Advances in management of in-stent restenosis

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TCT-AP Apr. 29, 2019

Seoul, South Korea

Definition of In-stent Restenosis

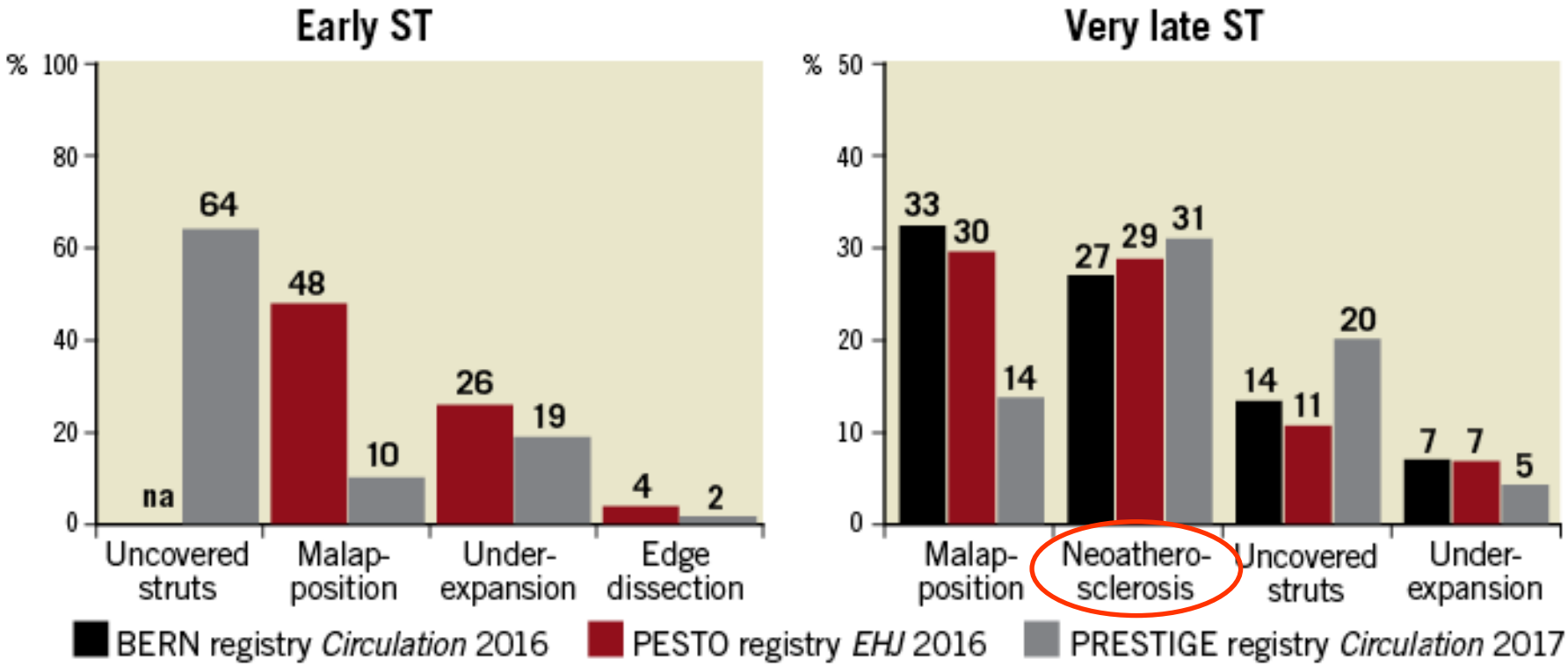
- > 50% reduction in luminal area within the stent or in the adjacent native vessel (5 mm of the proximal or distal stent edge)

Instent restenosis (ISR) presenting as Acute coronary syndrome (ACS)

- In the clinical database APPROACH, ISR manifested in 52.2% of cases as UAP/NSTEMI, in 18.5% as STEMI and only in 25.3% as stable AP
- Neoatherosclerosis and thin fibroatheroma plaque rupture major etiology
- IVUS or OCT may be helpful in differenting between Neoatherosclerosis and delayed endothelization.

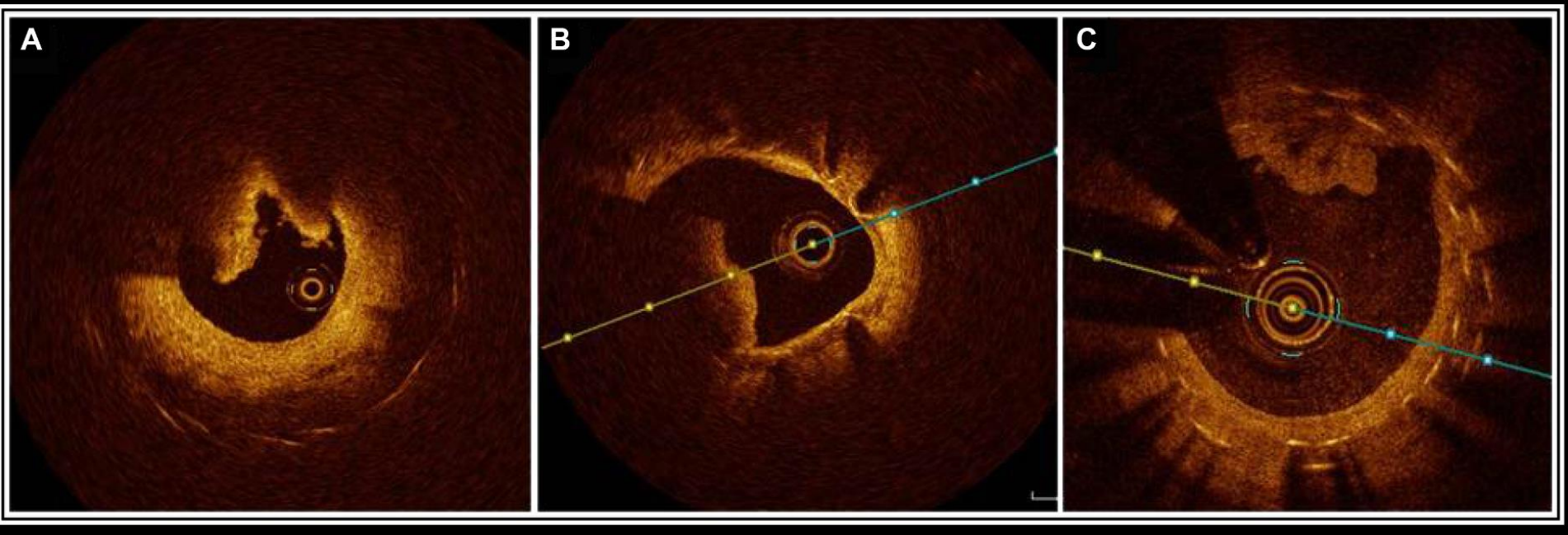
Bainey KR, Norris CM, Graham MM, *et al.* Clinical in-stent restenosis with bare metal stents: Is it truly a benign phenomenon? *Int J Cardiol* 2008; 128: 378–382

EuroIntervention

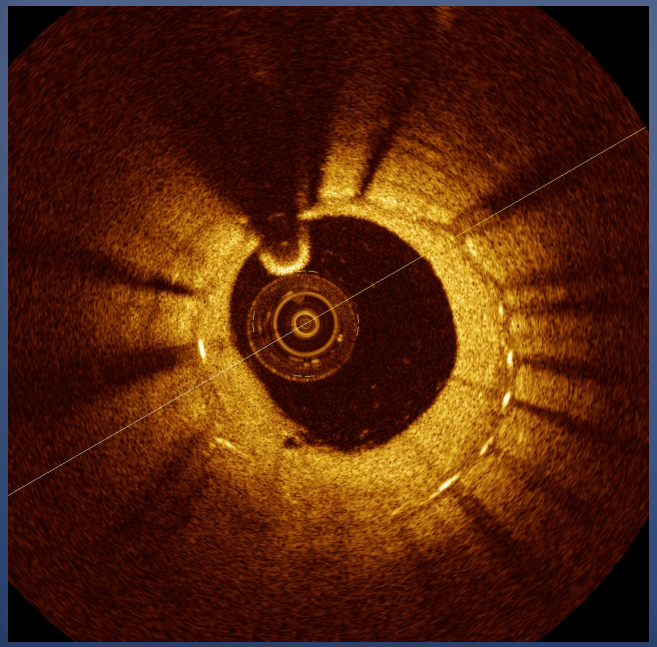


EuroIntervention 2018;14-online publish-ahead-of-print June 2018

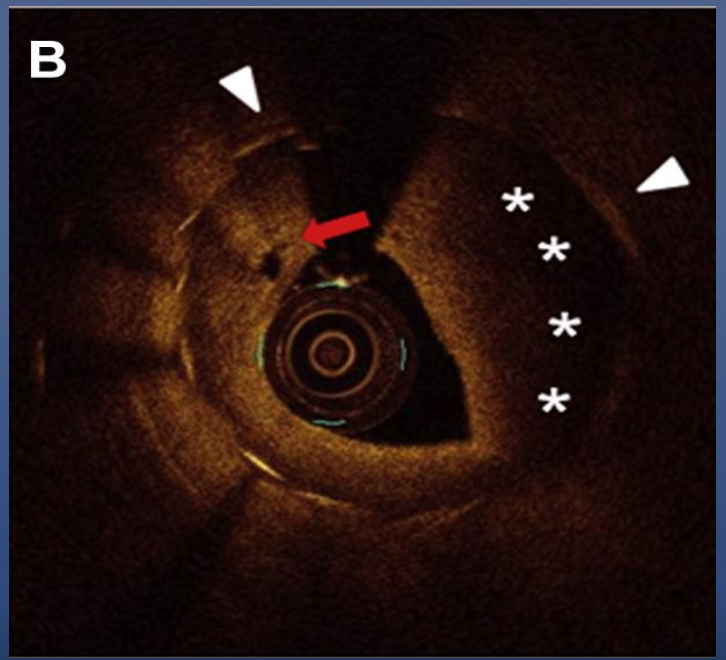
Clinical use of intracoronary imaging. Part 1: guidance and optimization of coronary interventions. An expert consensus document of the European Association of Percutaneous Cardiovascular Interventions



Fibrous neointimal proliferation



Lipid rich neo-atherosclerosis with plaque rupture & thrombus formation (above A, B, C)



ANGIOGRAPHIC RESTENOSIS & CLASSIFICATION

Diameter stenosis ≥ 50%

Type I focal ≤ 10 mm in length

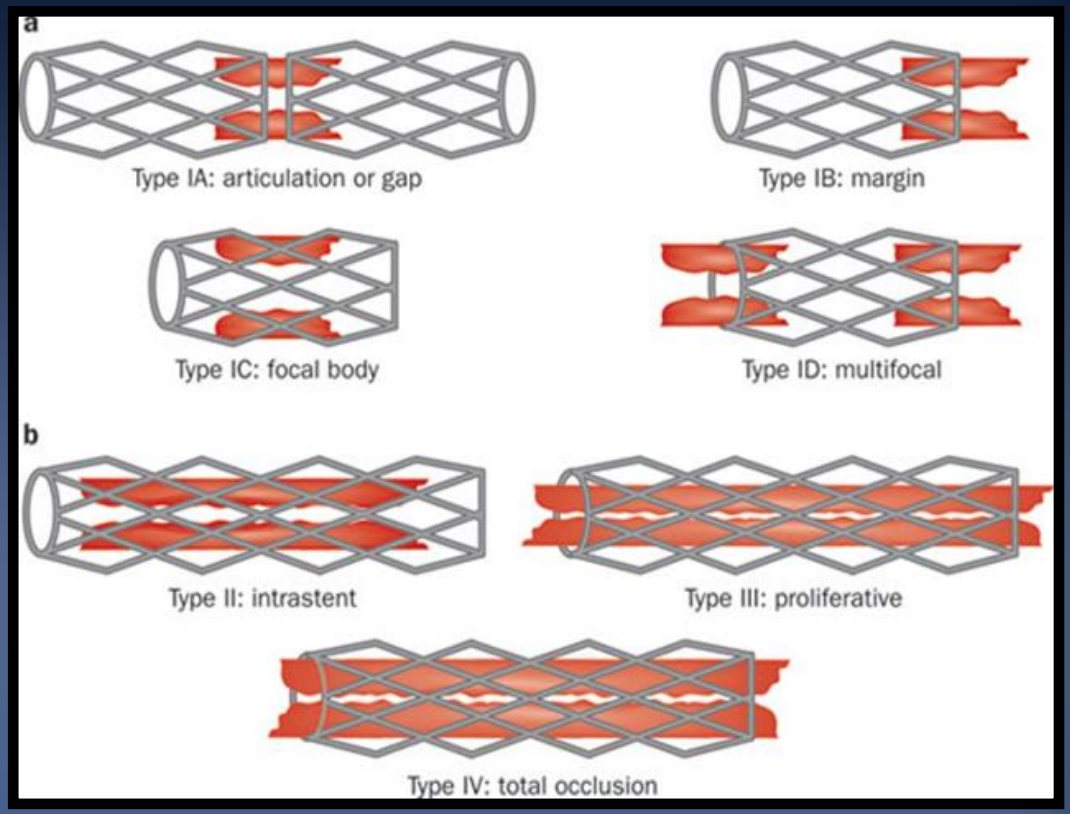
- IA articulation or gap
- IB margin
- IC focal body
- ID multifocal

Type 2 diffuse > 10 mm intrastent

Type 3 proliferative > 10 mm extending beyond stent margins

Type 4 total occlusion;

restenotic lesions with TIMI



Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long- term outcome. *Circulation* 1999;100:1872-78. PMID: 10545431

Restenosis rates

POBA	BMS	DES
30-50%	20-30%	<10%

Factors Influencing the Development of ISR

Pharmacological

- Drug resistance (dual antiplatelet therapy)
- Hypersensistivity to drug
- Hypersensistivity to

Mechanical

- Stent malappostion
- Stent underexpansion
- Edge trauma
- Geographical miss
- Stent fracture

Patient

- Diabetes
- Older Age
- Female
- Genetic

Biological

- Plasma proteolytic enzymes

Lesion

- Type B/C
  Long> 20mm
- Small vessel < 3mm
- Calcified Bifurcation disease
- Chronic total occlusion
- Ostial lesions

Developments in understanding risk factors for ISR

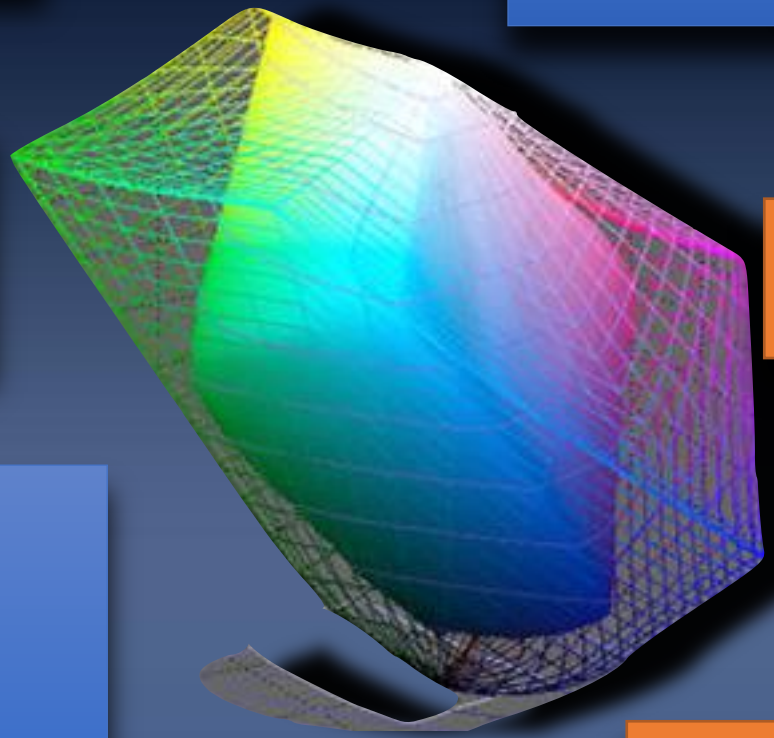
- Mainly higher plasma levels of matrix metalloproteinases (MMPs), the proteolytic enzymes that degrade the extracellular matrix (ECM)- associated with a higher risk of in-stent restenosis
- The association between some SNPs in *AGTR, GPX1, KAT2B, MMP12, FGB* and *VDR* genes and an increased risk of ISR.

Verschuren JJW, Trompet S, Postmus I, *et al.* Systematic testing of literature reported genetic variation associated with coronary restenosis: results of the GENDER Study. *PLoS One* 2012; 7: e42401

Conventional Balloon Angioplasty

Vascular Brachytherapy – outdated by 2 DES studies (SISR and TAXUS V ISR trials)

Cutting/Scoring Balloon: Prevents "watermelon seeding"



Repeat Stenting for ISR (BMS/DES)

Debulking Techniques

1. Directional atherectomy(Outdated)
2. Laser
3. ROTA:undilatable ISR/calcified but DES-ISR (not been evaluated)
4. Oribital atherectomy

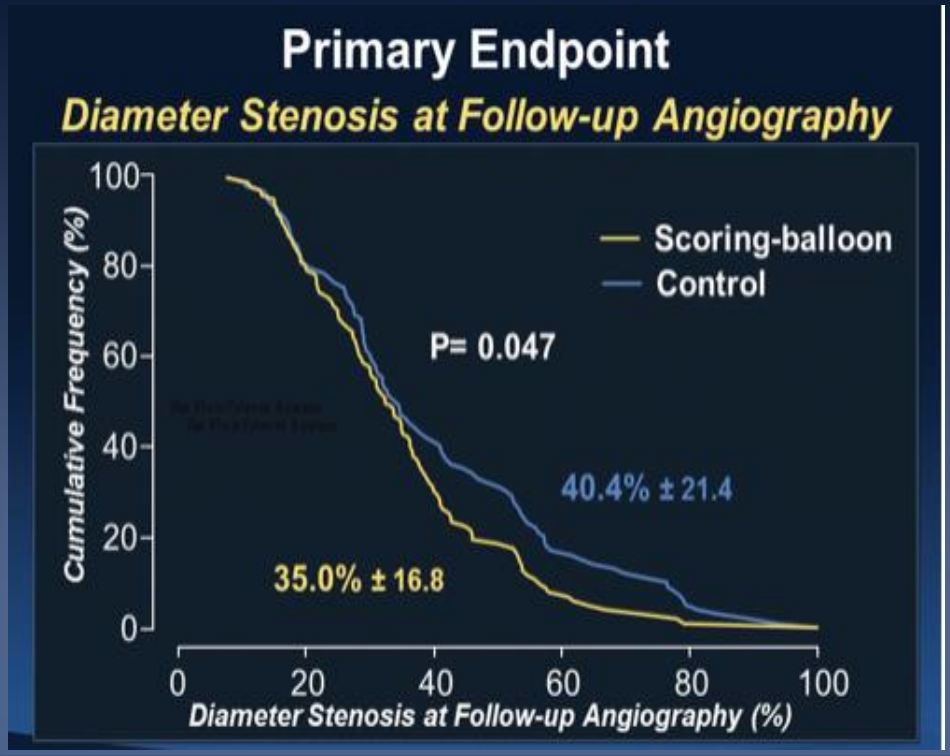
Drug eluting balloon (DEB) Angioplasty

Gamut of therapies for instent restenosis

POBA for ISR

- Favorable in "focal" ISR
- balloon-to-artery ratio of 1.1:1
- "dog bone" effects should tackled with high pressure non compliant balloon
- "watermelon seeding" phenomenon should be attended, therefore, Scoring/Cutting balloon is a better solution.
- Limited experience in DES ISR

Cutting/scoring balloon & DCB



Secondary endpoint results

6-8-month angiographic follow-up	SCB + DCB	POBA + DCB	p
Binary restenosis	18.5 %	32.0 %	0.03

12-month clinical follow-up	SCB + DCB	POBA + DCB	p
Target lesion revascularization	16.8 %	22.6 %	0.25
Death & MI	3.3 %	3.4 %	>0.99
Target lesion thrombosis	0 %	0 %	-

Conclusion

- DES ISR in limus-eluting stents, that paclitaxel-coated balloon-based strategies confirmed a high clinical safety profile out to 1 year.
- Neointimal modification with scoring balloon significantly improves the 6-mo restenosis (18.5% vs 32%, P = 0.03)

Intracoronary Stenting and Angiographic Results: Optimizing treatment of Drug Eluting Stent In-Stent Restenosis 4

DES for BMS ISR :RIBS II and ISAR-DESIRE trials-DES > POBA better

ISAR-DESIRE (Intracoronary Stenting or Angioplasty for Restenosis Reduction-DRE for ISR) trial was the first randomized study assessing the value of DES in patients with BMS-ISR) showed satisfactory results but….

SES is better than PES

Kastrati A, Mehilli J, von Beckerath N, *et al.* A. Sirolimus- eluting stent or paclitaxel-eluting stent *vs* balloon angioplasty for prevention of recurrences in patients with coronary in-stent restenosis: A randomized controlled trial. *JAMA* 2005; 293: 165-171

Incidence, Procedural Management, and Clinical Outcomes of Coronary In-stent Restenosis (real practice in U.S.A)

- VA data on 6,872 pts who underwent PCI 2006 – 2014 and subsequently required revascularization for ISR (DCB not available at the period).
- The number of revascularizations for ISR increased 0.28% per year, although the trend was nonsignificant ($P = 0.05$)
- Mortality was lower for those treated with a DES vs POBA or other non-DES method (HR 0.73; 95% CI 0.64–0.83), as was rate of TVR (HR 0.62; 95% CI 0.51–0.76)
- After adjustment for known risk factors, DES continued to be associated with lower mortality than other methods

Implications: There is a trend toward more interventions for ISR, with a suggestion of DES being associated with less TVR and mortality.

Waldo SW, et al. *Catheter Cardiovasc Interv.2017;Epub ahead of print.*

Drug eluting balloon for ISR

- Effective in patients with both BMS-ISR and DES-ISR
- RIBS V (ISR: DCB vs. EES) trial:
  2nd generation DES is better than DCB in BMS ISR
- ISAR-DESIRE 3 (Intracoronary Stenting and Angiographic Results: DES for ISR) :
  DCB is non-inferior to paclitaxel DES

J Interv Cardiol. 2016 Oct;29(5):469-479. doi: 10.1111/joic.12327. Epub 2016 Aug 8.

Full Text Online

Comparison of Clinical Results Following the Use of Drug-Eluting Balloons for a Bare-Metal Stent and Drug-Eluting Stent Instent Restenosis.

Lee WC[1], Fang YN[1], Fang CY[2], Chen CJ[1], Yang CH[1], Yip HK[1], Hang CL[1], Wu CJ[1], Fang HY[1].

Author information

RESULTS: The average age of the patients was 64.99 ± 10.35 years, and 76.9% of the patients were male. After multivariate Cox regression analyses about 1-year recurrent **restenosis** in DES-ISR group, only end stage renal disease (ESRD) (P = 0.047) and previous DEB failure (P < 0.001) were identified with significant difference. After propensity score matched analysis, the bias of baseline characteristics showed no significant difference. The DES-ISR group experienced more myocardial infarctions (2.8% vs 8.3%, P = 0.075), more TLR (8.1% vs 15.4%, P = 0.051), especially at nonostial lesion (5.7% vs 14.9%, P = 0.030) than the BMS-ISR group. Higher incidence of major cardiac cerebral adverse events happened in the DES-ISR group. (11.7% vs 22.1 %, P = 0.038) CONCLUSION: During the 1-year follow-up period, DEBs angioplasty for BMS-ISR had better clinical outcomes and less TLR than DES-ISR. ESRD and previous DEB failure were associated to TLR in DES-ISR group.

ESC European Society of Cardiology

European Heart Journal (2019) **40**, 87–165
doi:10.1093/eurheartj/ehy394

ESC/EACTS GUIDELINES

2018 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on myocardial revascularization of the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)

Restenosis		
DES are recommended for the treatment of in-stent restenosis of BMS or DES.[373,375,378,379]	I	A
Drug-coated balloons are recommended for the treatment of in-stent restenosis of BMS or DES.[373,375,378,379]	I	A
In patients with recurrent episodes of diffuse in-stent restenosis, CABG should be considered by the Heart Team over a new PCI attempt.	IIa	C
IVUS and/or OCT should be considered to detect stent-related mechanical problems leading to restenosis.	IIa	C

Drug eluting balloon for ISR

- Paclitaxel-effective antiproliferative agent in DEB. highly lipophilic and rapidly penetrates. Its concentrations used have stabilized at 3 µg/mm.
- The main factor influencing the efficacy- method of paclitaxel binding on the surface of the balloon catheter.
- Iopromide-coated PEB (Sequent® Please, B.Braun, Melsulgen, Germany) showed a significantly better angiographic outcomes than PEB without coating.
- Many other PEBs are currently used in clinical practice:
  1. DIOR® II (shellac-coated; Eurocor, Bonn, Germany),
  2. IN.PACT™ Falcon [urea-coated; Medtronic, Minneapolis, USA),
  3. Pantera™ Lux (BTHC-coated (butyryl-tri-hexyl citrate); Biotronik, Berlin, Germany]

DES vs DEB

The-more-you-gain-the-more-you-lose phenomenon

- As compared with DEB, DES provide better acute and long-term angiographic results
- As compared with DES, DEB provide a lower acute lumen gain and eventually a **similar or even lower late lumen loss**
- When absolute MLD or relative % DS at follow-up is selected as primary end point, DES outperform DEB in most head- to-head comparisons
- long-term clinical outcomes are largely favorable with both therapeutic strategies, some studies suggest that DES are more effective than DEB to reduce the need of repeat TLR, esp. with DES-ISR

Circ Cardiovasc Interv. 2018;11:e007109. DOI: 10.1161/CIRCINTERVENTIONS.118.0

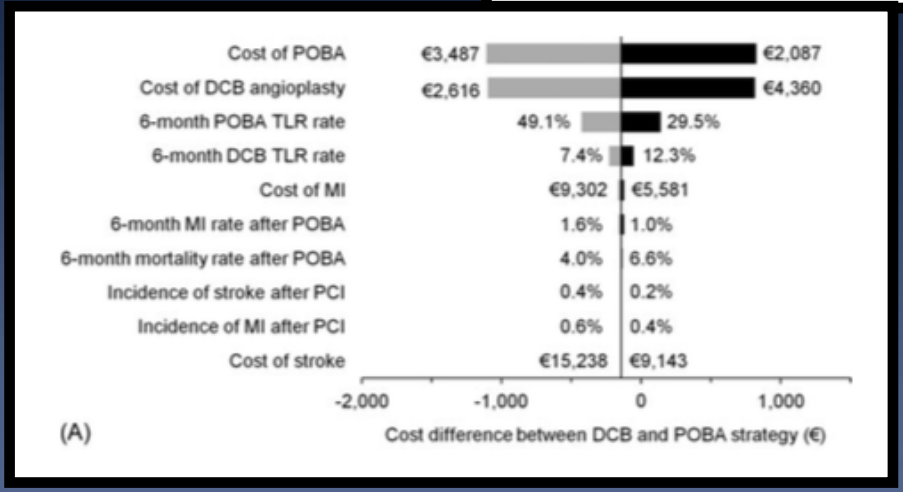
DES << DEB

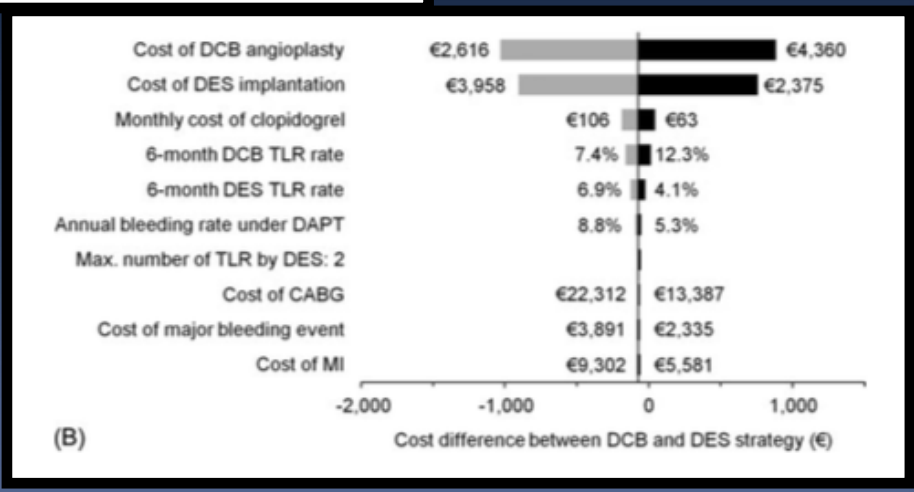
- DEB – More homogeneous distribution of anti-proliferative treatment into the vessel wall.
- Absence of polymers reduces chronic inflammatory response and the risk of subsequent late thrombosis.
- Faster neo-endothelization allows shorter DAPT Rx
- Almost no risk of the occlusion of side branches with another layer of metallic struts.

Clinical Investigations

Cost-Effectiveness of Paclitaxel-Coated Balloon Angioplasty in Patients With Drug-Eluting Stent Restenosis

Marc Dorenkamp, MD, MBA; Julia Boldt, Diplom (FH); Alexander W. Leber, MD; Christian Sohns, MD; Mattias Roser, MD; Leif-Hendrik Boldt, MD; Wilhelm Haverkamp, MD; Klaus Bonaventura, MD, MA





Conclusion - DCB angioplasty is a cost-effective treatment option for coronary DES-ISR. The higher initial costs of the DCB strategy compared to POBA or repeat DES implantation are offset by later cost savings.

- However cost of DEB varies in different countries, Some country as in China or CE Mark Countries, DEB cost is 3-5 times of DES cost

M. Dorenkamp et al: Cost-effectiveness of DCB angioplasty Clin. Cardiol. 36, 7, 407-413 (2013)

Dilemma of Recurrent ISR:

is DEB an elegant therapeutic strategy ?

- Implantation of a new DES is particularly worrisome in patients with multiple metal layers (good acute result and midterm clinical outcomes but keeps fueling a perverse vicious circle, so called "Onion skin" phenomenon").
- DEB represent an elegant strategy for these patients but provide unsatisfactory long-term outcomes in patients with ≥ 3 layers of stent
- Major efforts should be paid to aggressively tackle residual under-expansion and optimize procedural results

Yabushita H,et al. Clinical outcomes of drug-eluting balloon for in-stent restenosis based on the number of metallic layers: the New Tokyo Registry. *Circ*

Clinical Outcomes of Drug-Eluting Balloon for In-Stent Restenosis Based on the Number of Metallic Layers

The New Tokyo Registry

Hiroto Yabushita, Hiroyoshi Kawamoto, Yusuke Fujino, Satoko Tahara, Takeo Horikoshi, Miho Tada, Tatsuya Amano, Hirokazu Onishi, Akihiro Nakajima, Takayuki Warisawa, ... Show all Authors

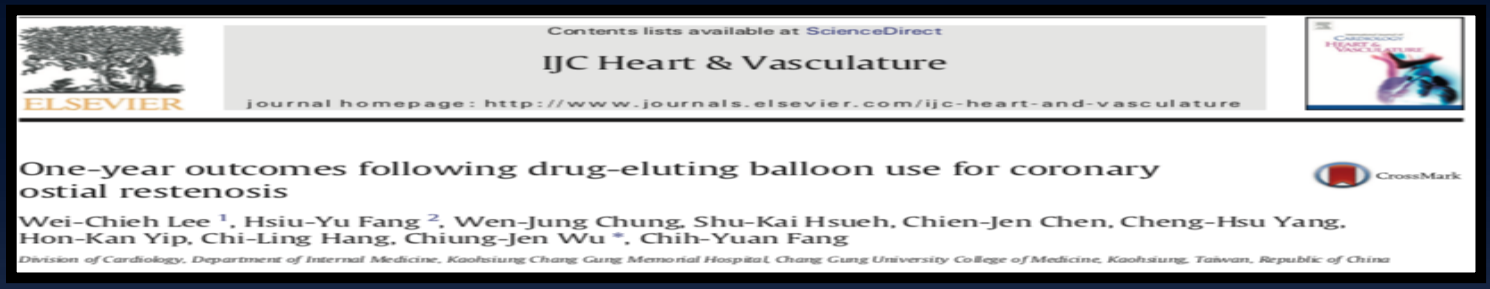
Originally published 13 Aug 2018 |
https://doi.org/10.1161/CIRCINTERVENTIONS.117.005935 |
Circulation: Cardiovascular Interventions. 2018;11

Conclusions:

Seemingly, drug-eluting balloon is less effective for ≥3L in-stent restenosis lesions. Hemodialysis and in-stent restenosis with the number of metallic layers are independent predictors for MACE.

Coronary ostial restenosis

- Procedural success and clinical outcomes of these lesions are inferior to those of non-ostial lesions
- Stent in stent' treatment causes lumen loss, and additional stenting may not be a desirable PCI for ostial ISR (especially in presence of co-morbidities like DM, HTN, ESRD etc)
- The use of DEBs has emerged as an adjunctive strategy



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IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

One-year outcomes following drug-eluting balloon use for coronary ostial restenosis

Wei-Chieh Lee [1], Hsiu-Yu Fang [2], Wen-Jung Chung, Shu-Kai Hsueh, Chien-Jen Chen, Cheng-Hsu Yang, Hon-Kan Yip, Chi-Ling Hang, Chiung-Jen Wu *, Chih-Yuan Fang

Division of Cardiology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan, Republic of China

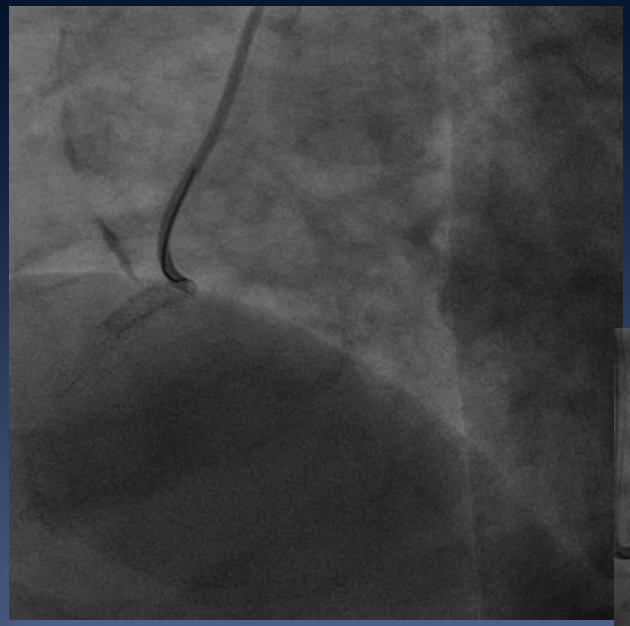
- 85 patients were diagnosed with coronary ostial ISR in our hospital. A total of 93 coronary ostial ISR lesions were treated with DEBs.
- More than half of the study patients had comorbidities, including hypertension, diabetes, and hyperlipidemia, 77.6% of the study patients had triple vessel coronary artery disease, and 54.1% of the study patients had left main coronary artery disease.
- TLR were performed in 19.2% in all groups; 11.5% in ostial LAD, 29.0% in ostial LCX, and 21.4% were in ostial RCA,
- 24.0% of the patients had MACE at 12-month F/U

Conclusion : PCI with DEB are an alternative strategy for coronary ostial ISR when additional stenting is not desirable.

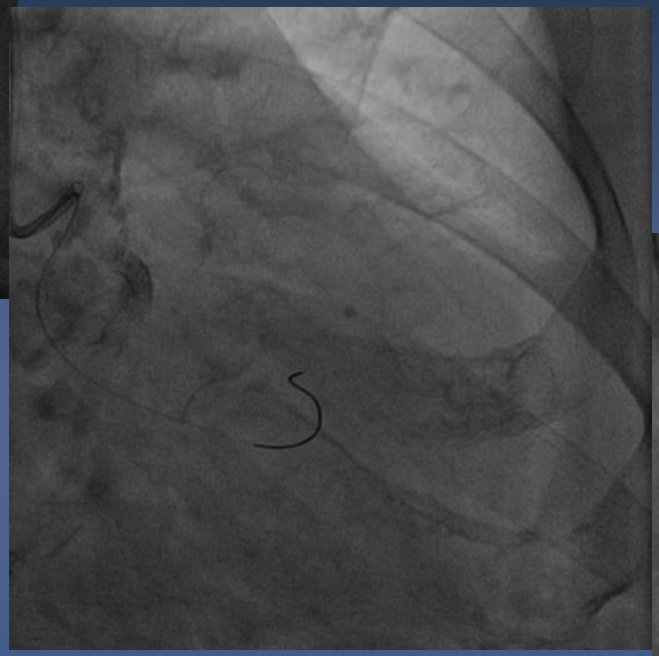
Case example-1

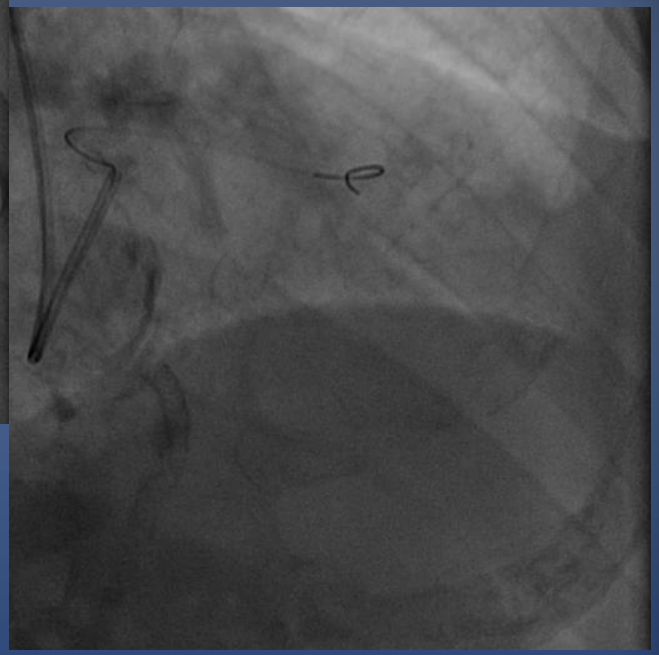
- 79 y/o male: H/T, Hyperlipidemia; h/o CVA and Left internal carotid artery stenting (2017)
- Prior DES at ostial RCA and ostial PLB (2016)—> DES x1 for ostial-RCA In-stent restenosis (2017)
- Presented with stable angina since 6 mo
- TET : positive at 2 min 15 sec ex. / 4.5 METS/ >1 mm ST depression in II,III,aVF and V4-V6
- Echo: Normal chambers; no regional wall motion abnormalities; LVEF~67%

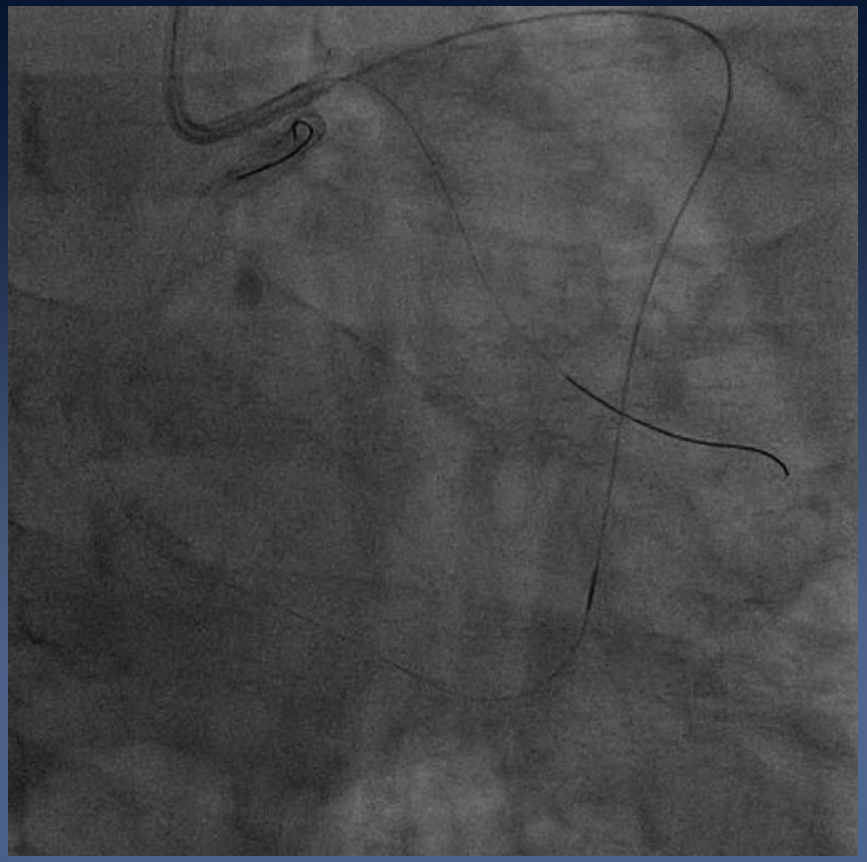
Catheterization thought Left snuffbox artery (d-RA) – 6 F IL 4.0 guiding catheter.

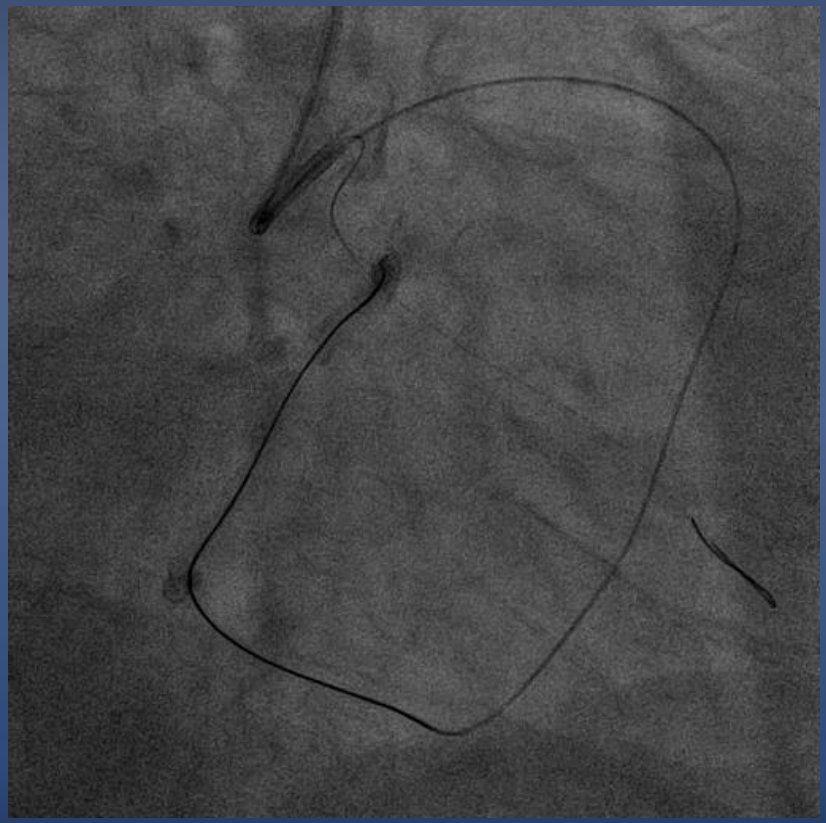


- Right coronary ostium had **instent CTO (J-CTO score- 2);** lesion length ~20 mm; **no stump.**
- Three visible septal collateral connections from LAD.



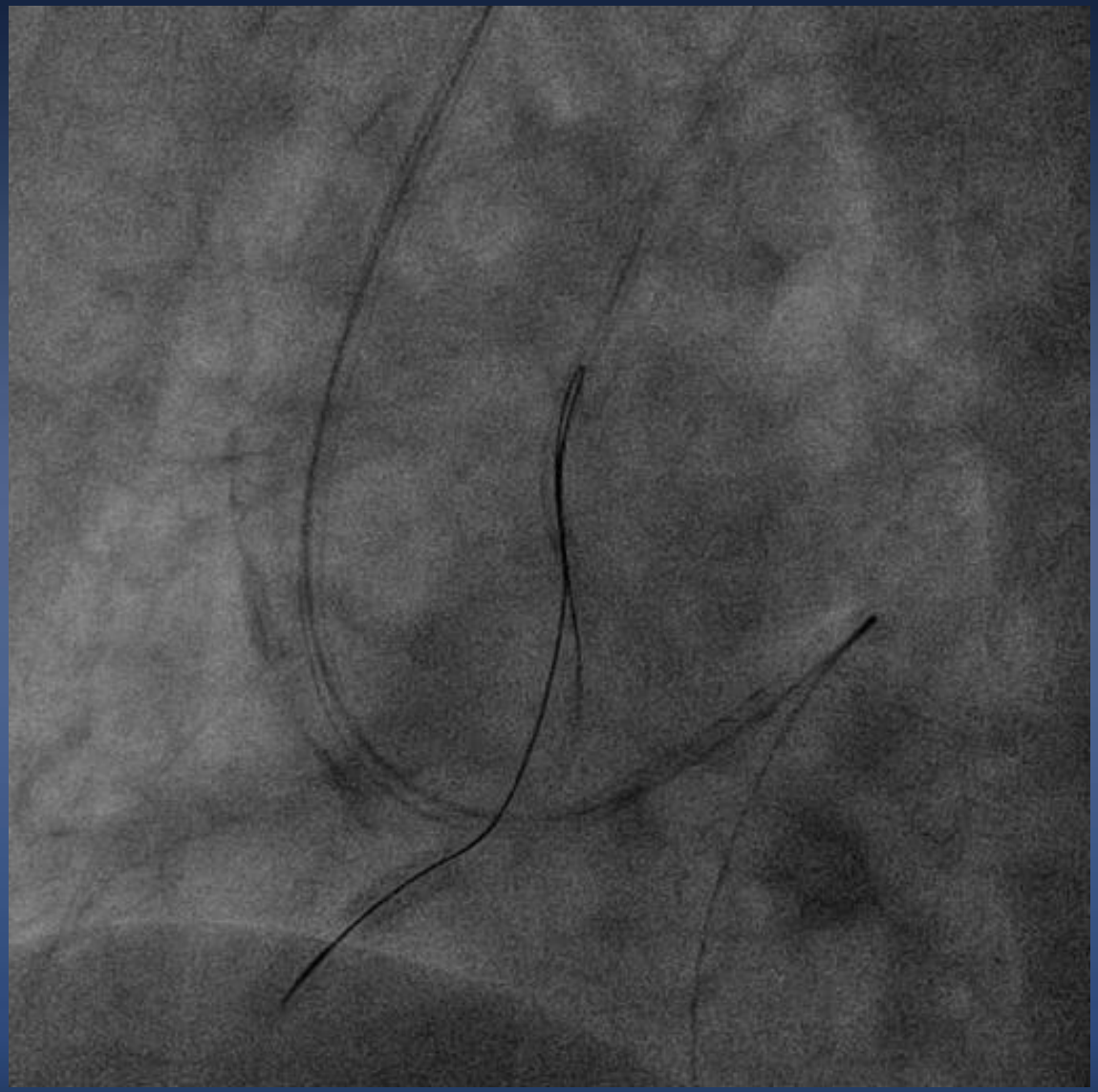




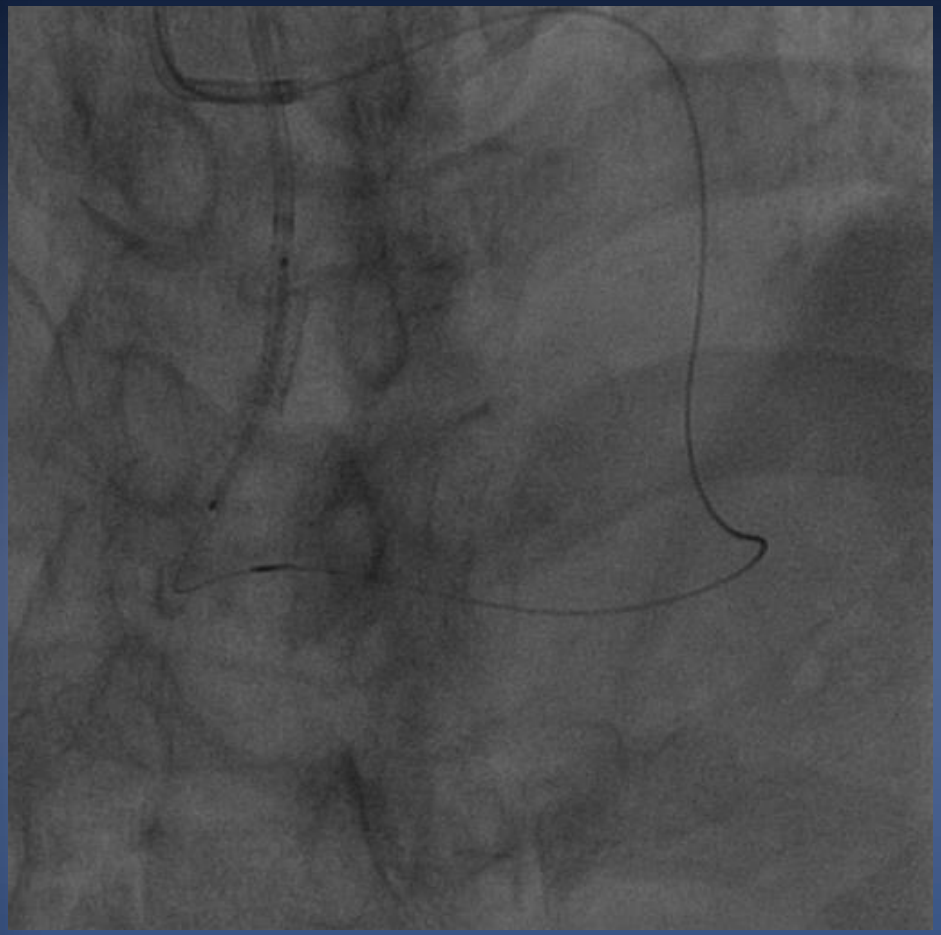


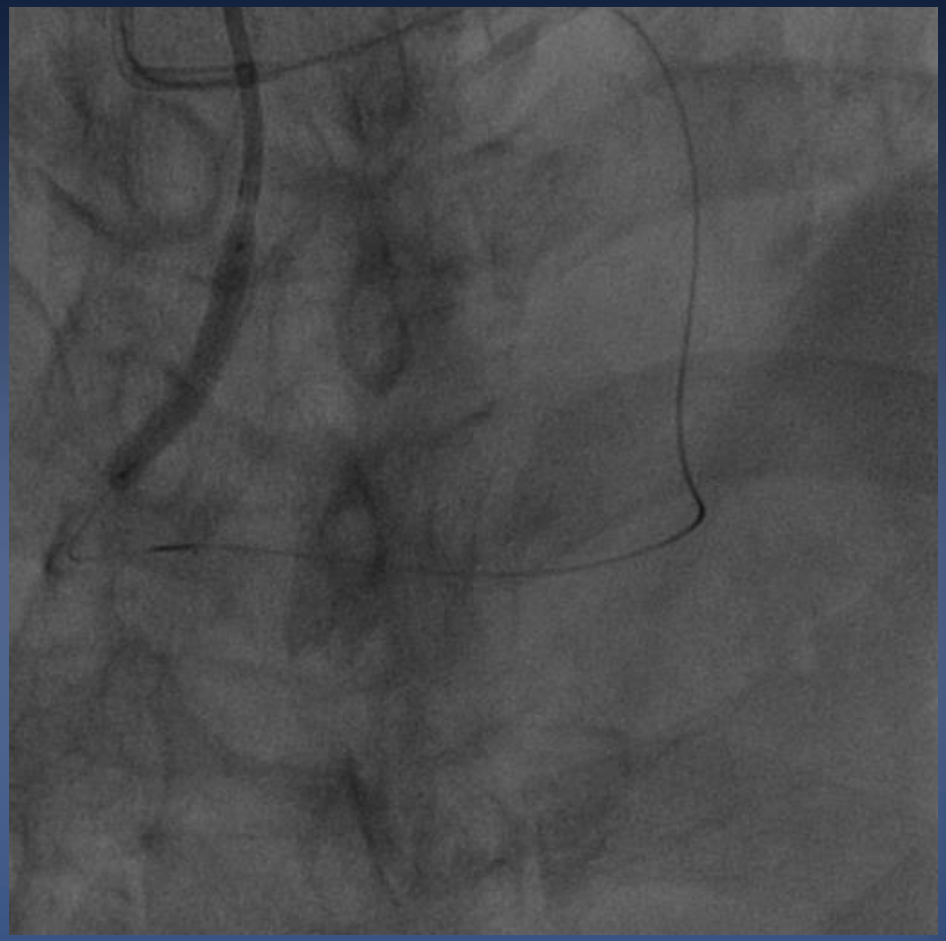
- Retrograde crossing with 7 F EBU 3.75 guide-UB3 wire and 1.6 F Caravel MC

Snaring the wire with hand-made snare

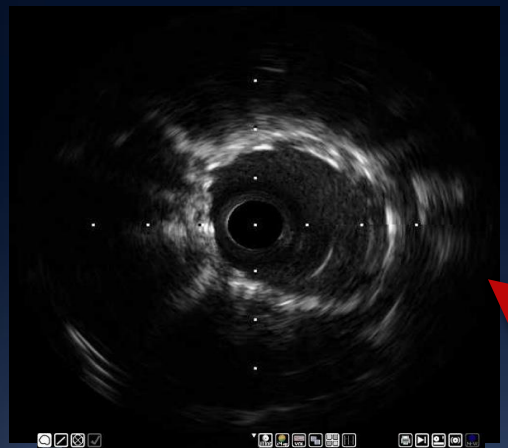


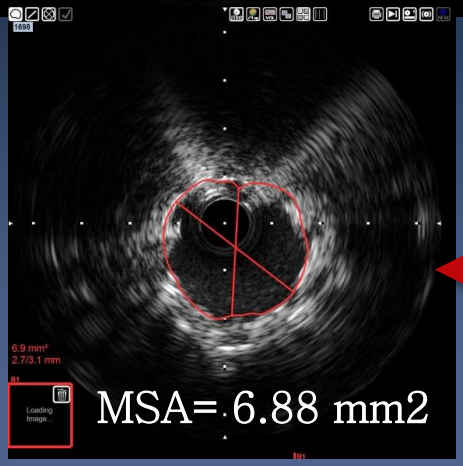
DES 3.5 x 28 mm was deployed at os-proximal RCA followed by post-dilation with 4.0 mm balloon upto 28 atm.

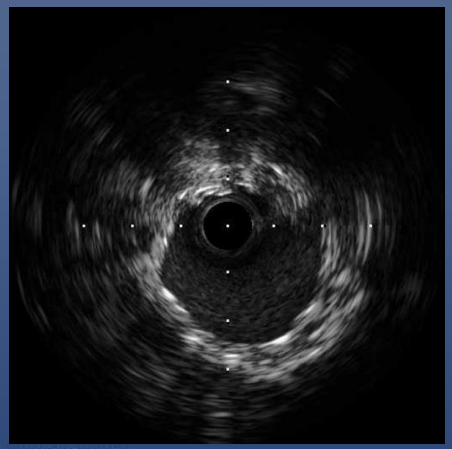


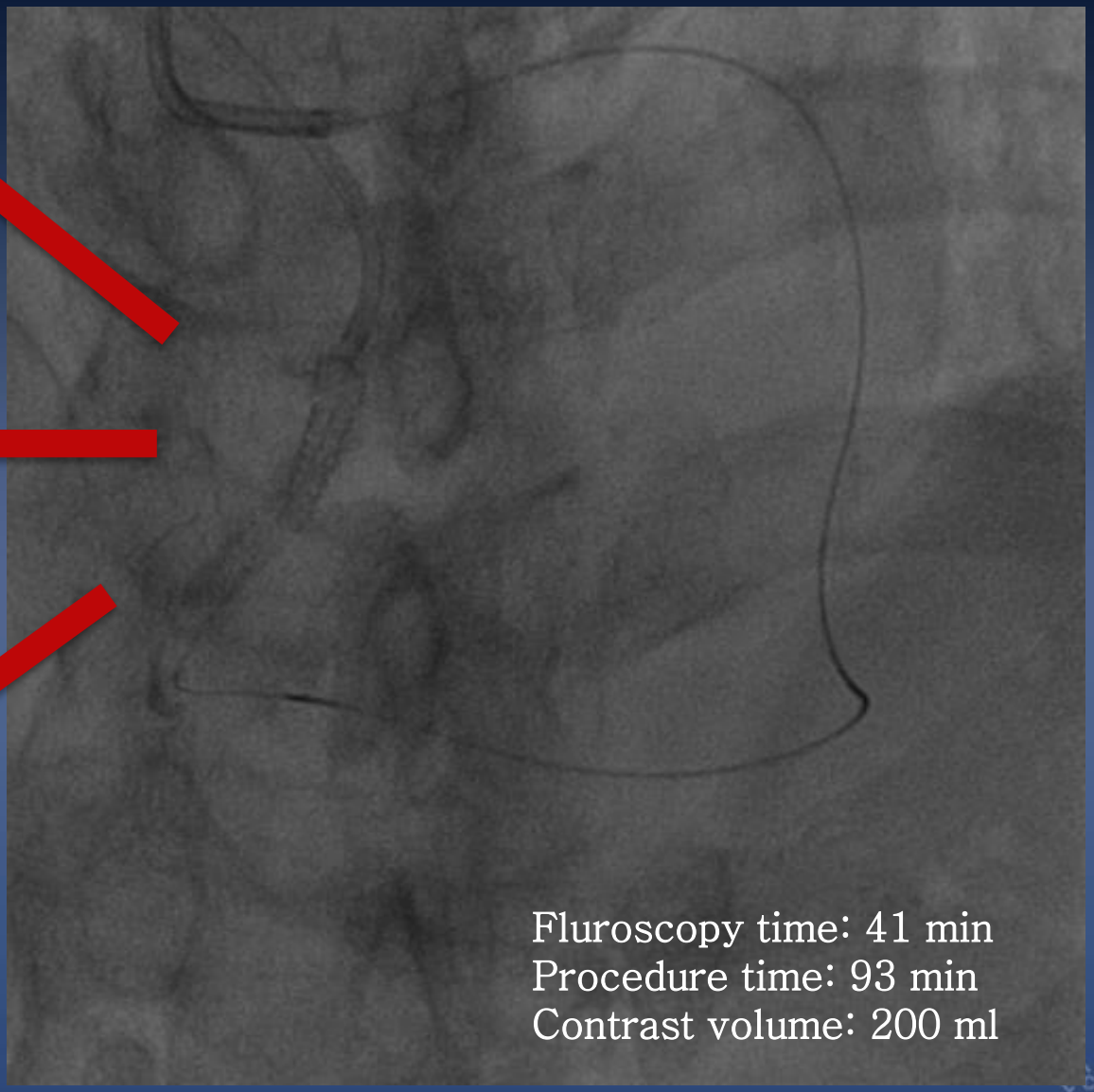


FINAL RESULT









Strategies for ISR under-expansion and under-sizing

- NC balloon
- Scoring/cutting balloon
- Rotational/ orbital atherectomy (need bigger burr for debulking of stent strut & tissue behind stent)
- Excimer Laser atherectomy (some reports)
- Intravascular lithotripsy (IVL)

Rotational vs. Orbital Atherectomy

	Rotablator	CSI Diamond back
Profile	Distal Cutting Profile 0.3 mm (.012”) 	Nose Cone 5 mm (.20”)  Crossing Profile ~0.66 mm (.026”) 1.25 mm Distal Cutting Profile*
Cutting Mechanism	**Front cutting**	**Circumferential cutting**
Target Lesion Opening	✓ **0 - < 1.25 mm**	✗ **0 - < 1.25 mm**
	✓ **1.25 mm-1.84 mm**	✓ **1.25 mm-1.84 mm**
	✓ **> 1.84 mm**	✗ **> 1.84 mm**

*CSI Classic Crown. Data presented by J. Moses at CRF Fellows 2014. Diamondback 360 Coronary Orbital Atherectomy System IFU.

Intravascular lithotripsy (IVL) for instent restenosis

- Principles similar to urologic lithotripsy – pulsatile sonic pressure waves that pass through soft tissue and selectively interact strongly with high-density calcium, producing significant shear stresses that have the ability to fracture the calcium.
- Could be useful for 1. calcific , un-dilatable neoatherosclerotic lesions 2. underlying under expanded stent.
- Ease of use (delivering a balloon to the lesion on any 0.014-inch guidewire), short learning curve and less procedural complications could facilitate rapid uptake

ROLE OF IMAGING

- IVUS is an indispensable tool in the evaluation of ISR- able to exclude possible mechanical causes of ISR (under-expansion, stent fracture, etc.) and provide detailed information on the extent of neointimal hyperplasia
- OCT- more detailed assessment of stented segment (superior axial resolution 10 – 20 um) enabling better characterization of neointimal tissue within stents, esp. of neo-atherosclerosis (lipid component or calcification)

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European Heart Journal (2019) **40**, 87–165
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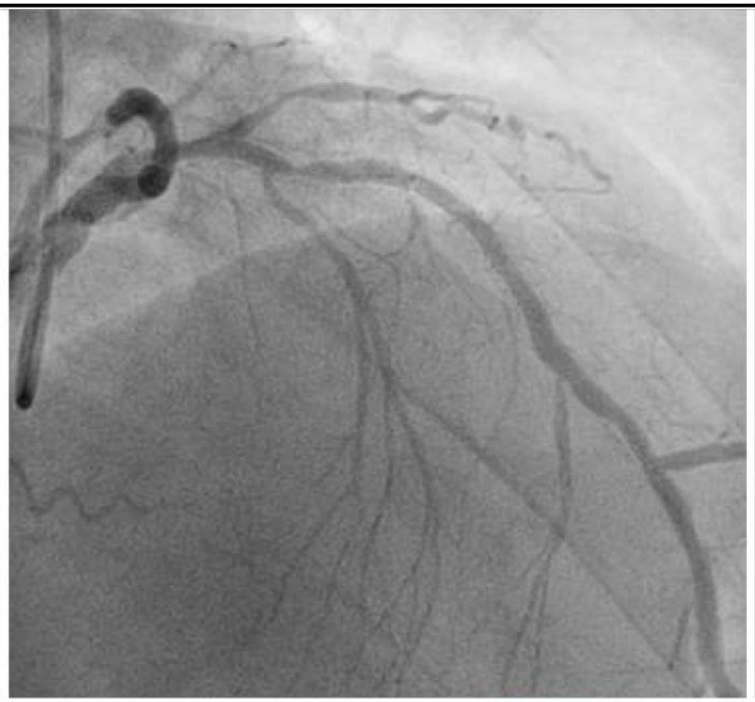
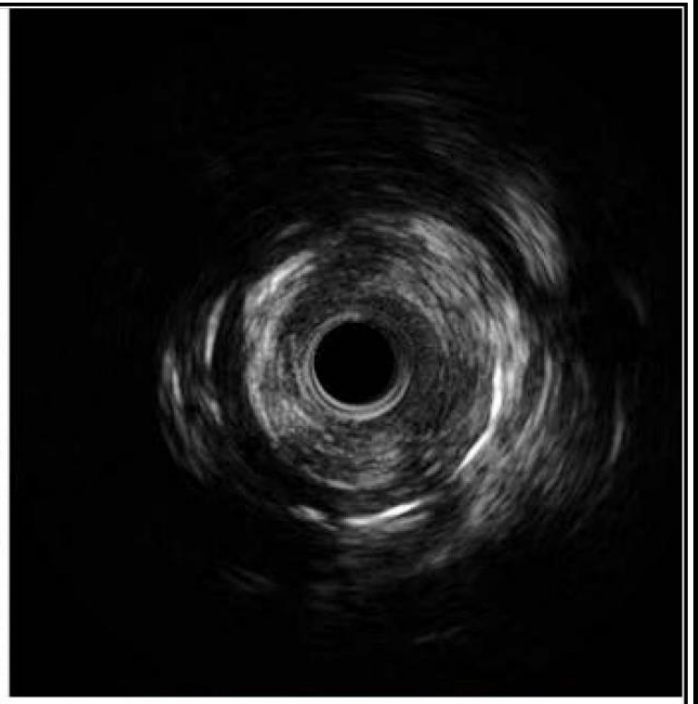
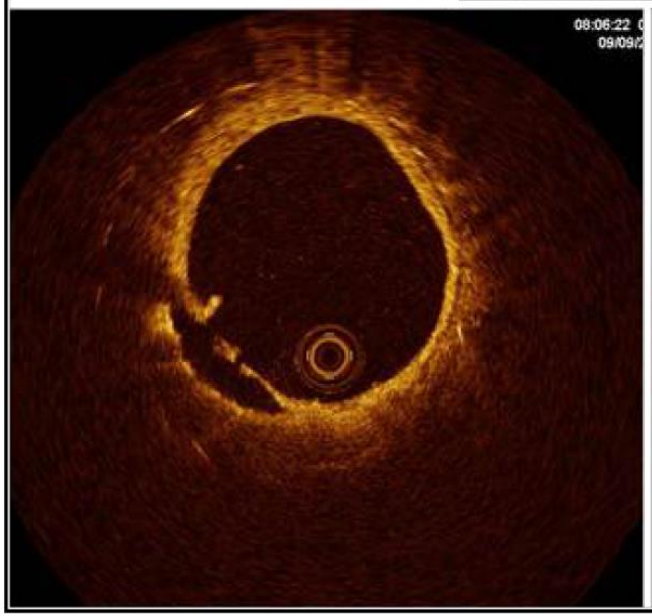
IVUS and/or OCT should be considered to detect stent-related mechanical problems leading to restenosis.	IIa	C



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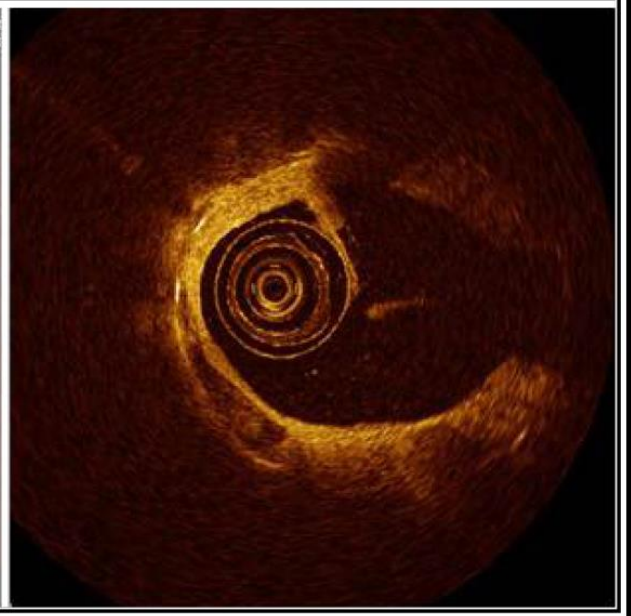

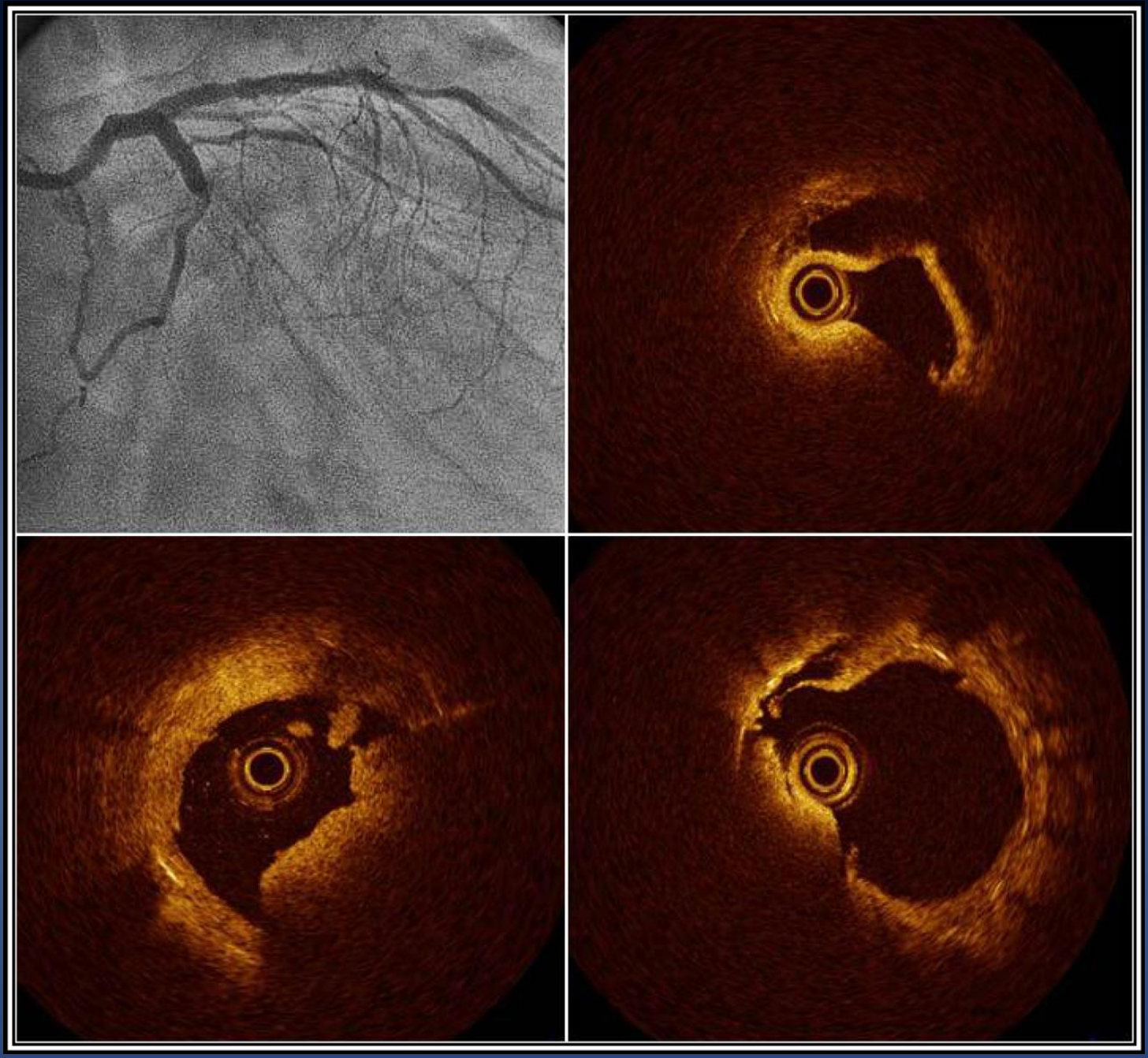

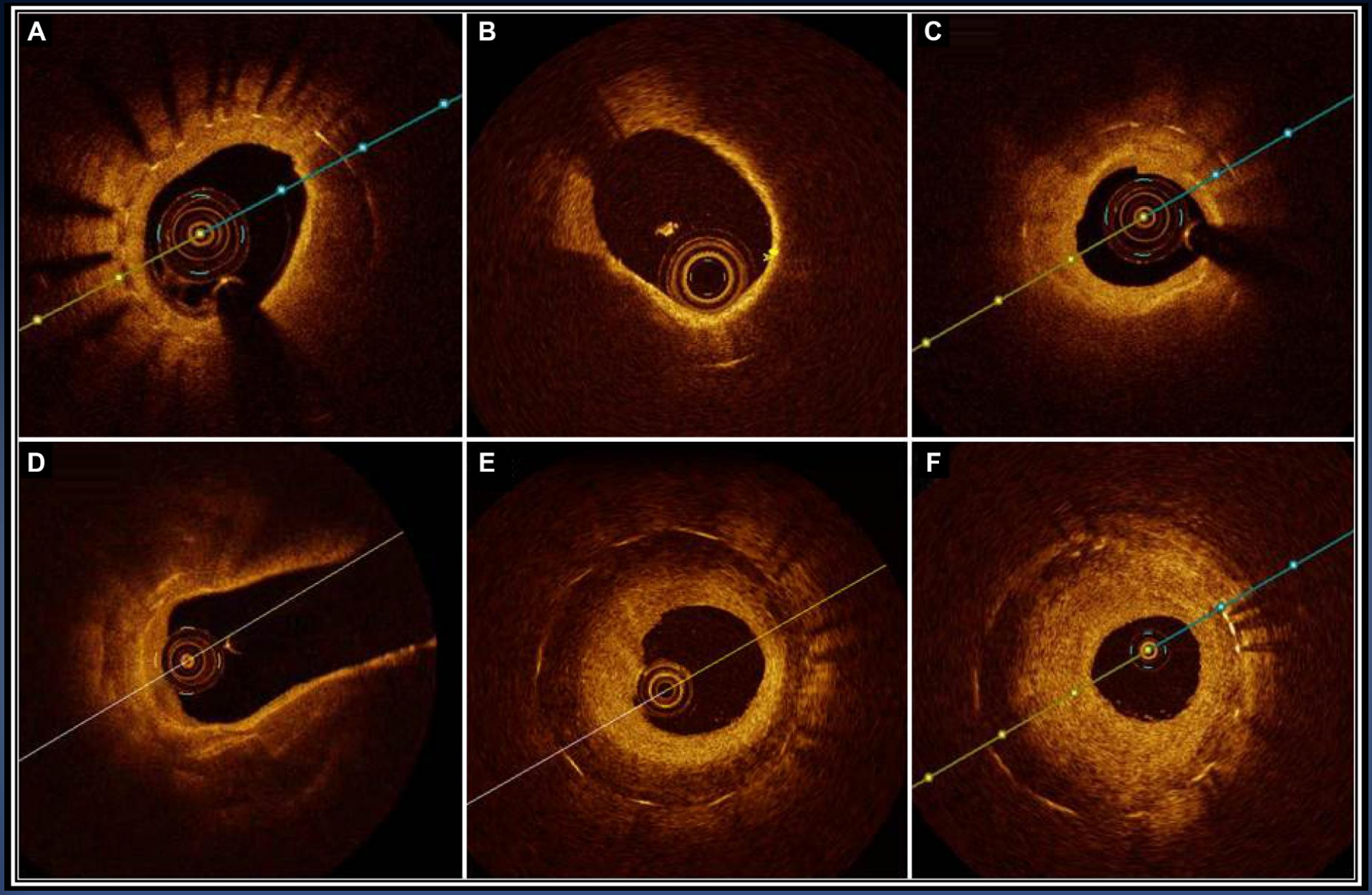
A
B
C
D
E
F

NEOATHROSCLEROSIS

- Incomplete regeneration of the endothelium leading to excessive uptake of circulating lipids and accelerated development of atherosclerotic plaques in the nascent neointima.
- Independent predictors of neoatherosclerosis included: Younger age, Longer durations, SES or PES implantation and Underlying unstable plaques.
- Neoatherosclerosis in DES shows unstable characteristics (Thin-Cap Fibroatheromas or plaque rupture) earlier (about two years) after implantation, whereas similar features in BMS occur relatively later (about six years)

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CLINICAL RESEARCH Interventional Cardiology

Appearance of Lipid-Laden Intima and Neovascularization After Implantation of Bare-Metal Stents

Extended Late-Phase Observation by Intracoronary Optical Coherence Tomography

Masamichi Takano, MD,* Masanori Yamamoto, MD,† Shigenobu Inami, MD,*
Daisuke Murakami, MD,† Takayoshi Ohba, MD,† Yoshihiko Seino, MD,† Kyoichi Mizuno, MD*
Tokyo and Chiba, Japan

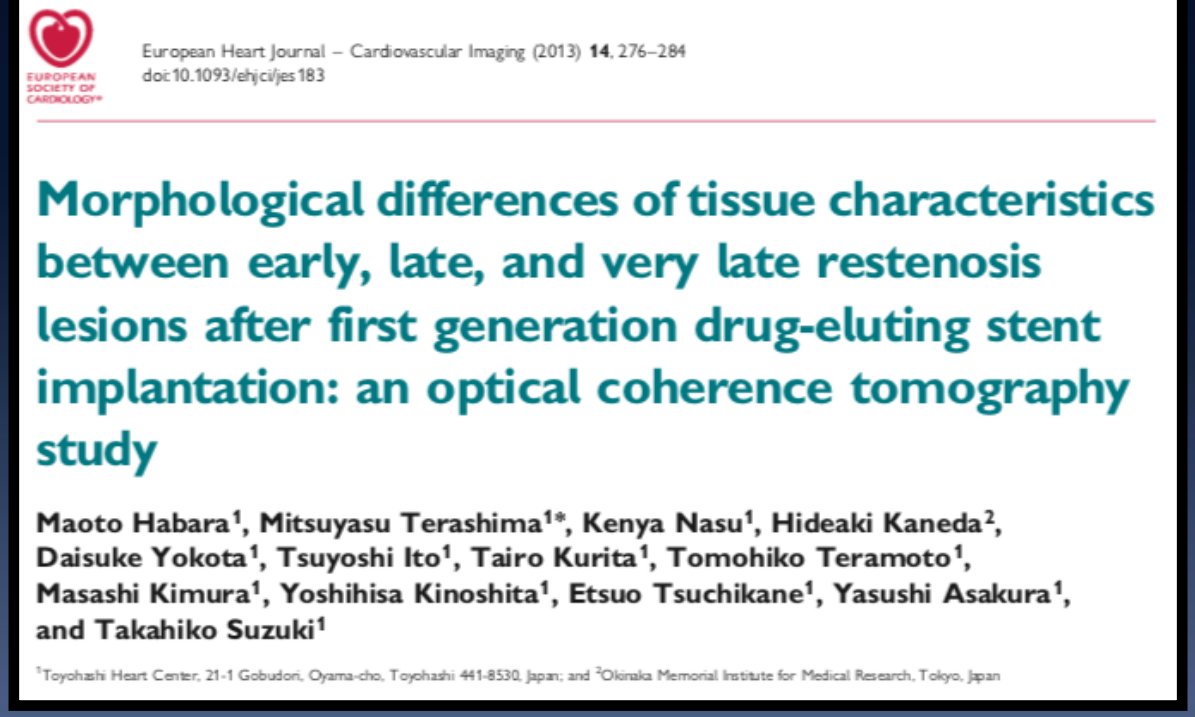
- This extended late-phase (> 5 years) OCT observation after BMS implantation demonstrated that:

1) Neointima often transforms into lipid-laden tissue with lumen narrowing.

2) Neovascularization expanding from the peri-stent area into the intima

may be responsible for atherosclerotic change.

3) Advanced atherosclerotic progression such as intimal disruption and



European Heart Journal – Cardiovascular Imaging (2013) **14**, 276–284
doi:10.1093/ehjci/jes183

Morphological differences of tissue characteristics between early, late, and very late restenosis lesions after first generation drug-eluting stent implantation: an optical coherence tomography study

Maoto Habara[1], Mitsuyasu Terashima[1]*, Kenya Nasu[1], Hideaki Kaneda[2], Daisuke Yokota[1], Tsuyoshi Ito[1], Tairo Kurita[1], Tomohiko Teramoto[1], Masashi Kimura[1], Yoshihisa Kinoshita[1], Etsuo Tsuchikane[1], Yasushi Asakura[1], and Takahiko Suzuki[1]

[1]Toyohashi Heart Center, 21-1 Gobudori, Oyama-cho, Toyohashi 441-8530, Japan; and [2]Okinaka Memorial Institute for Medical Research, Tokyo, Japan

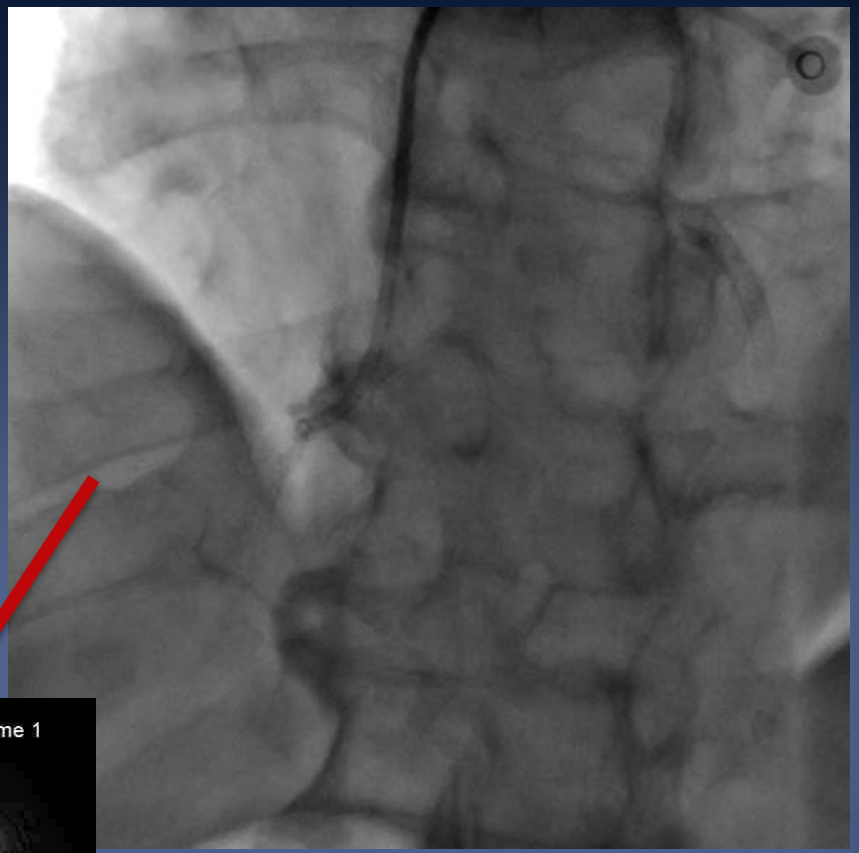
- The OCT morphological characteristics of DES restenotic tissue were different over a prespecified time course.
- OCT images in DES E-ISR might be associated with delayed arterial healing.
- Neoatherosclerosis might contribute to the DES late catch-up phenomenon including L-ISR and VL-ISR

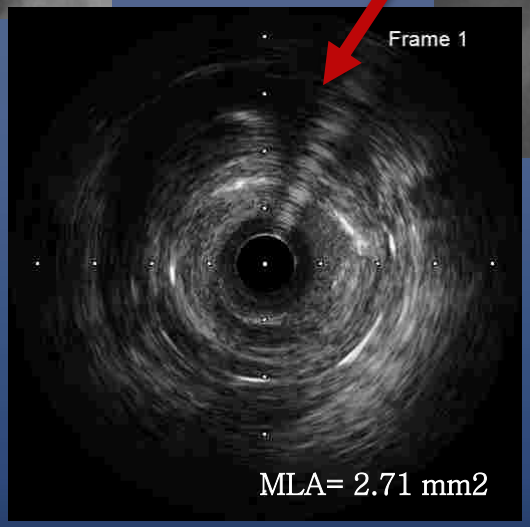
Case 2

- 83 yrs old gentleman
- Hypertension; ESRD stage IIIb; h/o CVA
- Prior history of stenting to p-LAD and p-m RCA with Taxus DES (2008).
- 2013 -Xience V 3 x 38 mm for p-LAD ISR in 2013. p-RCA stent had 40% diffuse ISR.
- 2019 - Unstable angina - large area reversible schema in inferior territory on Thallium scans.

2013

2019

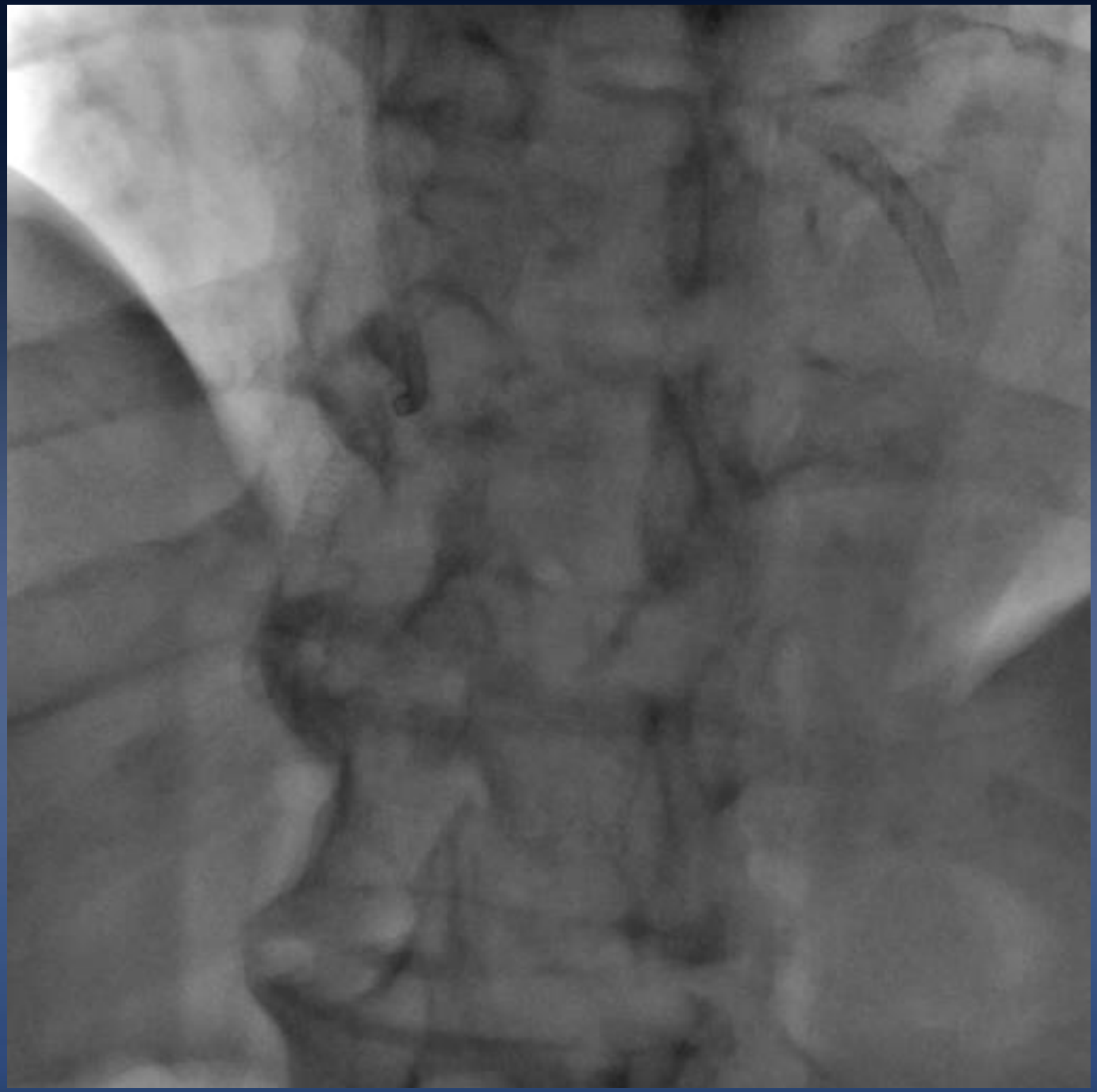




Late catch-up phenomenon

Lesion prepared with Accuforce 3.5 x 20 mm at 24 atm

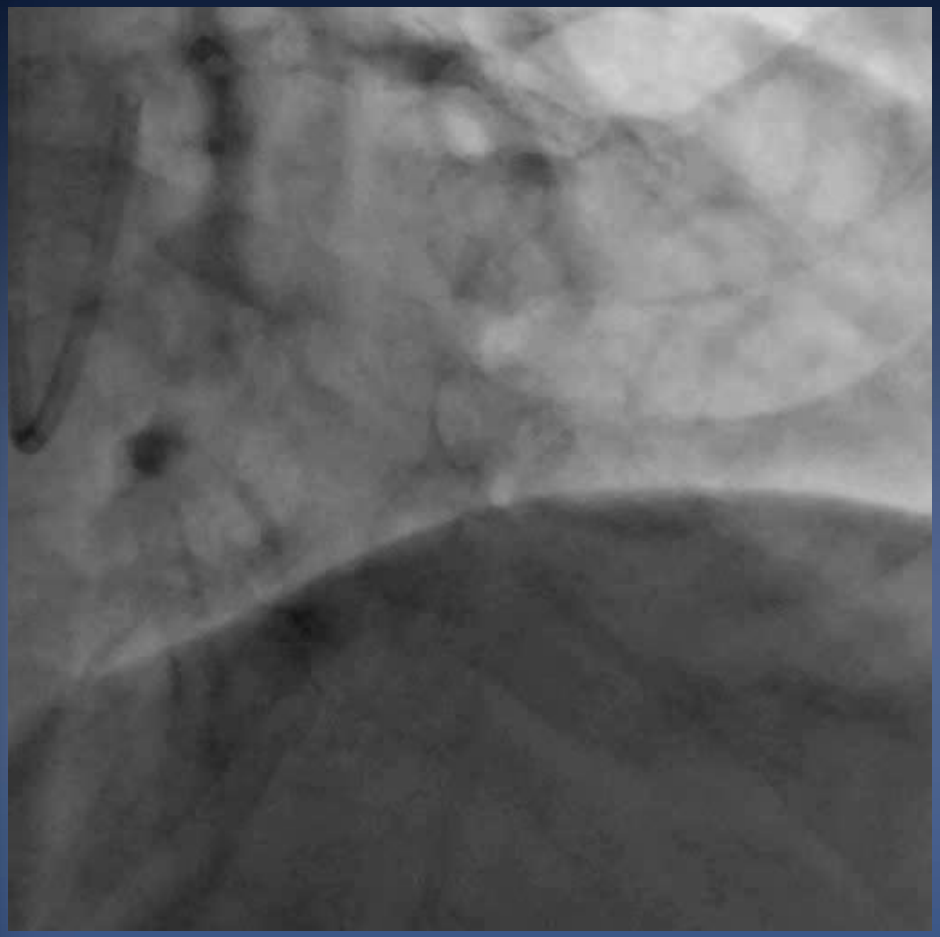
Xience Alpine 3x38 mm at 16 atm f/b postdilation with Accuforce 3.5 x 20 mm at 28 atm

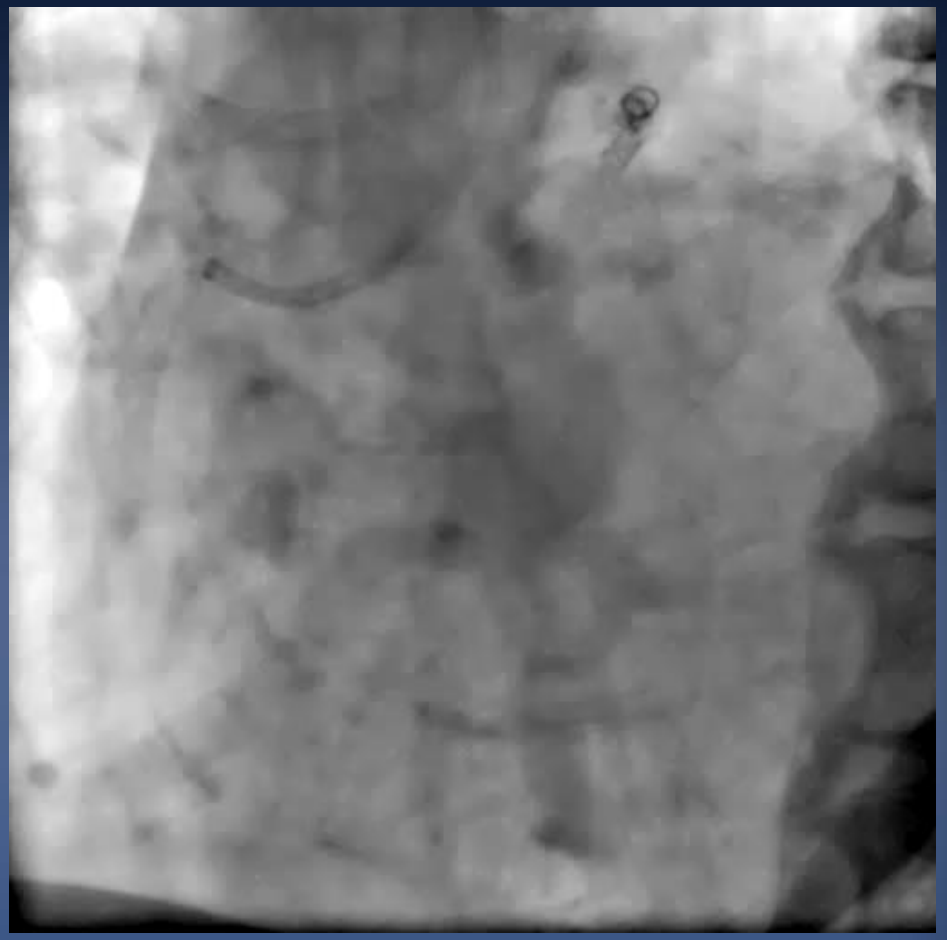


Case 3

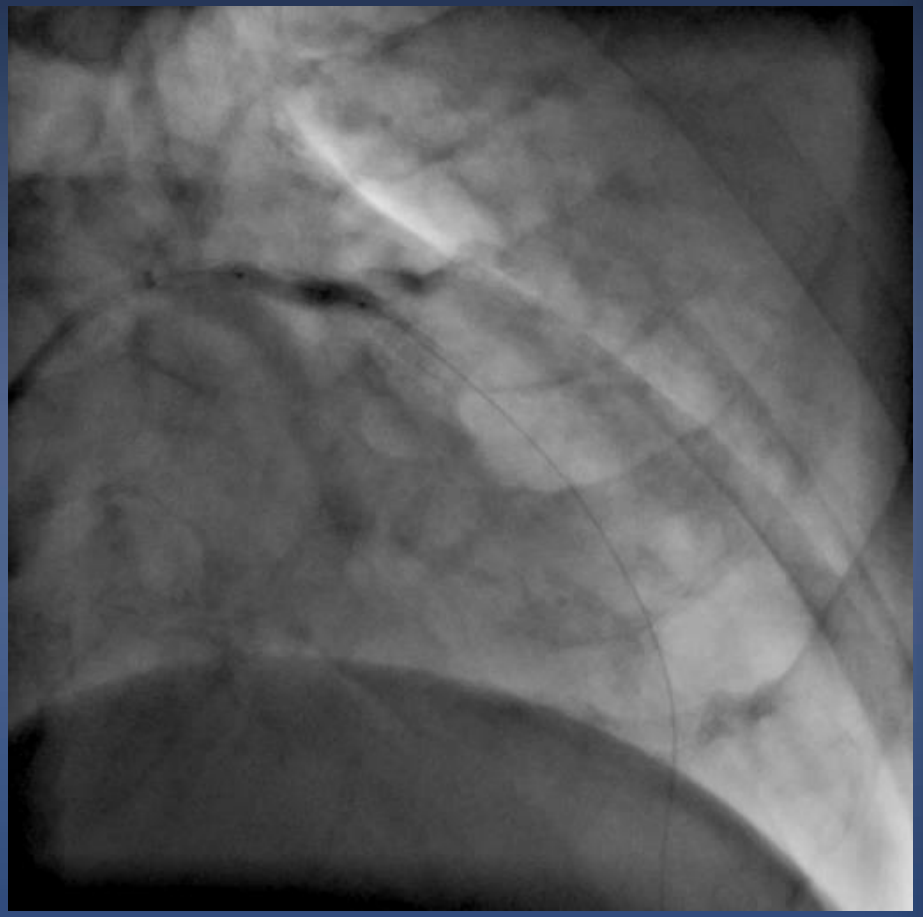
- A 70 y/o man presented with UA. He had medical history of DM, HTN, old MI, CAD S/P Taxus DES 3.5x24 mm to RCA-P and 2.75x32 mm Taxus for LAD-P and POBA to LCX since 2004-05-12.
- **Echo**: Dilated LV, LA, deteriorating LVEF from 40% to 23 %
- **Thallium Scan**: Probably irreversible myocardial ischemia in the apex, apical-anterior, apical-lateral, mid-inferolateral and basal-inferolateral segments of left ventricle.

- Through a L't Snuffbox, a 6Fr. Ikari-Left 4.0 was used to engage the LM and RCA



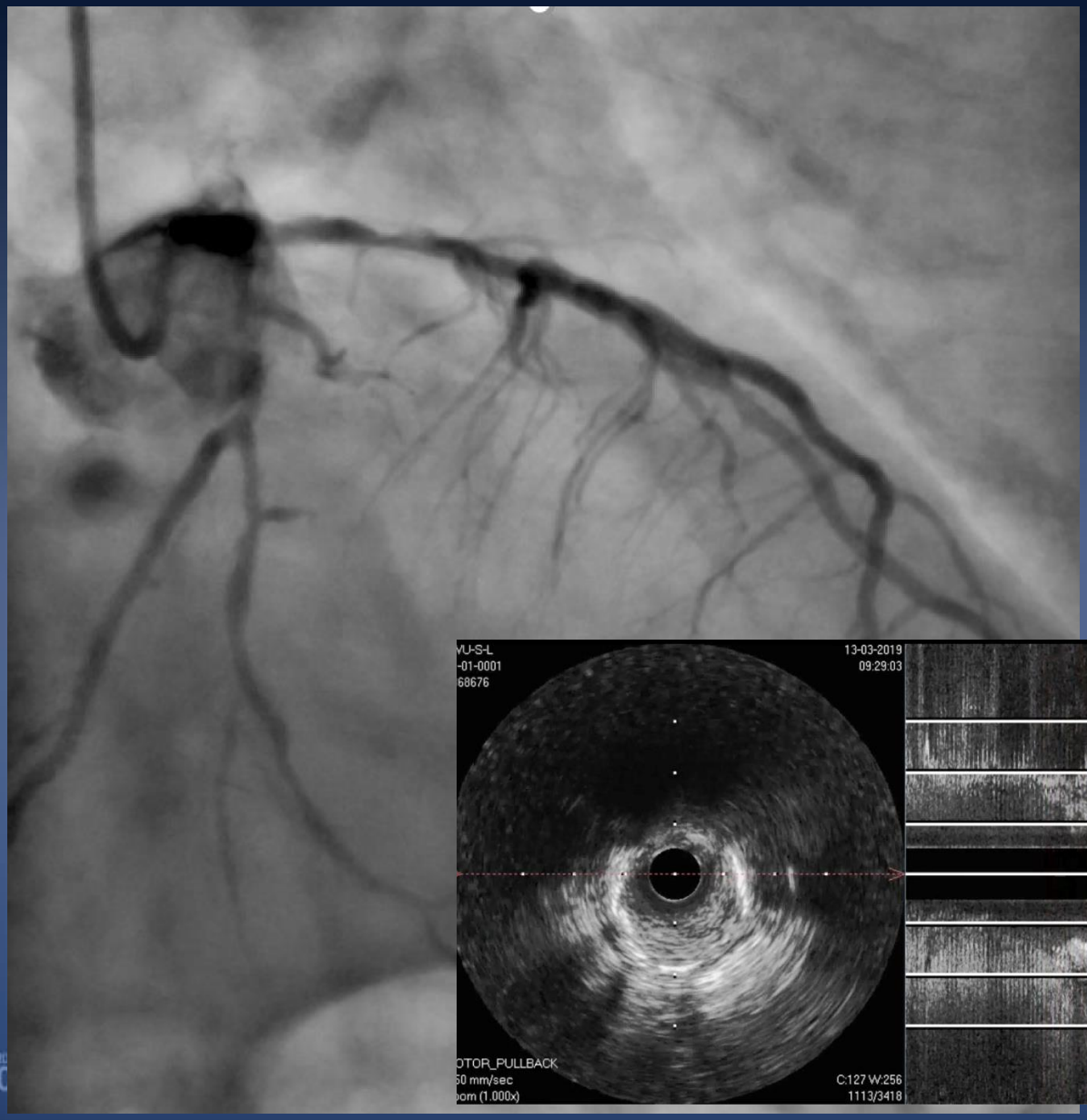


LAD Dilatation

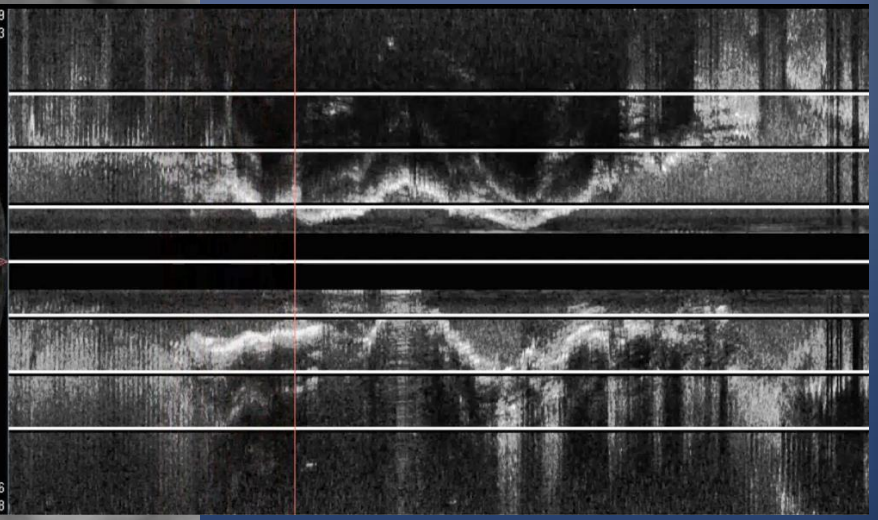


Accuforce balloon 3.0 X 15 up to 16-24 atm for LAD proliferative type ISR with neoatherosclerosis

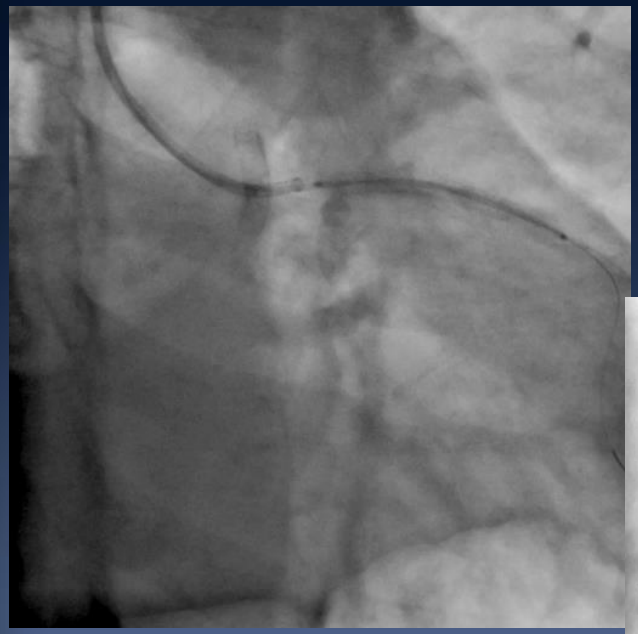
IVUS LAD: Taxus proliferative type ISR diffuse with neo-atherosclerosis & severe calcification

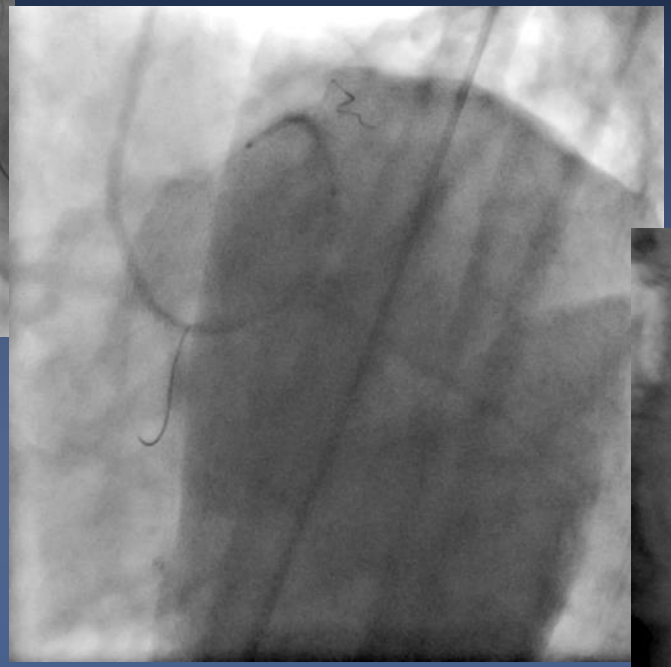


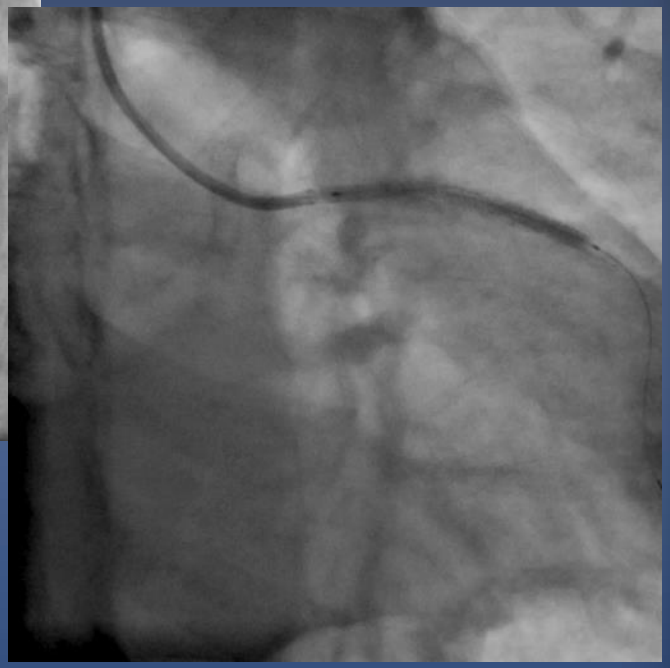
MLA 2.9 mm2



LAD Stenting



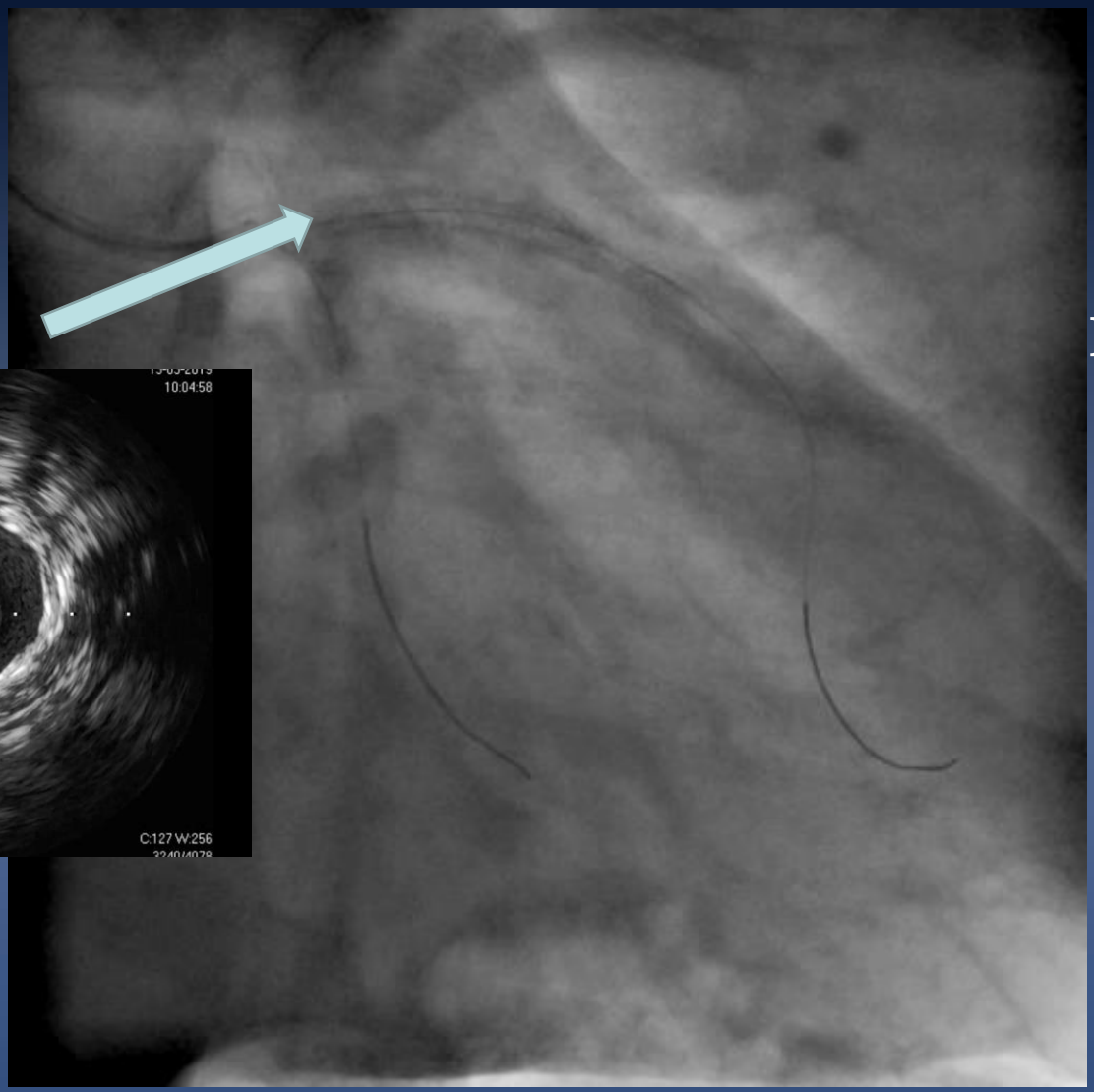


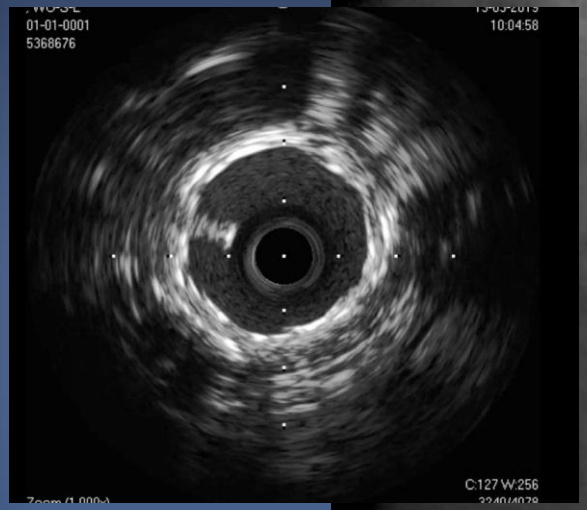


DES 3.0 X 48 up to 16 ATM

Post dilated using Accuforce HPB 3.0 X 15 mm up to 24 atm

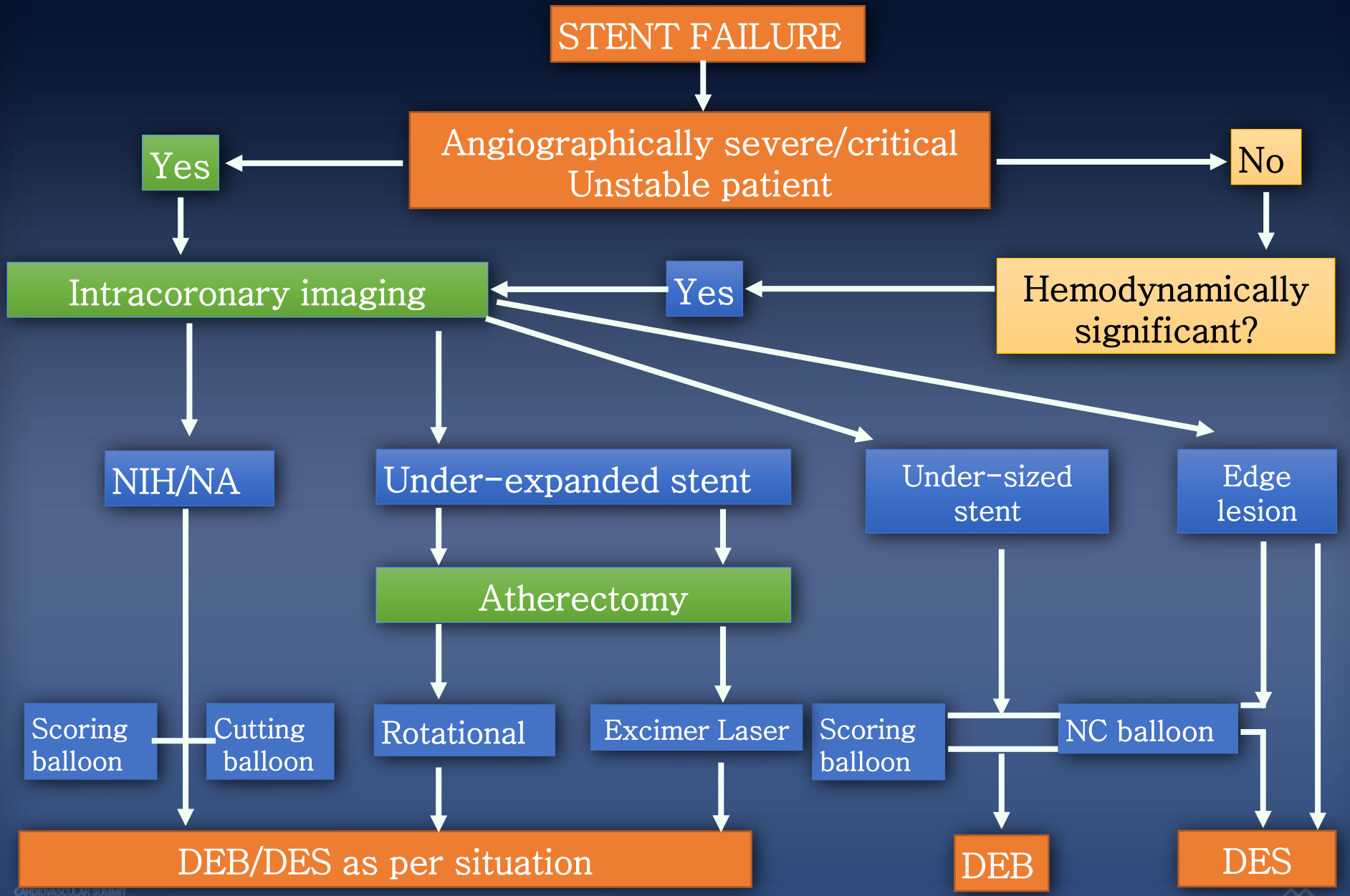
LAD Final





MSA 5.8 mm2

Simplified Approach to Stent Failure Cases



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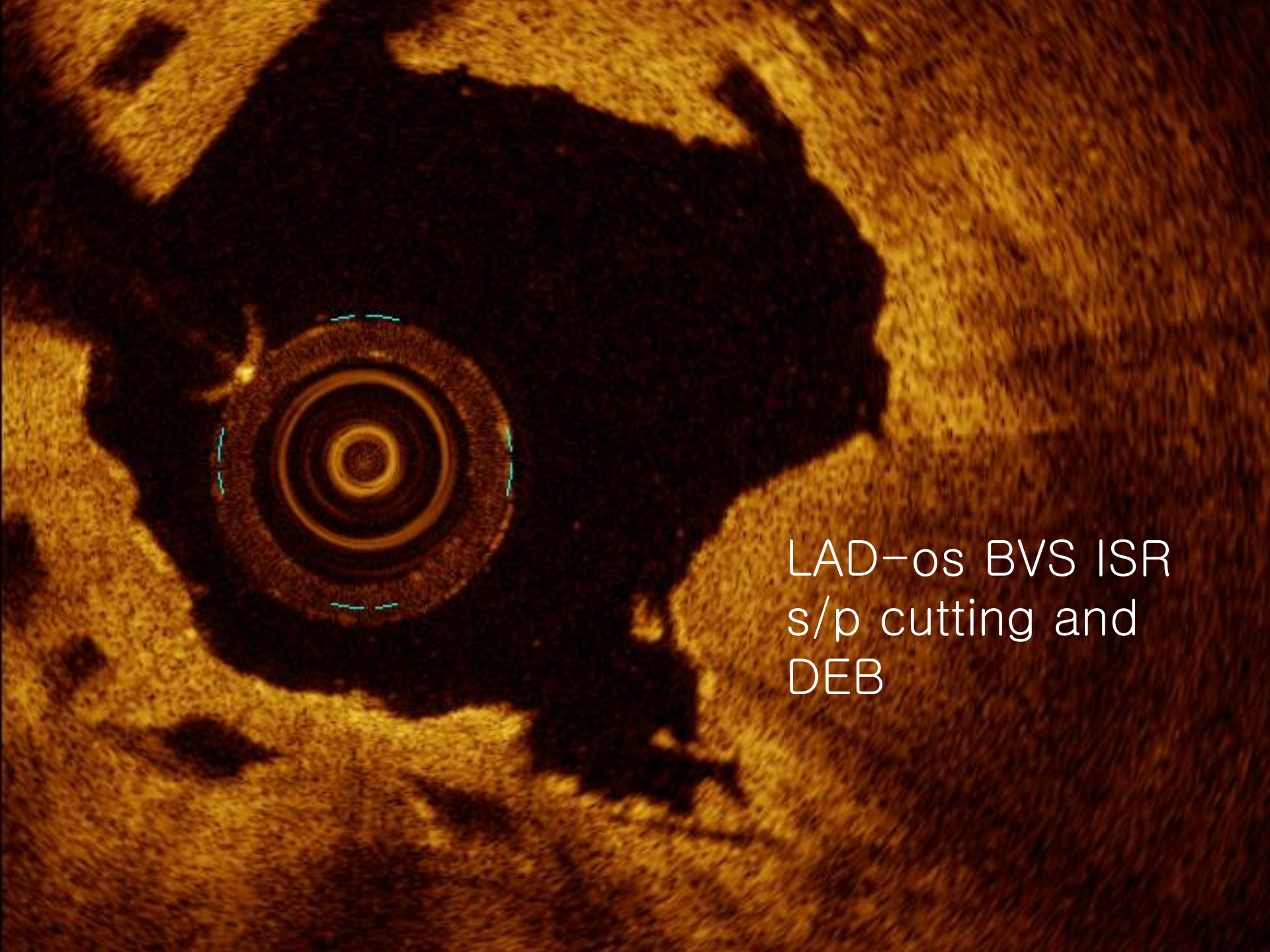
Future unsettle Issues:

- Biodegradable stent ISR
- Un-dilatable ISR (lithotripsy, Laser or Rotar ?
- Ostia location ISR ?
- Management of Neo-atherosclerosis ISR
- ESRD with DES failure


LAD-os BVS ISR
s/p cutting and
DEB


Thank you
長庚 高雄
高雄長庚紀念醫院
Kaohsiung Chang Gung Memorial Hospital