Can Routine IVUS Assessment (±RF Plaque Characterization) Reduce Stent Thrombosis and Restenosis?

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Premise

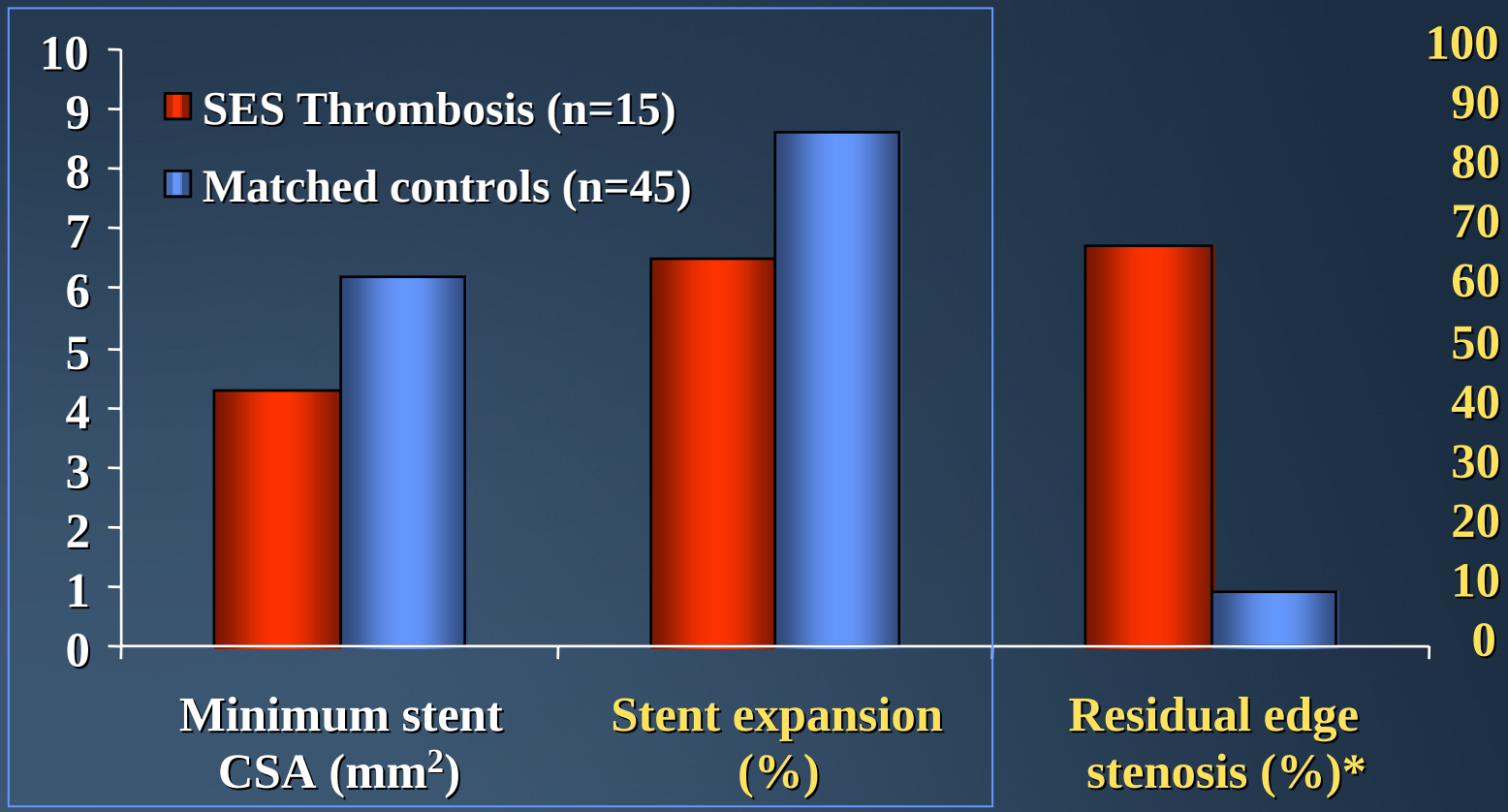
- Understanding reasons for DES thrombosis or restenosis will improve implantation techniques and lead to better patient outcomes. This was true in the bare metal stent era, and it should also be true in the DES era.

	Important?
Expansion	+
Residual Edge Stenosis/Dissection	+
Complications	+
Malapposition	±
Plaque Prolapse	-
Stent Asymmetry	-

- Stent underexpansion = inadequate stent dimensions
- Stent malapposition = lack of complete stent-vessel wall contact

Stent Underexpansion

Predictors of Cypher Thrombosis within 1 year @ CRF



- 12/15 SES thrombosis lesions has stent CSA <5.0mm² (vs 13/45 controls)

(Fujii et al. J Am Coll Cardiol 2005;45:995-8)

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Predictors of DES Thrombosis Within 1 Year @ WHC

	Stent Thrombosis	Matched Controls	P-value
N	14	30	
Proximal reference			
Smallest lumen CSA (mm^2)	4.7±1.1	6.0 ±2.3	0.067
Largest plaque burden (%)	66±8	56±10	0.0018
Stent			
Proximal edge CSA (mm^2)	6.1±1.7	7.0±2.1	0.17
MSA (mm^2)	4.6±1.1	5.6±1.7	0.0489
Distal edge CSA (mm^2)	5.6±1.6	6.8±2.2	0.079
Distal reference			
Smallest lumen CSA (mm^2)	4.3±1.7	5.3±2.1	0.12
Largest plaque burden (%)	53±15	45±14	0.14

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(Okabe et al., Am J Cardiol. 2007;100:615-20)

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Predictors of Cypher Thrombosis within 1 year @ CRF/CUMC

	Stent thrombosis (n=20)	Control (n=45)	p
Proximal edge plaque burden	56±15%	41±15%	0.006
MSA	3.8±1.0mm^2	6.0±1.7mm^2	<0.0001
MSA <5.0mm^2	85%	29%	<0.0001
MSA <4.0mm^2	65%	14%	<0.0001
Stent symmetry	1.3±0.4	1.2±0.1	0.005
Stent malapposition	45%	36%	NS
Distal edge plaque burden	46±18%	38±17%	NS

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(Liu et al., unpublished)

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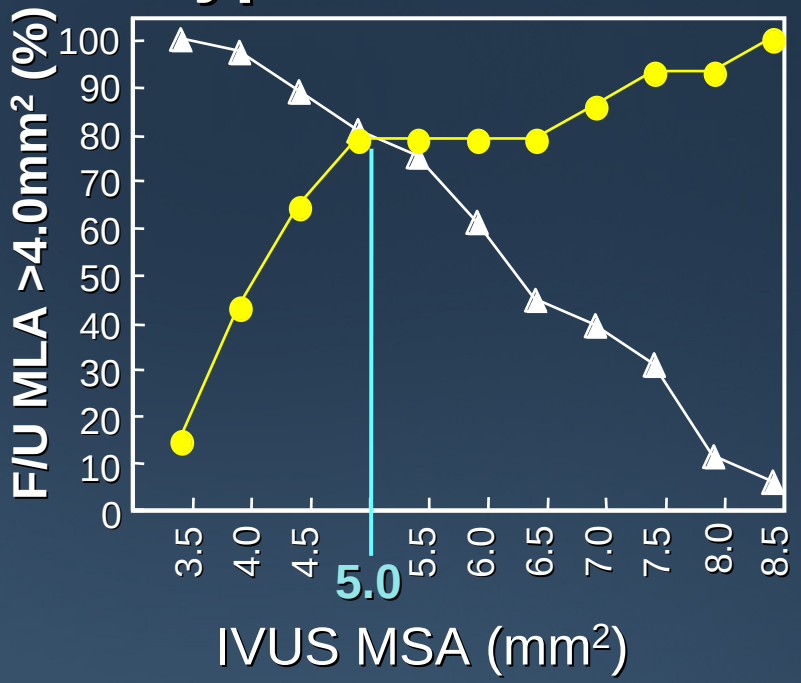
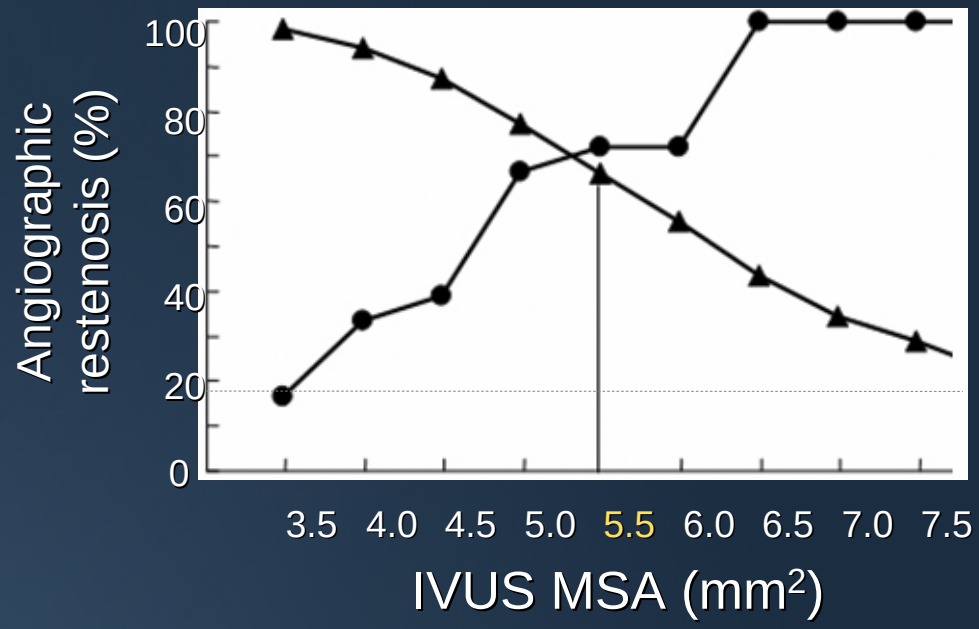
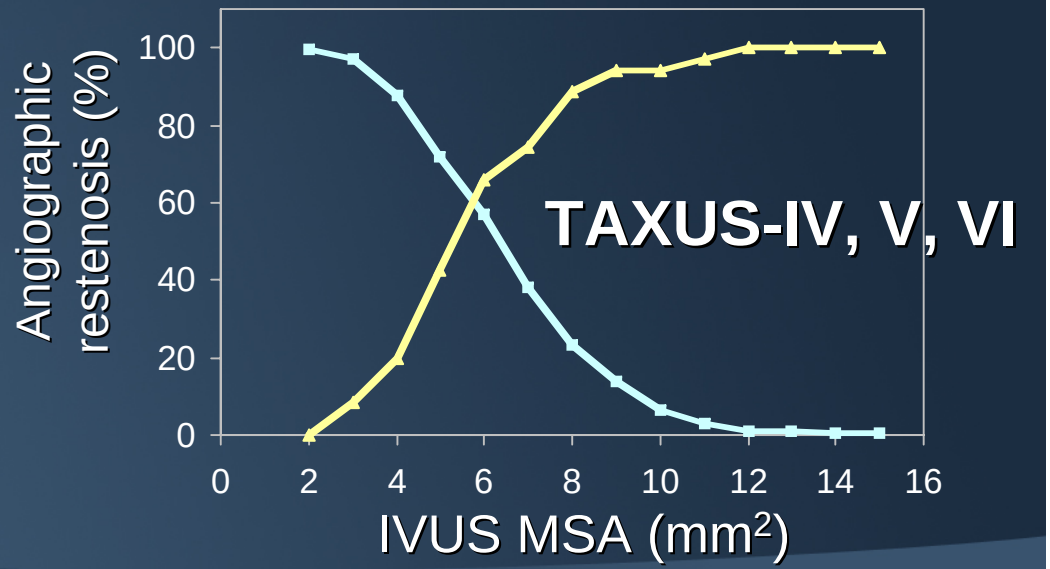
Cypher in SIRIUS*



Cypher at AMC**



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



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

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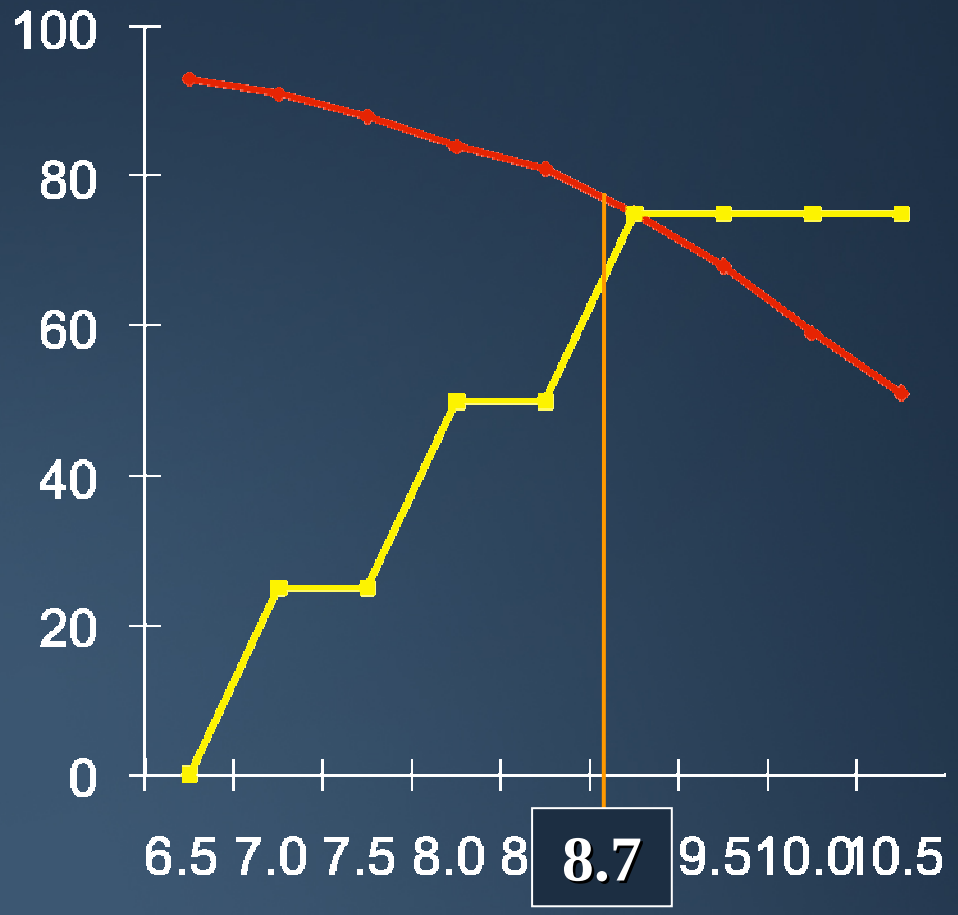
- Although sensitivity/specificity curve analysis in these 3 studies showed that the MSA that *best* separated DES restenosis from no restenosis was 5.0-5.5mm^2, all 3 studies also showed that a larger MSA was associated with a lower rate of DES restenosis.
- Therefore, “vessel appropriate” stent dimensions are still important.

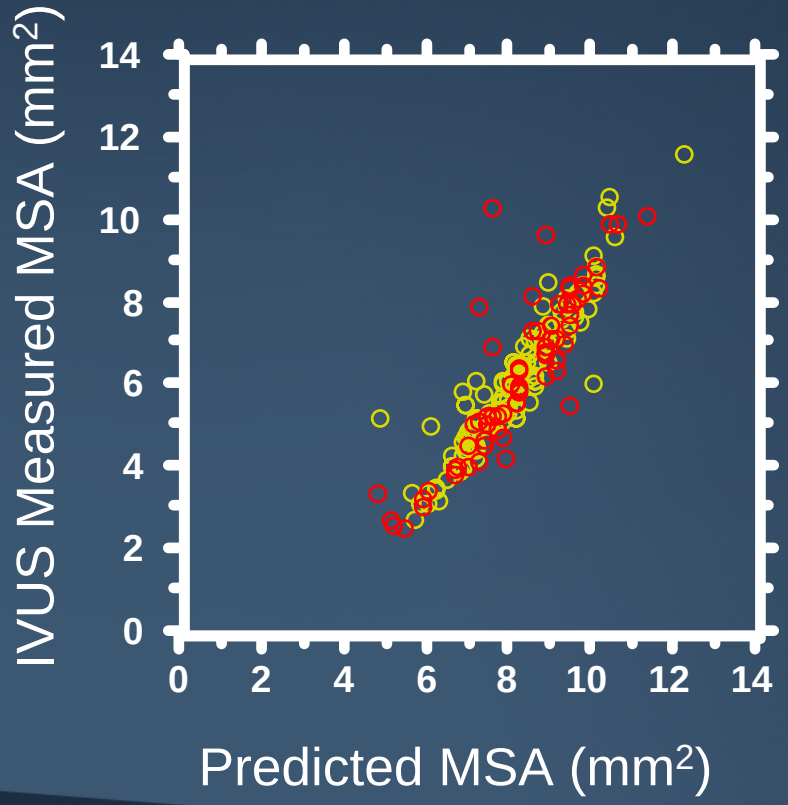
“Optimal” MSA and TLR after DES Implantation (n=595)

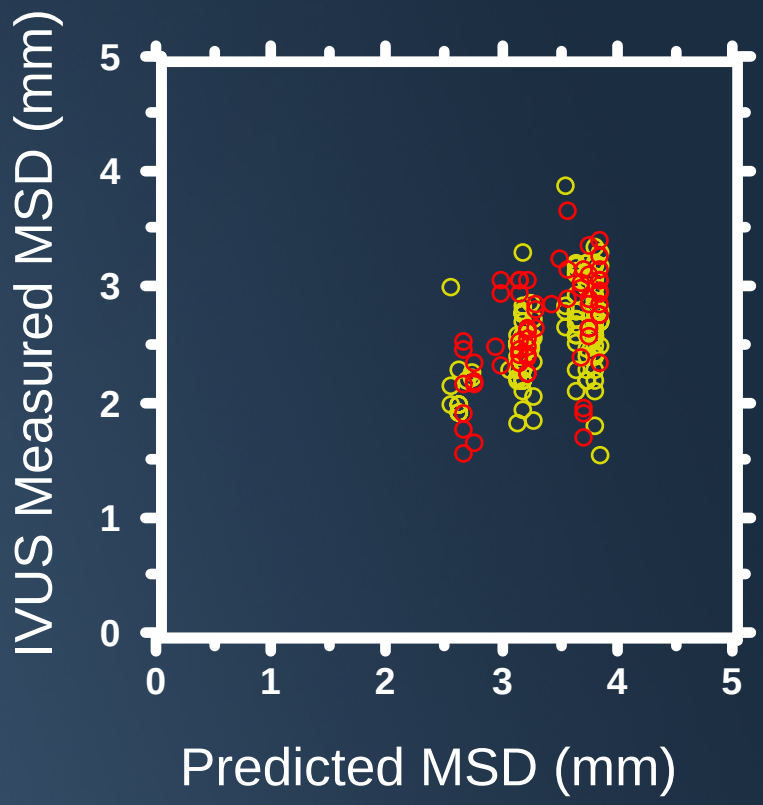


(SJ Park et al. TCT 2007)

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)





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

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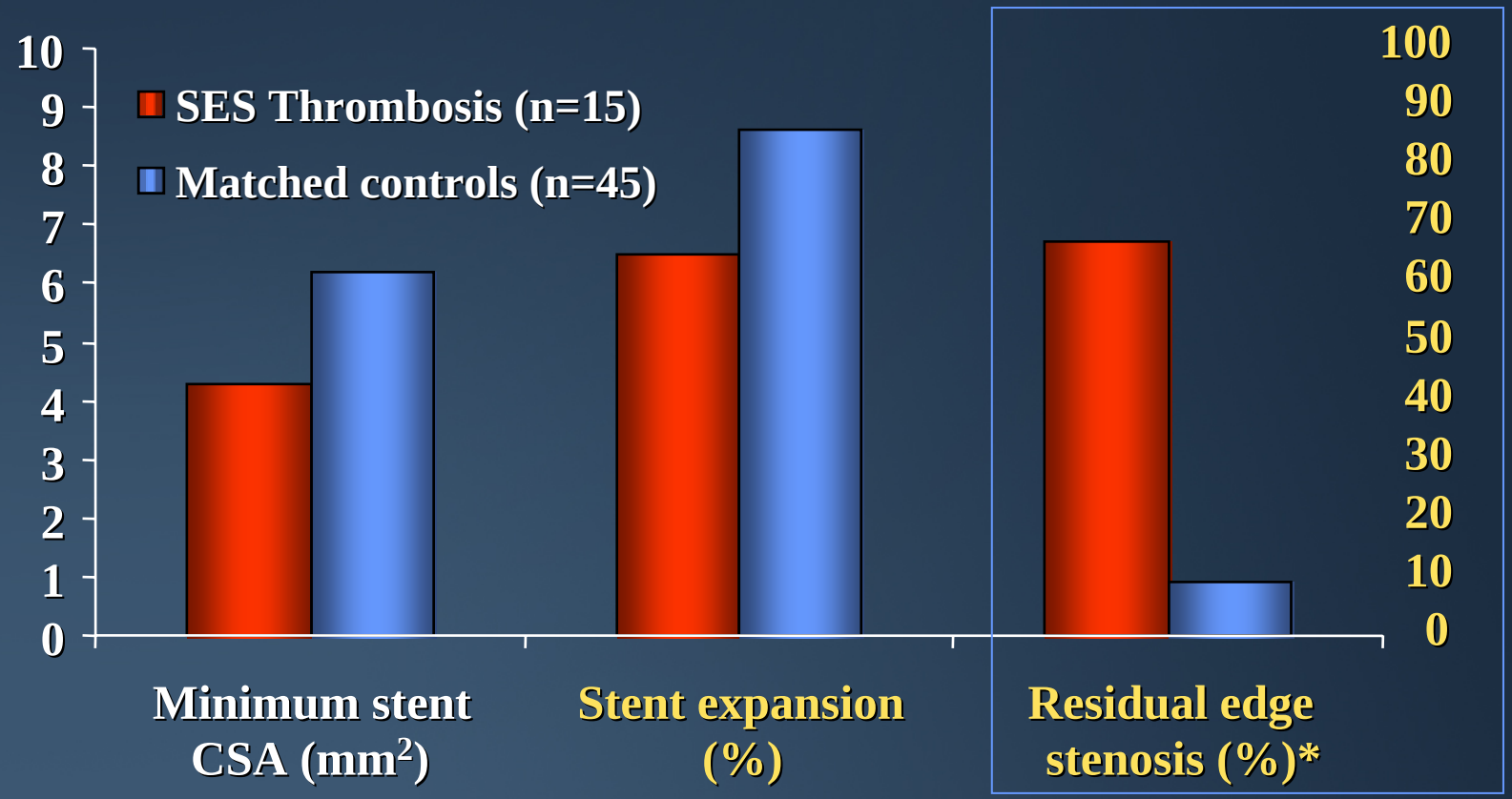
“Unstented” Secondary Edge Stenoses, Dissections, or Other Complications - AKA Longitudinal Geographic Miss

Predictors of Cypher Thrombosis within 1 year @ CRF



*Residual edge stenosis = edge lumen CSA <4.0mm² & plaque burden >70%.

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(Fujii et al. J Am Coll Cardiol 2005;45:995-8)

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IVUS Predictors of Stent Edge Restenosis in SIRIUS

Baseline Parameters	Peri-stent Stenosis	No Peri-stent Stenosis	p
Reference MLA (mm^2)	4.7±2.3	6.5±2.3	0.06
Reference Residual Plaque Burden (%)	*60.5±9.0*	*49.1±11.5*	*0.03*
Edge SA / Reference MLA	*1.5±0.3*	*1.2±0.3*	*0.03*
Maximum Pressure (mm)	15.4±3.2	16.9±2.7	ns
Balloon / Artery Ratio	0.9±0.1	1.0±0.1	ns

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(Sakurai et al. Am J Cardiol 2005;96:1251-3)

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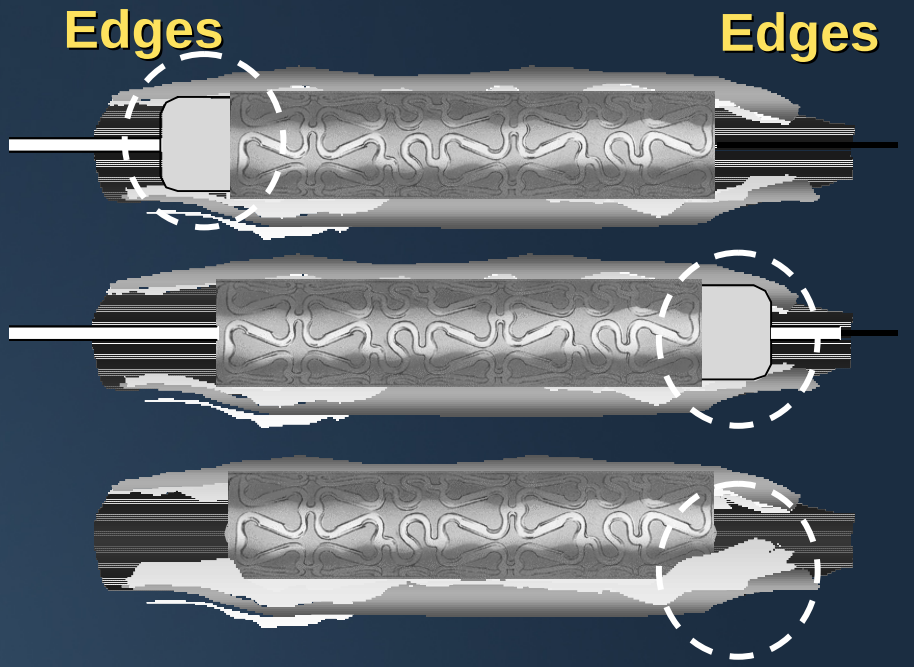
S.T.L.L.R. Registry

Longitudinal Geographic Miss

Balloon Injury
- *Proximal*
- *Distal*

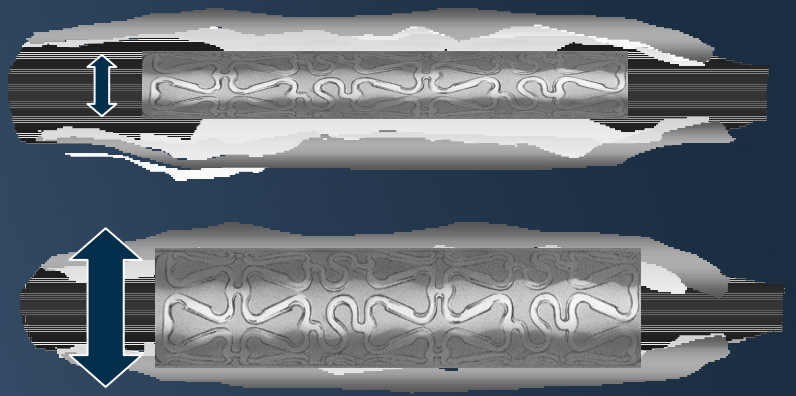
Uncovered plaque



Axial Geographic Miss

Stent/Balloon:Artery ≤ 0.9

Stent/Balloon:Artery >1.3



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(Costa et al, Am J Cardiol, in press)

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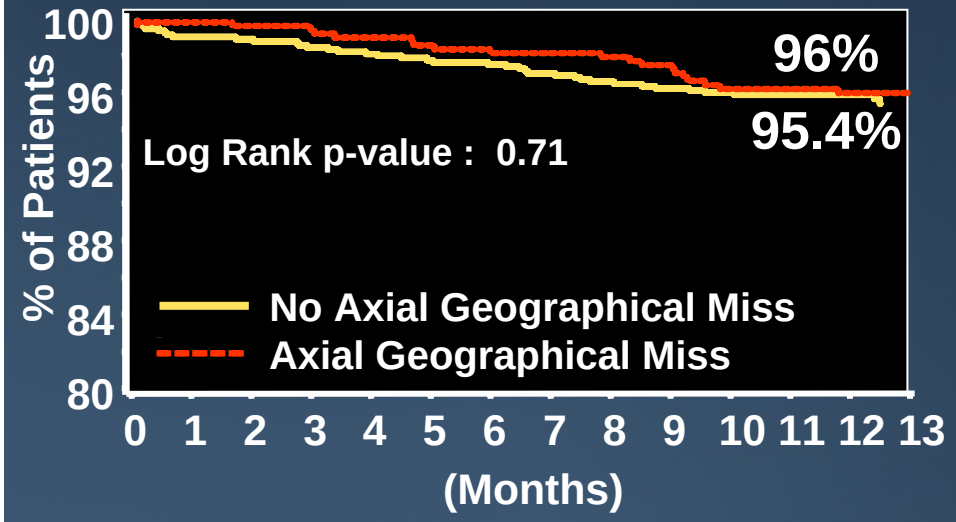
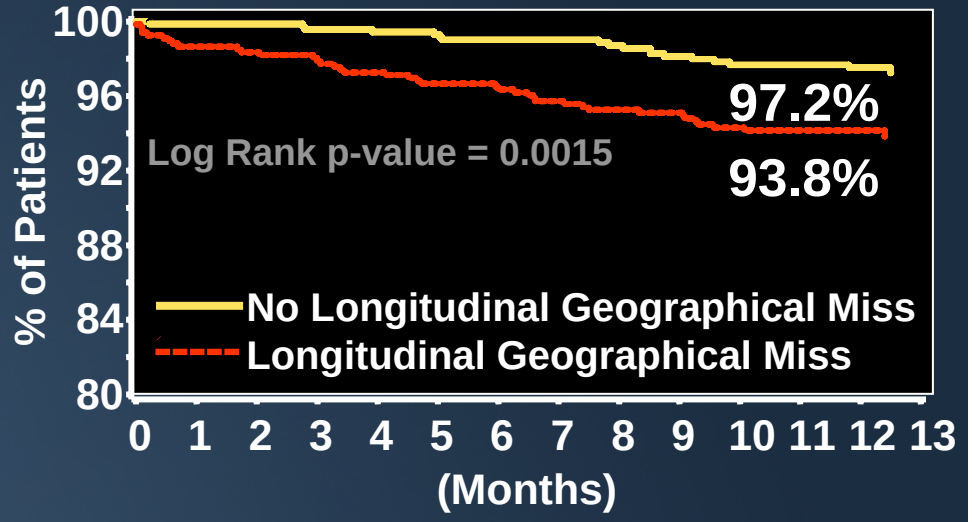
Freedom from 1-Year Clinically Driven TLR by Type of Geographic Miss





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(Costa et al, Am J Cardiol, in press)

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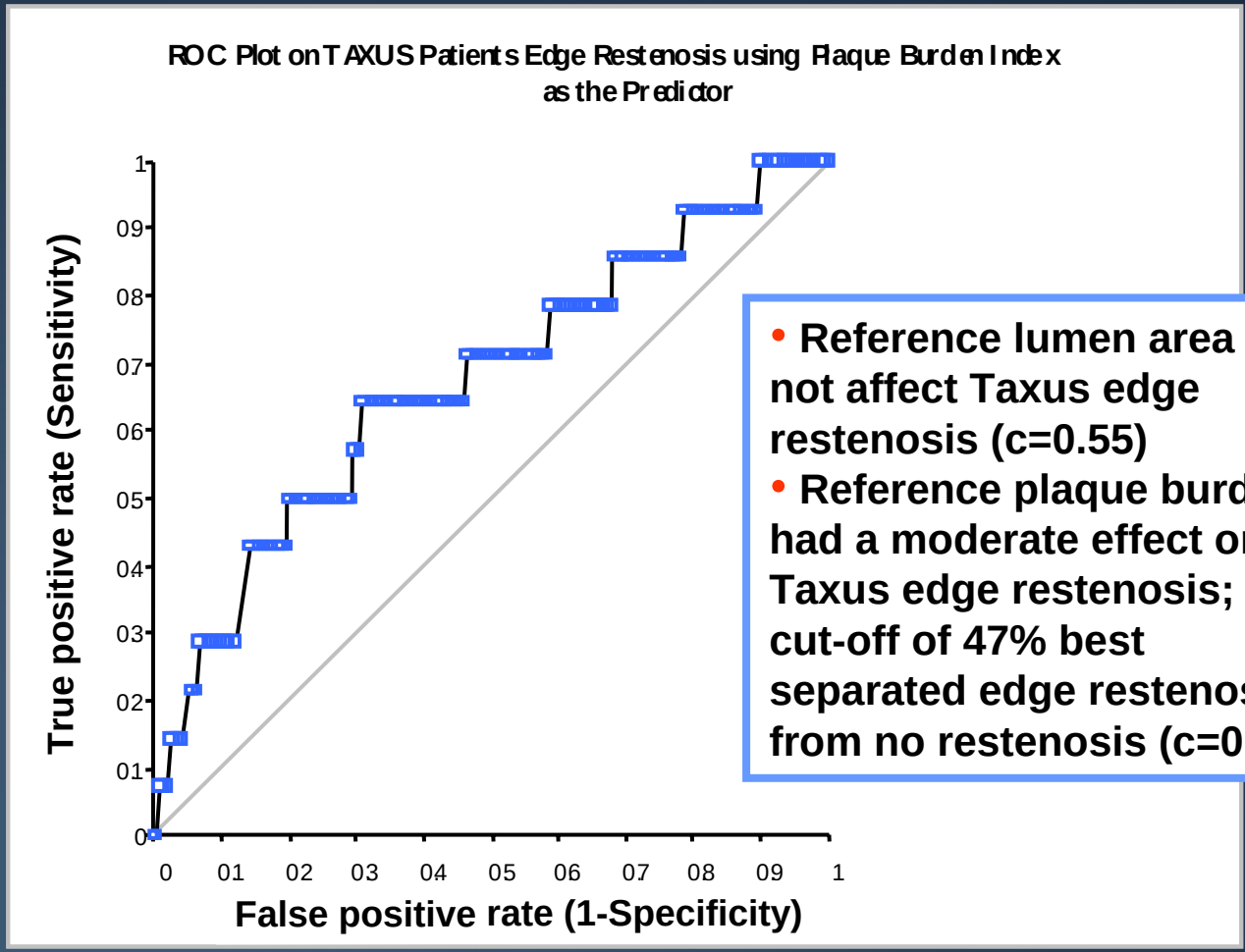
Comparison of 9-month QCA edge restenosis vs reference lumen area and plaque burden in TAXUS-IV, V, and VI (n=810)



- 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 47% best separated edge restenosis from no restenosis (c=0.67)

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(Liu et al, ACC 2008)

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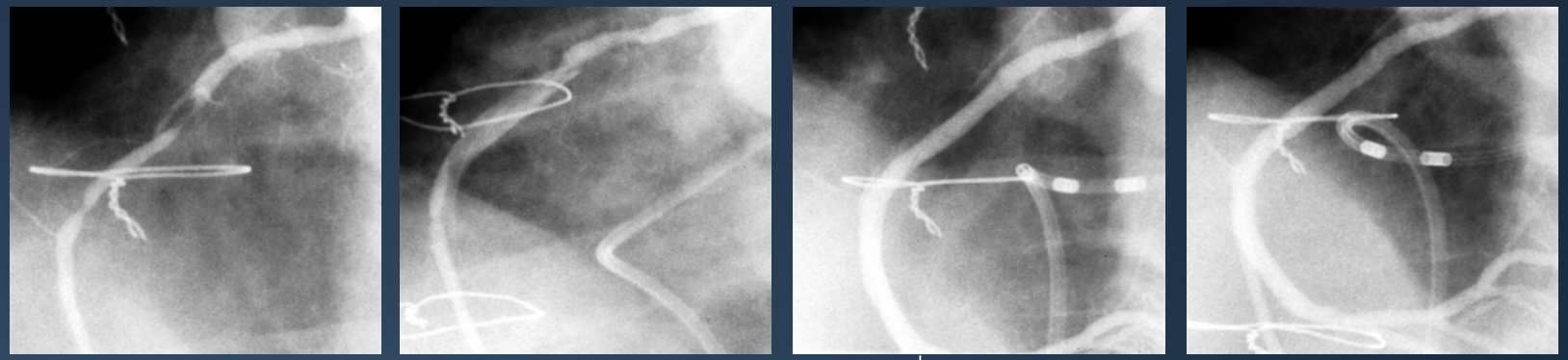
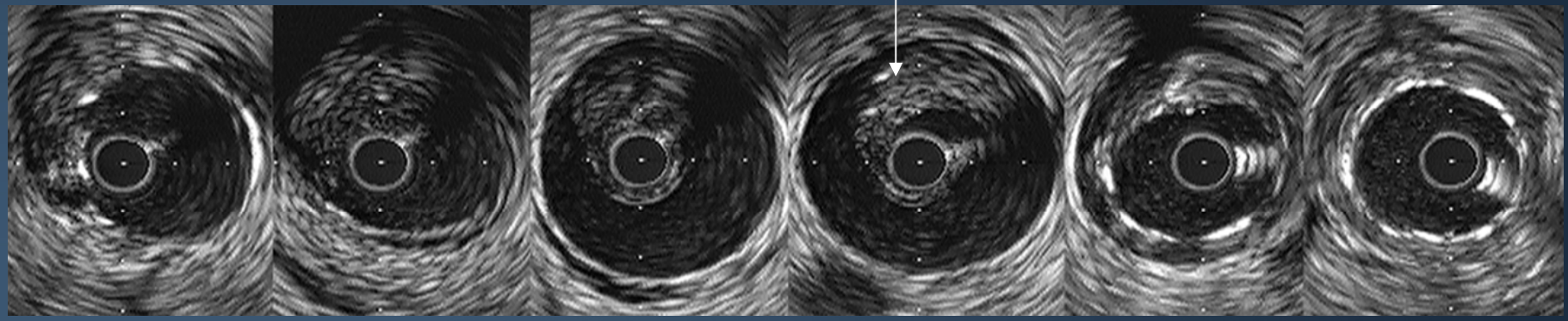
Major Dissection





0 → 5.0mm → 25.0mm

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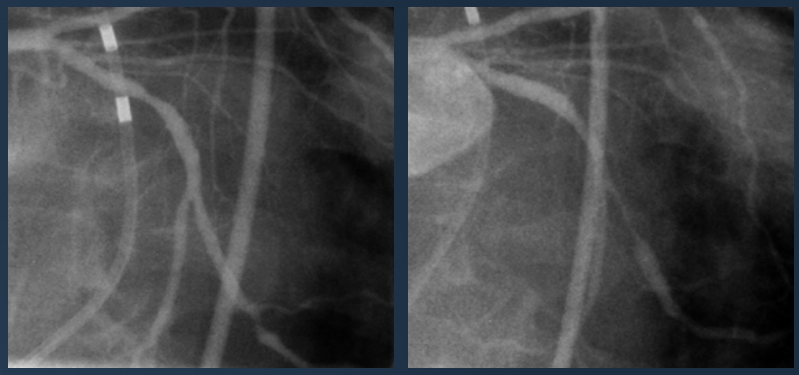
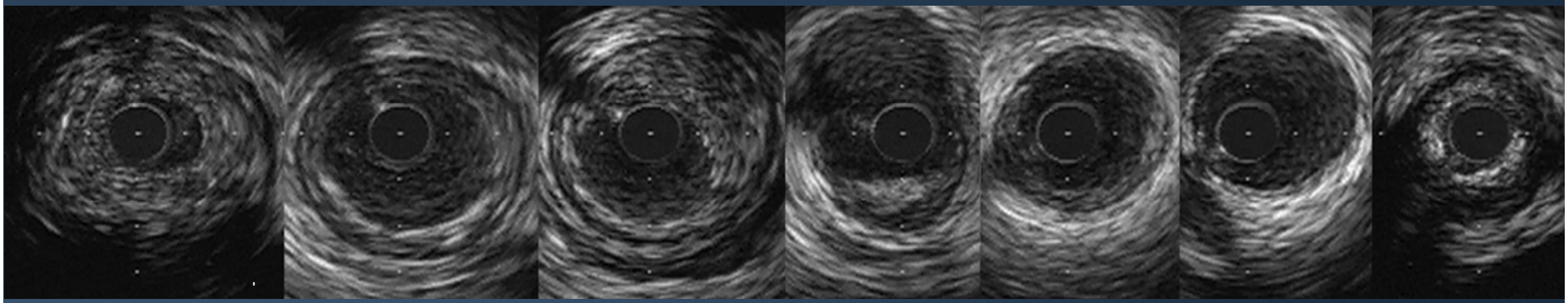
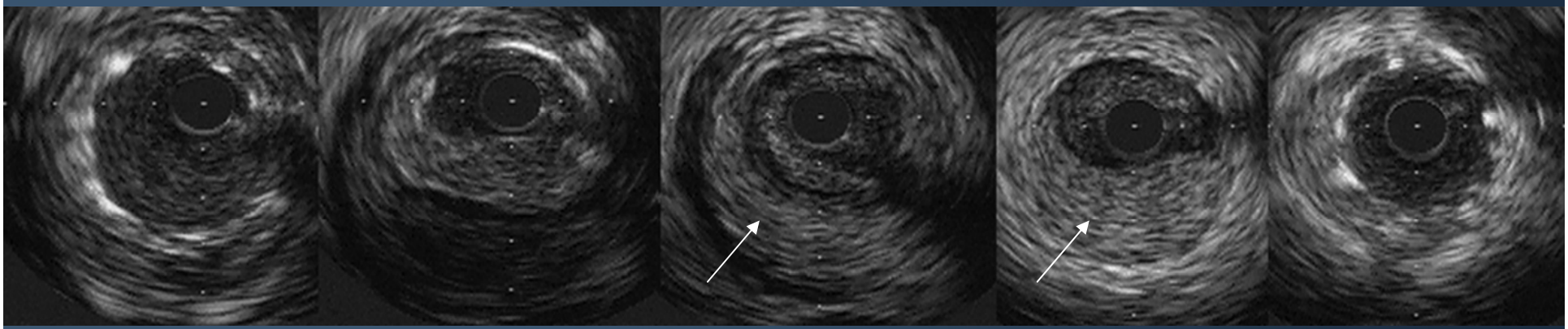
Intramural & Extramural Hematoma





0 → 7.5mm → 45.0mm



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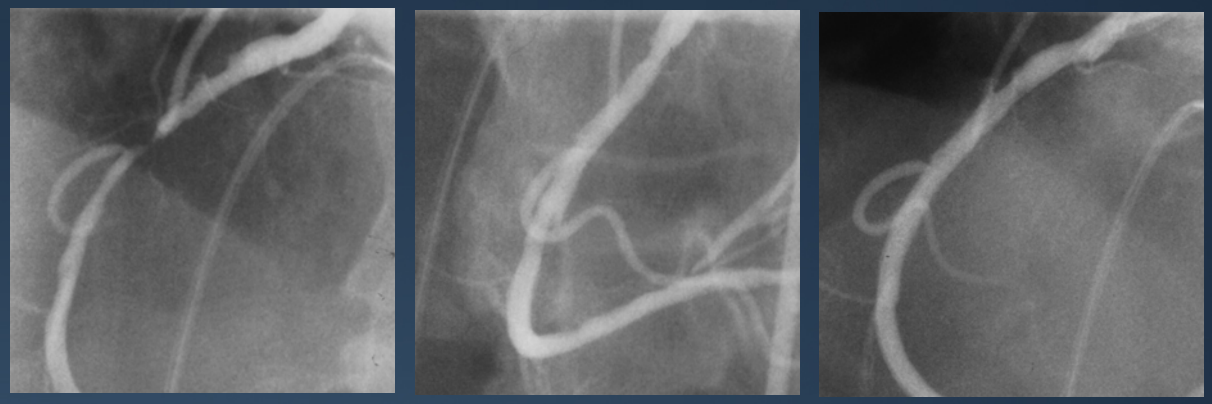
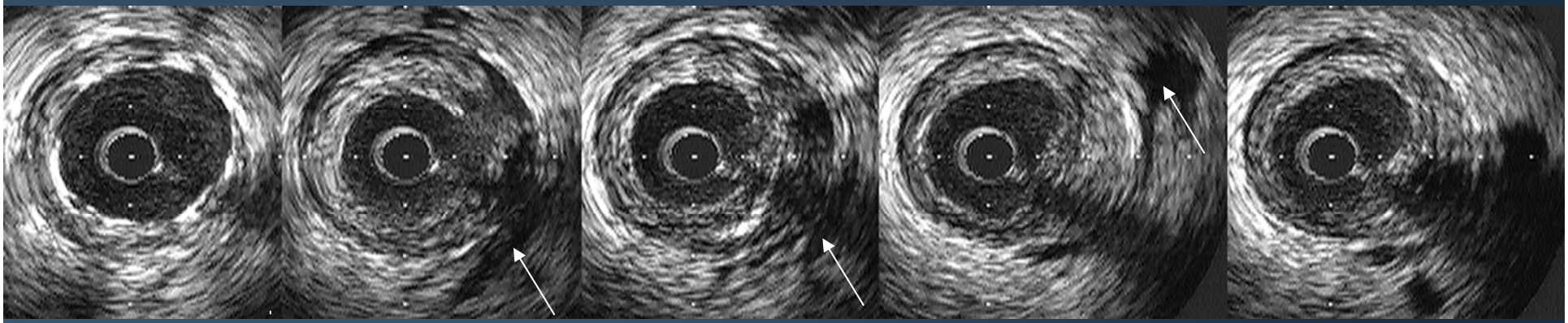
Perforation





0 → 1.5mm → 6.0mm

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Stent Malapposition

Acute Stent Malapposition

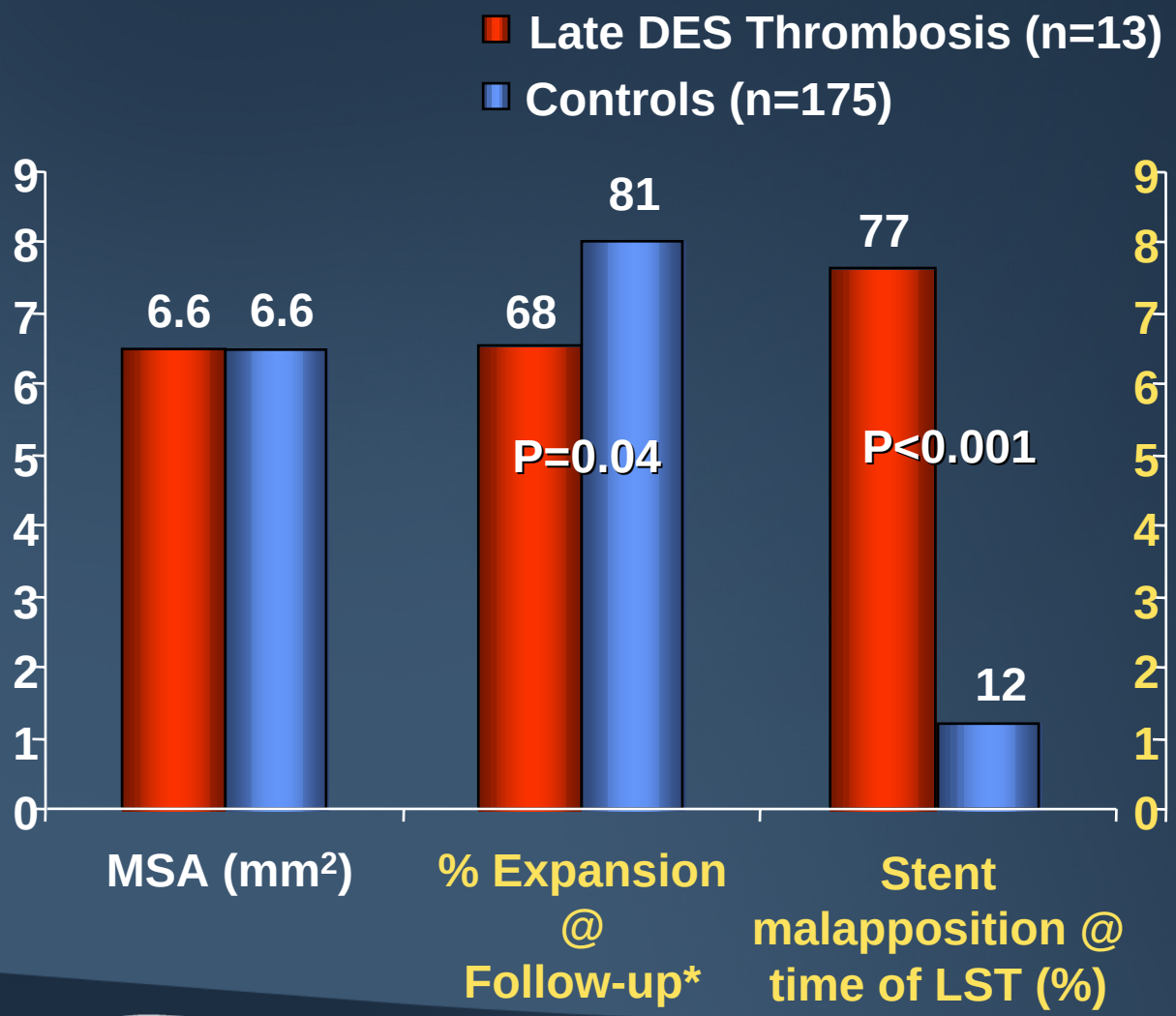
- **Most acute stent malapposition is modest in size.**
- **Although it was one of the original Colombo criteria, there is little or no data linking *isolated* acute stent malapposition to adverse clinical events including DES thrombosis.**
- **Persistent stent malapposition is associated with *less* intimal hyperplasia – presumably because the drug can cross small stent vessel-wall gaps**
  (*Balakrishnan et al., Circulation 2005;111:2958-65)*

Two Cases of Very Late Stent Thrombosis after DES Implantation

- LSM @ 6 months occurred in 10/195 (5.1%) lesions overall
  - 7/175 sirolimus-eluting stents
  - 3/20 paclitaxel-eluting stents
- Subsequent follow-up of 19±9 months
- ***Two patients developed late stent thrombosis (331 and 1152 days). These patients had a 20% (50mm^3) and a 39% (135mm^3) increase in EEM volume and, presumably, severe LSM***

(Siquiera et al. J Am Coll Cardiol 2006;47:365A)
(Feres et al. Cath Cardiovasc Intervent 2006;68:83-8)
(Siquiera et al. Eur Heart J 2007;28:1304-9)

IVUS Predictors of Very Late (>12 months) DES Thrombosis



Expansion was assessed at follow-up. "Underexpansion" may have represented an increase in reference vessel size (positive remodeling) rather than true underexpansion.

(Cook et al. Circulation 2007;115:2426-34)

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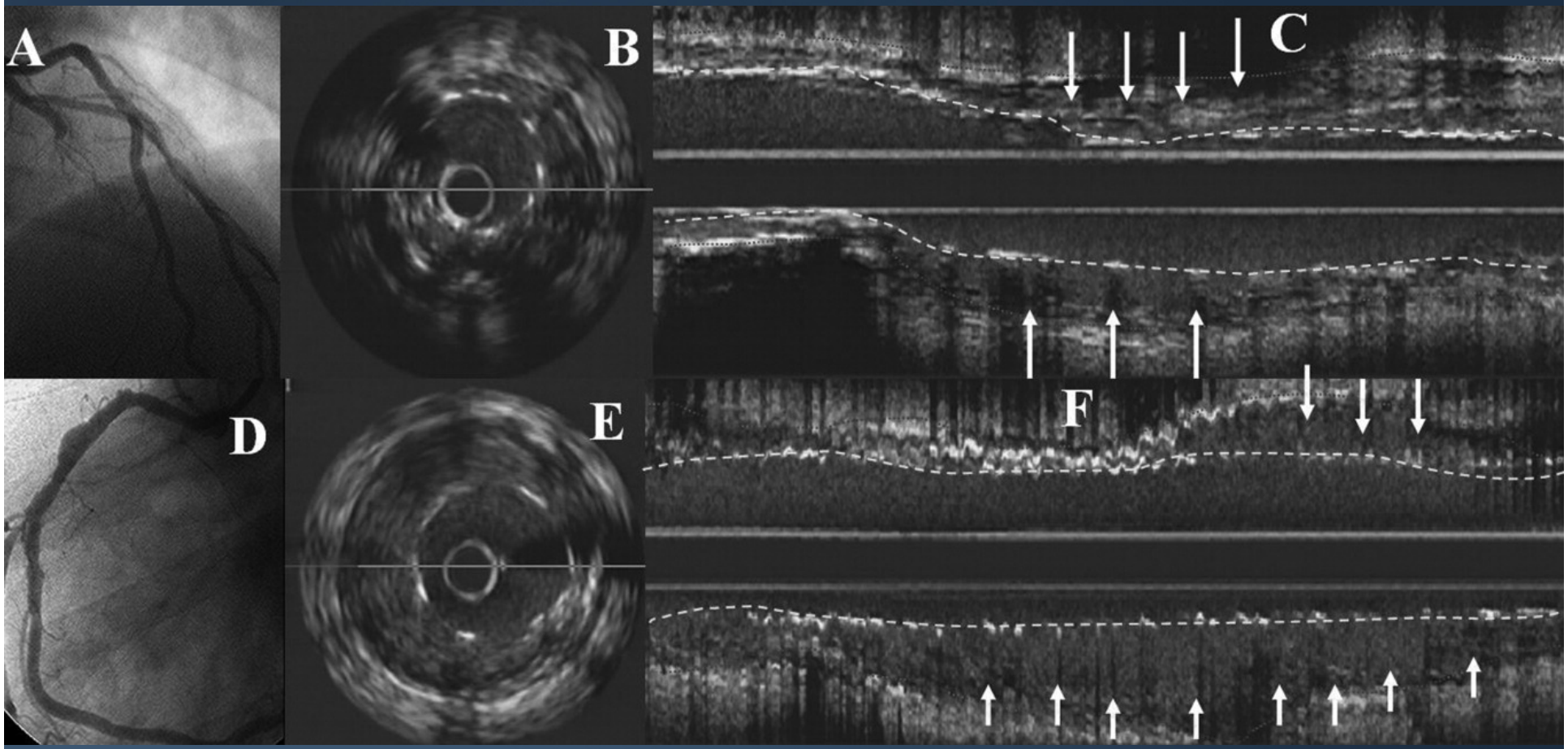

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Frequency and Predictors of Late Stent Malapposition

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Cypher Stent Trials

	Cypher	BMS	p
RAVEL	N=48	N=47	
All late malapposition	20%	4%	<0.015
SIRIUS	N=80	N=61	
Persistent malapposition	7.5%	9.8%	
New late malapposition	8.7%	0	<0.05
All late malapposition	16.3%	9.8%	

(Serruys et al. Circulation 2002;106:798-803)
(Ako et al. J Am Coll Cardiol 2005;46:1002-5)

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Taxus Stent Trials

	MR	SR	BMS	p
TAXUS-II	**N=116**	**N=113**	**N=240**	
Persistent malapposition	**0**	**4.4%**	**3.3%**	**NS**
New late malapposition	**9.5%**	**8.8%**	**5.4%**	**NS**
All late malapposition	**9.5%**	**13.2%**	**8.7%**	**NS**
TAXUS-IV, V, VI	**N=78**	**N=209**	**N=367**	
Persistent malapposition	**10.3%**	**2.4%**	**3.3%**	**0.0059**
New late malapposition	**16.7%**	**5.3%**	**3.3%**	**<0.0001**
All late malapposition	**27.0%**	**7.7%**	**6.6%**	**<0.0001**

Predictors in TAXUS-II: Lesion length, unstable angina, no DM
Predictors in TAXUS-IV, V, VI: Lesion length

(Tanabe et al. Circulation 2005;111:900-5)
(Weissman et al. Eur Heart J 2007;28:1574-82)

AMC Experience

- LSM occurred in 85/705 (12.1%) lesions overall
  - 71/538 (13.2%) sirolimus-eluting stents
  - 14/167 (8.4%) paclitaxel-eluting stents
  - 25.0% (4/16) after DCA before stenting
  - 27.5% (14/51) in CTO lesions
  - 31.8% (7/22) after primary stenting in acute MI
- Independent predictors of LSM were
  - total stent length (OR=1.02, p=0.001)
  - primary stenting in acute MI (OR=4.26, p=0.003)
  - CTO lesions (OR=2.59, p=0.007).

(Hong et al. Circulation 2006;113:414-9)

Clinical Consequences?

RAVEL, SIRIUS and E-SIRIUS

- 180 Cypher and 145 BMS with follow-up IVUS
  - Stent malapposition in 25% of Cypher and 8.3% of BMS ($p<0.001$)
  - Cypher patients with late malapposition had
    - Less diabetes, worse angina, and longer lesions at baseline
    - Larger EEMs at follow-up
- Clinical follow-up at 4 years
  - No difference in K-M event-free survival curves comparing patients with vs without late stent malapposition
  - Only one late stent thrombosis in the entire cohort – a patient with a Cypher stent and stent malapposition

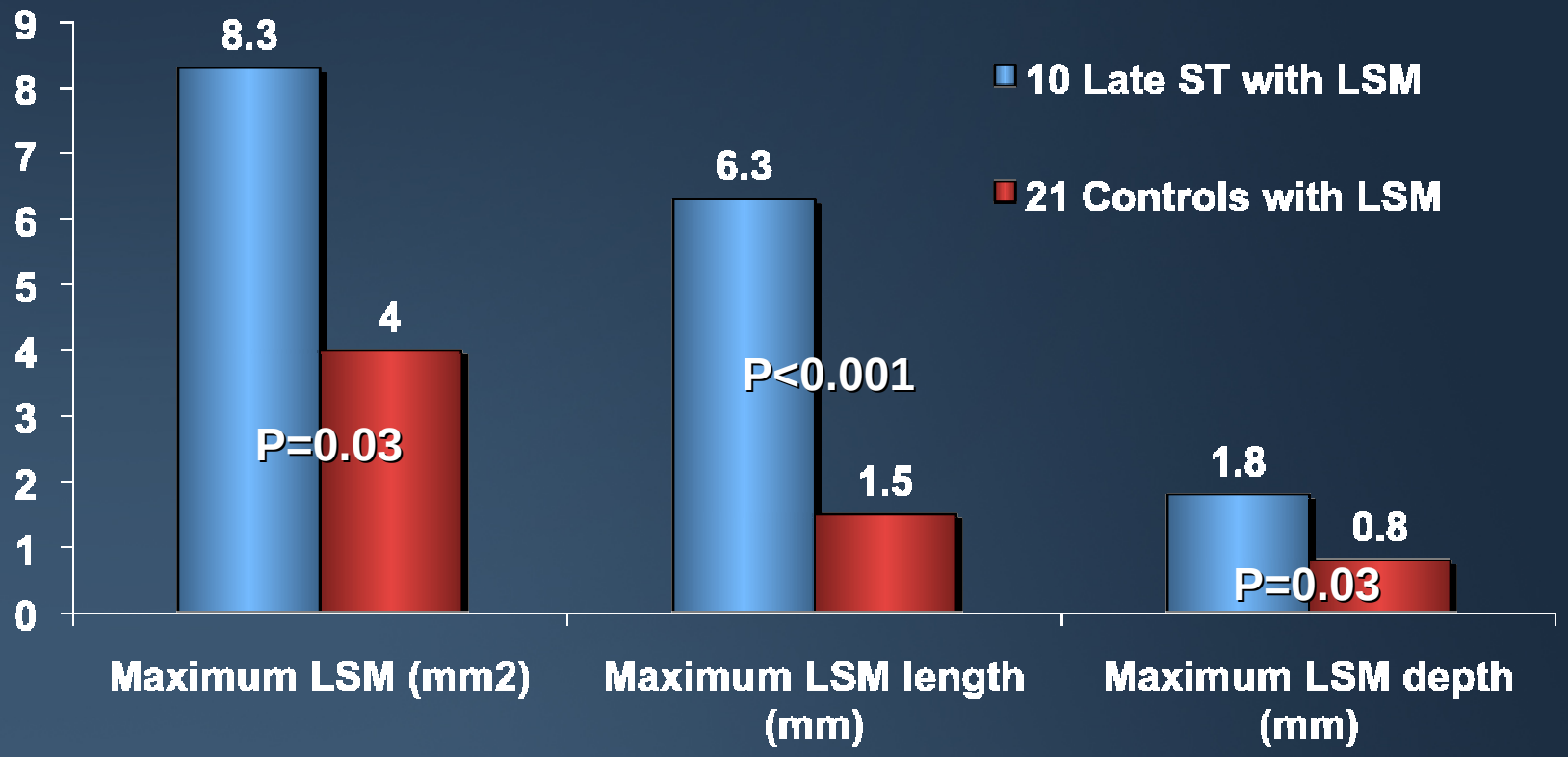
(Hoffmann et al. Heart 2008;94:322-8)

AMC Experience

- LSM occurred in 85/705 (12.1%) lesions overall
- At 10 months follow-up after detection of LSM. . .
  - Except for only one death in the non-LSM group, there were no MACE in either LSM or non-LSM patients
- At 30 month follow-up after detection of LSM (and 27 months after cessation of dual antiplatelet therapy)
  - There was one cardiac death and one MI due to very late stent thrombosis in the LSM group and two cardiac deaths and two MIs due to very late stent thrombosis in non-LSM patients.
  - There were no significant difference in overall MACE (3.8% versus 2.6%, respectively, p=0.4)
  - LSM was not an independent predictor of long-term MACE events.

(Hong et al. Circulation 2006;113:414-9)
(Hong et al, J Am Coll Cardiol 2007;50:1515-6)

Quantification of LSM in Patients with Very Late DES Thrombosis



(Cook et al. Circulation 2007;115:2426-34)

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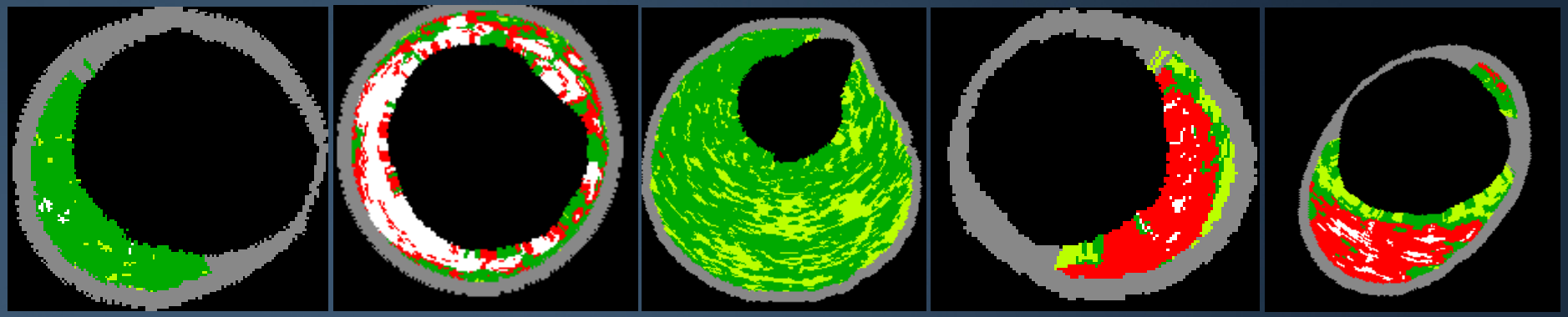
It is not clear that LSM alone - as an isolated rheologic phenomenon - can cause late stent thrombosis. . .

"We have shown that in humans delayed healing is common with current DES and that in those that thrombose, other factors, such as hypersensitivity reaction, bifurcating and ostial stenting, penetration of a necrotic core, stent malapposition, and restenosis, may also be important predictors of thrombosis."

(Luscher et al. Circulation 2007;115:1051-8)

- **But it is interesting to speculate that the composition of the plaque and the size and location of the necrotic core - either at the lesion site or at the edge of the stent - is important in late events (thrombosis and acute coronary syndromes).**



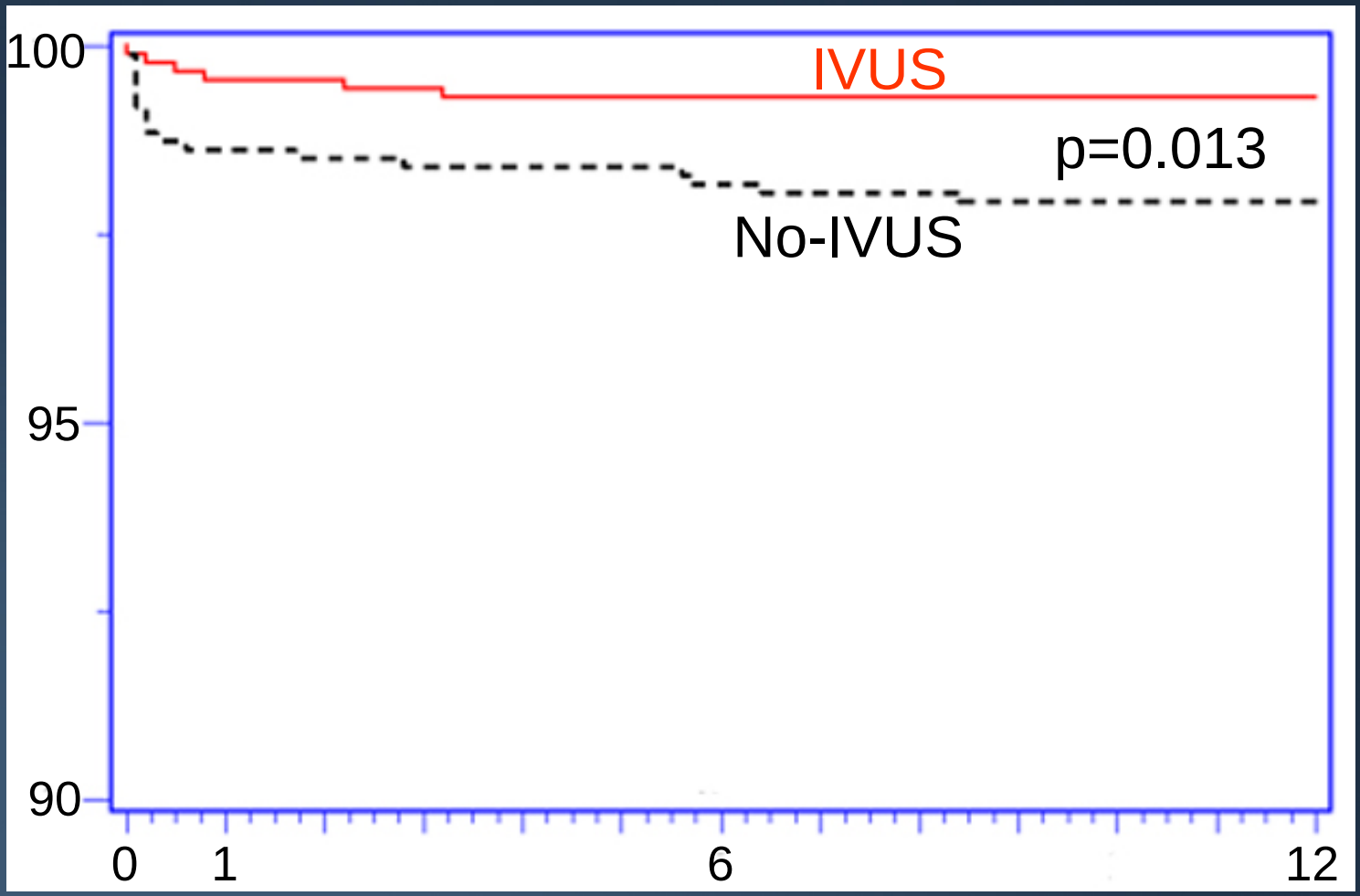
This will be studied in ADAPT-DES

1296 IVUS-guided, DES-treated lesions in 884 pts vs 1312 propensity-score-matched, angio-guided, DES-treated lesions in 884 pts

	IVUS-guided	Angio-guided	p
30 day			
MACE	2.8%	5.2%	0.01
Stent thrombosis	0.5%	1.4%	0.045
TLR	0.7%	1.7%	0.045
1 year			
MACE	14.5%	16.2%	0.3
Definite stent thrombosis	0.7%	2.0%	0.014
Probably stent thrombosis	4.0%	5.8%	0.08
TLR	5.1%	7.2%	0.06
Late definite stent thrombosis	0.2%	0.7%	0.3

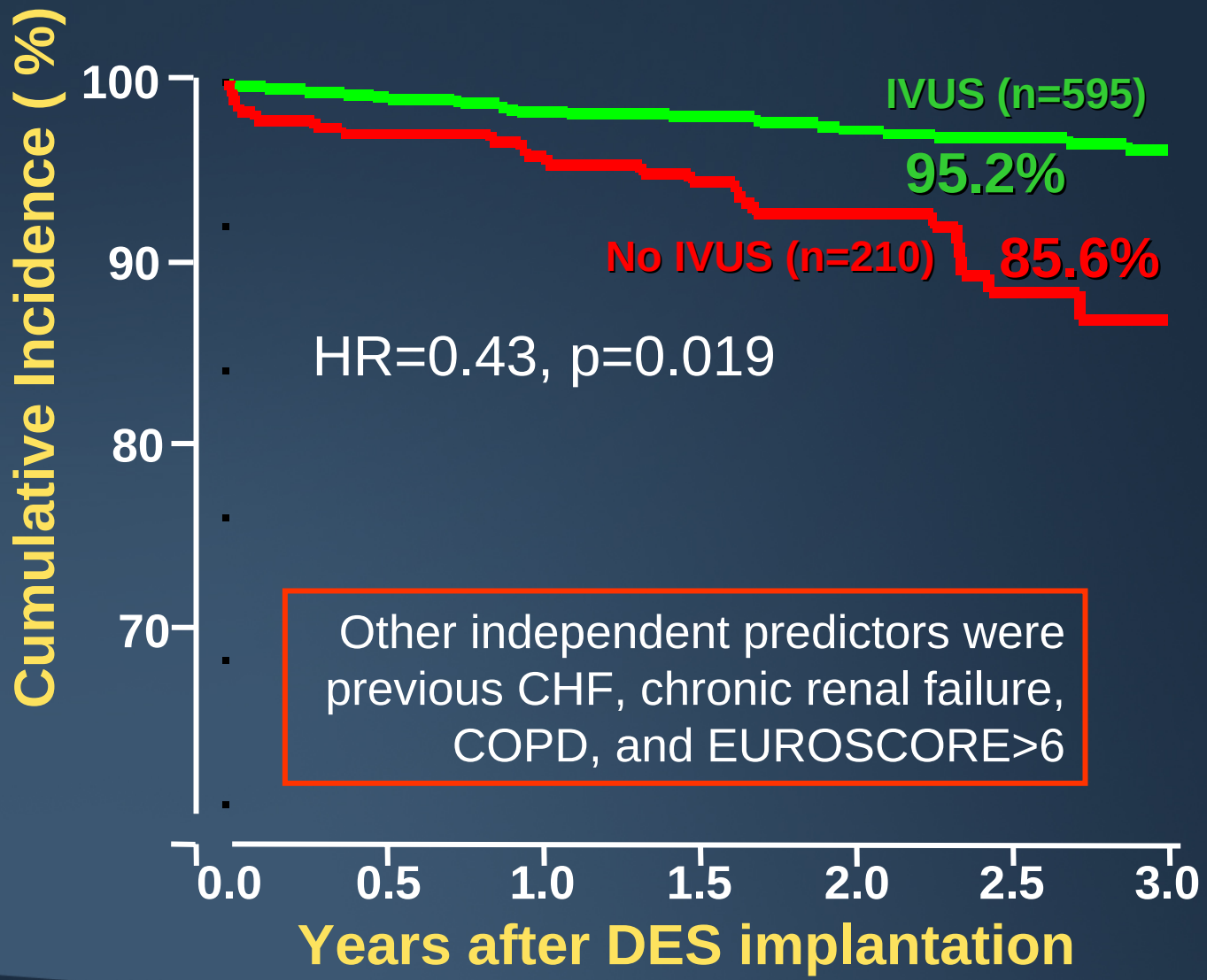
(Roy et al. Eur Heart J, in press)

Stent-thrombosis Free Survival (%)



(Roy et al. Eur Heart J, in press)

All-Cause Mortality After LMCA DES Implantation: Impact of IVUS Guidance



(SJ Park et al. TCT 2007)

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Conclusion

- Especially in high risk patient and lesion subsets, it is likely that routine IVUS use during DES implantation will improve patient outcomes and reduce acute, subacute, and late DES thrombosis and restenosis . . . By. . .
  - identifying acute implantation issues - primarily underexpansion, secondary edge stenoses, and complications
  - guiding appropriate remedies
- However, the effect of acute, mechanical implantation problems on DES complications decreases over time. Therefore, unless IVUS can identify plaque or lesion morphology associated with delayed healing (?large superficial necrotic core), the impact of IVUS guidance on very late stent thrombosis is likely to be minimal.