

**Perspectives on Drug-eluting  
Stent Safety and Efficacy  
with Regulatory Recommendations**

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# Conflict of interest disclosure

- **Consultant to and lecture fees: Boston Scientific, Abbott Vascular, BMS Imaging**
- **Equity: Devax, Xtent**
- **Board of directors: Devax**



# Overview

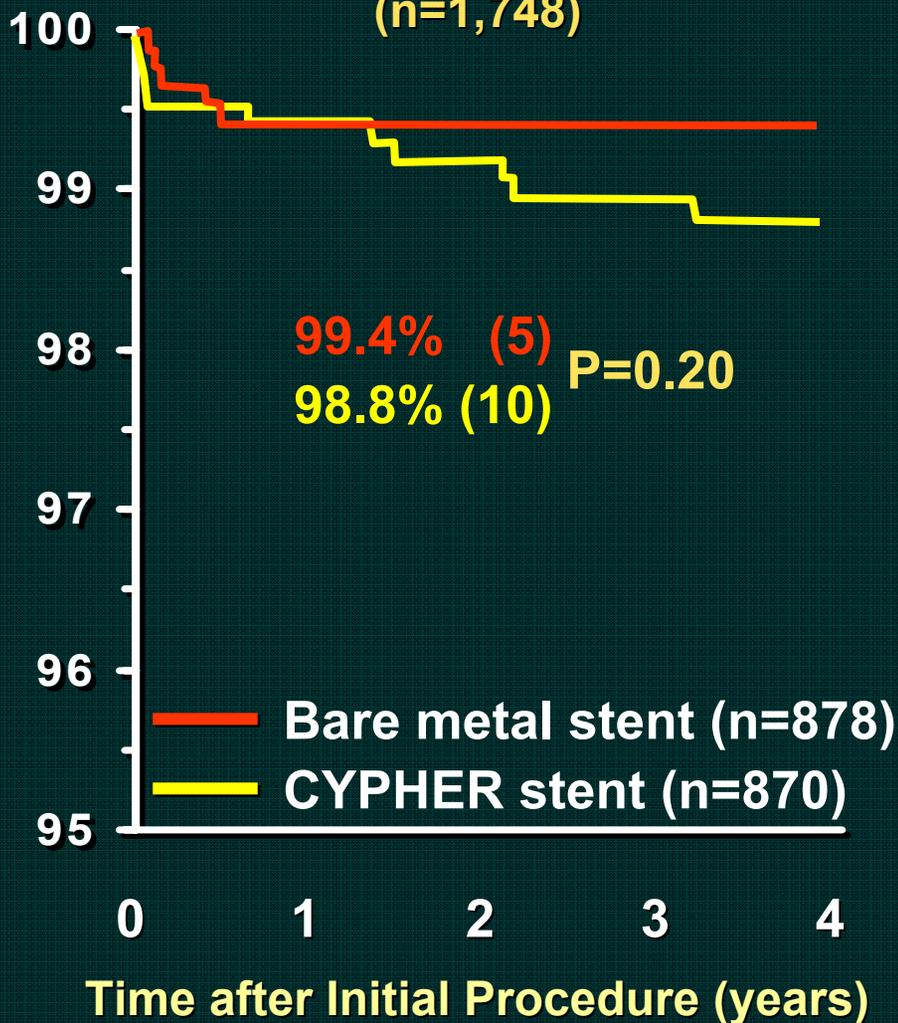
- **Drug-eluting stents markedly reduce clinical and angiographic restenosis compared to BMS**
  - **⇒ decreased recurrent ischemia requiring repeat hospitalization and revascularization procedures, (including CABG) and improved quality of life**
- **Safety concerns have arisen from reports of late stent thrombosis, and increased composite death and Q-wave MI rates**
- **Most studies have been inconclusive due to insufficient sample size, use of historical controls, limited follow-up duration or lack of access to original source data (requiring use of partial published data, abstracts and internet sources)**

# DES RCTs: Methodology

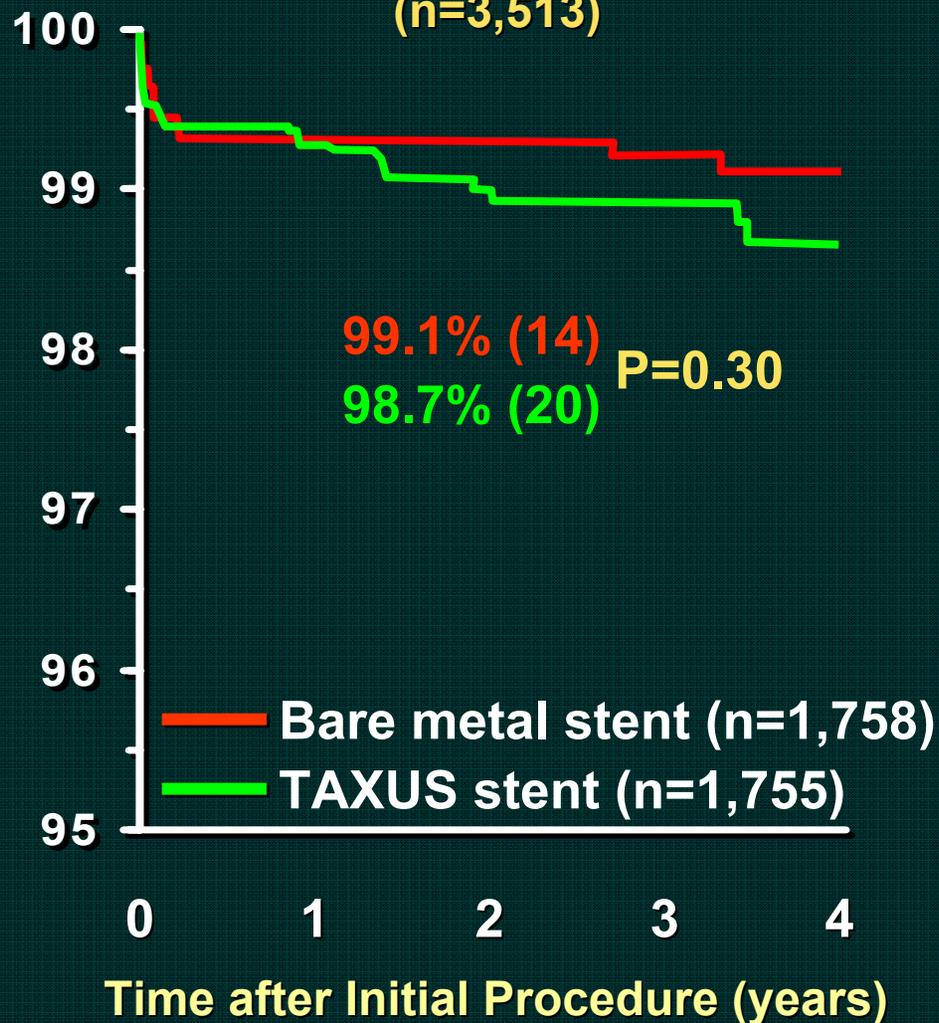
- Clinical trial databases (n=9) were obtained from Cordis and BSC by the Cardiovascular Research Foundation with permission for unrestricted academic analyses (Stone, Leon, Mehran, Kirtane and Pocock), performed by a CRF academic statistician (Martin Fahy)
  - RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS, TAXUS I, II, IV, V, VI
- Pre-specified analysis plan prior to data review
  - Intention to treat – no patients censored at baseline
  - Variables
    - Safety: death (all, cardiac and non-cardiac), MI (all, Q-wave and non Q-wave), death and MI, cardiac death and MI, death and Q-wave MI, stent thrombosis (protocol defined)
    - Efficacy: TLR and TVR
    - Note – no MACE/TVF composites
  - Time intervals: Latest FU (4 years), 0 - 30 days, ≥30 days, 30 days - 1 year, and ≥1 year to 4 years
  - Kaplan-Meier analysis to maximally utilize all available FU information, with log-rank or exact log-rank analysis

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

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

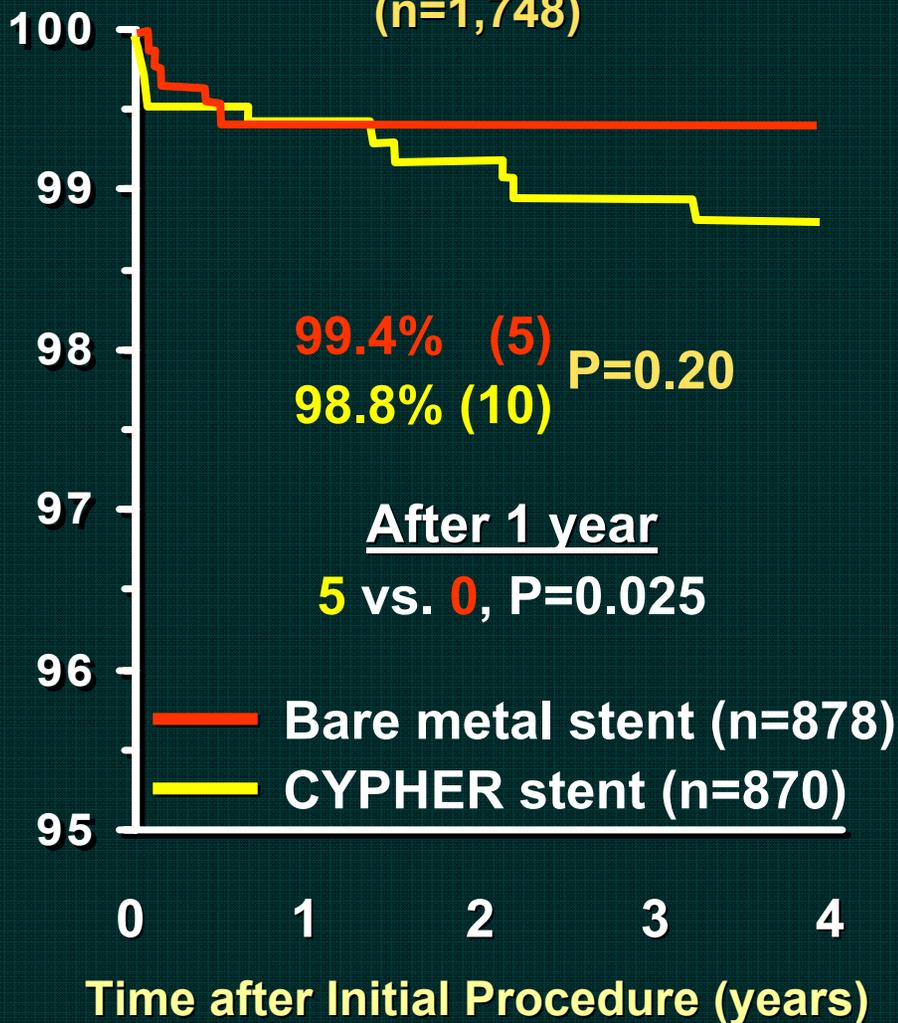


**TAXUS I, II, IV, V, VI**  
(n=3,513)

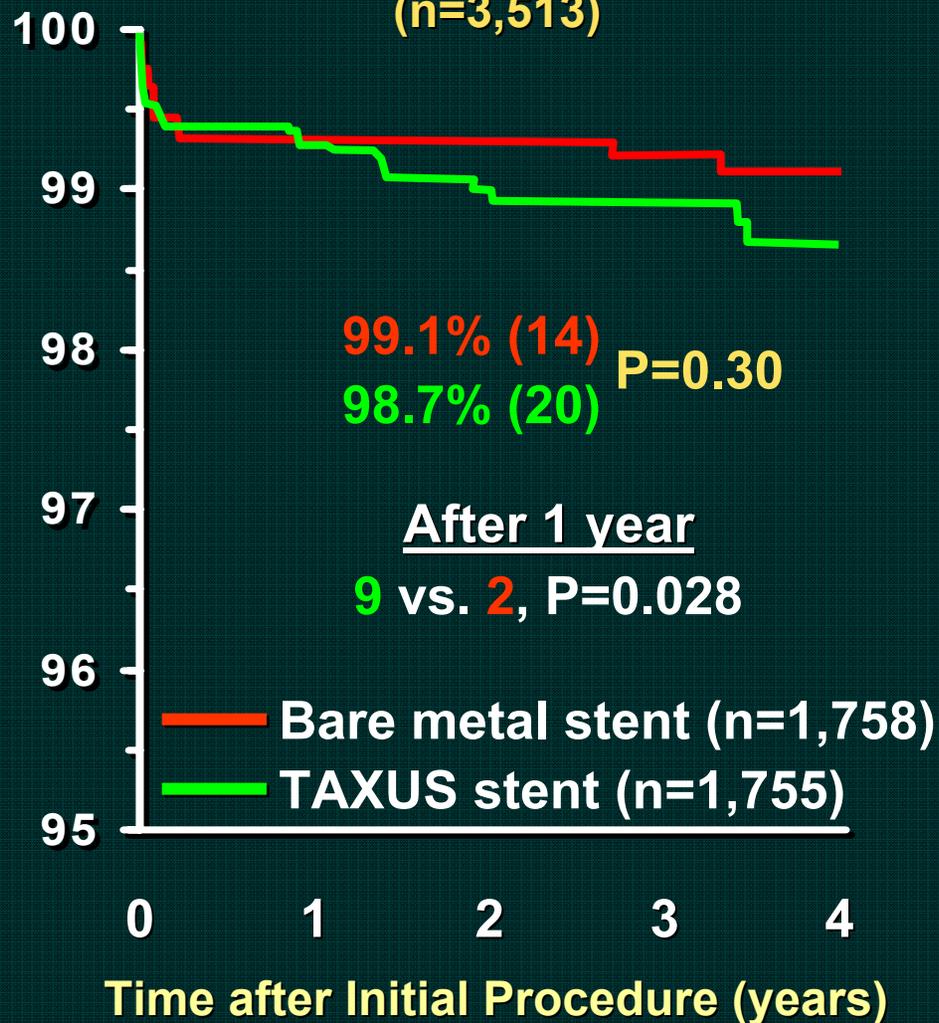


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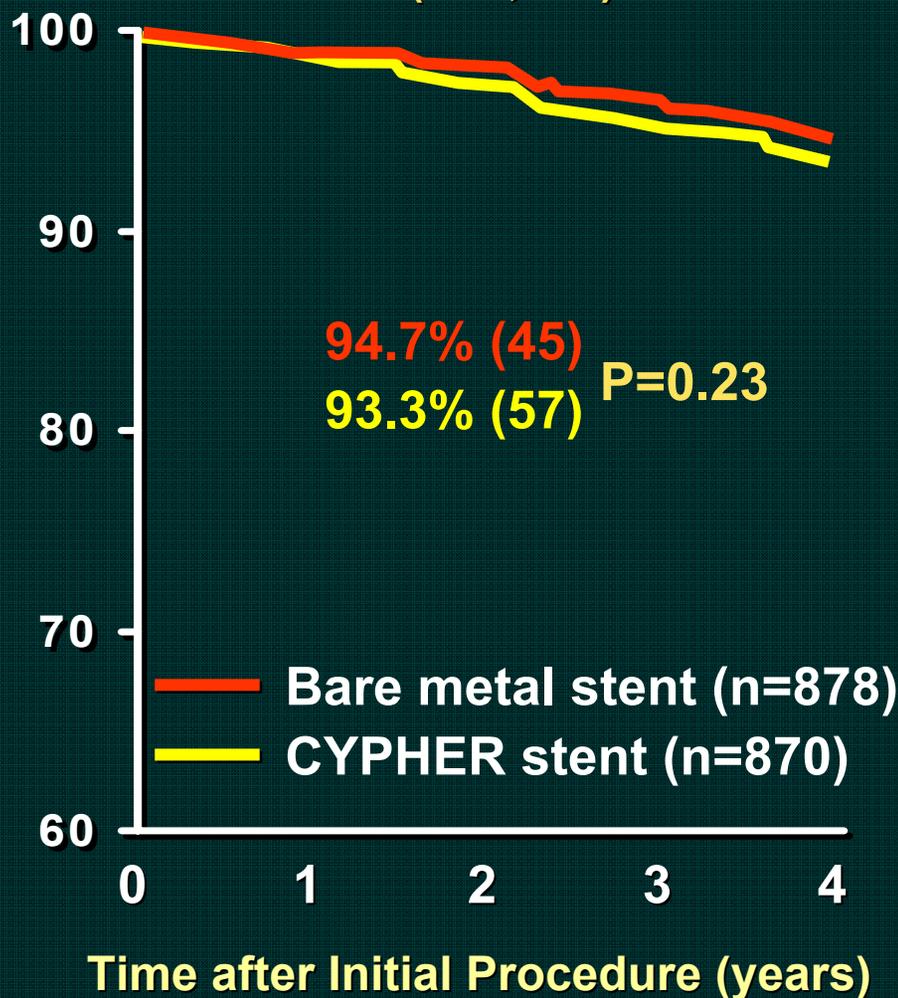


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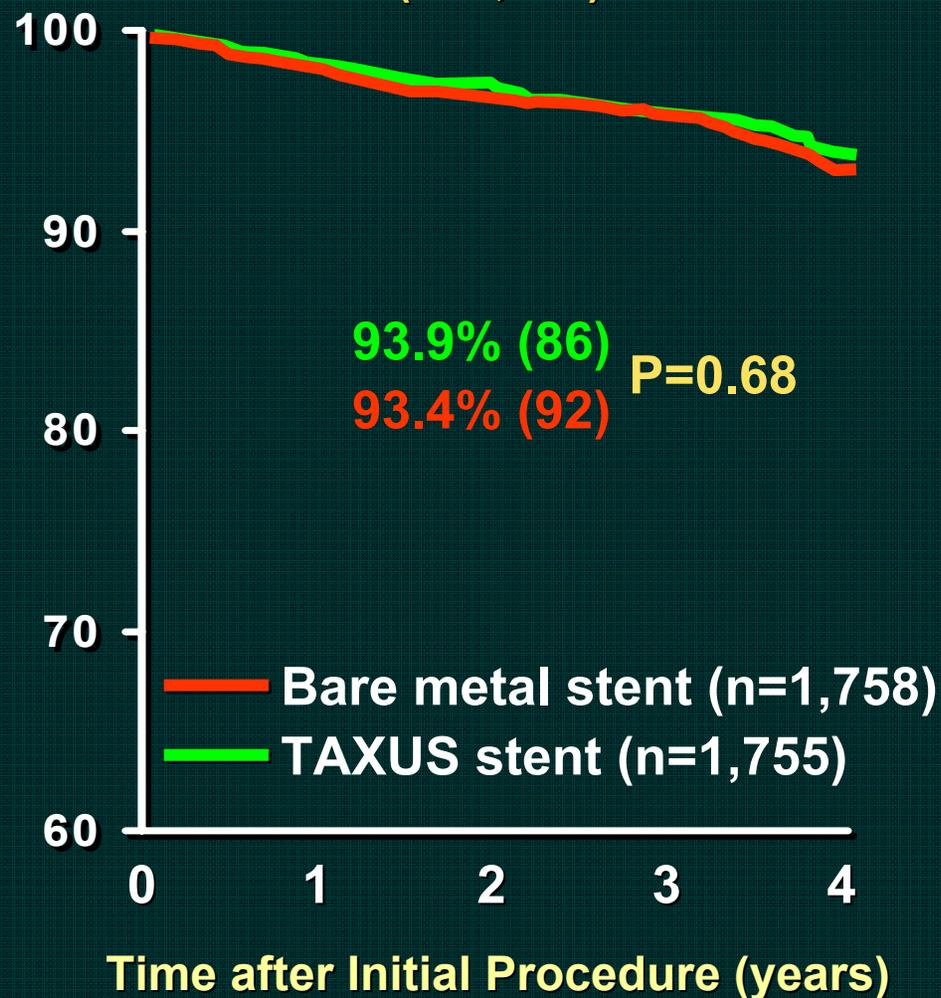


# 9 Prospective, Double-Blind, Randomized Trials Freedom From All Cause Death

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

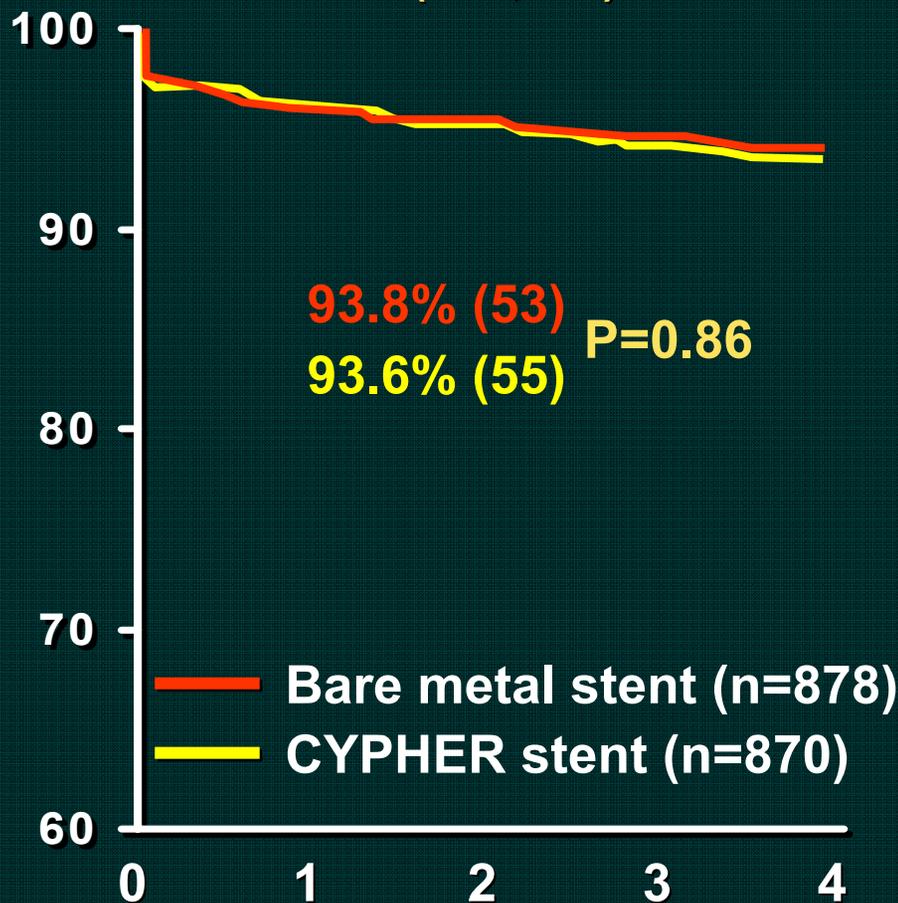


**TAXUS I, II, IV, V, VI**  
(n=3,513)



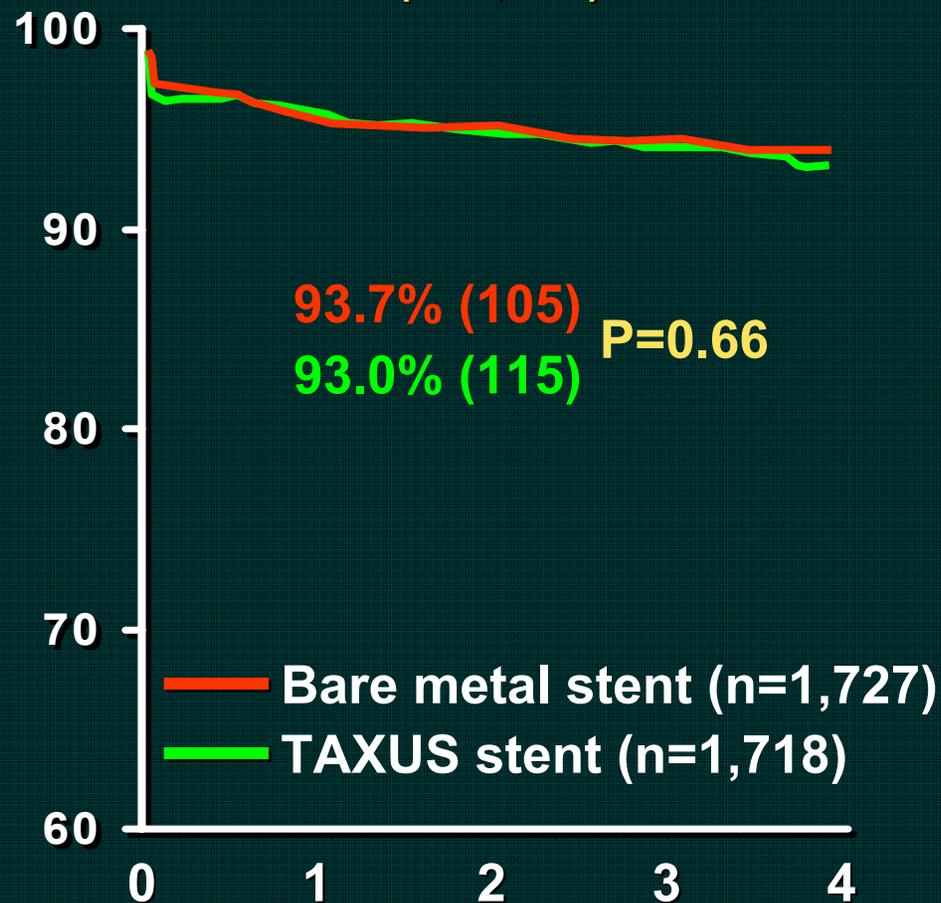
# 9 Prospective, Double-Blind, Randomized Trials Freedom From Myocardial Infarction

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



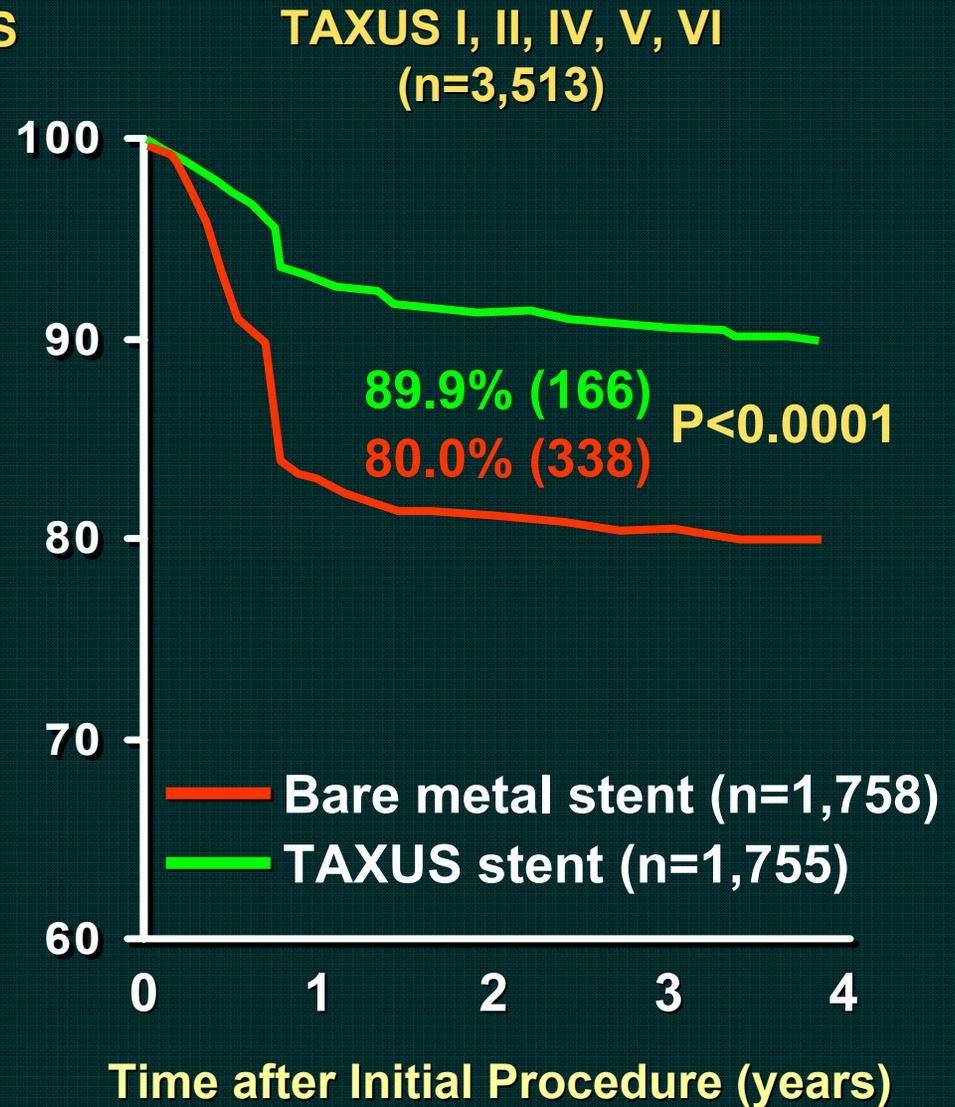
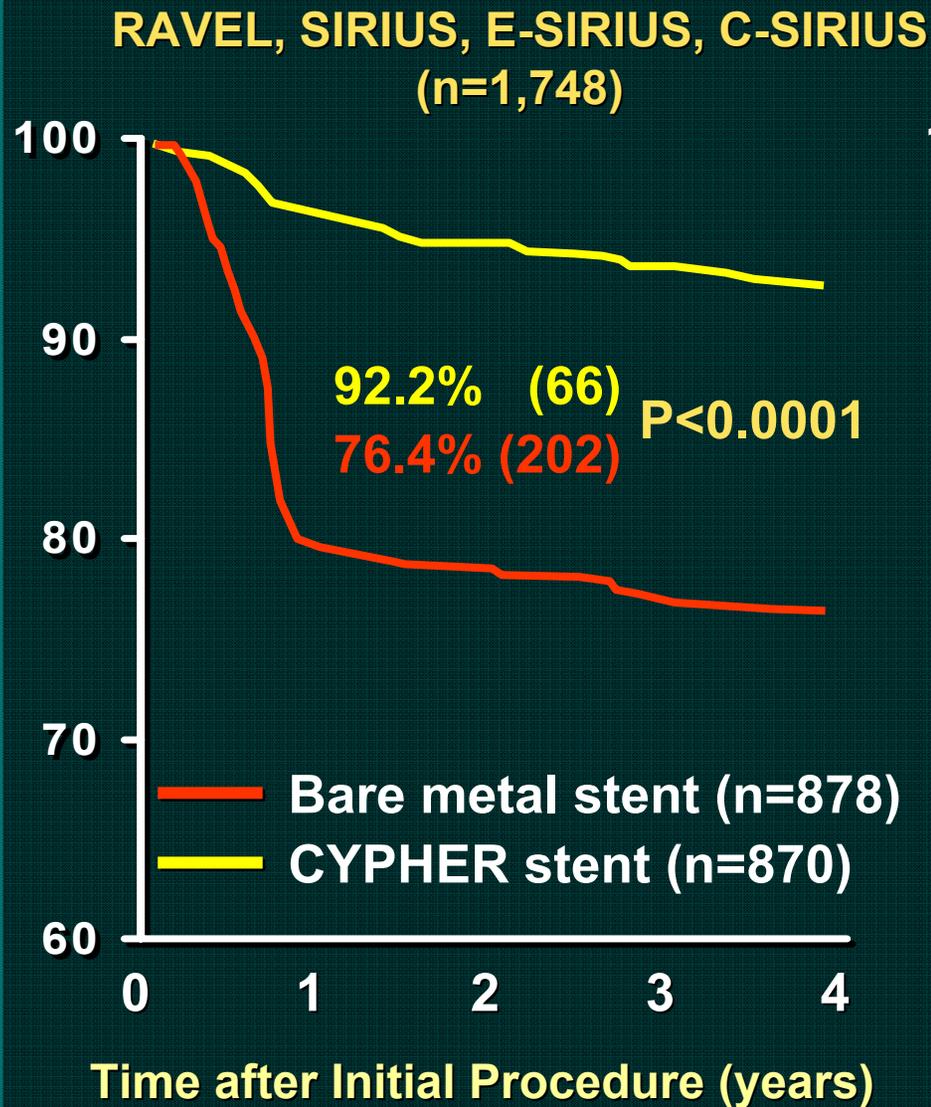
Time after Initial Procedure (years)

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



Time after Initial Procedure (years)

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



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

## All events: 0 – 4 Years (part 1)

	Cypher (N=870)	BMS (N=878)	RR [95% CI]	P value
<b>Death</b>	6.7% (57)	5.3% (45)	1.27 [0.86,1.88]	0.23
- <b>Cardiac</b>	3.5% (29)	2.7% (23)	1.26 [0.73,2.18]	0.40
- <b>Non cardiac</b>	3.3% (28)	2.7% (22)	1.27 [0.73,2.23]	0.40
<b>MI</b>	6.4% (55)	6.2% (53)	1.03 [0.71,1.51]	0.86
- <b>Q-wave</b>	2.1% (18)	1.3% (11)	1.64 [0.77,3.47]	0.19
- <b>Non Q-wave</b>	4.5% (38)	5.0% (43)	0.88 [0.57,1.36]	0.55

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

*Kaplan-Meier estimates*

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

## All events: 0 – 4 Years (part 2)

	Cypher (N=870)	BMS (N=878)	RR [95% CI]	P value
<b>Death or MI</b>	11.6% (100)	10.4% (89)	1.12 [0.84,1.49]	0.44
<b>Death or Q-MI</b>	8.2% (70)	6.4% (54)	1.30 [0.91,1.86]	0.14
<b>Cardiac death or MI</b>	8.8% (75)	8.2% (70)	1.07 [0.77,1.48]	0.69
<b>Stent thrombosis</b>	1.2% (10)	0.6% (5)	2.00 [0.68,5.85]	0.20
<b>Ischemic TLR</b>	7.8% (66)	23.6% (202)	0.29 [0.22,0.39]	<0.0001
<b>Ischemic TVR</b>	12.1% (102)	27.5% (235)	0.38 [0.30,0.48]	<0.0001

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

*Kaplan-Meier estimates*

# TAXUS 5-Study RCT Meta-Analysis (N=3,513)

## All events: 0 – 4 Years (part 1)

	Taxus (N=1745)	BMS (N=1758)	RR [95% CI]	P value
<b>Death</b>	6.1% (86)	6.6% (92)	0.94 [0.70,1.26]	0.68
- <b>Cardiac</b>	2.4% (36)	3.0% (42)	0.86 [0.55,1.35]	0.51
- <b>Non cardiac</b>	3.8% (50)	3.7% (50)	1.01 [0.68,1.49]	0.98
<b>MI</b>	7.0% (111)	6.3% (105)	1.06 [0.81,1.39]	0.66
- <b>Q-wave</b>	1.4% (22)	1.1% (17)	1.30 [0.69,2.45]	0.42
- <b>Non Q-wave</b>	5.8% (91)	5.3% (90)	1.02 [0.76,1.36]	0.92

TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI

Kaplan-Meier estimates

# TAXUS 5-Study RCT Meta-Analysis (N=3,513)

## All events: 0 – 4 Years (part 2)

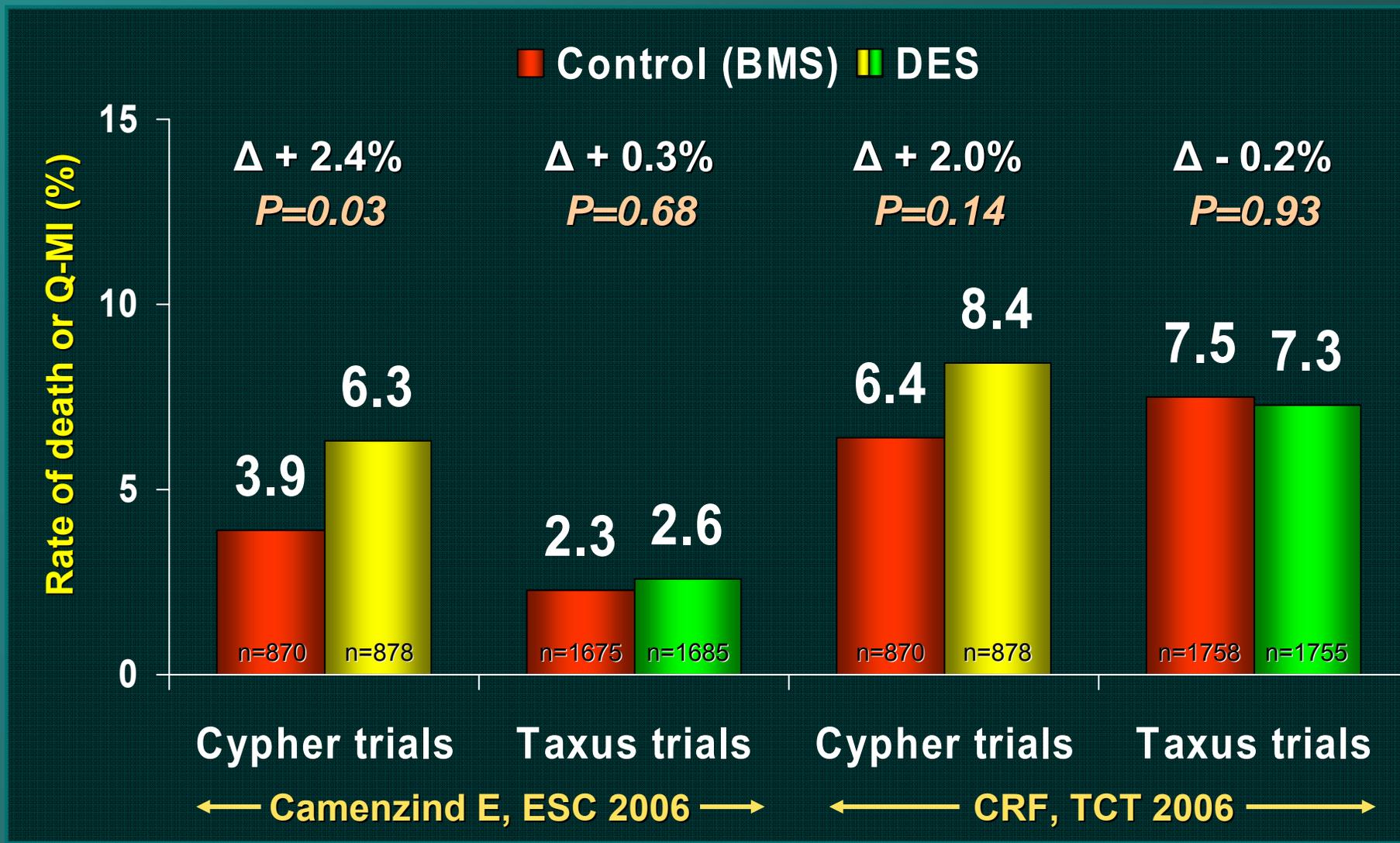
	Taxus (N=1745)	BMS (N=1758)	RR [95% CI]	P value
<b>Death or MI</b>	12.4% (187)	11.8% (183)	1.03 [0.84,1.26]	0.79
<b>Death or Q-MI</b>	7.3% (105)	7.5% (107)	0.99 [0.76,1.29]	0.93
<b>Cardiac death or MI</b>	8.9% (139)	8.5% (136)	1.03 [0.81,1.30]	0.82
<b>Stent thrombosis</b>	1.3% (20)	0.9% (14)	1.44 [0.73,2.84]	0.30
<b>Ischemic TLR</b>	10.1% (166)	20.0% (338)	0.46 [0.38,0.55]	<0.0001
<b>Ischemic TVR</b>	17.2% (272)	24.7% (409)	0.62 [0.53,0.73]	<0.0001

TAXUS I, TAXUS II, TAXUS IV, TAXUS V, TAXUS VI

Kaplan-Meier estimates

# Death or Q-wave MI

All randomized studies up to latest available follow-up



# Why is there no increase in death/MI with DES despite an increase in late stent thrombosis?

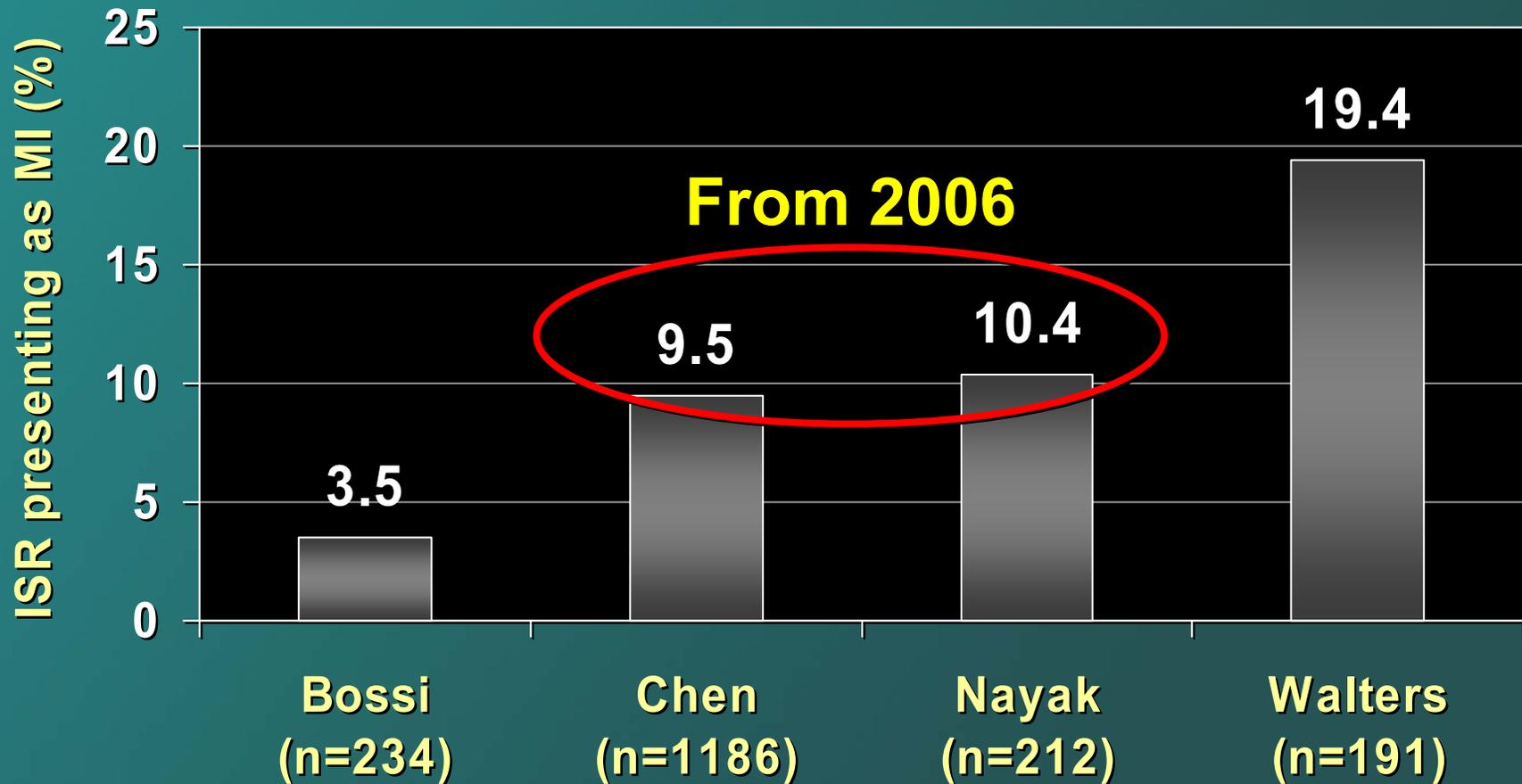
## 3 Possibilities

- 1) Causes of death and MI in pts with CAD undergoing stent implantation are multifactorial, and often remote from stent site
  - Relatively small excess risk of late stent thrombosis leading to death or MI might be lost against this greater non-stent related background rate
- 2) The excess in death and MI from late stent thrombosis with DES is offset by reduction of death and MI by preventing restenosis
- 3) The definition of stent thrombosis used in the pivotal trials censored thrombotic events after TLR, biasing against DES
  - By ITT there are no differences in the rates of late stent thrombosis between DES and BMS



# Is In-stent Restenosis a Benign Entity?

## Presentation of BMS ISR as Acute MI



Nayak AK et al. *Circ J* 2006;70:1026-29

Bossi I et al. *JACC* 2000;35:1569-76

Walters DL et al. *AJC* 2002;89:491-4

Chen MS et al. *AHJ* 2006,151:1260-1264



# Is ISR a Benign Entity?

## 1186 cases of single lesion bare metal ISR at the Cleveland Clinic

<b>64.1%</b>	<b>Effort Angina</b>
<b>26.4%</b>	<b>Unstable Angina</b>
<b>9.5%</b>	<b>Acute MI</b>
<b>- 7.3%</b>	<b>- NSTEMI</b>
<b>- 2.2%</b>	<b>- STEMI</b>

**Treatment**

**8 (0.7%)  
procedural  
deaths**

Chen MS et al. *AHJ* 2006,151:1260-1264

**106 cases (8.9%) totally occluded**



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

Total intent-to-treat population: 3445 patients

Control 1727

TAXUS 1718

Stent thrombosis  
14 pts

Ischemia-driven TLR  
290 pts

Ischemia-driven TLR  
135 pts

Stent thrombosis  
20 pts

12 patients with death or MI

11 patients with death or MI

4 patients with death or MI

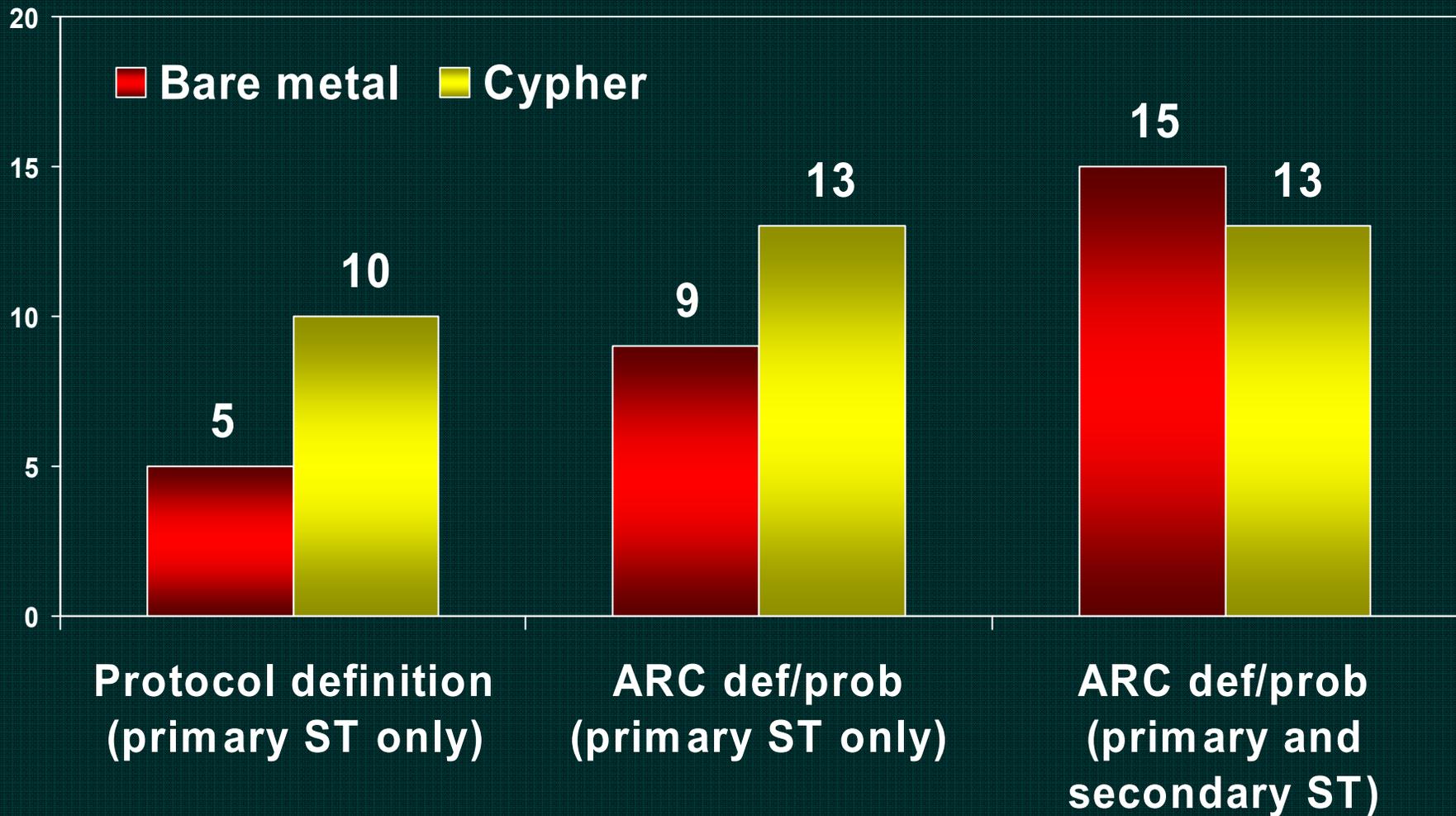
19 patients with death or MI

Σ: 23 Pts with Death or MI  
(4 Deaths + 21 MIs)

Σ: 23 Pts with Death or MI  
(3 Deaths + 23 MIs)

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

## Stent Thrombosis: 0 – 4 Years



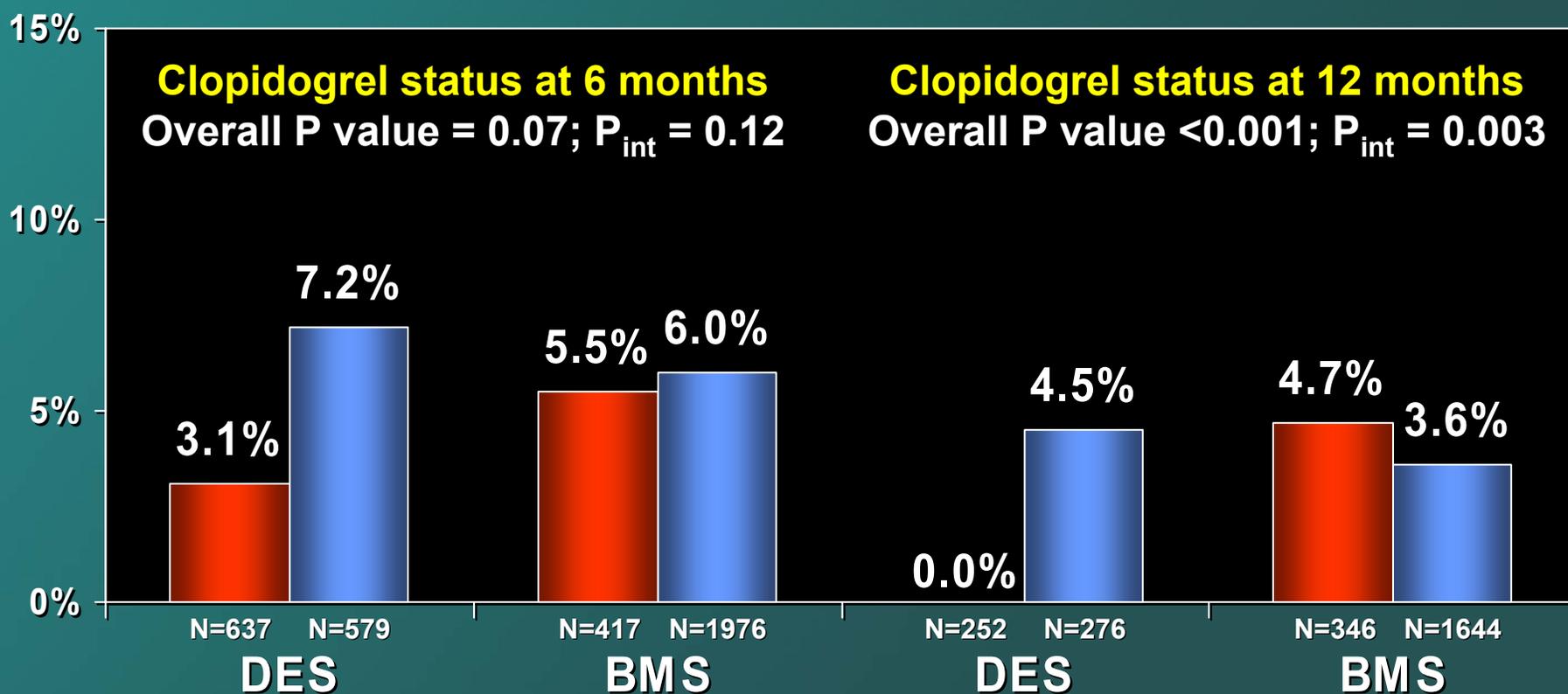
*RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS*

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

# Duke Database Death/MI Analysis

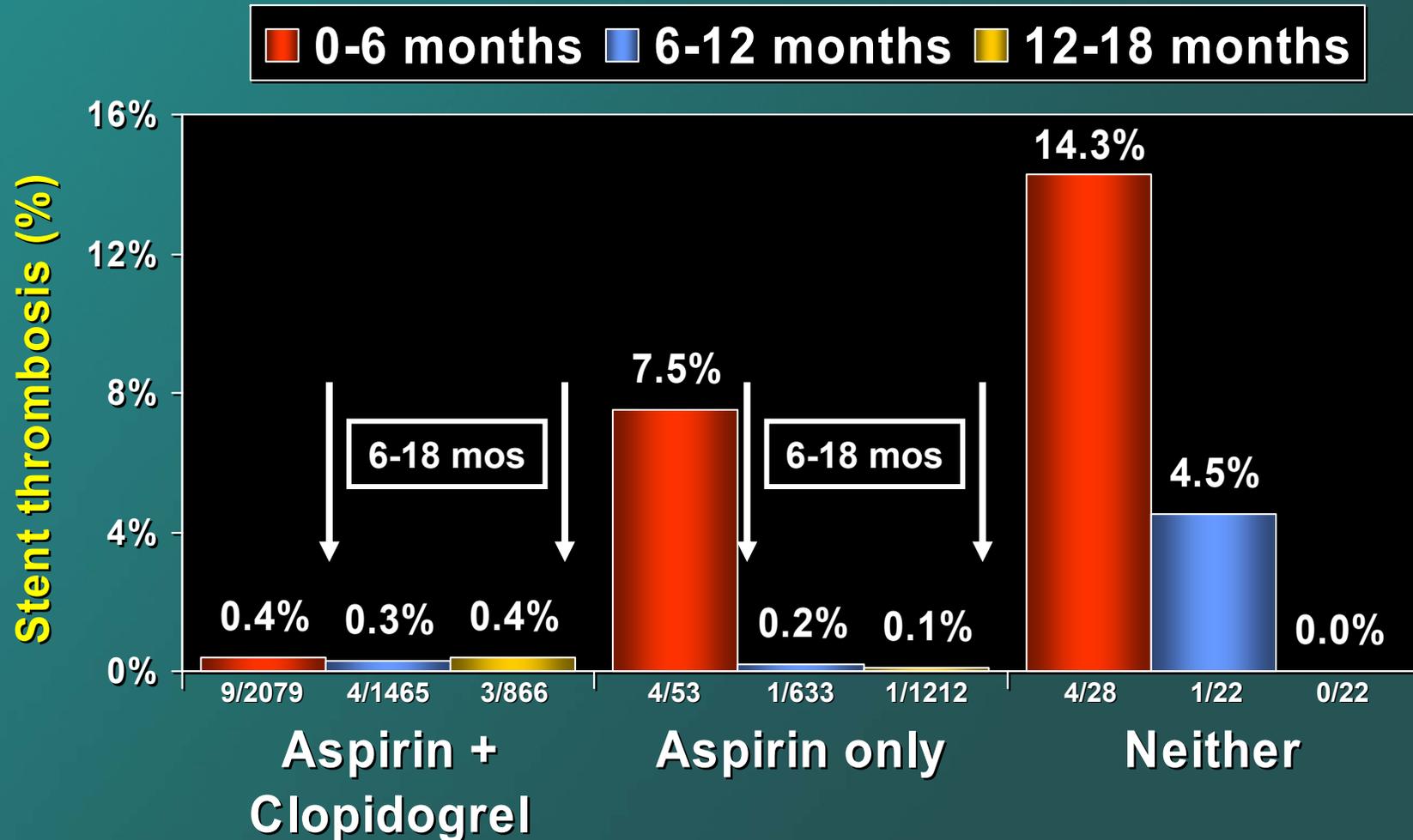
Adjusted death/MI rates at 24 months  
in patients without events at 6 months

■ On clopidogrel ■ Off clopidogrel



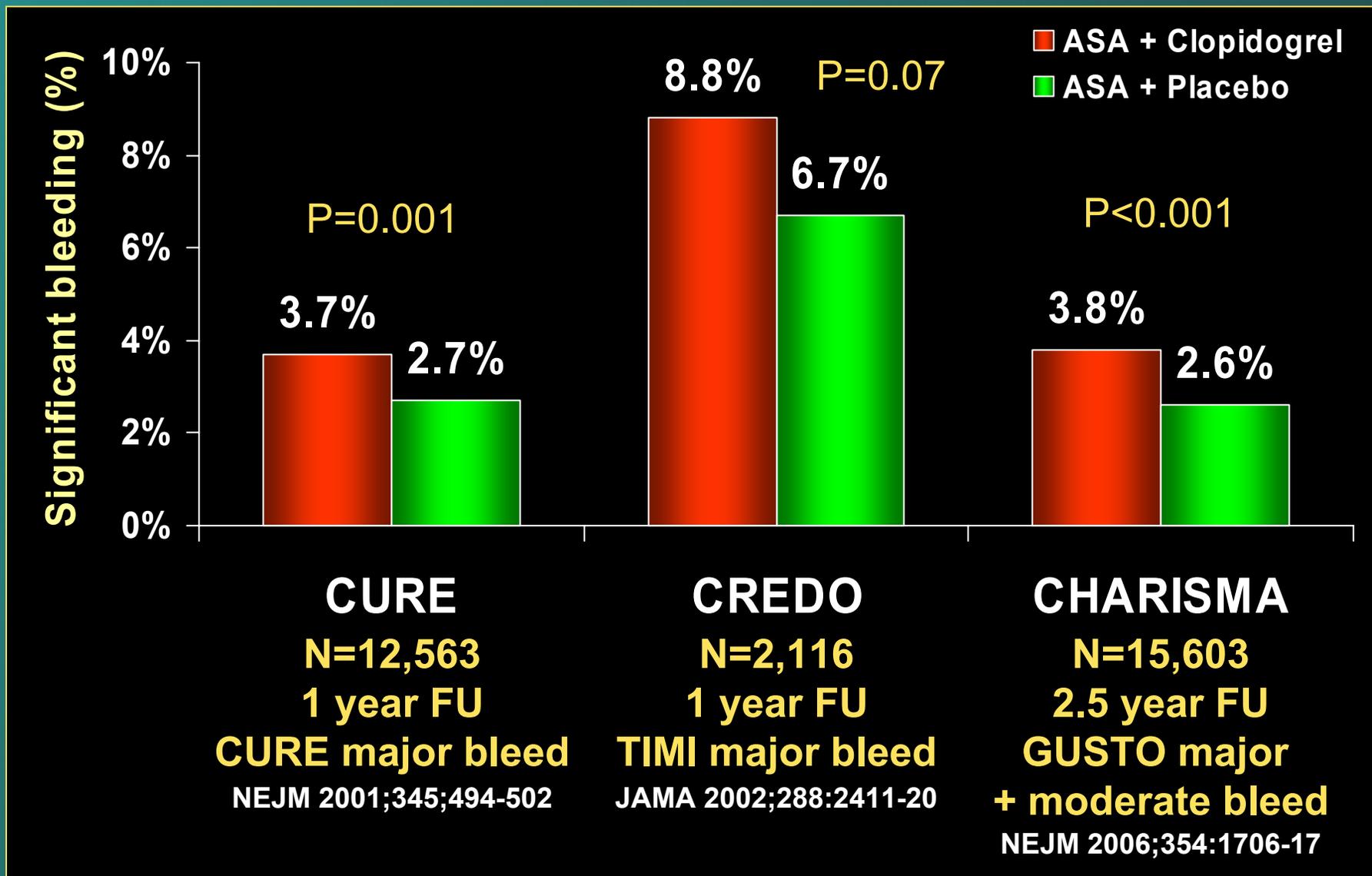
# Milan Stent Thrombosis Experience

2,160 consecutive pts with DES implanted



# Safety of Long-Term Clopidogrel

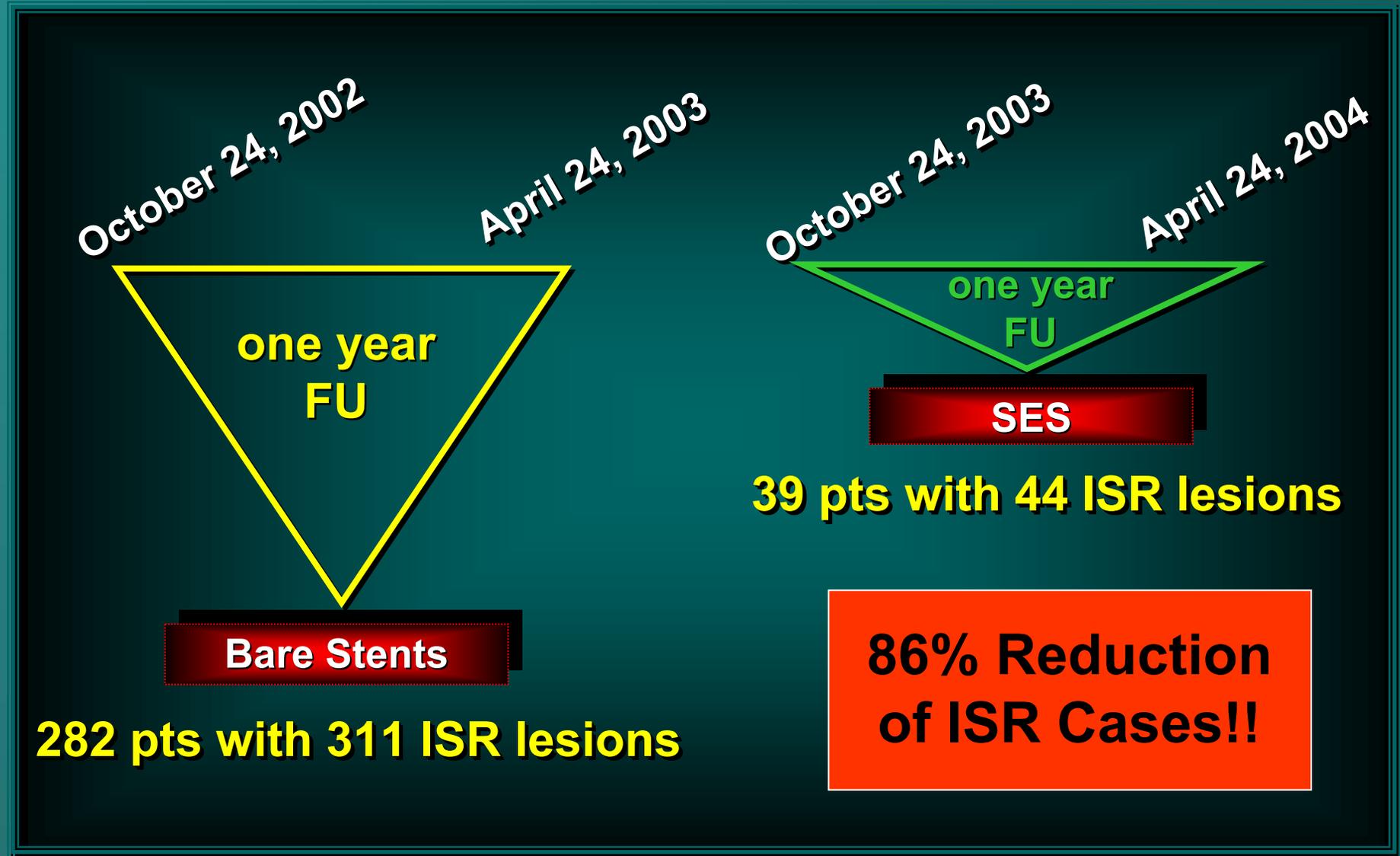
## 3 Placebo Controlled Trials



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

- 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**

# Frequency of In-stent Restenosis - CRF



# Drug-Eluting Stents: **Safety vs. Efficacy**

- 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 hundreds of thousands of patients.
- Like any medical advance, DES have side effects, the most concerning of which is an increased incidence of primary late stent thrombosis of ~2 per 1000 pts per year (~1 event per every 500 patient-years) compared to BMS, though this is offset by an excess rate of secondary thrombotic events from treatment of BMS restenosis.
- Moreover, the highest quality data to date suggest that with 4 years follow-up, DES when used on label do not increase overall death and MI rates, in part because of prevention of adverse events associated with restenosis.



# Drug-Eluting Stents: **Recommendations**

- Given the similar (low frequency) rates of death, MI and total (primary + secondary) stent thrombosis with on label use of DES and BMS, current DES approval pathways are for the most part acceptable – to modify approval trials to be powered for safety or to require longer-term FU is unnecessary and would be excessively burdensome.
- More rigorous post market surveillance (with greater rates of monitoring required to ensure event rate accuracy) is appropriate, as is an FDA “Dear Doctor” letter reinforcing the need to carefully weigh the risks and benefits of DES on a per patient basis, especially when considering off-label use.



# Drug-Eluting Stents: **Recommendations**

- **Long-term clopidogrel:** Whether long-term clopidogrel would reduce late stent thrombosis, thus warranting the risks and cost, is completely unknown. In the U.S. we don't change practice recommendations based on hope or need without firm evidence-based medicine. Therefore, pending the completion of an adequately powered randomized trial, the FDA-regulated "label" mandate (3 months for Cypher, 6 months for Taxus) shouldn't change. The ACC/AHA guidelines currently recommend 1 year of clopidogrel for DES, which is sufficient.