

# FDA Panel on Drug-eluting Stent Safety

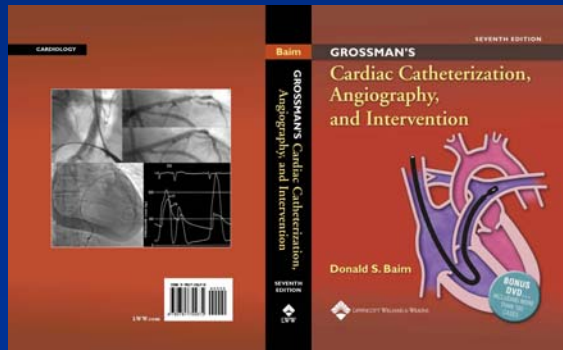
December 7 and 8<sup>th</sup>, 2006

## Boston Scientific Presentation: Part I

### On-label Use of the TAXUS<sup>®</sup> Drug-eluting Stent System

Donald S. Baim, M.D.  
Executive Vice President  
Chief Medical and Scientific Officer  
Boston Scientific Corporation

# Donald S. Baim, MD



**Faculty member since 1981**  
**Professor of Medicine, 1994-2006**

**Founder and Chief**  
**Interventional Cardiology Section 1981-2000**

**Senior Physician**  
**Interventional Cardiologist 2000-2006**

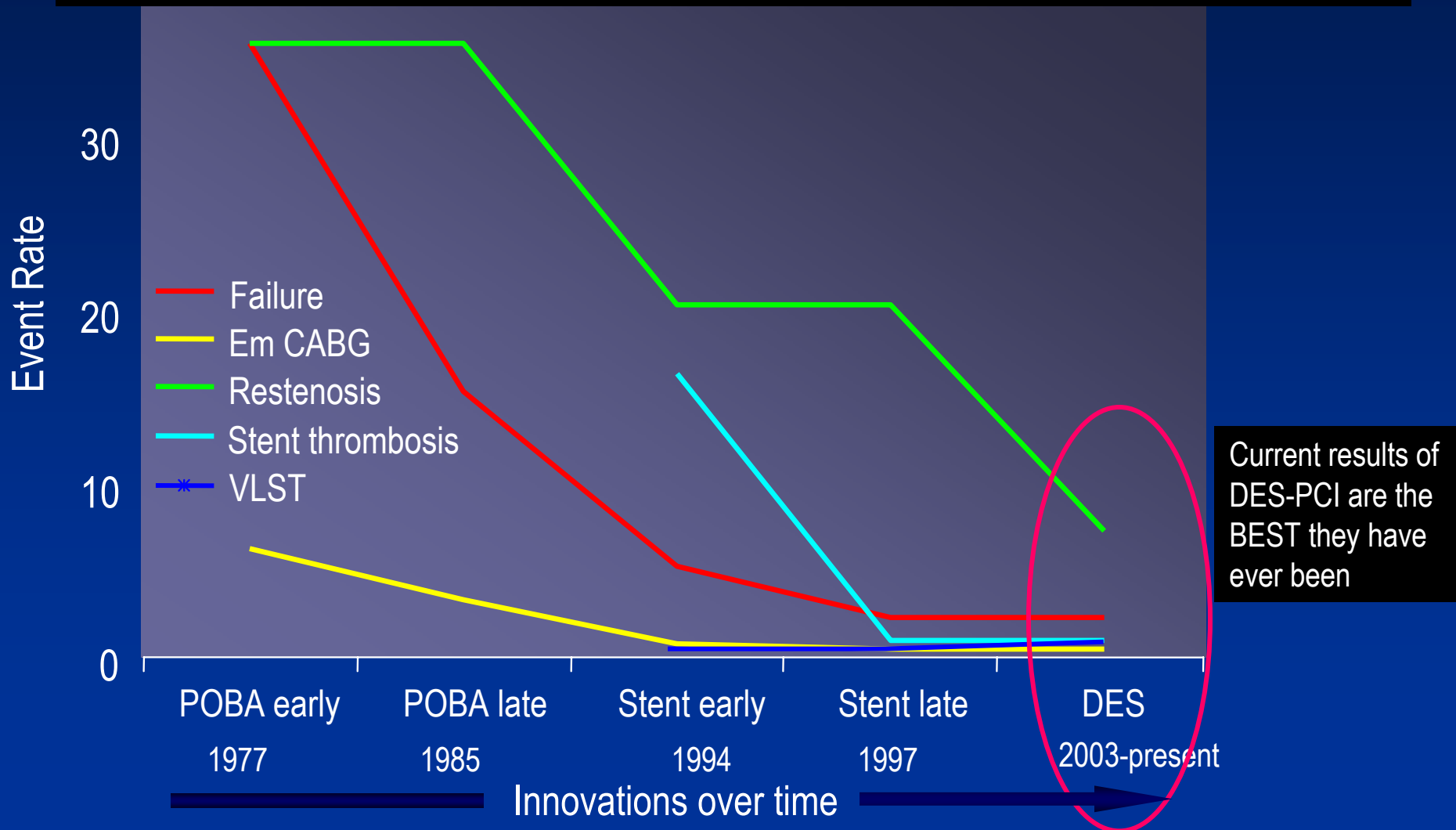
**Co-founder (with Dr. Kuntz)**  
**Chief Scientific Officer**  
**Harvard Clinical Research Institute**

**Editor-in-Chief, (4<sup>th</sup> through 7th edition [2006])**  
***Grossman's Cardiac Catheterization,***  
***Angiography and Intervention***

**Now (July 1, 2006) Executive Vice President**  
**Chief Medical and Scientific Officer**  
**Boston Scientific Corporation**

# Evolution of PCI: The dominant coronary revascularization since 1990

Over the last 30 years, percutaneous coronary intervention (PCI) has undergone progressive improvements in success, safety, and durability, as serial new technologies have been launched. While each innovation solved a serious prior problem, it has sometimes introduced rare new adverse events (e.g., in-stent restenosis, stent thrombosis).



# TAXUS® SR Stent Randomized Clinical Data

The Taxus I, II, IV, and V randomized trials compared the TAXUS® Slow-Release (SR) Stent to Bare Metal Stent (BMS) controls in 2,797 patients, median 4 year follow-up:

- a PROFOUND *clinical benefit* reduction in repeat revasc. ( $\Delta - 9.7\%$ , or 48 % relative)
- with trends towards LESS Death ( $\Delta -0.3\%$ ) or Q-MI ( $\Delta -0.1\%$ ) through last follow-up

This favorable risk benefit was seen in all studied sub-groups, with TLR reductions of :

- Diabetics (n=715)  $\Delta - 11.5\%$ , (46% relative),  $p < 0.0001$
- Small vessels ( $\leq 2.5\text{mm}$ ) (n=965)  $\Delta - 13.2\%$ , (48% relative),  $p < 0.0001$
- Long Lesions  $\geq 28\text{ mm}$  (n=341)  $\Delta - 18.2\%$ , (58% relative),  $p < 0.0001$
- Multiple Stents/vessel (n=497)  $\Delta - 23.1\%$ , (64% relative),  $p < 0.0001$

Stent thrombosis rates were not statistically different from the BMS Control for either :

	<u>4 years cum.</u>	or	<u>beyond 1 year (VLST)</u>
per protocol	1.3 vs. 0.8 %		$\Delta +0.4\%$ , $p = 0.057$
ARC 1 <sup>o</sup> def.+prob.	1.8 vs. 1.1 %		$\Delta +0.5\%$ , $p = 0.081$
ARC Total	3.5 vs. 3.6 %		$\Delta - 0.1\%$ , $p = 0.786$

Plavix use beyond 6 months with TAXUS showed a trend towards reduced Death or MI

# Agenda

## Background

Stent Thrombosis – ARC Definitions

TAXUS Meta-Analysis – All Patients

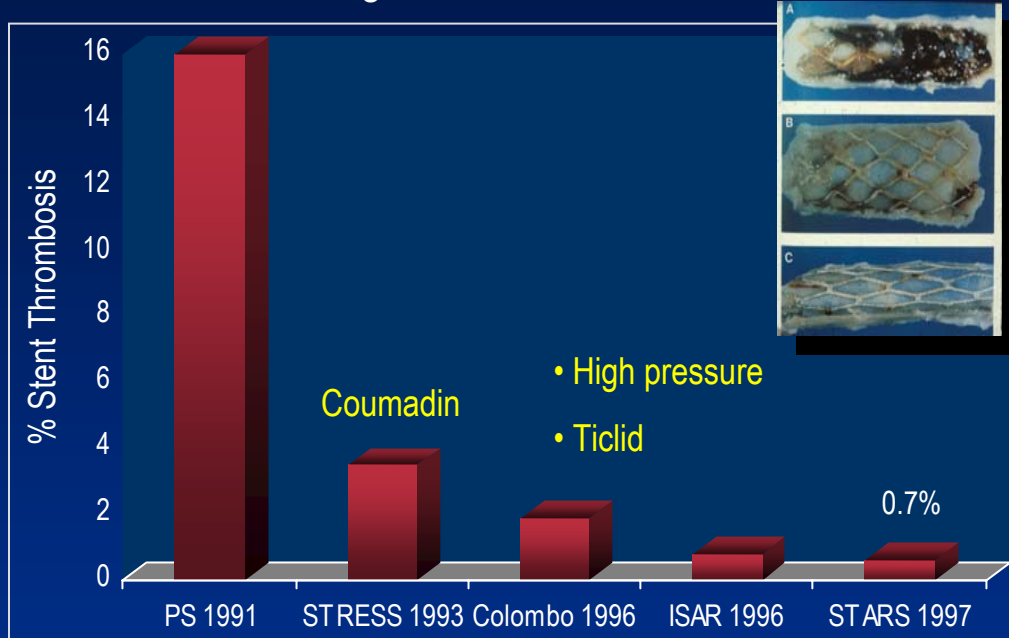
TAXUS Meta-Analysis – Subgroups

Antiplatelet Usage

Summary and Conclusions

# A Brief History of Stent Thrombosis

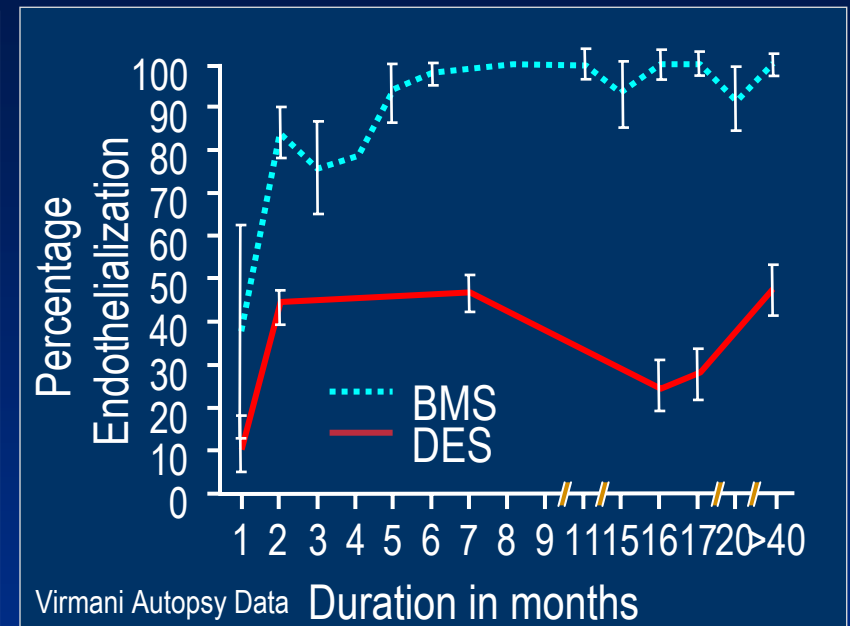
Decreasing incidence of ST with BMS



Stent thrombosis with BMS decreased progressively due to the use of high-pressure stent deployment and 1 month of dual anti-platelet Rx (aspirin, and ticlopidine or clopidogrel).

*SAT almost always occurred within 1 month of implantation.*

Incomplete/delayed endothelial coverage with DES



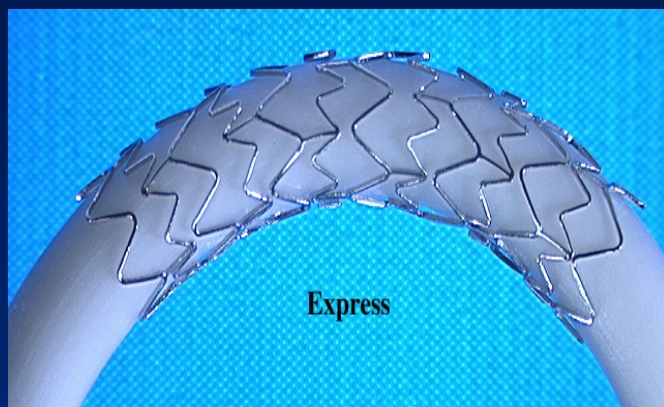
While the main benefit of DES (↓ in-stent tissue) has decreased restenosis, the associated drugs or polymers may interfere with rapid complete endothelial coverage, at least in some patients



Delayed endothelialization of DES was anticipated, as shown by longer (3 – 6 months) anti-platelet therapy, but it *may* have unmasked a new (but rare, ~ 0.5%) event : Very Late ST > 1 year after implantation.

# The TAXUS<sup>®</sup> Express<sup>®</sup> Stent – Boston Scientific Corporation

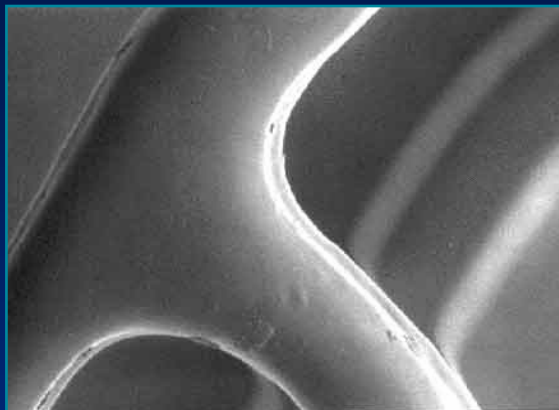
## Stent



## Express<sup>®</sup>

Stainless steel Tandem  
Architecture<sup>™</sup> Stent Design  
Maverick<sup>®</sup> Balloon Catheter  
Flexible, deliverable

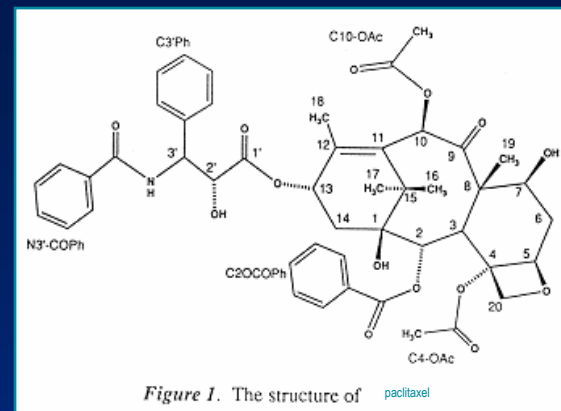
## Polymer



## Translute<sup>™</sup>

ABA triblock thermoplastic elastomer  
Styrene- b isobutylene- b styrene  
biostable and biocompatible  
provides controlled matrix release

## Drug



## Paclitaxel

Binds tubulin  
Stabilizes microtubular  
deconstruction  
Suppresses migration and  
proliferation (cytostatic) at low  
concentrations

Studied clinically in 2 different versions:

- Slow-release (SR)
  - commercialized version
- Moderate release (MR)
  - roughly 3x released dose compared to SR
  - never commercialized in any country

## DES Trials and Follow-up

*Currently, only TAXUS® and Cypher® stents have enough patients with enough long-term follow-up to accurately assess VLST and late clinical events*





# The TAXUS® SR Stent Trials (N = 2,797)

## *Patients randomized to Taxus SR vs BMS*



Cohort 1 (SR)

Stent Platform	 NiRx™	 NiRx™	 Express	 Express <sup>2</sup>
Study Objective	Safety and feasibility	Efficacy, dose-response	Pivotal	Indication expansion
n = ITT patients	61	266	1,314	1,156
1° endpoint	Safety and procedural success	% net volume obstruction (IVUS)	TVR Non-TVR	TVR Non-TVR
Long-term F/U available	5 years	4 years	4 years	2 years
RVD* (mm)	3.0 -3.5	3.0 -3.5	2.5 -3.75	<u>2.25</u> -4.0
Lesion	Single	Single	Single	<u>Multiple overlap</u>
Lesion length* (mm)	≤12	10 -12	10 - 28	10 - <u>46</u>
Max. # planned study stents per lesion/patient	1	1	2	2

RVD=Reference Vessel Diameter; \* As per trial inclusion/ exclusion criteria

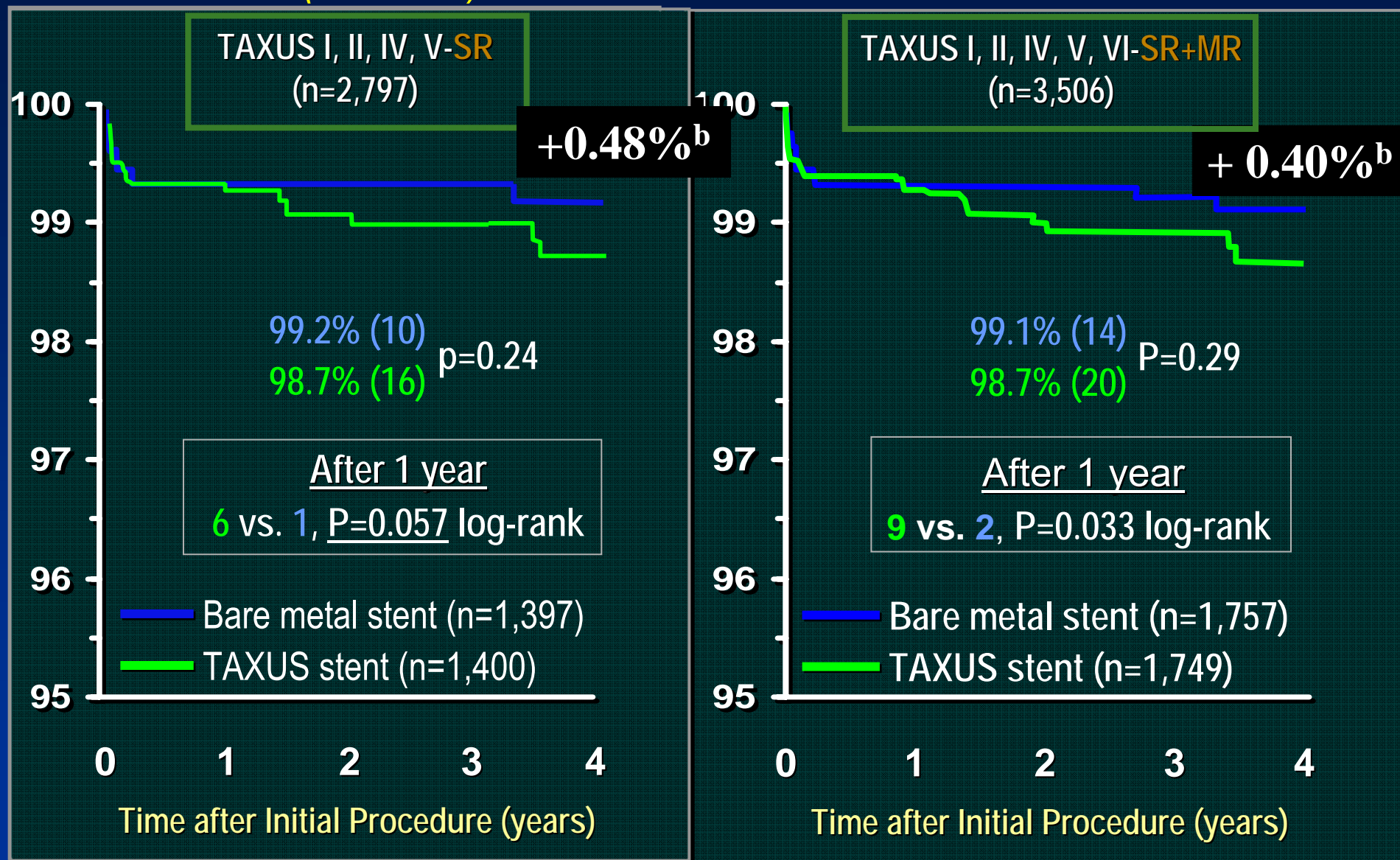
NiRx is a trademark of Medinol, Ltd., Jerusalem, Israel

# Methodology

- Pilot, pivotal and label extension randomized trials (IDE)
- Full monitoring and FDA audits of source data
- Independent Core Laboratories (angio, IVUS, EKG)
- Outside adjudication of all endpoints
  - HCRI for ARC stent thrombosis adjudication
- Internal (Boston Scientific) data entry and analysis
- Independent review and analysis of all patient-level data
  - ✓ Pocock Global Data and Safety Monitoring (October 2006)
  - ✓ Cardiovascular Research Foundation (November 2006)
  - Serruys (pending)

# Independent CRF patient-level meta-analysis

## *Freedom From (Protocol) Stent Thrombosis*



a. Difference = BMS – Cypher

b. Difference = BMS – Taxus

# Agenda

Background

Stent Thrombosis – ARC Definitions

TAXUS Meta-Analysis – All Patients

TAXUS Meta-Analysis – Subgroups

Antiplatelet Usage

Summary and Conclusions

# ARC Definitions – a large and needed step towards clarity

## Definite/Confirmed

Acute coronary syndrome AND [either  
Angiographic confirmation of thrombus or occlusion  
OR  
Pathologic confirmation of acute thrombosis]

## Probable

Unexplained death within 30 days  
OR

Target vessel MI, [even] without angiographic confirmation of  
thrombosis or other identified culprit lesion

## Possible

Unexplained death after 30 days

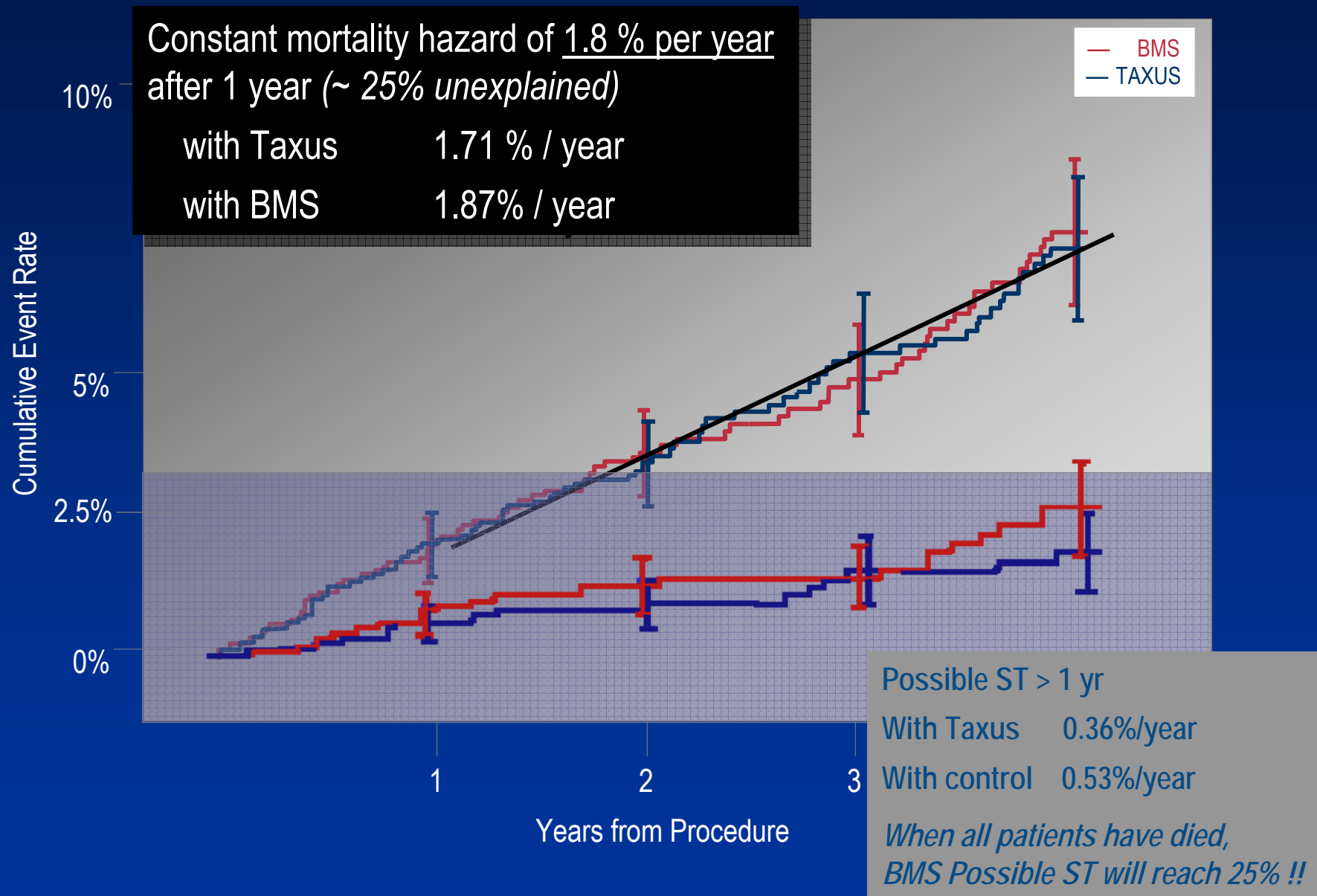
# ARC Definition (not a single definition, but a set of definitions)

	Primary (TLR censored)	Total (post-TLR retained)
Definite	Too Narrow <i>(specific, but not sensitive and may miss adverse events)</i>	Too Broad
Definite + Probable*	Best Balance* <i>(optimal sensitivity and specificity best suited for examining any differential ST mechanism)</i>	Too Broad
Definite + Probable+ Possible	Too Broad <i>(sensitive, but not specific and may dilute out any true safety signal)</i>	Too Broad

\*Also almost identical to the Protocol definition used in the Taxus trials

# Possible Stent Thrombosis is Too Broad

Death in the TAXUS<sup>®</sup> SR Stent Studies (2,797) reflect mostly natural history, and not stent thrombosis



## Inclusion of Post-TLR Stent Thrombosis is Too Broad

Differential use of post-brachytherapy in BMS arm obscures any mechanistic difference

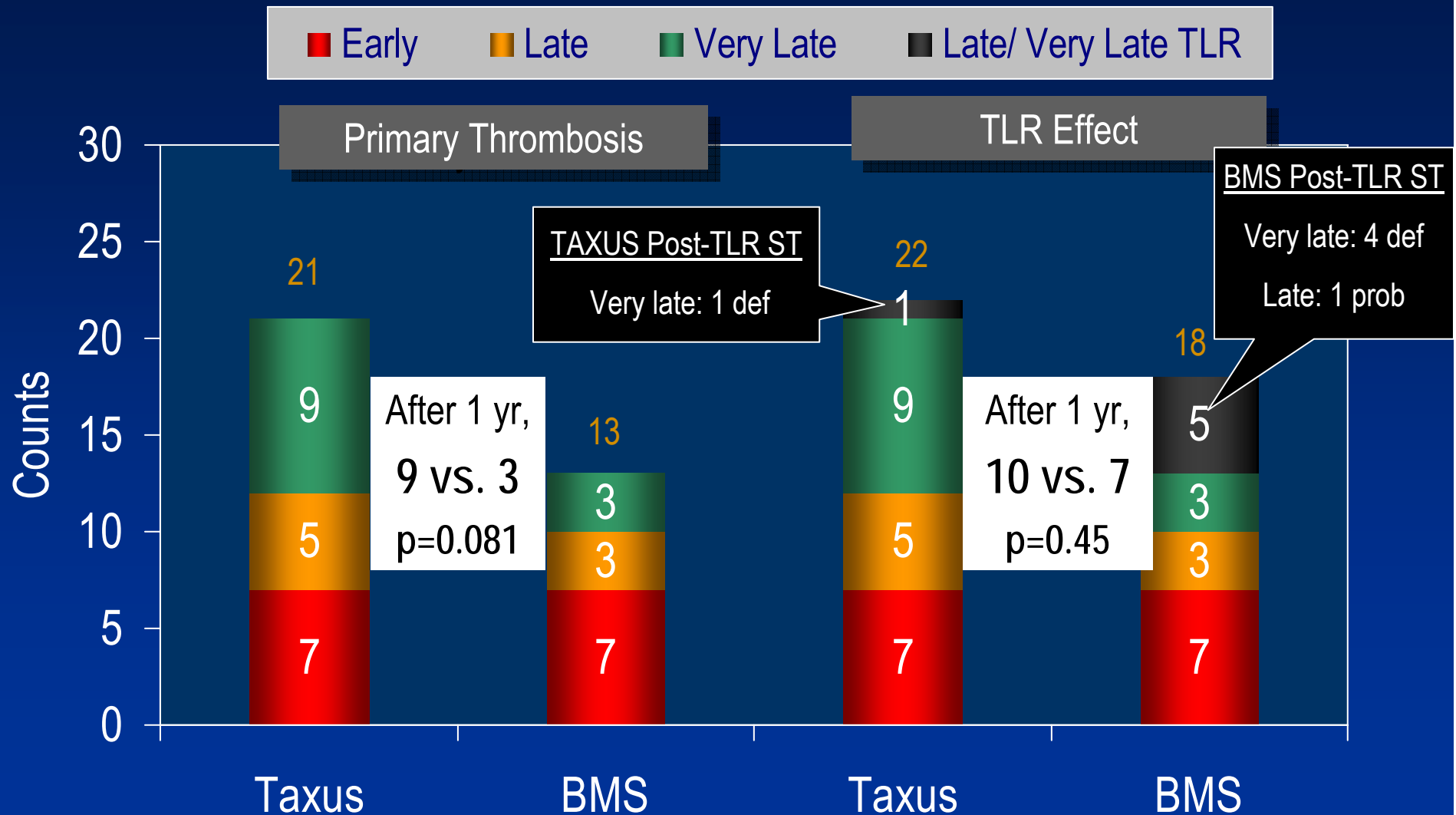
It is preferable to censor post-TLR thrombosis, and capture any missed events in ITT Death/ MI

	TAXUS ST (any) N = 39	BMS ST (any) N = 41
Prior TLR	3 / <u>133</u> TLR	8 / <u>266</u> TLR
Time from TLR to ST, mean (min, max)	269 (70, 407)	362 ( 3, 846)
ST Classification		
Definite/Probable	1	5
Possible	2	3
TLR Procedure	3	8 (7/8 Brachy)
BMS	2	1
PTCA	1	0
Brachytherapy/Atherectomy	0	1
Brachytherapy/PTCA	0	4
Brachytherapy/PTCA/BMS	0	2

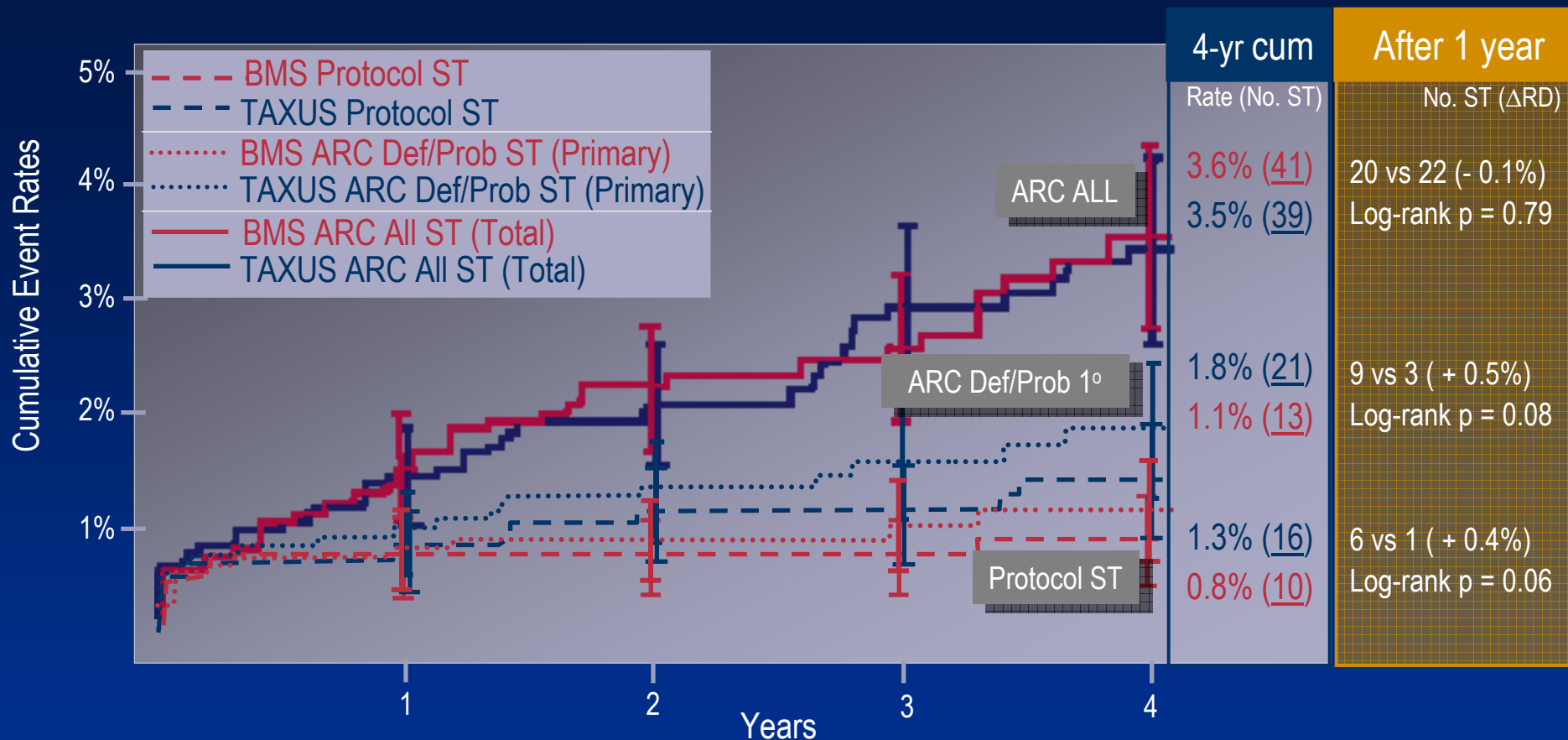


# ARC Definite/Probable Thrombosis

Inclusion of Prior TLR Events *hinders* (not helps) out understanding of whether any DES increase the Very Late Stent Thrombosis mechanism warrants increased anti-platelet therapy duration !!



# Taxus<sup>®</sup> SR Stent has no significant increase in stent thrombosis by *any* definition



	Years	1			2			3			4		
		Prot	Prim	Total	Prot	Prim	Total	Prot	Prim	Total	Prot	Prim	Total
TAXUS	# Entered	1400	1400	1400	1338	1336	1337	1217	1216	1217	733	730	730
	# Events	10	12	19	4	5	9	0	2	7	2	2	4
BMS	# Entered	1397	1397	1397	1342	1334	1341	1238	1231	1233	750	746	747
	# Events	9	10	20	0	1	10	0	1	3	1	1	8

ΔRD = Rate difference

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TAXUS Meta-Analysis – Subgroups

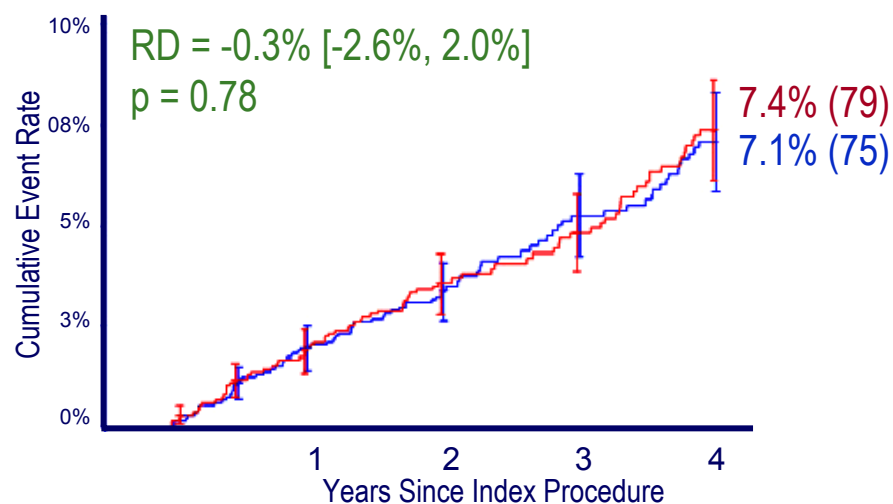
Antiplatelet Usage

Summary and Conclusions

# Overall TAXUS<sup>®</sup> Stent Analysis (N = 2,797)

## - Sample of Presentation Format

### All Death



TAXUS (N=1400)

BMS (N=1397)

RD = Rate Difference = TAXUS — BMS

[95% confidence intervals]

Log-rank p value

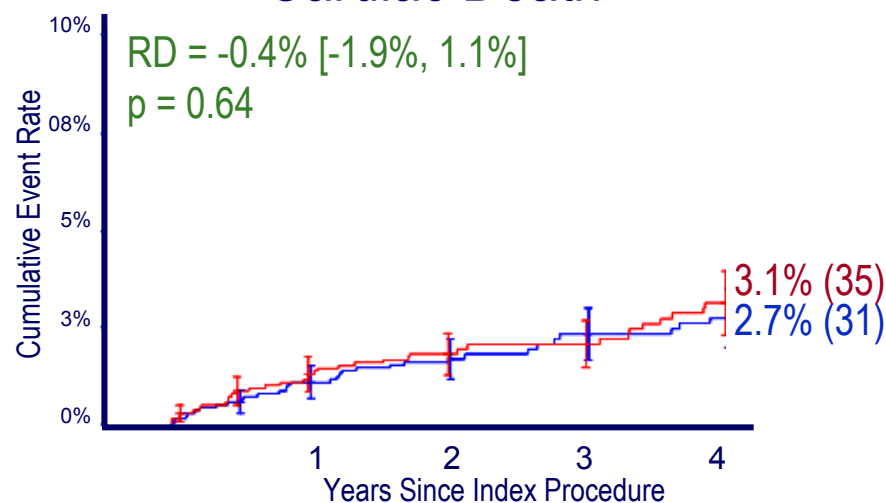
Decrease/ No increase

Increase

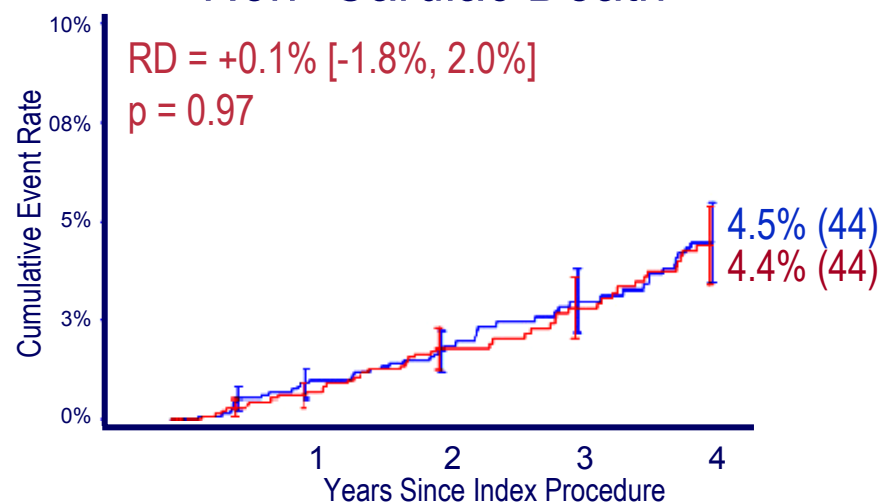
Decrease/No increase

Increase

### Cardiac Death



### Non- Cardiac Death



# Overall TAXUS® Stent Analysis (N = 2,797)

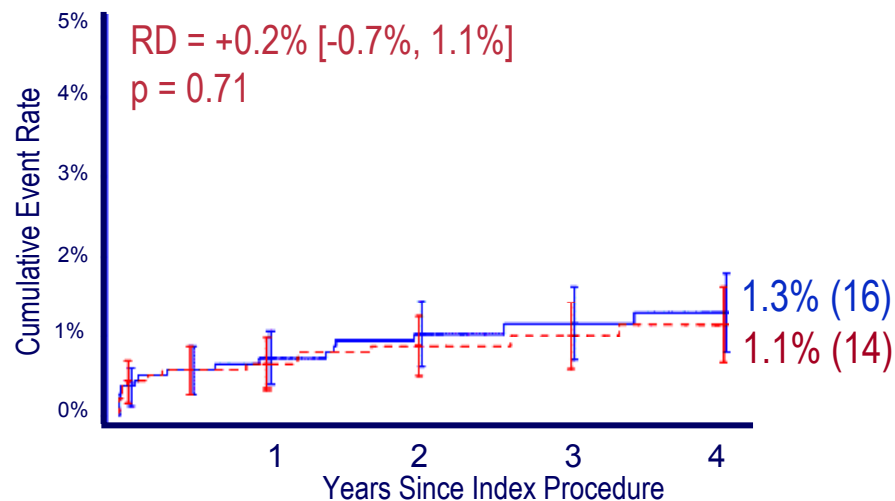
## ARC ST (Total = Including post-TLR)

— TAXUS (N=1400) — BMS (N=1397)

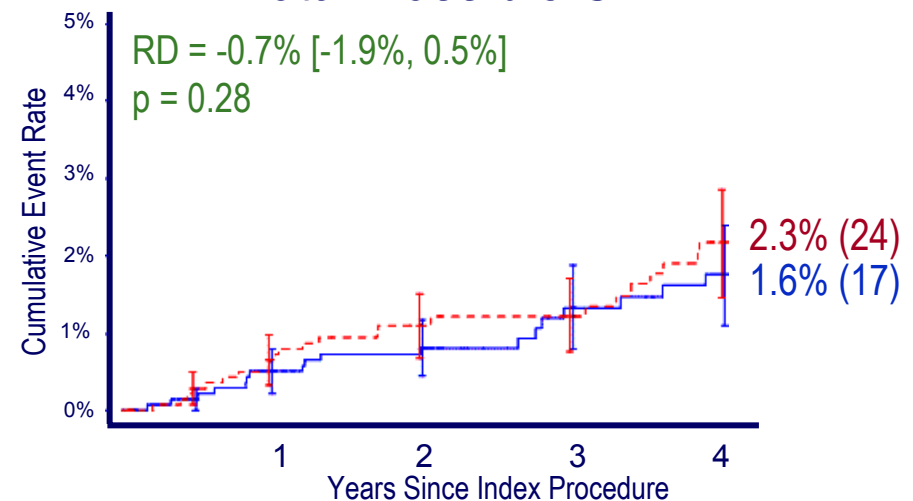
RD = Rate Difference = TAXUS — BMS

No increase Increase

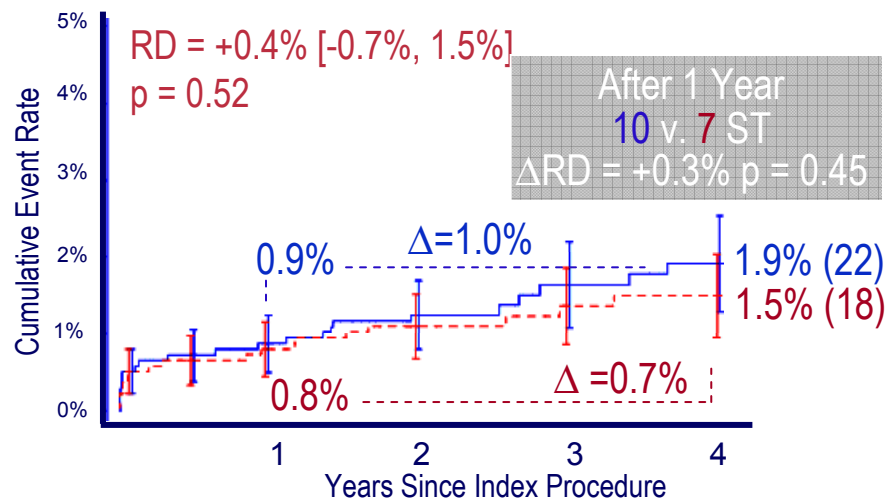
### Total Definite ST



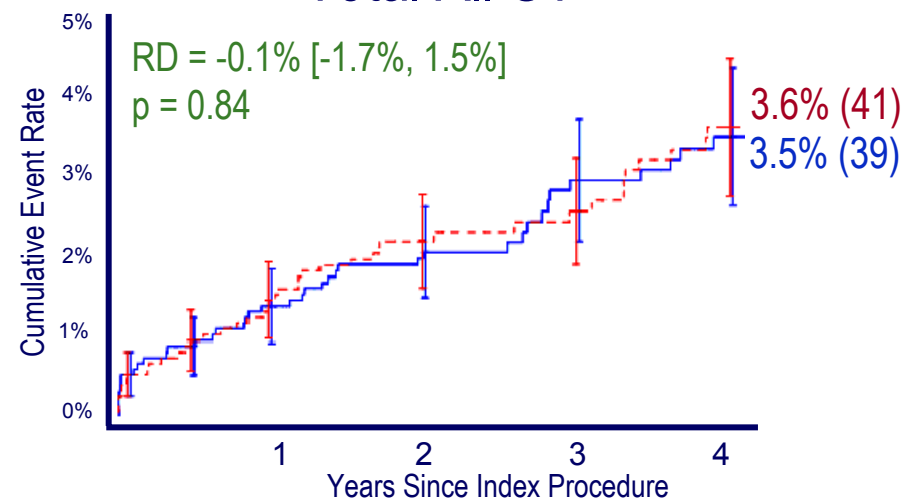
### Total Possible ST



### Total Definite/Probable ST



### Total All ST



# Overall TAXUS<sup>®</sup> Stent Analysis (N = 2,797)

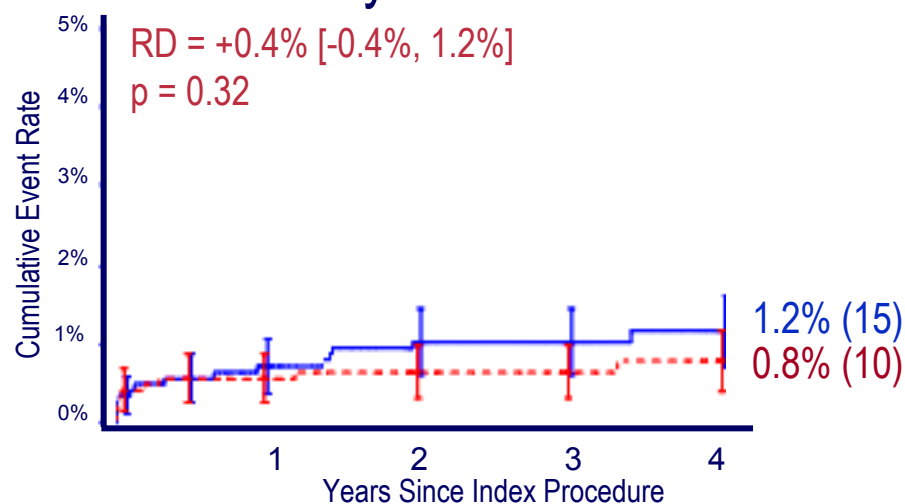
## ARC ST (Primary = Censoring ST post-TLR)

— TAXUS (N=1400) — BMS (N=1397)

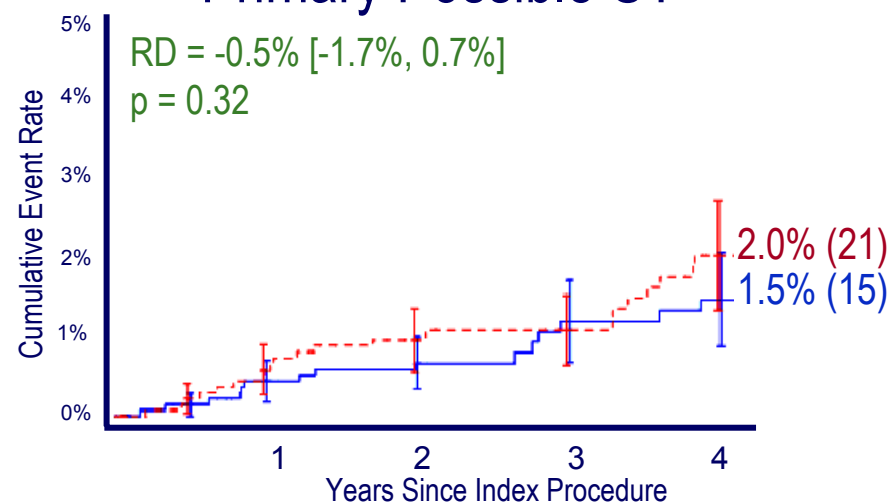
RD = Rate Difference = TAXUS — BMS

No increase Increase

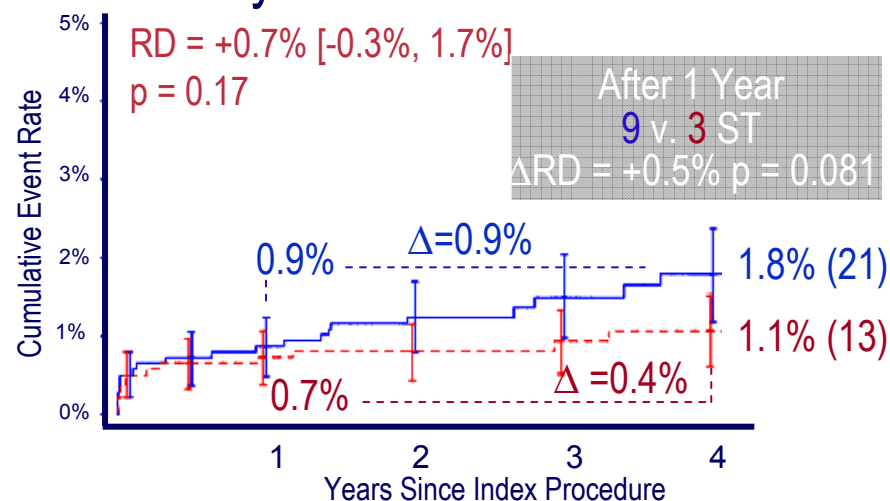
### Primary Definite ST



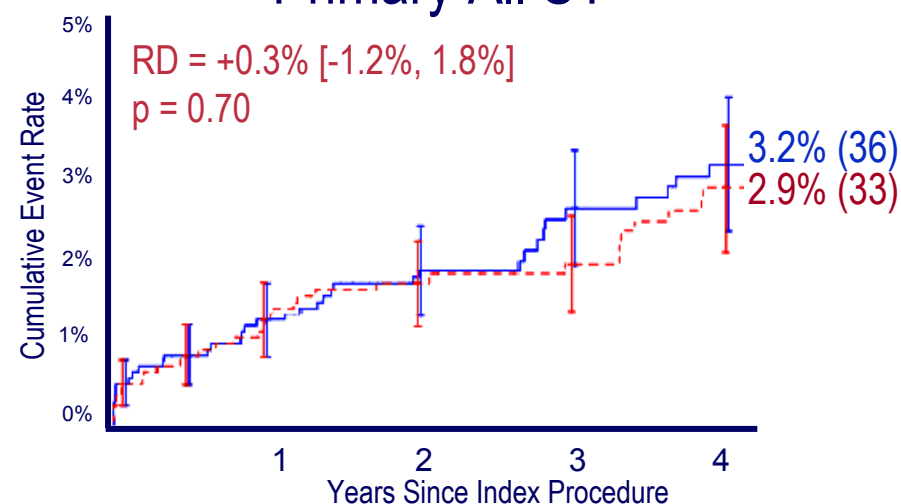
### Primary Possible ST



### Primary Definite/Probable ST



### Primary All ST



But have we spent so much time thinking about the hole,  
that we are forgetting about the doughnut?



Late stent thrombosis is just *one*  
of several causes of late death  
and MI (along with natural history  
and restenosis)

Death

Q-wave MI

Repeat procedures

# Overall TAXUS Analysis (N = 2,797)

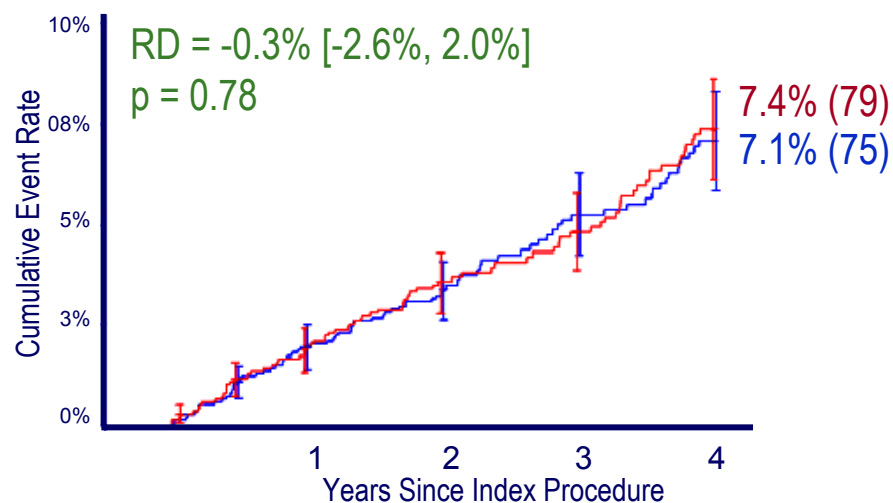
## Death -- Alternative Endpoints

— TAXUS (N=1400) — BMS (N=1397)

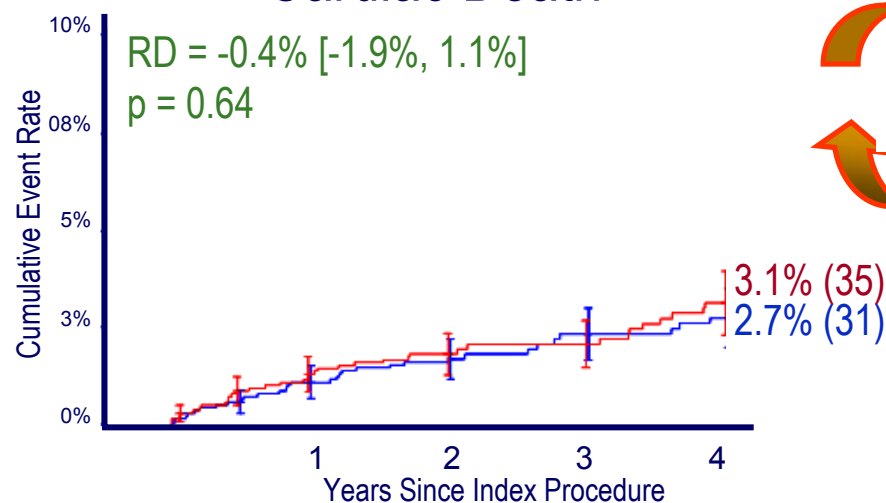
RD = Rate Difference = TAXUS — BMS

No increase Increase

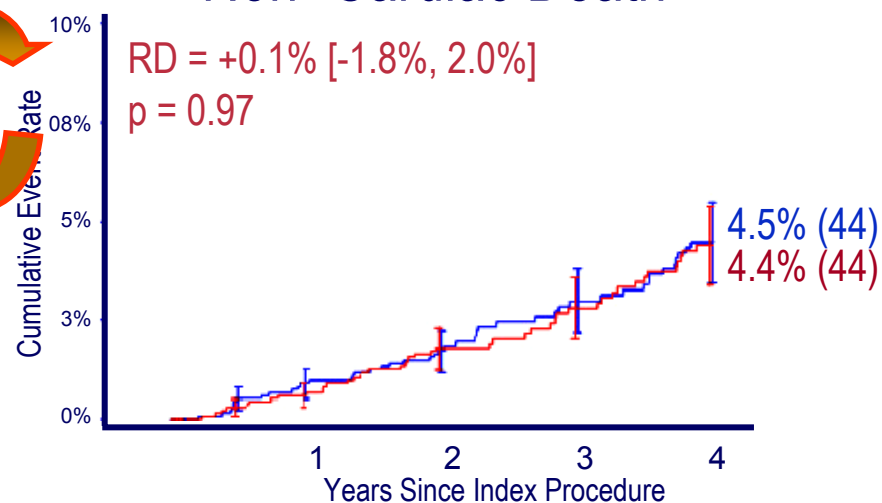
### All Death



### Cardiac Death



### Non- Cardiac Death





# Overall TAXUS<sup>®</sup> Stent Analysis (N = 2,797)

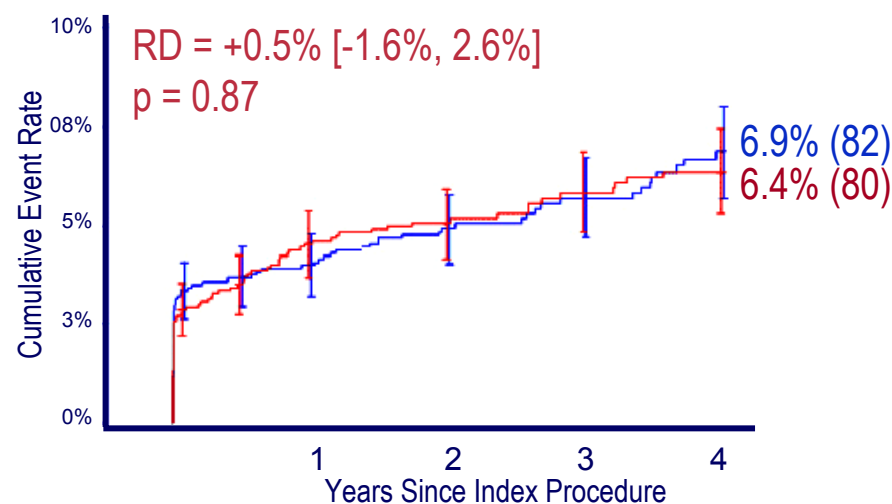
## MI -- Alternative Endpoints

— TAXUS (N=1400) — BMS (N=1397)

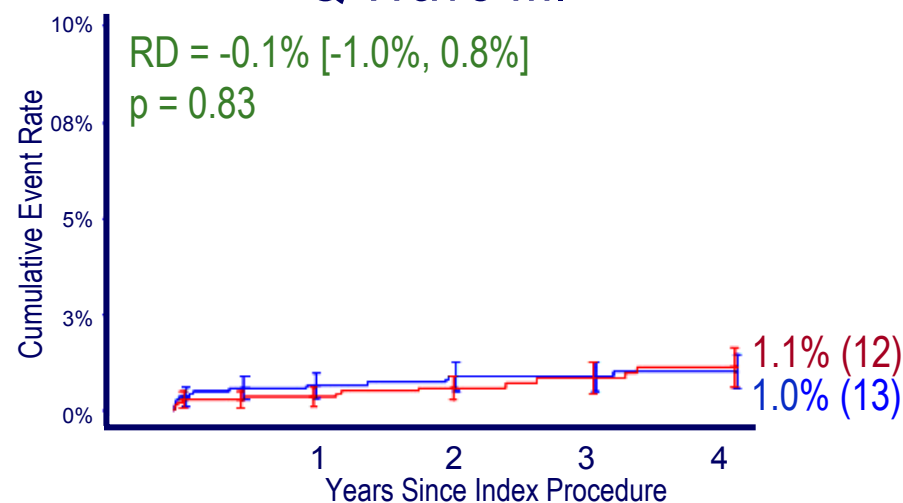
RD = Rate Difference = TAXUS — BMS

No increase Increase

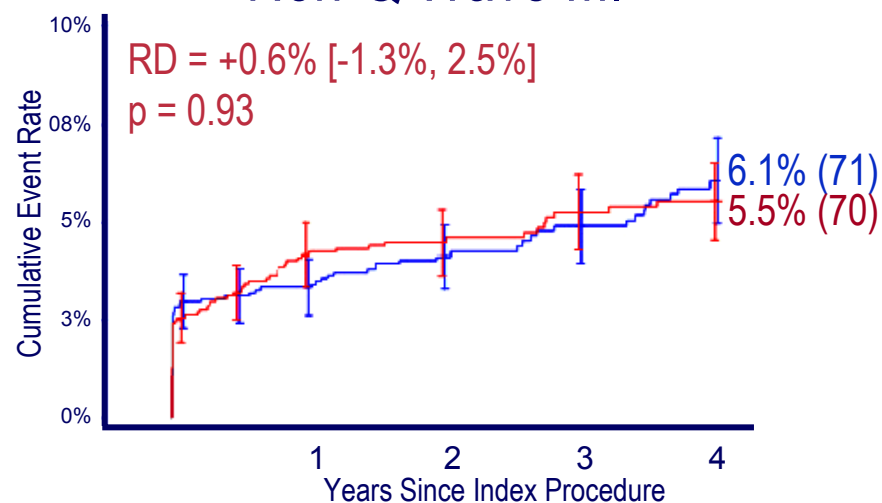
### All MI



### Q Wave MI



### Non-Q Wave MI



# Overall TAXUS<sup>®</sup> Stent Analysis (N = 2,797)

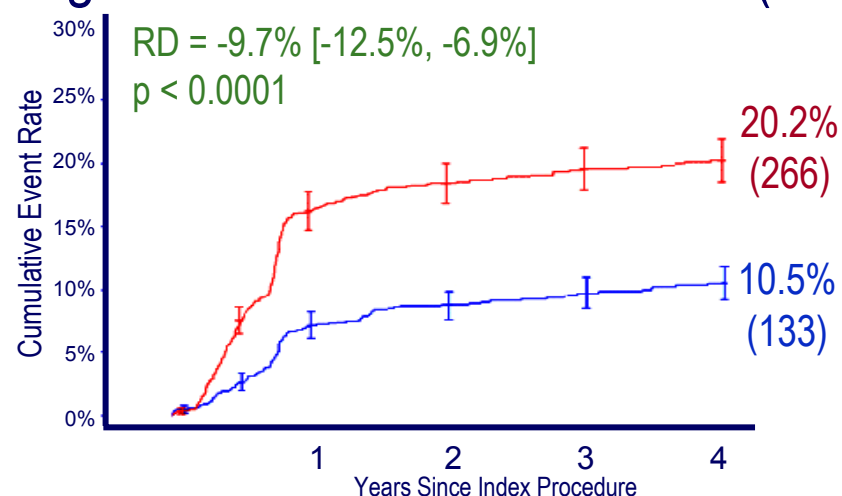
## Revascularization

— TAXUS (N=1400) — BMS (N=1397)

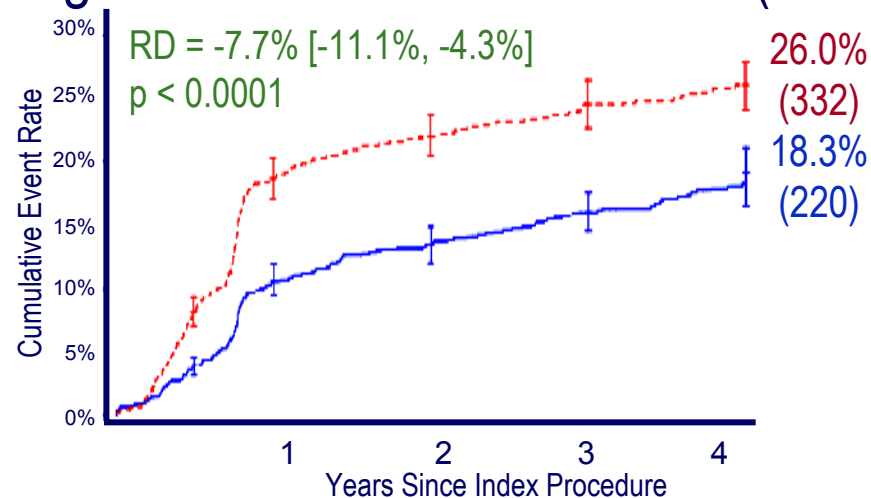
RD = Rate Difference = TAXUS — BMS

No increase Increase

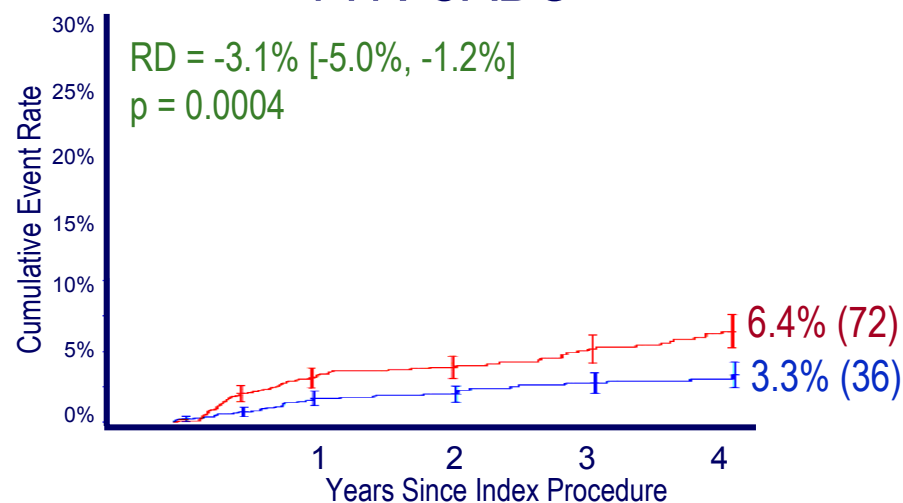
### Target Lesion Revascularization (TLR)



### Target Vessel Revascularization (TVR)



### TVR-CABG



# Overall TAXUS<sup>®</sup> Stent Analysis (N = 2,797)

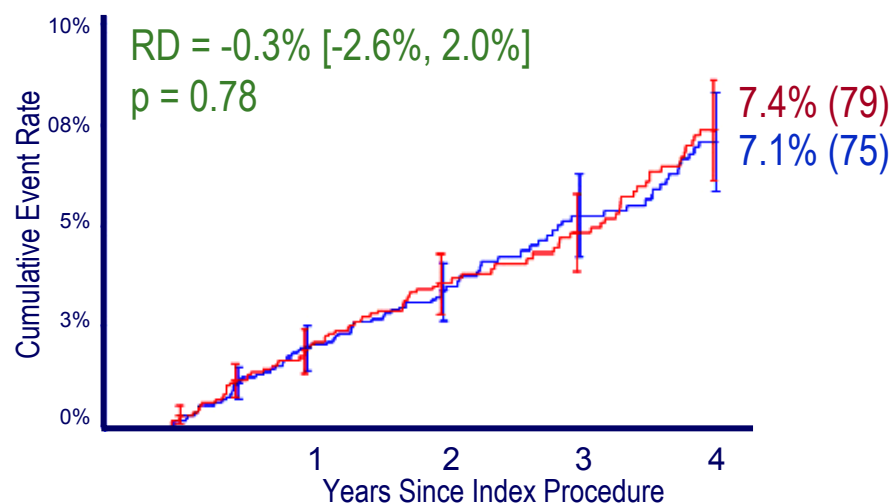
## Major Events Overview

— TAXUS (N=1400) — BMS (N=1397)

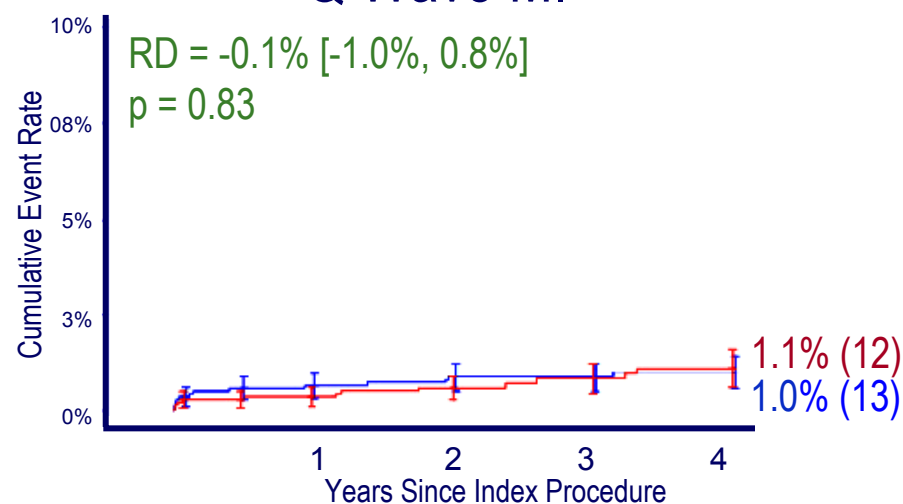
RD = Rate Difference = TAXUS — BMS

No increase Increase

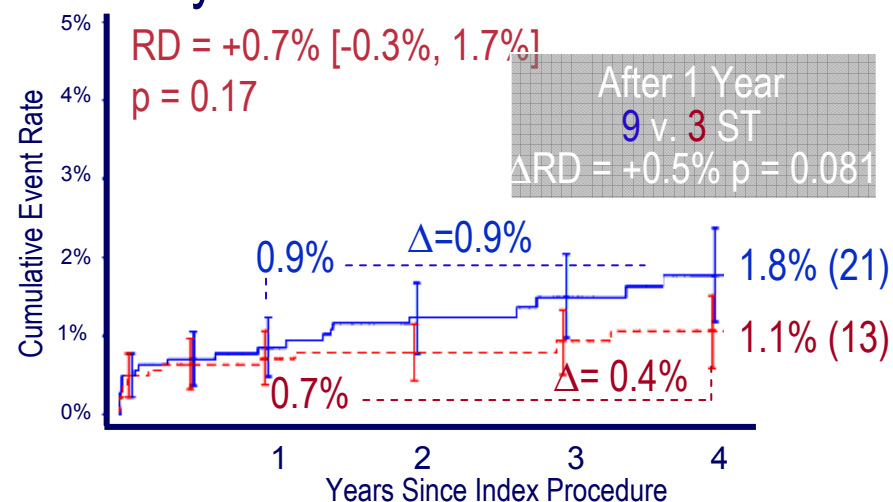
### All Death



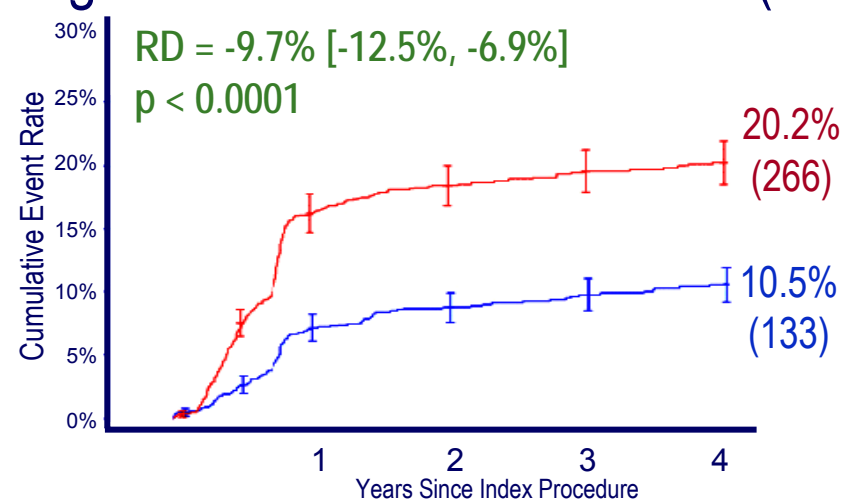
### Q Wave MI



### Primary ARC ST Definite/Probable



### Target Lesion Revascularization (TLR)



# Overall TAXUS<sup>®</sup> Stent Analysis (N = 2,797)

## ANNUAL HAZARD RATES

Δ = Rate Difference = TAXUS — BMS  
 No increase      Increase

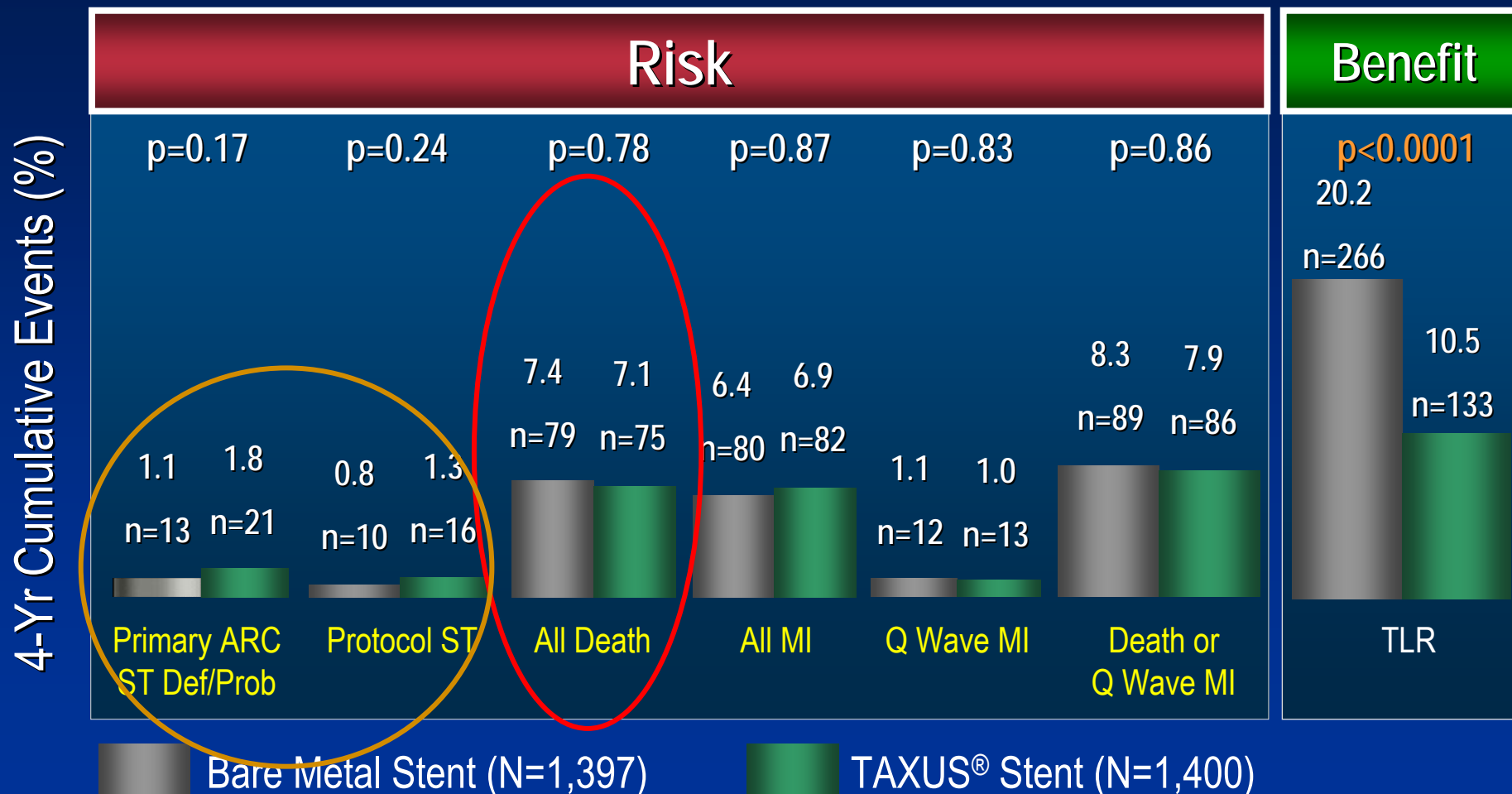
Event	0-1 Year (% / patient-year)			
	Taxus	BMS	Risk Difference	
			Δ	p
All Death	1.97	1.90	0.08	0.89
Cardiac Death	1.10	1.31	-0.22	0.60
All MI	4.24	4.76	-0.51	0.52
QWMI	0.66	0.37	0.30	0.28
Total ARC ST All	1.39	1.46	-0.07	0.88
Total ARC ST Def/Prob	0.88	0.81	0.07	0.83
TLR	7.37	17.59	-10.21	<0.0001
TVR-CABG	1.69	3.19	-1.50	0.01

1-4 Years* (% / patient-year)			
Taxus	BMS	Risk Difference	
		Δ	p
1.71	1.87	-0.16	0.65
0.57	0.60	-0.03	0.88
1.01	0.71	0.3	0.23
0.18	0.25	-0.07	0.57
0.72	0.78	-0.06	0.79
0.36	0.25	0.11	0.45
1.57	2.34	-0.77	0.04
0.47	1.04	-0.57	0.01

4-year Cumulative Rates (K-M estimate [%])			
Taxus	BMS	Risk Difference	
		Δ	p
7.1	7.4	-0.3	0.78
2.7	3.1	-0.4	0.64
6.9	6.4	0.5	0.87
1.0	1.1	-0.1	0.83
3.5	3.6	-0.1	0.84
1.9	1.5	0.4	0.52
10.5	20.2	-9.7	<0.0001
3.3	6.4	-3.1	0.0004

# TAXUS® Stent 4-Year Meta-Analysis reinforces the positive benefit / risk profile

TAXUS I, II-SR, IV, V (N=2,797)

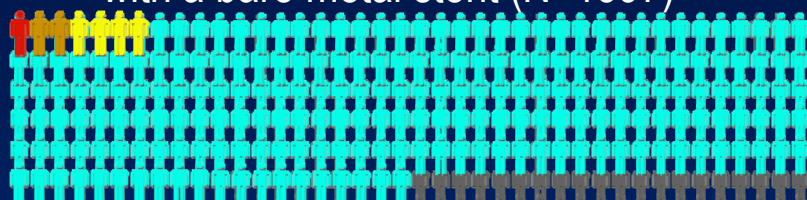


\*TAXUS Stent 4-year meta-analysis includes TAXUS I (5 yr), II-SR cohort I (4 yr), IV (4 yr), V (2 yr) (N=2,797). Kaplan Meier estimate and p values from log rank

# Restenosis is not benign

Any excess in Death or MI from the 6 additional Protocol-defined stent thromboses with TAXUS is counter-balanced by an offsetting 142-pt reduction in first TLR and TLR-related events

with a bare metal stent (N=1397)



260 TLRs<sup>a</sup> 1 Death 2 QMI 5 NQMI

10 STs 3 Deaths 4 QMI 4 NQMI

Stent-Related 4 Deaths 6 QMI 9 NQMI

Other Cardiac 31 Deaths 6 QMI 61 NQMI

Non-cardiac 44 Deaths

**TOTAL 79 Deaths 12 QMI 70 NQMI**



= TLR = Death = ST = QW MI = Non-QW MI

with a TAXUS stent (N=1400)



118 TLRs<sup>b</sup> 0 Death 0 QMI 4 NQMI

16 STs 3 Deaths 7 QMI 7 NQMI

Stent-Related 3 Deaths 7 QMI 11 NQMI

Other Cardiac 28 Deaths 6 QMI 60 NQMI

Non-cardiac 44 Deaths

**TOTAL 75 Deaths 13 QMI 71 NQMI**



a.Exclude 6 TLR due to ST

b.Exclude 13 TLR due to ST; and 2 TLR ≤ 30days.



# Agenda

Background

Stent Thrombosis – ARC Definitions

TAXUS Meta-Analysis – All Patients

TAXUS Meta-Analysis – Subgroups

- *Patient groups that traditionally have higher event rates*
  - *Diabetics*
  - *Small vessels ( $\leq 2.5$  mm)*
  - *Long lesions ( $\geq 28$  mm)*
  - *Multiple stents in single vessels*

Antiplatelet Therapy Usage

Summary and Conclusions

# TAXUS<sup>®</sup> Stent Subgroup Analysis

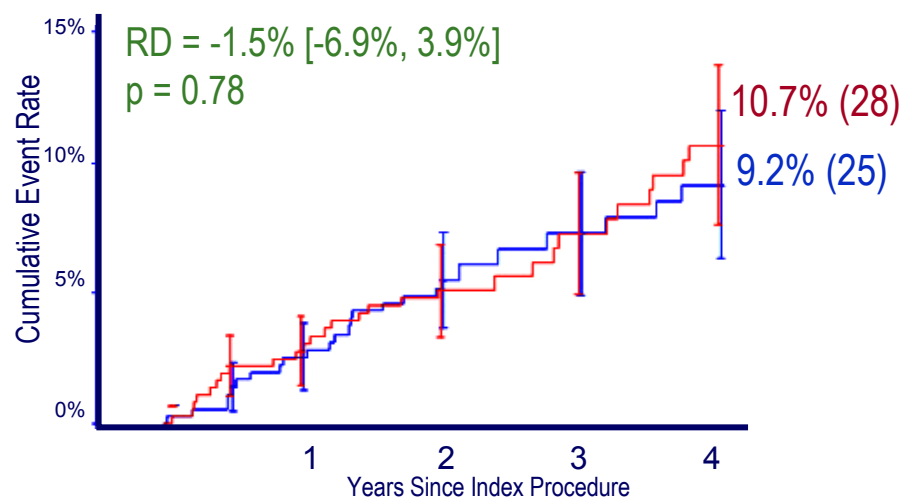
## Diabetics (N = 715)

— TAXUS (N=356) — BMS (N=359)

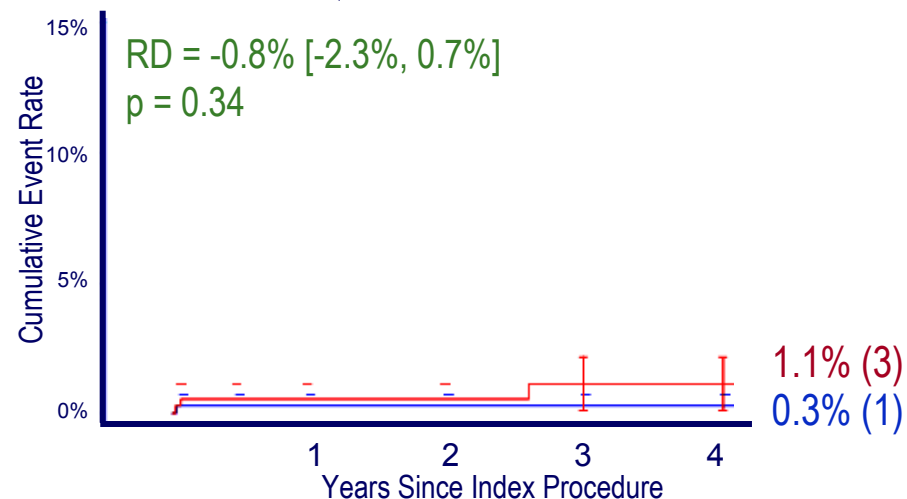
RD = Rate Difference = TAXUS — BMS

No increase Increase

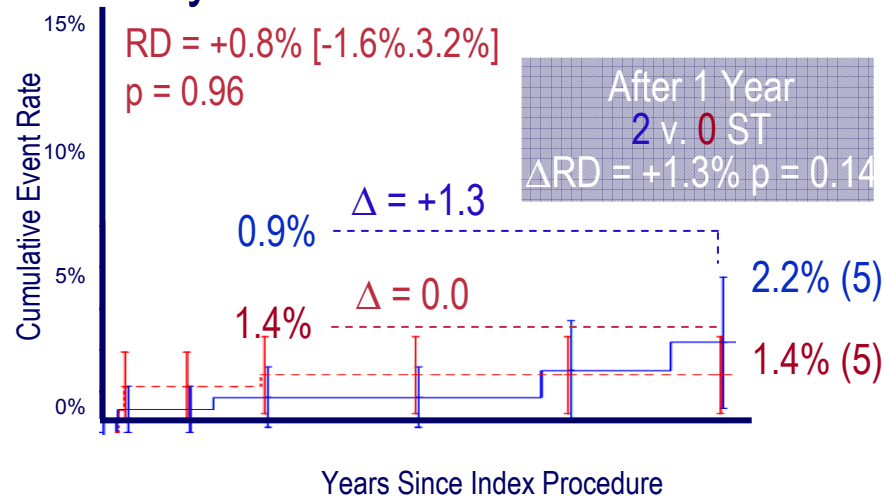
### All Death



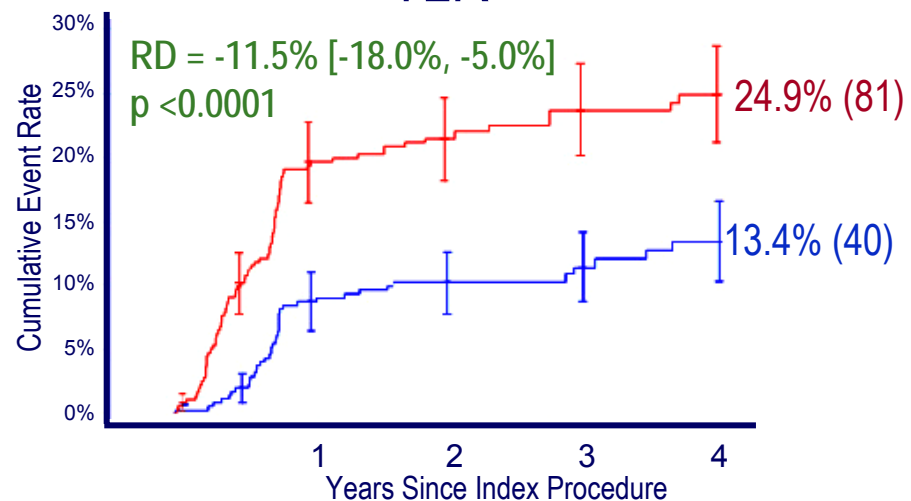
### Q Wave MI



### Primary ARC ST Definite/Probable



### TLR





# TAXUS<sup>®</sup> Stent Subgroup Analysis

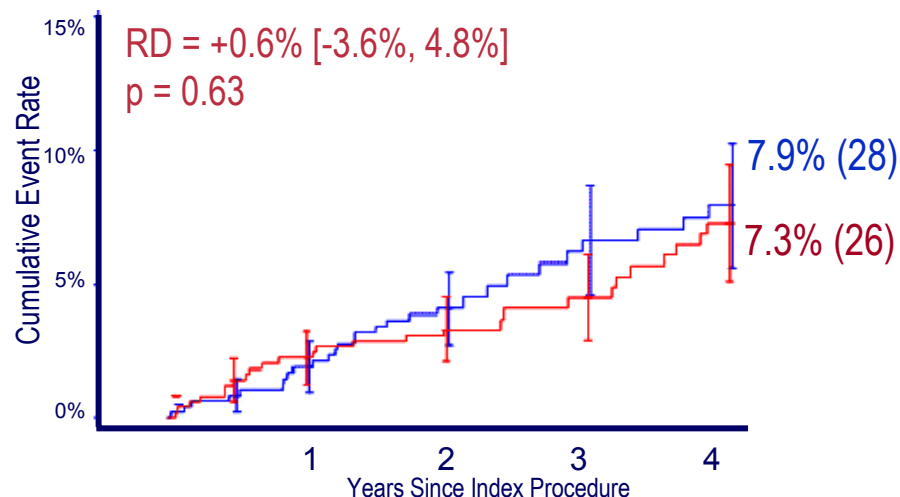
## Small Vessels RVD $\leq 2.5\text{mm}$ Visual (N = 965)

— TAXUS (N=475) — BMS (N=490)

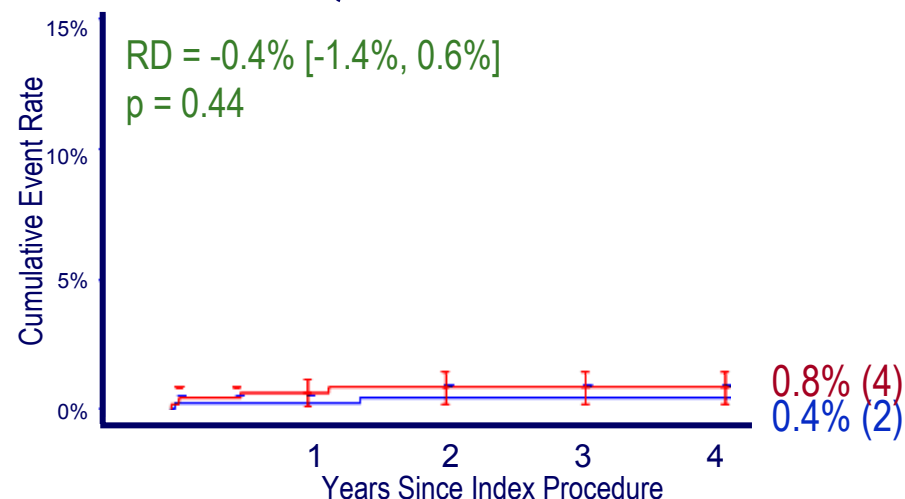
RD = Rate Difference = TAXUS — BMS

No increase Increase

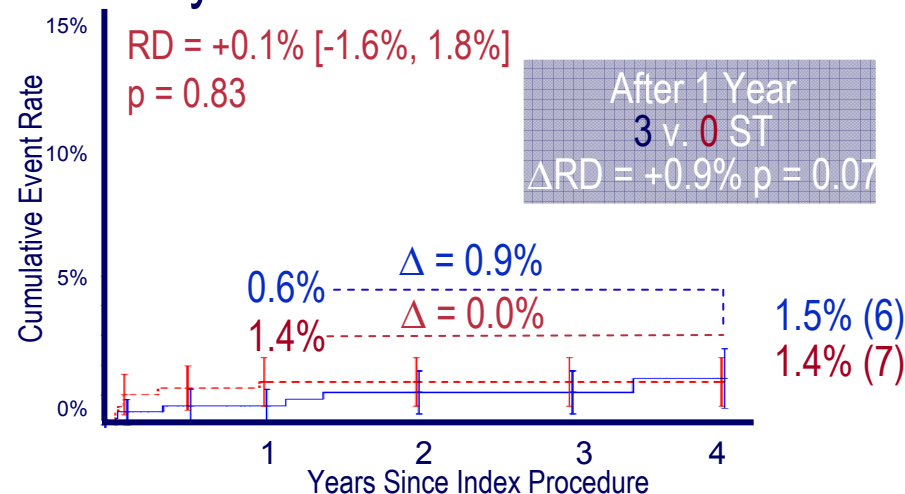
### All Death



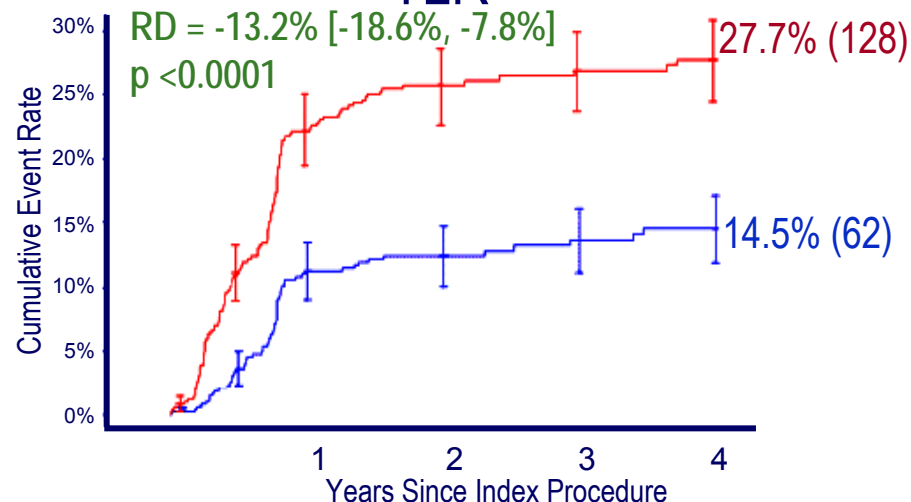
### Q Wave MI



### Primary ARC ST Definite/Probable



### TLR



# TAXUS<sup>®</sup> Stent Subgroup Analysis

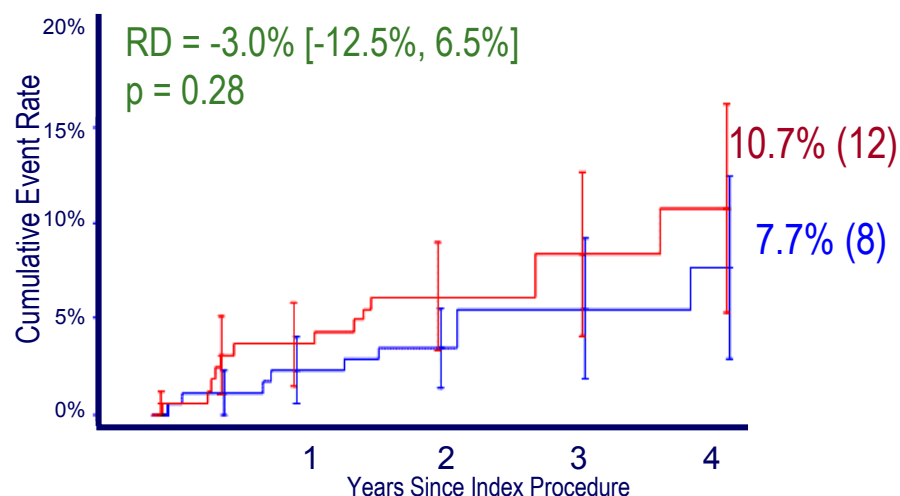
## Long Lesions $\geq 28\text{mm}$ Visual (N = 341)

— TAXUS (N=178) — BMS (N=163)

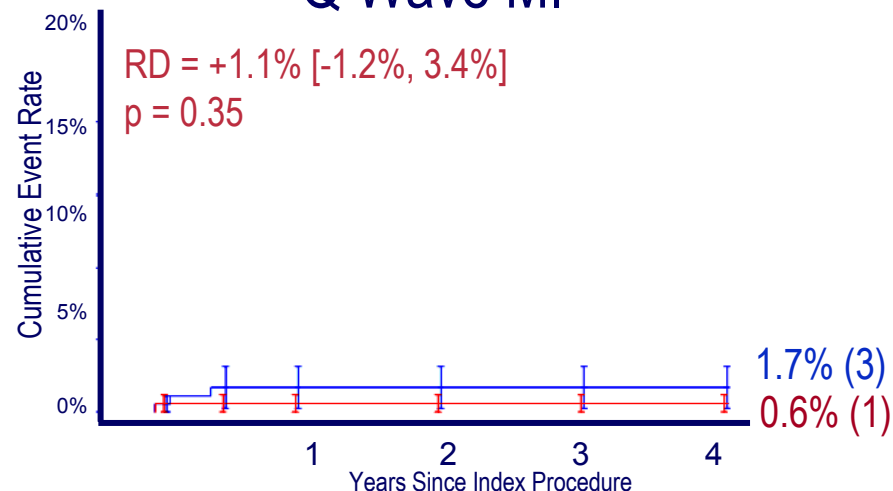
RD = Rate Difference = TAXUS — BMS

No increase Increase

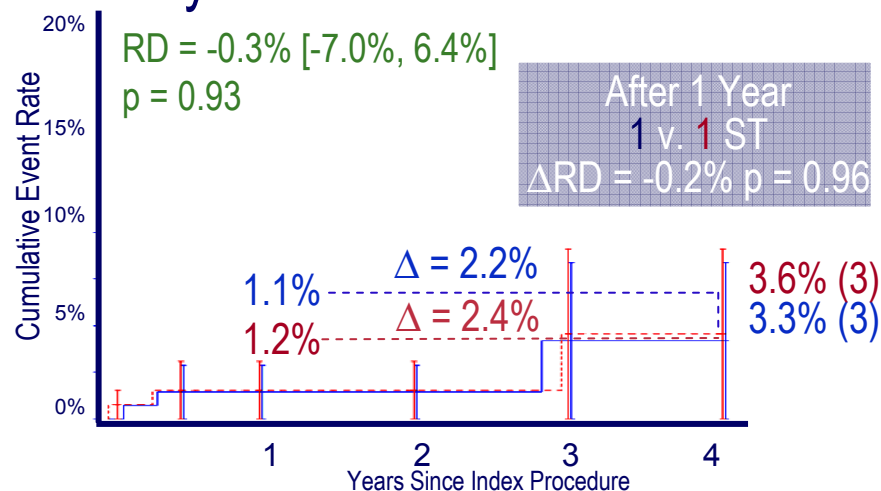
### All Death



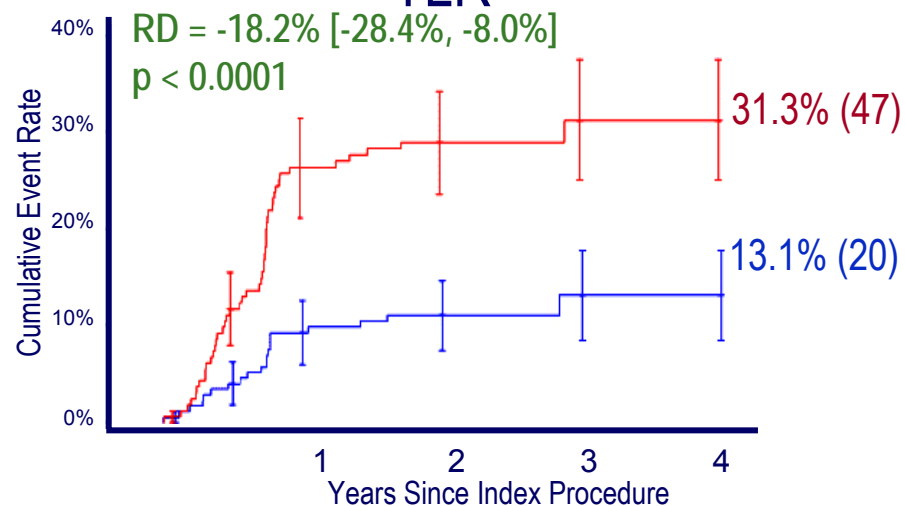
### Q Wave MI



### Primary ARC ST Definite/Probable



### TLR



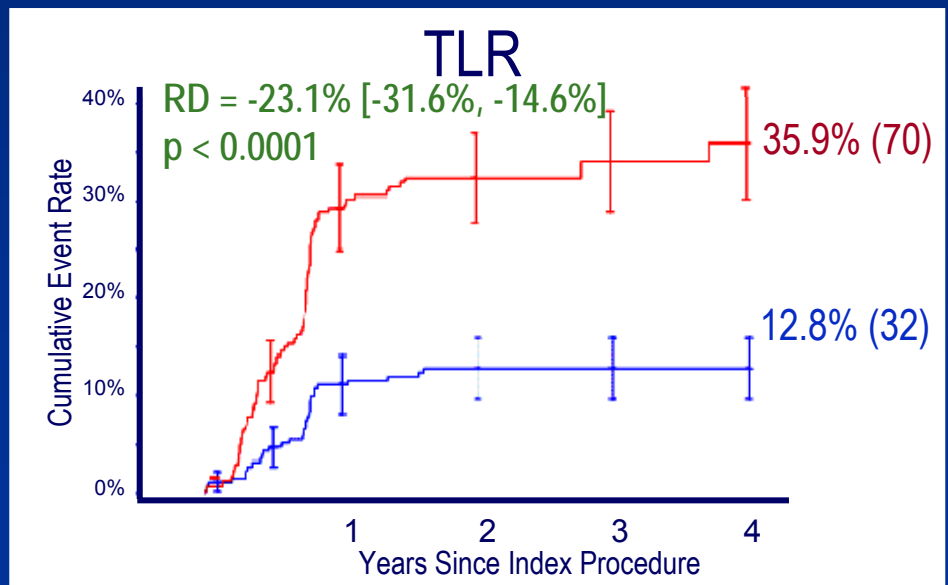
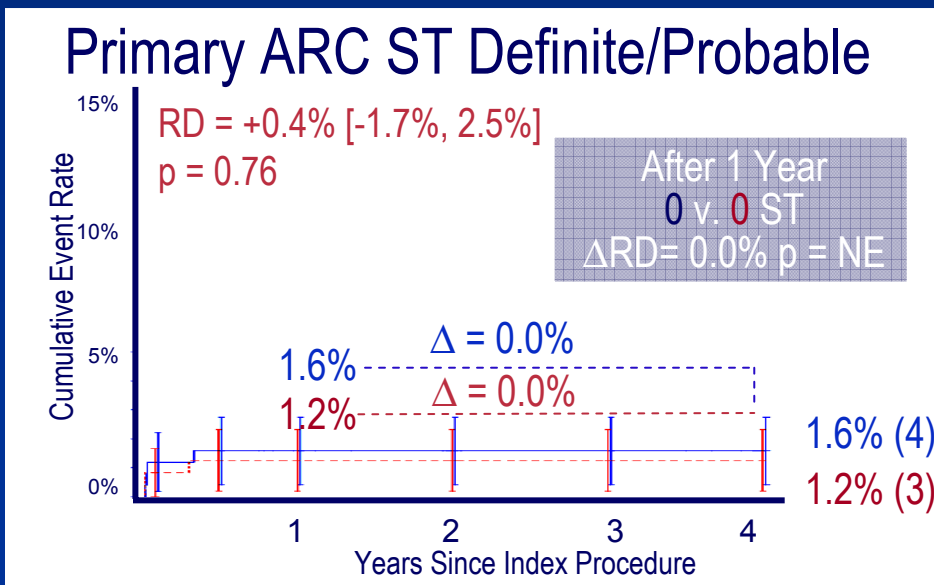
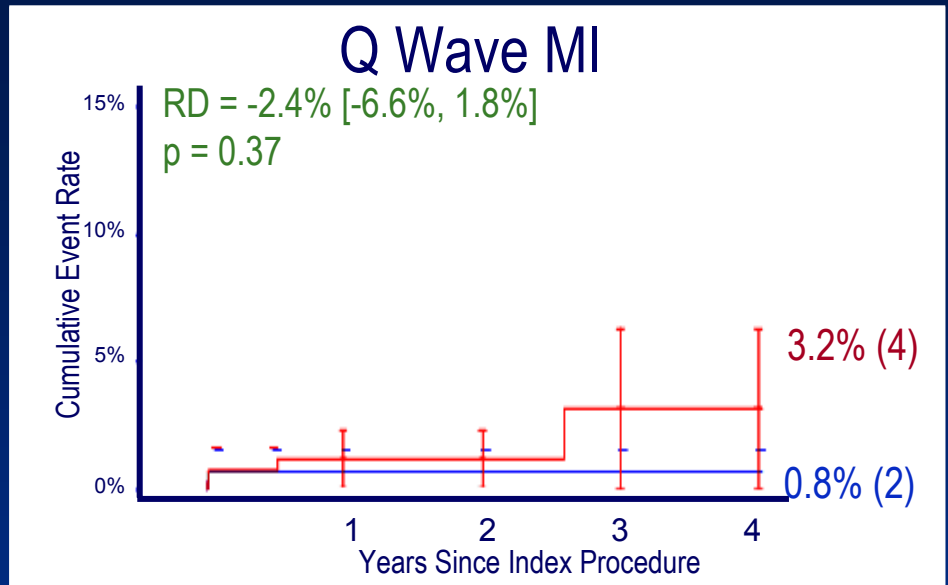
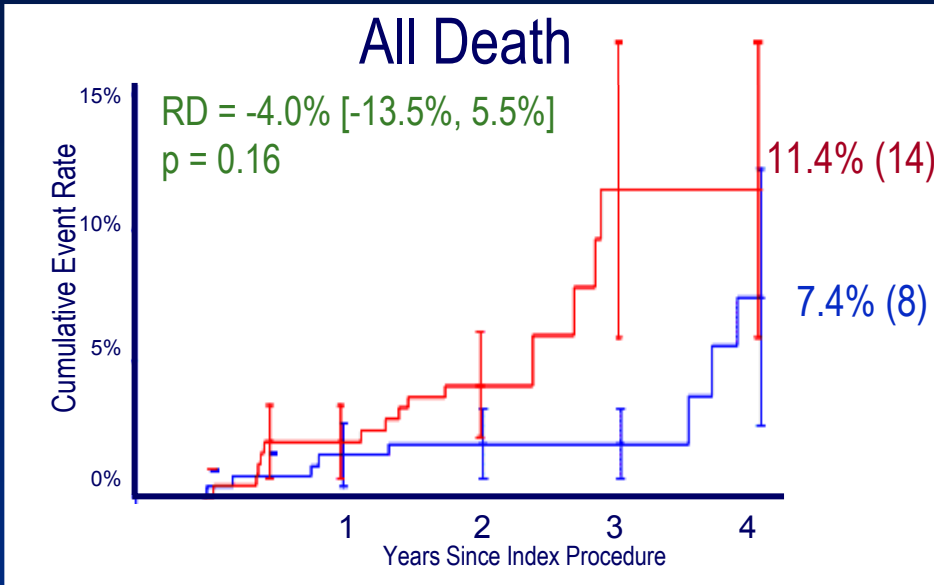
# TAXUS<sup>®</sup> Stent Subgroup Analysis

## Multiple Stents in Single Vessels (N = 497)

— TAXUS (N=255) — BMS (N=242)

RD = Rate Difference = TAXUS — BMS

No increase Increase



# Summary: TAXUS<sup>®</sup> Stent Subgroup Difference Signals

$\Delta$  = Rate Difference = Taxus - BMS

No increase

Increase

Event	1 year	4 year cum	4 year cumulative			
	Overall N= 2797	Overall N=2797	Diabetics N=715	RVD $\leq$ 2.5mm N= 965	Lesion $\geq$ 28 N =341	Multiple Stents N=497
All Death	0.08 p=0.89	-0.3 p=0.78	-1.5 p=0.78	0.6 p=0.63	-3.0 p=0.28	-4.0 p=0.16
Cardiac Death	-0.22 p=0.60	-0.4 p=0.64	1.0 p=0.64	-0.4 p=0.95	3.0 p=0.44	2.2 p=0.53
All MI	-0.51 p=0.52	0.5 p=0.87	-0.2	-0.6 p=0.28	9.5 p=0.01	-1.9 P=0.53
QWMI	0.30 p=0.28	-0.1 p=0.83	-0.8 p=0.34	-0.4 p=0.44	1.1 p=0.35	-2.4 p=0.37
Total ARC ST All	-0.07 p=0.88	-0.1 p=0.84	1.5 p=0.79	-0.7 p=0.56	1.1 p=0.90	-0.1 p=0.93
Total ARC ST Def/Prob	0.07 p=0.83	0.4 p=0.52	0.8 p=0.96	-0.4 p=0.48	1.1 p=0.91	-0.1 p=0.94
TLR	-10.21 p<0.0001	-9.7 p<0.0001	-11.5 p<0.0001	-13.2 p<0.0001	-18.2 p<0.0001	-23.1 p<0.0001
TVR-CABG	-1.50 p=0.01	-3.1 p=0.0004	-2.6 p=0.13	-5.1 p=0.0006	-6.9 p=0.02	-5.3 P=0.08

# Agenda

Background

Stent Thrombosis – ARC Definitions

TAXUS Meta-Analysis – All Patients

TAXUS Meta-Analysis – Subgroups

Antiplatelet Usage

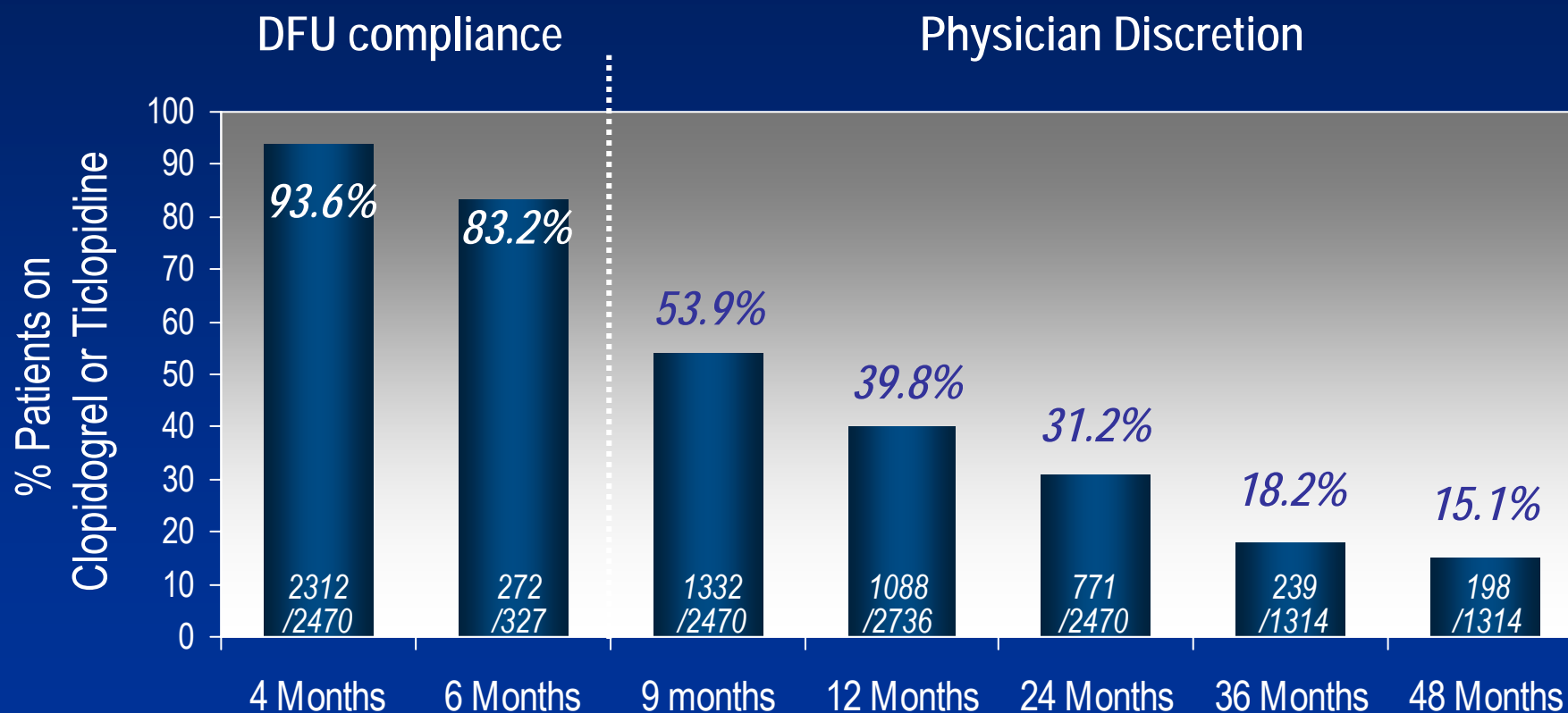
Summary and Conclusions

# Long-Term-Thienopyridine Intake in TAXUS Clinical Trial Program

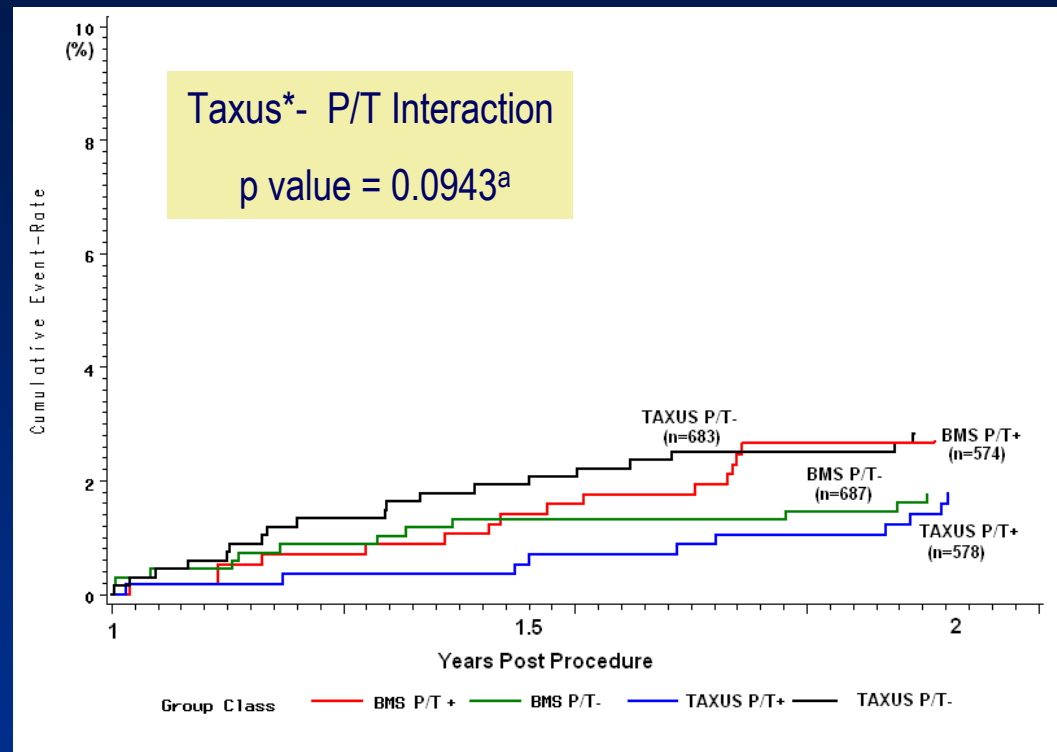
## Limitations

No formal medication log

Incomplete data collection between trials at various time points



# Death or MI During Follow-up to 2 Years Post-Procedure According to Plavix<sup>®</sup> /Ticlid<sup>®</sup> Usage at 12 Months



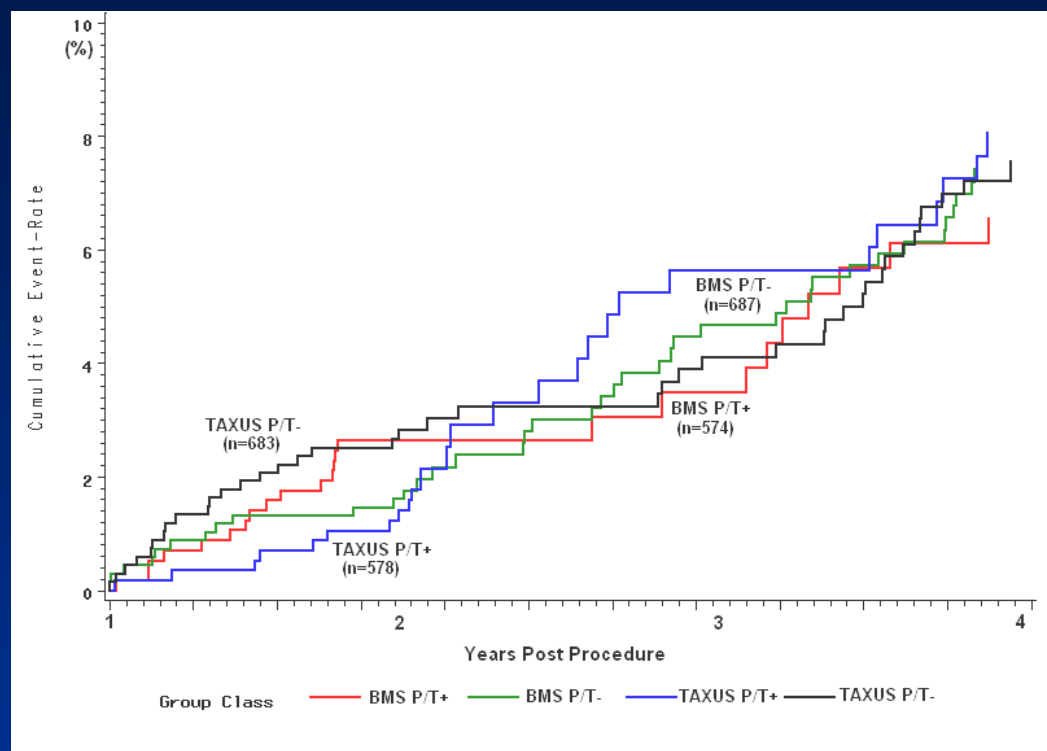
(n=2,522)		Plavix/Ticlid Use Overtime		ASA Use Overtime	
Group	n	12 M Landmark	24 M*	12 M Landmark†	24 M*
BMS P/T+	574	100%	75.9%	97.7%	96.5%
BMS P/T-	687	-	-	97.3%	96.1%
TAXUS P/T+	578	100%	73.7%	96.9%	96.5%
TAXUS P/T-	683	-	-	96.1%	93.2%

† Medication data available in TAXUS 2, 4, and 5 only

\* Medication data available in TAXUS 4, 5 only

a. adjusted Cox regression model, additionally adjusted for patient baseline and lesion characteristics  
Plavix and Ticlid are trademarks of Sanofi-Aventis

# Death or MI During Follow-up to 4 Years Post-Procedure According to *Plavix*<sup>®</sup> /*Ticlid*<sup>®</sup> Usage at 12 Months



† Medication data available in TAXUS 2, 4, 5

\* Medication data available in TAXUS 4, 5, only

\*\* Medication data available in TAXUS 4 only

(n=2,522)		Plavix/Ticlid Use Overtime				ASA Use Overtime			
Group	n	12 M Landmark	24 M*	36 M**	48 M**	12 M Landmark†	24 M*	36 M*	48 M**
BMS P/T+	574	100%	75.9%	70.1%	63.6%	97.7%	96.5%	93.2%	92.7%
BMS P/T-	687	-	-	-	-	97.3%	96.1%	95.0%	91.7%
TAXUS P/T+	578	100%	73.7%	66.2%	60.6%	96.9%	96.5%	92.5%	89.5%
TAXUS P/T-	683	-	-	-	-	96.1%	93.2%	91.3%	90.4%



## Summary -- On-label uses of the Taxus<sup>®</sup> SR Stent System

The Taxus I, II, IV, and V randomized trials compared the TAXUS<sup>®</sup> Slow-Release (SR) Stent to Bare Metal Stent (BMS) controls in 2,797 patients, median 4 year follow-up:

- a PROFOUND *clinical benefit* reduction in repeat revasc. ( $\Delta - 9.7\%$ , or 48 % relative)
- with trends towards LESS Death ( $\Delta -0.3\%$ ) or Q-MI ( $\Delta -0.1\%$ ) through last follow-up

This favorable risk benefit was seen in all studied sub-groups, with TLR reductions of :

- Diabetics (n=715)  $\Delta - 11.5\%$ , (46% relative),  $p < 0.0001$
- Small vessels ( $\leq 2.5\text{mm}$ ) (n=965)  $\Delta - 13.2\%$ , (48% relative),  $p < 0.0001$
- Long Lesions  $\geq 28\text{ mm}$  (n=341)  $\Delta - 18.2\%$ , (58% relative),  $p < 0.0001$
- Multiple Stents/vessel (n=497)  $\Delta - 23.1\%$ , (64% relative),  $p < 0.0001$

Stent thrombosis rates were not statistically different from the BMS Control for either :

	<u>4 years cum.</u>	or	<u>beyond 1 year (VLST)</u>
per protocol	1.3 vs. 0.8 %		$\Delta +0.4\%$ , $p = 0.057$
ARC 1 <sup>o</sup> def.+prob.	1.8 vs. 1.1 %		$\Delta +0.5\%$ , $p = 0.081$
ARC Total	3.5 vs. 3.6 %		$\Delta - 0.1\%$ , $p = 0.786$

Plavix use beyond 6 months with TAXUS showed a trend towards reduced Death or MI

Thank you

# DISCUSSION SLIDES

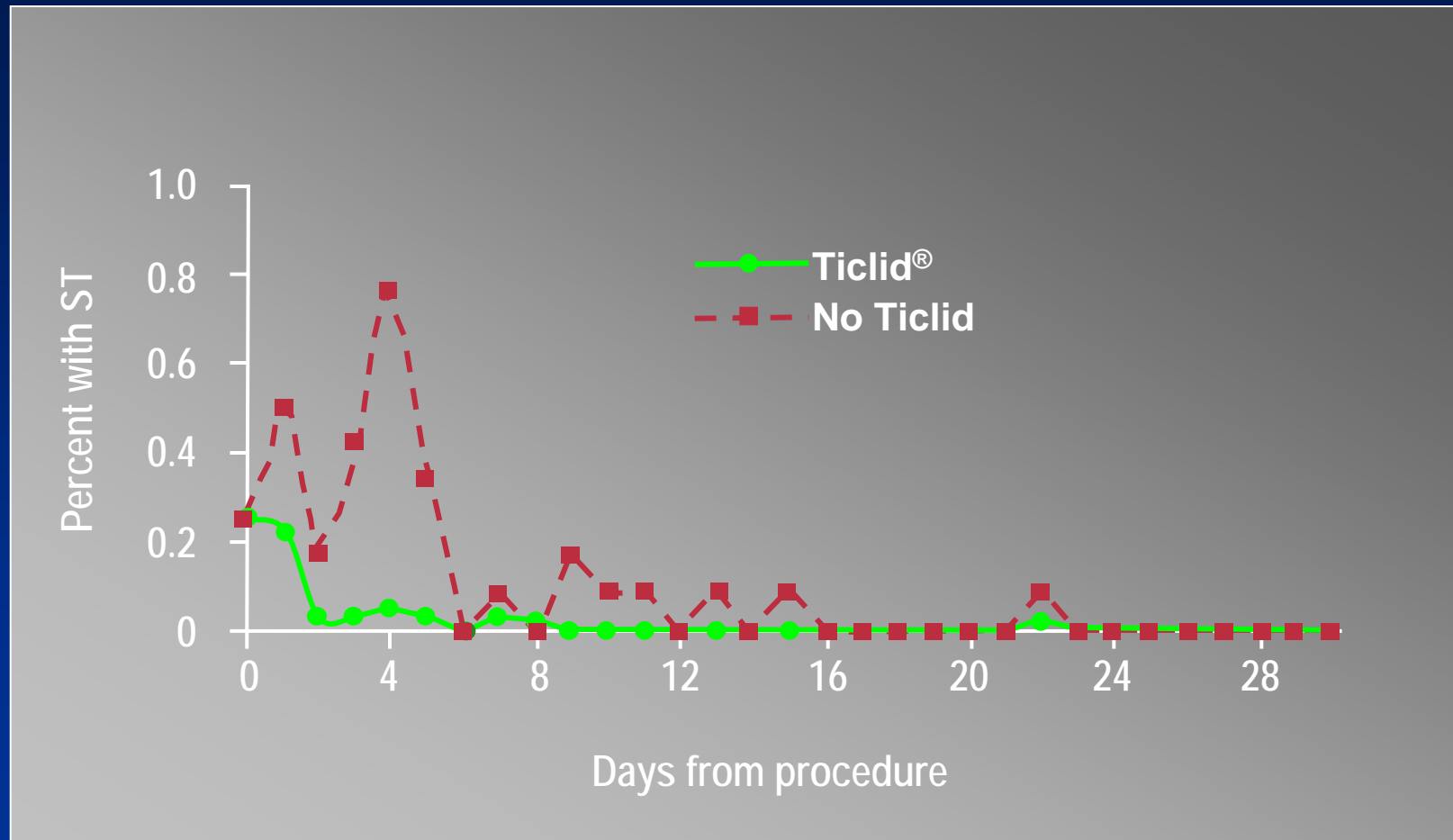
# Background

- Drug-eluting stents are a major new breakthrough for reducing restenosis and the need for re-intervention in PCI procedures
- The potent anti-proliferative drugs and the polymers that release them clearly and significantly alter vascular biological reaction, with the benefit of reduced in-stent restenosis and repeat revascularization
- They may, however, also cause *unintended consequences* such as delayed or incomplete endothelial coverage, inflammation, or positive remodeling, each of which have now been observed in man
- There have been suggestions that these consequences may lead to increases in adverse events (stent thrombosis after 1 year, late MI, or late death) compared to traditional bare metal stents
- If there were net increases in late death or MI with DES versus BMS, they might offset the potential benefits of reduced restenosis, and potentially lead to restrictions on DES use

## Background

### Time course of Stent Thrombosis with BMS

*Rationale for 1 month Duration of Anti-platelet Therapy*



2-4 weeks duration of anti-platelet therapy adequate for BMS

BMS = bare metal stent; ST = stent thrombosis.  
Cutlip DE et al. *Circulation*. 2001;103:1967.

# Number of Stent Thrombosis Cases

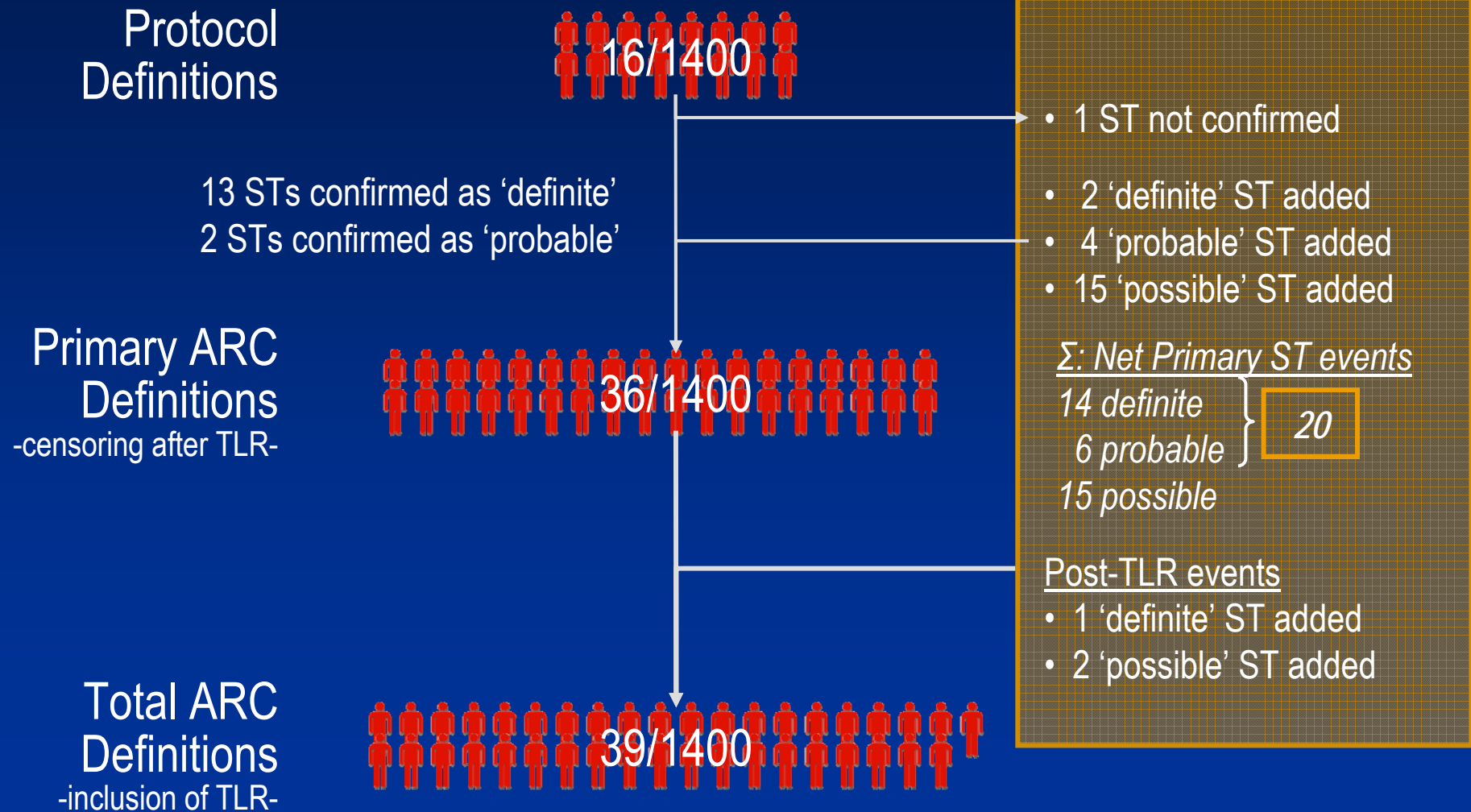
## *BSC vs. ARC Definitions*

ALL Stent Thrombosis Grouped by Days from Index Procedure

		Days from Index Procedure				
		0 - 1	2-30	31-365	366+	TOTAL
BSC Protocol	TAXUS	3	4	3	6	16 <sup>a</sup>
	Control	3	6	2	1	10 <sup>a</sup>
All ARC Definitions (Primary = Not post-TLR)	TAXUS	3	4	3 + 8	6 + 12 = 18	36 <sup>a</sup>
	Control	3	6	2 + 9	1 + 15 = 16	33 <sup>a</sup>
All ARC Definitions (Total = with post-TLR)	TAXUS	3	4	3 + 9	6 + 14 = 20	39 <sup>a</sup>
	Control	3	6	2 + 11	1 + 21 = 22	41 <sup>a</sup>

a. Patients may have multiple ST in different categories.

# Patient flow in TAXUS Group – Impact of ARC reassessment



# Patient flow in Control Group – Impact of ARC reassessment

## ARC Reassessment

- 2 'definite' ST added
- 2 'probable' ST added
- 20 'possible' ST added \*

### $\Sigma$ : Net Primary ST events

10 definite  
3 probable  
20 possible

13

### Post-TLR events

- 4 'definite' ST added
- 1 'probable' ST added
- 3 'possible' ST added

10/1397

Protocol  
Definitions

8 STs confirmed as 'definite'  
1 ST confirmed as 'probable'  
1 ST confirmed as 'possible'

33/1397

Primary ARC  
Definitions  
-censoring after TLR-

41/1397

Total ARC  
Definitions  
-inclusion of TLR-

- One patient had a probable and possible event



# Details about ST after TLR in TAXUS



## Case 1

Definite ST on day 924 – after 3 (!! ) TLRs attempts with cutting balloon and brachytherapy each on days 517, 593, and 924



## Case 2

Possible ST on day 185 - 70 days after TLR with a BMS plus brachytherapy



## Case 3

Possible ST on day 439 – 229 days after TLR with two BMS

# Details about ST after TLR in Control -1-



## Case 1

Definite ST on day 329 – 137 days after TLR with cutting balloon and brachytherapy (subsequent 90% restenosis)



## Case 2

Two (!! ) definite STs on days 429 and 569 – after 3 revascularizations (day 85 with cutting balloon and brachytherapy, day 283 with 2 TAXUS stents (no restenosis), and day 429 with CYPHER (!! ) in neighboring side branch)



## Case 3

Three (!! ) definite STs on days 607, 611, and 640 – after 4 revascularizations (day 293 with cutting balloon and brachytherapy, day 607 with TAXUS outside of target vessel, day 610 with TAXUS in target lesion, and day 640 (failed attempt) with medical therapy)



## Case 4

Definite ST on day 941 – 669 days after TLR with cutting balloon and brachytherapy

## Details about ST after TLR in Control -2-



### Case 5

Probable ST on day 553 – 245 days after TLR with stent



### Case 6

Possible STs on day 143 – 3 days after TLR with atherectomy and brachytherapy



### Case 7

Possible ST on day 620 – 258 days after TLR with brachytherapy

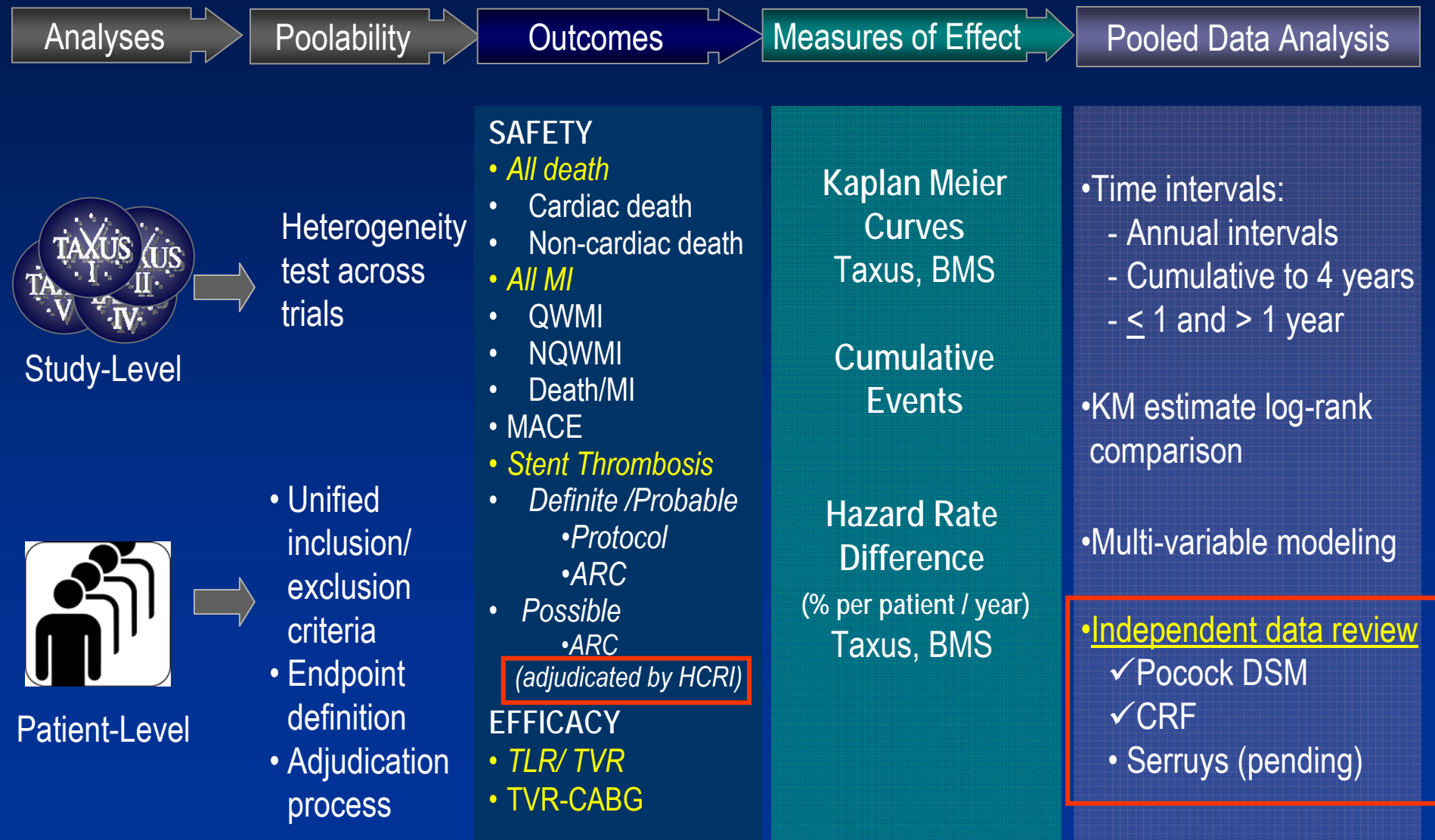


### Case 8

Possible ST on day 1125 – 846 days after cutting balloon and brachytherapy

# Methodology and *Data Synthesis*

Outside adjudication of all endpoints; independent review of all data



# Cypher® Prior TLR and Stent Thrombosis

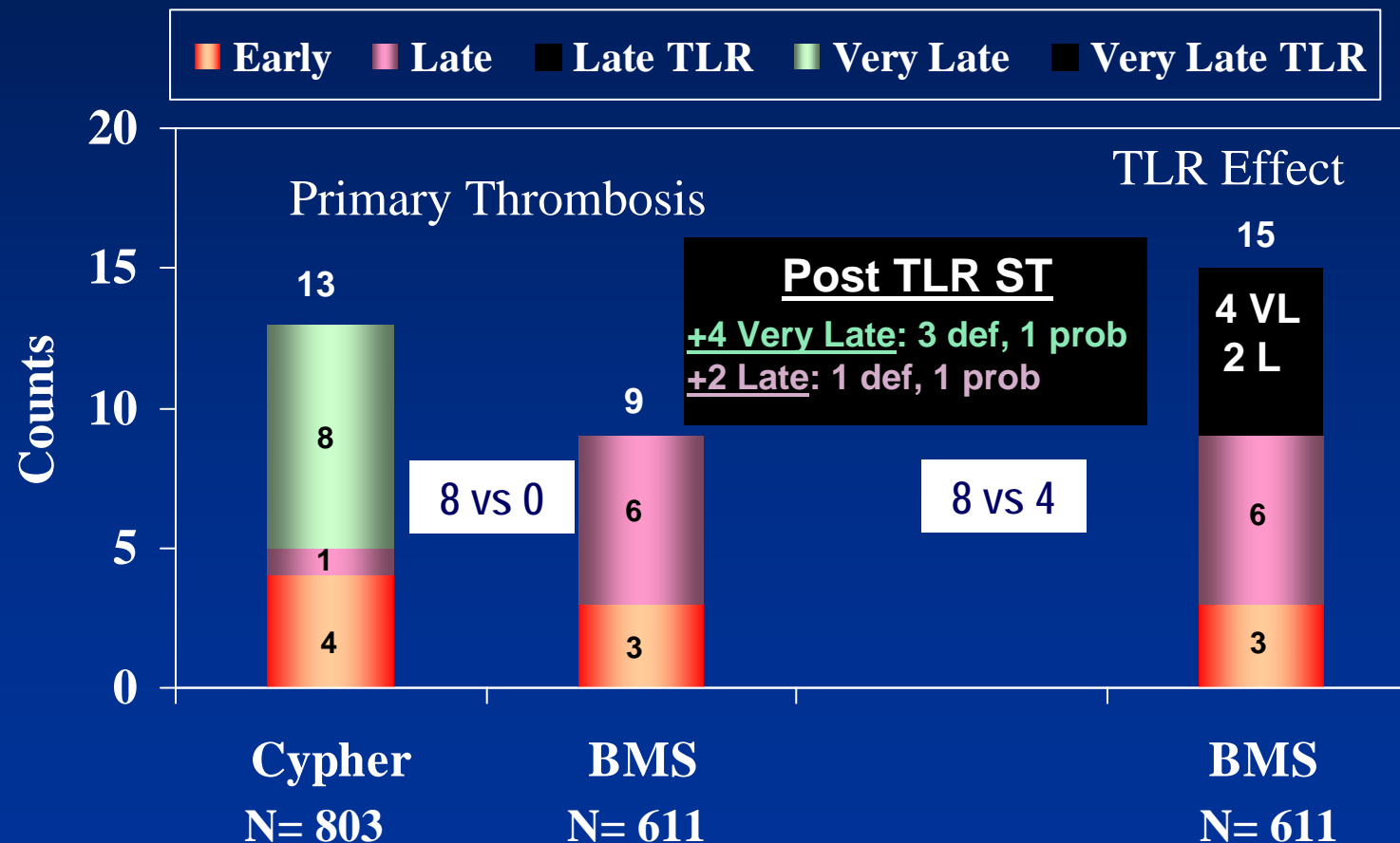
Don Cutlip, presentation at TCT 2006

	DES ST (any) N = 27	BMS ST (any) N = 27
Prior TLR	<p>QUESTION: Does a late thrombosis following brachytherapy to treat a BMS in-stent restenosis REALLY count <i>mechanistically</i> as a BMS stent thrombosis?</p> <p>Or is it preferable to still censor such events from our <i>mechanistic</i> understanding of whether DES thrombose more than BMS, knowing that we can capture any missed events in our intent to treat analysis of Death and MI?</p>	
Time from		
ST Classifi		
TLR Procedure	0	10 (7/10 brachy)
BMS only	0	0
Any SES	0	1
PTCA only	0	2
Brachytherapy/PTCA	0	5
Brachytherapy/stent	0	2

\* 1 Patient had stent thrombosis 1539 days after procedure.

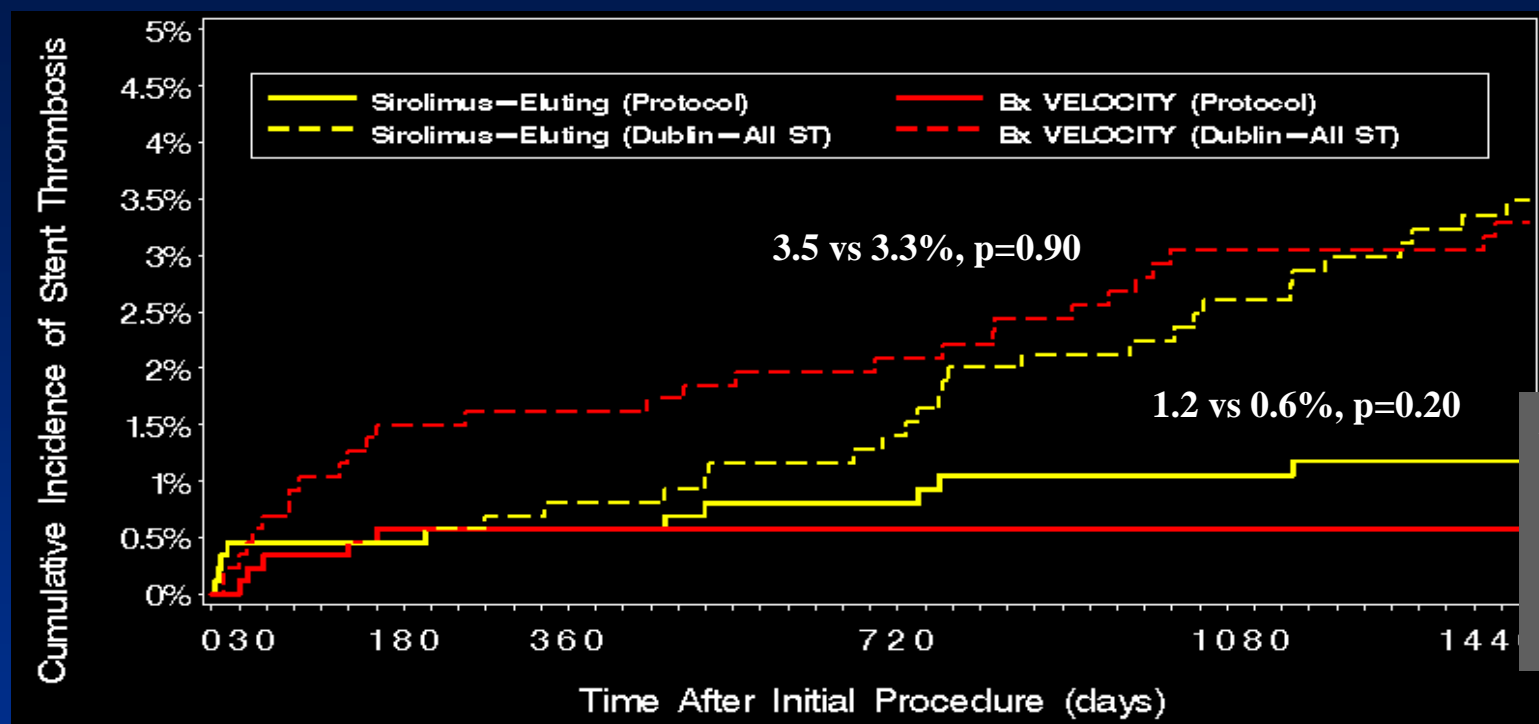
# Cypher® Primary Stent Thrombosis

## Counts of Definite/Probable Thrombosis – Prior TLR Effect



Modified minimally from Don Cutlip, presentation at TCT 2006

# The difference is profound!



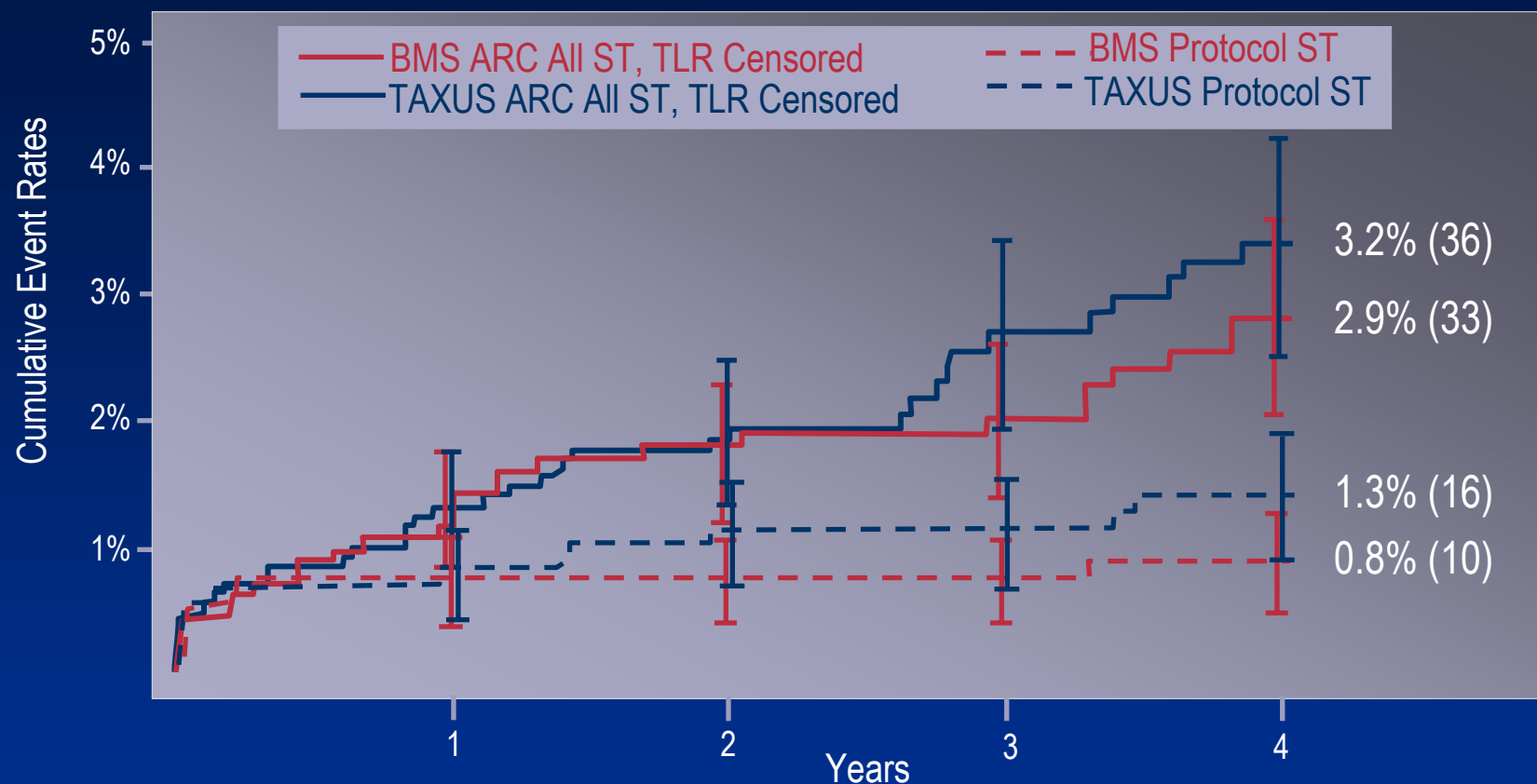
Cypher

BMS

Days	30	90	360	720	1080	1440
# Entered	878	872	860	831	806	801
# Events	4	0	2	5	10	8
# Entered	870	867	853	830	809	805
# Events	3	5	6	4	9	1

Cutlip TCT 2006

# Taxus the difference is profound!



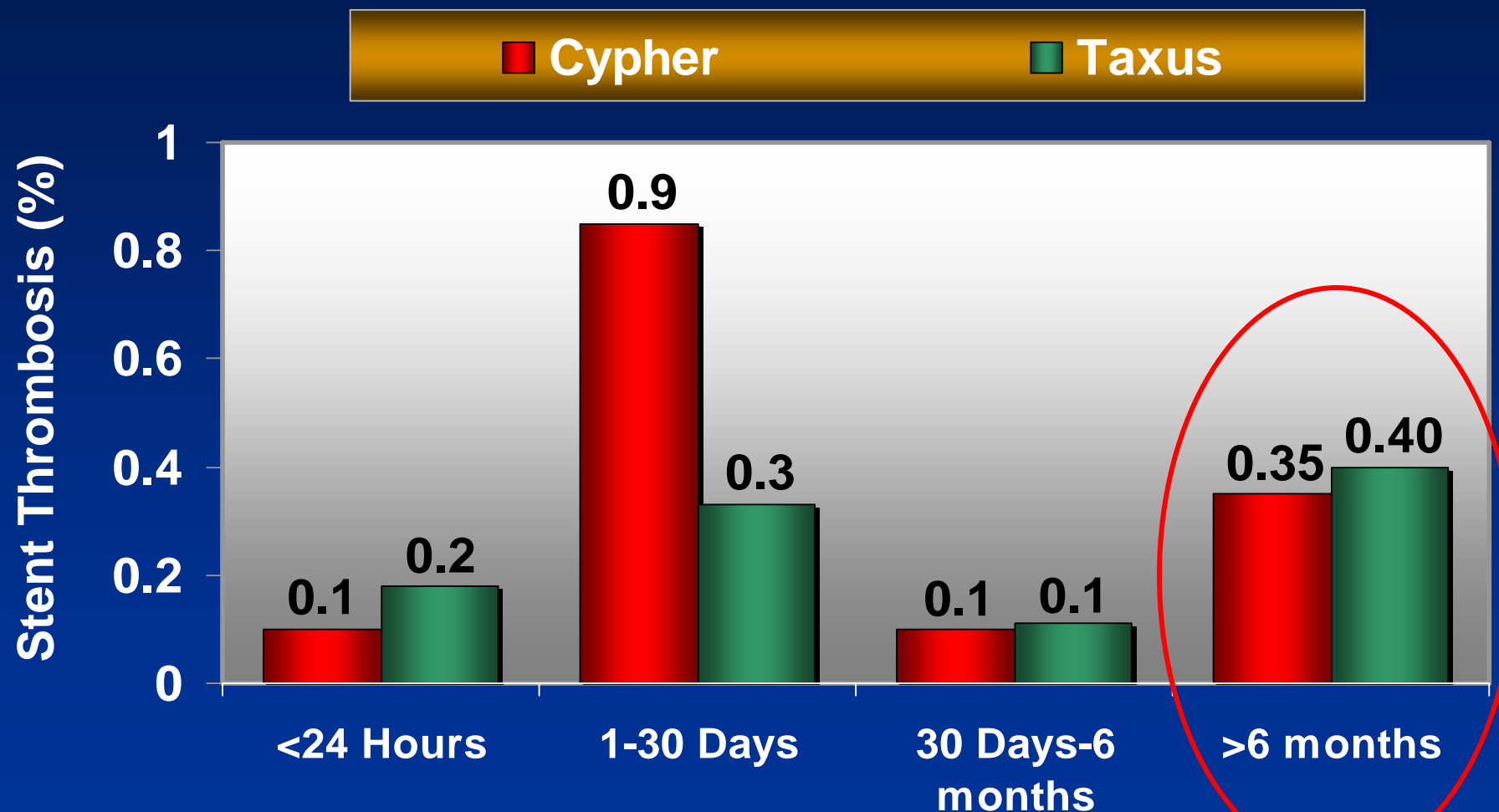
	Years	1		2		3		4	
		ARC	Protocol	ARC	Protocol	ARC	Protocol	ARC	Protocol
TAXUS	# Entered	1400	1400	1359	1361	1336	1338	1216	1217
	# Events	18	10	8	4	6	0	4	2
BMS	# Entered	1397	1397	1362	1363	1335	1342	1231	1238
	# Events	18	9	6	0	2	0	7	1



## Background

*Parity confirmed in broader data sets*

*ESTROFA : Stent thrombosis incidence*



Dr. de la Torre, TCT 2006

(13,500 DES @15 Spanish Centers)

# TAXUS Diabetics (N = 715)

## Annual Event Rates

$\Delta$  = Rate Difference = TAXUS — BMS  
 No increase      Increase

Event	0-1 Year (% / patient-year)			
	Taxus	BMS	Rate Difference	
			$\Delta$	p
All Death	2.60	2.84	-0.25	0.84
Cardiac Death	1.73	1.99	-0.26	0.80
All MI	3.57	6.28	-2.72	0.12
QWMI	0.29	0.57	-0.28	0.57
ST Protocol	0.58	1.43	-0.86	0.27
Total ARC ST All	1.74	2.29	-0.56	0.61
TLR	8.95	21.81	-12.86	<0.0001
TVR-CABG	2.62	4.67	-2.05	0.16

1-4 Years (% / patient-year)			
Taxus	BMS	Rate Difference	
		$\Delta$	p
2.52	2.70	-0.18	0.85
1.11	0.60	0.50	0.33
1.28	0.61	0.68	0.21
0.00	0.15	-0.15	0.34
0.16	0.00	0.16	0.30
0.95	0.60	0.35	0.48
2.09	2.46	-0.37	0.66
0.95	1.37	-0.41	0.53

4-year Cumulative Rates (K-M estimate [%])			
Taxus	BMS	Rate Difference	
		$\Delta$	p
9.2	10.7	-1.5	0.78
4.4	3.4	1.0	0.64
7.2	7.4	-0.2	0.57
0.3	1.1	-0.8	0.34
1.2	1.4	-0.2	0.50
4.6	3.1	1.5	0.79
13.4	24.9	-11.5	<0.0001
7.2	9.8	-2.6	0.13

p-value from Log rank test of no difference in the Kaplan-Meier curves between groups

# Taxus Subgroup Analysis

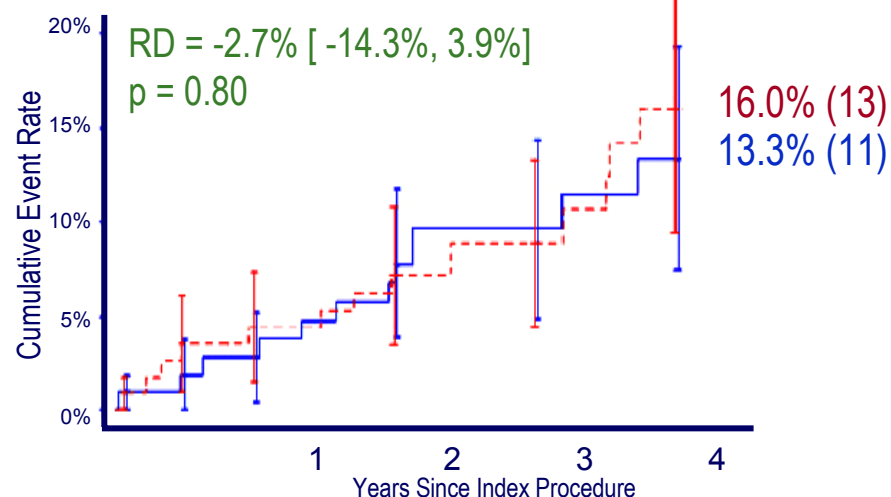
## Insulin-Requiring Diabetics (N = 221)

— TAXUS (N=107) — BMS (N=114)

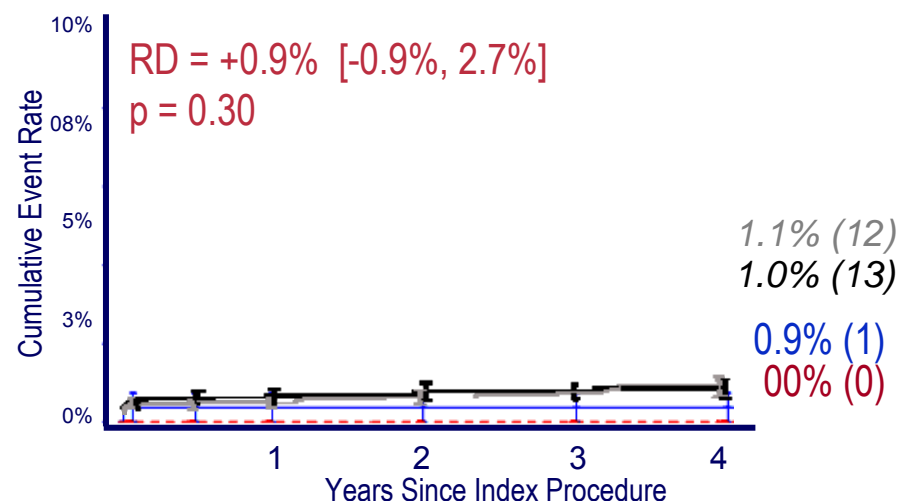
RD = Rate Difference = TAXUS — BMS

No increase Increase

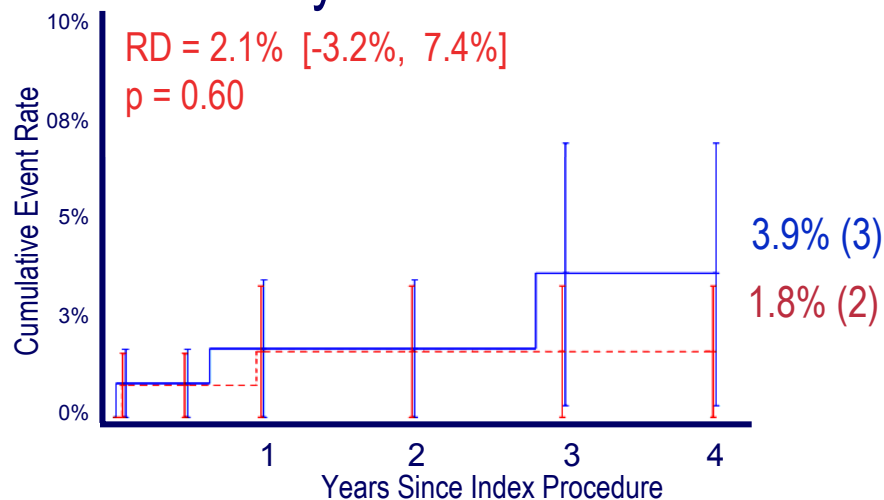
### All Death



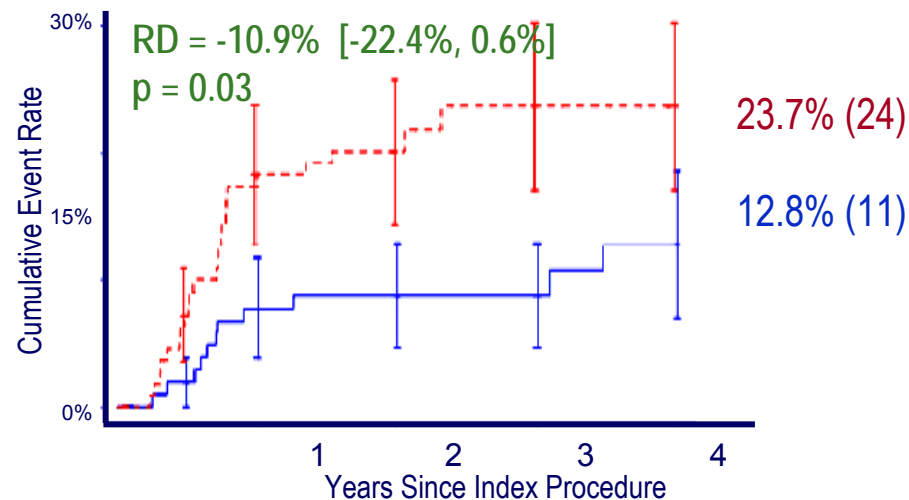
### Q Wave MI



### ARC Primary ST Definite/Probable



### TLR



# TAXUS Insulin-Requiring Diabetics (N=221)

## Annual Event Rates

$\Delta$  = Rate Difference = TAXUS — BMS  
 No increase      Increase

Event	0-1 Year (% / patient-year)				1-4 Years (% / patient-year)				4-year Cumulative Rates (K-M estimate [%])			
	Taxus	BMS	Rate Difference		Taxus	BMS	Rate Difference		Taxus	BMS	Rate Difference	
			$\Delta$	p			$\Delta$	p			$\Delta$	p
All Death	2.89	4.54	-1.65	0.53	4.06	3.85	0.21	0.89	13.3	16.0	-2.7	0.80
Cardiac Death	1.93	3.63	-1.71	0.46	2.03	0.96	1.07	0.36	6.9	6.4	0.5	0.90
All MI	4.00	6.61	-2.60	0.42	1.02	0.48	0.54	0.53	7.8	8.3	-0.5	0.66
QWMI	0.97	0.00	0.97	0.30	0.00	0.00	0.00	NE	0.9	0.0	0.9	0.30
ST Protocol	0.96	0.91	0.06	0.96	0.51	0.00	0.51	0.31	3.0	0.9	2.1	0.53
Total ARC ST All	2.90	2.73	0.17	0.94	1.53	0.96	0.57	0.59	6.9	3.6	3.3	0.45
TLR	7.96	19.70	-11.74	0.02	2.60	2.98	-0.37	0.86	12.8	23.7	-10.9	0.03
TVR-CABG	4.89	1.84	3.05	0.22	1.03	0.97	0.05	0.95	7.8	5.9	1.9	0.31

p-value from Log rank test of no difference in the Kaplan-Meier curves between groups

# TAXUS Small Vessels RVD $\leq 2.5$ mm Visual (N = 965)

## Annual Event Rates

$\Delta$  = Rate Difference = TAXUS — BMS  
 No increase (green)  
 Increase (red)

Event	0-1 Year (% / patient-year)			
	Taxus	BMS	Rate Difference	
			$\Delta$	p
All Death	1.95	2.30	-0.35	0.71
Cardiac Death	1.52	1.46	0.05	0.95
All MI	3.35	5.63	-2.29	0.10
QWMI	0.22	0.63	-0.41	0.33
ST Protocol	0.43	1.05	-0.62	0.28
Total ARC ST All	1.52	2.10	-0.58	0.51
TLR	11.77	25.08	-13.31	<0.0001
TVR-CABG	1.96	6.26	-4.30	0.001

1-4 Years (% / patient-year)			
Taxus	BMS	Rate Difference	
		$\Delta$	p
2.17	1.60	0.57	0.37
0.68	0.75	-0.06	0.87
1.04	0.76	0.28	0.53
0.11	0.11	0.01	0.98
0.23	0.00	0.23	0.14
0.80	0.96	-0.16	0.71
1.62	3.22	-1.60	0.03
0.69	1.30	-0.61	0.20

4-year Cumulative Rates (K-M estimate [%])			
Taxus	BMS	Rate Difference	
		$\Delta$	p
7.9	7.3	0.6	0.63
3.3	3.7	-0.4	0.95
6.8	7.4	-0.6	0.28
0.4	0.8	-0.4	0.44
1.1	1.0	0.1	0.79
3.7	4.4	-0.7	0.56
14.5	27.7	-13.2	<0.0001
5.0	10.1	-5.1	0.0006

p-value from Log rank test of no difference in the Kaplan-Meier curves between groups



# TAXUS Long Lesions $\geq 28\text{mm}$ (N = 341)

## Annual Event Rates

$\Delta$  = Rate Difference = TAXUS — BMS  
 No increase      Increase

Event	0-1 Year (% / patient-year)				1-4 Years (% / patient-year)				4-year Cumulative Rates (K-M estimate [%])			
	Taxus	BMS	Rate Difference		Taxus	BMS	Rate Difference		Taxus	BMS	Rate Difference	
			$\Delta$	p			$\Delta$	p			$\Delta$	p
All Death	2.33	3.77	-1.44	0.45	1.59	2.60	-1.01	0.44	7.7	10.7	-3.0	0.28
Cardiac Death	2.33	1.88	0.45	0.78	1.19	0.43	0.76	0.36	5.5	2.5	3.0	0.44
All MI	9.49	3.22	6.28	0.03	1.62	0.87	0.75	0.46	15.1	5.6	9.5	0.01
QWMI	1.77	0.63	1.14	0.35	0.00	0.00	0.00	NE	1.7	0.6	1.1	0.35
ST Protocol	0.58	0.63	-0.05	0.96	0.00	0.00	0.00	NE	0.6	0.6	0.0	0.96
Total ARC ST All	1.76	2.52	-0.77	0.63	1.20	0.87	0.33	0.72	6.6	5.5	1.1	0.90
TLR	9.71	29.83	-20.12	<0.0001	2.46	4.63	-2.17	0.23	13.1	31.3	-18.2	<0.0001
TVR-CABG	1.18	4.48	-3.31	-0.07	0.40	1.76	-1.36	0.15	1.8	8.7	-6.9	0.02

# TAXUS Multiple Stents in Single Vessels (N = 497)

## Annual Event Rates

Δ = Rate Difference = TAXUS — BMS  
 No increase      Increase

Event	0-1 Year (% / patient-year)				1-4 Years (% / patient-year)				4-year Cumulative Rates (K-M estimate [%])			
	Taxus	BMS	Rate Difference		Taxus	BMS	Rate Difference		Taxus	BMS	Rate Difference	
			Δ	p			Δ	p			Δ	p
All Death	1.60	2.12	-0.51	0.68	1.16	2.77	-1.61	0.13	7.4	11.4	-4.0	0.16
Cardiac Death	1.20	1.27	-0.07	0.95	0.58	0.00	0.58	0.17	3.5	1.3	2.2	0.53
All MI	9.63	6.65	2.98	0.30	0.58	1.25	-0.67	0.37	9.5	11.4	-1.9	0.53
QWMI	0.81	1.28	-0.47	0.61	0.00	0.31	-0.31	0.30	0.8	3.2	-2.4	0.37
ST Protocol	1.21	0.85	0.36	0.70	0.00	0.00	0.00	NE	1.2	0.8	0.4	0.70
Total ARC ST All	2.02	2.12	-0.10	0.94	0.29	0.31	-0.02	0.97	2.4	2.5	-0.1	0.93
TLR	11.80	33.98	-22.19	<0.0001	2.05	4.87	-2.82	0.06	12.8	35.9	-23.1	<0.0001
TVR-CABG	2.45	4.76	-2.31	0.18	0.88	1.88	-1.00	0.28	5.0	10.3	-5.3	0.08

p-value from Log rank test of no difference in the Kaplan-Meier curves between groups

# EVENT HAZARD RATES - FIRST YEAR

## TAXUS By Subgroups

Event	Overall N =2797	Diabetics N =715	Insulin-requiring diabetics N =221	RVD $\leq$ 2.5mm N = 965	Lesions $\geq$ 28mm N =341	Multiple stents N=497
All Death	1.97	2.60	2.89	1.95	2.33	1.60
Cardiac Death	1.10	1.73	1.93	1.52	2.33	1.20
All MI	4.24	3.57	4.00	3.35	9.49	9.63
QWMI	0.66	0.29	0.97	0.22	1.77	0.81
ST Protocol	0.73	0.58	0.96	0.43	0.58	1.21
Primary ARC ST Def/ Prob	0.88	0.87	1.93	0.65	1.17	1.62
TLR	7.37	8.95	7.96	11.77	9.71	11.80
TVR-CABG	1.69	2.62	4.89	1.96	1.18	2.45



# EVENT HAZARD RATES - FIRST YEAR

## BMS By Subgroups

Event	Overall N =2797	Diabetics N =715	Insulin-requiring diabetics N =221	RVD $\leq$ 2.5mm N = 965	Lesions $\geq$ 28mm N =341	Multiple stents N=497
All Death	1.90	2.84	4.54	2.30	3.77	2.12
Cardiac Death	1.31	1.99	3.63	1.46	1.88	1.27
All MI	4.76	6.28	6.61	5.63	3.22	6.65
QWMI	0.37	0.57	0.00	0.63	0.63	1.28
ST Protocol	0.66	1.43	0.91	1.05	0.63	0.85
Primary ARC ST Def/ Prob	0.73	1.43	1.82	1.47	1.26	1.28
TLR	17.59	21.81	19.70	25.08	29.83	33.98
TVR-CABG	3.19	4.67	1.84	6.26	4.48	4.76

# ANNUAL HAZARD RATES - YEARS 1-4

## TAXUS - By Subgroup

Event	Overall N =2797	Diabetics N =715	Insulin-requiring diabetics N =221	RVD $\leq$ 2.5mm N = 965	Lesions $\geq$ 28mm N =341	Multiple stents N=497
All Death	1.71	2.52	4.06	2.17	1.59	1.16
Cardiac Death	0.57	1.11	2.03	0.68	1.19	0.58
All MI	1.01	1.28	1.02	1.04	1.62	0.58
QWMI	0.18	0.00	0.00	0.11	0.00	0.00
ST Protocol	0.21	0.16	0.51	0.23	0.00	0.00
Primary ARC ST Def/ Prob	0.32	0.32	0.51	0.34	0.40	0.00
TLR	1.57	2.09	2.60	1.62	2.46	2.05
TVR-CABG	0.47	0.95	1.03	0.69	0.40	0.88

# ANNUAL HAZARD RATES - YEARS 1-4

## BMS - By Subgroup

Event	Overall N =2797	Diabetics N =715	Insulin-requiring diabetics N =221	RVD $\leq$ 2.5mm N = 965	Lesions $\geq$ 28mm N =341	Multiple stents N=497
All Death	1.87	2.70	3.85	1.60	2.60	2.77
Cardiac Death	0.60	0.60	0.96	0.75	0.43	0.00
All MI	0.71	0.61	0.48	0.76	0.87	1.25
QWMI	0.25	0.15	0.00	0.11	0.00	0.31
ST Protocol	0.04	0.00	0.00	0.00	0.00	0.00
Primary ARC ST Def/ Prob	0.11	0.00	0.00	0.00	0.44	0.00
TLR	2.34	2.46	2.98	3.22	4.63	4.87
TVR-CABG	1.04	1.37	0.97	1.30	1.76	1.88

# ANNUAL EVENT RATE difference signals (Taxus – BMS)

## Year 1 By Subgroup

Event	Overall N =2797	Diabetics N =715	Insulin-requiring diabetics N =221	RVD≤ 2.5mm N = 965	Lesions ≥ 28mm N =341	Multiple stents N=497
All Death	0.08 p=0.89	-0.25 p=0.84	-1.65 p=0.53	-0.35 p=0.71	-1.44 p=0.45	-0.51 p=0.68
Cardiac Death	-0.22 p=0.60	-0.26 p=0.80	-1.71 p=0.46	0.05 p=0.95	0.45 p=0.78	-0.07 p=0.95
All MI	-0.51 p=0.52	-2.72 p=0.12	-2.60 p=0.42	-2.29 p=0.10	6.28 p=0.03	2.98 P=0.30
QWMI	0.30 p=0.52	-0.28 p=0.57	0.97 p=0.30	-0.41 p=0.33	1.14 p=0.35	-0.47 p=0.61
ST Protocol	-0.07 p=0.88	-0.86 p=0.27	0.06 P=0.96	-0.62 p=0.28	-0.77 p=0.63	0.36 p=0.70
Primary ARC ST Def/ Prob	0.07 p=0.83	-0.57 p=0.49	0.12 P=0.95	-0.82 P=0.23	-0.09 p=0.94	0.34 p=0.76
TLR	-10.21 p<0.0001	-12.86 p<0.0001	-11.74 p=0.02	-13.31 p<0.0001	-20.12 p<0.0001	-22.19 p<0.0001
TVR-CABG	-1.50 p=0.01	-2.05 p=0.16	3.05 p=0.22	-4.30 p=0.001	-3.31 p=0.07	-2.31 P=0.18

# ANNUAL EVENT RATE difference signals (Taxus – BMS)

## Years 1-4 By Subgroup

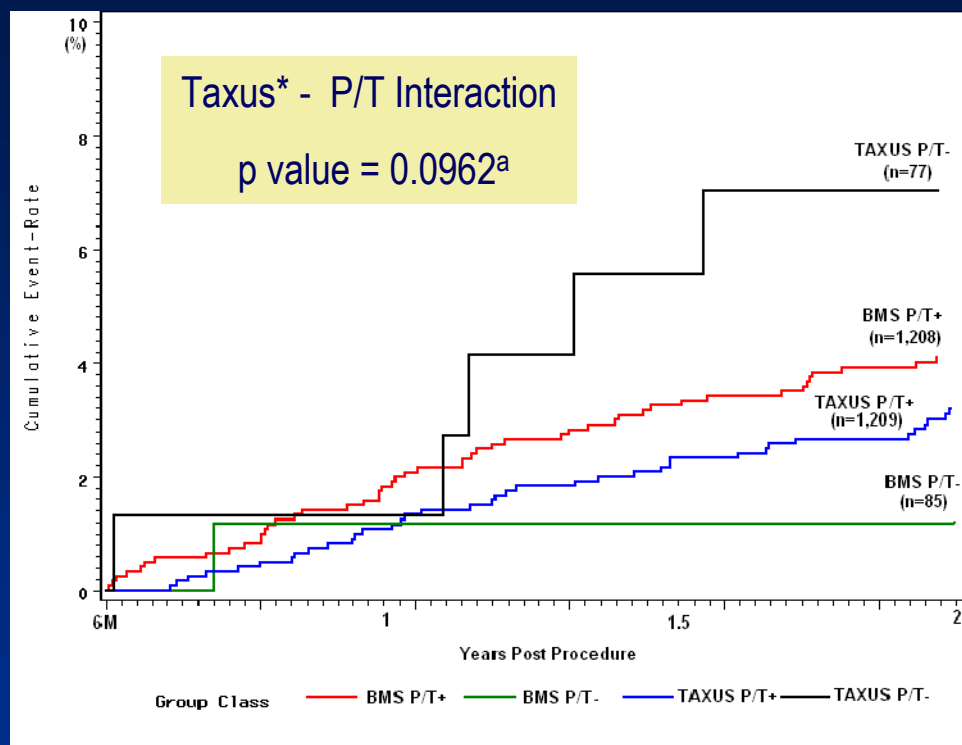
Event	Overall N =2797	Diabetics N =715	Insulin-requiring diabetics N =221	RVD≤ 2.5mm N = 965	Lesions ≥ 28mm N =341	Multiple stents N=497
All Death	-0.16 p=0.65	-0.18 p=0.85	0.21 p=0.89	0.57 p=0.37	-1.01 p=0.44	-1.61 p=0.13
Cardiac Death	-0.03 p=0.88	0.50 p=0.33	1.07 p=0.36	-0.06 p=0.87	0.76 p=0.36	0.58 p=0.17
All MI	-0.3 p=0.23	0.68 p=0.21	0.54 p=0.53	0.28 p=0.53	0.75 p=0.46	-0.67 P=0.37
QWMI	-0.07 p=0.57	-0.15 p=0.34	0.00 NE	0.01 p=0.98	0.00 NE	-0.31 p=0.30
ST Protocol	0.18 p=0.06	0.16 p=0.30	0.51 P=0.31	0.23 p=0.14	0.33 p=0.72	0.00 NE
Primary ARC ST Def/ Prob	0.22 p=0.08	0.32 p=0.14	0.51 P=0.30	0.34 p=0.07	-0.03 p=0.96	0.00 NE
TLR	-0.77 p=0.04	-0.37 p=0.66	-0.37 p=0.86	-1.60 p=0.03	-2.17 P=0.23	-2.82 p=0.06
TVR-CABG	-0.57 p=0.01	-0.41 p=0.53	0.05 p=0.95	-0.61 p=0.20	-1.36 p=0.15	-1.00 p=0.28



## CUMULATIVE TOTAL EVENT Differences Years 0-4 By Subgroup (Taxus – BMS)

Event	Overall N =	Diabetics N =	Insulin-requiring diabetics N =	RVD $\leq$ 2.5mm N =	Lesions $\geq$ 28mm N =	Multiple stents N =
All Death	-0.3 p=0.78	-1.5 p=0.78	-2.7 p=0.80	0.6 p=0.63	-3.0 p=0.28	-4.0 p=0.16
Cardiac Death	-0.4 p=0.64	1.0 p=0.64	0.5 p=0.90	-0.4 p=0.95	3.0 p=0.44	2.2 p=0.53
All MI	0.5 p=0.87	-0.2 p=0.57	-0.5 p=0.66	-0.6 p=0.28	9.5 p=0.01	-1.9 p=0.53
QWMI	-0.1 p=0.83	-0.8 p=0.34	0.9 p=0.30	-0.4 p=0.44	1.1 p=0.35	-2.4 p=0.37
ST Protocol	0.5 p=0.24	-0.2 p=0.50	2.1 p=0.53	0.1 p=0.79	0.0 p=0.96	0.4 p=0.70
Primary ARC ST Def/ Prob	0.7 p=0.17	0.8 p=0.96	2.1 p=0.60	0.1 p=0.83	-0.3 p=0.93	0.4 p=0.76
TLR	-9.7 p<0.0001	-11.5 p<0.0001	-10.9 p=0.03	-13.2 p<0.0001	-18.2 p<0.0001	-23.1 p<0.0001
TVR-CABG	-3.1 p=0.0004	-2.6 p=0.13	1.9 p=0.31	-5.1 p=0.0006	-6.9 p=0.02	-5.3 p=0.08

# Death or MI During Follow-up to 2 Years Post-Procedure According to Plavix® /Ticlid® Usage at 6 Months



(n=2,522)		Plavix/Ticlid Use Overtime			ASA Use Overtime		
Group	n	6 M Landmark	12 M†	24 M*	6 M Landmark†	12 M†	24 M*
BMS P/T+	1208	100%	49.5%	46.6%	98.1%	95.3%	96.3%
BMS P/T-	85	-	-	-	-	-	-
TAXUS P/T+	1209	100%	49.2%	43.3%	98.0%	94.3%	94.9%
TAXUS P/T-	77	-	-	-	-	-	-

† Medication data available in TAXUS 2, 4, and 5

\* Medication data available in TAXUS 4, 5 only

a. adjusted Cox regression model, additionally adjusted for patient baseline and lesion characteristics

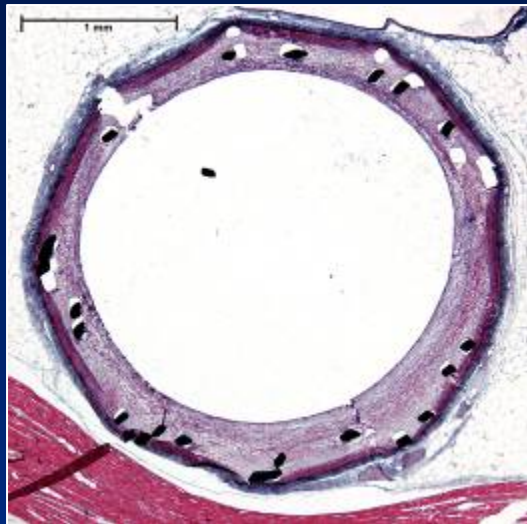
Plavix and Ticlid are trademarks of Sanofi-Aventis

# Translute™ Vascular Compatibility

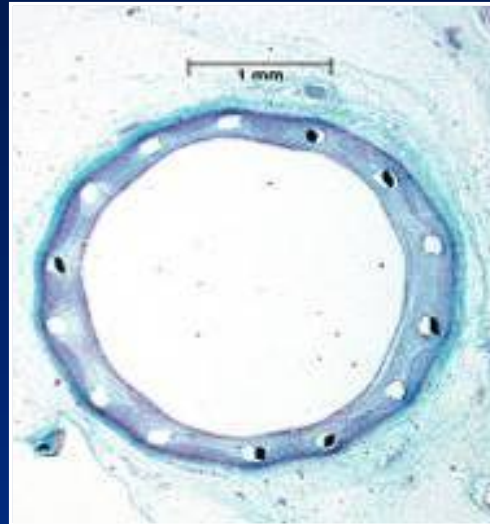
Porcine Coronary, SIBS coated Stents

**Bare  
Stent**

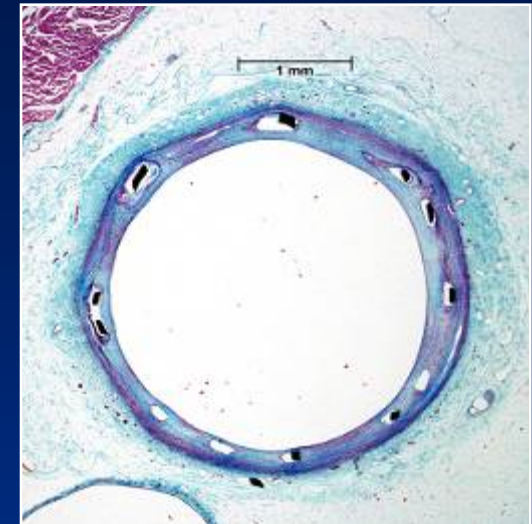
**30d**



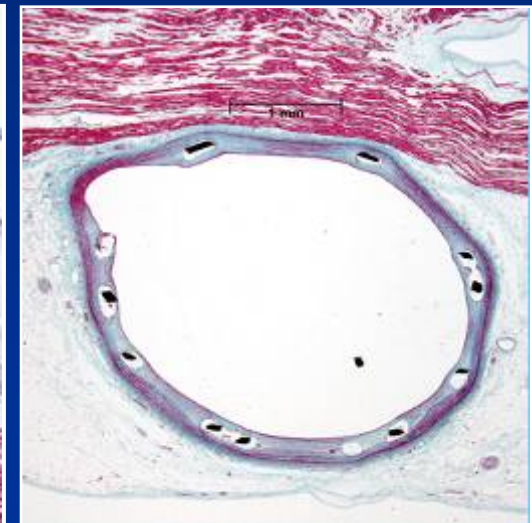
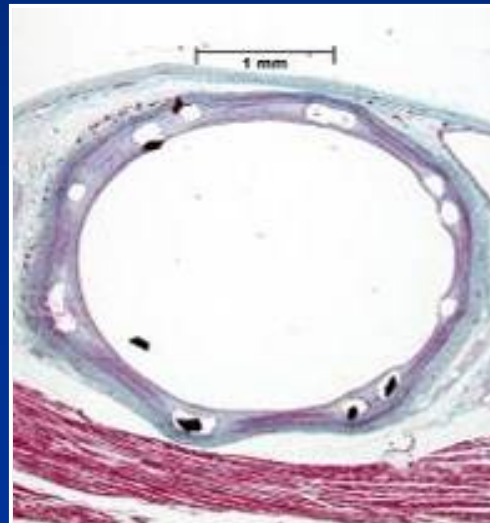
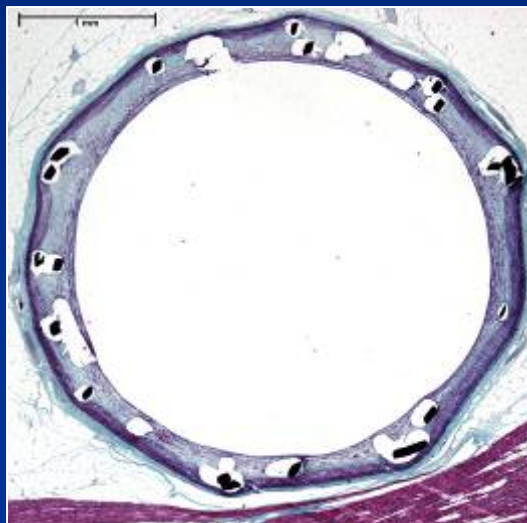
**90d**



**180d**



**Translute  
Coated  
Stent  
(no paclitaxel)**

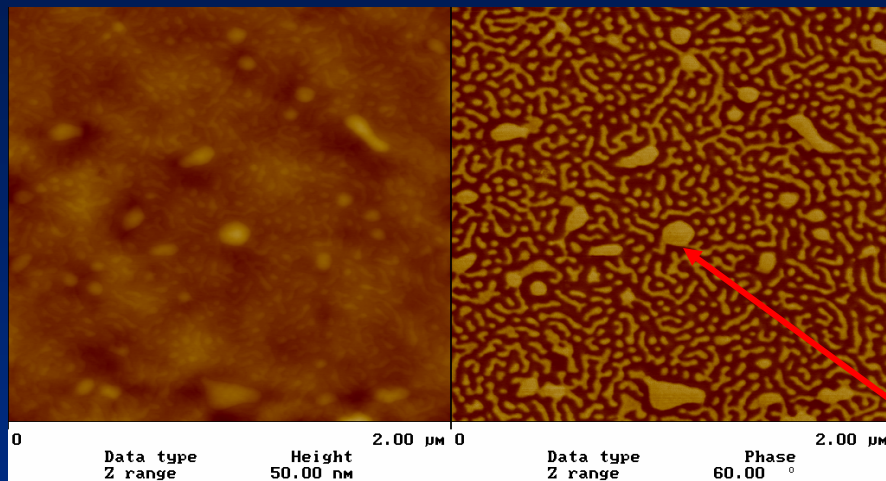


In collaboration with Dr. Rob Schwartz (Mayo Clinic) and Dr. Greg Wilson (Sick Children's-Toronto)

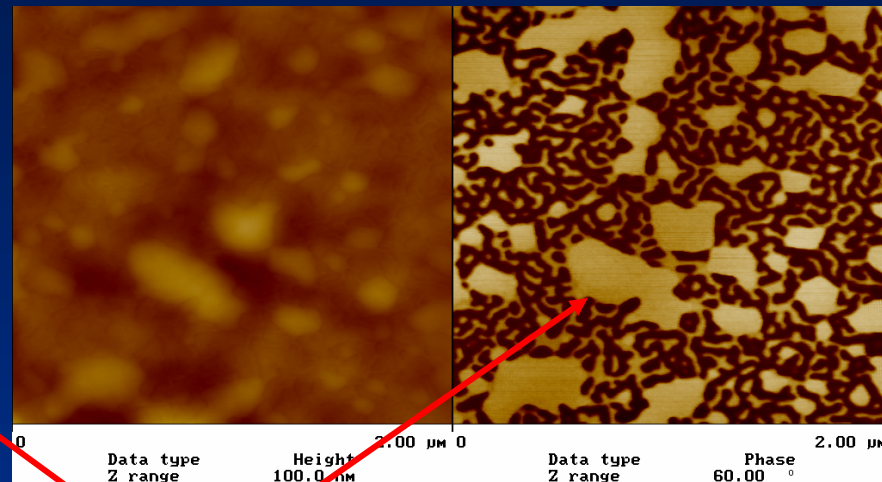


# AFM Images of TAXUS Stents of Varying Formulations

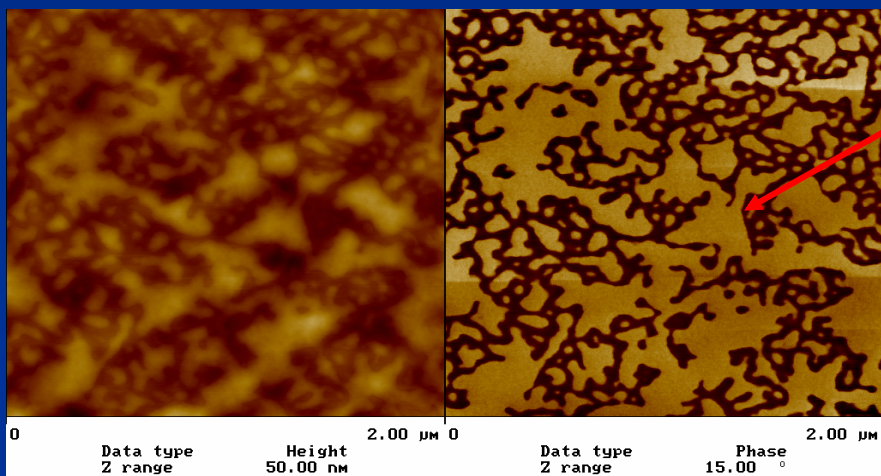
8.8% PTx (SR formulation)



25% PTx (MR formulation)



35% PTx (FR formulation)

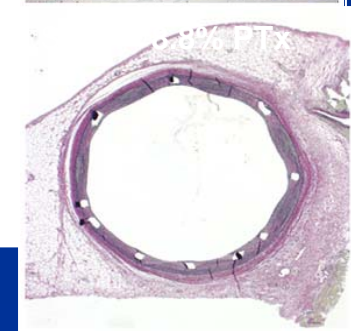
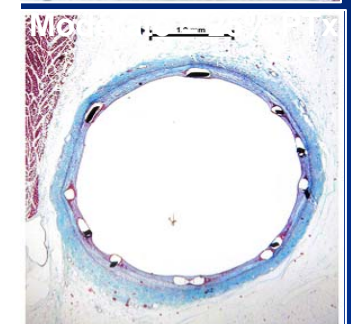
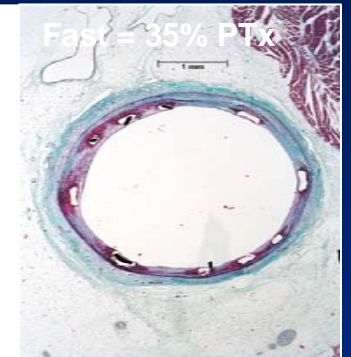
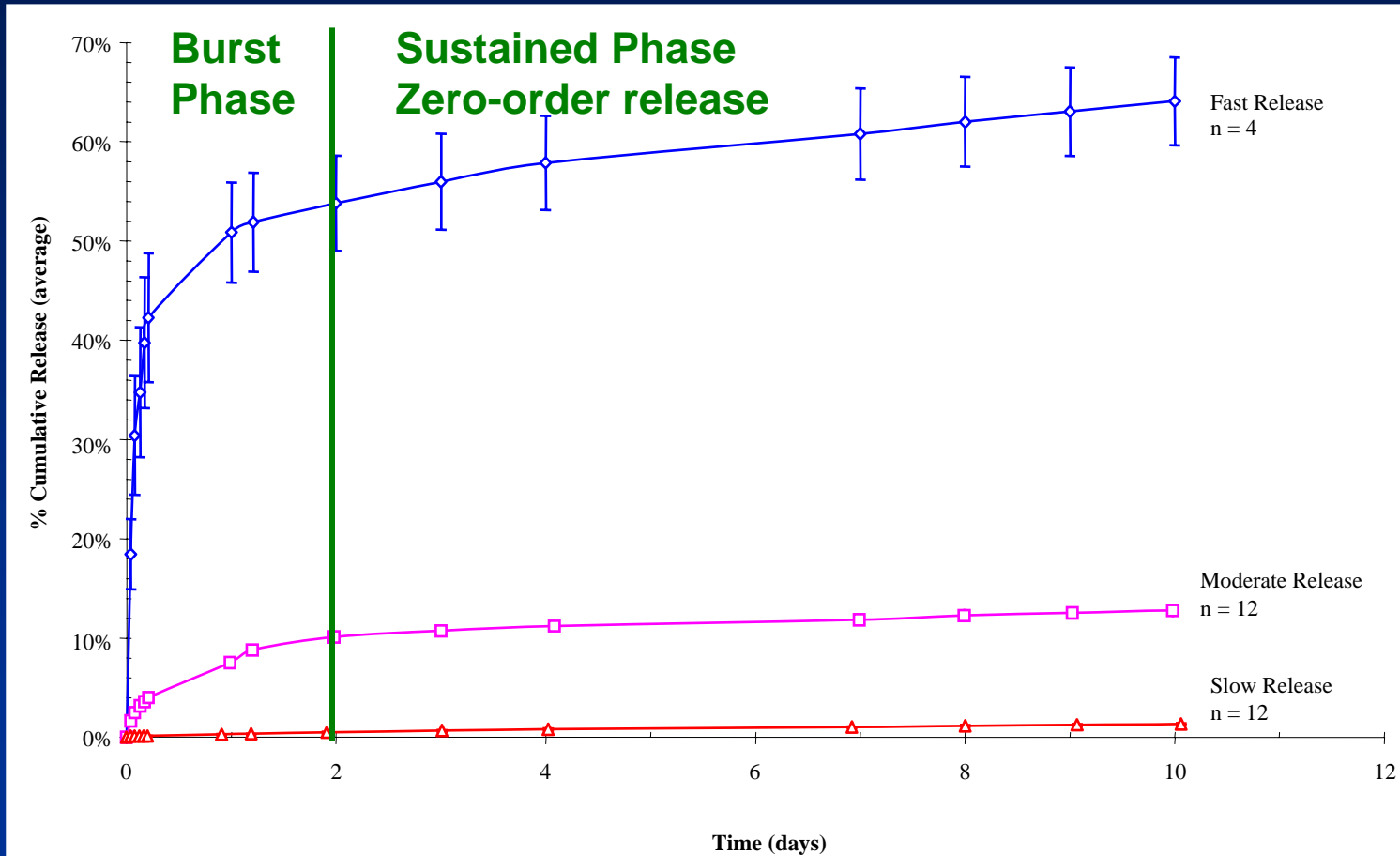


PTx Particles

*Increasing PTx concentration results in a more saturated matrix with more drug:drug interaction*

# Modulating Drug Release

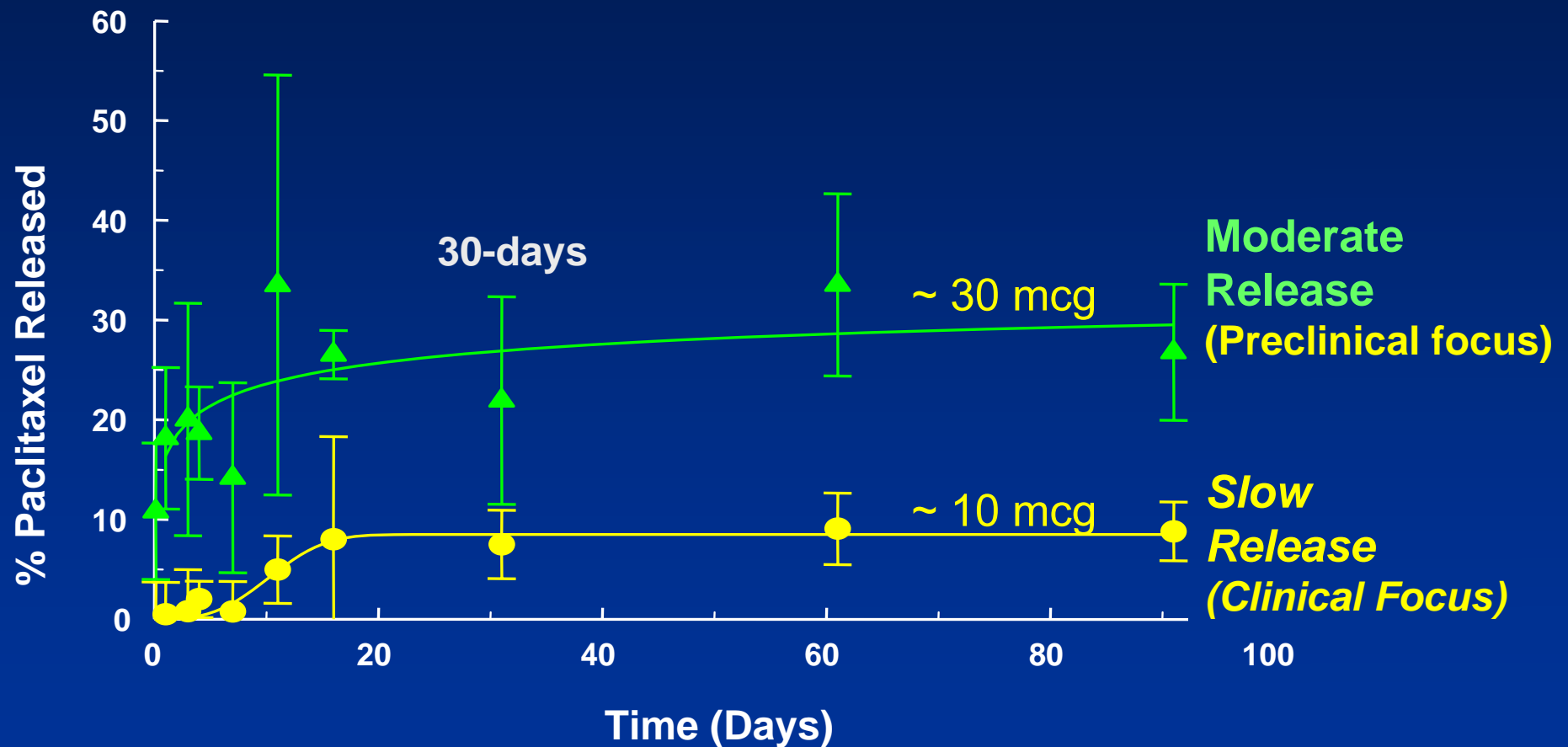
*Altering drug to polymer ratio to effect drug release and biological response*



Release Media - Physiological Saline w/ surfactant - pH 7.4 @ 37°C

Formulation in **Translute™** controls both drug release amount as well as time course

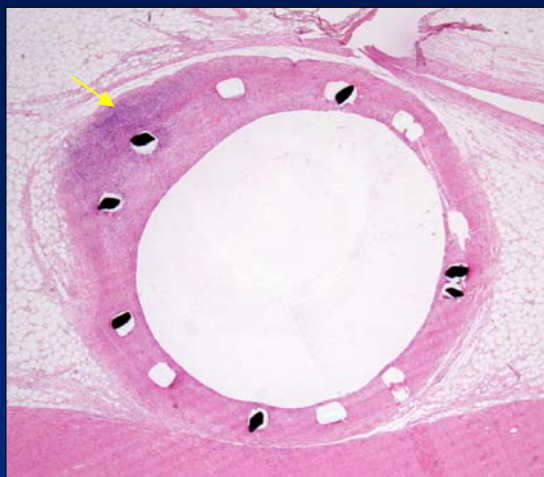
Rabbit Iliac Cumulative Release  
Plateau after 30 days



# CYPHER vs TAXUS Stents: Comparing the Inflammatory Response in Porcine Coronary Arteries

Robert S. Schwartz and Gregory J. Wilson

## Regional Patterns of Severe Inflammation (SI)



1520 LCX-4

X 20

Severe Unifocal



1517 LCX-3

X 20

Severe Multifocal



1517 LCX-4

X 20

Severe Circumferential

**Unifocal:** One focus of SI involving no more than one quadrant ( $90^\circ$ ) of the circumference

**Multifocal:** Two or more foci of SI involving no more than 3 quadrants ( $270^\circ$  maximum) of the circumference

**Circumferential:** Several foci of SI involving 4 quadrants of the circumference (usually every strut involved)



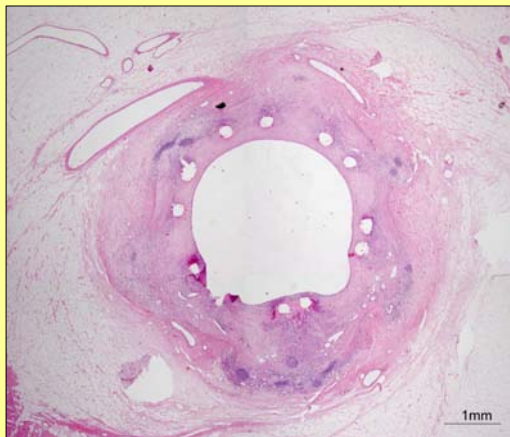
# CYPHER vs TAXUS Comparison of Circumferential Severe Inflammation (CSI) – X3

Proximal\*

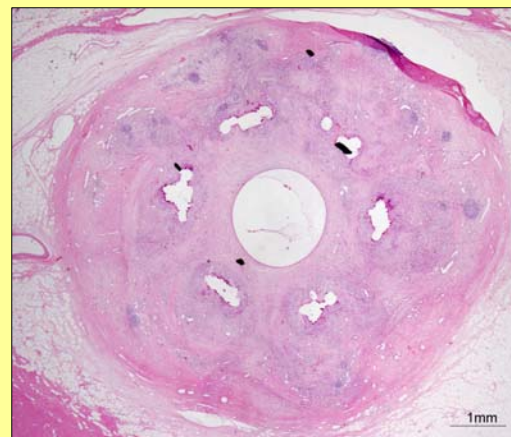
Overlap\*

Distal\*

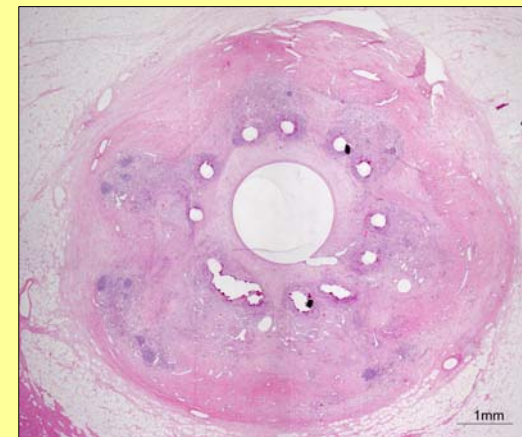
**CYPHER**  
CSI – X3  
43.1%  
(25/58)



4P590 RCA-B



4P590 RCA-C



4P590 RCA-D

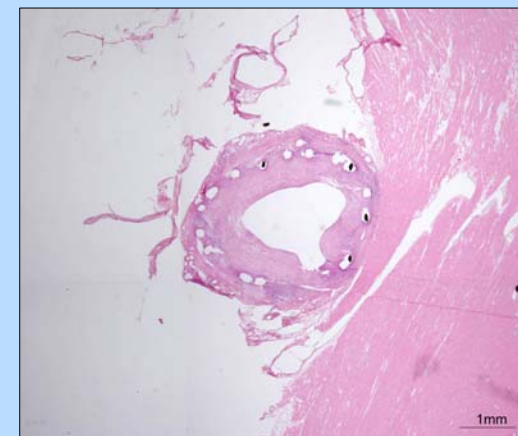
**TAXUS**  
CSI – X3  
1.7%  
(1/58)



1569 LAD-2



1569 LAD-3



1569 LAD-4

\*20X magnification

## Circumferential Severe Inflammation (CSI)- X3 All Studies Combined

Duration	CYPHER (%)	TAXUS (%)	<i>P</i> –Value*
30 Days	0.0 (0/24)	0.0 (0/24)	1.0
90 Days	52.3 (11/21)	5.0 (1/20)	0.0014
180 Days	60.9 (14/23)	0.0 (0/24)	< 0.0001

Significant increase over time in prevalence of CSI-X3<sup>†</sup> in CYPHER between 30 & 90 days (*P*=0.0008)

No significance difference over time in CYPHER between 90 & 180 days (*P*=0.27)

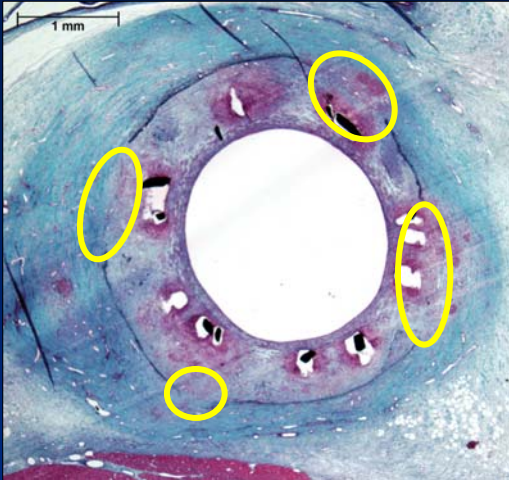
Prevalence of CSI-X3 in CYPHER significantly greater than TAXUS at 90 & 180 days

<sup>†</sup>Circumferential severe inflammation in all 3 sections

\*Fisher's Exact Test-Two Tailed

# Angiography Compared With Histology

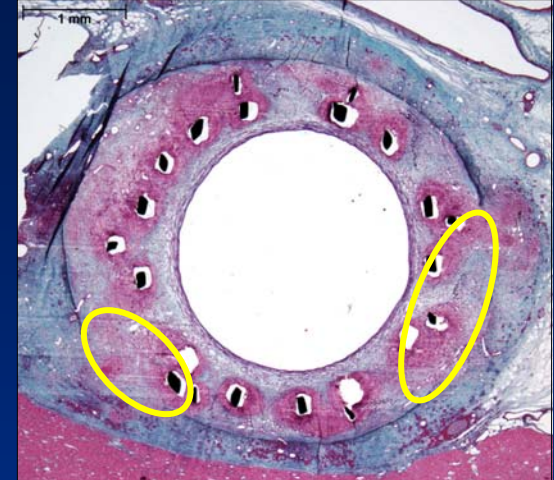
## Two DES Pairs



1502 LCX (overlap section) X 20



Animal 1502 (CYPHER)



1502 LAD (overlap section) X 20

### 90-Day Angiogram

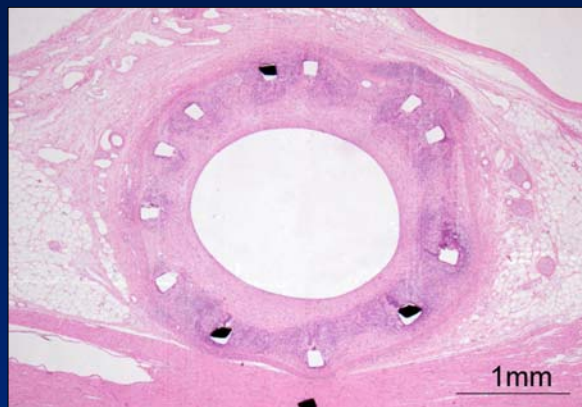
- Modest narrowing of both CYPHER stents
- No insight into existing inflammation

### 90-Day Histology

- Circumferential severe inflammation across 3 sections
- Substantial breakdown of black elastica (encircled)

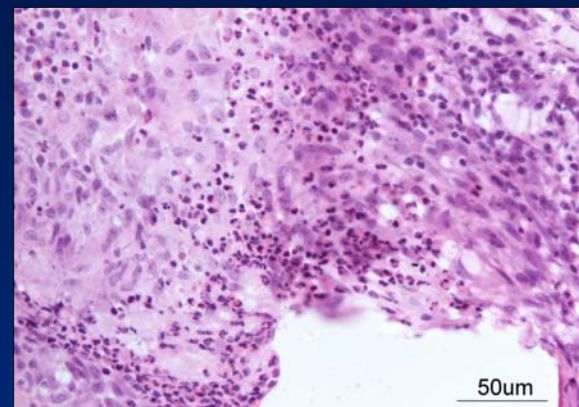


## Severe Inflammation Uncommon with either Bare Metal Control



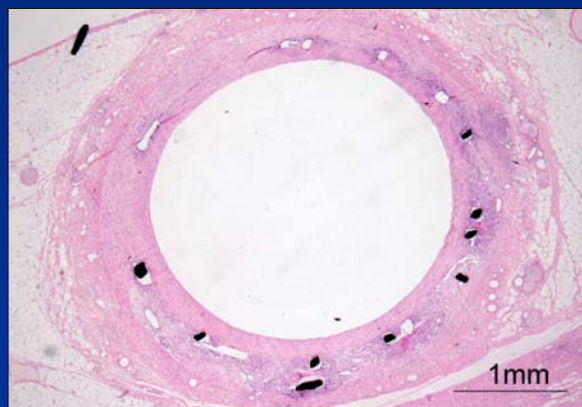
1517 LAD-2

BX Sonic  
@ 90 days



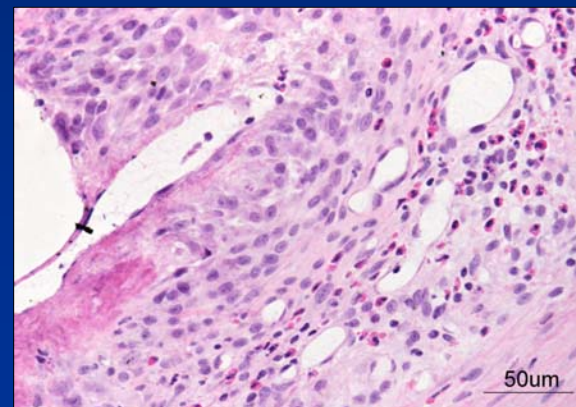
1517 LAD-2

Across Combined BX Velocity & BX Sonic: 2.7% (1/37) CSI-X3\*



1583 LAD-3

Liberté  
@ 90 days



1583 LAD-3

Across Combined Express & Liberté : 1.9% (1/52) SI-X2\*

\*CSI-X3: Circumferential severe inflammation in all 3 sections; SI-X2: Severe inflammation in 2 sections