Assessment of DES Restenosis: New IVUS Insights into the Mechanisms

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Cardiovascular Research Foundation

Editorial

Vascular Remodeling

Honey, I Think I Shrunk the Artery

Jeffrey M. Isner, MD

The mechanisms responsible for both favorable and unfavorable outcomes of balloon angioplasty continue to invite controversy. Nowhere is this more profound than in the case of restenosis, clearly the most frequent complication of percutaneous revascularization. Despite the fact that 185 patents describing treatment strategies designed to limit restenosis have been issued during the past decade,[1] until recently successful clinical application of derivative therapies has been virtually without success. There can be little doubt that our lack of understanding regarding the mechanisms responsible for restenosis has provided the underpinnings of our inability to successfully prevent its recurrence.

See p 2816

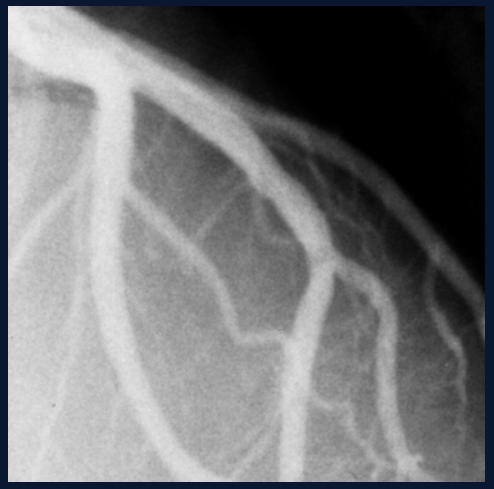
The vast majority of medical therapies designed to preempt restenosis have been predicated on the assumption that smooth muscle cell (SMC) proliferation constitutes the principal pathogenetic basis for restenosis. This concept has its origins in the fundamental studies of human atherosclerotic arteries that identified SMC accumulation within the neointima of (primary) lesions obtained at necropsy[2-4] and in supportive experimental observations in a variety of animal models.[5-10] Subsequently, beginning with the report of Austin et al,[11] necropsy examination of sporadic patients dying at various intervals after percutaneous revascularization[12-21] disclosed foci of hypercellularity, including cells with phenotypic characteristics of vascular SMCs, at the original site of balloon angioplasty.

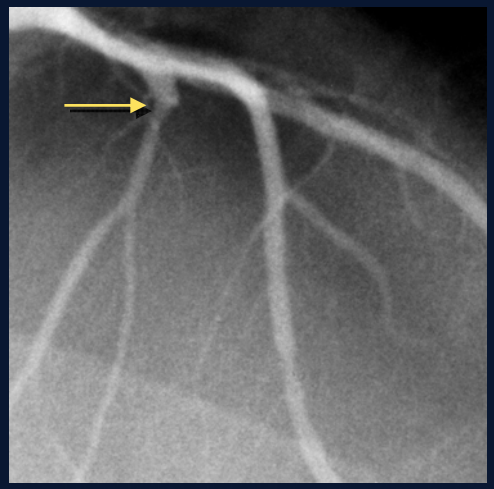
These reports were subsequently amplified by systemvascular SMCs, and the matrix surrounding these cells typically had a distinctly lighter hue and less-compact appearance than the matrix of primary or adjacent plaque.[26]

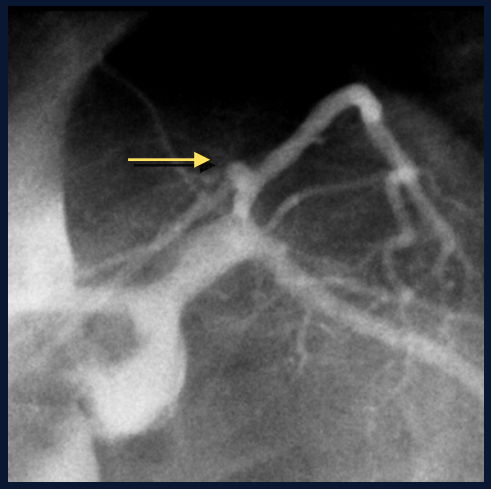
These contrasting findings regarding primary and restenotic lesions were perhaps best illustrated in a group of 18 patients studied in our laboratory[27] in whom directional atherectomy had been performed both as the primary intervention and again when the patient returned with restenosis. These 18 patients thus offered a unique opportunity to study the same lesion site in the same artery of the same patient at two different points in time. Light microscopic examination documented distinctive features, including hypercellular foci consisting of proliferative vascular SMCs surrounded by a loose neomatrix in 13 of 18 cases (72%). In 5 important exceptions, however, neither the primary nor the restenotic specimen demonstrated such a "restenosis focus." Of 253 restenosis specimens (65%) retrieved by directional atherectomy and studied in our laboratory,[27] a similar restenosis focus was identified in 165 (65%); among the remaining 88 specimens (35%), however, no distinctive histological features were observed.

Additional evidence supporting the proliferative nature of restenosis versus primary lesions is derived from ex vivo studies of SMCs cultured directly from explanted fragments of human atherectomy specimens.[28-38] These studies documented that the outgrowth kinetics of SMCs cultivated in this manner were indeed a reflection of the lesion type. Among 41 lesions retrieved by directional atherectomy and used in our laboratory to

Isner. Circulation 1994;89:2937-41

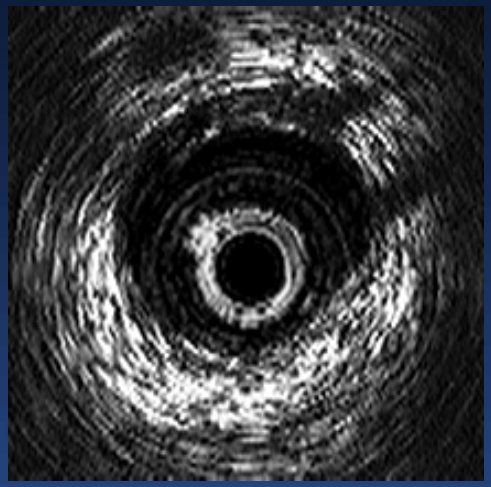


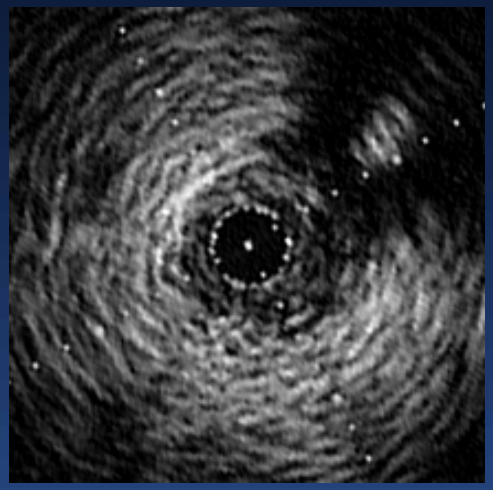




Post DCA+PTCA

7 month F/U



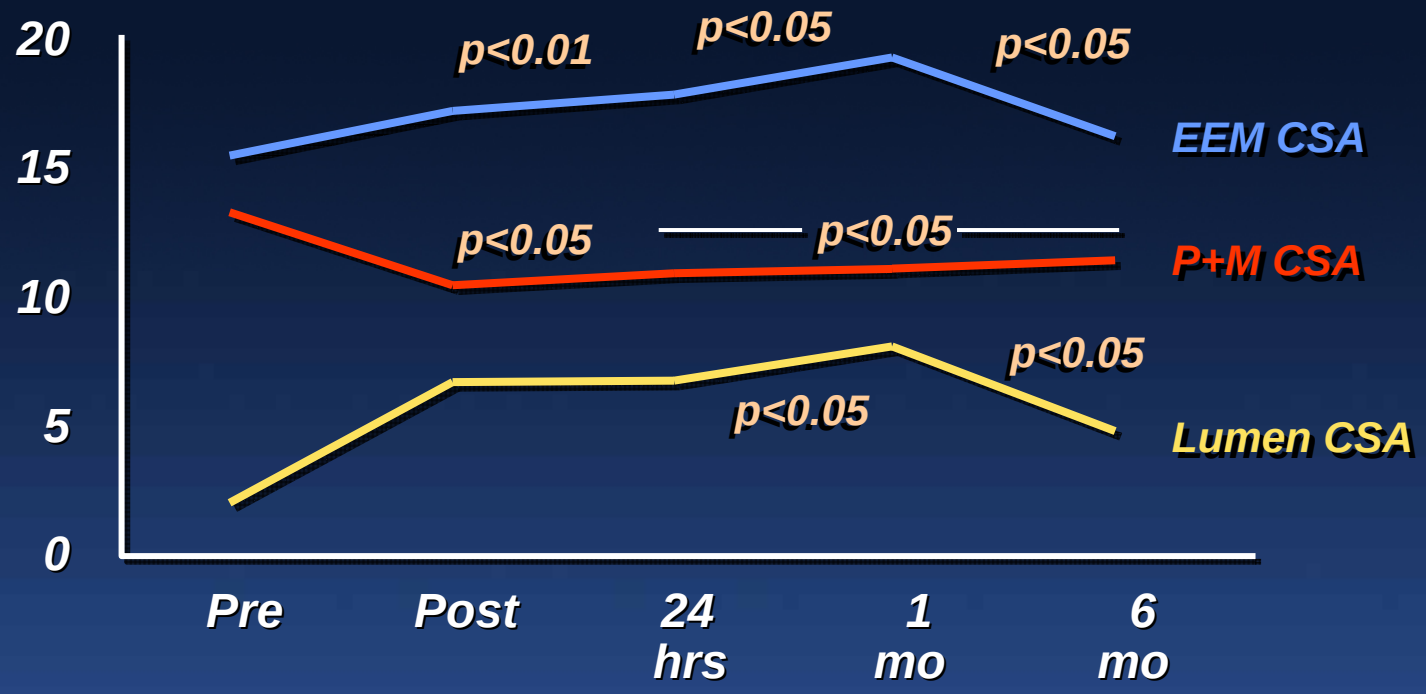


EEM =14.7mm²
Lumen = 10.2mm²
P&M = 4.6mm²

EEM = 5.5mm²
Lumen= 1.0mm²
P&M = 4.5mm²

SURE Trial: Restenosis in non-stented lesions

Average of the two image slices with the smallest pre-intervention and follow-up lumen CSA



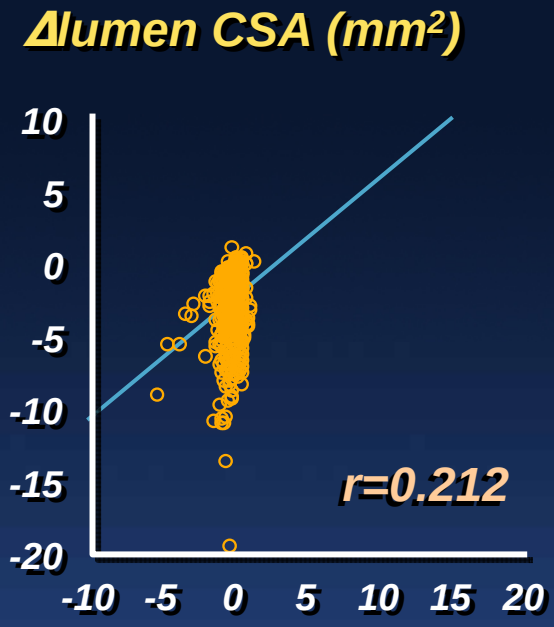
61 native vessel lesions (26 DCA, 35 PTCA) with complete serial IVUS studies (out of 79 lesions enrolled in the study)

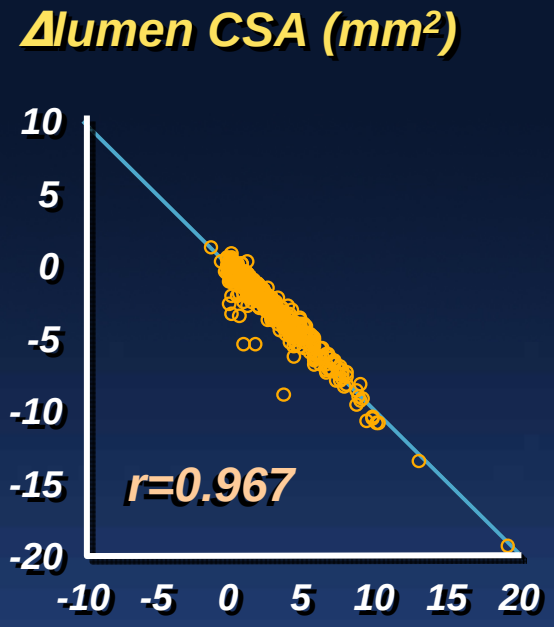
Kimura et al. Circulation 1997;96:475-83

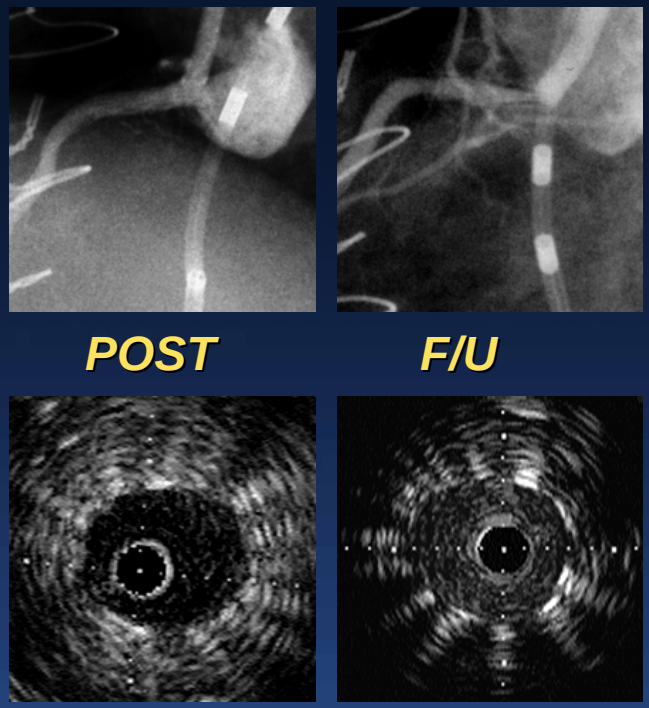
- **Stents reduce restenosis by achieving a better post-procedural result and by *eliminating* remodeling. This offsets a stent-related *increase* in tissue growth.**
- **In-stent restenosis is *solely* the result of tissue growth. However, stent edge restenosis is a combination of negative remodeling and intimal hyperplasia and is determined, in part, by the plaque burden at the edge at the time of implant.**
- **Mechanical problems - that occurred at the time of stent implantation - are present in a significant percentage of in-stent restenosis lesions.**

Hoffmann et al. Circulation 1996;94:1247-54
Mintz et al. AM J Cardiol 1996;78:18-22
Hoffmann et al Am J Cardiol 1997;79:951-3
Castagna et al. Am Heart J 2001;142:970-2

In-stent restenosis is all intimal hyperplasia

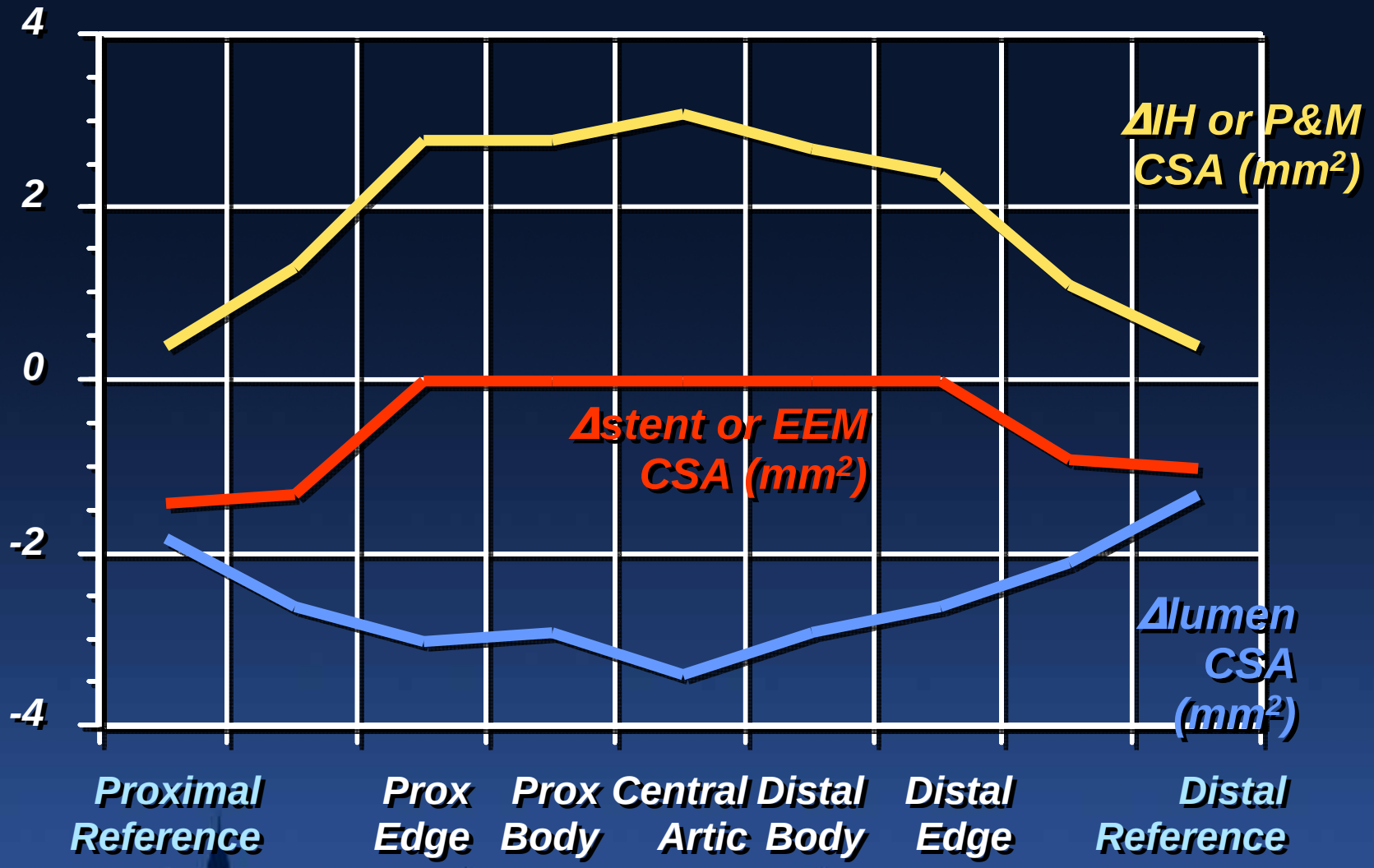






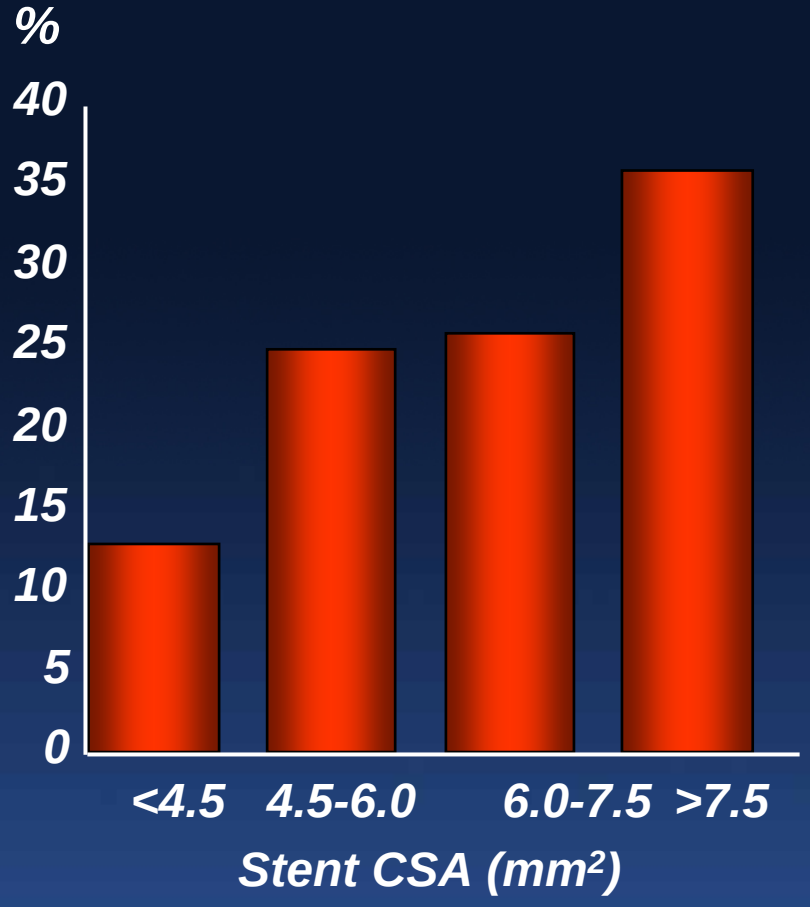
Hoffmann et al. Circulation 1996;94:1247-54

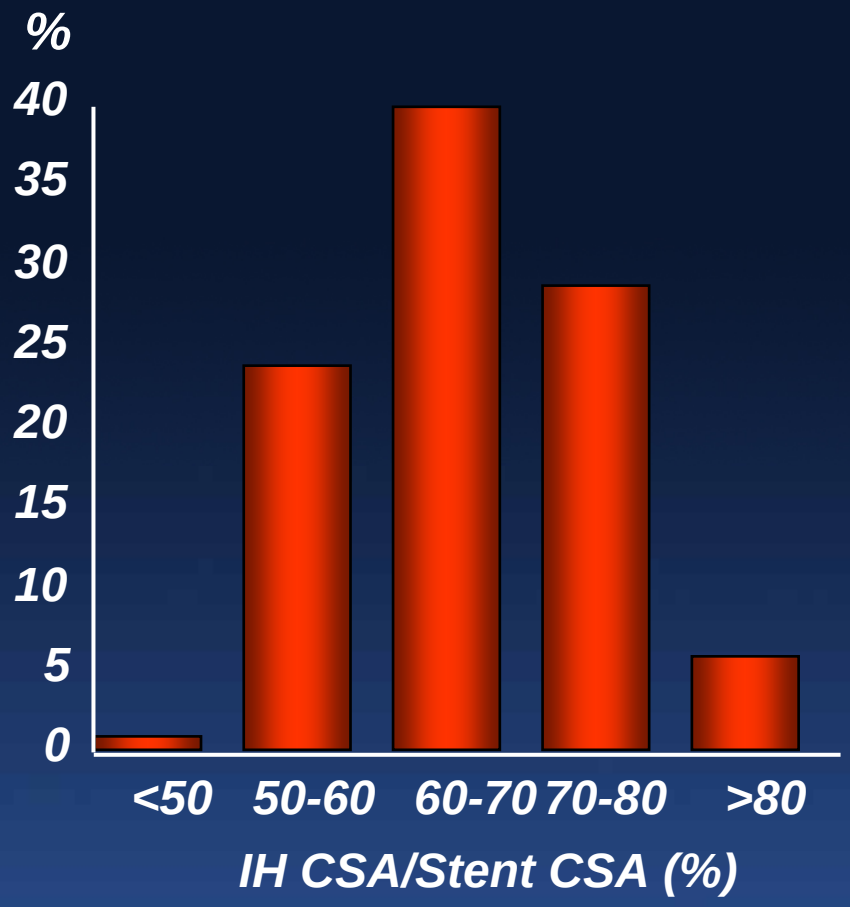
Restenosis in Stented Lesions



Hoffmann et al. Circulation 1996;94:1247-54

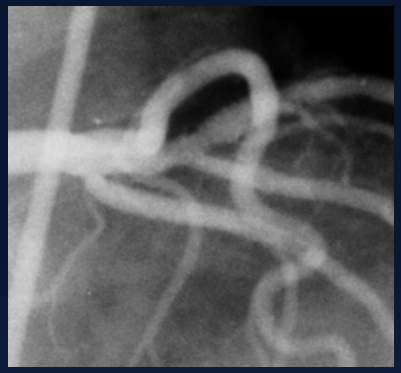
Analysis of 1089 Consecutive Patients With Bare Metal In-stent Restenosis

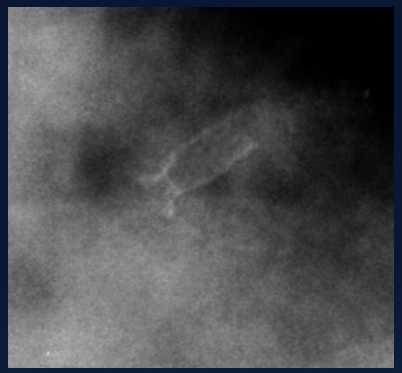


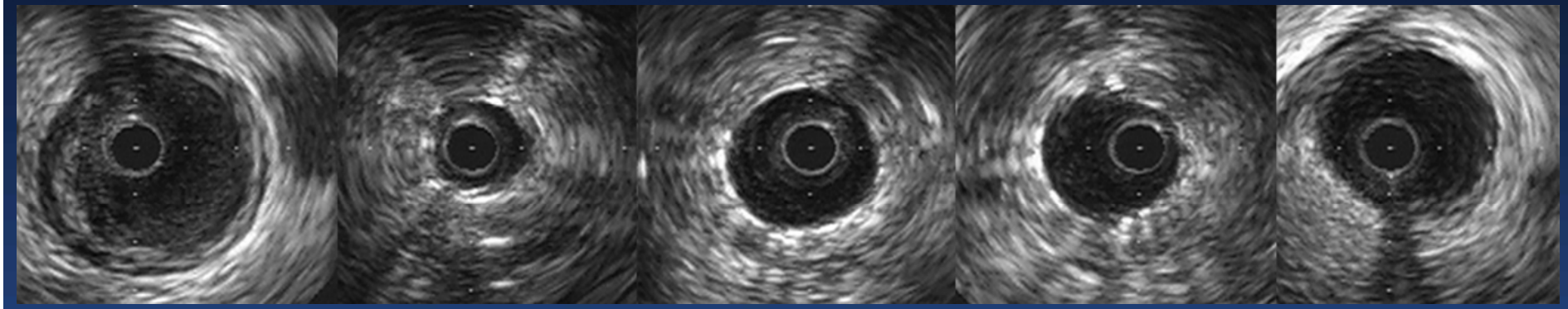


4.4% of cases had "unrecognized mechanical complications"
12% had severe chronic stent underexpansion (<4.5mm²)

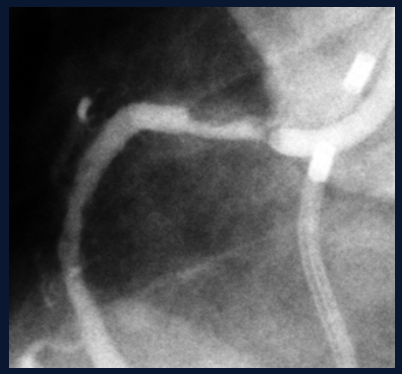
Castagna et al. Am Heart J 2001;142:970-4

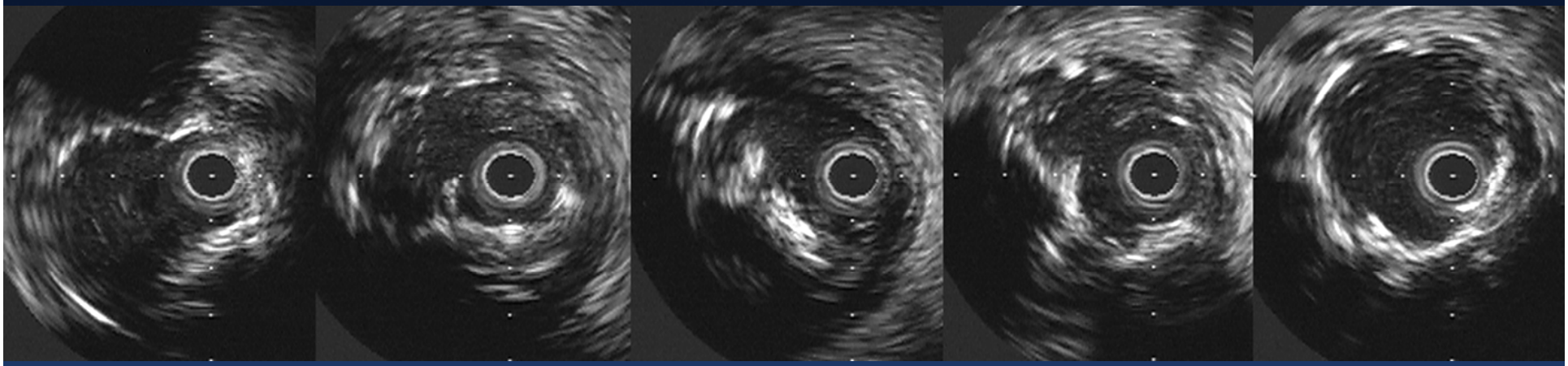






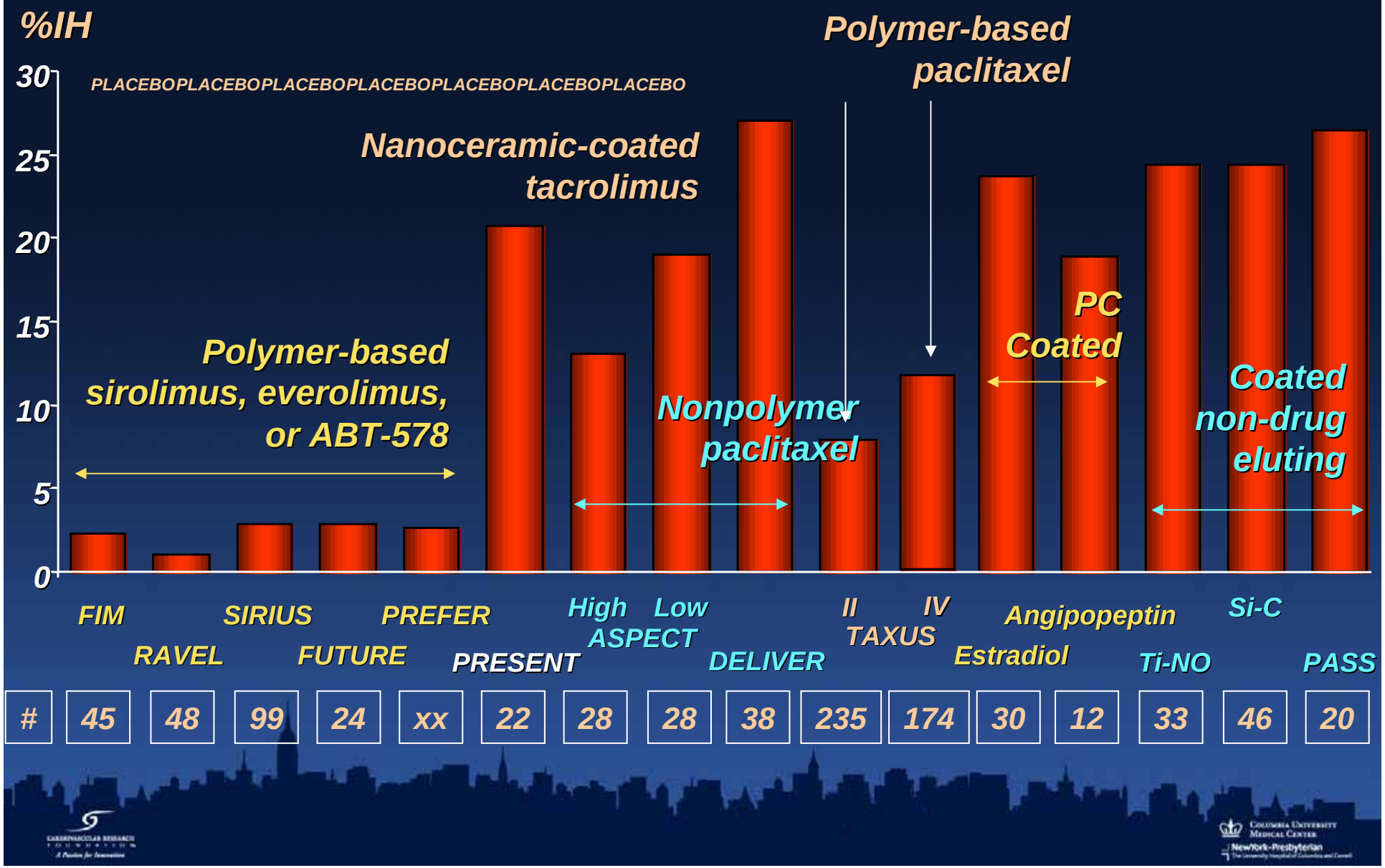
0 → 5.0 → 20.0mm





0 → 2.5 → 10.0mm

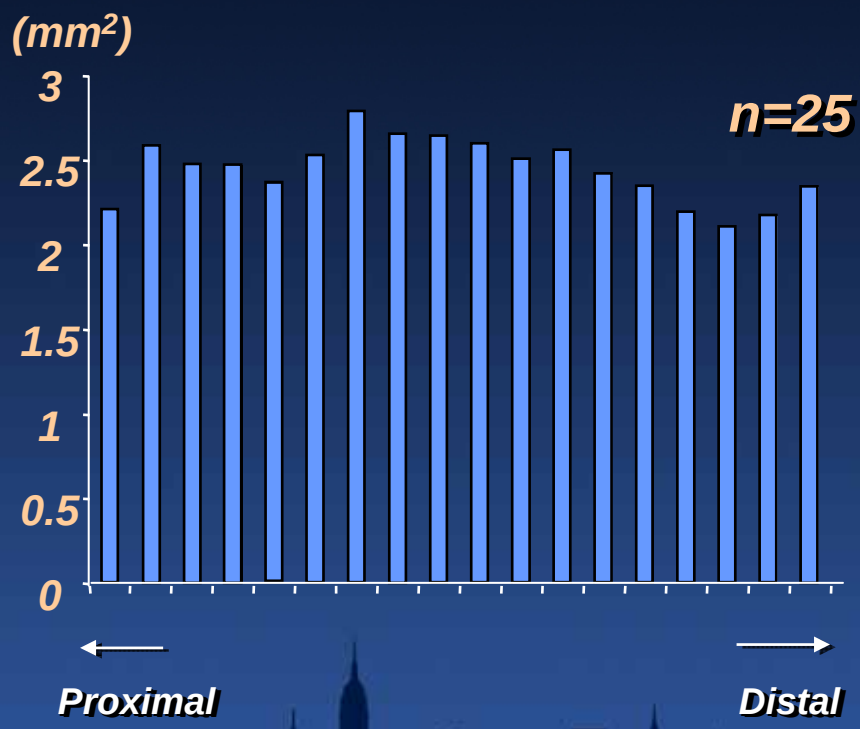
%IH in various DES trials



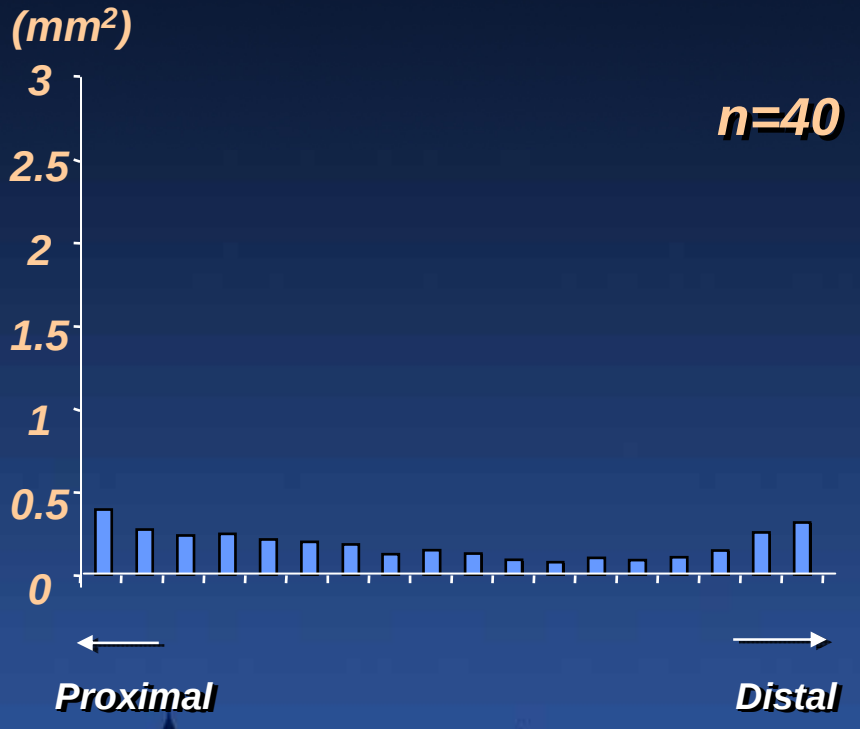
Distribution of Neointimal Proliferation

18 mm Single Stent

Bare Metal Stent



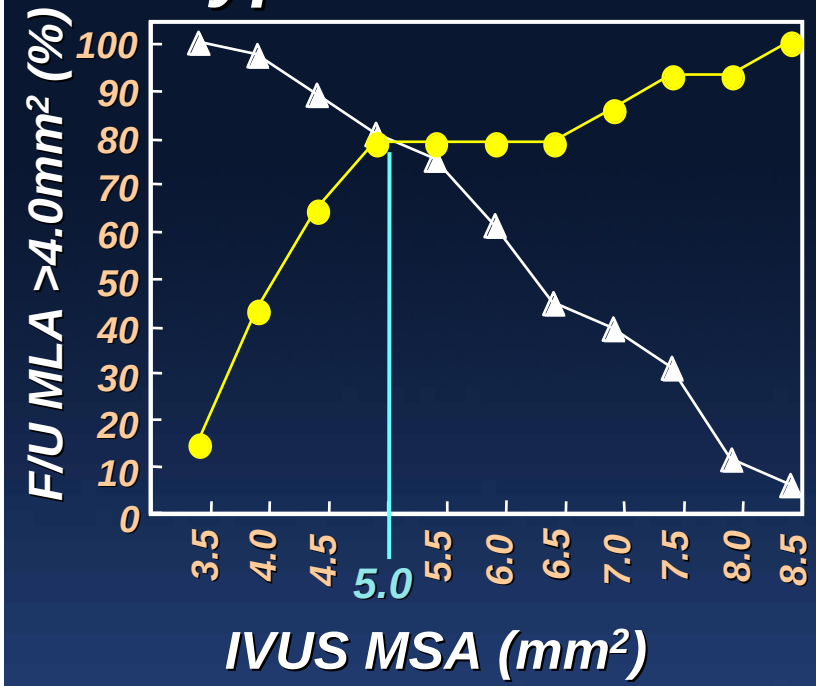
Sirolimus-Eluting Stent



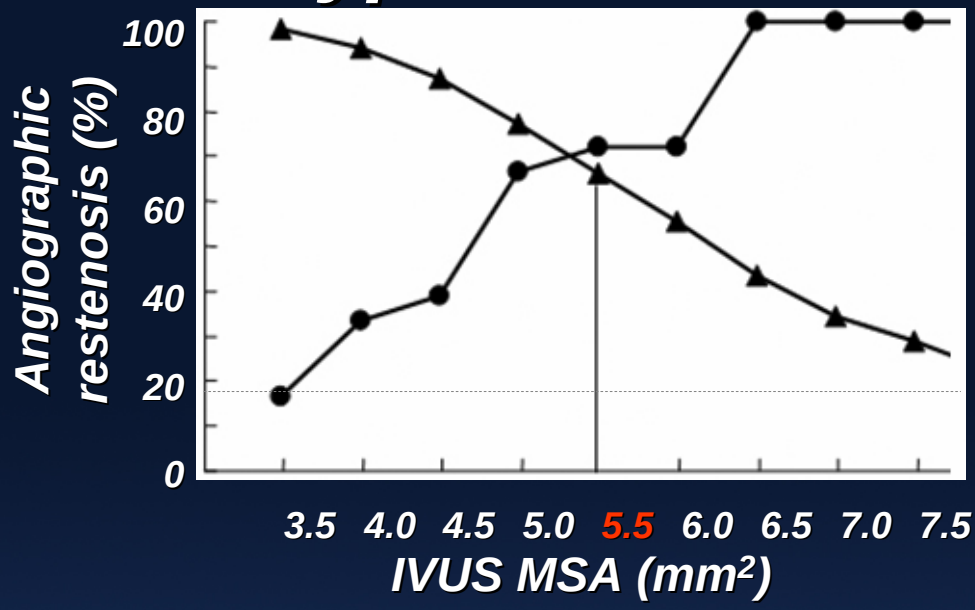
Predictors of DES Restenosis

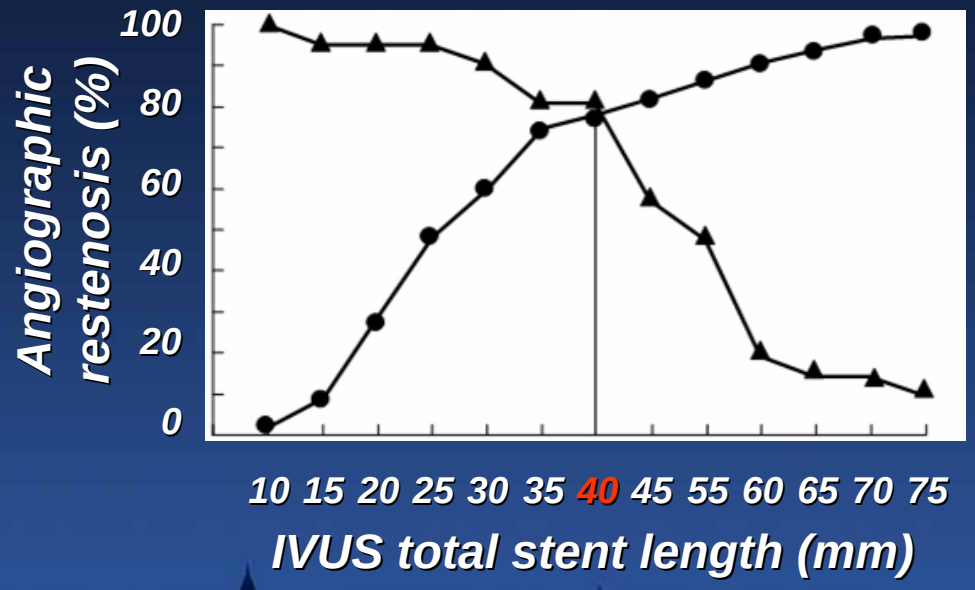
	DES Restenosis
Underexpansion or MSA	•*Sonoda et al. J Am Coll Cardiol 2004;43:1959-63* •*Hong et al. Eur Heart J 2006;27:1305-10* •*TAXUS IV, V, VI and ATLAS WH, LL, DS meta-analysis.* JACC Cardiovasc Interv. 2009;2:1269-75 •*Fujii et al. Circulation 2004;109:1085-1088* •*Choi. HORIZONS (unpublished)*
Edge problems (geographic miss, secondary lesions, large plaque burden, etc)	•*Sakurai et al. Am J Cardiol 2005;96:1251-3* •*Liu et al.Am J Cardiol 2009;103:501-6* •*Costa et al, Am J Cardiol, 2008;101:1704-11*

Cypher in SIRIUS



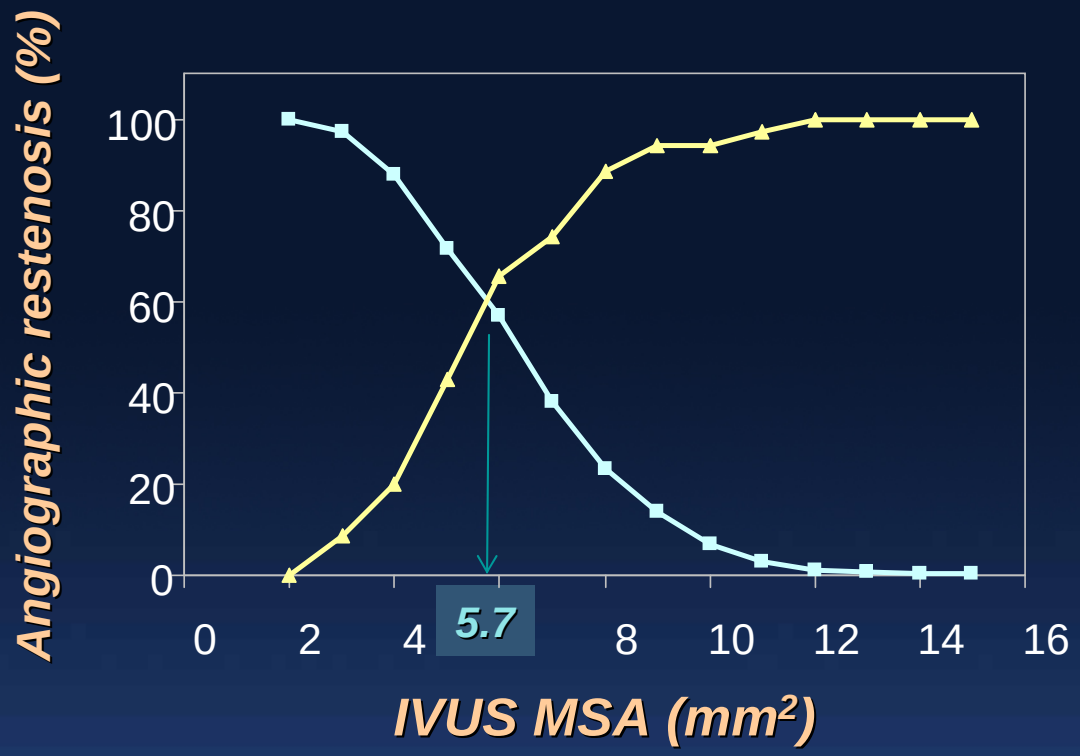
Cypher at AMC





Sonoda et al. J Am Coll Cardiol 2004;43:1959-63
Hong et al. Eur Heart J 2006;27:1305-10

TAXUS-IV, V, VI and ATLAS WH, LL, and DS



By definition, sensitivity/specificity curve analysis "must" identify a single MSA that best separates restenosis from no restenosis

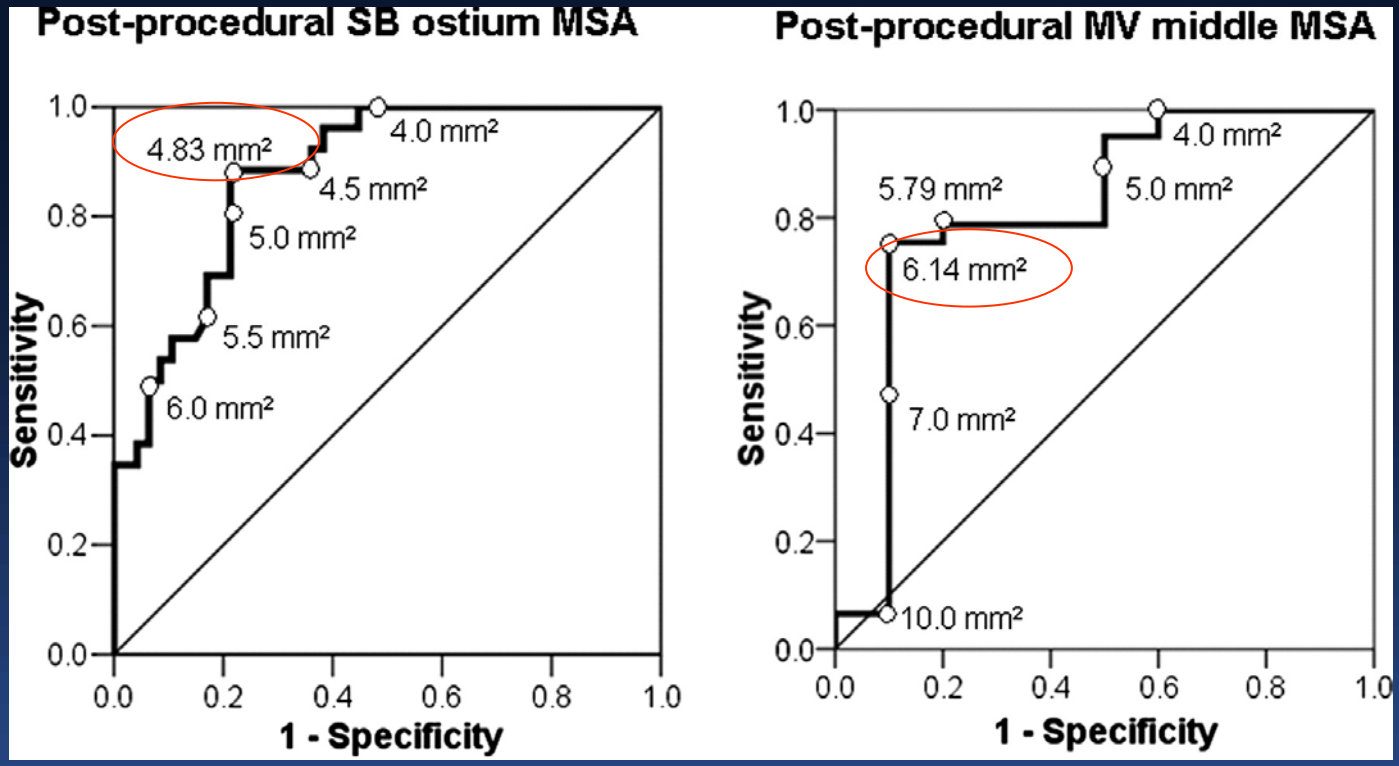
C-statistic for TAXUS was only 0.64

Doi et al. JACC Cardiovasc Interv. 2009;2:1269-75

There has to be some common sense in selecting IVUS endpoints.

- Is an MSA of 5.0-5.5mm^2 enough in big arteries? Probably not.
- Is it achievable in small arteries? Also, probably not.
- An optimum procedural end point cannot be determined using a cross-point of sensitivity and specificity curves, because the importance of those two diagnostic variables are not equivalent. An ideal procedural end point should be a clinically reasonable MSA that maximizes the probability of long-term stent patency while minimizing the risk of complications including restenosis.
- And if it were enough in all circumstances, we would only need 2.5mm stents since 100% expansion of a 2.5mm stent = 5mm^2

The Optimal Cutoff Value of Post-Procedural MSA to Predict a Follow-up MLA ≥4mm² After Bifurcatoin T-Stenting



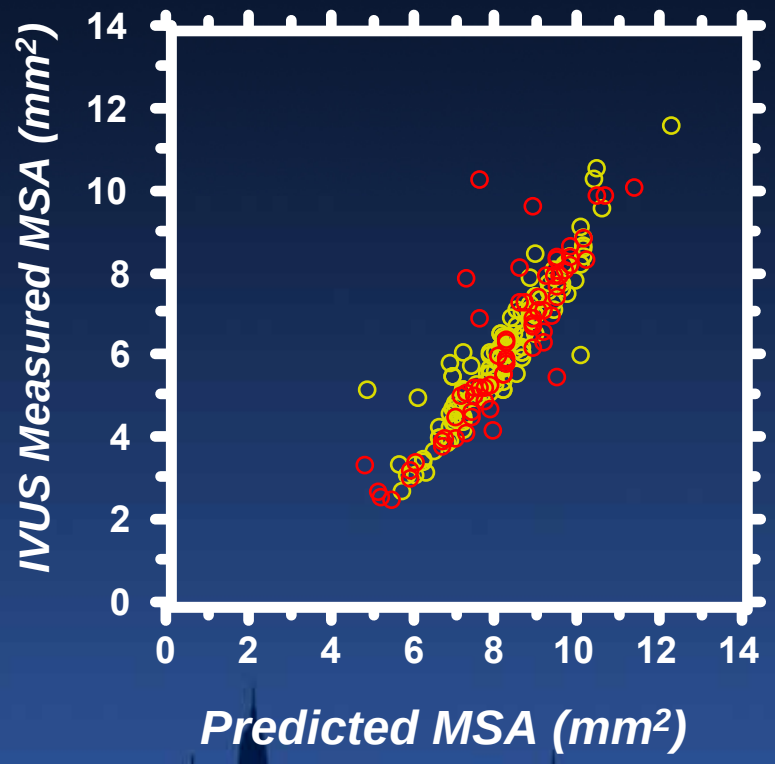
AUC=0.88
(95%CH=0.80-0.95)

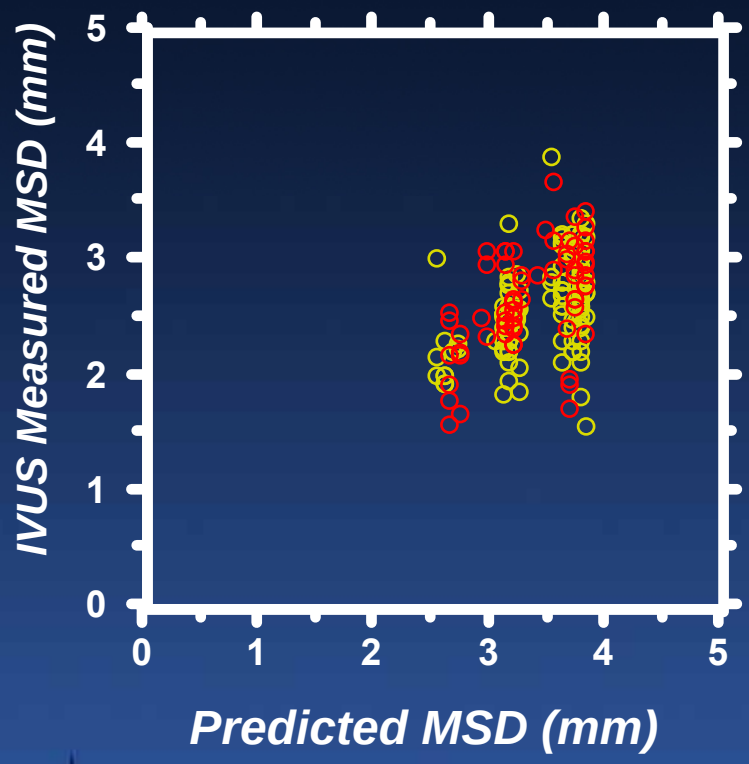
AUC=0.81
(95%CH=0.64-0.99)

Hahn et al. J Am Coll Cardiol 2009;54:110-7

Manufacturer's Compliance Charts Cannot Be Used to Guarantee Adequate Stent Expansion

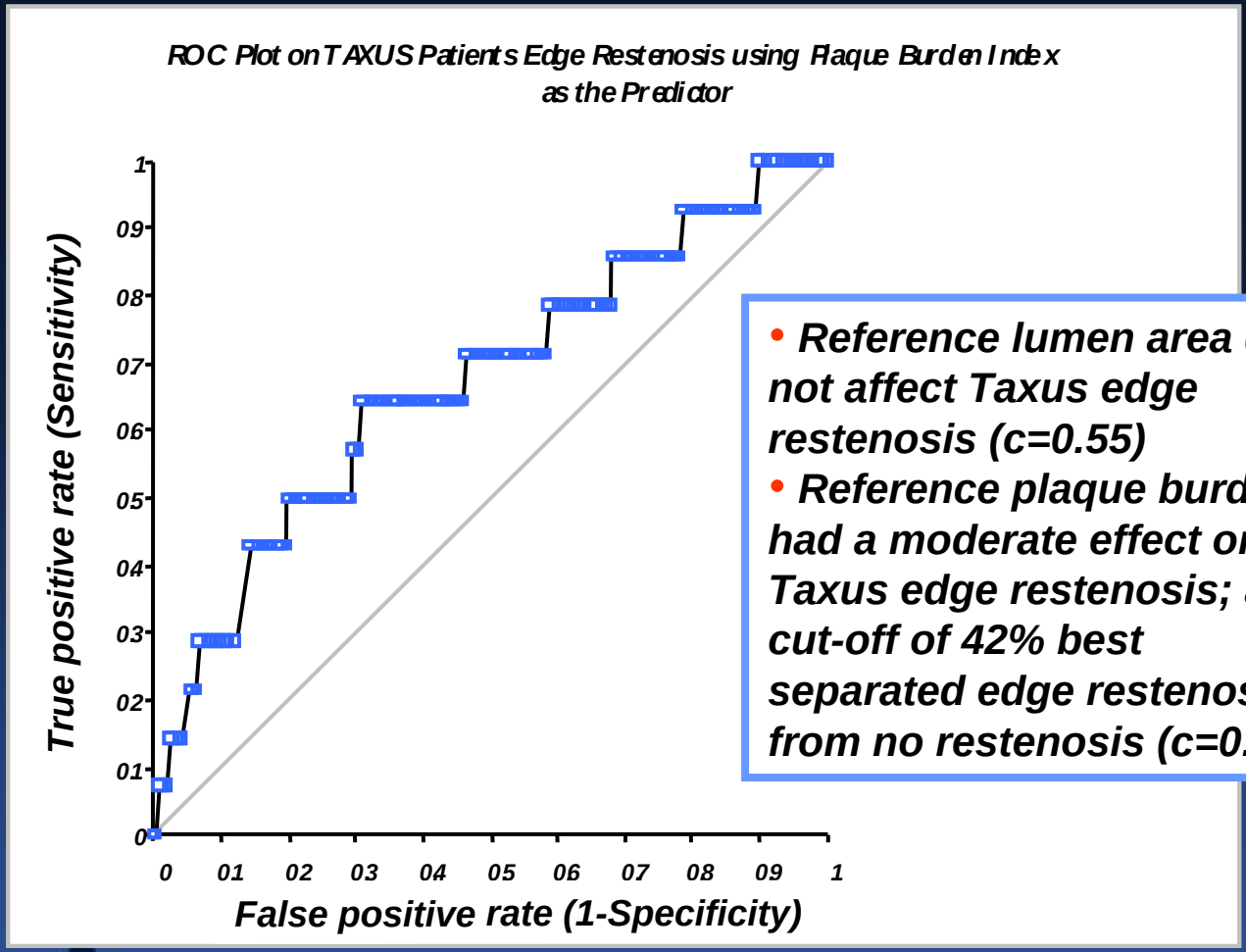
Comparison of IVUS-measured minimum stent diameter (MSD) and minimum stent area (MSA) with the predicted measurements from Cordis (Cypher in yellow, n=133) and BSC (Taxus in red, n=67). DES achieve an average of only 75% of the predicted MSD (66% of MSA)





(de Rebamar Costa et al, Am Heart J 2007;153:297-303)

Comparison of 9-month QCA edge restenosis vs reference lumen area and plaque burden in TAXUS-IV, V, and VI (n=810)



- *Reference lumen area did not affect Taxus edge restenosis (c=0.55)*
- *Reference plaque burden had a moderate effect on Taxus edge restenosis; a cut-off of 42% best separated edge restenosis from no restenosis (c=0.67)*

Liu et al, Am J Cardiol 2009;103:501-6

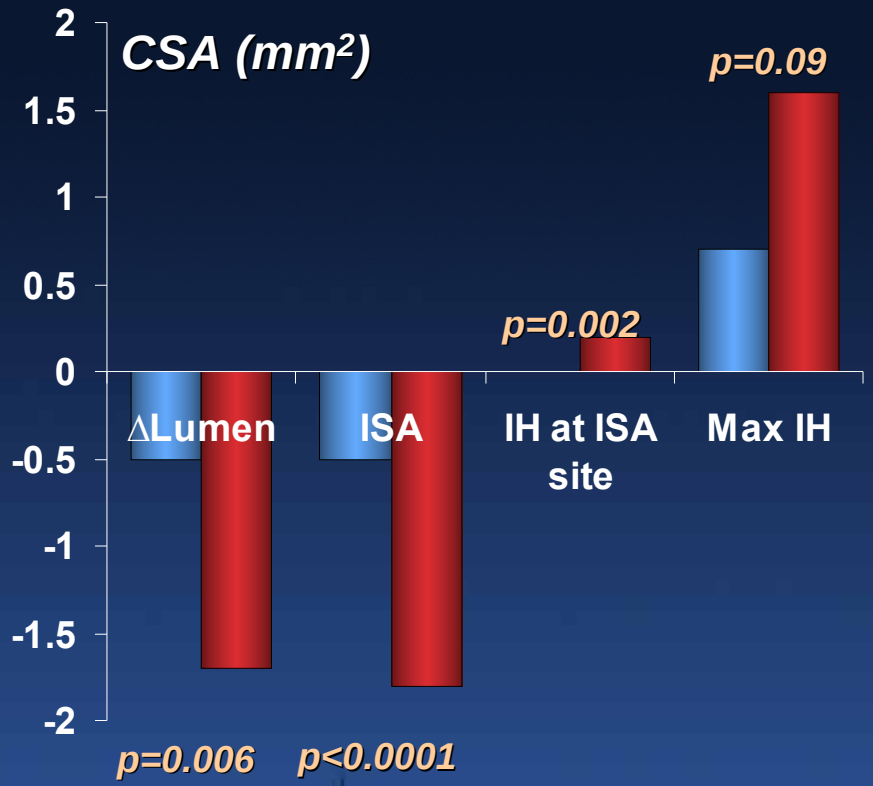
What about acute stent malapposition?

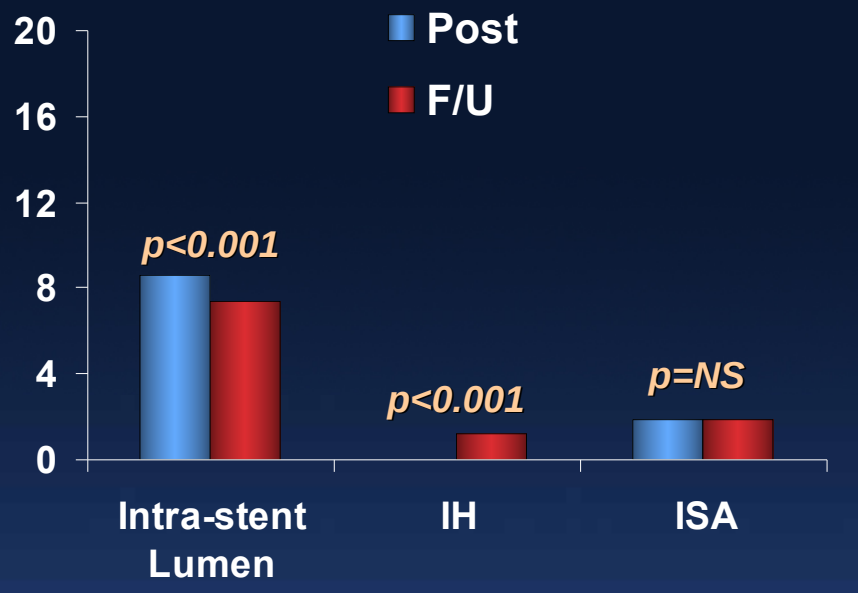
Although it was one of the original Colombo criteria, there is little or no data linking *isolated* acute stent malapposition to adverse clinical events including DES restenosis.

- **Persistent stent malapposition is associated with *less* intimal hyperplasia – the drugs can cross small stent vessel-wall gaps**
  - *Hong et al, Circulation. 2006;113:414-9*
  - *Balakrishnan et al. Circulation 2005;111:2958-65*
  - *Kimura et al. Am J Cardiol . 2006;98:436-42*
  - *Guo et al. Circulation. 2010;122:1077-1084*
- **In the integrated analysis of slow release formulation PES in TAXUS IV, V, and VI and TAXUS ATLAS Workhorse, Long Lesion, and Direct Stent Trial, there was no effect of acute stent malapposition on MACE (or stent thrombosis within the first 9 months) – whether BMS or DES**
  - *Steinberg et al, JACC Cardiovasc Intervent 2010;3:486-94*
- **In HORIZONS-AMI, post-intervention acute stent malapposition was detected in 33.8% of 68 lesions treated with PES and 38.7% of 24 lesions treated with BMS (p=0.7). There was no difference in MACE between patients with versus without acute stent malapposition in either BMS or PES cohorts.**
  - *Guo et al. Circulation. 2010;122:1077-1084*

Late incomplete Cypher Apposition and IH

- *Persistent ISA (n=40, 83% decreased in size)*
- *Completely resolved ISA (n=15)*



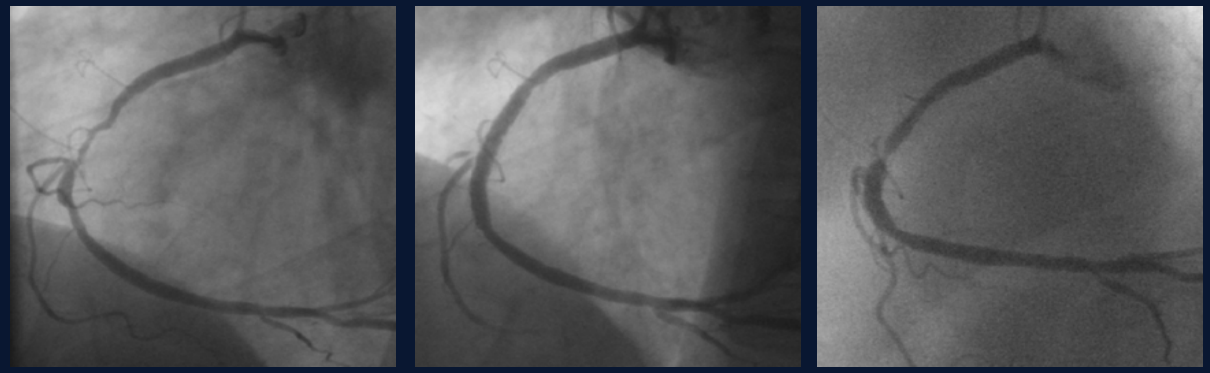


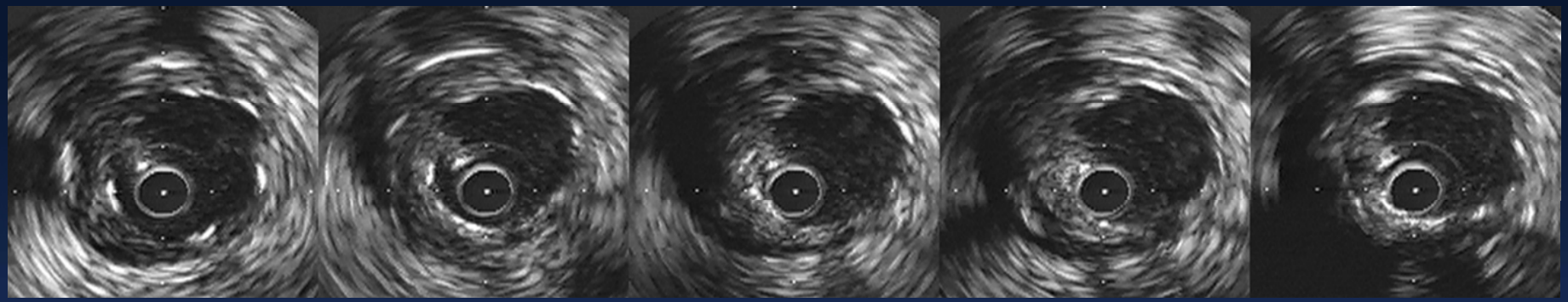
Kimura, et al. Am J Cardiol 2006;98:436-42
Hong et al. Circulation 2006;113:414-9

Analysis of 20 stent fractures in 17 patients

- 15 stent fractures were detected by angiography and IVUS, and 5 were detected only by IVUS
- 15 stent fractures in 13 patients were associated with in-stent restenosis (all focal); and 2 stent fractures in 2 patients were associated with very late stent thrombosis
- Five stent fractures occurred within a coronary aneurysm accompanied by malapposition despite the absence of a coronary aneurysm at index stenting.
  - Comparing stent fractures associated with an aneurysm to ones that did not occur in association with an aneurysm, complete stent fracture was more frequent (100% vs. 27%, p=0.008), and all presented >1 year after index stenting (vs. 33%, p=0.03).

Doi et al. Am J Cardiol 2009;103:818-23





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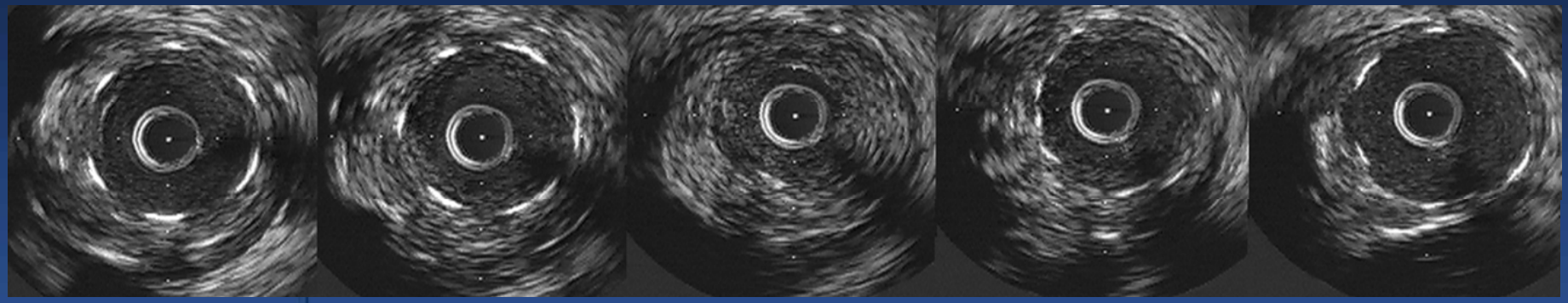

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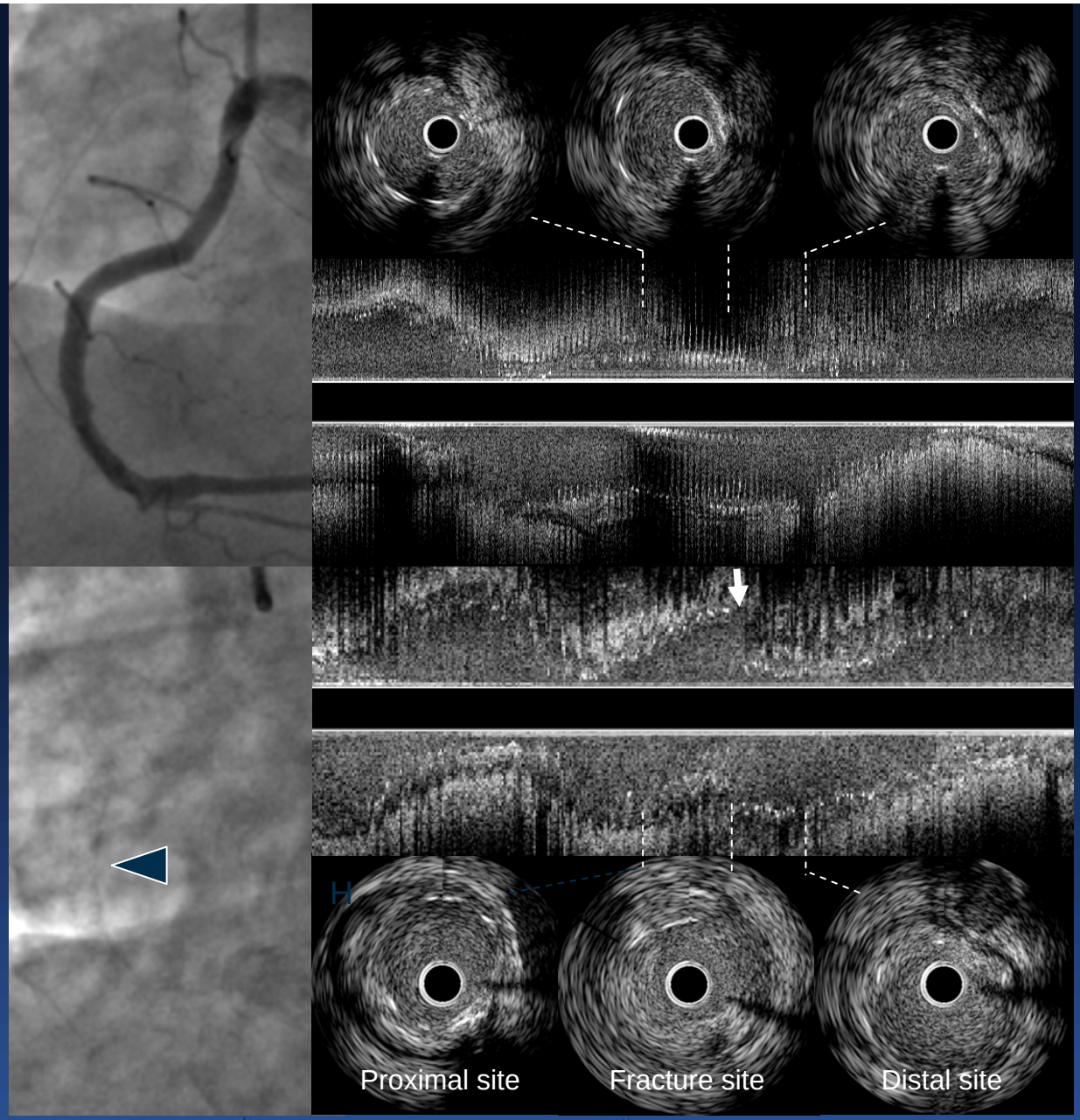

Proximal site
Fracture site
Distal site

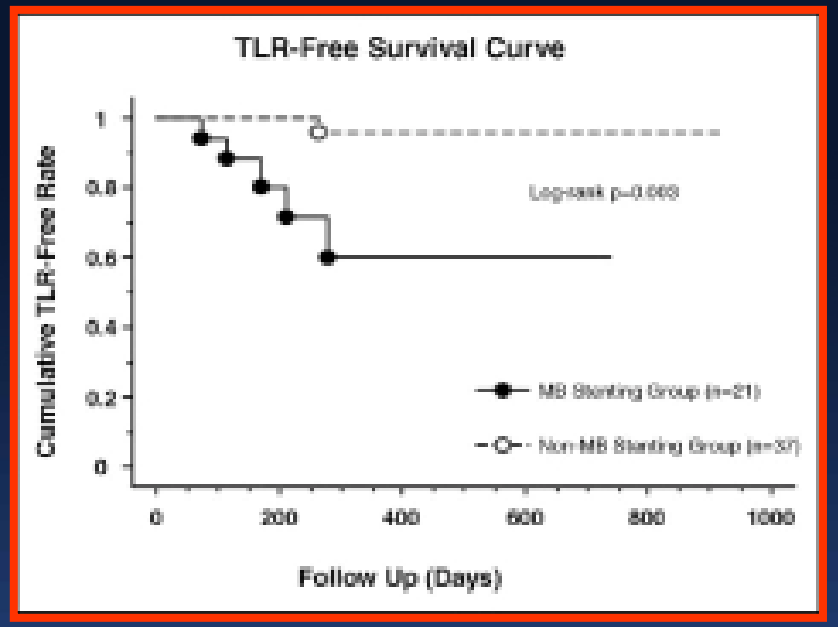
Comparing PES fractures to SES fractures

- Similar frequency of complete stent fracture (17% vs 21%, p >0.99)
- Similar frequency of fracture adjacent to calcified plaque or stent metal overlap (86% vs 100%, p = 0.99),
- Similar stent lengths (45.2 mm vs 39.3 mm, p >0.99)
- Similar fracture lengths (0.5mm vs 0.7mm, p = 0.14), and (6)
- Larger reference external elastic membrane area (15.0mm^2 vs 10.4mm^2, p = 0.01).
- More frequent complete malalignment of proximal and distal fragments in PES strut fractures compared to SES fractures (83% vs 7%, p = 0.002)

Doi et al. Am J Cardiol. 2010;106:952-7

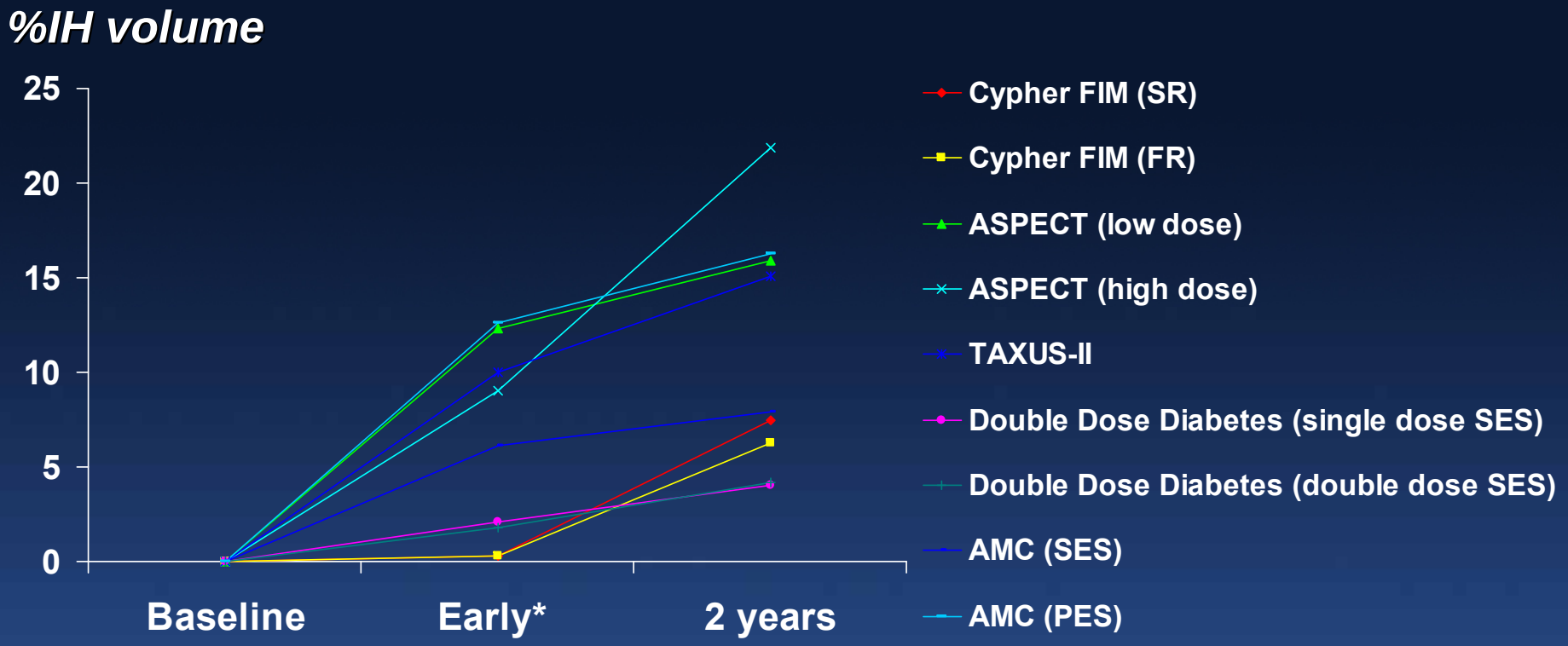
Impact of muscle bridge on DES restenosis

- IVUS identified muscle bridges in 70/317 patients undergoing LAD DES implantation.
- The DES extended into the MB segment beyond the obstructive lesion in 24 patients (34%), although significant plaque was not observed within any muscle bridge segment.
- MSA was significantly smaller in the MB stent group than non-MB stent group: 4.8 ± 1.1 vs $5.8 \pm 1.8 mm^2$ ($p = 0.02$).
- At a mean follow-up of 358 days, target-lesion revascularization, target-vessel revascularization, and MACE were more common in patients with versus without MB stent placement.

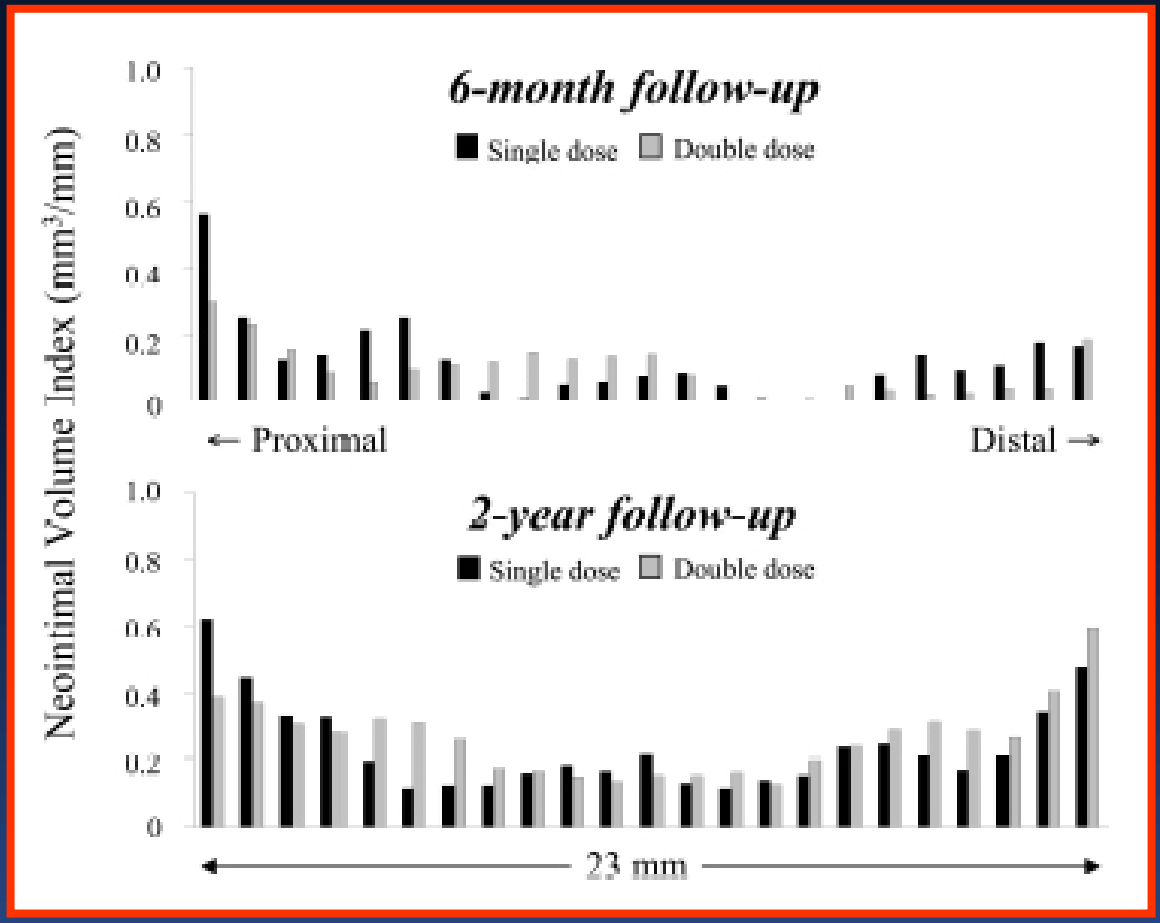


Tsujita et al Am J Cardiol. 2009;103:1344-8

Late DES Catch-Up Among IVUS Substudy Patients

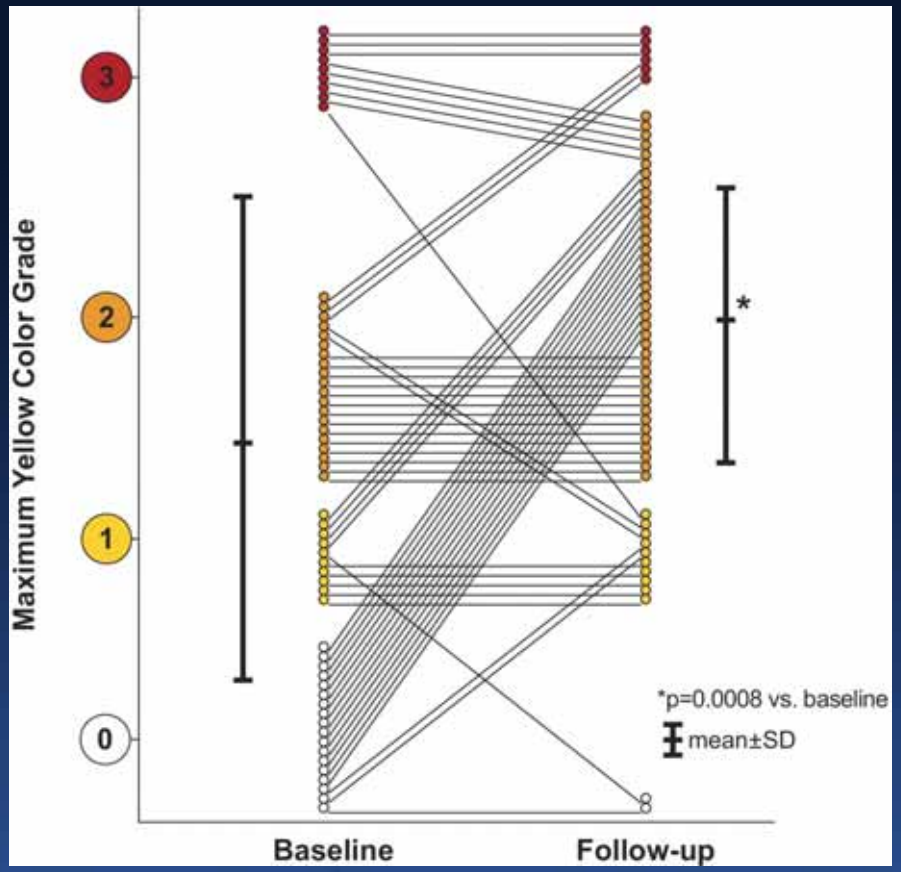


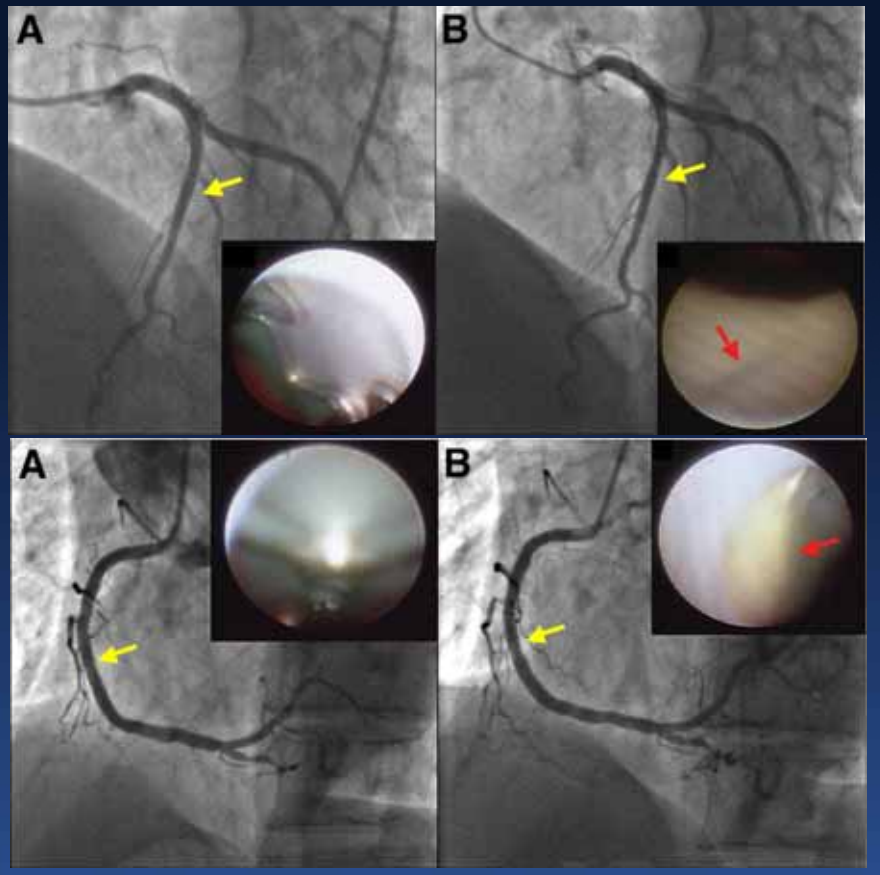
**defined as 4-9 months*



Hur et al. J Invasive Cardiol 2008;20:411-6

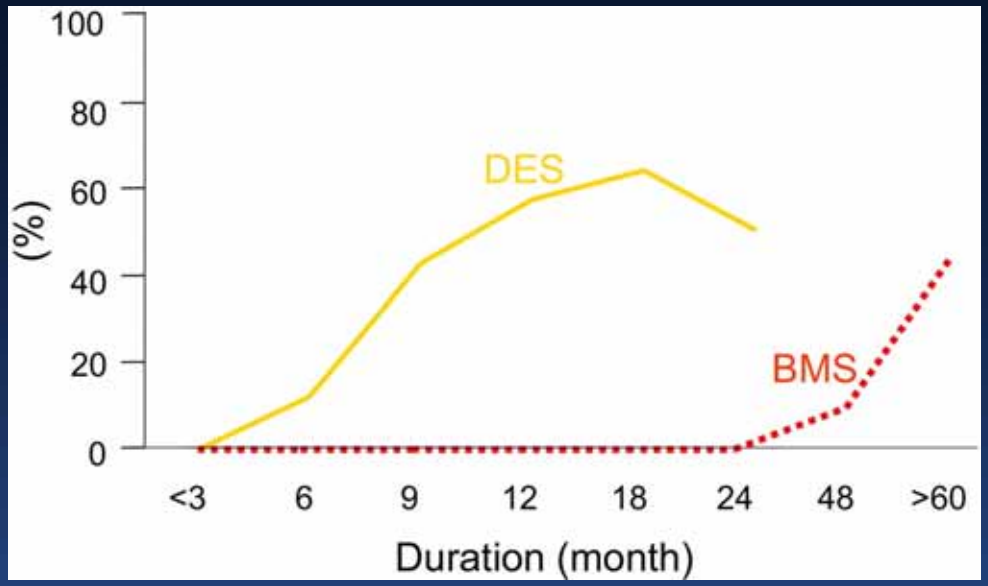
Changes in Maximum Yellow Color Grade From Baseline to Follow-Up in DES

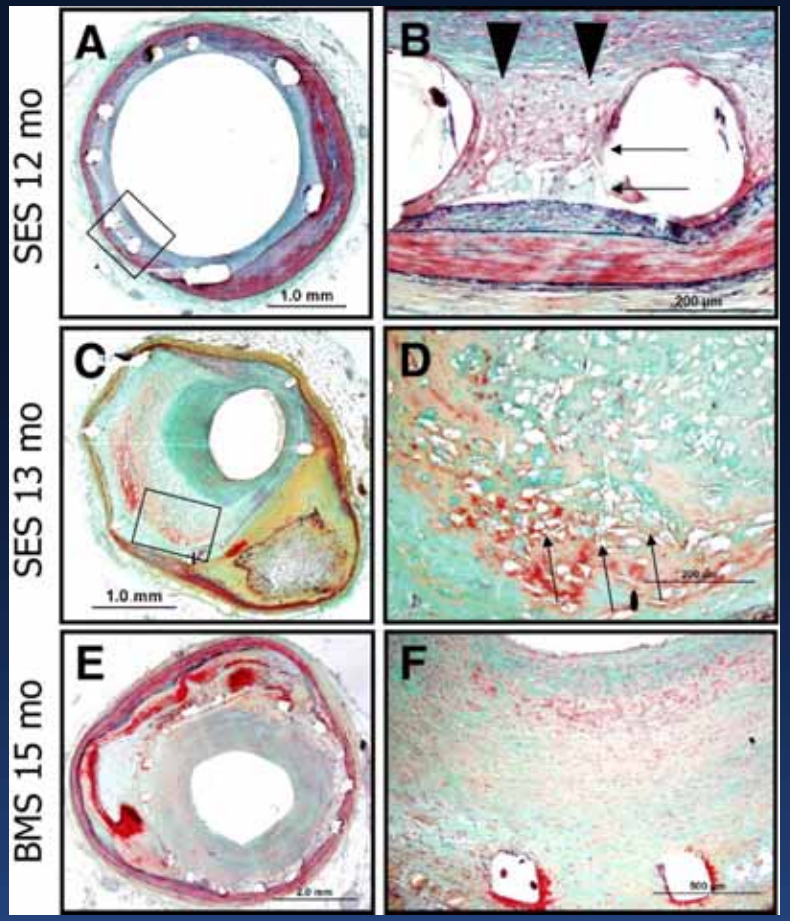




Higo et al. J Am Coll Cardiol Img 2009;2:616-24

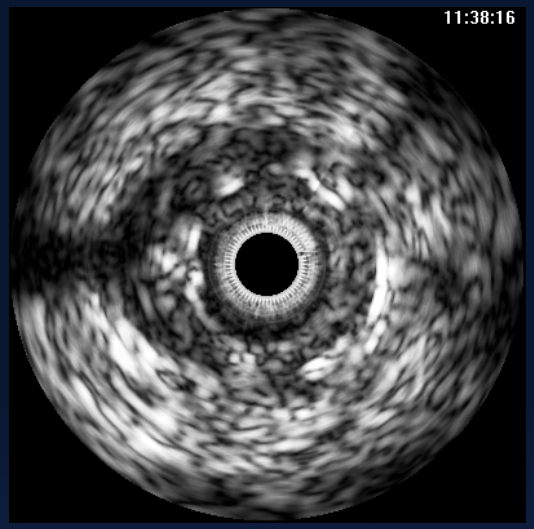
Percentage of Patients With Atherosclerotic Changes in DES Versus BMS in Relation to Duration of Implant at Autopsy

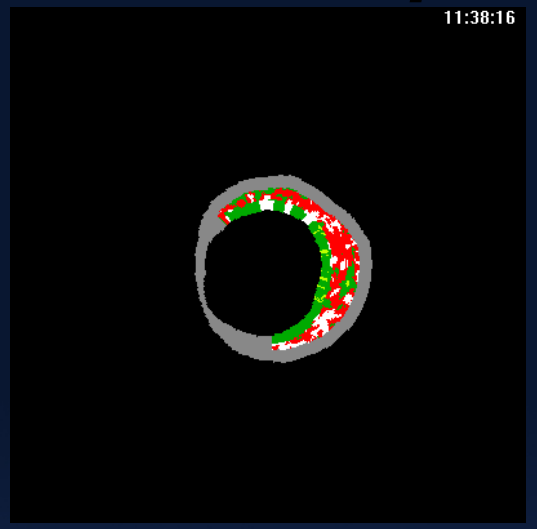




Nakazawa et al. J Am Coll Cardiol Img 2009;2:625-8

Taxus 22-month follow-up





BMS 57-month follow-up