National Heart Centre Singapore

Bioresorbable Vascular Scaffolds in PCI: Factors That Impact on Stent Thrombosis-An *In Vitro* Insight

Shengjie Lu [1], Valeria Paradies[1], Jaryl Ng[1], Philip E. Wong[1,2], Nicolas Foin [1, 2], Hector Alejandro Cabrera-Fuentes [1,2], Derek J. Hausenloy[1, 2,3,4,5,6], Huiying Ang[1]

1 National Heart Research Institute and National Heart Centre Singapore, Singapore
2 Cardiovascular and Metabolic Disorders Program, Duke-National University of Singapore
3 The Hatter Cardiovascular Institute, Institute of Cardiovascular Science, University College London, UK
4 Centre of Quantitative Medicine, Duke-National University of Singapore
5 Yong Loo Lin School of Medicine, National University Singapore, Singapore
6 The National Institute of Health Research University College London Hospitals Biomedical Research Centre, UK

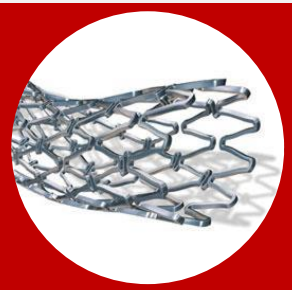
Evolution of Stent

1970s

Balloon Angioplasty

- Elastic recoil
- Acute closure
- Neointimal hyperplasia

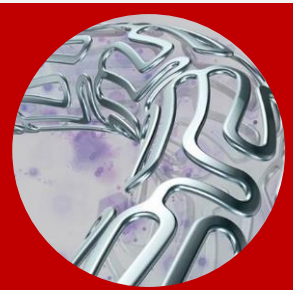
1980s



Bare Metal Stents (BMS)

- High incidence of in-stent restenosis (ISR)
- Neointimal hyperplasia

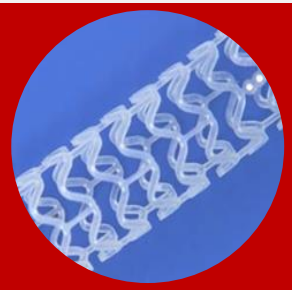
2000s



Drug-eluting Stents (DES)

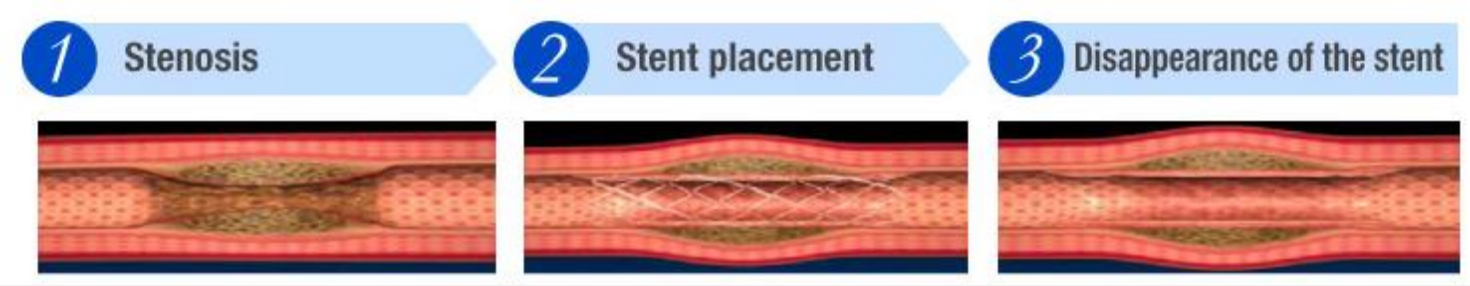
- Permanent caging, impaired endothelial function
- Reduced positive remodeling
- Late “catch-up” phenomena

2000 -

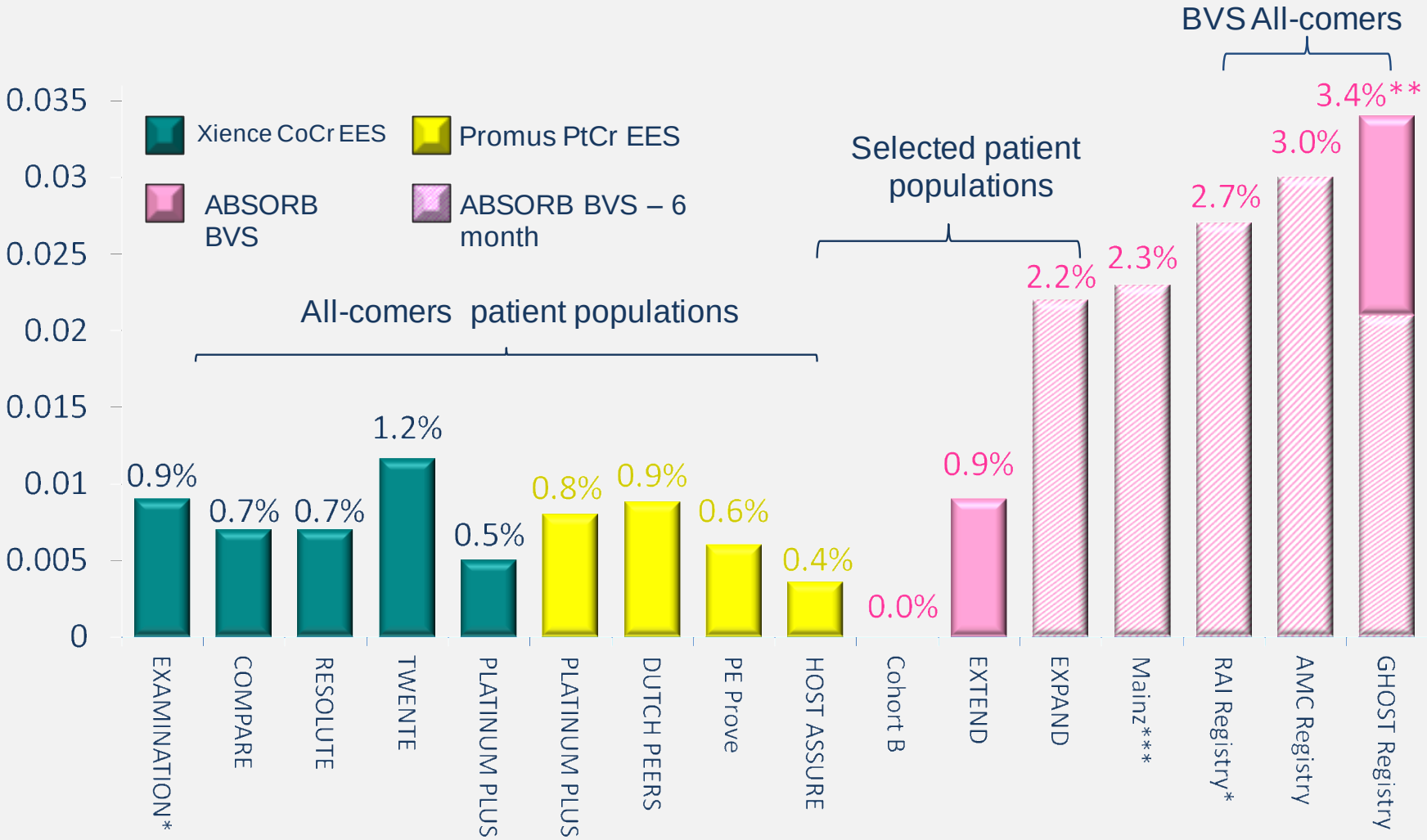


Bioresorbable Scaffolds (BRS)

- Potential long term benefits
- Large strut thickness, delivery issue (lesion prep)
- **Stent thrombosis**



Rates of Def/Prob ST (1 Year)



N:	751	897	1126	694	987	1862	905	1101	2503	101	660	171	133	74	135	1189

BVS twice as likely to have stent thrombosis compared to metallic DES

Capodanno et al. (2014) Eurointervention

Clinical Outcomes of BVS

02

- Criteria for non-inferiority not met
- A higher rate of device-oriented composite endpoint in BVS
- **8 definite scaffold thrombosis in BVS**

ABSORB II RCT
2Y Follow-up

Chevalier et al. *ABSORB II Clinical Outcomes at 3 Years.*
Presented at TCT 2016

Scaffold or Stent Thrombosis

	Absorb 335 patients	Xience 166 patients	p value
Definite	**2·5% (8)**	**0·0% (0)**	**0·06**
Acute (0–1 day)	0·3% (1)	0·0% (0)	1·0
Sub-acute (2–30 days)	0·3% (1)	0·0% (0)	1·0
Late (31–365 days)	0·0% (0)	0·0% (0)	1·0
Very late (>365 days)	1·8% (6)	0·0% (0)	0·19
Definite or probable	**2·8%(9)**	**0·0% (0)**	**0·03**
Acute (0–1 day)	0·3% (1)	0·0% (0)	1·0
Sub-acute (2–30 days)	0·3% (1)	0·0% (0)	1·0
Late (31–365 days)	**0·3% (1)**	**0·0% (0)**	**1·0**
Very late (>365 days)	1·8% (6)	0·0% (0)	0·19

8 Definite ScT (BVS) vs. 0 (Xience)

Objective and Methods

In vitro Scaffold Thrombosis Evaluation

Study effect of malapposition and strut thickness on thrombus formation

1.Strut Thickness,
2. Malapposition
3. Bifurcation PCI

In vitro perfusion model

Deployment of device

4 mins of porcine blood perfusion

+ 10% Acid-citrate-dextrose solution

Confocal Microscopy

Immunostaining with CD61 AB

Intensity, thrombus area

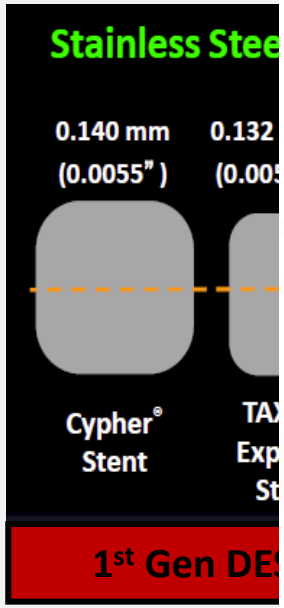
Student t-test ($p < 0.05$)

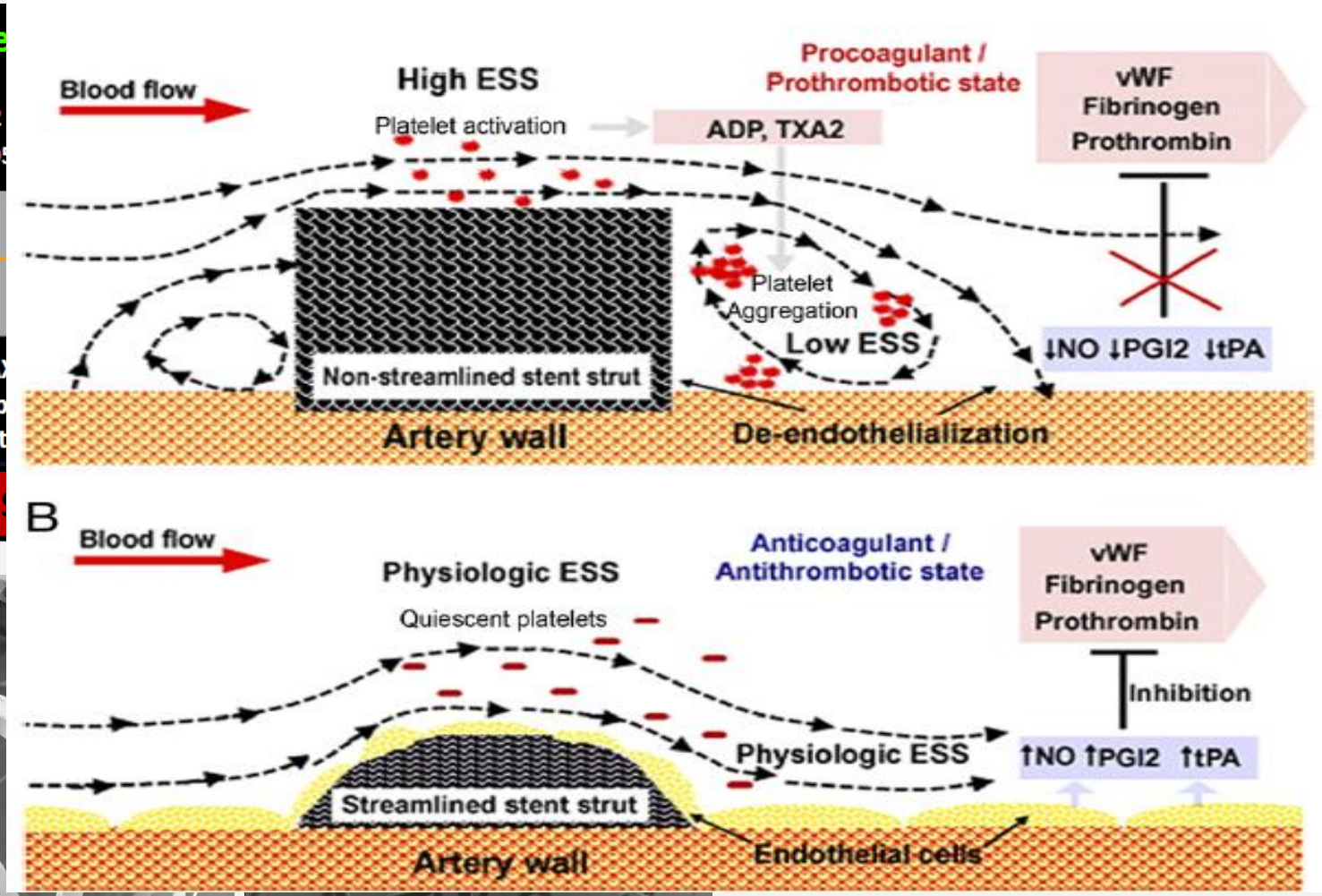
OCT Analysis

Cross sectional imaging

Thrombus area

1-Strut Thickness





High shear rate and shear stress will activate the platelet.

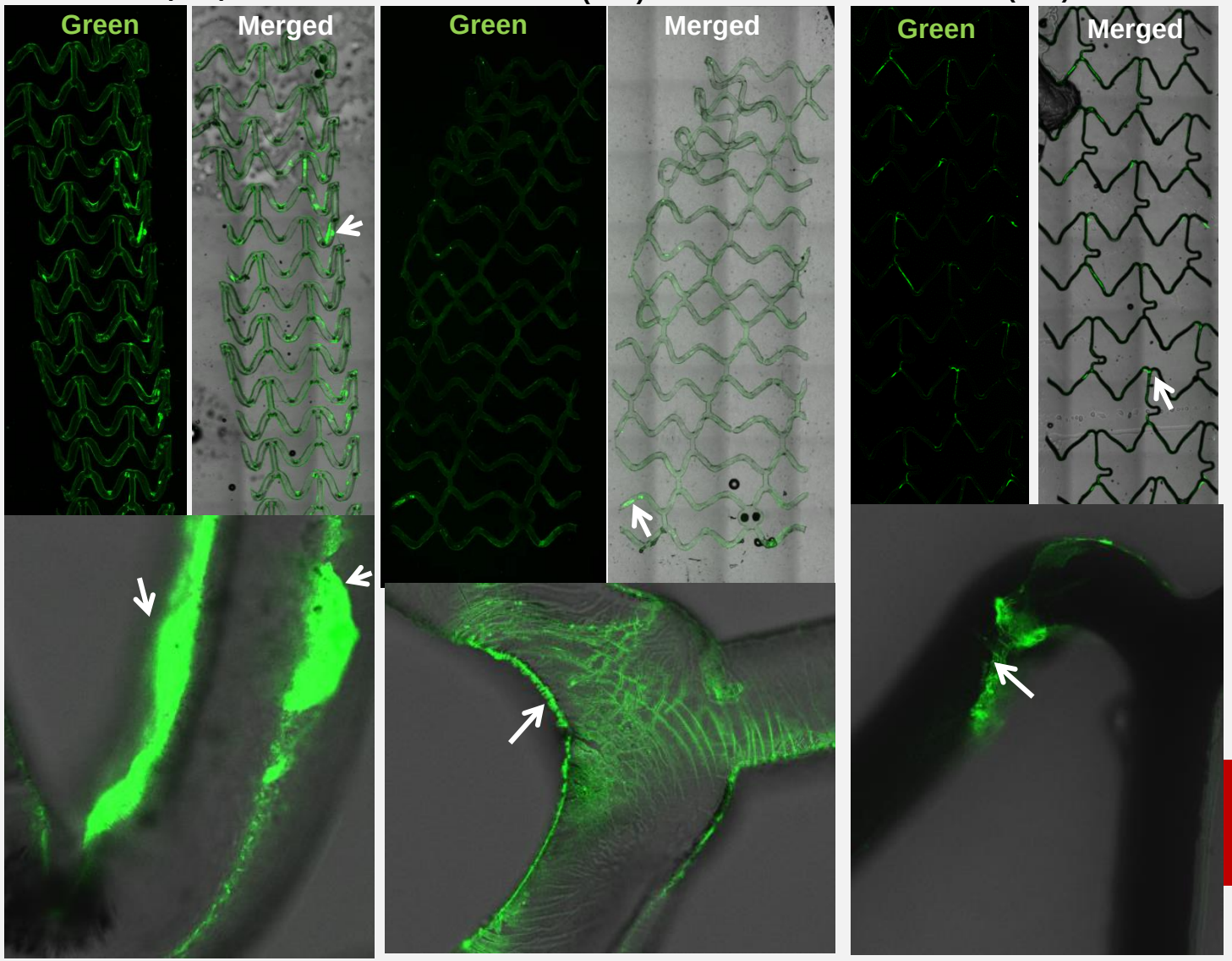
Koskinas et al. J Am Coll Cardiol 2012;59:1337–49

1-Effect of Strut Thickness

Abbott
BVS (157μm)
(N=6)

Arterius™
Thin-strut BRS (95μm)
(N=5)

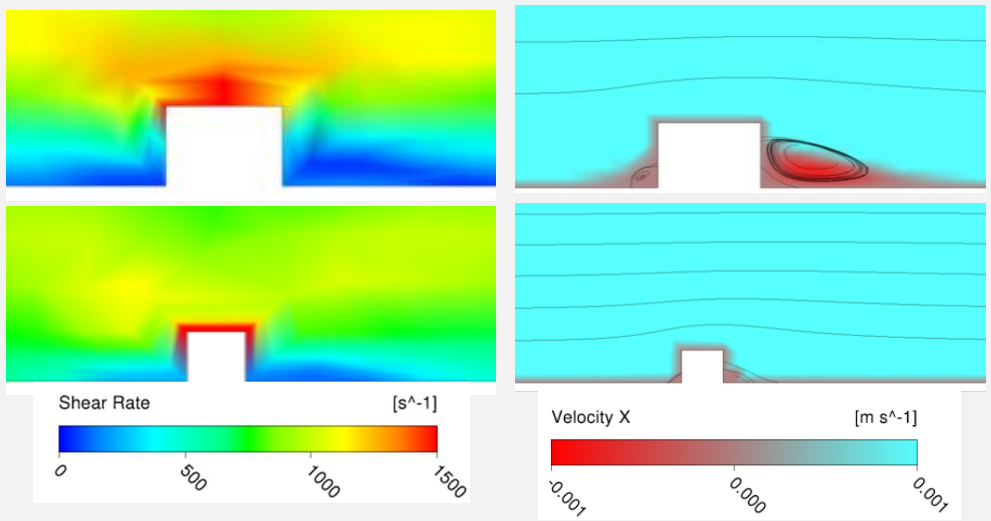
Abbott
Xience (81μm)
(N=5)



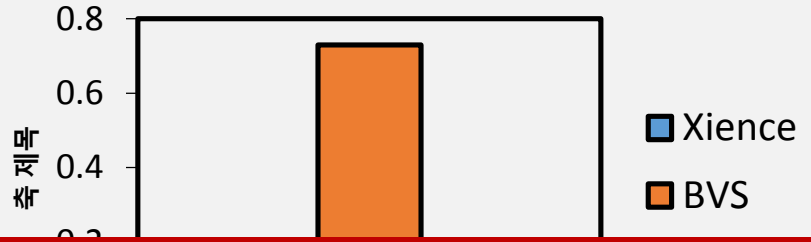
CFD

Shear Rate

Regions of Recirculation



Normalized Clot Area(mm^2/mm)



Thicker struts increase stent thrombogenicity (even in well-apposed model)

Lu SJ, Ng J, et al. (2018) **JACC: Cardiovasc. Interv**. 11(7); 714-716

2- Malapposition

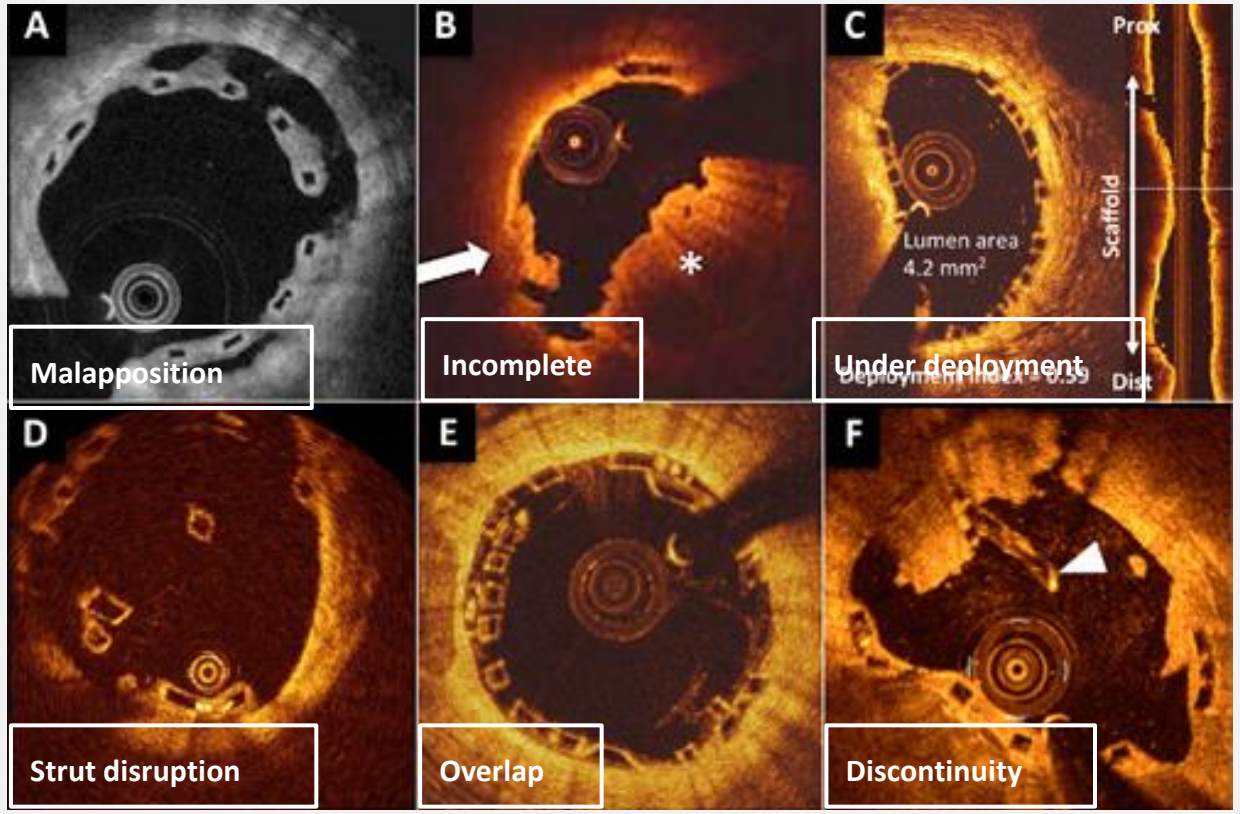
From a mechanical point of view – insights from intracoronary imaging

Acute/subacute Thrombosis

1. **Malapposition (under-sizing, lesion prep., inadequate post dilatation)**
2. Incomplete coverage of lesion
3. Under-deployment, lesion/device mismatch
4. Strut disruption

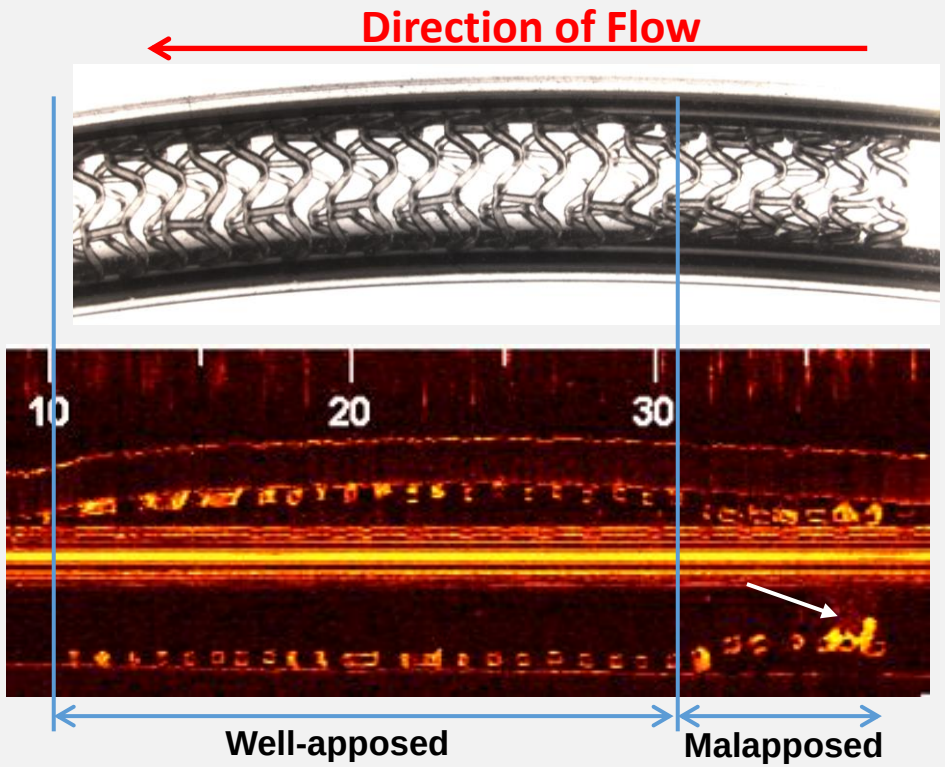
Late and very late Thrombosis

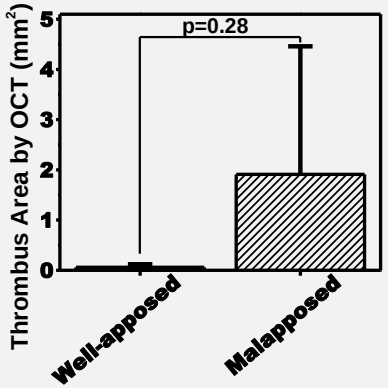
1. **Malapposition (under-sizing, lesion prep., inadequate post dilatation)**
2. Late discontinuity
3. Under-deployment, asymmetrical deployment
4. Uncovered struts (delayed healing)

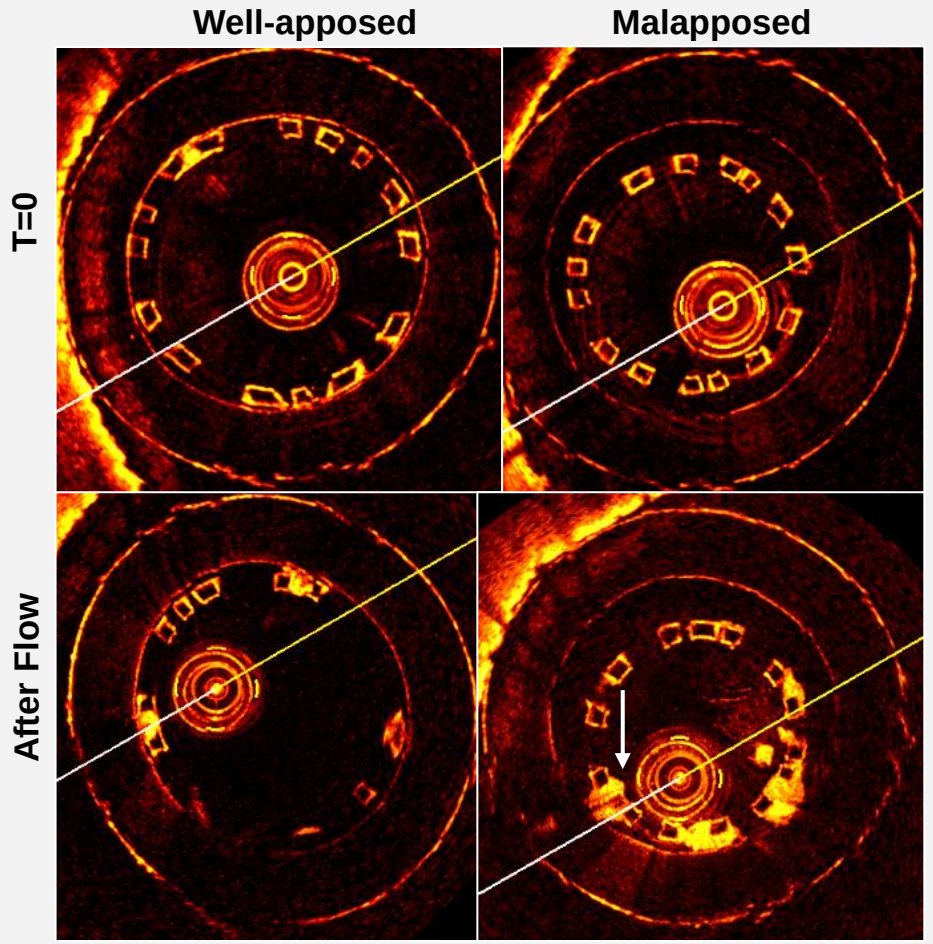


P. Serruys, PCRonline

2-Effect of Malapposition



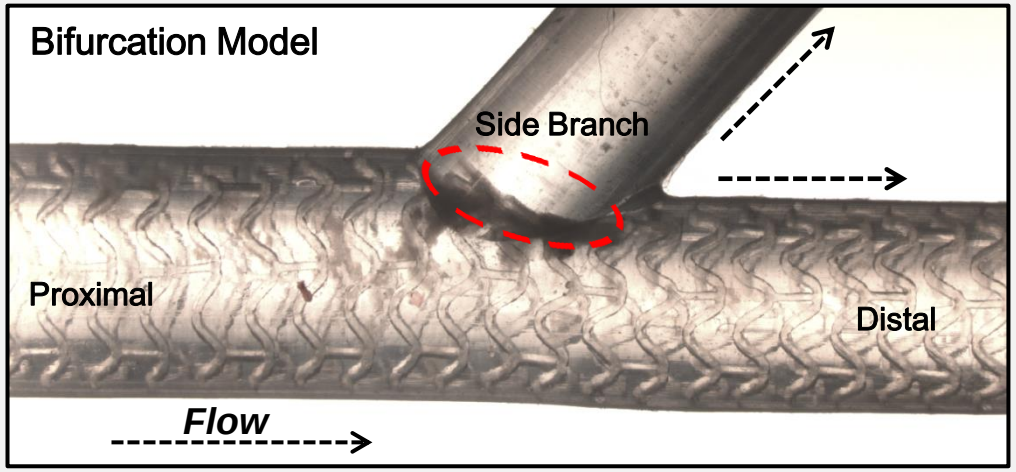


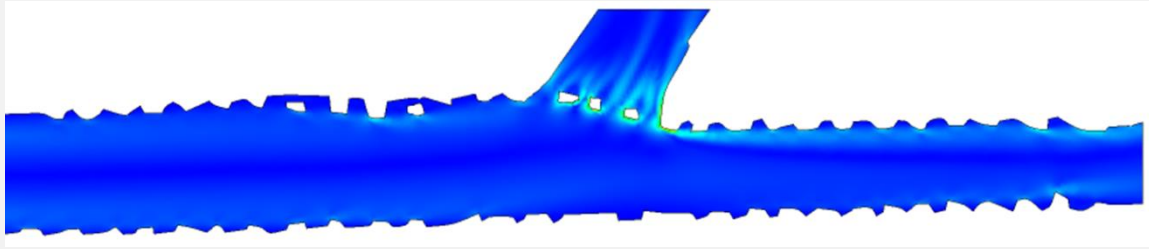


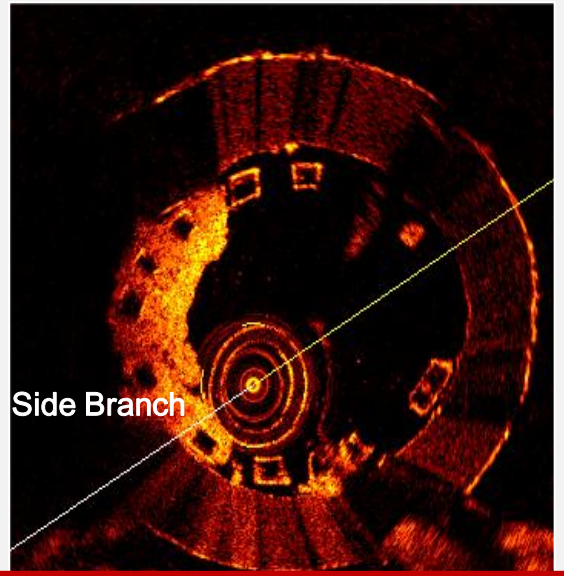
Significant thrombus formation when BVS strut is malapposed.

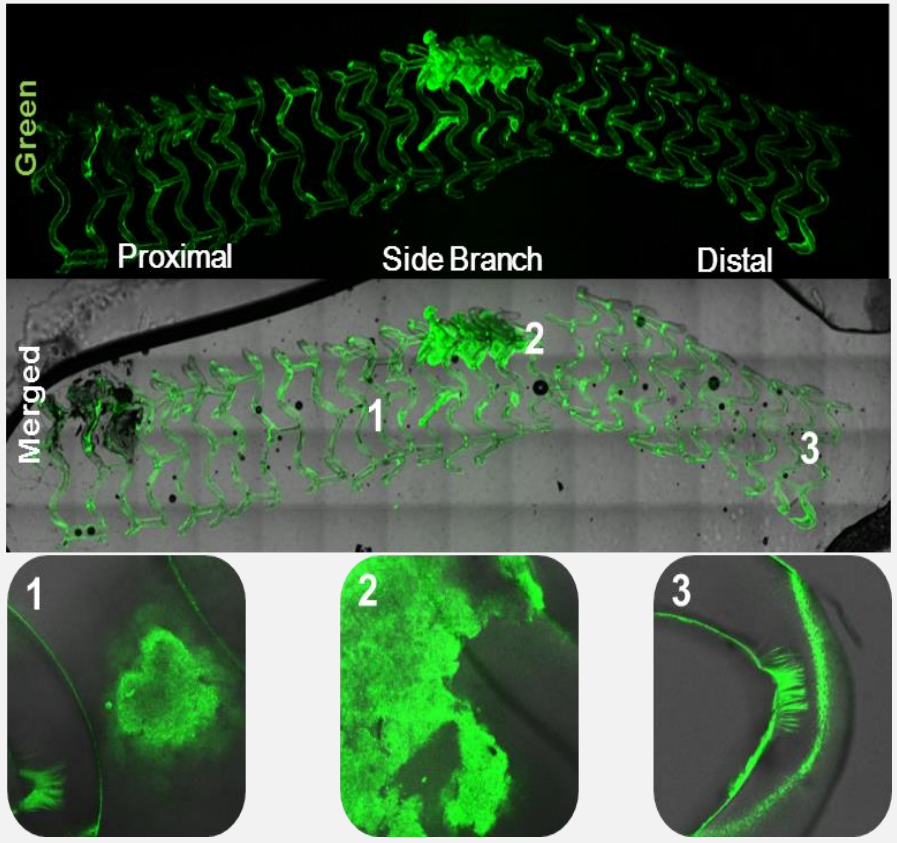
Foin, N., **Lu, S**., et al. (2017). **EuroIntervention**, 13(9), pp.e1096-e1098

3-Effect of Floating BVS Strut in Bifurcation







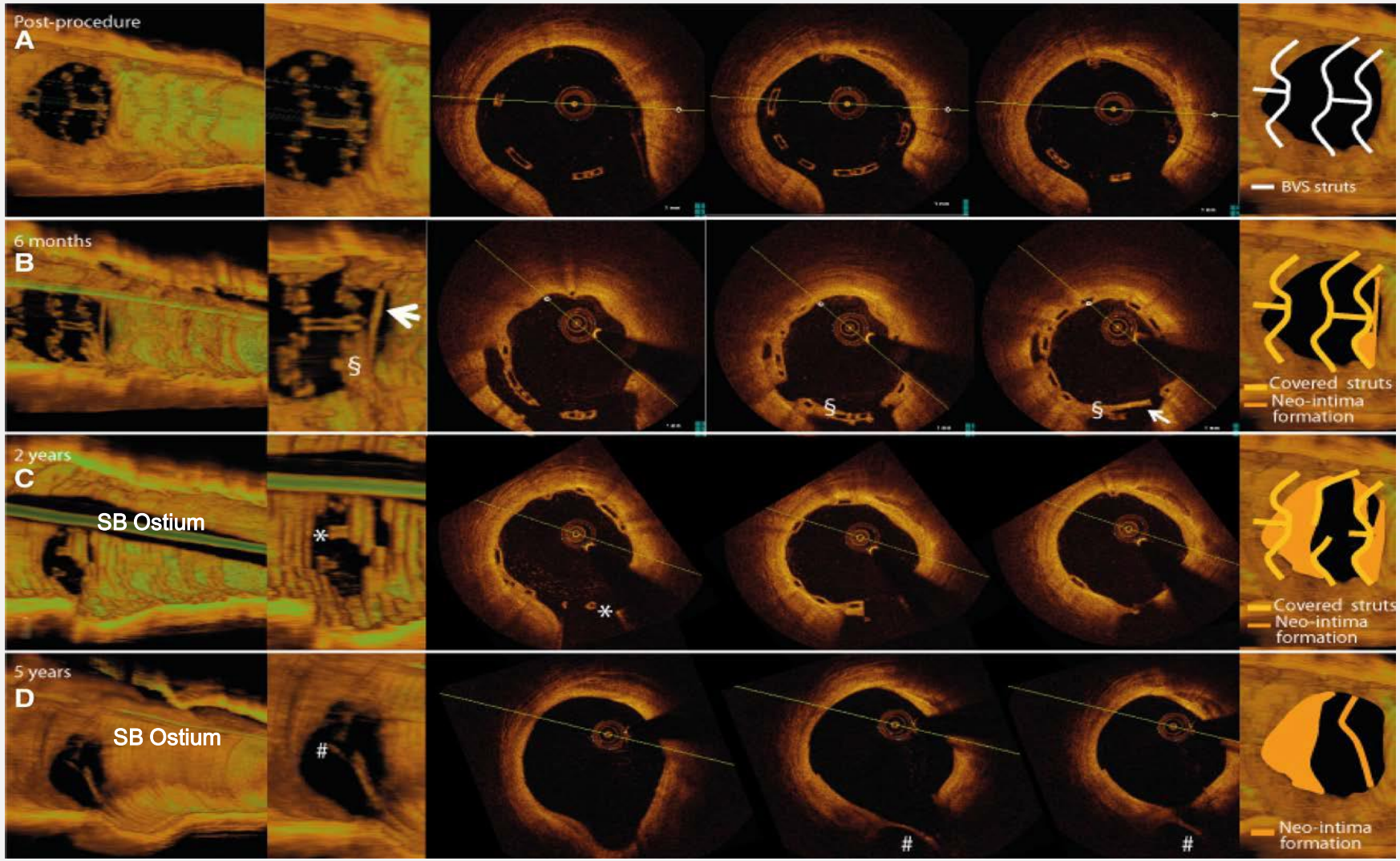


Significant thrombus formation at Side Branch ostium.

Paradies V, **Lu SJ***, et al. (2018) **Eurointervention**; pii: EIJ-D-18-00003. doi: 10.4244/EIJ-D-18-00003

3-BVS in Bifurcation

Pilot Trial -5 Years follow-up



Onuma et al. Circ Cardiovasc Interv. 2017;10:e004393.

Summary

1. ***In vitro*** **model is good to study stent/Scaffold thrombogenecity;**

2. **Strut thickness, malapposition, the use in bifurcation PCI are all important factors that trigger clots happening.**

Acknowledgements

National Heart Centre Singapore

A/Prof. Phillip Wong
Dr. Nicolas Foin
Dr. Huiying Ang
Dr. Valeria Paradies
Jaryl Ng

Duke-NUS

Prof. Derek Hausenloy
Dr Hector Alejandro Cabrera-Fuentes
Dr Sauri Hernández-Reséndiz
Prof Elisa A Liehn
Gustavo E. Crespo-Avilan
Whendy Contreras
Chrishan J. A. Ramachandra

Duke-NUS|SHF| National Health Innovation Centre(NHIC) |NMRC

Appendix

Causes of acute/subacute, late and very late ST

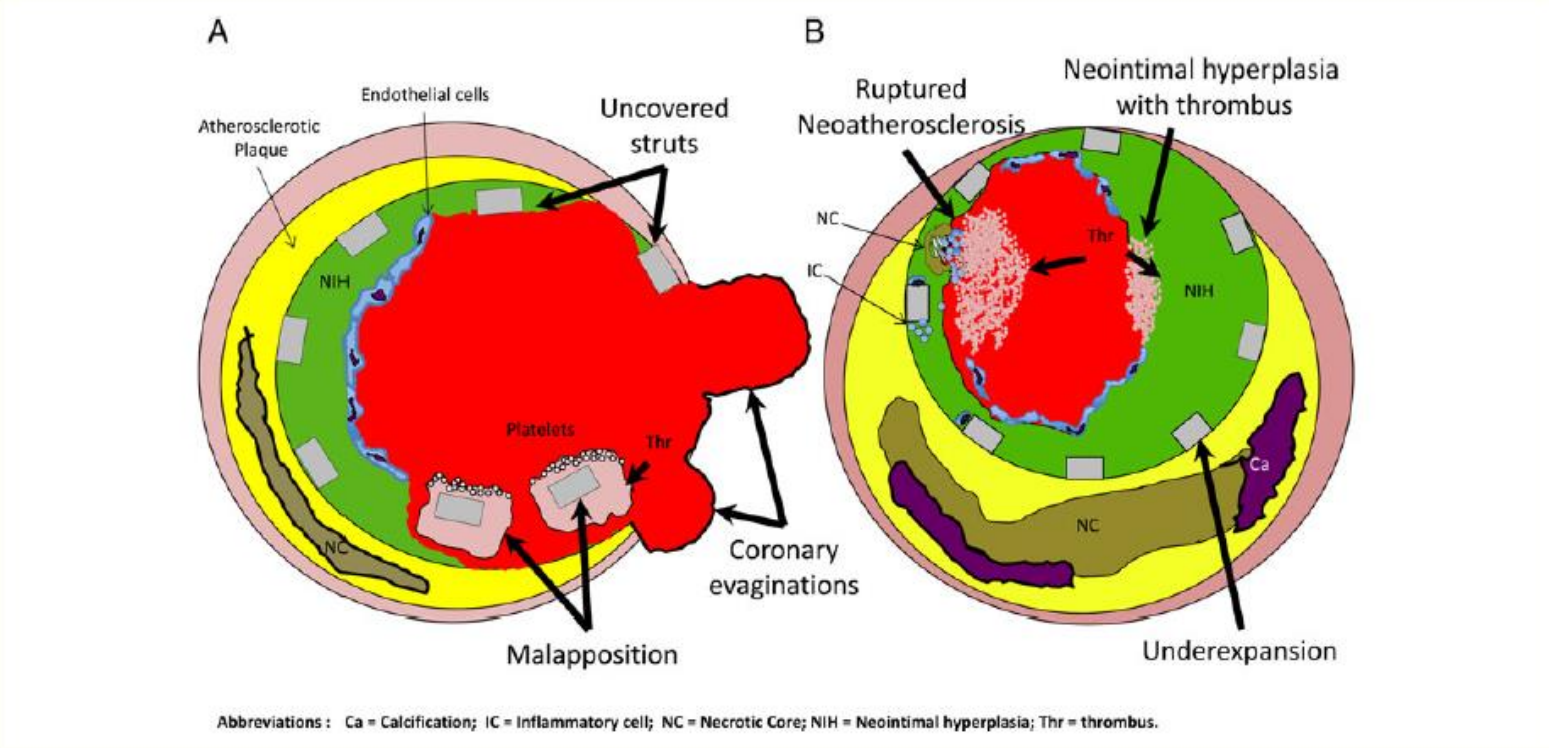
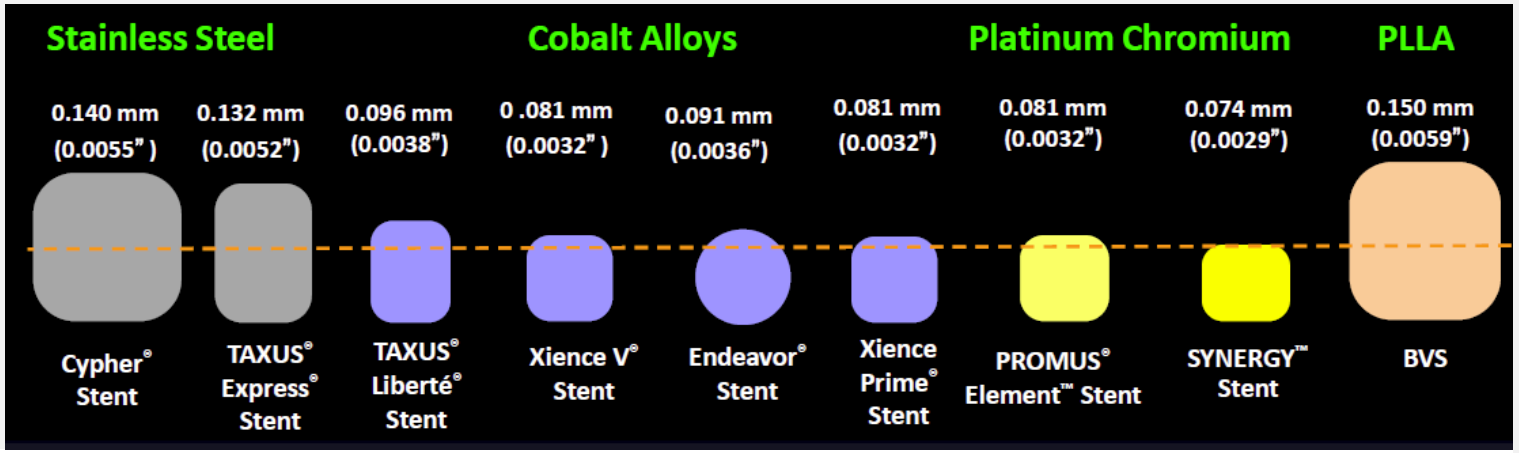
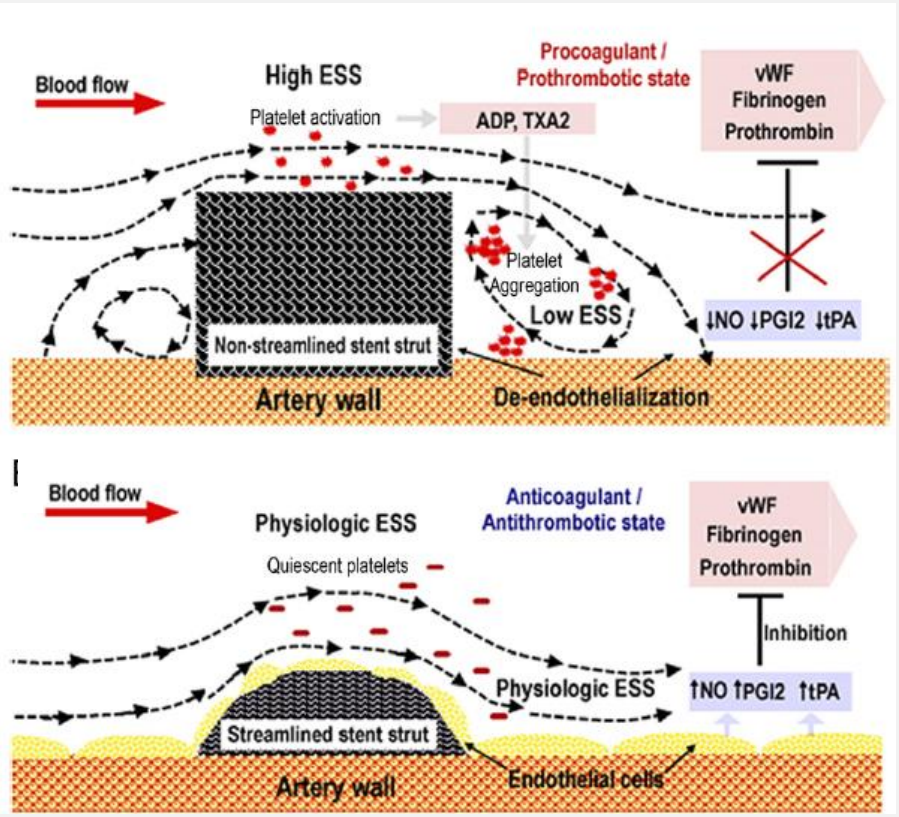


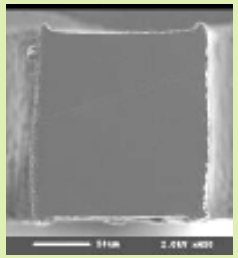
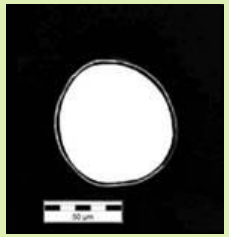
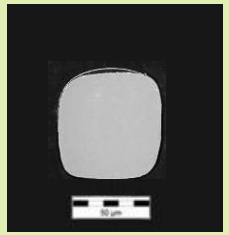
Figure 1 Causes of acute, subacute, late, and very late stent thrombosis. (*A*) Uncovered struts may be present in isolation or in the presence of malapposition, coronary evaginations, and also underexpansion (*B*). Malapposed stent struts are often covered by fibrin/platelet thrombus (Thr). Evaginations are defined as outward bulges in the luminal contour between struts and are a frequent finding in first-generation drug-eluting stents (DES) and less frequent in second-generation DES. (*B*) Underexpansion $<3.00\ mm^2$ may be a cause of uncovered struts and malapposition. Late stent thrombosis can occur form underlying excessive neointimal hyperplasia, and very late stent thrombosis from neoatherosclerosis.

Mori et al. *European Heart Journal* 2016; 37, 1217-1219

Strut Thickness from DES to BRS



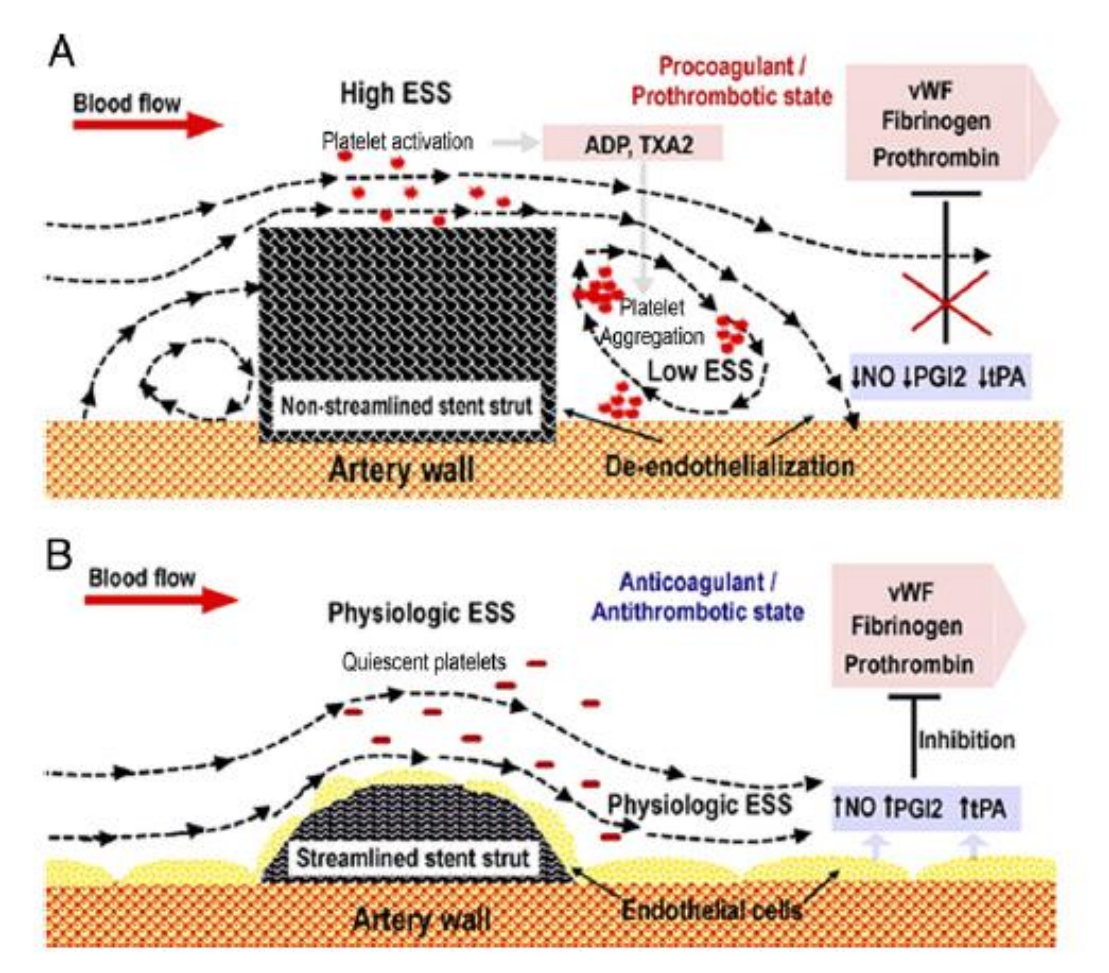


	Absorb Bioresorbable Vascular Scaffold System	Endeavor Resolute Stent	Xience PRIME	SYNERGY™	Orsiro Hybrid DES
SEM images					
Strut thickness	150 µm	91 µm	81 µm	74 µm	60 µm
Polymer thickness*	3 µm	4.8 µm	7.8 µm	4 µm	7.4 µm
Total thickness	156 µm	99 µm	95 µm	78 µm	71 µm

Int J. Cardiology 2014

Appendix

Effect of Strut Thickness on ST



- **High ESS region**: induces platelet activation
  - May trigger coagulation cascade
- **Low ESS region**: induces endothelial dsyfunciton, platelet aggregation
  - Pro-thrombotic state
- Thinner strut: faster re-endothelialization over struts, improves arterial healing

Koskinas et al. J Am Coll Cardiol 2012;59:1337–49

Treatment Options

Excercise/Medication

- Antiplatelet, statins, vasodilators, etc..
- Used for patients with stable CAD
- Not suitable for patients with severe stenosis or acute MI

Minimally Invasive: PCI with BMS

- Angioplasty with bare metal stenting
- Less invasive, mixed long term results. Balloon angioplasty was offered in early days of PCI to treat patients with MI
- Problem: high restenosis rates in CAD

By-pass Surgery

- LIMA, vein graft
- Viable option for those with good conduit
- Problem: Very Invasive and long hospital stay and recovery

Drug Eluting Stent

- Drug coating prevents early healing response and in-stent restenosis
- Offer equivalent treatment to by-pass
- Problem: Permanent metal implant remains in the artery after treatment