

Addressing the Lingering Concerns of Late DES Safety and Efficacy

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Conflict of Interest Disclosure

- **Ajay J. Kirtane**
 - **In the last 12 months, I have received honoraria/consultancy fees from Abbott Vascular, Boston Scientific, and Medtronic CardioVascular**
 - **Off-label use will be discussed**



Following the Introduction of DES

Things were going well...

- **Early Pivotal RCTs**
 - Marked efficacy compared to BMS at intermediate durations of follow-up
 - Limited pooled data (overall small numbers)
- **Supplemented by Observational data**
 - Single center analyses (AMC, Thoraxcenter)
- **Even demonstrated efficacy in RCTs and observational analyses of complex lesion subsets**
- **Clear, consistent effect on restenosis-related endpoints, but limited power to assess safety...**



DES Concerns in the Background

- **DES impair normal vascular healing**
 - Persistent (?toxic) polymer and drug effects
- **Vascular inflammation, incomplete endothelialization, fibrin deposition, platelet activation may all have clinical sequelae**
 - **Stent Thrombosis**
 - **Abnormal Vasomotion, Aneurysm Formation, Late Restenosis**

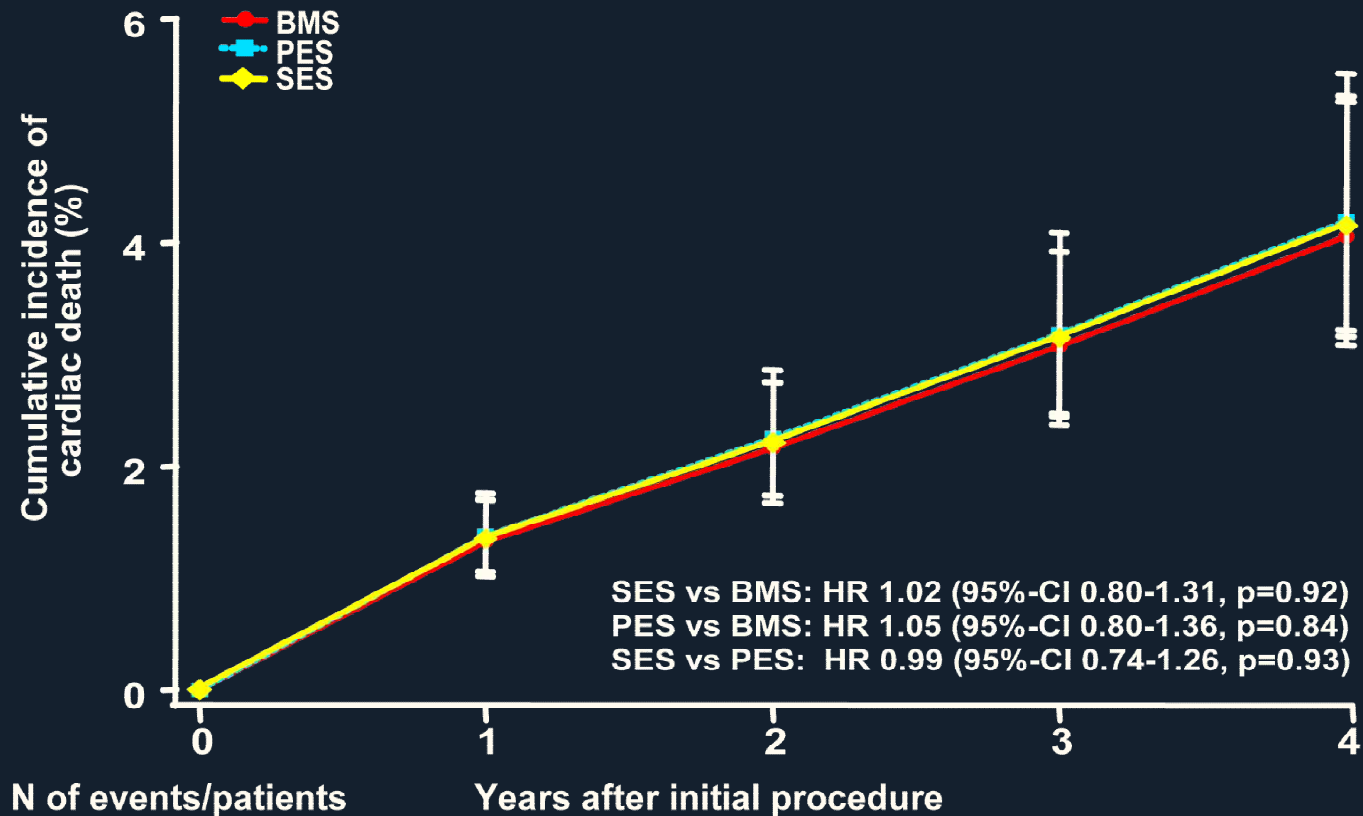


DES Studies: Initial Potential Concerns Explode in 2006!!!

- **SCAAR (the first time around)**
 - Large multicenter observational study
- **Camenzind and Nordmann meta-analyses**
 - Randomized data implicated with a signal of possible harm
- **Bern-Rotterdam Analysis**
 - The pathophysiologic link?



Network Meta-Analysis: Cumulative Incidence of Cardiac Death



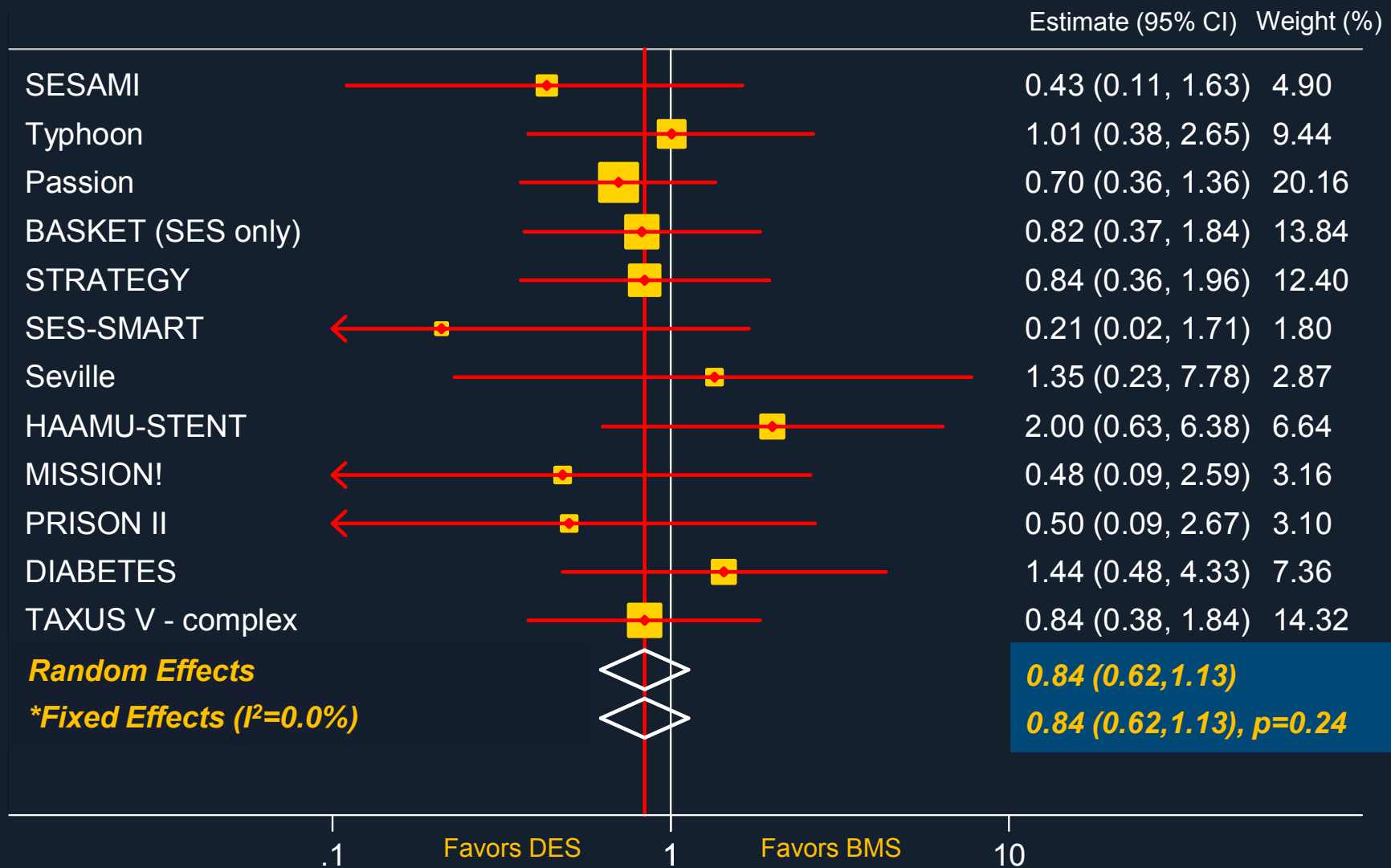
N of events/patients

Years after initial procedure

BMS	4763	78/4746	23/3310	13/2234	16/1845
PES	6300	97/6252	41/4232	13/2157	3/841
SES	6642	91/6601	34/4041	24/2340	14/1081

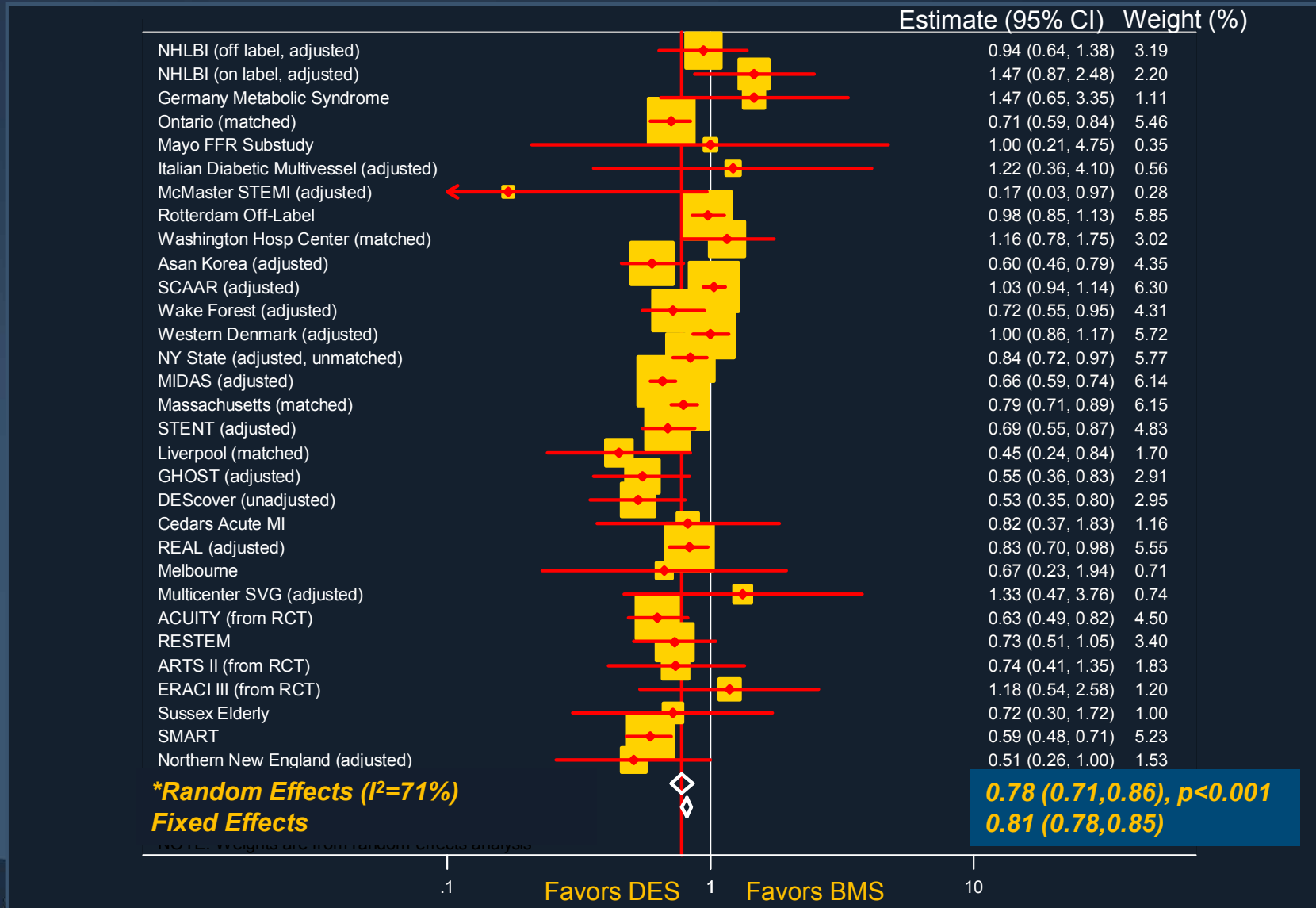
All-Cause Mortality: RCT's (Off-Label)

4,049 patients, 12 trials, mean F/U 1.5 years

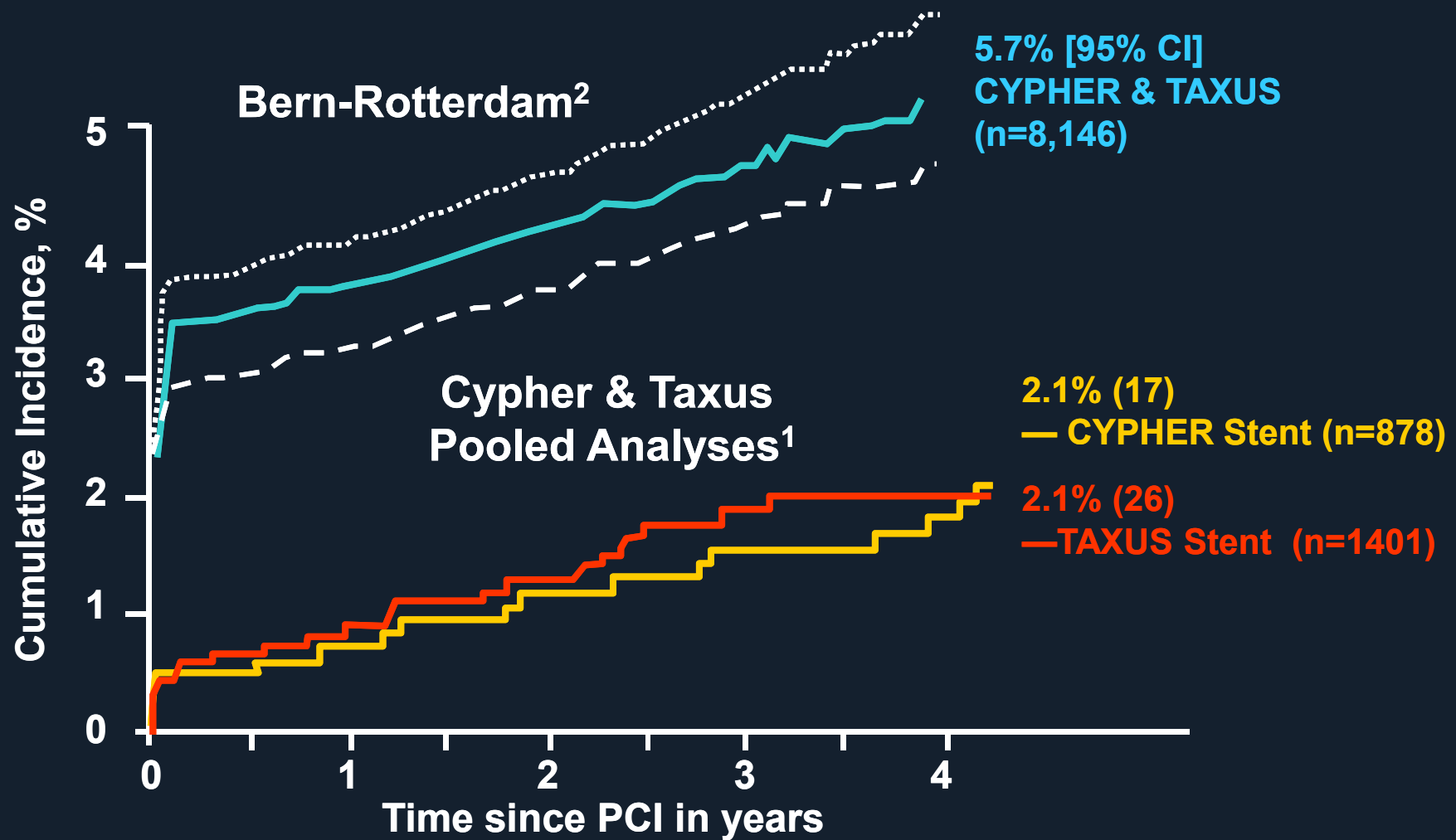


All-Cause Mortality: Observational Studies

169,595 patients, 31 registries, mean F/U 2.5 years



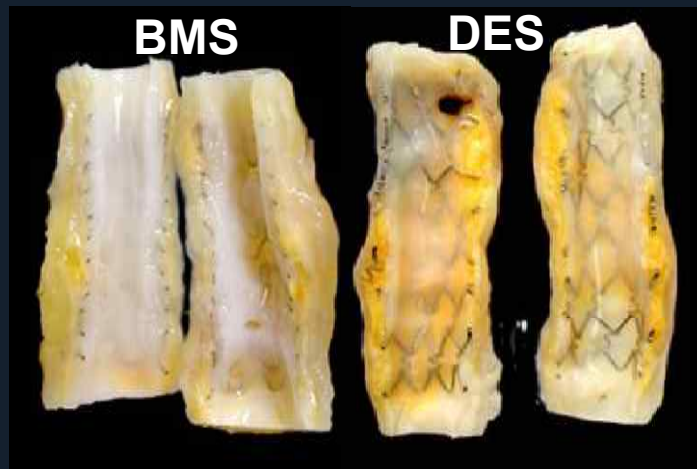
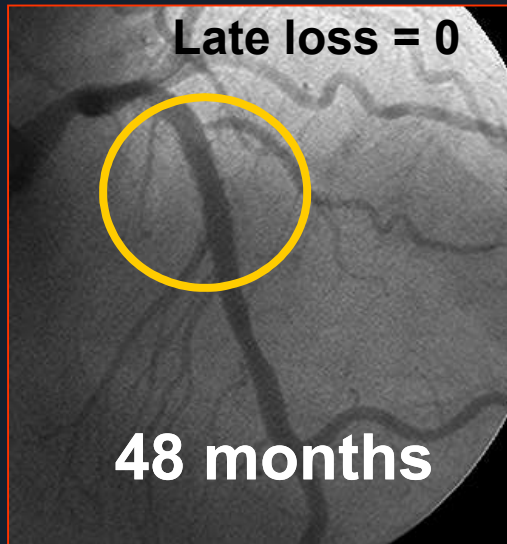
Cumulative Incidence of ARC Def/Prob ST over 4 yrs after DES (CYPHER & TAXUS)



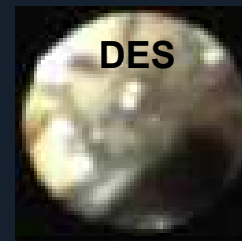
¹ Mauri et al; N Engl J Med 2007;356:1020-9

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

Drug-Eluting Stents.... the good, the bad, and the ugly!



Delayed Healing!



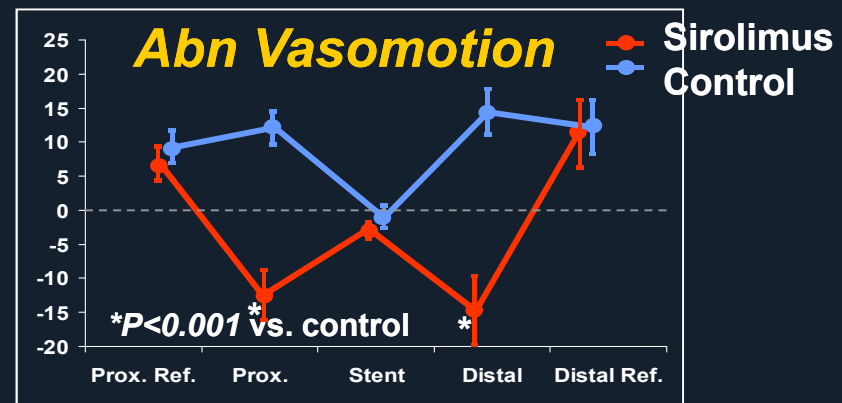
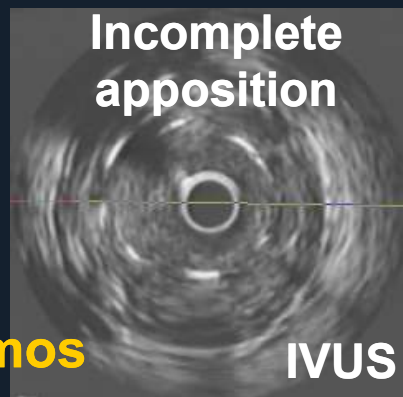
Angioscopy



Inflammation



40 mos



DES Use in 2010: Persistent Concerns

Linking pathology with clinical outcomes

- **Safety**

- We may feel better about mortality now, but LST is a real phenomenon!!
- Do we know how to prevent LST?

- **Efficacy**

- Late catch-up of ISR/TLR may limit the long-term absolute efficacy of DES



Potential Strategies to Address ST

- **Early ST (similar to BMS)**
 - PCI optimization (?IVUS), patient/lesion selection, antiplatelet therapy with appropriate response to it
- **Late ST**
 - DES designs to reduce inflammation and improve healing
 - Polymer adaptations / Drug duration
 - Polymer-free systems
 - ?DAPT duration



IVUS Correlates of VLST

	DES VLST (n=23)	BMS VLST (n=7)	P value
QCA: Index RVD	2.97	3.66	0.010
QCA: Post Stent MLD	2.70	4.08	<0.001

IVUS at Time of VLST (DES Median <3 yrs, BMS Median 9 yrs)

Total stented length	32.9	18.6	0.001
Minimal Lumen CSA	4.20	4.73	0.564
Miminal Stent CSA	6.15	7.42	0.413
Mean Neointimal Area	3.07	5.03	0.014
Neointimal Vol. index	0.42	0.51	0.069
Incomplete Apposition	17 (73.9%)	0 (0%)	0.001
Neointimal Rupture	10 (43.5%)	7 (100%)	<0.010

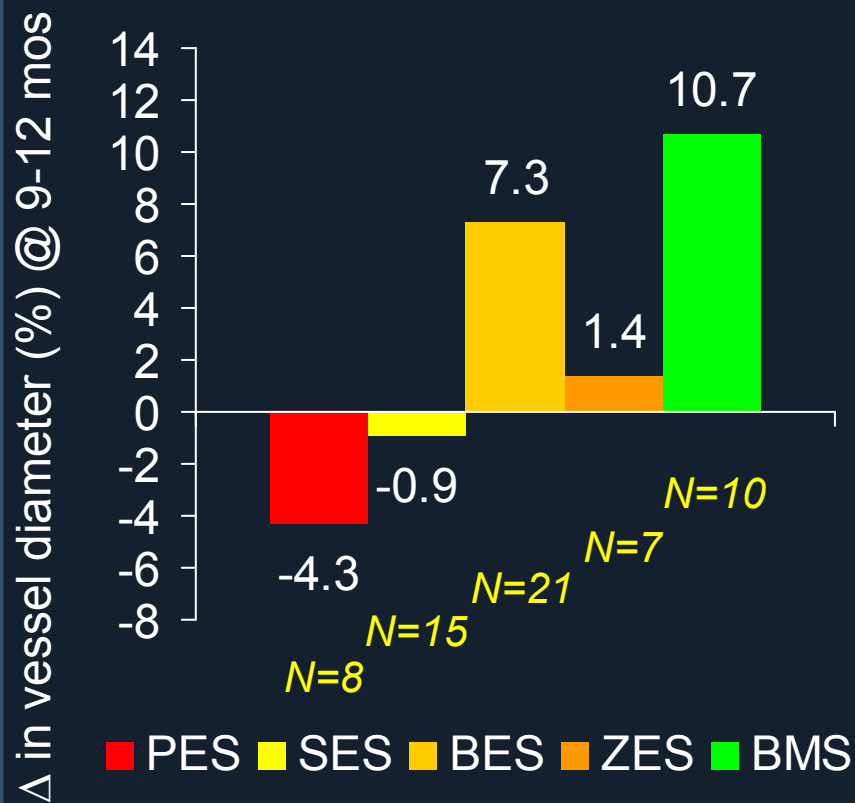


Pathologic Causes of LST: CV Path

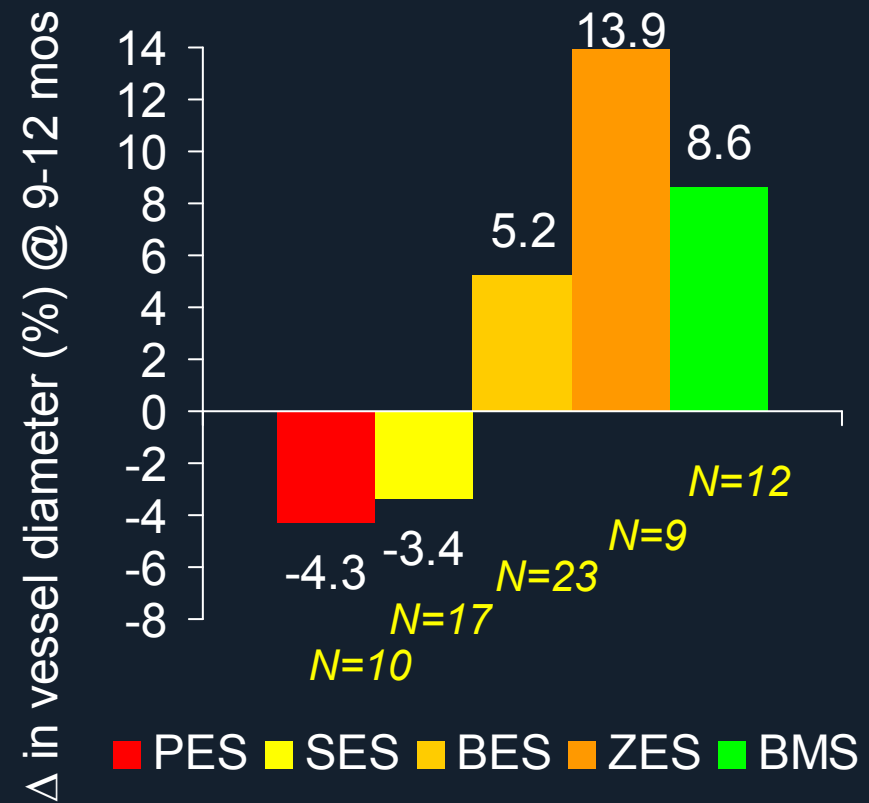
- **Stent Malapposition (40%)**
- **AMI Indication (40%)**
- **Bifurcation Indication (30%)**
- **Necrotic Core Penetration/Prolapse (25%)**
- **Long Stenting (>40 mm) (20%)**
- **Hypersensitivity Reaction (15%)**
- **Unknown/Other (5%)**
- **Stent Underexpansion (<5%)**

Comparison of Coronary Vasomotion Between DES and BMS

Proximal Segment

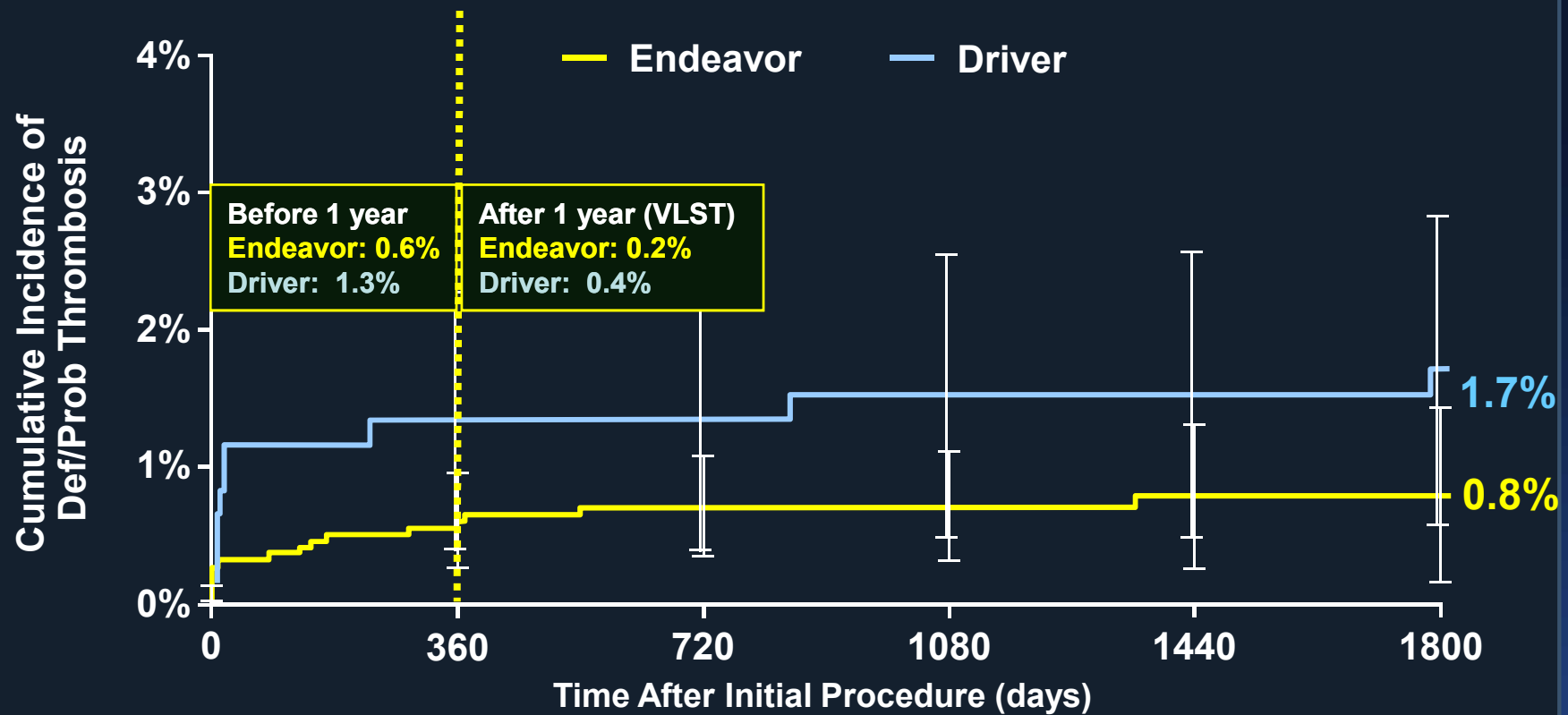


Distal Segment



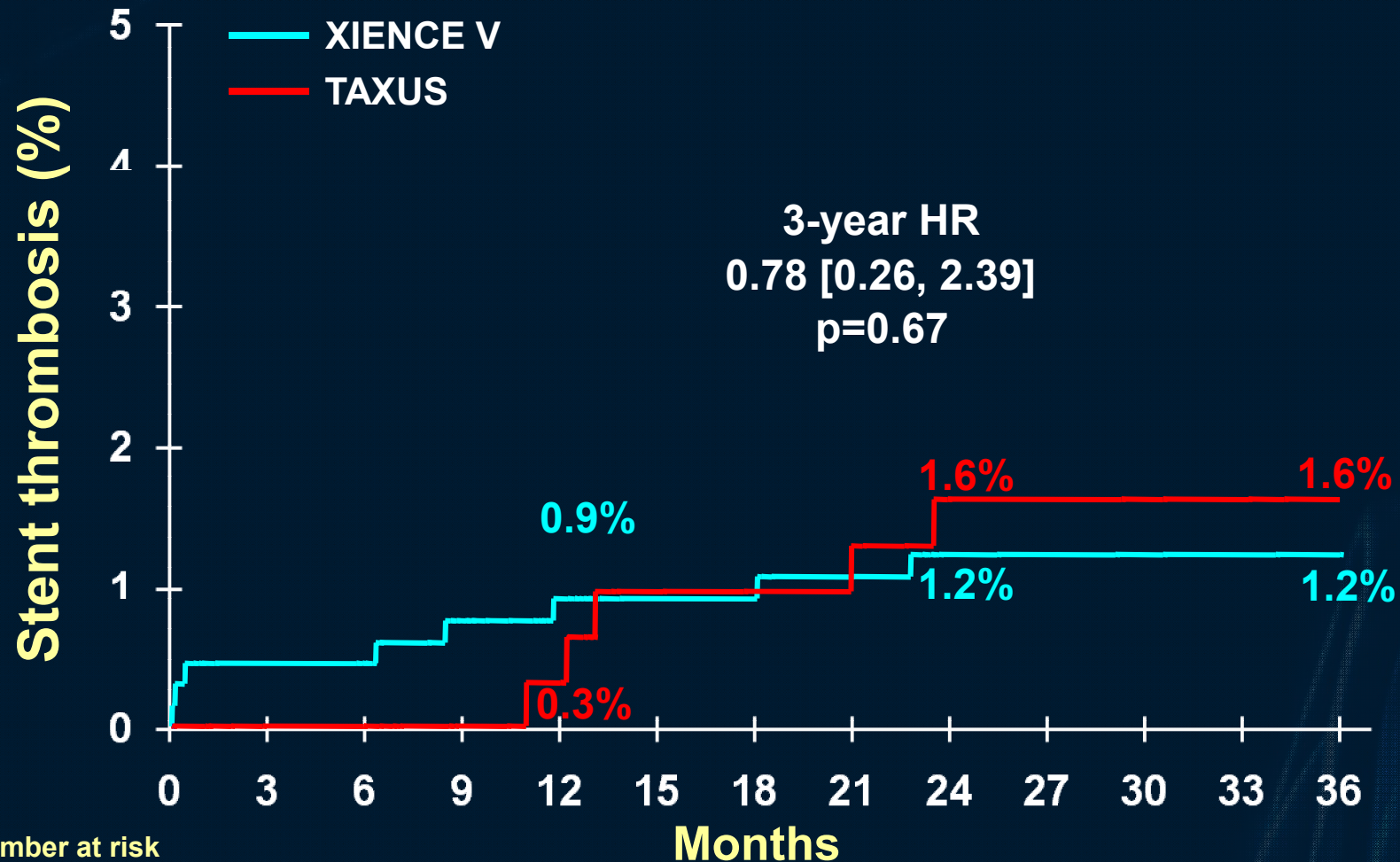
Endeavor Pooled Safety Analysis

ARC Definite/Probable ST to 5 years



Endeavor	2132	2131	2043	1987	1681	1116
% CI	0.05%	0.62%	0.71%	0.71%	0.80%	0.80%
Driver	596	595	570	559	543	538
% CI	0.17%	1.35%	1.35%	1.52%	1.52%	1.71%

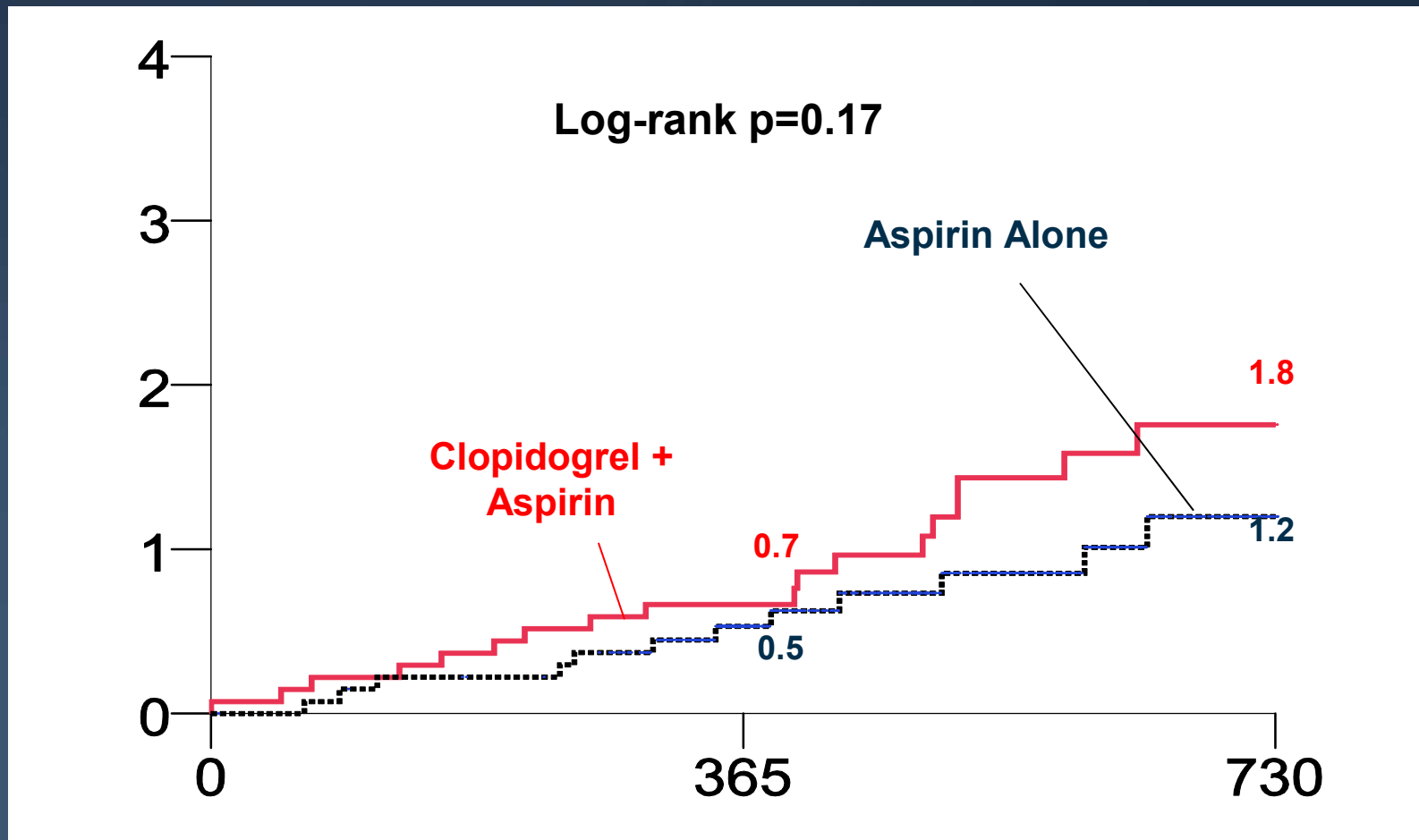
Stent Thrombosis (ARC Definite/Probable)



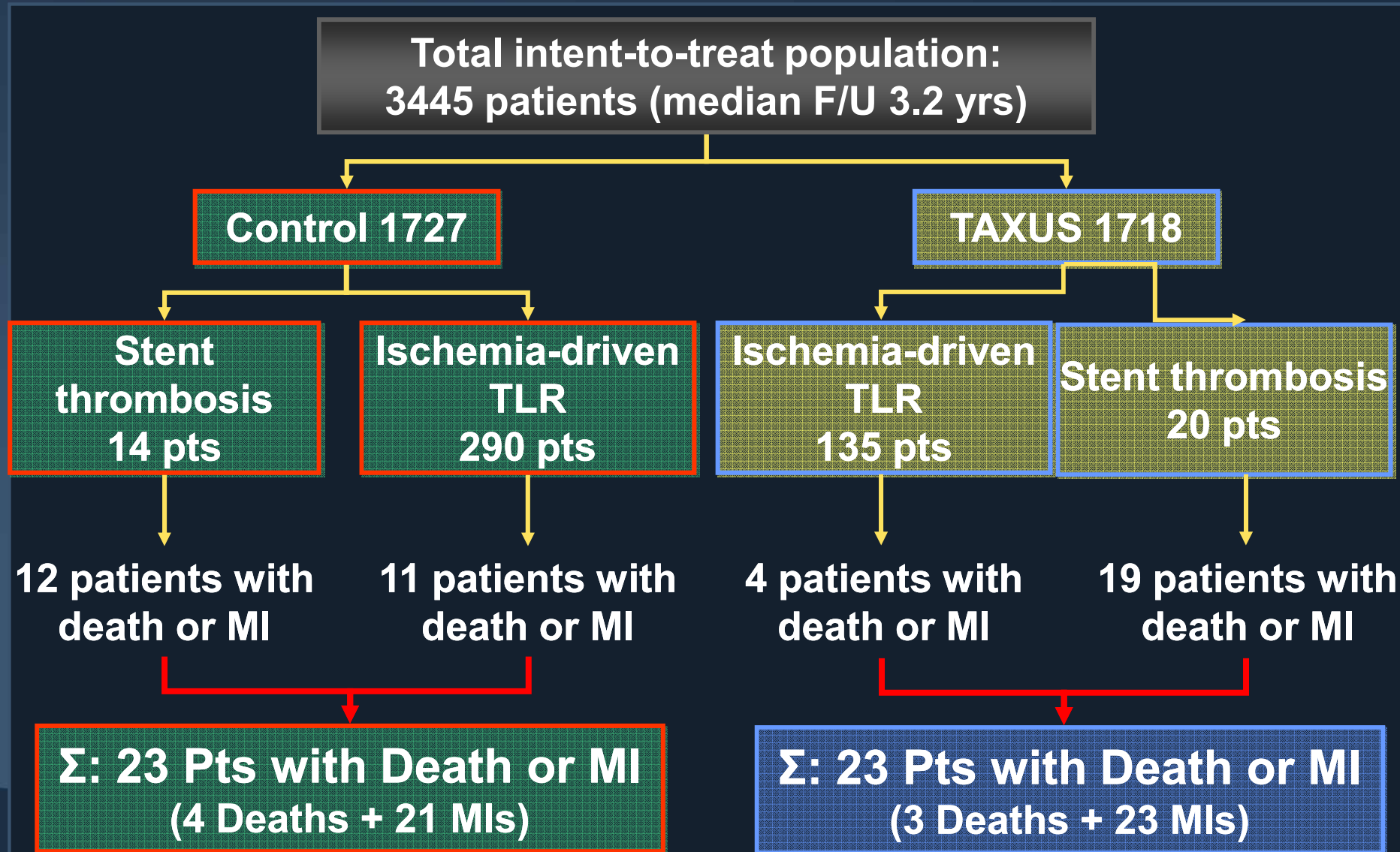
Number at risk

	0	3	6	9	12	15	18	21	24	27	30	33	36
XIENCE V	669	661	658	651	640	627	627	622	615	614	613	612	611
TAXUS	332	325	323	317	314	305	303	302	298	298	297	296	294

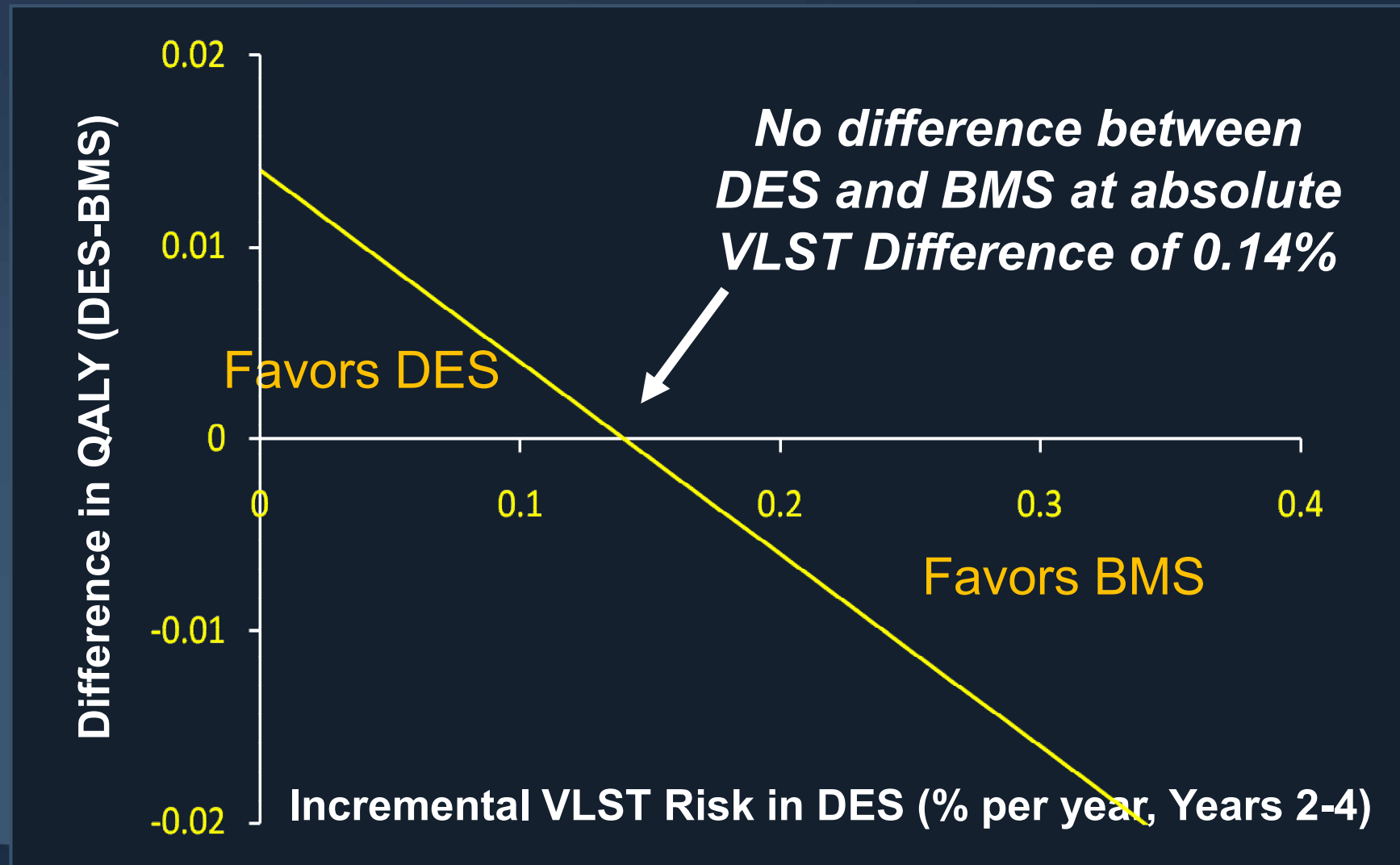
ZEST-LATE + REAL-LATE: Cardiac Death or Myocardial Infarction



TAXUS II, IV, V, VI: Death and MI within 7 Days of TLR and Stent Thrombosis



Potential Effect of Excess VLST with DES: A Decision Analysis

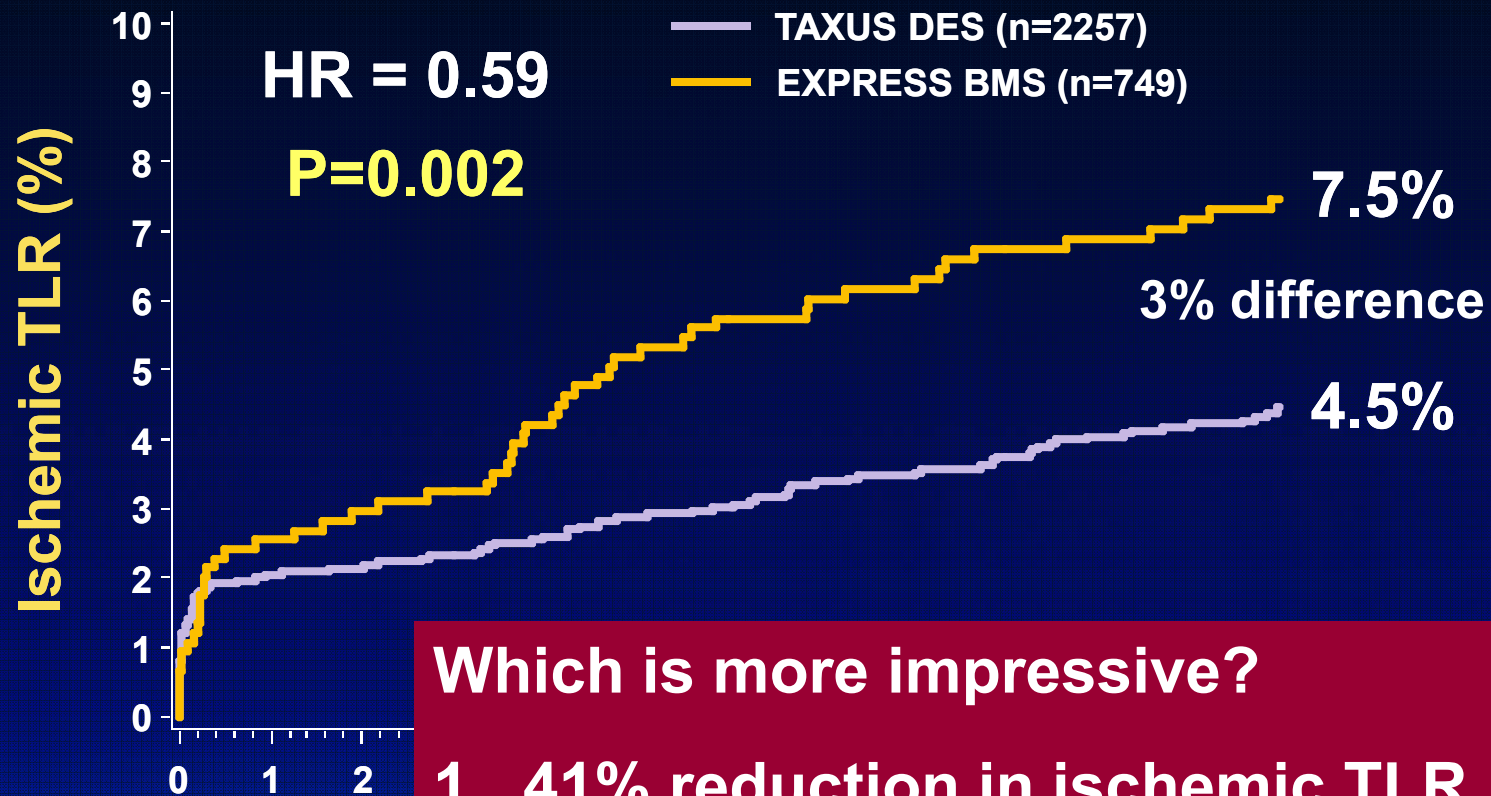


DES Efficacy Concerns

- **Overemphasis on relative risk reductions (40-50%) vs. absolute risk reductions (which are based upon baseline risk) may not be clinically sound**
 - **Routine angiographic follow-up may have exaggerated the benefits of DES over BMS**
- **Late catch-up ISR/TLR may limit the long-term efficacy of DES**



Primary Efficacy Endpoint: Ischemic TLR

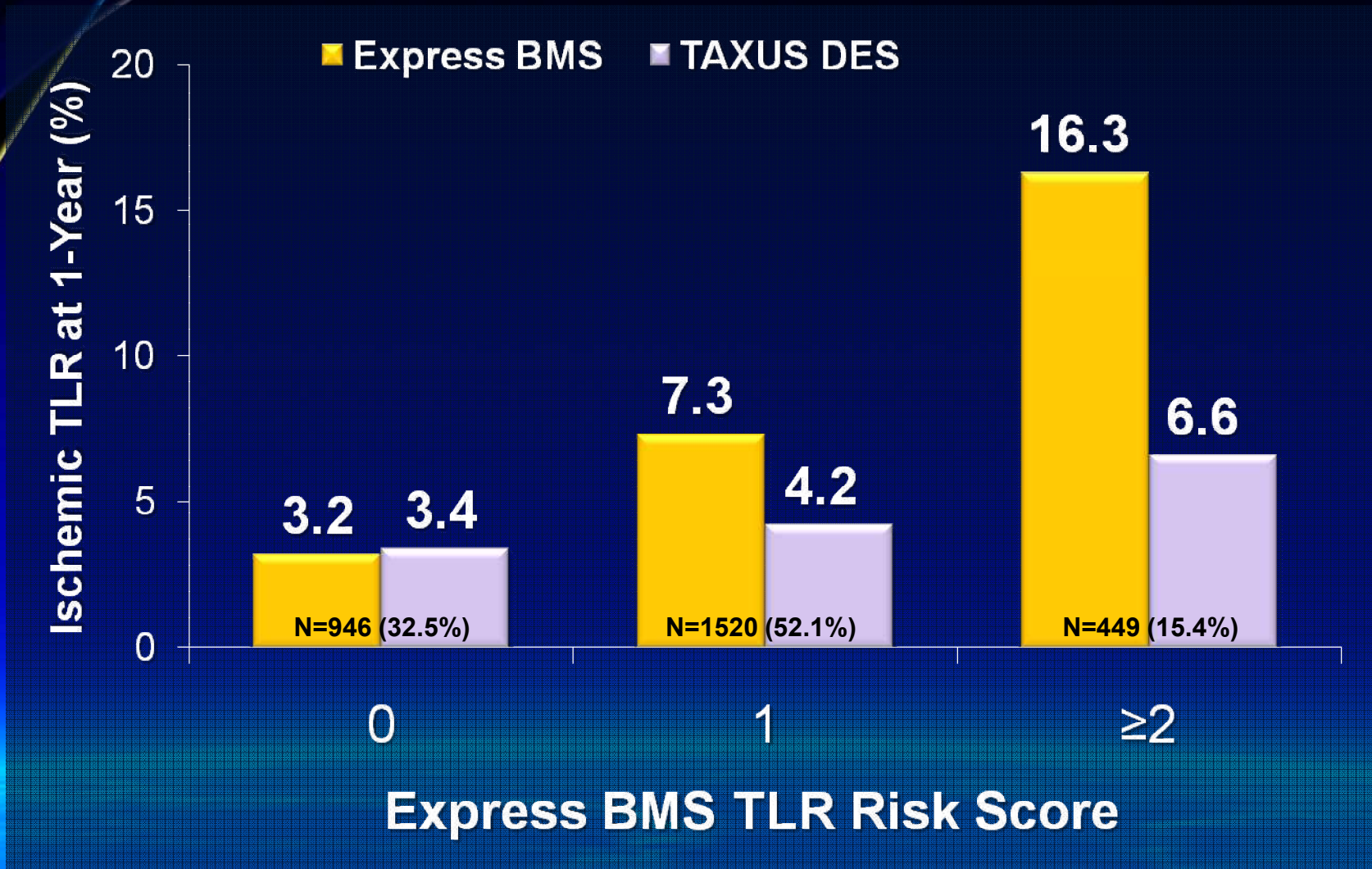


Number at risk	
TAXUS DES	2257
EXPRESS BMS	749

Which is more impressive?

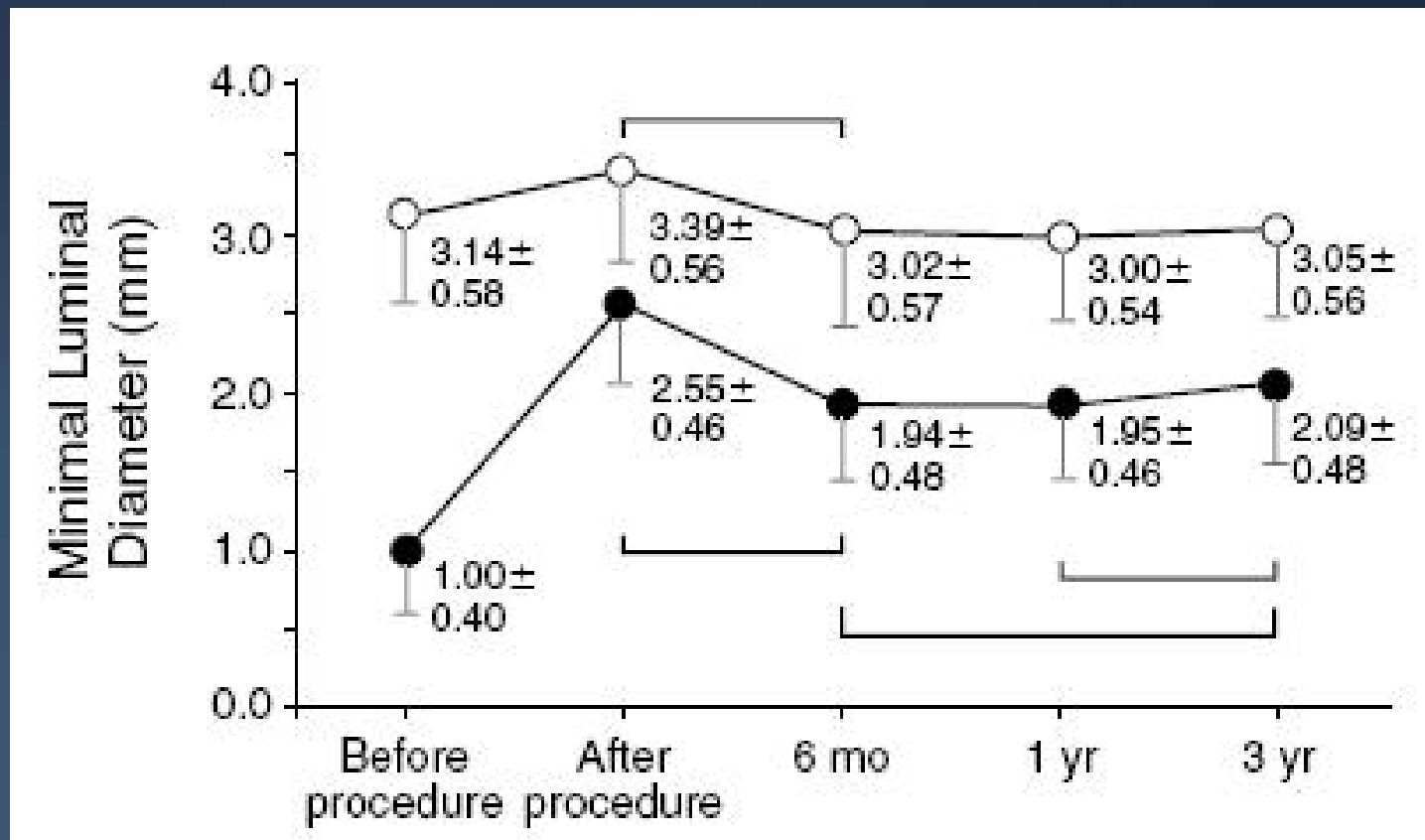
1. 41% reduction in ischemic TLR
2. Need to treat 33 patients with DES to prevent one BMS TLR event

1-Year TLR According to BMS Risk Score (N=2915)



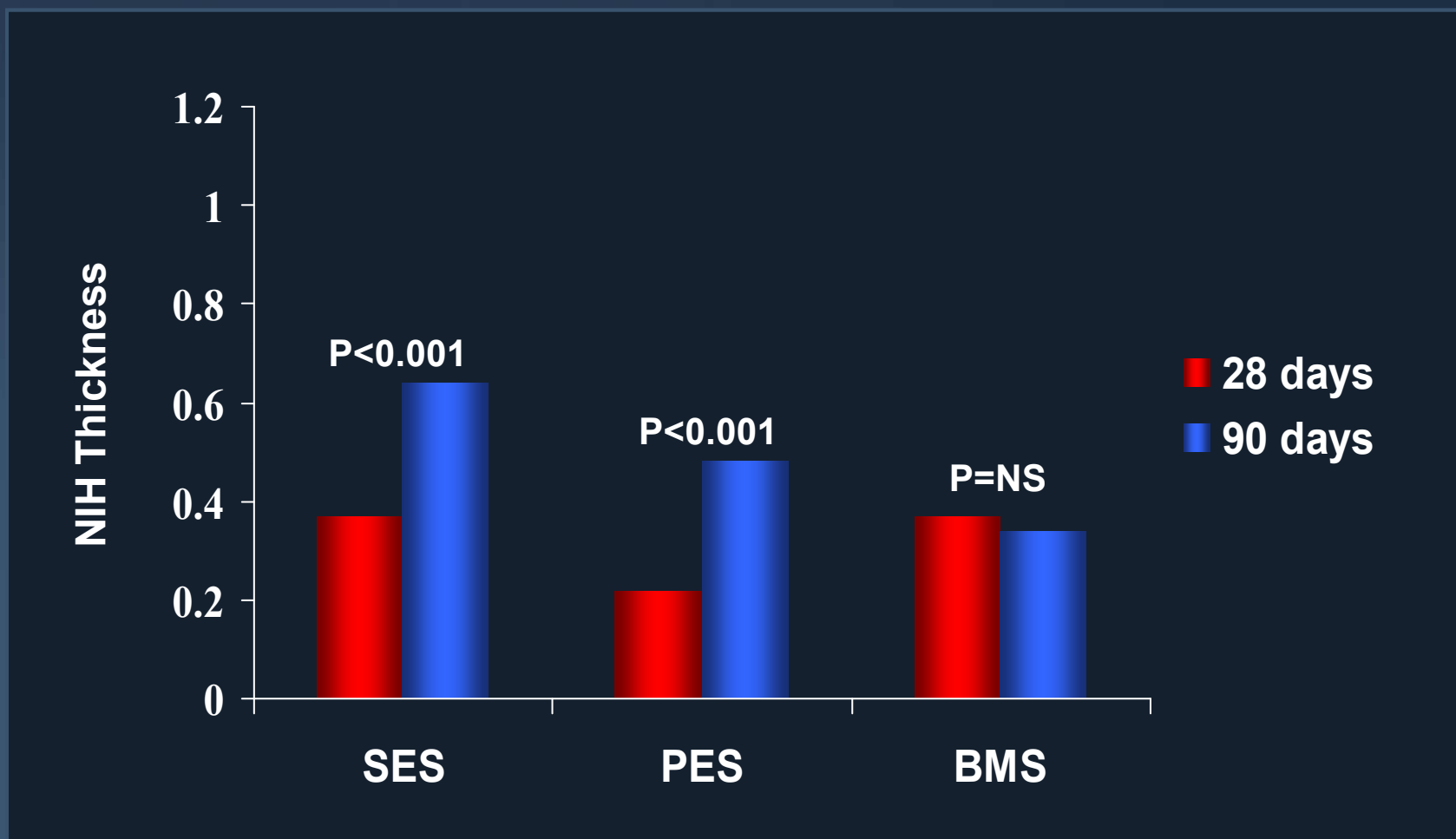
Regression of Neointima after BMS

72 lesions with sequential studies through 3 yrs

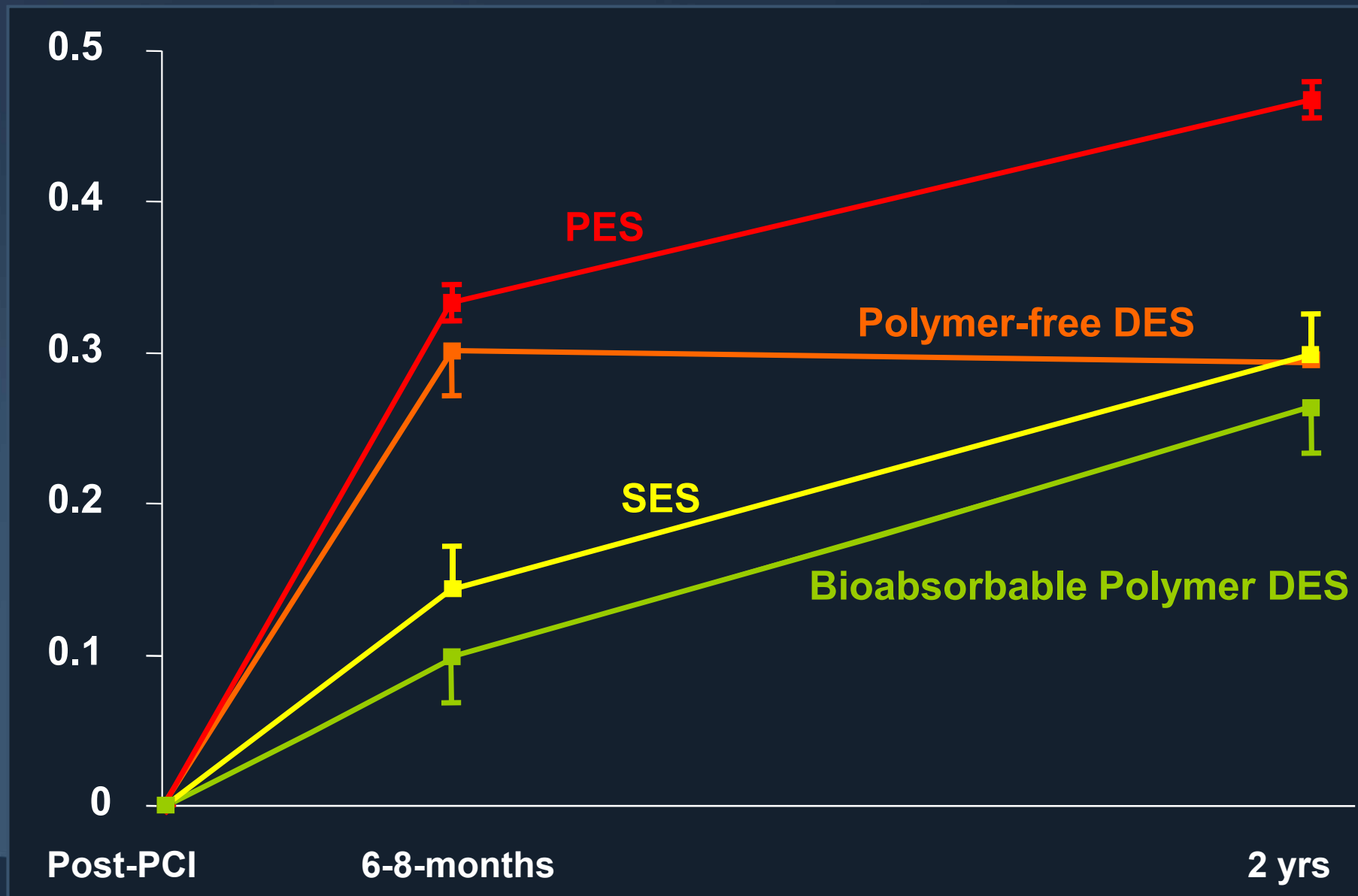


+0.14 mm Increase in MLD from years 1-3

Late Restenosis after DES? *Animal Data*

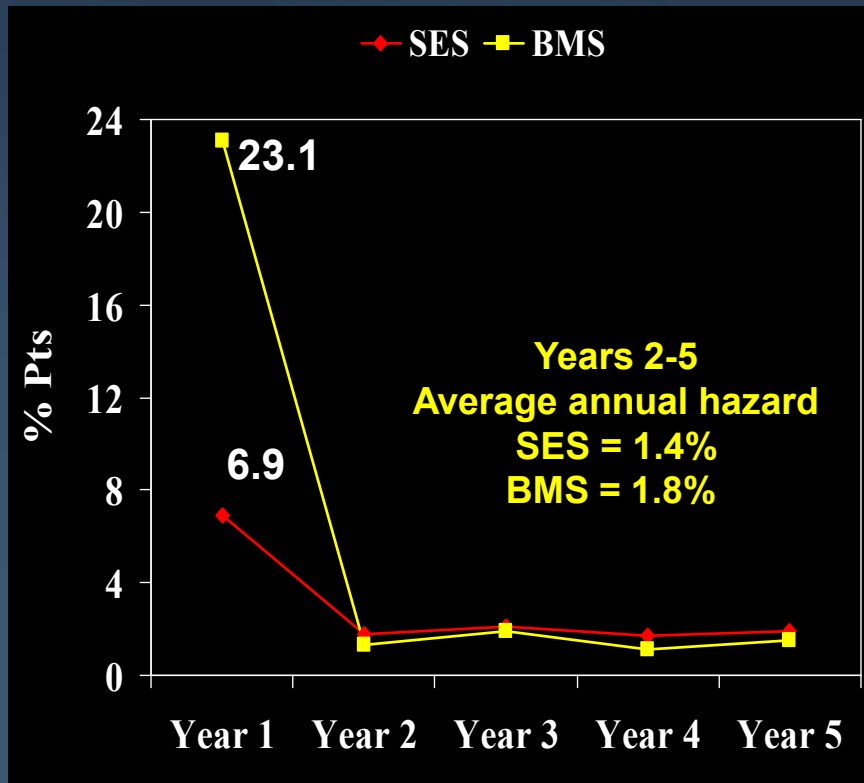


ISAR Data: Late Loss at 2 Years



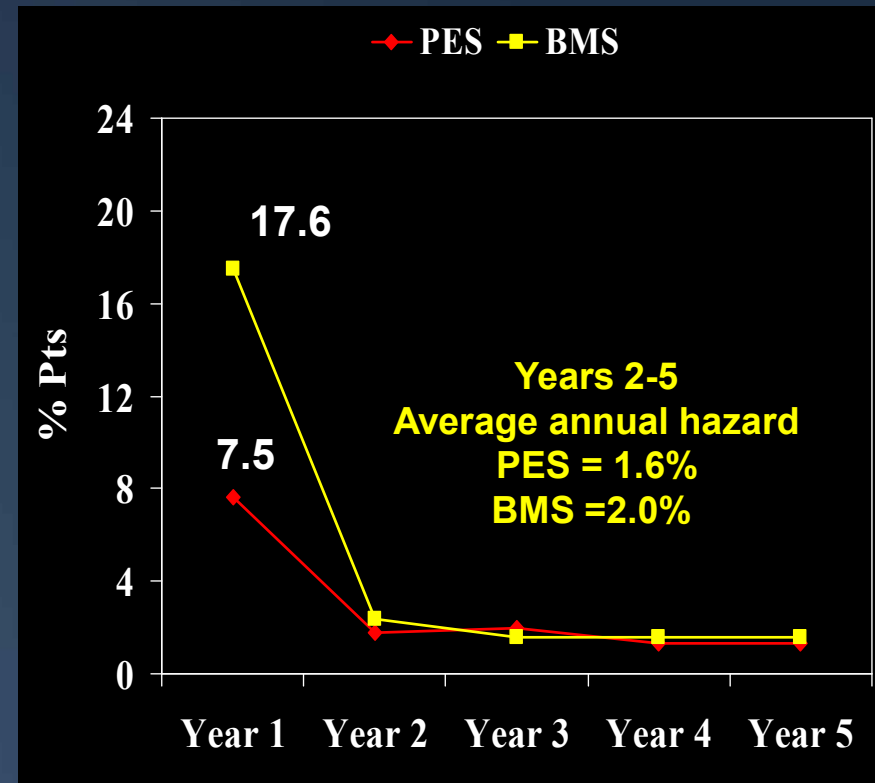
BMS versus DES Clinical Trials: Late Events

SIRIUS 5-Years



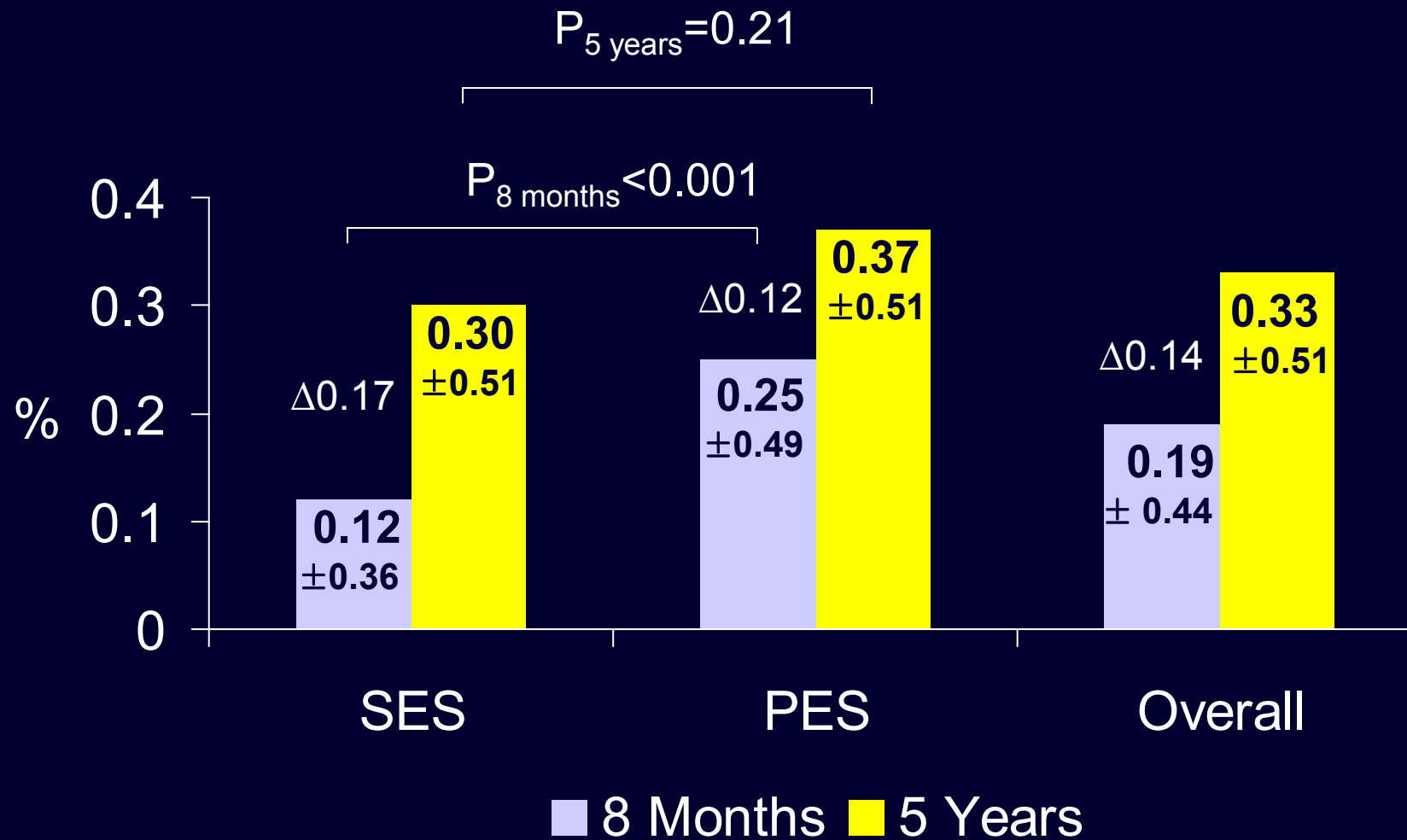
R. Chacko et al. JACC Intv. 2009;2:498-503

TAXUS 5-Years



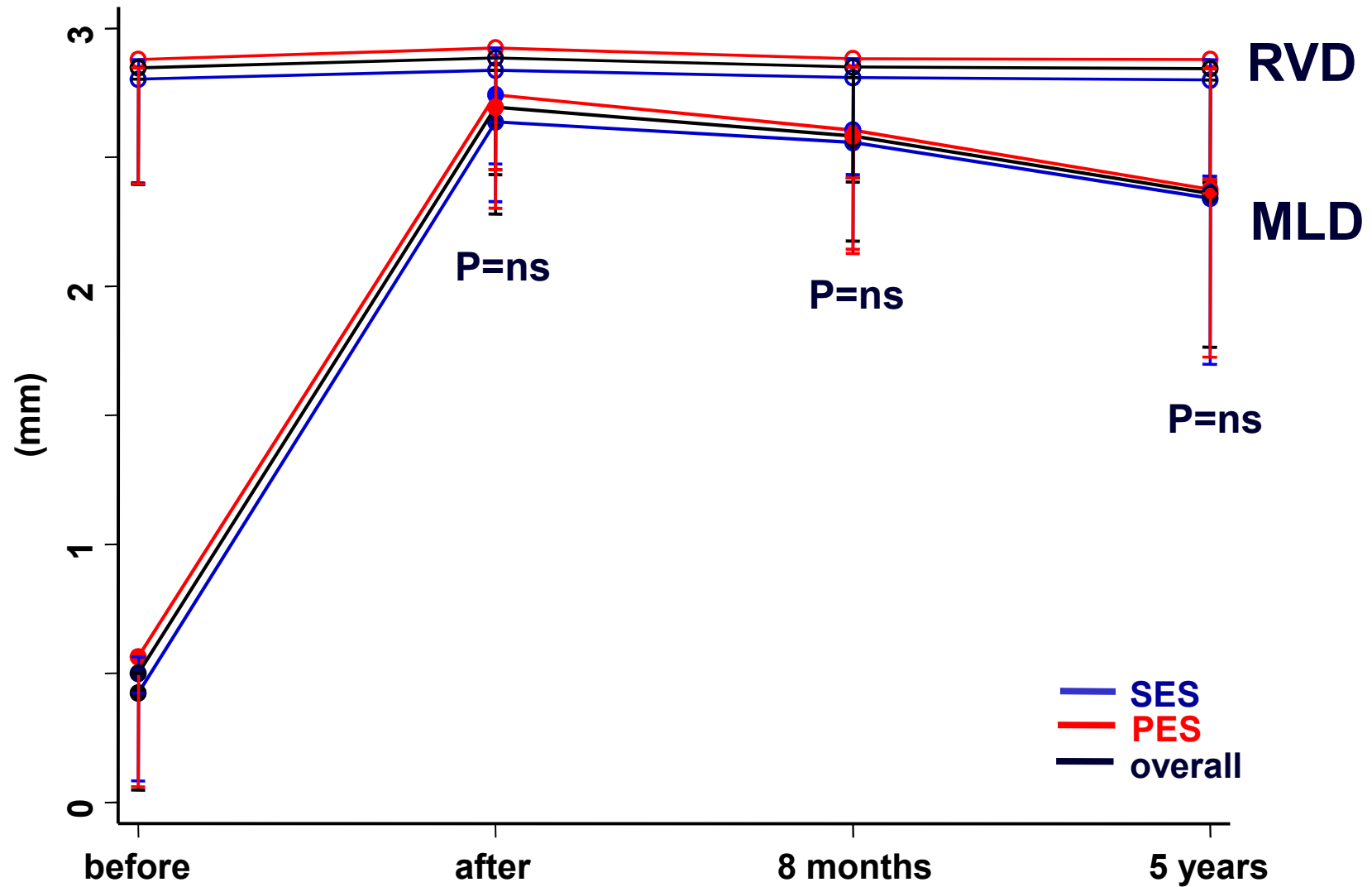
M. Leon et al. JACC Intv. 2009;2:504-12

SIRTAX-LATE: Late Loss Over Time

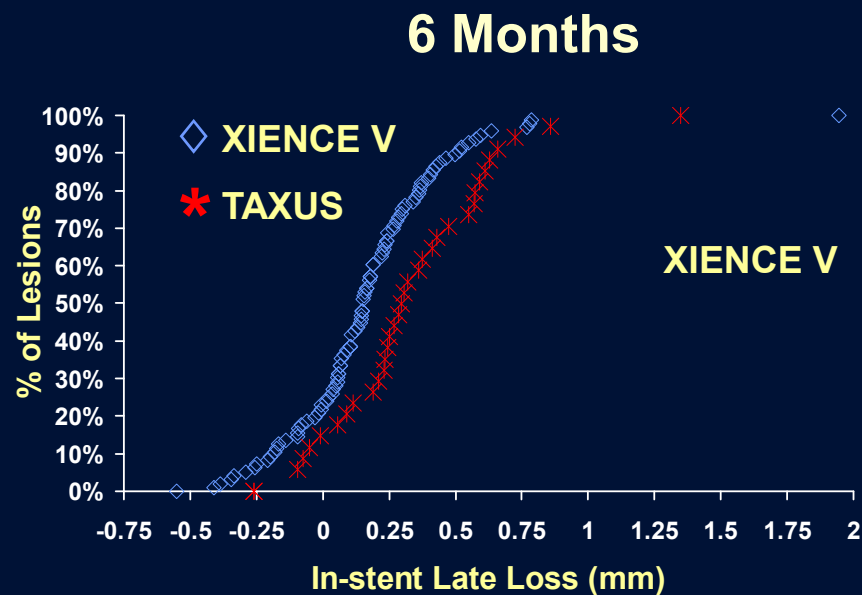


SIRTAX-LATE: Evolution of MLD

Paired Angiograms



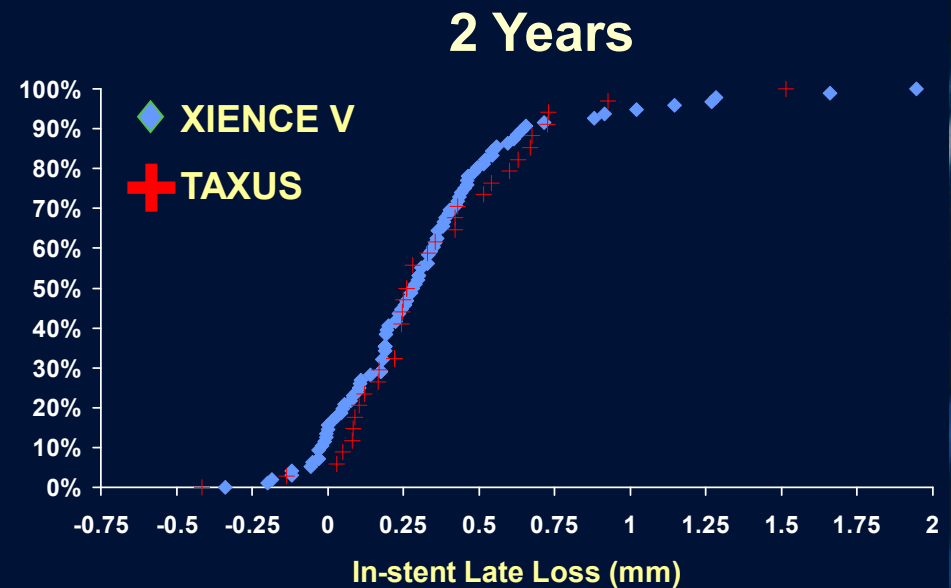
SPIRIT II: In-stent Late Loss in 132 Patients with Serial 6 Month and 2 Year Angio FU



XIENCE V: 0.17 ± 0.32 (nL=97)

TAXUS: 0.33 ± 0.32 (nL=35)

P=0.004



XIENCE V: 0.33 ± 0.37 (nL=97)

TAXUS: 0.34 ± 0.34 (nL=35)

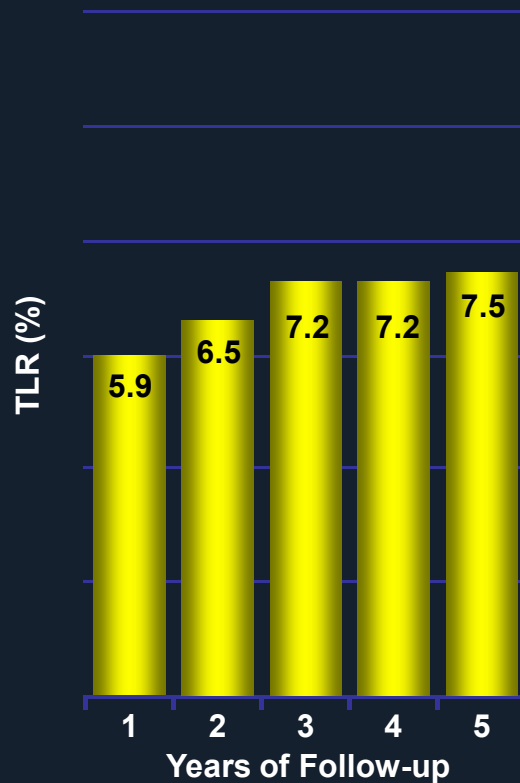
P=0.60

For patients having TLR, values of late loss observed prior to 6 month or 2 year FU were imputed

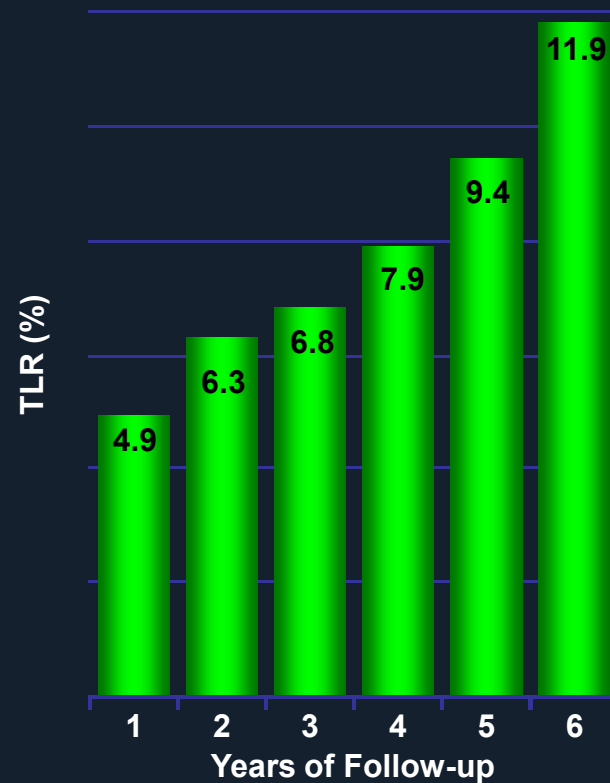
Pivotal Trials TLR: DES Arms

Rates of TLR Over Time

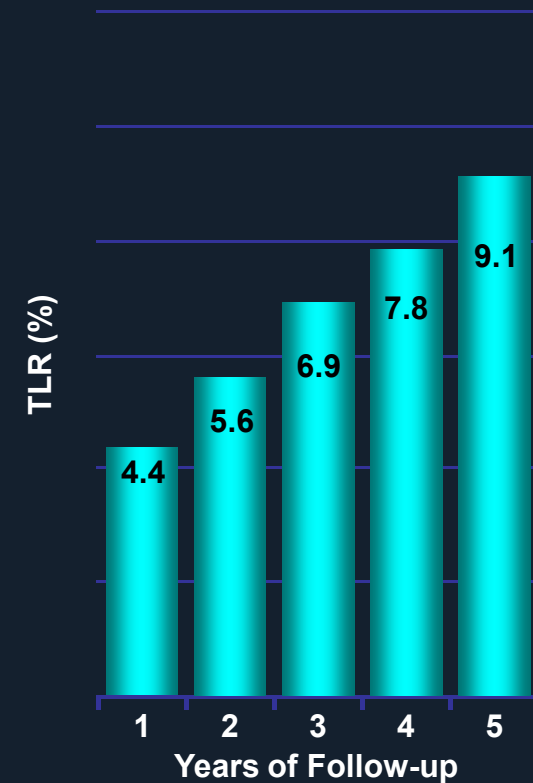
ENDEAVOR II
(Yr 5 N = 577/598)



SIRIUS
(Yr 5 N = 501/533)



TAXUS IV
(Yr 5 N = 618/662)



Late DES Issues: Safety and Efficacy

- Overall safety is very comparable to BMS with follow-up generally ≤ 5 years
 - DAPT adherence is critical early on
- Late stent thrombosis remains a concern, and real-world data 5 years and beyond is now emerging
 - How to prevent late stent thrombosis?
- Relative DES efficacy is unquestionably improved vs. BMS, but *absolute differences* in TLR rates may vary by overall patient risk and if late catch-up is a real phenomenon



What of These Lingerin Concerns?

- **Webster's Definition of "lingering"**
 - a: to remain alive although gradually dying
 - b : to remain existent although often waning in strength, importance, or influence

Improvements/Innovations in DES technology should hopefully allow these concerns to rest in peace!

