

The Next ERA: COMBO Dual Therapy Stent

The Unmet Need

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MEDICINE


CARDIOVASCULAR RESEARCH
FOUNDATION
A Passion for Innovation



Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

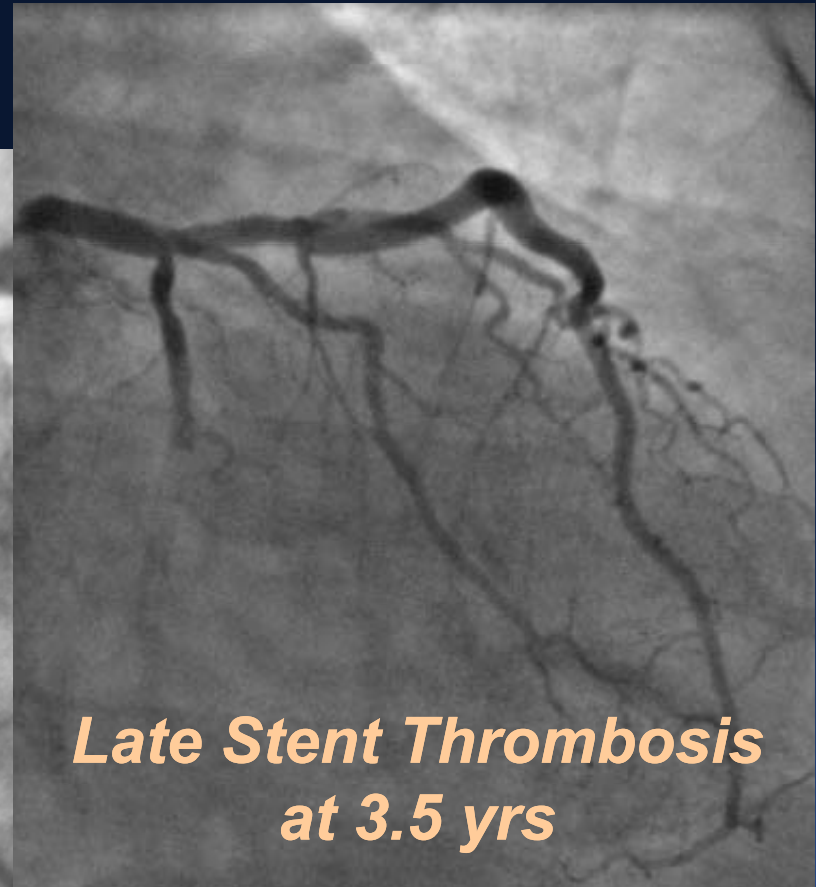
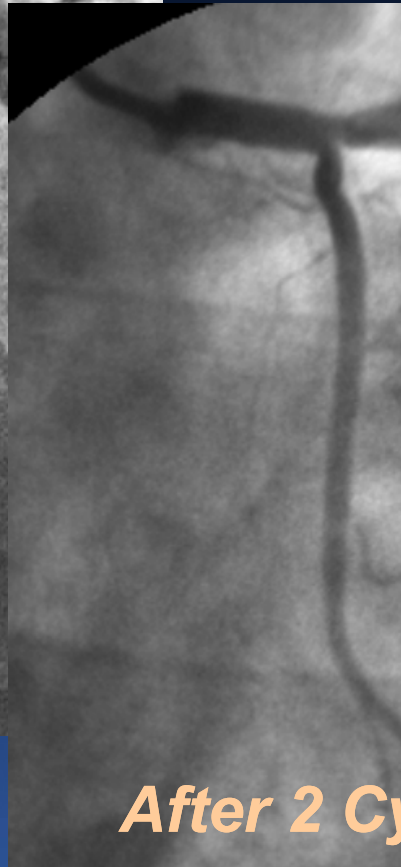
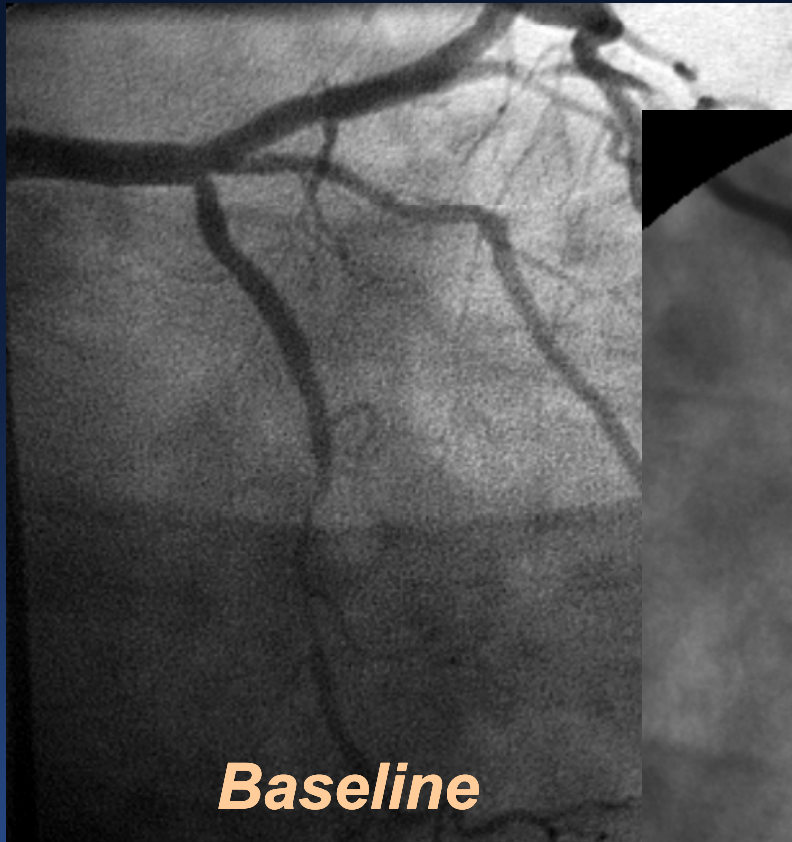
Affiliation/Financial Relationship

- **Grant/Research Support to Institution**
- **Consulting Fees/Honoraria**

Company

- Sanofi/BMS- Significant
- The Medicines Company
- Astra Zeneca, Abbott Vascular, Regado Biosciences, Janssen

Late Cypher Stent Thrombosis After 3 Years



Definition of Stent Thrombosis

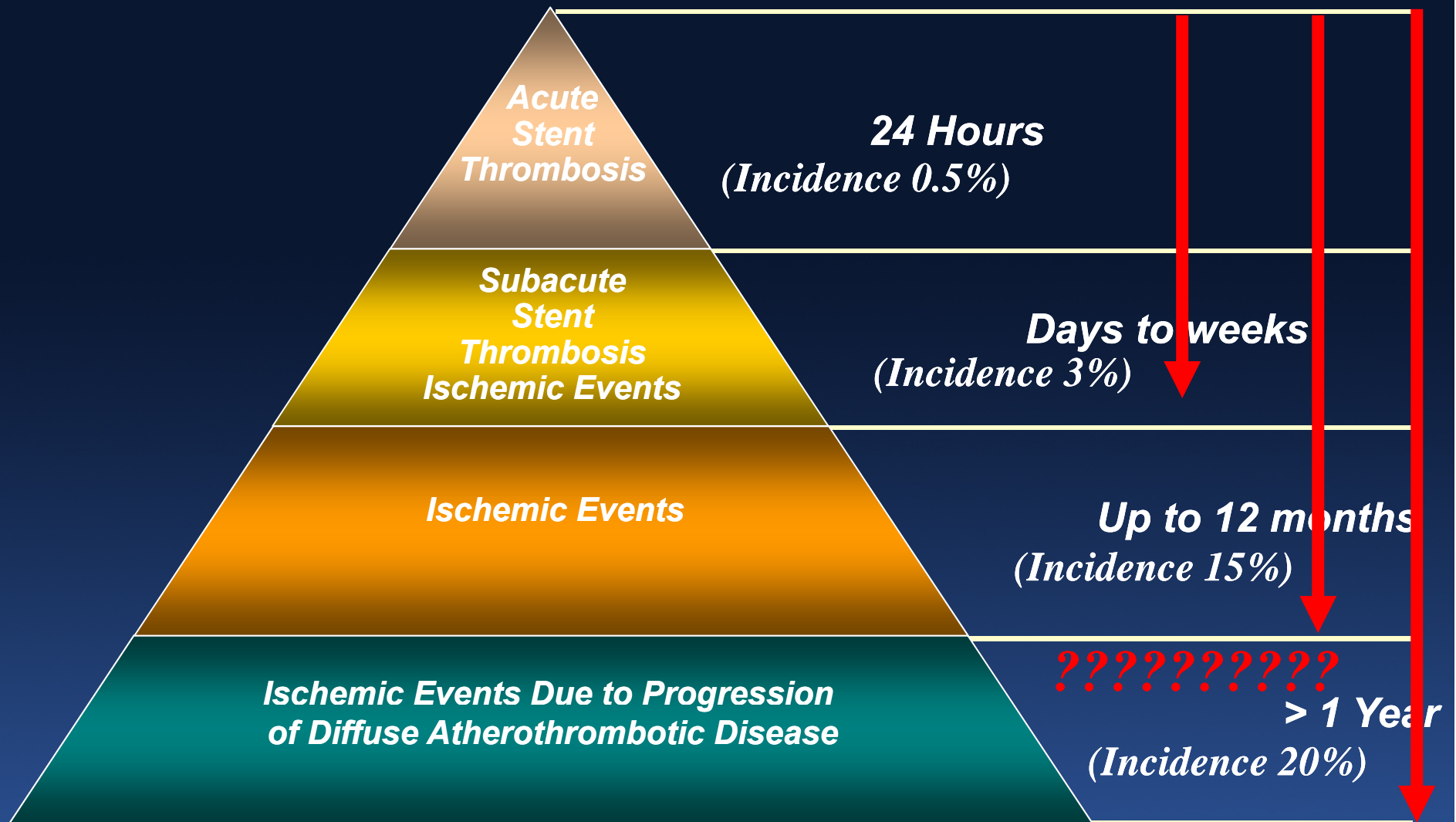
Cutlip D et al. *Circulation* 2007

- **Definite Stent Thrombosis**
 - Angiographic or pathologic confirmation of partial or total thrombotic occlusion within the peri-stent region

AND at least ONE of the following, additional criteria:

 - Acute ischemic symptoms
 - Ischemic ECG changes
 - Elevated cardiac biomarkers
- **Probable Stent Thrombosis**
 - Any unexplained death within 30 days of stent implantation
 - Any myocardial infarction, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
- **Possible Stent Thrombosis**
 - Any unexplained death beyond 30 days

“PYRAMID OF RISK” and BENEFIT w/ ADP Receptor Antagonism:

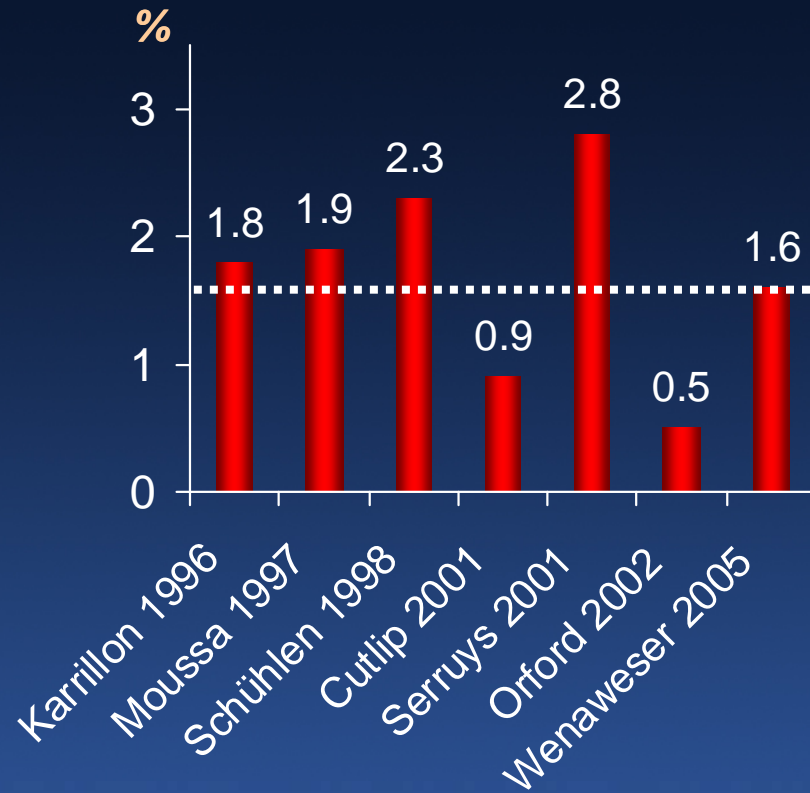


Adapted from Bhatt DL. J Invasive Cardiol. 2003;15:3B

Incidence of Stent Thrombosis

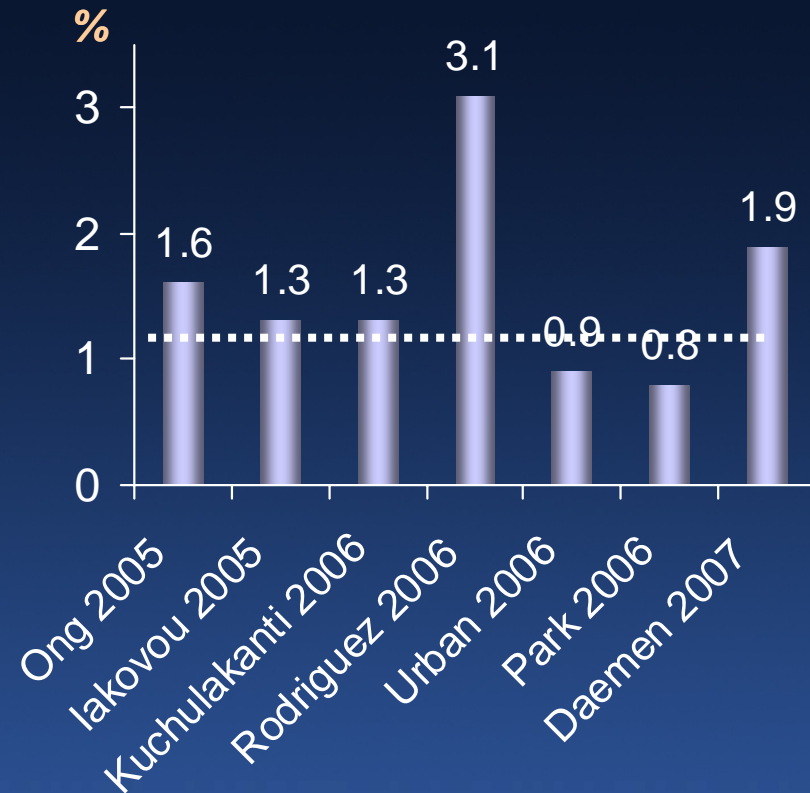
Bare Metal Stents

Mean = 1.4%

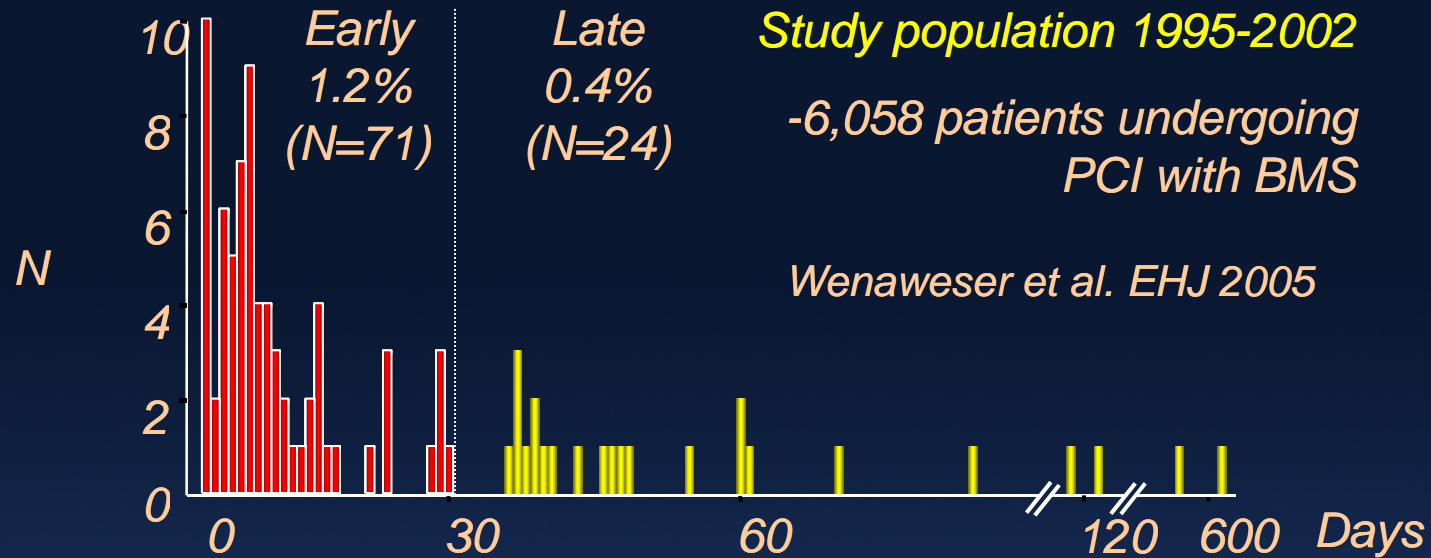


Drug-Eluting Stents

Mean = 1.2%



Late Stent Thrombosis and Bare Metal Stents

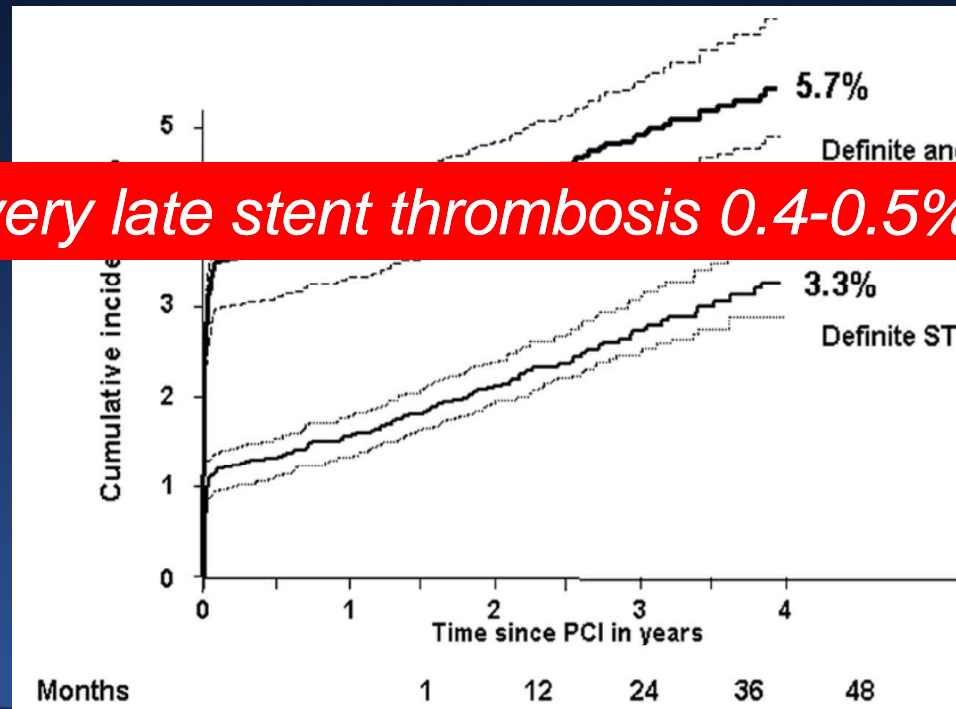


First Generation Drug-Eluting Stents and Very Late Stent Thrombosis Bern-Rotterdam Cohort Study @ 4 Years

Wenaweser P et al. J Am Coll Cardiol 2008, 52(14):1134-40

8,146 consecutive patients treated with 1st generation DES

Stent Thrombosis



Risk of very late stent thrombosis 0.4-0.5% per year

Multifactorial Nature of Stent Thrombosis

Device factors

- Surface
- Drugs
- Polymer
- Stent overlap

Procedural factors

- Dissection
- Incomplete stent apposition and stent expansion
- Brachytherapy

Patient factors

- Drug response/interactions
- Gene polymorphism
- LV function
- Acute coronary syndrome
- Renal failure
- Diabetes

STENT THROMBOSIS

Lesion factors

- Vessel size/length
- Thrombus
- Plaque characteristics
- Bifurcation
- Calcification
- Total occlusions

Stent-Artery-Interaction

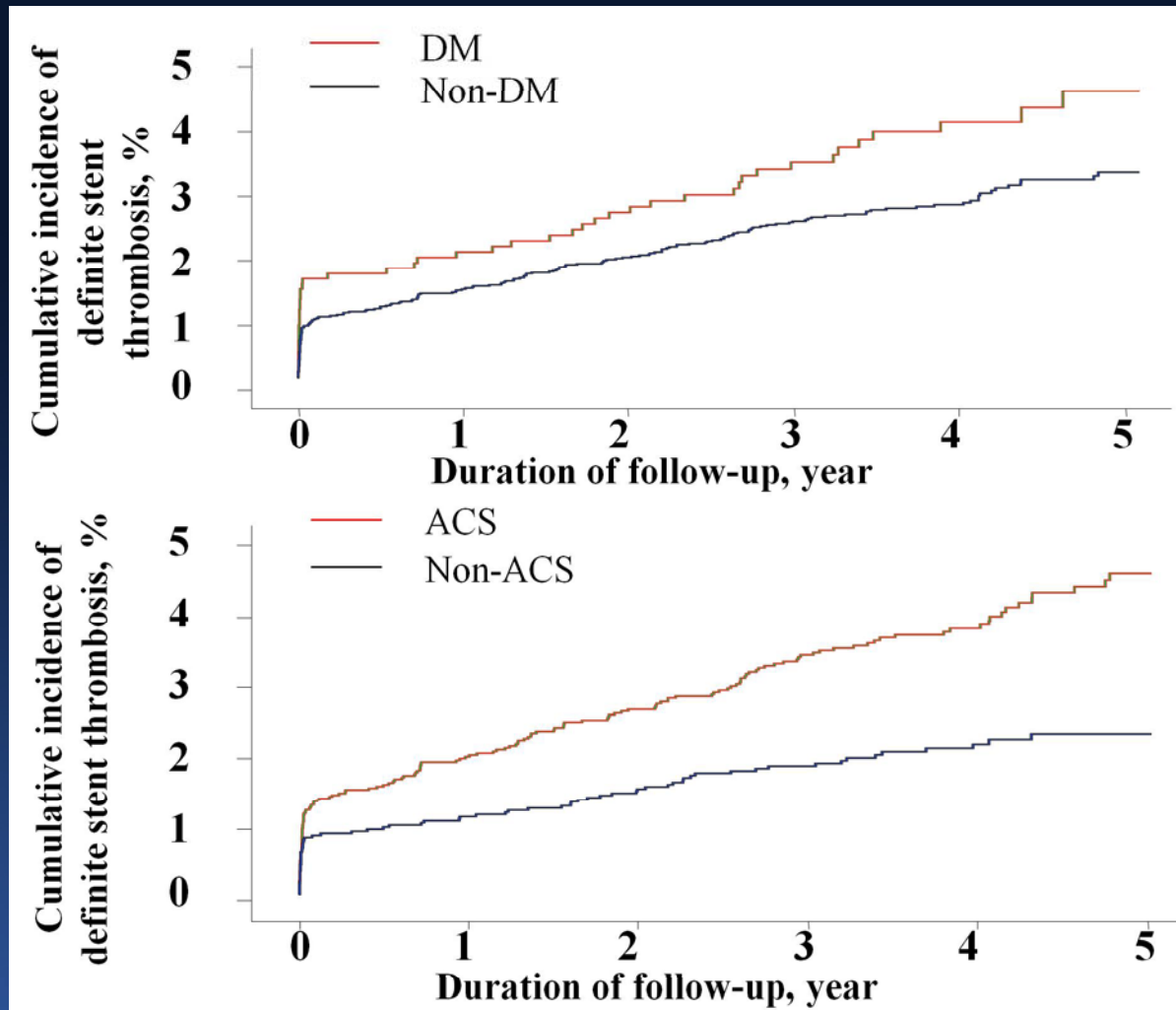
- Late Malapposition
- Hypersensitivity reaction

Platelet and Coagulation factors

- Coagulation activity
- Inhibition of platelet aggregation
- Inadequate response to anti-platelet therapy
- Premature anti-platelet therapy discontinuation

BR-Cohort Study @ 5 Years

Onuma Y. et al. ESC 2009



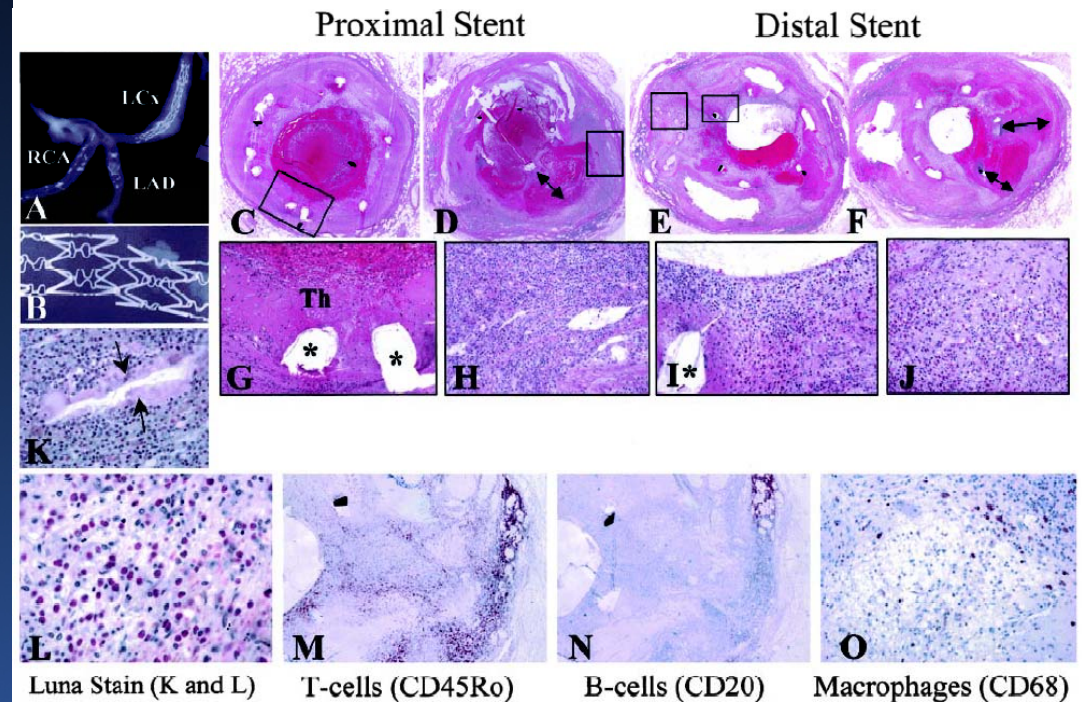
Hypersensitivity Associated With Drug-Eluting Stents

Virmani R et al. *Circulation* 2004;109:701-5

Nebeker J et al. *JACC* 2006;47:175-81

RADAR registry

- 262 of 5,783 DES related reports with hypersensitivity symptoms
- 17 cases probably or certainly related to DES
 - 4 cases of fatal stent thrombosis with focal hypersensitivity on autopsy (eosinophilic infiltrates)
 - Clinical manifestations
 - Rash, hives, dyspnea, myalgia/arthritis, itching
 - Laboratory findings
 - Eosinophilia
 - Elevated IgE titers

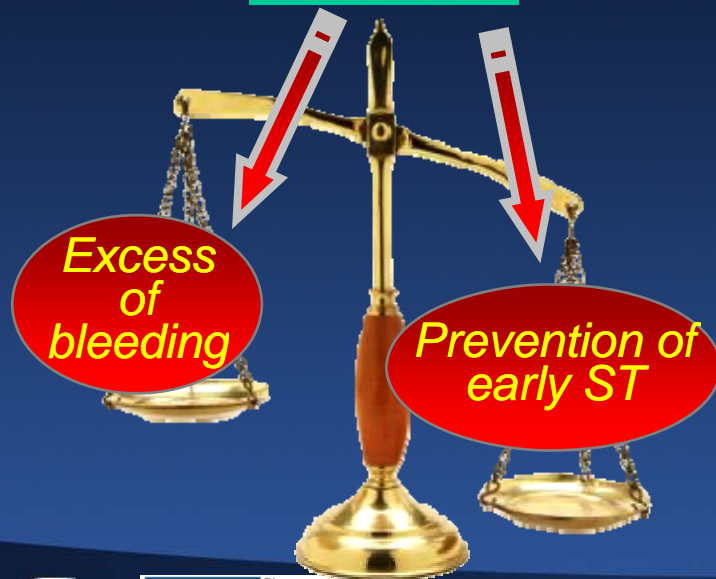


Prevention of Early ST

**Optimal
Platelet Inhibition**

**Optimal
Procedural Result**

*Extent of
platelet
inhibition*



No residual dissection

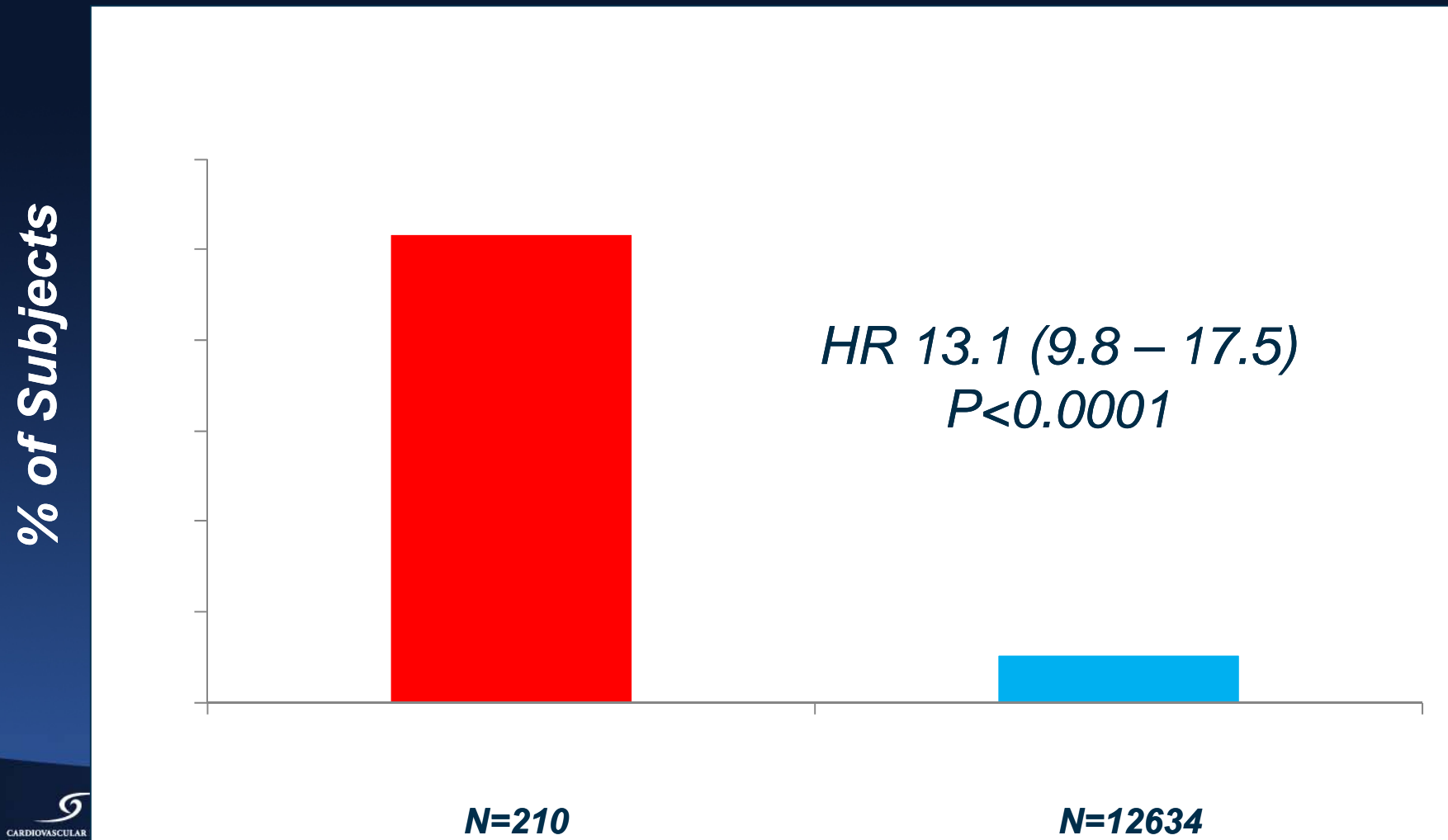
*Stent length as short as possible
and as long as needed*

Complete stent expansion

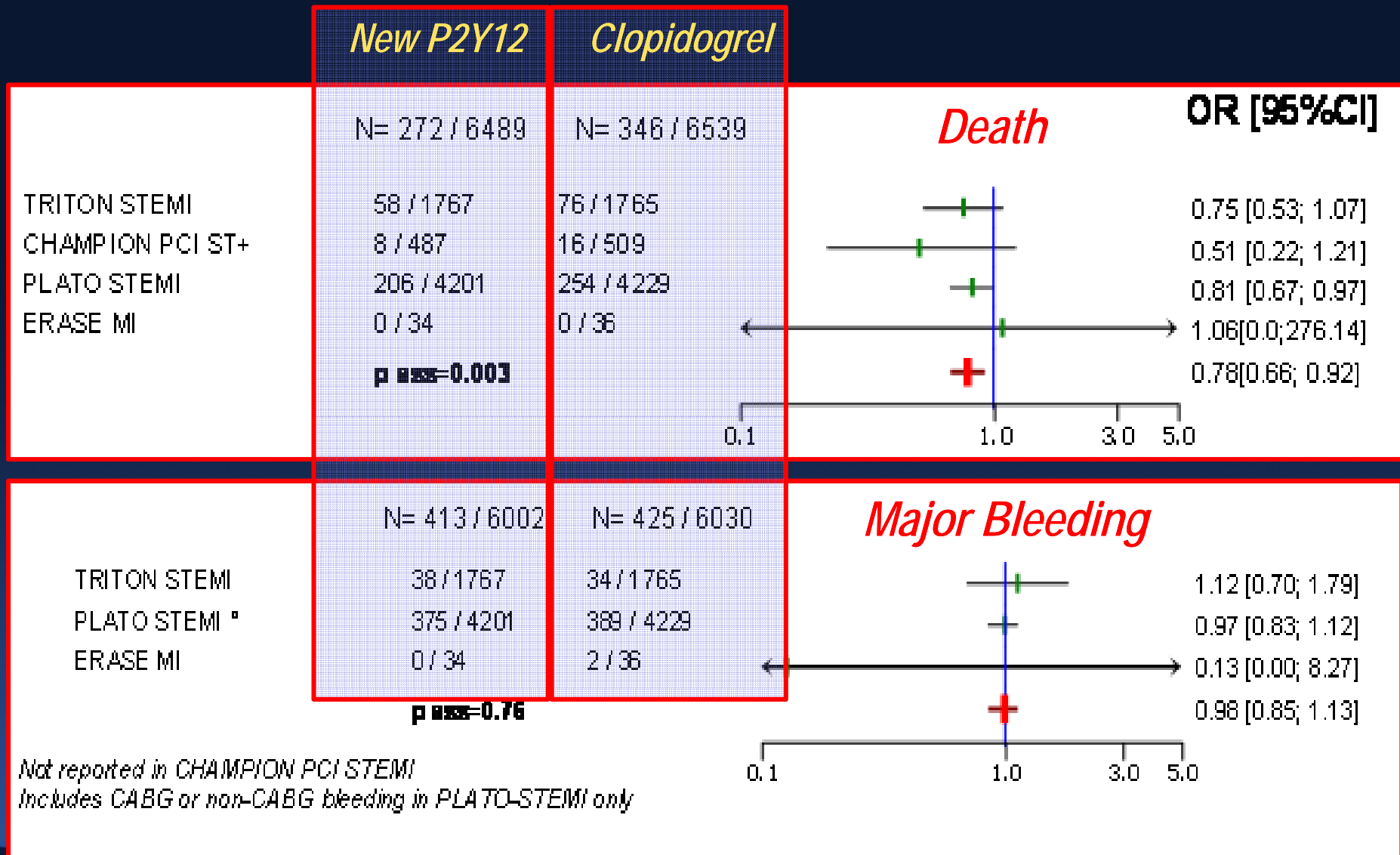
Death Following ST

STENT ANALYSIS

Mortality During Follow up (%) Post-Stent Thrombosis

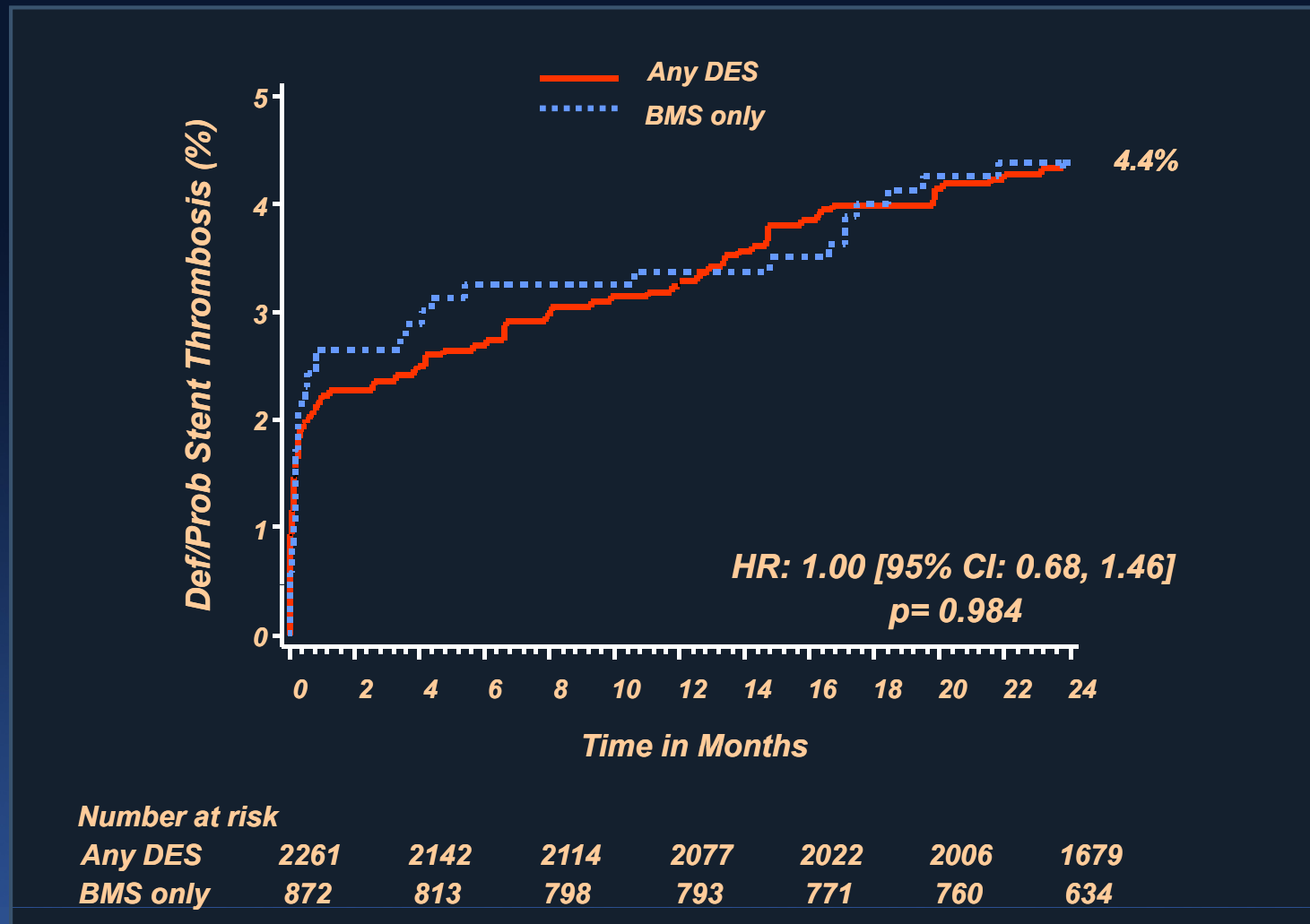


New P2Y12 in PCI for STEMI: ↓Death



HORIZONS-STENT THROMBOSIS: 2-year Events

Effect of DES Use







HORIZONS-STENT THROMBOSIS: 2-Year Events

Independent Predictors of ANY Definite/Probable ARC ST

<i>Variables</i>	<i>H.R. (95% C.I.)</i>	<i>p</i>
Insulin-Treated Diabetes	2.88 (1.64, 5.07)	0.0002
Angiographic Aneurysm	2.54 (1.04, 6.22)	0.041
History of Previous PCI	2.36 (1.53, 3.64)	0.0001
Angiographic Ulceration	2.25 (1.04, 4.86)	0.039
Current Smoking	1.66 (1.16, 2.38)	0.006
Baseline flow grade TIMI 0/1	1.59 (1.07, 2.36)	0.021
Baseline Platelet Count	1.0041 (1.0021, 1.0060)	<.0001
Pre-Randomization Heparin	0.55 (0.39, 0.79)	0.001

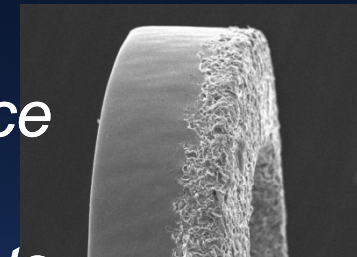
Prevention of Late ST – New Stent Technology

- *New Generation DES with smaller strut thickness*

CYPHER®	TAXUS®	ENDEAVOR	XIENCE V
			
Strut Thickness: 157 µm	Strut Thickness: 132 µm	Strut Thickness: 91 µm	Strut Thickness: 81 µm
Polymer Thickness: 12.6 µm	Polymer Thickness: 16 µm	Polymer Thickness: 5.3 µm	Polymer Thickness: 7.6 µm
Total: 169.6 µm	Total: 148 µm	Total: 96.3 µm	Total: 88.6 µm

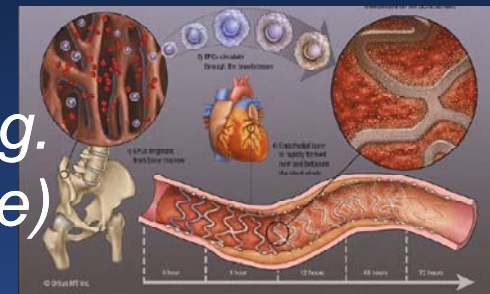
- *Biodegradable polymers*

- *Polymer free surface*



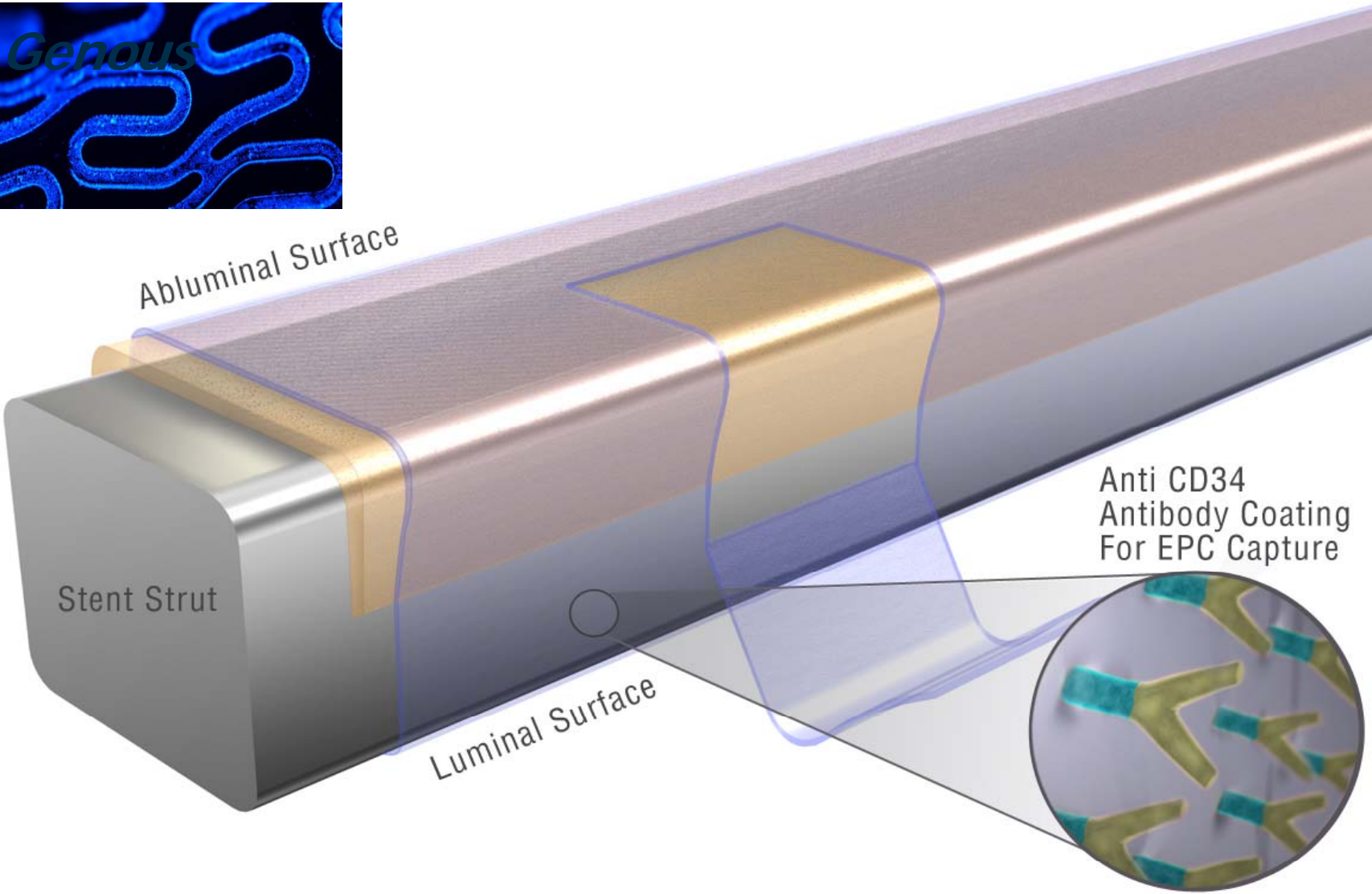
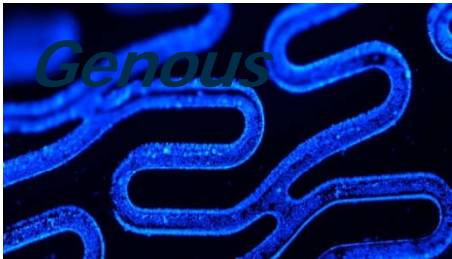
- *Bioabsorbable stents*

- *Concepts facilitating endothelial coverage (e.g. endothelial progenitor cell capture)*



- *Use of antithrombotic stent surface*

Combo Bio-engineered Sirolimus Eluting Stent



Combo Dual Therapy Stent

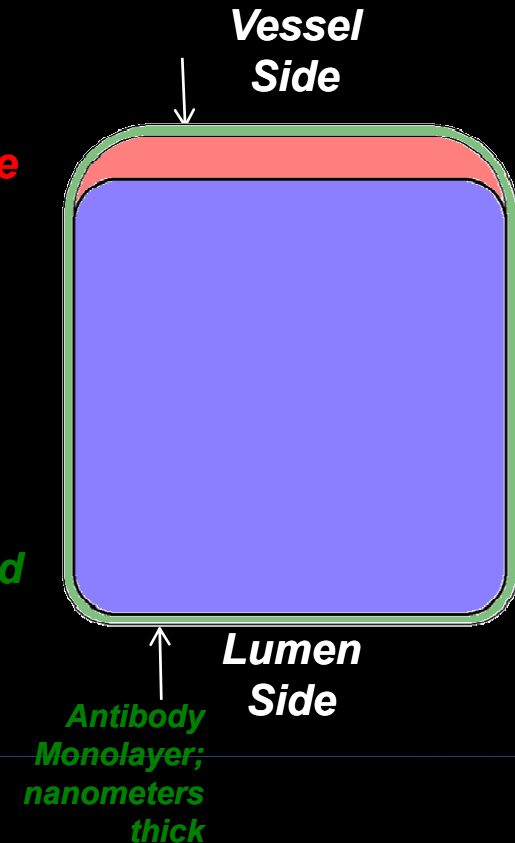
Design features:

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

**Abluminal
Sirolimus Release
Matrix**

**316L Stainless
Steel Stent Strut
Cross-section**

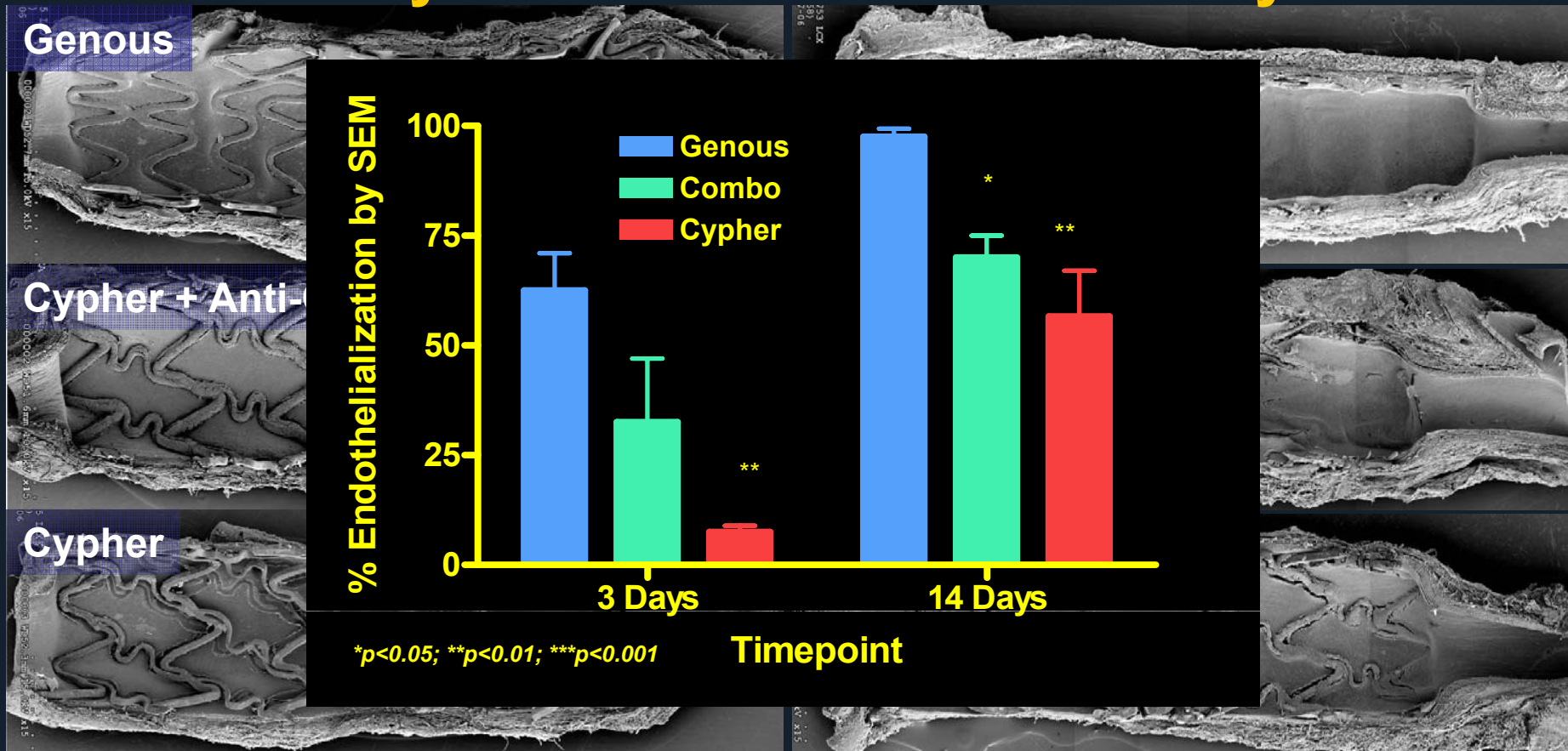
**Outer Immobilized
Anti-CD34
Antibody
Treatment**



Stent Surface Coverage by SEM in Stented Arteries at 3 and 14 Days

3 Days

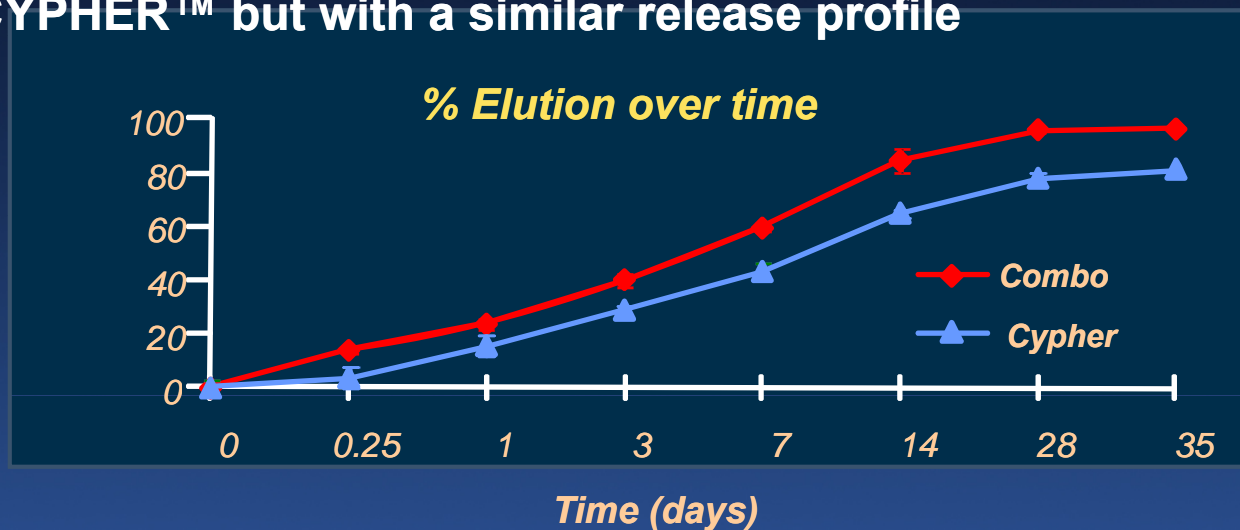
14 Days



Combo Stent

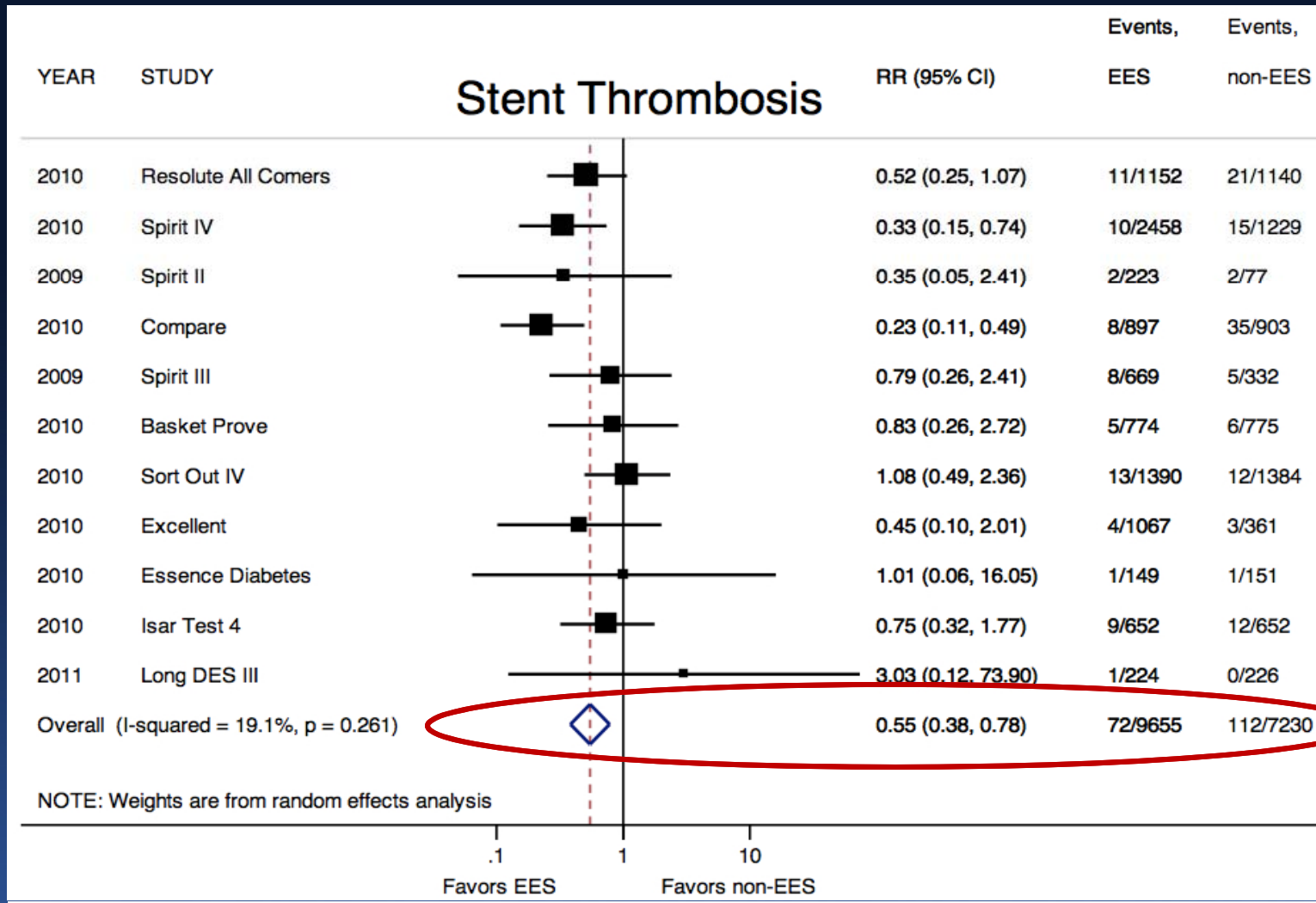
Sirolimus Drug Elution

- Drug – Sirolimus
- Polymer - biodegradable Surmodics SynBiosys™ proprietary blend of urethane-linked block co-polymers of lactide, glycolide, and ϵ -caprolactone; degradation time <90 days
- Drug content is 5 $\mu\text{g}/\text{mm}$ stent length, approximately half the dose of CYPHER™ but with a similar release profile

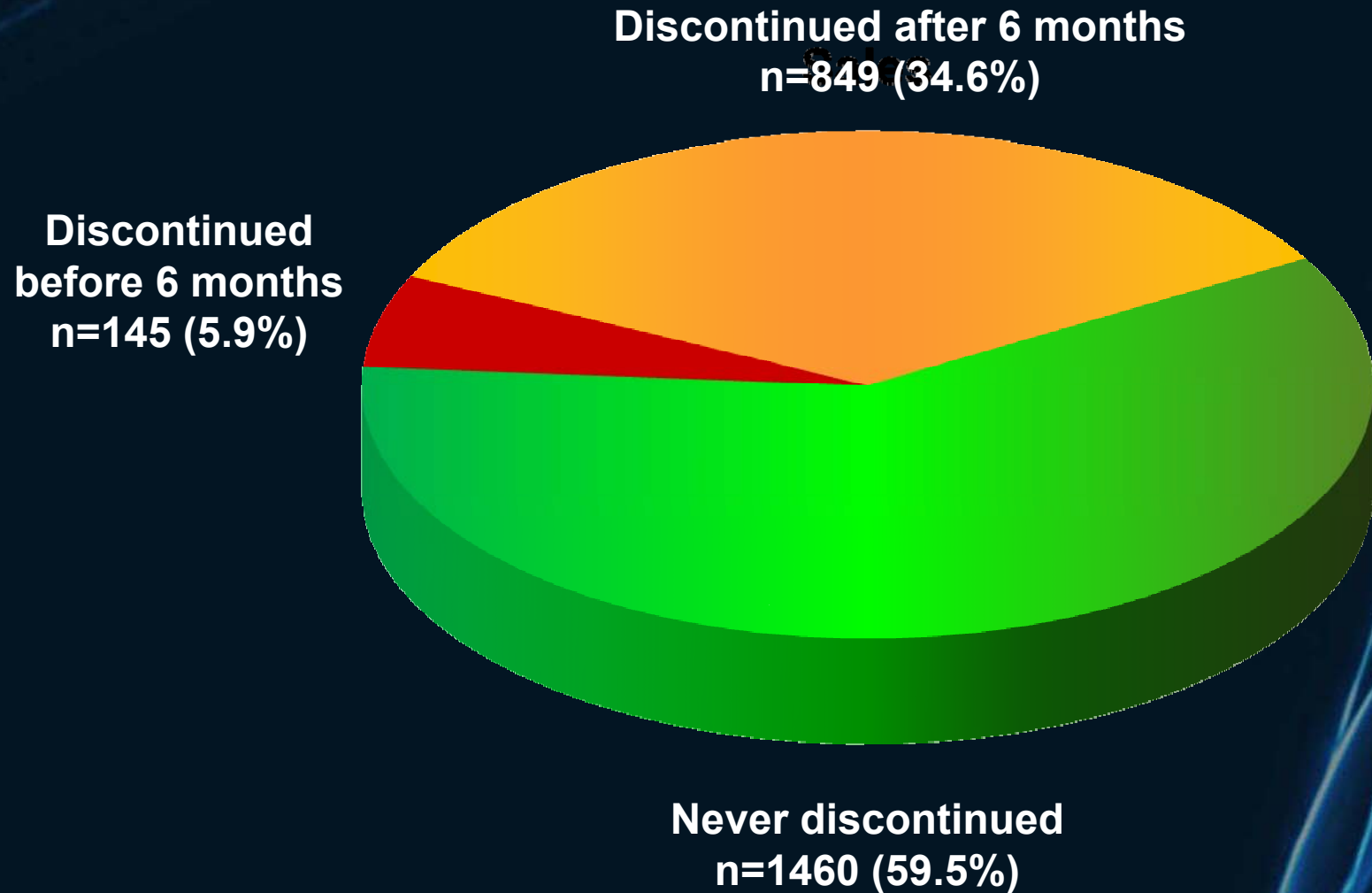


In vitro elution of Combo and CYPHER® (% of total drug eluted over time)

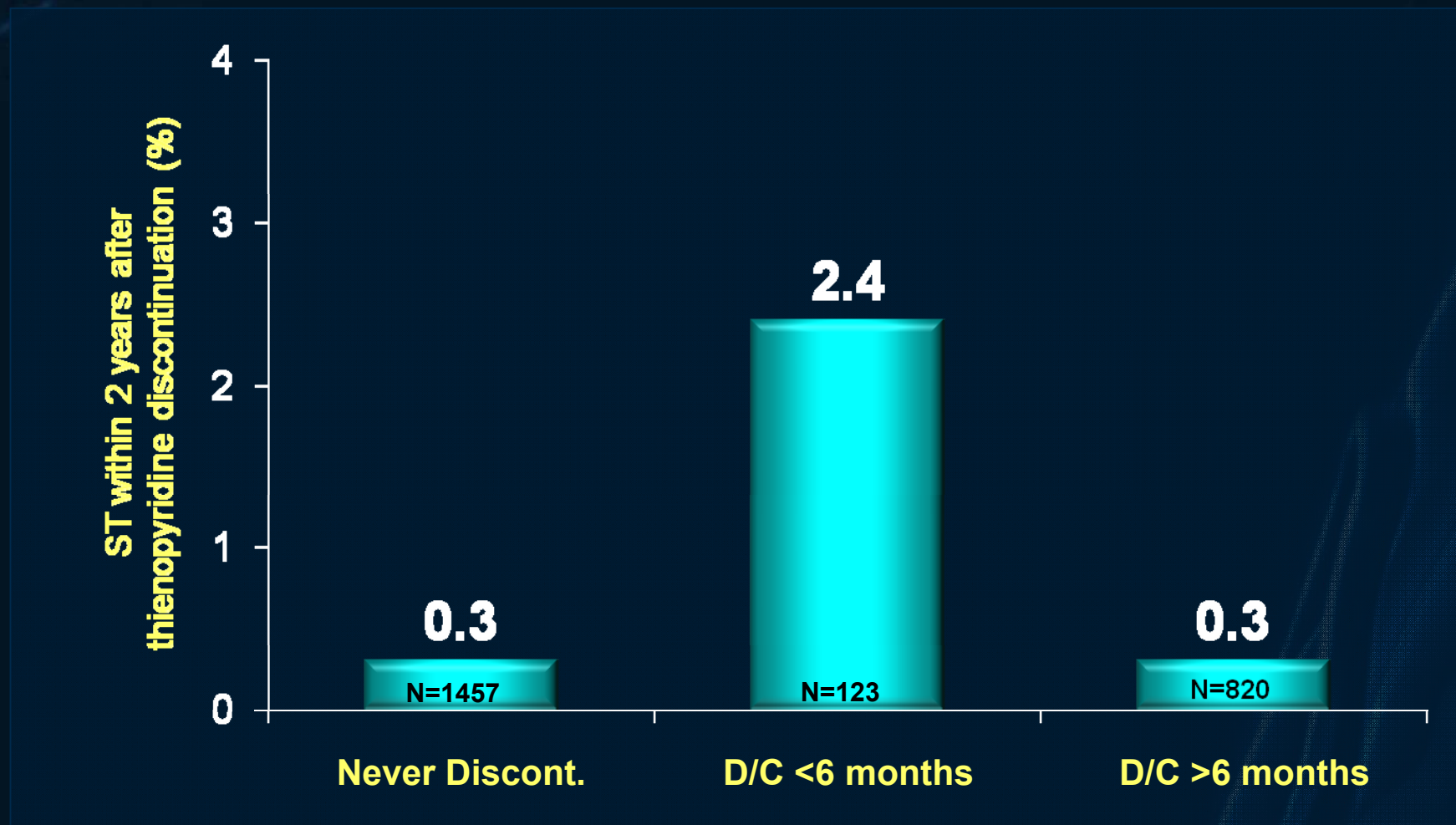
Stent Thrombosis



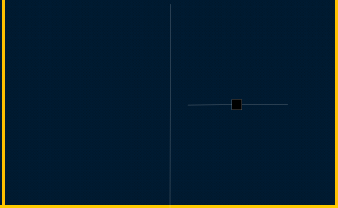
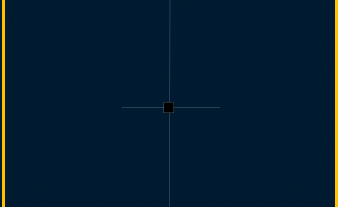
Timing of First Discontinuation of Thienopyridine Within 2 Years After XIENCE V Treatment (n=2454)



Timing of First Discontinuation of Thienopyridine and Subsequent Stent Thrombosis after XIENCE V Treatment



Multivariable Predictors of ARC Definite or Probable 2-Year Stent Thrombosis: XIENCE V Patients

Variable	Hazard Ratio [95% CI]	Hazard Ratio [95% CI]	P Value
First discontinuation of thienopyridine before 6 months (Yes vs. Never Discontinued)		8.06 [1.79, 36.22]	0.007
First discontinuation of thienopyridine after 6 months (Yes vs. Never discontinued)		1.06 [0.24, 4.73]	0.94

Conclusions

- **The safety profile of current DES technologies can still be enhanced- shorter duration of DAPT without risk for ST**
- **The additive effect of EPC recruitment with DES seems promising and needs further evaluation in large scale studies to evaluate this safety benefit**
- **The COMBO stent is the only stent that has employed this combination therapy, with early promising studies in humans**