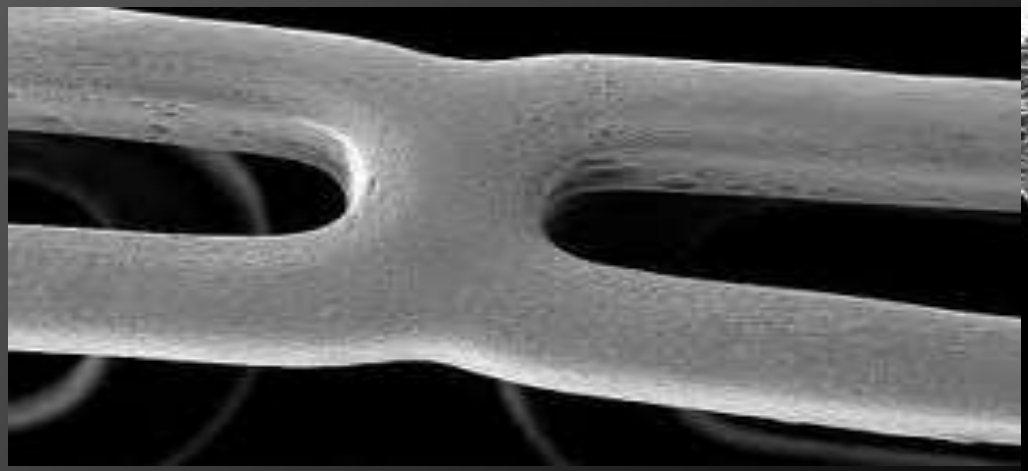
RESTENOSIS IN THE DES ERA
MECHANISMS AND TREATMENT



Α-Δ. ΜΑΥΡΟΓΙΑΝΝΗ
ΚΑΡΔΙΟΛΟΓΟΣ
ΑΙΜΟΔΥΝΑΜΙΚΟ ΕΡΓΑΣΤΗΡΙΟ
Γ.Ν.Θ. «Γ.ΠΑΠΑΝΙΚΟΛΑΟΥ» ΘΕΣΣΑΛΟΝΙΚΗ

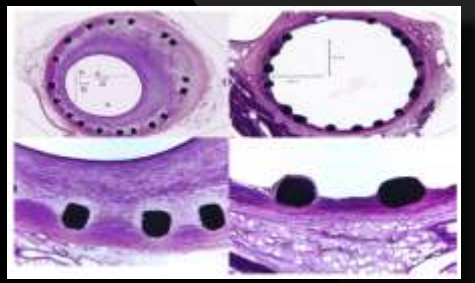
The NEW ENGLAND JOURNAL of MEDICINE

Nonoperative Dilatation of Coronary-Artery Stenosis — Percutaneous Transluminal Coronary Angioplasty

Andreas R. Grüntzig, M.D., Åke Senning, M.D., and Walter E. Siegenthaler, M.D.

N Engl J Med 1979; 301:61-68 | July 12, 1979

DES RESTENOSIS



- Restenosis after angioplasty and stent implantation has been historically considered the most significant problem in coronary interventional treatment

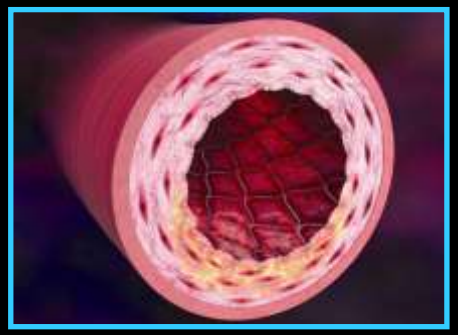
- Drug-eluting stents (DES) have dramatically reduced the rates of restenosis and TLR compared with bare metal stents (BMS)

Dangas G. Management of restenosis after coronary intervention. Am Heart J 1996;132:428

Stettler C et al. Outcomes associated withdrug-eluting and bare-metal stents: a collaborative network metaanalysis Lancet 2007;370:937

DES RESTENOSIS

- The widespread adoption of this technology into routine clinical practice has led to significant absolute numbers of patients presenting with DES treatment failure.



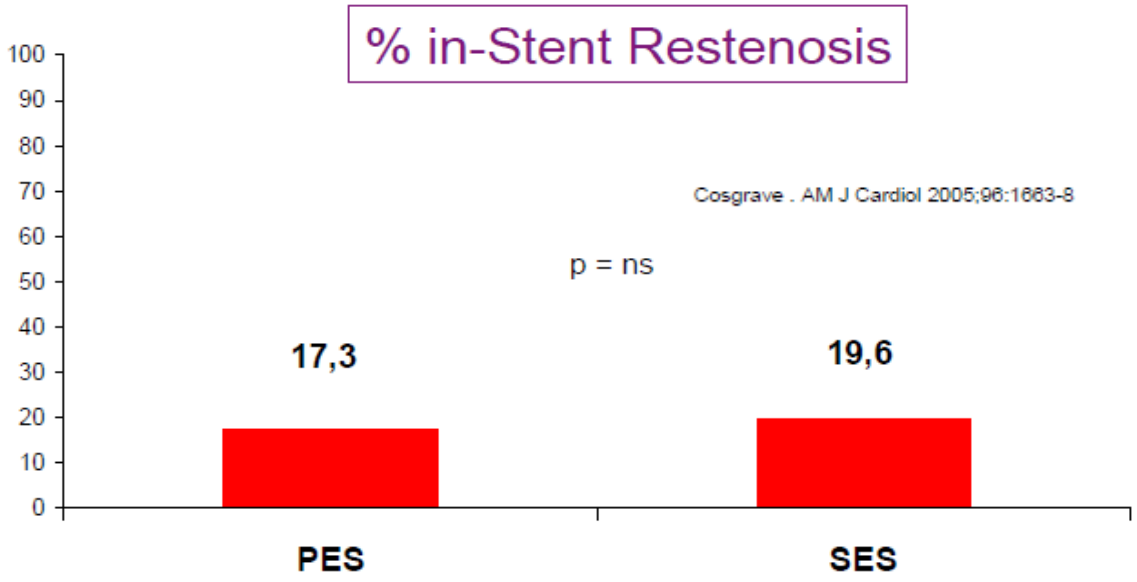
- In the U.S it is estimated that as many as 200,000 cases of DES restenosis may occur every year

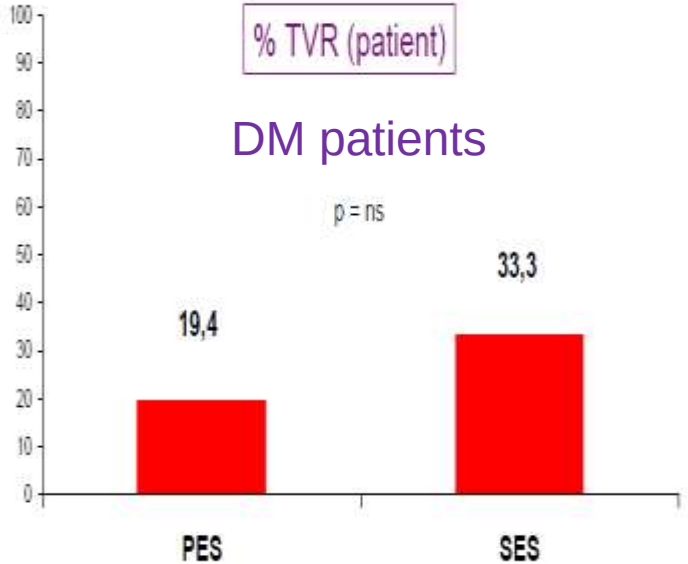
Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:480

DES restenosis: RCTs vs Real World

Cypher	0 - 6,4 %
Taxus	3 - 8,6 %
Endeavor	6,5 - 7 %
Xcience V	3,8 %

Left Main	14.1% *
Bifurcation	18.7-28% **
SVG	>10% (SECURE)
VBT Failure	>47.8% (SECURE)
Multivessel TAXUS	>12% (TAXUS V- TRUE)
Multivessel Cypher	>11% (RECIPE Registry)





DES RESTENOSIS: definition

- …or reduction in lumen diameter is the result of arterial damage with subsequent neointimal proliferation
- And a few terms one might need to know…

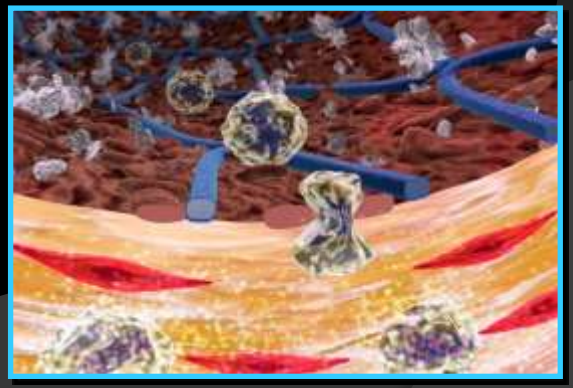
  -Late Lumen Loss = MLD post procedure - MLD fu

  -Binary restenosis

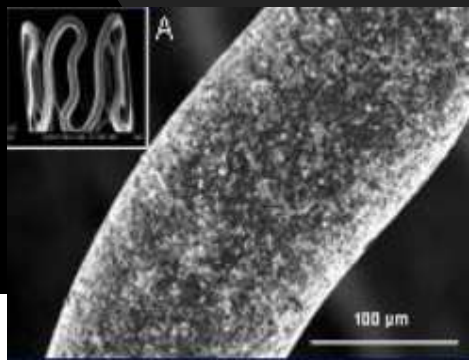
  -Percent diameter stenosis

  -TLR, TVR

  -MLA, RVD, MSA…etc

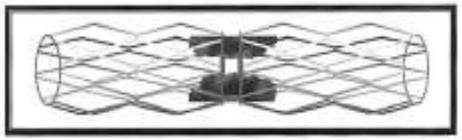


DES RESTENOSIS:classification

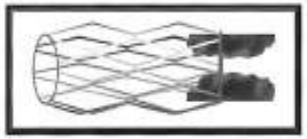


Angiographic Restenosis and Classification

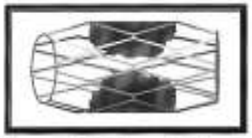
ISR Pattern I: Focal



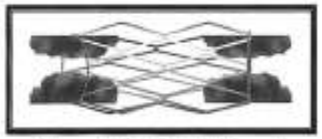
Type IA: Articulation or Gap



Type IB: Margin



Type IC: Focal Body

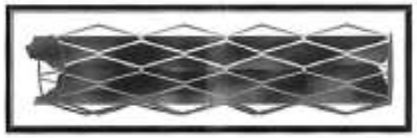


Type ID: Multifocal

ISR Patterns II, III, IV: Diffuse

ISR Pattern II: Intra-stent

ISR Pattern III: Proliferative



ISR Pattern IV: Total Occlusion

Clinical Restenosis: Assessed Objectively as Requirement for Ischemia-Driven Repeat Revascularization

Positive history of recurrent angina pectoris, presumably related to target vessel

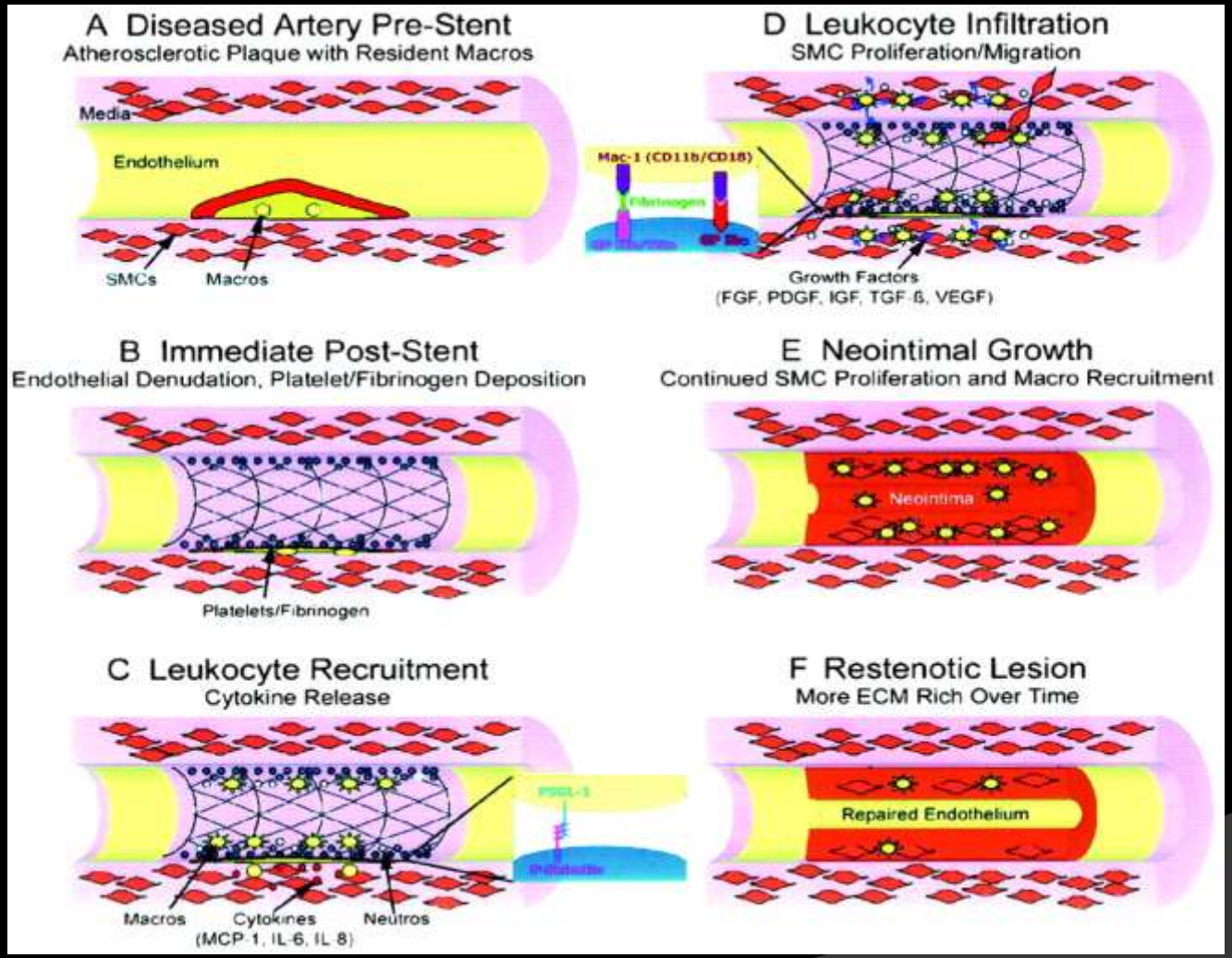
Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to target vessel

Abnormal results of any invasive functional diagnostic test (e.g., coronary flow velocity reserve, FFR <0.80); IVUS minimum cross-sectional area <4 mm^2 (and <6.0 mm^2 for left main stem) has been found to correlate with abnormal FFR and need for subsequent TLR (5–7)

TLR with diameter stenosis ≥70% even in absence of the above ischemic signs or symptoms

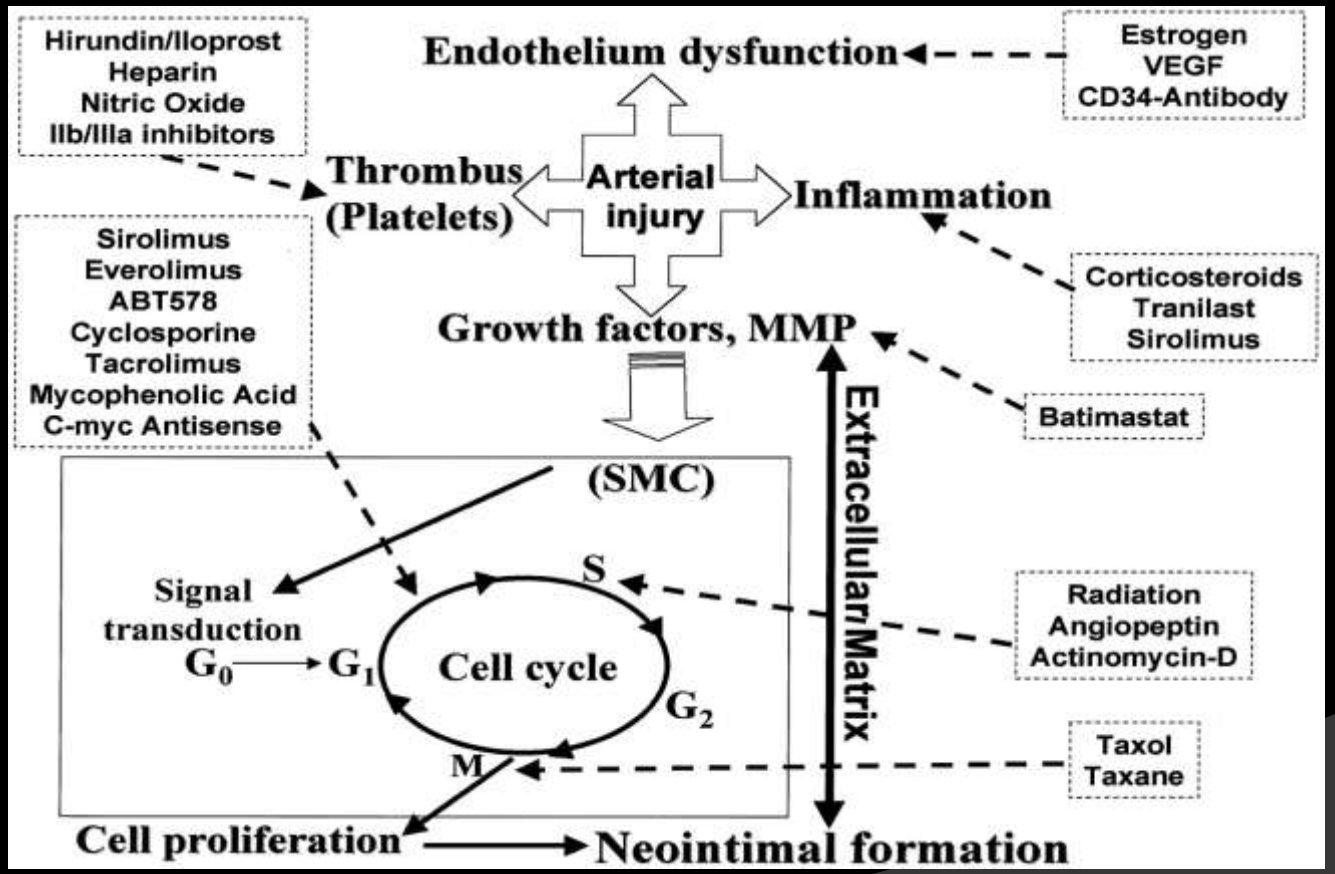
Mehran R et al. Angiographic patterns of in-stent restenosis Circulation 1999;100:1872
Cutlip D et al. Clinical end points in coronary stent trials Circulation 2007;115:2344

DES ISR: Schematic of an integrated cascade of restenosis

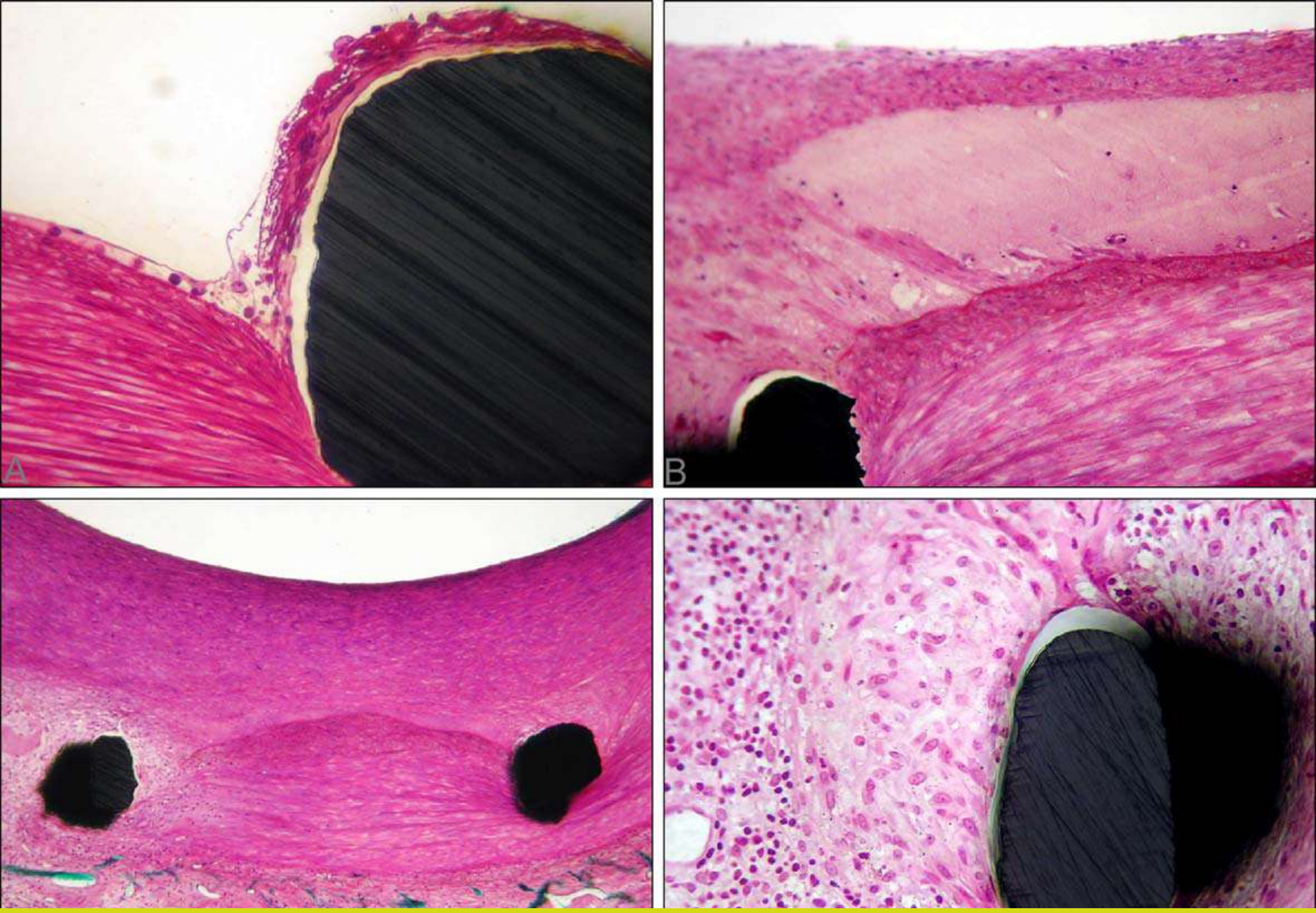


Welt FG. Inflammation and restenosis in the stent era. Artirioscler Thromb Vasc Biol 2002;22 : 1796

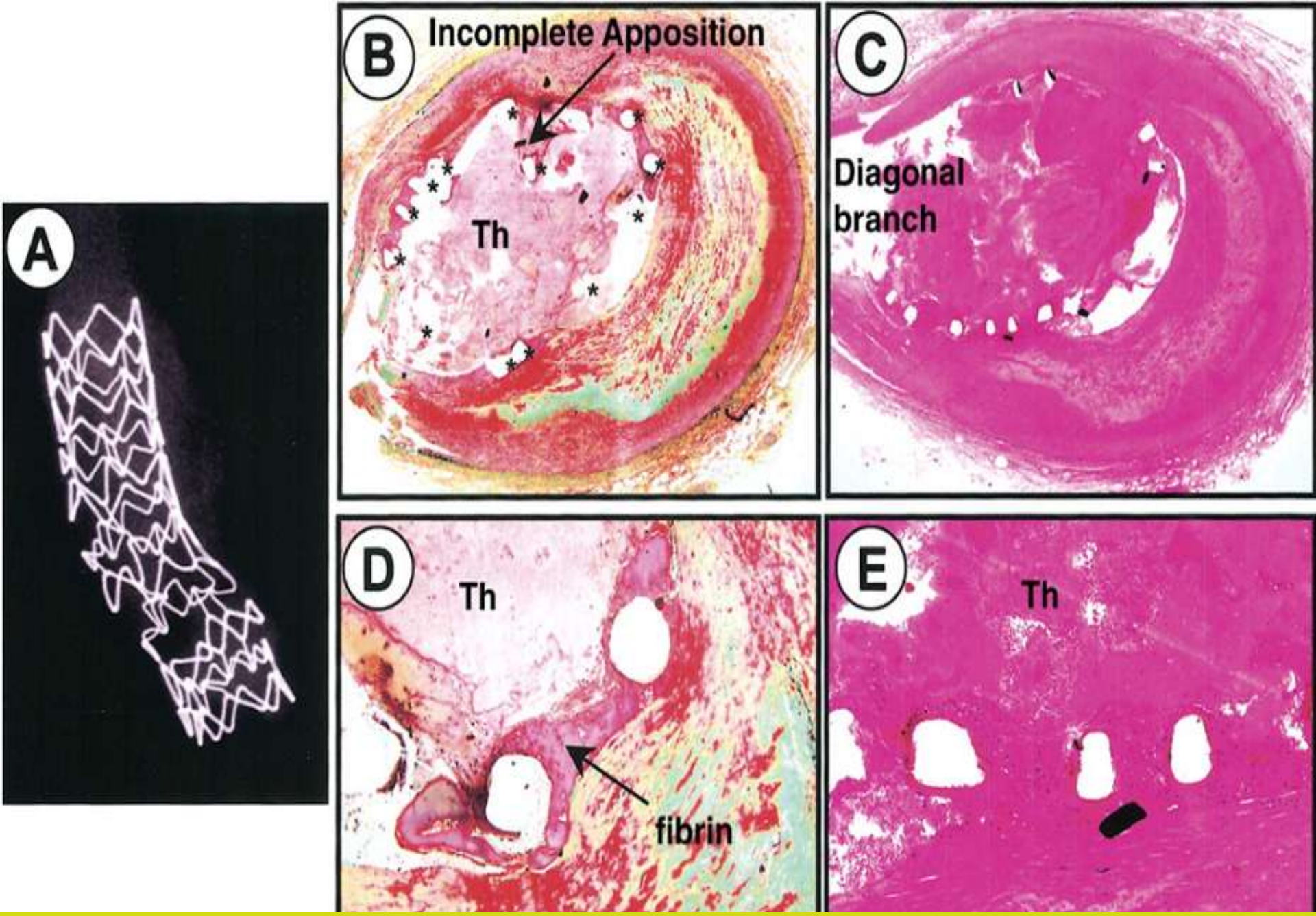
The leading processes of restenosis and correspondent inhibitory effects of different biological agents



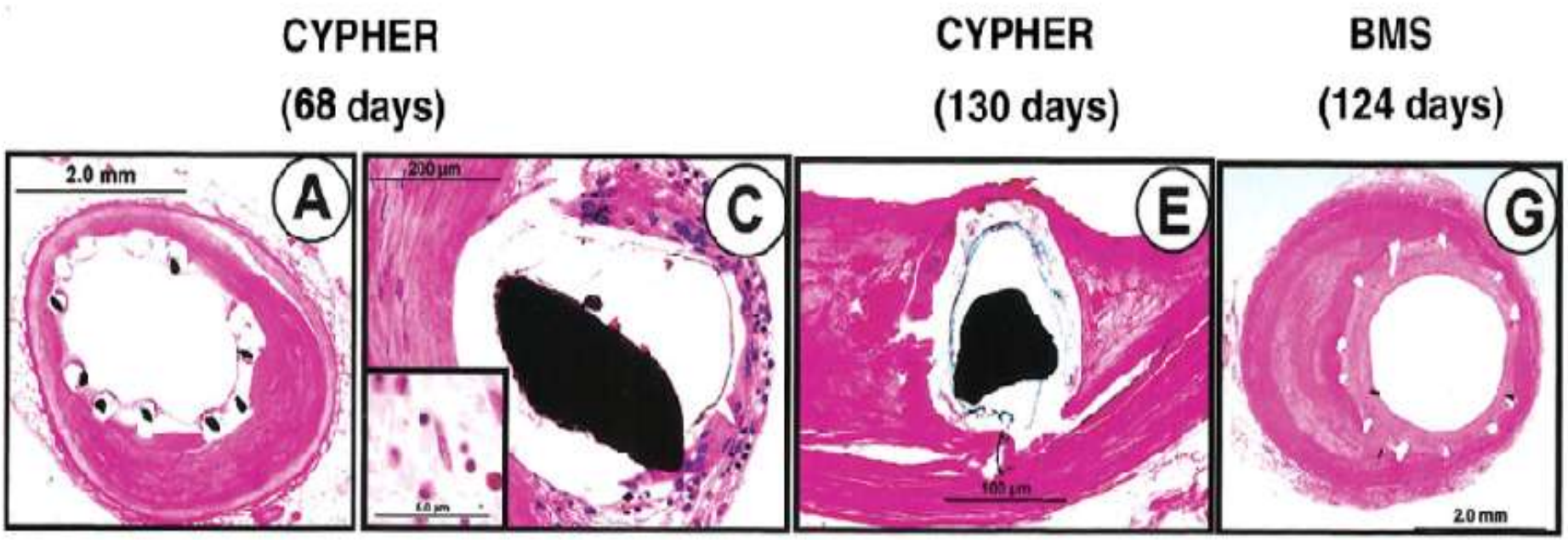
Sousa J E et al. Circulation 2003;107:2274-2279



Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model. Andrew J. Cartera et al. Cardiov. Res. 2004; 63: 617



Pathology of Drug-Eluting Stents in Humans: Delayed Healing and Late Thrombotic Risk. M Joner et al. JACC 2006; 48: 193



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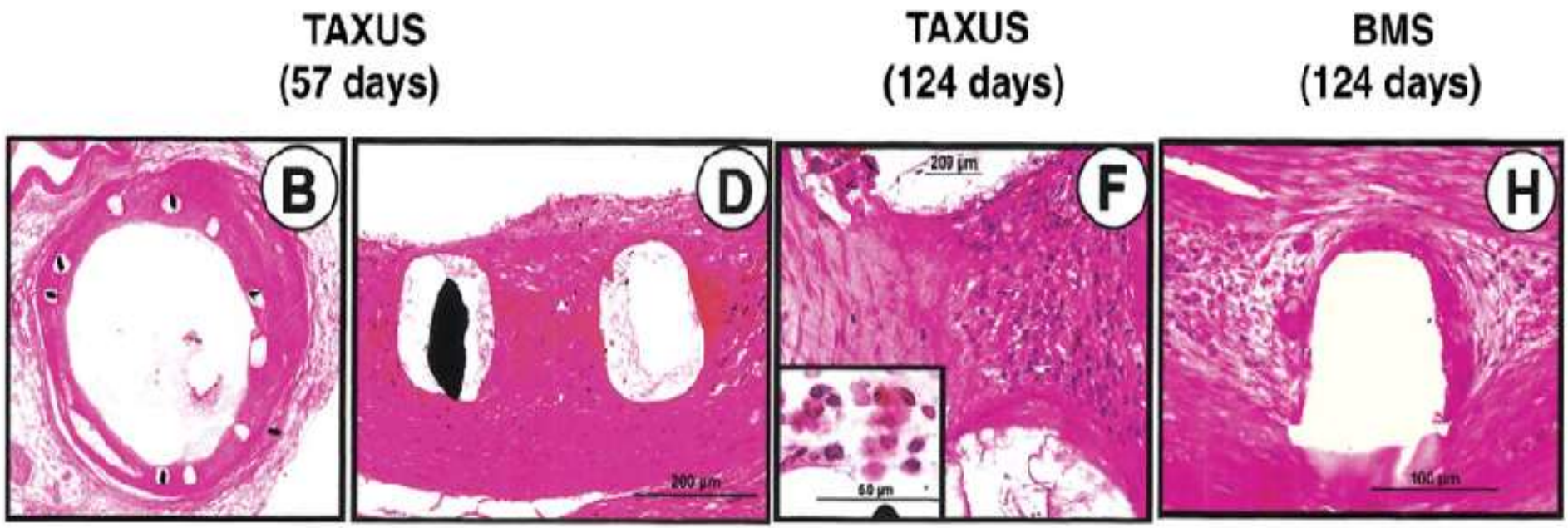
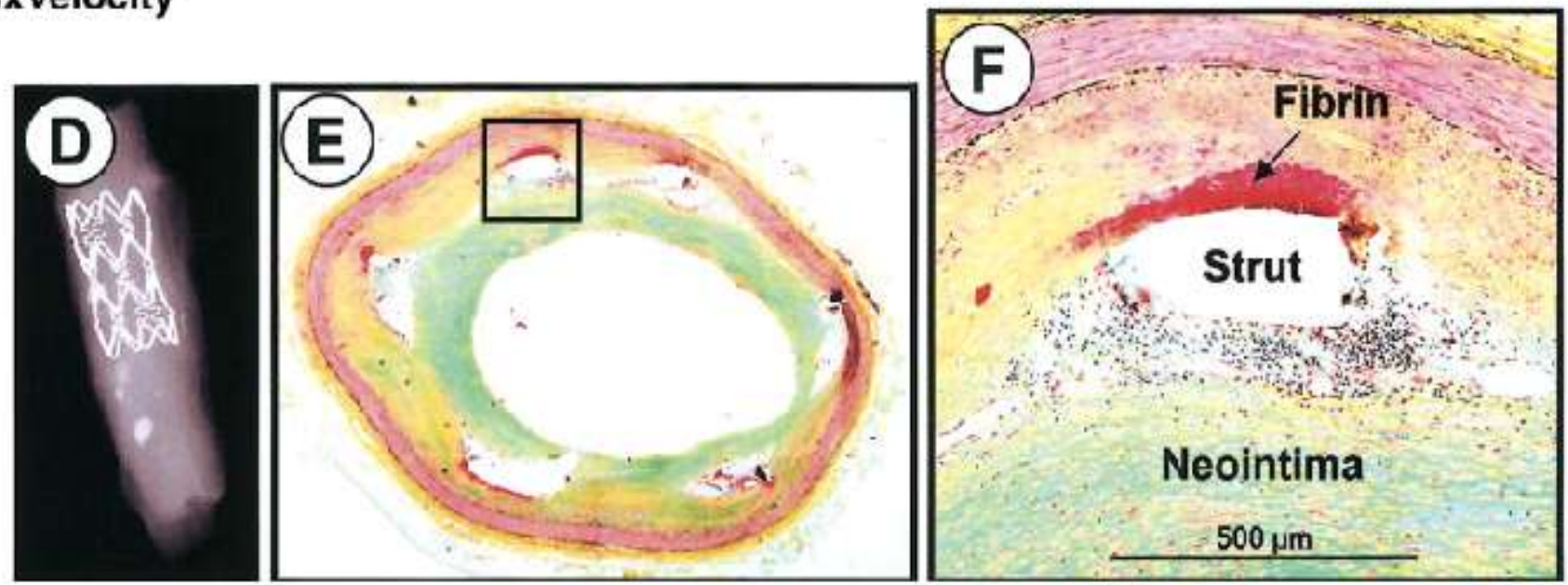


Cypher

Pathology of Drug-Eluting Stents in Humans: Delayed Healing and Late Thrombotic Risk. M Joner et al. JACC 2006; 48: 193

BxVelocity



DES ISR: not a benign clinical entity

- silent occlusive restenosis difficult to differentiate from a thrombotic event

- highly stenotic ISR can promote local nonocclusive thrombosis

→ NSTEMI TN (+) ACS

Rathore S et al. A comparison of clinical presentations, angiographic patterns and outcomes of in-stent restenosis between bare metal stents and drug eluting stents. EuroIntervention 2010; 5:841

DES ISR: not a benign clinical entity

BMS ISR

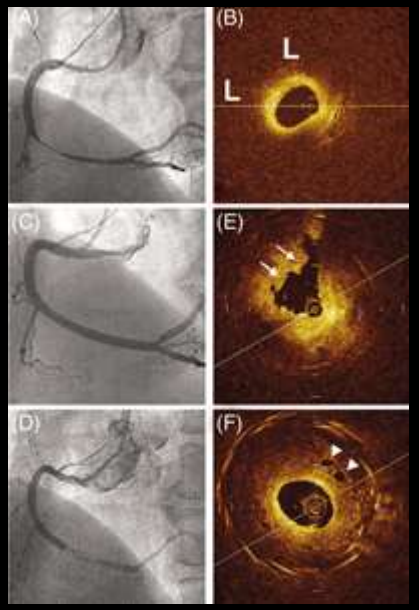
Unstable angina 26 – 53 %

MI 3.5 – 20 %

DES ISR

Unstable angina 16 – 66 %

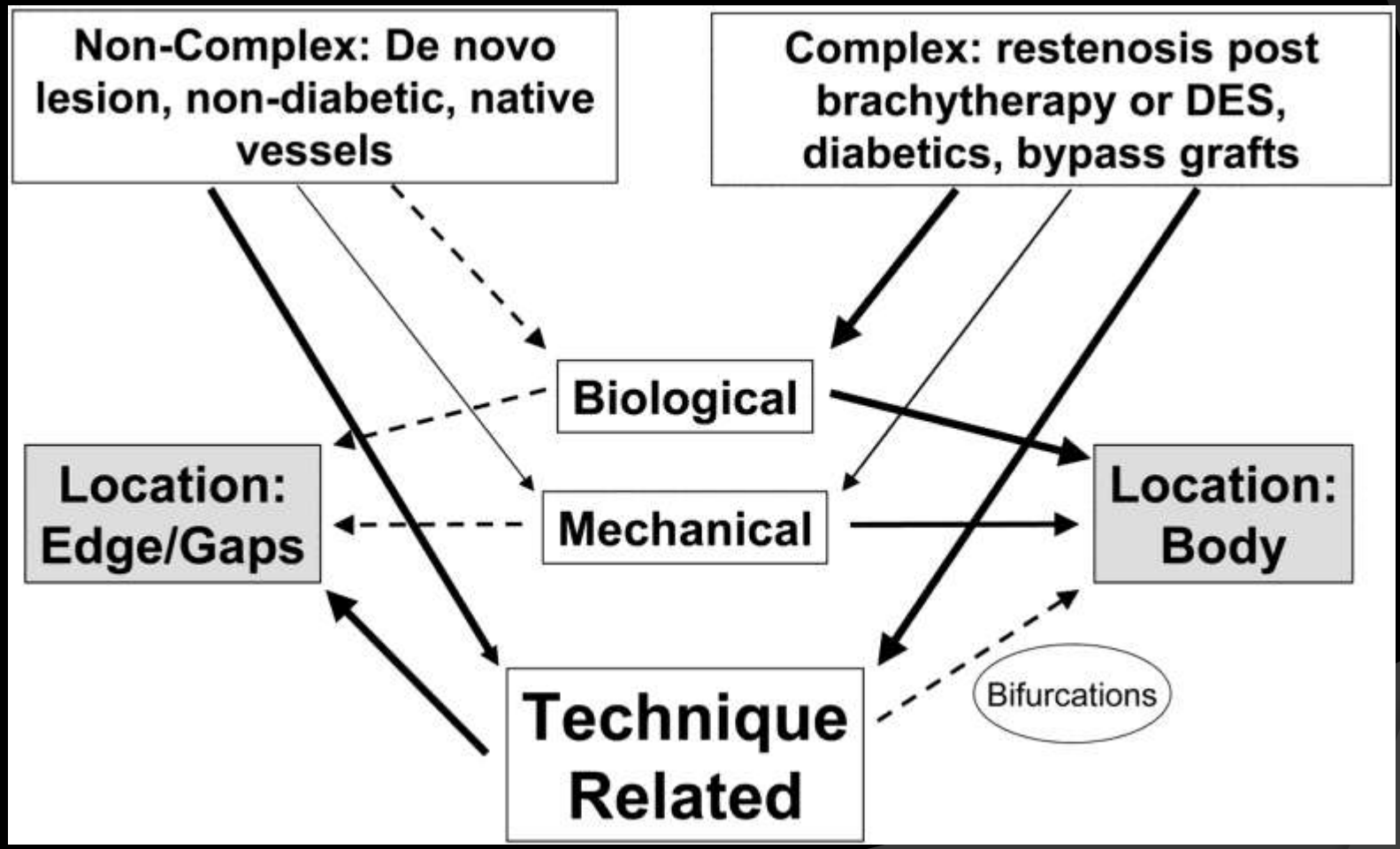
MI 1 – 20 %



Bossi I. et al. In-stent restenosis: long-term outcome and predictors of subsequent target lesion revascularization after repeat balloon angioplasty. J Am Coll Cardiol 2000;35:1569

Chen MS. Bare metal stent restenosis is not a benign clinical entity. Am Heart J 2006;151:1260

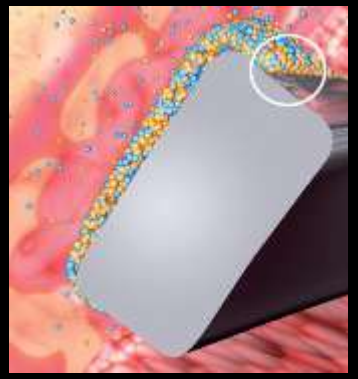
Possible mechanisms of restenosis after DES



Costa M A , Simon D I. Circulation 2005; 111:2257-2273

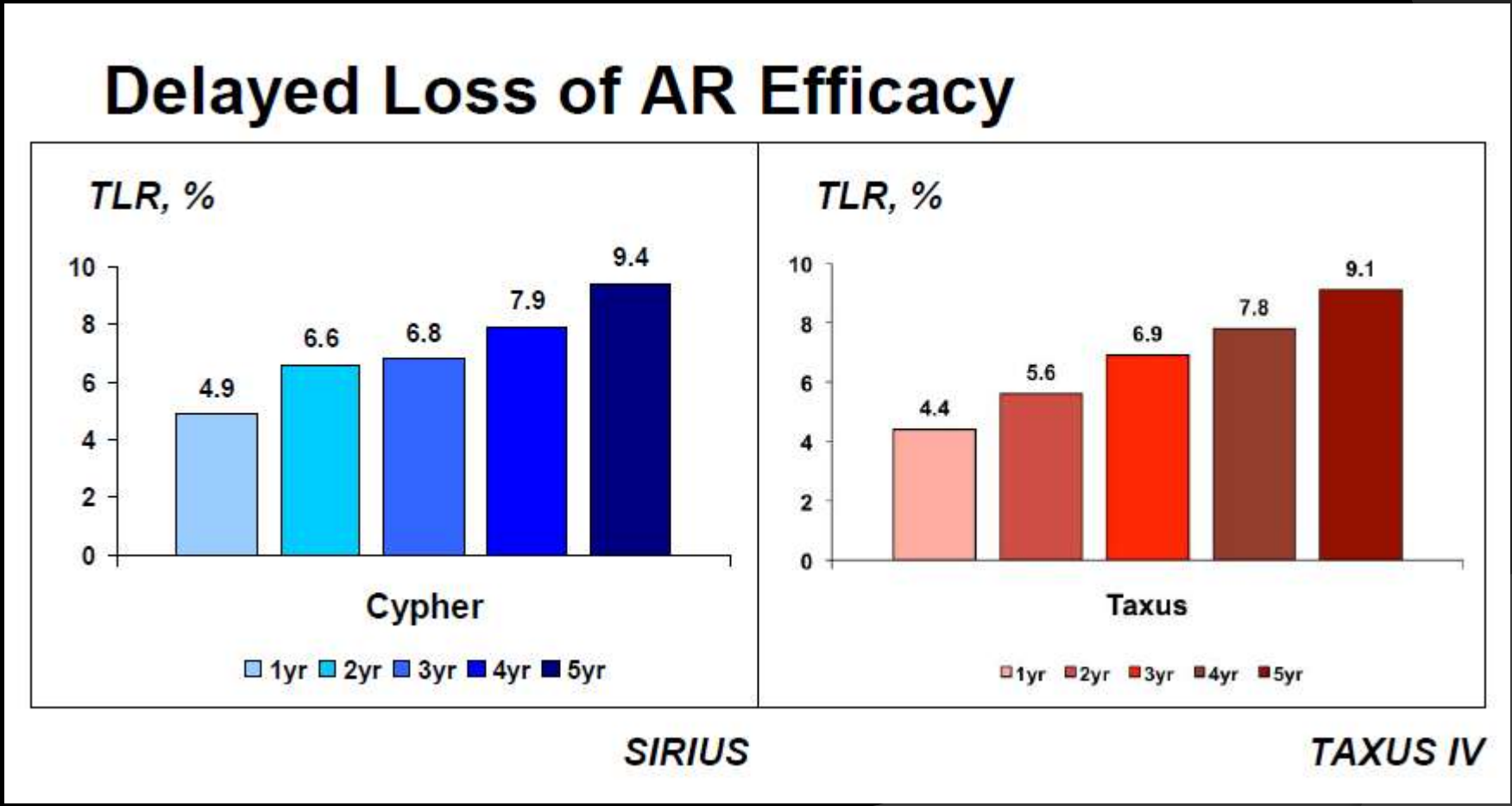
Clinical effects of DES depends on components :

- STENT PLATFORM
- ACTIVE PHARMACOLOGIC COMPOUND
- DRUG CARRIER



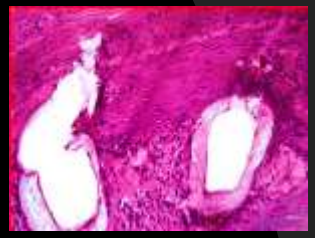
- Antiinflammatory immunomodulatory and /or antiproliferative agents

Late Luminal Creep: is our understanding of DES restenosis changing ?



Finn et al. JACC Interv. 2009

BIOLOGICAL FACTORS



- DRUG RESISTANSE genetic mutations
- HYPERSENSITIVITY 316 L stainless steel: release of molybdenum and nickel
- In 1st generation DES hypersensitivity reactions can be caused by any of the three components: alloy, polymer, drug

-Koster R et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. Lancet 2000; 356:1895

-Yusuf RZ.Paclitaxel resistance: molecular mechanisms and pharmacologic manipulation. Curr Cancer Drug Targets 2003; 3:1

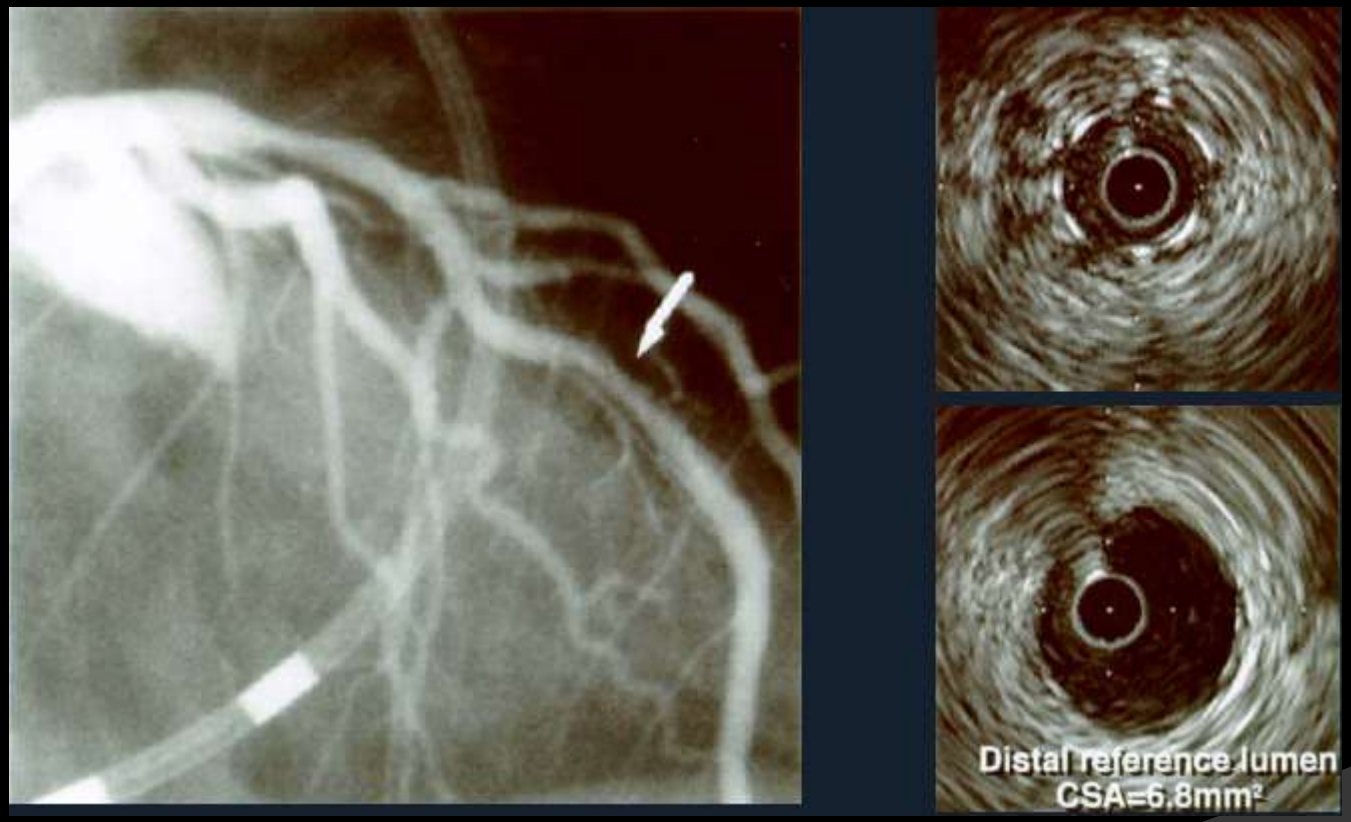
- Huang S, Houghton PJ. Mechanisms of resistance to rapamycins. Drug Resist Updat 2001;4:378

-Nebeker JR. et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. J Am Coll Cardiol 2006;47:175

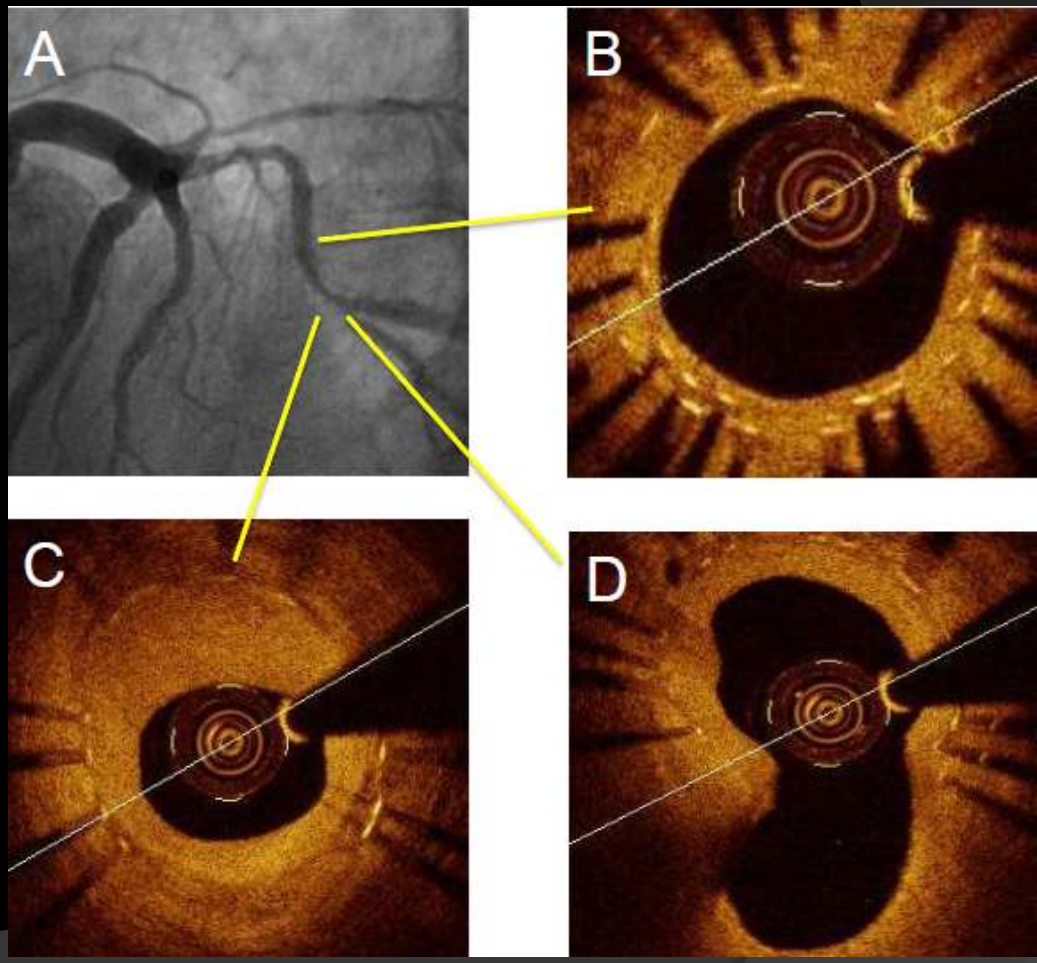
MECHANICAL FACTORS

- STENT UNDEREXPANSION (rather than chronic stent recoil)
- Excellent expansion when MLA in the stent ≥ 90% average RLA
- STENT MALAPPOSITION: undersized stents, significant tortuosity, fluctuation of reference lumen diameter

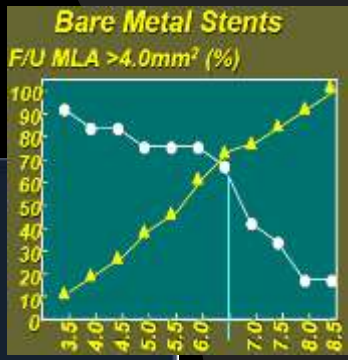
STENT UNDEREXPANSION



STENT UNDEREXPANSION



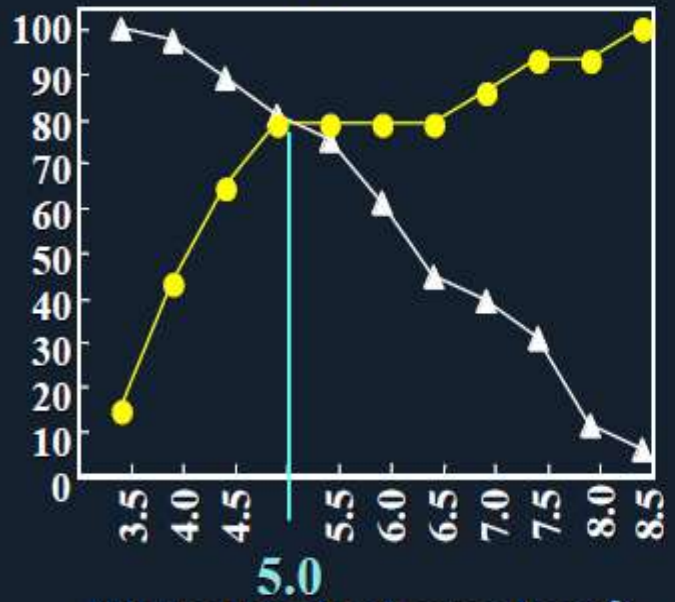
STENT UNDEREXPANSION



Post-Procedure MSA and Binary Restenosis

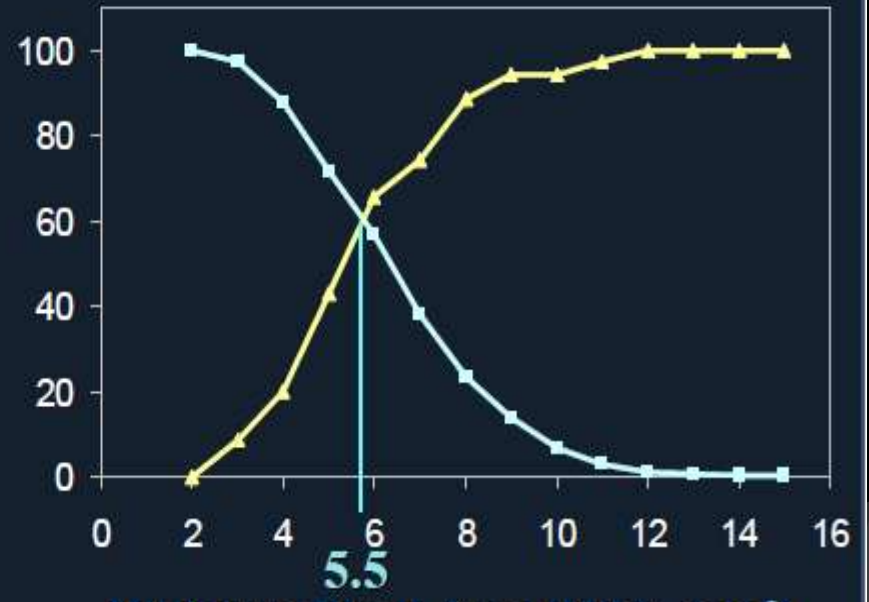
(sensitivity and specificity curves)

Cypher



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

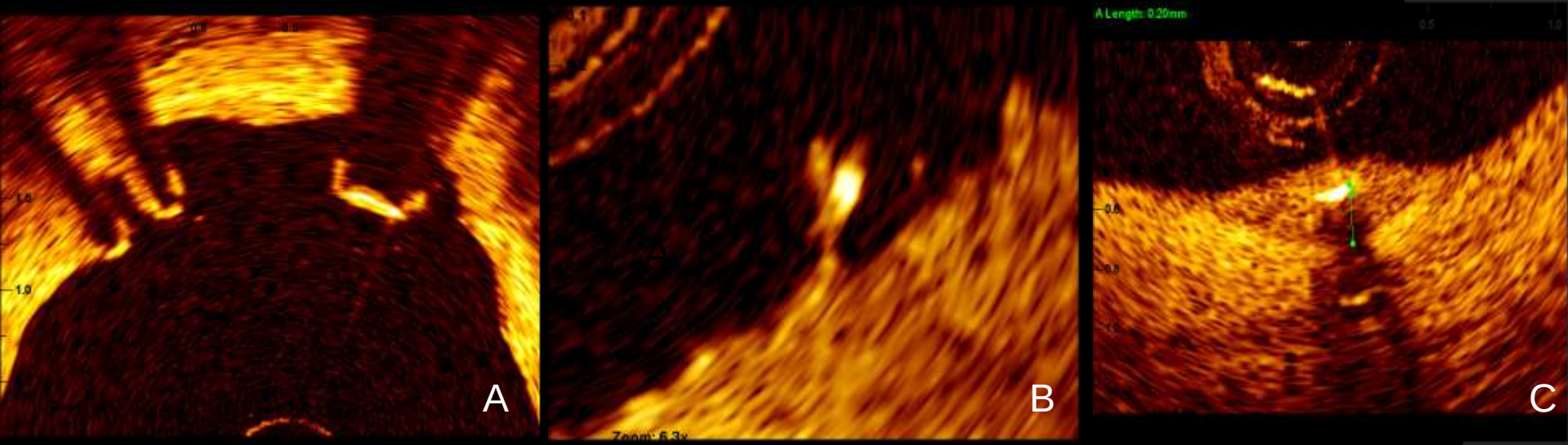
Taxus



Weissman N. TCT 2006

STENT MALLAPPOSITION

Evaluation by OCT of Neointimal Coverage of Sirolimus-Eluting Stent Three Months After Implantation

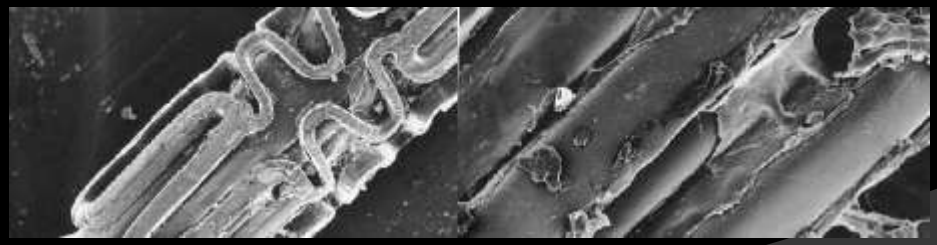


Different nonexposed strut types with malapposition. Although all struts were diagnosed as malapposed, there were intracoronary structures on them. (A) Struts seem to float into the lumen compared with the extra-stent lumen (arrowheads). (B) A strut is surrounded by an intracoronary structure with an irregular surface. This OCT finding likely indicates that a part of the analyzed strut has fibrin deposition. (C) Maximum distance between the strut surface and the vessel wall is 200 μm. This strut is completely buried under the intracoronary structure protruding into the lumen.

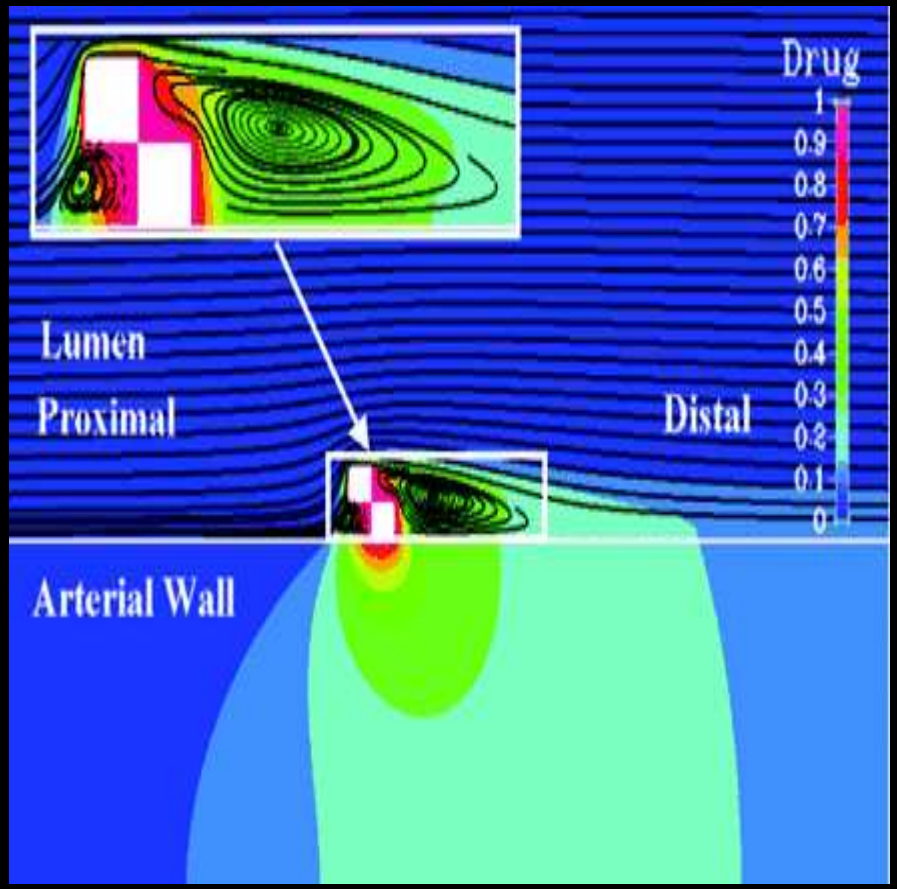
Takano, et al. Am J Cardiol 2007; 99: 1033-38

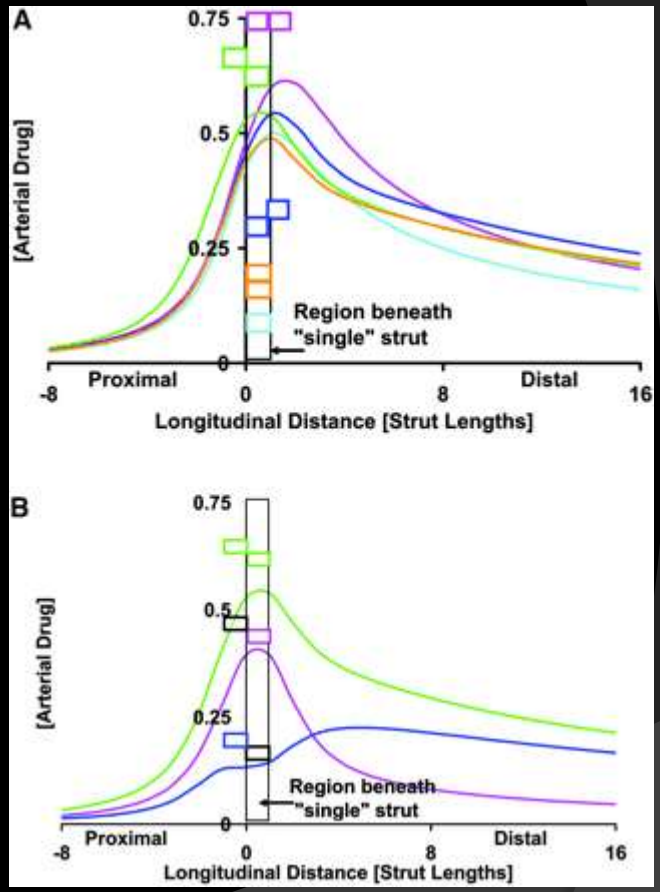
MECHANICAL FACTORS 2

- NON UNIFORM DRUG DISTRIBUTION (metal to artery ratio)
- STENT FRACTURE (eliminates metal scaffolding support - adversely impacts local drug delivery)



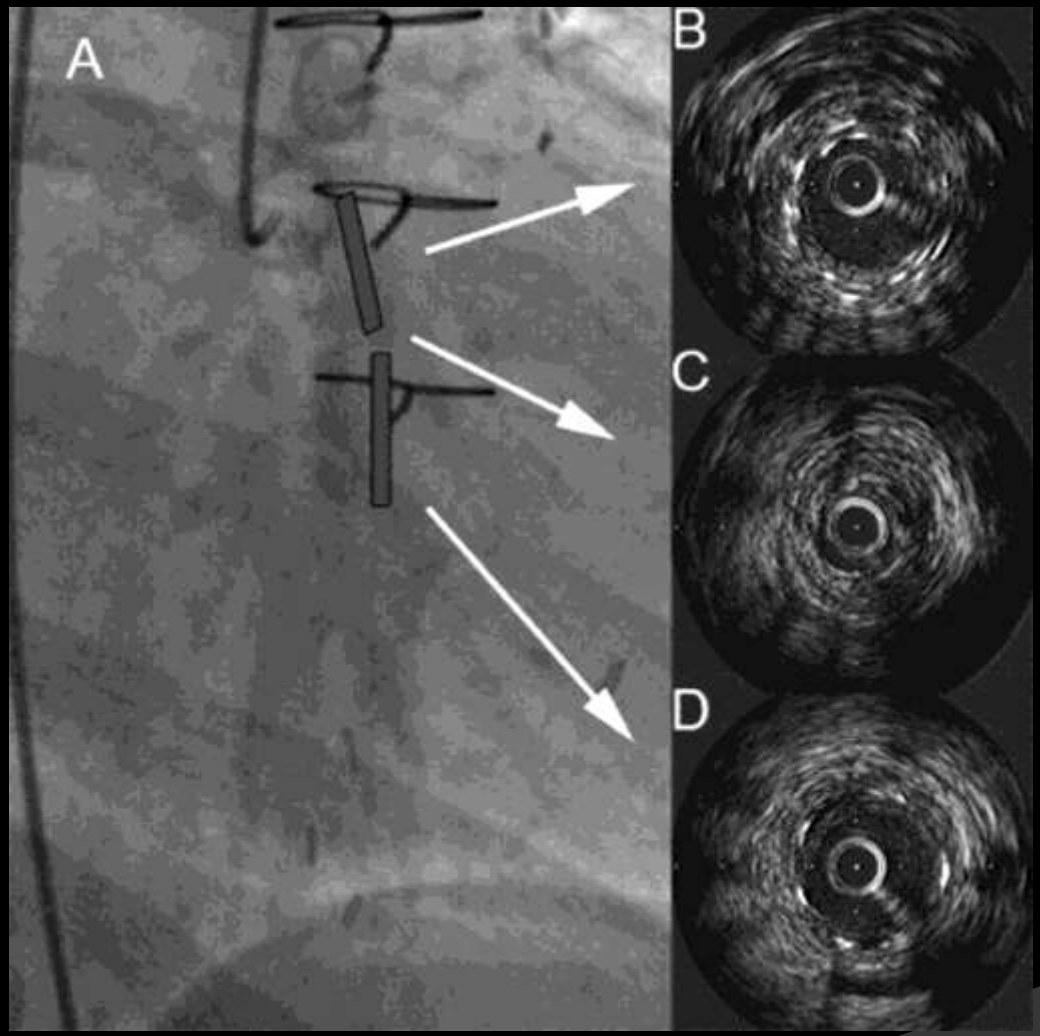
NON UNIFORM DRUG DISTRIBUTION





Balakrishnan B. Strut position, blood flow, and drug deposition: implications for single and overlapping drug-eluting stents. Circulation 2005;111:2958

STENT FRACTURE



Dangas, G. D. et al. J Am Coll Cardiol 2010; 56:1897-1907

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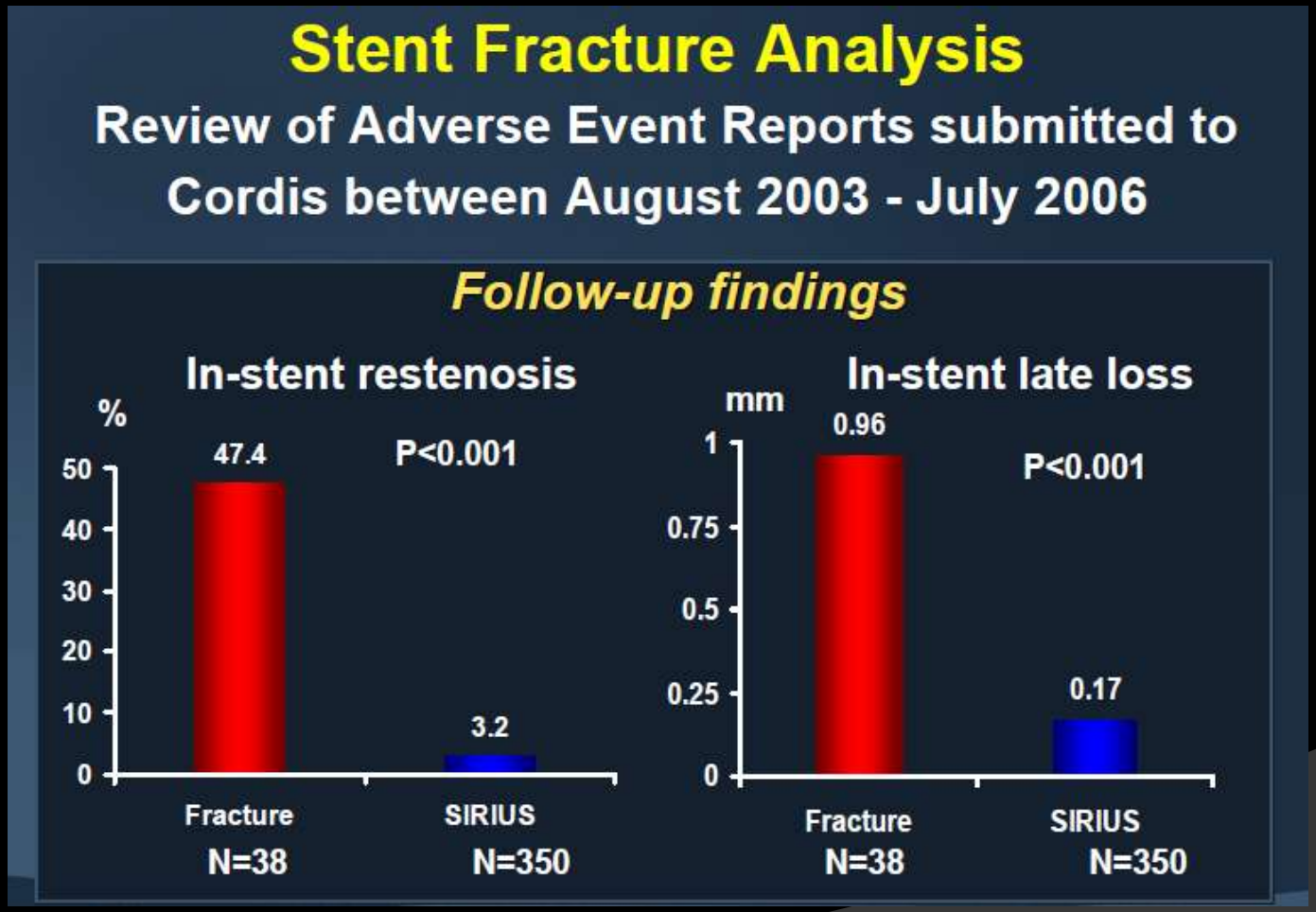
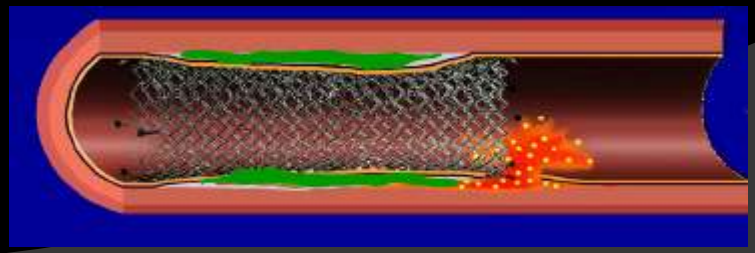
STENT FRACTURE



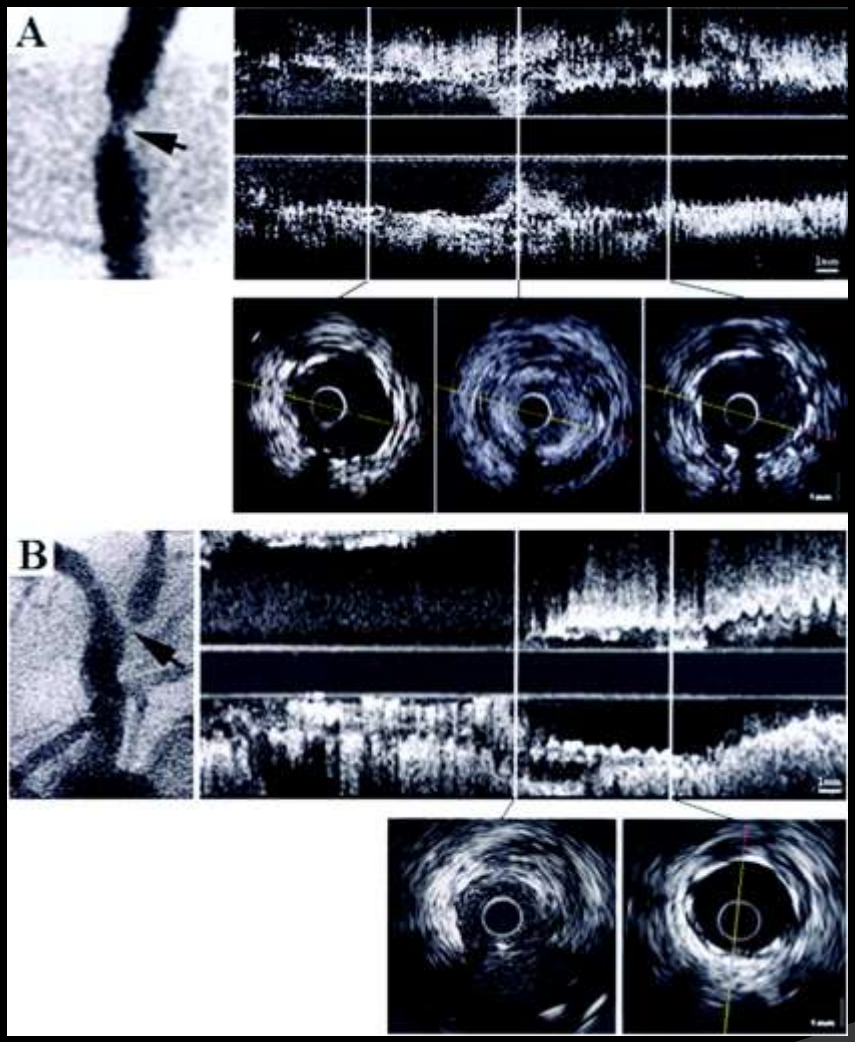
Popma JJ. et al. DES Revolution IV, 2007

TECHNICAL FACTORS

- BAROTRAUMA OUTSIDE STENTED SEGMENT
- STENT GAP
- RESIDUAL UNCOVERED ATHEROSCLEROTIC PLAQUES

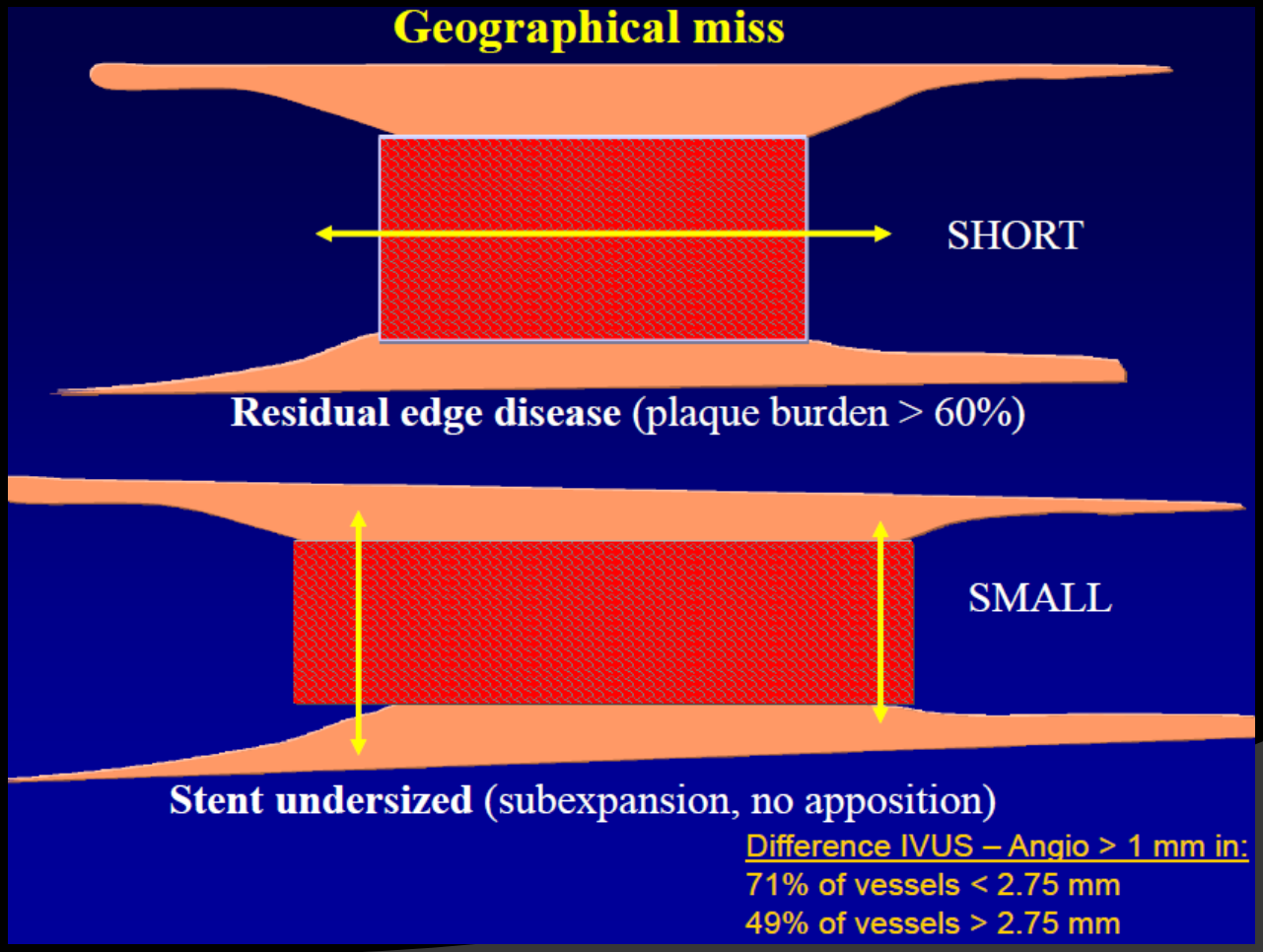


Focal restenosis at a gap between stents.

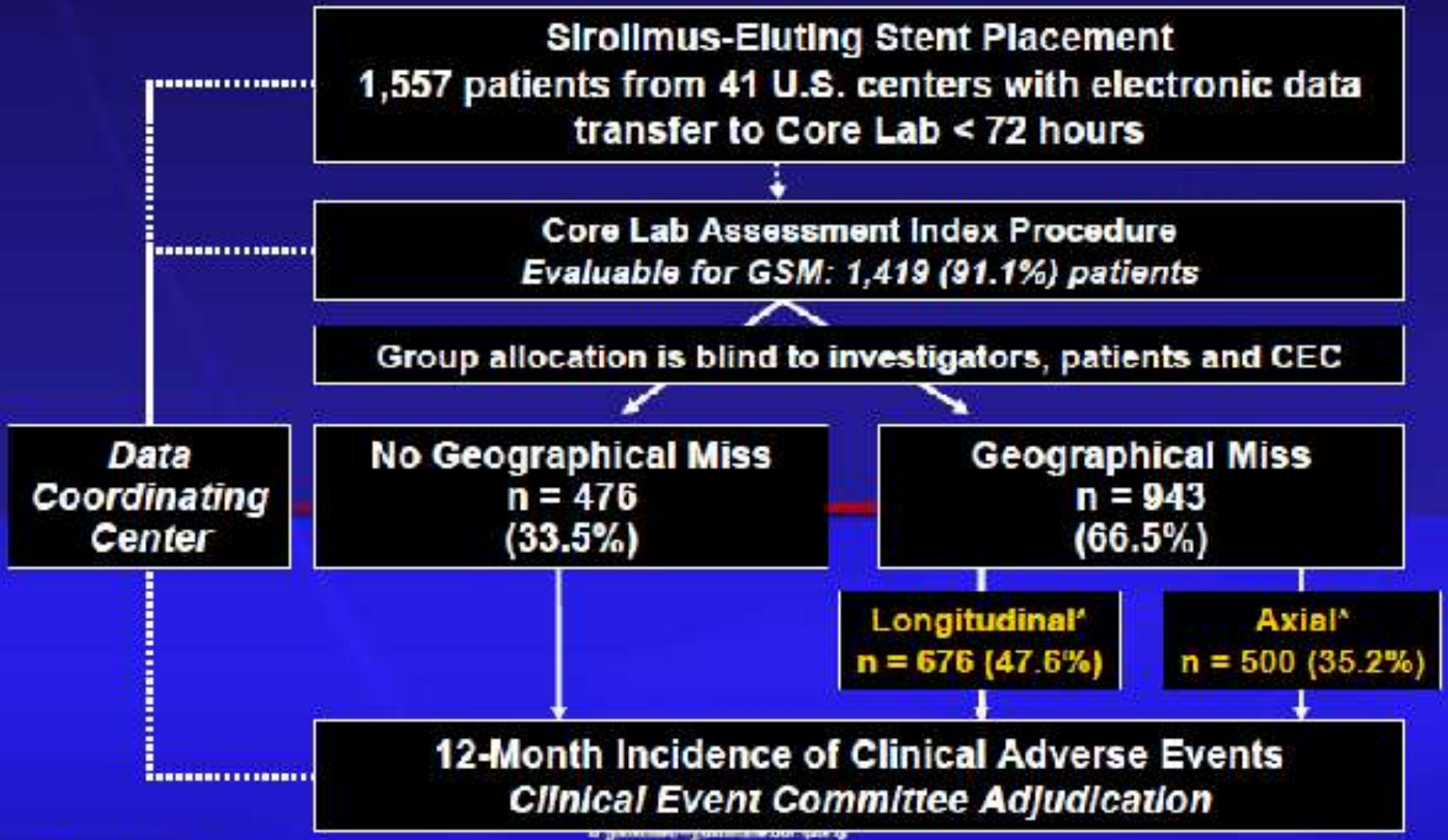


Lemos P A et al. Circulation 2003; 108:257-260

GEOGRAPHICAL MISS: how often do we miss the culprit of the culprit?



Impact of Stent Deployment Techniques on Long-term Clinical Outcomes of Patients Treated with Sirolimus-eluting Stents:



^ 234 (16.5%) patients experience both types of GM

Impact of Stent Deployment Techniques on Long-term Clinical Outcomes of Patients Treated with Sirolimus-eluting Stents: Results of The Multicenter Prospective S.T.L.L.R. Trial*

Freedom from 1-Year Clinically Driven TLR by Type of Geographic Miss

Costa MA, et al. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). Am J Cardiol 2008;101

INDEPENDENT PREDICTORS OF TLR AFTER DES IMPLANTATION

Randomized trials (on label)

SES arm in SIRIUS	Odds ratio
✓ Post procedure in-stent MLD	0.1840
✓ Total implanted stent length	1.0270

PES arm in TAXUS IV	Hazard ratio (95% CI)
✓ No study stents implanted	5.86 (1.36 - 25.27)
✓ No prior MI	3.70 (1.11 – 12.50)
✓ Female gender	2.33 (1.08 – 5.00)
✓ Lesion length	1.05 (1.01 – 1.10)

INDEPENDENT PREDICTORS OF DES RESTENOSIS

Registries (including off-label)

Rotterdam (Circulation. 2004)

- ✓ In-stent restenosis lesion
- ✓ Ostial lesions
- ✓ DM
- ✓ Vessel size
- ✓ LAD

Munich (Circulation. 2006)

- ✓ Vessel size
- ✓ Final Diameter stenosis
- ✓ DES type

Seoul (Am J Cardiol. 2006)

- ✓ DES type
- ✓ Final MLD
- ✓ Lesion length

Washington (ACC. 2007)

- ✓ Age
- ✓ Hypertension
- ✓ Procedural length
- ✓ Lack of IVUS guidance
- ✓ Total stented length

Milan (AHA. 2006)

- ✓ DM
- ✓ Unstable angina
- ✓ Reference vessel diameter
- ✓ Number of stents per lesion

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Journal of the American College of Cardiology

In-Stent Restenosis in the Drug-Eluting Stent Era

Predictors of ISR or TLR After DES Implantation

Patient Characteristics	Lesion Characteristics	Procedural Characteristics
Age	ISR	Treatment of multiple lesions
Female sex	Bypass graft	Type of DES
Diabetes mellitus	Chronic total occlusion	Final diameter stenosis
Multivessel coronary artery disease	Small vessels	
	Calcified lesion	
	Ostial lesion	
	Left anterior descending coronary artery lesion	

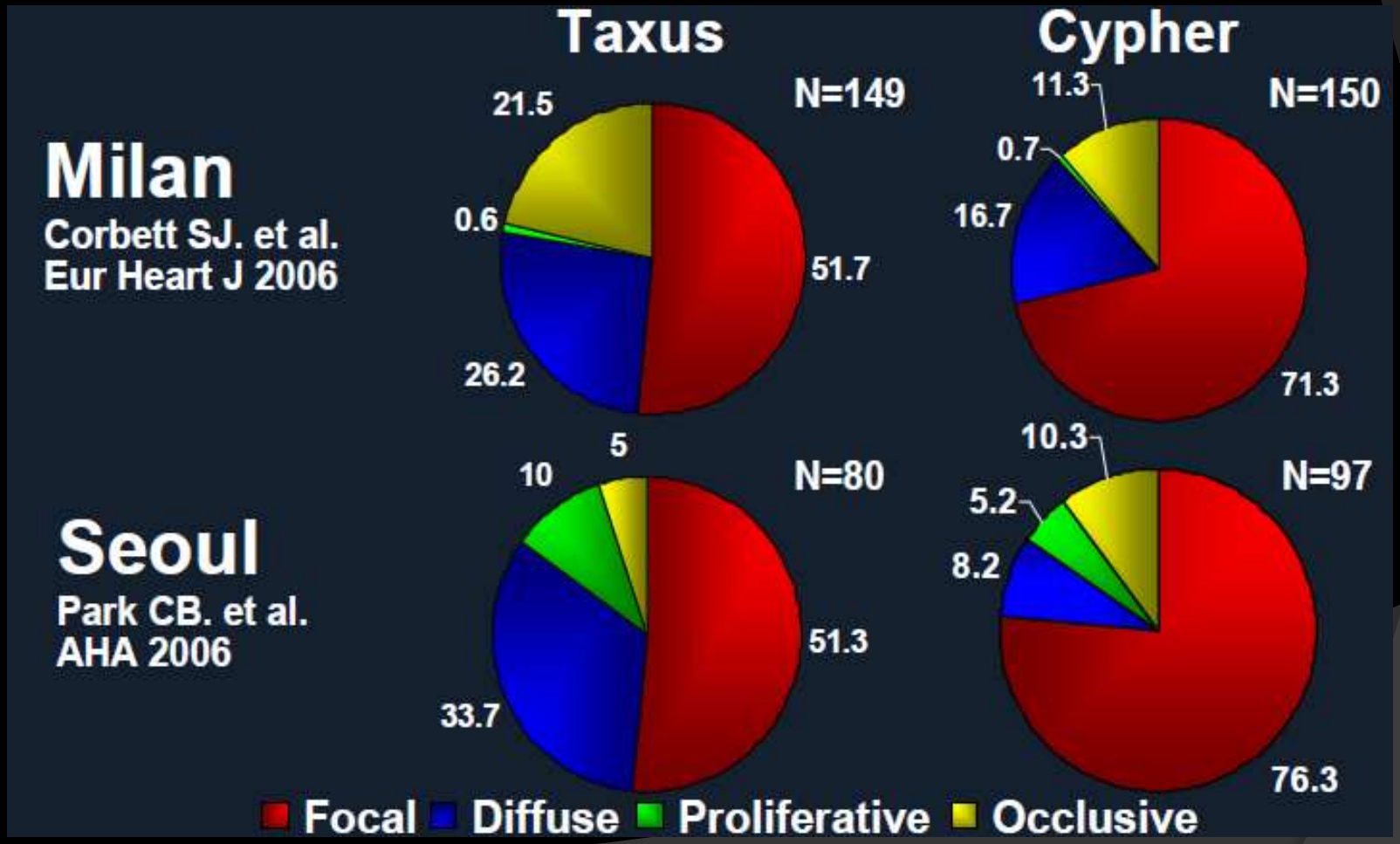
DES = drug-eluting stent(s); ISR = in-stent restenosis; TLR = target lesion revascularization.

Dangas, G. D. et al. J Am Coll Cardiol 2010;56:1897-1907

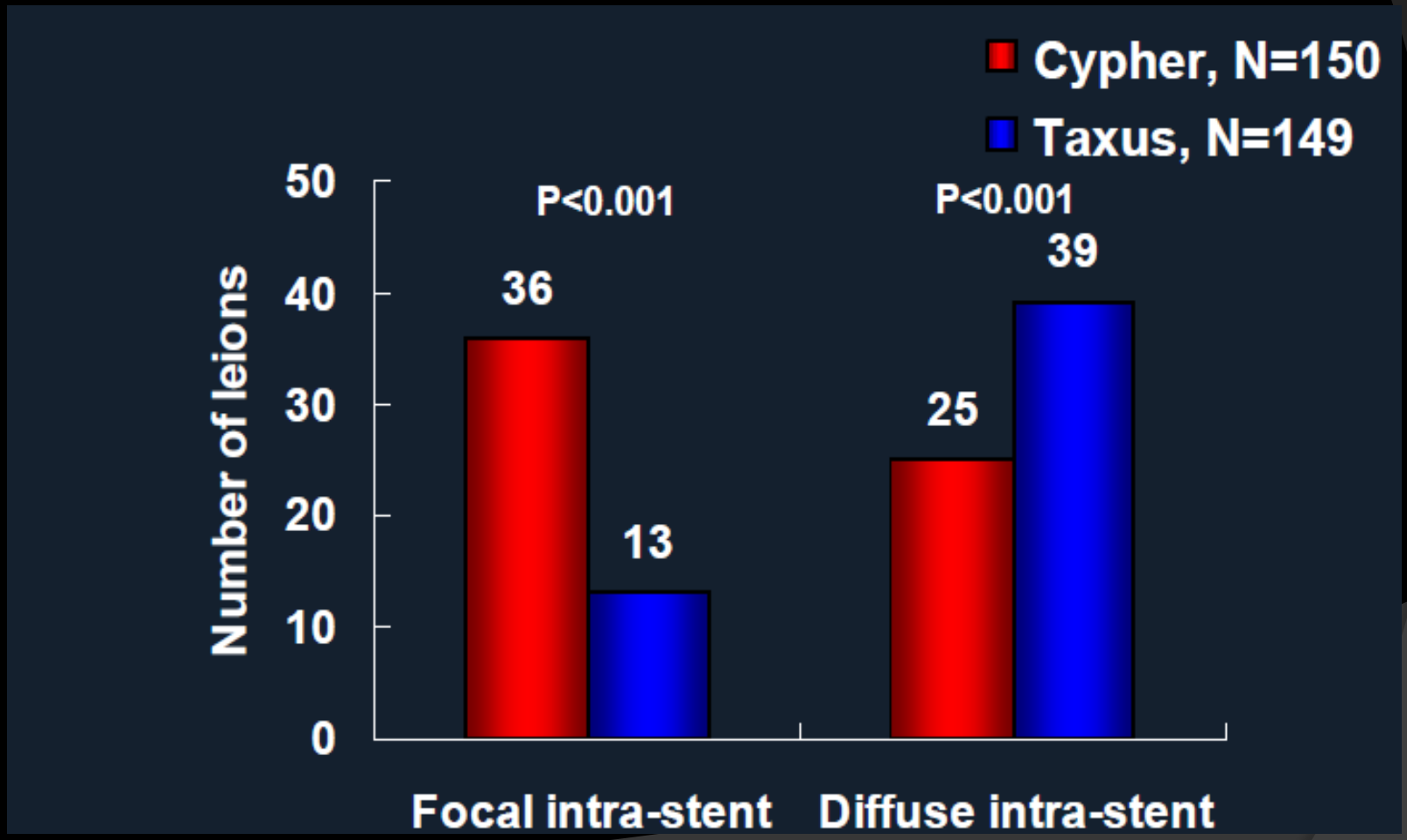
MORFOLOGIC PATTERNS OF DES ISR LESIONS

SIRIUS	Sirolimus (n=31)	Control (n=128)	P-value
I - focal	*87%*	*42%*	*<0.001*
II/III – diffuse or proliferative	6.5%	50%	<0.001
IV - total occlusion	6.5%	8%	0.895
TAXUS IV	**Paclitaxel (n=16)**	**Control (n=65)**	**P-value**
I - focal	*63%*	*31%*	*<0.001*
II/III – diffuse or proliferative	24%	66%	<0.001
IV - total occlusion	13%	3%	0.245

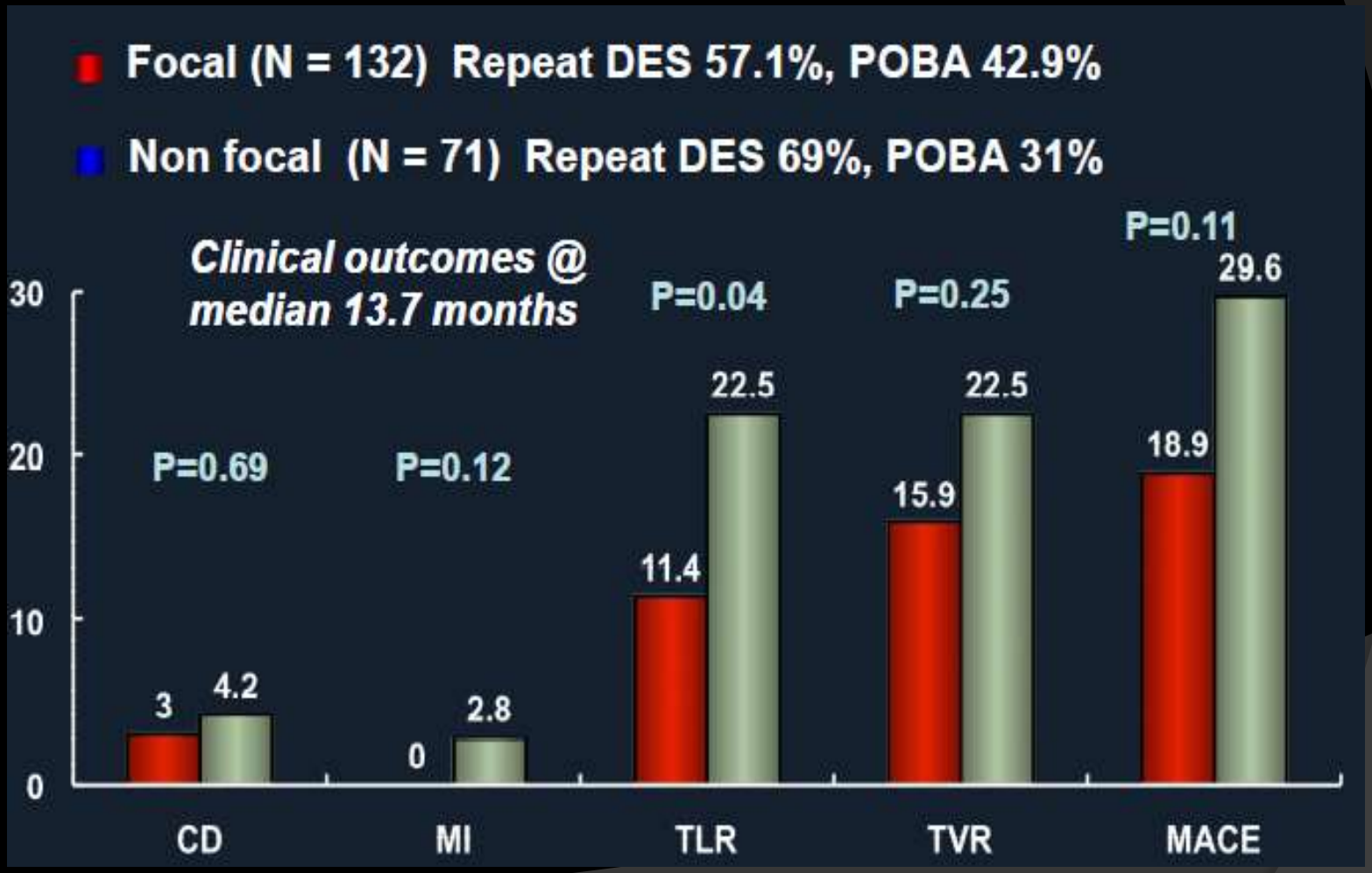
PATTERNS OF DES ISR: Cypher vs Taxus



PATTERNS OF ISR: the Milan experience



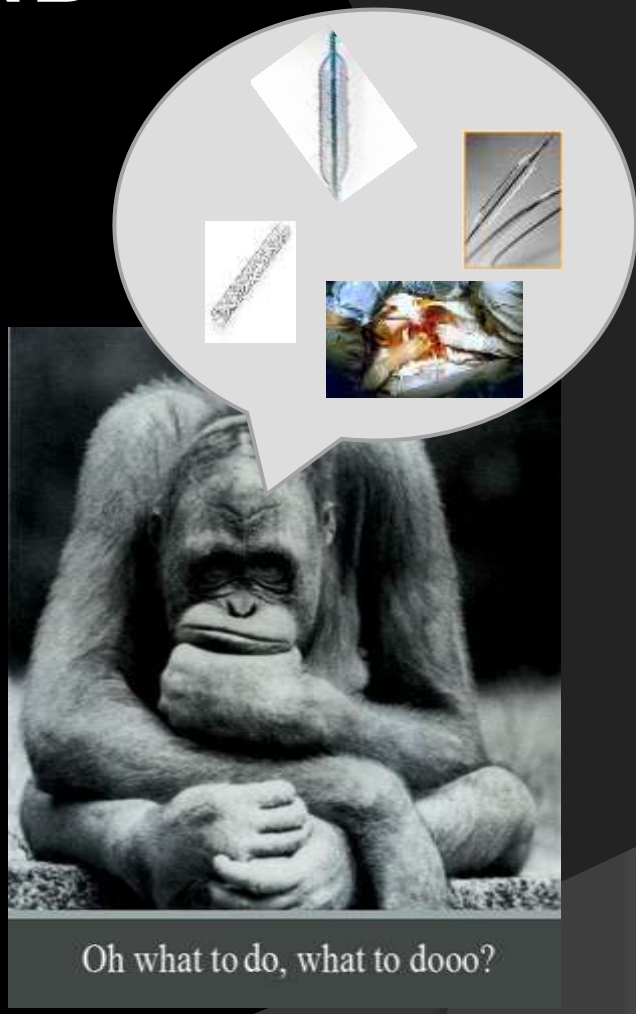
PATTERNS OF IN-STENT RESTENOSIS PREDICT OUTCOMES IN THE DES ERA?



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

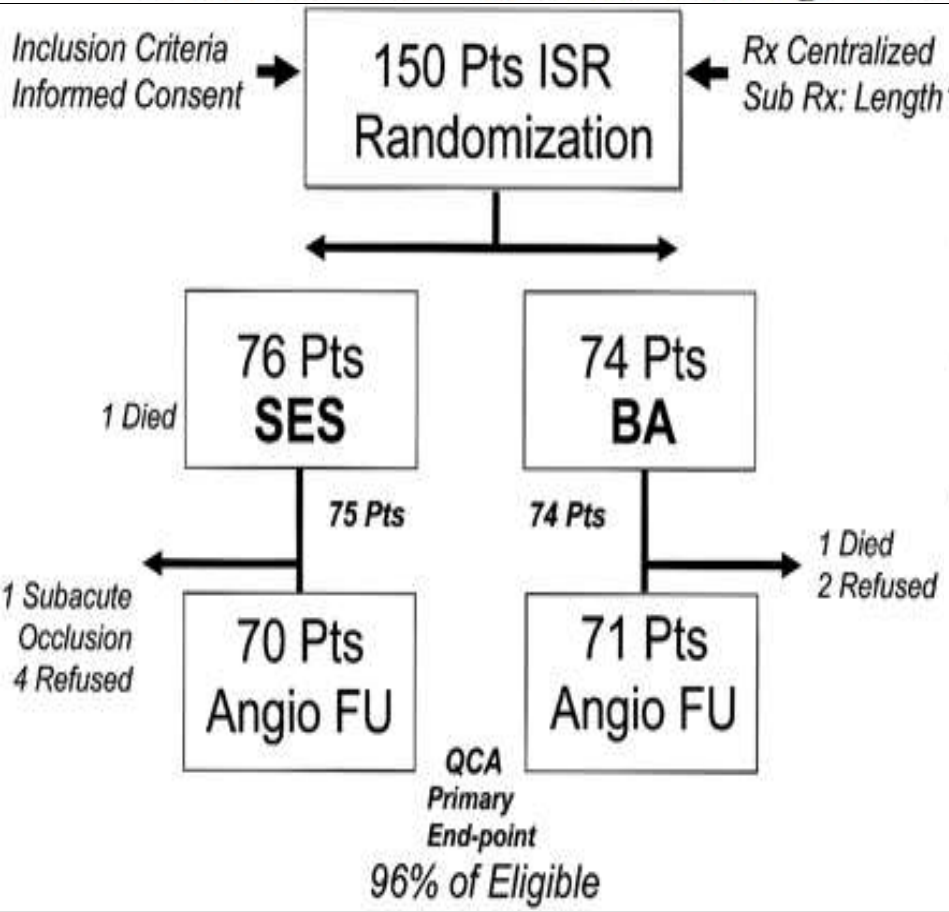
CLINICAL APPROACH AND TREATMENT OPTIONS

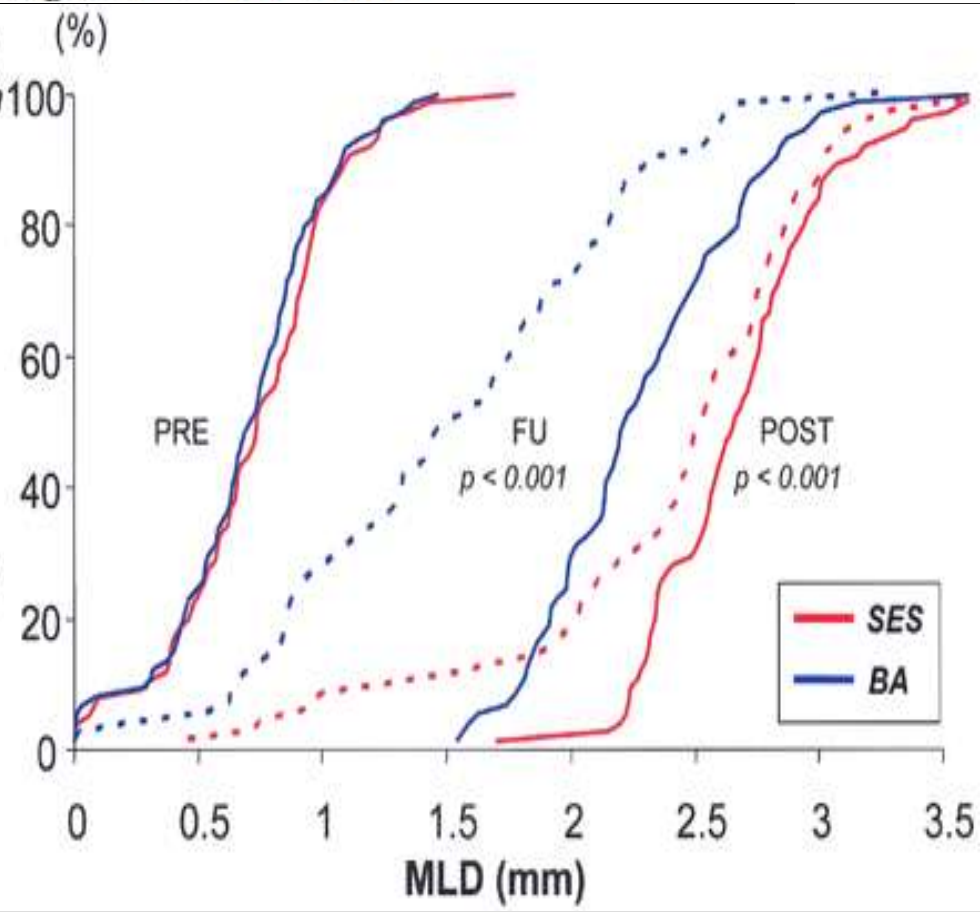
- Optimal treatment remains undefined
- Variety of treatment options – variable etiologies of DES ISR: difficult to determine optimal therapy
- Only 1 RCT
- Many obs. studies: small numbers of pts., treatment modalities too diverse, results too inconsistent to draw any definite conclusions



A Randomized Comparison of Sirolimus-Eluting Stent With Balloon Angioplasty in Patients With In-Stent Restenosis

Results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) Trial





Alfonso F. et al. A randomized comparison of sirolimus-eluting stent with balloon angioplasty in patients with in-stent restenosis: results of the Restenosis Intrastent: Balloon Angioplasty Versus Elective Sirolimus-Eluting Stenting (RIBS-II) trial. J Am Coll Cardiol 2006;47:2152

TAXUS V ISR Trial: Study Design

396 patients ≥ 18 years with stable or unstable angina or inducible ischemia undergoing percutaneous coronary intervention (PCI) of a single bare-metal in-stent restenosis (ISR) lesion in a native coronary artery.

Randomized.

34% female, median age 63 years, mean follow-up 9 months

Angiography (Baseline)

VBT using a beta-source radiation
n=201

PCI with paclitaxel-eluting stents
n=195

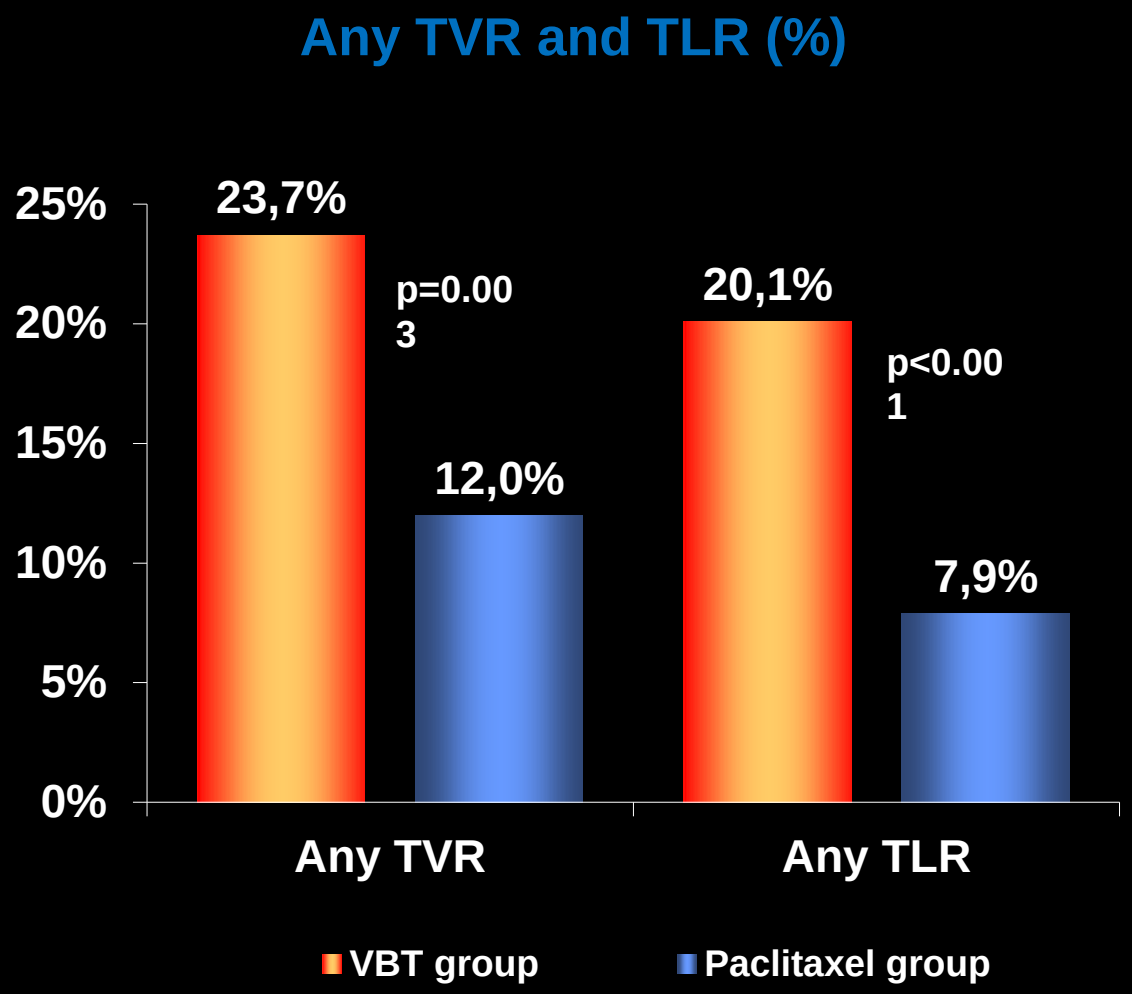
Repeat Angiography (9 months)

170 in VBT group and 172 in Paclitaxel group

- Primary Endpoint: Ischemia-driven target vessel revascularization at 9 months

Paclitaxel -eluting stents vs vascular brachytherapy for in-stent restenosis within bare metal stents: the TAXUS V ISR randomized trial. Stone GW et al. JAMA 2006; 295:1253

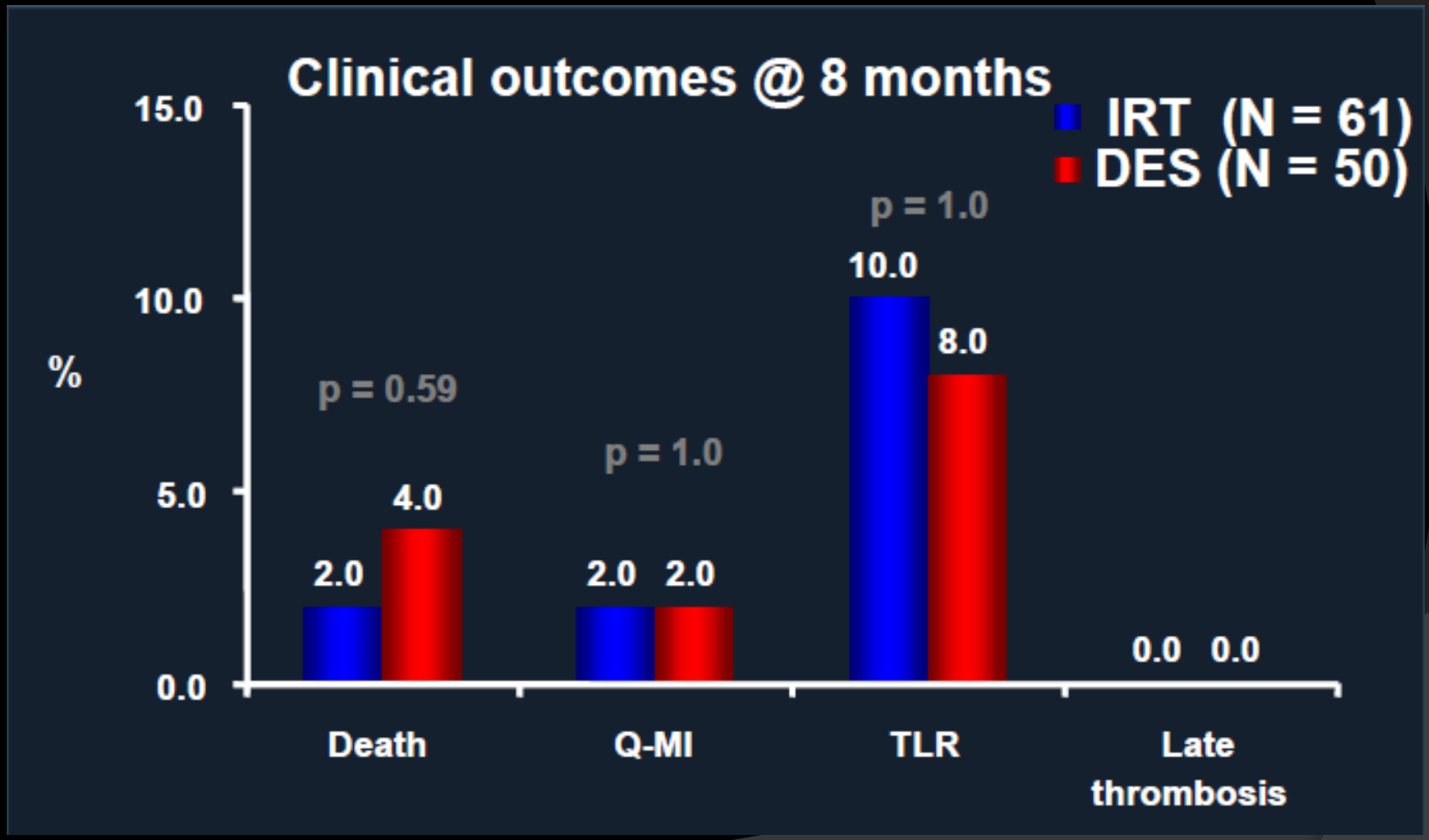
TAXUS V ISR Trial: 9 month Clinical Results



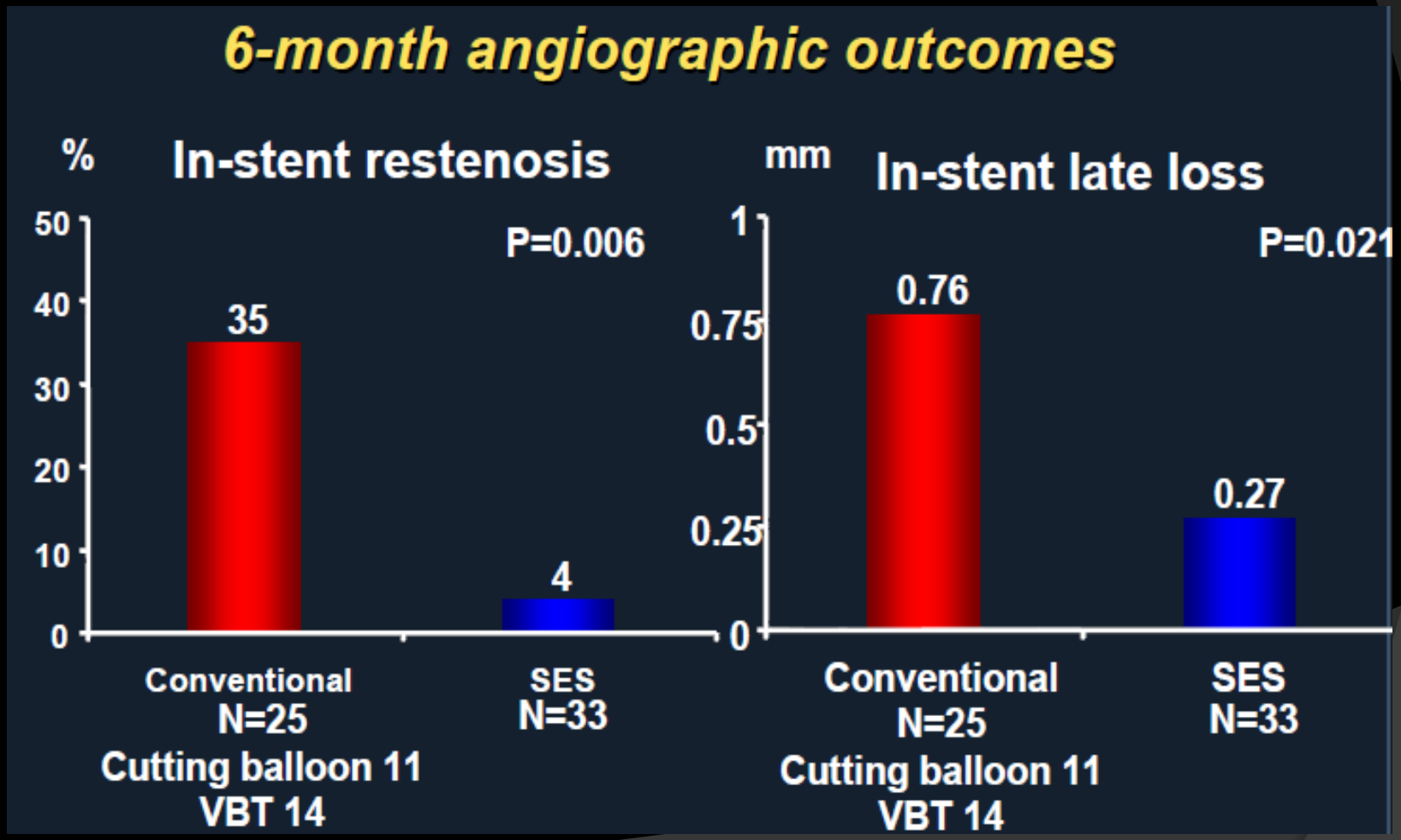
- Any incident of TVR was greater among the VBT group (23.7% vs 12.0%; p=0.003)
- Any incident of TLR was greater among the VBT group (20.1% vs 7.9%; p<0.001)

Presented at ACC 2006

Torguson R, Sabate M, Deible R, et al. Intravascular brachytherapy versus drug-eluting stents for the treatment of patients with drug eluting stent restenosis. Am J Cardiol 2006;98:1340–4.



Kim YH, Lee BK, Park DW, et al. Comparison with conventional therapies of repeated sirolimus-eluting stent implantation for the treatment of drug-eluting coronary stent restenosis.
Am J Cardiol 2006;98:1451– 4.



Long-Term Outcomes After Management of Restenosis or Thrombosis of Drug-Eluting Stents

Kaplan-Meier Estimates	Overall (n = 92)	Homo-Stents (n = 59)	Hetero-Stents (n = 18)	Other (n = 15)
6 Month	Percent of Patients (95% CI)			
Death	4.4 (1.7–11.3)	3.4 (0.9–12.9)	5.9 (0.9–35.0)	6.7 (0.9–38.7)
Myocardial Infarction	0	0	0	0
Target lesion revascularization†	9.7 (5.3–17.3)	8.1 (3.4–18.3)	14.3 (4.8–38.0)	10.0 (2.6–34.4)
All MACE, % of patients (95% CI)	12.7 (7.2–21.7)	9.1 (3.9–20.6)	17.6 (6.1–45.3)	21.0 (7.3–52.1)
12 Month	Percent of Patients (95% CI)			
Death	6.7 (3.1–14.3)	6.8 (2.6–17.2)	5.9 (0.9–35.0)	6.7 (0.9–38.7)
Myocardial Infarction	2.4 (0.3–16.1)	0	0	20.0 (3.1–79.6)
Target lesion revascularization†	28.2 (20.4–38.2)	28.5 (18.8–42.0)	19.0 (7.6–43.1)	36.5 (19.3–62.0)
All MACE, % of patients (95% CI)	42.9 (31.5–56.4)	43.0 (29.5–59.5)	25.1 (10.1–54.4)	76.3 (38.1–98.7)

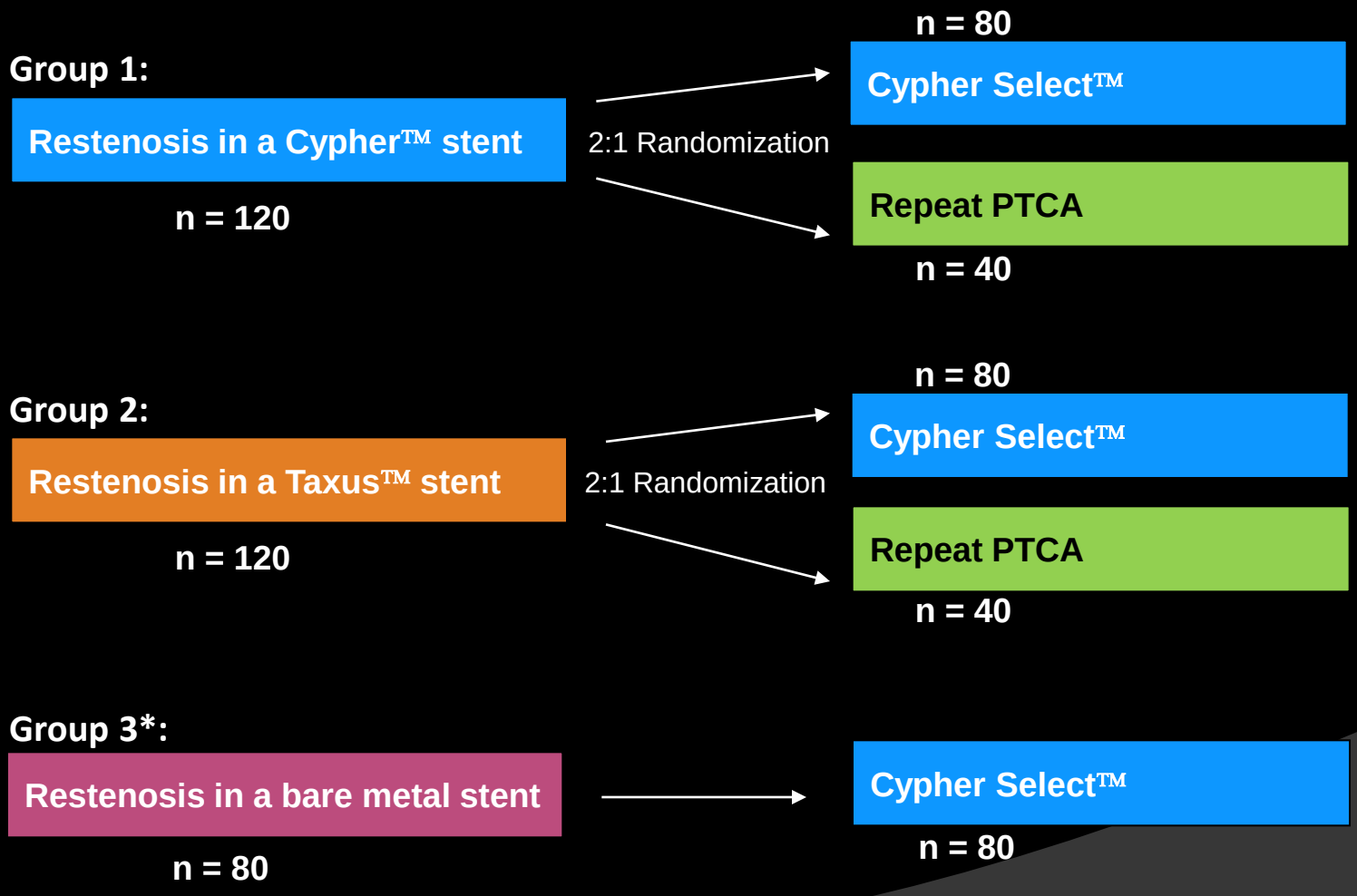
Mishkel GJ. Long-term outcomes after management of restenosis or thrombosis of drug-eluting stents. J Am Coll Cardiol 2007;49:181

CRISTAL: A Prospective Randomized Trial of Sirolimus-Eluting Stents Compared to Balloon Angioplasty for Restenosis of Drug-Eluting Coronary Stents

Bernard Chevalier, Jean Fajadet
on behalf of the CRISTAL investigators

TCT 2010, Late Breaking Trials and First Report Investigations; September 25, 2010

Study Design



*No randomization to PTCA, as already investigated in ISAR-DESIRE with poor outcome.

Clinical Endpoints

per Pooled Study Cohort

	Cypher Cypher/Taxus Pooled (n=136 patients) (n=141 Lesions)	PTCA Cypher/Taxus Pooled (n=61 patients) (n=61 Lesions)	p
Cardiac Death	0.7%(1/136)	1.6%(1/61)	0.52
Non-cardiac Death	2.2%(3/136)	1.6%(1/61)	1.000
Q-Wave MI	0.7%(1/136)	0.0%(0/61)	1.000
Non Q-Wave MI	2.2%(3/136)	1.6%(1/61)	1.000
TLR (Clinically Driven)	5.9%(8/136)	13.1%(8/61)	0.097
TVR (Clinically Driven)	2.2%(3/136)	0.0%(0/61)	0.55
Stent Thrombosis	0.7%(1/136)	0.0%(0/61)	1.000

ITT population

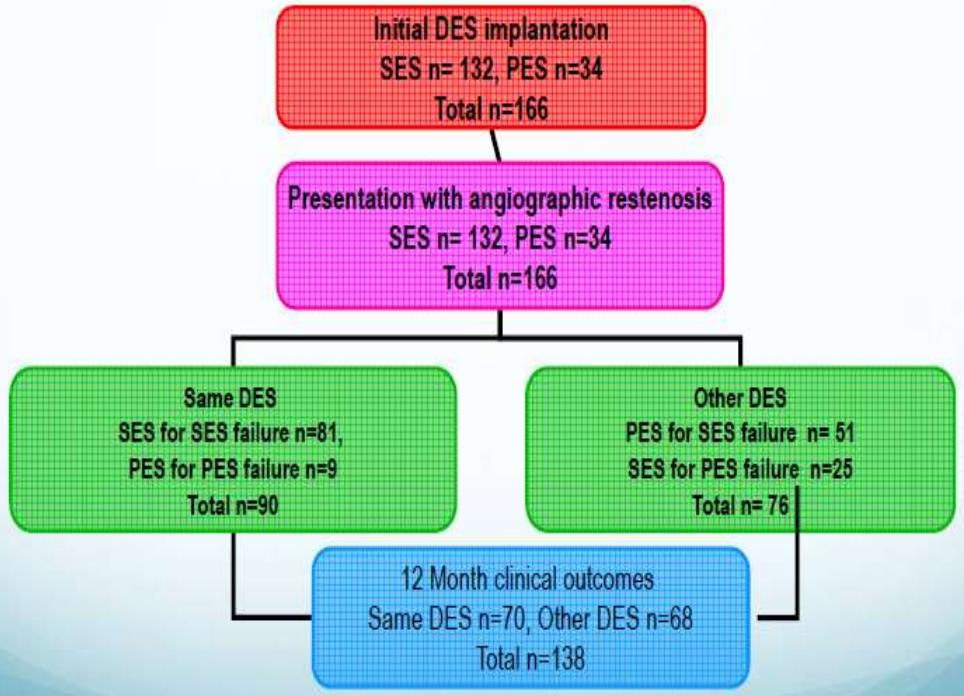
SAME DES or DIFFERENT DES?

- One of the etiologies of DES restenosis is drug resistance.
- What if…we change one DES for another?
- Few studies have investigated “homo” DES or “hetero” DES implantation for ISR
- SES vs PES

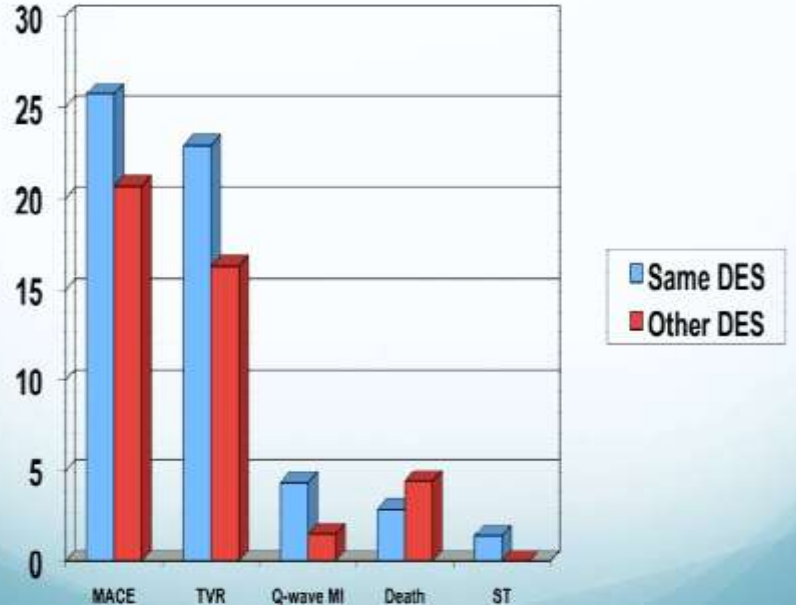
Treatment of Drug-Eluting Stent Restenosis with the Same or Different Drug-Eluting Stent: To Switch or not to Switch

Kimberly Smith Kaneshige, Rebecca Torguson, Zhenyi Xue, Daniel H. Steinberg, Tina L. Pinto Slottow, Probal K. Roy, Saquib Samee, Joseph Lindsay, Augusto D. Pichard, Lowell Satler, William O. Suddath, Kenneth Kent, Ron Waksman
Washington Hospital Center, Washington, DC

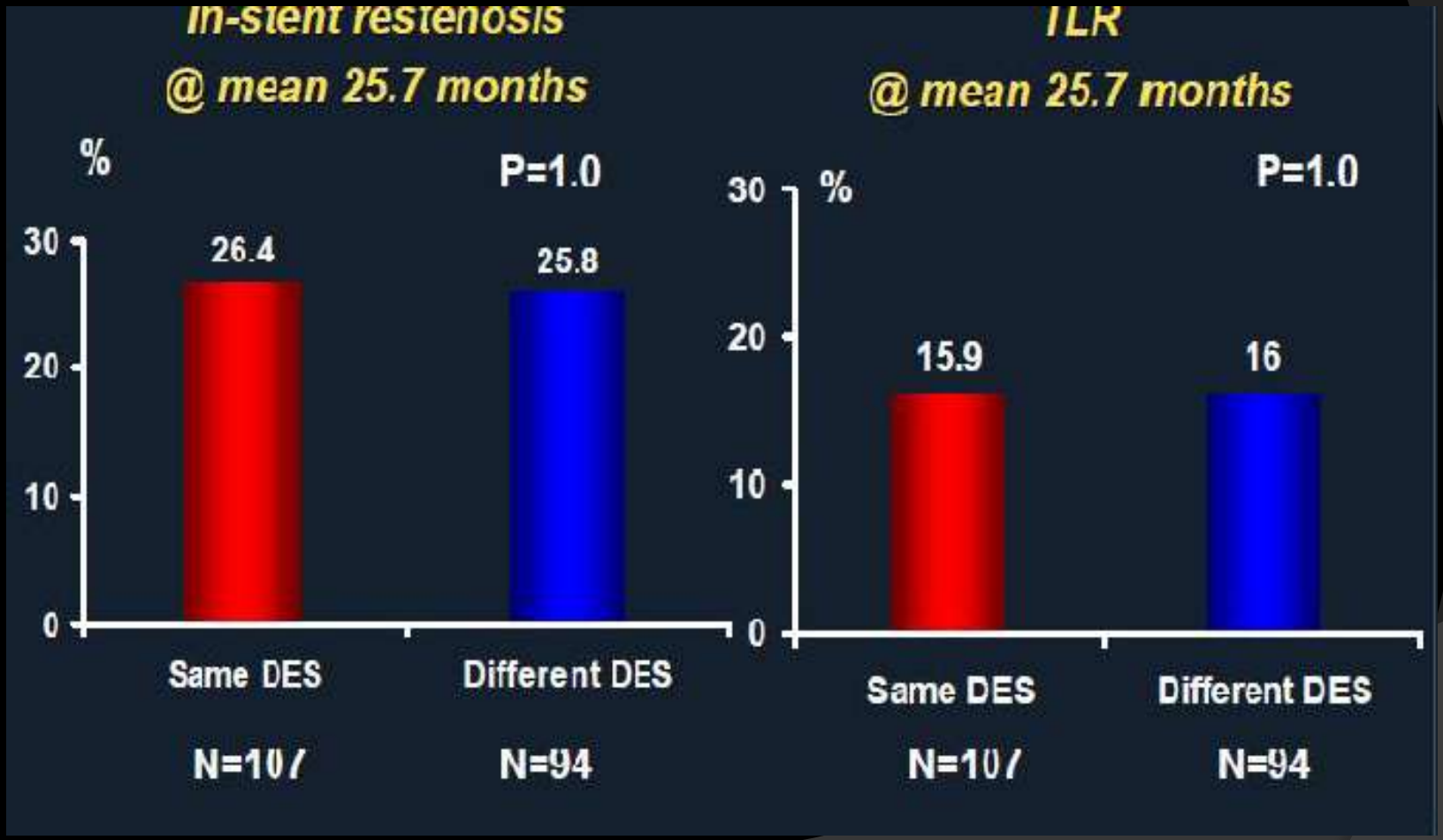
Study Design



12 Month Similar Between Same versus Other DES

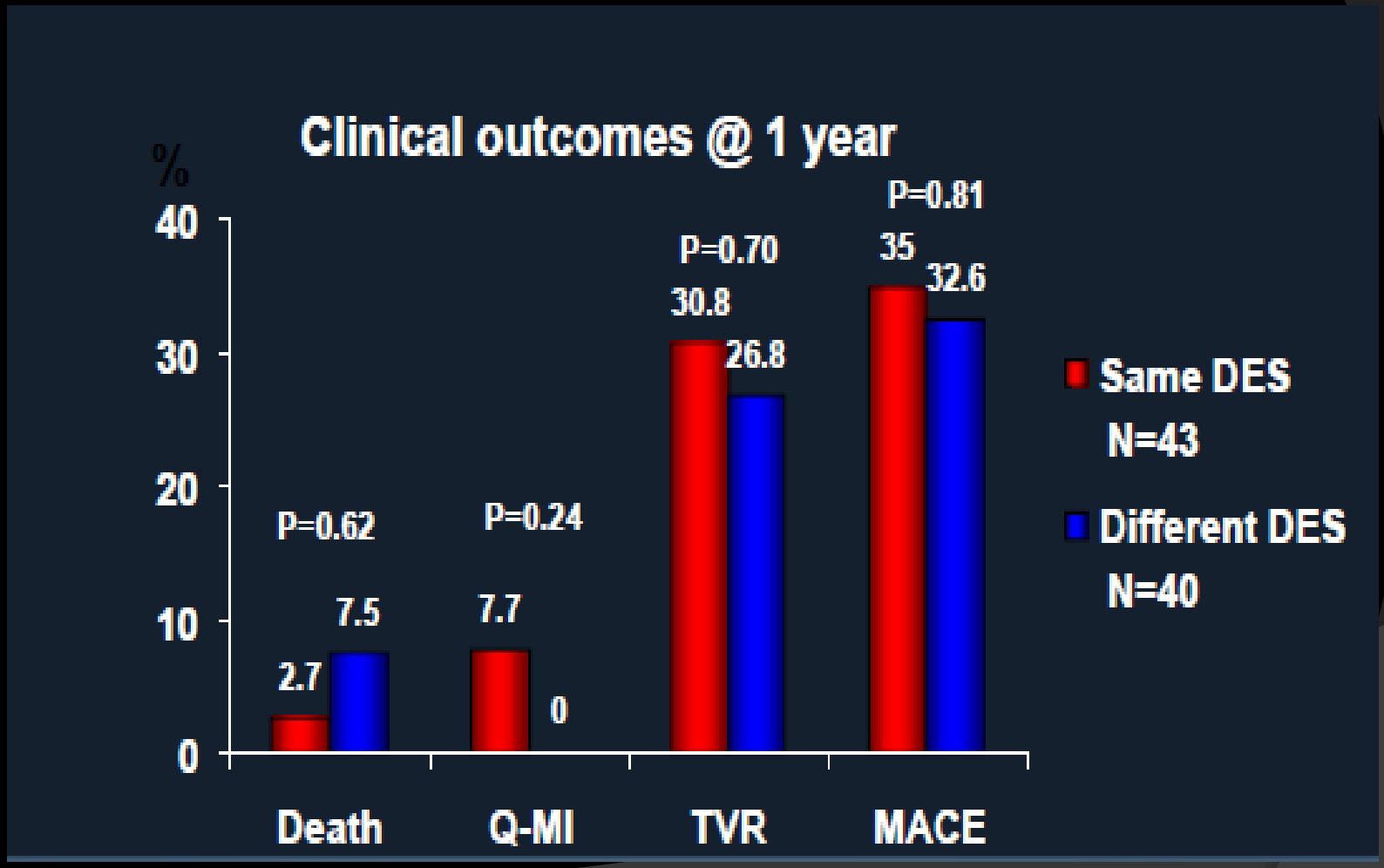


SAME DES vs other DES vs other treatment for DES failure. Does the SWITCH therapy work?



Cosgrave J et al. AHJ 2007; 153 : 354 - 9

SAME DES vs other DES vs other treatment for DES failure. Does the SWITCH therapy work?



Garg S et al. CCI 2007; 70: 9 - 14

PROSPECTIVE, RANDOMIZED TRIAL OF PACLITAXEL-VERSUS SIROLIMUS-ELUTING STENTS FOR TREATMENT OF CORONARY RESTENOSIS IN SIROLIMUS-ELUTING STENTS

Robert A. Byrne, Julinda Mehilli, Klaus Tiroch, Stefanie Schulz, Steffen Massberg, Karl-Ludwig Laugwitz, Albert Schömig, Adnan Kastrati

Deutsches Herzzentrum & 1. Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich. Germany

ISAR-DESIRE 2

Background

- The optimal treatment strategy for *in-stent restenosis* is based on the axiom:
  - maximize acute gain
  - minimize late loss

- **In *BMS*-restenosis this has most effectively been accomplished by DES**

ISAR-DESIRE *JAMA* 2005; RIBS-II *JACC* 2006
TAXUS-V-ISR *JAMA* 2006; SISR *JAMA* 2006

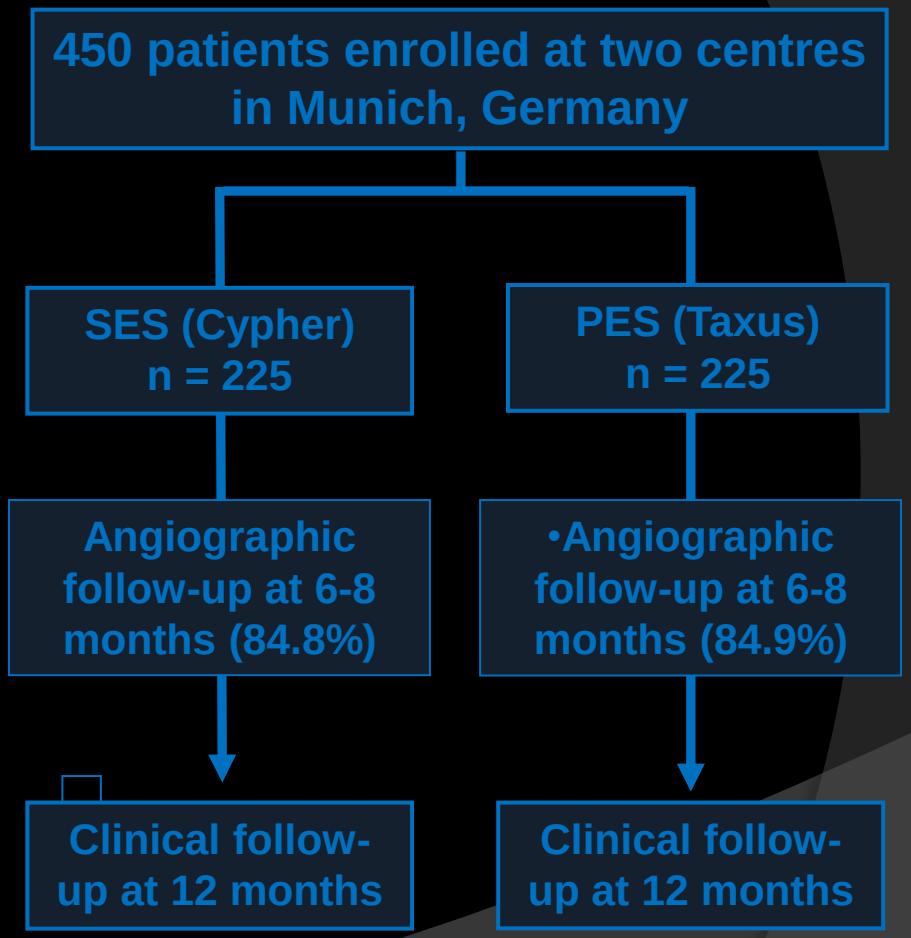
Background

- In DES-restenosis the most effective management strategy is unclear
- While repeat DES implantation seems preferable, optimal stent type is not known
  - Different DES (“hetero-DES”)
  - Same DES (“homo-DES”)

Lee et al. *AJC* 2006; Cosgrave et al. *AHJ* 2007
Garg et al. *CCI* 2007*; Byrne et al. Rev Esp Card* 2008

Study Organization Design

- **DESIGN: Randomized, open-label, active-control trial**
- **INCLUSION CRITERIA:**
  1. **In-SES restenosis > 50%**
  2. **Symptoms/signs of ischaemia**
- **EXCLUSION CRITERIA:**
  1. **Cardiogenic shock**
  2. **Lesion in LMCA or graft**
  3. **Acute myocardial infarction**
- **PRIMARY ENDPOINT:**
  In-stent late loss



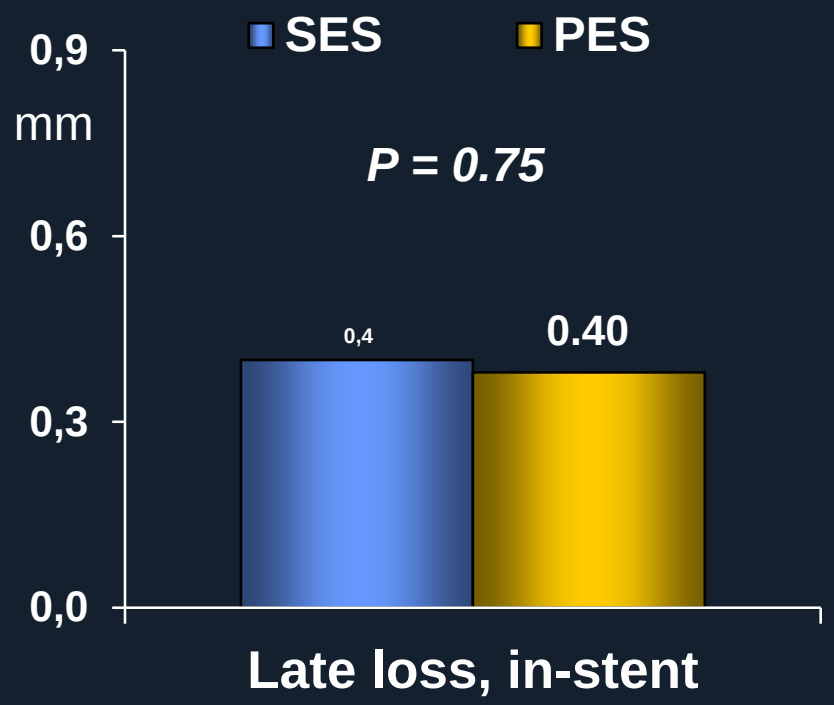
Baseline Characteristics

Lesions – Restenosis Morphology

	SES n = 243 (%)	PES n = 240 (%)
Focal margin	21.0	18.8
Focal body	37.5	34.6
Multifocal	6.6	7.5
Diffuse/proliferative	30.0	35.8
Occlusive	4.9	3.3

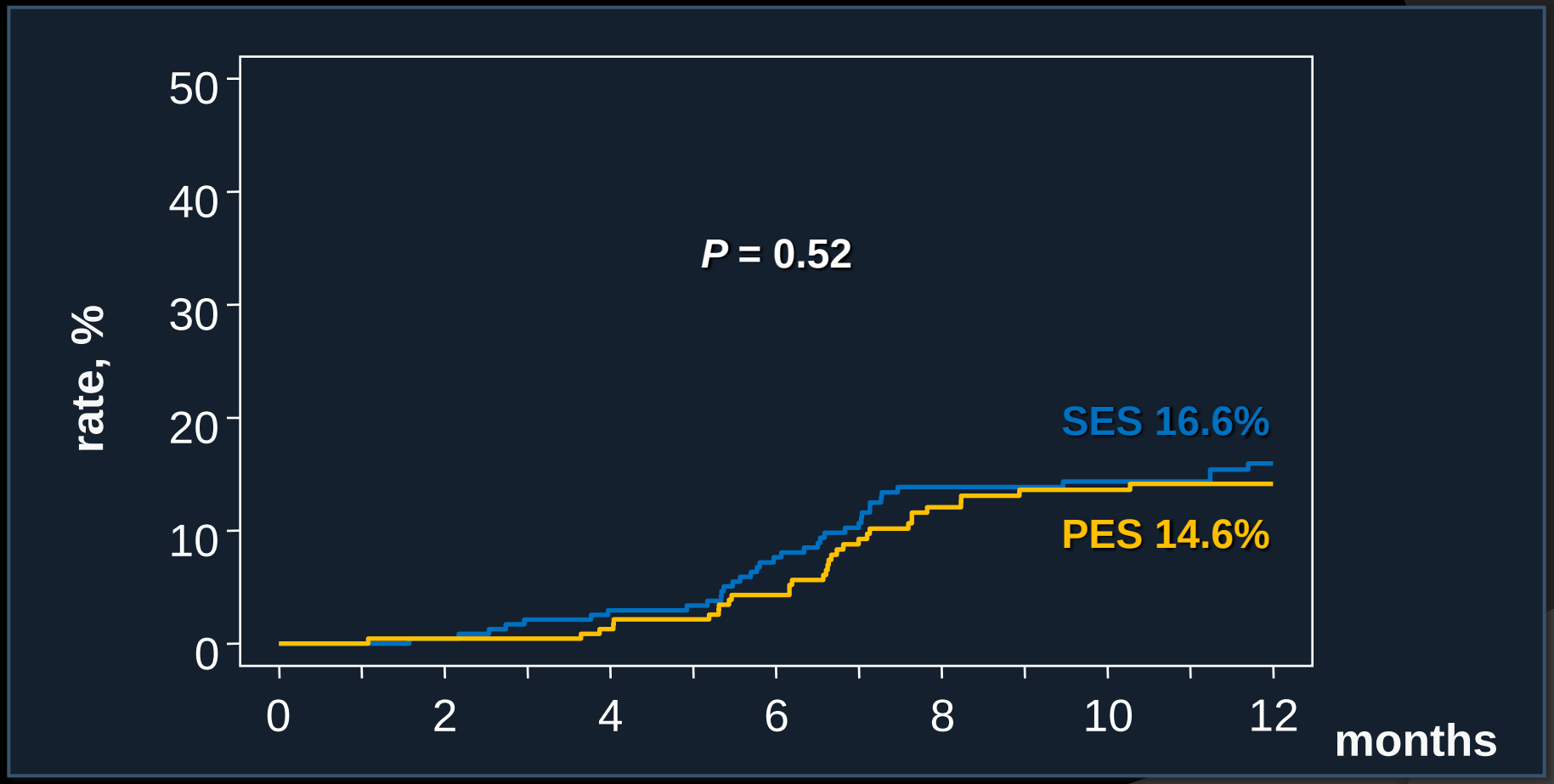
Primary Endpoint

Late Luminal Loss



Secondary Endpoint

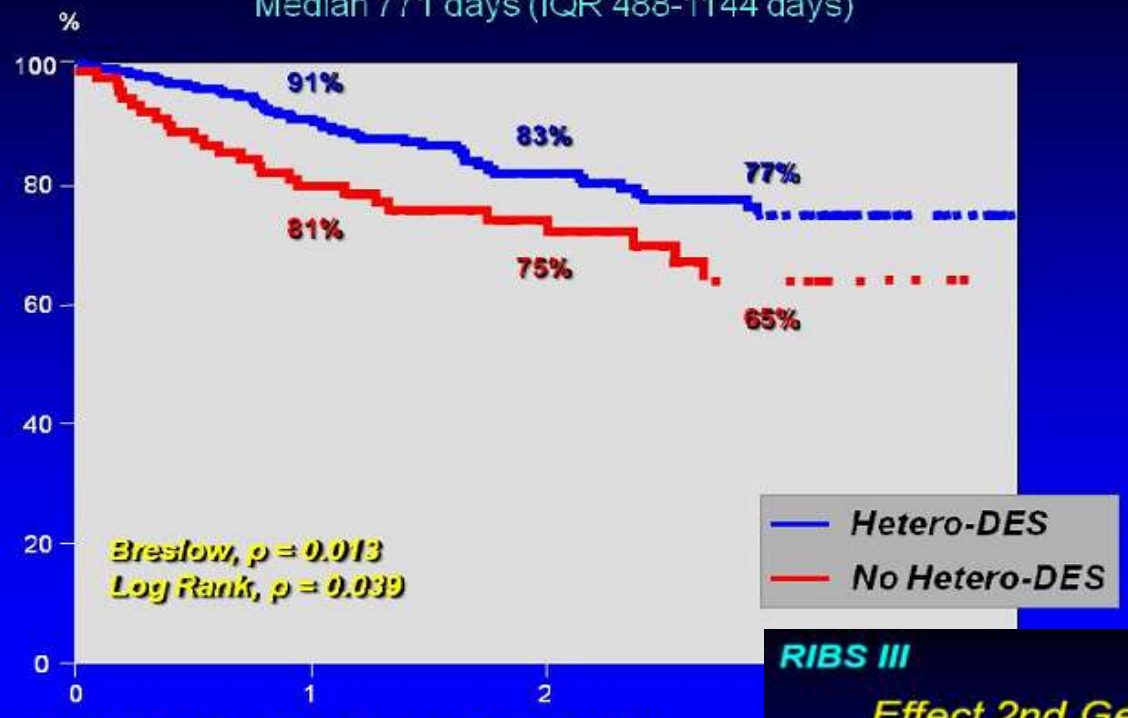
TLR



RIBS III

Event-Free Survival (MACE):

Median 771 days (IQR 488-1144 days)



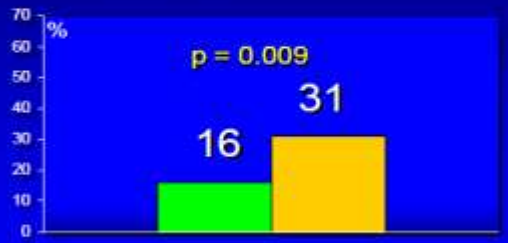
1ry Clinical End-point: MACE (Cardiac death, MI, TLR)

RIBS III

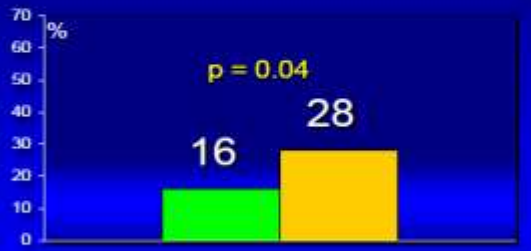
Effect 2nd Generation DES 33% (107/325 DES)

Recurrent Restenosis

All Patients



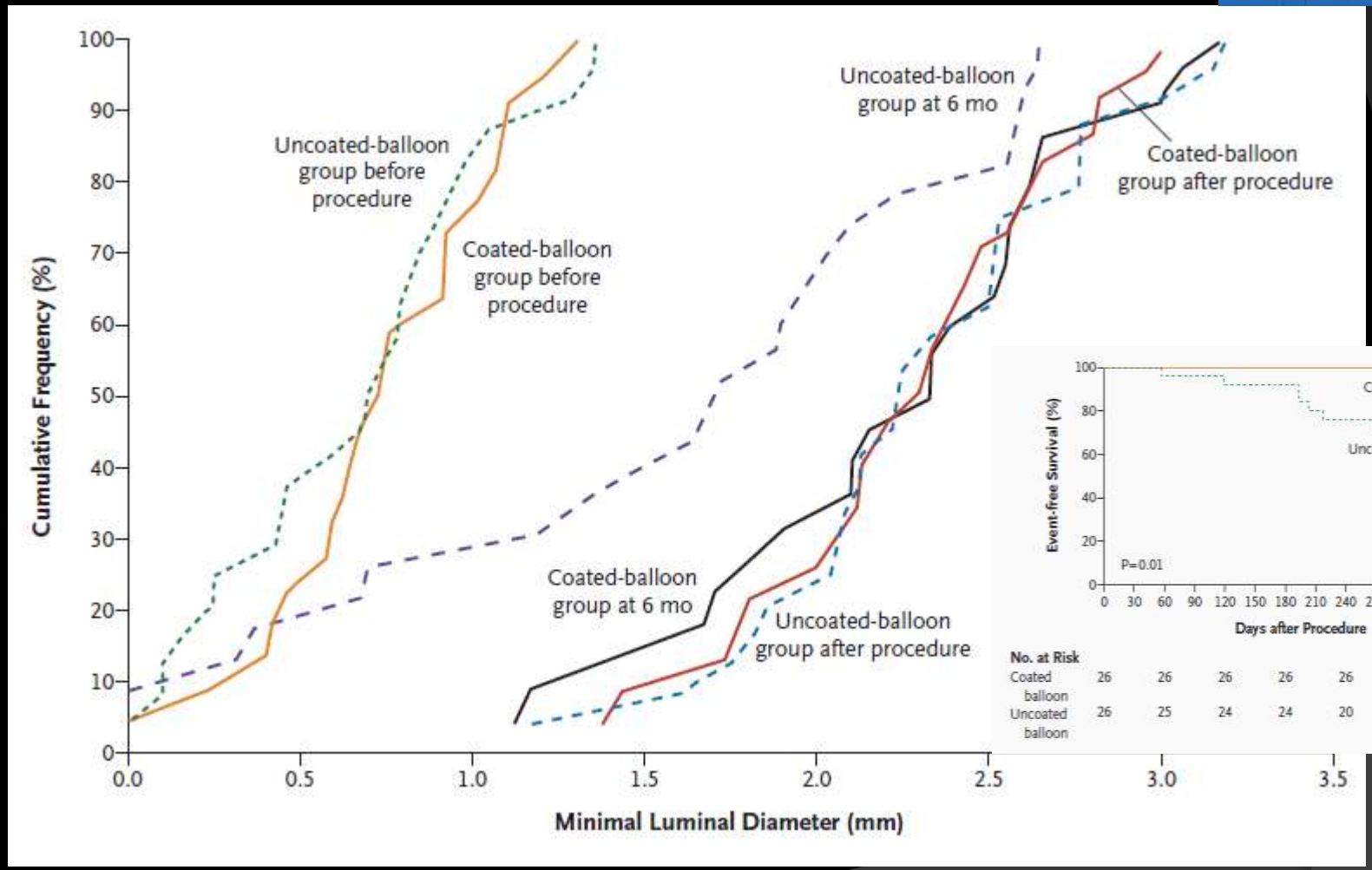
Patients treated with DES



DES in DES in DES in DES…

OR… something ELSE?

DRUG ELUTING BALLOONS



Scheller B, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med 2006;355:2113

TCT 2007 - LATE BREAKING STUDIES AND FIRST REPORT INVESTIGATIONS
WEDNESDAY, OCTOBER 24 2007, MAIN AREA

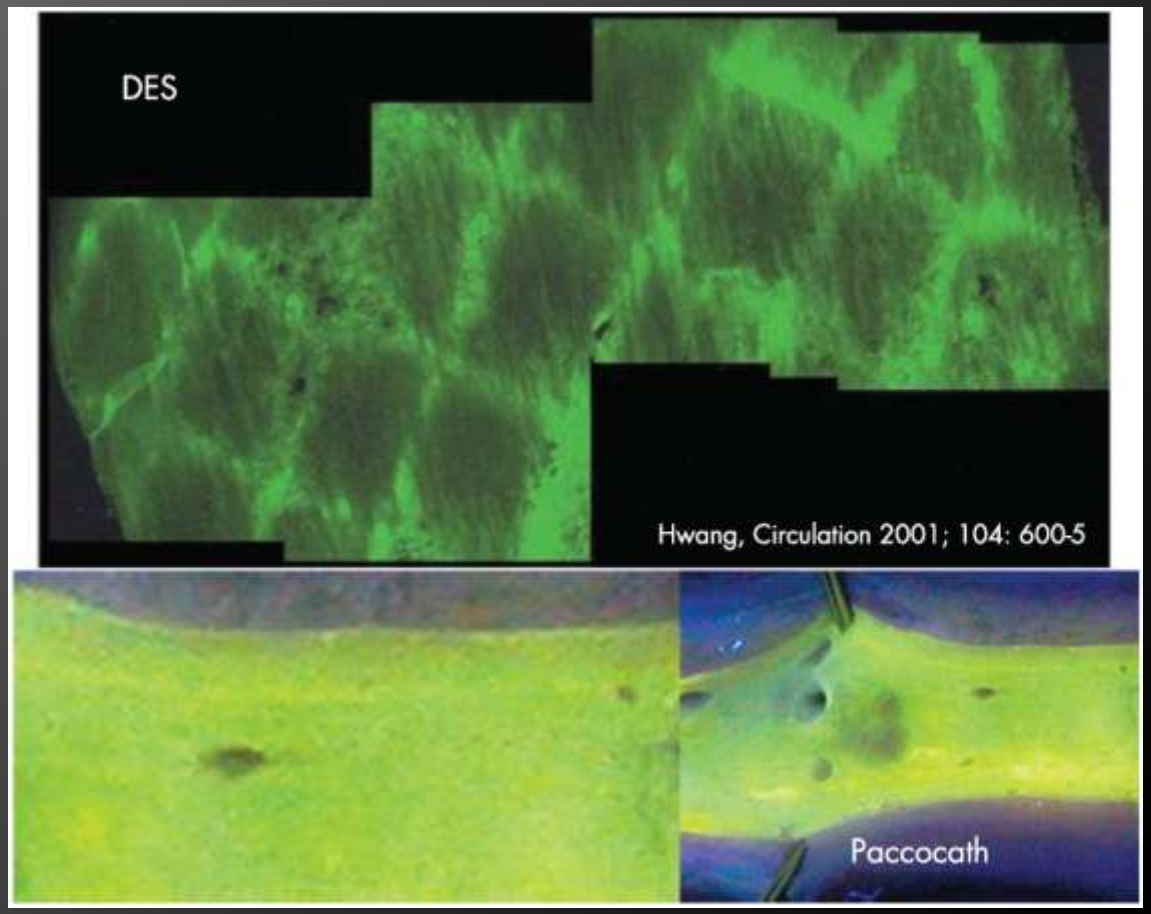
PACCOCATH ISR 1 AND 2: A PROSPECTIVE, RANDOMIZED TRIAL OF A PACLITAXEL-ELUTING BALLOON IN IN-STENT RESTENOSIS: 2-YEAR RESULTS

Bruno Scheller

for the Paccocath ISR Study Group

Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg / Saar, Germany

Drug-Eluting Balloon (DEB)



Drug-Eluting Stent

- Slow release
- Persistent drug exposure
- ~ 100 - 200 µg dose
- Polymer
- Stent mandatory

Drug-Eluting Balloon

- Immediate release
- Short-lasting exposure
- ~ 300 - 600 µg dose
- No polymers
- Premounted stent optional

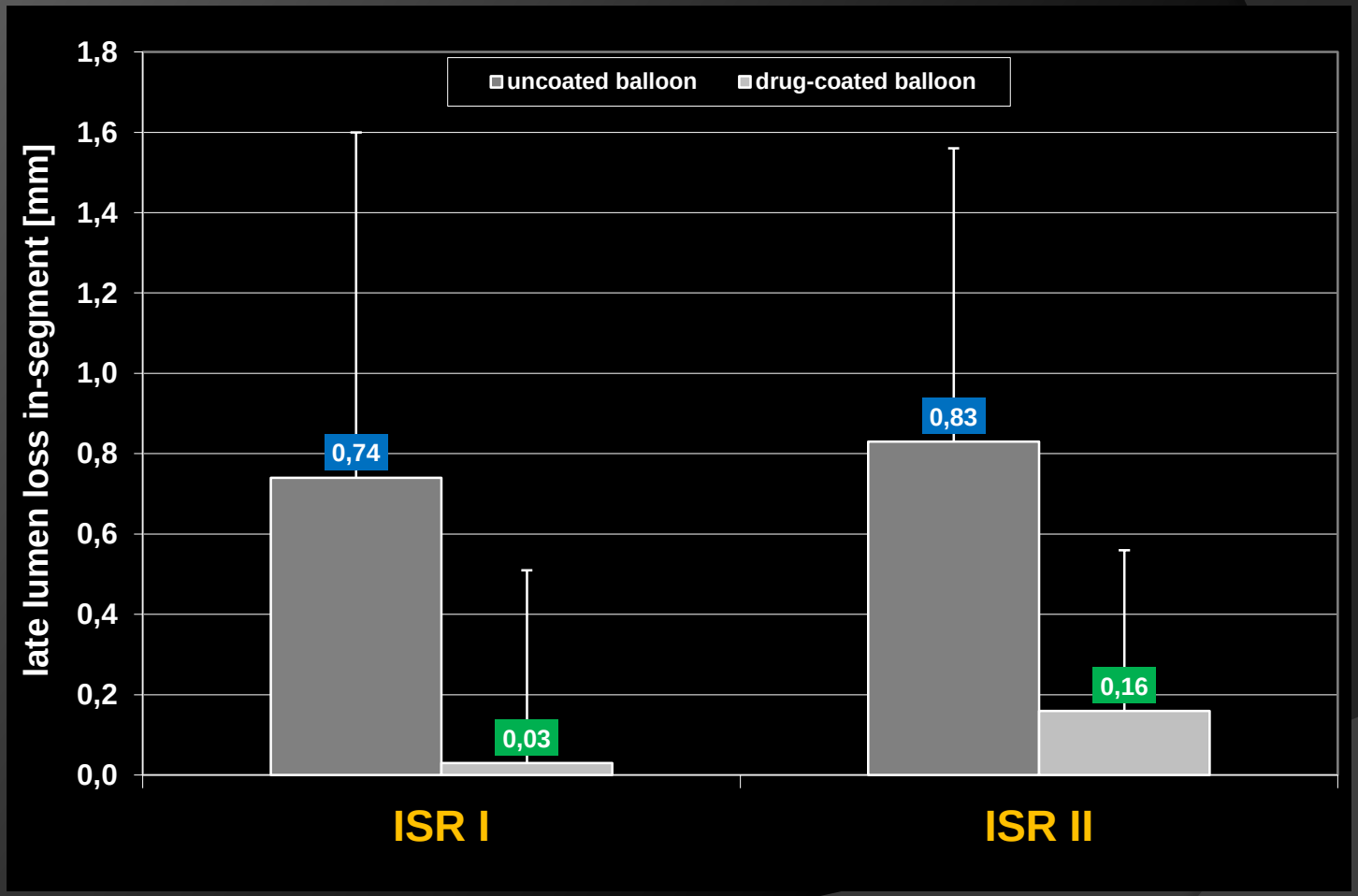
Heart 2007, 93: 539-41

Paccocath ISR I vs. II

	ISR I	ISR II	p
n	52	56	
Age	63.6 ± 10.8 years	68.0 ± 8.9 years	0.021
Female patients	15 (29 %)	20 (36 %)	0.289
Diabetes mellitus	10 (19 %)	18 (32 %)	0.095
Lesion length	18.0 ± 7.0 mm	18.8 ± 10.5 mm	0.669
Binary Restenosis in-segment	10 (43 %) vs. 1 (5 %) Δ 38 %	15 (56 %) vs. 2 (7 %) Δ 49 %	ISR I 0.002 ISR II 0.001
TLR 24 months	6 (23 %) vs. 0 Δ 23 %	14 (50 %) vs. 3 (11 %) Δ 39 %	ISR I 0.011 ISR II 0.001
MACE 24 months	9 (35 %) vs. 1 (4 %) Δ 31 %	16 (57 %) vs. 5 (18 %) Δ 39 %	ISR I 0.005 ISR II 0.003

Paccocath ISR I vs. II

Late lumen loss in-segment



PEPCAD II ISR Study: SeQuent™ DES vs. DEB

DES

- Slow and continuous drug release from stent struts
- ~100 -200 µg Paclitaxel / Sirolimus
- polymers with associated reactions
- Implies stent deployment DES

DEB (PACCOCATH)

- Instant and short term drug release from balloon
- ~ 300 -600 µg Paclitaxel
- No polymers
- No permanent mechanical irritation
- Stenting optional DEB

PEPCAD II ISR Study: Study Design

131 patients ≥ 18 years eligible for coronary revascularization for instent restenosis by means of PCI
Prospective. Randomized. Multi-center. Two-arm Phase-II Pilot Study

SeQuent™ Please
Drug Eluting Balloon Catheter
n=66

Taxus
Drug Eluting Stent
n=65

6 month, 1 and 3 year follow-ups

- Primary Endpoint: 6 month late lumen loss
- Secondary Endpoint: Procedural success (≤30% stenosis), 6 month binary restenosis, 6 month MACE, MACE at 1 and 3 years

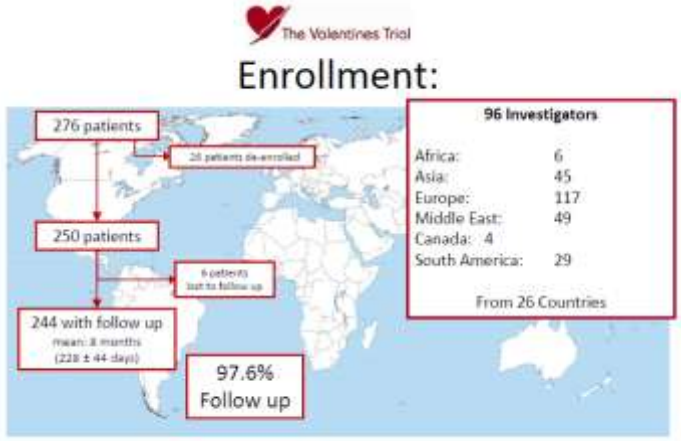
PEPCAD II ISR Study: Outcomes (AsT:N=126)

	DEB (n= 66)	DES (n=60)	P value=
Follow-up: clinical [months]	6.2 ± 0.8	6.2 ± 0.8	0.7
Follow-up: clinical [n]	64 (97.0%)	60 (100%)	0.4
Follow-up: angiographic	58 (87.9%)	54 (90.0%)	0.8
Late lumen loss [mm]	0.19 ± 0.38	0.47 ± 0.71	0.03
Binary restenosis in segment	2/58 (3.4%)	11/54 (20.4%)	0.007
TLR	2/64 (3.1%)	10/60 (16.7%)	0.02
Myocardial infarction	0/64 (0.0%)	*1/60 (1.7%)	1
Death	**2/64 (3.1%)	***1/60 (1.7%)	1
Total MACE (w/o noncardiac death)	3/64 (4.7%)	11/60 (18.3%)	0.02

*NSTEMI due to side branch occlusion
**1 cardiac, not lesion related; 2 non cardiac
*** non-cardiac death

The Valentines Trial

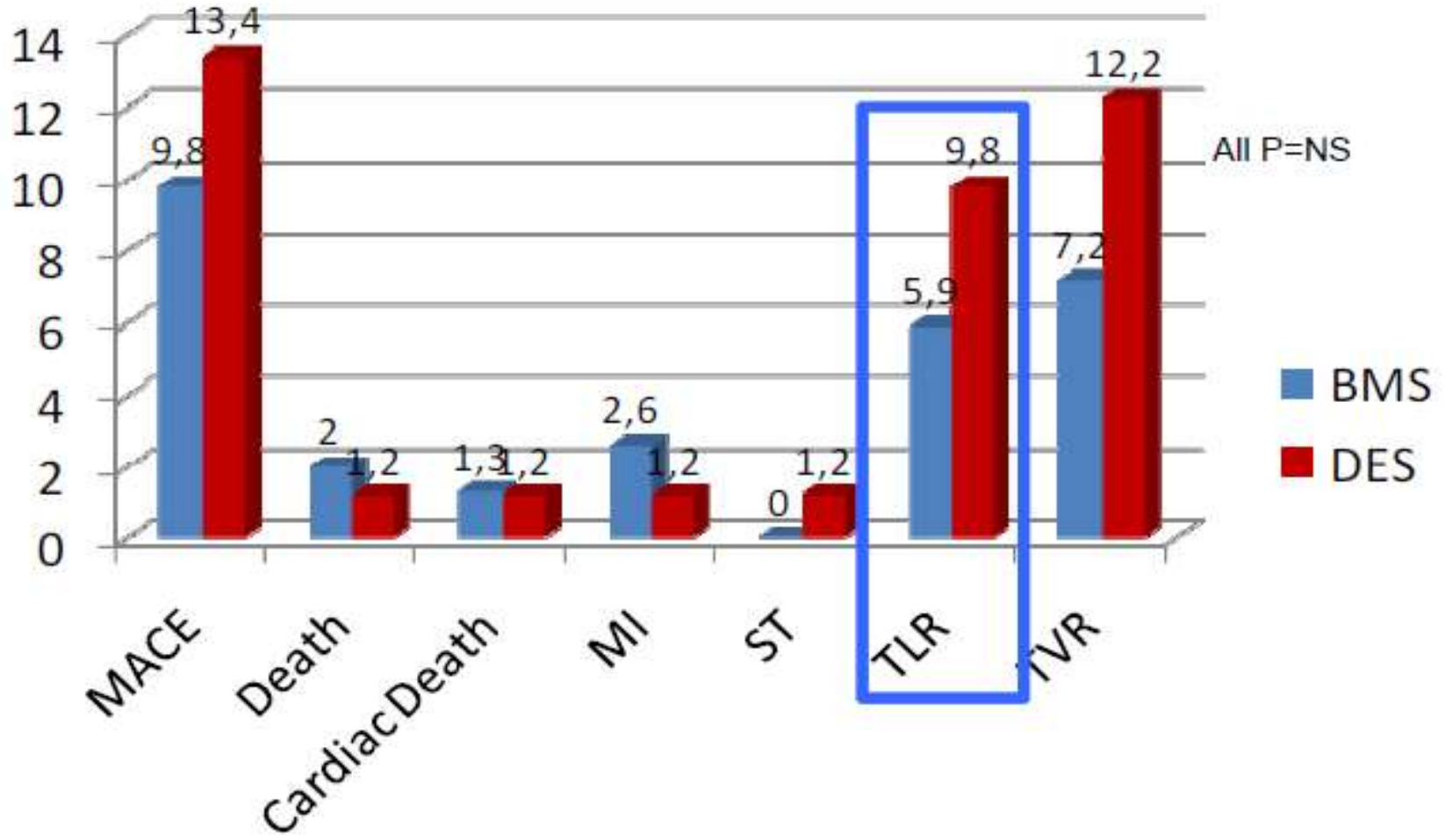
Professor Dr. Sigmund Silber, Munich, Germany
on behalf of the Valentines-I trial investigators



CRT2011 FEBRUARY 27 - MARCH 1
OMNI SHOREHAM HOTEL
WASHINGTON DC
iMPACT YOUR PRACTICE

The Valentines Trial

Results: BMS vs. DES: Follow-up (8 Months)

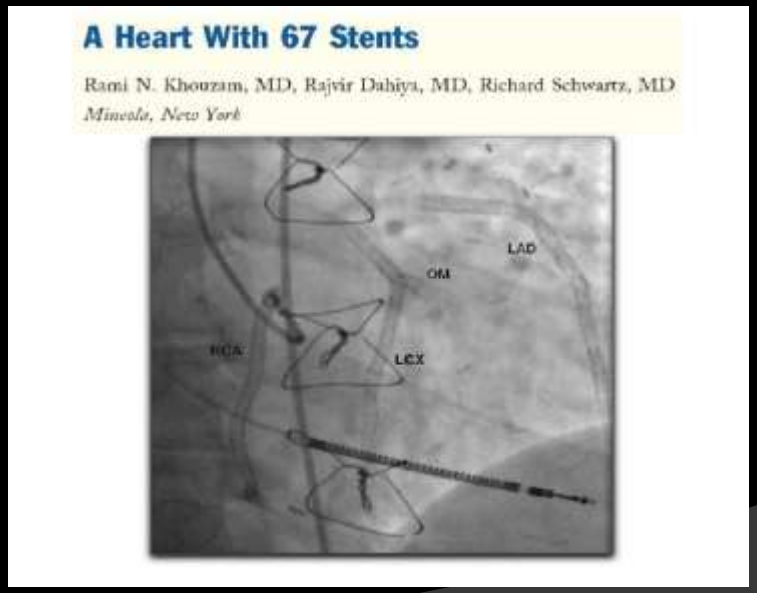


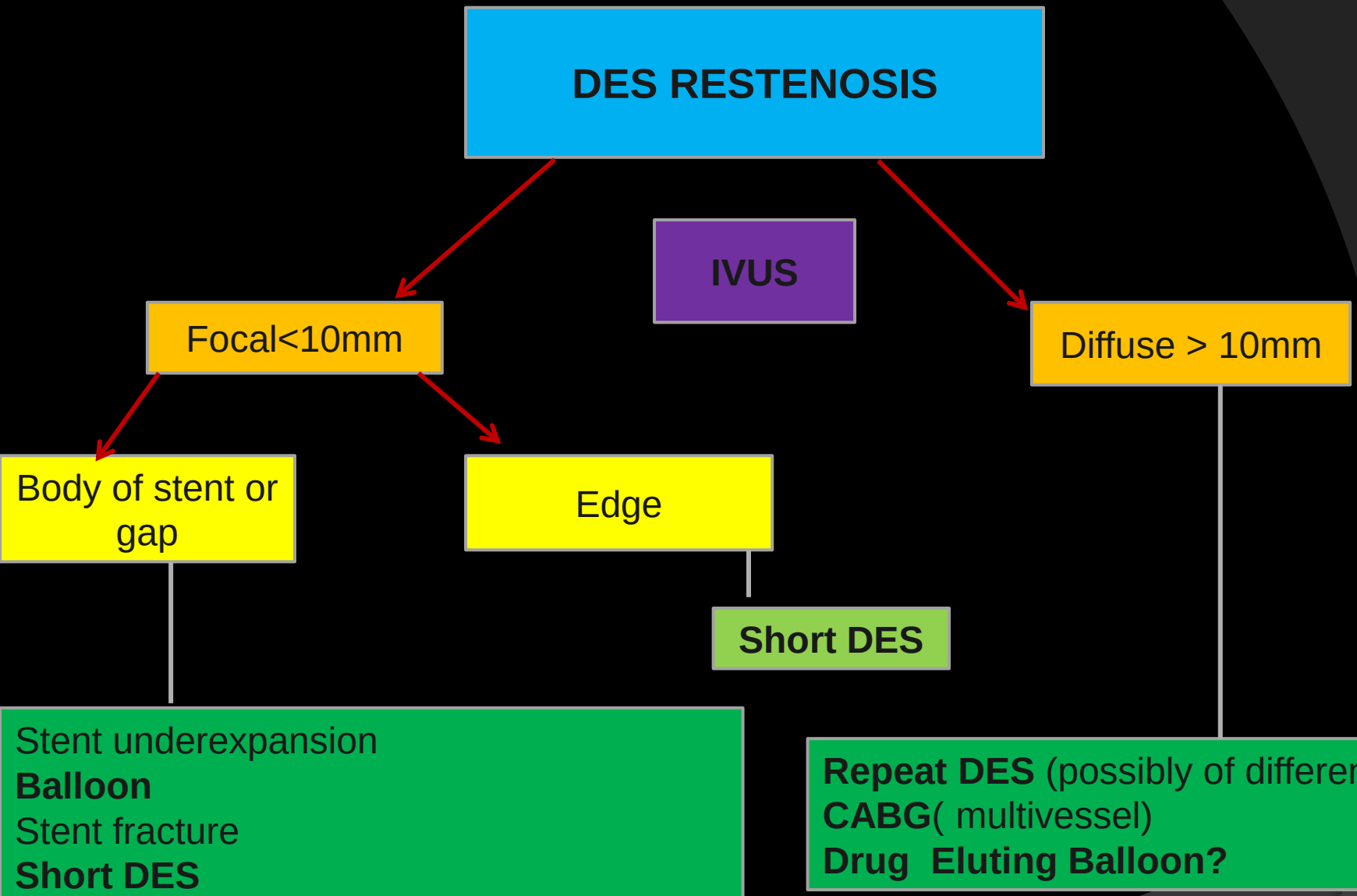
VascularBrachyTherapy

- DES obviate the need for VBT because of lower restenosis rates and comparitiveness in efficacy and logistics
- ST, edge effect stenosis, aneurysmal stenosis
- Most hospitals no longer perform the necessary set up
- Limited to pts. With DES ISR who are not candidates for reDES

CABG

- Multivessel DES with multivessel ISR
- single-vessel ISR at a very critical lesion location




DES RESTENOSIS
IVUS
Focal<10mm
Diffuse > 10mm
Body of stent or gap
Edge
Short DES
Stent underexpansion
Balloon
Stent fracture
Short DES
Others
Short DES (possibly of different type)
Balloon (consider cutting, scoring or DEB
Repeat DES (possibly of different type)
CABG(multivessel)
Drug Eluting Balloon?

Let's wrap it up…

- As the usage of DES in complex lesions increases, DES ISR will increase accordingly
- DES restenosis pattern differs from BMS: the predominant angiographic pattern is focal which in turn, is related to better prognosis
- Diffuse pattern does exist: high incidence of re-restenosis
- Multiple underlying mechanisms: mechanical, biological, technical
- Treat according to etiology

IICE "INNOVATIONS IN INTERVENTIONAL CARDIOLOGY AND ELECTROPHYSIOLOGY"

ΚΑΡΔΙΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ ΒΟΡΕΙΟΥ ΕΛΛΑΔΟΣ

4ο ΣΥΝΕΔΡΙΟ ΕΠΕΜΒΑΤΙΚΗΣ ΚΑΡΔΙΟΛΟΓΙΑΣ ΚΑΙ ΗΛΕΚΤΡΟΦΥΣΙΟΛΟΓΙΑΣ

24 | 25 | 26 ΝΕΜΒΡΙΟΥ 2011
ELECTRA PALACE HOTEL
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Table 6 Clinical and Angiographic Outcomes After Percutaneous Treatment of DES ISR

Study/First Author (Ref. #)	Year	No. of Lesions	Type of DES	Follow-up Duration	TLR	Angiographic Restenosis	Treatment Modalities Used
Randomized trial							
ISAR-DESIRE 2	2010	450	SES	6–8 months	16.7%	18.0%	PES 50%, SES 50%
Observational studies							
Lemos et al. (68)	2004	24	SES	9.3 months	20.8%	42.9%	BA 11%, BMS 4%, PES 41%, SES 44%
Moussa et al. (70)	2006	22	SES	12 months	23.0%	N/A	BA 13.5%, BMS 82%, VBT 4.5%
Lee et al. (67)	2006	140	SES	7.2 ± 1.8 months	14.0%	N/A	PES 100%
Torguson et al. (71)	2006	111	PES 22%, SES 78%	8 months	13.5%	N/A	PES 11%, SES 34%, VBT 55%
Kim et al. (66)	2006	58	PES 47%, SES 53%	12 months	5.2%	16.7%	BA 19%, SES 57%, VBT 24%
Cosgrave et al. (64)	2006	250	PES 34%, SES 66%	9 months	14.4%	28.4%	BA 38%, DES 62%
Mishkel et al. (69)	2007	108	SES, PES	15 ± 6 months	28.2%	N/A	BA 1%, BMS 18%, DES 80%, VBT 1%
Garg et al. (65)	2007	116	SES, PES	12 months	15.7%	N/A	SES, PES
Solinas et al. (20)	2008	152	PES 22%, SES 78%	12 months	8.3%	N/A	BA 16%, DES 84%
Bonello et al. (72)	2008	122	N/A	12 months	10.0%	N/A	VBT
Chatani et al. (73)	2009	140	SES	2 yrs	33.7%	32.5%	OTHER 35%, PES 22%, SES 43%
Steinberg et al. (22)	2009	119	N/A	12 months	22.2%*	N/A	DES
Rathore et al. (23)	2010	351	SES	9 months	37.0%*	41.1%	BA 67%, BMS 1%, PES 5%, SES 17%
Tagliareni et al. (75)	2010	252	PES 39%, SES 57%, ZES 4%	23 ± 10 months	11.8%	N/A	BA 53%, DES 47%
Singh et al. (74)	2010	319	N/A	3.2 yrs	15.0%	N/A	N/A

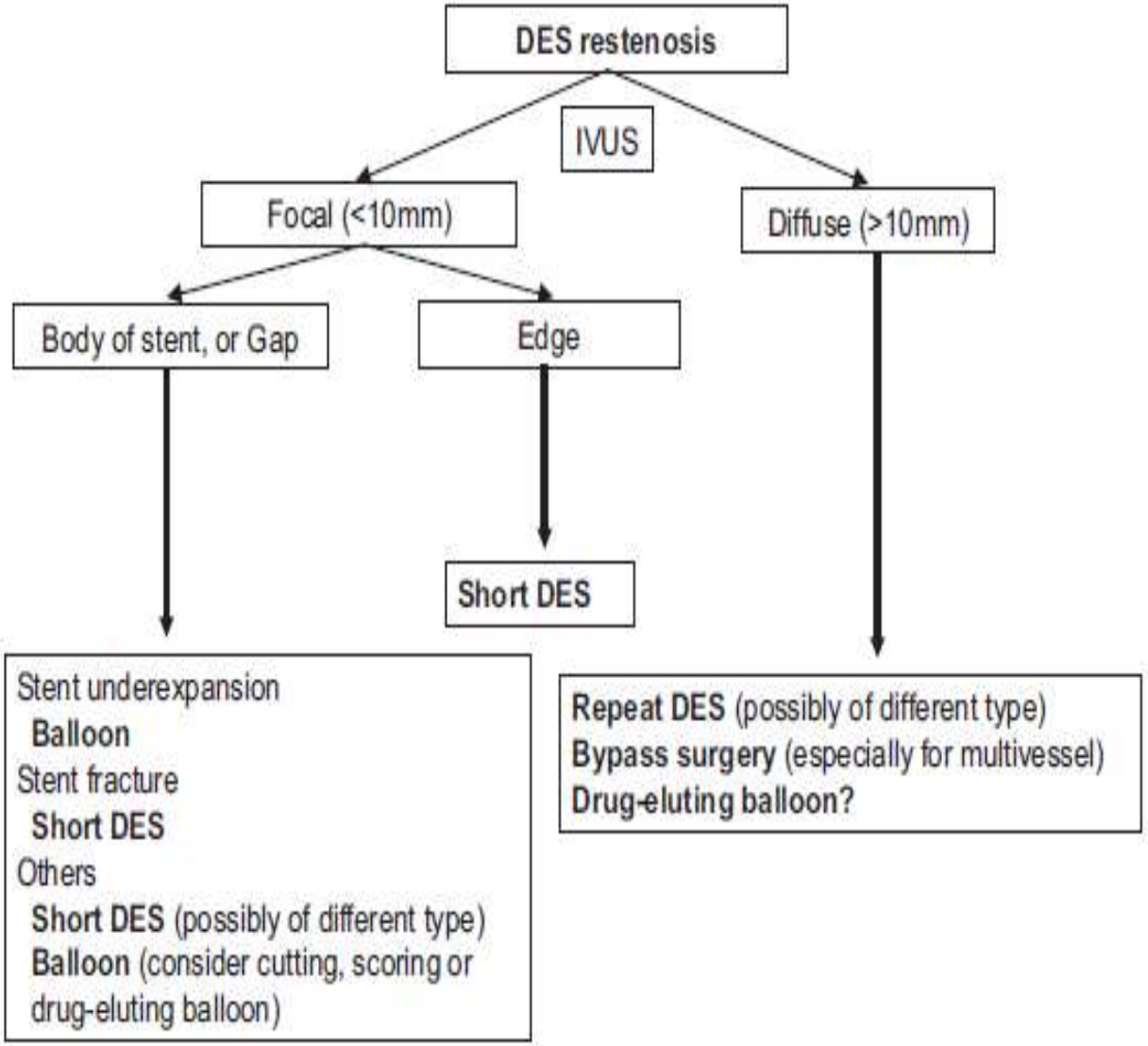
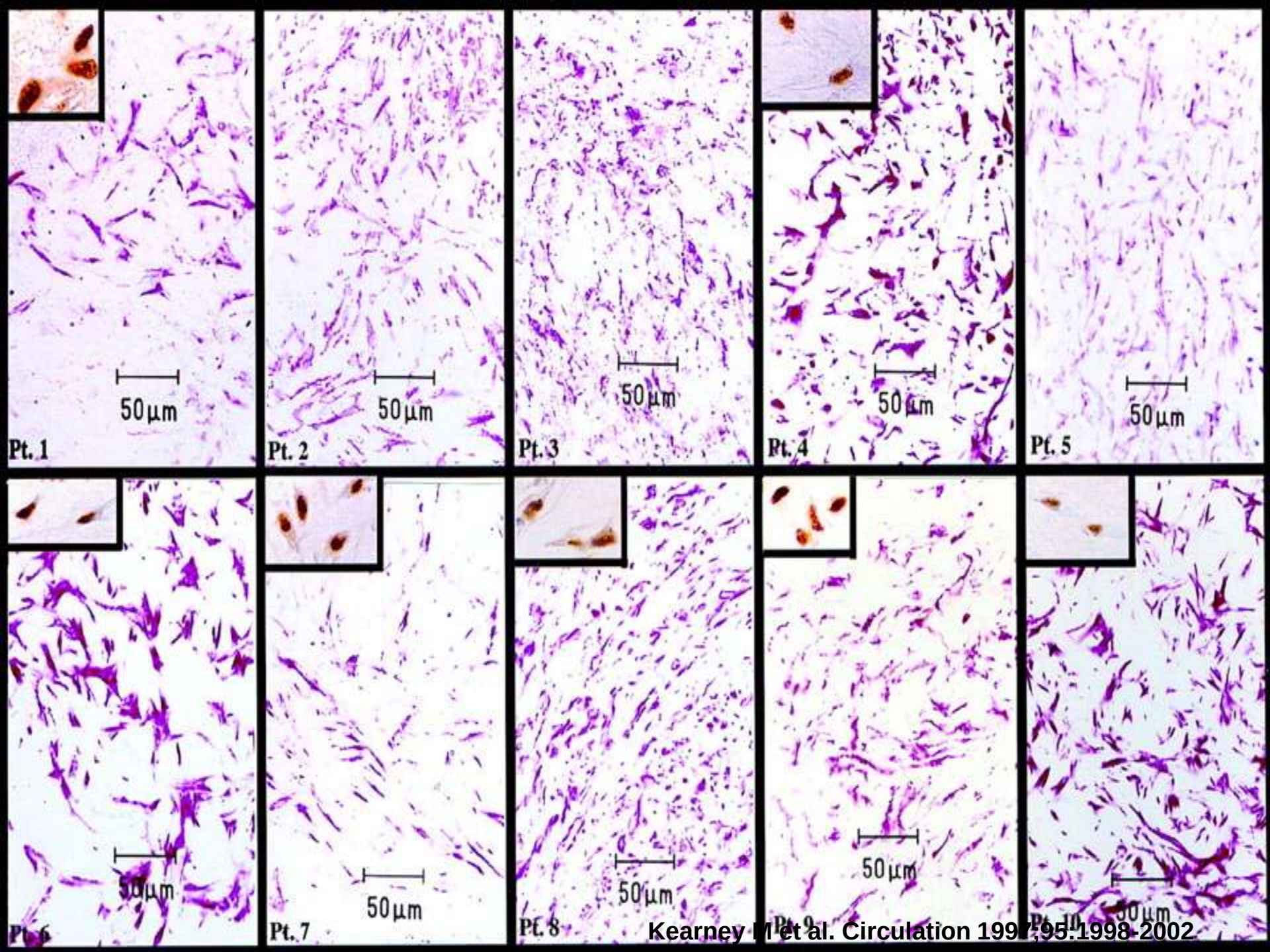


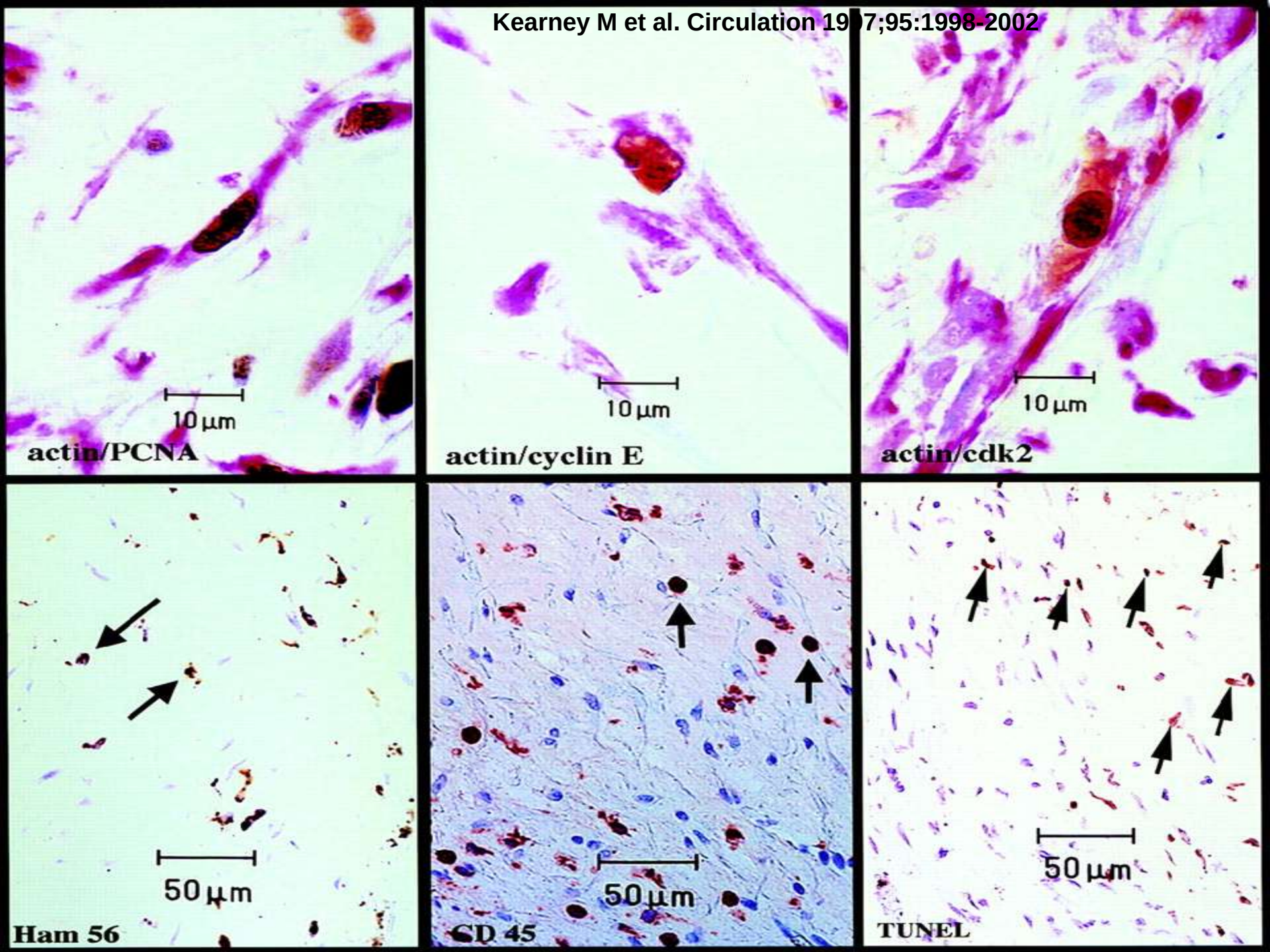
Figure 3 **Algorithm for the Treatment of DES Restenosis**

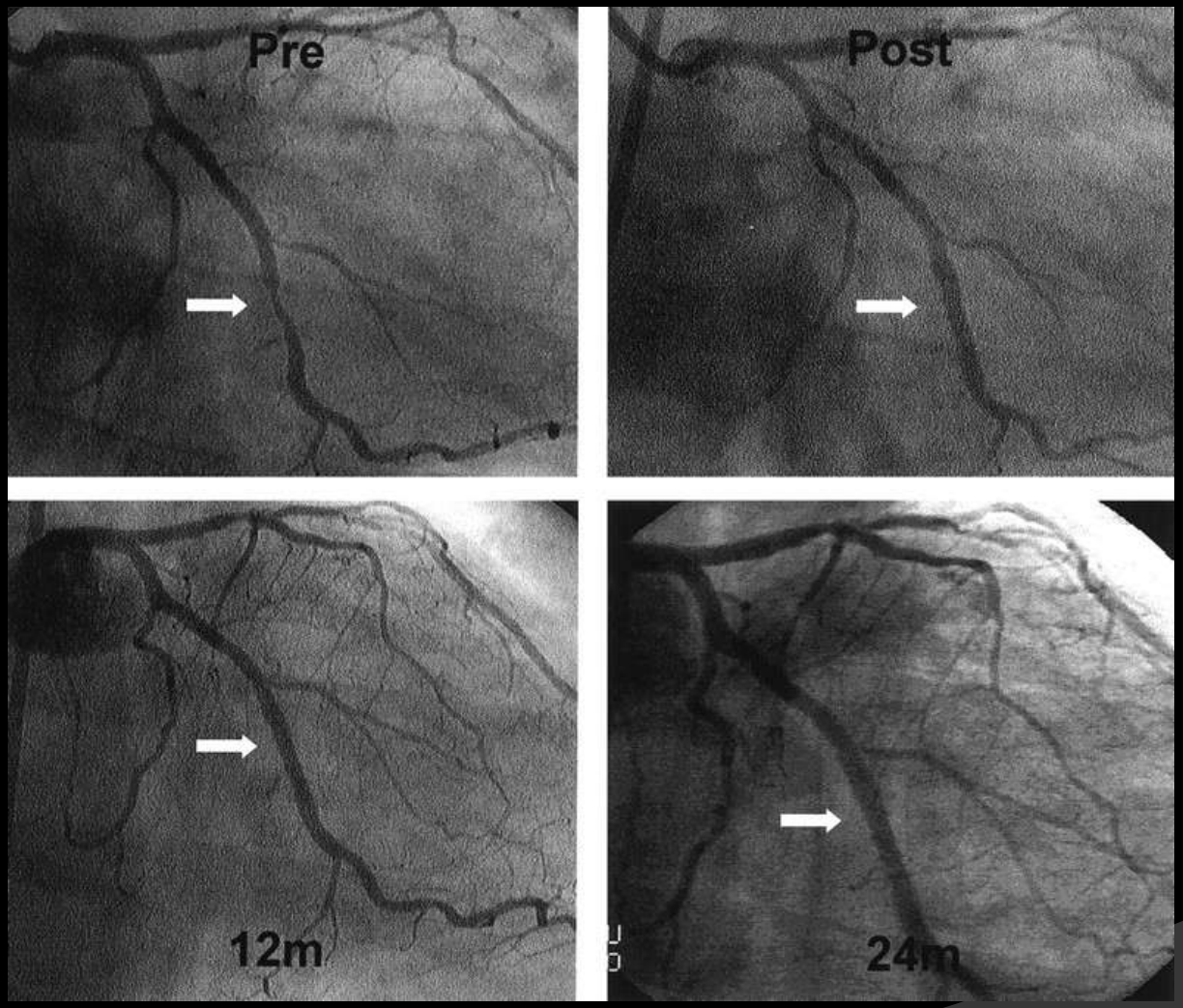
DES = drug-eluting stent(s); IVUS = intravascular ultrasound.



Kearney M et al. Circulation 1997;95:1998-2002

Kearney M et al. Circulation 1997;95:1998-2002

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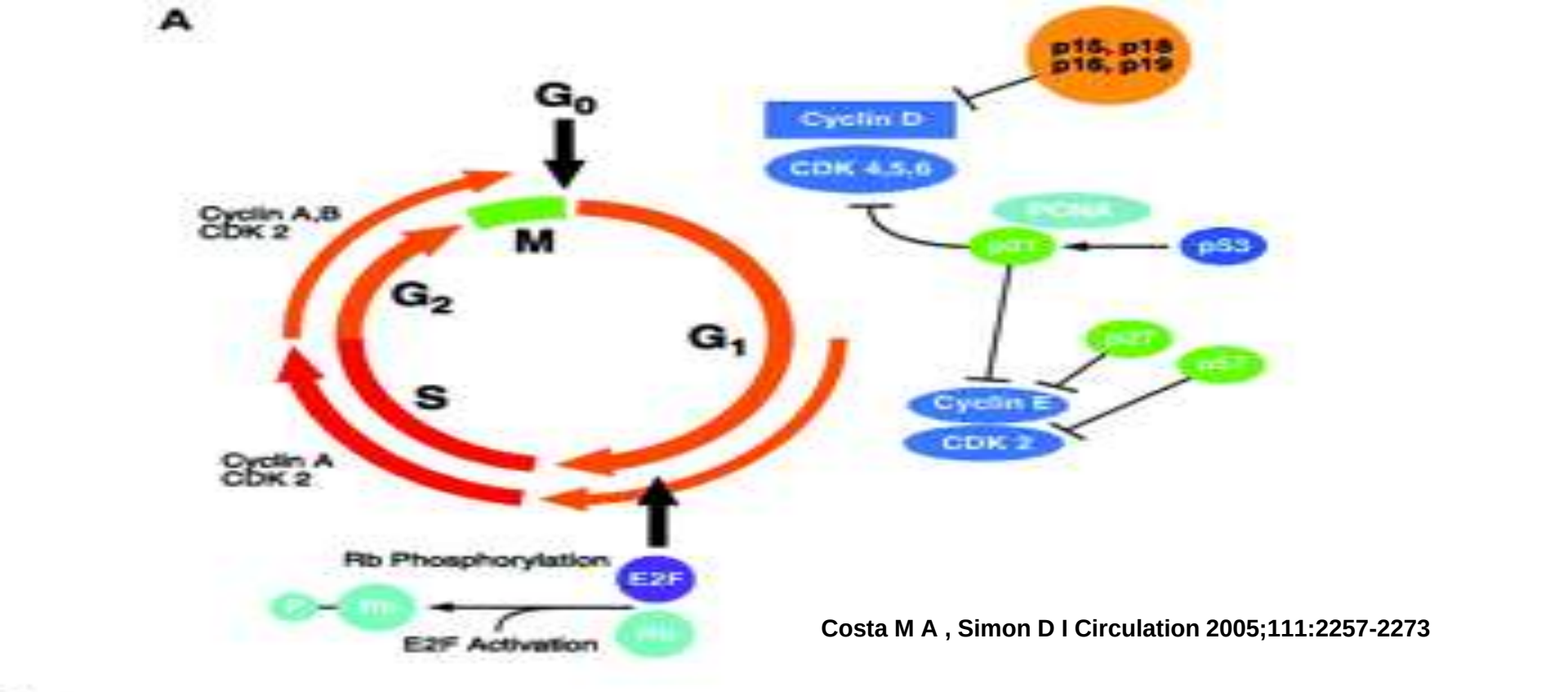
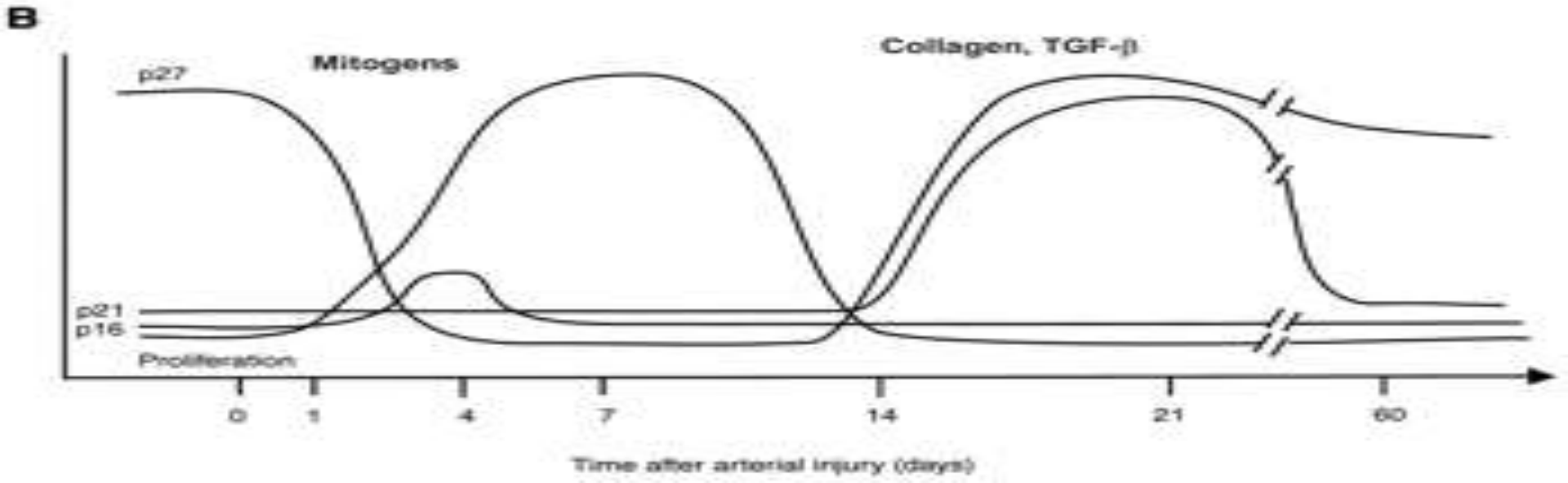
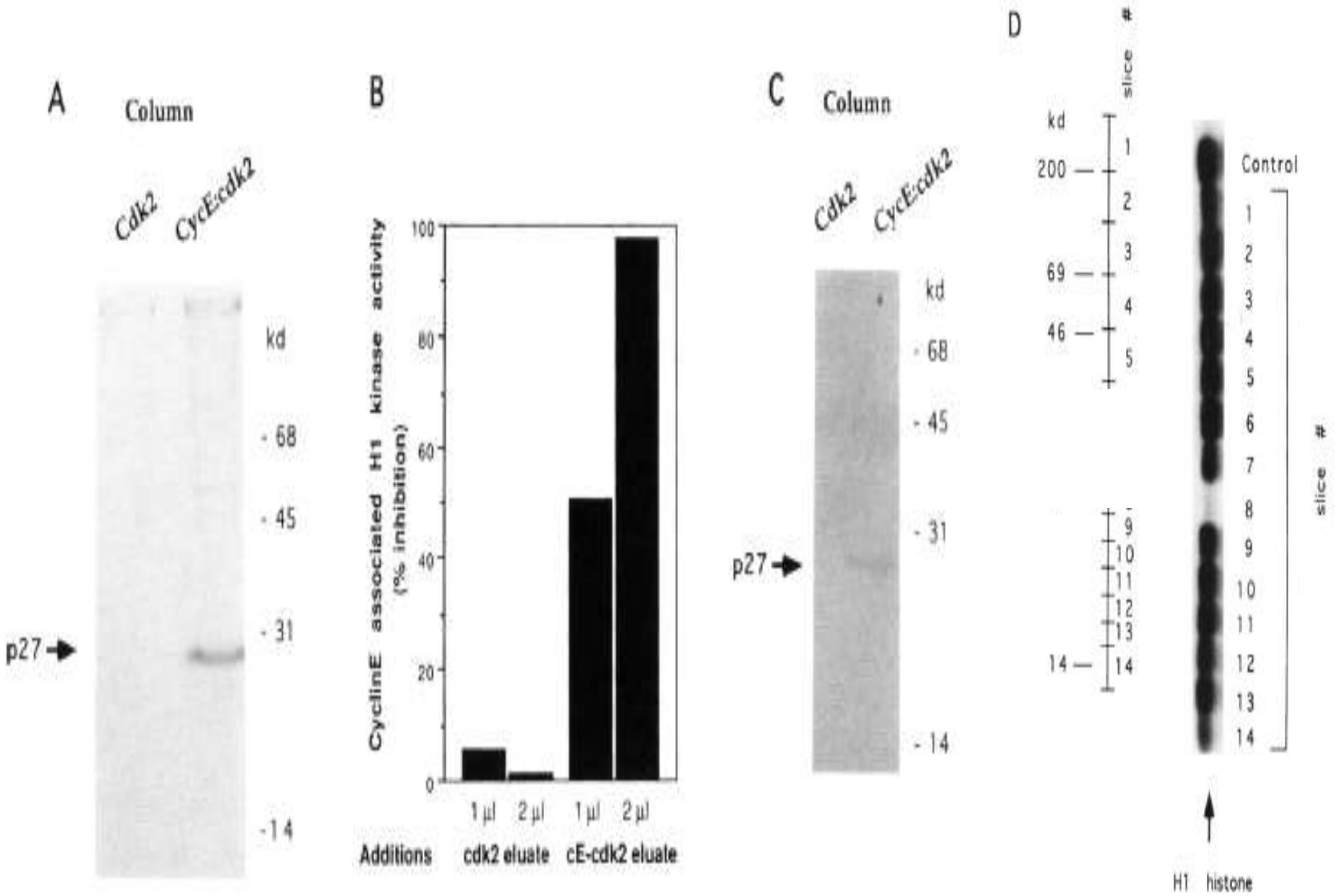


Costa M A , Simon D I Circulation 2005;111:2257-2273

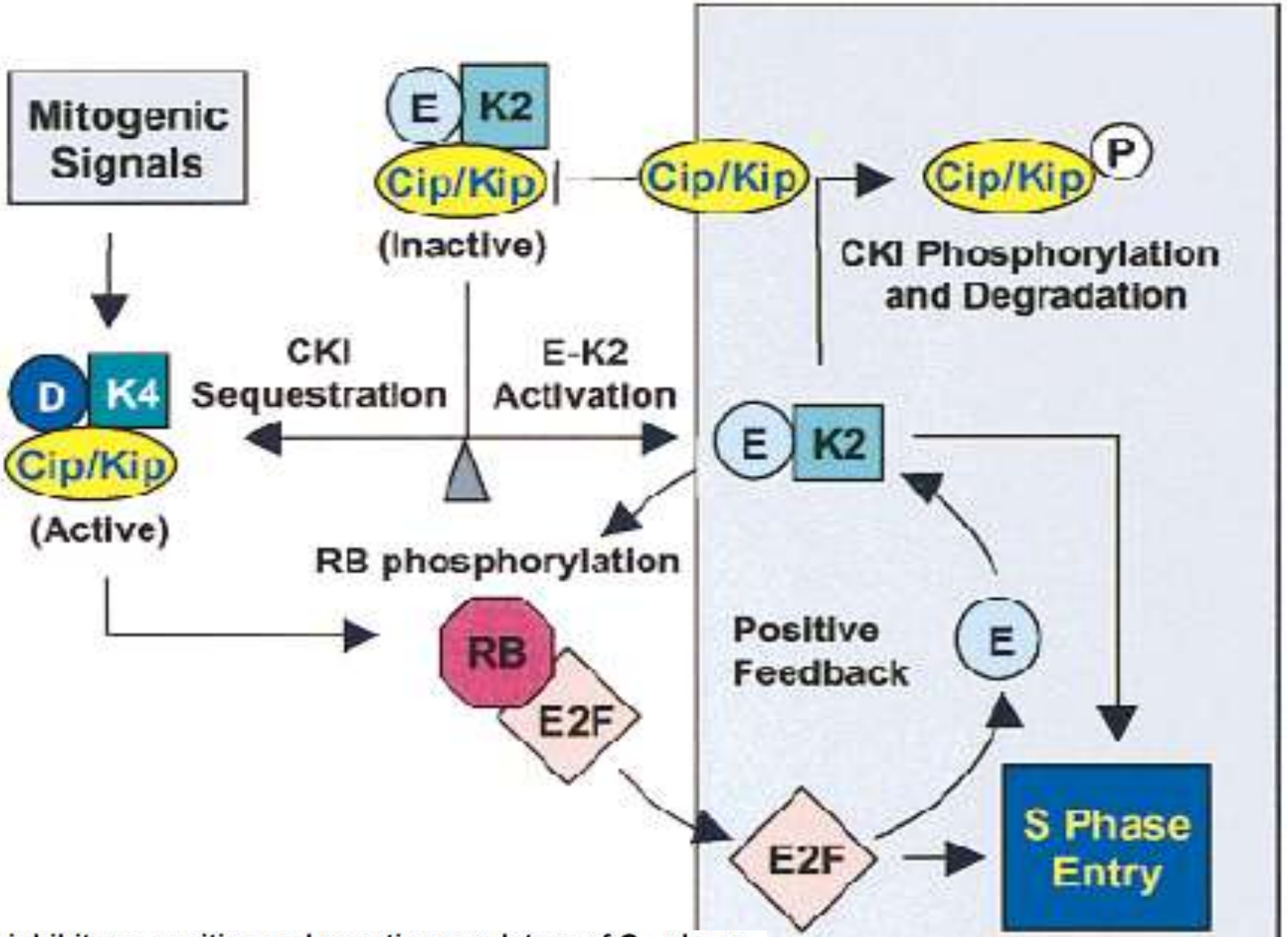




p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest.

K Polyak, J Y Kato, M J Solomon, et al.

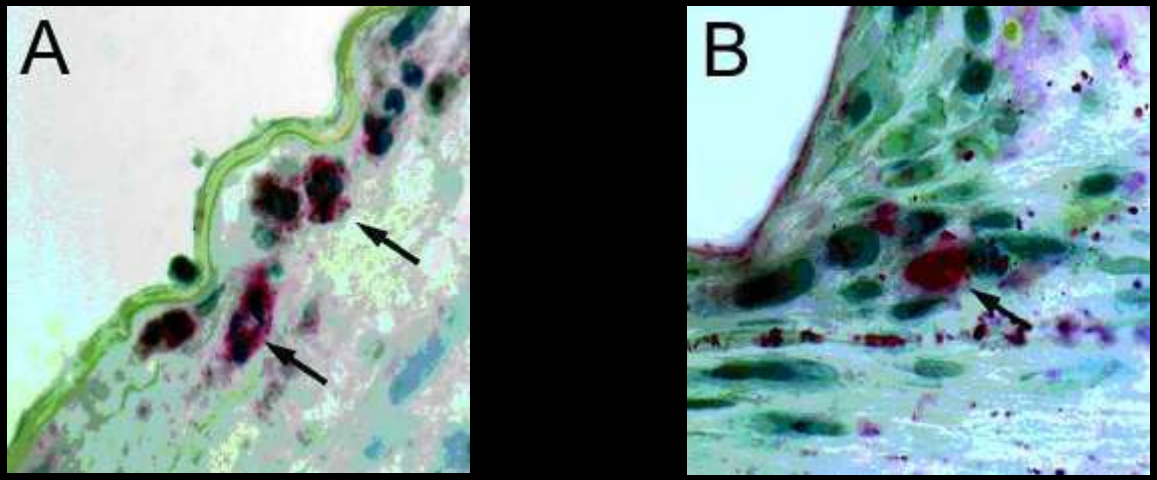
Genes Dev. 1994 8: 9-22



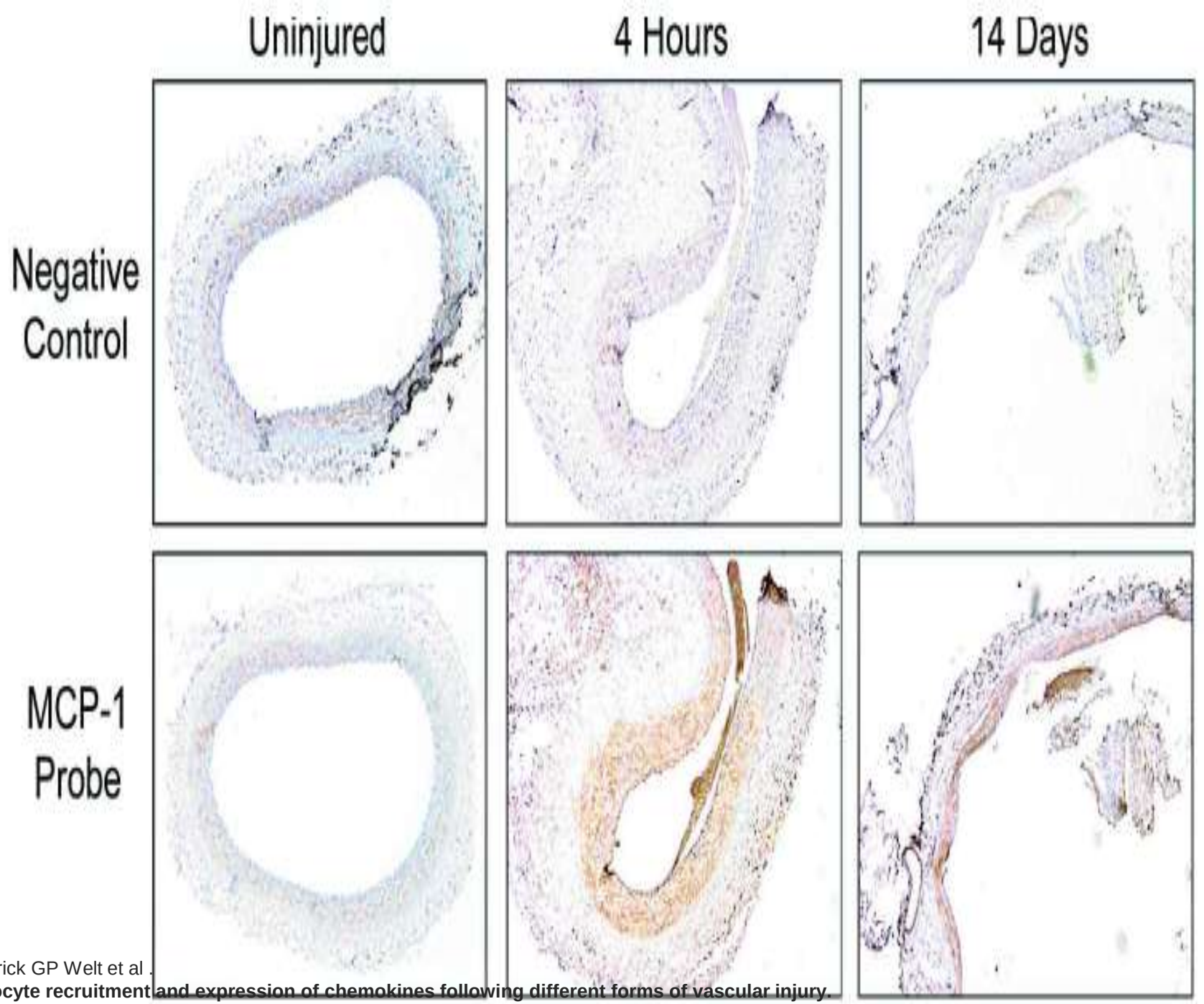
CDK inhibitors: positive and negative regulators of G_1-phase progression

Charles J. Sherr and James M. Roberts

Genes Dev. 1999 13: 1501-1512



Frederick GP Welt et al .
Leukocyte recruitment and expression of chemokines following different forms of vascular injury.
Vasc. Med. 2003 8: 1



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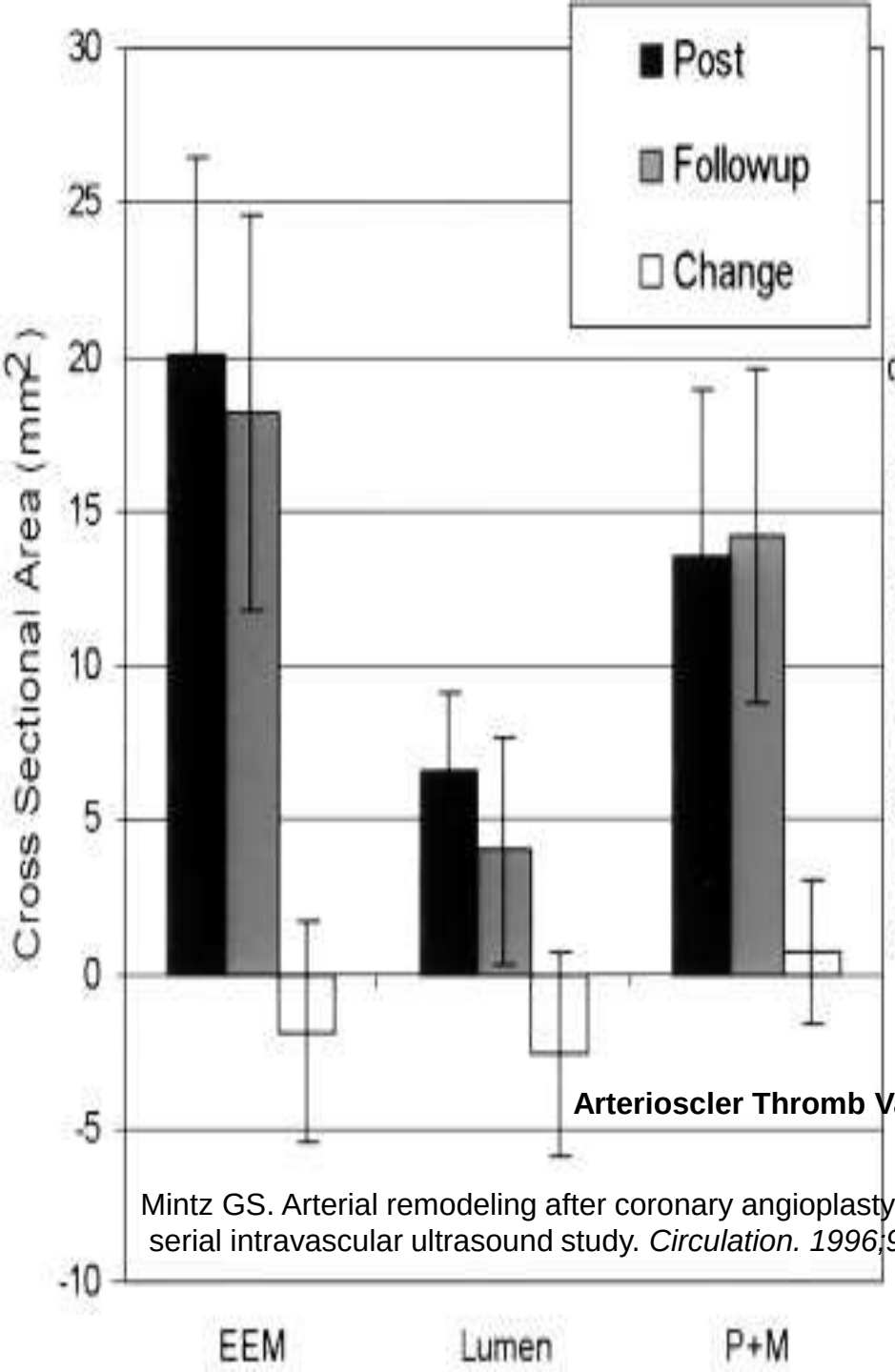
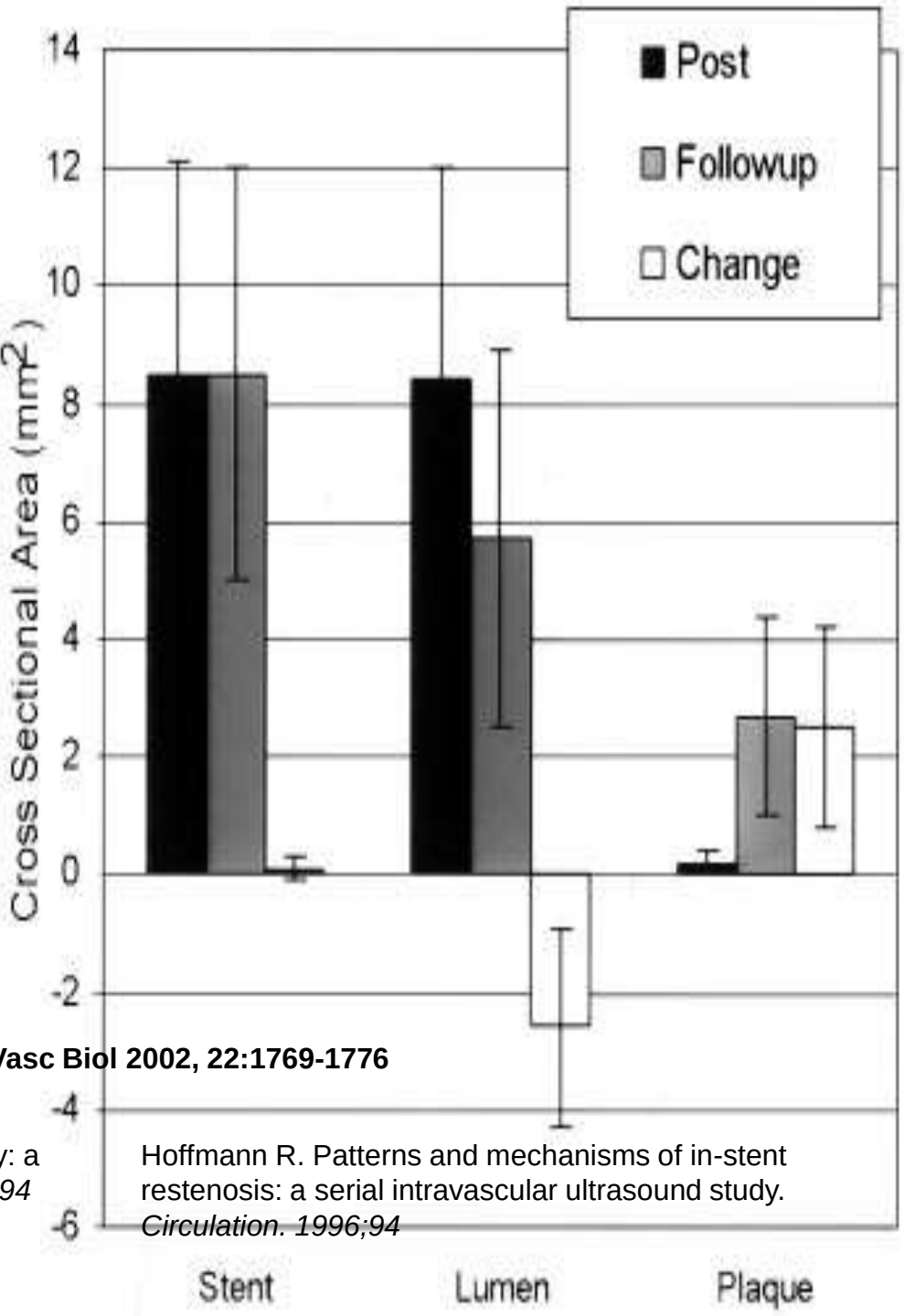
sc. Med. 2003 8: 1





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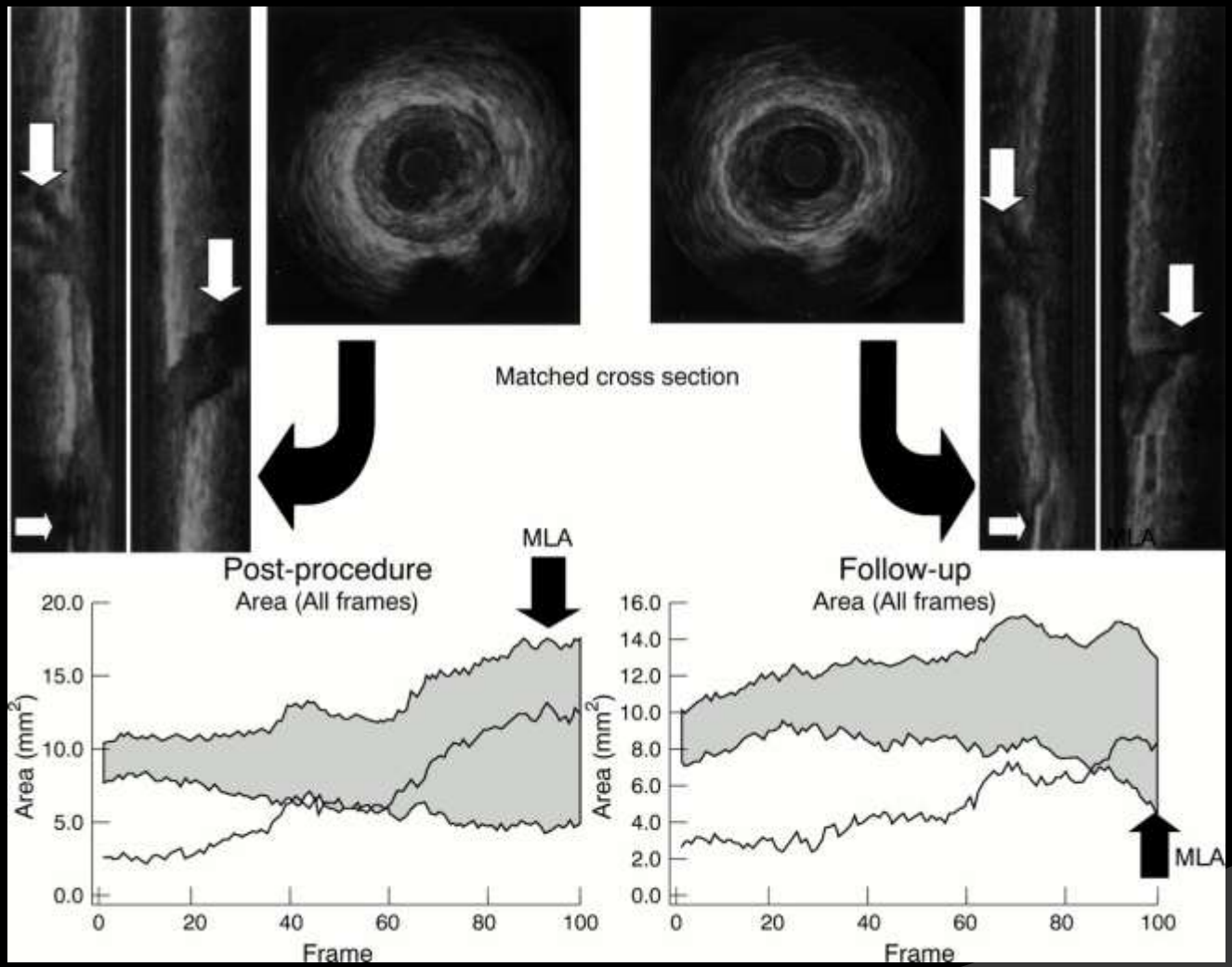

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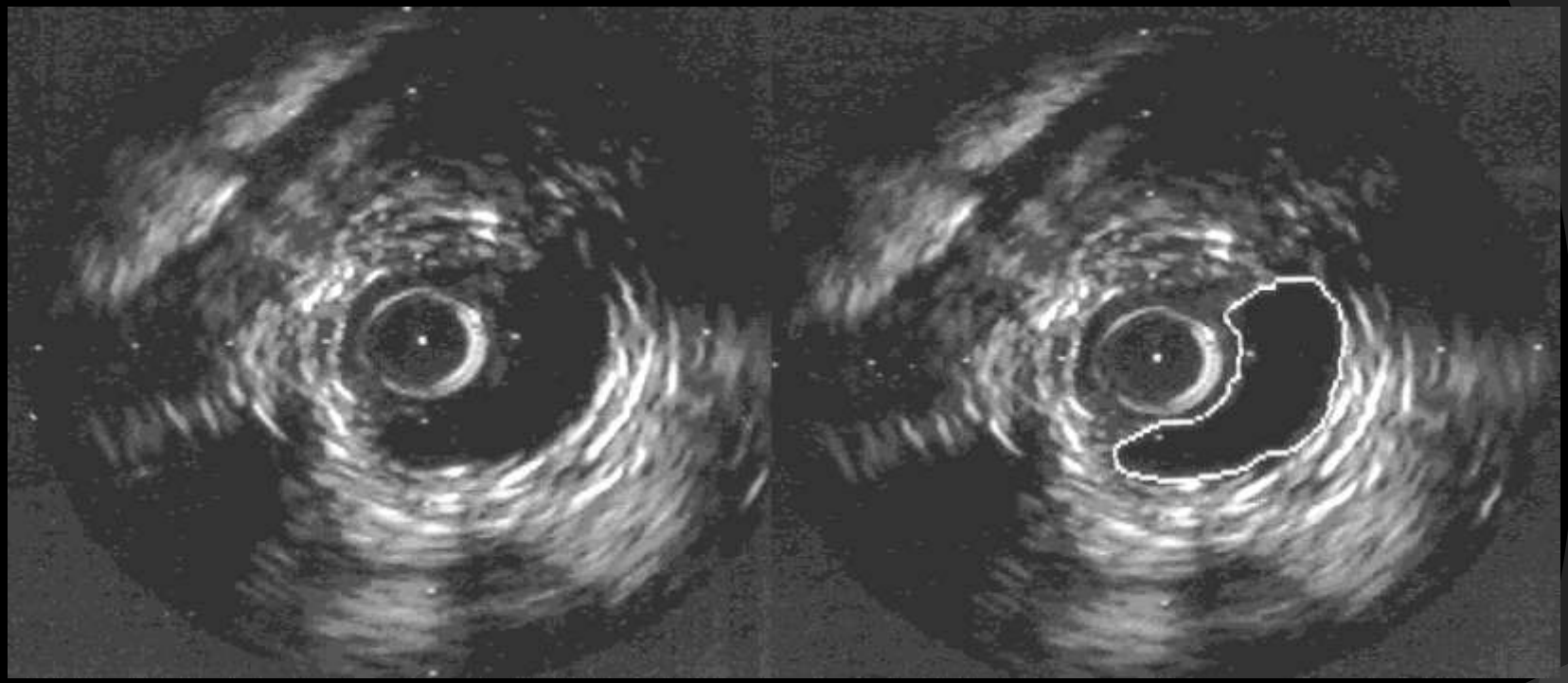

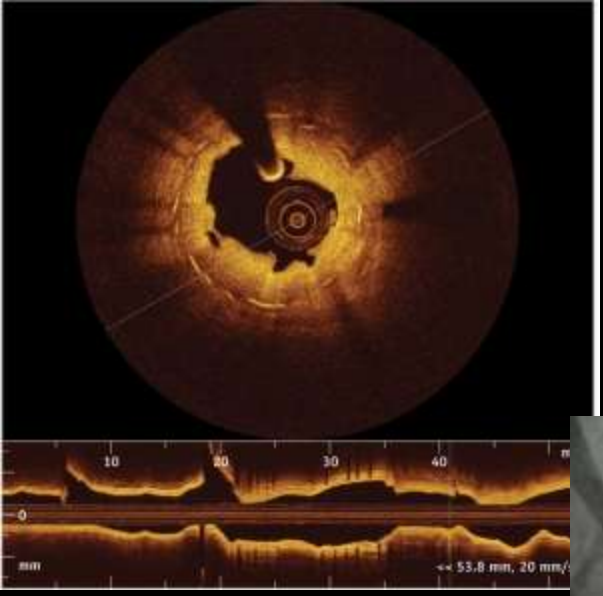
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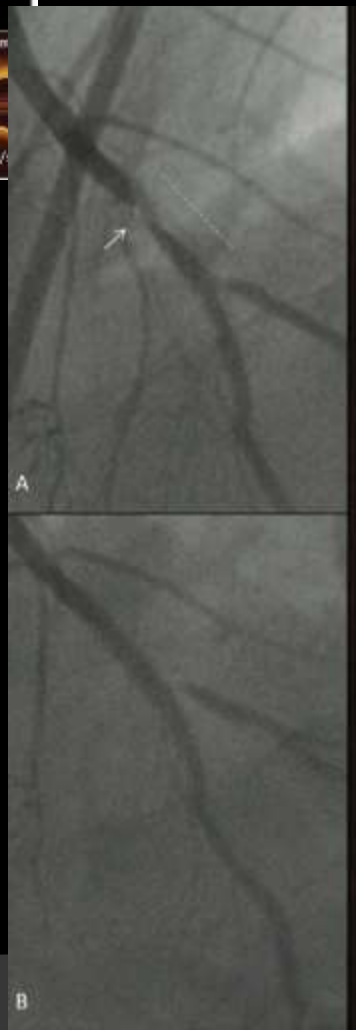
A
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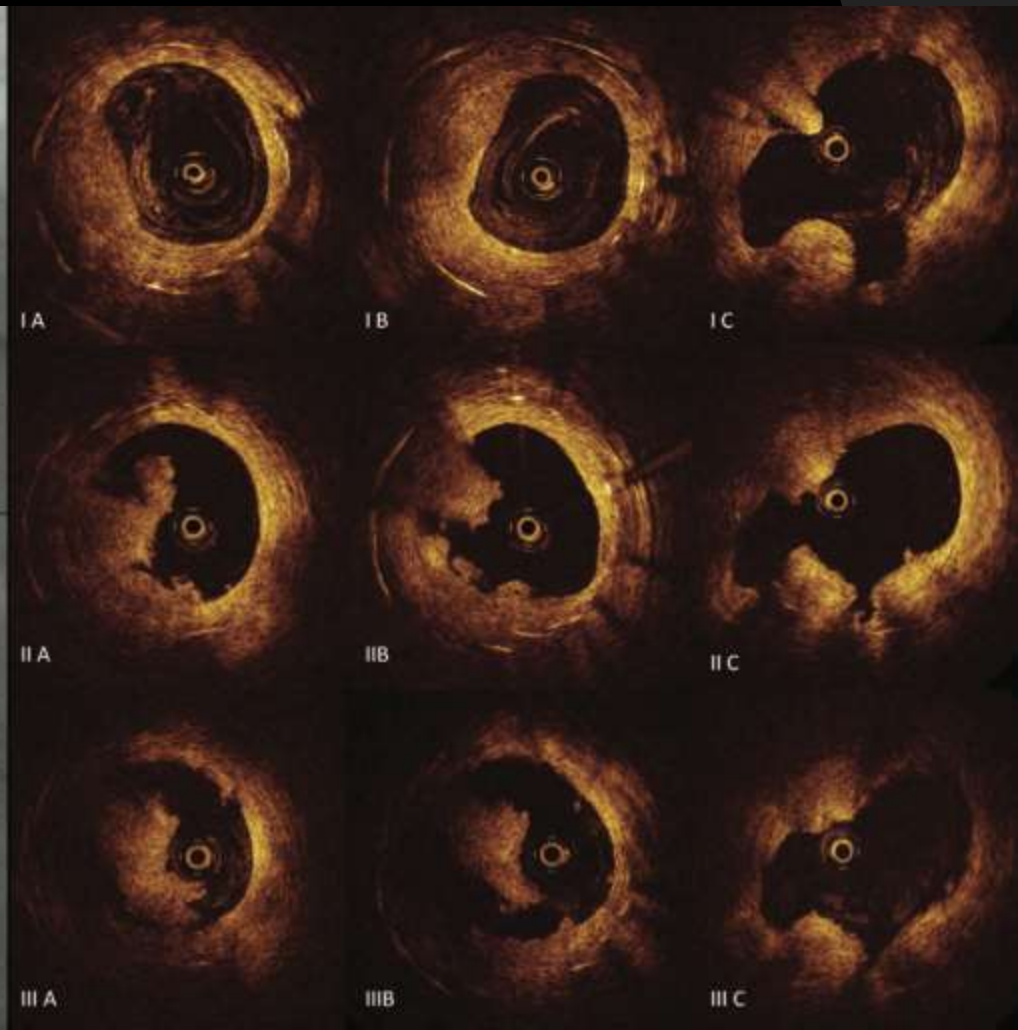
I A
I B
I C
II A
IIB
II C
III A
IIIB
III C

Do All Lesions Heal the Same?