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THE UNIVERSITY OF MELBOURNE

Drug-Coated Balloons in Complex Cases

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Why drug-coated balloons?

1. Ease of use in coronaries and peripheral (especially below knees)
2. Cost – balloon catheters have traditionally been less expensive than stents (and potential cost saving with less duration of DAPT)
3. Potential for improved safety – no chronic polymer effects, reduced drug exposure
4. Can be used in situations where DES can be problematic e.g. ISR, bifurcations (ostium side branch), diabetics, small vessels, diffuse disease, cant deliver stent

DCB: Components

Platform

Pantera balloon

- Semi-compliant
- Low profile
- Highly deliverable

Drug

Paclitaxel

- 3.0 µg/mm^2
- Anti-proliferative
- Lipophilic & quickly absorbed

Excipient

BTHC

- Butyryl-tri-hexyl citrate
- Biocompatible
- Degrades to citric acid and alcohol

Lux coating

- Homogenous
- Keeps paclitaxel in microcrystalline structure
- Optimal bioavailability

Pantera Lux

Clinically proven[1,2]

PEPPER and DELUX studies show high efficacy and safety in in-stent restenotic and de novo lesions

Indicated[3] for

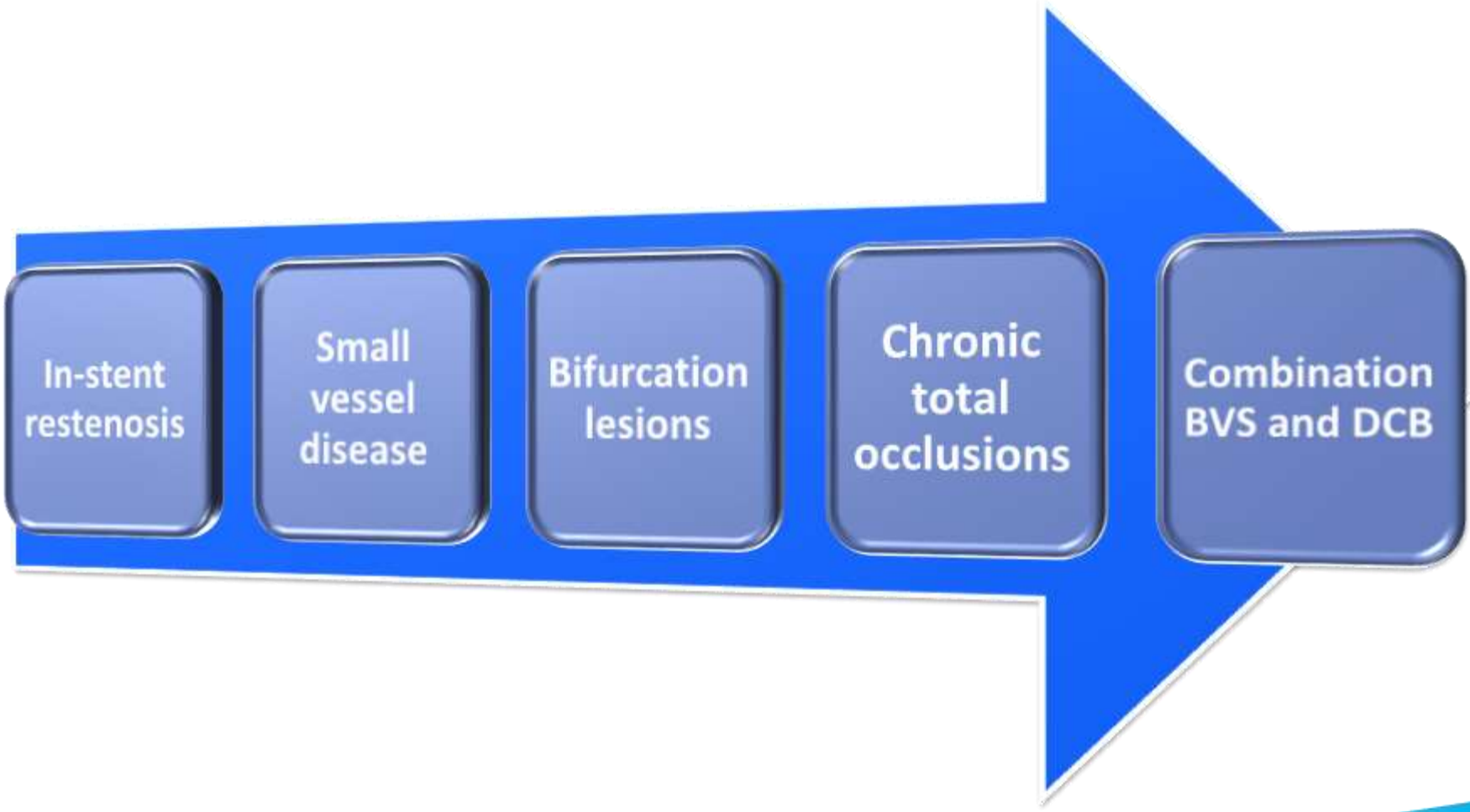
- in-stent restenosis
- de novo lesions
- small vessels
- acute occlusions

[1] Hehrlein C et al. Cardiovasc Revasc Med. 2012 Sep; 13(5): 260-4.

[2] Toelg R et al. EuroIntervention. 2014 Sep; 10(5): 591-9.

[3] Indications may differ in countries not accepting CE mark. Not for sale in the U.S.

The expanding use of drug-coated balloons in contemporary practice



In-stent restenosis

- Compared to the BMS era, the rate of in-stent restenosis (ISR) has been reduced by the introduction of DES
- With DES however, the rate of ISR is still about 5-10%, but higher in diabetics, small vessels, and bifurcations
- The first-line challenge is to reduce the frequency of ISR by using modern DES with proper implantation techniques
- When ISR does occur however, DCB's offer a proven therapeutic alternative to implantation of additional stents

ESC guidelines recommend DCB for ISR treatment

Recommendations for repeat revascularizations	Class	Level
Drug-coated balloons are recommended for the treatment of in-stent restenosis (within BMS or DES).	I	A

This is the strongest recommendation and highest level of evidence possible.

[Class 1 = general agreement that treatment is beneficial, useful and effective]
[Level of evidence A = derived from multiple randomized clinical trials or meta-analysis]

Source: Windecker et al. Eur Heart J. 2014 Oct 1; 35 (37): 2541-619.

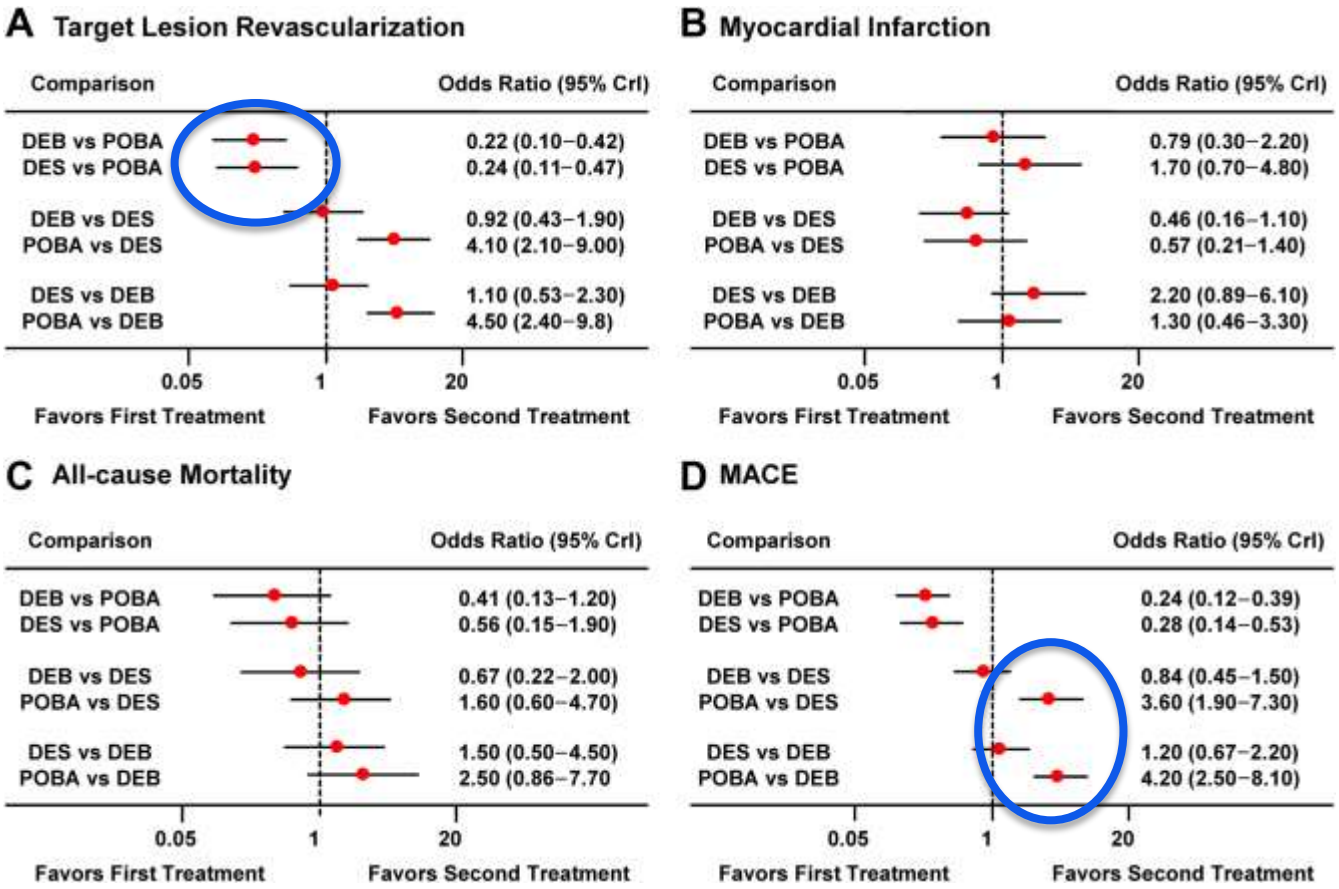


Figure 2 Results of Bayesian Network Meta-Analysis for Overall Rates of Clinical Outcomes in a Random Effects Model Results of a Bayesian network meta-analysis with a random-effects model for the risk of target lesion revascularization (A) , myocardial i...

Comparison Among Drug-Eluting Balloon, Drug-Eluting Stent, and Plain Balloon Angioplasty for the Treatment of In-Stent Restenosis : A Network Meta-Analysis of 11 Randomized, Controlled Trials

Joo Myung Lee , Jonghanne Park , Jeehoon Kang , Ki-Hyun Jeon , Ji-hyun Jung , Sang Eun Lee , Jung-Kyu Han , Hack-...

JACC: Cardiovascular Interventions, Volume 8, Issue 3, 2015, 382 - 394

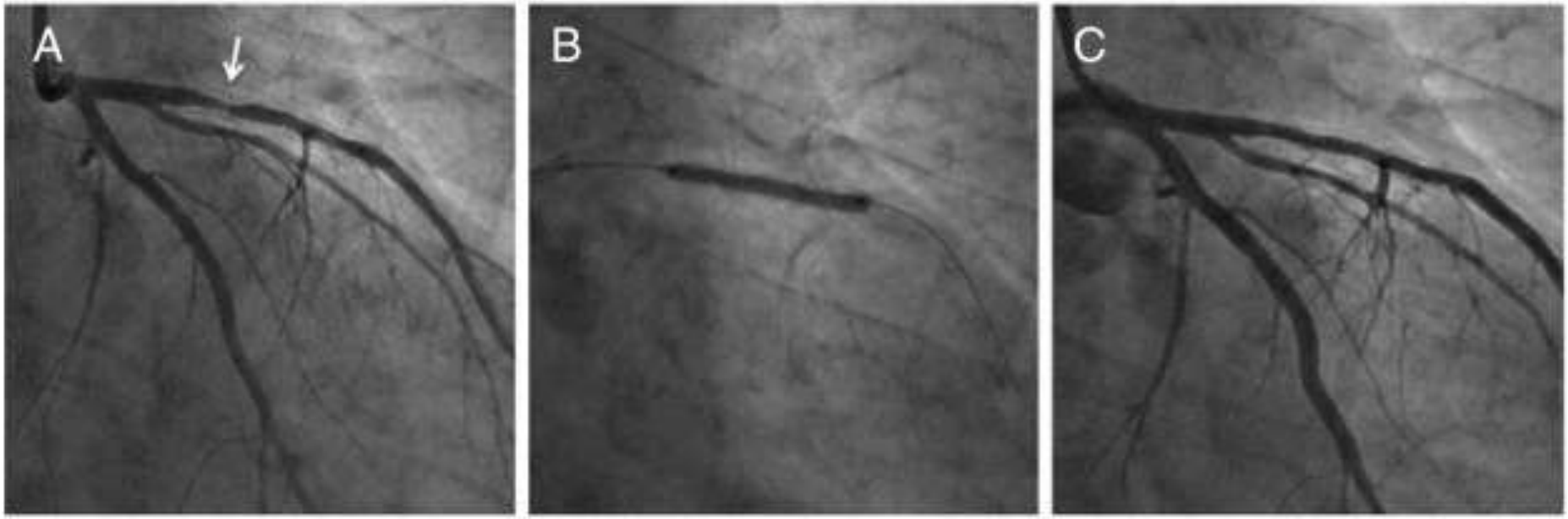
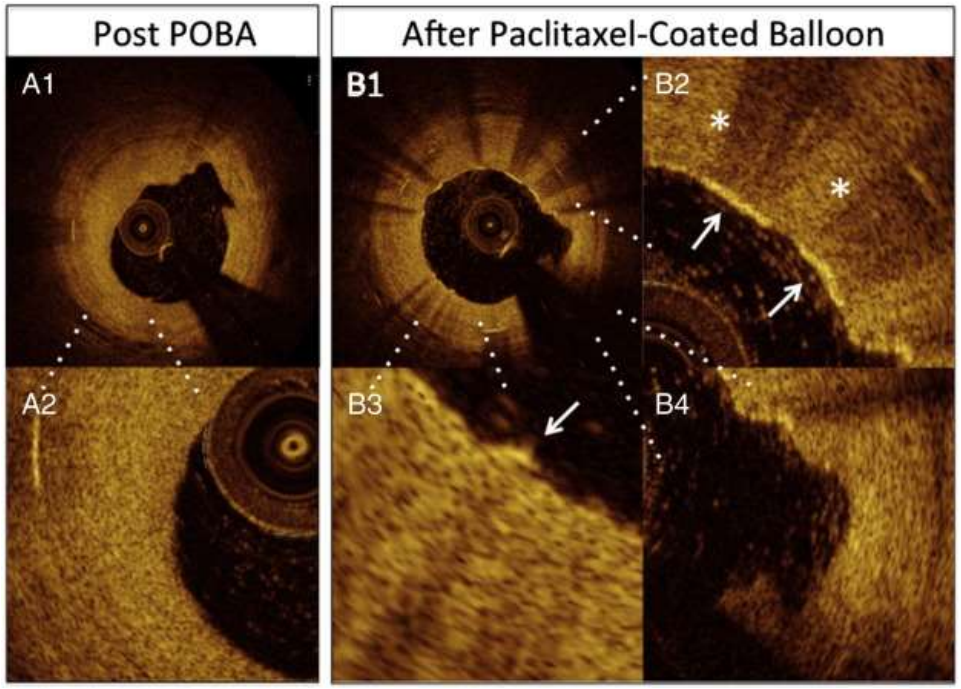


Fig. 1. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon.(A) Coronary angiography showing in-stent (bare-metal stent) restenosis at the proximal left anterior descending artery.(B) Drug-coating balloon after balloon angioplasty.(C) Fi...
Kihei Yoneyama, Kohei Koyama, Yasuhiro Tanabe, Takanobu Mitarai, Ryo Kamijima, Shingo Kuwata, Hiroshi Yamazaki, Emi Nakano, Ken Kongoji, Tomoo Harada, Yoshihiro J. Akashi

Coronary angioscopy and optical coherence tomography for confirmation of drug-coated neointimal plaque after paclitaxel-coated balloon angioplasty for in-stent restenosis

International Journal of Cardiology, Volume 176, Issue 3, 2014, 1207–1209



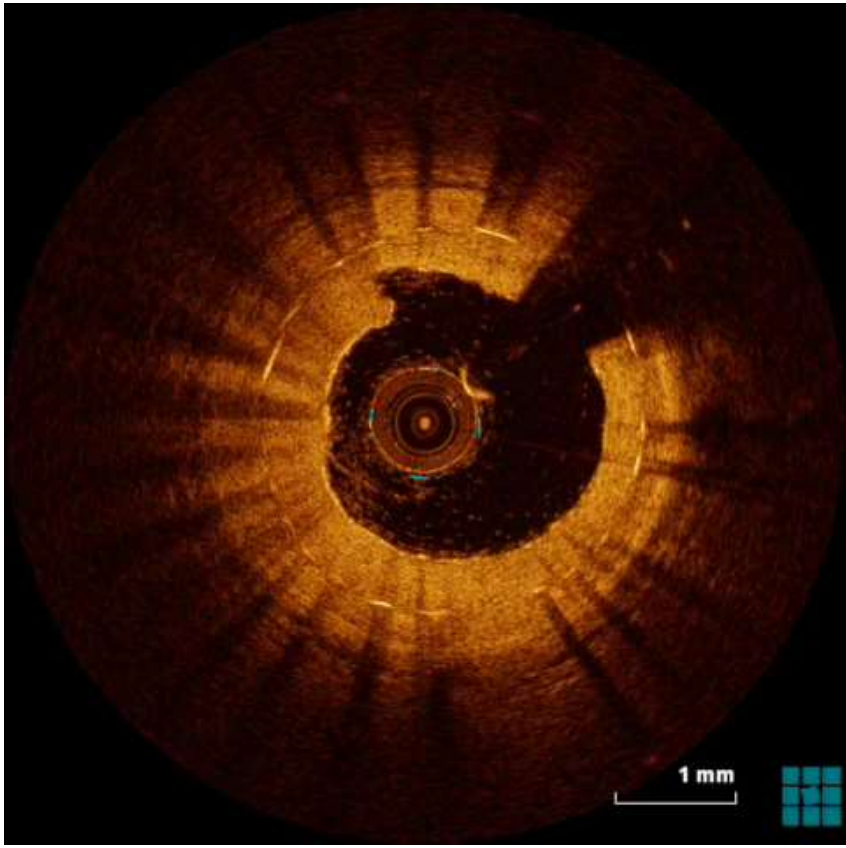


Fig. 2. Optical coherence tomography images of coronary in-stent restenosis with a paclitaxel-coated balloon.(A1) After balloon angioplasty, OCT revealed a severe neointimal plaque within the bare-metal stent.(A2) Neointimal coverage with a large view.(B1)

Kihei Yoneyama, Kohei Koyama, Yasuhiro Tanabe, Takanobu Mitarai, Ryo Kamijima, Shingo Kuwata, Hiroshi Yamazaki, Emi Suc...
Nakano, Ken Kongoji, Tomoo Harada, Yoshihiro J. Akashi

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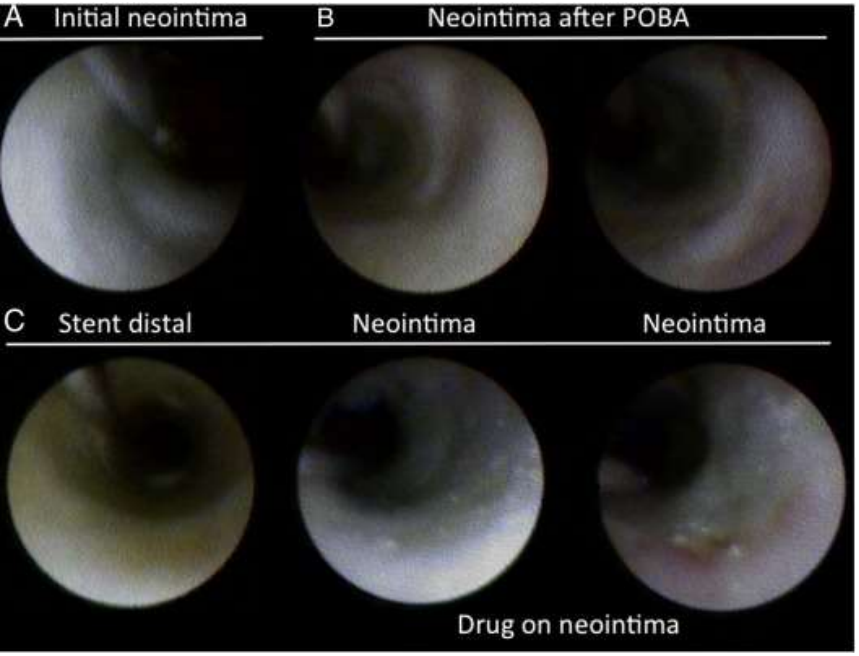

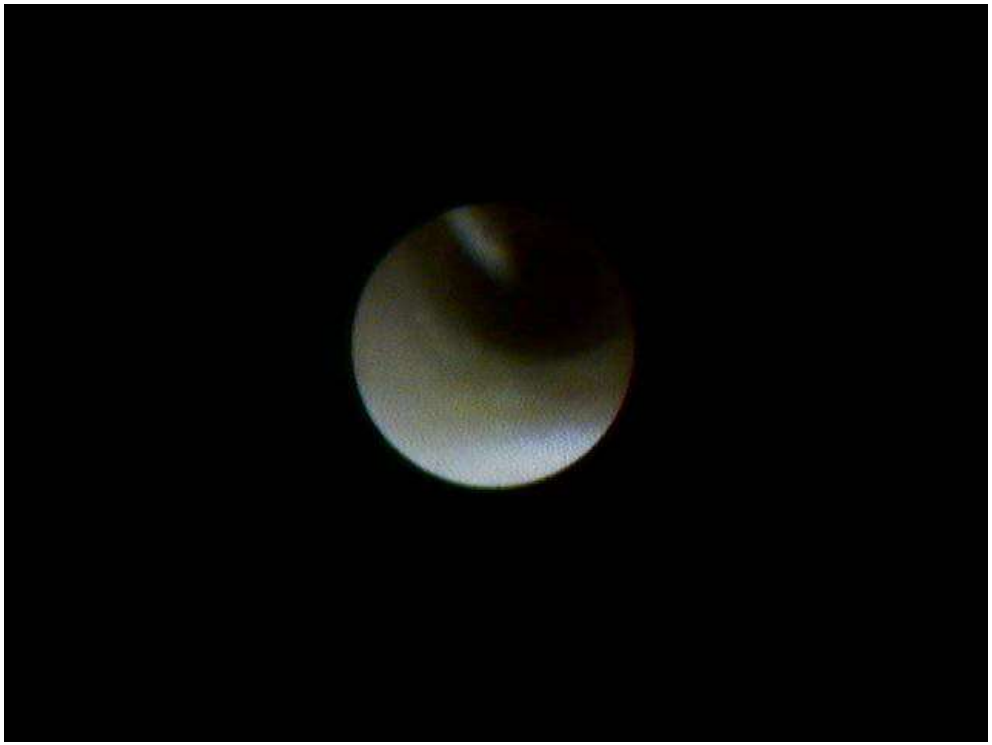

Fig. 3. Angioscopy of coronary in-stent restenosis with a paclitaxel-coated balloon.(A) Invisible stent struts with full neointimal coverage with white plaque.(B) Appearance of hemorrhage in neointimal plaque after plain old balloon angioplasty (POBA).(C) Conf...

Kihei Yoneyama, Kohei Koyama, Yasuhiro Tanabe, Takanobu Mitarai, Ryo Kamijima, Shingo Kuwata, Hiroshi Yamazaki, Emi Nakano, Ken Kongoji, Tomoo Harada, Yoshihiro J. Akashi

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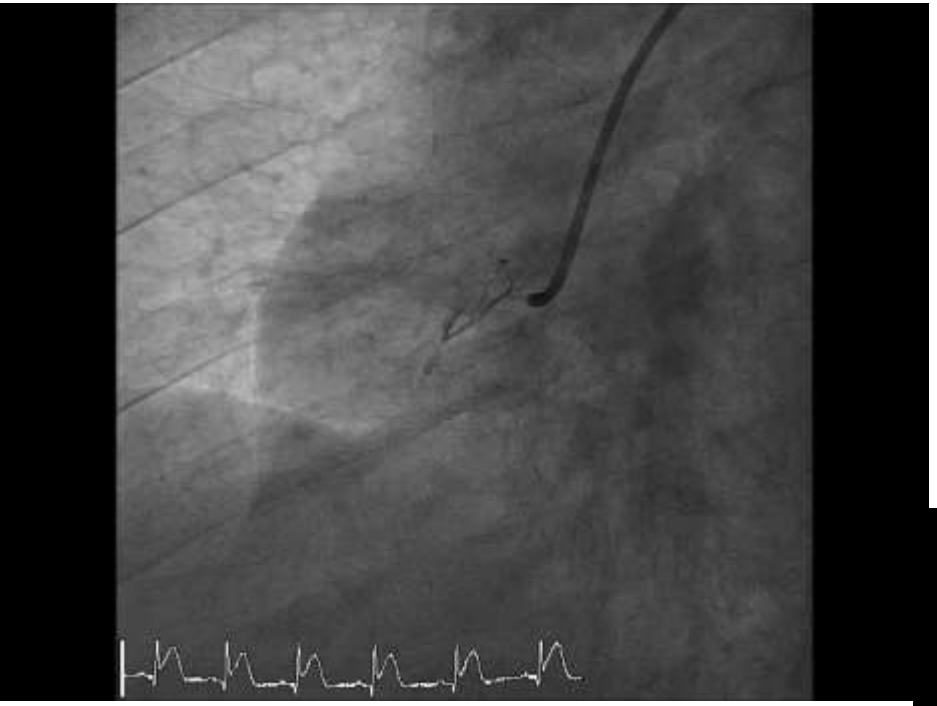
International Journal of Cardiology, Volume 176, Issue 3, 2014, 1207–1209

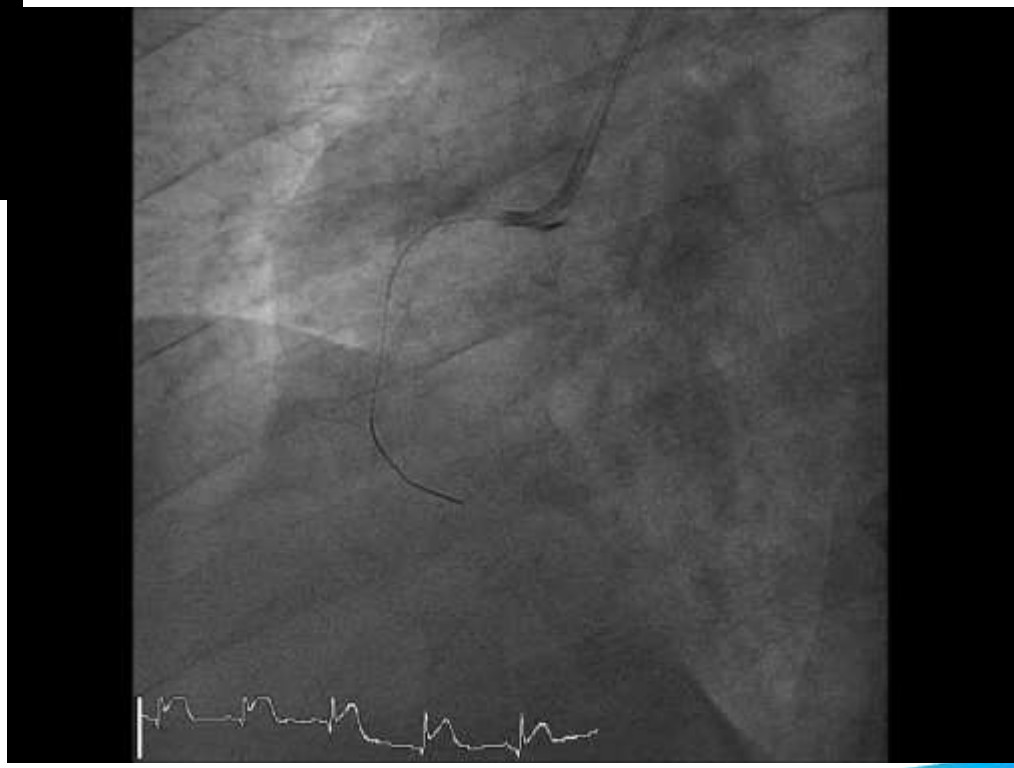
http://dx.doi.org/10.1016/j.ijcard.2014.07.224

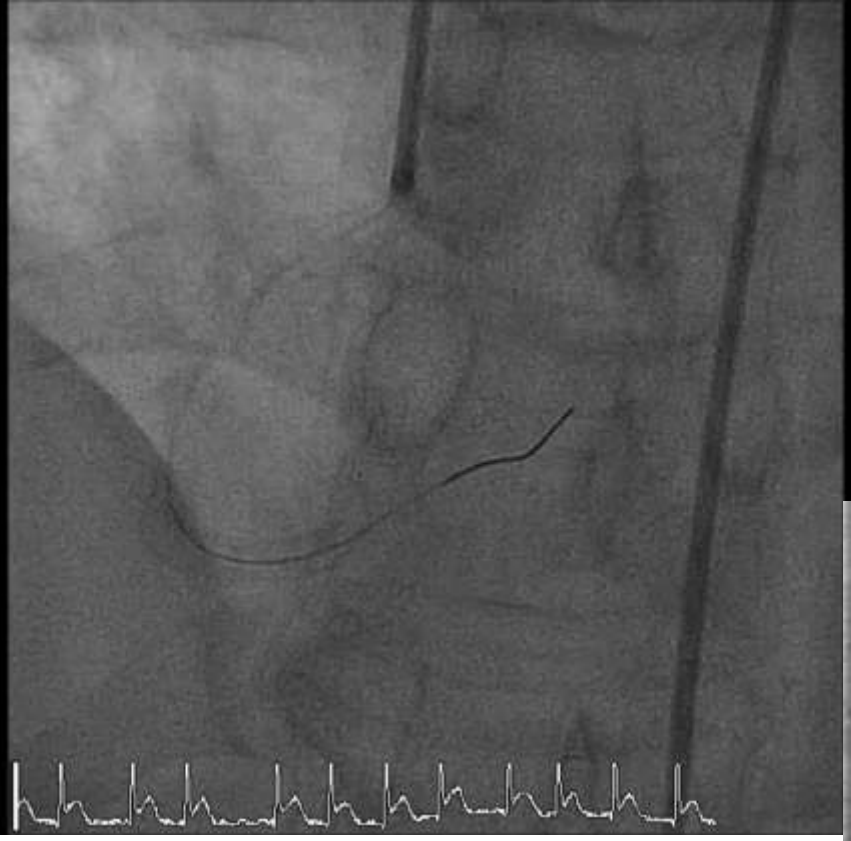
Case illustration

- 51 year-old male
- Hypertension, dyslipidaemia, prior smoker
- 2011: inferior STEMI – treated with 3 bare metal stents to the RCA
- 2015: New onset chest pain, positive inferior ischemia on stress echocardiography

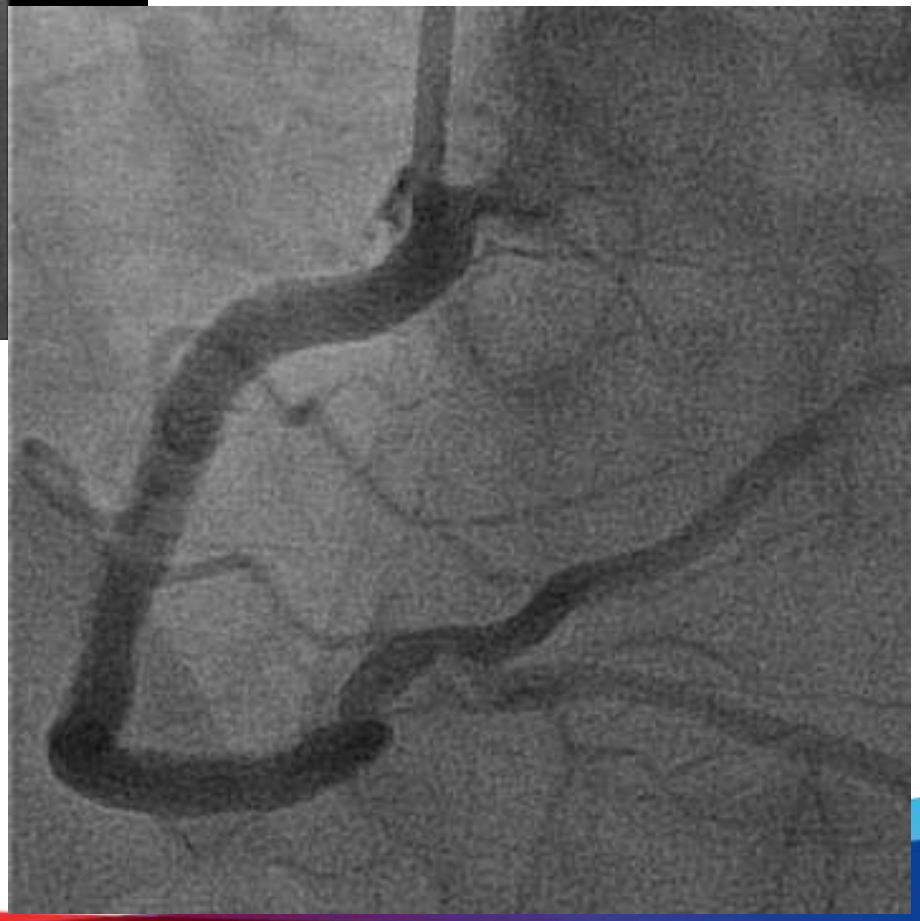
Inferior STEMI 2011



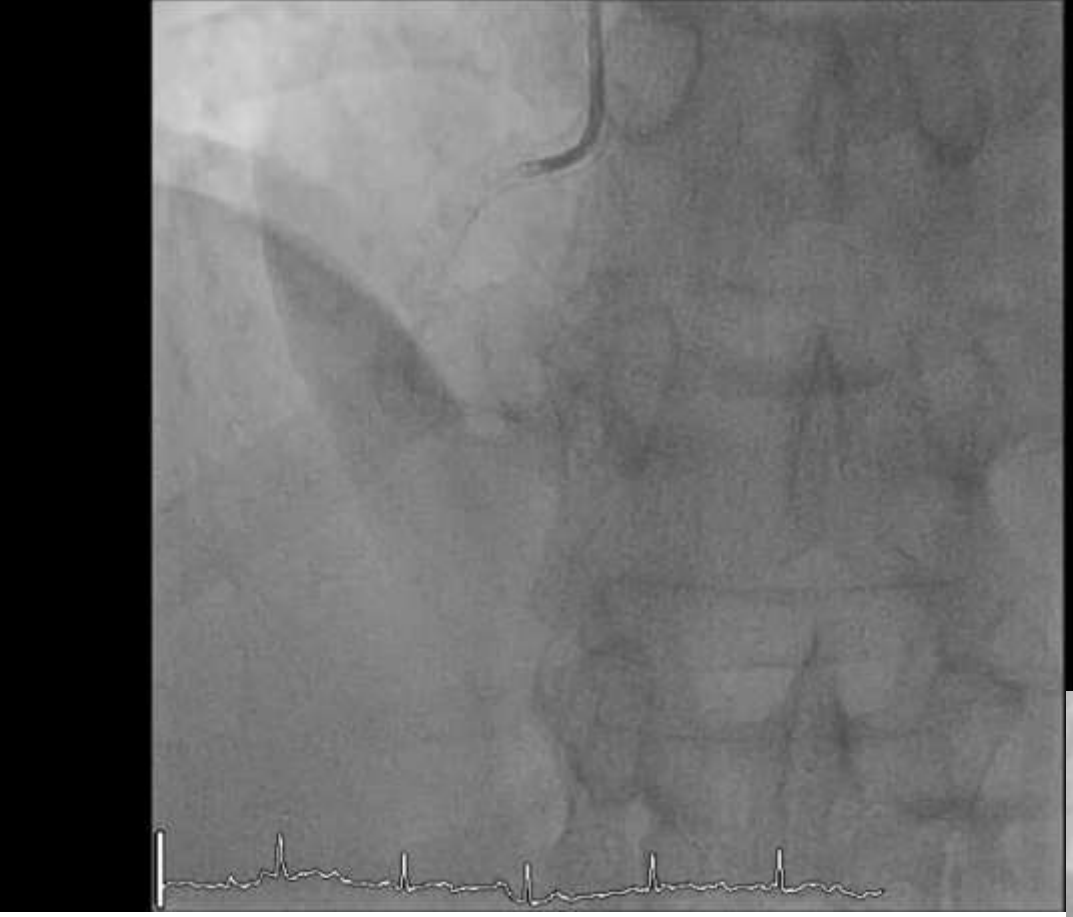


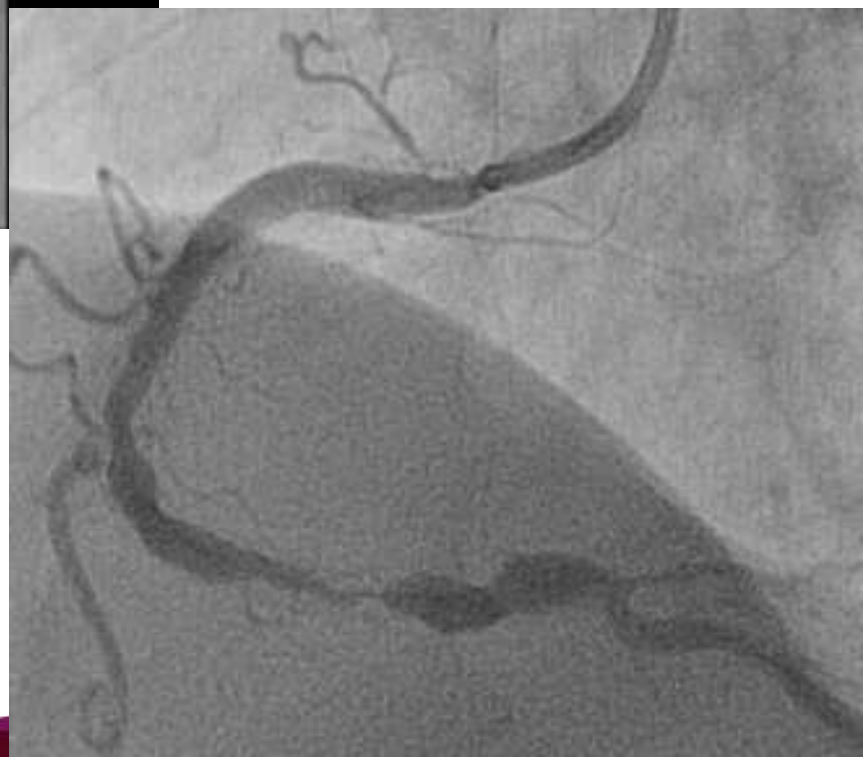


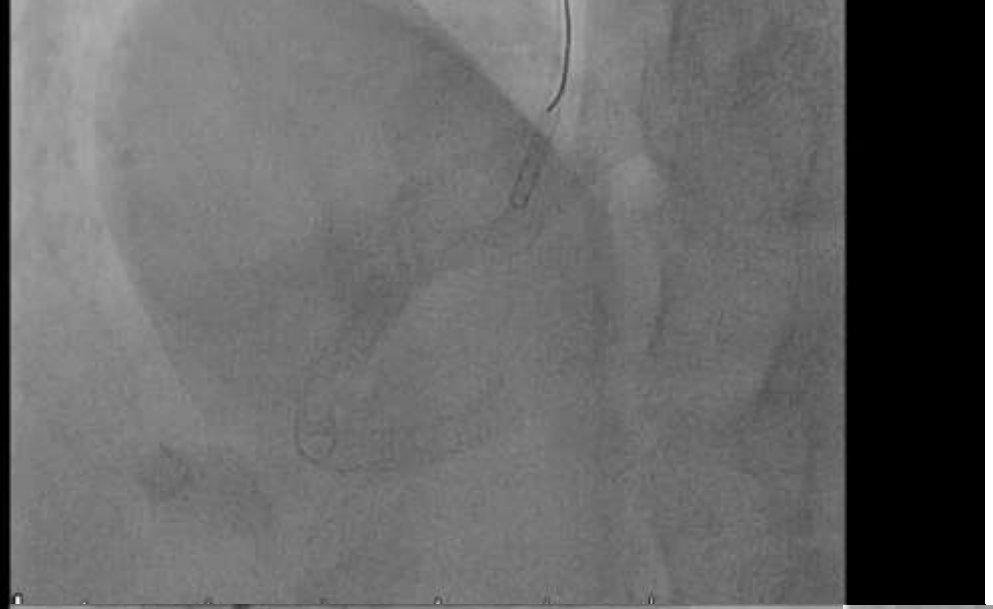
Post 3 bare metal stents
4.0x35mm
4.0x22mm
4.0x30mm



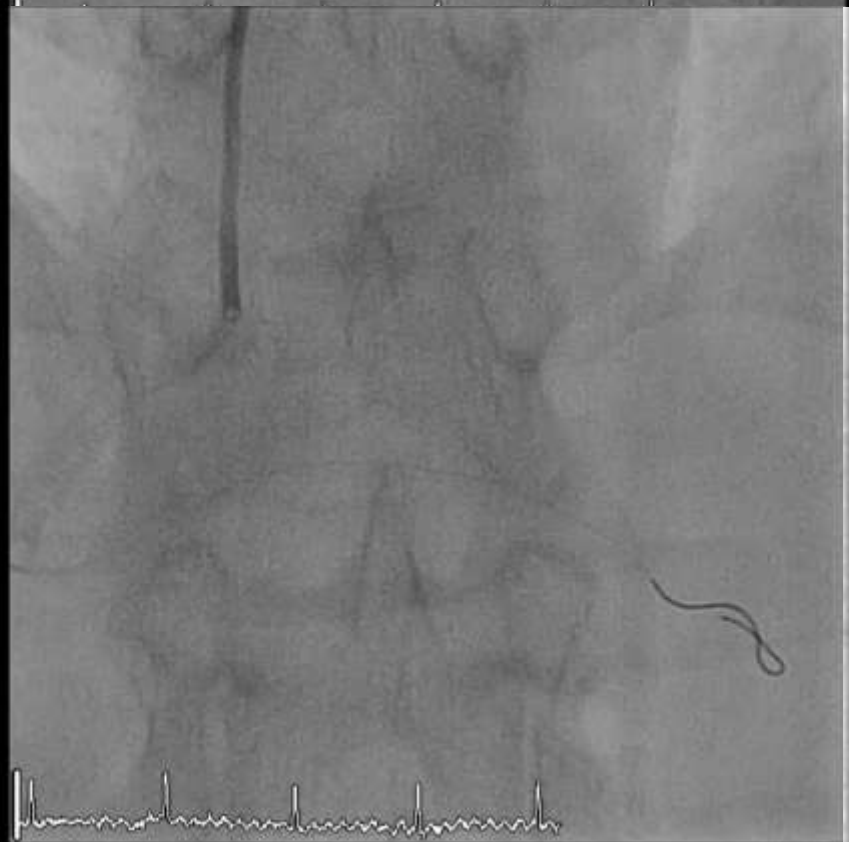
2015: recurrent angina

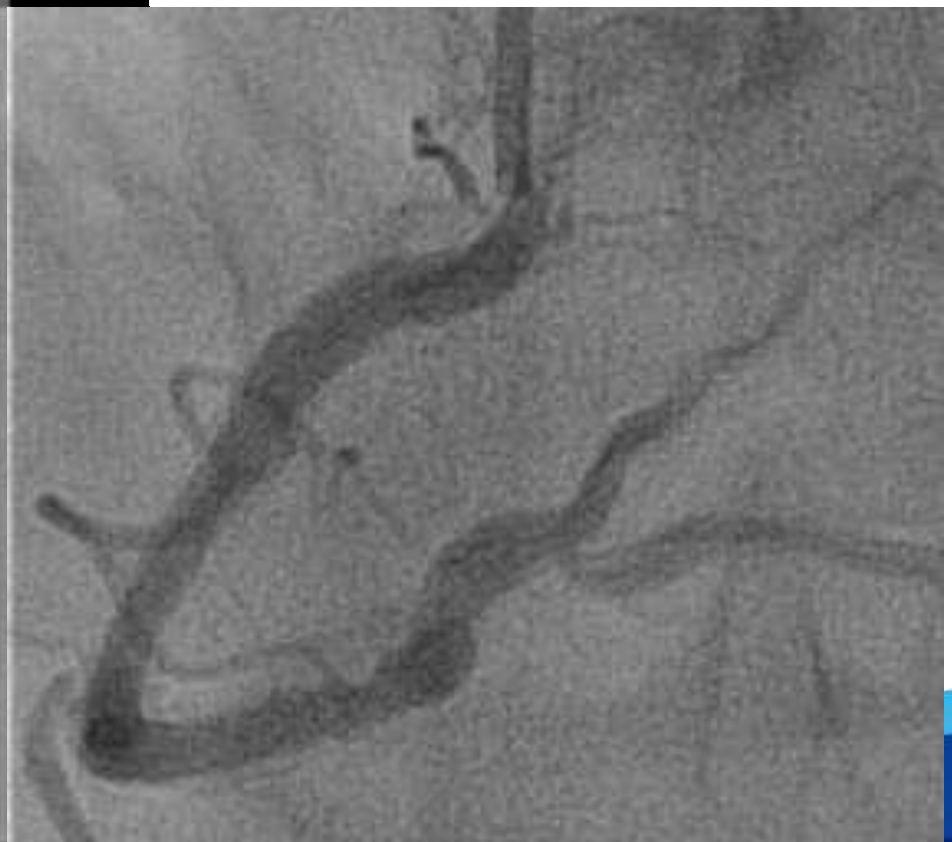






Procedure:
3.5mm NC balloon
BIOTRONIK Pantera Lux
DEBs
3.5x15mm
4.0x25mm
4.0x20mm

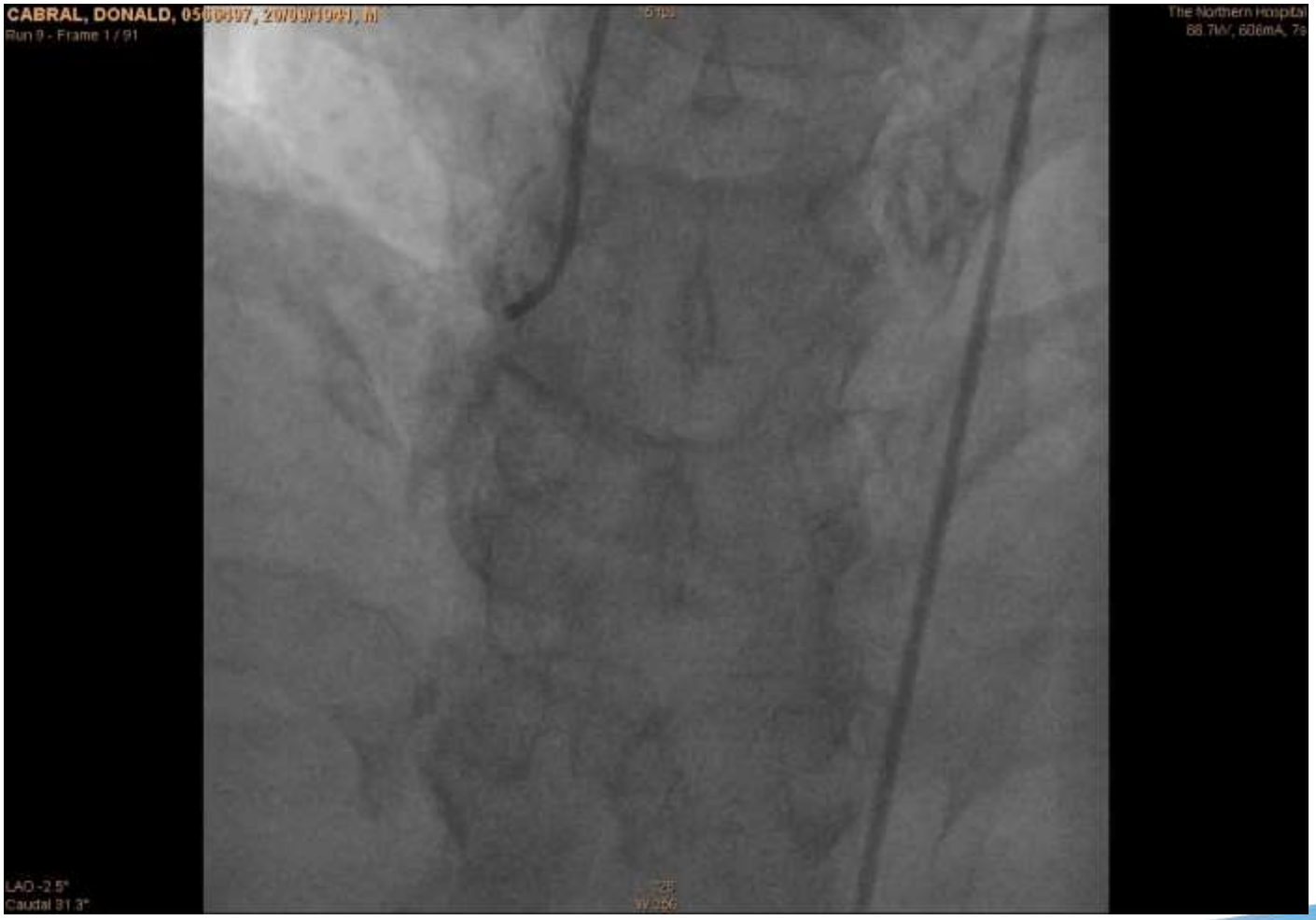




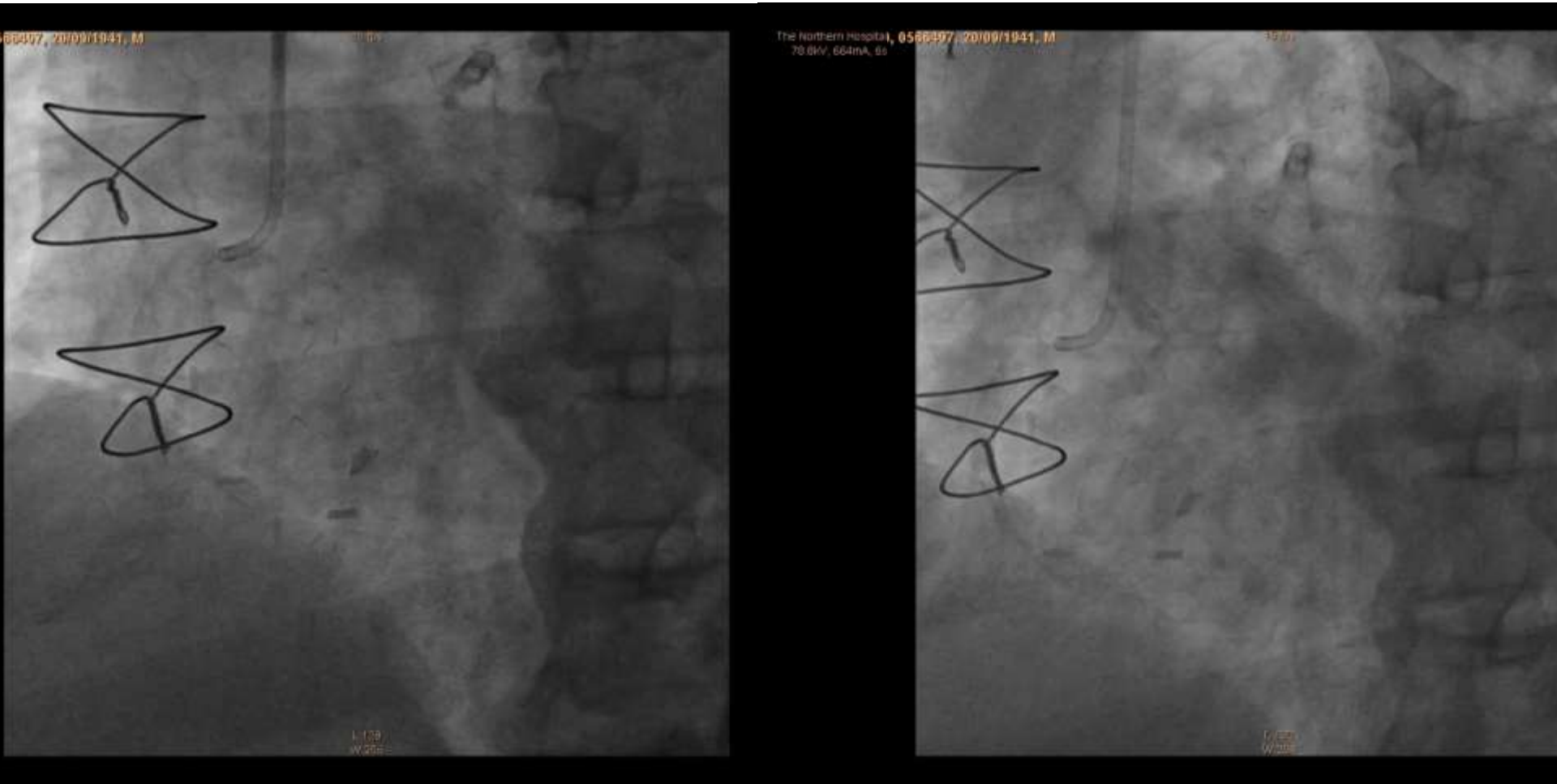
Case illustration 2

- 73-year-old male
- Hypertension, dyslipidemia, type 2 diabetes, obstructive sleep apnoea, chronic obstructive airways disease
- NSTEMI 2009 – triple vessel heavily calcified coronary disease
- CABG 2009 – LIMA to LAD, radial to OM, SVG-PDA

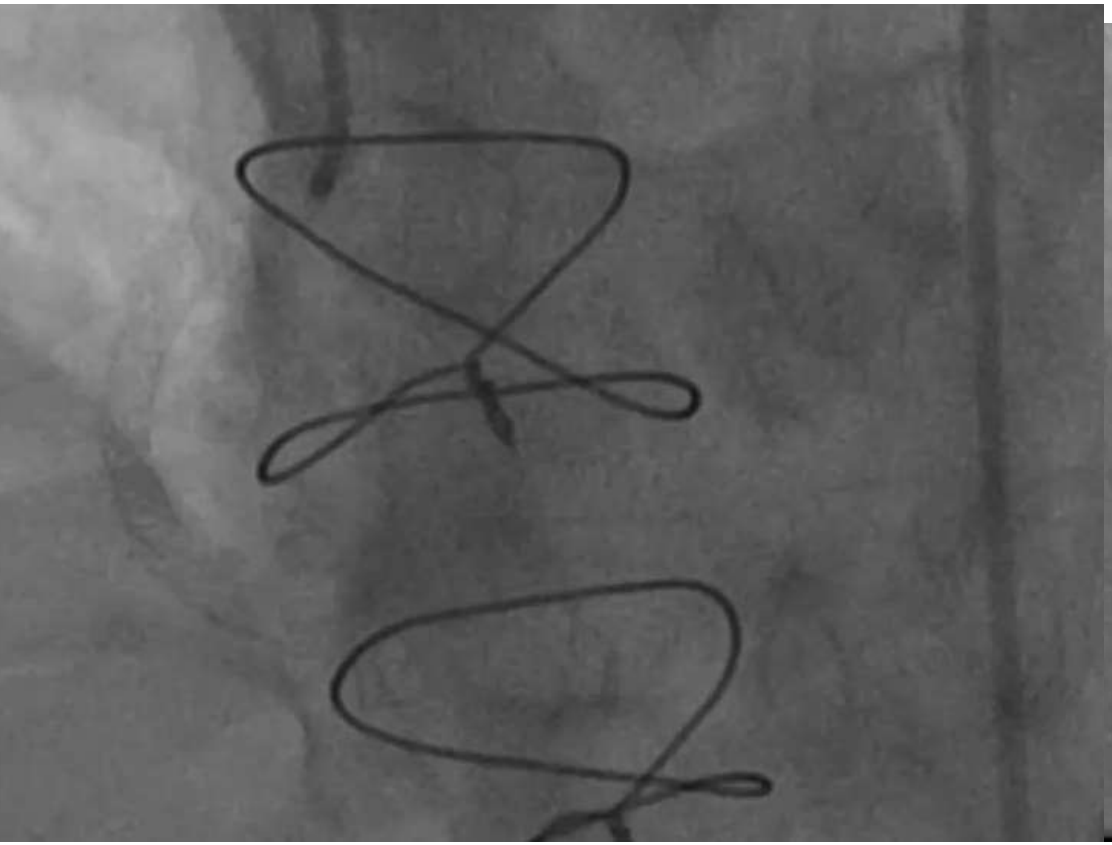
2009: NSTEMI, underwent CABGx3 (LIMA to LAD, RA-OM, SVG-PDA)

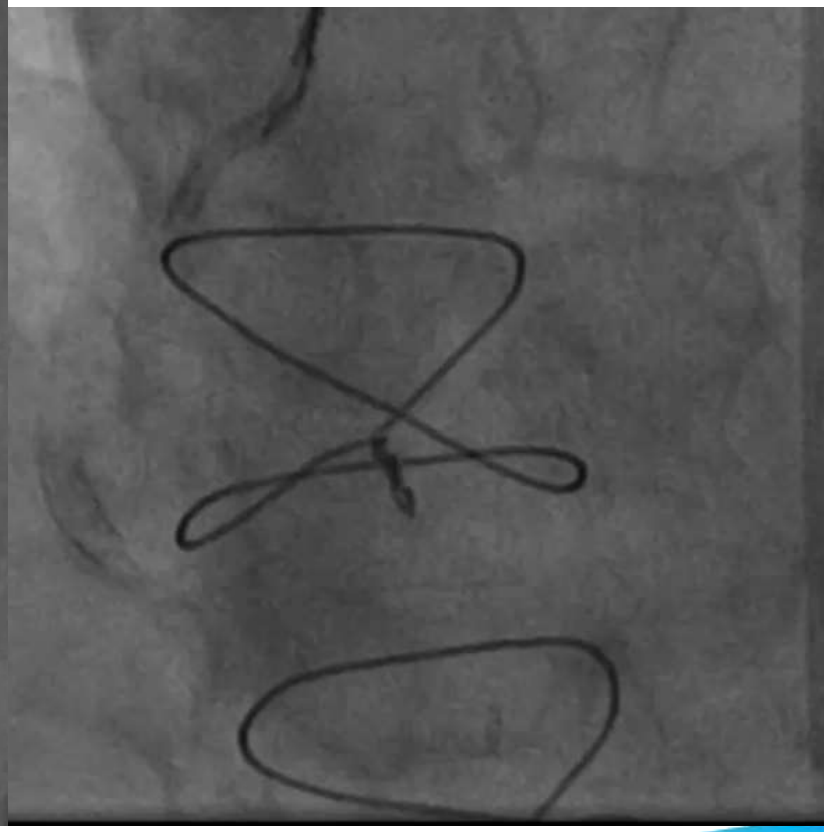


2011: Recurrent angina, NSTEMI
SVG graft occluded
PCI – RCA complex procedure, eventually two stents implanted
3.0x12, 3.5x24 Resolute stents

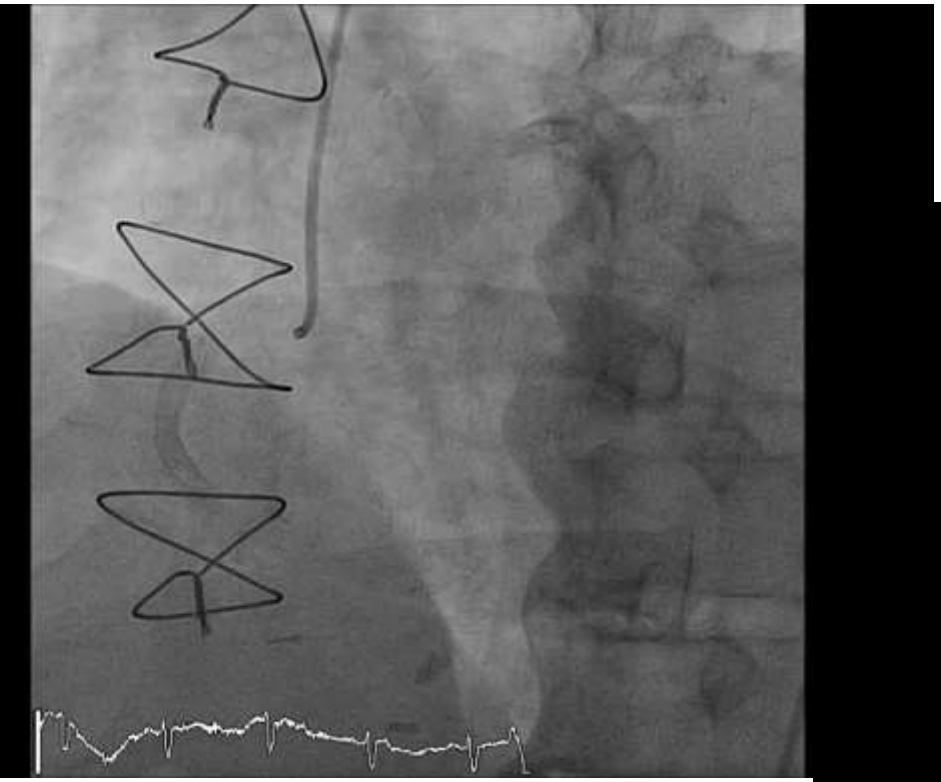


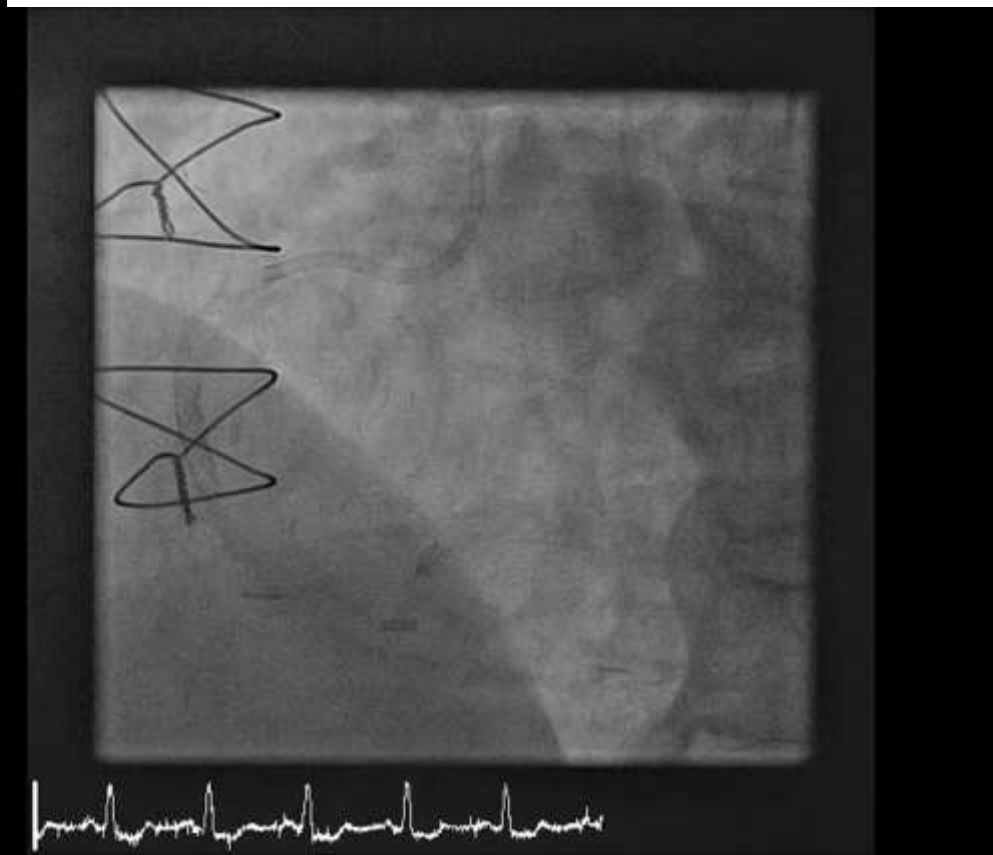
2012: 6 months post PCI, develops recurrent chest pain. Severe ISR – Xience 3.0x16mm stent deployed to ISR



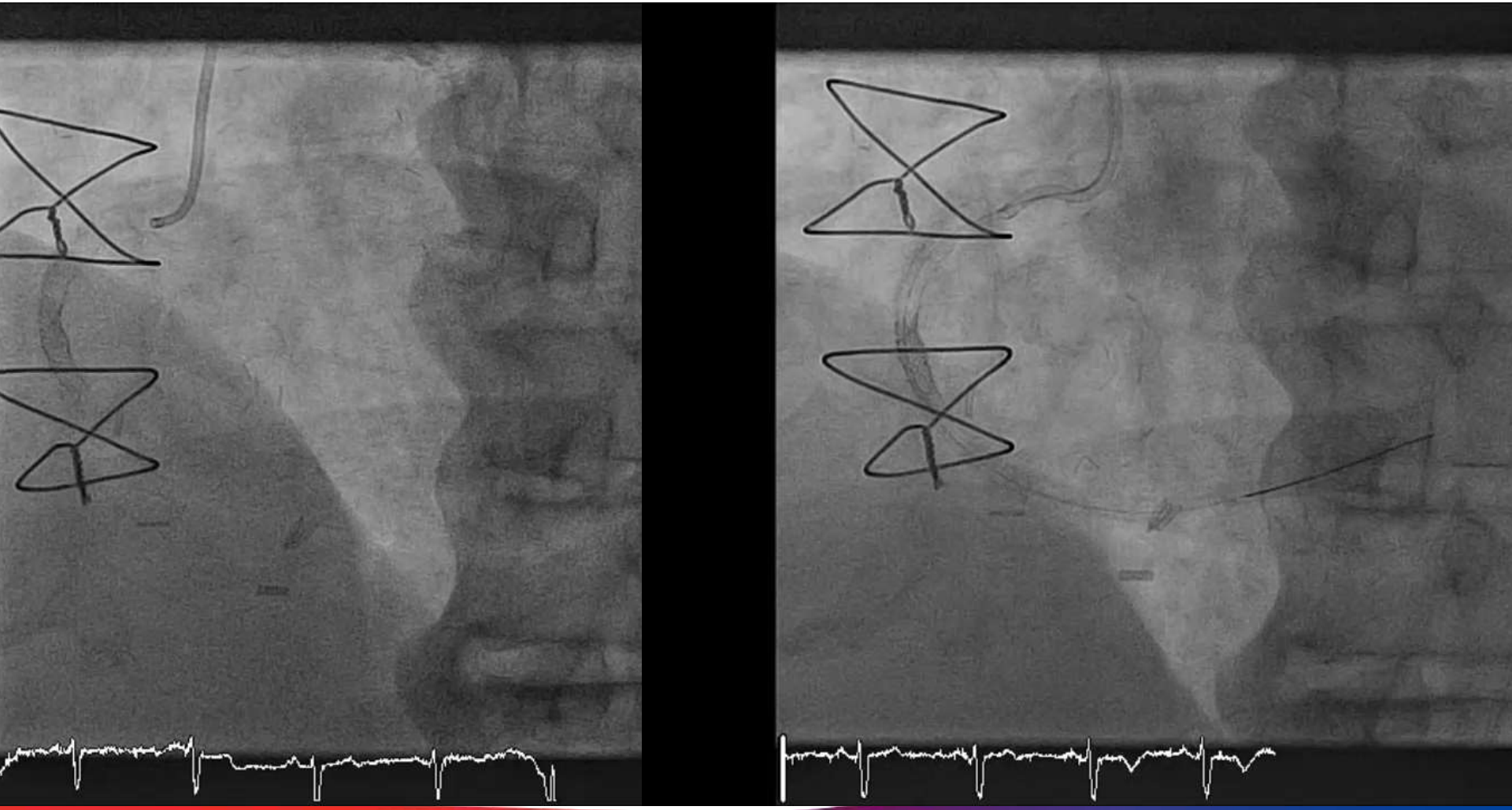


2013: 14 month later, develops recurrent chest pain, objective inferior ischemia on thallium
Further 3.5x12mm Xience Prime stent deployed



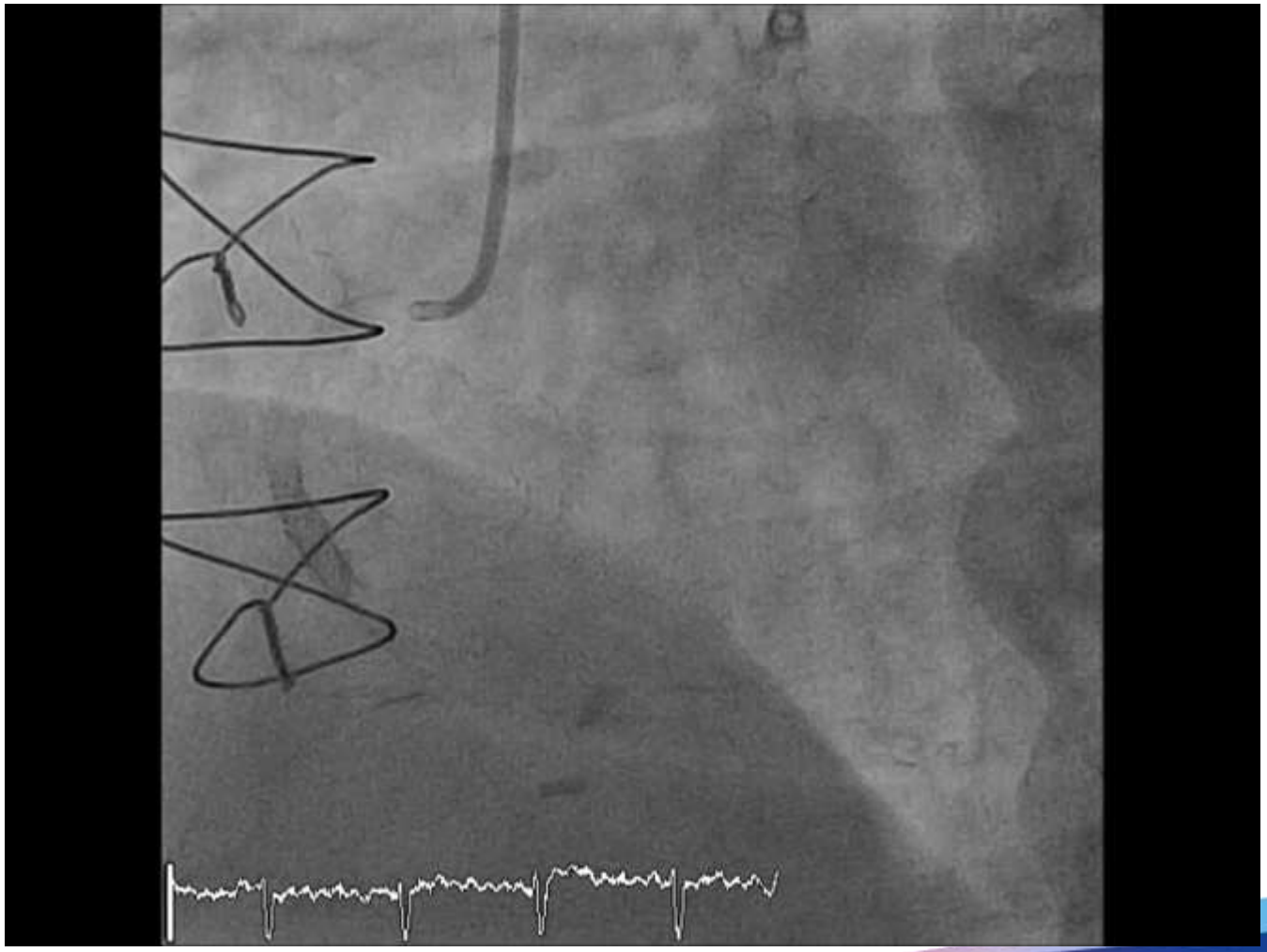


Sep 2014: Angina, 90% RCA restenosis
Promus Element deployed 3.5x12mm

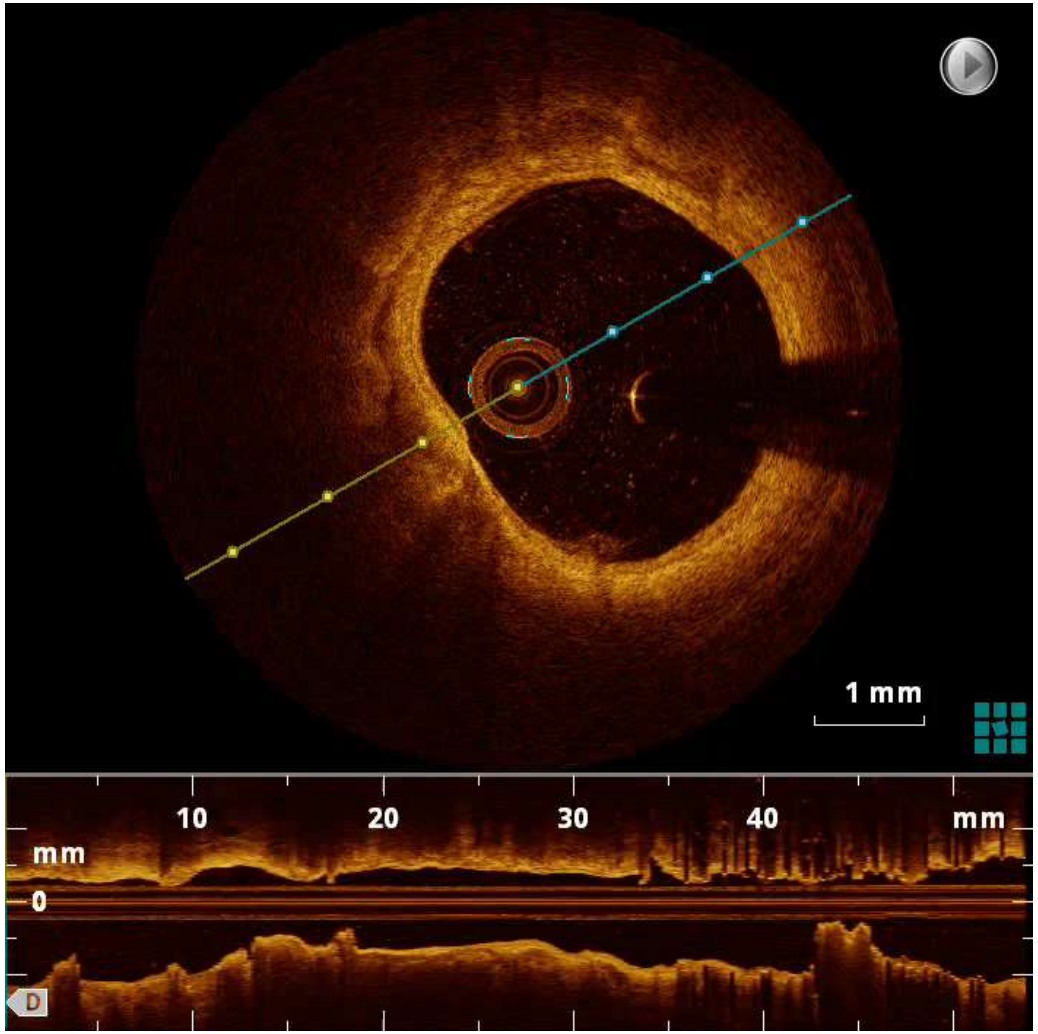


2015

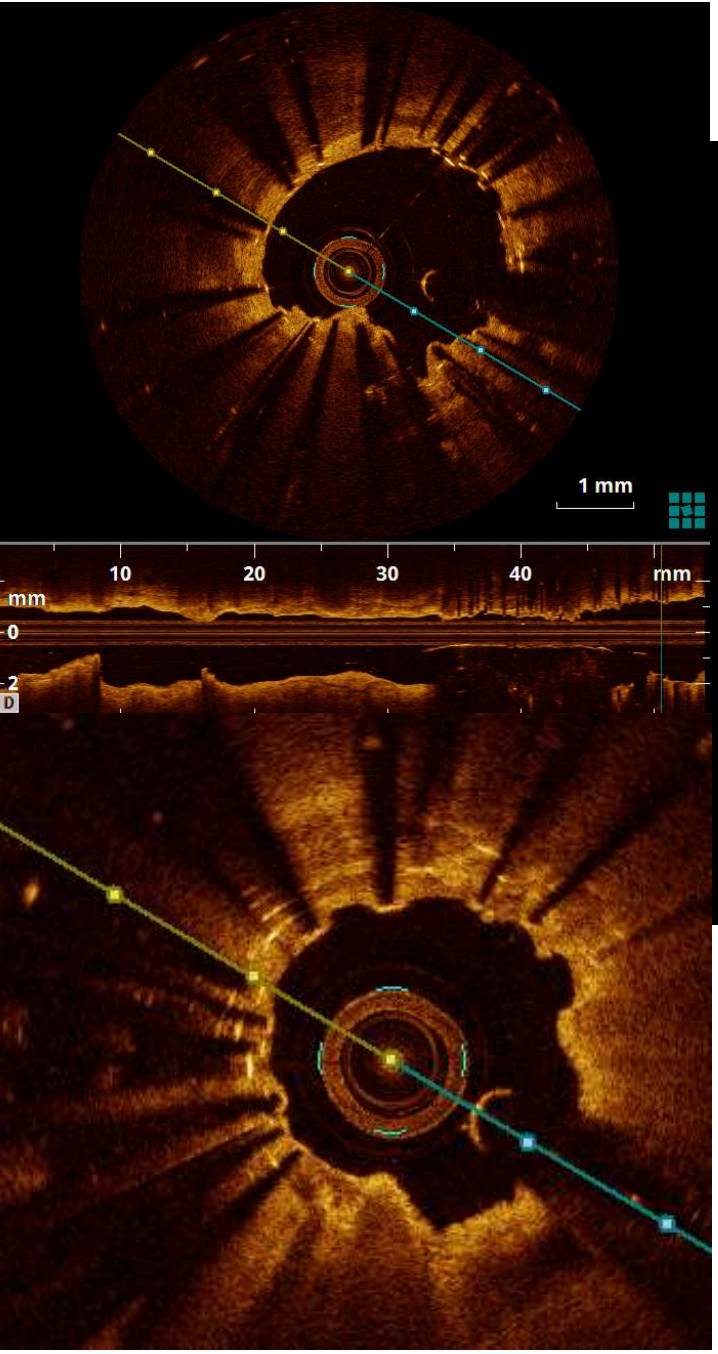
Having angiography to evaluate recurrent angina and positive stress echo

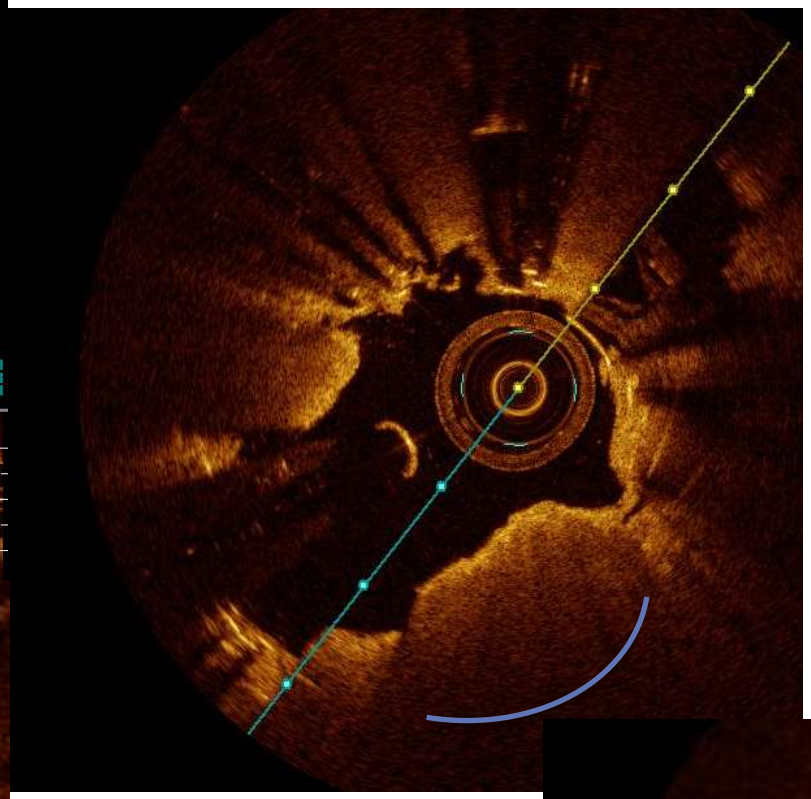


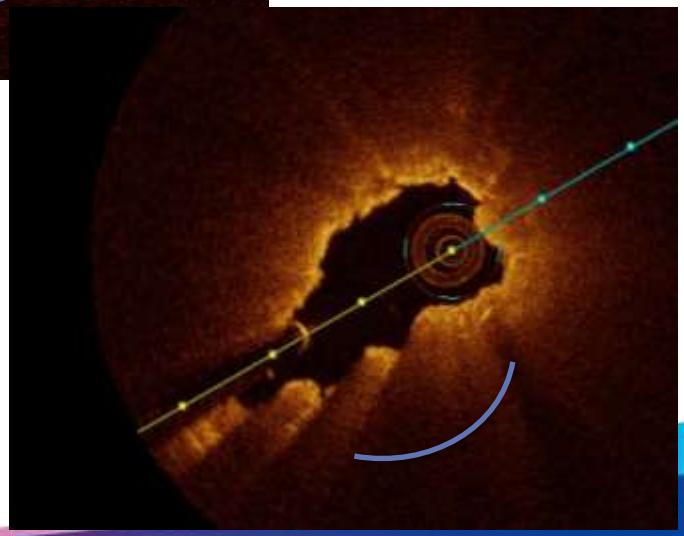
OCT Imaging - baseline



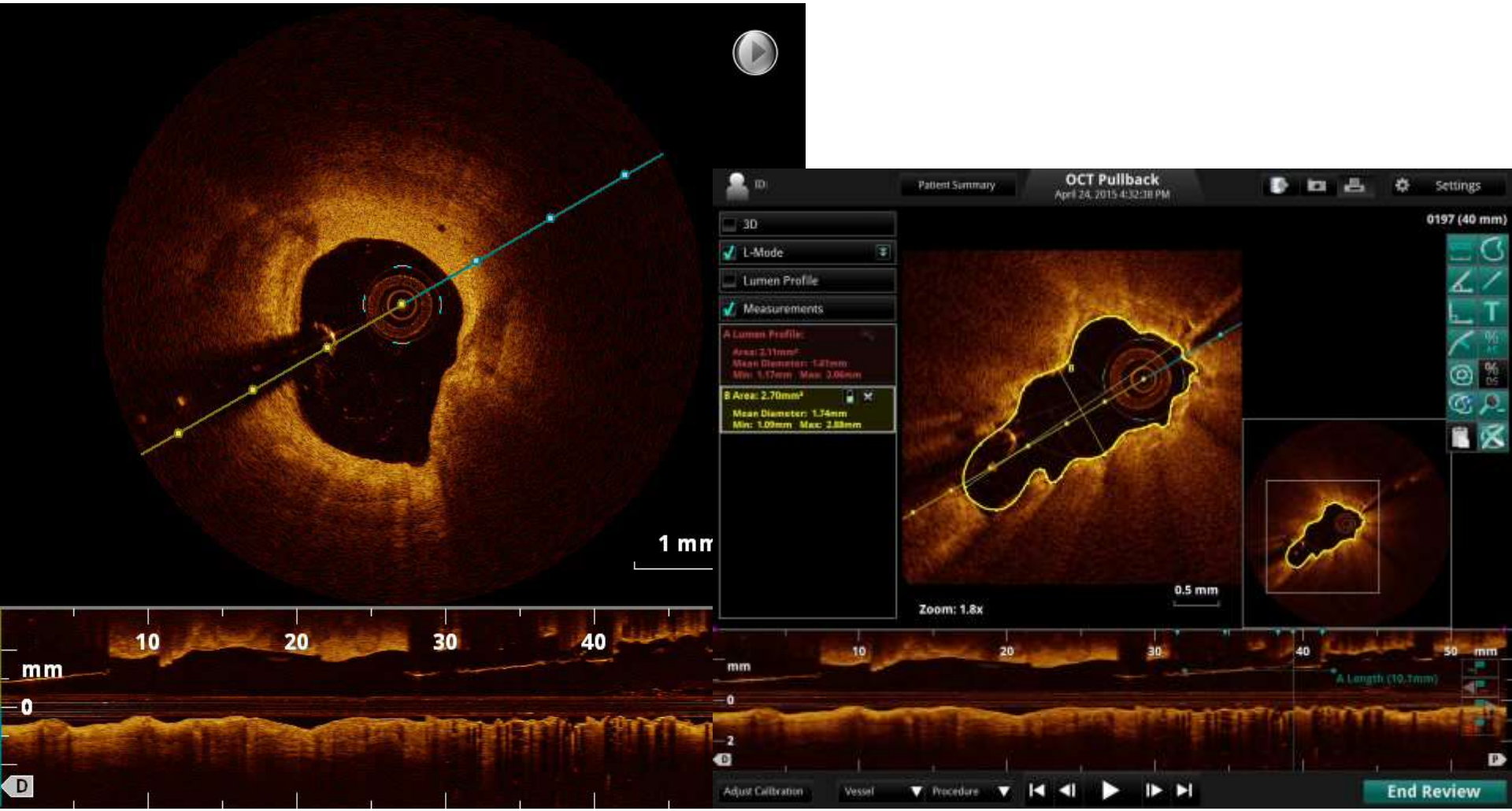
OCT – baseline – stent fracture



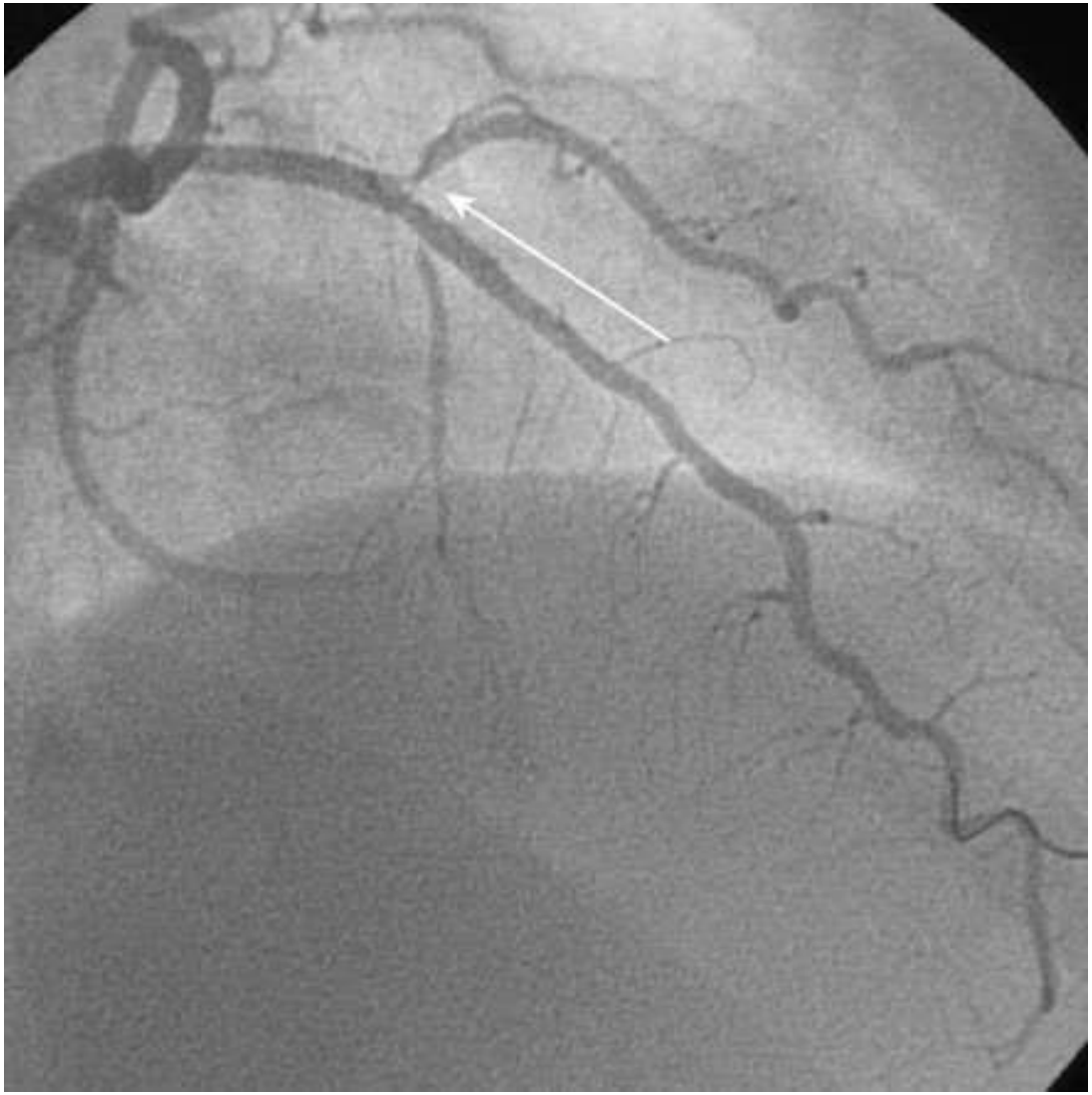




Post DCB


1 mm
10
20
30
40
mm
0
D
ID
Patient Summary
OCT Pullback
April 24, 2015 4:32:38 PM
Settings
0197 (40 mm)
3D
L-Mode
Lumen Profile
Measurements
A Lumen Profile:
B Area: 2.70mm²
Mean Diameter: 1.74mm
Min: 1.09mm Max: 2.88mm
0.5 mm
Zoom: 1.8x
10
20
30
40
50
mm
0
2
A Length (10.1mm)
Adjust Calibration
Vessel
Procedure
End Review

67year old, STEMI 12 months prior, LAD occlusion stented with DES, with recurrent angina



What about DCB for Acute STEMI

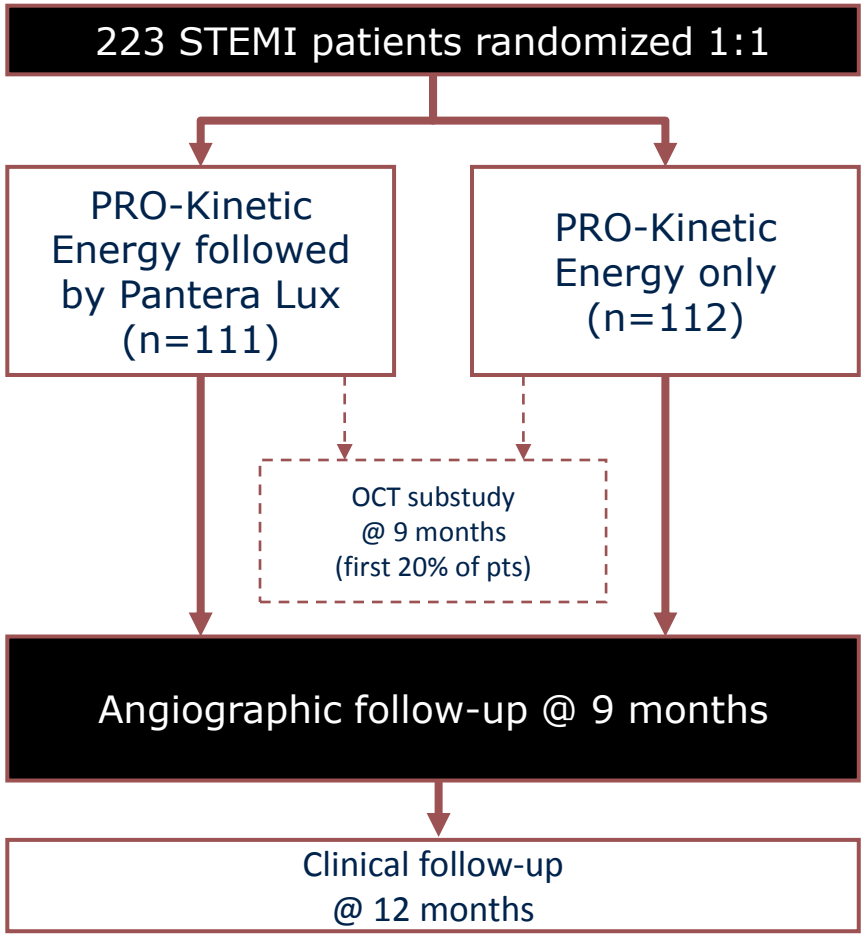
PEBSI: A Randomized Trial of Paclitaxel-Eluting Balloon After Bare Metal Stent Implantation vs Bare Metal Stent in ST Elevation Myocardial Infarction

PEBSI

DESIGN
Prospective, multi-center, randomized, clinical trial

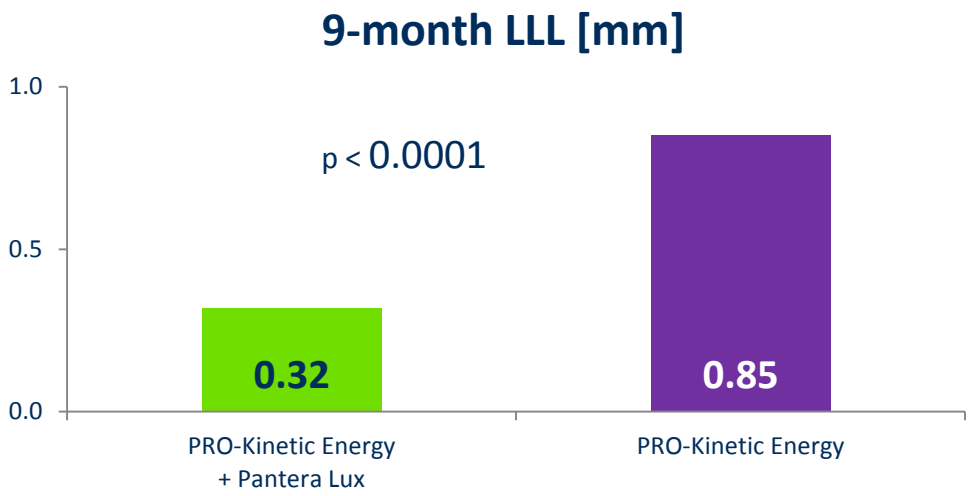
OBJECTIVE
To compare the efficacy and safety of the combined treatment of BMS plus DCB vs the conventional treatment (BMS only) in patients with STEMI within 12 hours of symptoms onset

PRINCIPAL INVESTIGATORS
Arturo Garcia-Touchard
Javier Goicolea
Hospital Universitario Puerta de Hierro
Madrid, Spain



Sources: Garcia-Touchard, oral presentation, ACC 2015
Clinicaltrials.gov, NCT01839890

Primary endpoint result



	BMS + DCB N = 111	BMS N = 112	p
9-month angiographic follow-up	N = 88	N = 83	
Primary endpoint: Late Lumen Loss (LLL)	0.32 ± 0.49 mm	0.85 ± 0.67 mm	<0.0001
Minimal lumen diameter	2.48 ± 0.57 mm	1.79 ± 0.71 mm	<0.0001
Binary restenosis	2.2 %	29.8 %	<0.0001

Source: Garcia-Touchard, oral presentation ACC 2015

Secondary clinical endpoint results

	BMS + DCB N = 111	BMS N = 112	p
12-month clinical follow-up	N = 105	N = 107	
TLR	1.8 %	7.1 %	0.0558
TVR	1.8 %	8.9 %	0.0192
Reinfarction	1.8 %	1.8 %	1.0000
Cardiac death	0.9 %	1.8 %	1.0000
Stent thrombosis	0.9 %	0.0 %	0.4955
Target Vessel Failure	3.6 %	11.6 %	0.0256

- Cardiac death and reinfarction at the end of 1 year were low, and similar in both groups
- MACE, TVF, and TVR were significantly lower in the BMS + DCB group
- There was a trend to a lower TLR in the BMS + DCB group
- ST, stroke, major bleeding requiring transfusion were also low, and similar in both groups

Source: Garcia-Touchard, oral presentation ACC 2015

Secondary OCT endpoint results

	BMS + DCB N = 111	BMS N = 112	p
9-month OCT follow-up	N = 25	N = 19	
Mean lumen area (mm^2)	7.43 ± 2.36	5.33 ± 1.93	0.0031
Neointimal thickness (mm)	0.14 ± 0.12	0.30 ± 0.16	0.0004
Strut coverage (%)	99.52±1.11	100 ± 0.0%	0.03

BMS + DCB showed better efficacy by OCT with:

- Greater lumen area
- Less neointimal thickness

Strut coverage excellent in both groups but greater in the BMS group.

Source: Garcia-Touchard, oral presentation EuroPCR 2015

A future of ‘no more metal jackets’?

EuroIntervention

Table 1. Baseline demographic and clinical characteristics.

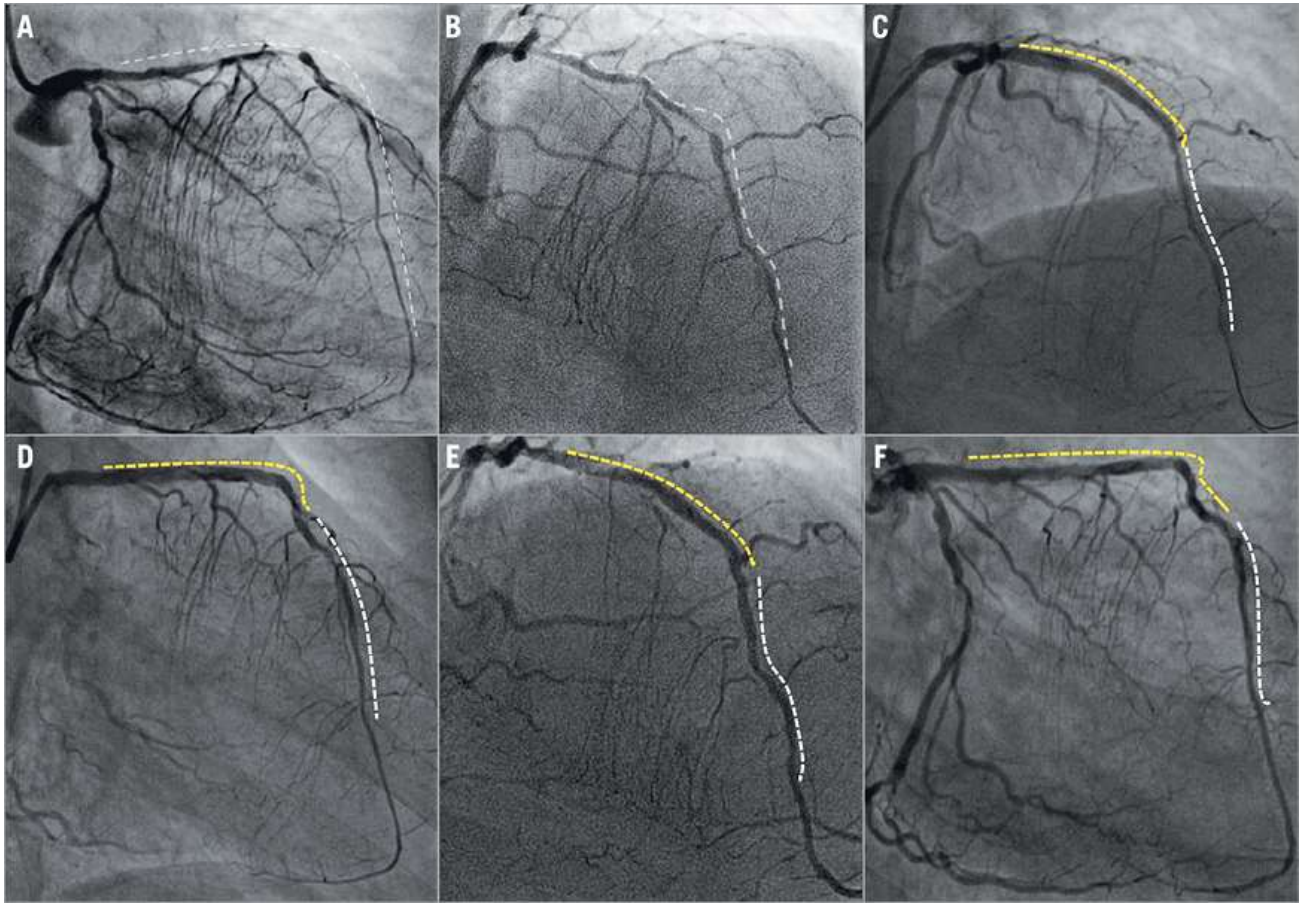
Patients, n (%)	n=42
Age (years), mean±SD	62.0±1.0
LVEF (%), mean±SD	55.0±6.1
Male gender	37 (88.1)
Cardiovascular risk factors	
Family history of CAD	18 (42.9)
Hypertension	29 (69.0)
Hypercholesterolaemia	25 (59.5)
Current smoker	7 (16.7)
Diabetes mellitus	12 (28.6)
Insulin-dependent diabetes	4 (33.3)
Prior MI	10 (23.8)
Prior PCI	17 (40.5)
Prior CABG	2 (4.8)
Stable angina	26 (61.9)
Acute coronary syndrome	16 (38.1)
Multivessel CAD	19 (45.2)

Values are expressed as mean±standard deviation (SD) or number and percentages. CABG: coronary artery bypass graft; CAD: coronary artery disease; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention

EuroIntervention 2016;11:e1589-e1595 published online e-edition April 2016

Hybrid strategy with a bioresorbable scaffold and a drug-coated balloon for diffuse coronary artery disease: the “no more metallic cages” multicentre pilot experience

EuroIntervention



EuroIntervention 2016;11:e1589-e1595 published online e-edition April 2016

Hybrid strategy with a bioresorbable scaffold and a drug-coated balloon for diffuse coronary artery disease: the “no more metallic cages” multicentre pilot experience

EuroIntervention

Table 2. Lesion and procedural characteristics.

	Patients, n=42
Target vessel	
Left anterior descending	29 (69.0)
Left circumflex	8 (19.0)
Right coronary artery	5 (12.0)
Radial approach	17 (40.5)
Hybrid (BRS plus DCB) indication	
De novo diffuse or tandem coronary disease	37 (88.1)
CTO	2 (5.4)
Bifurcation (side branch >2.0 ≤2.75 mm)	9 (24.3)
Diffuse BMS ISR	5 (11.9)
Rotational atherectomy	1 (2.4)
Scoring balloons	5 (11.9)
Intracoronary imaging	
OCT	5 (11.9)
IVUS	18 (42.9)

BMS: bare metal stent; BRS: bioresorbable scaffold; CTO: chronic total occlusion; DCB: drug-coated balloon; ISR: in-stent restenosis; IVUS: intravascular ultrasound; OCT: optical coherence tomography; PCI: percutaneous coronary intervention

EuroIntervention 2016;11:e1589-e1595 published online e-edition April 2016

Hybrid strategy with a bioresorbable scaffold and a drug-coated balloon for diffuse coronary artery disease: the "no more metallic cages" multicentre pilot experience

EuroIntervention

Table 4. Clinical outcomes following BRS plus DCB hybrid strategy.

	Patients, n=42
Procedural success, n (%)	42 (100)
Periprocedural MI (CK MB >5 times the upper limit of normal), n (%)	2 (4.7)
Median follow-up period, months	12 (IQR 6-18)
Angiographic follow-up, n (%)	22 (52.4)
Events from hospital discharge to the longest available follow-up	
All-cause death, n (%)	0
TLR per patient, n (%)	5 (11.9)
ID-TLR per patient, n (%)	2 (4.7)
BRS segment TLR, n (%)	4 (9.5)
BRS segment ID-TLR, n (%)	2 (4.7)
DCB segment TLR, n (%)	1 (2.3)
Definite/probable BRS/DCB segment thrombosis, n (%)	0

BRS: bioresorbable scaffold; CK MB: creatine kinase MB; DCB: drug-coated balloon; ID: ischaemia-driven; MI: myocardial infarction; TLR: target lesion revascularisation

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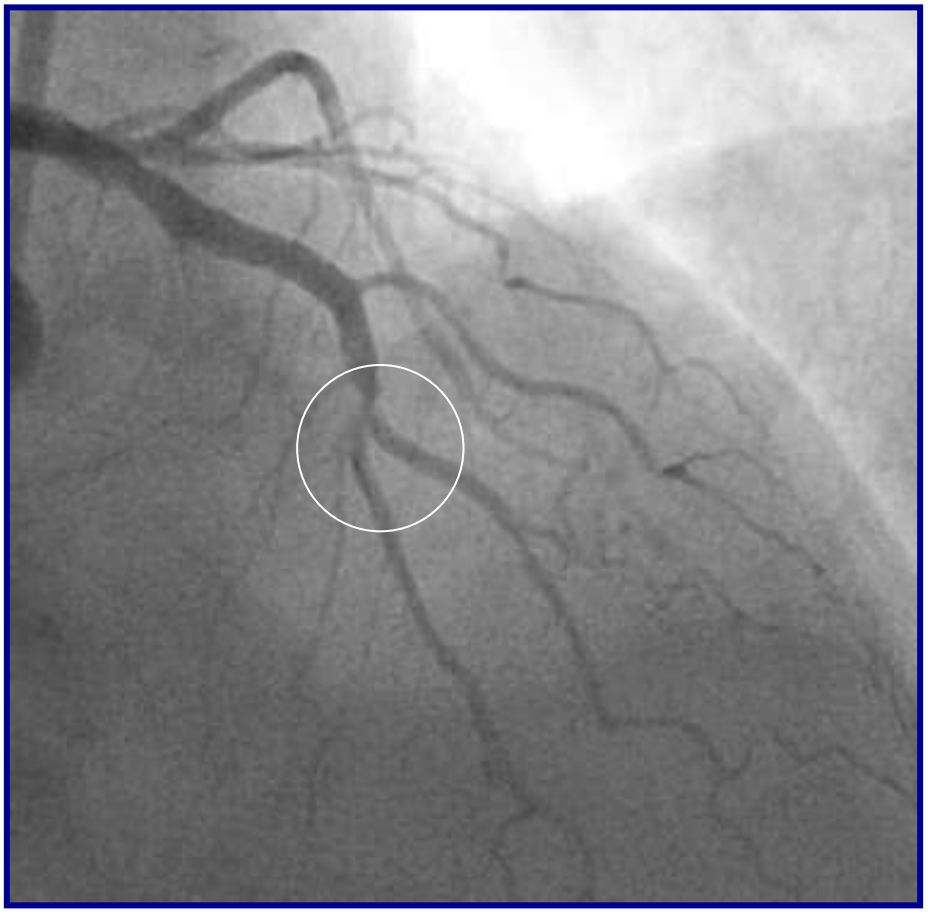
Hybrid strategy with a bioresorbable scaffold and a drug-coated balloon for diffuse coronary artery disease: the "no more metallic cages" multicentre pilot experience

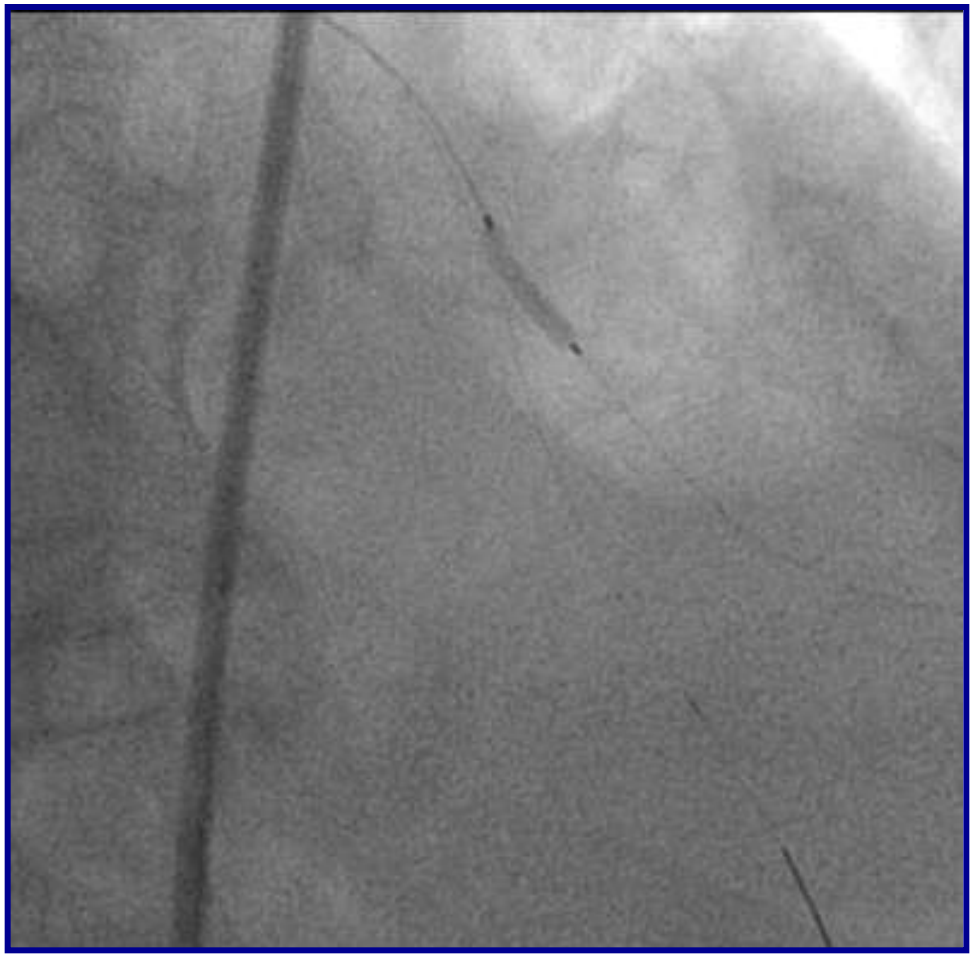
DCB for Bifurcation lesions

Bifurcation stenosis LAD/D2

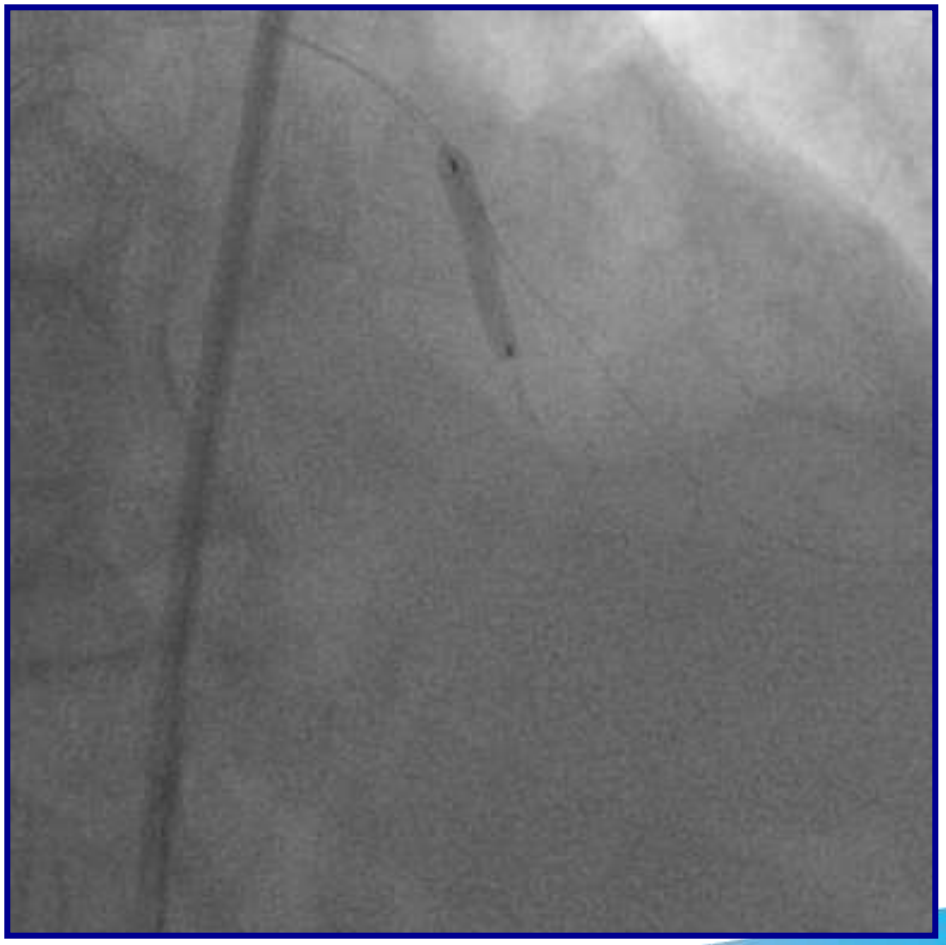


Courtesy Zhaoping Liu, Peking University First Hospital

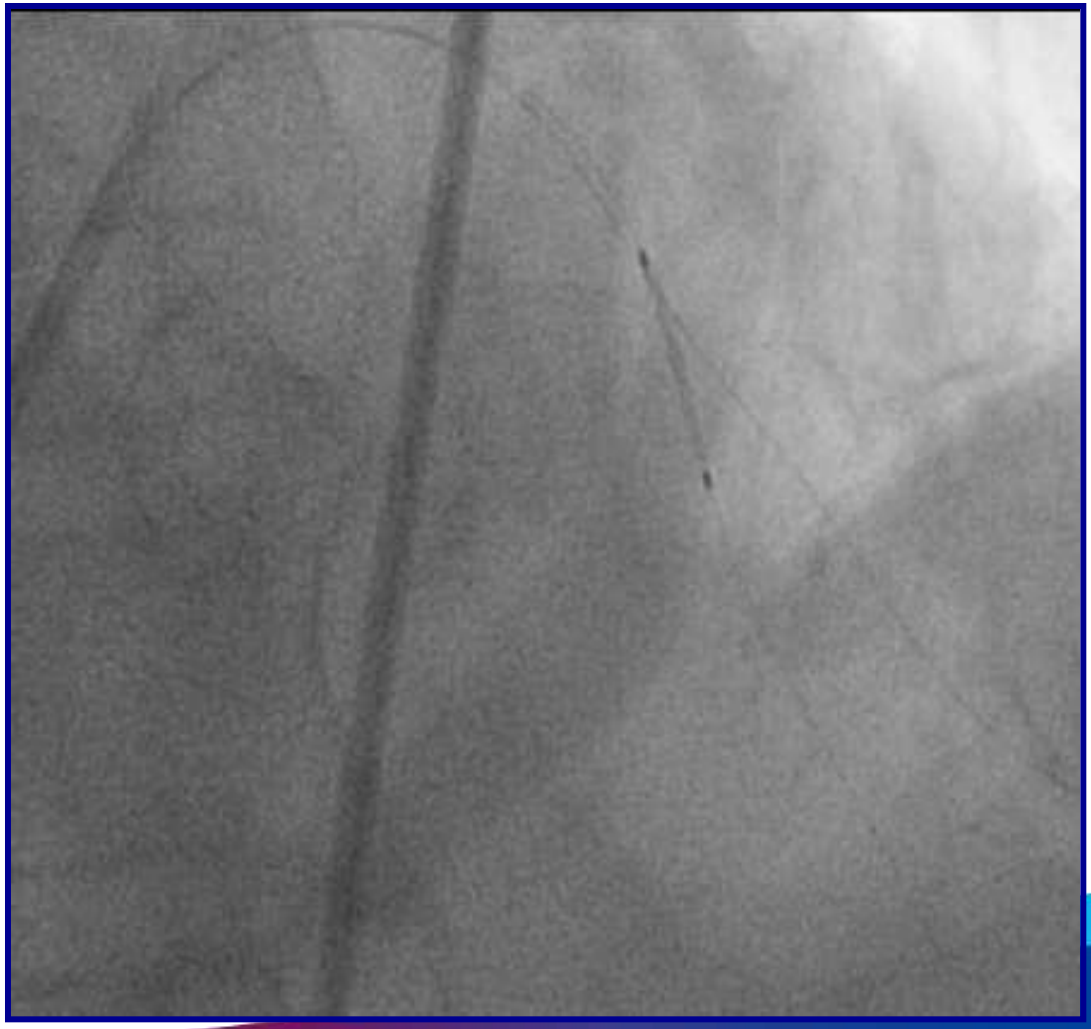
1. DCB Dilation of SB



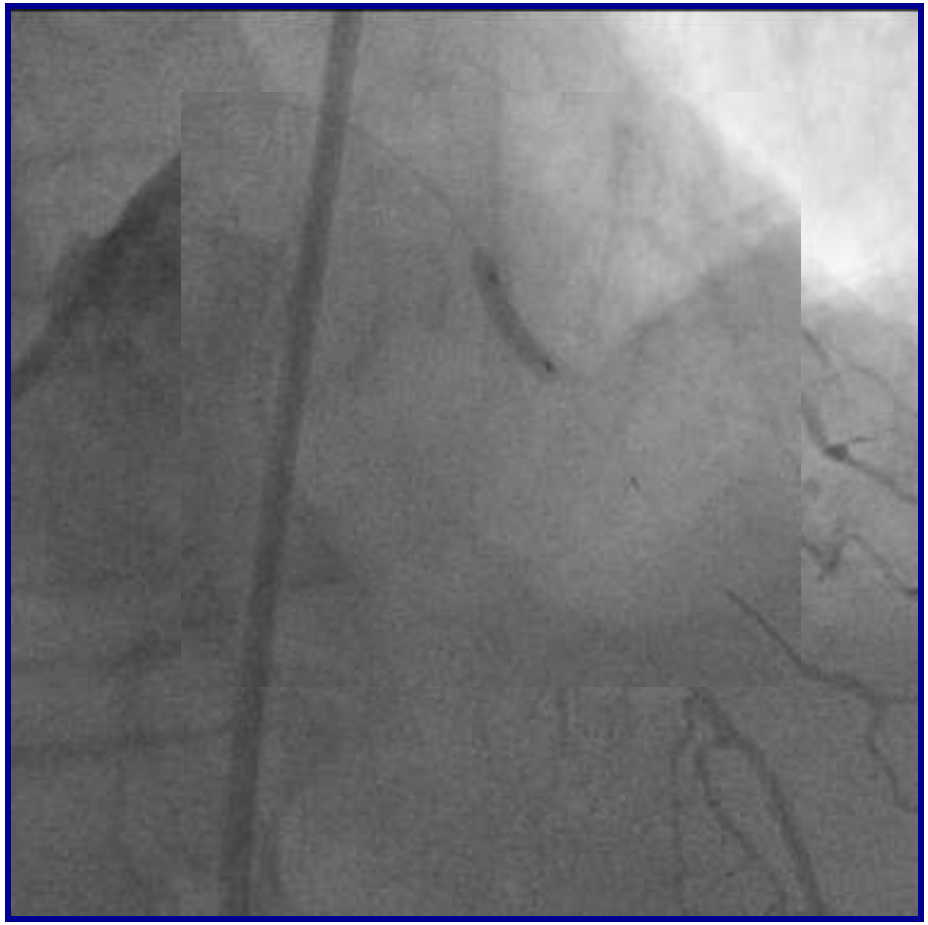
2. Dilatation of **MB** with second, usually larger DEB



3. Implantation of open-cell design **BMS** (Coroflex)



4. Dilatation of SB ostium with an uncoated balloon

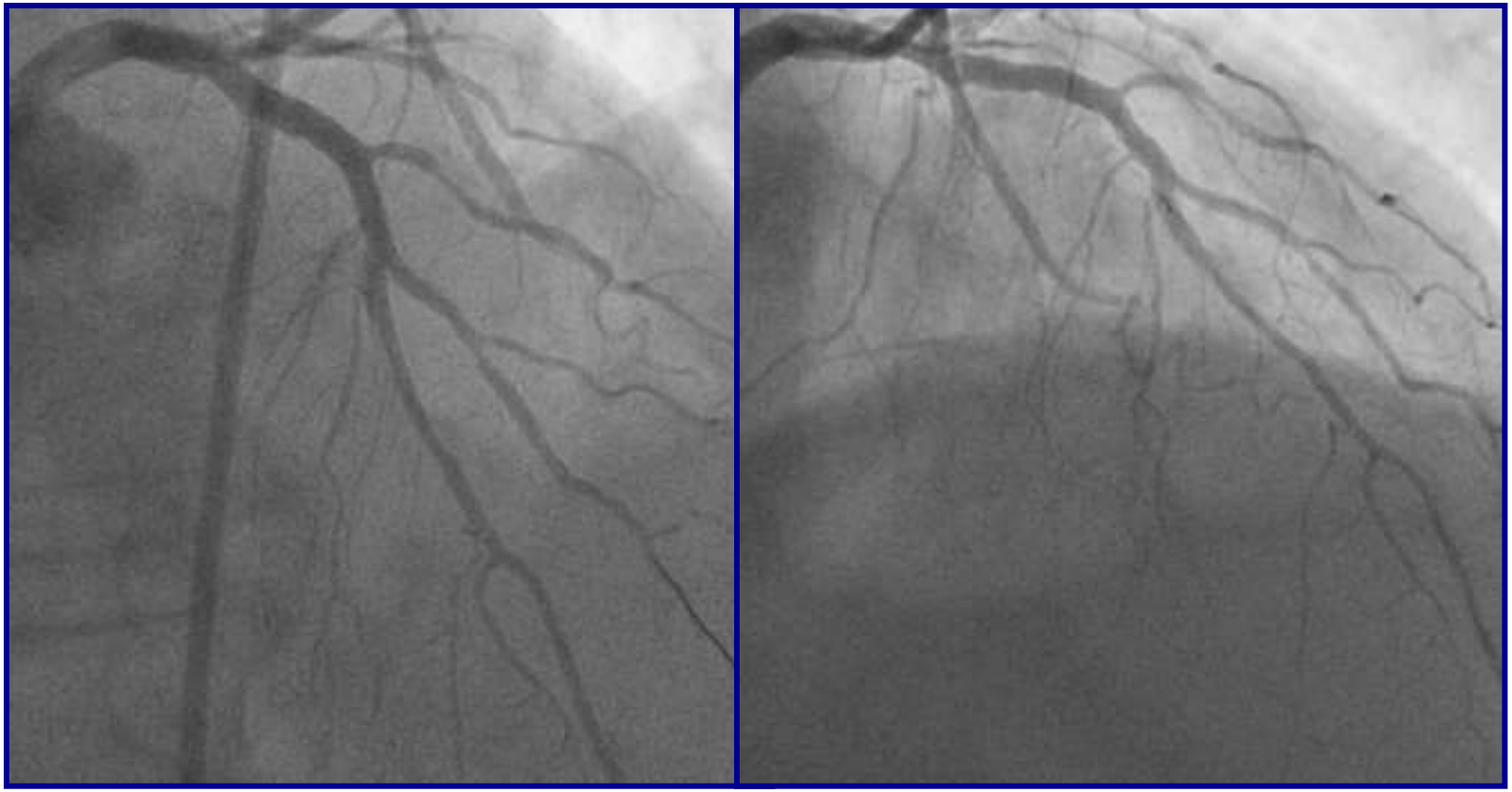


Stenosis at side branch ostium

9 months FU

Acute Result

After 9 month



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Serial Morphological Changes of Side-Branch Ostium after Paclitaxel-Coated Balloon Treatment of *De Novo* Coronary Lesions of Main Vessels

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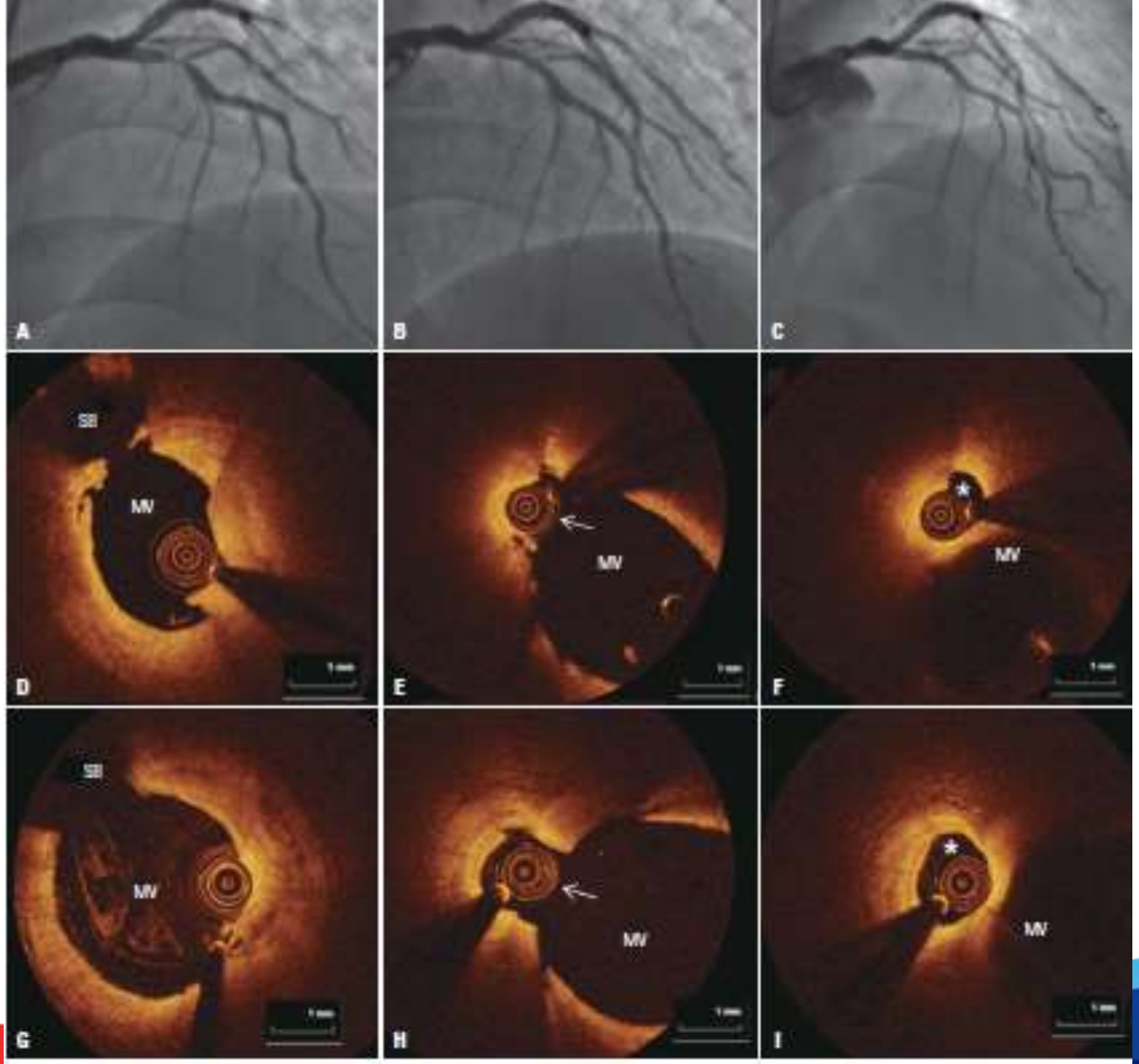
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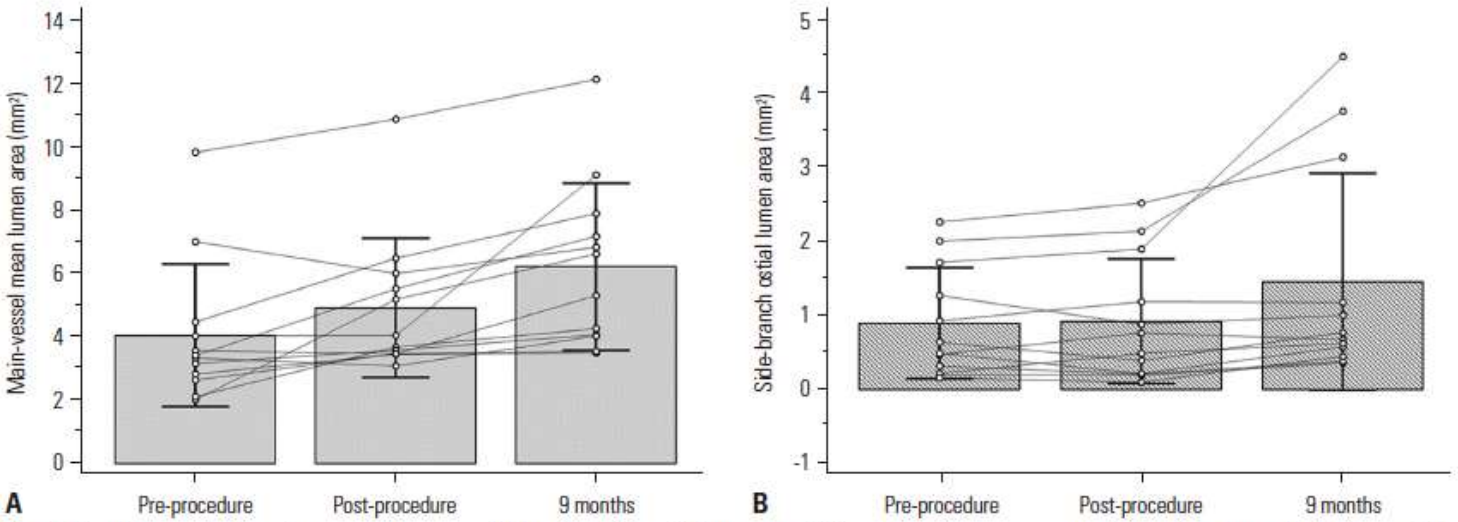

Fig. 4. The changes in the main vessel lumen area (A) and the SB ostial lumen area (B) pre-procedure, post-procedure and at 9-months follow-up. SB, side-branch.

The lumen area of the proximal rim of the SB ostium in main vessel increased at 9-months follow-up (3.74±2.64 mm2 pre-procedure, 5.03±1.95 mm2 post-procedure and 6.14±2.21 mm2 at 9-months). The lumen area of distal rim of the SB ostium in main vessel also increased at 9-months follow-up (4.35±2.11 mm2 pre-procedure, 4.71±1.92 mm2 post-procedure and 5.88± 2.10 mm2 at 9-months). The SB ostial lumen area increased at 9-months follow-up (0.92±0.68 mm2 pre-procedure, 1.03±0.77 mm2 post-procedure and 1.42±1.18 mm2 at 9-months).

Table 4. Complex coronary lesions.

Study	Devices	Number of patients	Primary outcome/follow-up	TLR, %/follow-up	Bail-out stent rate, %	Reference
Diffuse lesion						
Pilot long lesion study	DCB+BMS	12	LLL 0.48 mm/6 mos	16/6 mos	–	34
Diabetes mellitus						
PEPCAD IV	SeQuent Please+BMS vs. TAXUS	84	LLL 0.51 mm vs. 0.53 mm/6 mos	7.7 vs. 8.3/9 mos	–	35
DEAR	DIOR II+BMS (vs. DES vs. BMS)		MACE 13.2% (vs. 18.6% vs. 32.3%) /12 mos	6.6/12 mos	–	36
Chronic total occlusion						
PEPCAD CTO	BMS+SeQuent Please (vs. TAXUS)	48	LLL 0.64 mm (vs. 0.43 mm)/6 mos	14.6 (vs. 14.6)/12 mos	–	37
Acute myocardial infarction						
DEB-AMI	SeQuent Please+BMS	30	TLR 17%/12 mos	17/12 mos	–	38
DEB-AMI	DIOR II+BMS vs. BMS vs. TAXUS	149	LLL 0.64 mm vs. 0.74 mm vs. 0.21 mm/6 mos	20 vs. 17.6 vs. 2%/6 mos	–	39
Bifurcation						
DEBIUT registry	DIOR I (MB+SB) followed by BMS MB	20	No MACE/4 mos	0/4 mos		41
DEBIUT trial	DIOR I (MB+SB) followed by BMS MB vs. BMS MB vs. DES MB	117	MB: LLL 0.41 mm vs. 0.49 mm vs. 0.19 mm SB: LLL 0.19 mm vs. 0.21 mm vs. –0.11 mm/6 mos	20 vs. 27 vs. 15/18 mos	7.5 (SB)	42
PEPCAD V	SeQuent Please (MB+SB) followed by BMS MB	28	MB: LLL 0.38 mm SB: LLL 0.21 mm/9 mos	3.8/9 mos	14	43
Sgueglia et al	BMS MB followed by kissing DCB (SeQuent Please, IN.PACT Falcon, DIOR II, Pantera Lux)	12	Procedural success 100% No MACE/8 mos			44

BMS: bare metal stent; DCB: drug-coated balloon; LLL: late luminal loss; MACE: major adverse cardiac events; MB: main branch; SB: side branch; TLR: target lesion revascularisation

EuroIntervention 2013;9:979-988

The current status of drug-coated balloons in percutaneous coronary and peripheral interventions

Table 7. Vessel Thrombosis Rate in DCB Use and Duration of DAPT

Study	Device	Vessel Thrombosis Rate, % (n/N)	Duration of DAPT, Month(s)	Clinical Follow Up, Months
PEPCAD I	SeQuent Please	0 (0/82) in DCB only 6.3 (2/32) in DCB + BMS	1 3	6
PICCOLETTO	Dior I	0 (0/18) in DCB only 0 (0/10) in DCB + BMS	1 3	9
Spanish DIOR registry	Dior I/II	1 (1/103)	Not available	12
BELLO	In.Pact Falcon	0 (0/94)	Not available	6
LOCAL TAX	Genie + BMS	0 (0/67)	6	6
PEPCAD III	Coroflex DEBlue	2 (6/310)	6	9
PERfECT	SeQuent Please + EPC-capturing stent	0 (0/62)	3	6
INDICOR	SeQuent Please + BMS	6.1 (3/49) in DCB 1st 3.1 (1/48) in BMS 1st	3	12
De Novo Pilot study	Moxy + BMS	0 (0/26)	3	6
PEPCAD IV	SeQuent Please + BMS	0 (0/45)	3	6
PEPCAD CTO	SeQuent Please + BMS	0 (0/48)	3	6
DEBAMI	SeQuent Please + BMS	6.7 (2/30) (1 patient at 2 months, 1 patient at 6 months)	3	12
DEB-AMI	Dior II + BMS	4 (2/50) (1 patient at day 4, 1 patient at day 5)	Not available	6
Valentines II	Dior II	0 (0/103)	3	7.5
Pilot Long Lesion study	DCB (+ provisional BMS)	0 (0/12)	Not available	6
DEBIUT registry	Dior I + BMS	0 (0/20)	3	4
DEBIUT trial	Dior I + BMS	0 (0/40)	3	12
PEPCAD V	SeQuent Please + BMS	7 (2/28) (1 patient at 6 months, 1 patient at 8 months)	3	9
Sgueglia et al.	4 different DCB + BMS	0 (0/12)	3	8

Take Home Messages

- Drug coated balloons are proving to be a ‘multi-talented’ tool in the modern cardiac catheterisation laboratory
- Each case of ISR needs to be considered individually as there are several factors to think about including:
  - Patient characteristics (e.g. diabetes, ability to take prolonged DAPT)
  - Lesion/vessel factors (e.g. vessel geometry, calcification, distal versus proximal ISR, small vs large vessel, angulation, tortuosity)
  - Stent factors (e.g. stent type, likely mechanism for ISR such as fracture, versus neointimal proliferation versus malapposition)
- Following on from the positive results in the management of in-stent restenosis, drug coated balloons are showing promise in other challenging lesions subsets to treat native coronary artery disease with reassuring long term safety profile and, by negating the need for prolonged DAPT, offer a strategic benefit to treating patients with coronary disease in a cost effective way