Imaging Guidance for Treatment of In-stent Restenosis

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Cardiovascular Research Foundation

Disclosure Statement of Financial Interest

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

Affiliation/Financial Relationship	Company
Grant/Research/Fellowship Support	*Boston Scientific, Philips, InfraReDx, Abbott*
Consulting Fees/Honoraria	*Boston Scientific, Philips, Infraredx, Abbott*

Causes of Metallic Stent failure

	Bare Metal Stents				Drug-eluting Stents				
	Stent Thrombosis		**Restenosis**		Stent Thrombosis			**Restenosis**	
	<30d	>1y	**<5y**	**>5y**	<30d	30d - 1y	>1y	**<18m**	**>18m**
Intimal hyperplasia		x	**x**				x	**x**	
Procedure-related complications incl. underexpansion	x		**x**		x			**x**	
Late malapposition or aneurysm							x		
Vessel wall inflammation							x		
Stent fracture	x	x			x		x		**x**
Delayed healing						x			
Uncovered stent struts/fibrin deposition						x	x		
Neoatherosclerosis		x		x			x		**x**

Analysis of 298 ISR lesions (52 BMS, 73 SES, 52 PES, 16 ZES, and 105 EES) at CUMC

	BMS	1st generation DES	2nd generation DES	p-value
#	52	125	121	
Diabetes mellitus	19 (36.5%)	68 (48.9%)	57 (53.3%)	0.14
ACS presentation	28 (53.9%)	81 (58.3%)	56 (52.8%)	0.7
Total stent length (mm)	21.8±13.5	29.4±16.1	32.2±18.7	0.001
Average reference lumen area (mm^2)	**6.3±2.3**	**6.3±1.8**	**6.4±1.9**	**1.0**
Minimum stent area (MSA)	**6.4±2.2**	**4.9±1.6**	**4.7±1.6**	**<0.001**
MSA <5 mm^2	**28.8%**	**56.8%**	**69.2%**	**<0.001**
%NIH at MLA site	**60.9±12.8**	**56.1±16.0**	**52.3±16.9**	**0.006**
Diffuse ISR	28.8%	30.2%	28.0%	1.0
Neointimal calcification (%)	19.2%	13.0%	18.5%	0.41
Stent fracture, n (%)	0.0%	5.8%	6.5%	0.18
Stent malapposition, n (%)	7.7%	10.1%	10.3%	0.9

Goto et al. Am J Cardiol 2015;116:1351-7

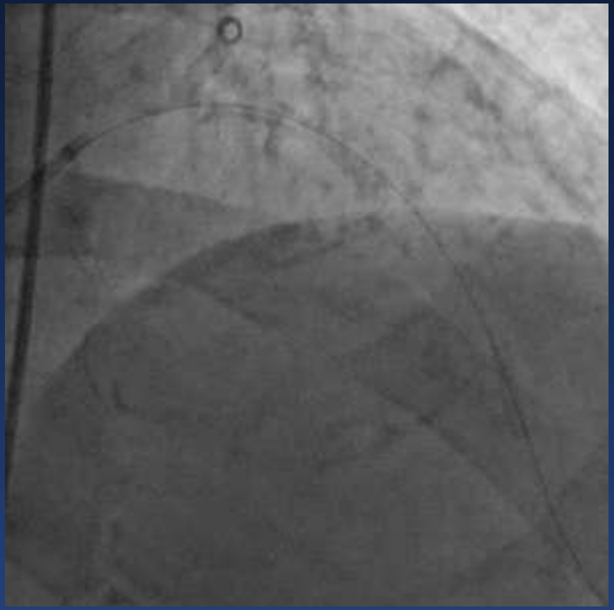
Two reasons for a small MSA. . .

- **Undersizing**

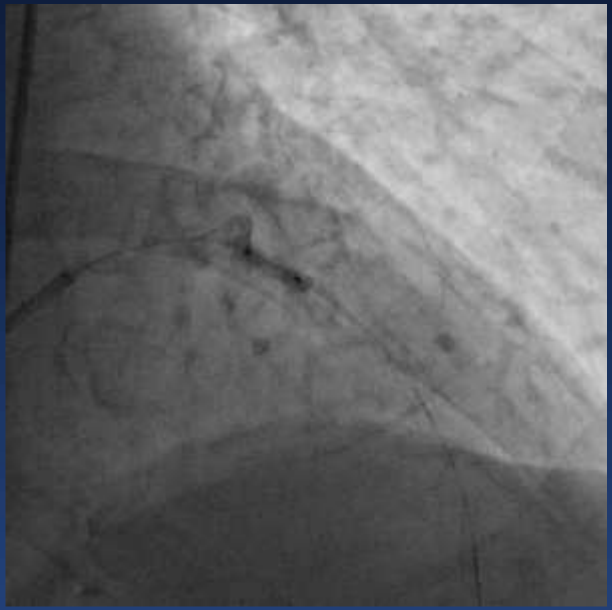
Size of the lumen in a normal artery		
	Area (mm^2)	Diameter (mm)
LM	18.1	4.8
Proximal LAD	10.8	3.7
Proximal LCX	10.2	3.6
Montreff et al. Eurointervention 2010;5:709-15		

- **Underexpansion . . . Inability to expand the stent despite high-pressures. . . most commonly due to calcium**

1st PCI in Dec 2012



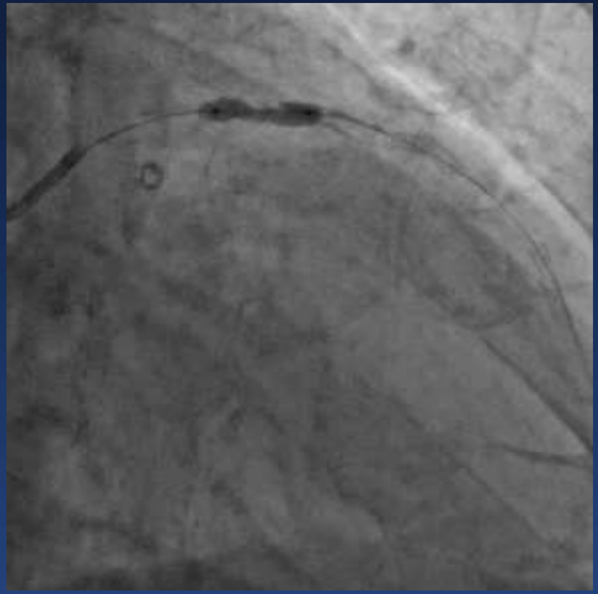
2.75x22mm
stent
@ 14 atm



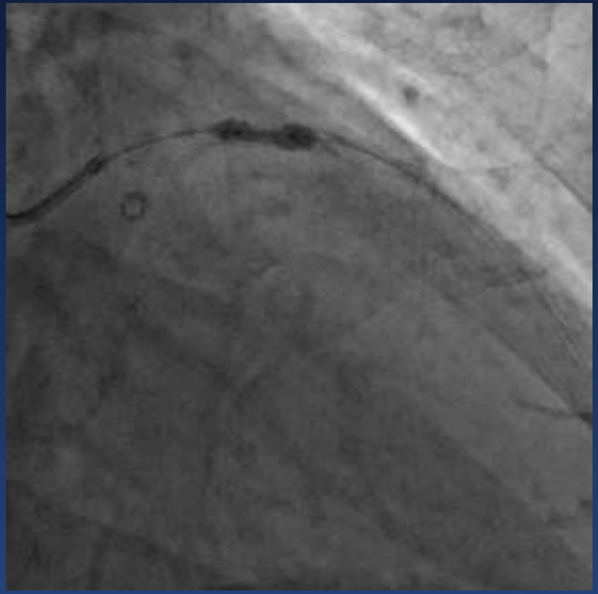
3.0x9mm NC
Balloon
@ 22 atm

Final diameter
stenosis
28 %

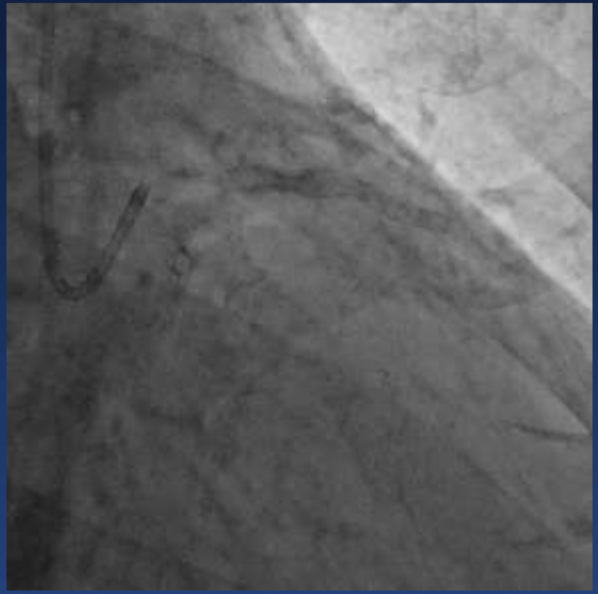
2nd PCI



3.5x12mm stent overlapping with prior stent @ 16 atm

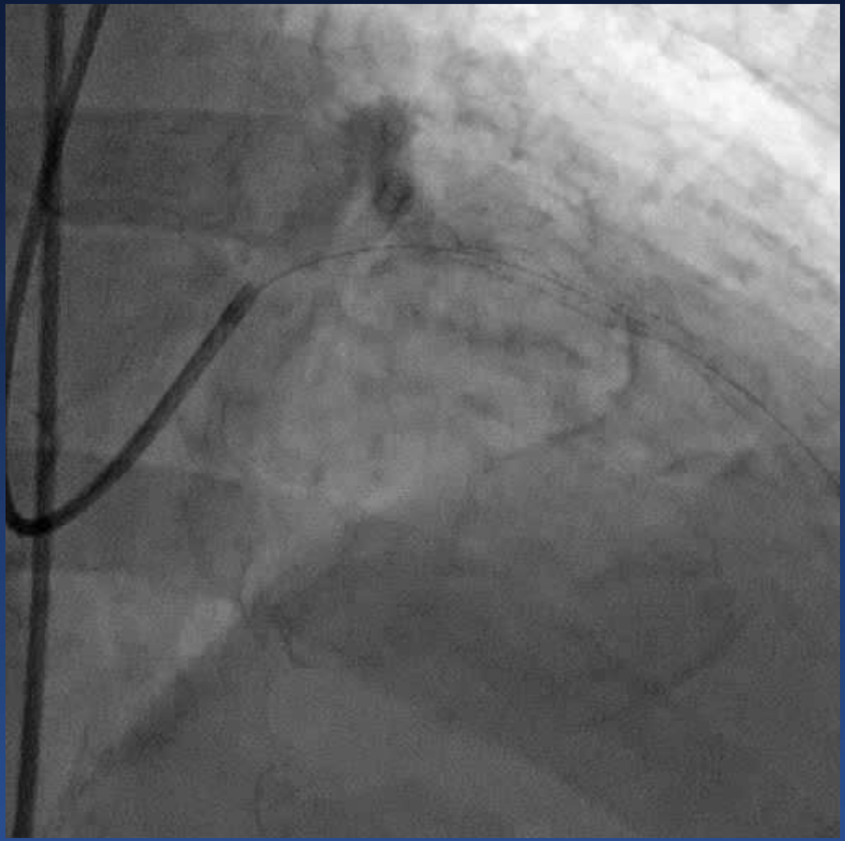


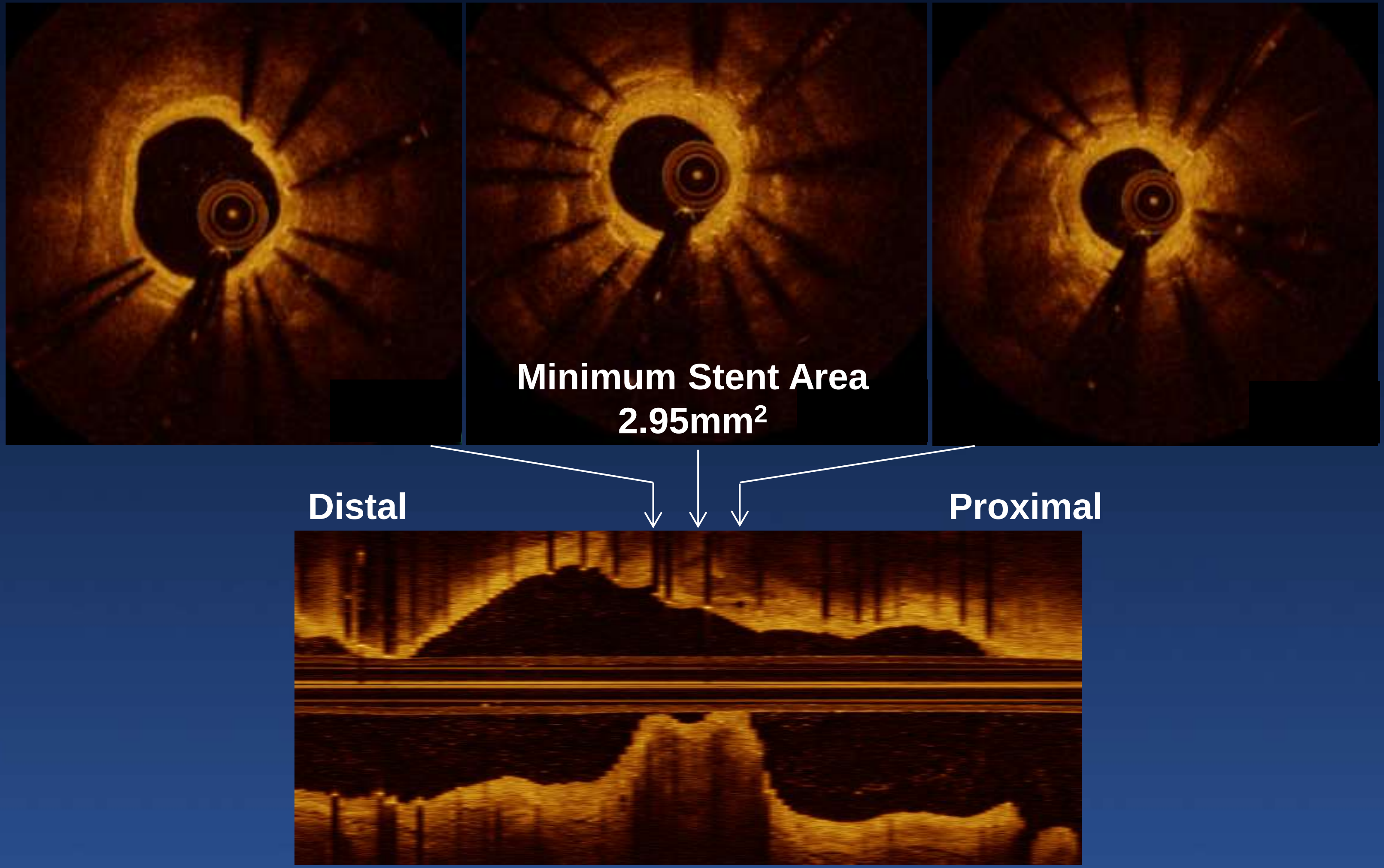
4.0x9mm NC balloon @ 26 atm



Final diameter stenosis 40%

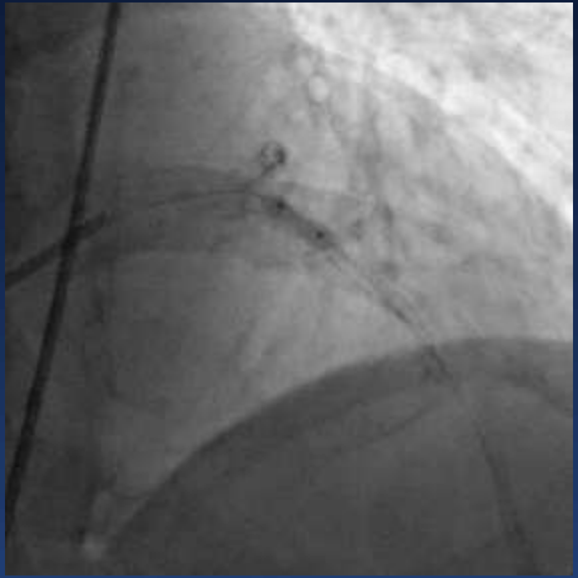
3rd PCI in March 2014



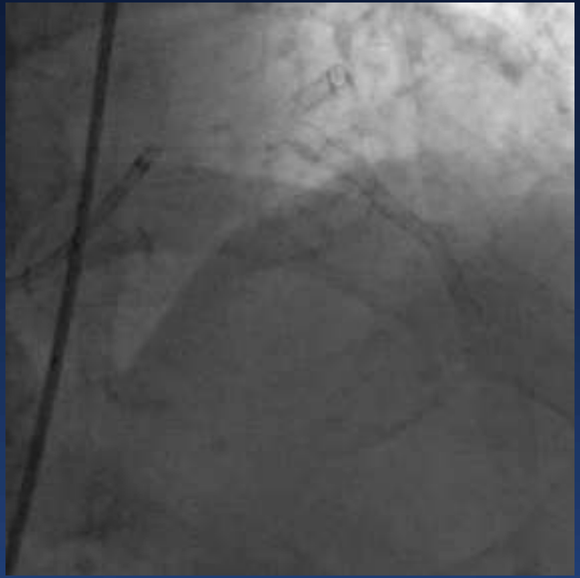


3rd PCI

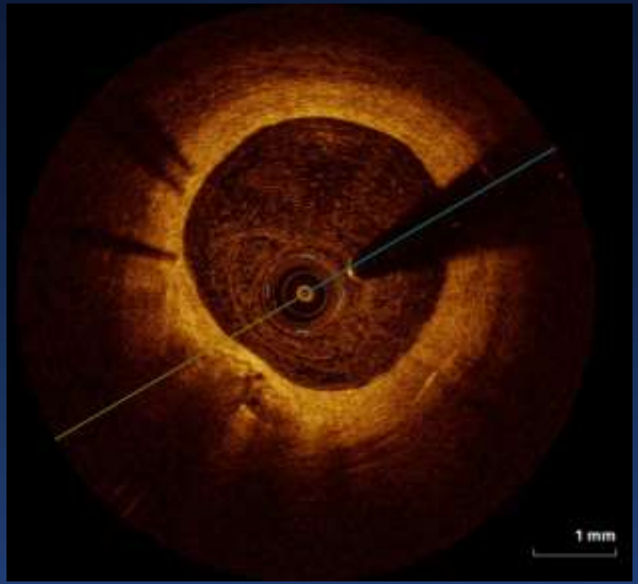
1.4mm excimer laser coronary atherectomy @ fluence of 60mJ/mm^2 and frequency of 80Hz



3.5x9mm NC Balloon @ 22 atm

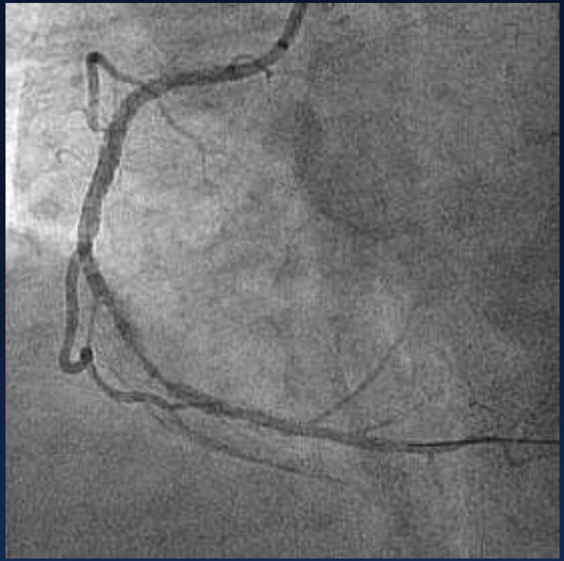


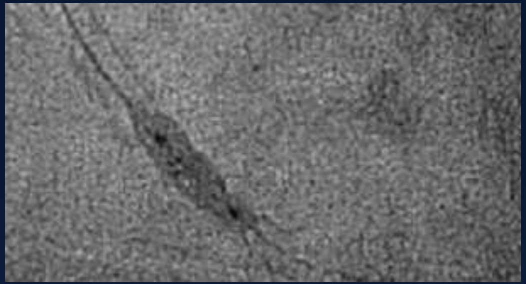
Final diameter stenosis 10%



Options for Treating Chronic Stent Underexpansion

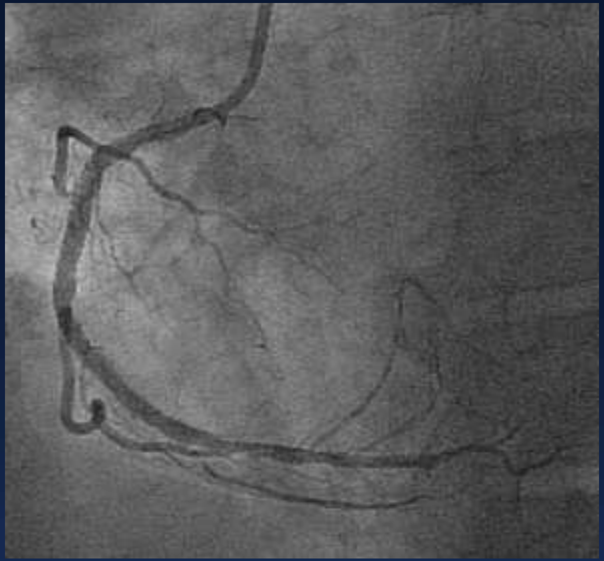
- **Aggressive ultra-high pressure balloon inflations**
  - OPN NC High-Pressure (RBP=35atm) PTCA Balloon (SIS Medical AG, Switzerland)
- **ELCA, ideally in a contrast filled lumen at the time of lasing to maximize photoacoustic effect**
  - Successful in 27/28 pts (Latib et al Cardiovasc Revasc Med 2014;15:8-12)
  - Successful in 23/23 and was associated with more calcium fracture and larger final MLA and area of previously implanted stent (6.15 mm^2 vs 4.65 mm^2). Contrast injection was associated with multiple calcium fractures and fractures even in thicker calcium (Lee et al, Eurointervention, in press.)
- **Rotational atherectomy**
  - Successful in 14/16 pts (Ferri et al Cather Cardiovasc Interv 2017;90:E19-E24)
- **Shockwave (lithotripsy)** (Ali et al. JACC Cardiovasc Imaging 2017;10:897-906)
- **Cutting or Scoring Balloon or Buddy-wire techniques**

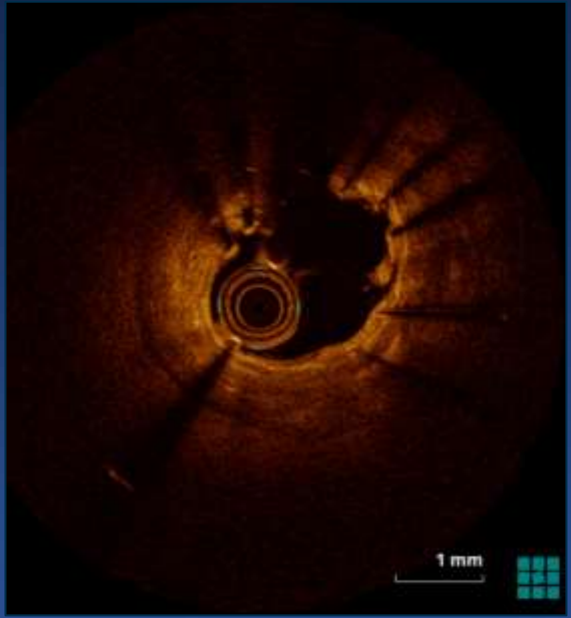


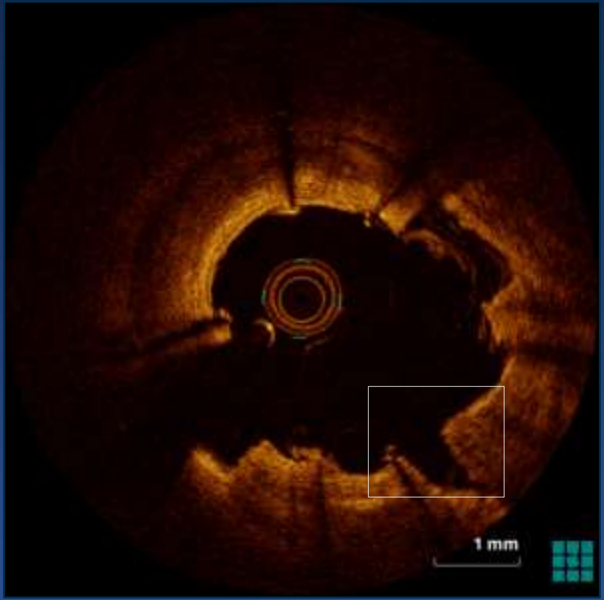


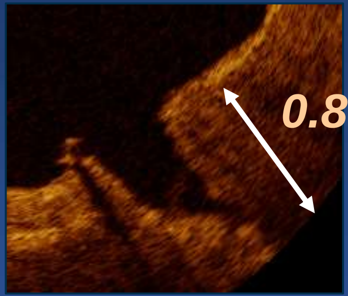
3.5mm@22atm

ELCA then 3.75mm@22atm







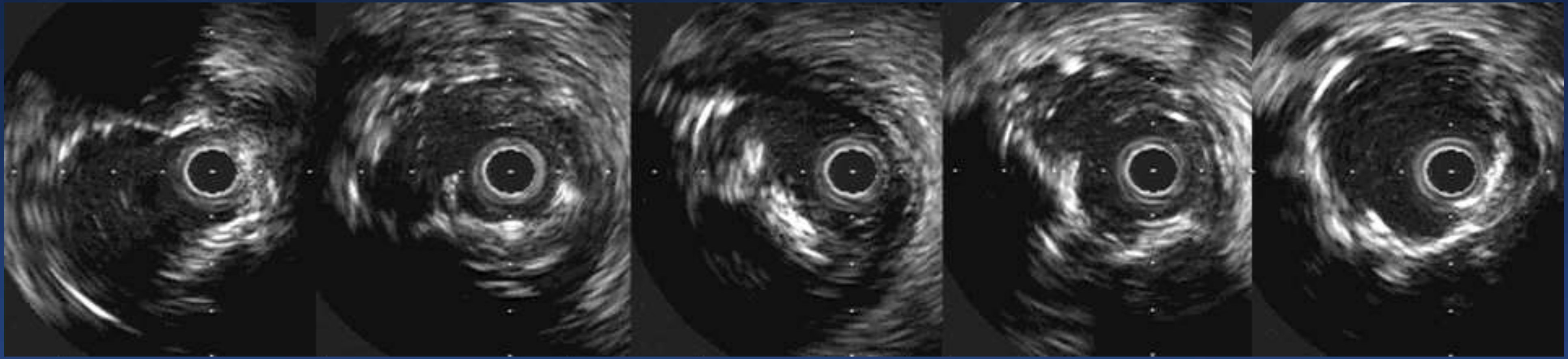


Lee et al, Eurointervention, in press.

Mechanical complications in restenotic lesions

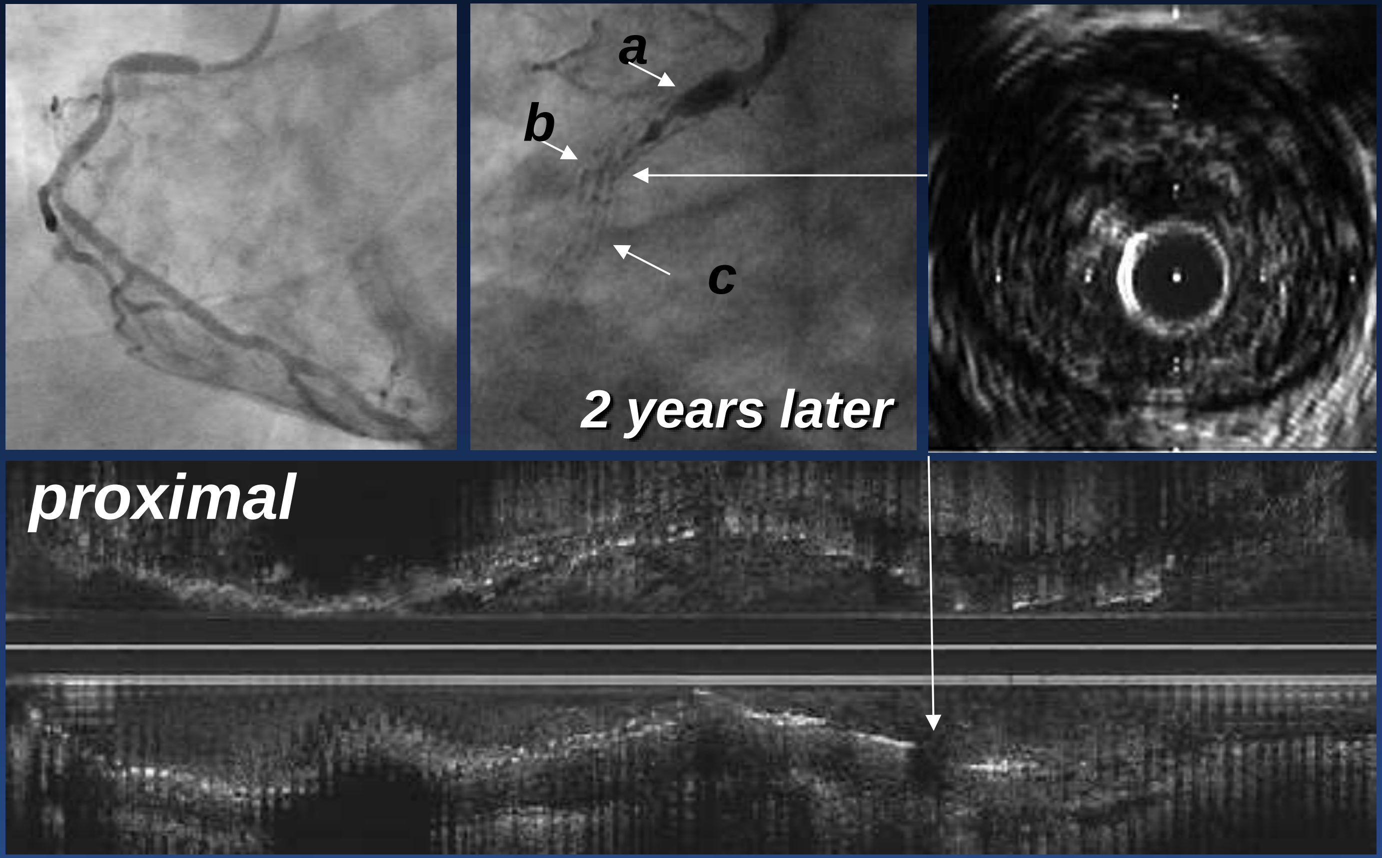
- 1090 pts with bare metal stent restenosis were evaluated at the Washington Hospital Center
  - In 49 (4.5%), there were mechanical complications: (1) missing the lesion, (2) stent "crush," and (3) having the stent stripped off the balloon during the implantation procedure.
  - Twenty percent of lesions had a MSA <5.0 mm^2 and an additional 18% had a minimum stent area of 5.0 to 6.0 mm^2.
  - *Castagna et al. Am Heart J 2001;142:970-4*
- 177 pts with EES restenosis were evaluated at Columbia University Medical Center
  - In 17 (9.6% there were mechanical complications: (1) complete stent fracture with separation, (2) partial stent fracture with separation, and (3) longitudinal deformation or stent strut fracture (n=11) with overlapping of the proximal and distal stent fragments.
  - *Inaba et al. EuroIntervention 2014;9:1301-8*

Proximal



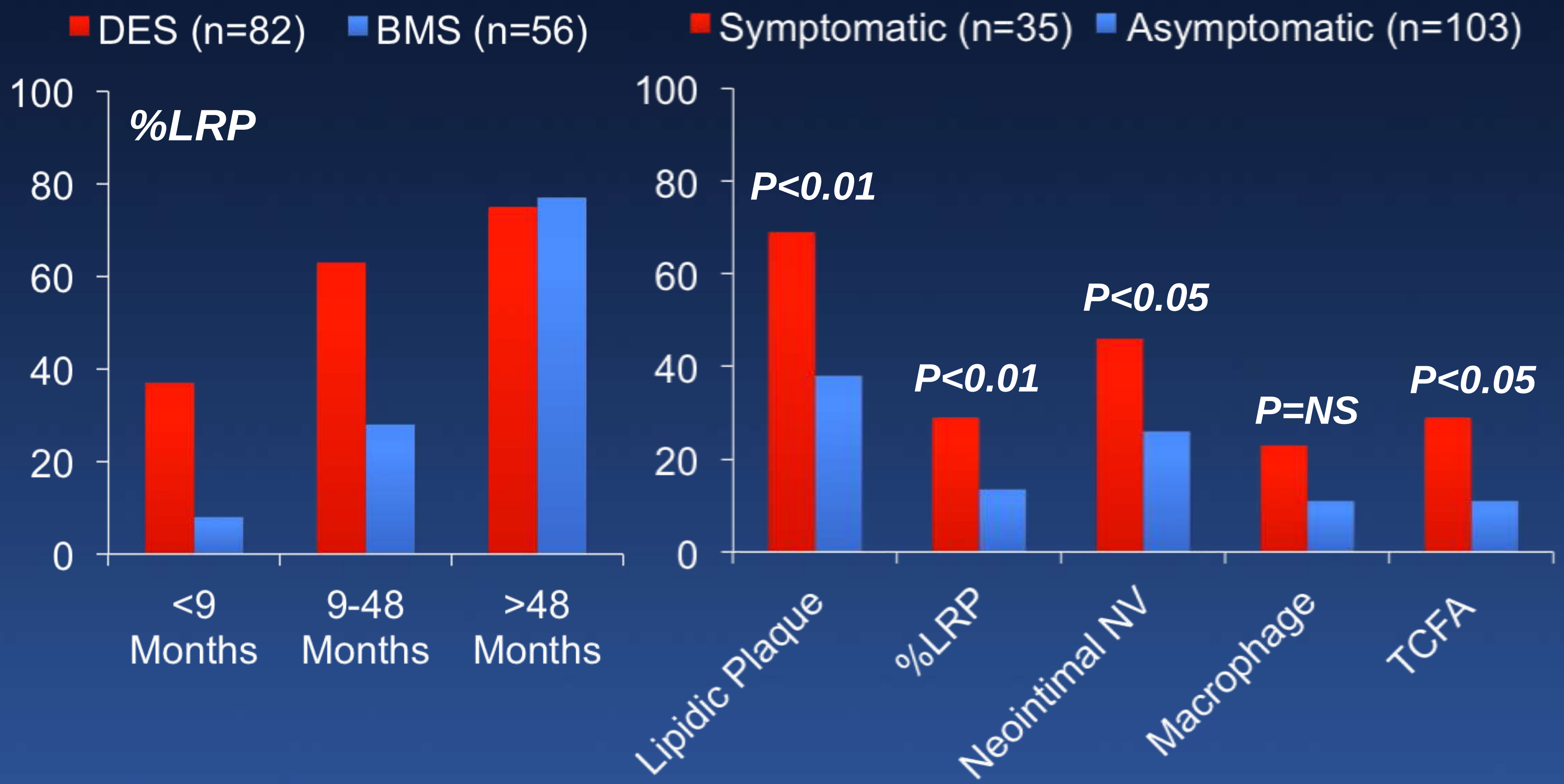
0 → 2.5mm → 10.0mm

DES after VBT failure for Rx of BMS Restenosis



- **Of 135 stent fracture cases, 67 (49.6%) cases were treated with repeat DES, whereas 68 (50.4%) were treated with POBA. None with DCB.**
- **The MACE rate at 3 years was significantly lower in the repeat DES group vs the POBA group largely driven by less TLR (25.7 vs. 55.8%, P < 0.001).**
  - *Mitomo et al. J Interv Cardiol 2015;28:365-73*

Neoatherosclerosis:
Incidence & time course from the MGH OCT Registry



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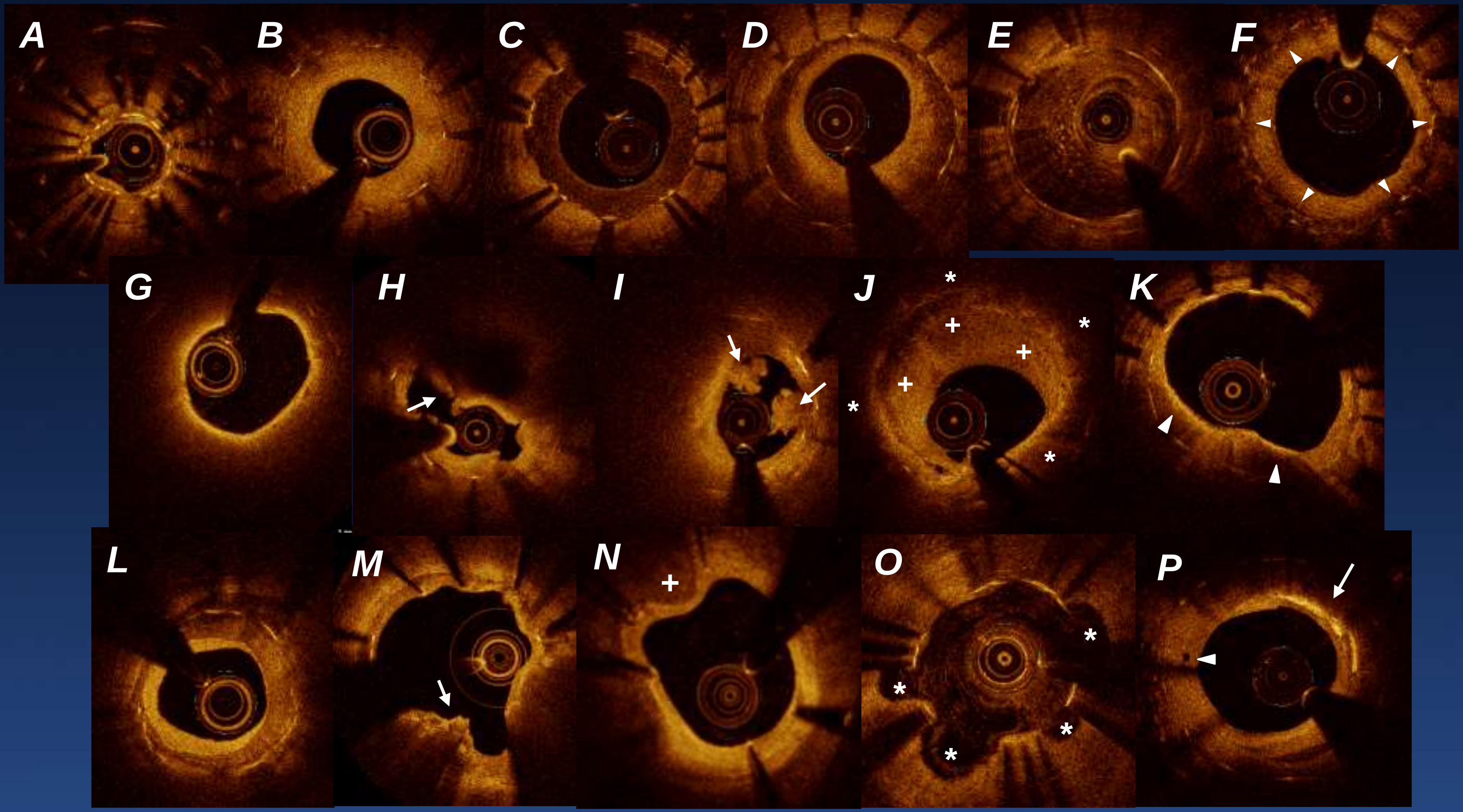
Yonetsu et al. Am J Cardiol 2012;110:933–9



A. Intimal thickness <100μm (underexpanded stent); B. Homogenous hyperplasia, high-intensity; C. Homogenous hyperplasia, low-intensity; D. Heterogeneous hyperplasia, layered; E. Heterogeneous hyperplasia, non-layered; F. Peri-strut low intensity; G. Lipidic neointima; H. Lipidic neointima rupture with thrombus; I. Lipidic neointima hyperplasia, thrombus without rupture; J. Multilayer neoatherosclerosis; K. Macrophages; L. Calcification in neointima; J. Calcified nodule in neointima; N. Native calcium protruding through stent struts; O. Evaginations; P. Cholesterol crystals with a microvessel

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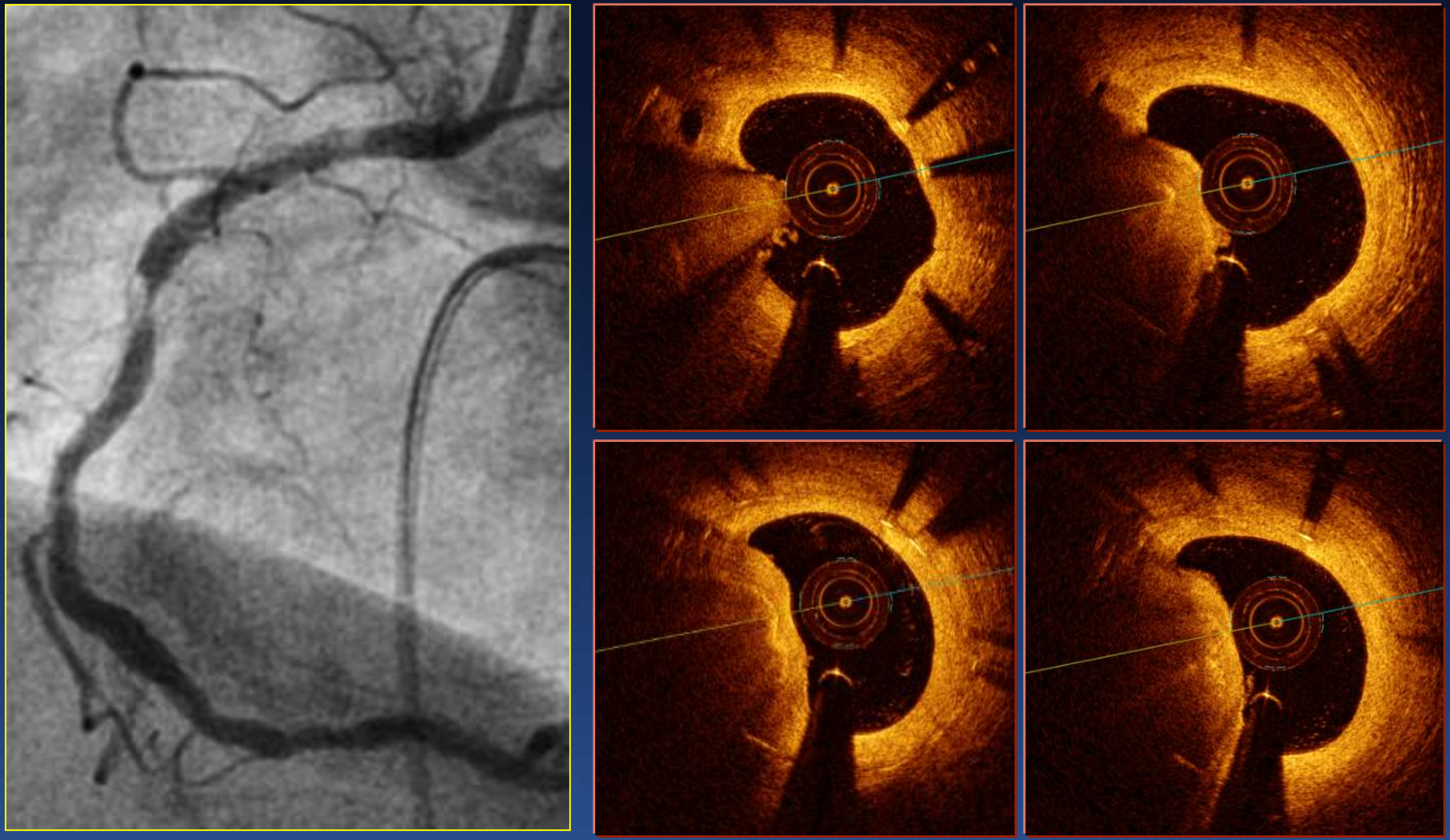

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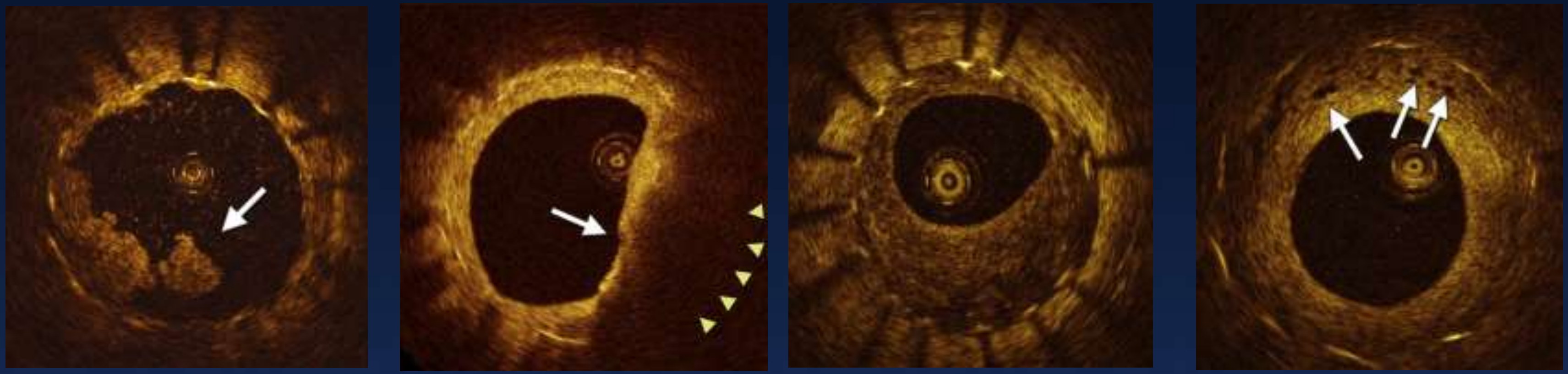
Alfonso et al. Can J Cardiol. 2016;32:830.e1-3.

Serial OCT in 76 DES-treated lesions



	Thrombus	Lipidic neointima	TCFA	Heterogeneous	Neovascularization
9 mos	10.5%	14.5%	3.9%	64.5%	44.7%
2 yrs	9.2%	27.6%	13.2%	61.8%	73.7%
P-value	1.0	0.0009	0.07	1.0	<0.001

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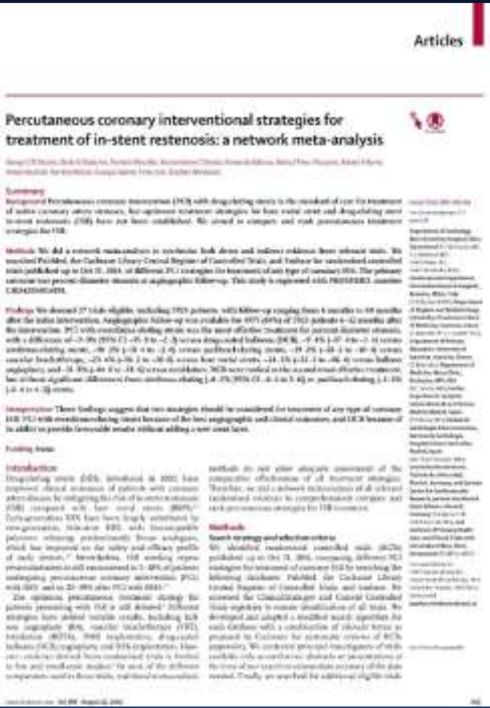
Kim et al. JACC Cardiovasc Imaging 2012;5:1147-55

Comparison of outcomes after treatment of in-stent restenosis using newer generation drug-eluting stents versus drug-coated balloon


Articles

Percutaneous coronary interventional strategies for treatment of in-stent restenosis: a network meta-analysis

- PCI with EES was the most effective treatment vs DCB, SES, PES, vascular brachytherapy, BMS, balloon angioplasty, and rotablation.
- DCB ranked as the second most effective treatment, but without significant differences from SES or PES.
- Two strategies should be considered for treatment of coronary ISR: PCI with EES because of the best angiographic and clinical outcomes and DCB because of its ability to provide favourable results without adding a new stent layer.


International Journal of Cardiology

Comparison of outcomes after treatment of in-stent restenosis using newer generation drug-eluting stents versus drug-eluting balloon: Patient-level pooled analysis of Korean Multicenter in-Stent Restenosis Registry

- The risks of TLF and a composite of all-cause mortality, all-cause myocardial infarction,
- or any revascularization were significantly lower in the DES group, even after being adjusted by an inverse probability weighted model, mainly driven by the significantly lower risk of TLR.
- Treatment of ISR with DCB independently predicted TLF.
- In unselected patients of ISR, clinical outcome at 1 yr was mainly dependent on difference in TLR and found to be better with contemporary DES than DCB.

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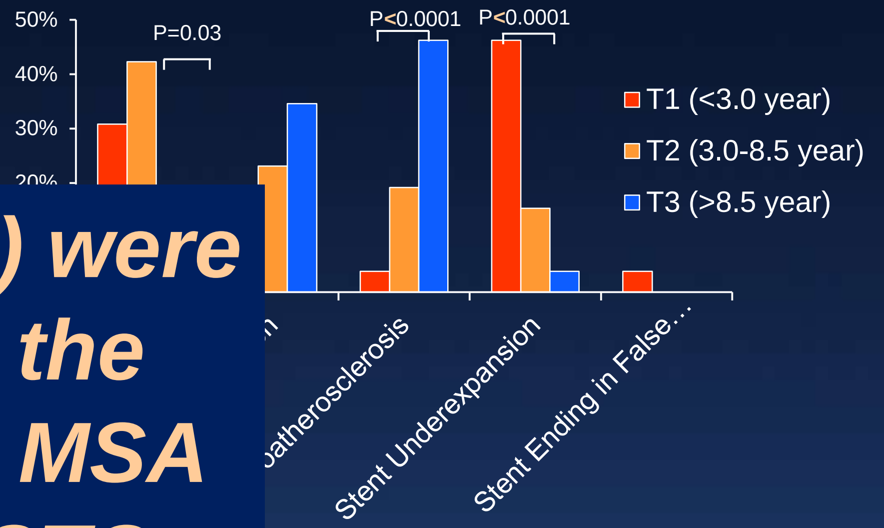
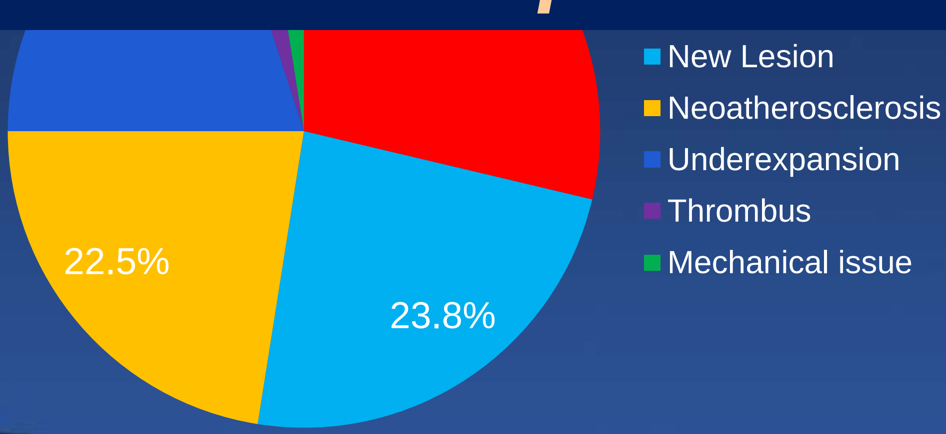
Siontis et al. Lancet. 2015;386:655-64
Lee et al. Int J Cardiol. 2017;230:181-90

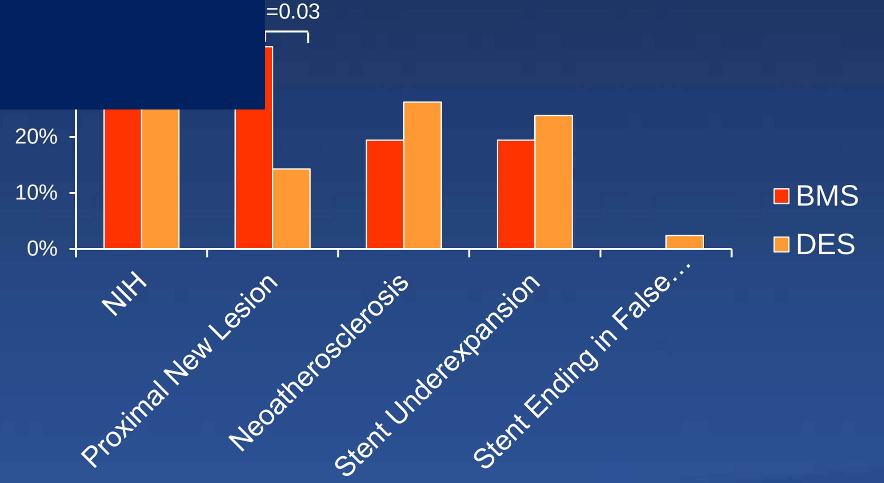
84 successfully recanalized in-stent CTO lesions were evaluated using IVUS. Although multiple morphologies were common, the primary morphologies were

- *excessive neointimal hyperplasia with good stent expansion -32%*
- *proximal or distal new lesion - 23%*
- *neoatherosclerosis - 19%*
- *stent underexp*
- *thrombus or ca*
- *crushed/deform*



Seventy-five ISR CTOs (97.4%) were treated with restenting, and the overall final (post–new stent) MSA was similar among the ISR CTO patterns





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Yin et al. JACC Cardiovasc Interv 2018;11:711-14

Options for treating ISR not caused by stent underexpansion

	Re-stenting	Drug-coated balloon
Stent fracture	x	
Stent deformation	x	
Intimal hyperplasia		
First time ISR	x	
Second time ISR*		x
Edge restenosis	x	
CTO	x	
Neoatherosclerosis	?	?


Original Contribution

Repeated Stenting of Recurrent In-Stent Restenotic Lesions: Intravascular Ultrasound Analysis and Clinical Outcome

*Kim et al. J Invasive Cardiol. 2007;19:506-9


CORRESPONDENCE

New Stent Implantation for Recurrences After Stenting for In-Stent Restenosis

Implications of a Third Metal Layer in Human Coronary Arteries

*Alfonso et al. J Am Coll Cardiol. 2009 Sep 8;54(11):1036-8

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Conclusions

- Intravascular imaging (IVUS or OCT) should be performed in every case of in-stent restenosis to identify mechanical problems that should be corrected first – especially stent underexpansion - whether caused by undersizing or related to peri-stent calcium
- Similarly, ISR presenting as a CTO should be imaged to identify one of the many potential mechanisms

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