22nd CARDIOVASCULAR SUMMIT
TCTAP 2017 April 25-27, 2017
Coex, Seoul, Korea

Future Perspective on Next BRS

Yoshinobu Onuma MD. PhD.[1]

Yohei Sotomi MD.[2], Taku Asano, MD. [2],

Erhan Tenecioglu, MD[1], Yosuke Miyazaki, MD.[1], Yuki Katagiri, MD[2]

Patrick W. Serruys MD. PhD.[3]

1. Erasmus University/ Cardialysis, Rotterdam, the Netherlands

2. Academisch Medisch Centrum, Amsterdam, the Netherlands

3. NHLI, Imperial College London, London, United Kingdom

Review

Bioresorbable Scaffold
The Emerging Reality and Future Directions

Yohei Sotomi, Yoshinobu Onuma, Carlos Collet, Erhan Tenekecioglu, Renu Virmani, Neal S. Kleiman, Patrick W. Serruys

Abstract: **In the era of drug-eluting stents, large-scale randomized trials and all-comer registries have shown excellent clinical results. However, even the latest-generation drug-eluting stent has not managed to address all the limitations of permanent metallic coronary stents, such as the risks of target lesion revascularization, neoatherosclerosis, preclusion of late lumen enlargement, and the lack of reactive vasomotion. Furthermore, the risk of very late stent, although substantially reduced with newer-generation drug-eluting stent, still remains. These problems were anticipated to be solved with the advent of fully biodegradable devices. Fully bioresorbable coronary scaffolds have been designed to function transiently to prevent acute recoil, but have retained the capability to inhibit neointimal proliferation by eluting immunosuppressive drugs. Nevertheless, long-term follow-up data of the leading bioresorbable scaffold (Absorb) are becoming available and have raised a concern about the relatively higher incidence of scaffold thrombosis. To reduce the rate of clinical events, improvements in the device, as well as implantation procedure, are being evaluated. This review will focus on the current CE-mark approved bioresorbable scaffolds, their basic characteristics, and clinical results. In addition, we summarize the current limitations of bioresorbable scaffold and their possible solutions.** (*Circ Res*. 2017;120:1341-1352. DOI: 10.1161/CIRCRESAHA.117.310275.)

Key Words: bioresorbable scaffold ■ magnesium ■ polymers ■ thrombosis

Mechanical properties of metal vs. PLLA

Composition	Tensile modulus of elasticity (Gpa)	Tensile strength (Mpa)	Elongation at break (%)	Degradation time (months)	Products
Poly (L-lactide)	3.1-3.7	60-70	2-6	>24	Absorb (platform), DESolve (platform), Magmaris (coating)
Poly (DL-lactide)	3.1-3.7	45-55	2-6	6-12	Absorb (coating)
Magnesium alloy	40-45	220-330	2-20	1-3	Magmaris (platform)
Cobalt chromium	210-235	1449	~40	Biostable	Xience

Onuma and Serruys Circulation 2011

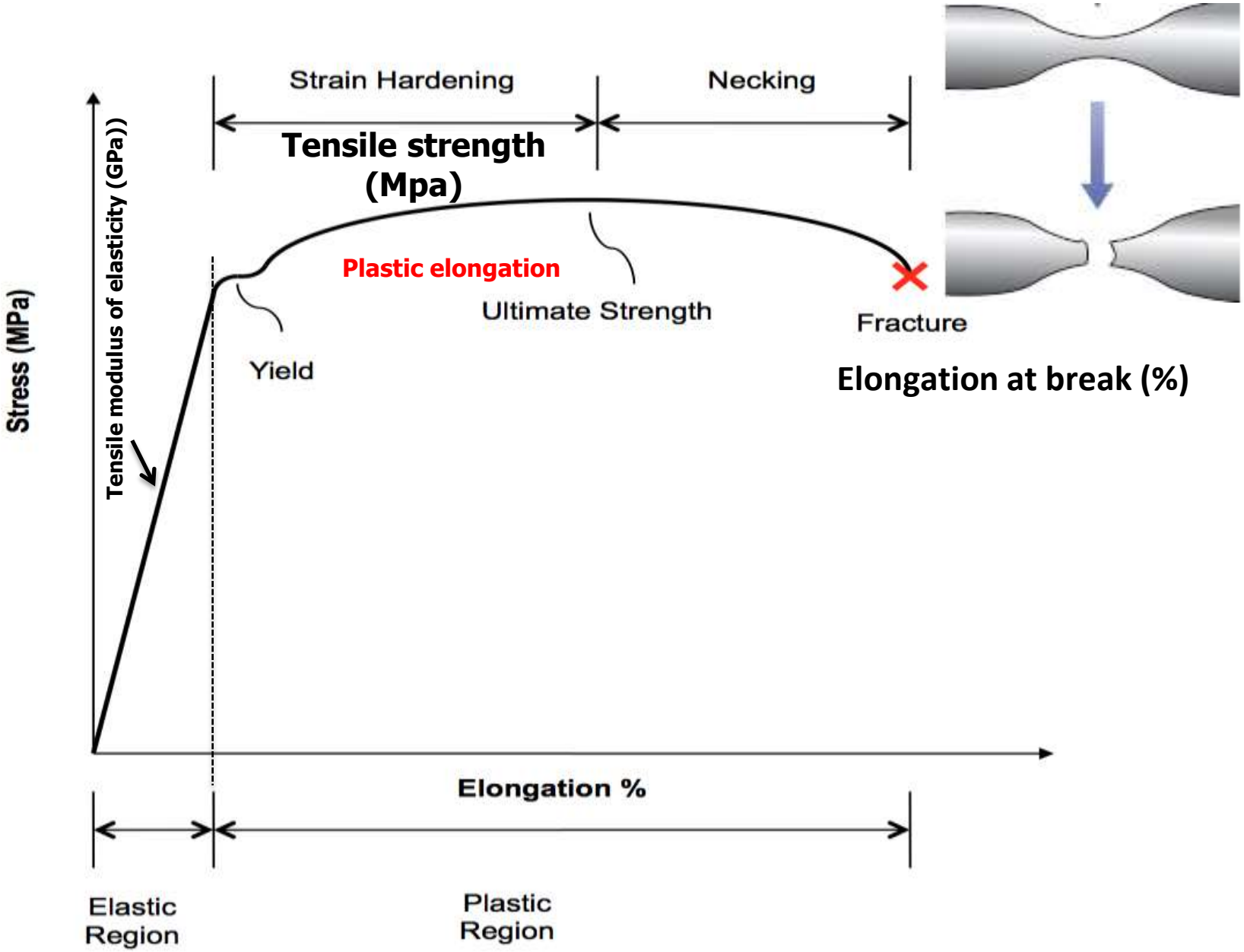
Current limitation of BRS

If a bioresorbable scaffold is ultimately expected to have the same range of applicability as a durable metal stent, the gap in mechanical properties must be reduced.

Currently, three primary limitations exist:

- **Low tensile strength and stiffness which require thick struts to prevent acute recoil**
- **Insufficient ductility which impacts scaffold retention on balloon catheter and limits the range of scaffold expansion during deployment**
- **Instability of mechanical properties during vessel remodeling if bioresorption is too fast**

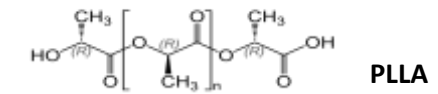
Let's take a "crash course" of material science



Bioresorption profiles

Sotomi et al. Circ Research 2017

Bioresorption process of current CE-mark approved BRSs



PLLA → Hydrolysis → Lactic acid → Krebs cycle → $CO_2 + H_2O$

(A) Absorb

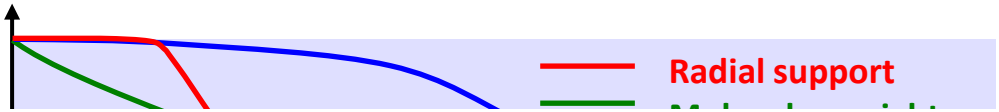
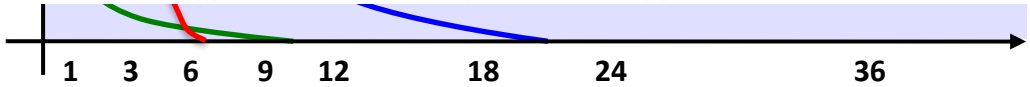


Table 1. CE-Mark Approved Bioresorbable Scaffolds

Stent Name (Manufacturer)	Stent Platform	Strut Thickness	Coating Material	Coating Thickness	Drug	Reported Release Profile	Drug Dose
BVS 1.1 (Abbott)	PLLA	157 μm	PLLA	2–4 μm	Everolimus	75% of loaded everolimus within 30 days	100 μg/cm²
DESolve (Elixir)	PLLA	150 μm	Bioresorbable polymer	<3 μm	Novolimus	More than 85% of the drug is released over 4 wk	5 μg/mm
ART Pure (ART)	PDLLA	170 μm	…	…	No drug	NA	NA
Magmaris (Biotronik)	93% Mg and 7% rare earth elements	150 μm	PLLA	1 μm	Sirolimus	Over 3 to 6 mo	1.4 μg/mm²

BVS indicates bioresorbable vascular scaffold; NA, data not available; PDLLA, poly(L-lactide-co-D,L-lactide); and PLLA, poly-L-lactide.

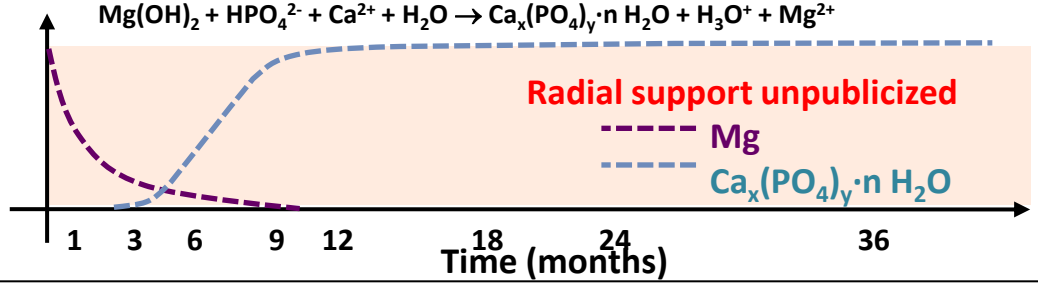


Magnesium

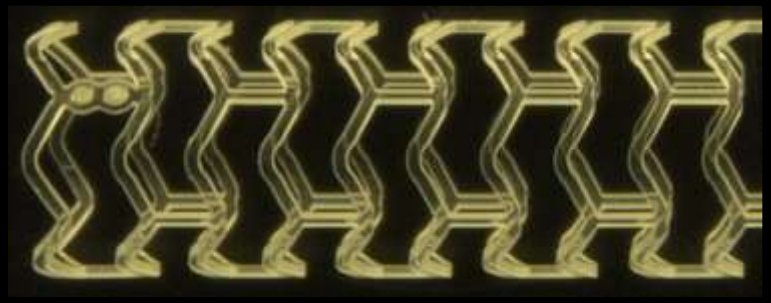
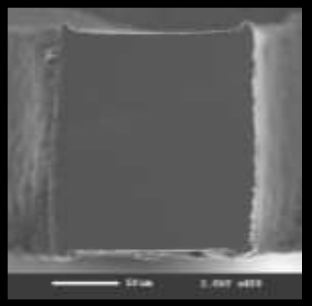
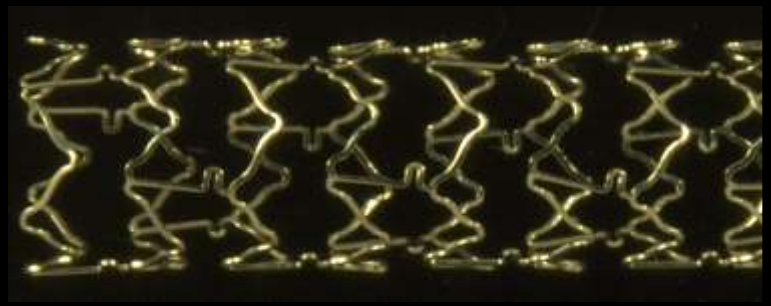
(D) Magmaris

$Mg + 2\ H_2O \rightarrow Mg(OH)_2 + H_2$

$Mg(OH)_2 + HPO_4^{2-} + Ca^{2+} + H_2O \rightarrow Ca_x(PO_4)_y \cdot n\ H_2O + H_3O^+ + Mg^{2+}$



Design of Absorb and Xience

	Macroscopic appearance	Material	Cross-section	Strut thickness
Absorb scaffold		PLLA + PDLLA		157 μm
Xience V		Co-Cr + durable fluoropolymer		89 μm

Covered vessel wall area (footprint [3.0mm device]):
26% (Absorb scaffold) vs. 12% (Xience V)

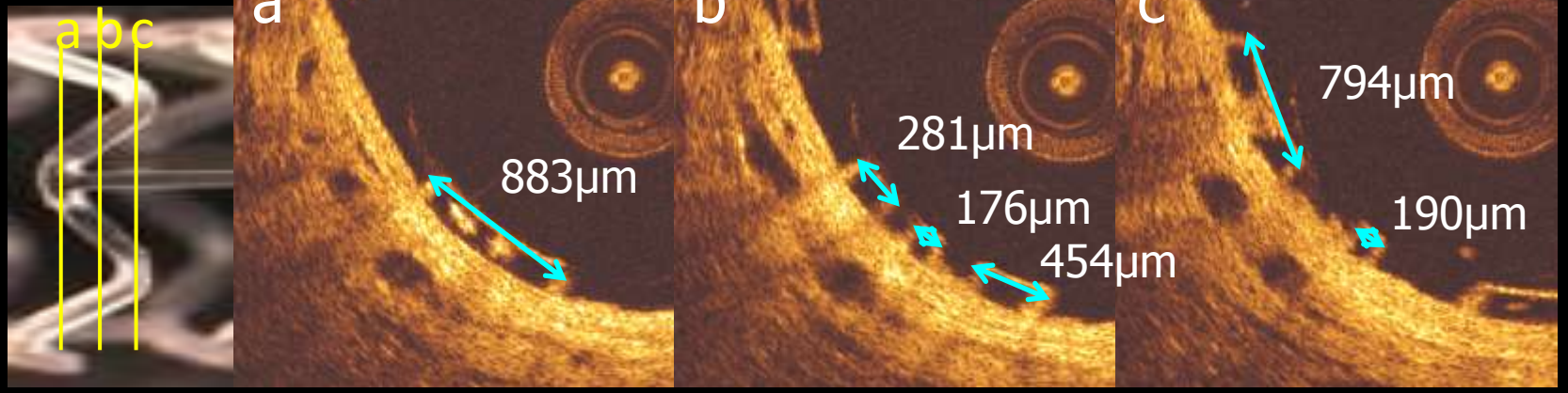
Muramatsu et al. JACC interv 2013

Snowshoe Versus Ice Skate for Scaffolding of Disrupted Vessel Wall*

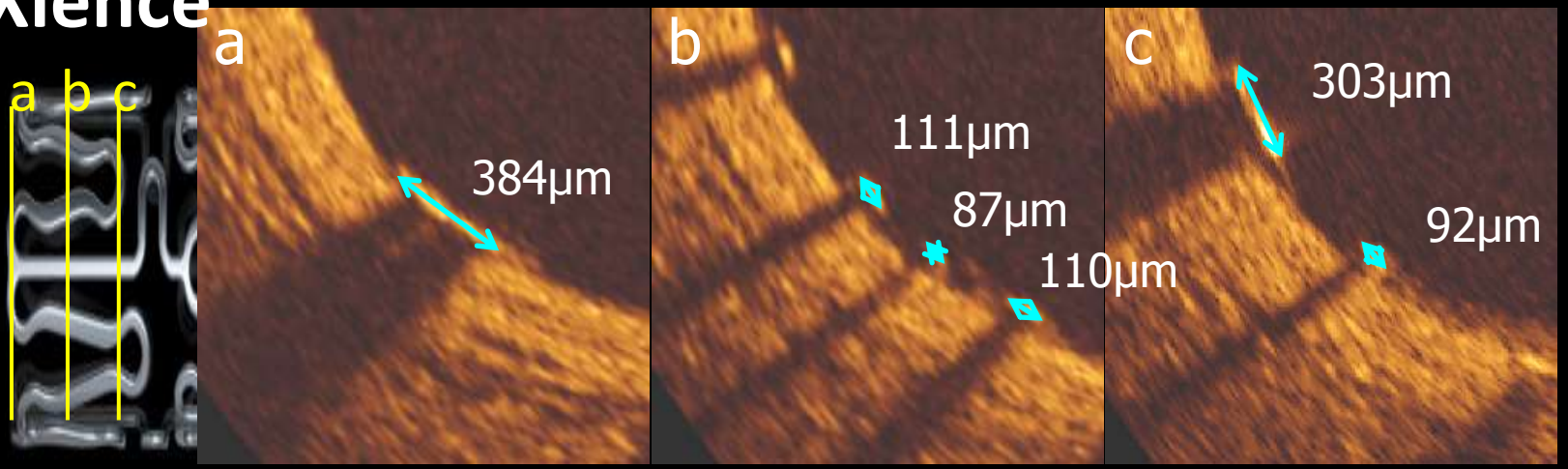
Patrick W. Serruys, MD, PhD,† Pannipa Suwannasom, MD,‡ Shimpei Nakatani, MD,‡ Yoshinobu Onuma, MD, PhD‡

Difference of Strut Width in each part (Hinge, Link, Ring)

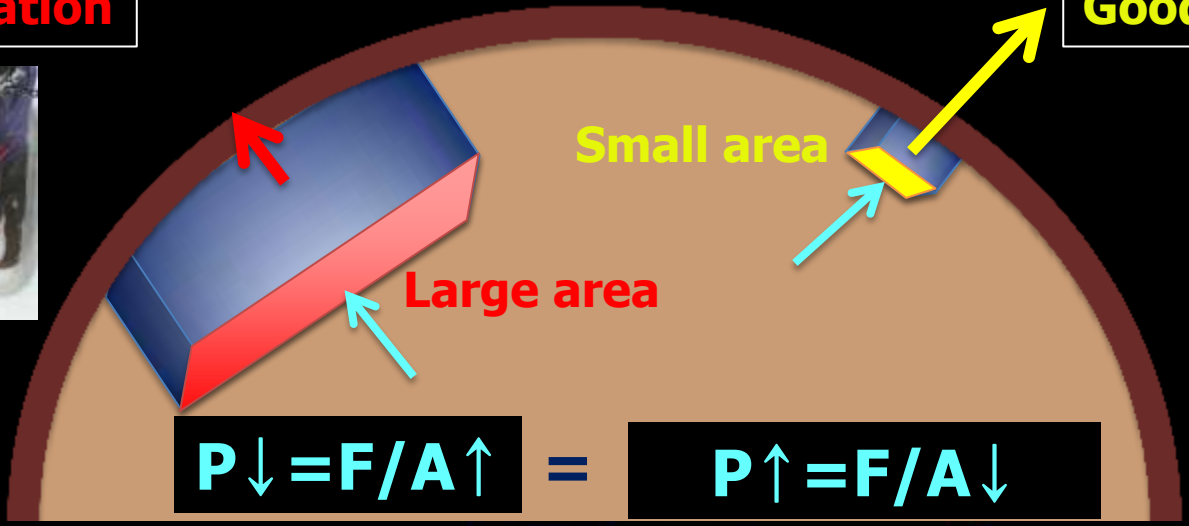
Absorb



Xience

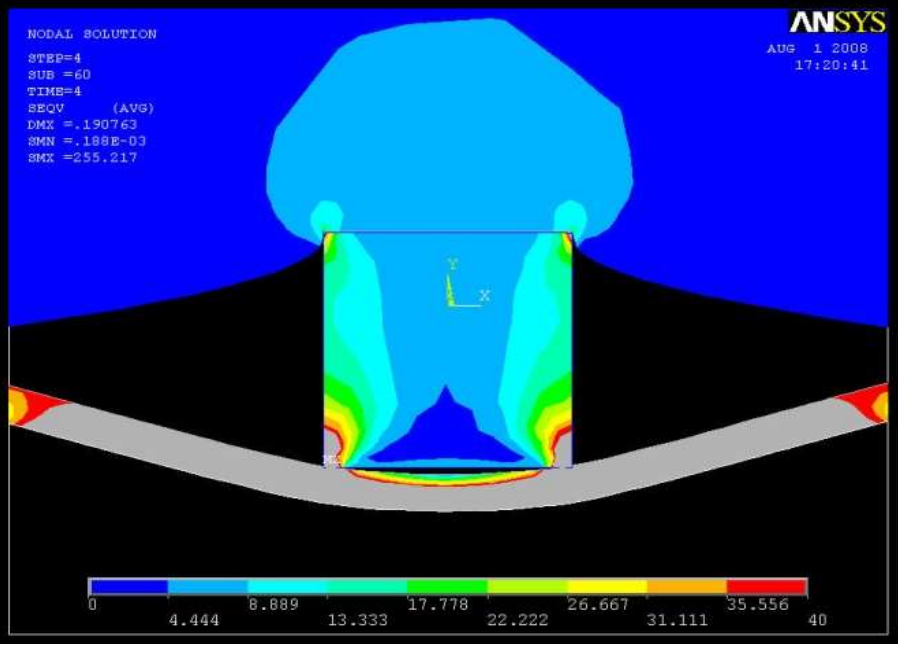


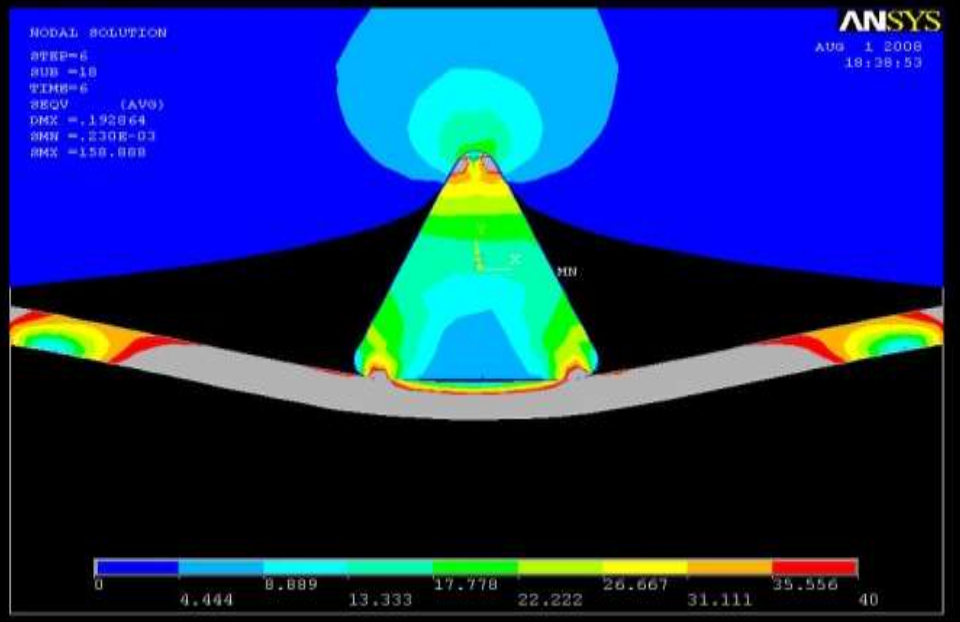
Poor penetration



Good penetration

$P\downarrow = F/A\uparrow$ = $P\uparrow = F/A\downarrow$





Large strut area →Poor penetration → Small expansion

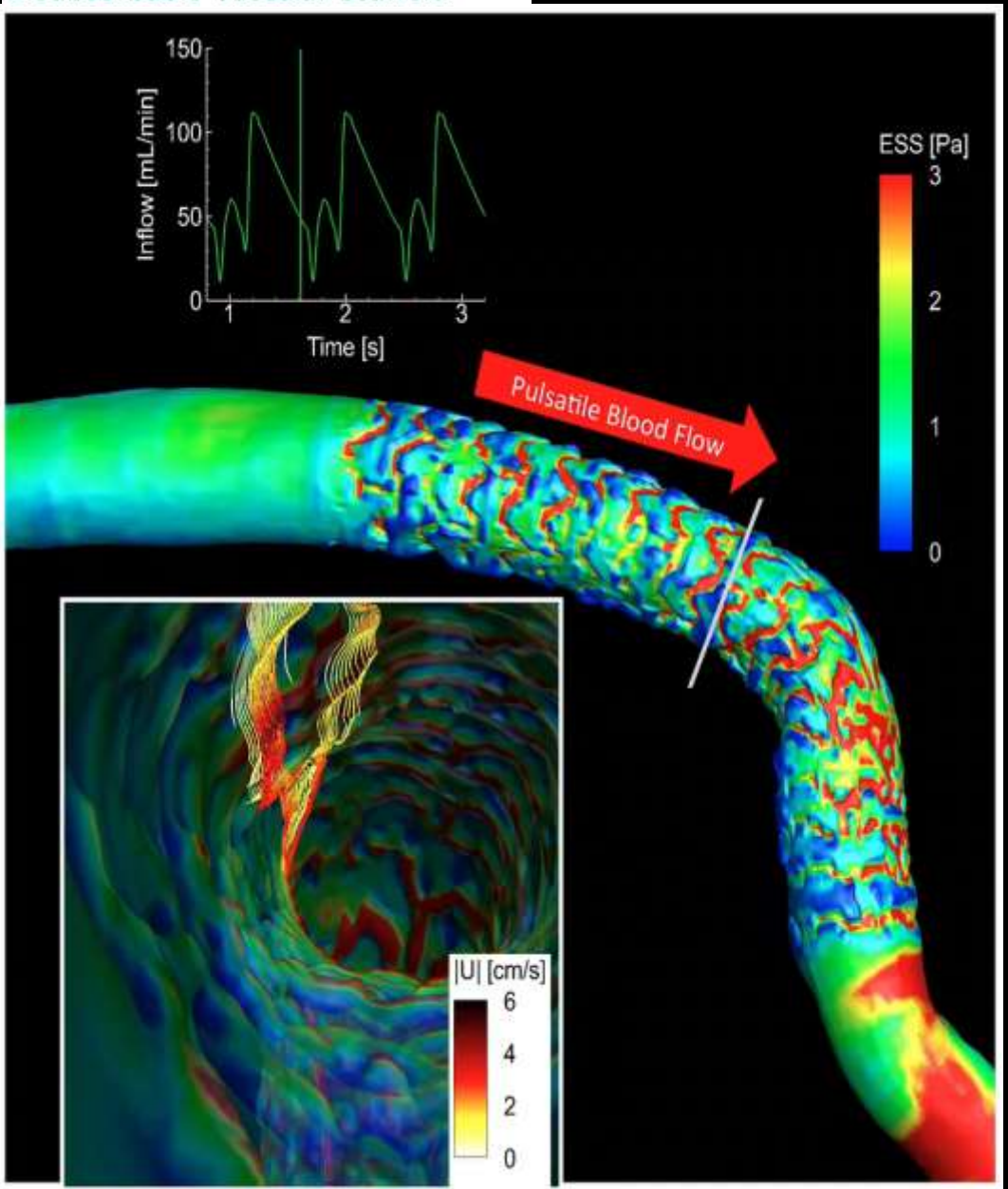
Small strut area →Good penetration → Large expansion

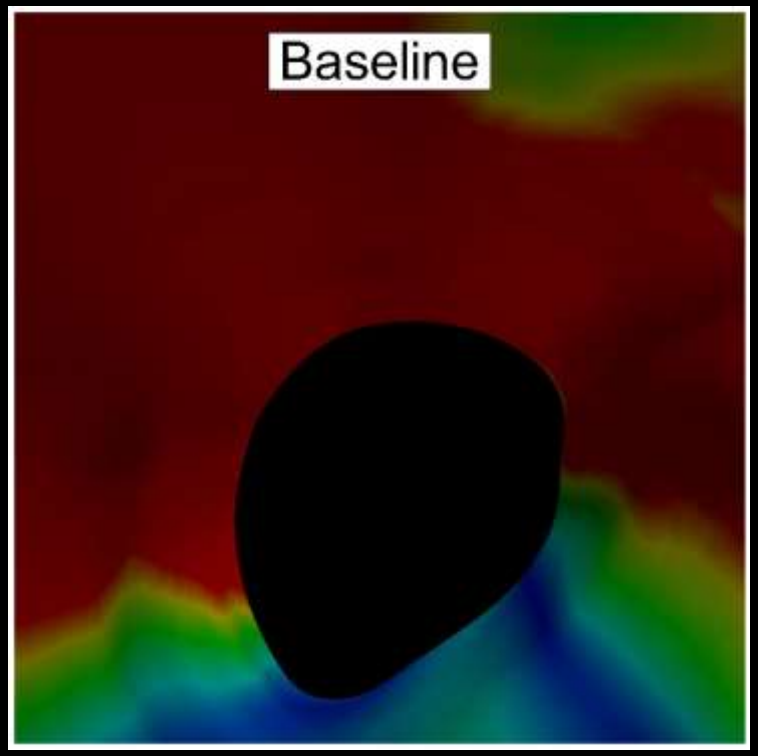
Serruys, Suwannason et al. JACC CI

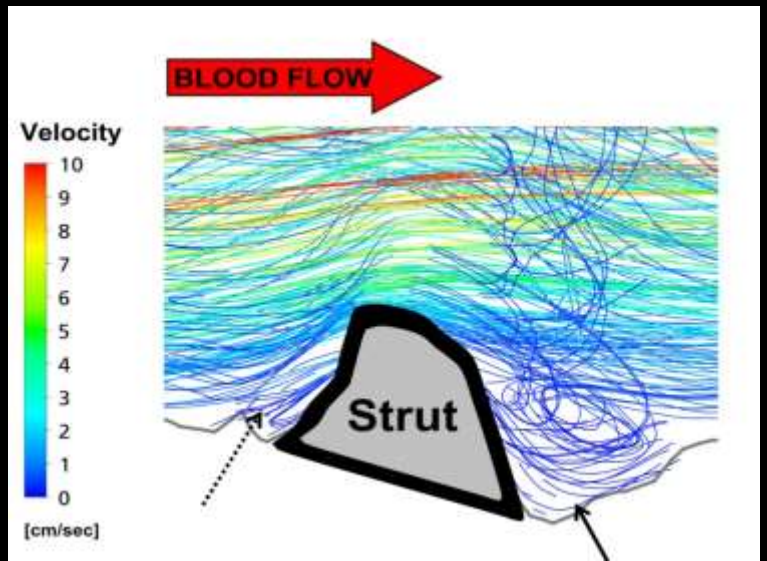
The Nidus for Possible Thrombus Formation

Insight From the Microenvironment of Bioabsorbable Vascular Scaffold

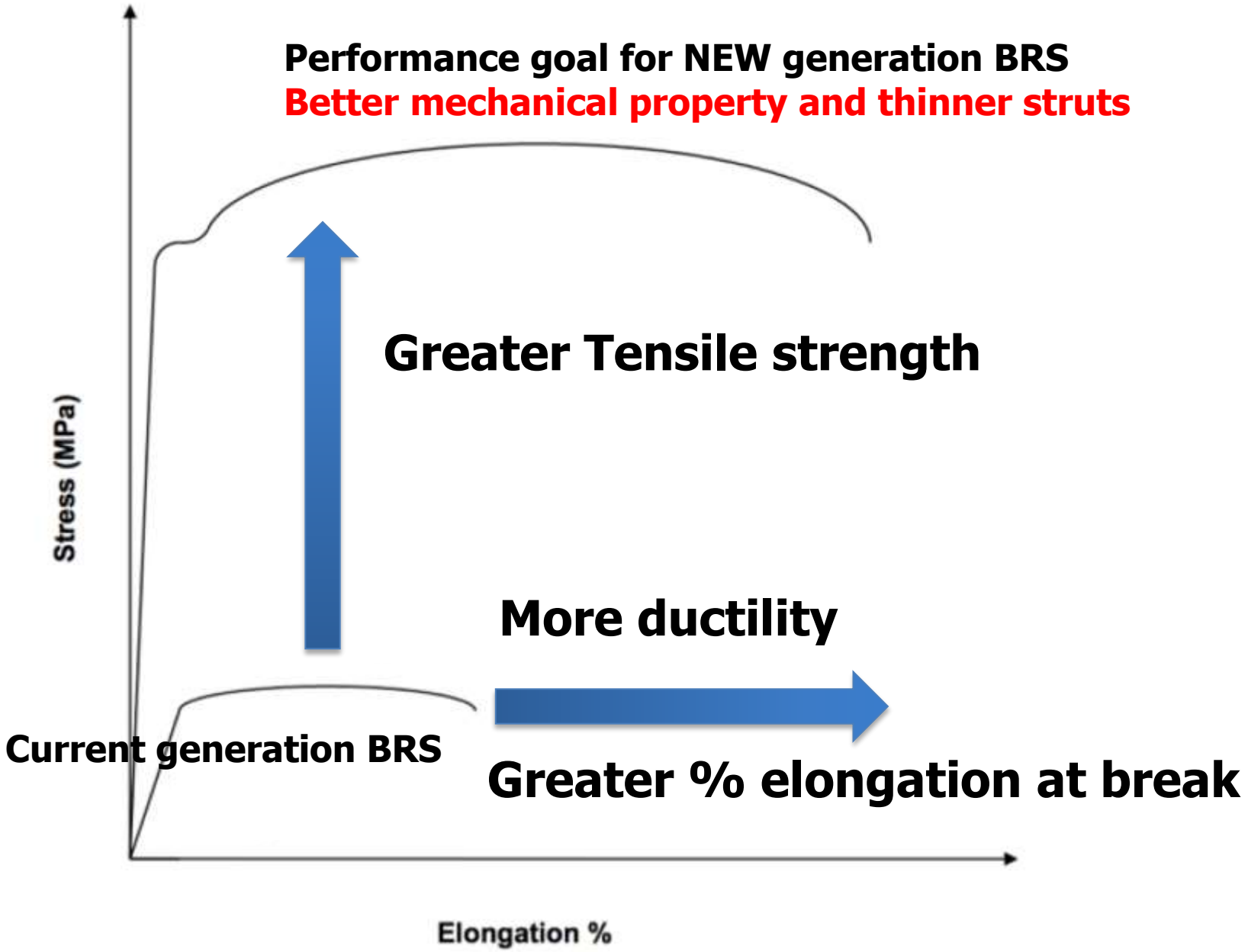
Tenekecioglu et al. JACC intervention 2016
Bourantas et al. JACC intervention

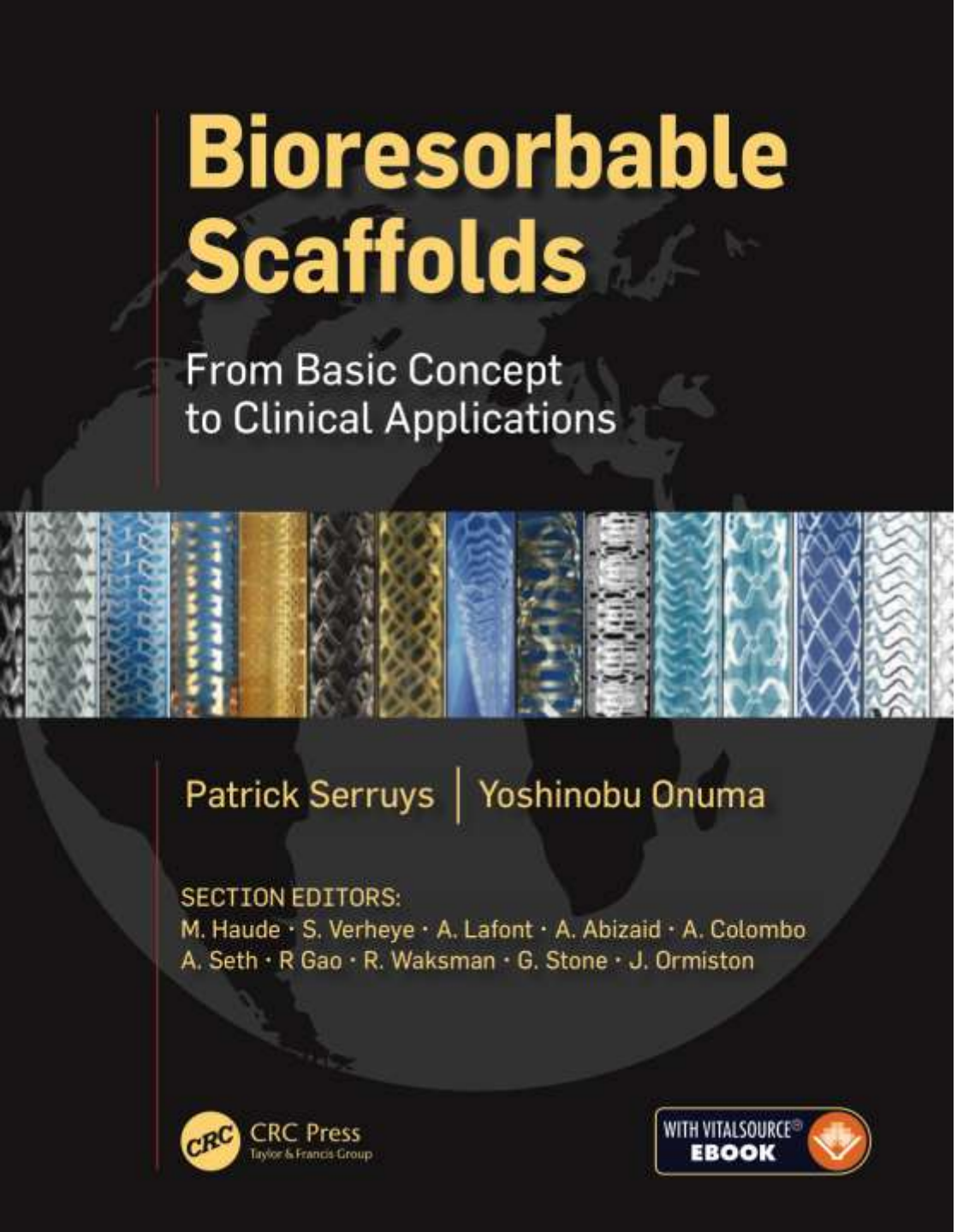






Performance goal and mechanical dilemma





Chapter 10
Emerging technologies (Pre-CE mark, Pre FDA, pre PMDA and pre CFDA)

Lifetech

Qualimed

Meril life

Orbus Neich

Abbott: New generation Absorb scaffold

Arterius

Manli

Boston Scientific

Huaan tech

Lepu

"Playing" with molecular orientation and mechanical property of PLLA

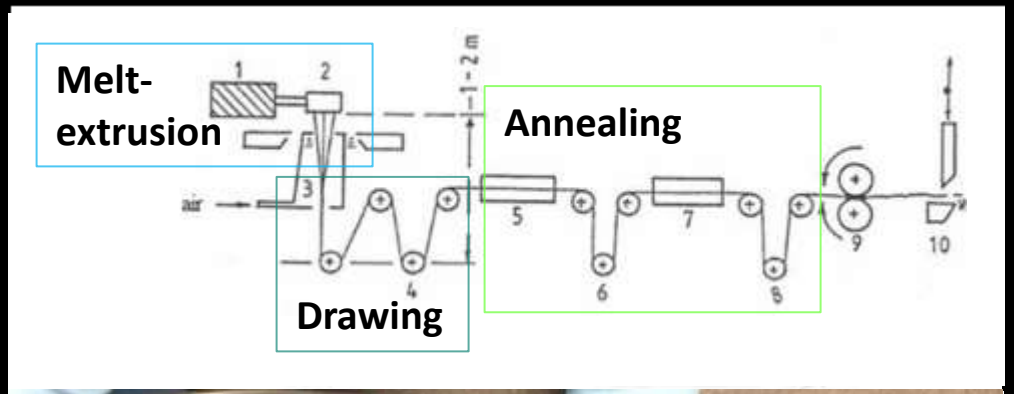
e.g. Manli Cardiology's Microfiber Technology

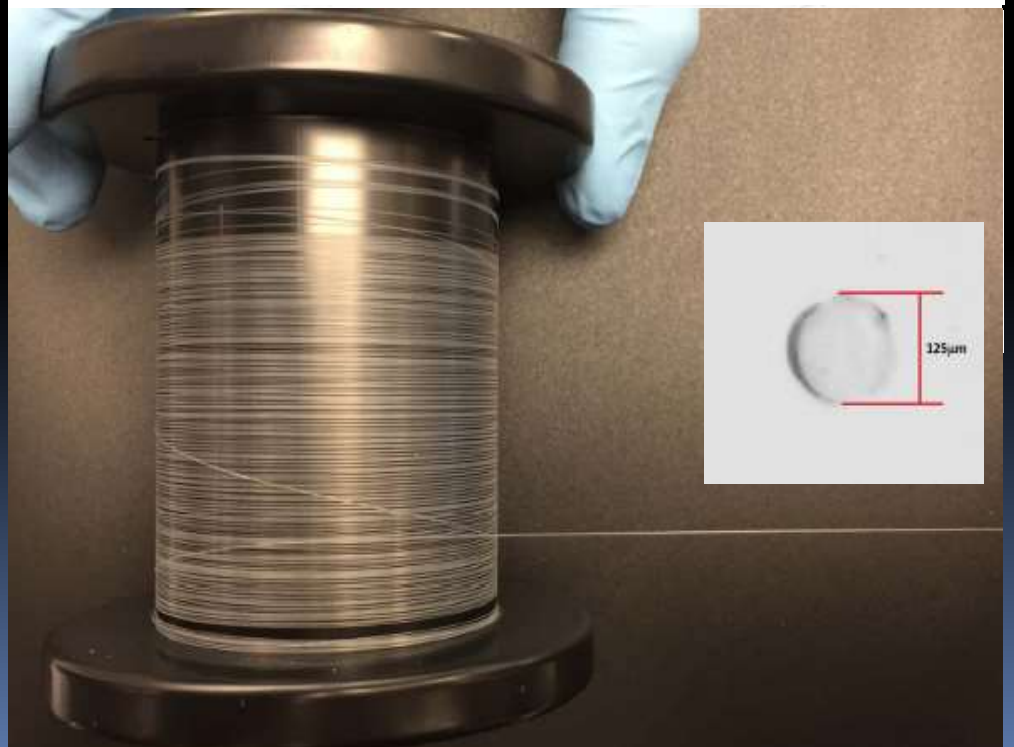
1. Highly oriented polylactide constituting a circular monofilament with preferred directional mechanical properties.

2. Convert monofilament's directional mechanical properties into scaffold's radial mechanical properties.

3. Transform circular monofilament into a scaffold with circular strut geometry.

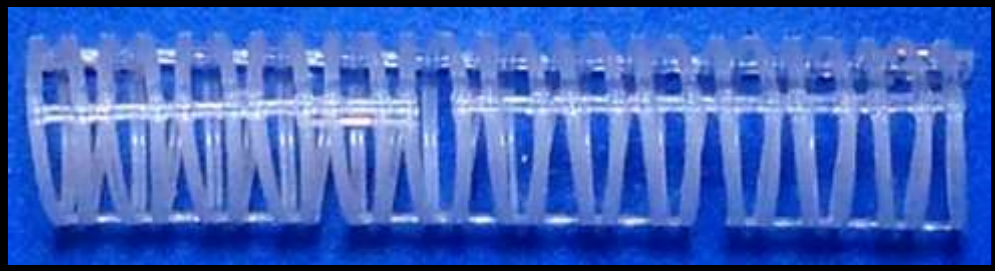
Amorphous Polymer Oriented Polymer Chain

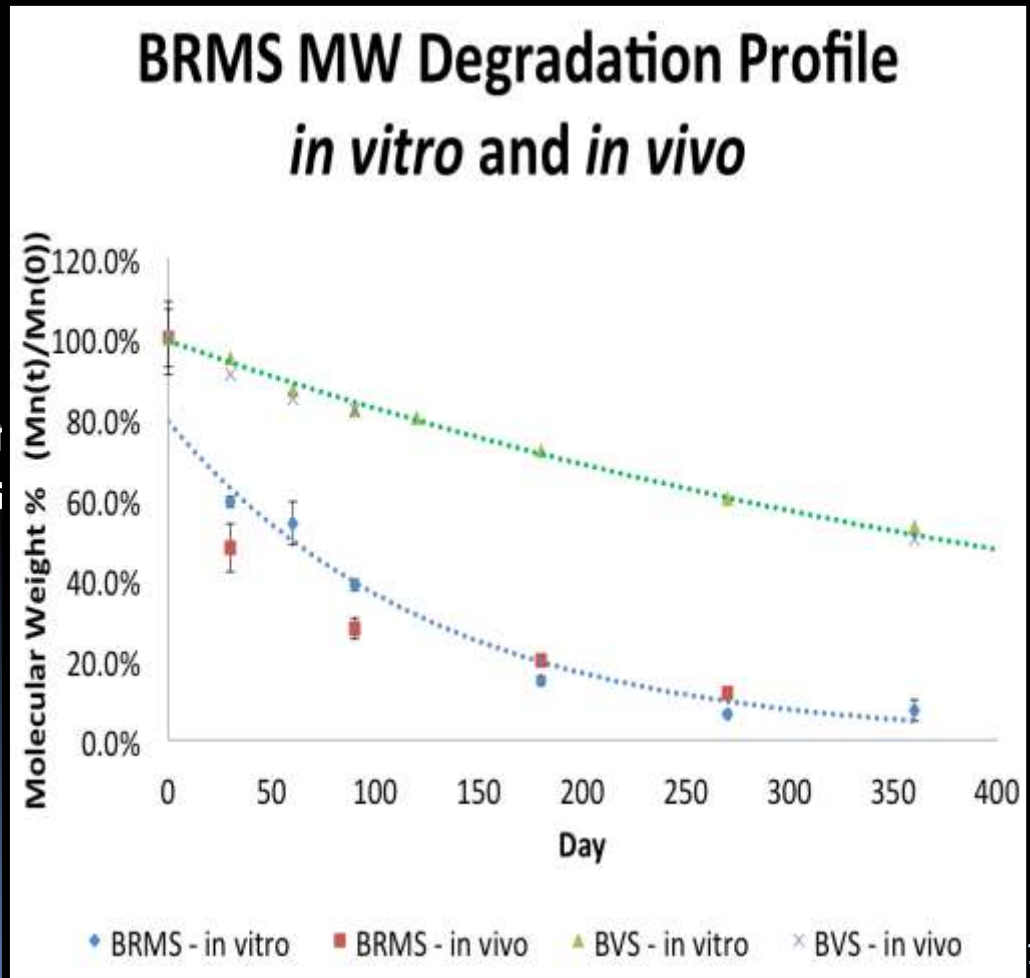




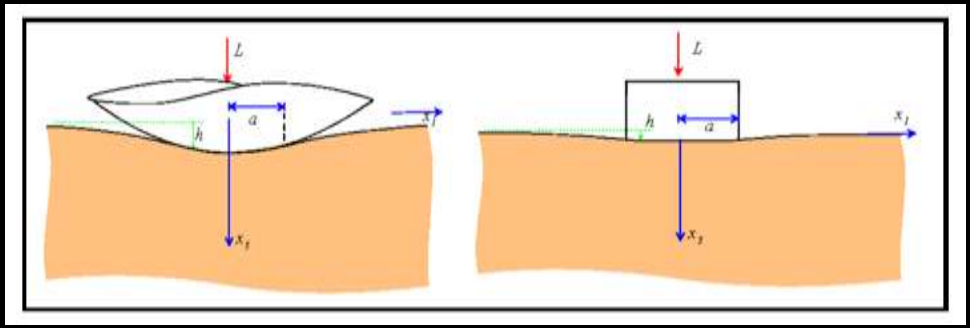
Manli Cardiology's Microfiber Technology

1. Start with highly oriented circular polylactide monofilament with preferred directional mechanical properties.
2. Convert monofilament's directional mechanical properties into scaffold's radial mechanical properties.
3. Make monofilament's circular geometry into scaffold strut's circular geometry.
4. Ambient temperature assembly process





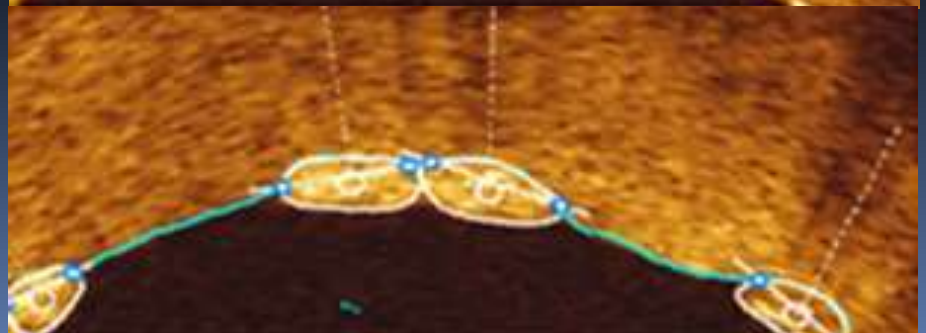
CIRCULAR STRUTS (mono fiber) PENETRATE INTO THE VESSEL WALL BETTER THAN THE *QUADRATIC* STRUTS

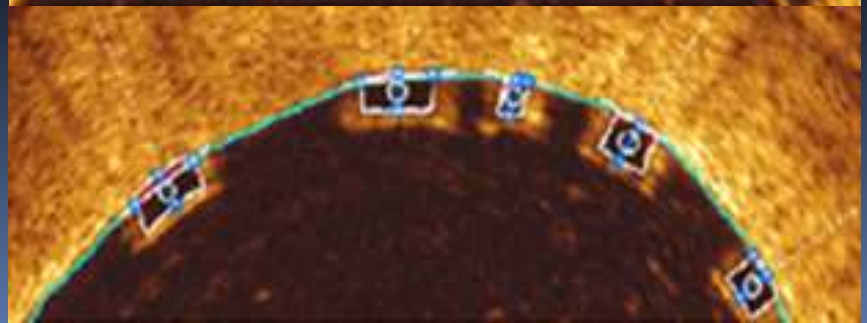


$$p(\rho) = \frac{2\mu h}{\pi(1-\nu)\sqrt{a^2-\rho^2}}$$

Axisymmetric contact pressure distribution is in an inverse relation with the initial contact radius (a in the figure).

Green, A.E. and Zerna, W., Theoretical Elasticity. 1968
Ting, T. T. C. Anisotropic Elasticity Theory and Applications, 1996





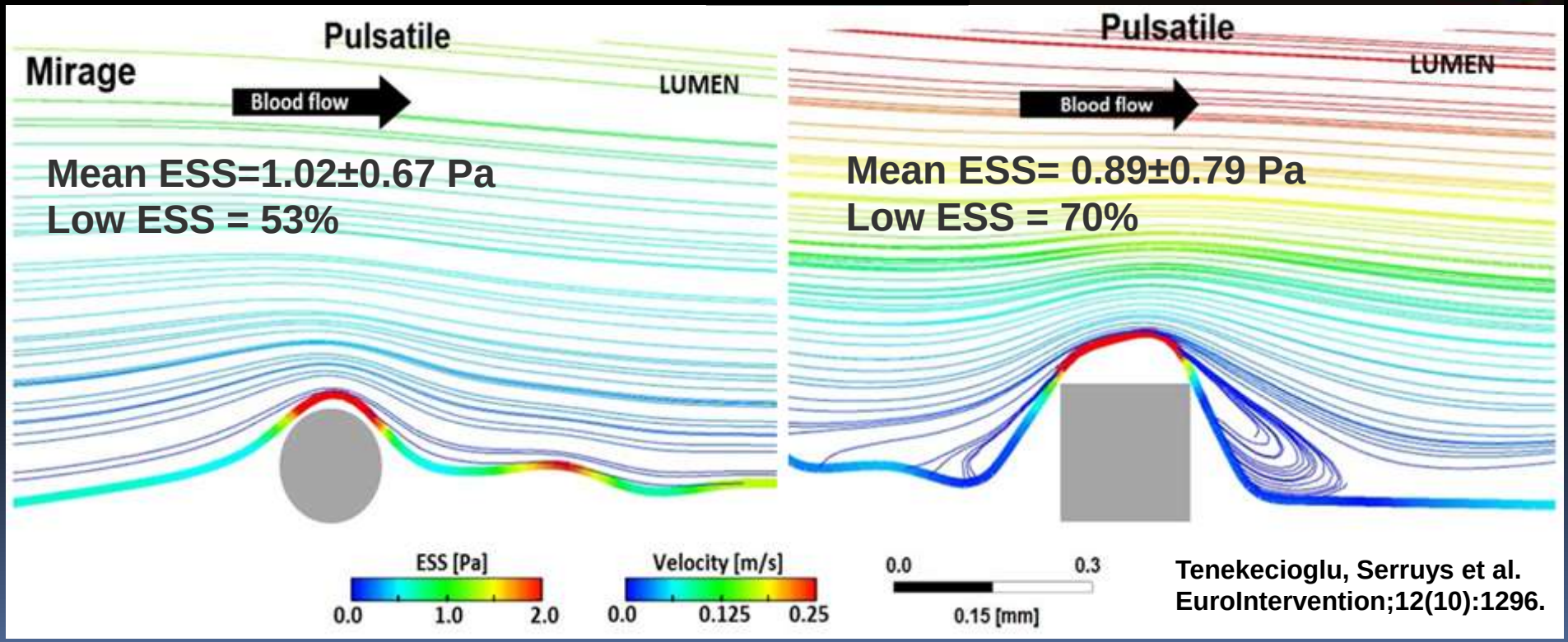
In a porcine model (n=8), flow and endothelial shear stress simulation differentiated the two devices

Tenekecioglu et al. Int J Cardiovasc Imaging. 2017 Apr 1.

MIRAGE BRMS(n=11)

ABSORB BVS (n=6)

Serruys PW, et al. Int J Cardiol. 2017; 227:467-473.



Tenekecioglu, Serruys et al. EuroIntervention;12(10):1296.

Note the intense recirculation area behind the quadratic strut

Matched OCT Cross-Sections

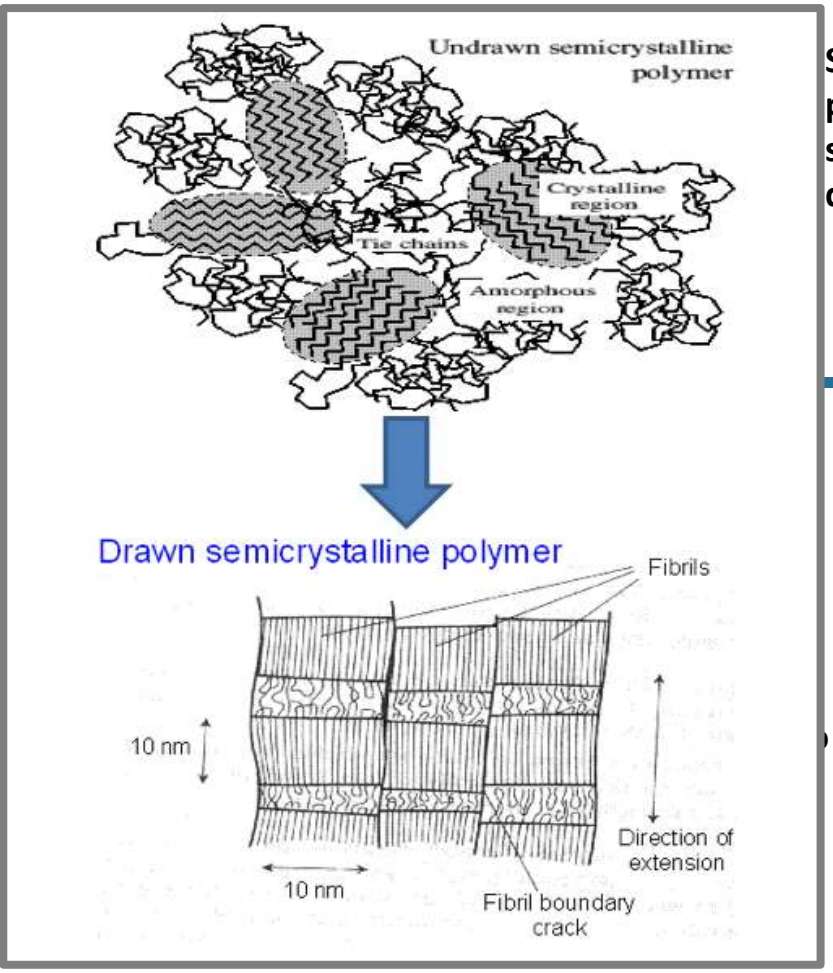
JACC: CARDIOVASCULAR INTERVENTIONS VOL. ■, NO. ■, 2017

ISSN 1936-8798/$36.00
http://dx.doi.org/10.1016/j.jcin.2017.03.015

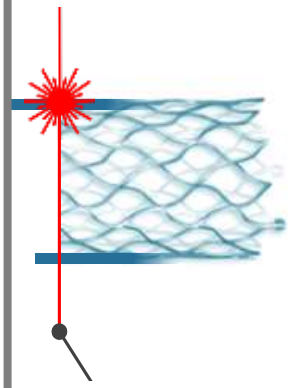
Randomized Comparison of Absorb Bioresorbable Vascular Scaffold and Mirage Microfiber Sirolimus-Eluting Scaffold Using Multimodality Imaging

Erhan Tenekecioglu, MD,[a] Patrick W. Serruys, MD, PhD,[a,b] Yoshinobu Onuma, MD, PhD,[a] Ricardo Costa, MD,[c] Daniel Chamié, MD,[c] Yohei Sotomi, MD,[d] Ting-Bin Yu, PhD,[e] Alexander Abizaid, MD, PhD,[c] Houng-Bang Liew, MD,[f] Teguh Santoso, MD, PhD[g]

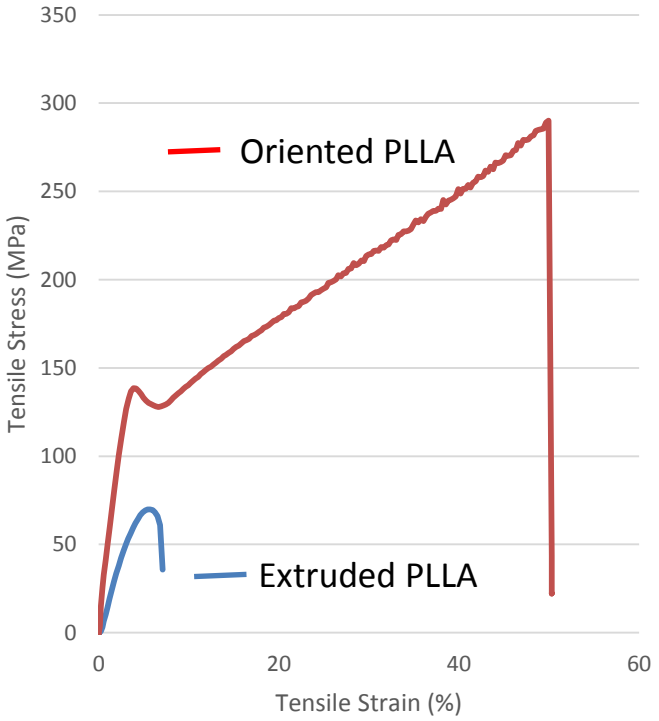
#2 "Playing" with molecular orientation and mechanical property of PLLA: ArterioSorb™ scaffold of ARTERIUS



Semi-crystalline polymer created by stretching or drawing the fibers



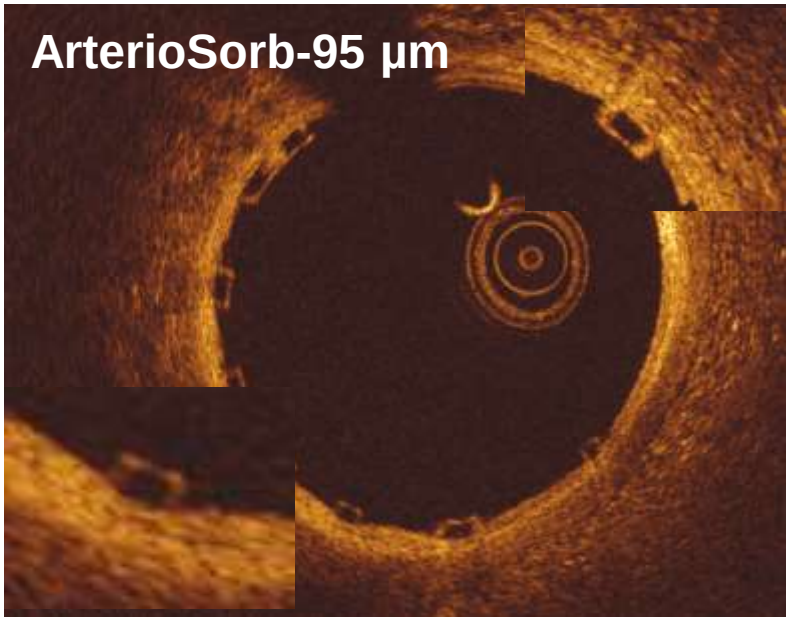
Laser cutting of stent (standard technology)

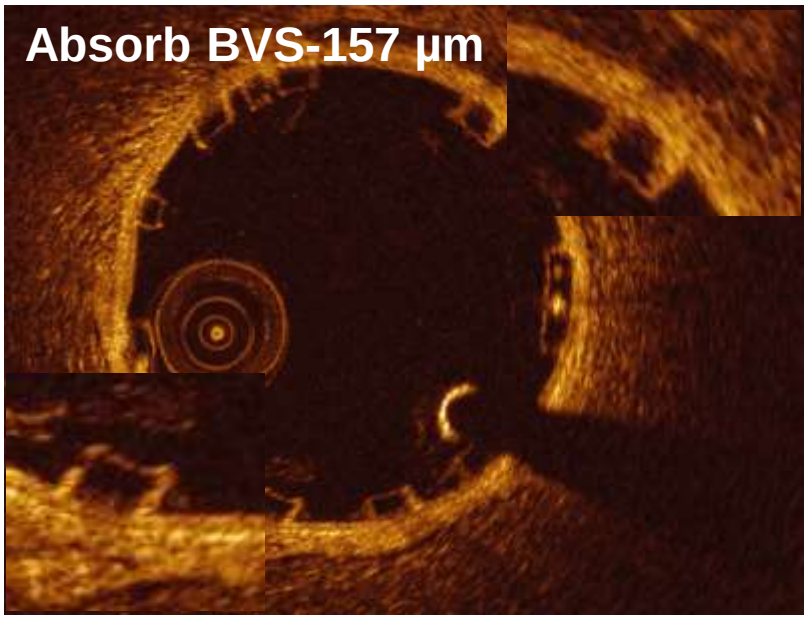


- **Tube wall thickness of < 95 µm can be achieved**
- **Scaffold tube thickness comparable to metallic DES**

Reducing the protrusion of the strut (stronger and thinner strut ,polylactatide oriented)

Scaffold	Lumen diameter (mm)	Balloon-artery ratio	Scaffold-artery ratio	Acute recoil (%)
Arteriosorb-95 (n=6)	2.97±0.15	1.08±0.06	1.05±0.04	2.7±3.9





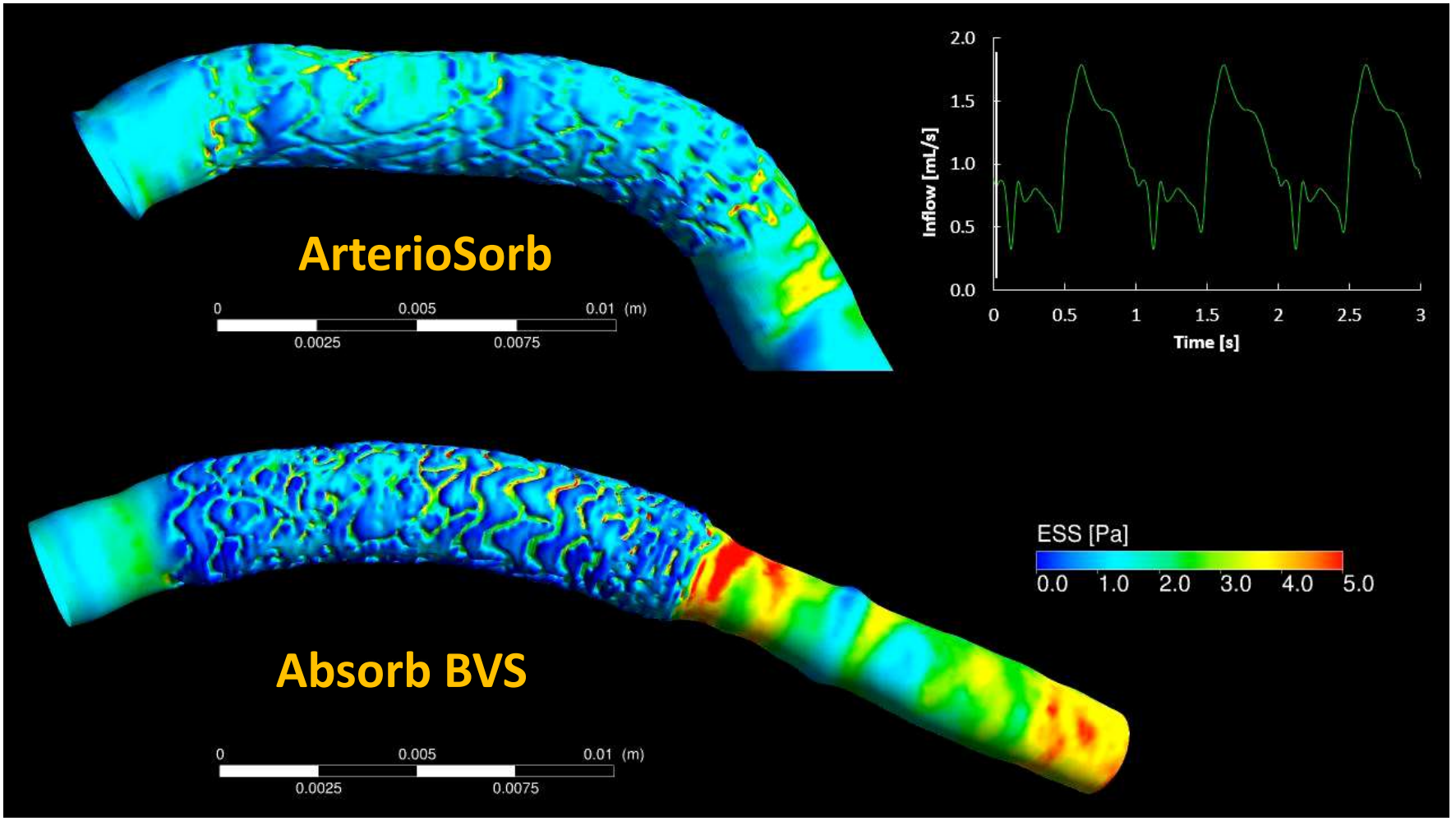
Protrusion distance: 89±7 µm

Protrusion distance: 150±9 µm

Arteriosorb from Arterius

Absorb from Abbot

Non-Newtonian Pulsatile Simulation of Coronary Flow in Scaffold Implanted Vessel Segments

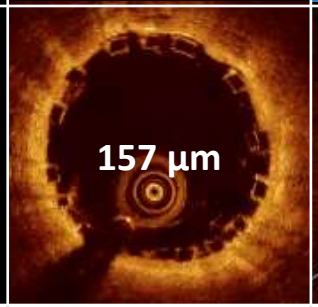
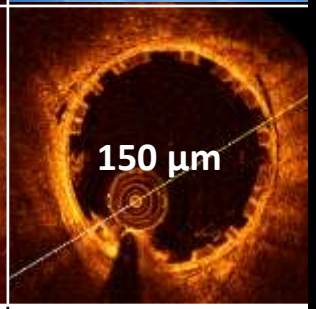
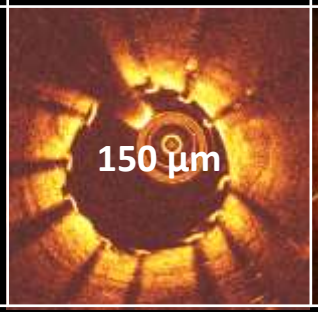
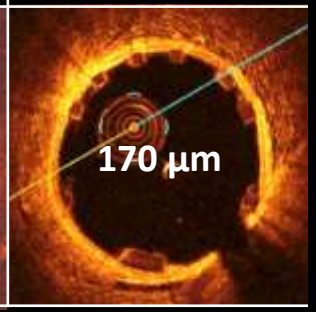


Serruys, Bourantas, Torii, Teneciogulu, Al-Lamee, Onuma et al. Optics in Cardiology 2017

Aiming at thinner struts

From 150 µm to 100 µm…

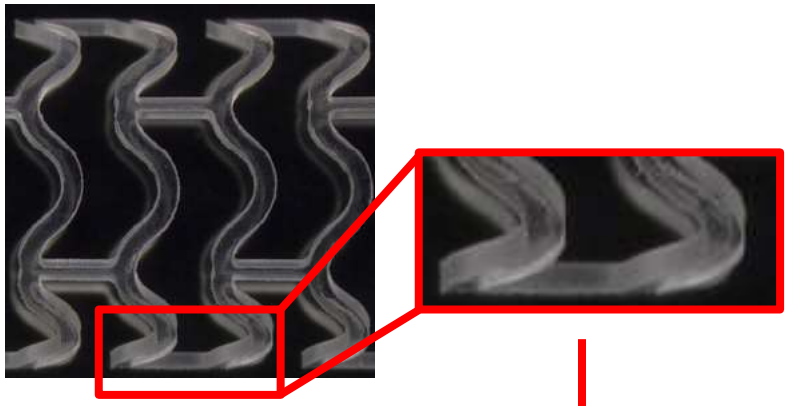
Sotomi et al. submitted

	1st generation BRS	
Scaffold	Absorb BVS 1.1	DESolve
Design		
OCT appearance	 157 µm	 150 µm
Scaffold	Magmaris	ART
Design		
OCT appearance	 150 µm	 170 µm

Next Generation BVS:

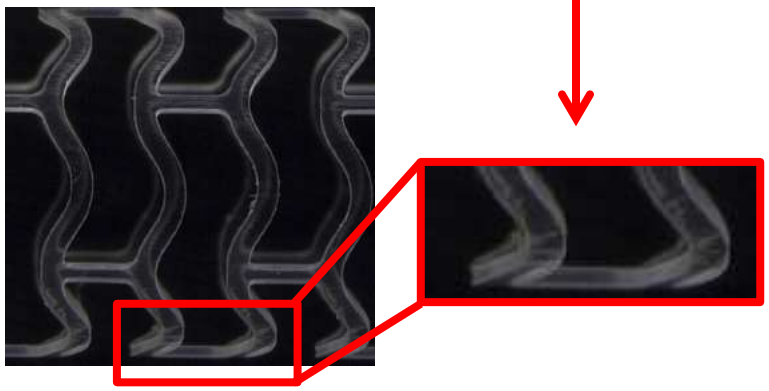
designed to expand the size matrix and Reduce strut thickness

Absorb GT1™



Reduced strut thickness

Next Gen BVS



More Treatment Flexibility

- Broader size matrix, including longer lengths

Improved Deliverability

- Smaller crossing profile
- **Enhanced catheter**
- **Strut thickness reduced** substantially compared to Absorb GT1™

Optimized Healing

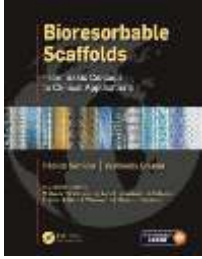
- Same drug and elution rate as Absorb GT1

Data and images on file at Abbott Vascular

Overview of current status of BRS

Product name	Company	Biodegradable material used for backbone	Coating	Development	Pre-clinical	Clinical	CE mark approved
Absorb	Abbott	PLLA	PDLLA	YES	YES	YES	YES
Absorb GT1	Abbott	PLLA	PDLLA	YES	YES	YES	YES
ART Pure	ART	PDLLA	none	YES	YES	YES	YES
Magmaris	BIOTRONIK	WE43 alloy, 93% Mg, and 7% rare earth elements	PLLA	YES	YES	YES	YES
DESolve 100	Elixir	PLLA	bioresorbable polymer	YES	YES	YES	YES
DESolve 150	Elixir	PLLA	bioresorbable polymer	YES	YES	YES	YES
DESolve XL	Elixir	PLLA	bioresorbable polymer	YES	YES	YES	YES
IGAKI-TAMAI	Kyoto Medical	PLLA	none	YES	YES	YES	YES only for PVD
Fantom	REVA	Desaminotyrosine polycarbonate	Desaminotyrosine polycarbonate	YES	YES	YES	
APTITUDE	Amaranth Medical	PLLA	NA	YES	YES	YES	
FORTITUDE	Amaranth Medical	PLLA	bioresorbable polymer	YES	YES	YES	
FAST	Boston Scientific	PLLA	PLGA	YES	YES	YES	
XINSORB	Huaan	PLA/PCL/PGA	PDLLA+PLLA	YES	YES	YES	
NeoVas	Lepu	PLLA	PDLA	YES	YES	YES	
Mirage	Manli Cardiology	PLLA	PLLA	YES	YES	YES	
MeRes100	Meril	PLLA	PDLLA	YES	YES	YES	
Firesorb	MicroPort	PLLA	PDLLA	YES	YES	YES	
Ideal BioStent	Xenogenics	polylactide anhydride mixed with a polymer of salicylic acid with a sebacic acid linker	Salicilate linked with adipic acid	YES	YES	YES	
ArterioSorb	Arterius	PLLA	Bioresorbable polymer	YES	YES		
ReNATURAL (M) ReNATURAL (P)	Cardionovum	(M)=metal, (P)=PLLA	NA	YES	YES		
AMITY	Elixir	PLLA	bioresorbable polymer	YES	YES		
DESolve Cx	Elixir	PLLA	bioresorbable polymer	YES	YES		
IMBI BE	Envision Scientific	magnesium	Nanocarrier layer: Top-coat that [illegible]	YES	YES		
LifeTech Iron-Based BRS	LifeTech	Nitrided Iron	"special" polymer	YES	YES		
Mg Spiral	Medtronic	Magnesium	"family of degradable polymers"	YES	YES		
On-AVS	OrbusNeich	PLLA, PLGL, PDLA	PLLA+PDLA	YES	YES		
Unity BRS	QualiMed	Magnesium	PLGA	YES	YES		
Avatar	[illegible]	[illegible]	[illegible] polymer	YES	YES		
Scitech MBRS	Scitech	Magnesium	NA	YES	YES		
Terumo/ART DCBS	Terumo Corporation	PDLLA	Bioresorbable polymer	YES	YES		
ZMED	Zorion Medical	Magnesium/PLGA	NA	YES	YES		
Next-Gen Absorb	Abbott	PLLA	PDLLA	YES			
Sahajanand Bioabsorbable	Sahajanand	PLLA	Bioresorbable polymer	YES			
MAGNITUDE	Amaranth Medical	PLLA	Bioresorbable polymer	YES			
Firefalcon	MicroPort	PLLA	NA	YES			
Galaxy	Shanghai Bio-Heart	PLA	Bioresorbable polymer	YES			

- **10 products under evaluation in clinical studies**
- **13 products under evaluation in pre-clinical studies**
- **5 products still under development**
- **28 PLLA products/ 6 magnesium products**



Summary

- Current version of BRSs still have limited mechanical properties as compared to metallic stents due to its material characteristics. To compensate, the current generation BRS have relatively thick and wide struts.

- To overcome inherent material properties, various modifications to polymer are being attempted. (Stronger and ductile scaffold, Thinner/round struts, Fast resorption without inflammation)

- The development of next generation BRS with thinner struts (≤100 μm) is ongoing.

- >35 products are currently being in development, or evaluated in pre-clinical and clinical situations.