

DES of the Future: Design Goals and Challenges

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**Presenter Disclosure Information for
TCTAP 2010; April 27-30, 2010**

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Scientific Advisory Board:
Abbott Vascular, Boston Scientific,
Medinol, and Medtronic

First Generation DES

TAXUS

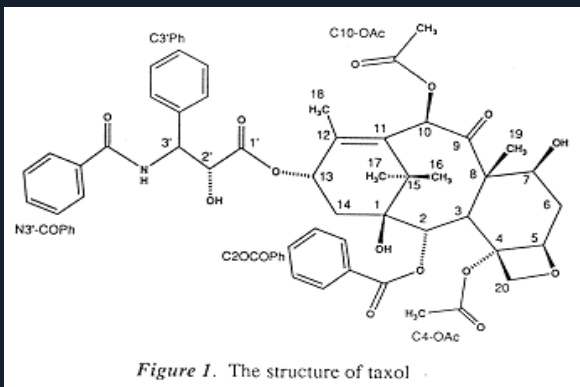
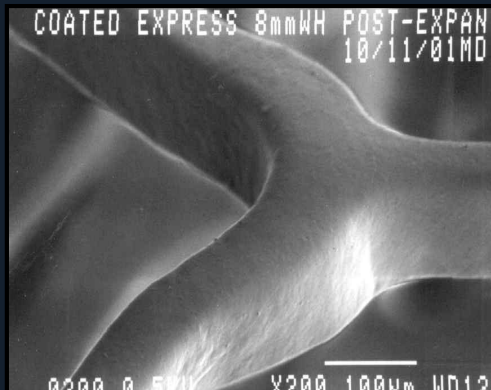


Figure 1. The structure of taxol

Paclitaxel
Drug

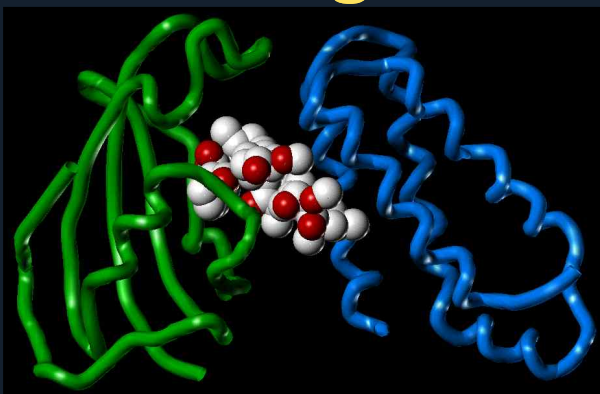


Polyolefin derivative
Polymer

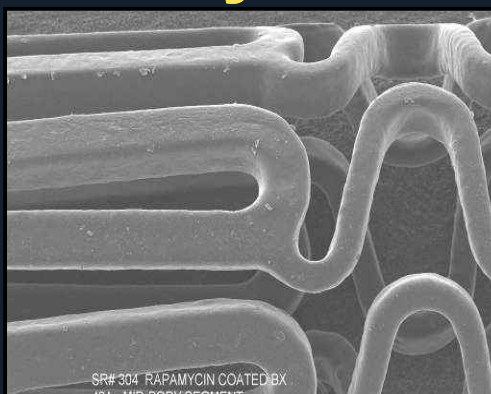


Express²
Stent

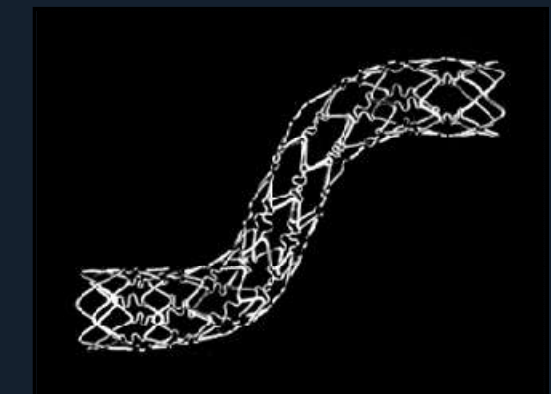
Cypher



Sirolimus



PEVA + PBMA blend



BX Velocity

DES - A Transforming Technology



***My Rosey Prophecy:
Restenosis is CURED!***

12 months

24 months

48 months

The Early Days of DES

Belief, hope, and hyperbole > the evidence

Potential DES over-exuberant use

2005 →

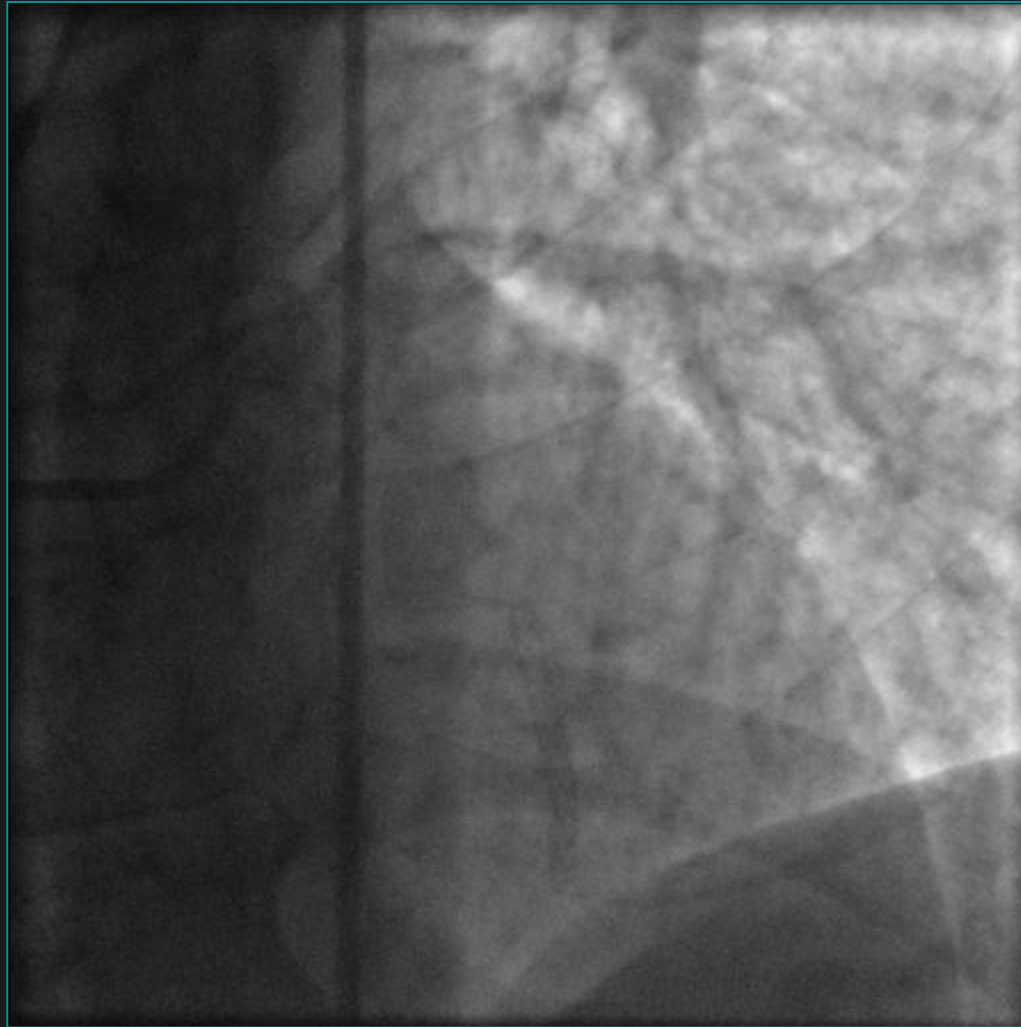
- DES solves restenosis
- Pivotal data look good (safety and efficacy)
- *Maybe they are good for all lesions types and in all patients*

~90%
penetration

Late DES thrombosis after discontinuation of antiplatelet therapy

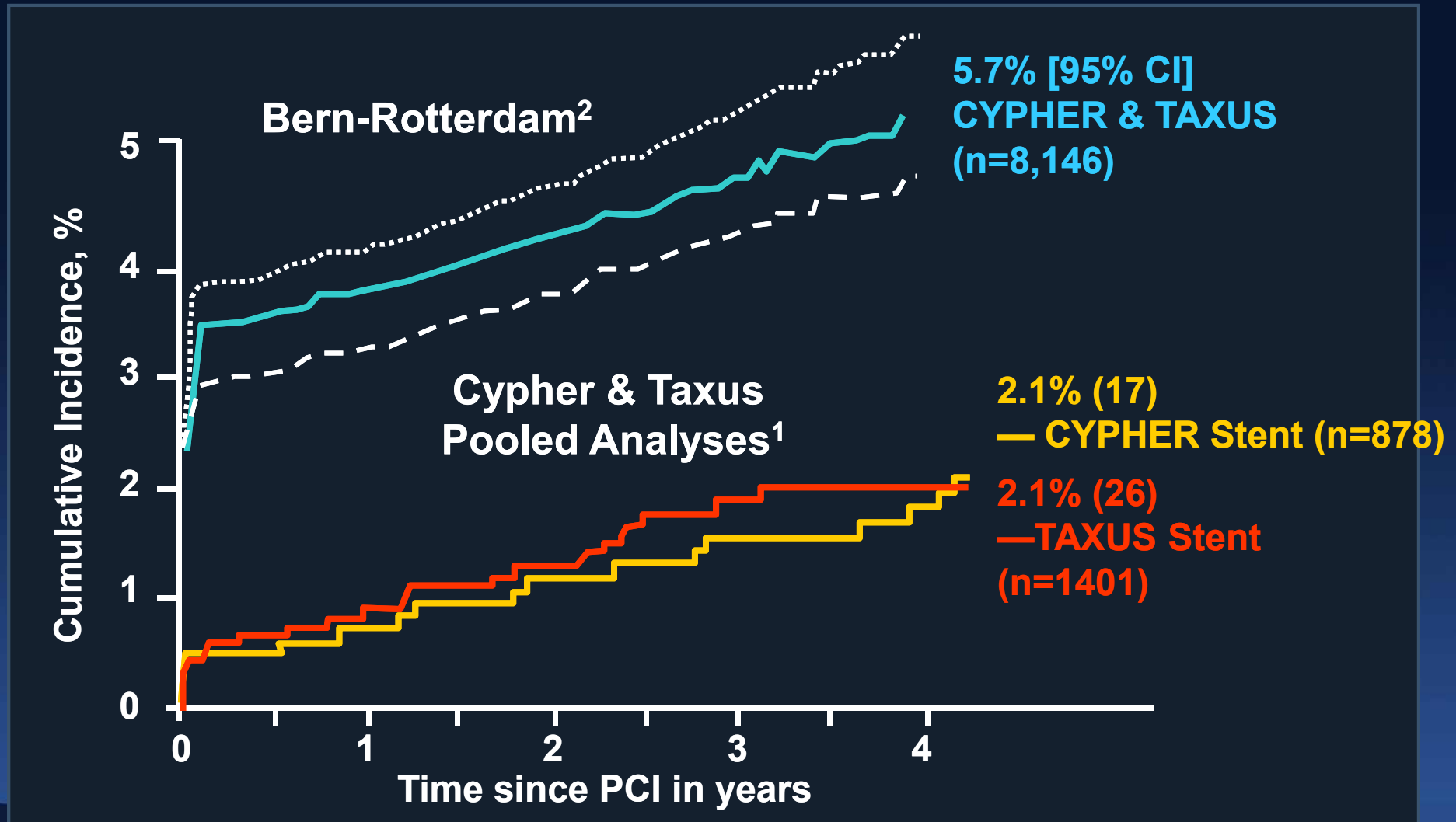


Late Stent Thrombosis - Cypher



- **57 yo WM with ACS**
 - **3 mm X 23 mm Cypher without complications**
 - **6 mos of ASA + Plavix**
- **6 days after stopping Plavix, sudden onset CP and evolving acute anterior MI**
- **Stent thrombosis at proximal stent site**

Cumulative Incidence of ARC Def/Prob ST over 4 yrs after DES (CYPHER & TAXUS)



¹ Mauri et al; N Engl J Med 2007;356:1020-9

² Wenaweser et al; J Am Coll Cardiol 2008;52:1134-40

GOOGLE VS. MICROSOFT
THE RACE TO REV UP THE SEARCH ENGINE

America's Largest Private Companies
Howard Stern—Is Anyone Listening?
SCORE! Hockey Is Hot Again

NOVEMBER 27, 2006 | WWW.FORBES.COM

Forbes

STENTS
DEFIBRILLATORS
SPINAL DISCS
ARTIFICIAL KNEES

**Are These
As Safe As
You Think?**

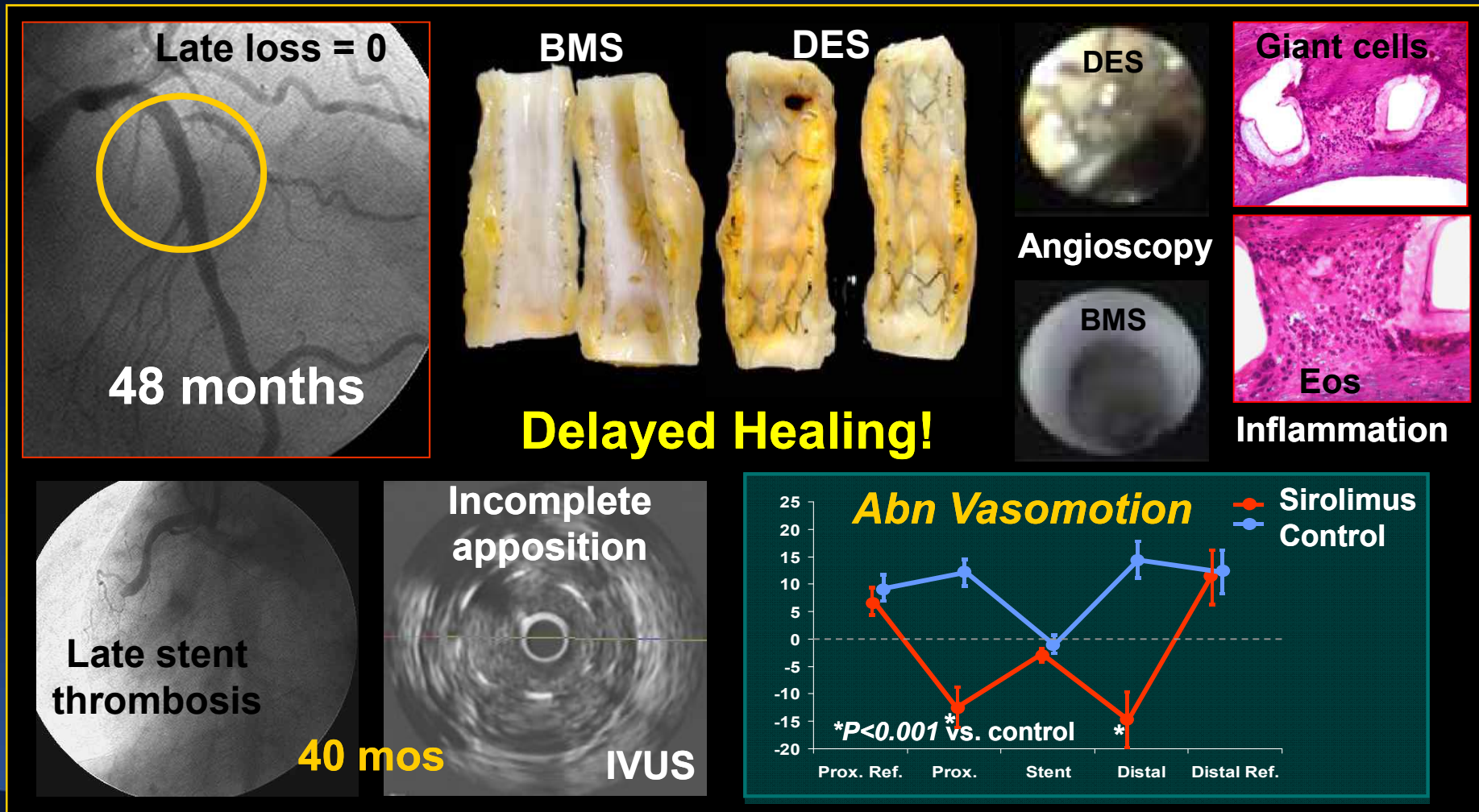
\$4.99 | CANADA \$6.99



**DES =
“a million
ticking time
bombs”**

Drug-Eluting Stents

the good, the bad, and the ugly!



The Dark Days of DES

*Fear-based avoidance and distortions
> the (true) evidence*

Definite DES under-use

← 2006-07

- DES = ↑ thrombosis and ↑ mortality
- COURAGE drives more medical Rx
- *Maybe DES use should be dramatically reduced*

~60%
(<50% EU)
penetration

DES Design Goals

Lessons Learned...

- 1. Don't be “seduced” by early favorable DES angiographic or clinical outcomes; the time domain for DES vascular biology effects and procedure-related clinical outcomes is years (not months) and is more protracted than BMS.**
- 2. There is no “generic” DES system; each DES is uniquely differentiated (unlike BMS)**
 - ❖ Safety and efficacy considerations are DES-specific and require long-term (≥ 5 years) follow-up**

Drug-Eluting Stents

First Generation

Stent design and delivery system

Pharmacologic agent

Drug-Eluting Stent

Drug carrier vehicle

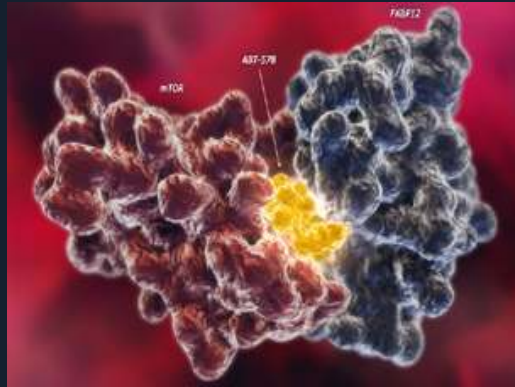
“Off the shelf” outdated stent and delivery system

Known FDA-approved drugs with approximated release kinetics

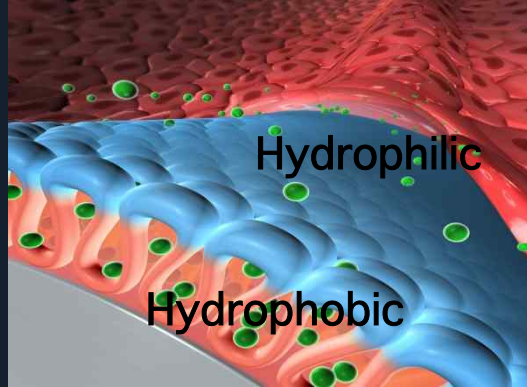
Available, FDA-approved biostable polymers

Second Generation DES

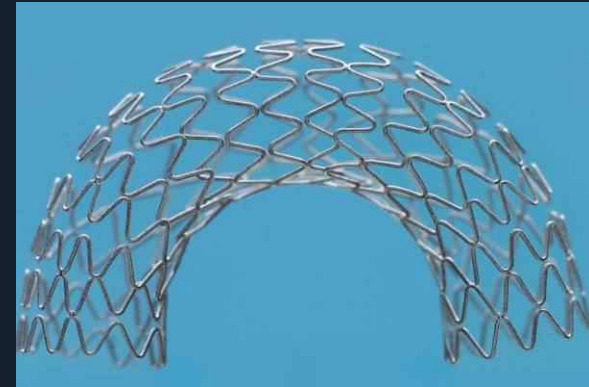
Endeavor**



Zotarolimus
Drug

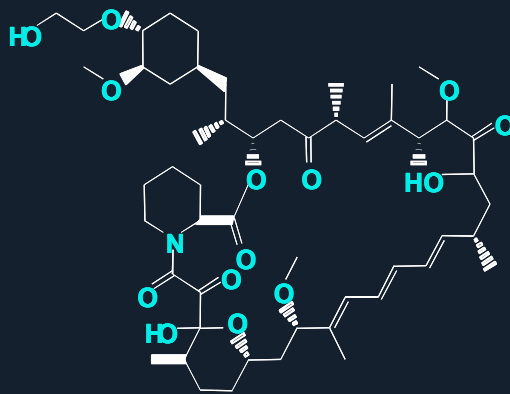


BioLinx
Polymer



Driver
Stent

Xience V*



Everolimus



VDF + HFP copolymer



Vision

A Slow Return to DES “Normalcy”

Reliance on overwhelming evidence

Can we regrow the DES forest?

2007 (late) → now

- PCI better for Sx relief and reducing ischemia
- DES doesn't ↑ mortality or MI (on or off-label use) and reduces TVR ~50% (real world)
- *More confident DES use, but with careful DAPT*

~75%
penetration

Next Generation DES

The Holy Grail?



No restenosis
No clinical safety issues

Future DES *Design Goals*

Deliverability

Efficacy

Safety

Future DES

Design Goals

Deliverability

DES Design Goals

Deliverability...what counts?

- *Ease-of-use delivery in complex anatomies (tortuous vessels) and in complex lesions (calcified, angulated, distal)...*
 - ✓ Low profile
 - ✓ Conformability
 - ✓ Stent within stent (surface friction)
- *Sidebranch access...*
 - ✓ Cell geometry
- *Favorable delivery system characteristics...*
 - ✓ Balloon compliance
 - ✓ Minimal balloon over-hang (edge dissections)

Future DES

Design Goals

Efficacy

DES Design Goals

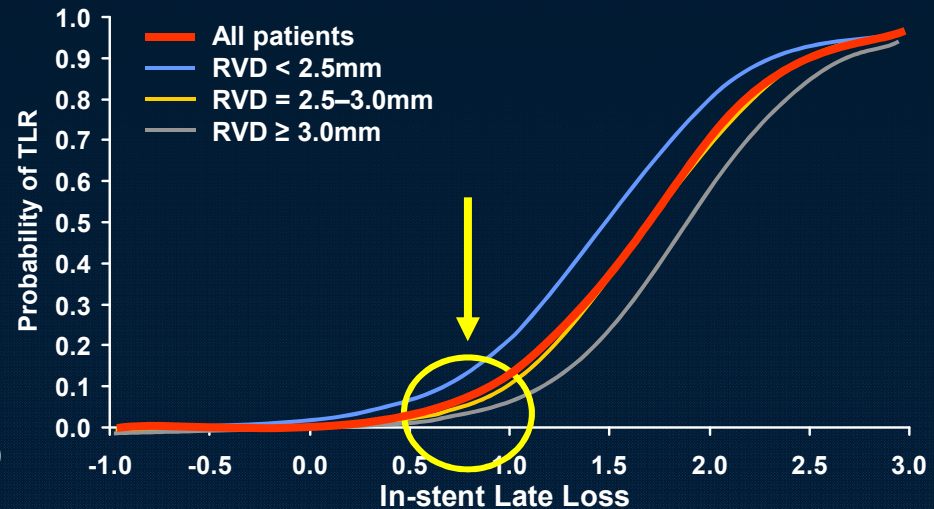
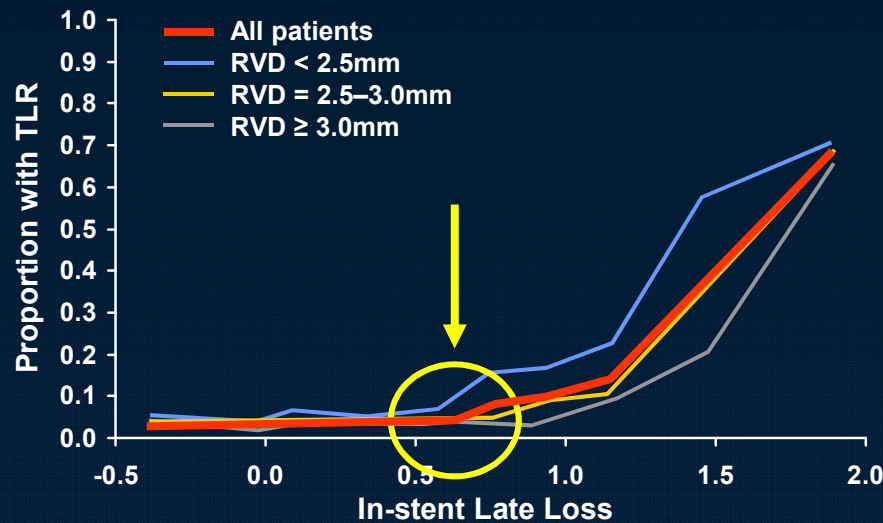
Efficacy...what counts?

- **Biologic efficacy...** reduction in neointimal hyperplasia
 - ✓ Angio = in-stent late loss
 - ✓ IVUS = neointimal volume and % volume obstruction
- **Angiographic efficacy...** reduction in angiographic stenosis
 - ✓ Angio = in-segment % diameter stenosis
- **Clinical efficacy...** reduction in repeat revascularization events (ischemia-driven)
 - ✓ Clinical – TLR and TVR (? Composites TVF/TLF)

11 RCTs with Cypher, Taxus, Endeavor, and BMS (5381 pts)

Surrogate Angiographic Endpoints for Clinical Outcomes

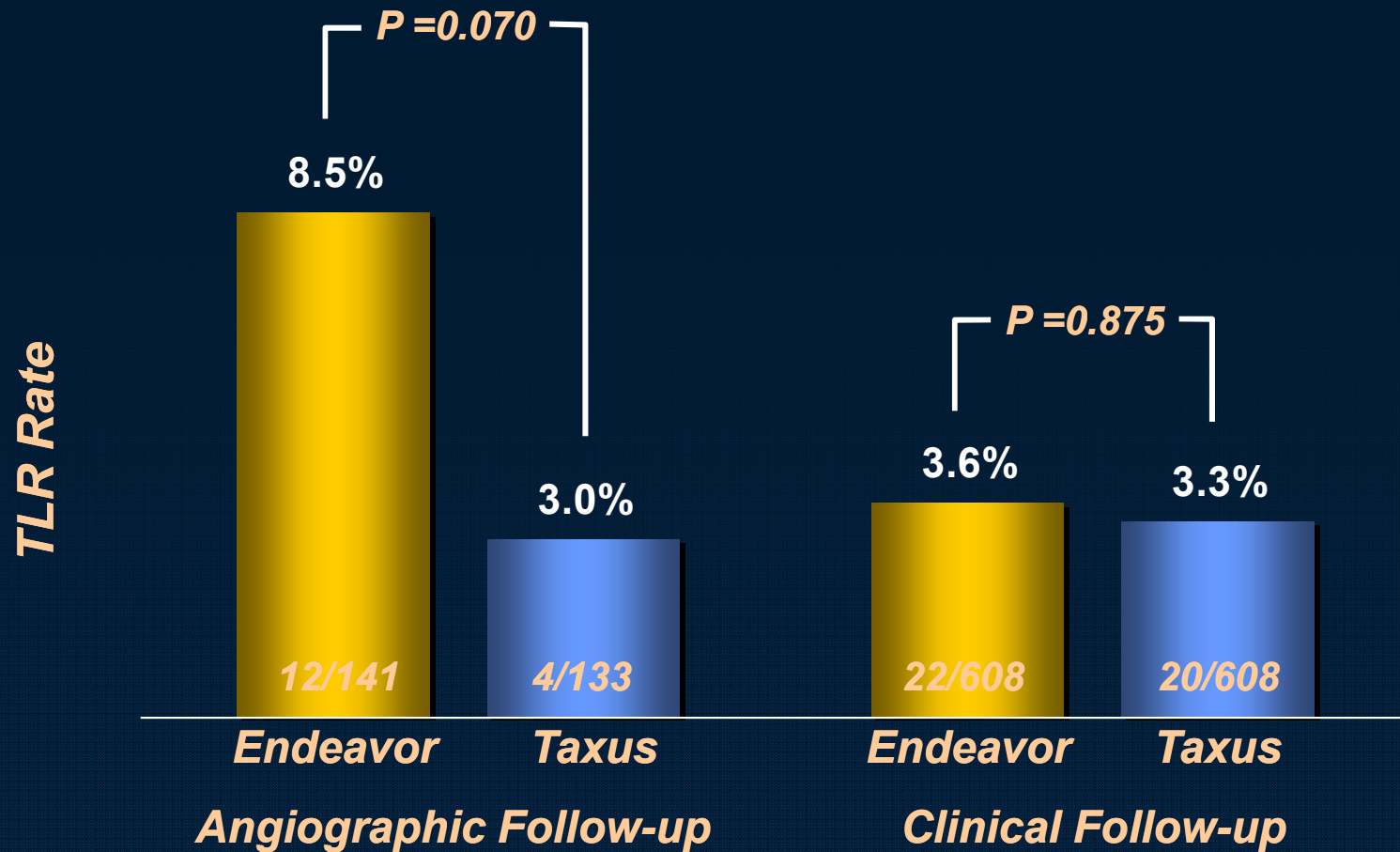
LL vs. TLR – A monotonic but curvilinear relationship



N 256 273 447 570 581 586 498 413 434 331 486 440

Endeavor IV

TLR by Angiographic Follow-up at 12 months

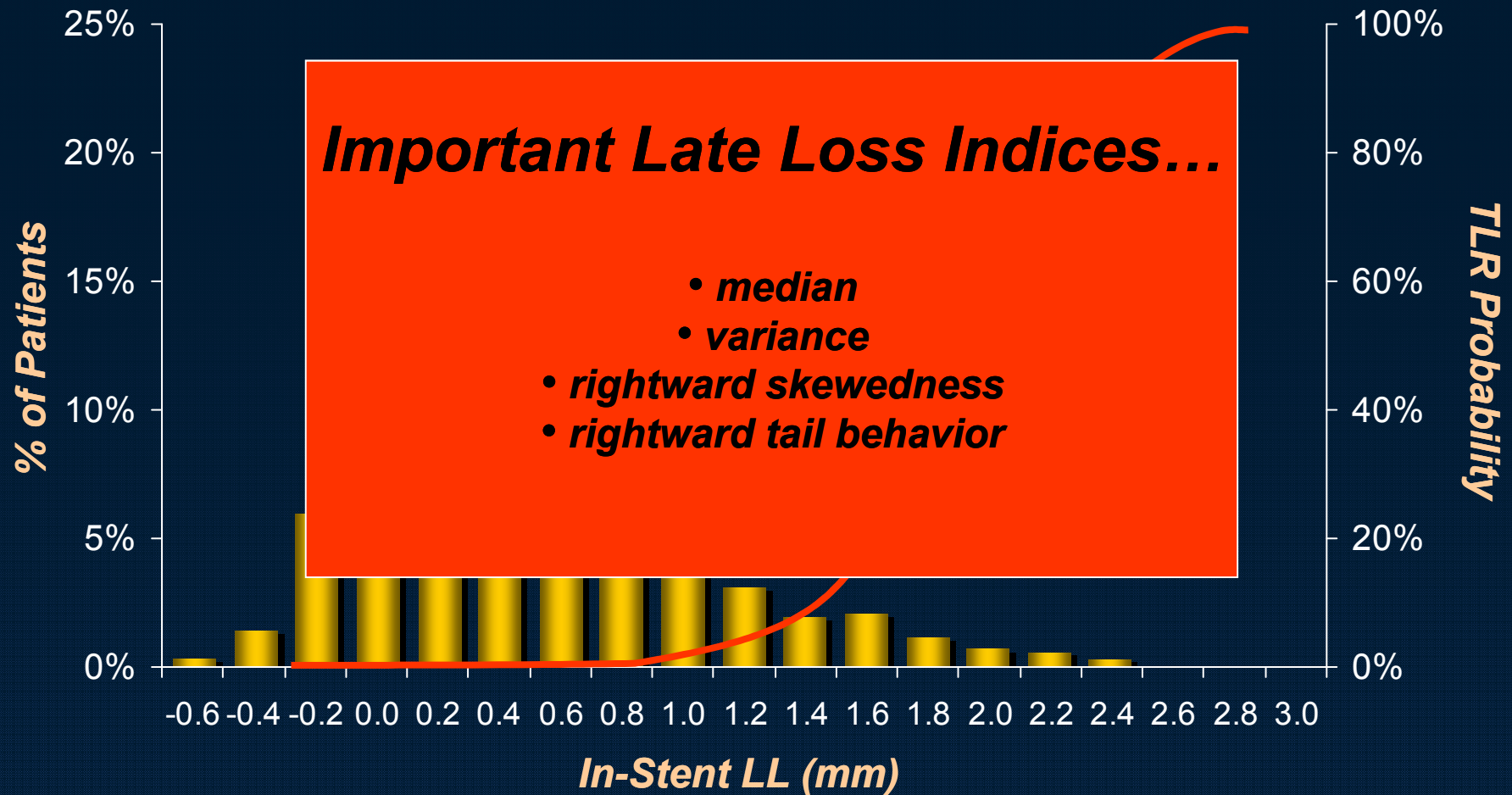


18% of pts

82% of pts

Endeavor In-Stent Late Loss

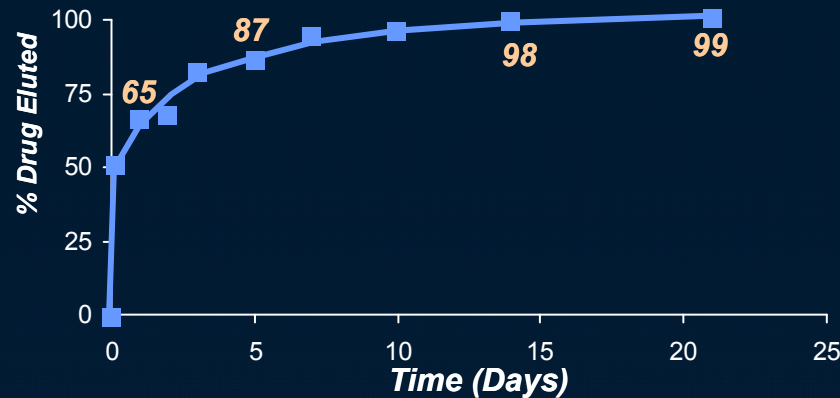
Endeavor II, II CA, III and IV



800 pts with angio FU at 8 mos

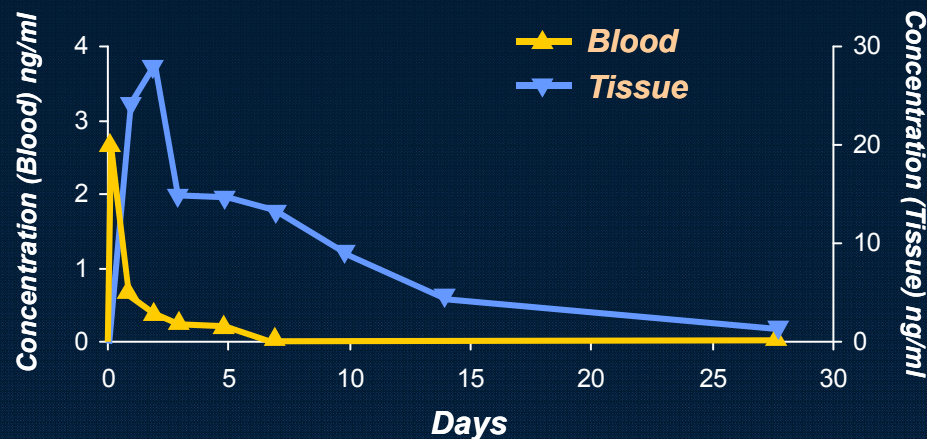
Porcine Drug Elution Kinetics and PK

Drug Elution by Recovered Drug from Stent



- Zotarolimus is hydrophobic and rapidly elutes from the hydrophilic PC polymer matrix within 14 days*

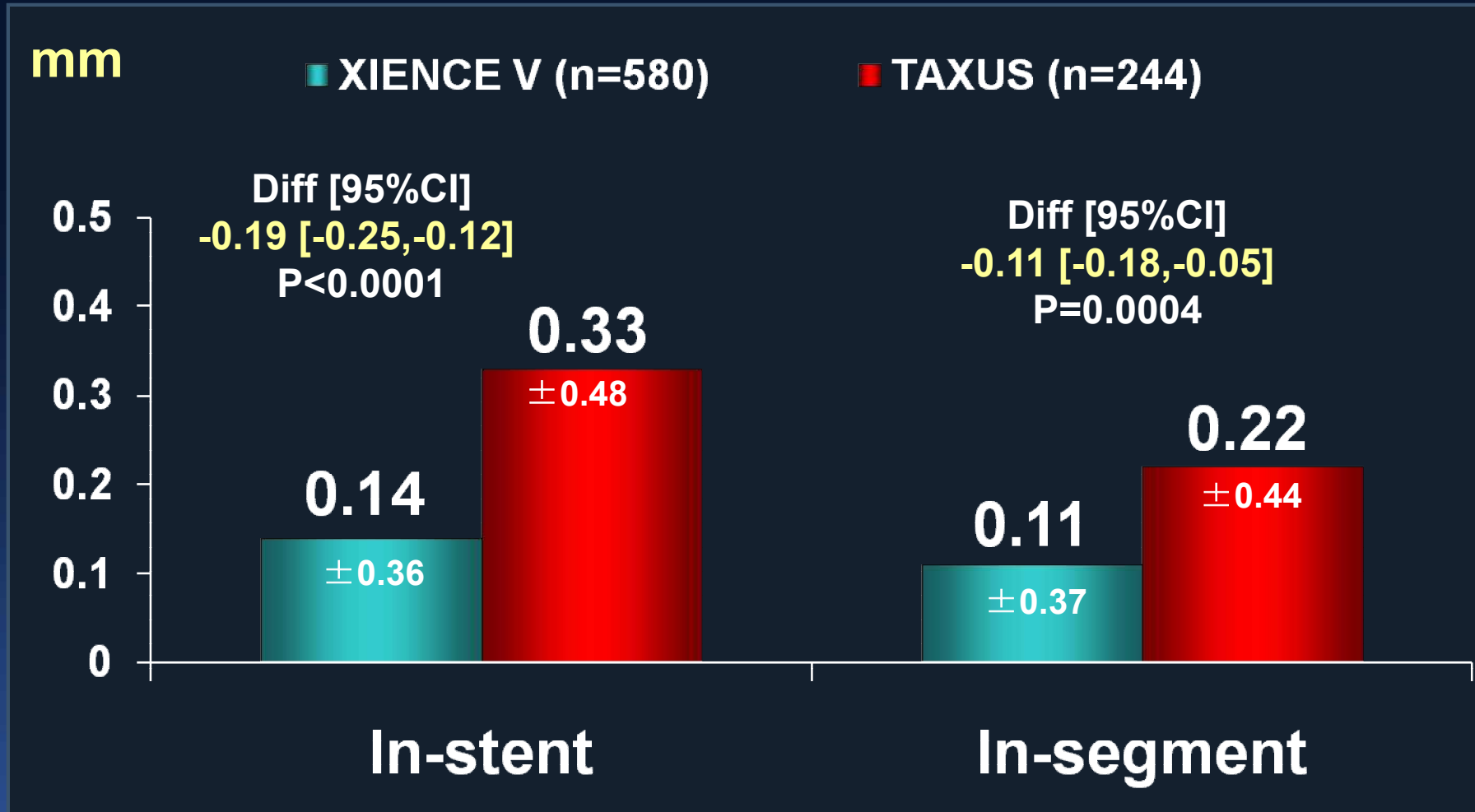
Blood and Arterial Tissue Zotarolimus Concentration



- Zotarolimus is highly lipophilic enabling rapid arterial tissue loading and drug retention which is sustained for ~28 days*

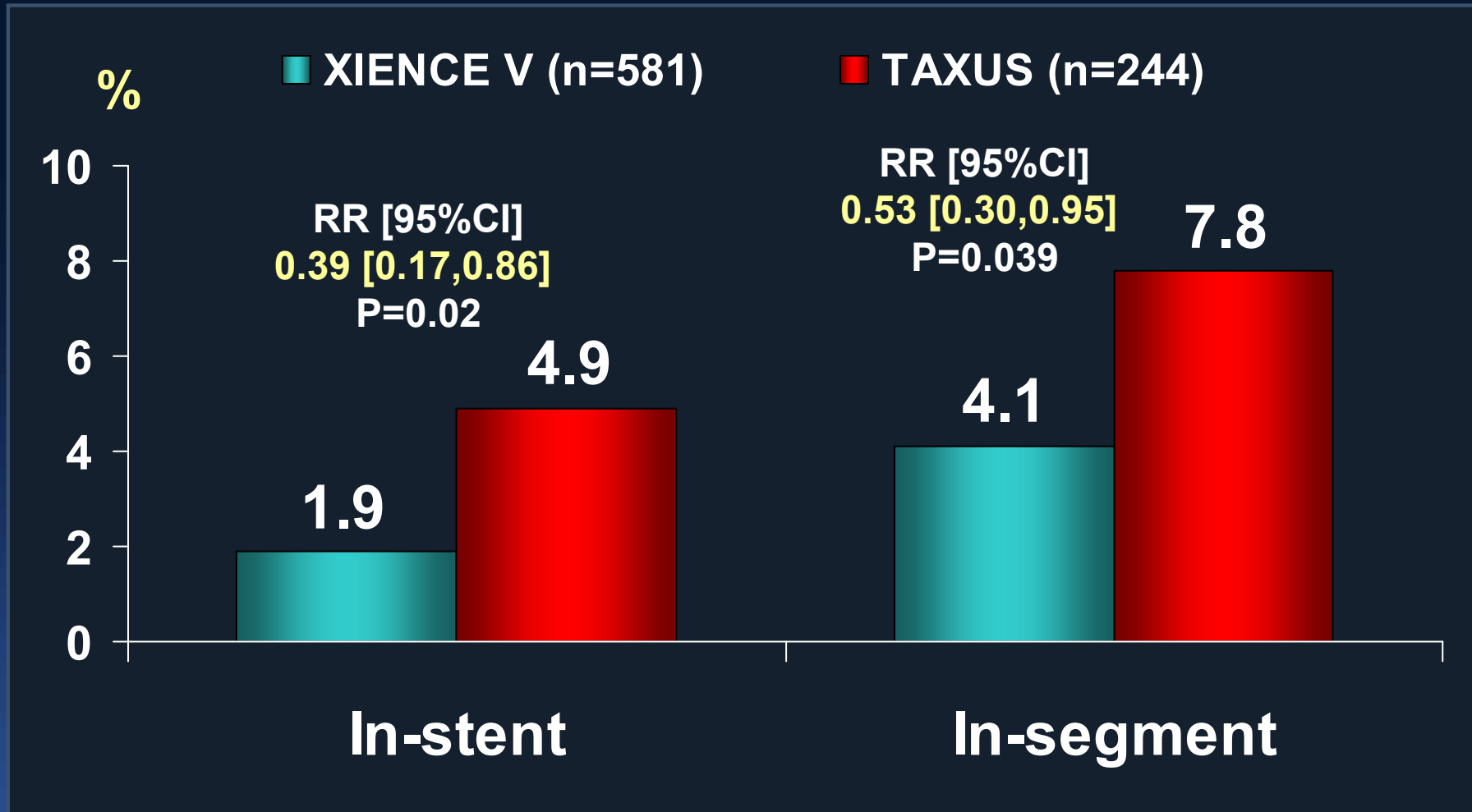
Rapid drug release

SPIRIT II + III Pooled Meta-analysis Late Loss



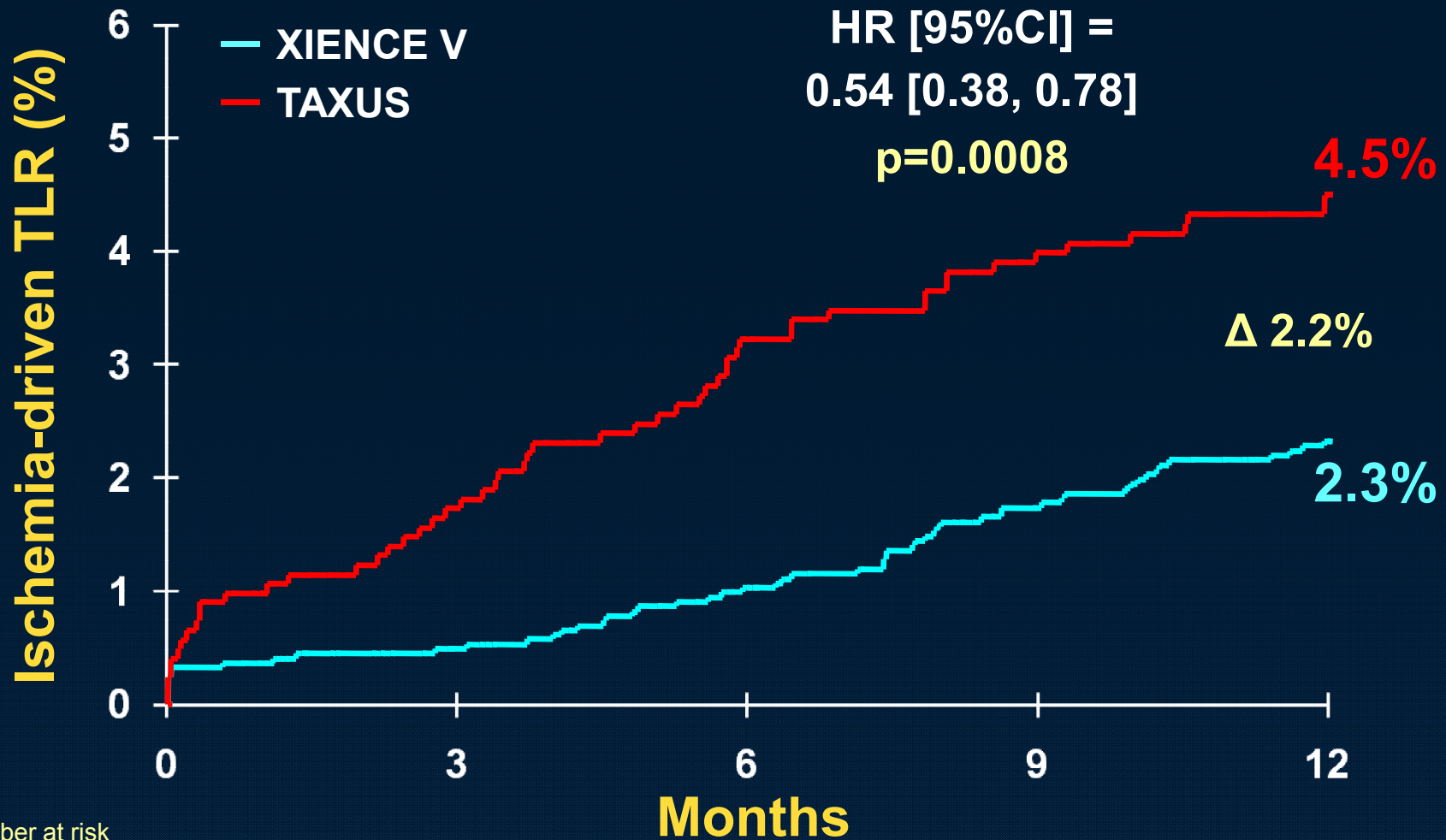
SPIRIT II + III Pooled Meta-analysis

Binary Restenosis



Ischemia-Driven TLR - 1 Year

Spirit IV



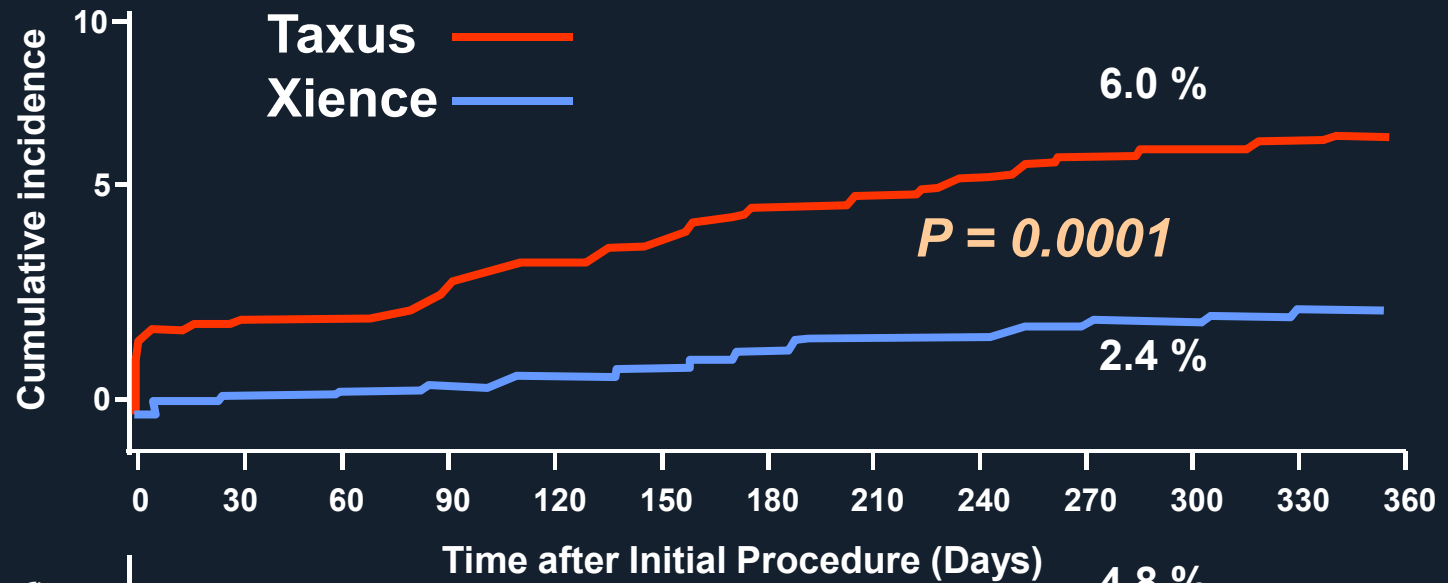
Number at risk

XIENCE V	2458	2419	2392	2353	2328
TAXUS	1229	1185	1158	1140	1125

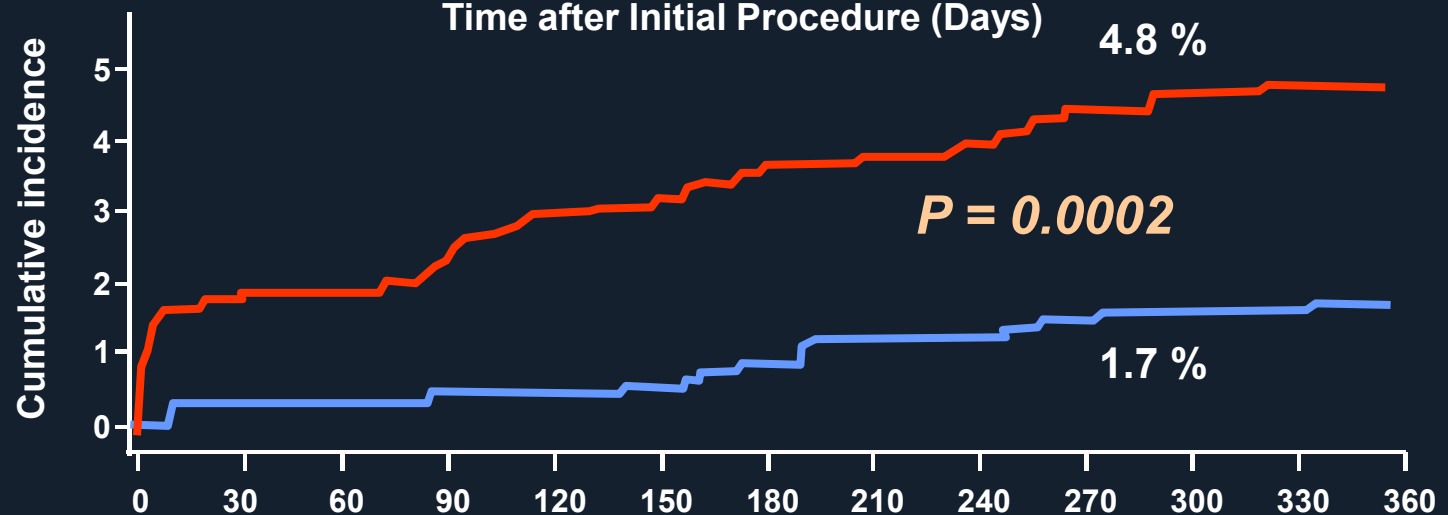
COMPARE – 2^{ry} Endpoint Analysis

TVR & Ischemia Driven TLR

TVR

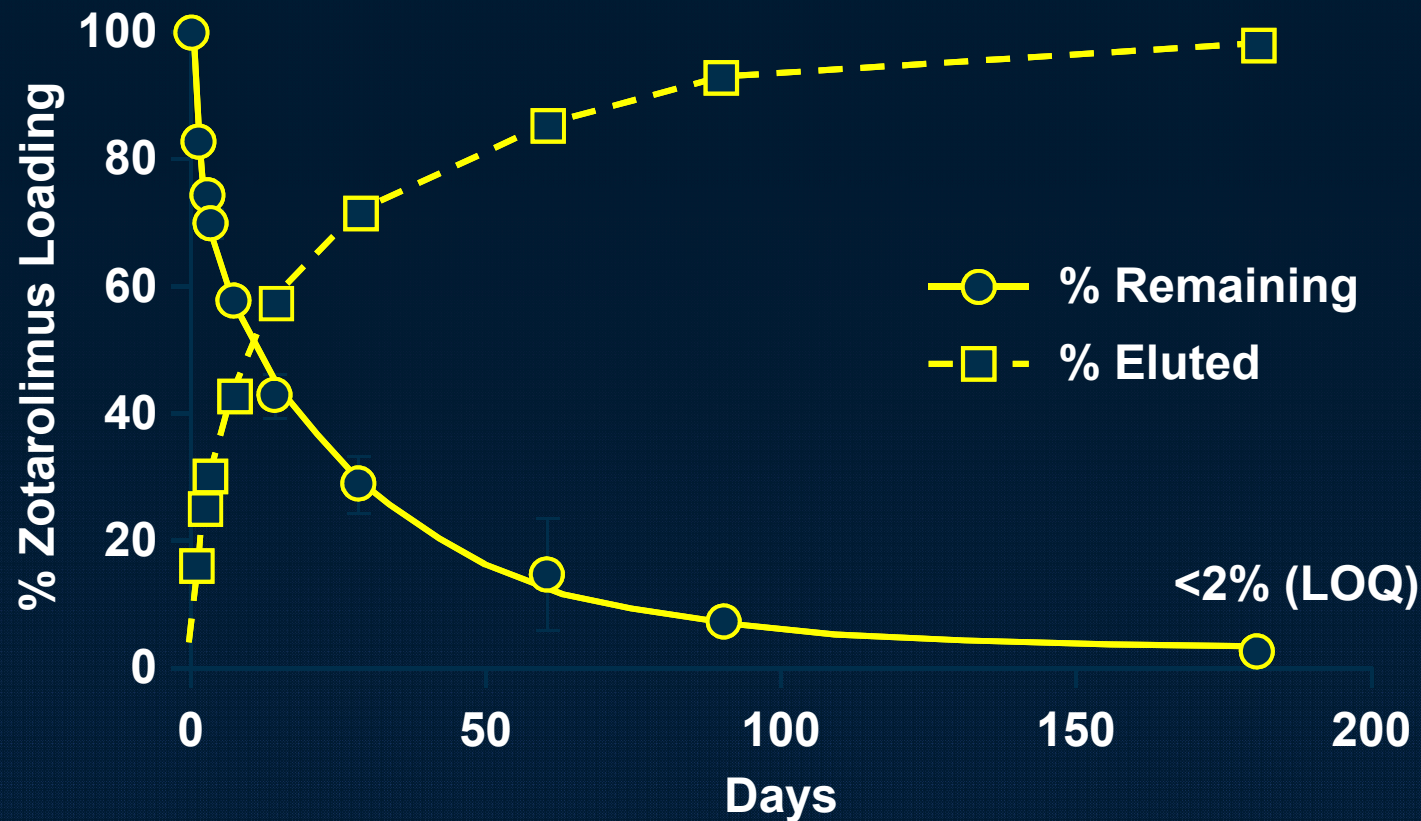


TLR



Endeavor RESOLUTE

BioLinx Polymer in vivo Elution

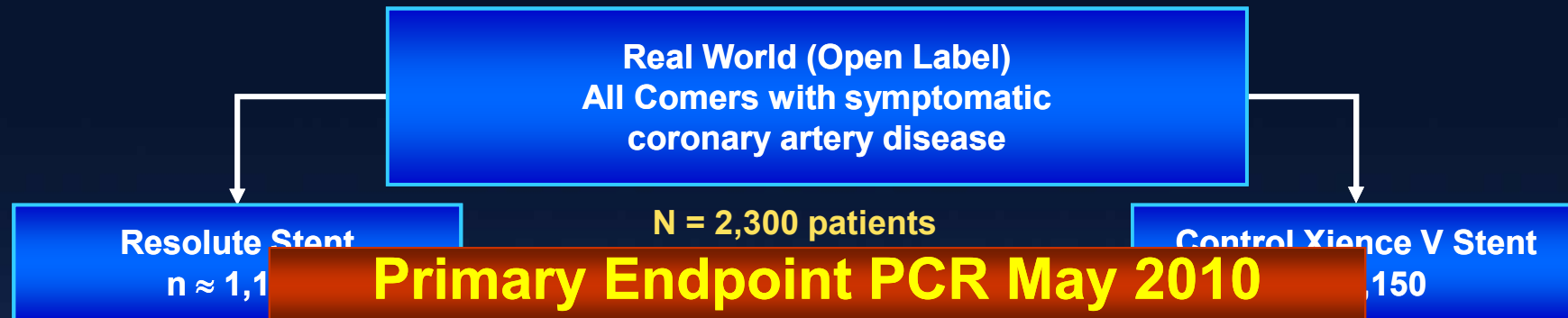


Greater than 85% of the drug is eluted at 60 days
Complete drug content exhausted by 180 days

RESOLUTE All Comers

Co-PIs: Profs. Serruys, Silber, Windecker

Enrollment Complete



Clinical Endpoints

Clinical/MACE



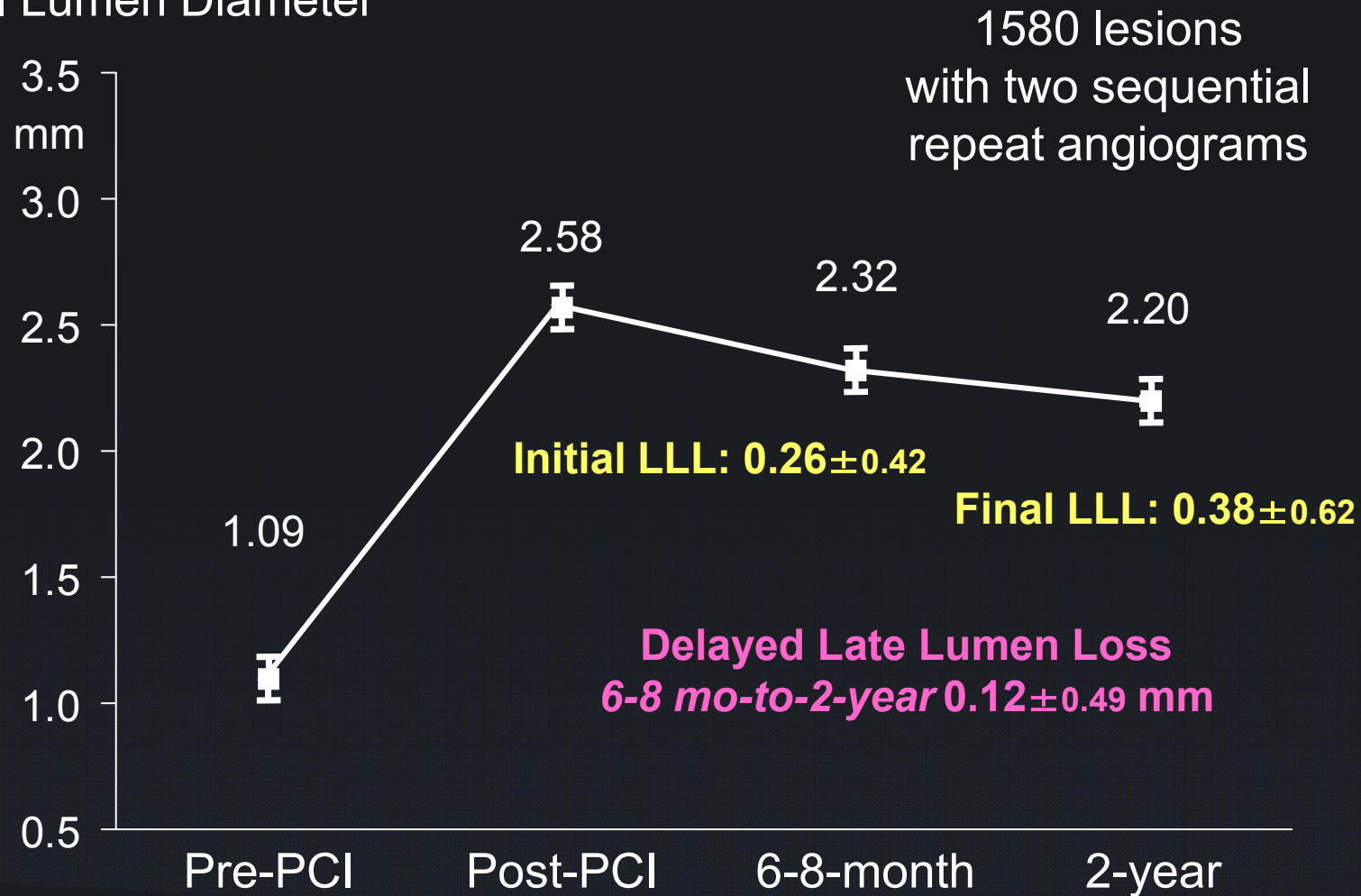
Angio/IVUS

460 (20%) QCA subset
50 (2%) OCT Subset

Primary Endpoint: Composite – Cardiac Death, Target Vessel MI, TLR @ 12mo
Secondary Endpoints: Composite @ 30d, 6mo, 2 – 5 yr; angiographic & optical coherence tomography (OCT) parameters @ 13 mo
Drug Therapy: ASA and clopidogrel/ticlid ≥ 6 months (per guidelines)

Temporal Course of Restenosis after DES Implantation

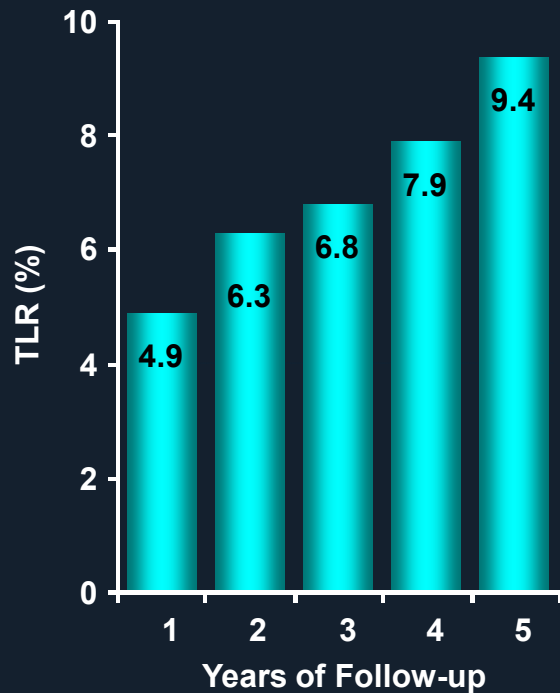
Minimal Lumen Diameter



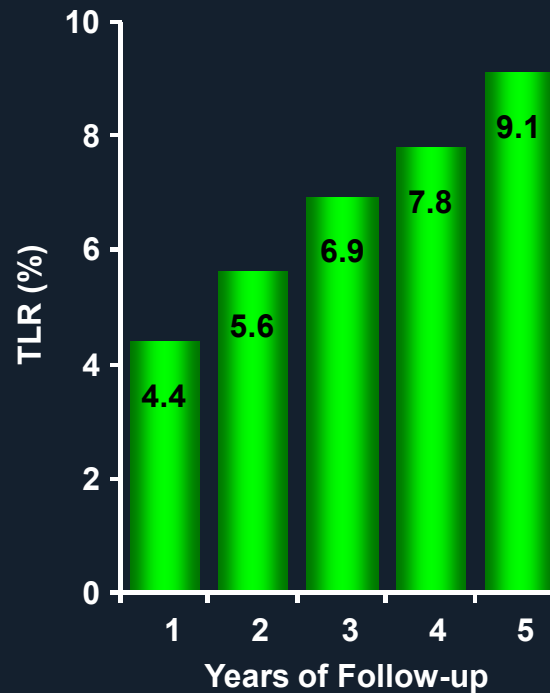
Pivotal Trials TLR - DES Arms

SIRIUS, TAXUS IV and ENDEAVOR II

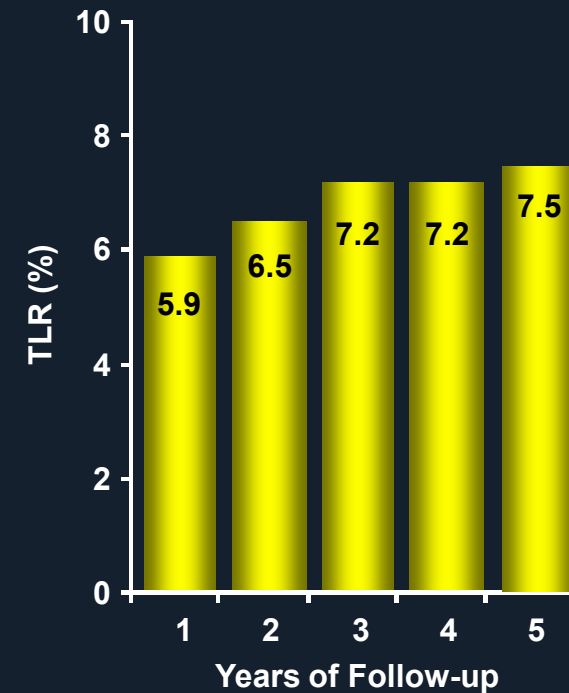
SIRIUS
(n=501/525)



TAXUS IV
(n=618/650)

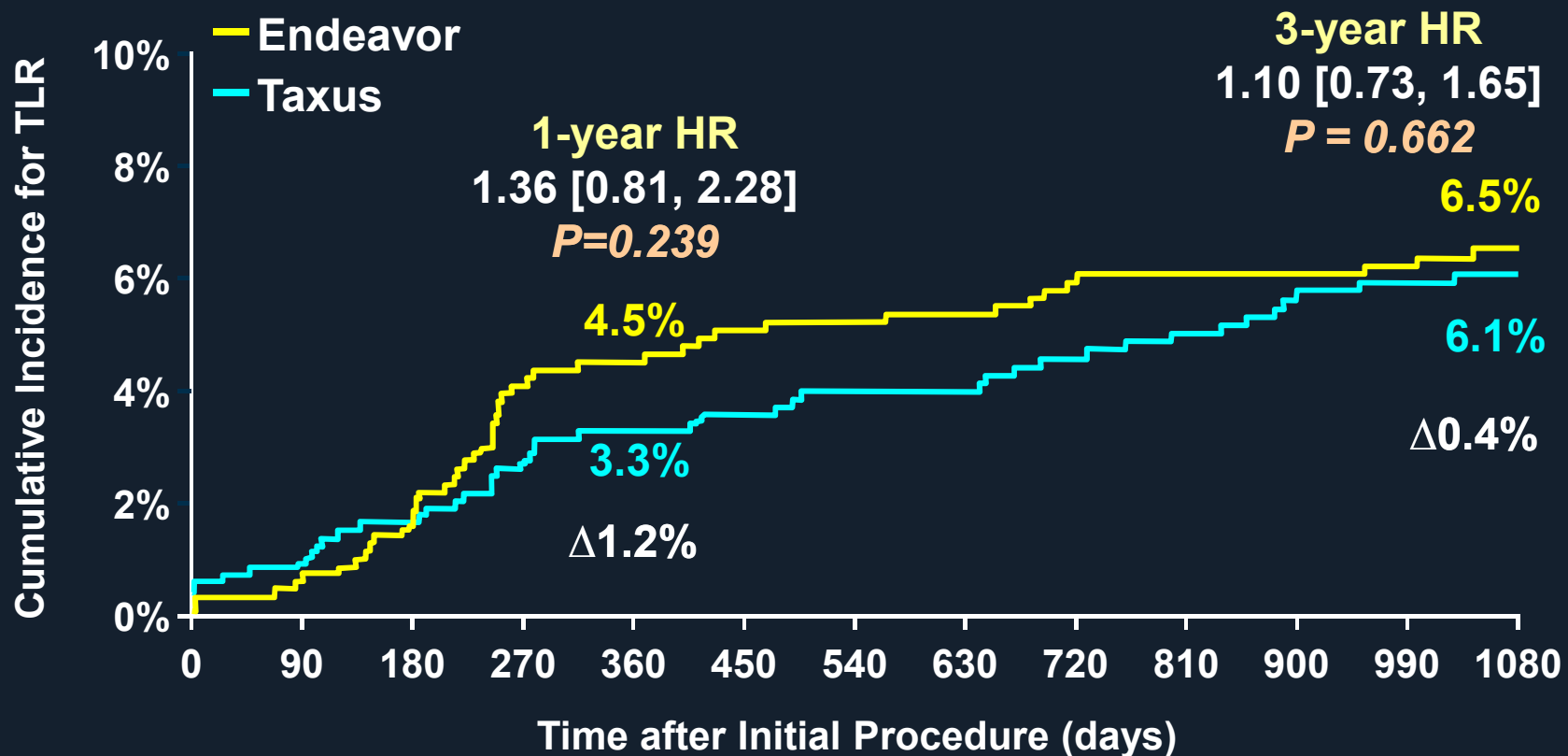


EII
(n=581/598)



ENDEAVOR IV – 3yr FU

TLR to 36 months



Endeavor	773	773	755	744	706	690	676	672	665	651	639	635	630
Taxus	775	771	758	742	712	695	682	677	674	659	646	635	628

Values are the KM estimates
P values were calculated by Log Rank Test

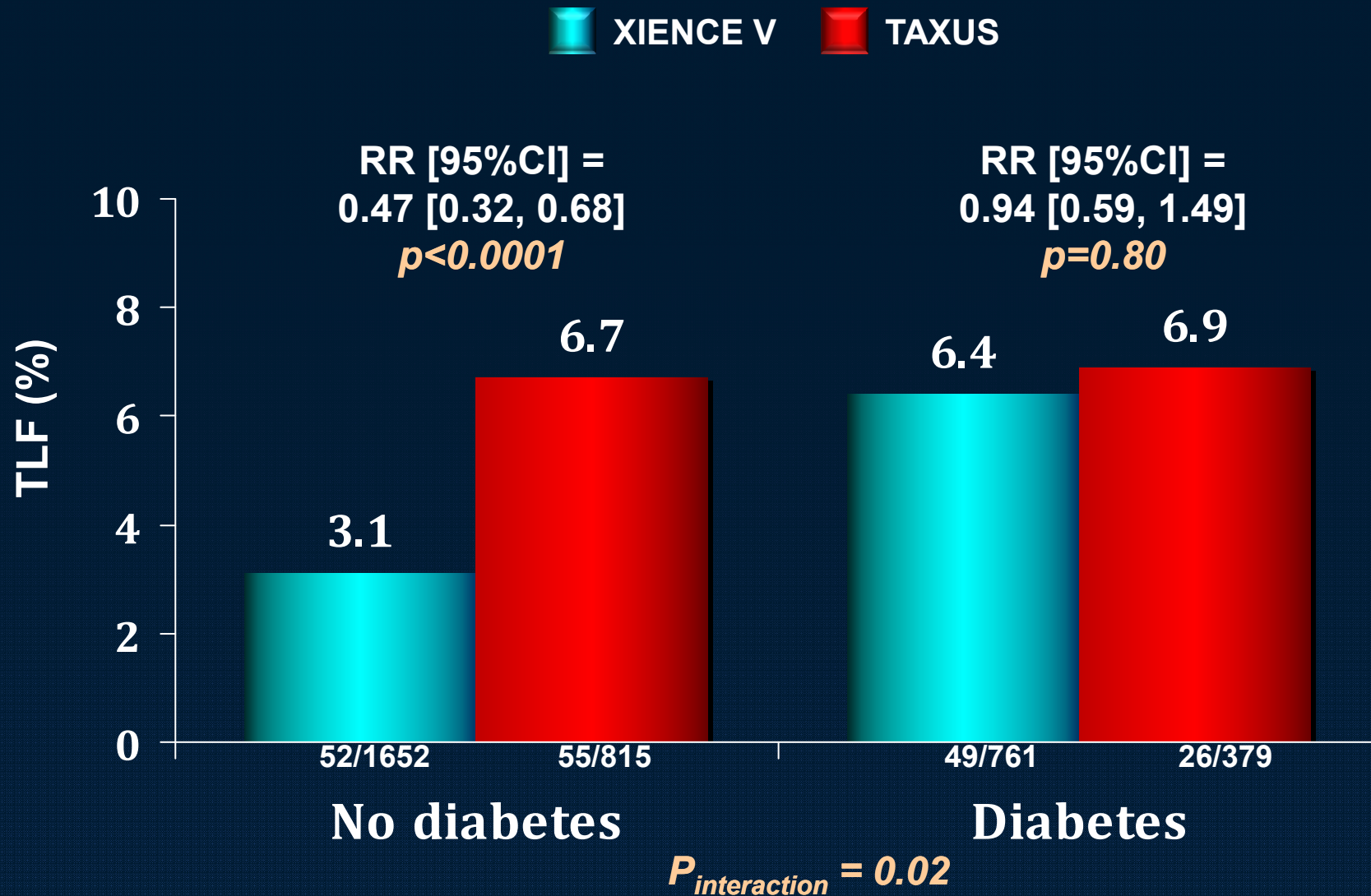
DES Design Goals

Lessons Learned...

- 3.** Once the delicate pathobiologic balance is achieved for a DES in a particular clinical and anatomic circumstance, the impact on restenosis is striking and the clinical benefits are profound.
 - ❖ The relationship between TLR and angio in-stent late loss is monotonic BUT non-linear; emphasizes the impact of angio FU on TLR and the importance of TLR as the primary efficacy endpoint
 - ❖ Some 2nd generation DES (Xience/Promus) have more potent anti-restenosis efficacy than some 1st generation DES (Taxus)
 - ❖ Some 1st generation DES may be associated with an attenuated late restenosis response (unlike BMS)

Impact of Diabetes on TLF

Spirit IV



Clinical Outcomes Through 1 Year - Diabetes Mellitus -

	XIENCE V 786 pts	TAXUS 399 pts	P value
Death, all	1.6%	0.8%	0.41
- Cardiac death	0.9%	0.3%	0.28
MI, all	2.6%	3.7%	0.36
- Target vessel MI	2.6%	3.4%	0.46
Cardiac death or TV-MI	3.4%	3.7%	0.87
TLR	4.2%	4.7%	0.65
TLF	6.4%	6.9%	0.80
MACE	6.4%	7.1%	0.71
TVF	8.4%	8.4%	1.00
ST, protocol	0.53%	1.33%	0.17
ST, ARC def/prob	0.80%	1.33%	0.52

TLF = cardiac death, target vessel MI, or ID-TLR; MACE = cardiac death, all MI, or ID-TLR;
TVF = cardiac death, all MI, or ID-TVR. 1 Year = 365 ± 28 days

DES Design Goals

Lessons Learned...

- 4. Variations in anatomic targets, lesion subsets, and underlying patient-related factors importantly influence the anti-restenosis effects of DES.**
 - ❖ In particular, diabetics demonstrate differential responses to different DES systems

Future DES

Design Goals

S**afety**

DES Design Goals

Safety...what counts?

- ***Pre-clinical assessments...*** “biocompatibility”
 - ✓ Animal models = reduced inflammation, hypersensitivity, and thrombogenicity; normal healing and downstream vasoreactivity
- ***Clinical endpoints...*** “BMS-like” clinical events during extended FU
 - ✓ Death and MI
 - ✓ Stent thrombosis (esp. late/very late); protocol and ARC definitions
- ***IVUS findings...*** no pathobiologic responses
 - ✓ Late incomplete apposition → aneurysms

Stent Thrombosis

Procedure, Product, Patient

Procedure

- *Post Dilation*
- *Flush apposition*

Stent Thrombosis

Product

- *Polymer integrity and reactions*
- *Drug effects*

Patient

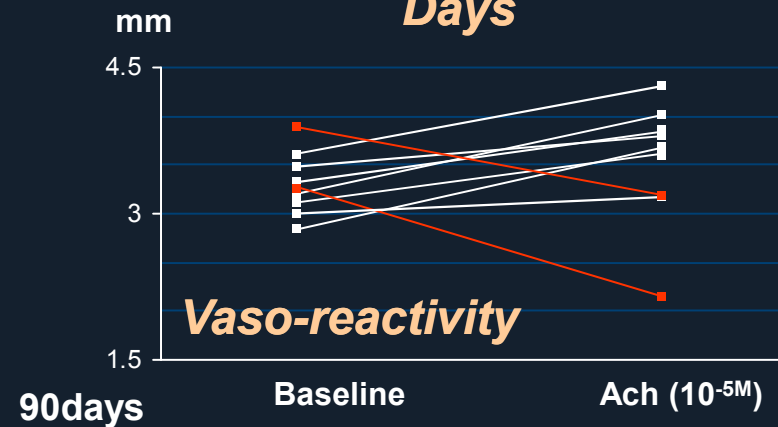
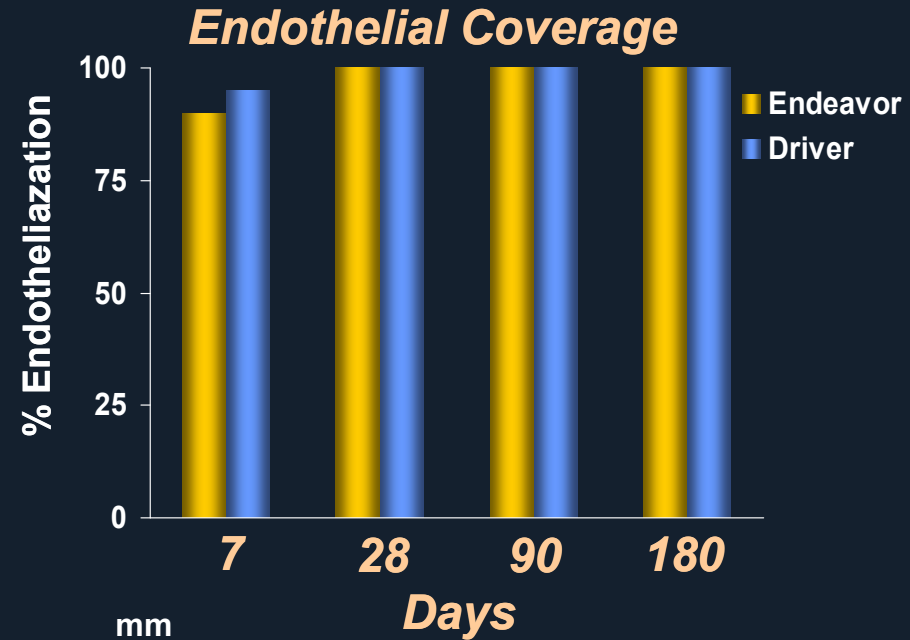
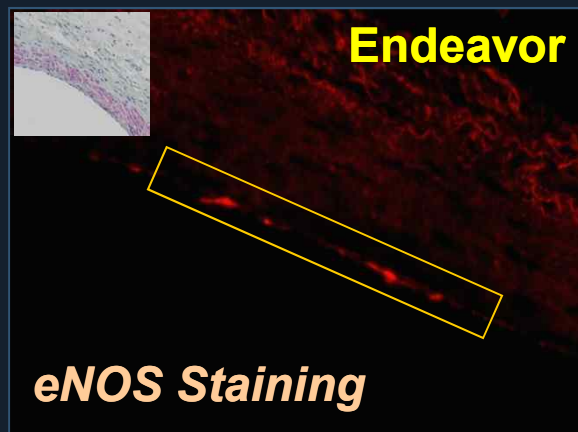
- *Higher Risk*
- *AP Compliance and Resistance*

ENDEAVOR Safety Considerations

Animal Studies (rabbits and pigs)



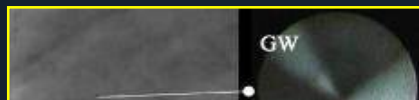
Histopathology



ENDEAVOR Safety Considerations

Human Results

Angioscopy



ZES (n=14) vs. SES (n=16)
@ 8 mos FU
ZES improved neointimal coverage
(P=0.0004) and fewer thrombi
Awata et al; J Am Coll Cardiol 2008;52;789-90



541 ZES pts @ 8 mos FU
0.4% late incomplete apposition; no
positive remodeling; homogeneous
neointimal distribution
Fitzgerald et al; Stanford IVUS core lab

OCT

44 overlapped ZES in 17 pts
@ 6 mos FU (24,076 struts analyzed)
ZES no malapposed or uncovered
struts; no intraluminal thrombus

Guagliumi et al; ESC 2008

Proximal to stent

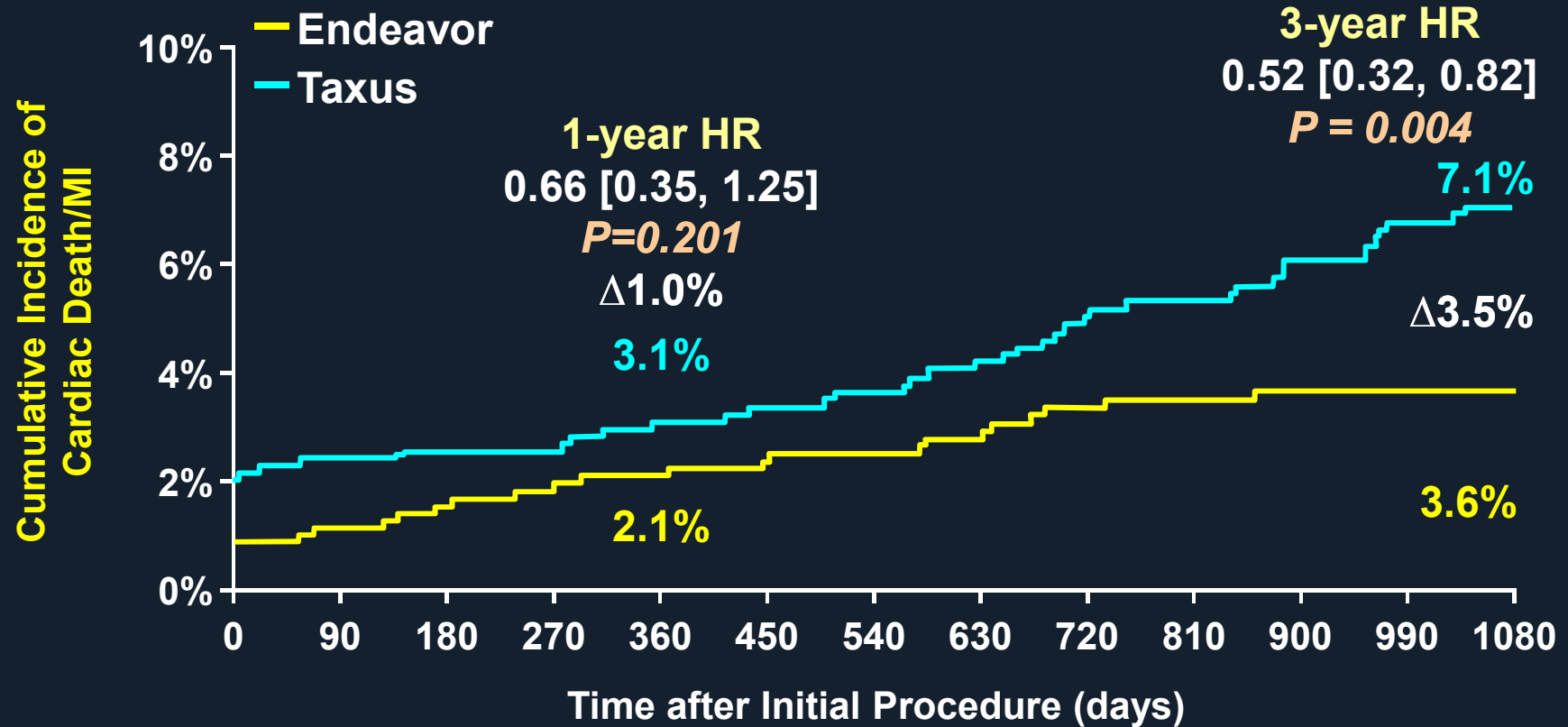
Distal to stent

ZES (n=20) vs. SES (n=20) vs.
BMS (n=10); Ach infusions
@ 6 mos; ZES improved
endothelial function cw SES
(P<0.001) and similar to BMS

Kim et al; ACC 2008

ENDEAVOR IV – 3yr FU

CD/MI to 36 months

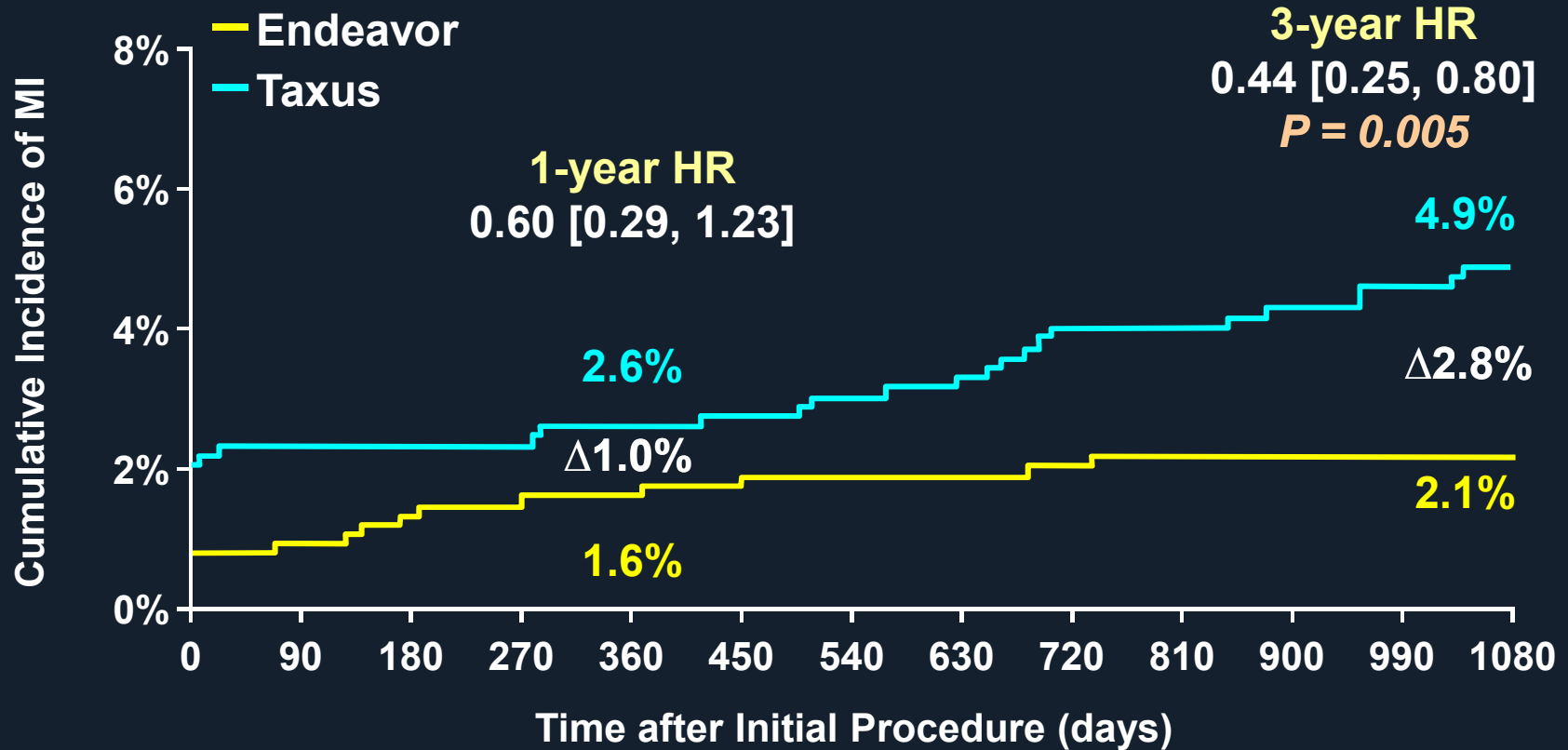


Endeavor	773	769	754	747	734	720	706	703	697	685	673	669	666
Taxus	775	758	747	738	727	715	702	698	693	678	667	658	650

Values are the KM estimates
P values were calculated by Log Rank Test

ENDEAVOR IV – 3yr FU

Myocardial Infarction to 36 months

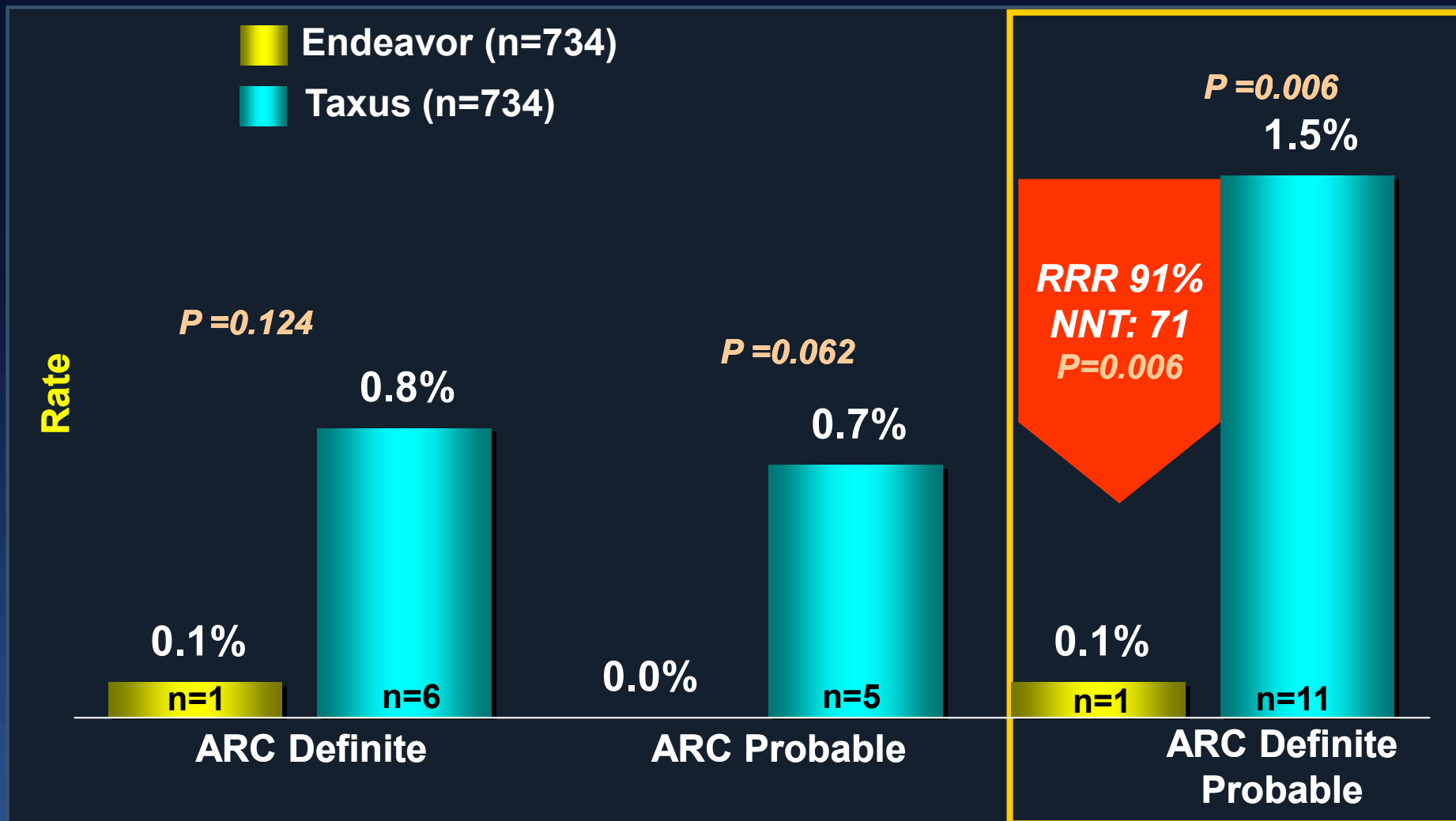


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ENDEAVOR IV – 3yr FU

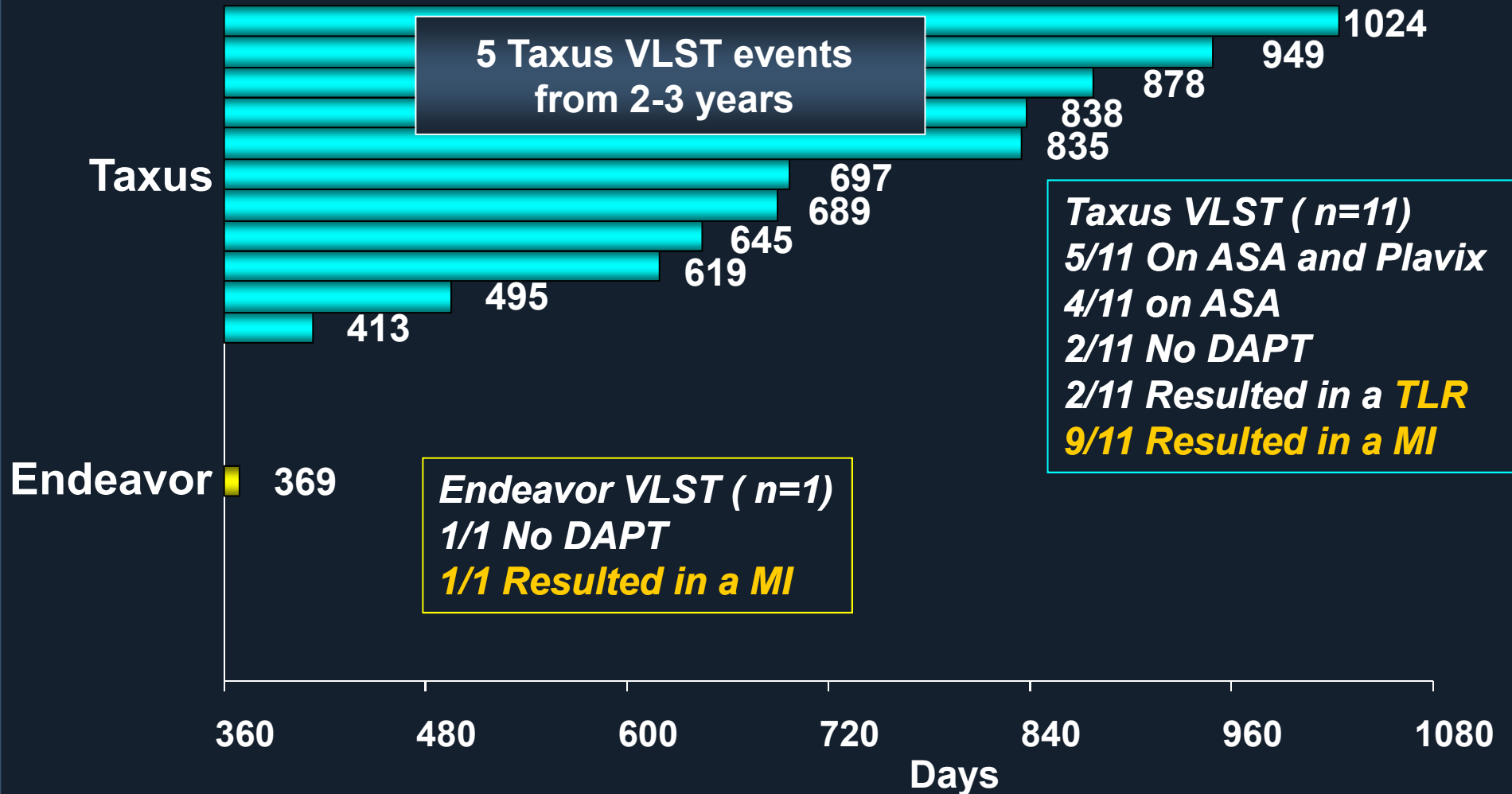
ARC VLAST 12-36 mos



Values are the event rates
P values were calculated by Fisher Exact Test

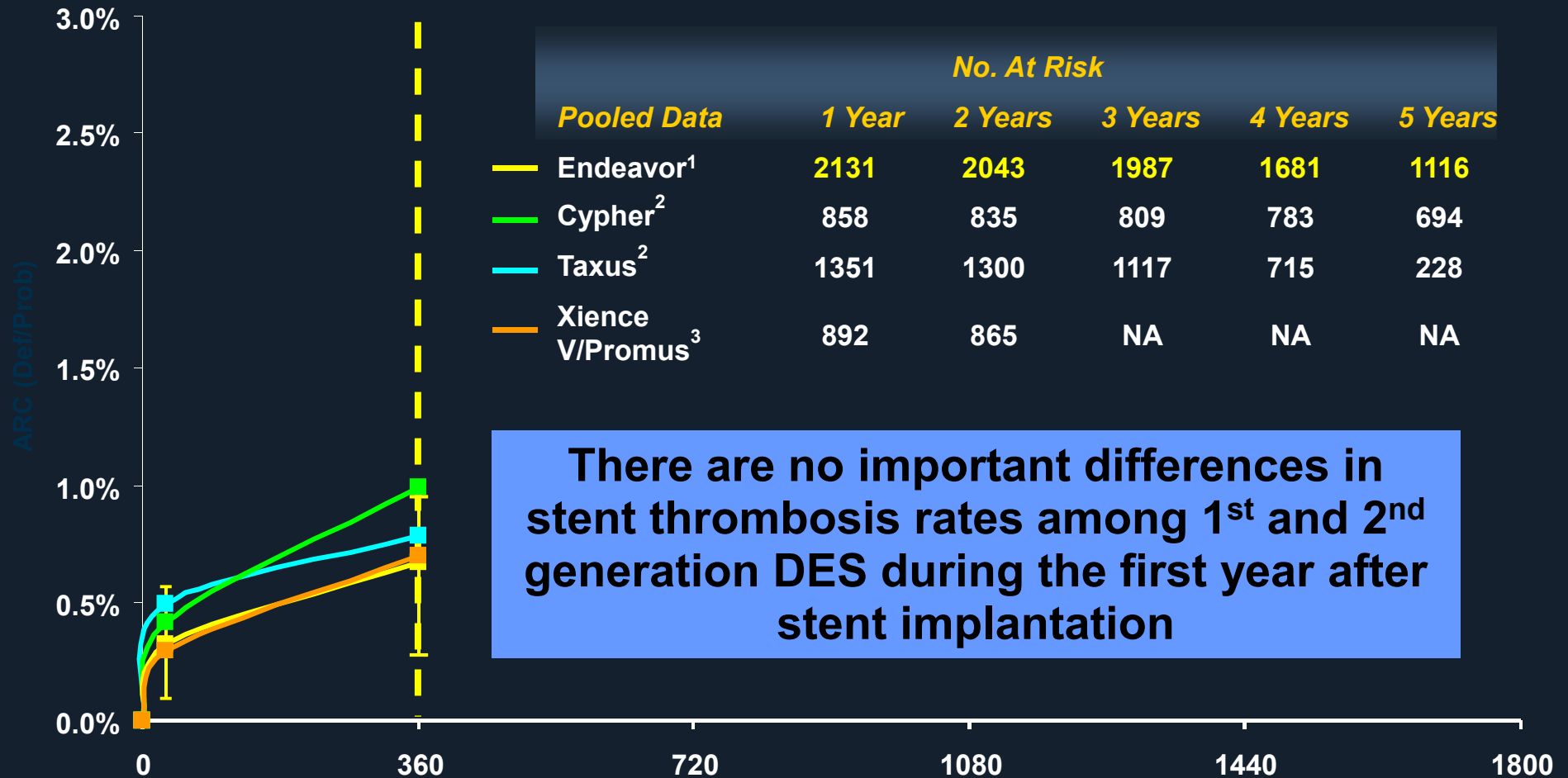
ENDEAVOR IV – 3yr FU

Timing of ARC Def/Prob VLST



DES Pooled Programs

ARC Def/Prob ST Landmark to 5 Years



There are no important differences in stent thrombosis rates among 1st and 2nd generation DES during the first year after stent implantation

1. Mauri et al. PCR 2009.

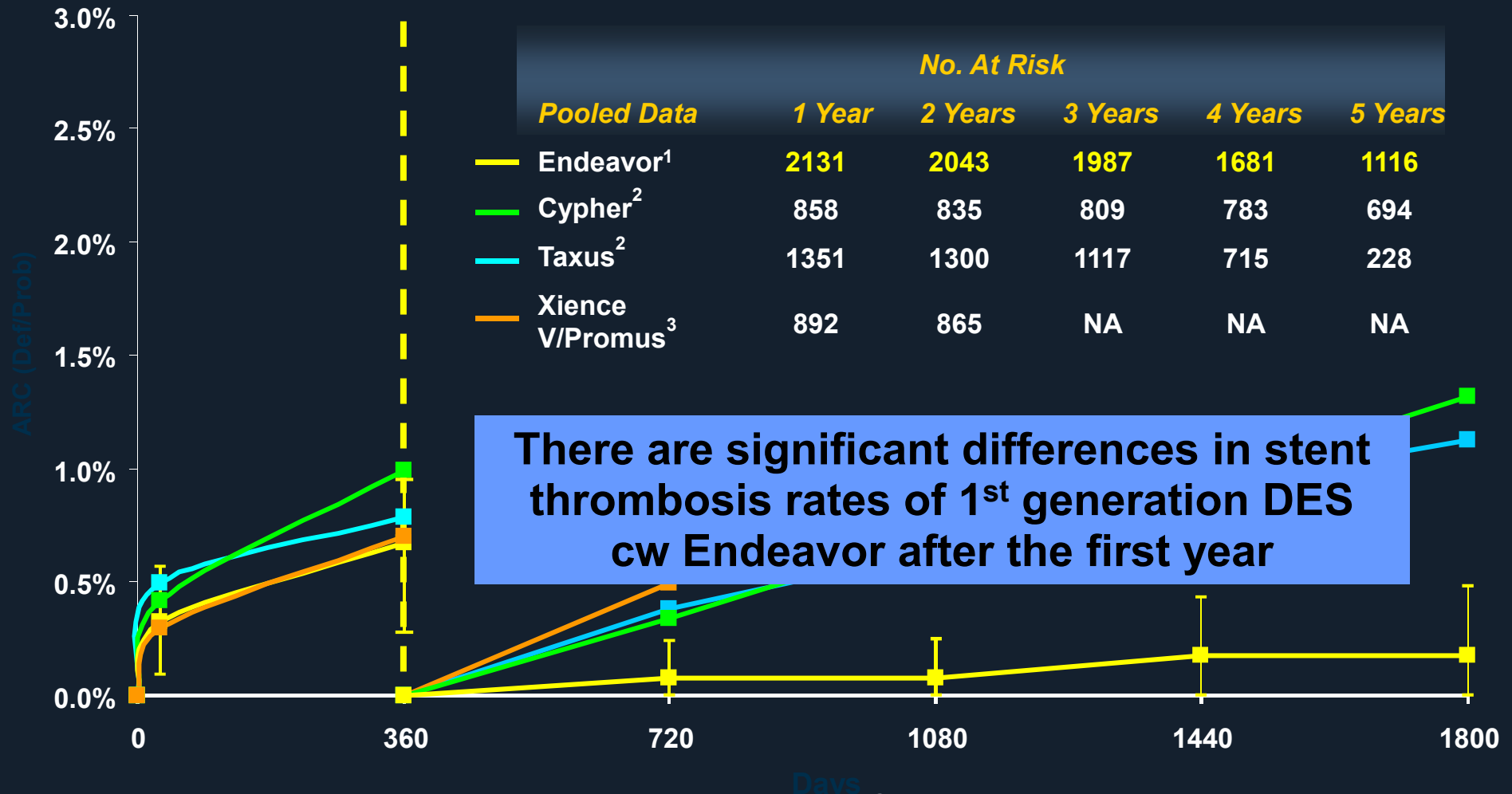
2. 5 year Outcomes in the Sirius Trial, Weisz et al. JACC Vol. 53, No. 17, 2009

3. Mauri L et al. N Engl J Med. 2007;356:1020-1029.

4. Stone, G et al., New SPIRIT Clinical Data, ACC. 09.

DES Pooled Programs

ARC Def/Prob ST Landmark to 5 Years



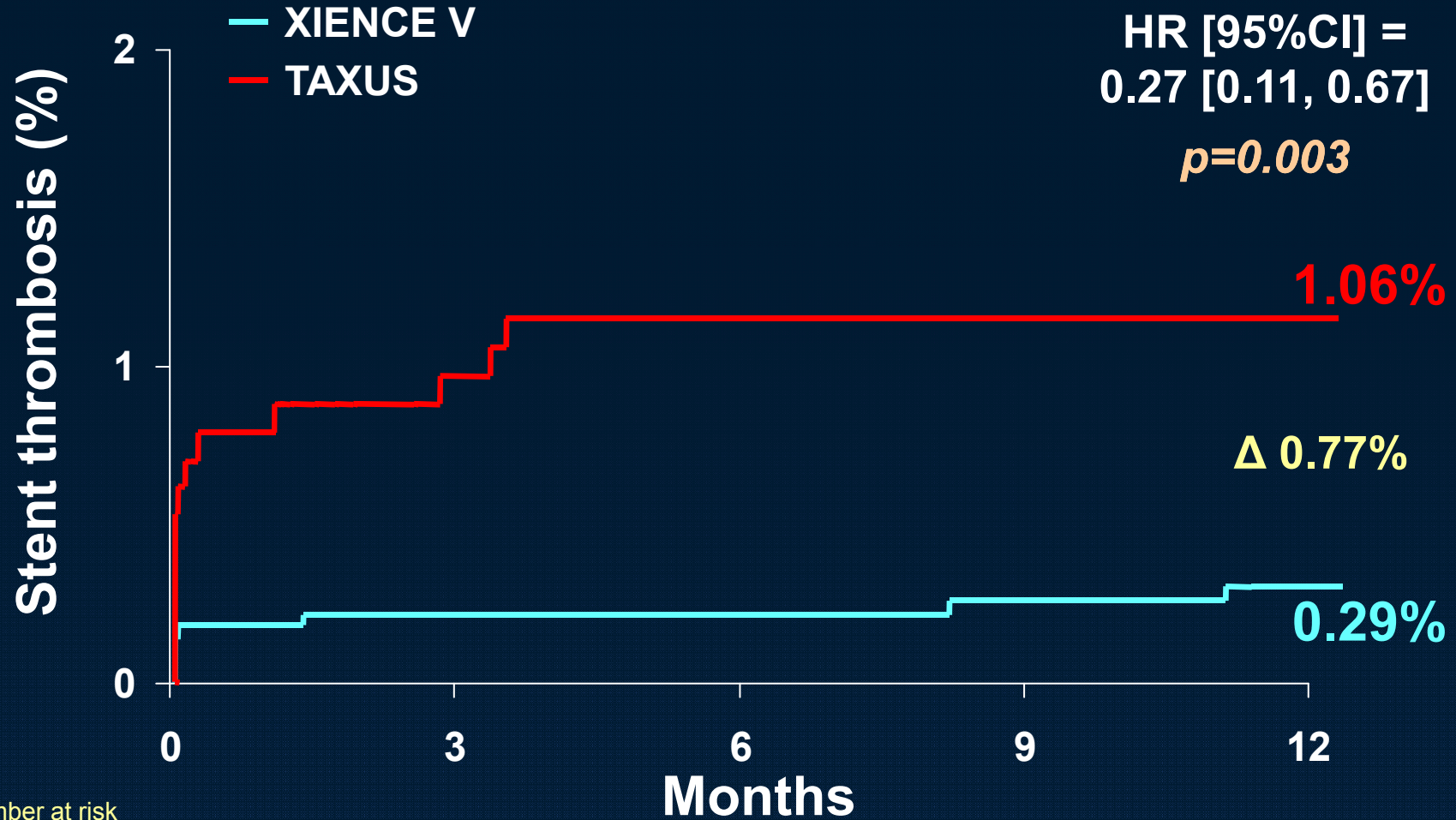
1. Mauri et al. PCR 2009.

2. 5 year Outcomes in the Sirius Trial, Weisz et al. *JACC* Vol. 53, No. 17, 2009

3. Mauri L et al. *N Engl J Med.* 2007;356:1020-1029.

4. Stone, G et al., New SPIRIT Clinical Data, ACC. 09.

Spirit IV Stent Thrombosis (ARC Def or Prob)

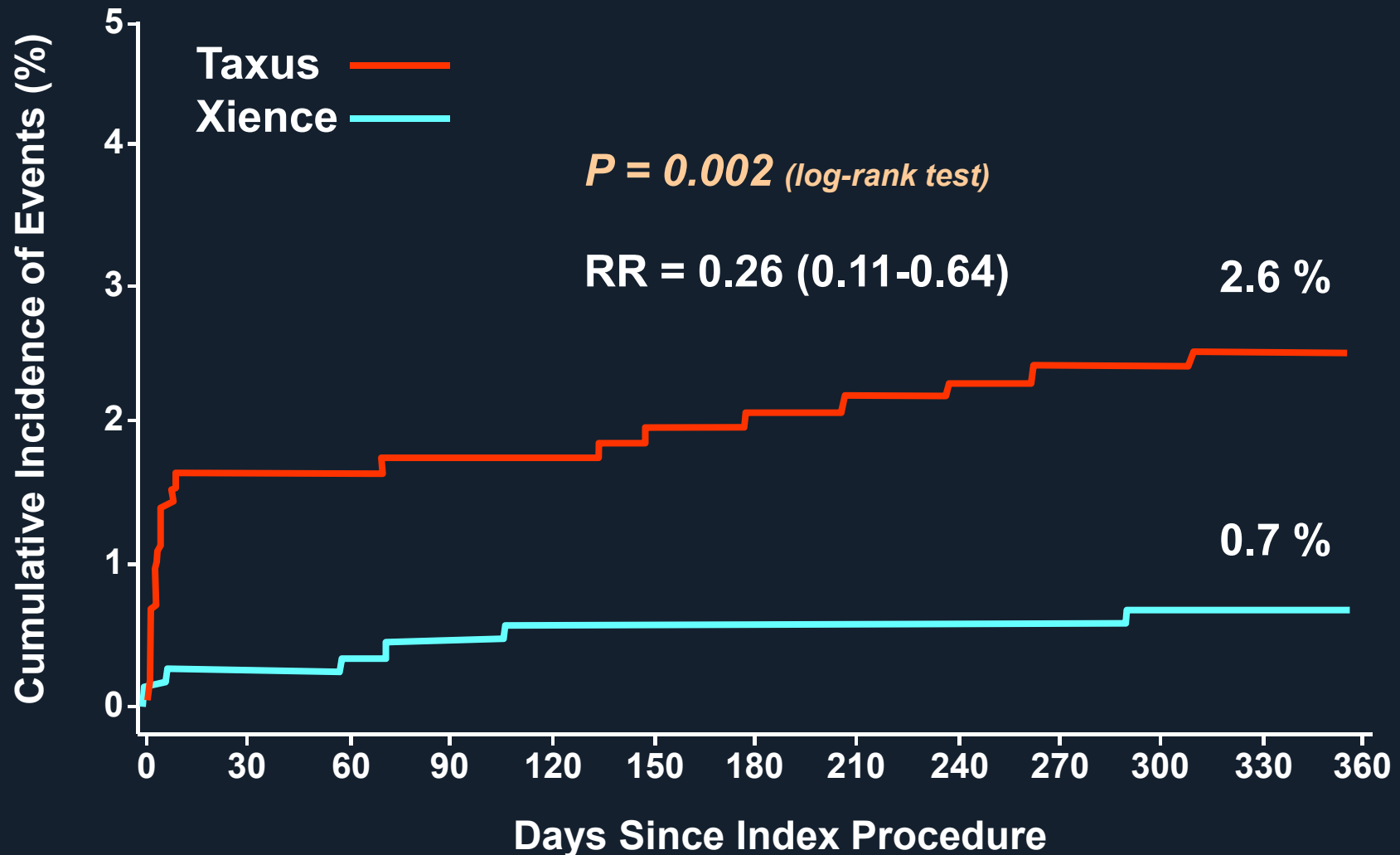


Number at risk

XIENCE V	2458	2426	2412	2388	2376
TAXUS	1229	1195	1184	1174	1166

COMPARE – 2^{ry} Endpoint Result

Early and Late Stent Thrombosis (definite & probable according ARC)



DES Design Goals

Lessons Learned...

- 5. Unlike BMS technologies, DES are uniquely differentiated with active/dynamic properties resulting in both early and late clinical effects which can be simulated in animal models and in small clinical studies using surrogate safety endpoints.**
- 6. Advanced 2nd generation DES technologies with improved deliverability and more biocompatible drug carriers with optimized drug dosing/kinetic release patterns are clearly preferred – both safety and efficacy!**

Future DES

Challenges

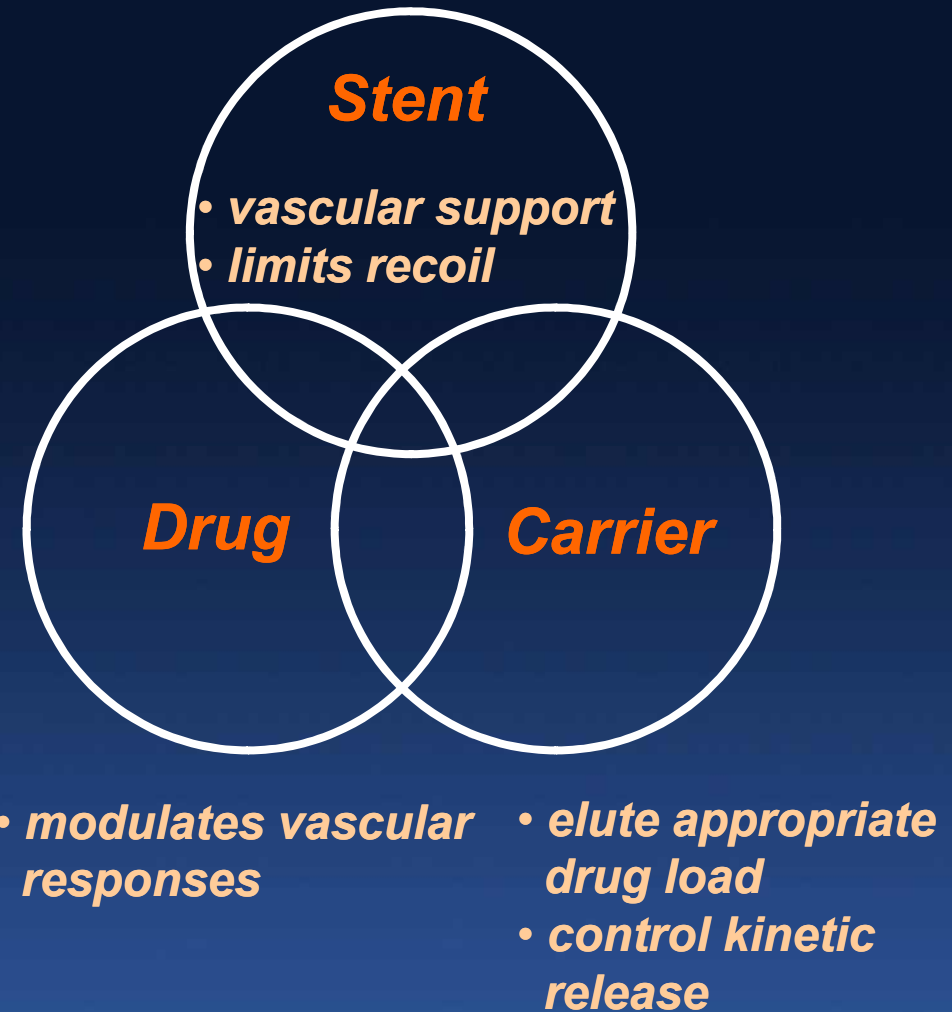
- Remarkably difficult to develop a highly deliverable DES with a biocompatible drug carrier which elutes a potent anti-proliferative drug with optimized release kinetics – safe + lowest possible restenosis
- Increasing regulatory hurdles for approval of iterative and new DES (almost cost prohibitive)
- Healthcare economic considerations (declining reimbursement and prices) are contributing to the unfavorable climate for future DES development.

**Lucius Quinctius
Cincinnatus
(519–430 BCE?)**



**A.Colombo, E. Karvouni,
Biodegradable stents: "Fulfilling the
mission and stepping away",
Circulation 102 (2000) 371-373**

WHICH NEEDS TO GO AND WHICH NEEDS TO STAY



**Lucius Quinctius
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(519–430 BCE?)**



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Biodegradable stents: "Fulfilling the
mission and stepping away",
Circulation 102 (2000) 371-373**

WHICH NEEDS TO GO AND WHICH NEEDS TO STAY

Stent

- ***vascular support***
- ***limits recoil***

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Cincinnatus
(519–430 BCE?)**



**A.Colombo, E. Karvouni,
Biodegradable stents: "Fulfilling the
mission and stepping away",
Circulation 102 (2000) 371-373**

***WHICH NEEDS TO GO AND
WHICH NEEDS TO STAY***

Future DES

New Drug Carrier Systems

- ***New DES with...***
 - **Bioabsorbable polymers**
 - **Polymer-free drug delivery**
- ***Bioabsorbable DES***
- ***Drug-eluting Balloons***

Next Generation DES

The Holy Grail?



No restenosis
No clinical safety issues

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