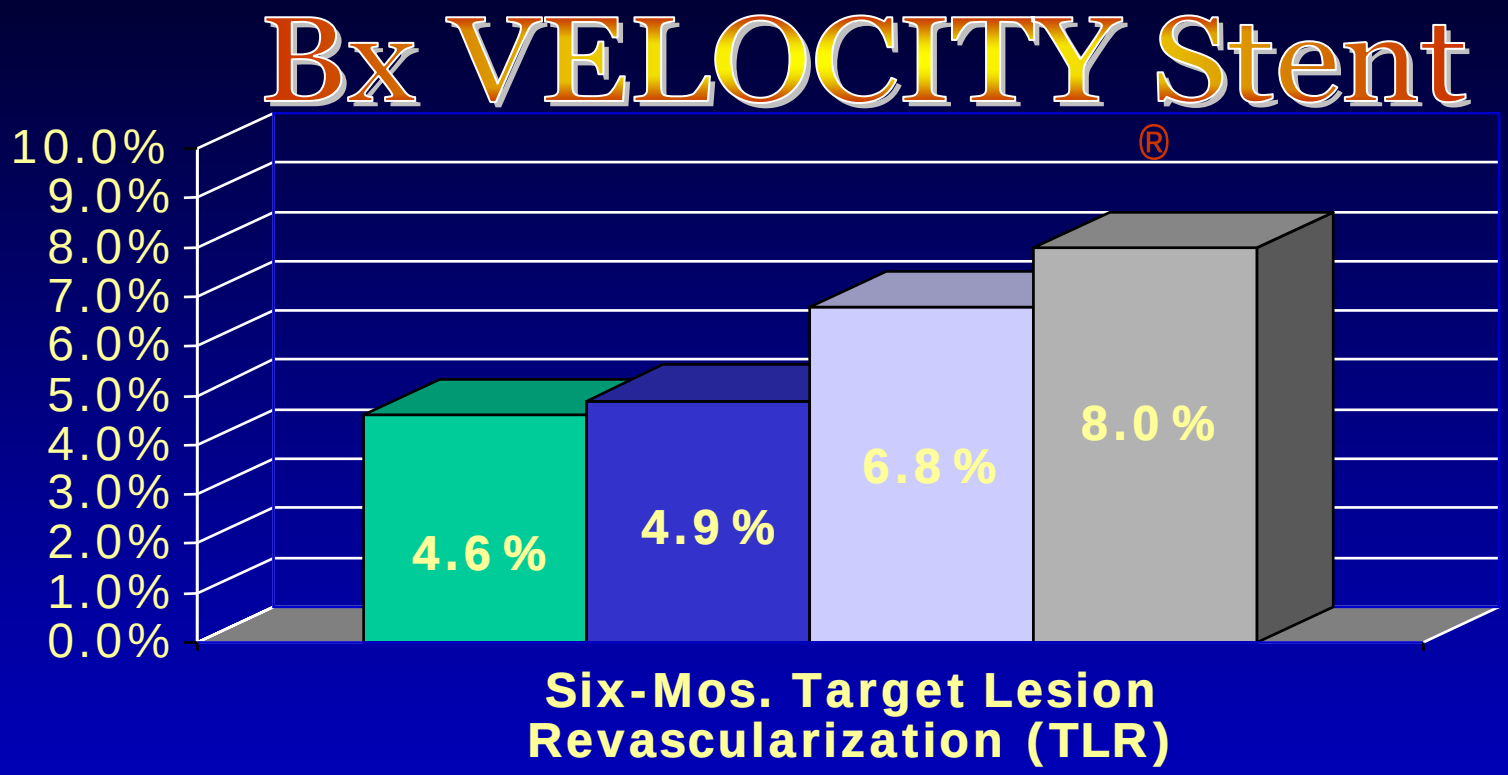


When does BAR becomes TLR?

- 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

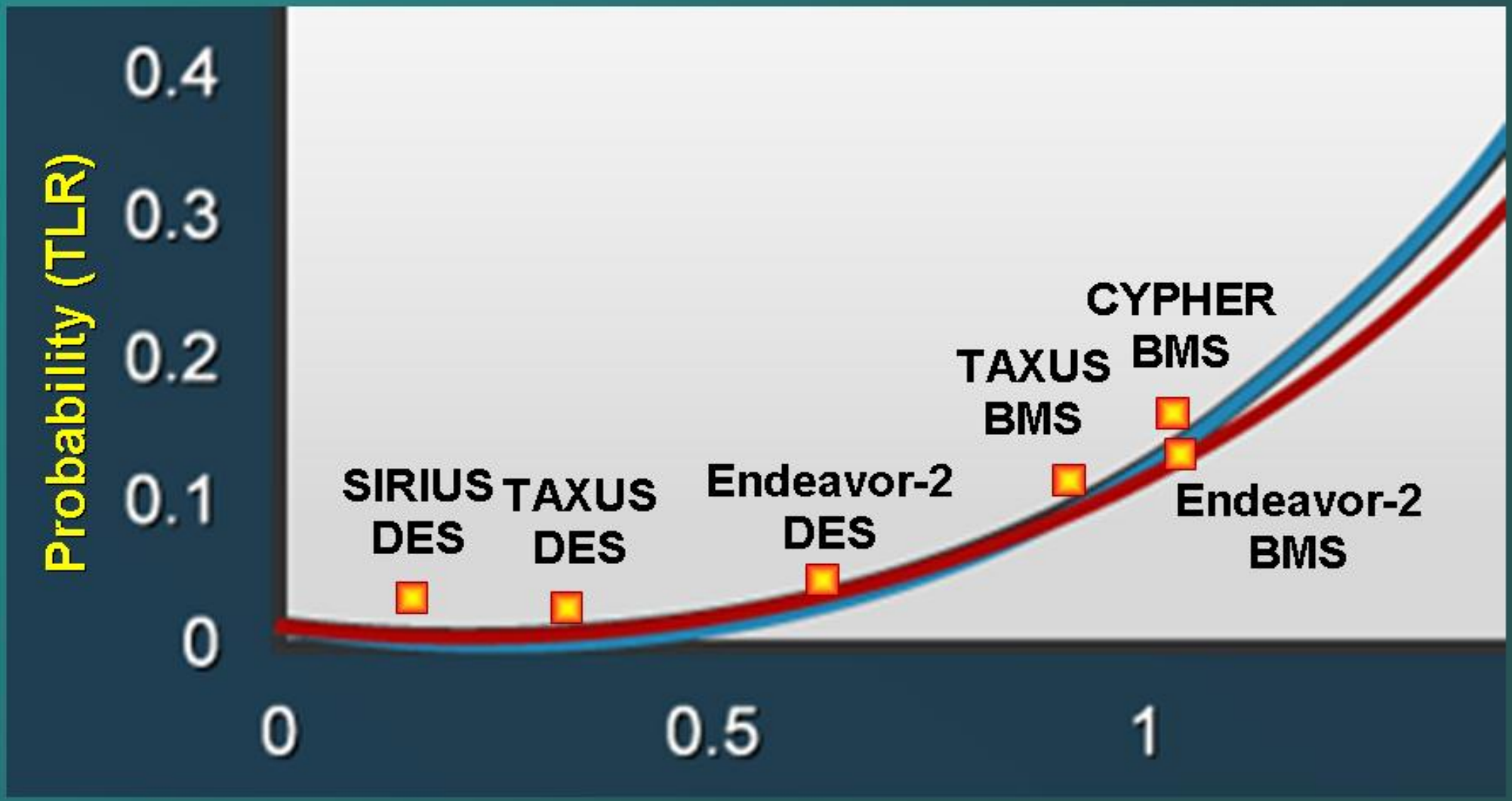
Trial Design Drives Outcomes

TLR Is also Influenced by Trial Design



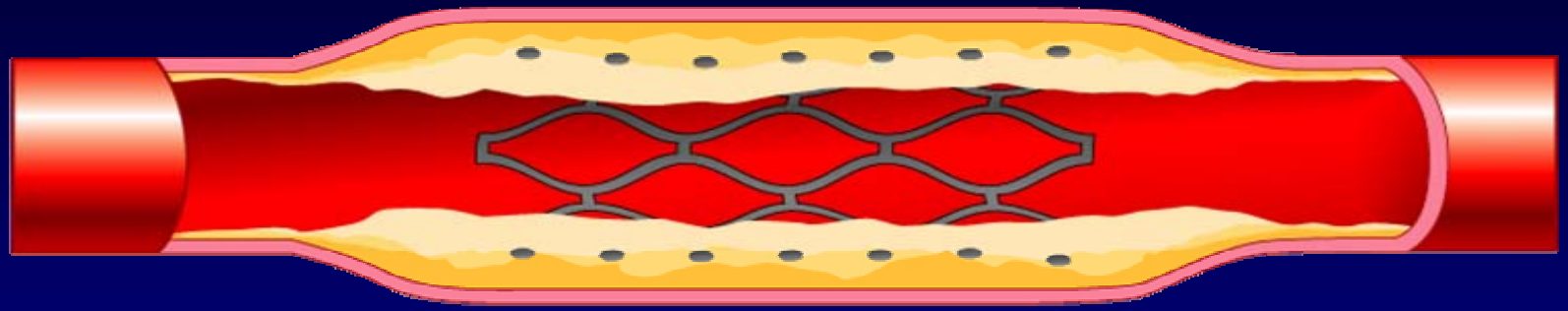
	VENUS	VENTANA	RAVEL/CHI	SIRIUS/CHI
Diabetics	*23.4%*	*10.7%*	*21.2%*	*28.2%*
MLD-post	*2.90 mm*	*2.55 mm*	*2.41 mm*	*2.68 mm*
Stented Length	*16.3 mm*	*18.0 mm*	*18.0 mm*	*21.2 mm*

De Novo "Pivotal" RCTs



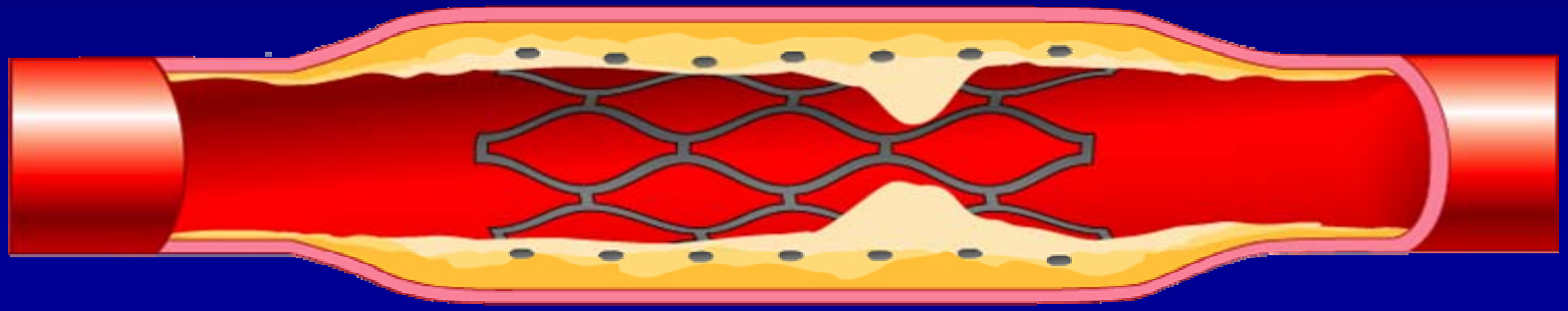
3D-IVUS: Diffuse vs Focal Neointima

Diffuse NIH



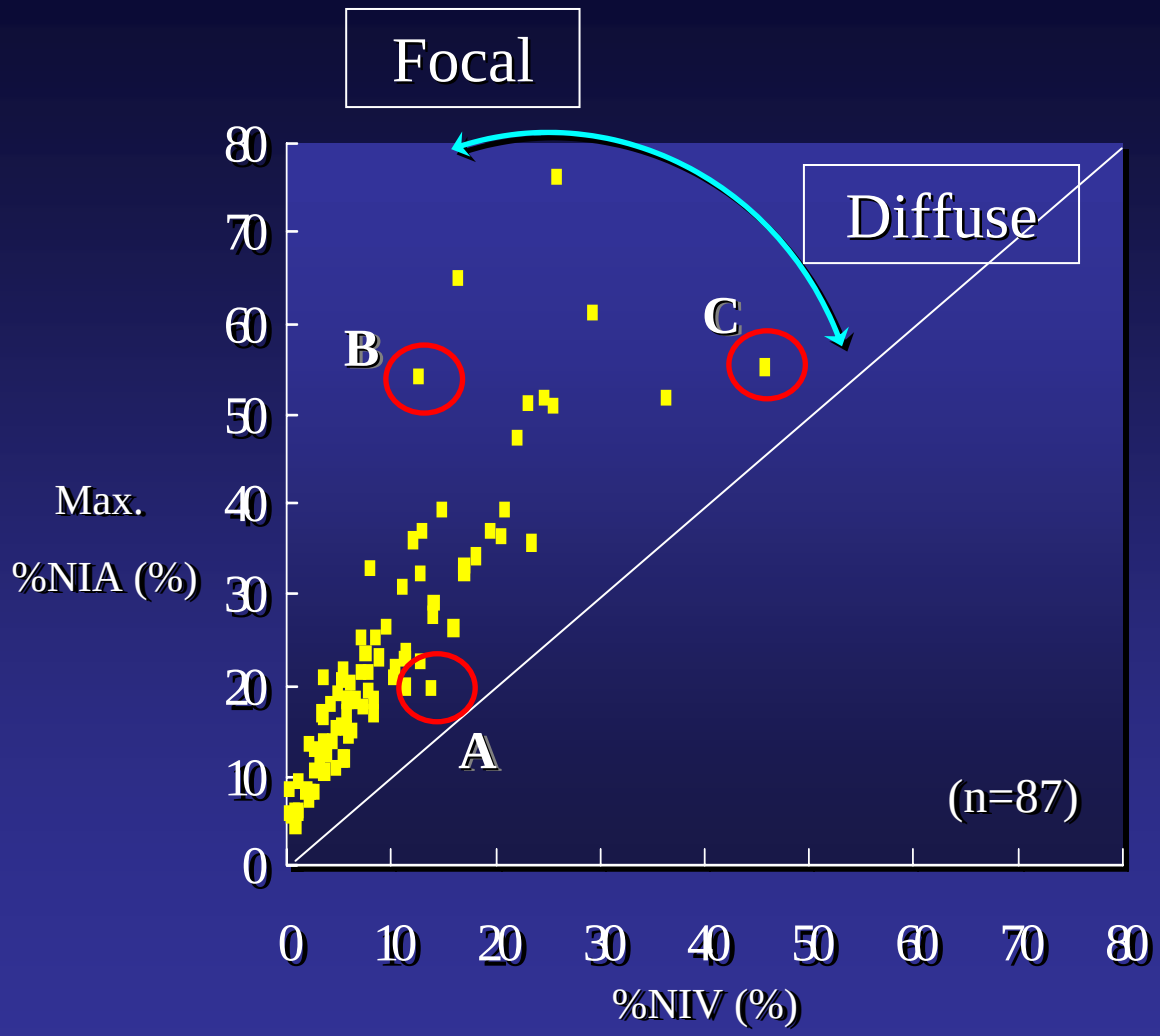
%NI Volume = 10%

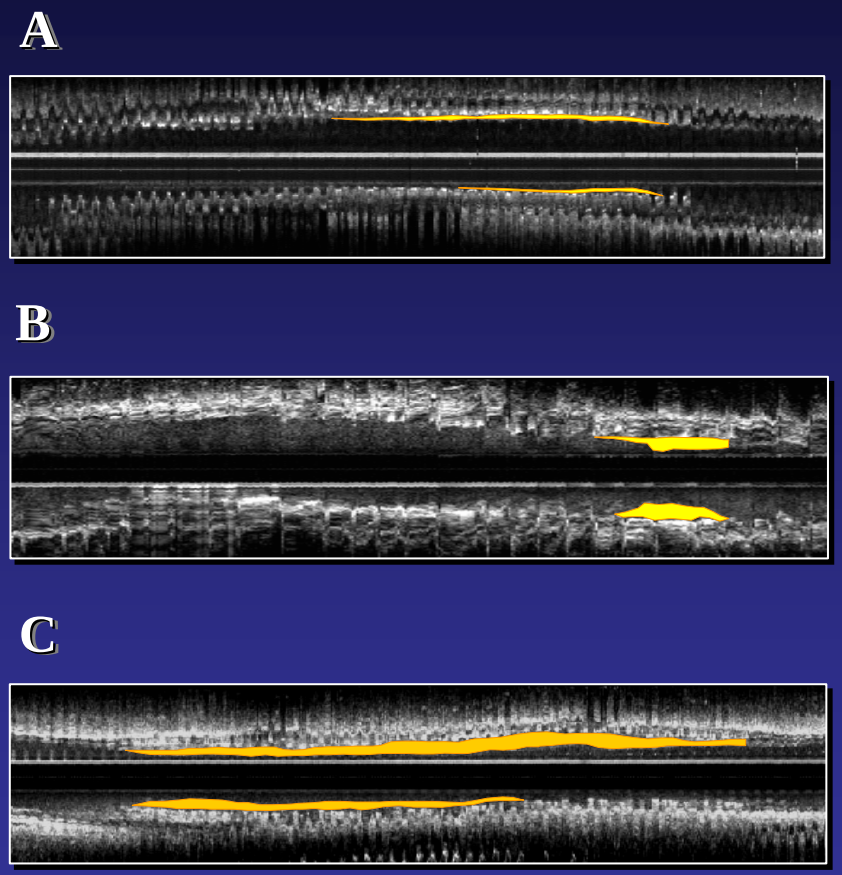
Focal NIH



%NI Volume = 10%

Relationship between Volume and Area Obstruction

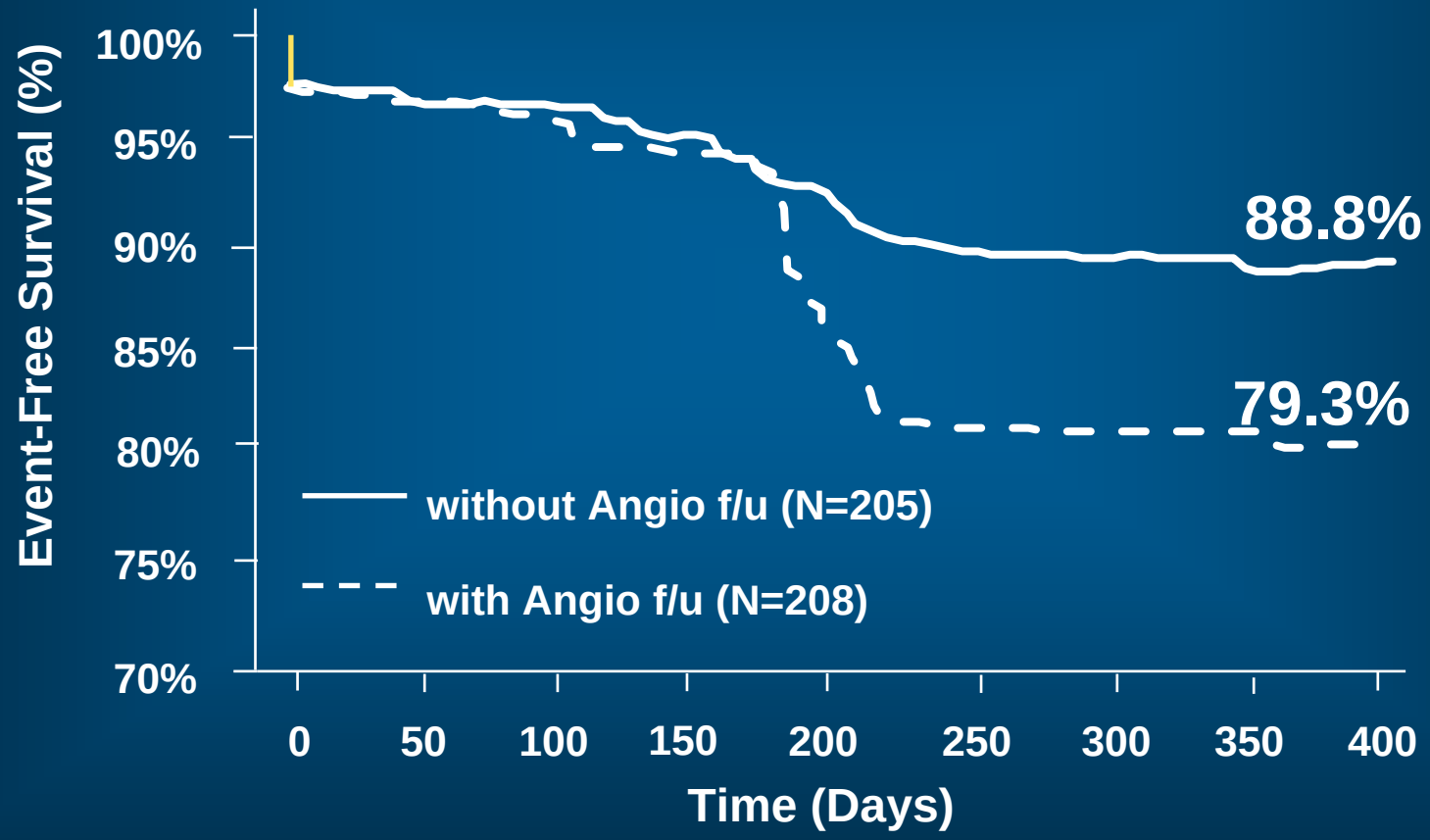




Impact of angiographic follow-up: Benestent II

Benestent II Clinical Results:

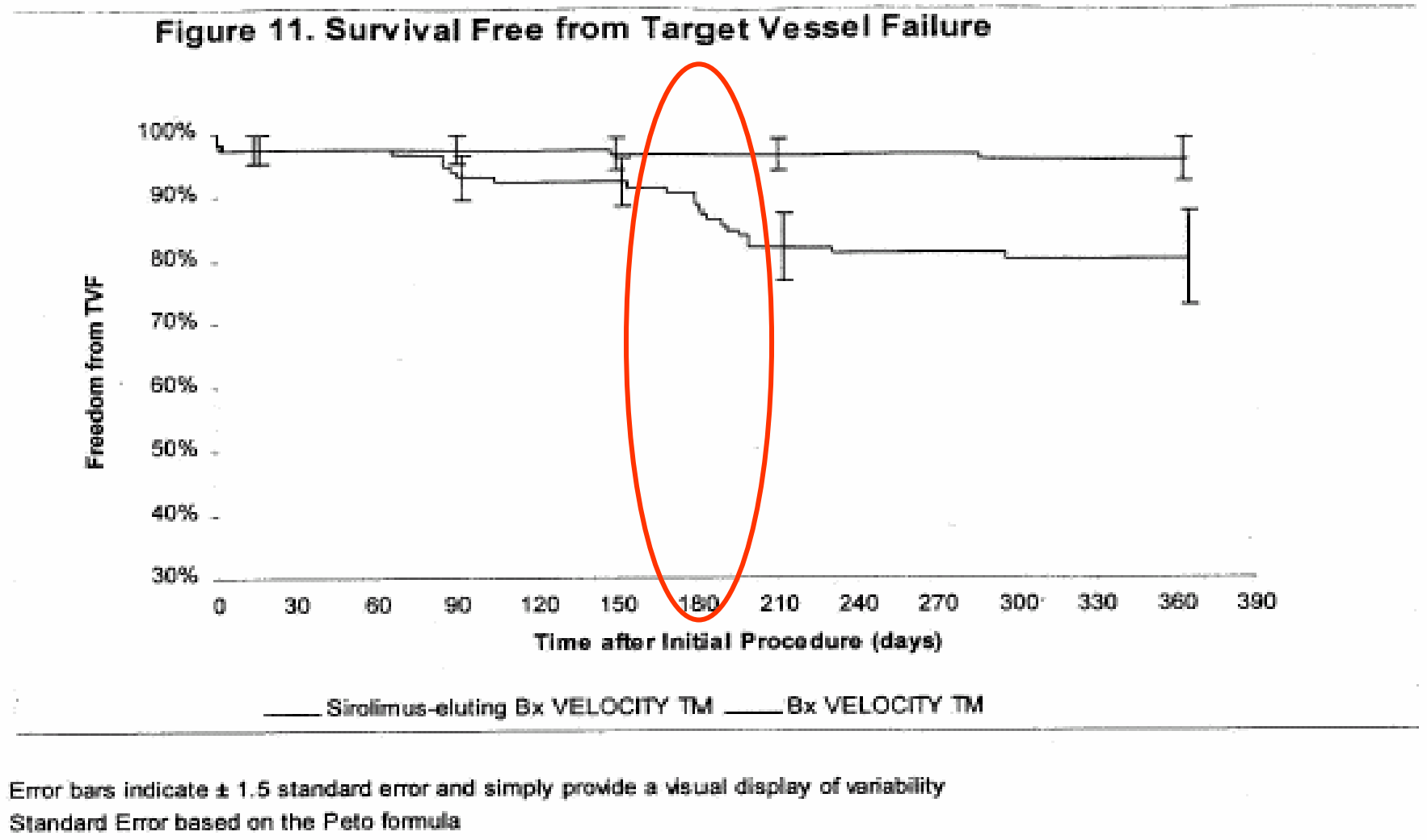
Event-Free Survival at One Year with and without angio follow-up



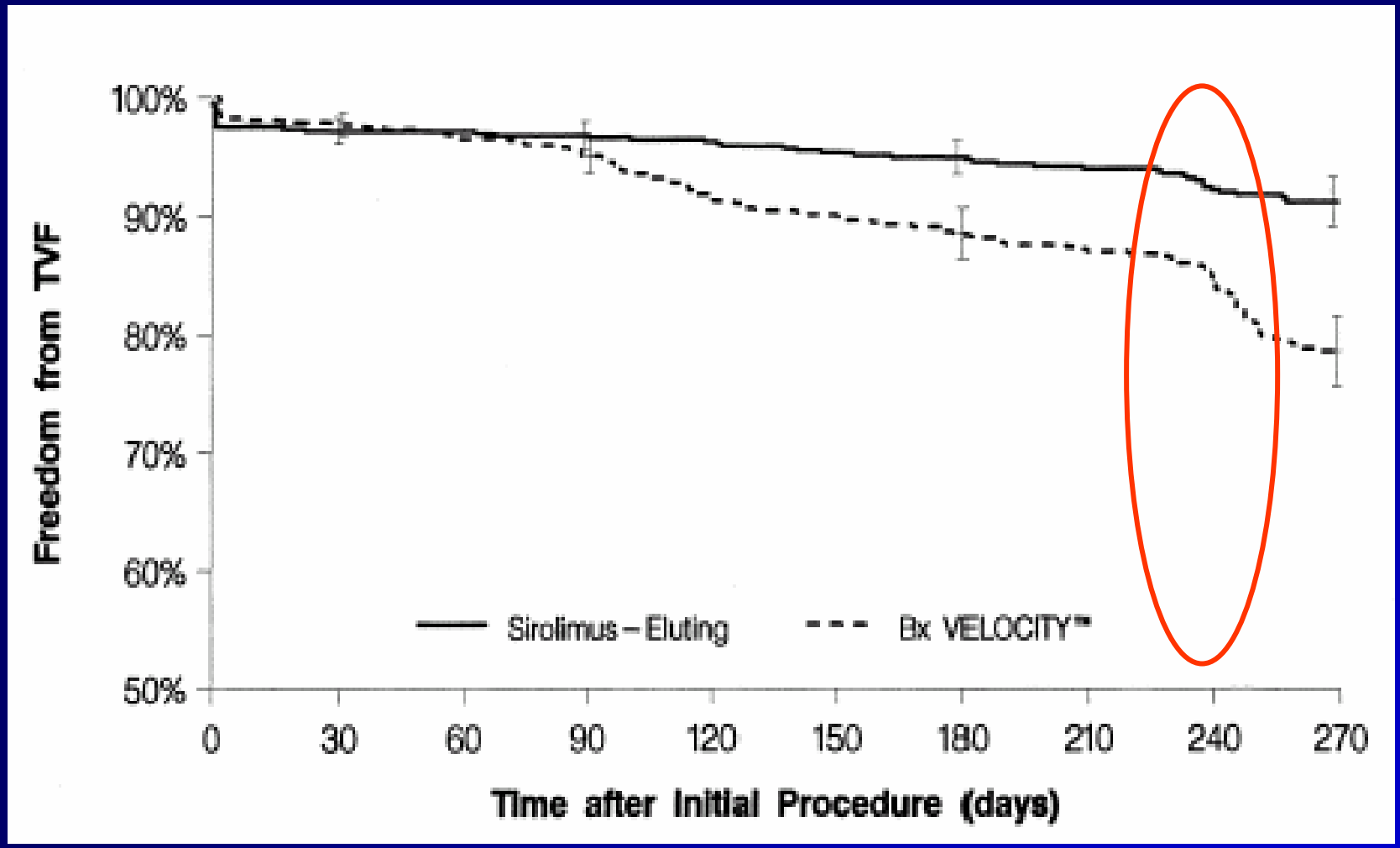
P.W. Serruys, MD, ThoraxCenter, Rotterdam, Netherlands
European Society of Cardiology, August, 1997

Ranking Scale

Influence of Angiography RAVEL



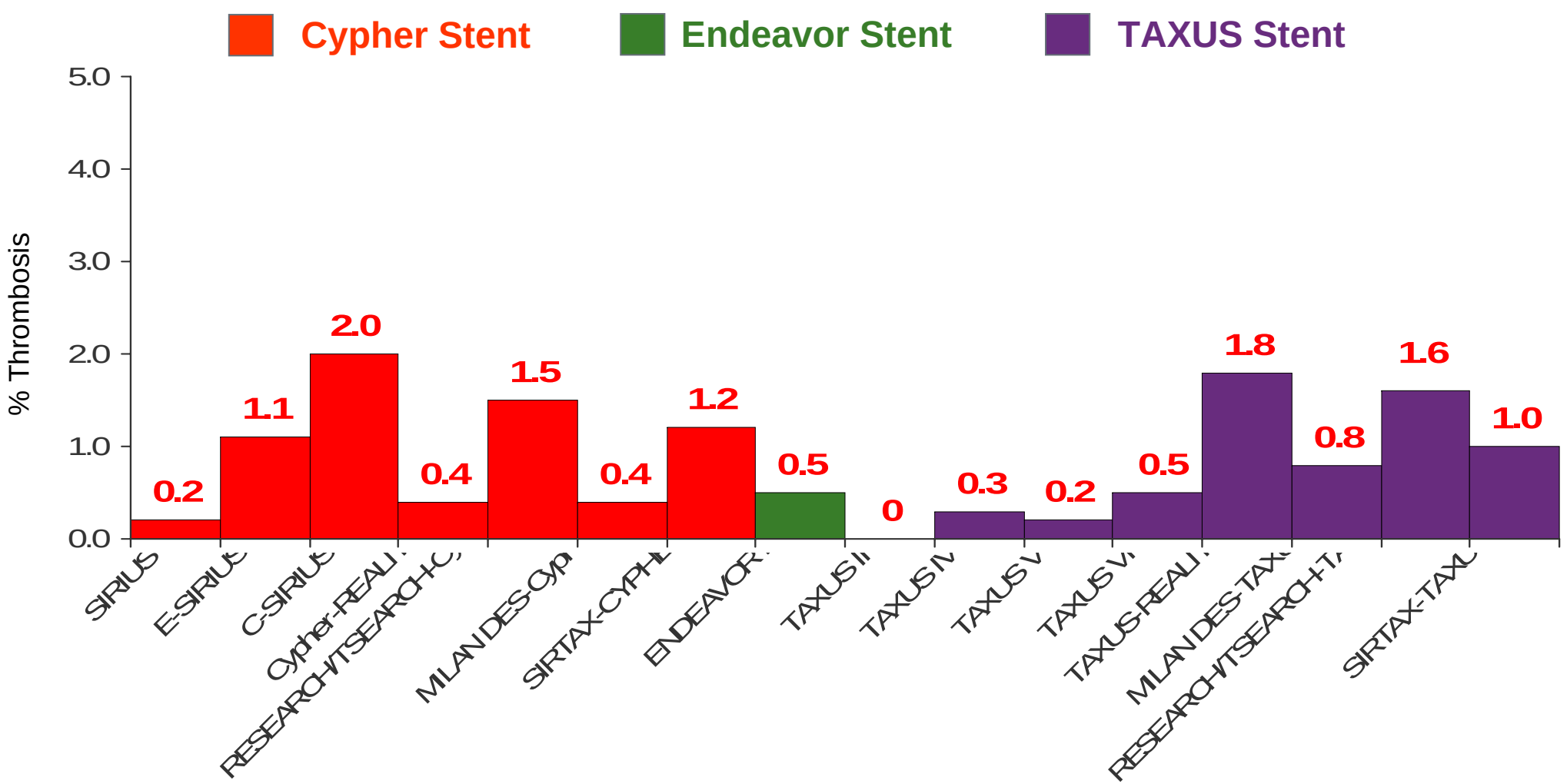
Influence of Angiography SIRIUS



John Hyde, Ph.D., M.D. Interventional Cardiology Devices Branch
Center for Devices & Radiological Health
DHHS/FDA/CDRH

SAT Rates Across Trials

Out of Hospital to 30 Days



Data sources available on file.

TAXUS Stent = TAXUS® Express²™ 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