

# **Sirolimus-Eluting Stents in the Real World: Is There a Safety Concern?**

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New York City***

**DES Safety, Efficacy, and Future innovations  
Angioplasty Summit TCT Asia-Pacific 2007  
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# Presenter Disclosure Information for Angioplasty Summit 2007

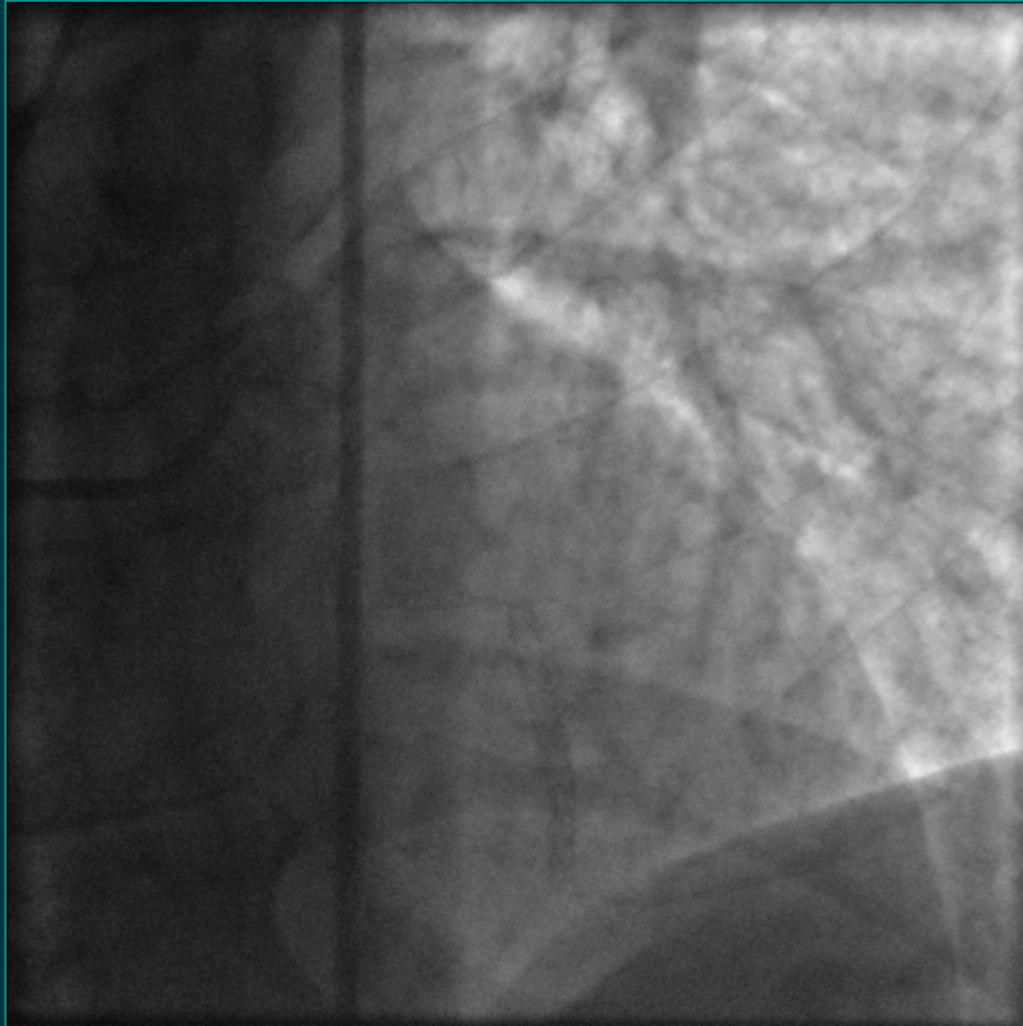
***Martin B. Leon, M.D.***

***Consultant or Advisory Board:***  
BSC, Cordis-JNJ, Medtronic, Abbott

***Stockholder or other Equity:***  
None



# Late Stent Thrombosis - Cypher



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

# SES Real World: Safety Concerns?

## The Four Questions...

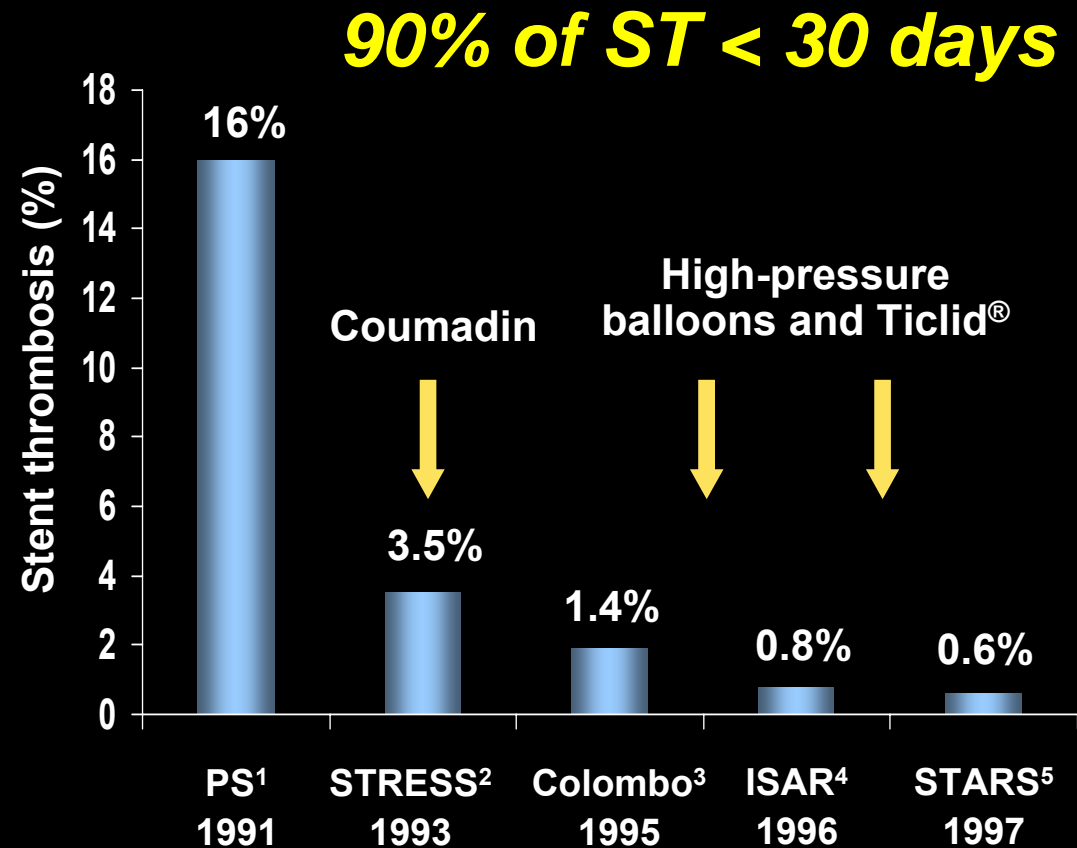
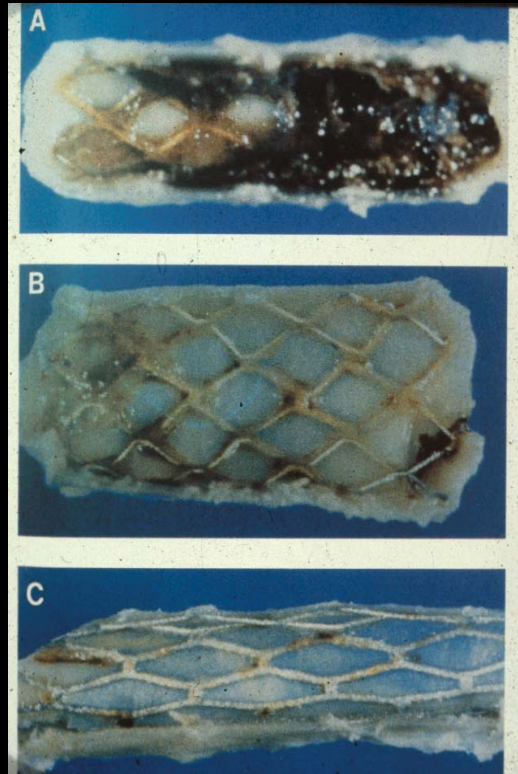
- **Is there an increase in stent thrombosis with SES vs. BMS (ARC definitions, continuous hazard, and causes)?**
- **Is there an increase in death (and MI) with SES vs. BMS (on-label vs. off-label, diabetics)?**
- **Should the anti-platelet therapy be adjusted due to SES stent thrombosis considerations?**
- **Should SES use be modified in response to safety concerns?**

# SES Real World: Safety Concerns?

## The Four Questions...

- *Is there an increase in stent thrombosis with SES vs. BMS (ARC definitions, continuous hazard, and causes)?*
- Is there an increase in death (and MI) with SES vs. BMS (on-label vs. off-label, diabetics)?
- Should the anti-platelet therapy be adjusted due to SES stent thrombosis considerations?
- Should SES use be modified in response to safety concerns?

# History of Stent Thrombosis



1. Schatz et al. *Circulation*.1991;83:148; 2. Fischman et al. *N Engl J Med*. 1994;331:496; 3. Colombo et al. *Circulation*.1995;91:1676; 4. Schömig et al. *Circulation*.1994;90:2716; 5. Leon et al. *N Engl J Med*. 1998;339:1665; 6. Joner et al. *J Am Coll Cardiol*. 2006;48:193.

# Late DES thrombosis after discontinuation of antiplatelet therapy

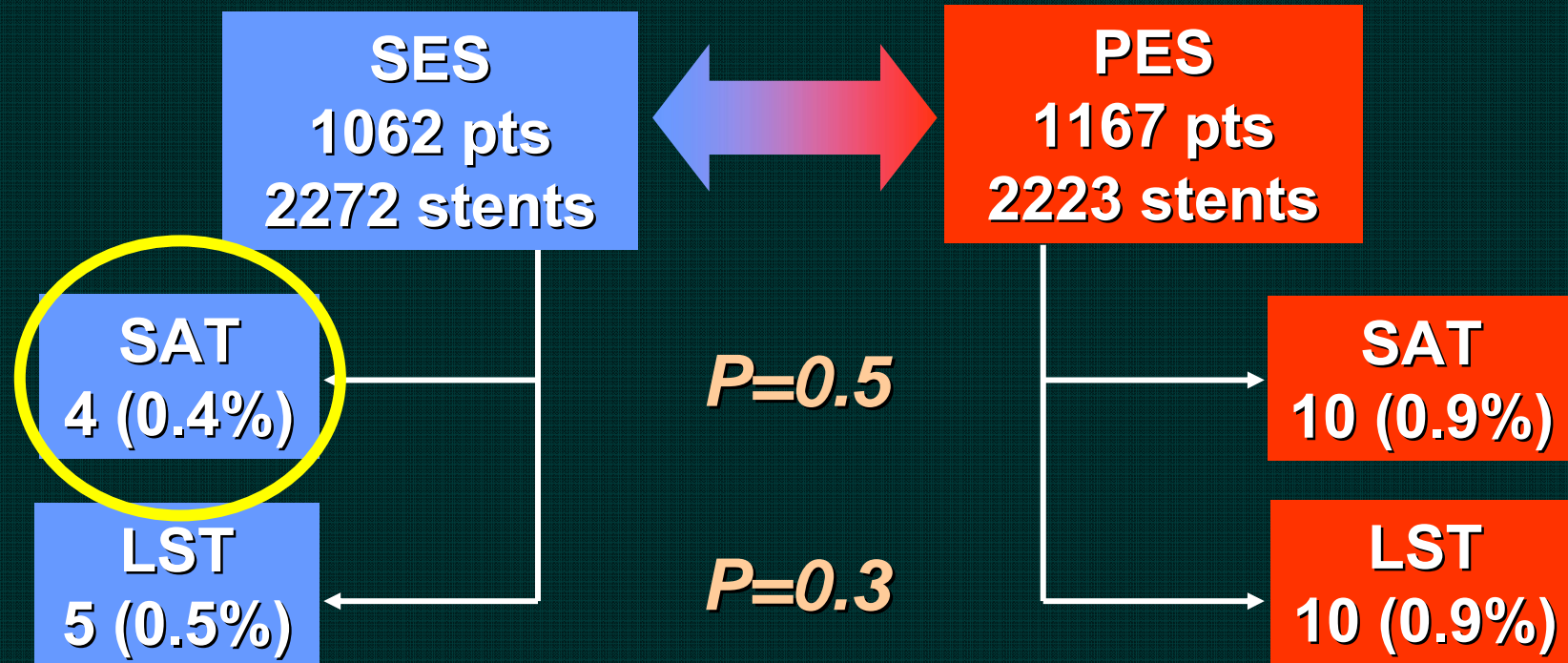


*McFadden EP et al. Lancet 2004; 364:1519-21*



# Stent Thrombosis after DES

2229 patients after successful DES implantation



10.2 ± 4.4 m

9.3 ± 5.6 months

7.9 ± 3.6 m

Total SES  
9 (0.9%)

Total DES 29/2229 (1.3%)

$P=0.09$

Total PES  
20 (1.7%)





# Stent Thrombosis after DES

2229 patients after successful DES implantation

**SES**  
1062 pts  
2272 stents

**PES**  
1167 pts  
2223 stents



**SAT**  
4 (0.4%)

**SAT**  
10 (0.9%)

$P=0.5$

**LST**  
5 (0.5%)

**LST**  
10 (0.9%)

$P=0.3$

10.2 ± 4.4 m

9.3 ± 5.6 months

7.9 ± 3.6 m

**Total SES**  
9 (0.9%)

**Total DES** 29/2229 (1.3%)

**Total PES**  
20 (1.7%)

$P=0.09$

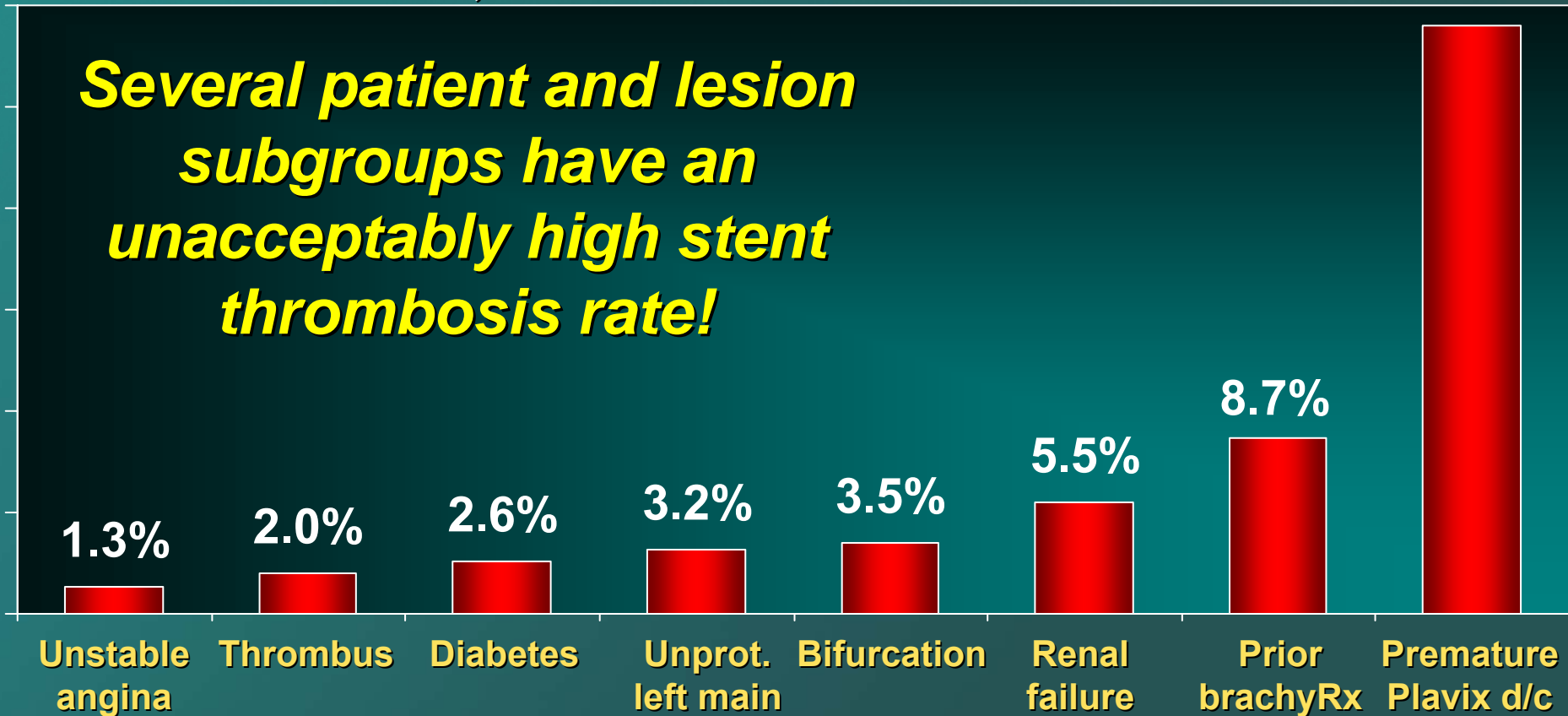


**Stent thrombosis after DES (SES or PES) occurred in 29/2229 pts (1.3%) at 9 mos (45% mortality)**

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

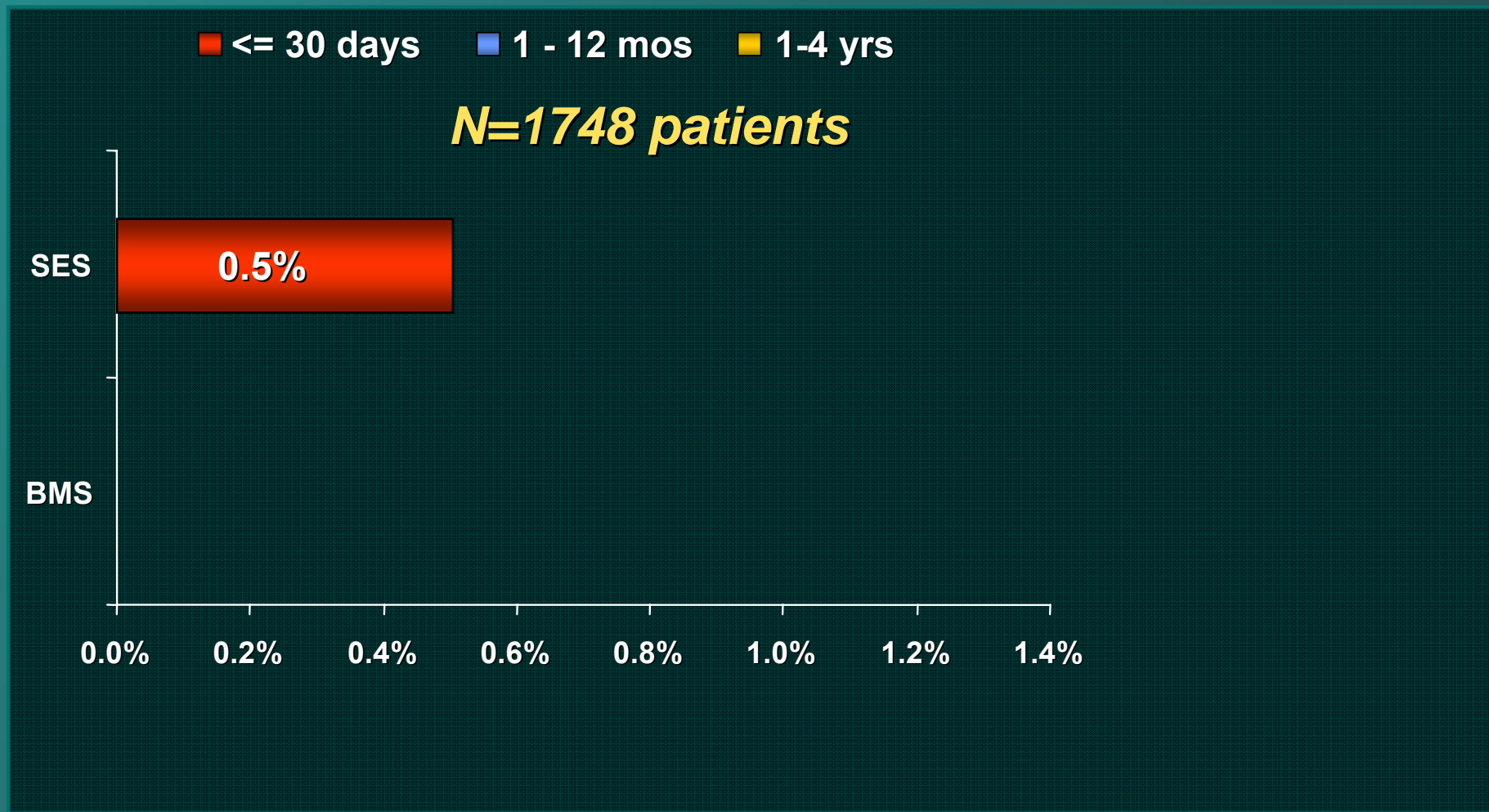
29%

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



# Cypher RCT Meta-analyses

## *Combined Stent Thrombosis\**

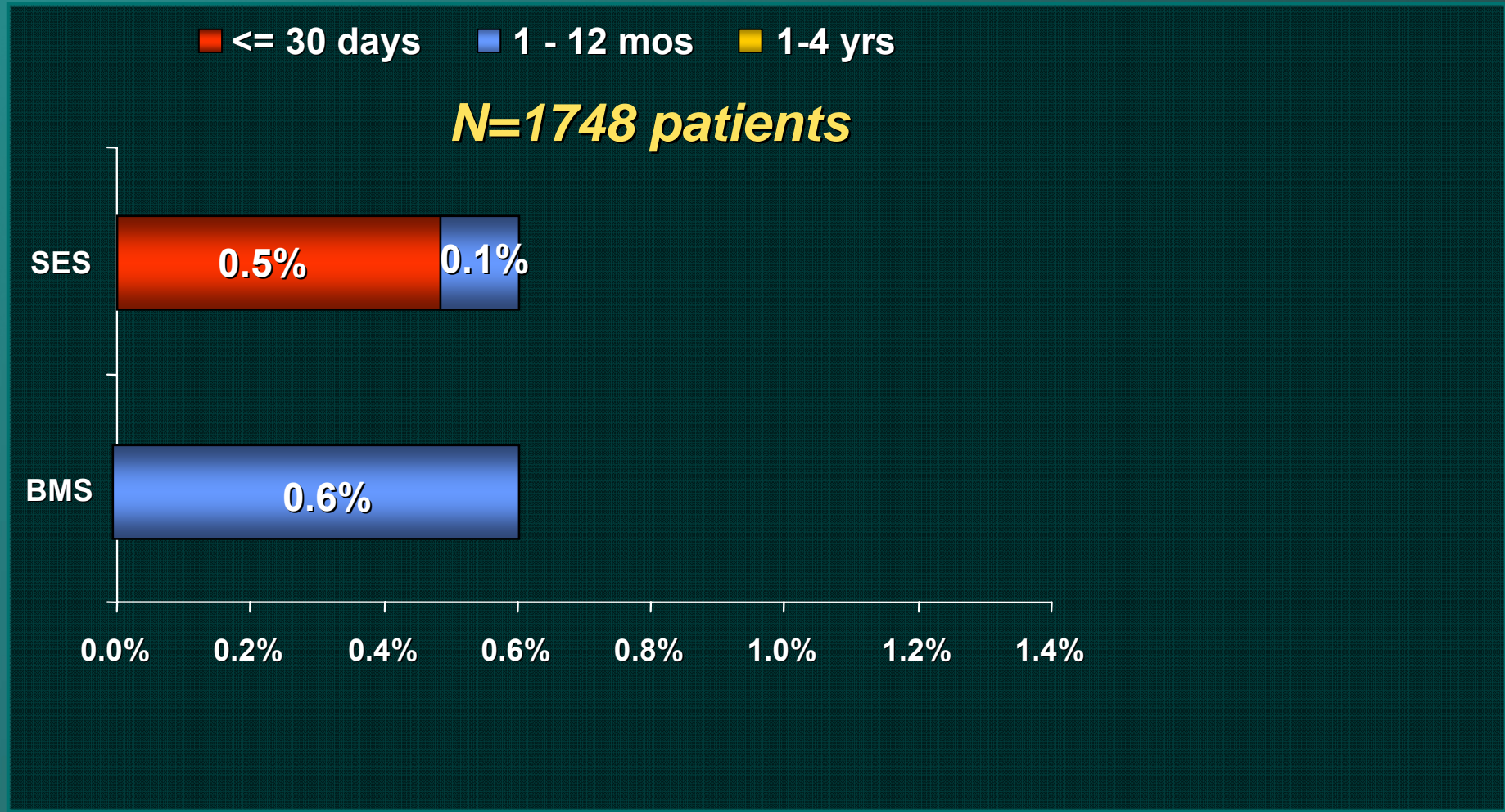


\* RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS



# Cypher RCT Meta-analyses

## *Combined Stent Thrombosis\**

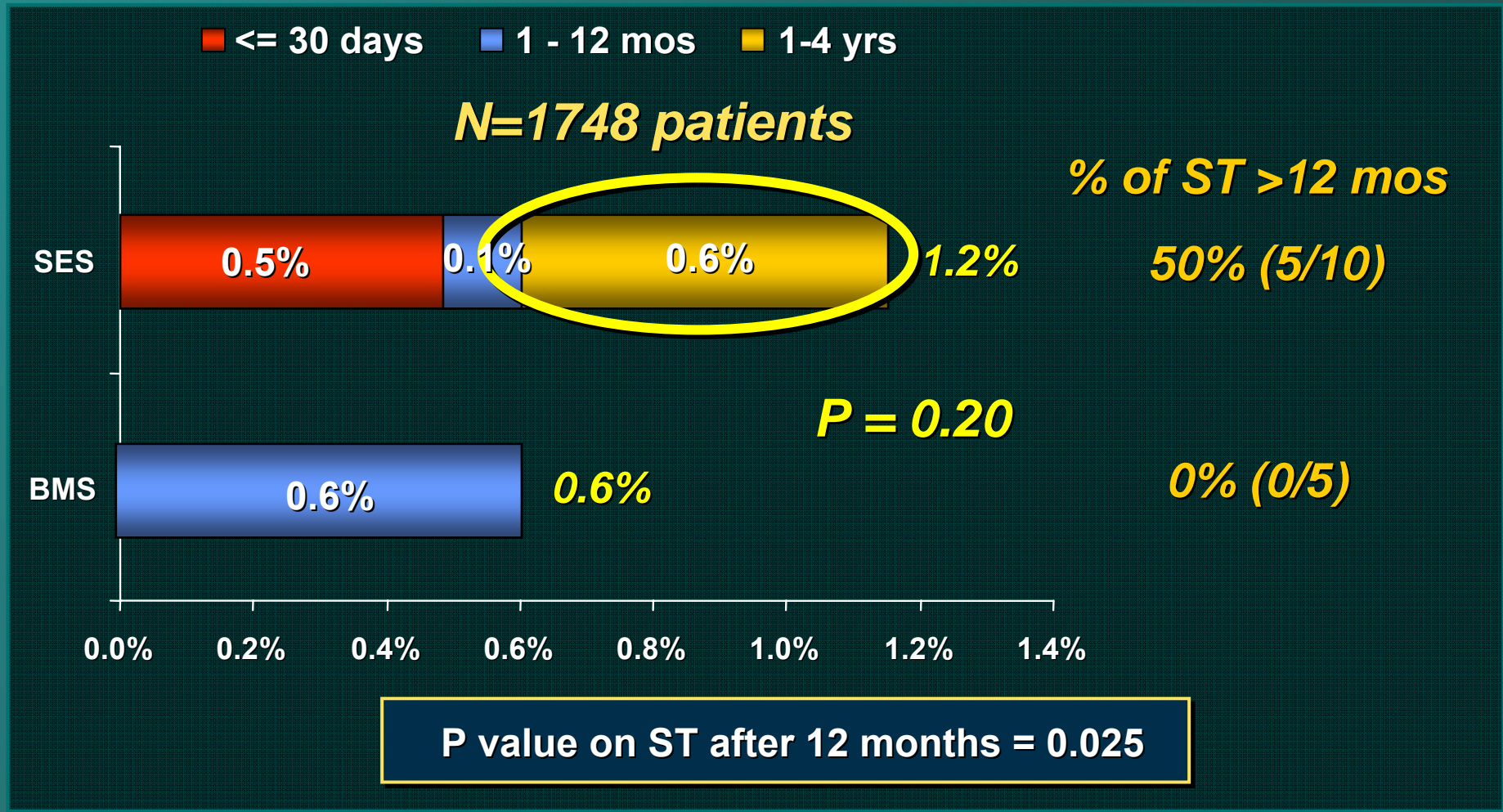


\* RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS



# Cypher RCT Meta-analyses

## Combined Stent Thrombosis\*



\* RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

# ***Expanded* Stent Thrombosis Definition**

## **Timing**

<b>Acute Thrombosis*:</b>	<b>0 – 24 hrs. post</b>
<b>Sub-acute Thrombosis*:</b>	<b>&gt;24 hrs – 30 days post</b>
<b>Late Thrombosis:</b>	<b>30 days – 1 year post</b>
<b>Very Late Thrombosis:</b>	<b>&gt; 1 year post</b>

- 1. Definite/Confirmed**
- 2. Probable**
- 3. Possible**

*\* Acute/Sub-acute can also be replaced by early stent thrombosis. Early stent thrombosis = 0-30 days.*

# ***Expanded* Stent Thrombosis Definition**

## **1. Definite/Confirmed**

***Angiographic confirmed stent thrombosis (definite)*** is considered to have occurred if:

**1. TIMI flow is:**

- a. Grade 0 with occlusion originating in the stent or segment 5mm proximal or distal to the stent region in the presence of thrombus**
- b. Grade 1, 2, 3 originating in the stent or in the segment 5mm proximal or distal to the stent region in the presence of thrombus**

**AND** at least one of the following criteria within 48 hrs:

- 2. New onset of ischemic symptoms at rest (typical chest pain with duration >20 minutes)**
- 3. New ischemic ECG changes suggestive of acute ischemia**
- 4. Typical rise and fall in cardiac biomarkers (>2x ULN of CK)**

The incidental angiographic documentation of stent occlusion in the absence of clinical syndromes is not considered a confirmed stent thrombosis (silent thrombosis).



# ***Expanded* Stent Thrombosis Definition**

## **2. Probable**

***Probable stent thrombosis*** is considered to have occurred in the following cases:

- 1. Any unexplained death within the first 30 days.**
- 2. Irrespective of the time after the index procedure, any MI in the absence of any obvious cause which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis.**

## **3. Possible**

***Possible stent thrombosis*** is considered to have occurred with any unexplained death beyond 30 days.



# CYPHER RCT Stent Thrombosis

## 4 yr Follow-up: *Expanded Definition*

### *definite + probable*

Thrombosis	CYPHER N=878 Patients	BMS N=870 Patients	P Value*
Early (0-30 days)	0.5% (4)	0.3% (3)	0.4702
Late (31-360 days)	<b>0.2% (2)</b>	<b>0.9% (8)</b>	<b>0.0098</b>
Very Late (361-1440)	0.9% (7)	0.5% (4)	0.3632
<b>Summary:</b>			
Late + Very Late	1.1% (9)	1.4% (12)	0.5043
All Thrombosis	1.5% (13)	1.7% (15)	0.6985

Data from 4 pooled RCT: SIRIUS, E and C SIRIUS and RAVEL

\* *Log Rank (exact) Test P-value*



# CYPHER RCT Stent Thrombosis 4 yr Follow-up: *Expanded Definition* *definite + probable*

Thrombosis	CYPHER N=878	BMS N=870	P-Value*
<b>Expanded Definition</b>	1.5% (13)	1.7% (15)	0.6985
<b>Standard Definition</b>	1.5% (13)	1.7% (15)	0.6985
<b>All Thrombosis</b>	1.5% (13)	1.7% (15)	0.6985

***Why the difference?***

***The protocol definitions of stent thrombosis censored all stent thrombosis events after an intervening TLR!***

Data from 4 pooled RCT: SIRIUS, E and C SIRIUS and RAVEL

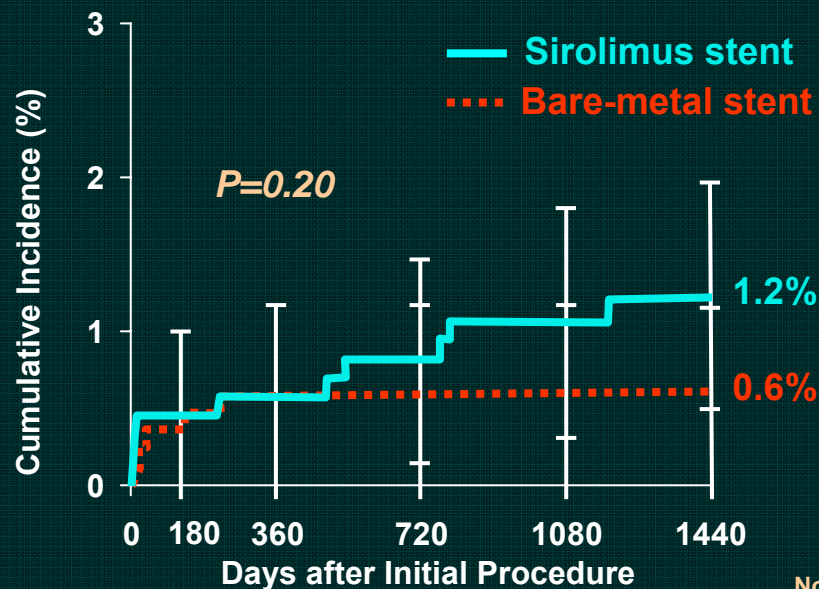
\* ***Log Rank (exact) Test P-value***



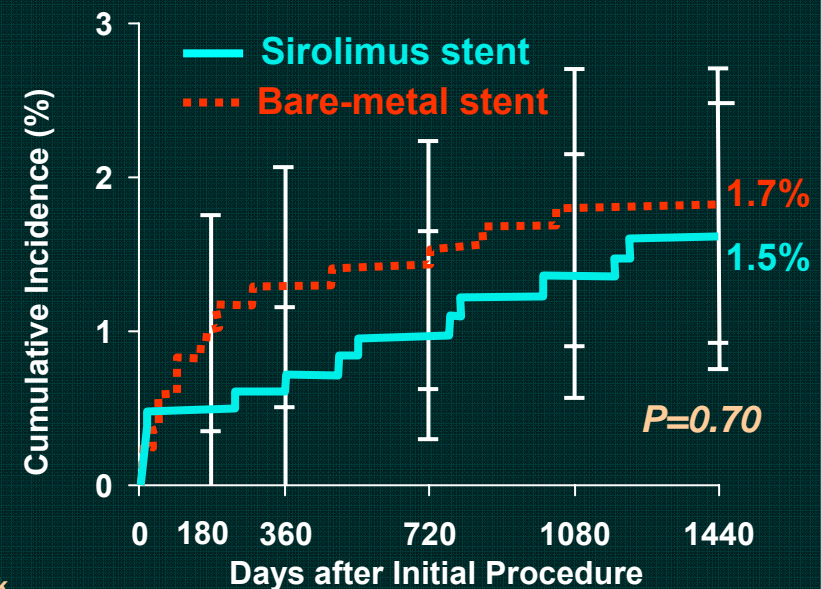
# Stent Thrombosis in Randomized Clinical Trials of Drug-Eluting Stents

*Protocol and ARC definitions of stent thrombosis; SES randomized trials; Follow-up to 4 yrs*

**Sirolimus Stent (Protocol)**



**Sirolimus Stent (ARC)\***

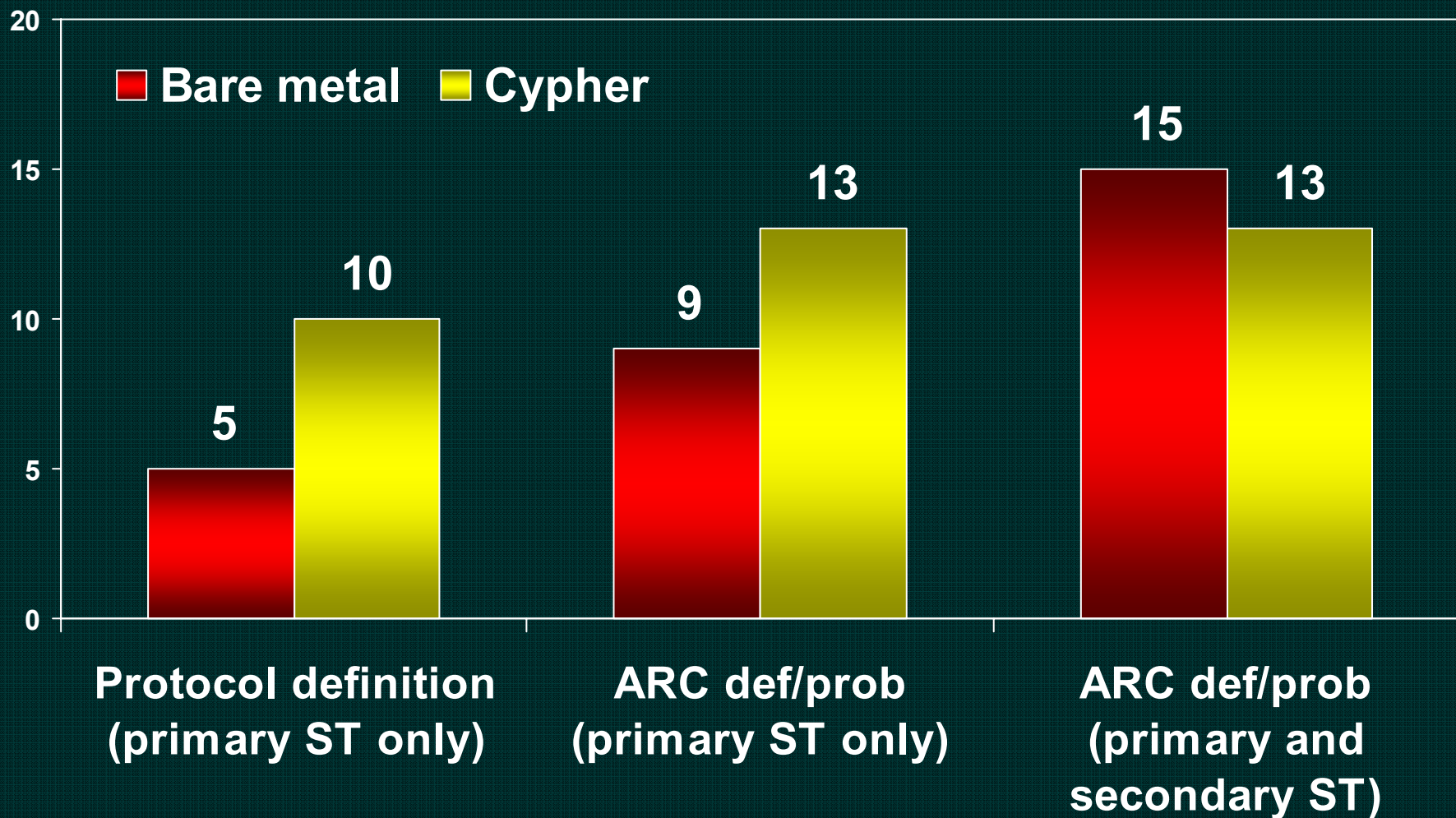


*\*def + prob*



# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

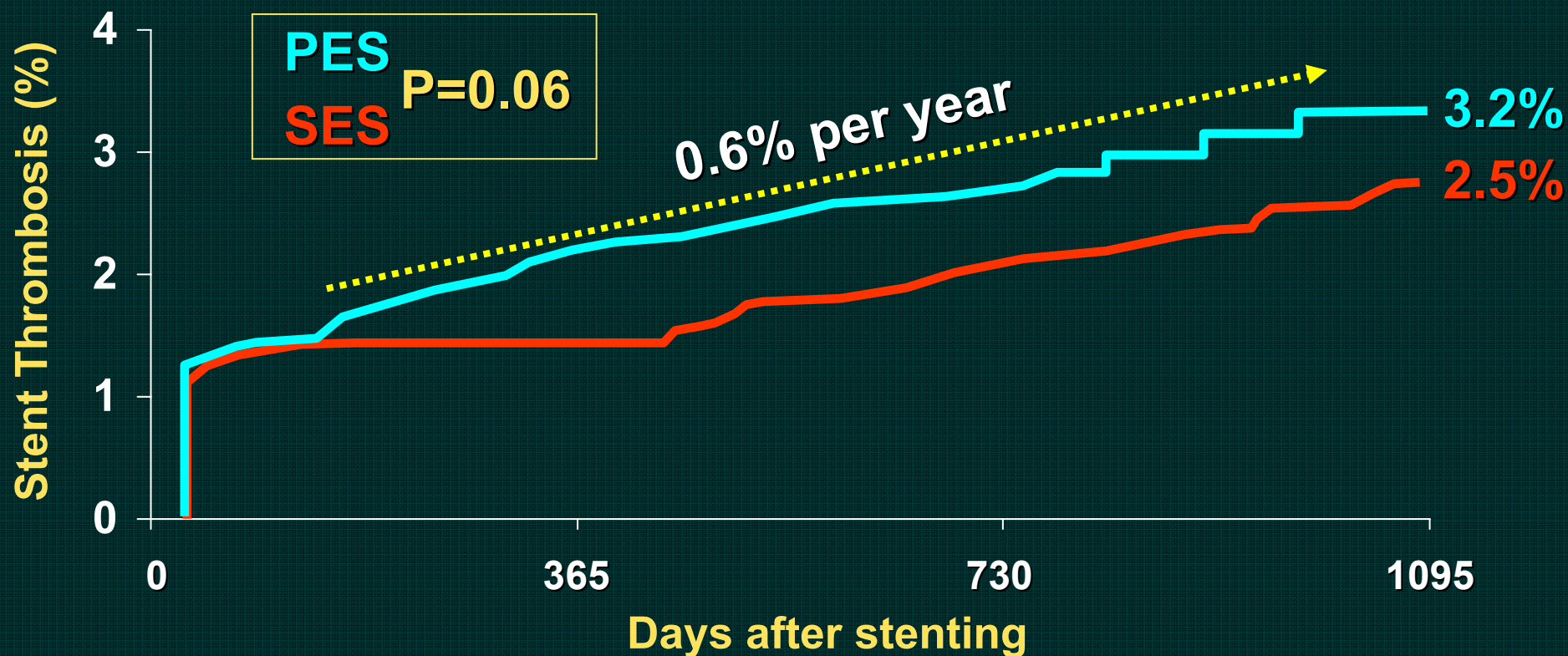
## Stent Thrombosis: 0 – 4 Years



*RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS*



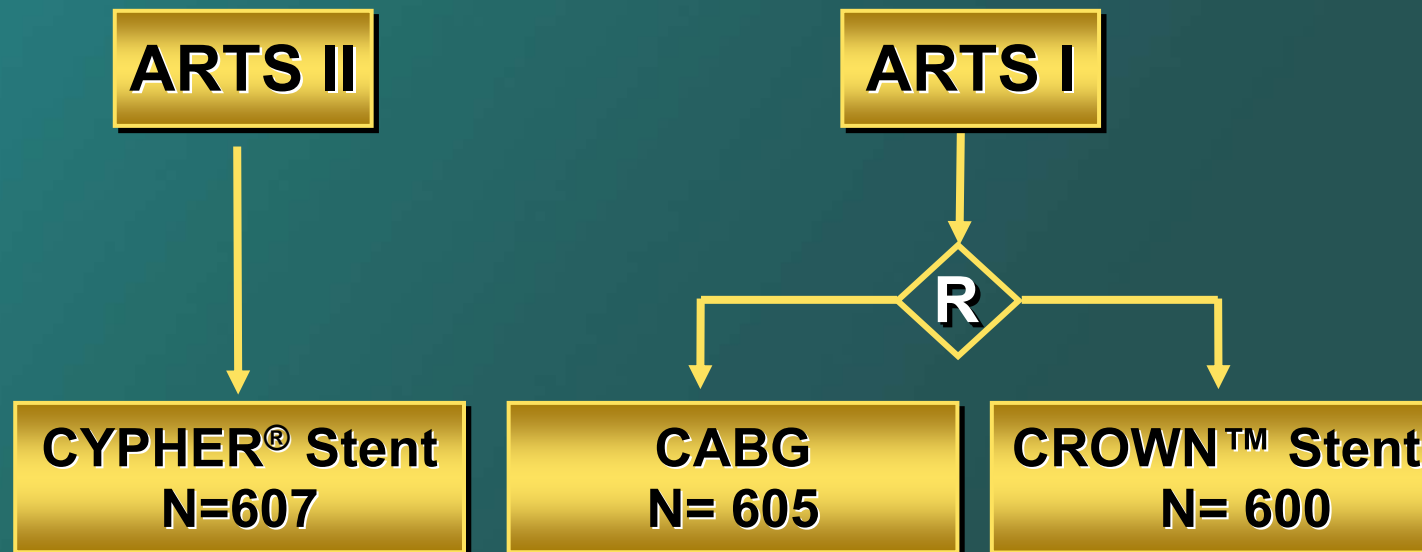
# Bern/Rotterdam 2 Center Experience



Days after PCI	9	30	365	730	1095
Incidence <b>SES</b> (%)	1.0	1.1	1.3	1.9	2.5
Incidence <b>PES</b> (%)	1.2	1.3	2.0	2.7	3.2
Pts at risk	8146	7162	7002	2841	971

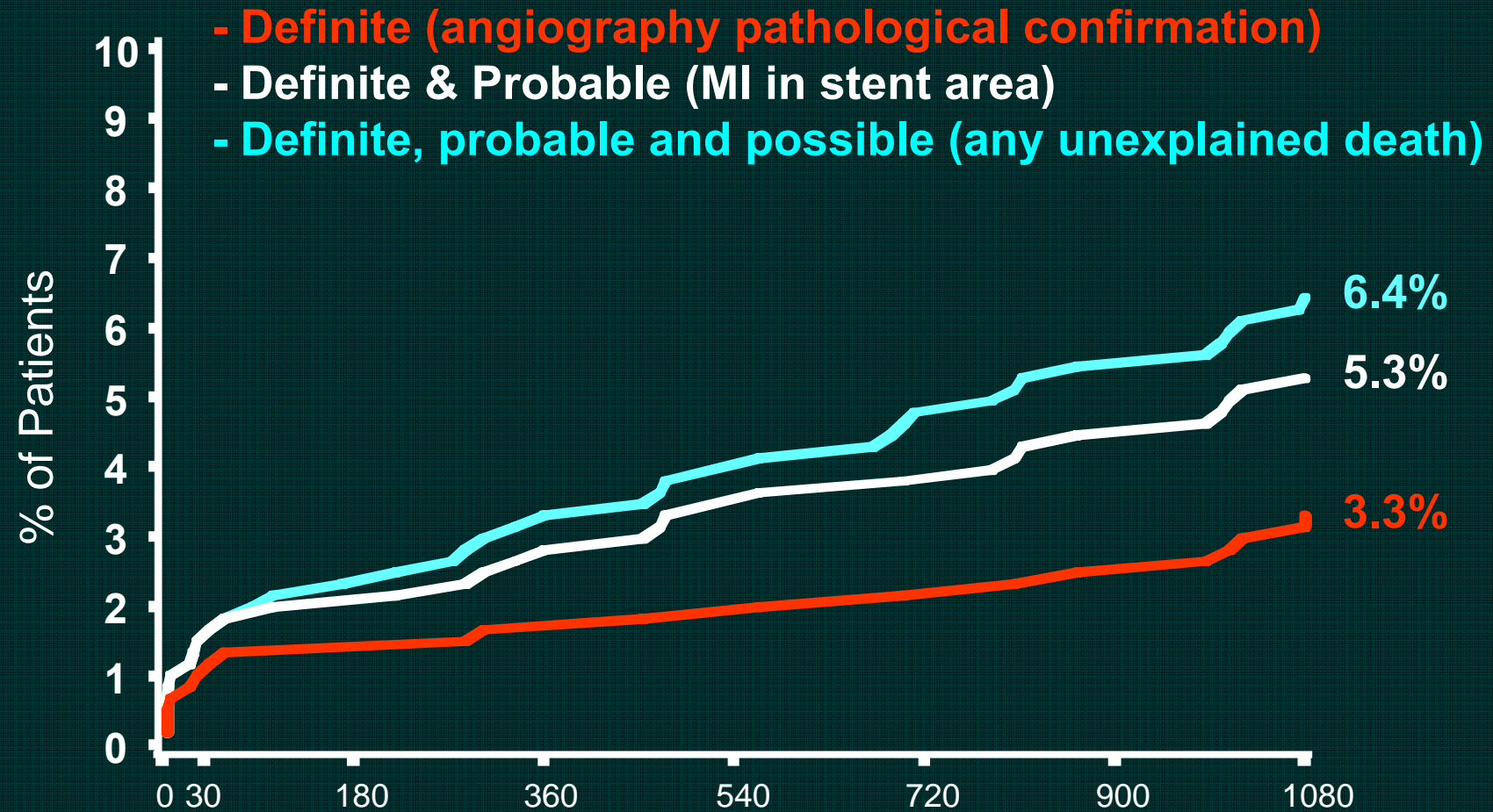
# ARTS II – Study Design

- Multicenter, non-randomized trial
- 607 patients in 45 centers from 19 countries
- The main goal of the ARTS II trial is to assess a non-inferiority in treatment effectiveness and in cost-effectiveness with respect to the previous results of the ARTS I trial

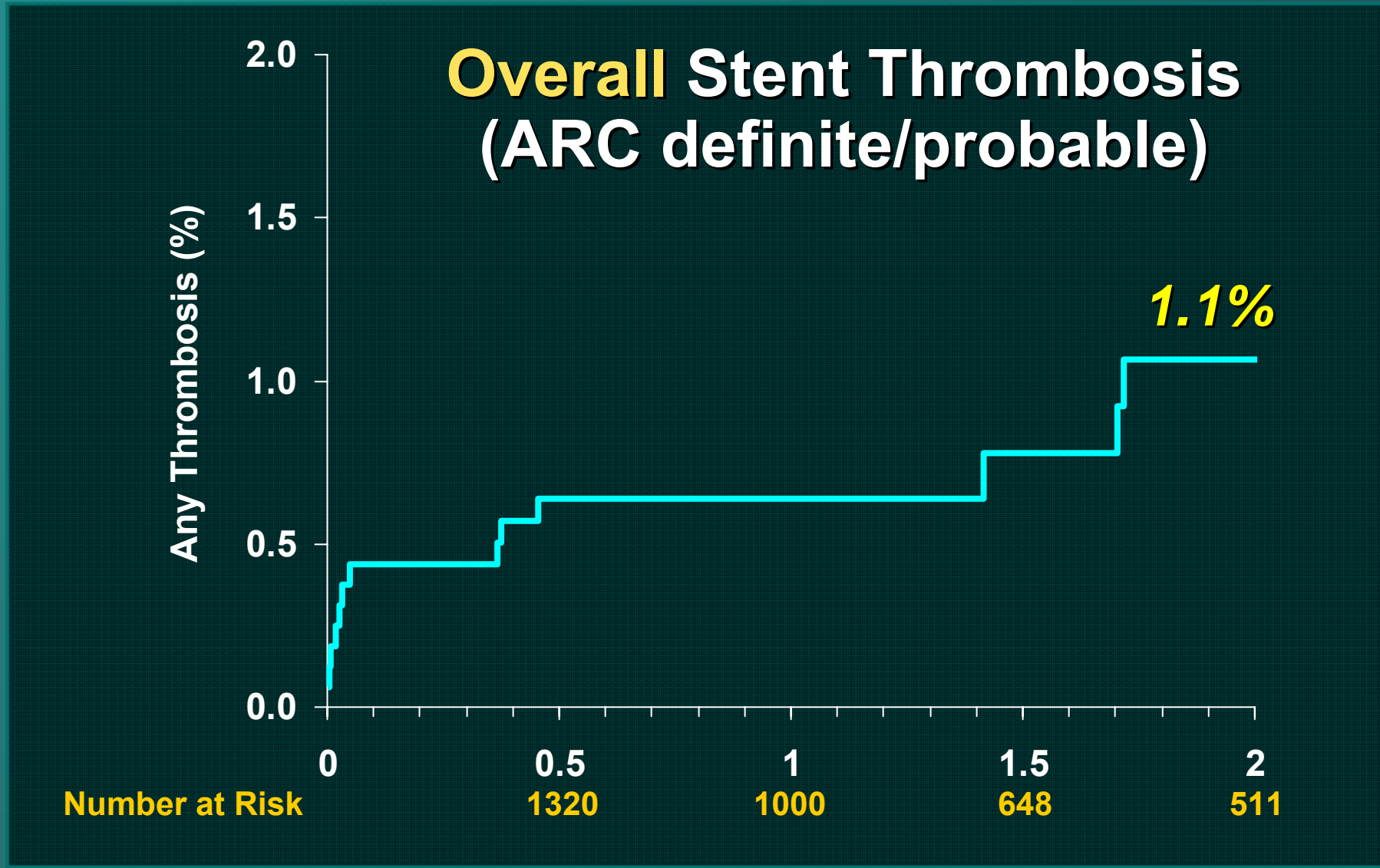


# ARTS II: Stent thrombosis to 3 yrs\*

\* Re-adjudication according to ARC definitions

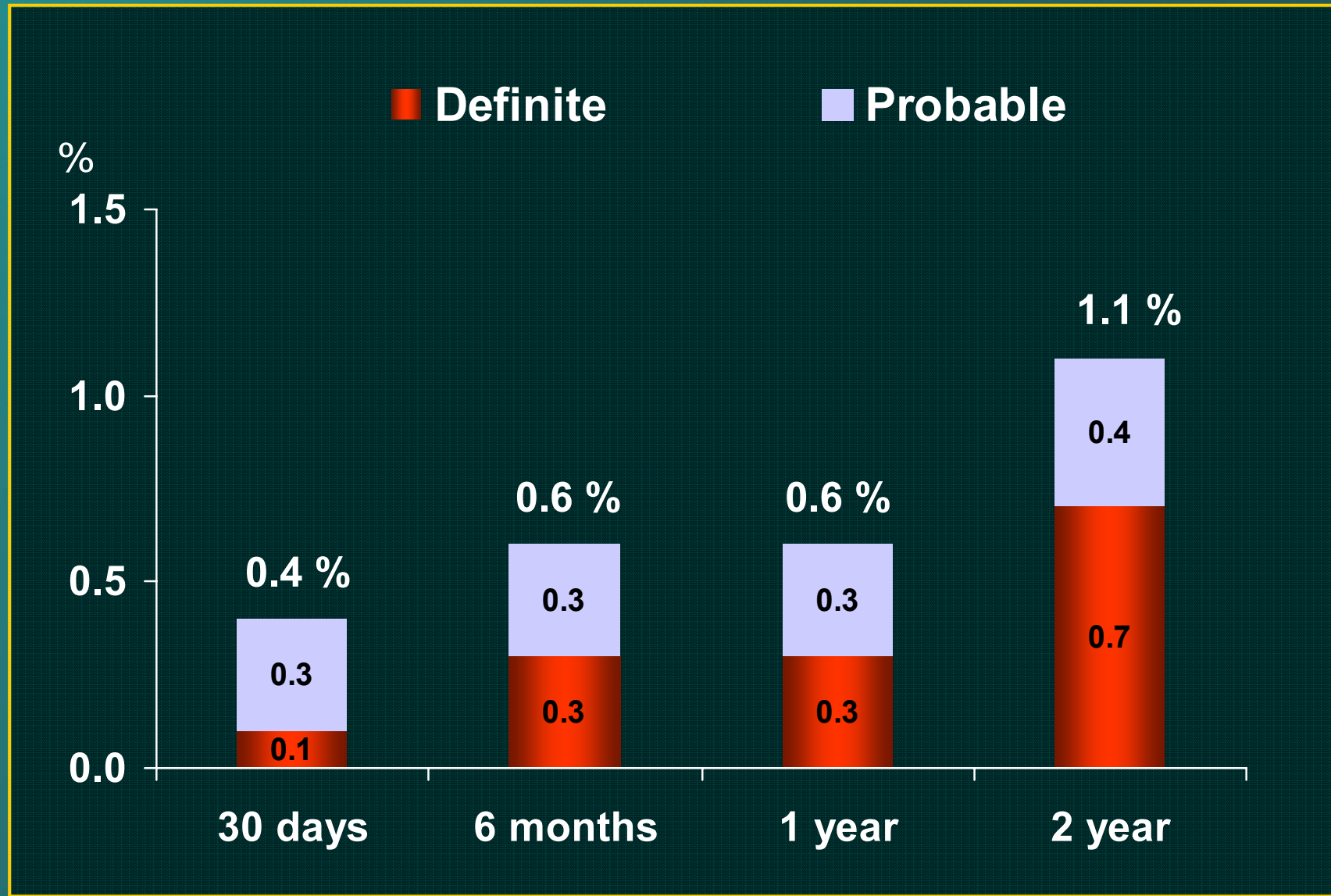


# **MATRIX:** 1,522 “real world” pts (86% off label)

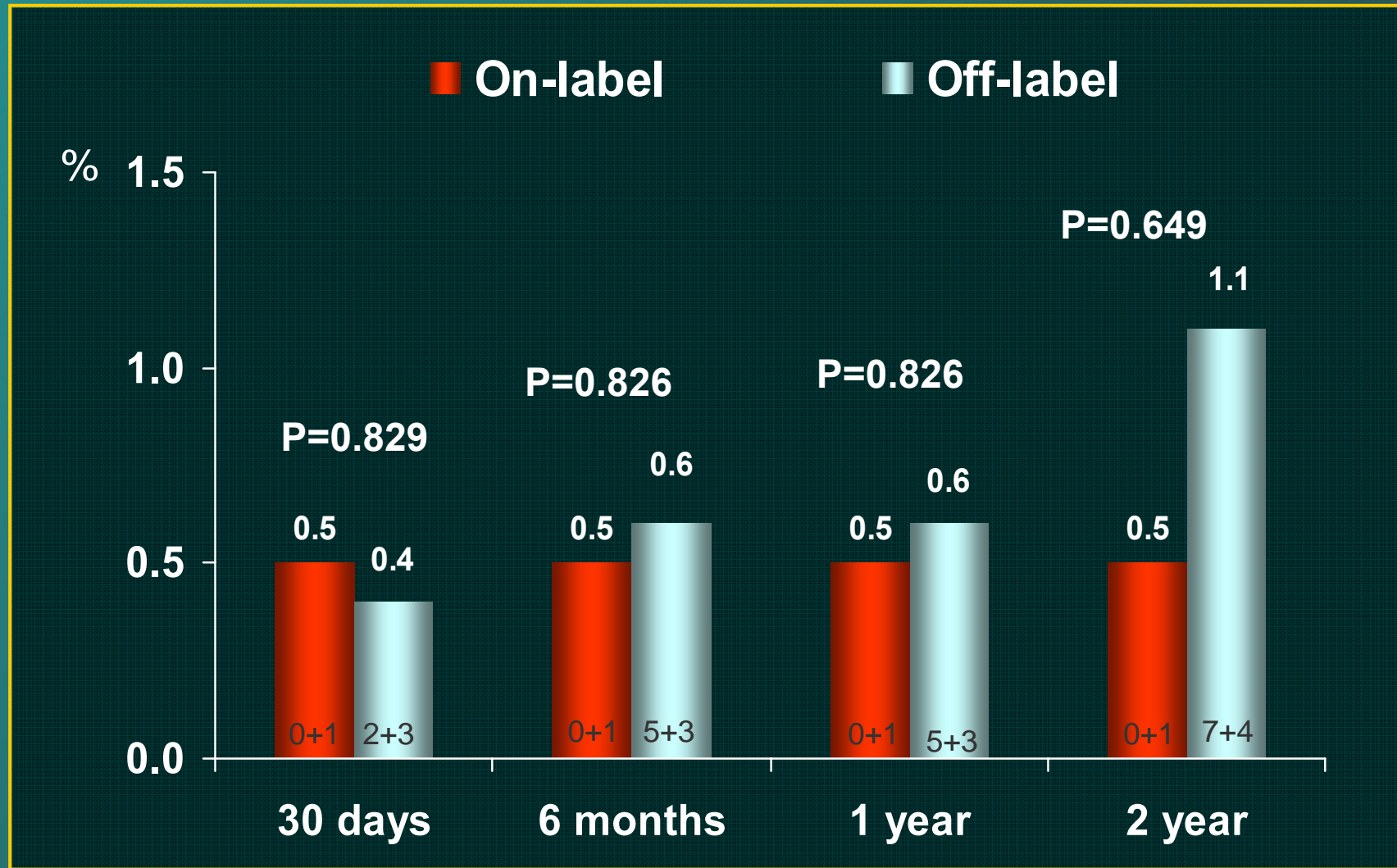




# **MATRIX: 1,522 “real world” pts (86% off label)**



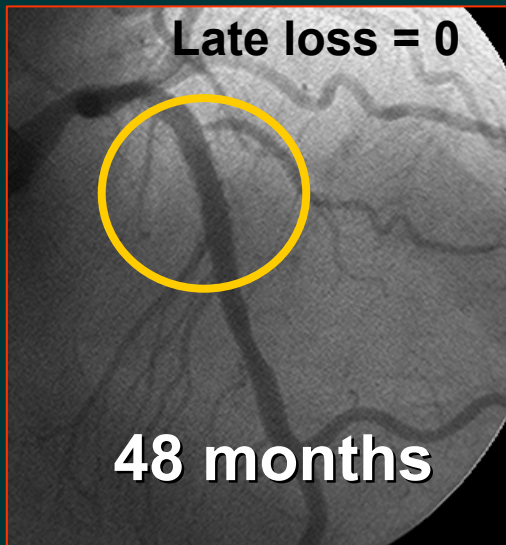
# **MATRIX: ST\* on-label vs. off-label use**



\* Stent thrombosis includes ARC definite and probable



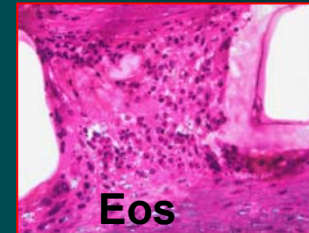
# Drug-Eluting Stents.... the good, the bad, and the ugly!



**Delayed Healing!**



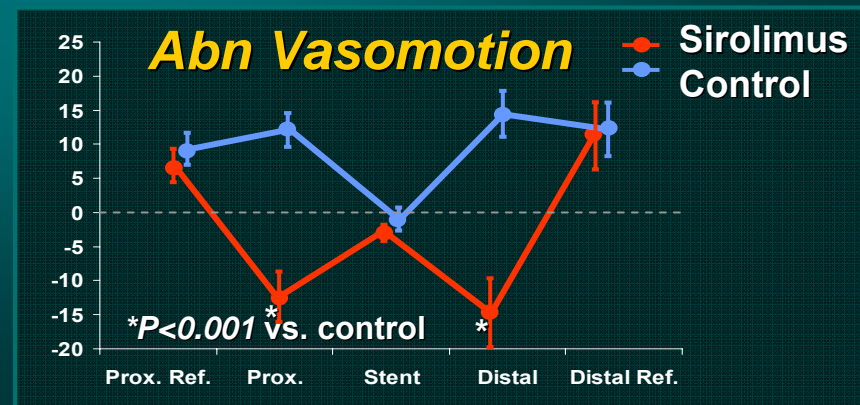
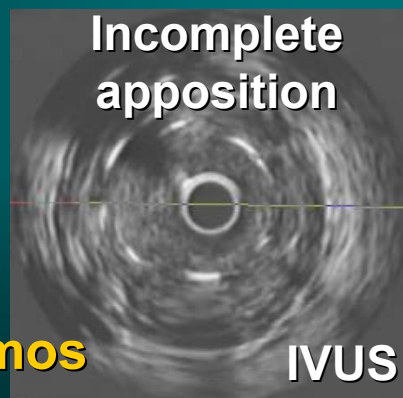
Angioscopy



Inflammation

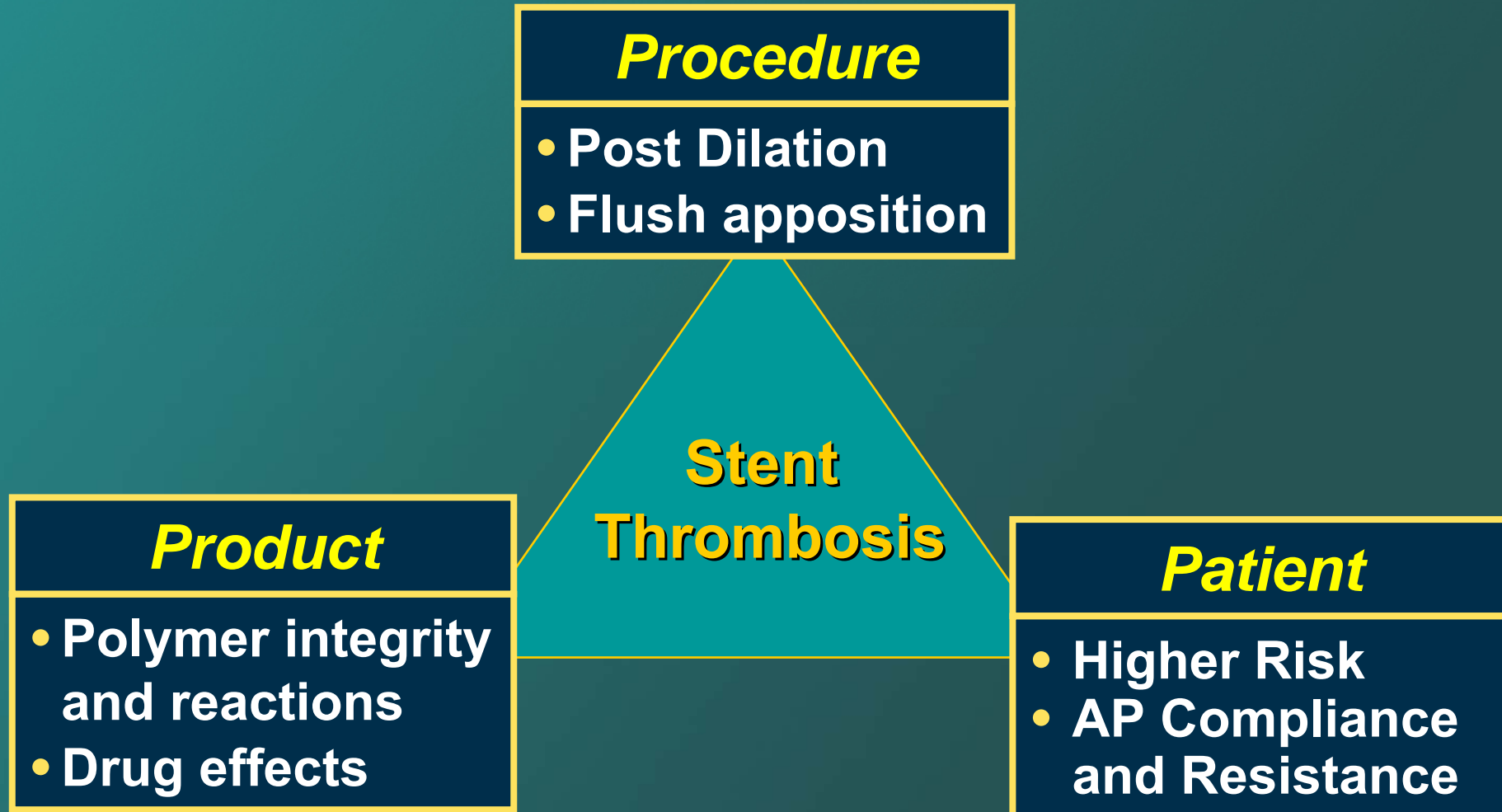


40 mos



# Stent Thrombosis

## *Procedure, Product, Patient*



# SES Real World: Safety Concerns?

## The Four Questions...

- Is there an increase in stent thrombosis with SES vs. BMS (ARC definitions, continuous hazard, and causes)?
- *Is there an increase in death (and MI) with SES vs. BMS (on-label vs. off-label, diabetics)?*
- Should the anti-platelet therapy be adjusted due to SES stent thrombosis considerations?
- Should SES use be modified in response to safety concerns?

# 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**

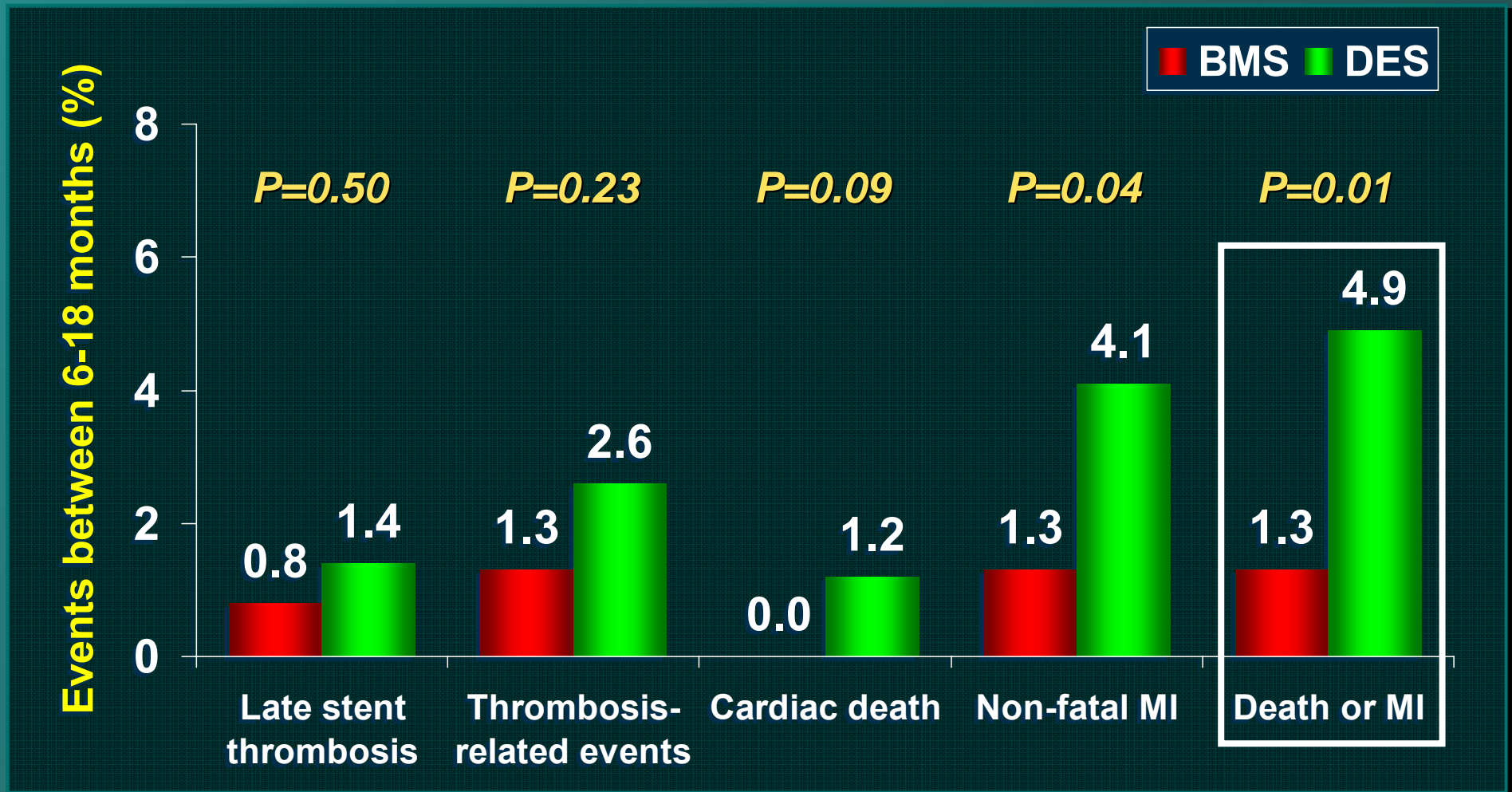
**Bare metal  
VISION stents (BMS)  
n=244**

***Followed for 1 year off clopidogrel***

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

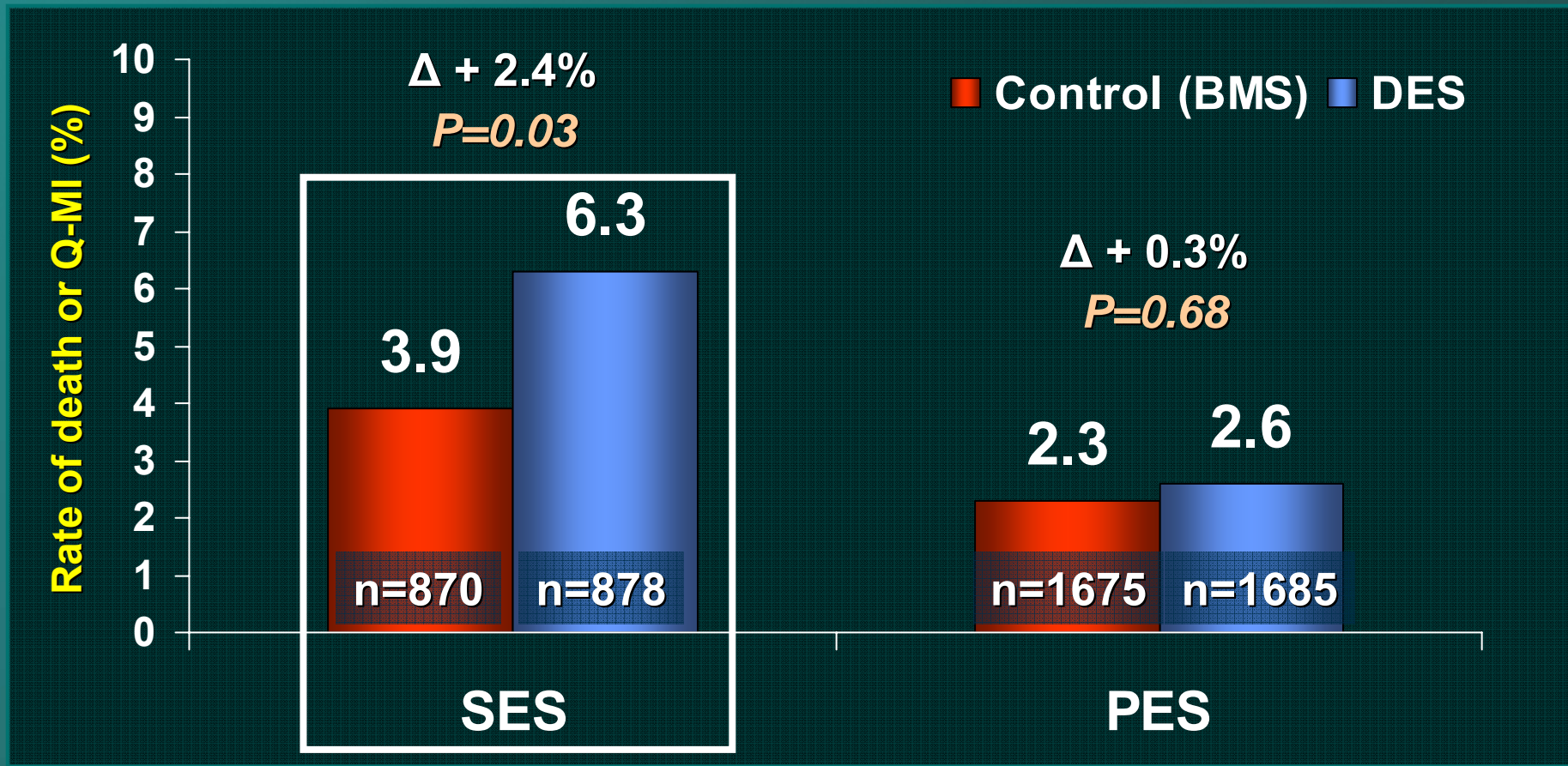
# BASKET LATE Trial: 6-18 Mo MACE

N=743 (pts with early events excluded)



# Incidence of Serious or Adverse Events Death or Q-Wave MI

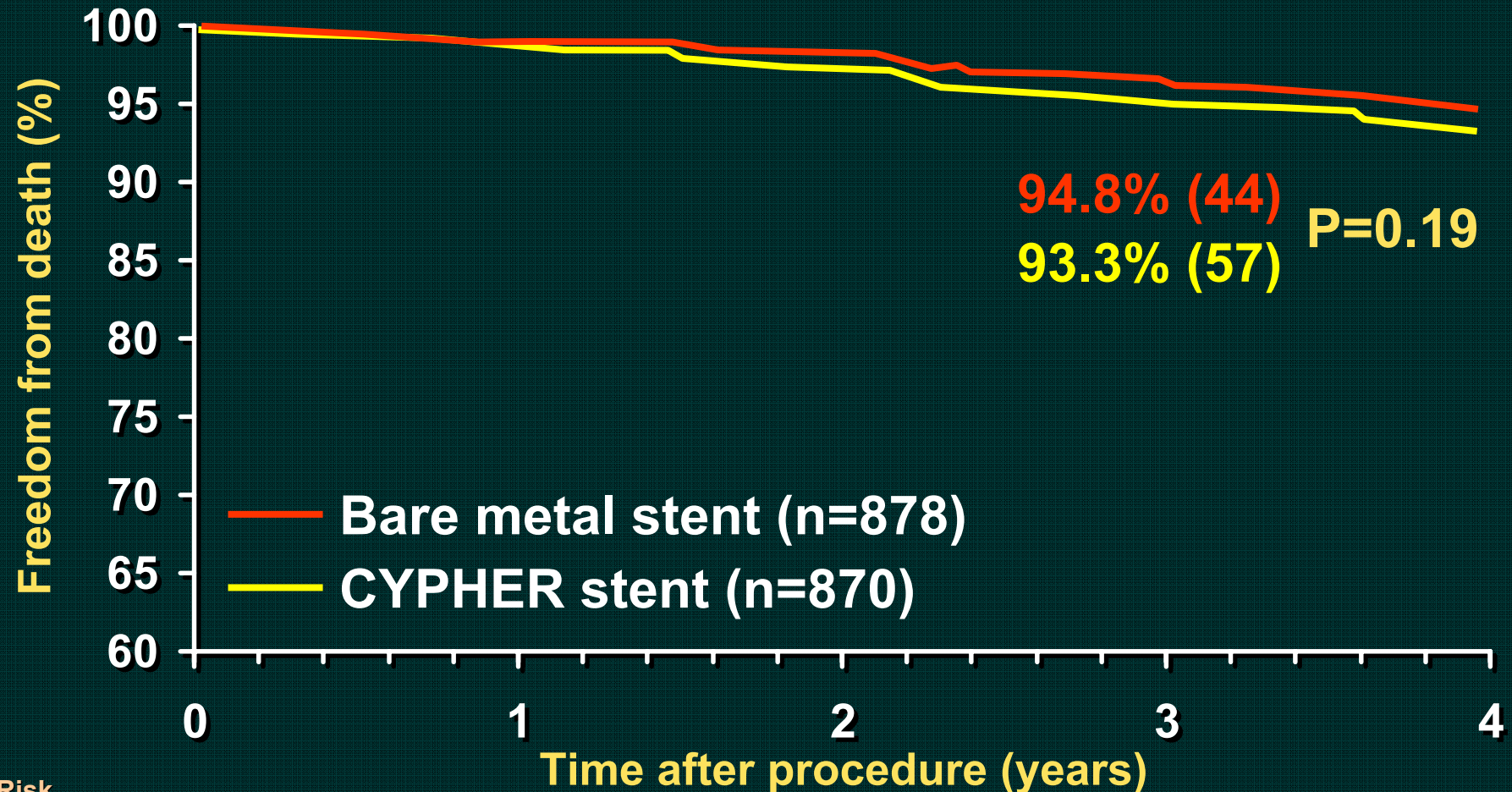
All randomized studies up to latest available follow-up





# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

## Freedom From Death (all cause): 0 – 4 Years

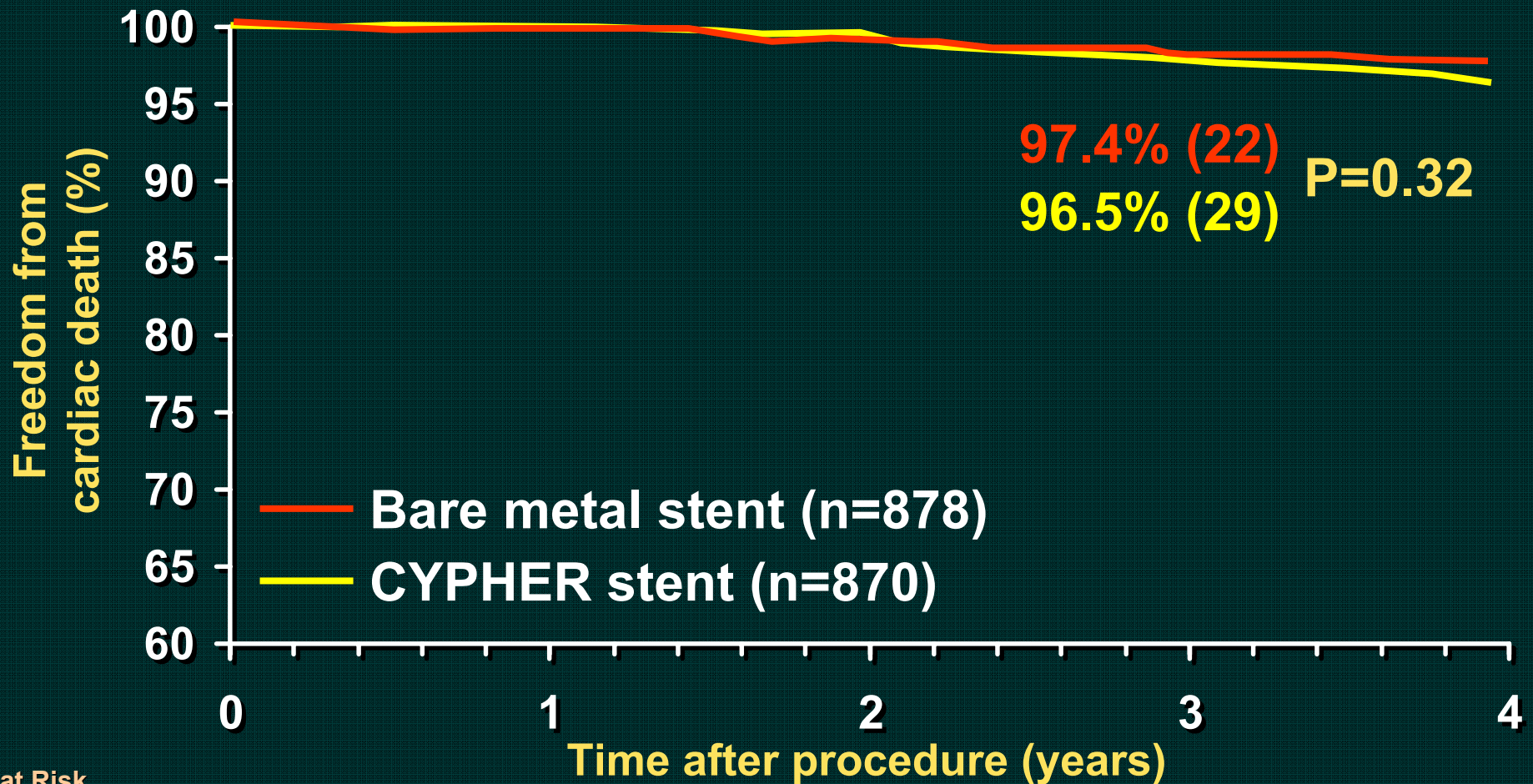


# at Risk

BMS	870	855	835	809	745
CYPHER	878	859	832	801	738

# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

## Freedom From Cardiac Death: 0 – 4 Years

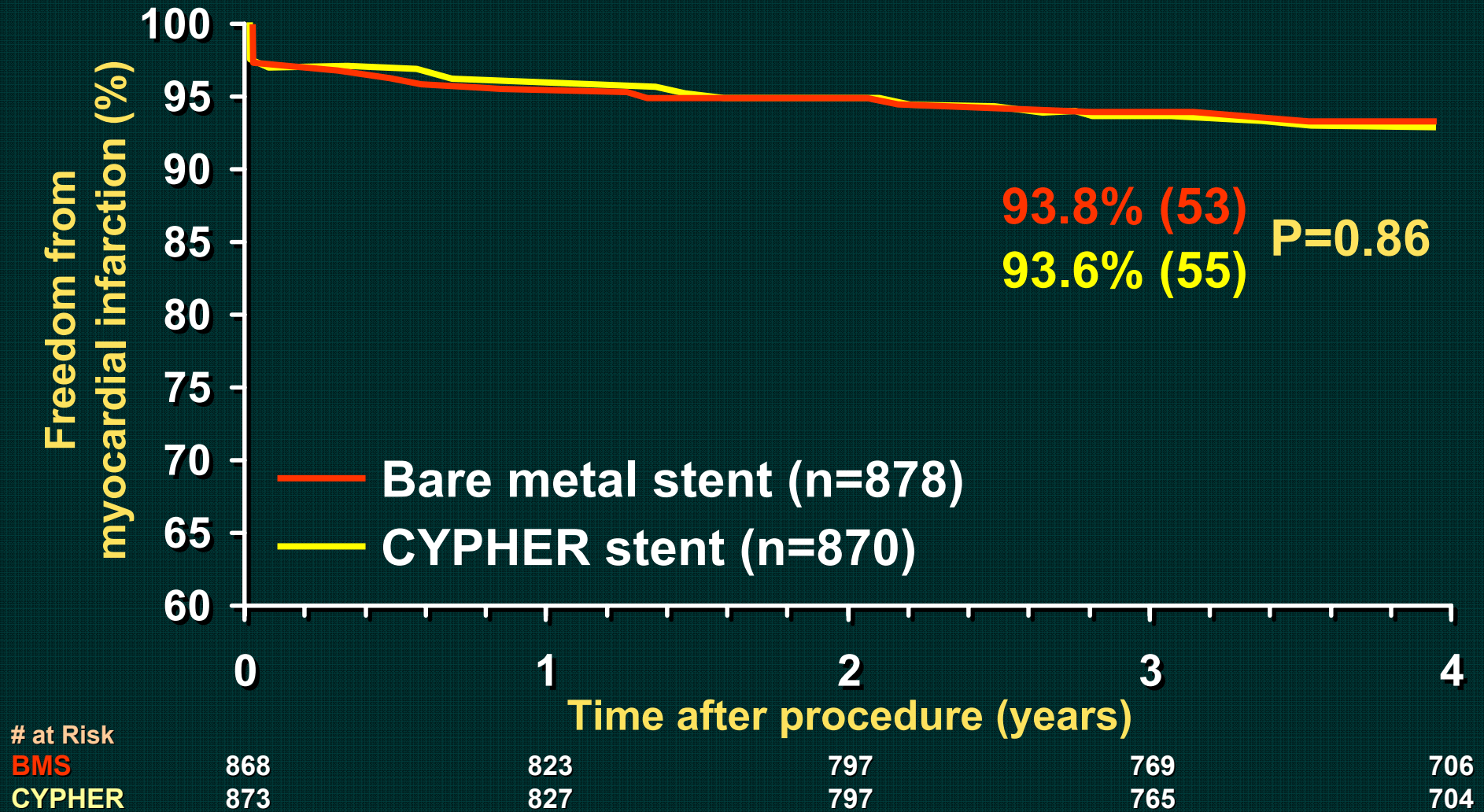


# at Risk

BMS	870	855	835	809	745
CYPHER	878	859	832	801	738

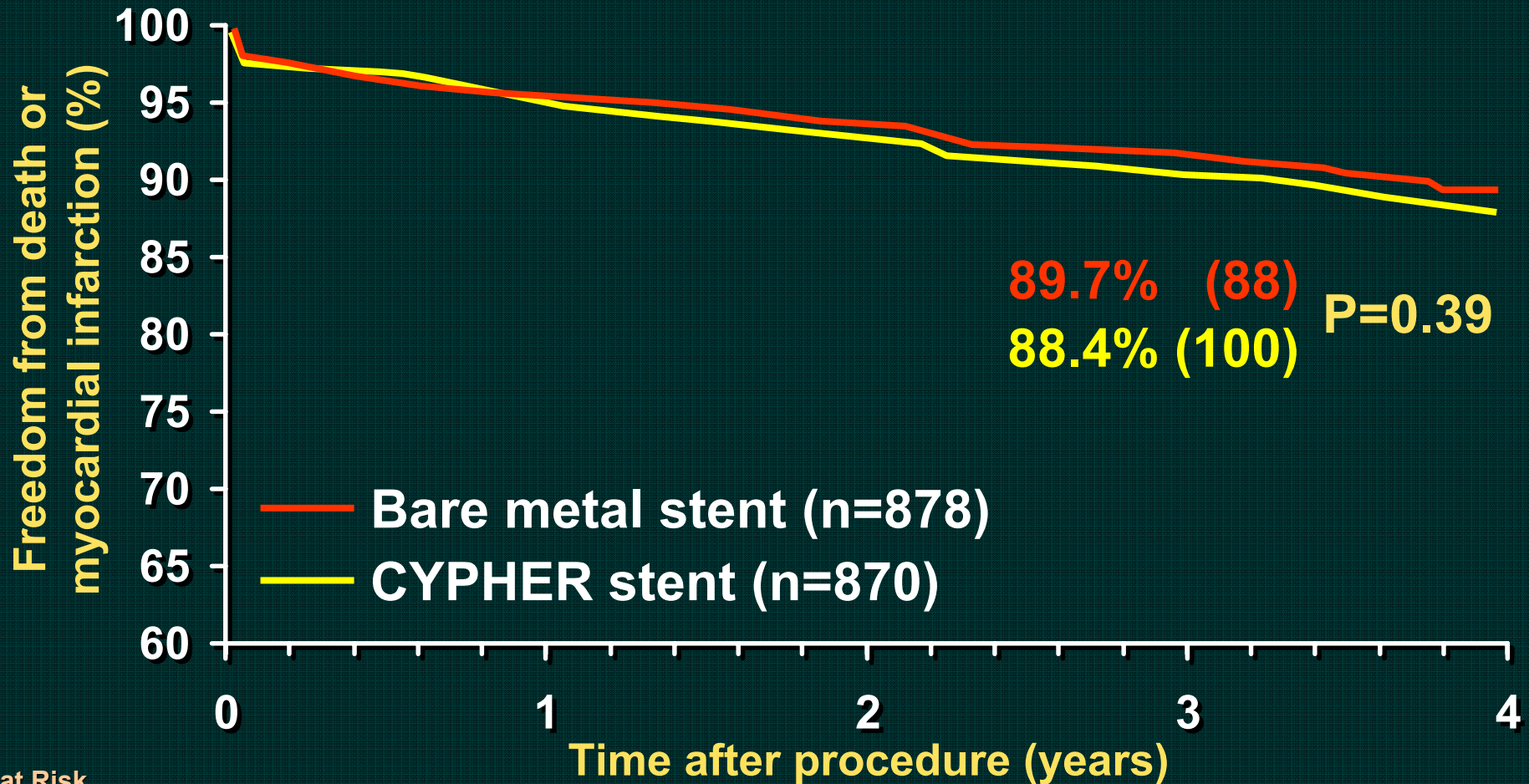
# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

## Freedom From Myocardial Infarction: 0 – 4 Years



# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

## Freedom From Death or MI: 0 – 4 Years

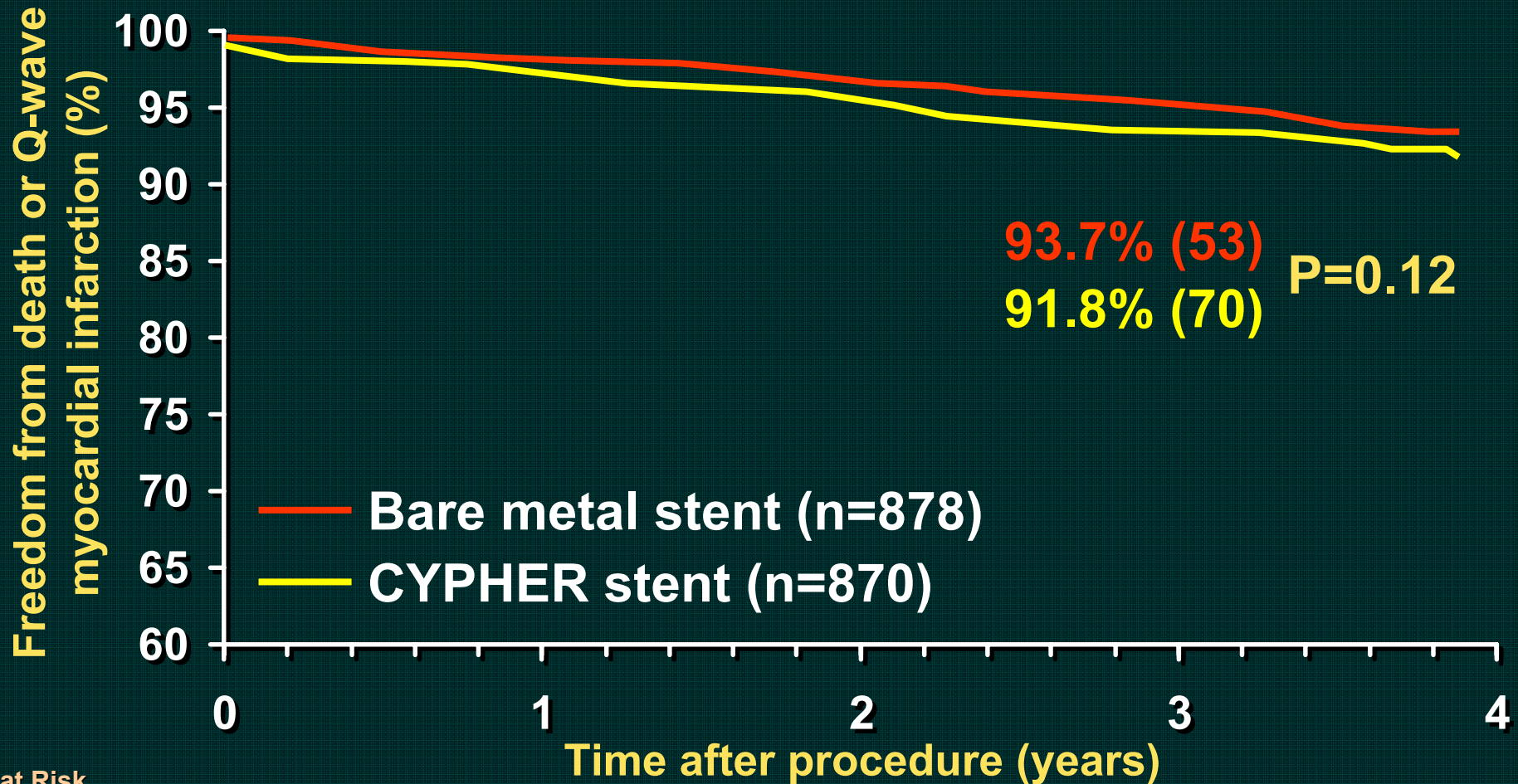


# at Risk

BMS	868	823	797	769	706
CYPHER	873	827	797	765	704

# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

## Freedom From Death or Q-wave MI: 0 – 4 Years

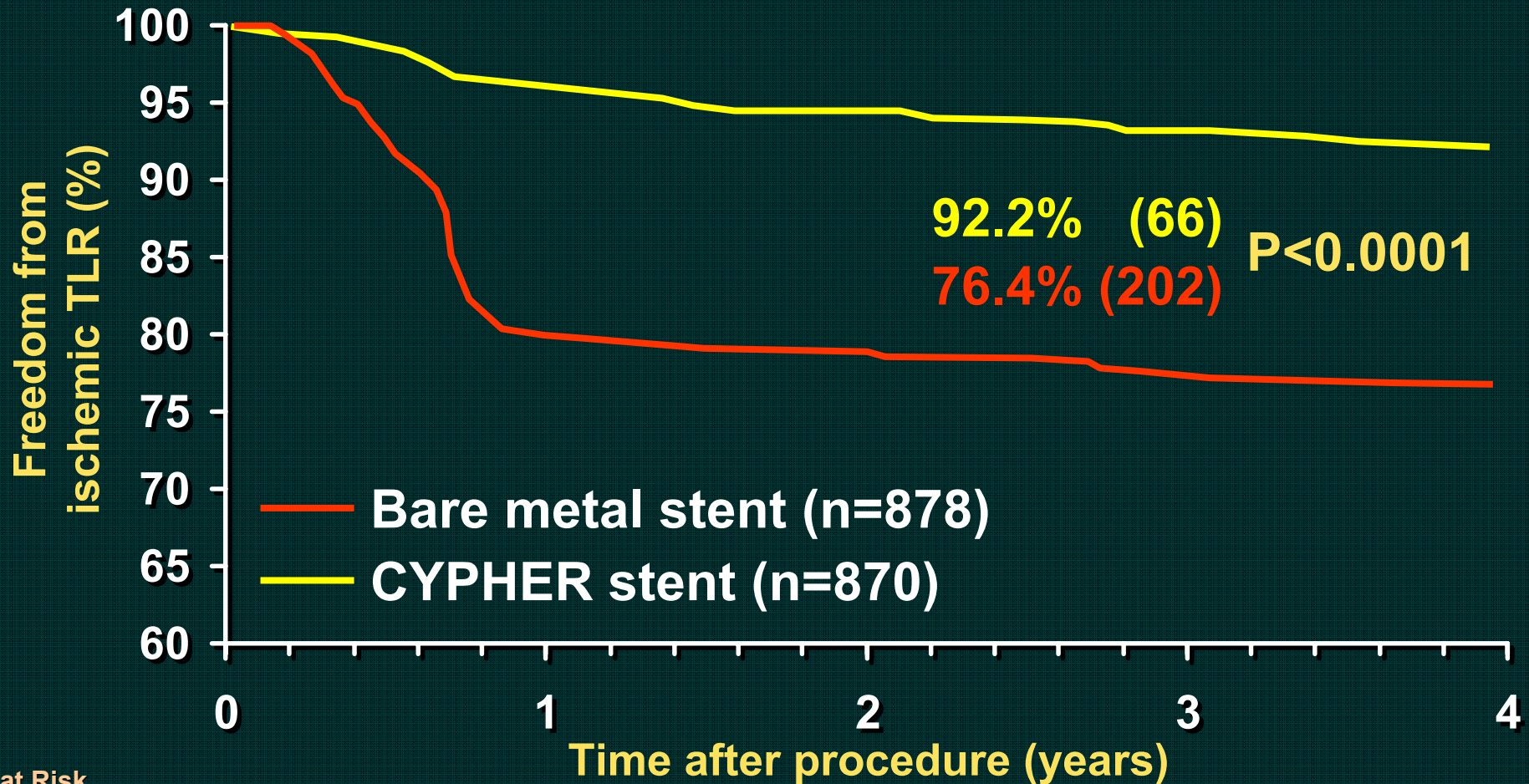


# at Risk

BMS	869	851	829	802	738
CYPHER	877	849	822	789	727

# CYPHER 4-Study RCT Meta-Analysis (N=1,748)

## Freedom From Ischemic TLR: 0 – 4 Years



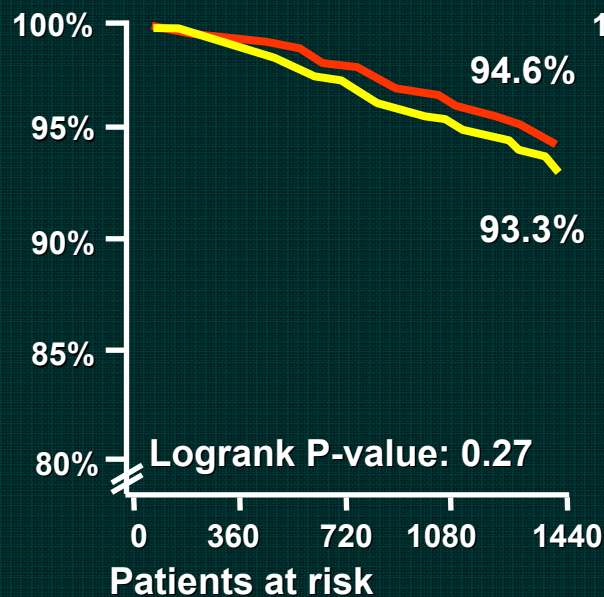
# at Risk

BMS	870	679	653	621	569
CYPHER	877	823	788	753	685

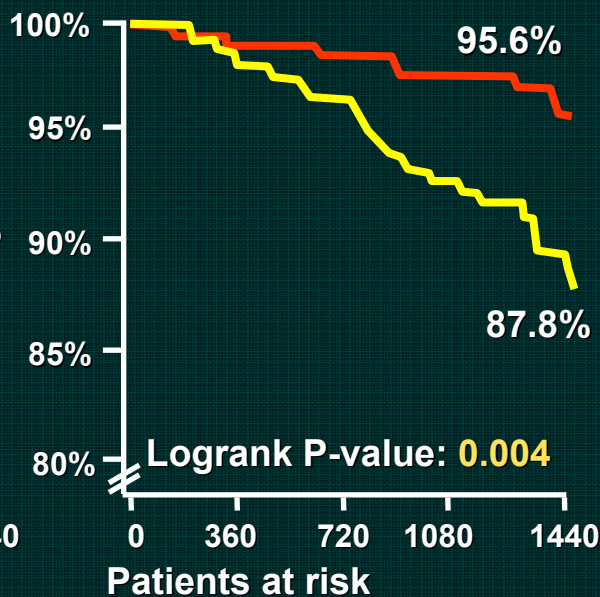
# All-cause Mortality in Pooled Analysis

## RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

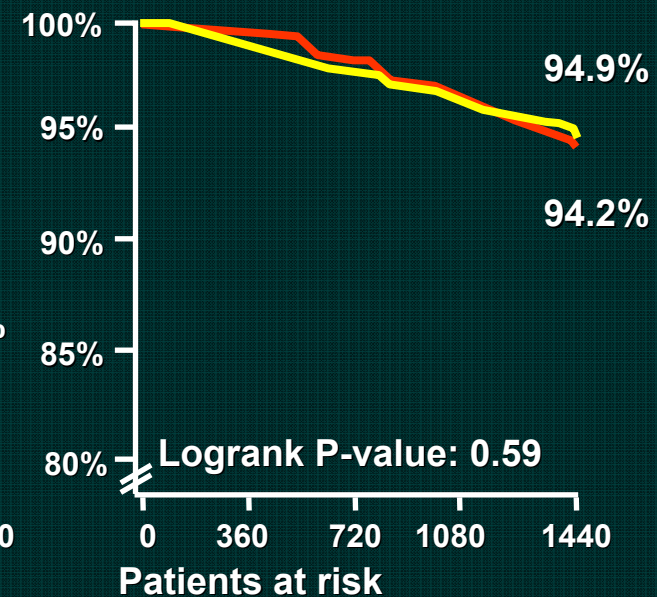
### Total population N=1748



### Diabetic patients N=428



### Non-diabetic patients N=1318



BMS	869	855	838	816	763
SES	877	860	835	809	740

232	230	227	221	197
194	188	185	175	158

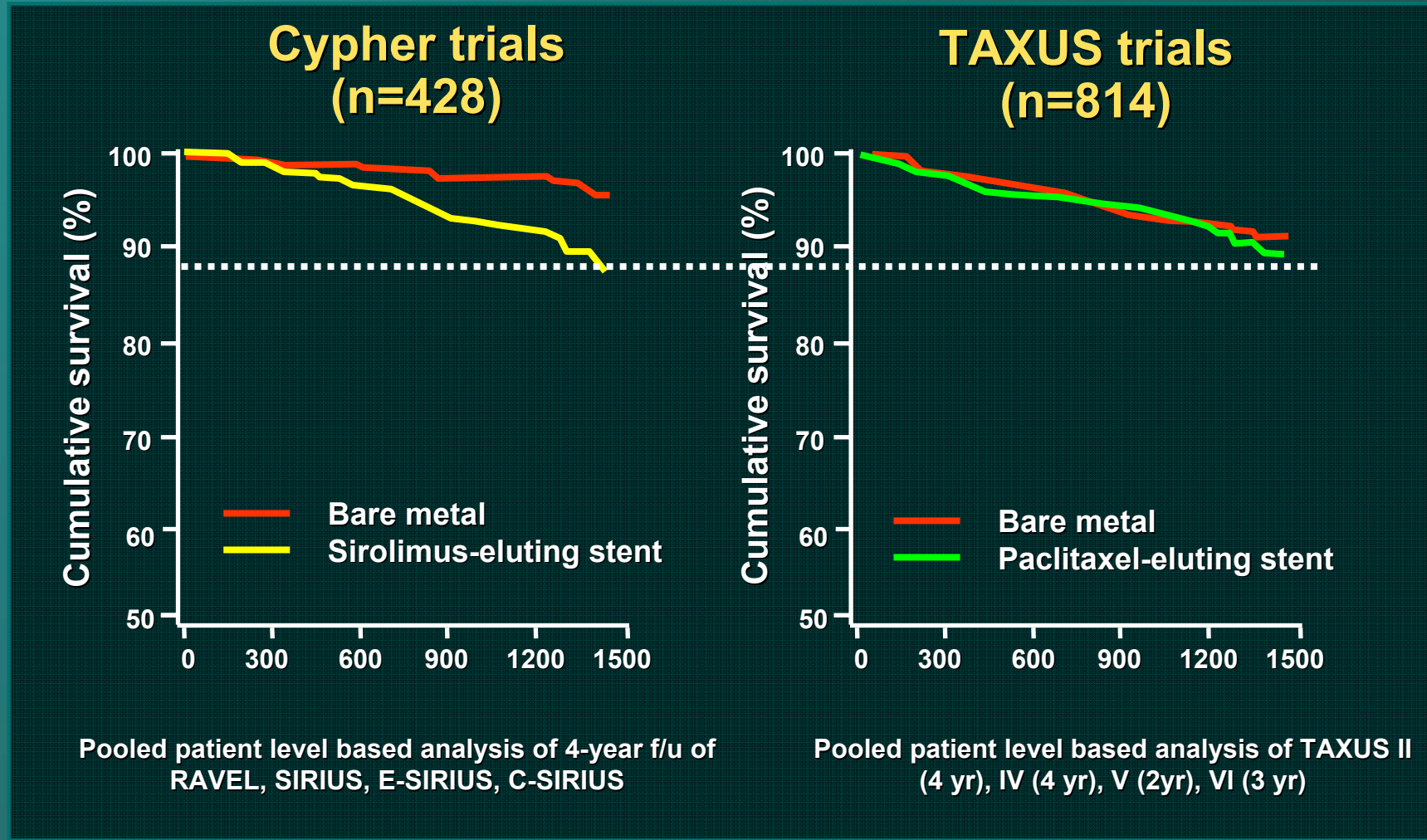
634	623	608	593	545
672	672	650	634	579

— Bare metal  
— Sirolimus-eluting stent



# Mortality in Pooled Analyses

## Diabetic subset





# DES: Off-label use

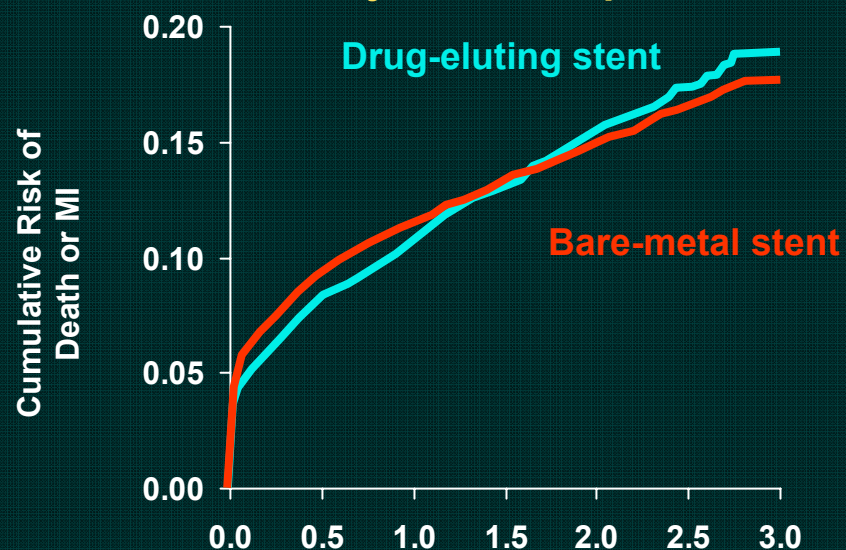
- **More complex and unapproved indications**
  - **Very small vessels and very long lesions**
  - **Chronic total occlusions**
  - **Bifurcations**
  - **Left main disease**
  - **In-stent restenosis**
  - **Multivessel disease**
  - **Saphenous vein grafts**
  - **Acute myocardial infarction**



# Long-term Outcomes with DES vs. BMS in Sweden

- 6033 pts with DES and 13,738 pts with BMS in 2003 and 2004 from the **Swedish Coronary Angiography and Angioplasty Registry (SCAAR)**
- FU up to 3 yrs based on 1424 deaths and 2463 MIs and adjusted for differences in baseline characteristics

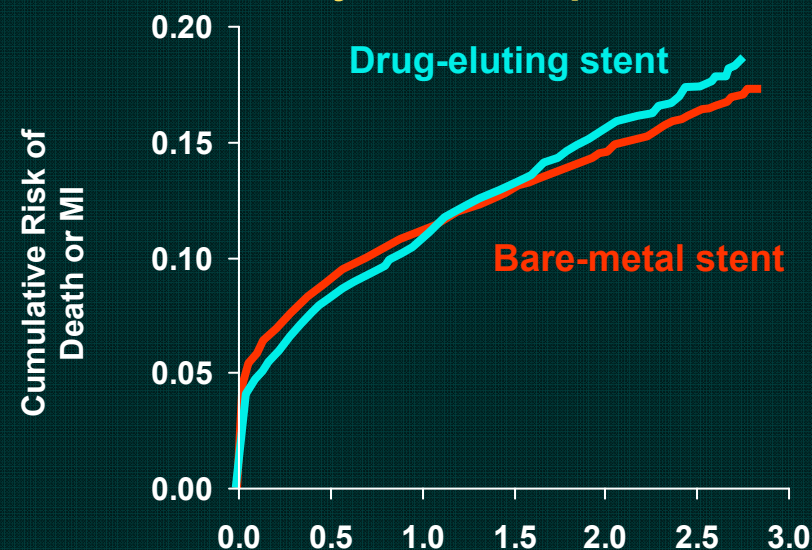
**Unadjusted Composite Event**



No. at Risk

<b>BMS</b>	13,735	12,467	12,172	9,295	5,965	3,205	7
<b>DES</b>	6,033	5,547	5,388	3,379	1,676	606	0

**Adjusted Composite Event**



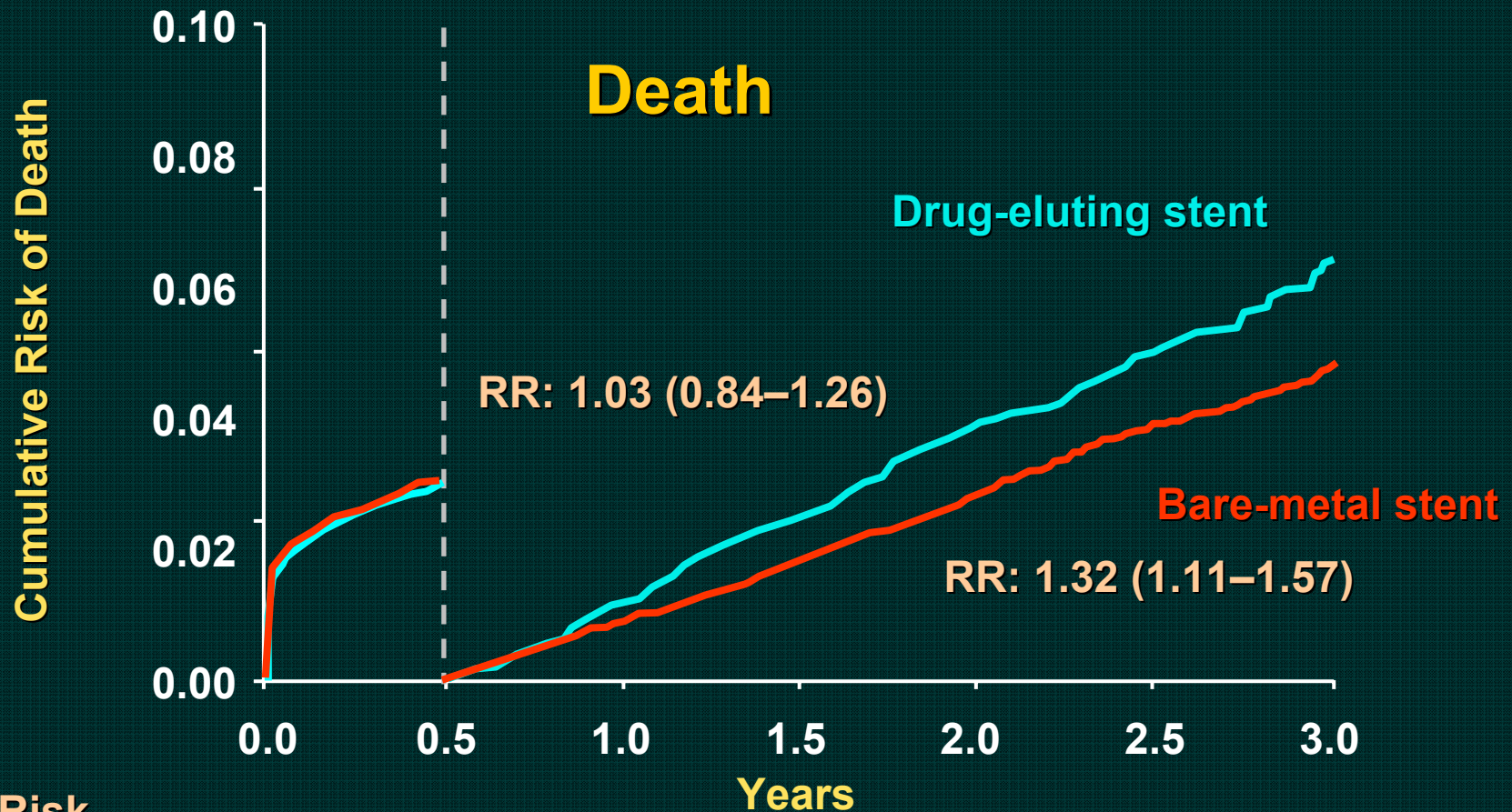
No. at Risk

<b>BMS</b>	12,880	11,706	11,432	8,665	5,520	2,963	7
<b>DES</b>	5,770	5,307	5,158	3,216	1,608	580	0



# SCAAR: Landmark Analysis of ALL Pts

*(Propensity Score Adjusted Cumulative Event Rates)*



**No. at Risk**

<b>BMS</b>	12,880	12,473	12,354	12,228	9,298	5,966	3,199
<b>DES</b>	5,770	5,605	5,541	5,471	3,434	1,777	626



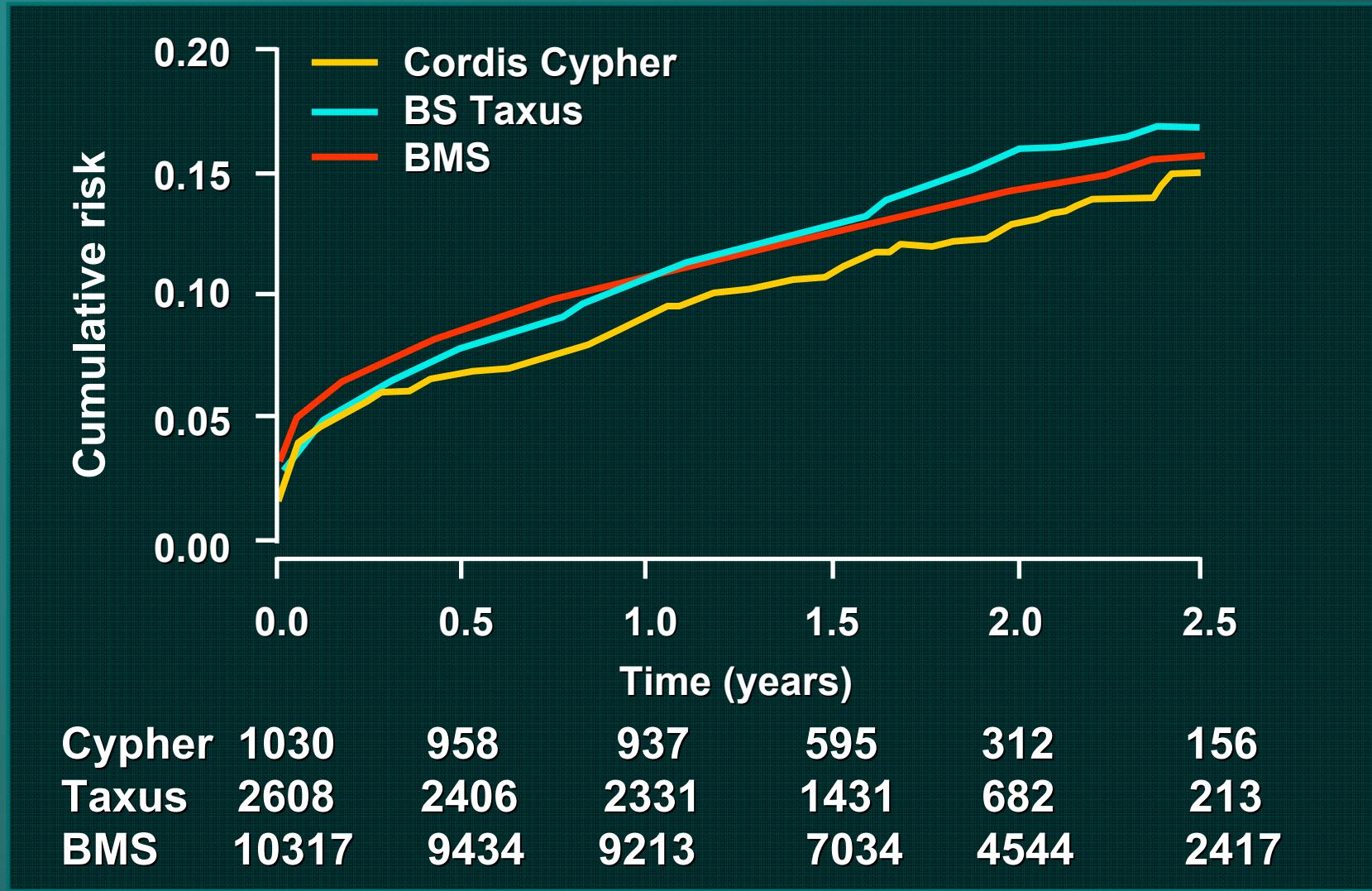
# SCAAR: Patient Characteristics and Procedural Factors (ONE STENT)

*Differences all highly significant!*

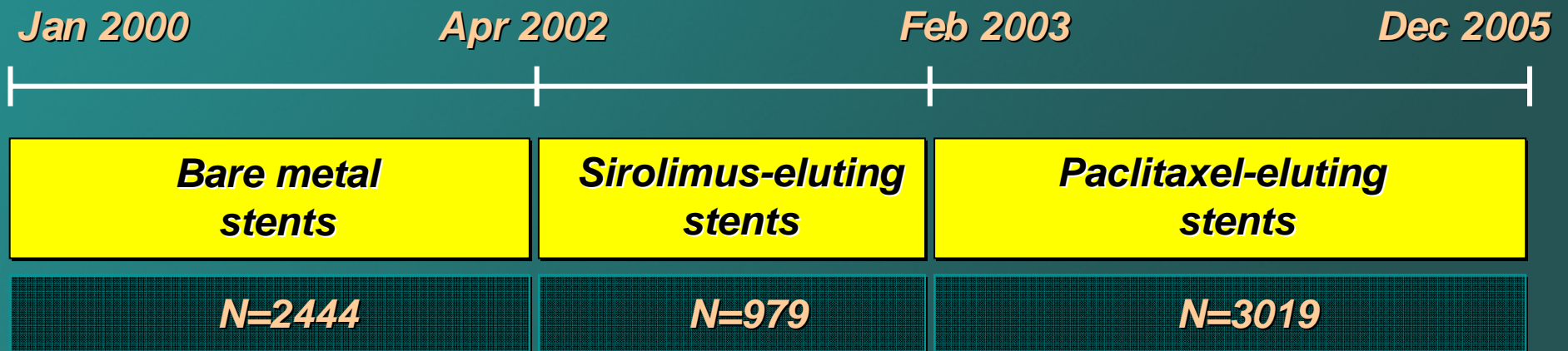
	BMS	DES
<b>STEMI (%)</b>	25.8	17.7
<b>Diabetes (%)</b>	15.7	23.5
<b>Previous PCI (%)</b>	10.6	16.9
<b>≥ 2 Stents (%)</b>	24.9	39.7
<b>Stent Diam &lt; 3mm (%)</b>	25.8	42.4
<b>Stent Length ≥ 20 mm (%)</b>	22.1	41.8
<b>Restenotic Lesion (%)</b>	1.2	6.7
<b>LM Coronary (%)</b>	1.0	2.3
<b>LAD Location (%)</b>	38.5	62.1



# SCAAR: Unadjusted Cumulative Incidence of Death and MI (Single Stent)



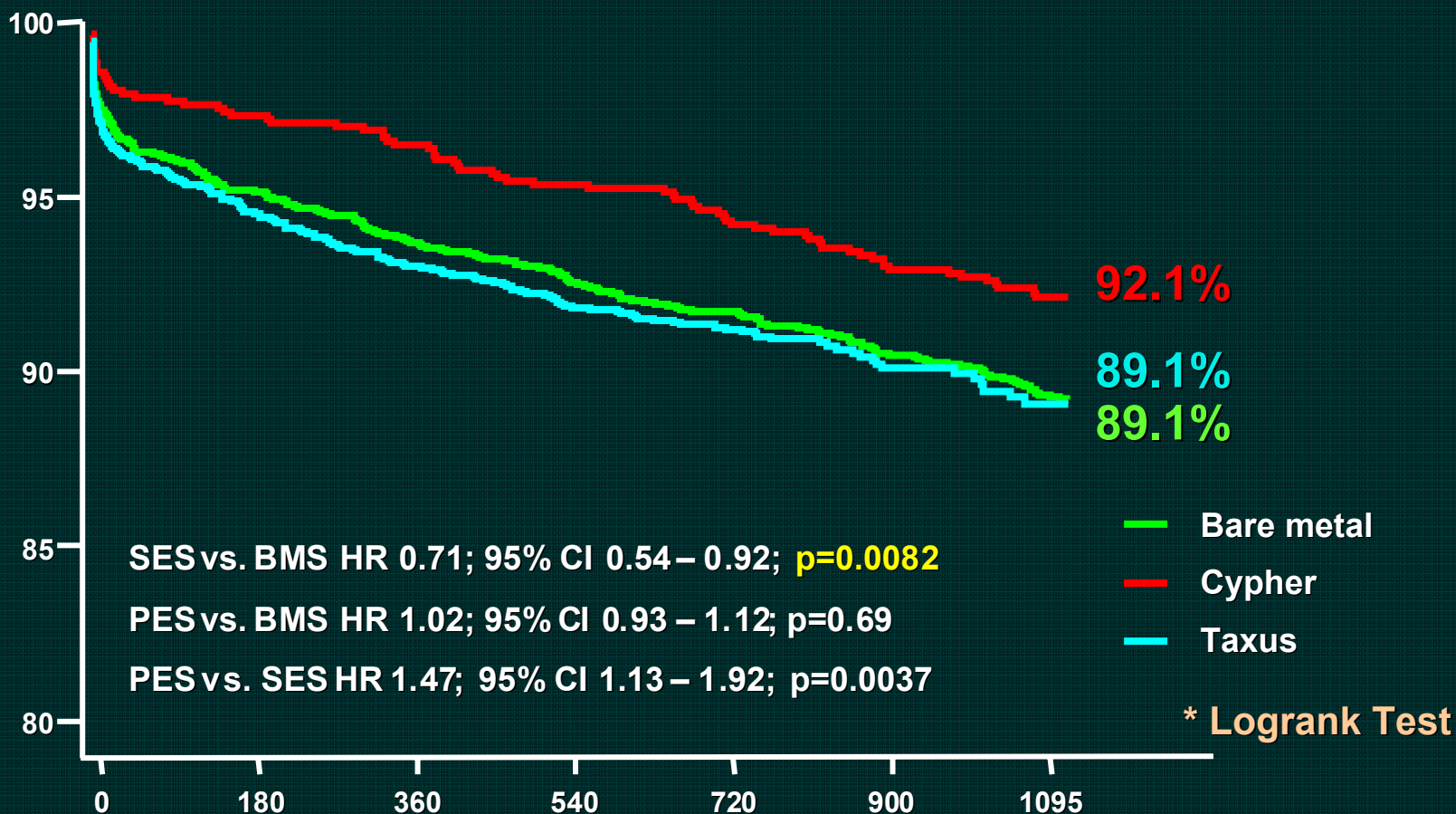
# Thoraxcenter Real World Experience



**6442 patients**  
**13,150 stents**

**Serruys PW et al. FDA 12/06**

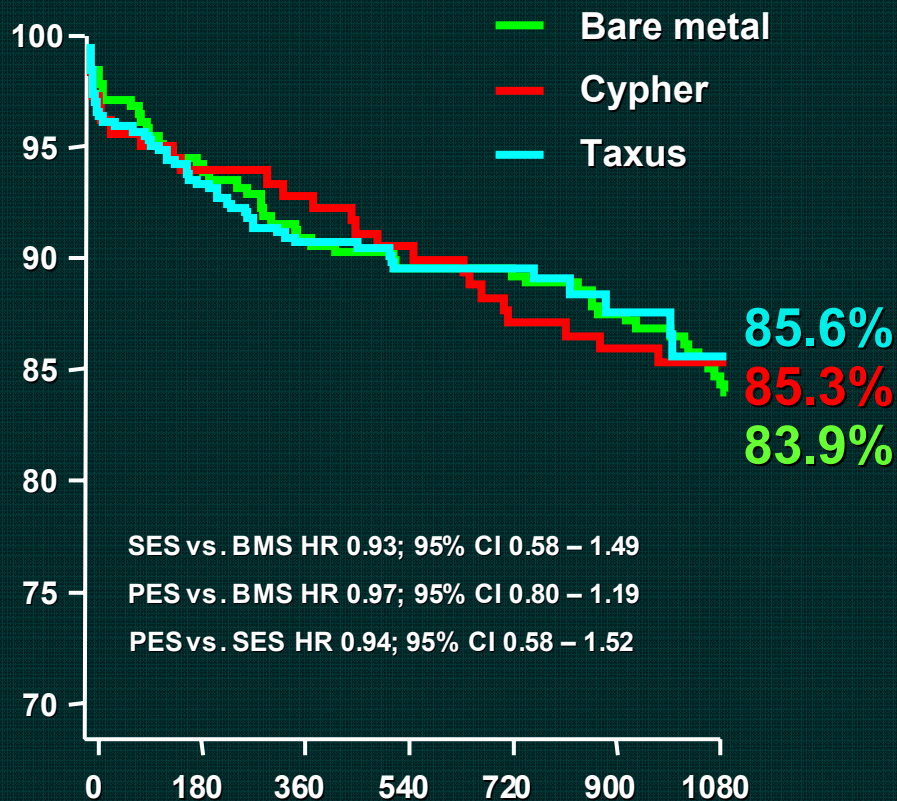
# All-cause Mortality at 3 Years



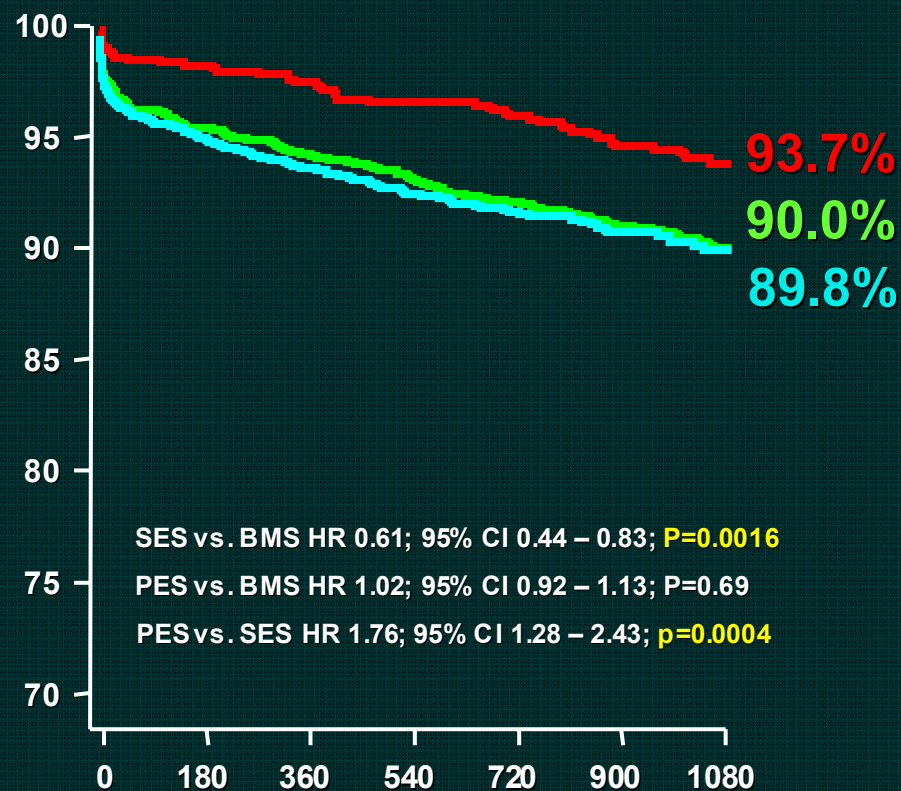
Group	0	30	90	180	360	720	1095
<b>BMS</b>	2287	2211	2195	2170	2126	1990	1862
<b>SES</b>	976	955	951	946	936	888	833
<b>PES</b>	2776	2620	2537	2499	2414	1432	491

# All-cause Mortality at 3 Years

## Diabetics



## Non-Diabetics

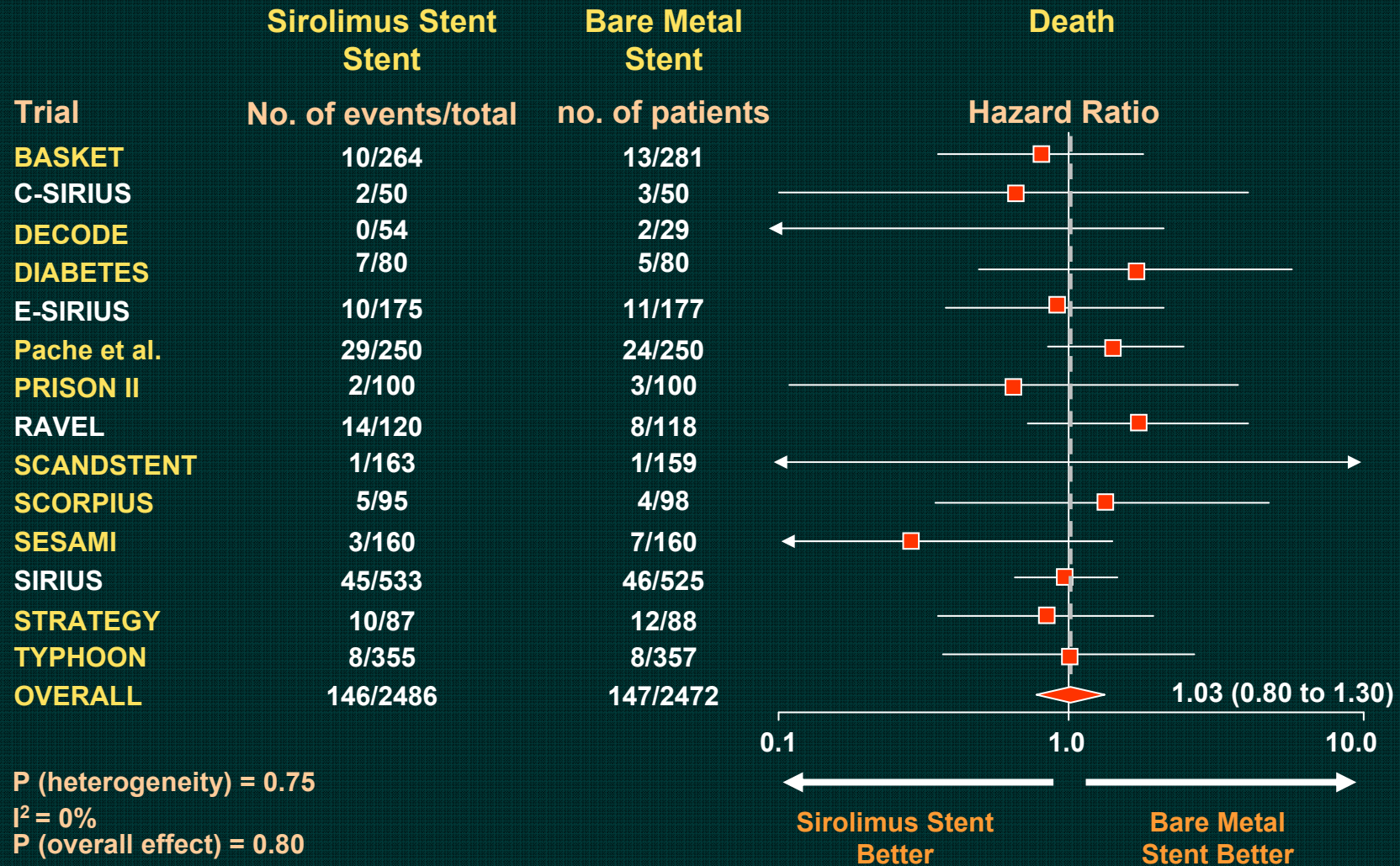


Group	0	180	360	720	1080
<b>BMS</b>	306	288	276	267	237
<b>SES</b>	179	168	165	152	142
<b>PES</b>	484	433	408	258	85

Group	0	180	360	720	1080
<b>BMS</b>	1980	1882	1850	1723	1625
<b>SES</b>	796	778	771	730	691
<b>PES</b>	2291	2066	2006	1174	402

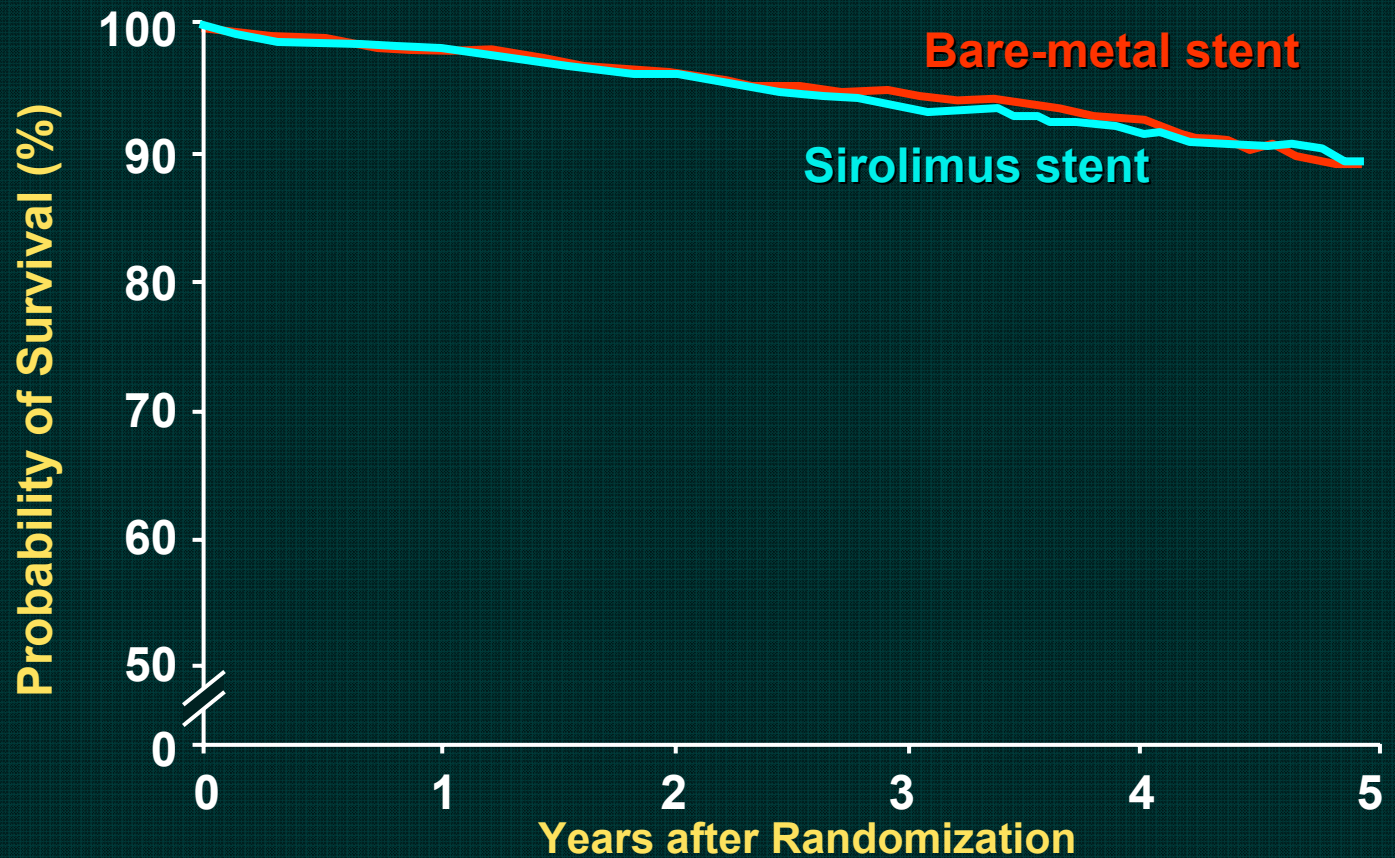


# Analysis of 14 Randomized Trials Comparing SES with BMS



# Analysis of 14 Randomized Trials Comparing SES with BMS

## Freedom from Death

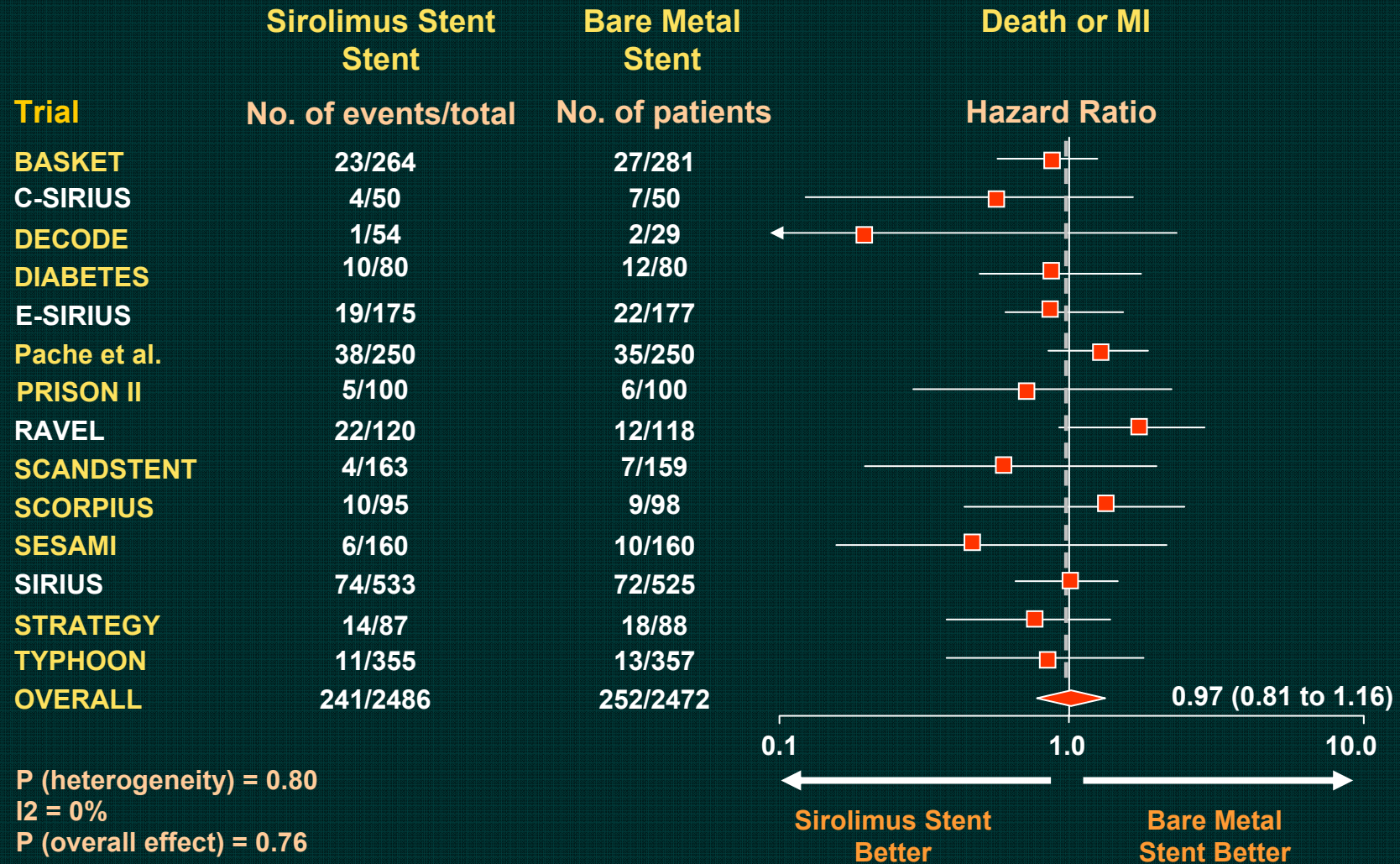


No. at Risk

Sirolimus stent	2,486	2,056	1,218	1,028	765	548
BMS	2,472	2,063	1,207	1,044	842	530

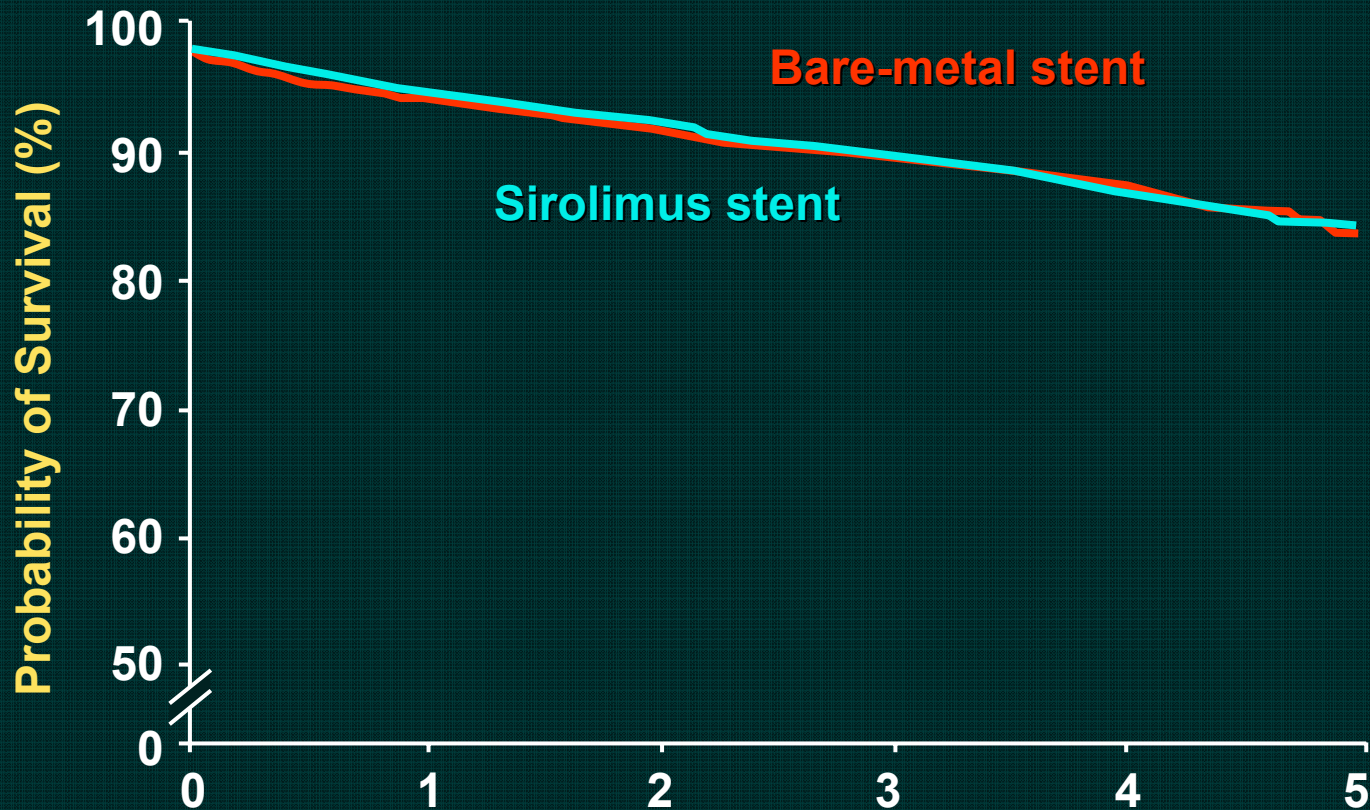


# Analysis of 14 Randomized Trials Comparing SES with BMS



# Analysis of 14 Randomized Trials Comparing SES with BMS

## Freedom from Death or MI



No. at Risk

Sirolimus stent  
BMS

2,486  
2,472

1,985  
1,983

Years after Randomization

1,168  
1,148

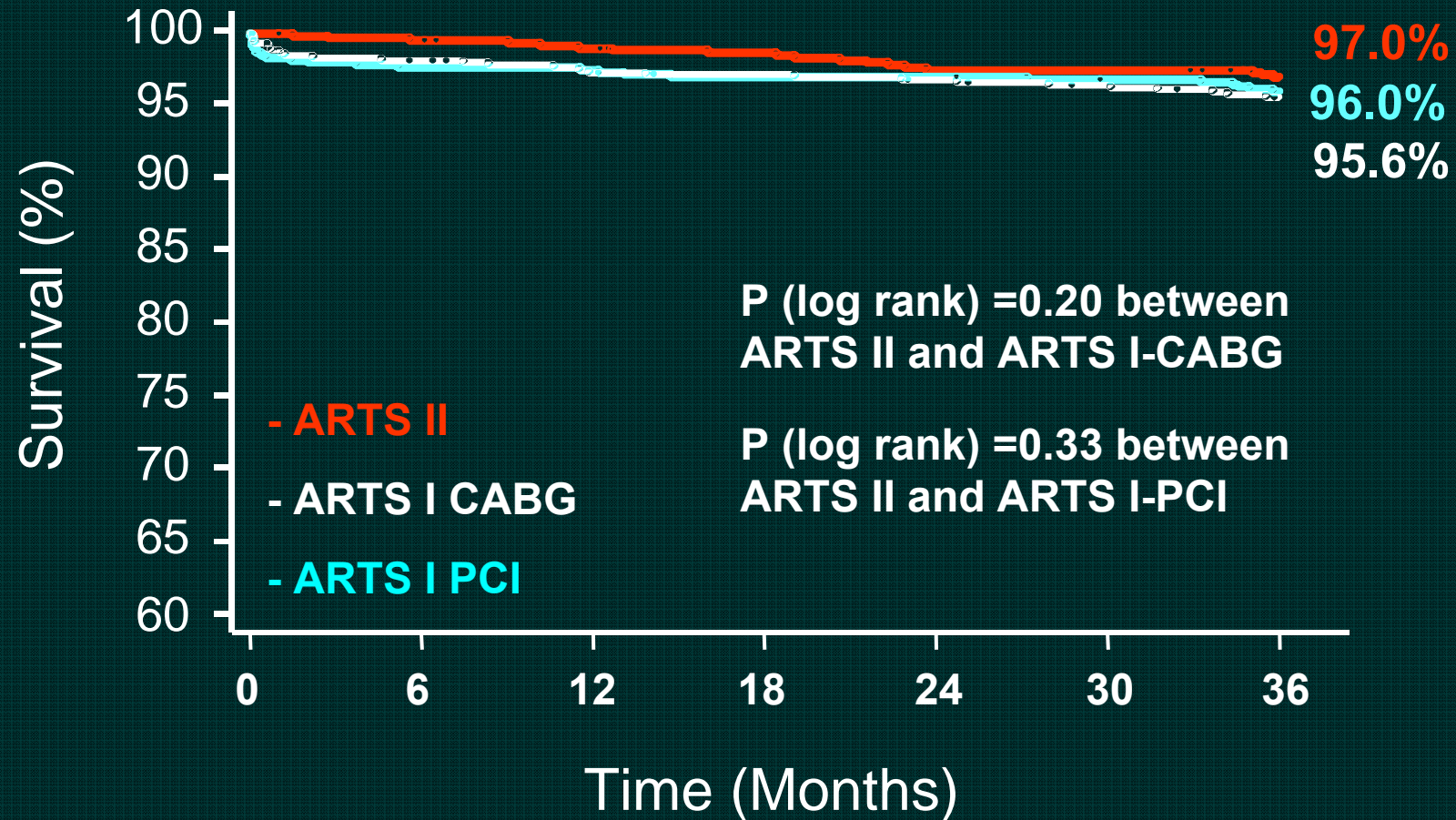
983  
992

728  
798

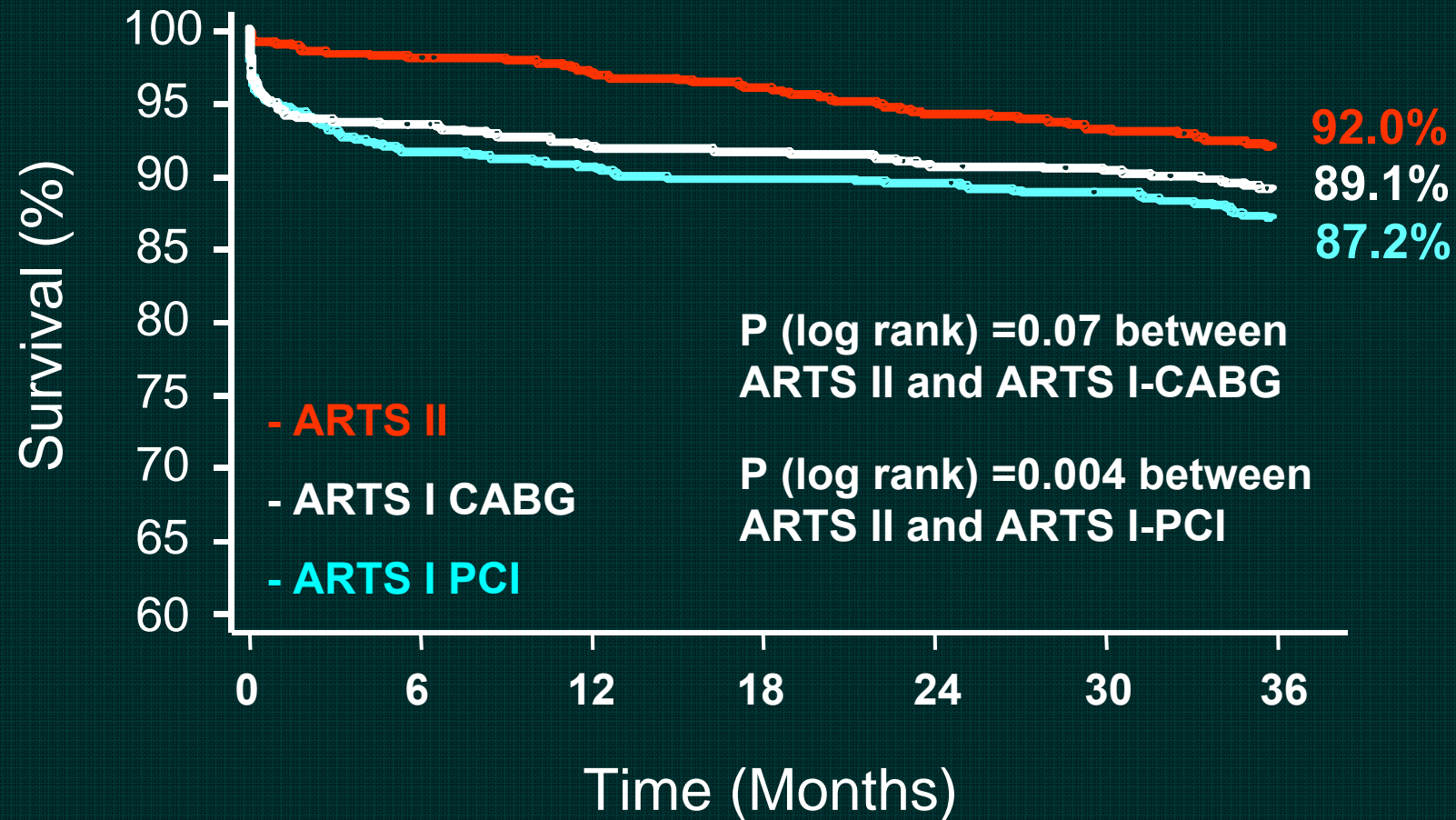
516  
505



# ARTS II: Death to 3 yrs

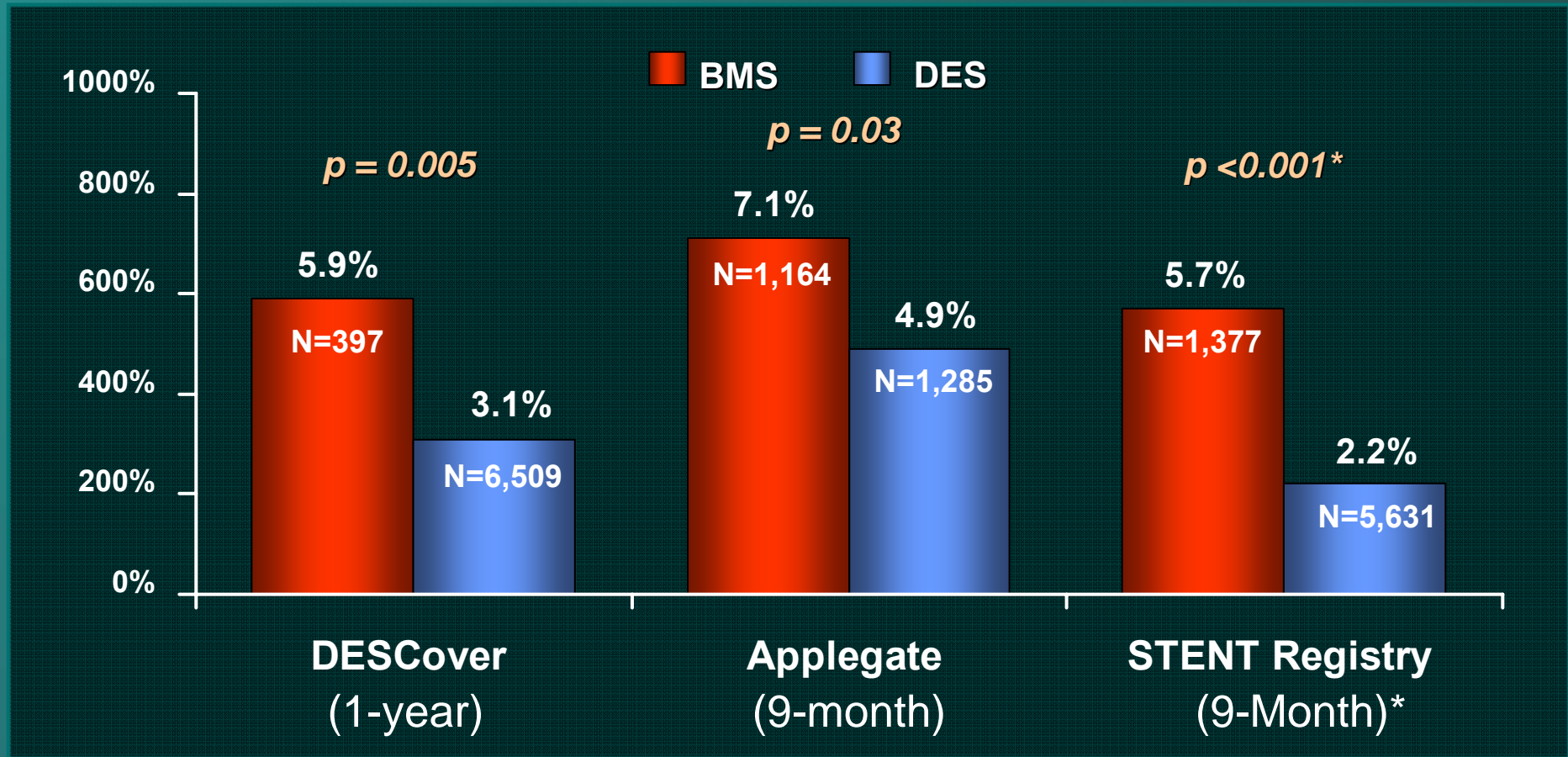


# ARTS II: Death/CVA/MI to 3 yrs



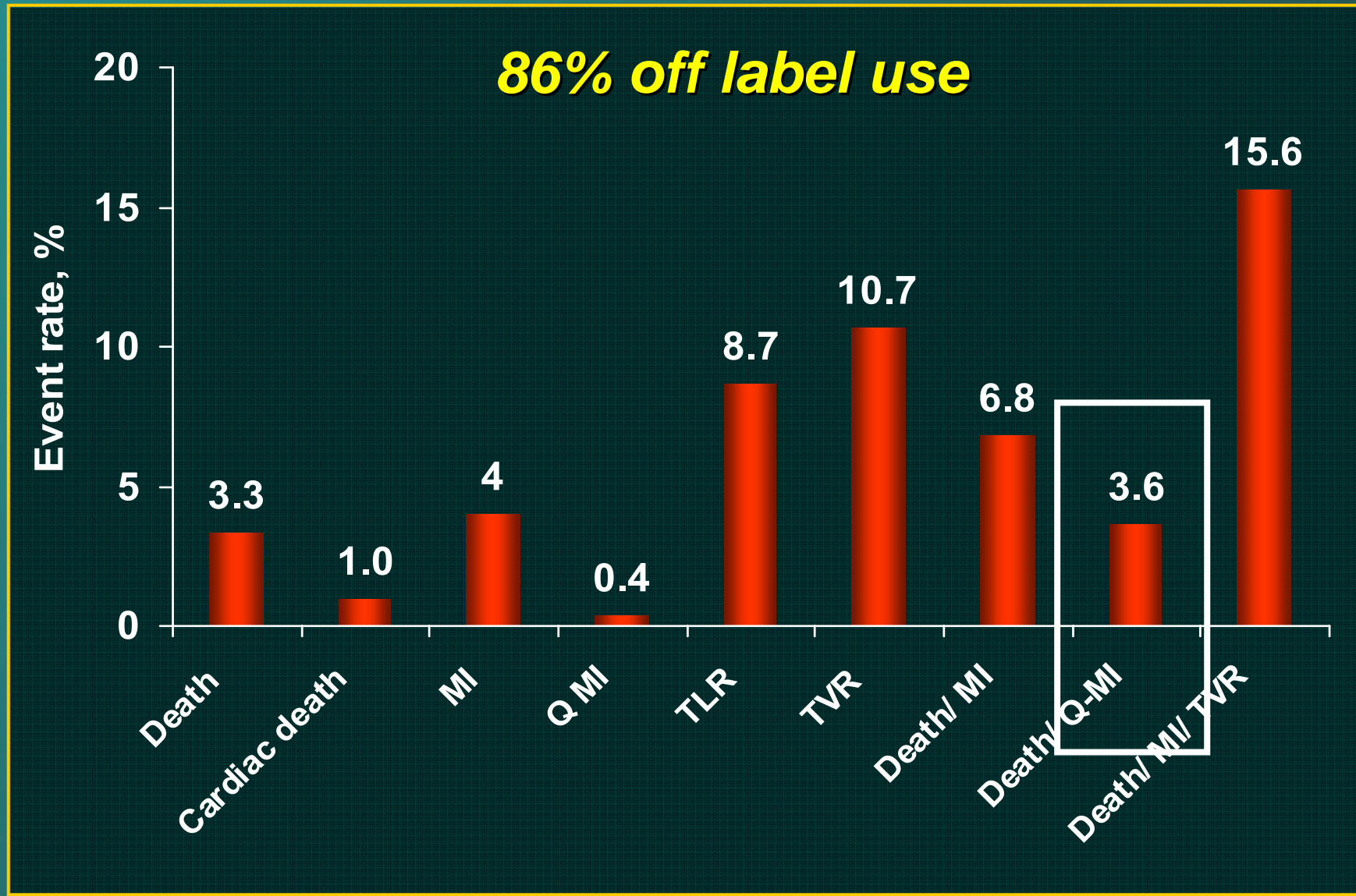
# Real World Registries: DES vs. BMS

## All Cause Mortality Rates (%)



\* Adjusted HR = 0.56 (95% CI 0.4,0.8),  $p=0.0013$

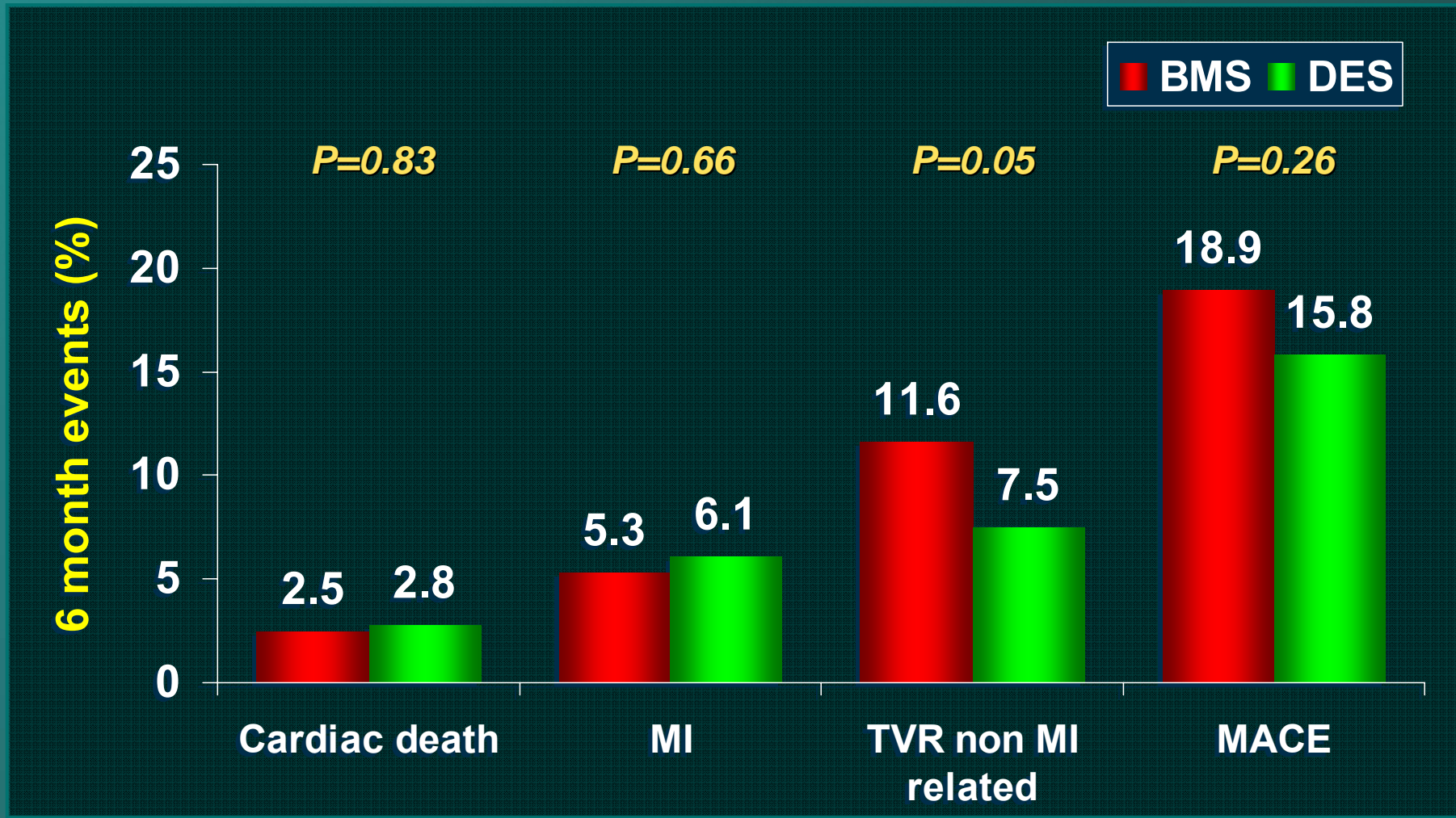
# **MATRIX: 2-Year Clinical Outcomes**





# BASKET Trial: 18 Month MACE

N=836 (All pts with 18 month FU)



# SES Real World: Safety Concerns?

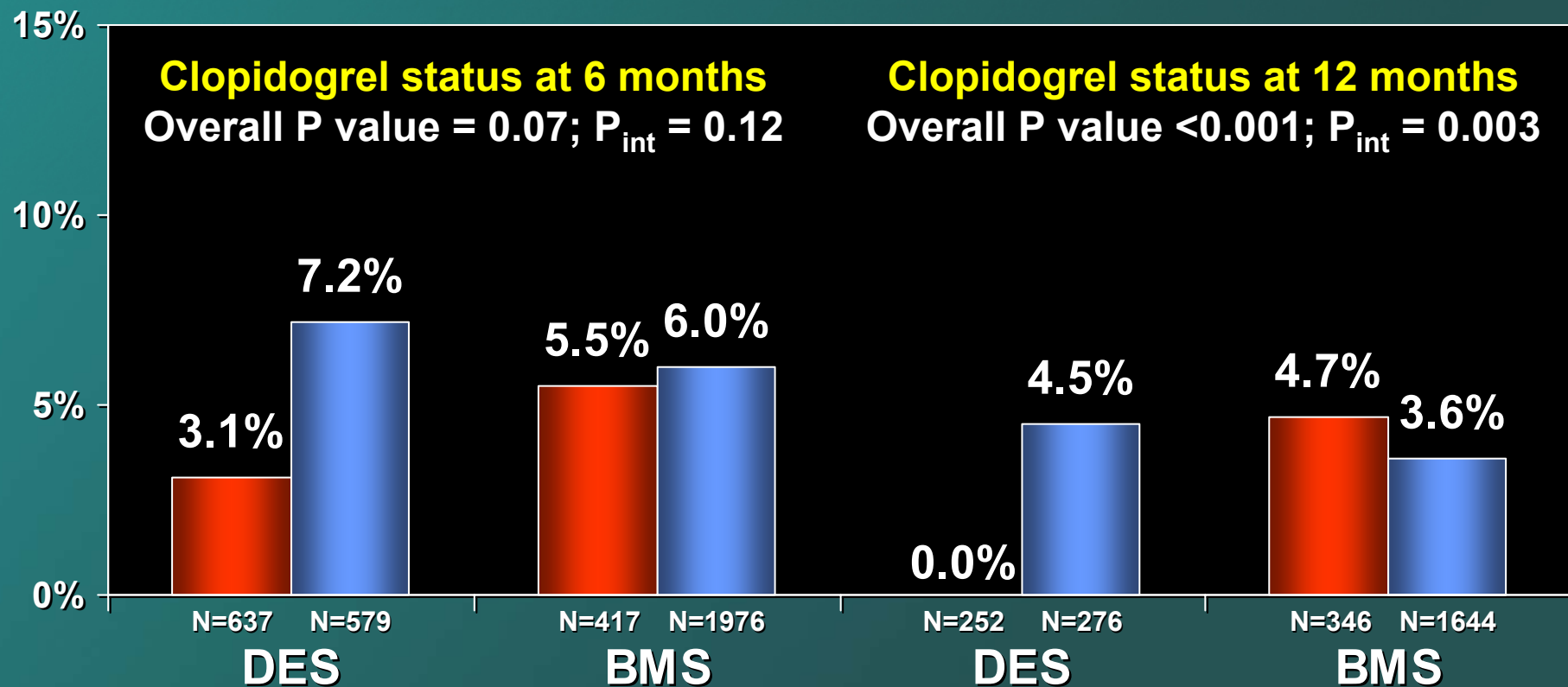
## The Four Questions...

- Is there an increase in stent thrombosis with SES vs. BMS (ARC definitions, continuous hazard, and causes)?
- Is there an increase in death (and MI) with SES vs. BMS (on-label vs. off-label, diabetics)?
- *Should the anti-platelet therapy be adjusted due to SES stent thrombosis considerations?*
- Should SES use be modified in response to safety concerns?

# Duke Database Death/MI Analysis

Adjusted death/MI rates at 24 months  
in patients without events at 6 months

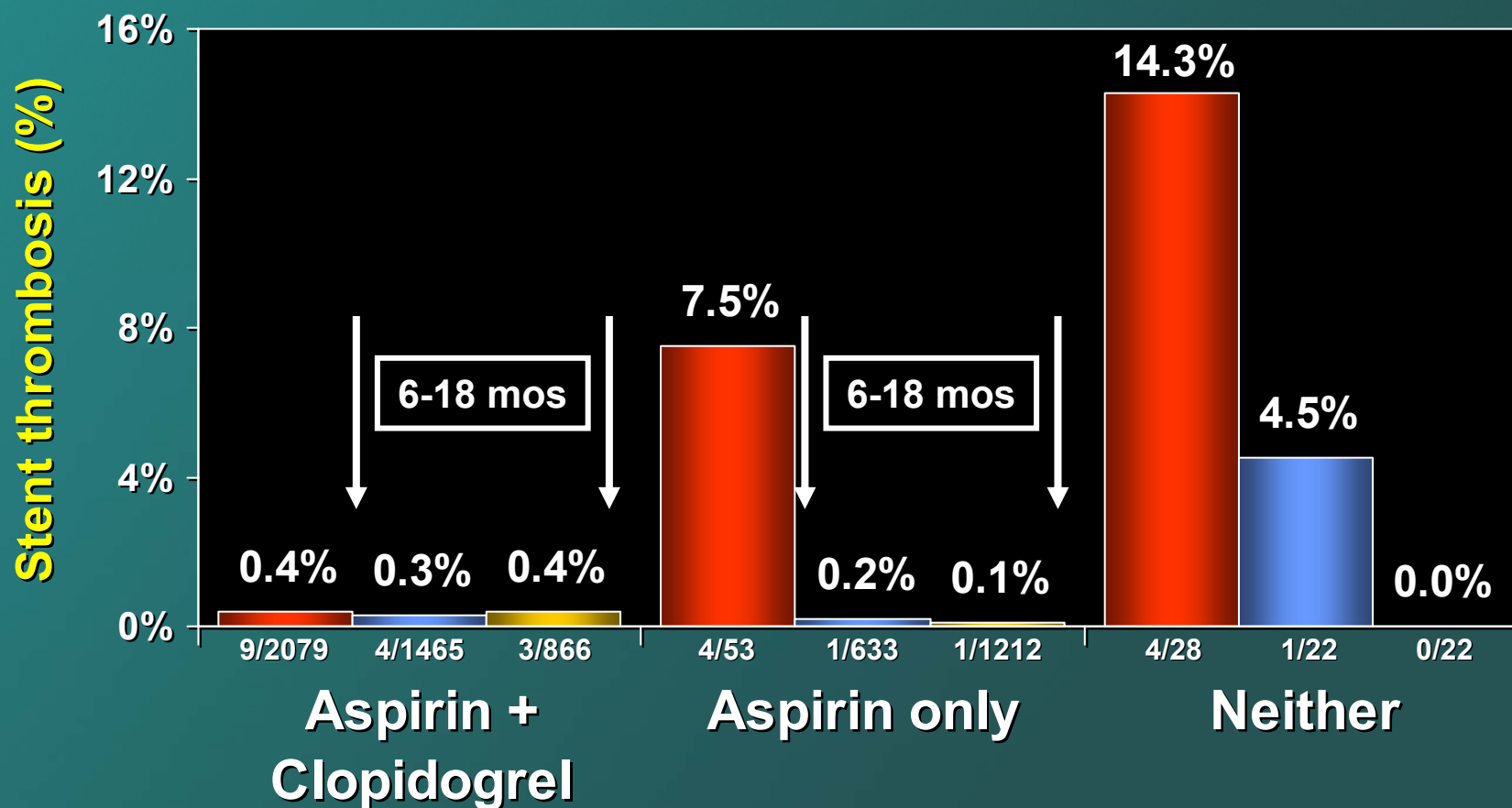
■ On clopidogrel ■ Off clopidogrel



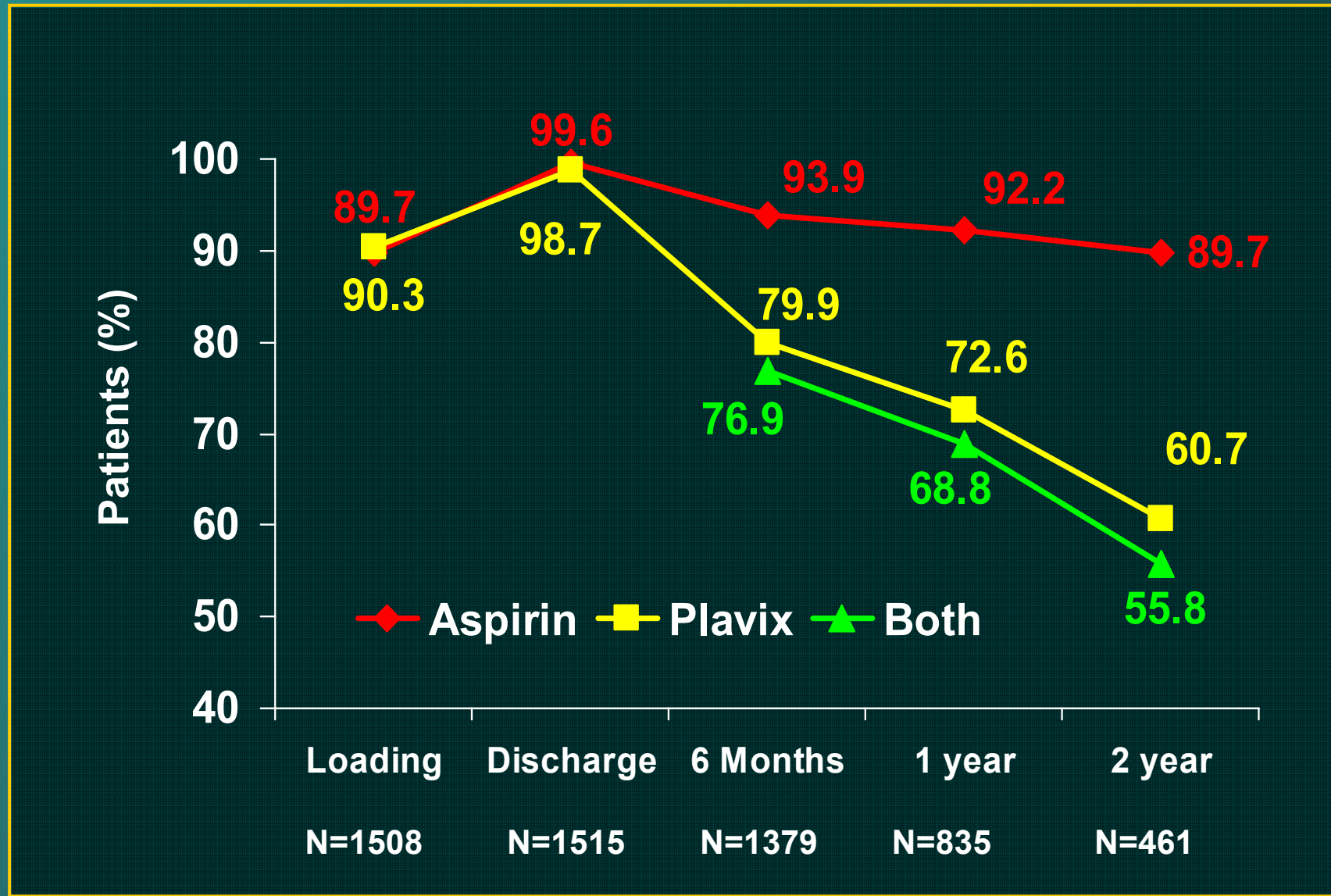
# Milan Stent Thrombosis Experience

2,160 consecutive pts with DES implanted

0-6 months 6-12 months 12-18 months



# **MATRIX:** Antiplatelet Rx Adherence



# **MATRIX: Impact of Clopidogrel Adherence**

## **6-Month Use and Outcomes > 180 Days**

	<b>On-Plavix (N=1096)</b>	<b>Off-Plavix (N=276)</b>	<b>p</b>
<b>Death</b>	<b>2.4 %</b>	<b>1.4 %</b>	<b>0.321</b>
<b>Cardiac death</b>	<b>0.4 %</b>	<b>0.5 %</b>	<b>0.993</b>
<b>Non-cardiac death</b>	<b>1.2 %</b>	<b>0.9 %</b>	<b>0.712</b>
<b>Unknown death</b>	<b>0.9 %</b>	<b>0</b>	<b>0.170</b>
<b>Myocardial infarction</b>	<b>0.7 %</b>	<b>2.3 %</b>	<b>0.061</b>
<b>Q wave</b>	<b>0</b>	<b>0.4 %</b>	<b>0.071</b>
<b>Non-Q wave</b>	<b>0.7 %</b>	<b>1.9 %</b>	<b>0.173</b>
<b>TLR</b>	<b>7.9 %</b>	<b>3.8 %</b>	<b>0.091</b>
<b>TVR</b>	<b>9.2 %</b>	<b>4.6 %</b>	<b>0.074</b>
<b>Death/ MI</b>	<b>2.9 %</b>	<b>3.7 %</b>	<b>0.665</b>
<b>Death/ MI/ TVR</b>	<b>11.3 %</b>	<b>7.5 %</b>	<b>0.154</b>
<b>Stent thrombosis</b>	<b>0.7 %</b>	<b>0</b>	<b>0.248</b>



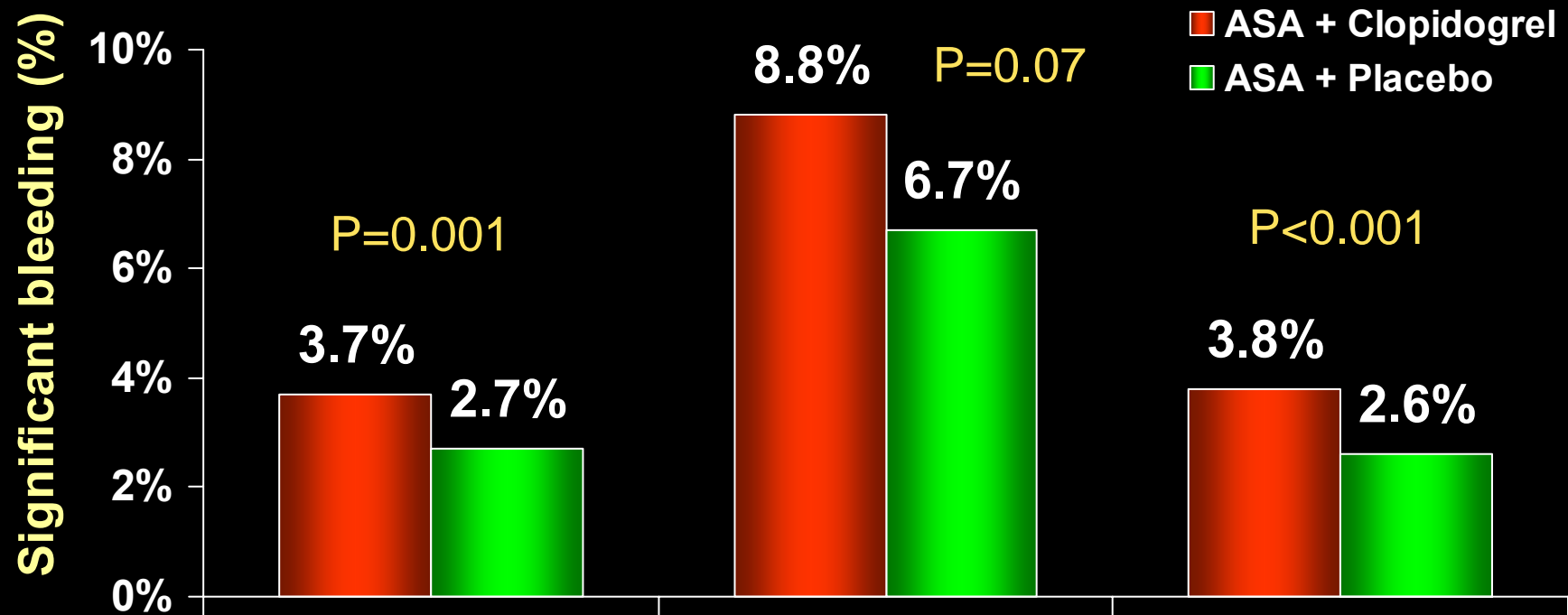
# **MATRIX:** Impact of Clopidogrel Adherence 1-Year Use and Outcomes > 365 Days

	On-Plavix (N=780)	Off-Plavix (N=294)	p
<b>Death</b>	1.2 %	2.0 %	0.276
<b>Cardiac death</b>	0	0.5 %	0.168
<b>Non-cardiac death</b>	0.7 %	1.2 %	0.397
<b>Unknown death</b>	0.5 %	0.4 %	0.993
<b>Myocardial infarction</b>	0.7 %	1.4 %	0.409
<b>Q wave</b>	0	0	N/A
<b>Non-Q wave</b>	0.7 %	1.4 %	0.409
<b>TLR</b>	5.5 %	0.8 %	<b>0.003</b>
<b>TVR</b>	5.7 %	1.2 %	<b>0.006</b>
<b>Death/ MI</b>	1.6 %	3.4 %	0.109
<b>Death/ MI/ TVR</b>	6.7 %	3.7 %	0.130
<b>Stent thrombosis</b>	0.7 %	0	0.209



# Safety of Long-Term Clopidogrel

## 3 Placebo Controlled Trials



**CURE**  
**N=12,563**  
**1 year FU**  
**CURE major bleed**  
**NEJM 2001;345:494-502**

**CREDO**  
**N=2,116**  
**1 year FU**  
**TIMI major bleed**  
**JAMA 2002;288:2411-20**

**CHARISMA**  
**N=15,603**  
**2.5 year FU**  
**GUSTO major + moderate bleed**  
**NEJM 2006;354:1706-17**

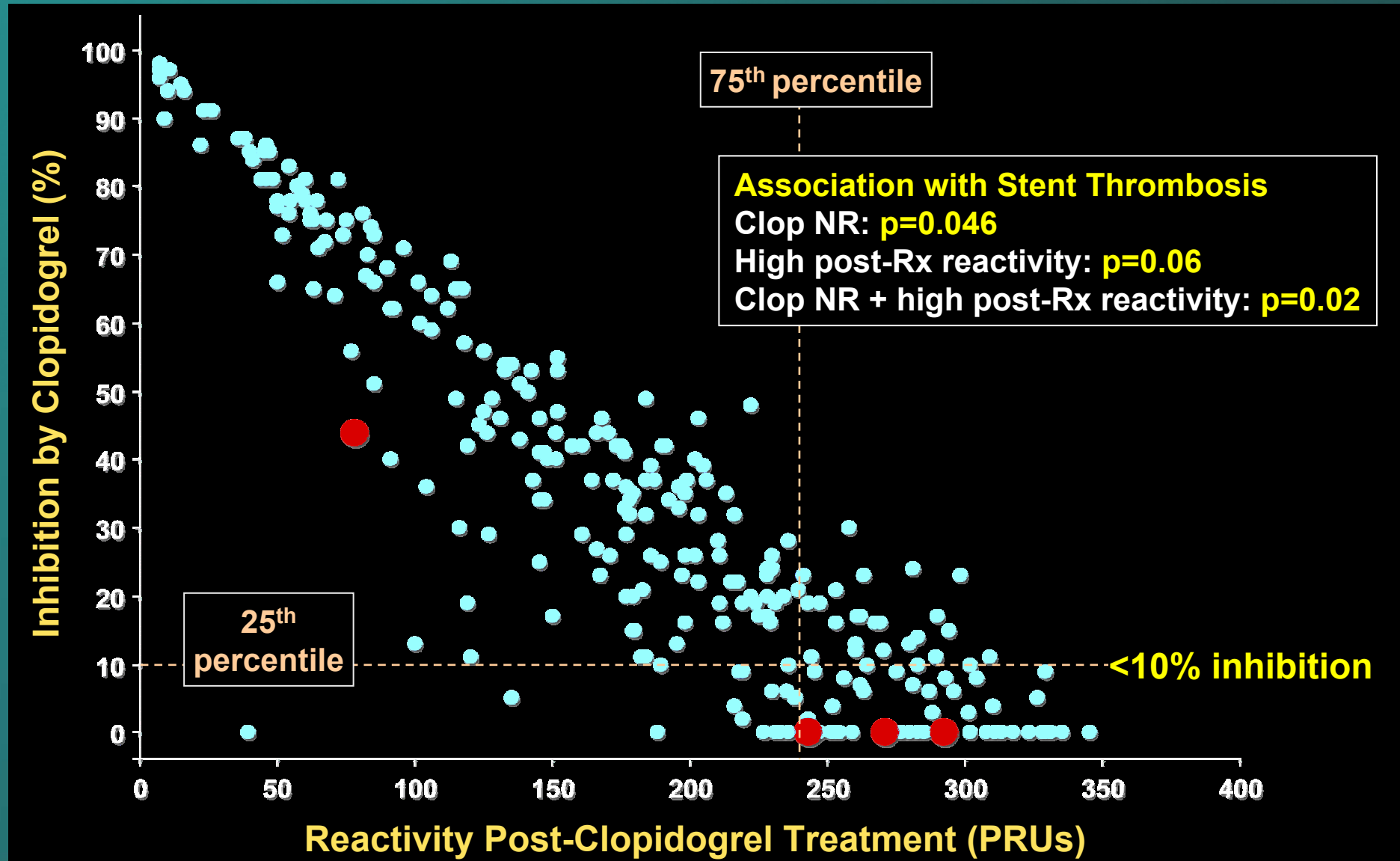




# U.S. Cost Implications of Long-term Clopidogrel Therapy

- At \$4 per day, Clopidogrel costs ~\$1500 per year
- As many as 1 million U.S. patients per year receive DES ⇒
- **One year of Clopidogrel would cost ~\$1.5B**
- For 4 million U.S. patients with DES implanted ⇒
- **One year of Clopidogrel would cost ~\$6.0B**

# Clonidogrel Responsiveness at the Time of PCI and Stent Thrombosis After Cypher w/i 30 Days: N=280



# **Announcing** **The ADAPT DES Study**

**10,000 consecutive pts receiving DES  
at up to 12 sites**

**Aspirin and Clopidogrel responsiveness evaluated  
(Accumetrics VerifyNow system)**

**Clinical FU for 2-5 years**

**Angiographic core lab assessment of all  
stent thromboses and 1:3 matching controls**

**PIs: Gregg W. Stone and Chuck Simonton  
Sponsors: CRF and the Dickinson Inst.  
Principal study group: STENT Registry investigators**

**Funded by grants from Boston Scientific  
(lead supporter), Accumetrics, Abbott  
Vascular, Cordis, and Medtronic**

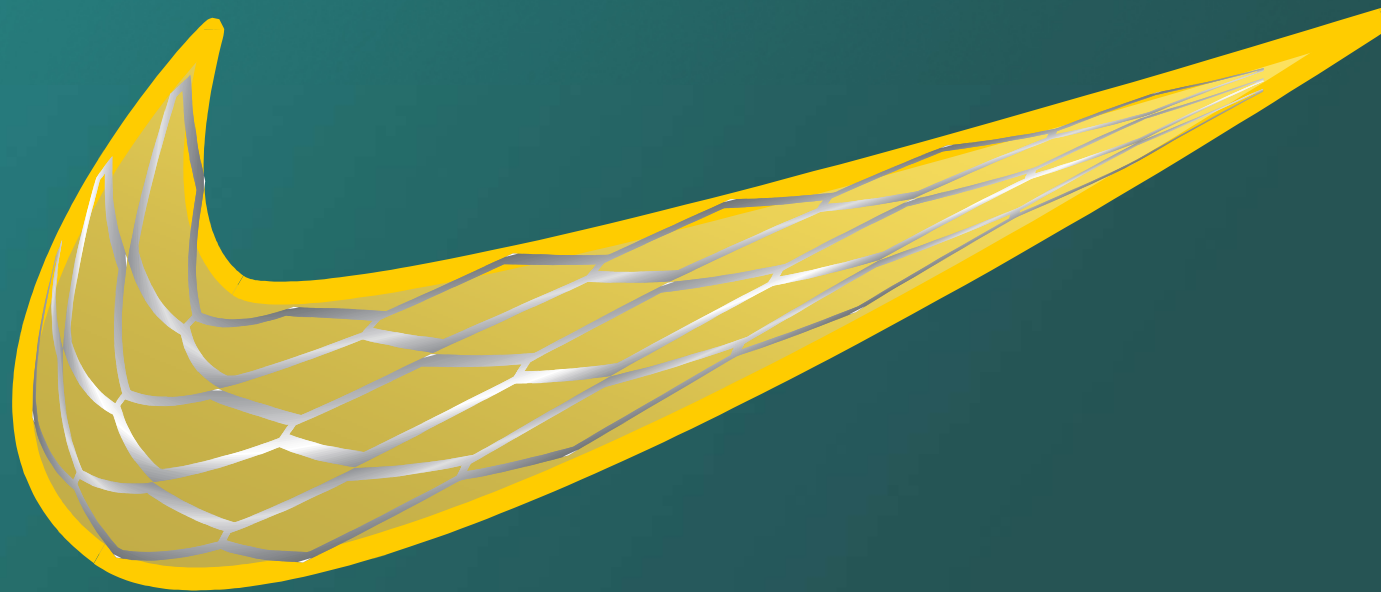
# SES Real World: Safety Concerns?

## The Four Questions...

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- Is there an increase in death (and MI) with SES vs. BMS (on-label vs. off-label, diabetics)?
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- *Should SES use be modified in response to safety concerns?*

# Intervention 2007

*Just Do the  
“Right” Thing!*



# SES Use - 2007

## ***How can we minimize the risk of late DES thrombosis NOW?***

- ***Upfront careful patient screening for extended Plavix therapy*** – conservative approach re: compliance, bleeding risk, and co-morbidities
- ***Case selection based on risk-benefit analysis***  
DES use is now restricted and not assumed!  
(consider CABG in complex MVD)
- ***Optimize procedural operator technique***
- ***Prolonged dual anti-platelet Rx*** (at least 1 yr)
- ***Meticulous patient FU and communication***



# SES Use - 2007

***If Death and MI aren't increased,  
why reduce DES use?***

- ***Incomplete data*** (esp. long-term FU) in several important areas, including the “continuous hazard” of late DES over time and unknown risks in several “off label” use categories. Additional large RCTs needed to make recommendations (e.g. FREEDOM, CARDIA, SYNTAX, and HORIZONS ongoing).

# SES Use - 2007

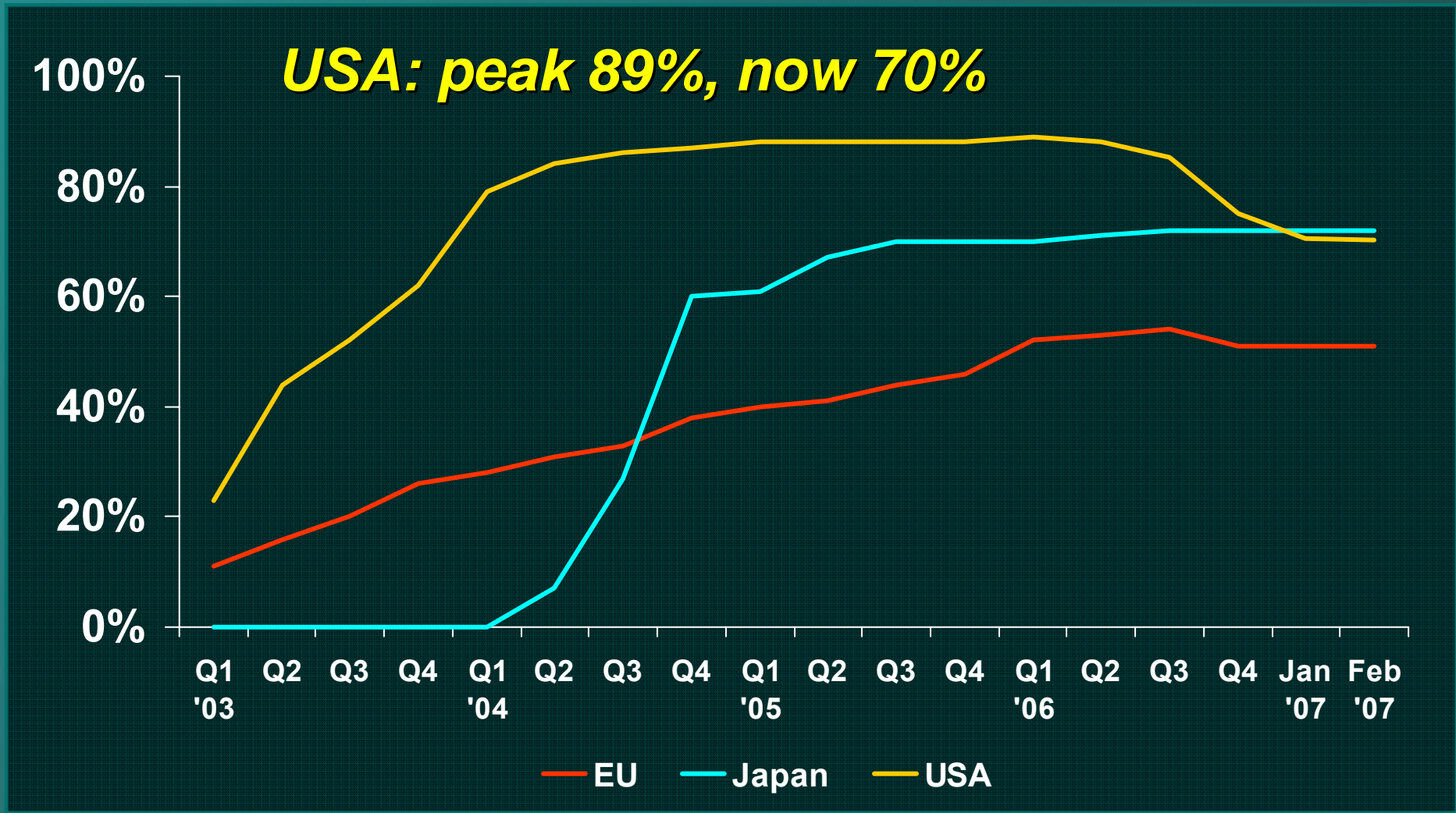
***If Death and MI aren't increased,  
why reduce DES use?***

- ***Problems associated with obligatory long-term Plavix dependence*** - unknown duration of therapy, compliance concerns, cost and reimbursement issues, bleeding risks, and anxiety associated with the “unknowns” of premature cessation. It's very difficult to maintain a co-morbid CAD population on long-term Plavix Rx!

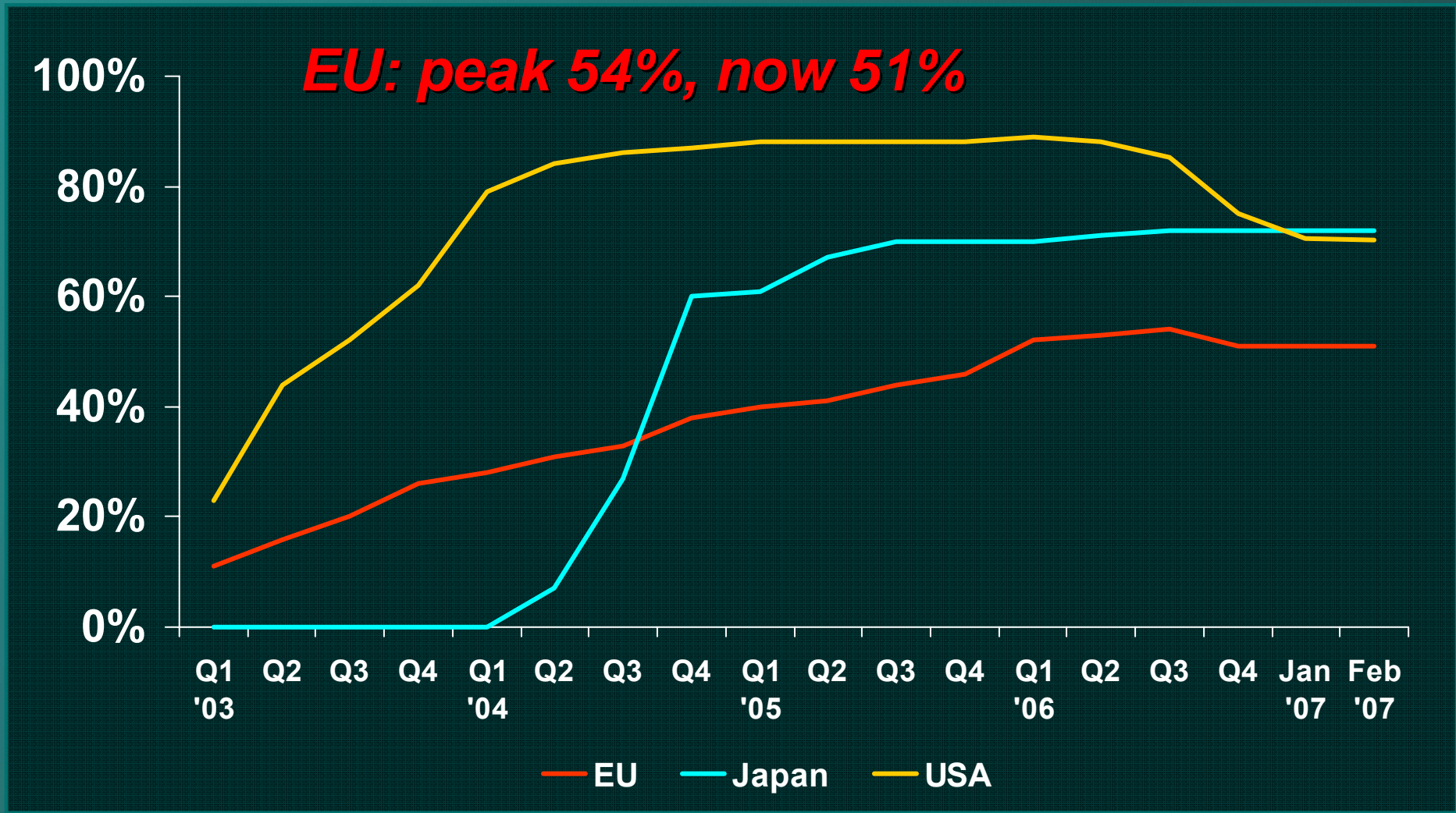




# World-wide DES Penetration (USA, EU, and Japan)

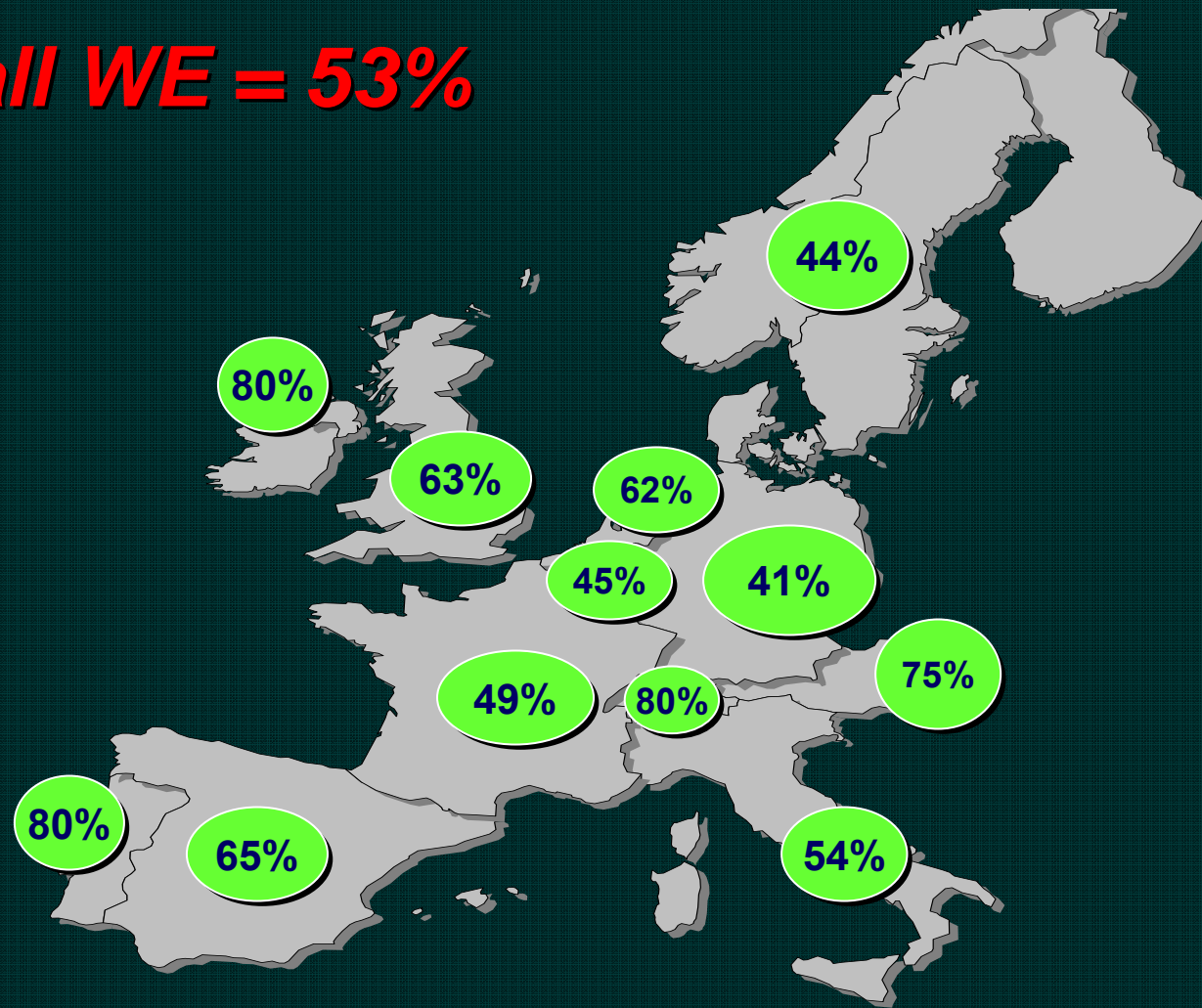


# World-wide DES Penetration (USA, EU, and Japan)

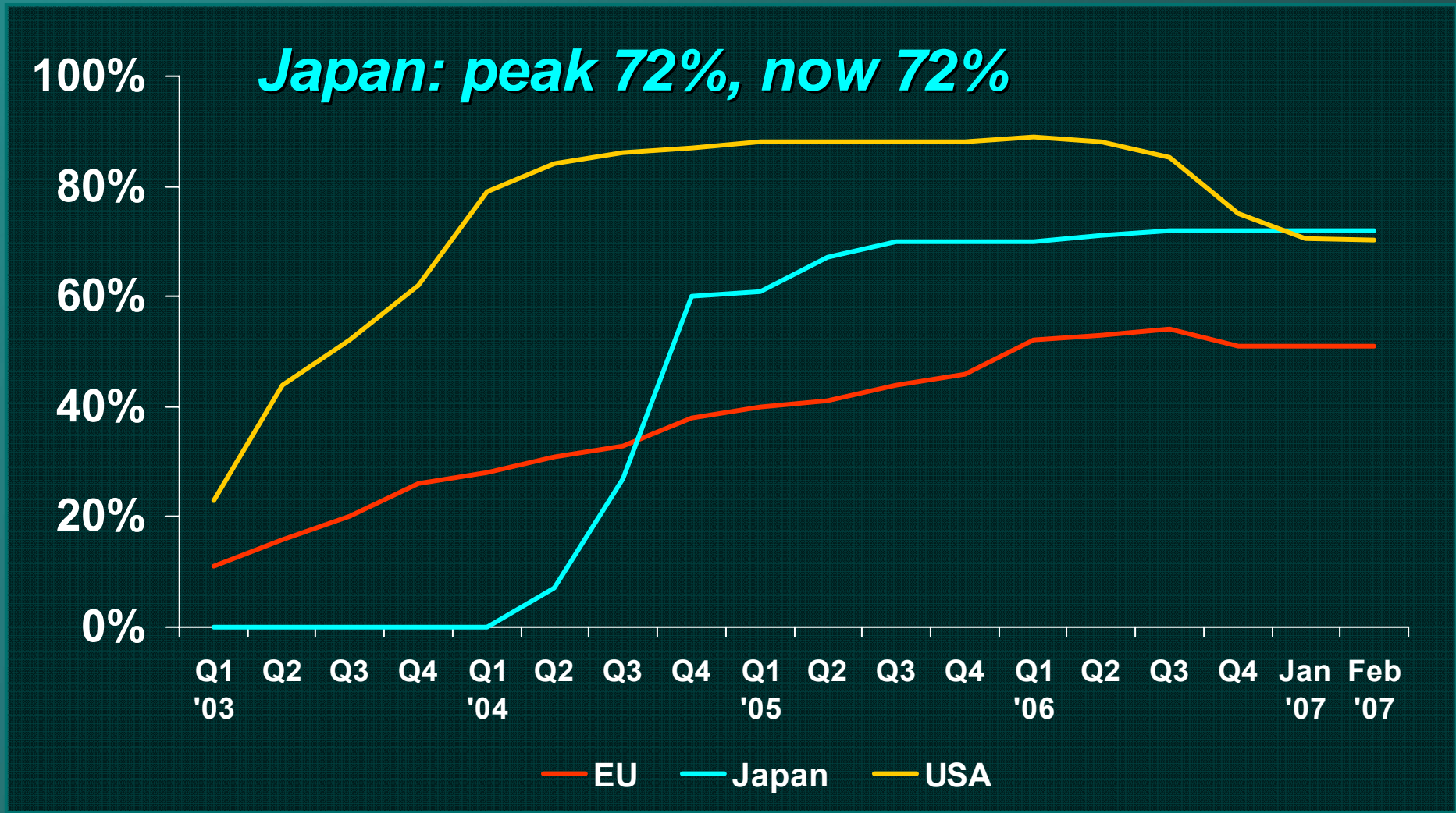


# DES Penetration in Western Europe (November, 2006)

**Overall WE = 53%**



# World-wide DES Penetration (USA, EU, and Japan)



# ***Major Determinants of BMS vs. DES Use***

- Interpretation of the safety-benefit equation for and against DES use
- Patient and lesion complexity factors (referral patterns, practice mix)
- Plavix compliance concerns
- ***Socioeconomic considerations (intangibles)***
  - ✓ ***peer pressure***
  - ✓ ***patient pressure***
  - ✓ ***liability issues***
  - ✓ ***reimbursement (economic factors)***



# Life is a Matter of “Balance”

## *The Scale Favors DES!*

