

SOLACI 2012

Mexico City- July, 2012

**Late and Very Late Stent Thrombosis:
*Differences in Presentation and
Outcome that are Germane to
Management Decisions***

Fausto Feres, MD

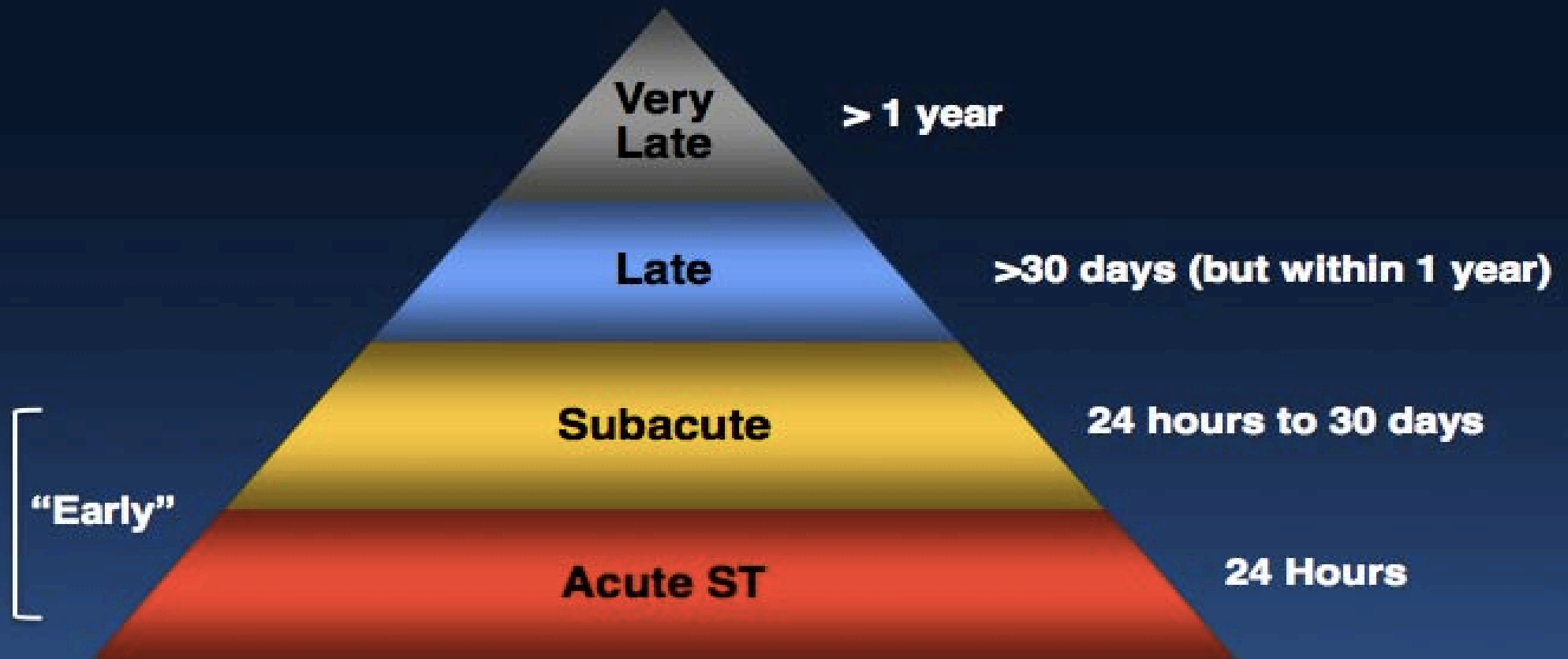
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Late and Very Late Stent Thrombosis

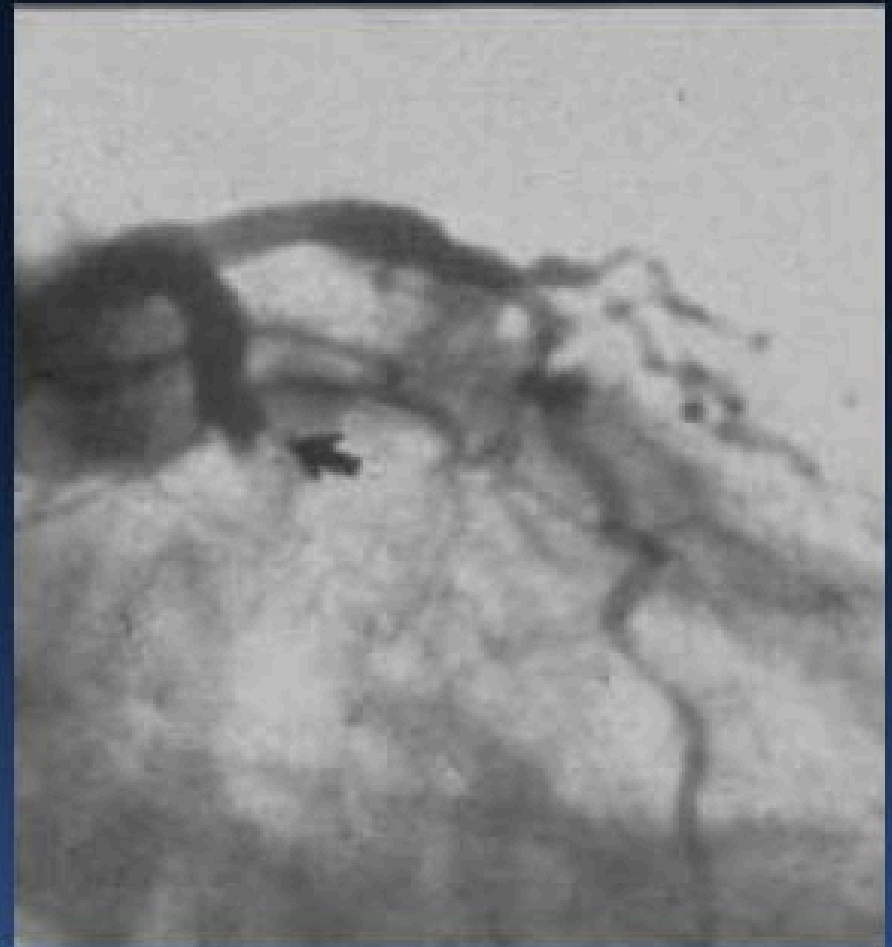
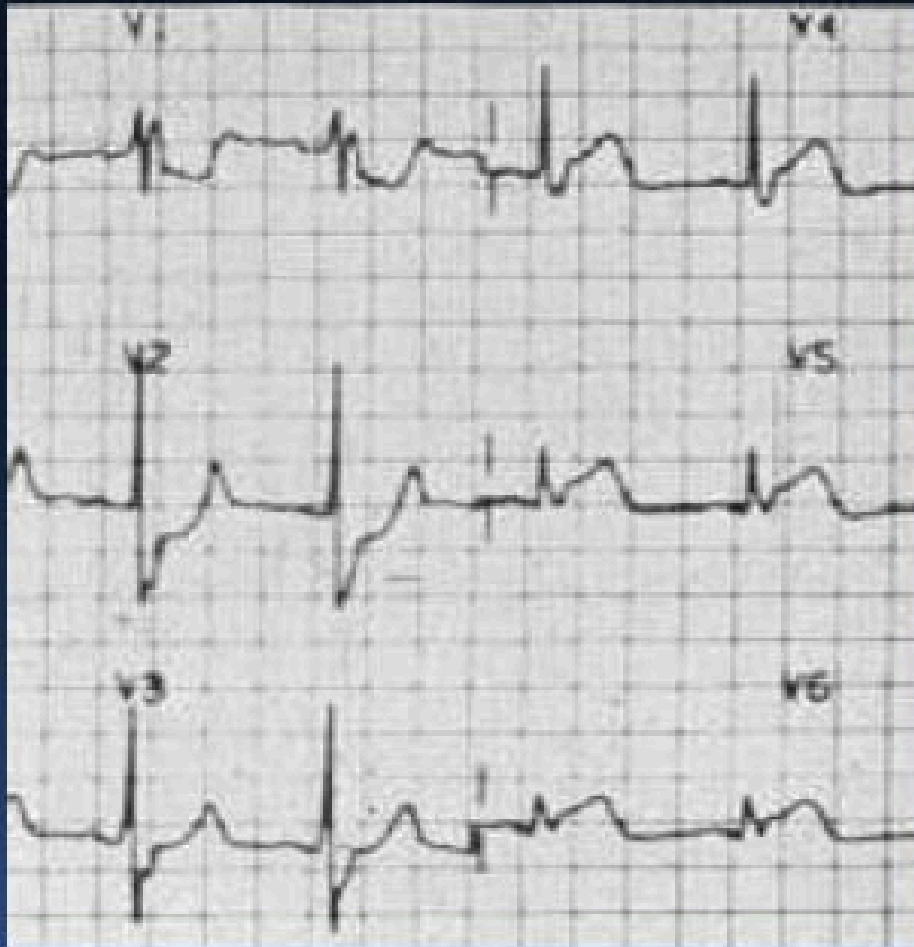
■ Introduction & Presentation

Timing of ST After Stent Implantation



Cutlip et al. *Circulation* 2007;115:2344-51

A Reminder of the Significance of Stent Thrombosis



ST typically presents as a large MI, with high rates of subsequent mortality

Late and Very Late Stent Thrombosis

- Introduction & Presentation

- Mechanism & Outcome: First Generation DES

Late Stent Thrombosis: *why does it happen ?*

Very Late Thrombosis After Drug-Eluting Stents

Fausto Feres,¹ MD, PhD, J. Ribamar Costa, Jr.,² MD, and Alexandre Abizaid,^{1*} MD, PhD

Stent thrombosis is a rare but potentially fatal complication of percutaneous treatment of coronary disease. Its occurrence after drug eluting stent (DES) placement has raised concerns, especially when it occurs late after the stent implantation. The mechanisms of late thrombosis after DES have yet to be completely understood. By means of serial angiography and intravascular (IVUS) images we described a relatively new and unusual vessel response to drug-eluting stents (e.g. huge positive remodeling in all vessel extension), leading to impressive late-acquired incomplete stent apposition and finally causing stent thrombosis and acute myocardial infarction. After describing the two cases, one after Cypher stent implantation and one after Taxus stent implantation, we briefly reviewed the literature available on stent thrombosis with special emphasis on its late occurrence. • 2006 Wiley-Liss, Inc.

Key words: drug-eluting stents; late thrombosis; positive remodeling

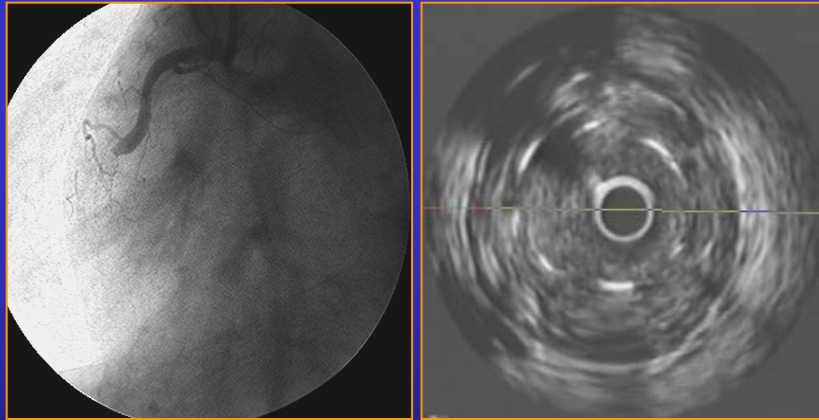
INTRODUCTION

follow-up angiography and IVUS imaging. Quantitative coronary angiography demonstrated an absence of

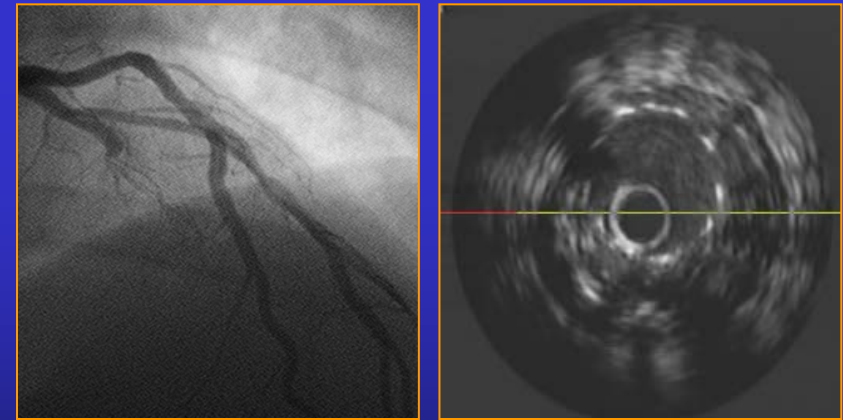
Catheterization 2006; 68:83-88

Late and Very Late Stent Thrombosis

Late Incomplete Stent Apposition



Cypher ® 1216 days pos procedure



Taxus™ 331 days pos procedure

Hong M e cols . *Circulation* 2004 ; 109 : 881-886

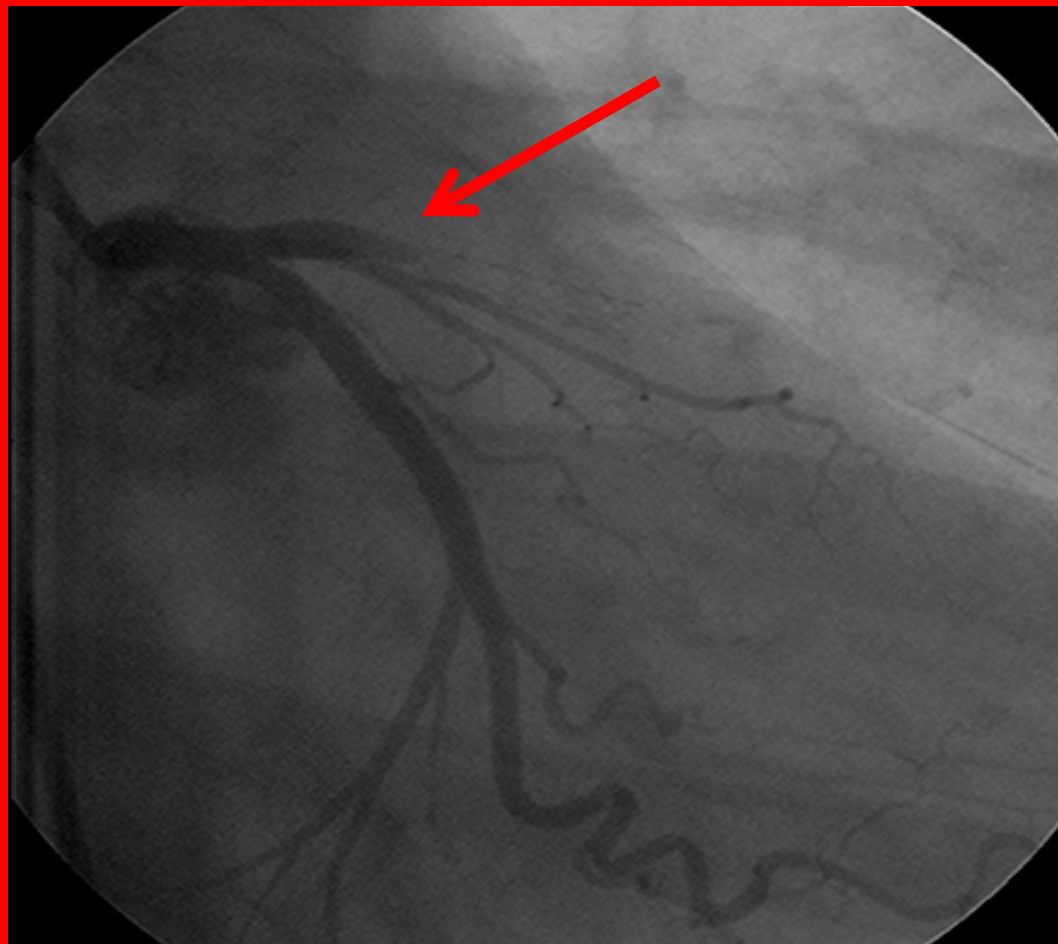
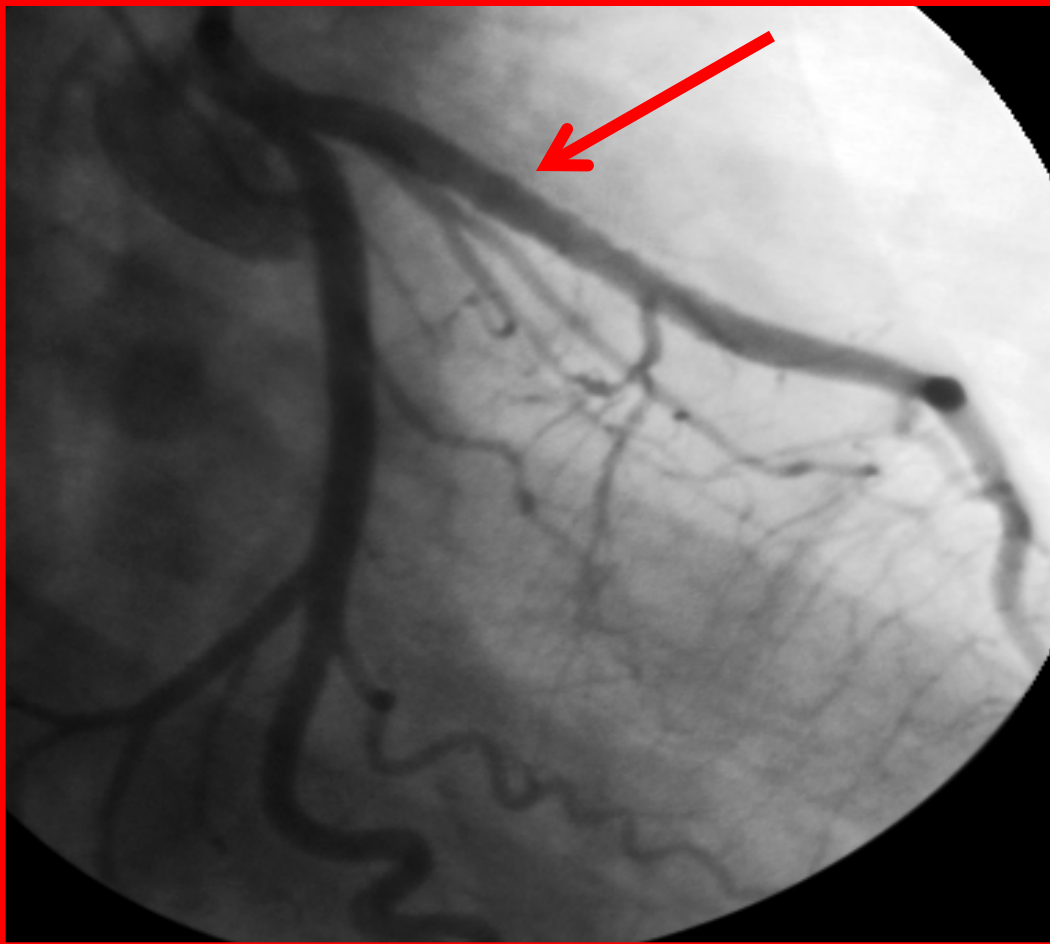
Serruys PW e cols . *Circulation* 2002 ; 106 : 798-803

Tanabe K e cols . *Circulation* 2005 ; 111 : 900-905

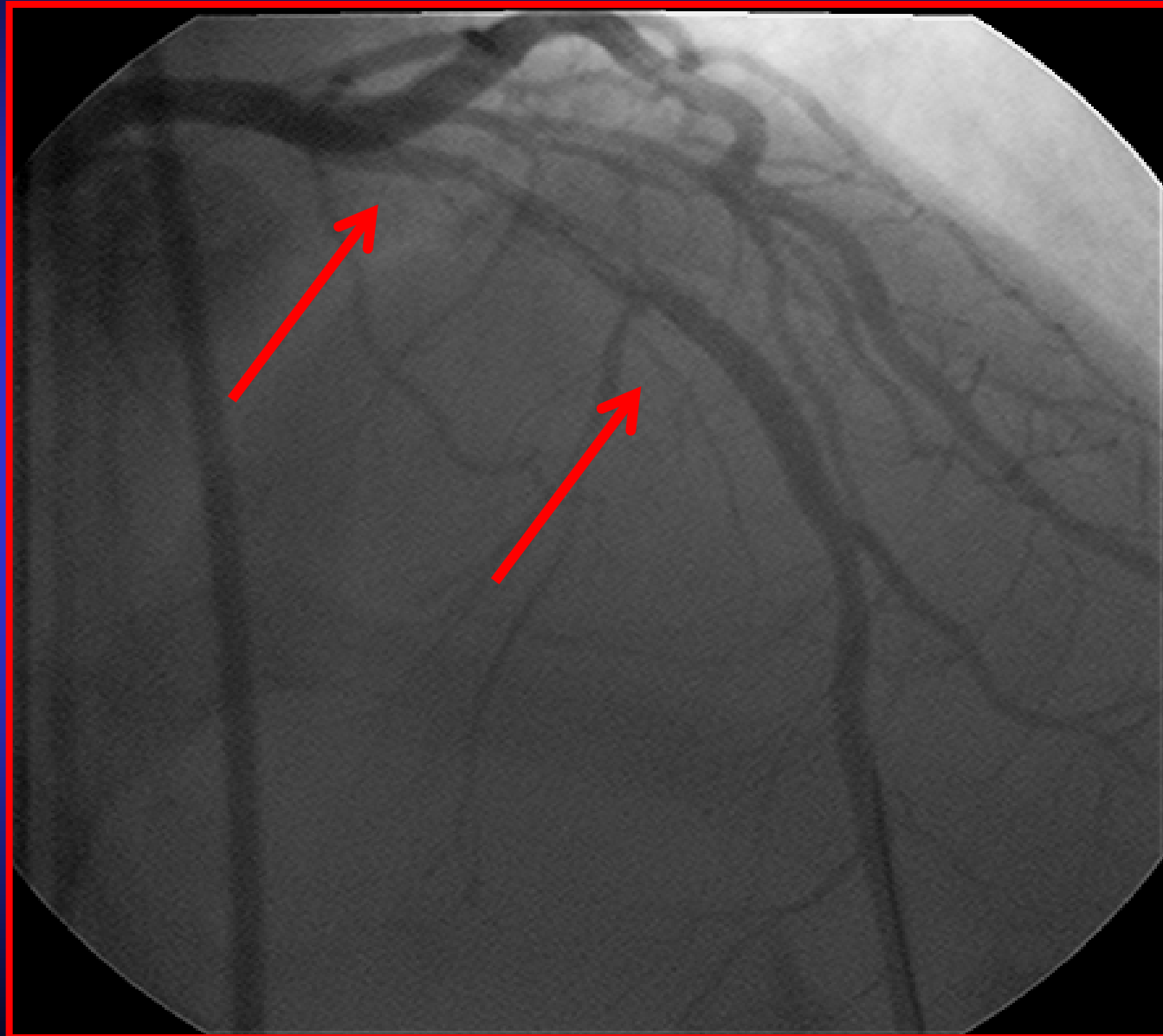
Late Stent Thrombosis: *why does it happen ?*

Post SES
December/2005

October/2008
(34 months later)

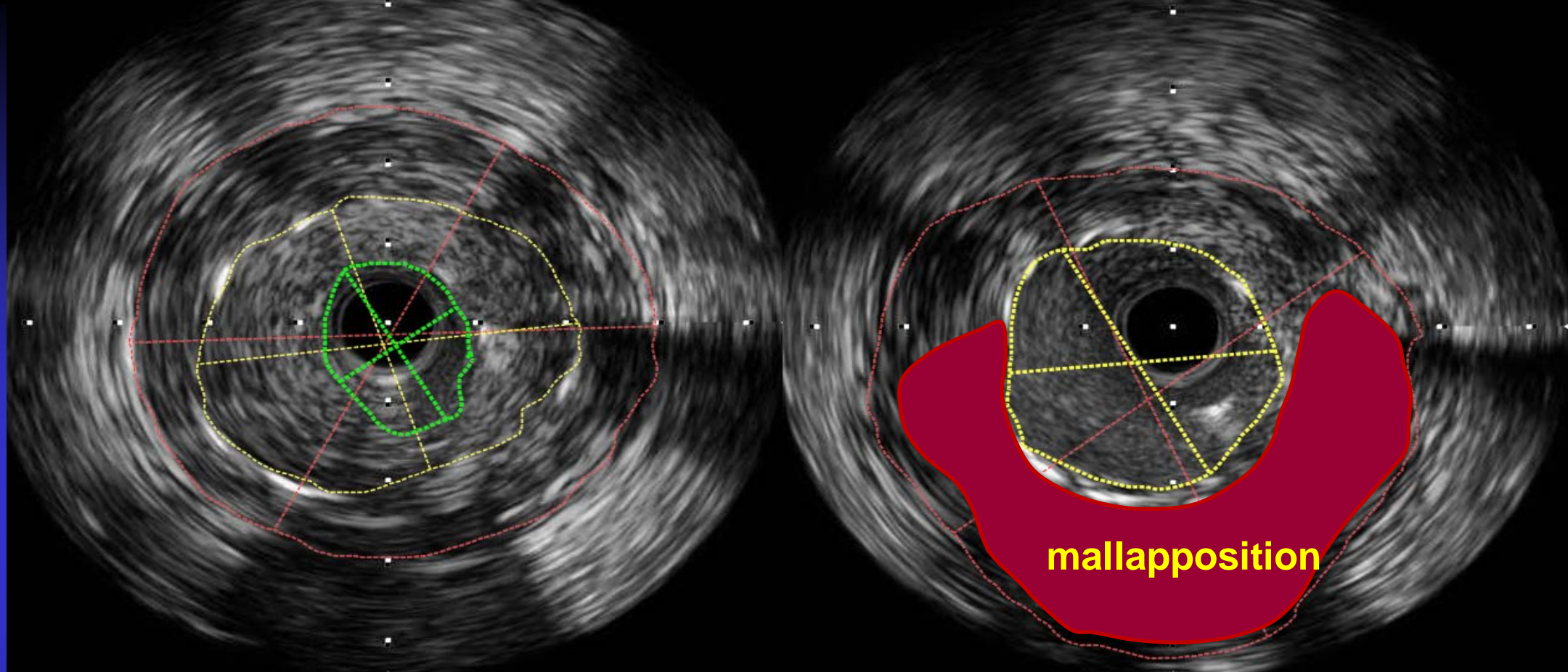


Post Thrombus Aspiration






Post Thrombus Aspiration







Measurements

iA1		25,09 mm ²
<hr/>		
iA2		11,64 mm ²
<hr/>		
iA3		2,66 mm ²

5,46/5,83 mm
3,41/4,25 mm
1,59/2,18 mm

Measurements

iA1		28,89 mm ²
<hr/>		
iA2		7,58 mm ²

5,78/6,32 mm
2,98/3,27 mm

Predictors of DES Thrombosis

35 Autopsy Examinations Following Stent Placement (N=32 DES, 7 BMS)

- SAT 8/39 stents, LST 11/39 stents
- All BMS with complete endothelialization
- Predictors
 - Stent across ostia of major sidebranch
 - Strut penetration of necrotic core
 - **Stent malapposition**
 - Increasing stent length
 - Hypersensitivity
 - Focal delayed no healing (absence of intima)

Joner, Virmani et al. *Circulation* 2005;112:3210

Late and Very Late Stent Thrombosis

Interventional Cardiology

Correlation of Intravascular Ultrasound Findings With Histopathological Analysis of Thrombus Aspirates in Patients With Very Late Drug-Eluting Stent Thrombosis

Stéphane Cook, MD*; Elena Ladich, MD*; Gaku Nakazawa, MD; Parham Eshtehardi, MD; Michel Neidhart, PhD; Rolf Vogel, MD, PhD; Mario Togni, MD; Peter Wenaweser, MD; Michael Billinger, MD; Christian Seiler, MD; Steffen Gay, MD; Bernhard Meier, MD; Werner J. Pichler, MD; Peter Jüni, MD; Renu Virmani, MD; Stephan Windecker, MD

Background—Intravascular ultrasound of drug-eluting stent (DES) thrombosis (ST) reveals a high incidence of incomplete stent apposition (ISA) and vessel remodeling. Autopsy specimens of DES ST show delayed healing and hypersensitivity reactions. The present study sought to correlate histopathology of thrombus aspirates with intravascular ultrasound findings in patients with very late DES ST.

Methods and Results—The study population consisted of 54 patients (28 patients with very late DES ST and 26 controls). Of 28 patients with very late DES ST, 10 patients (1020±283 days after implantation) with 11 ST segments (5 sirolimus-eluting stents, 5 paclitaxel-eluting stents, 1 zotarolimus-eluting stent) underwent both thrombus aspiration and intravascular ultrasound investigation. ISA was present in 73% of cases with an ISA cross-sectional area of $6.2 \pm 2.4 \text{ mm}^2$ and evidence of vessel remodeling (index, 1.6 ± 0.3). Histopathological analysis showed pieces of fresh thrombus with inflammatory cell infiltrates (DES, 263 ± 149 white blood cells per high-power field) and eosinophils (DES, 20 ± 24 eosinophils per high-power field; sirolimus-eluting stents, 34 ± 28 ; paclitaxel-eluting stents, 6 ± 6 ; P for sirolimus-eluting stents versus paclitaxel-eluting stents = 0.09). The mean number of eosinophils per high-power field was higher in specimens from very late DES ST (20 ± 24) than in those from spontaneous acute myocardial infarction (7 ± 10), early bare-metal stent ST (1 ± 1), early DES ST (1 ± 2), and late bare-metal stent ST (2 ± 3 ; P from ANOVA = 0.038). Eosinophil count correlated with ISA cross-sectional area, with an average increase of 5.4 eosinophils per high-power field per 1-mm^2 increase in ISA cross-sectional area.

Conclusions—Very late DES thrombosis is associated with histopathological signs of inflammation and intravascular

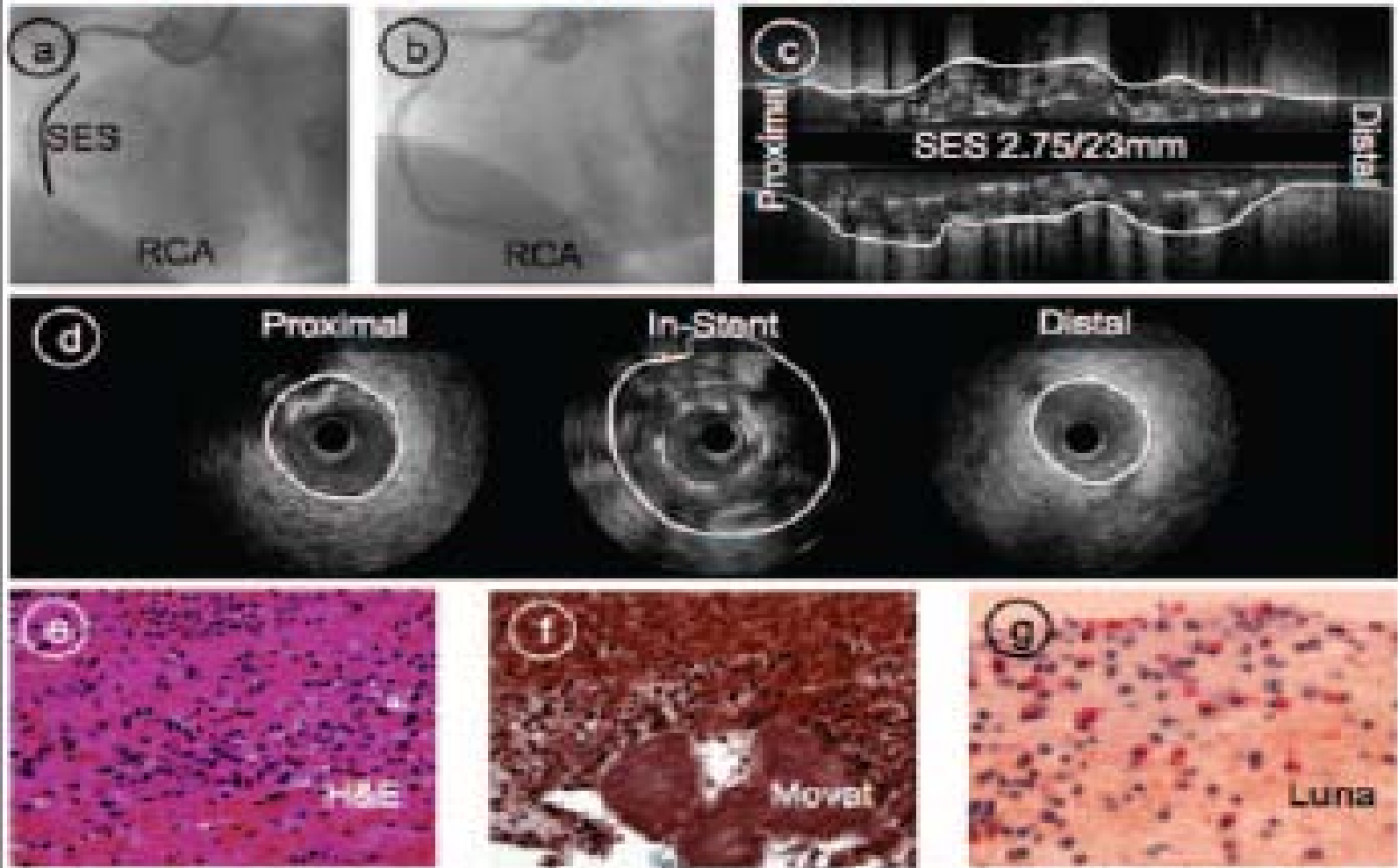
Late and Very Late Stent Thrombosis

- 28 pts with VLST (DES) and 26 controls in 2007
- **ISA in 73%; index of vessel remodeling, 1.6 ;**
- Maximal CSA, mm² was 20.2!
- Fresh thrombus with inflammatory cell
- Eosinophil count correlated with ISA!

Cook , Ladich et al.Circulation 2009; 120:391-399

Late and Very Late Stent Thrombosis

A. Very Late ST (790 days after Implantation)



Cook , Ladich et al. *Circulation* 2009; 120:391-399

Pathology Findings from Different Coronary Arteries in the Same Patient (delayed healing)

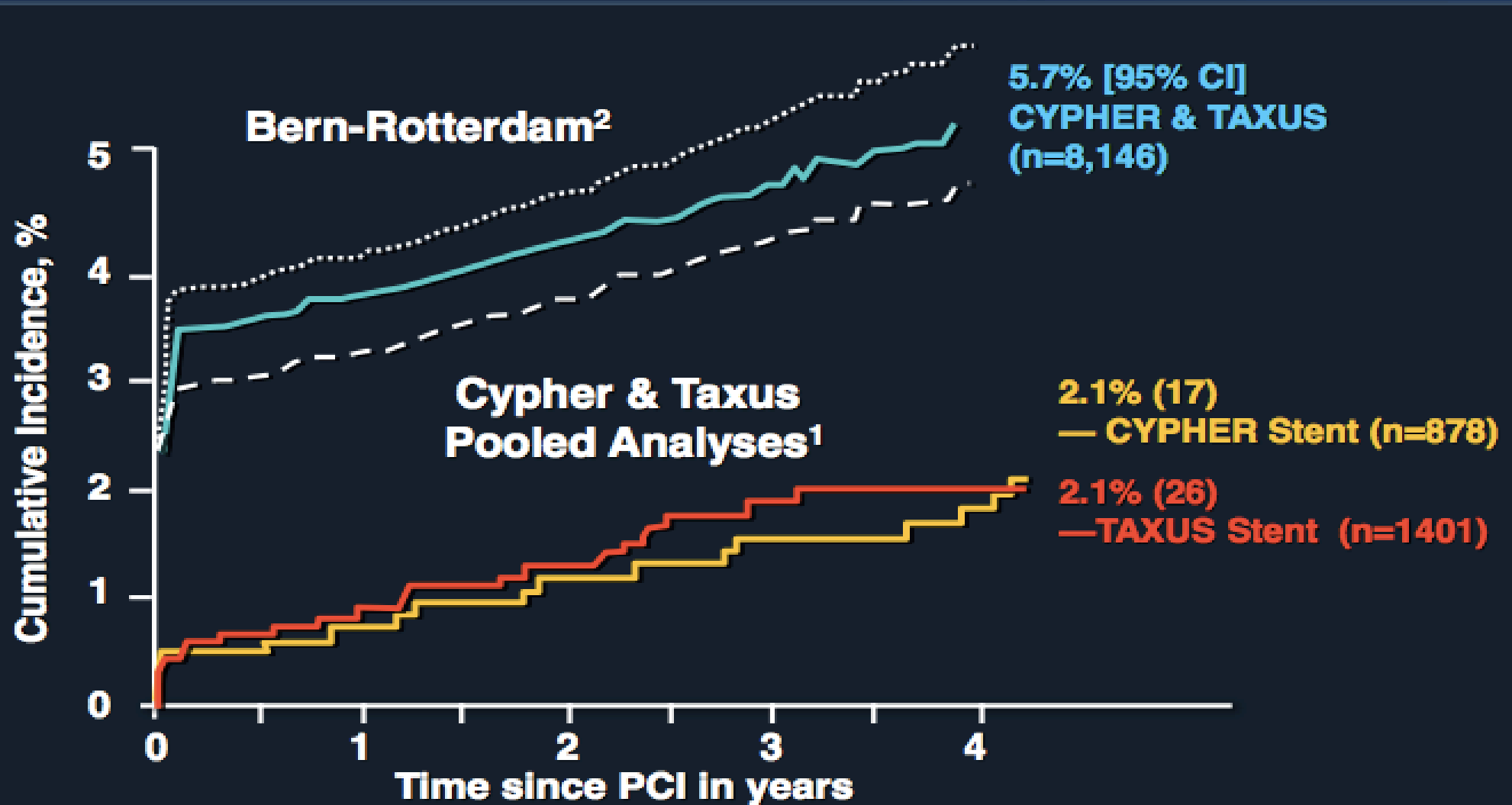


**BMS 24 Months after
Deployment**



**SES 16 Months after
Deployment**

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

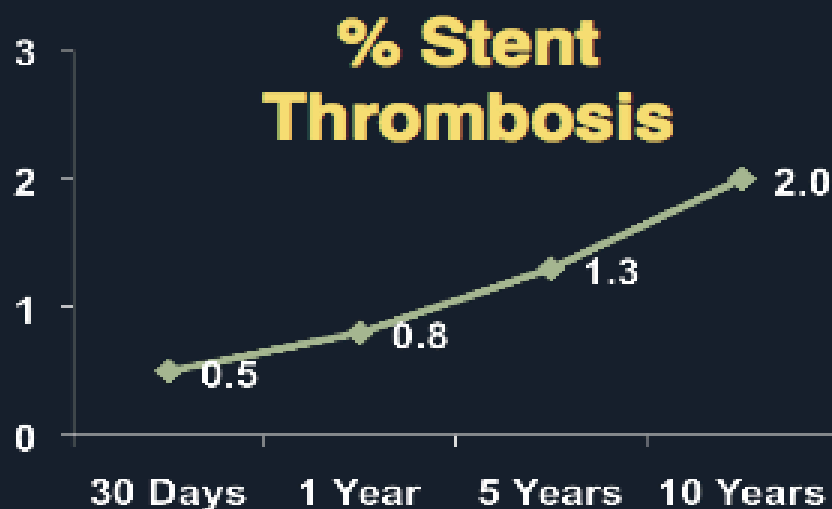


¹ Mauri et al; N Engl J Med 2007;356:1020-9

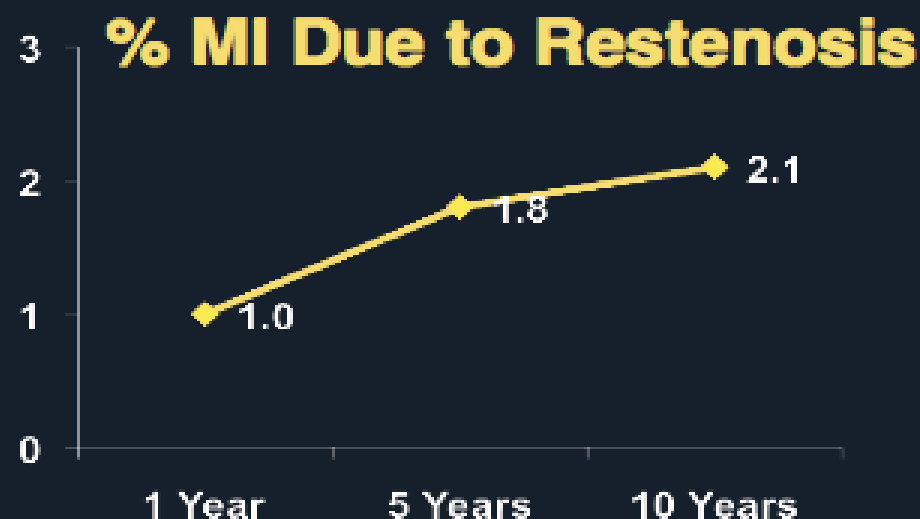
² Wenaweser et al; J Am Coll Cardiol 2008;52:1134-40

Stent Thrombosis and Restenosis During Extended Follow-up of Pts Treated With BMS (n=4503)

	1 Year % (95% CI)	5 Years % (95% CI)	10 Years % (95% CI)
All stent thrombosis	0.8 (0.6-1.1)	1.3 (1.0-1.7)	2.0 (1.5-2.5)
On-label patients	0.6 (0.2-0.9)	1.0 (0.5-1.2)	1.4 (0.9-2.0)
Off-label patients	1.1 (0.7-1.5)	1.7 (1.2-2.2)	2.5 (1.7-3.3) ^b



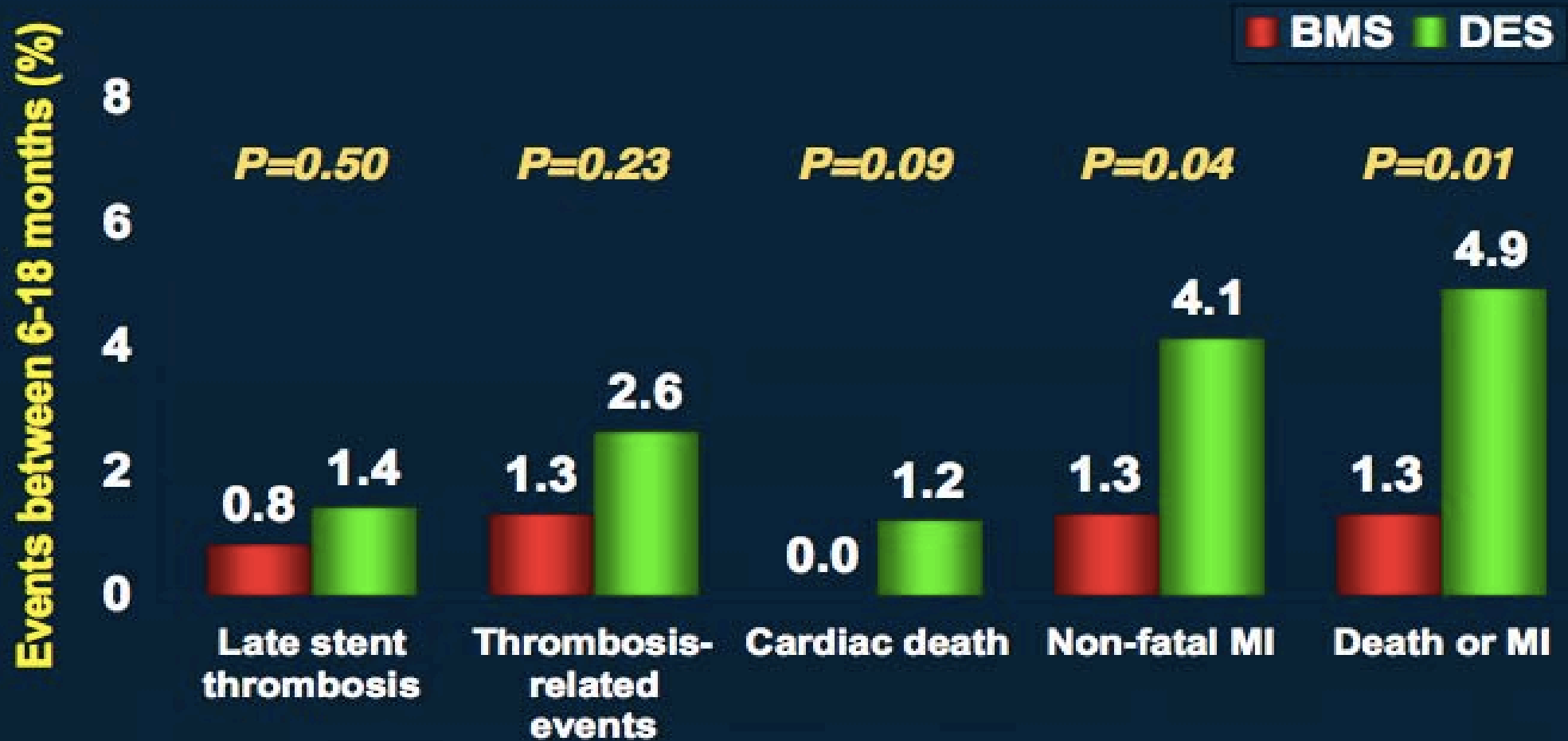
↑ **Mortality Risk: HR=22, P<0.001**



↑ **Mortality Risk: HR=2.4, P<0.001**

BASKET LATE Trial: 6-18 Mo MACE

N=743 (pts with early events excluded)

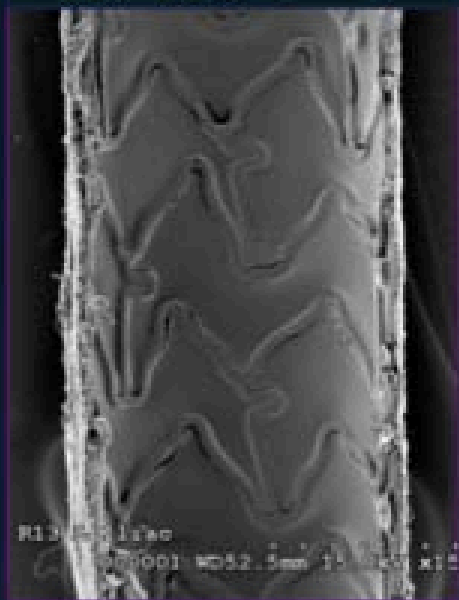


Late and Very Late Stent Thrombosis

- Introduction & Presentation
- Mechanism & Outcome: First Generation DES
- Outcome: Second Generation DES

14 Day Endothelialization: Rabbit Iliac Model

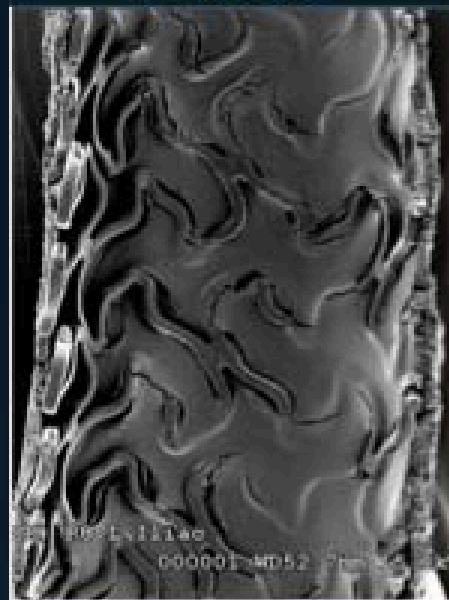
XIENCE™ V



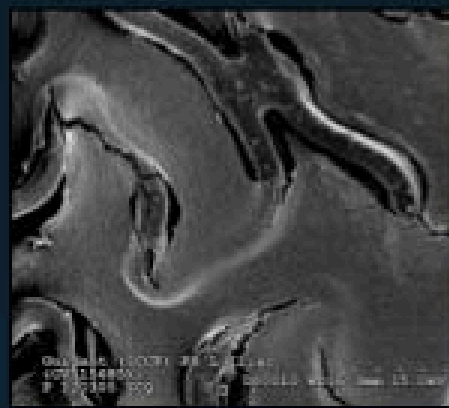
CYPHER®



TAXUS®



ENDEAVOR™



Late Incomplete Apposition post 2nd generation DES

Interventional Cardiology

Comparison of vascular response to zotarolimus-eluting stent versus sirolimus-eluting stent: Intravascular ultrasound results from ENDEAVOR III

Akiyoshi Miyazawa, MD,^a Junya Ako, MD,^a Yoichiro Hongo, MD,^a Seung-Ho Hur, MD, PhD,^a Ichizo Tsujino, MD, PhD,^a Brian K. Courtney, MD,^a Ali H.M. Hassan, MD,^a David E. Kandzari, MD,^b Yasuhiro Honda, MD,^a and Peter J. Fitzgerald, MD, PhD^a for the ENDEAVOR III Investigators
Stanford, CA; and Durham, NC

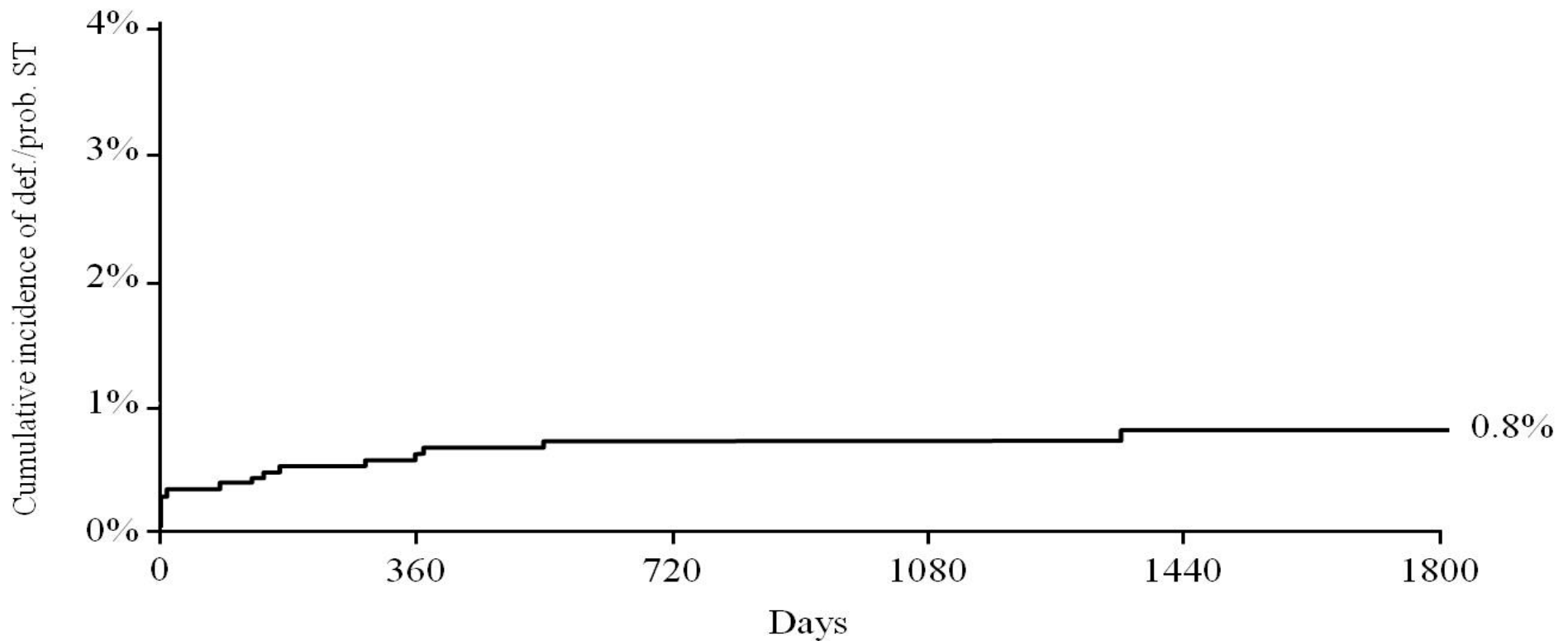
Miyazawa et al. Am Heart J 2008; 155: 108-13

Late Incomplete Stent Apposition

Table II. Qualitative IVUS analysis

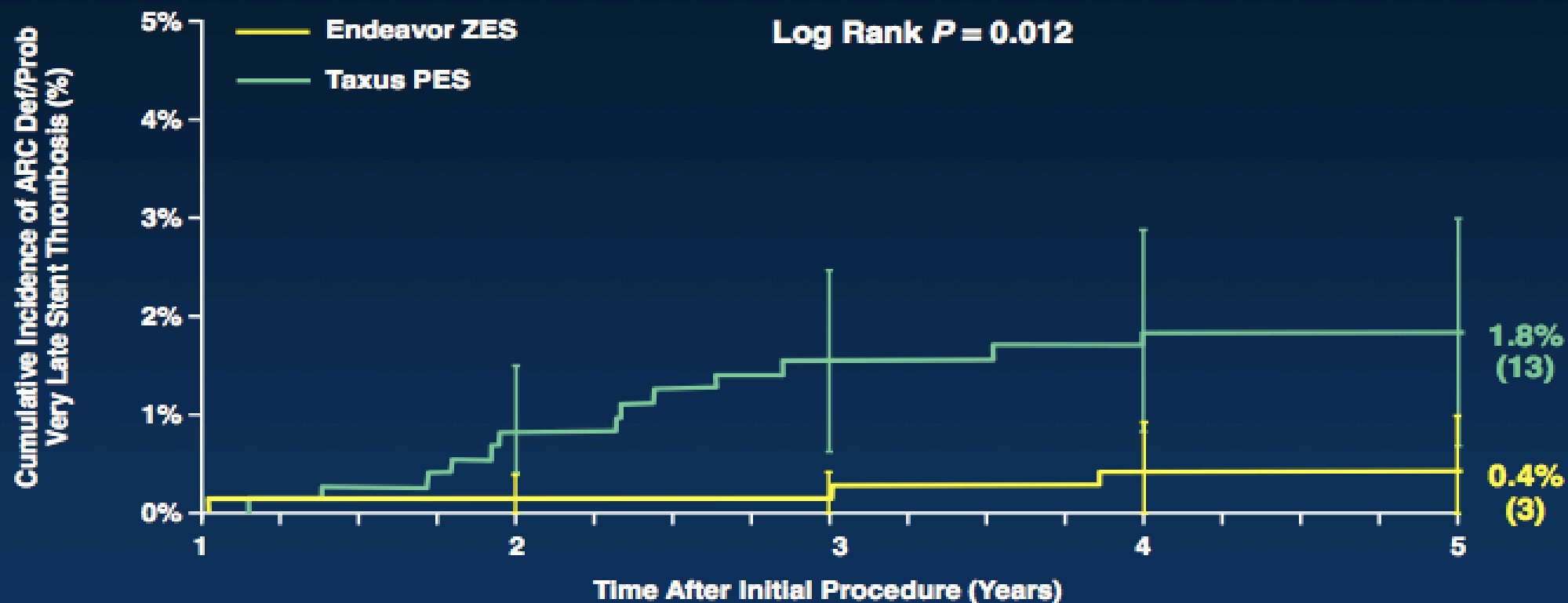
	ZES (n = 190)	SES (n = 68)	P
Dissection			
Proximal edge	2 (1.1%)	2 (2.9%)	NS
Distal edge	3 (1.5%)	2 (2.9%)	NS
Intraluminal tissue *	23 (12.1%)	21 (30.8%)	<.01
ISA			
ISA at baseline	24 (12.6%)	13 (19.1%)	NS
Resolved ISA	11	5	
Persistent ISA	13	8	
Late-acquired ISA	1 (0.5%)	4 (5.9%)	.02

Cumulative Stent Thrombosis Rate with the E-ZES



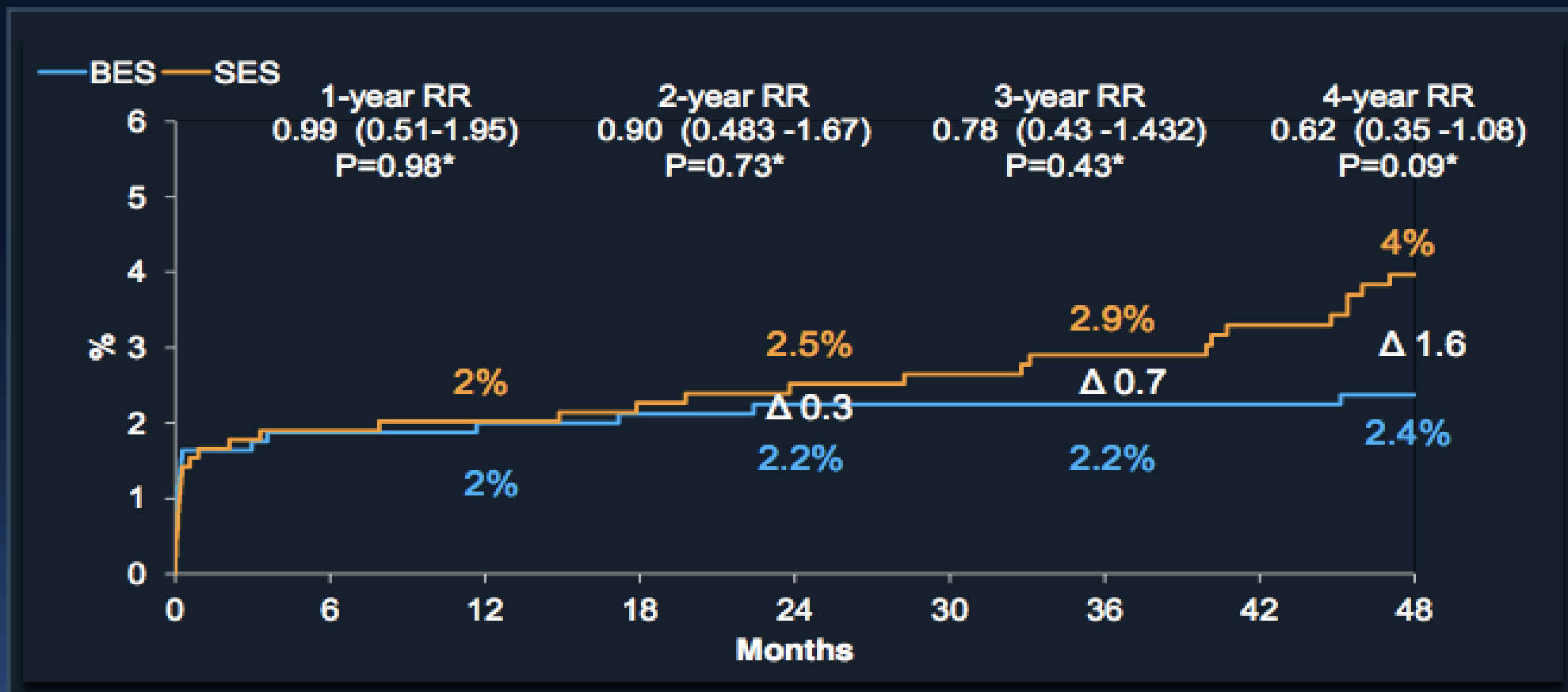
ENDEAVOR IV

Cumulative Incidence of Very Late ST to 5 Years



Endeavor	737	737	710	689	648
Taxus	734	734	707	675	644

LEADERS: Definite ST (ARC)

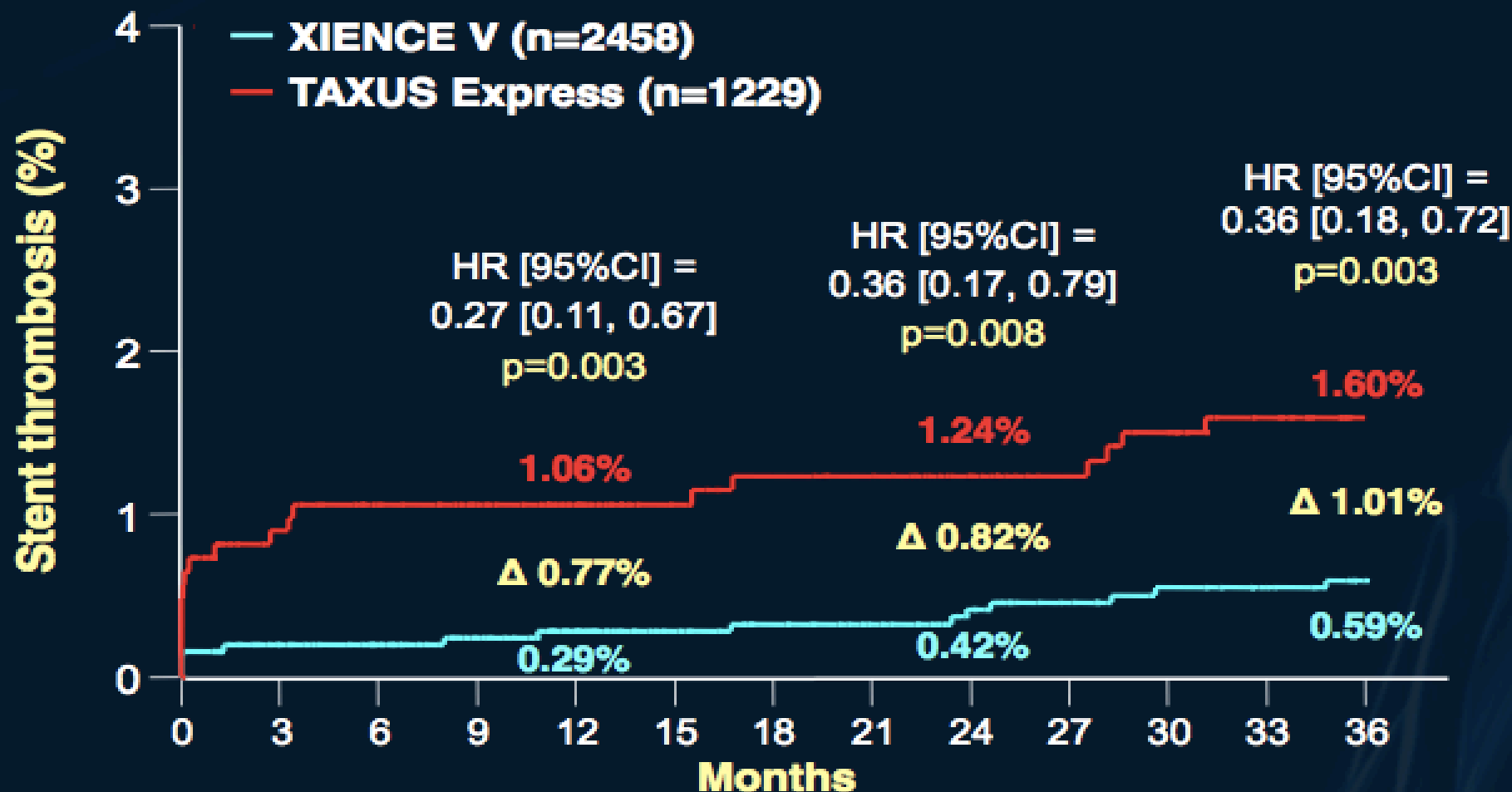


Number
s at risk

SES	850	817	801	787	776	759	750	730	714
BES	857	821	804	792	787	780	774	757	746

G. Stefanini et al. Lancet, 2011

Stent Thrombosis (ARC Def or Prob)

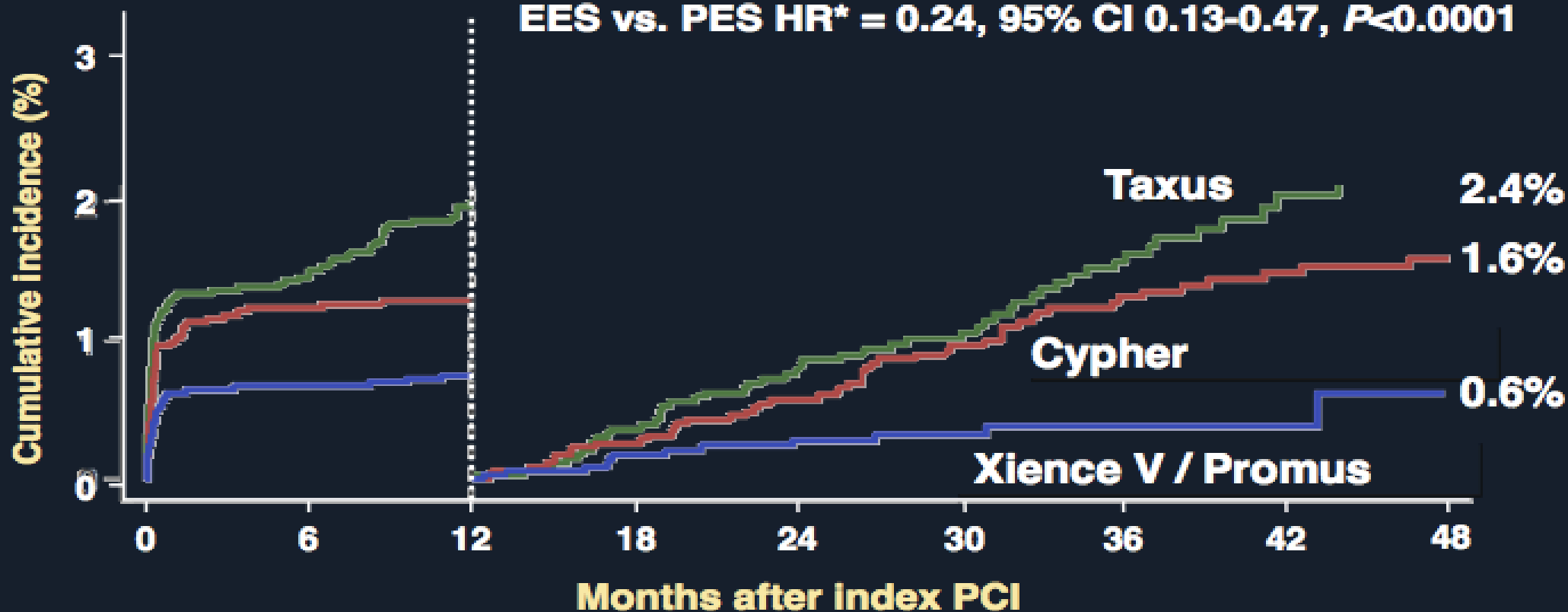


Number at risk

XIENCE V	2458	2427	2413	2387	2358	2331	2319	2311	2296	2272	2263	2254	2242
TAXUS	1229	1196	1186	1175	1157	1137	1131	1127	1115	1106	1098	1086	1073

Bern Rotterdam (n=12,339 pts) ARC Definite ST: Landmark analysis

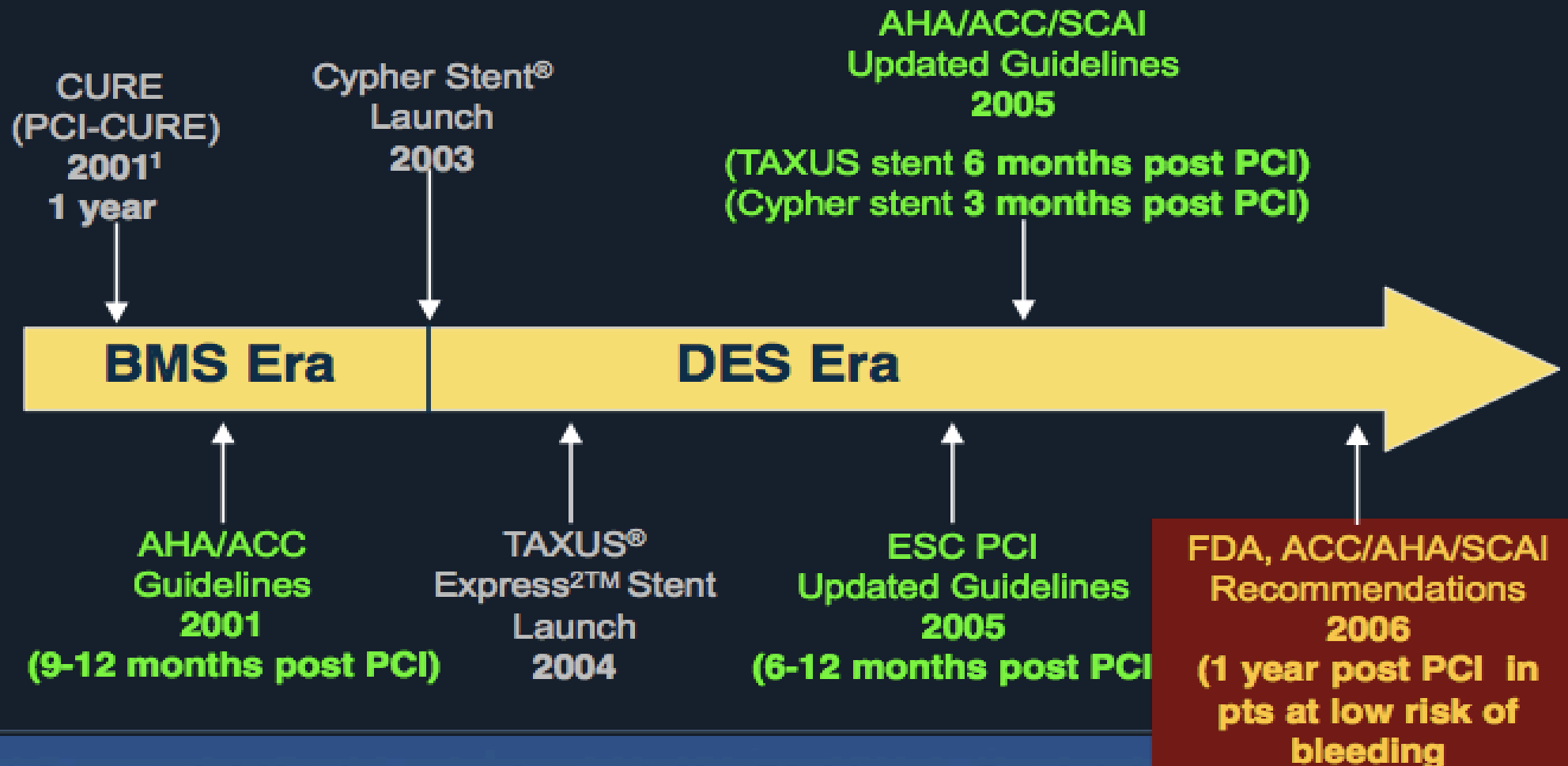
EES vs. SES HR* = 0.33, 95% CI 0.15 – 0.72, P=0.006
EES vs. PES HR* = 0.24, 95% CI 0.13-0.47, P<0.0001



Late and Very Late Stent Thrombosis

- Introduction & Presentation
- Mechanism & Outcome: First Generation DES
- Outcome: Second Generation DES
- Management Decisions

Optimal Duration of Anti-platelet Therapy Post DES Still Unclear



How to Minimize Stent Thrombosis

- **Better Patient selection**
 - Screening for adherence and bleeding risk / ability to tolerate DAPT
 - No upcoming surgical procedures (6 wk for BMS, 6–12 m for DES)
- **Better Stent selection and deployment**
 - Consider use of stents with proven lower stent thrombosis rates
 - Appropriate vessel sizing, high-pressure deployment/post-dilation
 - Ensuring absence of edge dissections and adequate inflow/outflow
 - Avoiding the use of 2 stents in bifurcation lesions (if possible)
- **Better Peri- and post-procedure care**
 - Use of more potent oral antiplatelet regimens in appropriately indicated clinical scenarios (e.g. ACS with acceptable bleeding risk)
 - Patient education and clinical follow-up are critical
 - Continuation of DAPT without interruption whenever possible

How to Treat Stent Thrombosis

- **Upstream**
 - Rapid reperfusion for STEMI
 - Low threshold to for invasive management
- **Performance of PCI**
 - Thrombectomy
 - IVUS or OCT (to establish why)
 - POBA to optimize expansion
 - Stent if edge issues (particularly early)
- **Escalation of pharmacotherapy**
 - Genetic testing?

What We Have Learned

- Stent thrombosis remains the most devastating complication of stent implantation!
 - Increasing incidence?
- Different mechanisms seem to be at play for Early vs. Very Late ST
- Risk factors are multifactorial
 - Patient / Response to Pharmacotherapy
 - Device
 - Procedure

Muchas Gracias!!

Após uma consulta médica :



**Prof. Lineu J. Miziara,
de Uberaba-MG**

*“que o médico é seu amigo,
que o médico é honesto,
que o médico se mostrou
preocupado em resolver
seus problemas, e que
faria tudo que estivesse
ao seu alcance para
solucioná-los”.*