Bioabsorble stents have a promising future : YES

Jacques Koolen

Catharina Hospital Eindhoven

TCTAP-2012

Background

- **Who wants a corpus alienum in the body ?**
- To treat a diseased vessel, only a temporary mechanical scaffold is needed. Therefore bioabsorbable scaffolds have been developed.
- Bioabsorbable scaffolds temporarily support the vessel and additionally can release a drug similar to a permanent DES.
- During and after the absorption process, these devices change their mechanical scaffolding, the artery becomes uncaged.
- The natural physiology of the artery returns with features like late expansive remodeling, bending flexibility and vasomotion. This is called “Vascular Restoration Therapy (VRT)”.

- This may reduce the risk of late and very late thrombotic events and provide the option for reducing long-term dual antiplatelet therapy.
- In addition, non-invasive imaging of the scaffolded vessel lumen with CT or MRI should become possible.

DREAMS: 1st generation DRug-Eluting Absorbable Metal Scaffold
- Design Overview -

Scaffold Backbone

- Proprietary Mg-alloy
- 120µm strut thickness

Drug carrier

- 1 µm bioabsorbable PLGA Polymer

Delivery system

- Modified PRO-Kinetic Energy
- 6F compatible

Drug

- Paclitaxel
- Proven elution behaviour

BIOSOLVE-I study design

Study objective

Evaluate safety and clinical performance of DREAMS

Study design

Prospective, multi-center, first-in-man trial, single de novo coronary artery lesions with RVD between 3.0 and 3.5 mm and lesion lengtl ≤ 12 mm

Primary endpoint

Cohort 1: TLF* at 6 months
Cohort 2: TLF* at 12 months

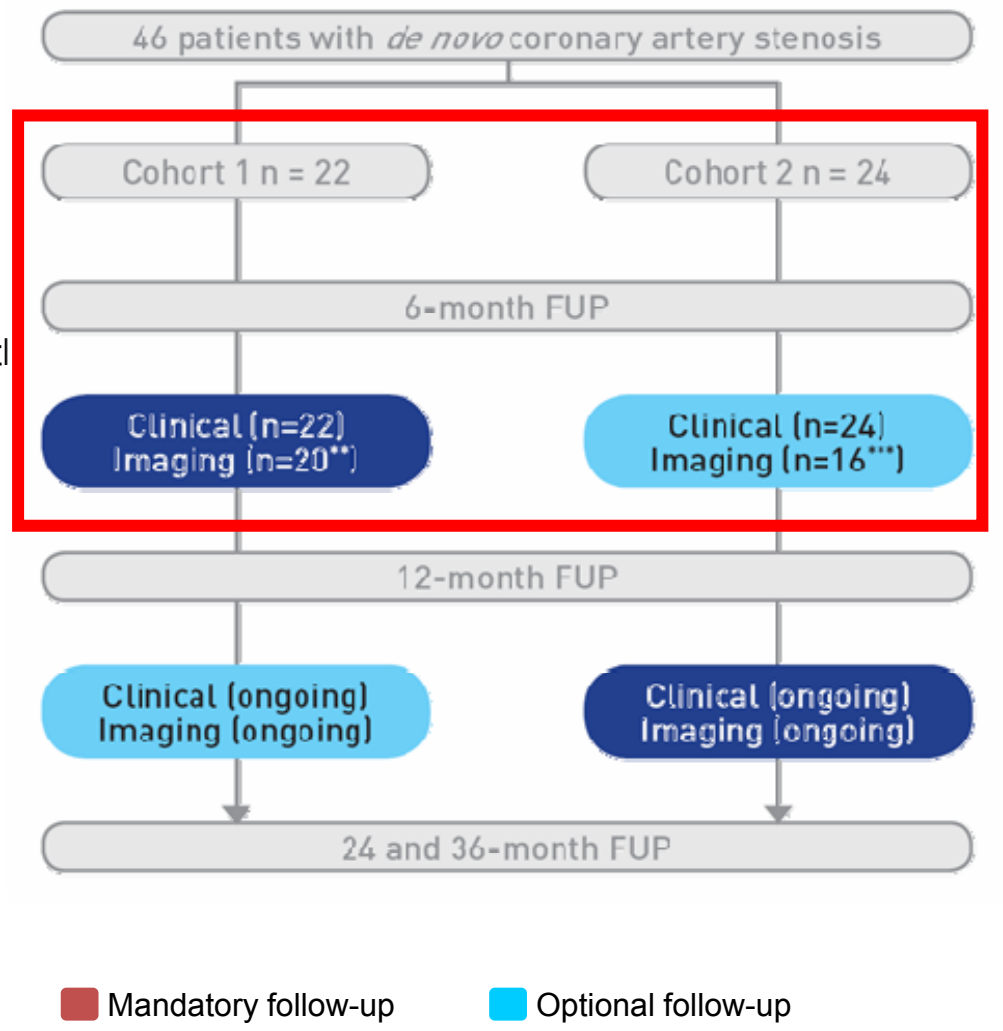
Primary investigator

Jacques Koolen, Catharina Ziekenhuis, Eindhoven, The Netherlands

* Composite of cardiac death, target vessel myocardial infarction and clinically driven TLR

** 2 pts withdrew consent for imaging FUP at 6 months

*** 16 pts from cohort 2 consented for the optional 6-month imaging FUP



Baseline clinical and angiographic characteristics

Cohort 1+2	N=46	
Age (mean ± SD)	**65.3 ± 9.7**	
Men (N/%)	**34**	**73.9 %**
Hypertension	**40**	**87.0 %**
Hyperlipidemia	**41**	**89.1 %**
History of MI	**15**	**32.6 %**
Previous PCI	**27**	**58.7%**
Renal Insufficiency	**12**	**26.1%**
Congestive Heart Failure	**7**	**15.2%**
Diabetes	**7**	**15.2%**
Smoking	**6**	**13.0%**
History of stroke of TIA	**3**	**6.5%**

Pre-Procedure (N=46)	
RVD (mm)	**2.73 ± 0.48**
MLD (mm)	**1.21 ± 0.52**
% Diameter stenosis	**55.9 ± 16.7**
Mean lesion length (mm)	**10.99 ± 4.6**

Procedure (N=46)	
Scaffold length used (mm)	**16**
Scaffold ∅ used (mm)	**3.25 / 3.5**

Procedural and primary endpoints for both cohorts up to 6 months

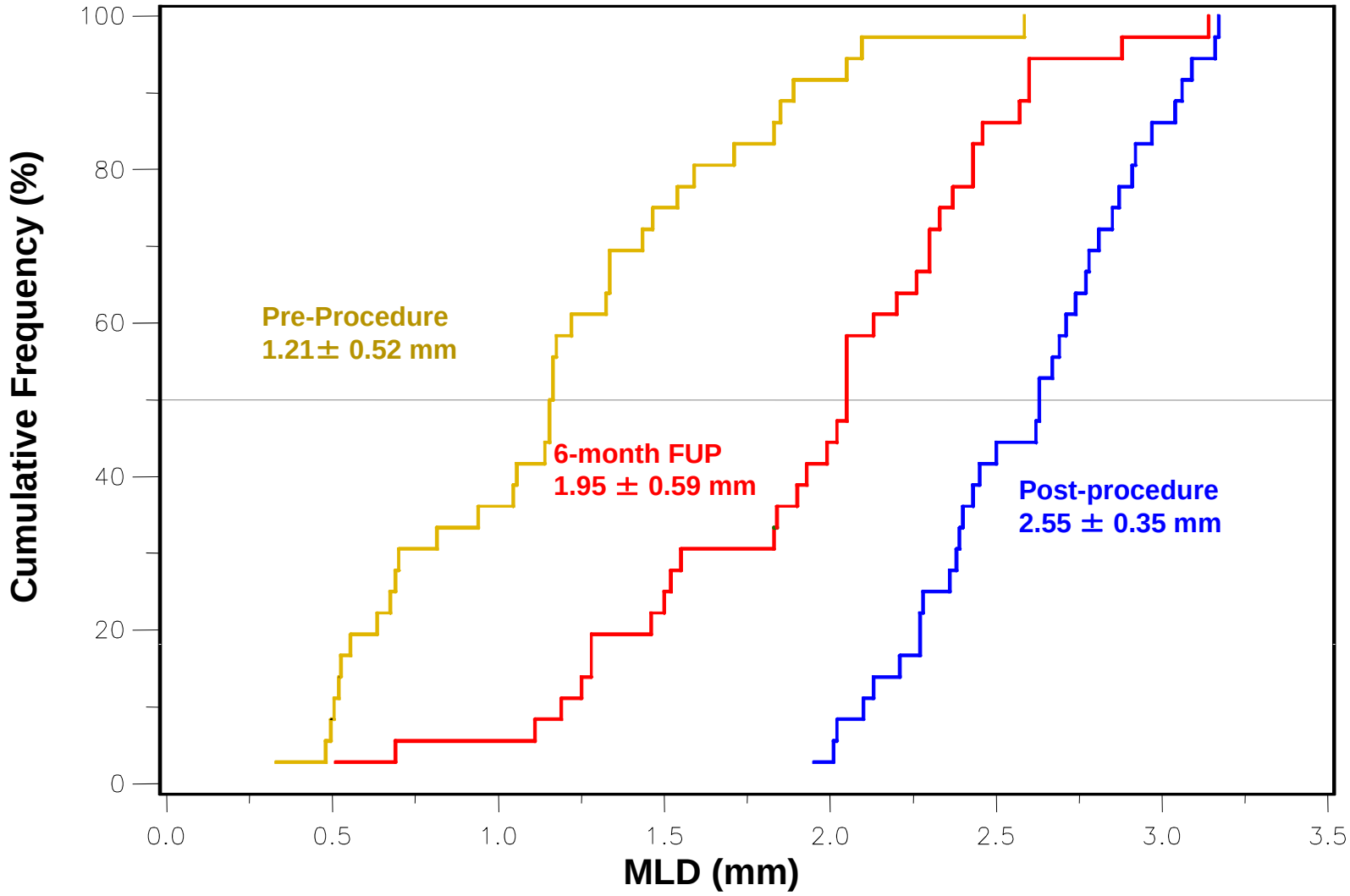
	N	%
Device success*	46	100
Procedural success**	46	100
6-month clinical results	46	100
TLF	2	4.3
Cardiac death	0	0.0
MI	0	0.0
Scaffold thrombosis	0	0.0
TLR (clinically-driven)***	2	4.3

* Defined as:
- successful delivery of the scaffold to the target lesion site in the coronary artery
- appropriate scaffold deployment
- successful removal of delivery system after release of the scaffold
- safe removal of the device in case of deployment failure

** Defined as:
- device success plus attainment of a final residual stenosis of < 50% of the target lesion
- absence of a major adverse cardiac event during the hospital stay to a maximum of first seven days post procedure

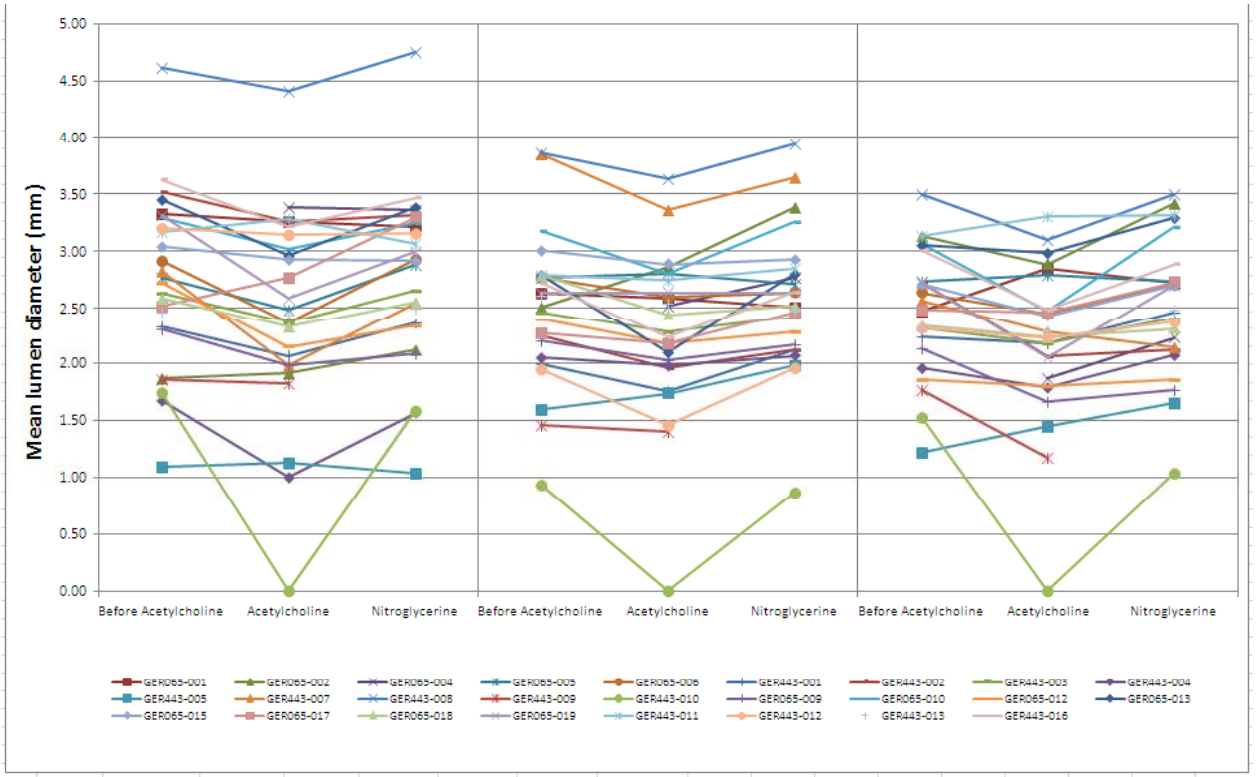
*** TLR occurred during 6 M FUP, both pts had angina, 1 pt received an additional DREAMS in the target lesion during the initial procedure because of a flow-limiting bailout situation

Cumulative frequency of in-scaffold Minimal Lumen Diameter



Vasomotion result - Cohort 1+2 (n=26)

	Proximal Segment	Scaffolded Segment	Distal Segment
	P=0.370	P=0.710	P=0.744
Mean	2.76 _____ 2.47 _____ 2.78	2.50 _____ 2.30 _____ 2.57	2.48 _____ 2.21 _____ 2.51
	p=0.001 p=0.001	p=0.001 p=0.001	p=0.003 p=0.0001



*All p values are paired t-tests between time points (top: Before Acetylcholine and Nitroglycerine, Bottom left: Before Acetylcholine and Acetylcholine, Bottom Right: Acetylcholine and Nitroglycerine), no multiple comparison adjustment was made in this figure.

Conclusions

- The DREAMS device demonstrates an excellent safety profile without death, MI, or scaffold thrombosis at 6 months
- A TLF rate of 4.3% at 6 months after DREAMS implantation is comparable to permanent DES
- DREAMS demonstrated significantly improved efficacy compared to the bare AMS:

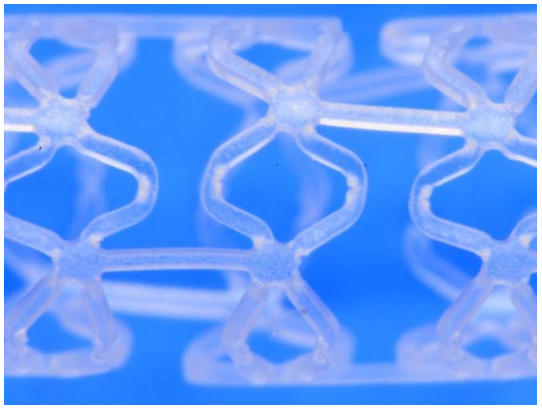
  Reduction in LLL of 41% (1.08 vs. 0.64mm)

  Reduction of TLR rate by 82% (23.8 vs 4.3%
- Future directions: continued improvement in design, markers and moving to a Limus drug

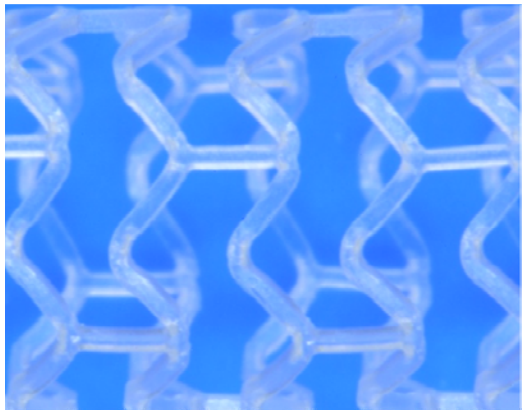
Background

The scaffold was improved by modified polymer processing and by design change so that the Cohort B device provides more uniform vessel support and for a longer duration

The scaffold used in Cohort A

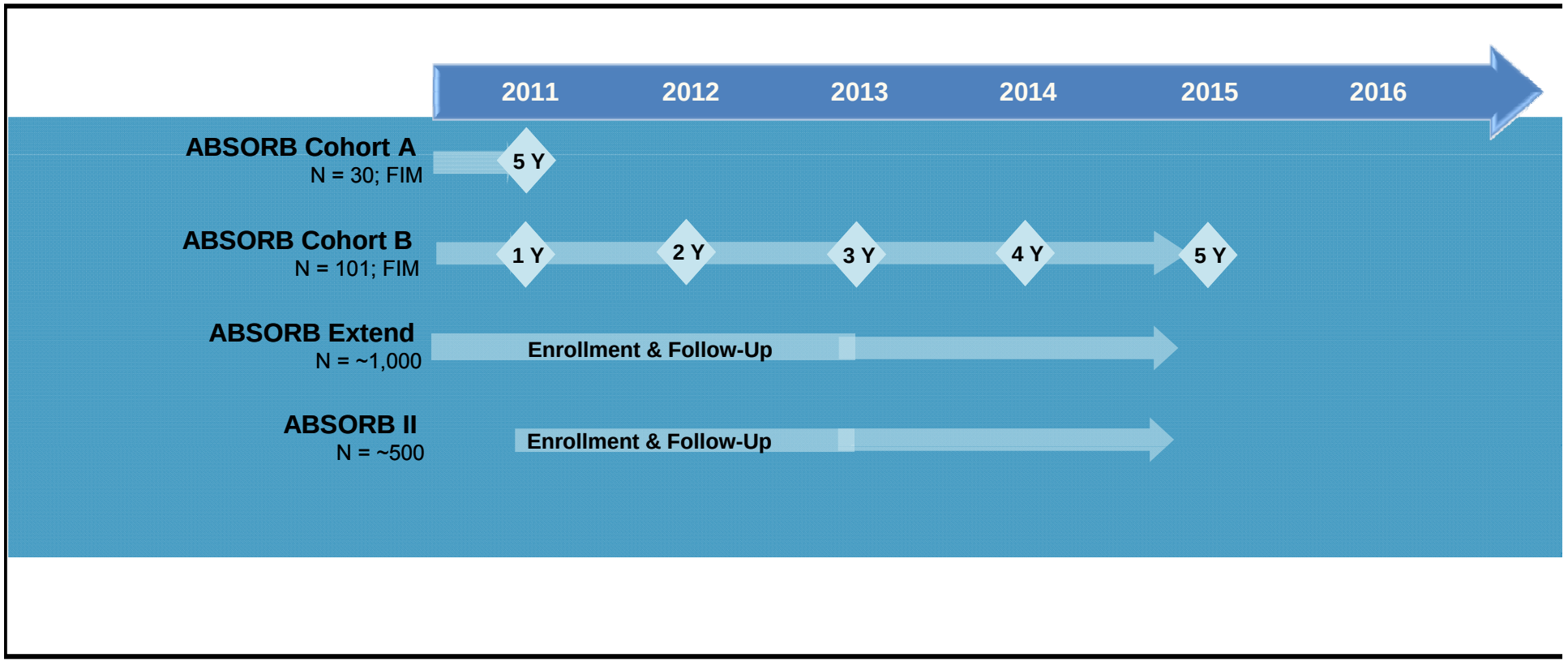


Improved scaffold Cohort B



The Cohort B scaffold elutes the same drug (everolimus) with the same dose and rate as that used for Cohort A

The ABSORB Clinical Trial Program



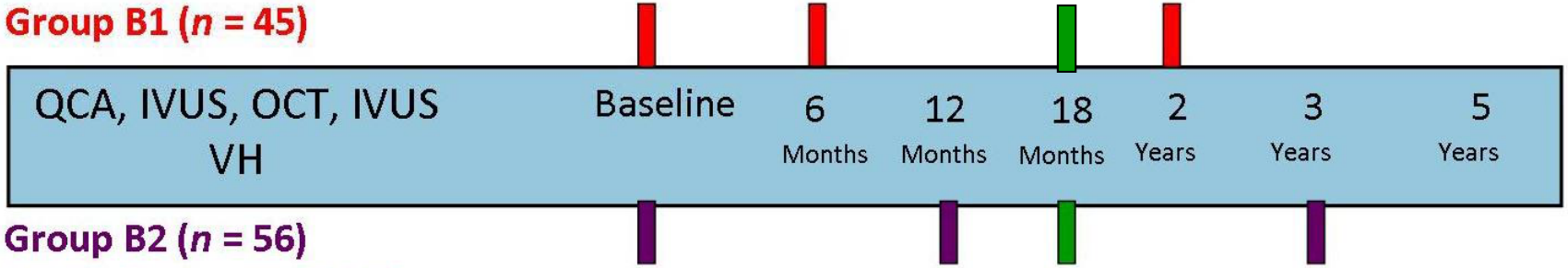
ABSORB A - 5 Year Clinical Results

Hierarchical	6 Months 30 Patients	12 Months 29 Patients*	4 Years 29 Patients*	5 Years 29 Patients*
Ischemia Driven MACE, %(n)	3.3% (1)**	3.4% (1)**	3.4% (1)**	3.4% (1)**
Cardiac Death, %	0.0%	0.0%	0.0%	0.0%
MI, %(n)				
Q-Wave MI	0.0%	0.0%	0.0%	0.0%
Non Q-Wave MI	3.3% (1)**	3.4% (1)**	3.4% (1)**	3.4% (1)**
Ischemia Driven TLR , %				
by PCI	0.0%	0.0%	0.0%	0.0%
by CABG	0.0%	0.0%	0.0%	0.0%

No new MACE events between 6 months and 5 years
No scaffold thrombosis up to 5 years

*One patient withdrew consent after 6 months
**This patient also underwent a TLR, not qualified as ID-TLR (DS = 42%) followed by post-procedural troponin qualified as non-Q MI and died from his Hodgkin's disease at 888 days post-procedure.

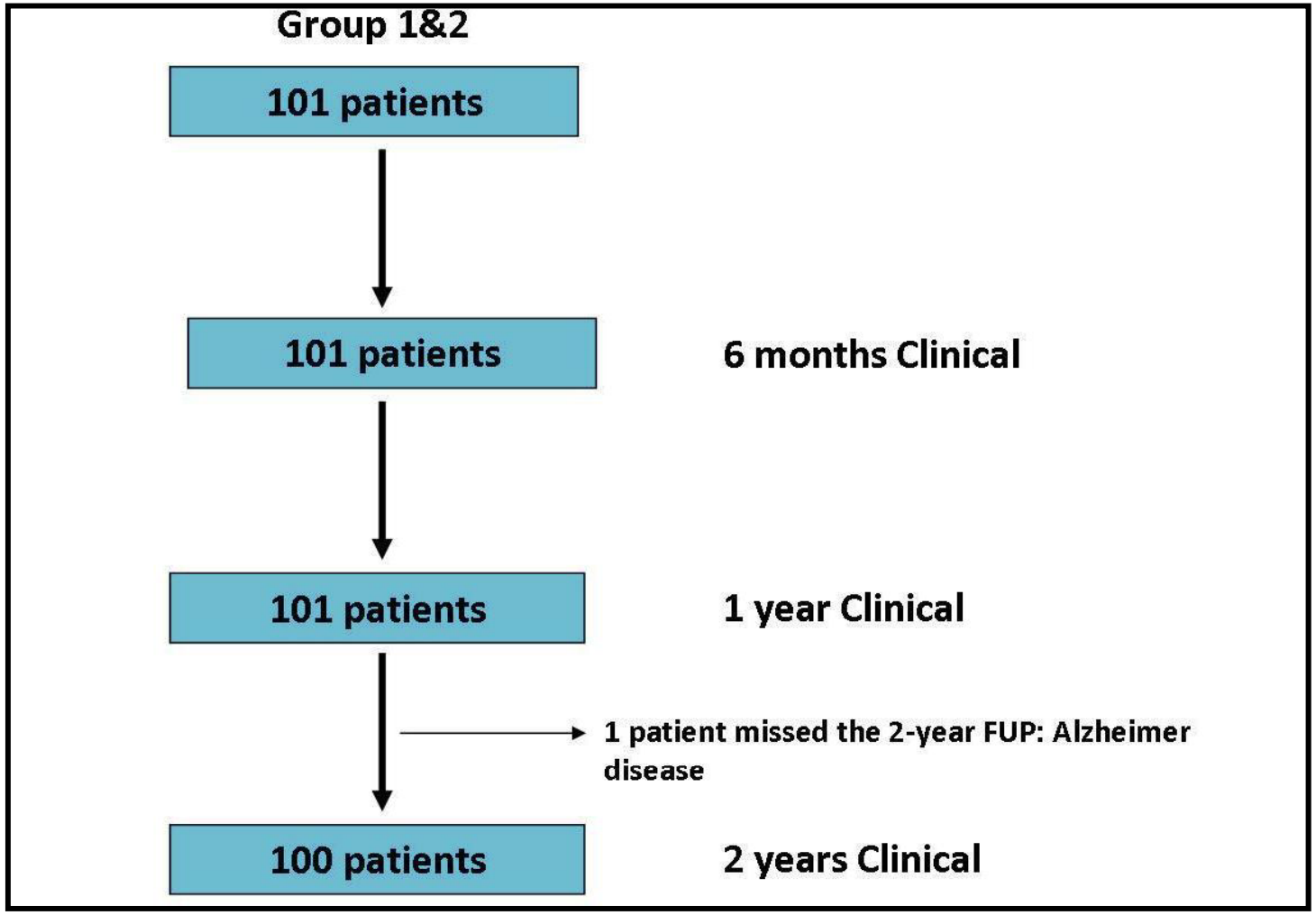
ABSORB B – Trial Design



- Sponsor: Abbott Vascular
- Primary Investigators:
  - PW Serruys MD, PhD
  - J Ormiston MD
- DSMB: J Tijssen PhD, M Wiemer MD, P Urban MD
- CEC: C Hanet MD, R Tölg MD, V Umans MD
- Angiographic, IVUS and OCT Corelab: Cardialysis
- Prospective, open label, FIM
- 3.0 x 18mm devices to treat up to 2 lesions ≤ 14mm in length

- 12 sites Europe, Australia, New Zealand
- B de Bruyne, MD
- R van Geuns, MD
- J Ormiston, MD
- D Dudek, MD
- L Thuesen, MD
- P Smits, MD
- B Chevalier, MD
- D McClean, MD
- J Koolen, MD
- S Windecker, MD
- R Whitbourn, MD
- I Meredith, MD, PhD
- 101 patients enrolled between 19 Mar - 6 Nov 09

ABSORB B - Patient Inclusion



ABSORB B - Baseline Demographics

	Group 1 & 2 n = 101
Male (%)	72
Mean age (years)	62
Previous MI (%)	25
Prior Cardiac Intervention on Target Vessel (%)	6
Diabetes mellitus (%)	17
Hypercholesterolemia req. med. (%)	78
Hypertension req. med. (%)	62
Current smoker (%)	17

ABSORB B
Lesion Characteristics/Acute Success

	N = 101 $N_{Lesions}$ = 102
Location of lesion (%)	
LAD	43
RCA	33
LCX	23
Ramus	1
Lesion classification (%)	
A	1
B1	55
B2	40
C	4
Clinical Device success (%)	**100**
Clinical Procedure success (%)	**98**

Clinical Device Success = Successful delivery & deployment of the BVS at intended target lesion & successful withdrawal of the BVS delivery system w/ attainment of final residual stenosis of less than 50% of the target lesion by QCA (by visual estimation if QCA unavailable). Standard pre-dilation catheters & post-dilatation catheters (if applicable) may be used. Bailout patients will be included as device success only if the above criteria for clinical device are met.

Clinical Procedure Success = Same as definition above and/or using any adjunctive device without occurrence of ischemia driven major adverse cardiac event (MACE) during the hospital stay w/ a maximum of first seven days post index procedure.

ABSORB B Group 1&2
Clinical Results - Intent to treat

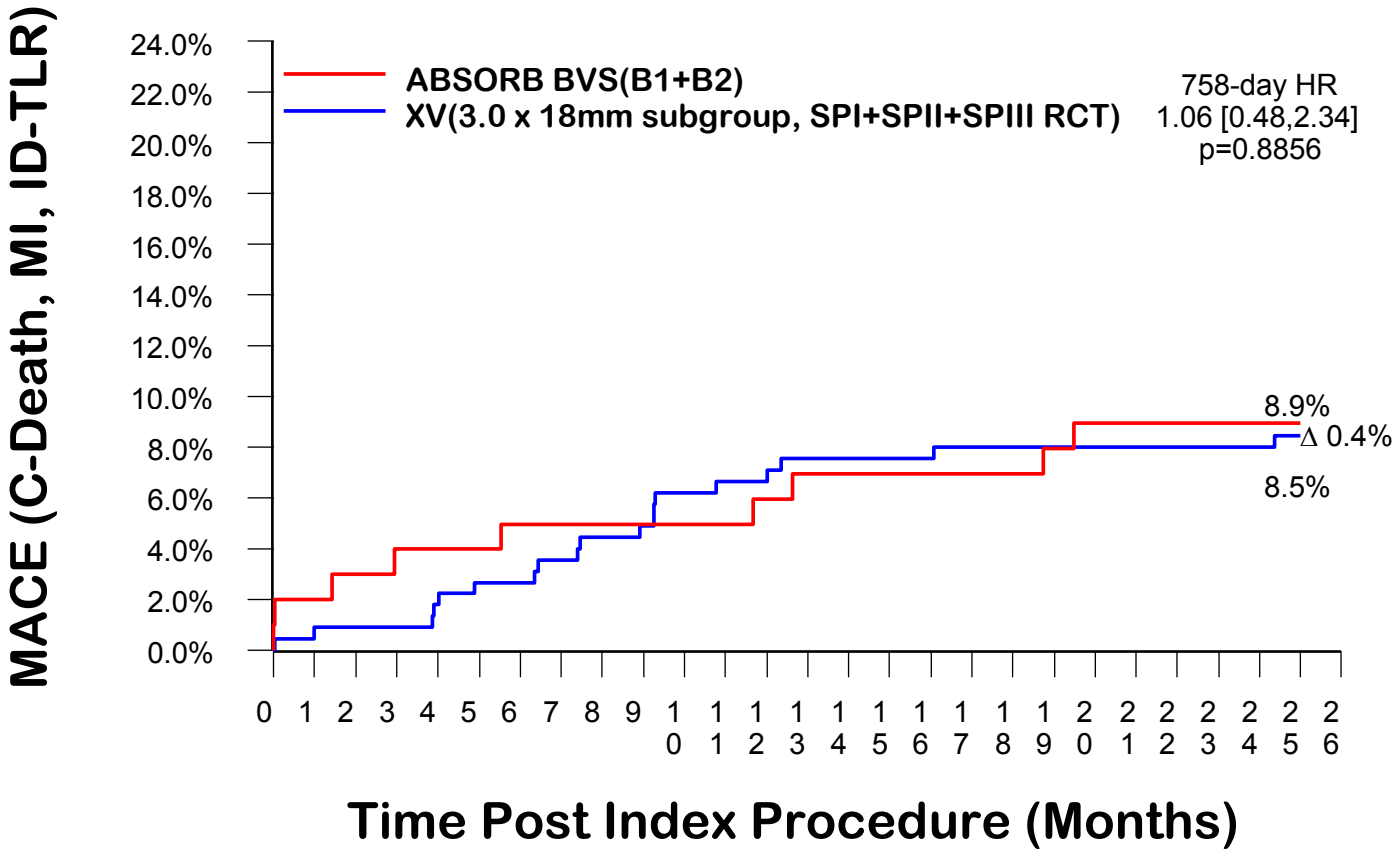
Non-Hierarchical	30 Days N = 101	6 Months N = 101	1 Year N = 101	2 Years N = 100*
Cardiac Death %	0	0	0	0
Myocardial Infarction % (n)	2.0 (2)	3.0 (3)	3.0 (3)	3.0 (3)
Q-wave MI	0	0	0	0
Non Q-wave MI	2.0 (2)	3.0 (3)	3.0 (3)	3.0 (3)
Ischemia driven TLR % (n)	0	2.0 (2)	4.0 (4)	6.0 (6)
CABG	0	0	0	0
PCI	0	2.0 (2)	4.0 (4)	6.0 (6)
Hierarchical MACE % (n)	2.0 (2)	5.0 (5)	6.9 (7)	9.0 (9)

*One patient missed the 2-year FUP

No scaffold thrombosis by ARC or Protocol out to 2-Year
Only 2 additional TLR events between 1 year and 2 years

MACE: Cardiac death, MI, ischemia-driven TLR
TVF: Cardiac death, MI, ischemia-driven TLR, ischemia-driven TVR

KM estimate of MACE rate in patients treated with Absorb BVS (ABSORB Cohort B, n=101) vs. patients treated with a single 3x 18 mm metallic XIENCE V (SPIRIT First+II+III, n=227)



	0	194	393	758
ABSORB BVS(B1+B2) At Risk	101	96	94	91
XV(3.0 x 18mm subgroup, SPI+SPII+SPIII RCT) At Risk	227	219	204	191

- Absorbable stents are as good as DES stents in up to 5 years follow-up.
- The limitation is in the manufacturing process
- Untill now limited sizes and lenght are available and thus mainly relative simple lesions have been treated
- The systems and manufacturing process will be improved further

Conclusion

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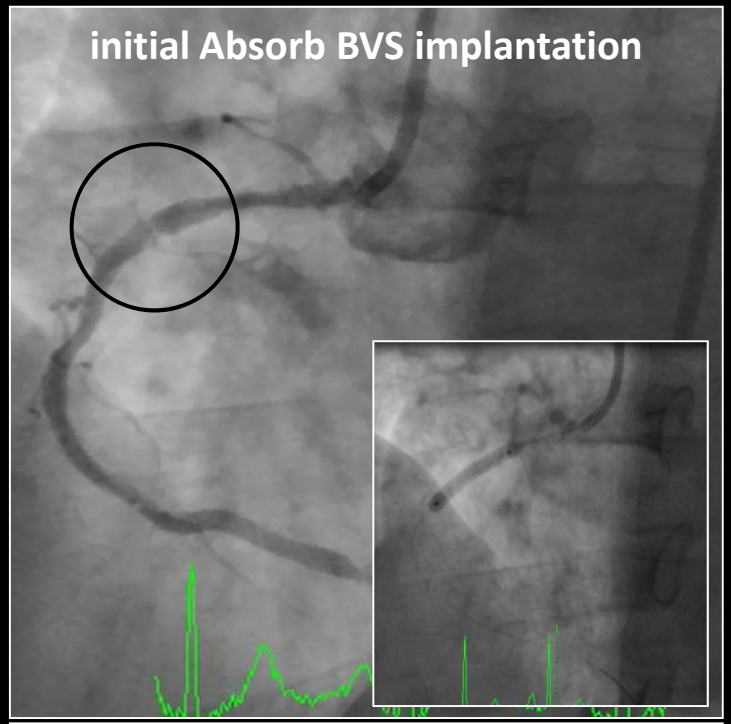
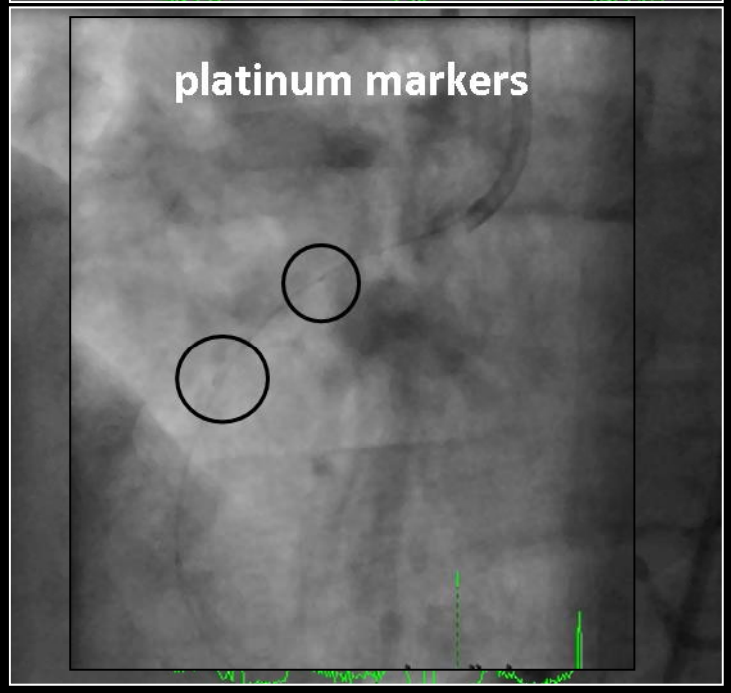




ID-TLR # 5:

The patient experienced UA on day 363

Angio:

1. **patent Absorb BVS**
2. 60% DS distal LM
3. 80% DS ostial LCx
4. 70% DS ostial RCA

} CABG with 3 grafts (day 439)

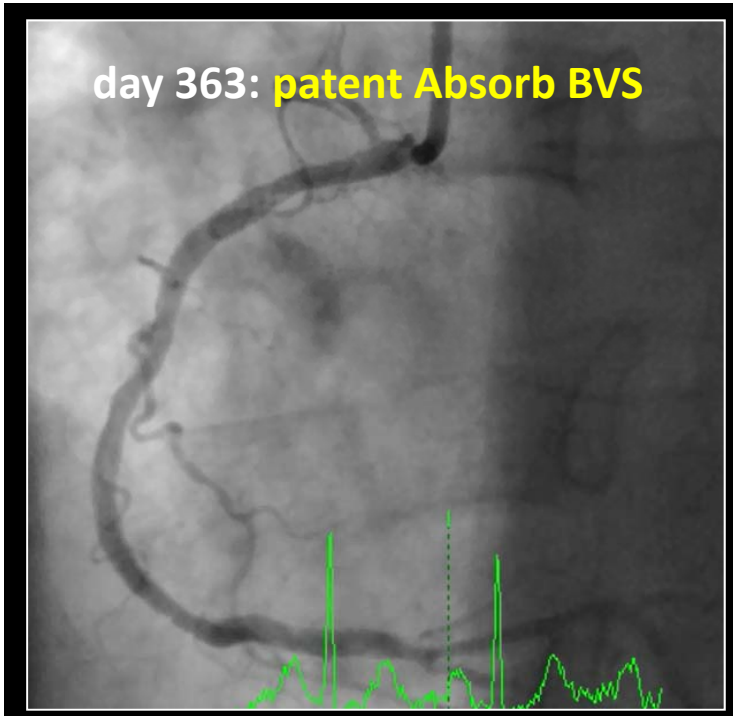
The patient experienced UA on day 590

Angio:

1. 16% DS prox RCA
2. 60% DS mid-RCA

Revascularization with 4.0 x 38 mm Promus Element across the mid-RCA lesion, at the edge of the Absorb BVS

SE2936417 Rev. A
Absorb BVS is neither approved nor available for sale in the U.S.
Note: Absorb BVS is currently CE marked. Information provided for educational purposes only.



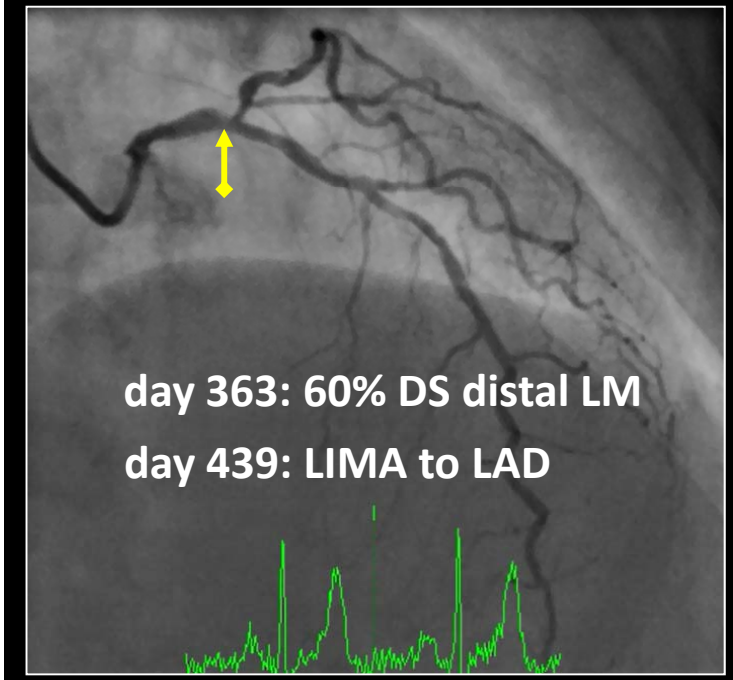
ID-TLR # 5:

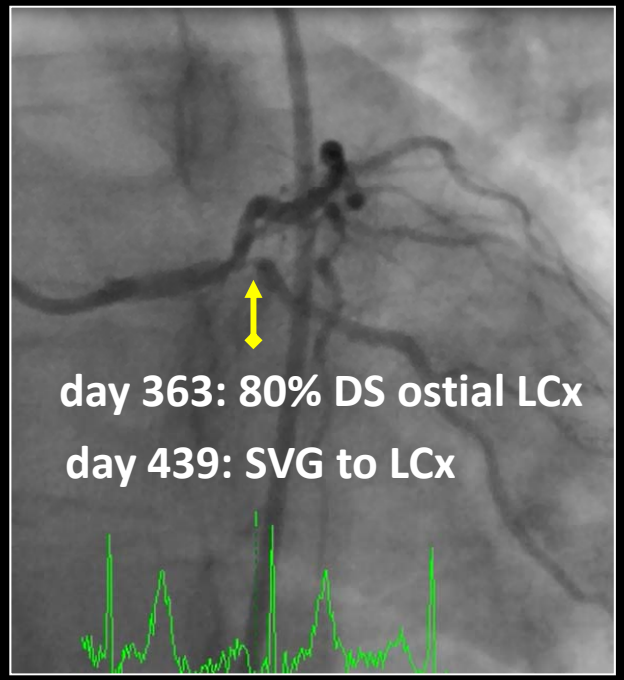
The patient experienced UA on day 363

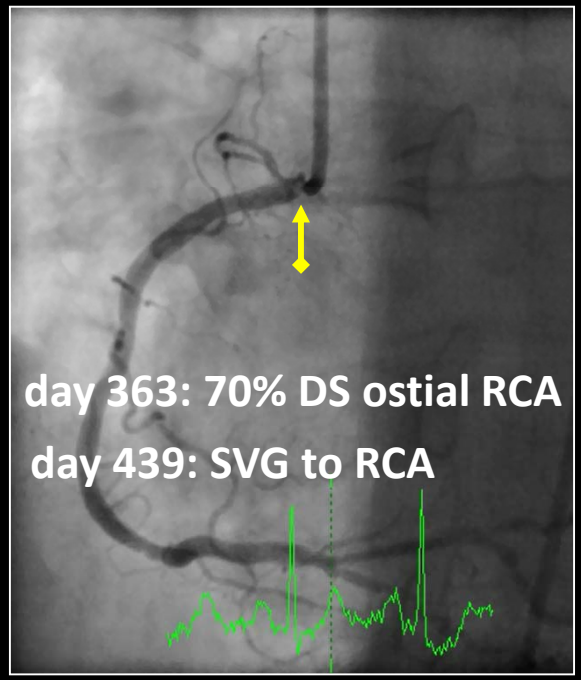
Angio:

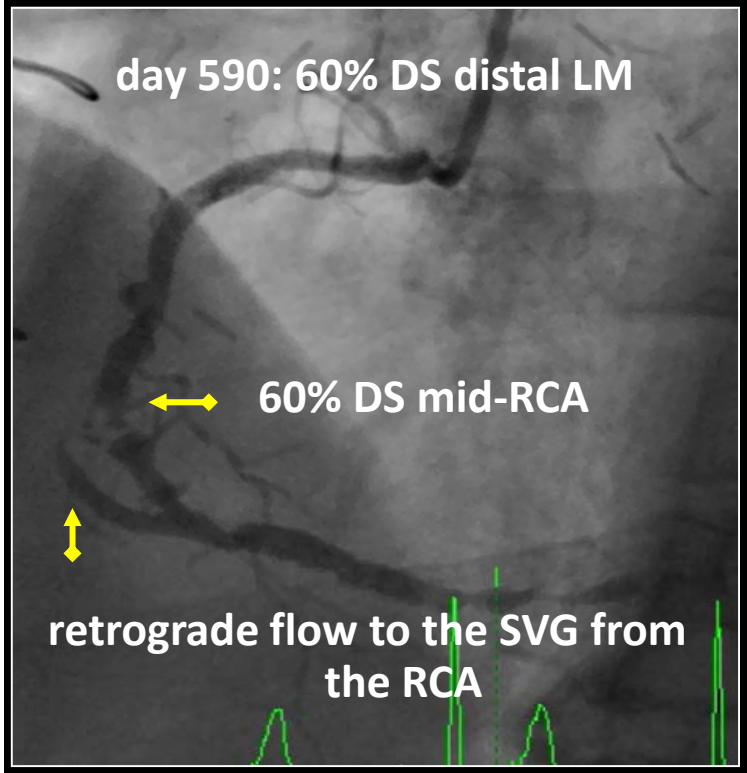
1. patent Absorb BVS
2. 60% DS distal LM
3. 80% DS ostial LCx
4. 70% DS ostial RCA

} CABG with 3 grafts (day 439)









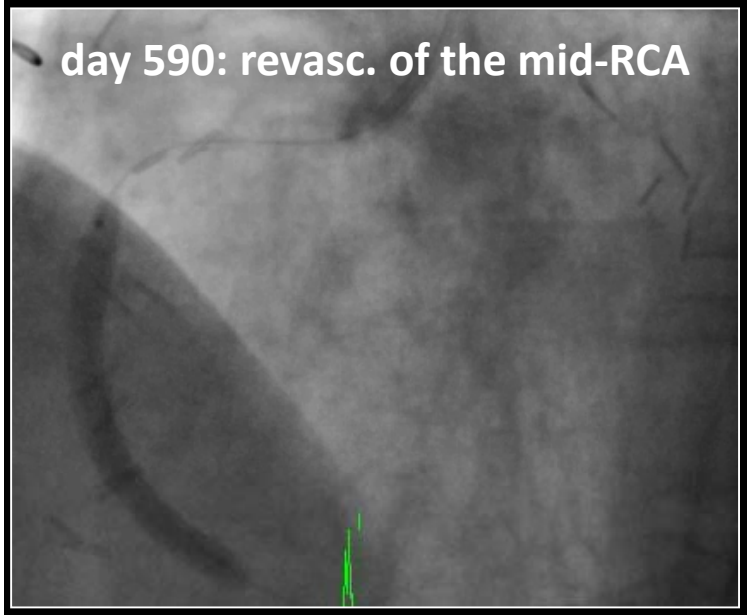
ID-TLR # 5:

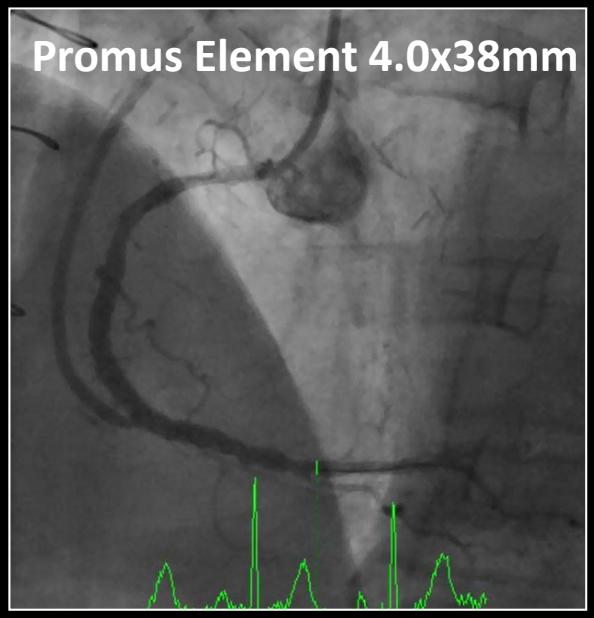
The patient experienced UA on day 590

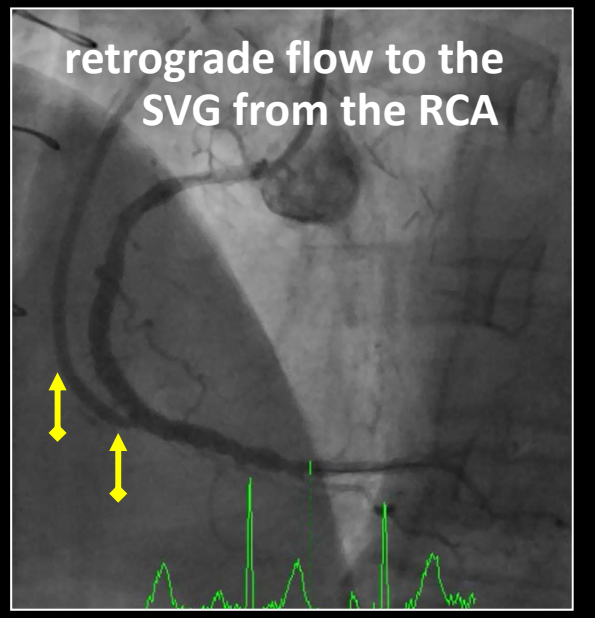
Angio:

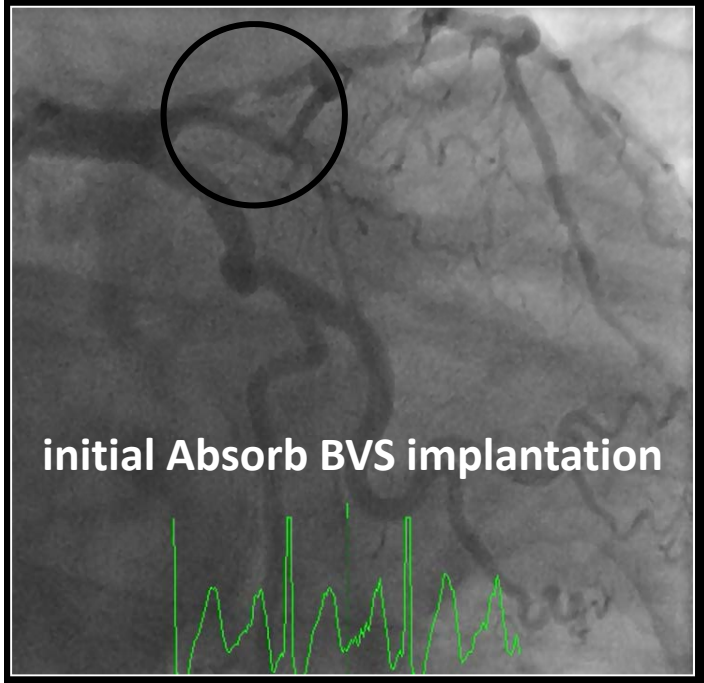
1. 16% DS prox RCA
2. 60% DS mid-RCA

Revascularization with 4.0 x 38 mm Promus Element across the mid-RCA lesion, at the edge of the Absorb BVS









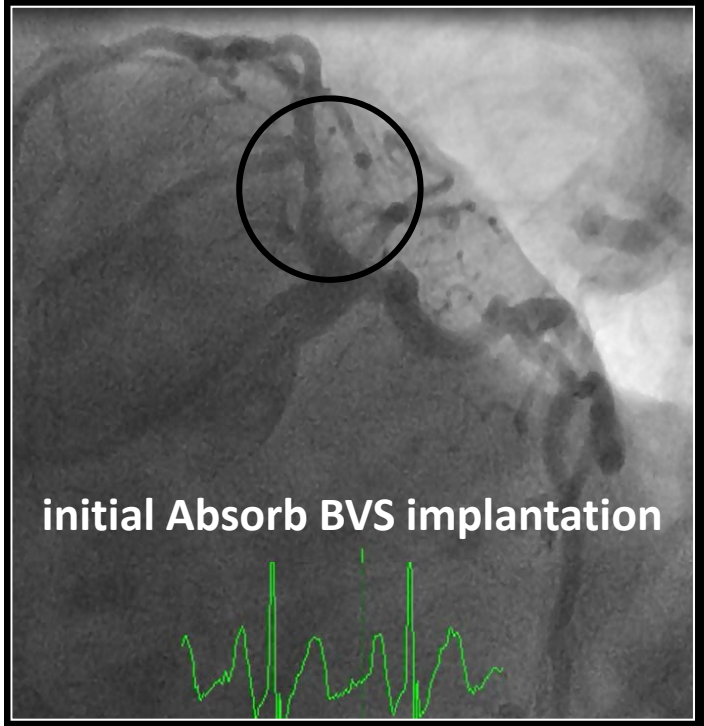
ID-TLR # 6:

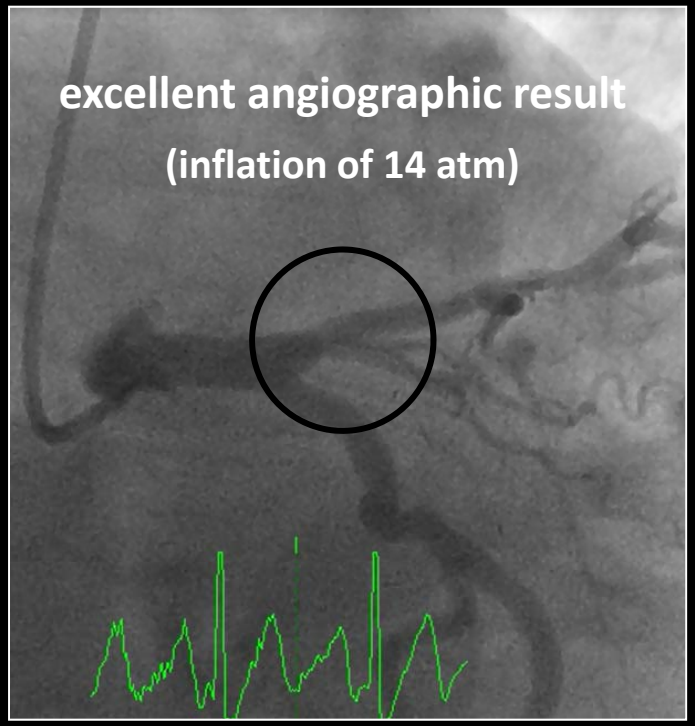
The patient experienced UA on day 564

Angio: (day 567)

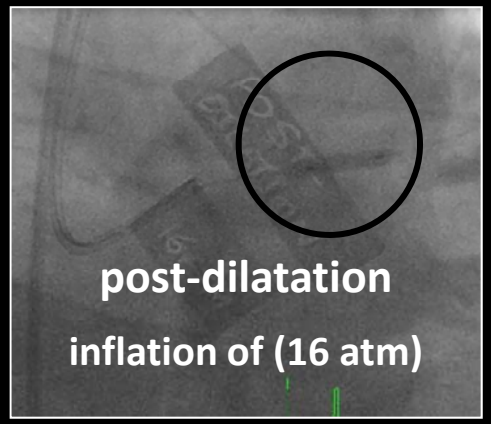
1. 74% DS in-scaffold restenosis in proximal LAD with no thrombosis or occlusion. Troponin was elevated with a peak value of 1.66 ng/ml (ULN 0.04 ng/ml) with normal CK.

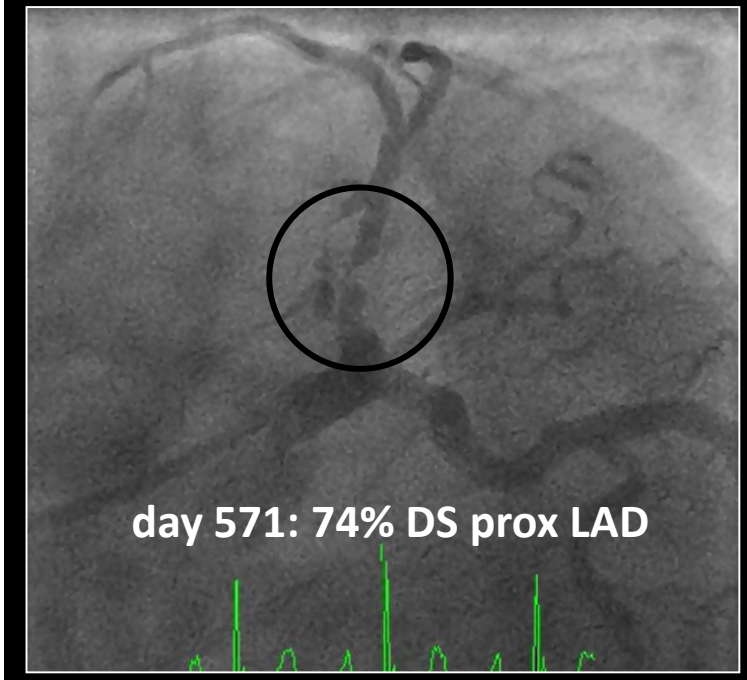
Revascularization on day 571, with 3.0 x 18 mm XIENCE V





potential axial geographical miss?





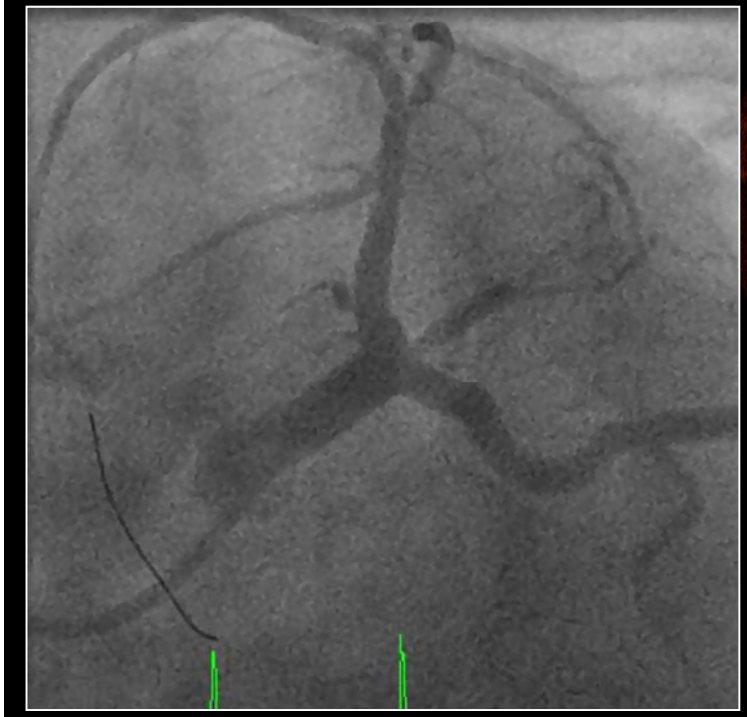
ID-TLR # 6:

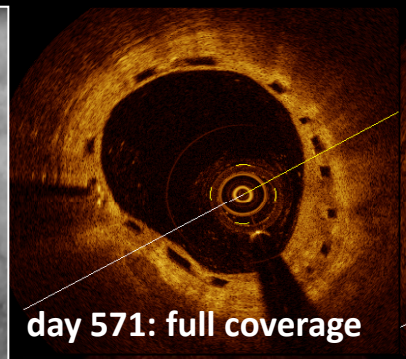
The patient experienced UA on day 564

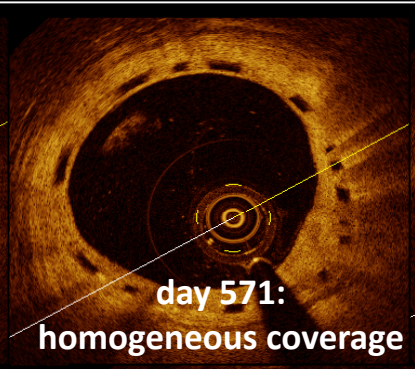
Angio: (day 567)

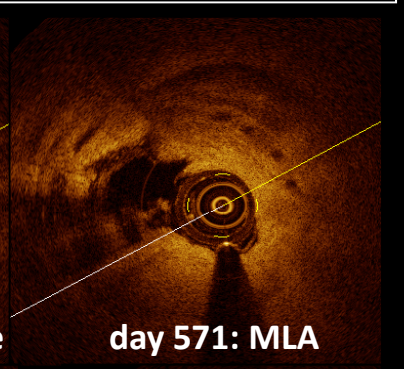
1. 74% DS in-scaffold restenosis in proximal LAD with no thrombosis or occlusion. Troponin was elevated with a peak value of 1.66 ng/ml (ULN 0.04 ng/ml) with normal CK.

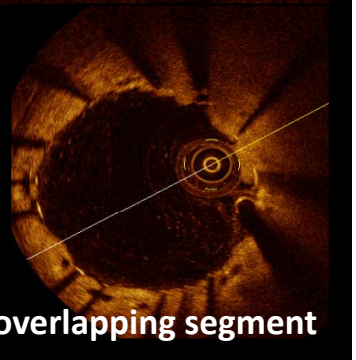
Revascularization on day 571, with 3.0 x 18 mm XIENCE V











Baseline Demographics Absorb BVS (ABSORB Cohort B, n=101) vs. patients treated with a single 3x 18 mm metallic XIENCE V (SPIRIT First+II+III, n=227)

	ABSORB B n = 101	XV (SPI + SPII + SPIII RCT) n = 227
Male (%)	72	64
Mean age (years)	62	64
Previous MI (%)	25	23
Diabetes mellitus (%)	17	26
Hypercholesterolemia req. med. (%)	78	73
Hypertension req. med. (%)	62	74*
Current smoker (%)	17	25

*p=0.05

Baseline Lesion Characteristics Absorb BVS (ABSORB Cohort B, n=101) vs. patients treated with a single 3x 18 mm metallic XIENCE V (SPIRIT First+II+III, n=227)

	ABSORB B N = 101 $N_{Lesions}$ = 102	XV (SPI + SPII + SPIII RCT) N = 227 $N_{Lesions}$ = 227
Location of lesion (%)		
LAD	43	55
RCA	33	21*
LCX	23	25
Ramus	1	0
Lesion classification (%)		
A	1	5
B1	55	45
B2	40	47
C	4	3

*p=0.02

Back-up Slides

ABSORB Cohort B, Adverse Events

3 NQMI

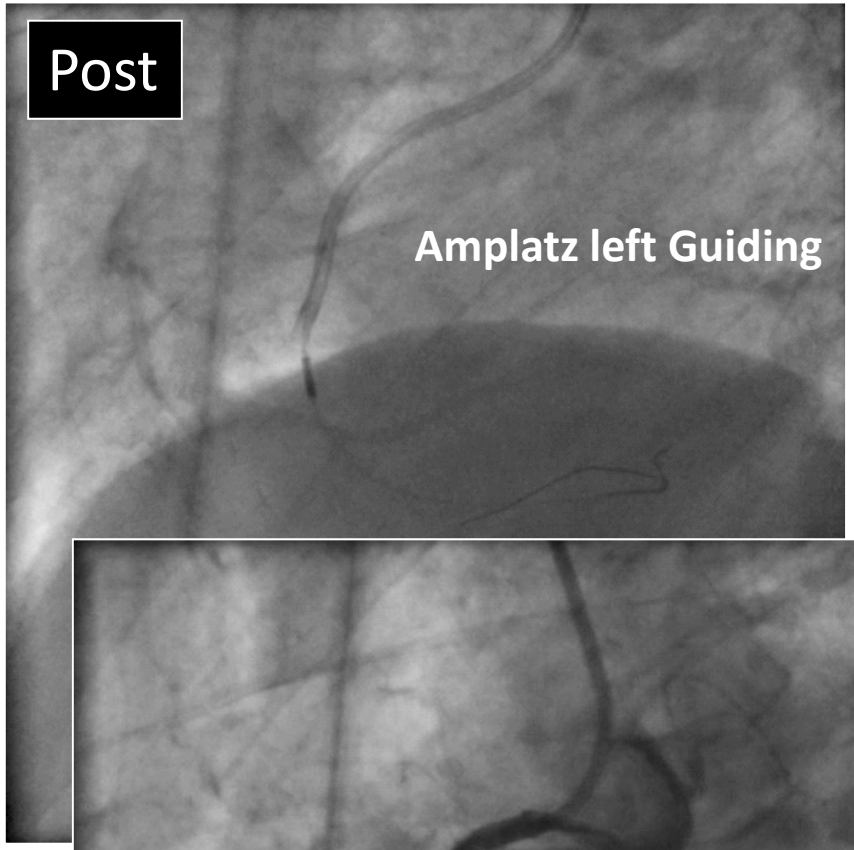
- #1 (Group 1): edge dissection requiring everolimus eluting stent; enzyme bump on day 1 post-procedure (Troponin 0.8 ng/ml, CK 521 U/L (ULN = 180), and CKMB 48 U/L (ULN = 4))
- #2 (Group 2): dissection following pre-dilatation which persisted after scaffold deployment, left alone; enzyme bump on day 1 post-procedure (Troponin 0.81 µg/L, CK 667 U/L (ULN = 150), CKMB 97.2 ng/ml (ULN = 4)
- #3 (Group 2): patient experienced unstable angina on day 43 post-procedure, repeat angio performed, during IVUS a thrombus (inadequate anticoagulation) formed on the guidewire – ruled iatrogenic thrombus with ECG changes and enzyme bump (Troponin 2.9 ng/ml , CK 300 U/L (ULN = 170), CKMB 40 U/L (ULN = 30))

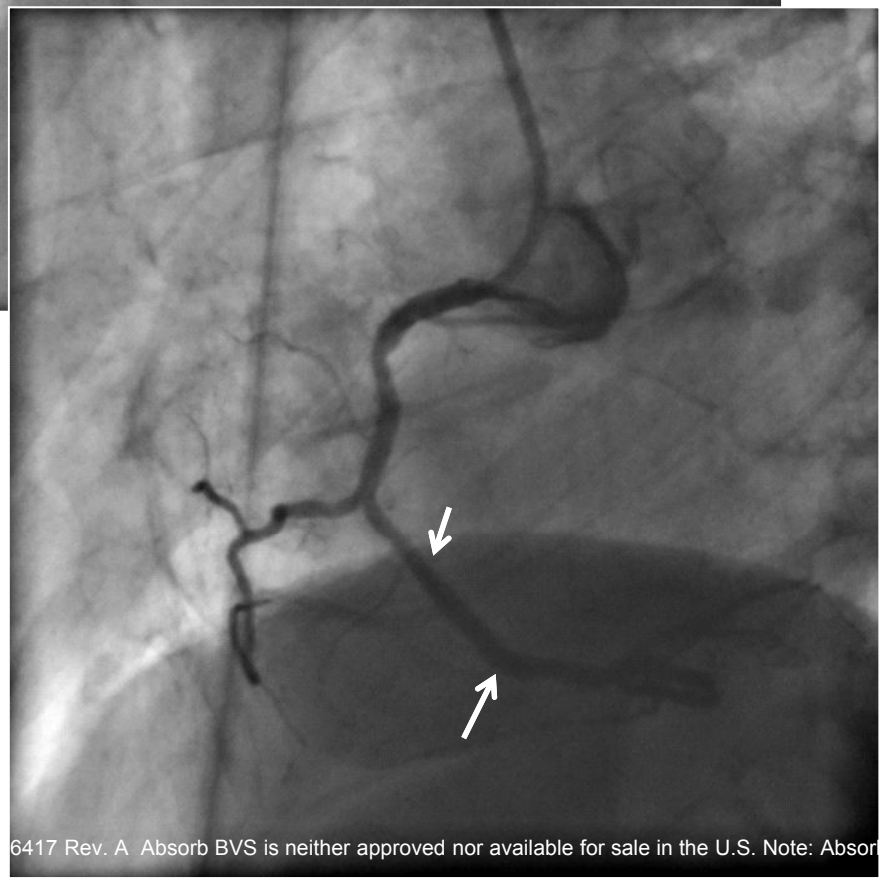
ABSORB Cohort B, Adverse Events

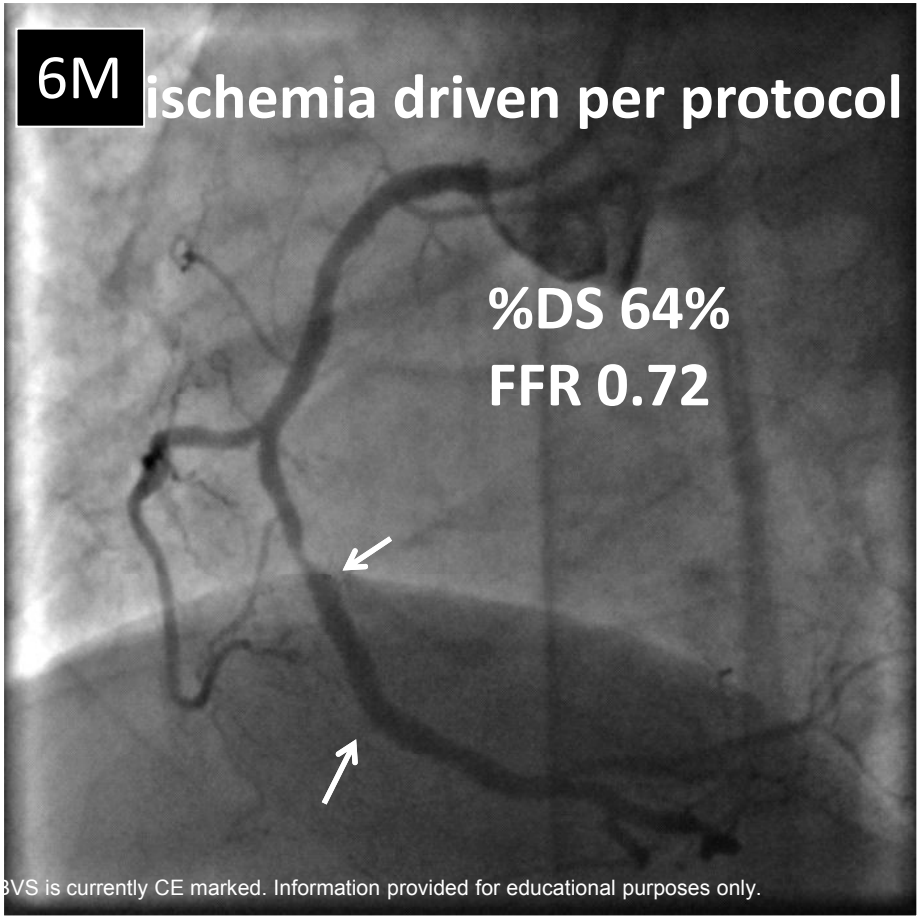
6 ID-TLR

- #1 (Group 1): patient returned on day 168 post-procedure with angina, found to have a mid-RCA stenosis extending into the proximal end of the target lesion, treated with XIENCE V – restenosis thought to be caused by vessel injury caused by deep seating of the guiding catheter during the index procedure to facilitate passing the IVUS catheter
- #2 (Group 2): patient experienced angina on day 59 post-procedure, came back for an angiogram on day 89; found to have a diffuse mid-LAD lesion extending into the proximal portion of the scaffold – core lab determined this was a myocardial bridge
- #3 (Group 1): during index procedure, scaffold deployment resulted in plaque shift that occluded the first diagonal branch; branch was opened with PTCA; patient returned on day 358 post procedure with progressive angina, angiography on day 383 noted sub-total stenosis proximal to the scaffold, revascularized with XIENCE V – restenosis thought to be related to vessel injury caused during recanalization of occluded diagonal branch
- #4 (Group 2): patient hospitalized on day 353 post-procedure due to stable angina CCS Class III with elevation of troponin (0.3µg/L, ULN=0.03µg/L), normal CK (89U/L, ULN=200U/L) and normal CK-MB (5.4µg/L, ULN=6.73µg/L). Angiography on day 354 noted intra-stent stenosis (64% corelab assessed) at the target lesion, revascularized with XIENCE V
- #5 (Group 2): patient experienced unstable angina on day 363 post-procedure, angiography revealed a patent study Absorb BVS, 60% DS lesion distal LMCA, 80% DS ostial lesion LCX and a 70% DS ostial lesion RCA. No intervention performed, patient referred for cardiac surgical fup. On Day 439, patient underwent CABG with SVG to distal RCA and proximal LCX, and LIMA to mid LAD. A left ICA endarterectomy was performed for critical stenosis without symptoms. On Day 590, patient hospitalized due to unstable angina with elevated CK-MB 25 U/L (ULN 24 U/L). Angiography revealed core lab assessed 16% DS lesion in proximal RCA and 60% DS lesion in mid RCA. On Day 591, revascularization with 4.0 x 38 mm PROMUS Element across the lesion in mid RCA (CASS # 2) on the edge of Absorb BVS (CASS #1) with good results confirmed by IVUS
- #6 (Group 2): Angiography on Day 346 (1-year imaging FUP): Absorb BVS in proximal LAD widely patent with a mild area of disease in mid LAD distal to scaffolded segment. IVUS and OCT showed the scaffold to be well apposed and expanded with thin neo-intimal coverage. On Day 564, patient hospitalized with unstable angina. Angiography performed on Day 567 noted a corelab assessed 74% DS in-scaffold restenosis in proximal LAD (CASS #12) with no thrombosis or occlusion. Troponin was elevated with a peak value of 1.66 ng/ml (ULN 0.04 ng/ml) with normal CK. On Day 571, patient underwent PCI revascularization with XIENCE V with good results

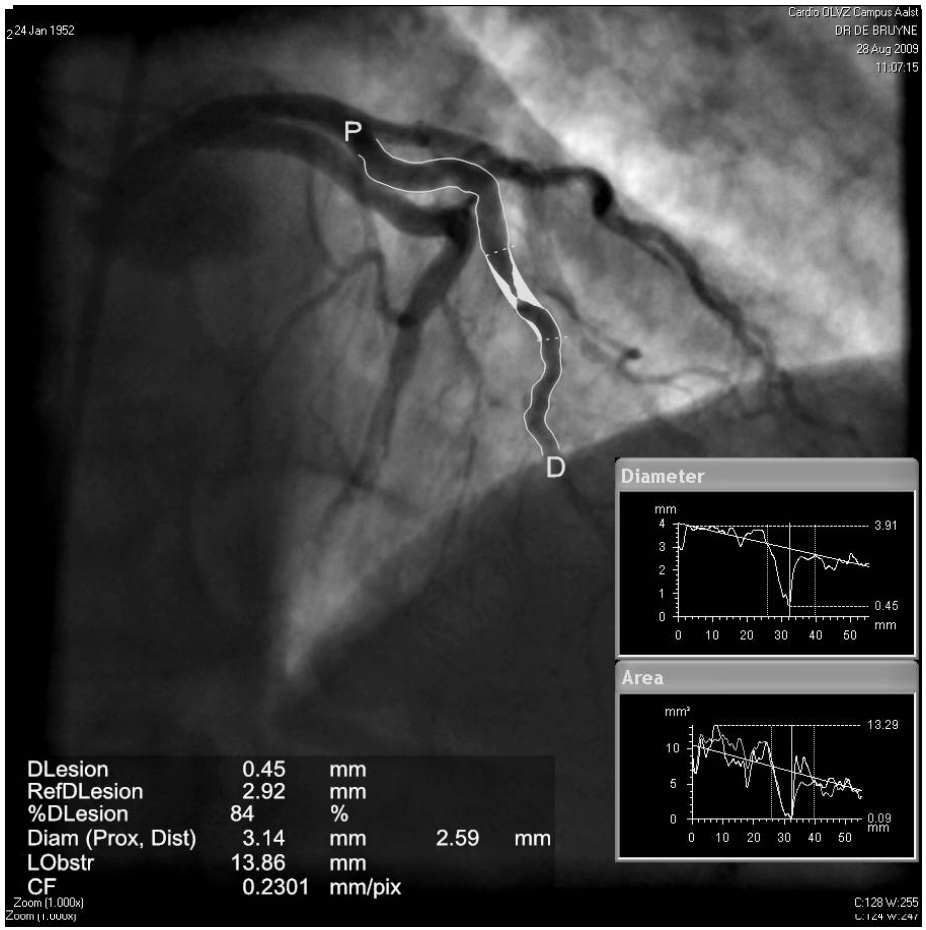
ID-TLR #1:

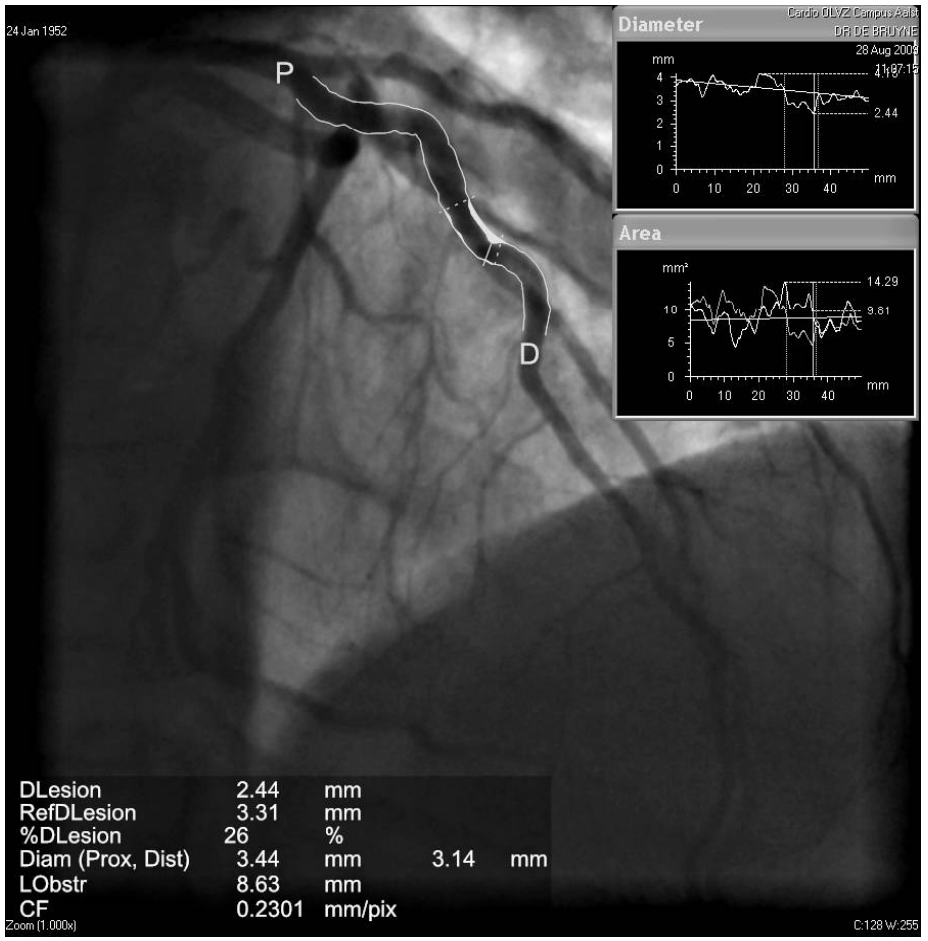






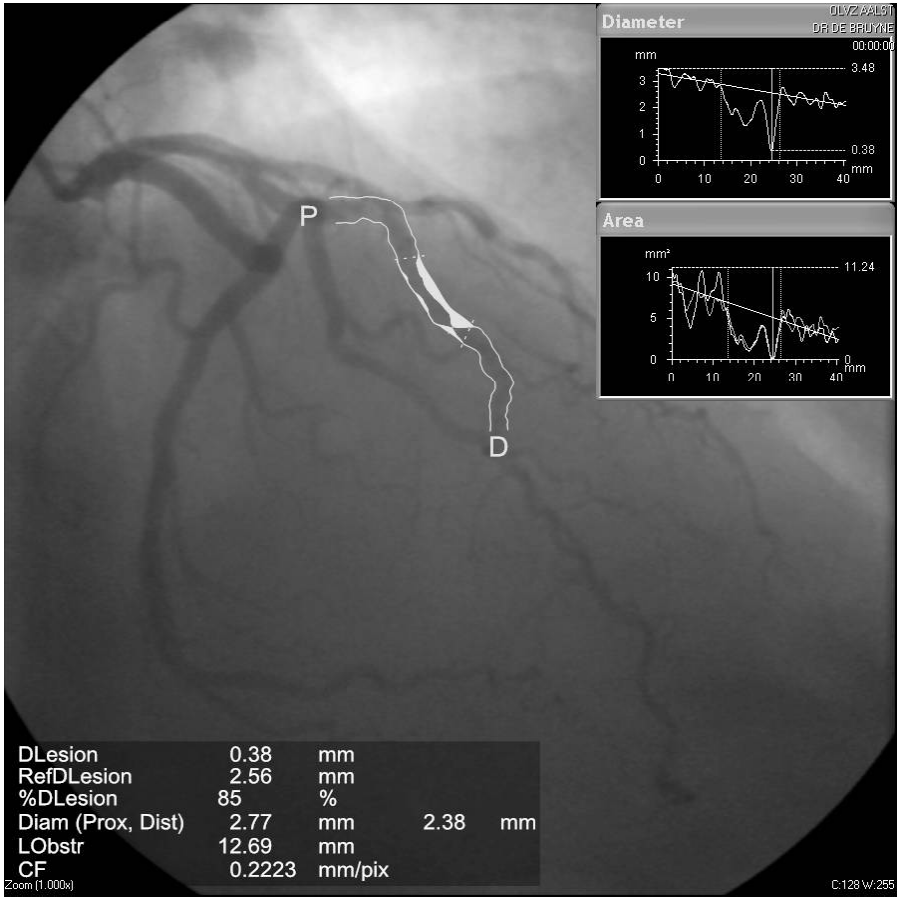
ID-TLR #2:

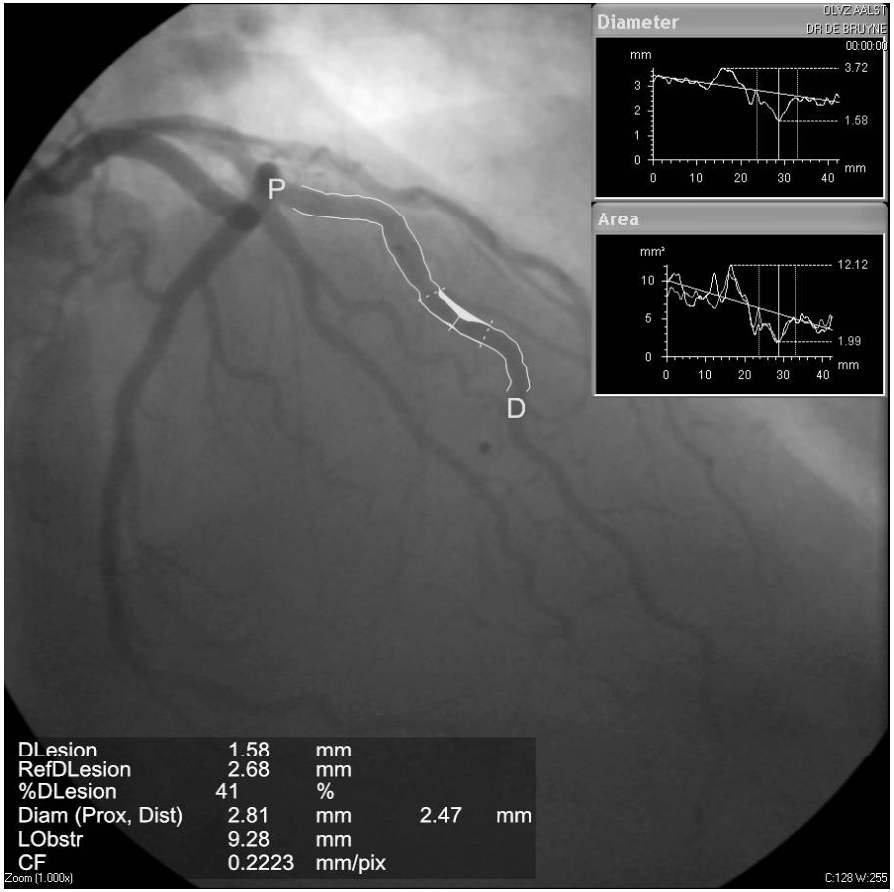




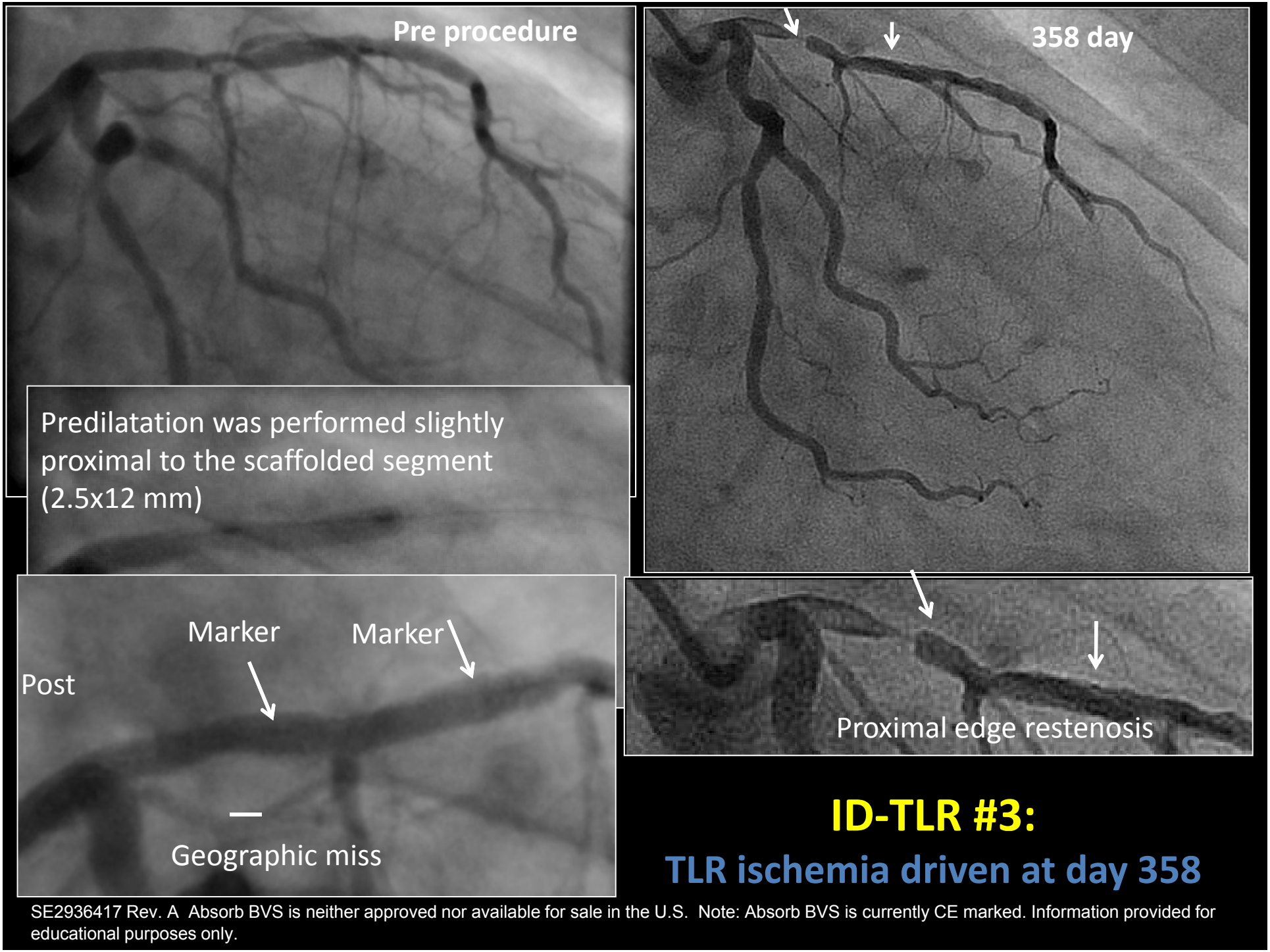
Myocardial Bridging

ID-TLR #2:

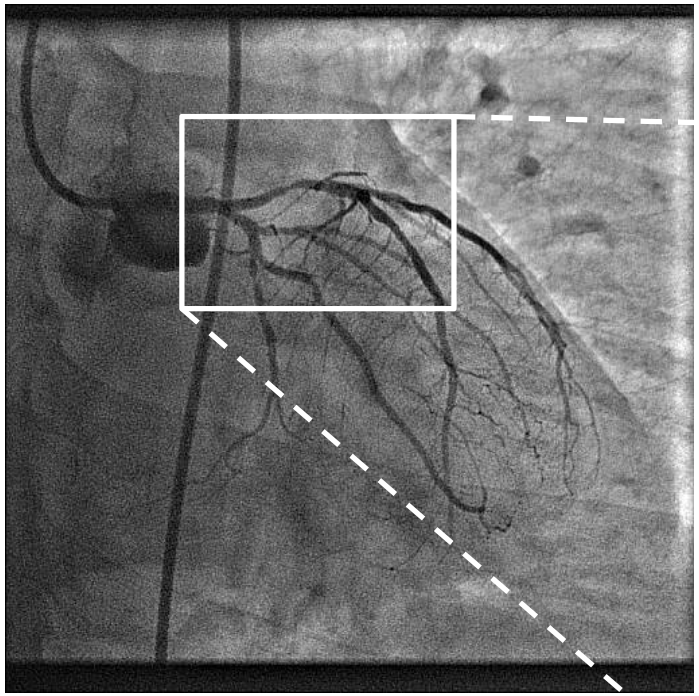


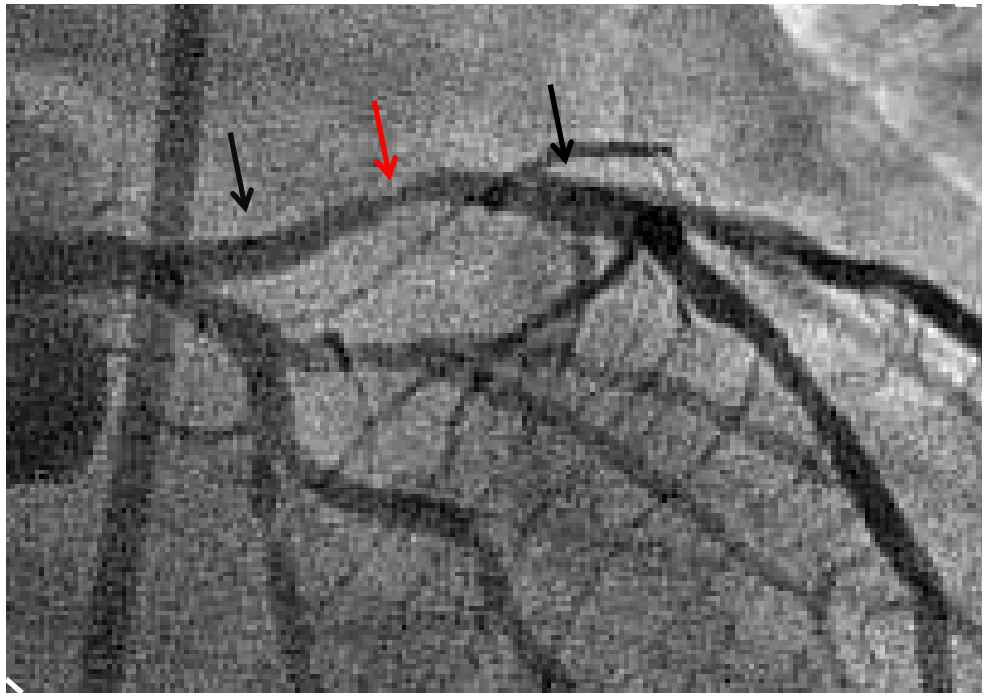


Myocardial Bridging



ID-TLR #4:
TLR ischemia driven at day 354





Procedural and primary endpoints for both cohorts up to 6 months

	N	%
Device success*	46	100
Procedural success**	46	100
6-month clinical results	46	100
TLF	2	4.3
Cardiac death	0	0.0
MI	0	0.0
Scaffold thrombosis	0	0.0
TLR (clinically-driven)***	2	4.3

* Defined as:
- successful delivery of the scaffold to the target lesion site in the coronary artery
- appropriate scaffold deployment
- successful removal of delivery system after release of the scaffold
- safe removal of the device in case of deployment failure

** Defined as:
- device success plus attainment of a final residual stenosis of < 50% of the target lesion
- absence of a major adverse cardiac event during the hospital stay to a maximum of first seven days post procedure

*** TLR occurred during 6 M FUP, both pts had angina, 1 pt received an additional DREAMS in the target lesion during the initial procedure because of a flow-limiting bailout situation