

# **Short DAPT in HBR patients**

## **-Are all stents created equal?**

**Gyu Chul Oh, MD**

**Seoul St. Mary's Hospital, South Korea**

# Disclosure

- I have nothing to disclose.

# CONTENTS

- Current issues in antiplatelet therapy after PCI
- The optimal DES - stent polymer
- Clinical evidence in HBR & DAPT duration (XIENCE 90 / XIENCE 28)

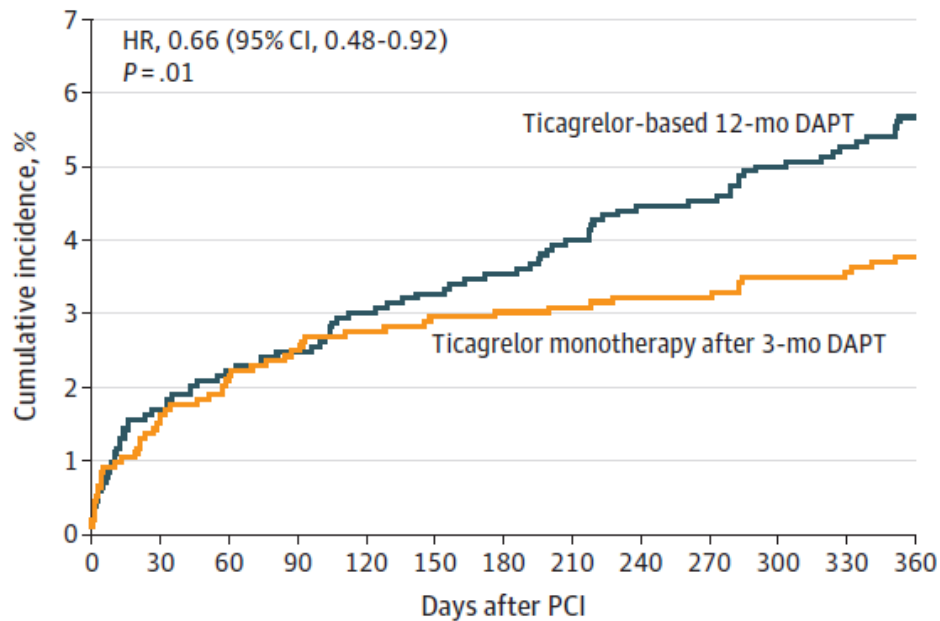
# Background

- DAPT is a key component in preventing ischemic events after PCI, however, it inevitably increased the risk of bleeding.
- There has been an increased prevalence of HBR patients in recent years.
- Hemorrhagic events following PCI affect prognosis, and recent trials have emphasized a shortened DAPT regimen.
- However, the optimal DAPT regimen / duration for these HBR patients have yet been set.

# Current issues in antiplatelet therapy

## TICO / TALOS-AMI

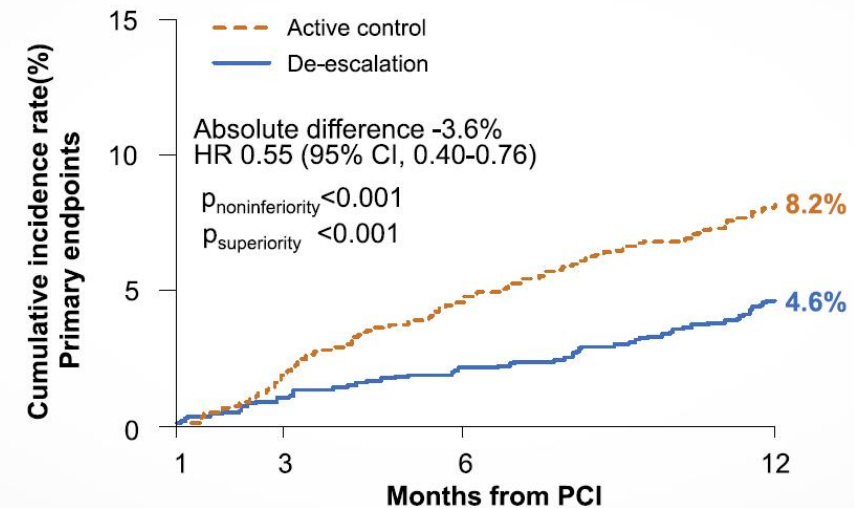
**A** Primary outcome of the net adverse clinical event



No. at risk

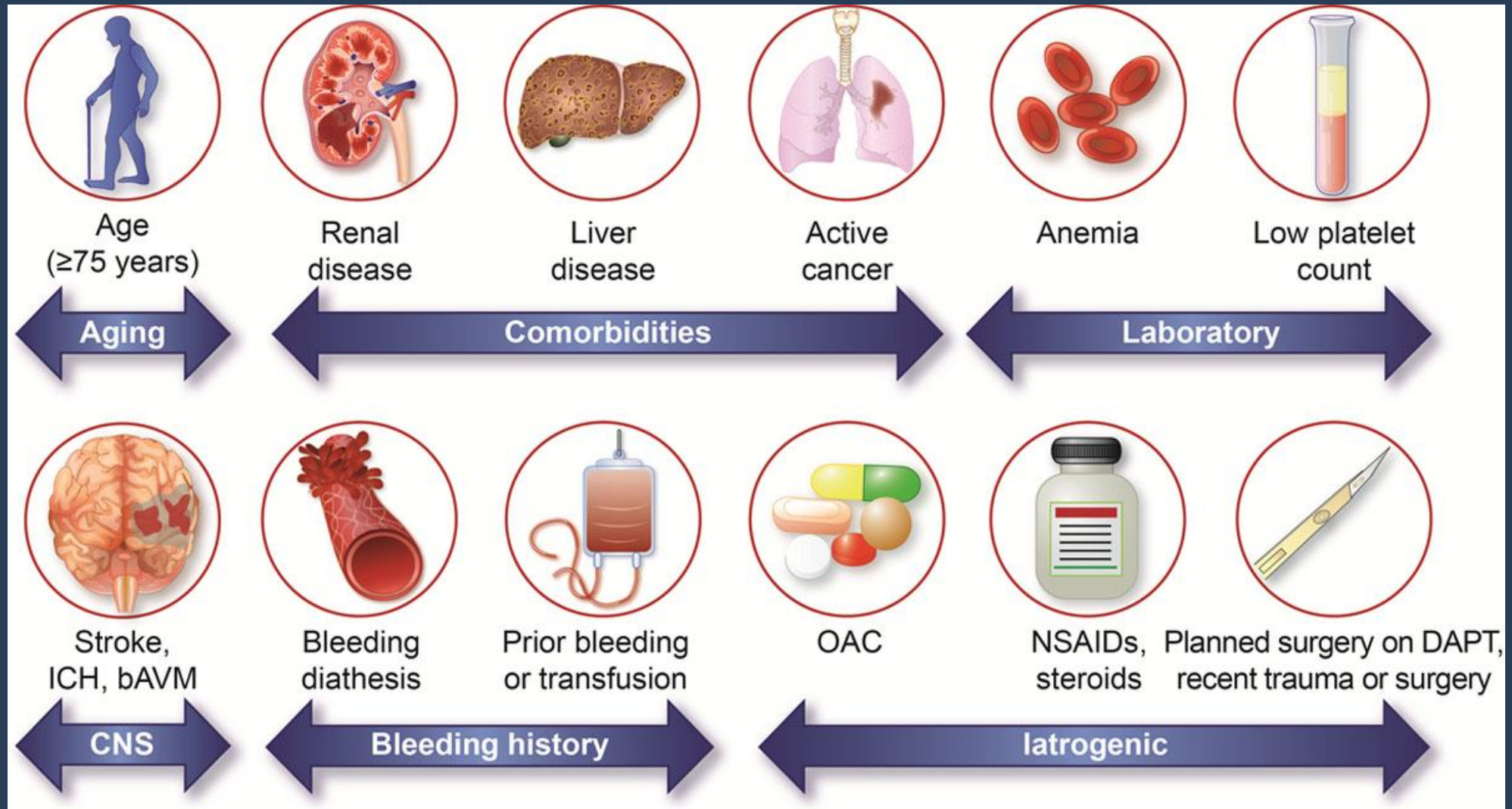
12-mo DAPT	1529	1500	1489	1481	1466	1460	1455	1442	1432	1430	1423	1418	1407
3-mo DAPT	1527	1498	1483	1471	1462	1456	1452	1442	1437	1437	1432	1430	1424

## Composite of cardiovascular death, MI, stroke and BARC bleeding (type 2,3, or 5)



	Number at risk			
De-escalation	1349	1291	1247	1172
Active control	1348	1273	1191	1099

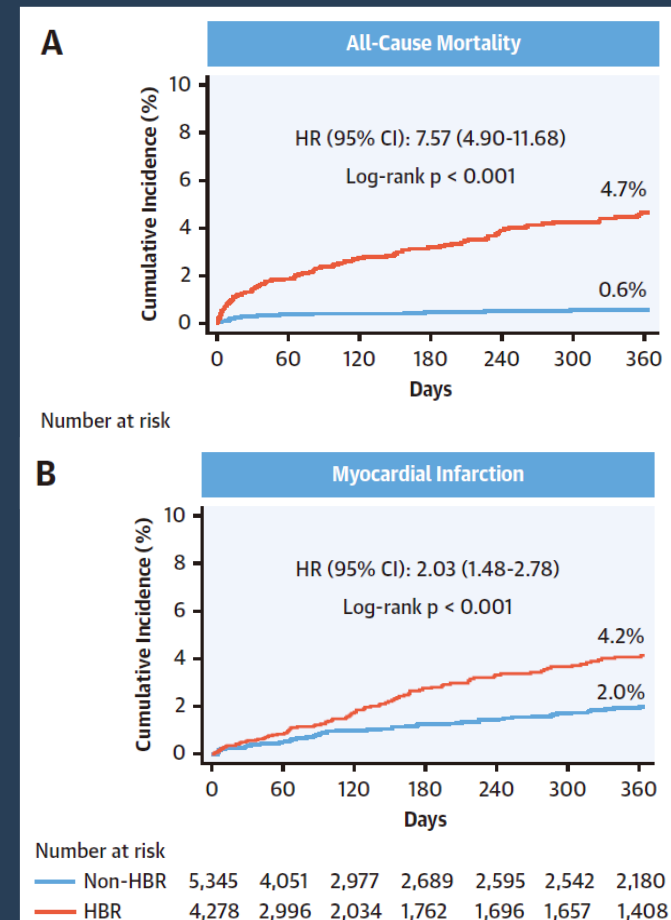
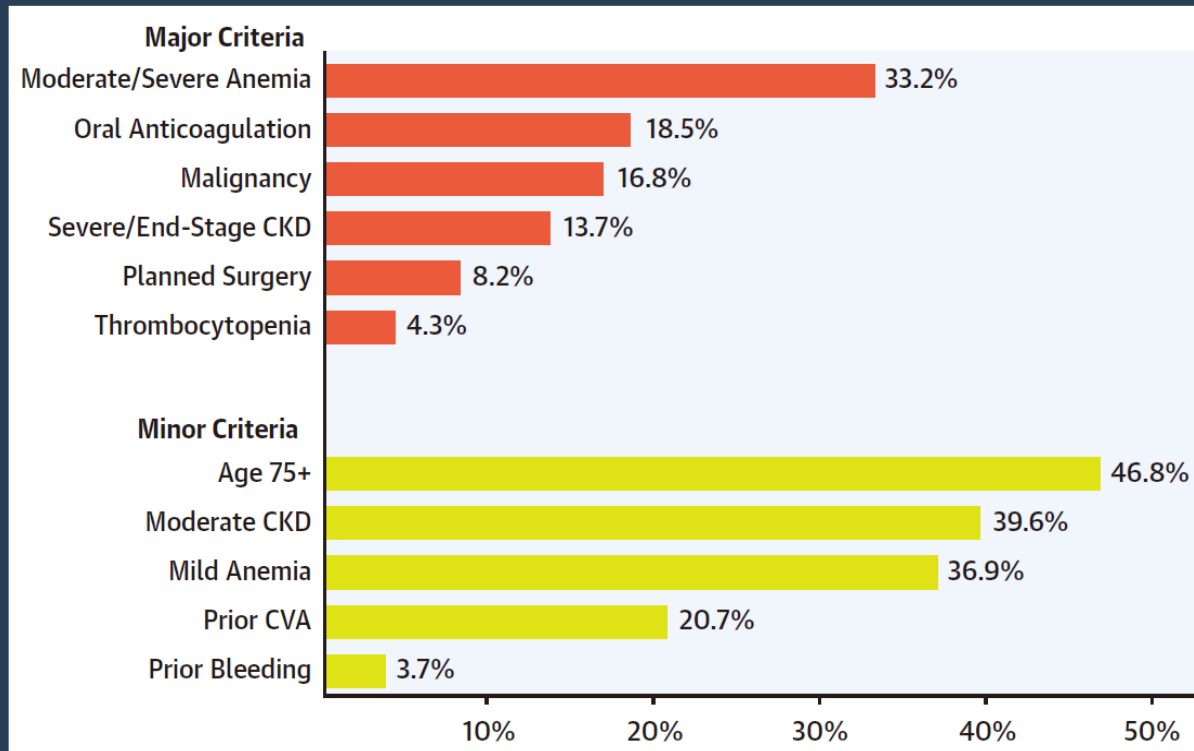
# HBR (High Bleeding Risk)



# Prevalence of HBR

*Among 9,623 patients undergoing PCI in a tertiary center*

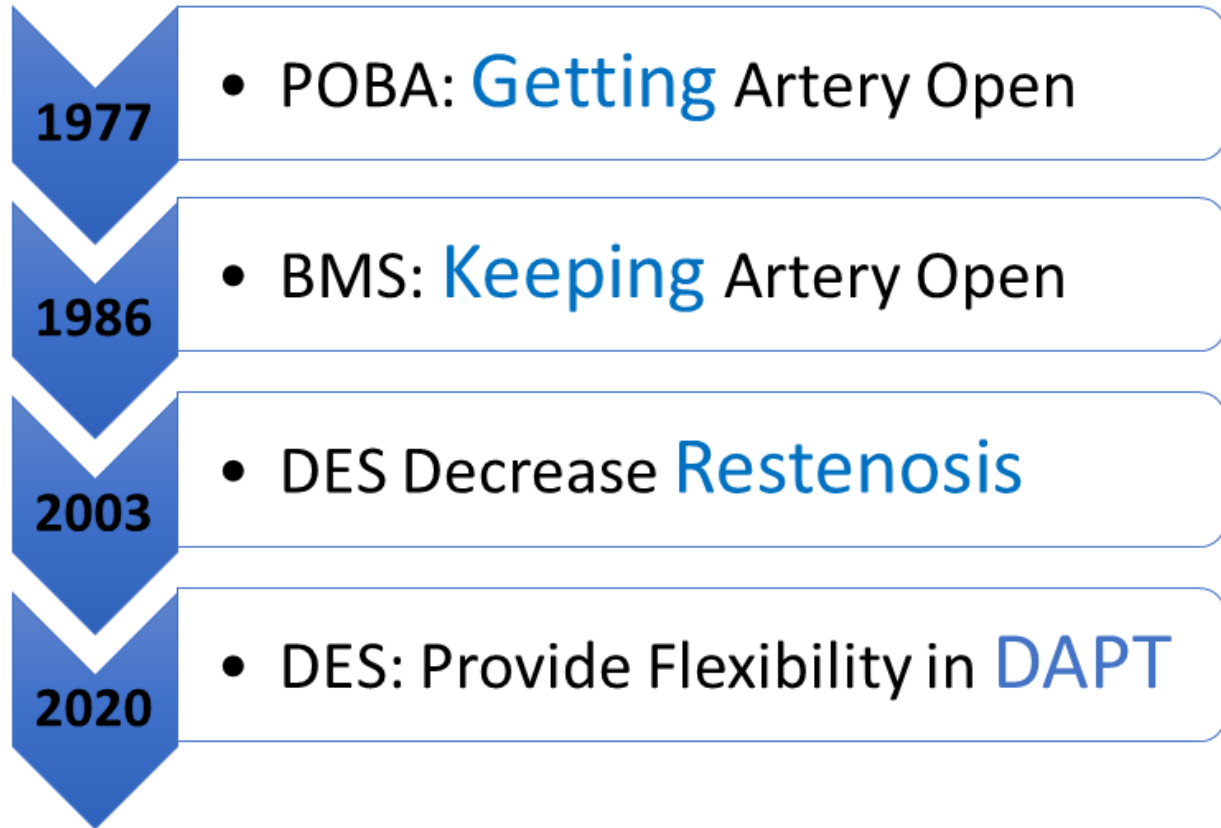
- 44.4% qualified as HBR (1 major or 2 minor ARC-HBR criteria)



# The Optimal DES

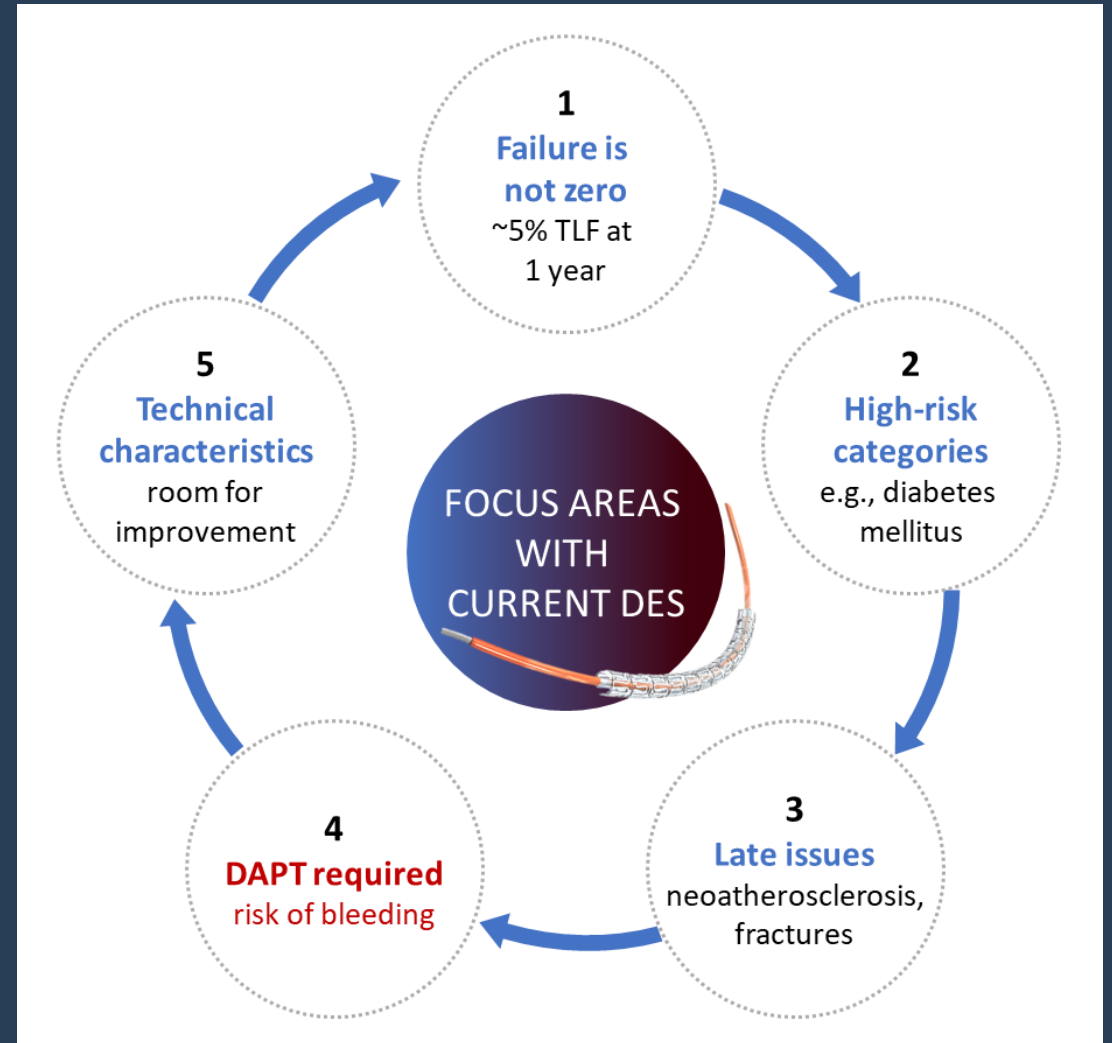


# The ROAD from PTCA to DES PCI



# The current status of DES

- Stent failure still persist
- Late stent failure issues
  - Neoatherosclerosis
  - Stent fracture
- Requirement of DAPT
  - Leads to increased bleeding
- Higher-risk patients needing PCI
  - HBR patients



# The OPTIMAL stent

Deliverability

Radial strength, uniform deployment

Minimize early thrombotic complications

Prevent restenosis

Minimal inflammation

# The OPTIMAL stent

Deliverability

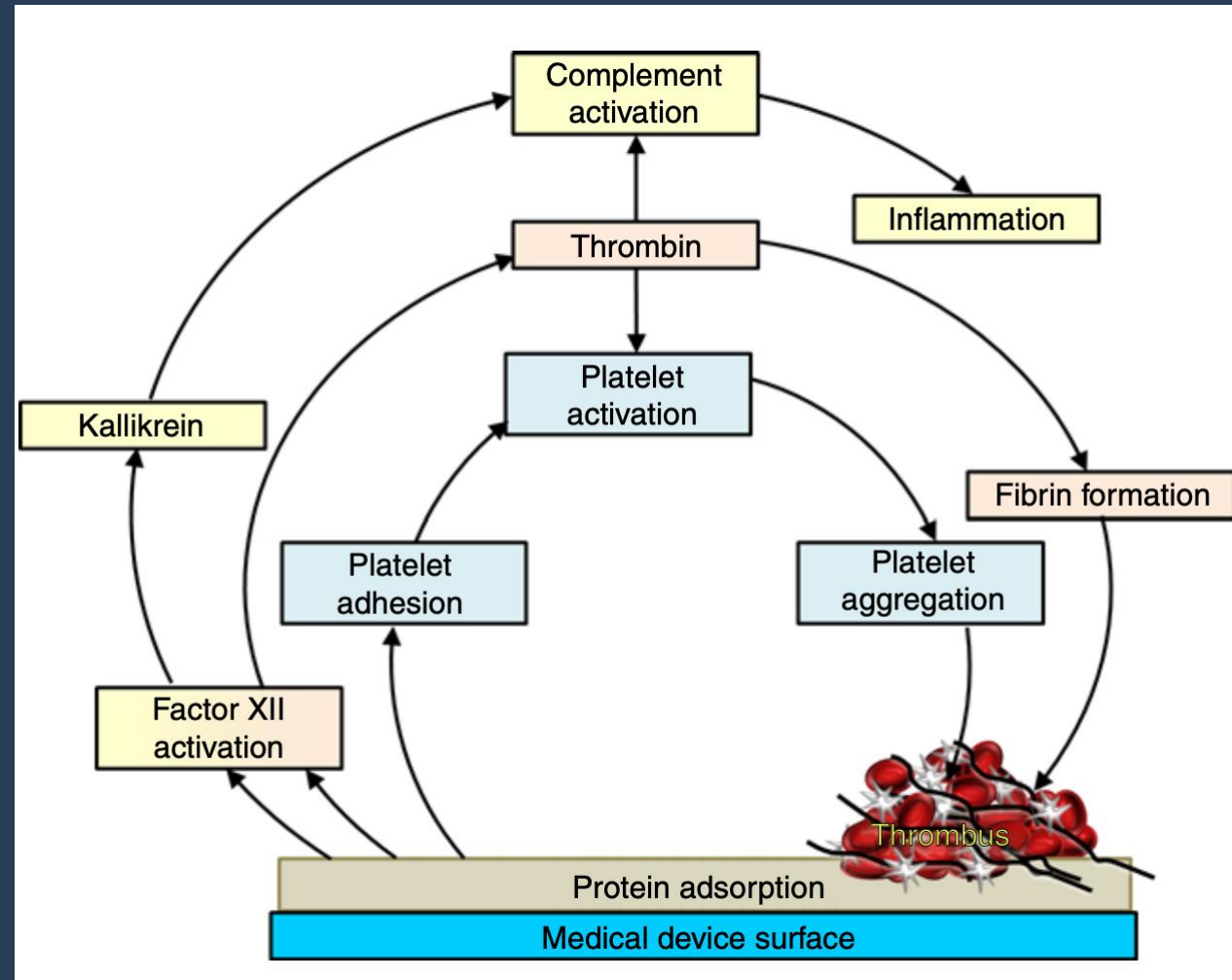
Radial strength, uniform deployment

Minimize early **thrombotic** complications

Prevent **restenosis**

Minimal **inflammation**

# Medical device-induced thrombosis











# Factors in thromboresistance

- Thin strut design and minimal flow disturbance
- The **Polymer**
  - Durable vs. Degradable vs. None
  - Conformal vs. Abluminal
- Healing characteristics

# Contemporary DES Platforms

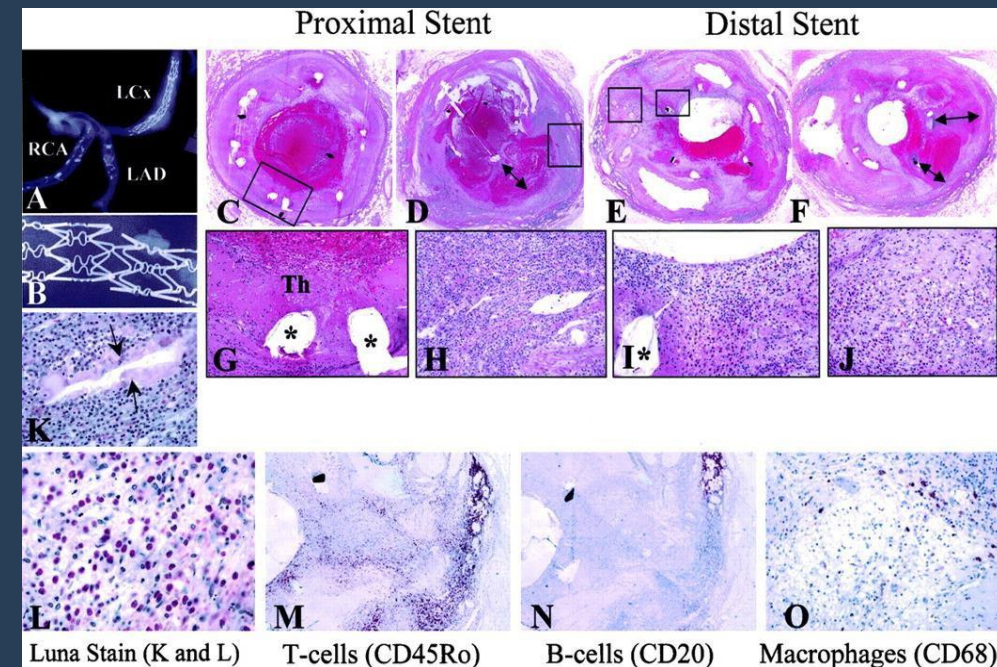
## *Strut and Coating Thickness In Perspective*

	Durable Polymer Coated		Bioabsorbable Polymer Coated					
	Xience CoCr-EES	Resolute /Onyx	Biomatrix	Nobori	Ultimaster	SYNERGY	MiStent	Orsiro
	Promus PtCr-EES	CoNi-ZES	316L-BES	316L-BES	CoCr-SES	PtCr-EES	CoCr-SES	CoCr-SES
								
Strut thickness	81 $\mu\text{m}$ 0.0032"	89/81 $\mu\text{m}$ 0.0035"	120 $\mu\text{m}$ 0.0046"	125 $\mu\text{m}$ 0.0047"	80 $\mu\text{m}$ 0.0031"	74 $\mu\text{m}$ 0.0029"	64 $\mu\text{m}$ 0.0025"	61 $\mu\text{m}$ 0.0024"
Polymer	PVDF	BioLINX	PLA	PLA	PDLLA + PCL	PLGA	PLGA	PLLA Probio*
Distribution / thickness	Conformal 7-8 $\mu\text{m}$ / side	Conformal 6 $\mu\text{m}$ / side	Abluminal 10 $\mu\text{m}$	Abluminal 20 $\mu\text{m}$	Abluminal 15 $\mu\text{m}$	Abluminal 4 $\mu\text{m}$	Conformal 5 $\mu\text{m}$ / 15 $\mu\text{m}$ *silicon carbide	Conformal 3.5 $\mu\text{m}$ / 7.5 $\mu\text{m}$

# What does the polymer do?

- A drug reservoir for controlled release of the antiproliferative drugs (ensure anti-restenotic efficacy)
- Polymers in 1st generation DES (TAXUS, CYPHER)
  - Poor biocompatibility
  - Increased risk of thrombosis
  - Localized inflammation

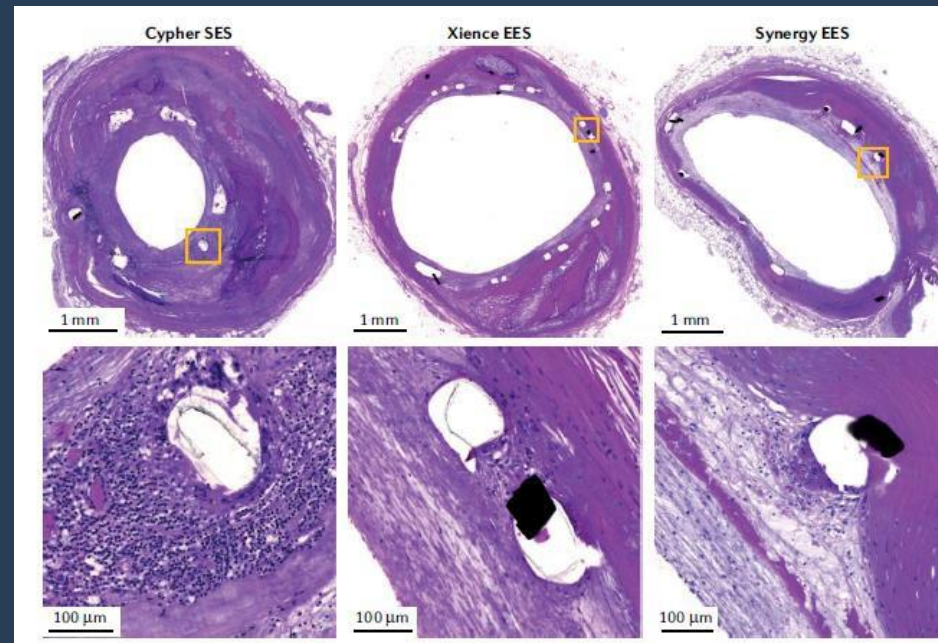
→ Prolonged use of DAPT





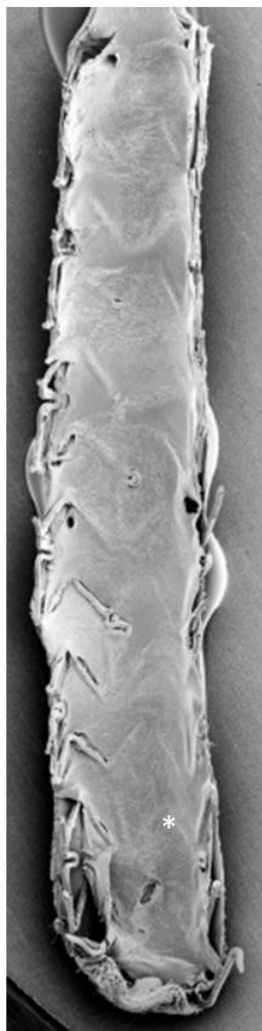
# Improvements in polymer technology

- More **biocompatible** polymers
  - PVDF- HFP: poly(vinylidene fluoride- co-hexafluoropropylene), a highly **fluorinated** polymer (fluoropolymer in Xience stents)
  - mixture of hydrophobic C10 polymer, a polyvinylpyrrolidone C19 polymer (BioLinx in Resolute stents)
- **Biodegradable** polymer

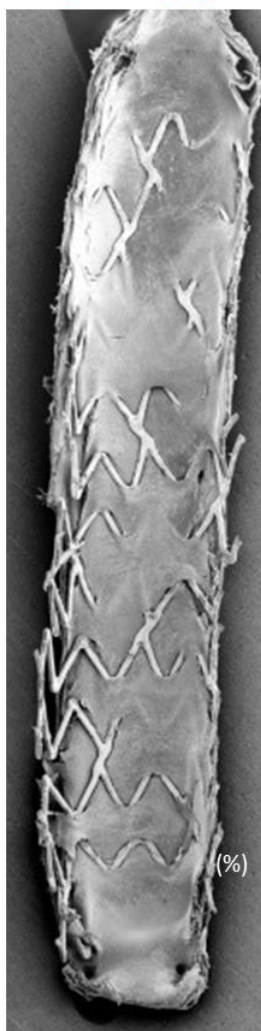


# Incomplete endothelialization after 28 days

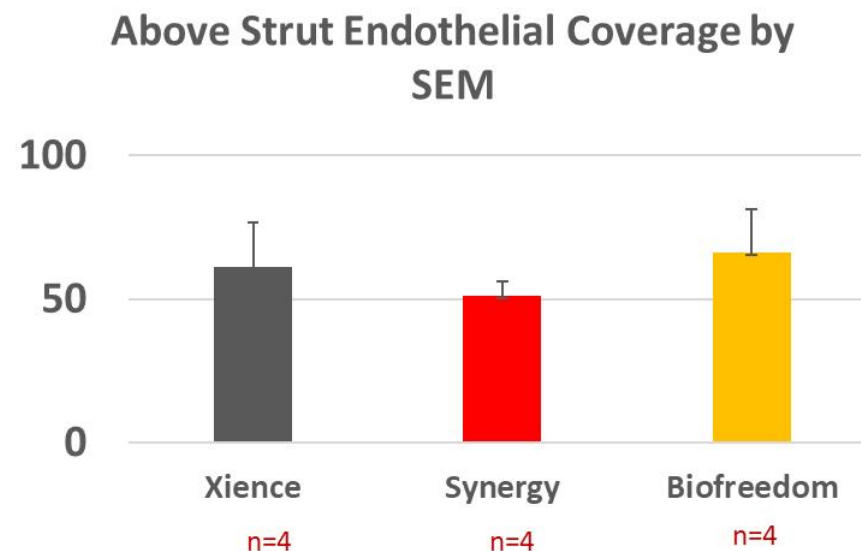
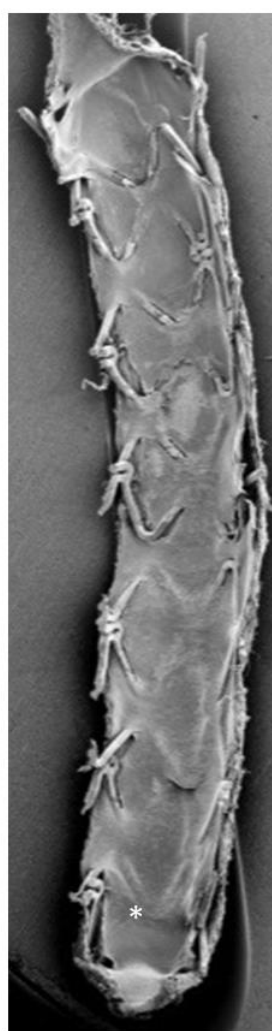
**Xience**



**Synergy<sup>†</sup>**



**BioFreedom<sup>‡</sup>**



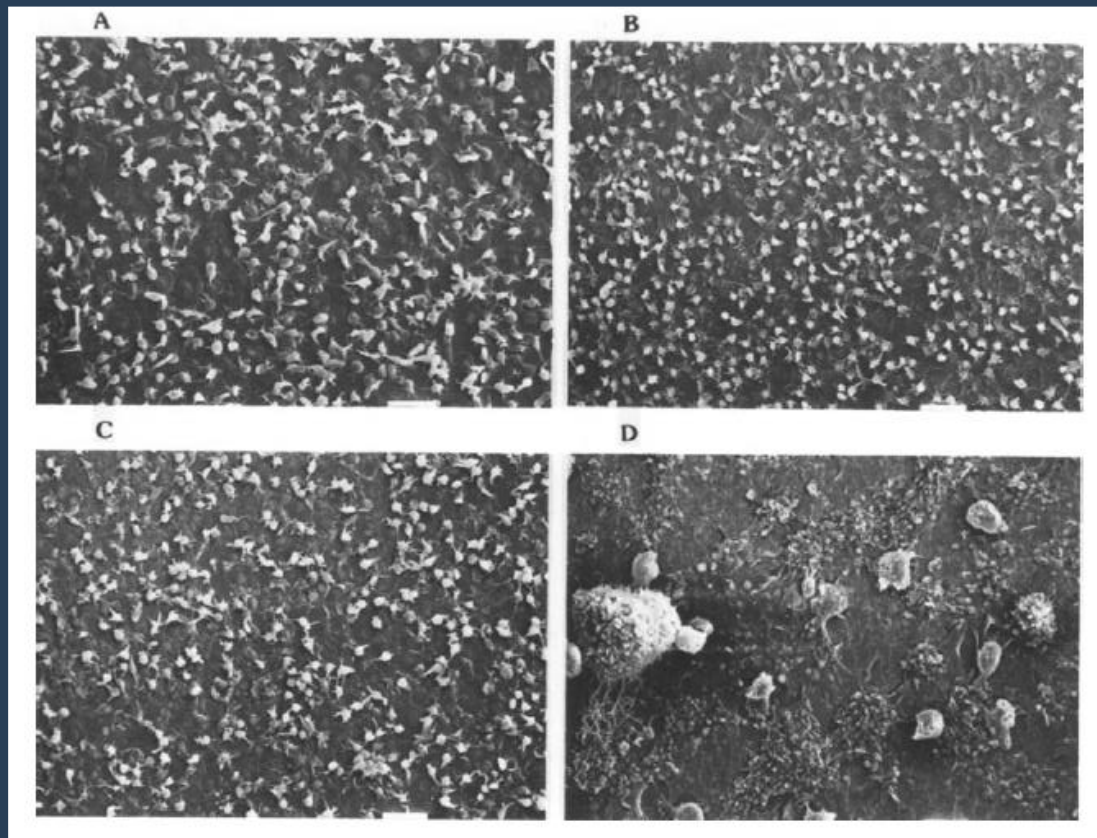
**Key Takeaway: At 28 Days in Animal Models DES are not fully healing → thus favorable blood biomaterials interactions are extremely important**



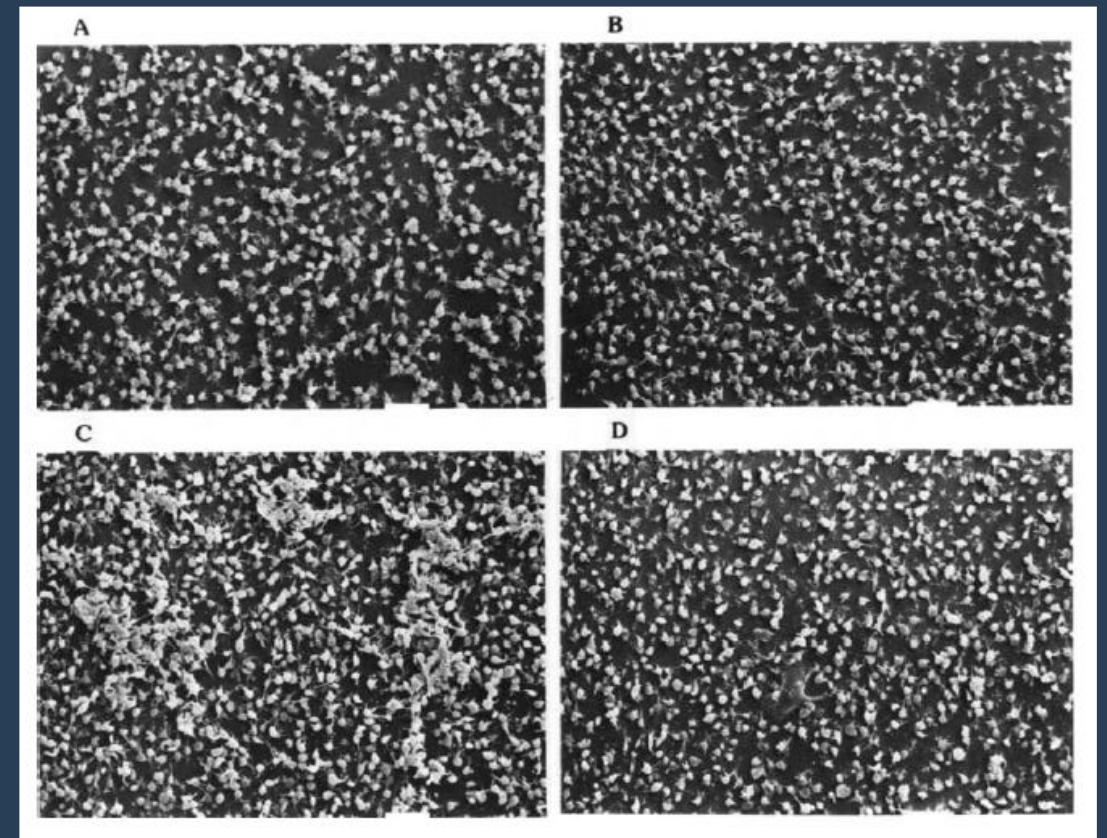
# Albumin as an inert thromboresistant coating

*Ex-vivo canine model*

PVC pre-absorbed with fibrinogen

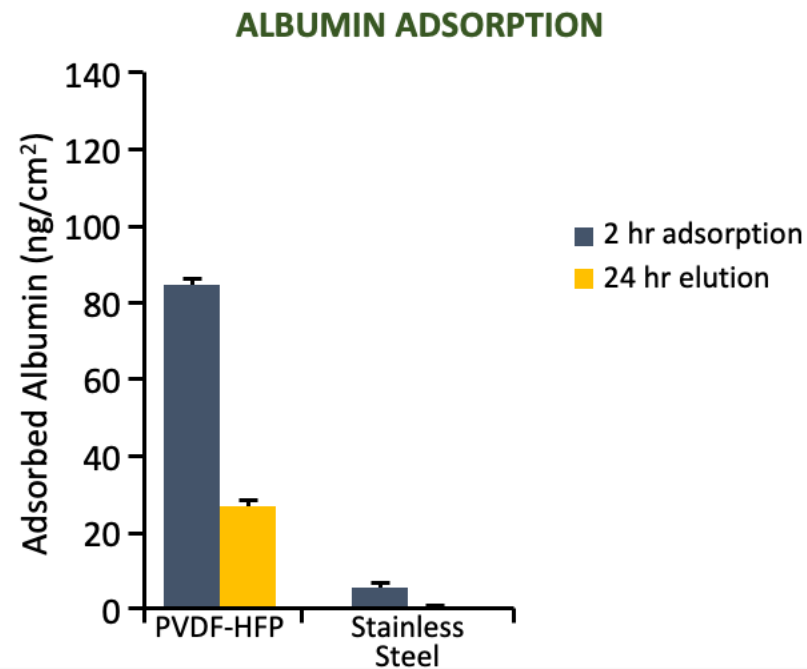


PVC pre-absorbed with albumin

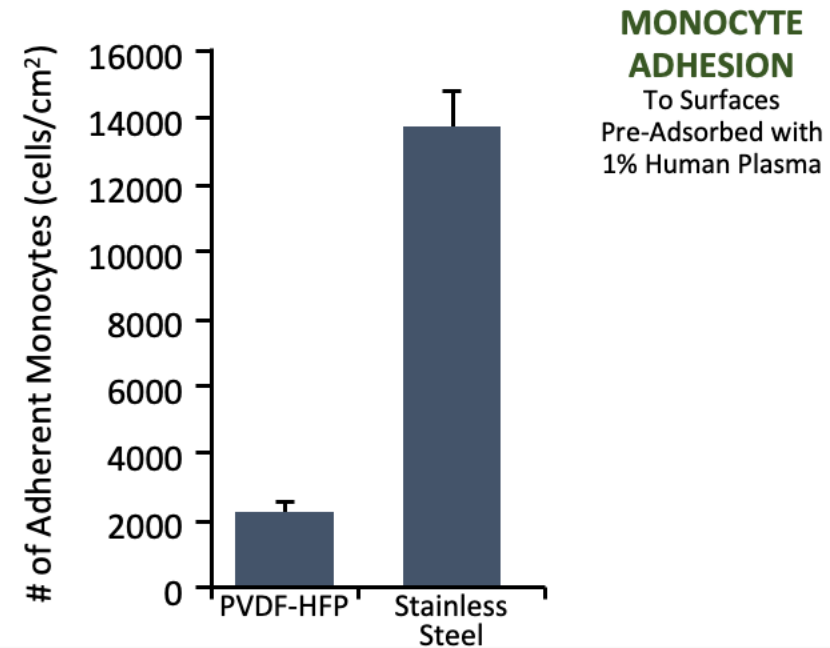


# Permanent polymers: Fluoropolymer

XIENCE™ Stent Fluoropolymer has higher albumin absorption/retention than bare metal



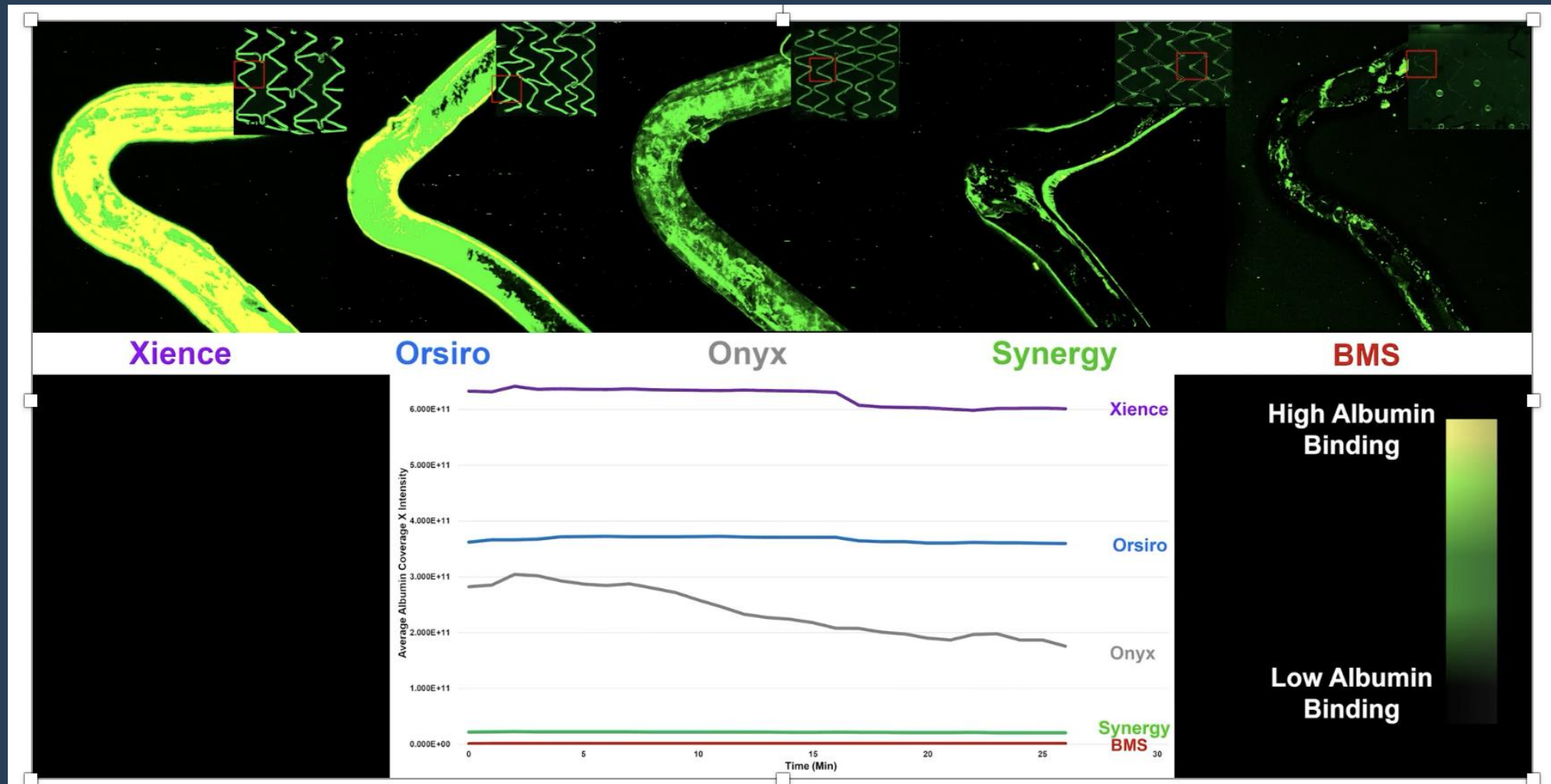
Preferential albumin adsorption of XIENCE™ Stent Fluoropolymer offers the lower monocyte adhesion than bare metal



**"Blood compatibility assessment of polymers used in drug eluting stent coatings"** Luisa Mayorga Szott, Colleen A. Irvin, Mikael Trollsas, Syed Hossainy, and Buddy D. Ratner Citation: *Biointerphases* **11**, 029806 (2016).

# Albumin retention in In Vitro Flow models

*Greatest albumin coverage and strongest signal with the Xience stent*



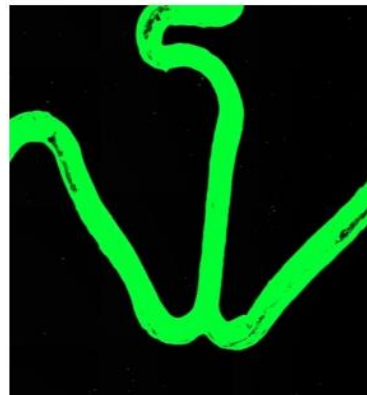
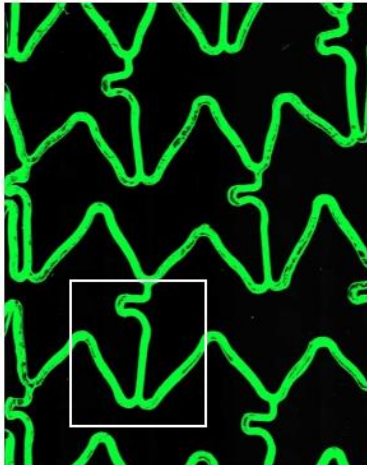


# Albumin retention in In Vitro Flow models

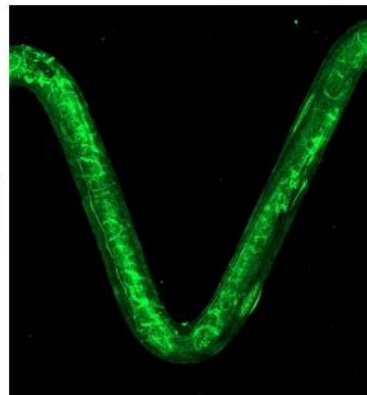
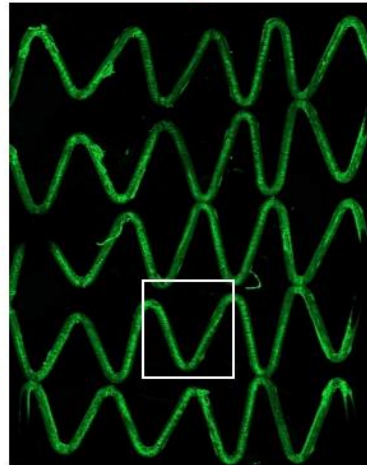
*Greatest albumin coverage and strongest signal with the Xience stent*

● Fluorescent Human Albumin

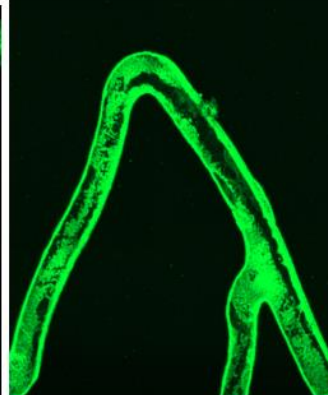
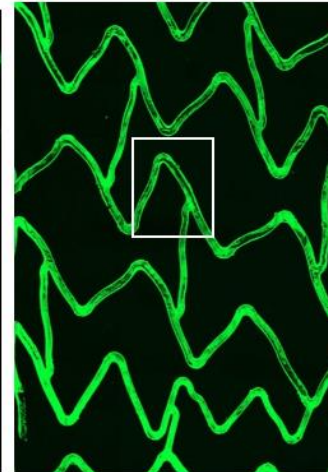
**XIENCE™**



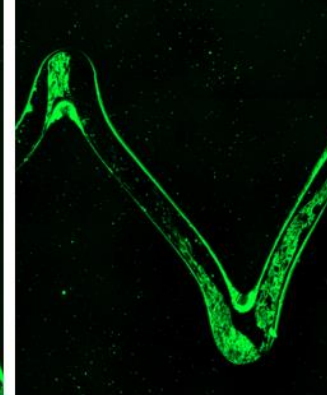
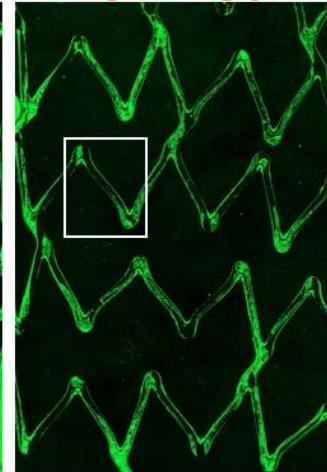
**Onyx†**



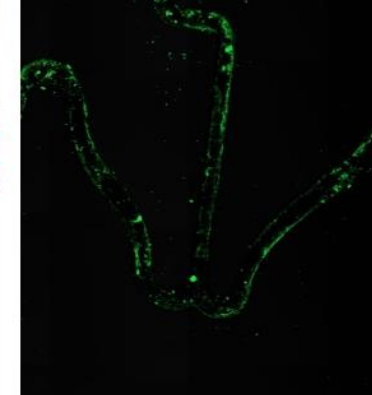
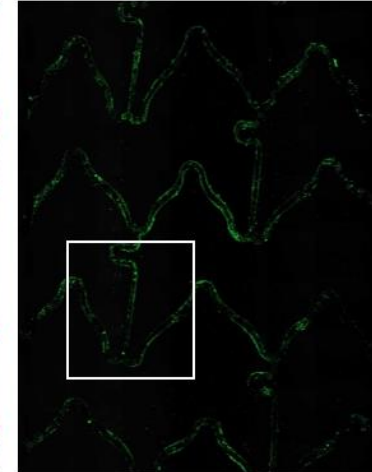
**Orsiro†**



**Synergy†**



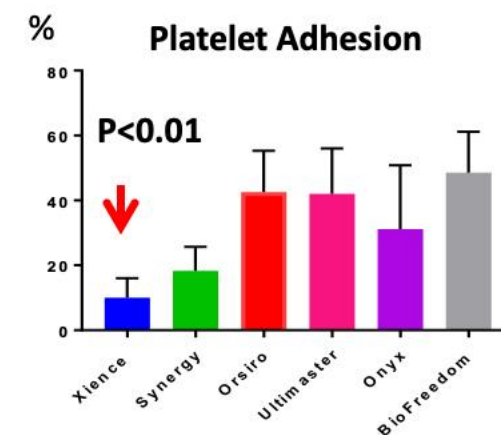
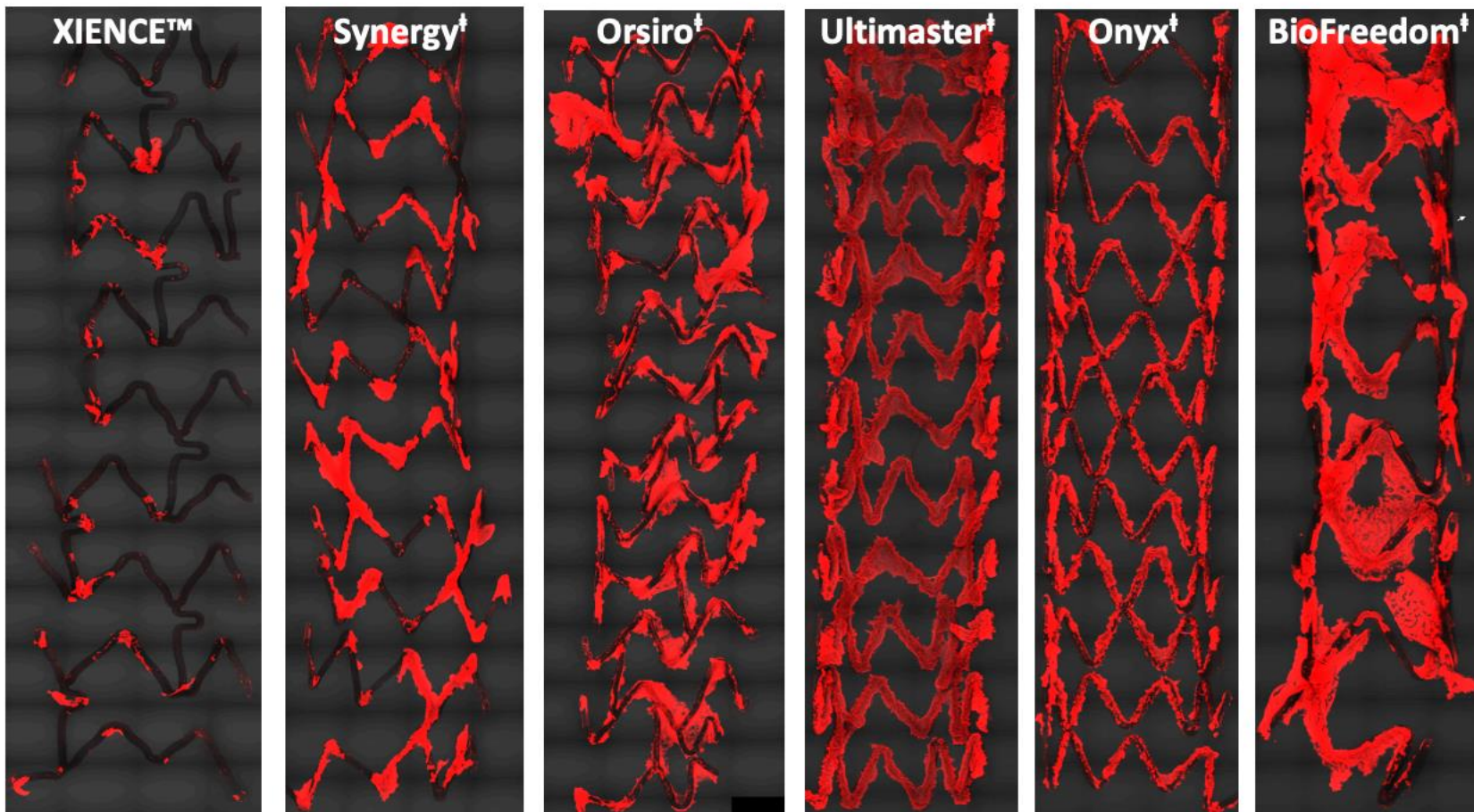
**BMS**



# Ex-vivo swine shunt models under ASA monotherapy

*Significantly lower platelet adhesion for the Xience stent*

Platelets (red)





# Ex-vivo swine shunt models under ASA monotherapy

*Significantly less inflammation with the Xience stent*

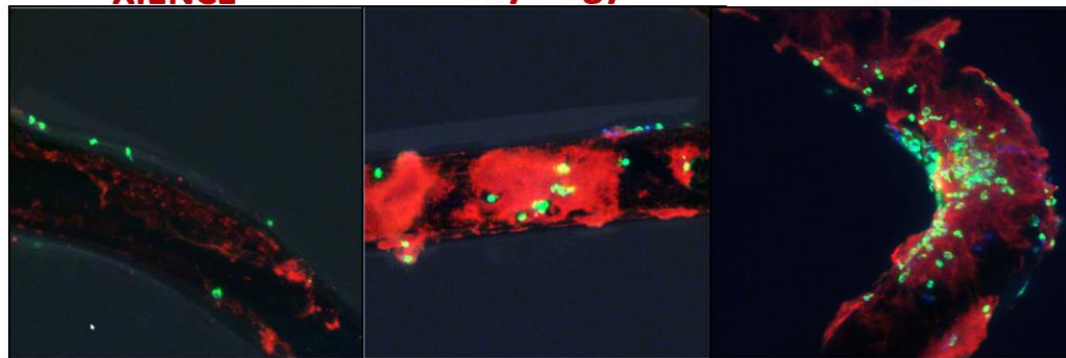
Neutrophils

Neutrophils (green)

XIENCE™

Synergy†

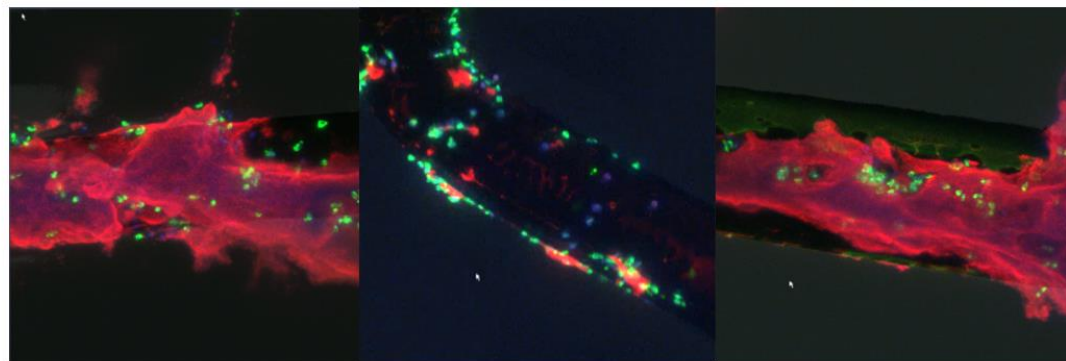
Orsiro†



Ultimaster†

Onyx†

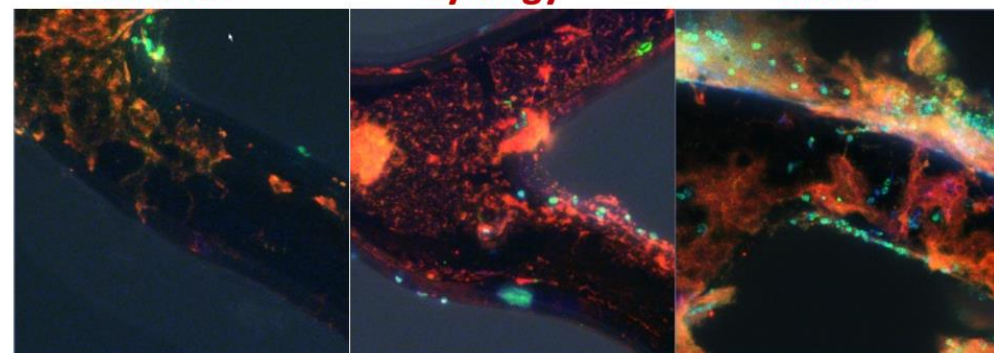
BioFreedom†



XIENCE™

Synergy†

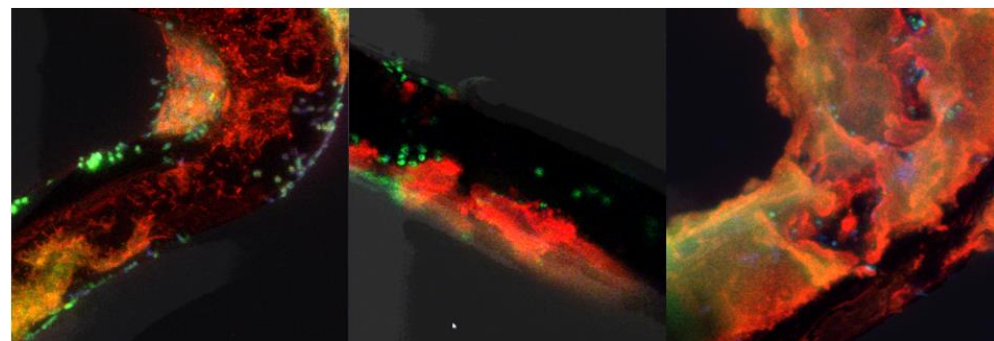
Orsiro†



Ultimaster†

Onyx†

BioFreedom†

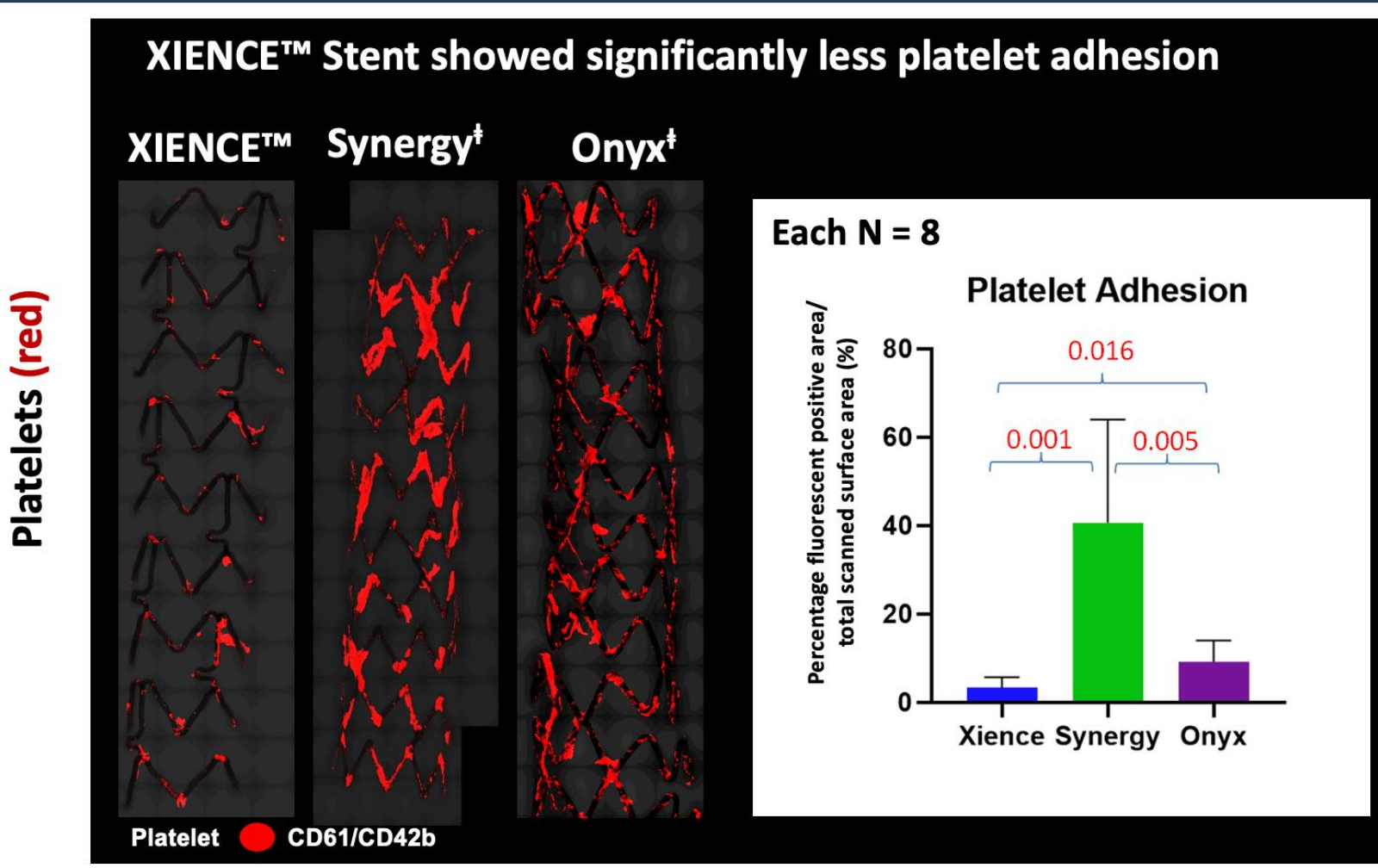


Monocytes (green)



# Ex-vivo swine shunt models under clopidogrel monotherapy

*Significantly lower platelet adhesion for the Xience stent*



# Ex-vivo swine shunt models under clopidogrel monotherapy

*Significantly less inflammation with the Xience stent*

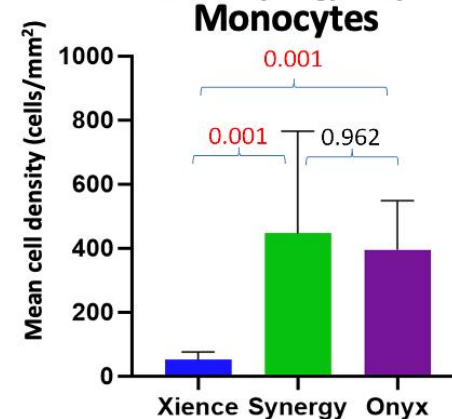
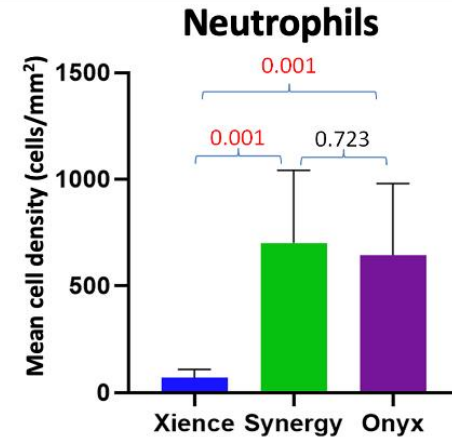
**XIENCE™ Stent showed significantly less inflammatory cell adhesion**

Neutrophils ● PM-1      Monocytes ● CD14

**XIENCE™**

**Synergy†**

**Onyx†**

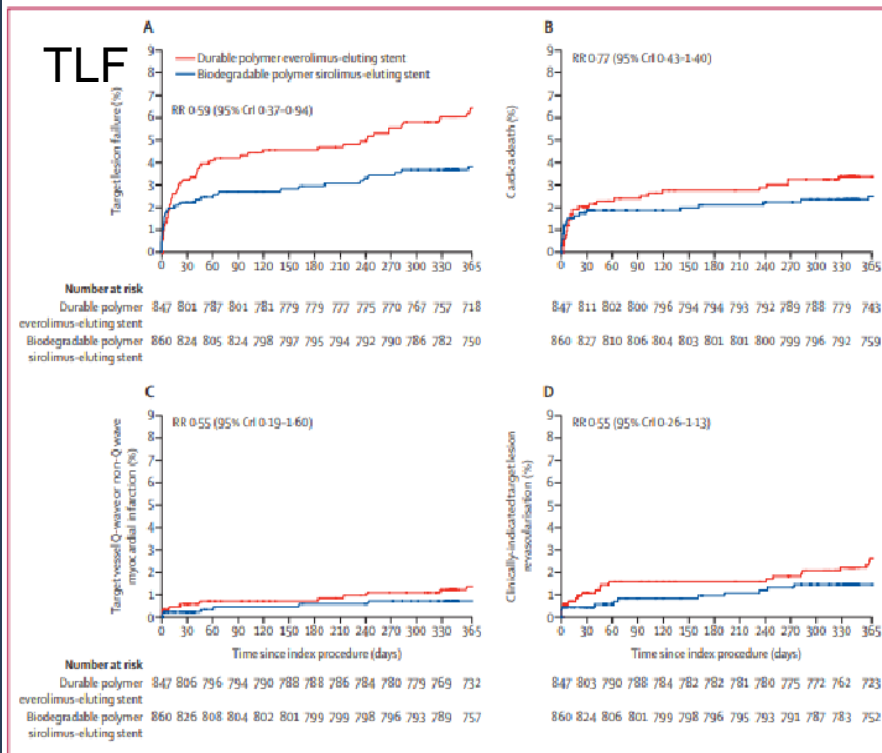


# Biodurable vs. Biodegradable

No winner yet

## Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI): a single-blind, prospective, randomised superiority trial

Juan F Iglesias\*, Olivier Muller\*, Dik Heg, Marco Roffi, David J Kurz, Igal Moorof, Daniel Weilenmann, Christoph Kaiser, Maxime Tapponnier, Stefan Storteky, Sylvain Losdat, Eric Eeckhout, Marco Valgimigli, Ayodele Odutayo, Marcel Zwahlen, Peter Juni, Stephan Windecker, Thomas Pilgrim

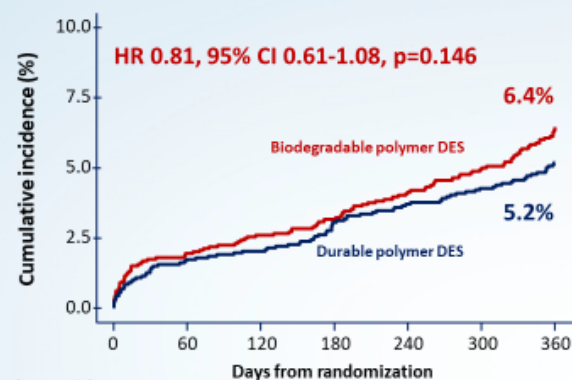


## Primary outcome (POCO at 1 year)



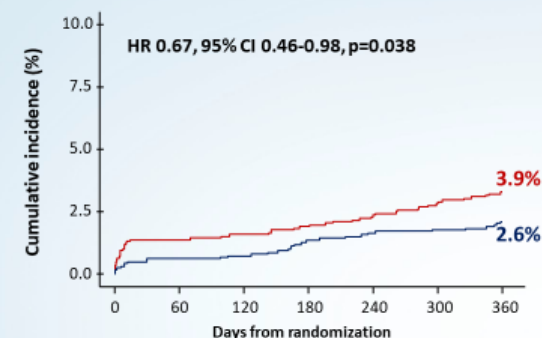
ACS patients who had a significant stenosis in coronary angiogram, eligible for stent implantation

Durable polymer DES group



## Key Secondary outcome at 12 months

- DOCO:** Cardiac death, Target vessel MI, Stent thrombosis, Target Lesion Revascularization



**How Short can we go?**

# Xience Short DAPT trials

ASA

1-month

**XIENCE 28** **HBR**

3-month

**XIENCE 90** **HBR**  
**STOPDAPT**

P<sub>2</sub>Y<sub>12</sub>i

1-month

**STOPDAPT-2**  
**STOPDAPT-2 HBR**  
**STOPDAPT-2 Complex**  
**STOPDAPT-2 ACS**

No DAPT

**STOPDAPT-3** **On going**

1. Mehran R, et al. TCT Connect 2020 - XIENCE 28 & XIENCE 90
2. Natsuaki M, et al. Cardiovasc Interv Ther. 2016 Jul ; 31(3): 196-209
3. Watanabe H, et al. JAMA. 2019; 321(24) 2414-2427
4. Watanabe H, et al. Circulation. 2019; 140:1957-1959
5. Watanabe H, et al. Presented at JCS2020
6. Watanabe H, et al. Presented at ESC2021
7. STOPDAPT-3 Trial Design: the U.S. National Library of Medicine, ClinicalTrials.gov Identifier: NCT04609111, <https://clinicaltrials.gov/ct2/show/NCT04609111>

# XIENCE 28 / XIENCE 90

## *Study Objectives*

- Among **HBR** patients undergoing successful PCI with Xience stents
- Primary objective
  - The safety (**all death / MI**) of a short DAPT regimen (1 / 3 months) vs. DAPT of 6-12 months
- Secondary objectives
  - The impact of shorter DAPT regimens on clinically significant **bleeding** (BARC 2-5)
  - **Stent thrombosis** rates, compared against a performance goal
- Control group – Xience V

# XIENCE 28 / XIENCE 90

## *Study population*

- Inclusion criteria
  - HBR patients undergoing PCI with Xience stents

- Exclusion criteria
  - STEMI
  - LVEF <30%
  - Overlapping stents
  - LM, ISR, CTO, graft PCI

### HBR Criteria



Age  $\geq 75$  years



Chronic OAC therapy



CKD (creatinine  $\geq 2.0$  mg/dl or dialysis)



Anemia (hemoglobin <11 g/dl)



Hematological disorders (platelet count <100,000/mm<sup>3</sup> or any coagulation disorder)



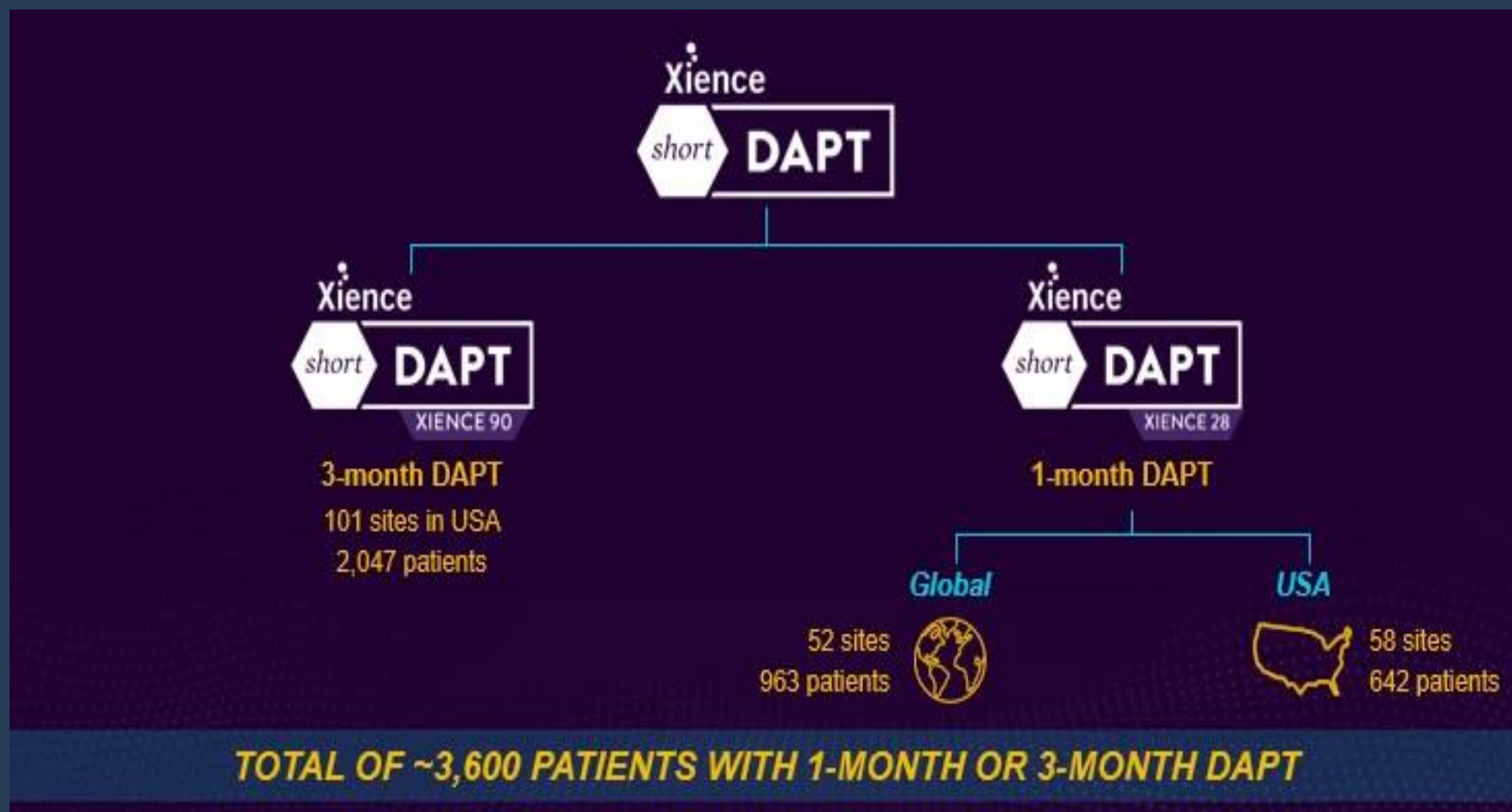
Major bleeding in the last 12 months



History of stroke



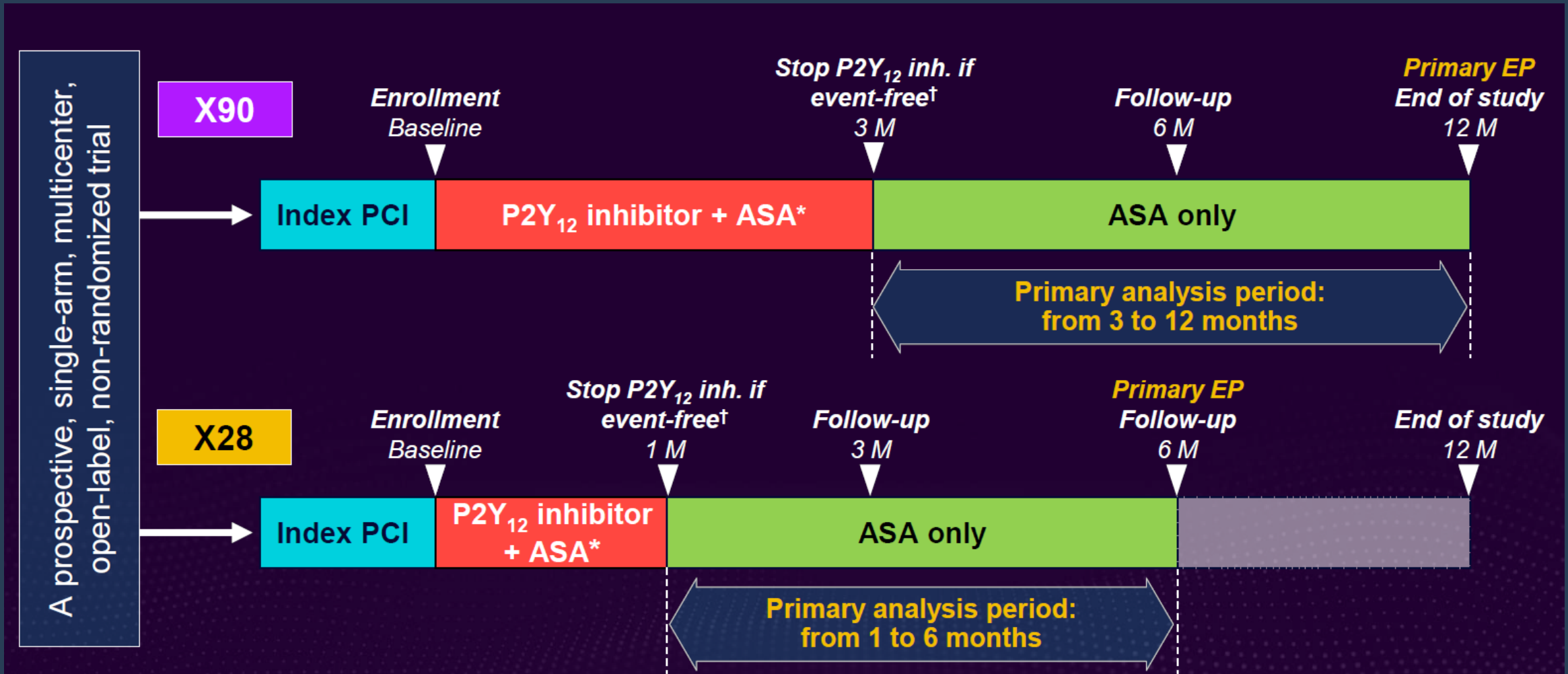
# XIENCE 28 / XIENCE 90



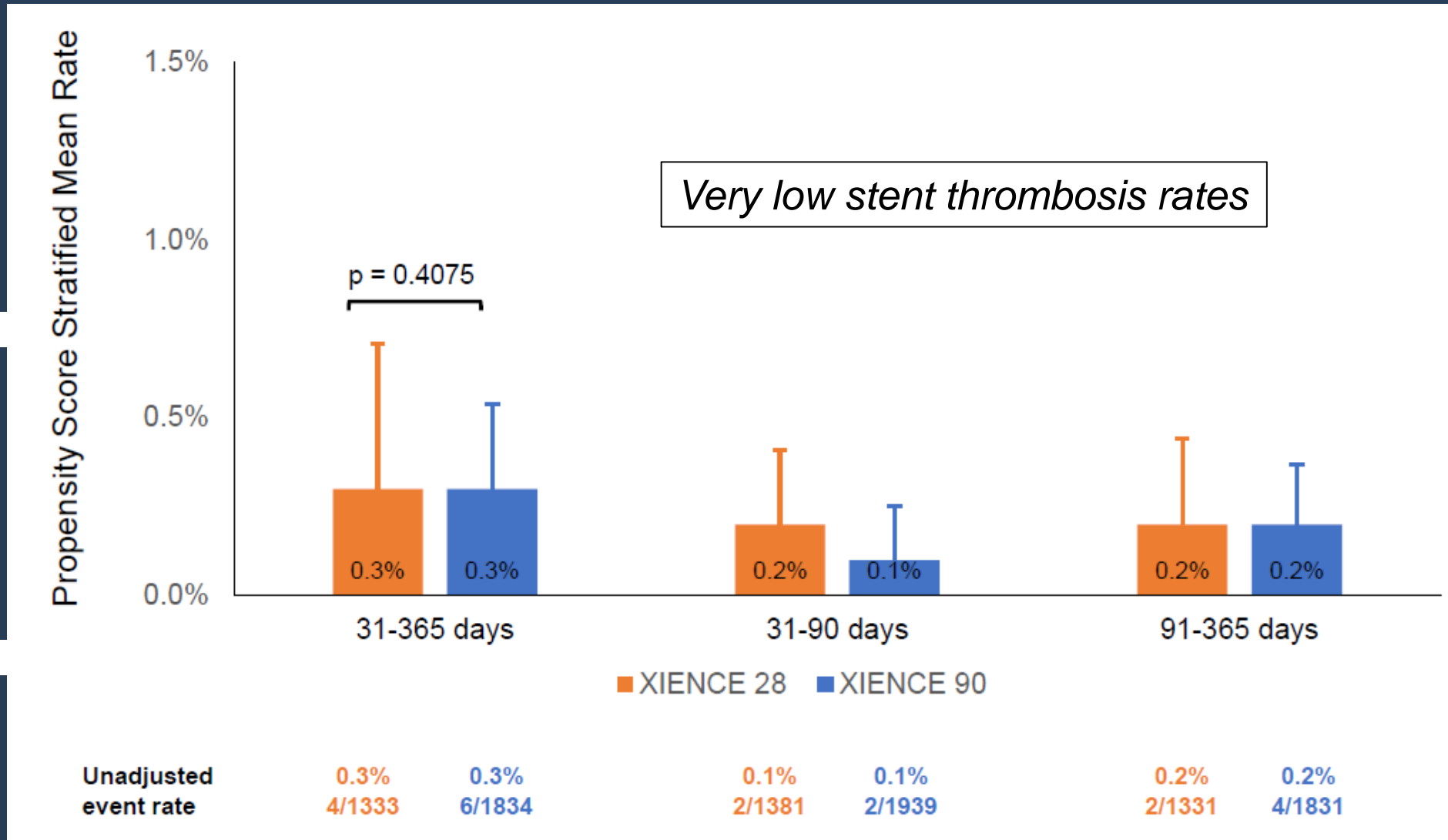


# XIENCE 28 / XIENCE 90

## Study Design

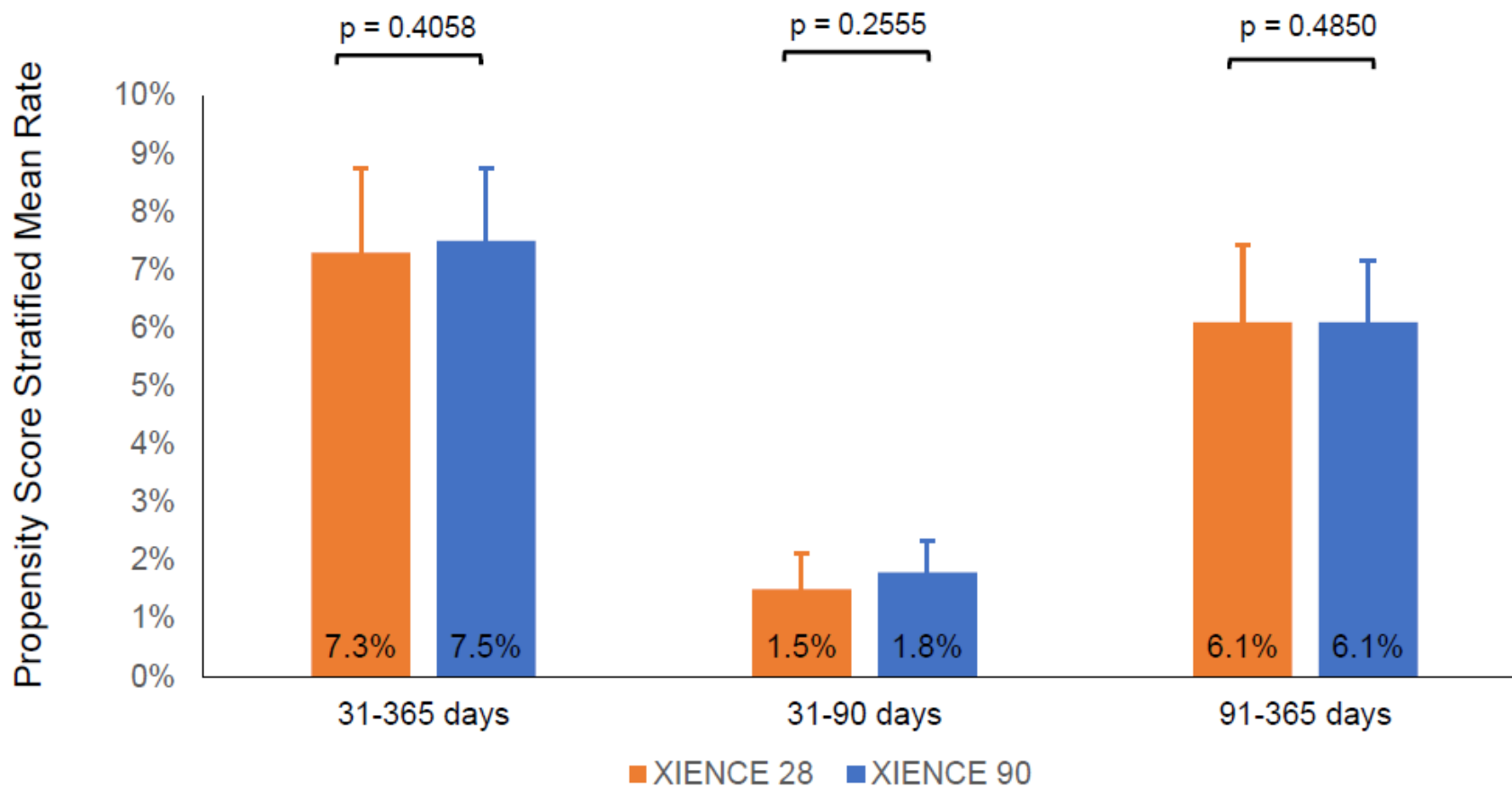


# XIENCE 28 & 90: Outcomes



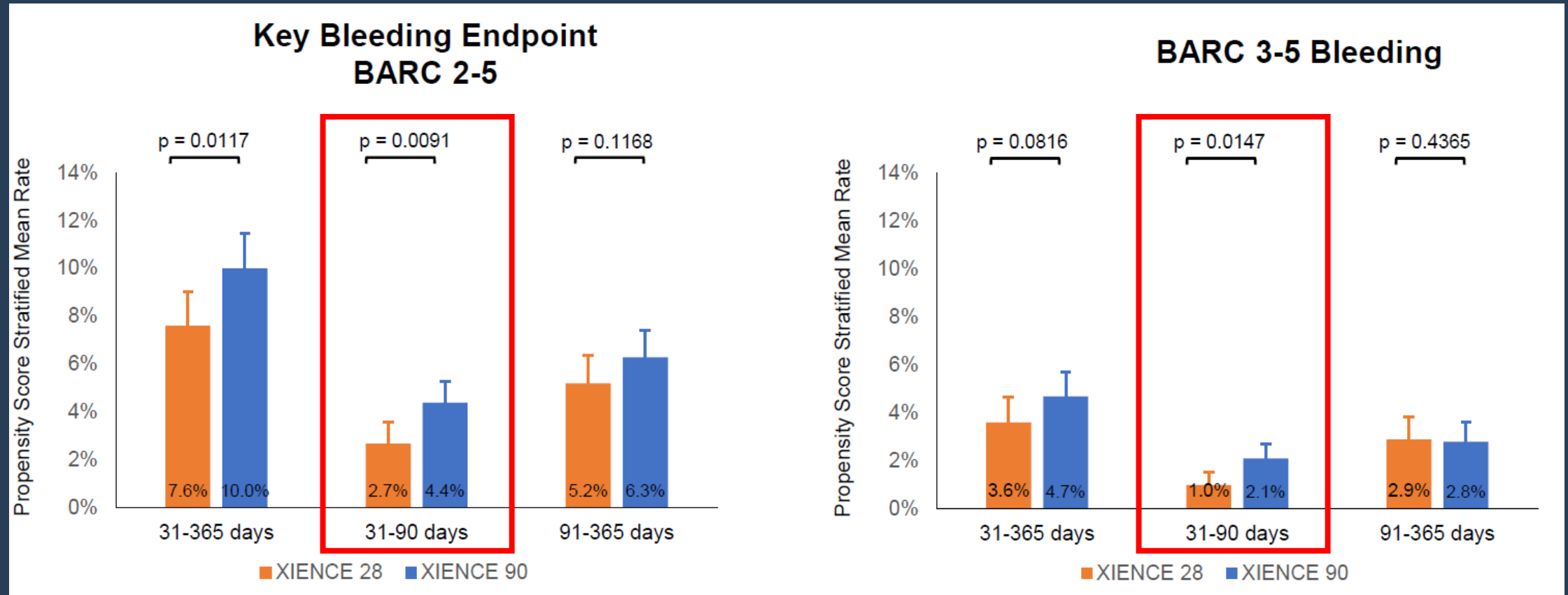
# XIENCE 28 vs XIENCE 90

*All death / MI*



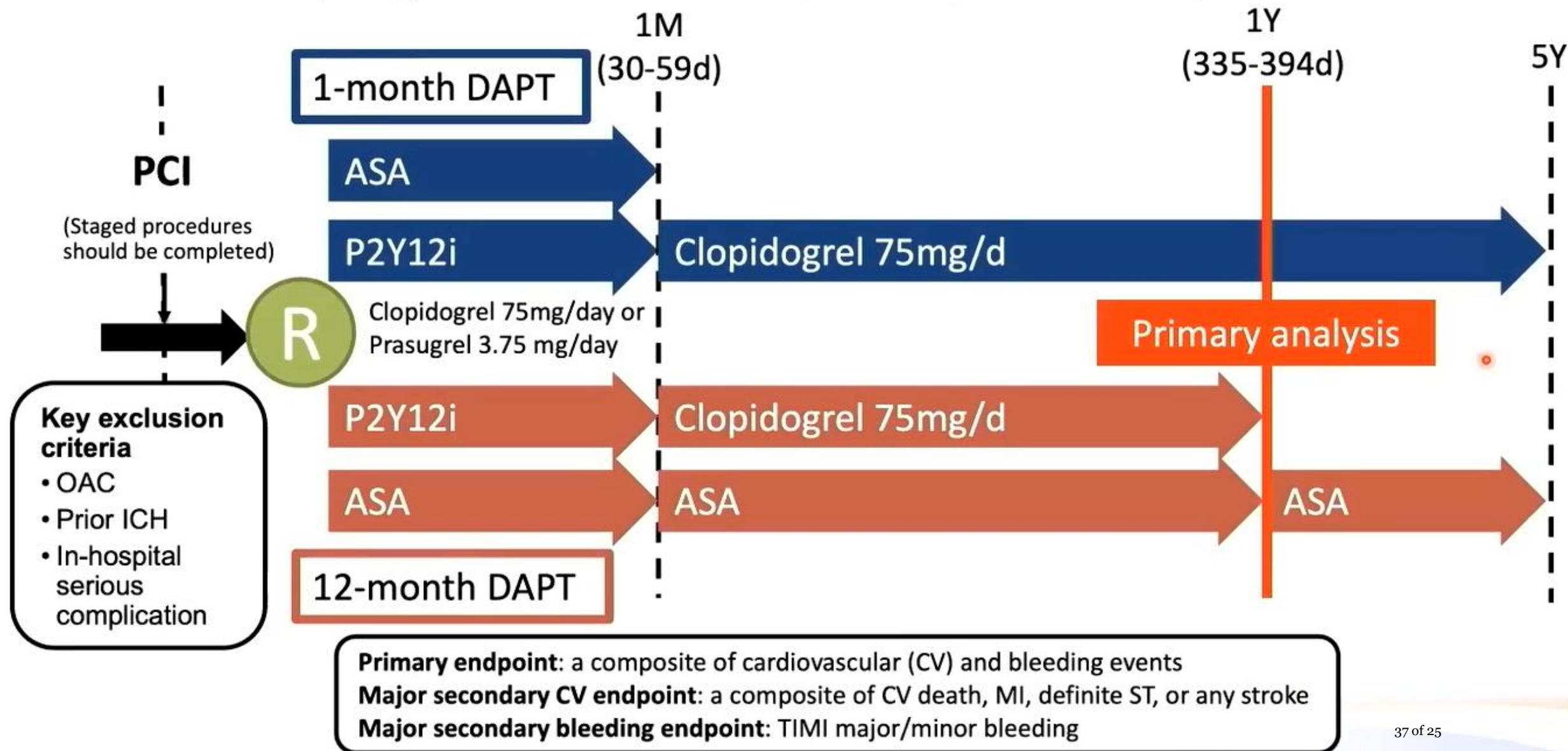
# XIENCE 28 vs XIENCE 90

## Bleeding



# STOPDAPT-2 and STOPDAPT-2 ACS

Prospective multicenter open-label randomized trials  
comparing 1-month versus 12-month DAPT after CoCr-EES implantation



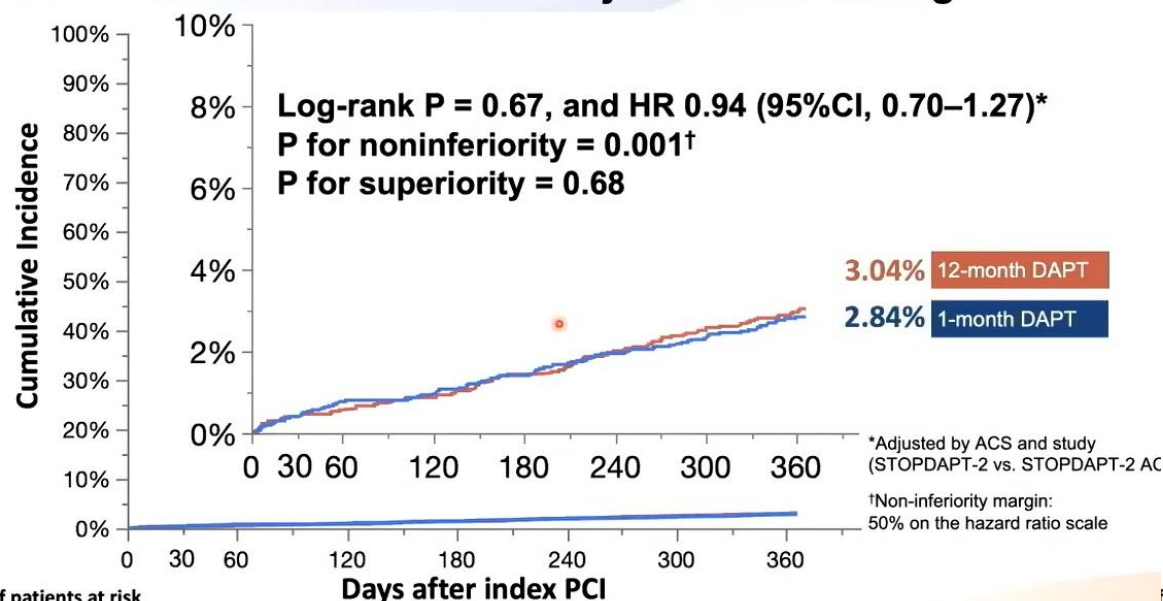


# STOPDAPT-2 Total cohort

STOPDAPT-2  
Total cohort

## Primary Endpoint

CV death/MI/ST/Stroke/TIMI major/minor bleeding

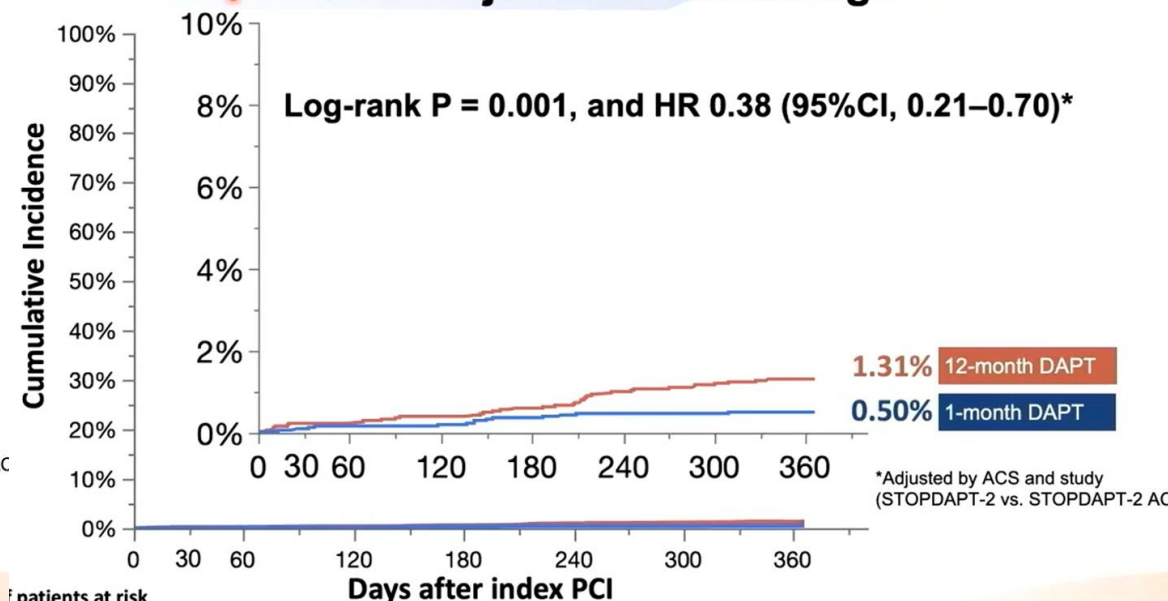


Number of patients at risk

	0	30	60	120	180	240	300	360
12-month DAPT	3004	2991	2970	2959	2941	2922	2902	2327
1-month DAPT	2993	2980	2956	2946	2928	2905	2885	2357

## Major Secondary Bleeding Endpoint

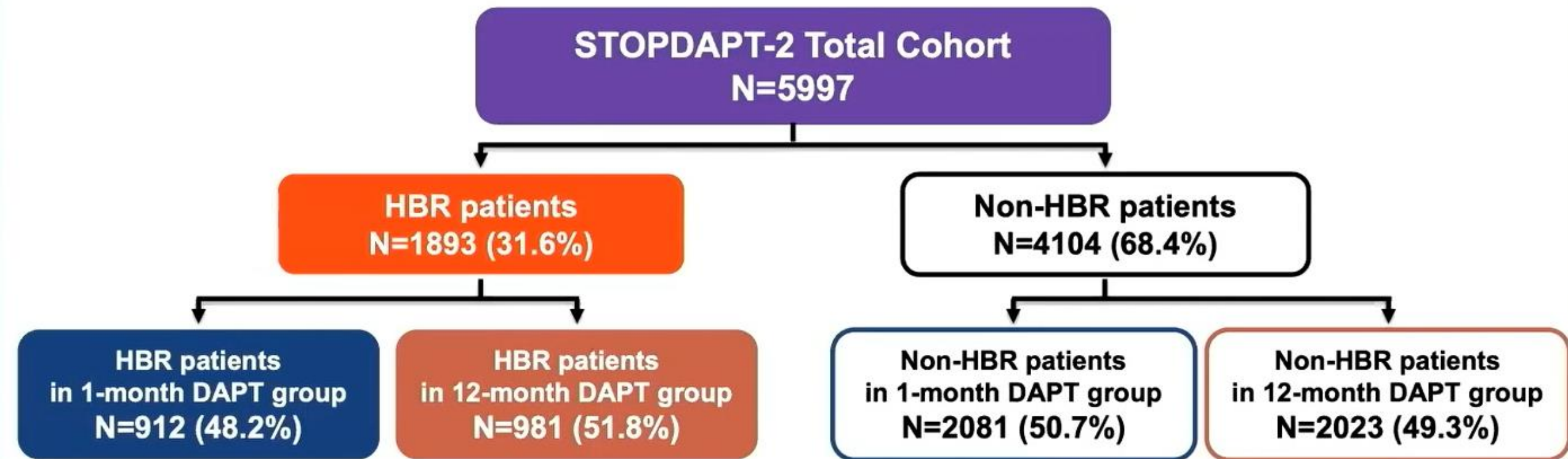
TIMI major/minor bleeding



Number of patients at risk

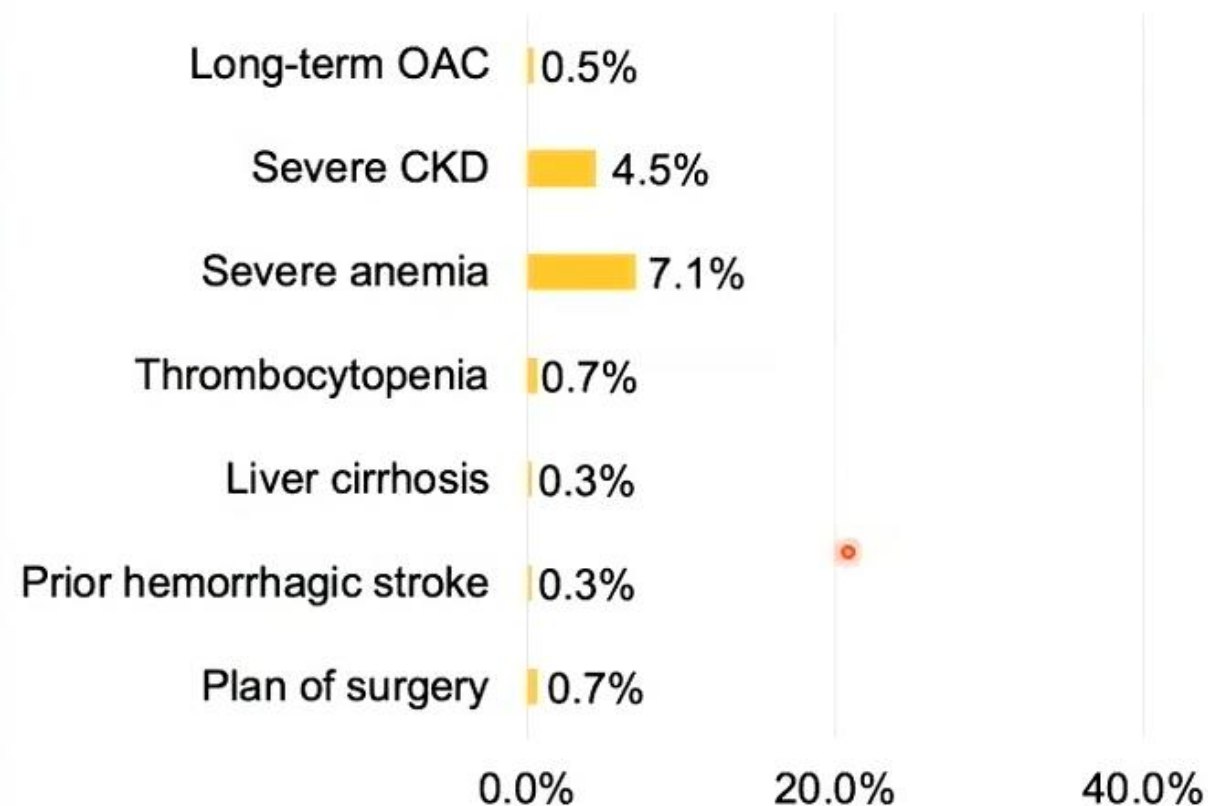
	0	30	60	120	180	240	300	360
DAPT	3004	2995	2977	2968	2957	2941	2929	2360
APT	2993	2985	2970	2965	2955	2941	2927	2400

# Subgroup analysis #2: HBR and Non-HBR

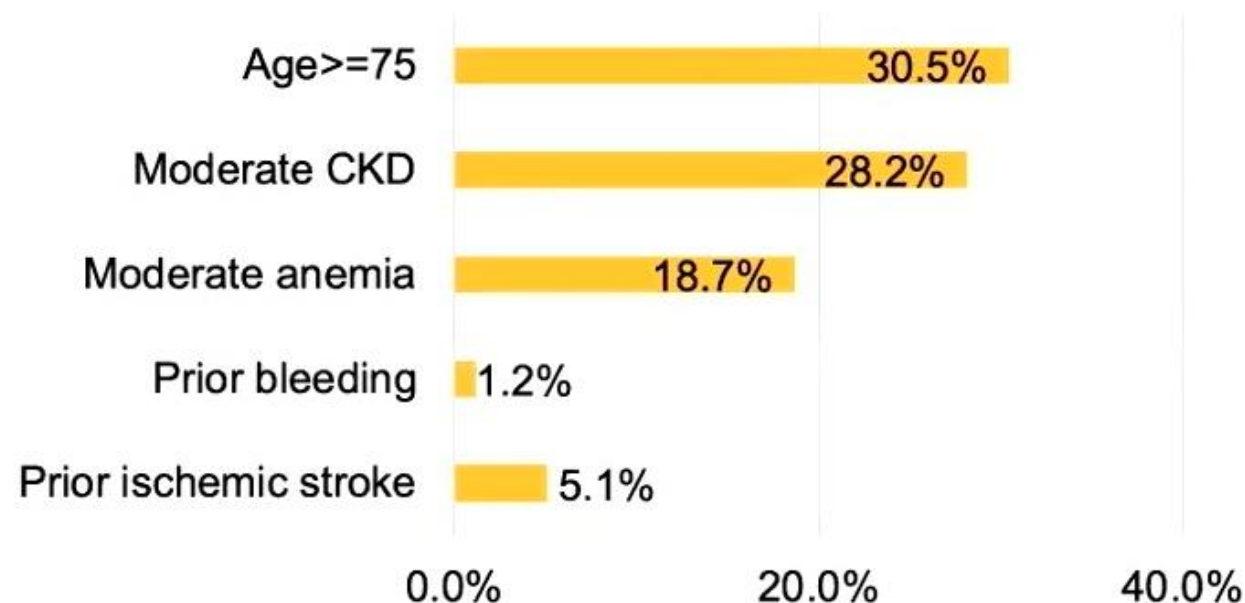


# Prevalence of HBR criteria

## Major criteria



## Minor criteria

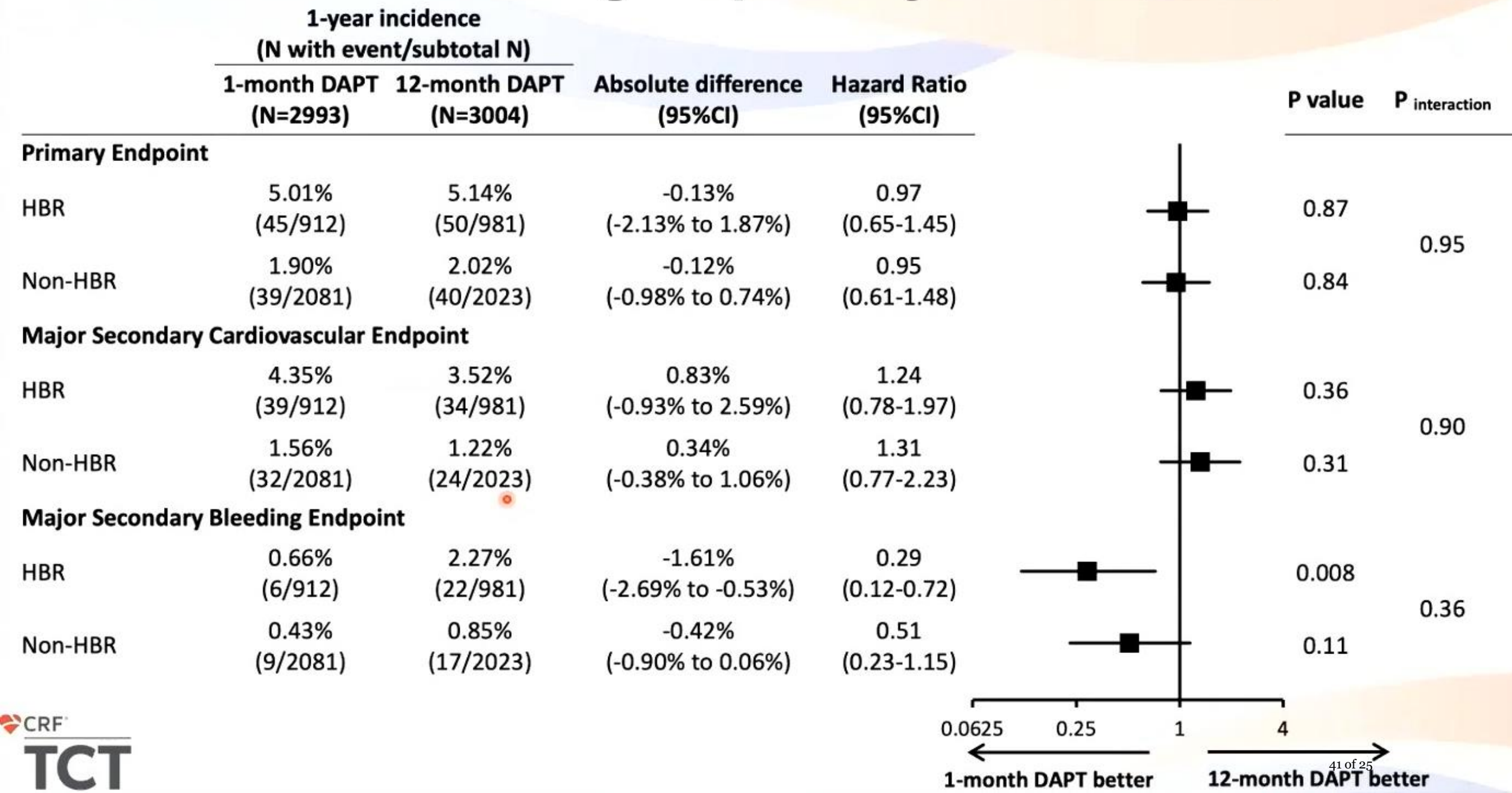


HBR was defined as having at least one major criterion or two minor criteria of ARC-HBR.<sup>1</sup>

We modified the ARC-HBR definitions, because some criteria of ARC-HBR were not exactly captured in this study.



# Subgroup analysis #2: HBR

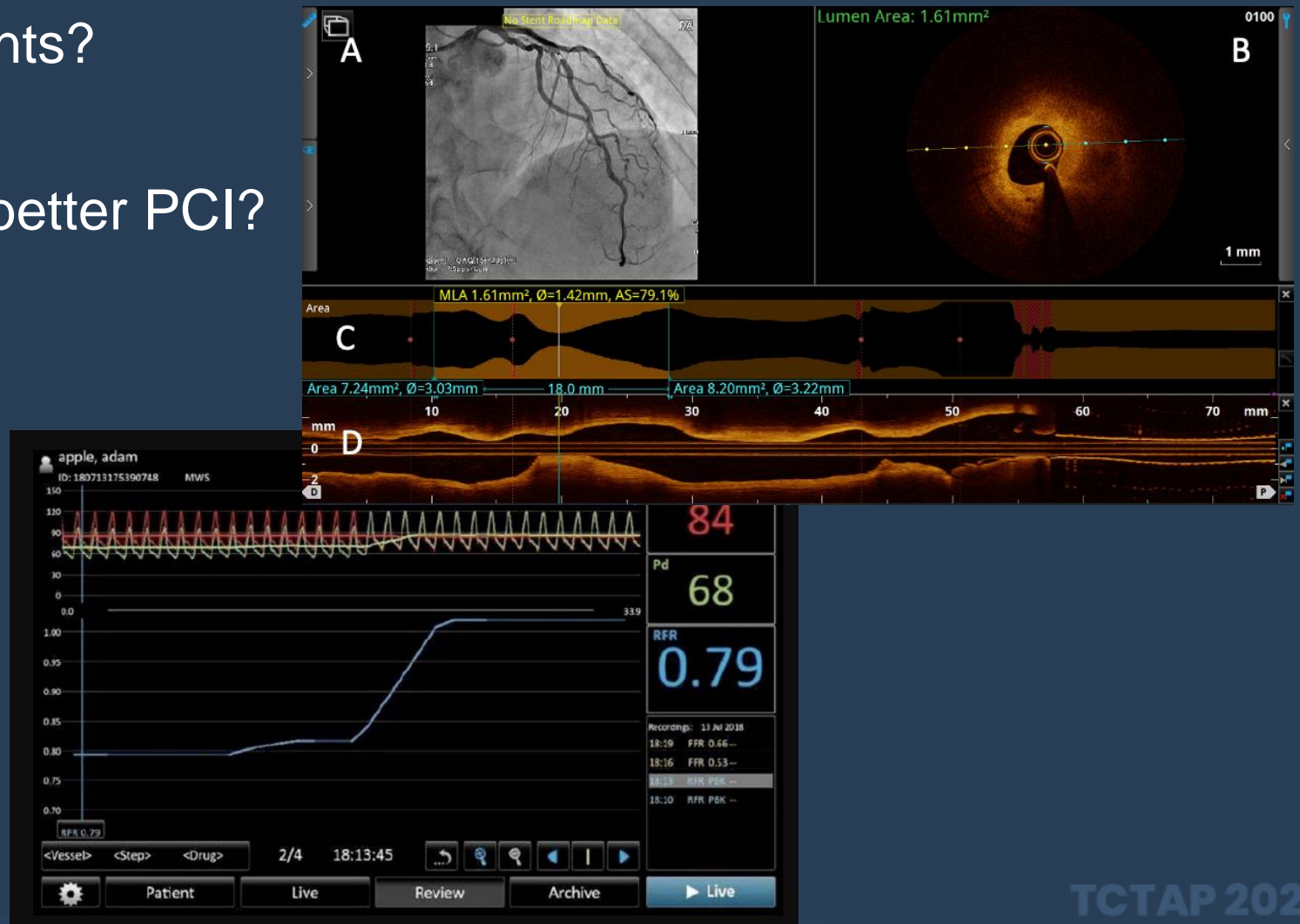


# SUMMARY of XIENCE 90/28, STOPDAPT-2

- Among HBR patients undergoing PCI with the XIENCE™ stent, a short DAPT regimen of 1 or 3 months compared with standard DAPT up to 12 months resulted in:
  - Non-inferior ischemic outcomes
  - Lower risk of bleeding outcomes
  - Very low incidence of stent thrombosis

# Is it the stent? Or is it us?

- Should there be better stents?  
or
- Should we be performing better PCI?
- Performing optimal PCI
  - Imaging
  - Physiology
  - Optimization



# Conclusion

- Antiplatelets are key in preventing thrombotic events after PCI, however, they inertly cause **bleeding**
- Recent studies are searching for a safe & effective **brief** DAPT regimen
- **Polymers**, a major component of DES, has evolved to become more biocompatible and **thromboresistant**.
- With biocompatible, **durable** polymers, a shorter DAPT can be used, which has shown to be safe in recent studies (XIENCE 90 / XIENCE 28)

**Thank You for your attention.**