CARDIOVASCULAR SUMMIT
TCTAP 2015

New Metallic DES: Bioresorbable Polymers or Polymer-Free (Novel concept)

Patrick W Serruys, M.D., Ph.D.

International Centre for Cardiovascular Health, Imperial College, London, UK

Yoshinobu Onuma, MD, PhD

Thoraxcenter, Erasmus MC, Rotterdam, The Netherlands

Cardialysis

11:00-10, April 29, 2015

TCT-AP, Main Arena

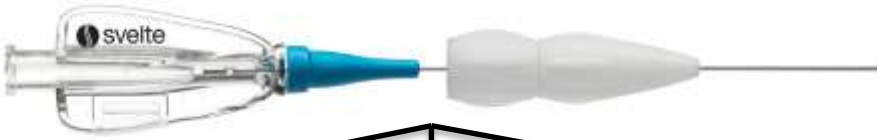
Overview of the presentation

1. Stent on wire and new coating in amino-acid (Svelte)
2. Surface treatment in Bare-metal stent (Axetis, Qvanteq)
3. Non-coated stent (Nano^{+} of Lepu)
4. Nanomeric electrografting for fast reendothelialization: short duration of elution (Sinomed)
5. Impaction of crystalized sirolimus in a vessel wall for long duration of neointimal inhibition: long duration of elution (Mistent)
6. Stent reservoir for AMI (Microport)

The Swelte stent "on a fixed wire" technology: Designed to Facilitate TRI, 'Slender' PCI

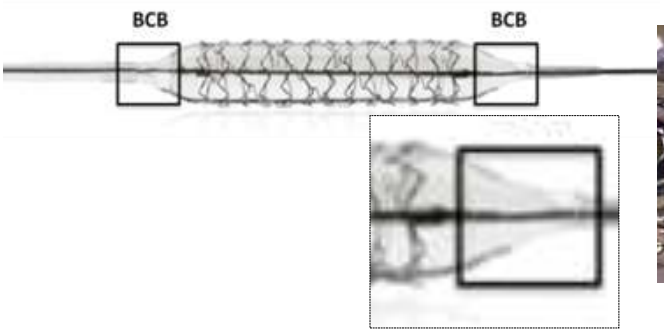
Integrated Delivery System (IDS)

- **'All-In-One' integrated wire design optimizes TRI / 'slender' PCI and direct stenting**
- **Lowest profile stent system available, downsizes sheaths and catheters**
- **Reduces procedural steps and costs of PCI**



Specialized Wire & Balloon Technology

- Balloon Control Bands (BCBs) prevent balloon expansion beyond stent edges, designed for multiple, high-pressure inflations: ***¼ sizes above RBP***

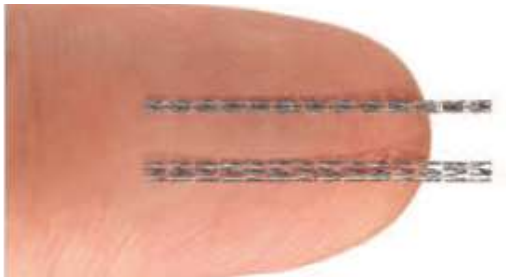


Bioresorbable Drug Coating

- Composed of natural occurring amino acids; high mechanical integrity
- ***Fully resorbed within 12-months*** via enzymolysis, leaving only BMS behind

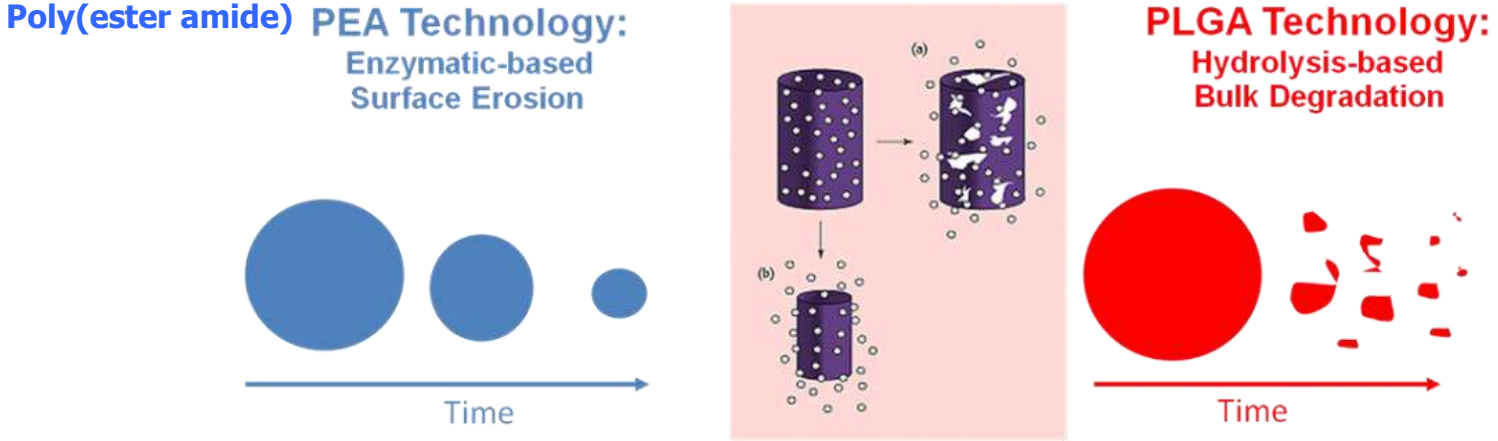
Hybrid Stent Design

- ***~ ½ the crimped cross-sectional profile*** of current generation stents*
- Provides optimal blend of flexibility and radial strength



New Class of Enzymatic-Mediated Bioresorbable Drug Coating Technology

- **Bioresorbable coating**
  - Composed of naturally-occurring Amino Acids with high mechanical integrity
  - ***Reduced secretion of pro-inflammatory cytokines (IL-6, IL-1ß) and increased secretion of anti-inflammatory mediators (IL-1ra) compared to PLGA****
  - Prevents pH change and activation of the complement cycle
  - Absorbed in ~9 mos. via enzymatic surface erosion (***enzymolysis, not hydrolysis***)
- **Mixed with sirolimus, applied to stent in single application**
  - Coating thickness ~ 6 µm; drug load ~ 220 µg/cm^2 (3.0 x 18mm drug dose: ~130 µg)
  - Elution profile, tissue concentration levels similar to Cypher, Xience



*DeFife, Grako et al. Poly(ester amide) Co-polymers Promote Blood and Tissue Compatibility. *Journal of Biomaterials Science 20 (2009): 1495-1511.*

Svelte DES First-In-Man Outcomes

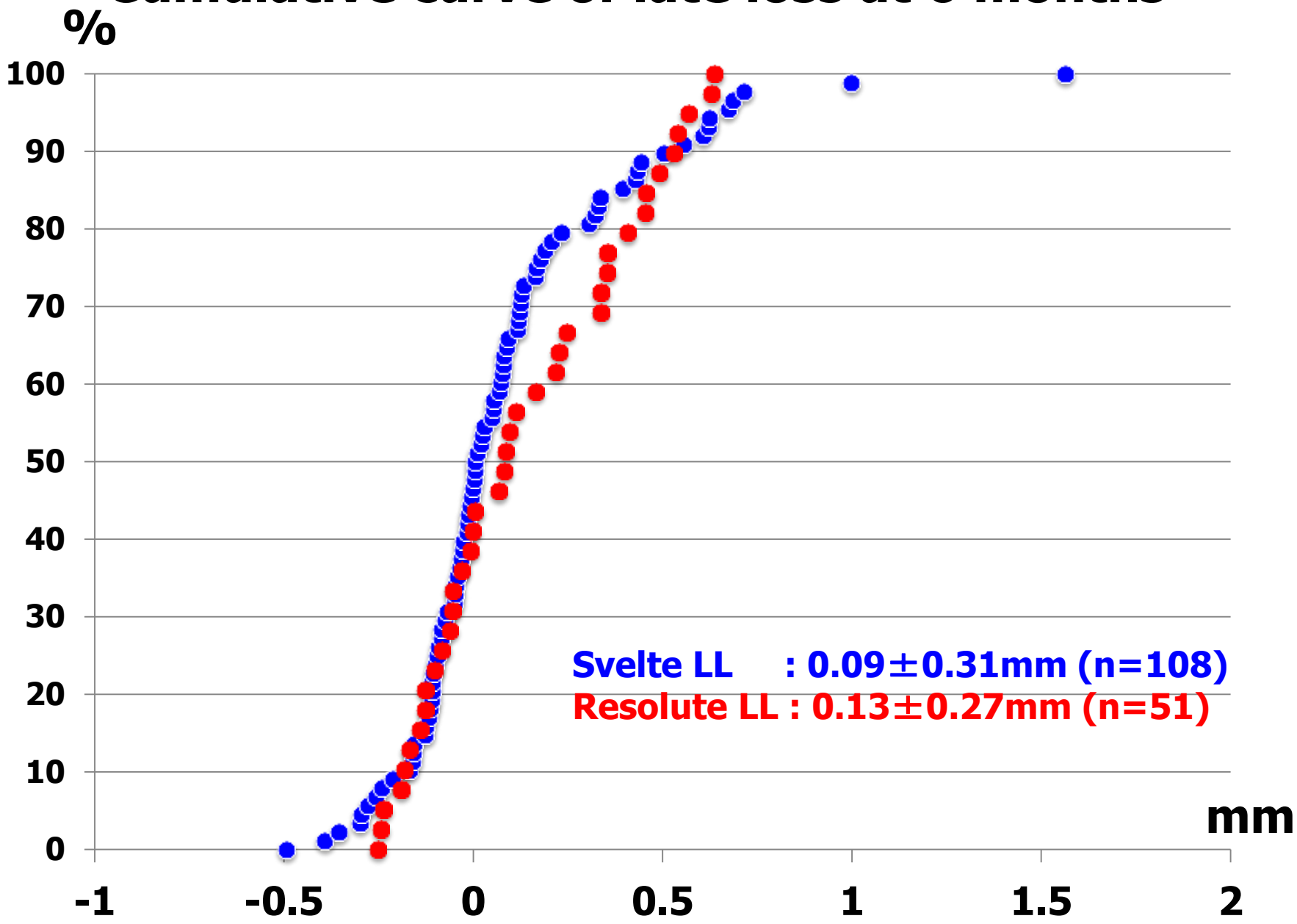
Key Baseline Characteristics	Svelte DES FIM DIRECT Study n=29
Reference Vessel Diameter	2.69 mm
Lesion Length	11.7 mm
Diabetics	17%
6-Month QCA	**n=29**
In-Stent Late Loss	**0.22 mm**
Diameter Stenosis	18%
6-Month IVUS	**n=28**
Neo Intimal Volume	3 mm^3
In-Stent Volume Obstruction	3%
24-Month Clinical Outcomes	**n=29**
Clinically-Driven TLR	0%
Clinically-Driven TVF	0%
MACE	0%
Stent Thrombosis	0%

Webster et al. *First-In-Human Evaluation of a Sirolimus-Eluting Coronary Stent on an Integrated Delivery System: the DIRECT Study*. EuroIntervention 2013; 9:46-53.

0% MACE sustained through 2-years

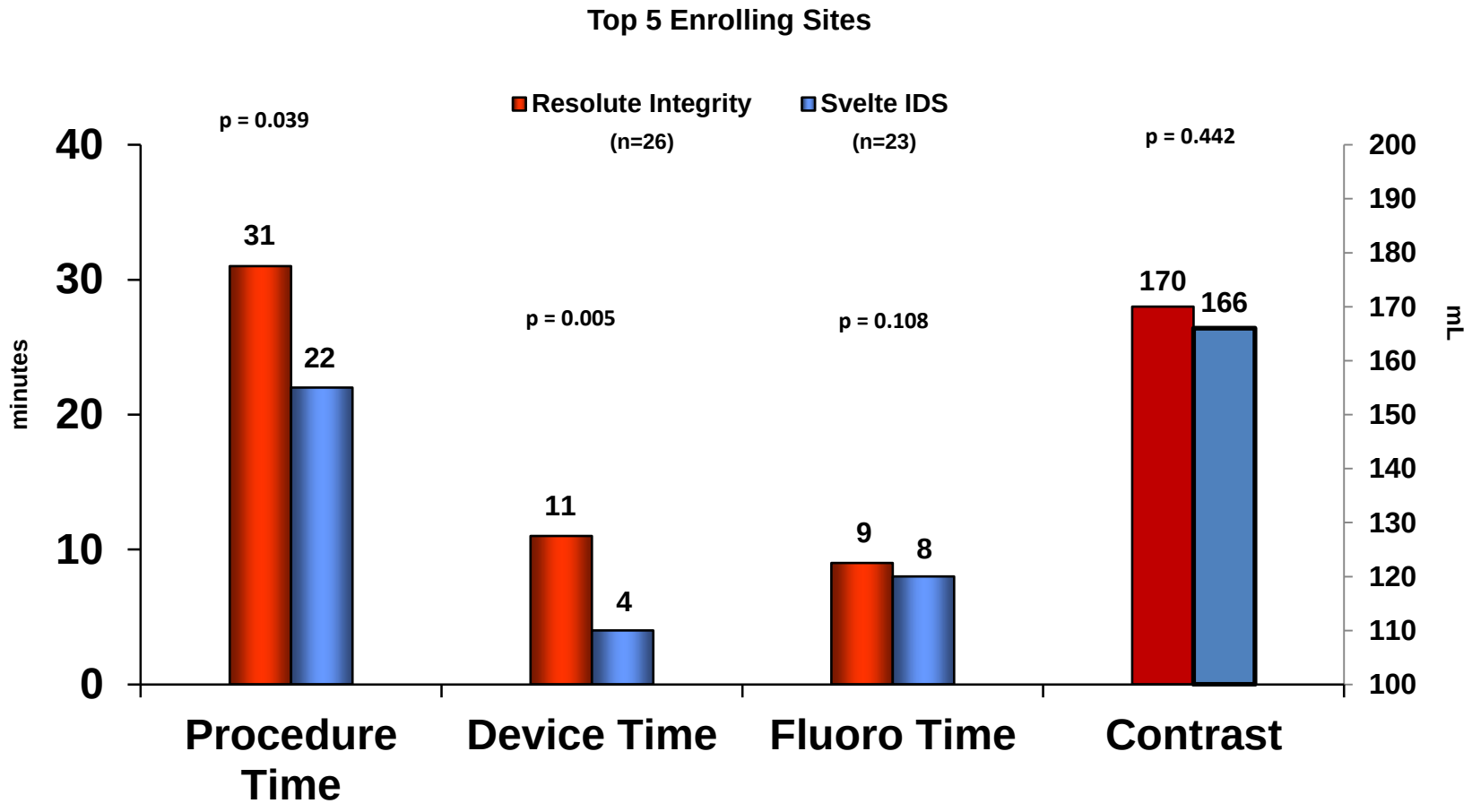
MACE defined as clinically-driven TLR, MI, cardiac death. TVF defined as clinically-driven TVR, TV MI, cardiac death. All data independent CEC / core lab adjudicated. Clinical follow-up continuing through 5-years.

DIRECT II trial (Svelte vs. Resolute)
Cumulative curve of late loss at 6 months



DIRECT II: Procedural Observations

Short learning curve (n=5) with IDS yields reduced procedure, device time:



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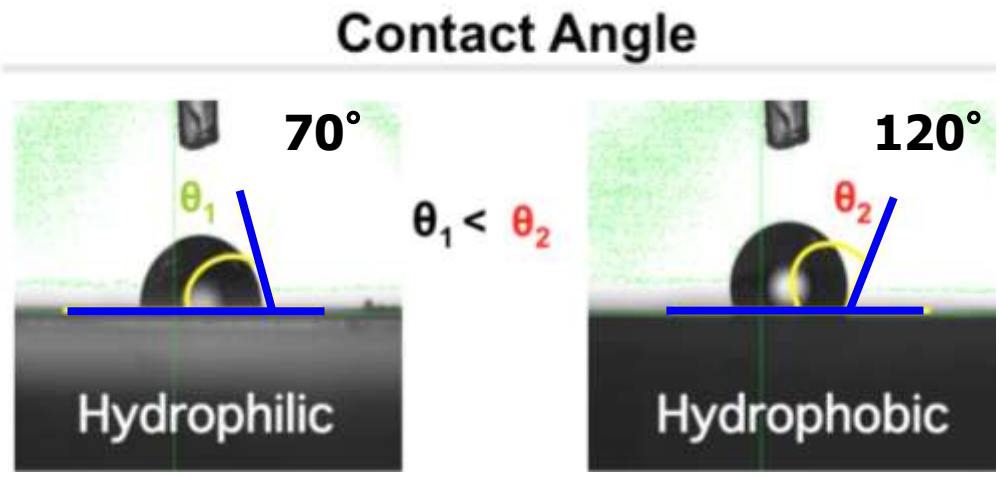
Relative Gene expression

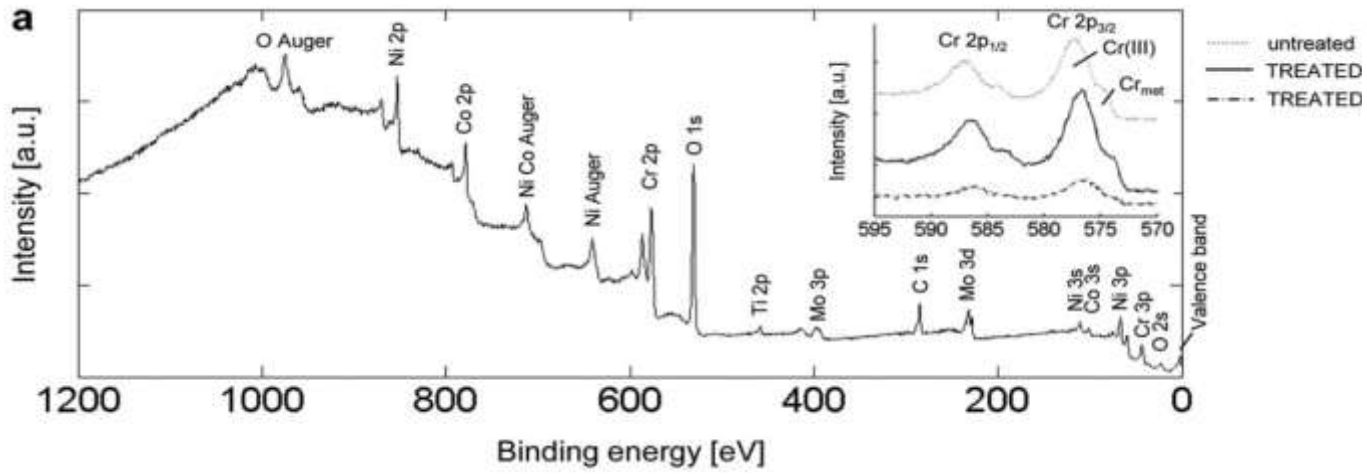
Hydrophobic polymers stimulate inflammatory and prothrombotic genes

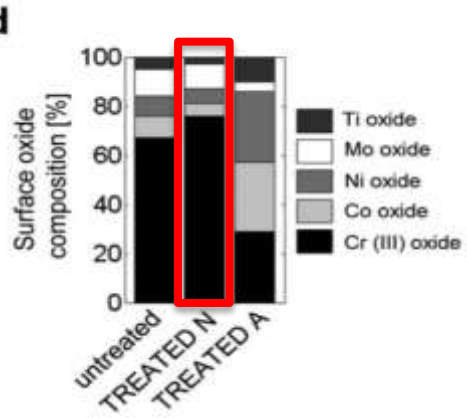
Polymer	**SIBS**	
Contact angle	**118°**	
	EC	**SMC**
TF	+	+
PAR-2	+	+
PAI-1	+	-
IL-8	+	-
MCP-1	-	+
TNF	-	+
Endothelin-1	++	+
TSP-1	-	-
CTCF	+	-
Total	**7**	**5**



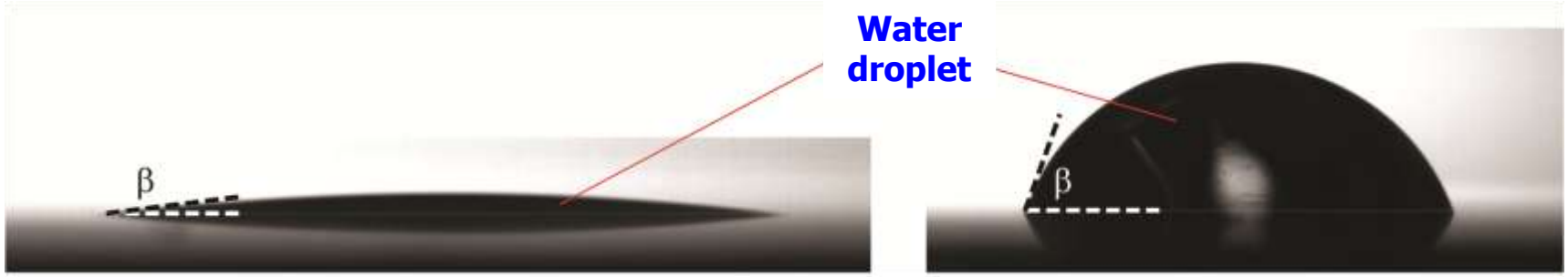
Qvanteq: Surface modification by oxygen plasma

Surface treatment with oxygen plasma creates the oxidized surface layer





The surface treatment makes it more hydrophylic



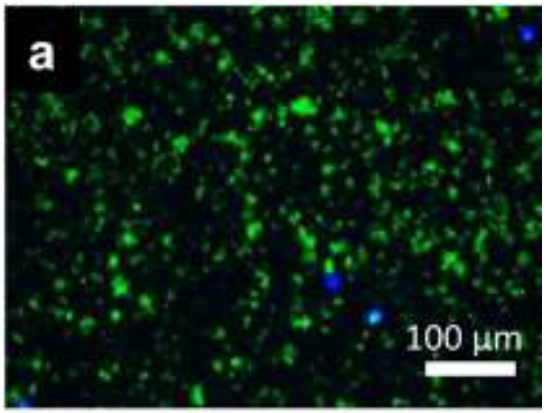
Treated surface
Contact angle ß <10º

Regular BMS surface
Contact angle ß = 70º

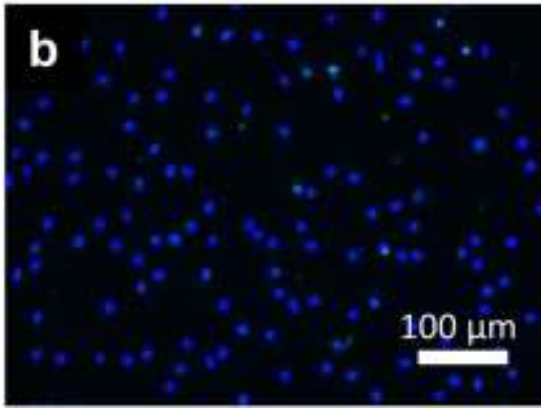
Qvanteq: Surface modification and hydrophilic status decrease platelet aggregation and promote endothelialization

The treated oxidized surface decreases platelet aggregation (CD41^{+} cells)

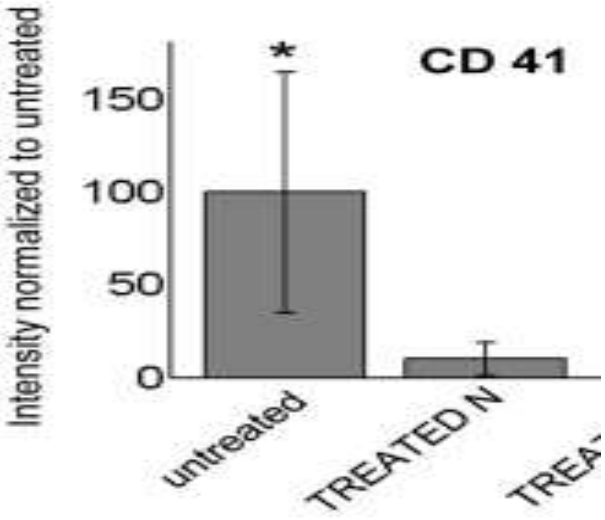
Untreated



Surface treated

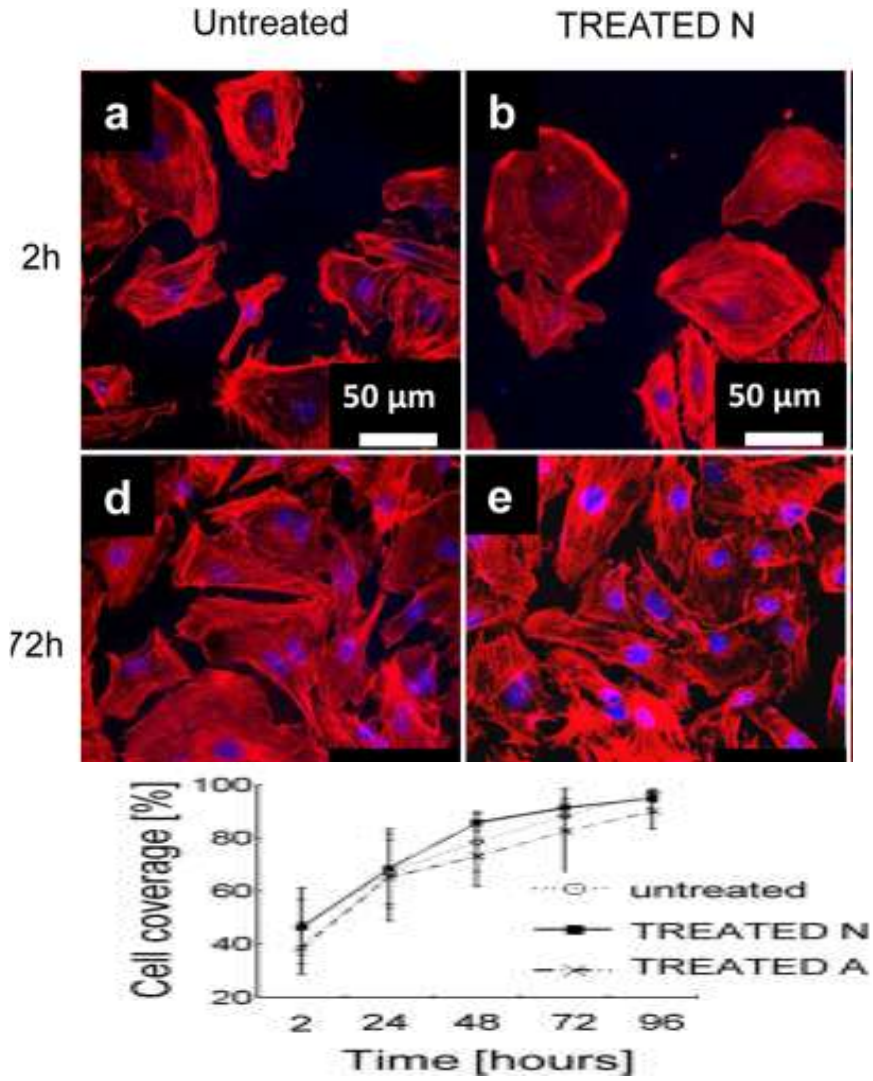


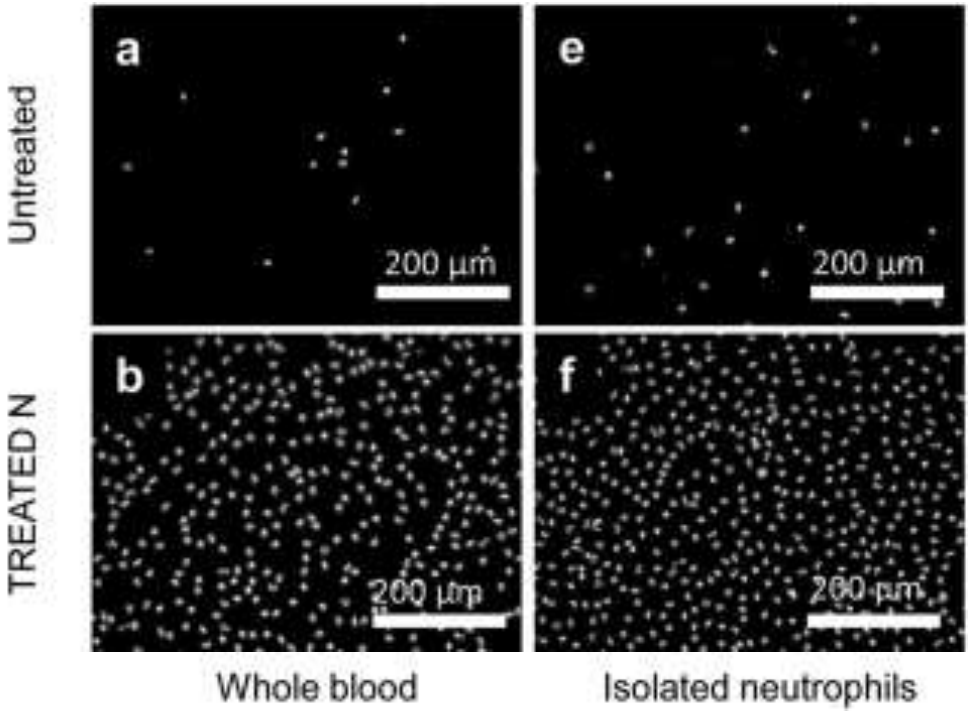
Green: CD41a



Blue: DAPI nuclei

Qvanteq: Surface modification promotes re-endothelialization and neutrophil aggregation

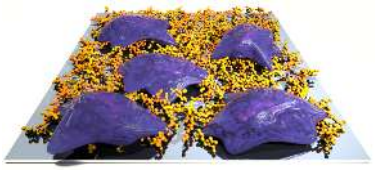




Mechanism of action: cell-selective surface recruits neointimal growth regulator

Qstent → **Protein** Adsorption → **Neutrophil** Recruitment → **Cathelicidin** Release from Neutrophils → **Controlled tissue response in swine coronary artery**

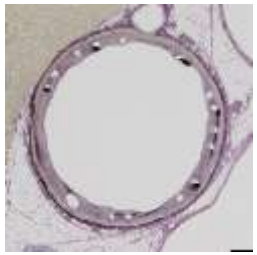
Qstent surface



Qstent surface

Qstent surface

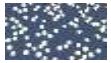
30 days



90 days

Neutrophil promoting Proteins

Neutrophil



LL37 / Cathelicidin protein regulates endothelialization

Animal studies performed at: CBSET, Lexington MA, USA
Animal models: Yorkshire swine (30 d) & Yucatan miniature swine (90d)
Data on file at : Qvanteq AG, Zurich, Switzerland

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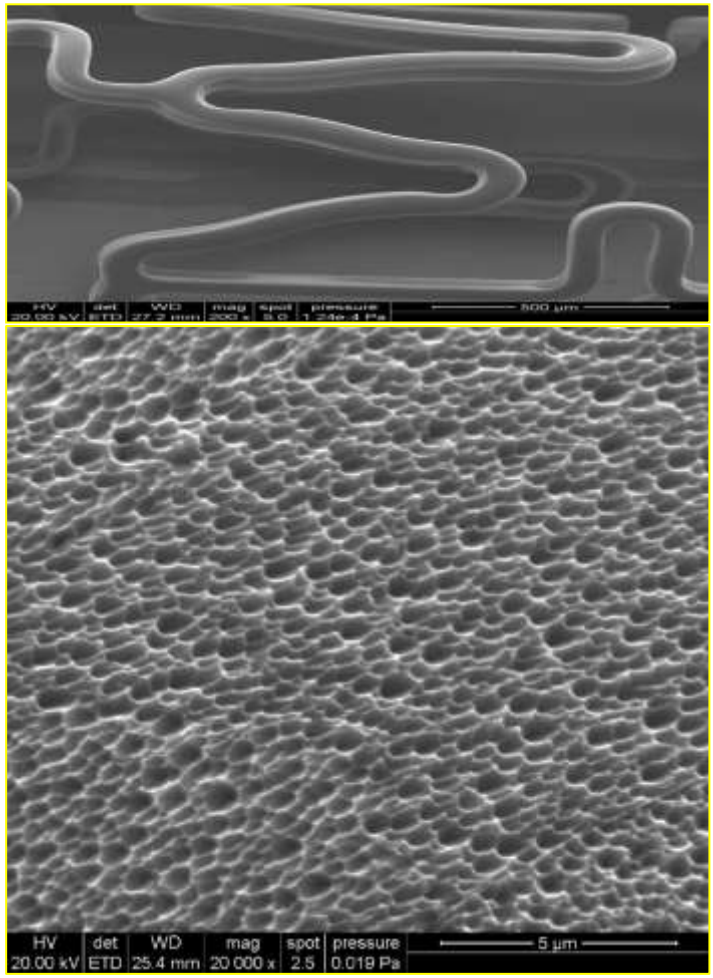
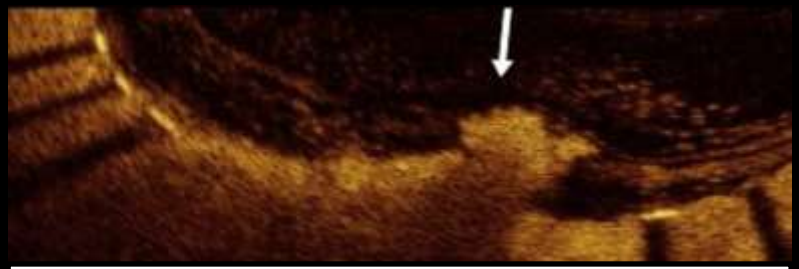
Nano+ OCT Polymer-free SES

Key Features:



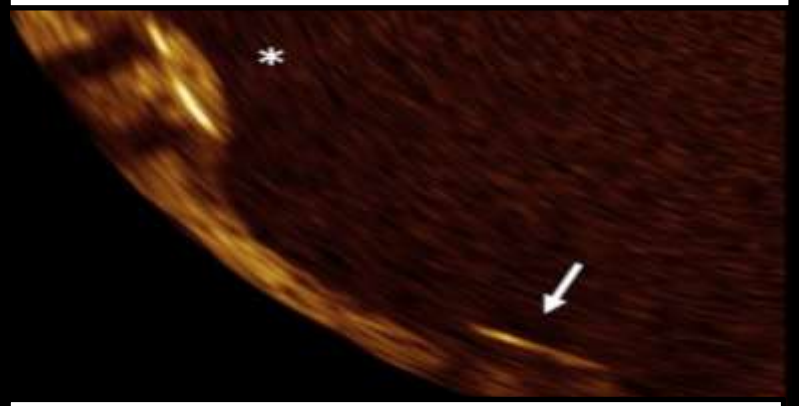
	Nano+ ™
Stent platform	316L Stainless steel
Strut thickness	91 µm
Surface modification	Abluminal Nanoporous surface
Drug, Dosage	Sirolimus (2.2µg/mm^2)
Drug release kinetics	80%, 30 days

However, to assess the degree of vascular healing in 2 time points, the healing index also calculated , the healing index in the composite of

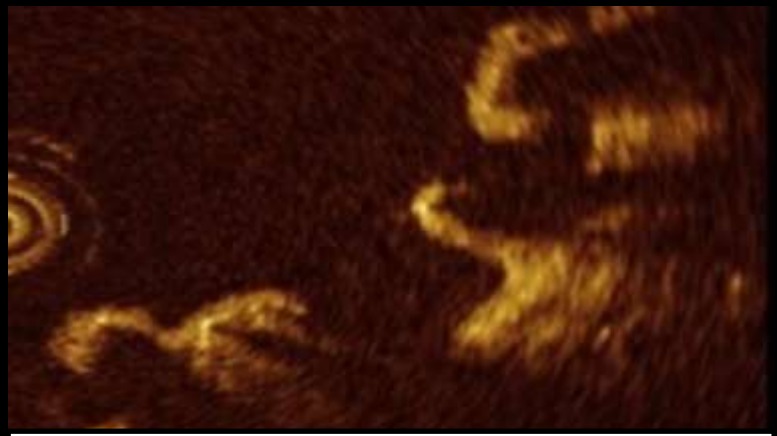


a)Intraluminal defect area (% ILD)

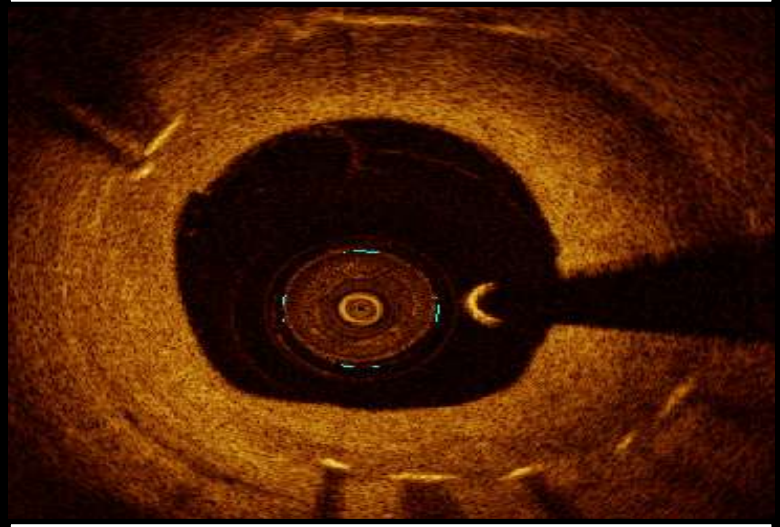
b)Malapposed and uncovered (% MU)



c)Uncovered alone (% U)

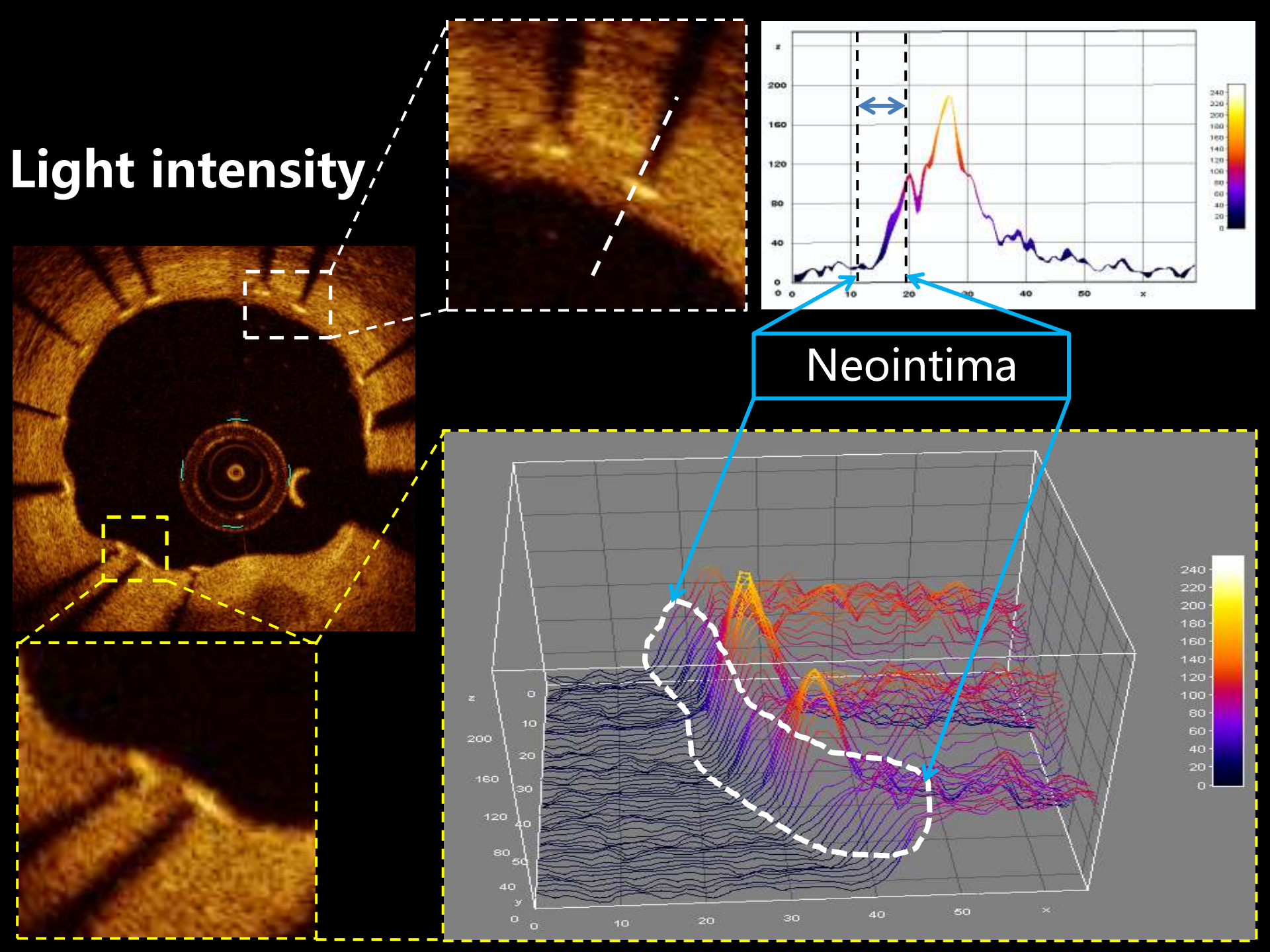


d)Malapposed alone (% M)

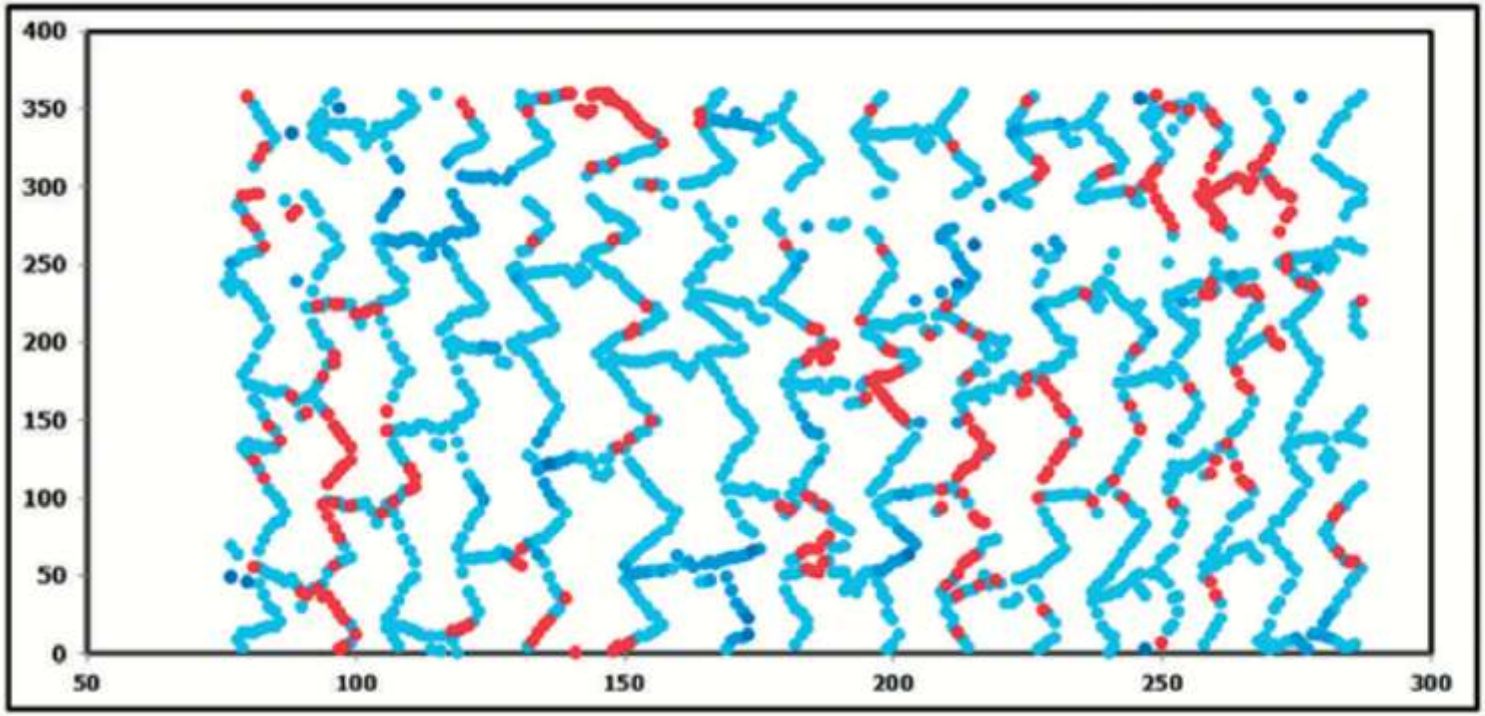


e)Neointimal volume obstructiontion (%NVO)

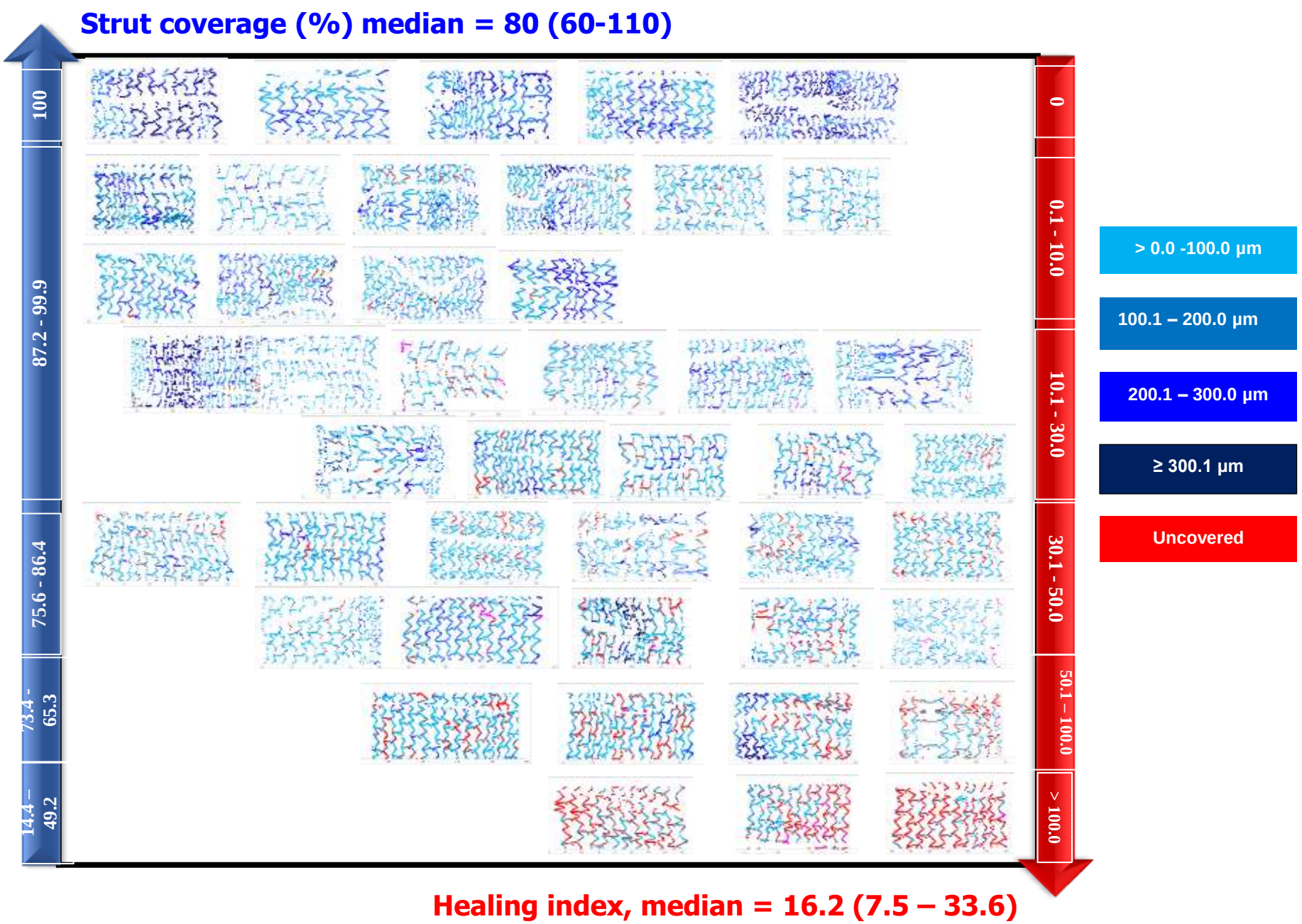
Healing index = [% ILDx4] + [% MUx3]+ [% Ux2]+ [% M] + [% NVO† -30]


Light intensity
Neointima

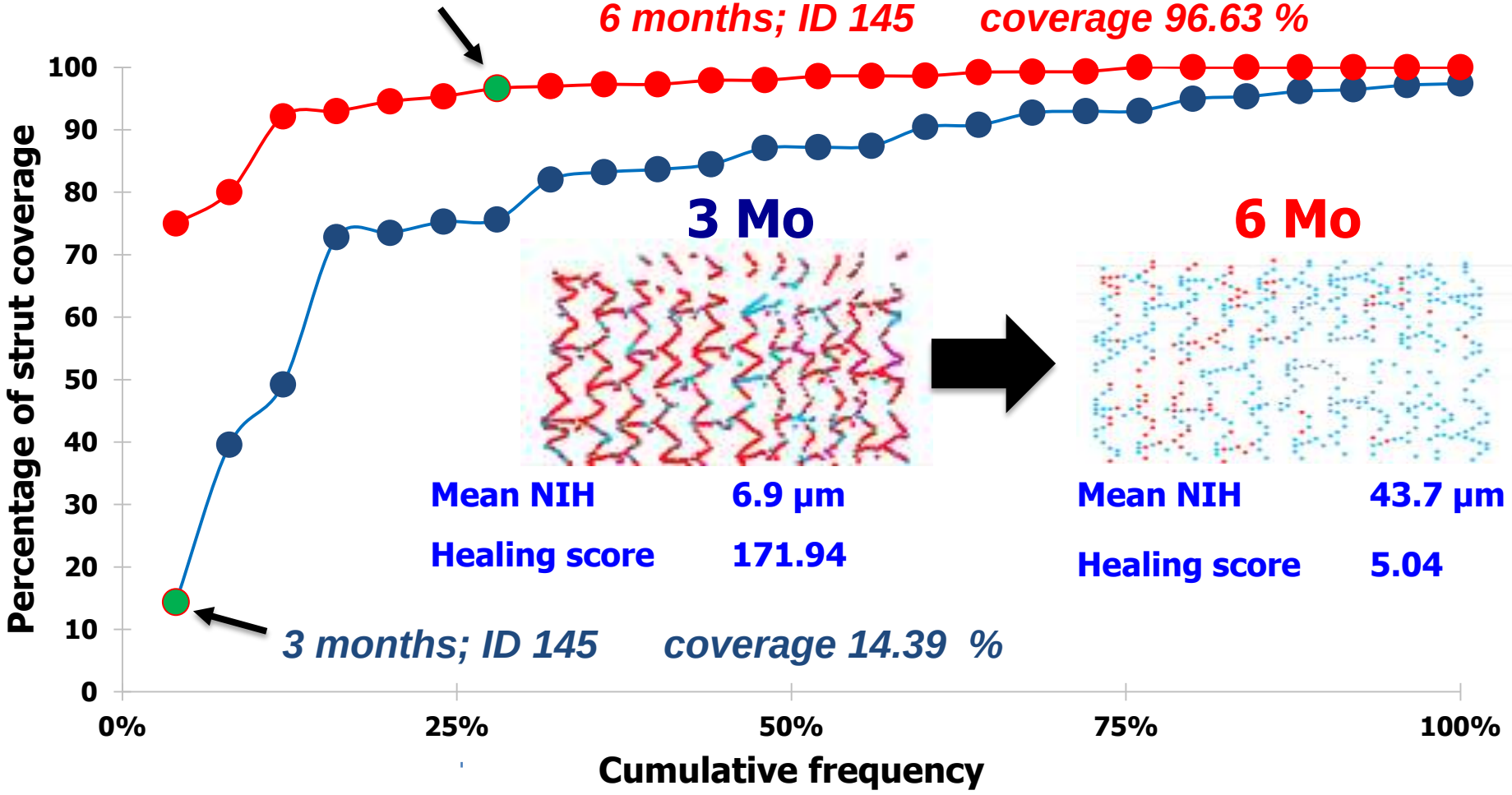
Status of strut coverage and healing index (n=45)



Status of strut coverage and healing index



Cumulative frequency curve of percentage of covered struts at 3 months and 6 months in paired 25 lesions



Comparison of healing index among different stent types with period of evaluation and patients setting

Patients status	n	time-point	mean ± SD	median (range)
In stable patients:				
Sirolimus polymer-free stent	45	3 mos	30.3 ± 38.9	16.2 (0.0 -177.7)
BVS-EES	28	6 mos	9.4 ± 13.3	3.1 (0.0 - 53.7)
Sirolimus polymer-free stent	25	6 mos	7.2 ±12.1	2.7 (0.3-9.3)
SES durable polymer	29	9 mos	43.3 ± 36.2	26.1 (4.6 - 127.4)
BES biodegradable polymer	22	9 mos	35.2 ± 25.0	36.7 (1.1 - 79.6)
ZES durable polymer	17	13 mos	18.7 ± 20.4	15.2 (0.0 - 79.0)
EES durable polymer	15	13 mos	10.8 ± 15.3	3.4 (0.0 - 47.7)
In STEMI patients:				
BES biodegradable polymer	25	Post PCI	202.8 ± 41.5	198.1 (67.9-344.3)
BES biodegradable polymer	25	6 months	13.4 ± 19.6	9.0 (0.0-97.2)
BES biodegradable polymer +TB	26	Post PCI	206.3 ± 38.7	200.6 (101.9-358.7)
BES biodegradable polymer +TB	26	6 months	20.1 ± 22.2	15.1 (0.0- 96.9)

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AsiaIntervention

ZES for multivessel and long lesions: RESOLUTE ASIA Registry

Thrombus aspiration for STEMI: Japanese PCI Registry

Second generation EES and vascular function

Site-specific neoatherosclerosis assessed by optical coherence tomography

Stent malapposition and contrast staining

How should I treat LAD disease progression?

Short-term effects of Nano+™ polymer-free sirolimus-eluting stents on native coronary vessels: an optical coherence tomography imaging study

Pannipa Suwannasom[1,2], MD; Edouard Benit[3], MD; Sjoerd H. Hofma[4], MD, PhD; Xu Bo[5], MD; Yuki Ishibashi[1], MD, PhD; Runlin Gao[2], MD

...yed drug-eluting stents (DES) aim to promote early endothelialisation and prevent stent ...cus. We sought to evaluate the extent of neointima growth by optical coherence tomography (OCT) three months after implantation of a polymer-free stent with a nano-sized-pore surface eluting sirolimus.

...hyperplasia
• polymer-free
• optical coherence tomography

Methods and results: In this prospective, multicentre, open-label study, patients were enrolled with documented stable angina or silent ischaemia and planned intervention for up to two *de novo* coronary lesions (in different vessels), with lesion length of ≤18 mm. The primary OCT endpoint was the percentage of in-stent neointimal volume obstruction at three months. The secondary endpoints included binary restenosis, stent thrombosis and device-oriented composite endpoints: a composite of cardiac death, myocardial infarction (MI) non-attributable to non-target vessel and clinically indicated target lesion revascularisation at three months. A total of 45 patients with 47 lesions were enrolled from four European sites. Eventually, 43 patients with 45 lesions underwent OCT examination at three months (one case was excluded for poor image quality and one case due to catheter dysfunction). The median and interquartile range of in-stent neointimal volume obstruction was 8.2% (4.7-10.7), of strut coverage was 93.0% (83.2-96.5) and of incomplete apposed struts was 0% (0.0-0.9), respectively. At three months, the mean angiographic in-stent late lumen loss was 0.17±0.27 mm. No case of stent thrombosis, cardiac death or clinically indicated target lesion revascularisation was reported at three months.

Conclusions: Polymer-free sirolimus-eluting stents with a nano-sized-pore surface are effective in inhibiting neointimal tissue proliferation and promoting early vascular healing with high strut coverage at three-month follow-up. (ClinicalTrials.gov number: NCT01925027).

*Corresponding author: P.O. Box 2125, 3000 CC Rotterdam, The Netherlands.
E-mail: patrick.w.j.c.serruys@gmail.com

For more details please see in 1st issue AsiaIntervention !!

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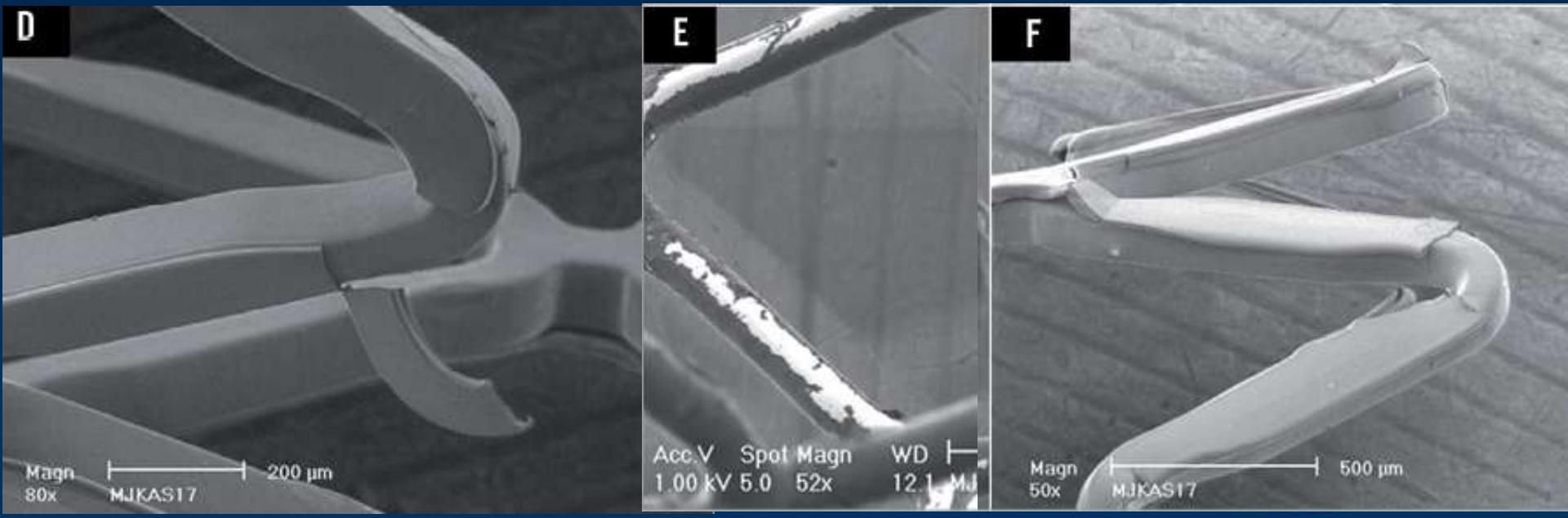
Background

non-erodable or erodable polymers as matrices for drug incorporation. show less compliant mechanical integrity towards cracking & delamination. When adhesion primers are used to improve this, their propensity to hinder/delay or promote recolonization is then under great concern as all of the matrix and drug are gone.

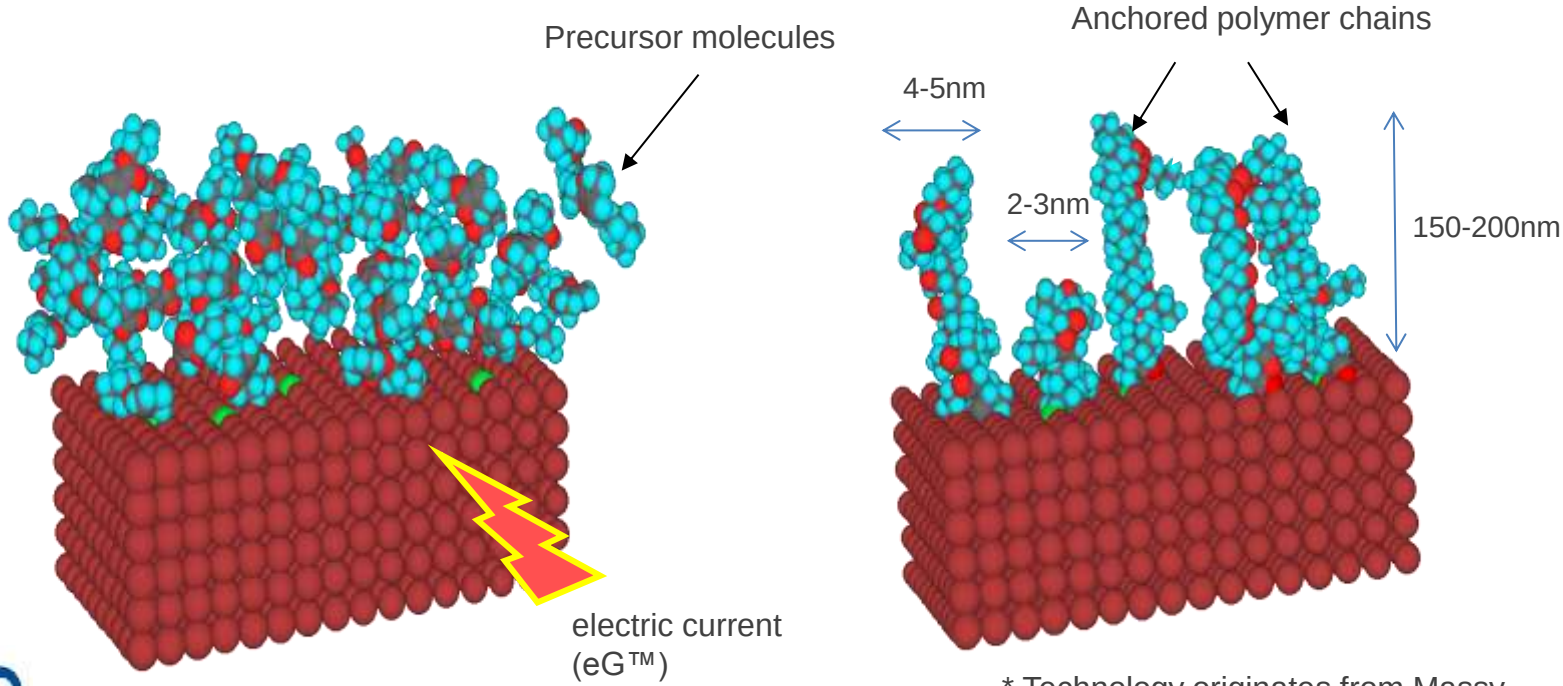


eG Coating Technology

What's eG coating?

Electro-grafting coating technology*: a passive coating where precursor molecules are electroplated, which generate polymer chains to grow perpendicularly in a helical shape on the surface of the stent.

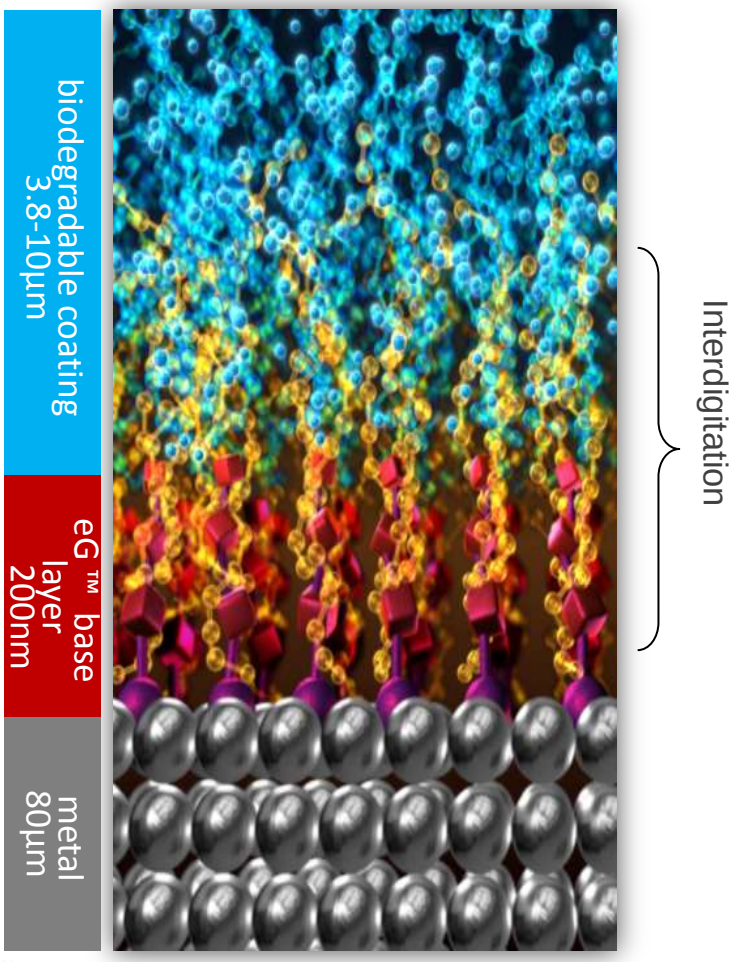
- Ultra-thin (nanometric 150-200nm) organic (polymeric) layers;
- **Covalent bonding;**
- Hyper conformal and uniform on complex shapes.

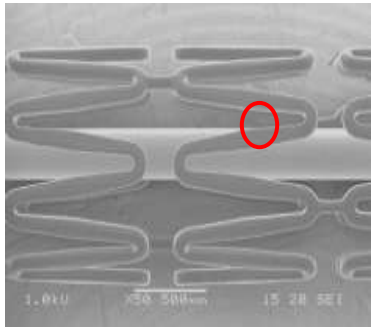


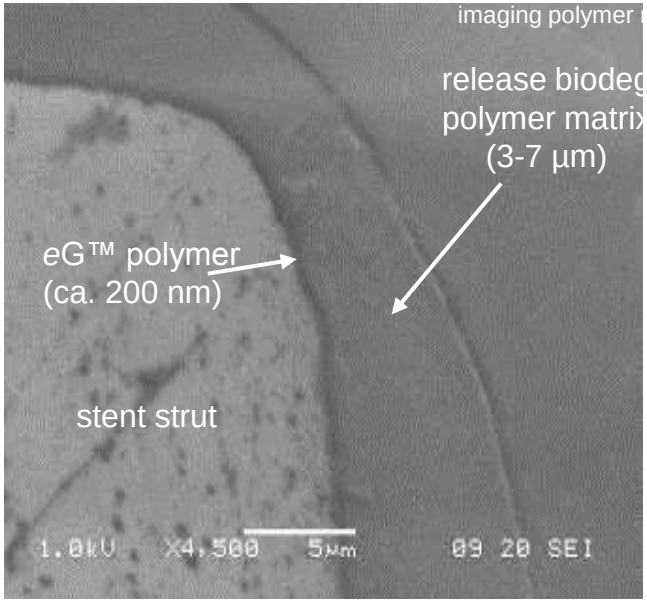
* Technology originates from Massy, France (subsidiary of SINOMED)

eG Coating Technology

Interdigitation: The process of intertwining electrified helical polymer chains of the eG base layer and the biodegradable coating (PLGA and Sirolimus).

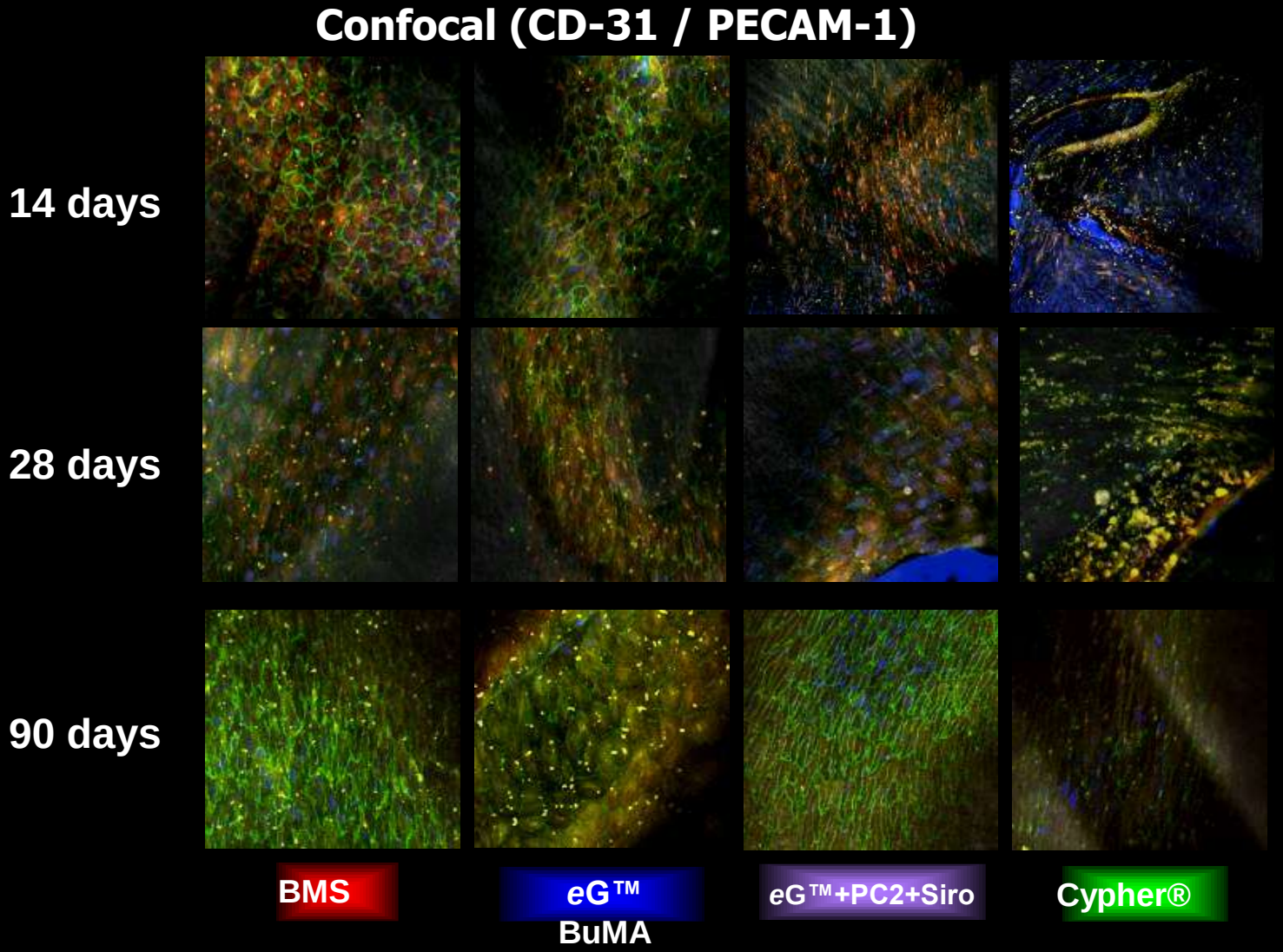






SINOMED

The BuMA stent using electro-grafting technology (*e*G™, AlchiMedics S.A., Massy, France) promotes recolonization by active EC's.



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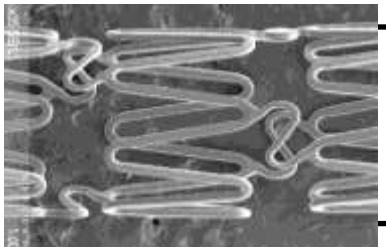
MiStent SES - Enhancing DES Design

MiStent SES optimizes stent design, polymer elimination & drug delivery



STENT - optimized for **faster healing** (CoCr)
Thin struts (64 µm) facilitate healing and lower acute thrombogenicity

POLYMER – optimized for **fast elimination** (PLGA)

Minimized polymer exposure - **eliminated from stent** in 45-60 days and **completely absorbed** from tissue within 90 days to allow healing

DRUG - optimized for **controlled prolonged elution**

Crystalline sirolimus allows **drug elution up to 9 months** for sustained inhibition of neointima

Continued Drug Delivery without Coating

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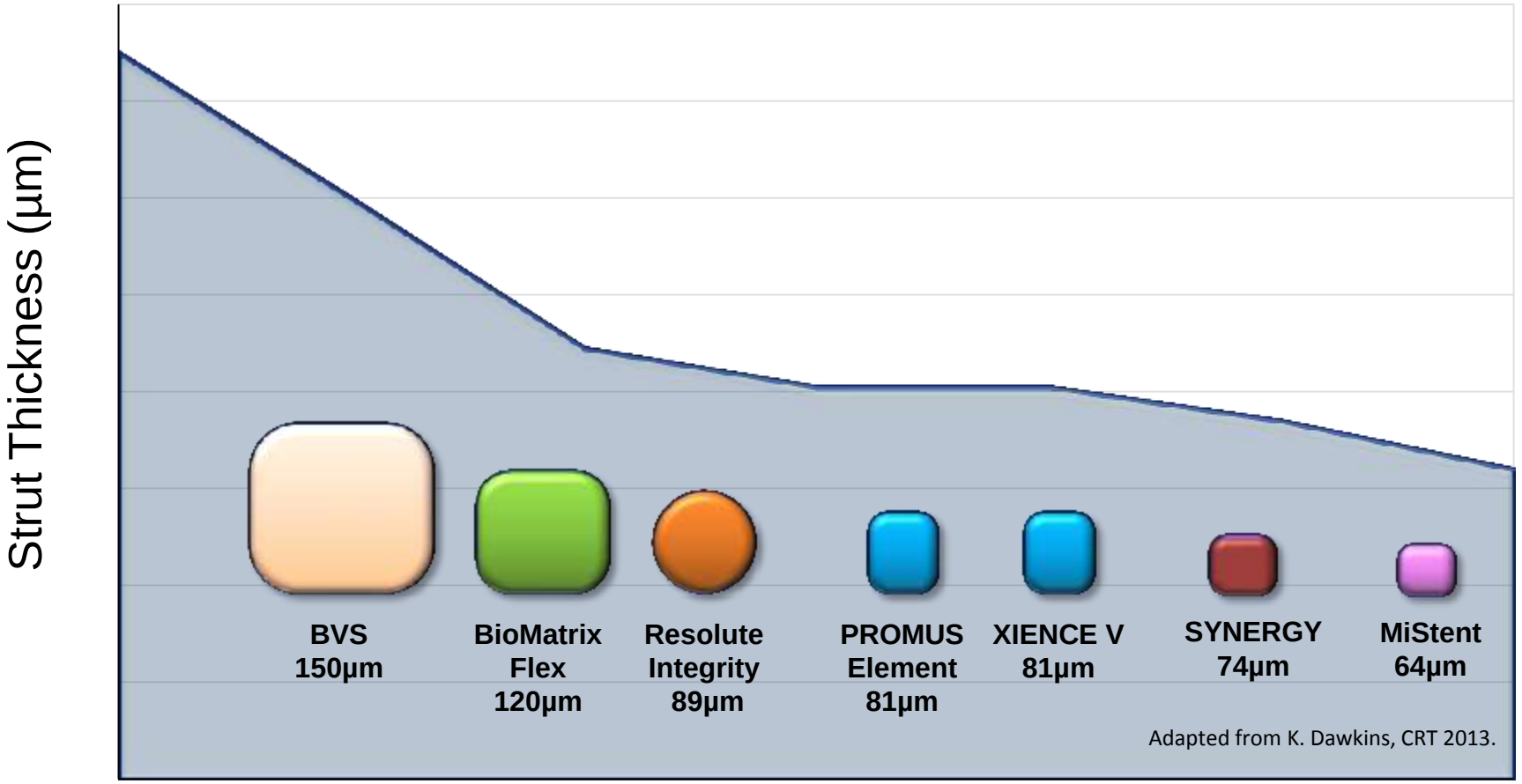

Thinner struts are associated with more rapid healing and lower risk of acute thrombogenicity

Ref: Kolandaivelu, K., et al. *Circulation* 2011, *123(13), 1*400-1409.

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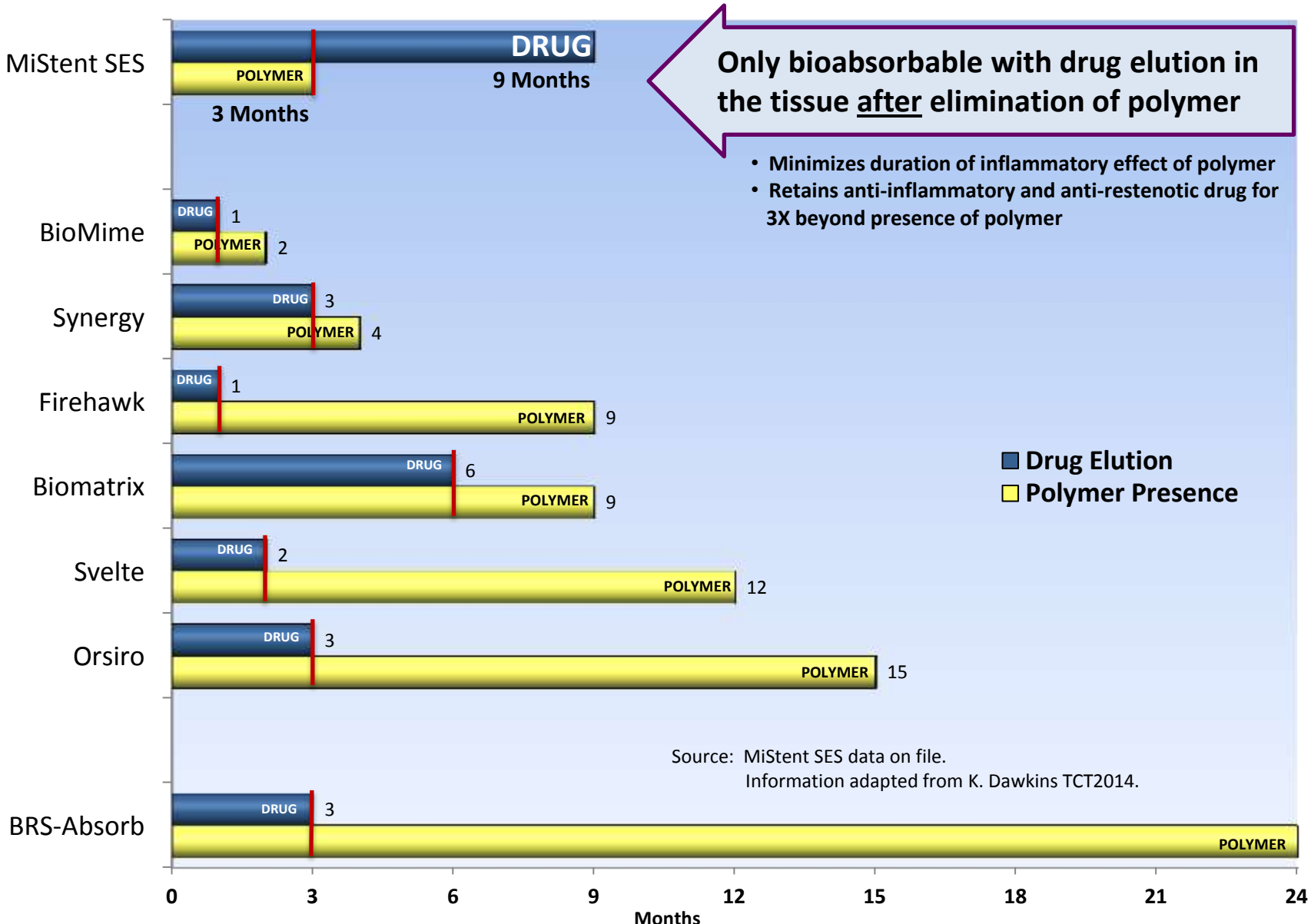
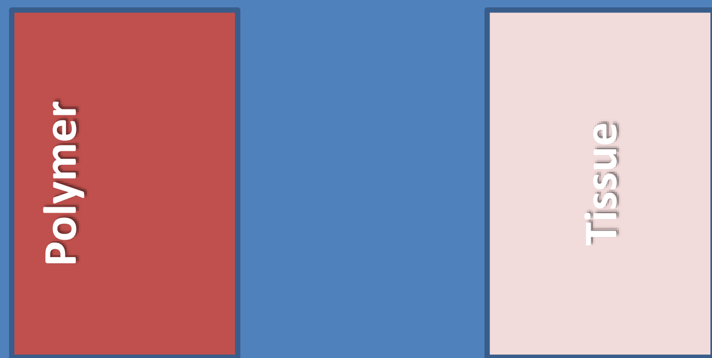
Time Course for Drug Delivery & Polymer Dissolution



"Conventional" Amorphous Elution

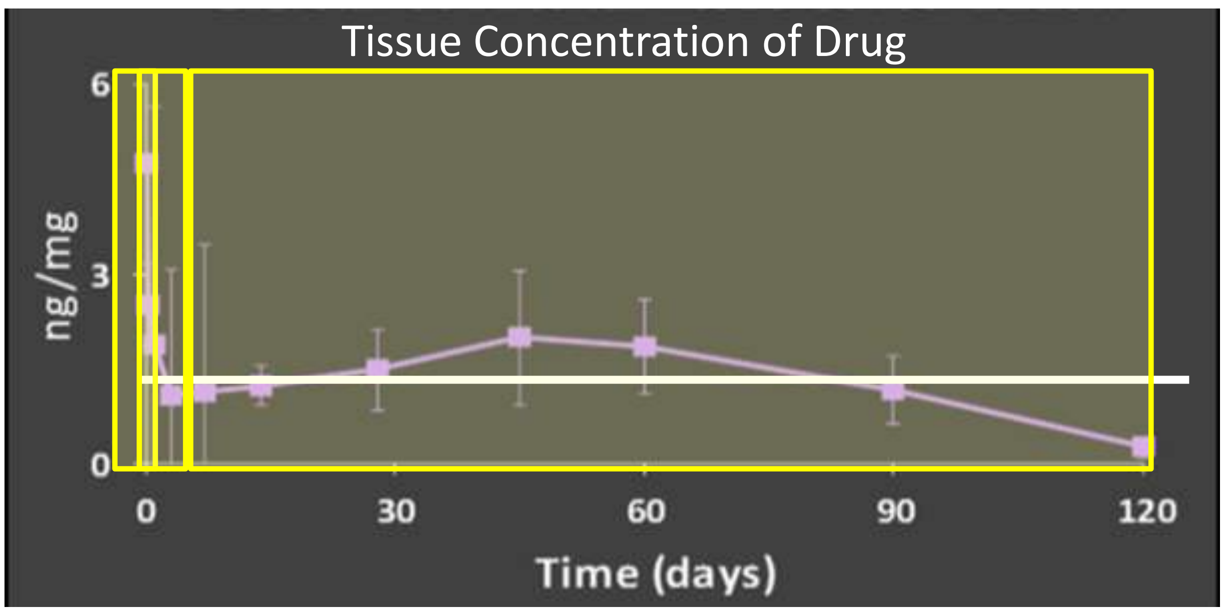
Amorphous Sirolimus in Polymer



Upon implantation the majority of the sirolimus is available for elution and the drug diffuses into the tissue due to a concentration gradient. This results in a rapid burst in tissue concentration of the drug

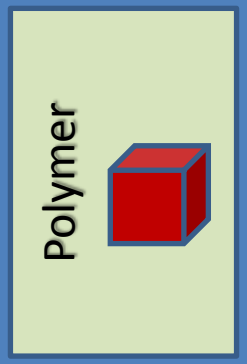
This rapid burst is followed by … there is no further therapeutic benefit of this burst of drug which may delay endothelisation

High Drug Concentration Low



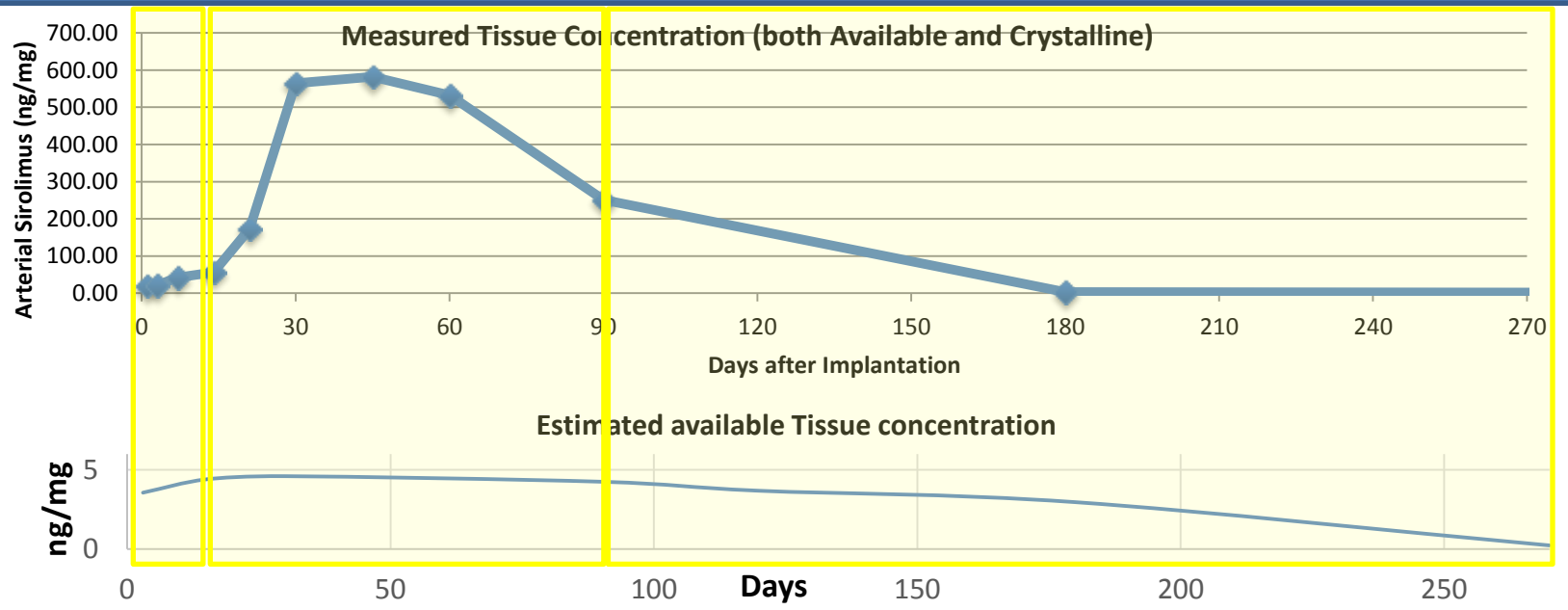
Mechanism of Action

Crystalline Sirolimus in Polymer



After the polymer is absorbed, still crystalline Sirolimus and diffuse a burst of Sirolimus which may impact (appear like a burst) but most of this Sirolimus is trapped in a crystalline form

High — Drug Concentration — Low



Conclusion

The stent technology is still alive and kicking.

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