A Clinician's Perspective on Drug-Eluting Stents: Balancing Safety and Efficacy

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FDA DES Thrombosis Panel
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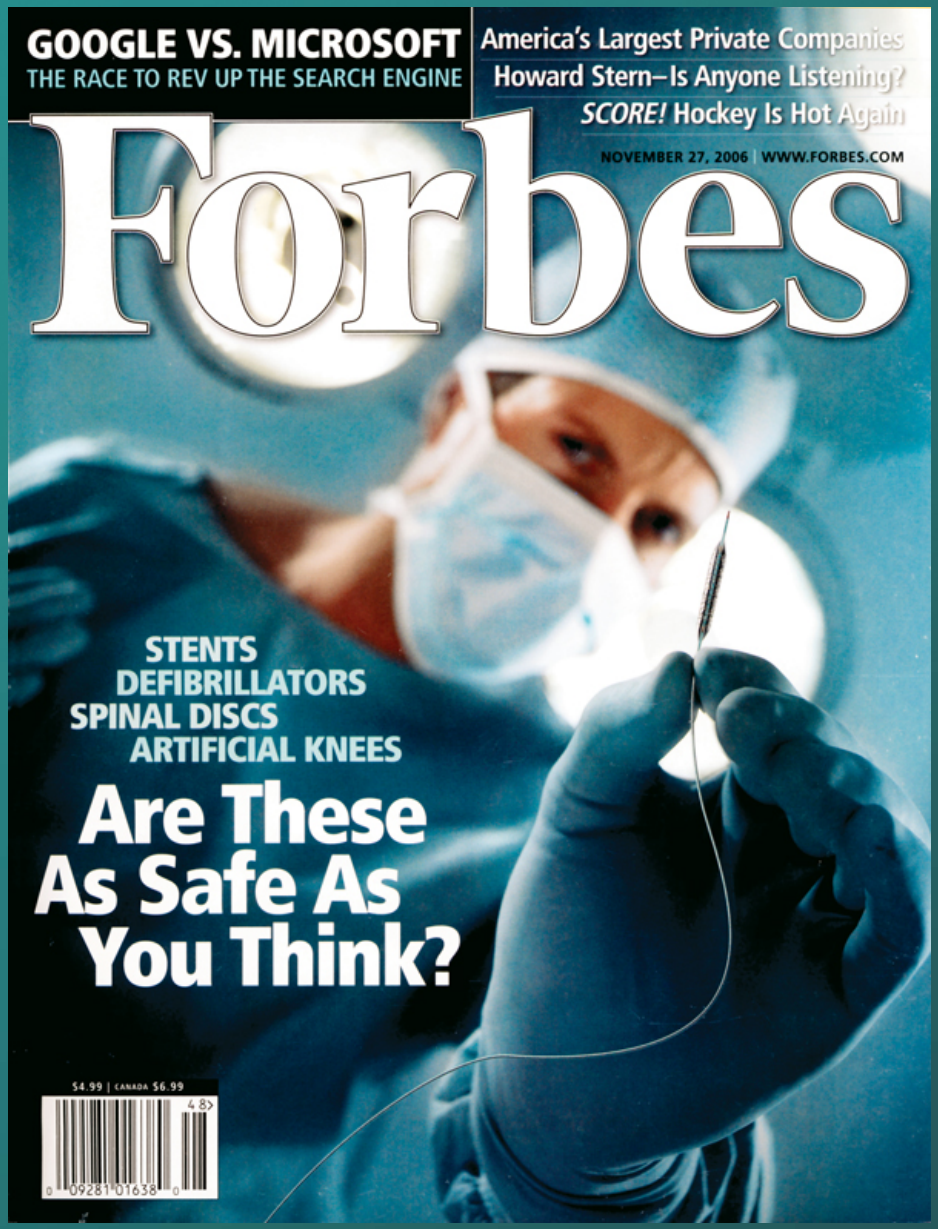
Presenter Disclosure Information for FDA DES Thrombosis Panel

Jeffrey W. Moses, M.D.

Consultant or Advisory Board:
Cordis-JNJ, BMS



The lay press negative characterization of DES safety (often fueled by physicians) has frightened both patients and referring physicians (unnecessarily), which has seriously compromised the interventionalist's ability to deliver optimal therapy in patients with complex CAD.

"An Epidemic of Madness!"

TUESDAY

ESC Congress News

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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 Clinical Perspectives

The "4" Questions

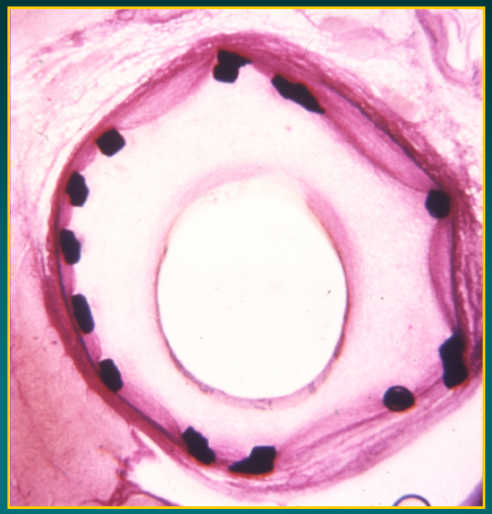
1. *What are the alternatives to DES treatment?* (safety and management of BMS in-stent restenosis)
2. *What is the incremental efficacy of DES vs. BMS?* (on-label and off-label patient cohorts)
3. *Does the balance of safety/efficacy still favor DES?*
4. *What is the current DES "dilemma" for clinicians (and prospective patients)?*

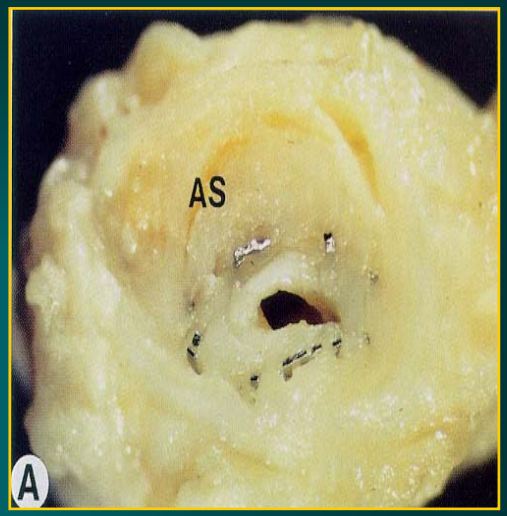
DES Clinical Perspectives

The "4" Questions

1. *What are the alternatives to DES treatment?*
   (safety and management of BMS in-stent restenosis)

Bare Metal Stents….
The bad old days





Restenosis After Bare Metal Stents
Scope of the Problem

- Coronary interventions worldwide 2005:
  2.4 million (~ 50% in US)
- Angiographic restenosis: *600,000/yr*
- Clinical events: **300,000/yr**
- Recurrent clinical events: 60,000/yr
- Ultimate bypass surgery: 100,000/yr

Economic Burden of Restenosis

1 million PCI procedures in US during in 2004[1]

↓

>70% of PCIs used bare metal stents (conservative)[2]

↓

Estimated TVR frequency (Centers for Medicine & Medicaid Services population) **14.4%** in the BMS era[3]

↓

Mean cost for each TVR event **$11,913**[4]

↓

Est. annual economic burden in the US **~$1.2 billion**

Thom T et al. Circulation 2006;113:e85-151[1]

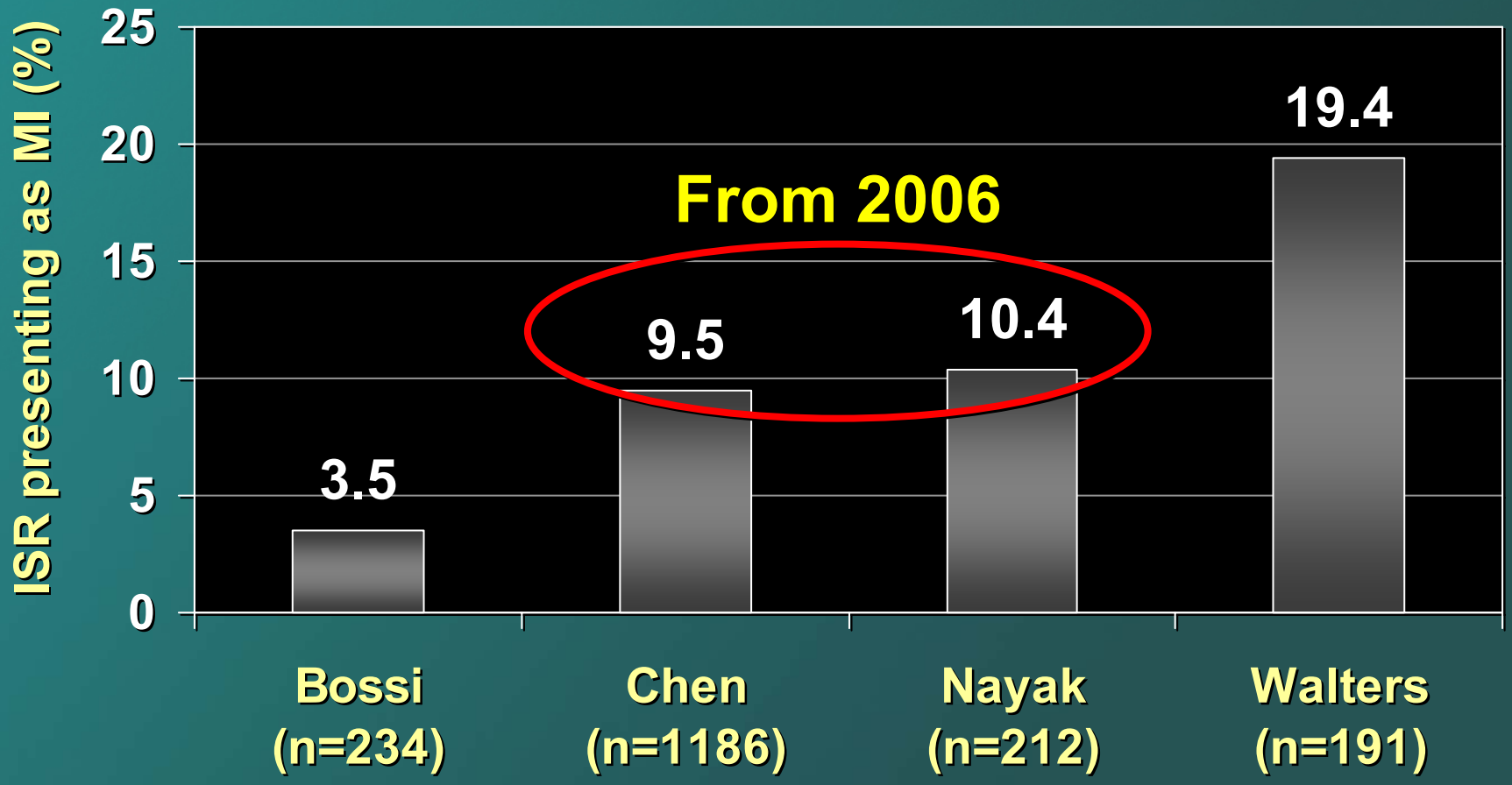
Laskey WK, et al. Am J Cardiol 2001; 87:964-9[2]

Cutlip DE, et al. JACC 2002;40:2082-9[3]

Cohen DJ et al. Circulation 2001;104: I:386-7[4]

Is BMS ISR a Benign Entity?

Presentation of BMS ISR as AMI



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

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

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

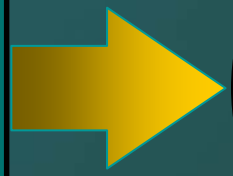
Chen MS et al. *AHJ* 2006,151:1260-1264

Is BMS ISR a Benign Entity?

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

64.1%	Effort Angina
26.4%	Unstable Angina
9.5%	Acute MI
- 7.3%	- NSTEMI
- 2.2%	- STEMI

Treatment

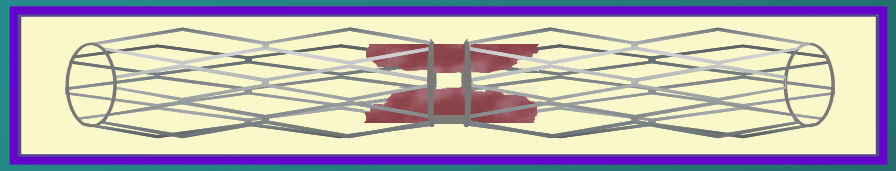


8 (0.7%) procedural deaths

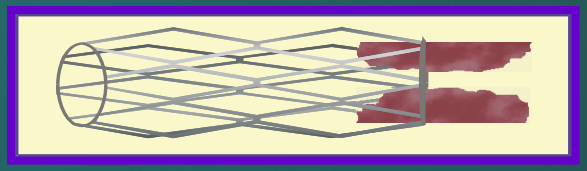
Chen MS et al. *AHJ* 2006,151:1260-1264

106 cases (8.9%) totally occluded

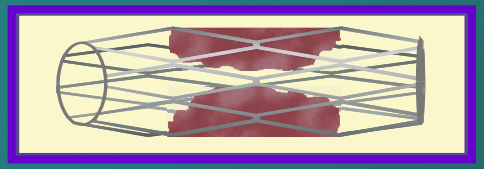
In-Stent Restenosis Patterns



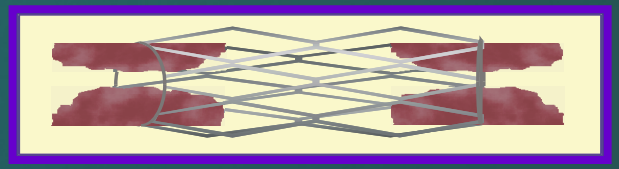
Pattern I (Focal) Type IA: Articulation / Gap



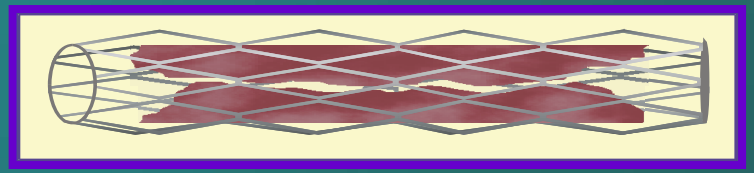
Pattern I (Focal) Type IB: Margin



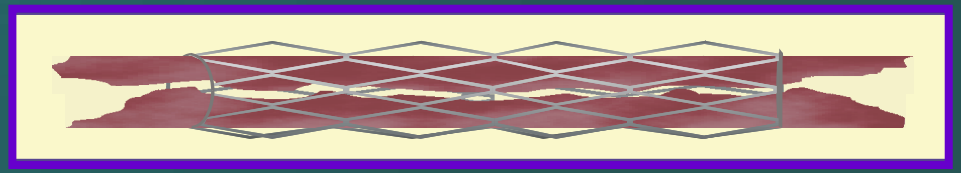
Pattern I (Focal) Type IC: Focal Body



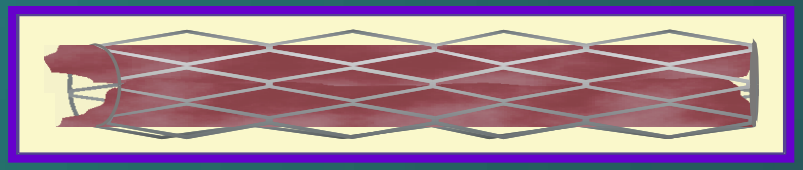
Pattern I (Focal) Type ID: Multifocal



Pattern II (Diffuse): Intra-stent



Pattern III (Diffuse): Proliferative

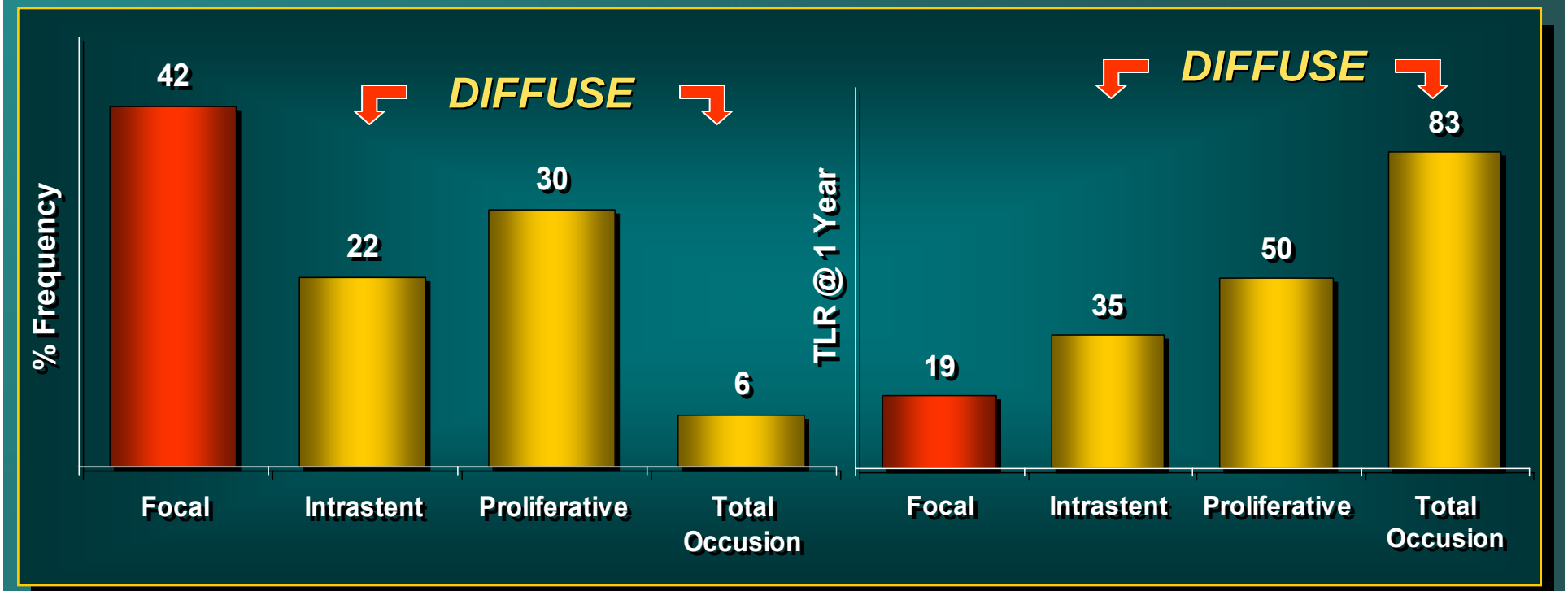


Pattern IV (Diffuse): Total Occlusion

Classification proposed by Mehran et al. Circulation 1999;100:1872-1878

Patterns of In-Stent Restenosis

282 lesions; restenosis patterns classified by angiography and confirmed by IVUS



Predictors of TLR : diabetes, previous ISR and ISR patterns

Mehran R et al. Circulation 1999;100:1872-78

BMS In-Stent Restenosis (CRF)

All Conventional Therapies

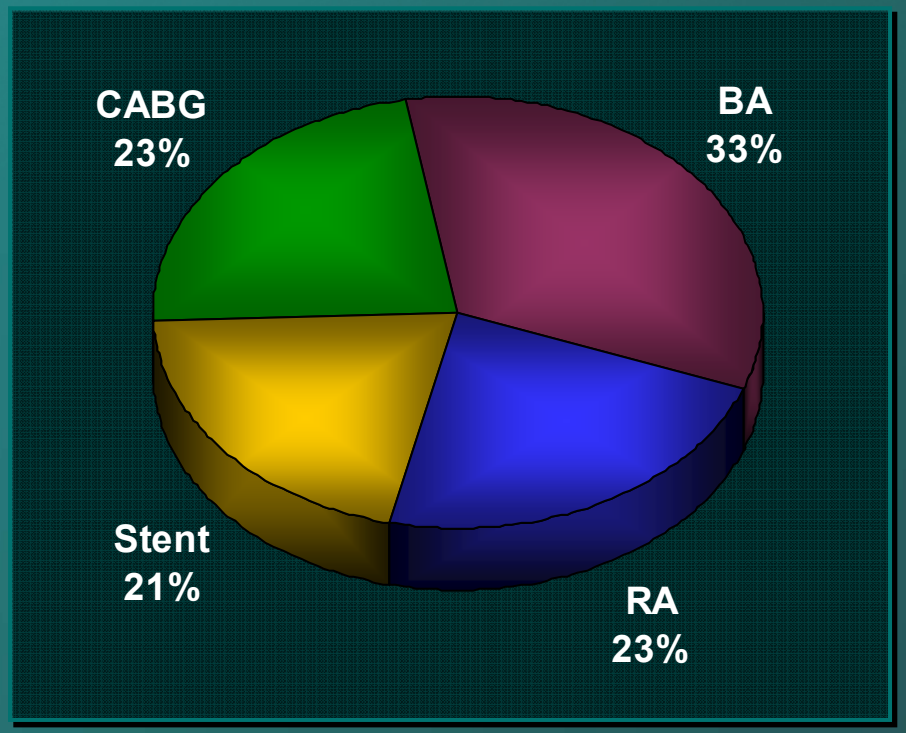
765 consecutive pts @ WHC with in-stent restenosis treated with ALL THERAPIES (PTCA n=267, ELCA n=208, RA n=130, stent n=160), excluding vascular brachytherapy, assisted by IVUS guidance

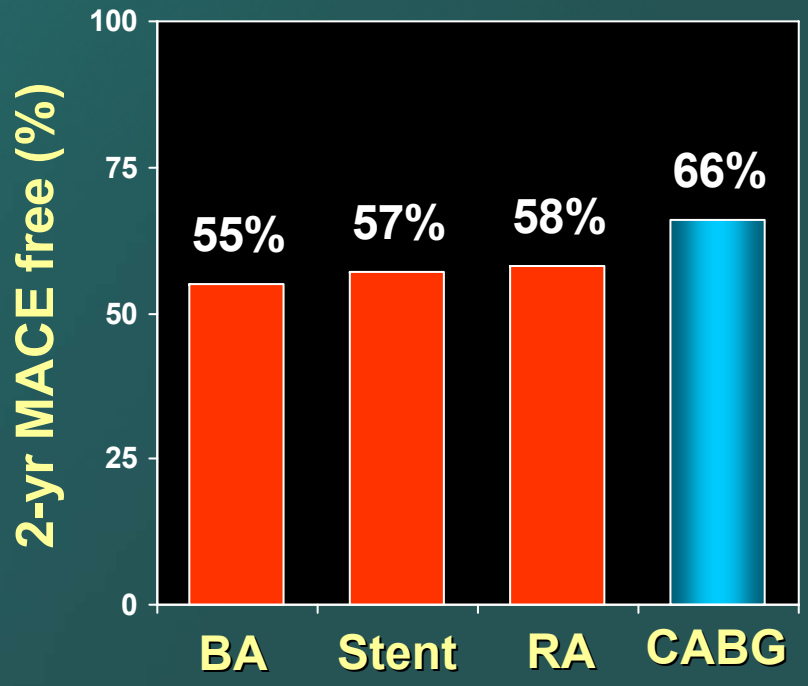
	All	PTCA	ELCA	RA	Stent
Diabetes (%)	34.5	36	36	37	28
Lesion Length (mm)	13±5	9±3	21±11	19±9	9±4
Final %DS	19±16	23±16	18±15	18±13	12±10
Final CSA (mm2)	7.3±3.2	6.6±0.8	6.9±1.0	6.5±0.5	9.7±1.0
TLR @ 1 Year	27.5	24.5	29.0	22.5	25.2

Treatment Strategies after Bare Metal ISR

510 consecutive pts with bare metal ISR.

Treatment strategy at the operators discretion.





Moustapha A, et al. J Am Col Cardiol 2001;37:1877-1882

Gamma-1: Five-Year FU

Clinical Outcomes (0-9 months)

	Placebo (n=121)	CRT (n=131)	P value
MACE*	54 (44.6%)	38 (29.0%)	0.013
Death	1 (0.8%)	4 (3.1%)	0.370
All MI	9 (7.4%)	16 (12.2%)	0.213
Q-wave	4 (3.3%)	6 (4.6%)	0.751
non-Q	5 (4.1%)	10 (7.6%)	0.293
All TLR	51 (42.1%)	33 (25.2%)	0.005
TLR-CABG	24 (19.8%)	13 (9.9%)	0.032
TLR-PTCA	34 (28.1%)	27 (20.6%)	0.187
Stent closure	3 (2.5%)	8 (6.1%)	0.031
0-30 days	2 (1.7%)	1 (0.8%)	0.613
30-270 days	1 (0.8%)	7 (5.3%)	0.067

** MACE = death, MI, all TLR (CABG and PCI)*

Gamma-1: Five-Year FU

Clinical Outcomes (0-60 months)

	Placebo (n=121)	CRT (n=131)	P value
MACE*	66 (54.5%)	64 (48.9%)	0.380
Death	12 (9.9%)	13 (9.9%)	1.000
All MI	11 (9.1%)	23 (17.6%)	0.064
Q-wave	4 (3.3%)	7 (5.3%)	0.544
non-Q	7 (5.8%)	17 (13.0%)	0.056
All TLR	58 (47.91%)	53 (40.5%)	0.254
TLR-CABG	32 (26.4%)	27 (20.6%)	0.300
TLR-PTCA	40 (33.1%)	35 (29.0%)	0.578
Stent closure	3 (2.5%)	11 (8.4%)	0.021
0-30 days	2 (1.7%)	1 (0.8%)	0.613
30-270 days	1 (0.8%)	10 (7.6%)	0.010

** MACE = death, MI, all TLR (CABG and PCI)*

SECURE - Events In & Out of Hospital to 1 year

252 patients with 1 yr follow-up

	Radiation Failure* (n=178 pts)	No Radiation Failure (n=74 pts)	P-value
TLR (%)	47.8	29.7	0.012
TVR (%)	51.1	32.4	0.008
TVF (%)	54.5	33.8	0.004
Stent thromb <30 days (%)	1.7	2.7	0.63
Stent thromb >30 days (%)	3.4	0	0.18

**patients with at least one lesion previously treated with brachytherapy*

SECURE – Events In & Out of Hospital to 1 year

252 patients with 1 yr follow-up

	Radiation Failure* (n=178 pts)	No Radiation Failure (n=74 pts)	P-value
Death (%)	5.1	4.1	1.00
MI (%)	7.9	2.7	0.16
Q-wave	4.5	1.4	0.29
Non-Q wave	4.5	1.4	0.29
MACE (death, MI, TLR)	52.3	36.5	0.027

**patients with at least one lesion previously treated with brachytherapy*

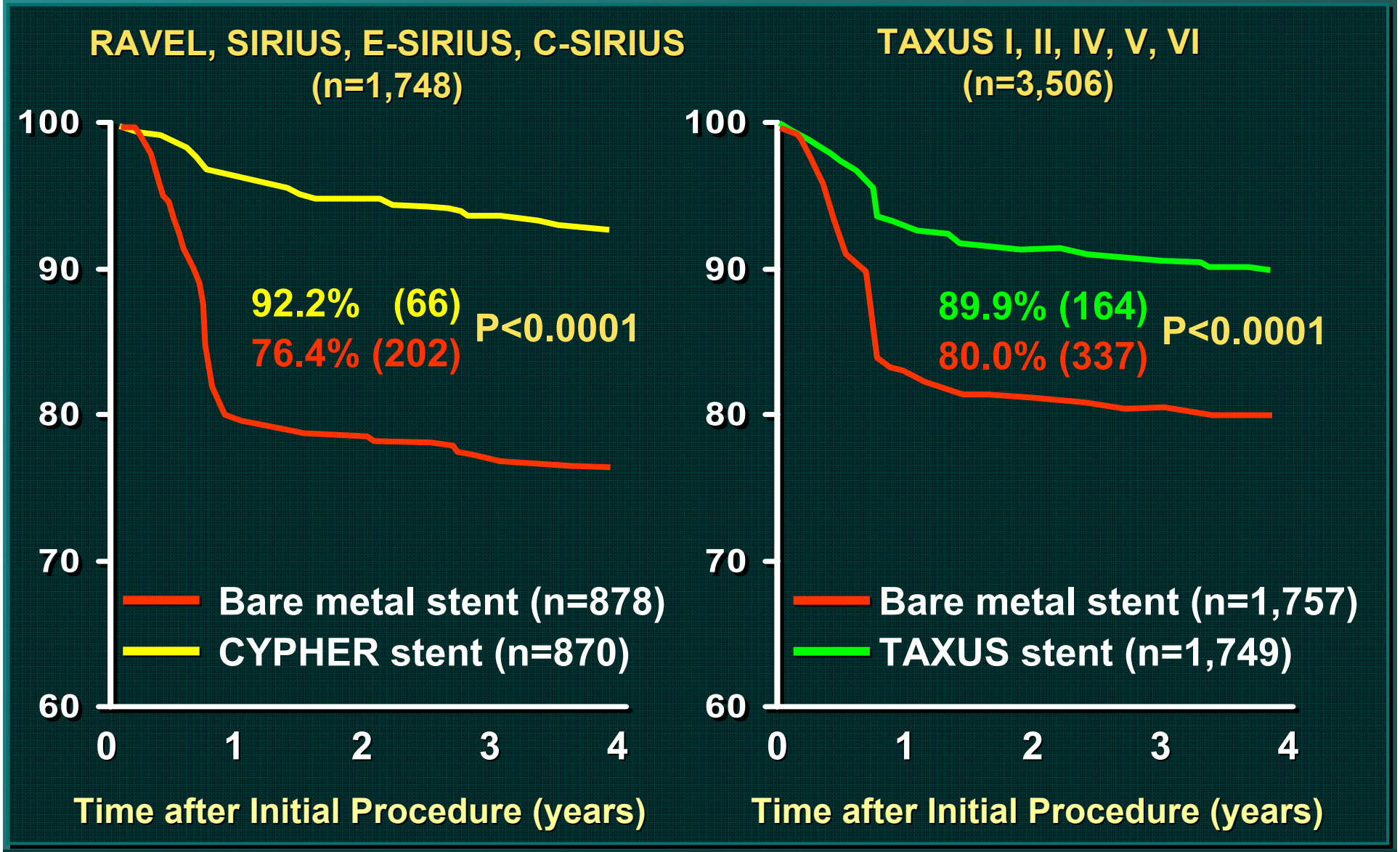
DES Clinical Perspectives

The "4" Questions

1. *What are the alternatives to DES treatment?* (safety and management of BMS in-stent restenosis)
2. *What is the incremental efficacy of DES vs. BMS?* (on-label and off-label patient cohorts)

9 Prospective, Double-Blind, Randomized Trials

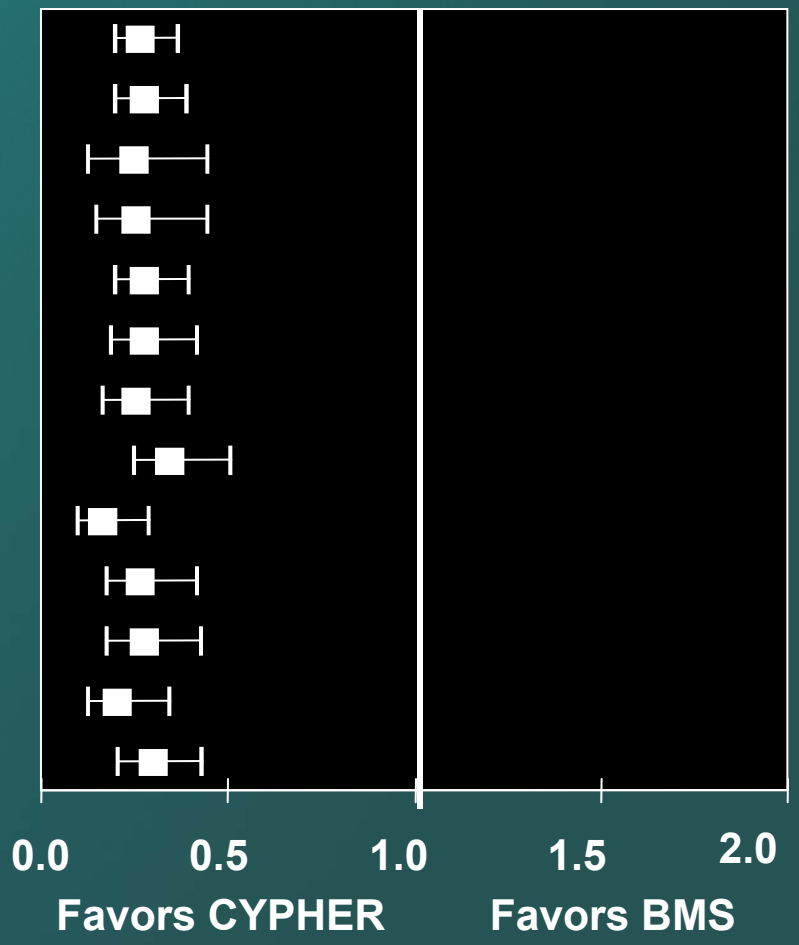
Freedom From Ischemic TLR



Pooled Data from RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS

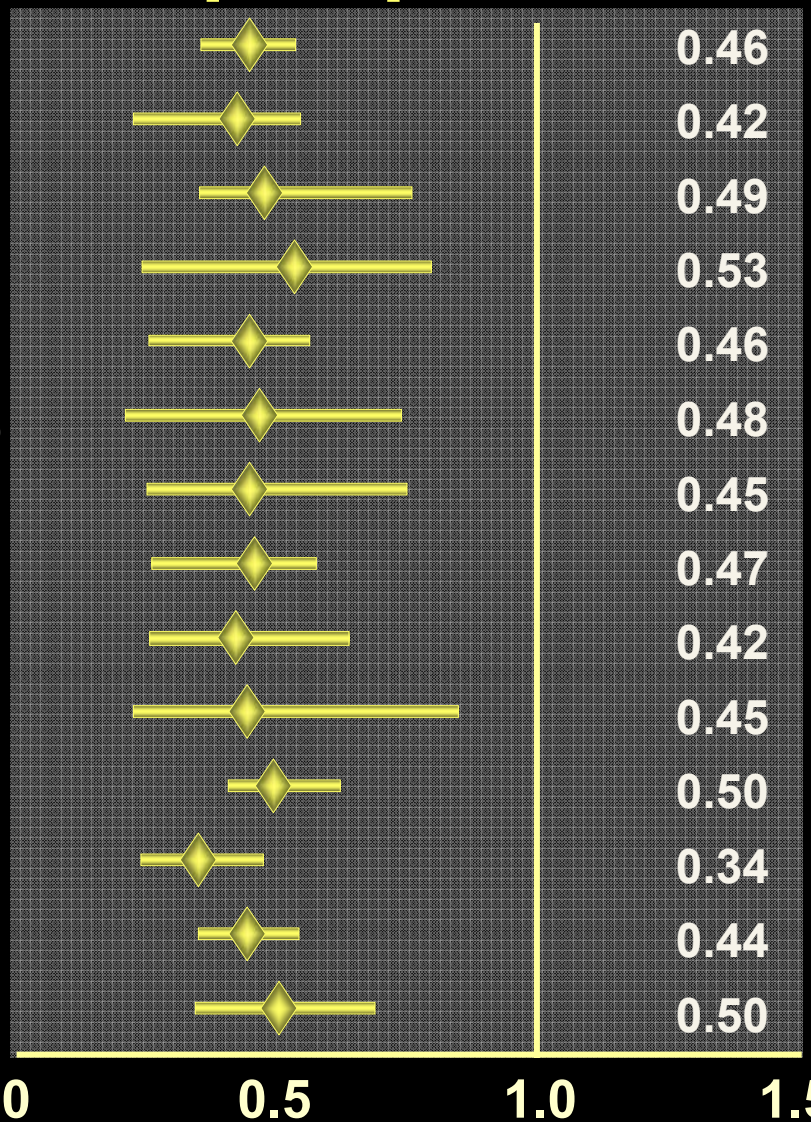
4-Year TLR: Subgroup Analyses

	CYPHER Stent	BMS	P-value
Overall	7.6%	23.3%	<0.0001
Female	8.3%	24.3%	<0.0001
Male	6.0%	20.6%	<0.0001
Diabetes	10.3%	30.5%	<0.0001
Non-Diabetes	6.9%	20.7%	<0.0001
LAD	8.8%	25.7%	<0.0001
Non-LAD	6.6%	21.4%	<0.0001
RVD < 2.75mm	10.0%	23.8%	<0.0001
RVD ≥ 2.75mm	4.7%	22.5%	<0.0001
Length > 13.5mm	9.1%	26.6%	<0.0001
Length ≤ 13.5mm	6.7%	20.5%	<0.0001
Overlap	9.5%	32.9%	<0.0001
Non Overlap	6.9%	19.7%	<0.0001



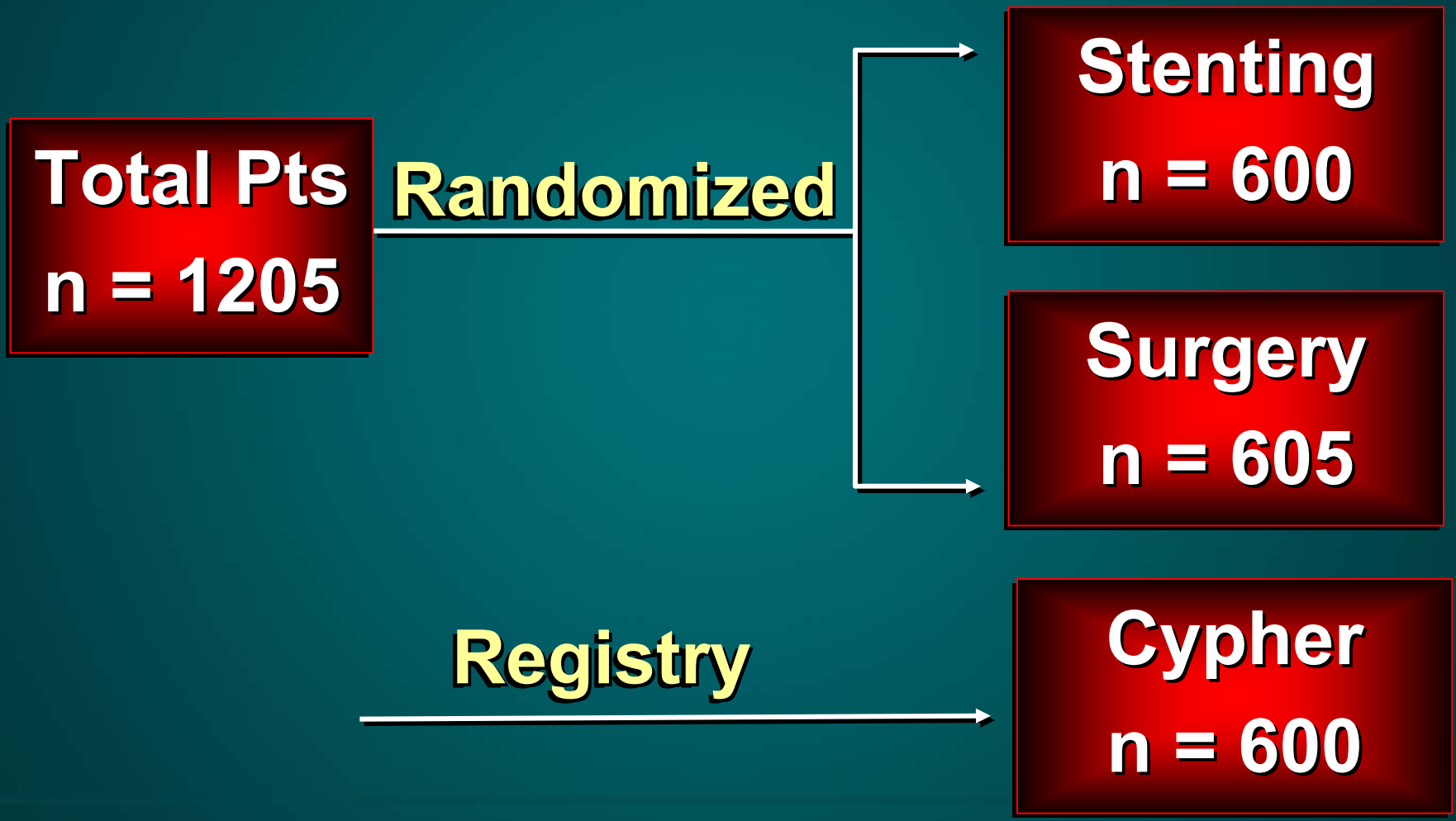
TLR up to 4 Years: Subgroup Summary

TAXUS II, IV, V, VI Meta-analysis



	HR	TAXUS	Control	P Value
All	0.46	10.3%	20.2%	<0.0001
RVD ≤2.5	0.42	13.2%	27.8%	<0.0001
RVD 2.5 - ≤3.0	0.49	9.8%	18.7%	<0.0001
RVD >3.0	0.53	7.3%	12.7%	0.002
Lsn Length <18	0.46	9.7%	19.1%	<0.0001
Lsn Length 18-26	0.48	11.0%	20.9%	0.0006
Lsn Length >26	0.45	12.9%	26.6%	0.002
Non-Diabetic	0.47	9.6%	18.7%	<0.0001
Diabetic-Oral	0.42	12.3%	25.7%	<0.0001
Diabetic-Insulin	0.45	13.6%	23.3%	0.01
Single Stent	0.50	9.6%	17.4%	<0.0001
Multiple Stents	0.34	12.1%	32.5%	<0.0001
Male	0.44	9.5%	19.9%	<0.0001
Female	0.50	12.2%	20.8%	<0.0001

ARTS II
Arterial Revascularization Therapy Study



ARTS II:
Lesion Characteristics

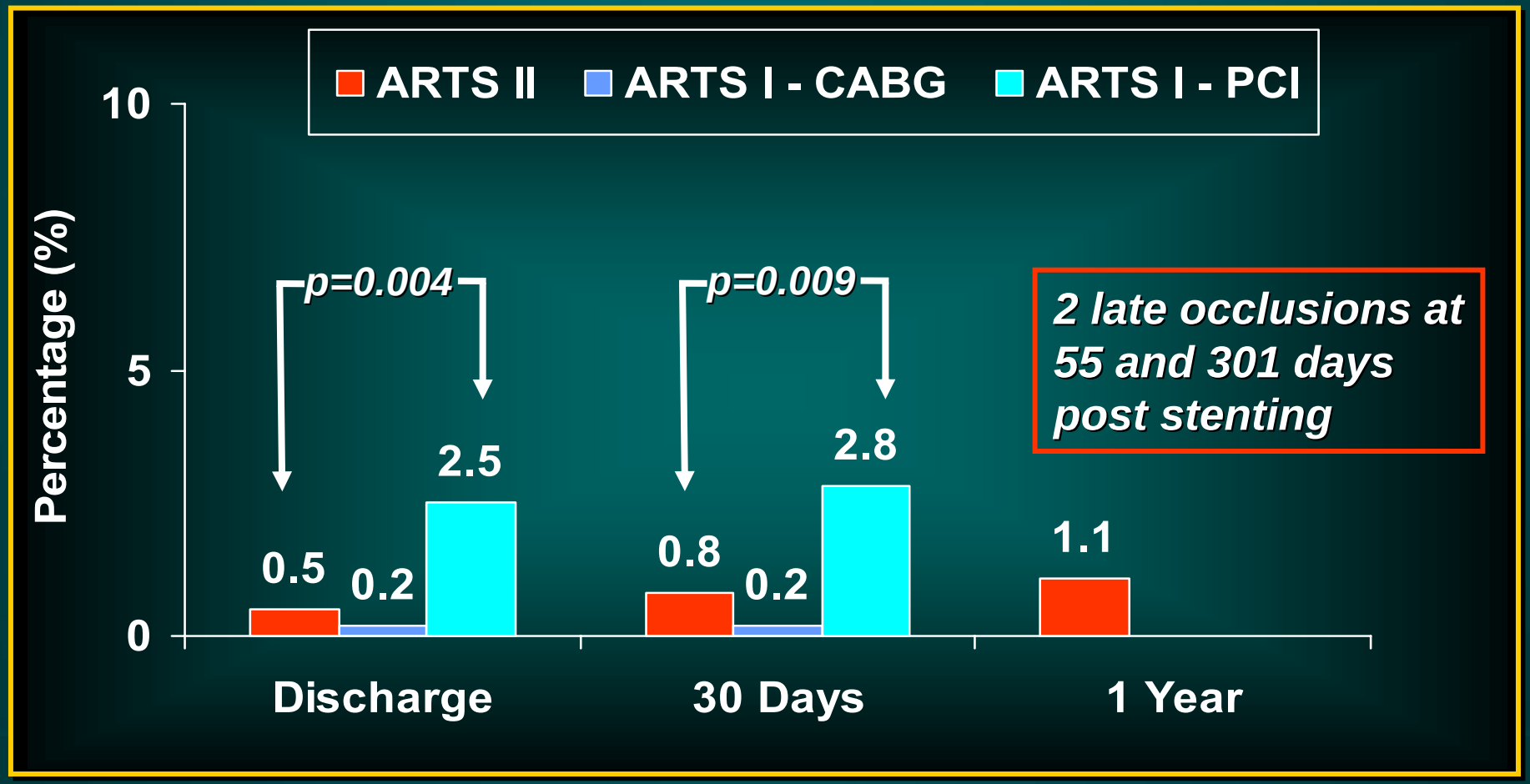
% of patients	ARTS II N=607 pts N=2160 les.	ARTS I (CABG) N=605 pts N=1638 les.	ARTS I (PCI) N=600 pts N=1606 les.
2-VD	46	66	69
3-VD	54 ↑	30	27
% of lesions			
LAD location	42	41	39
LCx location	29	29	29
RCA location	29	30	31
Discrete (<10mm)	61	68	66
Tubular (10-20mm)	27	25	27
Diffuse (>20mm)	12 ↑	7	7
Type C lesion	14 ↑	8	8
Side branch involvement	34	32	35

ARTS II:
Procedural Characteristics

	ARTS II N=607 pts N=2160 les.	ARTS I (CABG) N=605 pts N=1638 les.	ARTS I (PCI) N=600 pts N=1606 les.
Lesions, #	3.6 ↑	2.8	2.8
Stented les. / anast. seg., #	3.2 ↑	2.6	2.5
Stents, #	3.7 ↑	-	2.8
Direct stenting, %	35 ↑	-	3
Max. inflation pressure, atm	16.4 ↑	-	14.6
Total stent length, mm	73 ↑	-	48
Gp IIb/IIIa inhibitor use, %	33	-	-
Use of arterial conduit, %	-	93	-
Duration of procedure, mins	85	193	99
Hospital stay, days	3.4	9.6	3.9

ARTS II:
*Angiographic Occlusions**

*** Definition of thrombotic occlusion:** Angiographically proven occlusion (TIMI 0 or 1) or flow limiting thrombus (TIMI 1 or 2)



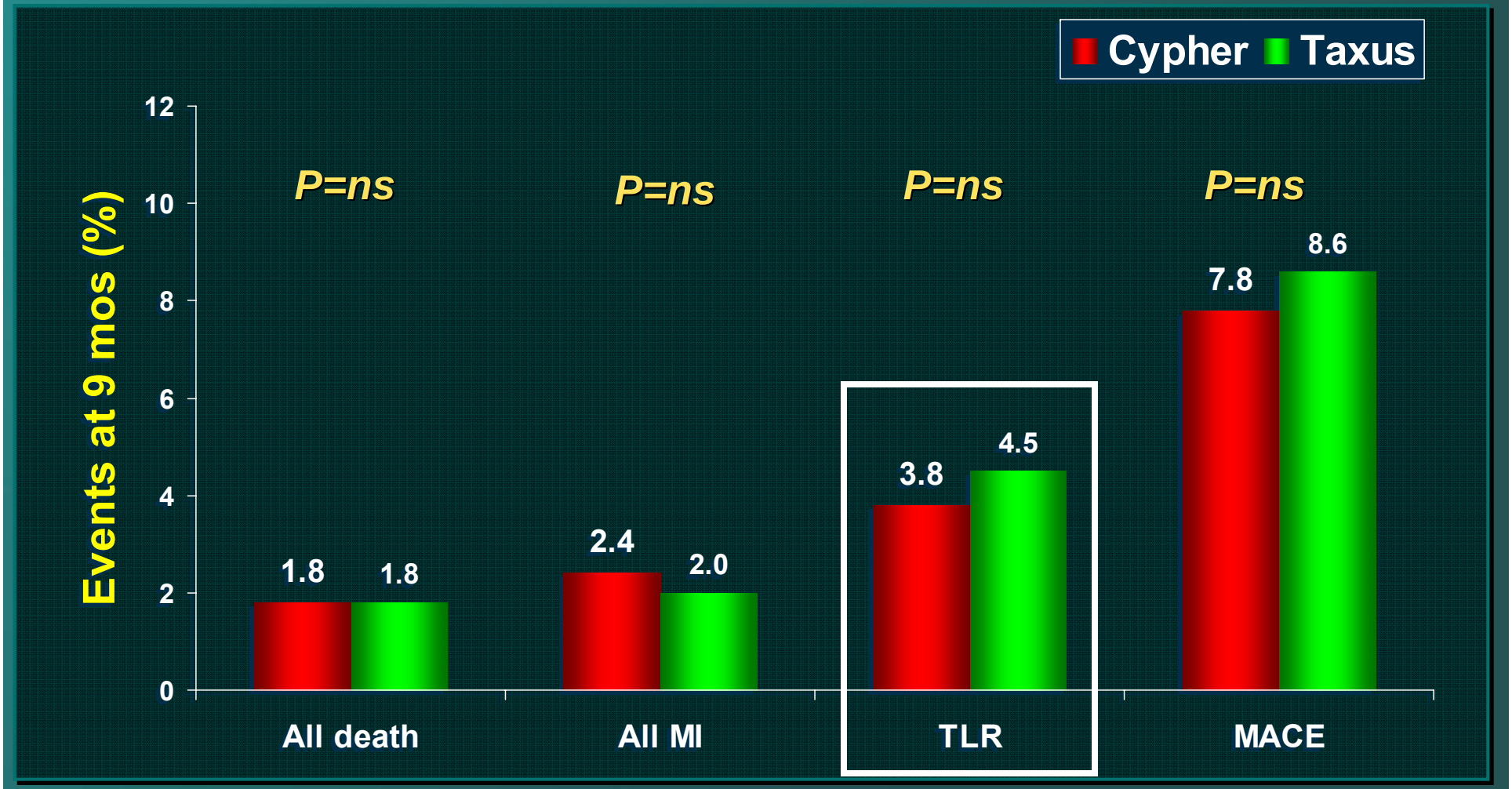
ARTS II:
*MACCE up to 1 year **

MACCE	ARTS II N=607	ARTS I (CABG) N=602	ARTS I (PCI) N=600
Death	1.0%	2.7%	2.7%
CVA	0.8%	1.8%	1.8%
MI	1.2%	3.5%	5.0%
(re) CABG	2.0%	0.7%	4.7%
(re) PCI	5.4%	3.0%	12.3%
Any MACCE	10.4%	11.6%	26.5%

* Complete follow-up in 97%

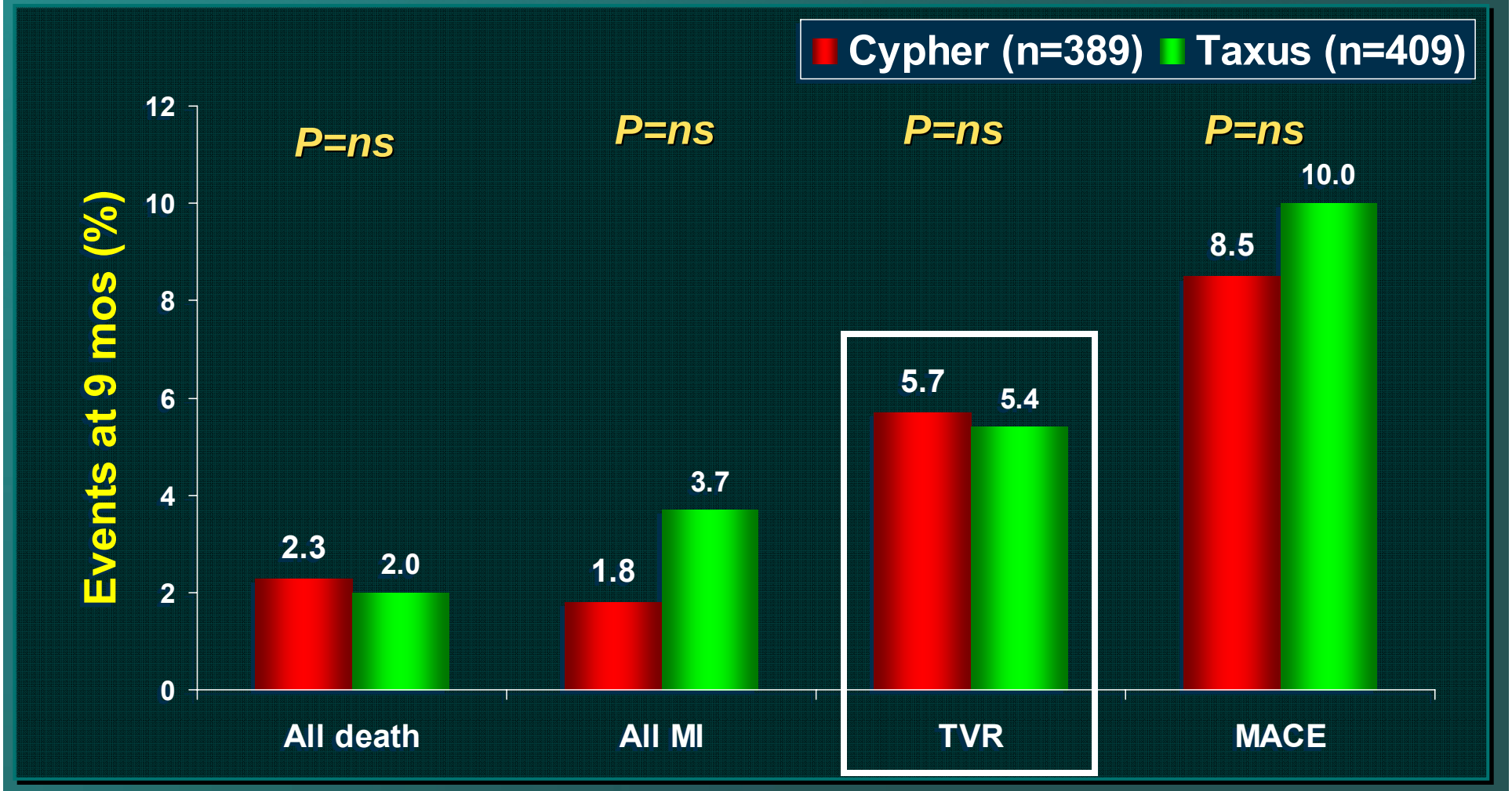
SORT OUT II: 9 Clinical FU

All 5 Danish university centers randomized Cypher vs. Taxus DES in 2,098 patients (2,889 lesions); open inclusion, only clinical FU



STENT Registry MVD: 9 Mo Clinical FU

"Real world" registry in 8 regional centers; 9,129 patients with either Cypher or Taxus; 798 patients (8.7%) with multivessel Rx; only clinical FU



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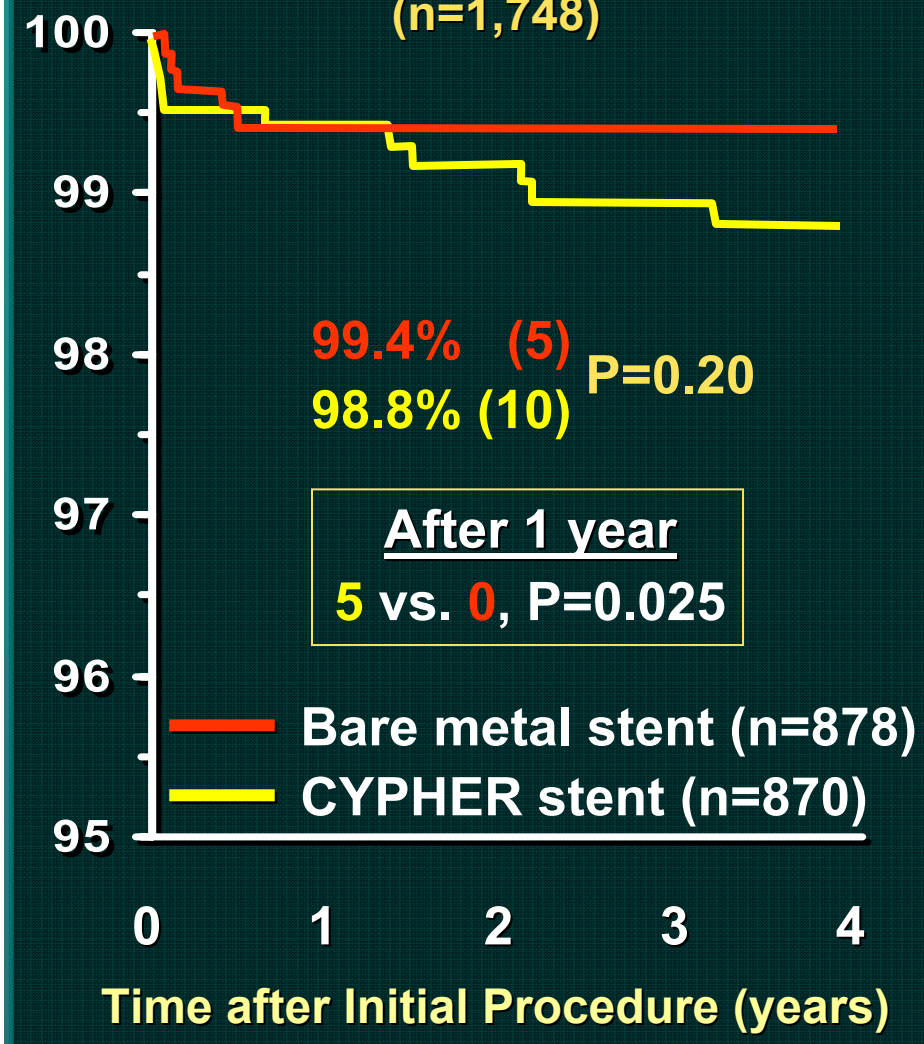
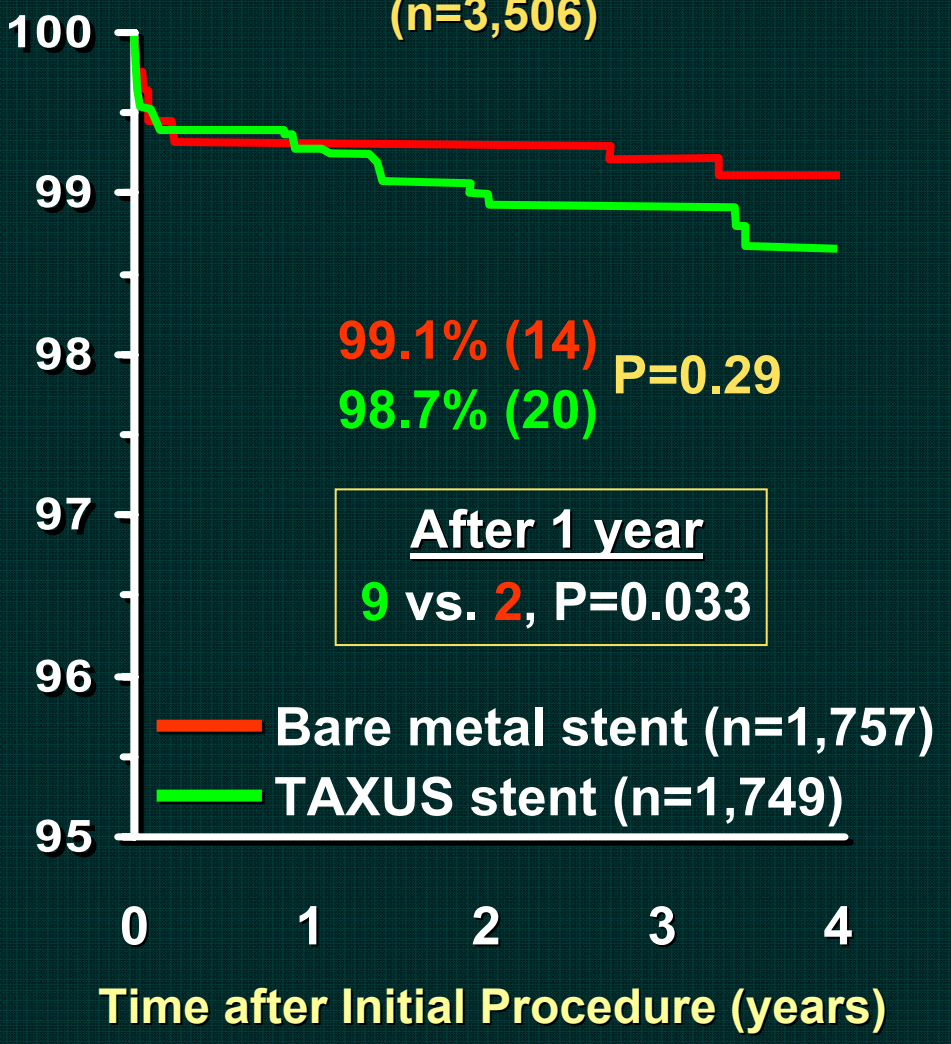
Freedom From (Protocol) Stent Thrombosis





CYPHER RCT Stent Thrombosis 4 yr Follow-up: *Expanded Definition*

definite + probable

Thrombosis	CYPHER N=878	BMS N=870	
Ea			
La			
Ve			
Su			
La			
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 RCT Stent Thrombosis 4 yr Follow-up: *Expanded Definition*

definite + probable

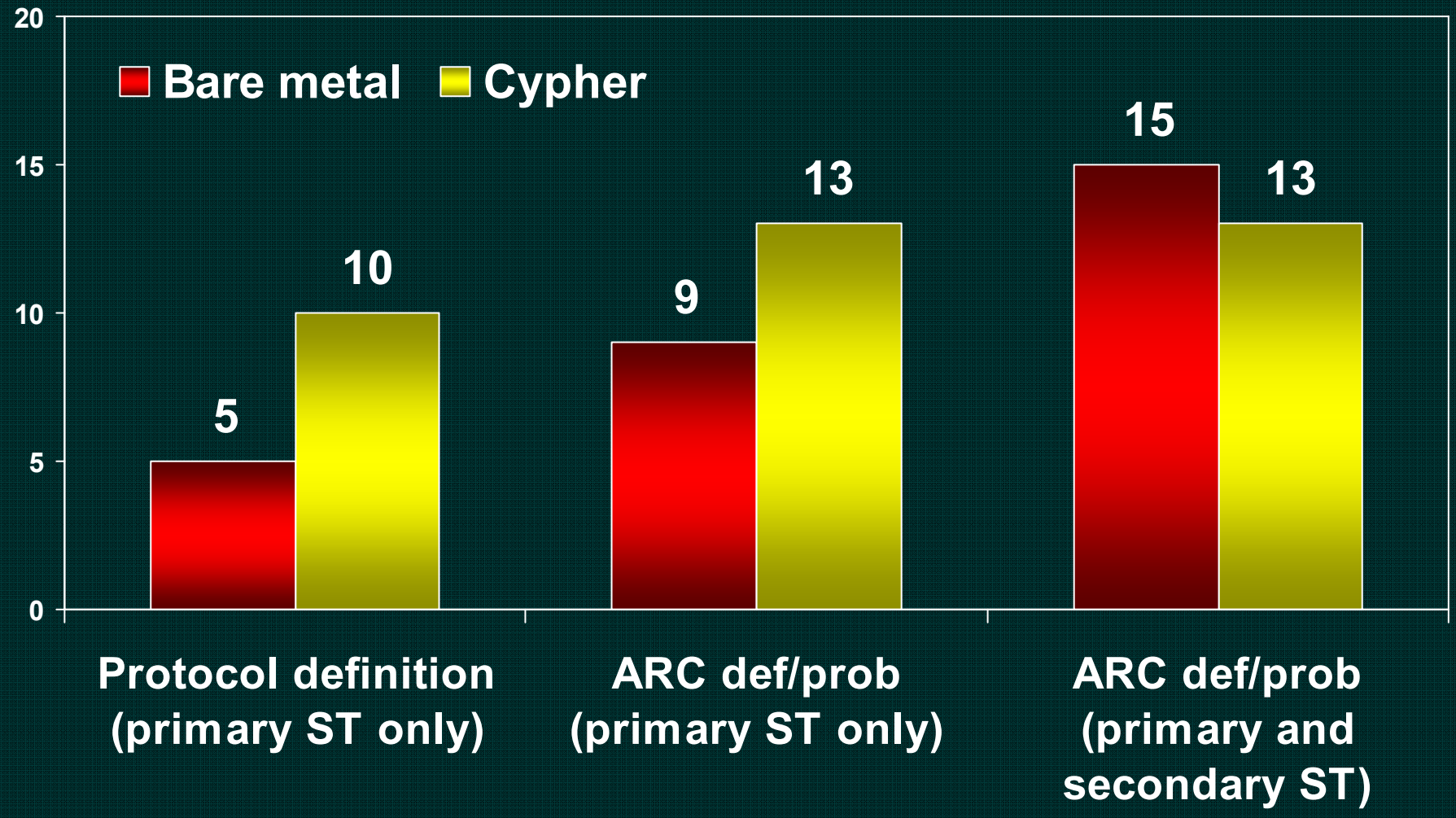
Thrombosis	CYPHER N=878 Patients	BMS N=870 Patients	P Value*
Early (0-30 days)	0.5% (4)	0.3% (3)	0.4702
Late (31-360 days)	*0.2% (2)*	*0.9% (8)*	*0.0098*
Very Late (361-1440)	0.9% (7)	0.5% (4)	0.3632
Summary:			
Late + Very Late	1.1% (9)	1.4% (12)	0.5043
All Thrombosis	1.5% (13)	1.7% (15)	0.6985

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

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

CYPHER 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

Frequency of In-stent Restenosis - CRF

282 pts with 311 ISR lesions

39 pts with 44 ISR lesions

86% Reduction of ISR Cases!!

Frequency of In-stent Restenosis - CRF

October 24, 2002

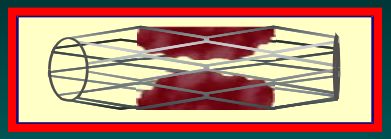
April 24, 2003

one year FU

Bare Stents

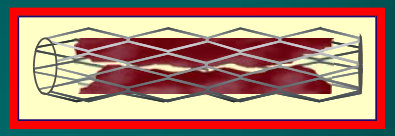
282 pts with 311 ISR lesions

Focal



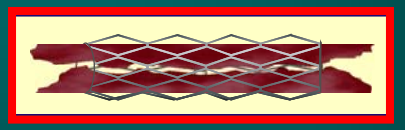
36%

Diffuse Intrastent



20%

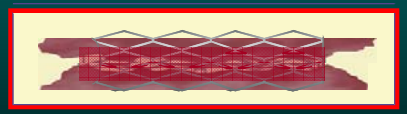
Proliferative



39%

64%

Total Occlusion



5%

Outcomes Bare Stent ISR:
Events to 1 year

Event	N= 282
Death (%)	4.2
MI (%)	6.1
Q-wave	3.1
Non-Q wave	3.0
Death/MI (%)	8.1%
TLR (%)	27.2%
MACE(%)	34.1%

Frequency of In-stent Restenosis - CRF

October 24, 2003

April 24, 2004

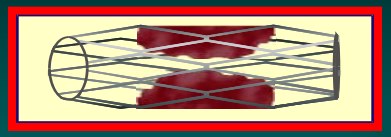
one year FU

SES

39 pts with 44 ISR lesions

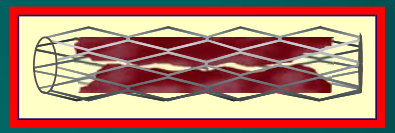
86% Reduction of ISR Cases!!

Focal



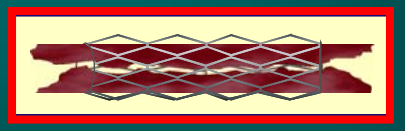
86%

Diffuse Intrastent



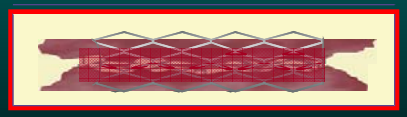
13%

Proliferative



0%

Total Occlusion



1%

14%

Outcomes DES Stent ISR:
Events to 1 year

Event	N= 39
Death (%)	0
MI (%)	0
Q-wave	0
Non-Q wave	0
Death/MI (%)	0
TLR (%)	0
MACE(%)	0

Expected Cost-Effectiveness: DES in 2005

Diabetes

Vessel Diameter	Lesion Length				
	10 mm	15 mm	20 mm	25 mm	30 mm
2.5 mm	23%	26%	29%	31%	34%
3.0 mm	15			%	24%
3.5 mm	10			%	16%
4.0 mm	6			%	10%

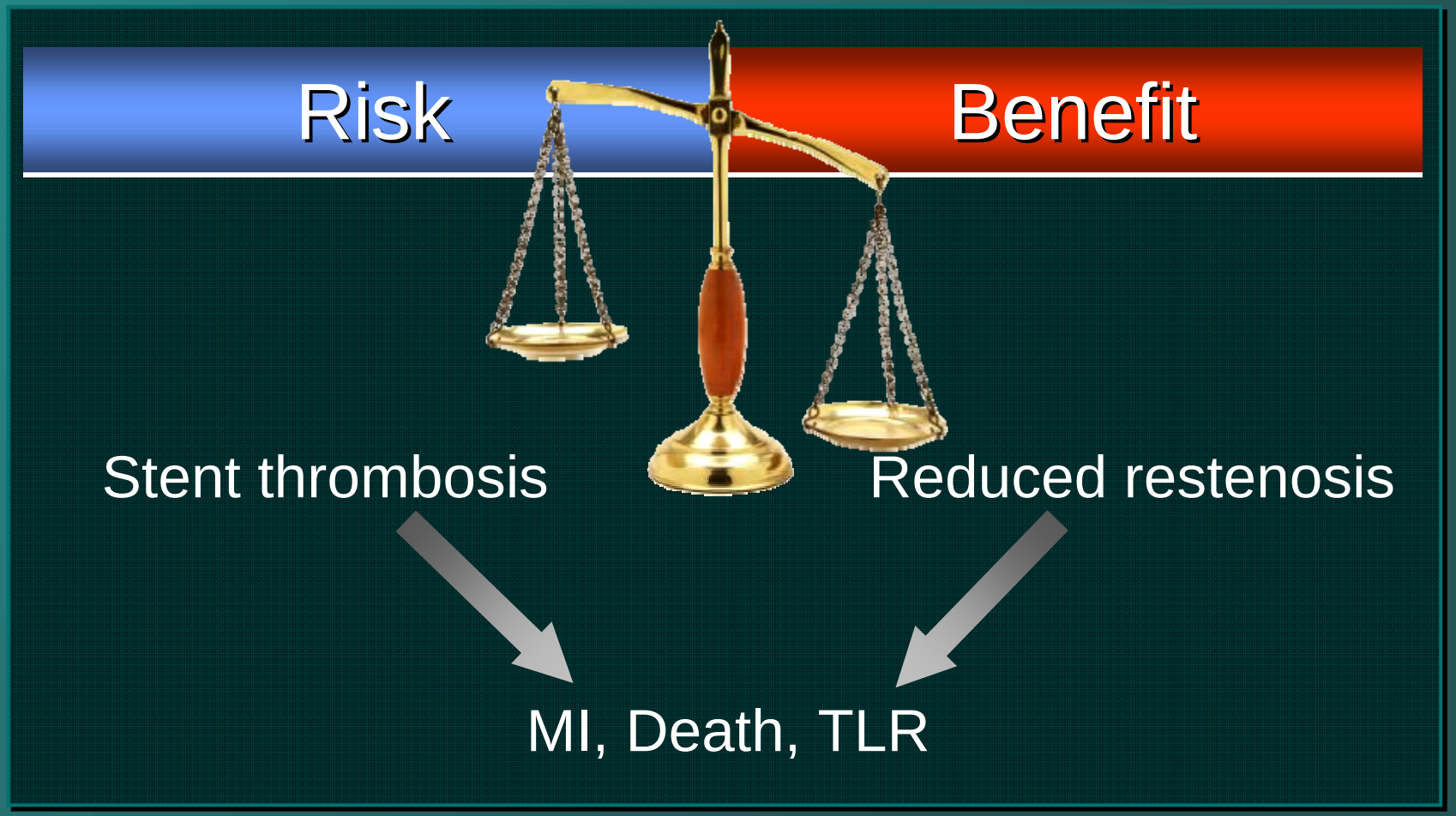
DES NOT Cost-efffective in only 15-20% of treated lesions

No Diabetes

2.5 mm	18			%	27%
3.0 mm	11%	13%	15%	17%	18%
3.5 mm	7%	8%	10%	11%	12%
4.0 mm	4%	5%	5%	7%	7%

Life is a Matter of "Balance"

The Scale Favors DES!



DES Clinical Perspectives

The "4" Questions

1. *What are the alternatives to DES treatment?* (safety and management of BMS in-stent restenosis)
2. *What is the incremental efficacy of DES vs. BMS?* (on-label and off-label patient cohorts)
3. *Does the balance of safety/efficacy still favor DES?*
4. *What is the current DES "dilemma" for clinicians (and prospective patients)?*

(v)LaST…Unanswered Questions

- Which patients are at higher risk for (v)LaST?
- What is the optimal duration and beneficial impact of dual anti-platelet therapy on (v)LaST?
- What are the consequences of long-term dual anti-platelet therapy?
- Is (v)LaST a continuous hazard function (i.e. linear over time)?
- Does (v)LaST occur more frequently in the « real world » (i.e. more complex patients and lesions)?
- Are there other patient-related factors which must be considered (drug resistance)?

DES Clinical Perspectives

Final Thoughts

- ***DES are unquestionably the "standard of care" PCI treatment alternative due to a marked "across the board" reduction in restenosis cw BMS!***
- **Given the data available, there is no evidence that DES cause a higher frequency of overall death and MI c/w BMS in on-label and off-label use indications.**
- **DES are "different" than BMS and are associated with a slightly higher frequency of very late stent thrombosis.**
- **The prolonged obligatory dual anti-platelet therapy and the attendant DES thrombosis anxiety has created significant logistic clinical practice adjustments.**

DES Clinical Perspectives

Final Thoughts

- *We recommend a more considered use of DES (e.g. routine 1 stent in bifurcations) and certainly a lower threshold for BMS use in situations where prolonged dual anti-platelet therapy is problematic.*
- **Presently, there are significant data gaps requiring new much larger clinical trials with longer FU.**
- **There are new DES technologies which may reduce these late safety concerns in the near future.**