Fellows Course, SOLACI-2014, Tuesday April 22nd

In Stent Restenosis: Diagnosis and Therapy

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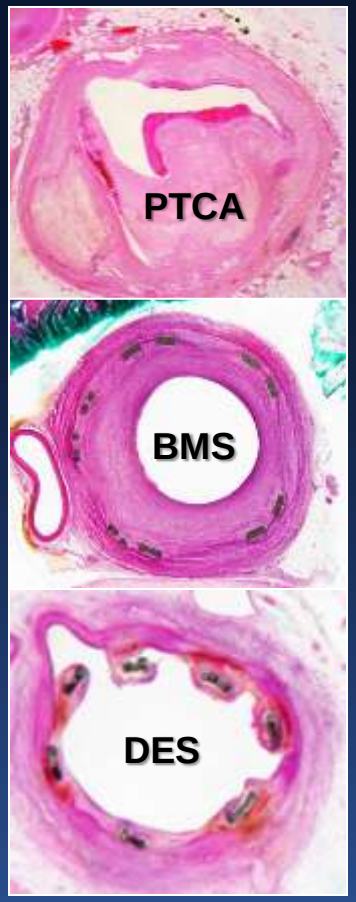
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below:

- Grant/Research Support: Abbott Vascular, Alumend, Amaranth Medical, Bioventrix Inc., Boston Scientific, Caliber Therapeutics Inc., Cardia Inc., Cardiosystems Inc., Cardiosolutions Inc., Circulite Inc., Corindus Vascular Robotics, Direct Flow Medical, Intact Vascular, Juventas, Lutonix, Meril Life Sciences, Mitralign, Orbus Neich Medical Inc., Stentys S.A., Surmodics, Thoratec, Tubrikar, Valve Medical, Volcano, WL Gore

The Technological Evolution of PCI

"A Band Aid Developmental Approach"



Acute dissections, abrupt vessel closure & chronic negative remodeling

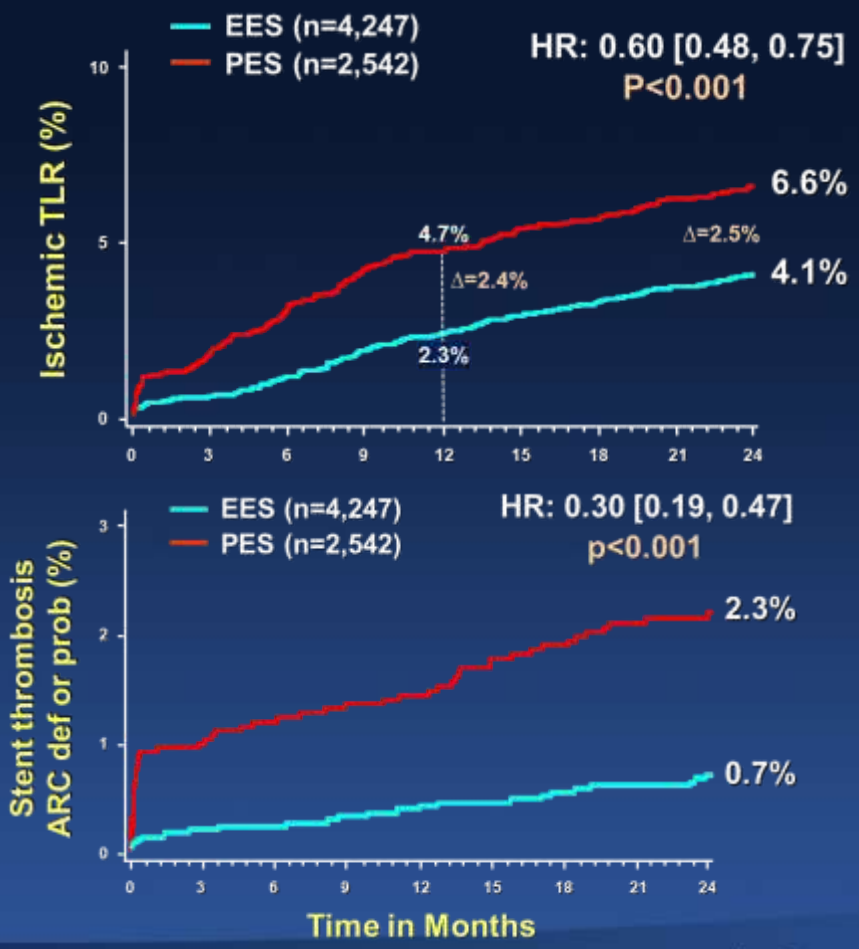
↓

Neointimal proliferation

↓

Delayed healing & stent thrombosis

SPIRIT II, III, IV and COMPARE trials
Pooled Database Analysis (n=6,789)

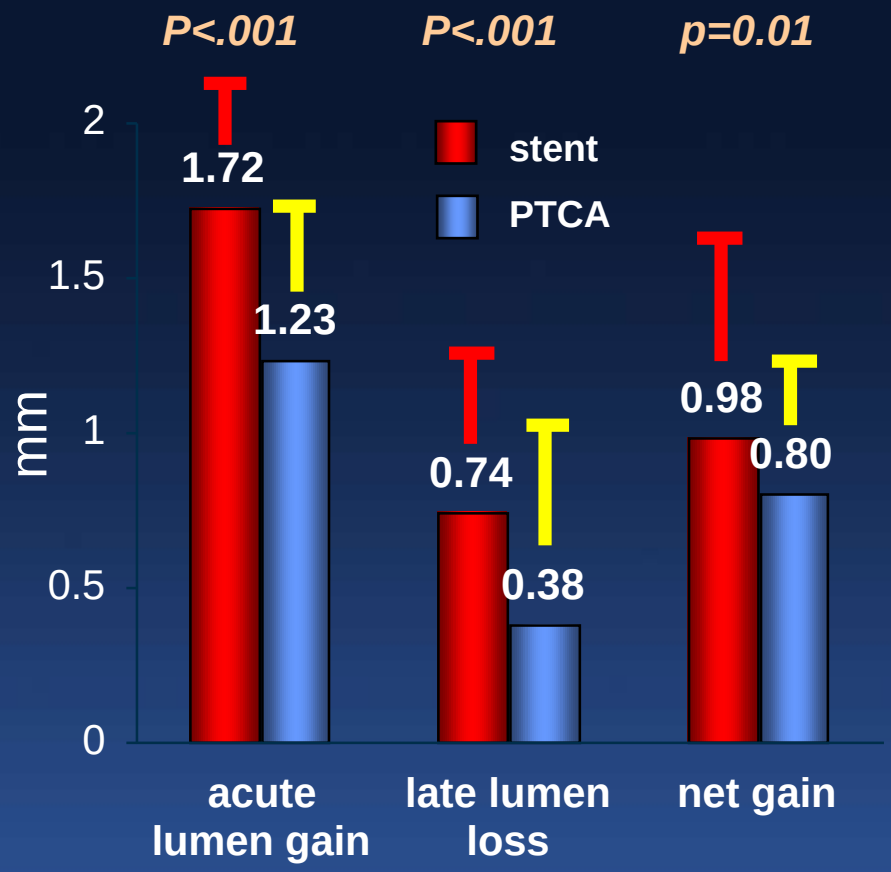


Kereiakes DJ et al. EuroIntervention 2011:7:74-83

Landmark PTCA vs. Stent Trials

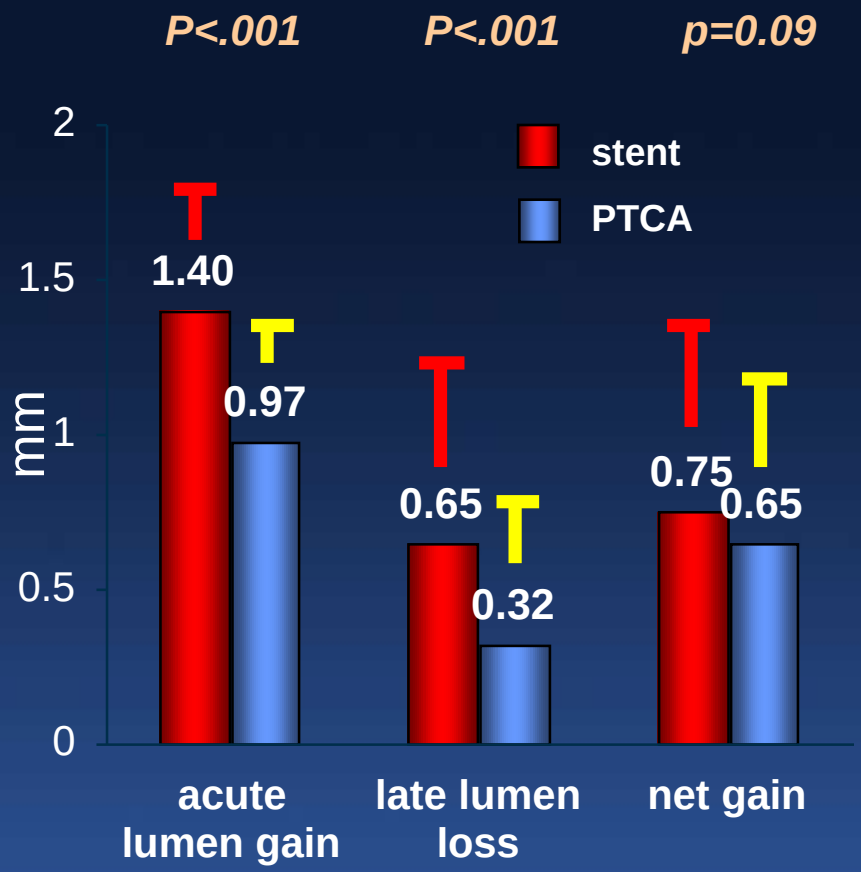
Early & Late Angiographic Results

STRESS n=410



DL Fishman et al., *N Engl J Med* 1994

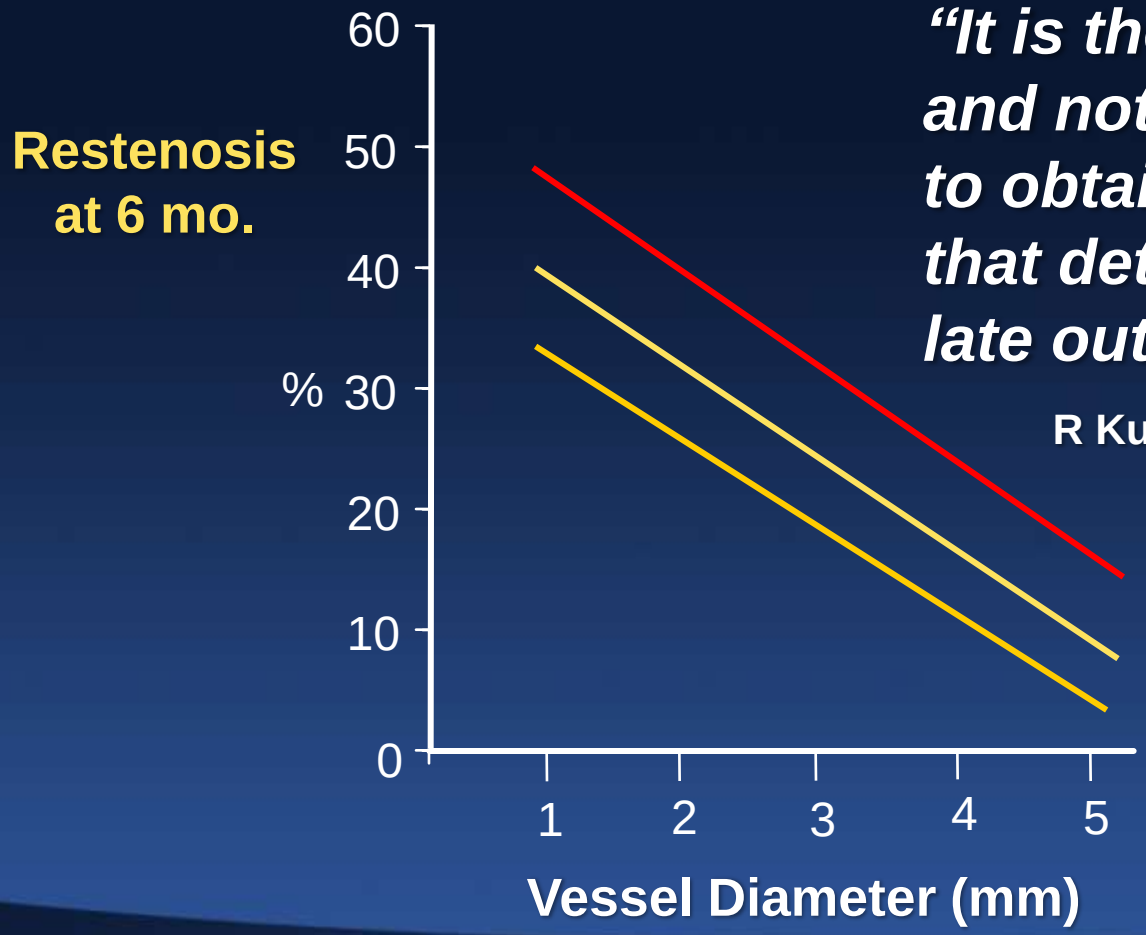
BENESTENT n=520



P Serruys et al., *N Engl J Med* 1994

Predictors of Long-Term Outcome

Device versus Procedural Results



The Bigger the Better Concept:

"It is the immediate result and not the device used to obtain the result that determines late outcome ..."

R Kuntz, *J Am Coll Cardiol* 1993

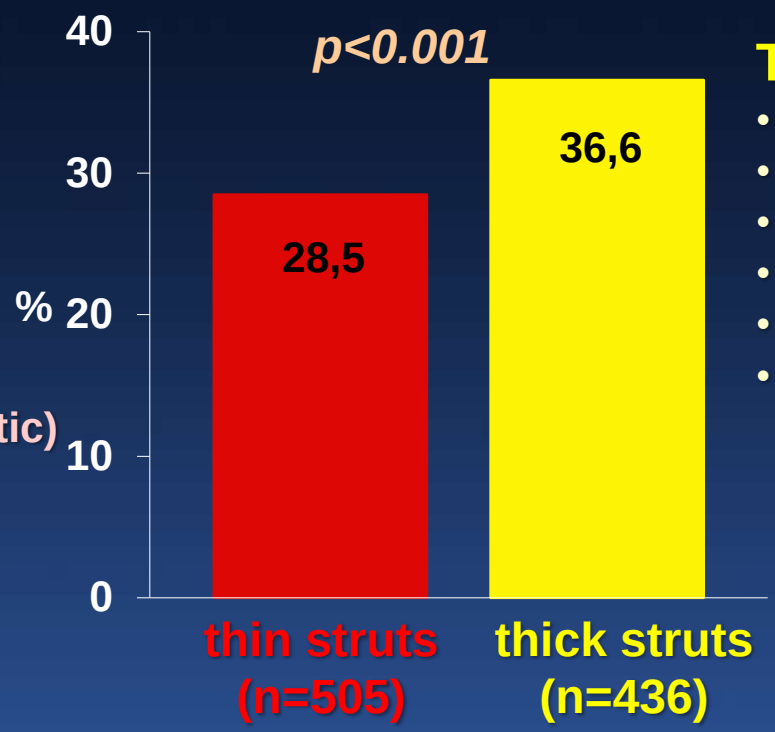
c/o Helmut Schühlen

Thin-Strut Versus Thick-Strut Stents

Retrospective analysis of 941 patients

Thin struts (<100 µm):

- Palmaz-Schatz
- ACS MULTI-LINK
- BiodivYsio
- BeStent
- JOSTENT Flex
- Diamond (Phytis)
- V-Flex (Global Therapeutic)
- Sorin Carbostent

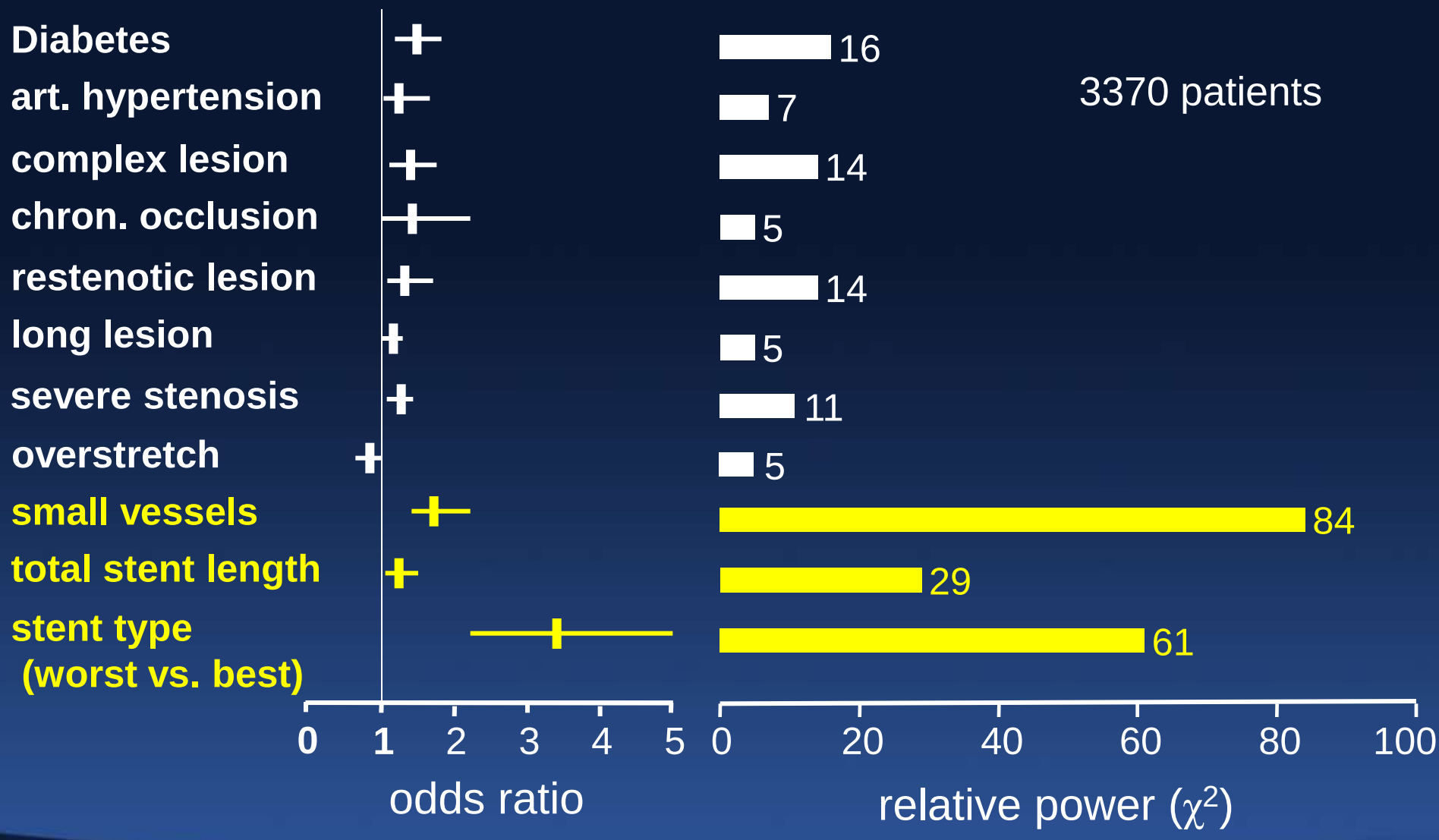


Thick struts (≥100µm):

- NIR
- ACS Duet
- BX Velocity
- AVE-II
- Cordis Crossflex LC
- Bard XT

Briguori et al., *J Am Coll Cardiol* 2002

Independent Risk Factors for ISR

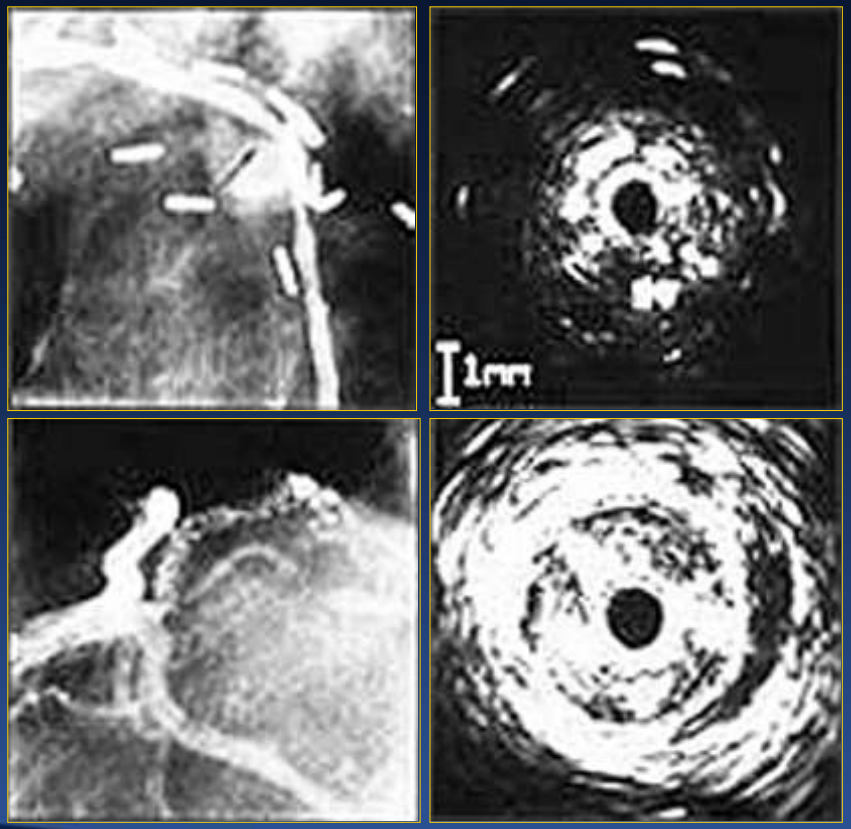


Kastrati et al., *Am J Cardiol* 2000

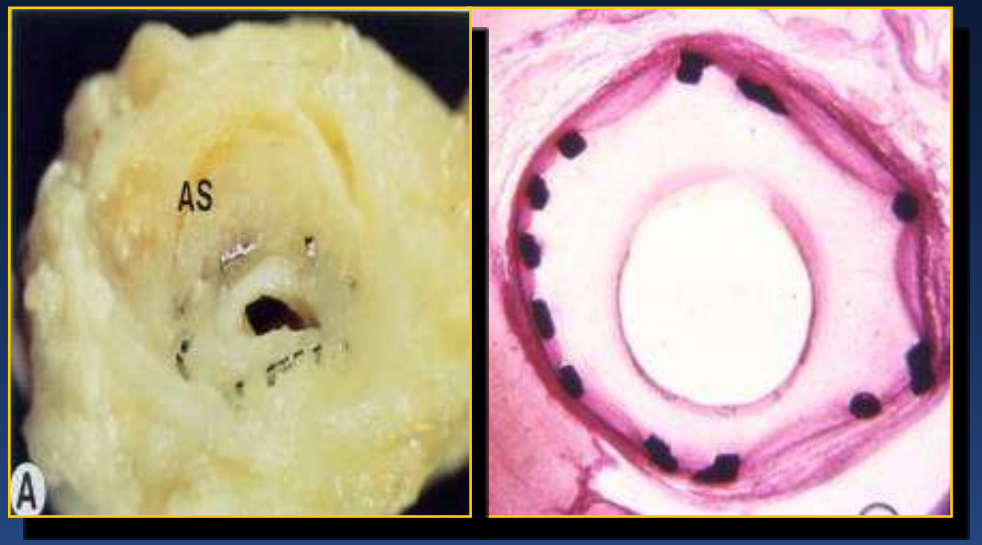
BMS In-Stent Restenosis

Mechanisms of Restenosis

Inadequate Initial Stent Expansion



In-Stent Restenosis = Intimal Hyperplasia



In-Stent Restenosis

Angiographic Classification

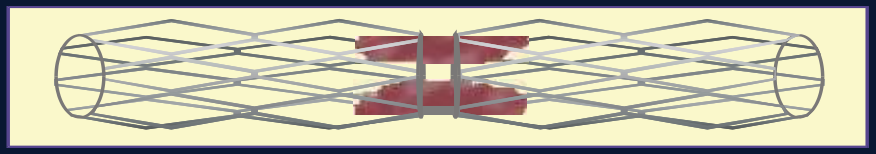
Focal (< 10mm)

- Unscaffolded (gap or articulation)
- Body (or edges)
- Margin
- Multifocal

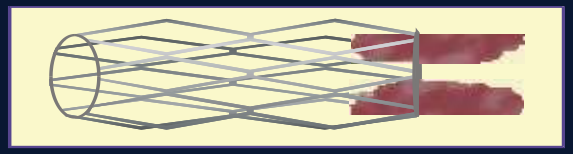
Diffuse (>10mm)

- Intrastent
- Proliferative (extends beyond margins)
- Total occlusion

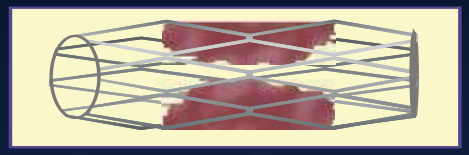
Patterns of In-Stent Restenosis



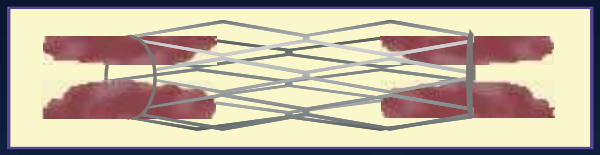
Pattern I (Focal) Type IA: Articulation / Gap



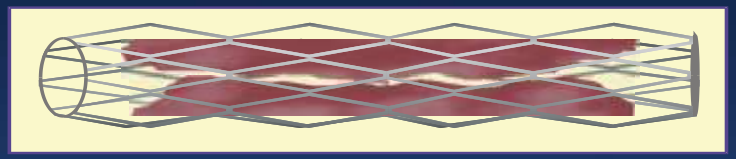
Pattern I (Focal) Type IB: Margin



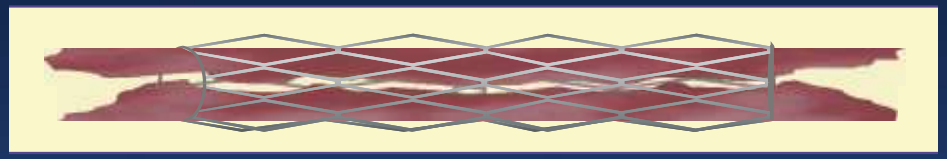
Pattern I (Focal) Type IC: Focal Body



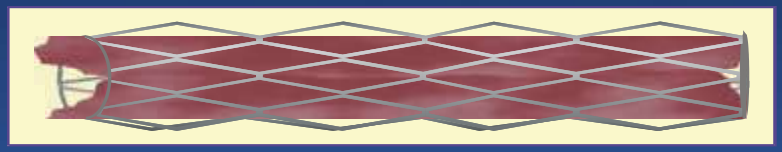
Pattern I (Focal) Type ID: Multifocal



Pattern II (Diffuse): Intra-stent



Pattern III (Diffuse): Proliferative



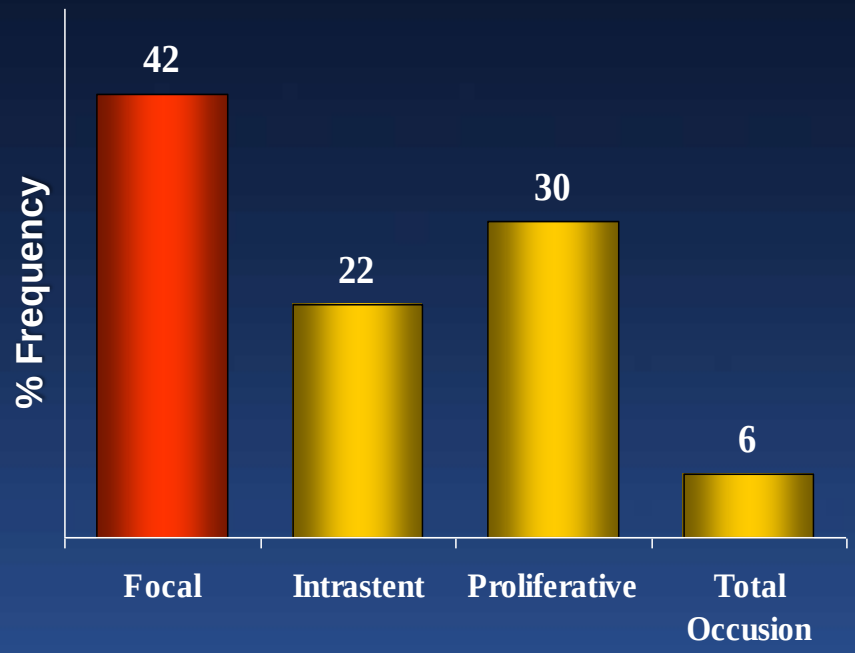
Pattern IV (Diffuse): Total Occlusion

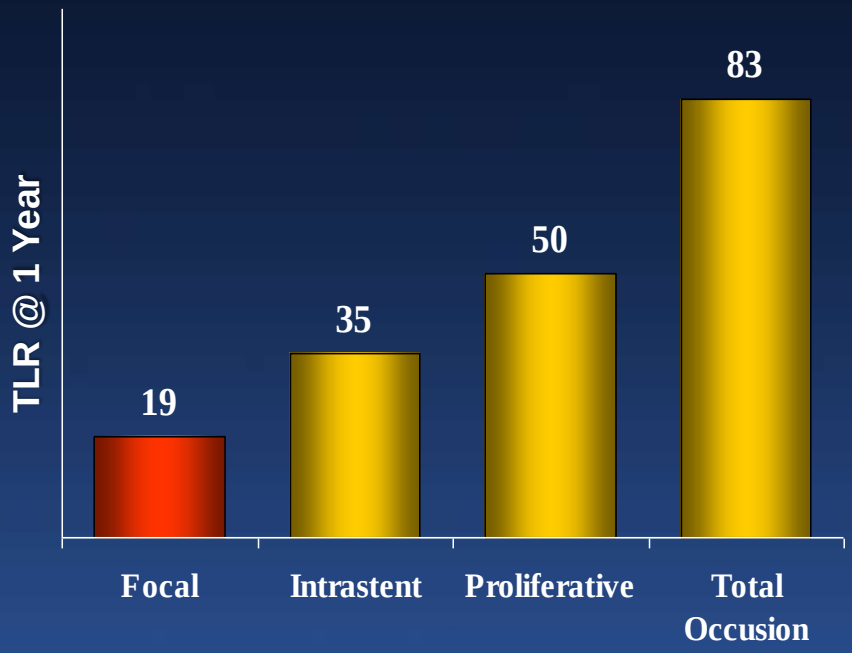
Mehran et al. Circulation 1999;100:1872-1878

Patterns of BMS In-Stent Restenosis

Implications for Clinical Outcomes

282 Lesions Reviewed; Restenosis Patterns Classified by Angiography and Confirmed by IVUS



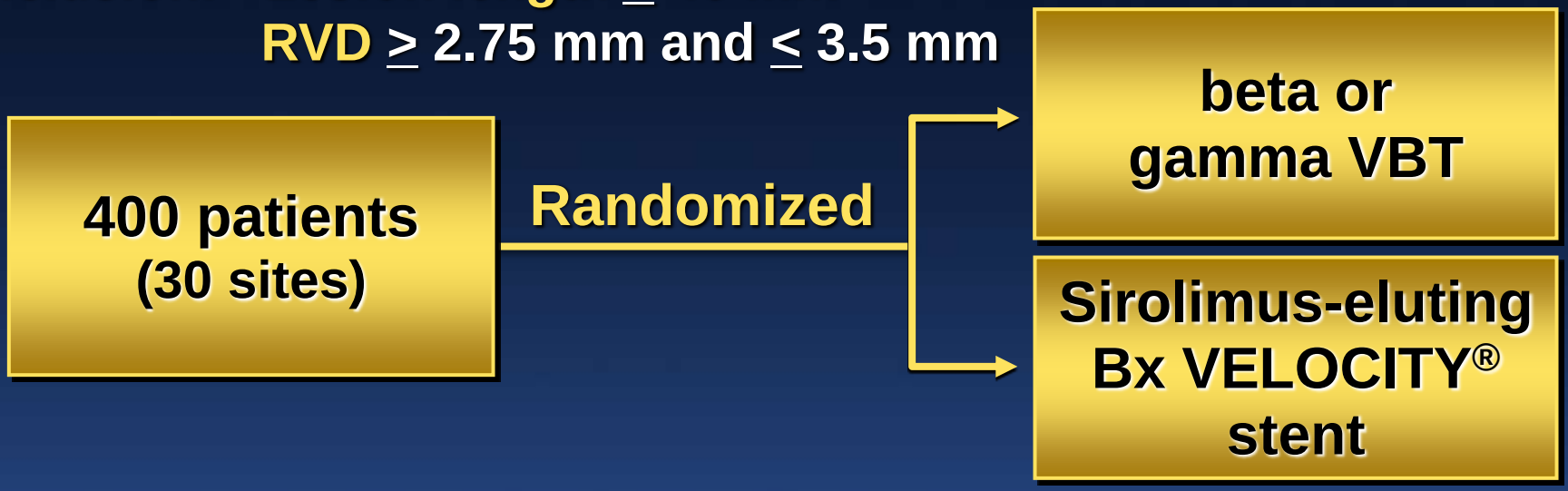


Mehran et al. Circulation 1999;100:1872-1878

SISR Trial

A Multicenter, Randomized Study of the Sirolimus-Eluting Bx Velocity® Balloon Expandable Stent vs. Intravascular Brachytherapy in the Treatment of Patients with In-Stent Restnotic Coronary Artery Lesions

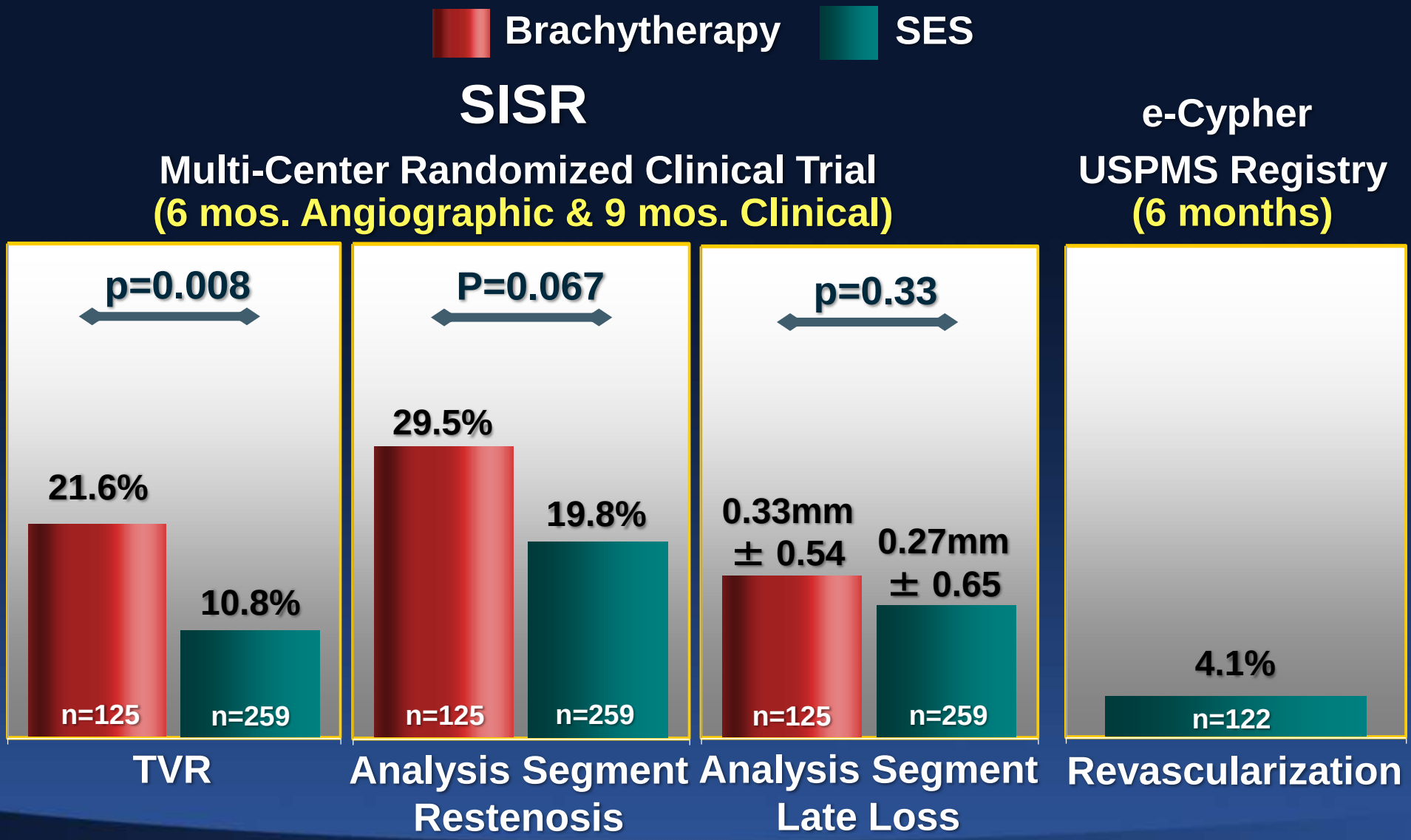
Inclusion: Lesion length ≤ 45 mm
RVD ≥ 2.75 mm and ≤ 3.5 mm



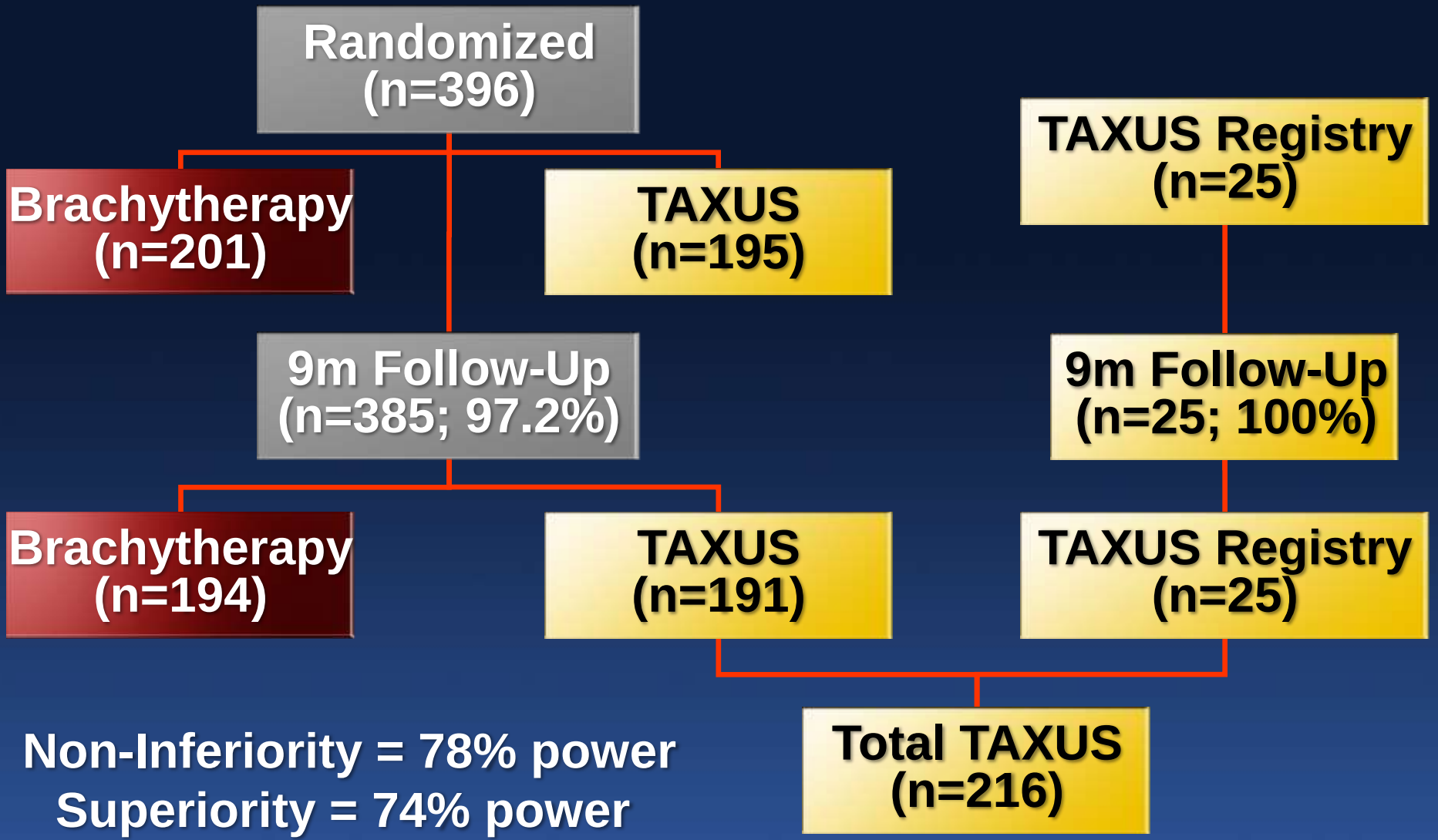
Endpoints 1ry: TVF @ 9 months
Angiographic: all patients @ 6 mos
IVUS: 5-7 center substudy @ 6 mos

Holmes, et al. TCT 2005

SES for BMS ISR

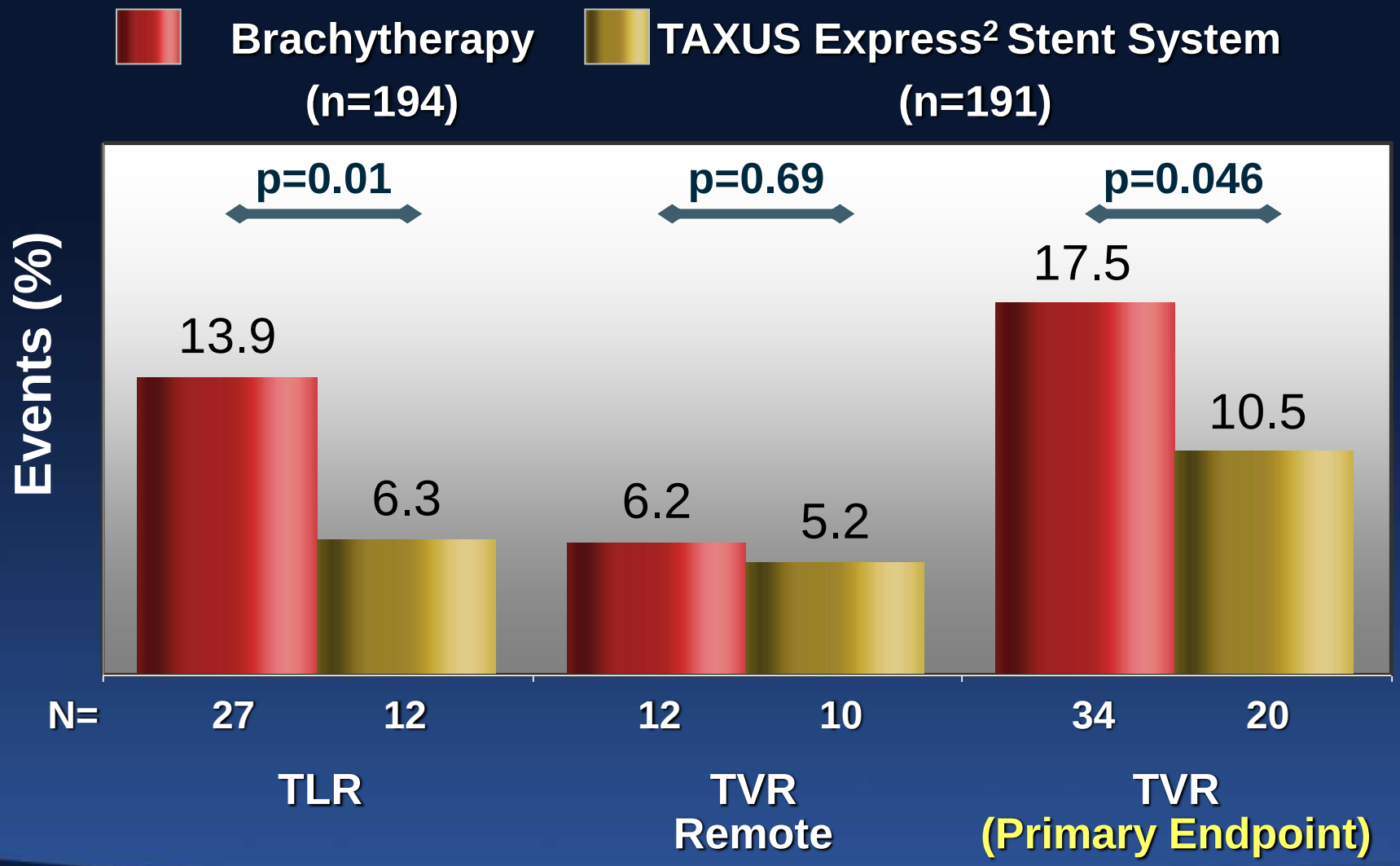


TAXUS V (ISR)



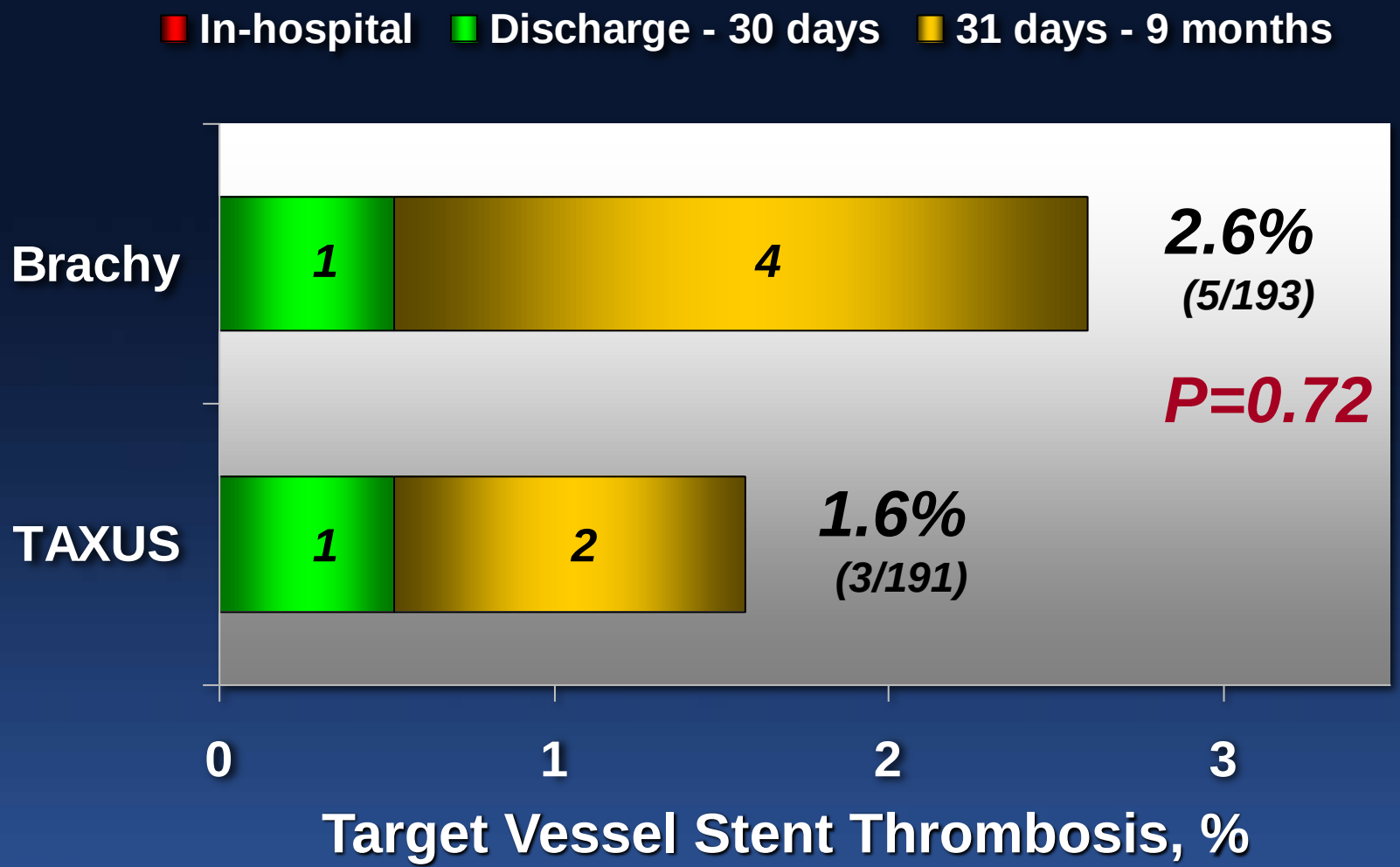
Non-Inferiority = 78% power
Superiority = 74% power

9 Month Revascularization Rates



Stone GW et al. JAMA 2006;295:1253-63

Stent Thrombosis



Mechanisms of DES Restenosis

- ***Biological Factors***
  - Drug resistance
  - Hypersensitivity
- ***Mechanical Factors***
  - Non uniform stent strut distribution
  - Stent fractures
  - Polymer peeling
  - Non uniform drug deposition
- ***Technical Factors***
  - Incomplete stent expansion
  - Stent gaps or “misses” (uncovered lesion segments)
  - Barotrauma to unstented segments

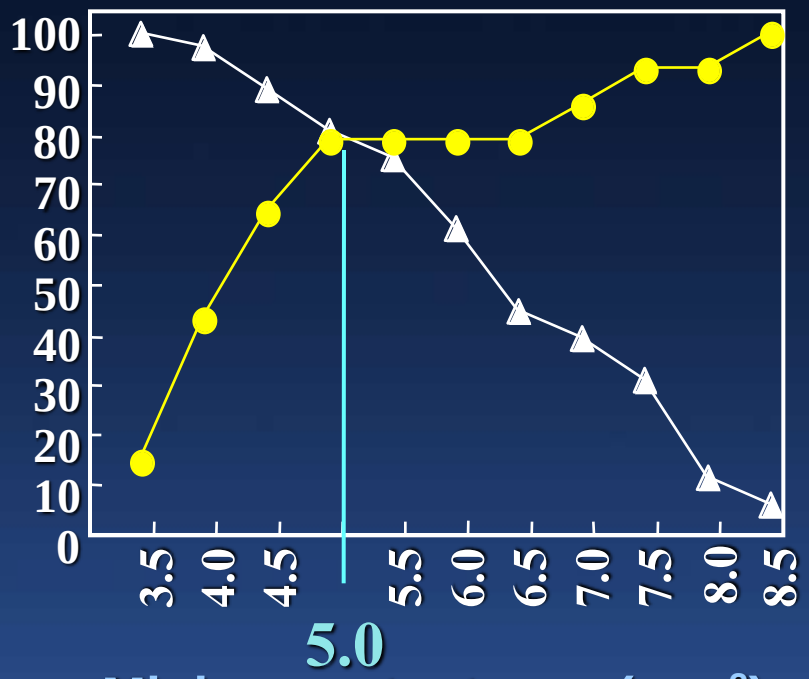
Technical Factors

Stent Underexpansion

Post-Procedure MSA and Binary Restenosis

(sensitivity and specificity curves)

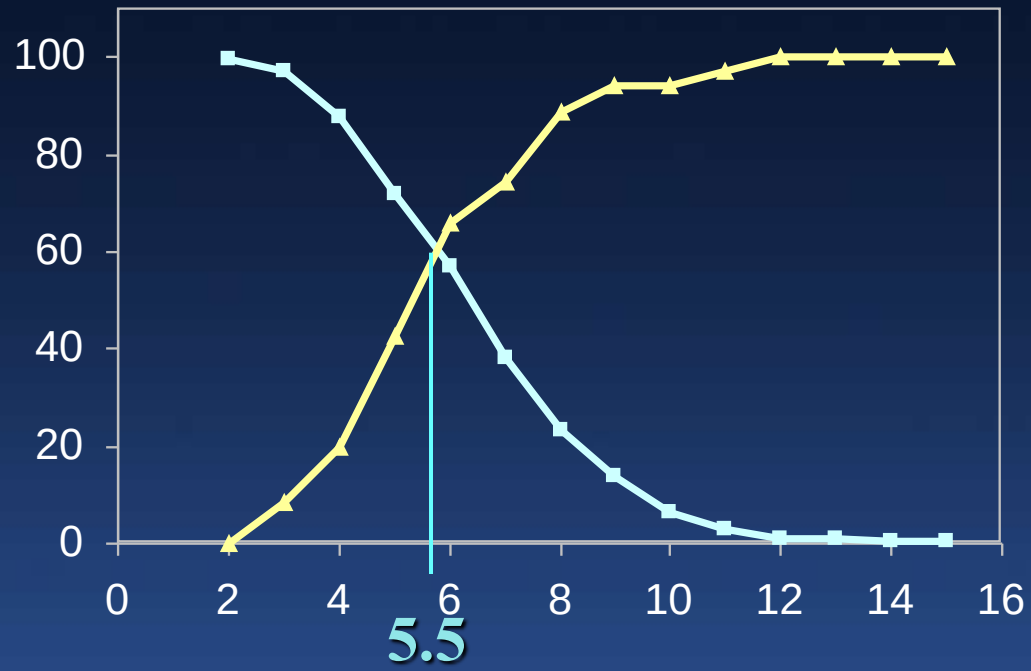
Cypher



Minimum stent area (mm^2)

Sonoda S. et al. J Am Coll Cardiol 2004;43:1959-63

Taxus

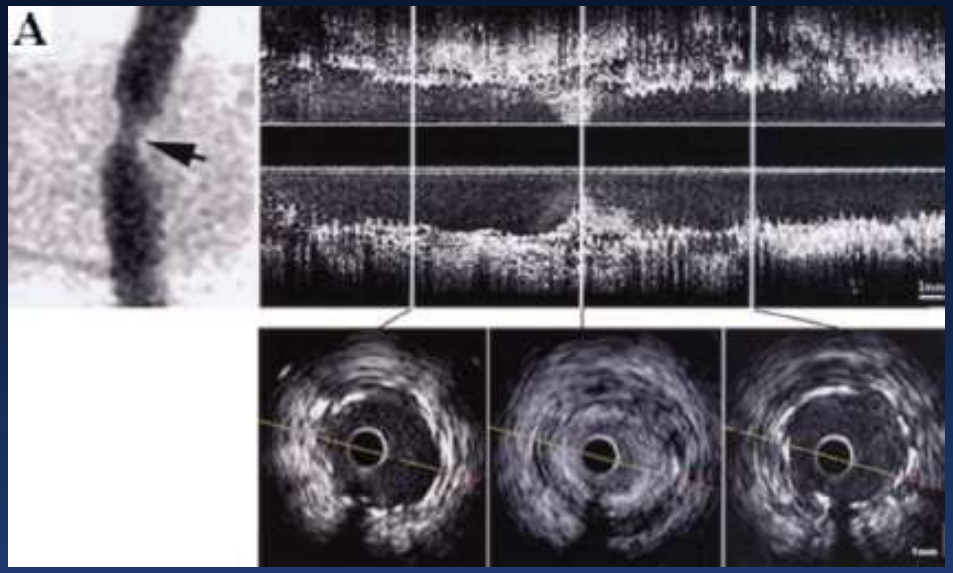


Minimum Stent Area (MSA, mm^2)

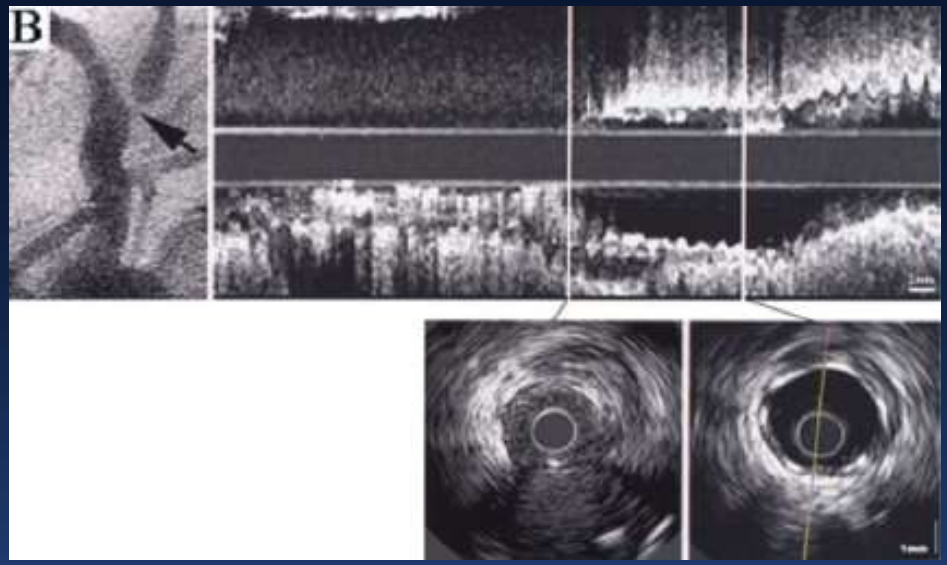
Weissman N. TCT 2006

DES ISR: Technical Factors

Gap



Incomplete Stent Coverage

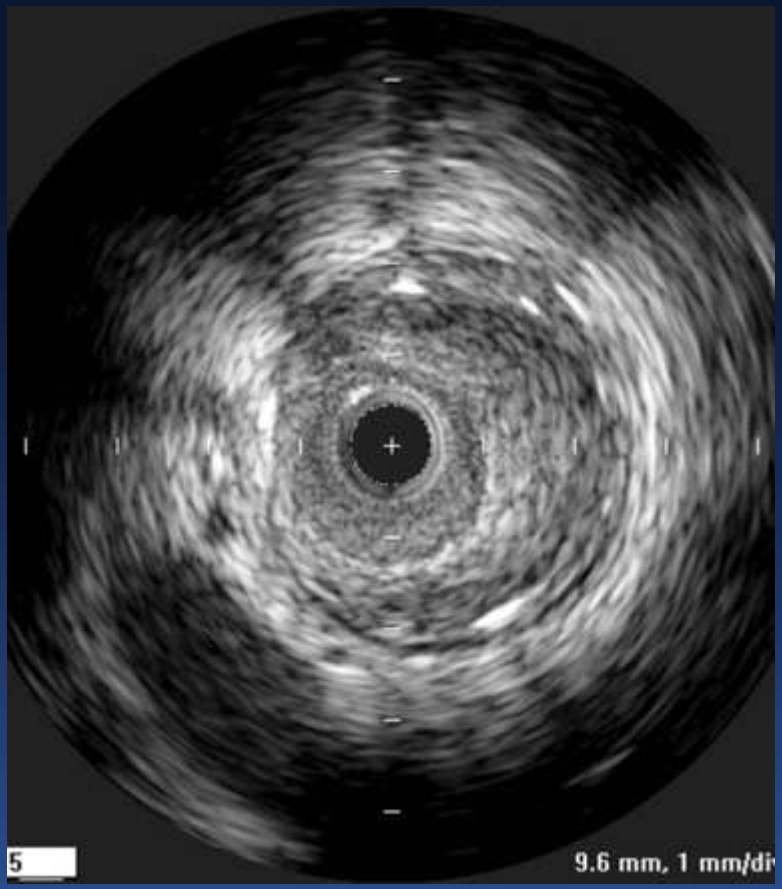


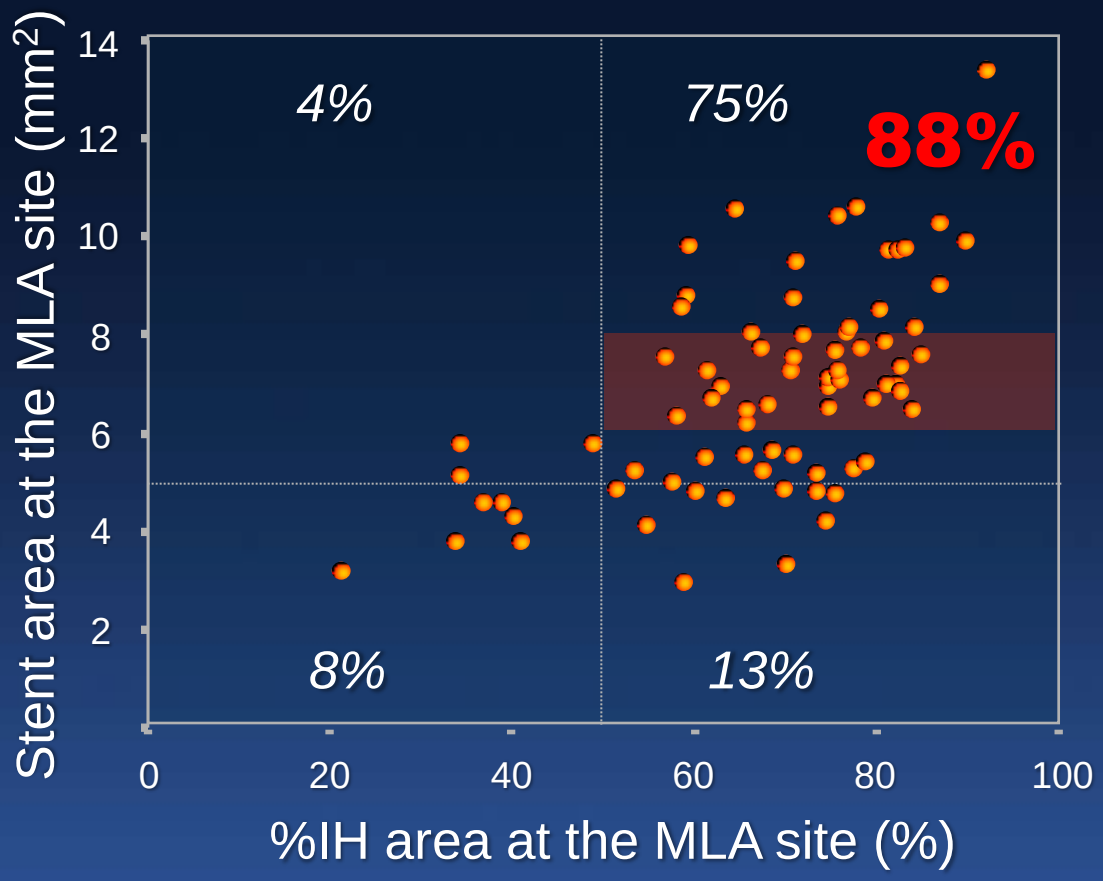
- **Stent edge restenosis is frequently associated with local trauma outside the stent.**
- **In-stent restenosis occurs as a localized lesion, commonly associated with a discontinuity in stent coverage.**

Lemos A. et al. *Circulation* 2003;108: 257-60

Intimal Hyperplasia

General Mechanism of ISR after DES

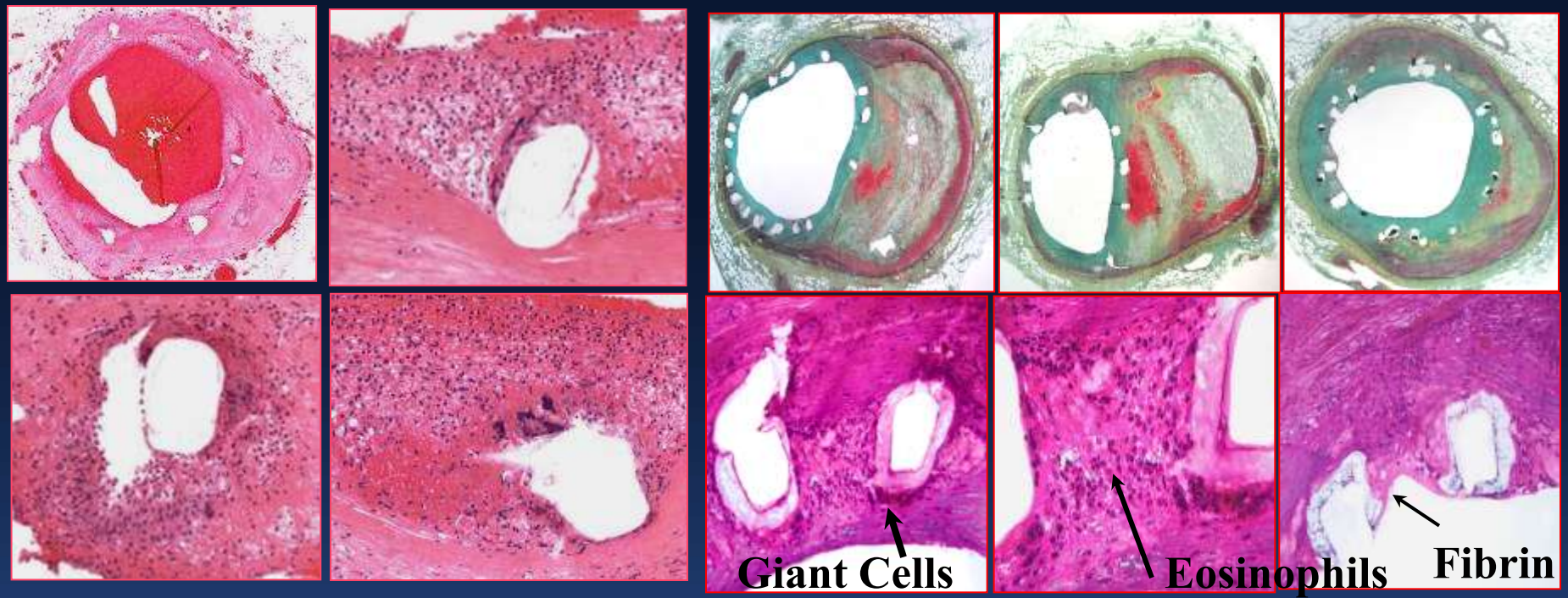




Kang et al. Circ Cardiovasc Interv 2011;4:9-14

Hypersensitivity Reactions

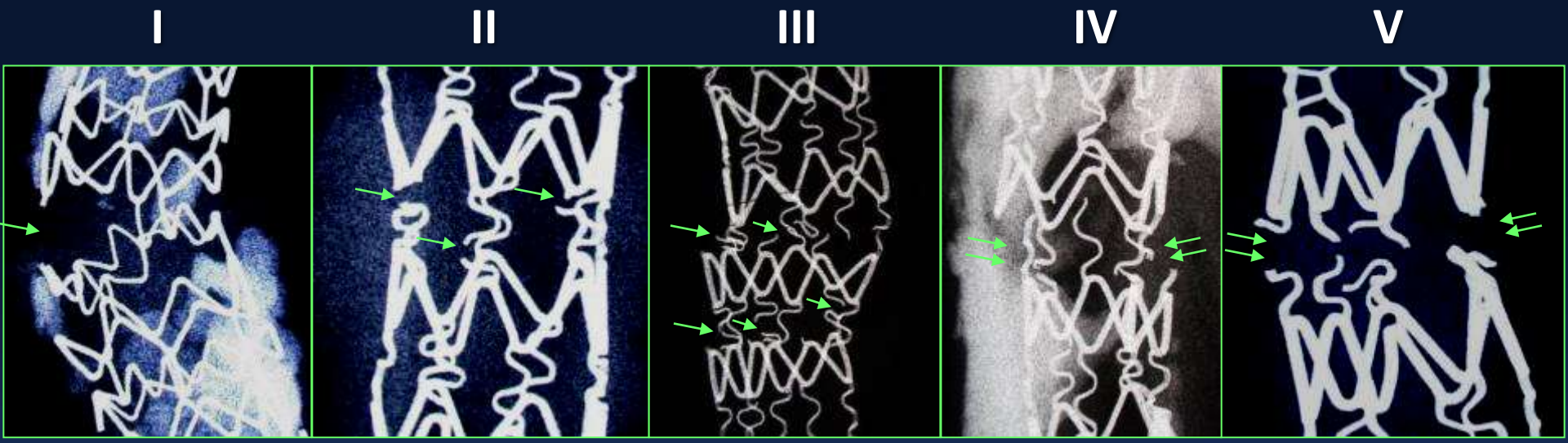
CYPHER in LCX @ 4 months ***Taxus in LAD @ 130 days***



Rash, hives, dyspnea, persistence after stopping Plavix, eosinophilia, elevated IgE, skin biopsy consistent with drug reaction when no drugs administered, Gallium scan consistent with inflammation at the stent site or LV draining lymph nodes, and eosinophils attacking the stent at autopsy.

Nebecker JR. et al. *JACC* 2006; 47: 175-181

Classification of Stent Fractures

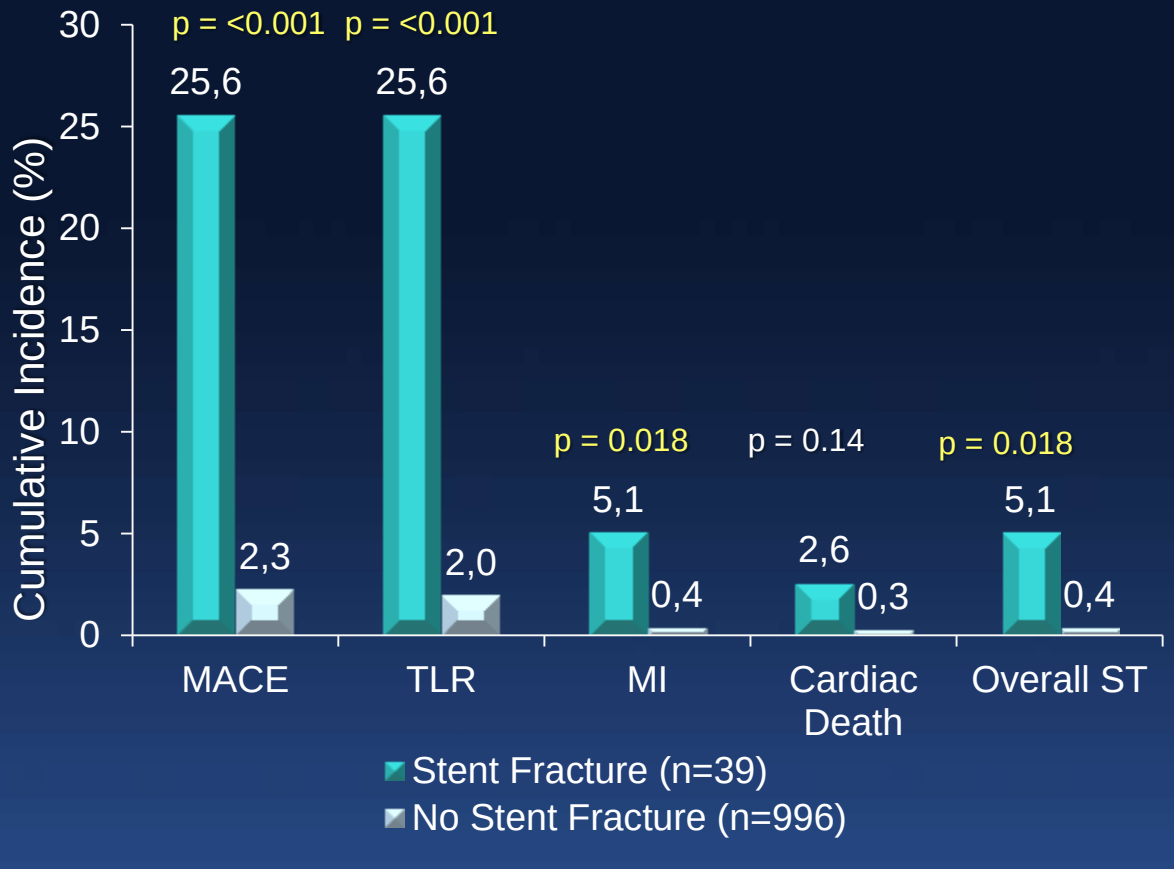


I=single strut fracture, II=2 or more struts fracture without deformation, III=2 or more struts fracture with deformation, IV=multiple fractures with acquired transection without gap, V=multiple fractures with acquired transections with gap

Among 177 DES lesions in the CVPath registry, stent fracture was documented in 51 (SES 32, PES 19) lesions (29%).
Grade V fracture was identified in 9 (SES 6, PES 3) lesions (5.1%).

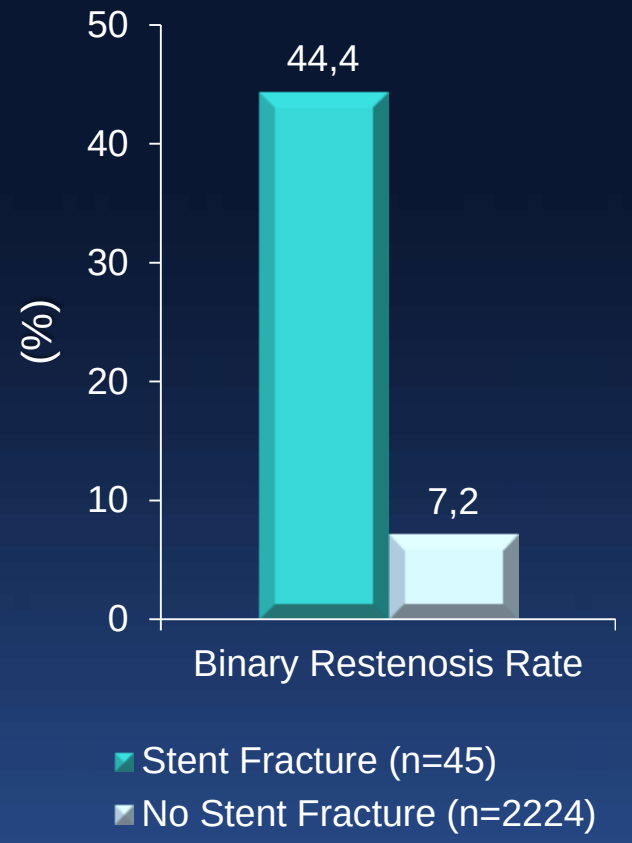
Nakazawa G, et al. JACC 2009;54:1924-31

Clinical Impact of Stent Fracture in Cobalt Chromium EES



CoCr-EES Fracture Rate: 2.9%

Kuramitsu et al. *Circ Cardiovasc Int* 2012; 5(5):663-71

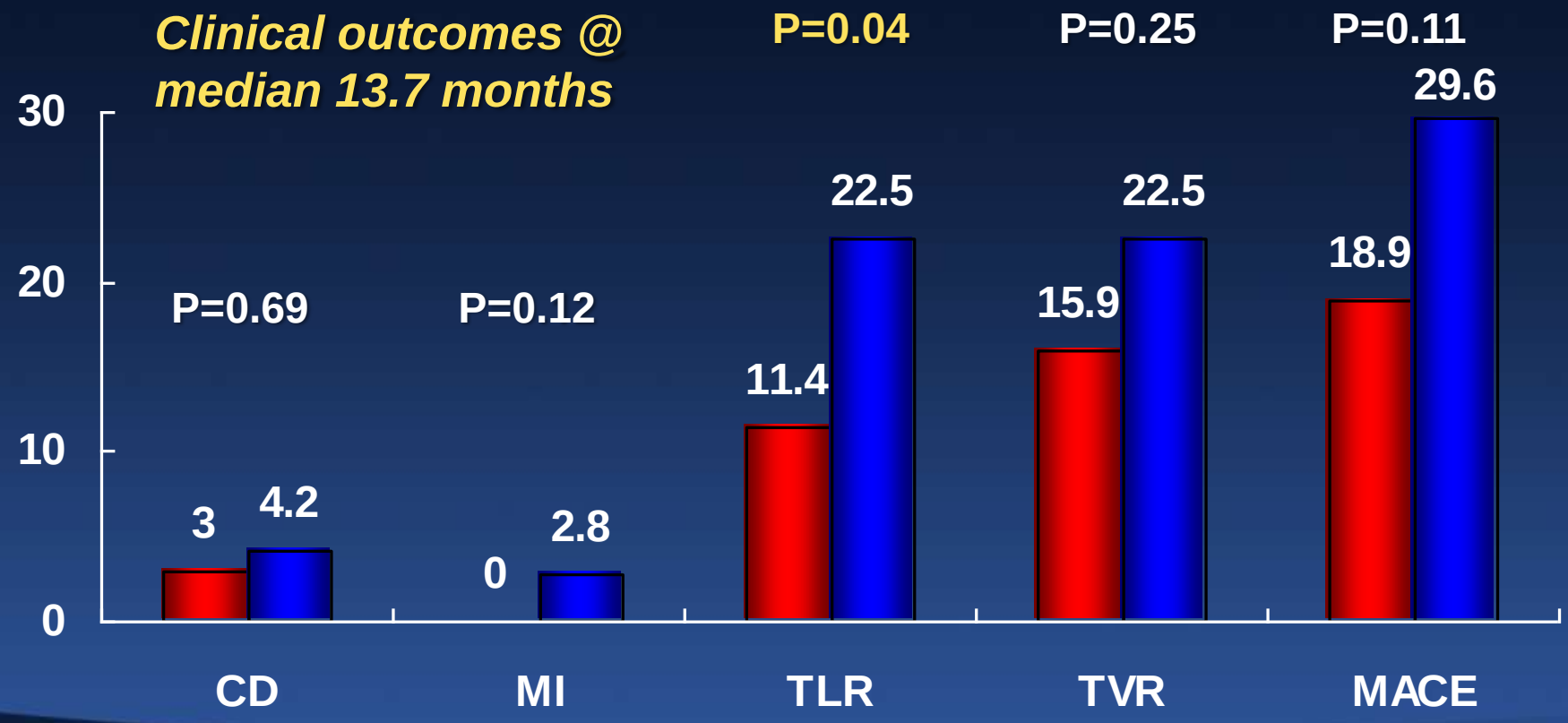


CoCr-EES Fracture Rate: 2.0%

Presented by Izawa et al at ACC 2013

Do Patterns of In-Stent Restenosis Predict Outcomes in the DES Era?

- Focal (N = 132) Repeat DES 57.1%, POBA 42.9%
- Non focal (N = 71) Repeat DES 69%, POBA 31%

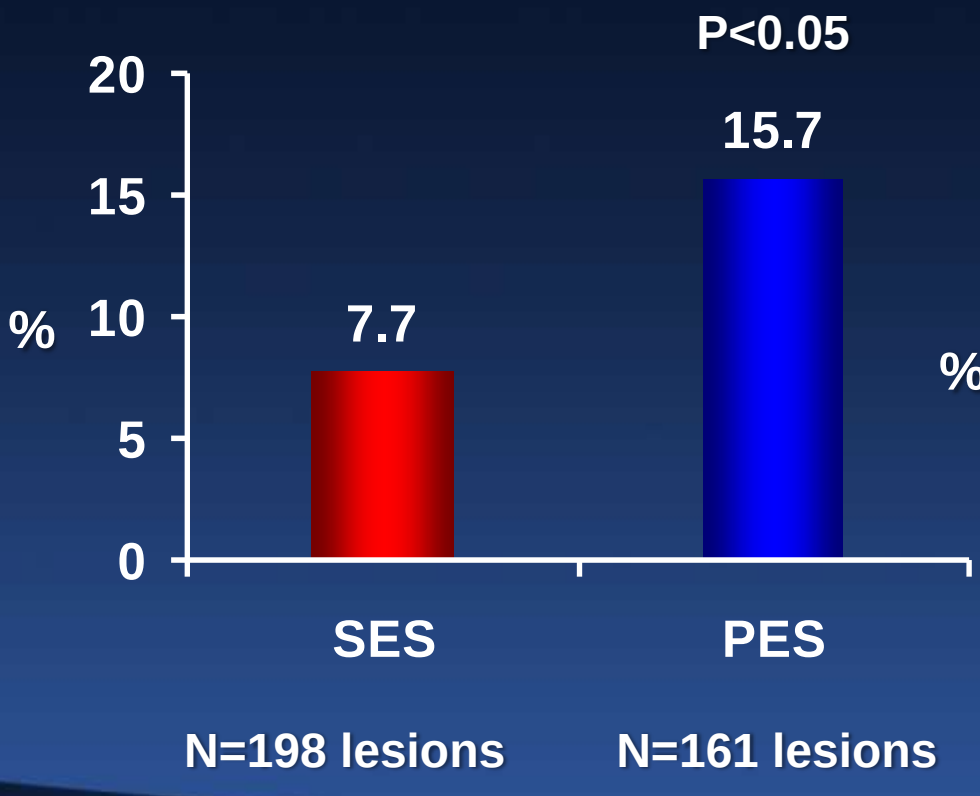


Cosgrave J. et al. *JACC* 2006;47: 2399-404

SES vs PES for SES Failures

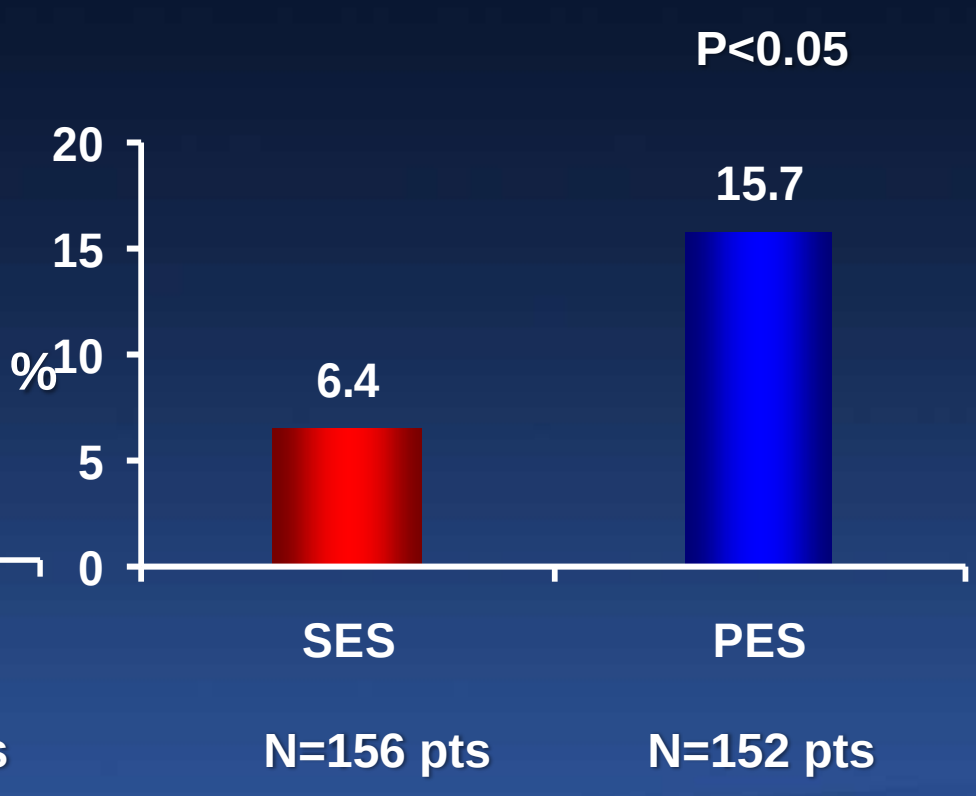
Multicenter Registry in Asia

Restenosis @ 1 year



N=198 lesions N=161 lesions

TLR @ 1 year

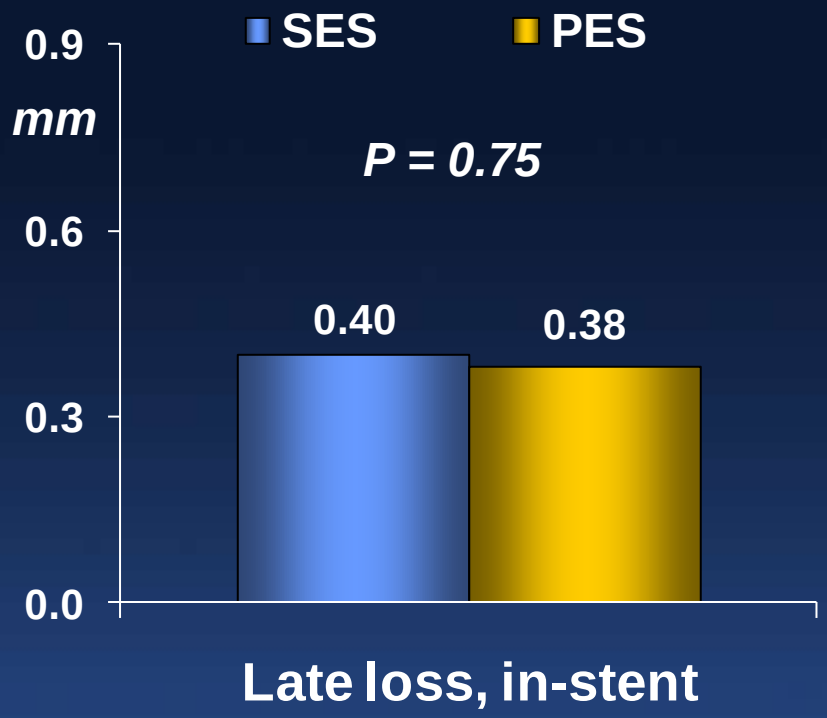


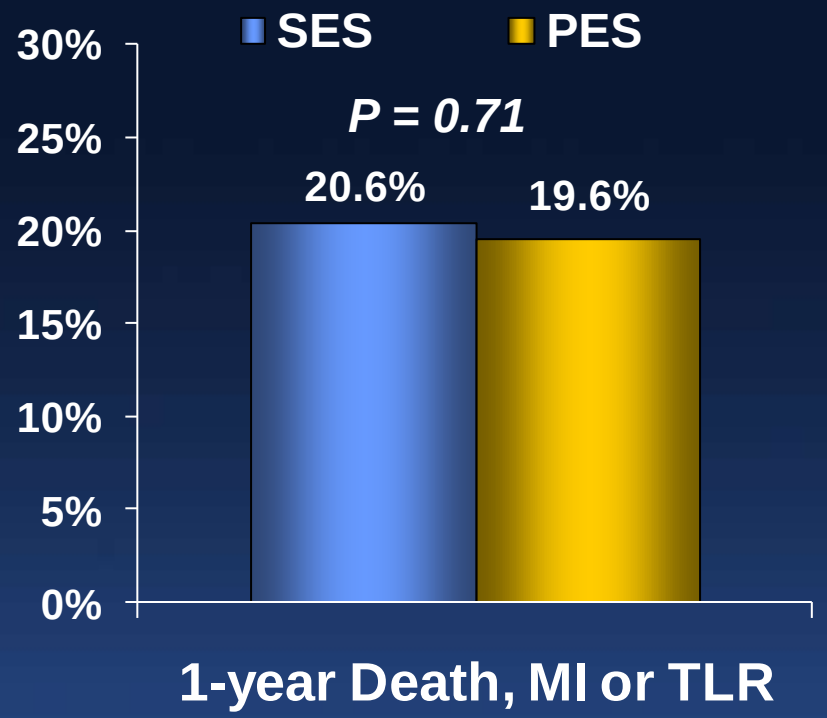
N=156 pts N=152 pts

Nakamura S. et al. ACC 2007

ISAR DESIRE-2

Patients with SES-ISR (n=225 per group)





- **No differences between same- or different DES treatment strategies**

R. Byrne, TCT 2009

RCT of Optimal Treatment Strategies for ISR After DES Implantation

162 patients stratified into focal (n = 96; randomized to SES or cutting balloons) or diffuse (n = 66; randomized to SES or EES) lesions.

- For focal restenosis, SES yield lower late loss (0.06 mm vs. 0.25 mm; *P* = 0.04), less recurrent restenosis (3.1% vs. 20.7%; *P* = 0.06) vs. cutting balloons
- For diffuse restenosis, SES, EES produce comparable rates of late loss (0.11 mm vs. 0 mm; *P* = 0.64), recurrent restenosis (5.0% vs. 14.3%; *P* = 0.32)
- Similar 1-year MACE, mortality, TVR rates for treatments in both cohorts

Implications: For focal DES restenosis, repeat SES are more effective than cutting balloons; for diffuse restenosis, SES, EES are equivalent

Song H-G, et al. J Am Coll Cardiol. 2012;59:1093-1100

DCB vs POBA/DES for BMS ISR: 3 RCTs

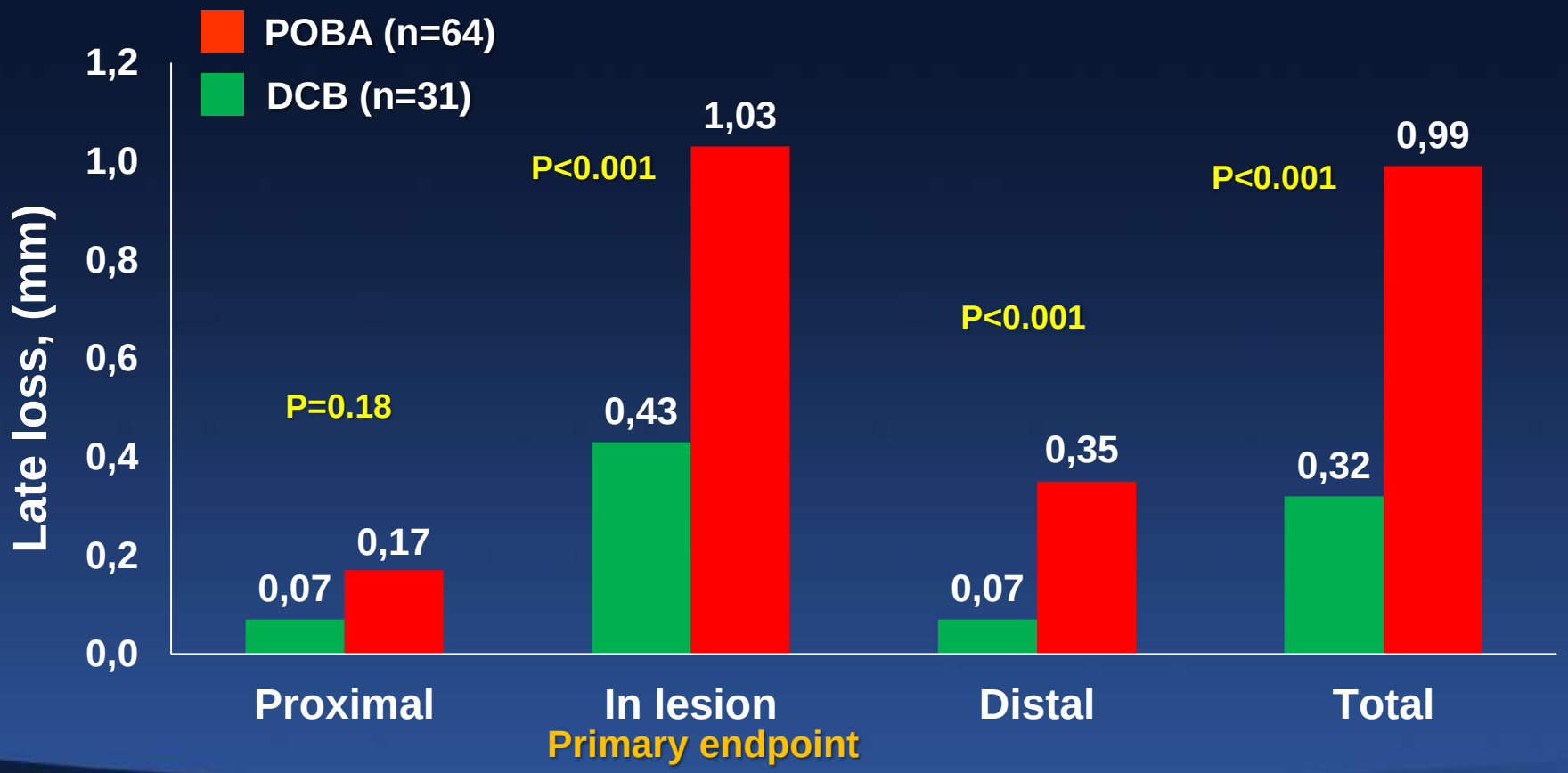
[1]PACCOCATH ISR I: 52 pts randomized to Paccocath vs. POBA
[2]PACCOCATH ISR II: 56 pts randomized to Paccocath vs. POBA
[3]PEPCAD II: 131 pts randomized to Sequent Please vs. TAXUS

	DCB	Control	P Value
Paccocath ISR I	N=26	N=26	
In-segment late loss – 6 mo	0.03 ± 0.48	0.74 ± 0.86	0.002
In-segment restenosis – 6 mo	4.5%	43.5%	0.002
TLR – 12 mo	0%	23.1%	0.02
Paccocath ISR I + II	N=54	N=54	
In-segment late loss – 6 mo	0.11 ± 0.45	0.81 ± 0.79	<0.001
In-segment restenosis – 6 mo	6.4%	51.0%	<0.001
TLR – 24 mo	5.6%	37.0%	<0.001
PEPCAD II	N=66	N=65	
In-segment late loss – 6 mo	0.17 ± 0.42	0.38 ± 0.61	0.03
In-segment restenosis – 6 mo	7.0%	20.3%	0.06
TLR – 12 mo	6.3%	15.4%	0.15

[1]Scheller B et al. N Engl J Med 2006;355:2113-24
[2]Scheller B et al. Res Cardiol 2008;97:773-81
[3]Unverdorben M et al. Circulation 2009;119:2986–2994

PEPCAD-DES: RCT at 6 German Centers

110 pts with non-occlusive single lesion DES restenosis (SES, PES or EES) randomized 2:1 to SeQuent Please vs. POBA
RVD 2.30 mm, LL 11.7 mm; 86.4% 6-month angio FU



Rittger H. TCT2011 Late Breaking Trial

ISAR DESIRE 3

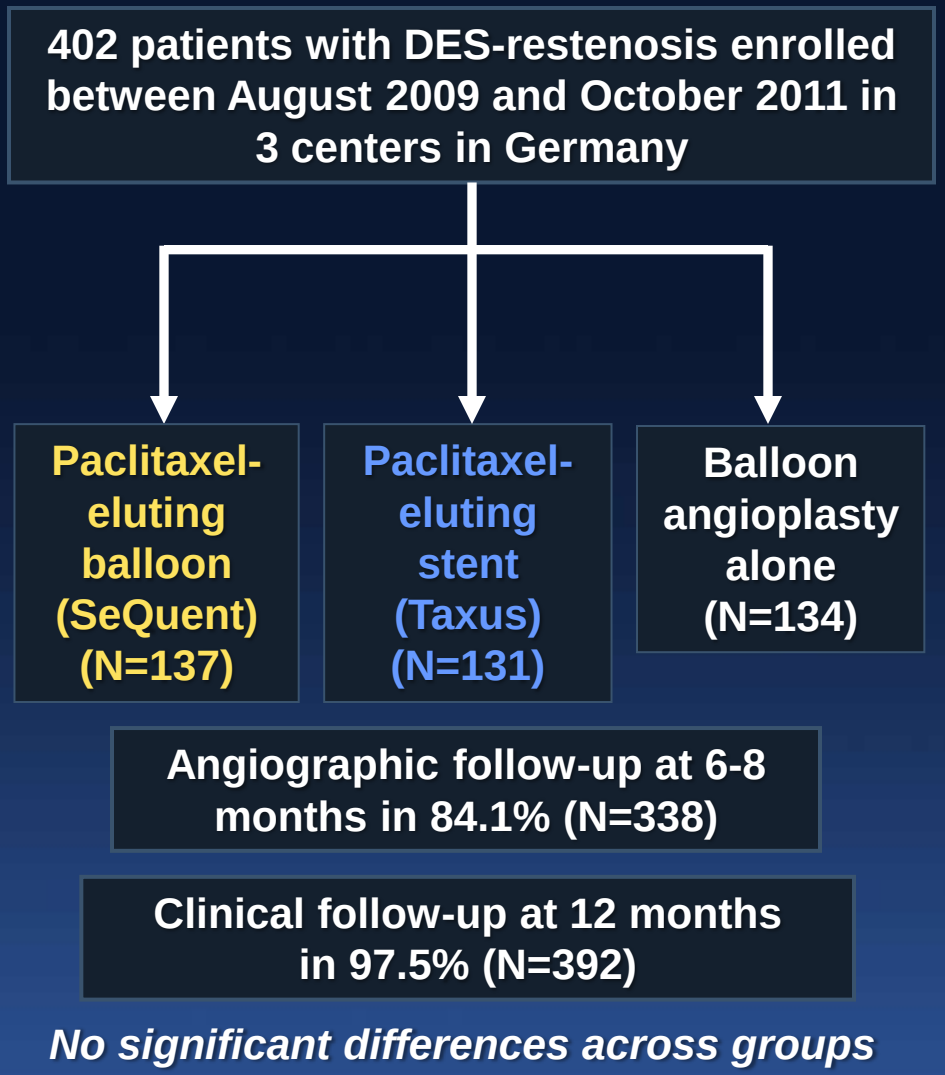
Design

DESIGN:
Prospective, randomized, active controlled, multicenter clinical trial

INCLUSION CRITERIA:
1. Stenosis > 50% in "limus"-eluting DES
2. Symptoms/signs of ischemia

EXCLUSION CRITERIA:
1. Lesion in left main stem
2. Acute STEMI
3. Cardiogenic shock

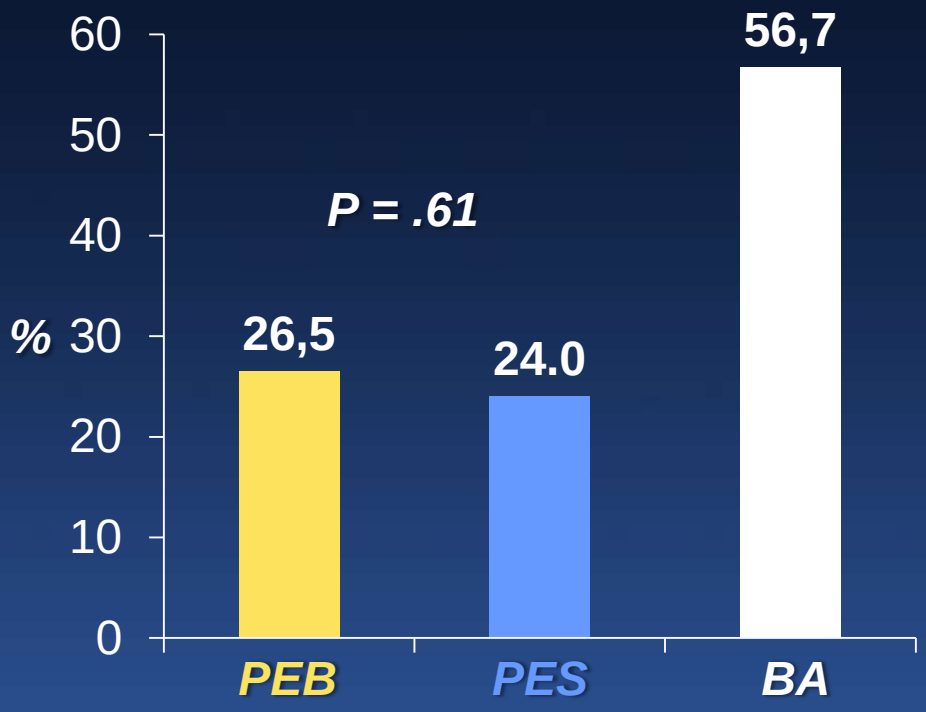
SPONSOR: Deutsches Herzzentrum



ISAR DESIRE 3: Restenosis

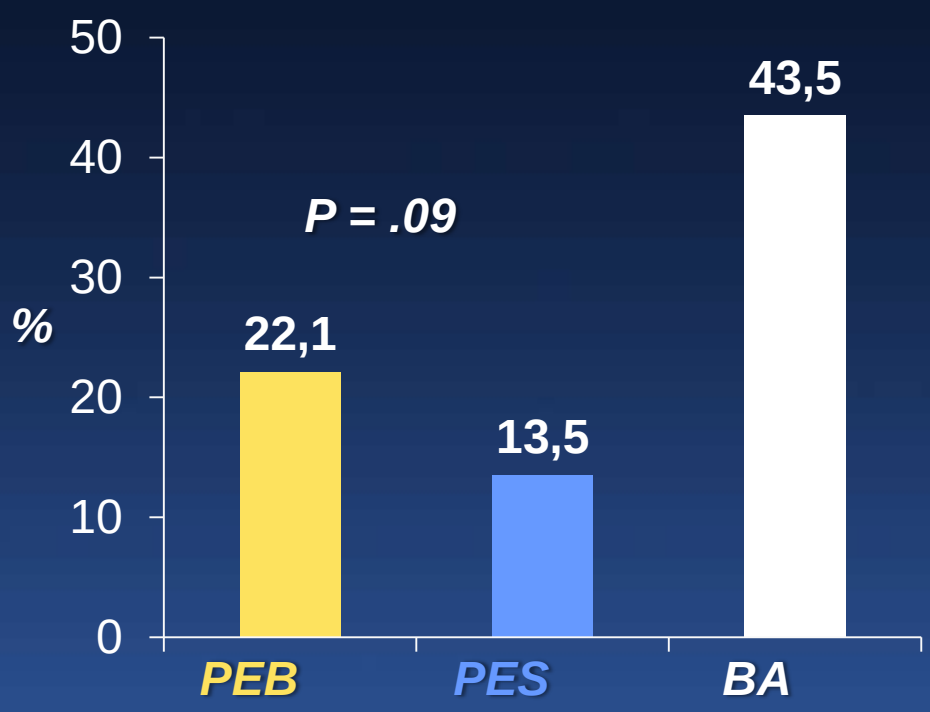
Binary Restenosis

PEB versus BA
PES versus BA
P <0.001



Target Lesion Revascularization

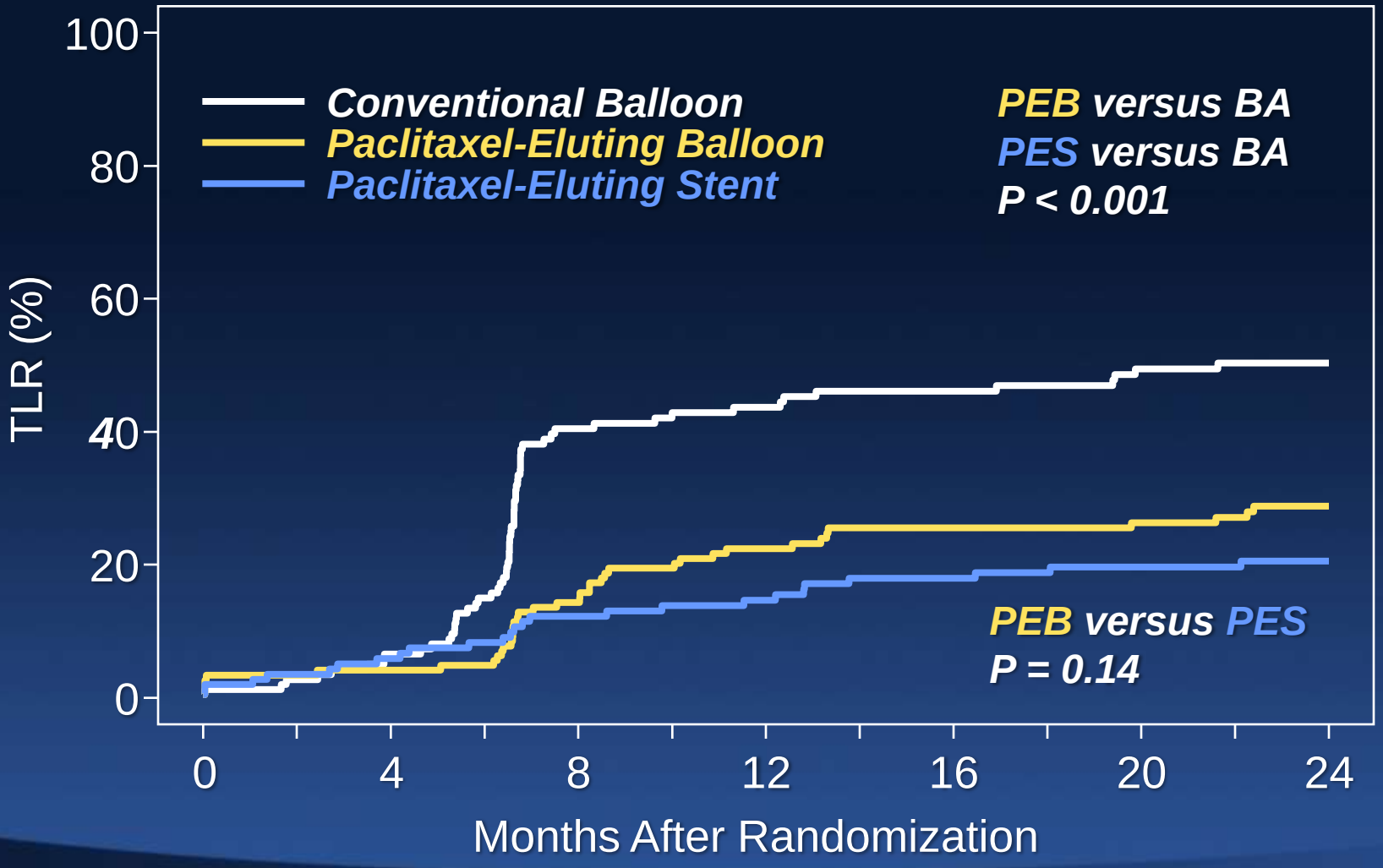
PEB versus BA
PES versus BA
P <0.001



R. Byrne, TCT 2012

ISAR-DESIRE 3: Two-Year Results

Target Lesion Revascularization



RIBS V

(January 2010 to January 2012)

Inclusion Criteria
Informed Consent

189 Pts BMS ISR Randomization

Rx Centralized
Stratification:
ISR Length & Edge

94 Pts **EES**

Xience Prime
(Abbott Vascular)

95 Pts **DEB**

SeQuent Please
(B. Braun Surgical)

100% Angiographic Success

8 Refused

3 Died
1 Thrombosis
7 Refused

86 Pts Angio FU

Mean: 270 days

QCA Primary End-point

84 Pts Angio FU

Mean: 271 days

(170 Patients: 92% of Eligible)

tct 25

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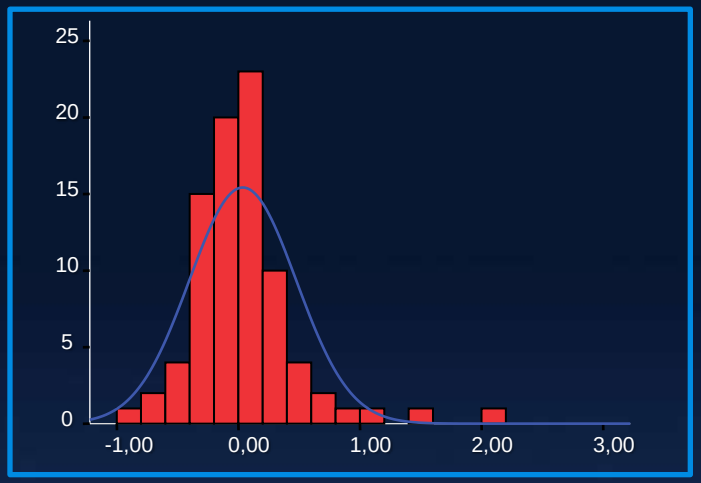
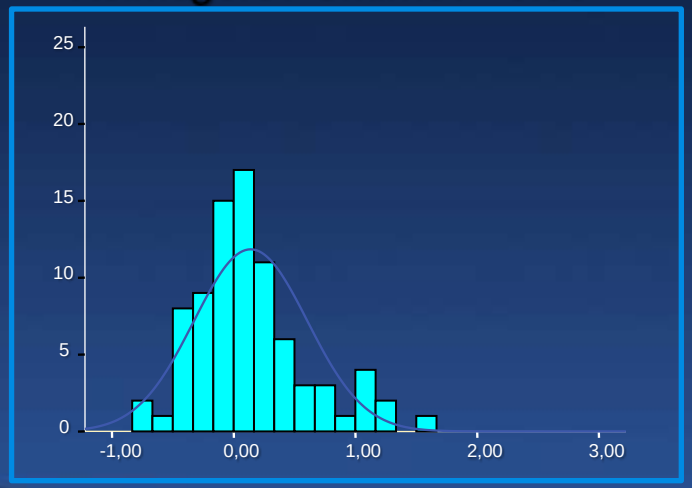
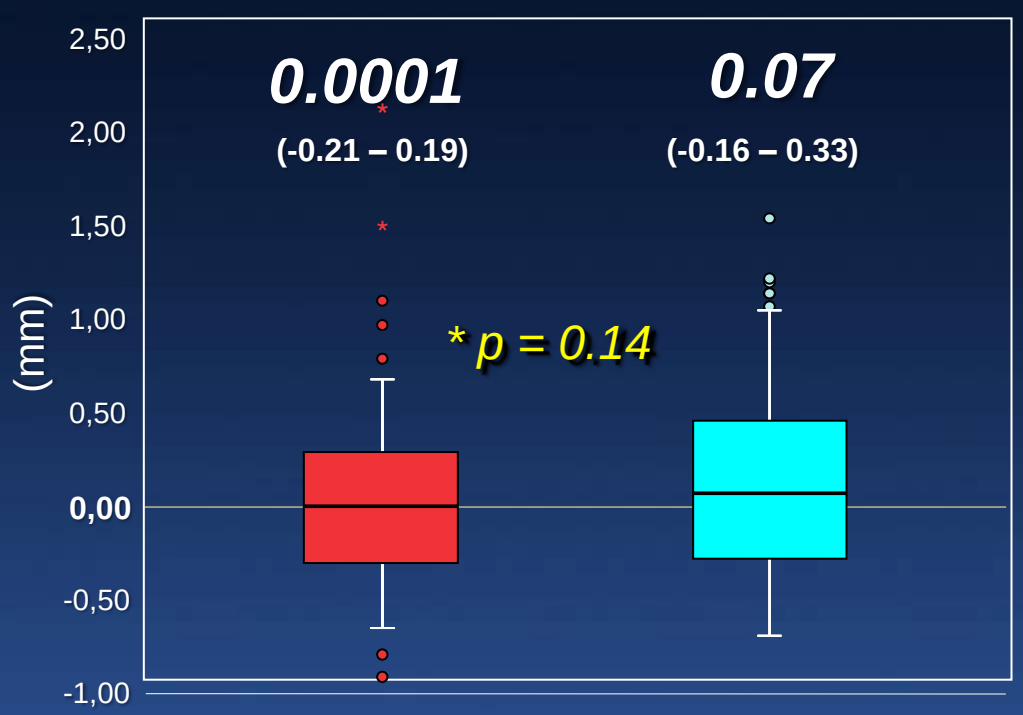
RIBS V
In-Segment Analysis (QCA)



Kolmogorov-Smirnov <0.05



Late Loss
0.04±0.5 vs 0.14±0.5 mm



* median (IQR); Mann-Whitney "U"

QCA = CASS II System

tct 25

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Current Therapeutic Options According to Mechanisms of ISR

Type of restenosis	Potential mechanisms	Treatment options
Focal in-stent	Underexpansion	PTCA, DCB
	Fracture	DES
	Local vessel biology	DCB
	Heterogeneous Drug Distribution	DES, DCB
Focal at stent edge	Geographic Miss	DES, DCB
	Plaque Progression	DES, DCB
Diffuse in-stent	Vessel Piology / Drug Resistance	DCB
Proliferative	Vessel Biology / Drug Resistance	DCB

Costa MA. et al. *AHJ*.2007;153: 447-9

Conclusions

- ISR is a man-made disease so the best approach is preventing it by the smart use of stents
- Once it is recognized; diagnose it (i.e., IVUS) as the mechanism of action may unveil the best way to treat it!
- DES restenosis rates are lower than ever but they are still associated with high morbidity and mortality rates
- Further engineering improvements in drug delivery will continue to reduce ISR cases and expand the therapeutic alternatives to treat this condition