Development and Commercialisation of Bioresorbable Polymer Medical Implants

Dr Nial Bullett, Dr Kadem Al-Lamee

Arterius Ltd (Leeds)

Polymer Process Engineering 2019

University of Bradford

10th July 2019

Arterius Ltd

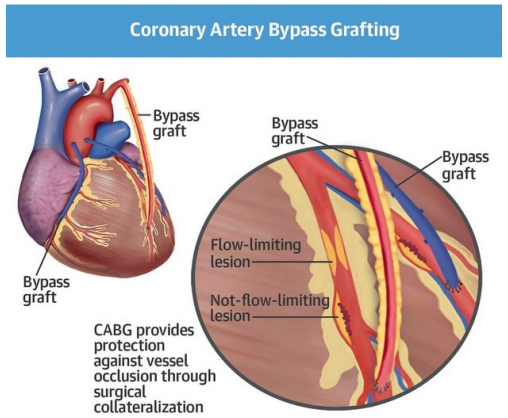
- Founded in Bradford in 2010 with the aim to develop a 2nd generation bioresorbable coronary scaffold (stent)

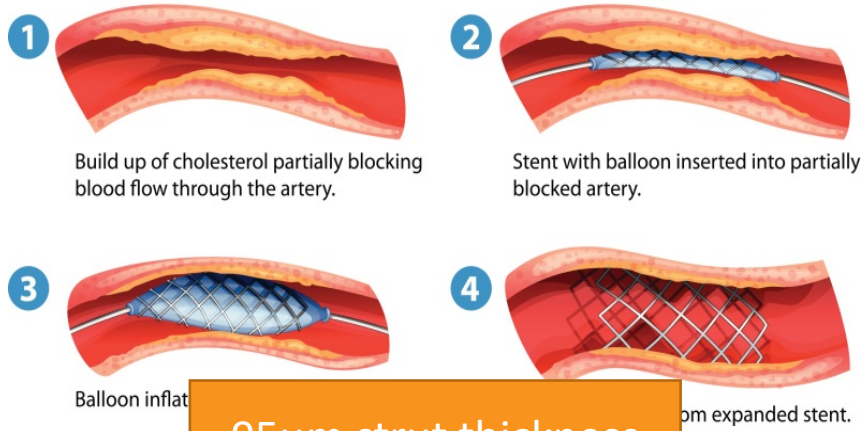
Dr Kadem Al-Lamee
30 years experience in biomaterials and medical devicesFounder of PolyBioMed (1996), acquired by Lombard Medical

Alistair Taylor
45 years Pharma and Medical Device experience
Former CEO of Schneider Worldwide Inc and Biocompatibles International plc

- Collaboration with Prof Coates' Polymer IRC group
  - Patent EP2909003 B1 "METHOD OF PRODUCING A TUBE FOR USE IN THE FORMATION OF A STENT"

Coronary Artery Disease and Evolution of Treatment Methods





157µm strut thickness
→ late stent thrombosis

95µm strut thickness
→ less flow disruption

1960
Bypass Graft

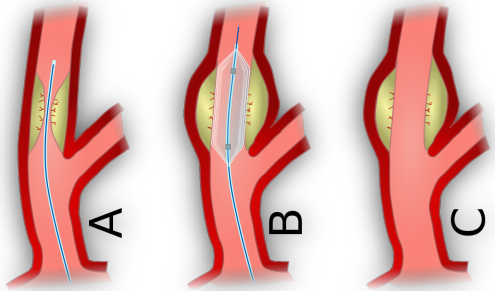
1977
Balloon Angioplasty

1986
Bare Metal Stents

Drug Eluti ts

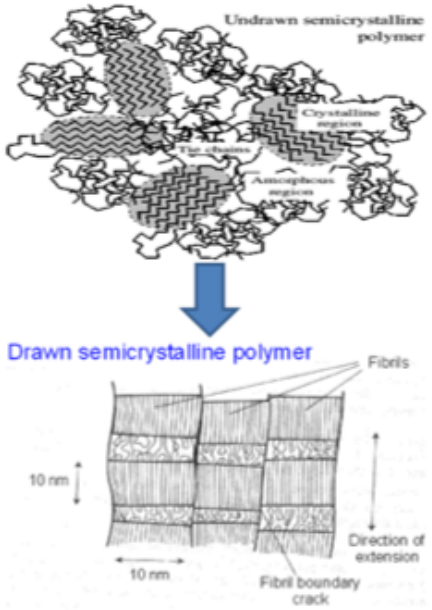
2011
1st Gen Bioresorbable Stents

20??
Bioresorbable Stents

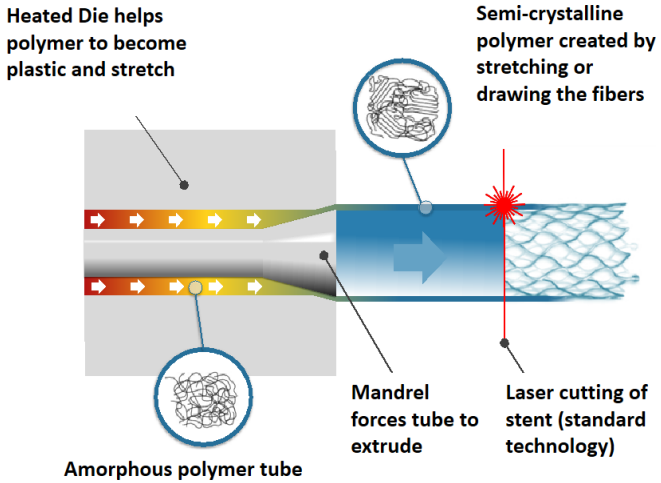


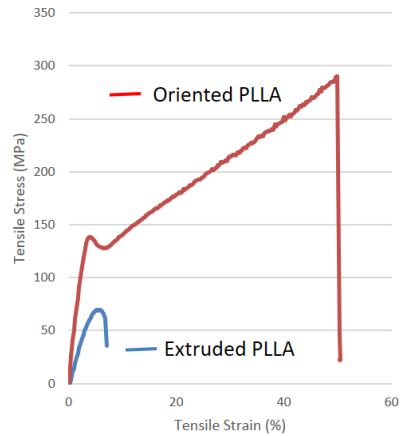
Solid Phase Tube Orientation for Stent Formation

A



B





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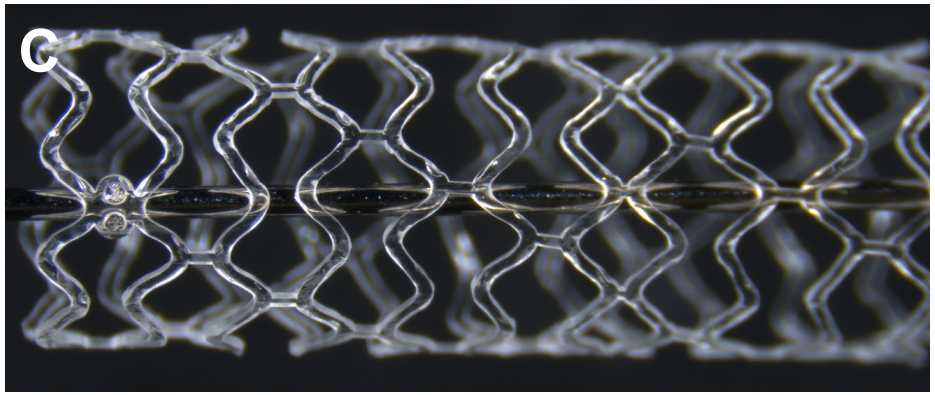

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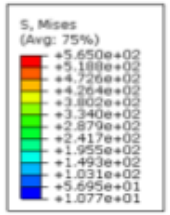
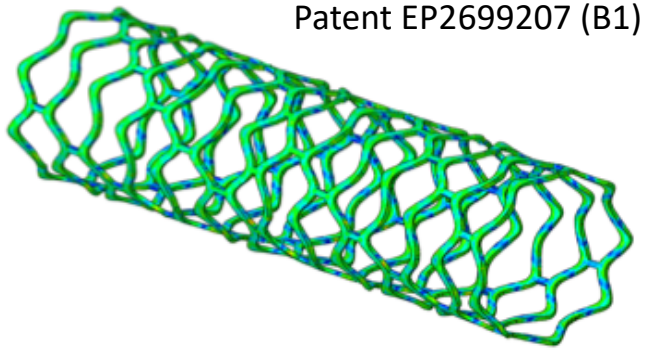
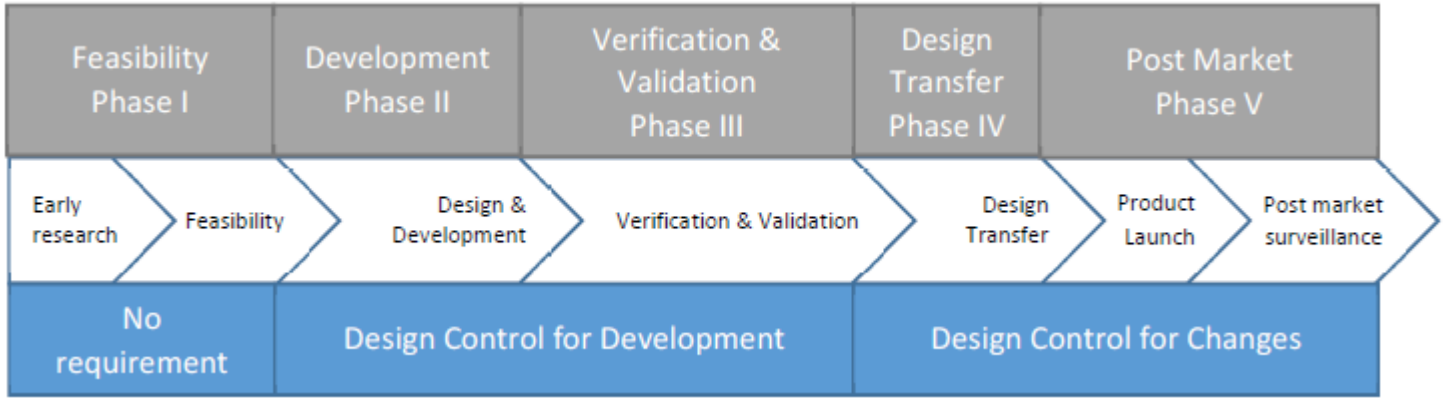


Collaboration with Prof Neil Bressloff (University of Southampton)

Patent EP2699207 (B1) "A STENT"



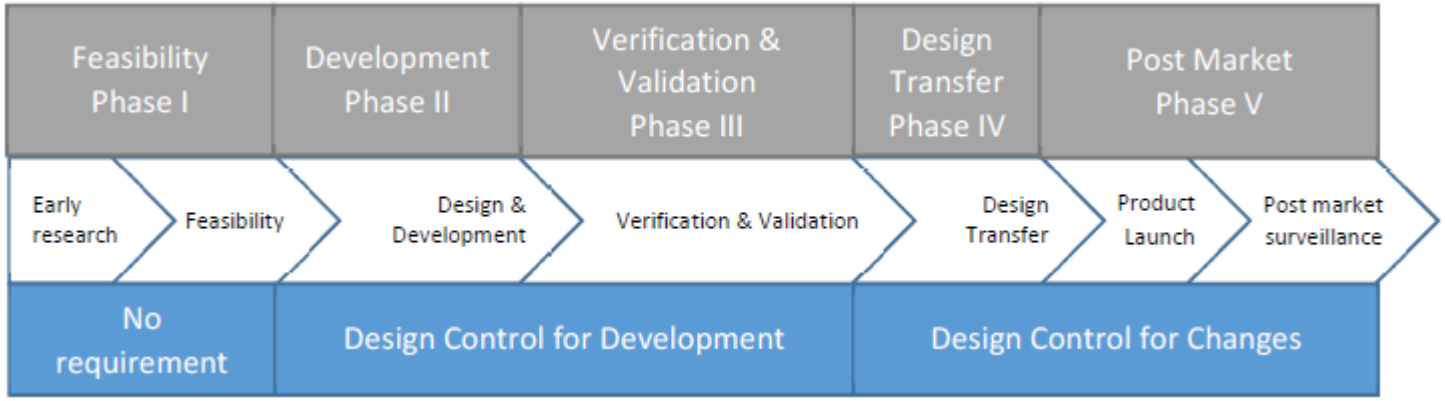
Medical Device Product Design and Development



- Proof of concept
- Prototype evaluation
- Design requirements
- Intended use
- Patent search
- Functionality
- Regulatory classification
- Sales & marketing planning
- Resource requirements

- Tasks required to take design to launch
- Establish team
- D&D plan
- Design inputs
- Risk management

Medical Device Product Design and Development

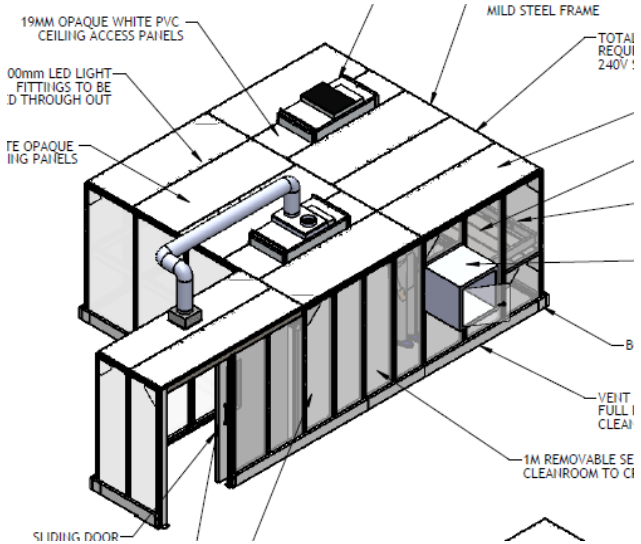


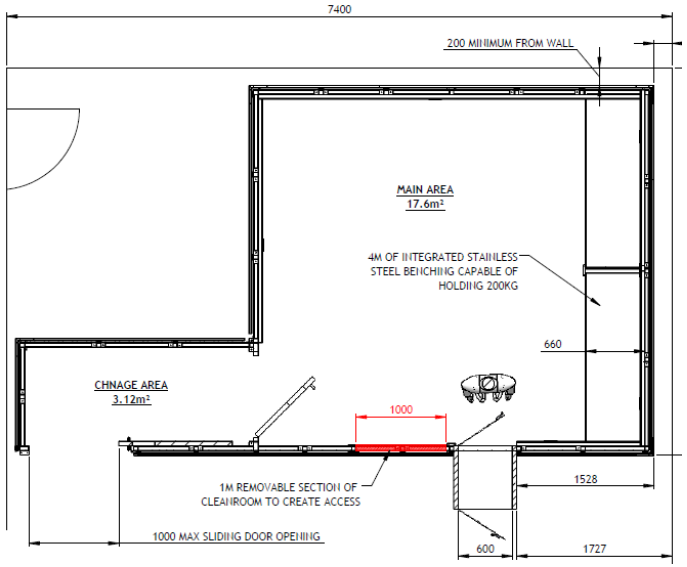
- Verification and validation – device conforms to user needs and intended uses given expected variations in components, materials, environment, processes
- Product bench testing
- Biocompatibility
- Preclinical evaluation
- Clinical evaluation

- Transfer to manufacturing
- Manufacturing protocols
- Final Production Specifications
- End of Design Control

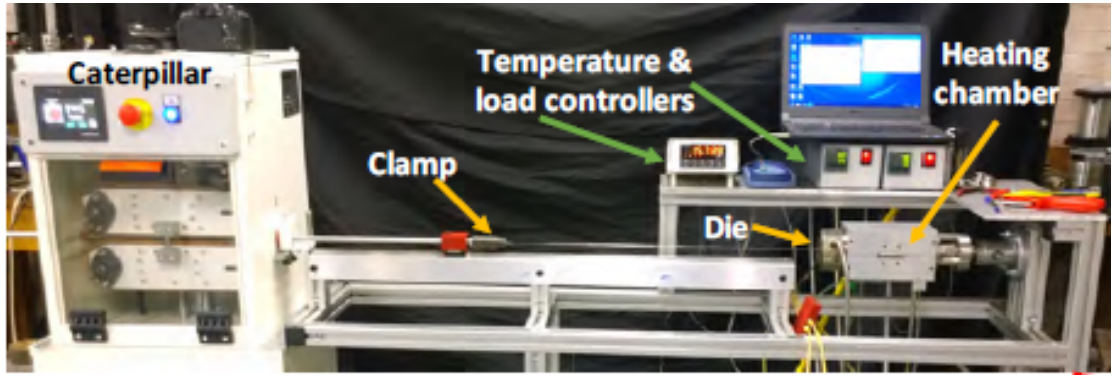
- Regulatory approval
- Production
- Sales & Marketing
- Change Control
- Feedback and Customer Complaints
- Adverse event reporting

Installation and Qualification of Class 8 Manufacturing Clean Room





Development of a Production Die Drawing System

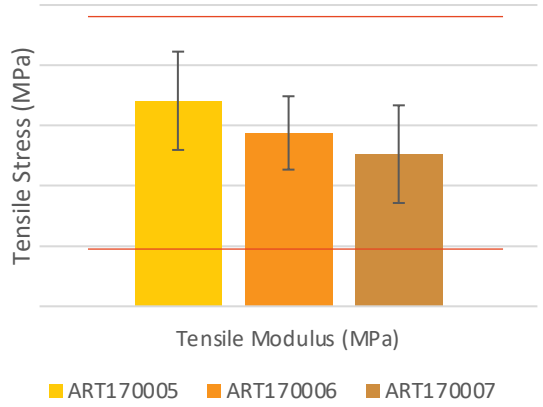


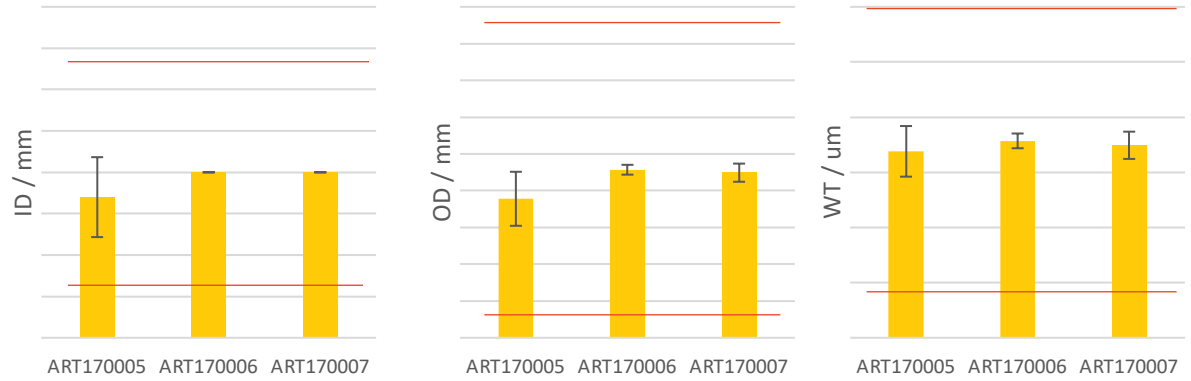
University of Bradford die drawing system used for feasibility and early development

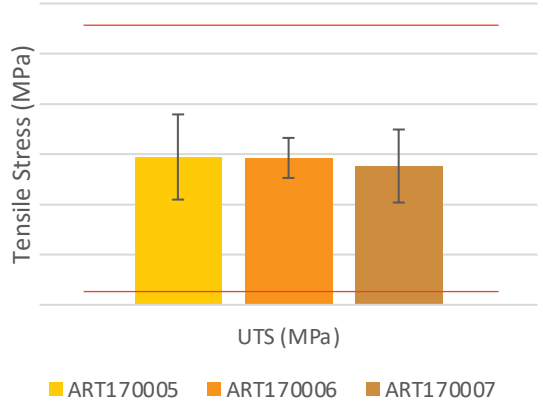
Arterius die drawing system produced in 2016 used for development and production

Validation of Processes

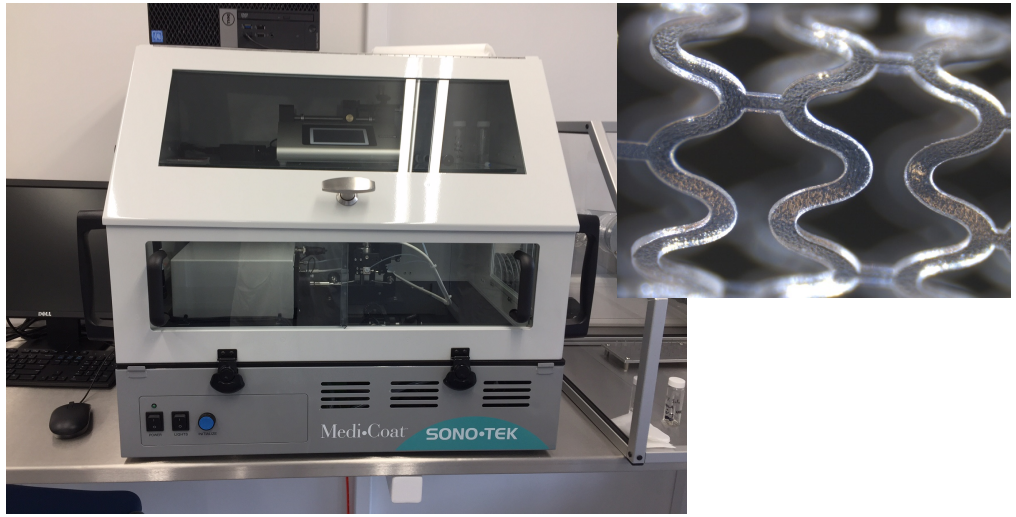
- Need to control quality of product – to be repeatable and reproducible
- Set acceptance criteria and evaluate repeatability and reproducibility of each manufacturing process
- Die drawing characterisation:
  - Dimensions (ID/OD/WT)
  - Tensile properties (modulus, UTS, yield, strain)
  - Thermal properties (Tg, crystallinity)

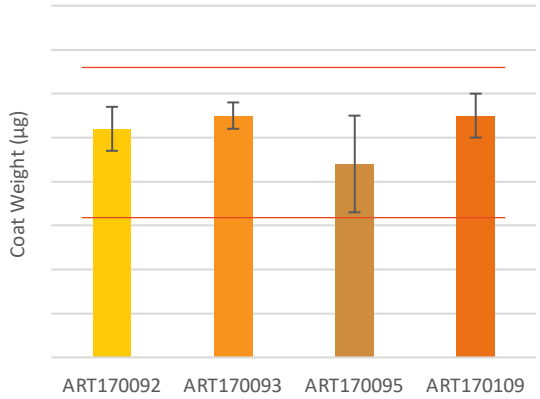


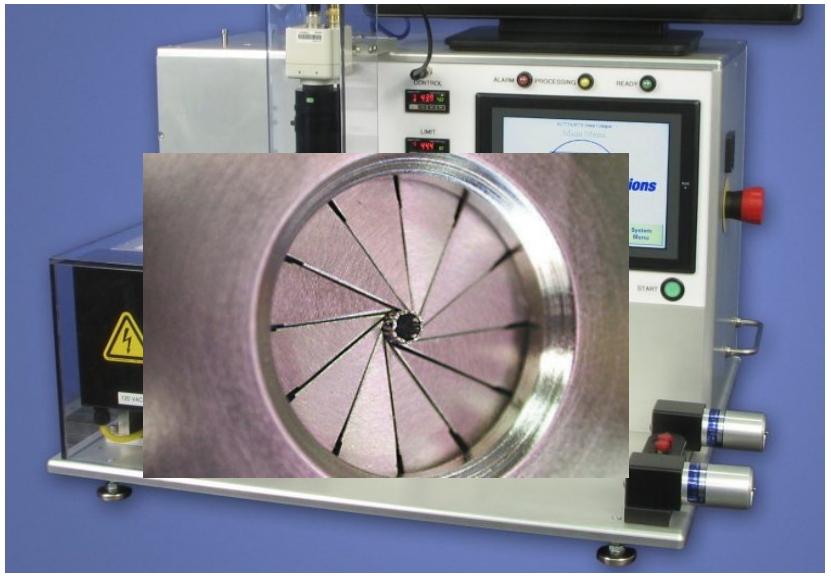


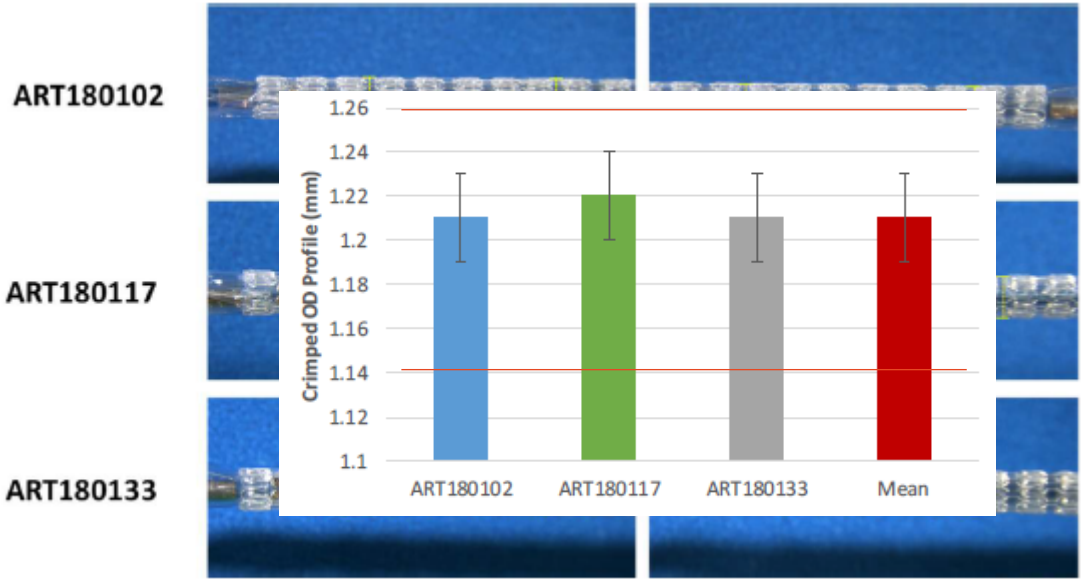


Validation of Stent Coating and Crimping





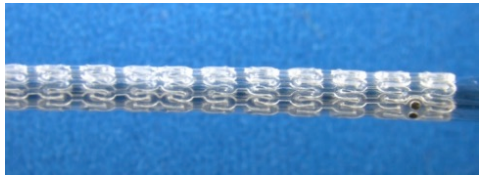


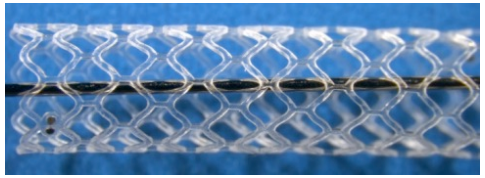


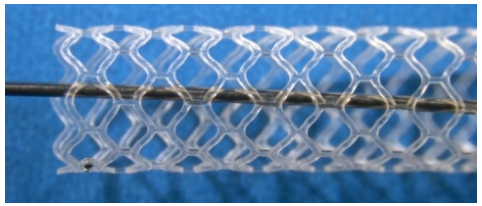
Verification and Validation

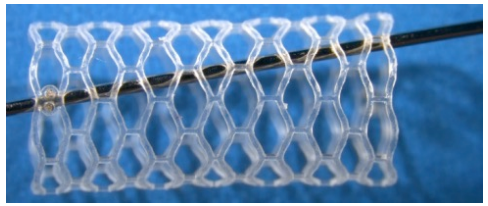
- Stability and Shelf Life

Refrigerated temperature storage (2 – 8 °C) – T = 0 Month

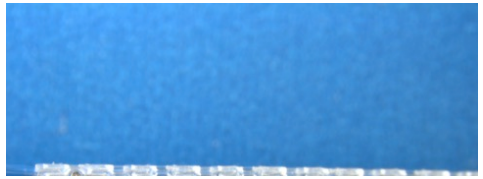

Crimped scaffold

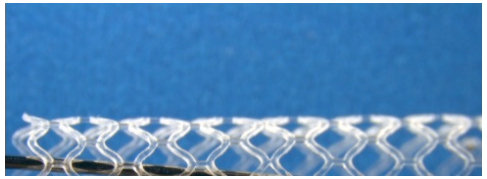

Expanded to 3.0 mm @ 16 atm

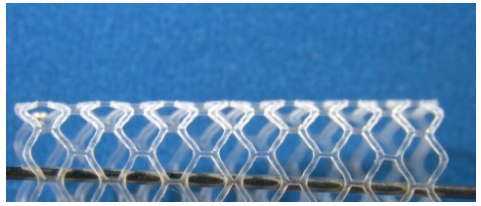

Expanded to 3.25 mm @ 22 atm

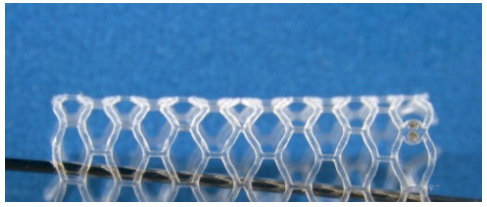

Expanded to 4.50 mm @ 8 atm

Refrigerated temperature storage (2 – 8 °C) – T = 1 Month

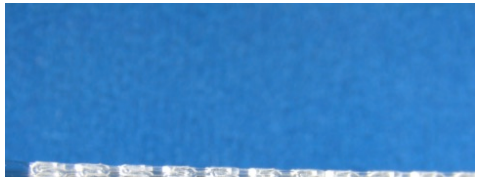

Crimped scaffold

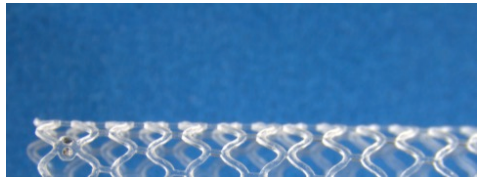

Expanded to 3.0 mm @ 16 atm


Expanded to 3.25 mm @ 22 atm


Expanded to 4.50 mm @ 8 atm

Refrigerated temperature storage (2 – 8 °C) – T = 3 Months


Crimped scaffold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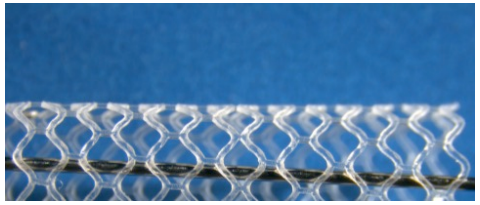
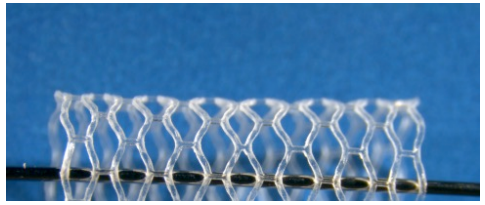
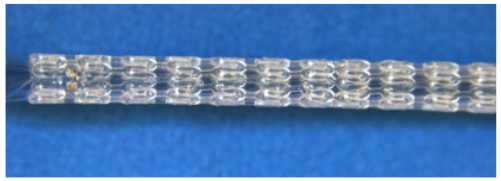
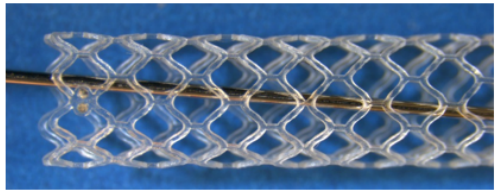
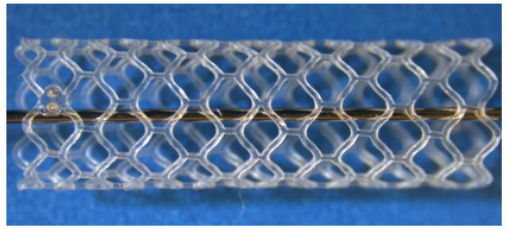

Expanded to 3.25 mm @ 22 atm

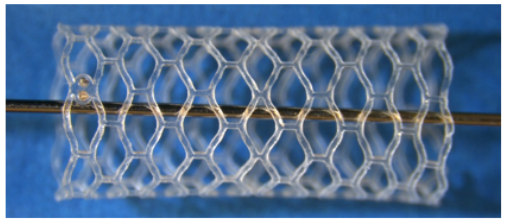

Expanded to 4.50 mm @ 8 atm

Refrigerated temperature storage (2 – 8 °C) – T = 6 Months


Crimped scaffold


Expanded to 3.0 mm @ 16 atm


Expanded to 3.25 mm @ 22 atm


Expanded to 4.50 mm @ 8 atm

Verification and Validation

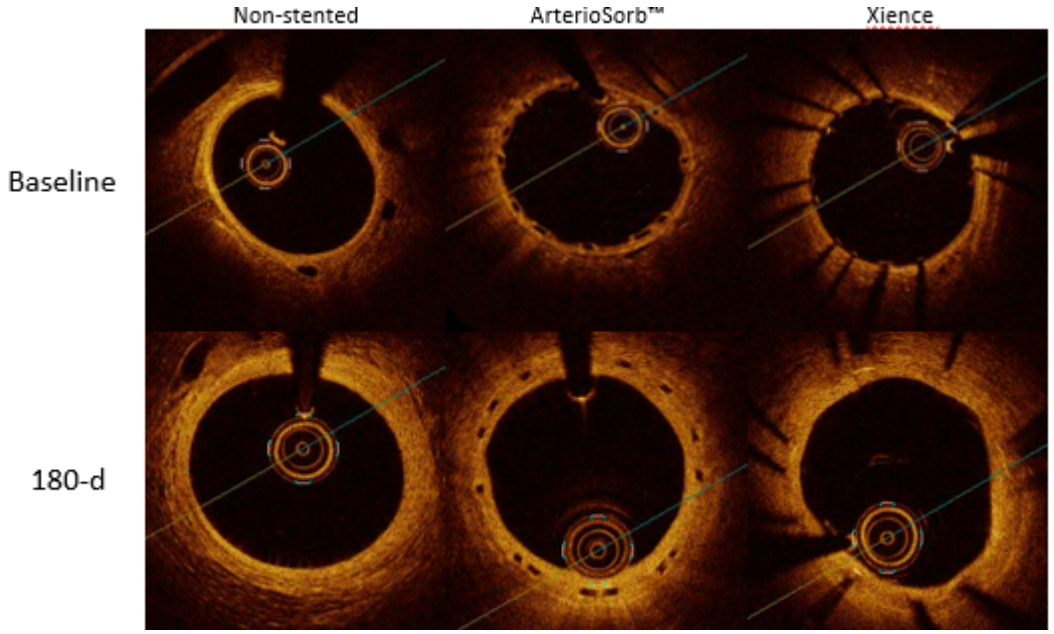
- Bench Testing
  - Radial strength testing
  - Degradation
- Stability and Shelf Life
- Biocompatibility
  - ISO 10993

	ArterioSorb Bioresorbable Scaffold	
	Testing	Rationale
Chemical Testing		
Exhaustive Extraction	T	
FTIR	T	
UPLC-MS	T	
GC-MS	T	
ICP	T	
IC	T	
Biological Testing		
Cytotoxicity:		
- MEM Elution Test	T	
- Direct Contact	T	
Sensitization	T	
Intracutaneous Reactivity/Irritation		R
Acute Systemic Toxicity		R
Material-Mediated Pyrogenicity		R

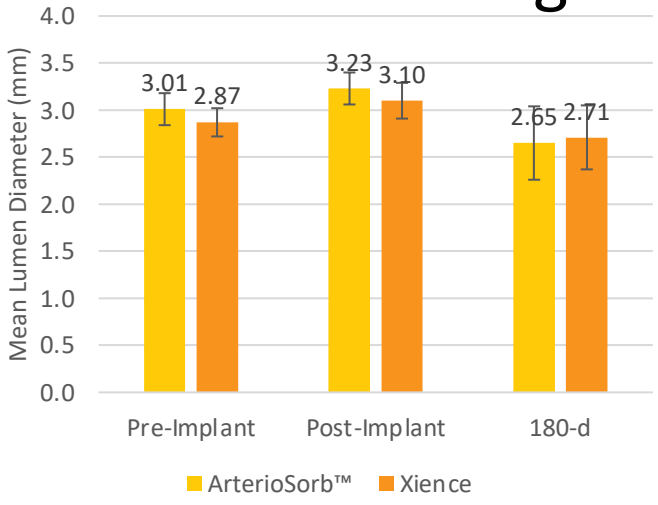
	ArterioSorb Bioresorbable Scaffold	
	Testing	Rationale
Hemocompatibility:		
- Hemolysis (Direct and Indirect)	T	
- Complement Activation	T	
- In vivo thrombogenicity**		R
Genotoxicity:		
- Bacterial Reverse Mutation Assay (Ames Test)	T	
- In vitro Mouse Lymphoma Assay Test	T	
Subacute/Subchronic Systemic Toxicity**		R
Muscle Implantation/Biodegradation Testing		R
Combined in vivo Thrombogenicity (ISO 10993-4), Subacute/Subchronic Toxicity (ISO 10993-11) and Local Tolerance (Vascular Implantation)/Biodegradation **	T	
Reproductive/Developmental		R
Carginogenicity		R

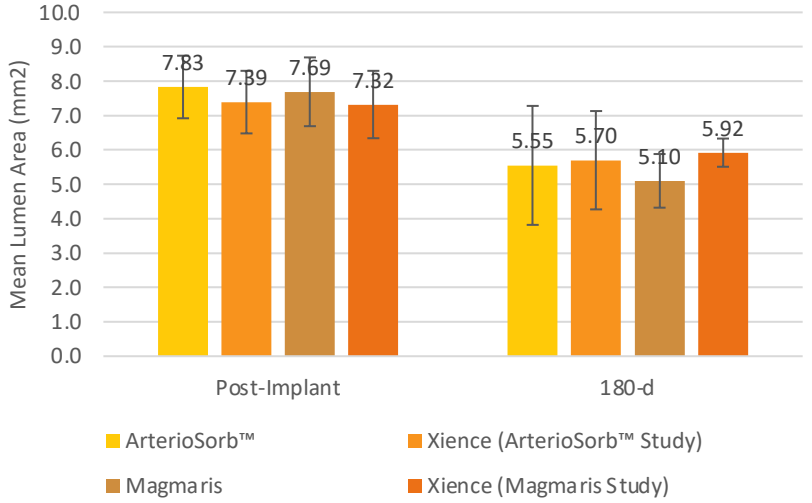
Verification and Validation

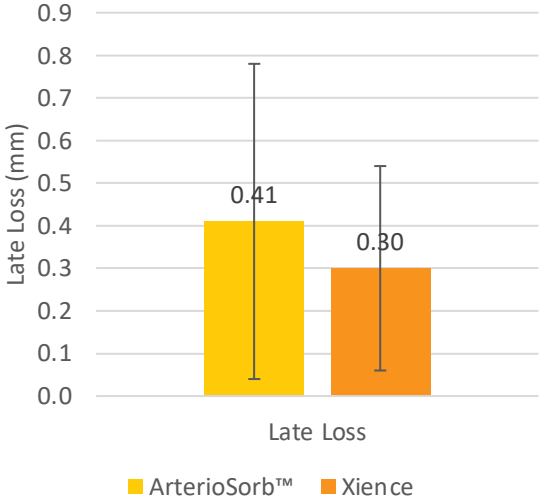
- Bench Testing
  - Radial strength testing
  - Degradation
- Stability and Shelf Life
- Biocompatibility
  - ISO 10993
- Preclinical testing



Optical Coherence Tomography Imaging in porcine model

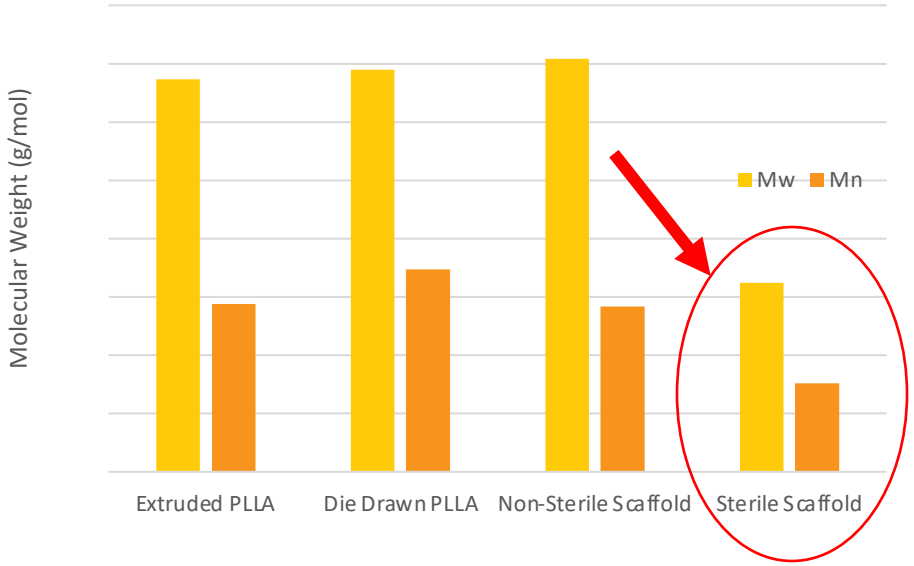






Verification and Validation

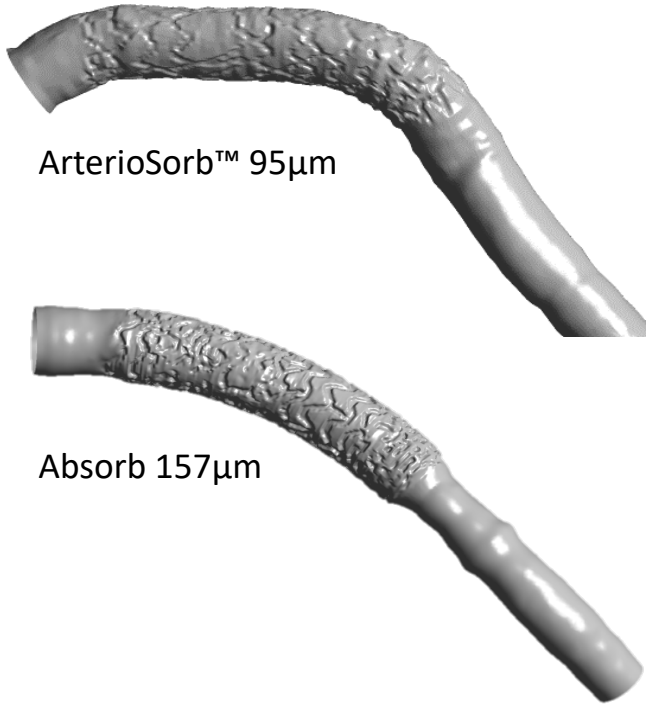
- Sterilisation
  - Product testing must be performed on “final device” – after sterilisation
  - Sterilisation method may seriously affect product performance



  - Sterilisation should be considered as early in product development as possible
    - In feasibility phase!

In vivo endothelial shear stress

- Arterial vessels reconstructed from in vivo OCT data
- Blood viscosity and arterial flow modelled using CFD



Tenekecioglu, Serruys et al.
Eur Heart J. 2017;38:2570

In vivo endothelial shear stress

- Arterial vessels reconstructed from in vivo OCT data
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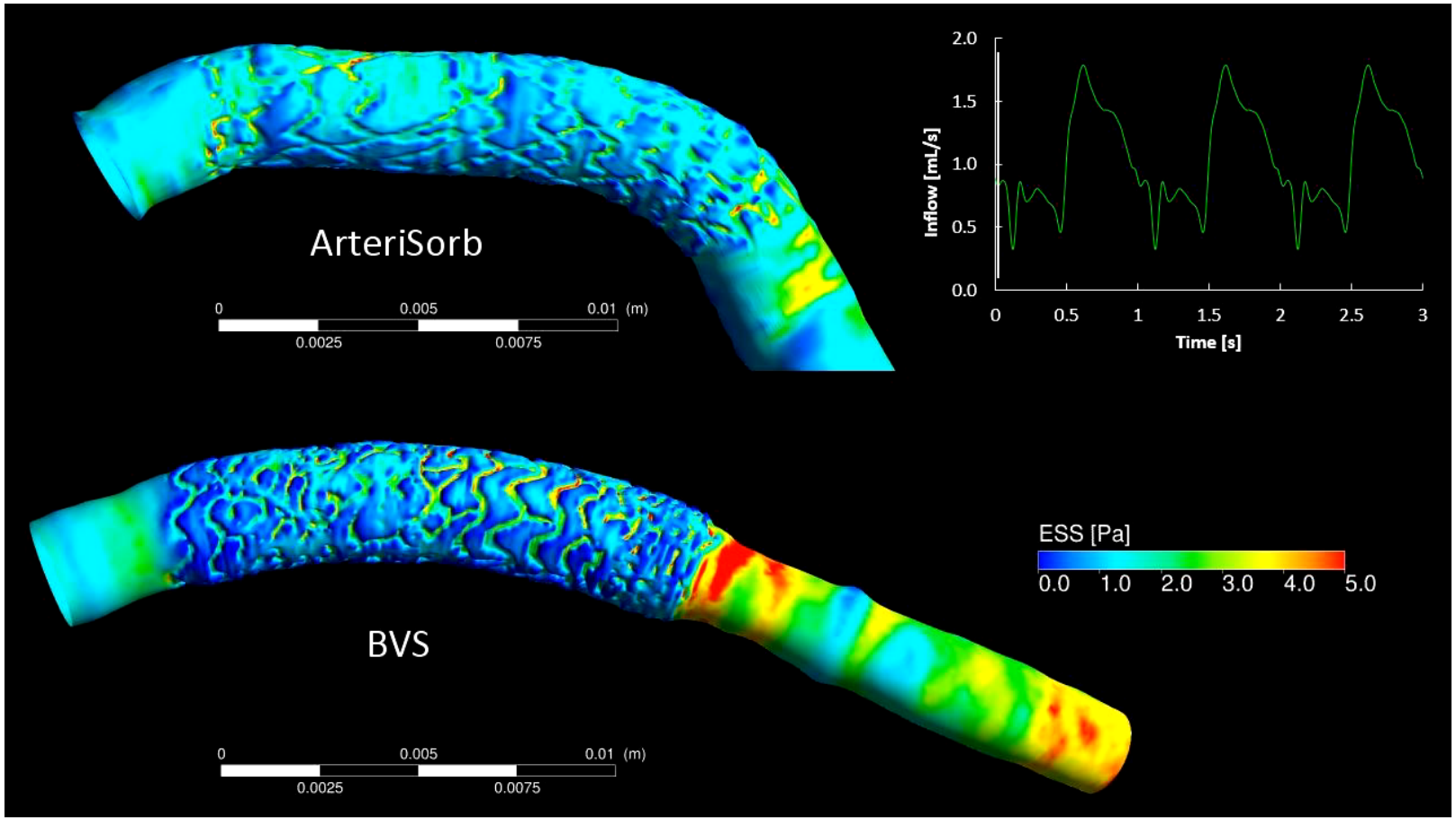
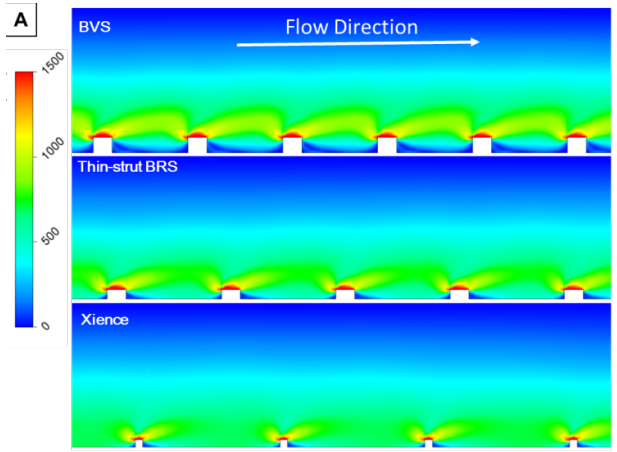


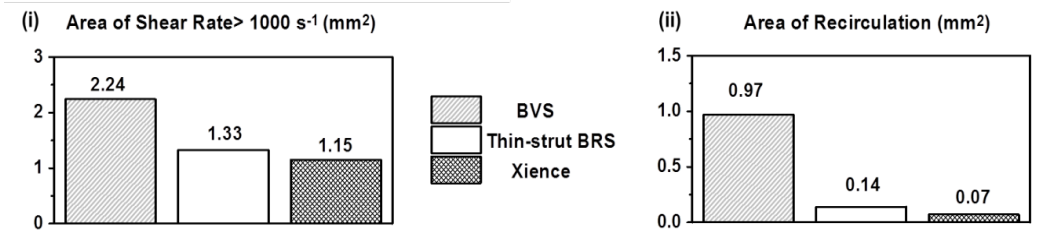
ESS in the inter-strut zones are lower in Absorb compared to the ArterioSorb scaffolds.
Lower ESS is associated with scaffold thrombosis due to turbulence and platelet aggregation.

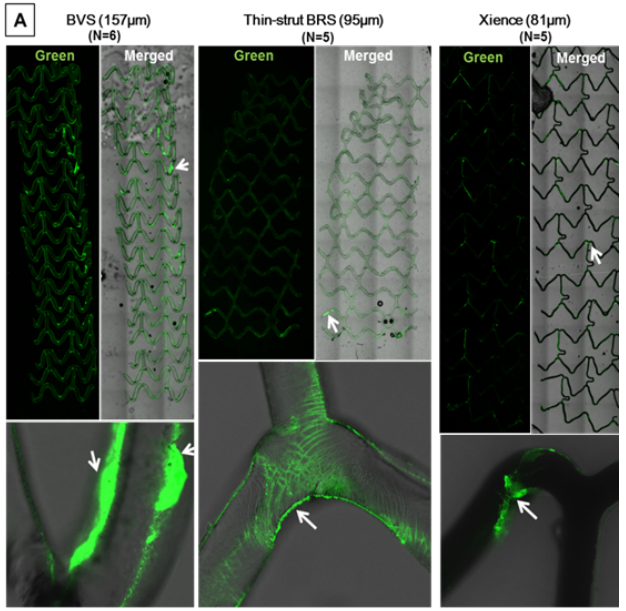
Tenekecioglu, Serruys et al. Eur Heart J. 2017;38:2570

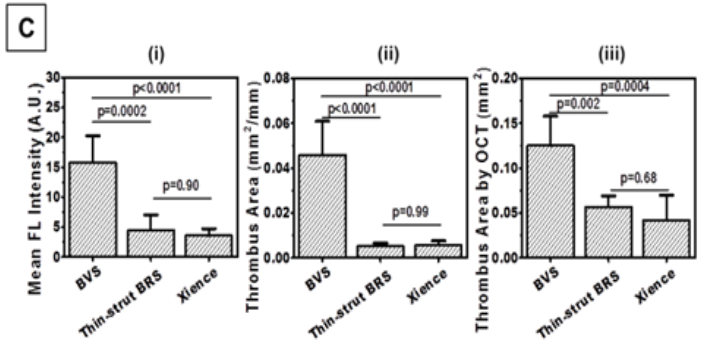
Simulation of the effect of 3 different strut profiles

- Problems with thrombosis in 1st generation BRS due to high strut thickness
  - 2D models of Absorb BVS (157µm), ArterioSorb™ (95µm) and Xience (81µm)
  - Flow reconstructed using computational simulation









- Perfusion of blood in coronary flow model (silicone vessels)
- Immunohistochemistry staining to show platelet aggregation

BRS: is there light at the end of the thin-strut tunnel? In-vitro insights on strut thickness impact on thrombogenicity in BRS

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Thank You!

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