DRUG COATED BALLOON: ESTABLISHED INDICATION & BEYOND

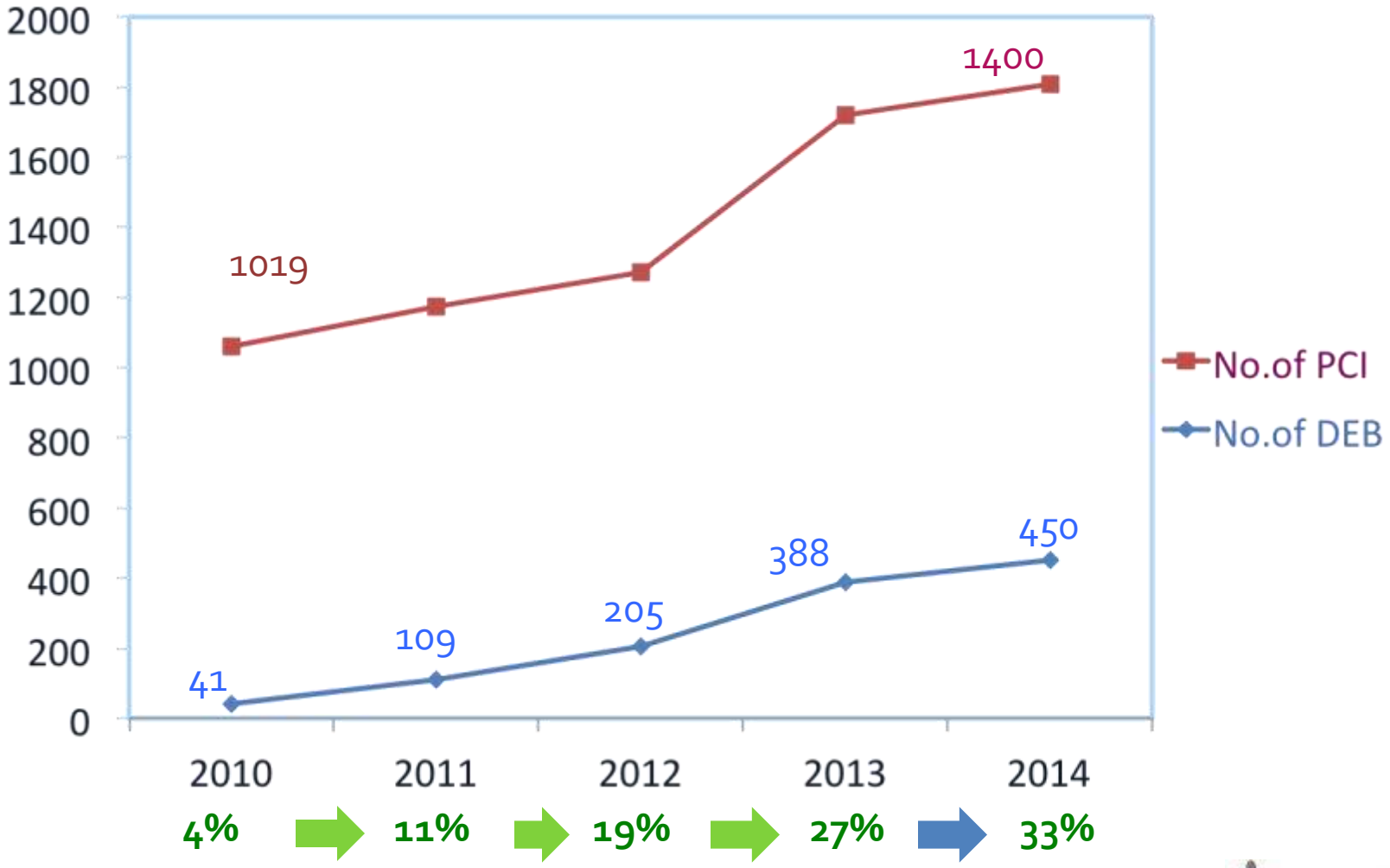
Paul Ong

Tan Tock Seng Hospital

Singapore

there’s more than one way to skin a cat

Angioplasty Trends in TTSH



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Essential Components of DCB

- Active Agent
  - Paclitaxel
- Additive
  - Butyryl-tri-hexyl citrate (BTHC)
  - Controls coating integrity and drug loss during transit
  - Facilitates tissue uptake: increases exposure, accelerates drug release & transfer to vessel wall
  - Necessary to achieve therapeutic drug levels

Pacific Yew Tree

Active Agent – Paclitaxel (Taxol)

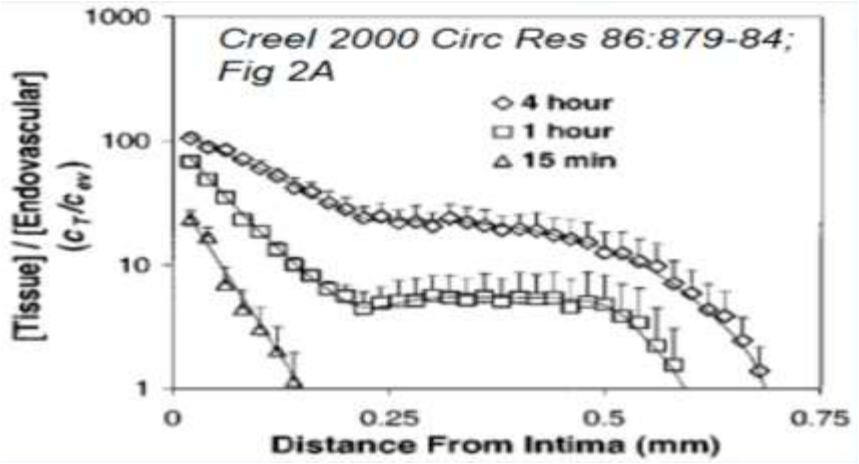
- First discovered in 1967 from the bark of the Pacific yew tree, ***Taxus*** brevifolia.
  - Developed commercially by Bristol-Myers Squibb the generic name was changed to paclitaxel.

- Paclitaxel is a mitotic inhibitor used in cancer chemotherapy.
  - It stabilizes microtubules and as a result, interferes with the normal breakdown of microtubules during cell division.
  - It is now used to treat patients with lung, ovarian, breast, head and neck cancer, and advanced forms of Kaposi's sarcoma.

- Paclitaxel is also used for the prevention of restenosis.

Active Agent – Paclitaxel (Taxol)

- Potently inhibits stenosis
  - Block proliferation and migration of smooth muscle cells
- *Very lipohilic (>> limus)*
  - Rapid uptake
  - Binds tissue at the target site and resist washout
- Diffuses from endothelial surface into medial and adventitial layers of arterial wall
  - Deep wall tissue paclitaxel concentration>10x level of endoluminal source



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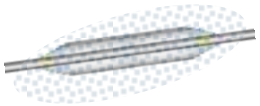
Why Drug Coated Balloon?
Drug Eluting Stent vs. Drug Coated Balloon

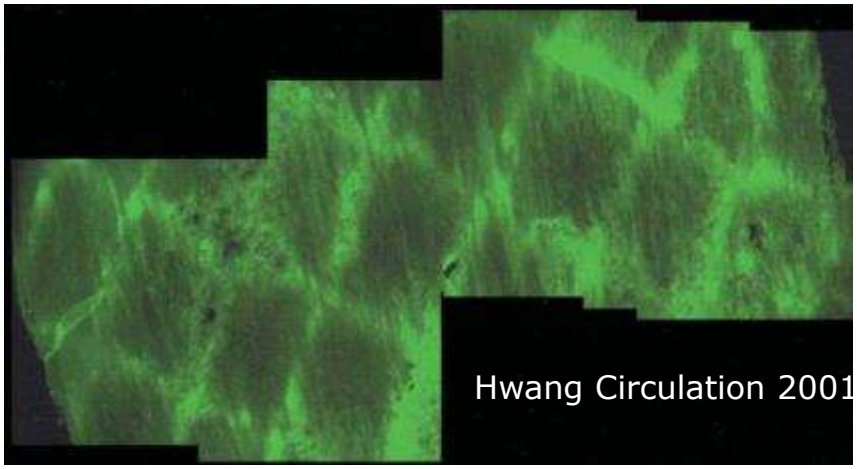


	Drug Eluting Stent	Drug Coated Balloon
Platform of drug delivery	Stent scaffolding	Balloon
Retention	Polymer based	Embedded imprinted
Drug dose	Low: 100 to 200 µg	High: 300 to 600 µg
Release kinetics	Slow and controlled	Fast release
Distribution	Strut-based vascular penetration	Balloon surface homogenous distribution

Source: R. Waksman and R. Pakala. *Drug-Eluting Balloon: The Comeback Kid?* Circ Cardiovasc Interv 2009;2;352-358.

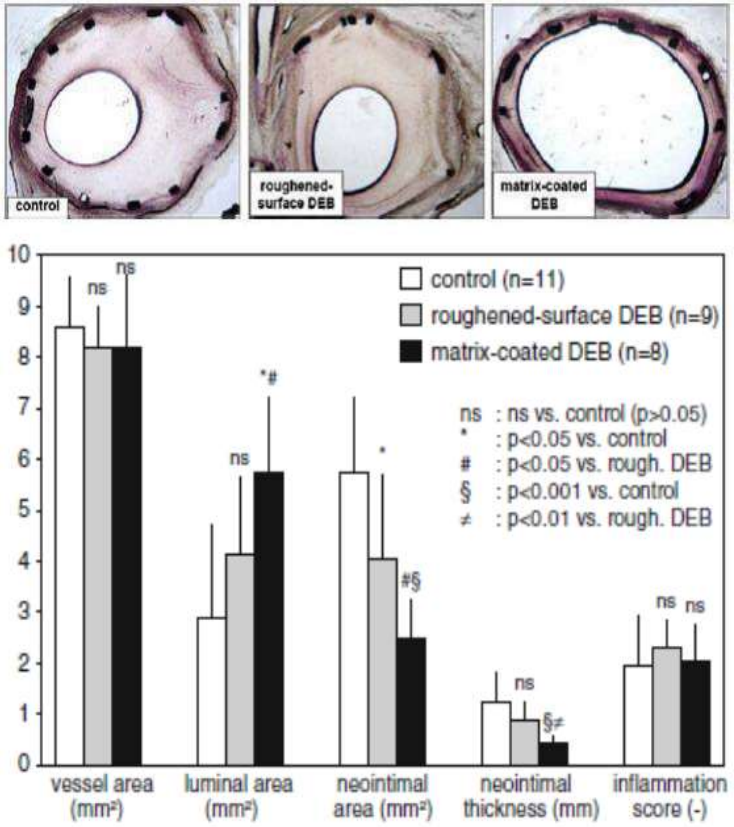
Drug distribution DES Vs DCB

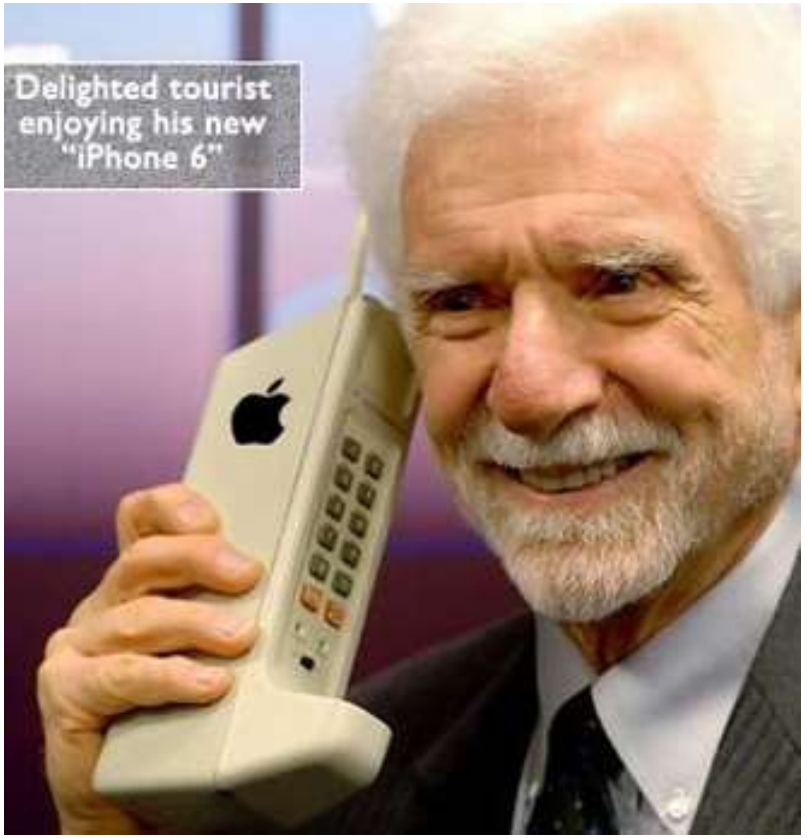
Unequal drug distribution with DES



Even drug distribution with DCB

Not all DCBs are created equal



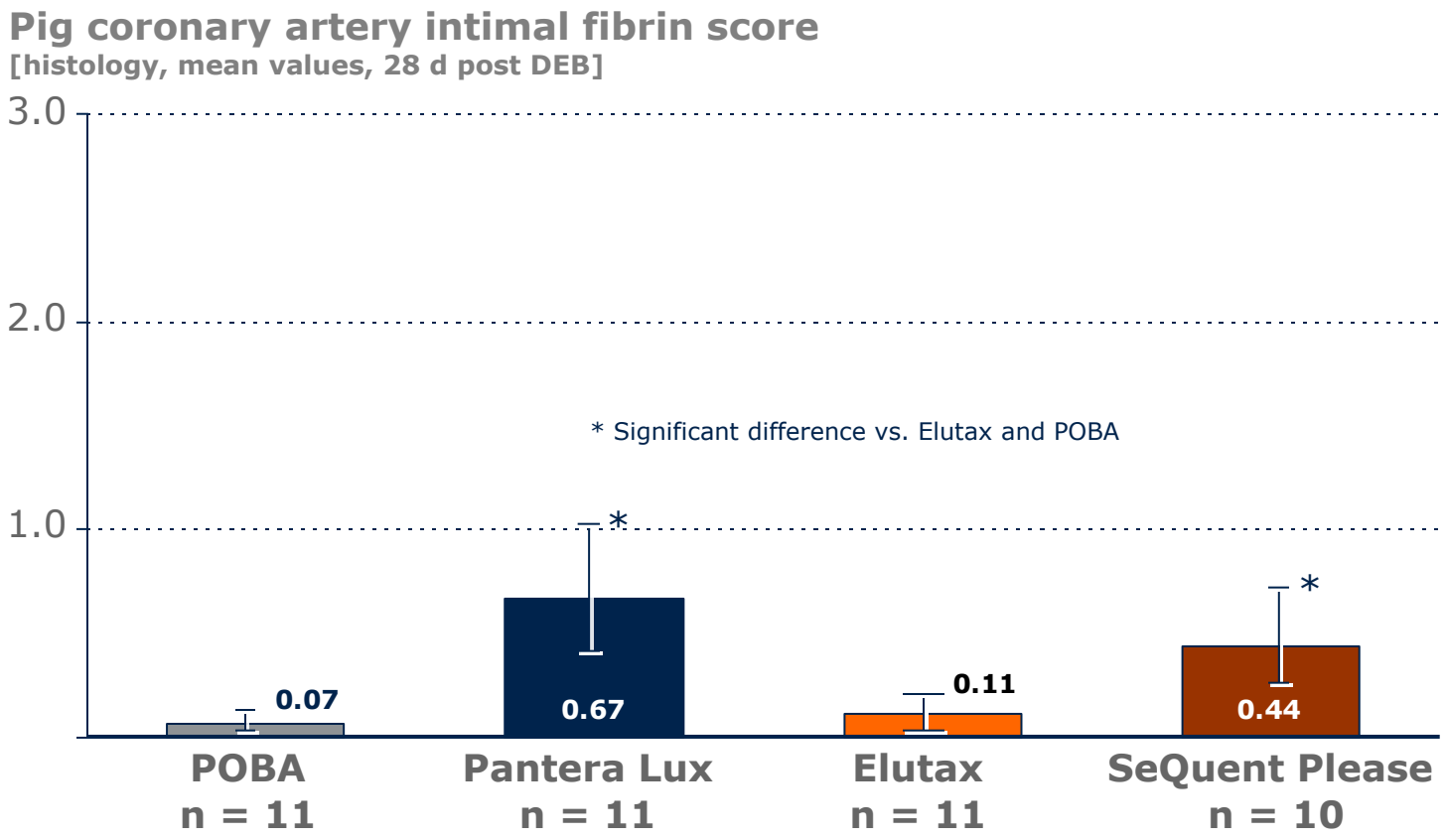


"When presenting our first preclinical data on DCB about 10 years ago, people said it would never work in humans. Today, the greatest threat to this technology is bad clinical science. As mentioned in the ESC/EACTS guidelines for coronary revascularization, one cannot assume a class effect for DCB.

Therefore, clinical evidence includes adequately powered RCTs in different indications for each type of DCB."

Drug efficacy of Pantera Lux is similar to SeQuent Please and significantly greater than POBA

Fibrin deposition serves as sign of delayed healing and surrogate for effective drug transfer



Source: Joner M et. al; Thromb Haemost 2011 May;105(5):864-72.

indications

- **ISR**
- **Small vessel de novo**
- **Primary PCI**
- **CTO**

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Repeat revascularization

Recommendations	Class[a]	LoE[b]	Ref[c]
Early post-operative ischaemia and graft failure			
Coronary angiography is recommended for patients with: • symptoms of ischaemia and/or abnormal biomarkers suggestive of perioperative myocardial infarction • ischaemic ECG changes indicating large area of risk • new significant wall motion abnormalities • haemodynamic instability.	I	C	
It is recommended to make the decision on redo CABG or PCI by *ad hoc* consultation in the Heart Team and based on feasibility of revascularization, area at risk, comorbidities and clinical status.	I	C	
PCI should be considered over re-operation in patients with early ischaemia after CABG if technically feasible.	IIa	C	
If PCI is performed, revascularization of the native vessels or IMA grafts rather than occluded or heavily diseased SVGs should be considered.	IIa	C	
Restenosis			
Repeat PCI is recommended, if technically feasible.	I	C	
DES are recommended for the treatment of in-stent re-stenosis (within BMS or DES)	I	A	501,502,508 511,524
Drug-coated balloons are recommended for the treatment of in-stent restenosis (within BMS or DES).	I	A	507– 511,524
IVUS and/or OCT should be considered to detect stent-related mechanical problems.	IIa	C	

DCB shows great results in ISR, against POBA …

PACCOCATH I/II : Randomized, multicenter trial	
Patient enrolment	108 (in two separate trials with identical protocol)
Device	Paccocath vs POBA
Lesion type	ISR
Primary endpoint	6 mo LLL (in-segment)

	DCB N=54	POBA N=54	p
6-months angio FUP	N=48	N=49	
LLL (in-segment)	0.11 ± 0.44 mm	0.80 ± 0.79 mm	0.001
12-months clinical FUP	N=54	N=54	
TLR	4 %	37 %	0.001
5 years clinical FUP	N=54	N=54	
TLR	9.3 %	38.9 %	0.004
MACE*	27.8 %	59.3 %	0.009

Conclusion:
At 6 month, Paccocath shows effective reduction of neointimal hyperplasia by low LLL values in ISR. Clinical results show lower TLR and MACE rate out to 5 years.

*MACE consists of TLR, MI, ST, stroke and death

Source: Scheller, JACC Cardiovasc Interv. 2012 Mar;5(3):323-30.

… and against DES

PEPCAD II: Randomized, multicenter trial	
Patient enrolled	131
Device	SeQuent Please vs Taxus
Lesion Type	ISR
Primary endpoint	6 mo LLL (in-segment)

Intention-to-treat analysis	DCB N=66	PES N=65	p
6-months angio FUP	N=57	N=59	
LLL (in-segment)	0.17 ± 0.42 mm	0.38 ± 0.61 mm	0.03
12-months clinical FUP	N=66	N=65	
TLR	6.3%	15.4%	0.15
3 years clinical FUP			
TLR	7.6%	18.5%	0.055
Stent Thrombosis	0	0	
MACE*	***15.2%***	***27.7%***	***0.062***

Conclusion

The SeQuent Please meets the primary endpoint and shows superiority over Taxus for the treatment of ISR out to 3 years.

*MACE consists of TLR, MI, stent thrombosis or cardiac death.

Source: Unverdorben, Circulation 2009;119;2986-2994
Unverdorben, oral presentation, EuroPCR 2011

Paclitaxel REleasing Balloon in Patients PresEnting with In-Stent Restenosis – FIM study

PEPPER

DESIGN
Prospective, multi-center, non-randomized, European clinical trial of the Pantera Lux Paclitaxel Releasing Balloon

OBJECTIVE
To evaluate the safety and efficacy of the Pantera Lux in patients with BMS and DES in-stent restenosis in coronary arteries

PRINCIPAL INVESTIGATOR
Ch. Hehrlein, MD
University Medical Center
Freiburg, Germany

Angiographic results assessed by independent core lab.
Clinical results adjudicated by clinical events committee.

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

Study Endpoints

Primary Endpoint

- Late Lumen Loss (in-stent[1]) at 6 month follow-up

Secondary Endpoints

- In-segment[2] LLL, % diameter restenosis @ 6 months
- In-stent[1] % diameter restenosis @ 6 months
- Cumulative MACE (composite of cardiac death, non-fatal MI, clinically driven TVR) @ 6 and 12 months
- Device success

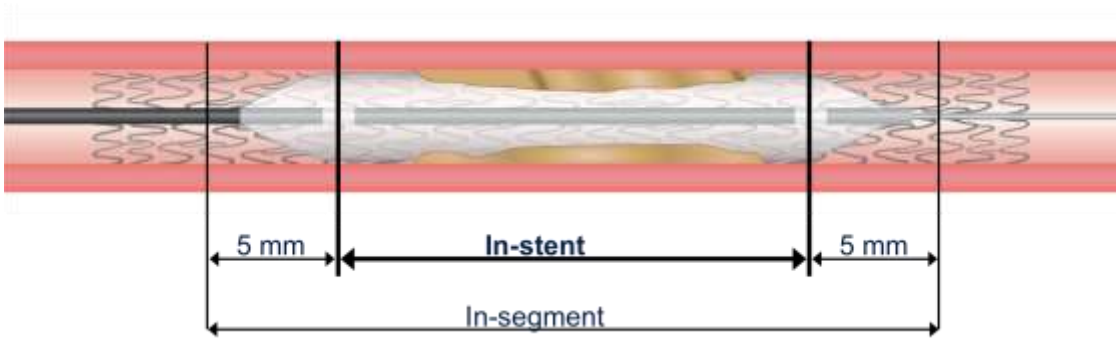
[1] In-stent length defined as restenotic area where the balloon was dilated (from shoulder to shoulder)
[2] In-segment length defined as in-stent plus 5 mm proximal and distal

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

Acute and 6-Month Angiographic Results[1]

	Pre-procedure	Post-procedure	6-month
In-stent			
Reference vessel diameter (mm)	2.84 ± 0.39	2.86 ± 0.39	2.82 ± 0.38
Minimum lumen diameter (mm)	0.91 ± 0.43	2.18 ± 0.39	2.08 ± 0.41[1]
Diameter stenosis (%)	68.1 ± 13.8	23.9 ± 9.8	25.9 ± 11.7
Late lumen loss (mm)			**0.07 ± 0.31[2]**
In-segment			
Late lumen loss (mm)			**0.02 ± 0.32**

[1] p=0.047 for BMS ISR (2.18 ± 0.46) vs DES ISR (1.98 ± 0.32)
[2] p=0.001 for BMS ISR (-0.05 ± 0.28) vs DES ISR (0.19 ± 0.29).
All other values without significant difference between BMS-ISR and DES-ISR subgroups



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

6- and 12-Month Clinical Results

	6 month				12 month			
	All	BMS[1]	DES[1]	P	All	BMS[1]	DES[1]	p
MACE[2]	**5 (6.5%)**	**2**	**3**	**0.66**	**9 (11.8 %)**	**2**	**7**	**.07**
Cardiac death	-	-	-	-	-	-	-	-
Non-fatal MI	1 (1.3 %)	1[3]	-	1.00	1 (1.3 %)	1	-	1.00
TVR (clinically driven)	4 (5.2 %)	1	3	.60	8 (10.5 %)	1	7	.021
TLR (clinically driven)	3 (3.9 %)	1	2	.60	7 (9.2 %)	1	6	.044
Death, non cardiac	2 (2.6 %)	1	1	1.00	2 (2.6 %)	1	1	1.00
Stent thrombosis	-	-	-	-	-	-	-	-

[1] Last layer of metal placed before DEB treatment
[2] Hierarchical order
[3] Within 24 hours after procedure

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

Conclusions

- Application of a paclitaxel coated balloon using BTHC as excipient is feasible and safe in a mixed population of patients with predominantly type I BMS ISR or DES-ISR lesions
- A short exposure of the vessel wall to paclitaxel results in very low late lumen loss, revascularization and MACE rates
- Pantera Lux application is a valuable treatment option for ISR in either BMS or DES patients

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

indications

- ISR
- **de novo**
- Primary PCI
- CTO

Asians have more DM (46.6% vs 34.8% p=0.06)

Angiographic features, procedural data and clinical outcomes.

	All Patients (N = 447)	Asian (N = 73)	Western (N = 374)	p-Value
Number of lesions	471	82	389	
Target vessel				
LAD, n,%	193 (41.0)	34 (41.4)	159 (40.9)	0.17
LCx, n,%	126 (26.8)	25 (30.5)	101 (26.0)	
RCA, n,%	94 (20.0)	19 (23.2)	75 (19.3)	
Others, n,%	58 (12.3)	4 (4.9)	54 (13.9)	
Calcification, n,%	112 (23.8)	8 (9.8)	104 (26.7)	0.001*
Bifurcation, n,%	45 (9.6)	6 (7.3)	39 (10.0)	0.43
Severe tortuosity, n,%	45 (9.6)	1 (1.2)	44 (11.3)	<0.001*
AHA/ACC type B2/C lesion	182 (38.6)	29 (35.4)	153 (39.3)	0.53
Reference vessel diameter, mm	2.14 ± 0.35	2.03 ± 0.17	2.17 ± 0.38	0.02*
Lesion length, mm	15.5 ± 7.0	17.9 ± 10.7	15.0 ± 6.0	0.003*
No. of PCB, n	478	82	396	
PCB diameter, mm	2.33 ± 0.31	2.29 ± 0.26	2.34 ± 0.32	0.06
PCB length, mm	19.2 ± 4.5	20.4 ± 4.6	18.9 ± 4.4	0.002*
Overall technical success, n,%	473 (99.0)	81 (98.8)	392 (99.0)	–
Clinical outcomes				
30-day MACE, n,%	1 (0.3)	0 (0)	1 (0.3)	0.62
9-month MACE, n,%	18 (4.7)	2 (2.7)	16 (5.1)	0.38
9-month TLR, n,%	14 (3.6)	1 (1.4)	13 (4.2)	0.25
9-month MI, n,%	7 (1.8)	1 (1.4)	6 (1.9)	0.75
9-month cardiac death, n,%	0 (0)	0 (0)	0 (0)	–

Ong et al 2014 Int J Cardiol

Asians have more DM (46.6% vs 34.8% p=0.06), more diffuse disease but good result with DCB only strategy

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9-month cardiac death, n,%	0 (0)	0 (0)	0 (0)	–

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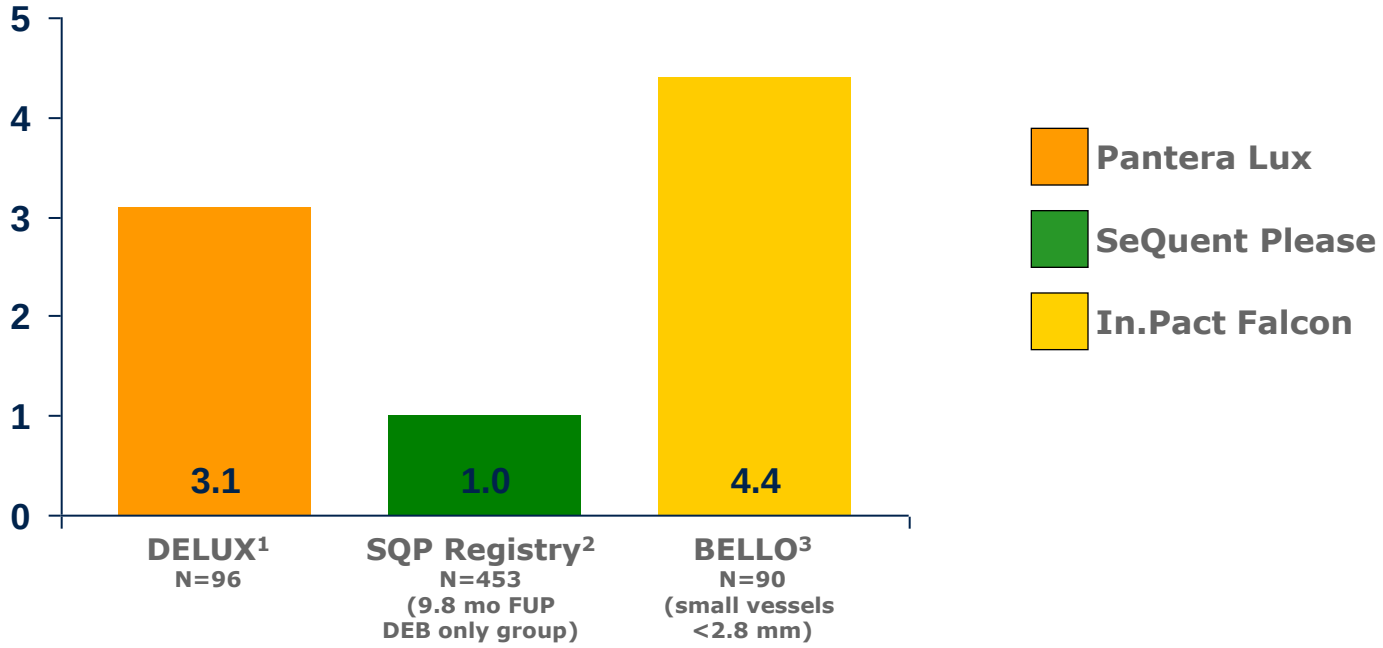
12-month clinical results
Comparison to published de novo lesion data

Comparison of published TLR rates at 12 months



1 Toelg R et al. EuroInterv 2013 Dec 19. [Epub]
2 Woehrle, JACC 2012;60(18):1733-8
3 Latib, JACC 2012;60(24):2473-80

DCB idea is to gently paint the coronary wall with paclitaxel

Positive Remodelling

Clin Res Cardiol
DOI 10.1007/s00392-014-0775-2

ORIGINAL PAPER

Local paclitaxel induces late lumen enlargement in coronary arteries after balloon angioplasty

Franz X. Kleber · Antonia Schulz · Matthias Waliszewski · Telse Hauschild · Michael Böhm · Ulrich Dietz · Bodo Cremers · Bruno Scheller · Yvonne P. Clever

F Kleber et al Clin Res Cardiol 2014

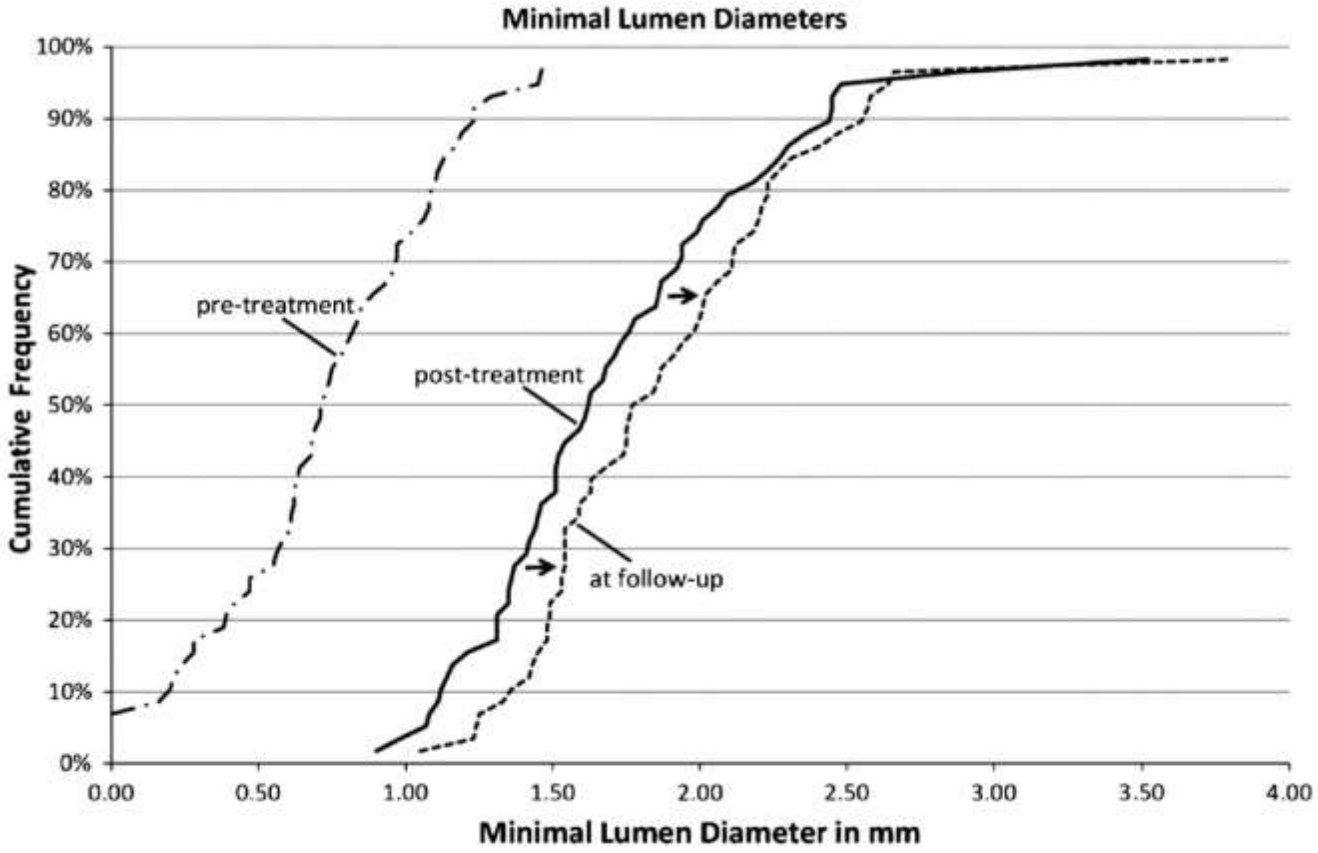
- Prospective non randomised study
- 56 consecutive patients
- 58 native coronary artery lesions mainly of small vessels (mean vessel reference diameter 2.58 ± 0.47 mm)
- angiographic follow-up at *4.1 ± 2.1 months*
- 41 of 58 lesions (69 %) showed a luminal increase while 29 % showed a luminal decrease

F Kleber et al Clin Res Cardiol 2014

9.1% gain in MLD at follow up

Angiographic measure	Pre-intervention	Post-intervention	Follow-up	*p* value pre vs. post	*p* value post vs. follow-up
Target lesion segment A					
Lesion length	8.49 ± 7.54	8.68 ± 7.35	8.48 ± 7.46	–	–
Minimal lumen diameter	0.81 ± 0.47	1.75 ± 0.58	1.91 ± 0.55	**<0.001**	**<0.001**
Mean lumen diameter	1.31 ± 0.44	2.03 ± 0.57	2.20 ± 0.56	**<0.001**	**<0.001**
Reference diameter	2.59 ± 0.45	2.60 ± 0.46	2.61 ± 0.47	0.394	0.185
Diameter stenosis	69.2 ± 14.0 %	33.8 ± 13.4 %	26.9 ± 13.8 %	**<0.001**	**<0.001**

Findings


Minimal Lumen Diameters
Cumulative Frequency
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0.00
0.50
1.00
1.50
2.00
2.50
3.00
3.50
4.00
pre-treatment
post-treatment
at follow-up
Minimal Lumen Diameter in mm

indications

- ISR
- Small vessel de novo
- **Primary PCI**
- CTO

3 Uses of DCB in PPCI

- POBA of de novo lesion (75%)
- POBA of late/very late stent thrombosis (8%)
- Adjunctive therapy for diffuse lesion (16%)

TTSH PPCI DCB Registry

Study Period: **Jan 2010 to April 2014**

- **Number of Patients: 97 patients**
- **Number of Lesions: 97 lesions**
- **Male: Female (%) = 83: 17**
- **Mean age : 60 ± 12 yrs**

Clinical Presentation:	**N/(%)**
Ant STEMI	**50(51)**
Inf/post STEMI	**47 (49)**

- **LVEF (%) : 42 ± 11**

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TTSH PPCI DCB Registry

CVS Risk Factors:	N/(%)
Smoking	48 (50)
Diabetes mellitus	33 (34)
Hyperlipidemia	50 (52)
Hypertension	55 (57)
Prior MI	13 (13)
Prior PCI	13 (13)

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TTSH PPCI DCB Registry

PCI details:	N/(%)
POBA (DCB-only)	93 (96)
Stent (DCB+BMS)	4 (4)
Post PCI TIMI flow	
TIMI 2	2 (2)
TIMI 3	95 (98)
Residual stenosis (%)	27 ± 14

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TTSH PPCI DCB Registry

Clinical Outcomes (1 Month):	N= 97/(%)
All cause mortality	4 (4)
MI	0 (0)
TLR	0 (0)
Lesion thrombosis	0 (0)

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TTSH PPCI DCB Registry

Clinical Outcomes (9 Month):	N=93/(%)
MACE	6 (6.4)
All cause mortality	1 (1)
MI	2 (2.1)
TLR	5 (5.4)
Lesion thrombosis	0 (0)

HH Ho, PJ Ong et al 2014 World J Cardiol

indications

- ISR
- de novo
- Primary PCI
- **CTO**

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CTO of LAD

- 55 year old
- Diabetic
- Committed smoker
- Recurrent angina and admission with CCF

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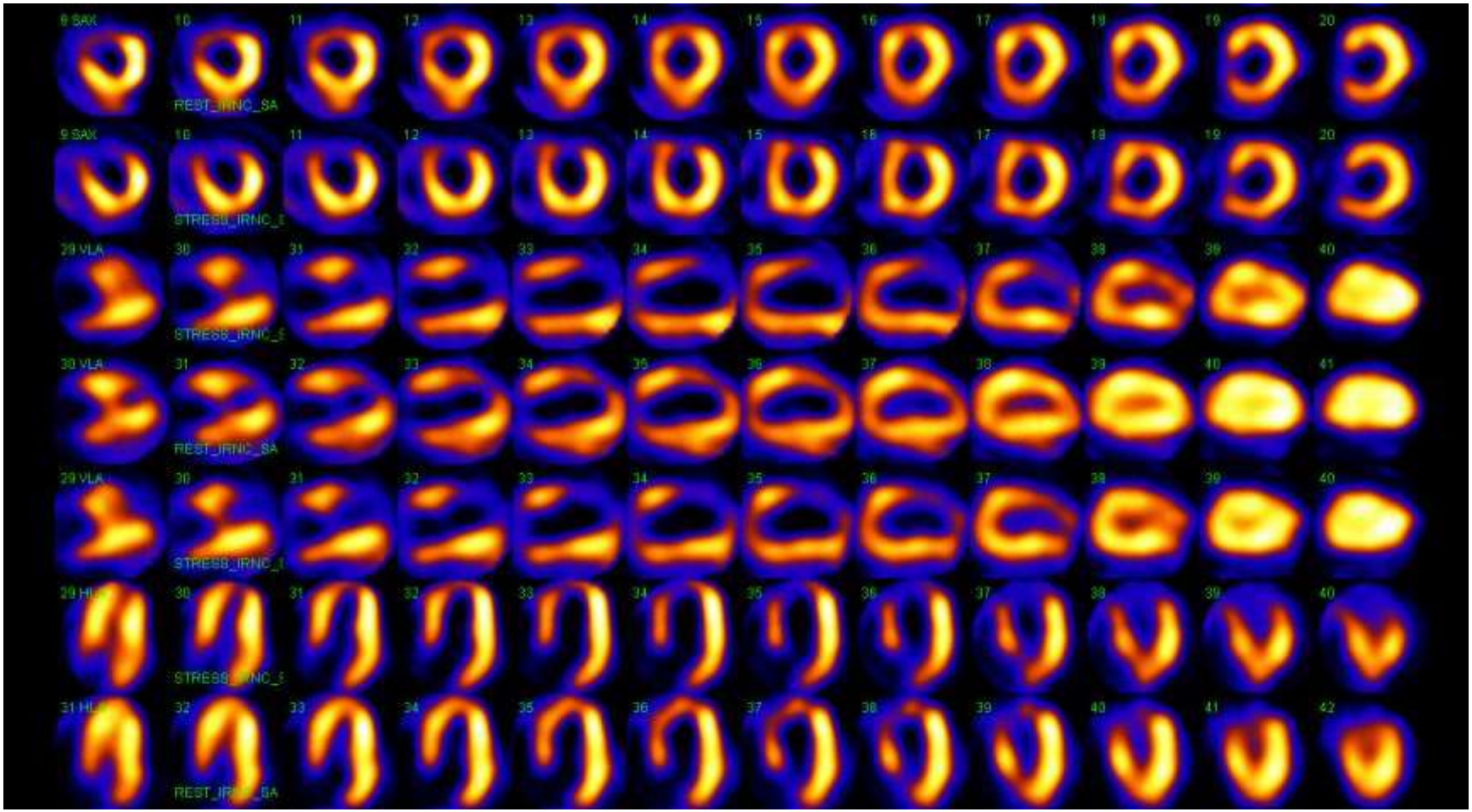
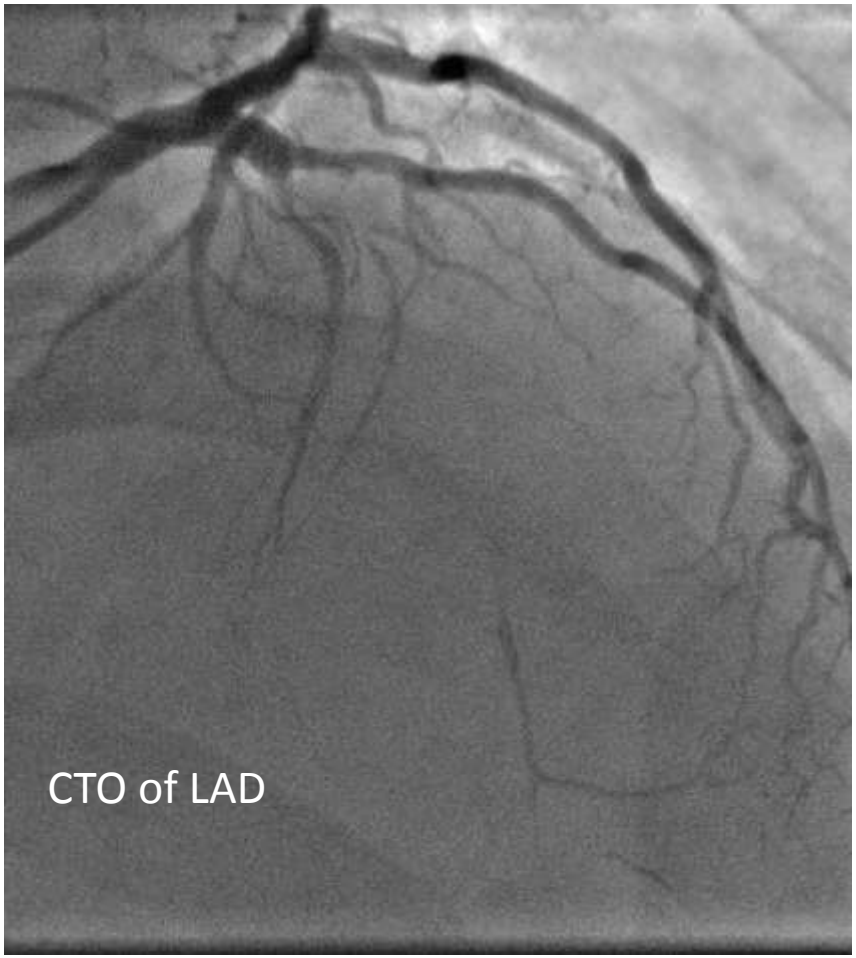
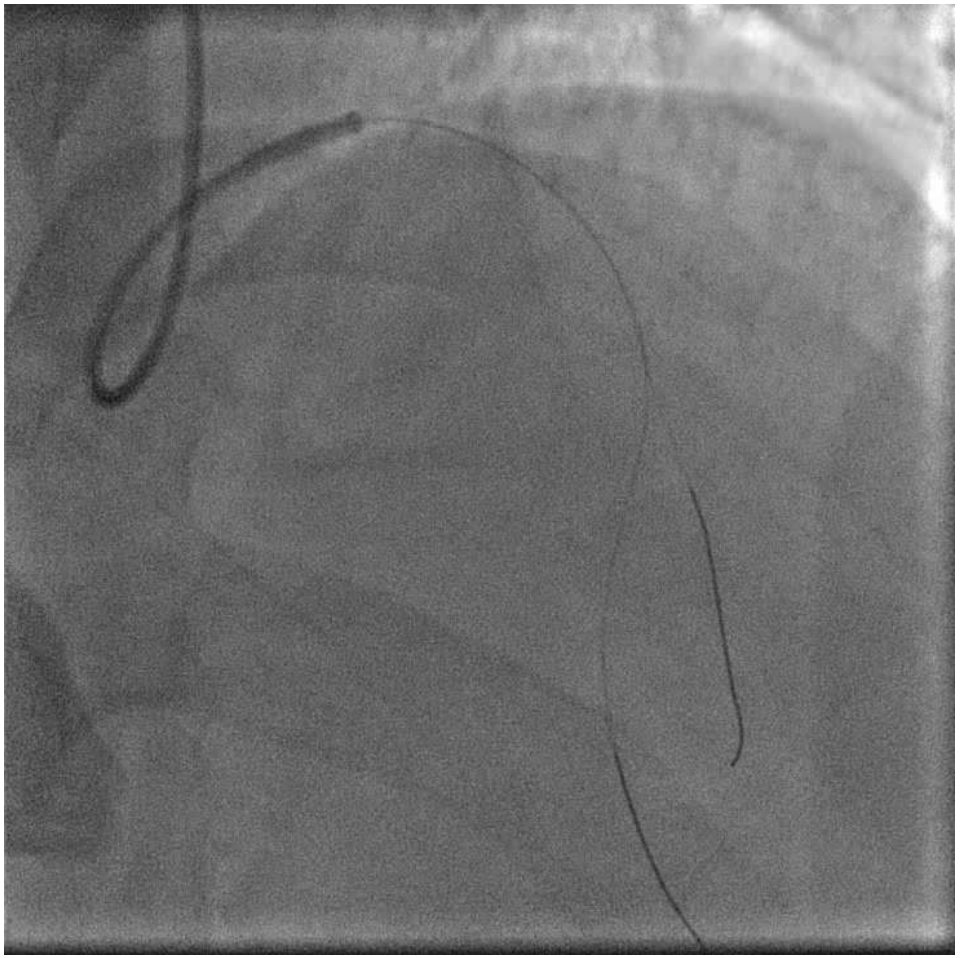
MIBI scan showed reversible ischaemia in the Anterior Wall



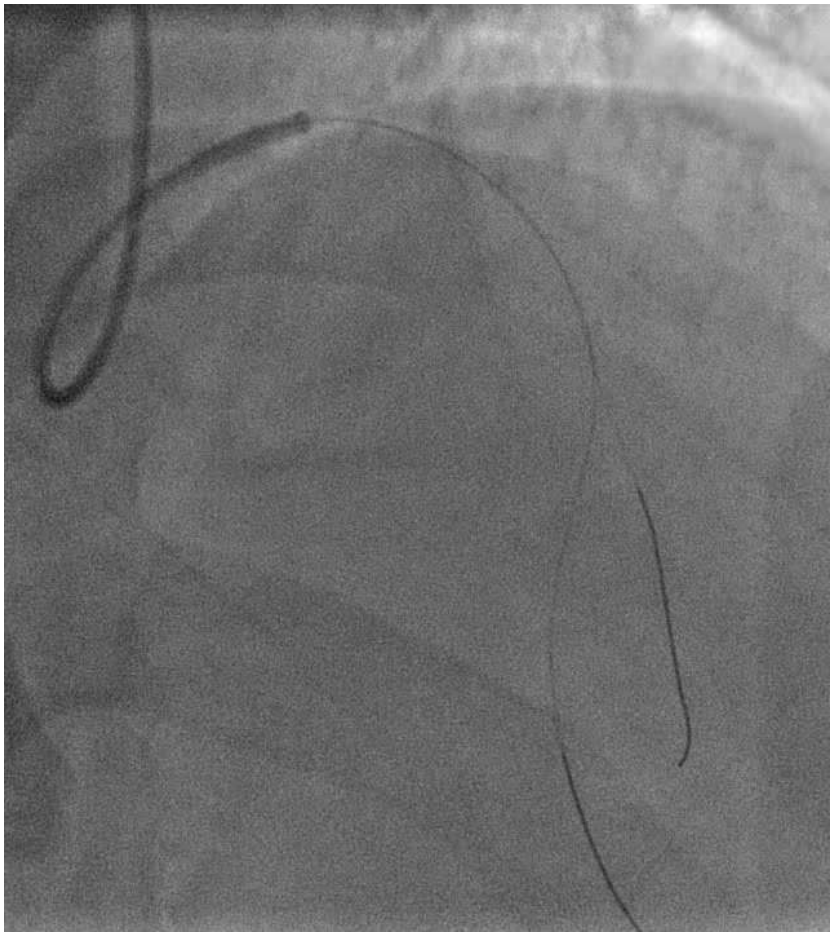
CTO of LAD



After balloon and nitrate

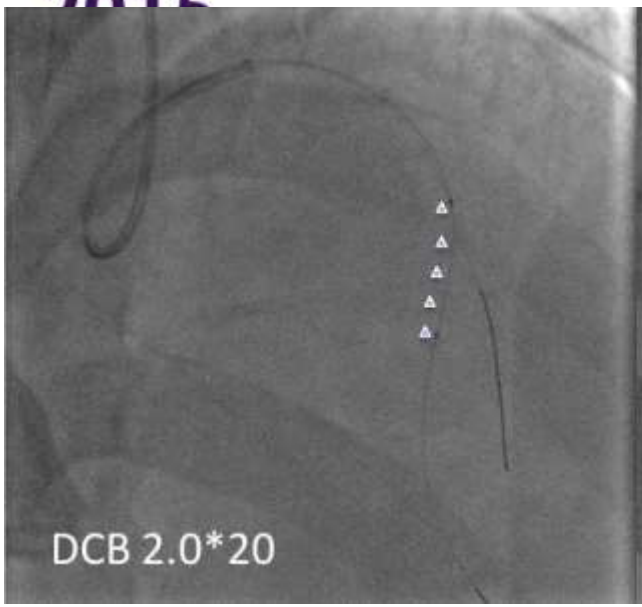


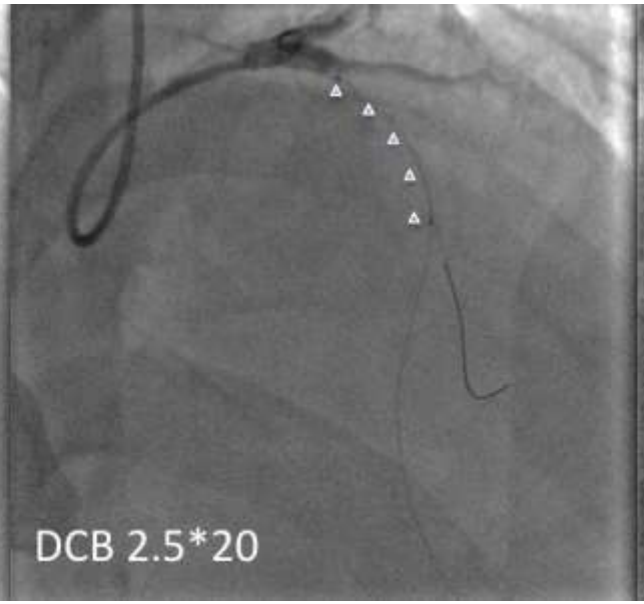
How will you treat?

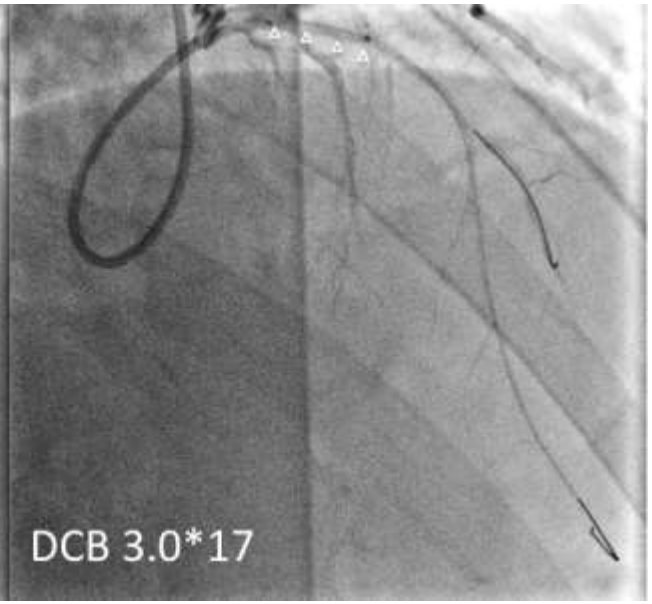


- Size difference
- Trification
- Small vessel
- Long lesion
- No clear landing zone

3 DCBs used



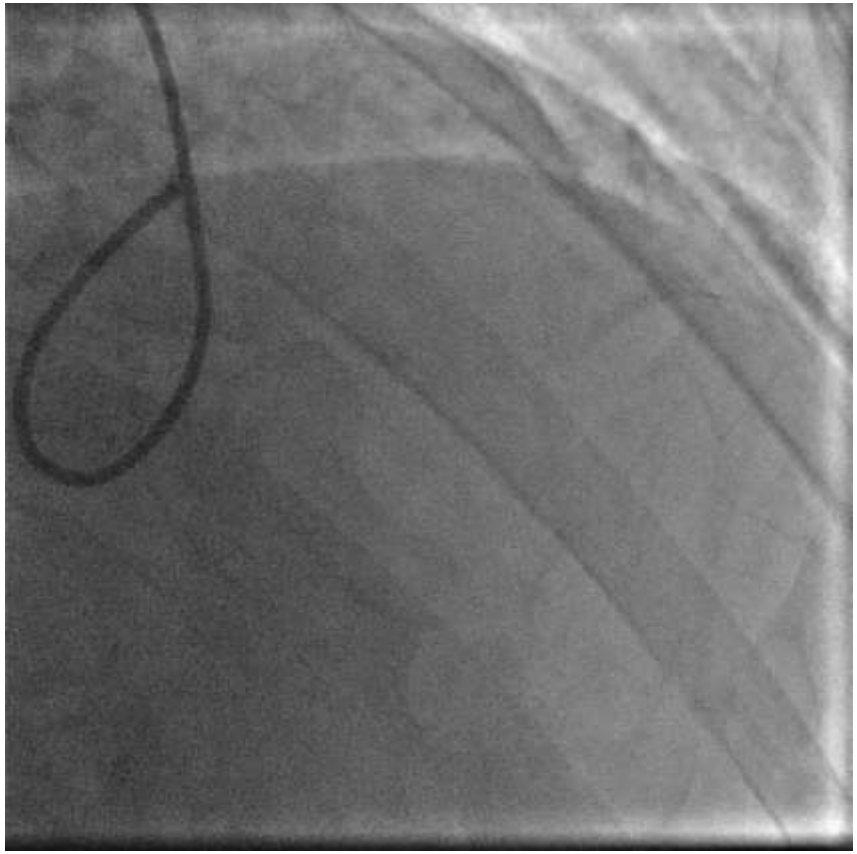




At end of procedure no major dissection. TIMI 3 flow
Still moderate disease after D1

Planned for elective re-angio at 6 to 8 months

Slightly underwhelming result



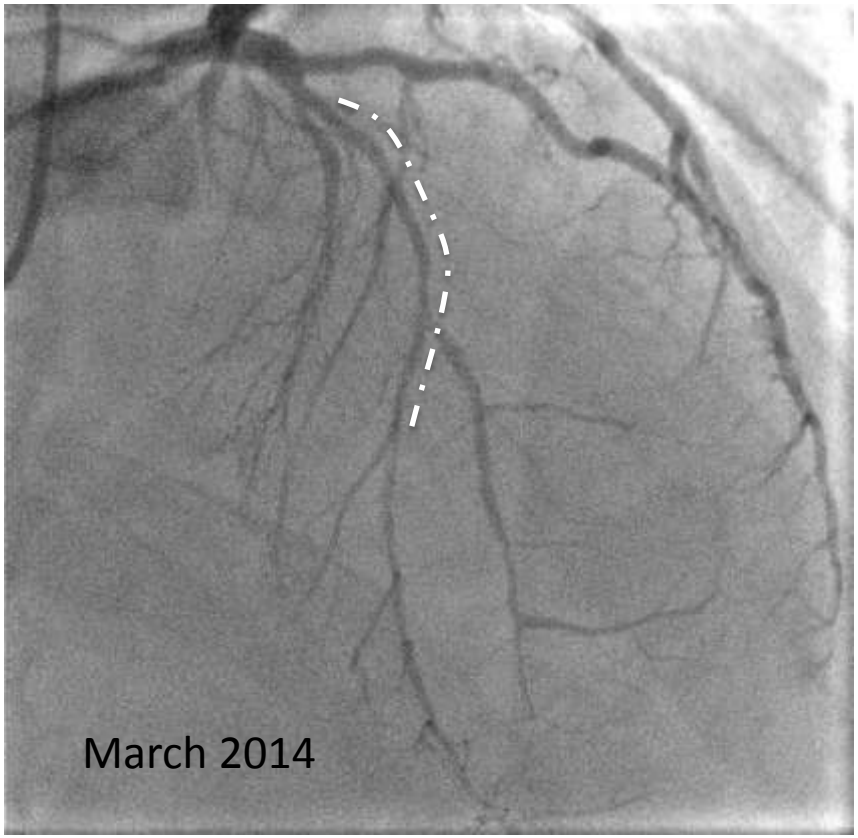
Nov 2014

- Completed 1 month DAPT
- Clinically well
- Angina free
- NYHA 1
- Elective Angiographic restudy 8 months later

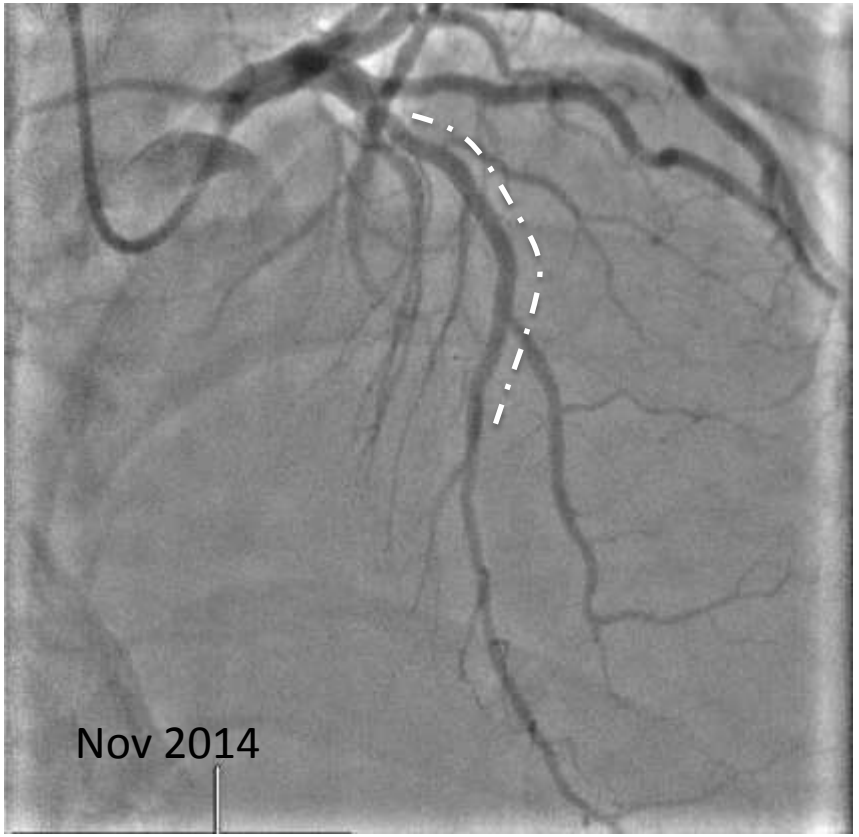
LAD still Patent !

8 months re-angiography
Positive remodelling of LAD

Before

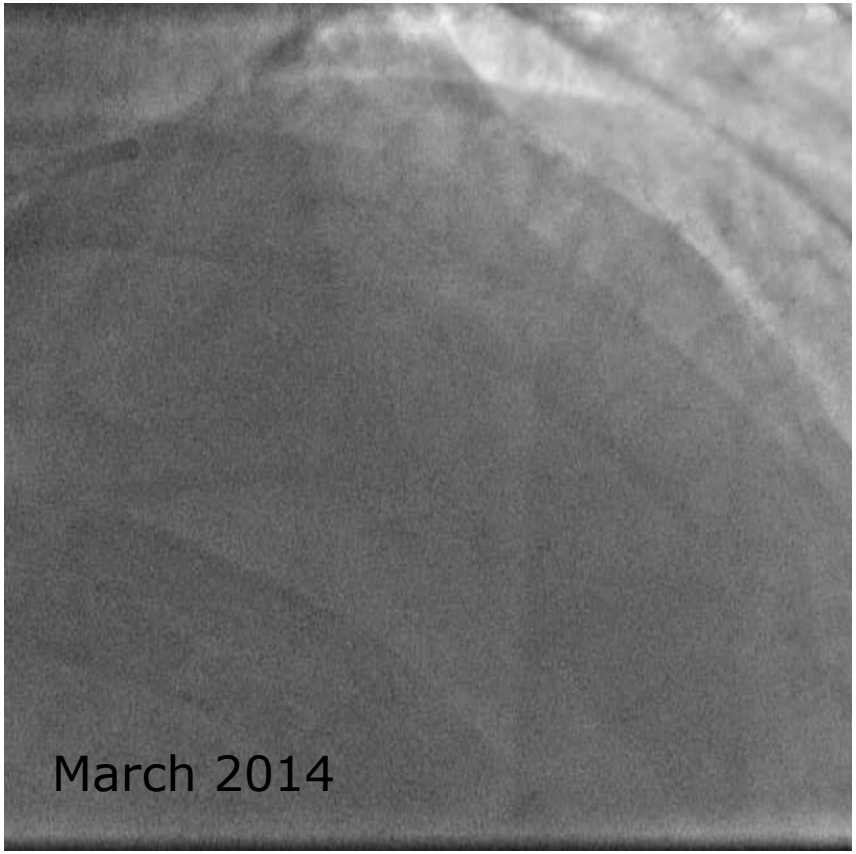


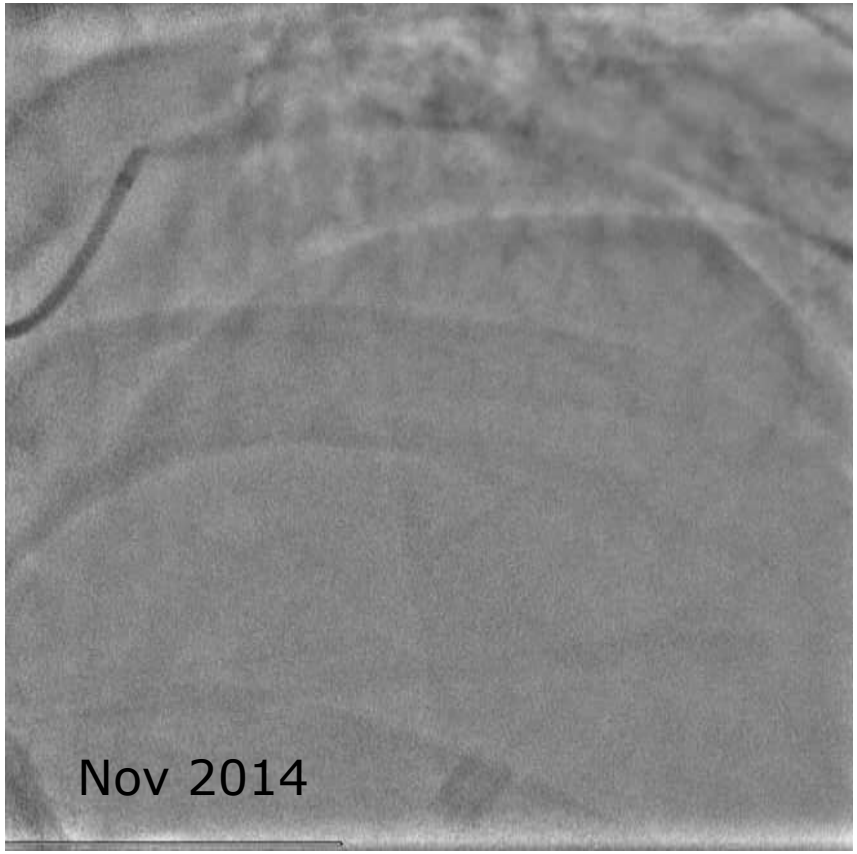
8 months later

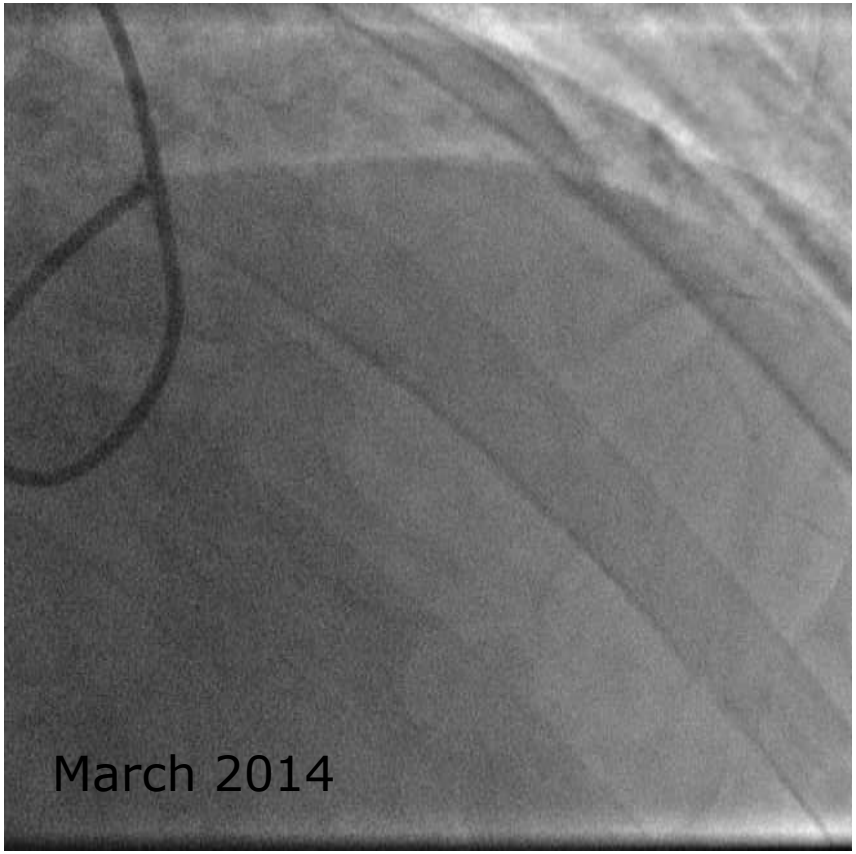


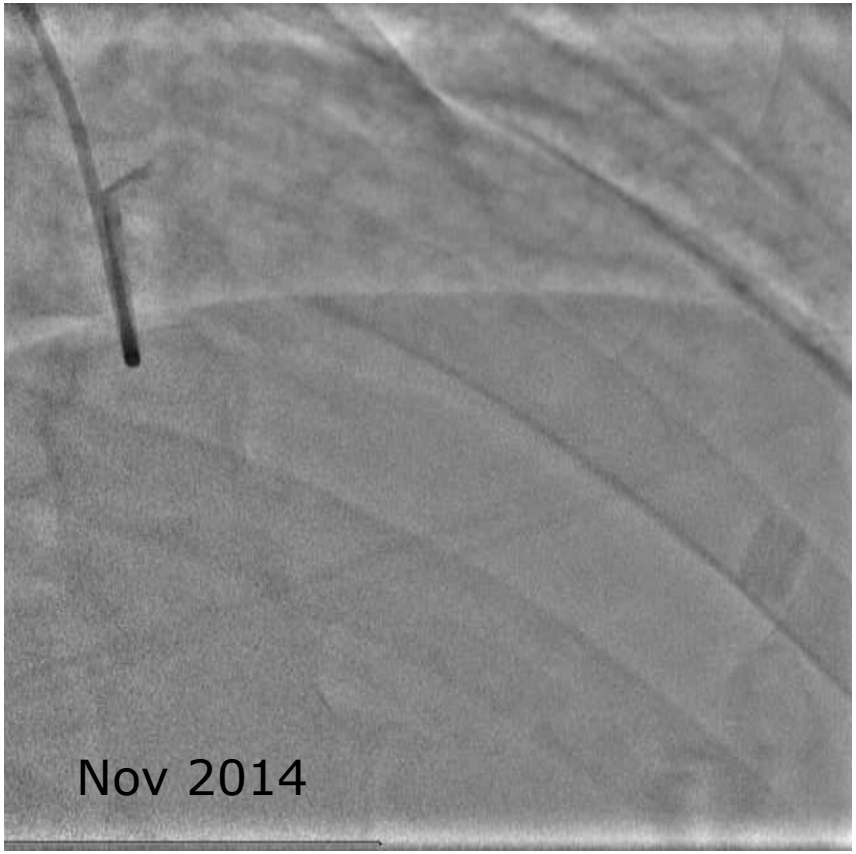
At 8 months clinically well and asymptomatic. Elective repeat angiogram.

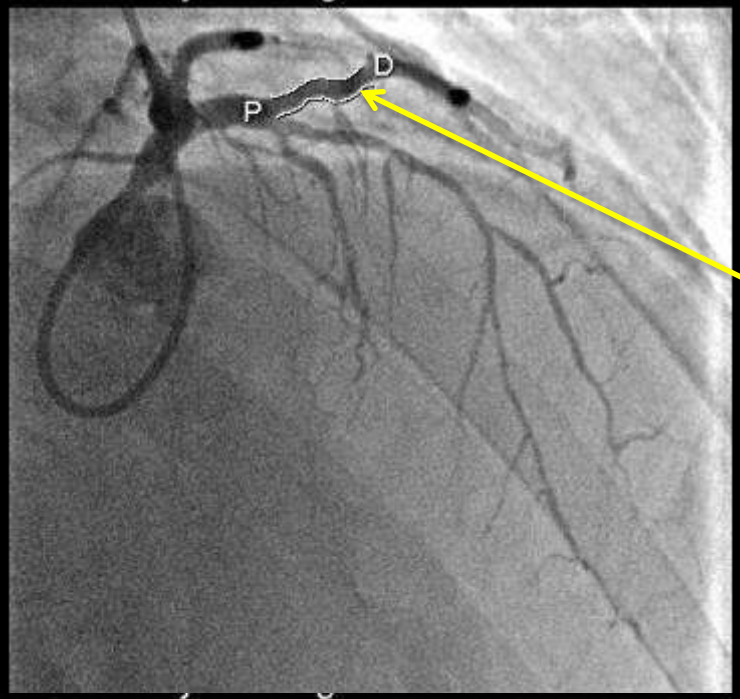
Positive Remodelling

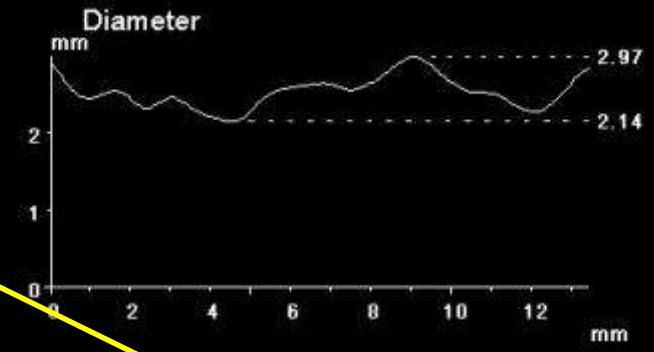


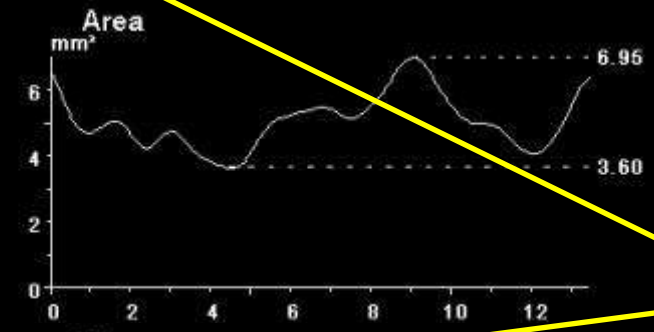



March 2014

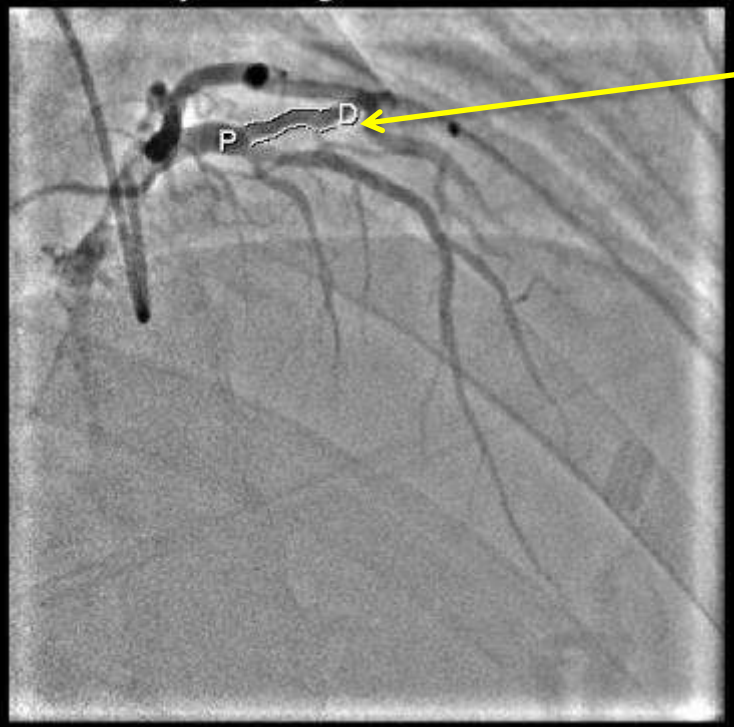

Nov 2014

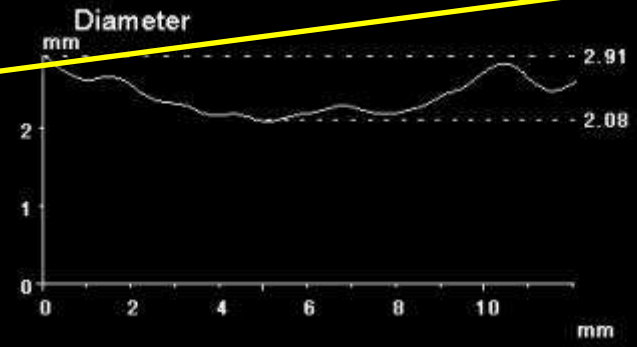


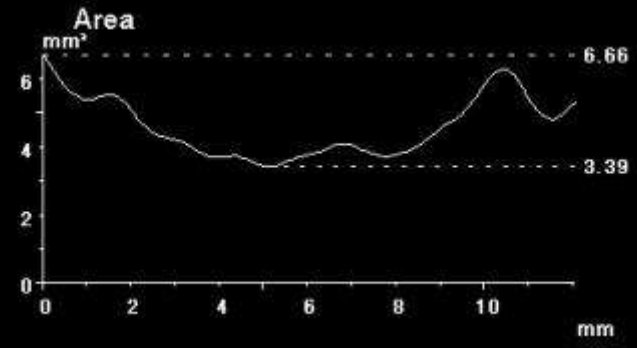


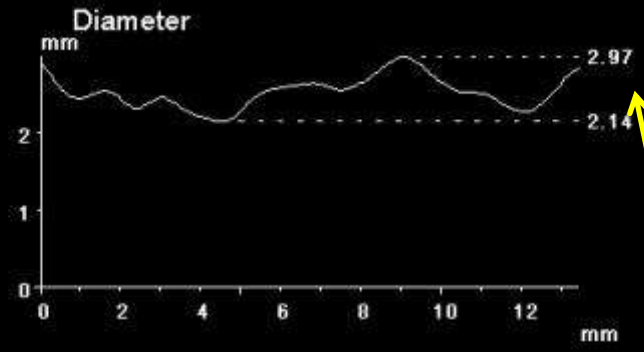


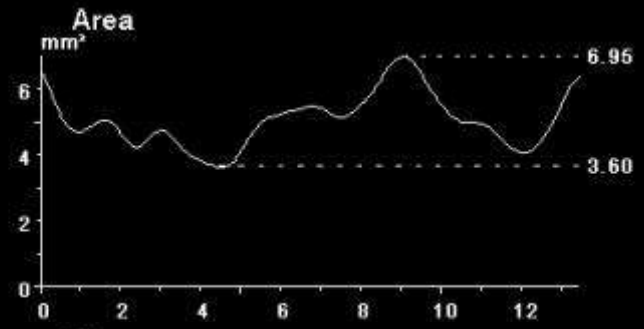
QCA Diagonal

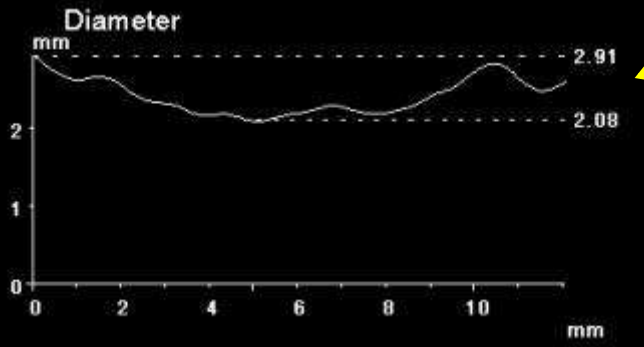


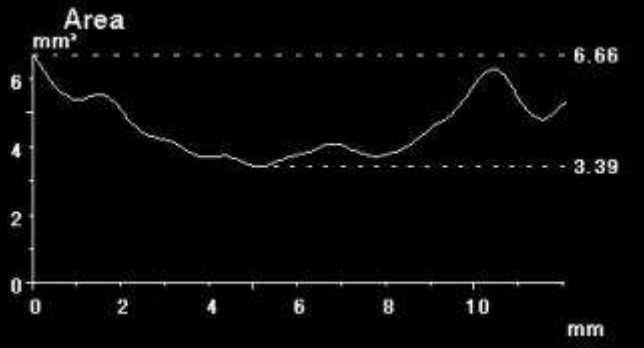






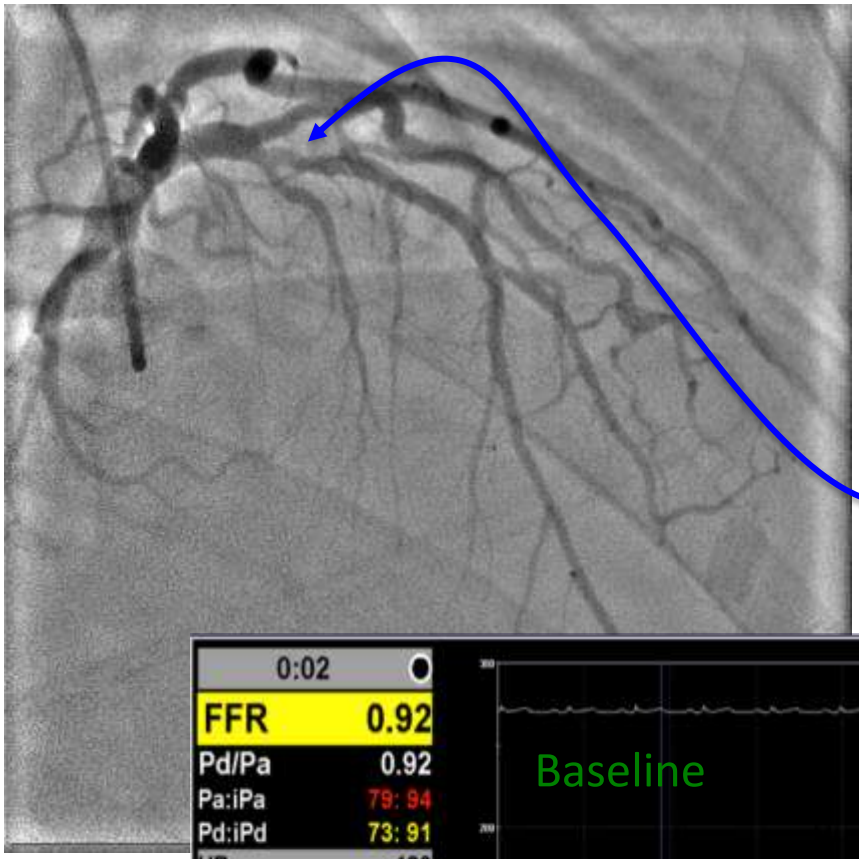




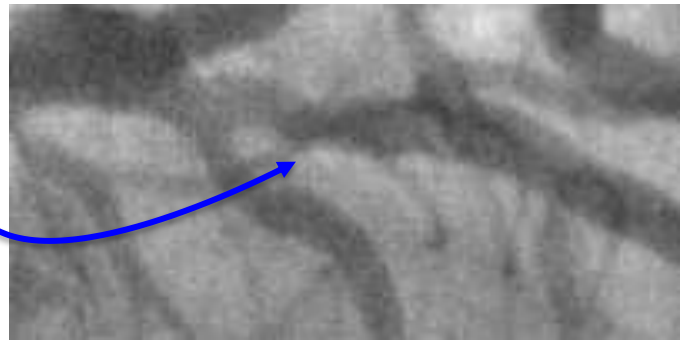


QCA Diagonal showing same measurement

8 months LAD not only patent but positively remodelled and no longer flow limiting



- Moderate lesion at previous CTO site - FFR



indications

- **ISR**
- **de novo**
- **Primary PCI**
- **CTO**

- **Bifurcation**
- **CABG**

D r u g C o a t e d B a l l o o n

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SAVE THE DATE!

15th & 16th AUGUST 2015

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