Platelet Involvement in Stent Thrombosis Would the Late Stent Thrombosis Disappear After the New Stents

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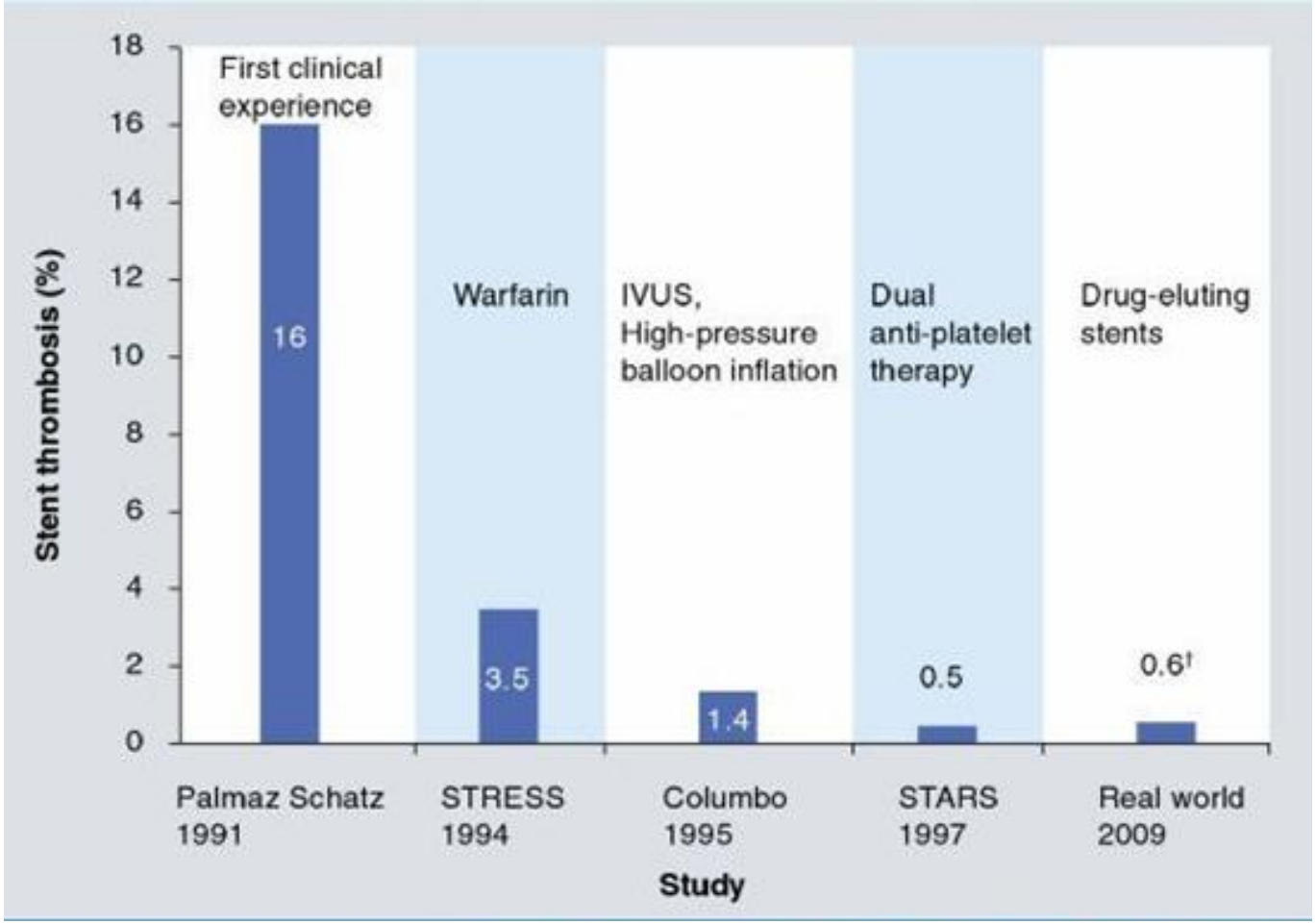
Stent Thrombosis

- ST is relatively rare, but still a major safety concern, especially with the use of DES
- The prognosis of ST is relatively poor
- The issue of very late ST specifically concerns the use of DES
- The occurrence of ST is multifactorial and largely unpredictable

Temporal Evolution of Stent Thrombosis

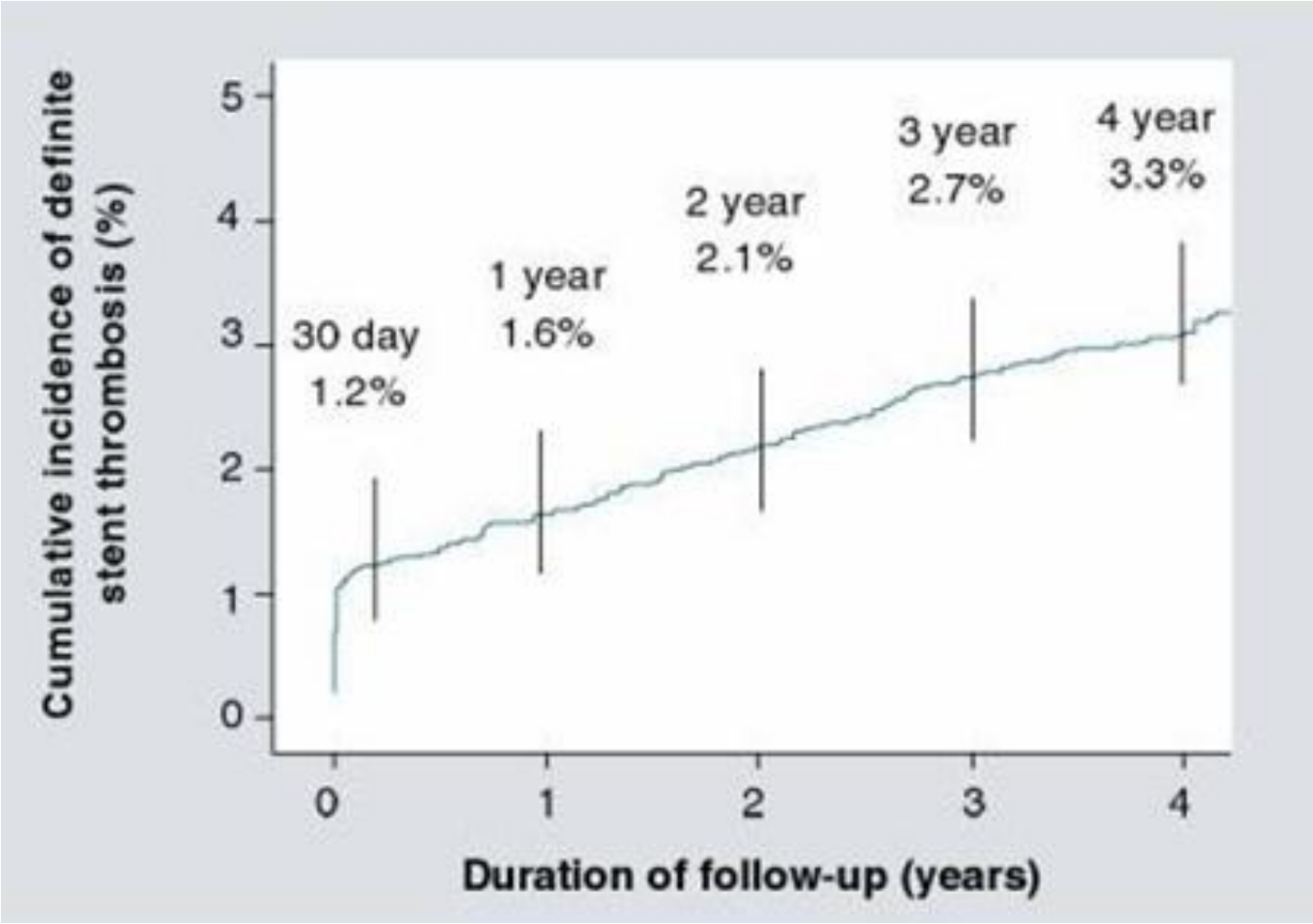


Stent Thrombosis. Definitions

- Definite stent thrombosis:
  - The highest level of certainty
  - Either angiographic or post-mortem evidence of thrombotic stent occlusion
- Probable stent thrombosis:
  - Any unexplained death within 30 days of stent implantation
  - Any myocardial infarction 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 until the end of follow-up

- Early stent thrombosis: stent thrombosis occurring within the first 30 days of stent implantation
- Late stent thrombosis: stent thrombosis occurring between 1 month and 1 year of stent implantation
- Very late stent thrombosis: stent thrombosis occurring after 1 year of stent implantation

Incidence of Stent Thrombosis During Long-Term F/up



Potential Predictors of Stent Thrombosis

Device factors

- Hypersensitivity to drug coating or polymer
- Incomplete endothelialization
- Stent design

Procedural factors

- Inadequate stent expansion
- Incomplete stent apposition
- Stent deployment in necrotic core

Lesion characteristics

- Lesion/stent length
- Vessel/stent diameter
- Complex lesions (bifurcation lesions or chronic total occlusions)

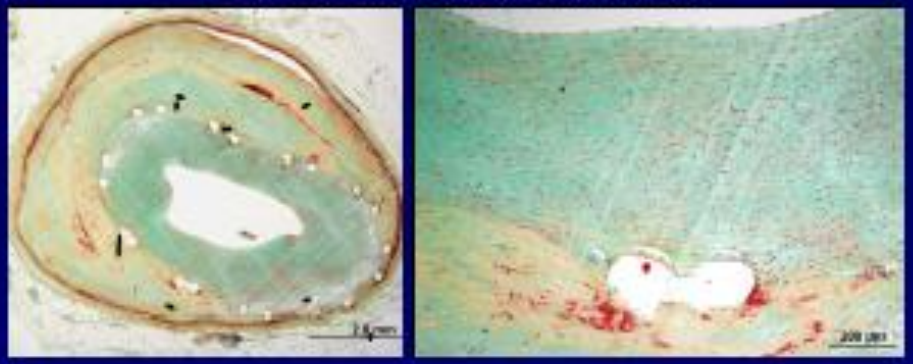
Patient factors

- Percutaneous coronary intervention for acute coronary syndrome/ST-elevation myocardial infarction
- Diabetes mellitus
- Renal failure
- Impaired left ventricular function
- Premature cessation of dual antiplatelet therapy
- Clopidogrel nonresponsiveness
- Prior brachytherapy

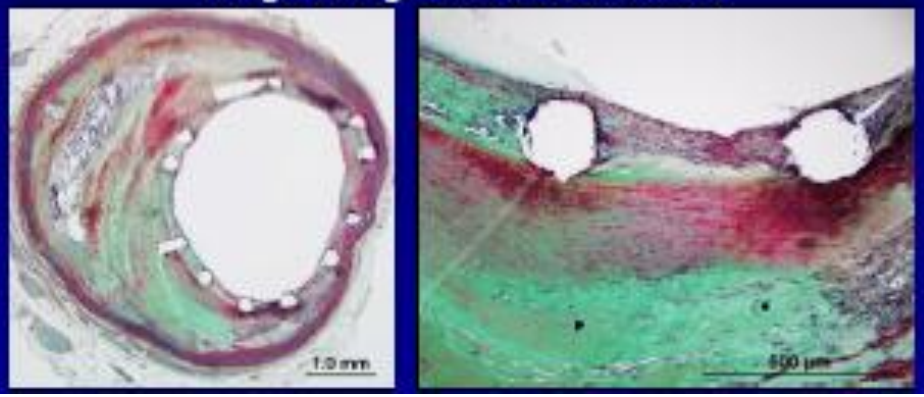
Stenting of Human Coronary Arteries

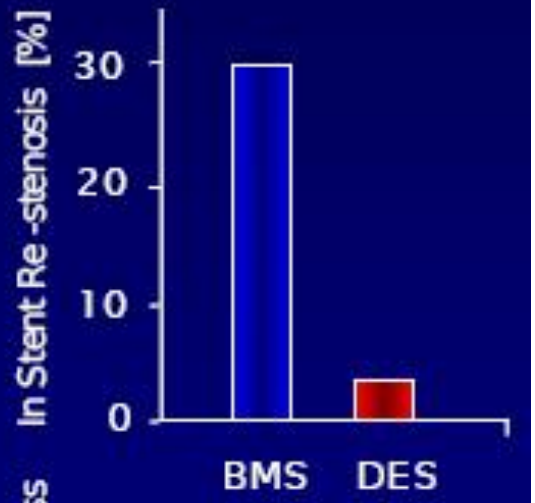
Drug Eluting *versus* Bare Metal Stents

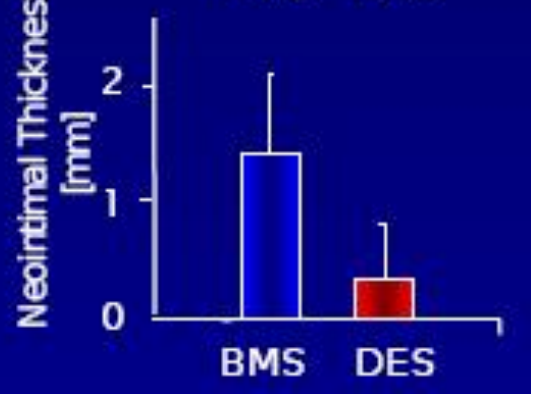
Bare Metal Stent (~15 months)



Drug Eluting Stent (~15 months)



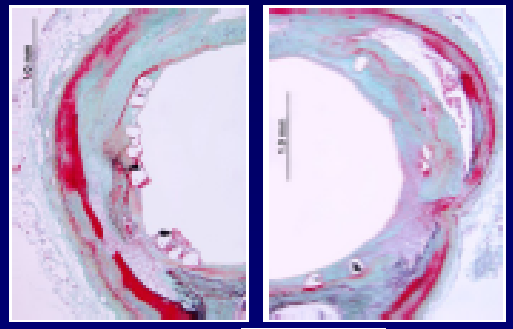


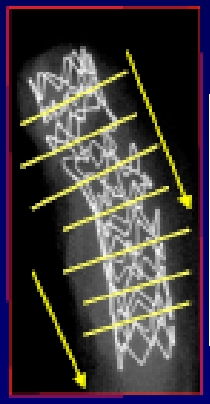


Pathological Correlates of Late DES Thrombosis: Strut Coverage as a Marker of Endothelialization

>30 days implants

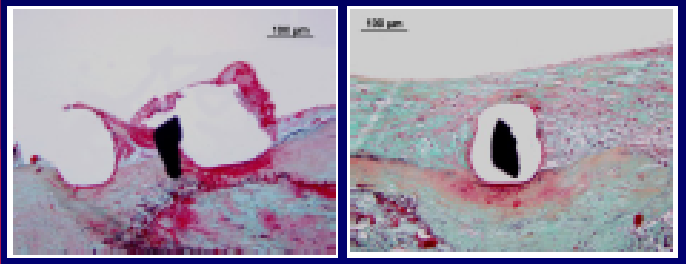
uncovered covered

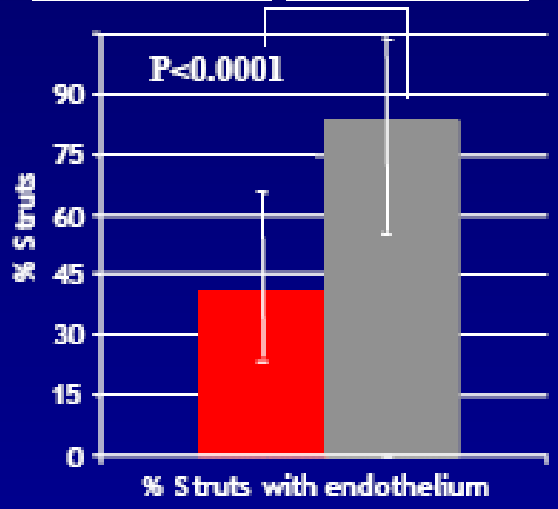


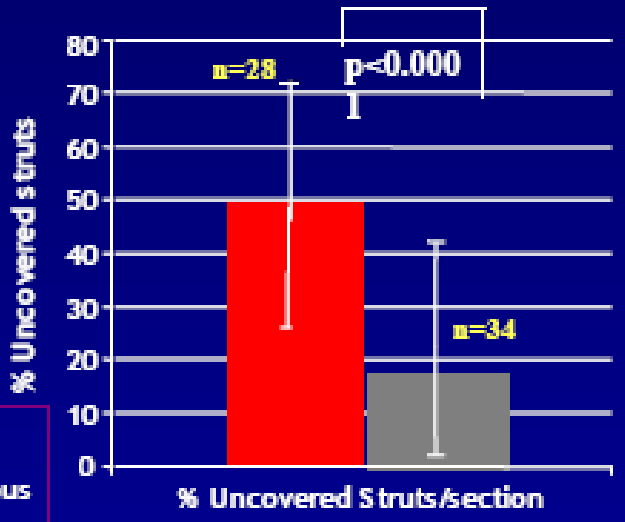


>30 days implants

uncovered covered





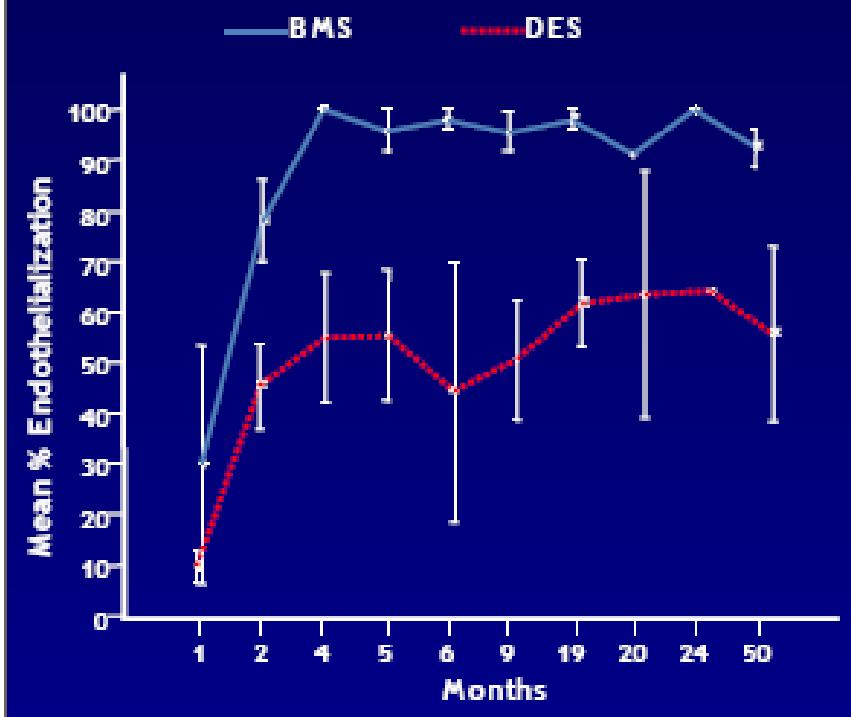


Finn AV, et al, Circulation 2007;115:2435-2441

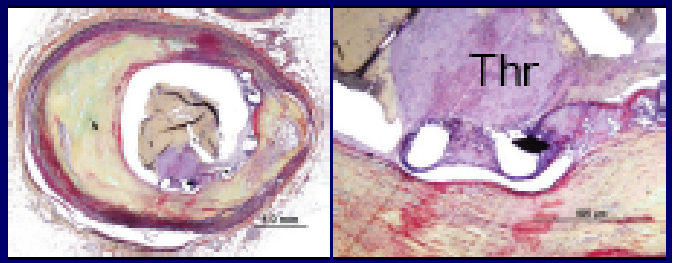
Incomplete Endothelialization

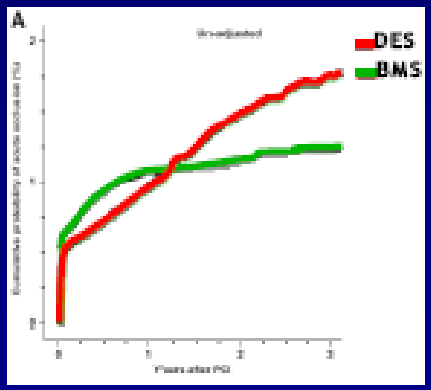
Late Stent Thrombosis (LST)

A Current Major Drawback of DES



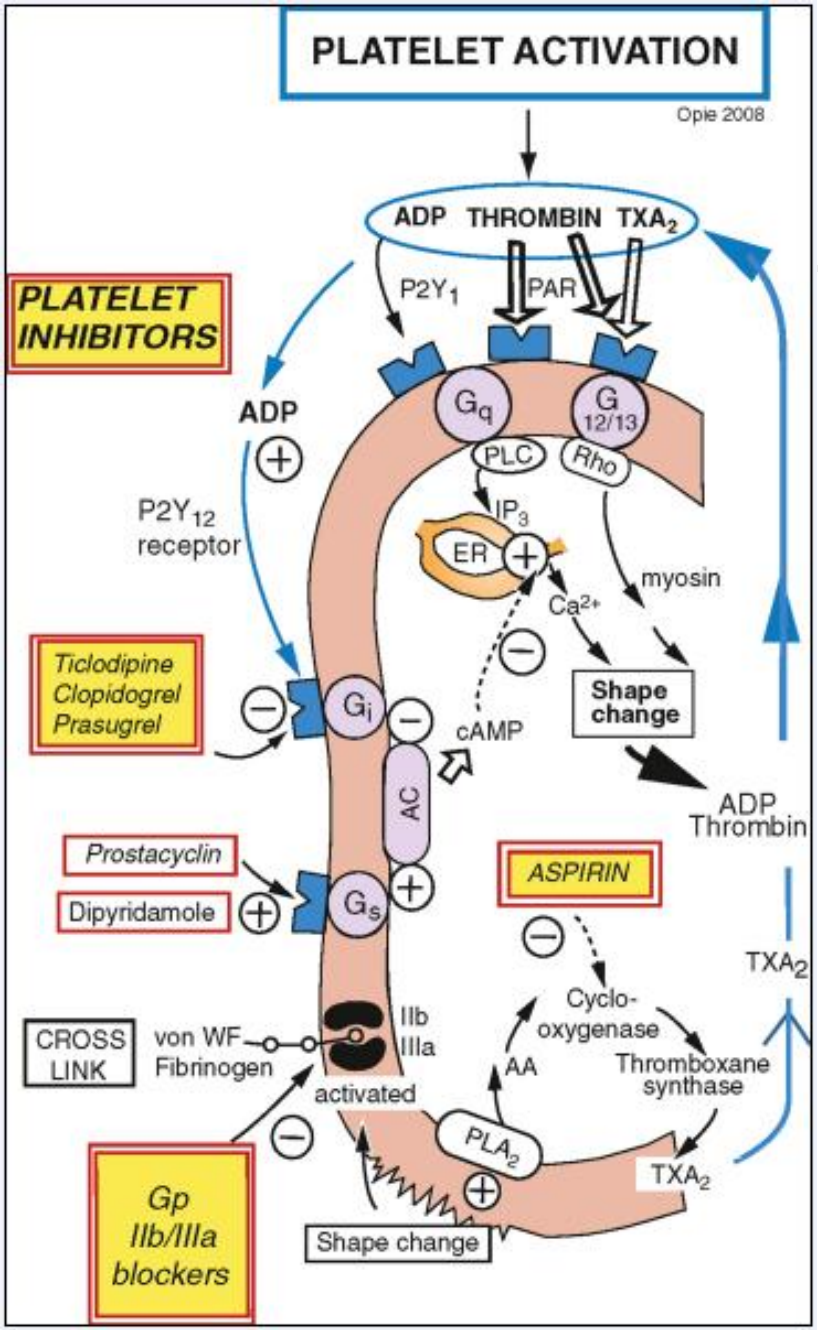
Joner M & Finn AV. J Am Coll Cardiol. 2006;48(1):193-202.



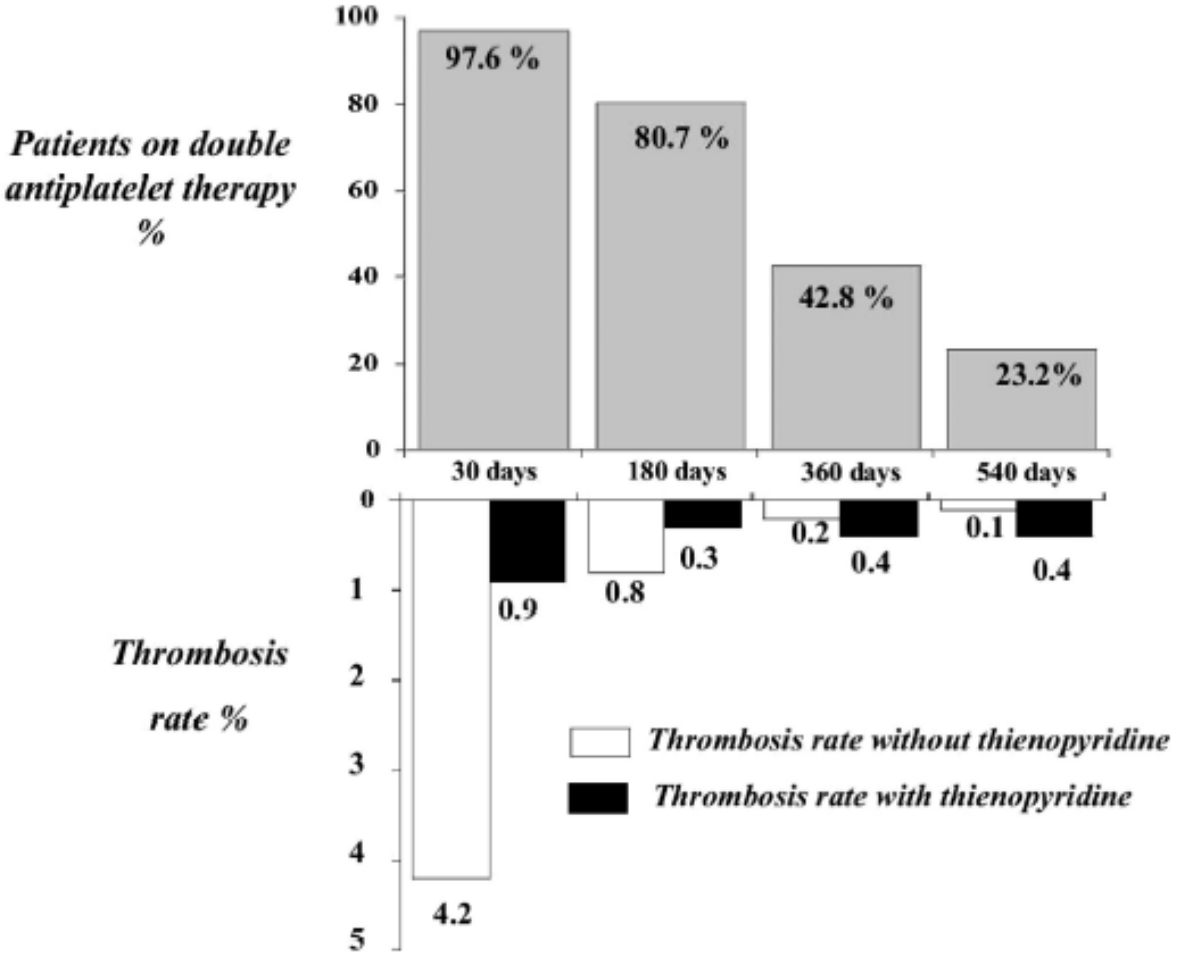


Langerqvist et al. Circulation Cardiovasc Interv 2009

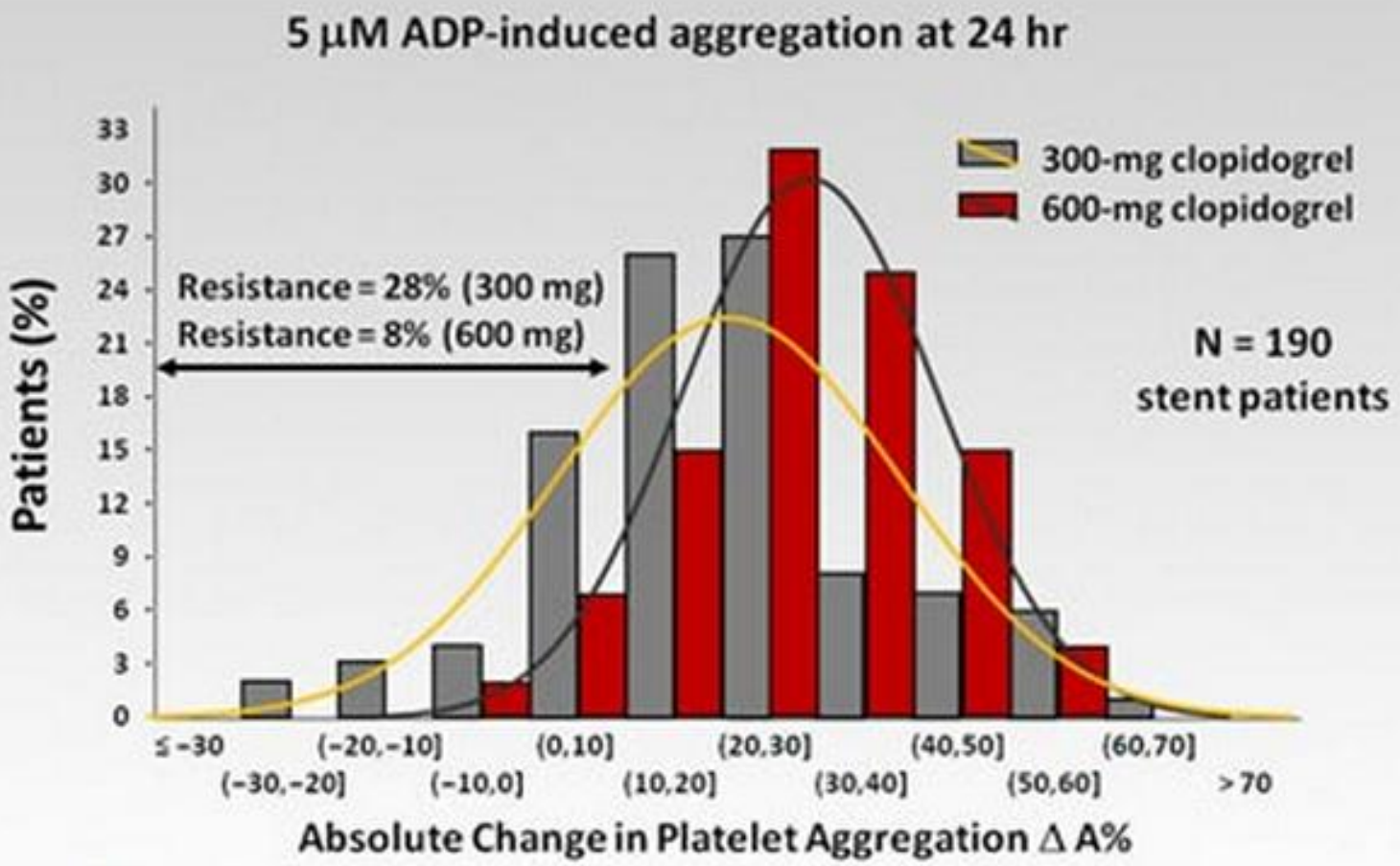
It Is All About the Platelet



Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Melzi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. *Circulation*. 2007;116: 745–754.



Marked Interindividual Response to Clopidogrel



Acute Coronary SYNDROMES

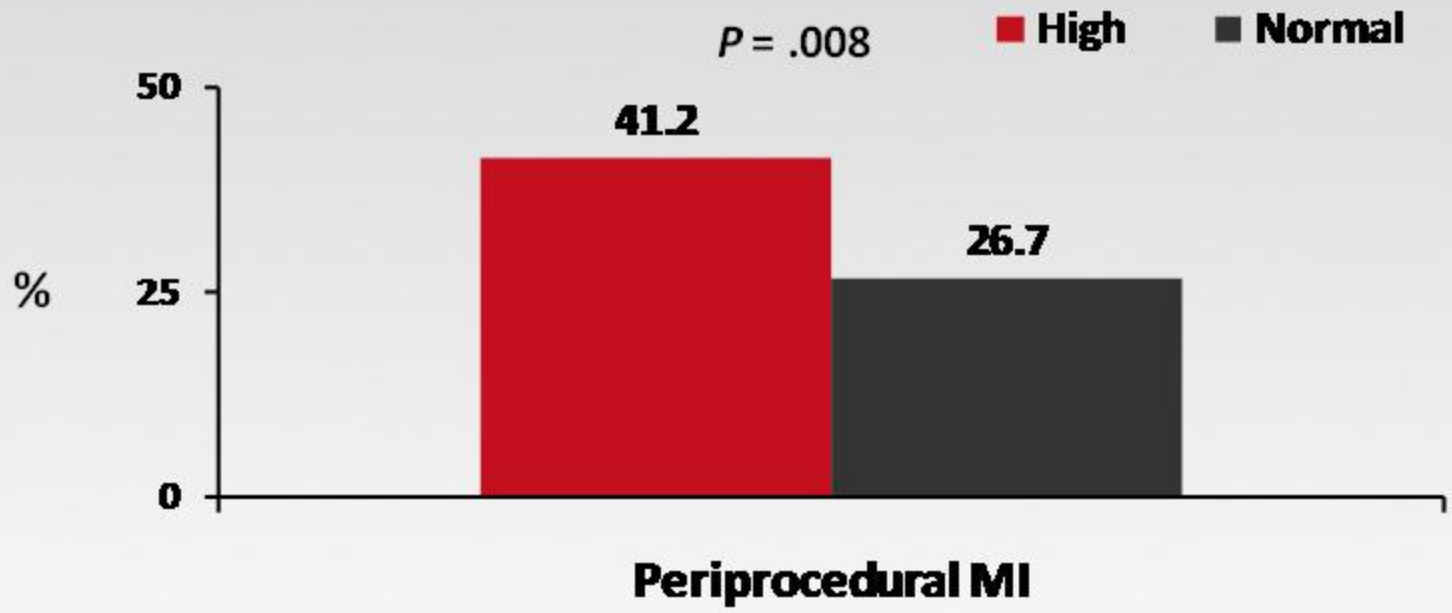
theheart.org MedscapeCME

Factors Influencing Platelet Aggregation/Drug Response

Suboptimal Clopidogrel Response

Genetic Factors	• Polymorphisms of CYP • Polymorphisms of GP Ia • Polymorphisms of $P2Y_{12}$ • Polymorphisms of GP IIIa
Cellular Factors	• Accelerated platelet turnover • Reduced CYP3A metabolic activity • Increased ADP exposure • Up-regulation of the $P2Y_{12}$ pathway • Up-regulation of the $P2Y_1$ pathway • Up-regulation of the P2Y-independent pathways (collagen, epinephrine, thomboxane A_2, thrombin)
Clinical Factors	• Failure to prescribe/poor compliance • Underdosing • Poor absorption • Drug-drug interactions involving CYP3A4 • **ACS** • **Diabetes mellitus/insulin resistance** • **Elevated body mass index**

High On-Treatment Platelet Reactivity Increases Risk for Periprocedural MI



High platelet reactivity: ≥ 240 PRU

N = 338 stable patients undergoing PCI with 600-mg clopidogrel

Mangiacapra F, et al. *JACC Cardiovasc Interv*. 2010;3:35-40.

Platelet Function Tests

Test Type	Normal Platelet Reactivity	High Platelet Reactivity*
Point-of-Care Tests		
Dade® PFA* (with collagen/ADP cartridge)	< 147 sec	≥ 147 sec
Innovance® PFA P2Y*	< 159 sec	≥ 159 sec
Plateletworks® Assay (using ADP tubes) Semi-automated, time dependent (≤ 10 min)	< 80.5%	≥ 80.5%
VerifyNow® $P2Y_{12}$ Assay (fully automated)	< 236 PRU	≥ 236 PRU
Dedicated Lab/Personnel/Labor Intensive		
IMPACT-R™ Assay (± ADP prestimulation)	- ADP: < 8.4% surface coverage + ADP: < 2.0% surface coverage	≥ 8.4% surface coverage ≥ 2.0% surface coverage
Light transmittance aggregometry (+ ADP)	5 µmol/L ADP: < 42.9% 20 µmol/L ADP: < 64.5%	≥ 42.9% ≥ 64.5%
VASP-P	≤ 50% PRI	> 50% PRI

ADP = adenosine diphosphate; PFA = platelet function analysis; PRI = platelet reactivity index; VASP-P = vasodilator-stimulated phosphoprotein phosphorylation

VerifyNow $P2Y_{12}$ Assay (Accumetrics, San Diego, California); Plateletworks Assay (Helena Laboratories, Beaumont, Texas); IMPACT-R Assay (Matis Medical Inc., Beersel, Belgium); PFA-100 and Innovance PFA P2Y (Siemens Healthcare Diagnostic GMBH, Marburg Germany).

*Not available for sale in the United States.

*Cutoffs per Breet N, et al. *JAMA*. 2010;303:754-762(corrected).

Consensus Cutoff Values by ROC Analysis

- LTA
  - MPA > 46% to 5 µM ADP
- VerifyNow $P2Y_{12}$
  - PRU > 235
- VASP-P
  - PRI > 50%
- MultiPlate®
  - MEA > 468 to ADP

LTA = light transmittance aggregometry; MEA = multiple electrode platelet aggregometry; ROC = receiver operating characteristic ; MPA = maximum platelet aggregation.
MultiPlate® (DiaPharma Group, Inc.)

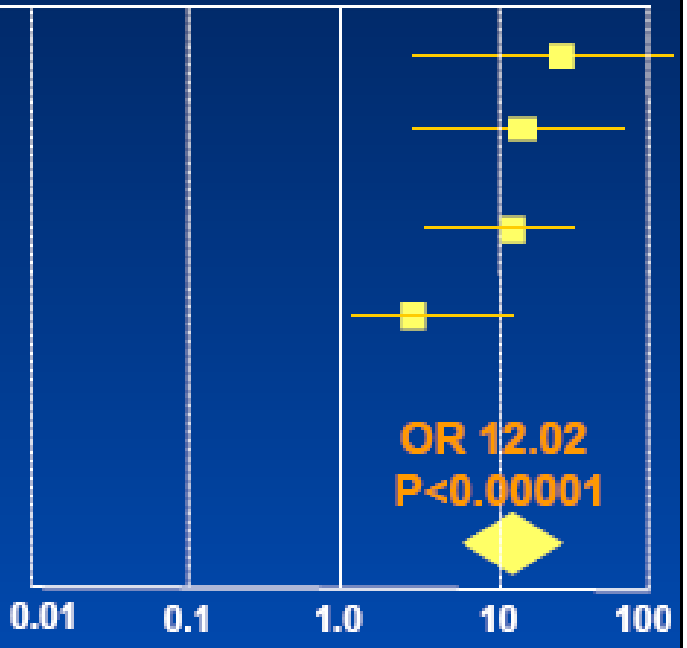
Bonello L, et al. *J Am Coll Cardiol.* 2010;56:919-933.

Clopidogrel resistance and Risk of CV event

Meta-analysis including pts treated with PCI in 25 studies (LTA, TEG, cytometry)

Clinical ischemic events (CV death, MI, stroke, revascularization, ST)

Study	CR	CS	Weight (%)
Matetzky	7/15	1/45	9.09
Cuisset (JTH)	9/23	3/83	14.08
Cuisset (JACC)	18/58	7/234	17.95
Geisler	5/22	19/357	16.63
Subtotal	**39/118**	**30/719**	**57.76**



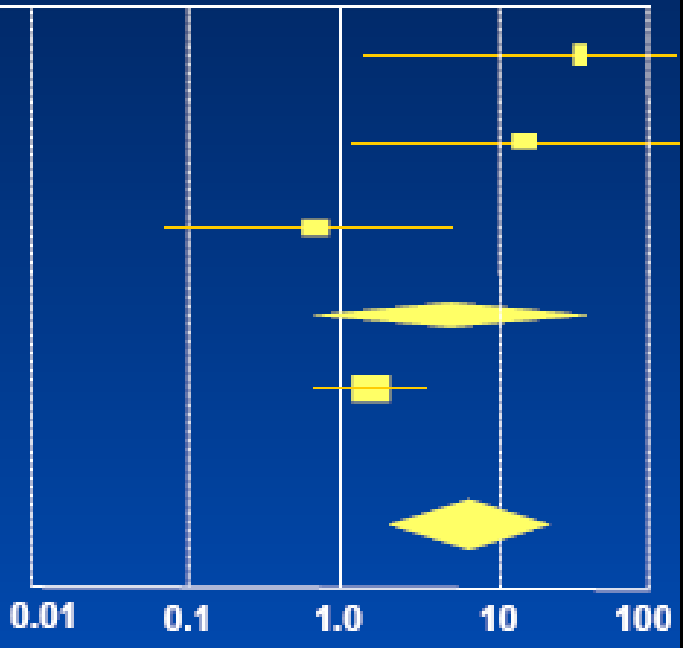
Snoep JD et al. Am Heart J 2007;154:221.

Clopidogrel resistance and Risk of CV event

Meta-analysis including 3688 pts in 25 studies (LTA, TEG, flow cytometry)

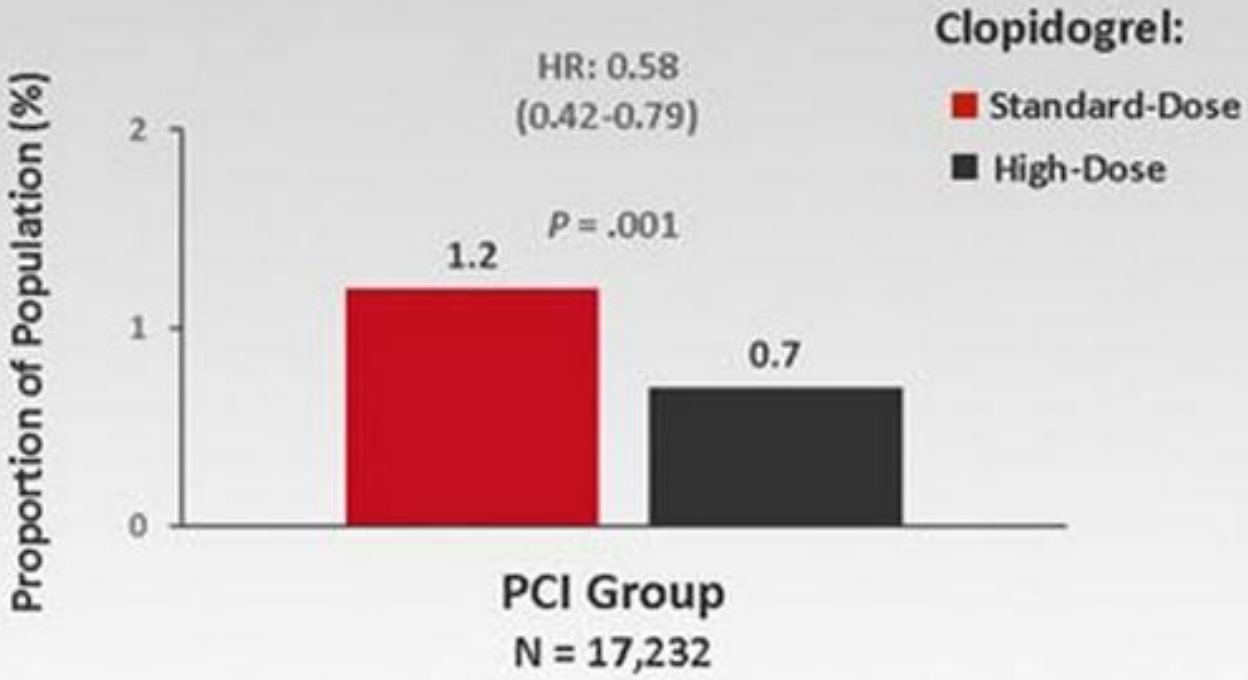
Subacute stent thrombosis

Study	CR	CS	Weight (%)
Muller	2/12	0/93	5.81
Klamroth	9/10	11/30	9.25
Wenaweser	1/4	22/69	8.65
Subtotal	12/26	33/192	23.72
Lev (myonecrosis)	11/36	19/114	18.53
Total	**26/440**	**184/634**	**100**



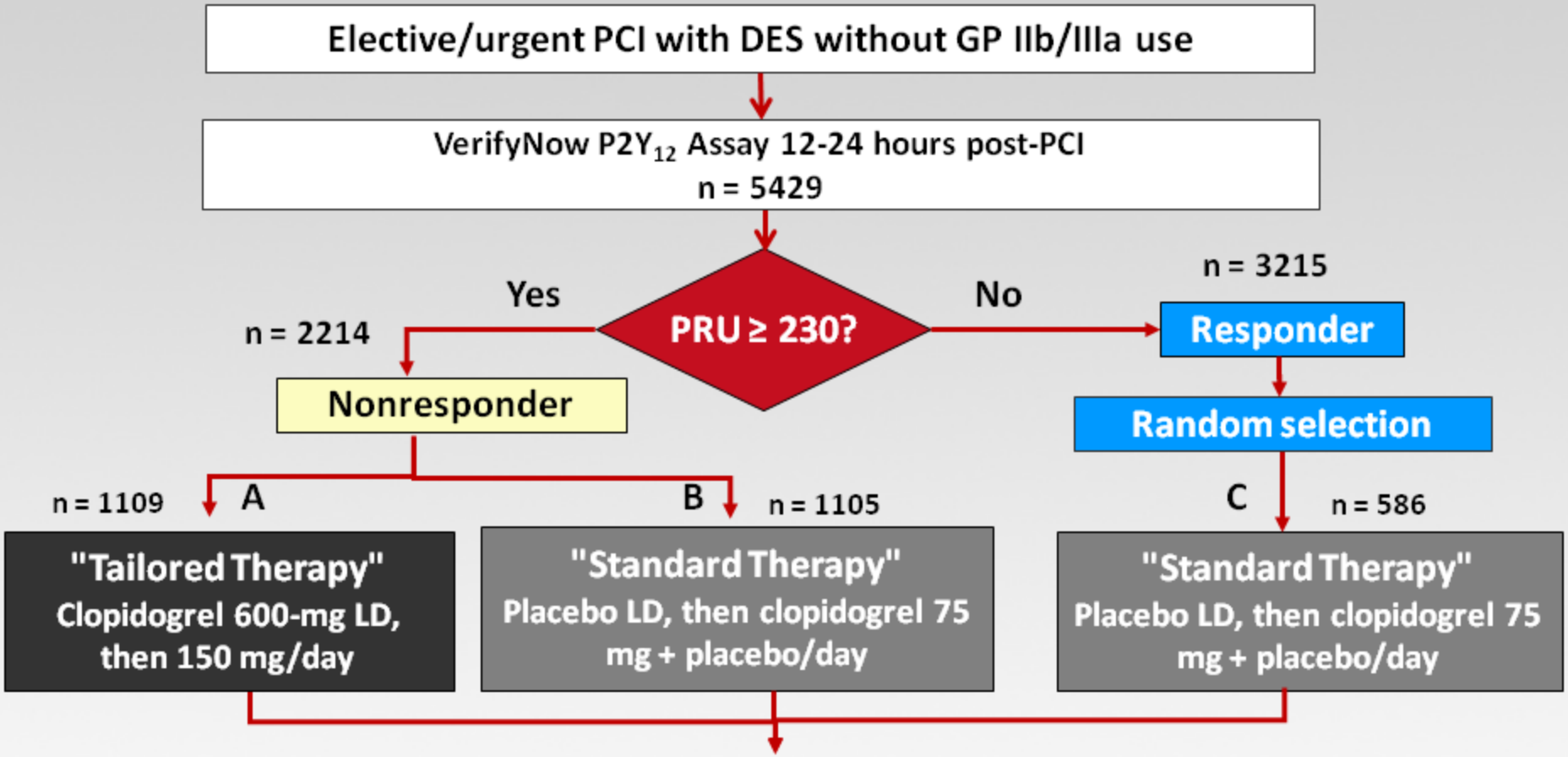
Snoep JD et al. Am Heart J 2007;154:221.

CURRENT-OASIS 7: Definite Stent Thrombosis at 30 Days



Standard = 300-mg loading, 75 mg daily
High = 600-mg loading, 150 mg x 7 days, 75 mg thereafter

GRAVITAS: Trial Design



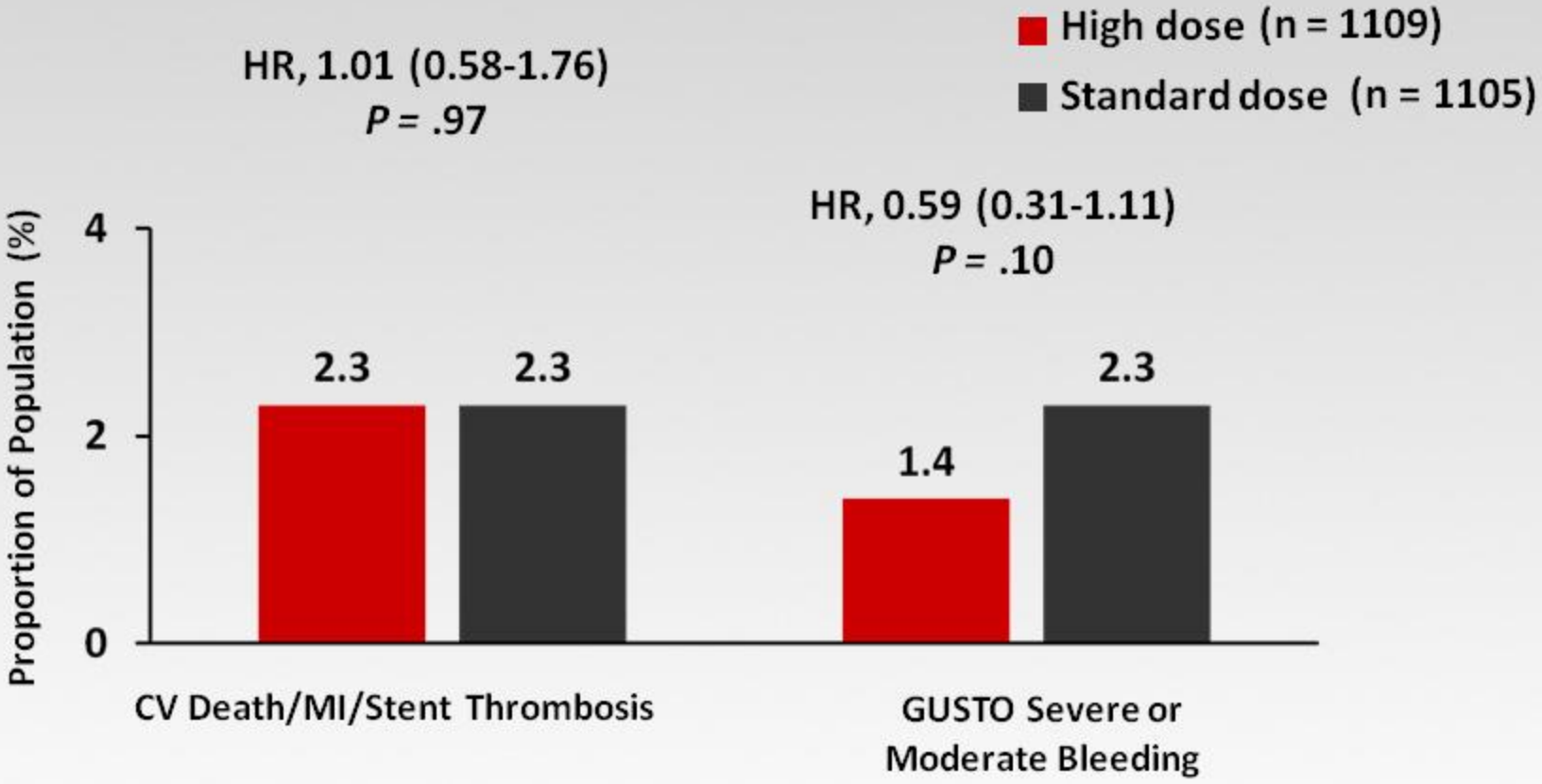
Clinical follow-up and VerifyNow assessment at 30 days, 6 months

Primary endpoint: 6-month CV death, nonfatal MI, ARC definite/probable stent thrombosis

ARC = Academic Research Consortium; DES = drug-eluting stent

Price MJ, et al. *JAMA*. 2011;305:1097-1105.

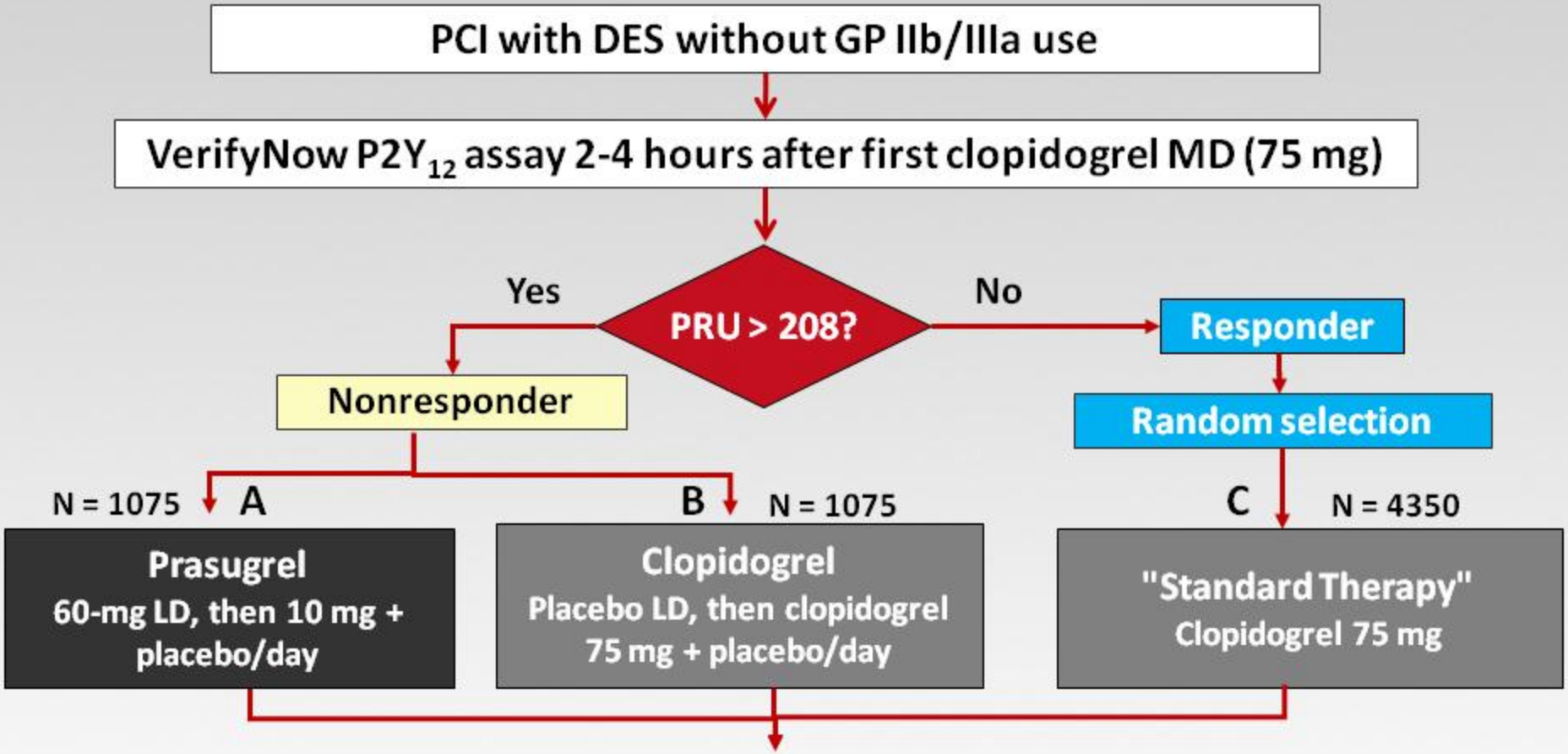
GRAVITAS: Primary Endpoint* and Bleeding at 6 Months



*Did not include periprocedural MI since platelet reactivity was measured after PCI

Price MJ, et al. *JAMA*. 2011;305:1097-1105.

TRIGGER-PCI: Trial Design



Clinical follow-up and VerifyNow assessment at 90 and 180 days

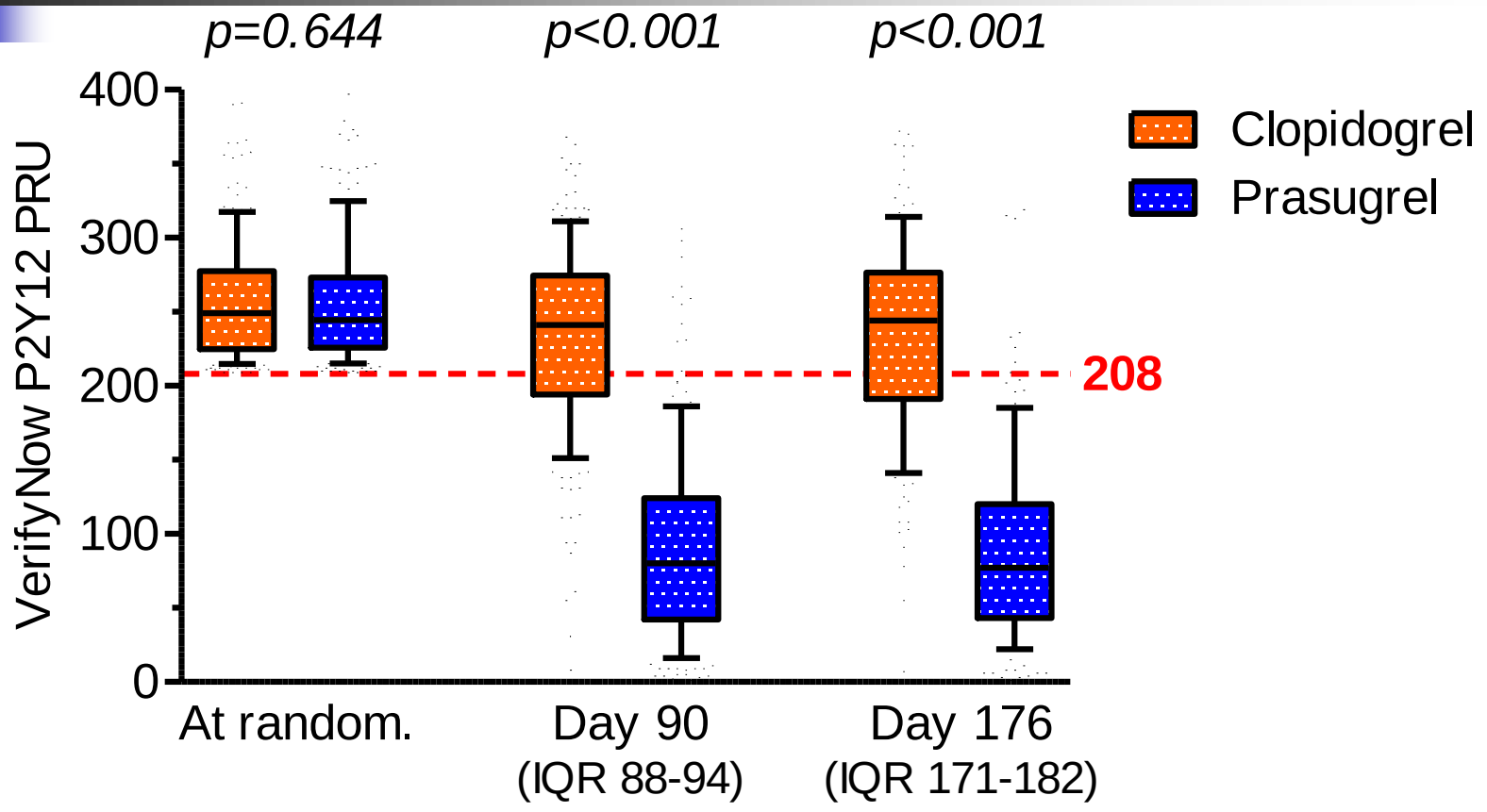
Primary endpoint: 6-month CV death, nonfatal MI

Study terminated due to the low rate of primary endpoint events

MD = maintenance dose

Platelet reactivity by VerifyNow P2Y12 assay: Prasugrel 10 mg oid vs. Clopidogrel 75 mg oid

ITT - population



Prasugrel	n=210	187	139
Clopidogrel	n=206	189	144

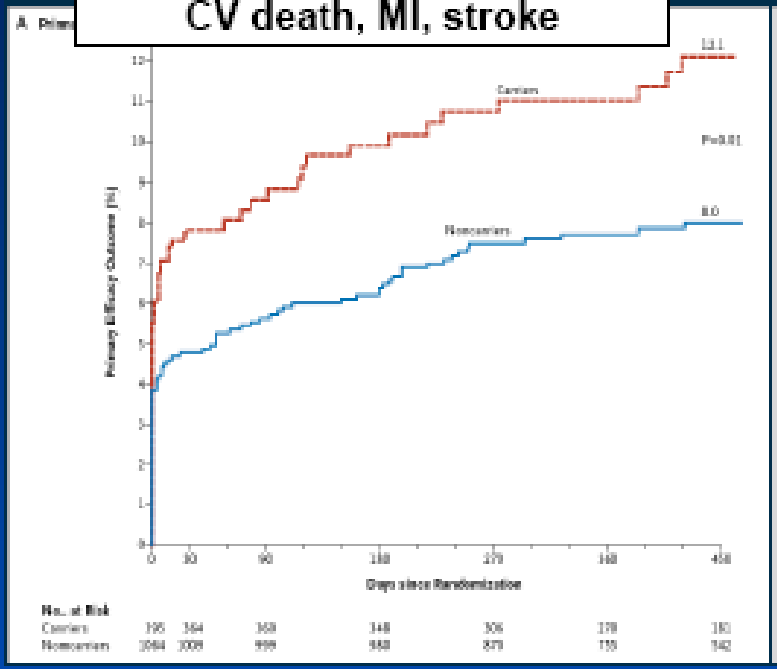
Median with interquartile range; 10-90% percentile

The impact of CYP450 Polymorphism in ACS pts on-clopidogrel

Substudy of TRITON-TIMI 38

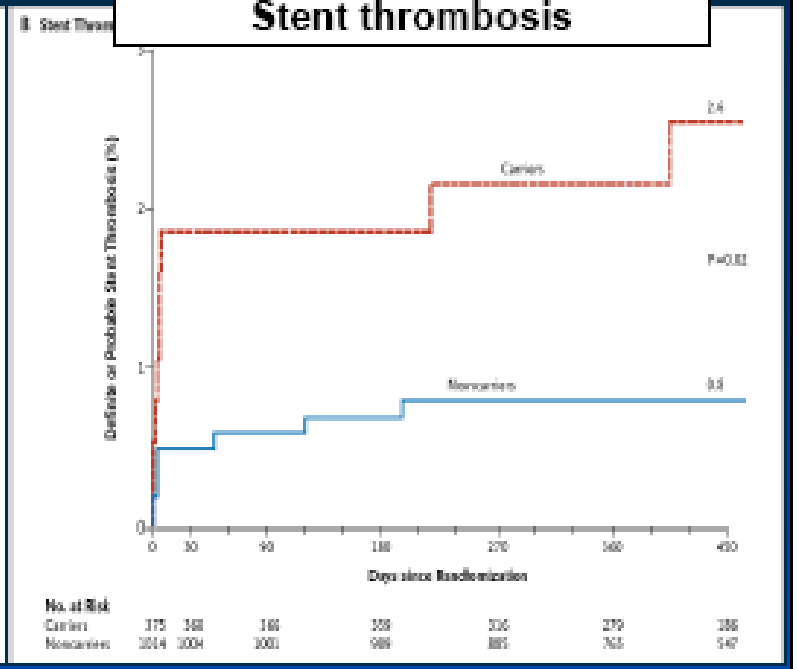
2C19 polymorphism: Carrier vs. Non-Carrier

CV death, MI, stroke



HR 1.53, 95% CI 1.07-2.19, P=0.01

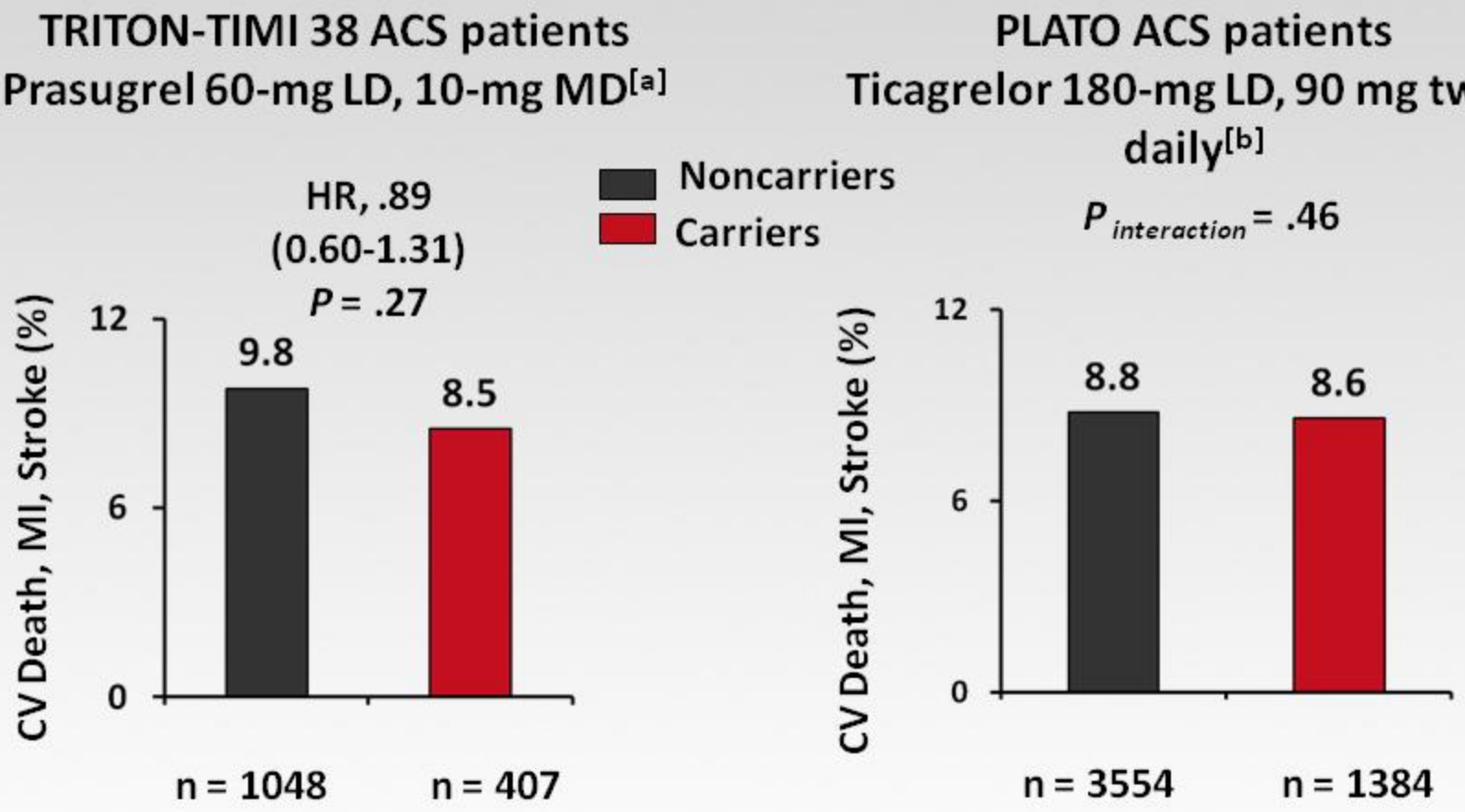
Stent thrombosis



HR 3.09, 95% CI 1.19-8.00, P=0.02

Mega JL, et al. NEJM 2009;360:354-

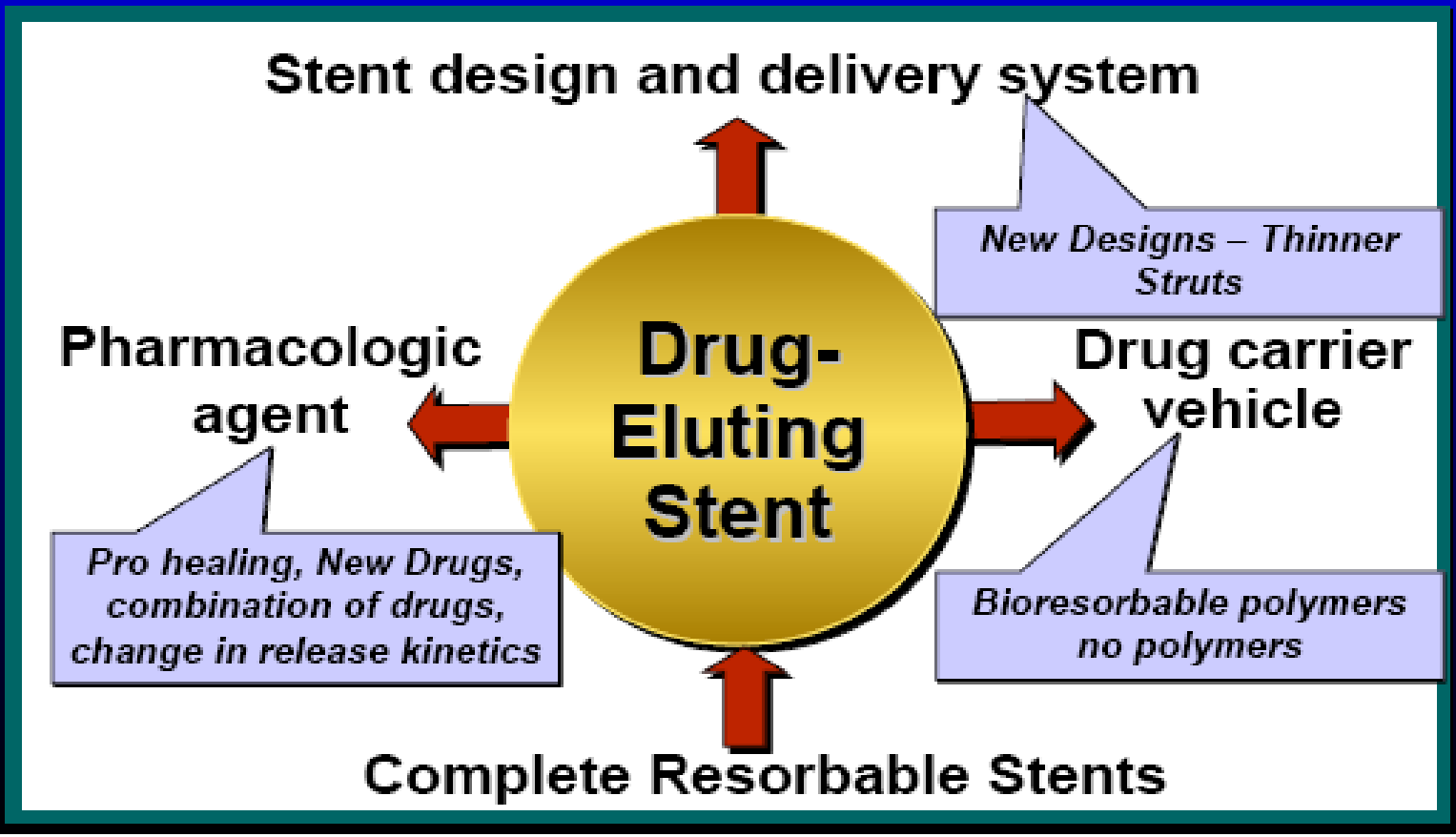
CYP2C19 Loss-of-Function Genotype Does Not Affect Prasugrel or Ticagrelor Efficacy



Ticagrelor is not approved by the FDA for use in the United States.

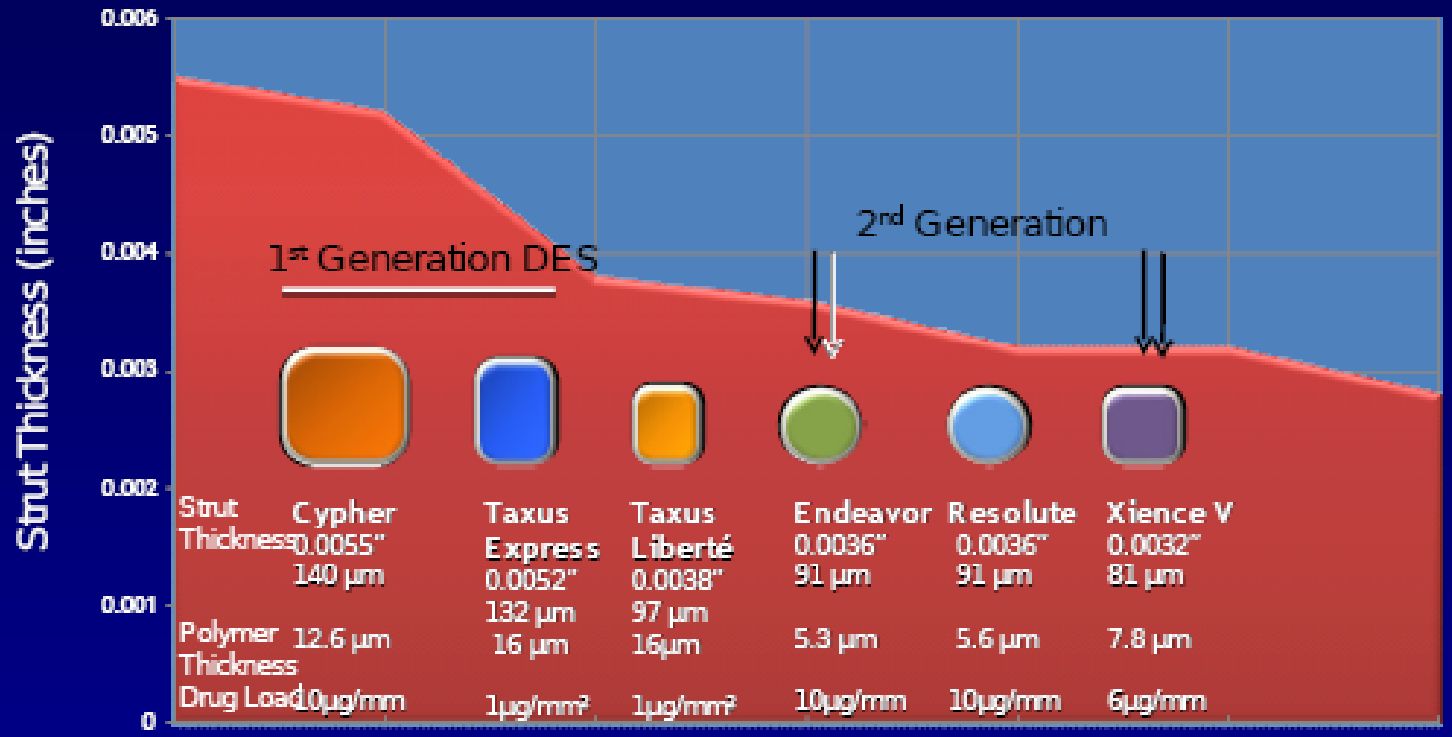
a. Mega JL, et al. *Circulation*. 2009;119:2553-2560.
b. Wallentin L, et al. *Lancet*. 2010;376:1320-1328.

Drug-Eluting Stents
Next Generation



Stent Strut and Polymer Thickness

- Thinner stent struts associated with improved clinical outcomes[1-4]

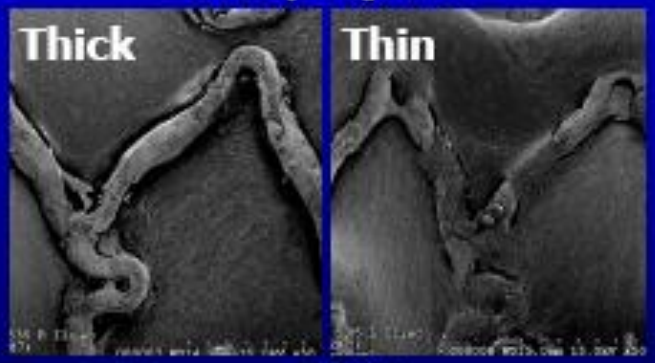


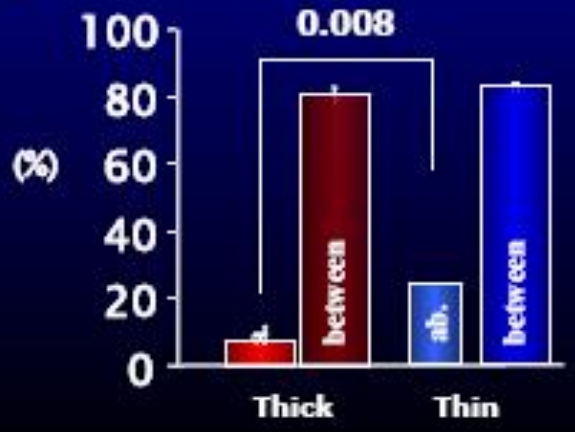
1. Kastrati, A, et al. *Circulation* 2001;103: 2816-2821.
2. Rittersma, SZ, et al. *Am J Cardiol* 2004; 93: 477-480
3. Pache, J , et al. *J Am Coll Cardiol* 2003; 41: 1283-1288
4. Turco, M., et al., *JACC CI* 2008; 1: 699-709.

Modified from Ian Meredith

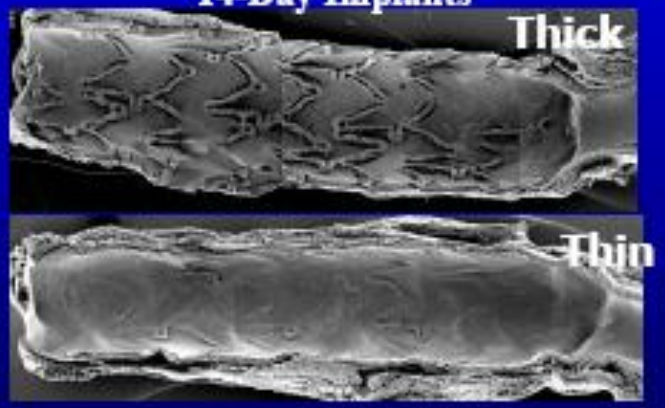
Optimization of Strut Thickness Leads to Rapid Re-Endothelialization

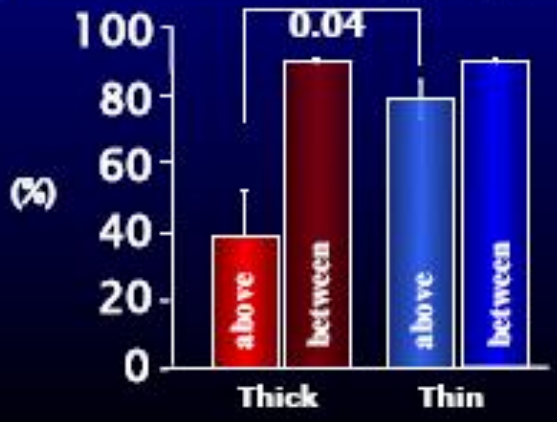
7-Day Implants

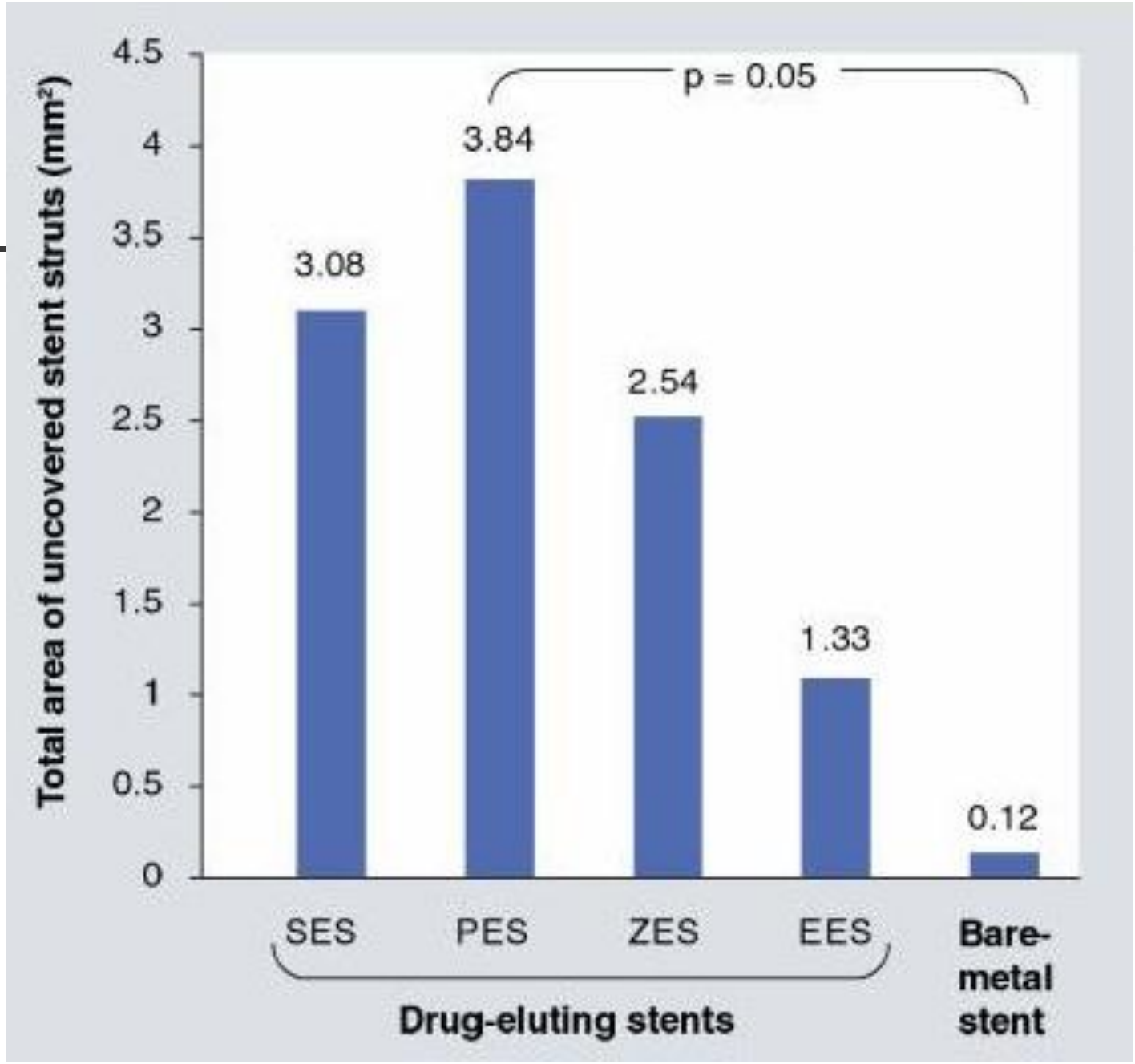




14-Day Implants





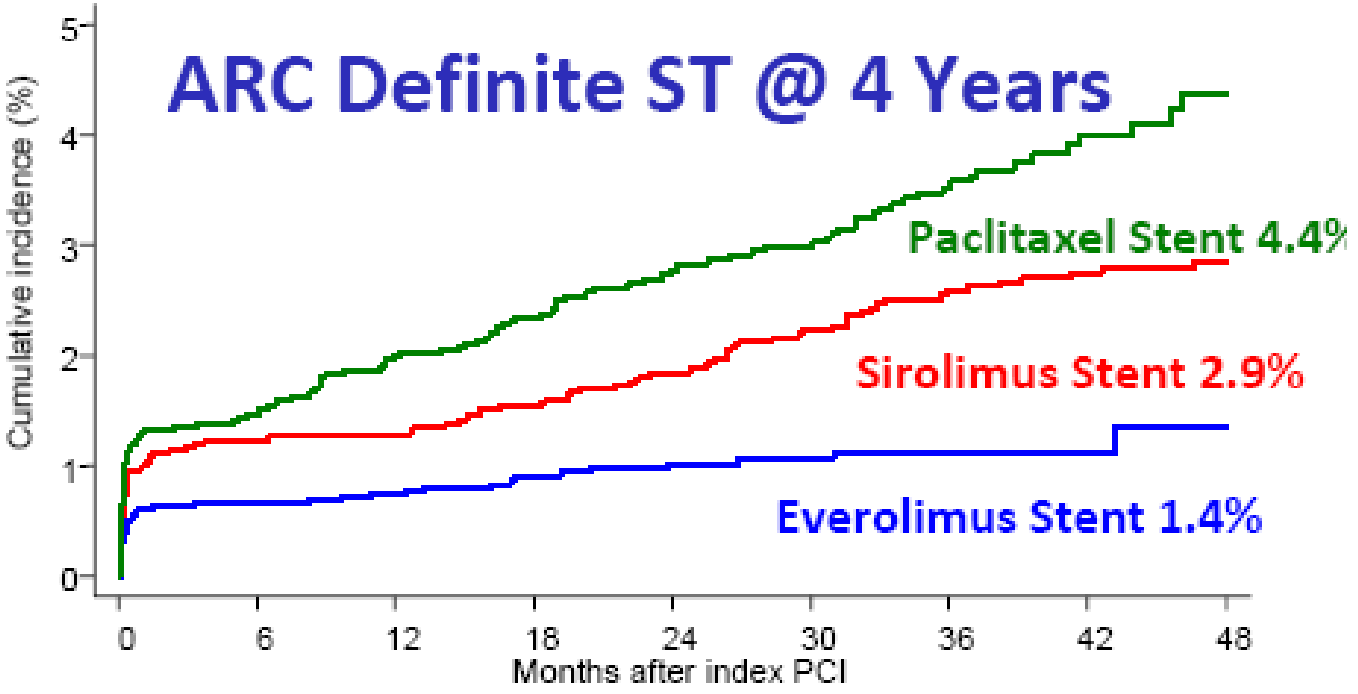

Total area of uncovered stent struts (mm²)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
p = 0.05
3.84
3.08
2.54
1.33
0.12
SES
PES
ZES
EES
Drug-eluting stents
Bare-metal stent

Bern-Rotterdam Cohort Study

Räber L, ESC 2011

EES vs. SES Hazard Ratio* = 0.41, 95% CI 0.27–0.62, P<0.0001

EES vs. PES Hazard Ratio* = 0.33, 95% CI 0.23-0.48, P <0.0001



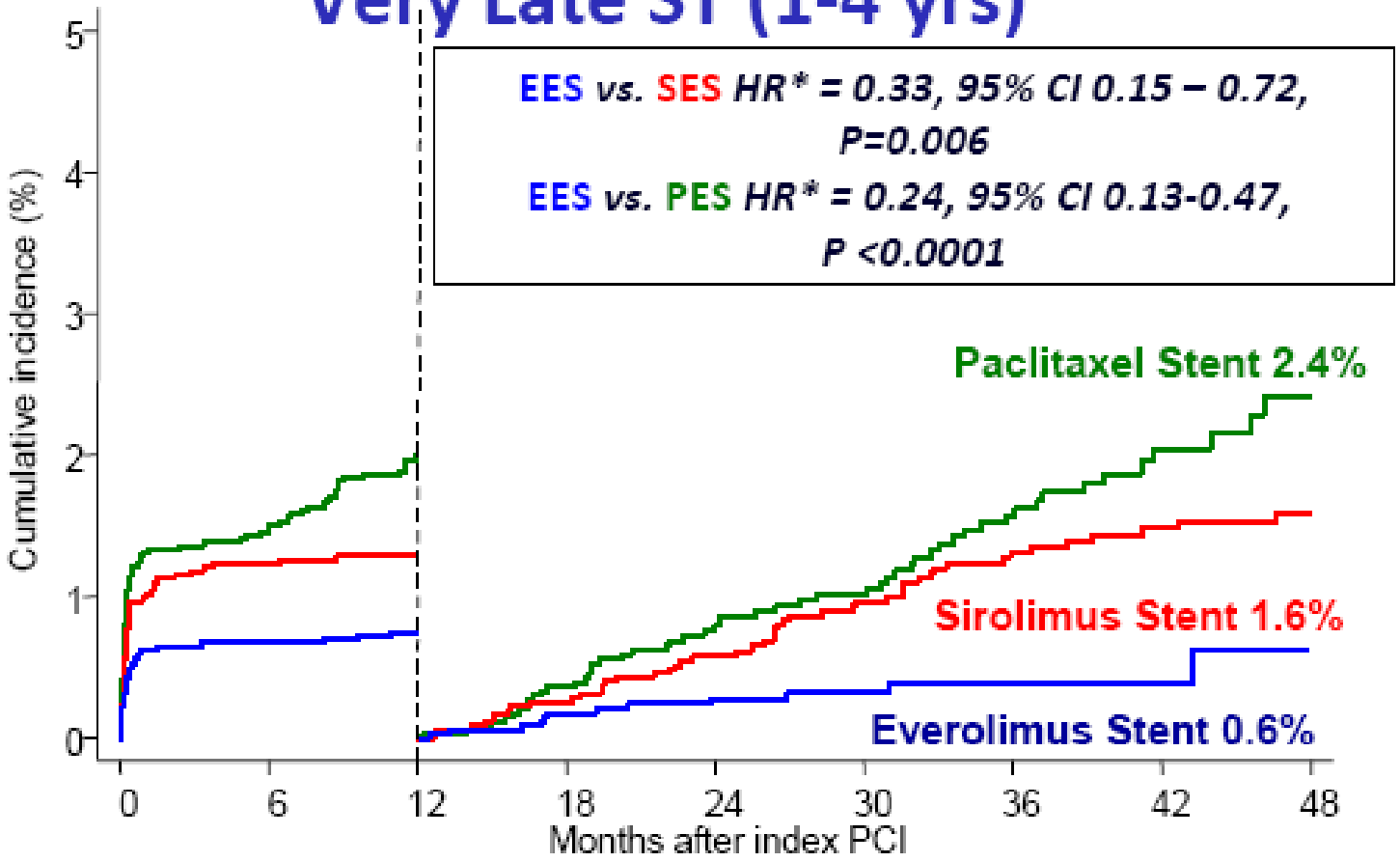
No. at risk

PES	4214	3916	3797	3176	2905	2344	1880	1077	686
SES	3784	3617	3569	3499	3404	3080	2521	2118	1734
EES	4135	3913	3793	3284	2604	1856	1041	514	208

*from Cox proportional hazards model

Bern-Rotterdam Cohort Study

Very Late ST (1-4 yrs)

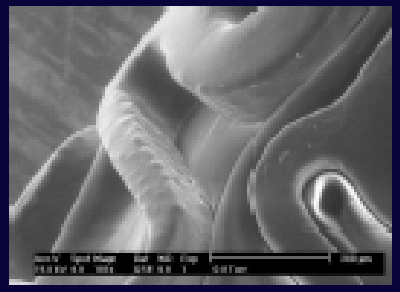


Räber L, ESC 2011

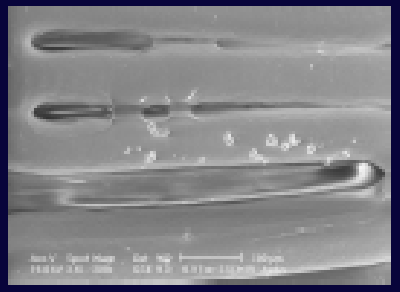
*from Cox proportional hazards model

Problems with Polymers

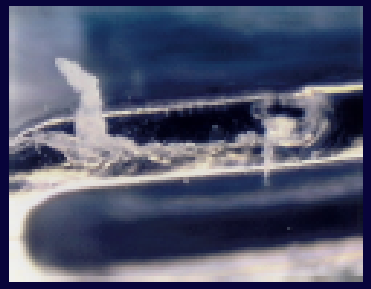
Shortcomings often associated with polymers during stent delivery



Non uniform polymer coating



"Webbed" polymer surface leading to stent expansion issues"



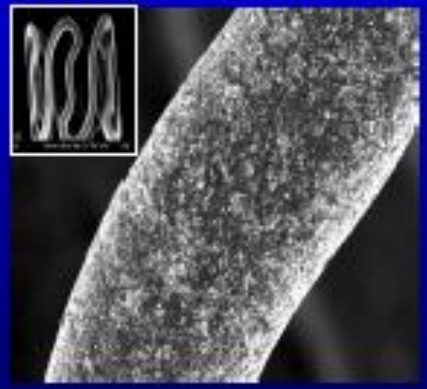
Polymer delamination

Durable Coatings-Potential for:

- Continuing source of inflammation
- Poor healing/thrombosis risk

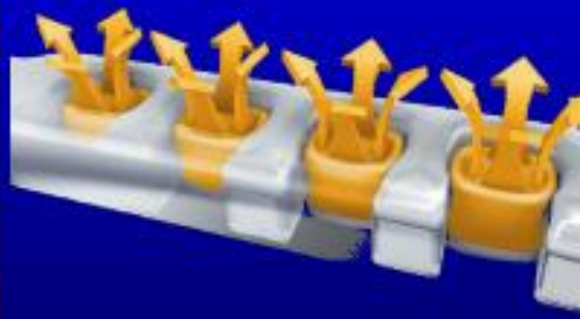
Biodegradable Polymer Based DES Platforms

Sirolimus – ISAR TEST

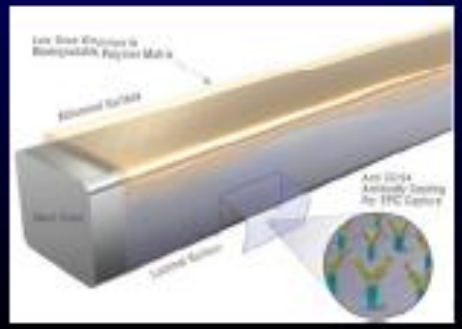


Biolimus A9 – BioMatrix
Nobori, Axxess, XTENT

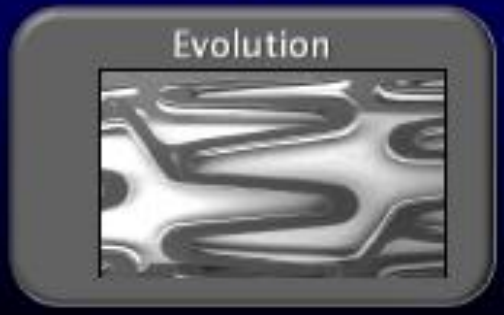
Sirolimus – NEVO



Sirolimus – Genous
Bioengineered R Stent



Everolimus - BSC

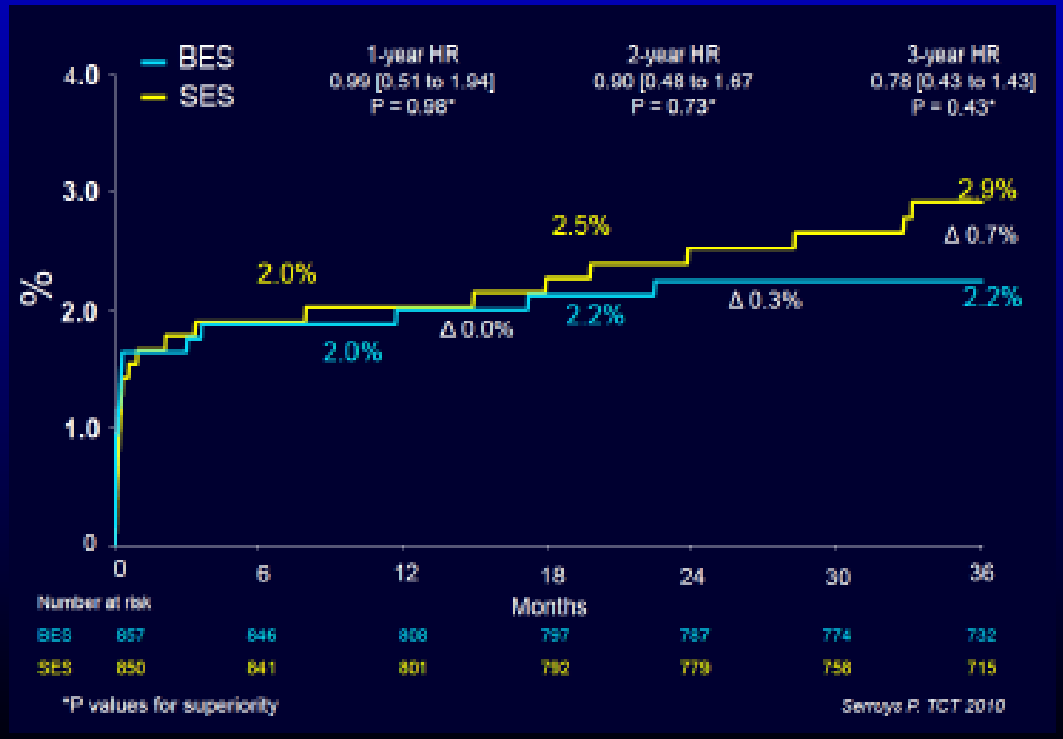


Myolimus – ELIXIR

Biodegradable Polymer Based DES Platforms and Risk of Stent Thrombosis

LEADERS- Definite ST

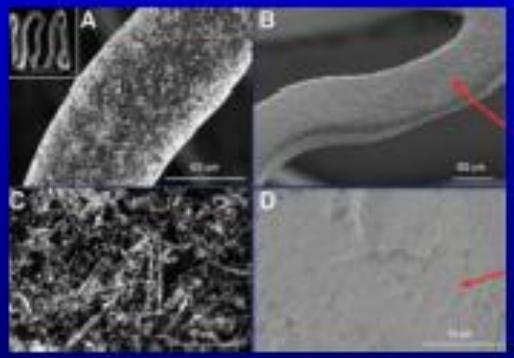
Serruys PW et al. TCT 2010



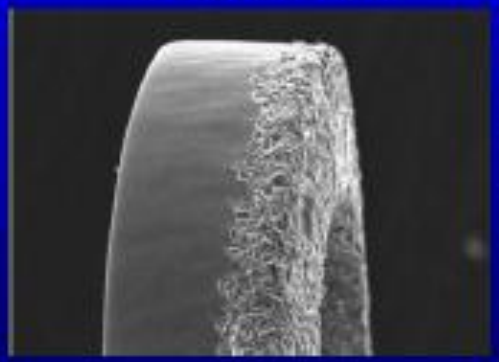
Polymer-Free DES Platforms

Abizaid A al. *Circ Cardiovasc Interv* 2010

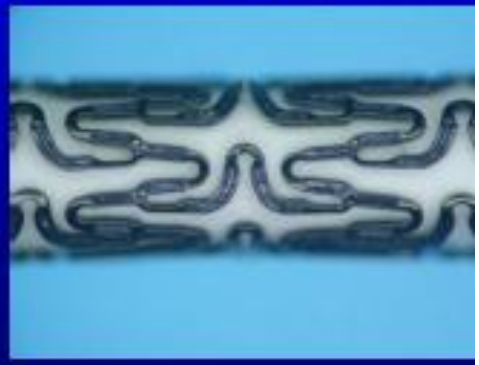
YUKON
Various Drugs



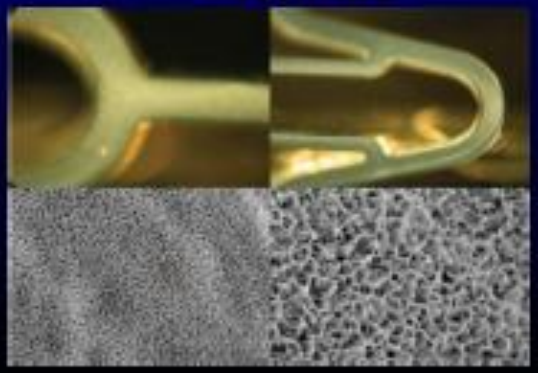
BioFreedom
Biolimus A9



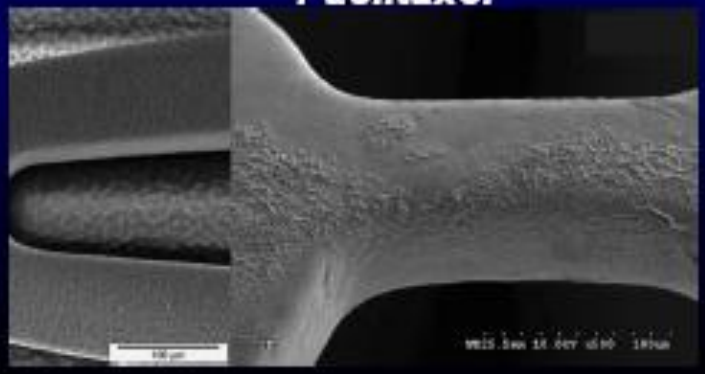
Optima
Tacrolimus



VESTAsync
Sirolimus



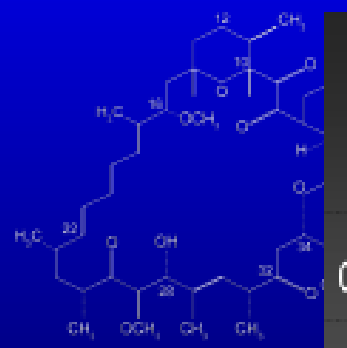
Amazon Pax
Paclitaxel



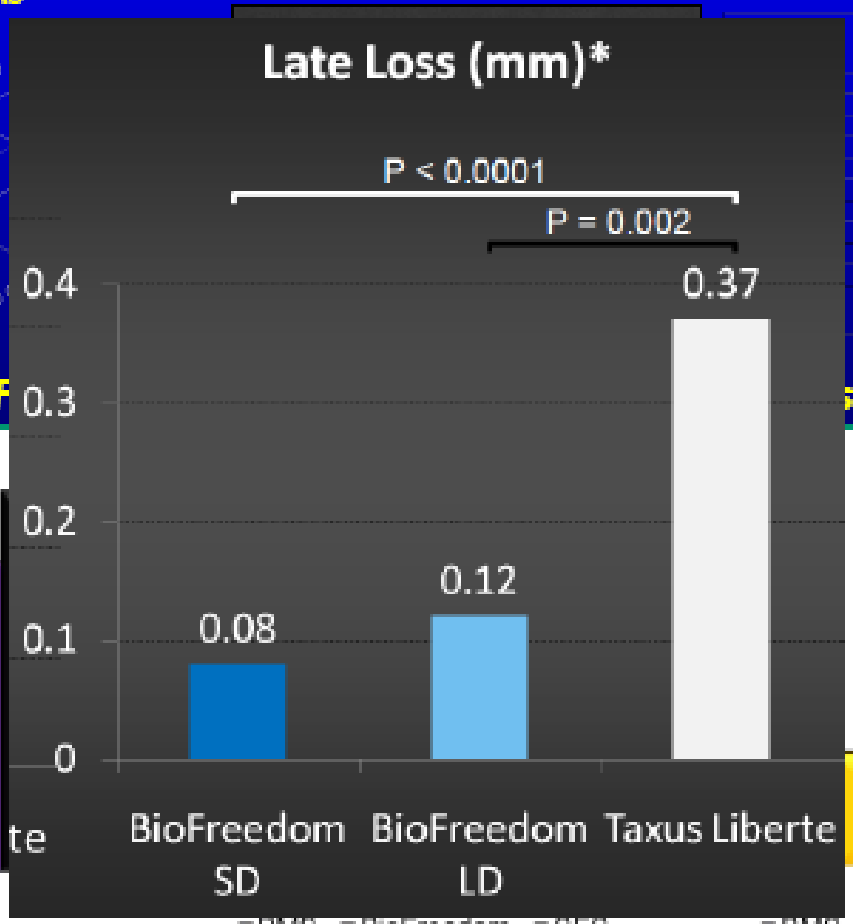
Biofreedom Polymer-Free Biolimus-A9 Coated Stent

Tada N et al. *Circ Cardiovasc Interv* 2010;3:174-83

Biolimus A9



Late Loss (mm)*



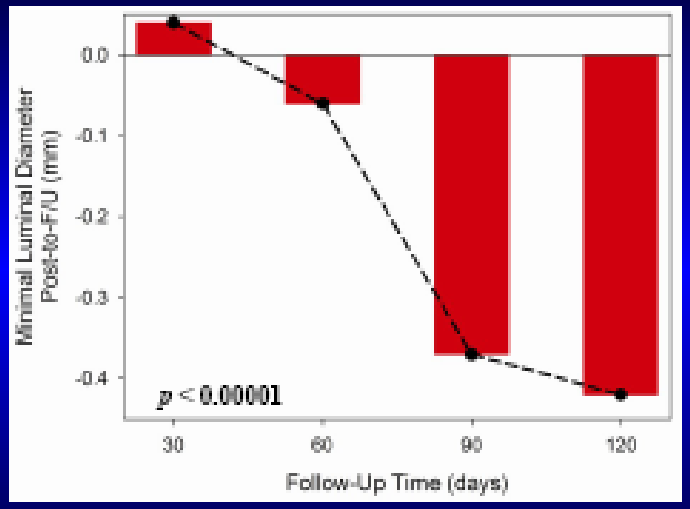
Struts With F ***s With Giant Cells***

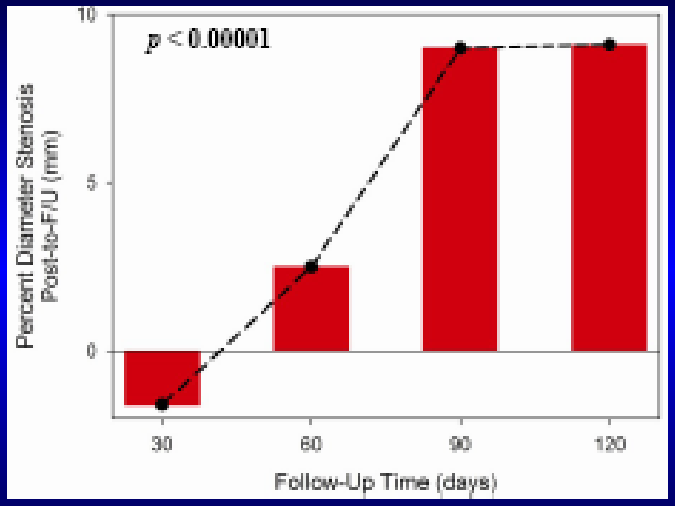
What is the Minimum Duration of Radial Scaffolding?

After DES Placement, Scaffolding of the Vessel is Only a Transient Need

Quantitative angiographic study in 342 consecutive patients at 1, 2, 3, and 4 months

n = 342 patients (*n* = 93 at 30-day F/U; *n* = 79 at 60-day F/U; *n* = 82 at 90-day F/U; *n* = 88 at 120-day F/U)





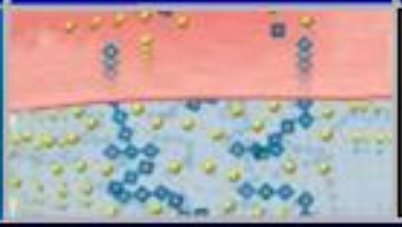
The lumen appears to stabilize approximately three months after PTCA

Serruys PW, et al., *Circulation* 1988; 77: 361.

Bioabsorbable Stent Programs

Igaki-Tamai		PLA
Biotronik		Magnesium
REVA		Tyrosine-Policarbonate
BIT		PAE-Salicylate PLA
BVS		

BVS: Bioresorbable Vascular Scaffold

Bioresorbable Device Platform	Bioresorbable Coating	Everolimus
• Poly (Lactic Acid) (PLLA) • Naturally resorbed, fully metabolized	• PDLLA coating • Fully biodegradable	• Similar dose and release rate to XIENCE V
		

Fully Bioabsorbable Everolimus-Eluting Stent

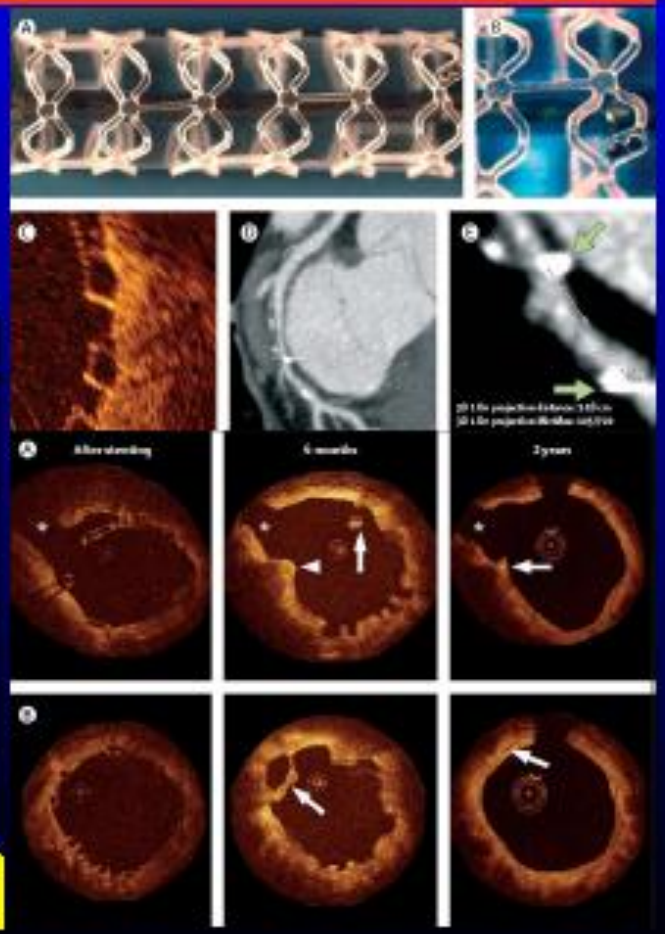
Serruys PW et al. *Lancet* 2009;373:897 – Onuma Y et al. *Circulation* 2011;123:779

Thin coating everolimus/PLLA matrix for controlled drug release

PLLA stent backbone for stent integrity

Cohort A - Clinical Outcomes Through Four Years

	1 Year	2 Years	3 Years	4 Years
Cardiac Death	0%	0%	0%	0%
MI	3.4%	3.4%	3.4%	3.4%
QWMI	0%	0%	0%	0%
NQWMI	3.4%	3.4%	3.4%	3.4%
TLR	0%	0%	0%	0%
Stent Thrombosis	0%	0%	0%	0%
MACE	3.4%	3.4%	3.4%	3.4%

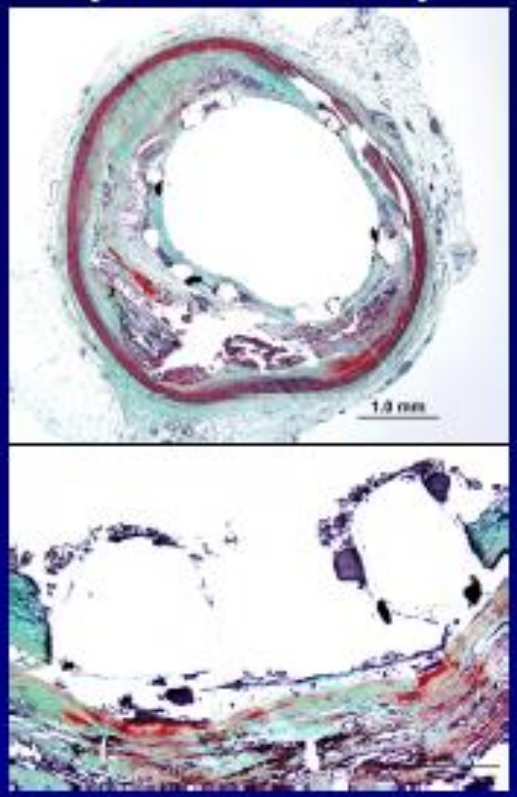


Stent Thrombosis and New Stents Conclusions

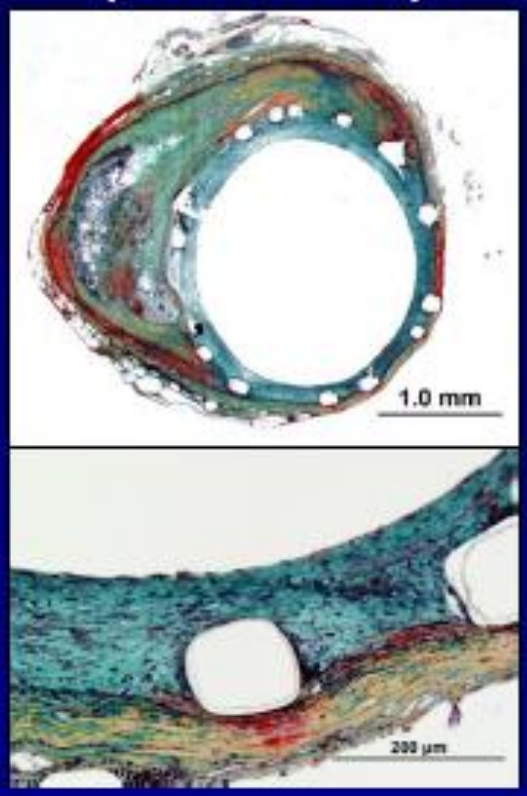
- ST although it affects a small percent of DES, remains an important safety issue
- ST is multifactorial, with central issues the stent design and platelet function
- Understanding ST mechanism has improved our preventing treatments
- New stents (bioabsorbable polymers, polymer free, fully bioabsorbable stents) and new antiplatelet agents will reduce significantly ST in the future

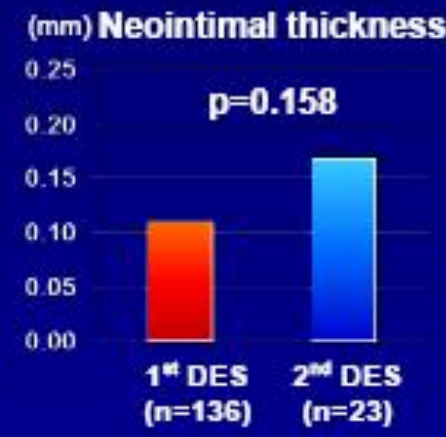
Vessel Healing Following Stent Implantation in Humans: 1st vs. 2nd generation DES

1st gen DES (SES 13 months)



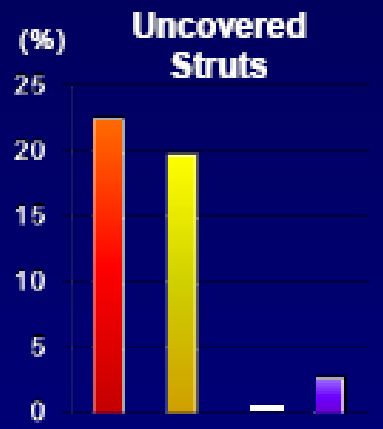
2nd gen DES (EES 6 months)

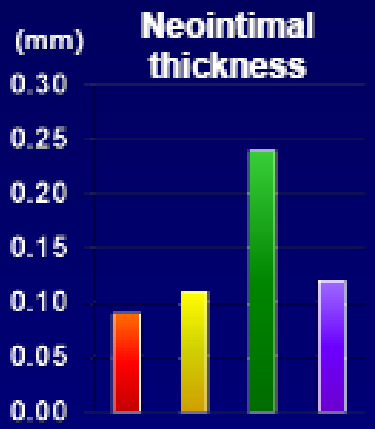


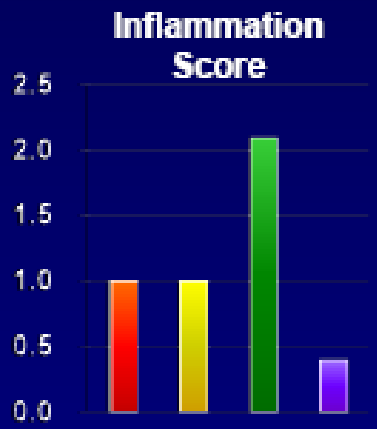


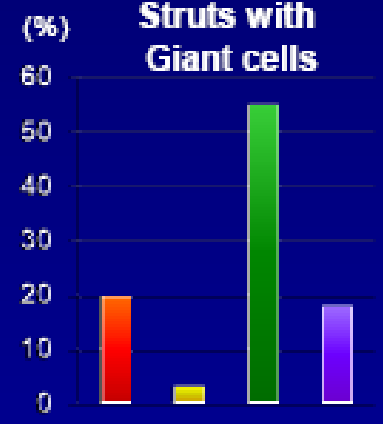
Histologic Assessment of 1st (SES and PES) and 2nd Generation (ZES and EES) DES (>30 days)

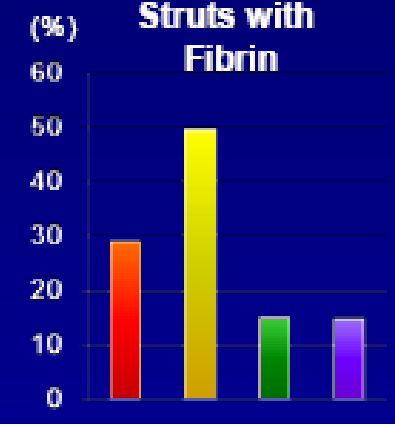
	SES (n=61)	PES (n=75)	ZES (n=6)	EES (n=17)
Median duration	(9.0 months)	(7.0 months)	(6.0 months)	(6.5 months)

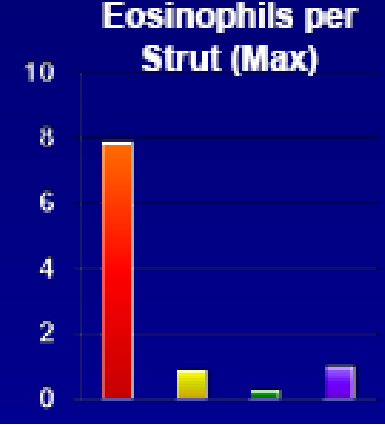




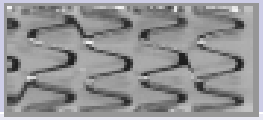








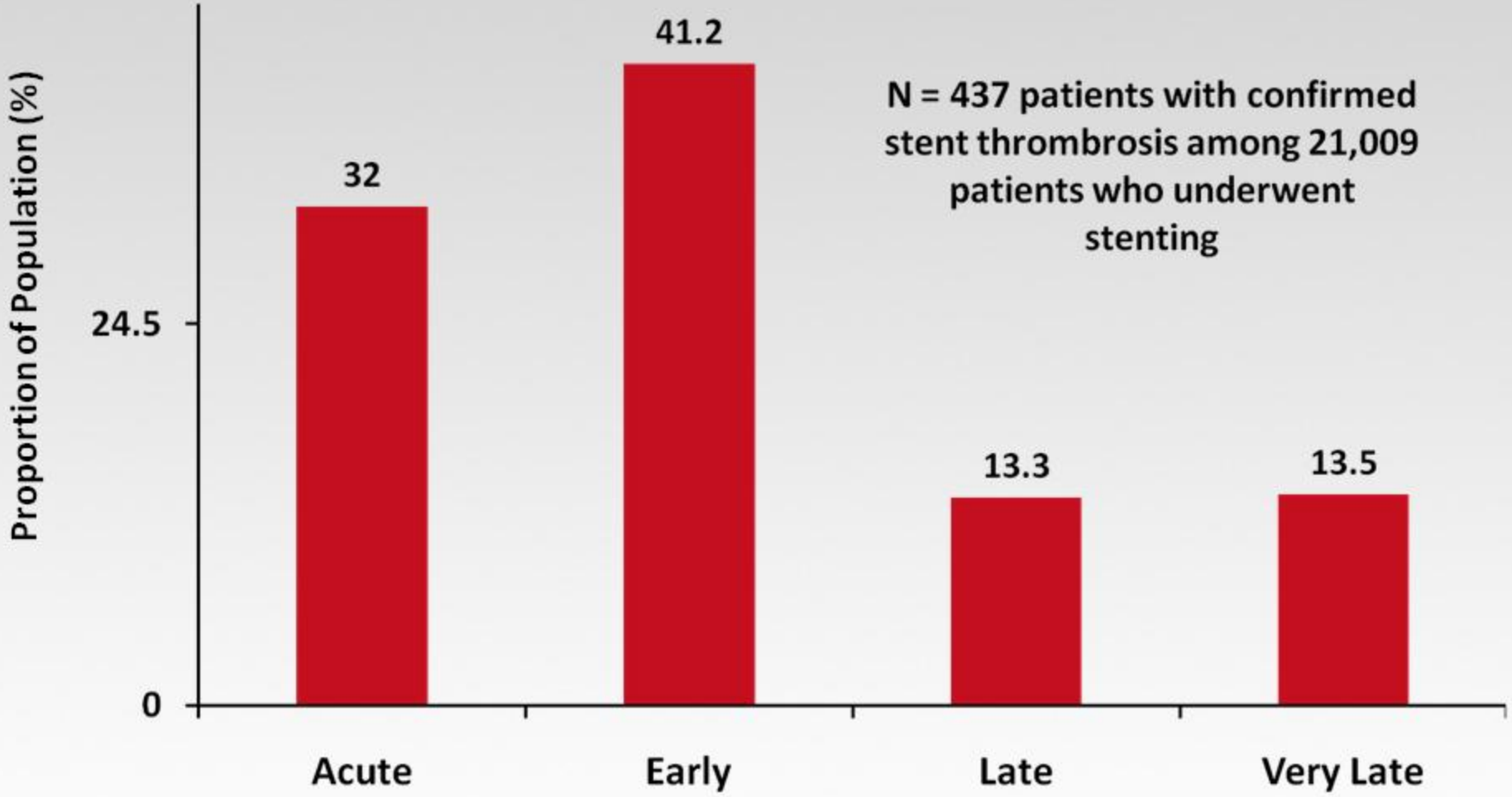
Practical Considerations

Stent	EES-Element Promus-Element	ZES - Resolute	EES - Xience Prime
Underlying Stent	PtCr – Element (Omega)	CoCr – Integrity	CoCr -– ML 8
Strut Thickness	0.0032”	0.0036”	0.0032”
Strut Pattern			
Lengths (mm)	8,12,16,20,24,28, 32, and 38 mm (38 for ≥2.7 mm diameter)	9,12,15,18,22,26, 30, 34 and 38 mm (34 and 38 for ≥3.0 mm diameter)	8,12,15,18,23,28, 33, and 38 mm (33 and 38 mm for ≥2.5 mm diameter)
Diameters (mm)	2.25, 2.5, 2 .75, 3.0, 3.5 and 4.0	2.25, 2.5, 2 .75 ,3.0, 3.5 and 4.0	2.25, 2.5, 2 .75, 3.0, 3.5 and 4.0

Practical Considerations

Stent	EES – PROMUS ELEMENT	ZES - Resolute	EES – Xience Prime
Max Expansion (mm)	2.25 to 2.75 2.5 & 2.75 to 3.5 3.0 & 3.5 to 4.25 4.0 to 5.25	2.25 – 2.75 to 3.25 3.0 – 4.0 to 4.75	2.25 & 2.5 to 3.25 2.75 &3.0 to 3.75 3.5 & 4.0 to 4.75
Sidebranch Cell Size (Max Expansion)	2.25 to 4.18 2.5 & 2.75 to 4.7 3.0 & 3.5 to 5.75 4.0 to 7.44	2.25 to 4.0 to 9.24 mm	6 Cresst -- 2.25 to 3.0 to 3.5mm 9 Crest – 3.5 & 4.0 to 4.2 mm
Polymer Drug	Fluorinated Copolymer - EES	Biolinx Polymer ZES	Fluorinated Copolymer - EES
In Stent Late Loss	≤0.2mm	≤0.2 mm	≤0.2 mm

Dutch Stent Thrombosis Registry: Most Events Early



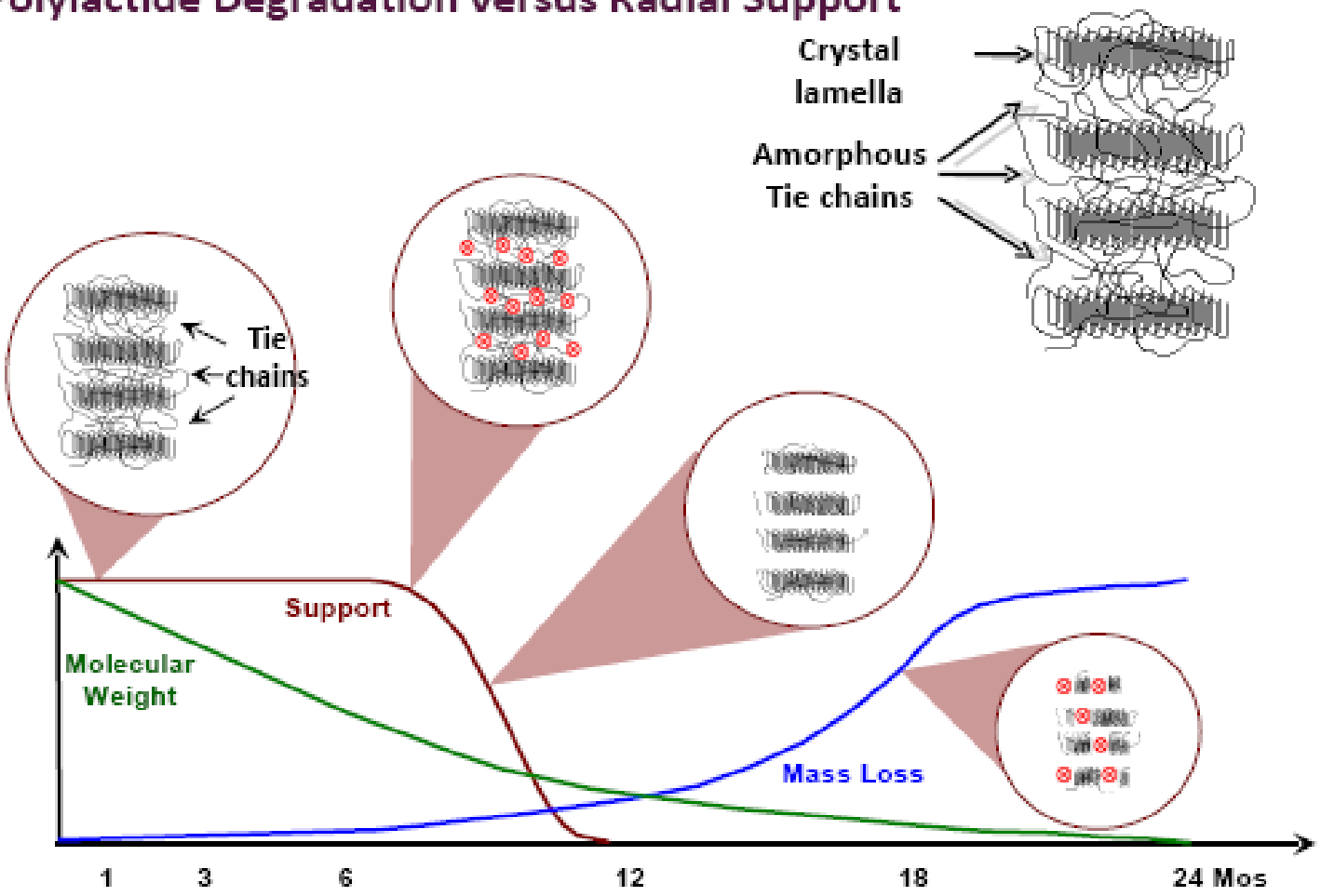
van Werkum JW, et al. *J Am Coll Cardiol*. 2009;53:1399-1409.

Conclusions

- HPR is a risk factor for thrombotic events during and after PCI.
- Several tests measuring HPR are validated to predict outcome
  - Define high-risk patients
  - Define low-risk patients
- The GRAVITAS trial showed that double-dose clopidogrel based on a single post-PCI measurement of platelet reactivity does not improve outcome.
- Randomized trials using stronger $P2Y_{12}$ inhibitors and serial testing (adjusting drugs per platelet function/genetic tests) are ongoing.

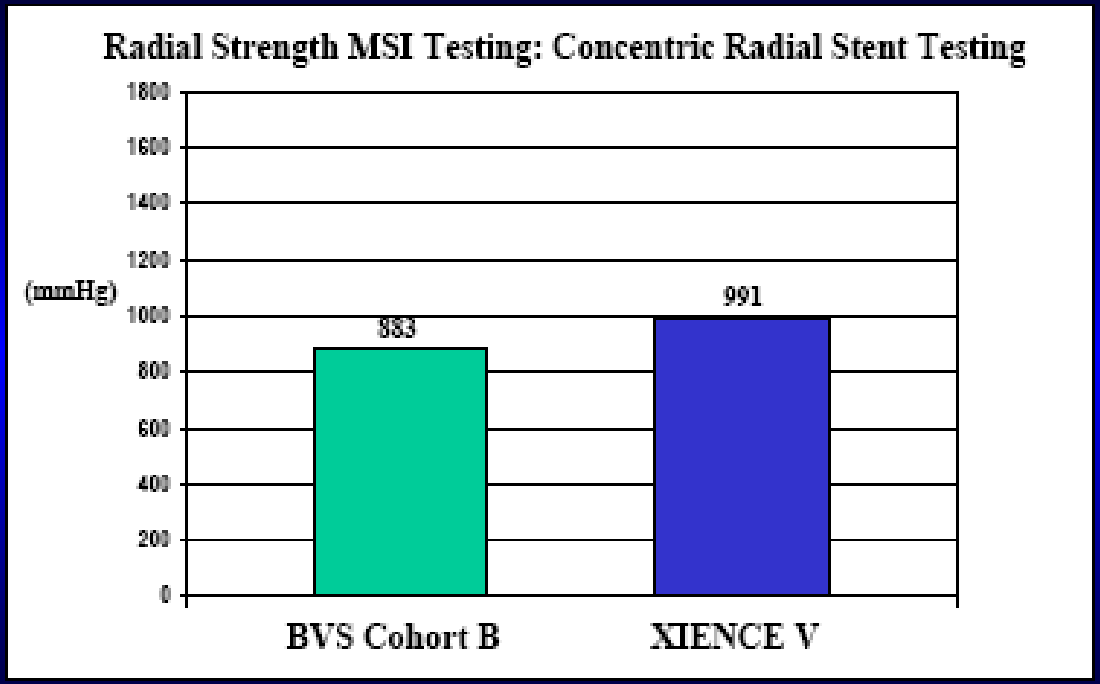
Bioabsorbable Drug Everolimus Eluting Stent (BVS)

Polylactide Degradation versus Radial Support



Radial Strength Testing

FDA mandates concentric radial strength measurements rather than flat plate measurements (more clinically relevant)



Radial strength comparable to metal stent at T=0

QCA results at 12 months

N=56	Proximal	In-scaffold	Distal
Minimal Luminal Diameter			
Post procedure	2.43	2.27	2.18
At 12 months	2.30	2.00	2.10
P value	0.003	<0.001	0.047
Late Loss, mm	0.12	0.27	0.07
Diameter Stenosis, %			
Post procedure	13	15	15
At 12 months	12	21	13
P value	0.75	<0.001	0.10
Binary restenosis	0%	3.57%	0%