The Role of IVUS and OCT in the Diagnosis and Treatment of Stent Thrombosis

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ARC Definitions

Level of Certainty	Timing
Definite	**Early**
Angiographic or pathologic confirmation of partial or total thrombotic occlusion within the peri-stent region AND at least ONE of the following, additional criteria:	Acute (<24 hrs)
Acute ischemic symptoms	Subacute (24 hrs – 30 d)
Ischemic ECG changes	**Late**
Elevated cardiac biomarkers	31 d – 1 yr
Probable	**Very Late**
Any unexplained death <30 days of stent implantation	> 1 yr
Any MI related to documented acute ischemia in the territory of the implanted stent w/o angiographic confirmation of stent thrombosis and in the absence of any other obvious cause	
Possible	
Any unexplained death beyond 30 days	

(Cutlip et al. Circulation. 2007;115:2344-51)

IVUS Predictors/Findings in Early Stent Thrombosis

	BMS	DES
Small MSA or MLA or underexpansion	•*Cheneau et al. Circulation 2003;108:43-7* •*Alfonso et al. Heart 2004;90:1455-9*	•*Fujii et al. J Am Coll Cardiol 2005;45:995-8)* •*Okabe et al., Am J Cardiol. 2007;100:615-20* •*Liu et al. JACC Cardiovasc Interv. 2009;2:428-34* •*Choi et al. Circulation Cardiovasc Interv. 20011;4:239-47*
Edge problems (geographic miss, secondary lesions, large plaque burden, dissections, etc)	•*Cheneau et al. Circulation 2003;108:43-7* •*Alfonso et al. Heart 2004;90:1455-9*	•*Fujii et al. J Am Coll Cardiol 2005;45:995-8* •*Okabe et al., Am J Cardiol. 2007;100:615-20* •*Liu et al. JACC Cardiovasc Interv. 2009;2:428-34* •*Choi et al. Circulation Cardiovasc Interv. 20011;4:239-47*

Although it was one of the original Colombo criteria and *although 2/3 of inteventional cardiologists believe otherwise*, there is little or no data linking *isolated* acute malapposition to adverse clinical events including stent thrombosis.

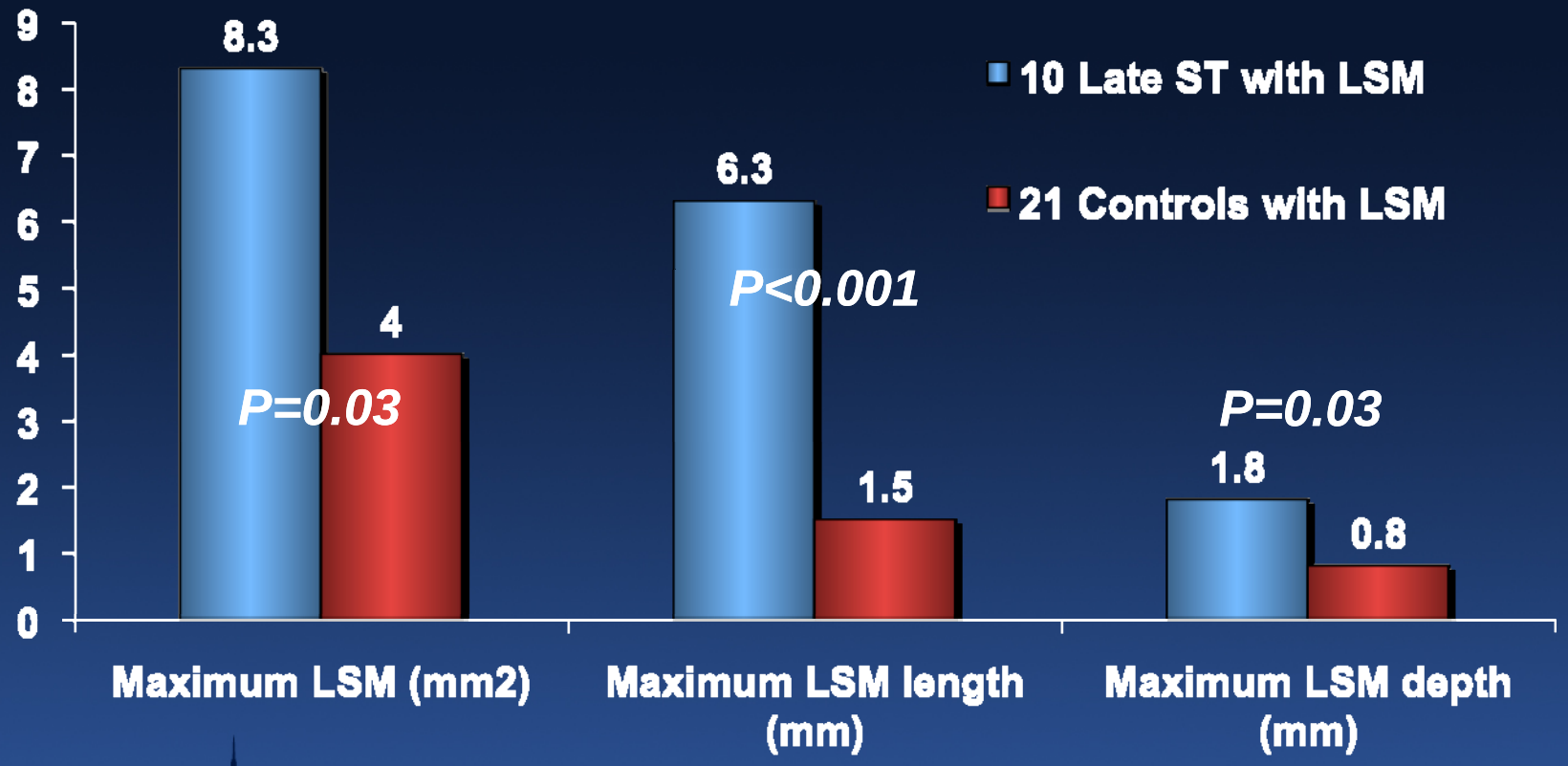
- **Stent malapposition is associated with *less* intimal hyperplasia – the drug can cross small stent vessel-wall gaps**
  - *Hong et al, Circulation. 2006;113:414-9*
  - *Kimura et al, Am J Cardiol . 2006;98:436-42*
  - *Steinberg et al, JACC Cardiovasc Intervent 2010;3:486-94*
  - *Balakrishnan et al., Circulation 2005;111:2958-65*
- **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 within the first 9 months – whether BMS or DES**
  - *Steinberg et al, JACC Cardiovasc Intervent 2010;3:486-94*
- **In HORIZONS-AMI, 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;122:1077-84*
  - *Choi et al. Circulation Cardiovasc Interv. 20011;4:239-47*

- There is almost no OCT data on early stent thrombosis. IVUS studies still show that mechanical problems – inadequate implantation – is a common cause of early stent thrombosis.
- Treatment of early stent thrombosis begins with establishing flow and involves correcting the mechanical problem.
- There is little or no IVUS or OCT data just on late stent thrombosis. A few late stent thrombosis patients are always included in studies of early or very late stent thrombosis.

The real concern is very late stent thrombosis, especially in first generation DES

- Fear that this will be an ongoing problem (indefinitely?) in patients who received Cypher or Taxus
- The mortality of patients with stent thrombosis is high
  - 25.5% 4 year rate of death/MI in 373 patients at the Thoraxcentre (1999-2011)
    - Daemen, TCT2011
  - 17% 2 year all-cause mortality in 111 patients from Denmark. (note: the moratlity of ISR presenting as NSTEMI in 38 patients was also high, 10.5%)
    - Thayssen, EuroPCR2010
- Increasing awareness of complications associated with prolonged clopidogrel use
    - SJ Park et al., N Engl J Med. 2010;362:1374-82
    - Valmigli, ESC 2011
- ***Much*** less of a problem with second generation DES

LSM was found in 77% of 13 VLST pts vs 12% of controls (p<0.0001)



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

IVUS Meta-Analysis of Late Stent Malapposition and VLST Frequency

- LSM: 17 studies with 4648 patients
  - LSM more common in DES than BMS (OR=2.5, p=0.02)
- VLST: 5 studies with 2080 patients
  - 3 Late ST (<12 mos), none in LSM
  - 6 Very late ST (>12 mos), 4 in LSM
  - Risk of very late ST was higher in LSM patients (OR=6.5, p=0.02), but only based on the expected numbers of very late ST

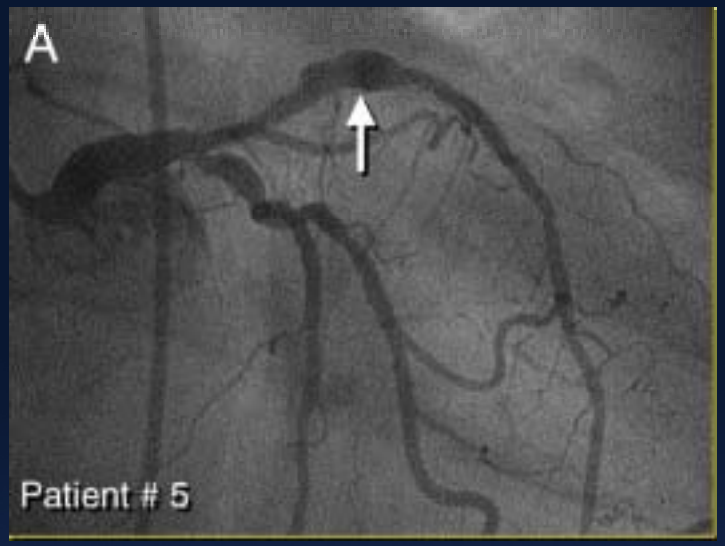
(Hassan et al. Eur Heart J 2010;31:1172-80)

	Clinical F-Up	Stent Type	LSM?	#	Observed LSM (#)		Expected VLST (#)
					LST	VLST	
Hoffmann	48 mos	SES+BMS	Y	57	0	1	0.18
			N	268	0	0	0.82
Tanabe	12 mos	PES+BMS	Y	46	0	NA	0.2
			N	423	2	NA	1.8
Hong	36 mos	SES+PES	Y	82	NA	1	0.44
			N	475	NA	2	2.56
Siqueira	29 mos	SES+PES	Y	10	0	2	0.11
			N	172	0	0	1.89
Weissman	24 mos	PES+BMS	Y	33	0	0	0.06
			N	514	1	0	0.94

Coronary Aneurysm Formation

- **Coronary aneurysms developed in 15/1197 (1.25%) consecutive pts with late angiographic follow-up after DES implantation.**
  - **Coronary aneurysms more frequently occurred when DES were implanted during acute myocardial infarction and were longer in length.**
  - **On IVUS, LSM area measured 12.1±8.6mm^2.**
  - **Two patients presented with acute myocardial infarction secondary to DES thrombosis, and 4 additional patients presented with unstable angina and underwent repeat PCI with a significant reduction in LSM area (11.6±3mm^2 to 5.5±0.6mm^2, p<0.05).**
- **After a mean follow-up of 399±347 days, the 1-year event-free survival was 49±14%; LSM area was 3.5x the size in patients with vs without subsequent events.**

(Alfonso et al. J Am Coll Cardiol. 2009;53:2053-60)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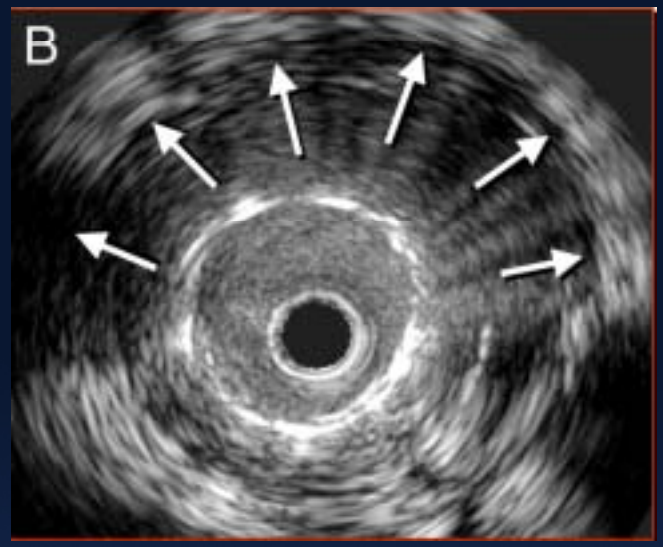
Patient # 5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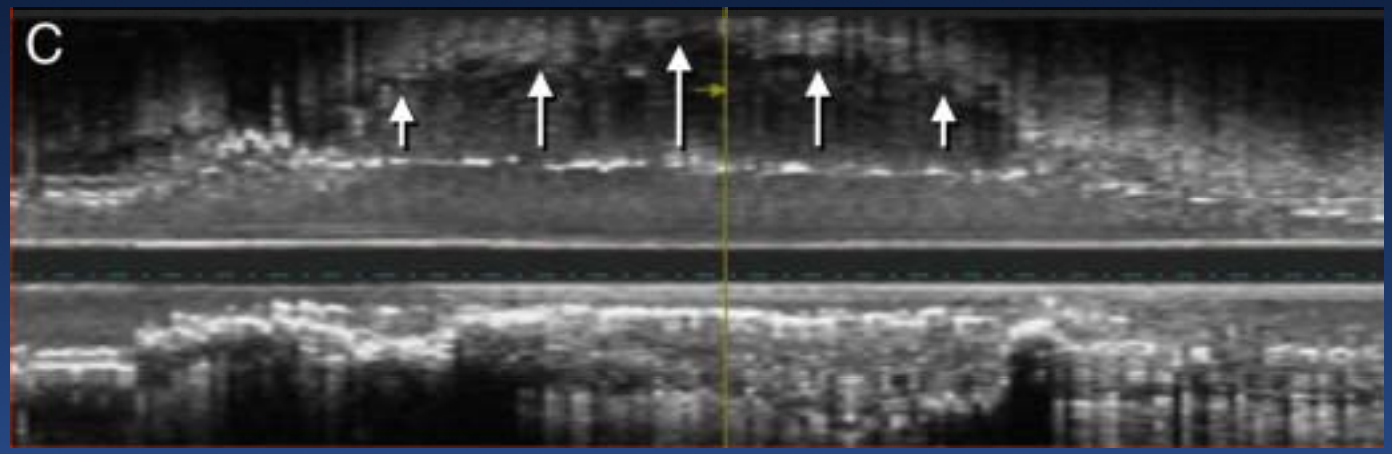
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Plus many, many case reports and case presentations. . .

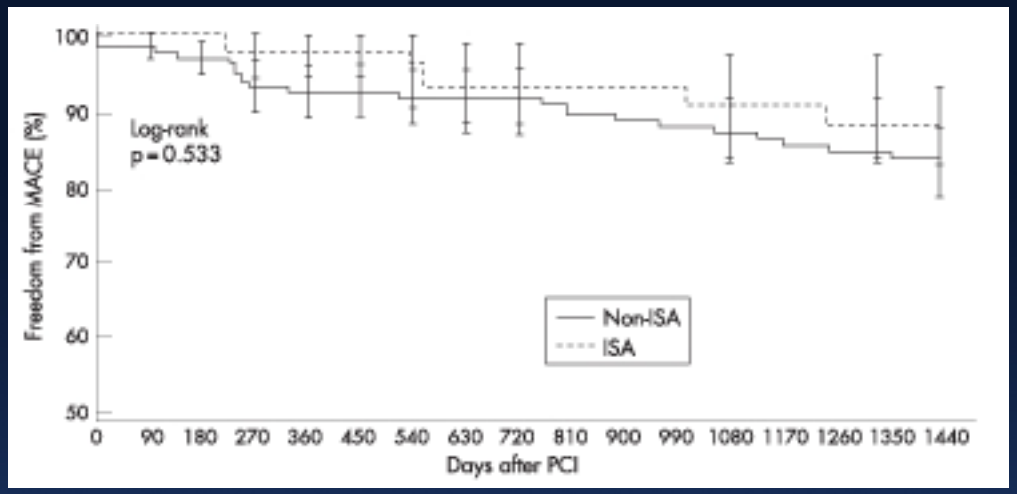
AMC Experience

- **LSM occurred in 85/705 (12.1%) lesions overall**
- **At 10 months follow-up after detection of LSM, here was one death in the non-LSM group and no MACE in the LSM group**
- **At 30 months 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% with versus 2.6% without LSM, 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)

RAVEL, SIRIUS, and E-SIRIUS

- LSM in 25% of 180 Cypher vs 8.3% of 145 BMS (p<0.001)
- Clinical follow-up at 4 years
  - No difference in K-M event-free survival curves

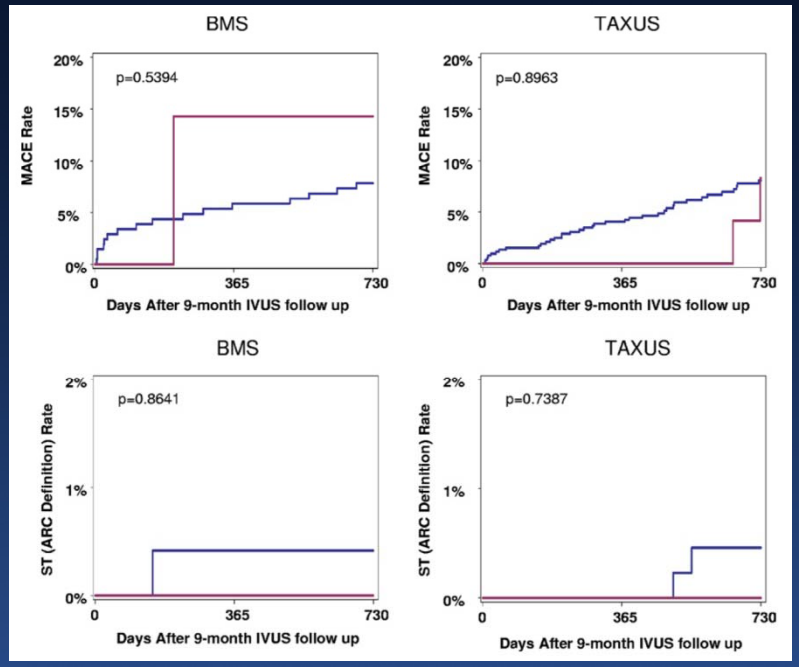


  - Trend toward more MIs in LSM groups (11.1% vs 4.4%, p=0.15, for Cypher, and 25% vs 5.3%, p=0.04, for BMS). But only 5/21 were target vessel related.
  - Only one VLST in the entire cohort in a patient with a Cypher stent and LSM
  - Independent predictors of 4-year MACE were use of BMS, # of stents, male gender – NOT LSM either overall or within Cypher and BMS groups, separately

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

TAXUS IV, V, and VI and ATLAS Workhorse, Long Lesion, and Direct Stent

- **Of the 4184 patients in these trials, 1580 patients (1098 PES and 482 BMS) were enrolled in IVUS sub-studies**
- **Two years after the 9-month IVUS follow-up. . .**
  - **MACE rates were similar in pts with vs without acquired LSM in BMS (14.3% vs 7.9%, p=0.54), TAXUS overall (8.3% vs. 8.1%, p=0.87), or TAXUS slow-release (0% vs 7.9%, p=0.28).**
  - **There were no incidences of definite/probable VLST in either BMS or TAXUS-treated patients with acquired LSM. Conversely, there were 2 incidences of definite/probable stent thrombosis in the BMS group (0.5%) and 3 in the TAXUS group (0.5%) with complete stent-vessel wall apposition.**



(Steinberg et al. J Am Coll Cardiol Intv 2010;3:486-94)

LSM in acute myocardial infarction

	Mission (AMI)		HORIZONS (AMI)	
	SES	BMS	TAXUS	BMS
Any malapposition at follow-up	37.5%	12.5%	46.3%	29.0%
Late acquired stent malapposition	25.0%	5.0%	30.8%	8.1%

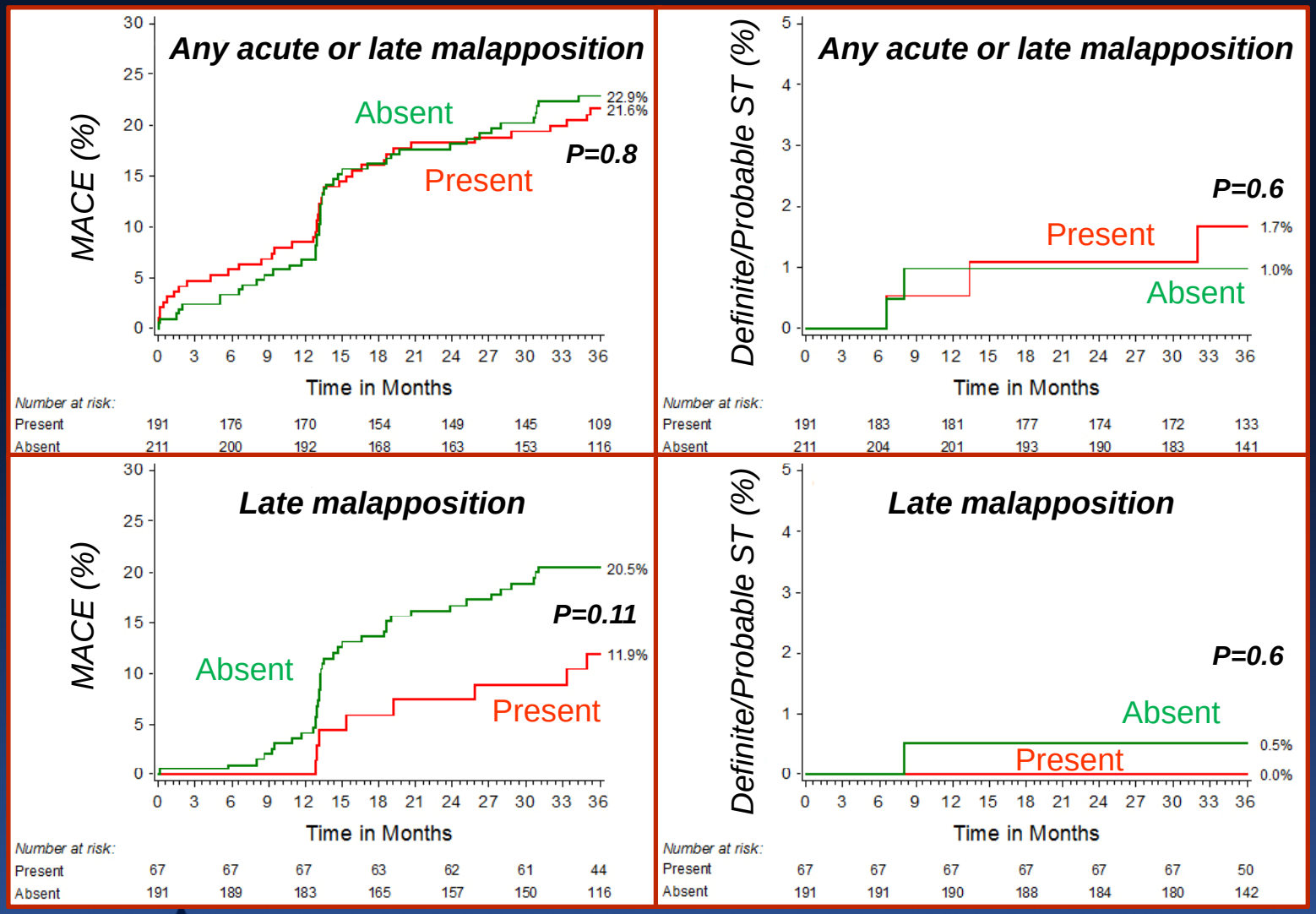
Frequency of late acquired stent malapposition in BMS presumably related to thrombus dissolution

Increased frequency of late acquired stent malapposition in DES vs BMS related to positive remodeling (77% of DES with LSM).

No increased frequency of events at 1 year post-stent implantation.

(van der Hoeven et al. J Am Coll Cardiol 2008;51:618-26)
(Maehara et al, Circulation. 2009;120:1875-82)
(Guo et al. Circulation 2010;122:1077-84)

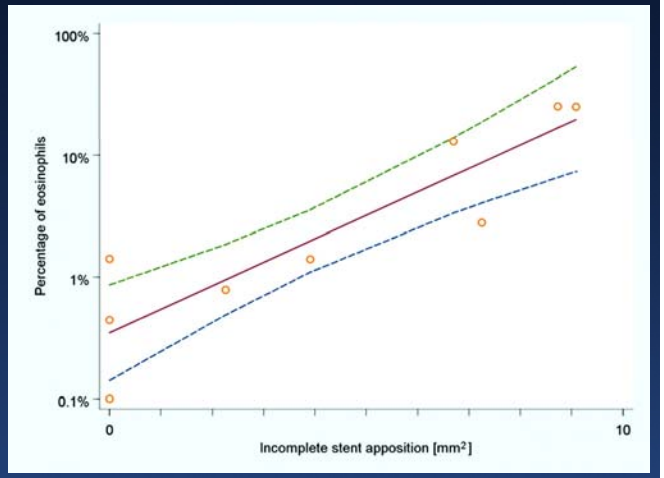
Three-year follow-up of HORIZONS-AMI



Correlation of IVUS Findings With Aspirates in 28 Pts with Very Late DES Thrombosis

- **28 pts with very late DES ST and 26 controls**
- **LSM in 73% of very late DES ST segments. Maximal LSM area measured 6.2±2.4mm², and length measured 9.4±9.5mm. LSM area exceeded 5.0mm² in 5 of 8 segments (63%)**

	WBCs	p	Eos	p
Controls		0.0001		0.038
Spontaneous MI	291±94		7±10	
Early ST-BMS	146±117		1±1	
Early ST-DES	73±117		1±2	
Very late ST-BMS	84±50		2±3	
Very late ST-DES	283±149		20±24	



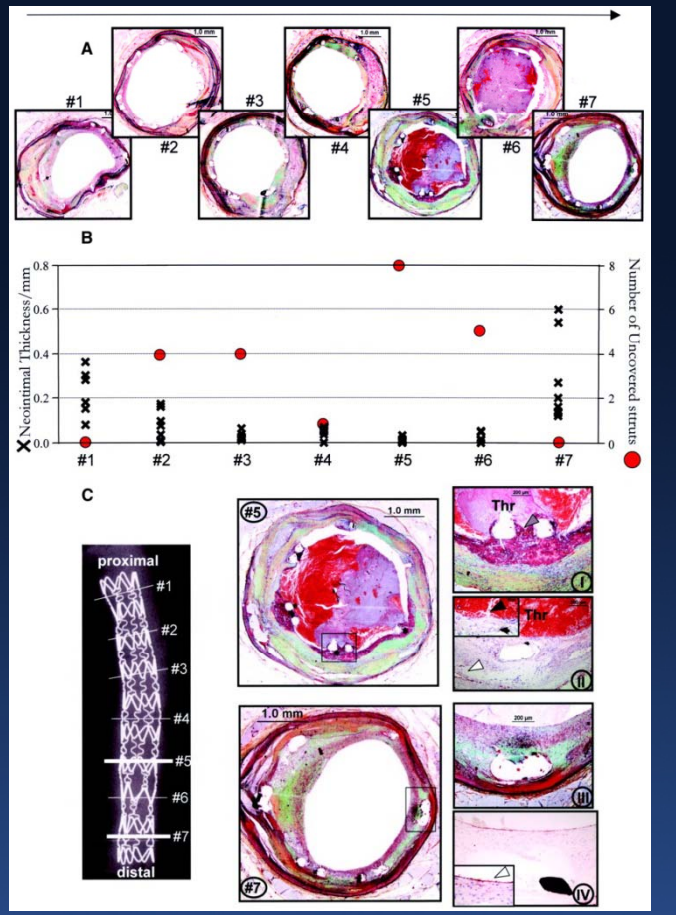
LSM area correlated with total eosinophil count (p=0.008)

(Cook et al. Circulation 2009;120:391-9)

Heterogeneity of neointimal healing after DES placement and the impact on late stent thrombosis

	DES Thrombosis (n=28)	No DES Thrombosis (n=34)	p
Fibrin score	2.4±1.3	1.2±1.1	0.002
Endothelialization, %	40.5±29.8	80.8±25.2	<0.0001
Uncovered strut per section, #	5.0±2.7	2.0±2.7	<0.0001
Stent length w/o neointima, mm	20.1±11.5	9.9±10.1	0.0004
Ratio of uncovered struts per total struts per section*	0.50±0.23	0.19±0.25	<0.0001

*The most powerful morphometric predictor of endothelialization was RUTSS. The odds ratio for LST in lesions having an RUTSS >30% is 9.0 (sensitivity=75%, specificity=76%)



(Finn et al Circulation. 2007;115:2435-41)

OCT and IVUS in DES with MI due to VLST

Median time to presentation 615 days (394, 1186)

	VLST	Controls*	P
Stents	18	36	
Cross-sections with uncovered struts (%)	33.3 (0, 43.7)	9 (0, 7.8)	0.003
Cross-sections with >30% uncovered struts (%)	21.6 (0, 43.7)	0 (0, 6.9)	0.002
Malapposed struts per patient (%)	5.9±6.3	1.8±1.5	0.001
Minimum stent CSA (mm^2)	5.7±1.4	5.9±1.4	1.0
Mean EEM CSA (mm^2)	19.4±5.8	15.1±4.6	0.003
"Remodeling index" (lesion/reference EEM CSA)	1.24 (1.06, 1.43)	0.99 (0.90, 1.11)	<0.001
Malapposition area (mm^2)	4.1±2.3	1.2±1.5	0.001

Thrombus aspiration demonstrated neutrophils and eosinophils in the majority of cases.

matched for: stent type and IVUS reference EEM and lumen CSA and stent diameter

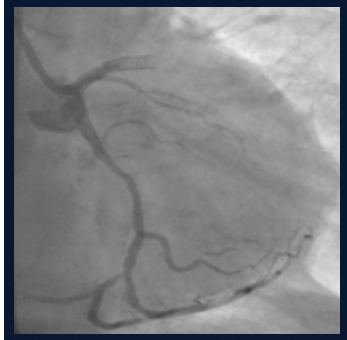
(Guagliumi et al, JACC Cardiovasc Intervent, in press)

Optical coherence tomography findings of very late stent thrombosis after drug-eluting stent implantation (n=18)

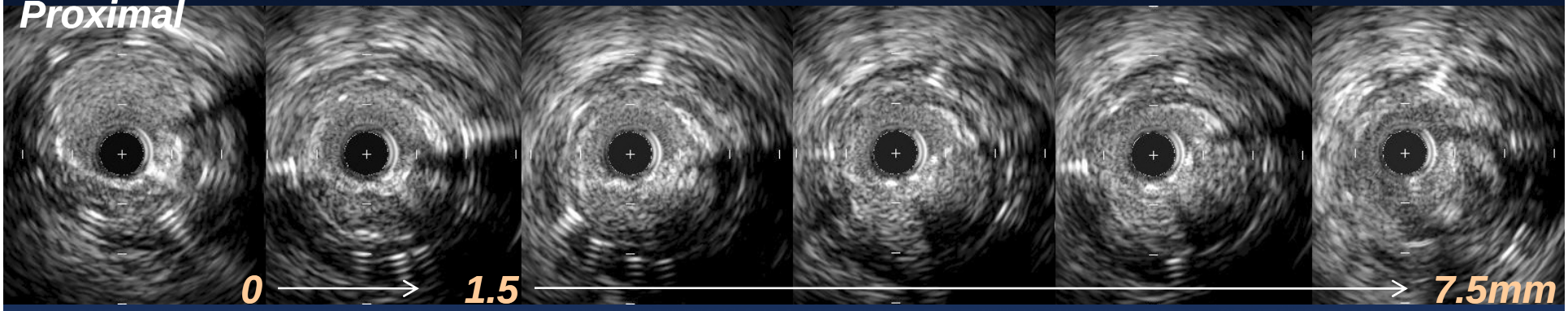
- 4 patients had ruptured and lipid-laden neointima, but no uncovered or malapposed stent struts.
- 14 patients without neointimal rupture had uncovered struts (n=9), malapposed struts (n=7), and/or lipid-laden neointima (n=4)

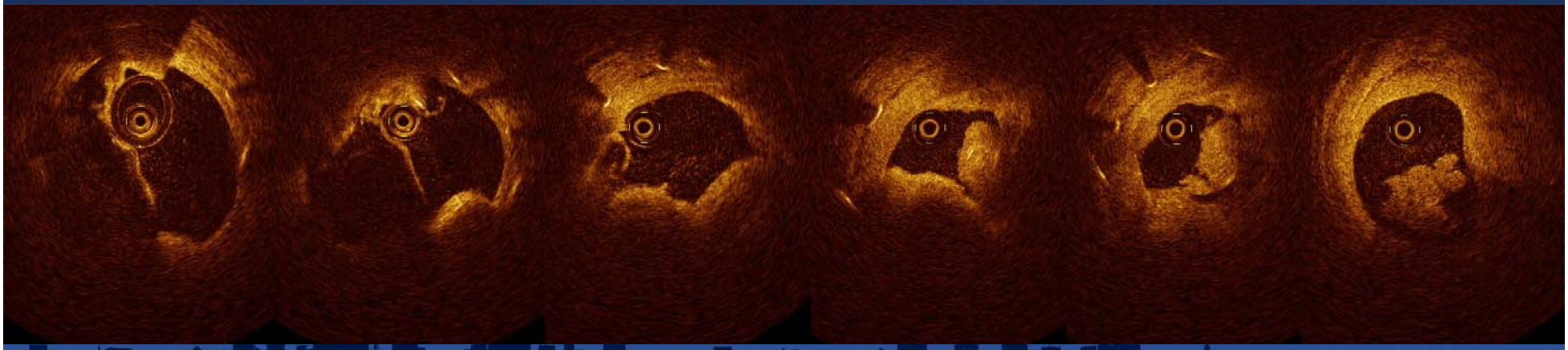
(Ko et al. Int J Cardiovasc Imaging, in press)

IVUS analysis of 23 very late DES thrombosis at Asan Medical Center

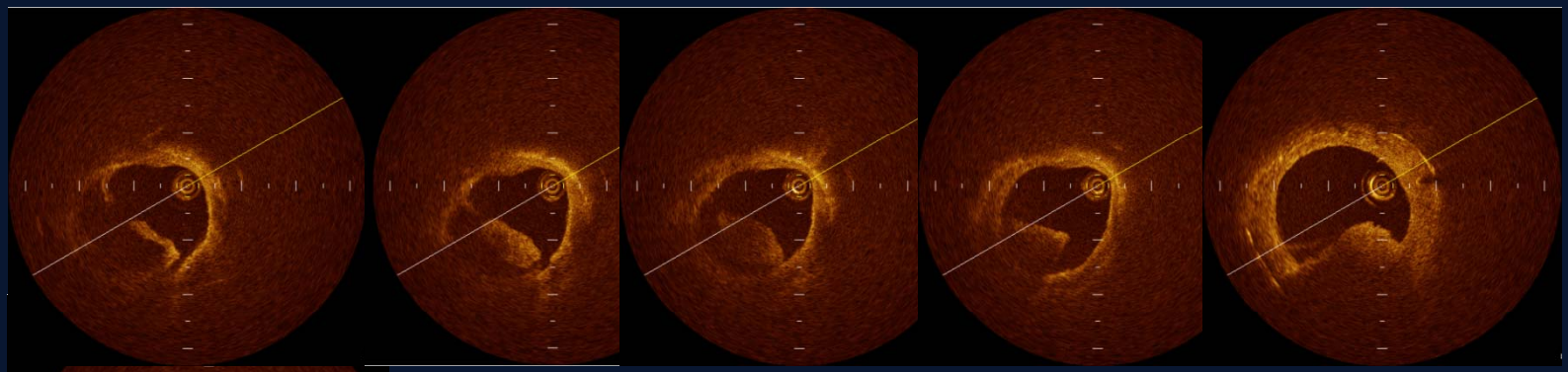


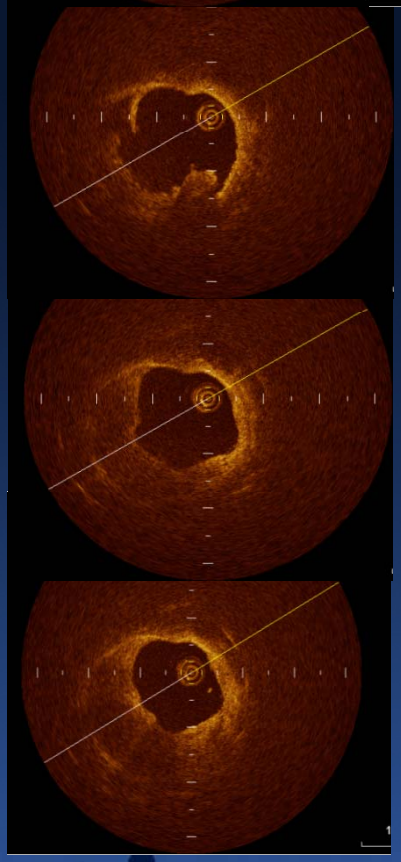
- LSM was observed in 17 DES pts (73.9%)
- In-stent neointimal rupture or peri-stent reference segment plaque rupture was observed in 15 DES pts (65.2%)

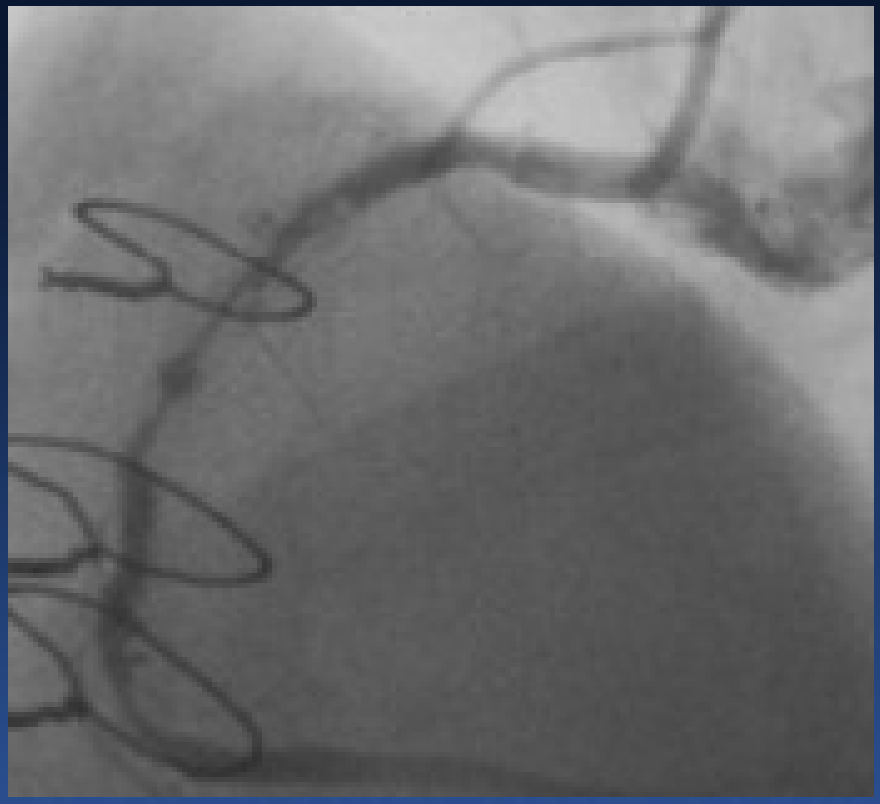




(Lee et al. J Am Coll Cardiol. 2010;55:1936-42)







Shibuya et al. Sakurabashi Watanabe Hospital, Osaka, Japan

Nordic IVUS Study (NIDUS): A registry of 124 stent thrombosis cases (87 DES, 37 BMS)

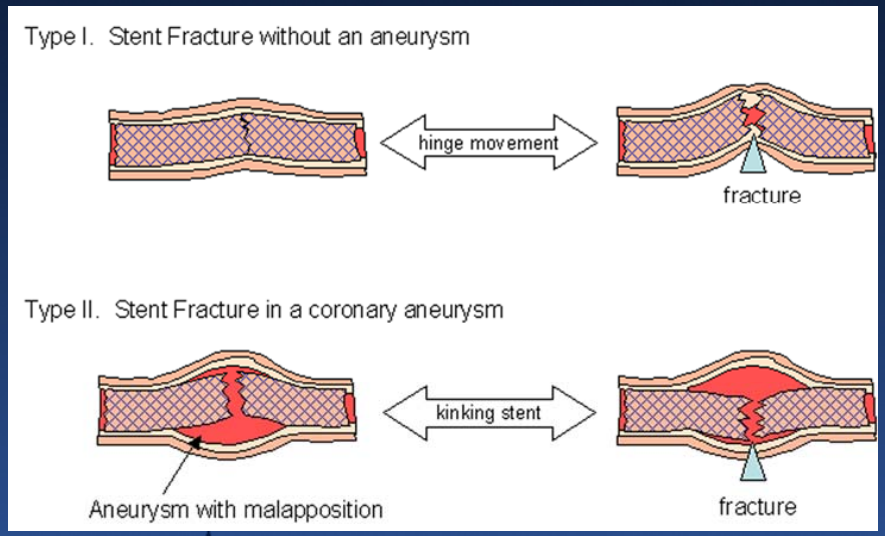
	DES	Stent fracture	Stent malapposition
Stent thrombosis	87	14 (16%)	37 (43%)
Acute/Early	20	4 (25%)	6 (30%
Late	6	0 (0%)	1 (17%)
Very Late	61	10 (16%)*	30 (49%)*

Both stent fracture and malapposition were seen in 4 VLST pts (7%); neither one was noted in 25 VLST pts (41%)

(Kosonen et al. EuroPCR 2010)

Analysis of 20 DES fractures in 17 patients

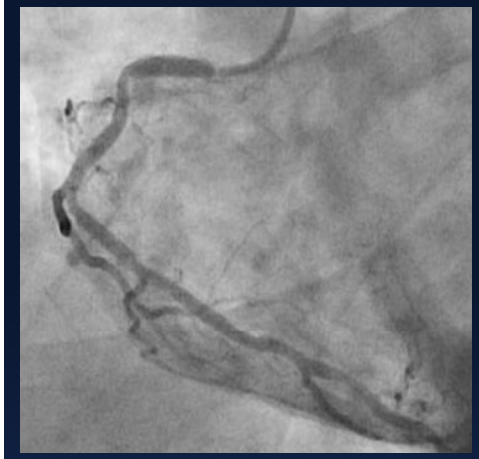
- **15 stent fractures in 13 pts were associated with in-stent restenosis (all focal); and 2 stent fractures in 2 pts were associated with very late stent thrombosis**
- **Five stent fractures occurred within a coronary aneurysm accompanied by malapposition despite the absence of a coronary aneurysm at index.**

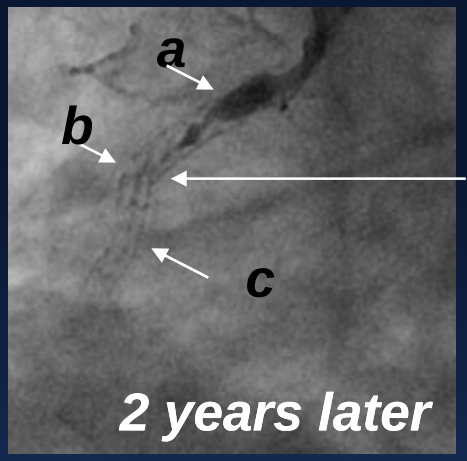


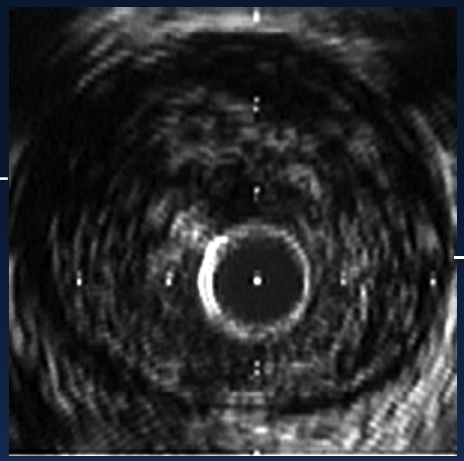
Comparing stent fractures with vs without an aneurysm, complete stent fracture was more frequent (100% vs. 27%, p=0.008), and all presented >1 year post-stenting (vs. 33%, p=0.03).

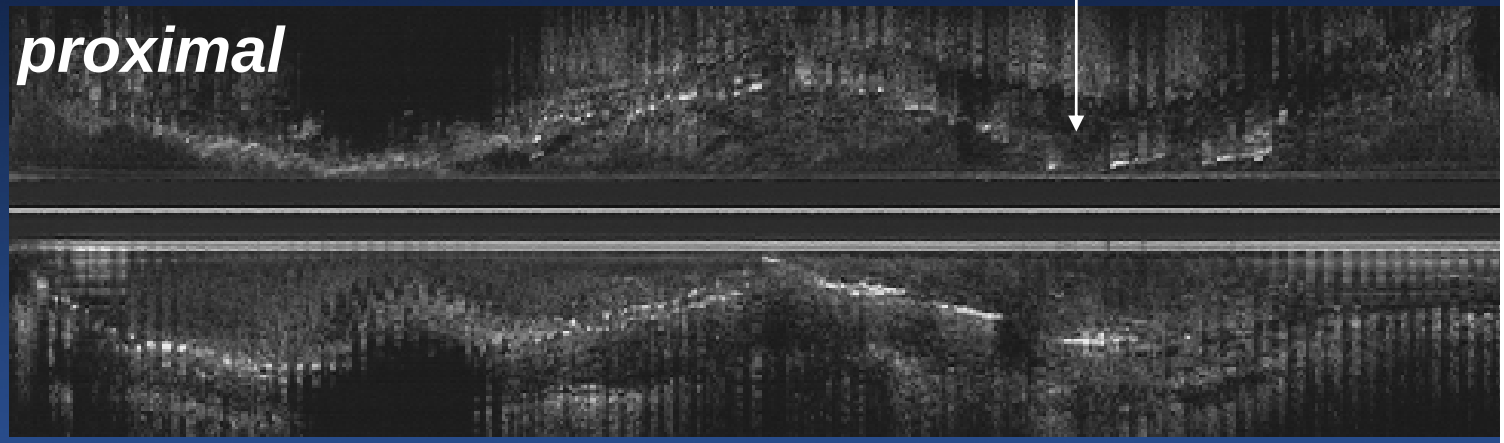
Doi et al. Am J Cardiol 2009;103:818-23

DES after VBT failure for Rx of BMS Restenosis









Recent studies of 1st generation DES have shown frequent, "asymptomatic" thrombi at follow-up.

		Imaging Modality		SES	PES
Awata, et al	Circulation 2008;118:S897	Angioscopy		26% (n=30)	57% (n=19)
Hara, et al	JACC Cardiovasc Interv 2010;3:215-20	Angioscopy	6 mos	12% (n=43)	50% (n=40)*
	Am Heart J 2010;159:905-10	Angioscopy	18 mos	11% (n=18)	70% (n=23)*
Higo et al	Thromb Res 2011;128:431-4	Angioscopy	12 mos	33%	
Otake, et al	Circulation 2008;118:S896	OCT		18% (n=35)	
Kim et al	Am Heart J 2010;159:278-83	OCT	9 mos	28% (n=27)	11% (n=7)
Murakami et al	Circ J 2009;73:1627-34	OCT		15% (n=3)	50% (n=10)
Takano et al	In J Cardiol 2011, in press	OCT	6 mos		48%

**** In paired comparison (n=19), prevalence of thrombus increased from 68% to 84% (Clin Cardiol 2011;34:322-6)***

Limitations

- IVUS*
  - Cannot distinguish between neointima and thrombus
  - Limits in resolution
    - Small amounts of neointima
    - Small areas of malapposition
- OCT*
  - Cannot penetrate red thrombus
  - Flow must be re-established before imaging

** Stent area measurements are not the same comparing IVUS and OCT*

- Very late stent thrombosis is multifactorial and patients often have multiple findings
  - Strut fracture and aneurysms
  - Neoatherosclerosis and late stent malapposition
  - Inflammation and late stent malapposition
  - Poor stent strut tissue coverage and late positive remodeling and remodeling
- Underexpansion is uncommon when the correct metric – minimum stent area – is used. Conversely, the use of the ratio of MSA to reference lumen (or EEM) area is problematic because of the frequency of positive remodeling that extends into the reference segments

	Early BMS Thrombosis (<30 days)	Early DES Thrombosis (< 30 days)	Late DES Thrombosis (30 days – 1 year)	Very Late DES Thrombosis (>1 year)
Underexpansion	+	+		
Inflow/outflow problems	+	+		
Acute malapposition	±	±		
Late acquired malapposition ± positive remodeling				+
Vessel wall inflammation				+
Strut fracture				+
Lack of stent strut tissue coverage				+
Neoatherosclerosis				+

- There is almost no data on the use of IVUS and/or OCT in the treatment of stent thrombosis – whether, early, late, or very late. Just clinical experience extrapolated from the use of IVUS during routine PCI
  - Reestablish flow
  - Identify and treat any mechanical abnormalities
  - Optimize the final result