

DES Safety Concerns: Impact on Clinical Practice

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**DES Safety and Efficacy: The Endeavor Perspective
Angioplasty Summit TCT Asia-Pacific 2007
April 25-27, 2007; Seoul, Korea**



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



DES Science

2002 - 2005

EFFICACY
(reduced
restenosis)

SAFETY

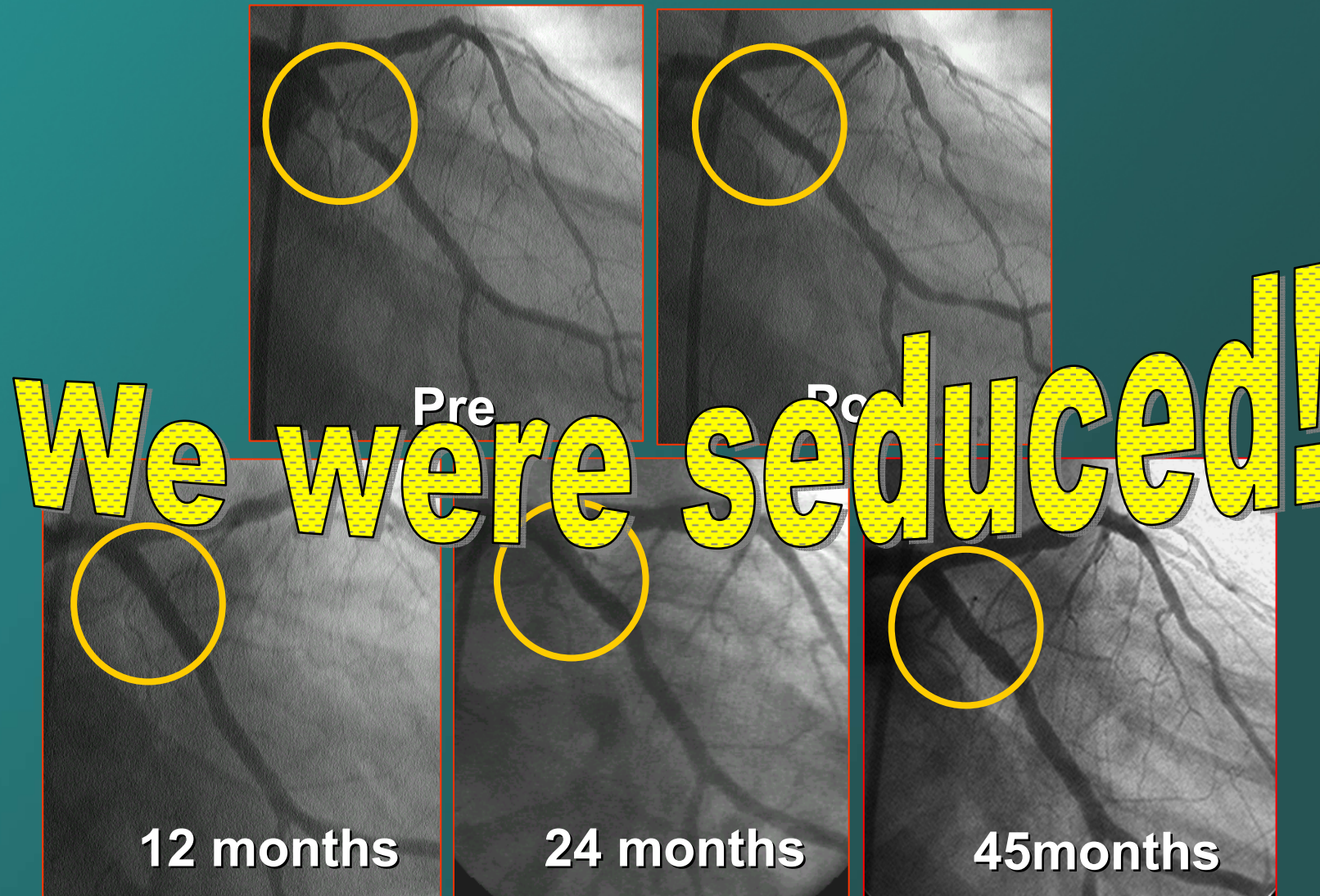
DELIVERABILITY

DURABILITY

COST-VALUE



CYPHER™ São Paulo: 45-Mos FU



DES Clinical Trials

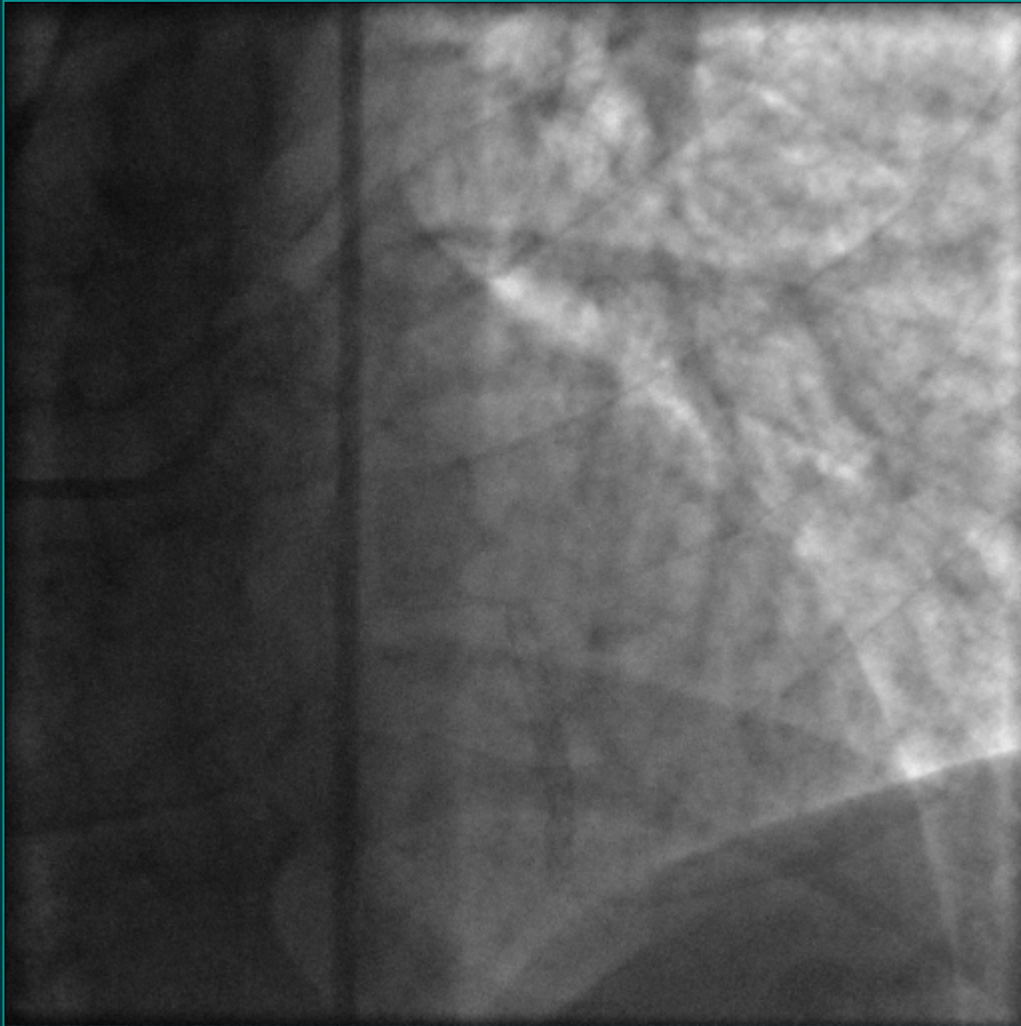
Over 1,000 peer review

***But obviously
it wasn't enough!***

2003 and 2006!



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

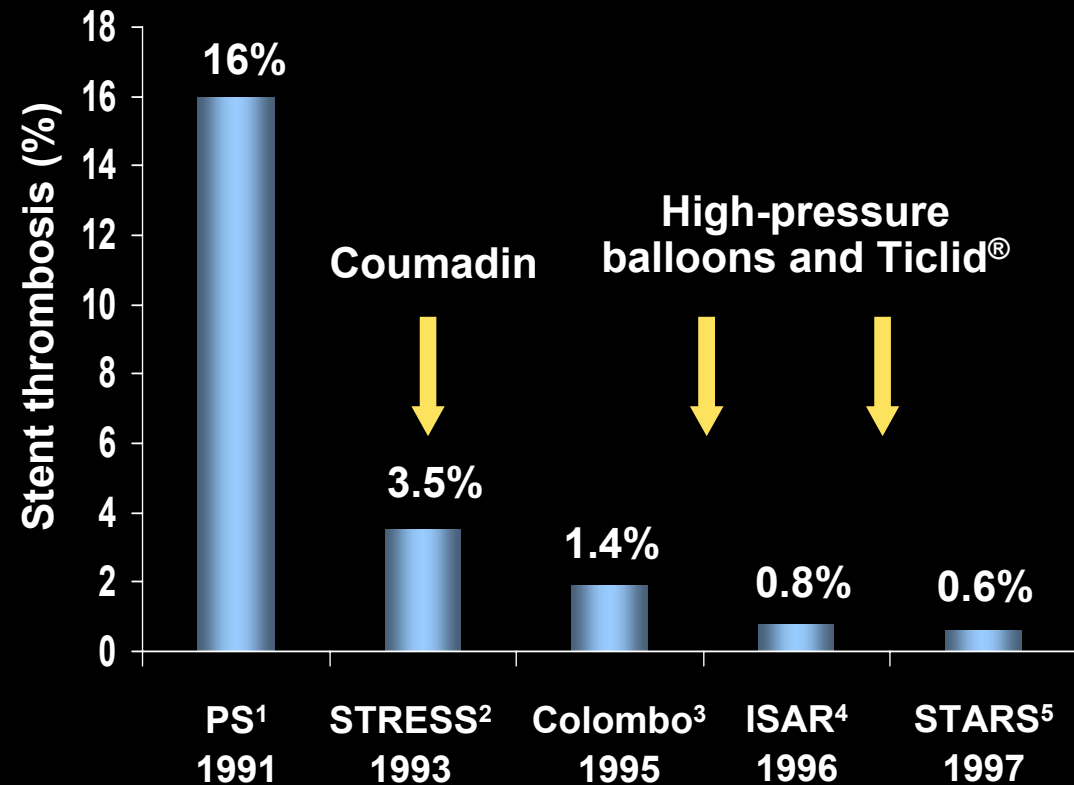
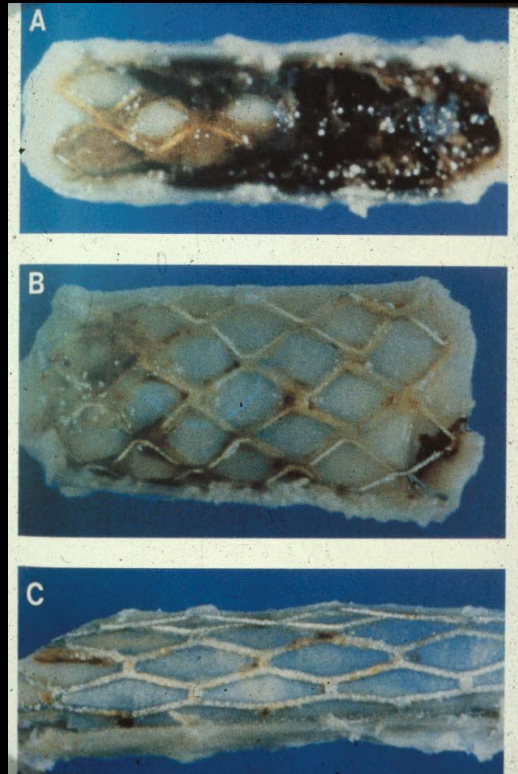


DES Safety Concerns

Stent Thrombosis (Late and Very Late)



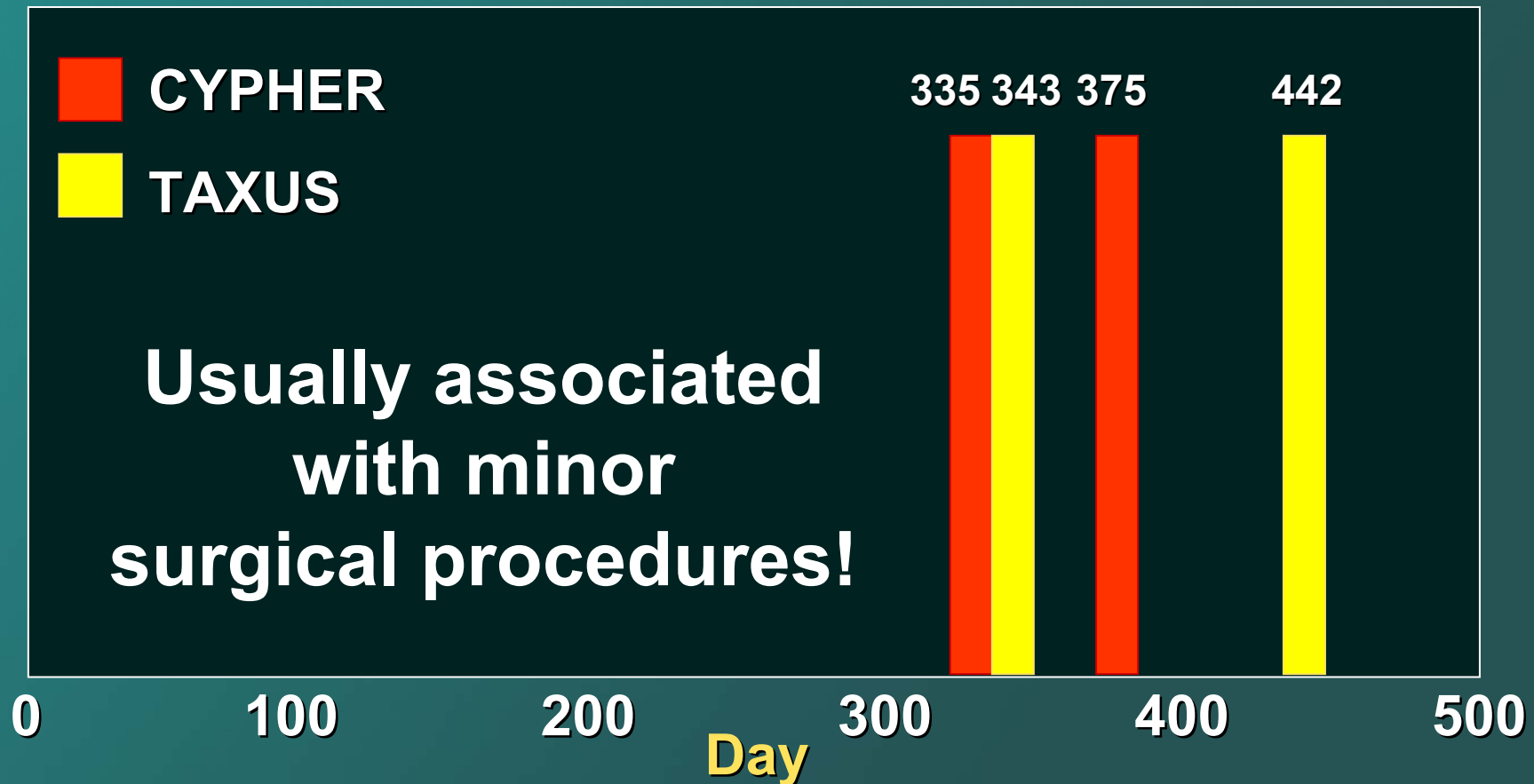
History of Stent Thrombosis



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



Milan/Siegburg Experience

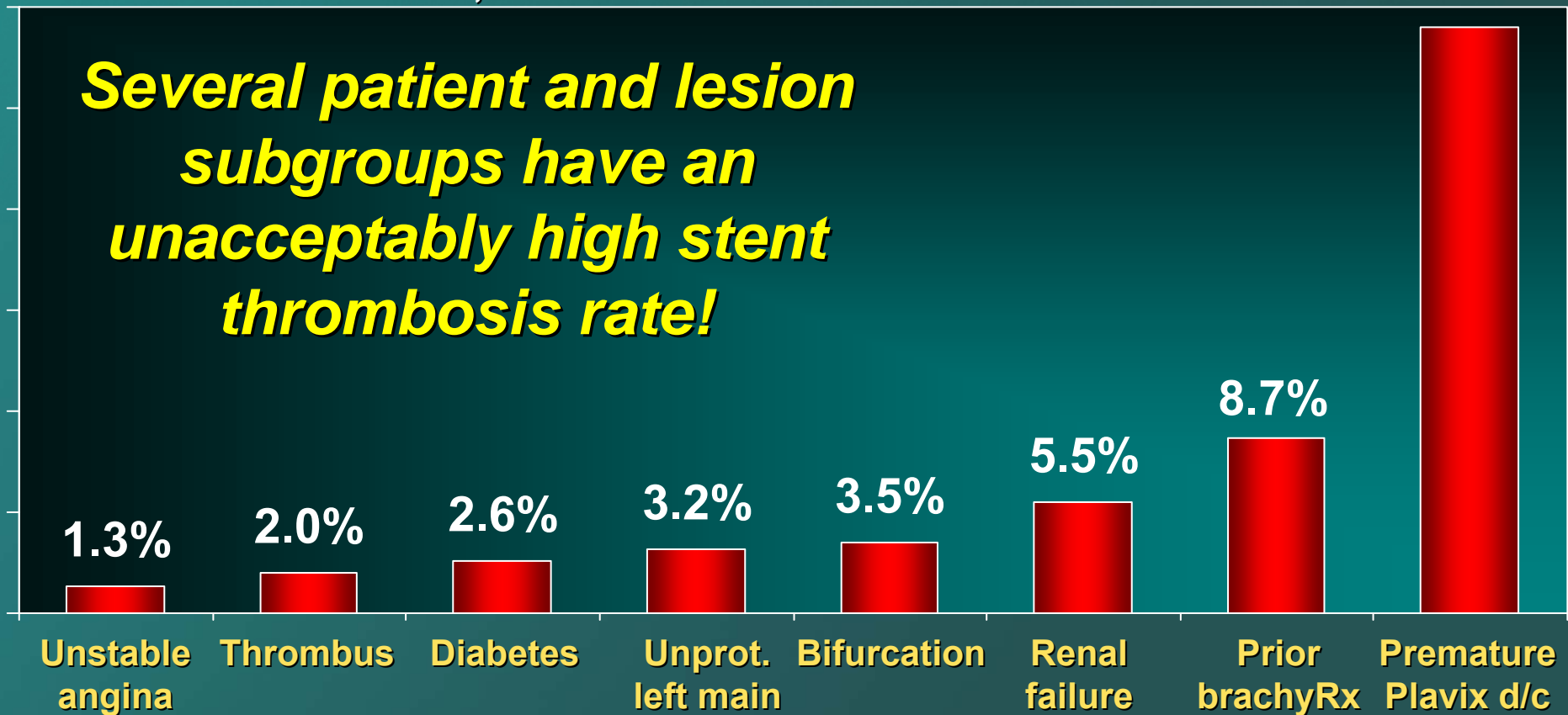


**Stent thrombosis after DES (SES or PES) occurred
in 29/2229 pts (1.3%) at 9 mos (45% mortality)**

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

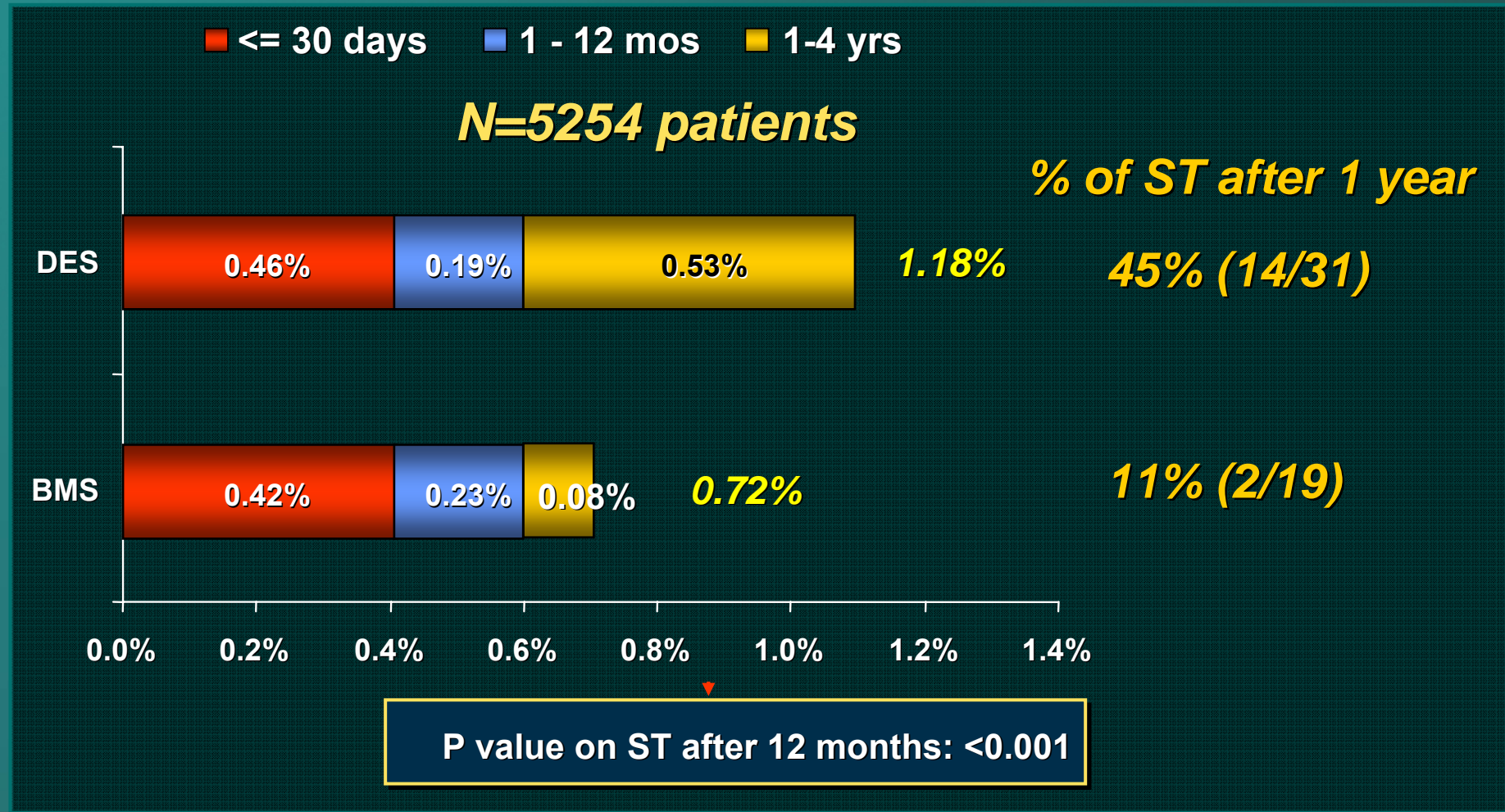
29%

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



Cypher and Taxus Meta-analyses

*Combined Stent Thrombosis**

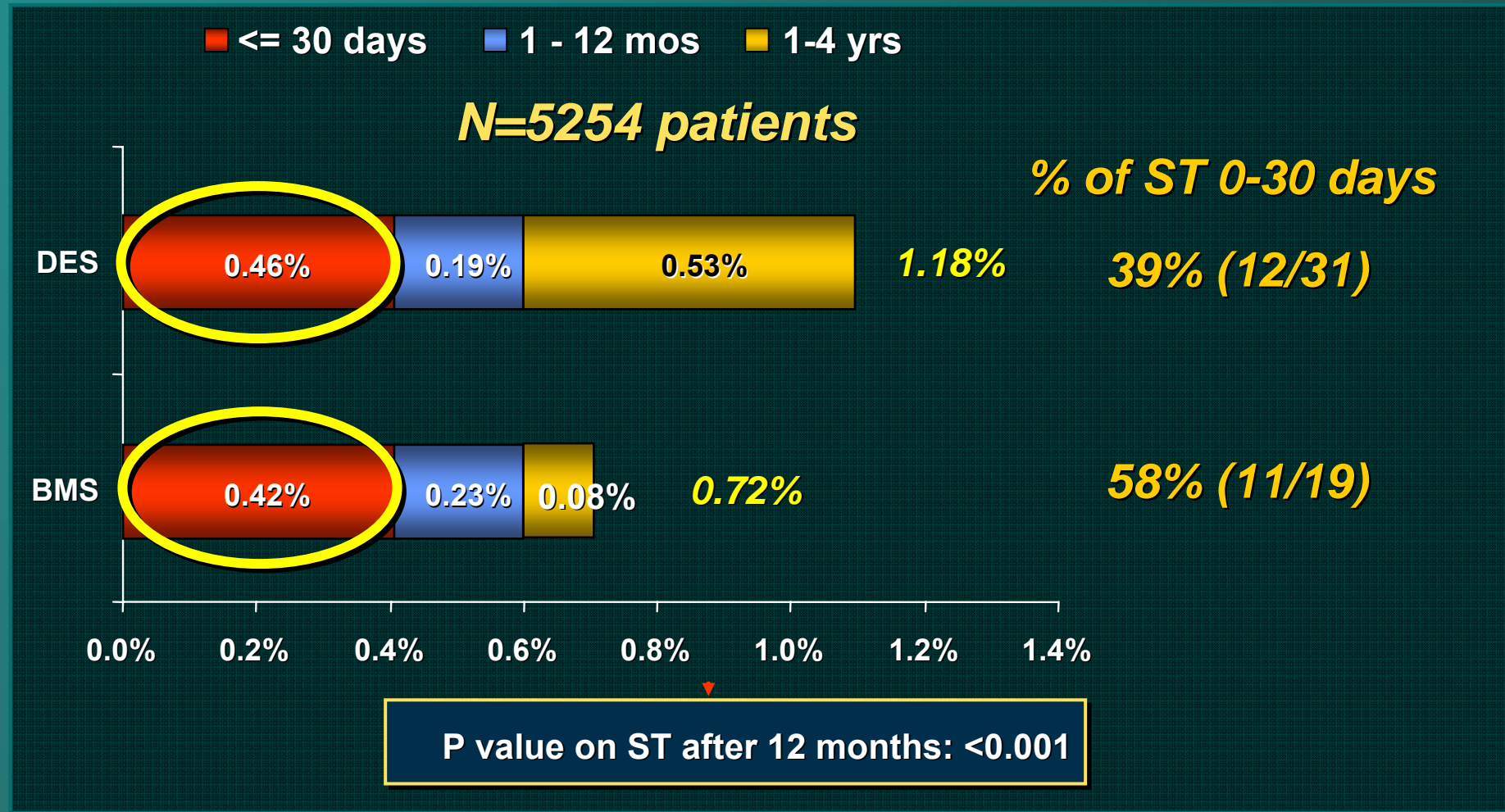


* TAXUS-I, II, IV, V, and VI; RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS



Cypher and Taxus Meta-analyses

*Combined Stent Thrombosis**

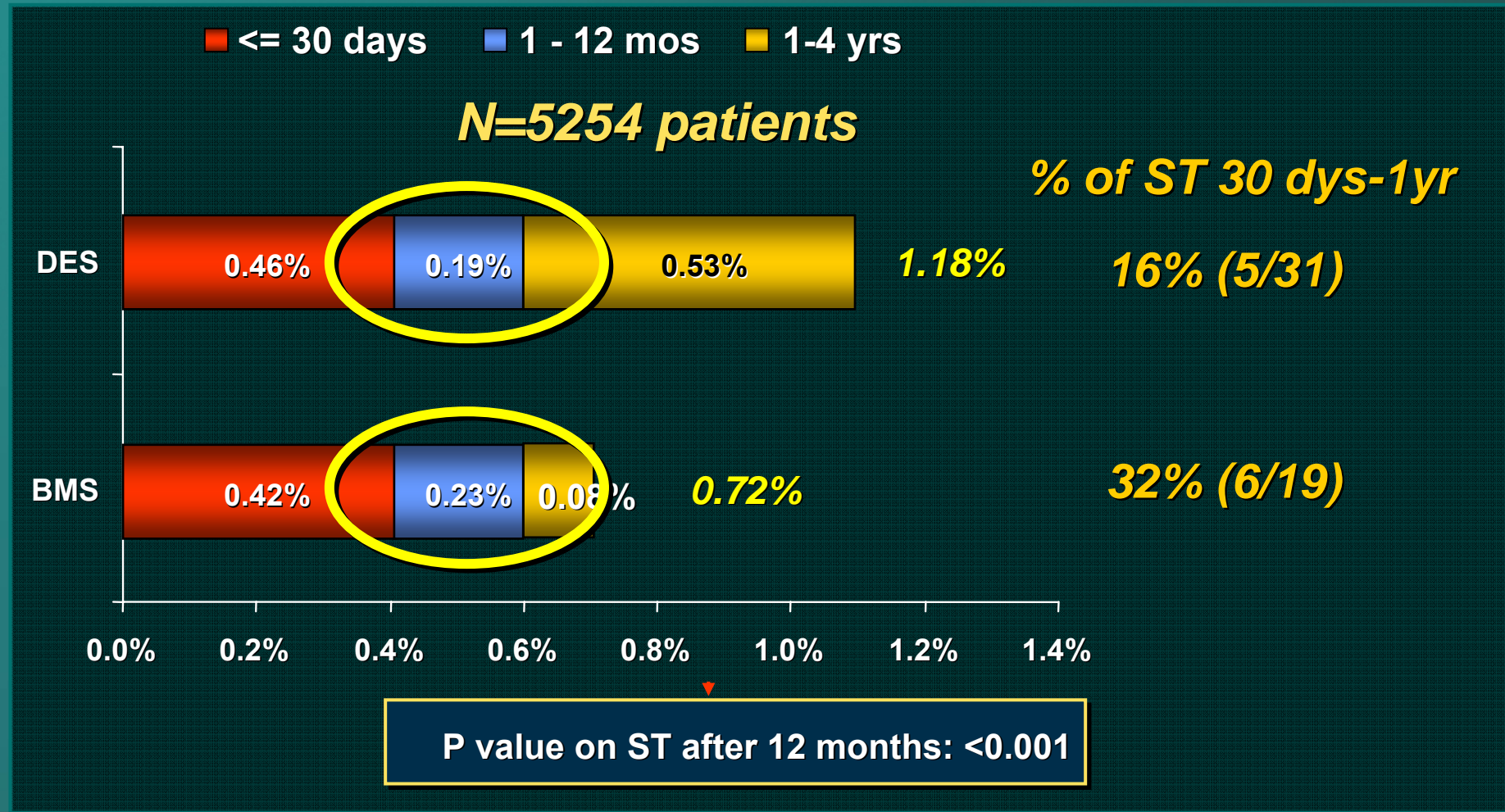


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Cypher and Taxus Meta-analyses

*Combined Stent Thrombosis**

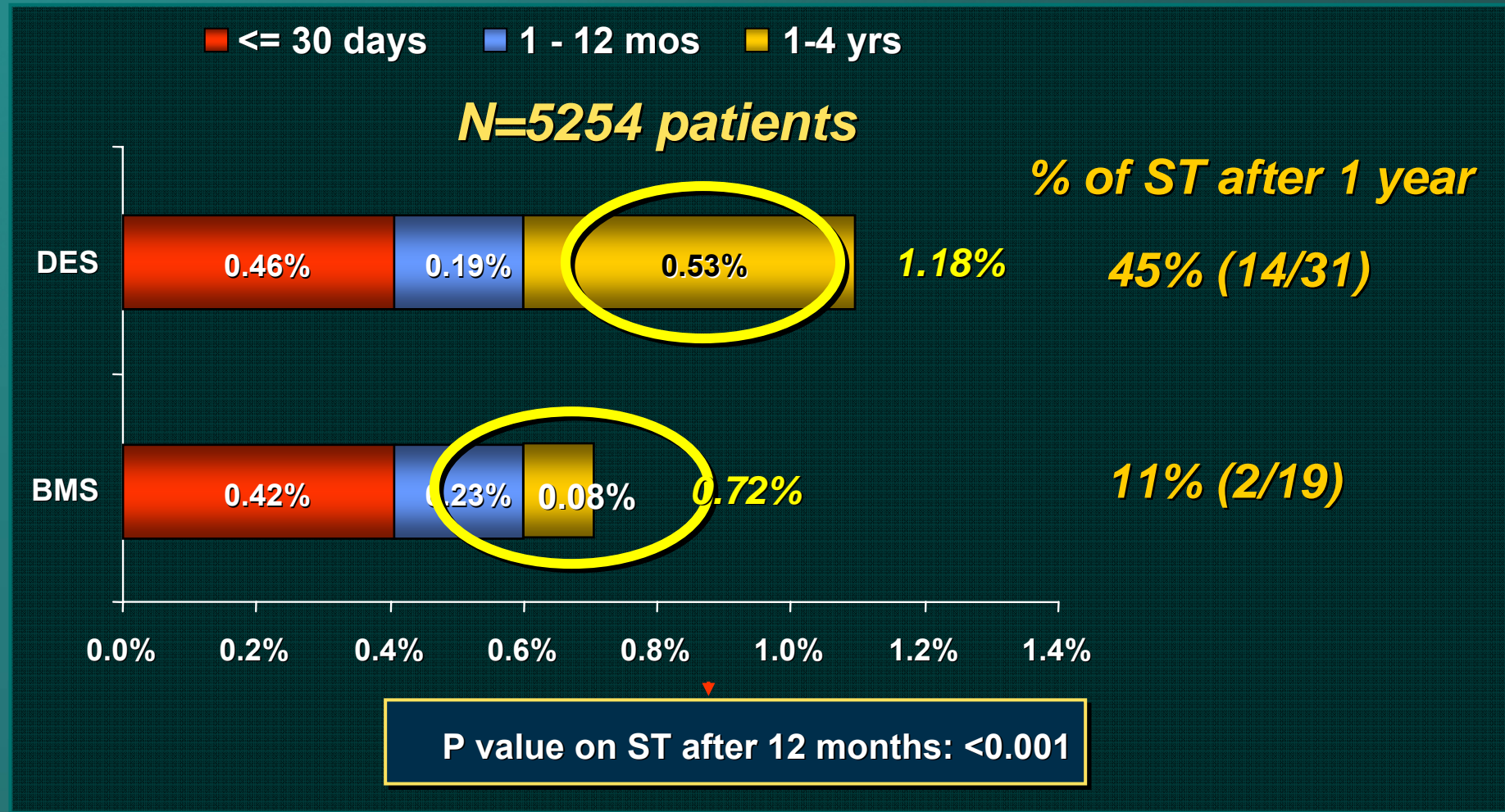


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Cypher and Taxus Meta-analyses

*Combined Stent Thrombosis**

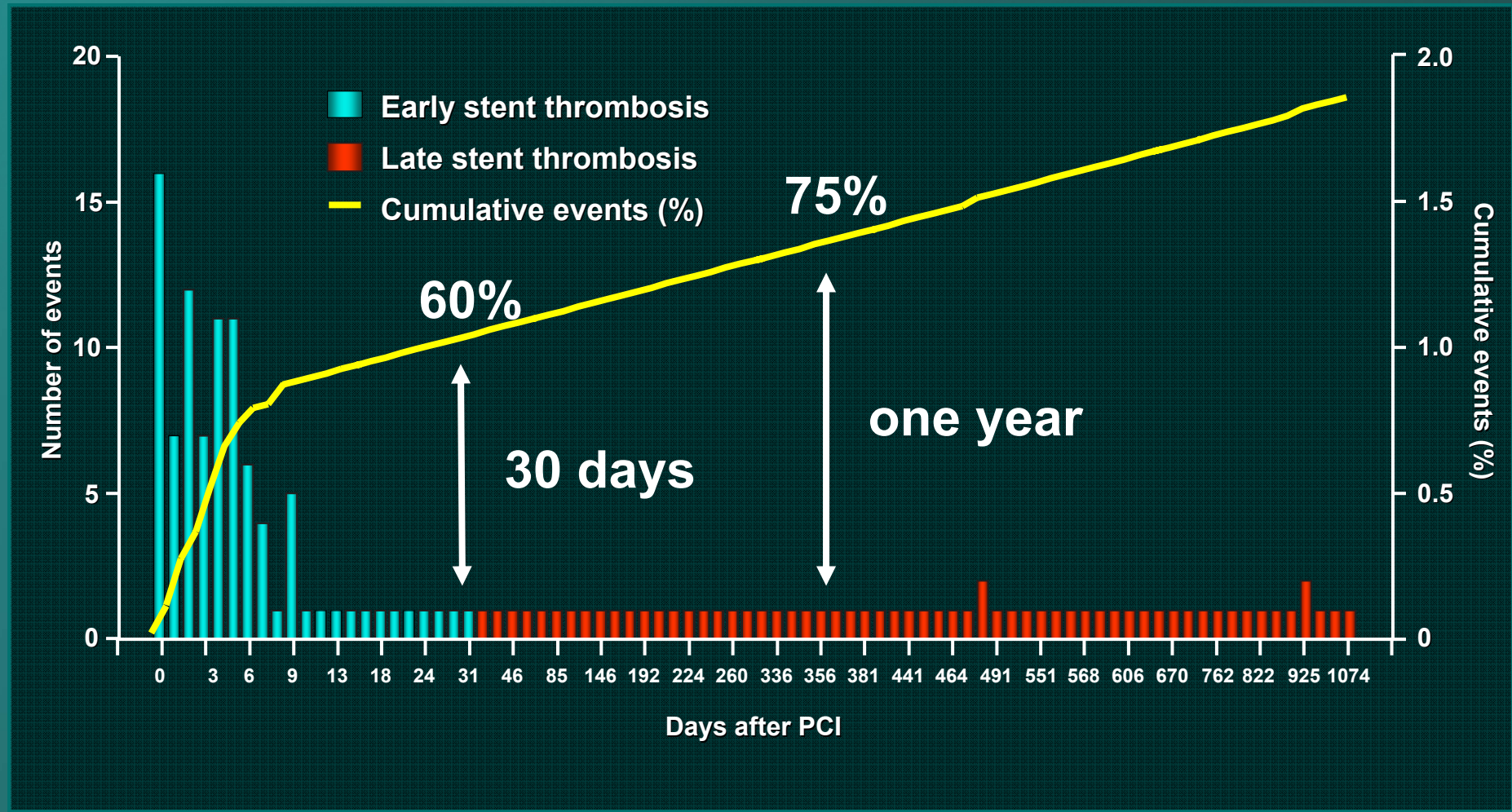


* TAXUS-I, II, IV, V, and VI; RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS



The Bern-Rotterdam Experience

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



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**

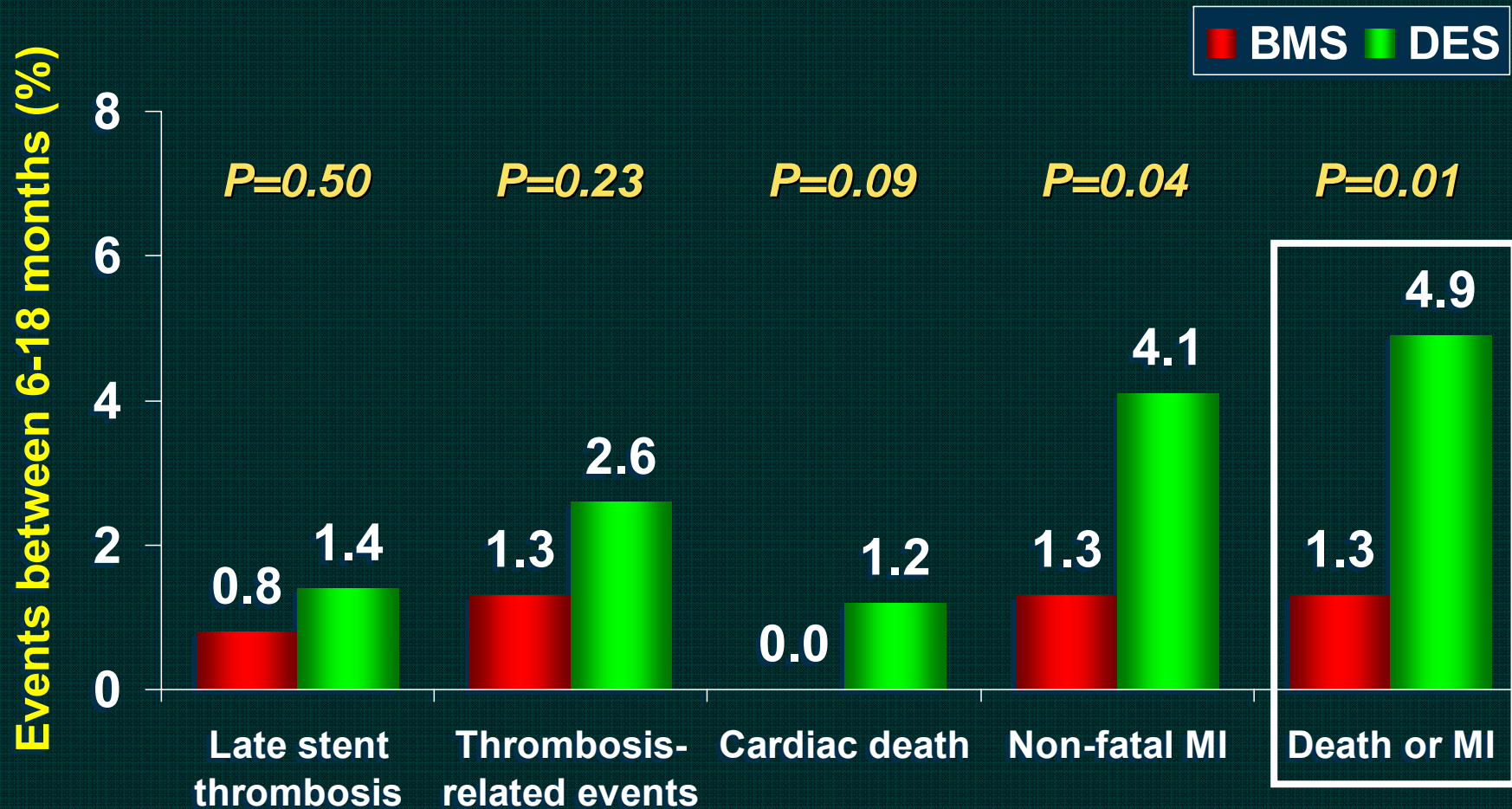
Followed for 1 year off clopidogrel

- **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)



THE WALL STREET JOURNAL

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WSJ.com

THURSDAY, JUNE 22, 2006 - VO

...the debate over the safety of drug-coated stents could signal turmoil in the booming industry.

Concerns Prompt Some Hospitals To Pare Use of Drug-Coated Stents

By SYLVIA PAGÁN WESTPHAL

Rising concern over potentially deadly blood clots has led some cardiac centers to cut back on use of drug-coated stents—tiny, wire-mesh tubes that have propped open the arteries of more than three million heart patients since their introduction in 2003.

The moves come as a growing number of studies question the effectiveness and safety of the stents, which are coated with drugs to prevent arterial scarring. They have quickly become by far the most common form of stent in use, generating \$5.3 billion in sales last year in a field dominated by Boston Scientific Corp. and Johnson & Johnson.

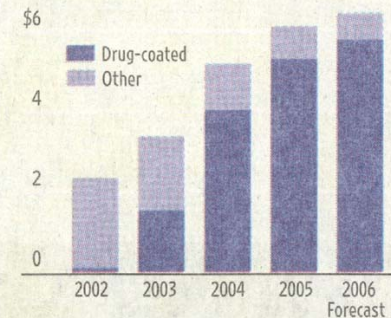
Hospitals aren't drastically curbing use of coated stents, and there's no indication yet of an overall decline in sales of them. But some leading hospitals have started substituting uncoated, bare-metal stents in some patients.

Moreover, the debate over the safety of drug-coated stents could signal turmoil in the booming industry. Drug-coated stents, which cost about \$2,300 apiece, are far more profitable than the uncoated variety, which sell for about \$700.

The new research also raises questions of long-term risks for patients who already have the devices. A recent Swiss study found 3.3 more heart attacks and deaths per 100 patients with drug-coated stents than with the uncoated, bare-metal ones, beginning six months after implantation and ending a year later. The heart attacks and deaths were mostly attributed to blood clots.

Expanding Pipeline

World-wide stent revenue, in billions



Source: Bank of America

Stents are designed to keep arteries open after they are cleared of fatty deposits. The idea is to prevent a future heart attack and avoid more risky heart-bypass surgery. Millions of heart patients have received stents since they won federal approval in the early 1990s.

But stents can trigger the growth of scar tissue that gradually narrows the artery again, a condition called restenosis. This rarely leads to deaths from heart attacks, but can affect a patient's quality of life by causing chest pain. If restenosis progresses, a patient must get the area opened up again—a process called "revascularization."

Drug-coated stents were designed to combat restenosis and reduce the need
Please Turn to Page A15, Column 1



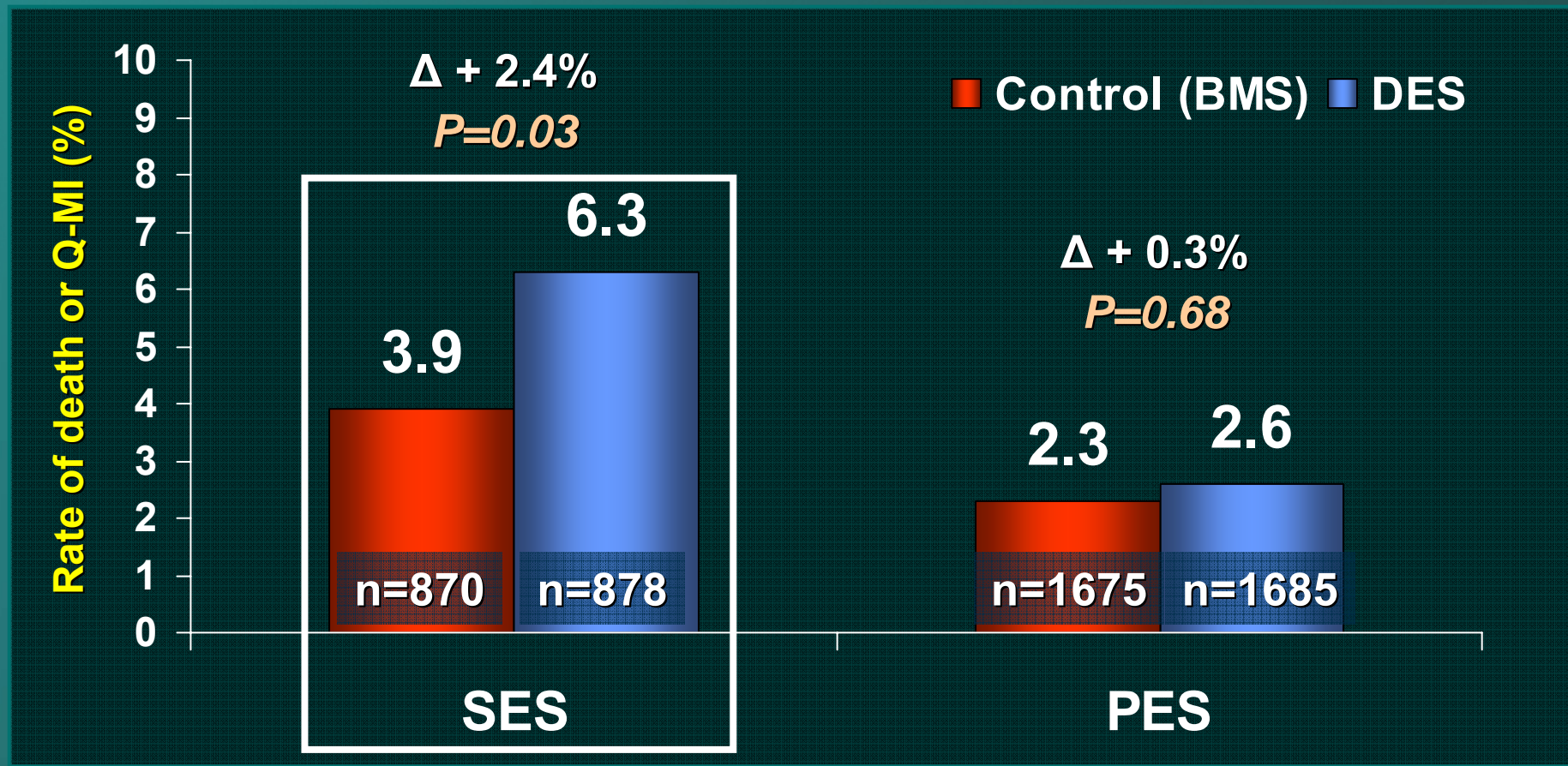
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Incidence of Serious or Adverse Events Death or Q-Wave MI

All randomized studies up to latest available follow-up



“An Epidemic of Madness!”

TUESDAY

ESC Congress News



 **WORLD HEART FEDERATION*** **World Congress of Cardiology 2006**
The unique meeting of the European Society of Cardiology Congress 2006 and the World Heart Federation's XVth World Congress of Cardiology



Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is 'unknown,'" said Yusuf. "I've a feeling the data we're seeing today is only the tip of the iceberg. We need to encourage more public access to the data."



obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality - PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but the



DES Science

2005 – Present/Future

SAFETY
(stent
thrombosis)

COST-VALUE

DURABILITY

DELIVERABILITY

EFFICACY



FDA DES Panel Meeting

Consensus Observations

- *There is an increase in “very late” (>1 yr) stent thrombosis associated with current DES*
 - ~2-4 per 1000 pts per year (? continuous hazard, ? patient and lesion predictors)
 - Data from multiple sources indicate that DES are associated with delayed healing responses and increased inflammation
 - The causes of late DES thrombosis are multifactorial; device, procedural, and patient factors (often multiple = perfect storm)



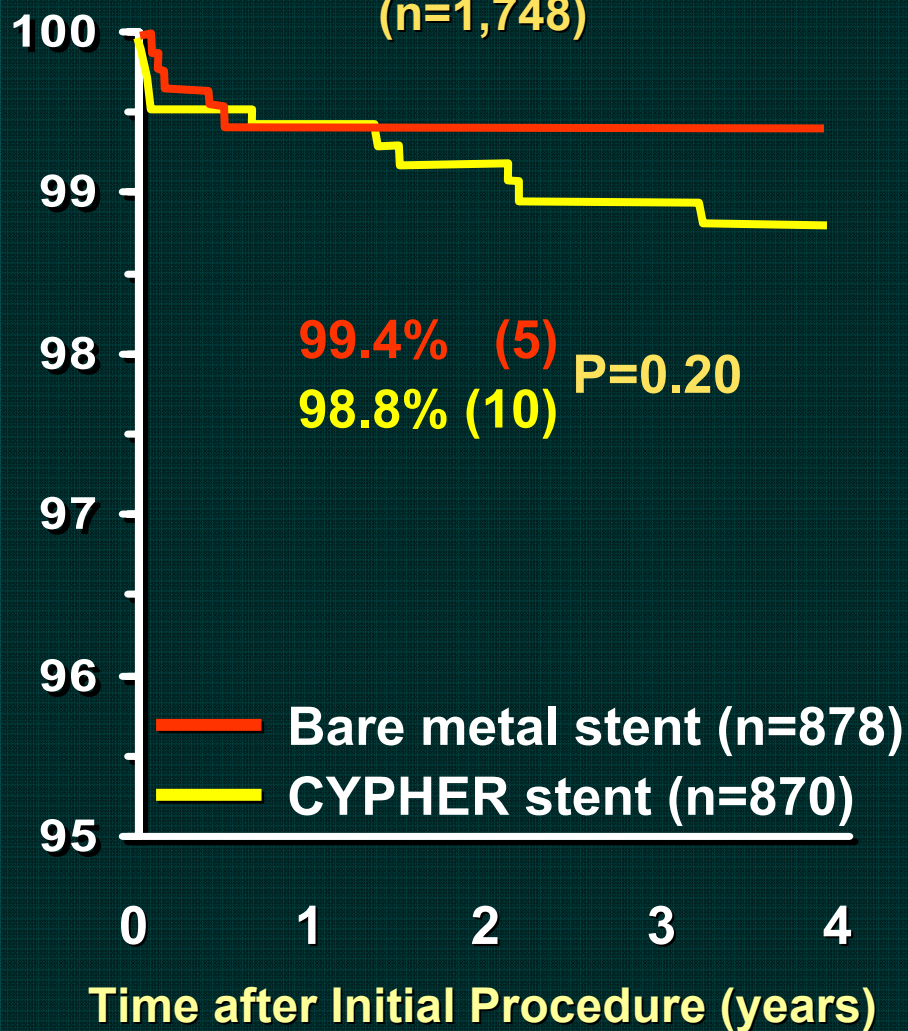
FDA DES Panel Meeting

Consensus Observations

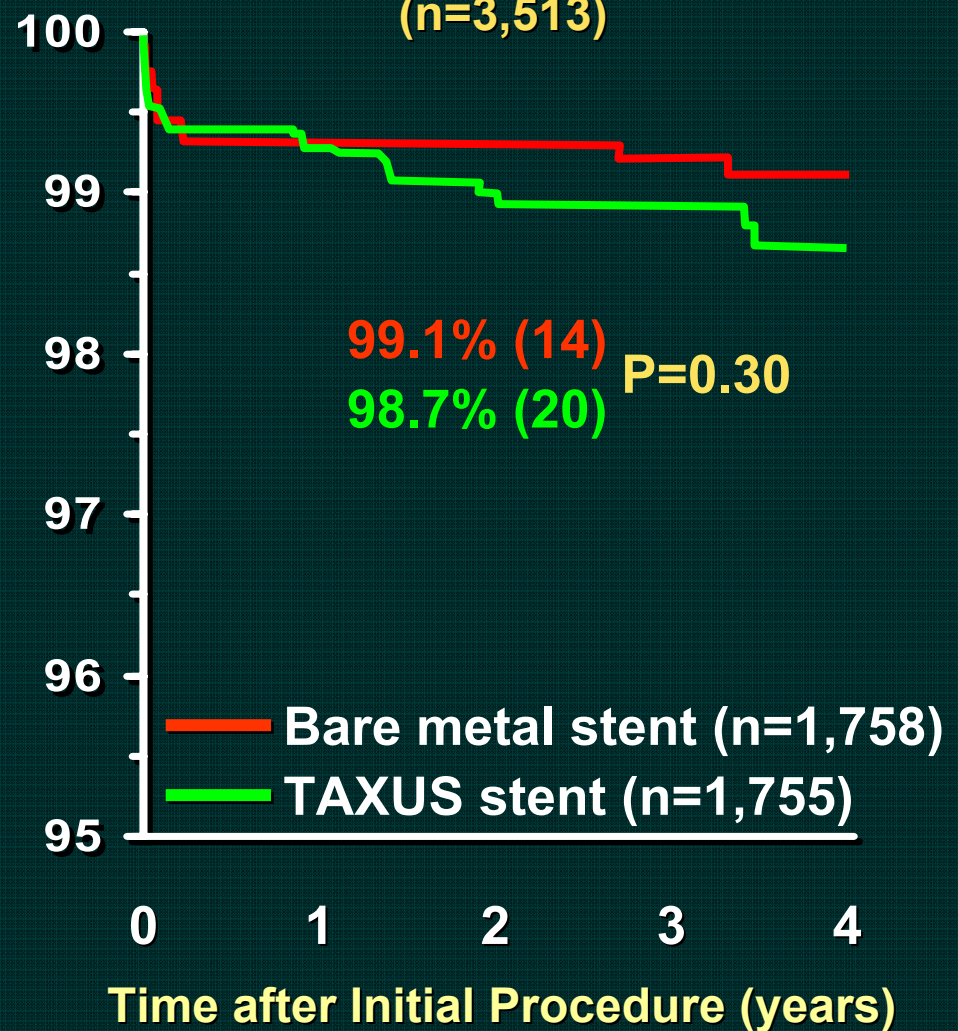
- There may be a link between post-DES reduced neo-intimal hyperplasia (late loss) and delayed late healing responses which contributes to late stent thrombosis
- DES stent thrombosis is highly definition dependent; need for revised standardized definitions and adjudication methods (ARC) to facilitate inter-study comparisons

9 Prospective, Double-Blind, Randomized Trials Freedom From (Protocol) Stent Thrombosis

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

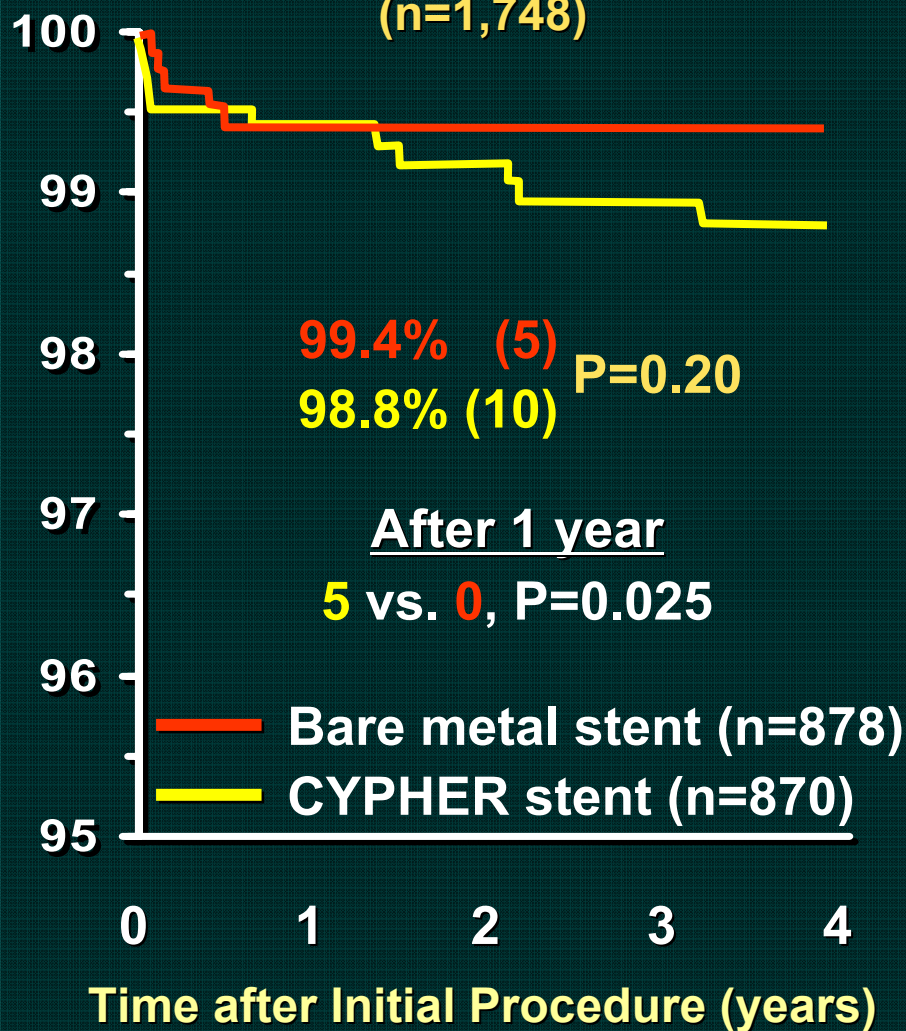


TAXUS I, II, IV, V, VI
(n=3,513)

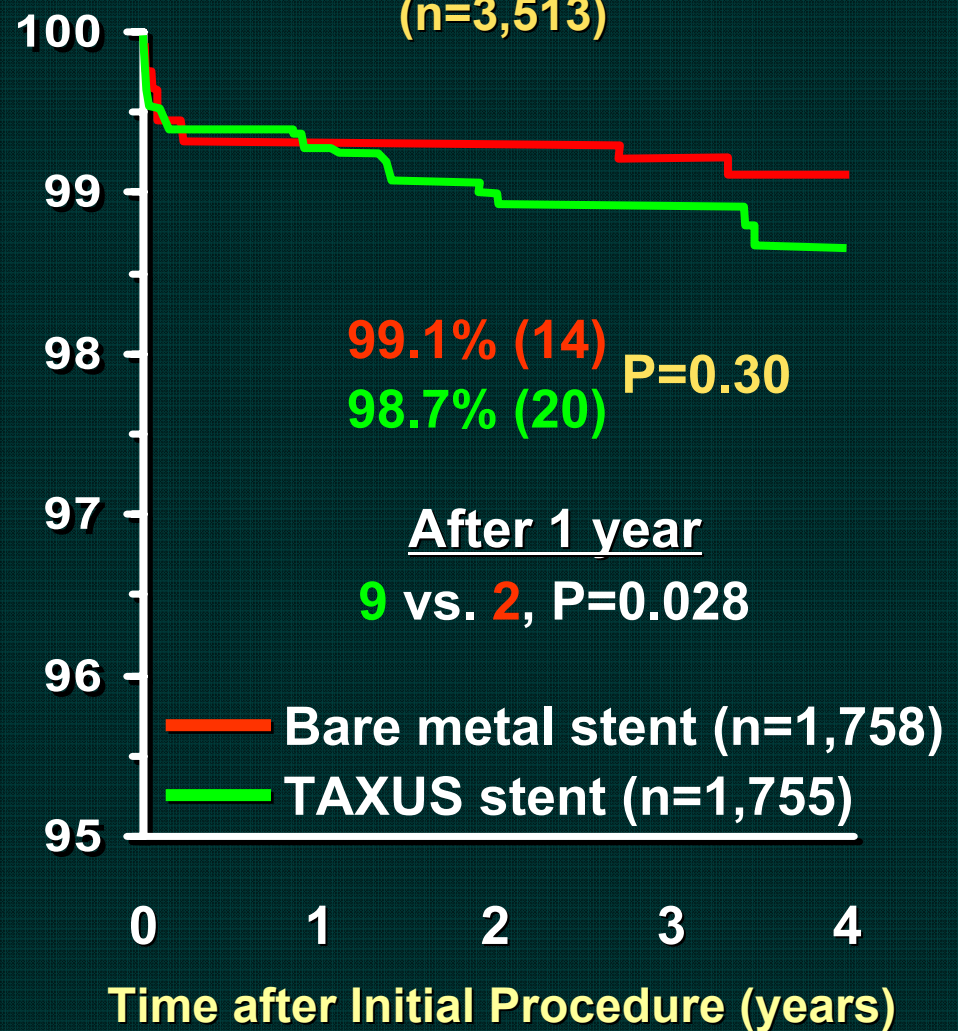


9 Prospective, Double-Blind, Randomized Trials Freedom From (Protocol) Stent Thrombosis

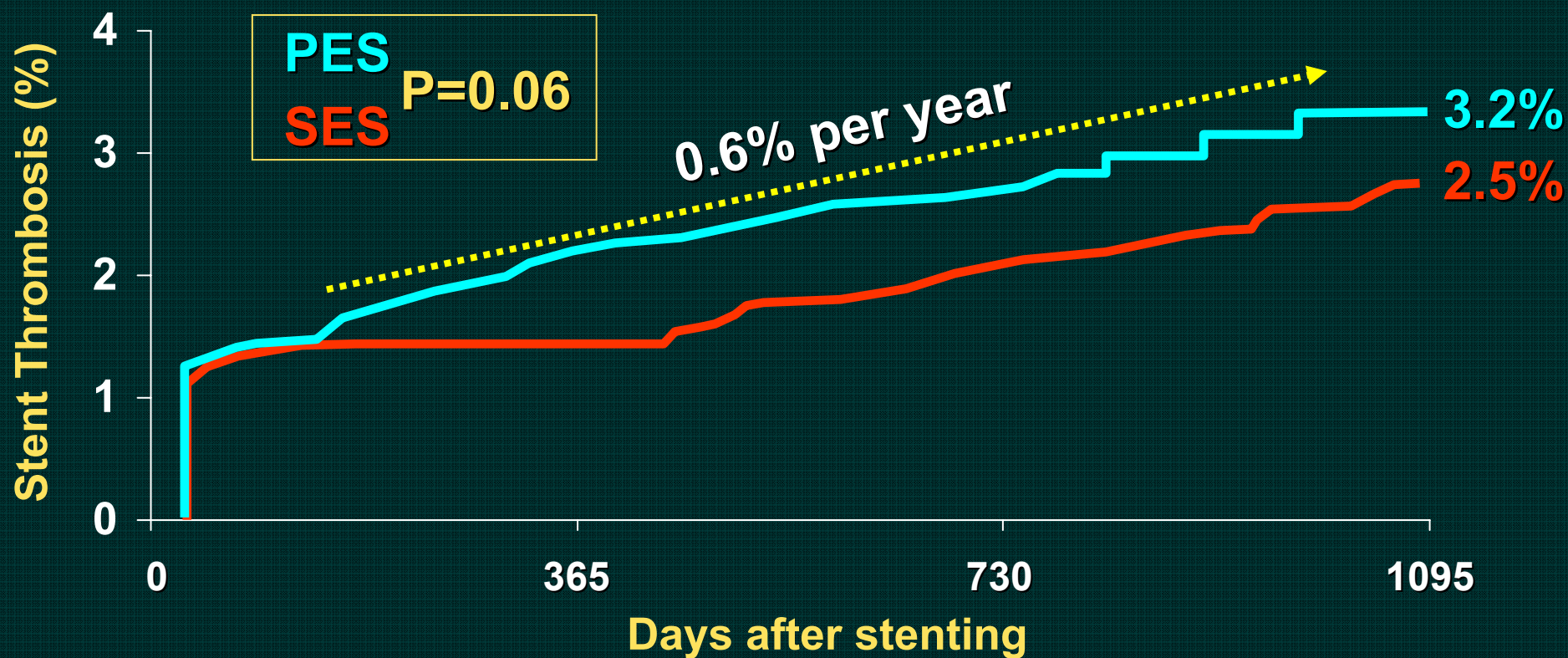
RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS
(n=1,748)



TAXUS I, II, IV, V, VI
(n=3,513)



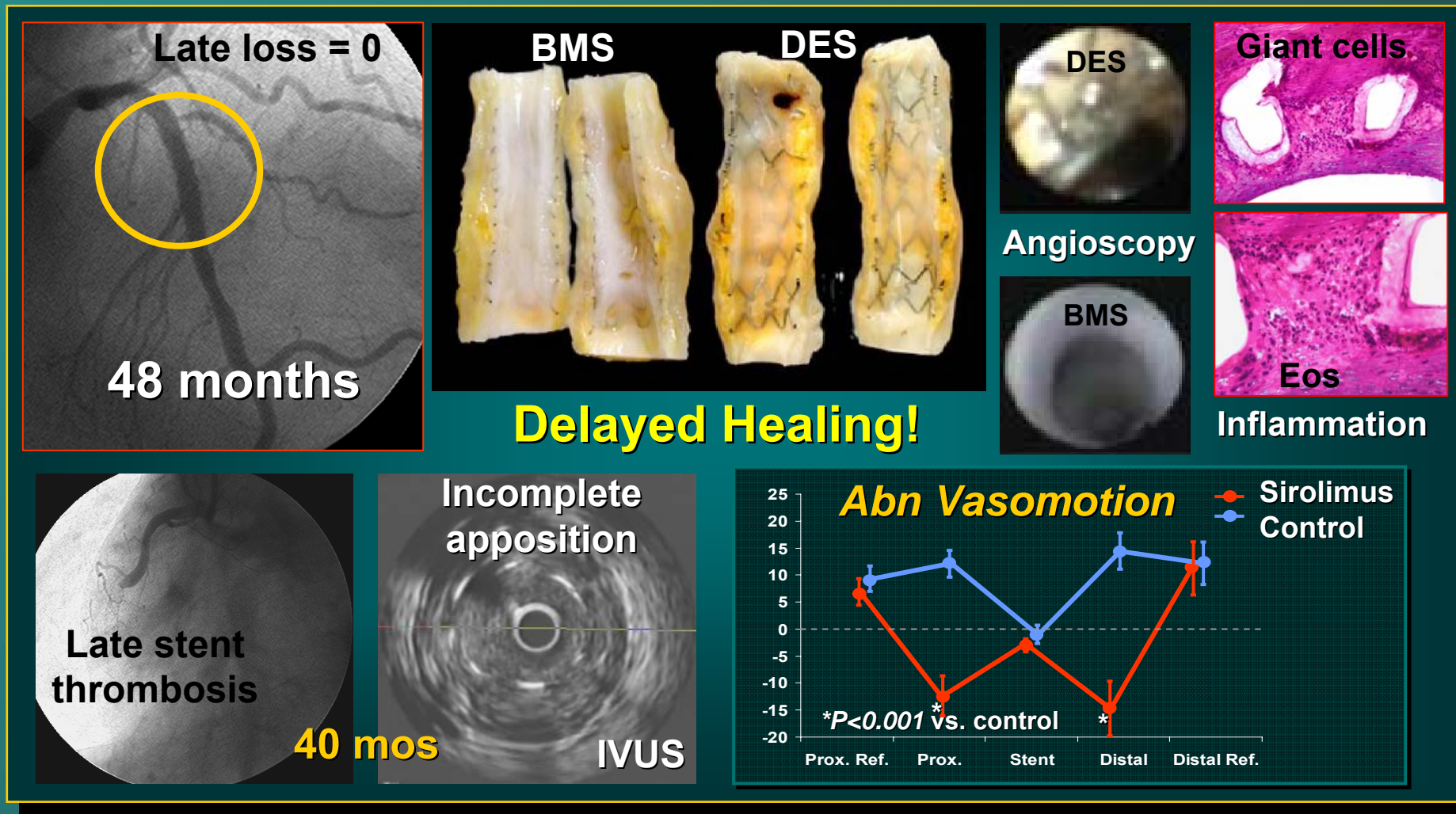
Bern/Rotterdam 2 Center Experience



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

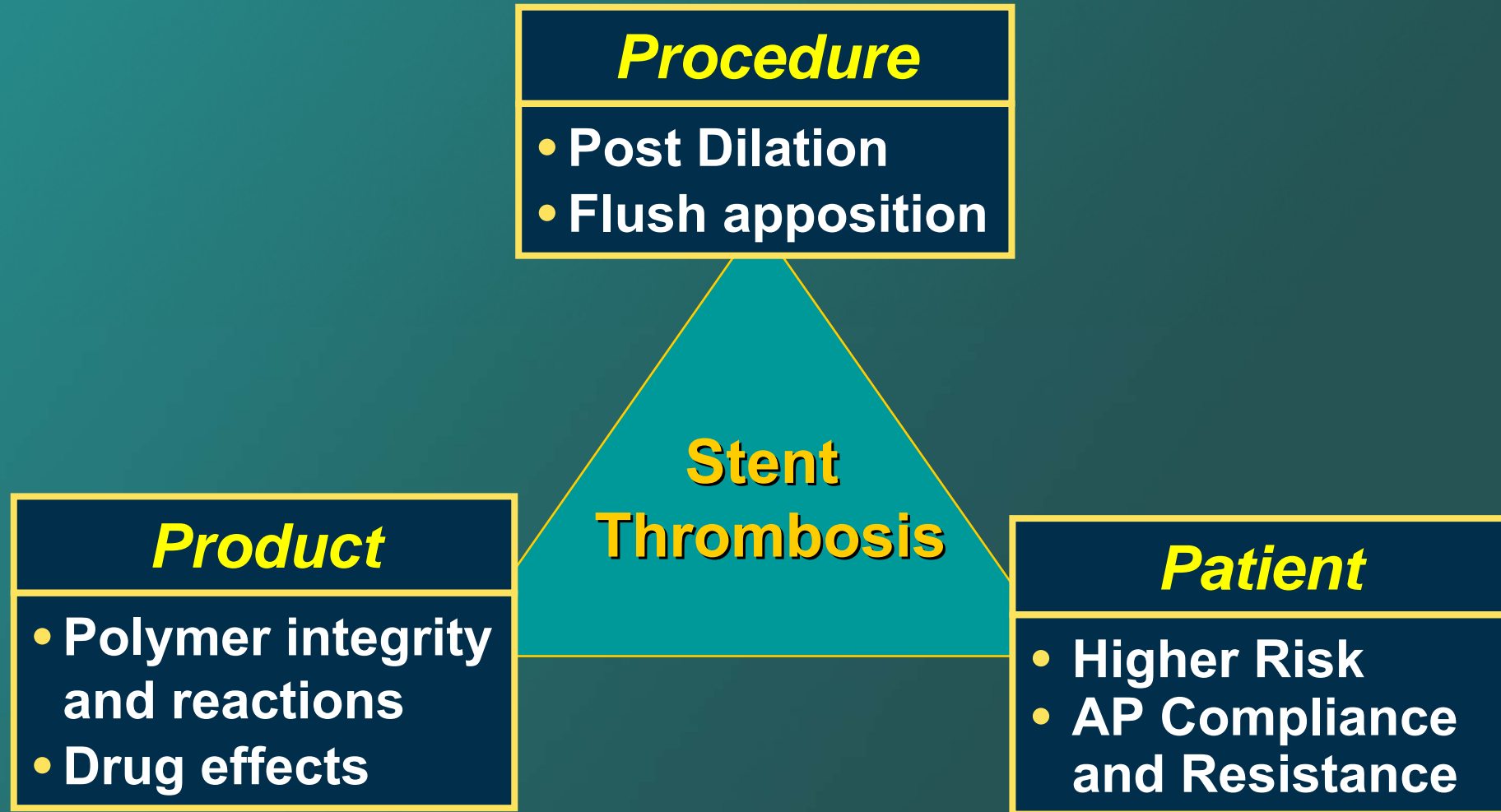


Drug-Eluting Stents.... the good, the bad, and the ugly!



Stent Thrombosis

Procedure, Product, Patient



CYPHER RCT Stent Thrombosis

4 yr Follow-up: *Expanded Definition*

definite + probable

	CYPHER N=878	BMS N=870	P-Value*
Thrombosis			
Expanded Definition			
Definite			
Probable			
Stent Thrombosis			
Definite			
Probable			
All Thrombosis	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!

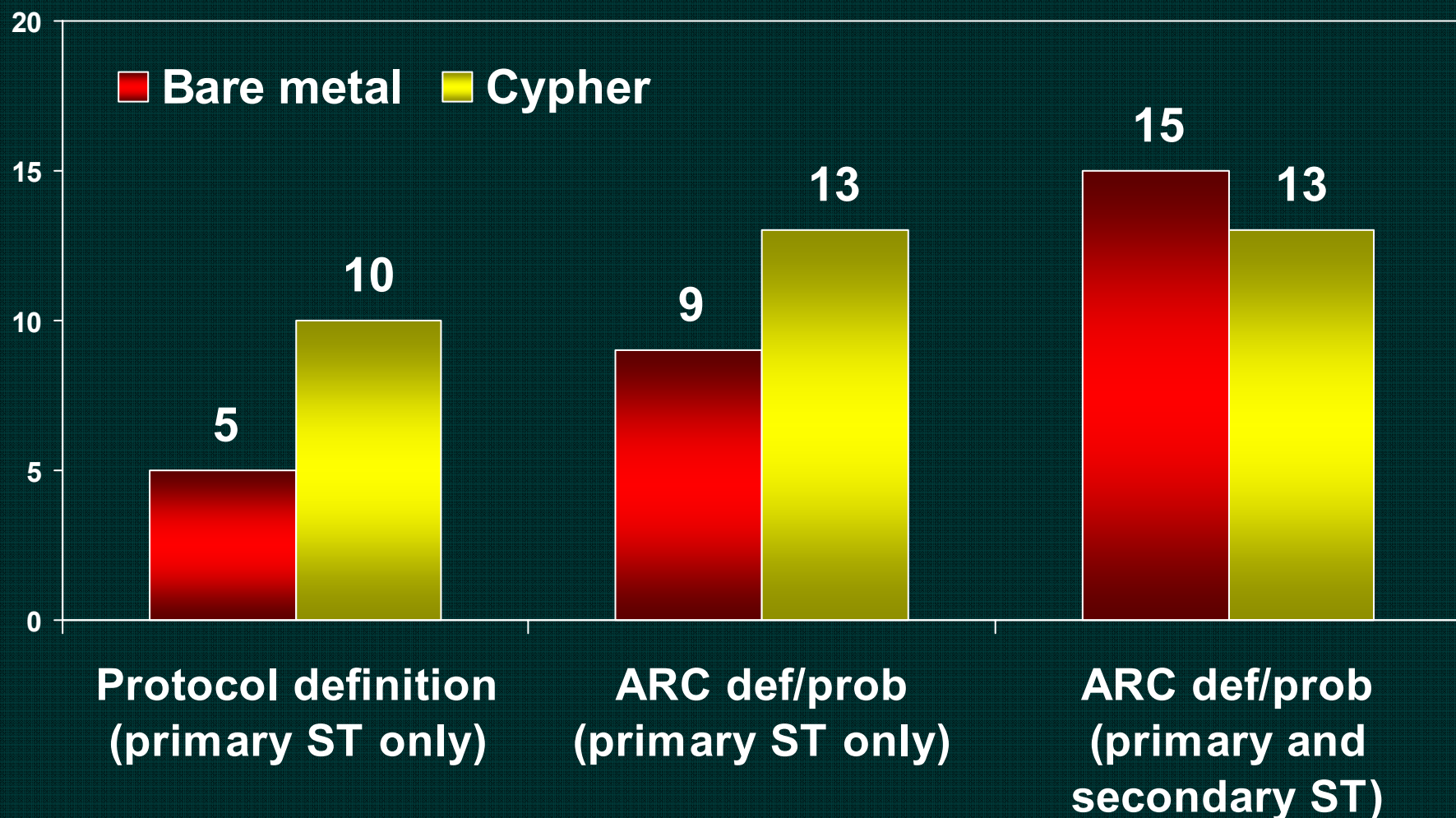
Data from 4 pooled RCT: SIRIUS, E and C SIRIUS and RAVEL

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



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

Stent Thrombosis: 0 – 4 Years



RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS



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Primary = Thrombotic episodes before TLR
Secondary = Thrombotic episodes after TLR

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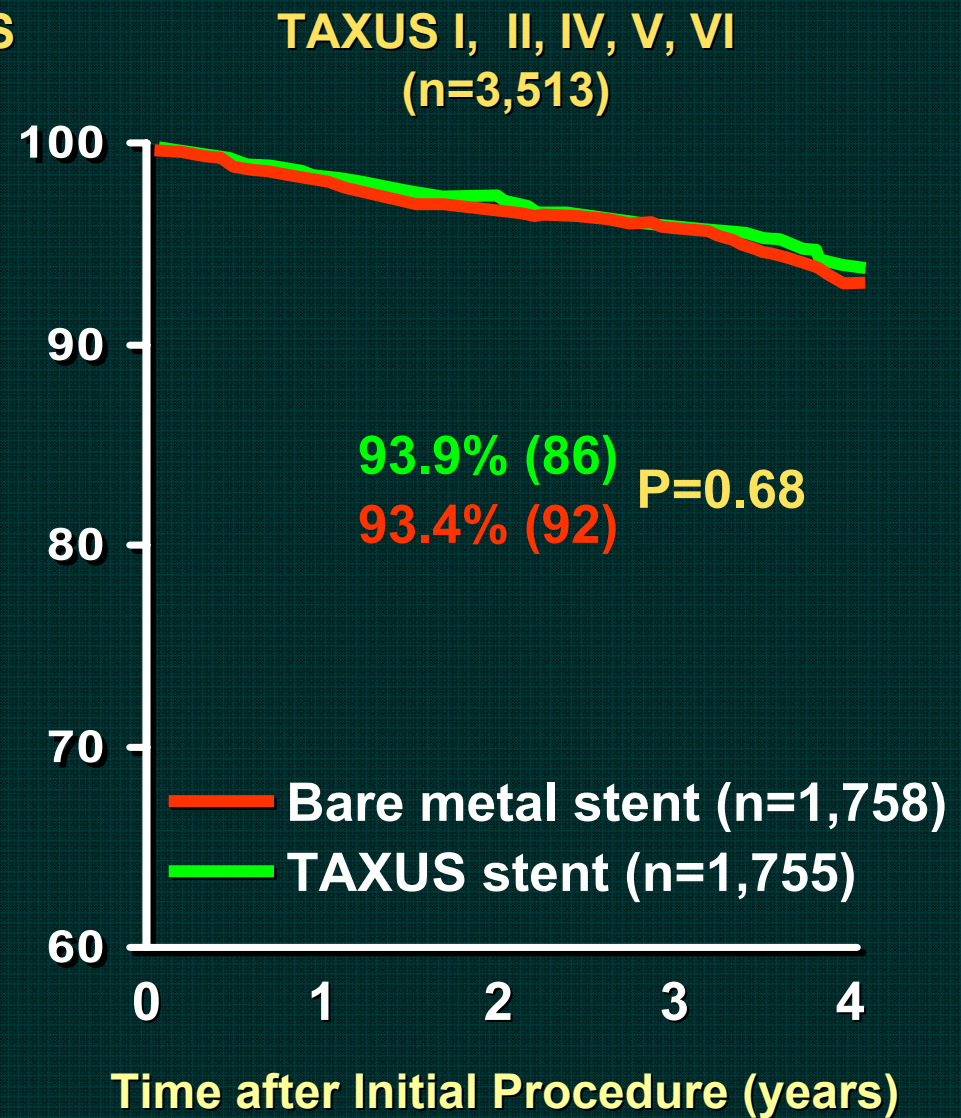
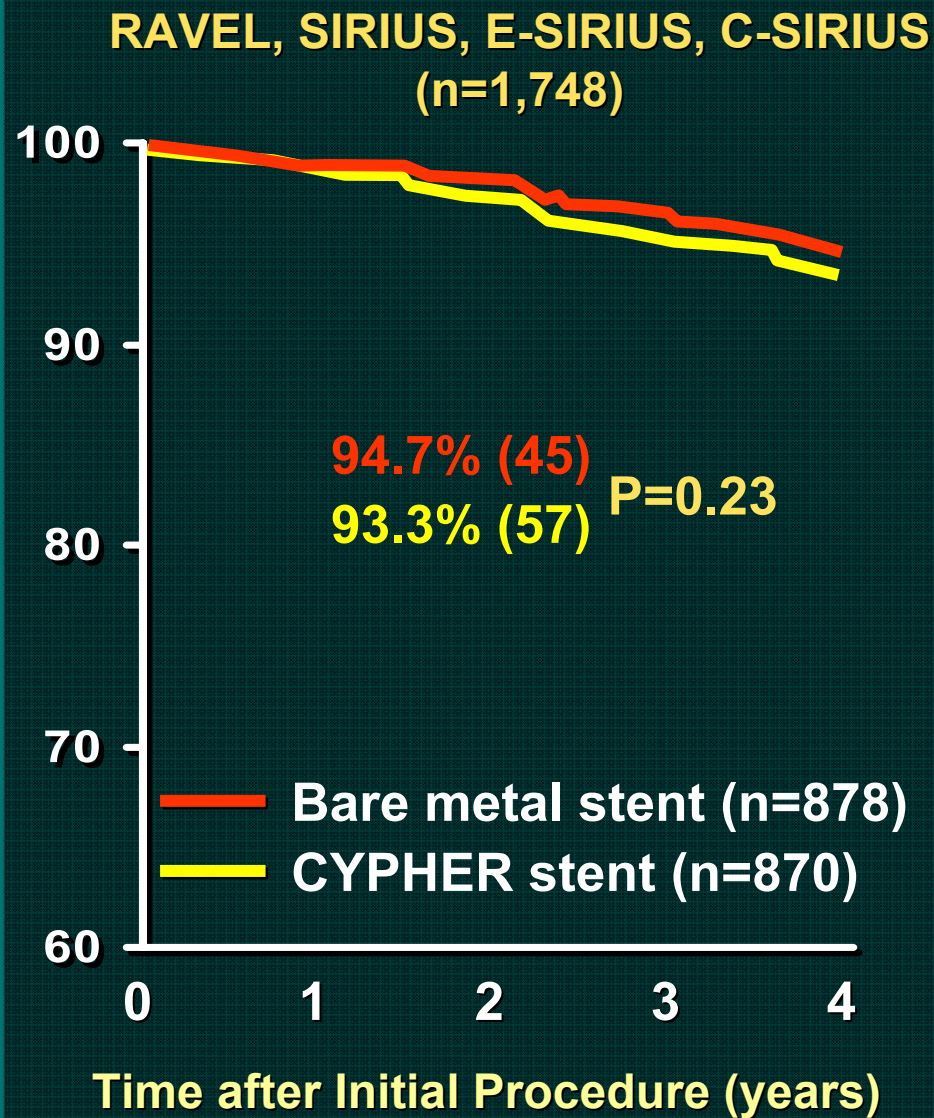


FDA DES Panel Meeting

Consensus Observations

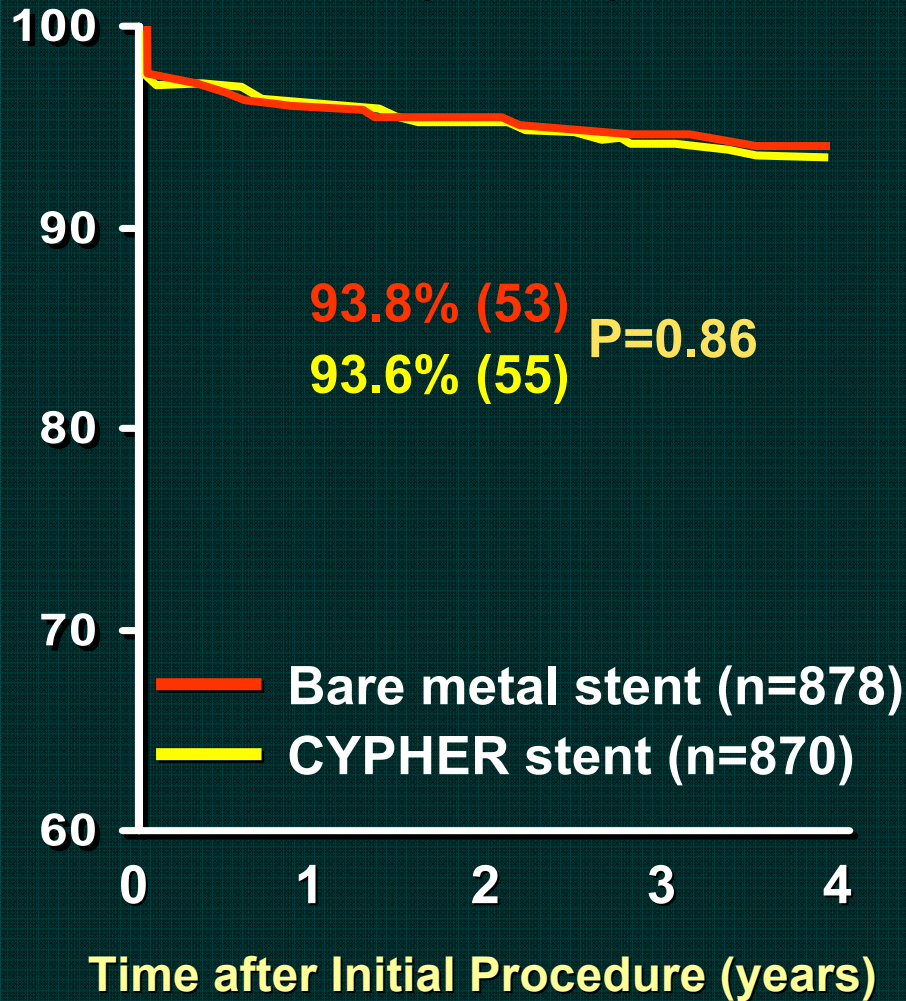
- ***“On-label” DES use – no significant increase in death/MI (despite higher late DES thrombosis)***
 - **Death/MI reduction from reduced restenosis balances death/MI increase from late DES thrombosis**
 - **Are there important safety differences in the diabetic subgroup?**

9 Prospective, Double-Blind, Randomized Trials Freedom From All Cause Death

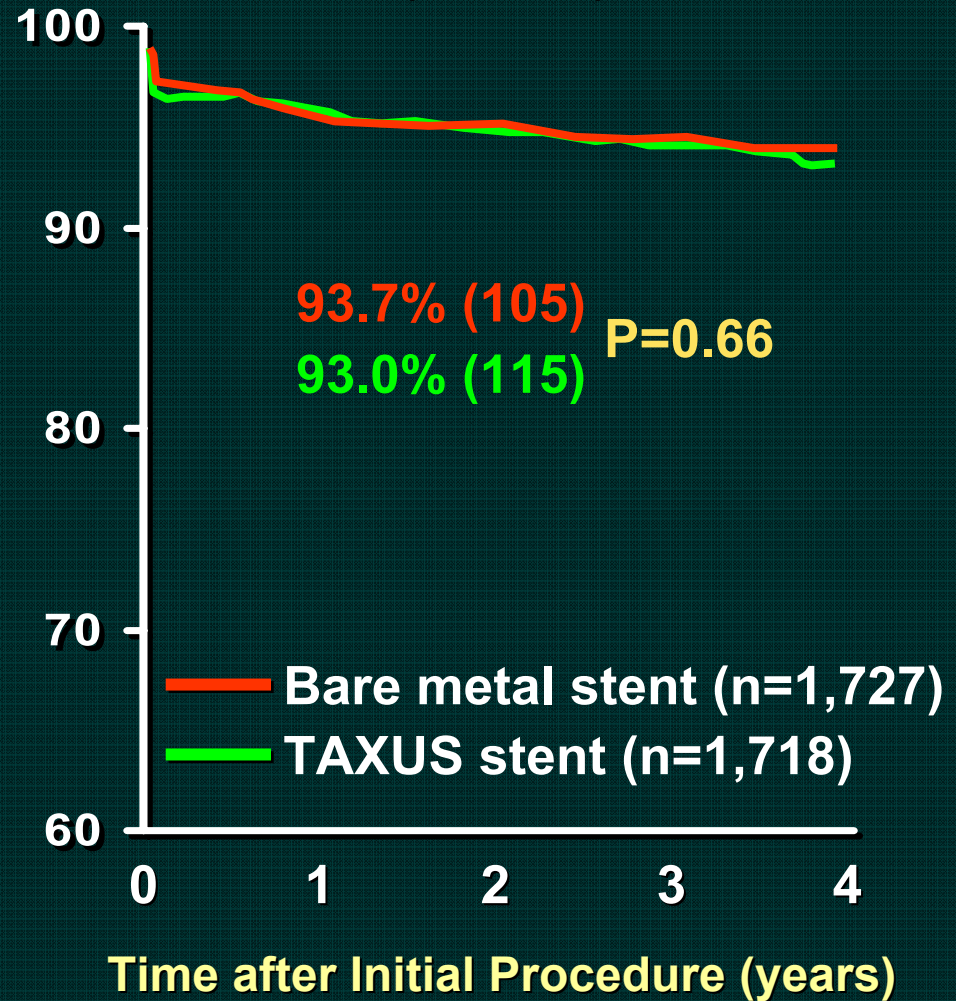


9 Prospective, Double-Blind, Randomized Trials Freedom From Myocardial Infarction

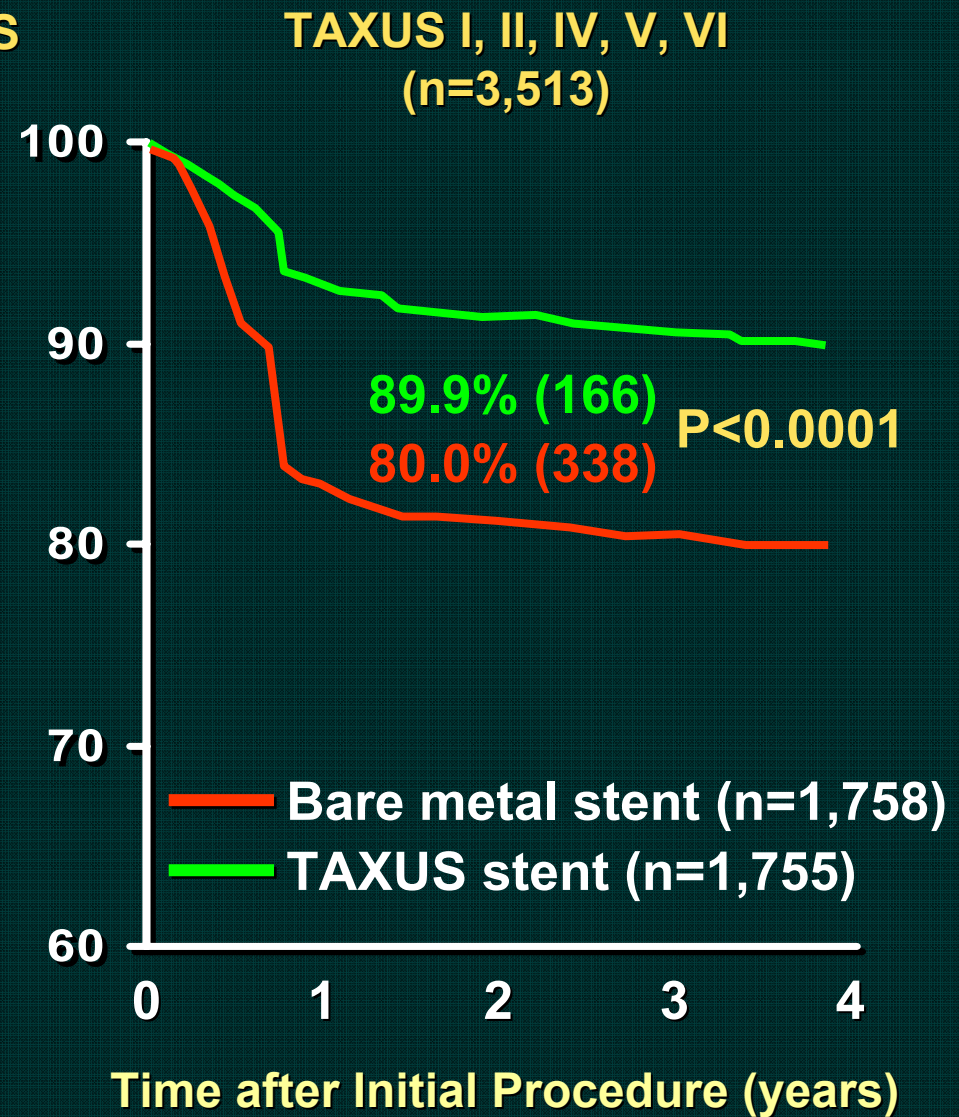
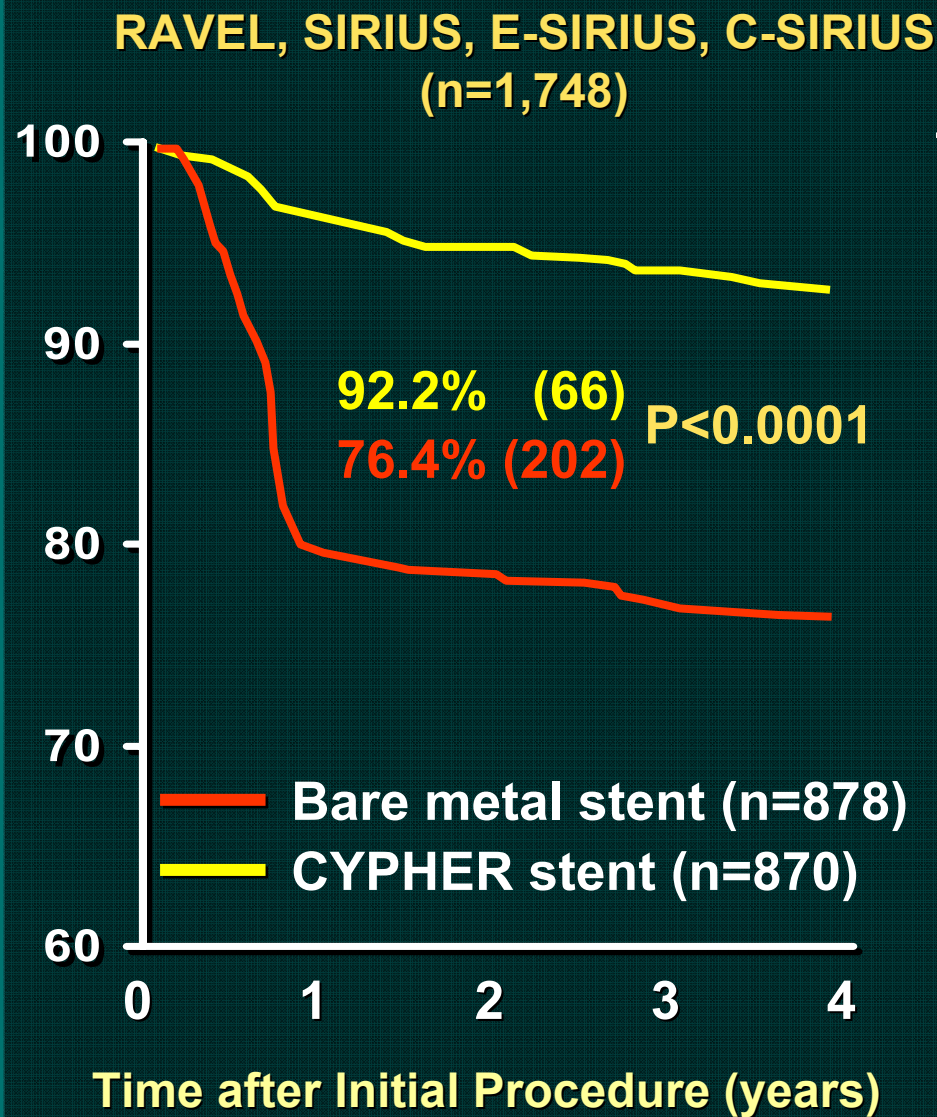
RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS
(n=1,748)



TAXUS I, II, IV, V, VI
(n=3,513)



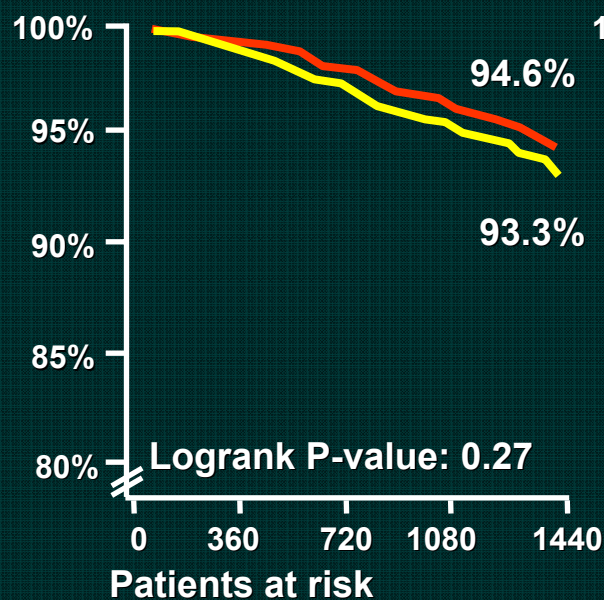
9 Prospective, Double-Blind, Randomized Trials Freedom From Ischemic TLR



All-cause Mortality in Pooled Analysis

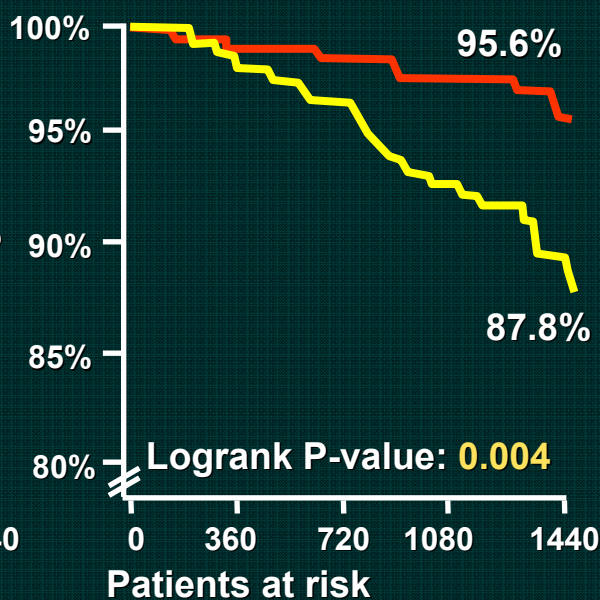
RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS

Total population N=1748



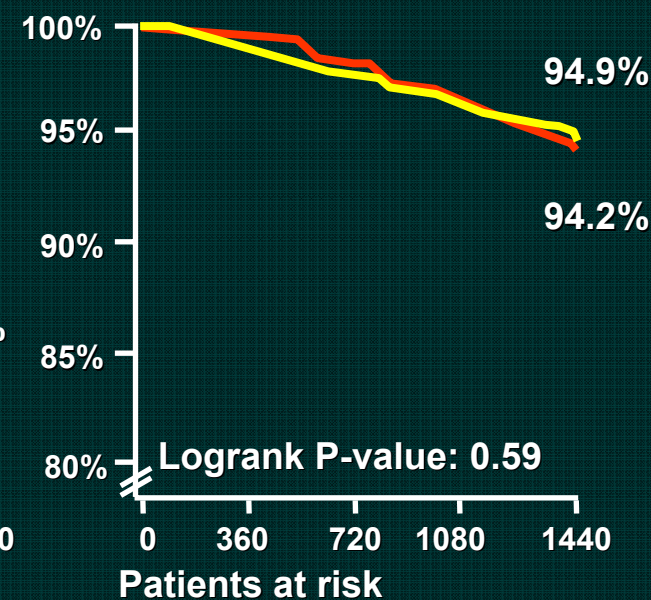
BMS	869	855	838	816	763
SES	877	860	835	809	740

Diabetic patients N=428



232	230	227	221	197
194	188	185	175	158

Non-diabetic patients N=1318



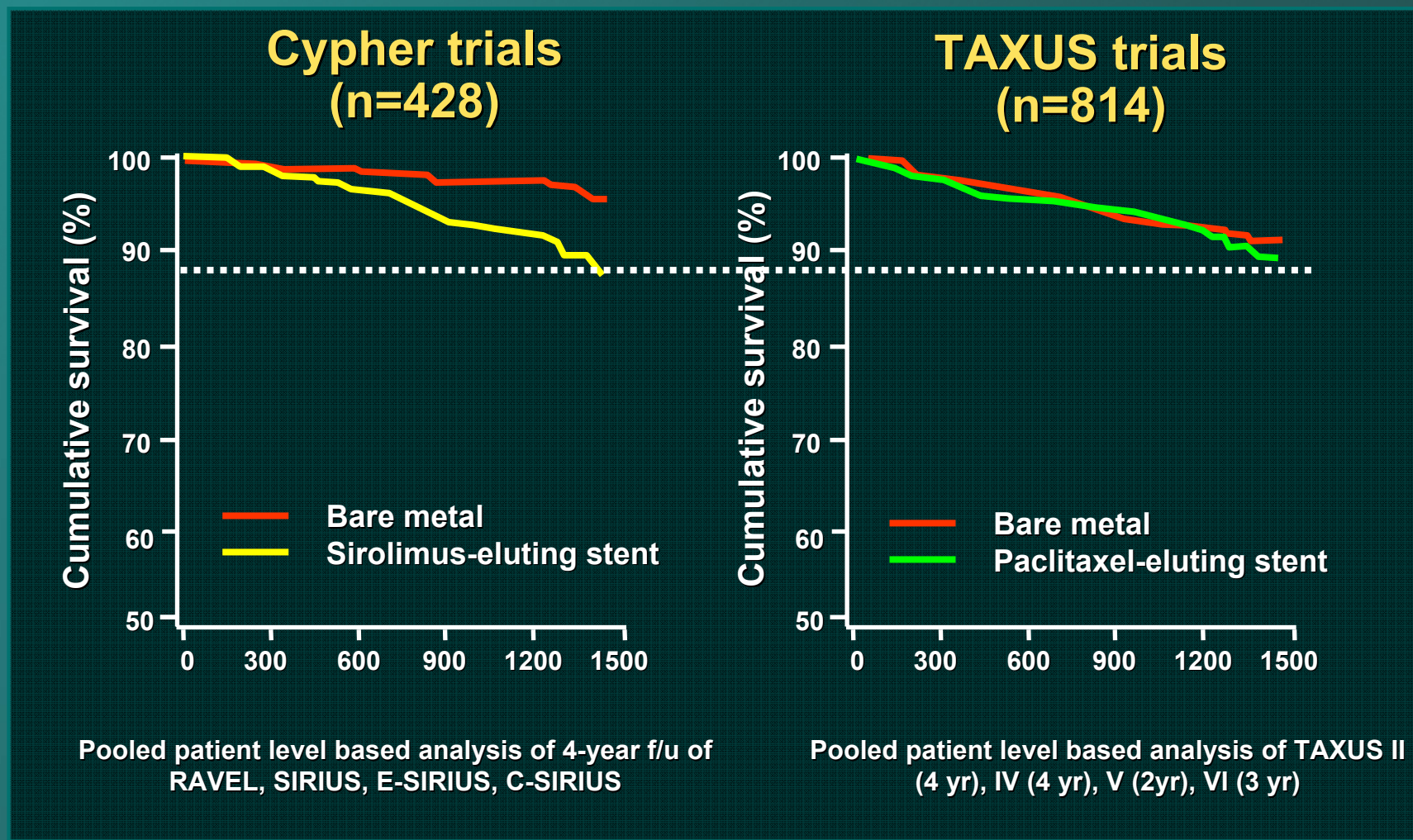
634	623	608	593	545
672	672	650	634	579

— Bare metal
— Sirolimus-eluting stent



Mortality in Pooled Analyses

Diabetic subset



FDA DES Panel Meeting

Consensus Observations

- ***“Off-label DES use – increased incidence of late DES thrombosis and death/MI cw “on-label”, but inadequate controls; results inconsistent!***
- **Few RCTs (underpowered); FDA sanctioned registries = insufficient sample size and FU, represents major data gap and source of concern**
- **Large population studies (SCAAR) fraught with methodologic flaws (e.g. risk adjustment issues)**



DES: Off-label use

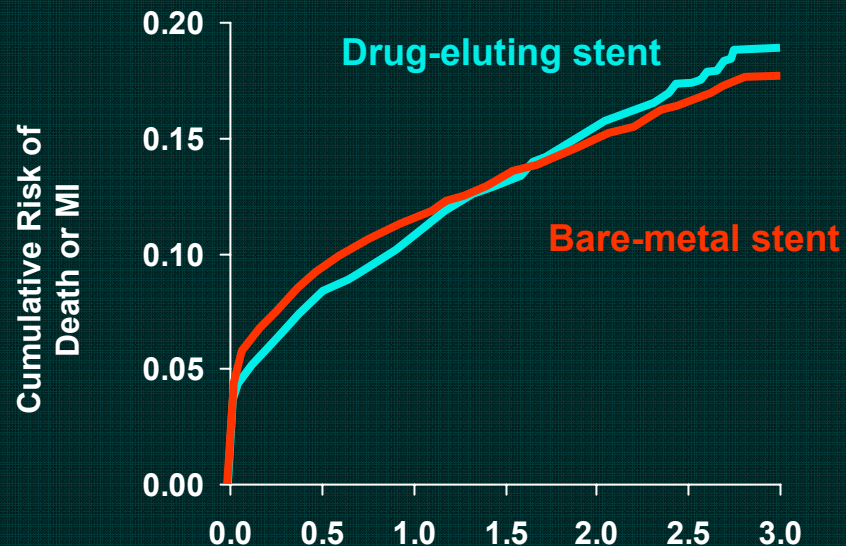
- **More complex and unapproved indications**
 - **Very small vessels and very long lesions**
 - **Chronic total occlusions**
 - **Bifurcations**
 - **Left main disease**
 - **In-stent restenosis**
 - **Multivessel disease**
 - **Saphenous vein grafts**
 - **Acute myocardial infarction**



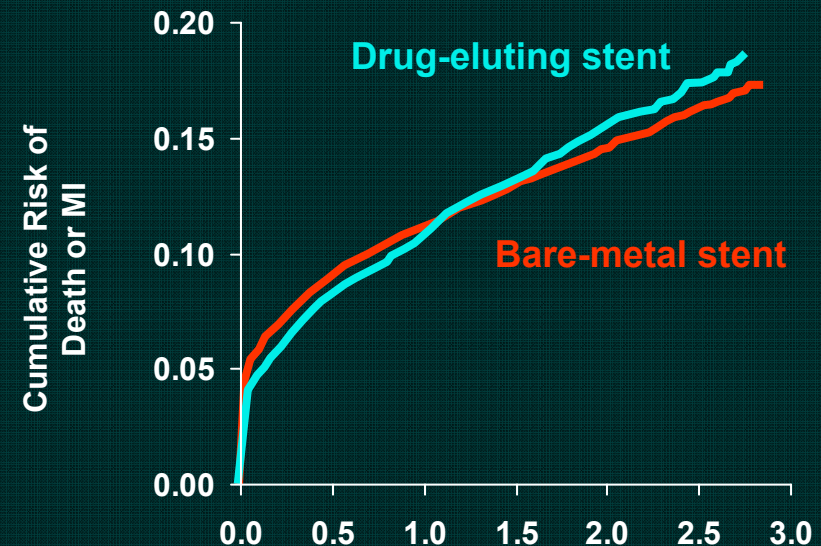
Long-term Outcomes with DES vs. BMS in Sweden

- 6033 pts with DES and 13,735 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

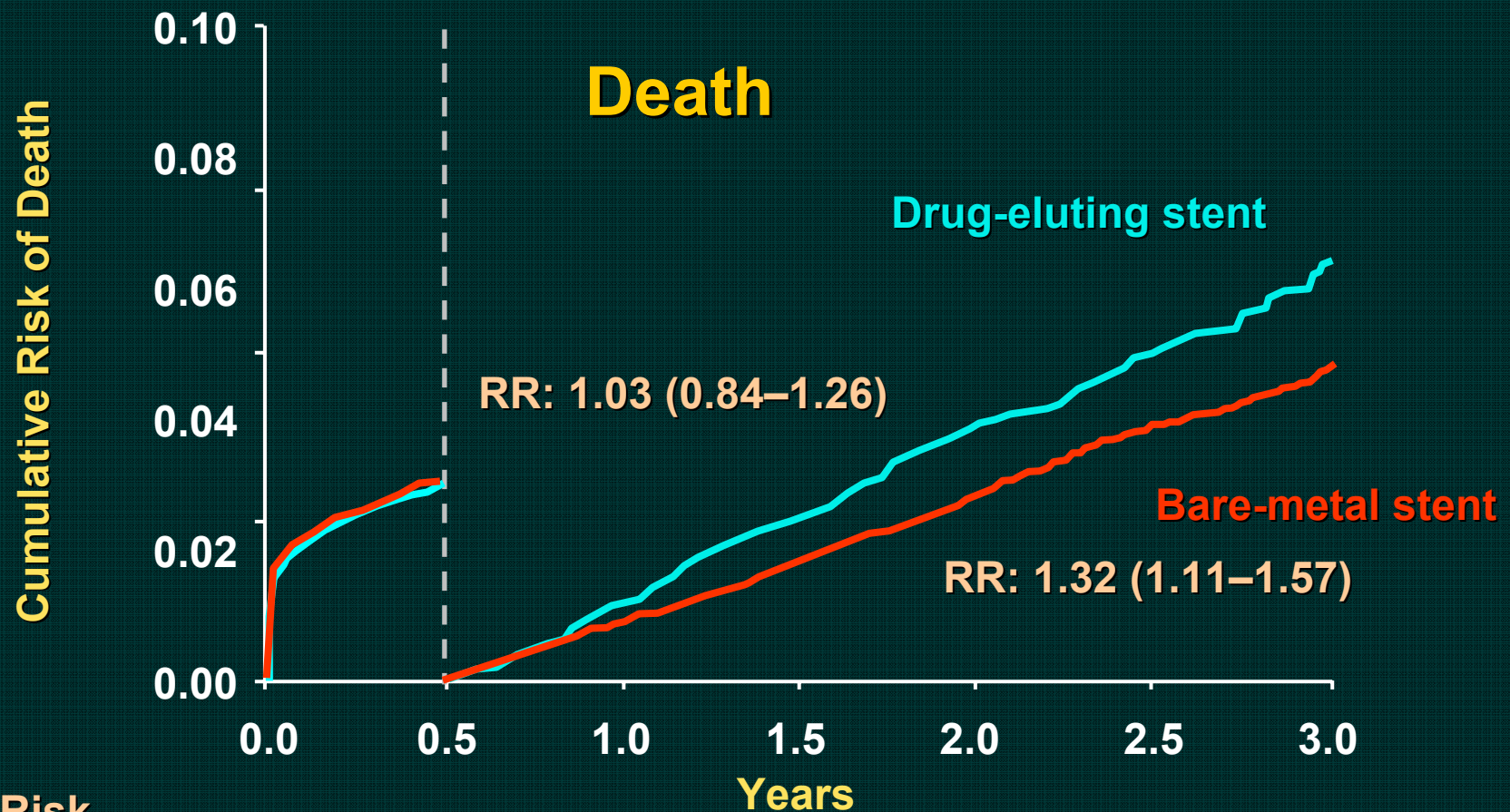


Adjusted Composite Event



SCAAR: Landmark Analysis of ALL Pts

(Propensity Score Adjusted Cumulative Event Rates)



No. at Risk

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



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Lagerqvist B. et al., NEJM 2007; 356:1009-19

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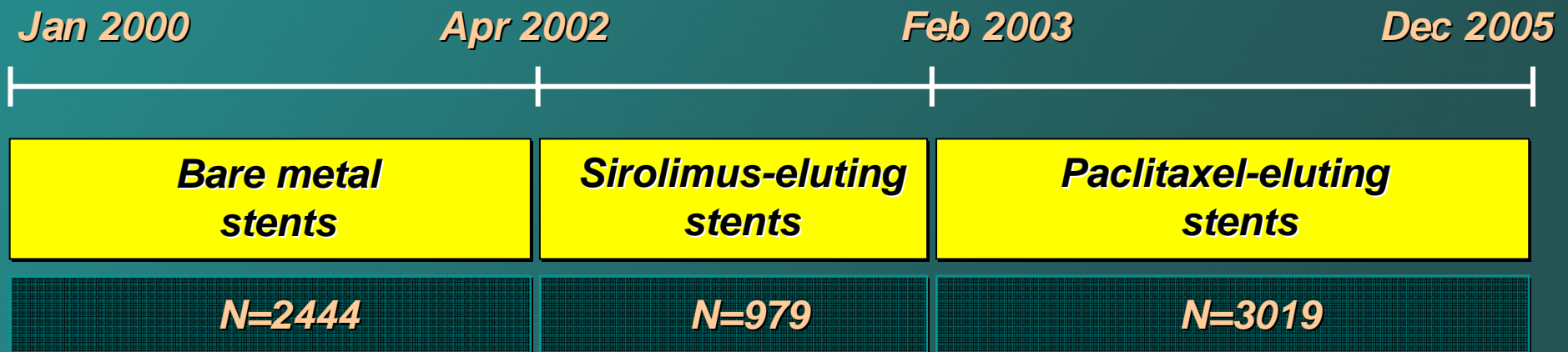
SCAAR: Patient Characteristics and Procedural Factors (ONE STENT)

Differences all highly significant!

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



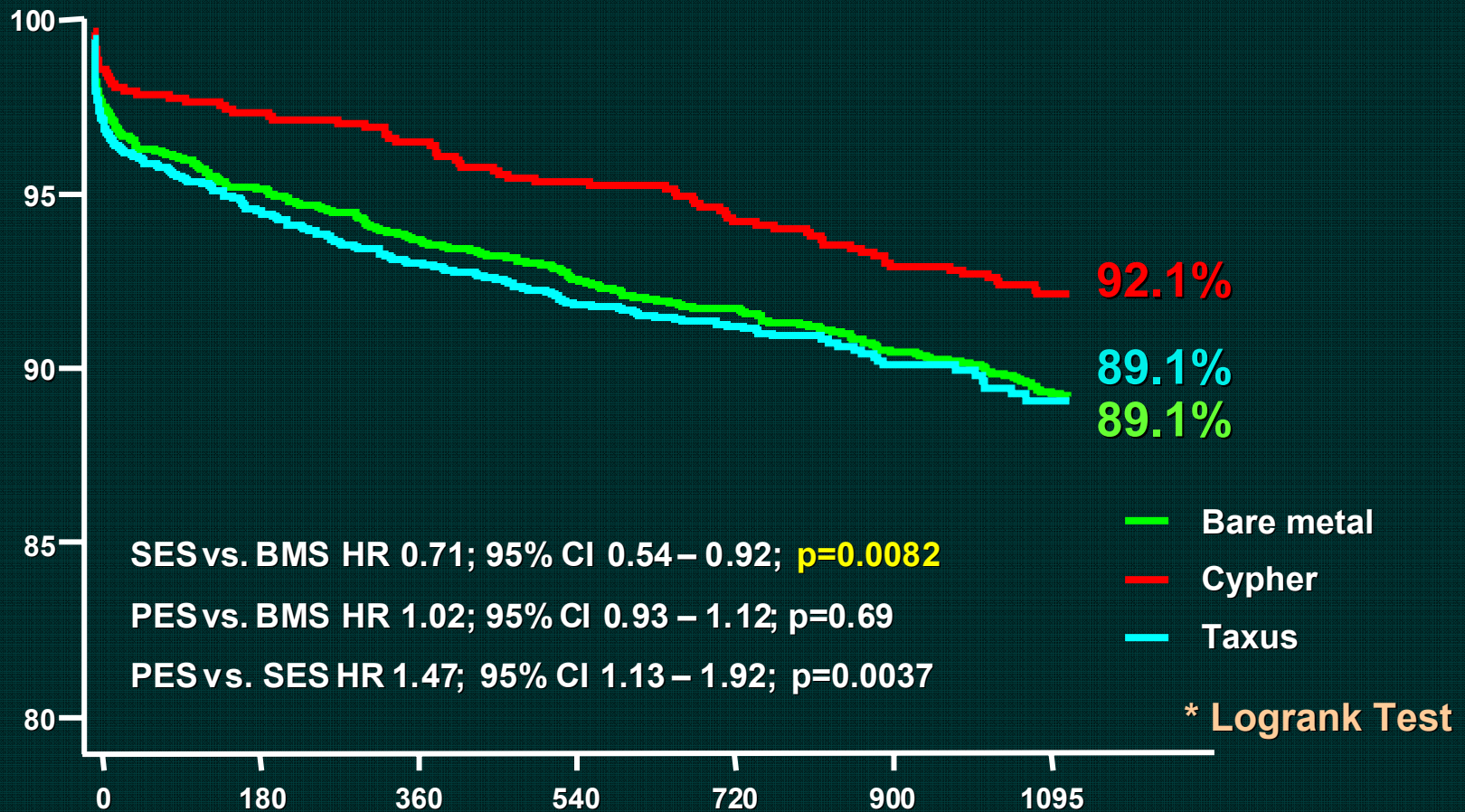
Thoraxcenter Real World Experience



6442 patients
13,150 stents

Serruys PW et al. FDA 12/06

All-cause Mortality at 3 Years

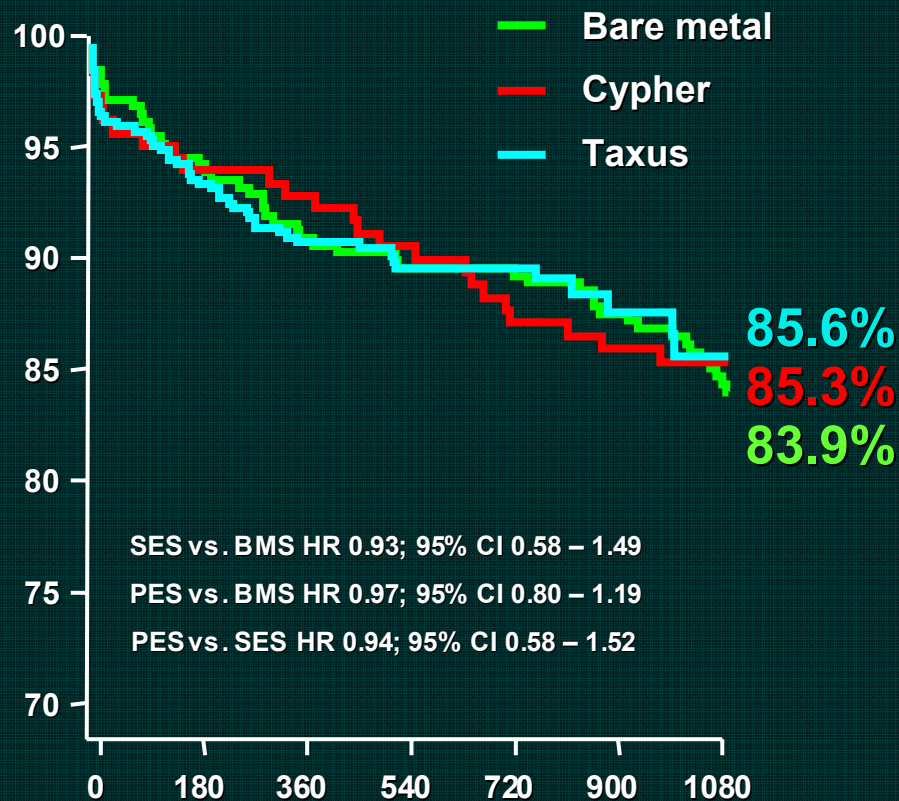


Group	0	30	90	180	360	720	1095
BMS	2287	2211	2195	2170	2126	1990	1862
SES	976	955	951	946	936	888	833
PES	2776	2620	2537	2499	2414	1432	491

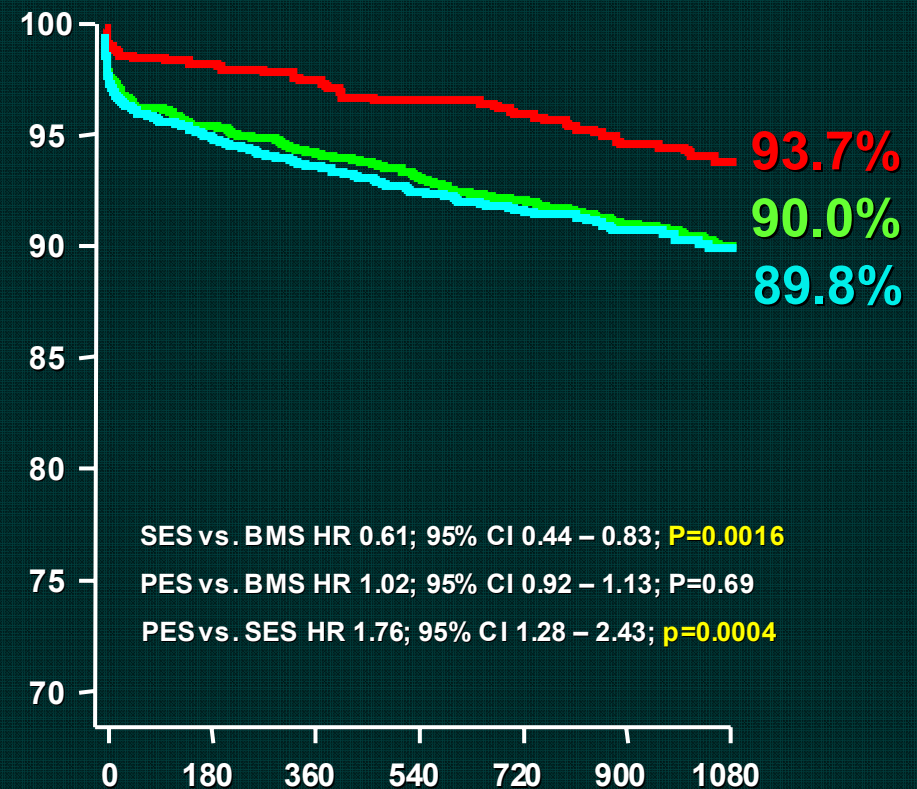


All-cause Mortality at 3 Years

Diabetics



Non-Diabetics



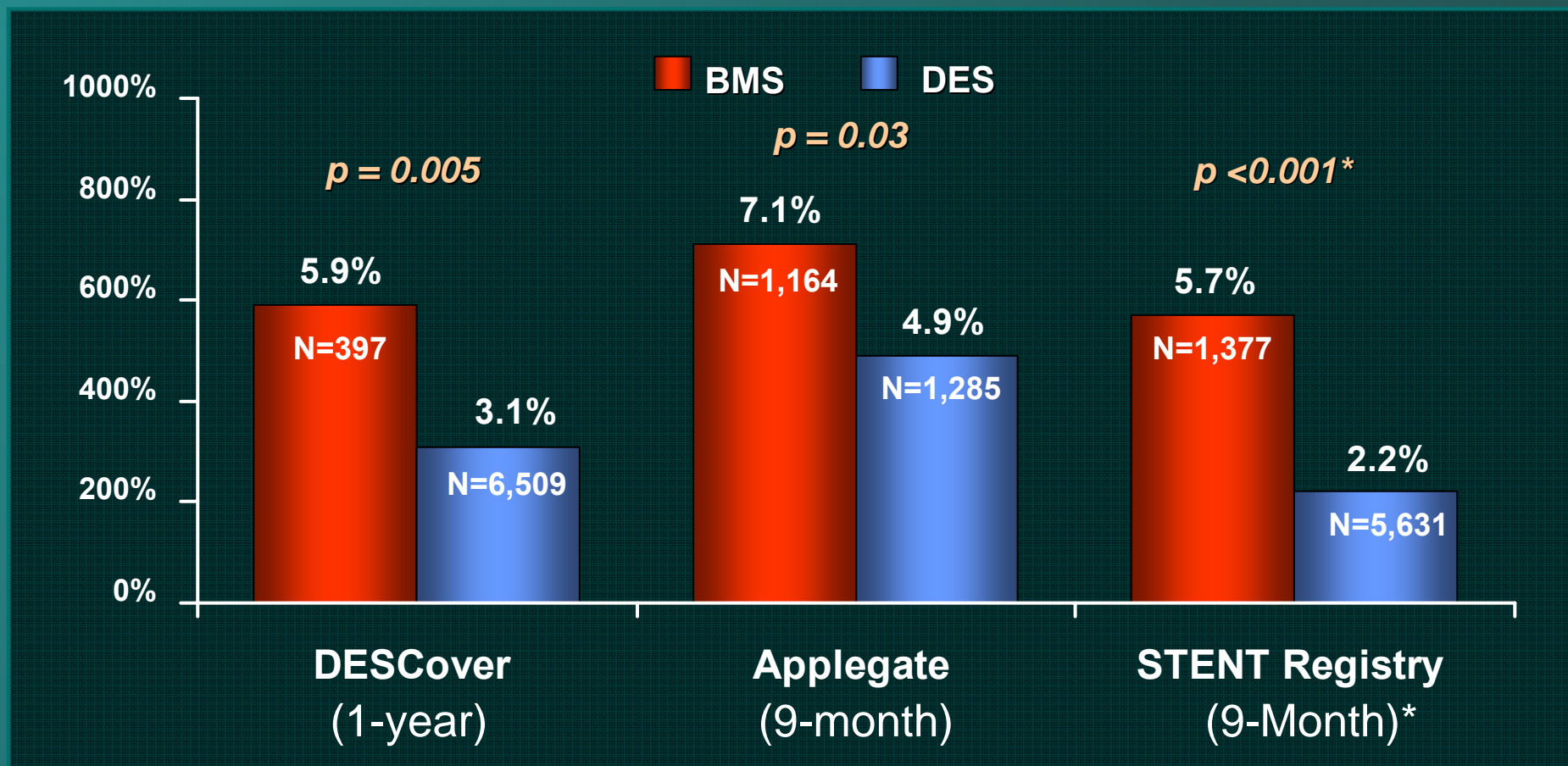
Group	0	180	360	720	1080
BMS	306	288	276	267	237
SES	179	168	165	152	142
PES	484	433	408	258	85

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



Real World Registries: DES vs. BMS

All Cause Mortality Rates (%)



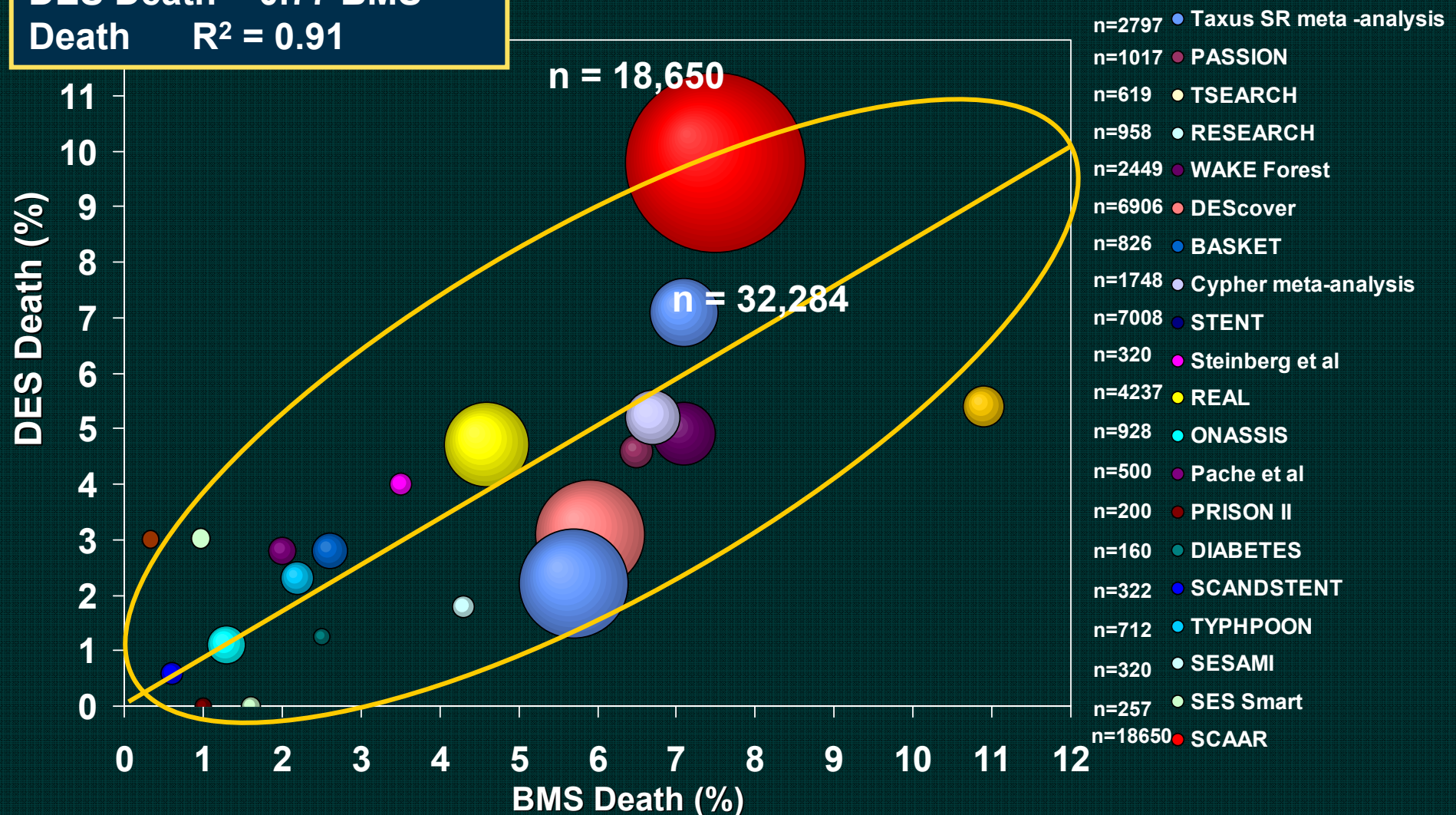
* Adjusted HR = 0.56 (95% CI 0.4,0.8), $p=0.0013$



Strategic Transcatheter Evaluation of New Therapies

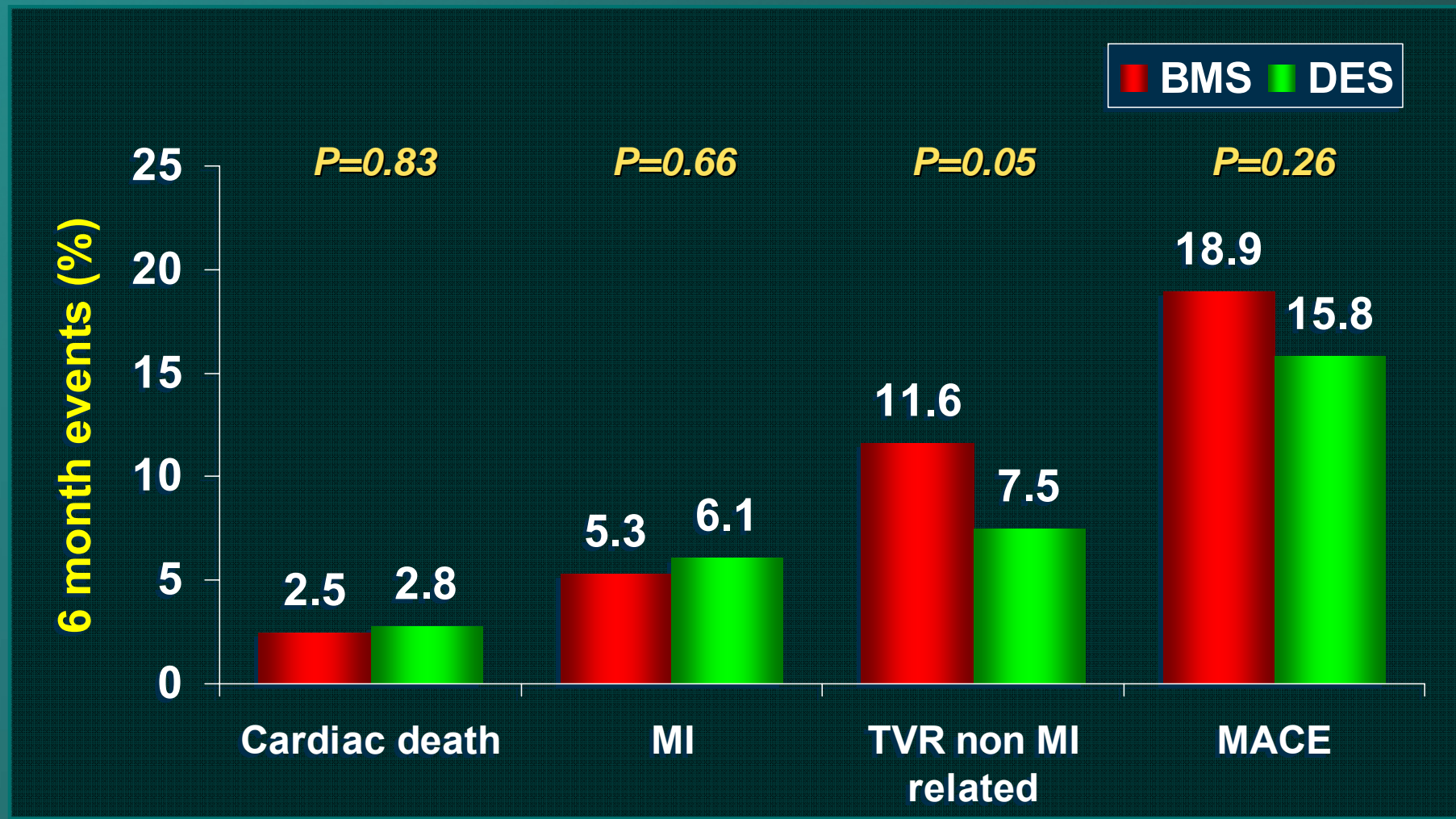
Patient-Year Weighted Regression for DES vs BMS Mortality

DES Death = 0.77 BMS
Death $R^2 = 0.91$



BASKET Trial: 18 Month MACE

N=836 (All pts with 18 month FU)



FDA DES Panel Meeting

Consensus Observations

➤ ***Duration of dual anti-platelet therapy should extend beyond the present product labels***

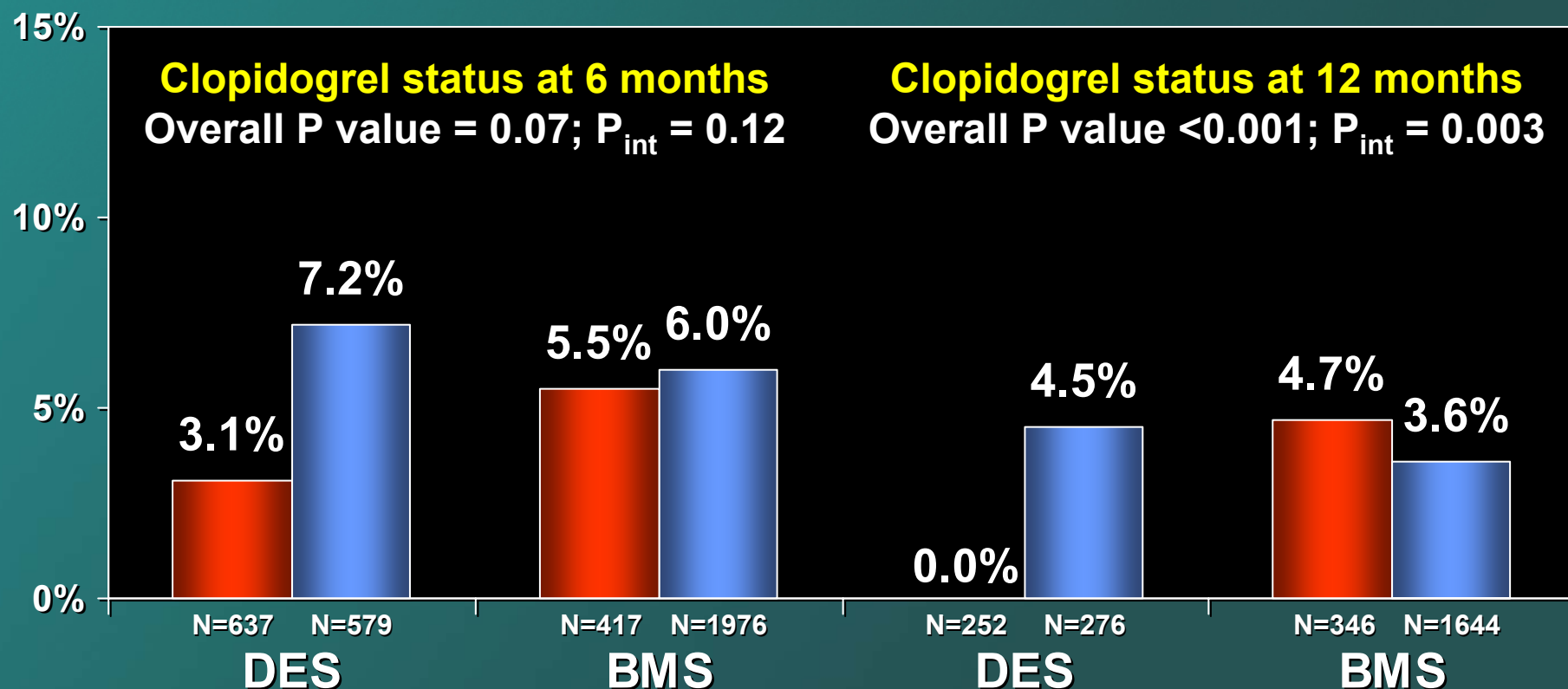
- One year is reasonable compromise (esp. for “off-label” DES use)
- Must balance against the increased risk of bleeding with dual anti-platelet therapy
- Additional studies immediately required to better clarify optimal anti-platelet therapy



Duke Database Death/MI Analysis

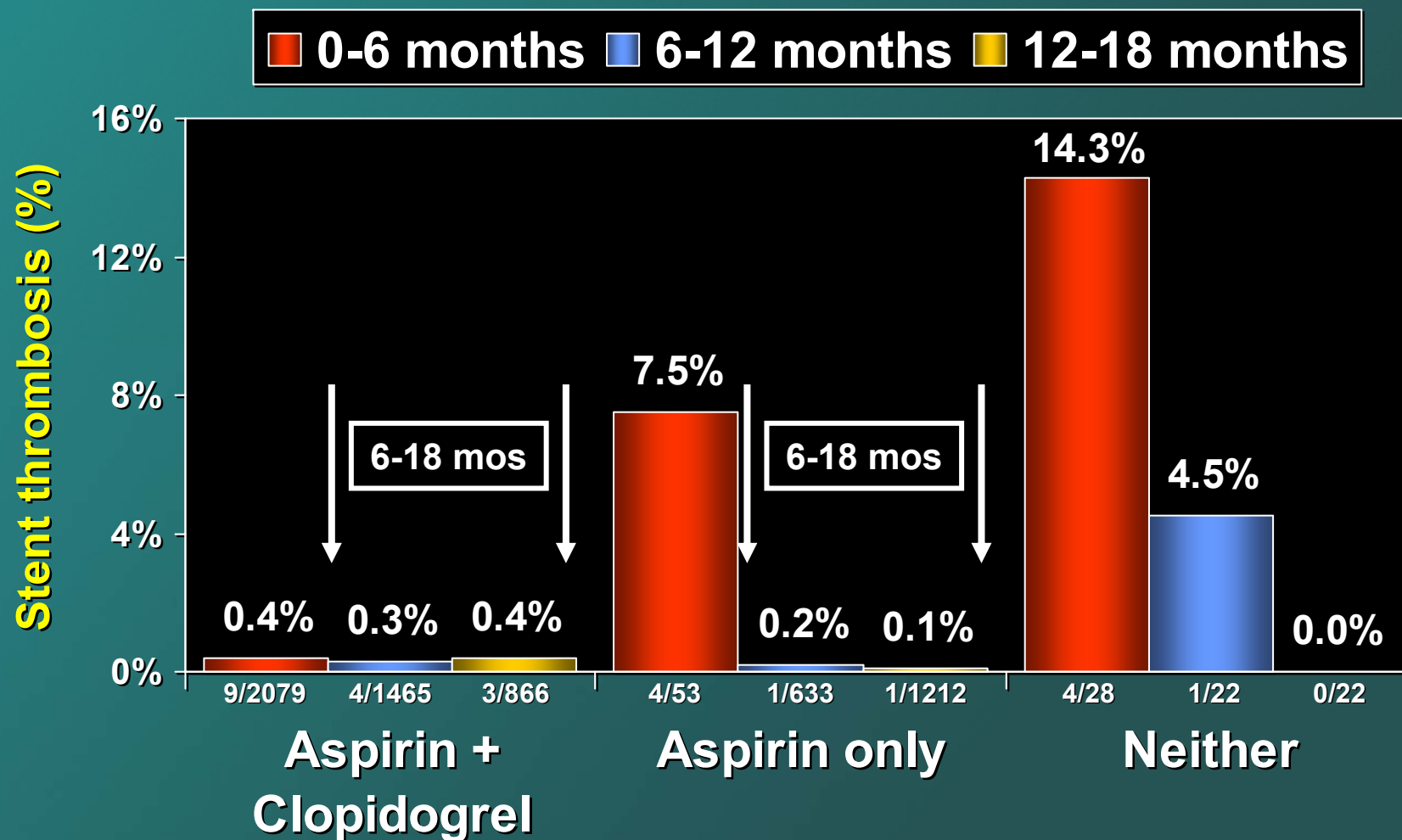
**Adjusted death/MI rates at 24 months
in patients without events at 6 months**

■ On clopidogrel ■ Off clopidogrel



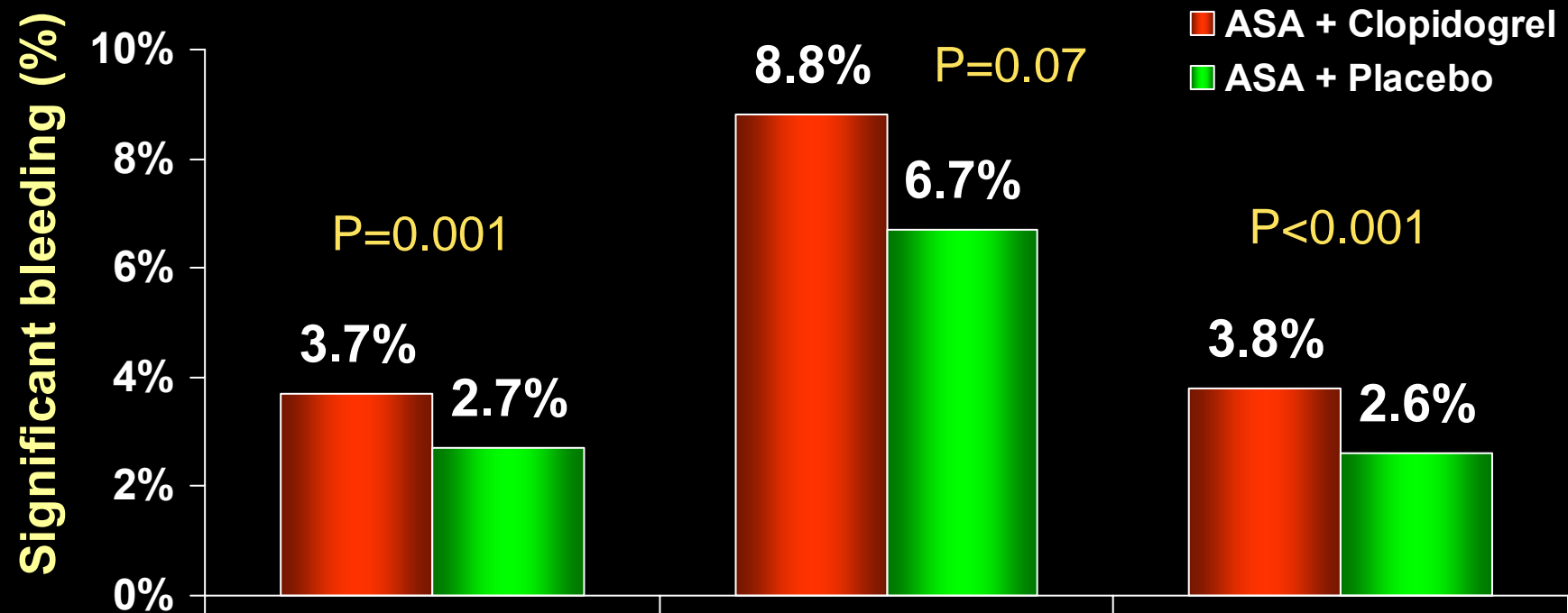
Milan Stent Thrombosis Experience

2,160 consecutive pts with DES implanted



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

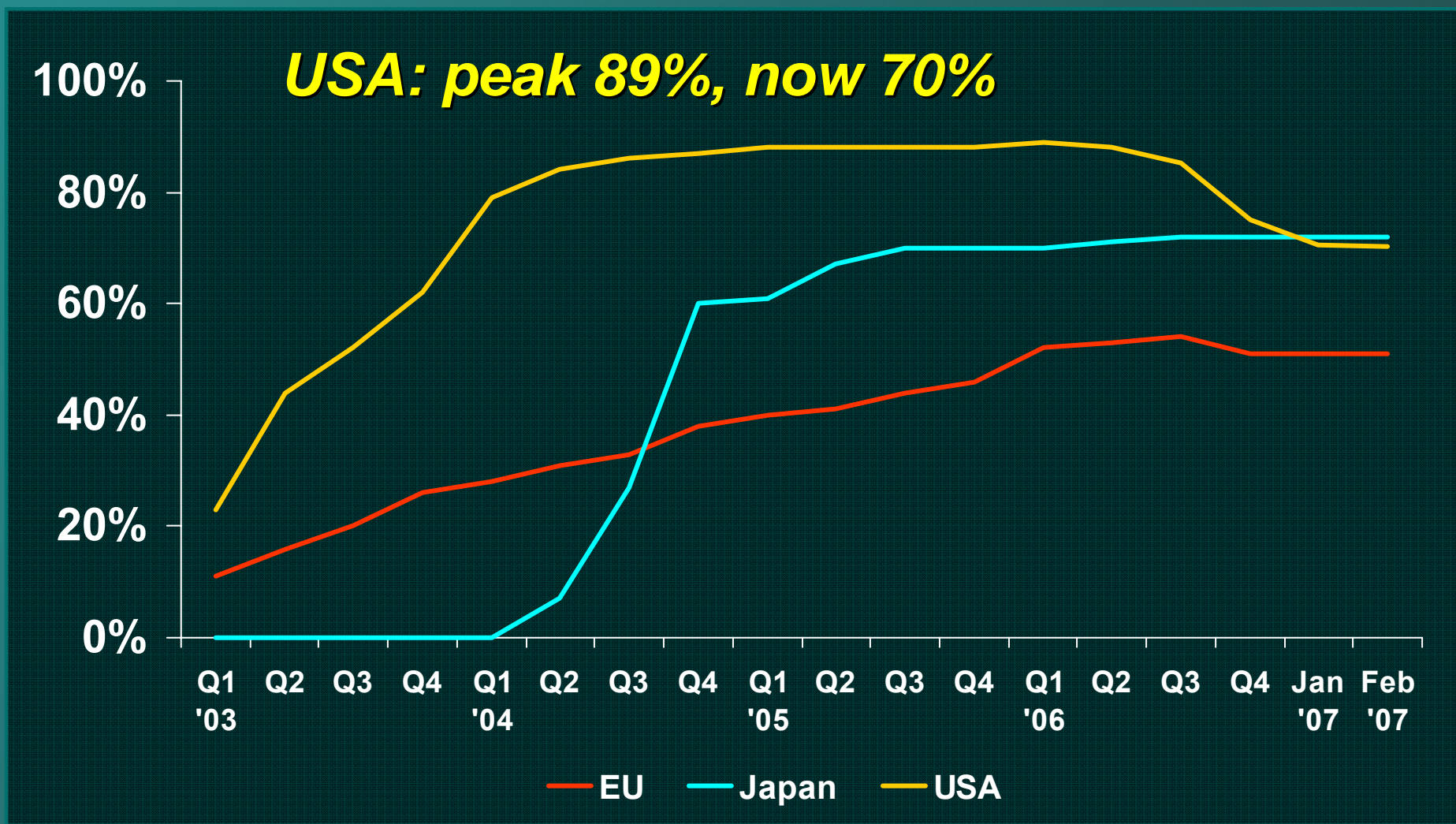
- At \$4 per day, Clopidogrel costs ~\$1500 per year
- As many as 1 million U.S. patients per year receive DES ⇒
- **One year of Clopidogrel would cost ~\$1.5B**
- For 4 million U.S. patients with DES implanted ⇒
- **One year of Clopidogrel would cost ~\$6.0B**



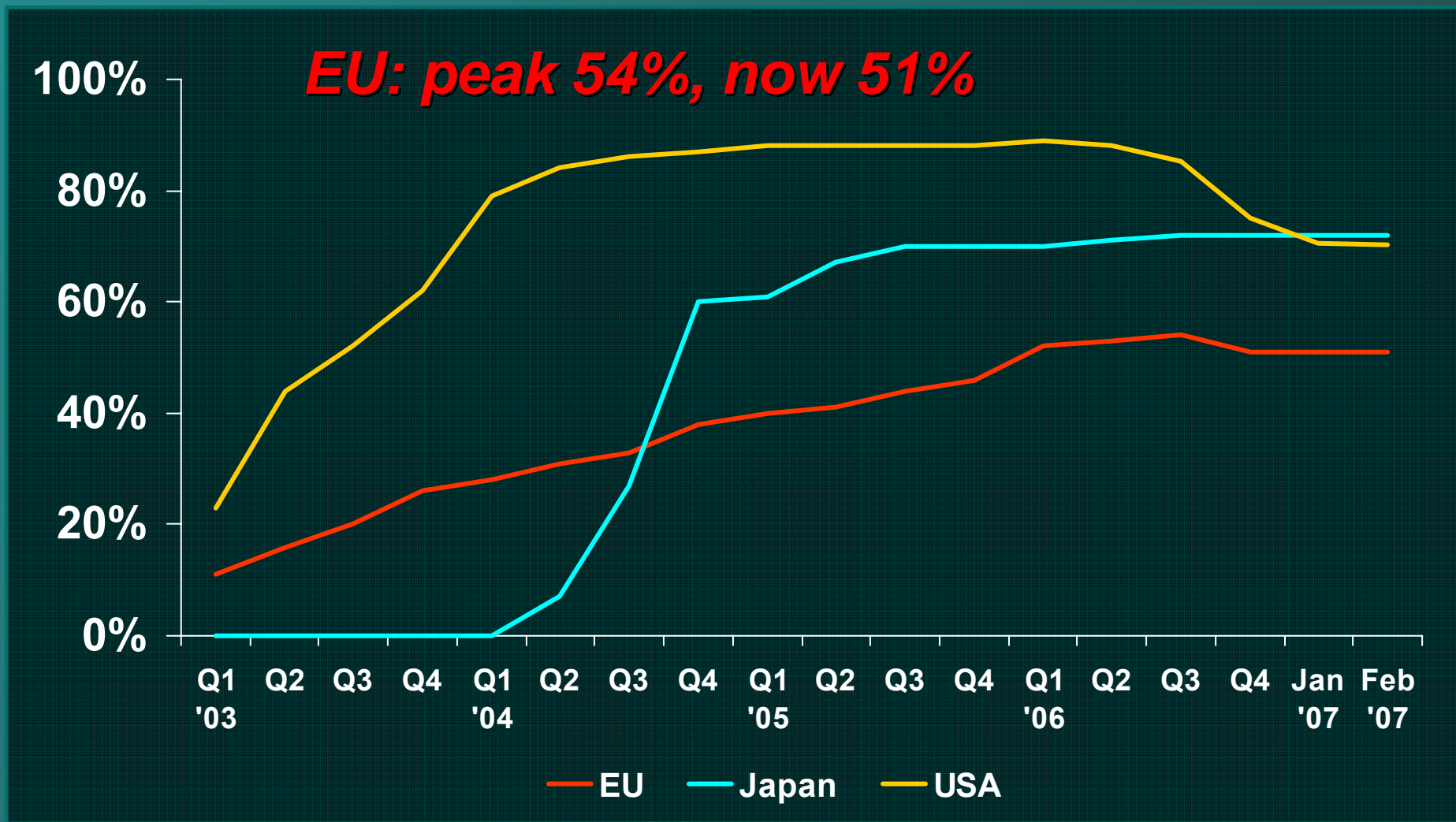
What is the impact on Clinical practice?

- **Reduced DES use**
- **Prolonged dual AP therapy**
- **Increased regulatory hurdles for new DES systems (U.S.)**
- **Search for a safer DES!!!**

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

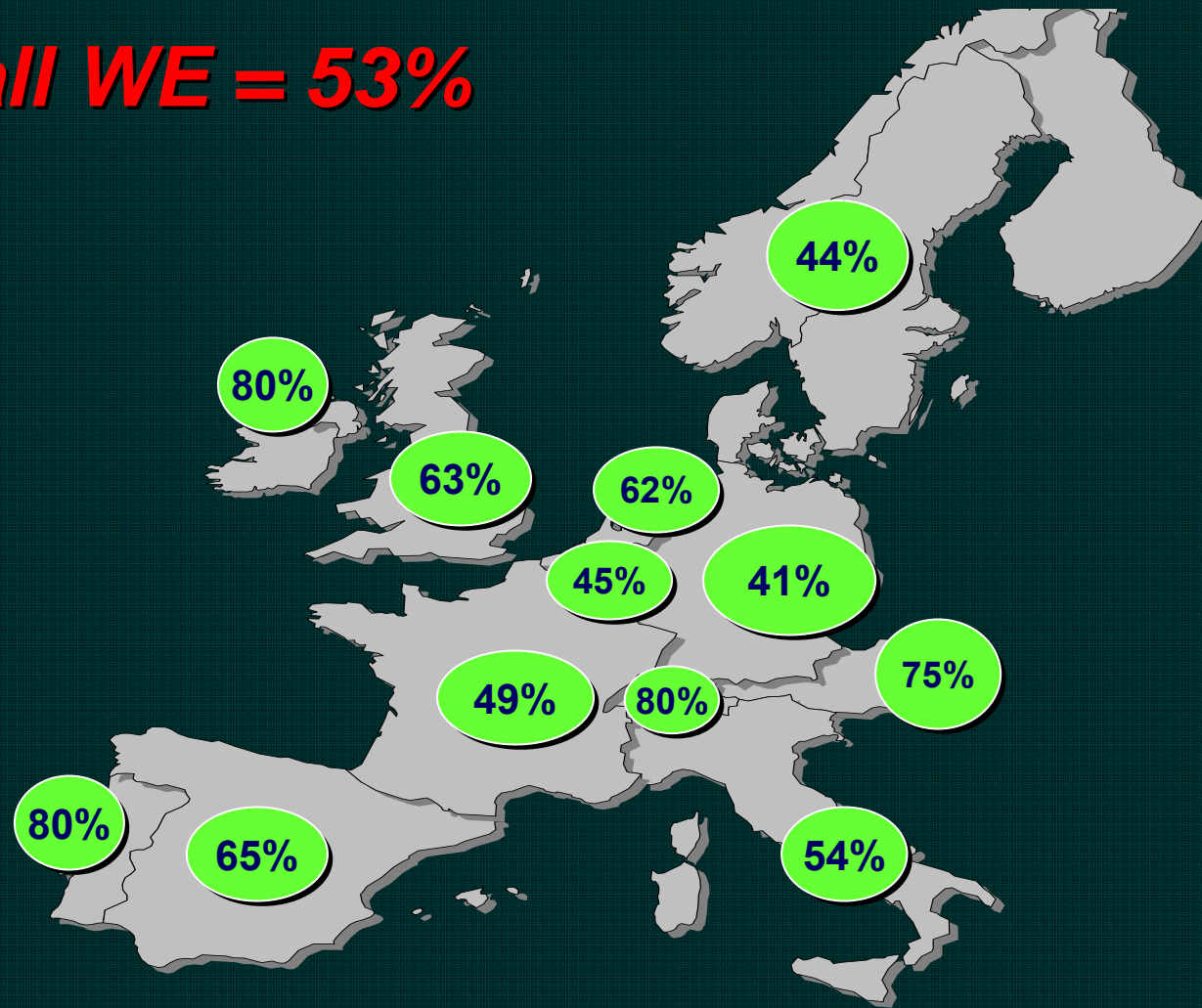


World-wide DES Penetration (USA, EU, and Japan)

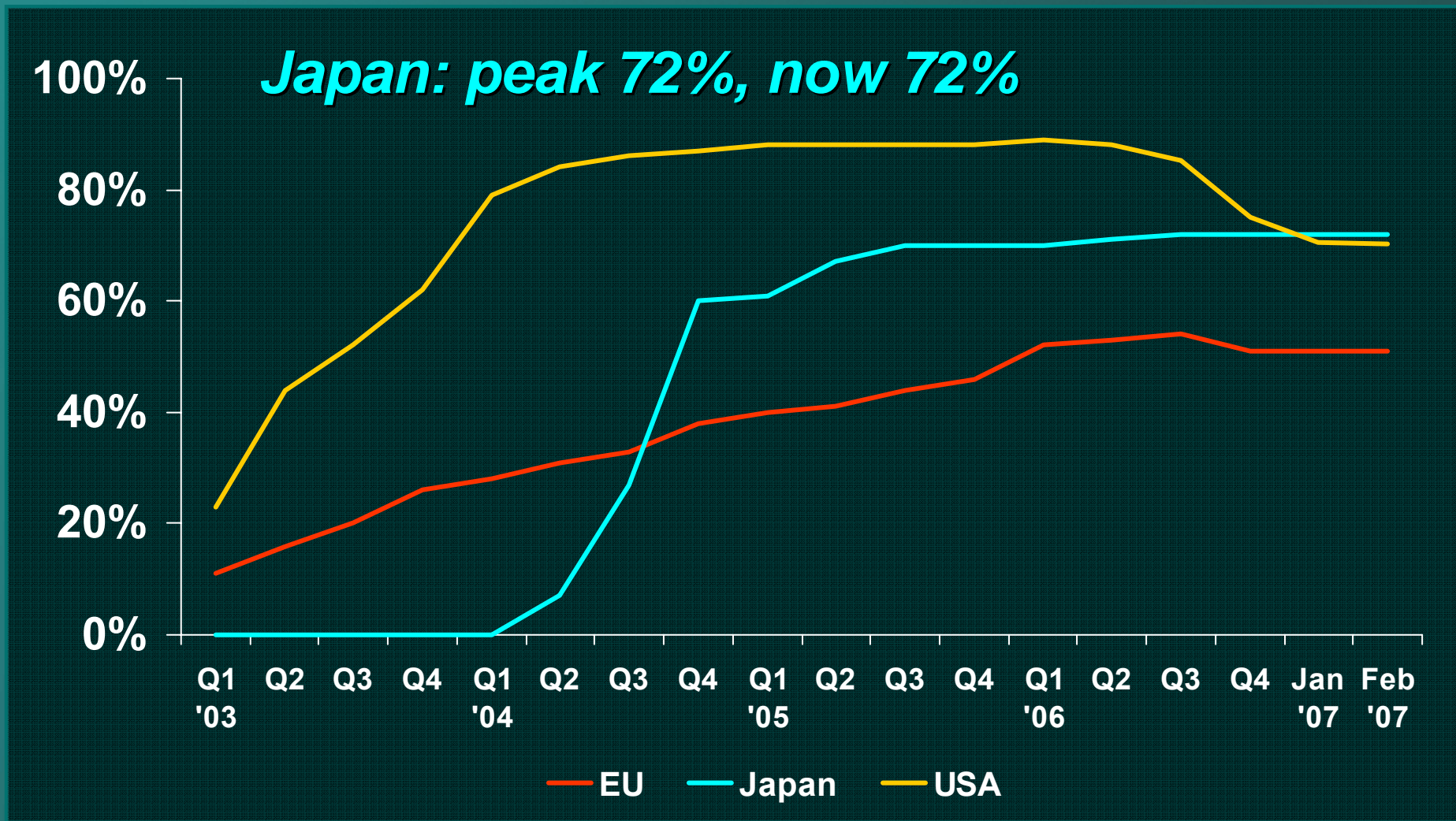


DES Penetration in Western Europe (November, 2006)

Overall WE = 53%



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



We need a safer DES!

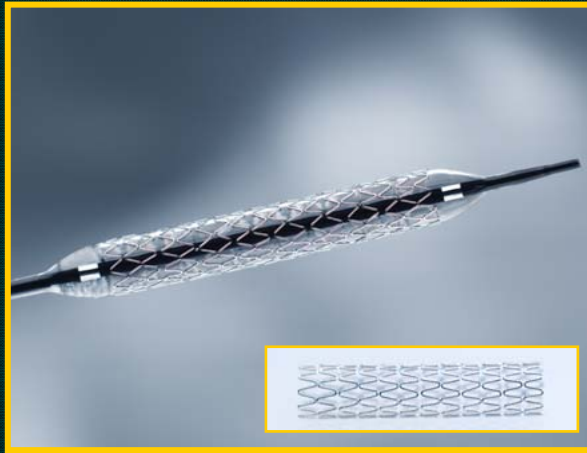
"I gotta have
my Plavix"



Endeavor DES System

Key Components

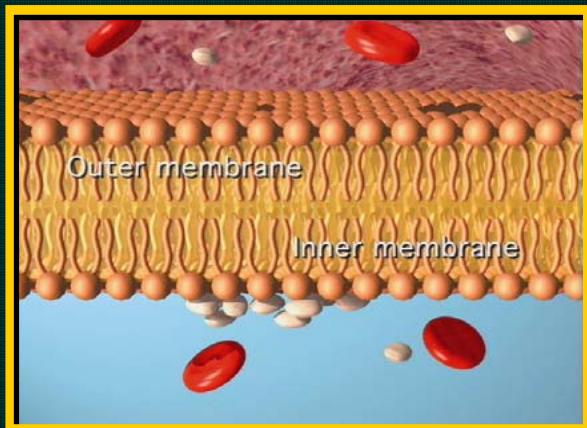
Driver Cobalt Alloy Stent



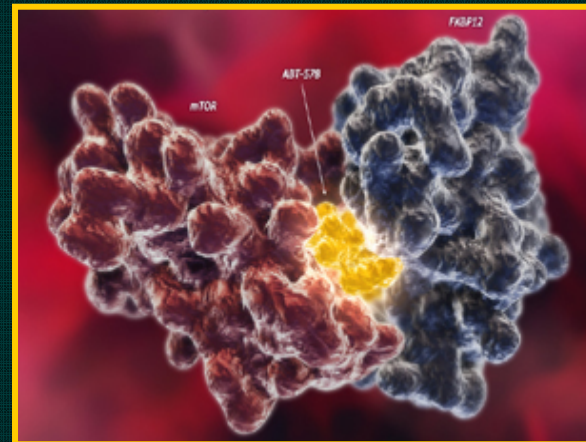
Stent Delivery System



PC Technology

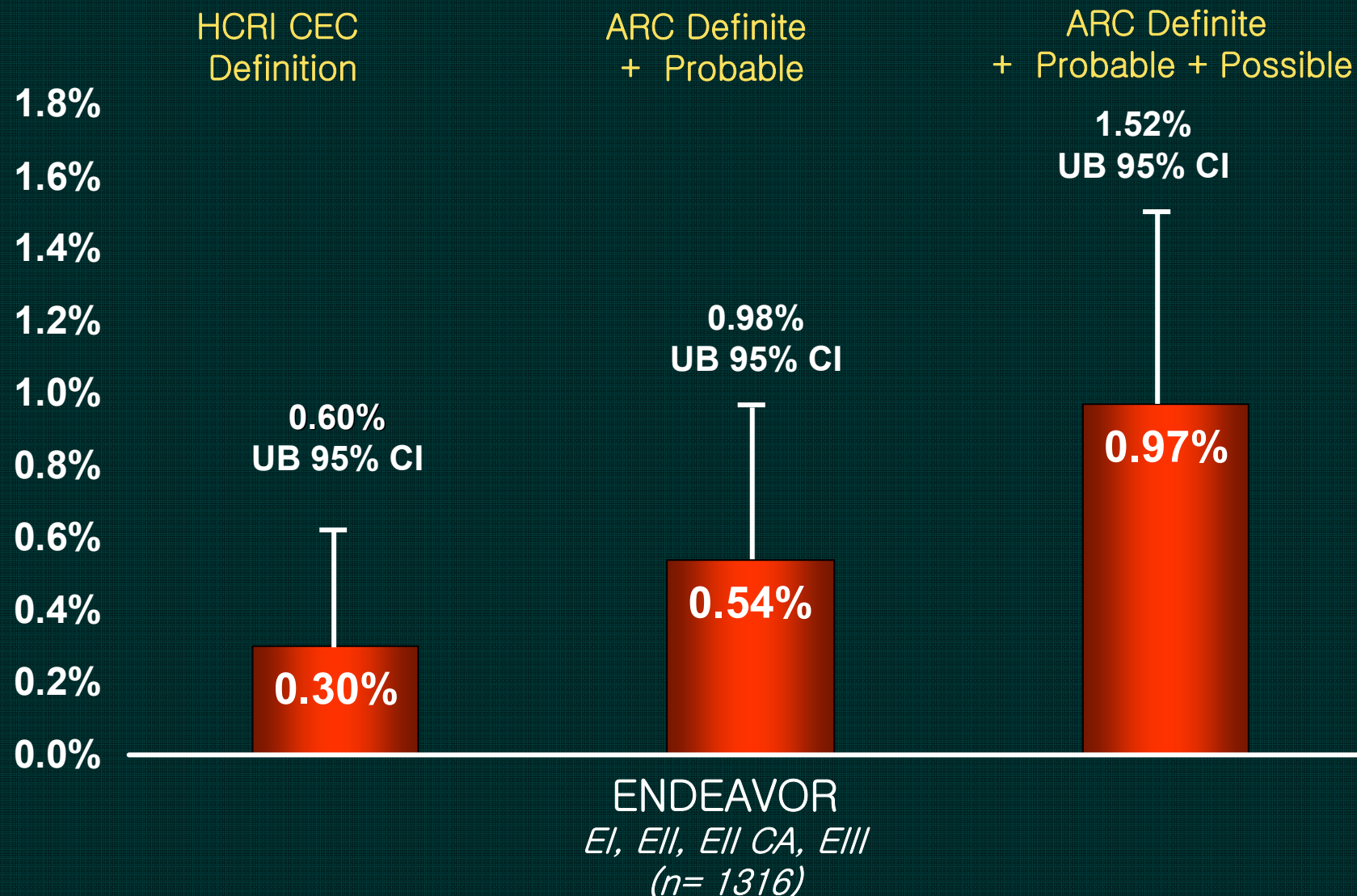


Drug: Zotarolimus



Endeavor Safety Analysis

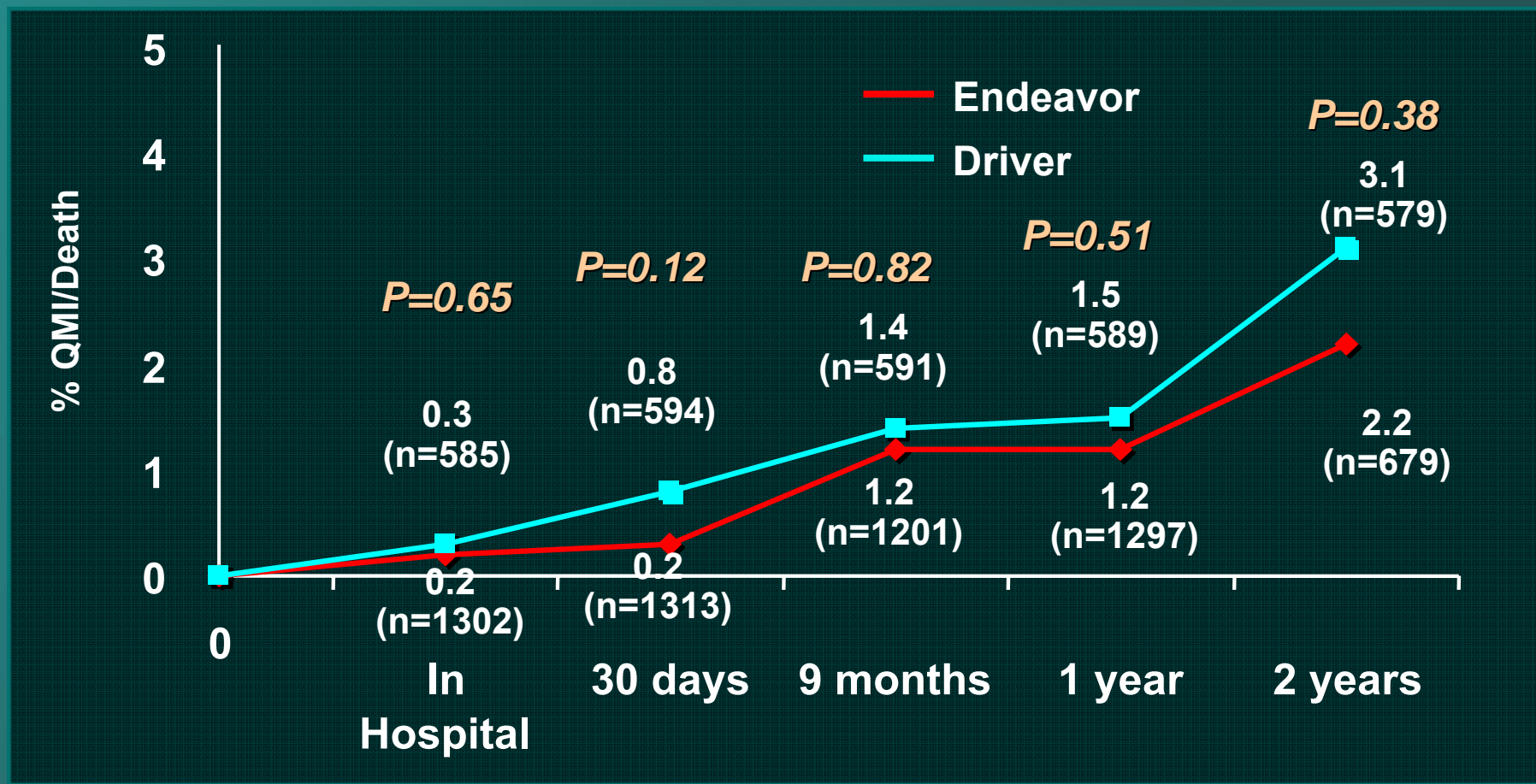
HCRI CEC and ARC Definitions 3yr K-M estimate



Endeavor Safety Analysis

Composite of Death and QMI

El, ElI, ElI CA, and ElII vs. ElI Driver



Endeavor Safety Analysis

IVUS Late Acquired Incomplete Apposition (IVUS core lab)

8 Month Results	EI* n=86	EII n=114	EIICA n=48	EIII n=190	Combined N=438
Late Incomplete Apposition (%)	0	0	0	0.5 (1) [†]	0.2 (1)

* EI results at 12 months

† Thrombus at baseline resolved during follow-up. No aneurysmal remodeling

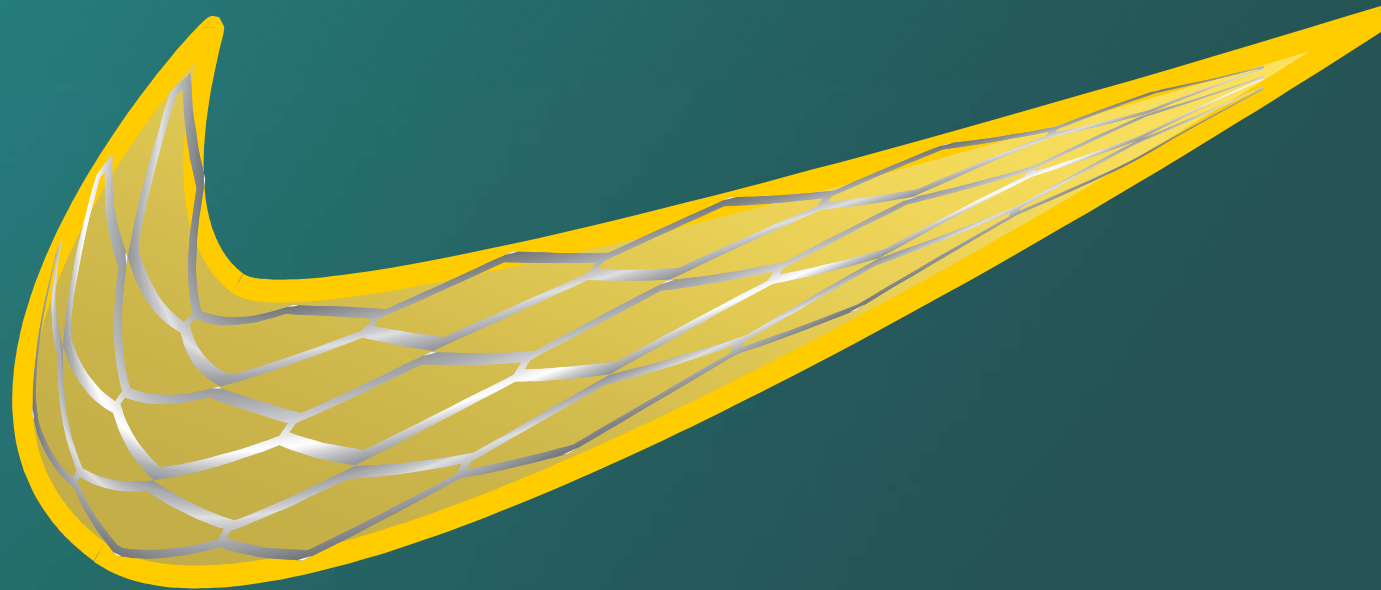


ENDEAVOR is a safer DES!



Intervention 2007

Just Do the “Right” Thing!



COLUMBIA UNIVERSITY
MEDICAL CENTER

CARDIOVASCULAR
RESEARCH FOUNDATION®



DES Use - 2007

Just do the “right” thing!

➤ ***Assess patient and lesion characteristics to establish restenosis risk profile***

- **Determine relative value of DES vs. BMS in every patient (no more “unrestricted” use)**
- **Consider both on-label and off-label situations (ironically, off-label use scenarios may be more compelling)**
- **Increased restenosis risk = favor DES**
- **Increased safety concerns = favor No DES**



DES Use - 2007

Just do the “right” thing!

- *Assess patient factors which may preclude long-term (at least one year) dual AP therapy*
 - Planned or possible intercurrent surgery
 - Bleeding Hx or tendencies
 - Other concomitant medications (e.g. coumadin)
 - Socio-economic factors which may affect Plavix compliance



DES Use - 2007

Just do the “right” thing!

➤ ***Consider alternatives to DES, if risk-benefit assessments prove unfavorable***

- CABG – unprotected LM disease, complex MVD (esp. diabetics), recurrent ISR (esp. VBT)
- BMS – Plavix dependence concerns, large (>4mm diameter) vessels, ? AMI pts, ? low restenosis risk lesions
- Balloon PCI – sidebranch in bifurcations (provisional stent only), small vessels in distal locations



DES Use - 2007

Just do the “right” thing!

➤ *Optimize DES implantation techniques*

- Adequate lesion preparation (pre-dilatation)
- High pressure implantation methodologies (like previous BMS strategies)
- Avoid undersizing and inflow/outflow obstruction (mod stenoses or dissections)
- Implant stent edges into normal reference segments
- Consider IVUS guidance (esp. LAD)



DES Use - 2007

Just do the “right” thing!

➤ ***Careful explanations and open communication with patients and families***

- **Careful pre-treatment history**
- **Discussion with EVERY pt re: risks and benefits of DES vs. alternative therapies**
- **Ongoing (post-Rx) communication and careful FU re: dual AP compliance (instructions = NO Plavix discontinuation without MD approval)!**



Life is a Matter of “Balance”

The Scale Favors DES!

