DES και θρόμβωση

Dimitrios Alexopoulos
30.10.2008

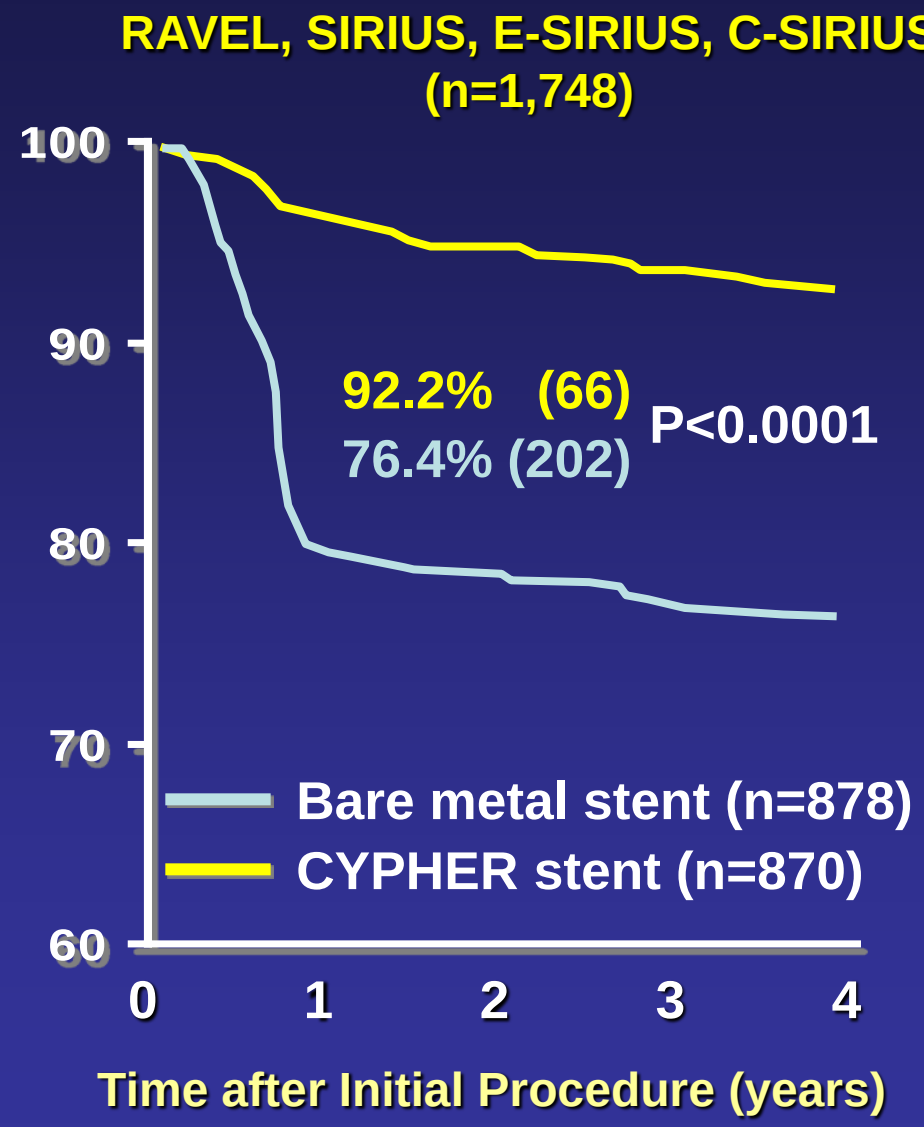
What is the Purpose of a Drug-eluting Stent?

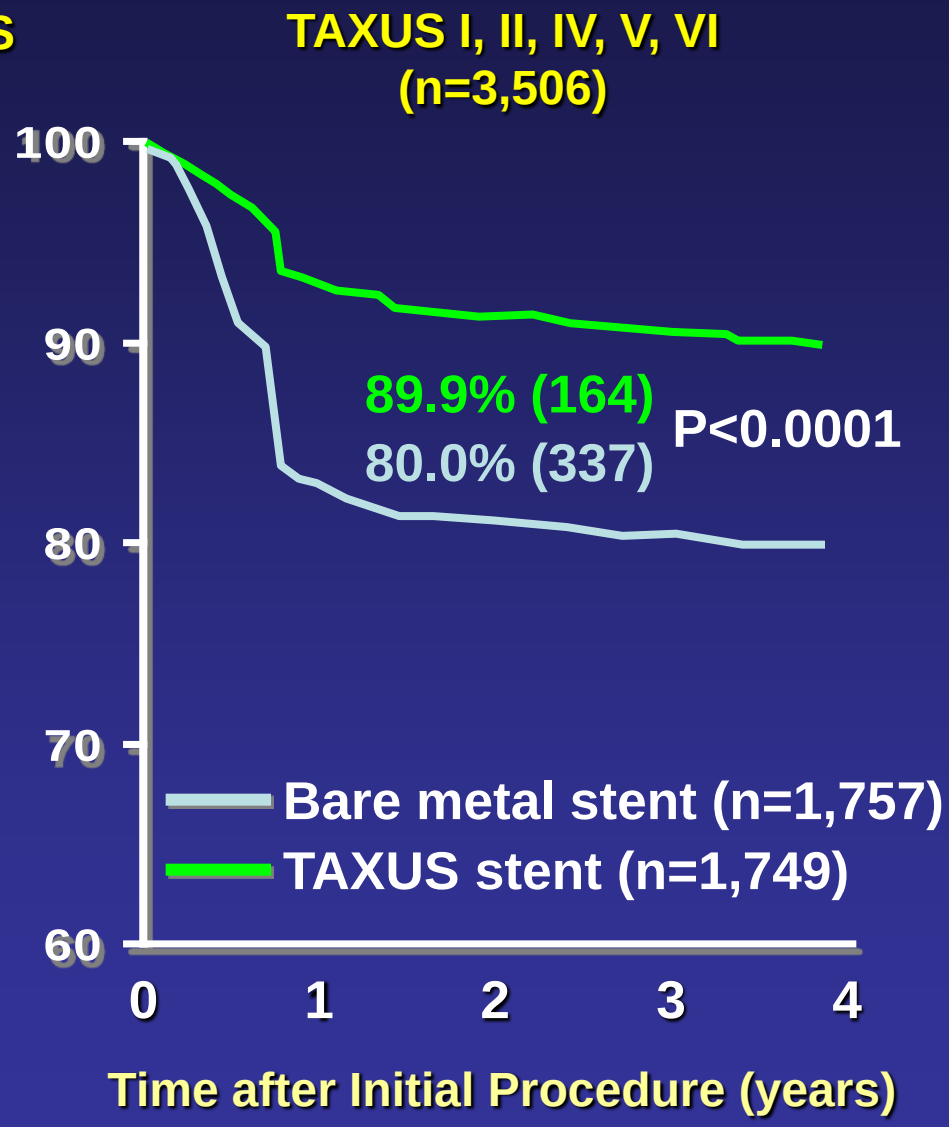
- To eliminate excess the neointimal proliferation that occurs with bare metal stents compared to balloon angioplasty

Restenosis 20-30%

9 Prospective, Double-Blind, Randomized Trials

Freedom From Ischemic TLR





Independent CRF patient-level meta-analysis from TCT 2006

Very Late Stent Thrombosis
Initial Cases and Discussion: Lancet 2004

Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paxlitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted. If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

McFadden EP et al. Lancet 2004; 364:1519–21

Time Frame of Stent Thrombosis

How did we get here?

0 day	to 1 day	Acute stent thrombosis
>1 day	to 1 month	Subacute stent thrombosis
>1 month	to 1 year	Late stent thrombosis
	> 1 year	Very late stent thrombosis

Acute Stent Thrombosis
Early BMS Experience

ARTICLES

Clinical experience with the Palmaz-Schatz coronary stent. Initial results of a multicenter study

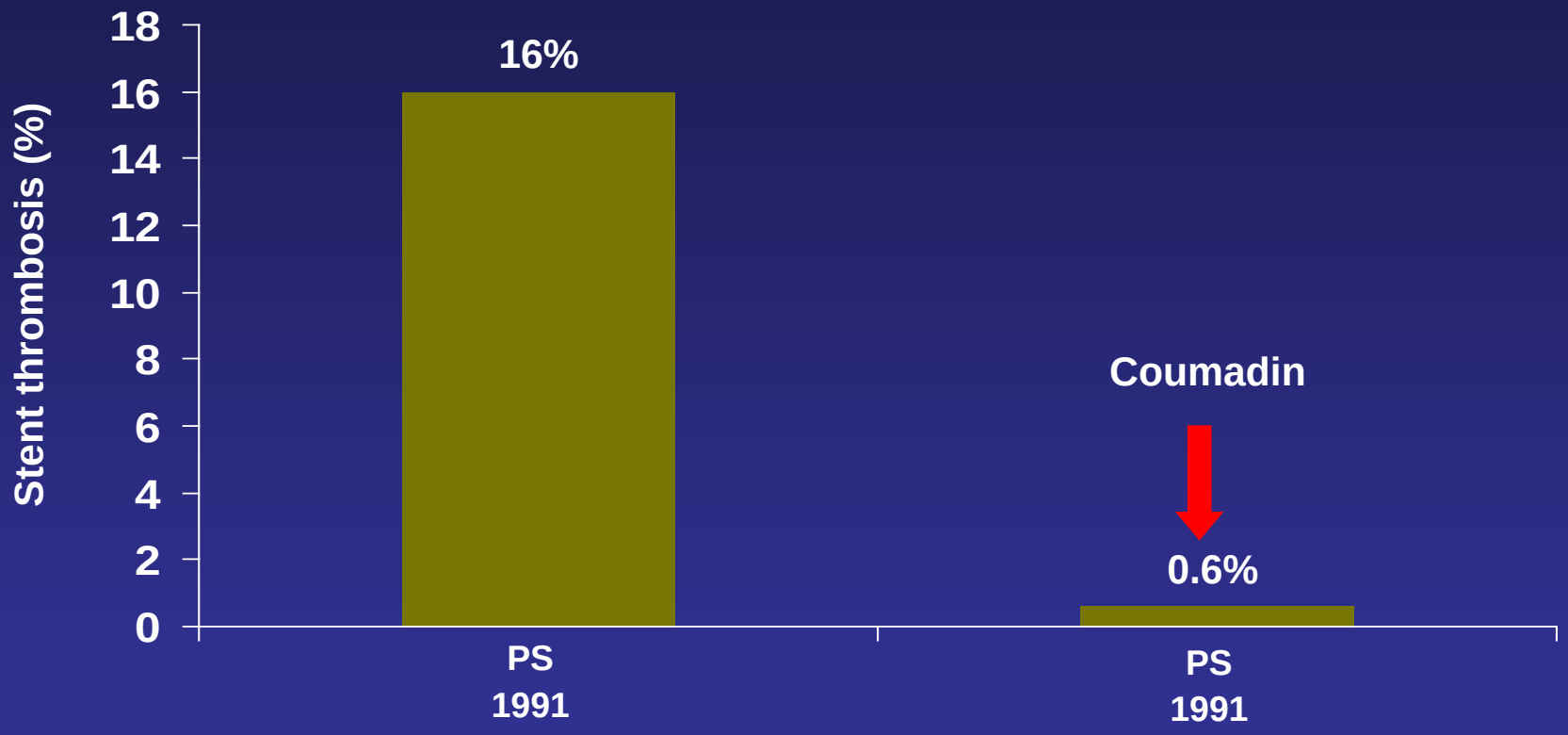
RA Schatz, DS Baim, M Leon, SG Ellis, S Goldberg, JW Hirshfeld, MW Cleman, HS Cabin, C Walker and J Stagg

Cardiology Division, Arizona Heart Institute Foundation, Phoenix.

We conclude that a high delivery success rate can be expected with this device and that clinical thrombosis is less frequent in anticoagulated patients than in nonanticoagulated patients.

Acute Stent Thrombosis

Early BMS Experience: With and Without Anticoagulation



Schatz et al. Circulation.1991;83:148;
Fischman et al. N Engl J Med. 1994;331496;

Early Stent Thrombosis

BMS Era Analysis: Trials Included

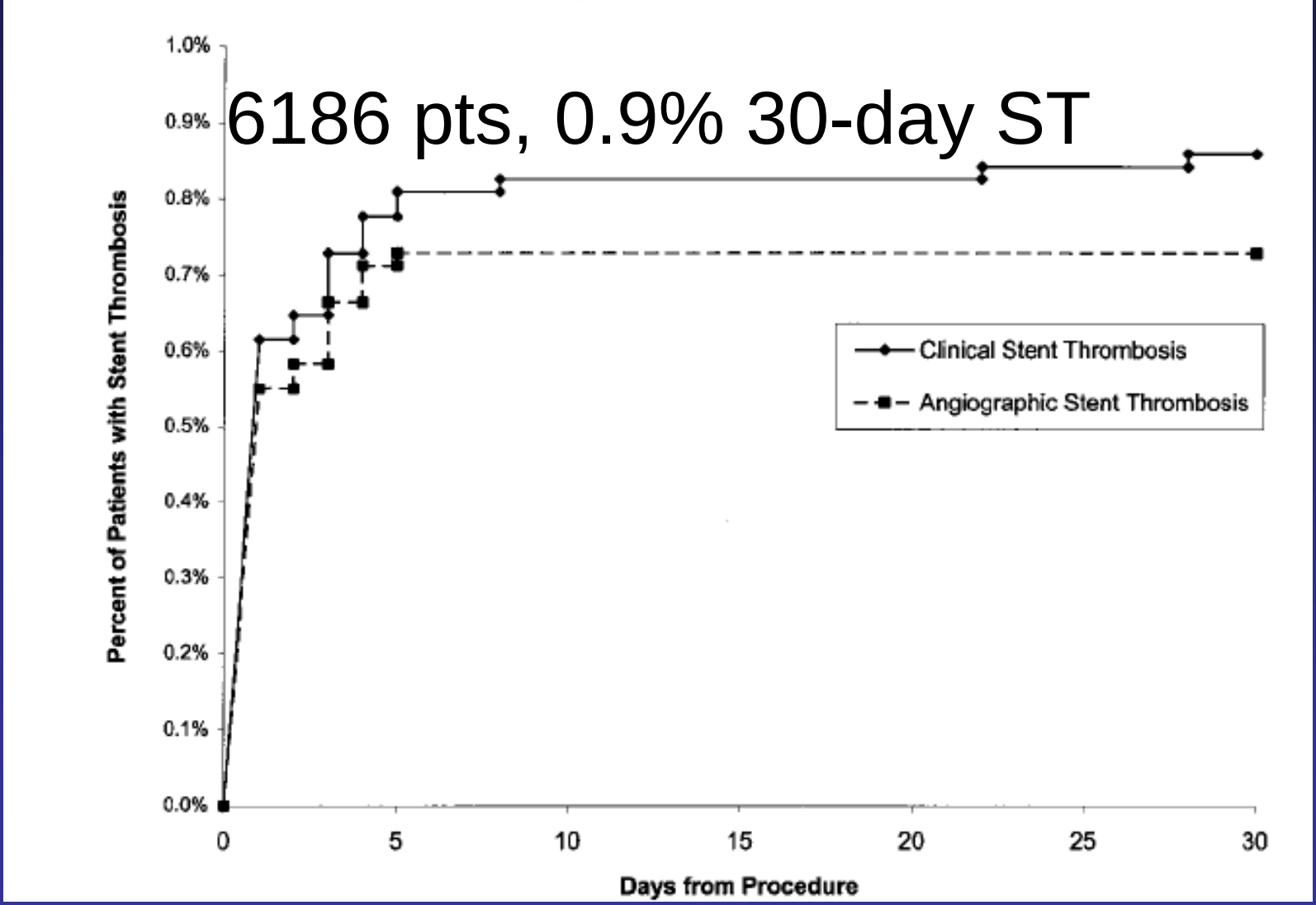
Study Name	Enrollment Period	Stent Types (Randomized), n	Registries (Stent Type, n)
STARS	9/95–10/96	Palmaz-Schatz, 546	Suboptimal stenting
			(Palmaz-Schatz, 233)
ASCENT	1/96–9/96	MULTILINK, 506	Pilot (Multilink, 143)
		Palmaz-Schatz, 513	Restenosis (Multilink, 198)
			RX/Long lesion (Multilink RX, 202)
SMART	1/96–5/97	Microstent, 326	Long lesion (Microstent, 159)
		Palmaz-Schatz, 320	Continuation (Microstent, 203)
			GFX stent (GFX, 229)
NIRVANA	1/97–5/97	NIR, 416	Pilot (NIR, 109)
		Plamaz-Schatz, 423	Abrupt/threatened closure (NIR, 193)
EXTRA	3/97–9/98	XT, 327	Pilot (XT, 143)
		Palmaz-Schatz, 313	Abrupt/threatened closure (XT, 28)
			Premounted (XT, 161)
CCS	5/98–3/99		(Crossflex LC, 495)

STARS indicates Stent Antithrombotic Regimen Study; ASCENT, ACS MultiLink Stent Clinical Equivalence Trial; SMART, Study of Micro Stent Ability to Limit Restenosis Trial; NIRVANA, NIR Vascular Advanced North American Trial; EXTRA, Evaluation of XT Stent for Restenosis in Native Coronary Arteries; and CCS, Crossflex Coronary Stent.

Cutlip et al: Circulation 2001;103;1967-1971

Early Stent Thrombosis

BMS Era: Results to 30 days



Cutlip et al: Circulation 2001;103;1967-1971

Early Stent Thrombosis
BMS Era:

Stent Thrombosis in the Modern Era

A Pooled Analysis of Multicenter Coronary Stent Clinical Trials

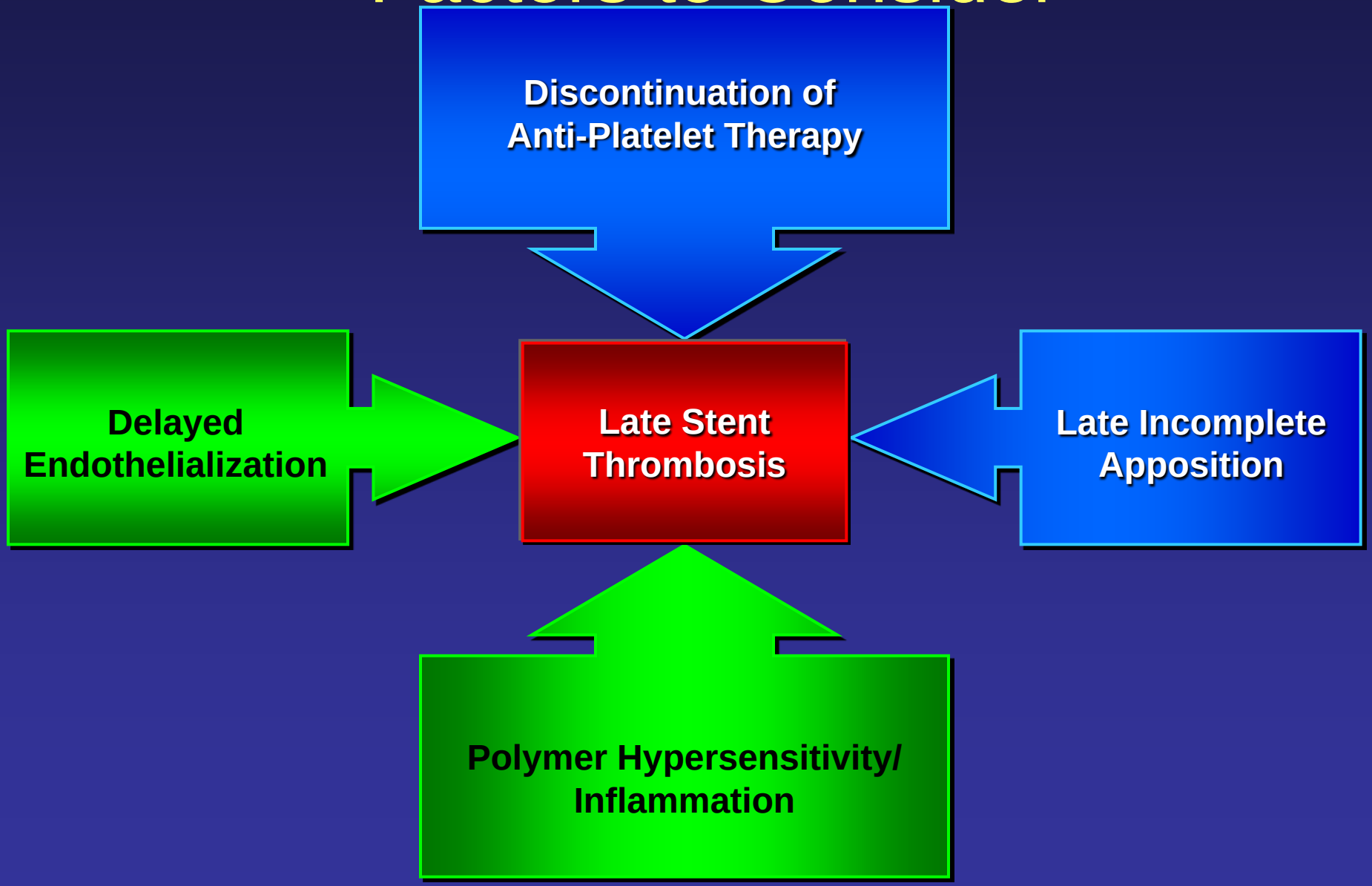
Donald E. Cutlip, MD; Donald S. Baim, MD; Kalon K.L. Ho, MD, MSc; Jeffrey J. Popma, MD;
Alexandra J. Lansky, MD; David J. Cohen, MD; Joseph P. Carrozza, Jr, MD;
Manish S. Chauhan, MD; Orlando Rodriguez, MD; Richard E. Kuntz, MD, MSc

Background—There are limited studies of stent thrombosis in the modern era of second-generation stents, high-pressure deployment, and current antithrombotic regimens.

Methods and Results—Six recently completed coronary stent trials and associated nonrandomized registries that enrolled 6186 patients (6219 treated vessels) treated with ≥1 coronary stent followed by antiplatelet therapy with aspirin and ticlopidine were pooled for this analysis. Within 30 days, clinical stent thrombosis developed in 53 patients (0.9%). The variables most significantly associated with the probability of stent thrombosis were persistent dissection NHLBI grade

Conclusions—Stent thrombosis occurred in ,1.0% of patients undergoing stenting of native coronary artery lesions and receiving routine antiplatelet therapy with aspirin plus ticlopidine. Procedure-related variables of persistent dissection,total stent length, and final lumen diameter were significantly associated with the probability of stent thrombosis.

Late Stent Thrombosis—Factors to Consider



Polymer Biocompatibility Issues

ELSEVIER

Cardiovascular Research

Cardiovascular Research 63 (2004) 617–624

www.elsevier.com/locate/cardiores

Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model

Andrew J. Carter[a,*], Meenakshi Aggarwal[b], Gregory A. Kopia[c], Fermin Tio[d], Philip S. Tsao[b], Ron Kolata[c], Alan C. Yeung[b], Gerald Llanos[c], Joh

[a] Providence Heart and Vascular Institute, Providence St. Vincent Medic
Portland, OR 97225-5218, USA
[b] Stanford University Medical Center, Stanford,
[c] Cordis Co., Warren, NJ, USA
[d] University of Texas at San Antonio Health Sciences Center,
[e] Ethicon Endo-Surgery, Inc., Cincinnati, OH

Received 1 March 2004; received in revised form 31 March 20
Available online 5 June 2004
Time for primary review 19 days

ELSEVIER

Cardiovascular Research

Editorial

The Cypher stent: no longer efficacious at three months in the porcine model?

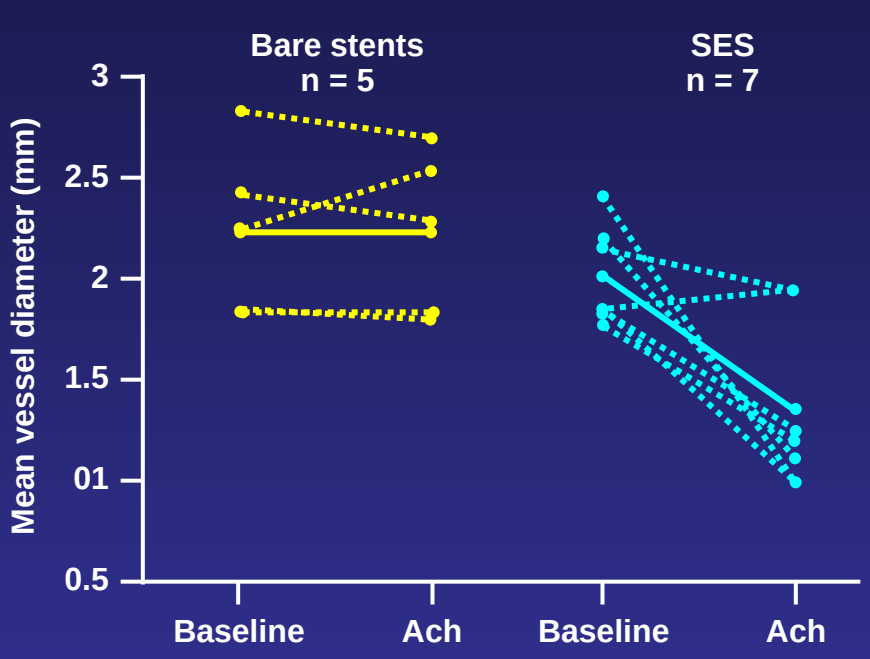
Antoine Lafont*

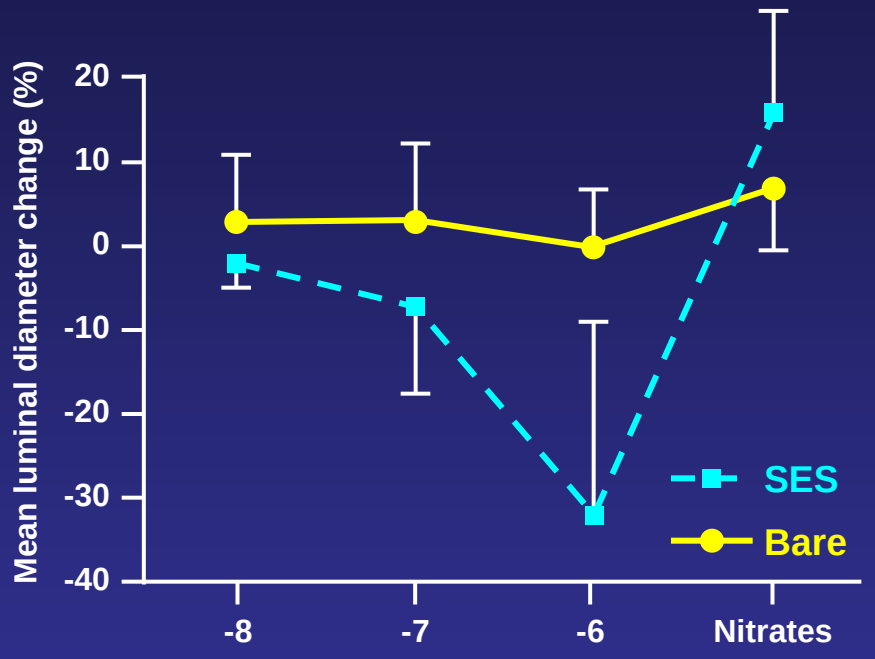
Once the drug is eluted from the stent, the remaining polymer if not biocompatible, may stimulate inflammation and late intimal development.

Carter, AJ et al. *Cardiovas Res*. 2004;63:617.
Lafont, A. *Cardiovas Res.* 2004;63:575.

Functional Endothelium

SES vs BMS



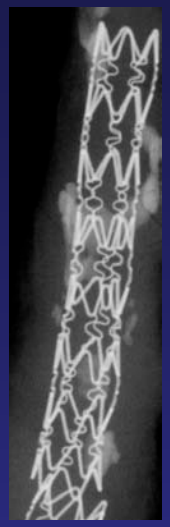


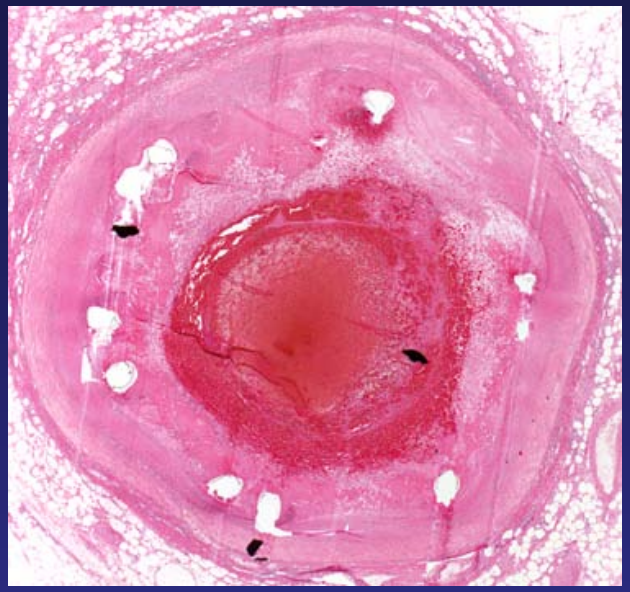
Conclusion:

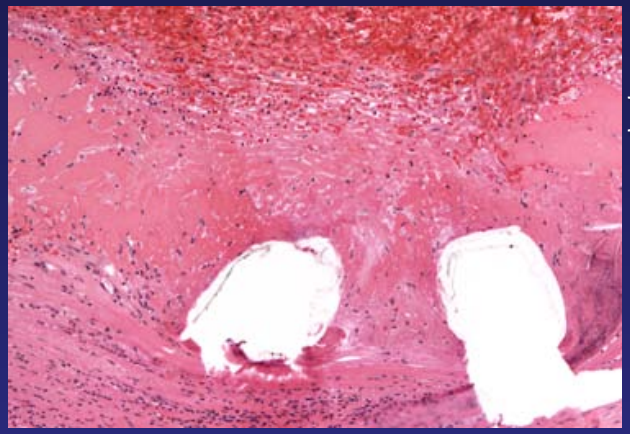
- BMS SES implantation may have an adverse effect on local endothelium-dependent vasomotor responses six months after SES compared to BS implantation

S.H. Hofma et al. *EHJ*. 2005.

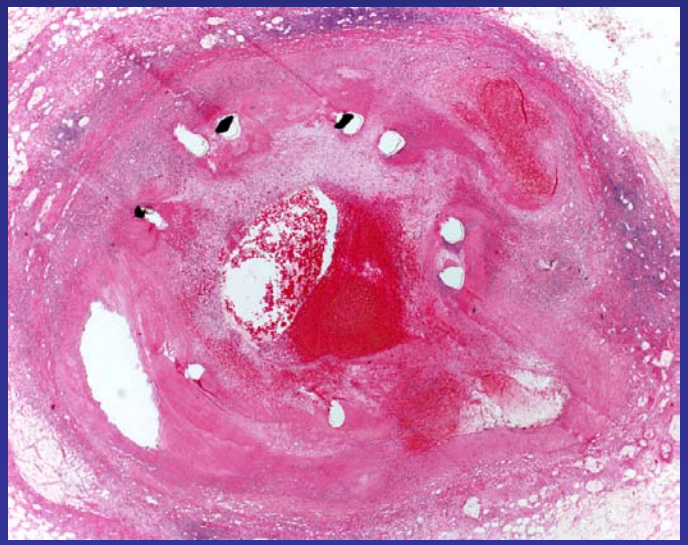
Late Stent Thrombosis 18 Months Post-SRL Stent Due to Hypersensitivity



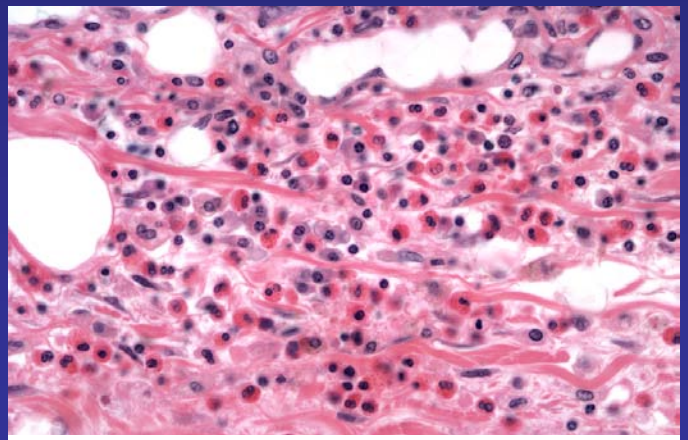




Impaired healing + Hypersensitivity (most likely to polymer)



Late DES thrombosis with aneurysm



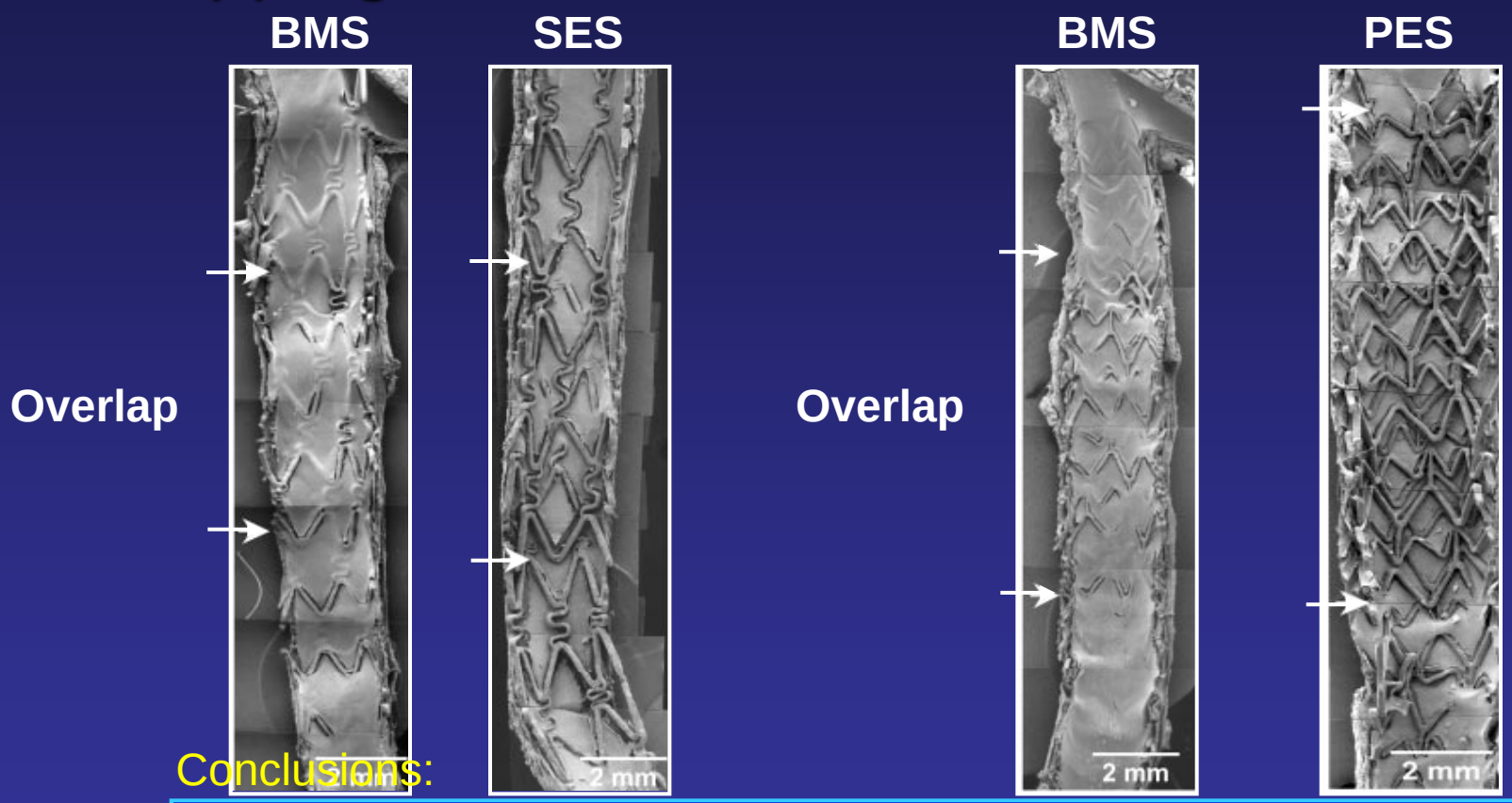
Marked chronic inflamm + eos

Iatrogenic SRL-Stent Induced Hypersensitivity, Aneurysm Formation, & Thrombosis

Virmani, Guagliumi, Farb
Circ 2004;109:701

Delayed Endothelialization

Overlapping SES vs PES



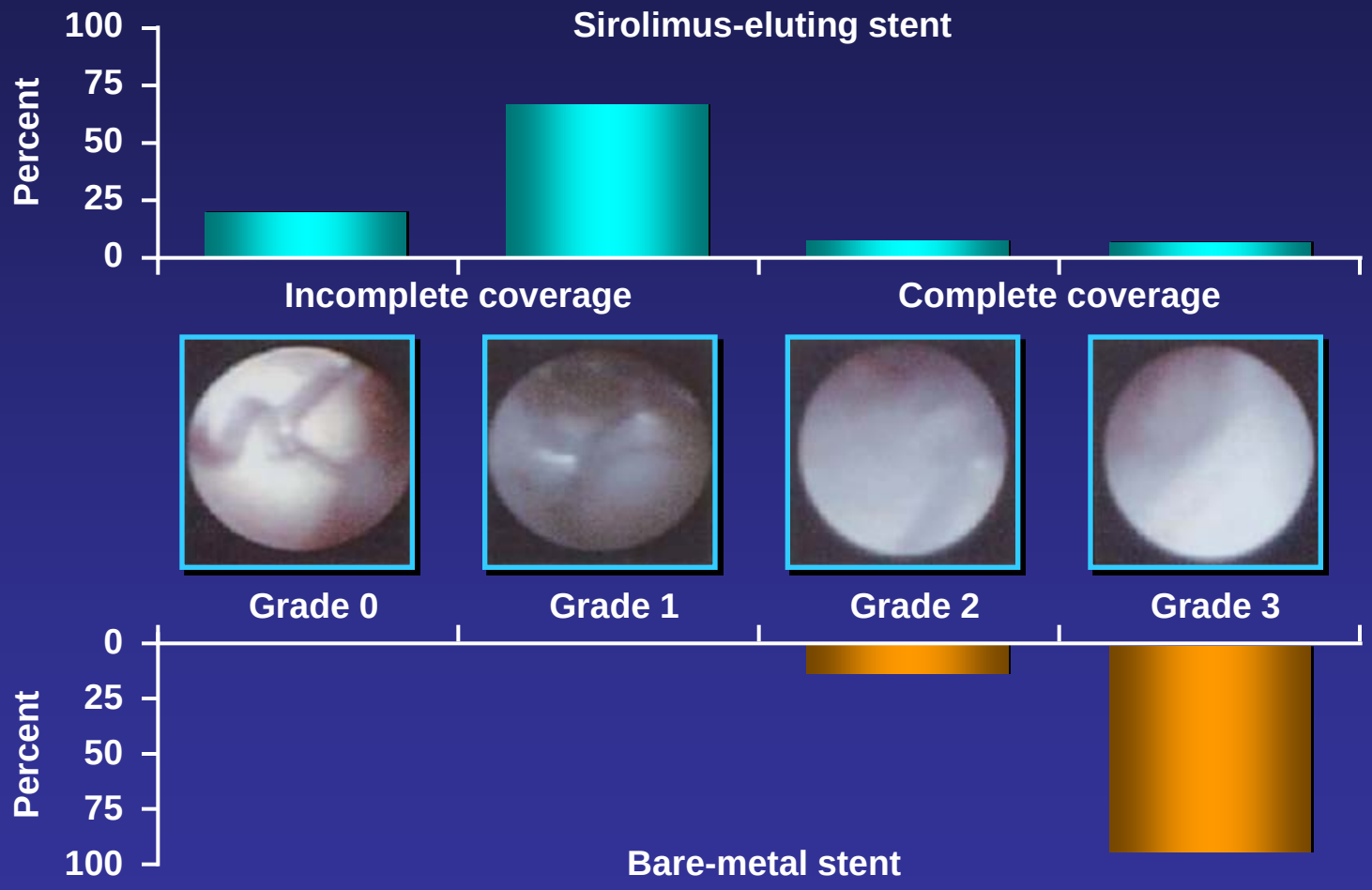
Conclusions:

- BMS showed far greater endothelialization than DES
- Lack of coverage highlighted in areas of overlap
- Less surface coverage by endothelial cells in PES than SES

Finn et al. (Circulation. 2005;112:270-278.)

Exposed Stent Struts at 6 Months

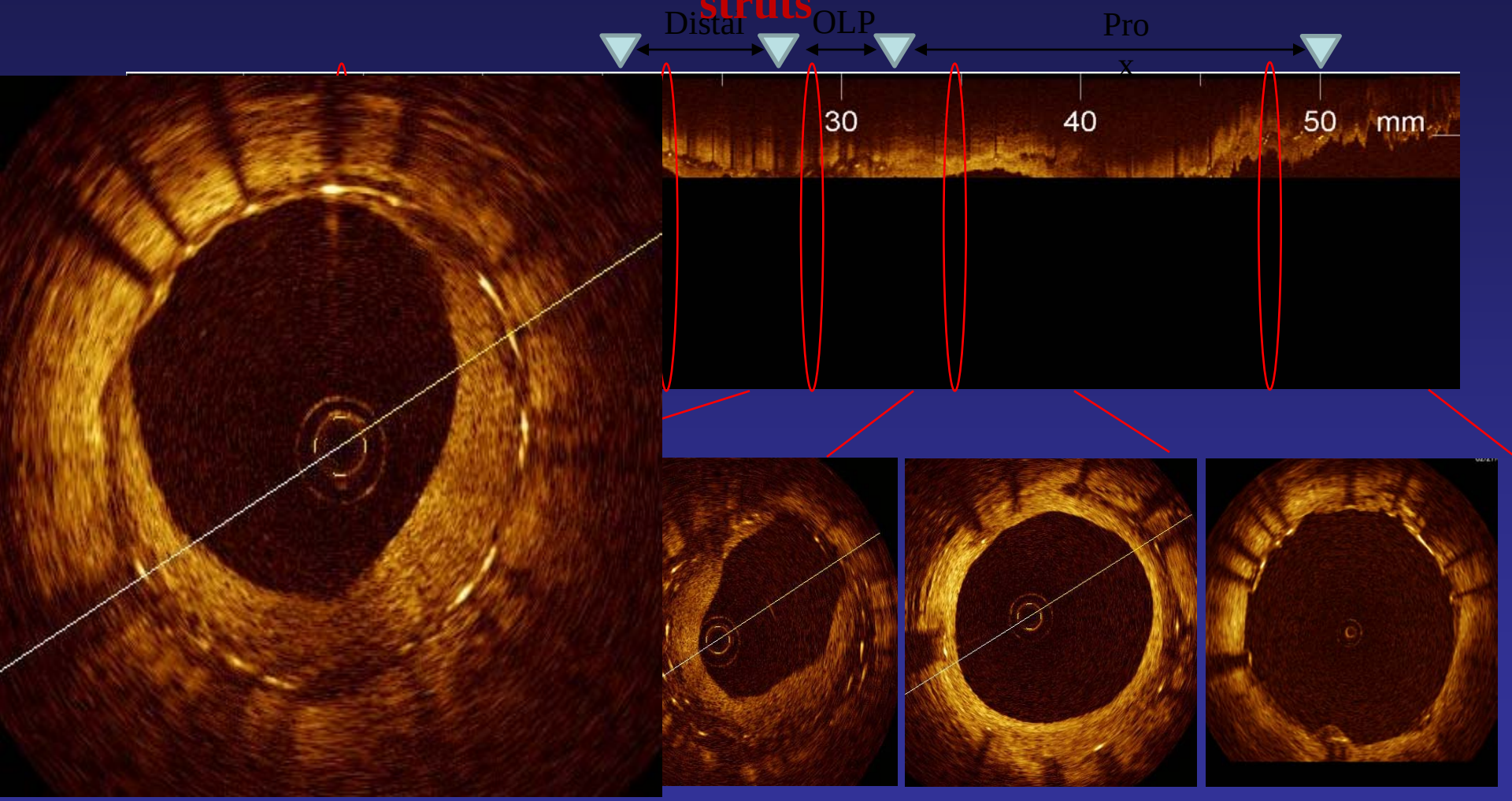
>80% Cypher Struts Exposed vs. BMS Struts



Kotani et al. JACC Vol. 47, No. 10, 2006.

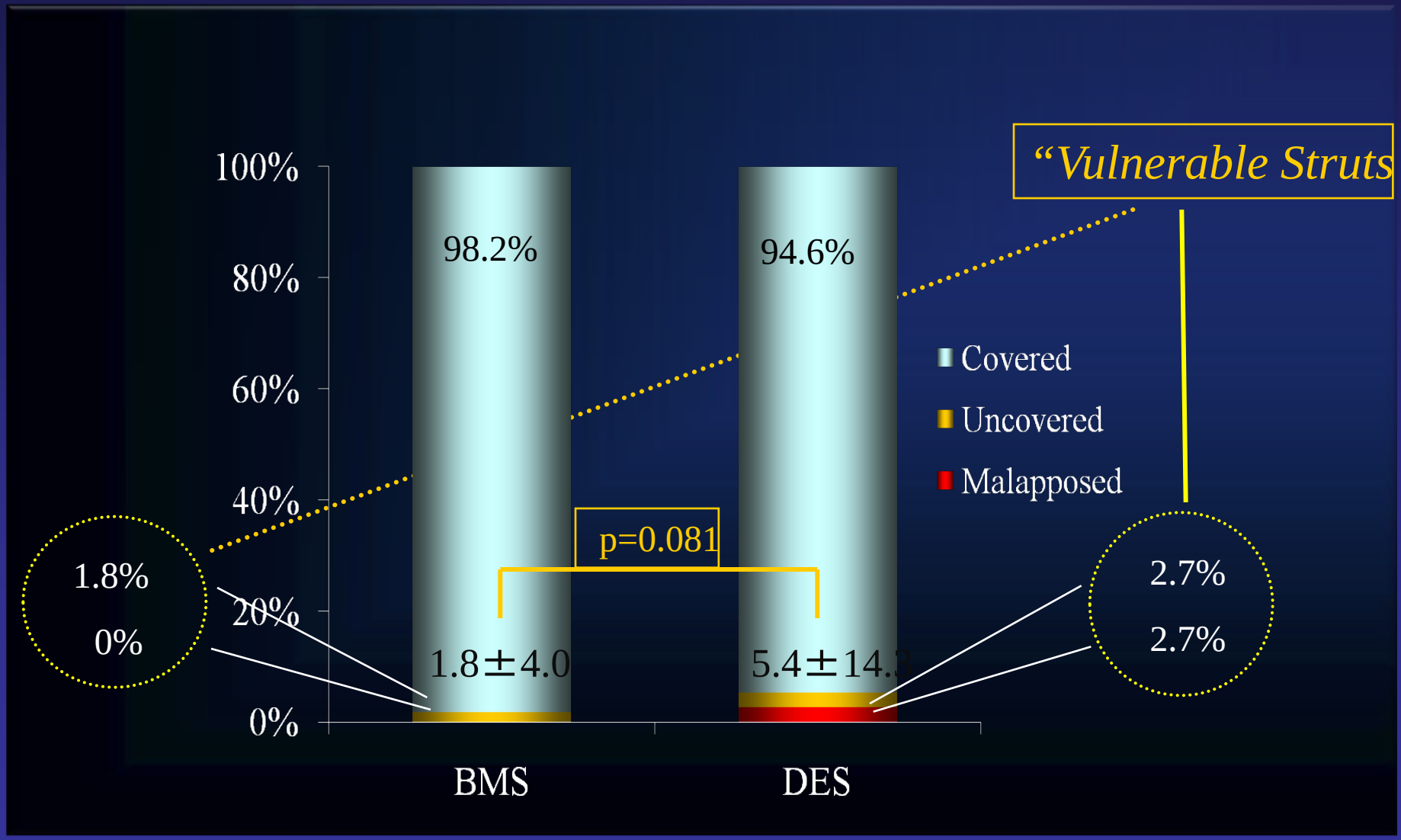
Six Month OCT: 75/76 eligible patients

Analyzed: 250 stented segments every 0.3 mm (6968 cross-sections) , 53.047 struts



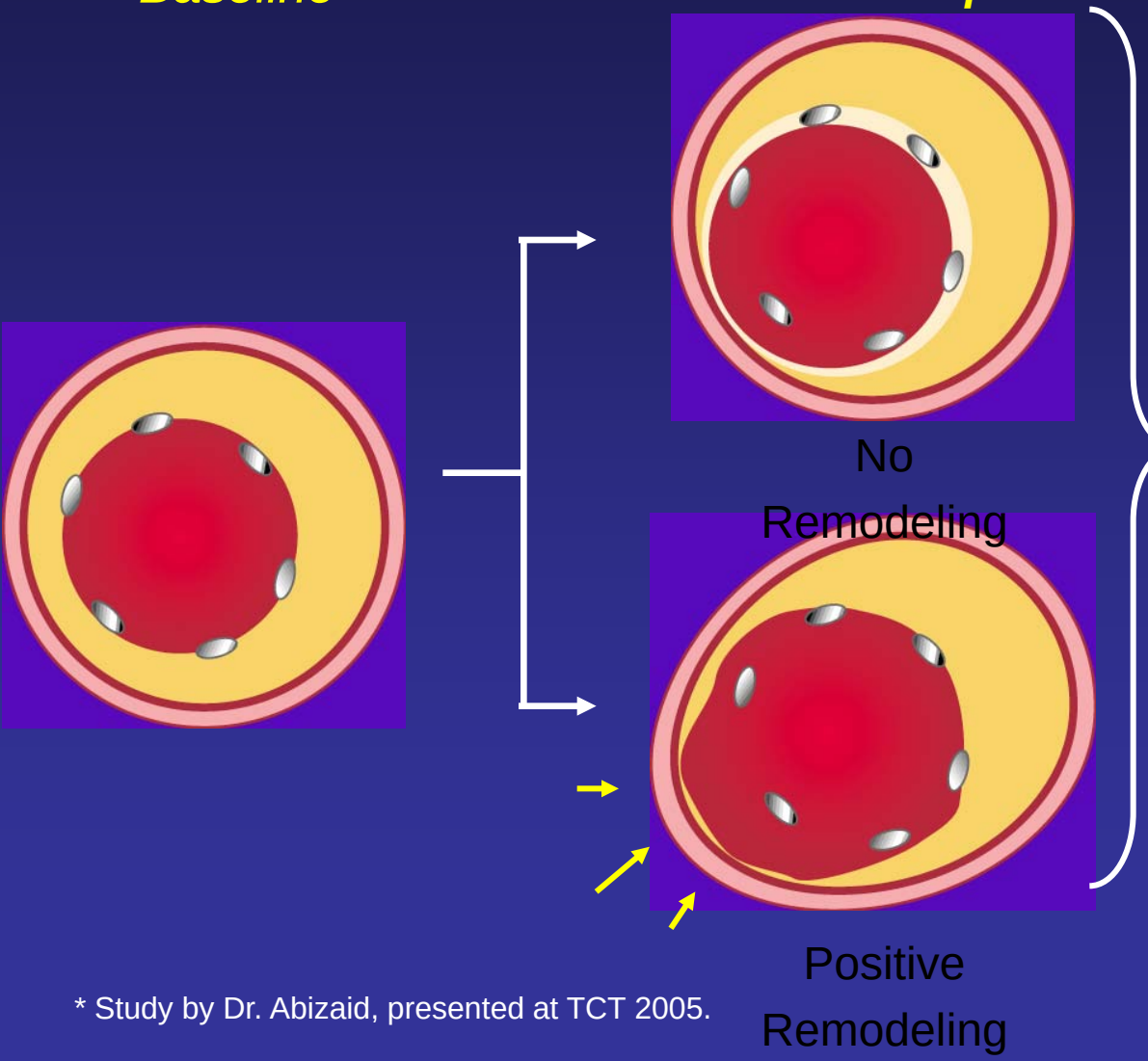
Ospedali Riuniti di Bergamo

Primary Endpoint: Overlap
Proportion of uncovered and/or malapposed struts in BMS vs DES



Late-Incomplete Apposition

Potential for Stent Thrombosis



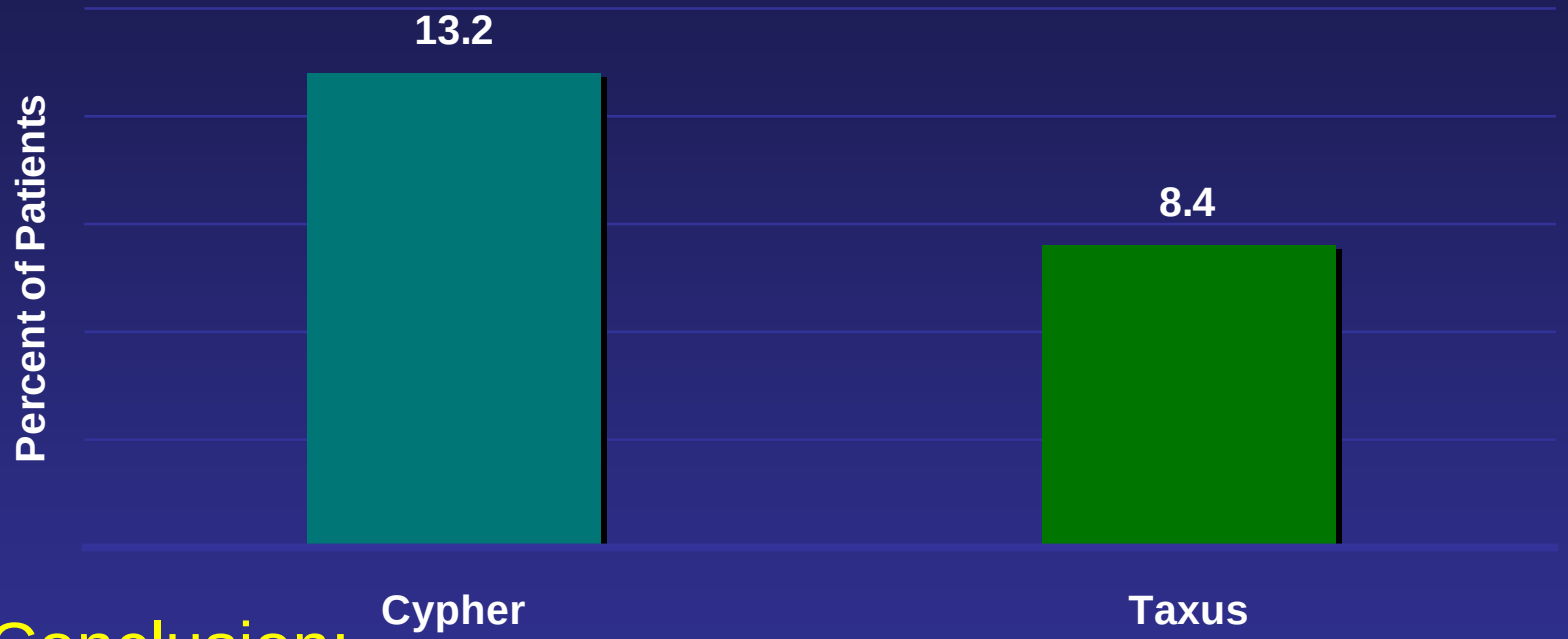
In a Taxus and Cypher study of patients with late incomplete apposition upon clopidogrel discontinuation:

20% had stent thrombosis*

* Study by Dr. Abizaid, presented at TCT 2005.

Incomplete Late Stent Apposition

Frequency and Implications



Conclusion:

- LIA occurs in 12% of cases after DES implantation
- The predictors of LSM are total stent length, primary stenting in acute myocardial infarction, and chronic total occlusion lesions

*Hong M.K. et al. *Circulation.* 2006;113:414-419.

Correlates of DES Thrombosis

Moreno, JACC 45:954, 2005
N=5030 (10 RCT)

- **Number of stents/patient**
- **Total stent length**

Iakovou and Colombo, JAMA 293:2126, 2005
N=2229 (3 Centers)

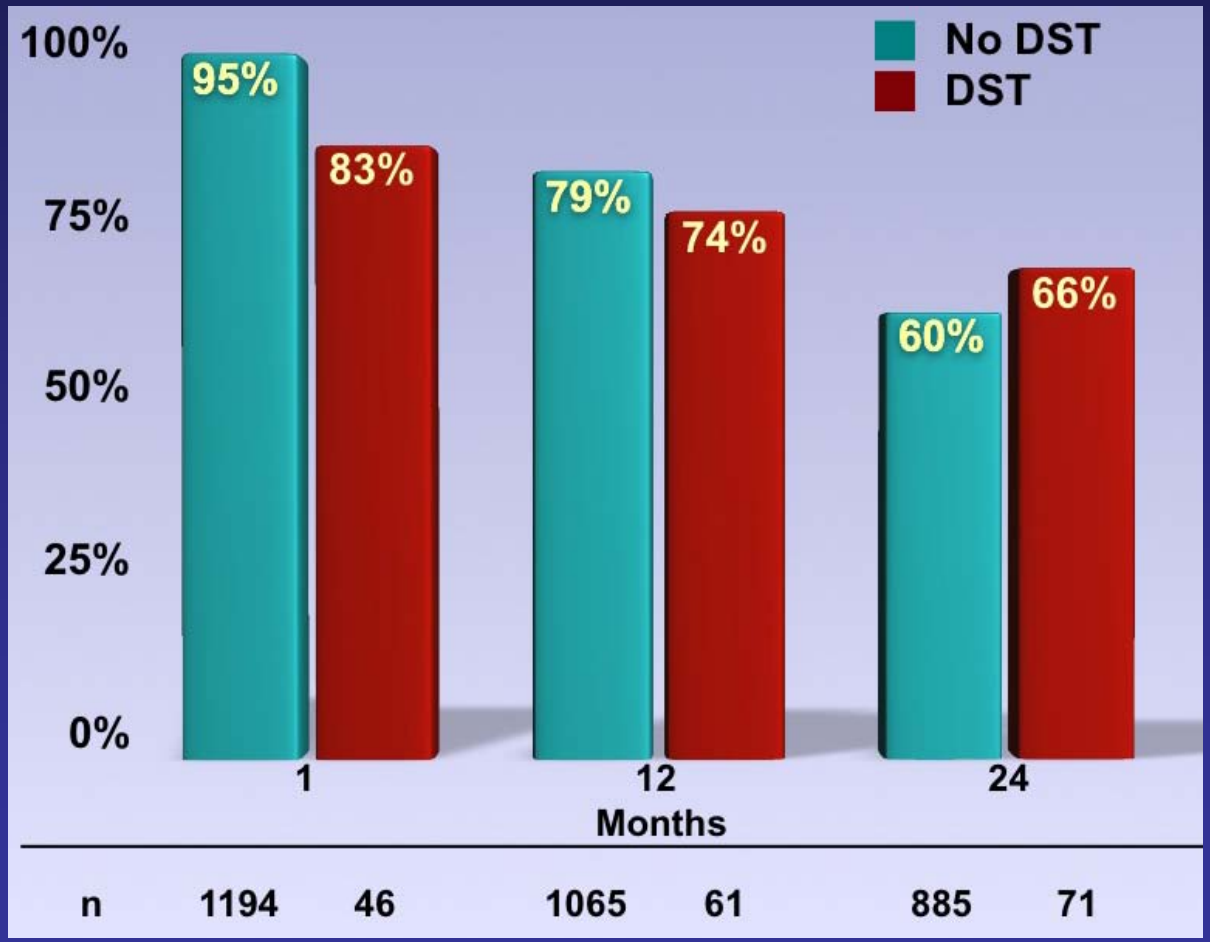
- **Premature antiplatelet rx d/c**
- **Renal failure**
- **Bifurcation lesion**
- **Diabetes**
- **↓ LVEF**

Kuchulakanti, Circulation 113:1108, 2006

- **Discontinuation of clopidogrel**
- **Renal failure**
- **Bifurcation lesions**
- **In-stent restenosis**

Washington Hospital Center

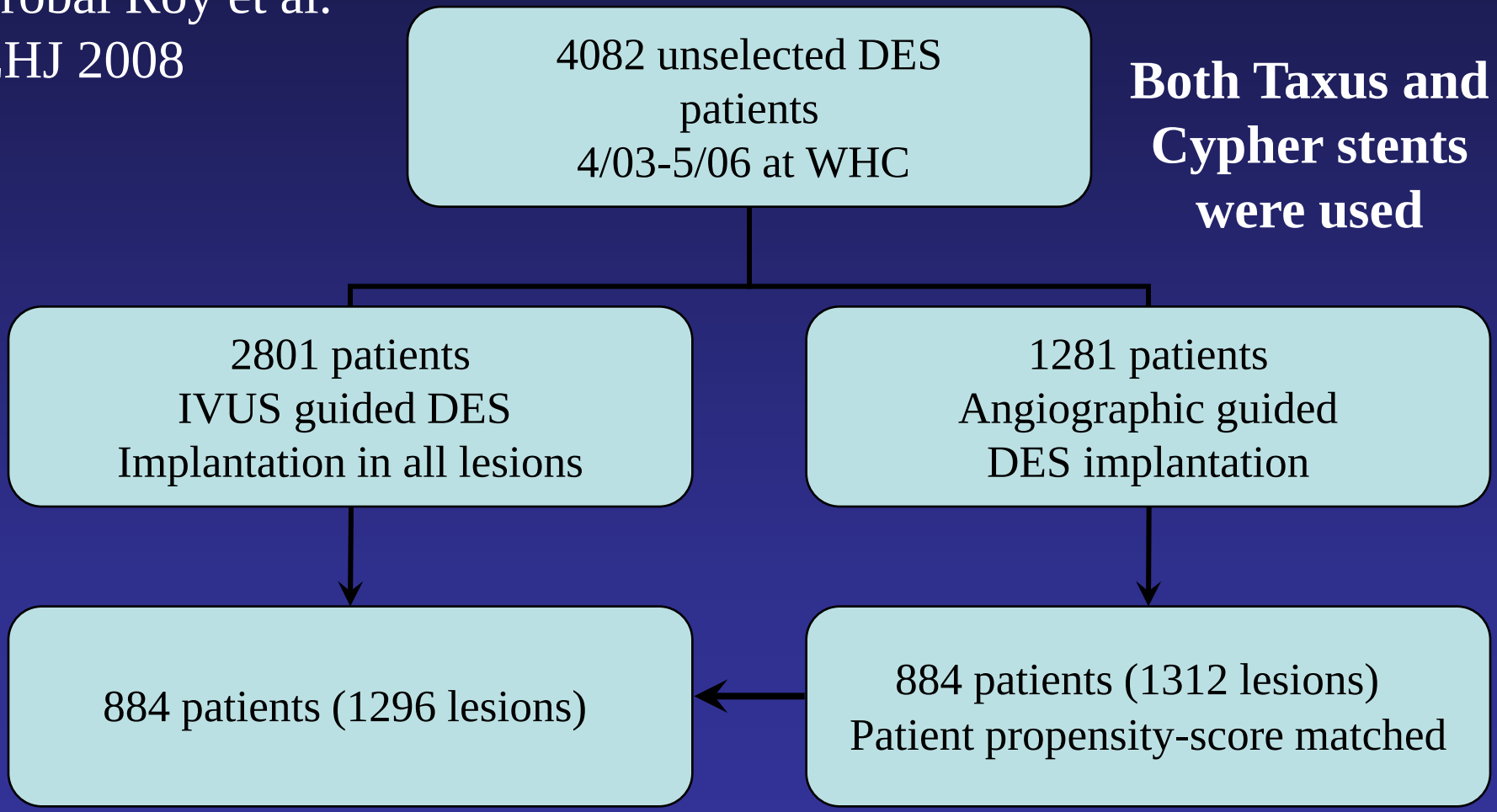
Clopidogrel Compliance



Pinto Slottow, TL et al. *Incidence and Correlates of Stent Thrombosis*

WHC Experience DES with and without IVUS

Probal Roy et al.
EHJ 2008



All patients completed 12 month clinical follow up

Probal Roy, et al. EHJ 2008 30 Day and 12 Months Outcomes

	IVUS (n=884)	No IVUS (n=884)	p Value
30-day Outcomes, n (%)			
Major adverse cardiac events	25 (2.8%)	46 (5.2%)	0.01
Death	15 (1.7%)	29 (3.3%)	0.03
Cardiac death	6 (0.7%)	14 (1.6%)	0.07
Q-wave myocardial infarction	6 (0.7%)	12 (1.4%)	0.15
Target vessel revascularization	10 (1.1%)	17 (2.0%)	0.17
Target lesion revascularization	6 (0.7%)	15 (1.7%)	0.045
Cumulative stent thrombosis	**4 (0.5%)**	**12 (1.4%)**	**0.045**
12-month Outcomes, n (%)			
Major adverse cardiac events	128 (14.5%)	143 (16.2%)	0.32
Death	50 (5.7%)	62 (7.1%)	0.23
Cardiac death			0.18
Q-wave myocardial infarction			0.21
Target vessel revascularization			0.69
Target lesion revascularization			**0.06**
Definite stent thrombosis			**0.014**
Probable stent thrombosis			**0.08**

Stent Thrombosis is Multi-Factorial

Lesion

Complexity, disease, healing:

- Long lesions
- Small vessels
- Multi-vessel, Multi stent
- AMI
- Diabetics
- Bifurcations

Technical

Operator Dependent:

- Under expansion
- Incomplete wall apposition
- Crush technique
- Vessel Preparation

Patient

Premature Antiplatelet Discontinuation

- Plavix® compliance
- Upcoming surgery
- Plavix® non responsive
- Plavix allergy /intolerance

DES

Injury & healing:

- Strut thickness
- Stent design (scaffolding/conformability)
- Polymer
- Drug and elution profile
- Stent delivery system
- Adequate or proper stent expansion

Modified from Honda and Fitzgerald, Circulation 2003:108, 2
Kereiakes D., et. al Rev Cardiovasc Med: 2004; 5 (1): 9-15

Defining Stent Thrombosis

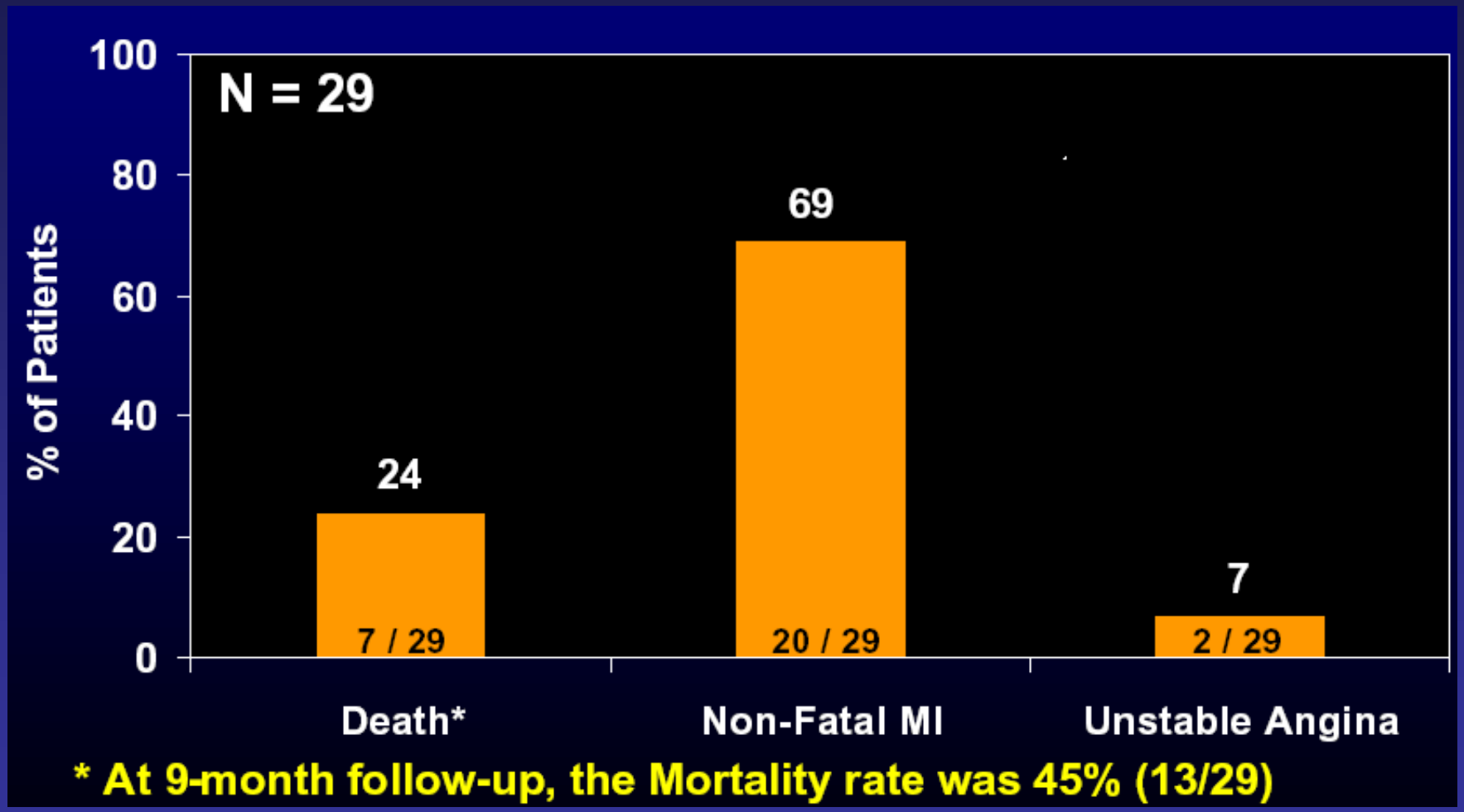
Clinical Presentation

- Most cases are dramatic.
  - Sudden death
  - Ventricular fibrillation
  - Large MI

Death or Large MI
>70%

- Are late silent occlusions also stent thrombosis?
  - Stenting to post-MI non-viable myocardium
  - Collateralized territory
    - Occlusion is usually sudden
    - Absent recent prior ischemia or preconditioning

Presentation with DES Thrombosis



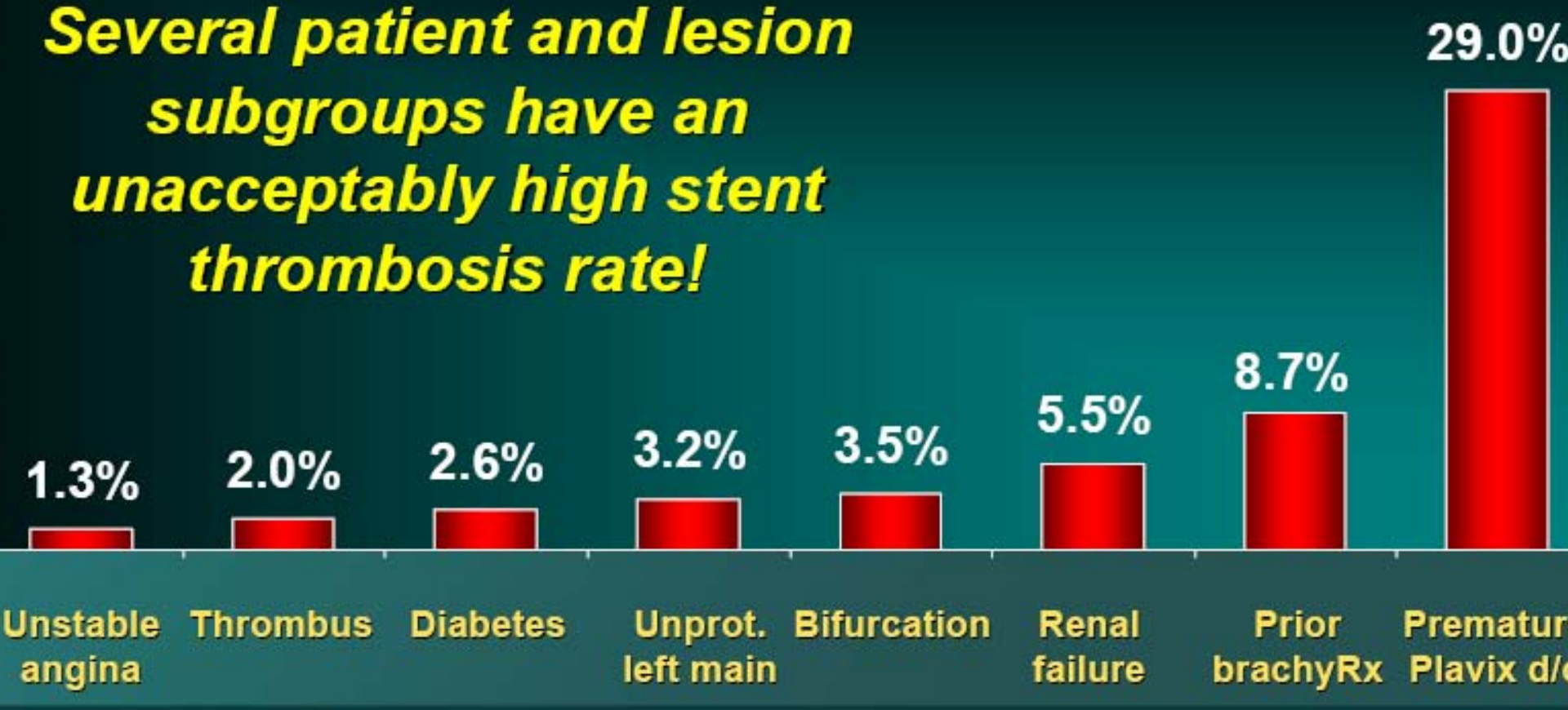
Iakovou: JAMA 2005; 293: 2126-30

Milan/Siegburg Experience

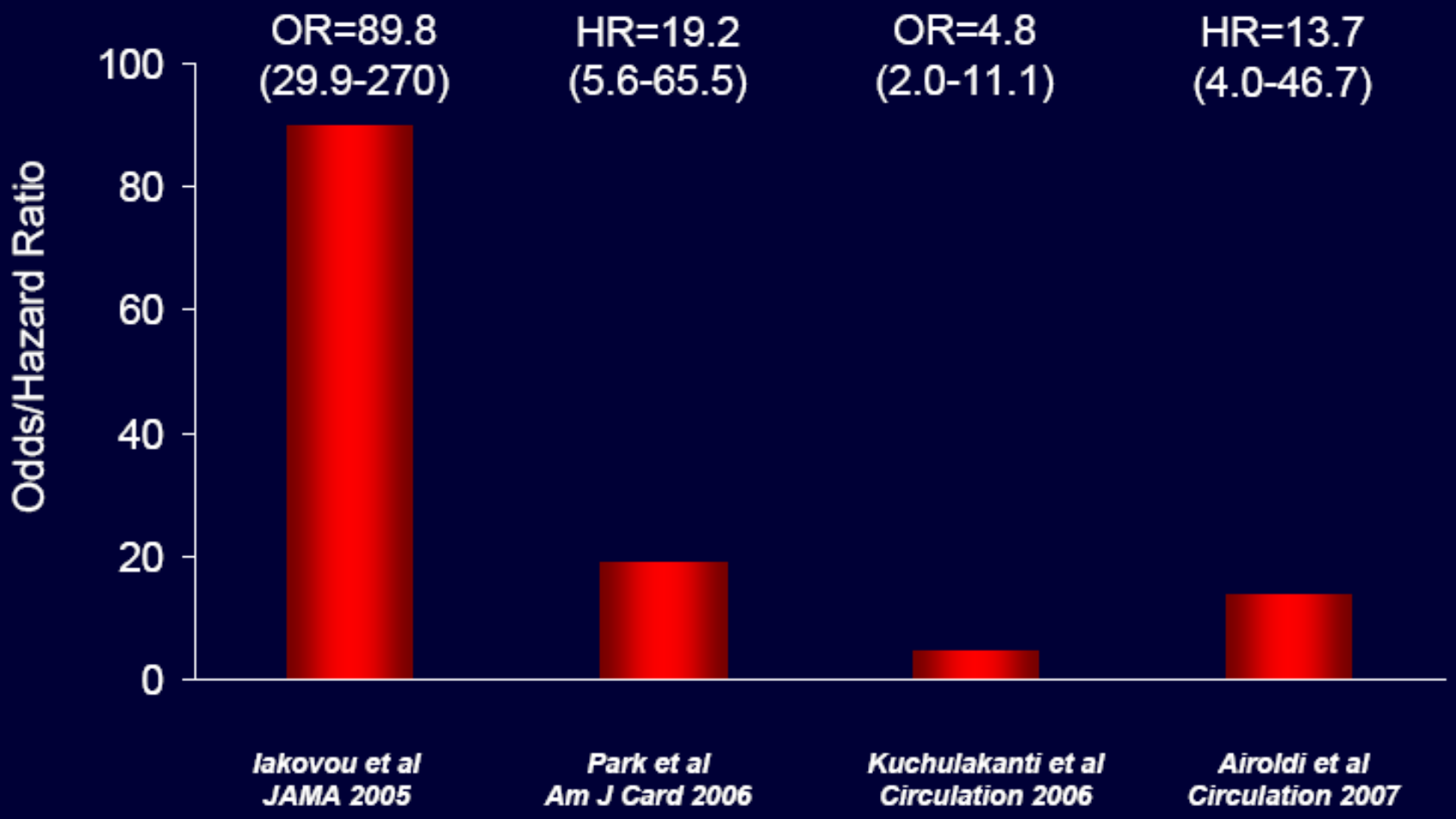
Stent thrombosis after DES (SES or PES) occurred in 29/2229 pts (1.3%) at 9.3±5.6 mos

Iakovou et al. JAMA 2005;293:2126-2130

Several patient and lesion subgroups have an unacceptably high stent thrombosis rate!

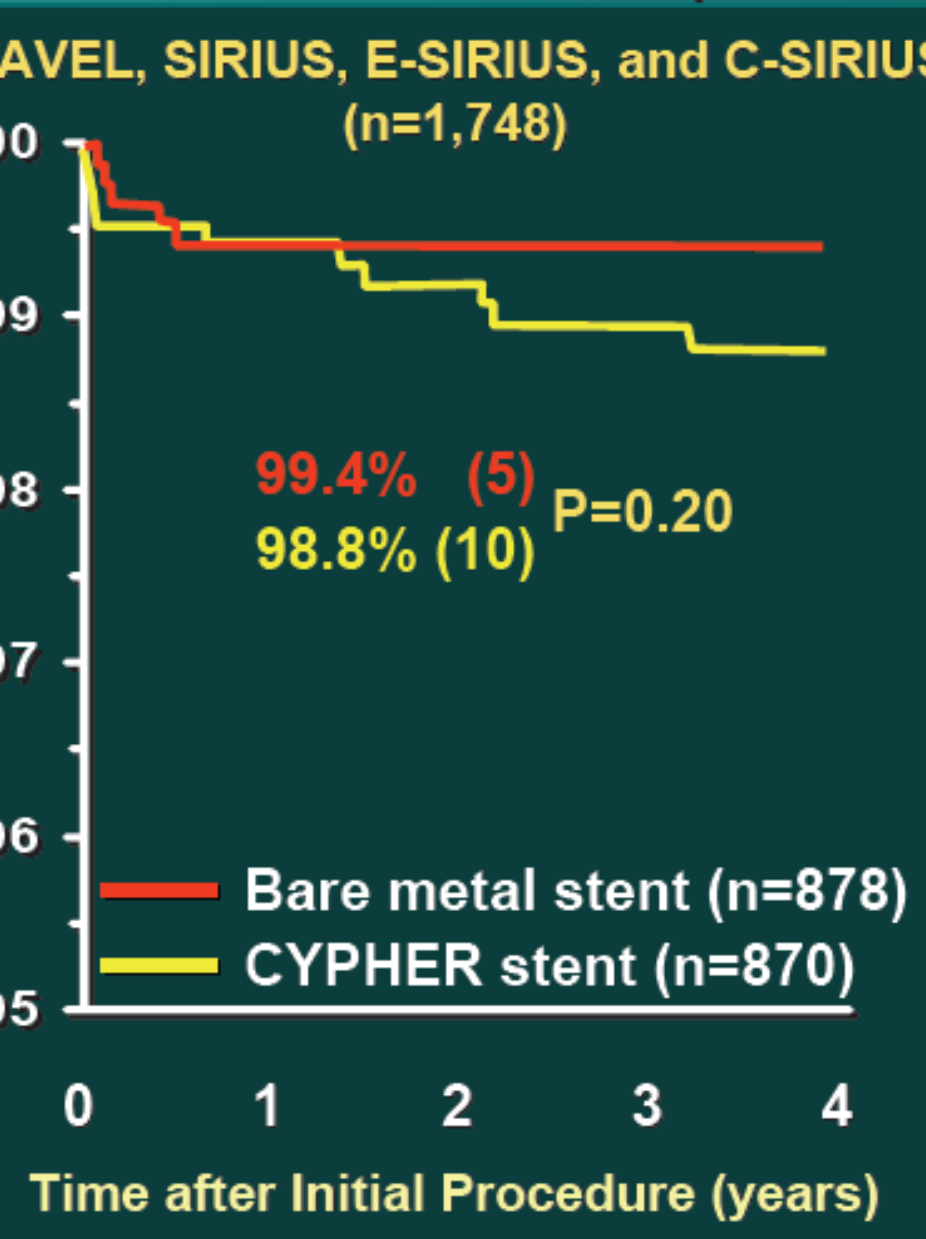


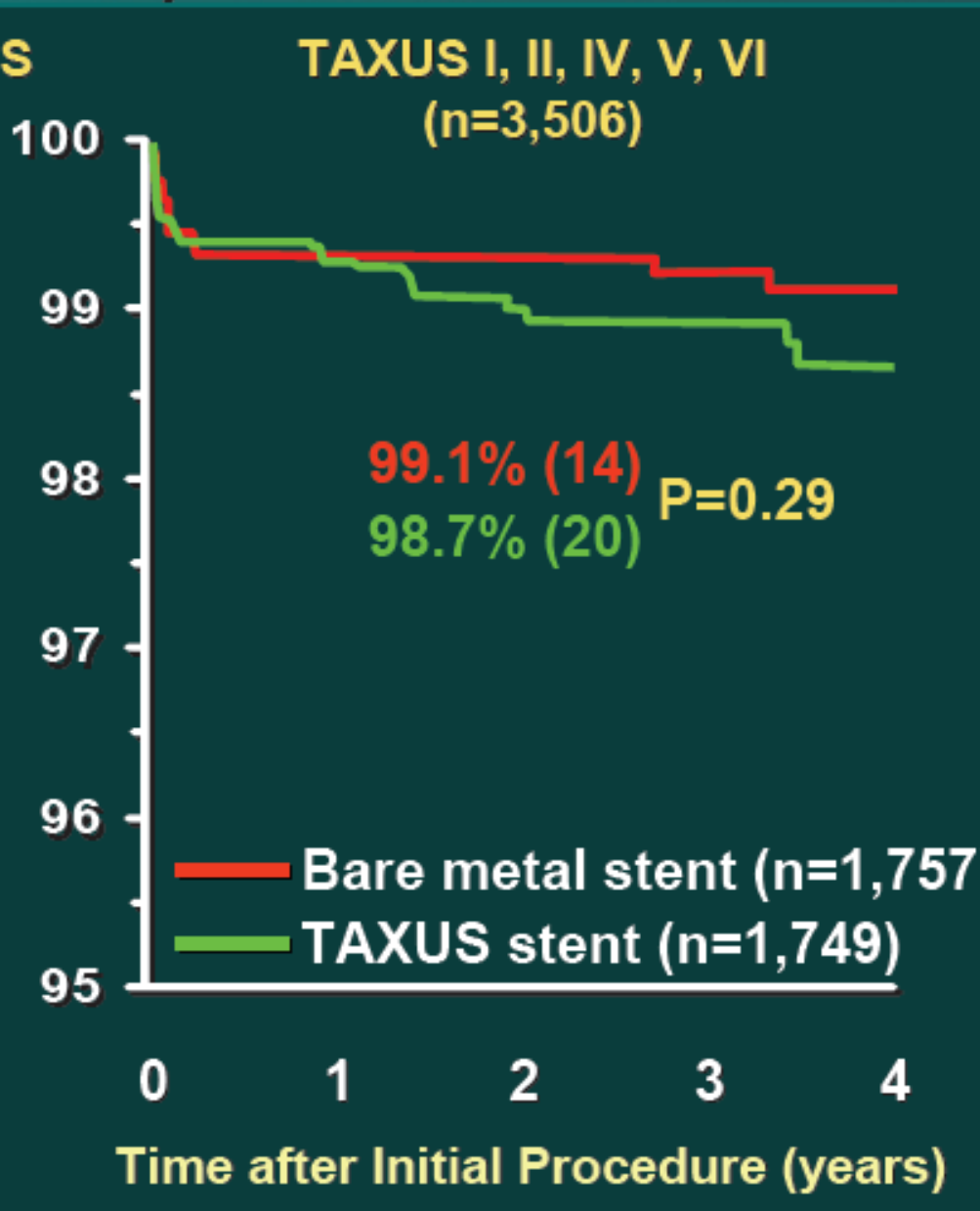
Premature Discontinuation of Antiplatelet Therapy as Predictor of Stent Thrombosis



9 Prospective, Double-Blind, Randomized Trials

Freedom From (Protocol) Stent Thrombosis





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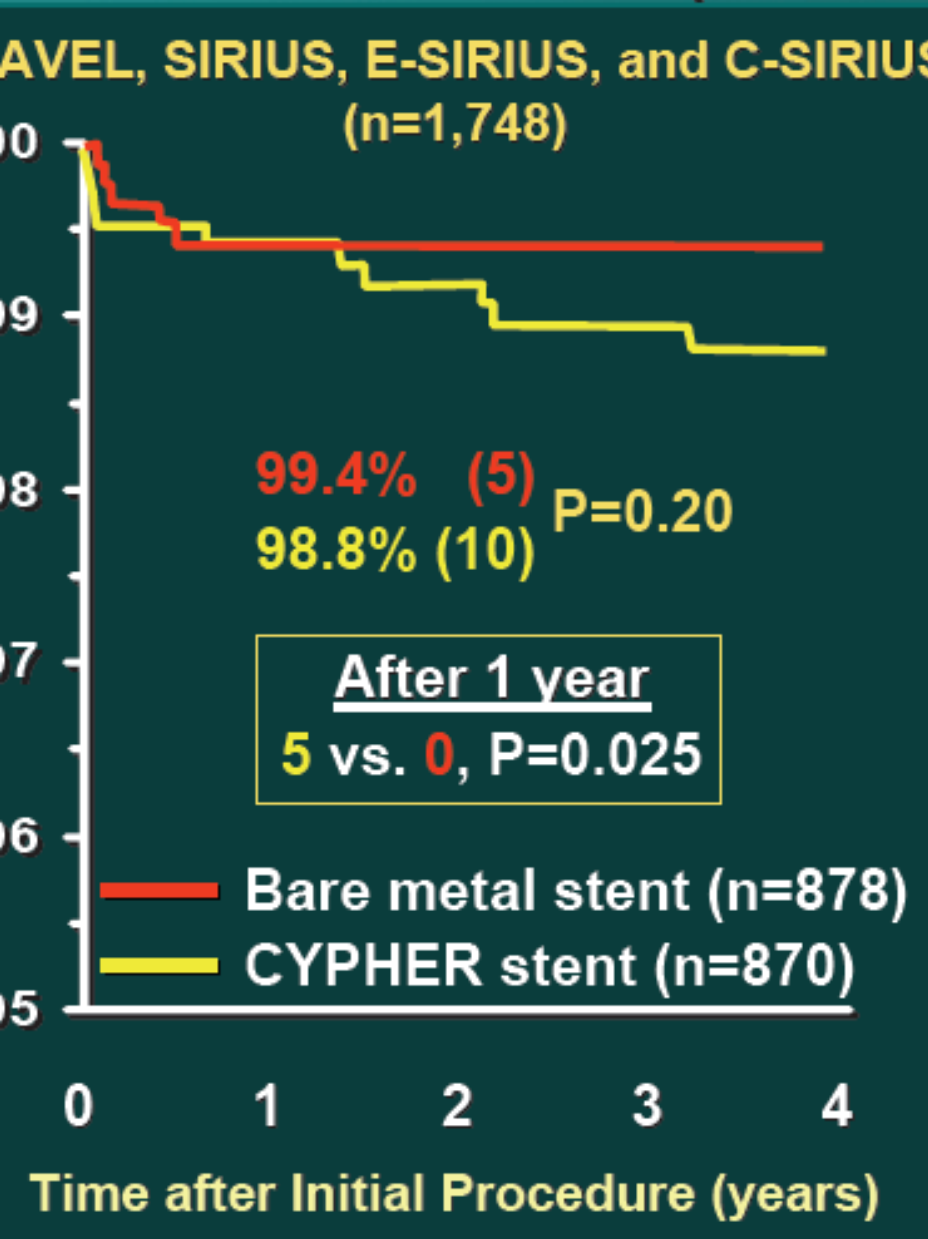
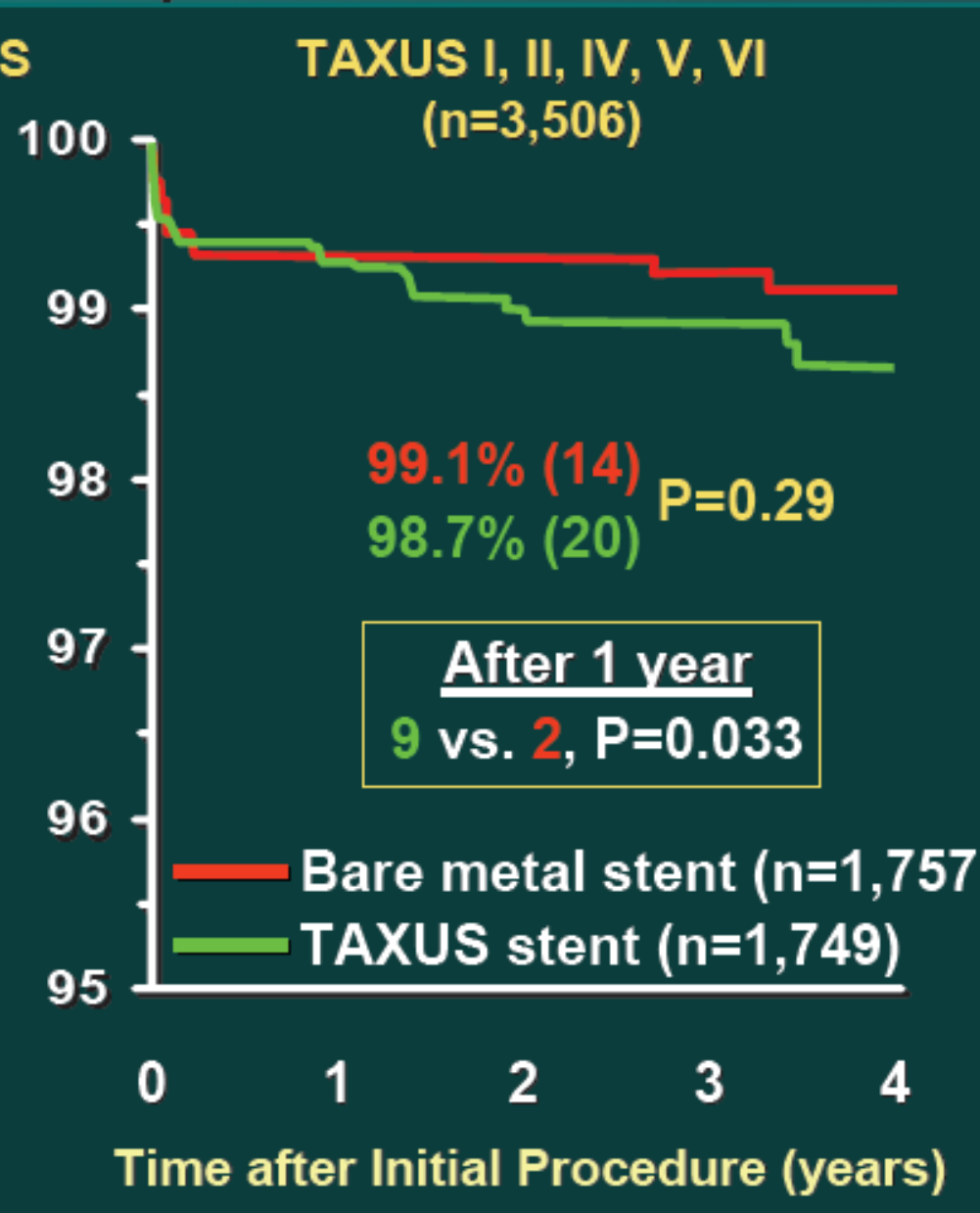
Freedom From (Protocol) Stent Thrombosis





ARC Proposed Standard Definitions

- **Definite/Confirmed**
  - Acute coronary syndrome AND
  - [Angiographic confirmation of thrombus or occlusion OR
  - Pathologic confirmation of acute thrombosis]
- **Probable**
  - Unexplained death within 30 days
  - Target vessel MI without angiographic confirmation of thrombosis or other identified culprit lesion
- **Possible**
  - Unexplained death after 30 days

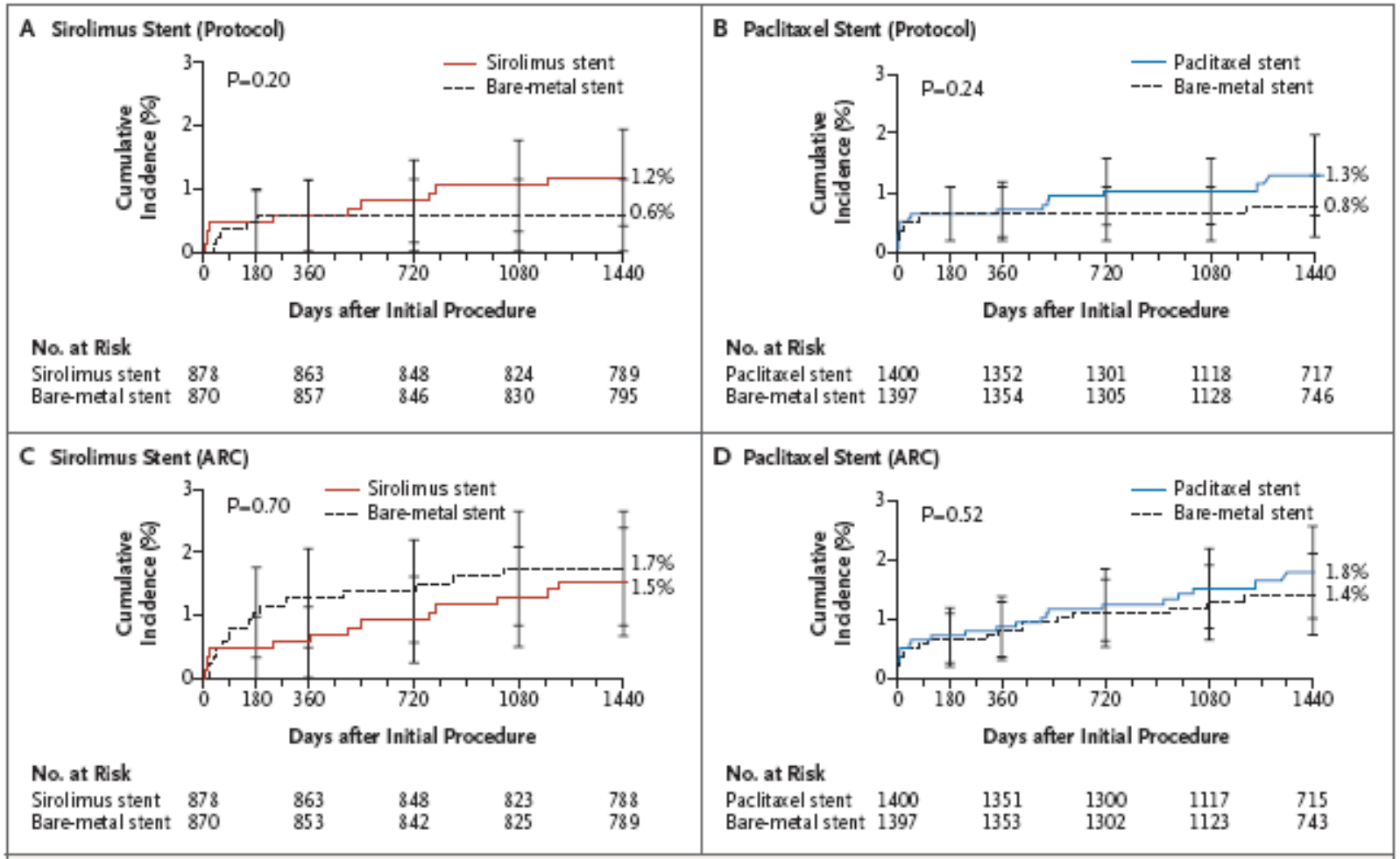


Figure 1. Cumulative Incidence of Stent Thrombosis at 4 Years after Implantation of FDA-Approved Drug-Eluting Stents, According to Definitions Used in Trial Protocol versus ARC Definite or Probable Categories.

Panels A and B show comparisons of the incidence of stent thrombosis in patients with sirolimus-eluting stents and paclitaxel-eluting stents, as compared with bare-metal stents, according to the definition of stent thrombosis used in the original cohort trials. Panels C and D show data from the same trials with the definition of definite or probable stent thrombosis recommended by the Academic Research Consortium (ARC). P values were calculated by the log-rank test. I bars indicate 95% confidence intervals.

revascularization vs. 1.1% of those without such ... certained in the trials of sirolimus-eluting stents

DES Thrombosis

Incidence of e-Cypher Registry of 20,503 SES in 15,157 pts

Acute	0.13%
Subacute	0.56%
Late (1-12 mo)	0.19%

Predictors of DES thrombosis

- IDDM
- Advanced age
- Stenting of multiple lesions
- Calcified or total occluded vessel
- ACS
- TIMI < 3
- Multivessel disease

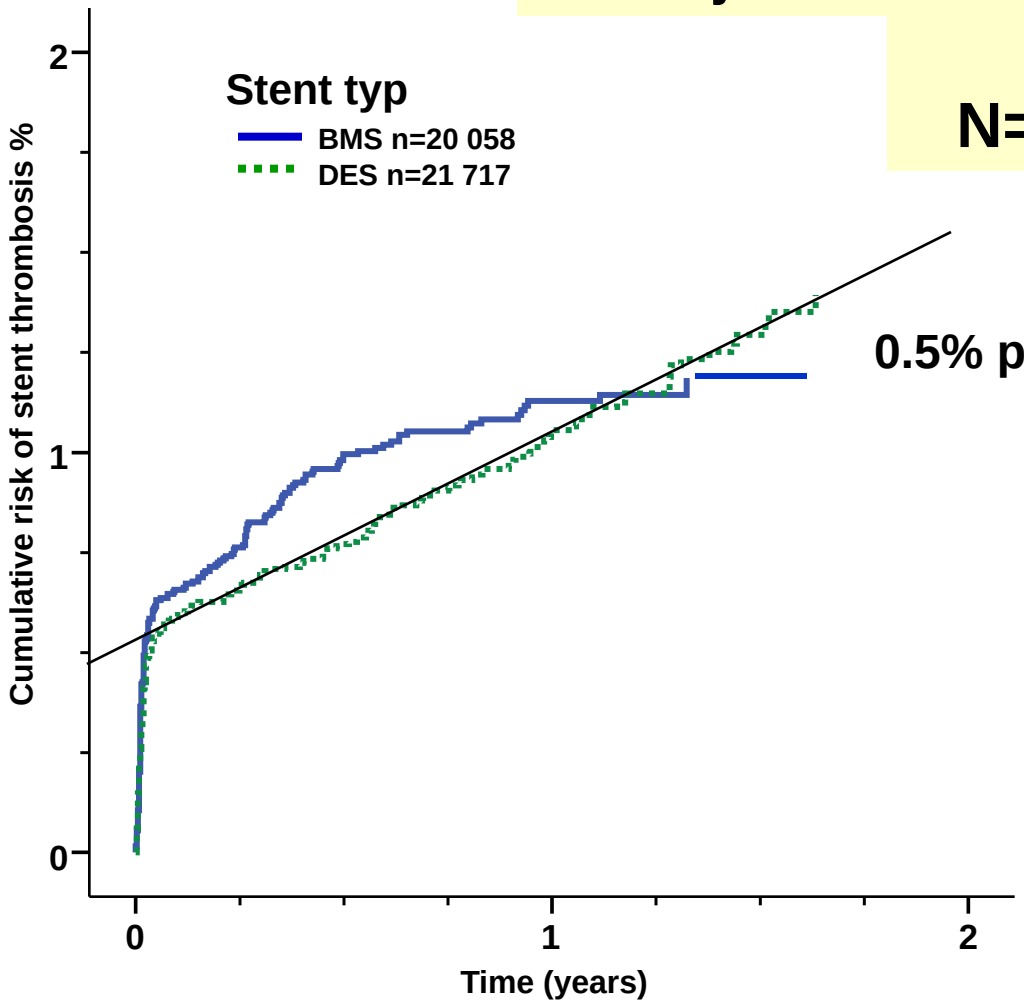
e-Cypher Registry, Circ 2006;113:1434

Stent thrombosis

Unadjusted

Total cohort

N=41 775 stents



0.5% per year

DES: Off-label use

- More complex and unapproved indications
  - Very small vessels and very long lesions
  - Chronic total occlusions
  - Bifurcations
  - Left main disease
  - In-stent restenosis
  - Multivessel disease
  - Saphenous vein grafts
  - Acute myocardial infarction

CUORE
COLUMBUS

In-Hospital And FU clinical Events: Milan Experience

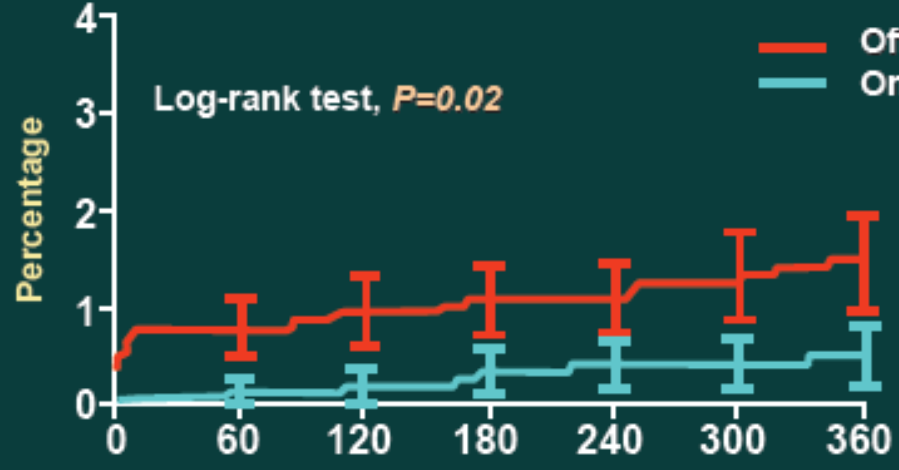
Variable	On Label	Off Label	P Value
Pts	364	680	
Acute Stent Throm	0	0.3%(2)	0.55
Sub-Acute ST	0	0.6%(4)	0.30
Late ST	1.4%(5)	1.2%(8)	0.78
MI	1.9%(7)	2.4%(16)	0.83
Total death	4.9%(18)	4.1%(28)	0.53
Cardiac death	2.7%(10)	2.5%(17)	1.00
MACE	17.6%(64)	28.2%(192)	0.0001

Are DES Adverse Event Rates Increased with Off-Label Use? EVENT Registry

(N=3,323 non STEMI pts, 51% SES, 49% PES, 55% off-label)

1-year Follow-up

Stent thrombosis

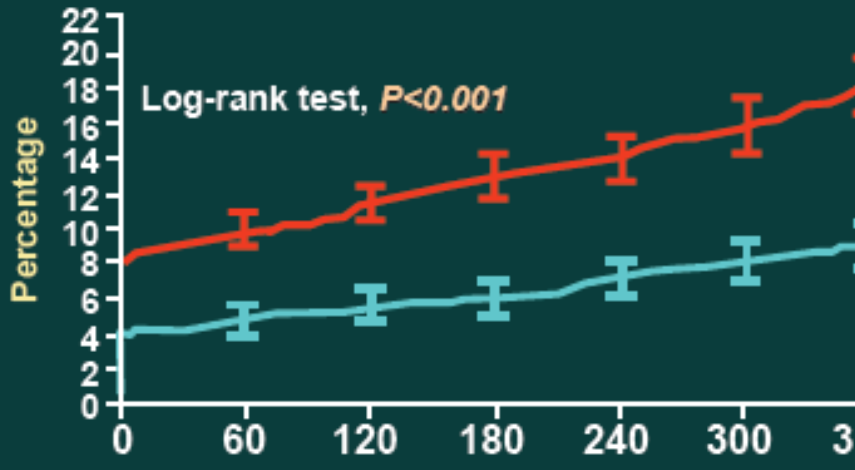


No. at Risk							
Off-label	1817	1769	1716	1711	1684	1551	1525
On-label	1506	1476	1451	1450	1431	1340	1327

Off-label: 1.6%
On-label: 0.9%

MV HR [95%CI]= 2.29 [1.02-5.16]
P<0.001

Death, MI or TLR



No. at Risk							
Off-label	1817	1757	1514	1476	1428	1313	1
On-label	1506	1475	1363	1343	1311	1215	1

Off-label: 17.5%
On-label: 8.9%

MV HR [95%CI] 2.16 [1.74-2.17]
P<0.001

BASKET LATE Trial: Study Design

743 patients randomized in the BASKET trial and WITHOUT AN EVENT DURING THE 6-MONTH CLOPIDOGREL PHASE

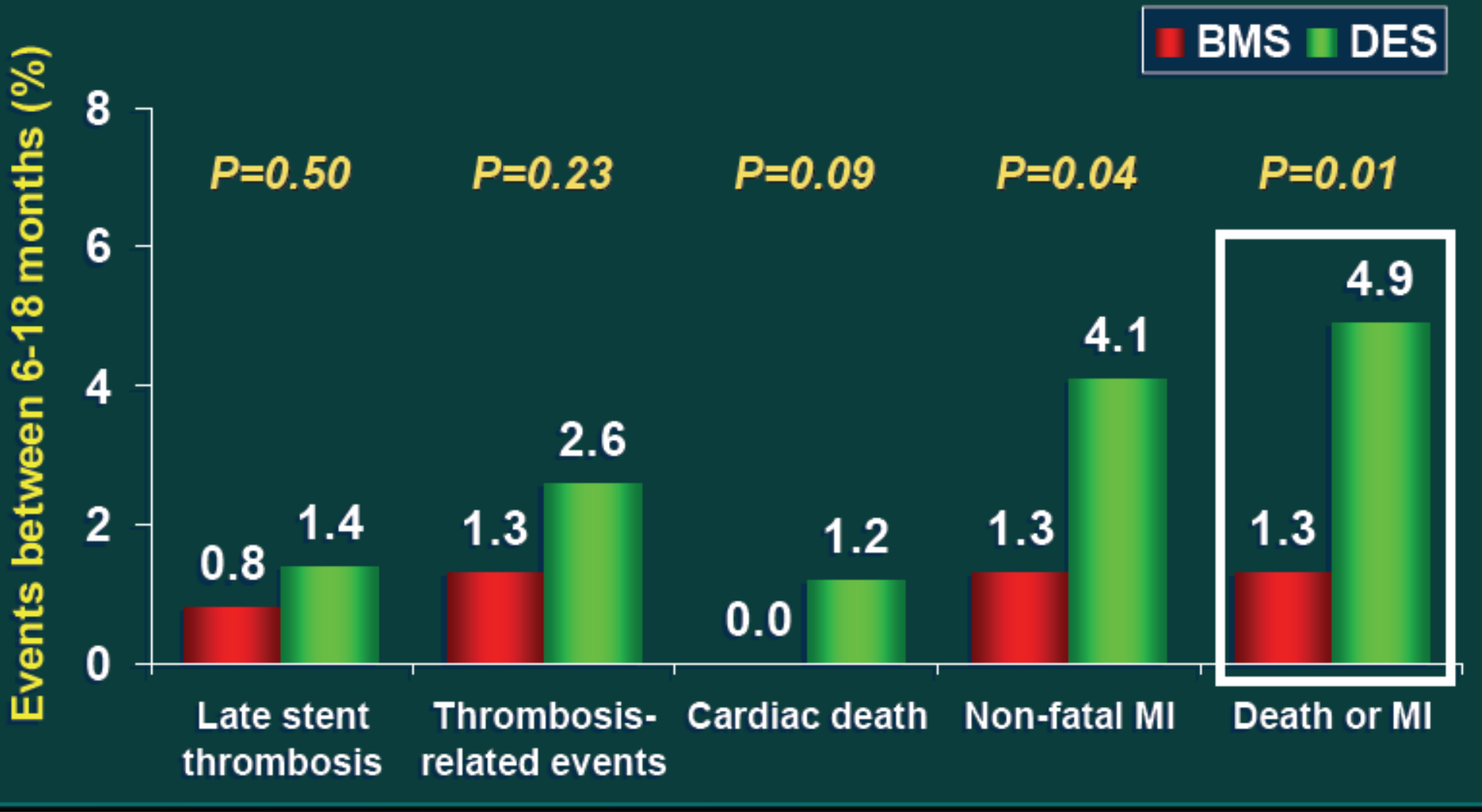
Drug-eluting stents (DES) (pooled paclitaxel and sirolimus DES groups) n=499	Bare metal VISION stents (BMS) n=244

Followed for 1 year off clopidogrel

- Primary Endpoint: Composite cardiac death or nonfatal MI.
- Other Endpoints: "Thrombosis-related events"

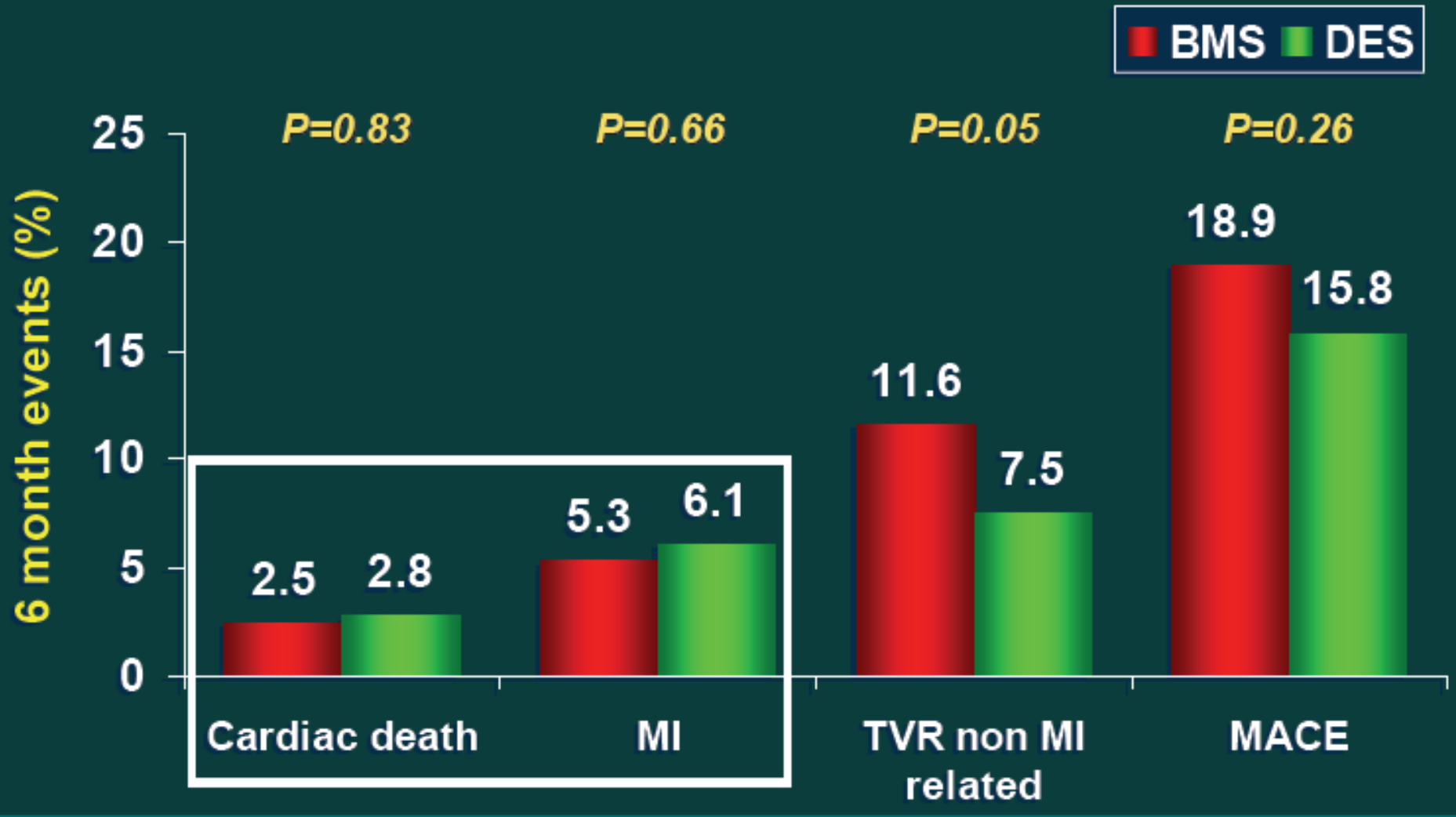
BASKET LATE Trial: 6-18 Mo MACE

N=743 (pts with early events excluded)



BASKET Trial: 18 Month MACE

N=836 (All pts with 18 month FU)

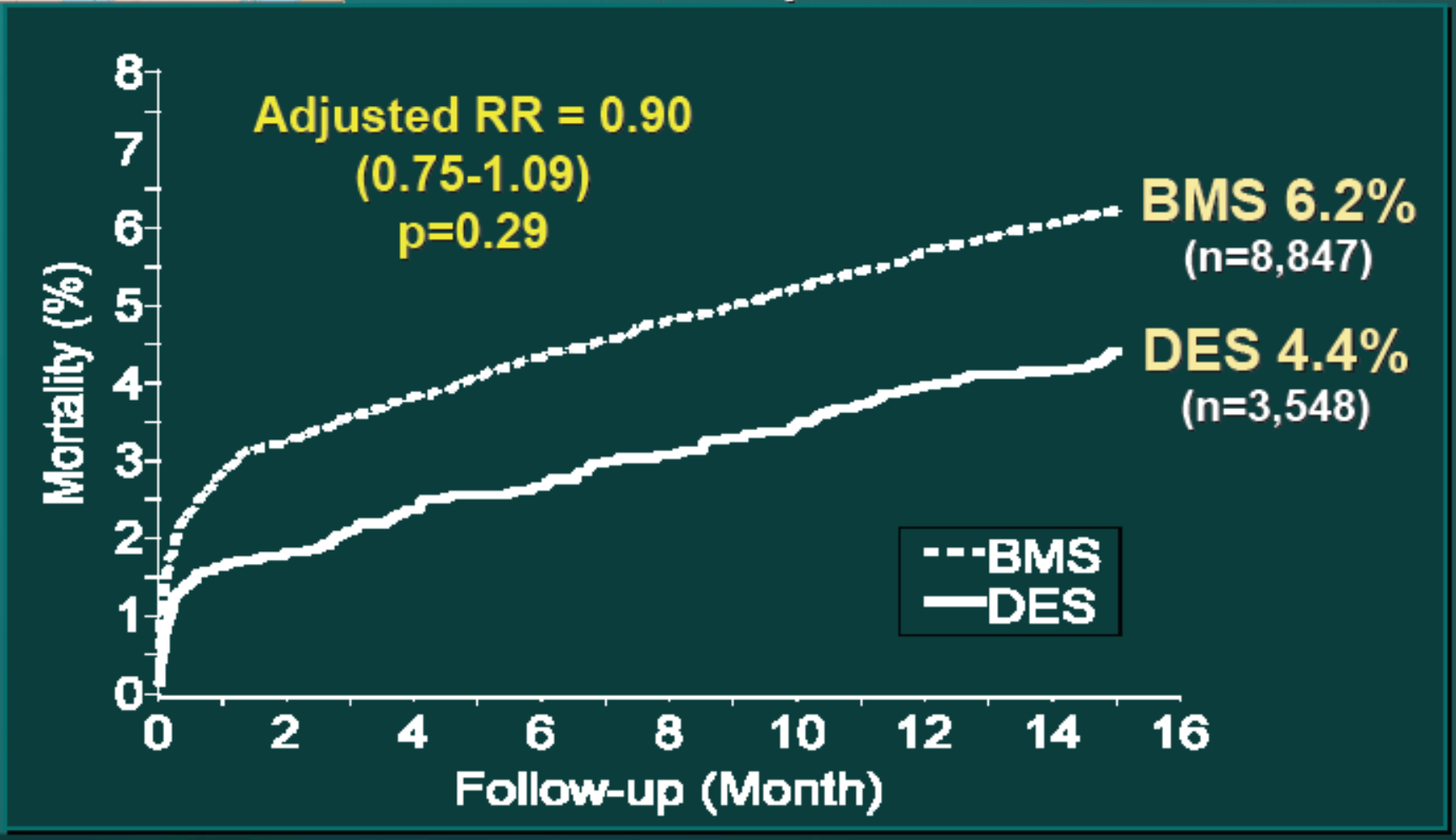


Western Denmark Registry

3 high volume centers covering 3 million inhabitants.

Mortality in all stented pts 1/02 – 6/05

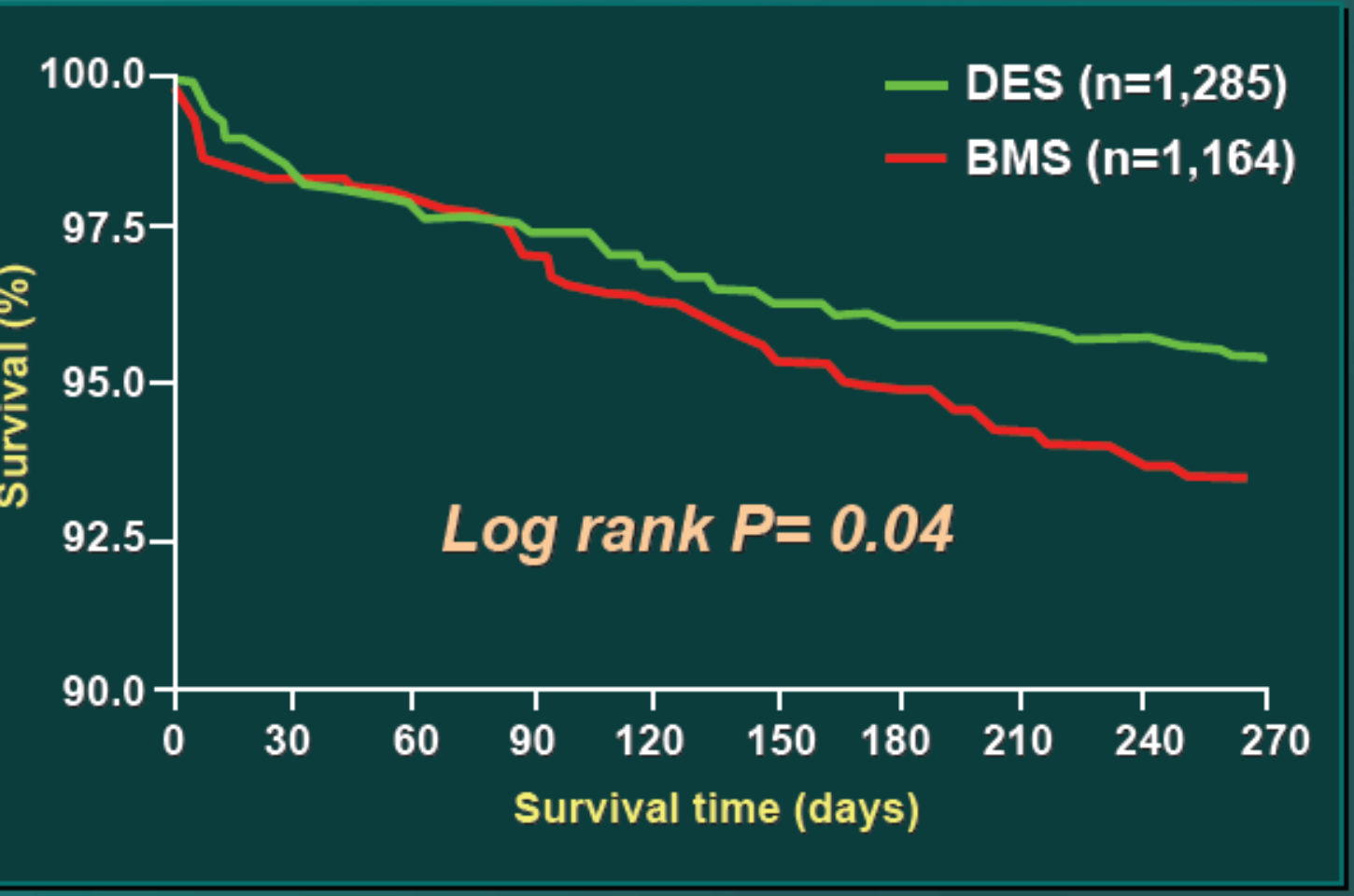
N=12,395 pts with 17,152 lesions



Wake Forest Experience (N=2,449)

BMS placed in 1164 pts the year before DES were available (4/02 – 4/03), and then DES placed in 1,285 comparable pts

72% ACS; Propensity score adjusted Cox MV analysis



Mortality

4.9% DES

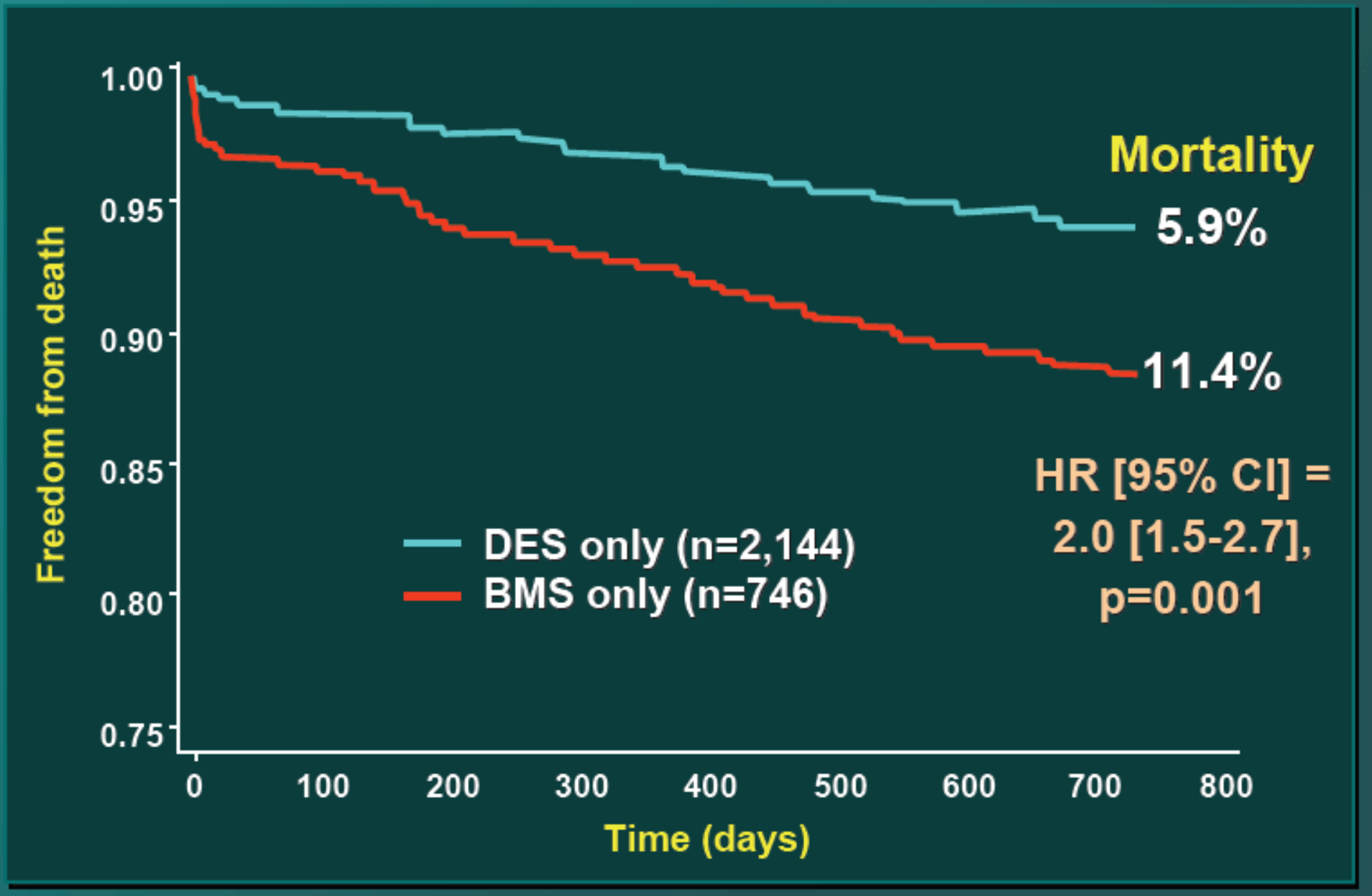
7.1% BMS

P=0.03

Propensity adjusted Cox

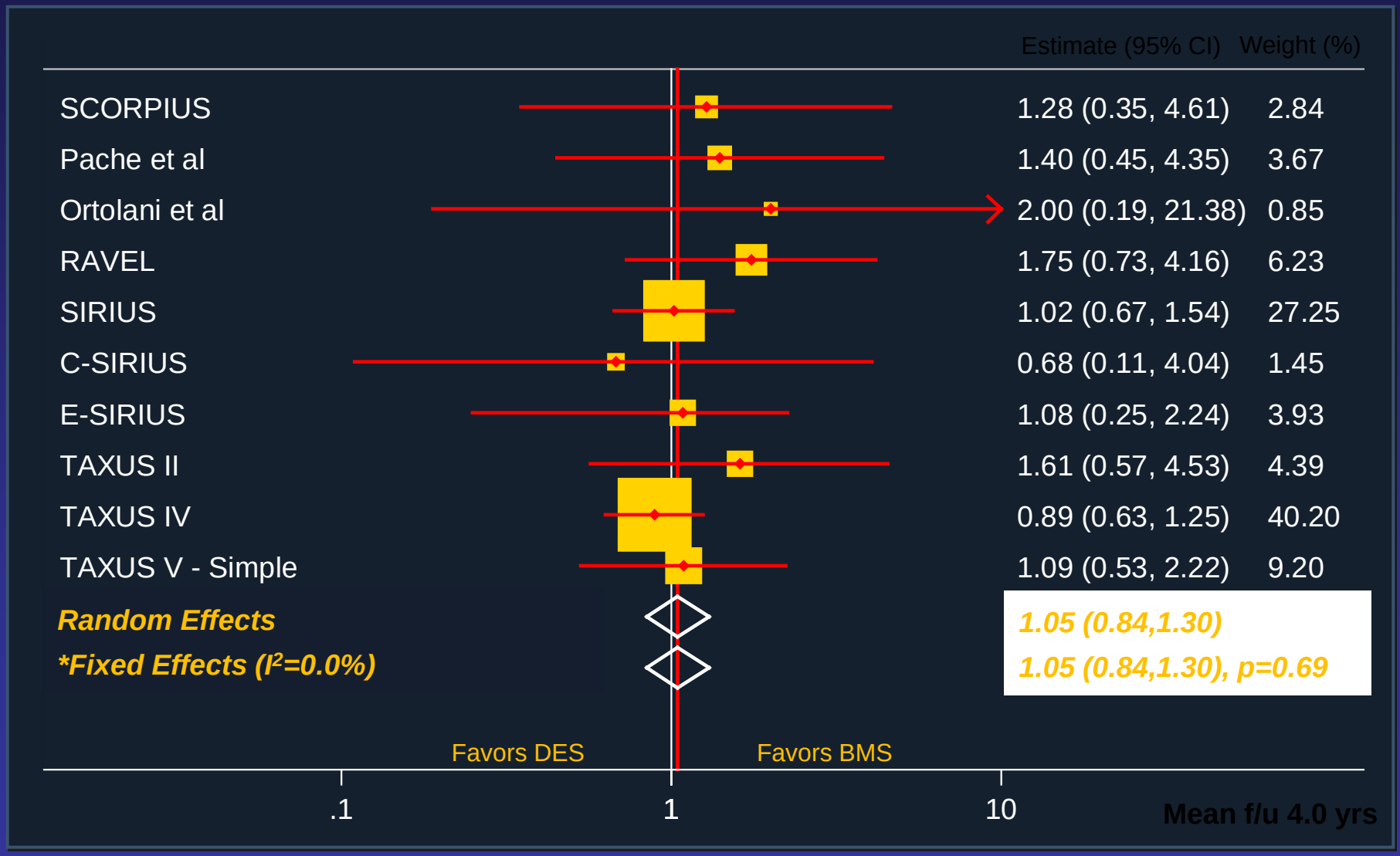
HR [95% CI] = 0.56 [0.36, 0.87

DES vs. BMS: Mortality (completed 2 yr F/U)



All-Cause Mortality: RCTs (On-Label)

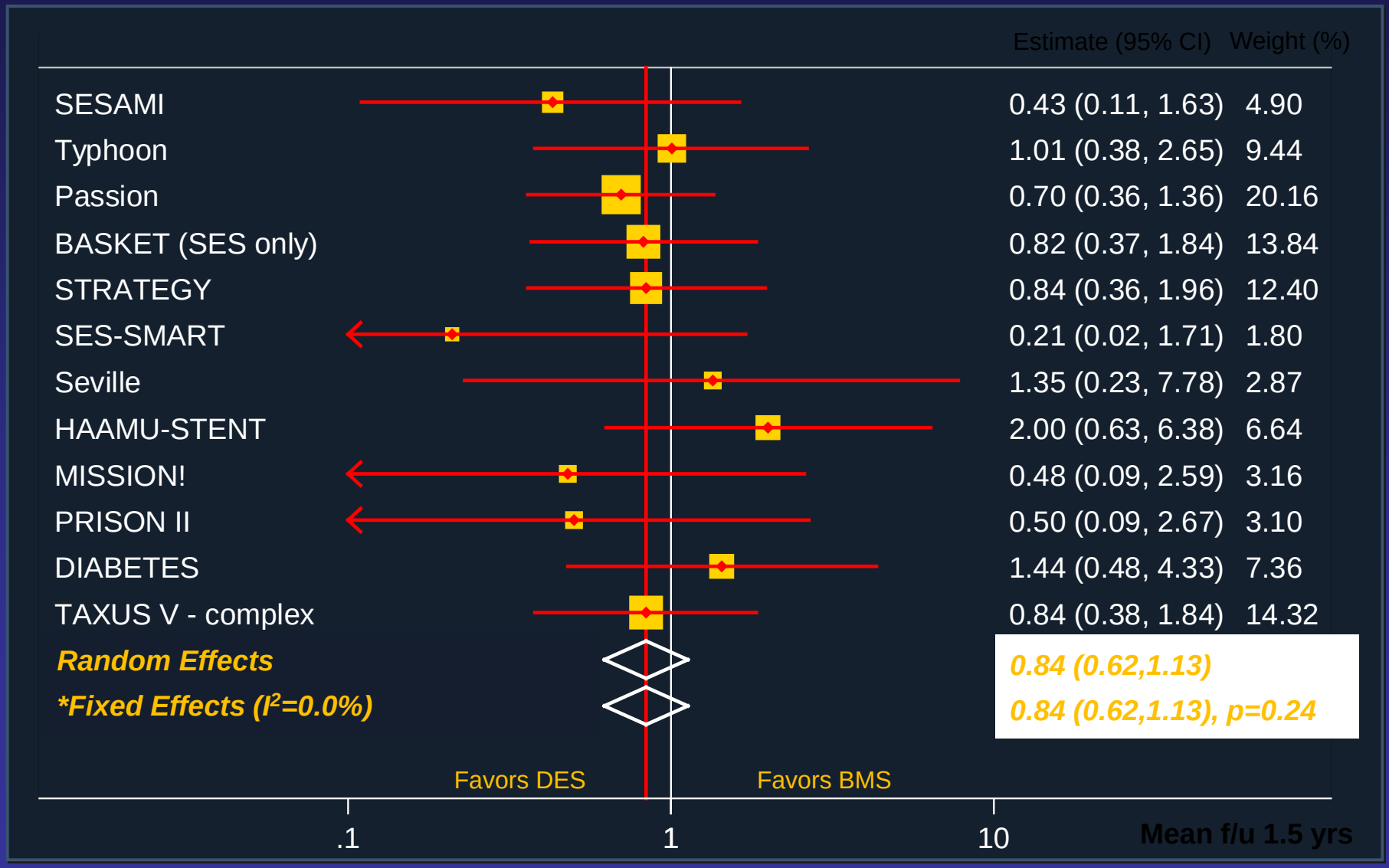
4,818 patients, 10 trials



Ajay J. Kirtane and Gregg W. Stone, 2008

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

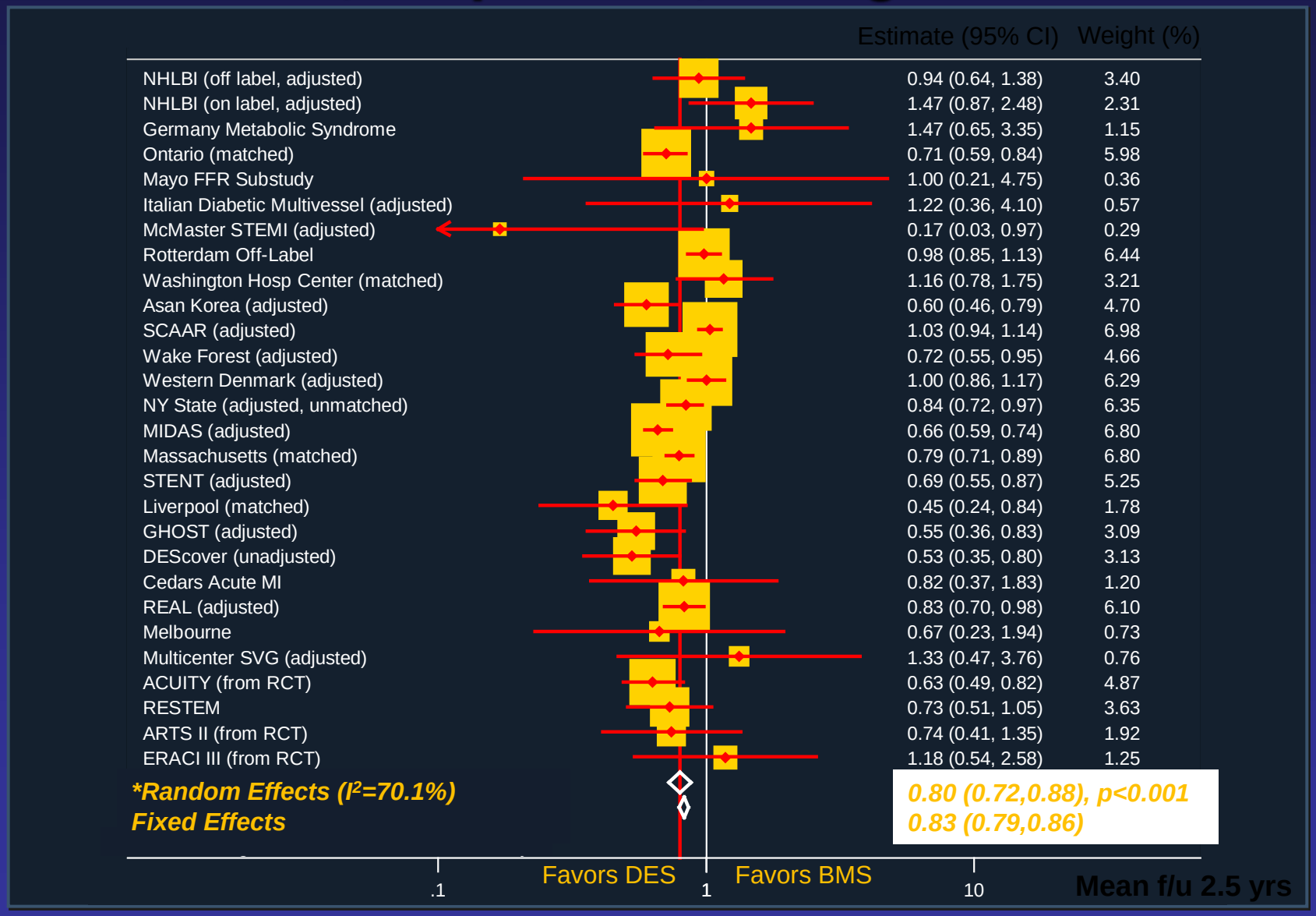
4,049 patients, 12 trials



Ajay J. Kirtane and Gregg W. Stone, 2008

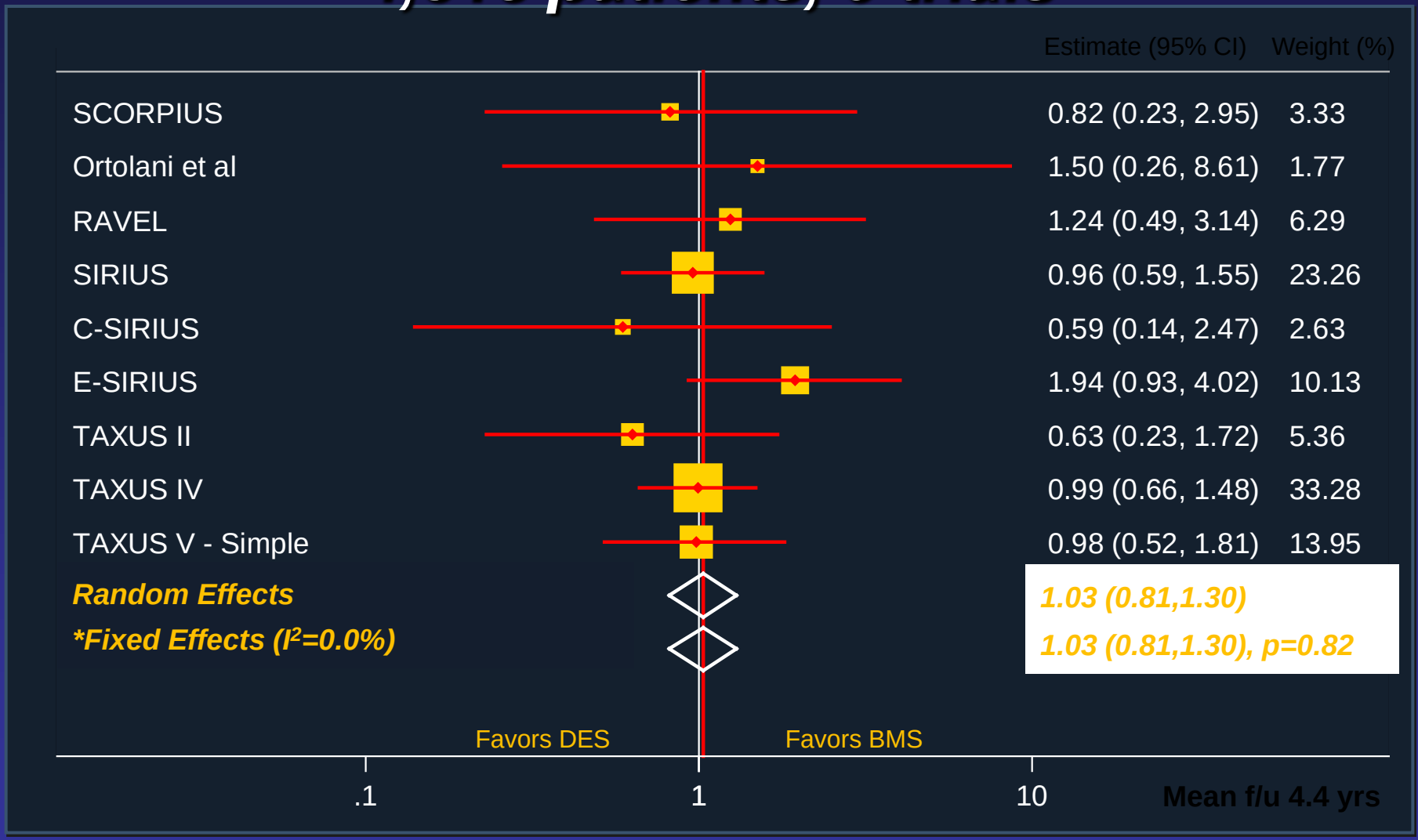
All-Cause Mortality: All Registries

161,232 patients, 28 registries



Ajay J. Kirtane and Gregg W. Stone, 2008

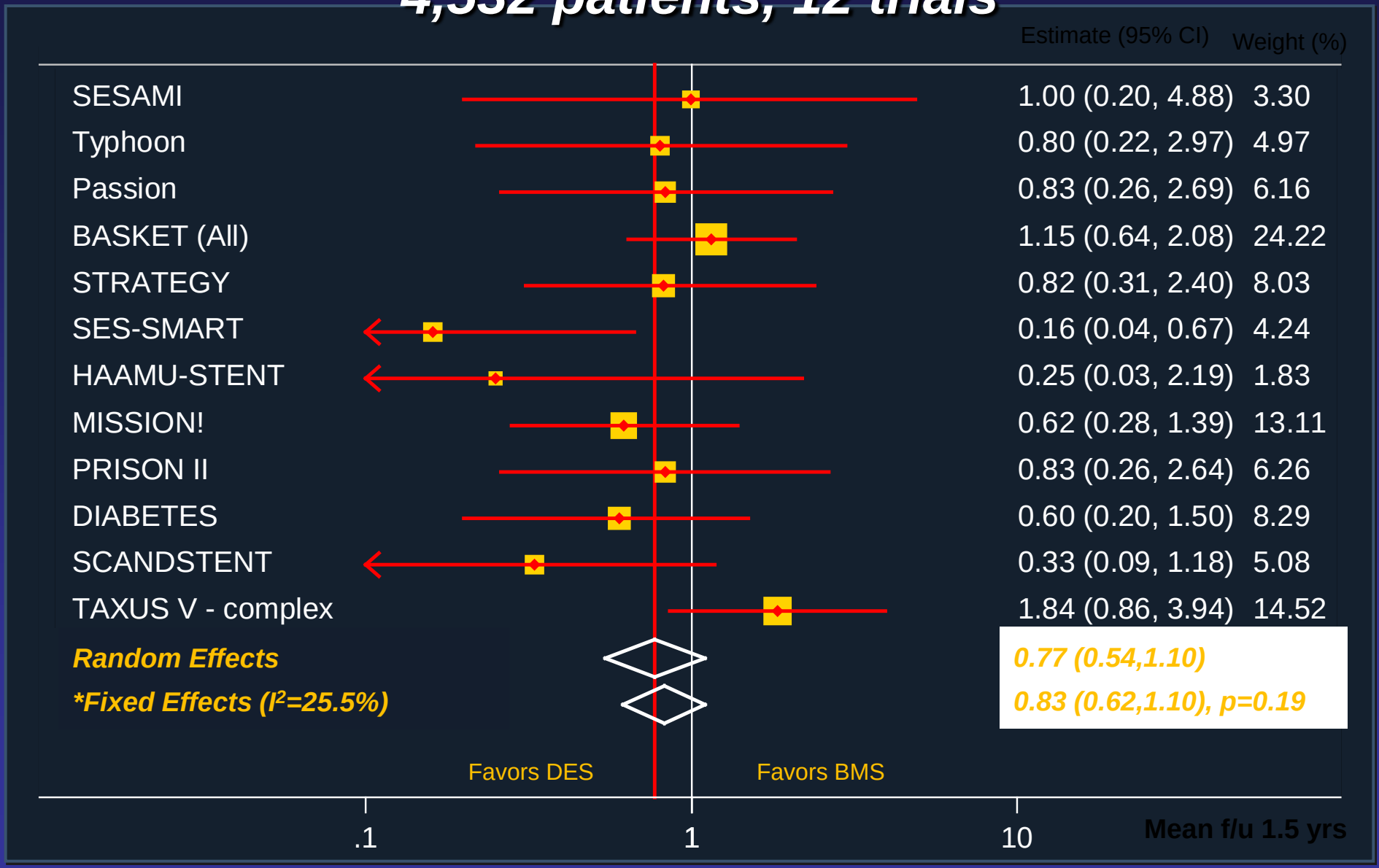
MI: RCTs (On Label)
4,318 patients, 9 trials



Ajay J. Kirtane and Gregg W. Stone, 2008

MI: RCT's (Off Label)

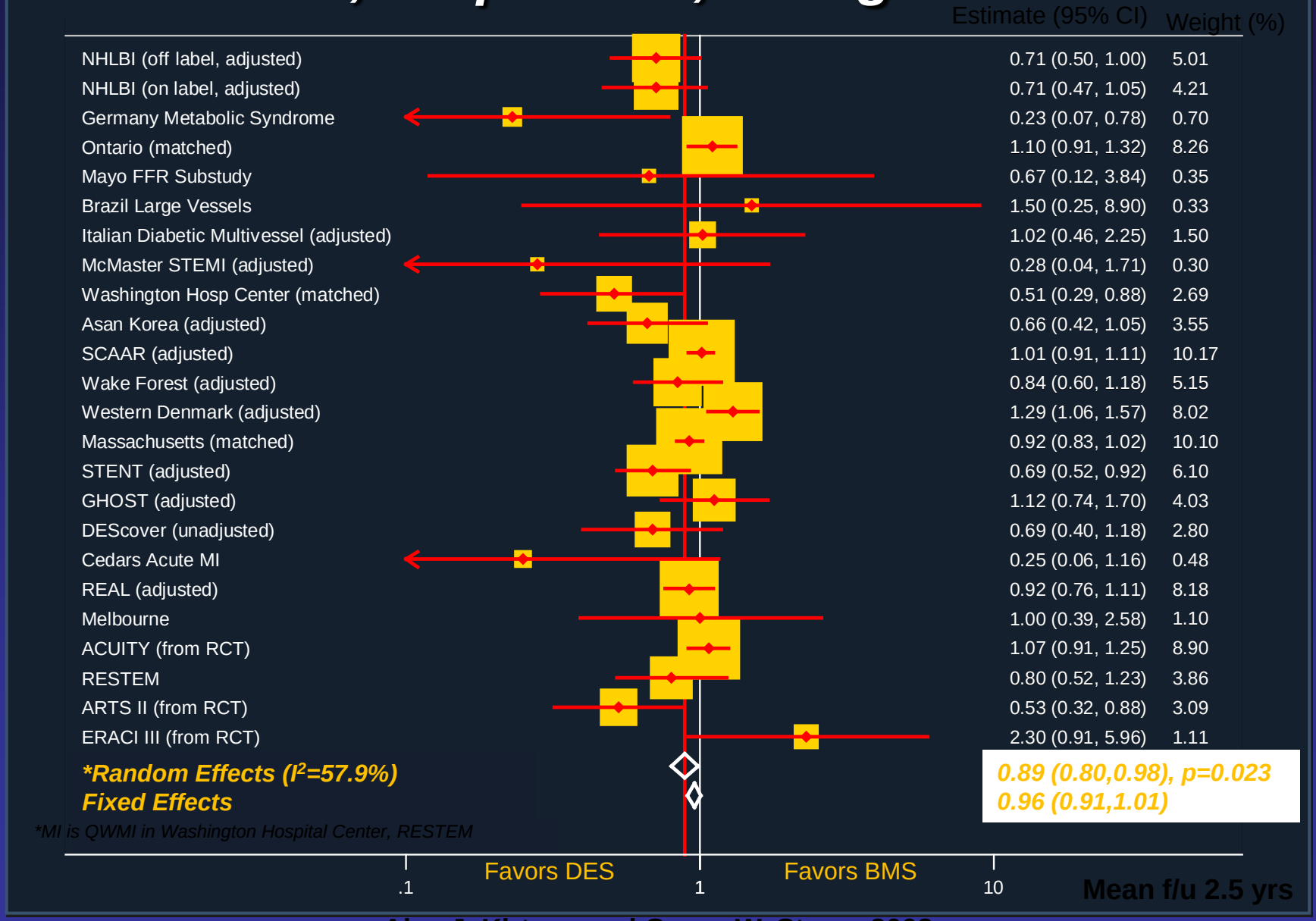
4,532 patients, 12 trials



Ajay J. Kirtane and Gregg W. Stone, 2008

MI: All Registries

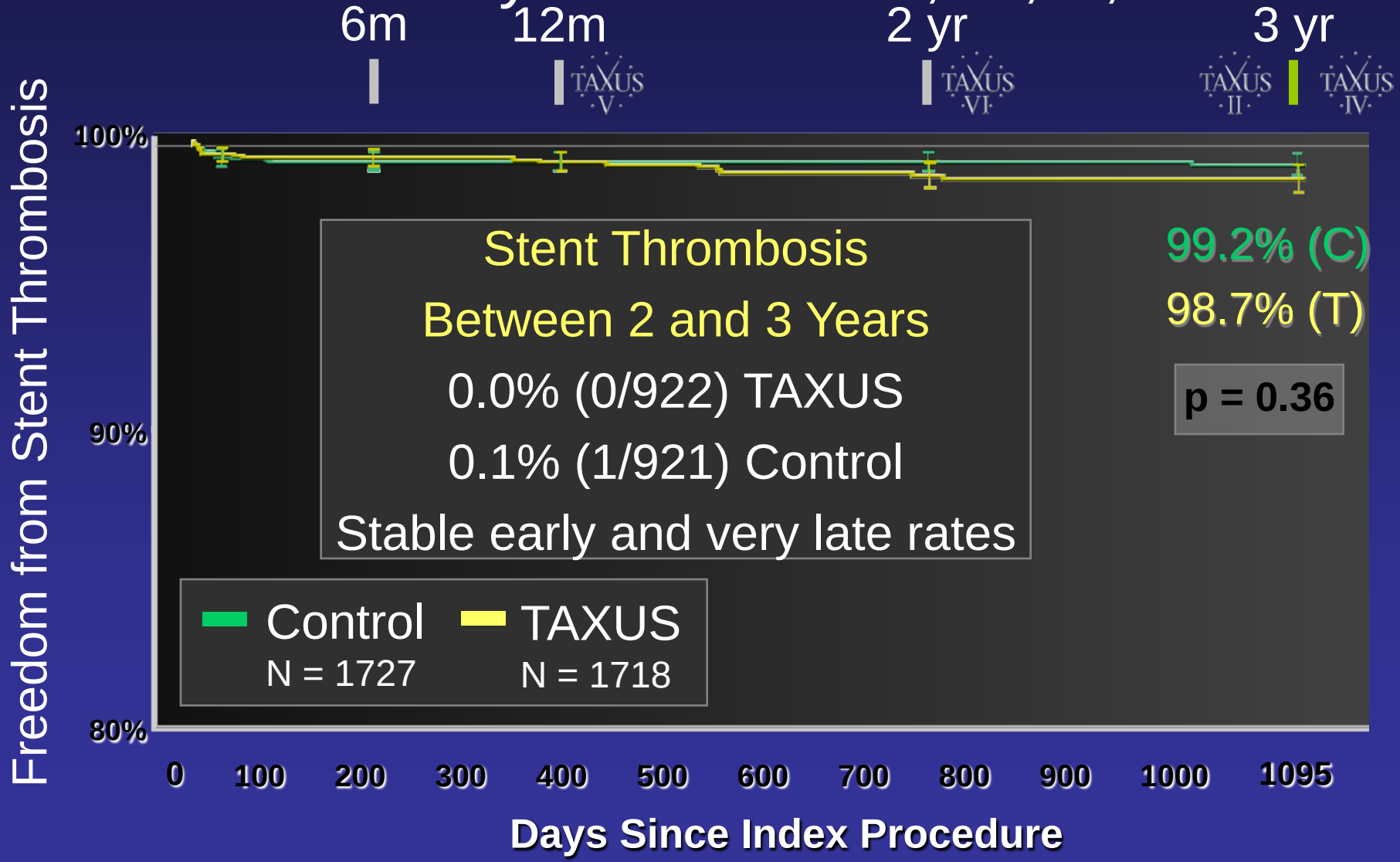
129,955 patients, 24 registries



Ajay J. Kirtane and Gregg W. Stone, 2008

Freedom from Stent Thrombosis out to 3-Years

Meta-Analysis: TAXUS II, IV, V, VI



Very Late TAXUS-SR ST Patients

Evaluation of Patients with Late ST

Patient	Days to ST	Angio. Conf.	Evidence of Disease Progression (Investigator Noted)	Dual Anti-Platelet Therapy
1	341	No	Yes	No
2	498	Yes	Yes	No
3	508	Yes	Yes	No
4	522	Yes	No	No
5	711	Yes	Yes	No

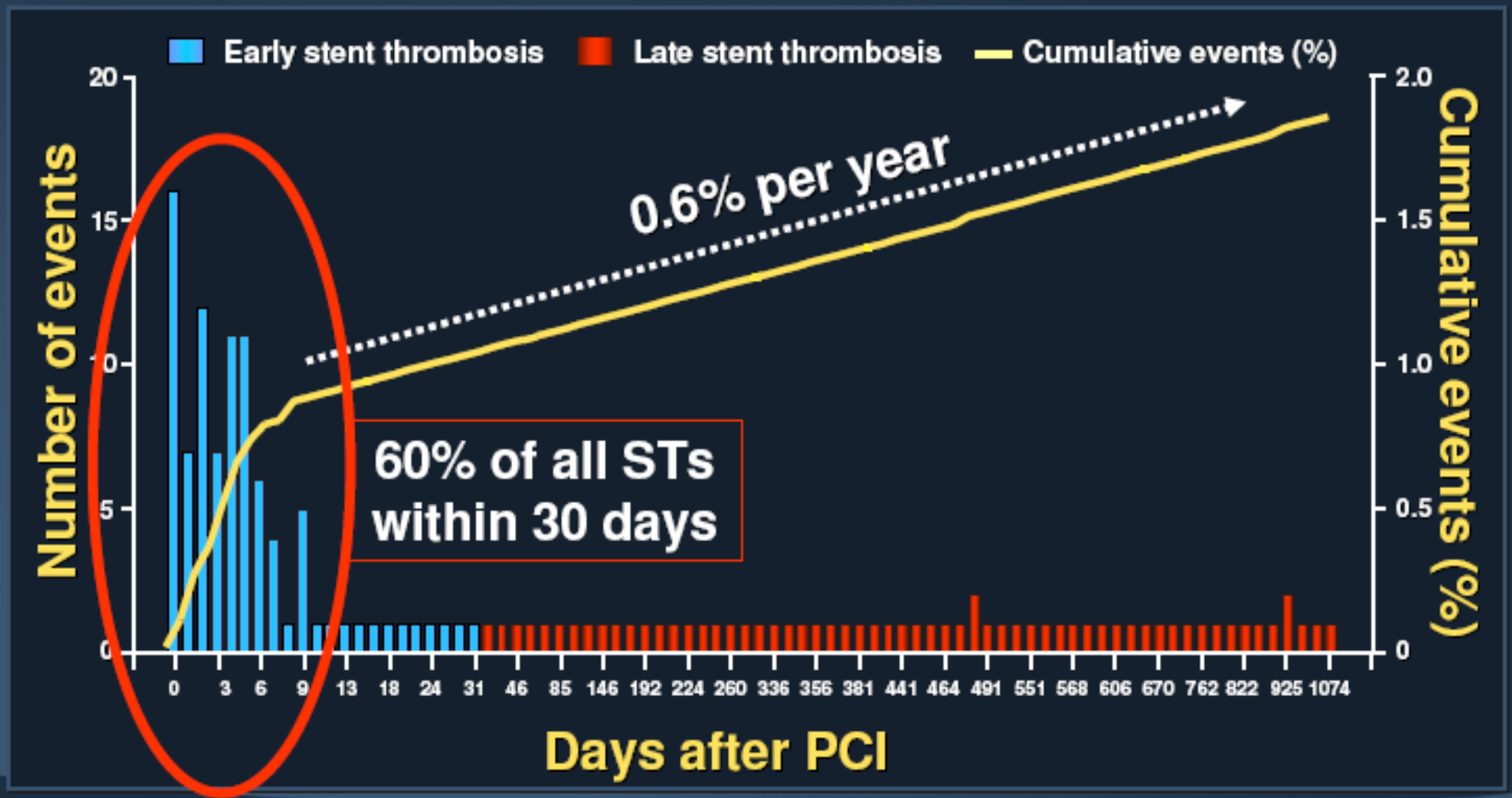
From TAXUS II-SR, IV, V

- 4 of 5 patients had disease progression
- All 5 patients were off dual anti-platelet therapy

Ellis: ACC 2006

Bern-Rotterdam Experience

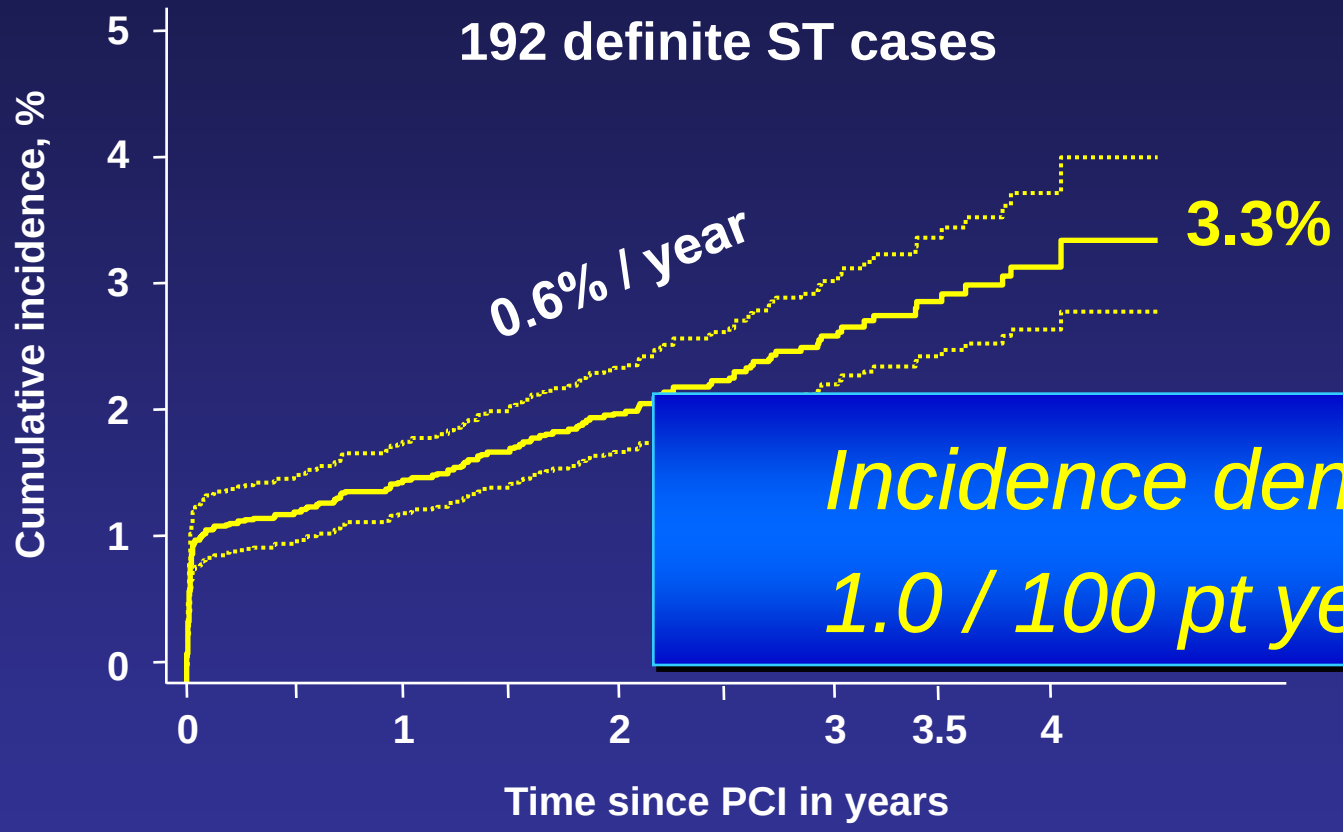
8146 pts. treated with SES (n=3823) or PES (n=4323) at 2 academic centers



Daemon J, et al, *Lancet* 2007;369:667–78

Definite Stent Thrombosis: DES

Patients Followed to 4 years

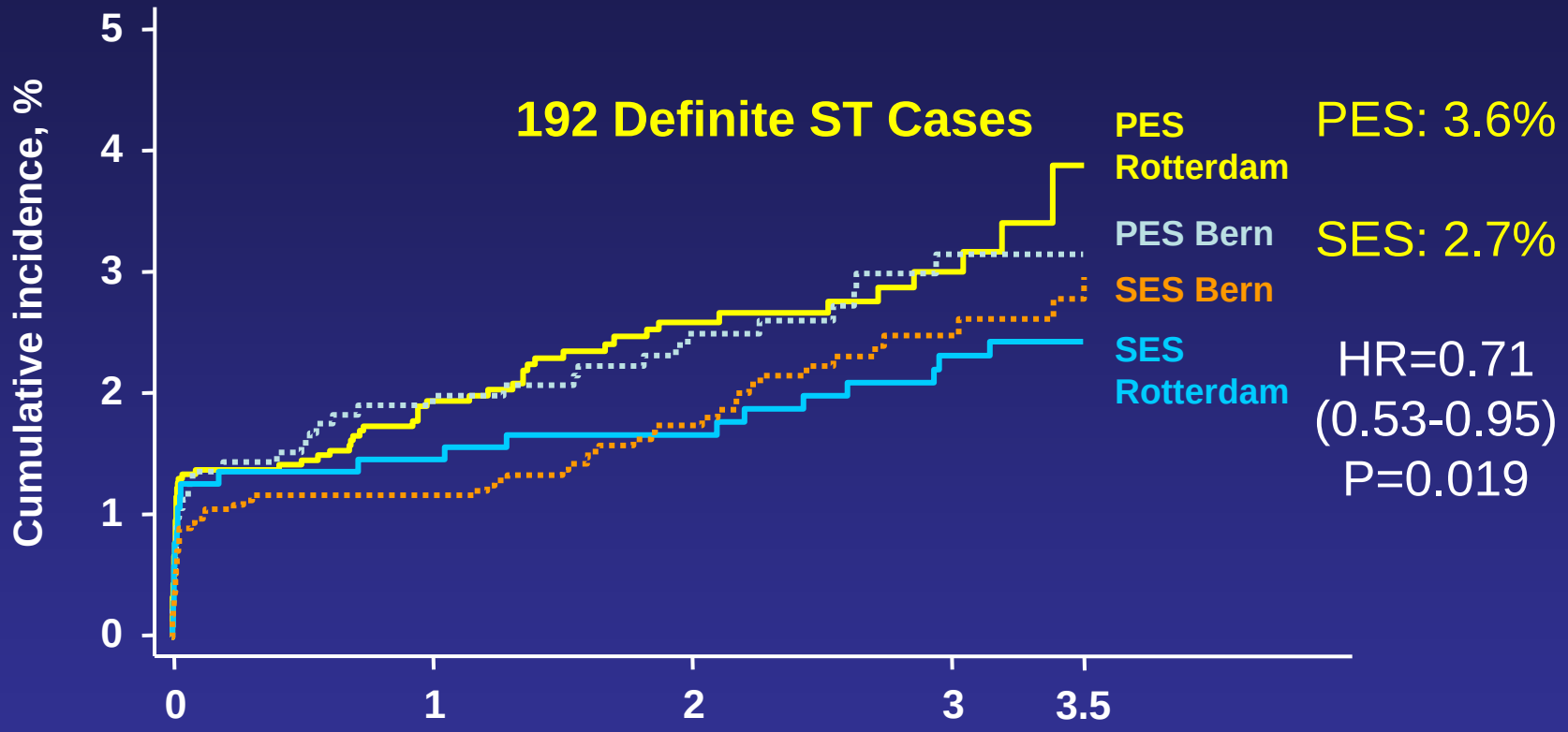


Incidence density
1.0 / 100 pt years

Months	1	12	24	36	48
Cumulative incidence, %	1.2	1.6	2.1	2.7	3.3
Patients at risk	7538	7210	5164	2790	1051

Definite Stent Thrombosis: DES Stent Type

Patients Followed to 4 years



Months	1	12	24	36	42
Cumulative incidence SES, %	1.0	1.2	1.7	2.4	2.7
Cumulative incidence PES, %	1.3	1.9	2.5	3.1	3.6

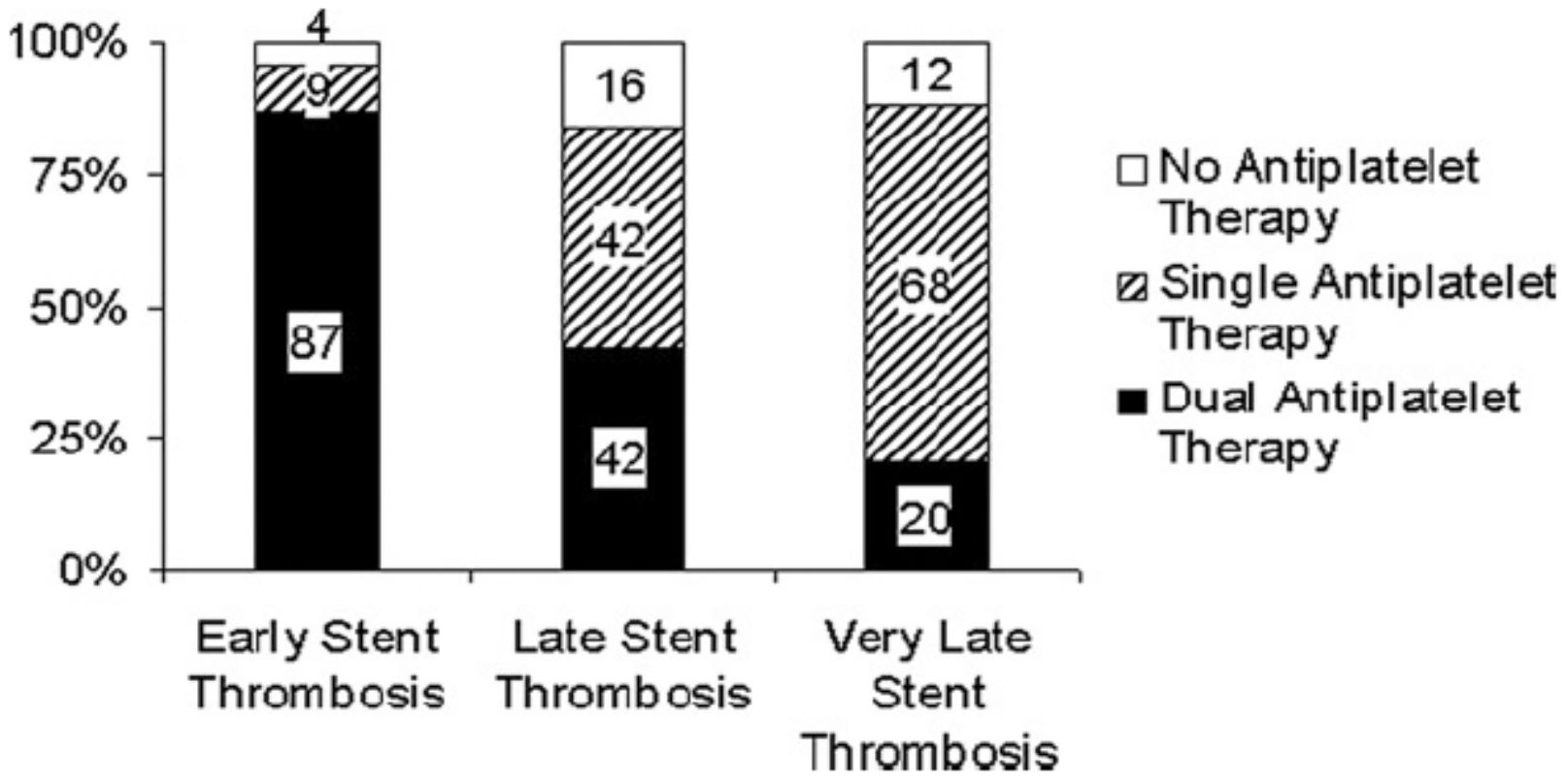


Figure 1 **Status of Antiplatelet Treatment at Time of Definite Stent Thrombosis**

Proportion of patients with early and late stent thrombosis treated with dual, single, or no antiplatelet therapy.

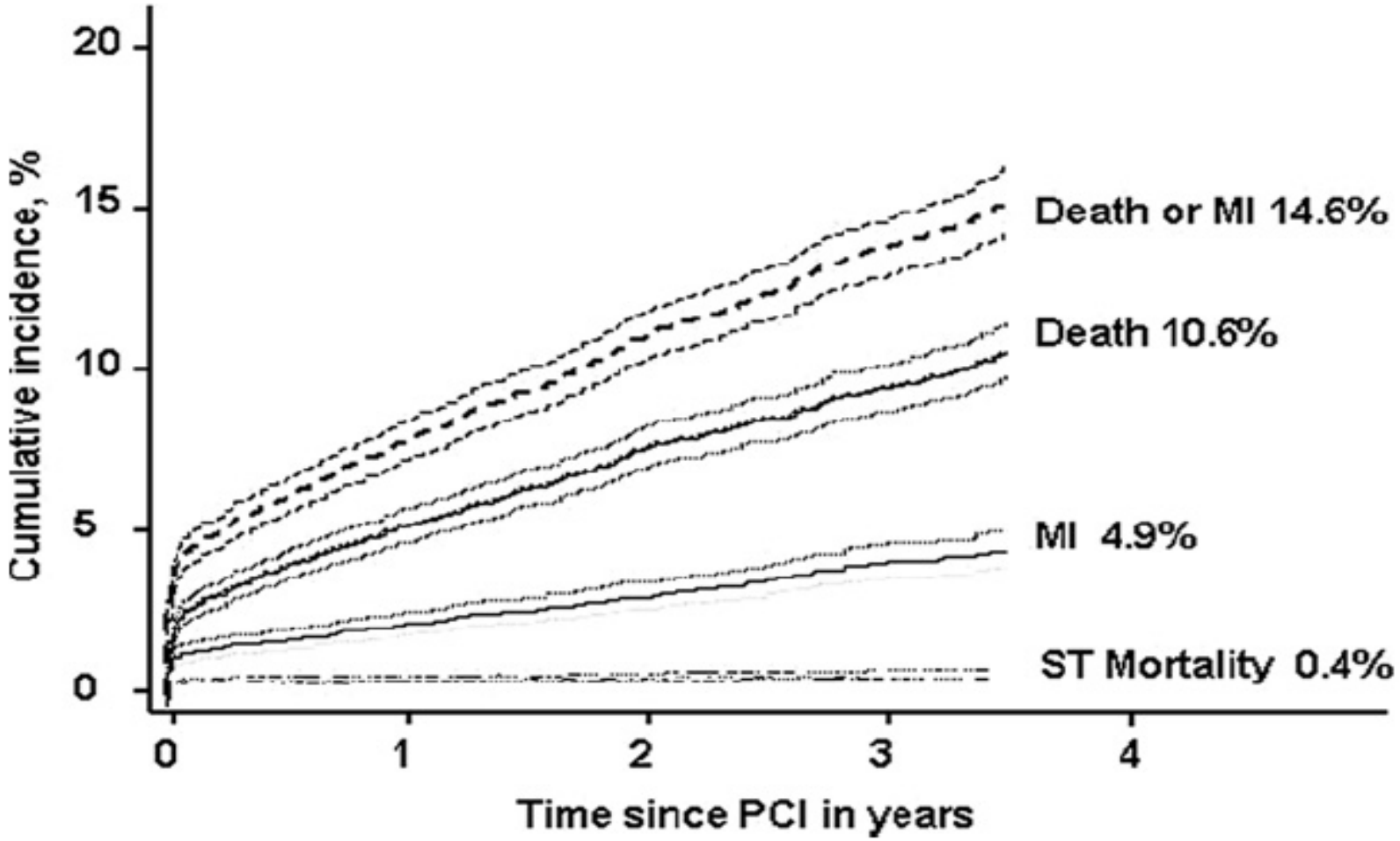
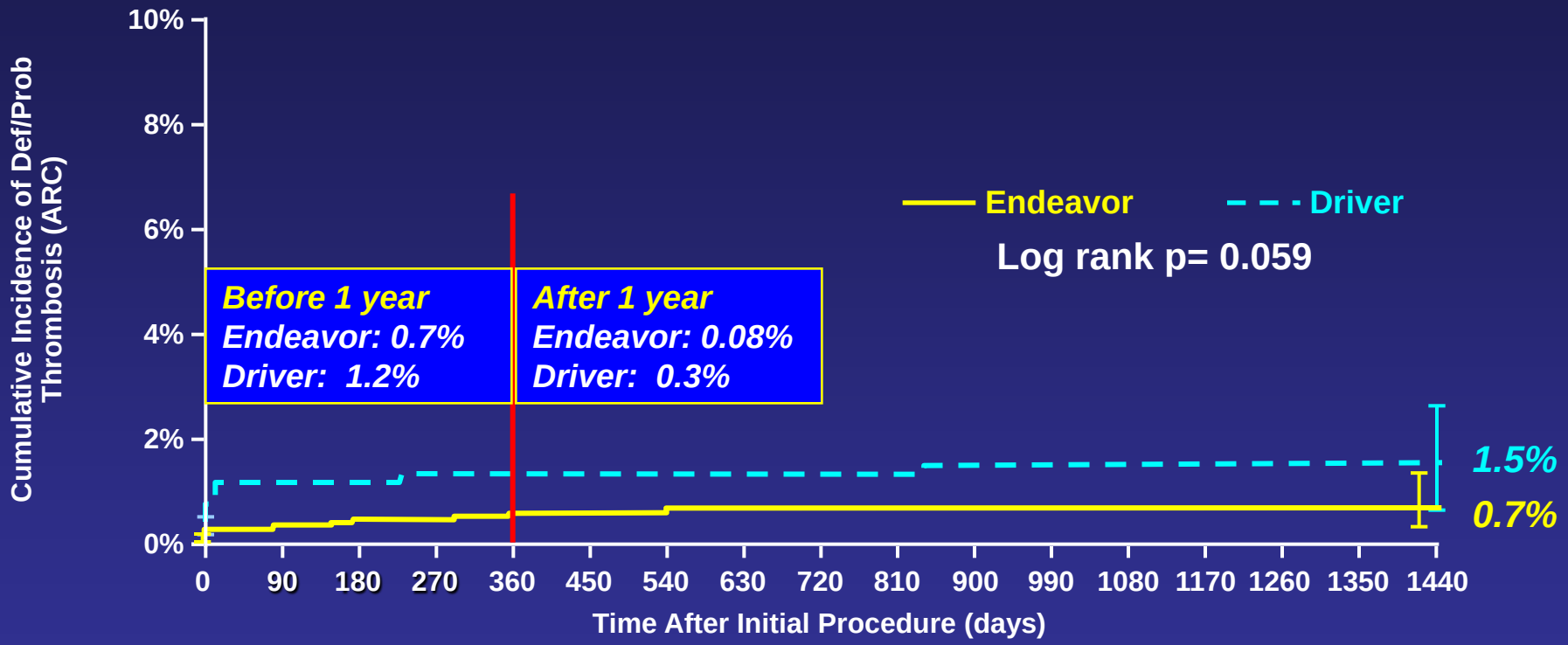


Figure 5 **Cumulative Incidence of Ischemic Adverse Events in 8,146 Patients During 4 Years of Follow-Up**

MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

Endeavor Safety Analysis
ARC Definite/Probable ST to 1440 Days

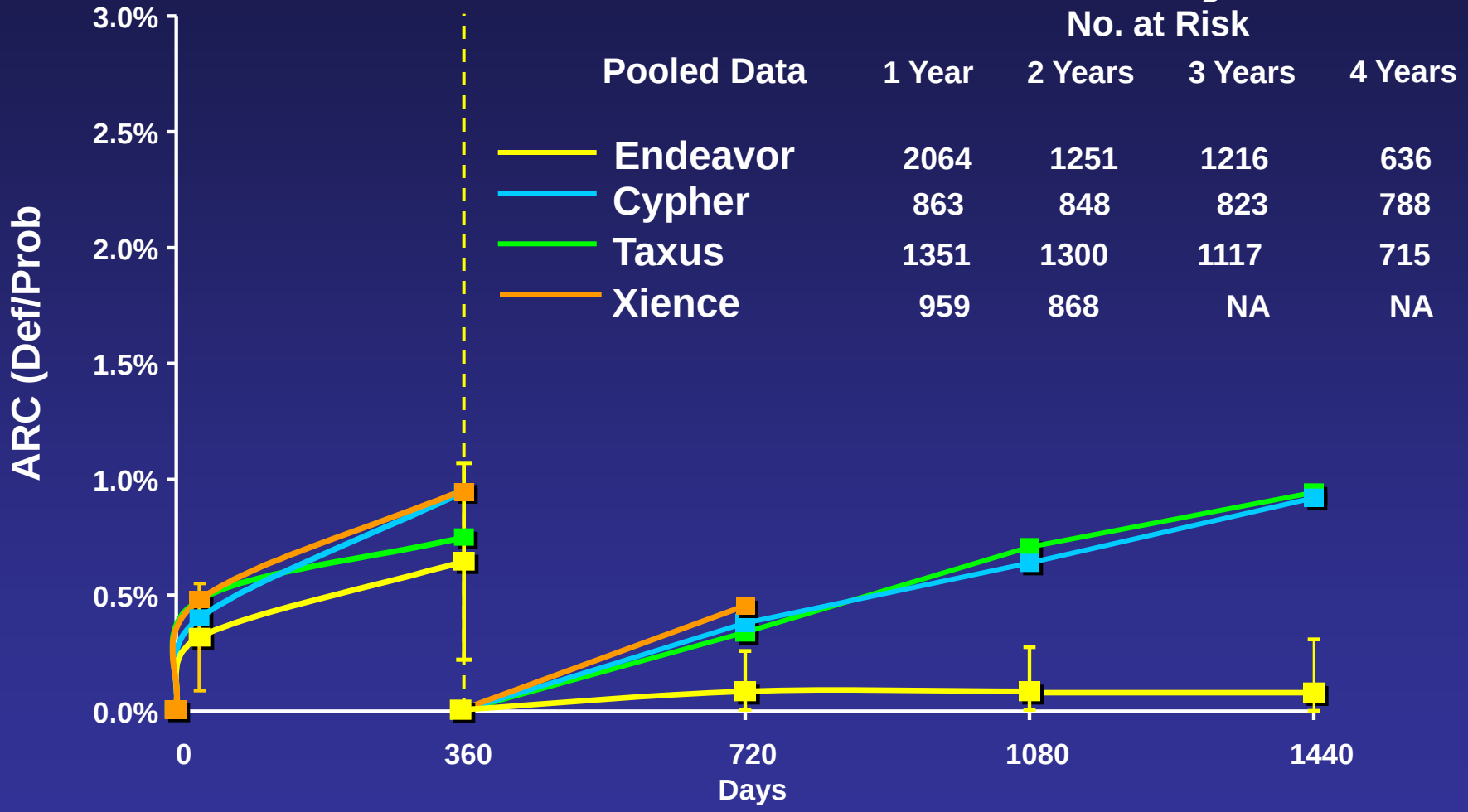


Def/Prob Thrombosis	0	30	270	360	720	1080	1440
Endeavor	*2132*	*2117*	*2085*	*2049*	*1247*	*1216*	*636*
# Events	1	6	4	2	1	0	0
% CI	0.0%	0.3%	0.5%	0.6%	0.7%	0.7%	0.7%
Driver	*596*	*585*	*581*	*575*	*560*	*549*	*539*
# Events	1	6	1	0	0	1	0
% CI	0.2%	1.2%	1.3%	1.3%	1.3%	1.5%	1.5%

Endeavor Pooled Safety Analysis: I Meredith et al. PCR 2008.

Endeavor Safety Analysis

ARC Definite and Probable ST to 4 years



Mauri et al. *N Engl J Med*. 2007;356:1020-1029.
Endeavor: Mauri et al. TCT. 2007.
Xience: Spirit II at ACC and Spirt III at PCR

PROTECT

International RCT Designed to Estimate VLST (>1 year)

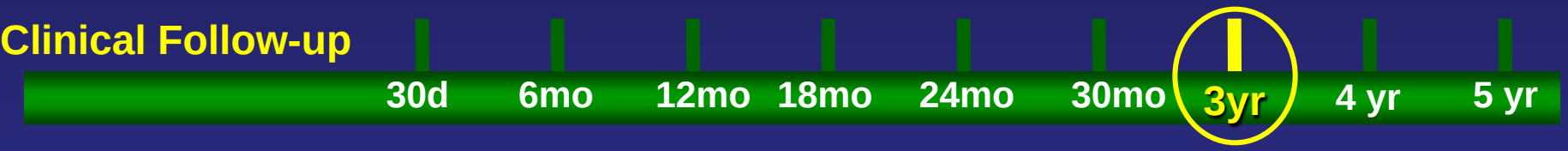
All Comer

Dual APT >3 to ≤12 months

Endeavor
N=4400

N = 8800
>200 International Sites
Randomization 1:1

Cypher
N=4400



Primary Endpoint: ARC Definite or Probable Stent Thrombosis at 3 years

Main Secondary Endpoints:

Death or Cardiac death combined all non-fatal MI as well as the number of patients with large non-fatal MI

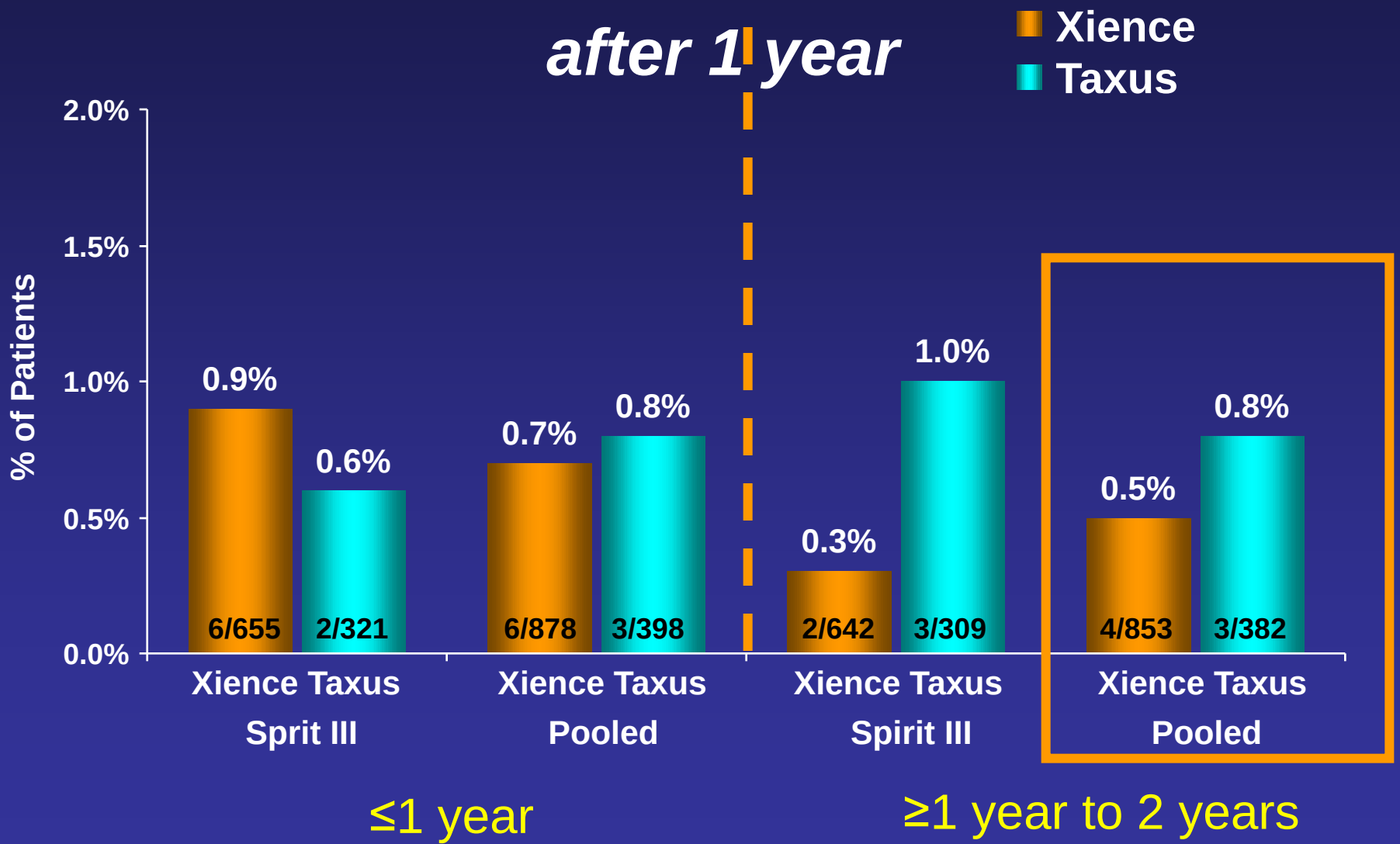
Clinical Follow up and Dual Antiplatelet Monitoring:

At 30 days, and every 6 months until 3 years, than each year until 5 years

Over 3500 Patients Currently Enrolled

Xience

ARC Definite and Probable ST before and after 1 year



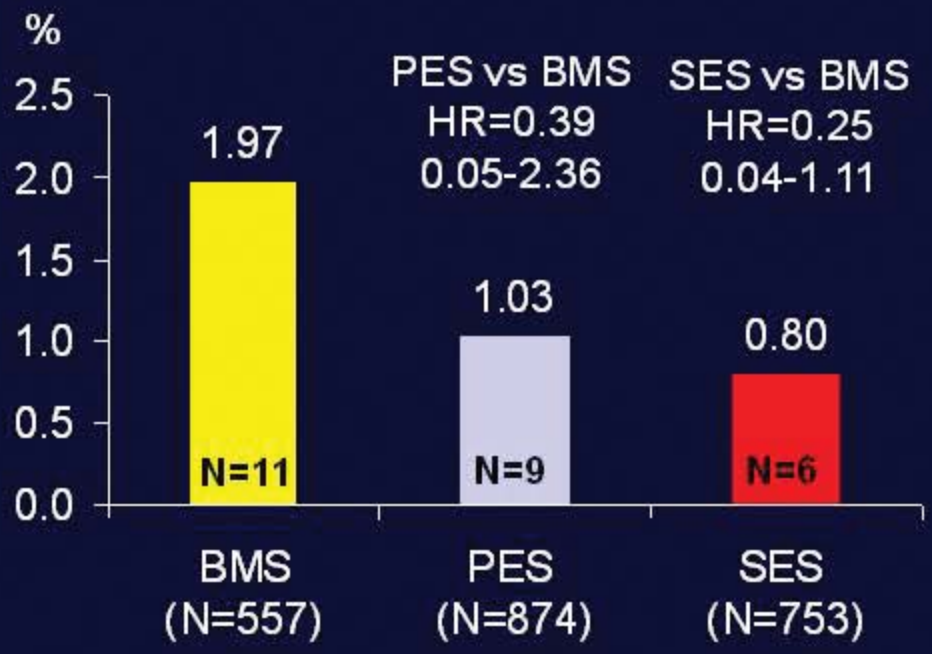
Endeavor: Fajadet et al. PCR 2008

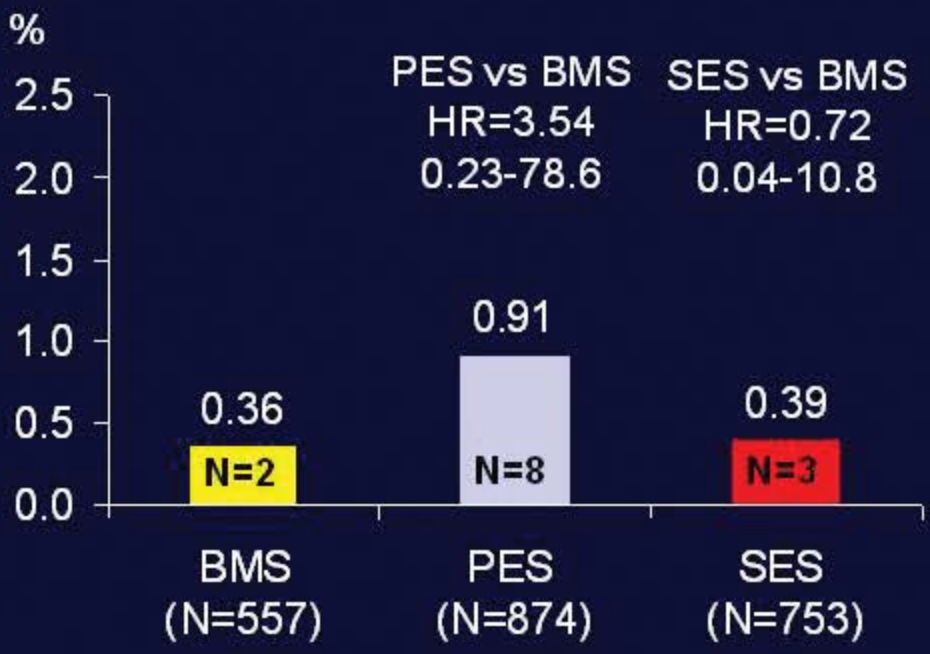
Early and Late Definite ST in Diabetic Patients Drug-Eluting vs. Bare Metal Stents

Early Stent Thrombosis (0 - 30 Days)
Stettler C et al. *BMJ 2008*

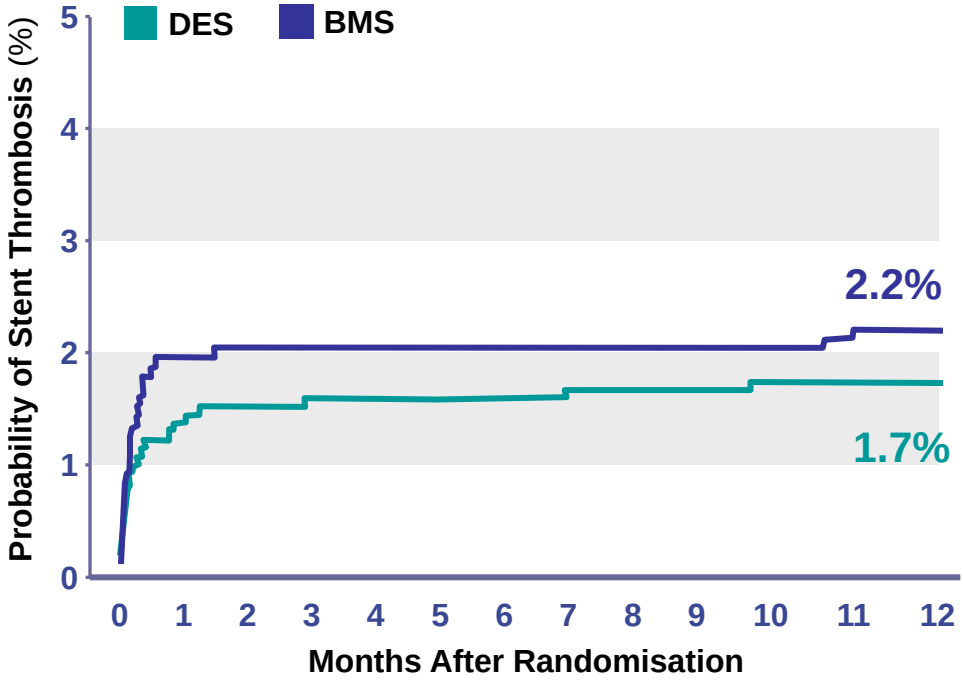
Late Stent Thrombosis (30 Days - 4 Years)
Stettler C et al. *BMJ 2008*

Network Meta-Analysis of 3,853 Diabetic Patients





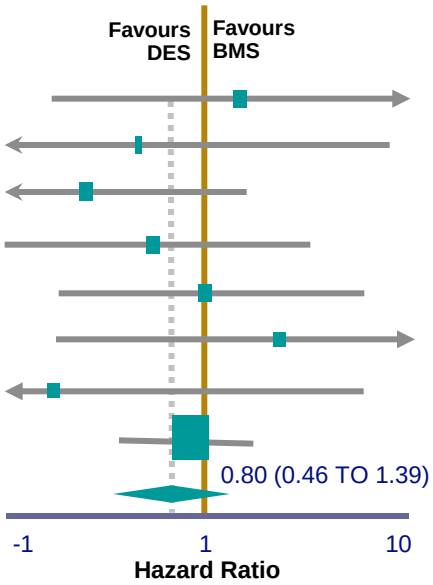
Meta-analysis of DES vs. BMS RCTs in AMI: Stent Thrombosis



No. of events/Total No. of patients

Trial	DES group	BMS group
BASKET-AMI	3/142	1/74
Di Lorenzo	1/180	1/90
HAAMU-STENT	2/82	5/82
MISSION	2/158	3/152
PASSION	3/310	3/309
SESAMI	2/160	1/160
STRATEGY	0/87	2/88
TYPHOON.	12/355	13/357
Overall	25/1,474	29/1,312

I^2 = 0%;
P (heterogeneity) =0.88;
P (Overall Effect) =0.43



Kastrati A, et al. Eur Heart J. 2007;28:2706-13.

Patients Unattractive For Stent (DES and BMS) Implantation

- Increased risk of bleeding
- Scheduled elective surgery
- Patients requiring oral anticoagulation
  - Atrial fibrillation
  - Pulmonary embolism
  - Prosthetic heart valves
- Non-compliance with dual antiplatelet therapy
  - Cost
  - Education
  - Psychiatric disorder

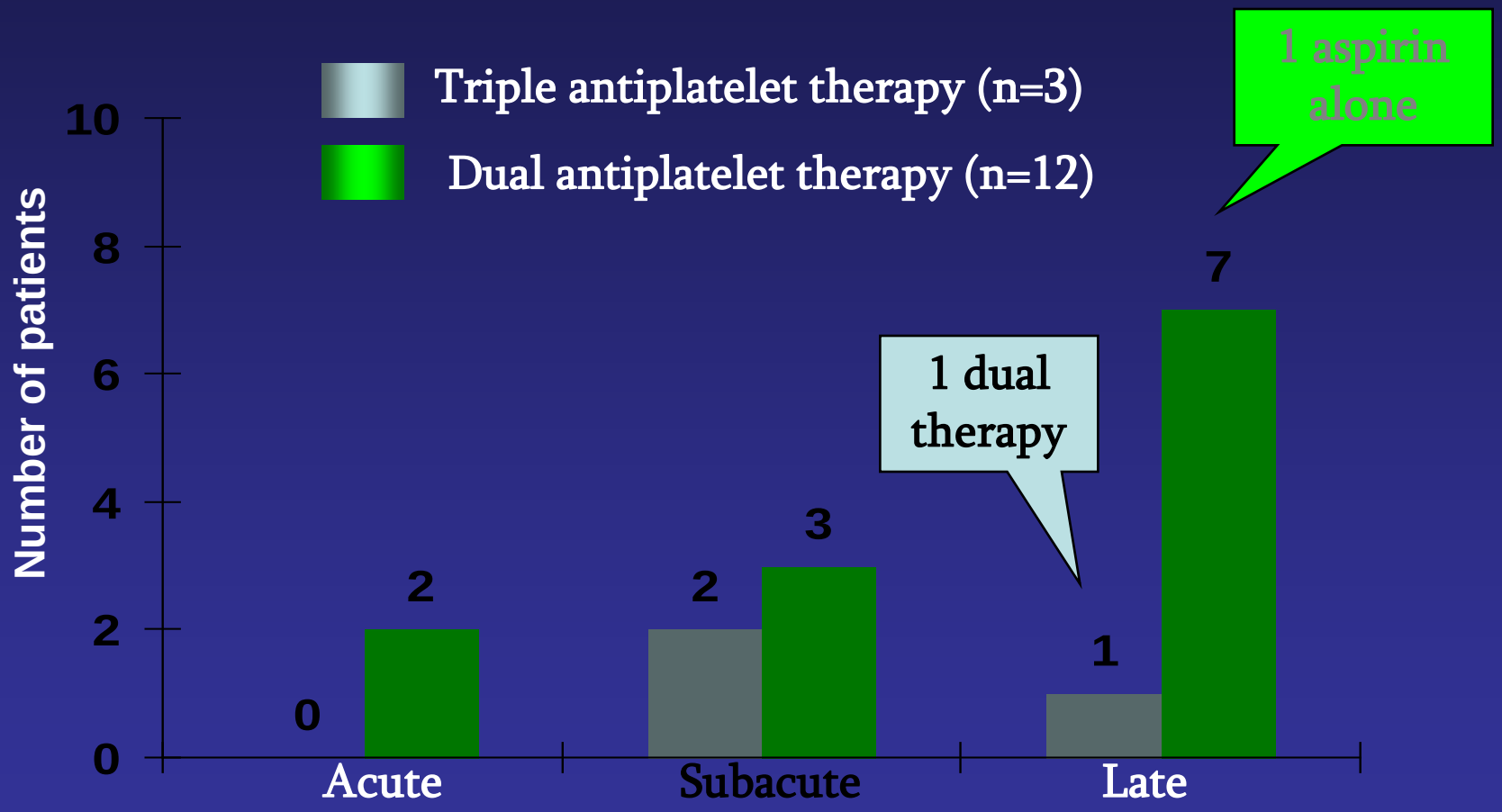
Triple Antiplatelet Therapy (*Aspirin, Clopidogrel and Cilostazol*) Significantly Reduces Ischemic Events after Drug-Eluting Stent Implantation

:*D*rug-*E*luting stenting followed by *C*ilostazol treatment *RE*duces *A*dverse *S*erious cardiac *E*vents

The DECREASE Registry

Seong-Wook Park, MD, PhD, FACC
Division of Cardiology, Asan Medical Center
University of Ulsan College of Medicine, Seoul, Korea

Timing of stent thrombosis and use of antiplatelet therapy



Drug-Eluting Stents: Restoring a Balance

Current Status, Future Projections

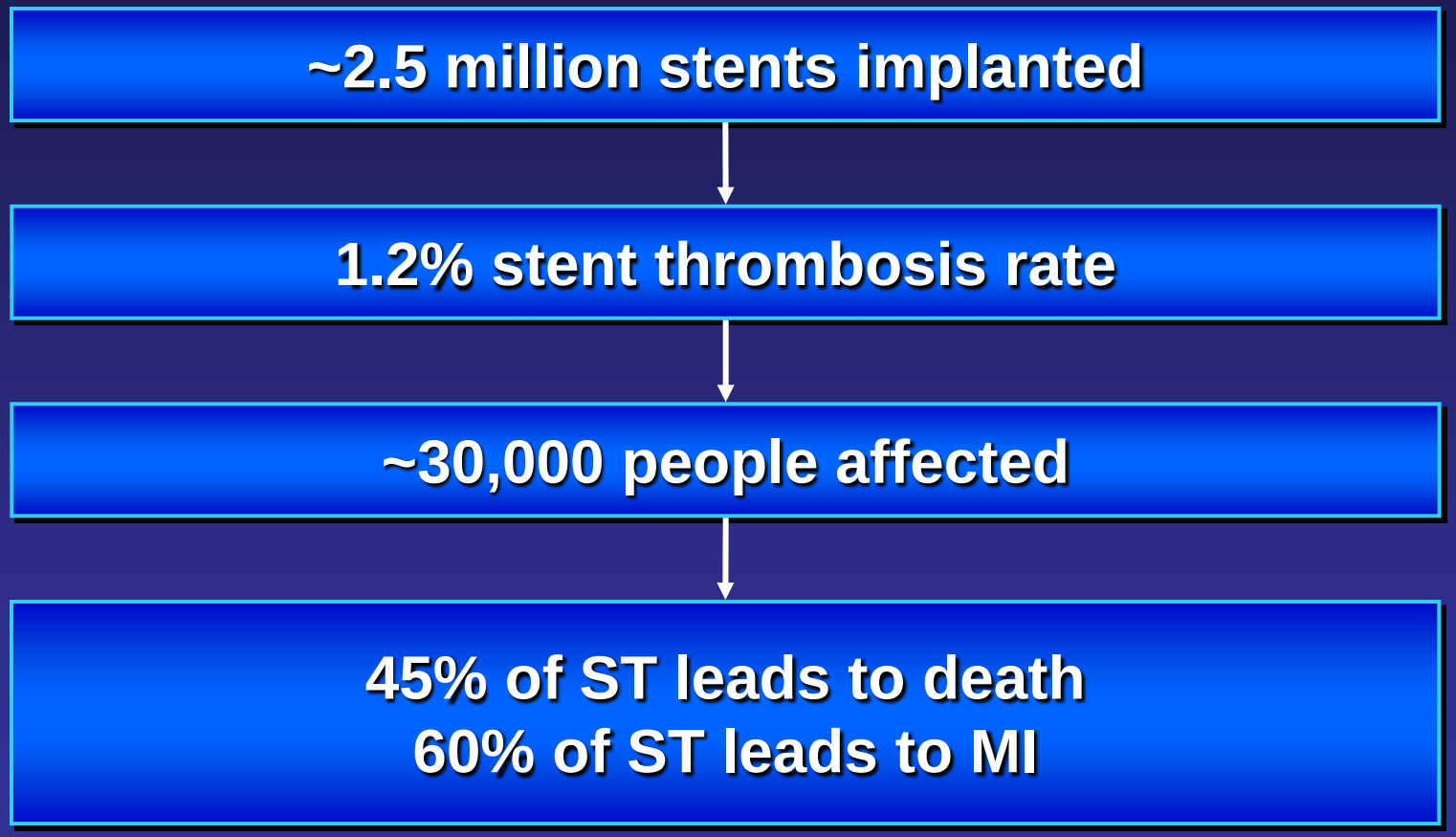
- DES represent a remarkable advance - by preventing restenosis DES have reduced the need for repeat PCI and CABG and improved the quality of life for millions of pts.
- Like any medical advance, DES have side effects, the most concerning of which is an increased incidence of late stent thrombosis in ~2-4 per 1000 pts per year.
- However, current studies suggest that on-label DES do not increase overall death and MI rates, likely because of prevention of adverse events associated with restenosis.

Drug-Eluting Stents: Restoring a Balance

Current Status, Future Projections

- Most large scale registries of DES for unrestricted use and randomized trials in off label pts do not suggest that DES increase mortality.
- Mega-trials have been initiated to examine the safety and efficacy of DES for off-label indications (MVD, LM ds., and AMI), to characterize the underlying causes of stent thrombosis, and to determine if stent thrombosis rates differ between different DES.
- In the interim, like with all drugs and devices, the risks and benefits of DES should be carefully weighed on a per pt basis, especially when considering off-label use.

A “Rare” Adverse Event Can Have Major Consequences



*Lakovou et al. *JAMA*. May 2005.
*Results are from 2005 US, www.devicelink.com.

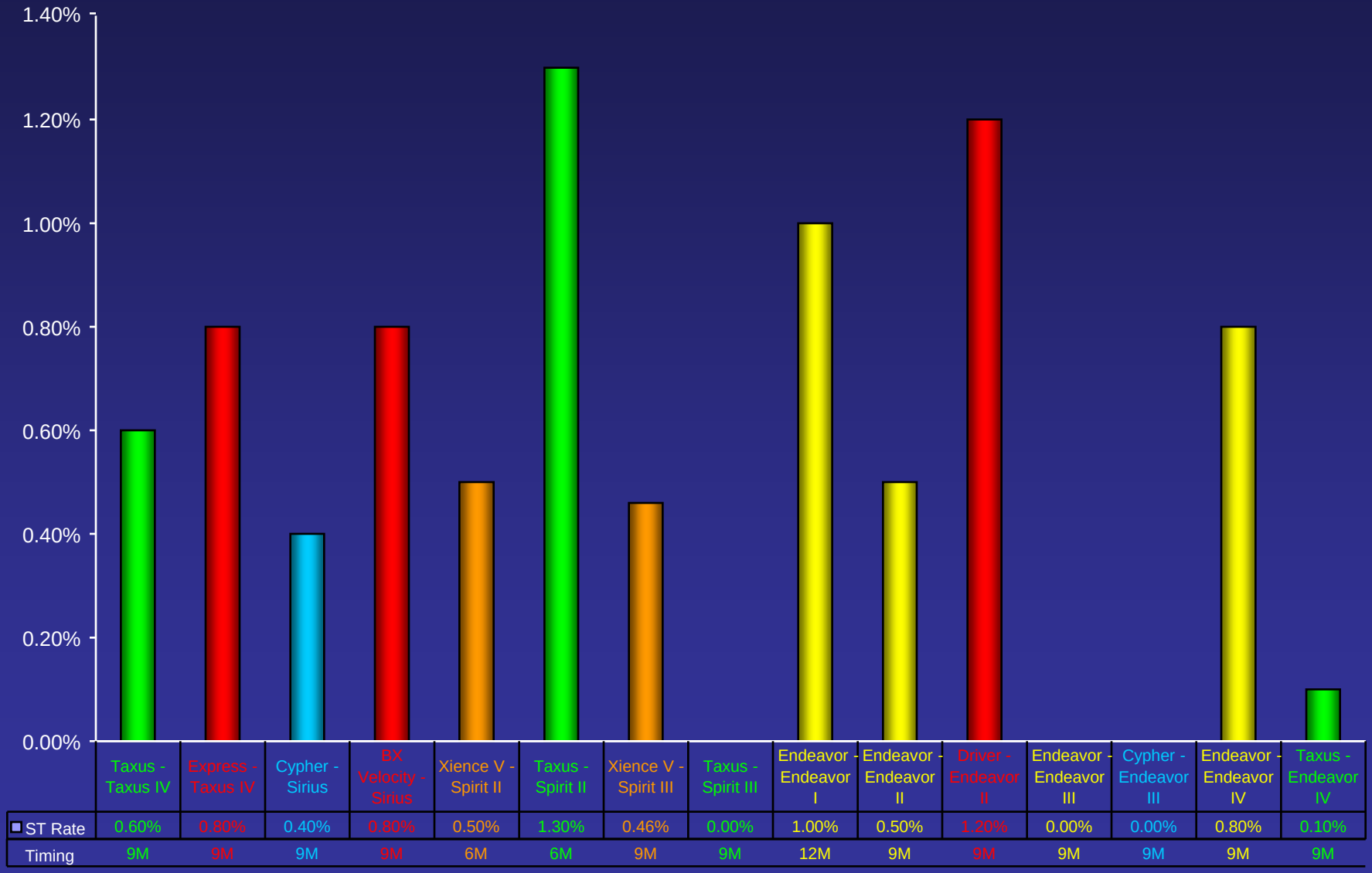
Endeavor Pooled Safety Analysis

Dual Antiplatelet Therapy (DAPT) Usage

Percent of patients on DAPT at:	1 year	2 years	3 years	4 years
ENDEAVOR (I, II, IICA)	29.1% (279/958)	11.2% (106/943)	8.5% (79/926)	8.3% (75/908)
Driver (II)	29.0% (166/572)	13.5% (76/562)	9.1% (50/548)	9.2% (50/945)

Late Stent Thrombosis: Total

ST Rates in key trials before 1 year



	Taxus - Taxus IV	Express - Taxus IV	Cypher - Sirius	BX Velocity - Sirius	Xience V - Spirit II	Taxus - Spirit II	Xience V - Spirit III	Taxus - Spirit III	Endeavor - Endeavor I	Endeavor - Endeavor II	Driver - Endeavor II	Endeavor - Endeavor III	Cypher - Endeavor III	Endeavor - Endeavor IV	Taxus - Endeavor IV
ST Rate	0.60%	0.80%	0.40%	0.80%	0.50%	1.30%	0.46%	0.00%	1.00%	0.50%	1.20%	0.00%	0.00%	0.80%	0.10%
Timing	9M	9M	9M	9M	6M	6M	9M	9M	12M	9M	9M	9M	9M	9M	9M

Late DES Thrombosis

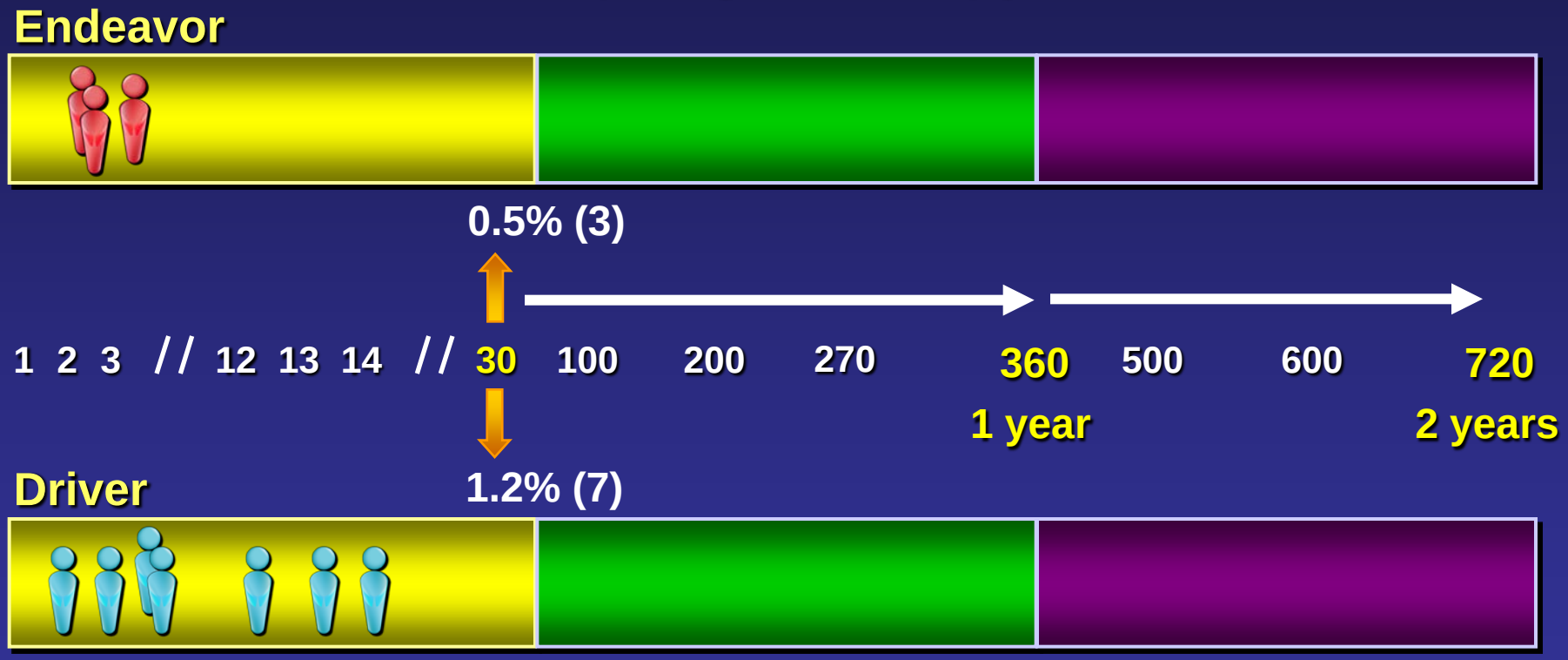
Conclusions

- Late DES thrombosis is uncommon but associated with high morbidity
- LST (beyond 1-2 yrs) is more frequent with DES than BMS
- LST is associated with D/C of antiplatelet Rx
- Etiology not well understood (likely related to delayed healing / hypersensitivity)
- Prolong dual antiplatelet Rx advisable in high risk pts

ENDEAVOR II

Safety Profile

ENDEAVOR II Clopidogrel Therapy for ≥3 months



Days Post Procedure

Defined as angiographic thrombus or subacute closure within the stented vessel at the time of the clinically driven angiographic re-study for documented ischemia (chest pain and ECG changes).
Any death not attributed to a non-cardiac cause within the first 30 days is considered a surrogate for stent thrombosis in the absence of documented angiographic stent patency.
Fajadet et al. *Circulation*. 2006;114:98-806.

Impact of Platelet Reactivity After Clopidogrel Administration on Drug-Eluting Stent Thrombosis

Piergiovanni Buonamici, MD, Rossella Marcucci, MD, Angela Migliorini, MD, Gian Franco Gensini, MD, Alberto Santini, MD, Rita Paniccia, MD, Guia Moschi, MD, Anna Maria Gori, MD, Rosanna Abbate, MD, David Antoniucci, MD

Florence, Italy

Objectives We sought to determine whether nonresponsiveness to clopidogrel as revealed by high in vitro post-treatment platelet reactivity is predictive of drug-eluting stent (DES) thrombosis.

Background No data exist about the impact of nonresponsiveness to clopidogrel on the risk of DES thrombosis.

Methods We conducted a prospective observational cohort study from July 2005 to August 2006 in an academic hospital. A total of 804 patients who had successful sirolimus- or paclitaxel-eluting stent implantation were assessed for post-treatment platelet reactivity after a loading dose of 600 mg of clopidogrel. Patients with platelet aggregation by 10 μmol adenosine 5′-diphosphate ≥70% were defined as nonresponders. All patients received chronic dual antiplatelet treatment (aspirin 325 mg and clopidogrel 75 mg daily) for 6 months. The primary end point was the incidence of definite/probable early, subacute, and late stent thrombosis at 6-month follow-up.

Results The incidence of 6-month definite/probable stent thrombosis was 3.1%. All stent thromboses were subacute or late. Of 804 patients, 105 (13%) were not responsive to clopidogrel. The incidence of stent thrombosis was 8.6% in nonresponders and 2.3% in responders ($p < 0.001$). By multivariate analysis, the predictors of stent thrombosis were as follows: nonresponsiveness to clopidogrel (hazard ratio [HR] 3.08, 95% confidence interval [CI] 1.32 to 7.16; $p = 0.009$), left ventricular ejection fraction (HR 0.95, 95% CI 0.92 to 0.98; $p = 0.001$), total stent length (HR 1.01, 95% CI 1.00 to 1.02; $p = 0.010$), and ST-segment elevation acute myocardial infarction (HR 2.41, 95% CI 1.04 to 5.63; $p = 0.041$).

Conclusions Nonresponsiveness to clopidogrel is a strong independent predictor of stent thrombosis in patients receiving sirolimus- or paclitaxel-eluting stents. (J Am Coll Cardiol 2007;49:2312–7) © 2007 by the American College of Cardiology Foundation

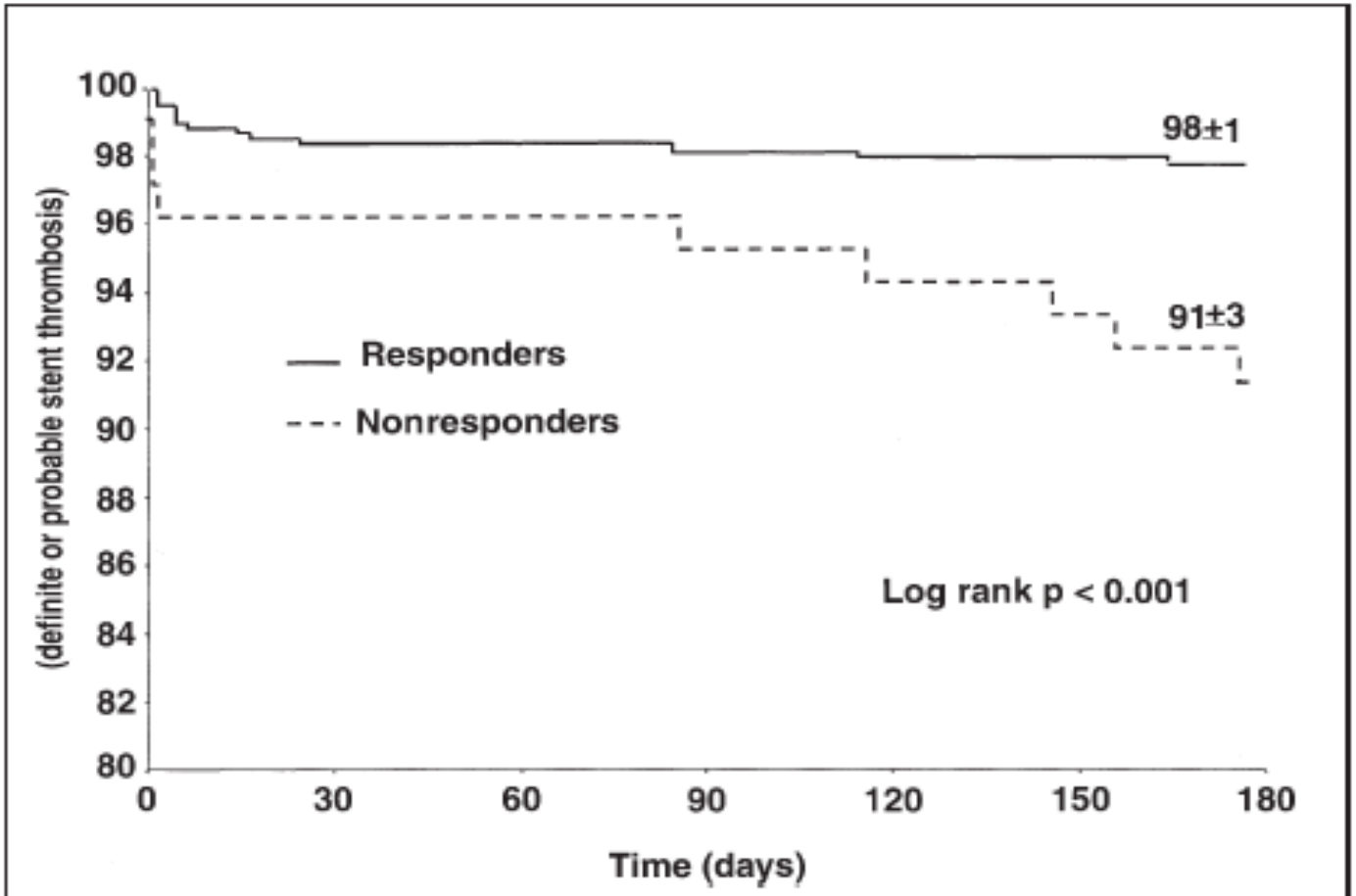


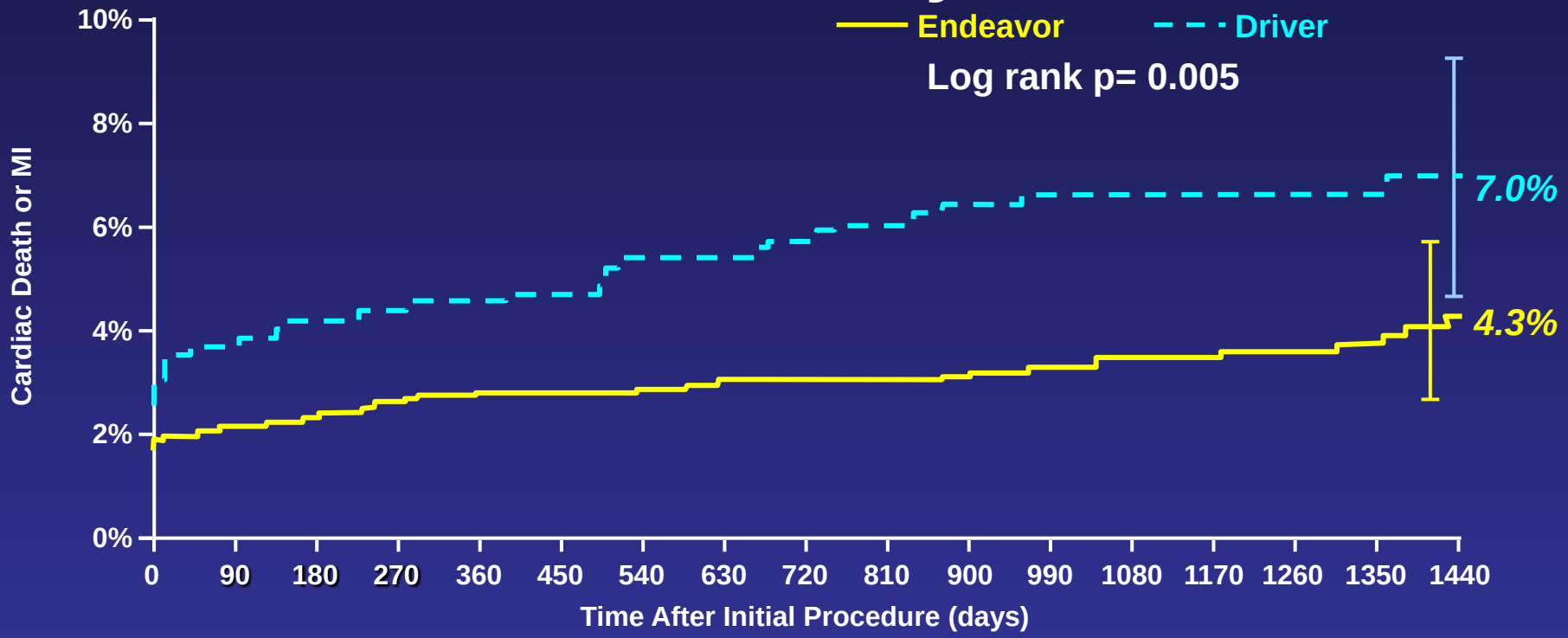
Figure 1 Kaplan-Meier Analysis of Primary End Point for Responders and Nonresponders to Clopidogrel

Conclusions

- Healing delay is inherent in the mechanism of benefit of DES's
- SAT rates appear to be similar to BMS for simple lesions
  - But the time window for risk is longer for DES's (i.e. late DES thrombosis)
  - Premature discontinuation of anti-platelet therapy increases risk of thrombosis
- Thrombosis rates likely increased for complex lesion and patient subsets
  - Major side branches, bifurcations, overlapped stents, thrombus containing lesions, poor distal runoff
  - Renal failure, diabetics

Endeavor Safety Analysis

Cumulative Incidence of Cardiac Death and MI to 1440 Days



Cardiac Death or MI	0	30	270	360	720	1080	1440
Endeavor	*2132*	*2083*	*2052*	*2014*	*1219*	*1186*	*622*
# Events	30	12	14	4	3	5	5
% CI	1.4%	2.0%	2.6%	2.8%	3.1%	3.5%	4.3%
Driver	*596*	*573*	*566*	*560*	*545*	*535*	*525*
# Events	15	6	5	1	7	5	2
% CI	2.5%	3.5%	4.4%	4.5%	5.8%	6.6%	7.0%

Endeavor Pooled Safety Analysis: J Meredith, et al. PCR. 2008.

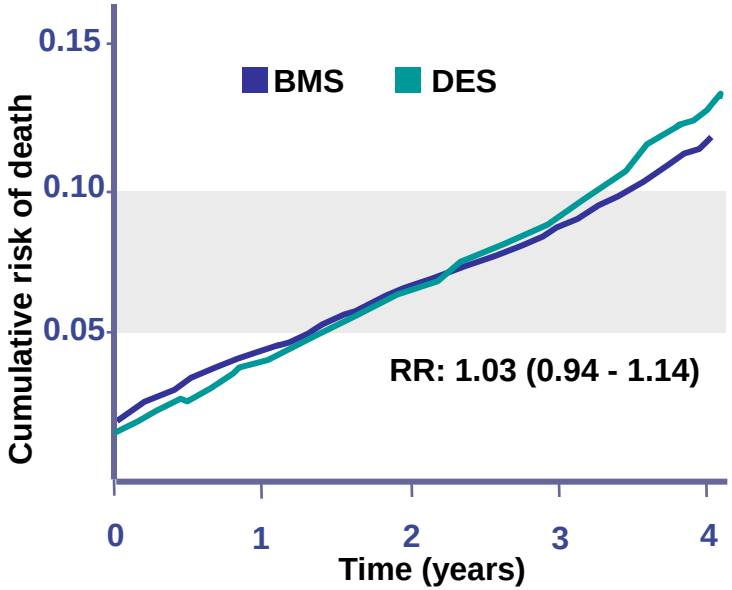
SCAAR 2007 Report

Composite of Death up to 4 years Post-Procedure

“During 4 years follow-up …

Total cohort n=35,262

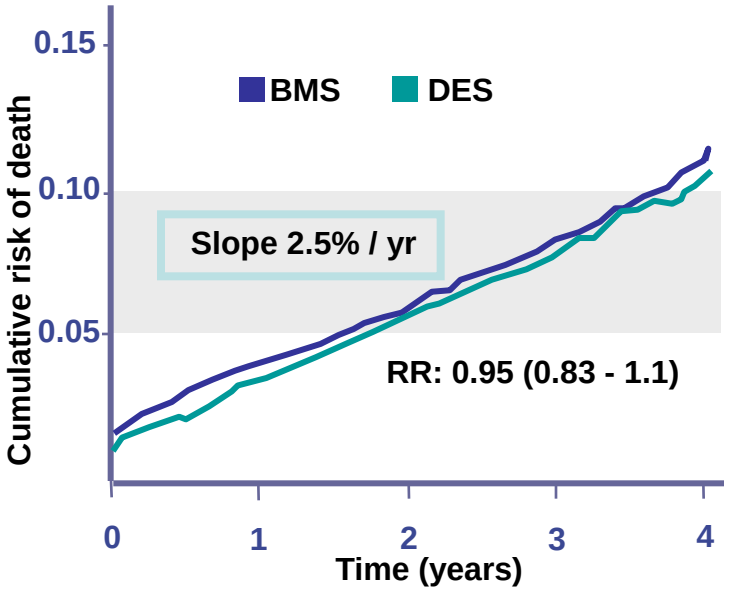
2003 – 2005 Adjusted Risk



BMS	18,769	18,136	17,948	16,109	13,401	10,326	7,158	3,970	1,179
DES	12,015	11,705	11,559	9,020	6,181	3,844	2,153	847	115

One stent cohort n=18,937

2003 – 2005 Adjusted Risk



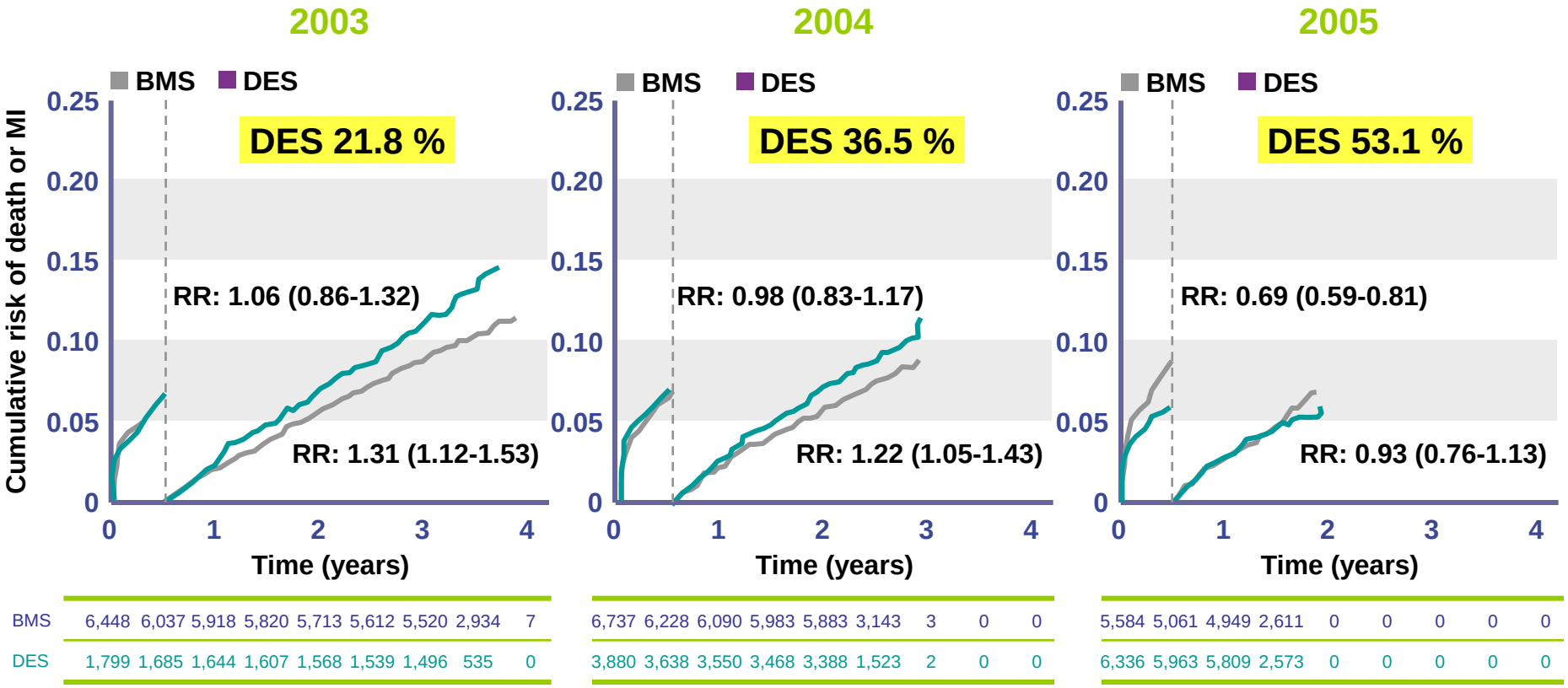
BMS	12,556	12,185	12,061	10,837	9,001	6,920	4,824	2,697	783
DES	6,381	6,237	6,161	4,844	3,280	2,038	1,140	462	58

…no more overall significant difference in mortality”

Lagerqvist B, et al. Oral Presentation. ESC 200

James S. Oral Presentation. TCT 2007

SCAAR 2007 Report
Landmark Analyses per Year
Total cohort (Death or MI: risk adjusted)
Prespecified landmarks at 6 months



11/11/2008

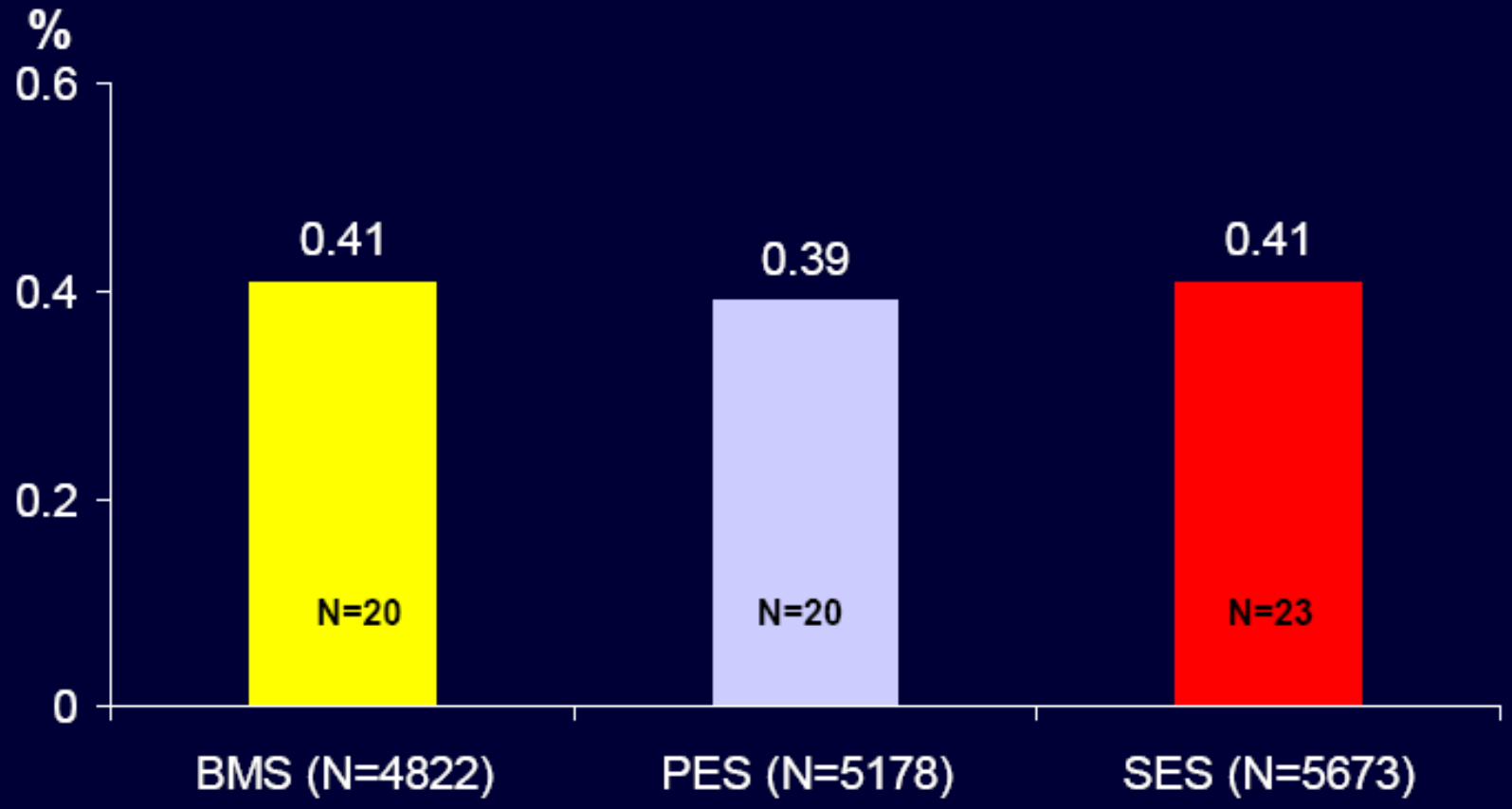
James S, et al. Oral Presentation. ESC 2007

James S. Oral Presentation. TCT 2007

Late Definite ST (>1 Month < 1 Year) Drug-Eluting vs Bare Metal Stents

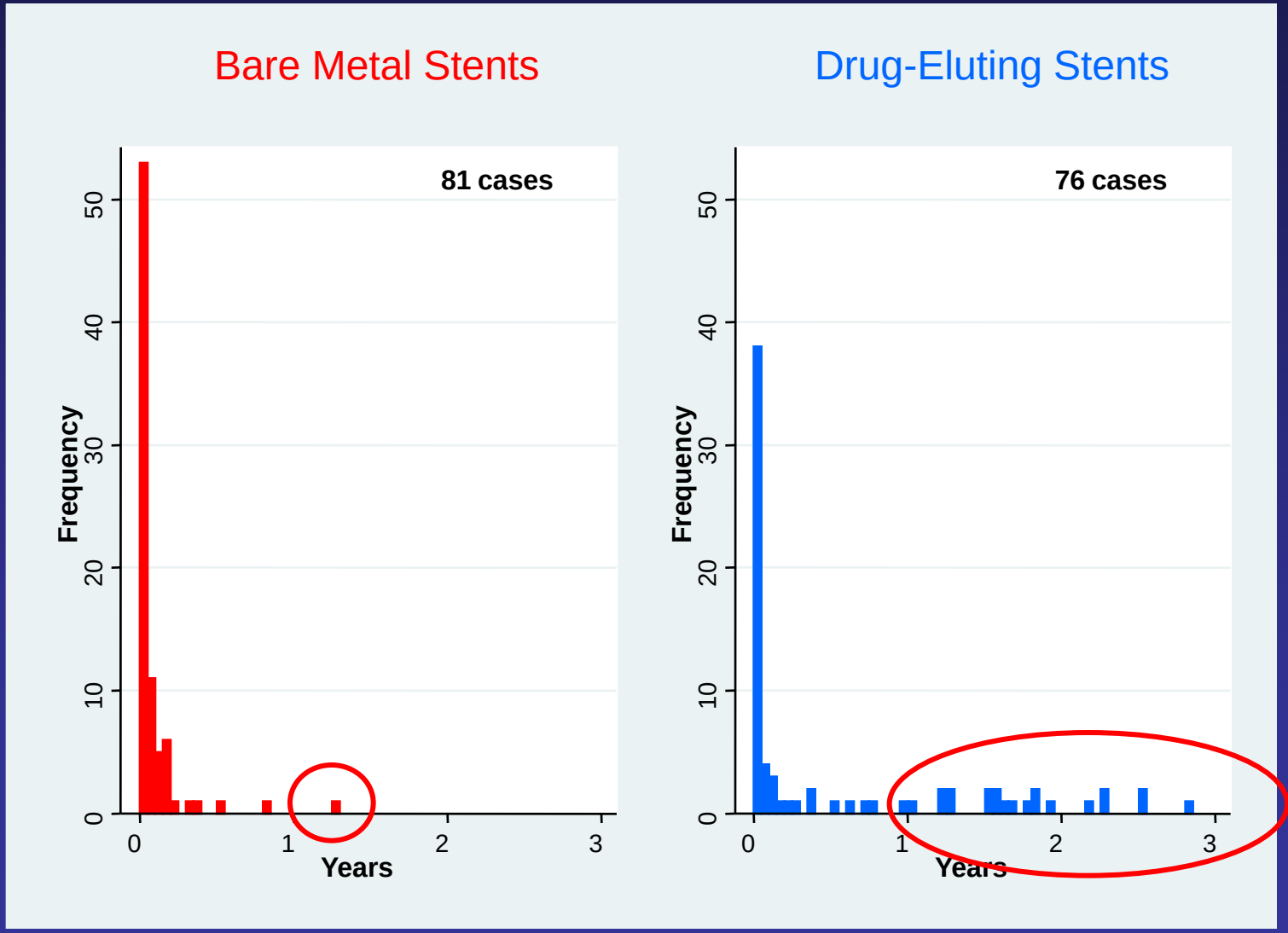
Stettler C et al. *Lancet* 2007;370:937-48

63 late ST cases (0.4%) of 18,023 patients



Definite Stent Thrombosis: BMS vs. DES

The Bern Experience 1995-2005



Endeavor Safety Analysis

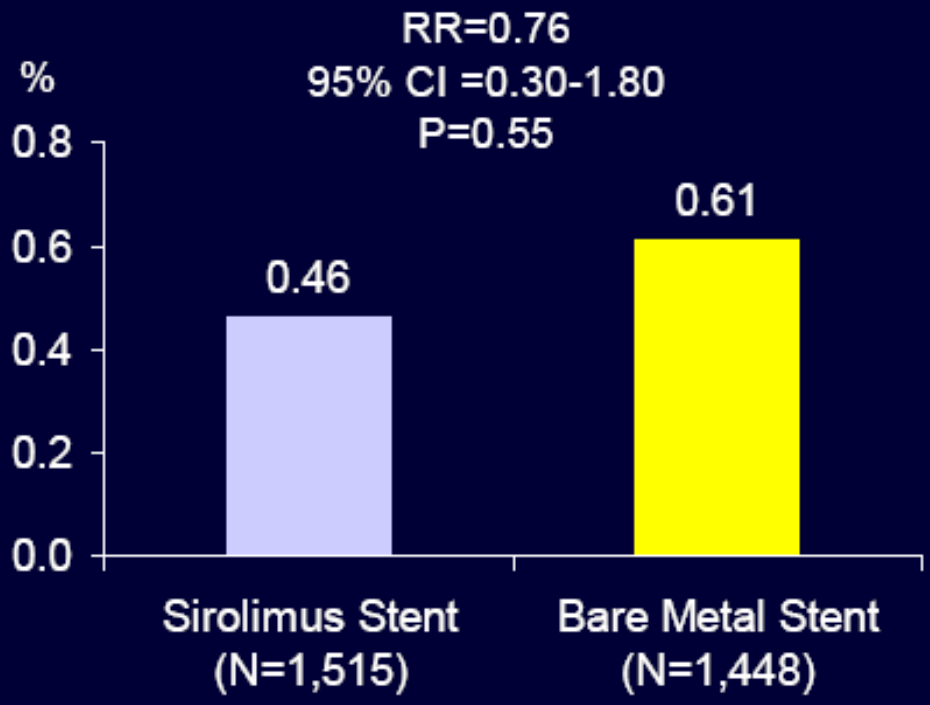
Cumulative Incidence of Stent Thrombosis by Time Interval (ARC definite and probable)

	Cumulative Incidence -%			
	Endeavor n = 2132	*[95% CI]*	Driver n = 596	*[95% CI]*
Early (0-30d)	0.3%	[0.09,0.57]	1.2%	[0.31,2.04]
Late (31-360d)	0.3%	[0.04,0.52]	0.2%	[0.00,0.51]
Very Late (361d-4y)	0.1%	[0.00,0.32]	0.2%	[0.00,0.56]
Cumulative (to 4y)	0.7%	[0.13,1.30]	1.5%	[0.41,2.64]

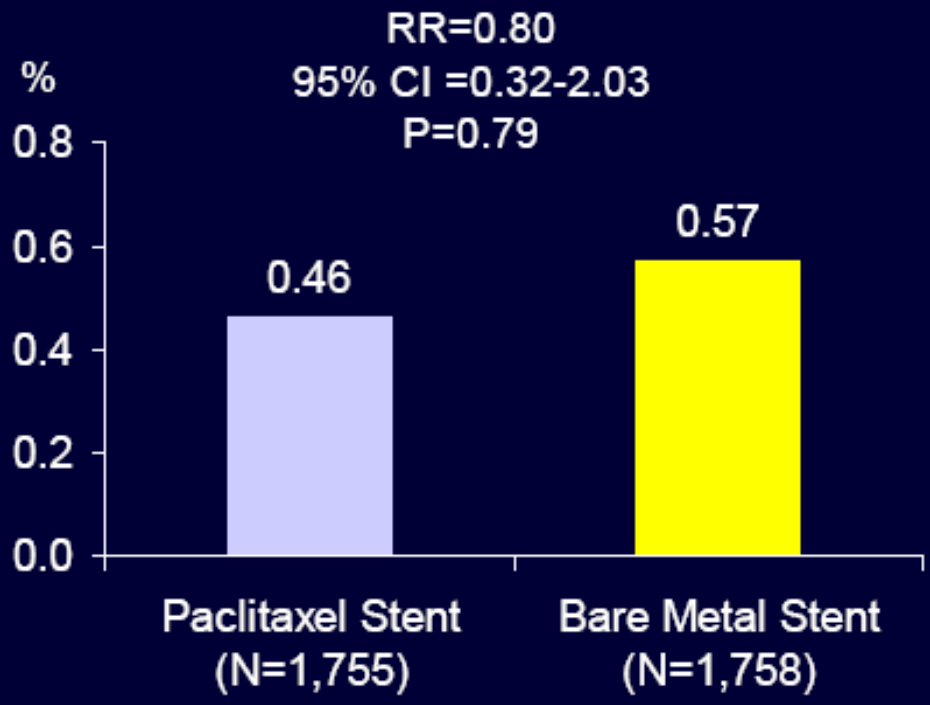
Standard error was estimated by Peto formula

Early Stent Thrombosis

Meta-analysis
SES vs BMS
Bavry A et al. *Am J Card* 2005

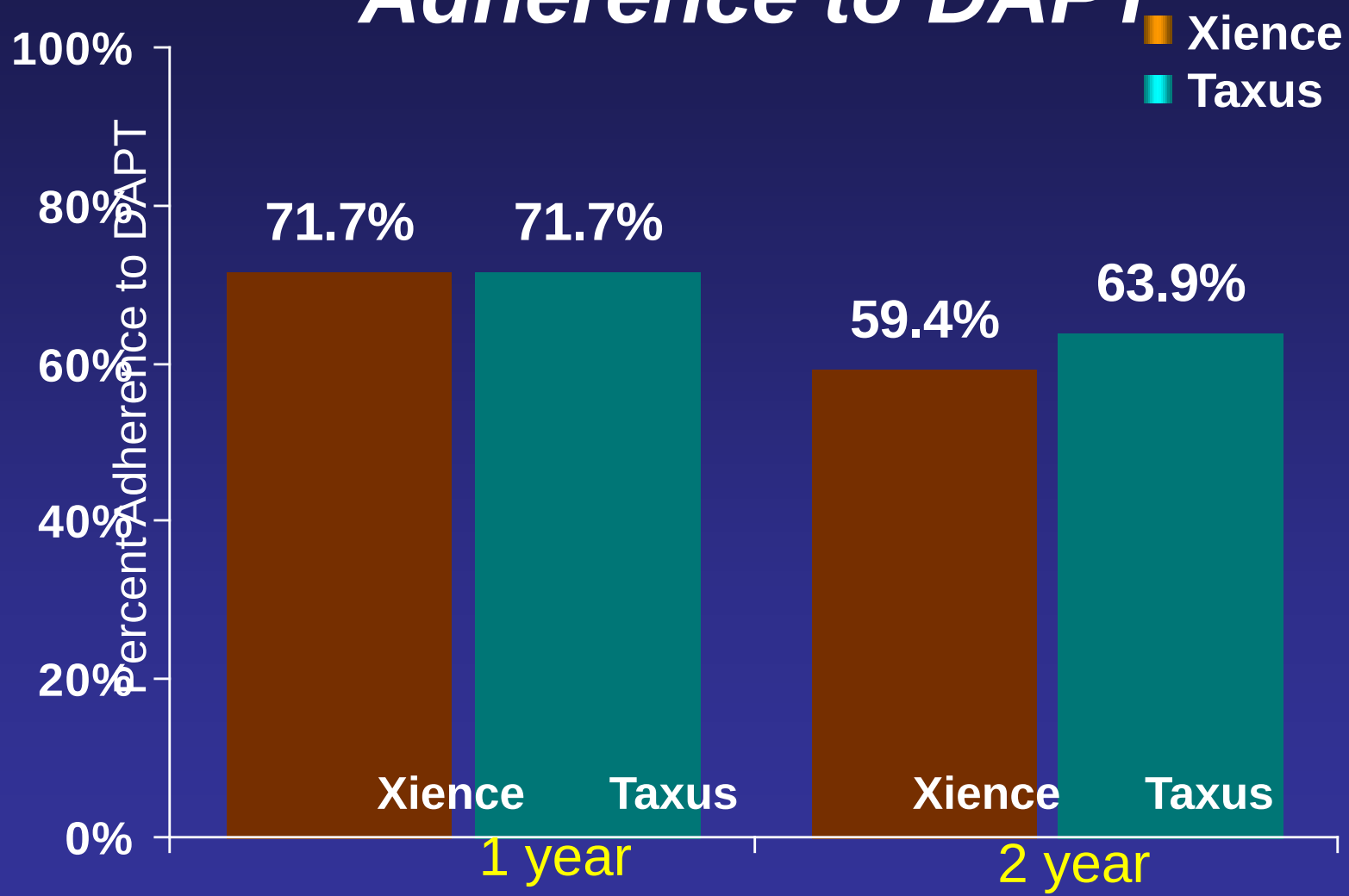


Meta-analysis
PES vs BMS
Stone G et al. *NEJM* 2007



Spirit III

Adherence to DAPT



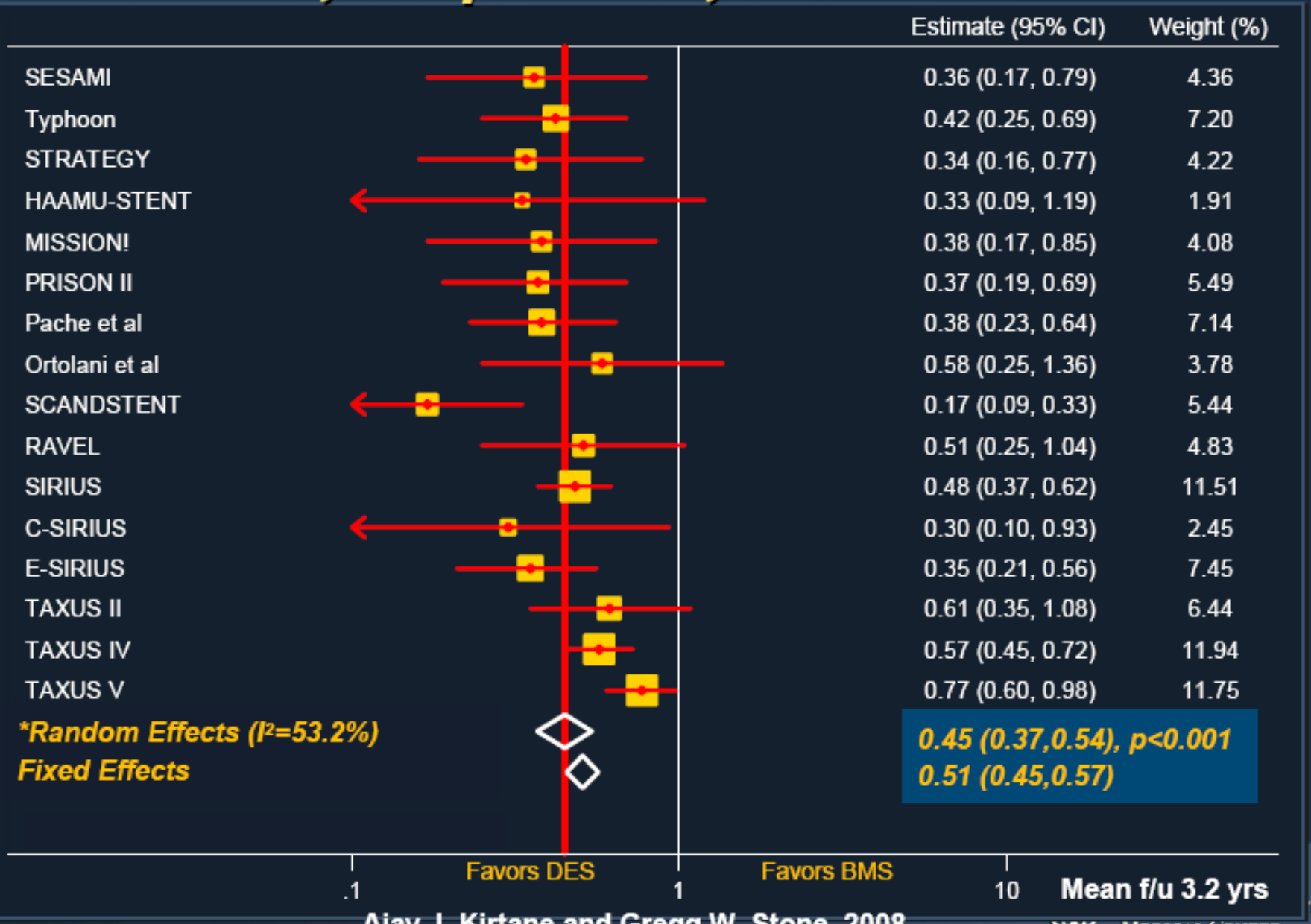
What About SCAAR?

SCAAR Expansion, ESC 2008

	2003–2004	2003–2005
Follow-Up	1–3 years	1–4 years
Stents implanted (BMS / DES)	37,750 (26,398 / 11,352)	61,896 (37,377 / 24,519)
Stent procedures (Only BMS / with DES)	24,215 (16,256 / 7,959)	39,432 (22,878 / 16,554)
Stented patients (Only BMS / with DES)	19,771 (13,738 / 6,033)	35,266 (21,480 / 13,786)
Endpoints:		
MI, 2003–2006*	2,463	4,160
Death, 2003–2006*	1,424	2,957

*From the Swedish hospital d/c and Riks-HIA registries; ** From the Swedish population registry

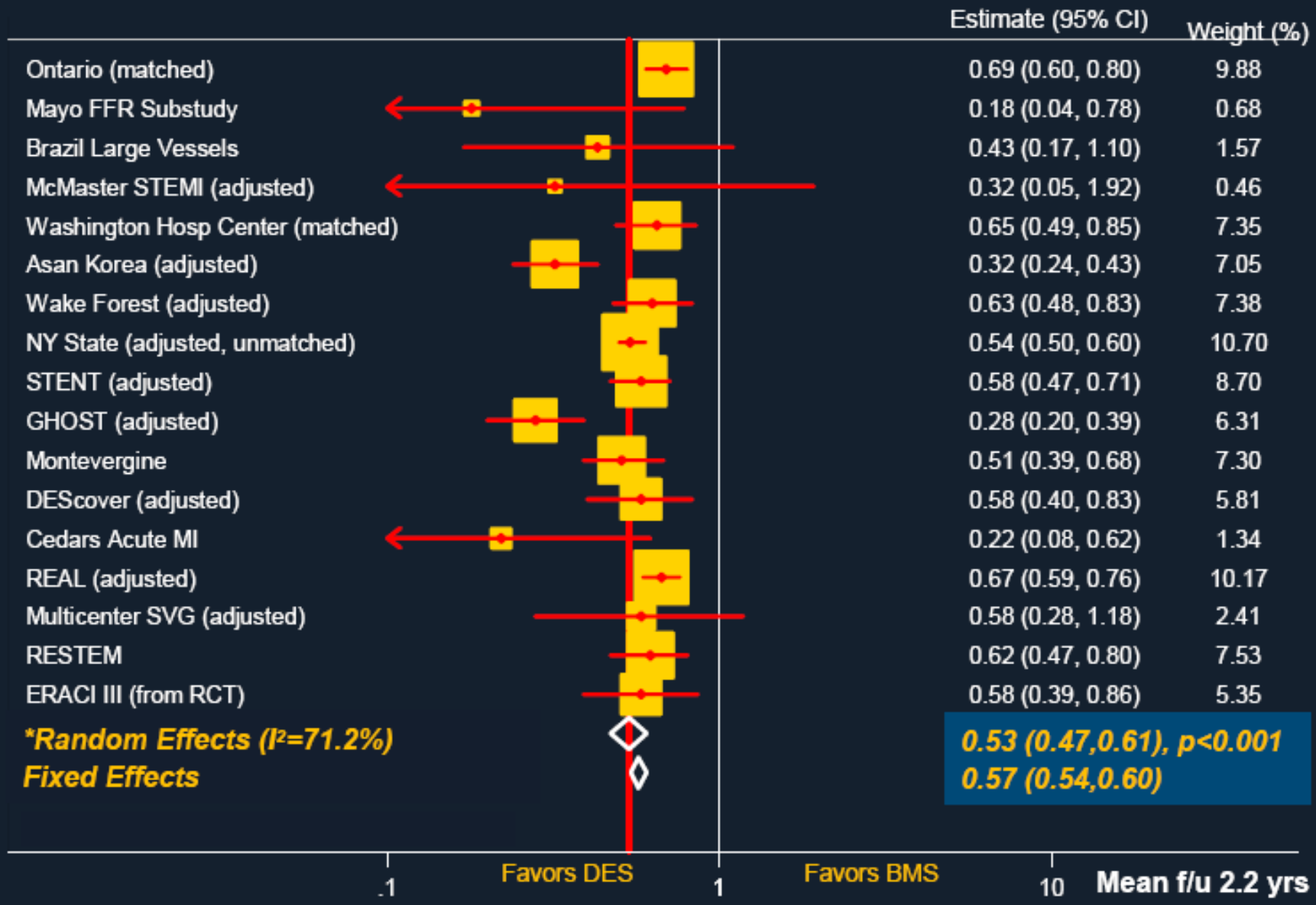
TVR: All RCTs
7,291 patients, 16 trials



Ajay J. Kirtane and Gregg W. Stone, 2008

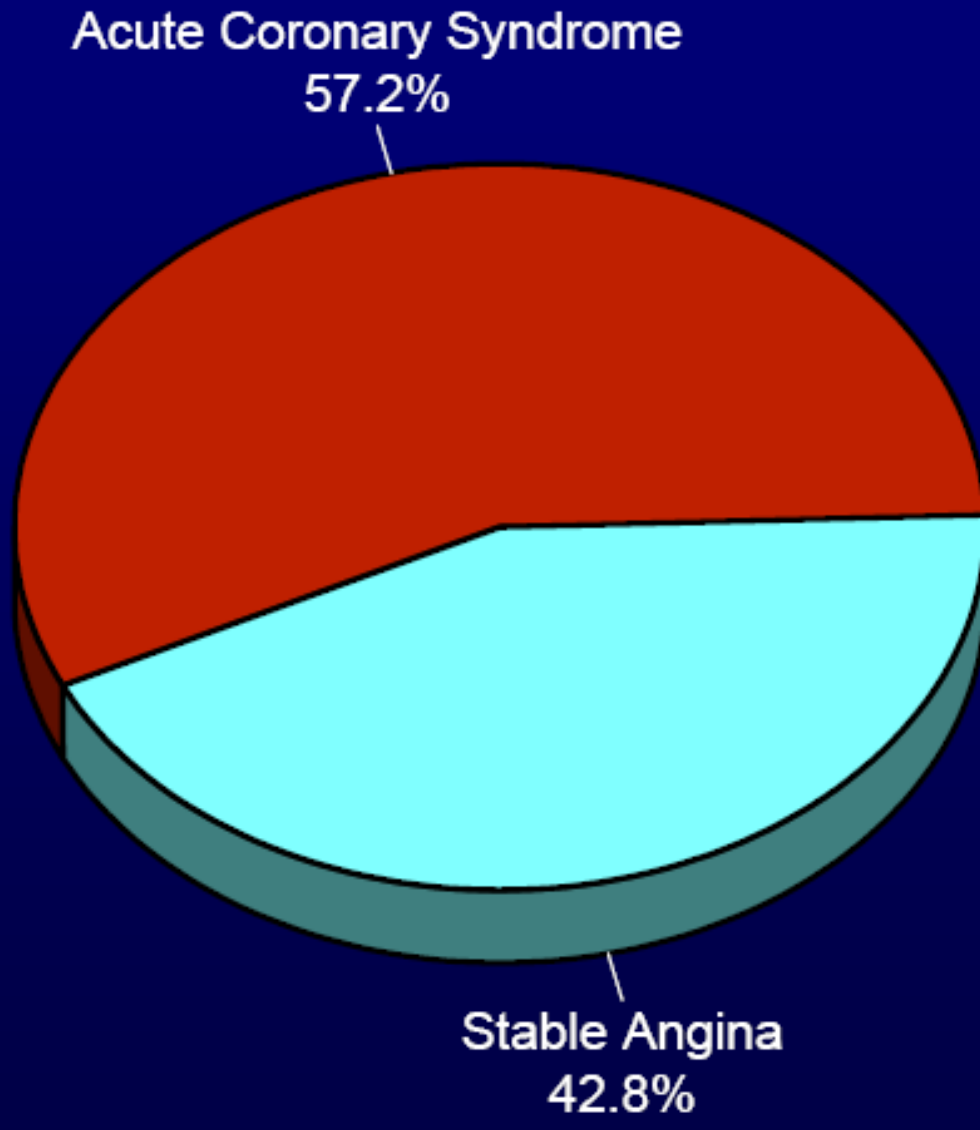
TVR: All Registries

73,819 patients, 17 registries



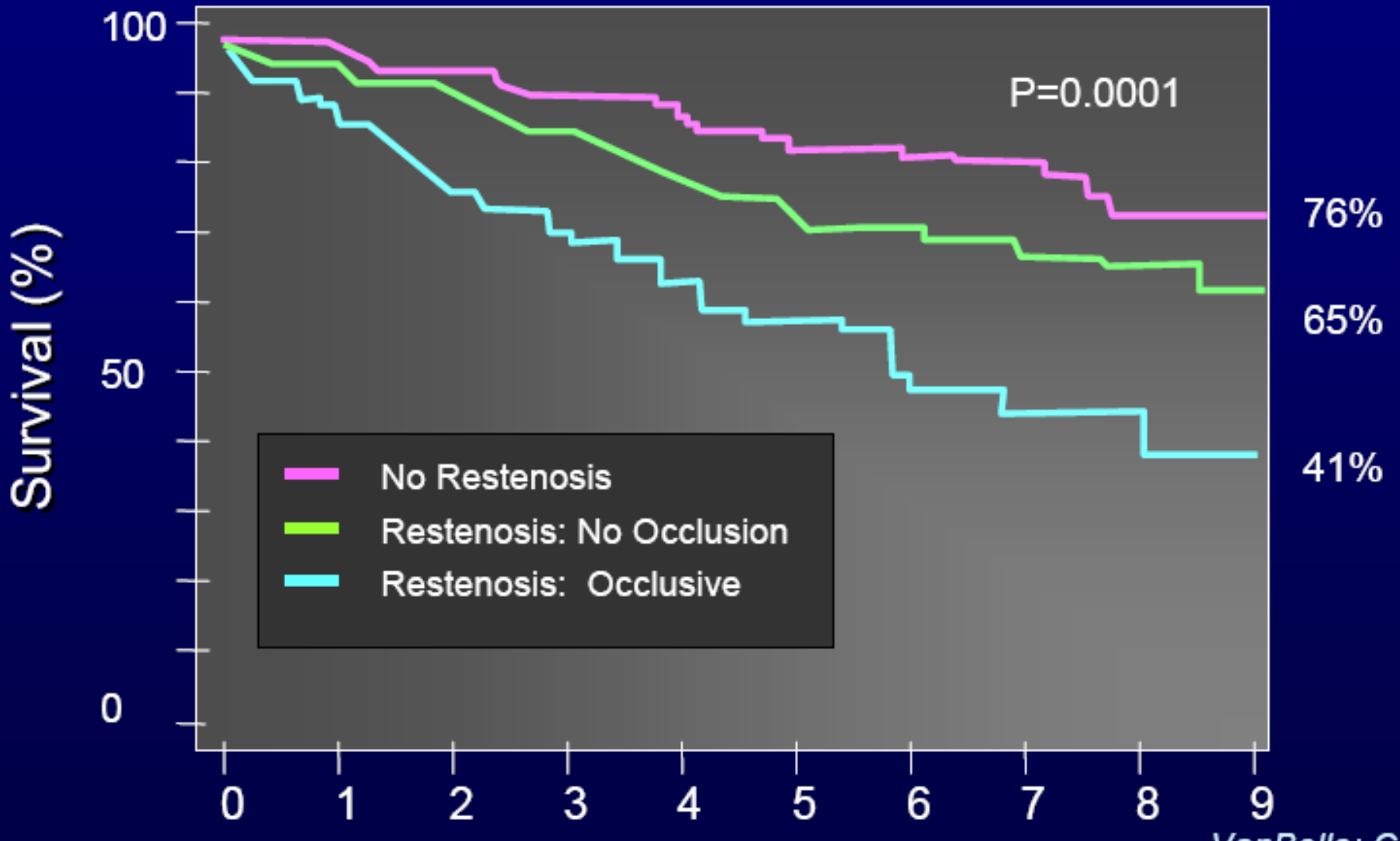
Presentation of In-stent Restenosis in the PRESTO Trial

- 1,441 of 11,484 patients had in-stent restenosis as an indication for PCI at the time of enrollment



Assali; AJC; 2006; 98; 729

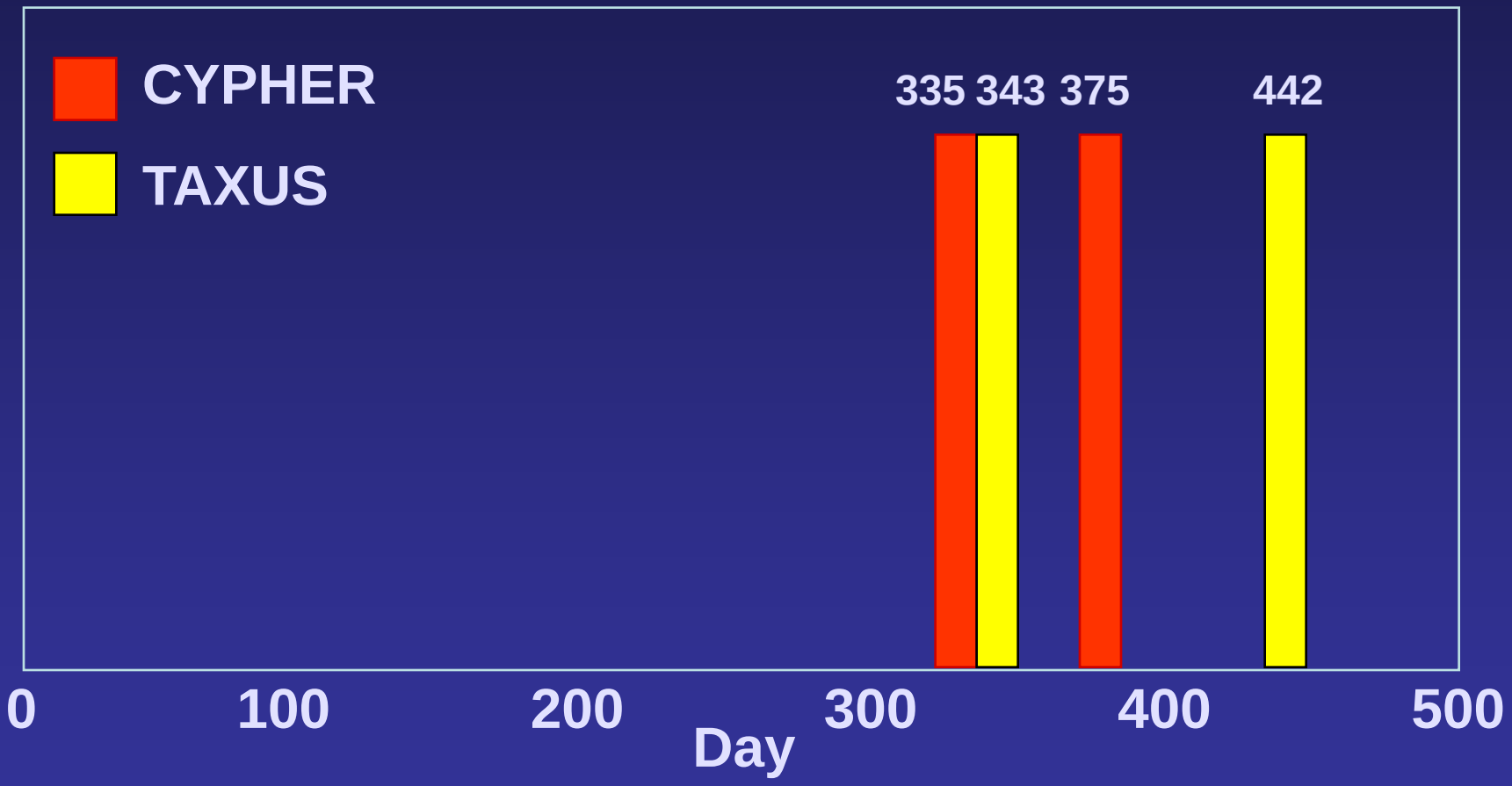
Mortality in Diabetic Patients with Restenosis *(N=603)*



VanBelle: Ci

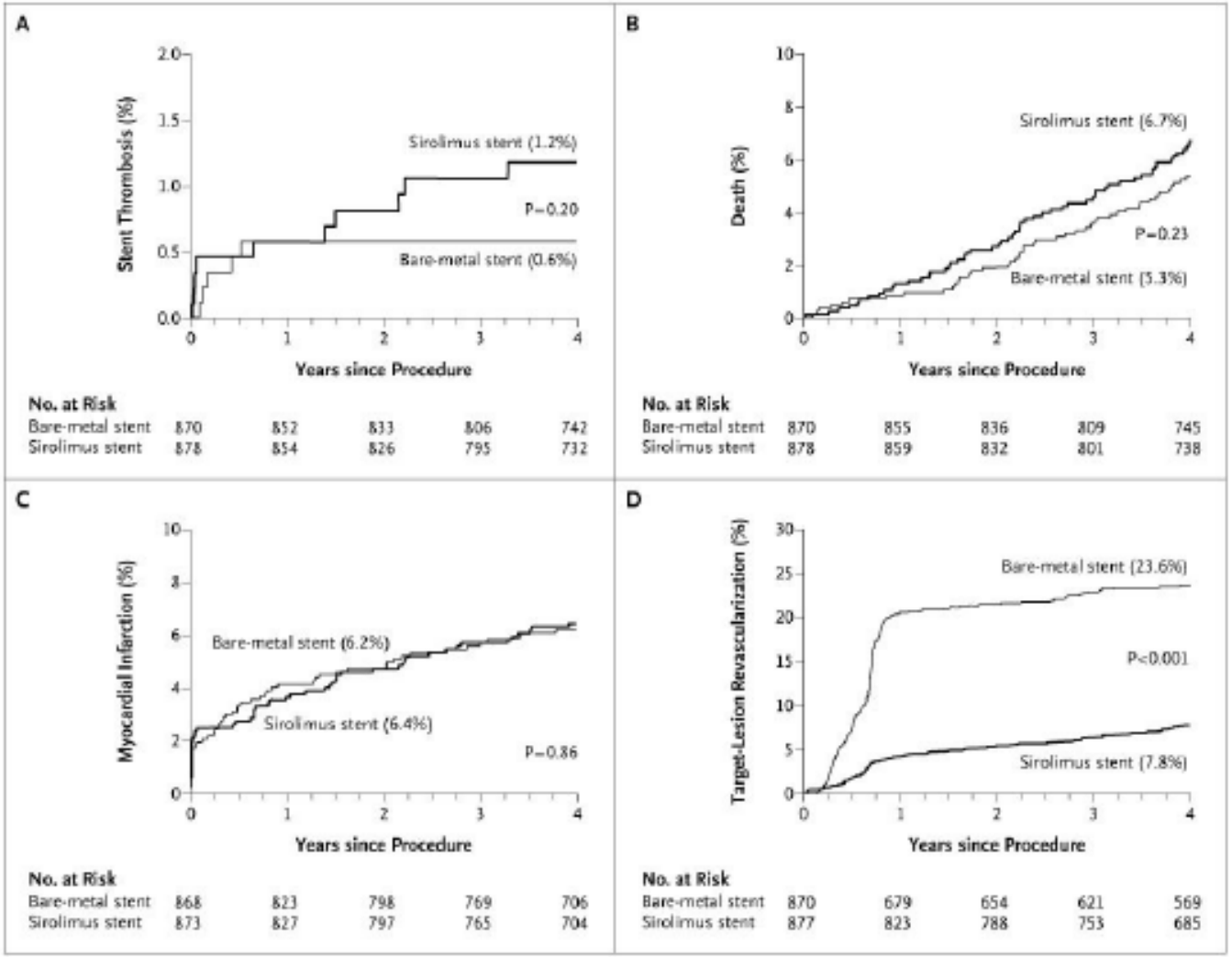
Very Late Stent Thrombosis

Initial Cases and Discussion: DAPT Prior



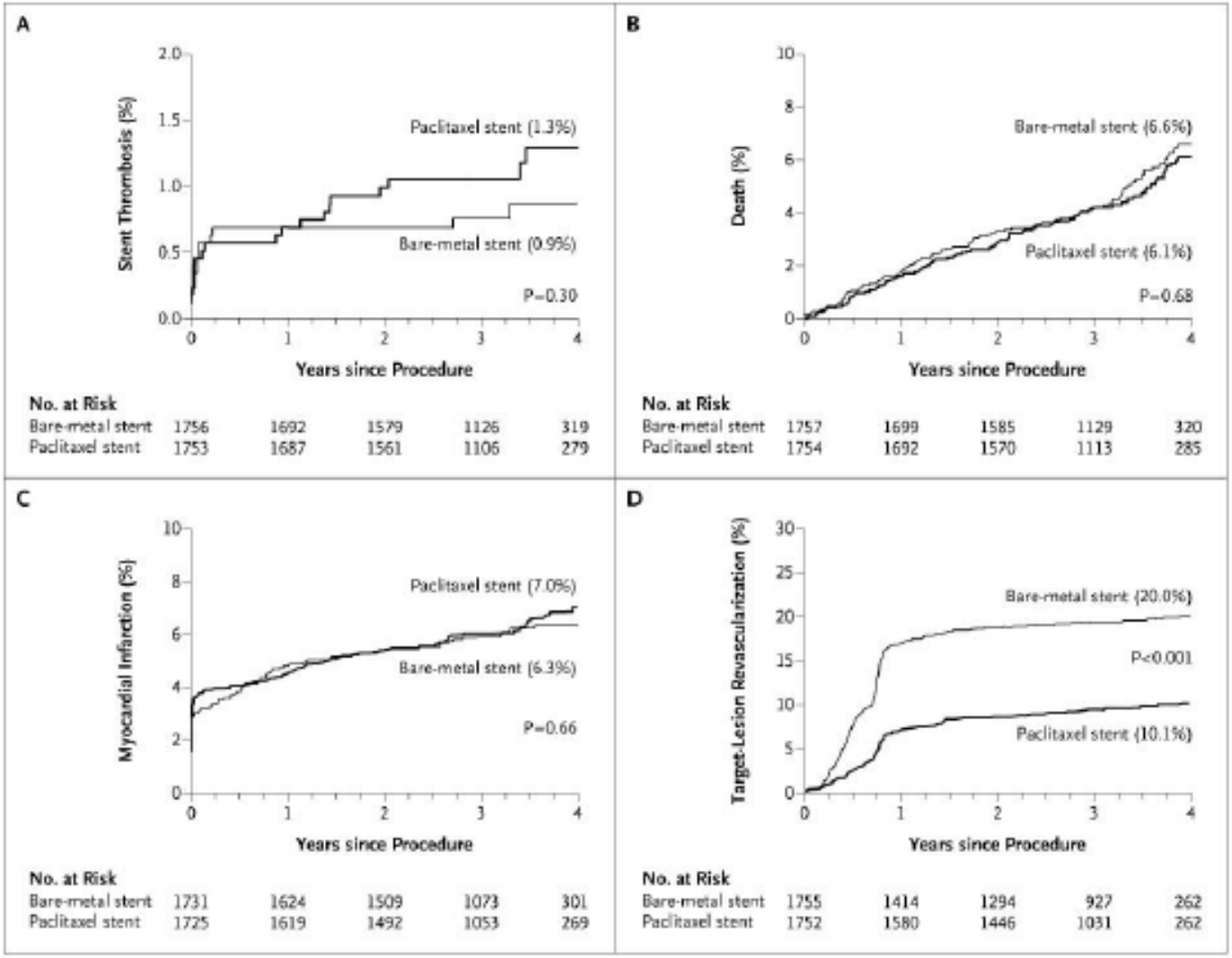
McFadden EP et al. Lancet 2004; 364:1519–21

Kaplan-Meier Curves Representing the Estimated 4-Year Cumulative Incidence Rates of Stent Thrombosis, Death, Myocardial Infarction, and Target-Lesion Revascularization for the Pooled Randomized Trials of Sirolimus-Eluting Stents and Bare-Metal Stents



Stone G et al. N Engl J Med 2007;356:998-100

Kaplan-Meier Curves Representing the Estimated 4-Year Cumulative Incidence Rates of Stent Thrombosis, Death, Myocardial Infarction, and Target-Lesion Revascularization for the Pooled Randomized Trials of Paclitaxel-Eluting Stents and Bare-Metal Stents

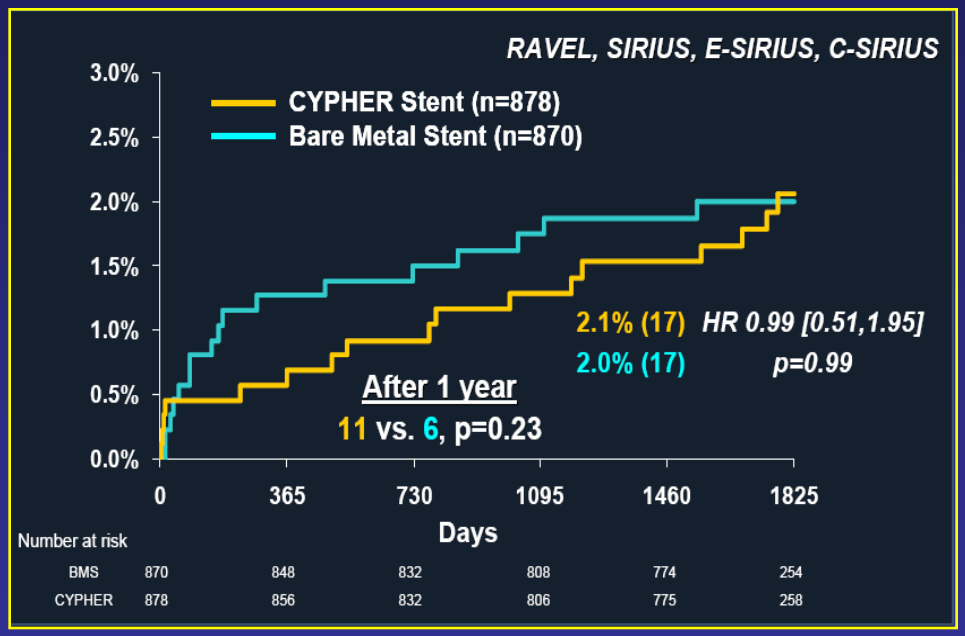


Stone G et al. N Engl J Med 2007;356:998-100

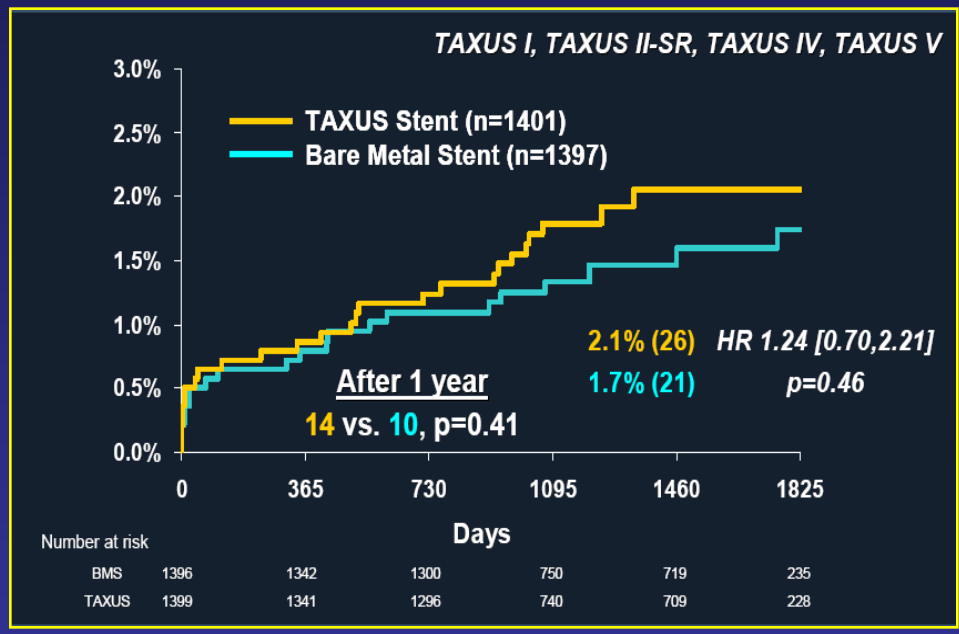
Stent Thrombosis

Freedom From (ARC Definite/Probable) Stent Thrombosis

RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS (n=1,748)



TAXUS I, II, IV, V, VI (n=3,506)



9 of 11 BMS patients who had an ST due to intervening TLR received brachytherapy

Kirtane et al. *TCT*. 2007.

*Includes intervening TLR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

Laura Mauri, M.D., Wen-hua Hsieh, Ph.D., Joseph M. Massaro, Ph.D., Kalon K.L. Ho, M.D., Ralph D'Agostino, Ph.D., and Donald E. Cutlip, M.D.

ABSTRACT

BACKGROUND

Definitions of stent thrombosis that have been used in clinical trials of drug-eluting stents have been restrictive and have not been used in a uniform manner.

METHODS

We applied a hierarchical classification of stent thrombosis set by the Academic Research Consortium (ARC) across randomized trials involving 878 patients treated with sirolimus-eluting stents, 1400 treated with paclitaxel-eluting stents, and 2267 treated with bare-metal stents. We then pooled 4 years of follow-up data. All events were adjudicated by an independent clinical-events committee.

RESULTS

The cumulative incidence of stent thrombosis according to the original protocol definitions was 1.2% in the sirolimus-stent group versus 0.6% in the bare-metal–stent group (P=0.20; 95% confidence interval [CI], −0.4 to 1.5) and 1.3% in the paclitaxel-stent group versus 0.8% in the bare-metal–stent group (P=0.24; 95% CI, −0.3 to 1.4). The incidence of definite or probable stent thrombosis as defined by the ARC was 1.5% in the sirolimus-stent group versus 1.7% in the bare-metal–stent group (P=0.70; 95% CI, −1.5 to 1.0) and 1.8% in the paclitaxel-stent group versus 1.4% in the bare-metal–stent group (P=0.52; 95% CI, −0.7 to 1.4). The incidence of definite or probable events occurring 1 to 4 years after implantation was 0.9% in the sirolimus-stent group versus 0.4% in the bare-metal–stent group and 0.9% in the paclitaxel-stent group versus 0.6% in the bare-metal–stent group.

CONCLUSIONS

The incidence of stent thrombosis did not differ significantly between patients with drug-eluting stents and those with bare-metal stents in randomized clinical trials, although the power to detect small differences in rates was limited.

CUORE
COLUMBUS

Baseline Clinical and Procedural Characteristics: Milan Experience

Variable	On Label	Off Label	P Value
Pts	364	680	
Male	325(89.3%)	603(88.7%)	0.84
Age (yrs)	63.8±10.6	63.4±10.6	0.38
EF (%)	54.2±9.1	53.2±9.6	0.56
Diabetes Mellitus	64(17.6%)	137(20.1%)	0.32
Nr Stents per Pt median (range)	2 (1-8)	3 (1-10)	0.0001
Total stent length (mm) Median (IQR)	33 (26-66)	60(36-99)	0.0001
Pts with >1 stent per les	79(21.7%)	192(28.2%)	0.02

ORIGINAL ARTICLE

Long-Term Outcomes with Drug-Eluting Stents versus Bare-Metal Stents in Sweden

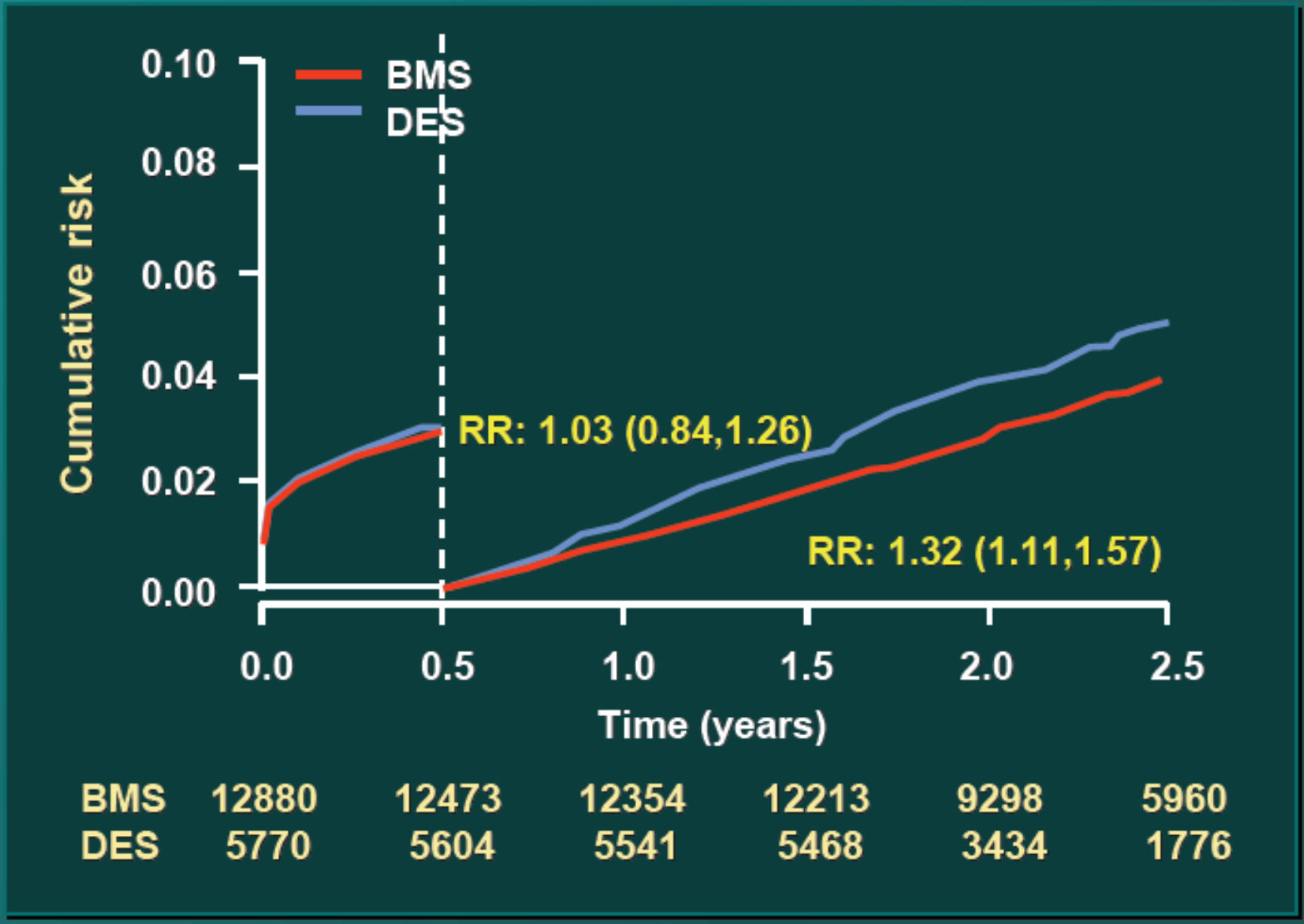
Bo Lagerqvist, M.D., Ph.D., Stefan K. James, M.D., Ph.D., Ulf Stenestrand, M.D., Ph.D., Johan Lindbäck, M.Sc., Tage Nilsson, M.D., Ph.D., and Lars Wallentin, M.D., Ph.D., for the SCAAR Study Group*

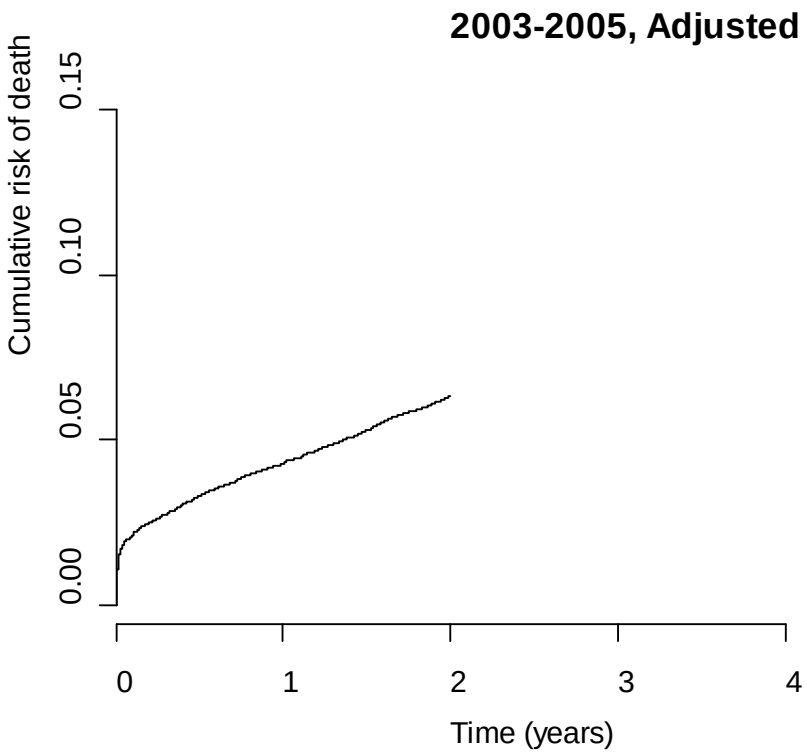
ooled analysis of 6033 patients treated with DES and
13,738 patients treated with BMS
ata from Swedish Coronary Angiography and Angioplasty Registry

utcome analysis was based on 1424 deaths and 2463 myocardial
farction during 3 years follow-up period and was adjusted for
fferences in baseline characteristics.

NEJM 2007;356:1009-

Death (Adjusted)




2003-2005, Adjusted
Cumulative risk of death
0.00
0.05
0.10
0.15
0
1
2
3
4
Time (years)

Death/MI-

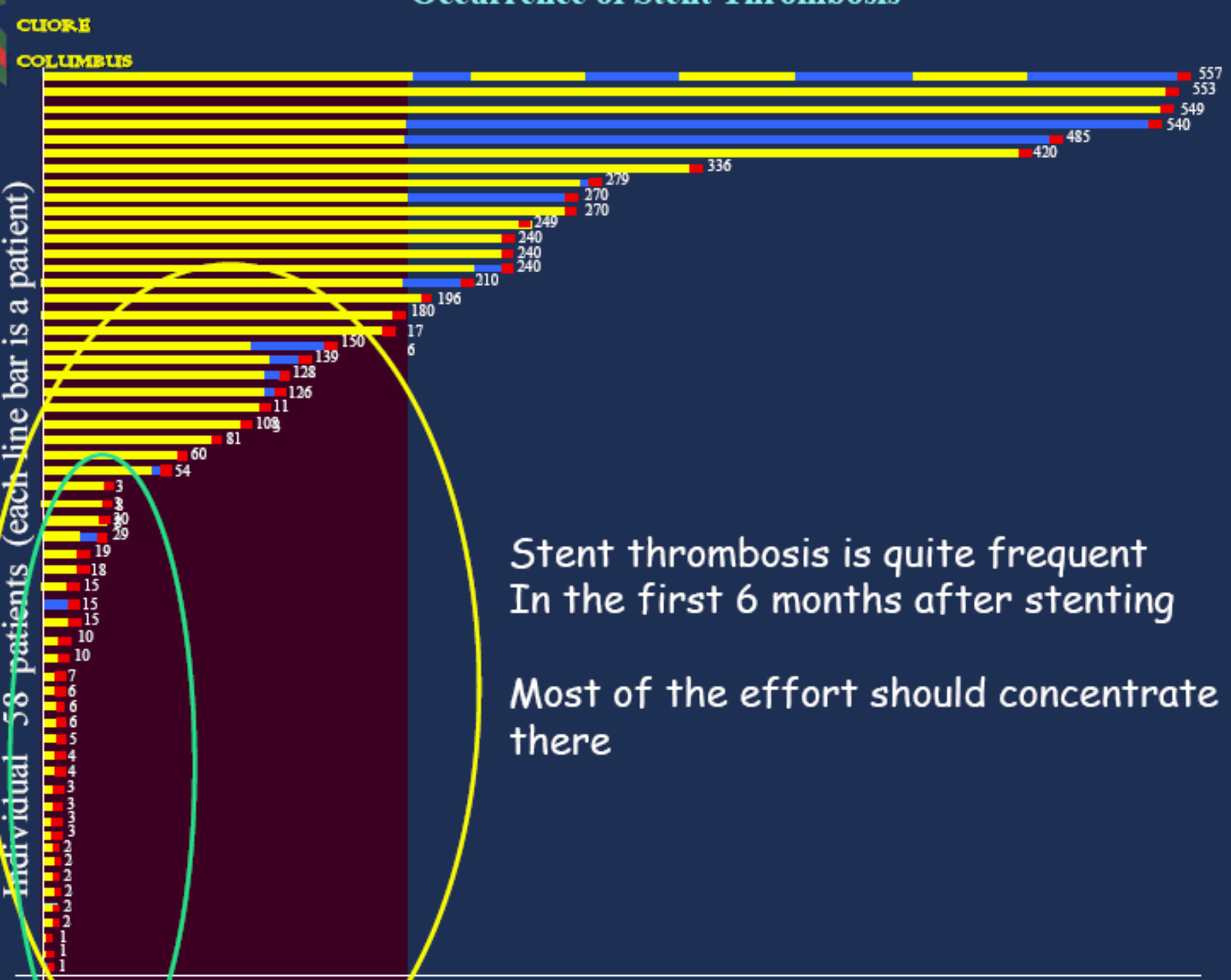
total cohort

Year by year

Occurrence of Stent Thrombosis

CUORE

COLUMBUS



Stent thrombosis is quite frequent
In the first 6 months after stenting

Most of the effort should concentrate there

Drug Eluting Stents
Assessing Stent Thrombosis

Timing of Event

- Acute (24 hours)
- Subacute (1-30 days)

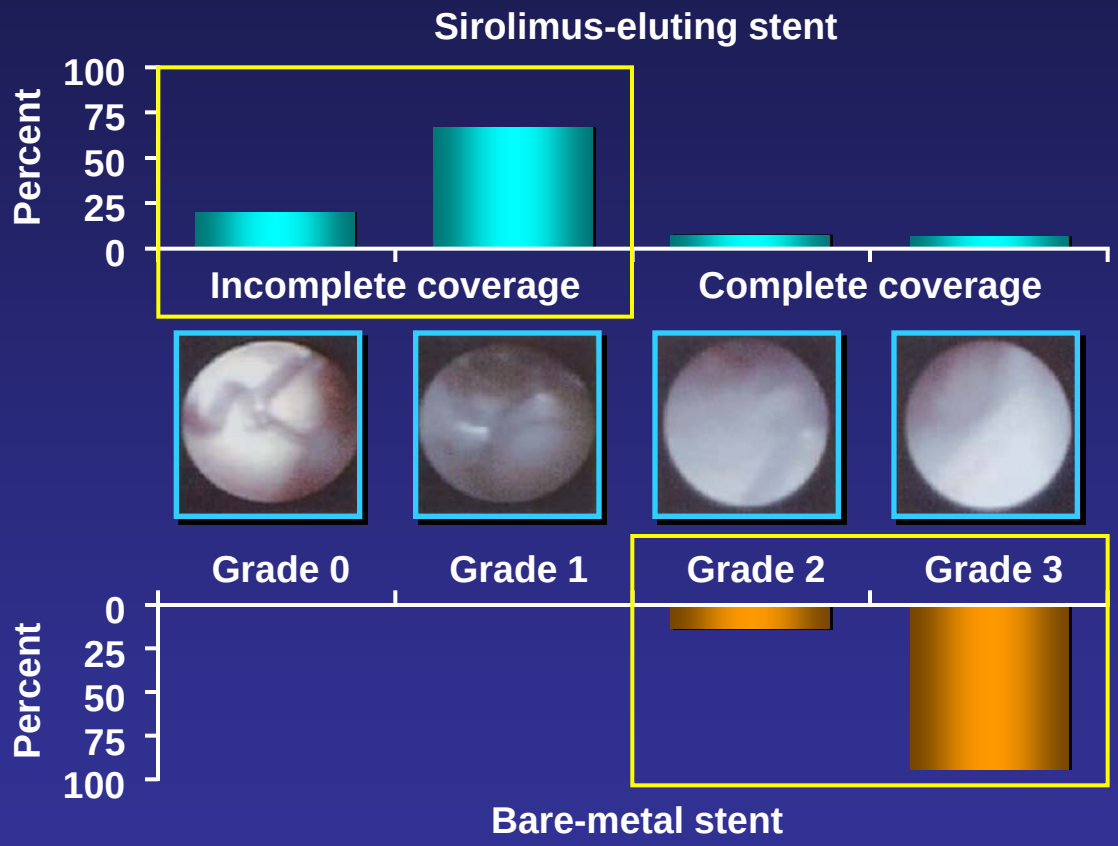
> "Early"

- Late (30 days – 1 year)
- Very Late (> 1 year)

Impact on Cardiac Death and MI

Delayed Endothelializat...

Cypher vs BMS



Conclusions:

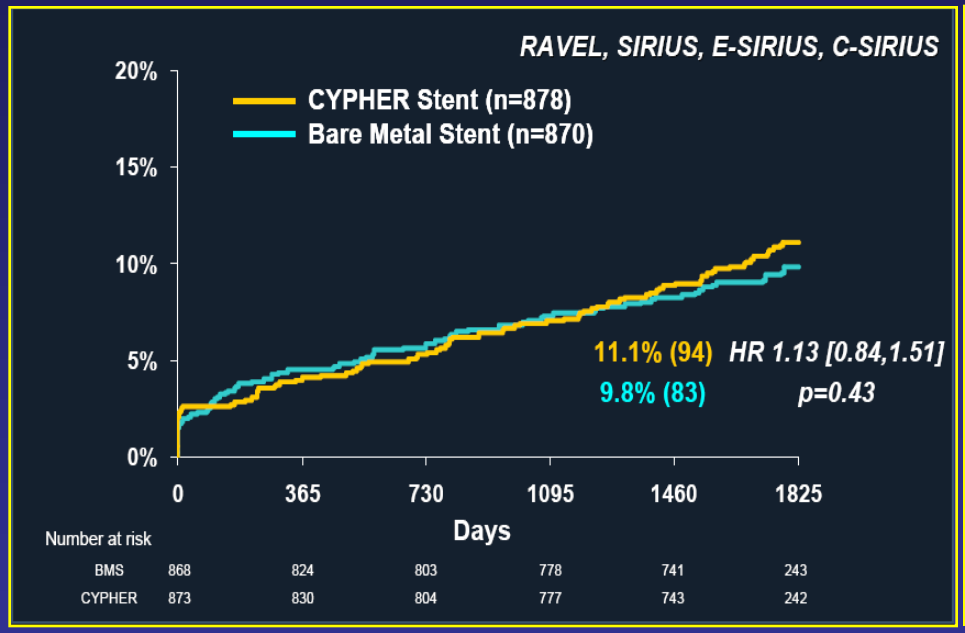
- 86.7% of Cypher stents had incomplete coverage (Grades 0-1)
- 0% of BMS had incomplete coverage (Grades 0-1)

Grade 0 was defined as stent struts that were fully visible, similar to immediately after implantation.
Grade 1 was defined as stent struts that bulged into the lumen and, although covered, were still transparently visible.
Grade 2 was defined as stent struts that were visible, but not clearly seen (ie, they were translucent).
Grade 3 was defined as stent struts that were not visible by angioscopy (ie, they were embedded in the neointima).
Kotani et al. JACC Vol. 47, No. 10, 2006.

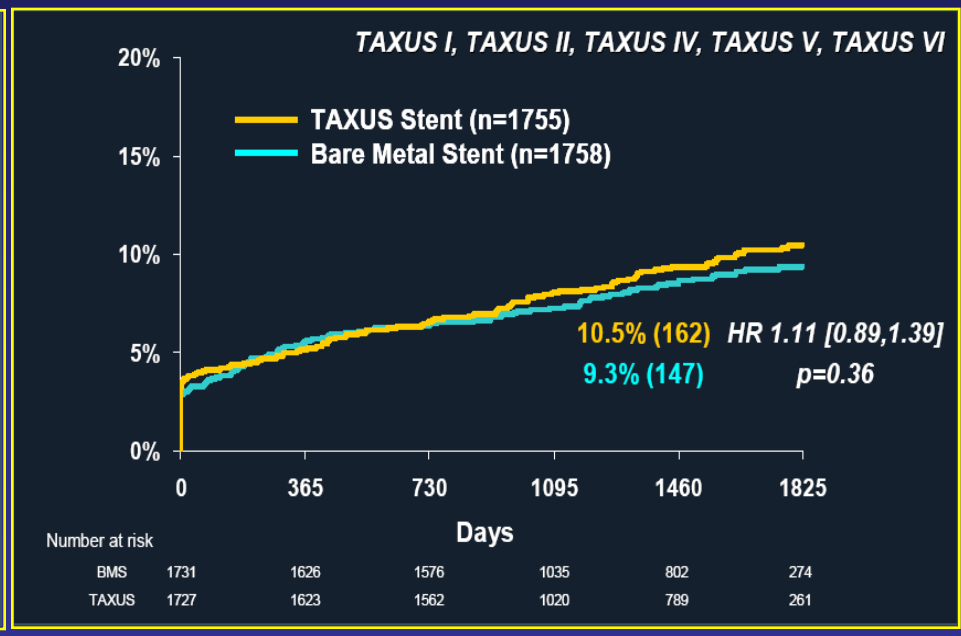
Cardiac Death and MI

Freedom from Cardiac Death and MI

RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS (n=1,748)



TAXUS I, II, IV, V, VI (n=3,506)



Kirtane et al. *TCT*. 2007.

Review of Very Late TAXUS-SR ST
Clinical Outcomes

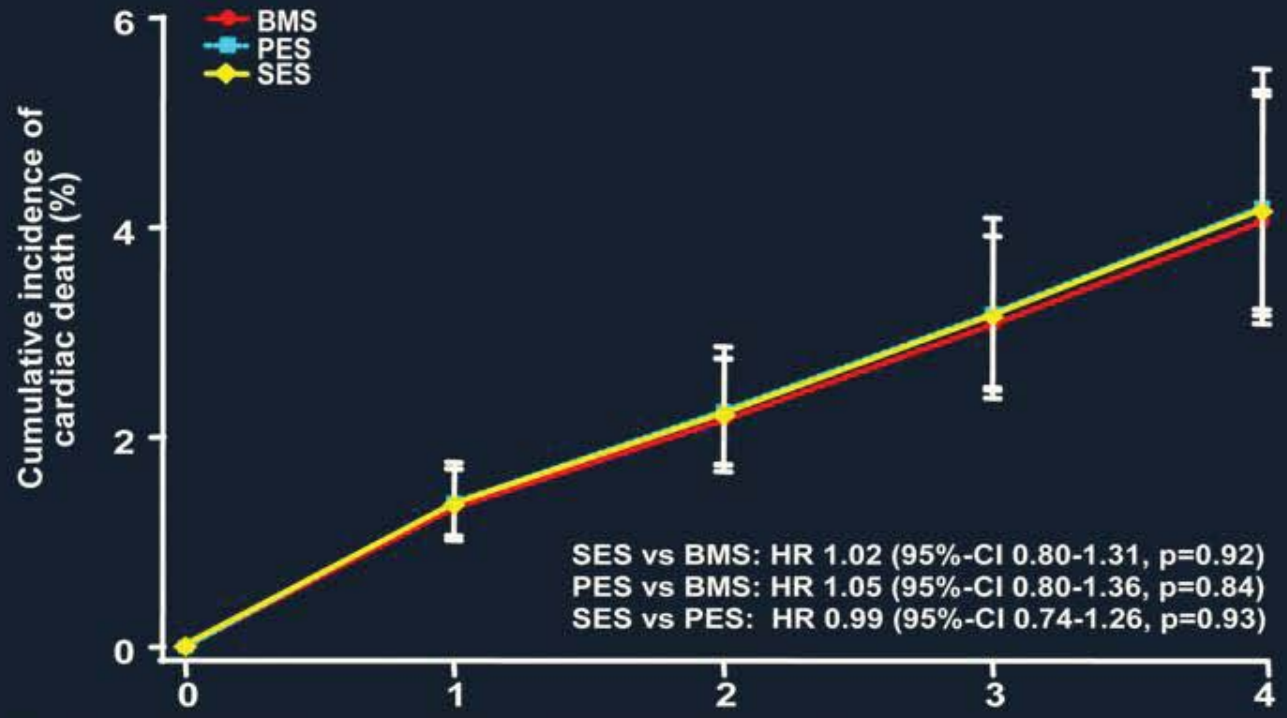
Patient	Days to ST	MACE Associated with ST: TVR	MACE Associated with ST: MI	MACE Associated with ST: Death	Add'l MACE Post ST
1	341	Yes	Yes	No	None
2	498	Yes	Yes	No	None
3	508	Yes	Yes	No	None
4	522	Yes	Yes	No	None
5	711	Yes	Yes	No	Cardiac Death, day 936

From TAXUS II-SR, IV, V

- High morbidity at time of very late events, as with early ST

Ellis: ACC 2006

Network Meta-Analysis: Cumulative Incidence of Cardiac Death



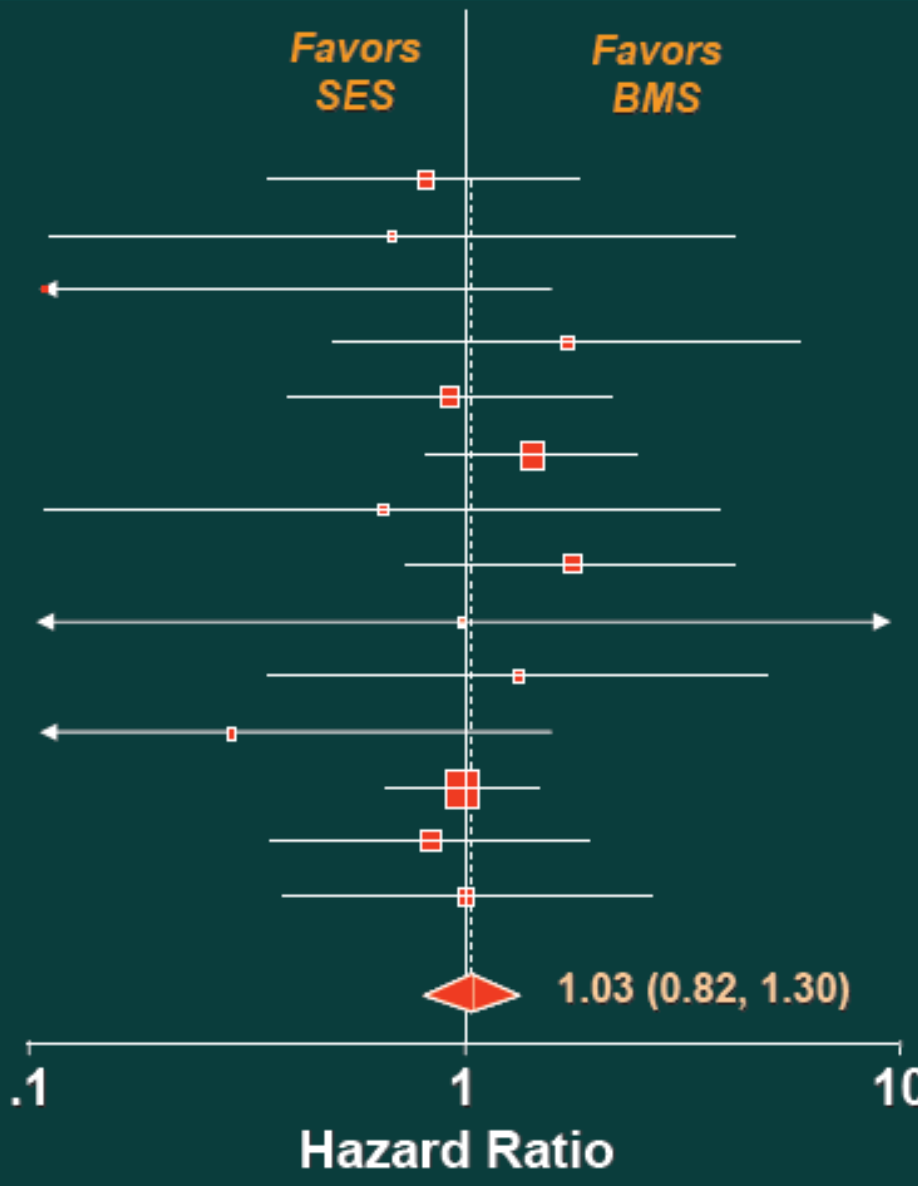
BMS	4763	78/4746	23/3310	13/2234	16/1845
PES	6300	97/6252	41/4232	13/2157	3/841
SES	6642	91/6601	34/4041	24/2340	14/1081

Stettler C., et al., Lancet 2007;370:937-48.

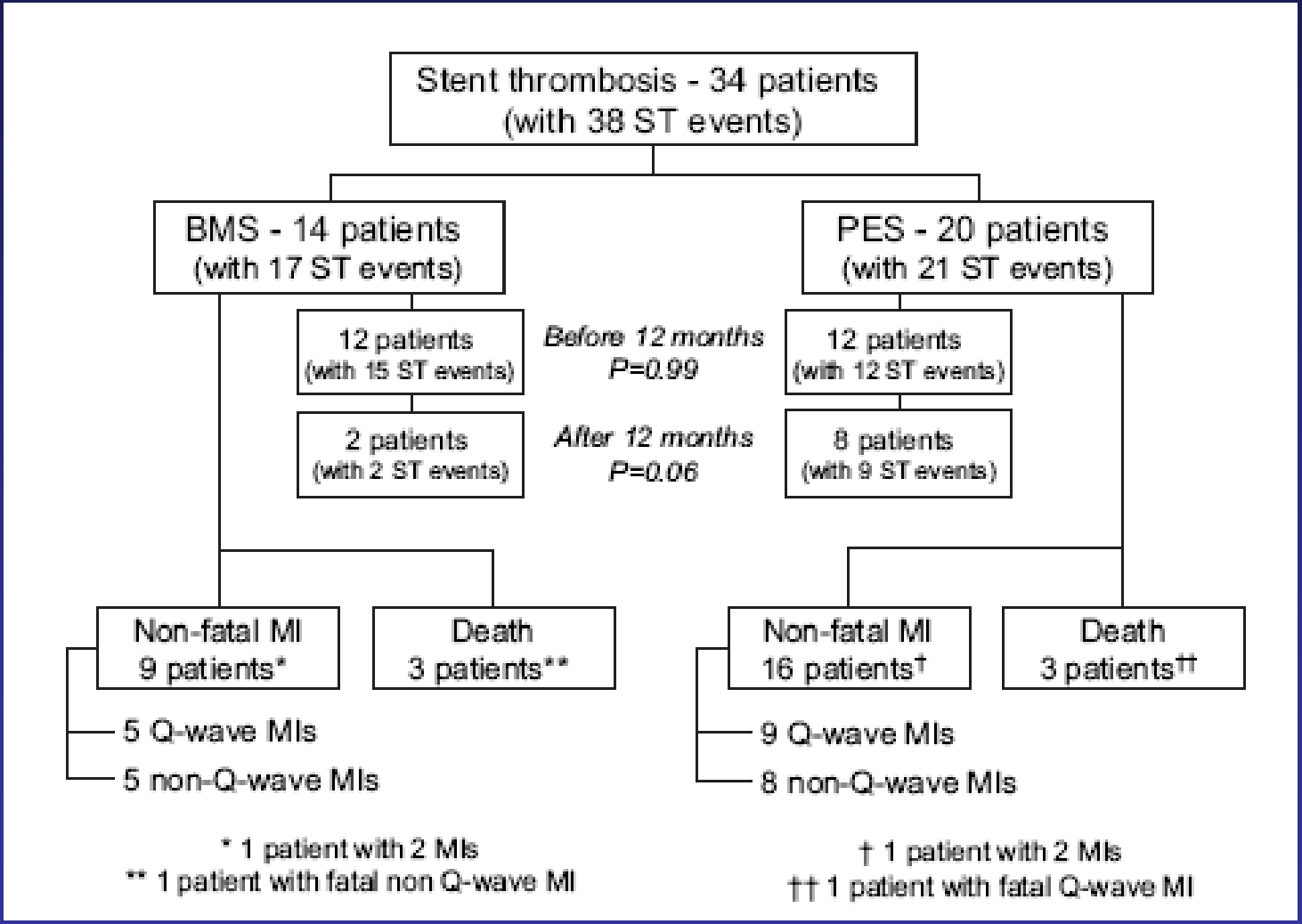
Randomized Trial Mortality: SES vs. BMS (N=4,958)

Trial (n=14)	No. of events / Total No. of patients: SES group	BMSgroup
BASKET	0/264	13/281
CSIRIUS	2/50	3/50
DECODE	0/54	2/29
DIABETES	7/80	5/80
ESIRIUS	10/175	11/177
PACHE	29/250	24/250
PRISON II	2/100	3/100
RAVEL	14/120	8/118
SCANDSTENT	1/163	1/159
SCORPIUS	5/95	4/98
SESAMI	3/160	7/160
SIRIUS	45/533	46/525
STRATEGY	0/87	12/88
TYPHOON	8/355	8/357
Overall	**146/2486**	**147/2472**

Test for Heterogeneity: Cochran Q=9.3
(d.f.=13) P=.75 . P (overall effect) = 0.80
Test for Inconsistency: I2 =0.0% Hazard Ratio

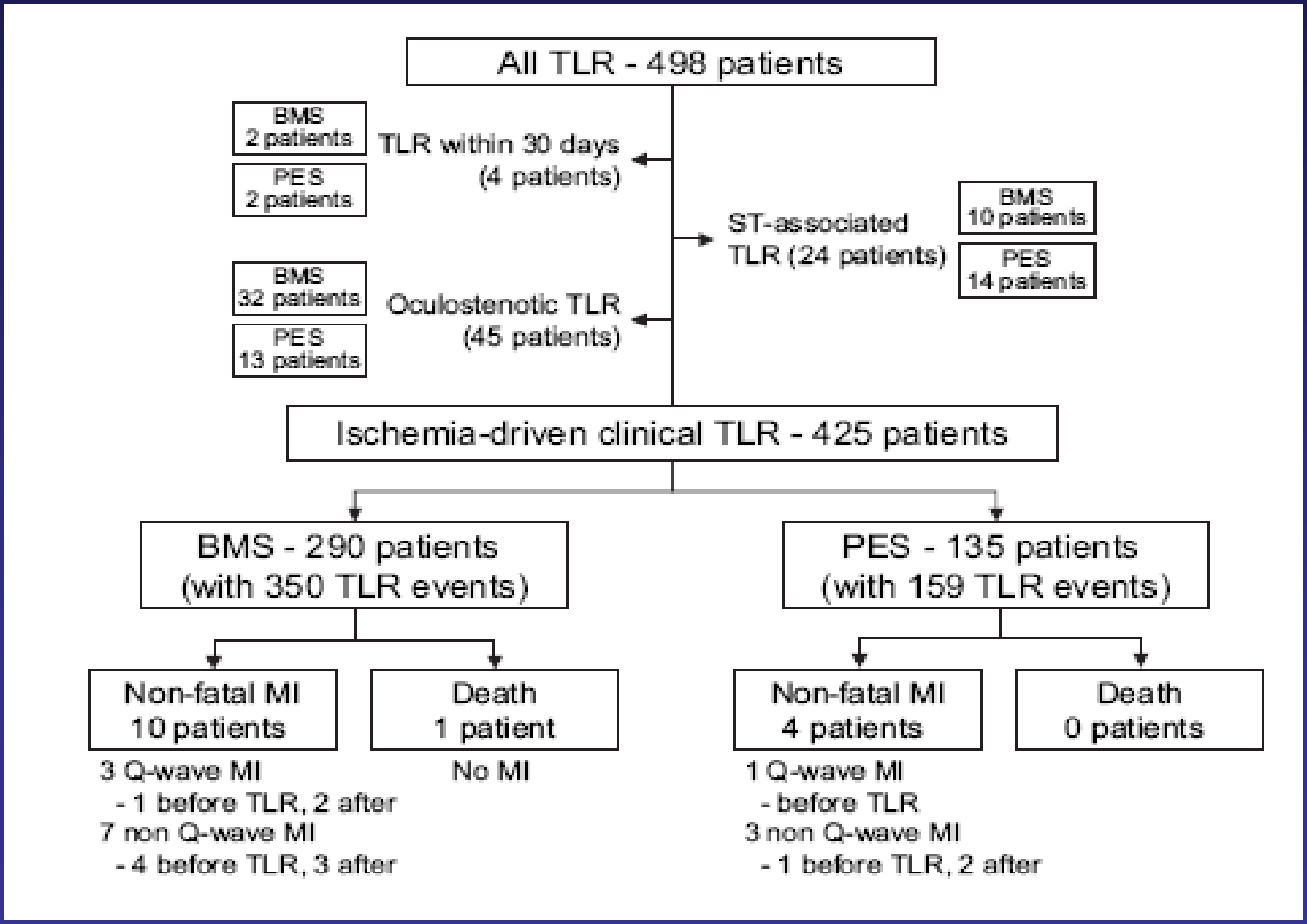


Pooled Analysis Taxus II, IV, V, VI, Trials
Stent Thrombosis Related Events



2007:Stone et al Circulation 2007;115;2842-2847

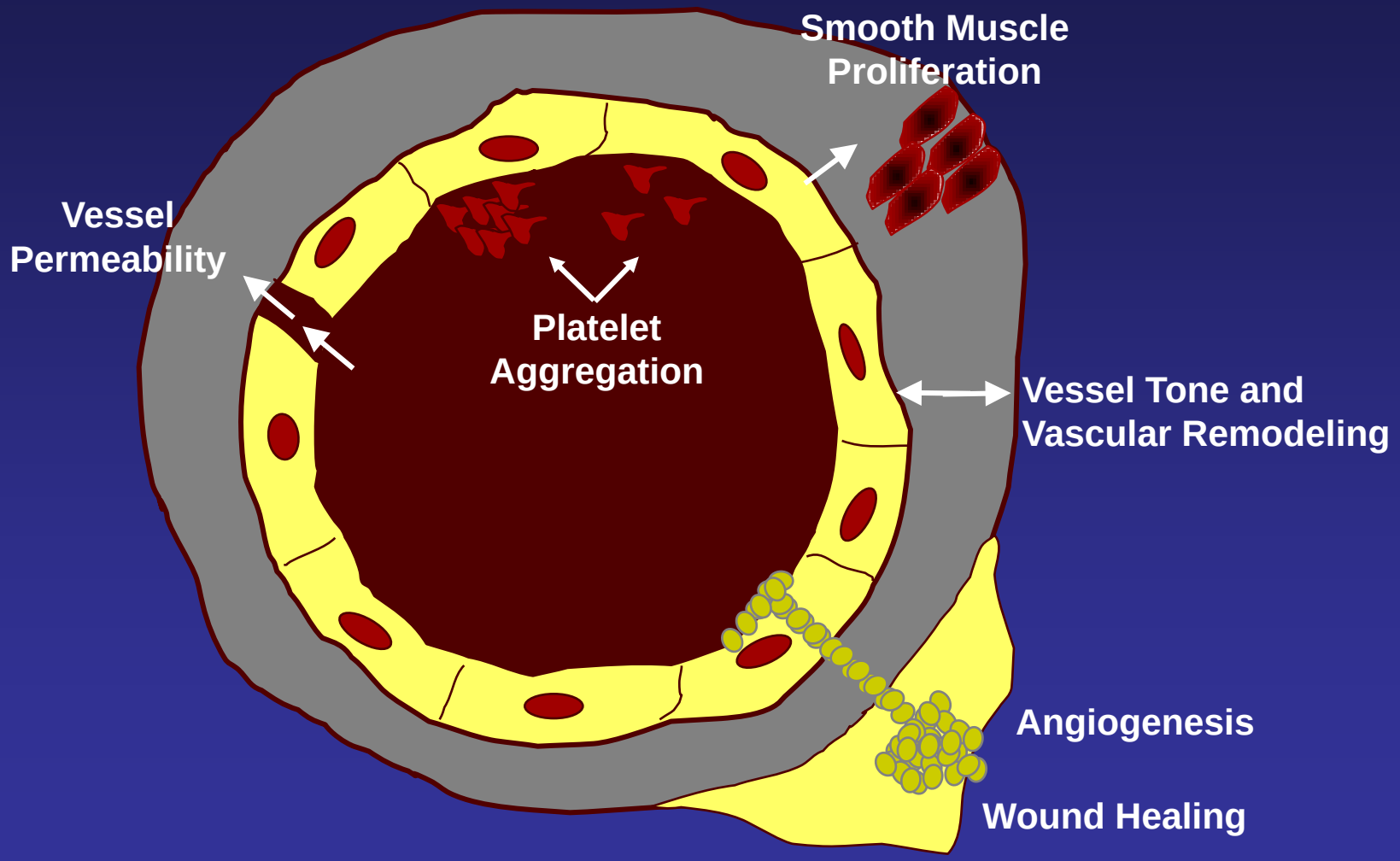
Pooled Analysis Taxus II, IV, V, VI, Trials
TLR Related Events



2007:Stone et al Circulation 2007;115;2842-2847

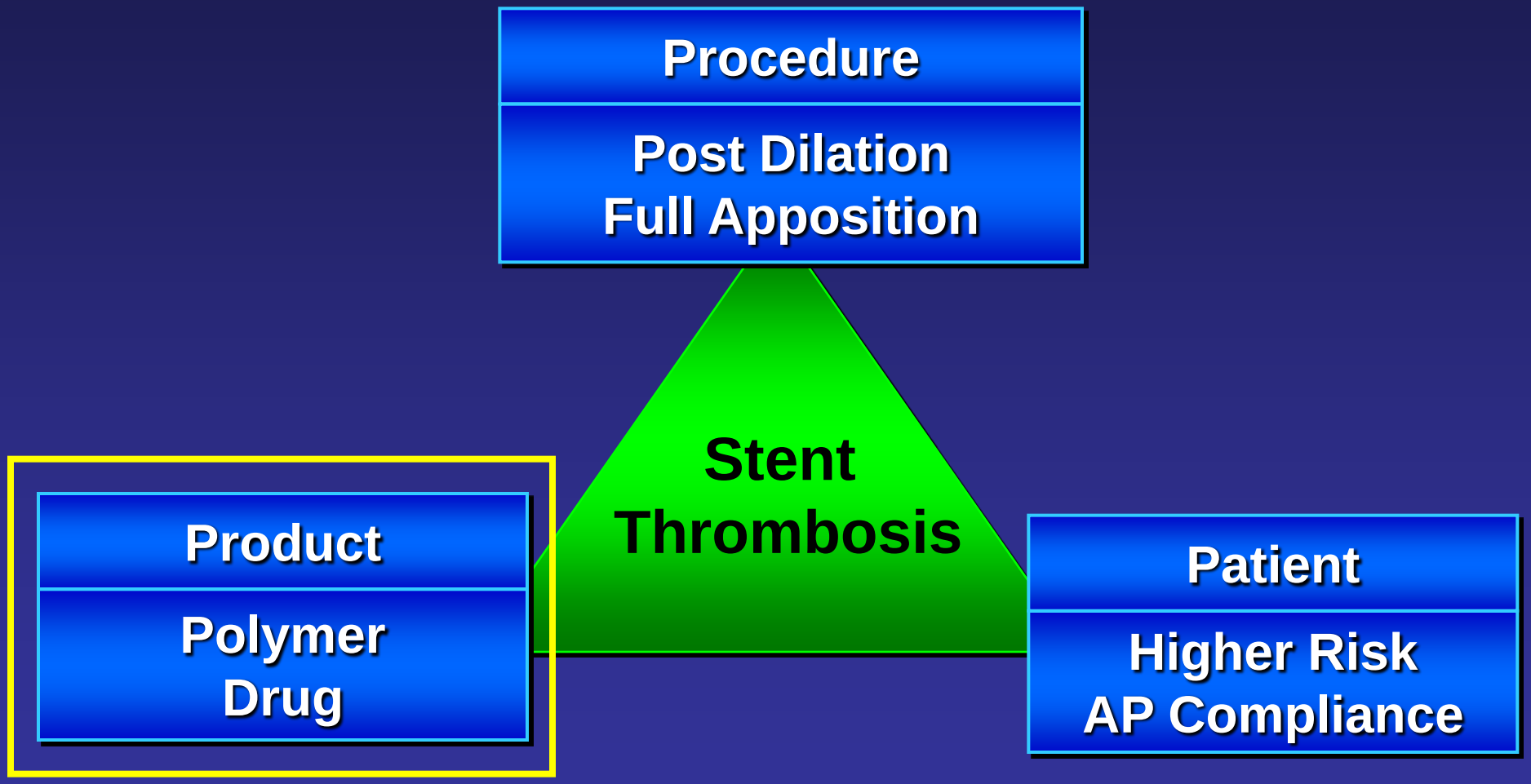
Nitric Oxide (NO)

Roles in Vasculature



Stent Thrombosis:

Procedure, Product, Patient

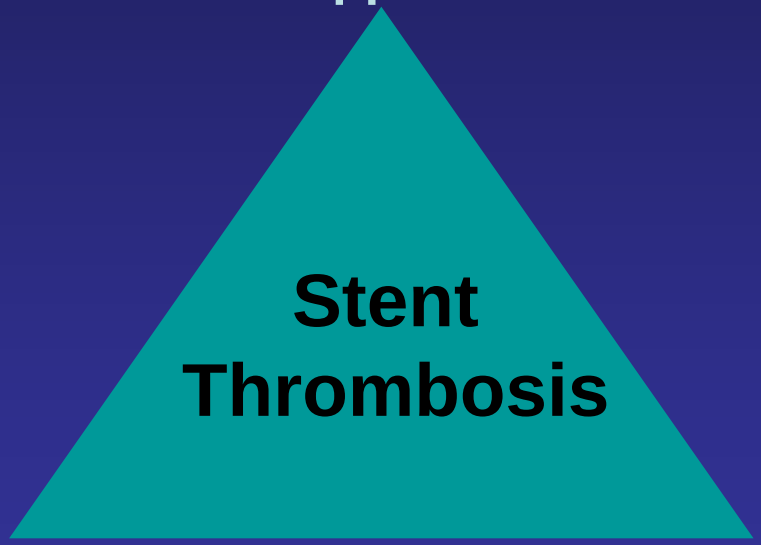


Stent Thrombosis

Procedure, Product, Patient

Procedure

- Post Dilation
- Flush apposition



Product

- Polymer integrity and reactions
- Drug effects

Patient

- Higher Risk
- AP Compliance and Resistance

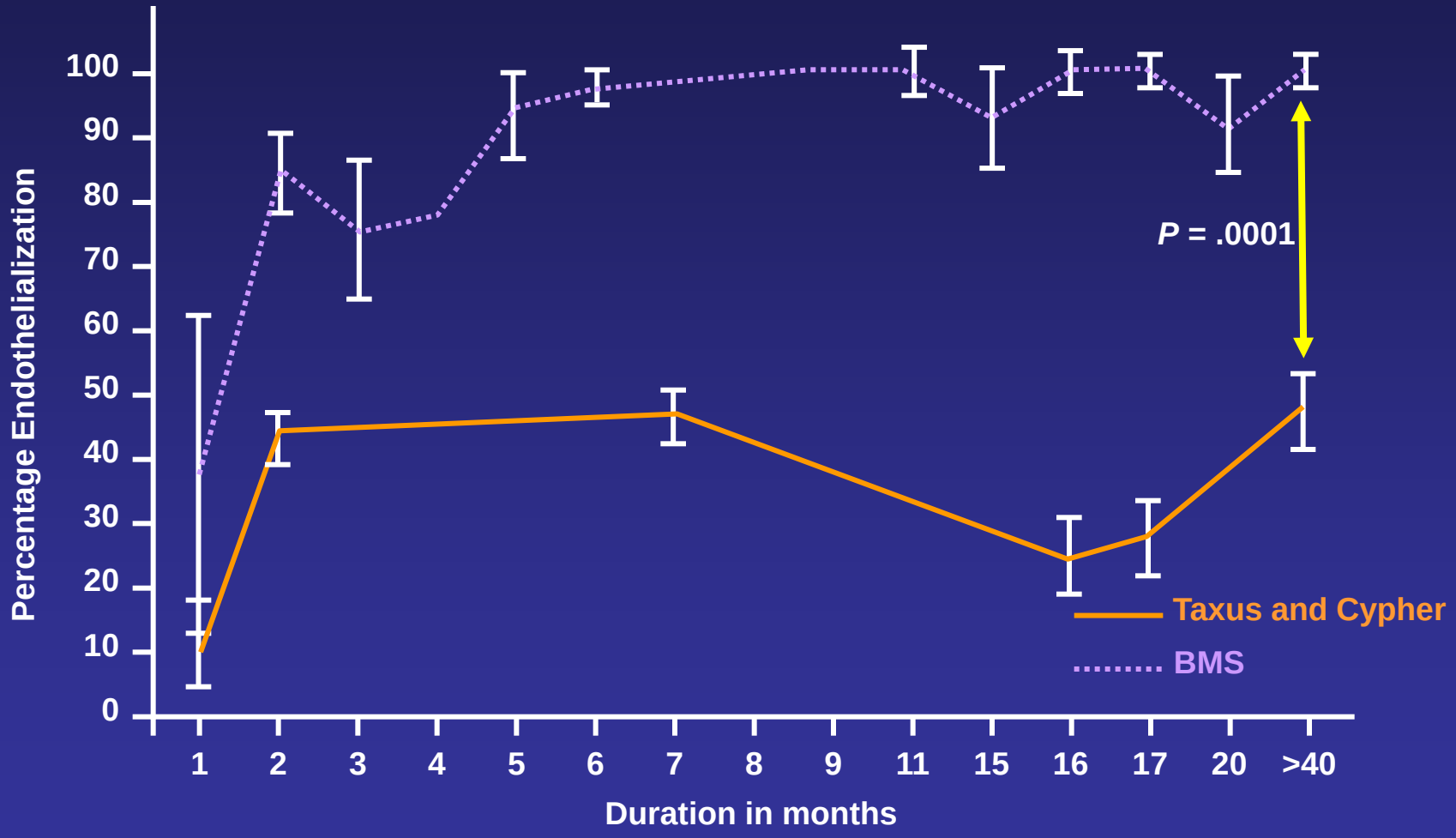
Causes of DES Thrombosis

- *The polymer* (hypersensitivity reactions, inflammatory and thrombogenic)!!!
- *The drug* (delayed healing and incomplete late stent apposition)
- *The procedure* (suboptimal stent deployment and inflow/outflow problems)
- *The patient* (anti-platelet resistance, intrinsic thrombogenicity and more complex lesions)

= increased sensitivity to obligatory prolonged dual antiplatelet regimens

Lack of Endothelial Strut Coverage

DES vs BMS >3 years in Humans



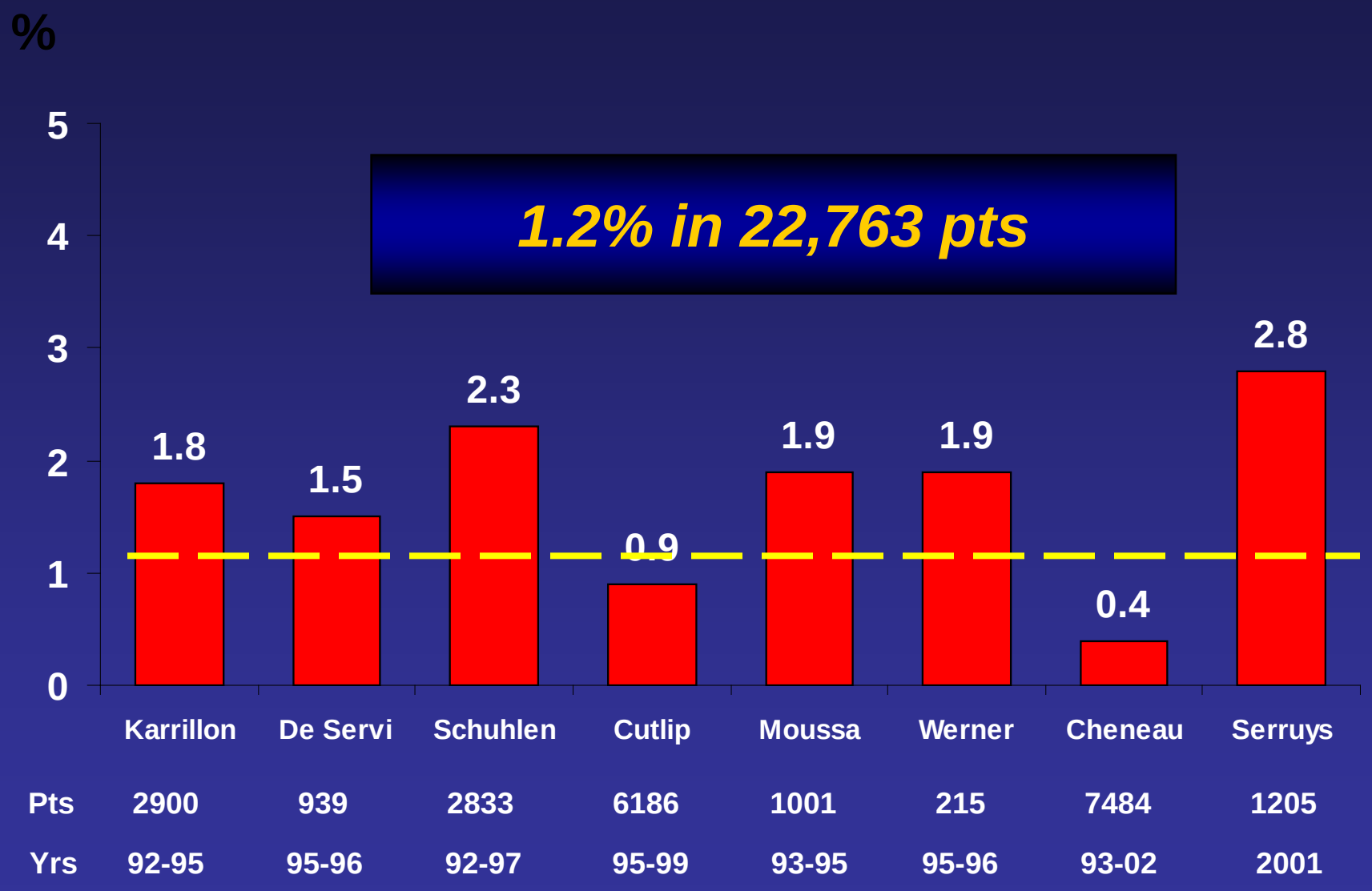
Joner, Virmani et al. *Circulation.* 2005;112:3210.

Correlates with Definite DES Thrombosis

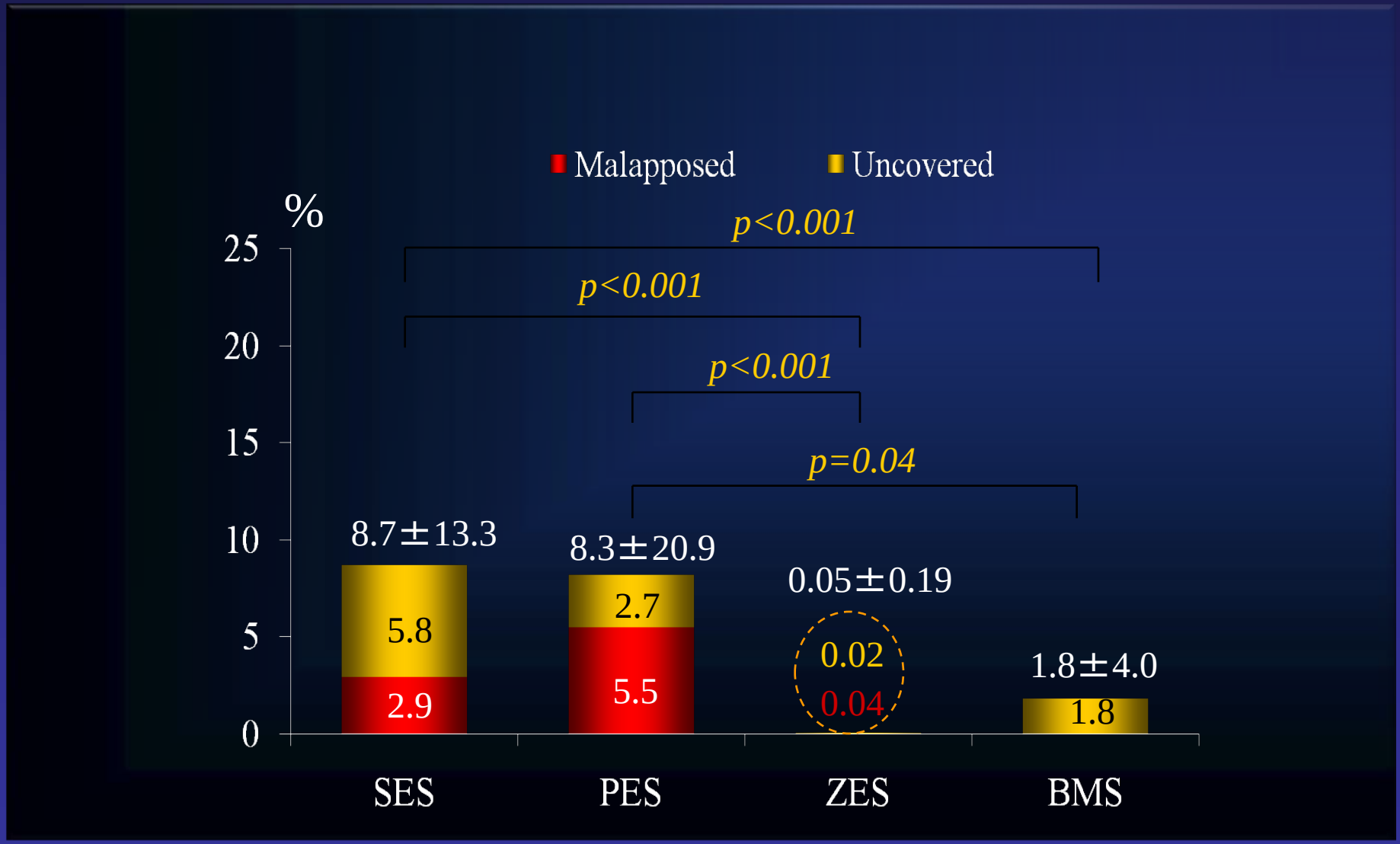
Definite ST Multivariate Logistic Regression Analysis			
Characteristic	Odds Ratio	Confidence Interval	p value
Diabetes mellitus	1.9	1.2-3.1	0.006
MI this admission	2.0	1.3-3.3	0.003
Number of stents	1.3	1.1-1.5	<0.001
Restenosis lesion	4.1	2.3-7.5	<0.001

Pinto T, Waksman R, et al. AHA 2007

Stent Thrombosis in Bare Metal Stents



Secondary Endpoint: Overlap
Proportion of uncovered and/or malapposed struts by stent type



Predictors of Stent Thrombosis Change with Time:

Up to 6 months:

Patient & Lesion complexity

Diabetes

Renal Failure

Long lesions

Small vessels

Bifurcations

Pharmacologic

Plavix® resistance

Early discontinuation

After 6 months:

Apparently not lesion complexity

Number of Stents ??

Apparently Not pharmacologic

Largely off Plavix

But will capture all meds.

Slow endothelialization

Genetics

Rupture Plaque ?

EPC levels

WHC Predictors of Stent Thrombosis in DES Era

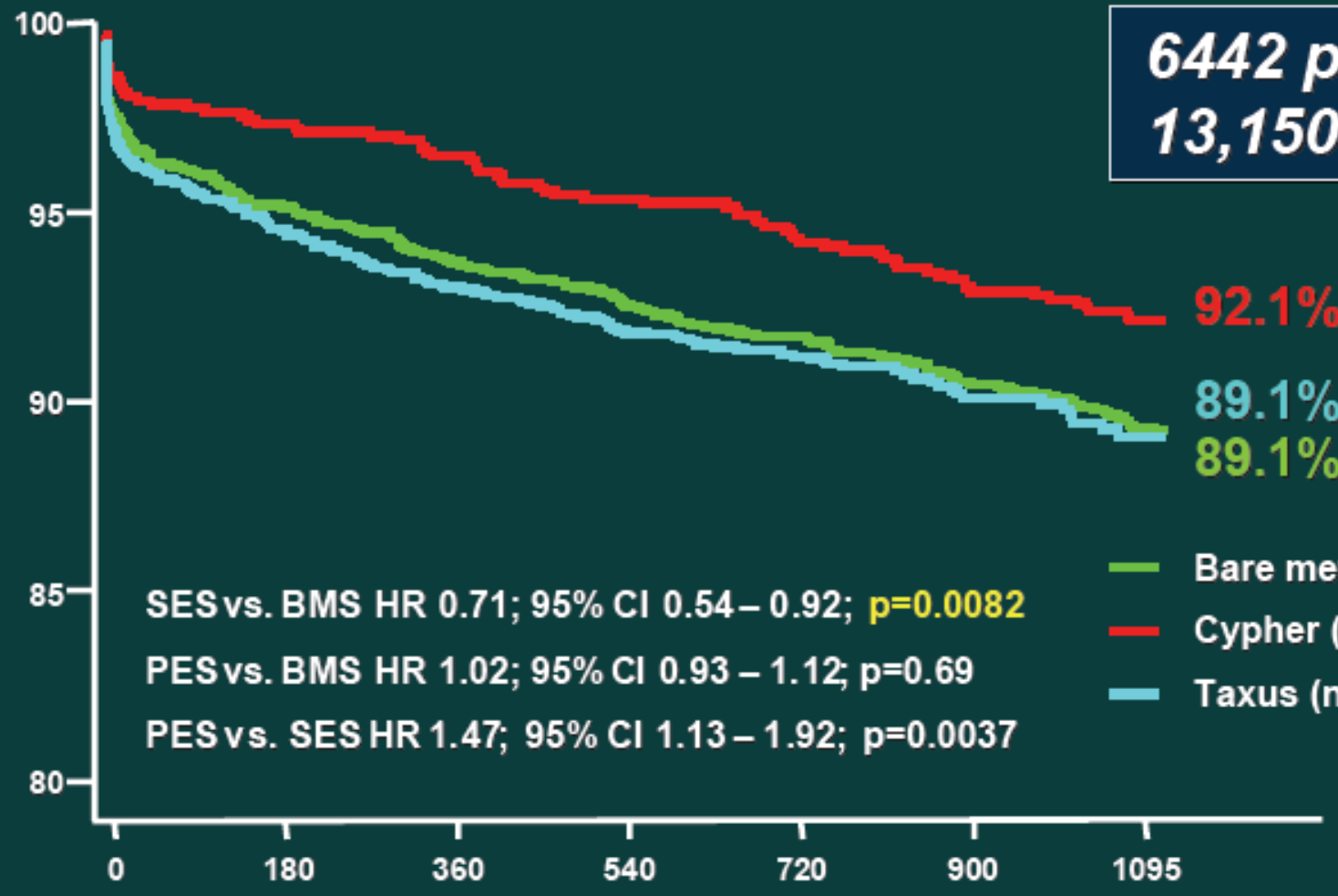
	OR	95% CI	*P* value
Age	0.97	0.94-1.0	0.06
Male	0.66	0.31-10.4	0.27
CABG History	0.15	0.01-1.2	0.07
Renal failure	3.75	1.2-11.3	0.02
IDDM	2.0	0.84-4.9	0.12
Bifurcation	4.4	1.96-10.0	0.0004
ISR	4.5	1.8-11.4	0.0013
	0.21	0.09-0.49	0.0003

el

Washington Hospital Center

Kuchulakanti, Waksman. Circulation 2005;113:1108-13

Thoraxcenter: All-cause mortality at 3 years



6442 patients
13,150 stents

Group	0	30	90	180	360	720	1095
BMS	2287	2211	2195	2170	2126	1990	1862
SES	976	955	951	946	936	888	833
PES	2776	2620	2537	2499	2414	1432	491

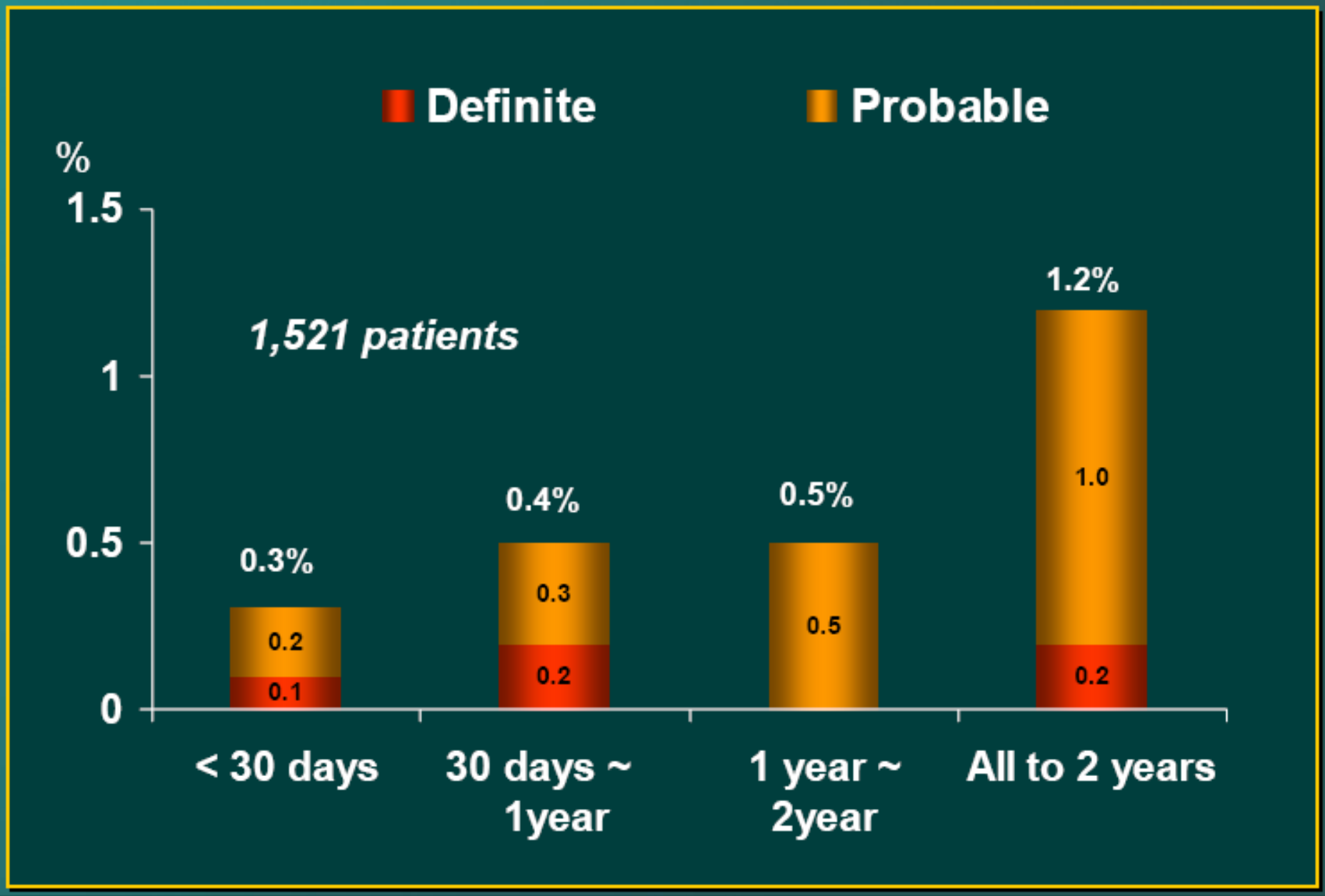
A Prospective "All Comers" Single Arm Study in Complex Patients: The MATRIX Trial

IDE: G030229/S003

CypherTM Sirolimus-Eluting Coronary Stent

FDA panel Meeting: Dec 7-8, 2006

Stent Thrombosis



Incidence and Correlates of Drug-Eluting Stent Thrombosis in Routine Clinical Practice

4-Year Results From a Large 2-Institutional Cohort Study

Peter Wenaweser, MD,* Joost Daemen, MD,‡ Marcel Zwahlen, PHD,† Ron van Domburg, PHD,‡ Peter Jüni, MD,† Sophia Vaina, MD, PHD,‡ Gerrit Hellige, MD,* Keiichi Tsuchida, MD,‡ Cyrill Morger, MD,* Eric Boersma, PHD,‡ Neville Kukreja, MBBS, MRCP,‡ Bernhard Meier, MD,* Patrick W. Serruys, MD, PHD,‡ Stephan Windecker, MD*

Bern, Switzerland; and Rotterdam, the Netherlands

Objectives We sought to determine the risk of late stent thrombosis (ST) during long-term follow-up beyond 3 years, searched for predictors, and assessed the impact of ST on overall mortality.

Background Late ST was reported to occur at an annual rate of 0.6% up to 3 years after drug-eluting stent (DES) implantation.

Methods A total of 8,146 patients underwent percutaneous coronary intervention with a sirolimus-eluting stent (SES) (n = 3,823) or paclitaxel-eluting stent (PES) (n = 4,323) and were followed up to 4 years after stent implantation. Dual antiplatelet treatment was prescribed for 6 to 12 months.

Results Definite ST occurred in 192 of 8,146 patients with an incidence density of 1.0/100 patient-years and a cumulative incidence of 3.3% at 4 years. The hazard of ST continued at a steady rate of 0.53% (95% confidence interval [CI]: 0.44 to 0.64) between 30 days and 4 years. Diabetes was an independent predictor of early ST (hazard ratio [HR]: 1.96; 95% CI: 1.18 to 3.28), and acute coronary syndrome (HR: 2.21; 95% CI: 1.39 to 3.51), younger age (HR: 0.97; 95% CI: 0.95 to 0.99), and use of PES (HR: 1.67; 95% CI: 1.08 to 2.56) were independent predictors of late ST. Rates of death and myocardial infarction at 4 years were 10.6% and 4.6%, respectively.

Conclusions Late ST occurs steadily at an annual rate of 0.4% to 0.6% for up to 4 years. Diabetes is an independent predictor of early ST, whereas acute coronary syndrome, younger age, and PES implantation are associated with late ST. (J Am Coll Cardiol 2008;52:1134–40) © 2008 by the American College of Cardiology Foundation

Stent Thrombosis, Clinical Events, and Influence of Prolonged Clopidogrel Use After Placement of Drug-Eluting Stent

Data From an Observational Cohort Study of Drug-Eluting Versus Bare-Metal Stents

Duk-Woo Park, MD,* Sung-Cheol Yun, PHD,† Seung-Whan Lee, MD,* Young-Hak Kim, MD,* Cheol Whan Lee, MD,* Myeong-Ki Hong, MD,* Sang-Sig Cheong, MD,‡ Jae-Joong Kim, MD,* Seong-Wook Park, MD,* Seung-Jung Park, MD*

Seoul and GangNeung, Korea

Objectives The purpose of this study was to evaluate the risk of stent thrombosis (ST), clinical outcomes, and the benefits of extended clopidogrel use after drug-eluting stent (DES) implantation.

Background Data are limited regarding uniform evaluation of ST and the influence of clopidogrel continuation beyond 12 months on late events after DES treatment.

Methods We identified 7,221 patients who received DES implantation (n = 3,160) or bare-metal stent (BMS) implantation (n = 4,061), and compared long-term adverse outcomes. Additionally, 2,851 patients with DES surviving 12 months without major events were analyzed according to clopidogrel continuation.

Results The adjusted-risk of overall ST was similar in the 2 groups. After 1 year, however, DES patients showed a higher risk of ST; definite/probable (hazard ratio [HR]: 3.55, 95% confidence interval [CI]: 1.26 to 9.99). The adjusted-risk of death (HR: 0.60, 95% CI: 0.46 to 0.79), death/myocardial infarction (HR: 0.63, 95% CI: 0.49 to 0.81), and target lesion revascularization (HR: 0.32, 95% CI: 0.24 to 0.43) were significantly lower in the DES group than in the BMS group. Continuing clopidogrel beyond 12 months was not associated with a reduced risk for ST (HR: 0.54, 95% CI: 0.07 to 4.23), death (HR: 1.20, 95% CI: 0.55 to 2.66), or death/myocardial infarction (HR: 1.16, 95% CI: 0.56 to 2.42) after DES implantation.

Conclusions As compared with BMS, DES showed a similar risk of overall ST, but a higher risk of very late ST. The rates of death, death/myocardial infarction, and target lesion revasuclarization were significantly lower in the DES group. Clopidogrel continuation beyond 1 year did not appear to reduce ST and clinical events after DES implantation. (J Am Coll Cardiol Intv 2008;1:494–503)
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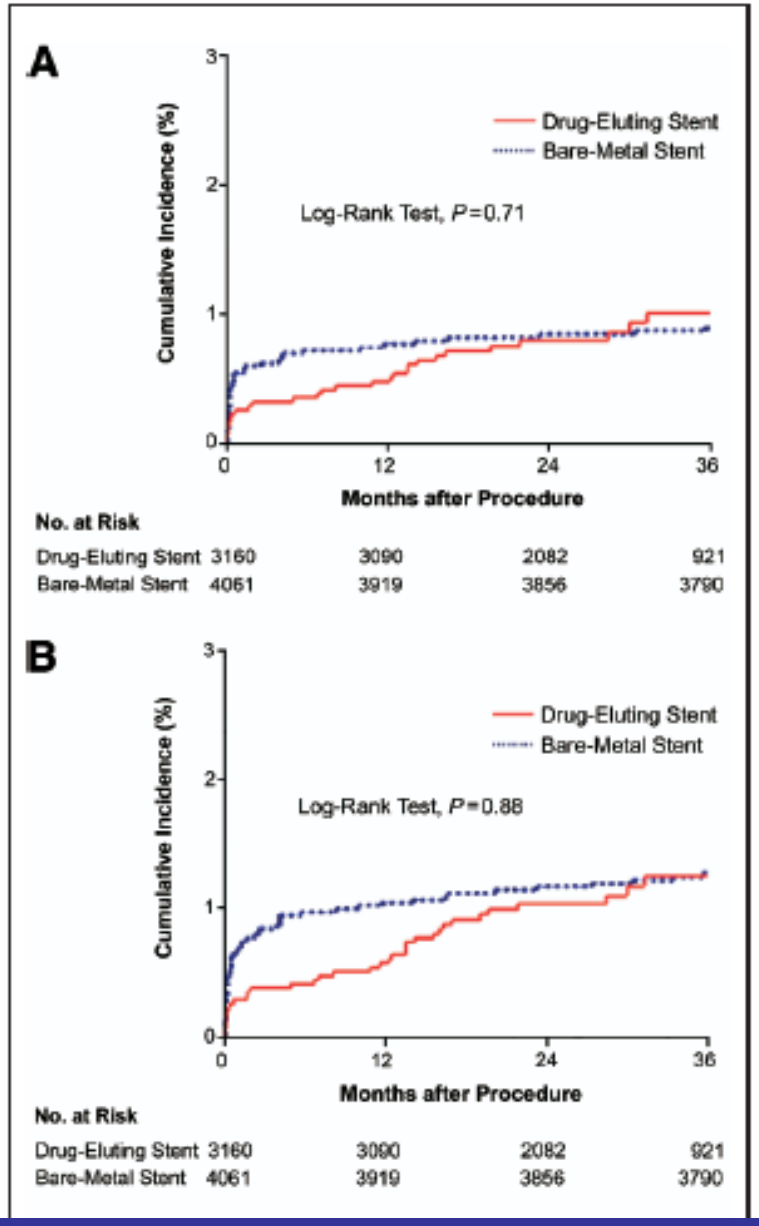
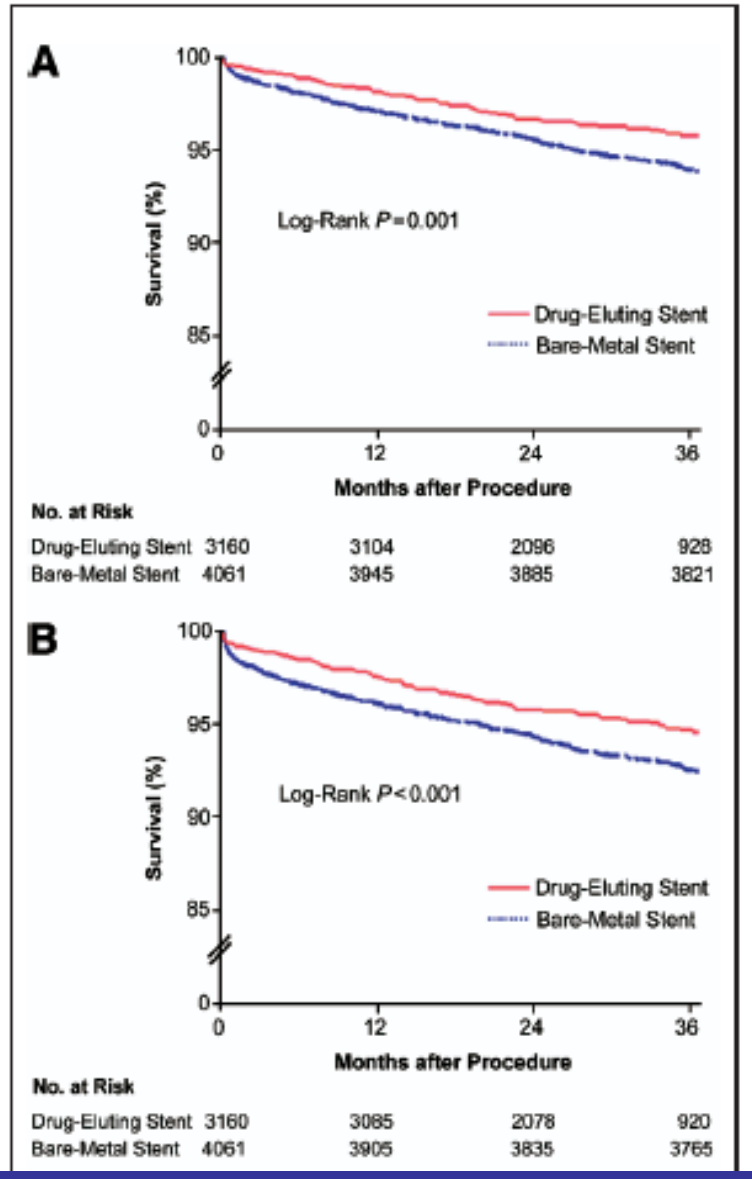

A
Cumulative Incidence (%)
Drug-Eluting Stent
Bare-Metal Stent
Log-Rank Test, P=0.71
Months after Procedure
No. at Risk
Drug-Eluting Stent 3160 3090 2082 921
Bare-Metal Stent 4061 3919 3856 3790
B
Cumulative Incidence (%)
Drug-Eluting Stent
Bare-Metal Stent
Log-Rank Test, P=0.88
Months after Procedure
No. at Risk
Drug-Eluting Stent 3160 3090 2082 921
Bare-Metal Stent 4061 3919 3856 3790


A
Survival (%)
Log-Rank P=0.001
Drug-Eluting Stent
Bare-Metal Stent
Months after Procedure
No. at Risk
Drug-Eluting Stent 3160 3104 2096 928
Bare-Metal Stent 4061 3945 3885 3821
B
Survival (%)
Log-Rank P<0.001
Drug-Eluting Stent
Bare-Metal Stent
Months after Procedure
No. at Risk
Drug-Eluting Stent 3160 3085 2078 920
Bare-Metal Stent 4061 3905 3835 3765