Clinical data: what do we learn from ABSORB II trial?

Bernard Chevalier

On behalf of ABSORB II Team

ABSORB II Study Organisation

- Principal Investigator: Patrick W. Serruys – Rotterdam, NL
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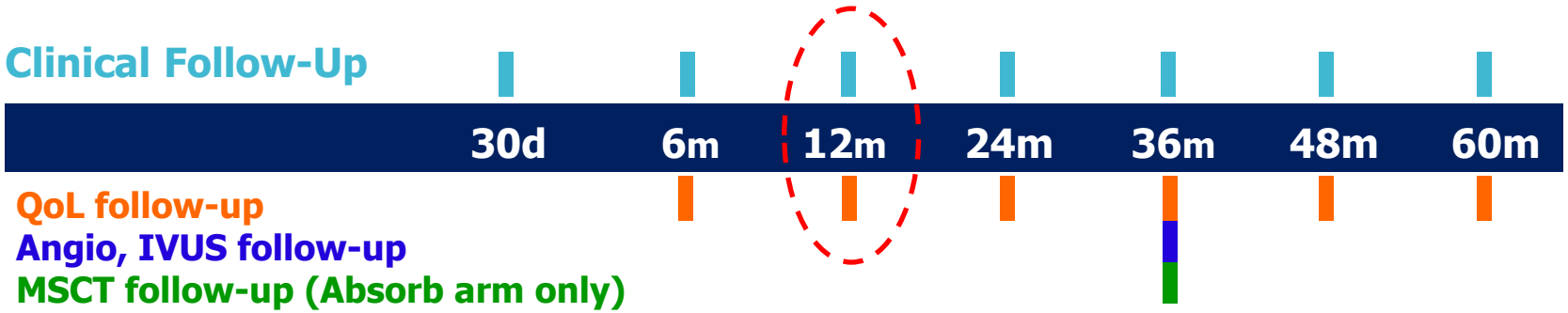
- Blood Sample Central Laboratory: ICON – Dublin, IE
- Sponsor: Abbott Vascular – Santa Clara, USA

In the last five years , I received research grants or speaker fees or I am/was consultant for: Abbott Vascular, Biotronik, Colibri, Cordis, Daichi-Sankyo, Eli-Lilly, Medtronic, Terumo. I am currently minor shareholder & general director of CERC (CRO)

ABSORB II Study Design

501 subjects

Randomized 2:1 Absorb BVS:XIENCE / 46 sites (Europe and New Zealand)



Study Objective	**Randomized against XIENCE control. First Patient In: 28-Nov-2011**
Co-primary Endpoints	**Vasomotion assessed by change in Mean Lumen Diameter between pre- and post-nitrate at 3 years (superiority)** **Minimum Lumen Diameter (MLD) at 3 years post nitrate minus MLD post procedure post nitrate (non-inferiority, reflex to superiority)**
Treatment	**Up to 2 *de novo* lesions in different epicardial vessels** **Planned overlapping allowed in lesions ≤ 48 mm**
Device Sizes	**Device diameters: 2.5, 3.0, 3.5 mm** **Device lengths: 12 (3.5 mm diameter only), 18, 28 mm**

Rapid worldwide adoption of Absorb resorbable scaffold without RCT

Decision to report 1 year secondary endpoints to communicate first randomized data to the medical community

Less acute gain

Angiography Assessment Pre and Post Procedure

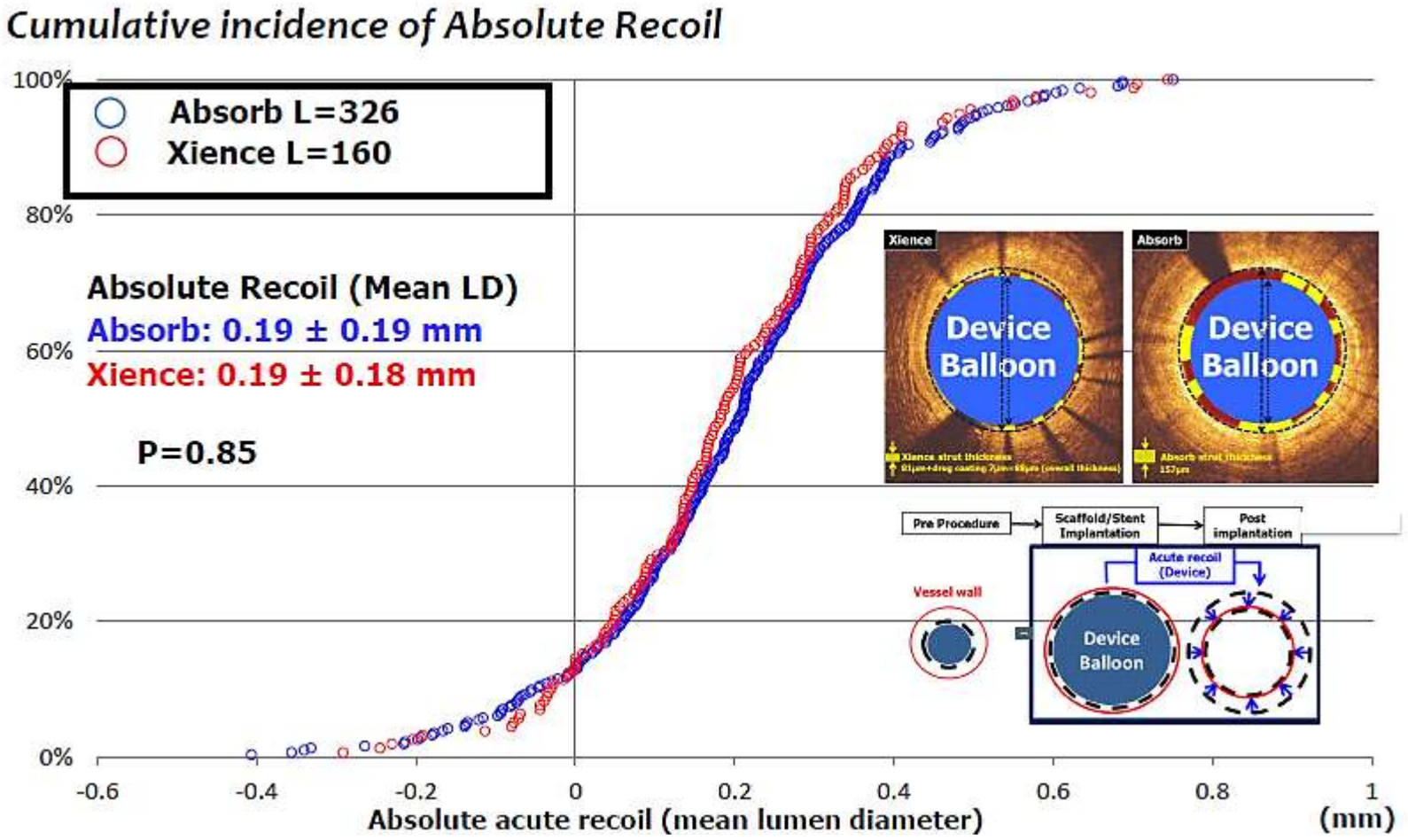
		Absorb 364 Lesions		Xience 182 Lesions	*p* value
Lesion length obstruction	mm	13.8 ± 6.5		13.8 ± 6.6	1.00
Total device length	mm	21.1 ± 8.8		20.9 ± 7.4	0.74
Pre-procedure RVD	mm	2.59 ± 0.4		2.63 ± 0.4	0.36
Post- procedure RVD	mm	2.64 ± 0.4	<	2.80 ± 0.3	<0.001
Pre-procedure MLD	mm	1.07 ± 0.3		1.05 ± 0.3	0.44
Post-procedure in-device MLD	mm	2.22 ± 0.3	<	2.50 ± 0.3	<0.001
Acute gain in-device	mm	1.15 ± 0.4	<	1.46 ± 0.4	<0.001
Pre-procedure %DS	%	59 ± 11		60 ± 12	0.30
Post-procedure in-device DS	%	16 ± 7	>	10 ± 5	<0.001

Serruys et al. Lancet 2015

IVUS Assessment Pre and Post Procedure

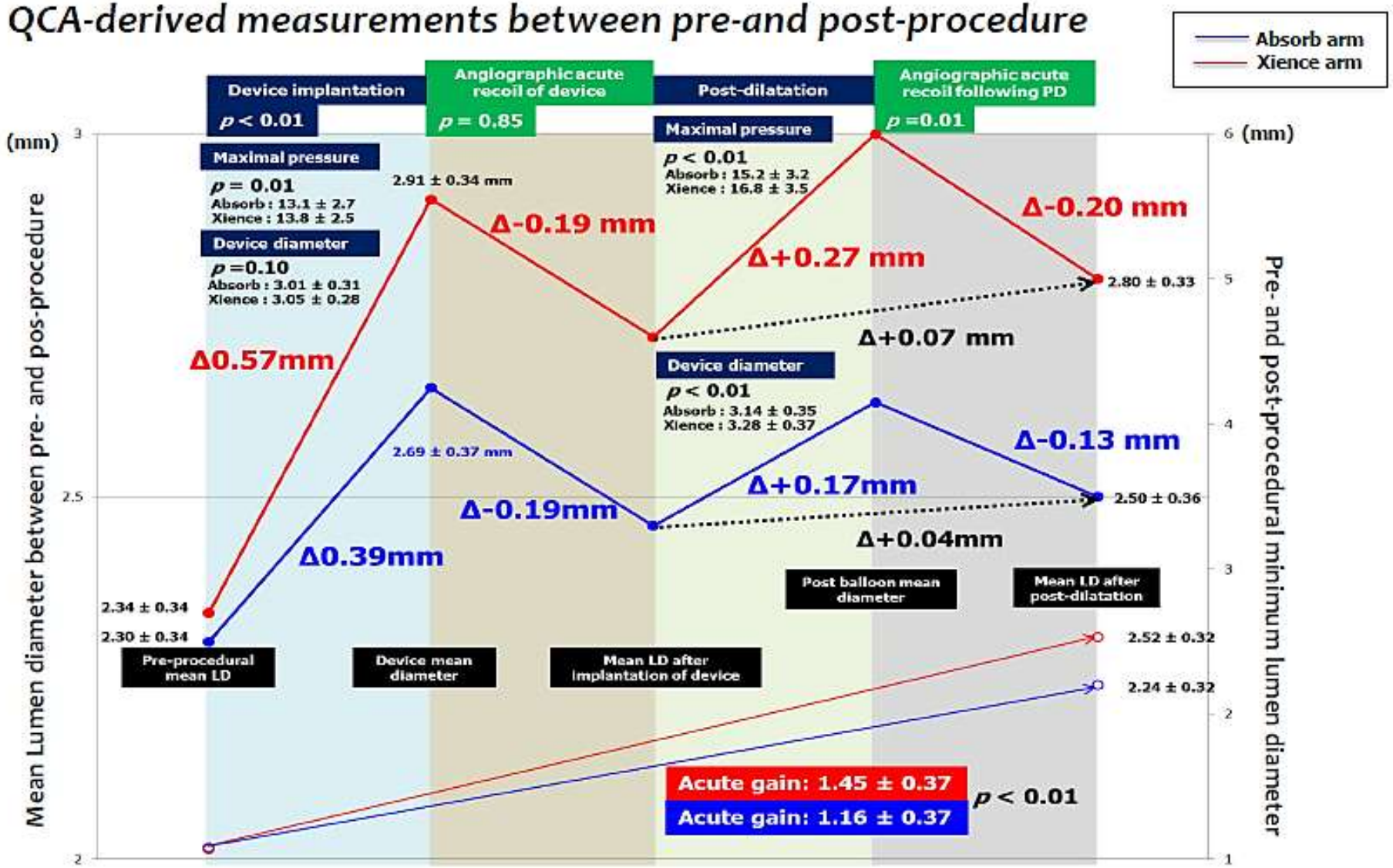
		Absorb 364 Lesions		Xience 182 Lesions	*p* value
Pre-procedure vessel area	mm^2	11.5 ± 3.4	<	12.3 ± 3.4	0.02
Post-procedure vessel area	mm^2	13.2 ± 3.6	<	14.3 ± 3.6	0.001
Pre-procedure plaque area / media	mm^2	6.7 ± 2.5	<	7.3 ± 2.7	0.01
Post-procedure plaque area / media	mm^2	7.1 ± 2.5		7.4 ± 2.4	0.18
Pre-procedure mean lumen area	mm^2	4.8 ± 1.4		5.0 ± 1.5	0.17
Post-procedure mean lumen area	mm^2	6.1 ± 1.4	<	6.9 ± 1.6	<0.001
Pre-procedure minimal lumen area	mm^2	2.0 ± 0.7		2.1 ± 0.8	0.20
Post-procedure minimal lumen area	mm^2	4.9 ± 1.4	<	5.7 ± 1.5	<0.001
Acute gain in minimal lumen area	mm^2	2.9 ± 1.3	<	3.6 ± 1.3	<0.001

Recoil?



	Absorb (L=326)	Everolimus-eluting metallic stent (L=160)	p value
Small vessel with RVD < 2.57mm (median)	0.21± 0.18	0.21± 0.16	0.87
Large device in a relatively small vessel with device / artery ratio >1.0	0.21± 0.18	0.20± 0.18	0.41
Lesion calcification	0.19± 0.15	0.20± 0.13	0.75

QCA-derived measurements between pre-and post-procedure



The difference in acute gain is derived from:

i) More gain at initial implantation with Xience than with Absorb (Δ+0.57mm vs. Δ+0.39 mm)

ii) More aggressive postdil with Xience than with A bsorb (Δ+0.07mm vs. Δ+ 0.04 mm)

Chevalier et al. ACC 2015

Good safety profile

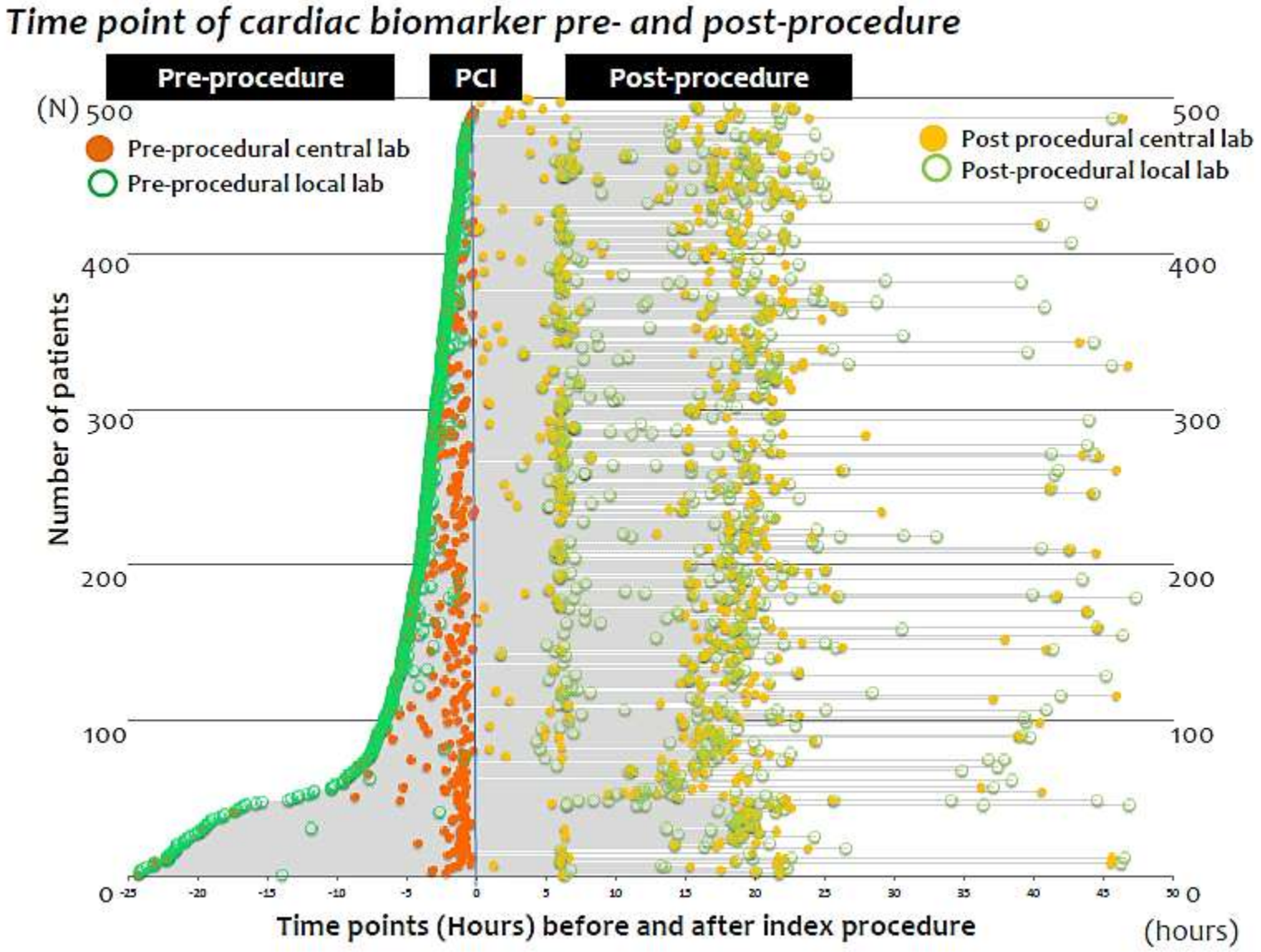
Clinical Outcomes

Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Composite of cardiac death, target vessel MI and clinically indicated target lesion revascularization (TLF, DoCE)	**4.8 %**	**3.0 %**	**0.35**
Cardiac death	0 %	0 %	1.00
Target vessel MI	4.2 %	1.2 %	0.07
Clinically indicated TLR	1.2 %	1.8 %	0.69
All TLR	1.2 %	1.8 %	0.69
Composite of all death, all MI and all revascularization (PoCE)	**7.3 %**	**9.1 %**	**0.47**
All death	0 %	0.6 %	0.33
All MI	4.5 %	1.2 %	0.06
All revascularization	3.6 %	7.3 %	0.08

Definite scaffold/stent thrombosis

Cumulative incidence in percentage	Absorb 335 pts	Xience 166 pts	*p* value
Definite scaffold/stent thrombosis			
Acute (0-1 day)	0.3 (1pt)	0.0	NS
Sub-acute (2–30 days)	0.3 (1pt)	0.0	NS
Late (31–365 days)	0.0	0.0	NS
Probable scaffold/stent thrombosis			
Acute (0-1 day)	0.0	0.0	NS
Sub-acute (2–30 days)	0.0	0.0	NS
Late (31–365 days)	0.3 (1pt)	0.0	NS

Biomarkers



Dudek et al. ACC 2015

Cardiac Biomarker Rise <48 Hours After the Index Procedure and Per Protocol Peri-procedural MI

	Troponin 485/501 (96.8%)			CKMB 487/501 (97.2%)			CK 476/501 (95.0%)		
	Absorb (n=325)	Xience (n=160)	P value	Absorb (n=324)	Xience (n=163)	P value	Absorb (n=315)	Xience (n=161)	P value
Mean ratio vs. ULN	13.4±30.6	9.1±21.0	0.12	1.3±2.0	1.1±1.6	0.22	0.7±0.6	0.6±0.6	0.36
	%	%	P value	%	%	P value	%	%	P value
>1×ULN	62.8	61.9	0.85	32.1	25.8	0.15	16.2	8.7	0.02
>2×ULN (~WHO)	48.6	45.6	0.54	13.3	9.8	0.27	5.1	1.9	0.09
>3×ULN	38.2	36.9	0.79	7.1	6.1	0.69	1.3	1.9	0.69
>5×ULN (TUD)	29.8	25.6	0.33	4.9	2.5	0.19	0	0.6	0.34
>10×ULN (SCAI)	19.1	15.0	0.27	0.6	0.6	1.00	0	0	1.00

Per Protocol PMI (WHO): elevation of total creatine kinase (CK) to >2 x normal along with elevated CKMB without clinical symptoms and ECG change

Per Protocol PMI: Absorb 3.9% (13/335) vs. Xience 1.2% (2/166) p=0.16

Incidence of per protocol PMI according to anatomic complications

anatomic complications assessed by angiography	Absorb (N=335 pts)	EES (N=166 pts)	p value
Per protocol peri-procedural MI	3.9% (13/335)	1.2% (2/166)	0.16
Type 1: Side Branch Occlusion, % (N)	2.7% (9/335)	0.6% (1/166)	0.18
Type 2: Angiographic Other Complication, % (N)	0.6% (2/335)	0.6% (1/166)	1.00
Abrupt closure	0% (0/335)	0.6% (1/166)	1.00
Distal embolization	0.3% (1/335)	0% (0/166)	1.00
coronary perforation	0% (0/335)	0% (0/166)	1.00
Flow limiting dissection (NHLBI type F)	0% (0/335)	0% (0/166)	1.00
coronary dissection after pre dilatation (NHLBI D or E)	0.3% (1/335)	0% (0/166)	1.00
coronary dissection after device implantation	0% (0/335)	0% (0/166)	1.00
Thrombus during procedure	0% (0/335)	0% (0/166)	1.00
Disruption of collateral flow	0% (0/335)	0% (0/166)	1.00
Non-indentifiable mechanism causes, % (N)	0.6% (2/335)	0% (0/166)	1.00

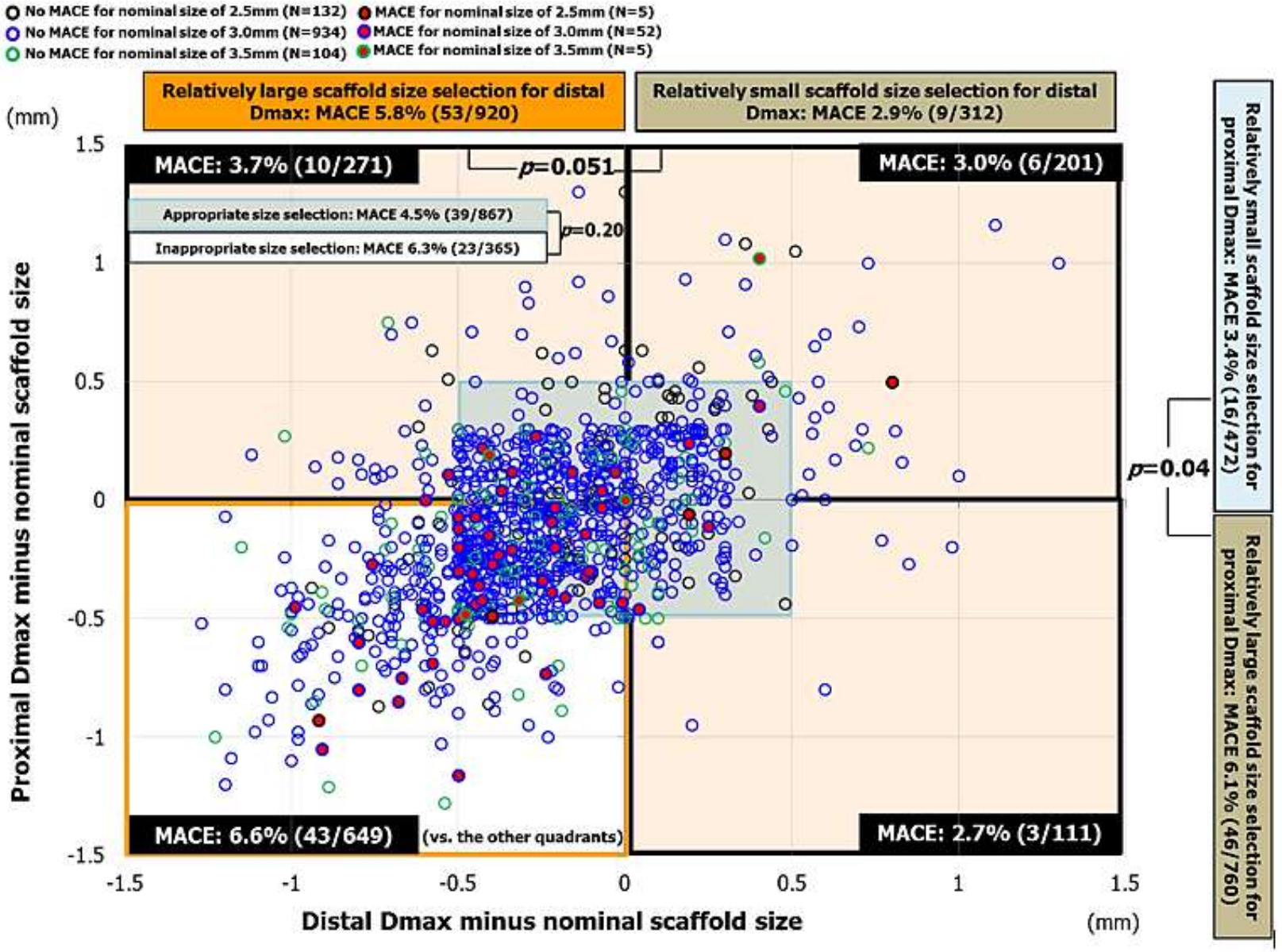
Post-procedural cardiac biomarker rise assessed by intravascular ultrasound

	No TUD PMI (N=346)	TUD PMI (N=138)	P value
IVUS gray scale assessment			
Pre-procedural total plaque volume (mm^3) in treated region	161.16±87.00	194.64±113.41	0.010
IVUS-VH assessment			
Pre-procedural mean necrotic core area (mm^2)	0.65±0.43	0.69±0.43	0.31

Predictors of per protocol peri-procedural myocardial infarction

	Multivariate logistic regression	
	OR (95%CI)	p Value
Treatment with overlapping devices	5.07 (1.78-14.41)	0.002
Device type (Absorb BVS vs. EES)	3.03 (0.67-13.74)	0.150

Role of sizing

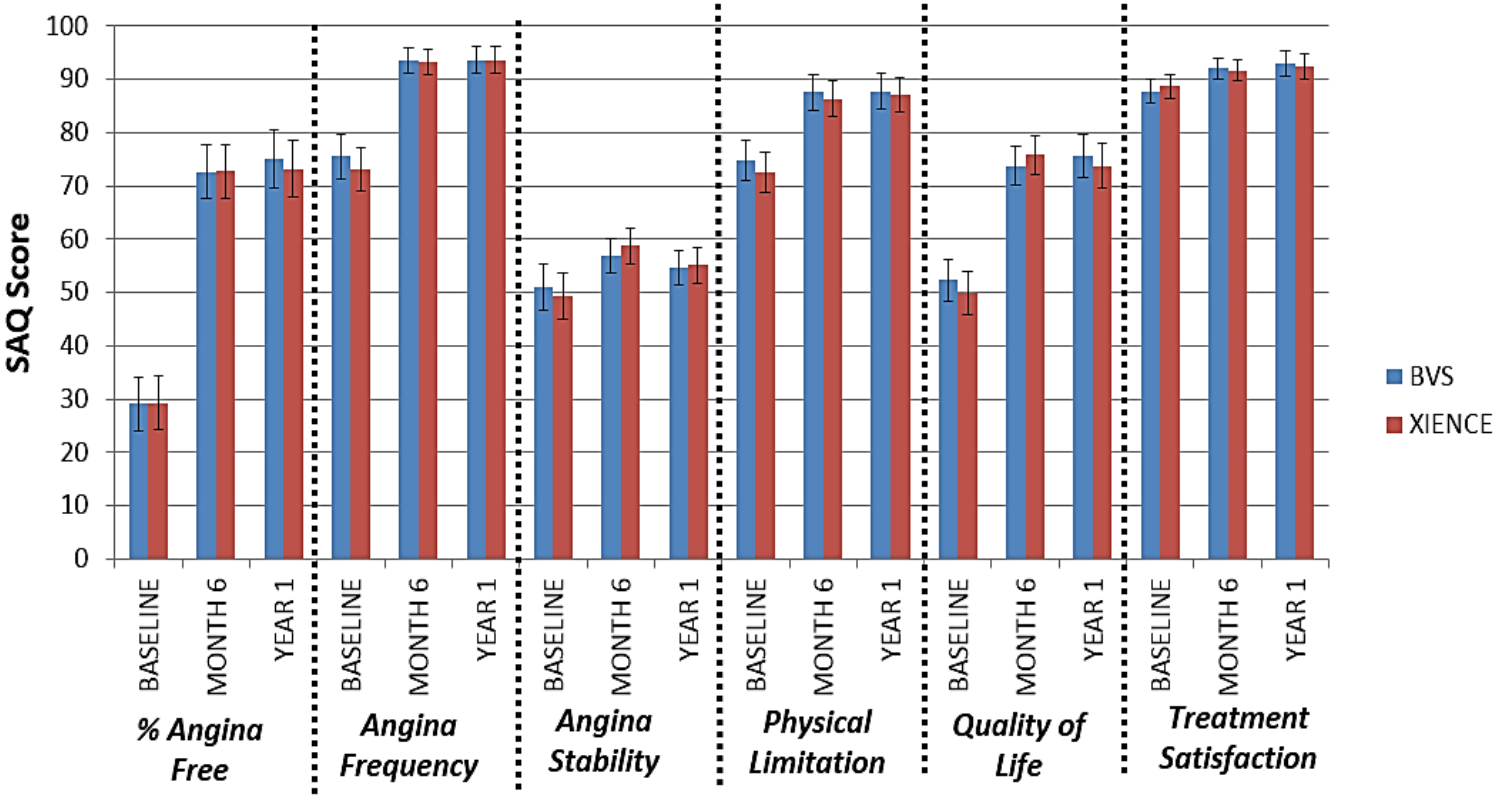


Ishibashi et al.

Impact on Angina?

ABSORB II Seattle Angina Questionnaire (SAQ)

- Cross-sectional SAQ analysis with a recall period of 4-weeks
- The higher SAQ score the better health status

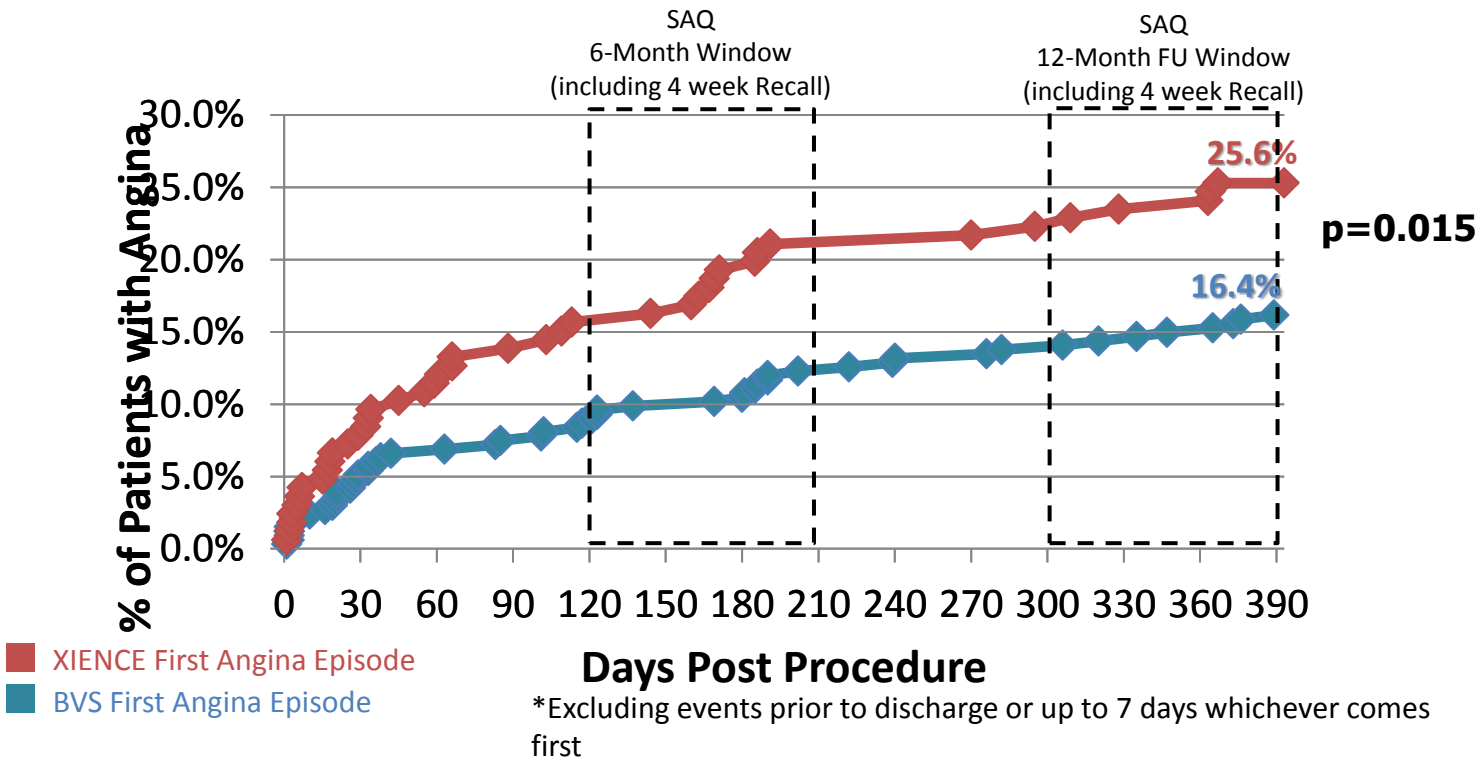


Site-Diagnosed Angina-Related Adverse Events

The angina related adverse events were collected using the adverse event case report forms

- At scheduled or unscheduled visit, the site will ask if the patient is experiencing any chest pain, tightness, shortness of breath….
- If the patient's reported symptoms deemed by the site to be cardiac in nature then an additional form (Cardiac Adverse Event Form) was completed
- The Cardiac Adverse Event Form asked the site to indicate whether the event was related to angina and if yes, what type of angina
  - No Angina, Stable, Unstable, Indeterminate, or Angina Equivalent
- Additionally, the form includes any diagnostic testing performed or treatment received that was either provided by the site or as reported to the site by the patient

Cumulative Post-PCI* Site-Diagnosed Angina- Related Adverse Events



*Excluding events prior to discharge or up to 7 days whichever comes first

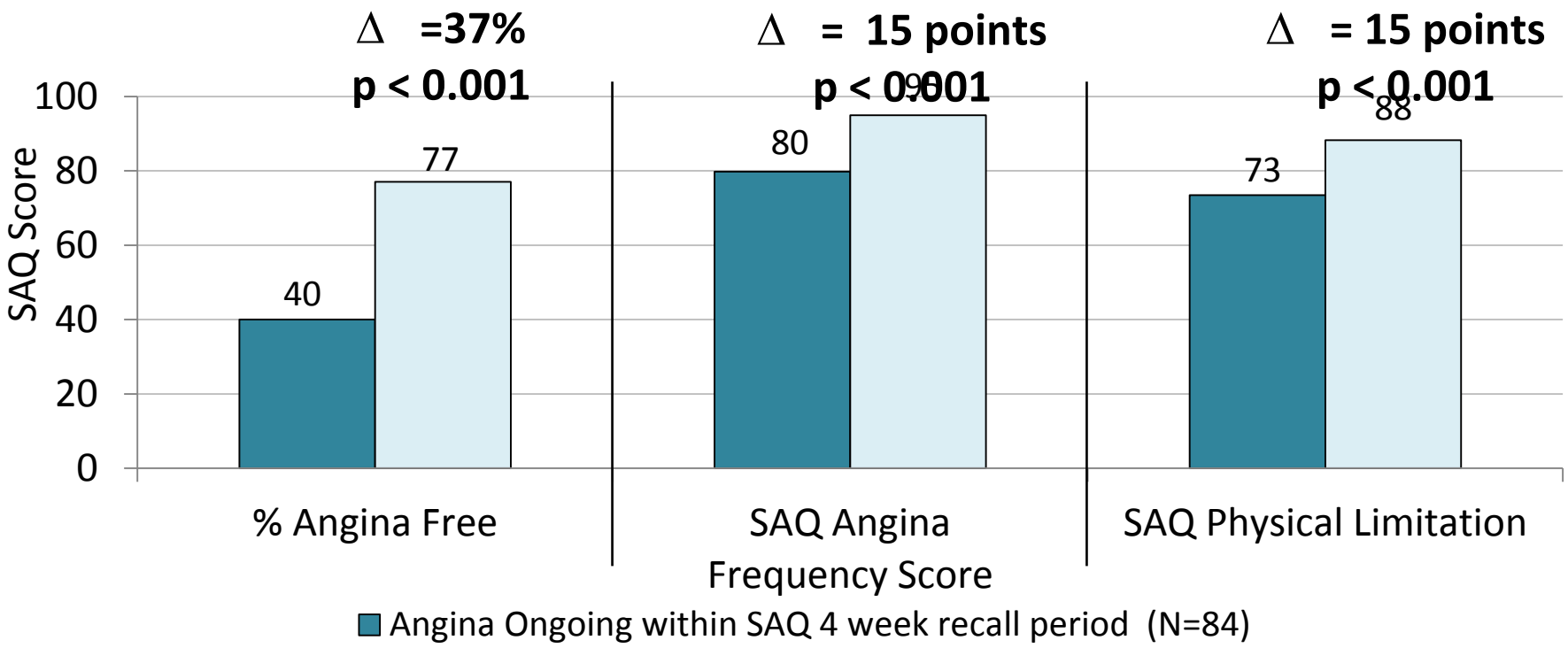
Site-Diagnosed Angina Subgroup Clinical Outcomes at 1 Year

Non-hierarchical events*	Angina* Cohort (N=96)	No Angina* Cohort (N=405)	P-value
Death	0.0% (0/95)	0.2% (1/401)	1.00
Cardiac death	0.0% (0/95)	0.0% (0/401)	1.00
MI	2.1% (3/95)	0.0% (0/401)	1.00
QMI	2.1% (2/95)	0.0% (0/401)	0.03
NQMI	0.0% (0/95)	0.0% (0/401)	1.00
All revascularization	21.1% (20/95)	0.7% (3/401)	<0.0001
All ID-revascularization	14.7% (14/95)	0.7% (3/401)	<0.0001
ID-TLR	5.3% (5/95)	0.2% (1/401)	0.0008
ID-TVR	8.4% (8/95)	0.7% (3/401)	<0.0001
ID-non-TL TVR	4.2% (4/95)	0.5% (2/401)	<0.0001
ID-NTVR	8.4% (8/95)	0.2% (1/401)	<0.0001
Patient Oriented Clinical Endpoints: All Death, All MI and All Revascularization	21.1% (20/95)	4.2% (17/401)	<0.0001

***Excluding events prior to discharge or up to 7 days whichever comes first**

*Excluding events prior to discharge or up to 7 days whichever comes first

Site-Diagnosed Angina Subgroup: relation with the SAQ window



Limitations

- Angina endpoint analysis: not pre-specified
- Post-hoc analysis : hypothesis generating and not confirmatory
- Adverse events reported by the patients at the time of the visits: risk of under reporting
- No review by an independent Clinical Events Committee.
- ABSORB II was a single blind trial: possible bias
- No mechanistic interpretation to explain differences in angina

Take home messages

Good one year safety/efficacy profile but trial underpowered

Sizing of artery is crucial to select appropriate devices

Angina data needs confirmation due to significant limitations

Two years follow-up will be presented @ TCT

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