Updated Evidence of BRS

Gachon University

Gil Hospital

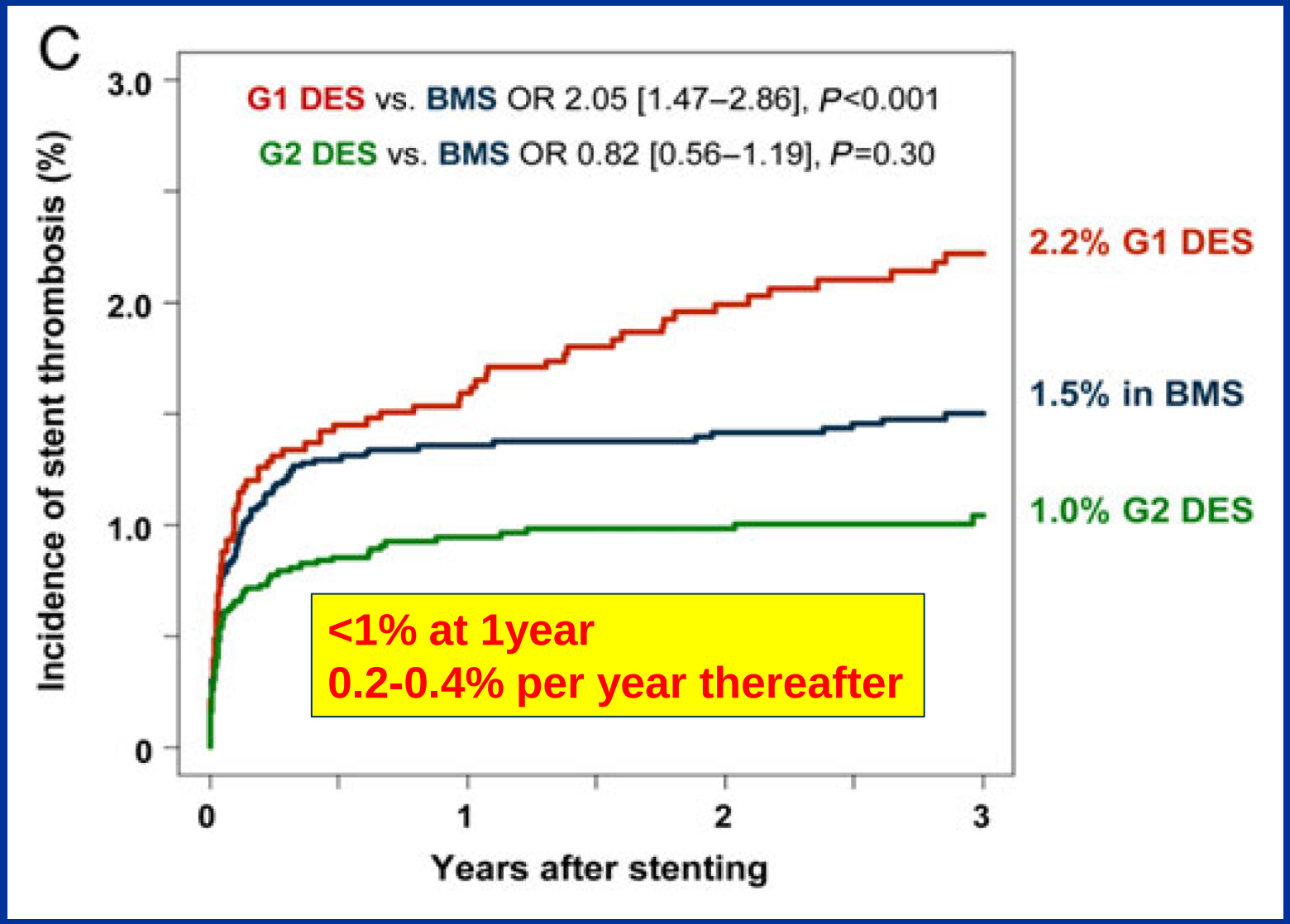
Seung Hwan Han

M.D., Ph.D. FACC

Contents

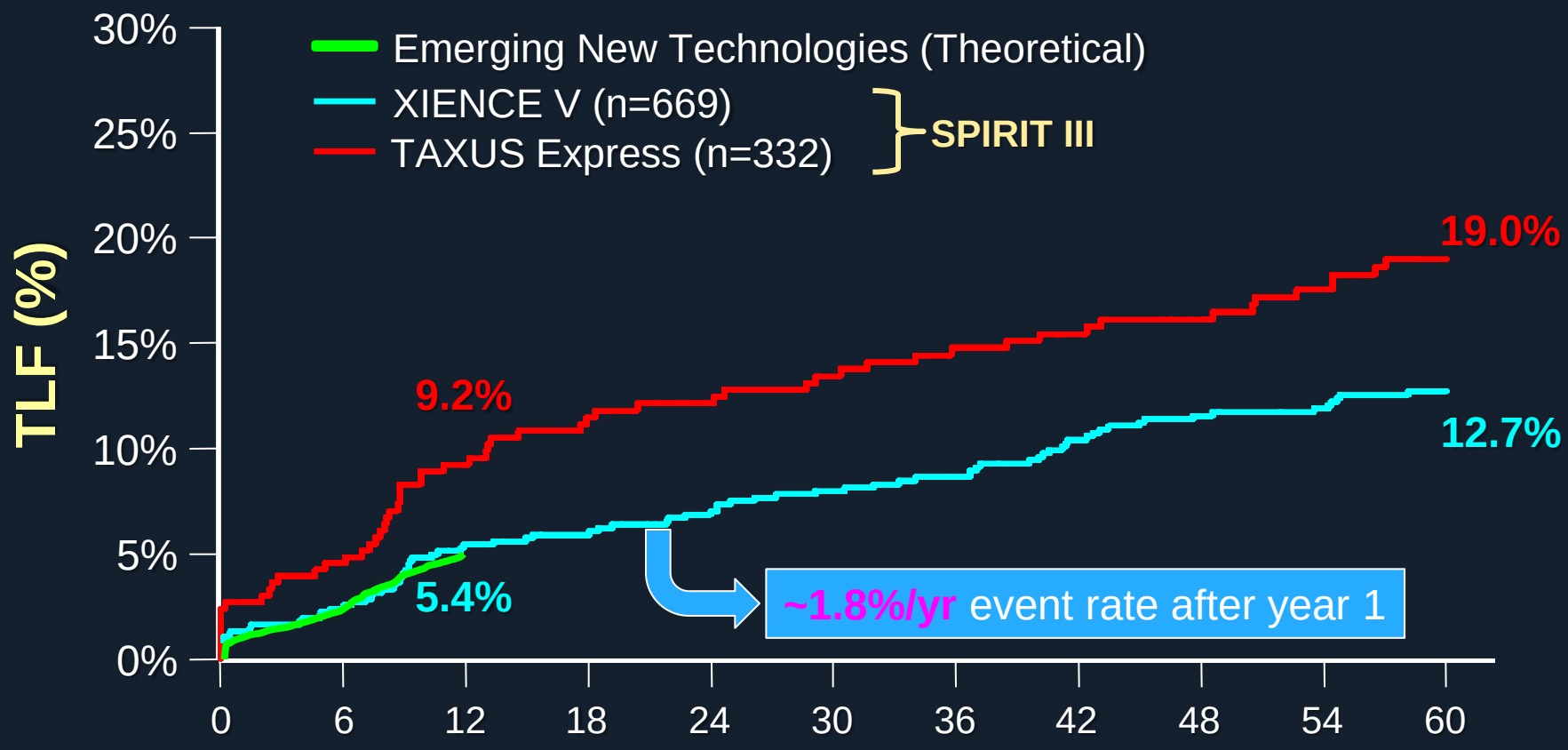
- **DES: Satisfactory strategy? Need for BRS**
- Updated Evidences based on randomized controlled trials (AII, AIII, A Japan, A China, Trofi II, Everbio II, AIDA, Meta-analysis)
- So what ? Which person, which lesions, How to do?
- Summary

ST Rates of Current DES



Byrne RA, at el, EHJ 2015

Long Term TLF Rates of DES



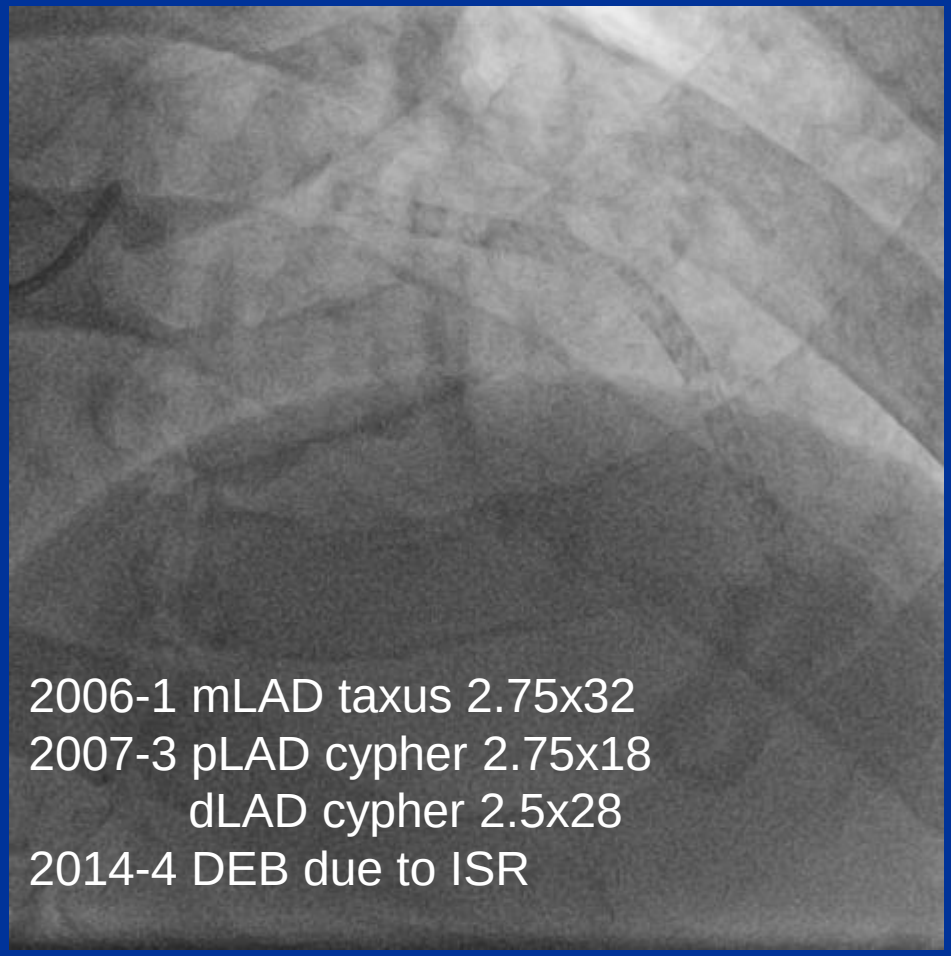
Number at risk

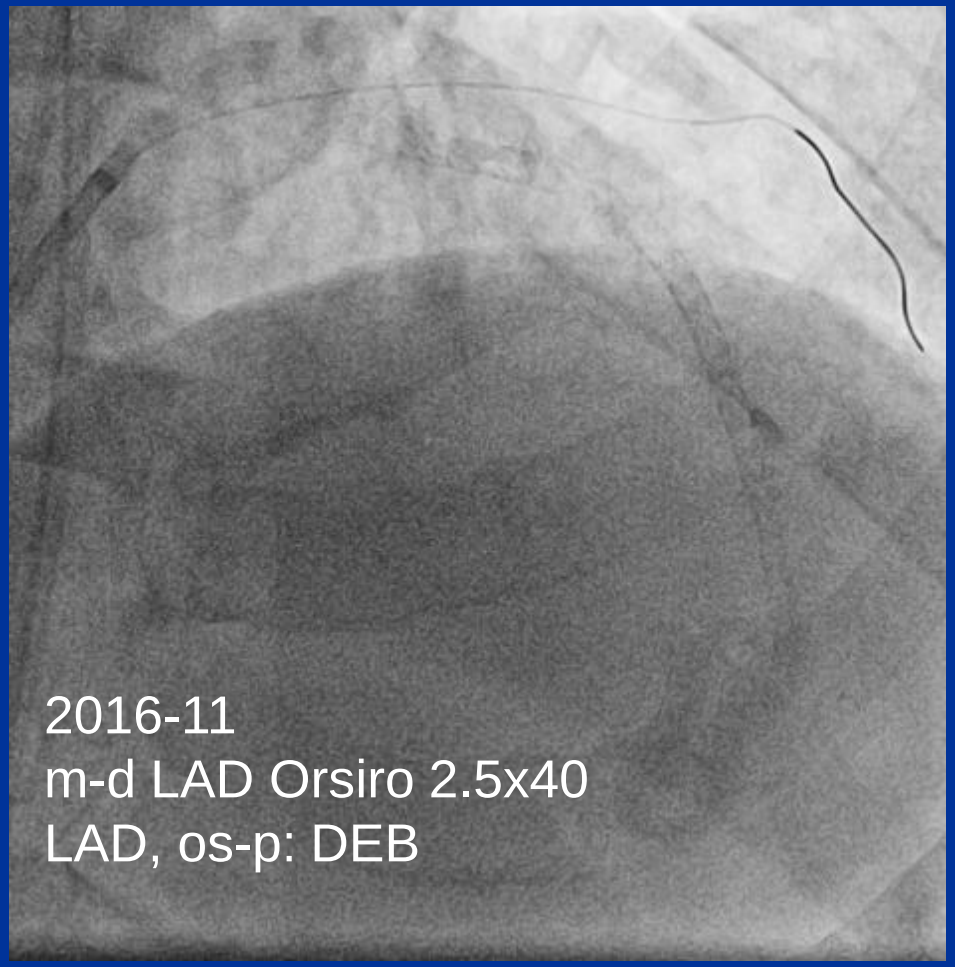
XIENCE V	669	646	616	601	582	571	565	548	537	529	521
TAXUS	332	310	288	274	269	262	255	248	243	231	223

TLF = cardiac death, target vessel MI, or ischemic-driven TLR

Spirit III: Gada H et al. J Am Coll Cardiol Intv 2013;6:1263–6

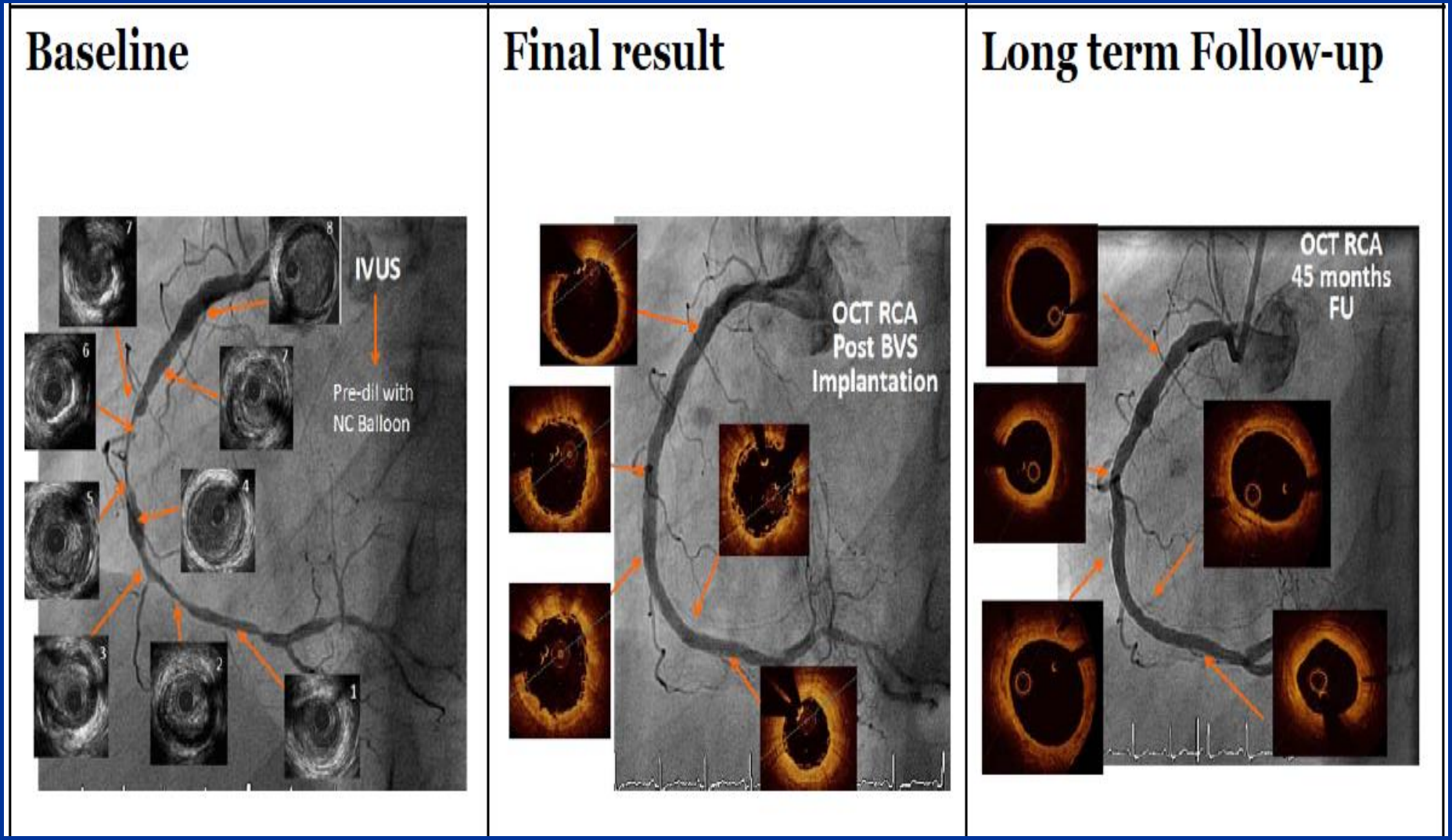
DES: Satisfactory strategy?





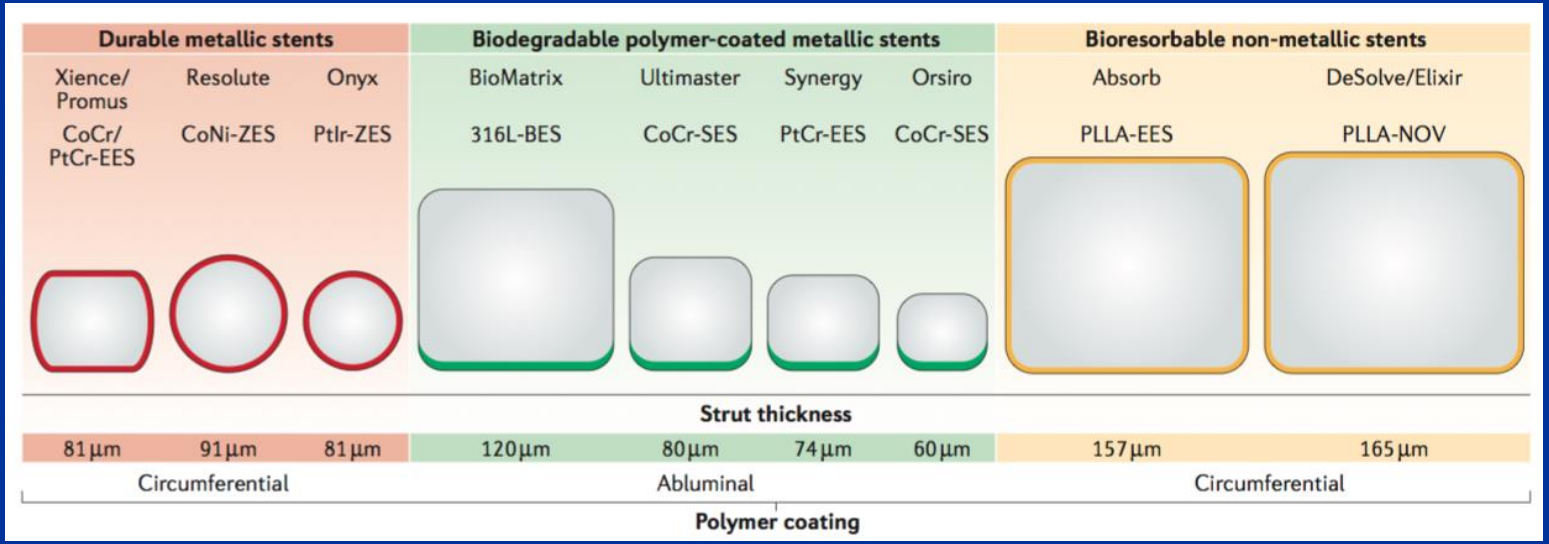
late target-lesion failure: maybe due to persistent presence of the **metallic stent frame** and **polymer** in the coronary vessel wall-→ **Neoatherosclerosis**

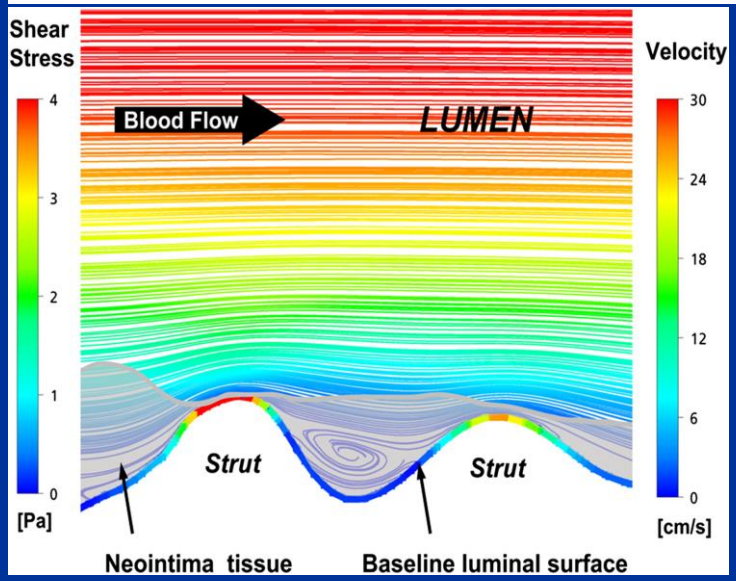
BRS: Expect always ideal Results?



Serra A, EuroPCR 2017

The Limitations of Current Version of BRS





-Bulky stent struts 150µm vs 80µm
-Higher shear stress
-Less cross ability
-Weak radial strength
-Limited expansion capability
-More device need for implantation (PSP, imaging device)
-Need for more prolonged DAPT

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- **Updated Evidences based on randomized controlled trials (AII, AIII, A Japan, A China, Trofi II, Everbio II, AIDA, Meta-analysis)**
- **Added data from TCT 2017**

- So what ? Which person, which lesions, How to do?

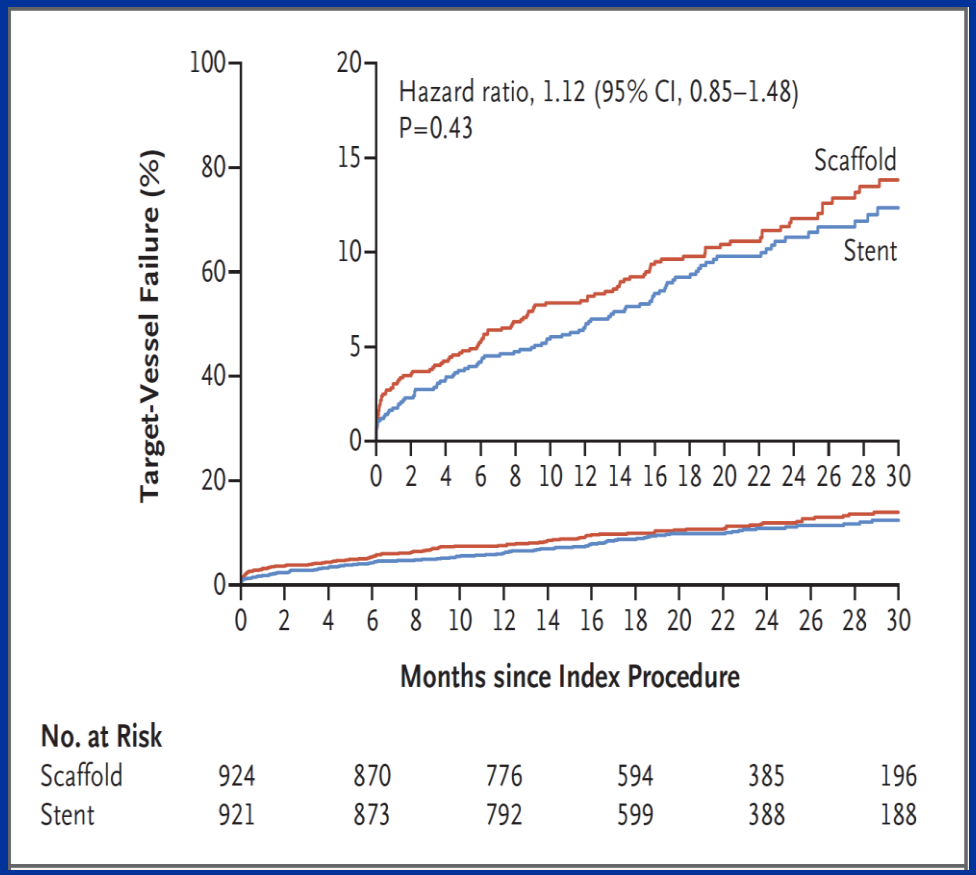
- Summary

Meta Analyses Comparing BRS to Metallic DES: 2 Years

			AMI	TLF	ST	Very late ST
Ali et al. Lancet 2017	A-II, A-Japan, A-China, A-III, EVERBIO II, TROFI II, AIDA	24 mo	1.52 (1.20-1.91)	1.29 (1.08-1.56)	3.35 (1.96-5.72)	9.67 (2.04-45.82)
			P=0.0004	P=0.0059	P<0.0001	P=0.0042
Collet et al. EHJ 2017	A-II, A-Japan, A-China, TROFI II, EVERBIO II	At least 24 mo	2.25 (0.81-0.19)	1.48 (0.90-2.42)	2.93 (1.37-6.26)	3.04 (1.20-7.68)
			P=0.09	0.09	P=0.01	P=0.03

Absorb vs. Xience in Routine PCI (AIDA, Routine PCI patients)

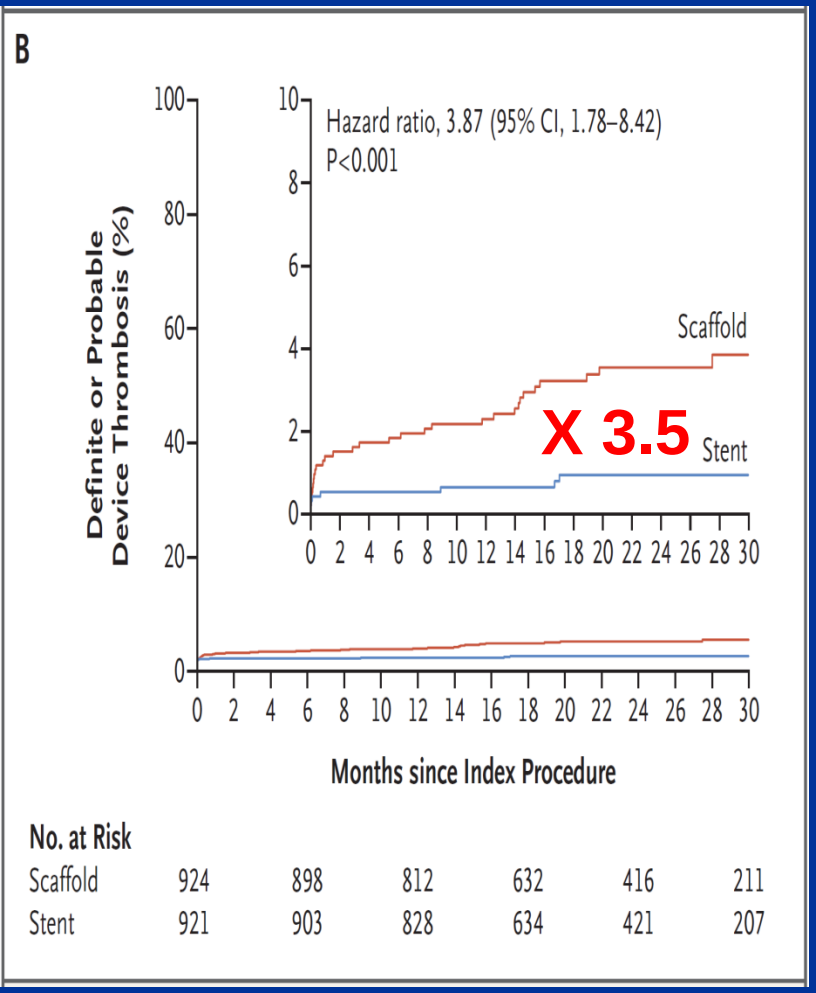
Clinical Outcomes	Absorb (N=924)	XIENCE (N=921)	P Value
TVF	11.7%	10.7%	0.43
Cardiac Death	2.0%	2.7%	0.43
TV-MI	5.5%	3.2%	0.04
TVR	8.7%	7.5%	0.37
TLF	10.3%	8.9%	0.31
TLR	7.0%	5.2%	0.15
Definite/ProbableST	3.5%	0.9%	<0.001



AIDA: Amsterdam Investigator Initiated Absorb Strategy All Comers Trial

NEJM 2017;376:2319-28

Absorb vs. Xience in Routine PCI (AIDA)



	No of Patients With event		2-yr cumulative event rate		HR	P
	Absorb	Xience	Absorb	Xience		
Definite or probable	31	8	3.5	0.9	3.87 (1.8-8.4)	<0.001
Acute (≤24hr)	3	3				
Subacute (1-30dyas)	10	2				
Late (31days -1yr)	8	2				
Very late (1-2yrs)	9	3				
Very late (>2-3yrs)	1	0				

- Vessel size ≤ 2.25mm, adequate device sizing, post-dilation
Not associated with the occurrence of scaffold thrombosis

- The rate of residual stenosis more than 30%:
Scaffold vs stent, 19% vs. 9% (P=0.05)

AIDA: Amsterdam Investigator Initiated Absorb Strategy All Comers Trial

NEJM 2017;376:2319-28

NEWS • INTERVENTIONAL

Absorb BVS Use Restricted in Europe

The CE Mark approval remains in place, but only centers participating in formal registries should be using the bioresorbable device for now.

May 31, 2017

By Michael O'Riordan | April 06, 2017

Based on recent results from the ABSORB II study

NEWS • INTERVENTIONAL | ACC 2017

FDA Warns of Risk of Major Adverse Cardiac Events With Absorb BVS

On the same day ABSORB III 2-year data are being presented at ACC, the agency is raising concerns.

The FDA is working with Abbott Vascular, Inc. to conduct additional analyses to better understand the cause(s) of the higher cardiac event and device thrombosis rates in patients treated with BVS compared to the XIENCE stent. The FDA will continue to monitor the performance of the BVS in ongoing clinical studies and in reports submitted to FDA through MedWatch. We will update this communication when additional information or analyses become available.

RECOMMENDATION: The FDA recommends that health care providers:

- Follow the instructions for target heart vessel selection (e.g., avoiding BVS use in small heart vessels) and optimal device implantation that are included in the BVS physician labeling.
- Advise patients experiencing any new cardiac symptoms such as irregular heartbeats, chest pain, or shortness of breath to seek clinical care. For more information about risks associated with the BVS, refer to the BVS physician labeling.
- Advise BVS patients to follow the recommendations for DAPT prescribed by their health care providers.
- Report any adverse events related to the BVS that come to your attention. If you suspect a problem with the BVS, we encourage you to file a voluntary report through MedWatch, the FDA Safety Information and Adverse Event Reporting Program. Health care personnel employed by facilities that are subject to the FDA's user facility reporting requirements should follow the reporting procedures established by their facilities.

Based on recent results from the 2-year data from ABSORB III study

CRF tct2017 daily
Transcatheter Cardiovascular Therapeutics Daily

INSIDE THIS ISSUE | DENVER, COLORADO | WEDNESDAY, NOVEMBER 1, 2017

Long-term Absorb BVS Data Continue to Disappoint

Lessons learned may inform future device design

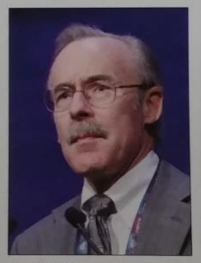
LATE-BREAKING TRIAL

By Michael O'Riordan

Longer-term follow-up data culled from the ABSORB II and III trials confirm the significantly increased risk of thrombotic events with the Absorb bioresorbable vascular scaffold (BVS; Abbott Vascular), with investigators reporting a higher risk of device thrombosis when compared with a metallic drug-eluting stent.

The results are unlikely to surprise physicians familiar with the device, nor are they likely to have much clinical impact given Abbott's recent decision to stop selling Absorb BVS due to low commercial sales.

Several meta-analyses published to date, as well as 3-year data from the ABSORB II trial, have also shown the Absorb device is associated with an increased risk of adverse events, particularly an increased risk of scaffold thrombosis, when compared with the Xience metallic everolimus-eluting stent (Abbott Vascular).



Stephen Ellis, MD

Stephen Ellis, MD (Cleveland Clinic, OH), who presented the 3-year ABSORB III results during a morning press conference, reported that use of Absorb was associated with a strong trend toward an increased risk of TLF, a composite endpoint that included cardiac death, target-vessel MI, and ischemia-driven target lesion revascularization (HR 1.31; 95% 0.99-1.73).

Ellis said that even if the device were available, it would not be frequently used. An eligible candidate might be a patient with diffuse disease in the left anterior descending artery, he suggested. "You don't want to put a metallic stent in there," said Ellis. "If you put a biodegradable scaffold in and allow the vessel to remodel, you won't block the patient from getting an opportunity for bypass

(Absorb BVS, continued on page 28)

Intermediate-Risk TAVR

Today's Highlights

See pages 4-6 for agenda with session times and locations.

Late-Breaking Clinical Trials

SENIOR: Randomized Trial of Bioabsorbable Polymer-Based Metallic DES vs BMS With Short DAPT in CAD Patients Older Than 75 Years

DAPT STEMI: Randomized Trial of 6-Month vs 12-Month DAPT After DES Implantation in STEMI

REDUCE: Randomized Trial of 3-Month vs 12-Month DAPT After Bioabsorbable Polymer-Based Metallic DES With Luminal CD34+ Antibody Coating in ACS Patients

First Report Investigations

MITRAL: 30-Day Outcomes of Transcatheter MV Replacement in Patients With Severe Mitral Valve Disease Secondary to Mitral Annular Calcification or Failed Annuloplasty Rings

INTREPID: 30-Day Outcomes of Transcatheter MV Replacement in Patients With Severe Mitral Regurgitation

TENDYNE: 1-Year Outcomes of Transcatheter MV Replacement in Patients With Severe Mitral Regurgitation

TRACER: 6-Month Outcomes of Transcatheter MV Neochordal Repair in Patients With Severe Primary Mitral Regurgitation

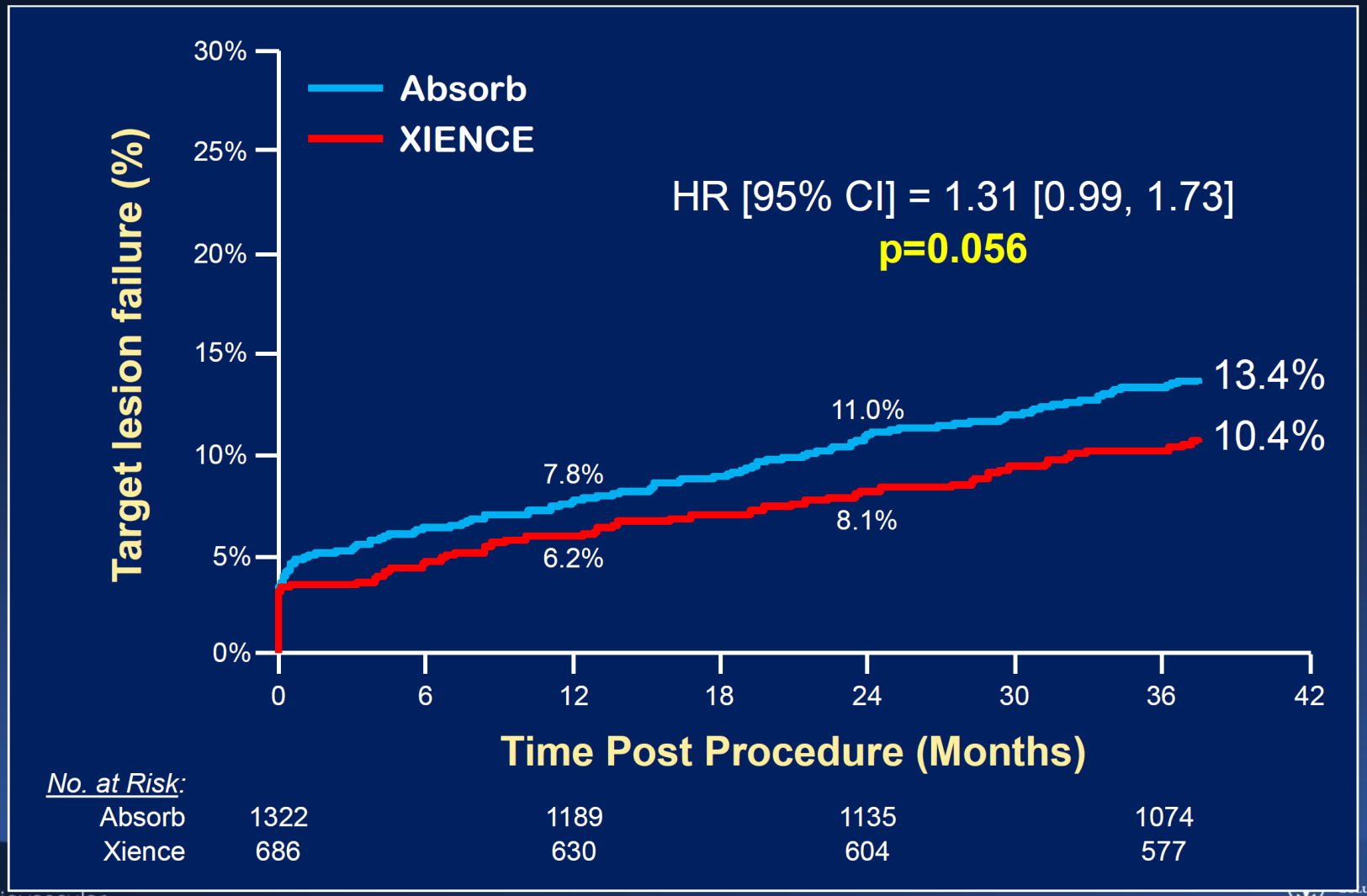
MAVERIC: 6-Month Outcomes of Transcatheter MV

ABSORB Randomized Trials
New Insights from TCT 2017

- Three ABSORB RCTs were presented as late breaking trials at TCT 2017 that reflect crucial time points that bear on BVS outcomes
  - ABSORB III (n=2,008) at 3 years: Time of complete bioresorption
  - ABSORB IV (n=2,604) at 30 days: Early outcomes with improved technique in a higher-risk population
  - ABSORB II (n=501) at 4 years: Very late outcomes after complete bioresorption

ABSORB III

ABSORB III 3-year
Target Lesion Failure
2,008 pts randomized 2:1 BVS vs. EES



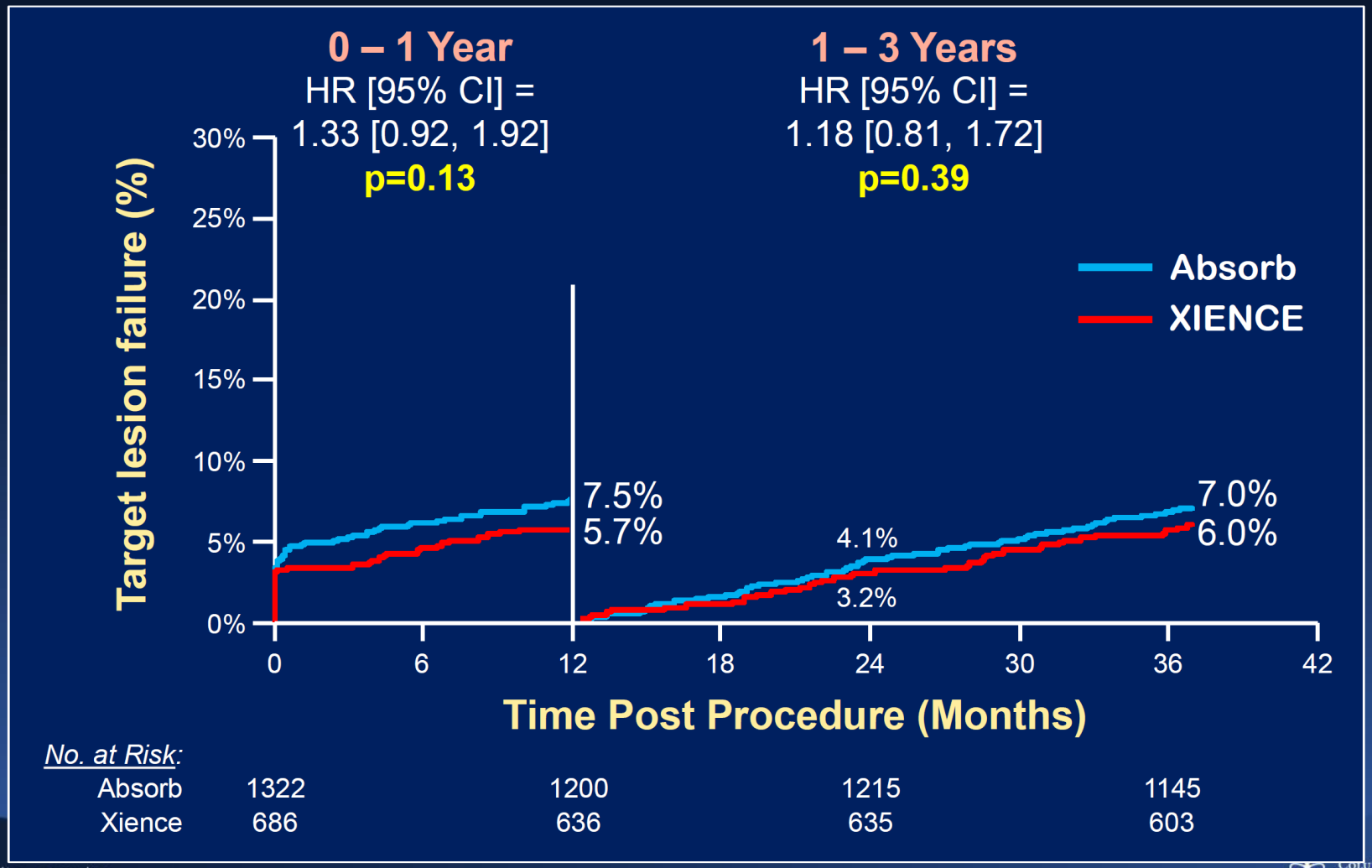
Cardiovascular Research Foundation

The 3-year window includes follow-up through 37 months

Columbia University Medical Center
NewYork-Presbyterian

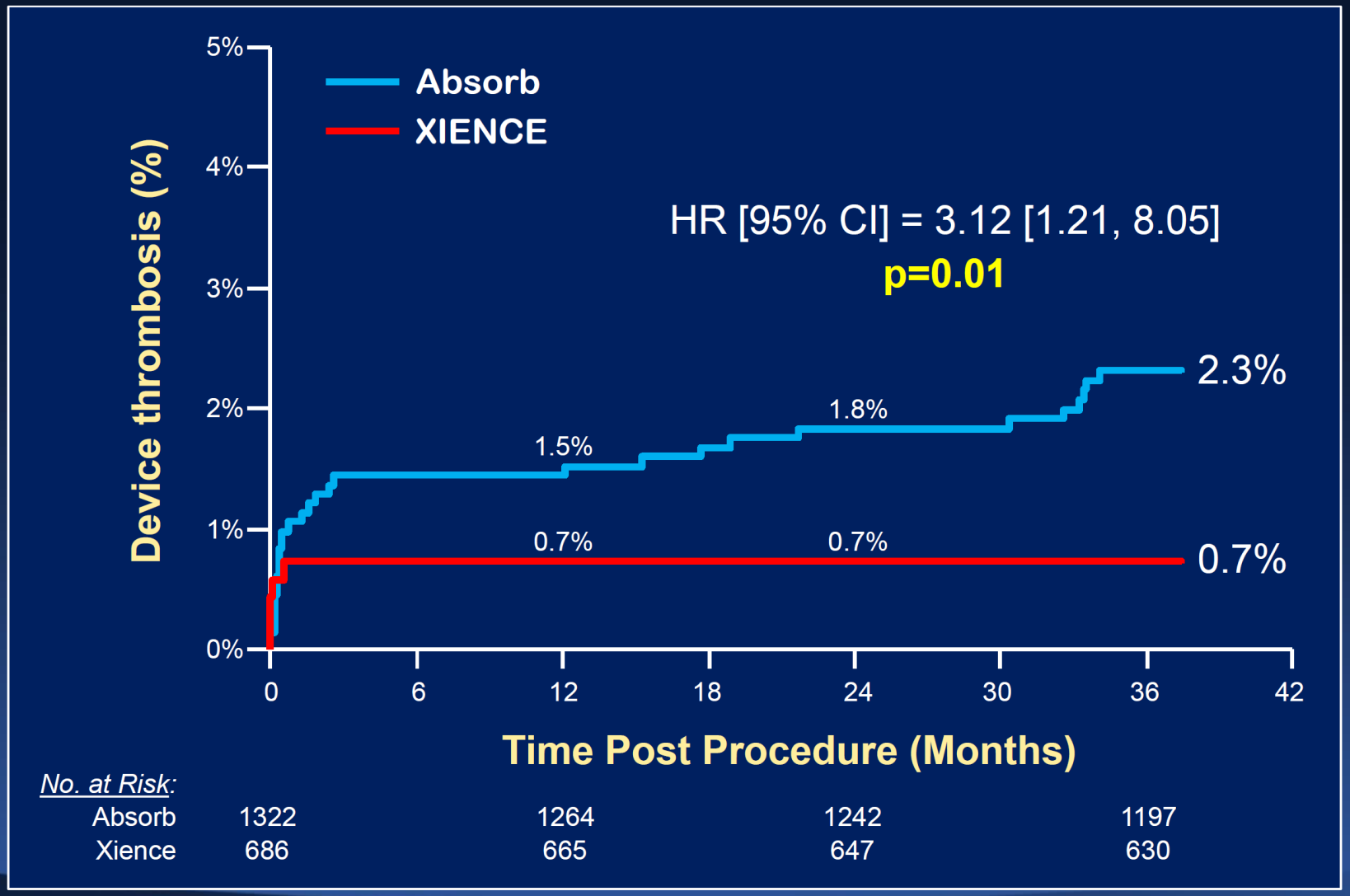
ABSORB III 3-year

Target Lesion Failure: Landmark Analysis



ABSORB III

ABSORB III 3-year
Device Thrombosis



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ABSORB III

ABSORB III 3-year
Device Thrombosis:
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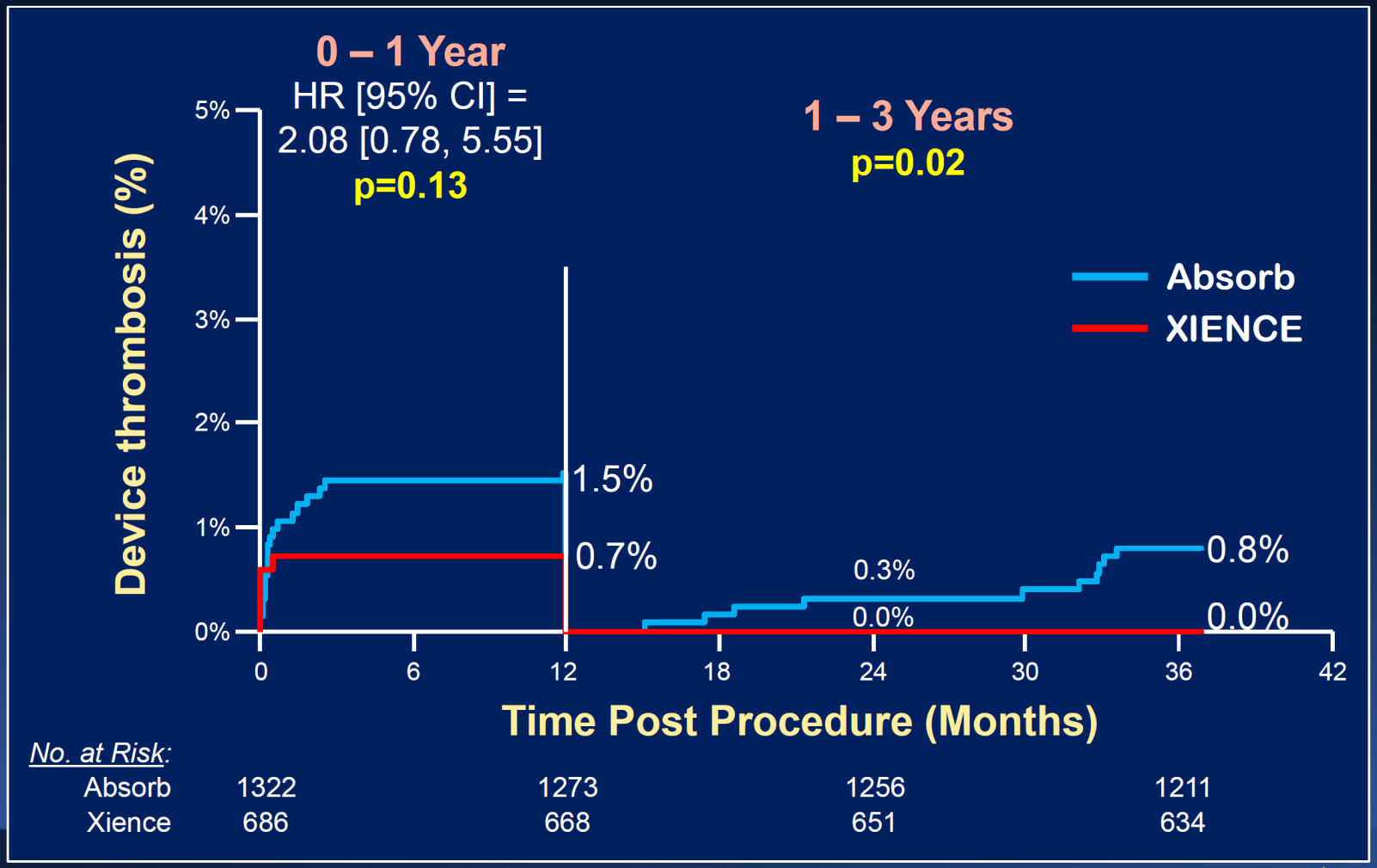


ABSORB IV: Trial Design

NCT01751906

Compared to ABSORB III:
Troponin pos ACS, thrombus and 3 lesions included

2,604 pts with SIHD or ACS
1 - 3 target lesions w/RVD
2.5-3.75 mm and LL ≤24 mm

Randomize 1:1
Stratified by diabetes and ABSORB III-like vs. not

ABSORB BVS
N=1,296

Xience EES
N=1,308

BVS technique:
Pre-dil: 1:1; NC balloon recommended
Sizing: IV TNG; QCA/IVUS/OCT strongly recommended if visually estimated RVD ≤2.75 mm and 2.5 mm device intended; <2.5 mm ineligible!
Post-dil: 1:1, NC balloon, ≥16 atm strongly recommended

DAPT for ≥12 months
Clinical/angina follow-up: 1, 3, 6, 9, 12 months, yearly through 7-10 years
SAQ-7 and EQ-5D: 1, 6, 12 months and 3 and 5 years
Cost-effectiveness: 1, 2, and 3 years

Primary endpoints: TLF at 30 days; TLF between 3 and 7-10 yrs (pooled with AIII)
Secondary endpoints: TLF at 1 year; angina at 1 year

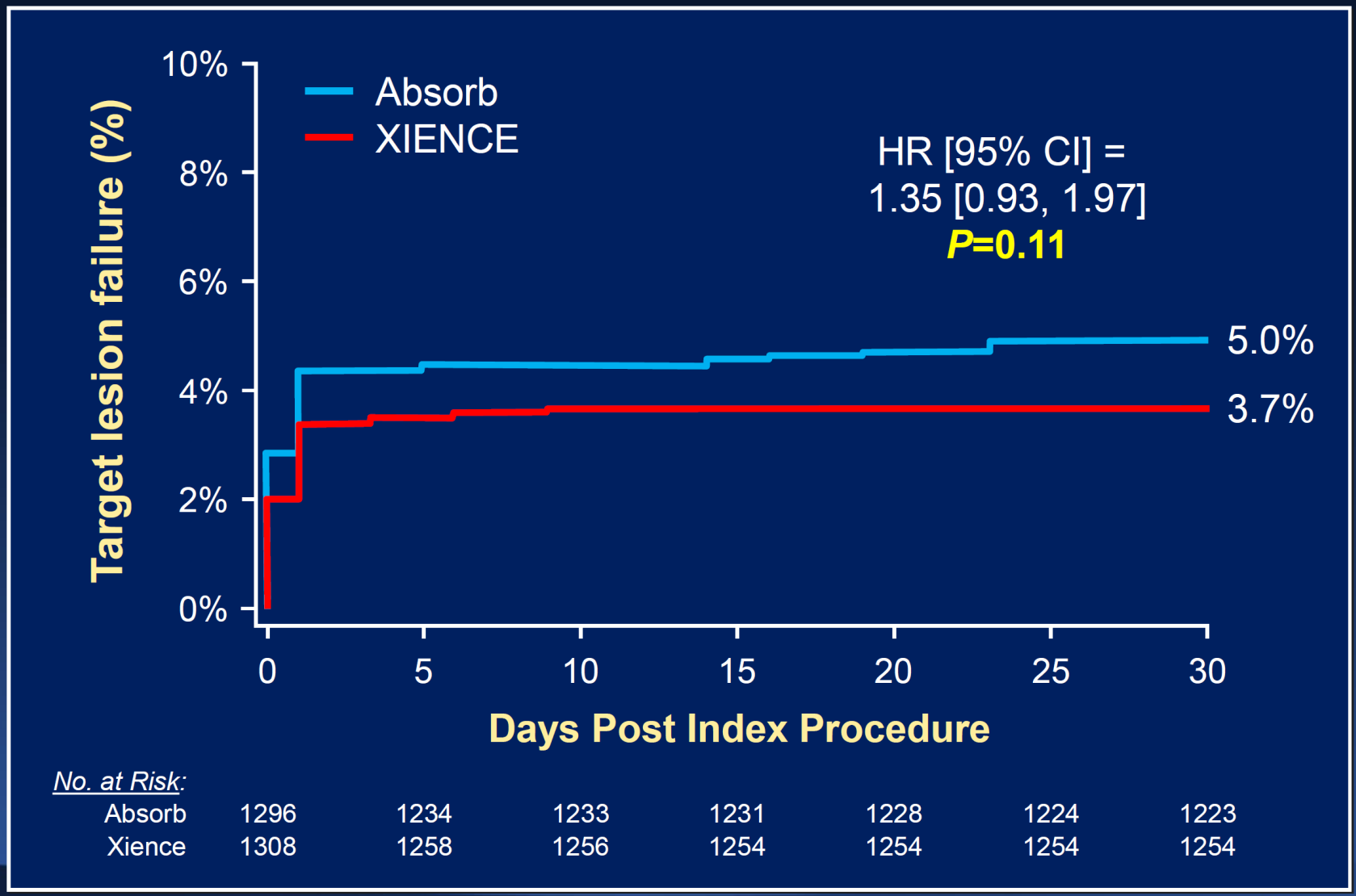
No routine angiographic follow-up

Cardiovascular Research Foundation

Columbia University Medical Center
NewYork-Presbyterian

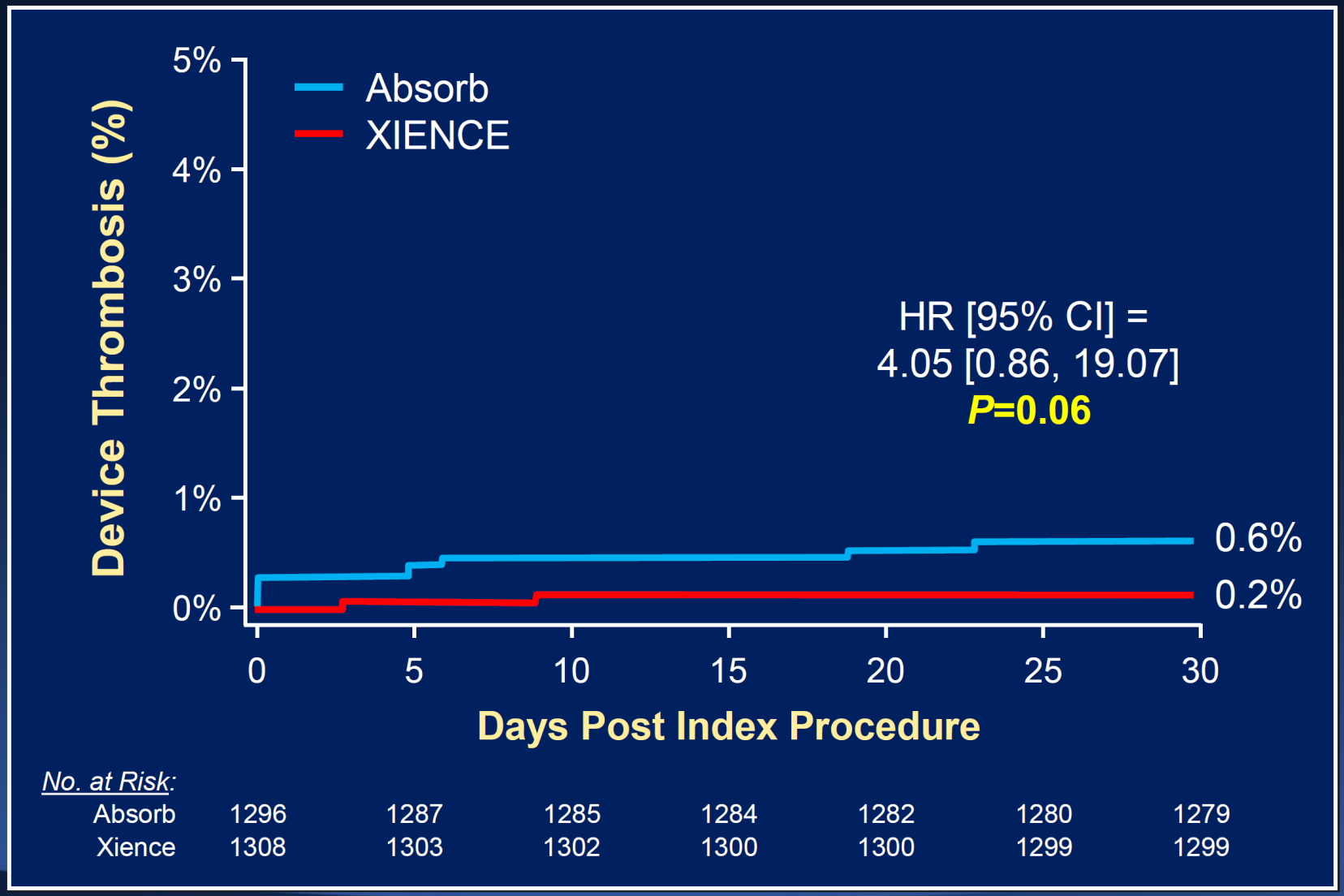
ABSORB IV

ABSORB IV 30-day
Target Lesion Failure



ABSORB IV

ABSORB IV 30-day
Device Thrombosis

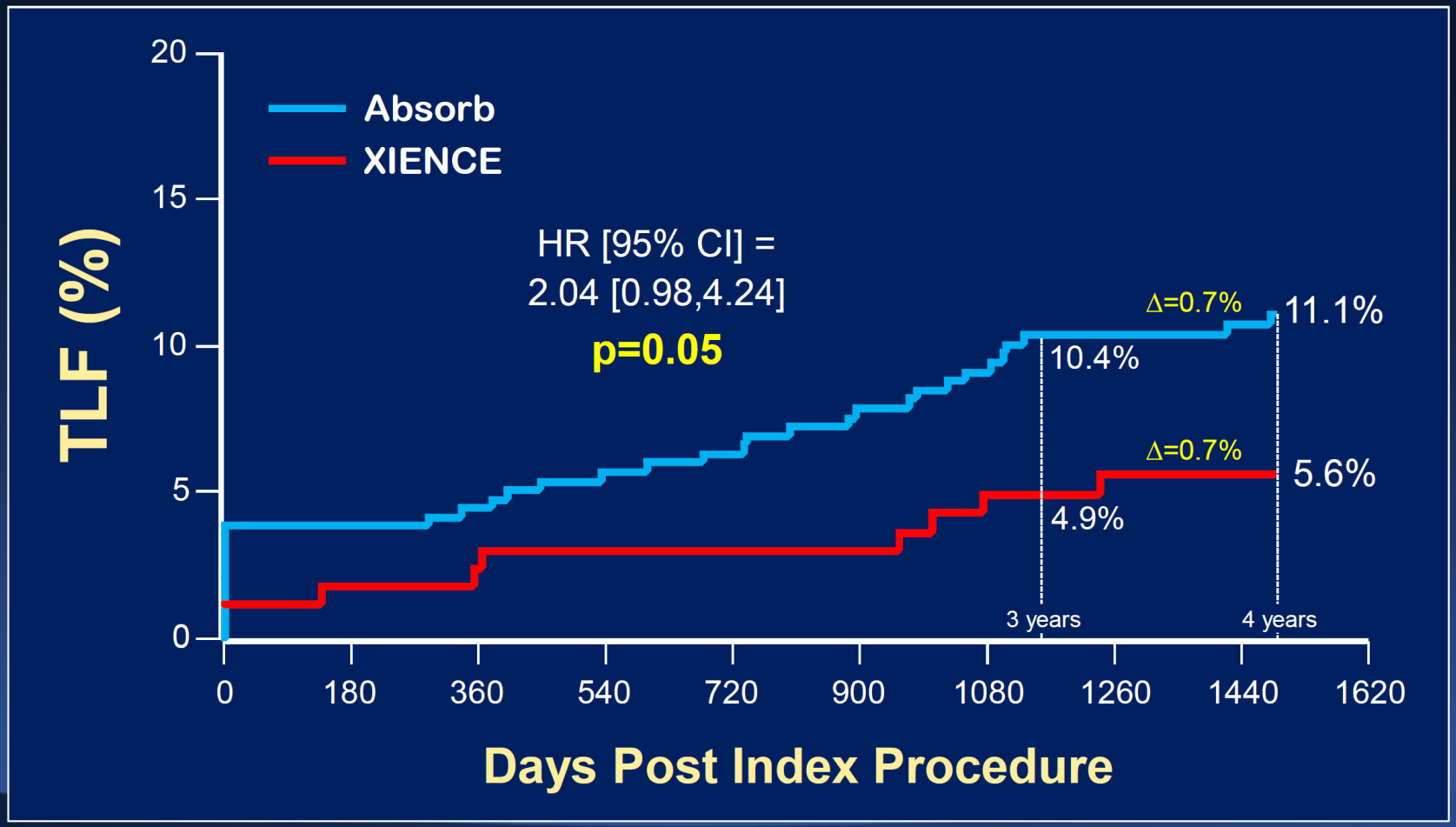


ABSORB II 4-year

Target Lesion Failure

501 pts randomized 2:1 BVS vs. EES

Routine angio FU at 3 yrs; 428 (85%) 4-year FU (re-consent required)

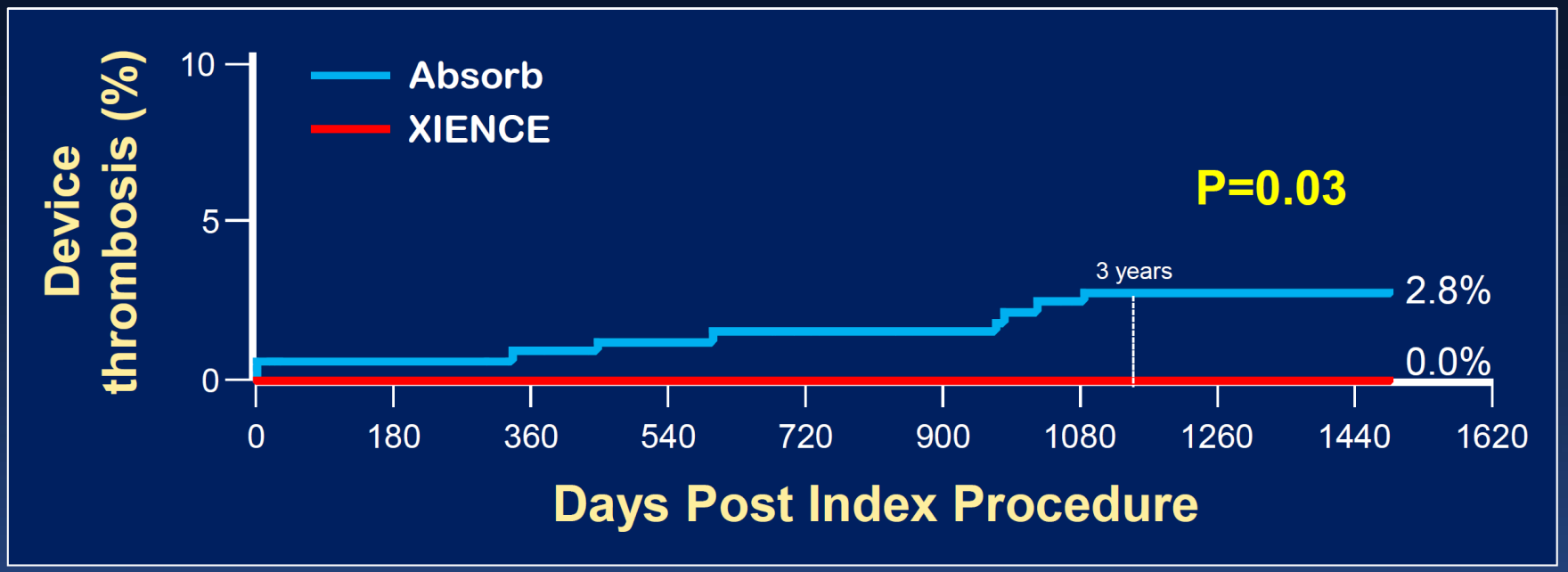


ABSORB II 4-year

Device Thrombosis (def/prob)

501 pts randomized 2:1 BVS vs. EES

Routine angio FU at 3 yrs; 428 (85%) 4-year FU (re-consent required)



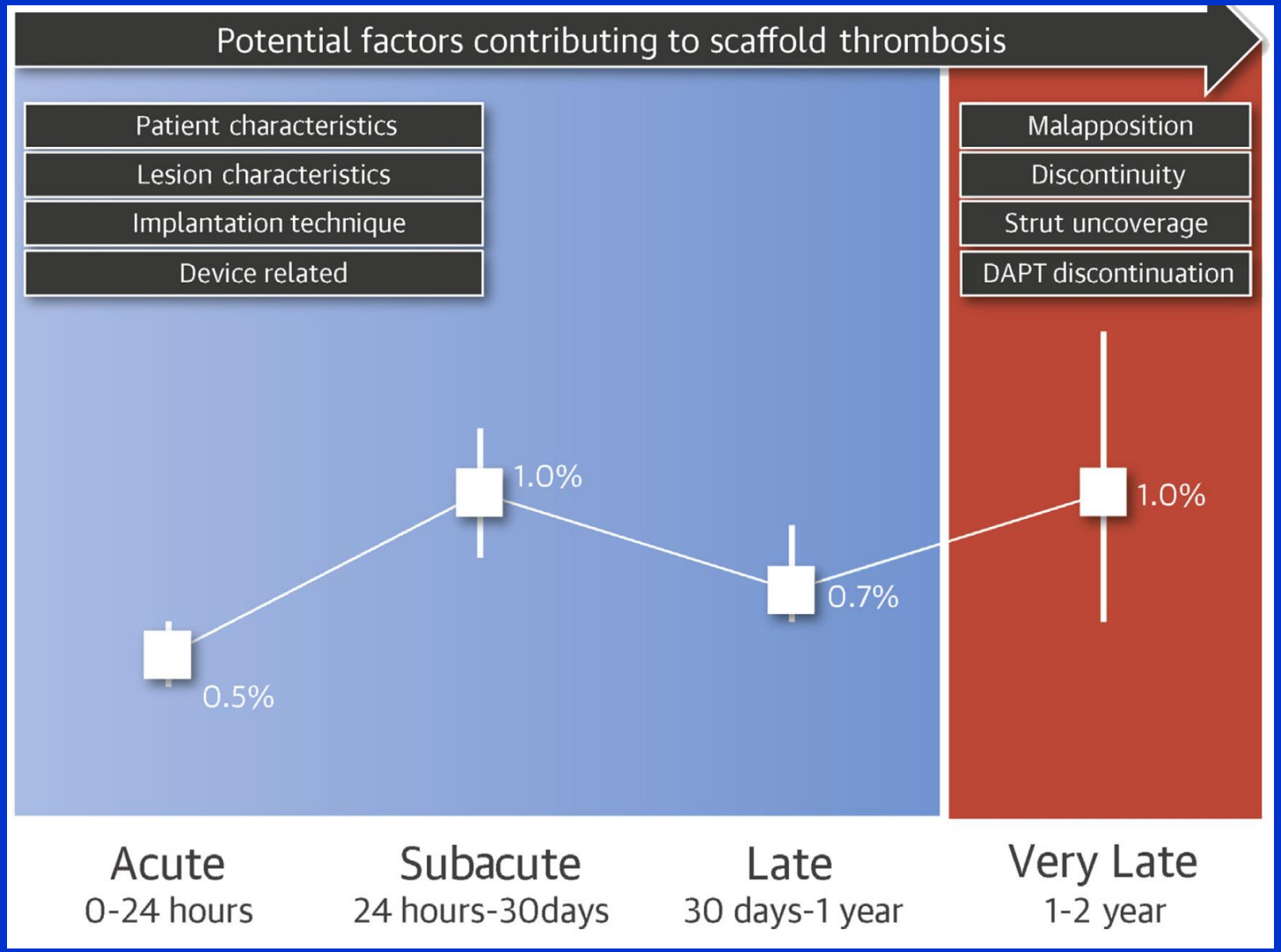
No device thromboses after 3 years

(in either arm)

Contents

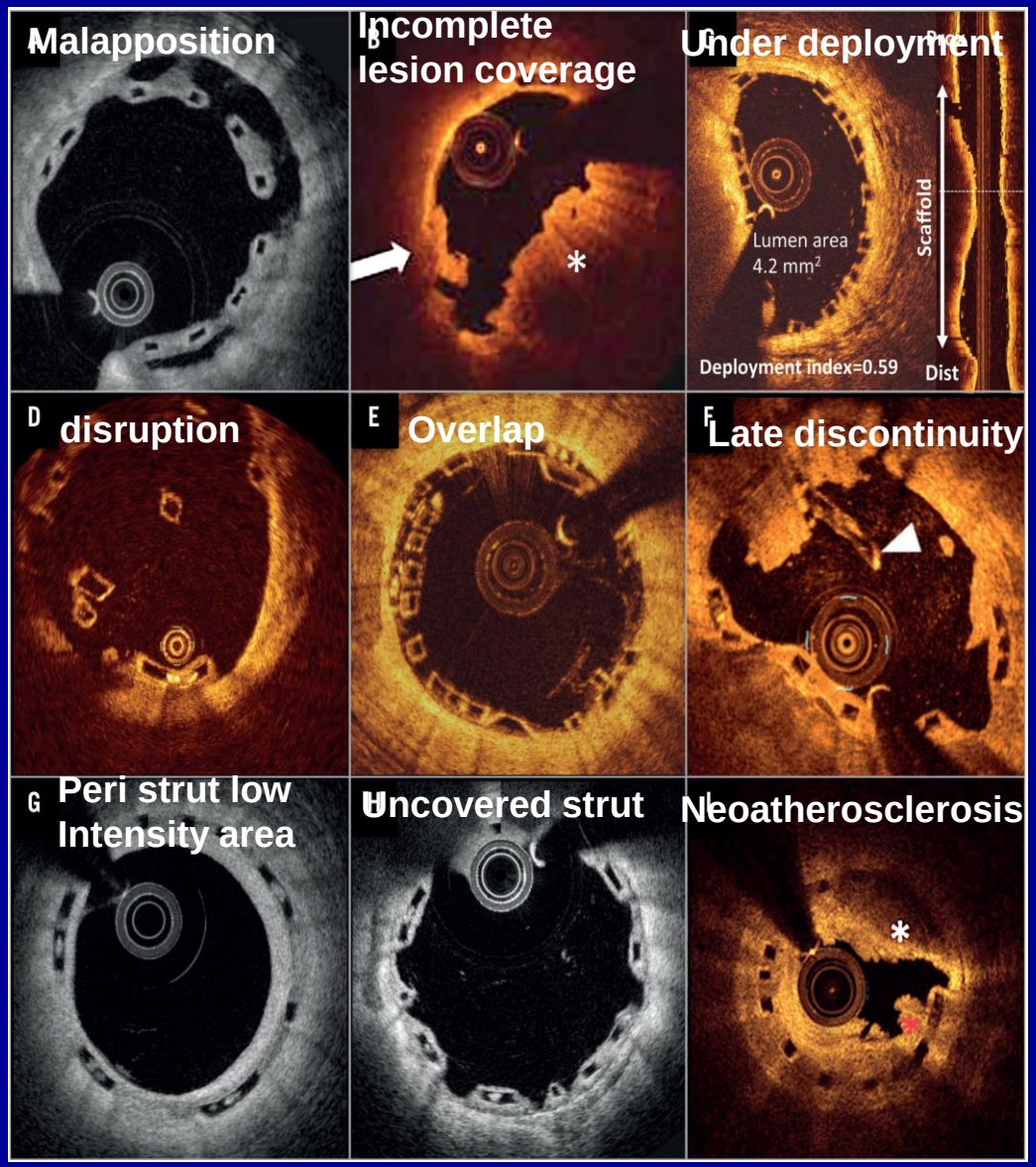
- So what ? Which person, which lesions, How to do?

Scaffold Thrombosis Rates and Potential Related Mechanisms at Different Time Intervals



Minerva Cardioangiol 2016;65:32-51
JACC cvInt 2017;5:425-37

The Cause of Scaffold Thrombosis



- **Suboptimal implantation**: Incomplete lesion coverage, under-deployment, malapposition
- **Thick stent struts**: blood flow alterations, thrombogenicity
- Late events: combination of non-embedded and non-absorbed scaffold struts and late structural discontinuity or device dismantling

Dismantling

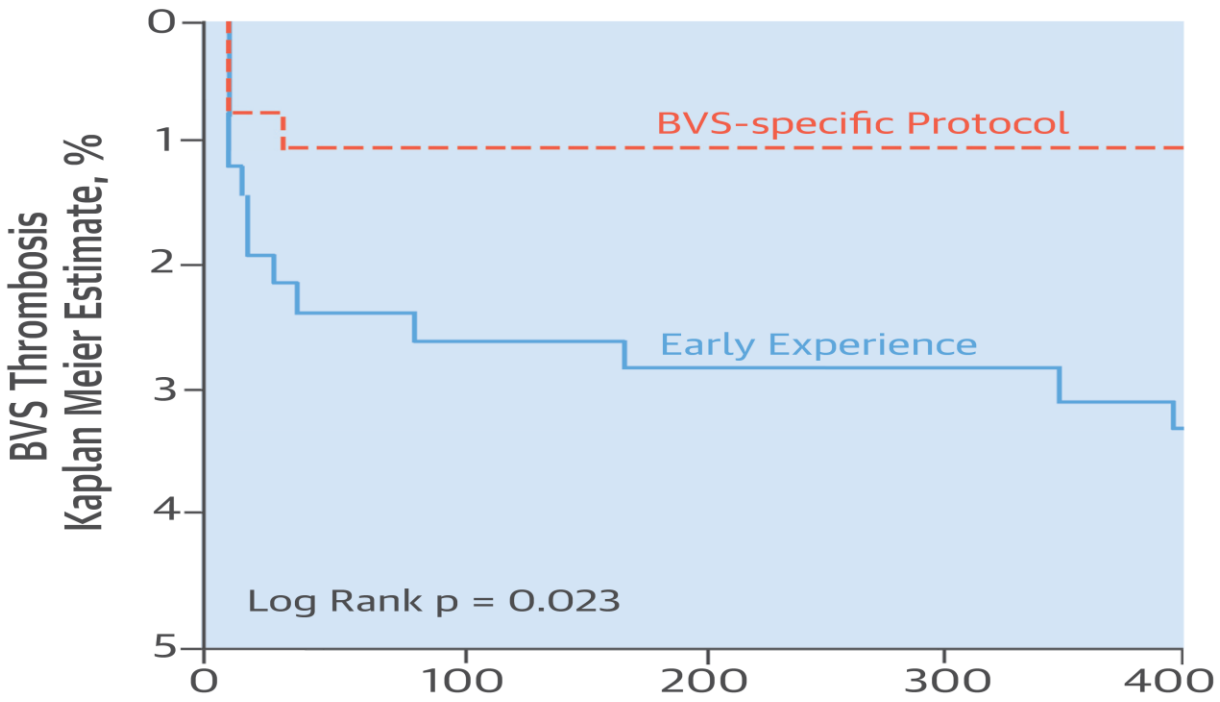
Circ Cardiovasc Interv 2015;8:e002369
EuroIntervention 2017;12:1747-56

Contents

- **So what ? Which person, which lesions, How to do?**
  - Select appropriate patients and lesions
  - Follow PSP technique and widely use of imaging devices
  - Maintain long term DAPT
  - Need for more improved scaffold

PSP is Very Important

CENTRAL ILLUSTRATION Thrombosis in Bioresorbable Scaffolds: Implantation Strategy



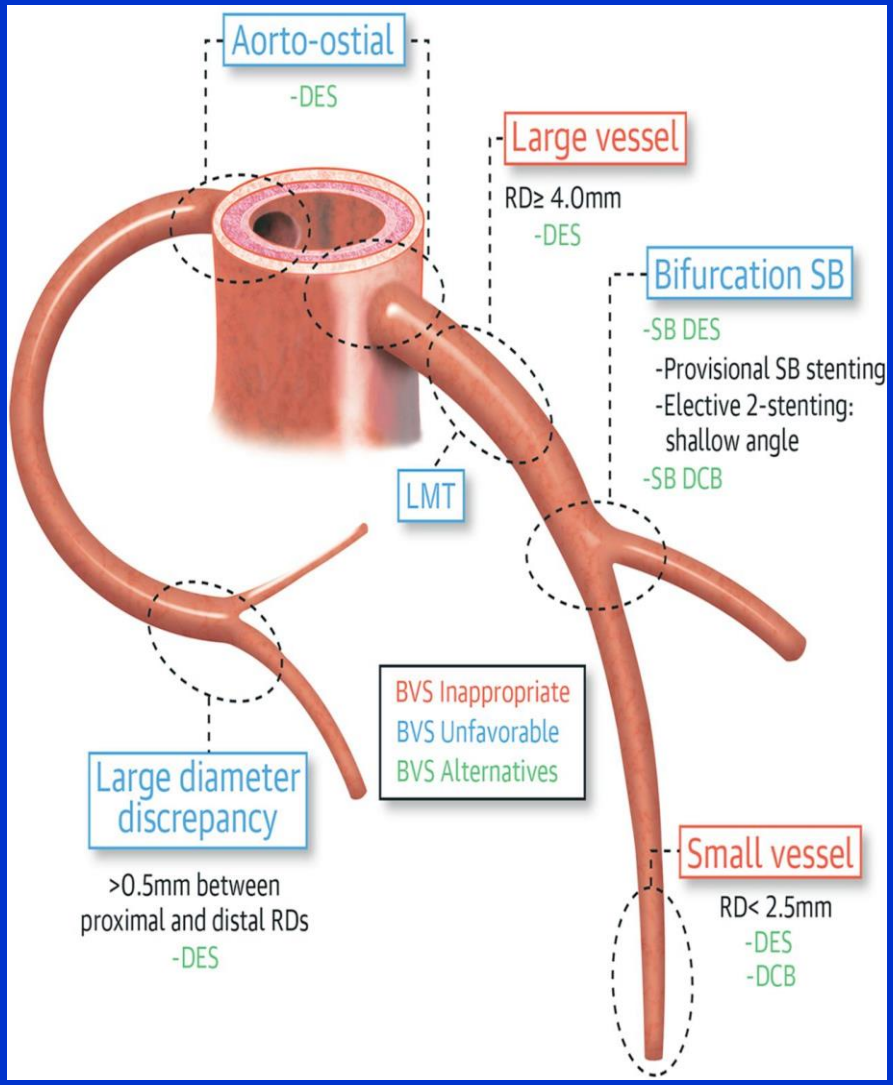
Patients					
Early Experience	369	369	369	369	369
BVS-specific	292	292	281	217	155

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

Kaplan-Meier curves describing the incidence of scaffold thrombosis (ScT) according to the implantation strategy used. **Orange** indicates bioresorbable vascular scaffold (BVS)–specific technique. The difference among the 2 curves remained significant in multivariable analysis.

Pruicel S, et al. JACC 2016;67:921

Hybrid Strategy of BRS in Combination with DES or DEB



Avoid BRS:

RD>4.0mm
RD<2.5mm

>0.5mm size discrepancy between pRD and dRD

Ostial lesion

Severe calcification: aggressive lesion preparation Needed

Bifurcation Lesion needed 2 stents

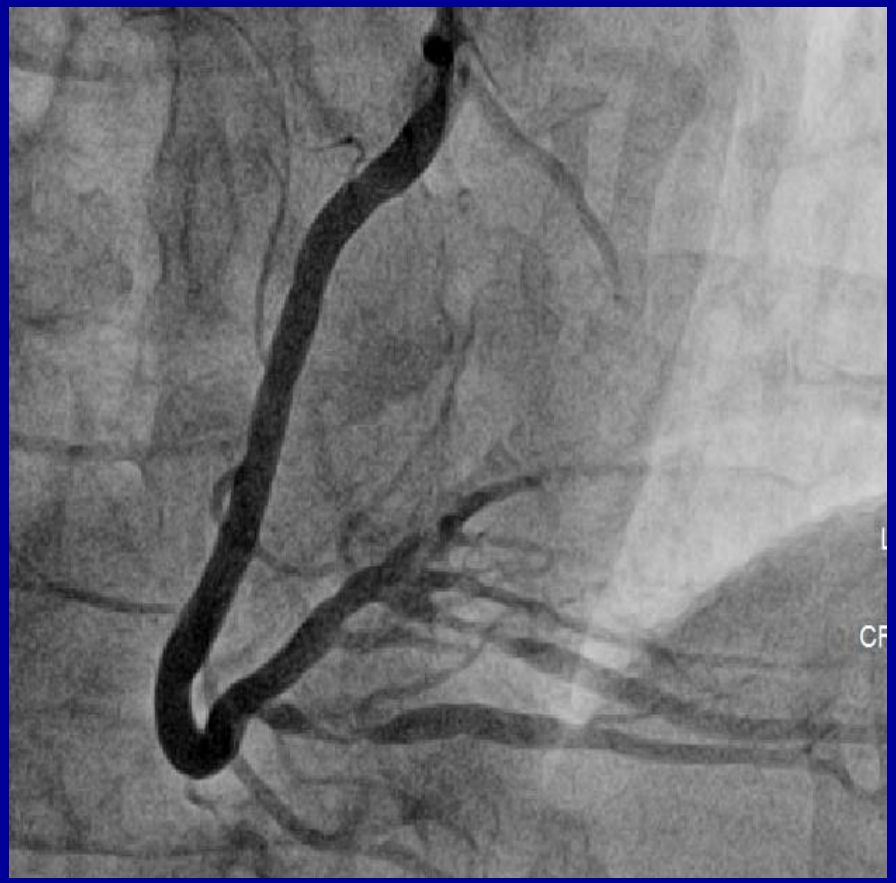
Side br, DES preferable or no excessive protrusion into the MB,

Avoid cullotte or crushing
Preferred T or small protrusion

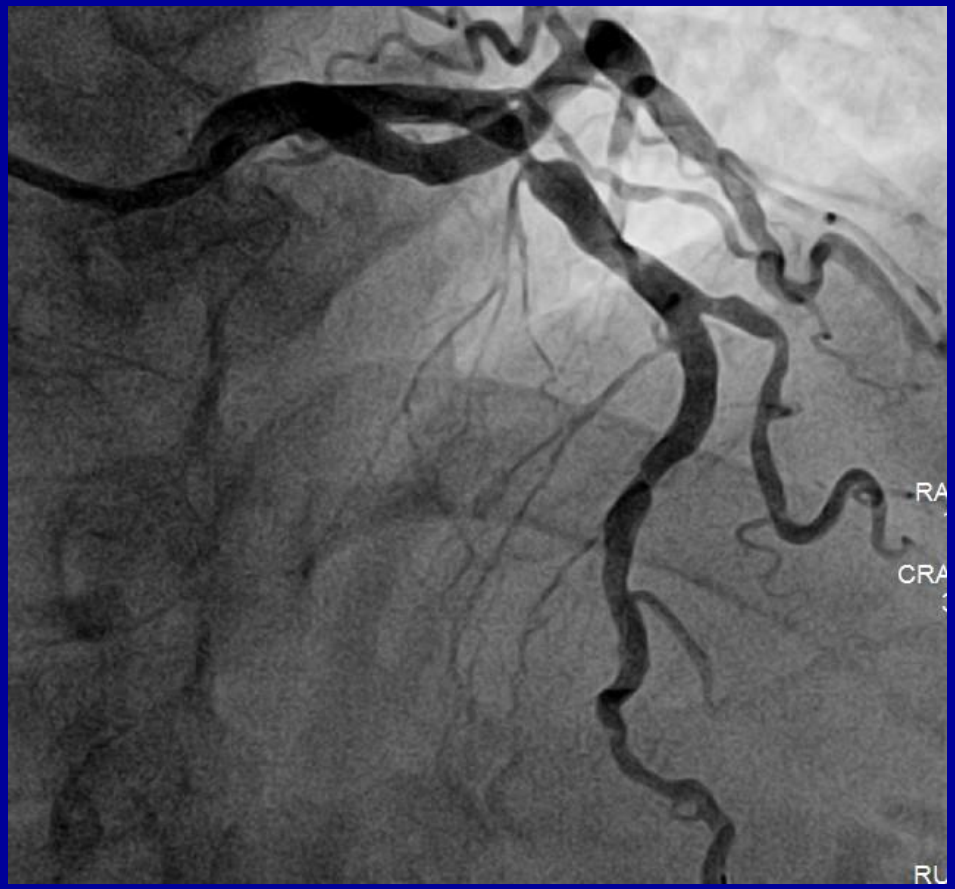
LM, should be cautious

Akihito Tanaka et al. JACC Int 2017;10:539-547

Patients and Lesion Selection: Avoid small vessel, Too large vessel

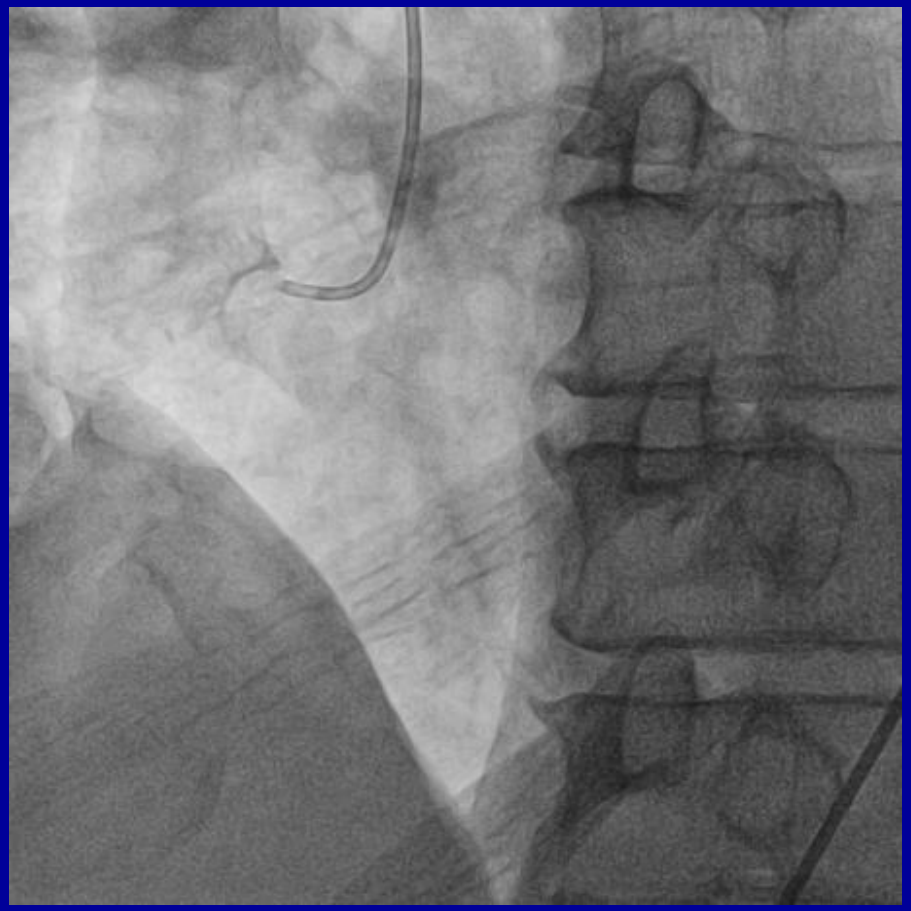


RD<2.5mm



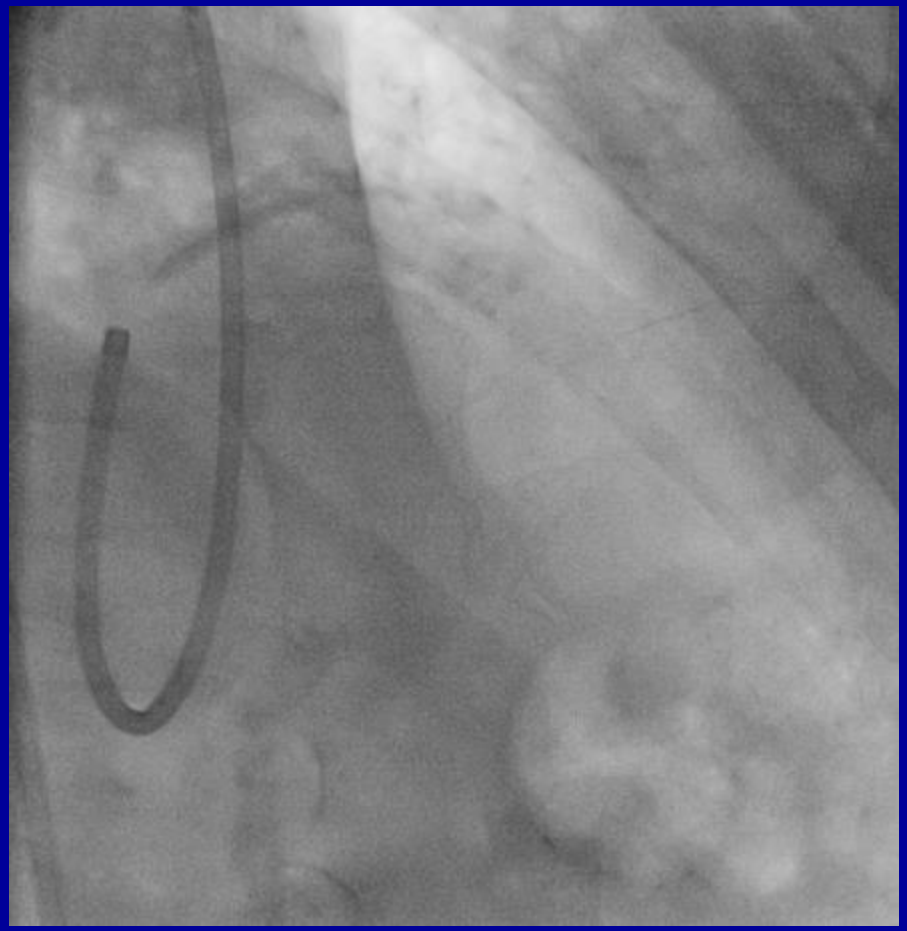
RD>4.0mm

Patients and Lesion Selection: Avoid lesions for high risk of No/slow flow



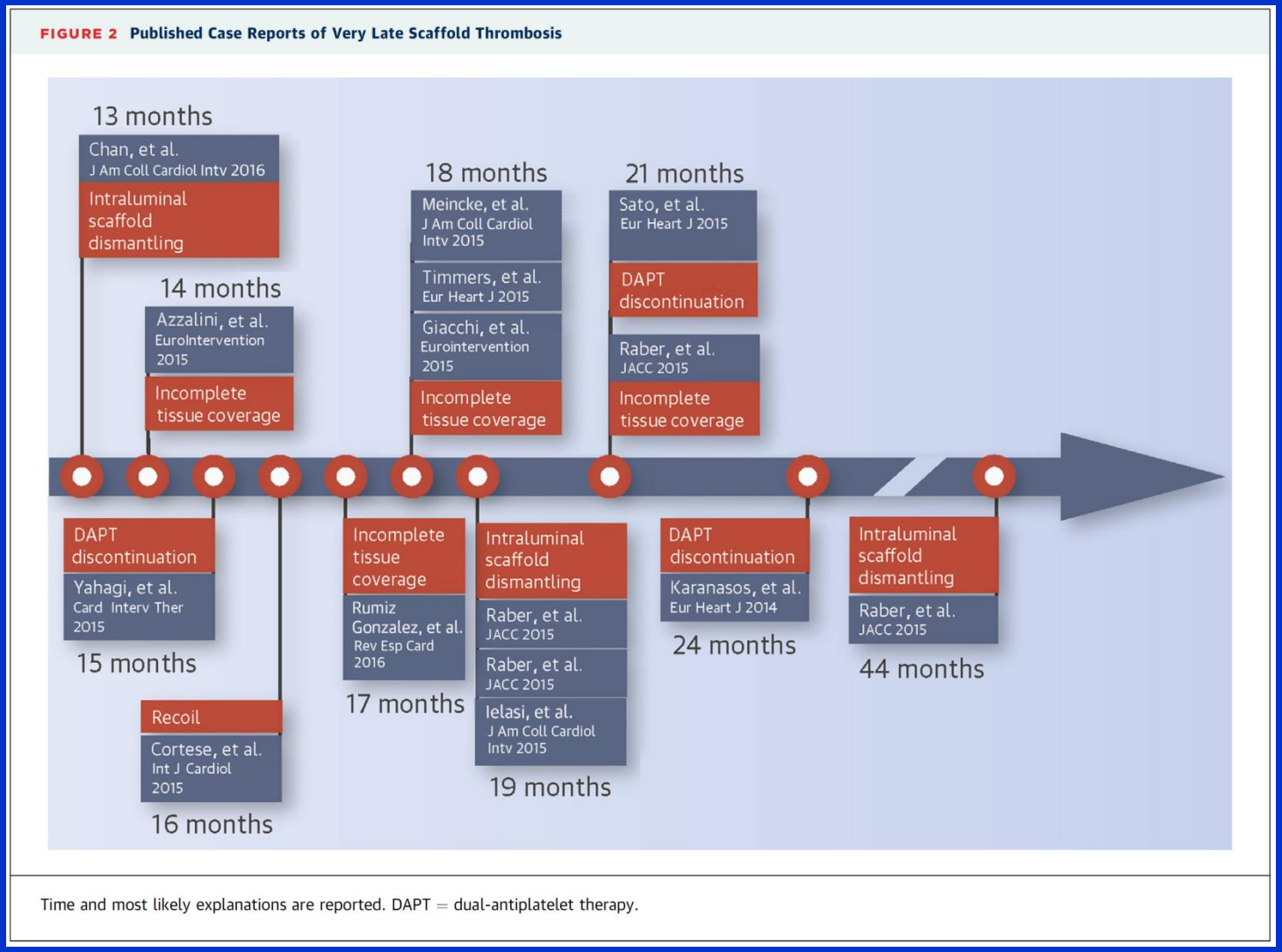
-Be careful patients with thrombus containing lesion due to no reflow by PSP technique

Patients and Lesion Selection: Avoid calcified and calcified ostial lesions



-Be careful patients with calcified lesion due to incomplete PSP

Scaffold Thrombosis Rates and Potential Related Mechanisms at Different Time Intervals



Minerva Cardioangiol 2016;65:32-51
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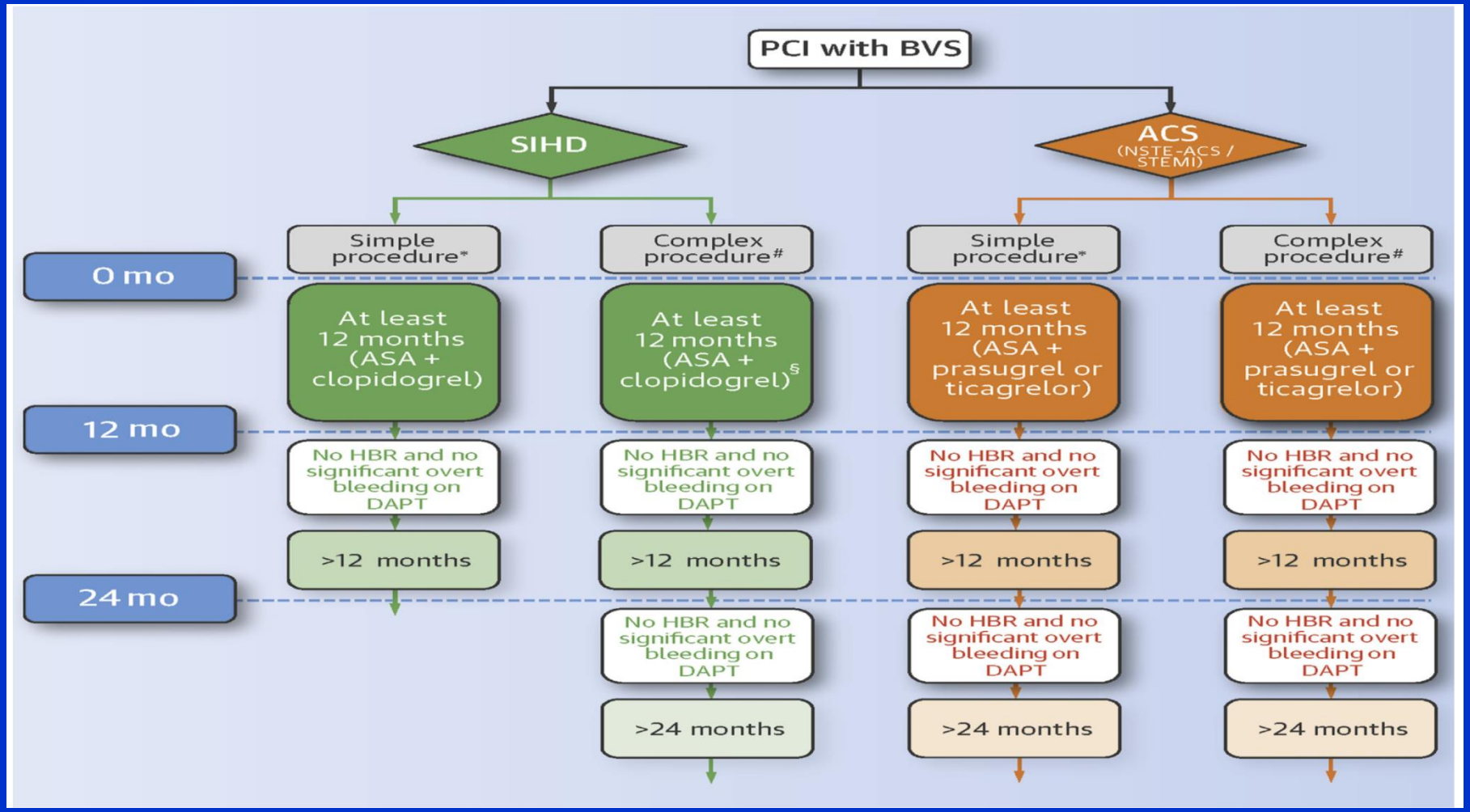
Importance of Long Term DAPT in Patients Undergoing PCI with BRS



- Avoid patients with high risk of bleeding such as AF

Minerva Cardioangiol 2016;65:32-51
JACC cvInt 2017;5:425-37

Abbott Nixes Absorb BVS Sales Worldwide

— Focus shifts to second-gen device development

by Nicole Lou, Reporter, MedPage Today/CRTonline.org

September 08, 2017

The current iteration of Absorb bioresorbable vascular scaffolds (BVS) will no longer be sold after next week, manufacturer Abbott announced.

"Physicians can implant Absorb with their available inventory. Abbott will discontinue all sizes of Absorb as of Sept. 14, 2017 or while supplies last, whichever comes first," an Abbott spokesperson told *MedPage Today* in an email.

Adopted from MedPage Today

An Abbott spokesperson said the decision to pull the device was made for business reasons: "Only a very small percentage of patients receive Absorb -- it makes up less than 1% of Abbott's overall stent sales. We took this decision for commercial reasons, not safety."

In the meantime, the company will follow implanted patients in existing Absorb clinical trials to assess long-term outcomes, as well as work on a next-generation bioresorbable device.

An Abbott statement said the company's "metallic Xience drug-eluting stent will continue to be the cornerstone of our portfolio, and we will focus efforts on a next-generation metallic drug-eluting product, Xience Sierra, that offers improved deliverability and expanded sizes; and on imaging and physiology assessment tools that help doctors perform complex interventional procedures."

"The second-generation device we're working on has a thinner profile and is easier to deliver," the company said. "Absorb is a first-generation device that took longer to implant to get the best results."

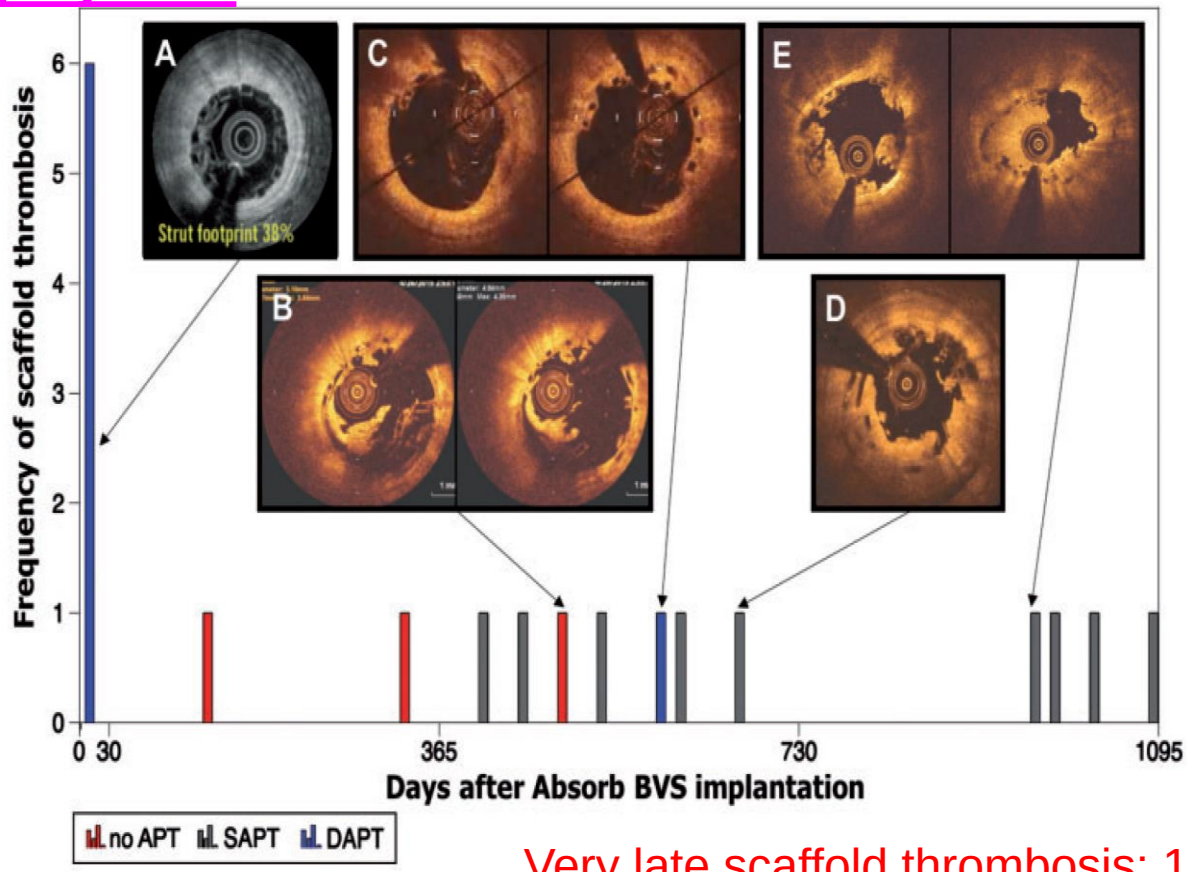
Summary

- 1st generation Absorb showed **higher rate of DOCE and scafford thrombosis rates** compared to EES throughout 2-3 years.
- **Select appropriate patient and lesions** for BRS implantation is most Important.
- **Follow PSP implantation technique** and **widely use imaging device**
- **Extended DAPT** in patients without high bleeding risk, **not recommended BRS implantation in patients with high risk of bleeding** or unlikely to comply with prolonged DAPT
- **Newer generations of BRS** with thinner struts, increased radial strength, different composition and faster resorption may be needed to improve outcomes of BRS.

Absorb vs. EES, Meta-analysis of Randomized Trials

(Absorb II, Japan, China, TROFI II, EVERBIO II)

Under deployment



Very late scaffold thrombosis: 1.4%

Scaffold discontinuity, malapposition, uncovered strut, fragmentation

Events rates at least 24 months f/u

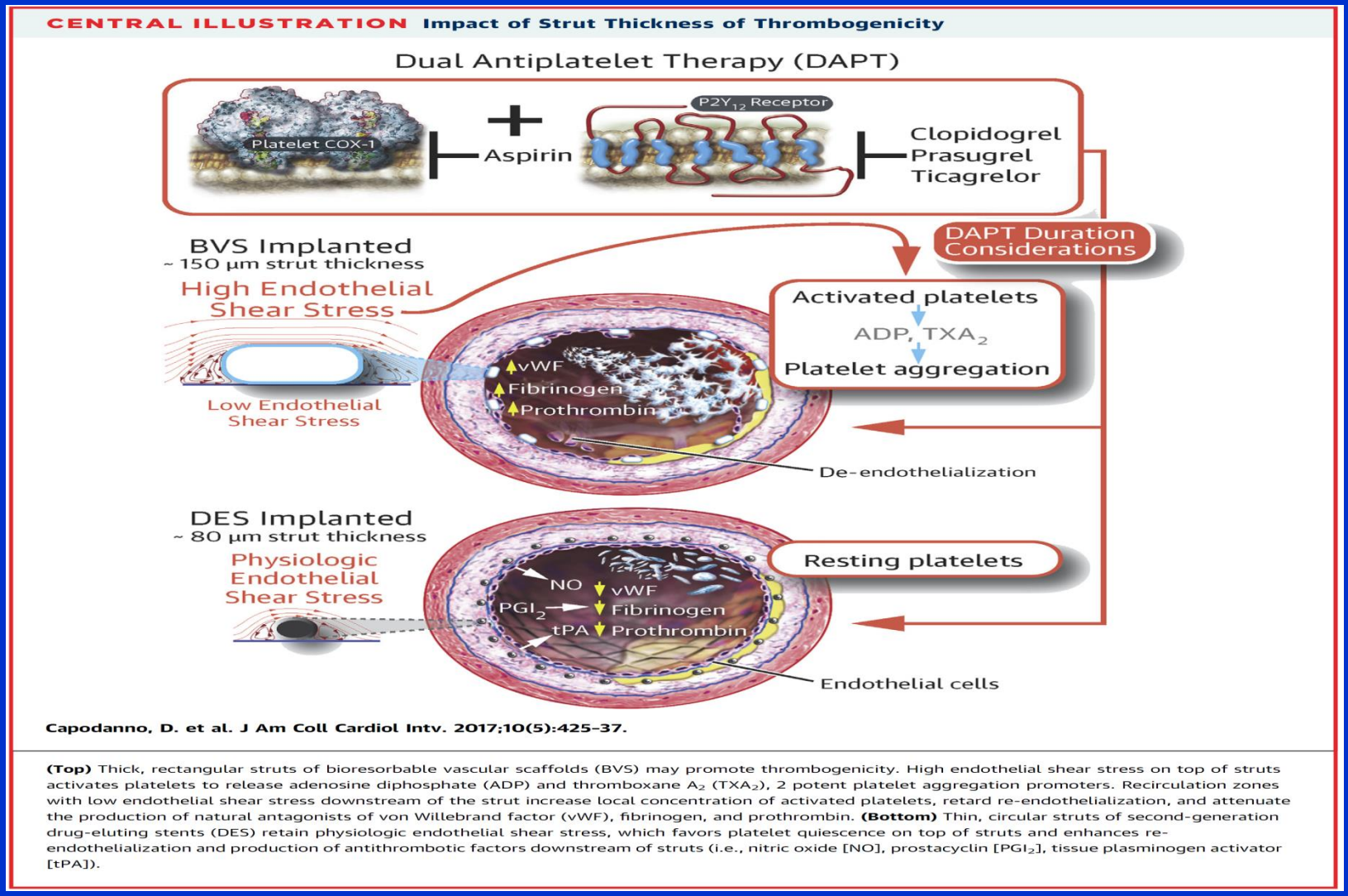
EHJ 2017; 0:1-8

PSP Technique

TABLE 1 Optimal Implantation Strategy

1. Careful lesion/patient selection and scaffold sizing
   - Full understanding of device specific features and limitations
   - Low threshold for intravascular imaging before BVS deployment
2. Adequate lesion preparation
   - Pre-dilation with noncompliant balloons (1:1 reference diameter and scaffold size)
   - Low threshold for adjunctive devices including scoring balloons or rotational atherectomy
3. Dedicated scaffold deployment
   - Slow and long inflation (2 atm per 5 s and >30 s)
   - Avoid high-pressure inflations with delivery balloon
   - Avoid excessive overlap when implanting multiple BVS
4. High pressure post-dilation with nonoversized balloon
   - Post-dilation with 1:1 noncompliant balloon with high pressure (more than 20 atm)
   - Maximum post-dilation balloon size allowed is +0.5 mm of scaffold size
5. Post-implantation evaluation
   - Careful observation to avoid suboptimal implantation by intravascular imaging
   - Underexpansion and malapposition should be managed aggressively
   - Low threshold to repeat steps 4 and 5 until an adequate result is achieved

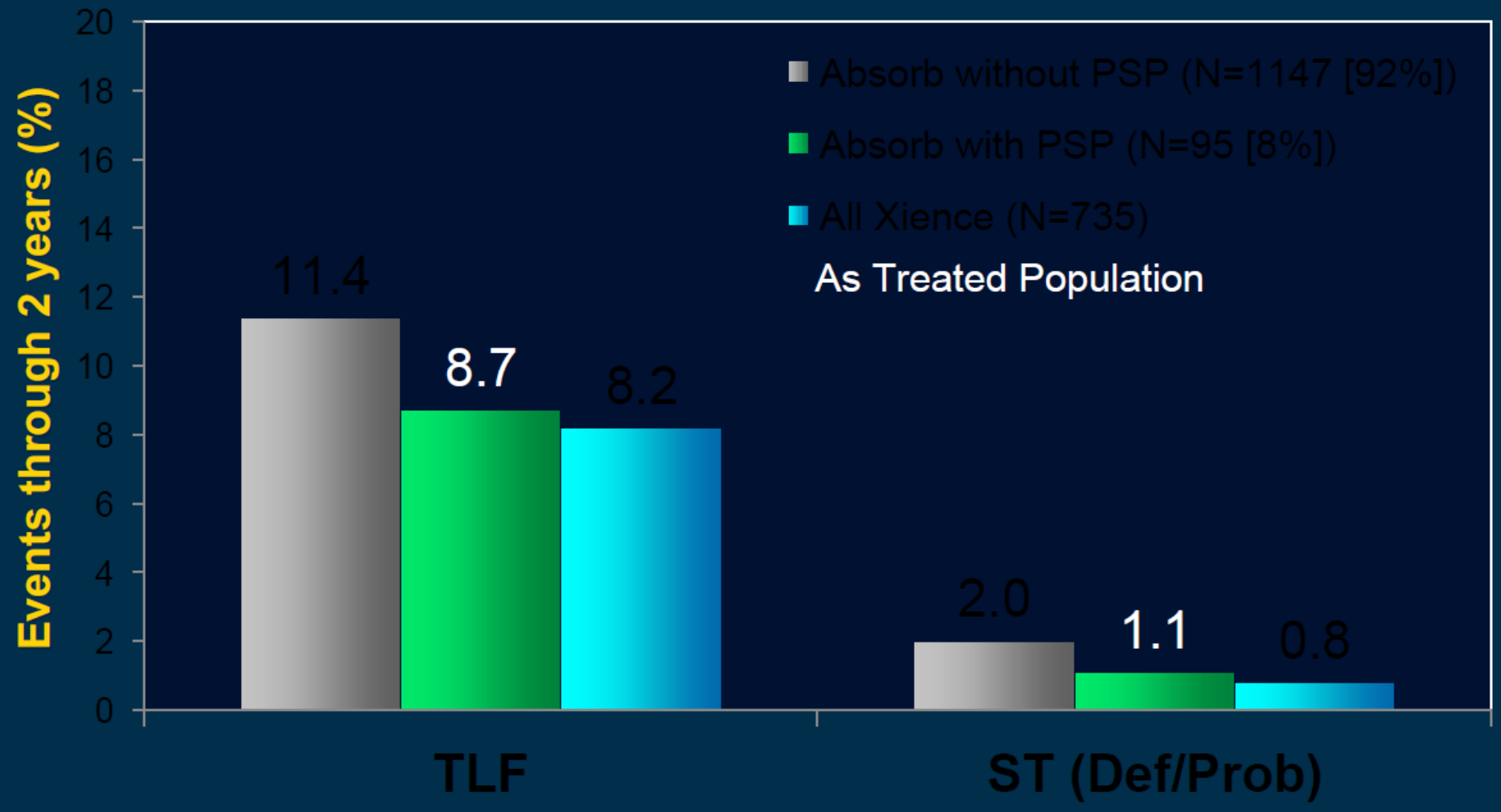
Scaffold Thrombosis Rates and Potential Related Mechanisms at Different Time Intervals



(Top) Thick, rectangular struts of bioresorbable vascular scaffolds (BVS) may promote thrombogenicity. High endothelial shear stress on top of struts activates platelets to release adenosine diphosphate (ADP) and thromboxane A_2 (TXA_2), 2 potent platelet aggregation promoters. Recirculation zones with low endothelial shear stress downstream of the strut increase local concentration of activated platelets, retard re-endothelialization, and attenuate the production of natural antagonists of von Willebrand factor (vWF), fibrinogen, and prothrombin. **(Bottom)** Thin, circular struts of second-generation drug-eluting stents (DES) retain physiologic endothelial shear stress, which favors platelet quiescence on top of struts and enhances re-endothelialization and production of antithrombotic factors downstream of struts (i.e., nitric oxide [NO], prostacyclin [PGI_2], tissue plasminogen activator [tPA]).

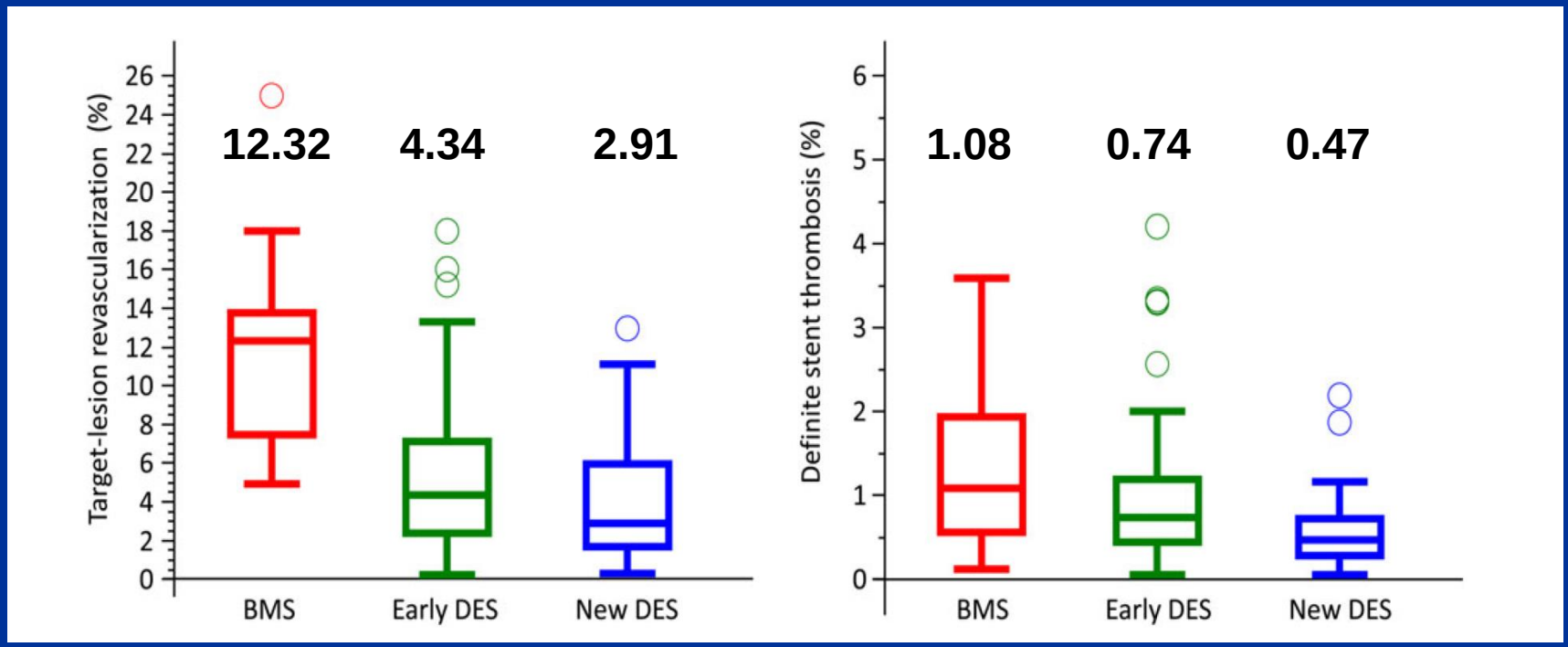
Minerva Cardioangiol 2016;65:32-51
JACC cvInt 2017;5:425-37

Impact of PSP* on TLF and ST (Def/Prob) by 2 Years (25 Months)



* Defined as patients with pre-dilatation, and QCA RVD ≥2.25mm-≤3.5mm, and post-dilatation performed at ≥18 atm, with post-dilatation balloon diameter > nominal scaffold diameter but ≤ nominal scaffold diameter + 0.5mm

ESC-EAPCI Systematic Review of Stents (Outcomes at 9-12 months)



Aggregate results from all RCTs* (n=158) with CE-marked stents 2002-2014

Byrne RA, at el, ESC-EAPCI Task Force. EHJ 2015

Absorb vs. EES, Meta-analysis of Randomized Trials

(Absorb II, Japan, China, TROFI II, EVERBIO II)

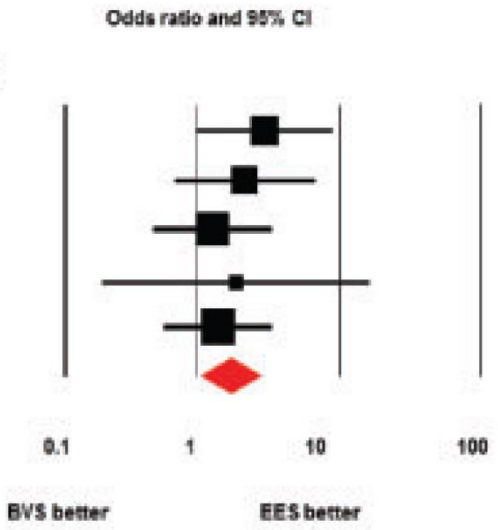
A Definite and Probable Device Thrombosis

D Very Late Device Thrombosis

E Ischemia-Driven Target Lesion Revascularization

Study name	ID-TLR / Total		Statistics for each study				
	BVS	EES	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
ABSORB II [19]	20 / 325	3 / 161	3.45	1.01	11.80	0.05	19.5%
ABSORB JAPAN [18]	14 / 261	3 / 130	2.40	0.68	8.50	0.18	18.4%
ABSORB CHINA [22]	8 / 237	6 / 237	1.35	0.50	3.94	0.60	25.5%
TROFI II [20]	2 / 95	1 / 96	2.04	0.18	22.92	0.56	5.0%
EVERBIO II [21]	11 / 78	8 / 80	1.48	0.56	3.90	0.43	31.4%
Summary	55 / 996	21 / 704	1.89	1.15	3.13	0.02	

Random effect-model OR 1.89 95%CI 1.15 to 3.13, p=0.02
Heterogeneity Cochran's Q=1.7, I²=0%, p=0.791

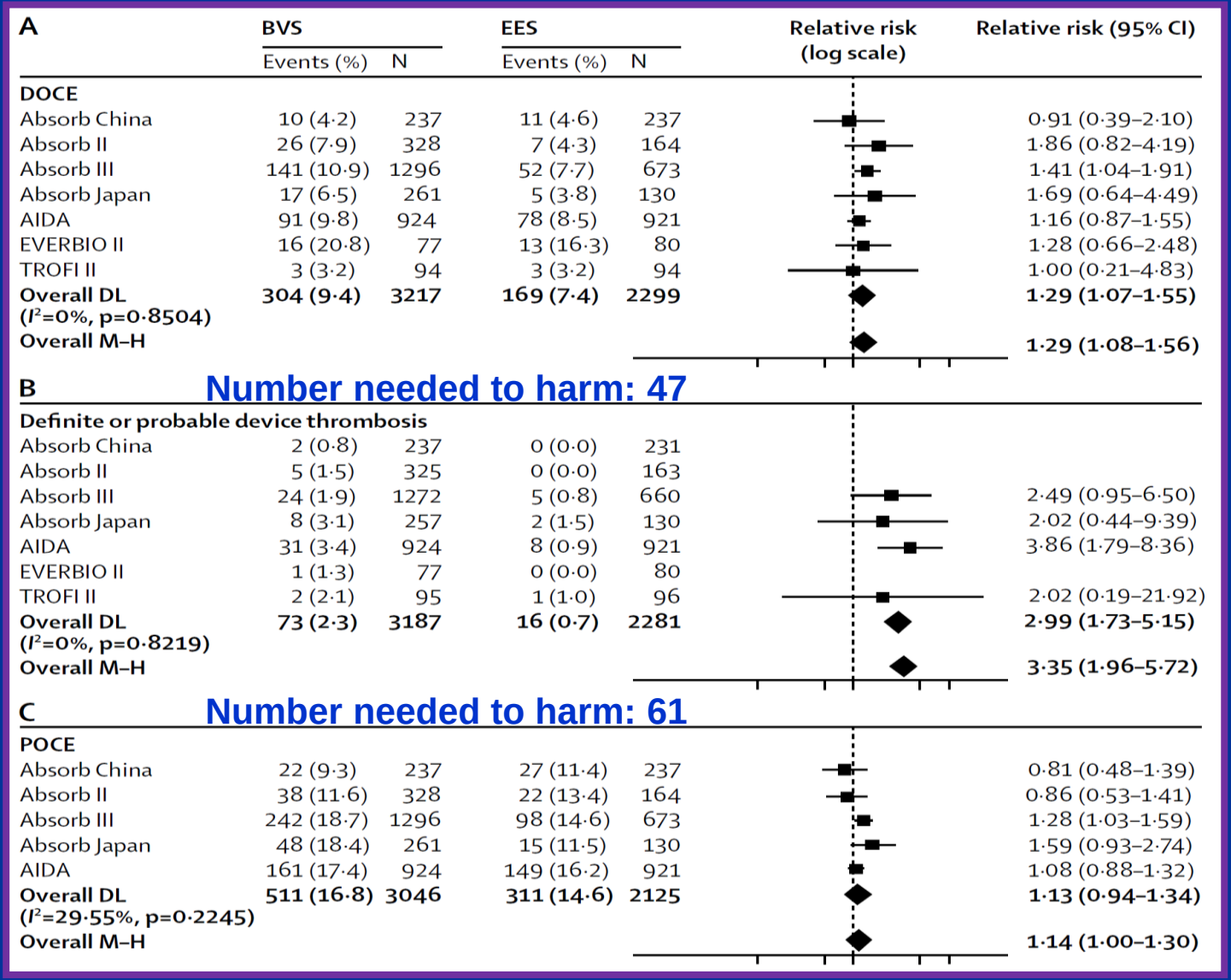


Events rates at least 24 months f/u

EHJ 2017; 0:1-8

Absorb (n=3261) vs. EES (n=2322) Meta-analysis

(Absorb II, III, Japan, China, EVERBIO II, TROFI II, AIDA)



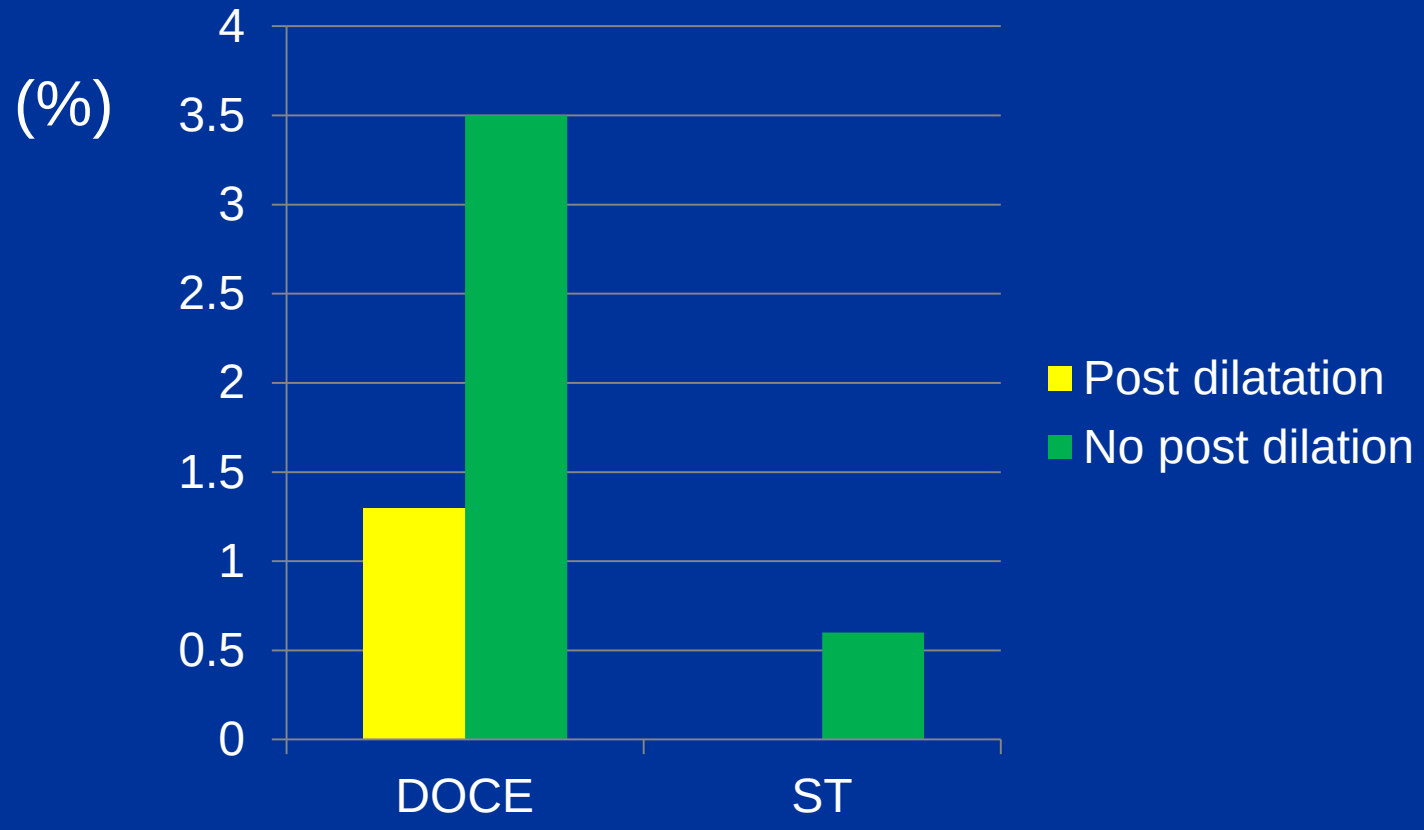
2-year cumulative events

Lancet 2017, in-press

Absorb: Effect of High Pressure (≥18atm) Post dilation

(Absorb II, III, Japan, China)

- Only 236 (11.4%) patients of 2070 BVS treated patients



Events rates of between 1-2 years

Lancet 2017, in-press

Blinded, Pooled, Interim ABSORB IV Outcomes: Comparison to ABSORB III

ABSORB III: 2008 pts randomized 2:1 BVS:EES (1322:686)
ABSORB IV: 3000 pts being randomized 1:1 BVS:EES

	ABSORB III Pooled (N=2008)[1]	ABSORB IV Pooled (N=2546)[2,3]
QCA RVD < 2.25 mm	19%	4%
Post-dilatation (BVS)	66%	84%
	Pooled Stent/Scaffold Thrombosis	
30 days	0.9%	0.4%
1 year	1.1%	0.5%

1. Assuming the observed event rates for each arm in ABSORB III, but adjusted for the 1:1 randomization ratio in ABSORB IV. The actual observed pooled ST rates in ABSORB III were 1.0% at 30 days and 1.3% at 1 year.
2. Based on February 15, 2017 data cut (N=2397 with 30-day FU and N=1415 with 1-year FU).
3. ABSORB IV includes ~25% non A-III like subjects (troponin+ ACS, 3 lesions treated, and planned staged procedures).

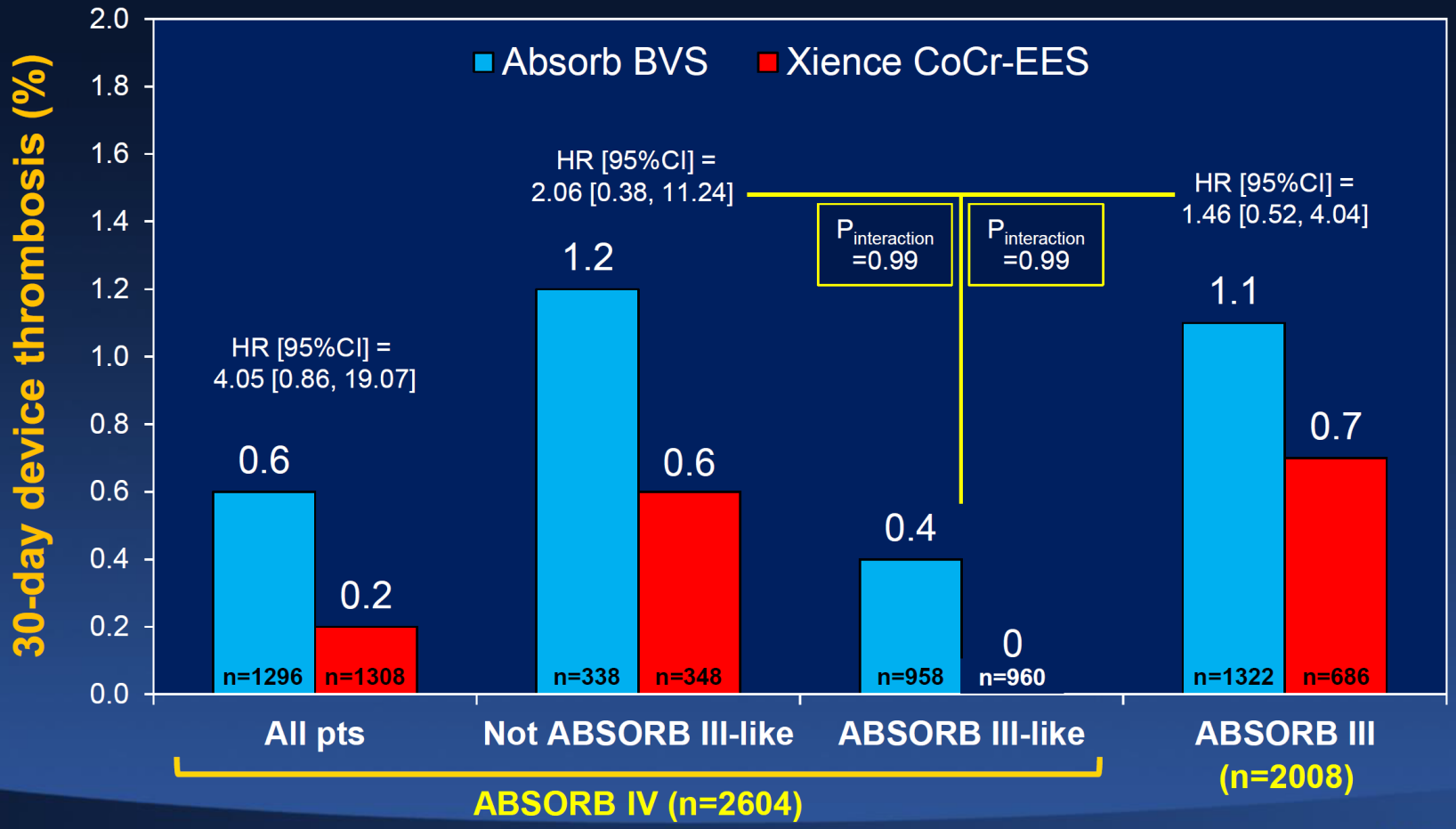
New Insights from the ABSORB RCTs: Conclusions

- In the large-scale ABSORB III trial, device-related events (TLF) continued to accrue between 1 and 3 years to a slightly greater extent with BVS (Δ1.0%, p=NS), mostly due to an ongoing risk of very late scaffold thrombosis
- In the ABSORB IV trial, 30-day outcomes with BVS vs. CoCr-EES were consistent in higher-risk troponin positive ACS and stable CAD pts; compared to ABSORB III, better technique (avoiding very small vessels) reduced early scaffold (and stent) thrombosis
- In the ABSORB II trial, event rates with BVS vs. CoCr-EES were similar between 3 and 4 years, and no further scaffold thromboses occurred beyond 3 years, the time point of complete PLLA polymer bioresorption

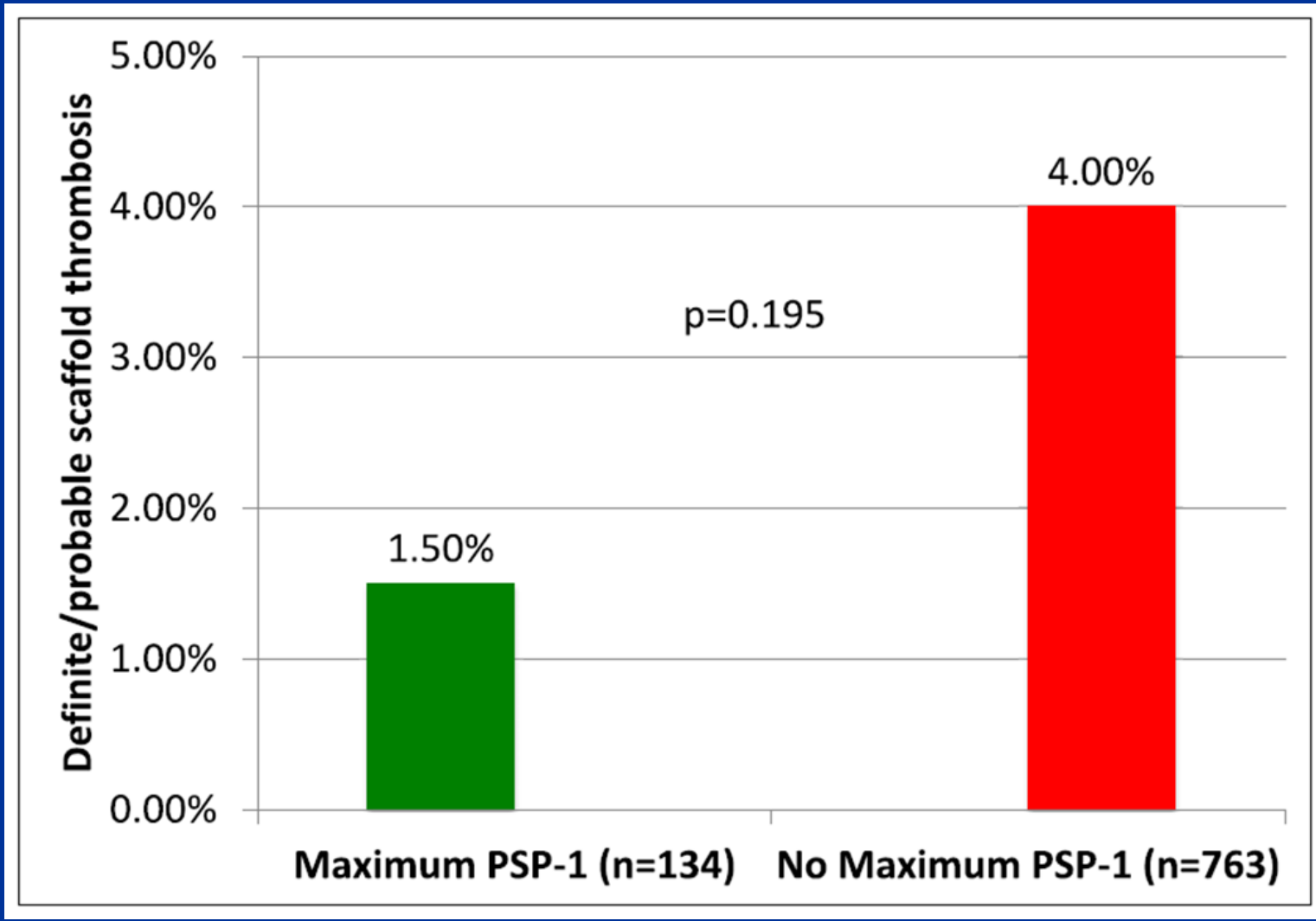
Device Thrombosis

ABSORB IV vs. ABSORB III

1918/2604 pts (73.7%) enrolled in ABSORB IV were “ABSORB III-like”; 686 were not (20.8% troponin+ ACS, 0.5% 3 lesions treated, 2.1% thrombus)



Absorb vs. Xience in Routine PCI (AIDA)



Influence of Dedicated PSP on ST rates