DES Thrombosis: Is It Real and Is It Worse? New Approaches to Solving It

Angioplasty Summit 2006
Seoul, Korea

David R. Holmes, M.D.

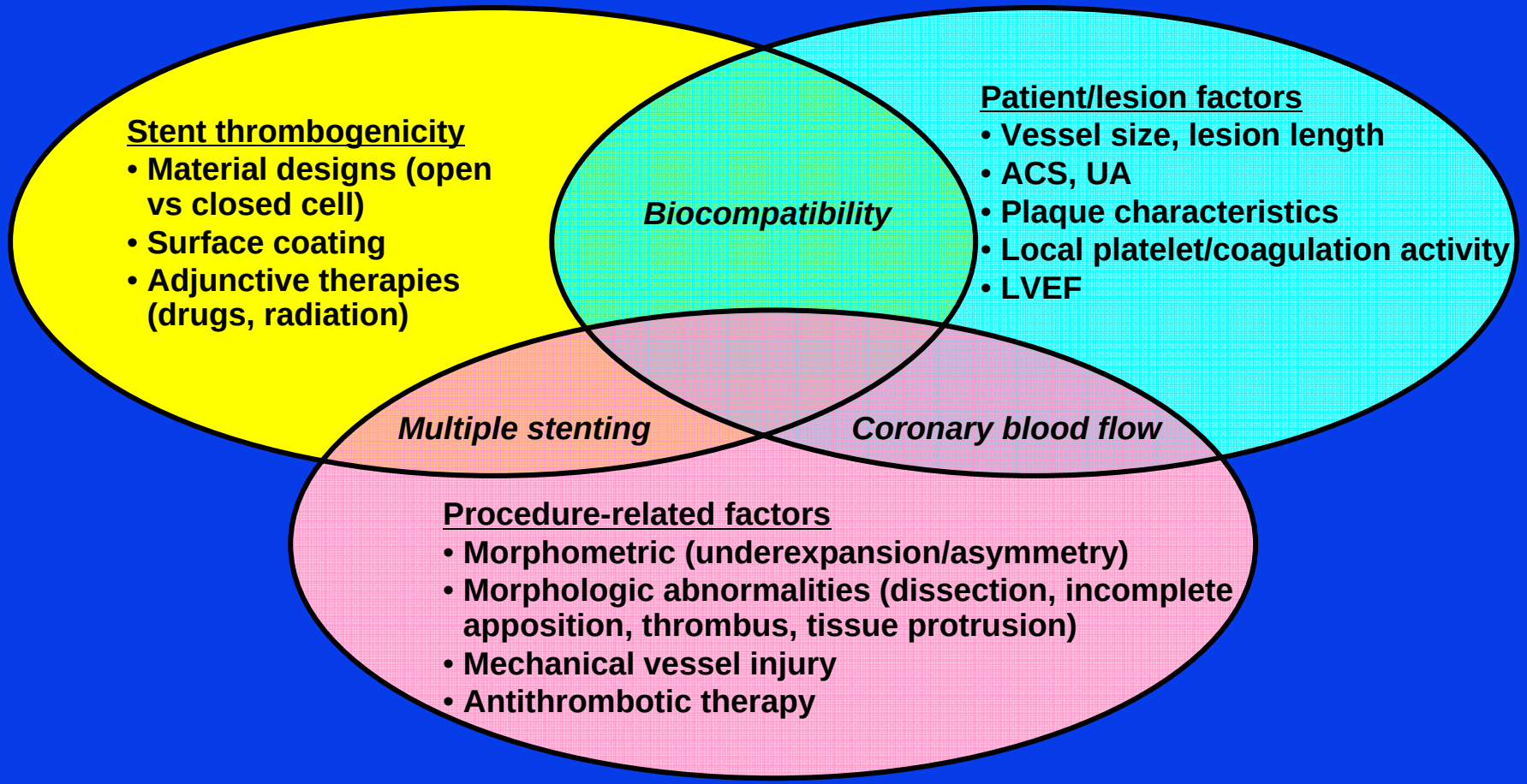
Mayo Clinic, Rochester, MN

MAYO CLINIC

MAYO CLINIC

Factors Associated with Stent Thrombosis

- The exact pathophysiology of stent thrombosis has not been fully elucidated
- However, multiple factors are involved in development of stent thrombosis



Honda and Fitzgerald: Circulation 108:2, 2003

DES and Stent Thrombosis

- Incidence
- Timing
- Clinical presentation
- Associations/Mechanisms
- Prevention
- Future

Drug-Eluting Stent Thrombosis Pooled Analysis

- 10 randomized trials of DES and BMS published prior to June 2004
- Included SES and PES

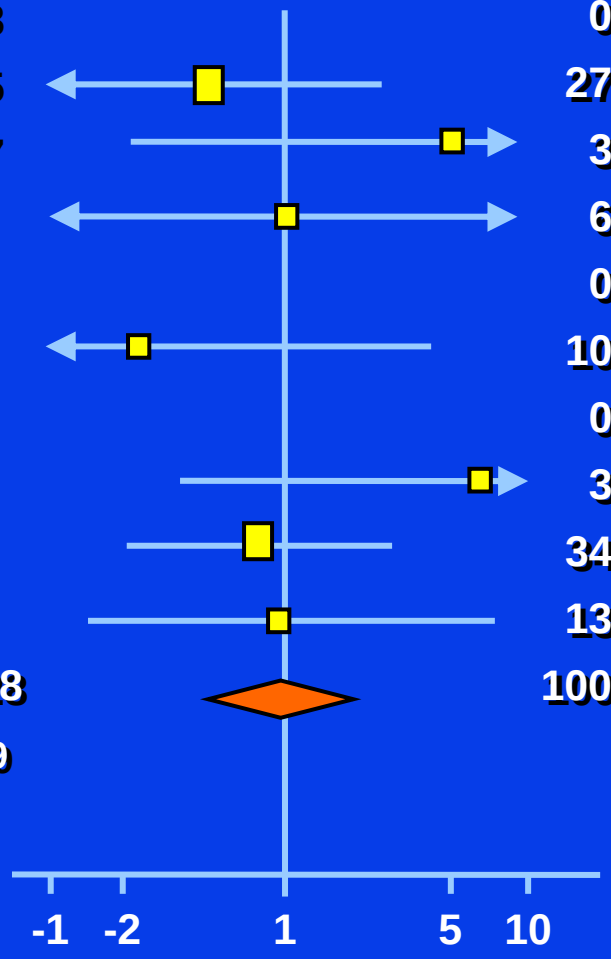
Moreno, JACC 2005; 45:954-9

Drug-Eluting Stent Thrombosis

Study	DES n/N	BMS n/N	OR (95% CI fixed)	Weight (%)	OR (95% CI fixed)
RAVEL	0/120	0/118		0.0	Not estimable
SIRIUS	2/533	4/525		27.6	0.49 (0.09, 2.69)
E-SIRIUS	2/175	0/177		3.4	5.12 (0.24, 107.32)
C-SIRIUS	1/50	1/50		6.7	1.00 (0.06, 16.44)
ASPECT	0/90	0/48		0.0	Not estimable
ELUTES	1/153	1/39		10.9	0.25 (0.02, 4.09)
TAXUS-I	0/31	0/30		0.0	Not estimable
TAXUS-II	3/266	0/270		3.4	7.19 (0.37, 139.80)
TAXUS-IV	4/662	5/652		34.4	0.79 (0.21, 2.94)
DELIVER	2/522	2/519		13.7	0.99 (0.14, 7.09)
Total (95% CI)	15/2,602	13/2,428		100.0	1.05 (0.51, 2.15)

Test for heterogeneity χ^2: 4.62; df=6; P=0.59

Test for overall effect: z=0.13; P=0.9



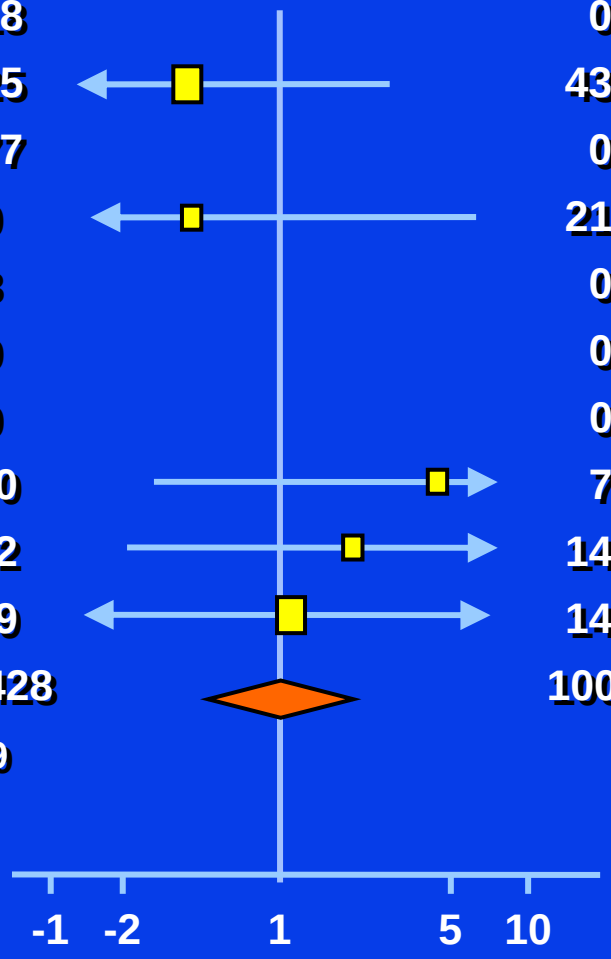
Moreno et al:
JACC 45:954, 2005

Drug-Eluting Late Stent Thrombosis

Study	DES n/N	BMS n/N	OR (95% CI fixed)	Weight (%)	OR (95% CI fixed)
RAVEL	0/120	0/118		0.0	Not estimable
SIRIUS	1/533	3/525		43.1	0.39 (0.09, 3.15)
E-SIRIUS	0/175	0/177		0.0	Not estimable
C-SIRIUS	0/50	1/50		21.2	0.33 (0.01, 8.22)
ASPECT	0/90	0/48		0.0	Not estimable
ELUTES	0/153	0/39		0.0	Not estimable
TAXUS-I	0/31	0/30		0.0	Not estimable
TAXUS-II	2/266	0/270		7.0	5.11 (0.24, 107.02)
TAXUS-IV	2/662	1/652		14.4	1.97 (0.18, 21.81)
DELIVER	1/522	1/519		14.3	0.99 (0.06, 15.94)
Total (95% CI)	6/2,602	6/2,428		100.0	0.99 (0.35, 2.64)

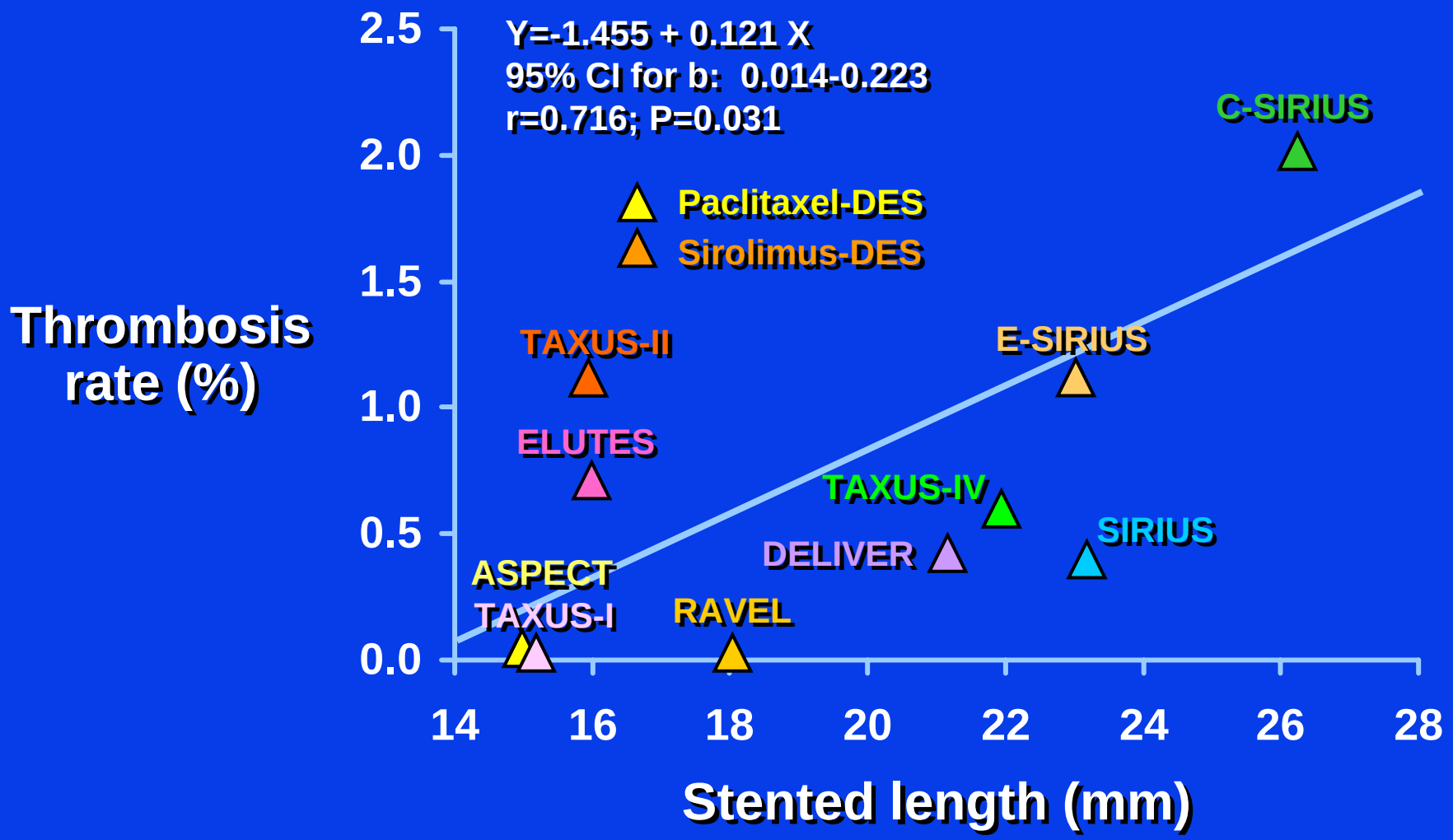
Test for heterogeneity χ^2: 2.81; df=4; P=0.59

Test for overall effect: z=0.01; P=1



Moreno et al:
JACC 45:954, 2005

Drug-Eluting Stent Thrombosis



Moreno et al: JACC 45:954, 2005

MAYO CLINIC

CP1223091-3

Drug-Eluting Stent Thrombosis Conclusions

"Drug-eluting stents do not increase the risk of stent thrombosis, at least under appropriate antiplatelet therapy"

Risk of stent thrombosis is related to stent length

Moreno, JACC 2005; 45:954-9

Cypher Late Thrombosis
720 Days

	CYPHER	Control
RAVEL	0/120 (0%)	1/118 (0%)
SIRIUS	2/553 (.4%)	3/525 (0.6%)
New SIRIUS	1/225 (.4%)	1/227 (0.4%)
Total	3/878 (.3%)	4/870 (0.5%)

Stent Thrombosis
Integrated TAXUS Program

	BMS n=1,367			PES n=1,369			
	No.	%	95% CI	No.	%	95% CI	P
Early (0-30 d)	7	0.51	0.23-1.1	7	0.51	0.22-1.1	1.0
Late							
31-180 d	2	0.15	0.03-0.59	2	0.15	0.03-0.59	1.0
>180 d	0			5	0.37	14-0.90	0.06
Total	9	0.66	0.33-1.29	14	1.02	0.50-1.76	0.4

Ellis: JACC 47:221A, 2006

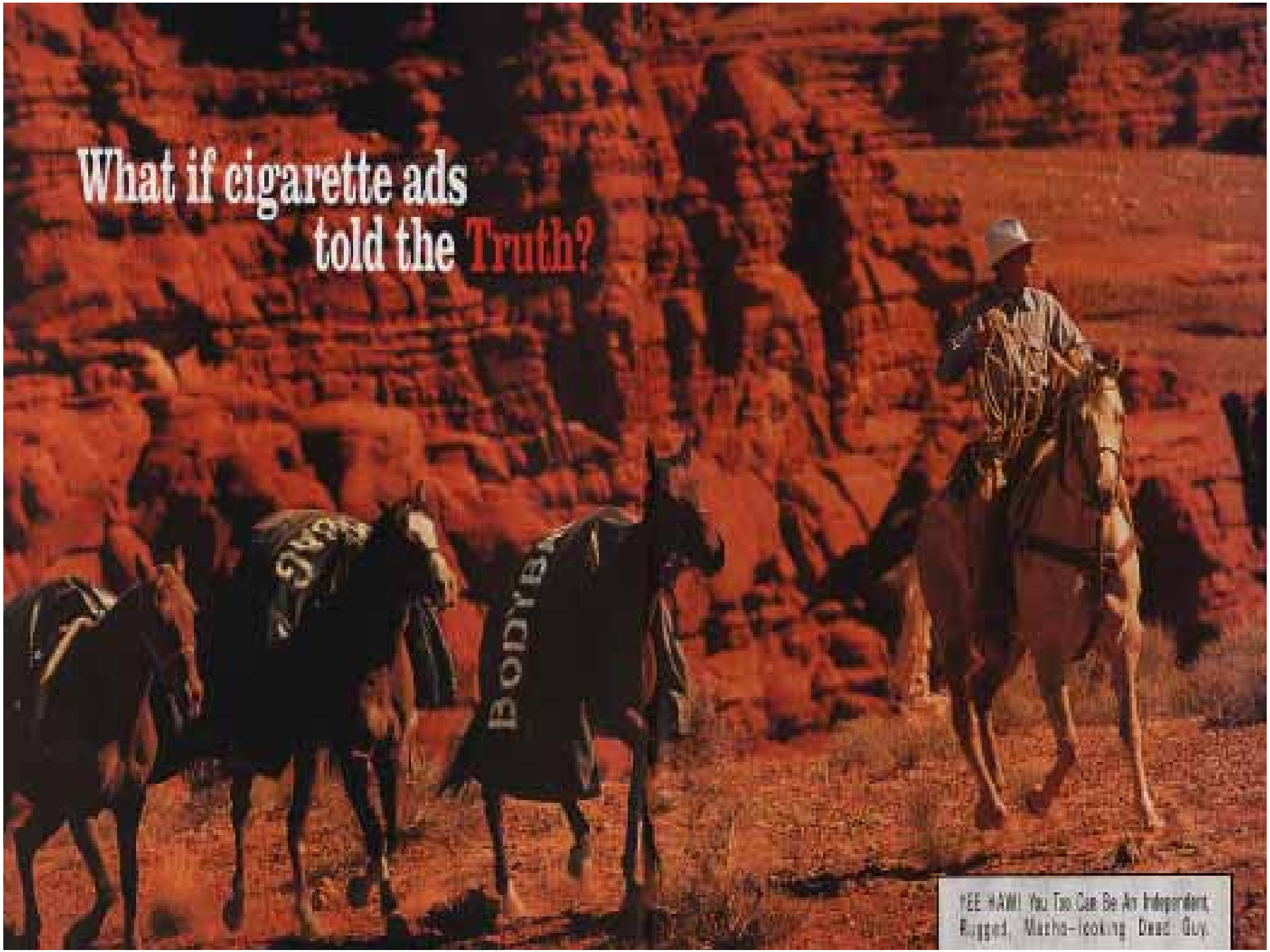
Stent Thrombosis
Issues

- Definition
  - Angiographic
  - Clinical
  - Presumed
- Adjunctive therapy
- Duration of follow-up

Incidence of Stent Thrombosis

Stent type	Pt (no.)	Angiographically-proven stent thrombosis			Possible stent thrombosis			All stent thrombosis		
		No.	%	95% CI	No.	%	95% CI	No.	%	95% CI
Bare metal	506	6	1.2	0.5-2.6	1	0.2	0.0-1.1	7	1.4	0.7-2.8
Sirolimus eluting	1,017	10	1.0	0.5-1.8	5	0.5	0.2-1.1	15	1.5	0.9-2.4
Paclitaxel eluting	989	10	1.0	0.6-1.9	6	0.6	0.3-1.3	16	1.6	1.0-2.6

Ong et al: J Am Coll Cardiol 45:947, 2005


What if cigarette ads
told the Truth?
YEE-HAW! You Too Can Be An Independent,
Rugged, Macho-looking Dead Guy.

The Downside of Stent Thrombosis
Angiographic Stent Thrombosis

- 30-day mortality 15%
- Non-fatal infarction 65%

Ong et al: JACC 45:947-53, 2005

The Downside of Stent Thrombosis

Possible Stent Thrombosis

n = 12

Mortality	75%
Non fatal infarction	25%

Ong et al: JACC 45:947-53, 2005

Factors Associated with the Probability of BMS Stent Thrombosis

- Complex baseline angiographic morphology
- Smaller maximal balloon diameter
- Stent underexpansion (<80%)
- Stent malapposition
- Inflow/outflow disease
- Persistent dissection
- Total stent length
- Final lumen diameter
- Platelet polymorphism
- Resistance to antiplatelet therapy

Cutlip et al: Circ 103:1967, 2001; Orford et al: JACC 40:1567, 2002; Uren et al: Eur H J 23:124, 2002; Dangas et al: AJC 94:983, 2004

What is it that washes everything else away?

Predictors of Stent Thrombosis

Variables	Hazard Ratio (95% CI)	P
Cumulative stent thrombosis		
Premature antiplatelet RX discon.	89.78 (29.90-269.60)	<.001
Renal failure	6.49 (2.60-16.15)	<.001
Bifurcation lesion	6.42 (2.93-14.07)	<.001
Diabetes	3.71 (1.74-7.89)	.001
LV ejection fraction/10% decrease	1.09 (1.05-1.13)	<.001

Iakovou, JAMA 2005; 293:2126-2130

Common Features for LAST

Characteristics of Patients with LAST

Pt (no.)	Age, gender	Months to event	DES type	Treated vessel	Nominal stent diam (mm)	Total stent length (mm)	Antiplatelet therapy at time of LAST	Notes	Clinical presentation	Clinical outcome at hospital discharge
1	74, male	2	SES	Mid LAD	2.5	23	Nil	Aspirin and clopidogrel stopped 5 days prior	STEMI	Alive
2	57, male	7	PES	RCA	3.0	68	Aspirin	Clopidogrel stopped 28 days prior	STEMI	Alive
3a	64, male	6	PES	Post LAD	3	32	Aspirin	Clopidogrel stopped 21 days prior	STEMI	Alive
3b	64, male	11	PES	Post LAD	3	16	Nil	Aspirin stopped 5 days prior to surgery	STEMI	Alive
4	74, male	14.5	PES	Post LAD	3.5	20	Nil	Aspirin stopped 7 days prior to surgery	STEMI	Alive
5	39, male	8	PES	Mid RCA	3	20	Aspirin	Clopidogrel stopped 2 months prior	STEMI	Alive
6	63, male	25	SES	Post LAD	3	46	Aspirin	Clopidogrel stopped 19 mo prior	STEMI with shock	Dead
7	71, male	26	SES	Post LAD	3	36	Aspirin	Clopidogrel stopped 23 mo prior	STEMI with shock	Dead

- Overall incidence SAT >180 days = 0.4%
- Most often occurs soon after discontinuation of clopidogrel
- Substantial morbidity and mortality

Associations

- Discontinuation of dual antiplatelet therapy
- Stent length
- Suboptimal deployment
- Lesion/patient complexity
  - Bifurcation stenting with AMI

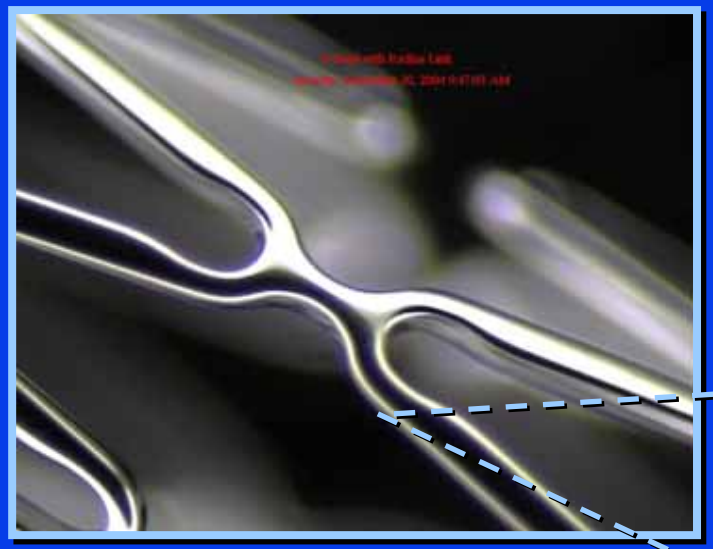
Prevention

- Optimize initial deployment
- Continue with dual antiplatelet therapy or at least ASA

Subsequent Non-Cardiac Surgery

- Within 3-6 months
  - Enhanced surveillance
  - Minimize or eliminate time without dual therapy
  - IV IIb/IIIa bridge
  - Early resumption of dual antiplatelet therapy

BioMatrix™ II Stent Platform

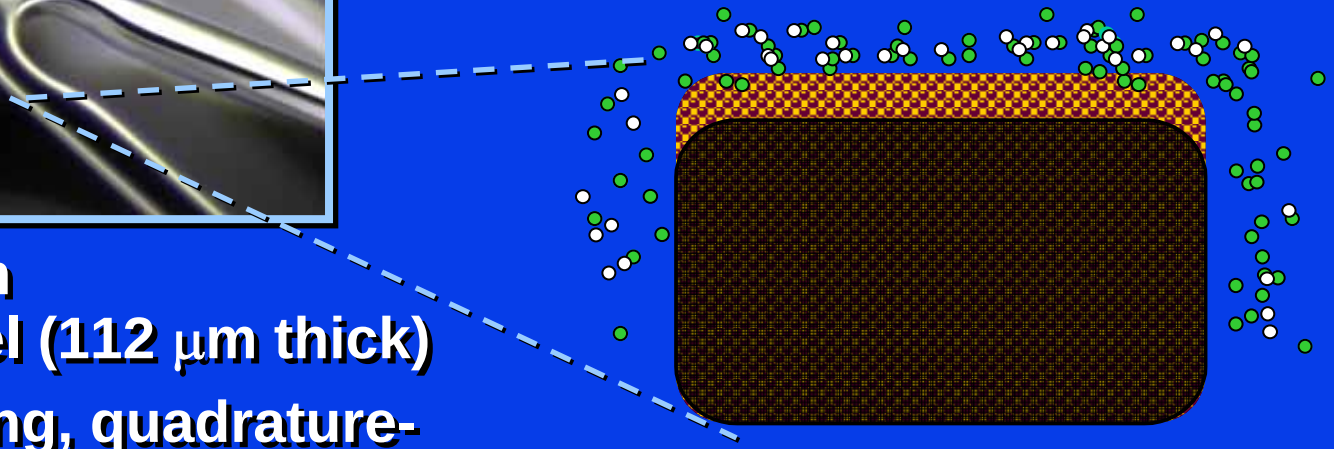


Drug: Biolimus A9™

15.6 μg/mm stent length

Drug carrier: Poly(lactic acid)

PLA:BA9 = 50:50



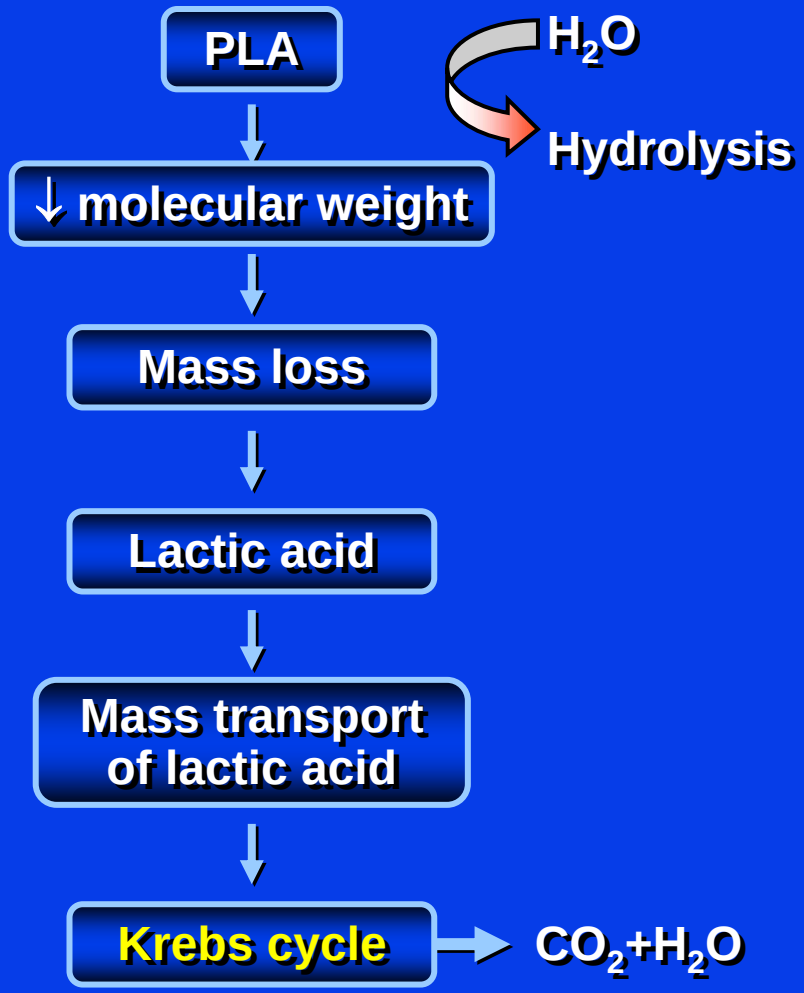
Stent platform
Stainless steel (112 μm thick)

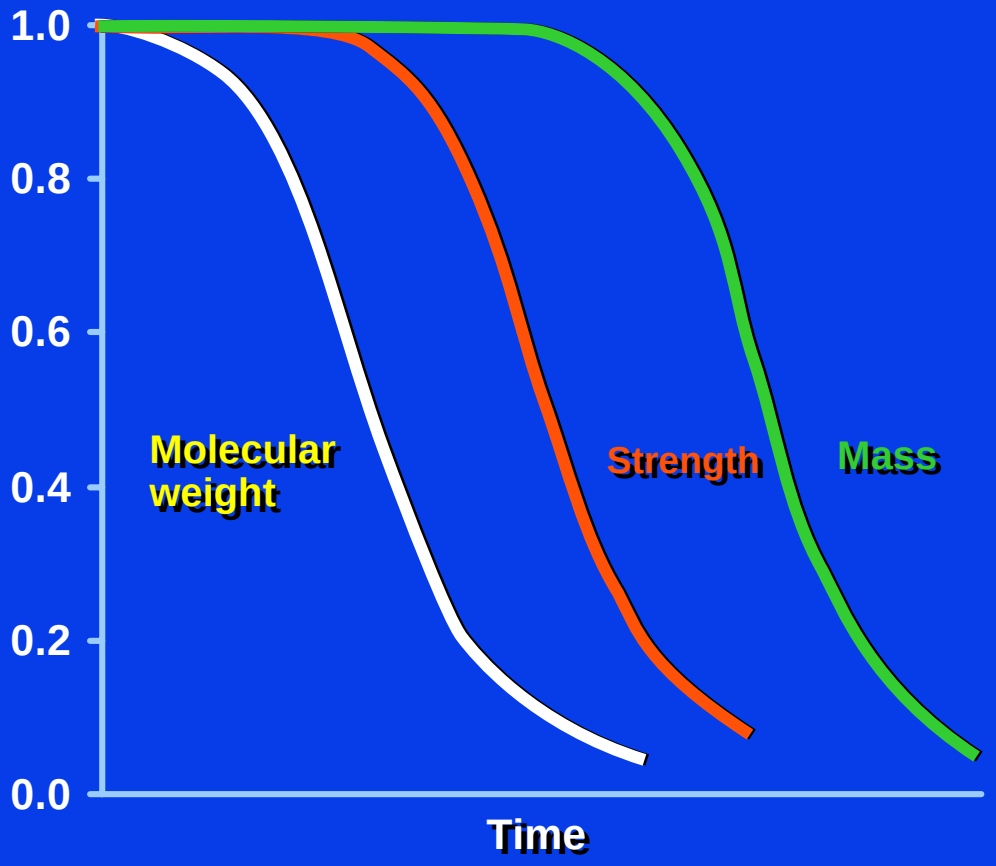
Corrugated ring, quadrature-link design for improved flexibility & axial fatigue resistance

Cross-section sketch of Biolimus A9 eluting stent

Abluminal surface coating

PLA Metabolic Pathway



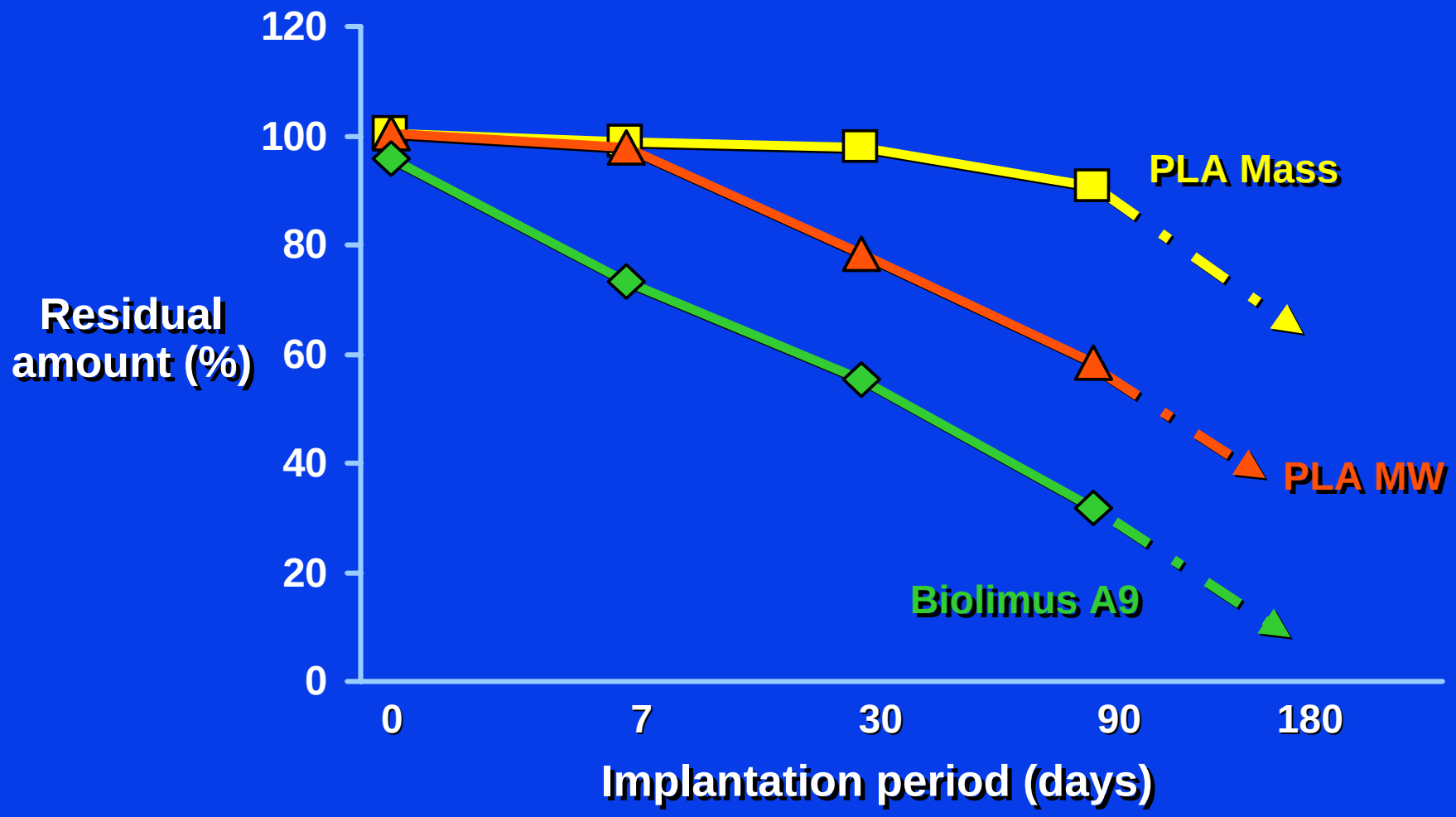


Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time

MAYO CLINIC

CP1221371-7

Degradation of Polymer and Release of Drug Over Time



Levels in the tissue wall return to BL after 180-270 days

Maximize Endothelialization

- Different drugs/polymers
- Different stent design
  - Magnetic stents
  - Bioabsorbable stents
  - Antibody coated stents

ENDEAVOR III
Multicenter Randomized Trial

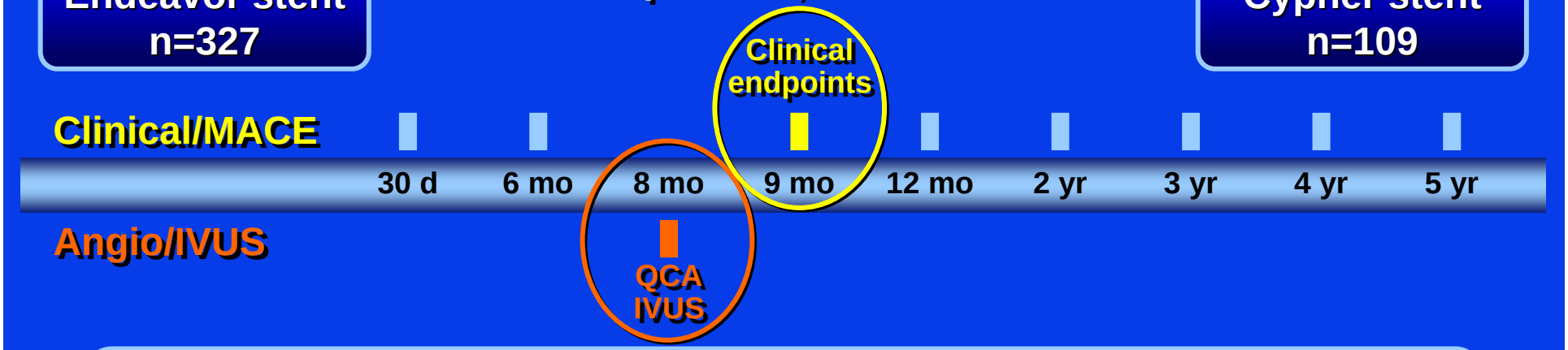
3:1 randomization
Single blind – single vessel – no staging

Single de novo native coronary lesion
Vessel diameter 2.5-3.5 mm
Lesion length 14-27 mm
Stent lengths 18-33 mm (8/9) mm bailout
Predilatation required

n=436 patients; 30 U.S. sites

Endeavor stent n=327

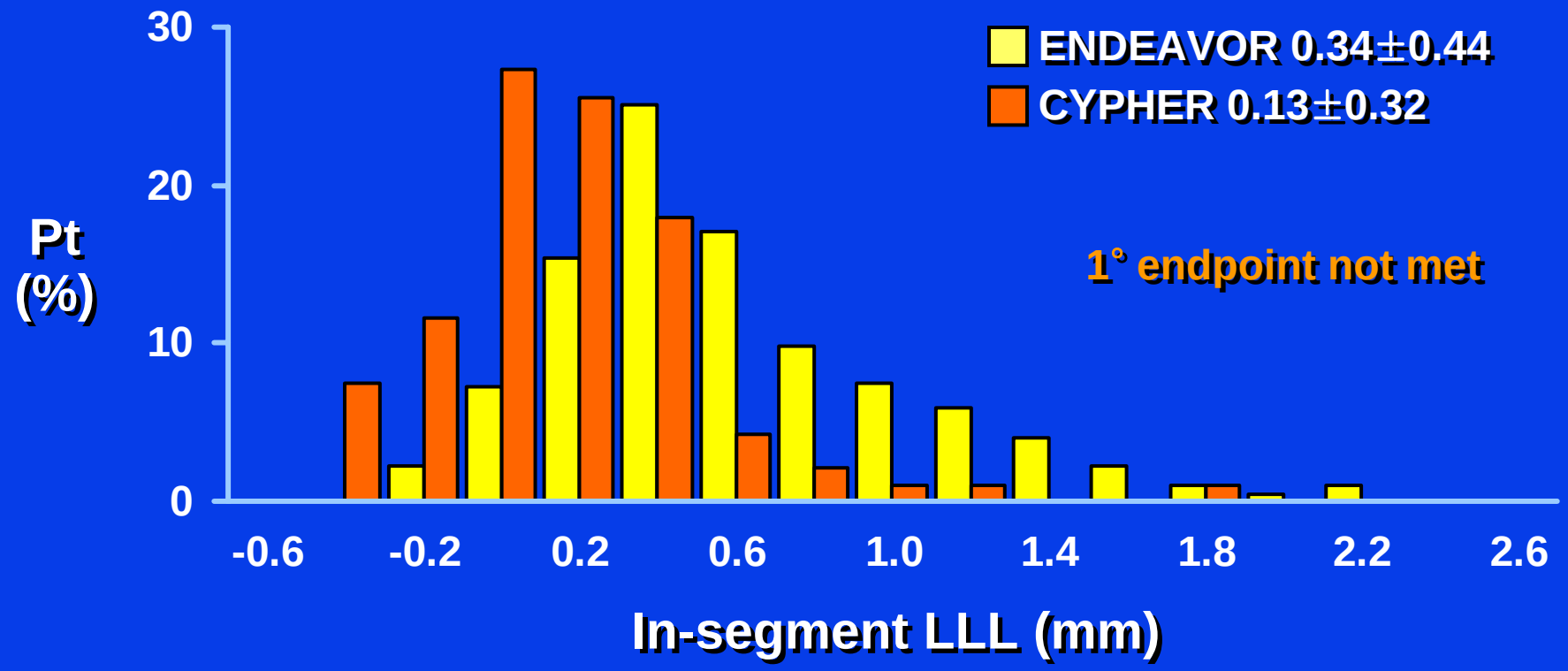
Cypher stent n=109



Primary endpoint: In-segment late lumen loss by QCA at 8 mo
Secondary endpoints: TLR, TVR, TVF at 9 months & ABR at 8 mo
Antiplatelet therapy for ≥3 mo, 10 μg zotarolimus per mm stent length

Primary Endpoint in-Segment LL

- Noninferiority margin of difference 0.20 mm
  90% power, 5% α-1 sided
- Observed difference 0.21 mm



Kandzari. TCT 2005; October 16-21, 2005; Washington DC

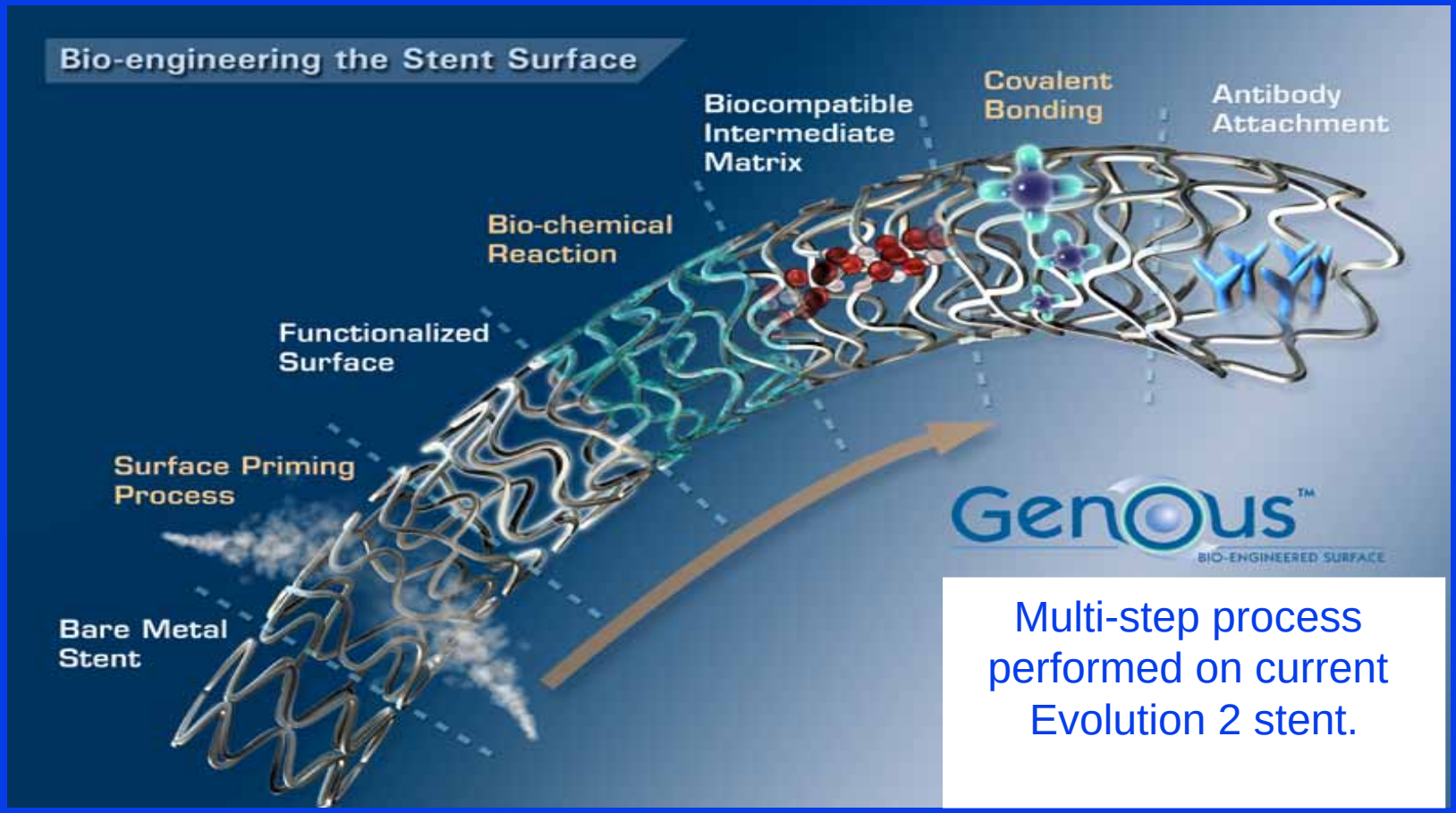
ENDEAVOR III
Clinical Results at 9 Months

	ENDEAVOR n=316	CYPHER n=113	P
MACE (%)	7.6 (24)	7.1 (8)	1.00
Death	0.6 (2)*	0	1.00
Q-wave MI	0	0	–
Non-Q-wave MI	0.6 (2)	3.5 (4)	0.04
CABG	0	0	–
TLR	6.3 (20)	3.5 (4)	0.34
CABG	0.9 (3)	0	0.57
PCI	5.4 (17)	3.5 (4)	0.61
Stent thrombosis (%)	0	0	–
TVR (non-TL) (%)	6.0 (19)	5.3 (6)	1.00
TVF (%)	12.0 (38)	11.5 (13)	1.00

*Noncardaic deaths (lung cancer, cerebral hemorrhage)

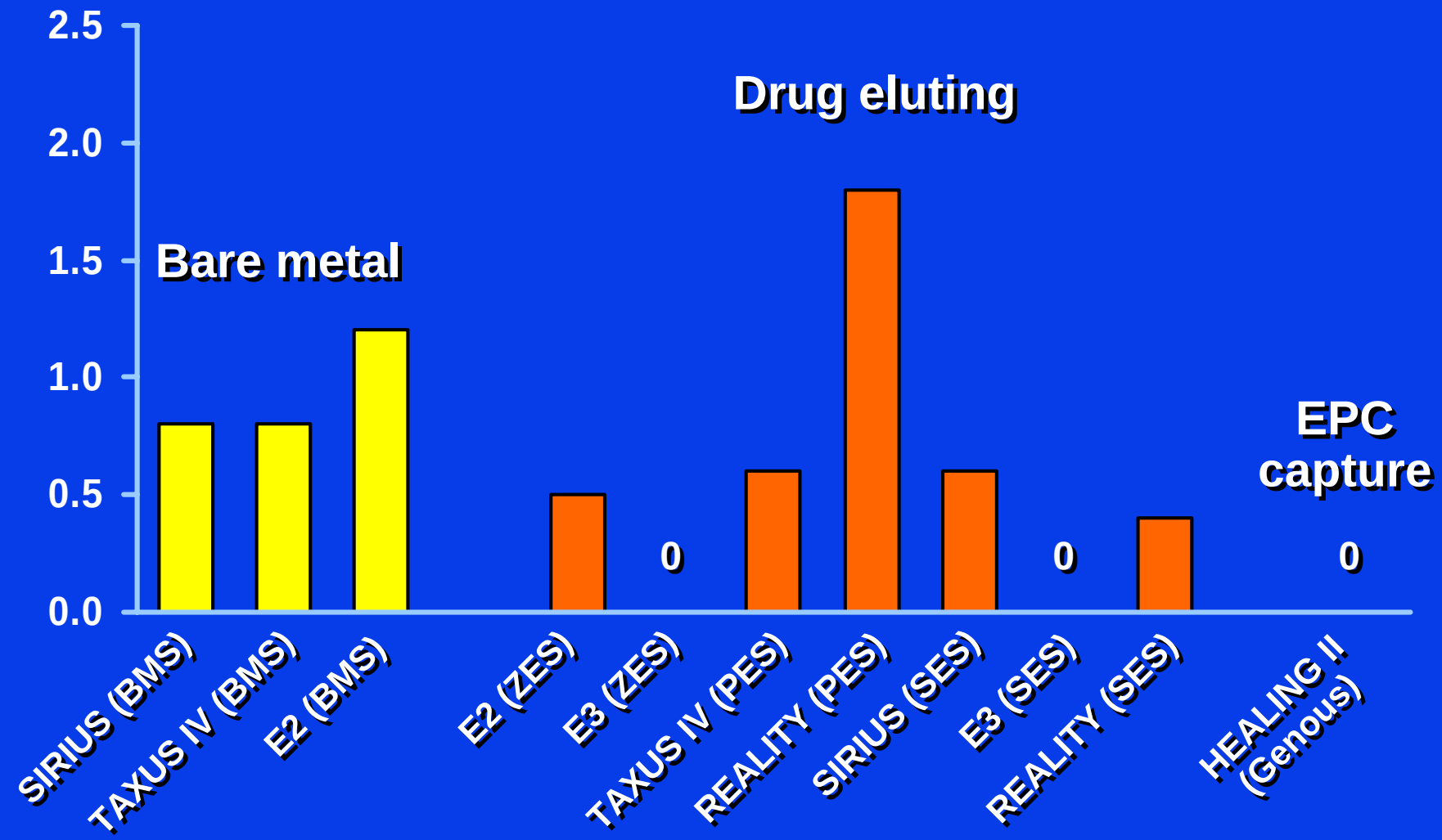
Kandzari: TCT 2005; October 16-21, 2005; Washington DC

Genous Processing

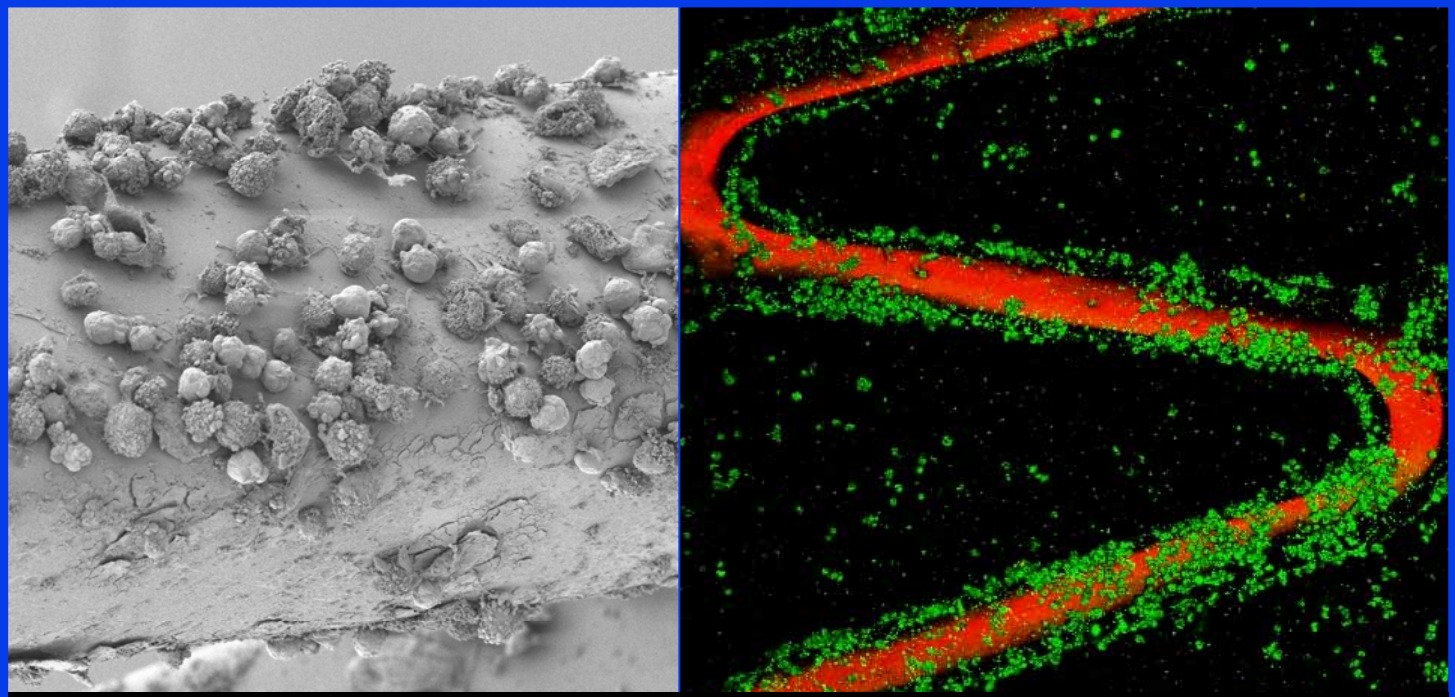


Multi-step process performed on current Evolution 2 stent.

Stent Thrombosis 8/9 Months

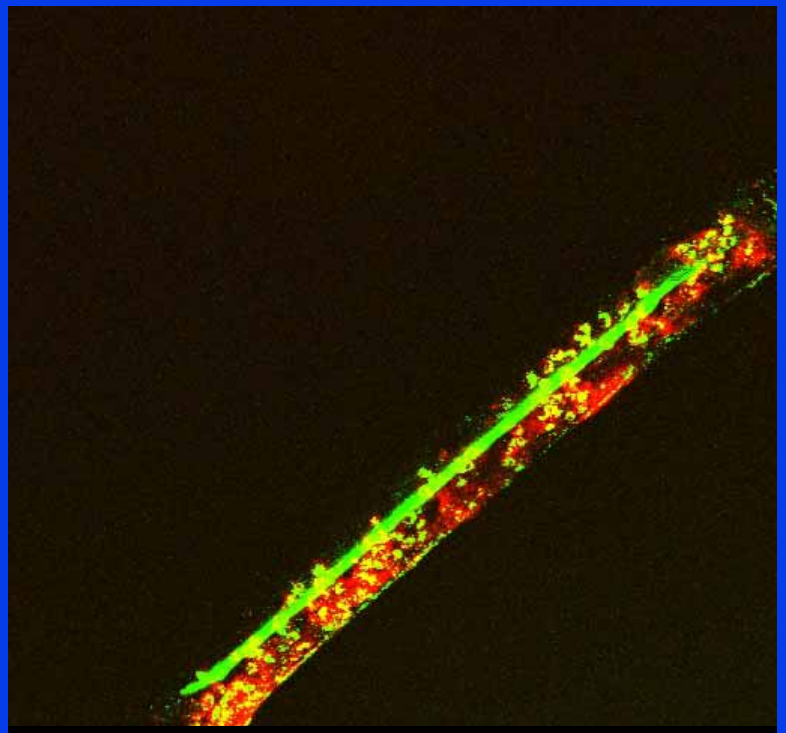


Cells on a magnetic stent - in vitro

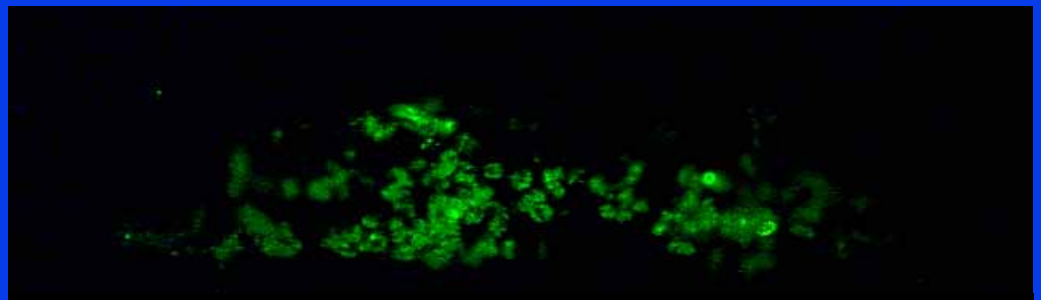


EM and Confocal images at time of cell capture

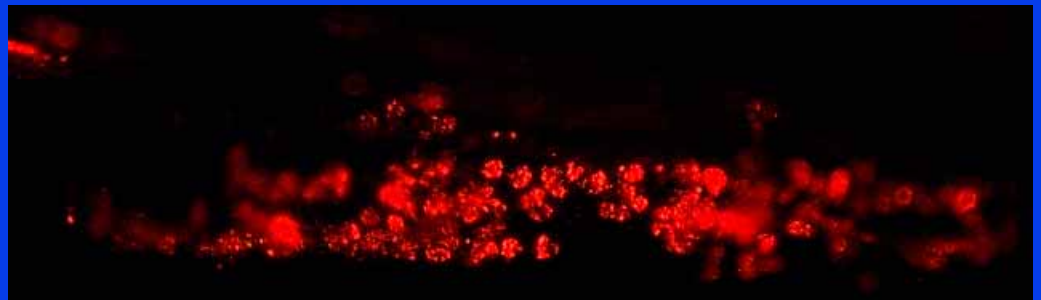
Rabbit carotid stent - in vivo



After in vivo cell delivery
and 2 hr blood flow



Paramagnetic particles - green



Cell surface marker - red

DES and Stent Thrombosis

- Incidence
- Timing
- Clinical presentation
- Associations/Mechanisms
- Prevention
- Future

Conclusions

- EPC titer directly correlates with angiographic and IVUS outcome and identifies patients likely to respond to EPC capture stenting.
- HEALING II suggested that patients with a normal EPC count responded favorably to EPC capture stenting (late loss index 0.19; late luminal loss 0.48 mm)
- TLR/TVR events were restricted to the low EPC group.
- Patients without statin therapy at the time of implant were generally restricted to the low EPC group.
- Low EPC count was associated with a significant late luminal loss, high TVR/TLR incidence and a lack of statin therapy.
- Since statin therapy has been shown to augment EPC number (and function), it may enhance the outcome of EPC capture stenting (Vasa *et al.* Circ 2001, Landmesser *et al.* Circ 2005).