Bioresorbale Stents

Just an Alternative or One-Way Street?

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29/10/2015

Bioresorbale Drug-Eluting Stents (BRS)

- Breakthrough technology (after biodegradable polymers)
- Stents disappear after their useful function (no local inflammatory reaction)
- Restore vasomotor tone and endothelialization
- Increase vessel diameter (positive remodeling)
- Improve coronary physiology
- Potentially decrease anginal burden

Bioresorbale Drug-Eluting Stents (BRS)

- Not currently all patients are candidates and lesions are suitable
- Stent deployment requires optimal pre and post dilatation
- Low threshold of intracoronary imaging techniques
- Higher rate of early post-procedural stent thrombosis

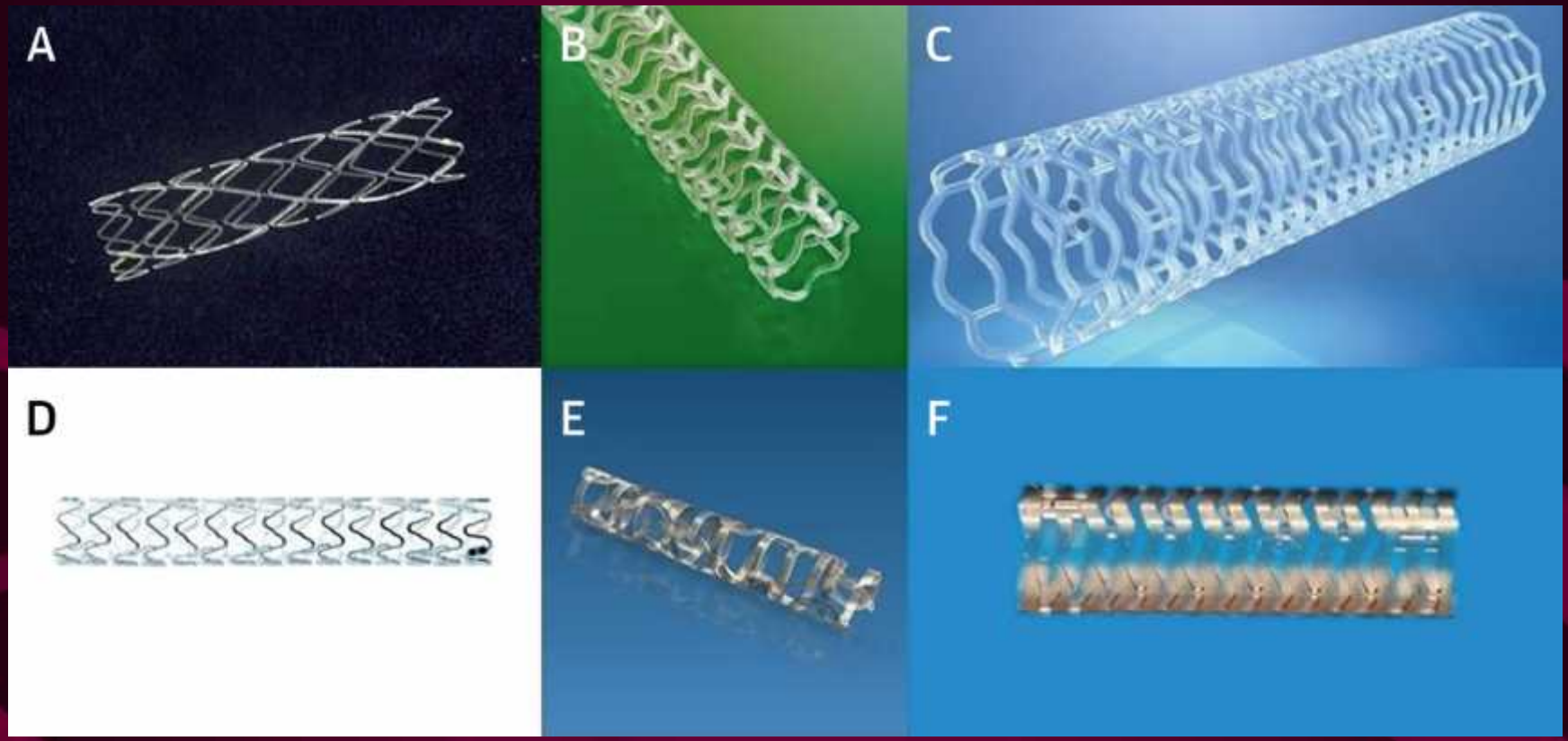
Optimal BRS

- Optimal short and mid term radial support with thin struts
- Adequate deliverability, handling and flexibility for insertion
- Consistency of drug elution
- Integrity during resorption

Strategies of developing BRS

- Backbone comprised of L-lactic acid polymer
  - ABSORB stent (BVS): Everolimus-eluting stent (CE Mark, Abbot Vascular)
  - DESolve stent: Myolimus/Novolimus-eluting stent (CE Mark, Elixir Medical Corporation)
  - ART stent: No eluting drug (CE Mark, Terumo Corporation)
- Magnesium-based scaffolds (with rare earth metals)
  - AMS/DREAMS: Paclitaxel/Sirolimus-eluting stent (Biotronic)
- Other (Desaminotyrosin, Polylactic anhydrate)
  - REVA BRS/ReZolve: Paclitaxel/Sirolimus-eluting stent (Reva Medical)
  - Ideal Biostent: Sirolimus-eluting stent (Xenogenics)

Types of BRS



A: Igaki-Tamai stent; B: ABSORB stent; C: DESolve stent; D: DREAMS Magesium alloy; E: ReZove BRS; F: Ideal BioStent

Igaki-Tamai Stent

- PLLA-based BRS
- Self-expandable when contrast dye heated at 80^0 C
- Initial results promising and vessel diameter increased at 3-year follow-up
- Requires 8F Catheter
- Heated contrast dye may cause injury

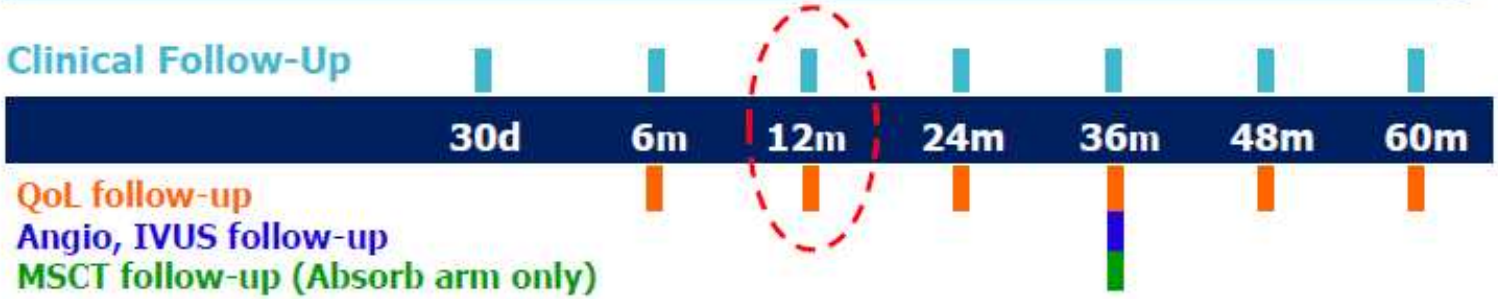
Absorb BVS

- PLLA-based stent
- 150 μm strut thickness (c/w 90 in current DES)
- 1:1 mixture of poly-D,L-lactic acid and everolimus
- Degrades over time to H_2O and CO_2
- Full hydrolytic degadration up to 3 years

ABSORB II Study Design

501 subjects

Randomized 2:1 Absorb BVS:XIENCE / 46 sites (Europe and New Zealand)



Study Objective	Randomized against XIENCE control. First Patient In: 28-Nov-2011
Co-primary Endpoints	Vasomotion assessed by change in Mean Lumen Diameter between pre- and post-nitrate at 3 years (superiority) Minimum Lumen Diameter (MLD) at 3 years post nitrate minus MLD post procedure post nitrate (non-inferiority, reflex to superiority)
Treatment	Up to 2 *de novo* lesions in different epicardial vessels Planned overlapping allowed in lesions ≤ 48 mm
Device Sizes	Device diameters: 2.5, 3.0, 3.5 mm Device lengths: 12 (3.5 mm diameter only), 18, 28 mm

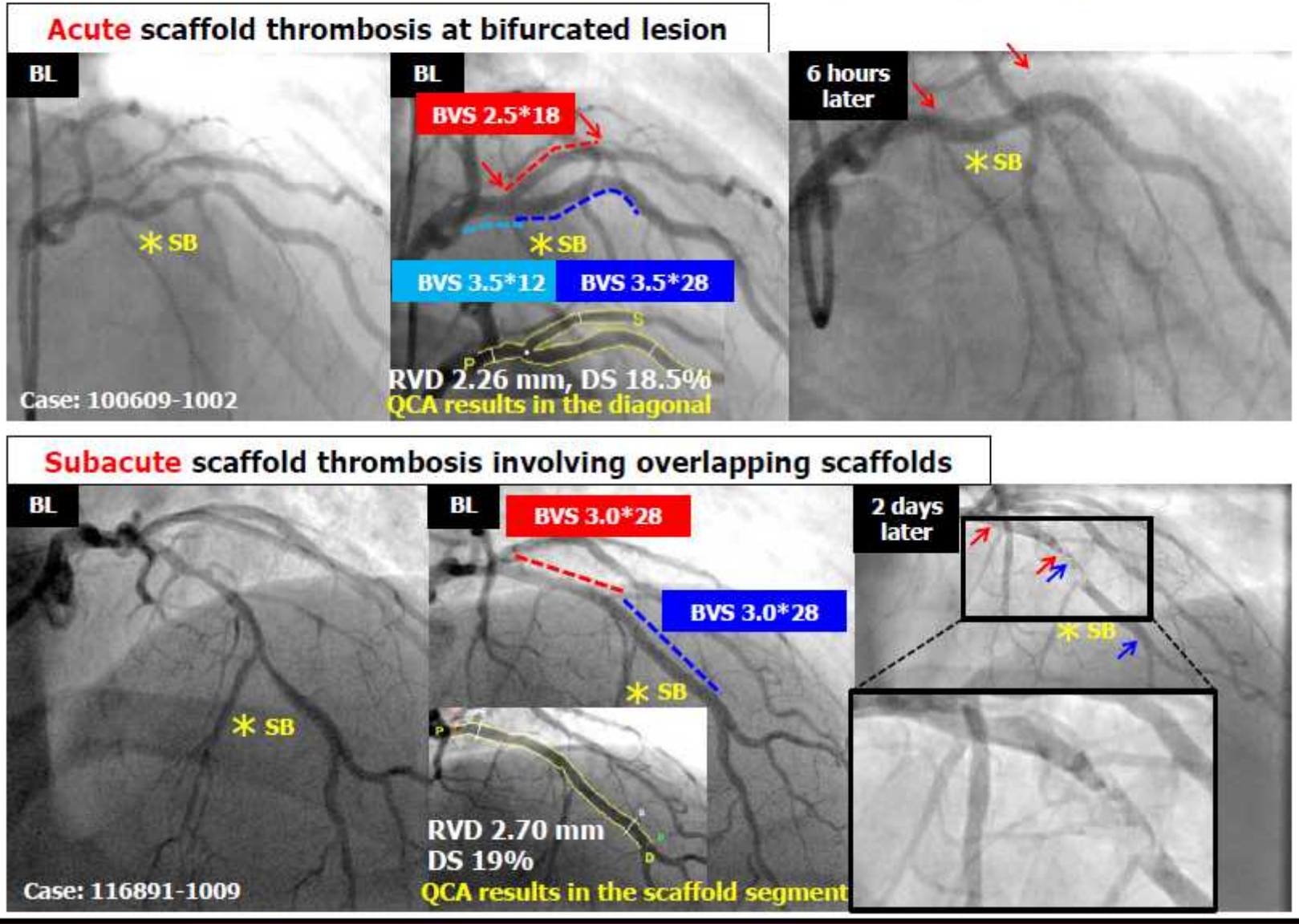
Clinical Outcomes

Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Composite of cardiac death, target vessel MI and clinically indicated target lesion revascularization (TLF, DoCE)	**4.8 %**	**3.0 %**	**0.35**
Cardiac death	0 %	0 %	1.00
Target vessel MI	4.2 %	1.2 %	0.07
Clinically indicated TLR	1.2 %	1.8 %	0.69
All TLR	1.2 %	1.8 %	0.69
Composite of all death, all MI and all revascularization (PoCE)	**7.3 %**	**9.1 %**	**0.47**
All death	0 %	0.6 %	0.33
All MI	4.5 %	1.2 %	0.06
All revascularization	3.6 %	7.3 %	0.08

Definite scaffold/stent thrombosis

Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Definite scaffold/stent thrombosis			
Acute (0-1 day)	0.3 (1pt)	0.0	NS
Sub-acute (2–30 days)	0.3 (1pt)	0.0	NS
Late (31–365 days)	0.0	0.0	NS
Probable scaffold/stent thrombosis			
Acute (0-1 day)	0.0	0.0	NS
Sub-acute (2–30 days)	0.0	0.0	NS
Late (31–365 days)	0.3 (1pt)	0.0	NS

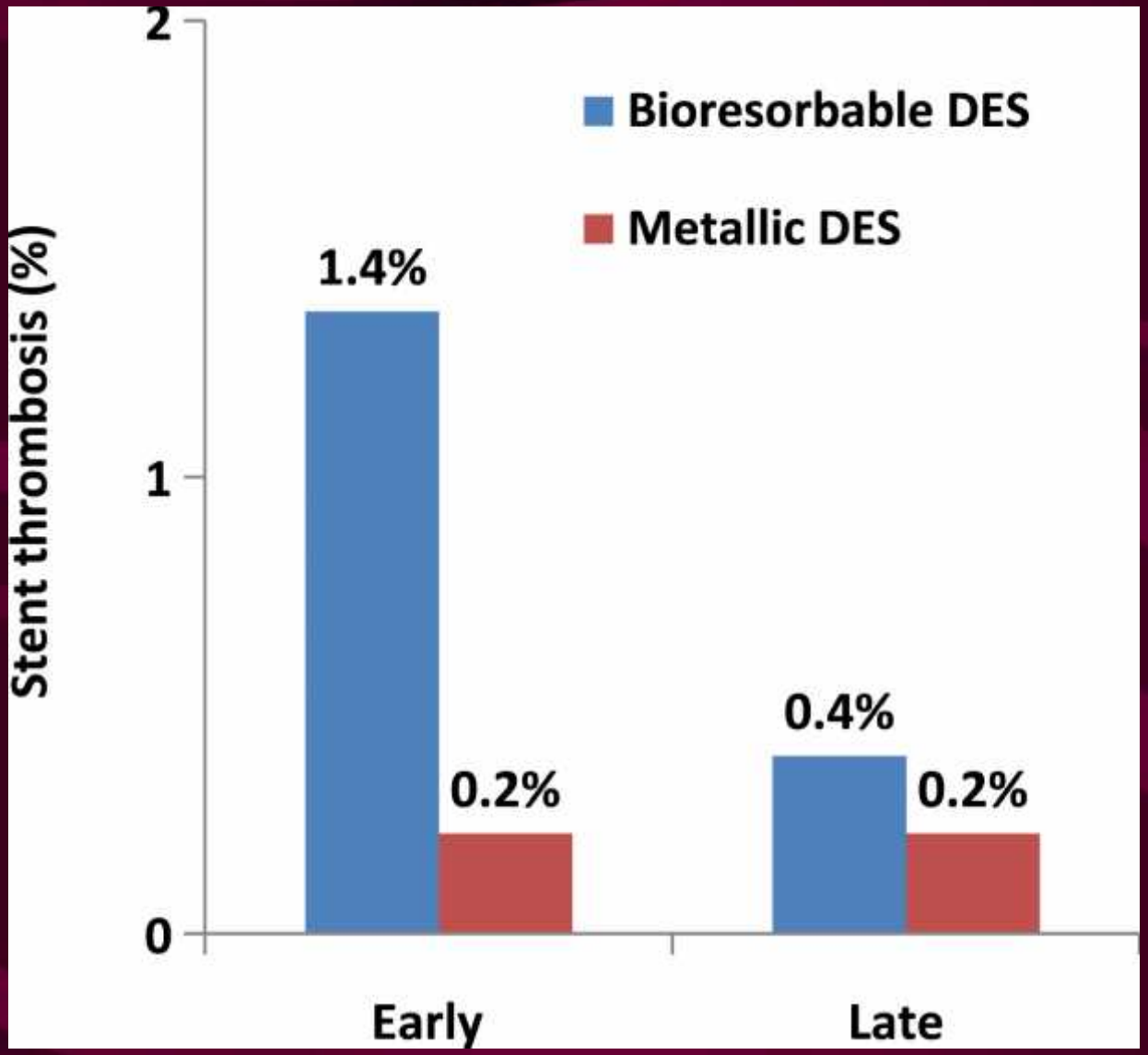
Definite scaffold/stent thrombosis



ABSORB III – 2008 Patients

Outcome	Absorb (1322) (%)	Xience (686) (%)	p
Target lesion failure	7.8	6.1	0.16
Cardiac death	0.6	0.1	0.29
Target vessel MI	6	4.6	0.18
Ischemia-driven target lesion revascularization	3	2.5	0.5
Ischemia-driven target vessel revascularization	5	3.7	0.18
Patient-reported angina	18.3	18.4	0.93
Definite or probable stent thrombosis	1.5	0.7	0.13

Rates of Stent Thrombosis after implantation of BRS vs BMS



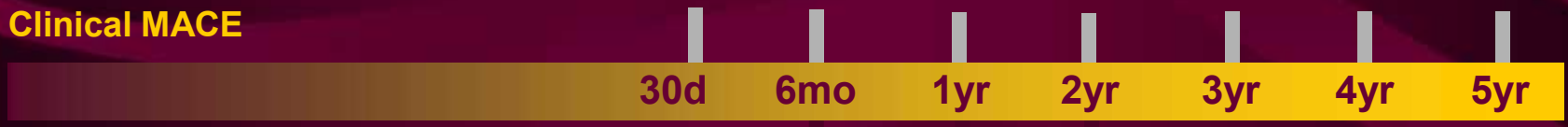
DESolve BRS

- PLLA based-stent
- 150 μm strut thickness
- Novolimus eluting drug
- Degrades to H_2O and CO_2 in 1 year
- Device resorption time is 2 years
- Wider range of expansion, reduced strut fracture, self-correction of minor malapposition

DESolve Nx Clinical Trial Design

Single *de novo* Coronary Artery Lesion
Reference vessel diameter: 2.75-3.0mm
Lesion length: <12mm, DAPT 12 months
3.0, 3.25, 3.5mm diameters; 14 and 18mm lengths

13 International Sites
Europe, New Zealand and Brazil
126 patients



Primary Endpoint: 6-month in-scaffold late lumen loss
Secondary Endpoints:

- **Clinical**: Major Adverse Cardiac Events (cardiac death, target vessel MI, and clinically indicated TLR), Scaffold thrombosis
- **QCA**: In-segment late lumen loss, binary restenosis, and percent diameter stenosis
- **IVUS**: In-scaffold percent volume obstruction, malapposition
- **OCT**: In-scaffold percent obstruction, strut coverage
- **MSCT**: Percent diameter stenosis, lumen area

DESolve Nx showed excellent acute performance and low events through 2 years

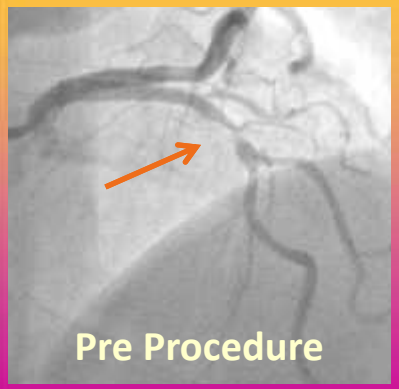
In-Scaffold Analysis	Baseline N_L = 126	Post procedure N_L = 128	6 months N_L = 113
RVD (mm)	3.06 ± 0.31	3.09 ± 0.26	3.01 ± 0.29
MLD (mm)	0.92 ± 0.40	2.67 ± 0.28	2.45 ± 0.44
Acute gain (mm)		1.73 ± 0.45	
Acute Recoil (%)		6.6%	
LLL at 6-months (mm)			0.21 ± 0.34
Median Late Loss (mm)			0.11 (0.04 , 0.21)
Diameter Stenosis (%)	69.9 ±12.3	13.5 ± 7.8	18.3 ± 13.6
In-Segment Binary Restenosis* n (%)			4 (3.5%)

Hierarchical Events 0 to 720 days, n (%)	6M (N=122)*	12M (N=122)*	24M (N=122)*
Major Adverse Cardiac Events	**3.3%**	**5.7%**	**7.4%**
Cardiac Death**	1 (0.8%)	2 (1.6%)	3 (2.5%)
Target vessel MI***	1 (0.8%)	1 (0.8%)	1 (0.8%)
Q-wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Q- wave MI	1 (0.8%)	1 (0.8%)	1 (0.8%)
Clinically Indicated-TLR PCI	2 (1.6%)	4 (3.3%)	5 (4.1 %)
Definite Stent Thrombosis+	0 (0.0%)	0 (0.0%)	0 (0.0%)

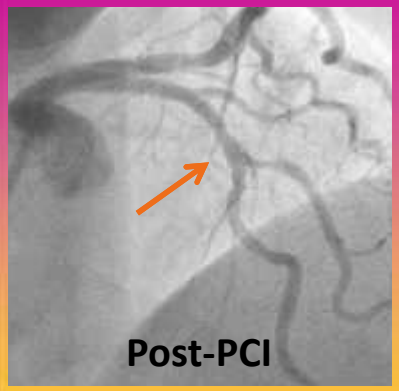
EKE 2015

Case Example 1 - Multi-modality Imaging

Angio's

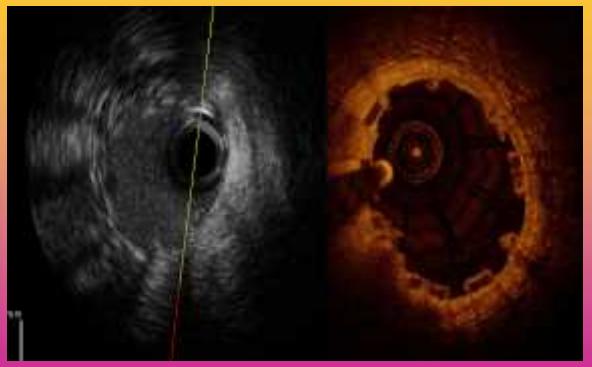


Mean Scaffold Diameter = 3.1mm

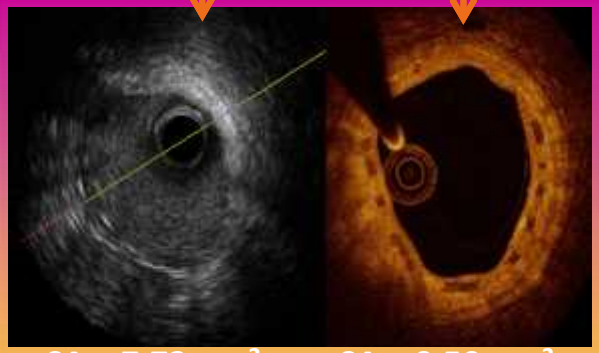


6 mos FU

IVUS/OCT



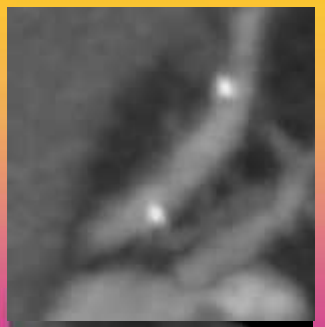
SA = 6.09mm^2 SA = 6.48mm^2

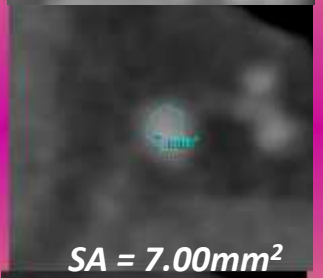


SA = 7.73mm^2 SA = 9.50mm^2

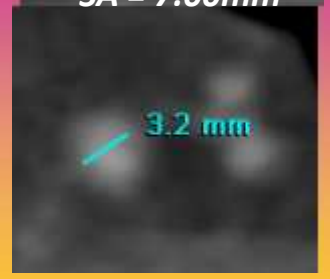
6 mos FU

MSCT





SA = 7.00mm^2



12 mos FU

ART BRS

- PLLA or PDLA based BRS
- No eluting drug – next generation with eluting drug (Terumo)
- Programmed dismantling at 3 months and resorption in 2 years
- CE Mark based on ARTDIVA study 6 months results

DREAMS 2G

- Magnesium-based BRS
- 120-150 μm strut thickness
- Electronegative charge emerges during degradation with antithrombotic function
- Paclitaxel to sirolimus (2G) eluting drug
- Resorption time up to 12 months

Evolution of the BIOTRONIK Absorbable Magnesium Scaffold

	 AMS	 DREAMS 1G	 DREAMS 2G
Alloy	Magnesium-based (WE43)	Refined Magnesium	Refined Magnesium
Drug	-	Paclitaxel	Sirolimus
Polymer	-	PLGA	PLLA
Scaffold Design	4 crown/4 link No marker	6-crown/3-link No marker	6-crown/2-link Two double markers
Strut Thickness	165 µm	120 µm	150 µm
Magnesium Absorption Time	1-2 months	3 months  28-day Faxitron	12 months  90-day Faxitron

* In-segment late lumen loss. Source: Erbel et al. Lancet 2007;369:1869-75. Haude et al. Lancet 2013;381(9869):836-844.

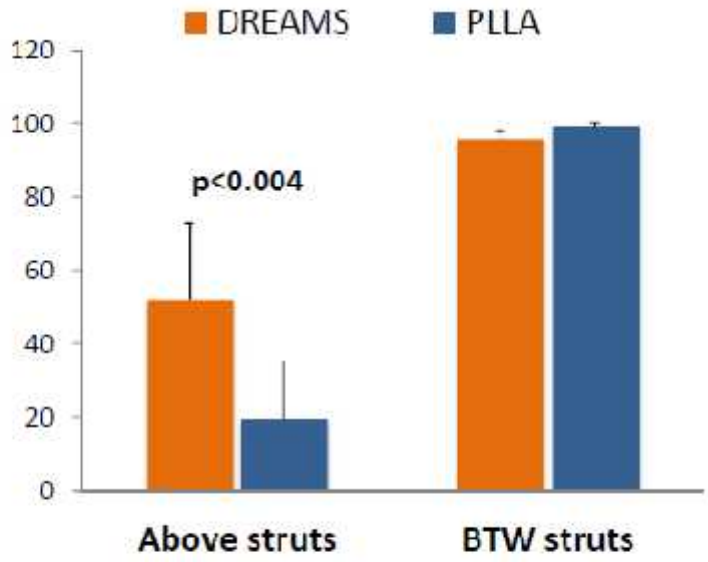
BIOSOLVE-I Results

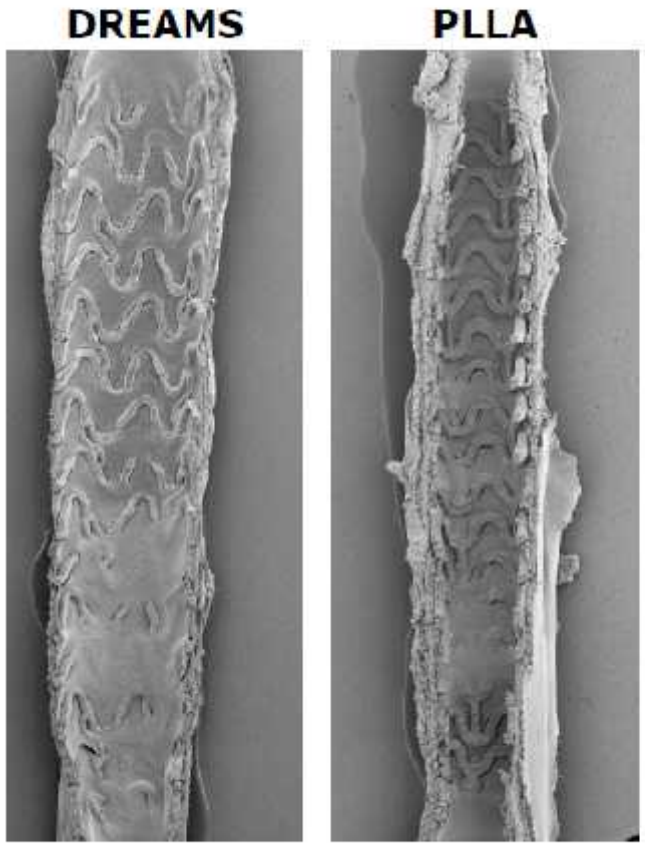
	6-month[1] N=26	12-month[1] N=44	24-month[2] N=44	36-month[3] N=44
TLF % (n)	4.3% (2)	6.8% (3)	6.8% (3)	6.8% (3)
Cardiac death % (n)	0.0%	0.0%	0.0%	0.0%
MI % (n)	0.0%	2.3% (1)	2.3% (1)	2.3% (1)
Scaffold thrombosis % (n)	0.0%	0.0%	0.0%	0.0%
Clinical TLR % (n)	4.3% (2)	4.5% (2)	4.5% (2)	4.5% (2)

Source: Haude. et al. Lancet 2013; 381:836-44. [2] M Haude, oral presentation EuroPCR 2013, [3] R Waksman, oral presentation EuroPCR 2014.

Endothelialization testing

in New Zealand white rabbits at 28-days





Source: Adapted from M. Joner, oral presentation, CRT 2015.

Safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de-novo coronary artery lesions (BIOSOLVE-II): 6 month results of a prospective, multicentre, non-randomised, first-in-man trial

- Between Oct 8, 2013, and May 22, 2015, we enrolled **123 patients** with 123 coronary target lesions. At **6 months**, mean in-segment late lumen loss was 0·27 mm (SD 0·37), and angiographically discernable vasomotion was documented in 20 (80%) of 25 patients. Intravascular ultrasound assessments showed a preservation of the scaffold area (mean 6·24 mm^2 [SD 1·15] post-procedure *vs*6·21 mm^2 [1·22] at 6 months) with a low mean neointimal area (0·08 mm^2 [0·09]), and optical coherence tomography did not detect any intraluminal mass. Target lesion failure occurred in four (3%) patients: one (<1%) patient died from cardiac death, one (<1%) patient had periprocedural myocardial infarction, and two (2%) patients needed clinically driven target lesion revascularisation. No definite or probable scaffold thrombosis was observed.

Conclusions

- BRS represent an advancement in the interventional treatment of coronary disease
- Current data are slightly inferior with respect to device success, recoil, MACE, lumen areas and TLR
- Some possible benefits are only demonstrated in animal testing and small human cohorts
- Data on various type of patients and lesions are limited
- Technical considerations of deployment and imaging
- Optimal duration of double antiplatelet therapy is unclear
- However, current BRS limitations will likely be resolved in the near future