Bioresorbable Scaffolds
Moving Forward or Backwards?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse have had a financial interest/arrangement or affiliation with the organization(s) listed below in relation this topic.

Affiliation/Financial Relationship

Company
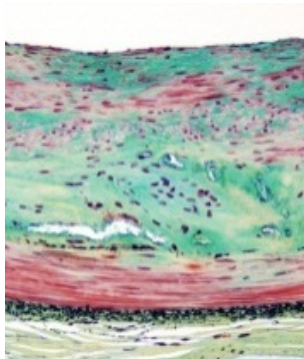
Consulting Fees or Speaker Honoraria

- Abbott Vascular

Potential Unique Benefits of BioResobableScaffolds

CELLS

- SMC differentiation to contractile phenotype through mechanotransduction
- Endothelium lined tissue coverage that responds to stimuli

PATIENT

- Stabilization of target lesion events (plaque capping)
- Recovery/preservation of epicardial-mediated portion of coronary flow reserve (remodeling/vasomotion)
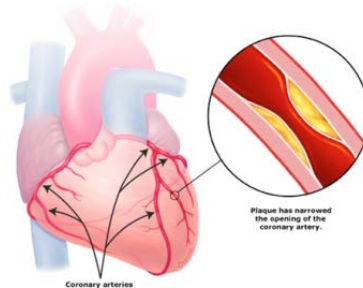
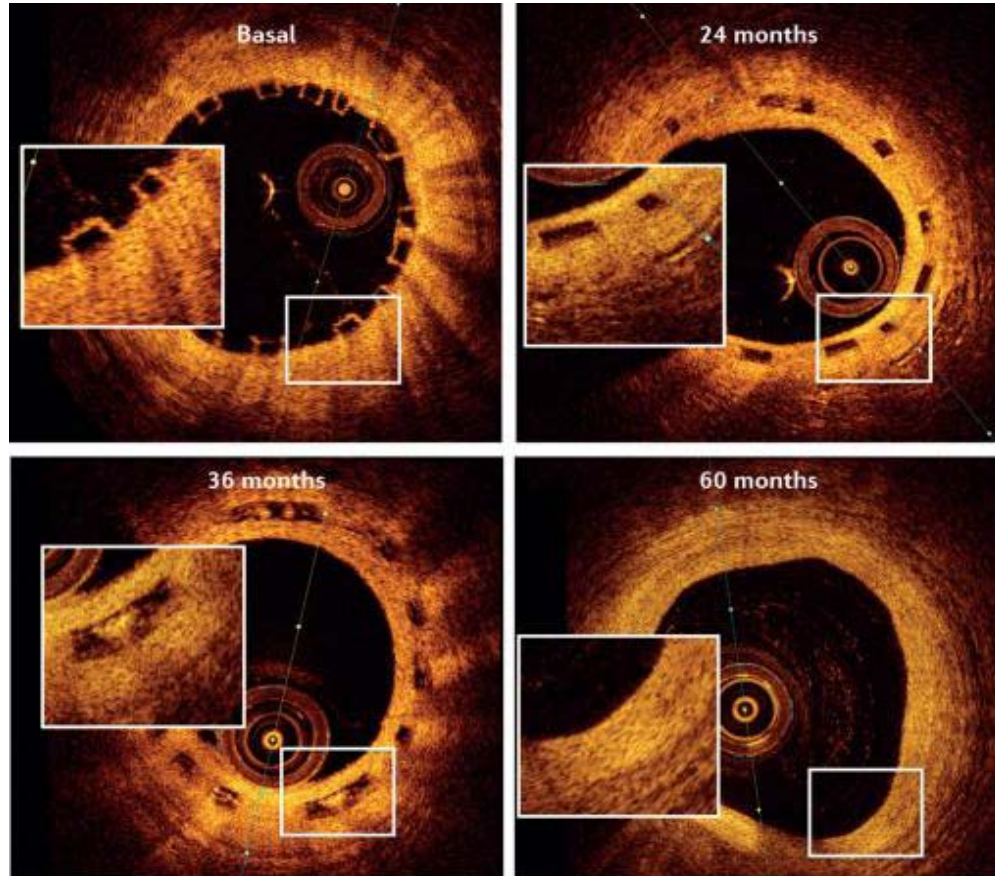## VESSEL

- Vessel remodeling allowed in the absence of metallic caging
- Vasomotion recovered through functional cellular tissue formation (mechanotransduction)
- Plaque capping with a "neo-intima" of ~ 200 µm
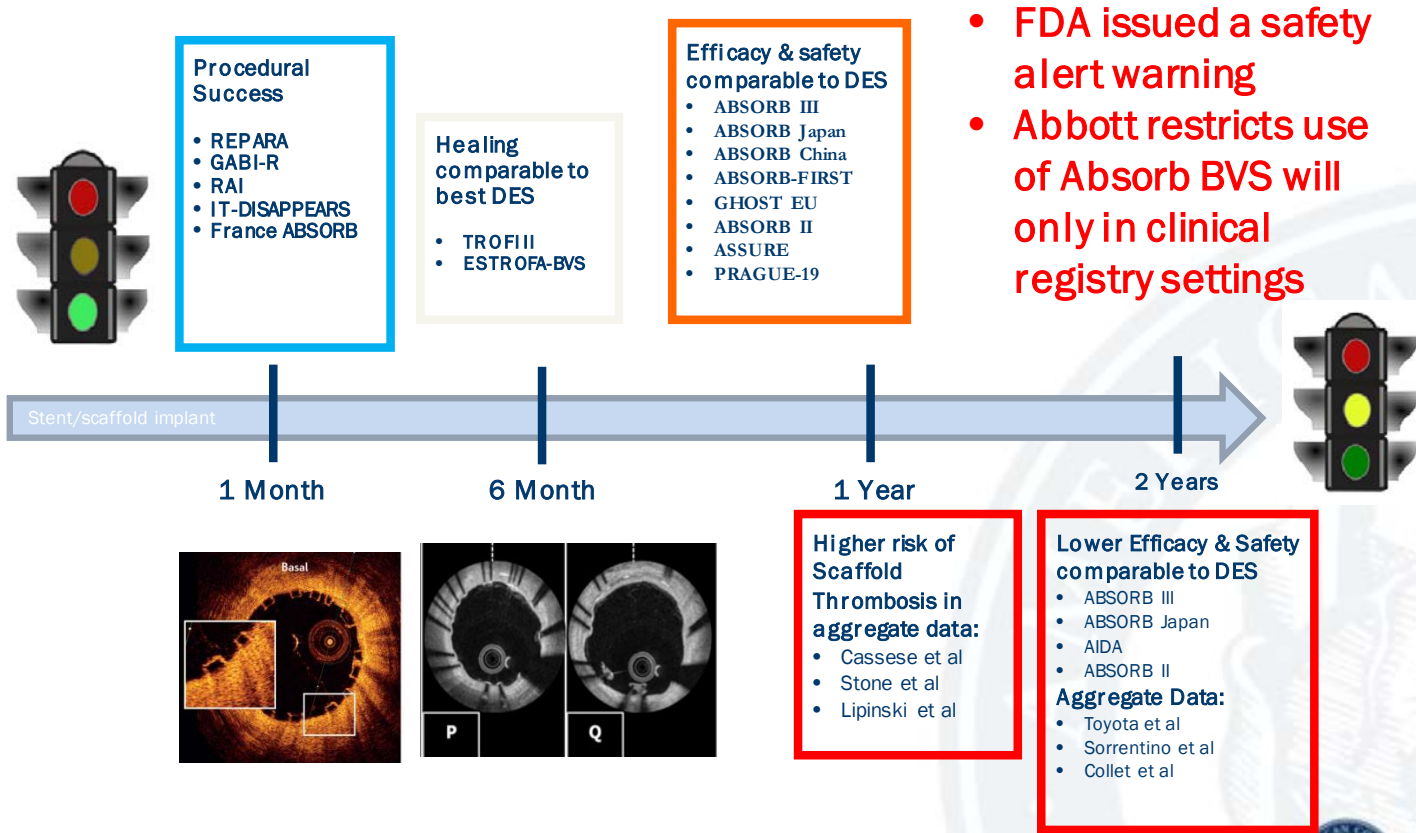- Plaque reduction
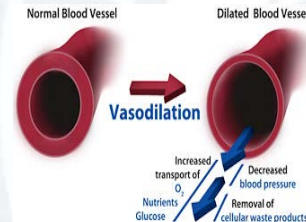
Evolution of Vascular Remodeling
As Assumed/Imagined from Animal Models

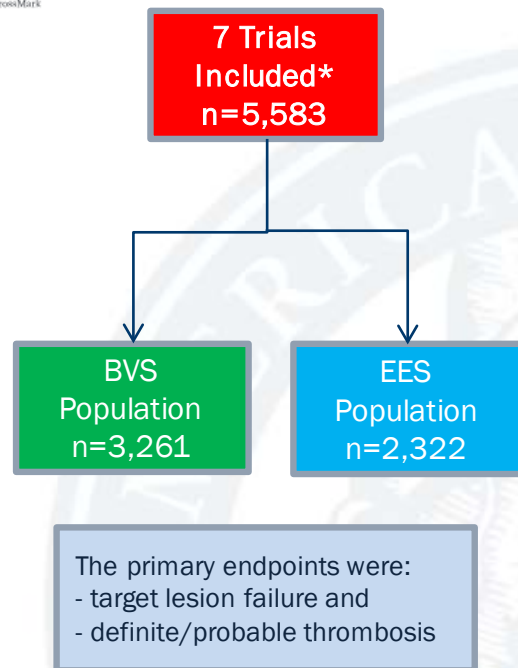Indolfi C, De Rosa S, Colombo A. Nat Rev Cardiol. 2016 Dec;13(12):719-729

Everolimus-Eluting Bioresorbable Scaffolds Versus Everolimus-Eluting Metallic Stents

Sabato Sorrentino, MD,[a,b] Gennaro Giustino, MD,[a] Roxana Mehran, MD,[a] Anapoorna S. Kini, MD,[a]
Samin K. Sharma, MD,[a] Michela Faggioni, MD,[a,c] Serdar Farhan, MD,[a] Birgit Vogel, MD,[a] Ciro Indolfi, MD,[b,d]
George D. Dangas, MD, PhD[a]

- **Selected studies:** Randomized Clinical Trials (RCTs) in which bioresorbable vascular scaffolds were compared to the best in class everolimus eluting stent

- Median time of follow-up was **2 years** (range 2 to 3 years).

* Only studies with at least 2-year of follow up were included

7 Trials Included*
n=5,583

BVS Population
n=3,261

EES Population
n=2,322

The primary endpoints were:
- target lesion failure and
- definite/probable thrombosis

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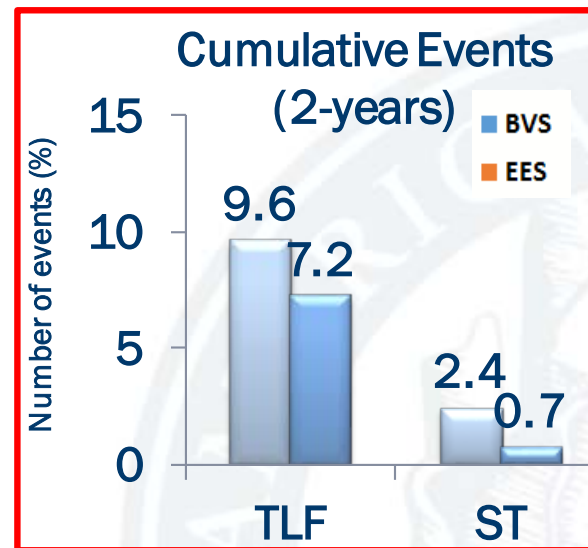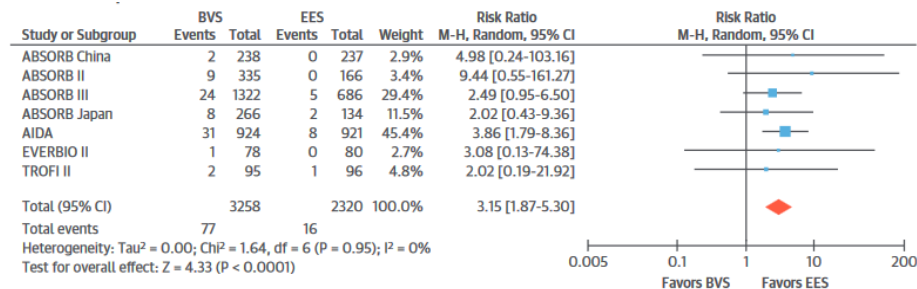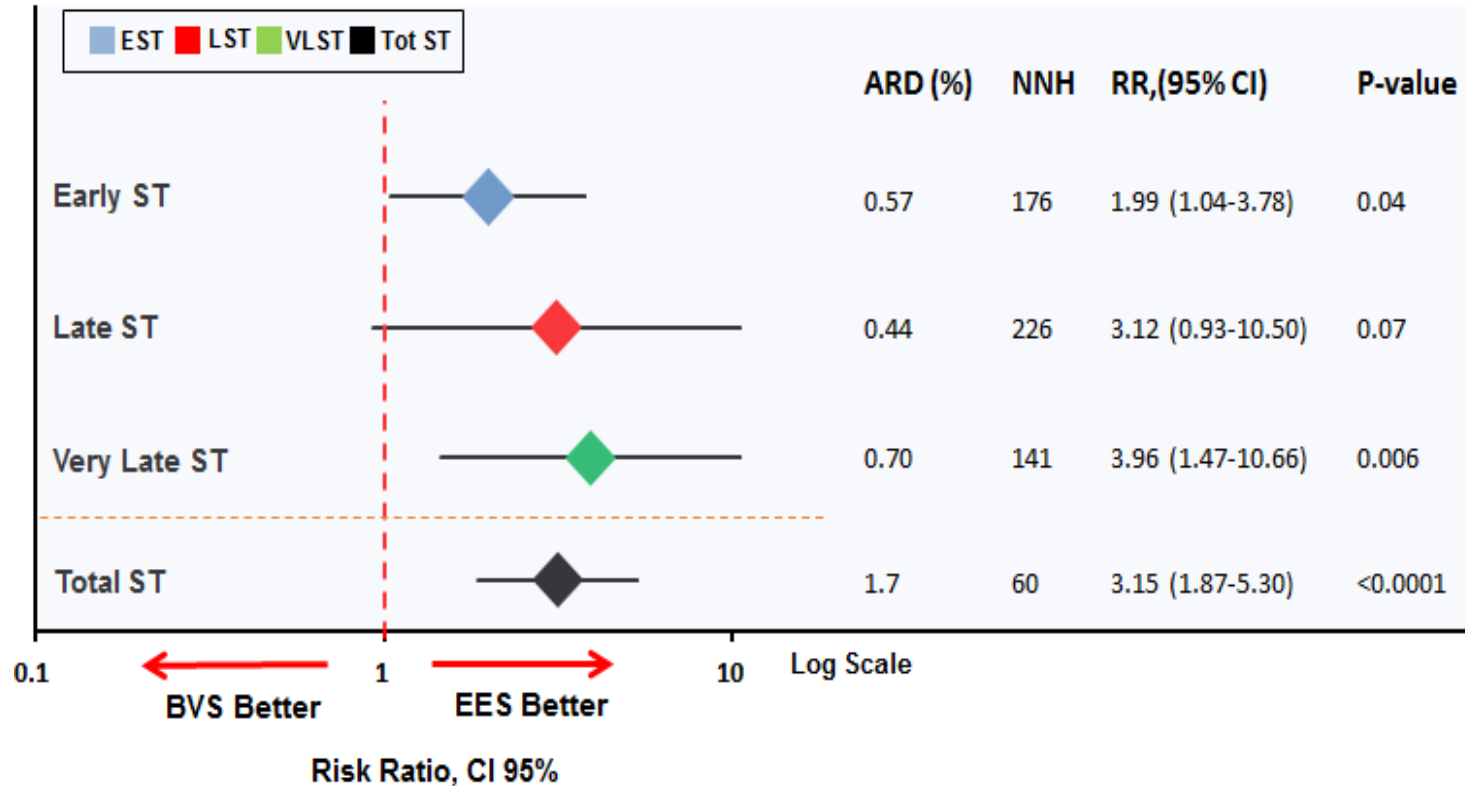# AbsorbBVS 7 trial Meta-Analysis Primary Outcomes

Target Lesion Failure

Study or Subgroup	BVS Events	Total	EES Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ABSORB China	10	238	11	237	4.9%	0.91 [0.39-2.09]
ABSORB II	34	335	8	166	6.1%	2.11 [1.00-4.45]
ABSORB III	143	1322	53	686	37.5%	1.40 [1.04-1.89]
ABSORB Japan	19	266	5	134	3.7%	1.91 [0.73-5.01]
AIDA	91	924	78	921	40.9%	1.16 [0.87-1.55]
EVERBIO II	14	78	9	80	5.6%	1.60 [0.73-3.47]
TROFI II	3	95	3	96	1.4%	1.01 [0.21-4.88]
Total (95% CI)		3258		2320	100.0%	1.32 [1.10-1.59]
Total events	314		167			

Heterogeneity: Tau² = 0.00; Chi² = 4.09, df = 6 (P = 0.66); I² = 0%
Test for overall effect: Z = 2.96 (P = 0.003)

Risk Ratio M-H, Random, 95% CI — Favors BVS / Favors EES (0.02, 0.1, 1, 10, 50)

Definite or Probable Scaffold/Stent Thrombosis (ST)

Study or Subgroup	BVS Events	Total	EES Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ABSORB China	2	238	0	237	2.9%	4.98 [0.24-103.16]
ABSORB II	9	335	0	166	3.4%	9.44 [0.55-161.27]
ABSORB III	24	1322	5	686	29.4%	2.49 [0.95-6.50]
ABSORB Japan	8	266	2	134	11.5%	2.02 [0.43-9.36]
AIDA	31	924	8	921	45.4%	3.86 [1.79-8.36]
EVERBIO II	1	78	0	80	2.7%	3.08 [0.13-74.38]
TROFI II	2	95	1	96	4.8%	2.02 [0.19-21.92]
Total (95% CI)		3258		2320	100.0%	3.15 [1.87-5.30]
Total events	77		16			

Heterogeneity: Tau² = 0.00; Chi² = 1.64, df = 6 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)

Risk Ratio M-H, Random, 95% CI — Favors BVS / Favors EES (0.005, 0.1, 1, 10, 200)

Cumulative Events (2-years)

BVS / EES

Number of events (%)

- TLF: 9.6 (BVS), 7.2 (EES)
- ST: 2.4 (BVS), 0.7 (EES)

Sorrentino S; Giustino G; Mehran R, Dangas GD et al
J Am Coll Cardiol. 2017 Apr 12. pii: S0735-1097(17)37013-4

AbsorbBVS 7 Trial Meta-Analysis: Thrombosis across overtime

Sorrentino S; Giustino G; Mehran R, Dangas GD et al
J Am Coll Cardiol. 2017 Apr 12. pii: S0735-1097(17)37013-4

ABSORB III 3-year
Device Thrombosis: Stratified by Vessel Size

RVD <2.25 mm
HR [95% CI] = 3.34 [0.75, 14.91]
p=0.09

RVD ≥2.25 mm
HR [95% CI] = 3.08 [0.91, 10.47]
p=0.06

Device thrombosis %

Absorb
XIENCE

4.6%   4.6%   5.0%

1.5%   1.5%   1.5%

Time Post Procedure (Months)

Absorb
XIENCE

0.8%   1.2%   1.7%
0.5%   0.5%   0.5%

Time Post Procedure (Months)

No. at Risk:

Absorb	242	224	222	216	1074	1036	1016	977
Xience	133	128	120	114	549	535	525	514

Stone G. Presented at TCT 2017

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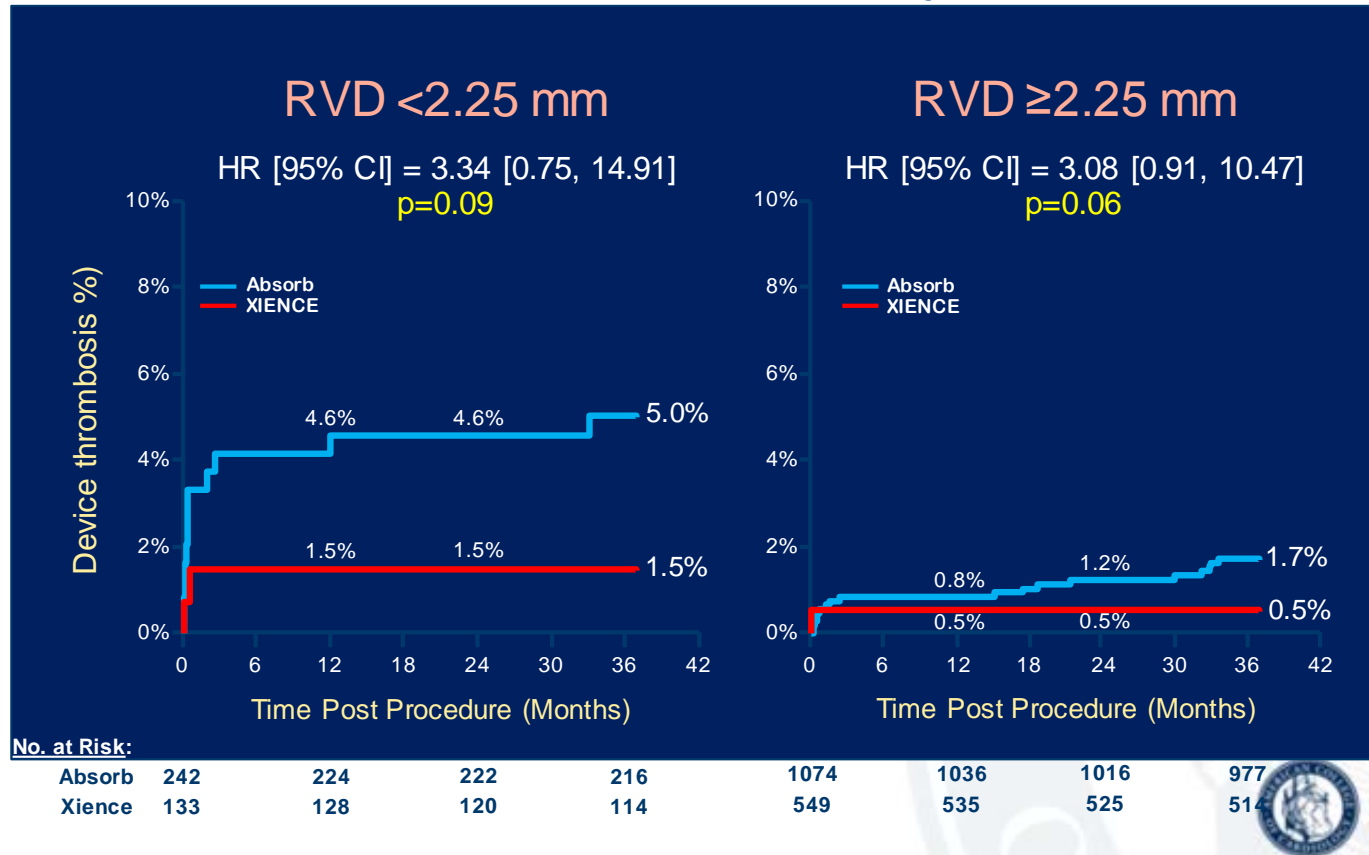
Late Series of Human Very Late scaffold thrombosis: The presence of malapposed-uncovered scaffold struts in direct contact with thrombus suggests a potential triggering role (all cases)"

Raber L et al J Am Coll Cardiol. 2015 Oct 27;66(17):1901-14
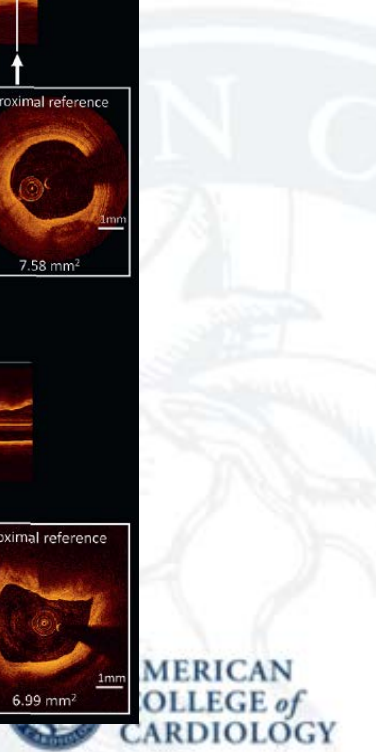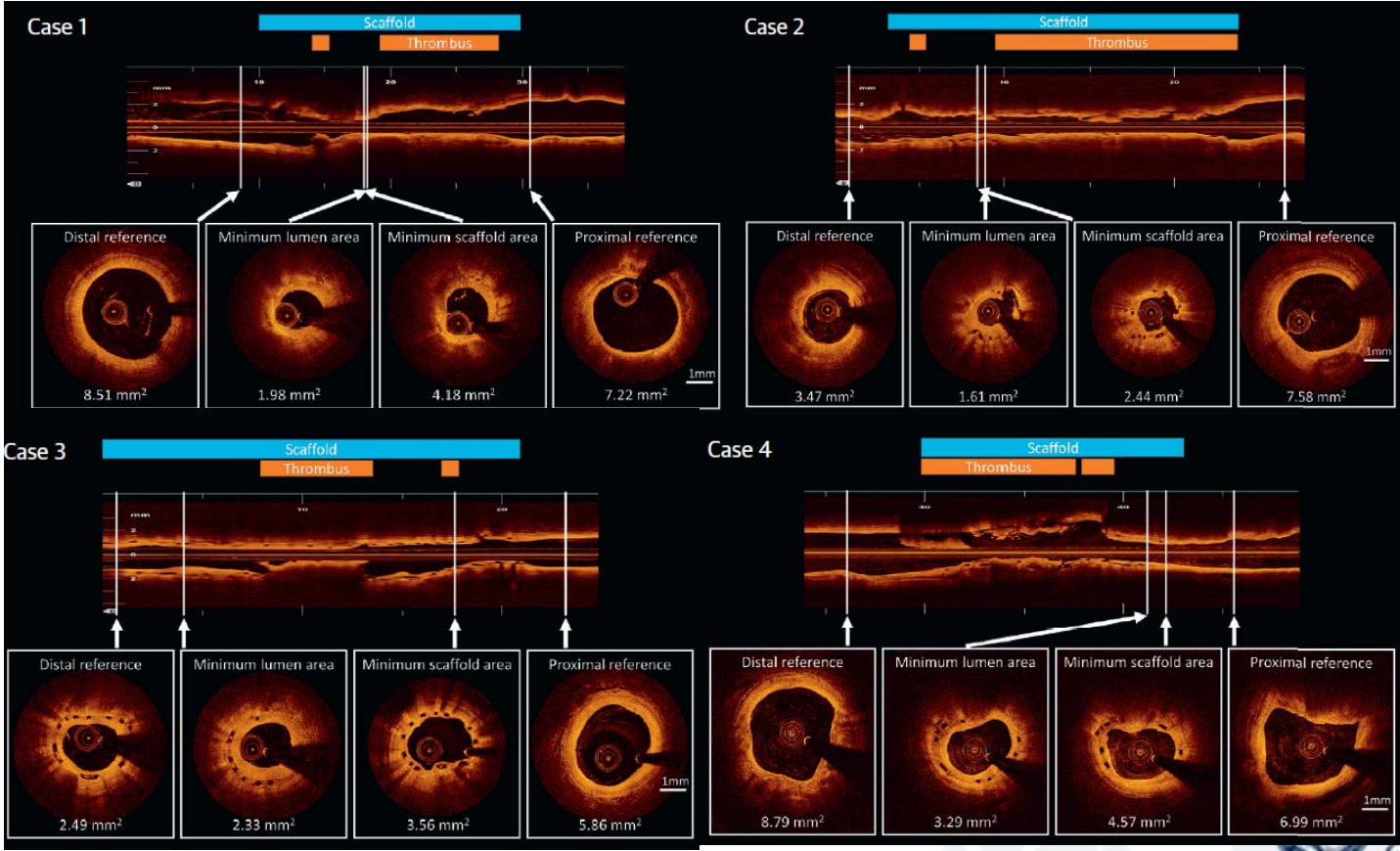
AbsorbBVS On-DAPT-status

Räber L. Presented at TCT 2017
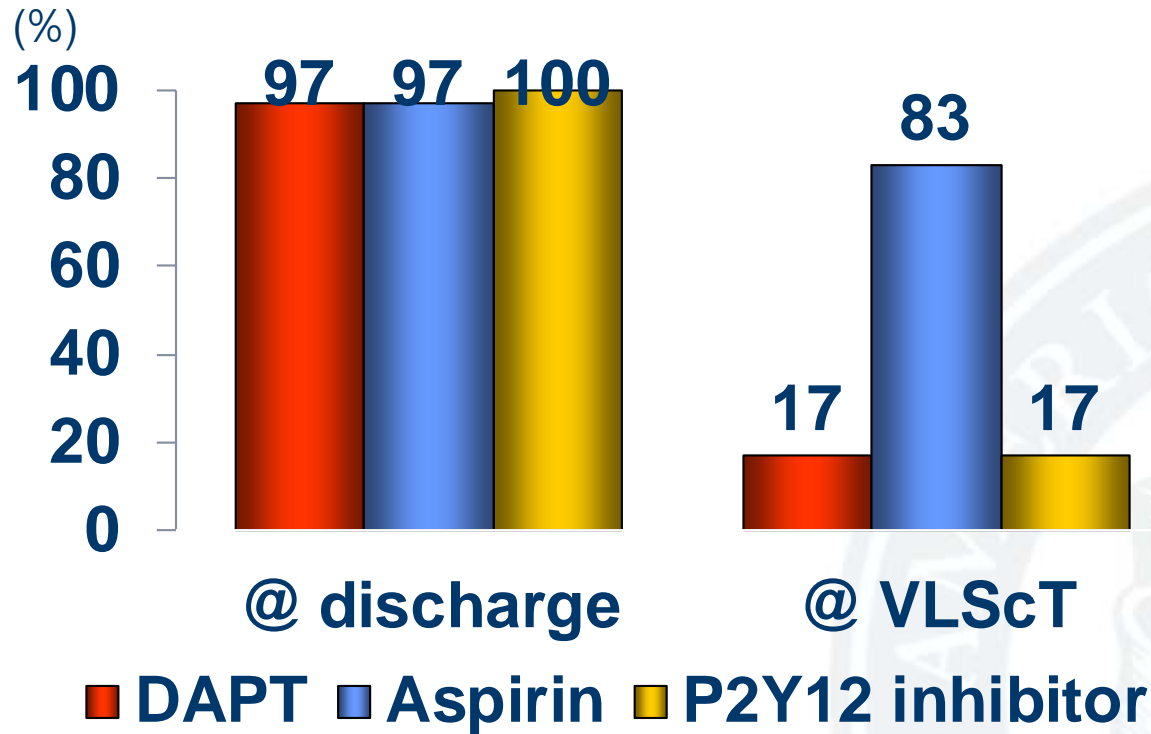
AbsorbBVS Rates of failure mechanisms

Underexpansion or scaffold shrinkage

Others

Scaffold discontinuity

11%

11%

42%

18%

18%

Neoatherosclerosis

Malapposition

n = 38
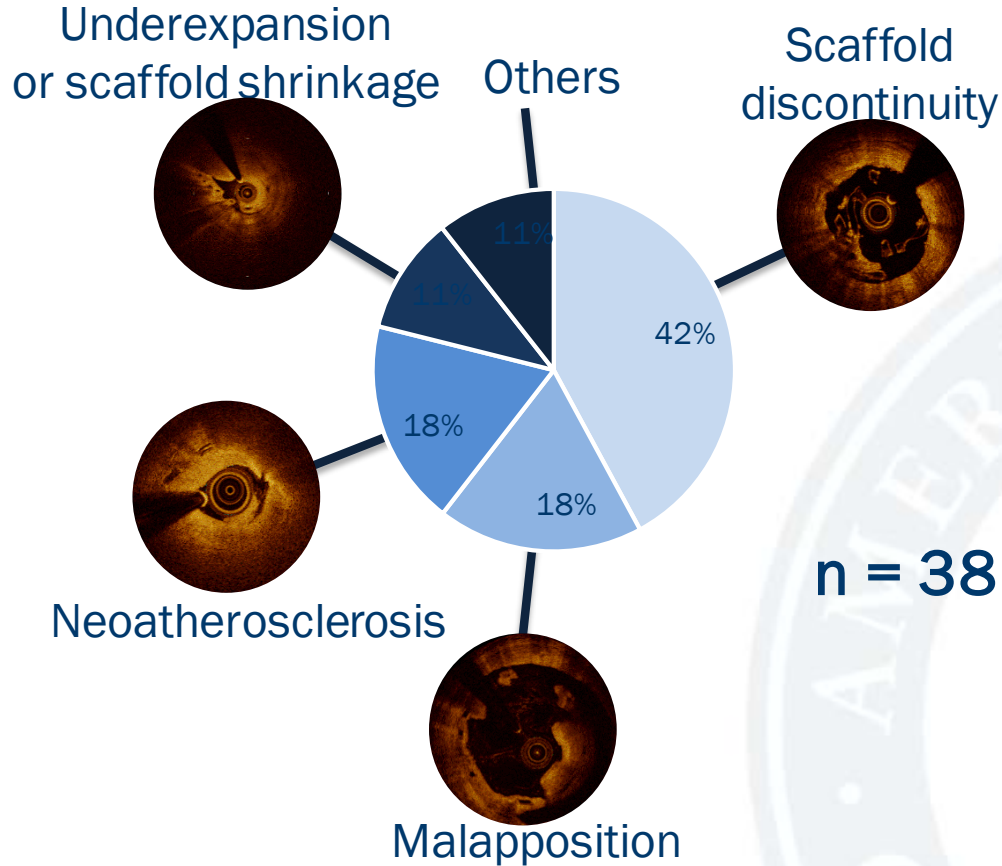
Räber L. Presented at TCT 2017

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Presumed specific mechanisms of increased events (ScT) with AbsorbBVS

- Mechanically less strong material
  - → Thicker struts/
    - Larger surface area
  - → Less embedment/
    - Under-expansion
  - → Disturbed microcirculation
  - → Predisposition to
    - Early thrombosis
- Late discontinuities/ dismantling without encapsulation
  - → Late/ Very Late Thrombosis
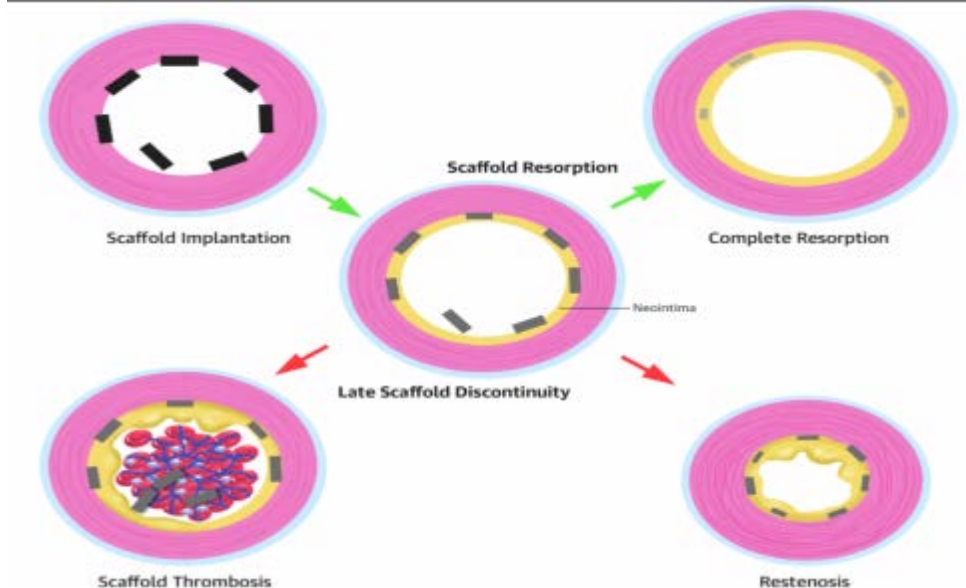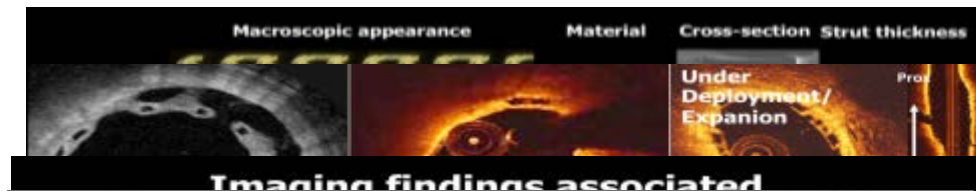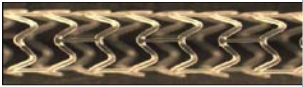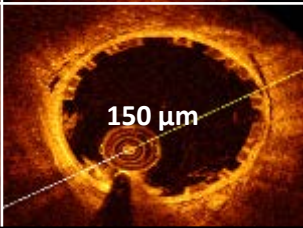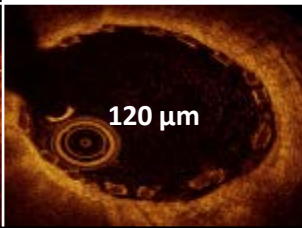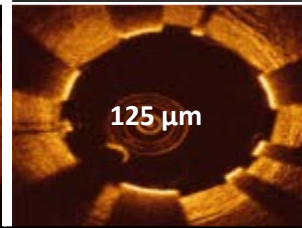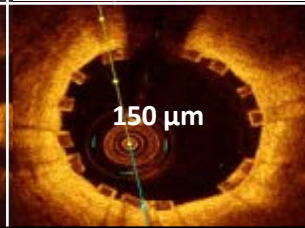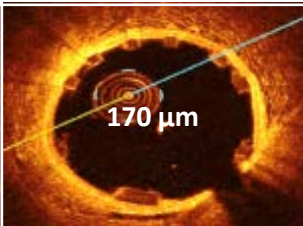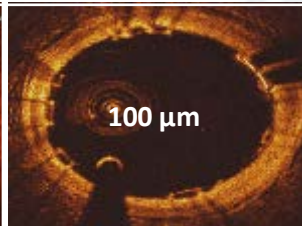
Strut thickness varies among BRS types

Scaffold	Absorb BVS 1.1	DESolve	DESolve Cx	Fantom	FORTITUDE
Design					
OCT appearance	157 µm	150 µm	120 µm	125 µm	150 µm
Scaffold	Magmaris	ART	MeRES 100	Mirage	Firesorb
Design					
OCT appearance	150 µm	170 µm	100 µm	125 µm	100-125 µm

Sotomi et al. Circ Res. 2017 Apr 14;120(8):1341-1352

Biodegradation process of CE-mark approved BRS.
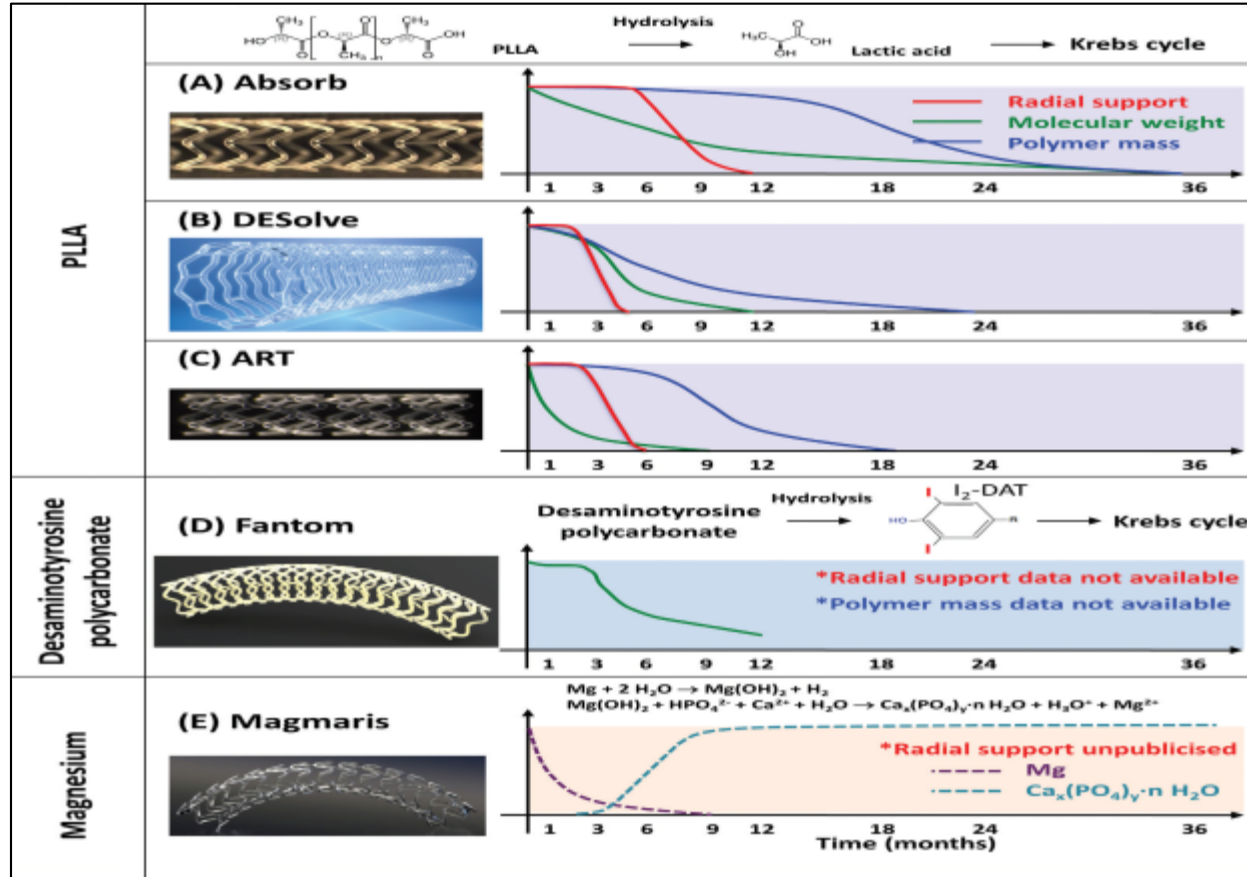
Evolution of the BIOTRONIK Magnesium Scaffold

	PROGRESS-AMS	BIOSOLVE-I	BIOSOLVE-II / III
Device generation	**AMS** **4-month**	**DREAMS 1G** **6-month**	**DREAMS 2G (Magmaris)** **6-month**
Design			
Sizes (mm)	Ø 3.0 & 3.5 Length: 15, 20	Ø3.25 & 3.5 Length: 15	Ø 2.5, 3.0 & 3.5 Length: 15, 20, 25
Backbone	Mg alloy	Refined Mg alloy	Refined Mg alloy
Strut thickness/width	165/80 μm	120/130 μm	120/120 μm (Ø 2.5) 150/150 μm (Ø 3.0 & 3.5)
Markers	none	none	Ta-composite
Coating - drug	none	PLGA/PTX	PLLA/SIR
Crossing profile in mm	1.6	1.5	1.75 (BIOSOLVE-II) 1.50 (BIOSOLVE-III)
Kinetics			
Drug elution kinetics	n.a.	like Taxus	like Orsiro
Absorption period in month	1-2	3-4 (Mg)	≈12 (Mg)
In-segment Late Lumen Loss (mm)	0.83±0.51	0.52±0.48	0.27±0.37 (BIOSOLVE-II)
Results			
TLF* (%)	23.8	4.3	3.3%
Definite or Probable Scaffold Thrombosis (%)	0.0	0.0	0.0

*Composite of cardiac death, target vessel myocardial infarction, clinically driven target lesion revascularization and CABG

Waksman R Presented at TCT 2017

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In a porcine arterio-venous shunt model, Magmaris was less thrombogenic than Absorb…

PLATELET

Waksman R et al. Circ CV Interv. 2017 Aug, published online
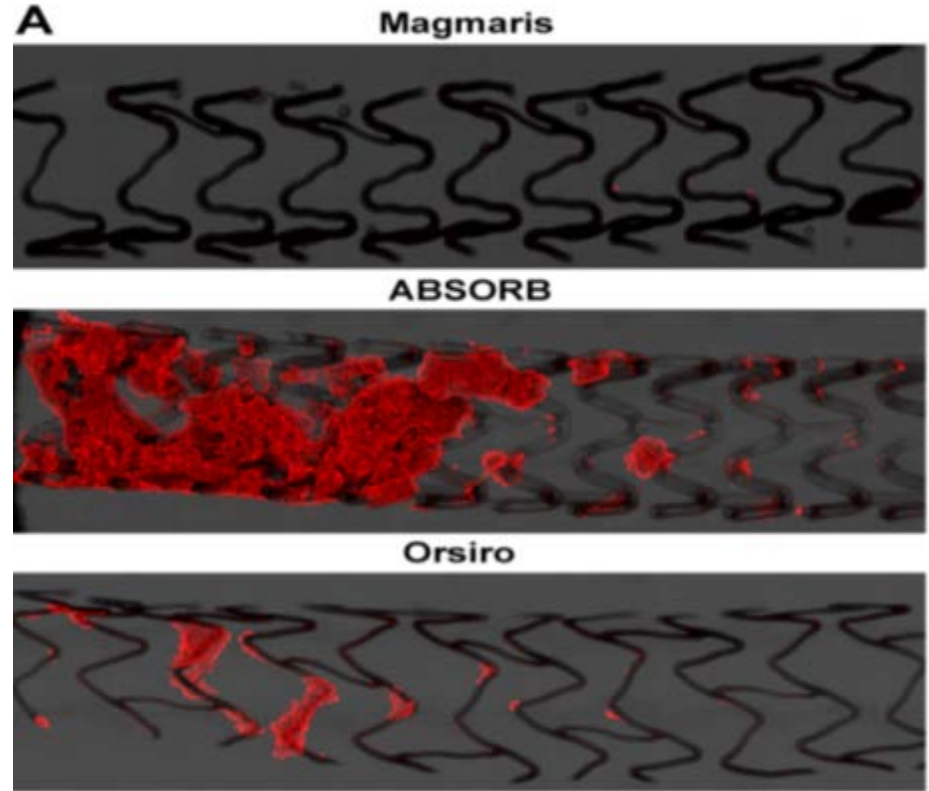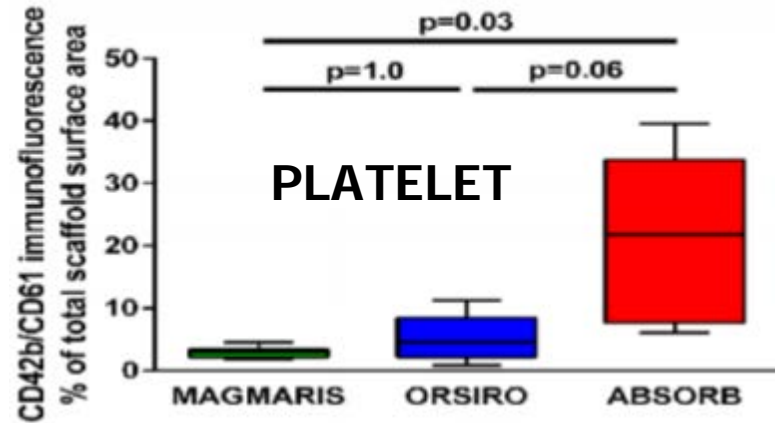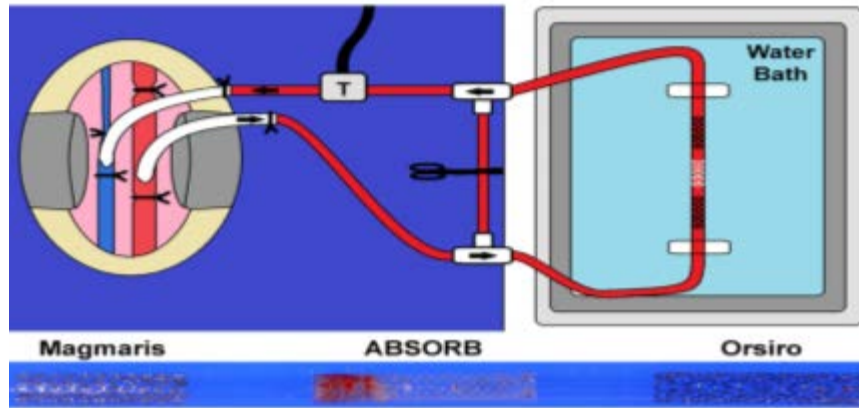
AMARANTH'S MINIATURIZATION PROCESS

150-μm

FORTITUDE
~20% SA*

1 mm

115-μm

APTITUDE
~21% SA*

800 μm

<100-μm

MAGNITUDE
~22% SA*

800 μm
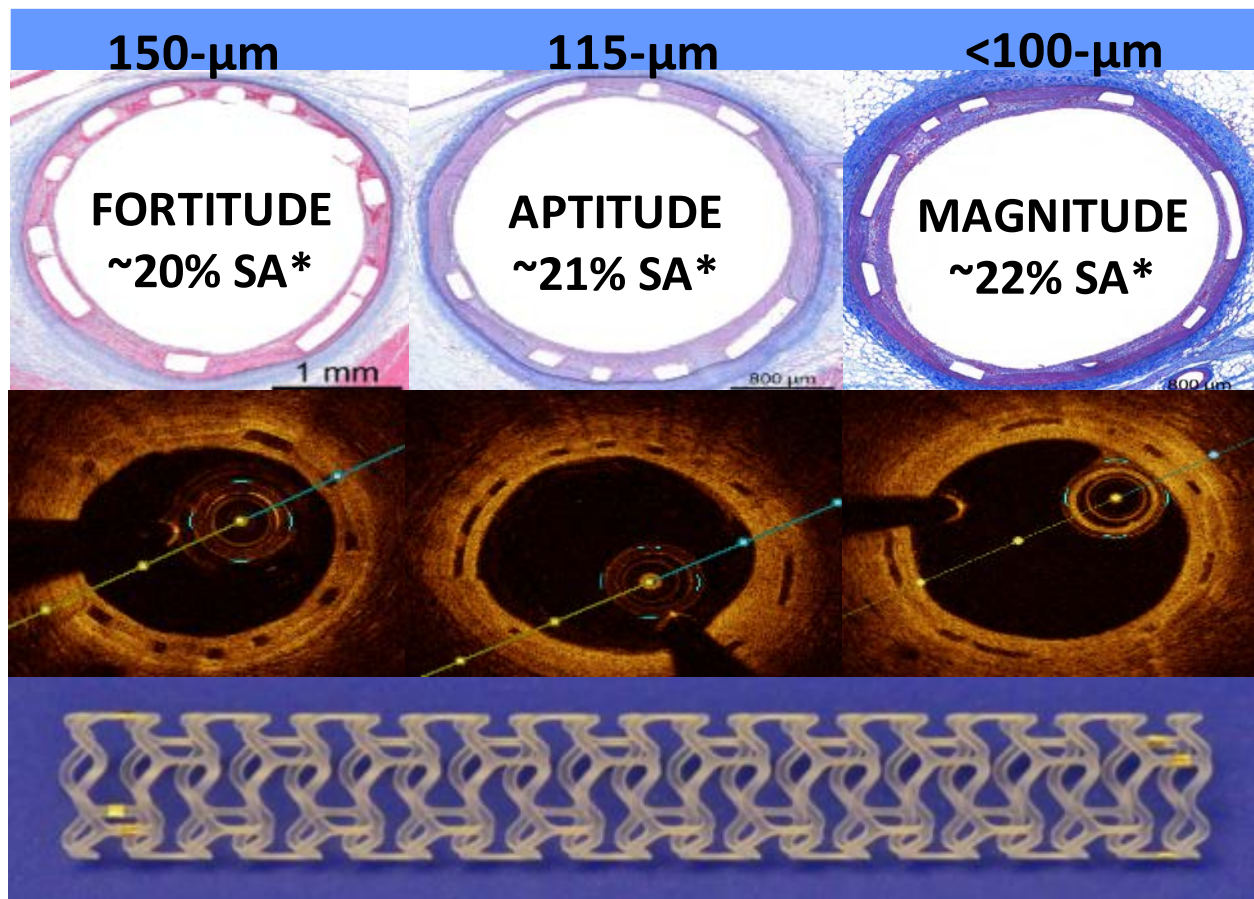
Strut miniaturization maintaining radial force to the <100μm range without compromising biomechanical behavior/properties

Small Studies Ongoing (n<200)

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*Surface Area at RBP, ABSORB BVS currently at ~27% at RBP

*Colombo A. First Report Investigation, TCT2016

DESolve Cx Bioresorbable Coronary Scaffold System

- **120 μm strut thickness**
  - Improved deliverability

- **System crossing profile (0.053" - 1.3mm*)**

- **6 Fr (0.71" – 1.8mm) guide catheter compatible**

- **0.014" wire compatible**
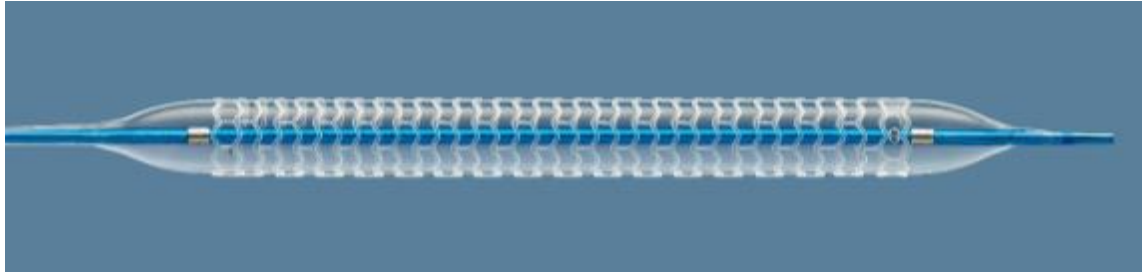
20%
Reduction
In Strut Thickness

DESolve (150 μm)

DESolve Cx

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Reva Fantom BRS Global Clinical Program

Enrollment Complete – In Follow Up

FANTOM I	**First-in-human safety study (n=7)**	🇪🇺 🇧🇷	Year 3
FANTOM II Cohorts A&B	**Multi-center safety and performance study (n=240)**	🇪🇺 🇧🇷	Year 2

Enrolling

FANTOM II Cohort C	**Long lesion and multiple vessel, multi-center study (n=50)**	🇪🇺	enrolling
FANTOM STEMI	**Single center pilot study in STEMI (n=20)**	🇪🇺	enrolling

Planning

FANTOM Registry	**European post-market multi-center registry (n=125+)**	🇪🇺	planning
FANTOM III (US pivotal trial)	**Multi-center RCT vs. metallic DES (n=1,800-2,200)**	🇺🇸 🇪🇺	planning
FANTOM Japan (pivotal trial)	**Multi-center RCT vs. metallic DES (n=350-400)**	🇯🇵	planning

J. Hermiller Presented at TCT 2017

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MeRes100 (developed in INDIA)
Sirolimus Eluting Bioresorbable Vascular Scaffold
100 micron strut thickness

100 µm

Hybrid cell design

Scaffold backbone PLLA 100 µm strut thickness

Drug coat of PDLLA + Sirolimus 1.25 µg/mm²

High radial strength, 22.30 N

Closed cell

Open cell

24% scaffold to artery ratio

Low recoil, 1.23%

Couplets of tri-axial RO markers at either end

Estimated degradation in 2-3 years

Optimal side branch access

MeRes-1

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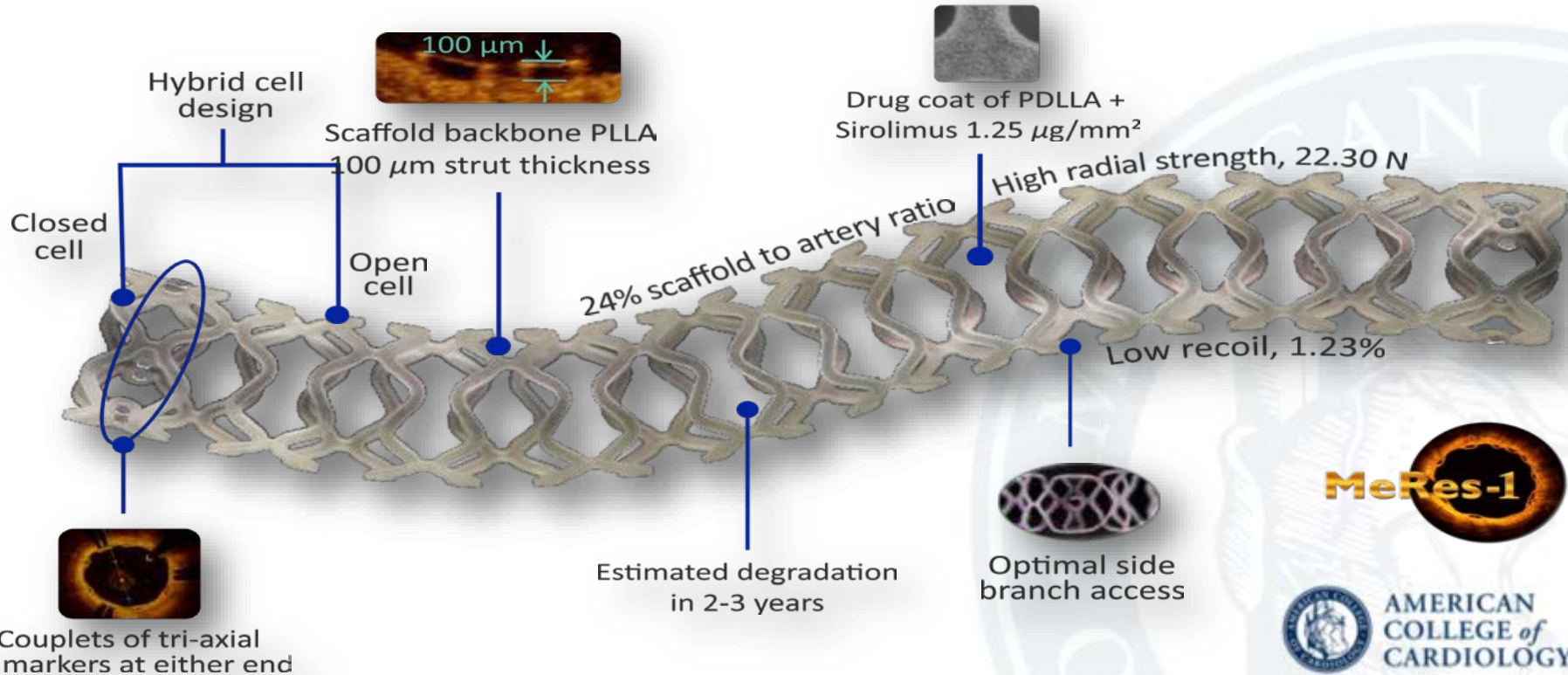
BRS Era: Conclusions 2017

We hoped for a stent that dissolves (*was it too much to ask?*)

- After it does its job
- And leaves no mark behind
- 1 was approved early indeed on long term promises...

Yet, our hopes were betrayed - BRS animal models inaccurate...

- DAPT came fast as a savior (*sounds familiar?*), but a bit too late...

We learnt a lot of lessons:

- Metallic EES may be super tough comparator!
- *Never Underestimate Endovascular Thrombosis...*
- Strut thickness is indeed a very basic factor to get right
- A BRS should, in fact, *Dissolve in time when in human coronaries*!

Bio-Engineering principles are improving steadily

A restart is expected – 2nd / 3rd Generation BRS

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Bioresorbable Vascular Scaffolds

The fourth revolution in interventional Cardiology?

Timeline:

- 1958 — Coronary angiography by F. Mason Sones
- 1964 — Angioplasty by Charles Theodore Dotter
- 1977 — Baloon angioplasty by Andreas Grüntzig
- 1986 — Palmaz-Schatz stent
- 1992 — Coronary angioplasty via radial artery
- 1993 — Primary angioplasty for STEMI
- 1996 — Coronary premounted NIR stent
- 2000 — Bioresorbable Igaki-Tamai stent
- 2002 — Drug-eluting Cypher stent
- 2005 — Second-generation drug-eluting stents
- 2006 — Bioresorbable absorb stent
- Bioresorbable magnesium alloy stent
- DESolve scaffold
- 2012
- 2014 — Reva Fantom scaffold