Addressing the Unmet Needs of Balancing Bleeding & Ischemic Events – *The Clinical View of PCI*

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Rheology:
The Balance of Coronary Thrombosis & Bleeding

Coronary Thrombosis:

- *ACS histopathology*:
  - Plaque rupture
  - Platelet activation
  - Thrombosis
- *PCI-related*
  - Trauma of stent impantation
  - Site healing (restenosis)
  - Site non-healing

Vulnerable patient
Vulnerable plaque
Anti-thrombotic agents

Vulnerable stent
DAPT
Stent design

ARC Stent Thrombosis:

- **Early**
- **Late**
- **Very late**

Cutlilp D et al, Circ 2007

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Special Reports

Clinical End Points in Coronary Stent Trials
A Case for Standardized Definitions

Donald E. Cutlip, MD; Stephan Windecker, MD; Roxana Mehran, MD; Ashley Boam, MSBE; David J. Cohen, MD; Gerrit-Anne van Es, PhD, MSc; P. Gabriel Steg, MD; Marie-angèle Morel, BSc; Laura Mauri, MD, MSc; Pascal Vranckx, MD; Eugene McFadden, MD; Alexandra Lansky, MD; Martial Hamon, MD; Mitchell W. Krucoff, MD; Patrick W. Serruys, MD; on behalf of the Academic Research Consortium

Background—Although most clinical trials of coronary stents have measured nominally identical safety and effectiveness end points, differences in definitions and timing of assessment have created confusion in interpretation.
Methods and Results—The Academic Research Consortium is an informal collaboration between academic research organizations in the United States and Europe. Two meetings, in Washington, DC, in January 2006 and in Dublin

The Vulnerable Patient

ACS Presentations & Bleeding

Major bleeding data elements and outcomes:

N=22,000 pts from REPLACE-2, ACUITY, HORIZONS-AMI

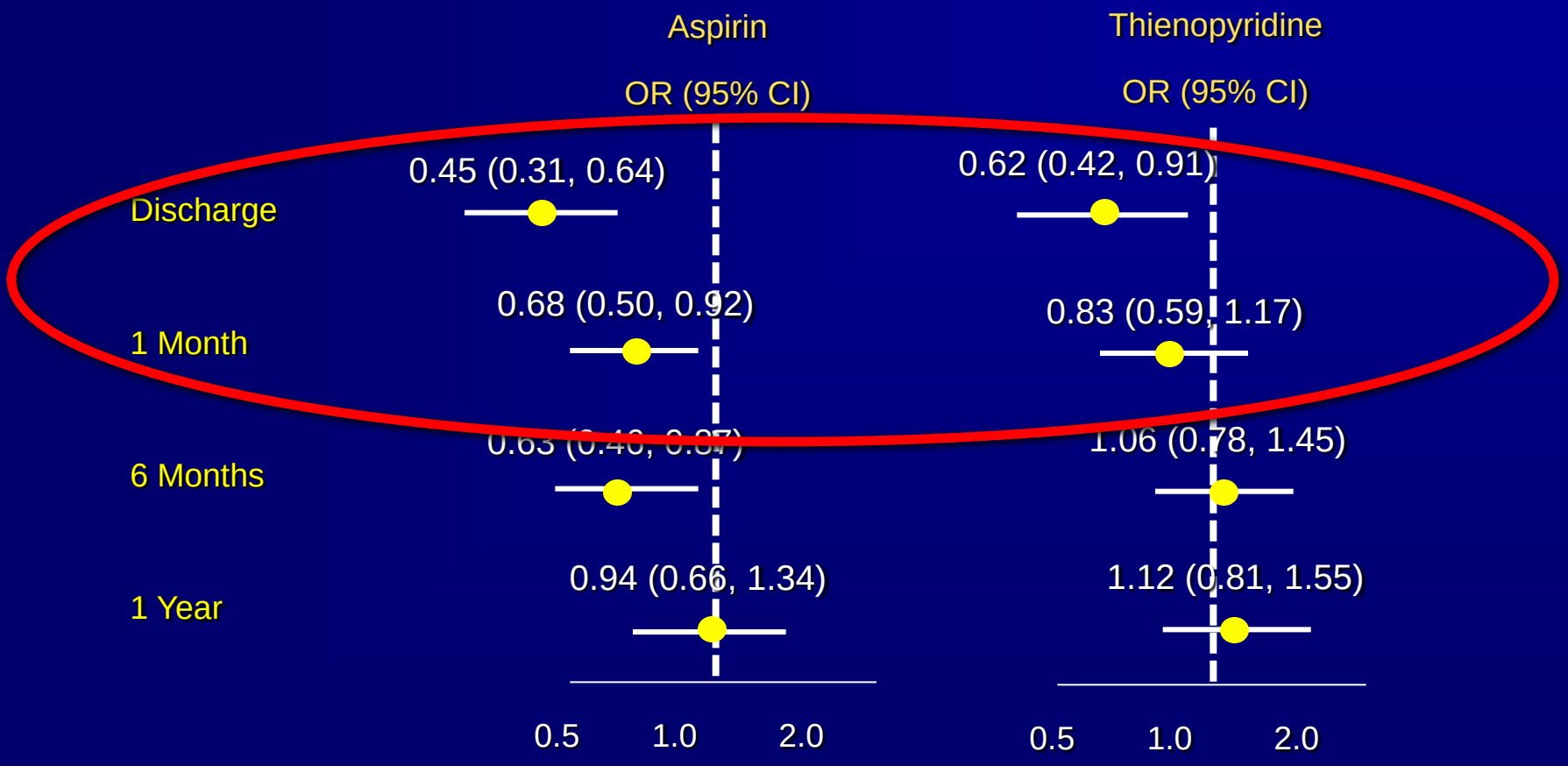
Event	Hazard ratio (95% CI)	Deaths within 1 y, n	p
TIMI major bleed	4.85 (3.56–6.60)	53	<0.001
Non-TIMI major bleed with transfusion	2.98 (2.10–4.24)	40	<0.001
Non-TIMI major bleed without transfusion	1.79 (1.09–2.93)	17	0.021
Large (≥5 cm) hematoma only	1.30 (0.58–2.92)	6	0.53

Mehran R, et. al. *EHJ* 2009

Interruption of DAPT

N=2498 ACS patients from the PREMIER Registry

Discharge ASA and thienopyridine
Pts. with bleeding vs. pts. without bleeding



Wang TY, et. al. Circulation 2008

The Vulnerable Stent

Safer Stent Designs

TUESDAY

ESC Congress News

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Do drug-eluting stents increase deaths?

TWO SEPARATE, independent meta-analyses, presented in Hot Line session I, suggest drug-eluting stents (DES) may increase death, Q-wave myocardial infarction (clinical surrogates of in-stent thrombosis) and cancer deaths, bringing the long-term safety of DES firmly into the spotlight. Discussant Salim Yusuf (McMaster University, Canada) hailed the data as one of the most important presentations to come out of this year's meeting.

"Six million people in the world have been implanted with DES, yet their long-term safety and efficacy is unknown," said Yusuf. "I've a ling the data we're seeing today is only the the iceberg. We need to encourage more ss to the data."

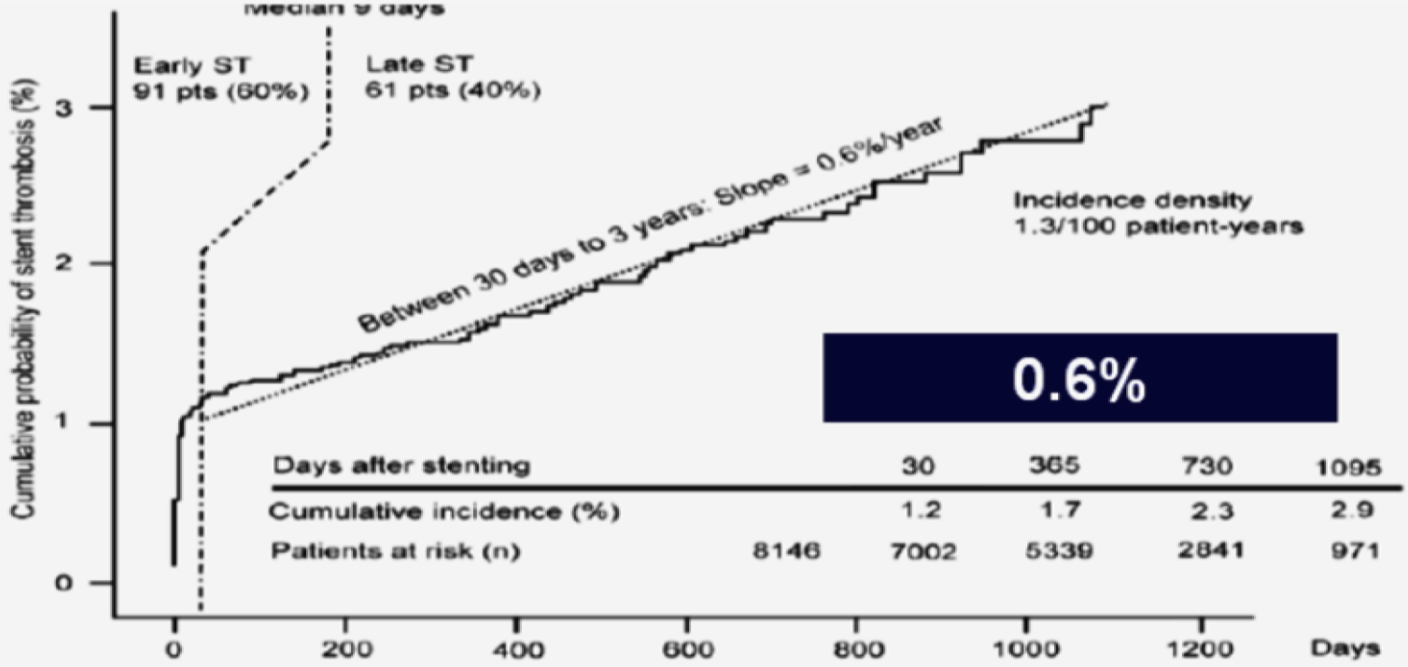
obtain this data from the manufacturer," said Nordmann. He speculated that the increase in cancer might be due to a rapid impairment of the immune system.

Yusuf widened the debate to include percutaneous coronary intervention (PCI). "The overuse of PCI is an insidious change in the culture of cardiology that needs to be reversed," he said. The use of PCI was established in MI, high-risk unstable angina and cardiogenic shock. However, its use in stable disease was a totally different question.

"There's no beneficial influence on mortality – PCI does nothing to prevent heart attack. All we are doing is providing short-term relief of chest pain. It's not re-stenosis that kills but

Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study

Joost Daemen, Peter Wenaweser, Keiichi Tsuchida, Linda Abrecht, Sophia Vaina, Cyrill Morger, Neville Kukreja, Peter Jüni, Georgios Sianos, Gerrit Hellige, Ron T van Domburg, Otto M Hess, Eric Boersma, Bernhard Meier, Stephan Windecker, Patrick W Serruys



DES = drug eluting stent; N = number; pts = patients; ST = stent thrombosis. Adapted from (67)

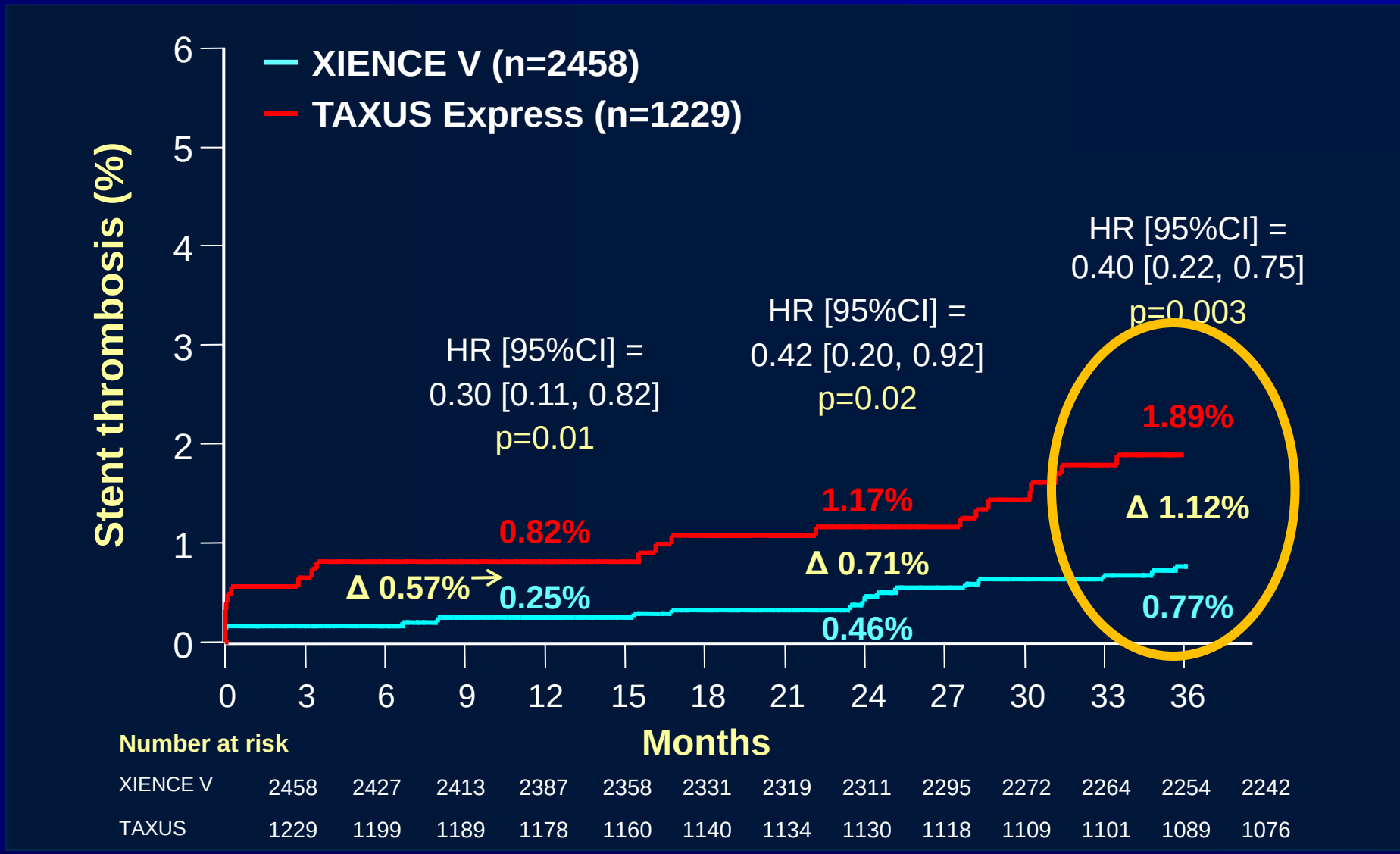
Daemen J et al, Lancet 2007; 369(9562):667-678.

Design Targets for Safer DES

ST contributing factors

- **The Patient: thrombotic lesions (STEMI, ACS)**
- **The Procedure: trauma, malaposition**
- **The Polymer: inflammation, allergy**
- **The Drug: mTor inhibition: collateral damage**
- **DAPT: how much, how long, bleeding & cost**

Spirit IV:
3 year Stent Thrombosis (Protocol Definition)*



DUKE UNIVERSITY MEDICAL CENTER

CRI Duke Clinical Research Institute

Why Do We Need Safer DES?

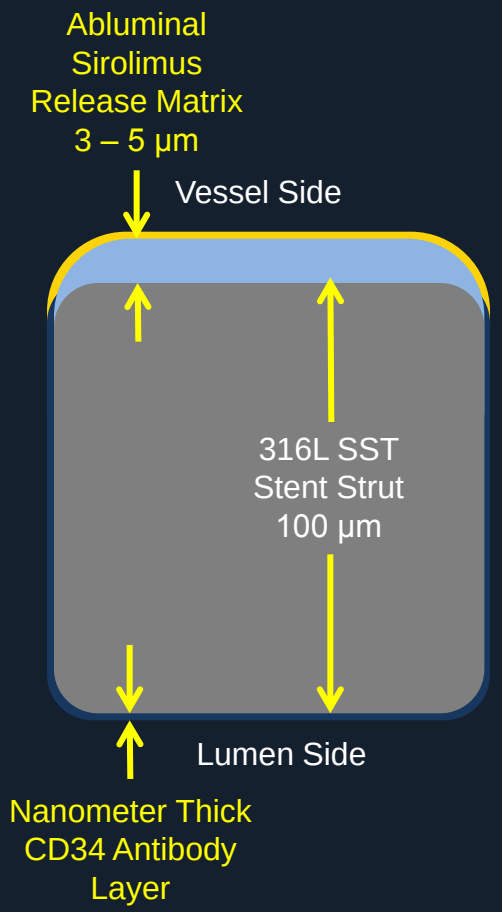
- **Modern state of the art DES are very good**
- **Stent thrombosis rates around 2%**
- **12 month DAPT or more still widely practiced**

- **Global PCI:**
  - **> 10 million DES patients**
  - **> 1 million more per annum**
- **2% Stent thrombosis:**
  - **>20,000 STEMI & death yearly**
- **For every 6 months of DAPT:**
  - **>180 million uncecessary doses**
  - **>30,000 bleeding events yearly**
- **Even worse in aging populations**

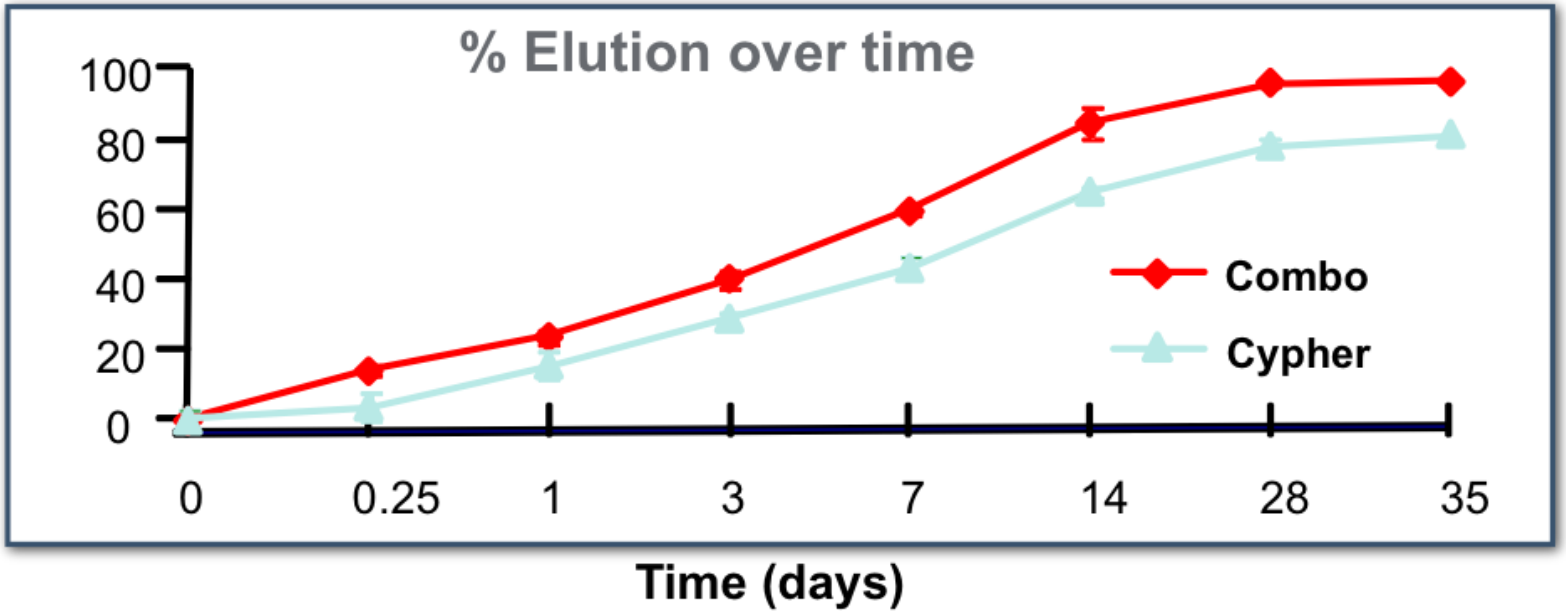
COMBO Dual Therapy Stent

Design features:

- Abluminal biodegradable polymer matrix
- Sirolimus elution
- Genous technology for accelerated endothelial coverage



Abluminal Sirolimus Drug Delivery from a completely biodegradable polymer matrix

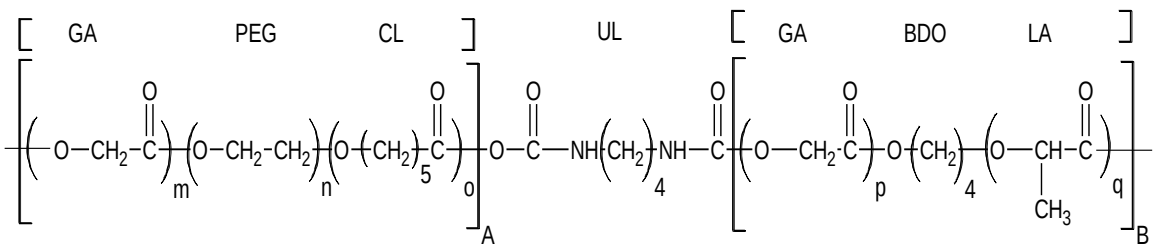


In vivo **elution profile of Combo and Cypher (% of total drug eluted over time)**

Polymer matrix degradation within 90 days

Granada et al., Circ Cardiovasc Intervent. 2010; 3:257-266

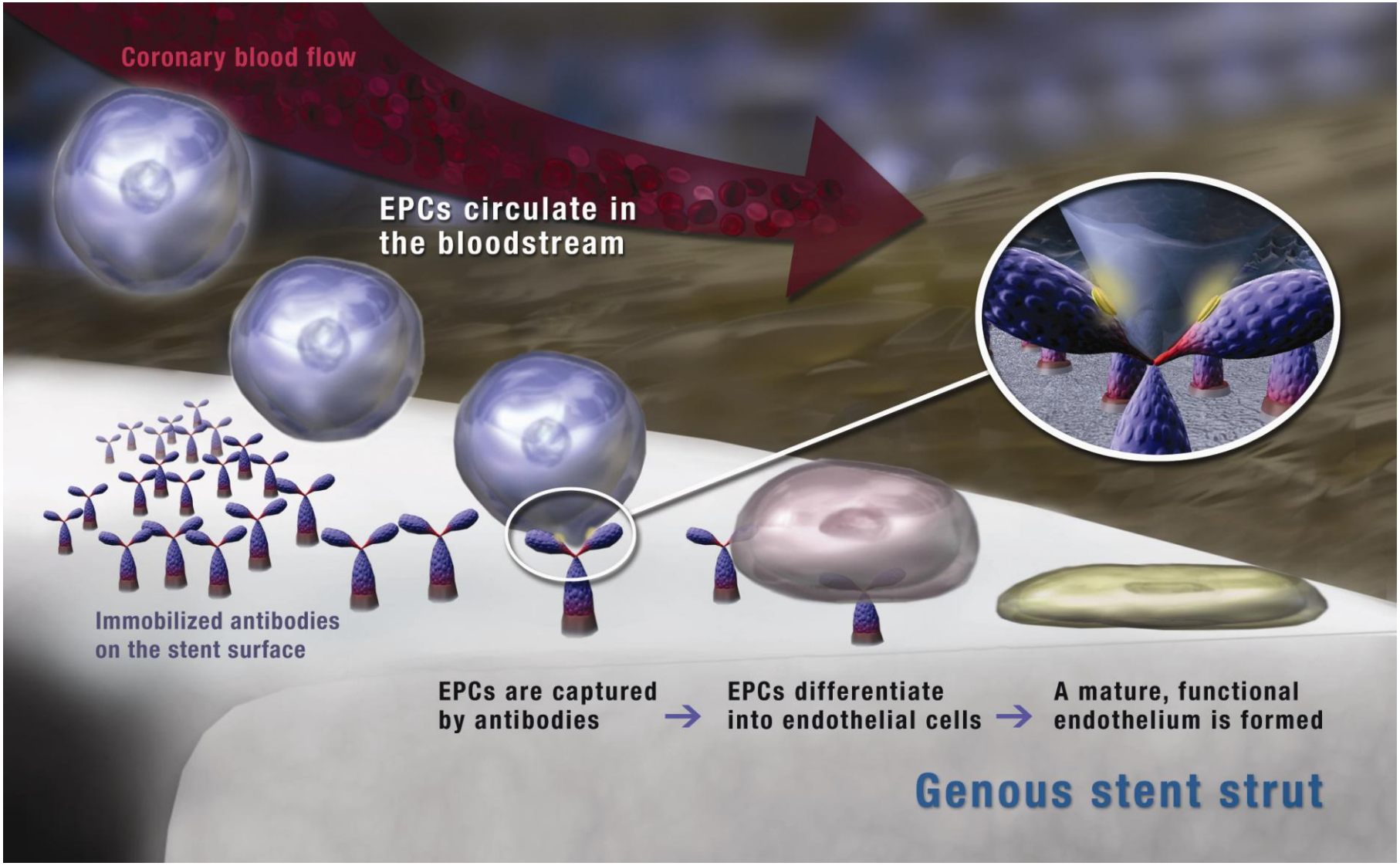
Abluminal Surmodics SynBiosys™ Polymer



GA=poly Glycolic Acid
PEG=Poly Ethylene Glycol
CL= poly ε-CaproLactone
UL=Urethane Linkage
BDO=Ester Linkage
LA=poly Lactic Acid

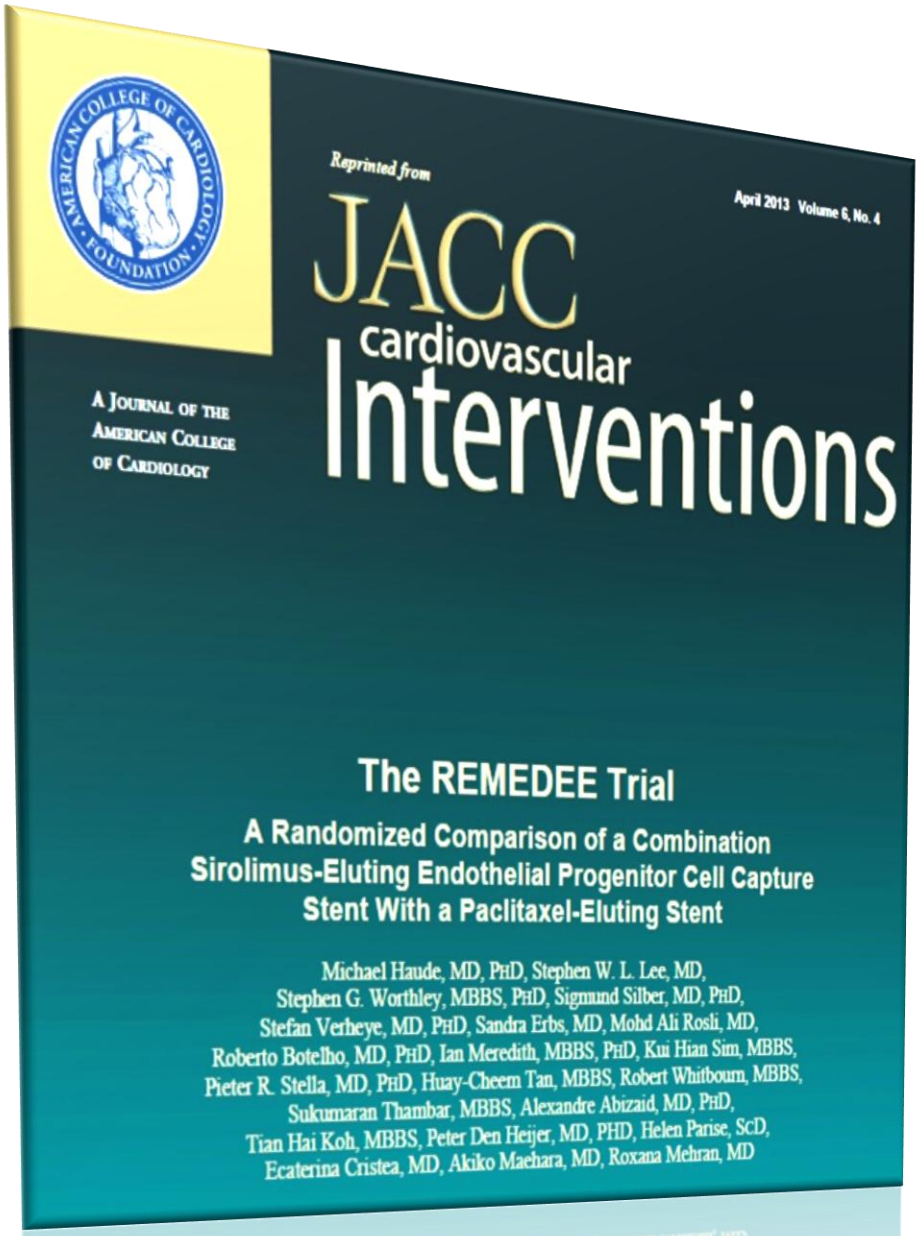
- **Lactide-glycolide block co-polymer**
- **Resorption within 90 days**
- **Degradation is by hydrolysis into small molecules that are excreted by the urinary and respiratory systems**

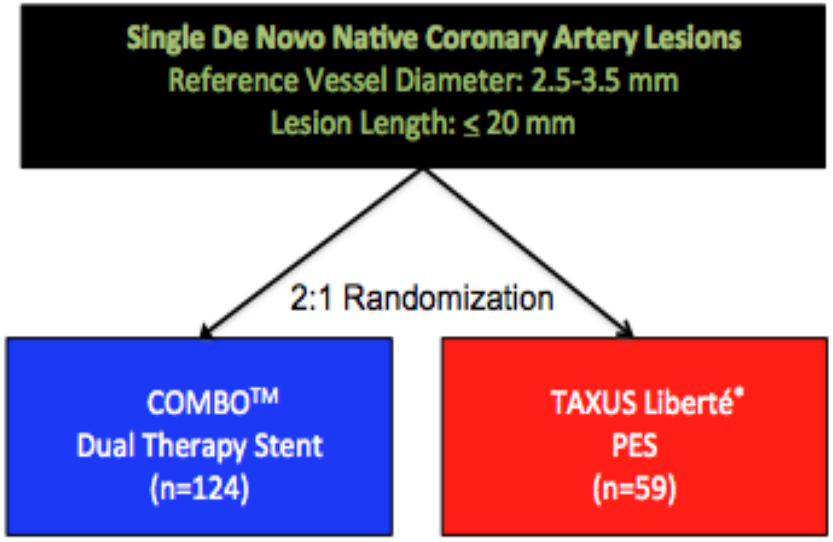
EPC Capture Concept



What is the interest of EPC capture?

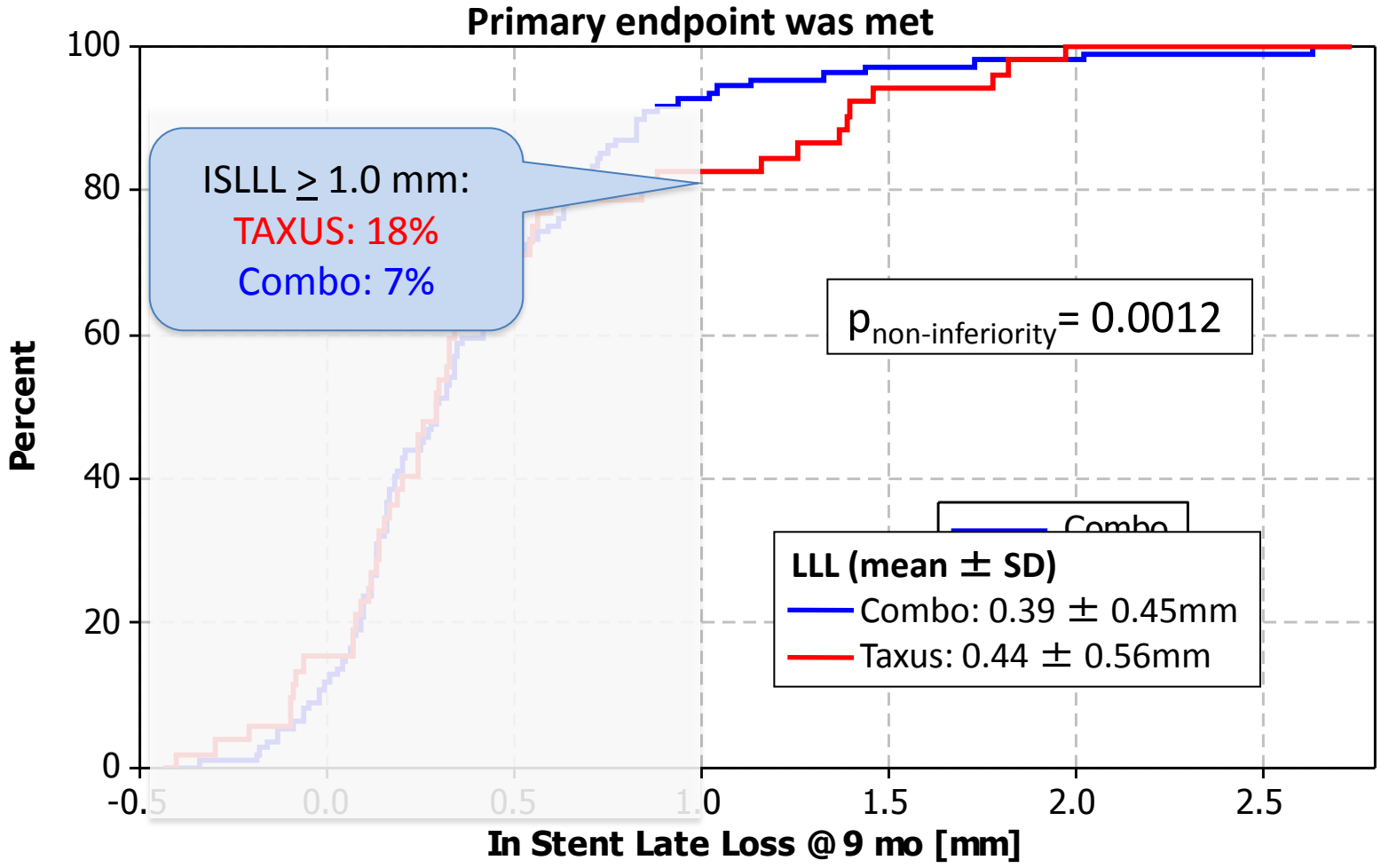
- **EPC capture design objective:**
  - **Faster endothelialization of stent struts**
  - **More complete endothelialization of stent struts**
  - **More rapid endothelialization between struts**
- **Clinical implications of better endothelialization:**
  - **Lower early stent thrombosis (vs. trauma)**
  - **Lower late & very late stent thrombosis (vs. non-healing)**
  - **Shorter DAPT**
  - **Safer for ruptured plaque (ACS, STEMI)**
  - **Safer for high risk of DAPT interruption pts (BMS)**



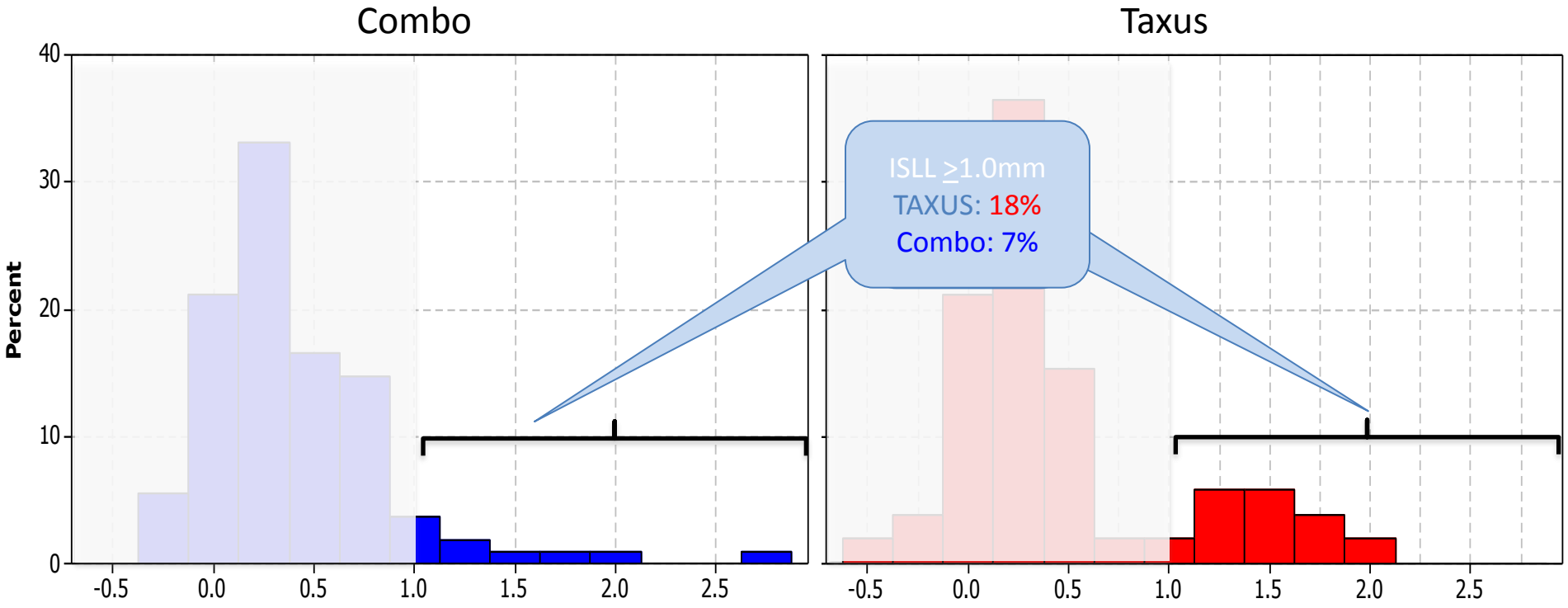


Primary endpoint:
Angiographic in-stent LLL at 9 months
tested for non-inferiority

In-stent Late Lumen Loss at 9 Months
Cumulative Frequency Distribution



Histograms of In-stent Late Loss at 9 Months



LLL distributions show different patterns:

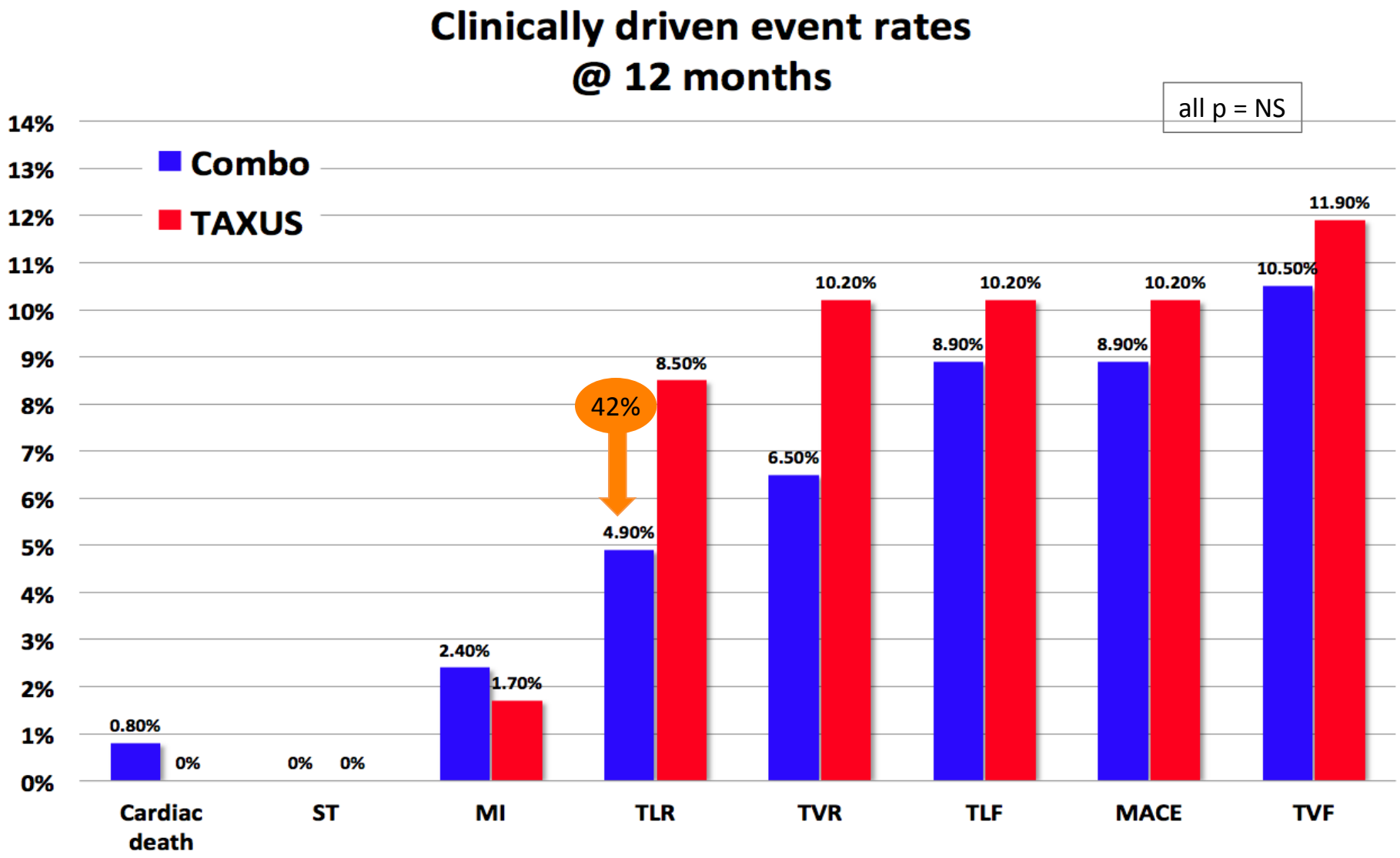
- Combo stent: slight tail (n= 109)
- Taxus stent: bimodal appearance (n= 52)

Angiographic Parameters at 9 Months

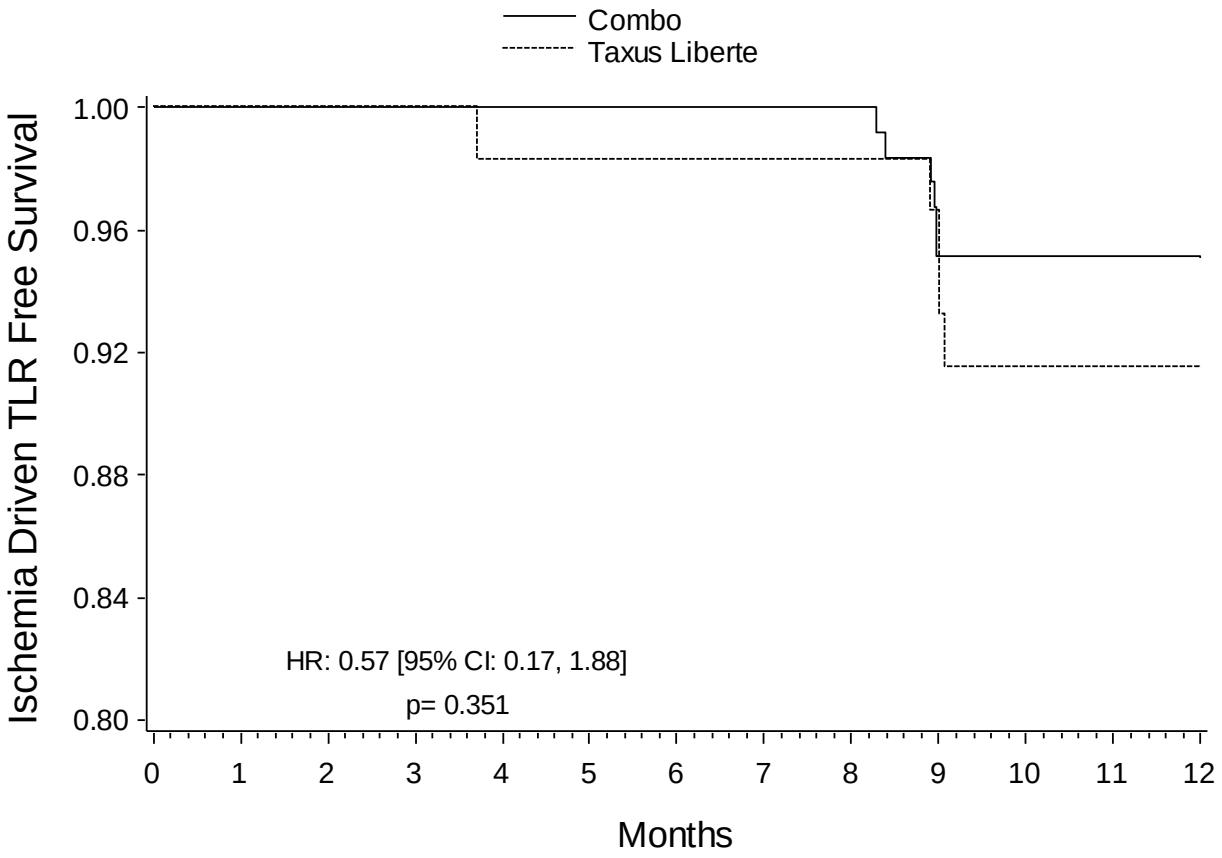
	Combo (N=124)	**TAXUS** (N=59)	**p-value**
Restenosis (%)			
In-stent	5.5%	9.6%	0.34
In-segment	8.3%	13.5%	0.30
Minimum Lumen Diameter (MLD) (mm)			
In-stent, mean ± SD	2.31 ± 0.58	2.30 ± 0.56	0.86
In-segment, mean ± SD	2.09 ± 0.56	1.97 ± 0.57	0.19
In-stent late lumen loss (mm)			
mean ± SD	0.39 ± 0.45	0.44 ± 0.56	0.55
	Non inf. P=0.0012		
In-segment late lumen loss (mm)			
mean ± SD	0.27±0.46	0.41±0.54	0.08
Proximal In-segment, mean ± SD	0.19 ± 0.44	0.29 ± 0.53	0.24
Distal In-Segment, mean ± SD	0.09 ± 0.30	0.13 ± 0.30	0.45

Met primary endpoint of non-inferiority

REMEDEE Clinical Results



Target Lesion Revascularization (KM Graph)

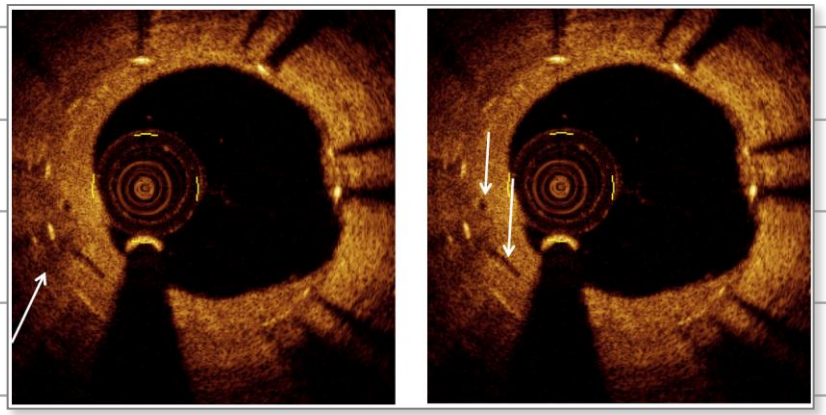


Number at risk / (Cumulative events) rate

Combo	124	124	124	117	63
	(0) 0.0%	(0) 0.0%	(0) 0.0%	(6) 4.9%	(6) 4.9%
Taxus Liberte	59	59	58	57	34
	(0) 0.0%	(0) 0.0%	(1) 1.7%	(2) 3.4%	(5) 8.5%

Qualitative Analysis (OCT)

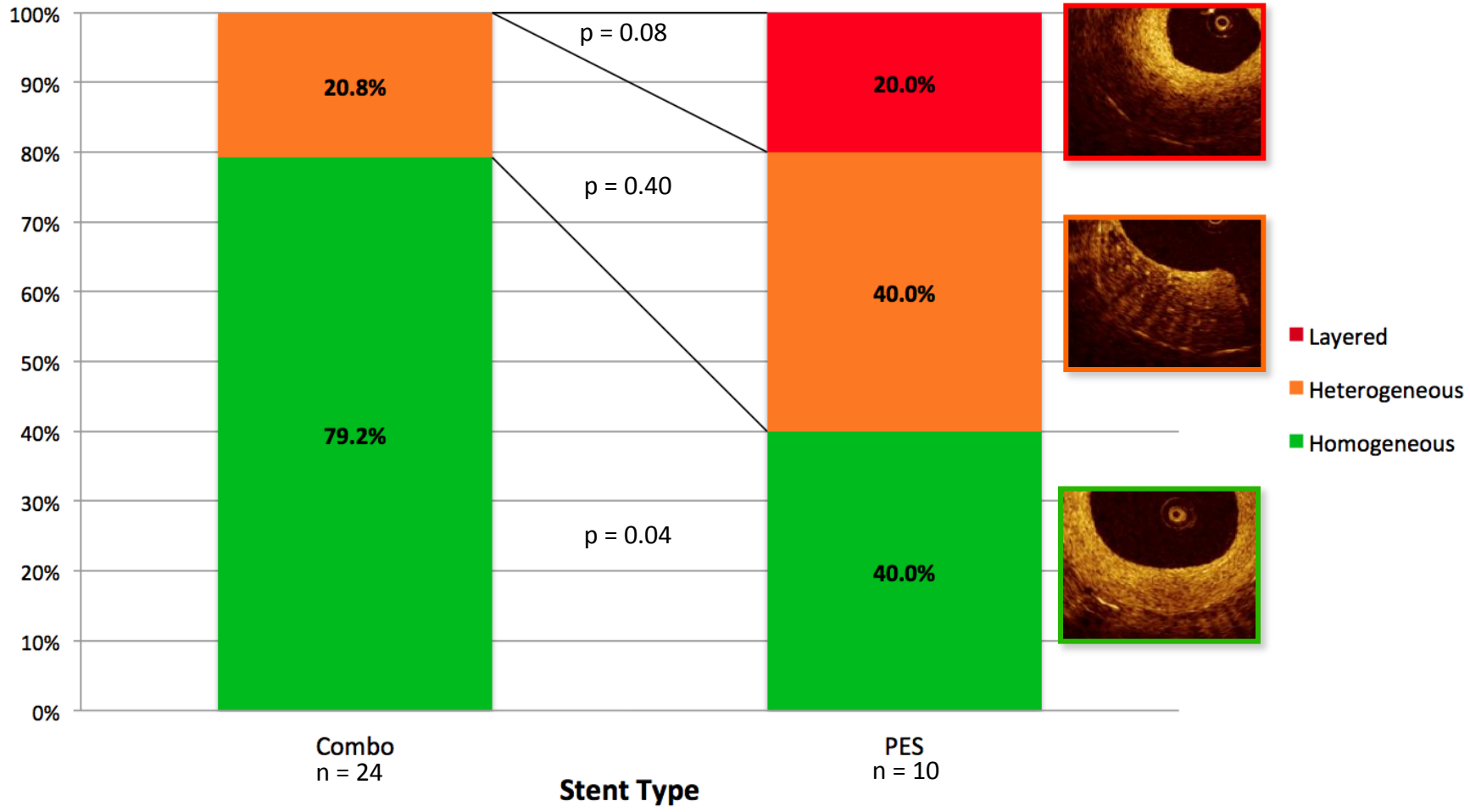
REMEDEE (9 month FU)



Wijns W, AsiaPCR 2013, Singapore

NI Tissue Characterization (OCT)

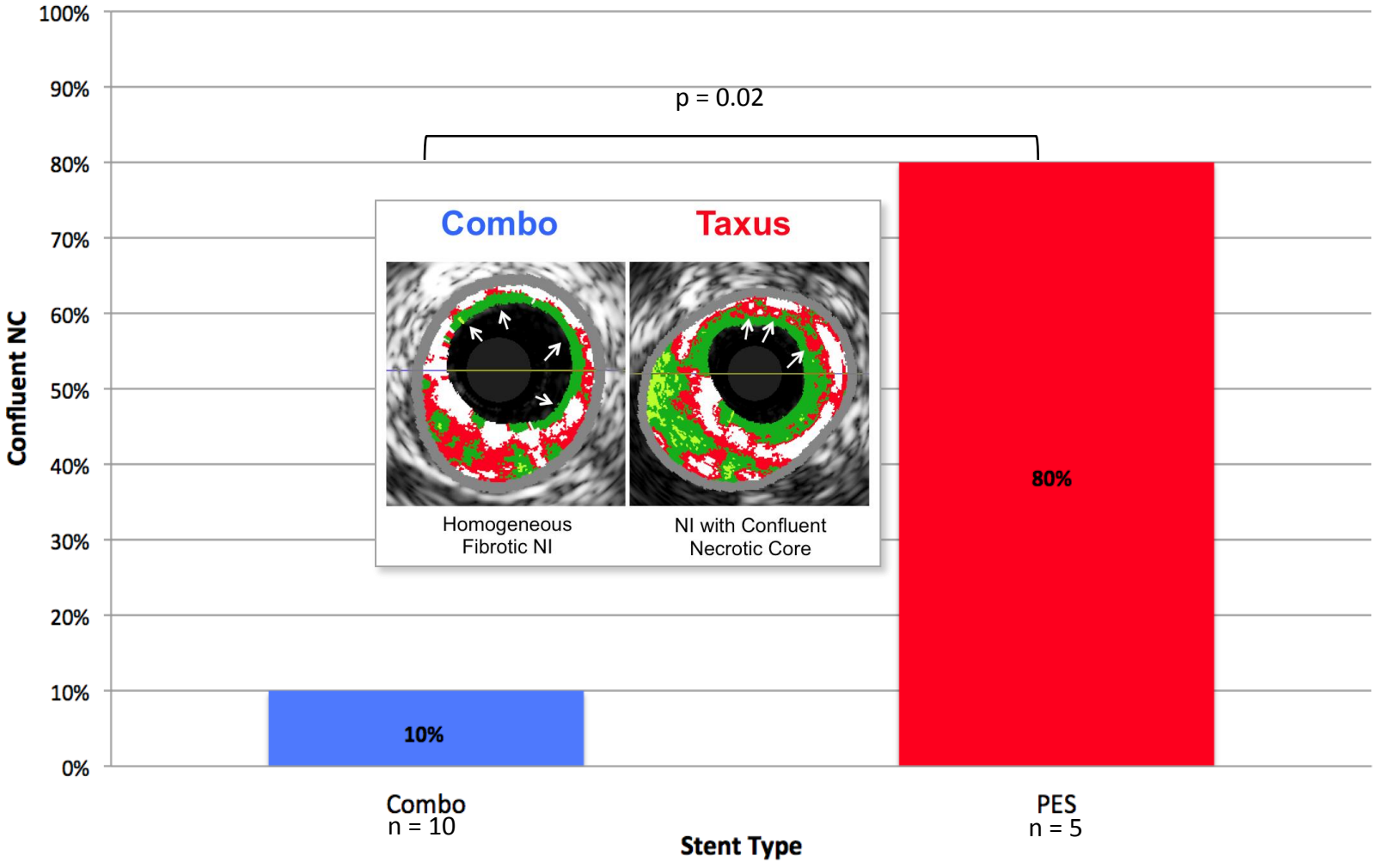
REMEDEE (9 month FU)



Wijns W, AsiaPCR 2013, Singapore

Confluent Necrotic Core in NI (IVUS-VH)

REMEDEE (9 month FU)



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Wijns W, AsiaPCR 2013, Singapore

Conclusions

- Balance of bleeding and thrombosis in PCI pts remains complex
- Improved stent design plays a significant role in addressing these issues
- COMBO stent combines:
  - Abluminal only polymer
  - Absorbable polymer
  - EPC capture anti-CD34 Ab
- COMBO design objectives could affect safety objectives:
  - Early ST rates
  - Late & very late ST rates
  - DAPT dependence, duration
  - Healing of thrombotic lesions (ACS, STEMI)
- COMBO Data to date:
  - Effective anti-proliferative DES technology
  - Mechanistic tissue “signature” of more complete and homogeneous endothelial healing than with Taxus

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