22nd CARDIOVASCULAR SUMMIT
TCTAP2017

Long-Term Safety Issue of BRS; Chance or True?

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Erasmus MC

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CARDIALYSIS
Clinical Trial Management - Core Laboratories

amc

Meta-analysis of 2-3Y outcomes after the ABSORB implantation

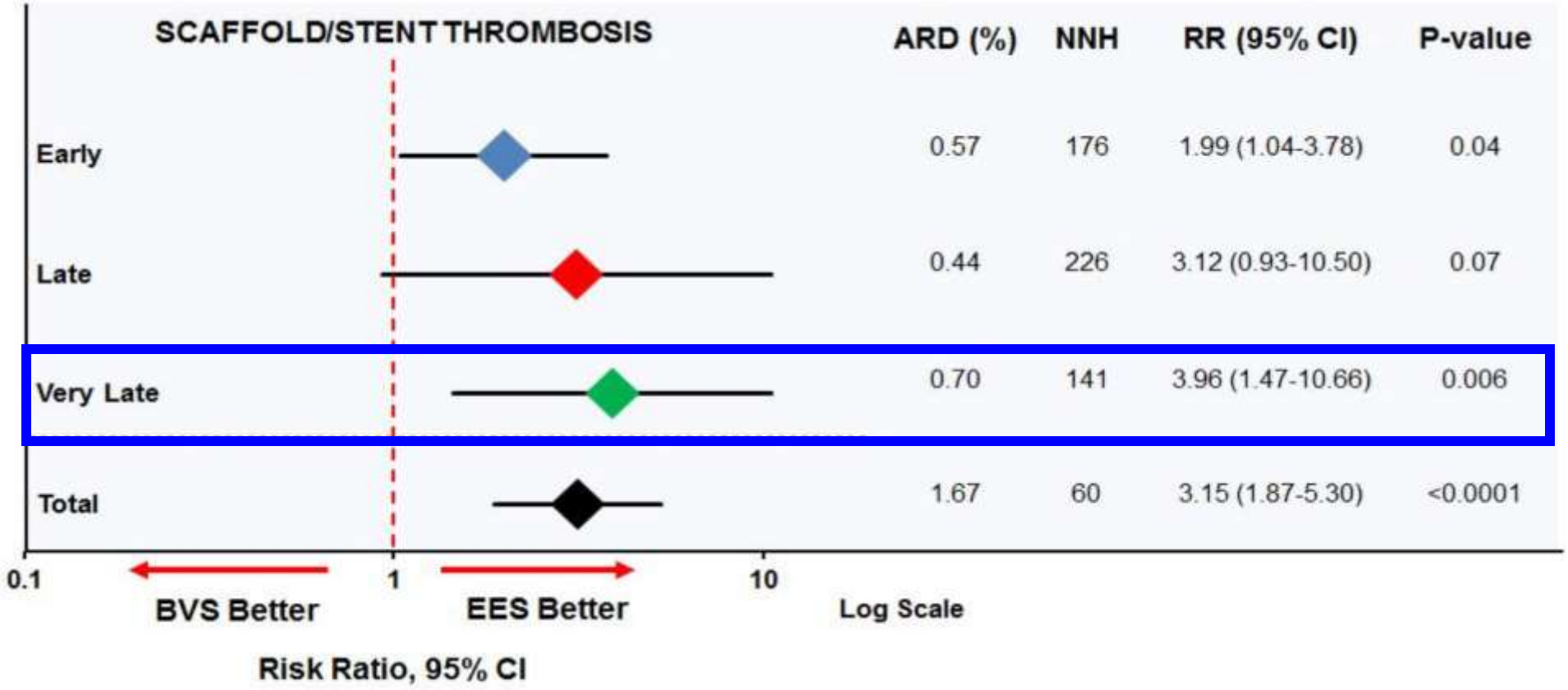
Study	Number of included patients	Included study	follow-up year	TLF rate (BVS vs EES) OR (95%CI)	TV-MI (BVS vs EES) OR (95%CI)	ID-TLR rate (BVS vs EES) OR (95%CI)	Definite/ probable ST rate (BVS vs EES) OR (95%CI)	Very late ST rate (BVS vs EES) OR (95%CI)
Collet et al.[1]	1,730 (1,015 vs. 715)	ABSORB II	**3Y**	9.3% vs. 6.6% **OR 1.48 (0.90-2.42)**	4.5% vs. 1.6% **OR 2.25 (0.81-6.19)**	5.6% vs. 3.0% **OR 1.89 (1.15-3.13)**	2.4% vs. 0.9% **OR 2.95 (1.37-6.26)**	1.4% vs. 0.5% **OR 3.04 (1.20-7.68)**
		ABSORB JAPAN	**2Y**					
		ABSORB CHINA	**2Y**					
		TROFI II	**2Y**					
		EVERBIO II	**2Y**					
Ha et al.[3]	2,582 (1,407 vs. 1,095)	ABSORB II	**3Y**	**OR 1.31 (0.93-1.83)**	**OR 2.59 (1.17-5.70)**	**OR 1.70 (1.02-2.83)**	**OR 2.35 (1.14-4.86)**	Not reported
		ABSORB JAPAN	**2Y**					
		ABSORB CHINA	**2Y**					
		ABSORB EXAMINATION	**2Y**					
		ABSORB EXTEND	**3Y**					
Sorrentino et al.[2]	5,583 (3,261 vs. 2,322)	ABSORB II	**3Y**	9.6% vs. 7.2% **OR 1.32 (1.1-1.59)**	5.8% vs. 3.2% **OR: 1.62 (1.24 to 2.12)**	5.7% vs. 4.1% **OR 1.40 (1.10-1.79)**	2.4% vs. 0.7% **OR 3.15 (1.87-5.30)**	0.84% vs. 0.13% **OR 3.96 (1.47-10.66)**
		ABSORB III	**2Y**					
		ABSORB JAPAN	**2Y**					
		ABSORB CHINA	**2Y**					
		AIDA	**2Y**					
		TROFI II	**2Y**					
		EVERBIO II	**2Y**					

1; EHJ. 2017, 2; JACC 2017, 3; JACC Cardiovasc Interv. 2017.

J Am Coll Cardiol. 2017 Apr 12. pii: S0735-1097(17)37013-4. doi: 10.1016/j.jacc.2017.04.011. [Epub ahead of print]

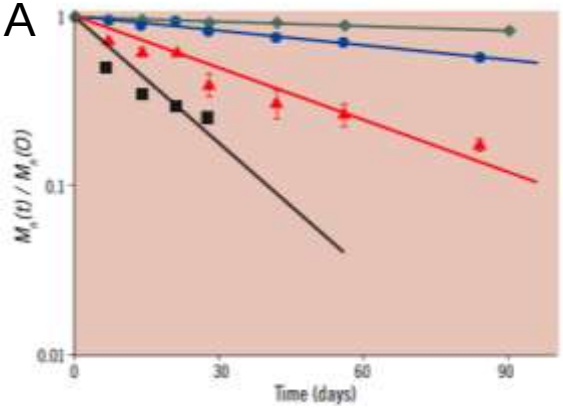
Everolimus-Eluting Bioresorbable Scaffolds versus Metallic Everolimus-Eluting Stents: Meta-Analysis of Randomized Controlled Trials.

Sorrentino S[1], Giustino G[2], Mehran R[2], Kini AS[2], Sharma SK[2], Faggioni M[3], Farhan S[2], Vogel B[2], Indolfi C[4], Dangas GD[5].



Molecular weight, Mechanical support and Mass loss

A



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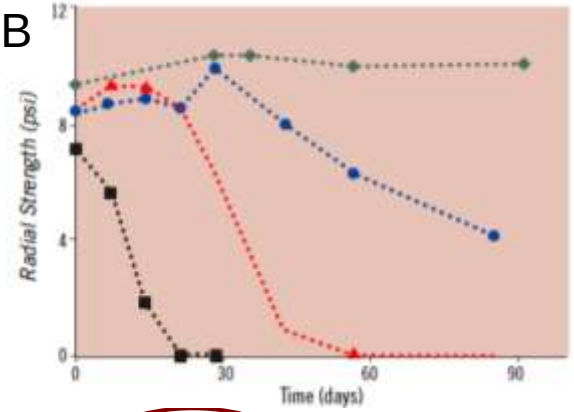

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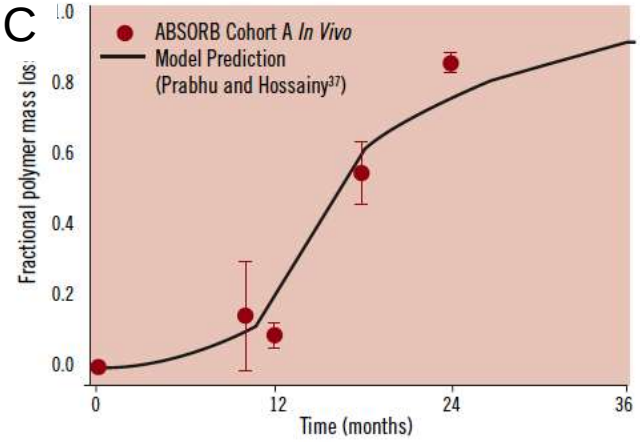
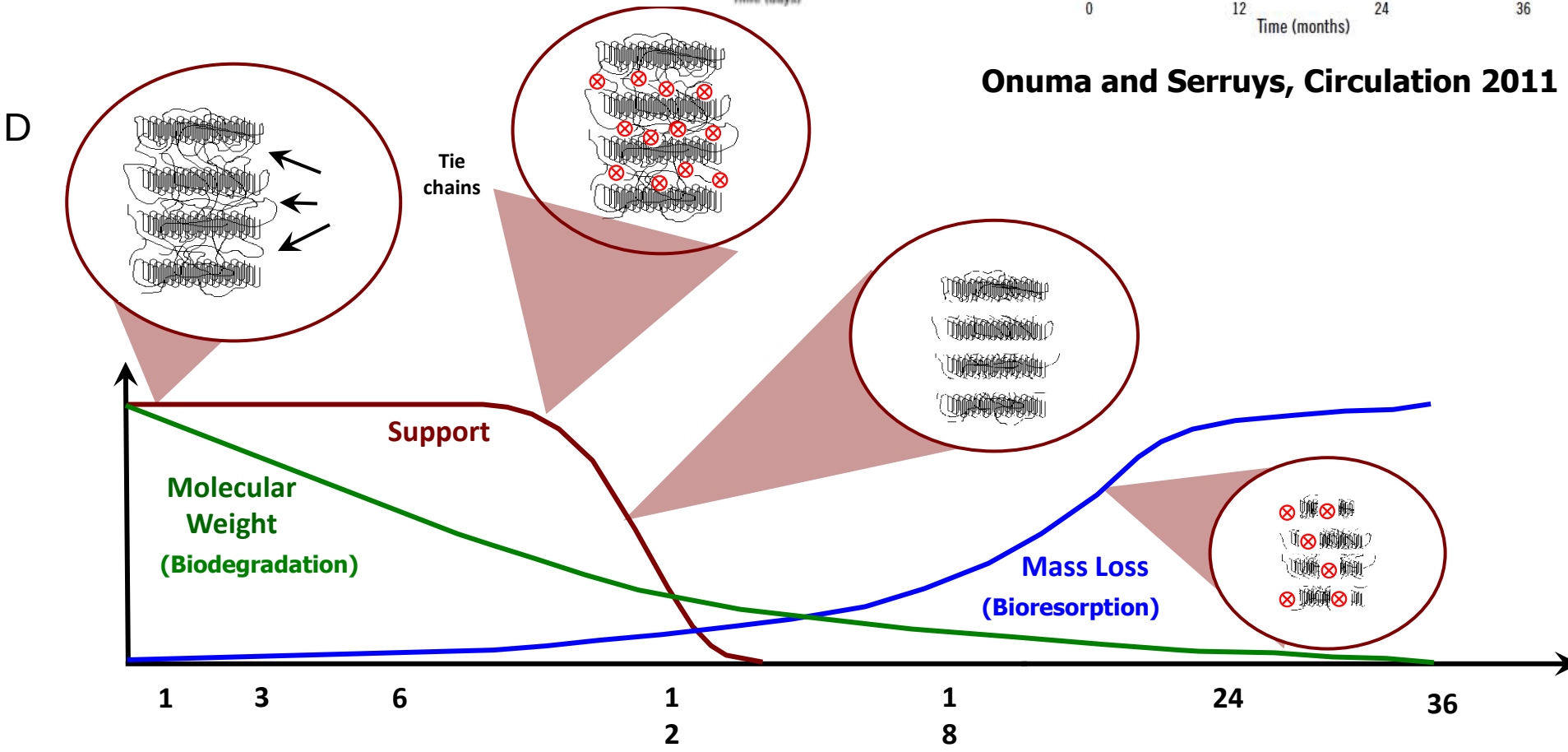


Onuma and Serruys, Circulation 2011

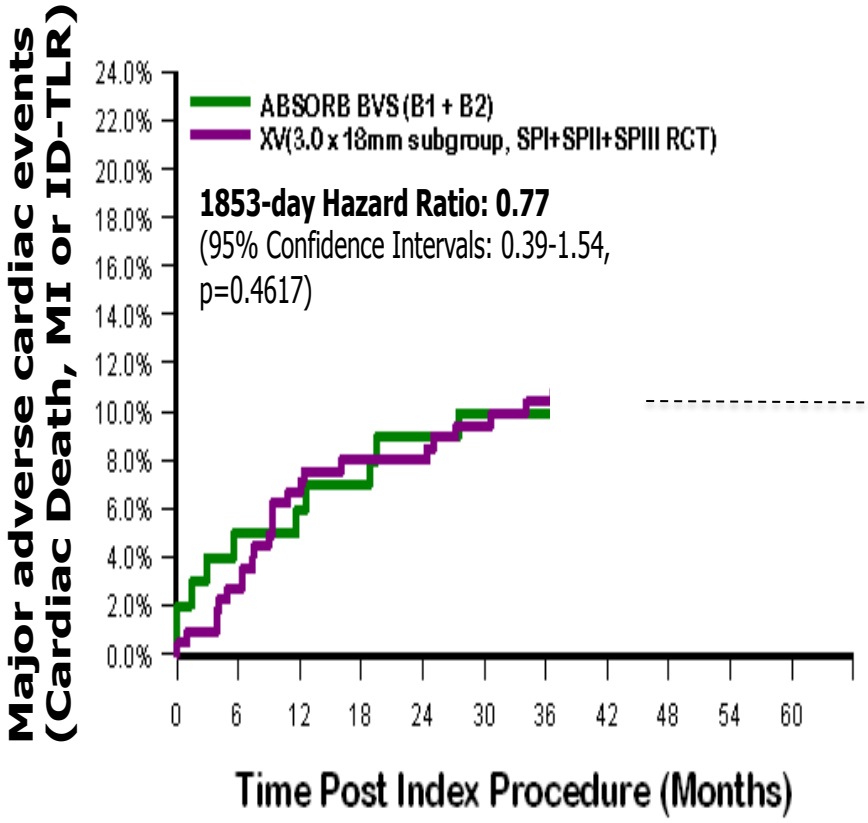
D



Kaplan-Meier estimates of cumulative major adverse cardiac events (Cardiac death, MI or ID-TLR) in ABSORB cohort B vs. ABSORB II trial at 3 years

ABSORB Cohort B

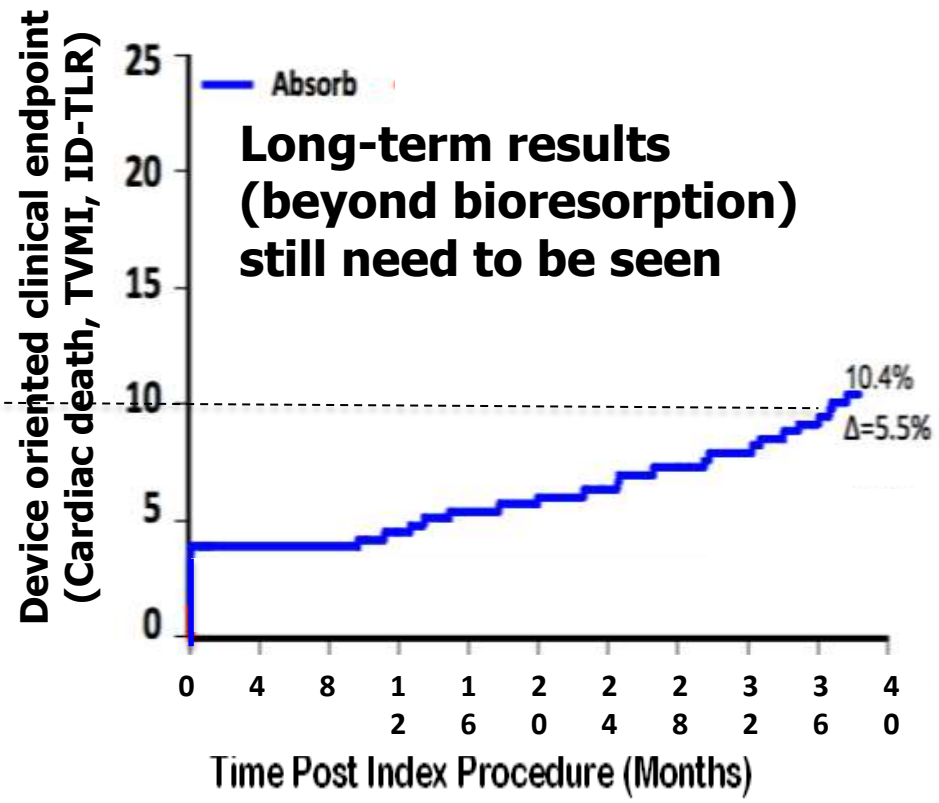
Serruys PW, Onuma Y, et al. EuroIntervention2014



Number of patients at Risk										
Time After Index Procedure (days)	0	37	194	284	393	573	758	1123	1488	1853
ABSORB	101	99	96	96	94	92	91	88	86	85
Xience V	227	224	219	211	204	202	191	182	174	169

ABSORB II

Serruys PW, Chevalier B et al. Lancet 2016



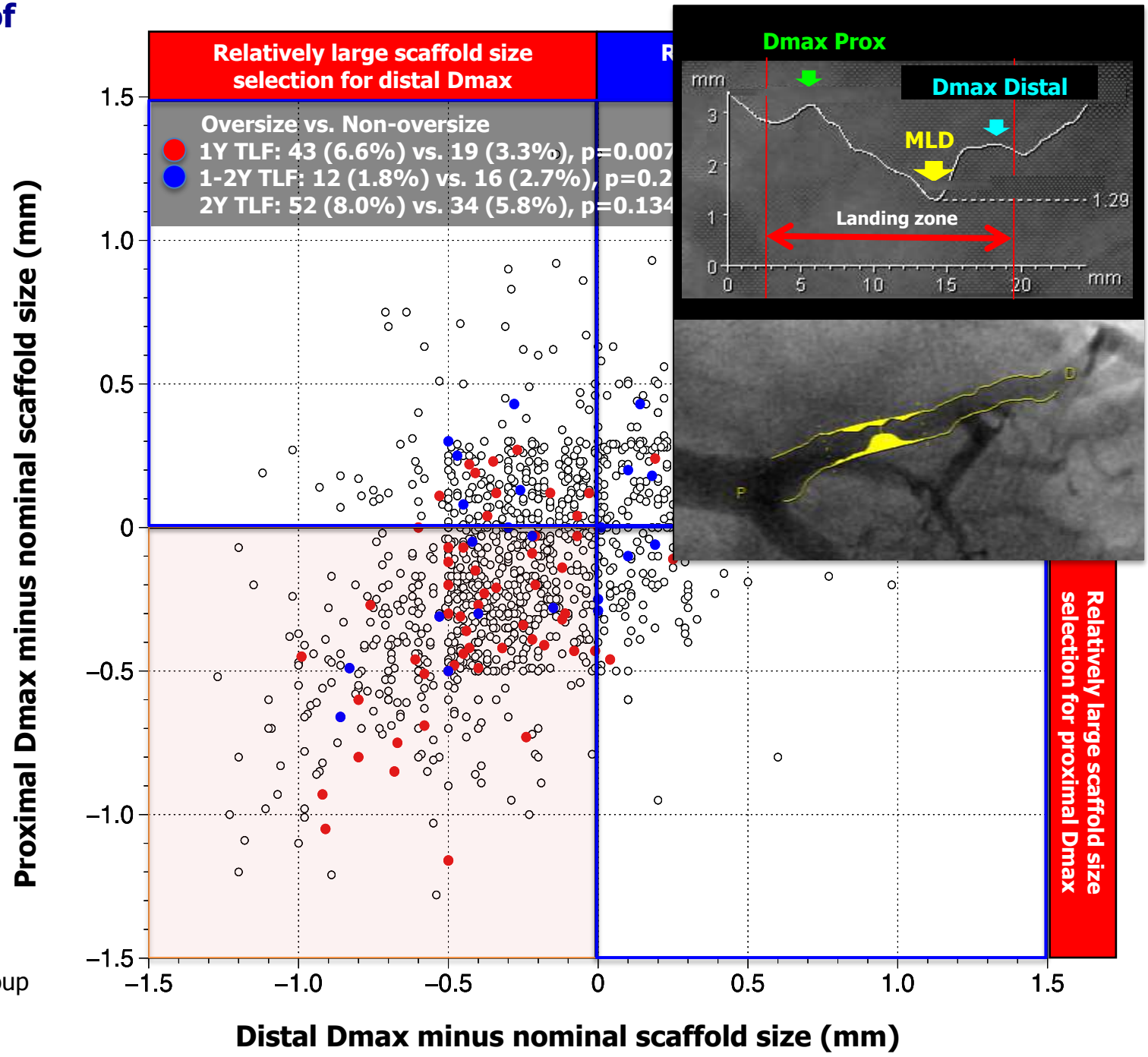
Time After Index Procedure (days)						
	0	37	194	393	758	1151
Absorb: # At Risk	335	318	318	312	300	282
% Event Rate	2.10%	3.90%	3.90%	4.80%	6.90%	10.40%
% SEM	0.80%	1.10%	1.10%	1.20%	1.40%	1.70%
XIENCE:# At Risk	166	164	161	158	156	149
% Event Rate	1.20%	1.20%	1.80%	3.00%	3.00%	4.30%
% SEM	0.80%	0.80%	1.00%	1.30%	1.30%	1.60%

- **Meta-analysis showed an increase of ScT (1-2Y) compared to Xience**

- **What is the underlying cause?**

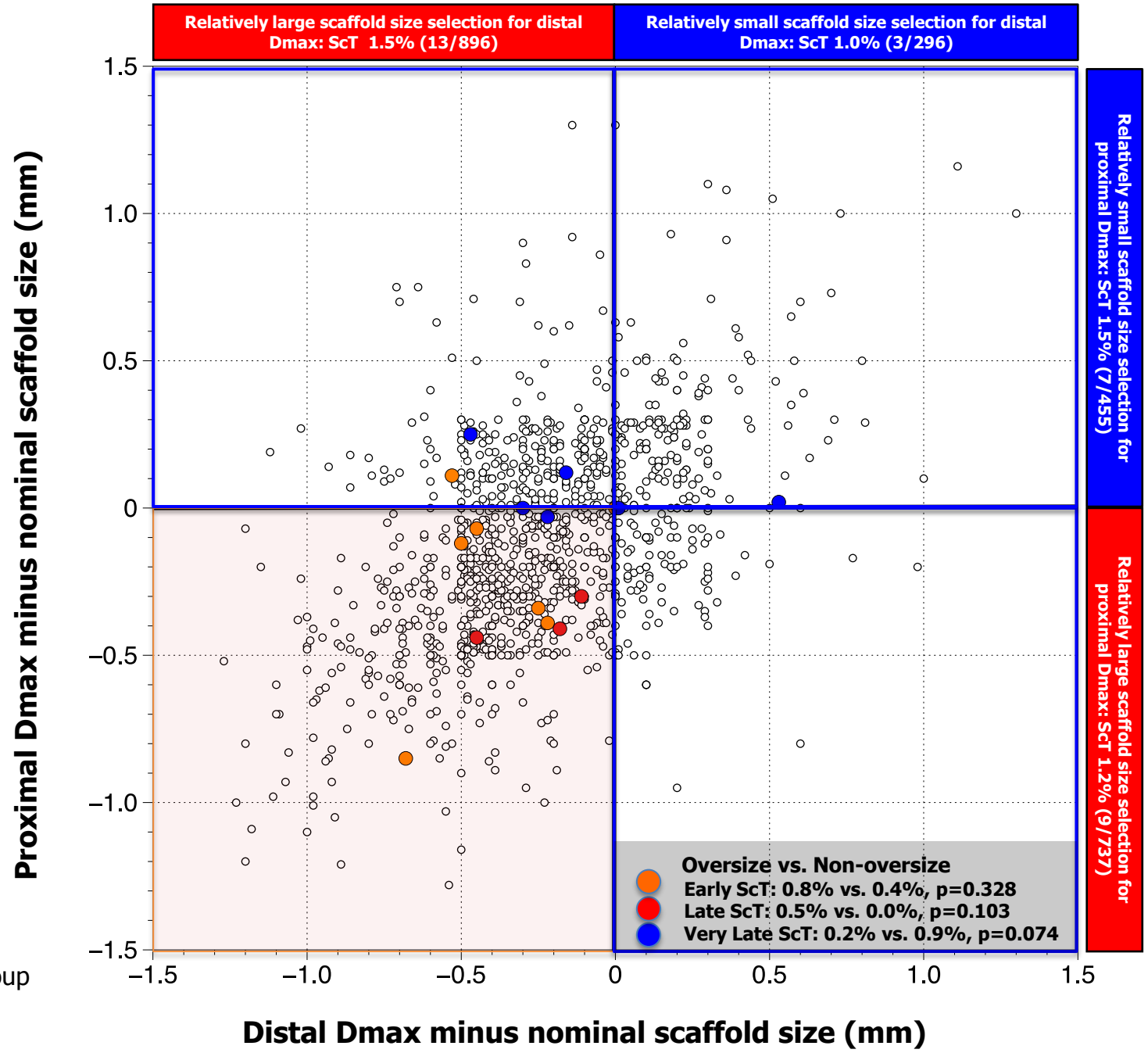
Pooled analysis of ABSORB B, Extend and Absorb II:

Device-vessel mismatch and TLF



Pooled analysis of ABSORB B, Extend and Absorb II:

Device-vessel mismatch and ScT



Possible mechanical causes of scaffold thrombosis: insights from case reports with intracoronary imaging

Yohei Sotomi[1], MD; Pannipa Suwannasom[1,2,3], MD; Patrick W. Serruys[4]*, MD, PhD; Yoshinobu Onuma[1], MD, PhD

Systematic review

Imaging findings in ScT cases

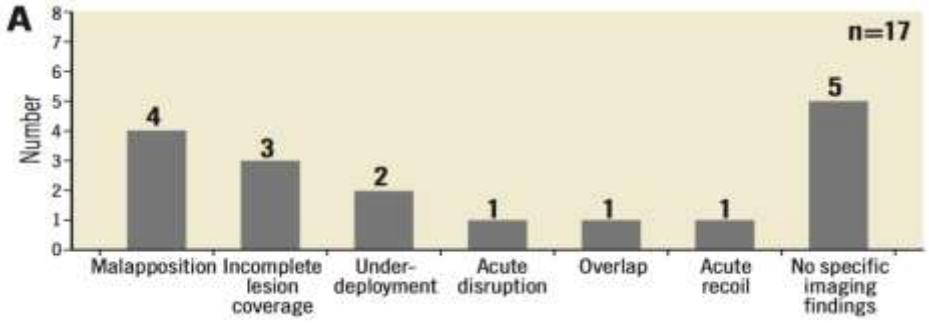
- **Early ScT (N=17)**

malapposition (24%), incomplete lesion coverage (18%), and underdeployment (12%)

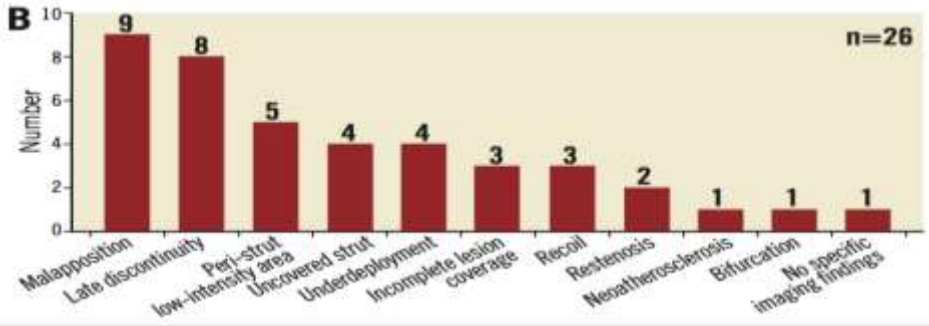
- **Late/very late ScT (N=26)**

malapposition (35%), late discontinuity (31%) and peri-strut low-intensity area (19%)

Early scaffold thrombosis



Late/very late scaffold thrombosis

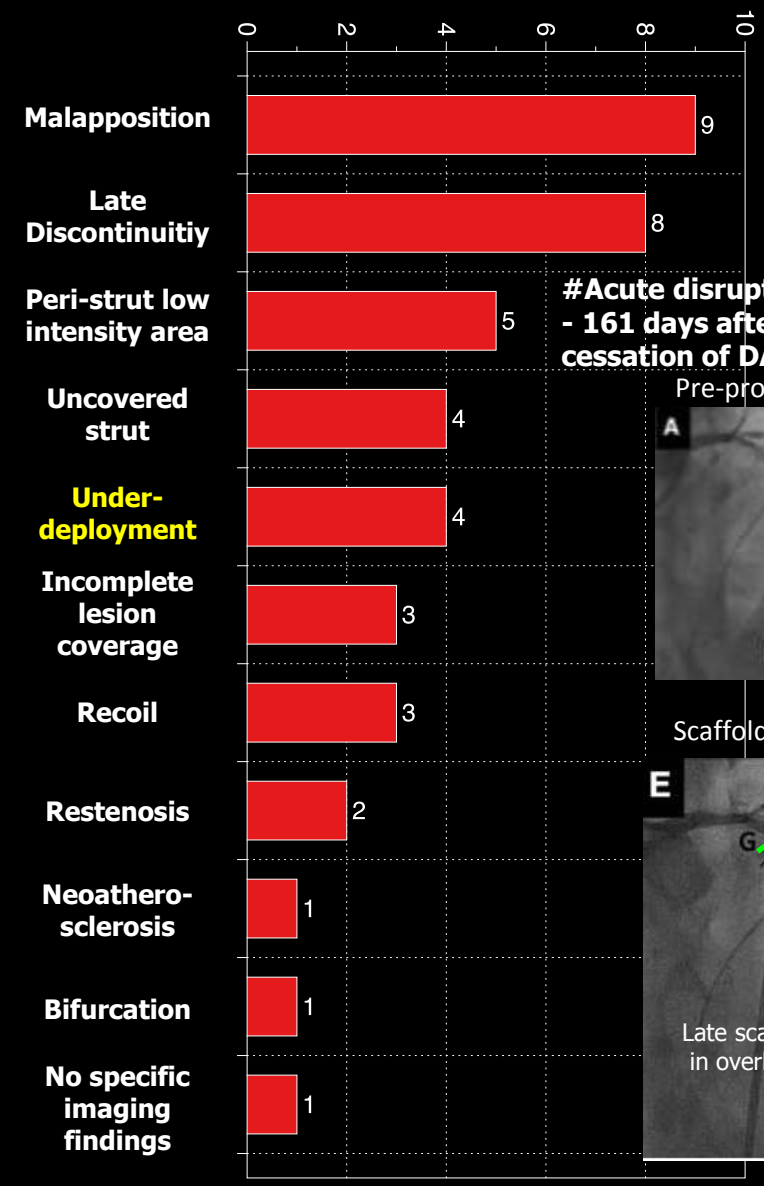


jaa Just accepted article

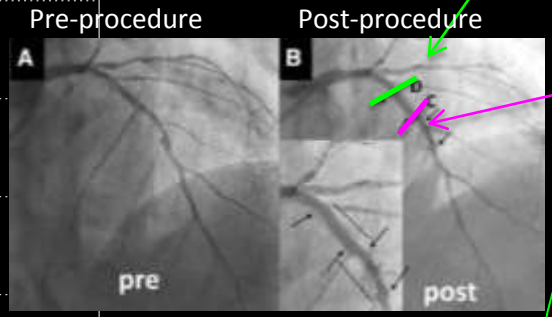
Sotomi et al. Eurointervention 2016

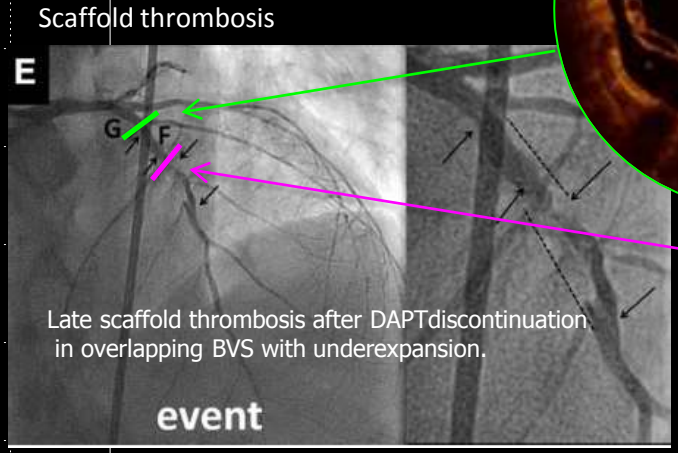
Imaging findings associated with Late/very late scaffold thrombosis

Karanasos A et al. Circ Cardiovasc Interv 2015;8.

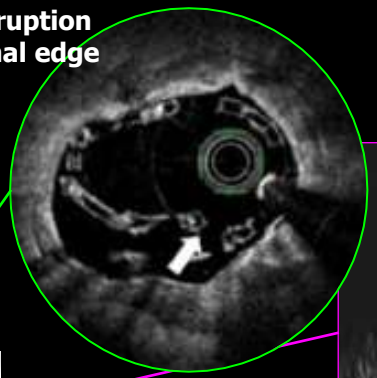


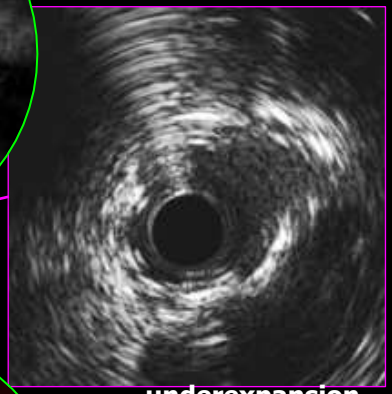
#Acute disruption and Late Thrombosis - 161 days after implantation, 2 days after cessation of DAPT



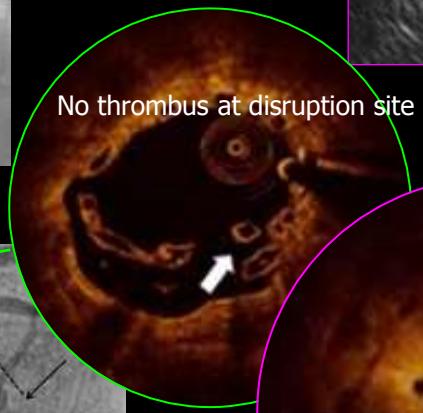


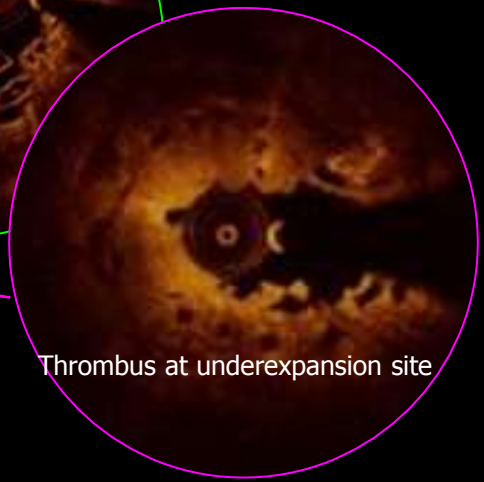
acute disruption at proximal edge





underexpansion at mid scaffolded part (overlap)

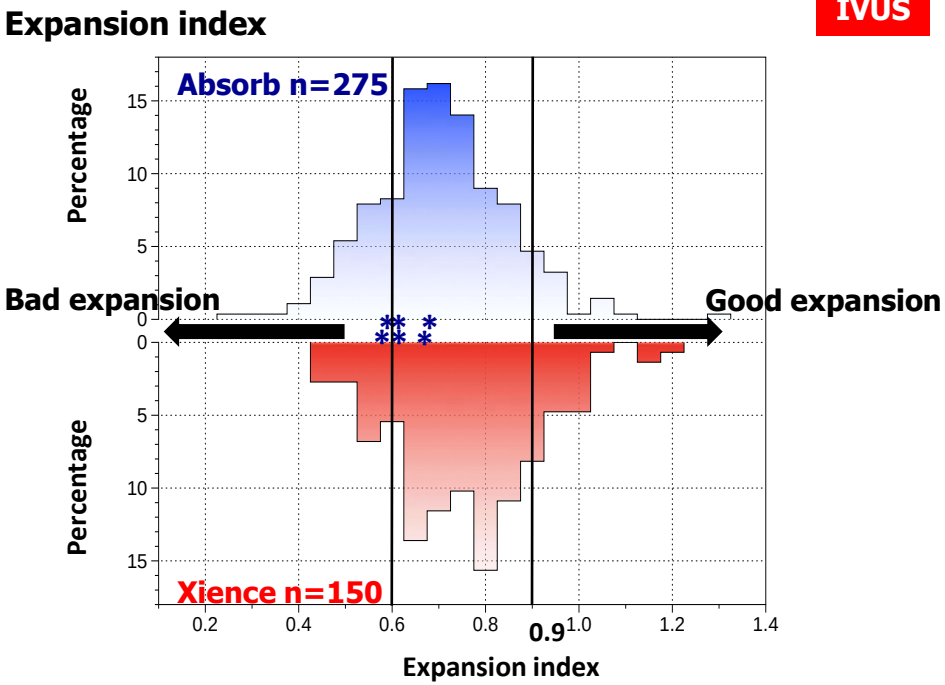




IVUS

In-depth insights into VLScT cases in ABSORB II trial

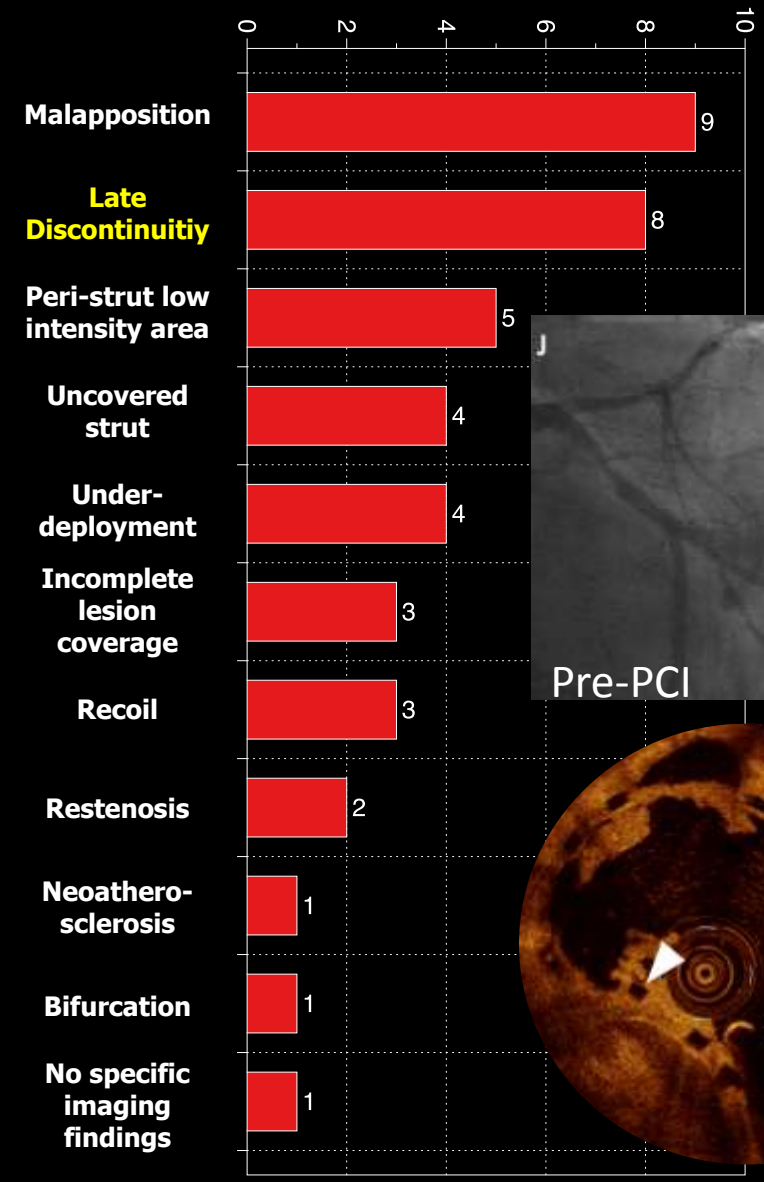
Expansion index < 0.6 and **lesion coverage ratio** were significantly associated with VLScT.



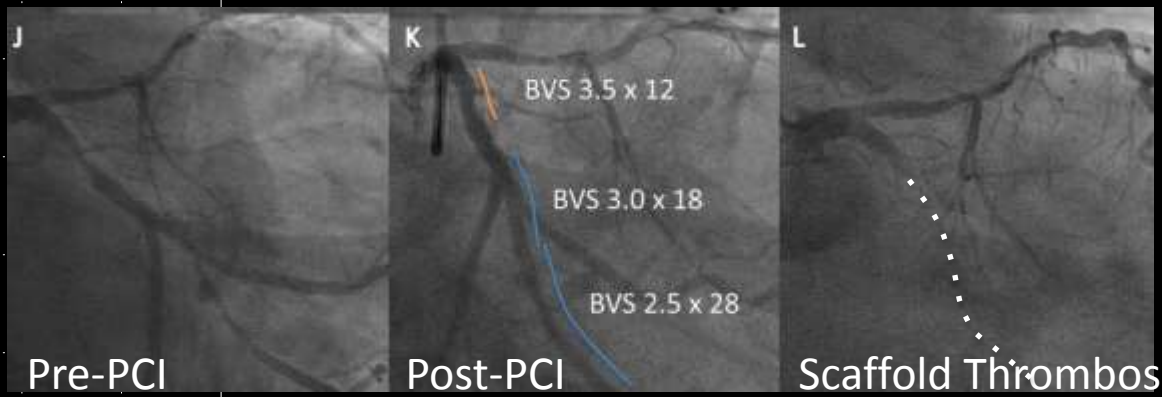
Predictors for VLScT:
Univariate Cox regression analysis

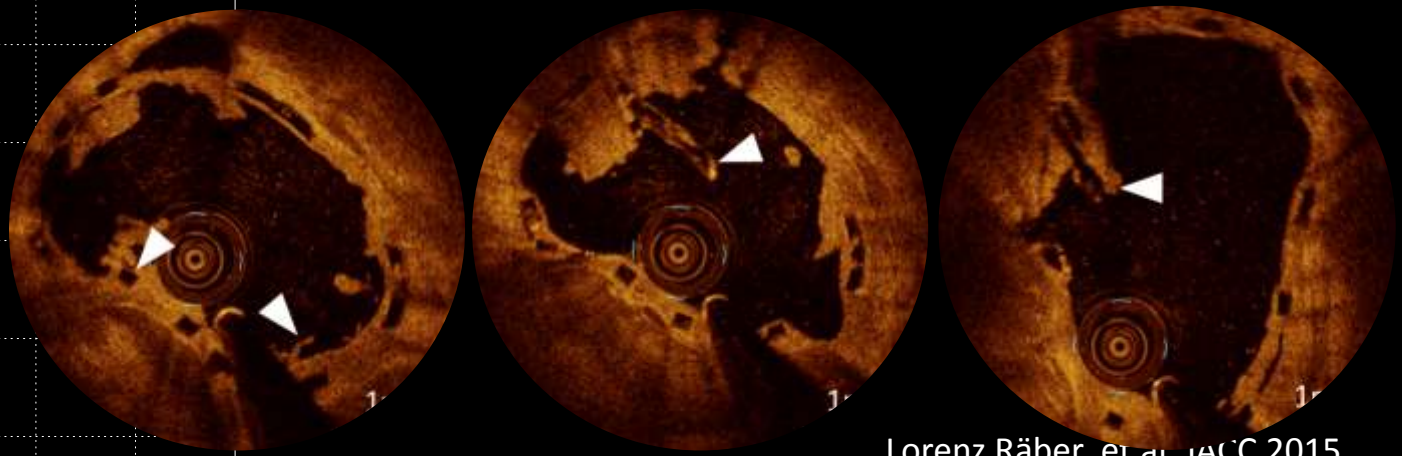
Variable	Odds ratio [95% confidence interval]	p value
QCA		
In-device % diameter stenosis (%)	1.07 [0.96-1.19]	0.218
In-device minimum lumen diameter (mm)	2.58 [0.25-26.08]	0.422
Lesion coverage ratio per 0.1 increase	**0.74 [0.56-0.98]**	**0.032**
IVUS		
Minimum lumen diameter (mm)	1.80 [0.18-17.74]	0.613
Asymmetry index per 0.1 increase	0.34 [0.10-1.18]	0.088
Expansion index per 0.1 increase	0.58 [0.32-1.04]	0.066
Minimum eccentricity index per 0.1 increase	2.29 [0.63-8.35]	0.208
Deployment index per 0.1 increase	1.78 [0.75-4.22]	0.188
Expansion index <0.6	**6.93 [1.24-38.82]**	**0.028**

Imaging findings associated with Late/very late scaffold thrombosis



VLST at 19 months



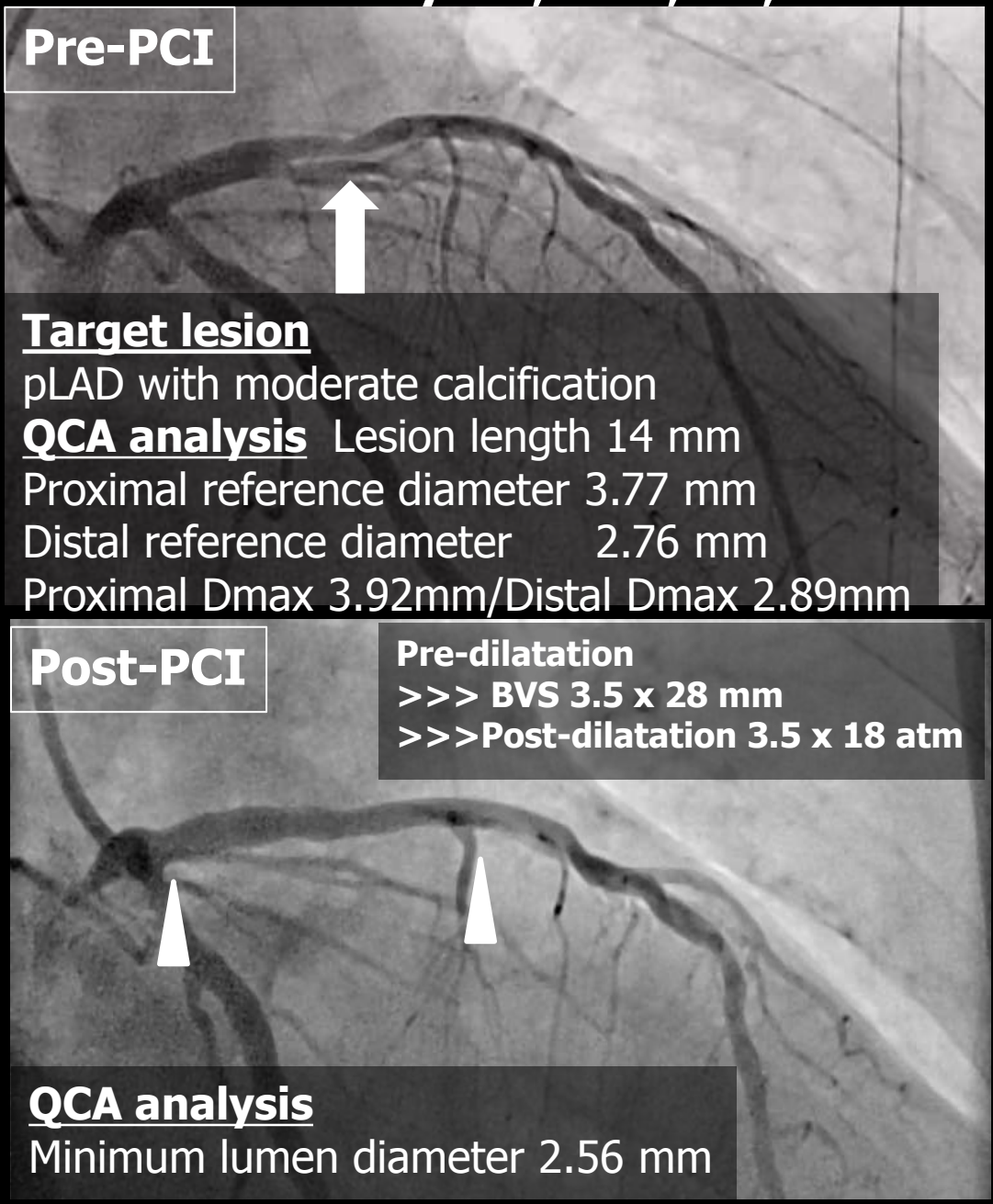


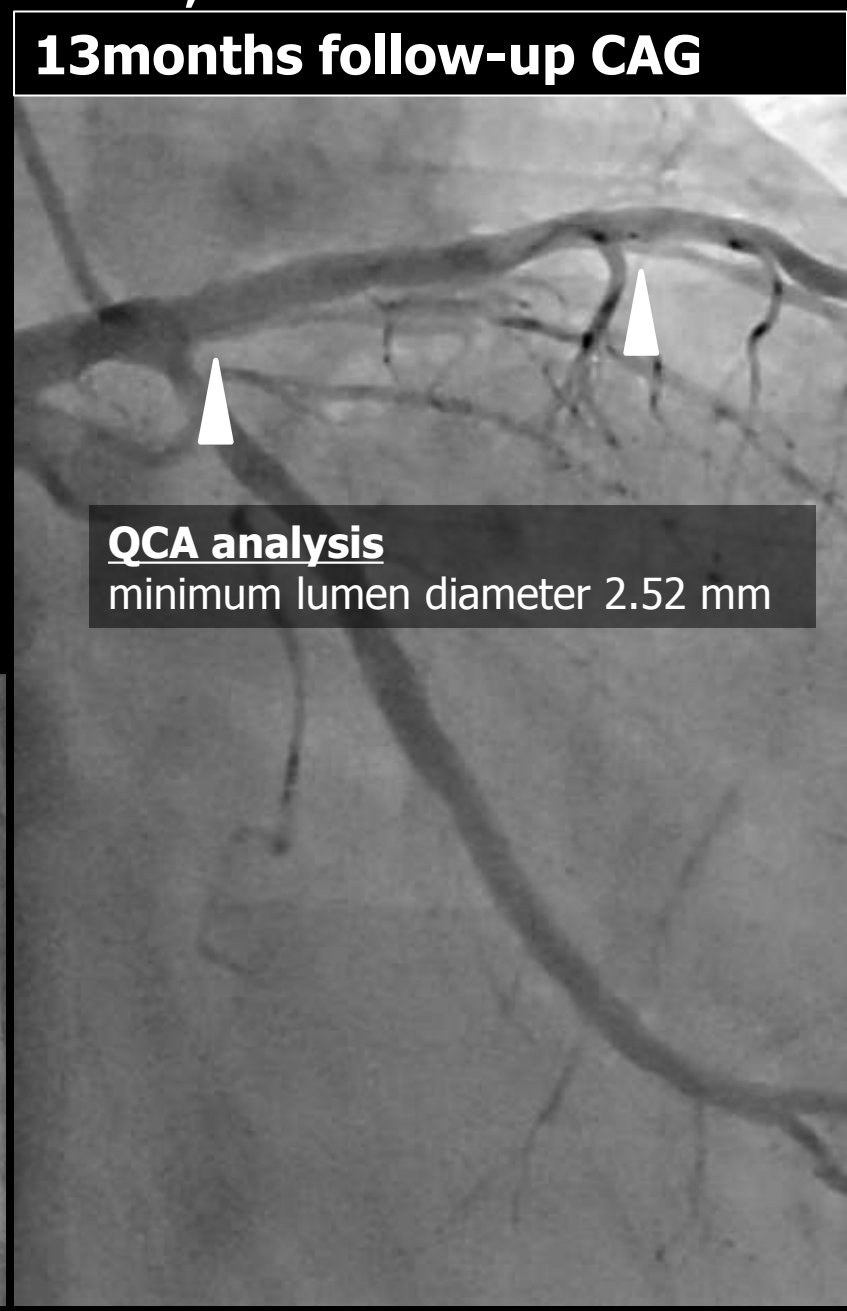
Lorenz Räber et al. JACC 2015

VLST case 1 (Day 494)

Onuma et al. Eurointervention 2016

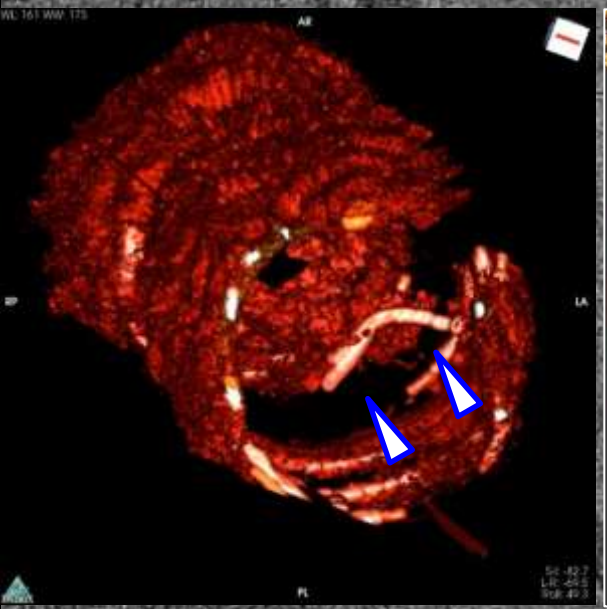
Risk factors: 79 yo M, HTN, HL, former smoker, DM II

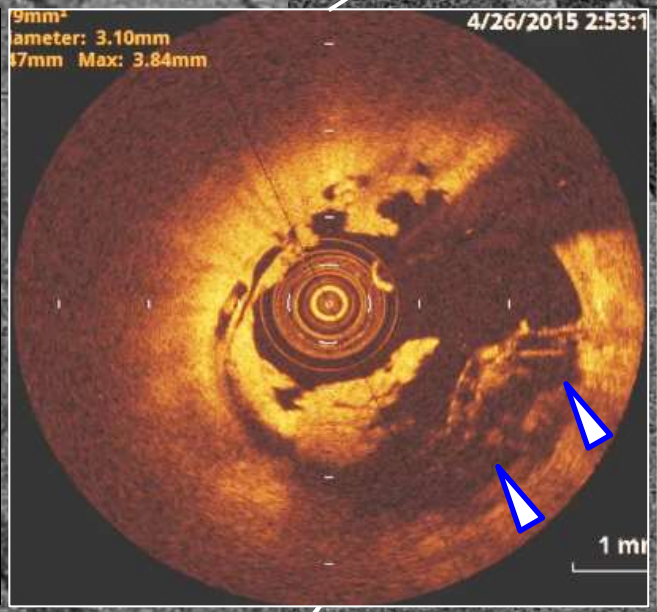




VLST (day 494) (TVQMI)

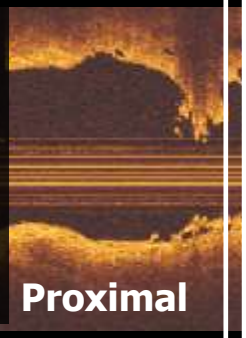
Post thrombectomy

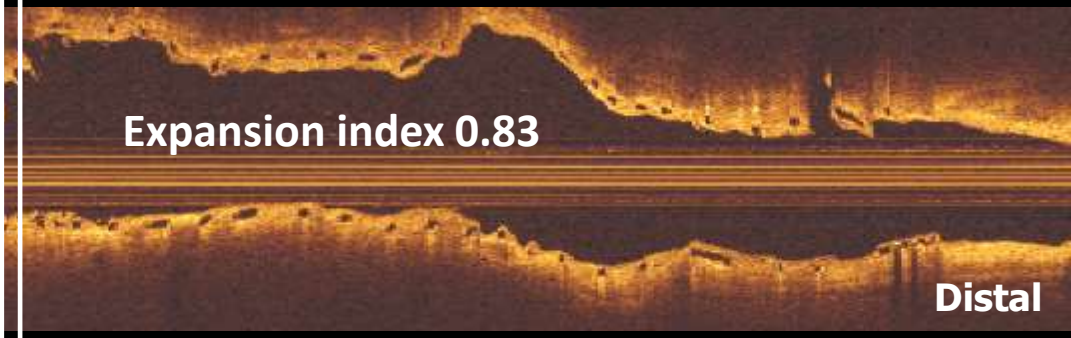




Status of antiplatelet therapy

ASA: quit at 487 days
(1 week before event)
Clopidogrel: quit at 1 year
Ciostazol: quit at 3 weeks





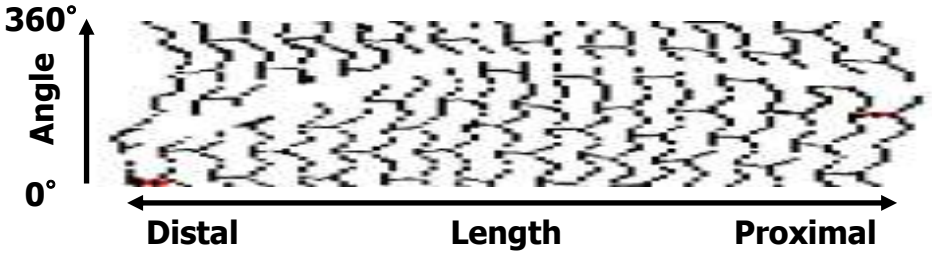
125 135 145 155 165

118 128 138 148 158 168 178 188 198 208

Late discontinuity is expected phenomenon related to bioresorption.

Serial changes of strut distribution

BRS textbook



Absorb Strut
Metallic marker

ABSORB Cohort B1

Baseline	6 months	24 months

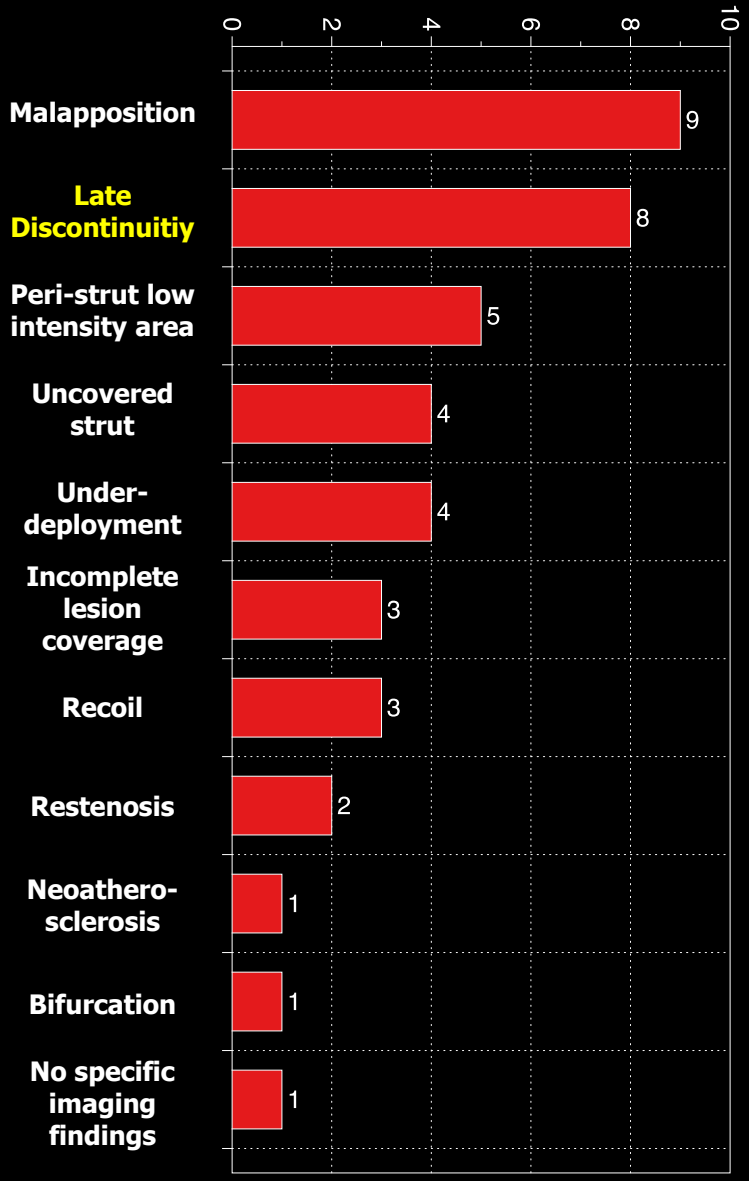
ABSORB Cohort B2

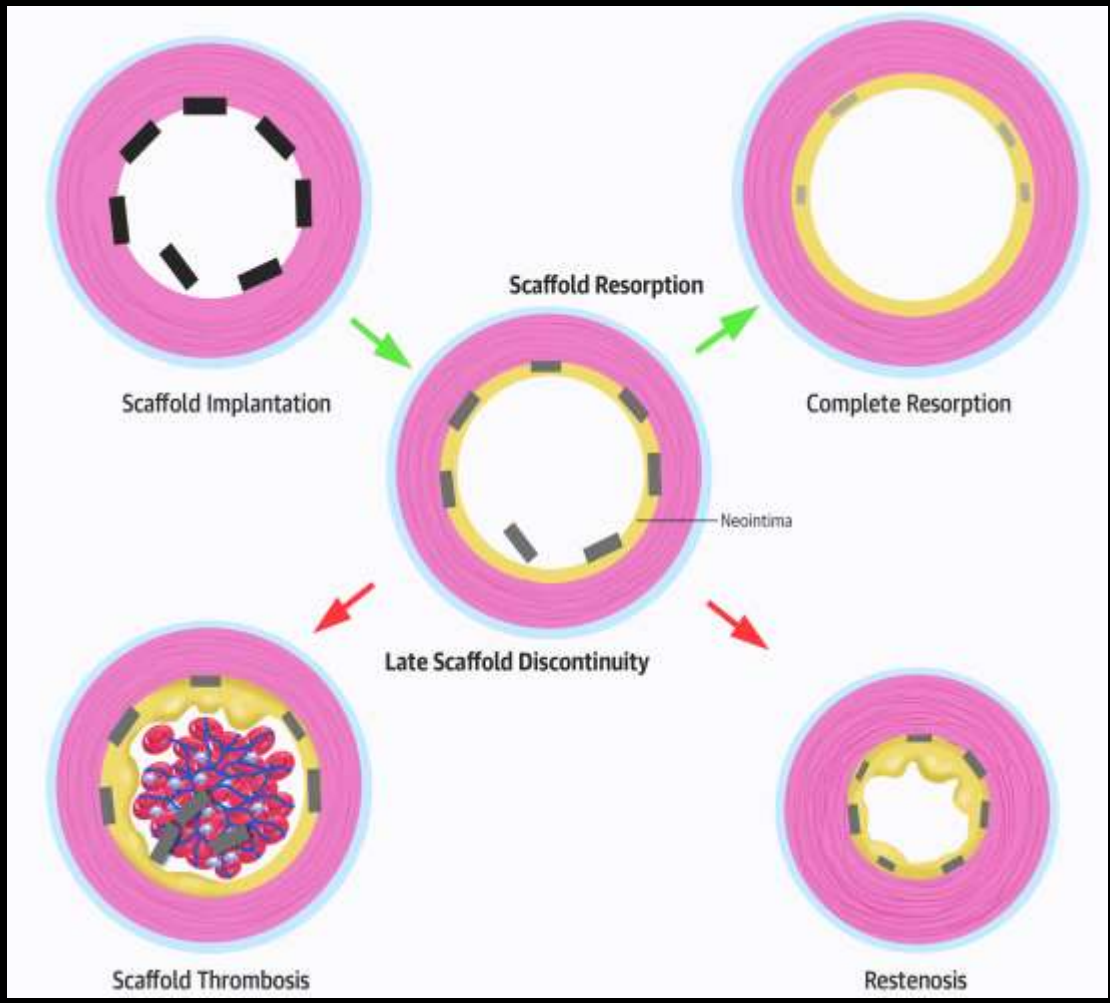
Baseline	12 months	36 months
	Not available	

In serial OCT observation up to 36 months, late discontinuities were observed in 43%, without clinical events

Onuma et al. JACC int 2014,

Imaging findings associated with Late/very late scaffold thrombosis



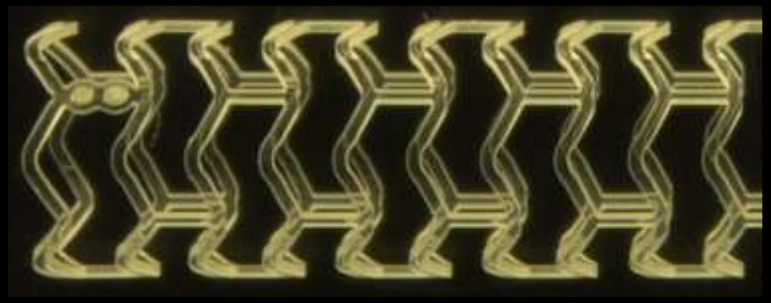
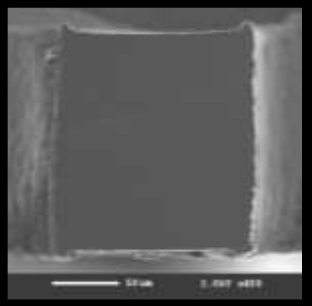
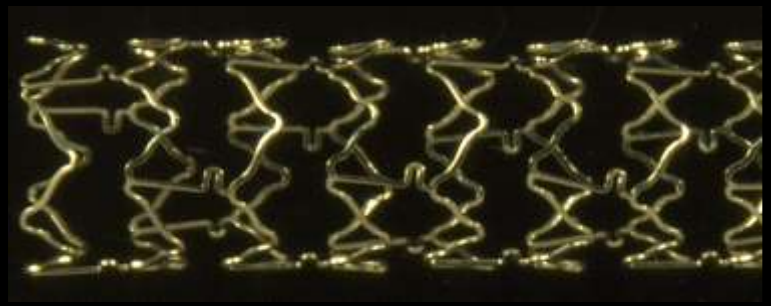


Lorenz Räber et al. JACC 2015, Onuma et al. JACC interv 2014, Sotomi et al. Submitted

How to avoid these and enhance coverage?

Sotomi et al. EI 2016

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)

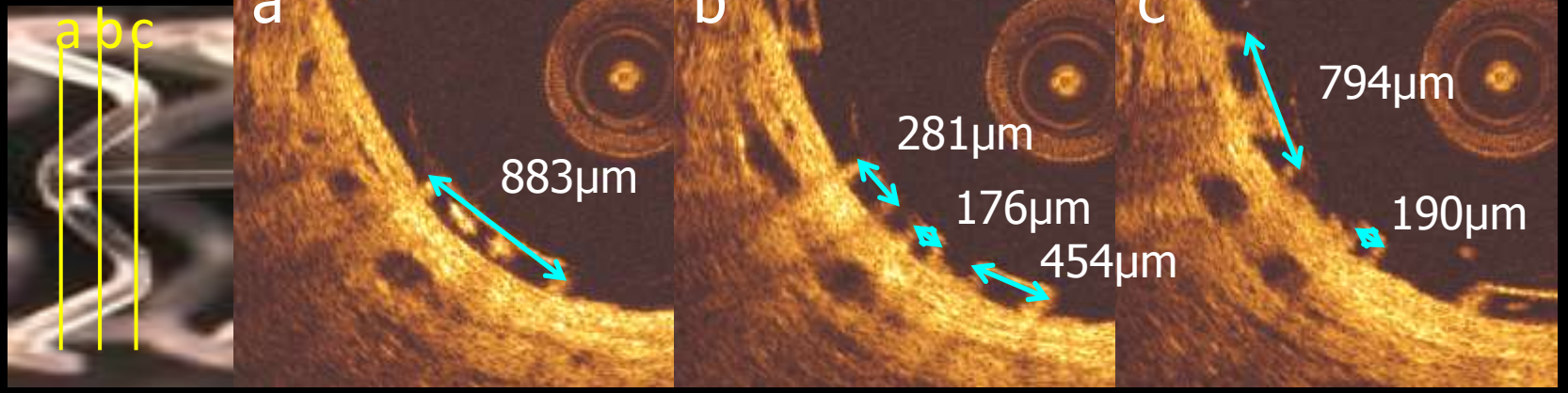
Muramatsu et al. JACC interv 2013

Snowshoe Versus Ice Skate for Scaffolding of Disrupted Vessel Wall*

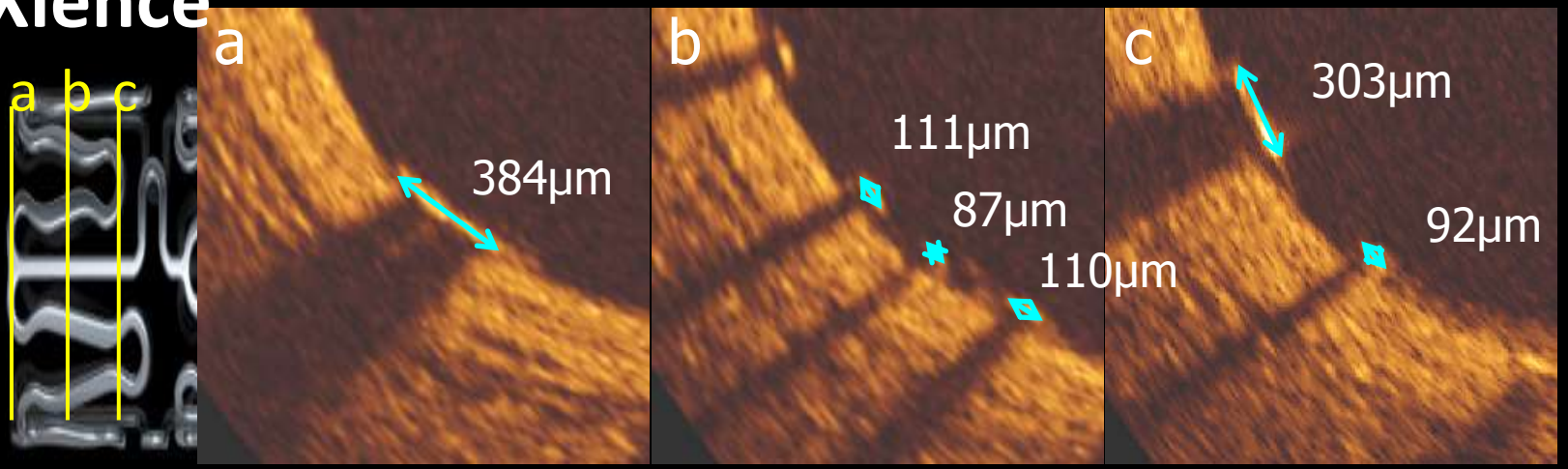
Patrick W. Serruys, MD, PhD,† Pannipa Suwannasom, MD,‡ Shimpei Nakatani, MD,‡ Yoshinobu Onuma, MD, PhD‡

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

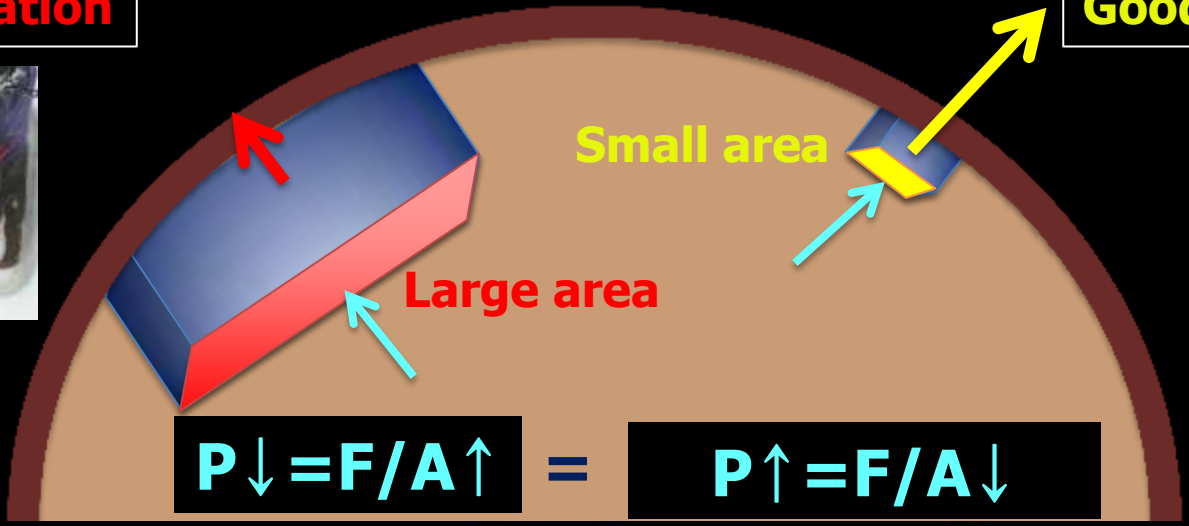
Absorb



Xience

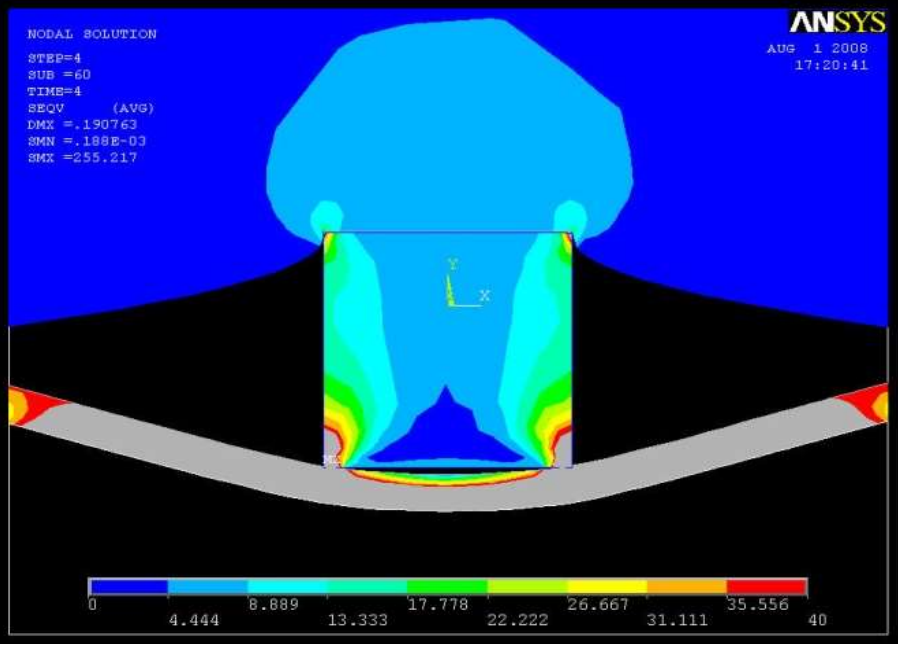


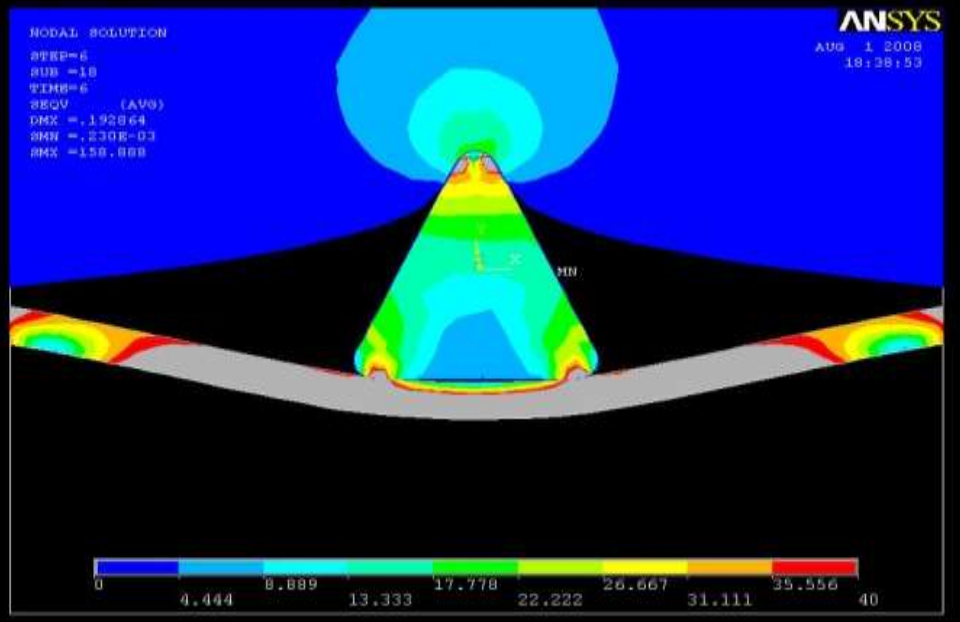
Poor penetration



Good penetration

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



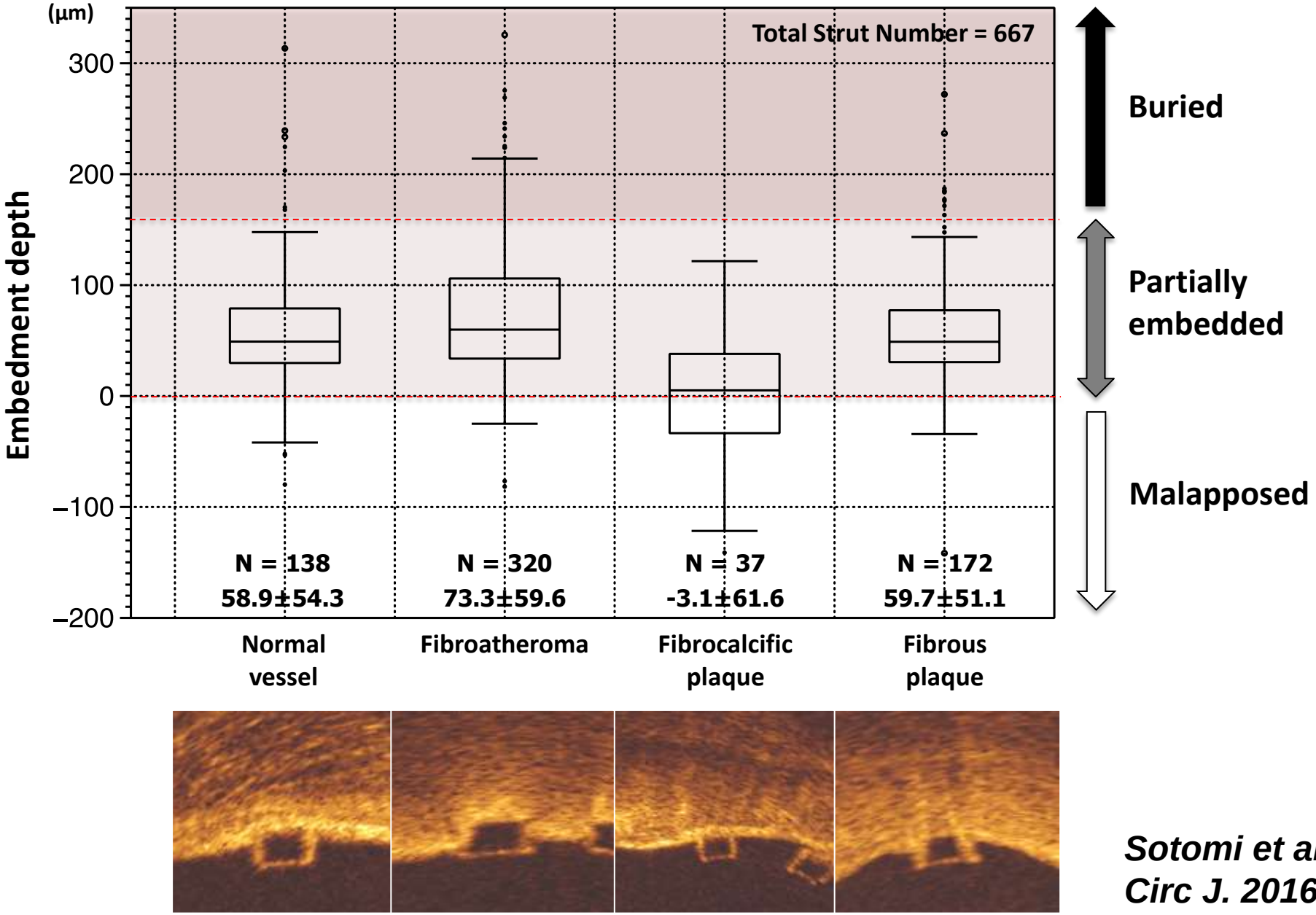


Large strut area →Poor penetration → Small expansion

Small strut area →Good penetration → Large expansion

Serruys, Suwannason et al. JACC CI

Influence of underlying plaque morphology

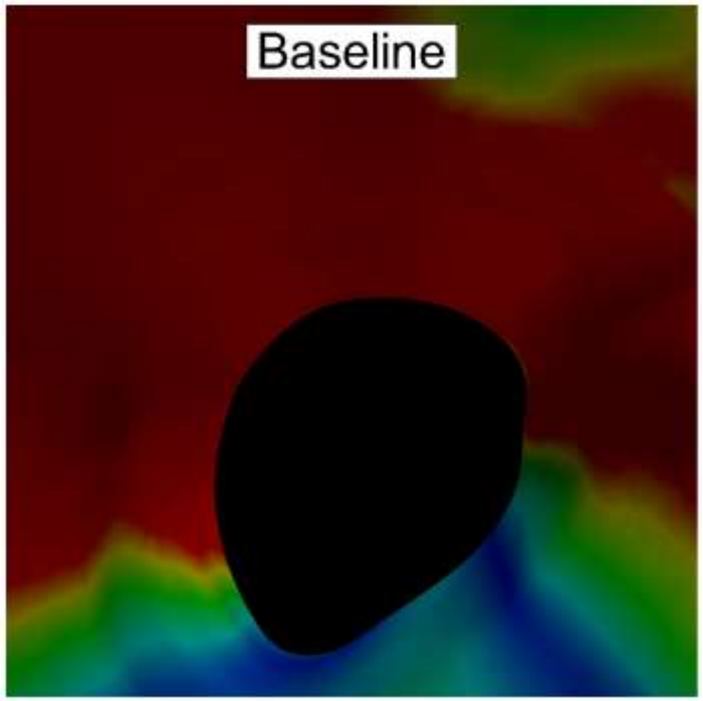


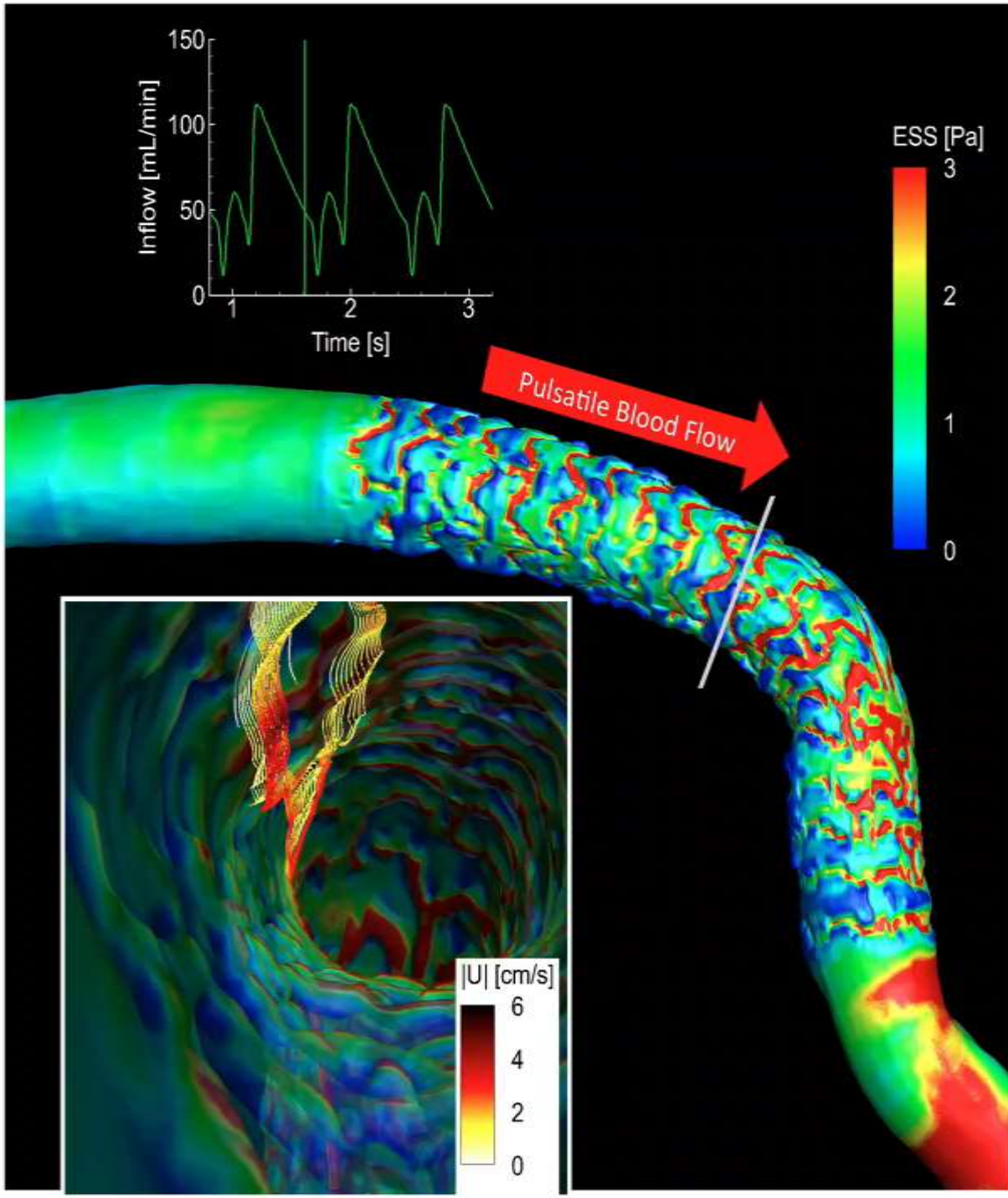
Sotomi et al. Circ J. 2016

The Nidus for Possible Thrombus Formation

Insight From the Microenvironment of Bioresorbable Vascular Scaffold

JACC interv 2016:2167-8
Tenekecioglu et al.





What determines long-term outcomes using fully bioresorbable scaffolds - the device, the operator or the lesion?

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Department of Cardiology, Bern University Hospital, Bern, Switzerland

Yamaji, Widencker et al. EuroIntervention 2017
Wykrzykowska et al. NEJM 2017

RCT	pre- / post-dilatation	ACS	B2/C	Calc.	Bif.	TLR	ScT
EVERBIO II (N=78)		37	30			8 (10)***	0 (0.0)
ABSORB TROFI II (N=95)		100		§		1 (1.1)	1 (1.1)
ABSORB II (N=335)		20	46	13§	#	4 (1.0)	3 (0.9)
ABSORB China (N=238)		65	75	18§	50#	7 (2.9)	1 (0.4)
ABSORB III (N=1,322)		27	69	§	#	42 (3.2)	20 (1.5)
ABSORB Japan (N=266)		10	76	35§	#	7 (2.6)	4 (1.5)

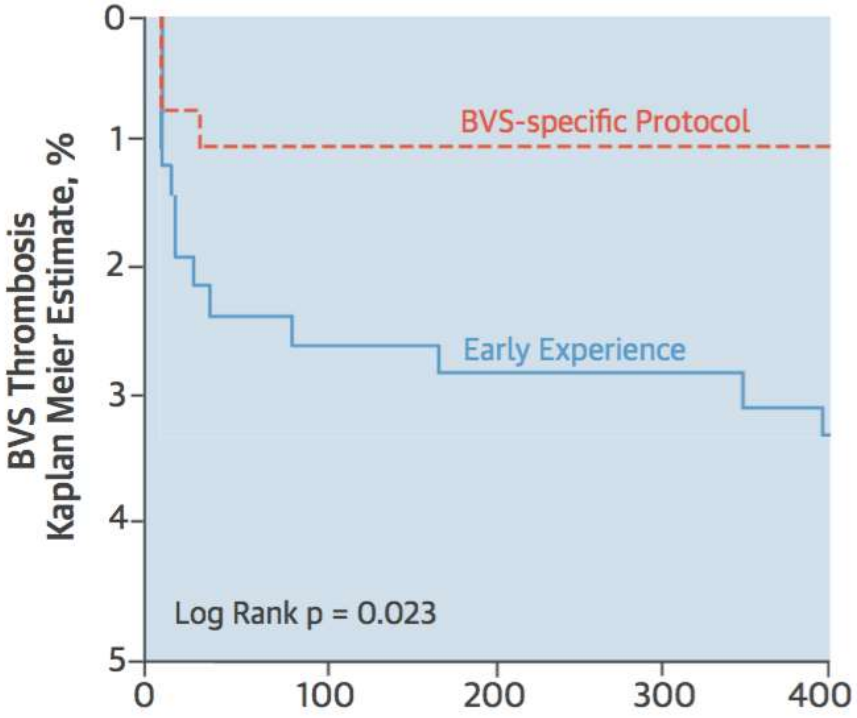
AIDA: Pre dil 97%, Post dil 74%

BVS-specific implantation strategy significantly reduced the rate of ScT

When a BVS-specific implantation strategy was implemented, 12-month ScT rates fell from 3.3% to 1.0%, an effect that remained significant when adjusted for multivariable propensity score (p = 0.012; **hazard ratio: 0.19**; 95% confidence interval: 0.05 to 0.70).

The BVS-specific implantation strategy

1. **Pre-dilatation with noncompliant balloon** up to the same size as the reference vessel diameter.
2. BVS implantation only in case of full expansion of the noncompliant percutaneous transcatheter coronary angioplasty balloon as demonstrated by angiography in 2 orthogonal planes.
3. Implantation of a BVS of the same size as the reference vessel diameter at 10 to 12 atm.
4. **Post-dilatation with noncompliant balloons** up to a maximum of 0.5 mm larger **at 14 to 16 atm.**

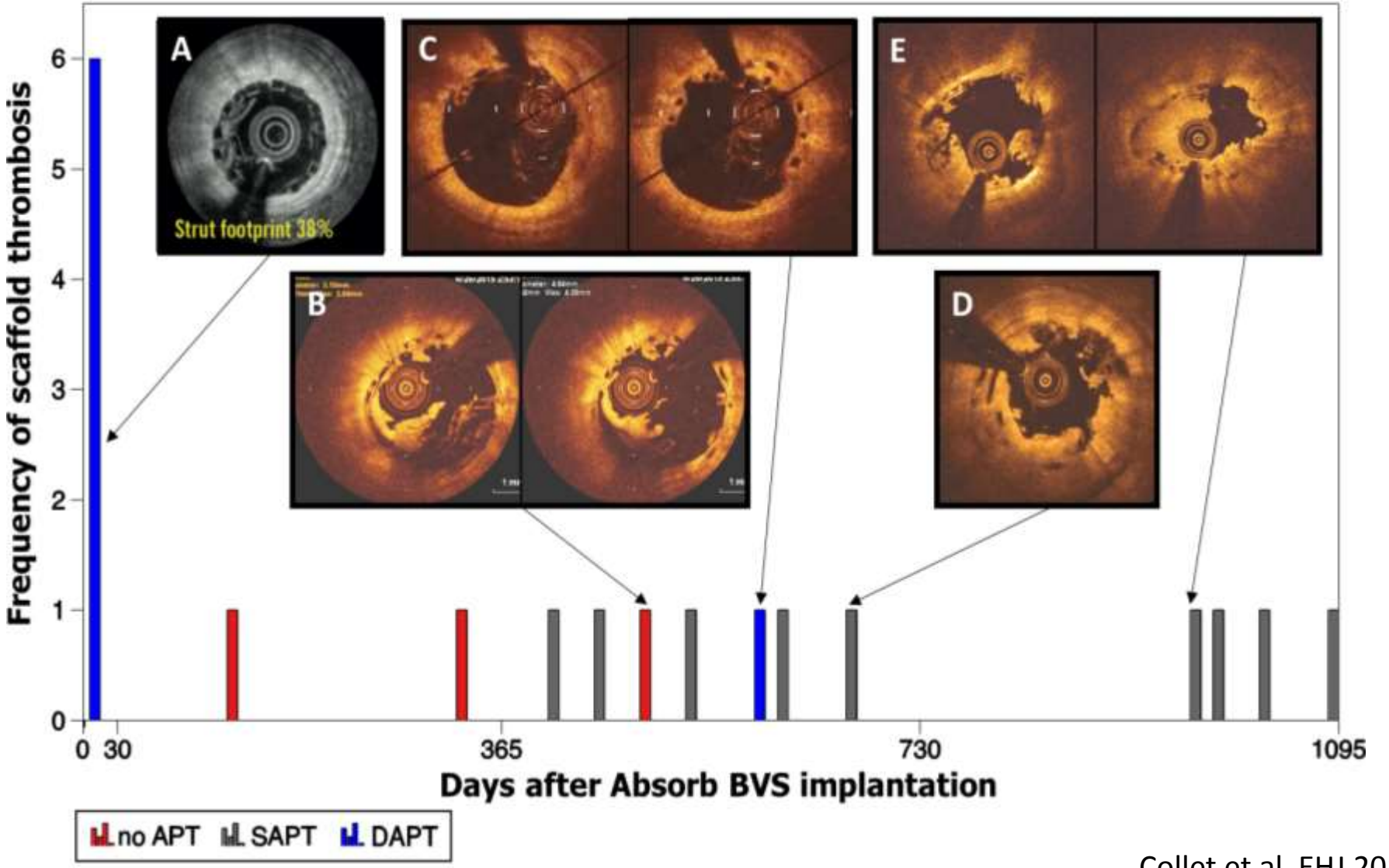


Patients					
Early Experience	369	369	369	369	369
BVS-specific	292	292	281	217	155

Puricel, S. et al. J Am Coll Cardiol. 2016; 67(8):921-31.

Puricel, et al. J Am Coll Cardiol. 2016

Review of literature with late (≥2y) outcomes: Timing of scaffold thrombosis and DAPT status

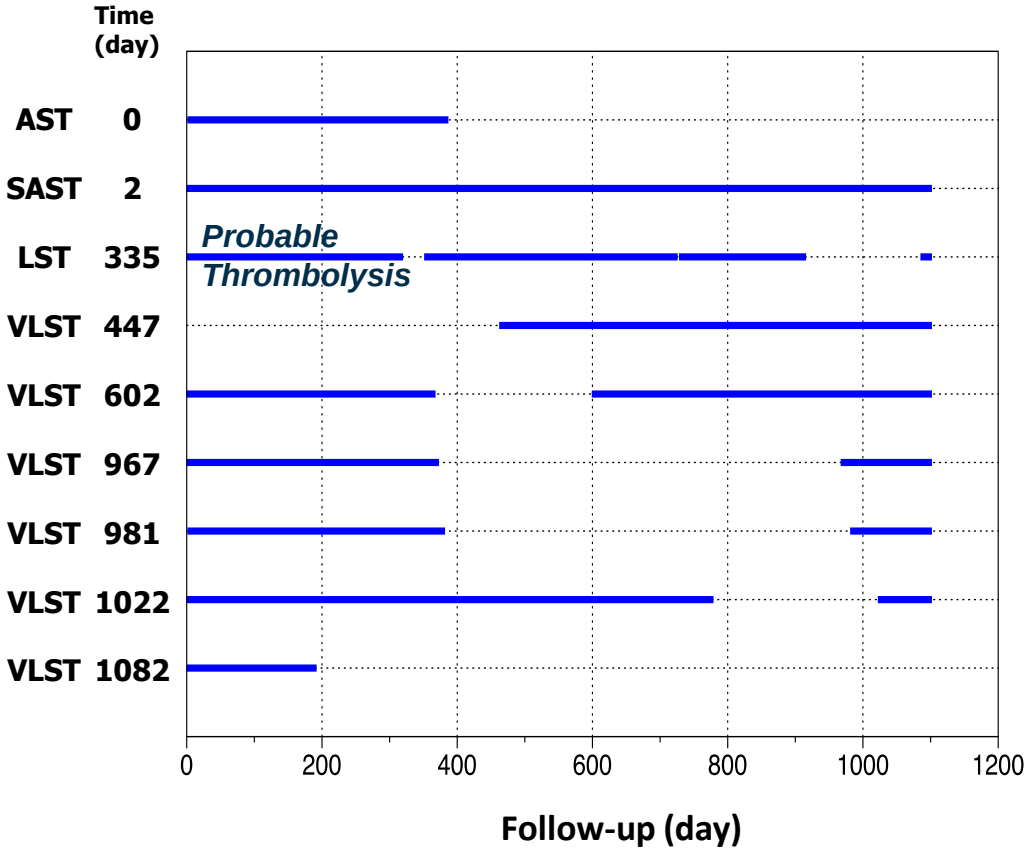


Collet et al. EHJ 2017

ABSORB II: Dual antiplatelet therapy in Absorb group (N=335)

VLST occurred in patients with DAPT discontinuation, while no VLST was observed in patients without DAPT discontinuation during 3 years.

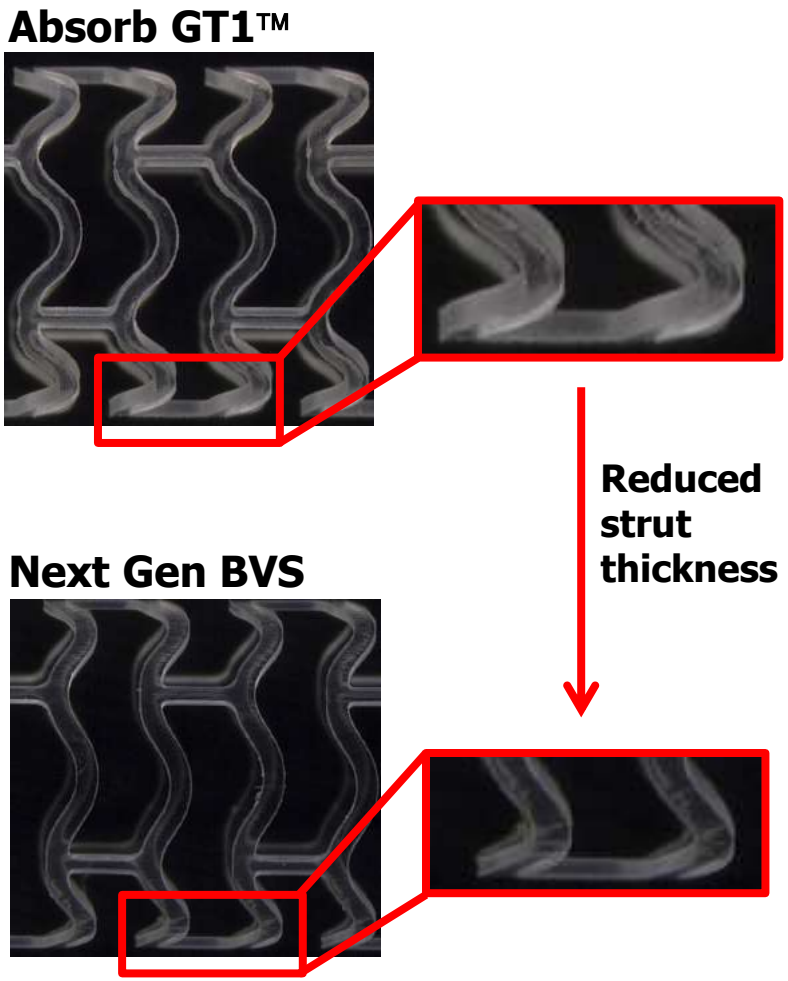
	VLScT	No VLScT	Total
DAPT discontinuation	6 (100)	257 (78.1)	263 (78.5)
DAPT 3 years without discontinuation >1week*	0 (0)	72 (21.9)	72 (21.5)
Total	6 (100)	329 (100)	335 (100)



Fisher's exact test: p=0.347

Next Generation BVS:

designed to expand the size matrix and Reduce strut thickness



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

Long-Term Safety Issue of BRS; Chance or True?

- Recent meta-analyses of mid-term outcomes (2-3 years) demonstrated increased rates of TV-MI, scaffold thrombosis and very late scaffold thrombosis of Absorb scaffold in comparison with Xience stent. **Long-term outcomes (beyond 3 years: bioresorption time)** still need to be seen in randomized trial.

- Theoretically, enhancement of neointimal coverage would be a key to prevent ScT associated with late discontinuity, which could be achieved by better expansion and better strut embedment.

- It remains to be proven that the **dedicated implantation technique** and potentially long DAPT could decrease the VLScT (e.g. Absorb IV). Eventually **the further iteration** of device with thinner struts will be available to mitigate early and long-term risk.