

Newer Generation Drug-Eluting Stents: What is the Promise?



Stephan Windecker



Department of Cardiology

Swiss Cardiovascular Center and Clinical Trials Unit Bern

Bern University Hospital, Switzerland

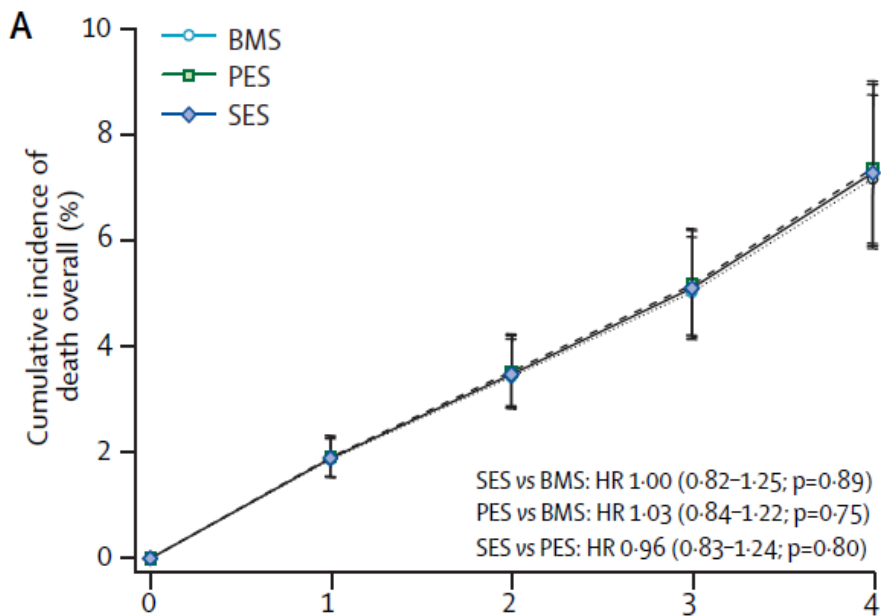
Drug-Eluting Stent Safety

Network Meta-Analysis: DES vs BMS

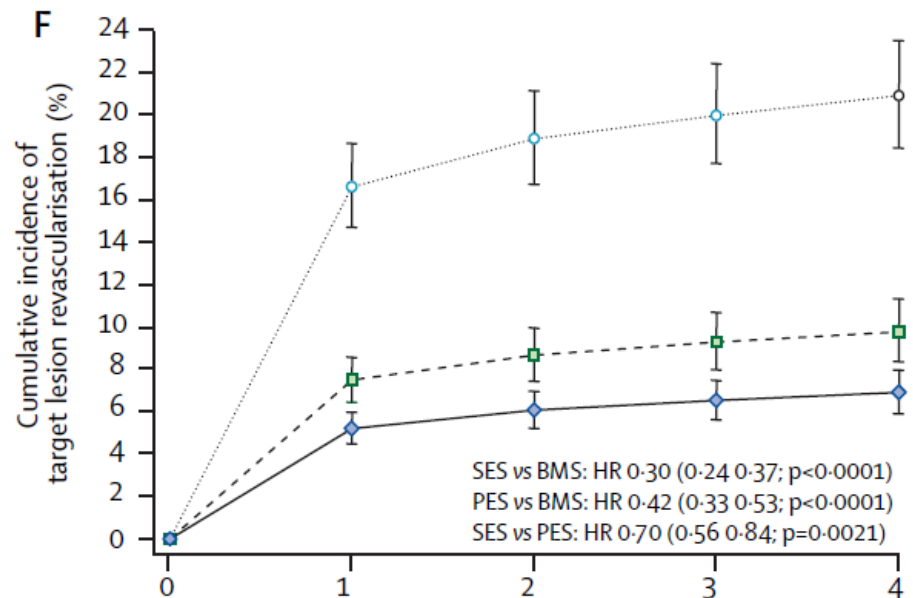
Stettler C et al. *Lancet* 2007;370:937-48

Mortality

Repeat Revasc



18,023 Patients



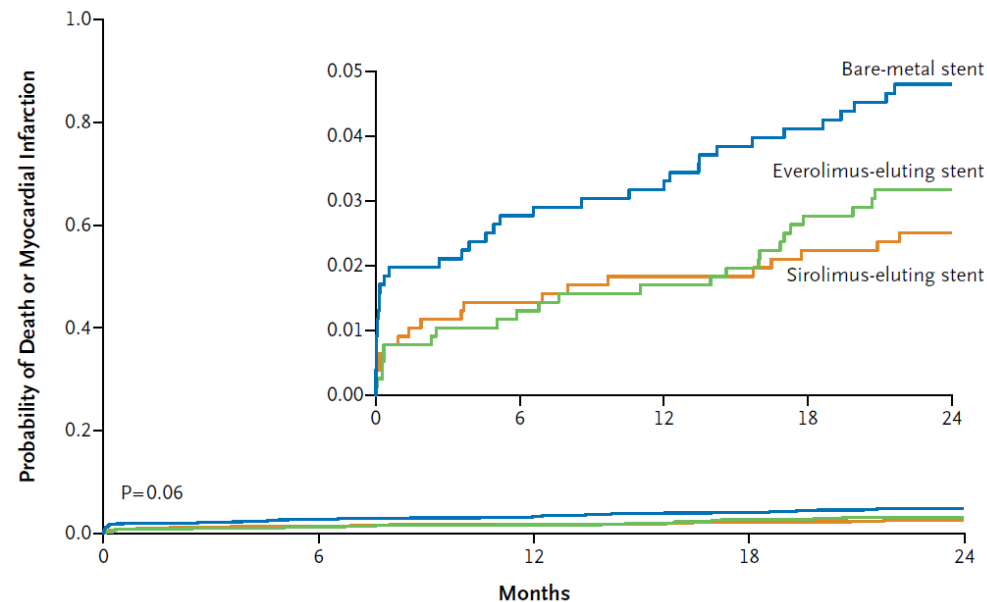
18,023 Patients

Drug-Eluting Stent Safety in Large Vessels

BASKET-PROVE: DES vs BMS

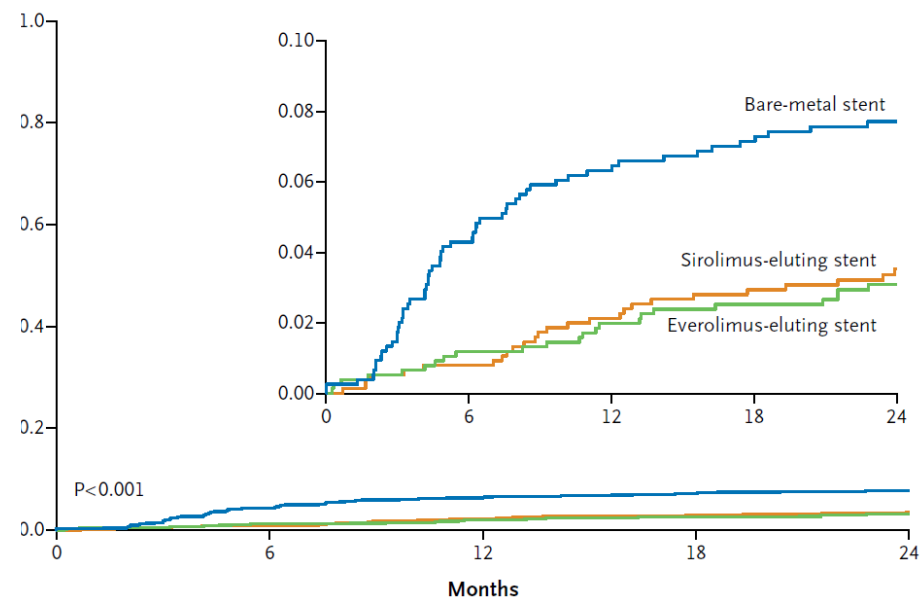
Kaiser C et al. *N Engl J Med* 2010

Death or MI



2,314 Patients

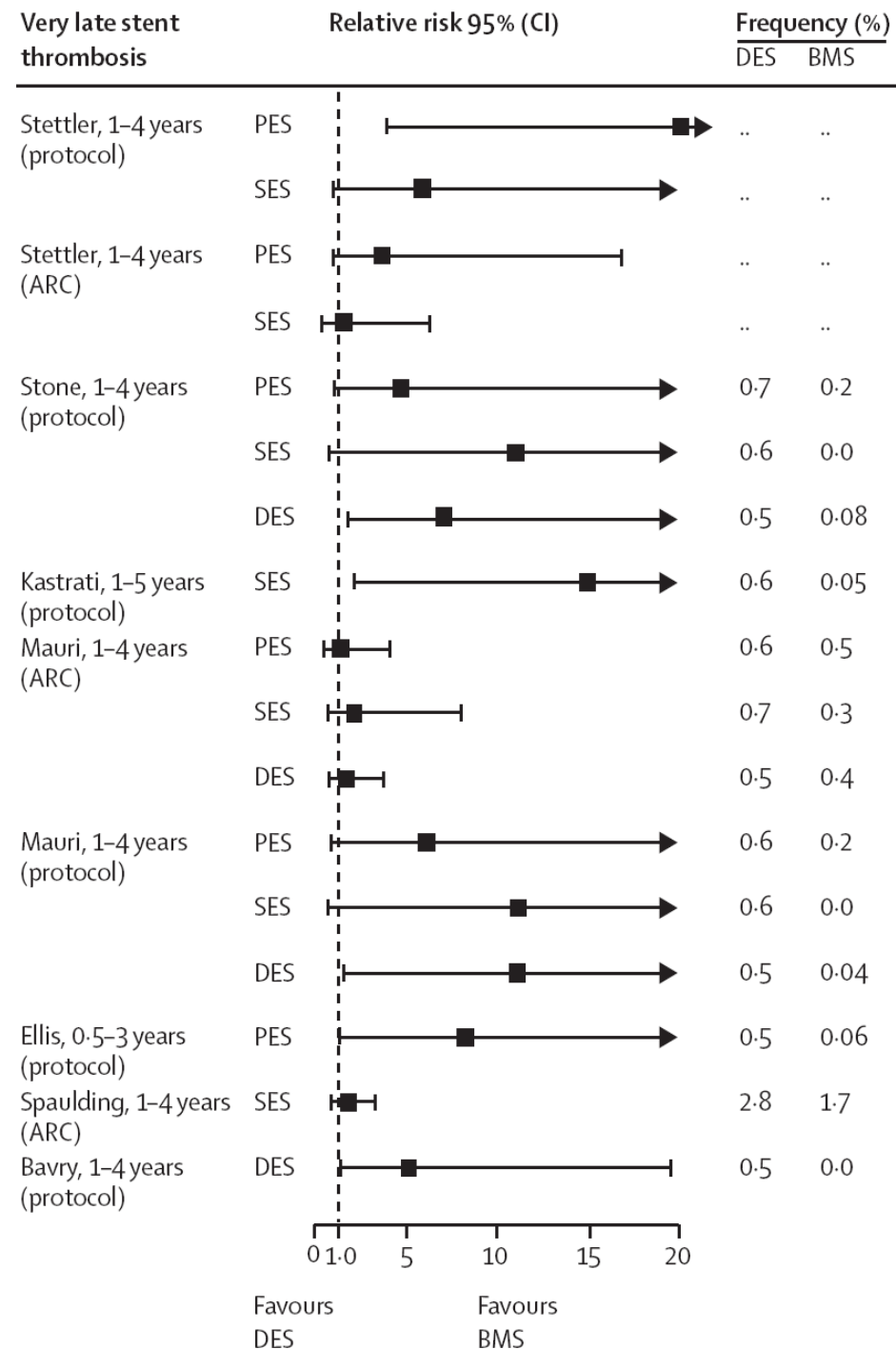
Repeat Revasc



2,314 Patients

Very Late Stent Thrombosis

Bavry A et al. Lancet 2008



Newer Generation Drug-Eluting Stents: What is the Promise?

Durable Polymer DES

Biodegradable Polymer DES

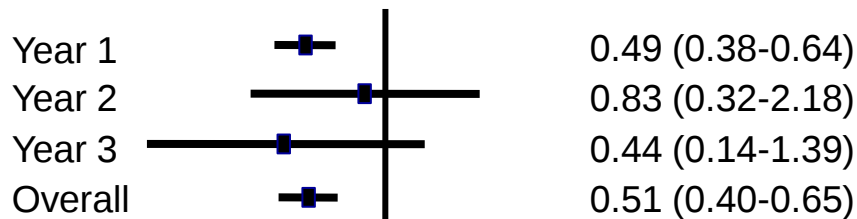
Polymer-free DES

Comparison of Everolimus-Eluting and Paclitaxel-Eluting Stents

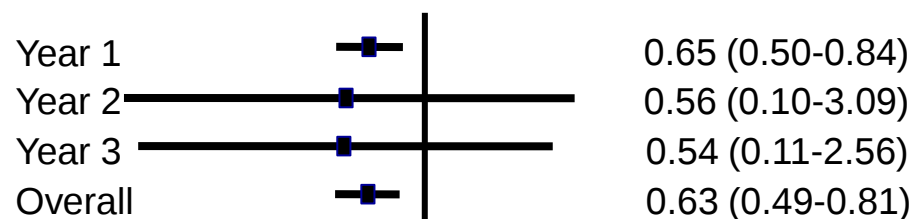
Meta-Analysis of SPIRIT II, III, IV and COMPARE

Clinical Outcomes Up to 3 Years

TLR



Cardiac Death or MI



Favors EES

Favors PES

Favors EES

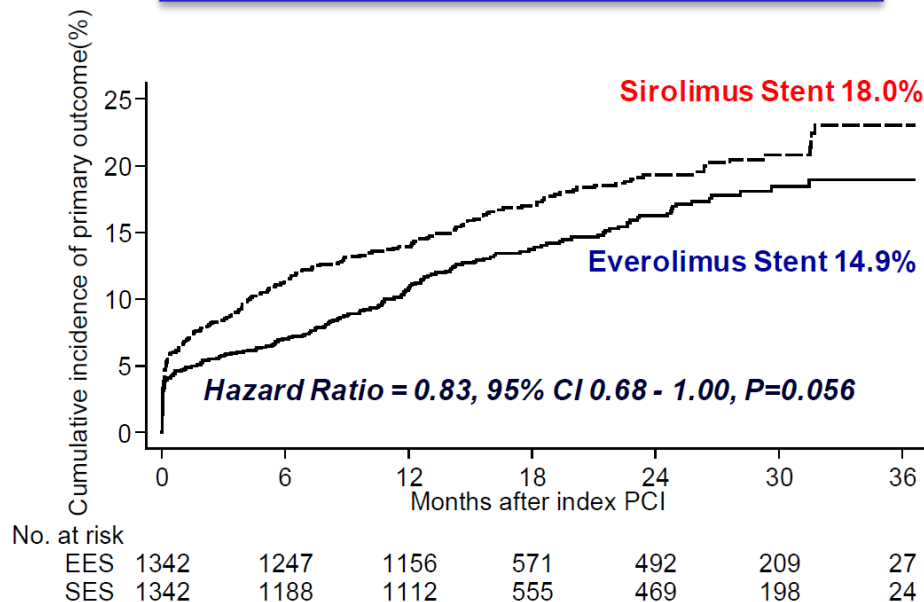
Favors PES

**6,789
Patients**

Long-term Propensity-Score Matched Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents (LESSON-I)

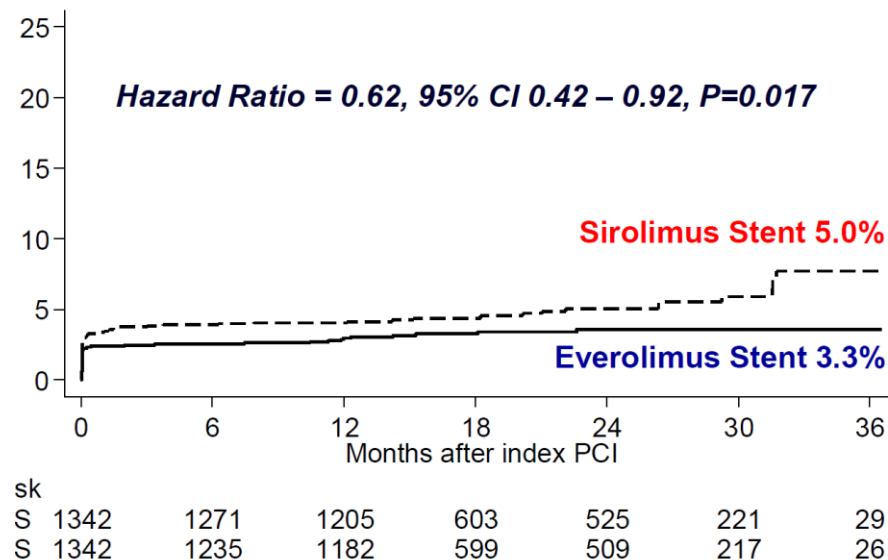
Räber L et al. *J Am Coll Cardiol* 2011, in press

Death, MI or TVR



1,342 Matched Pairs

Myocardial Infarction

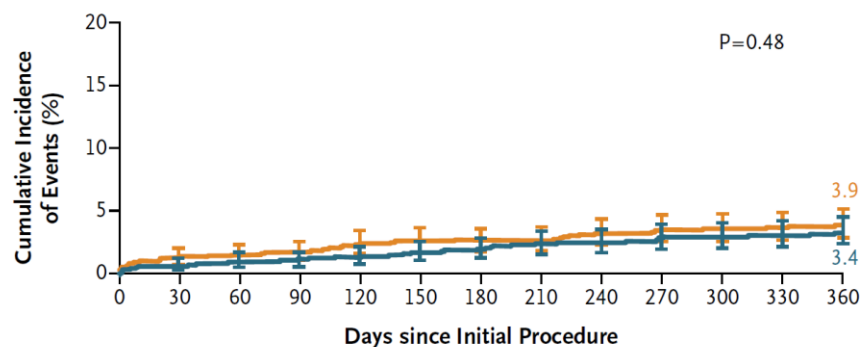


1,342 Matched Pairs

Everolimus-Eluting vs Zotarolimus-Eluting Endeavor Resolute Stent

Serruys PW et al. *N Engl J Med* 2010

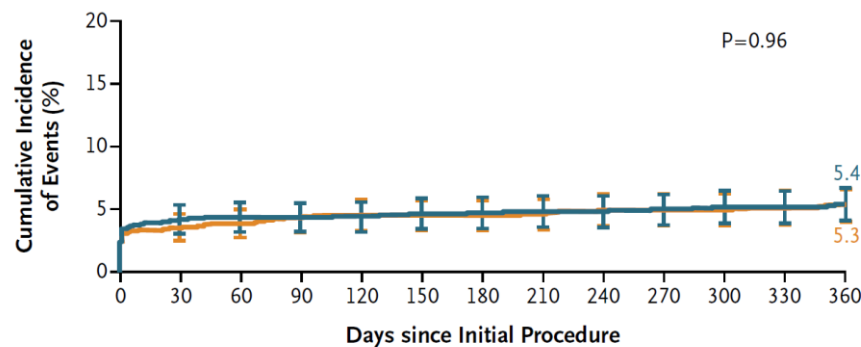
Target Lesion Revasc @ 1 Year



Zotarolimus													
No. of patients	1140	1135	1115	1108	1103	1093	1091	1089	1082	1073	1069	1068	1057
No. of events	4	11	3	2	8	2	1	0	6	3	1	1	2
Cumulative incidence (%)	0.4	1.3	1.6	1.8	2.5	2.7	2.7	2.7	3.3	3.6	3.6	3.7	3.9

Everolimus													
No. of patients	1152	1148	1126	1118	1116	1112	1105	1098	1085	1083	1075	1069	1056
No. of events	1	7	4	1	3	4	3	5	1	4	1	1	3
Cumulative incidence (%)	0.1	0.7	1.1	1.1	1.4	1.8	2.0	2.5	2.6	2.9	3.0	3.1	3.4

Cardiac Death or MI @ 1 Year



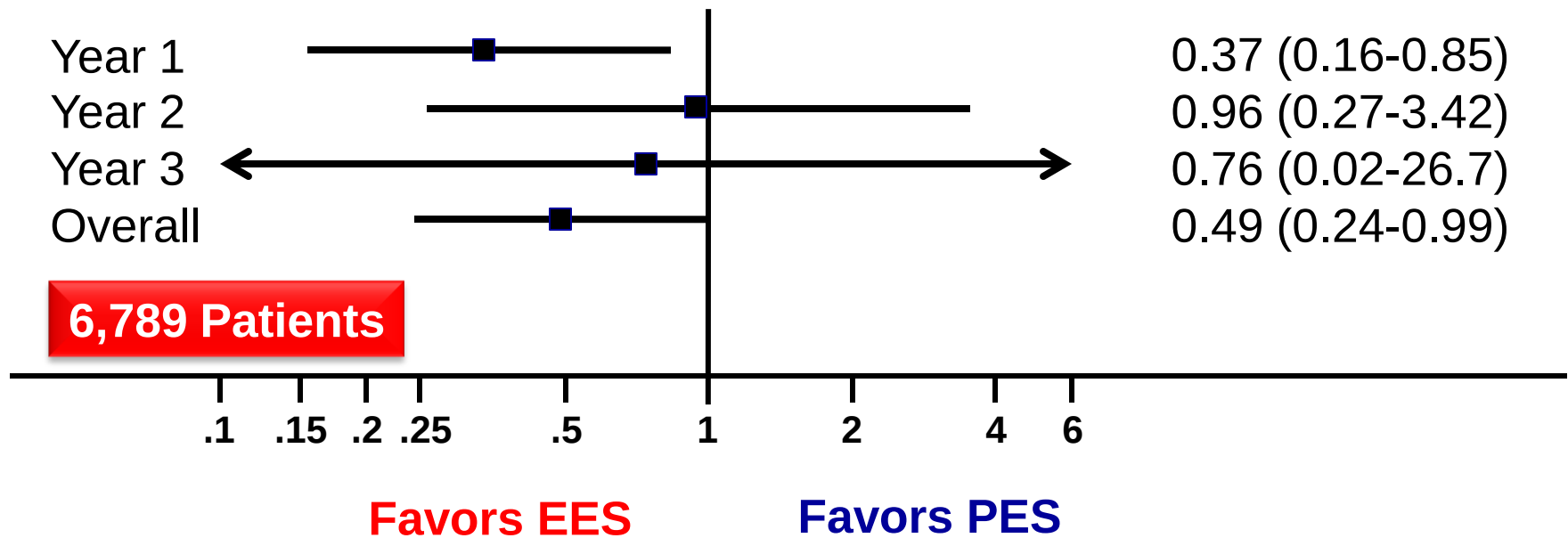
Zotarolimus													
No. of patients	1140	1113	1092	1086	1080	1078	1078	1077	1069	1065	1064	1064	1053
No. of events	26	14	4	5	2	0	0	1	4	0	0	2	2
Cumulative incidence (%)	2.3	3.5	3.9	4.3	4.5	4.5	4.5	4.6	4.9	4.9	4.9	5.1	5.3

Everolimus													
No. of patients	1152	1123	1094	1090	1089	1088	1085	1081	1072	1071	1067	1061	1049
No. of events	28	20	2	0	1	2	1	1	0	2	2	0	2
Cumulative incidence (%)	2.4	4.2	4.3	4.3	4.4	4.6	4.7	4.8	4.8	5.0	5.1	5.1	5.4

Comparison of Everolimus-Eluting and Paclitaxel-Eluting Stents

Meta-Analysis of SPIRIT II, III, IV and COMPARE

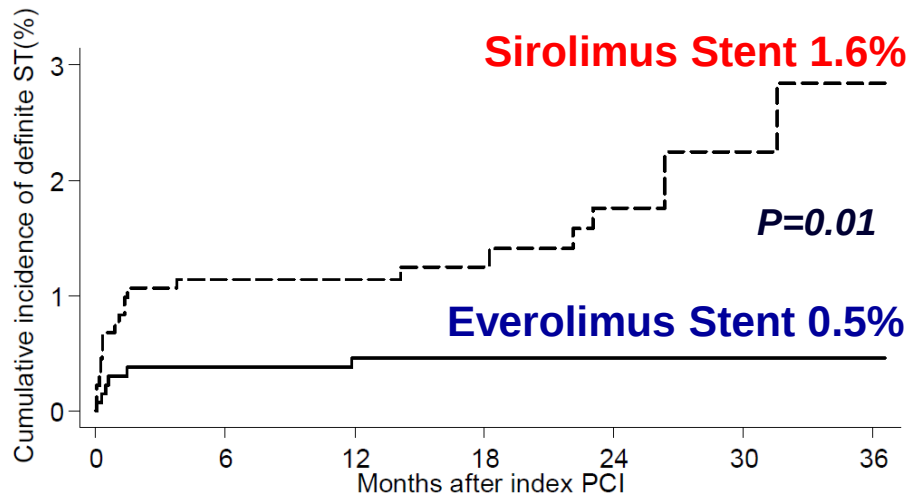
ARC Definite or Probable ST up to 3 Years



Long-term Propensity-Score Matched Comparison of Everolimus-Eluting and Sirolimus-Eluting Stents (LESSON-I)

Räber L et al. *J Am Coll Cardiol* 2011, in press

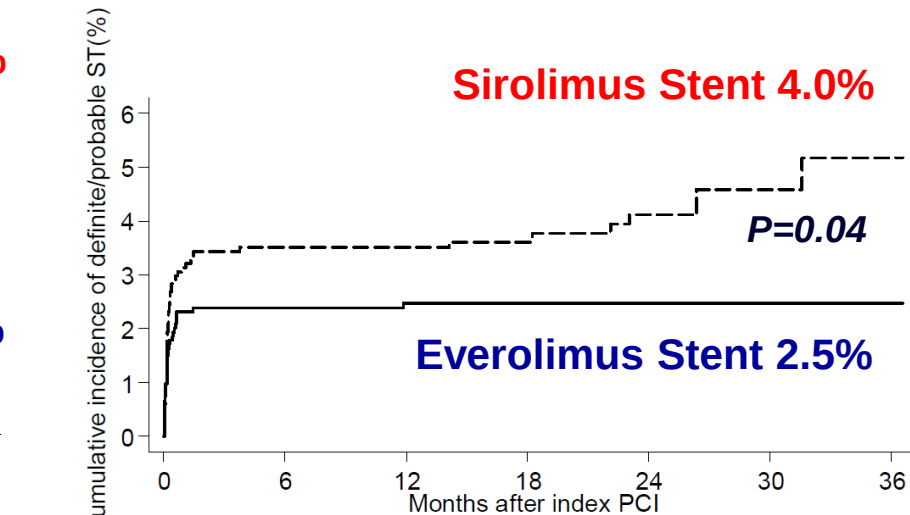
Definite ST



No. at risk							
EES	1342	1296	1234	620	543	226	29
SES	1342	1271	1216	619	527	223	28

1,342 Matched Pairs

Definite or Probable ST



No. at risk							
EES	1342	1296	1234	620	543	226	29
SES	1342	1271	1216	619	527	223	28

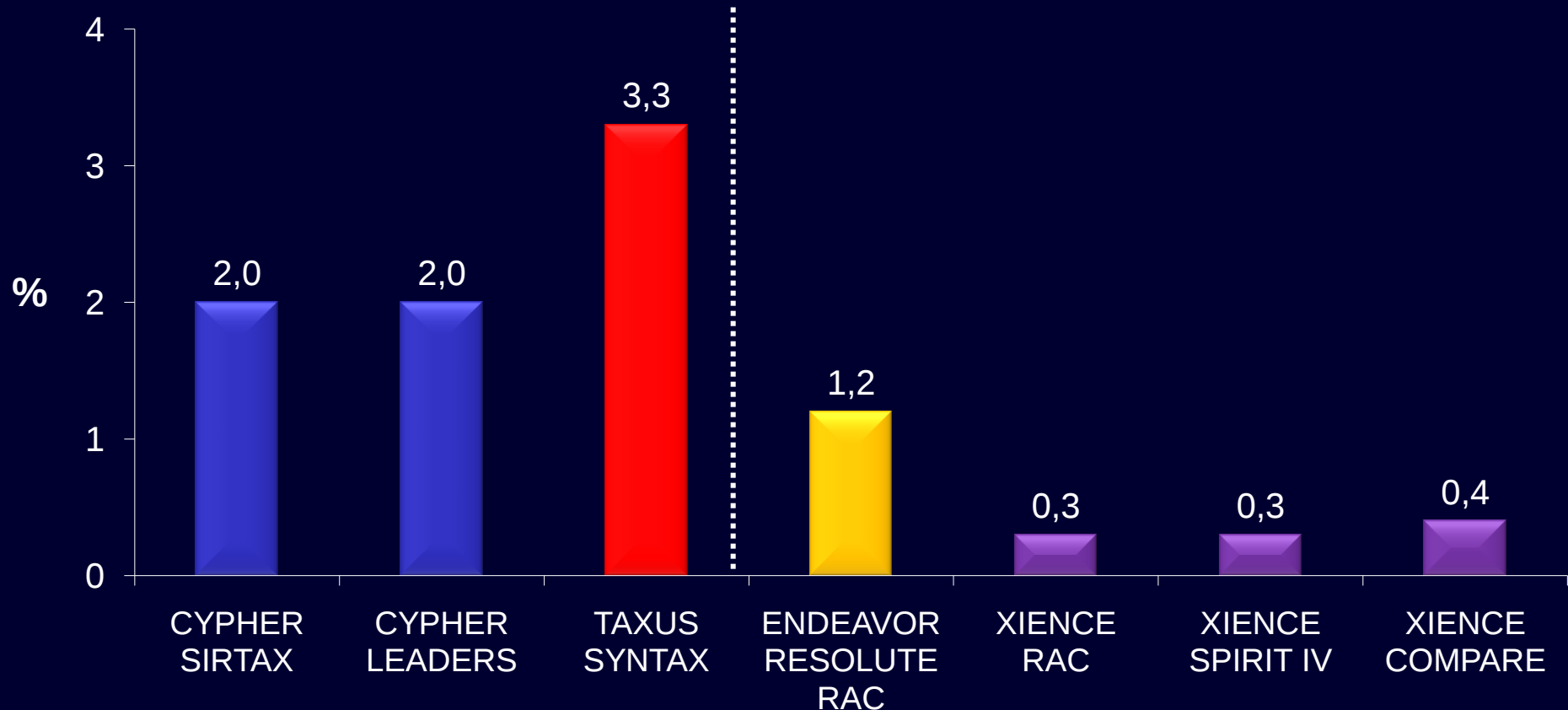
1,342 Matched Pairs

Stent Thrombosis in Perspective

Definite Stent Thrombosis in All Corner Trials @ 12 Months

Early Generation DES

Newer Generation DES

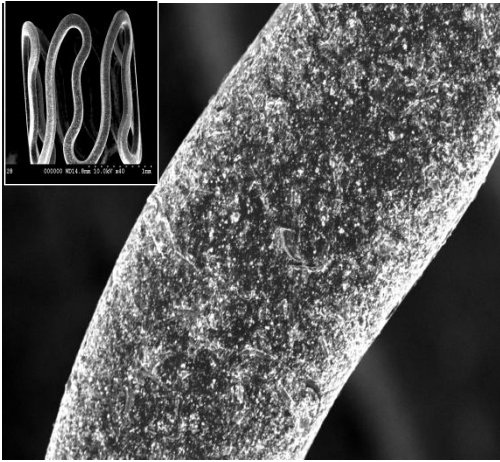


Durable Polymer Newer Generation DES

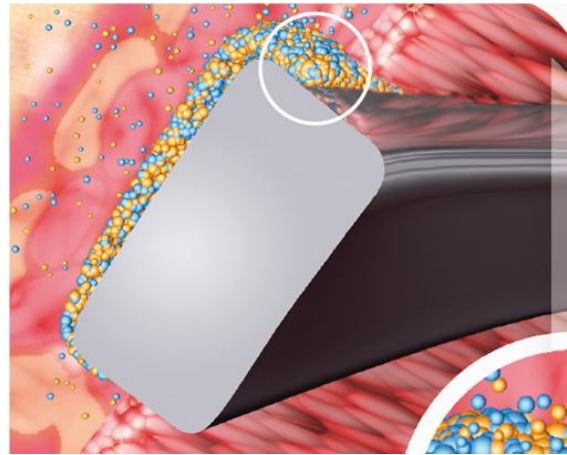
- Newer generation durable polymer DES are associated with a lower rate of MI compared with early generation DES
- The risk of very late ST appears lower with newer generation durable polymer DES but requires confirmation in larger and more complex patient cohorts
- Newer generation DES combine improved efficacy with improved safety profile and constitute a new standard of care in patients undergoing PCI
- Limus analogues are the drug of choice for current DES applications

Biodegradable Polymer Based DES Platforms

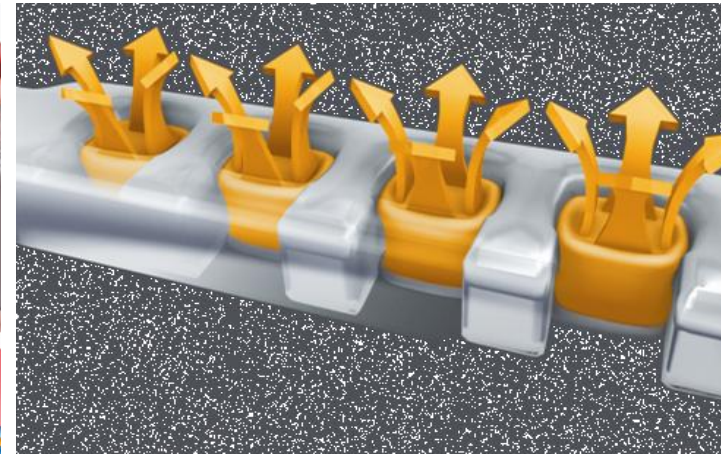
Sirolimus – ISAR TEST



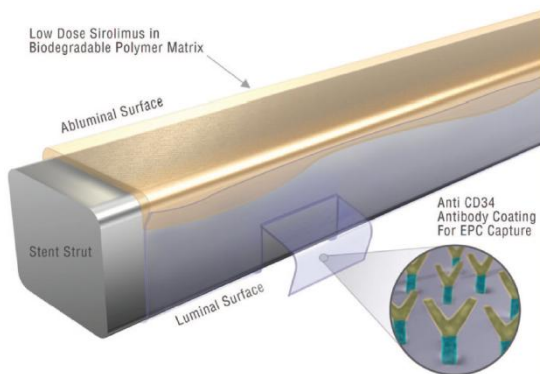
Biolimus A9 – BioMatrix Nobori, Axxess, XTENT



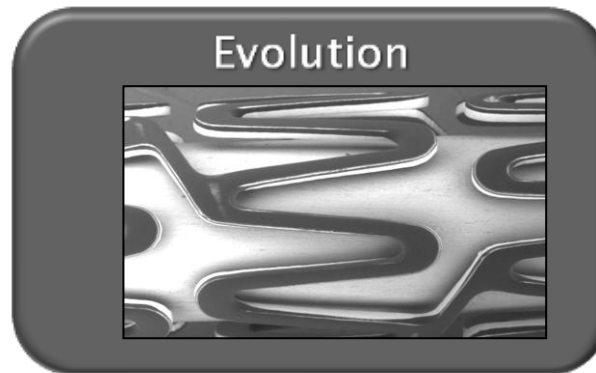
Sirolimus – NEVO



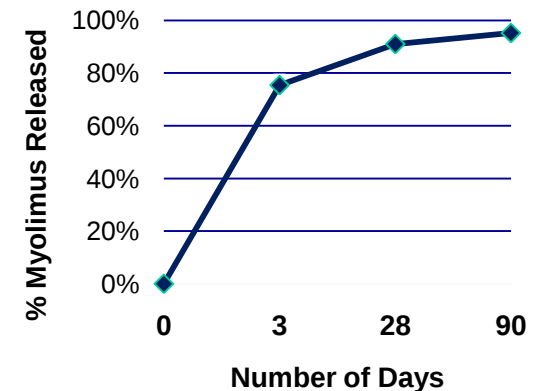
Sirolimus – Genous Bioengineered R Stent



Everolimus - BSC



Myolimus – ELIXIR



ISAR TEST 4 – Randomized Trial of 3 Limus-Eluting Stent Platforms With Different Polymer Coatings

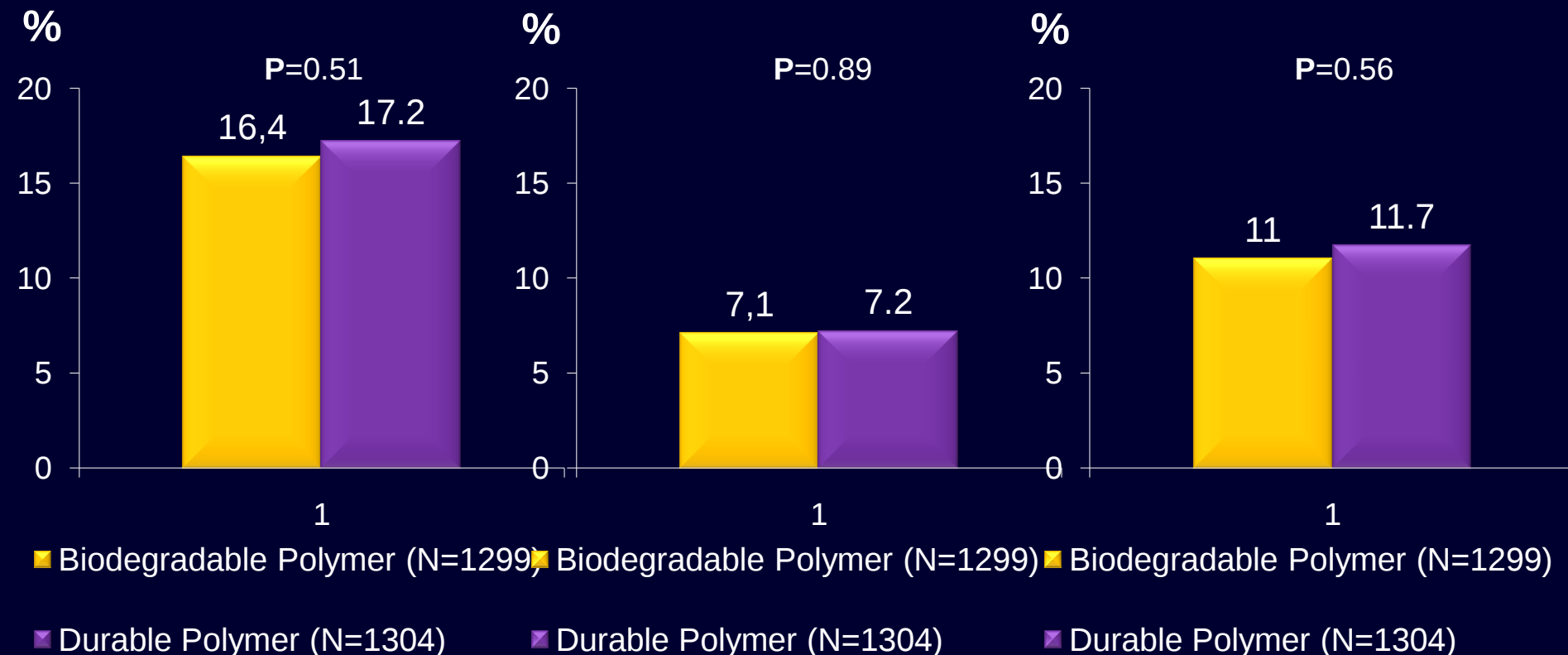
Byrne RA al. *Eur Heart J* 2009

Clinical Outcomes Through 2 Years (Byrne RA et al. CTU @ ESC 2010)

**Cardiac Death,
MI or TLR**

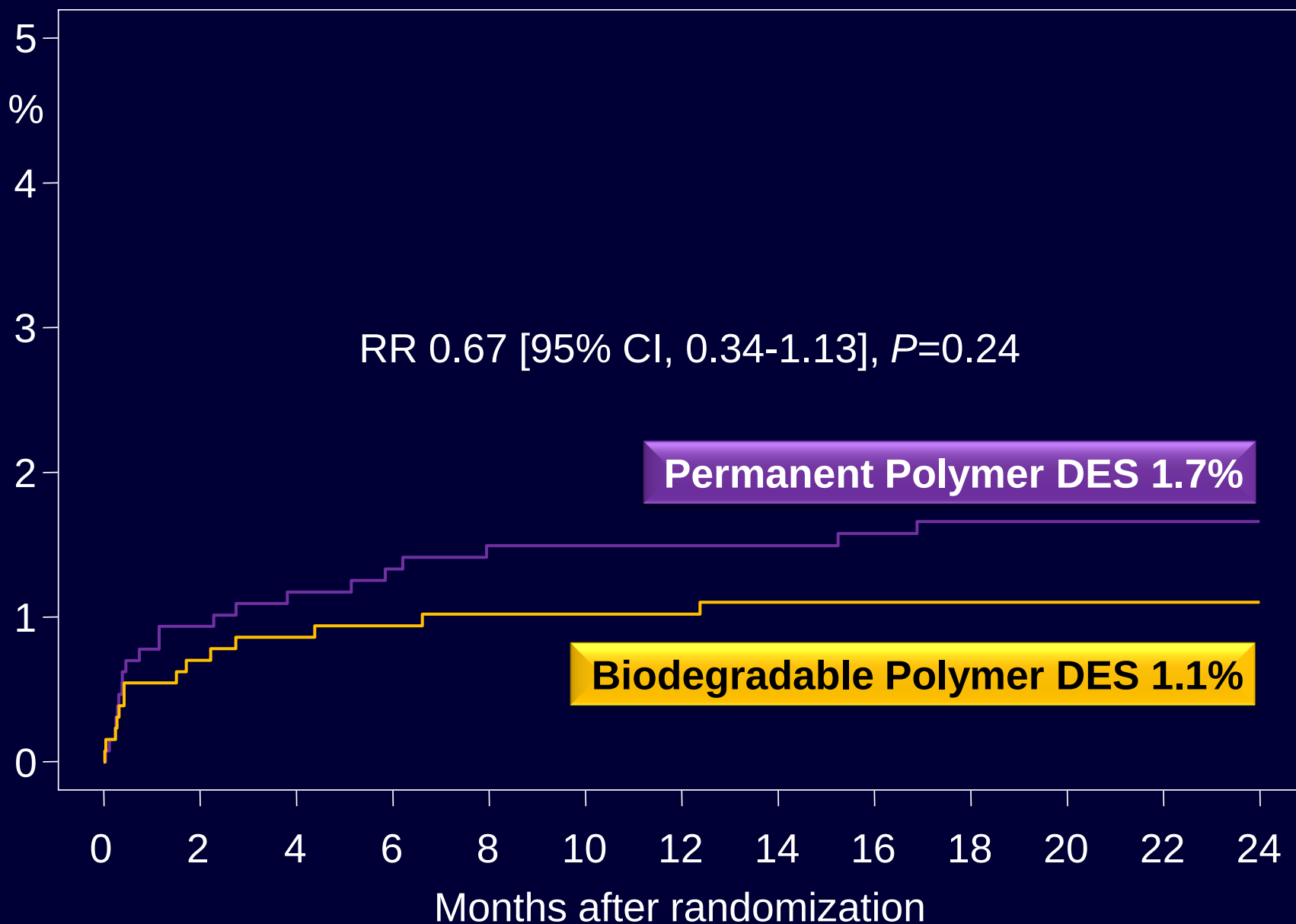
**Cardiac Death
or MI**

TLR



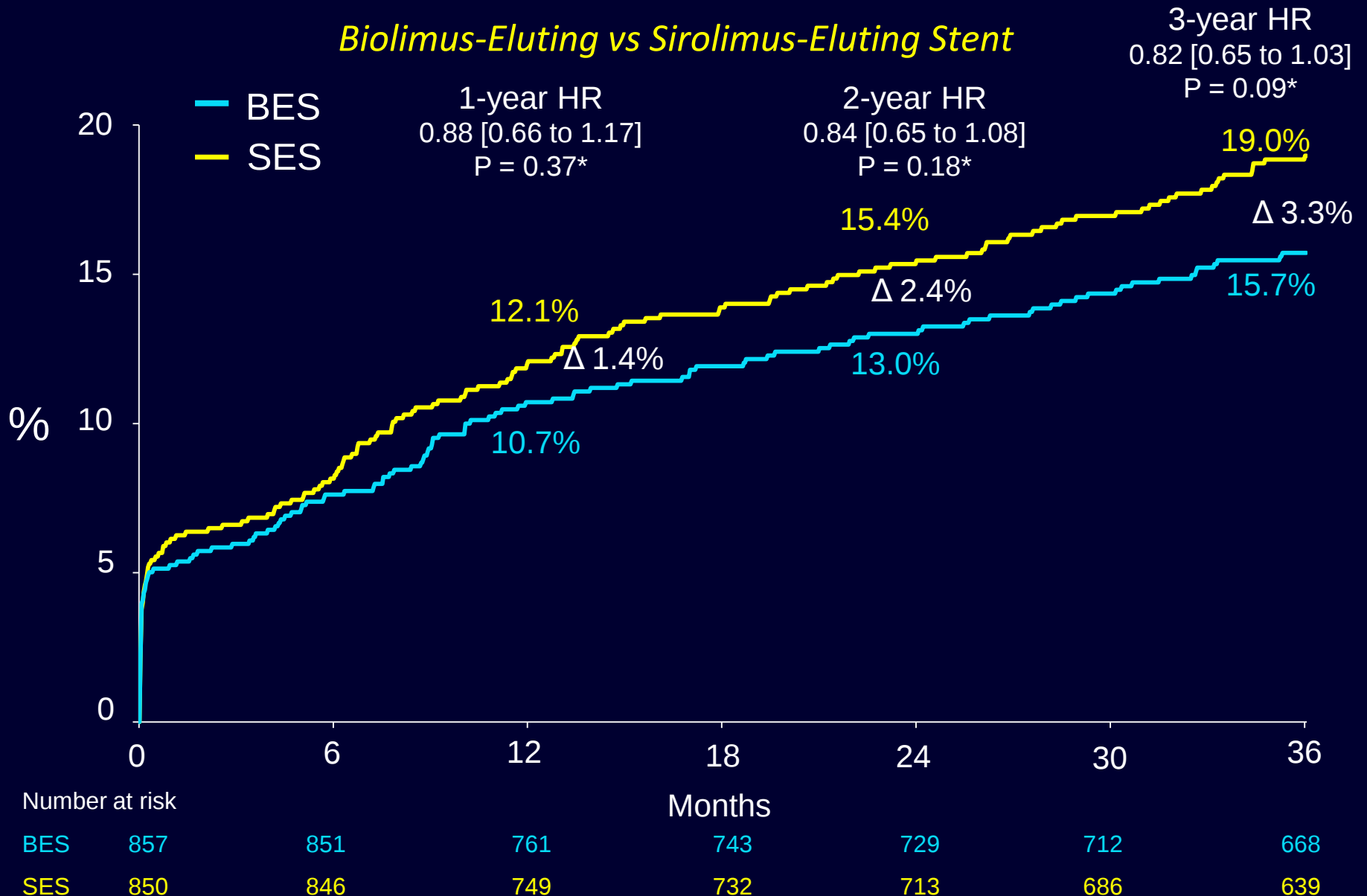
Definite/Probable Stent Thrombosis

Byrne RA et al. CTU @ ESC 2010



LEADERS – MACE

Biolimus-Eluting vs Sirolimus-Eluting Stent



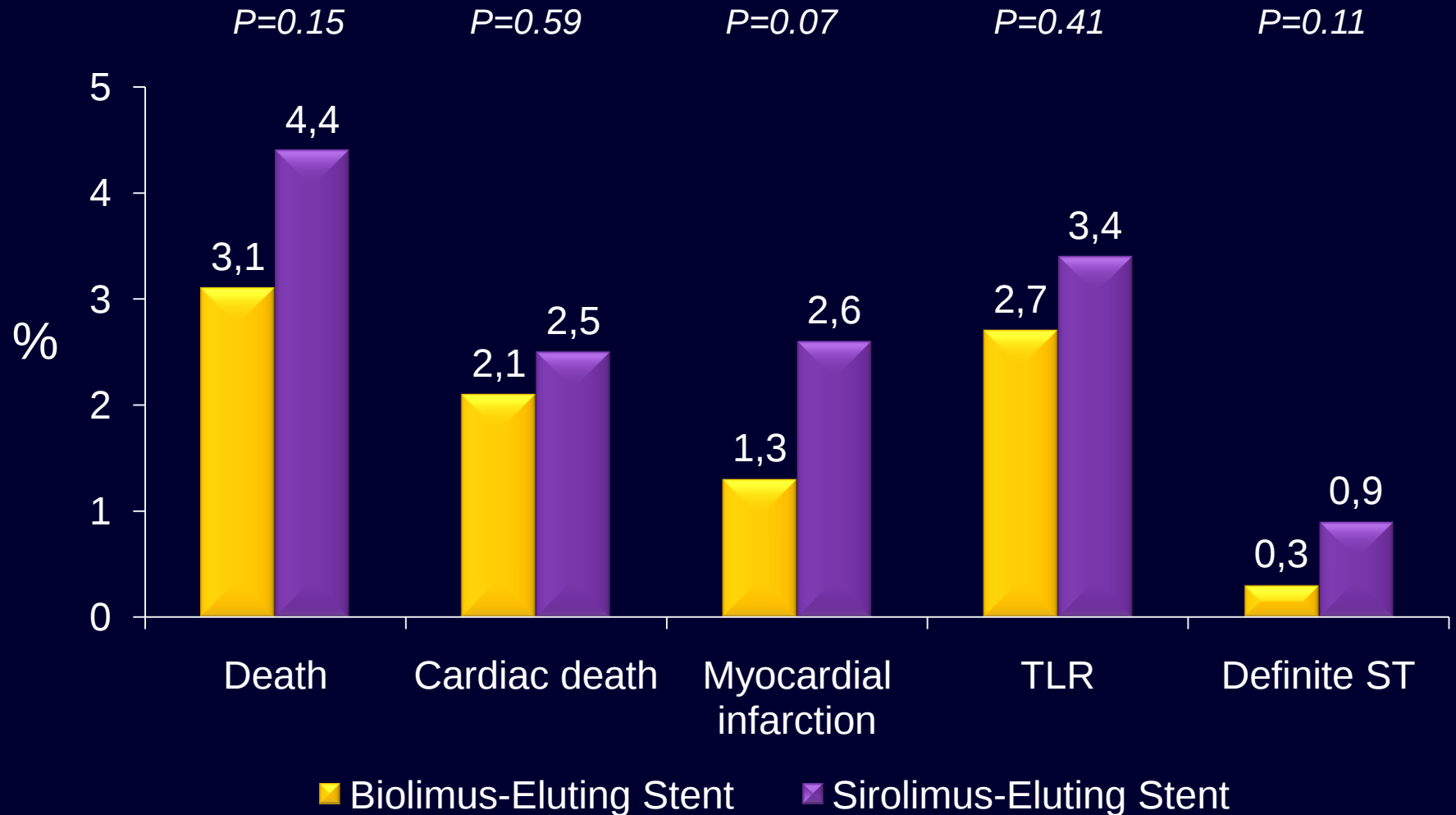
MACE = Cardiac Death, MI, or Clinically-Indicated TVR

* P values for superiority

Serruys P. TCT 2010

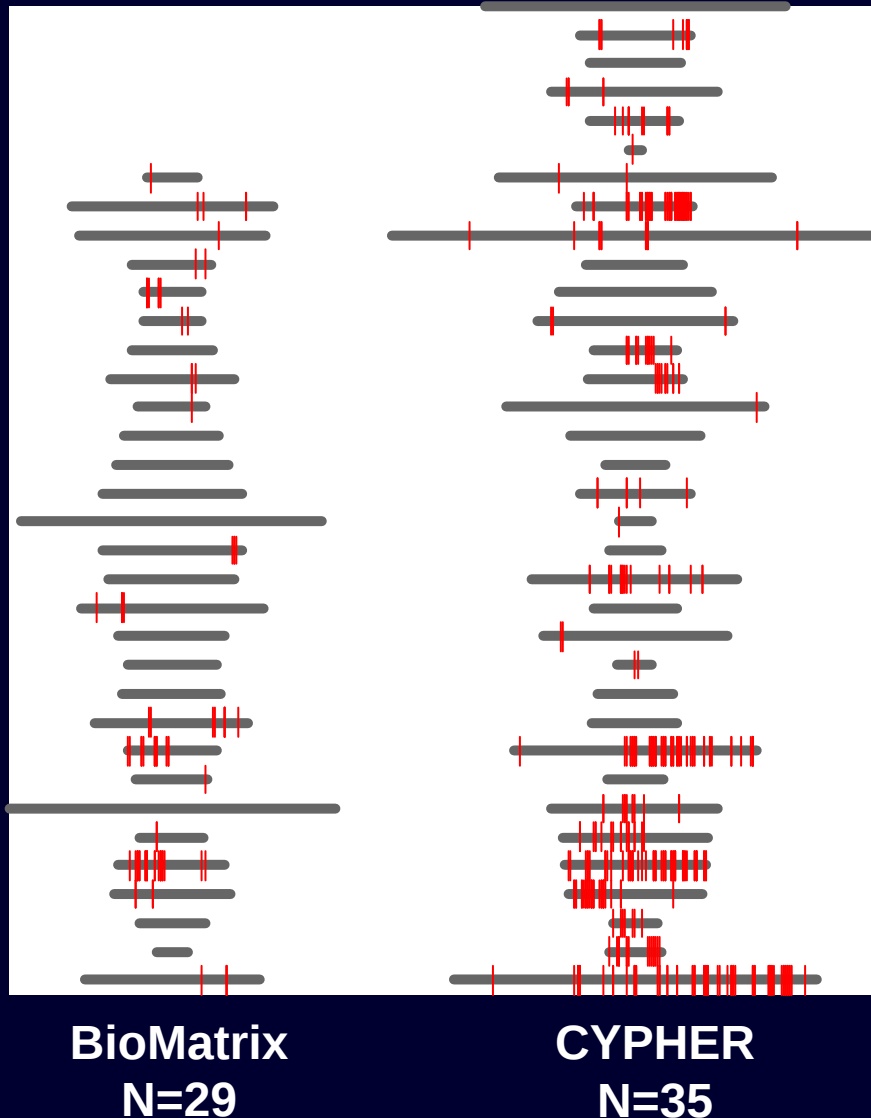
LEADERS – Landmark Analysis from 1 to 3 Years

Biolimus-Eluting vs Sirolimus-Eluting Stent

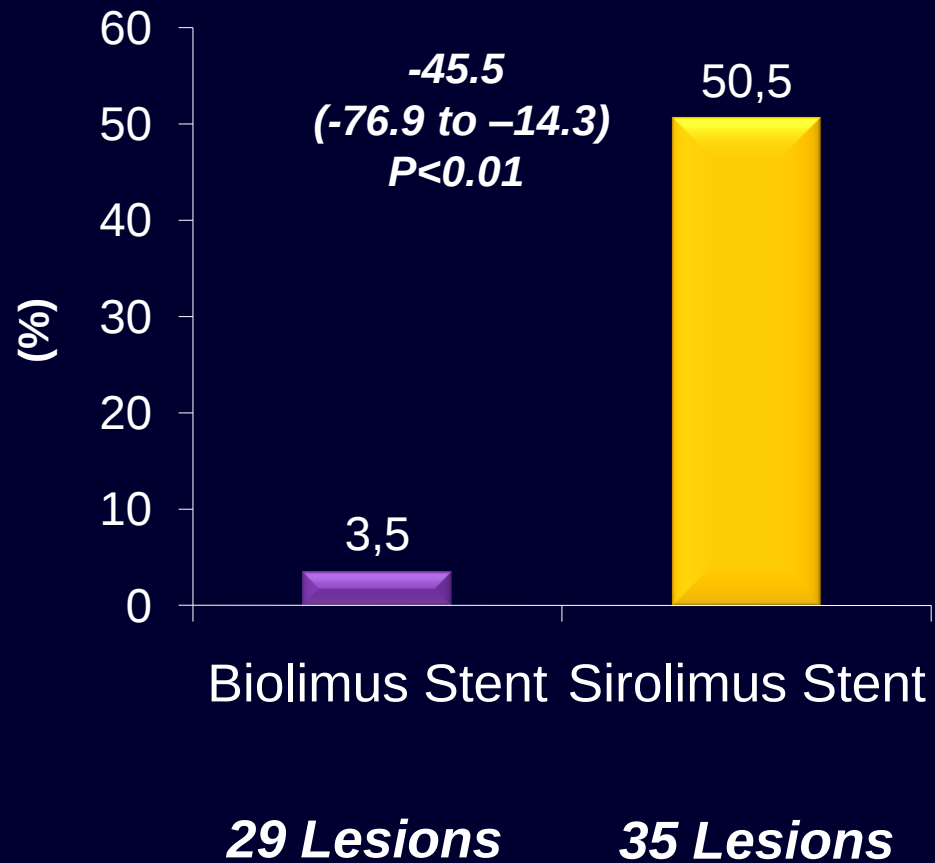


LEADERS - OCT Substudy

Barlis P et al. *Eur Heart J* 2010

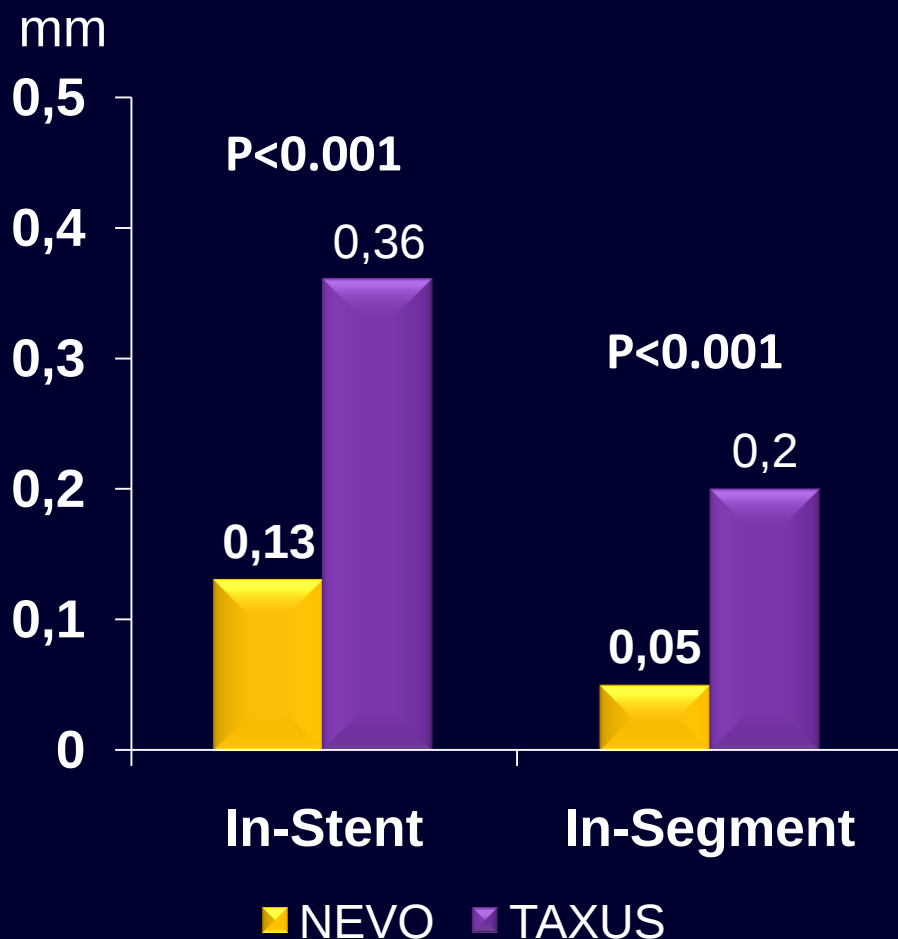


Lesions With At Least 5% Uncovered Struts

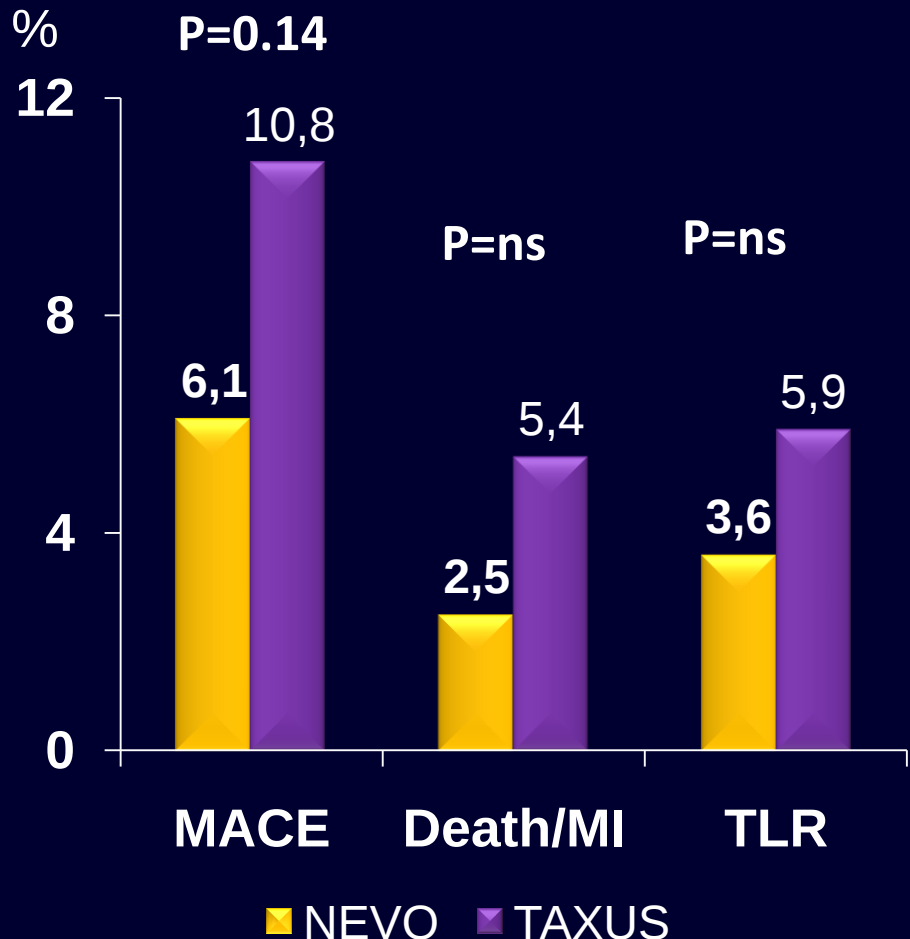


NEVO RES-I: Sirolimus Release From Biodegradable Polymer Reservoirs

Angiographic Outcome



Clinical Outcome



NEVO II Study Overview

All-Comers

~2500 patients @ 32 sites

2:1 randomization

NEVO™

Sirolimus-eluting Stent
(n~1667)

Off-label
~ 1000 pts

Near on-label
~ 667 pts (40%)

Xience V

Everolimus-eluting Stent
(n~833)

Off-label
~ 500 pts

Near on-label
~ 333 pts (40%)

**Primary Endpoint: 12M Composite Clinical Endpoint of Cardiac Death,
TV-related MI and Clinically Driven TLR**

**Sub-study: NEVO near on-label: 150 Angio/75 IVUS
Xience V near on-label: 75 Angio/38
IVUS**

Clinical/ MACE

30day

6M

1Yr

13M

18M

3Yr

5Yr

Angiographic sub

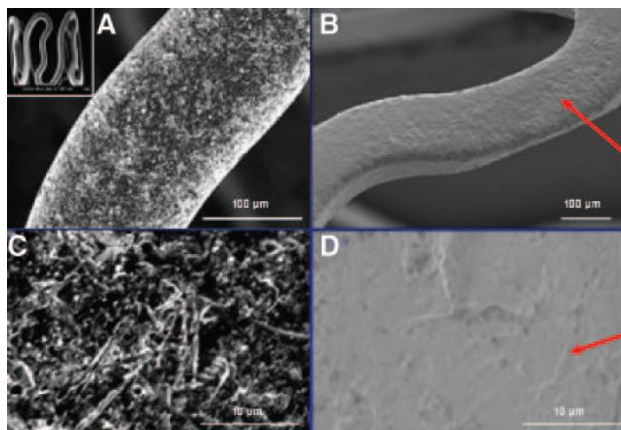
Biodegradable Polymer DES

- Safety and efficacy of biodegradable polymer based limus releasing DES is at least as good as first generation durable polymer based DES
- A large scale randomized trial is required to address whether biodegradable polymer based DES are superior to permanent polymer based DES in terms of safety and very late ST
- The majority of novel and upcoming newer generation DES are based on biodegradable polymer platforms owing to the appealing concept of leaving no polymer behind

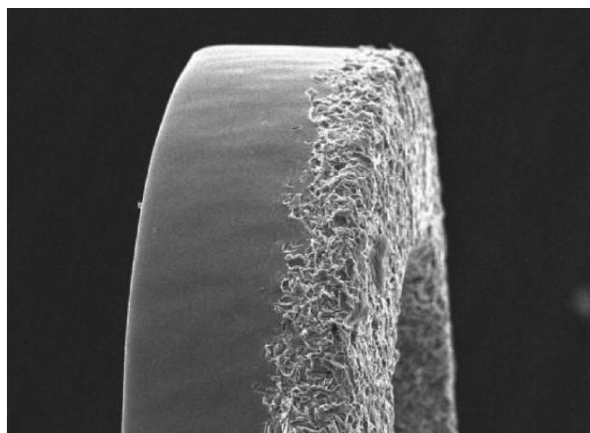
Polymer-Free DES Platforms

Abizaid A al. *Circ Cardiovasc Interv* 2010

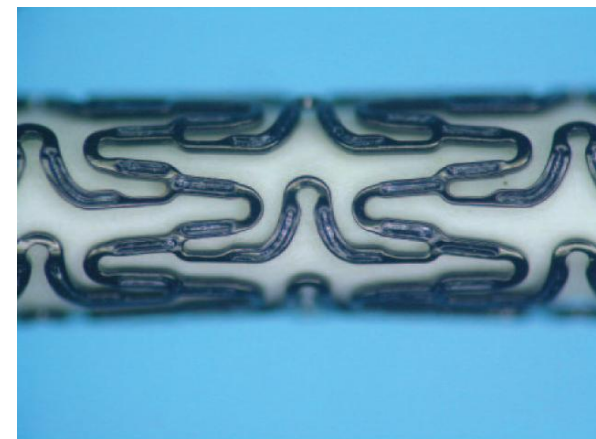
YUKON
Various Drugs



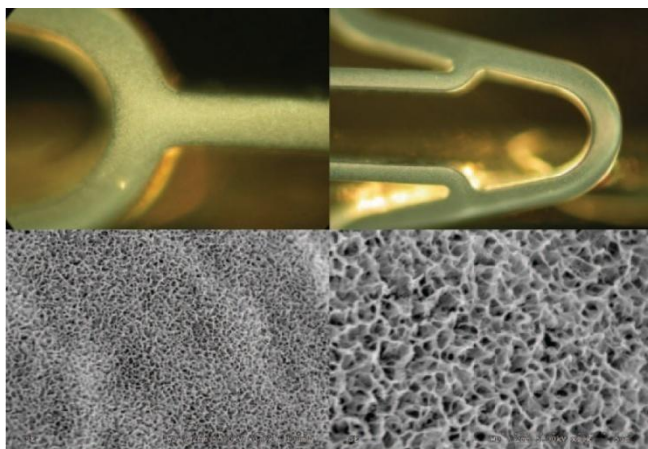
BioFreedom
Biolimus A9



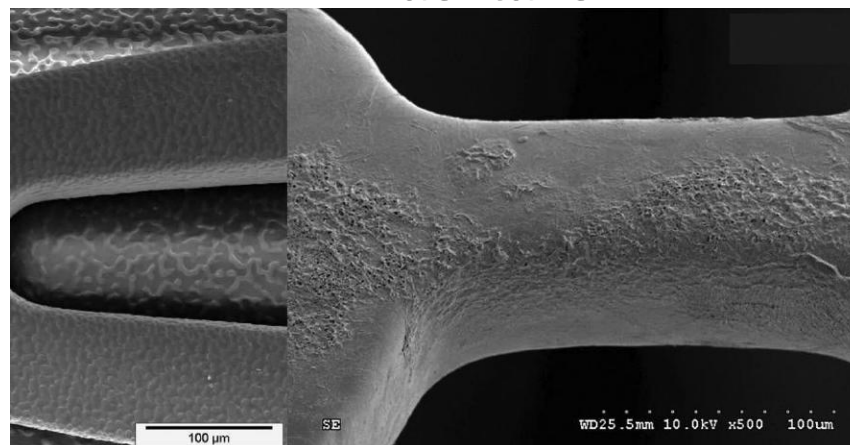
Optima
Tacrolimus



VESTAsync
Sirolimus



Amazon Pax
Paclitaxel



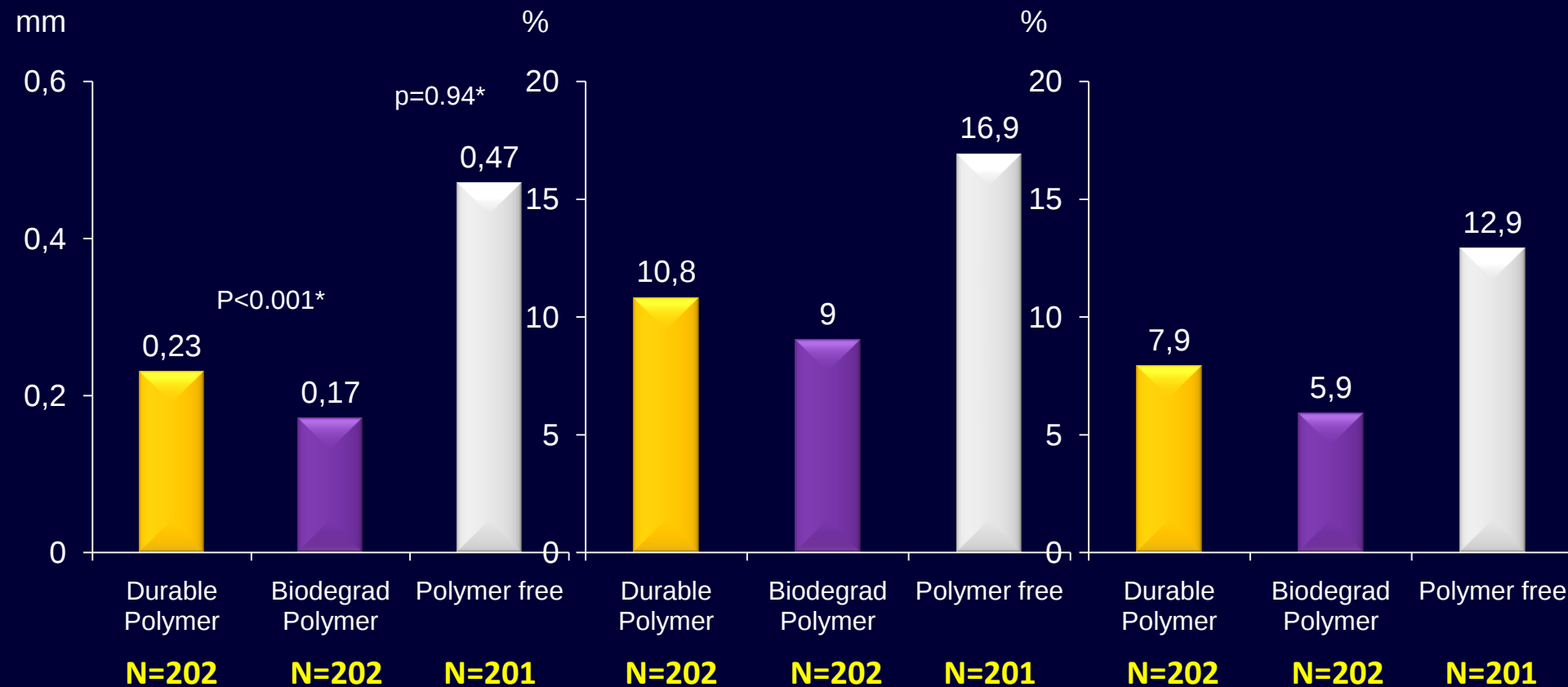
Sirolimus Release From Durable Polymer, Biodegradable Polymer and Polymer-Free Surfaces

Mehilli J et al. *Eur Heart J* 2008 (ISAR TEST 3)

In-Stent Late Loss

Binary Restenosis

Clinical TLR

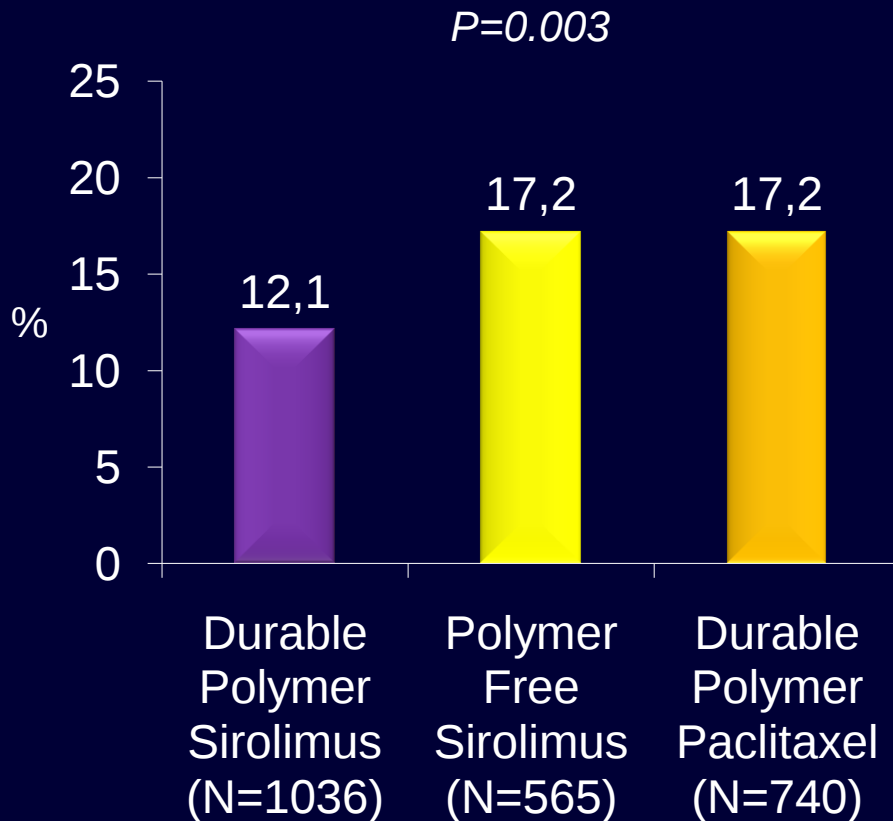


* P_{non-inferiority} vs durable polymer

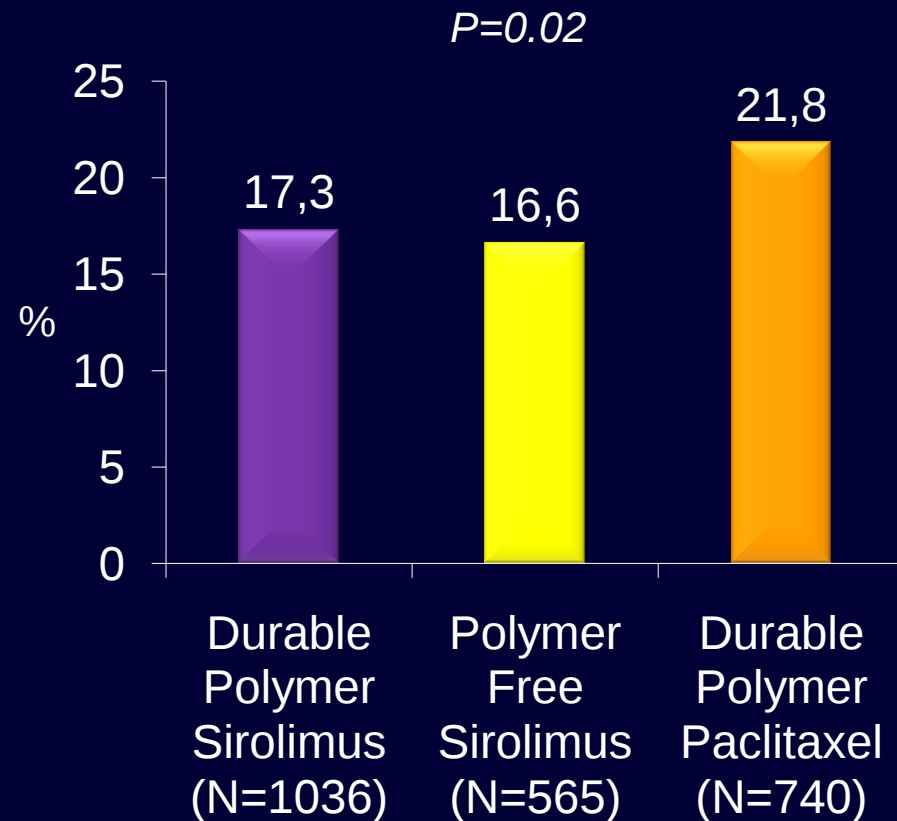
Durability of Antirestenotic Efficacy of DES

Byrne RA et al. *JACC Cardiovasc Interv* 2009;2:291-9

Restenosis @ 6-8 Months



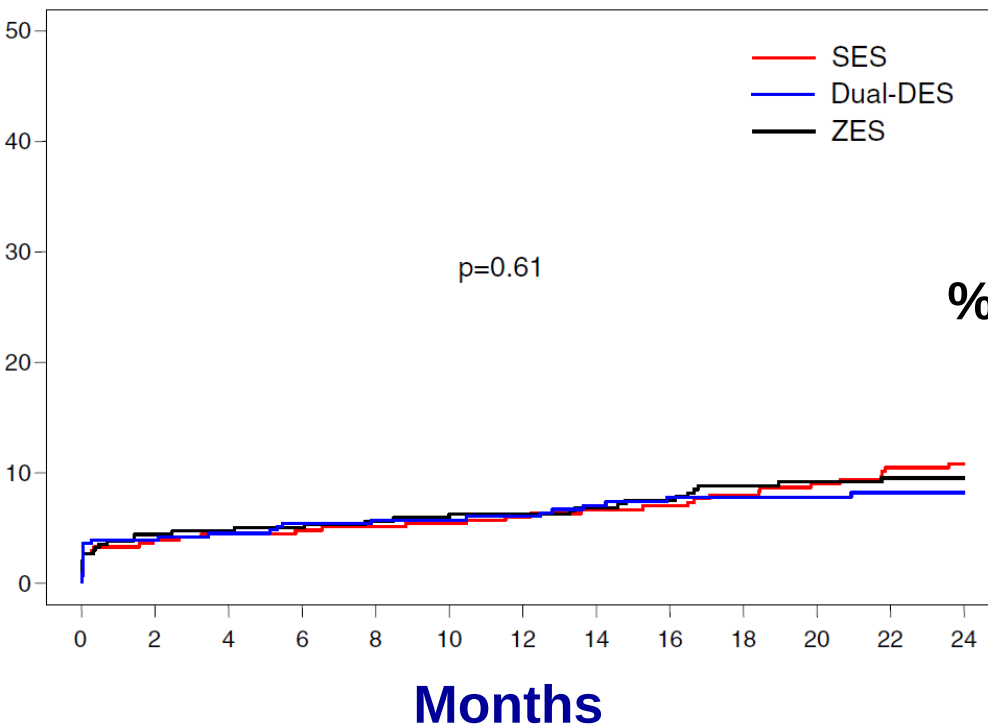
Restenosis @ 2 Years



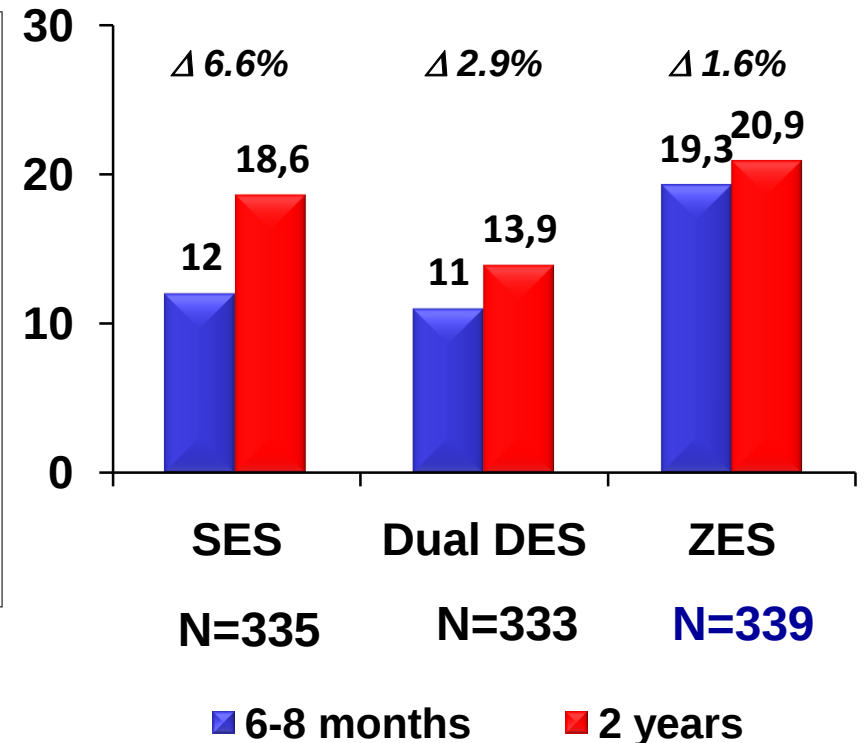
Two Year Angiographic and Clinical Outcome of Polymer-Free Dual Release DES Versus Durable Polymer Based Sirolimus and Zotarolimus Stents

Byrne R et al. *J Am Coll Cardiol* 2010 (ISAR TEST 2 Investigators)

Death or MI



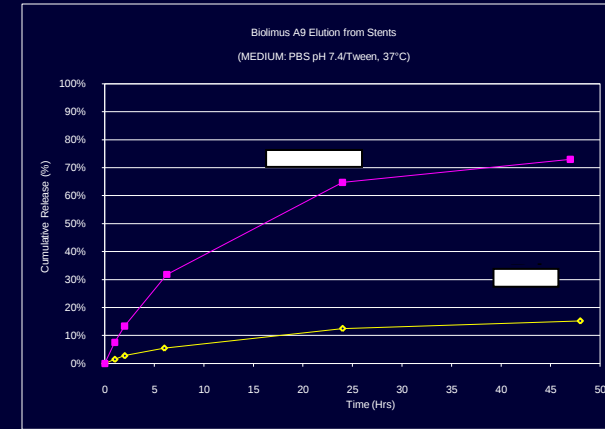
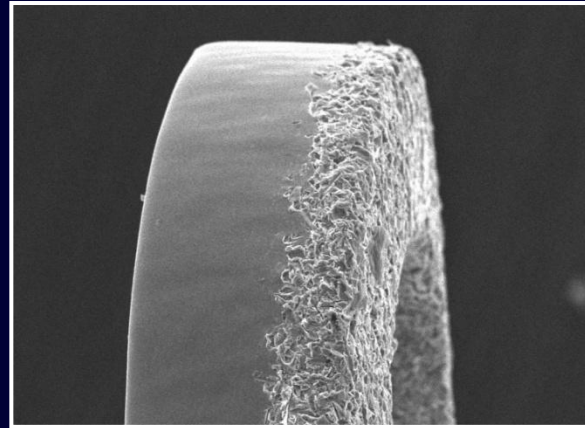
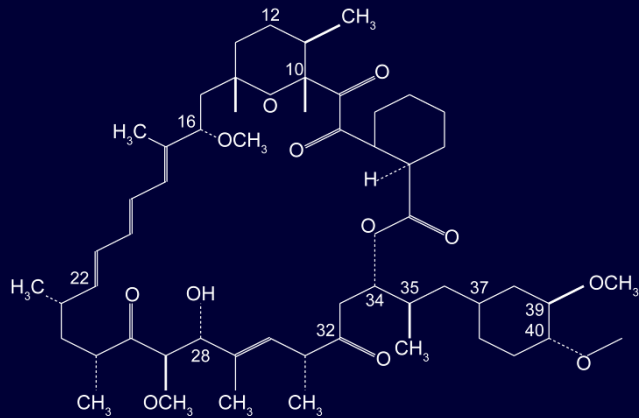
Angiographic Restenosis



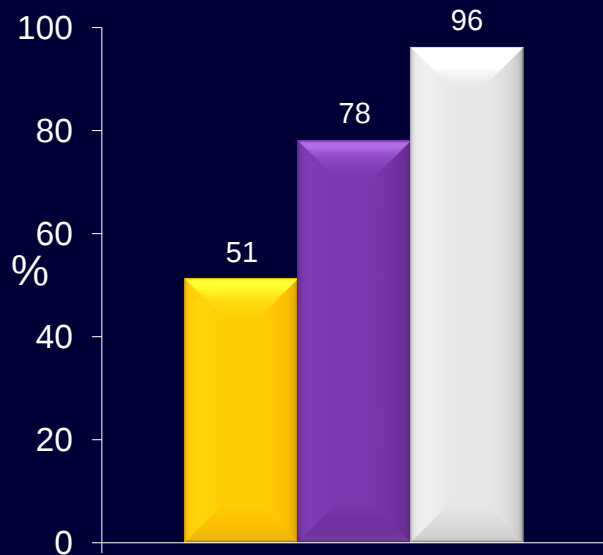
Polymer-Free Biolimus-A9 Coated Stent

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

Biolimus A9

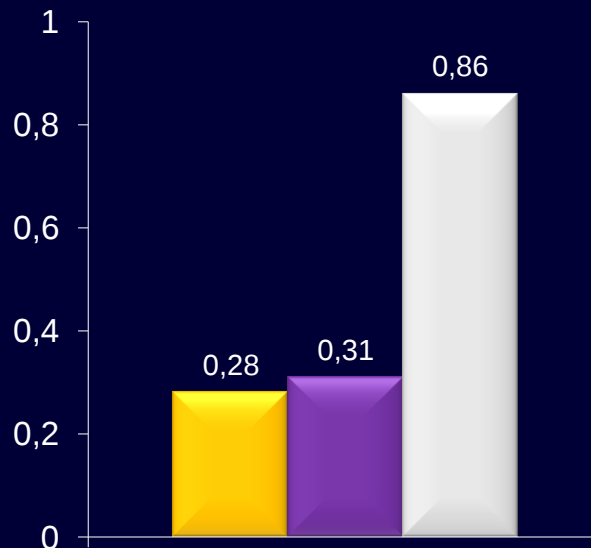


Struts With Fibrin



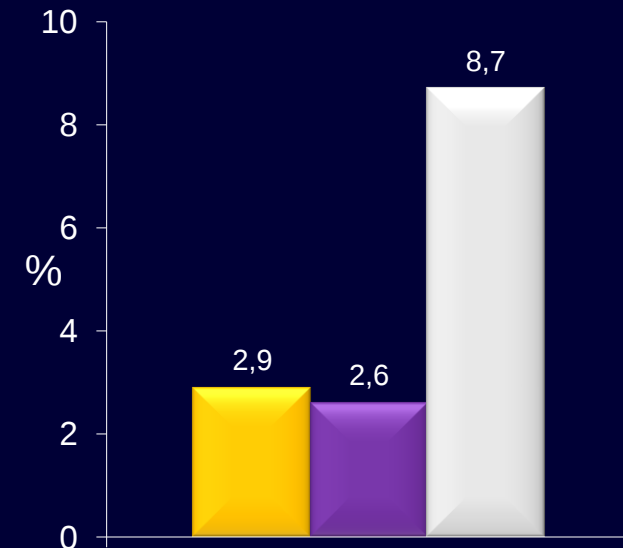
■ BMS ■ BioFreedom ■ SES

Inflammation Score



■ BMS ■ BioFreedom ■ SES

Struts With Giant Cells

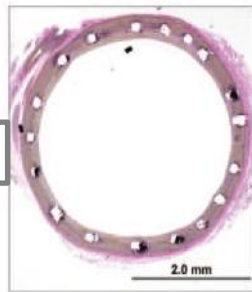


■ BMS ■ BioFreedom ■ SES

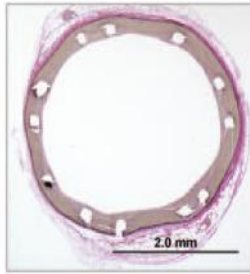
Pre-Clinical Study - Efficacy BES vs. SES & BMS

Tada et al.,
Circ Cardiovasc Interv
2010;3;174-183

28 Days



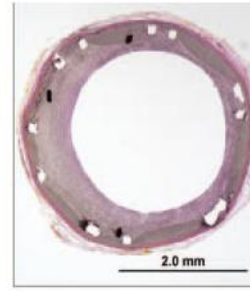
SD



LD

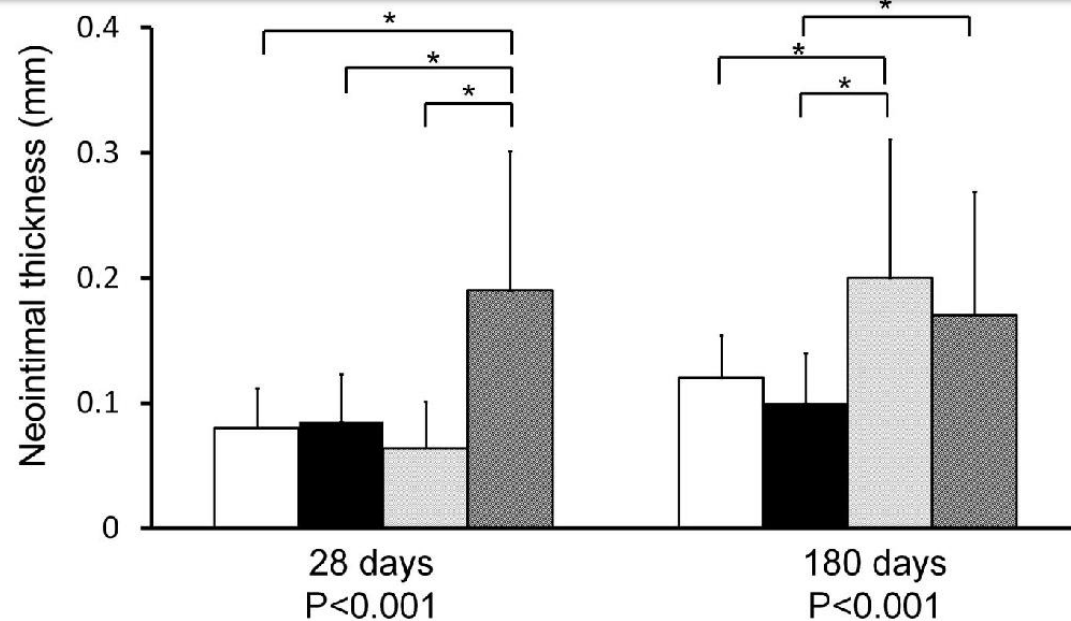
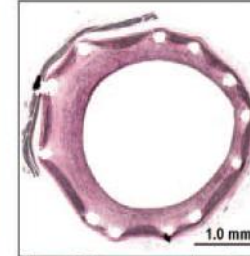
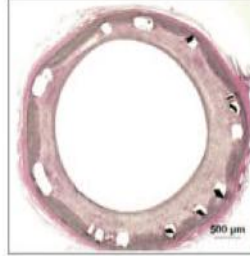
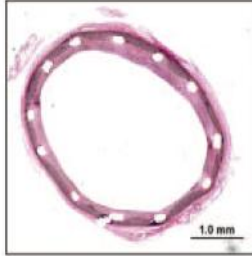
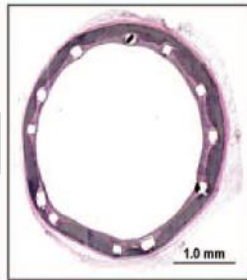


SES



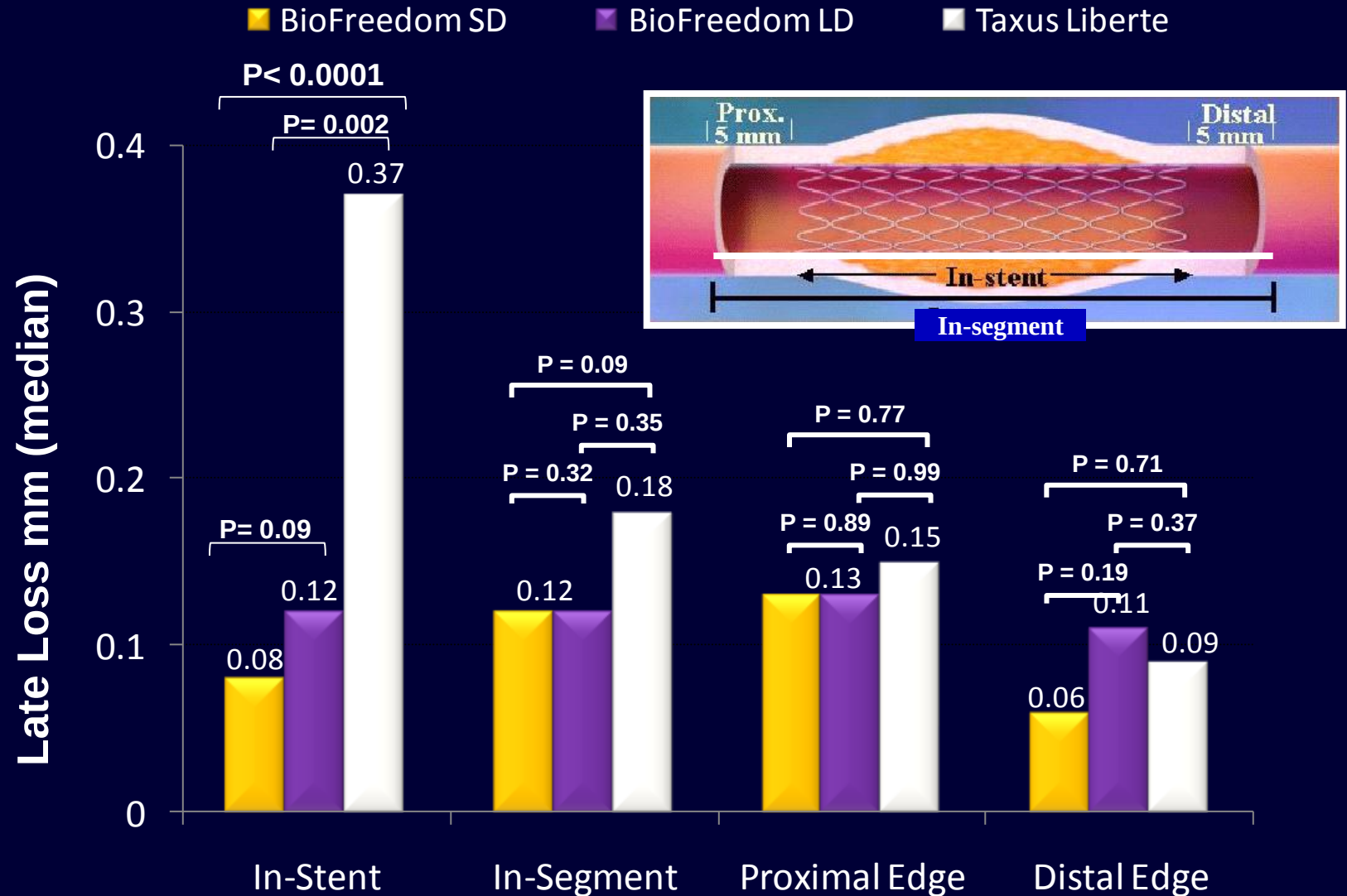
BMS

180 Days



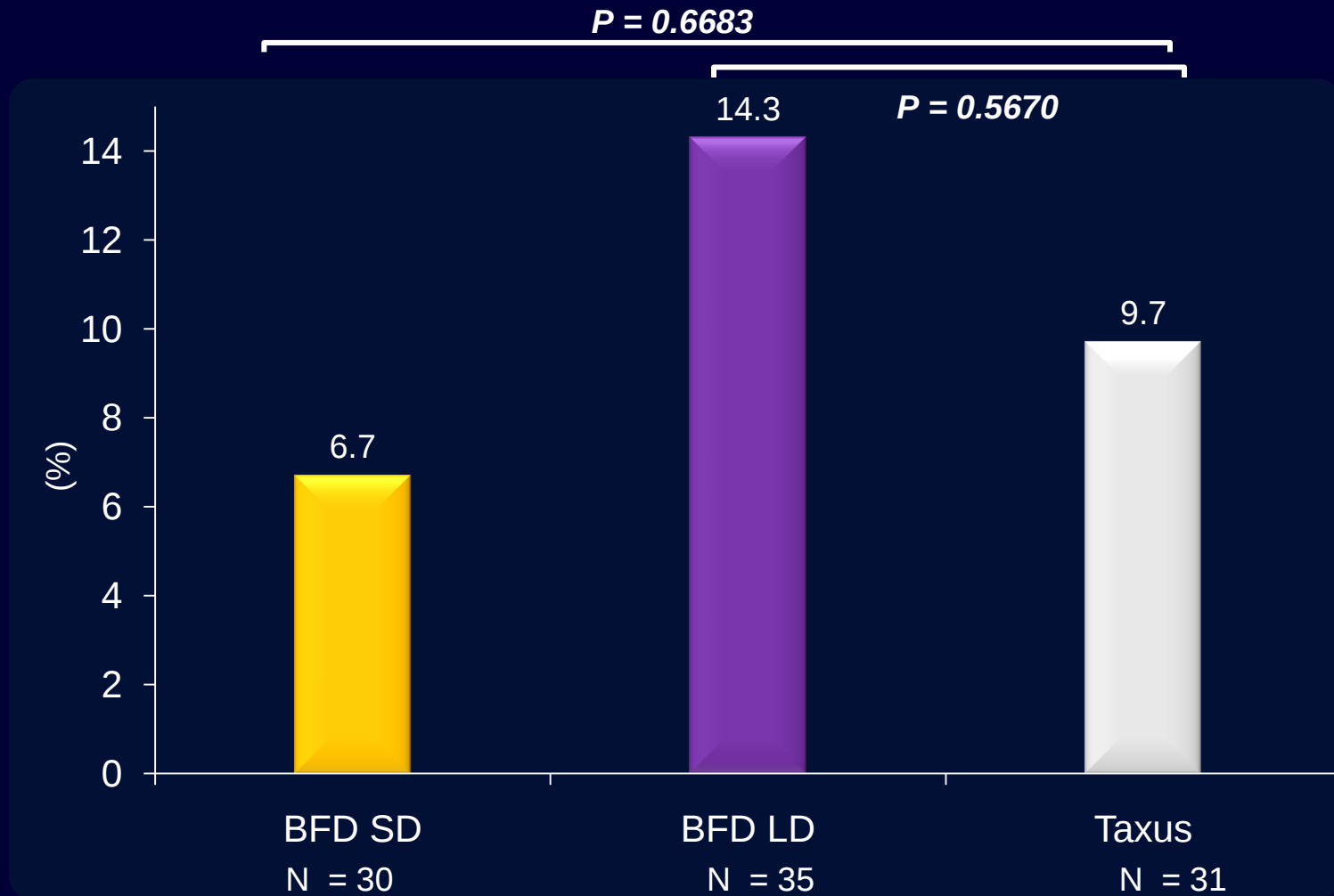
	n	28 days	180 days
☐ Standard dose Bio-freedom	24	24	23
☒ Low dose Bio-freedom	26	26	27
☐ Sirolimus-eluting stents	30	30	39
☒ Bare metal stents	24	24	24

Polymer-Free BioFreedom Stent – 4 Month Results



12 Month Angiographic FU

In-Segment Binary Restenosis: 2nd Cohort



BioFreedom - Clinical Outcomes @ 12 Months

	BioFreedom Standard Dose N=60	BioFreedom Low Dose N=62	Taxus Liberté N =50	P-value BFM SD vs. Taxus	P-value BFM LD vs Taxus
MACE	3 (5%)	7 (11.6%)	0 (0.0%)	N/A	0.09
Death	1 (1.8%)	0 (0.0%)	0 (0.0%)	N/A	N/A
MI*	1 (1.8%)	1 (1.6%)	0 (0.0%)	N/A	0.34
Q Wave MI	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A	N/A
Non-Q Wave MI*	1 (1.8%)	1 (1.6%)	0 (0.0%)	N/A	0.34
Emergent Bypass	0 (0.0%)	0 (0.0%)	0 (0.0%)	N/A	N/A
TLR**	1 (1.8%)	6 (10%)	3 (5%)	N/A	0.17
Stent Thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)		

Future of Newer Generation DES

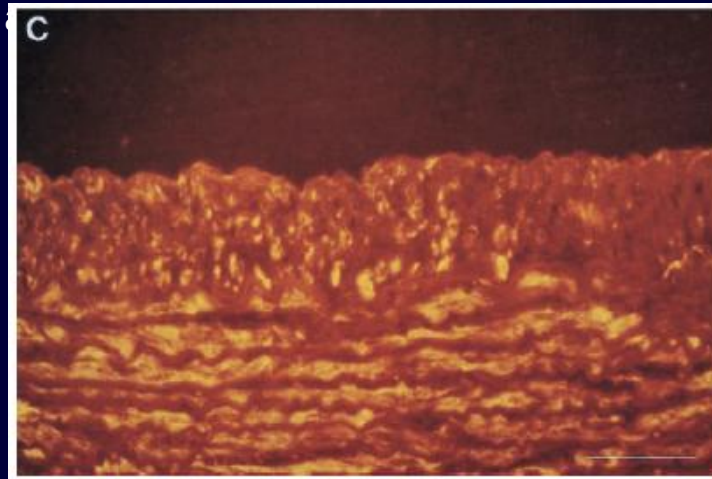
- Newer generation durable polymer DES provide improved safety and efficacy compared with early generation DES
- The majority of future generation DES are based on biodegradable polymer drug release providing similar safety and efficacy as durable polymer DES
 - Appealing concept requiring confirmation in adequate trials
- Polymer-free based DES may even further decrease polymer related adverse events, but potentially at the cost of reduced efficacy

Drug-Coated Balloon Catheters

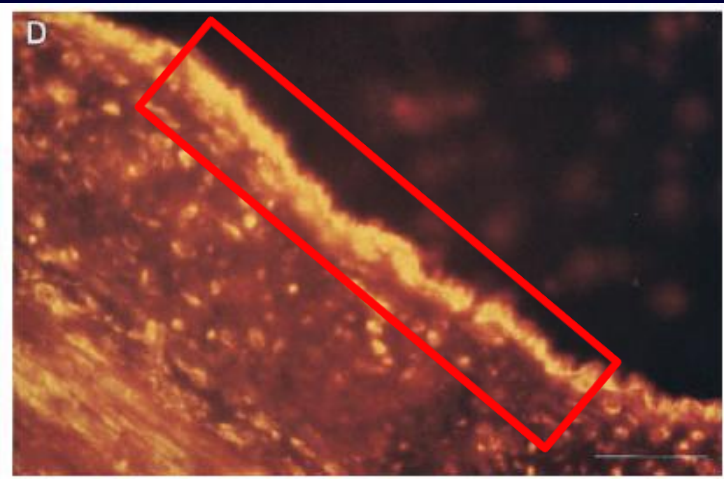
Mechanism of action

A lipophilic drug applied on a carrier is passively transferred to the intima of the coronary artery by balloon expansion. Variable tissue retention rates determine local inhibition of neointimal hyperplasia.

Immunofluorescence micrographs after staining with a monoclonal anti-tubulin AB



Control animal seven days after BD showing heterogeneous staining within the neointima



Histologic section seven days after local paclitaxel delivery showing an intensely stained "fluorescence band" at the luminal cell lining

Drug-Coated Balloon Catheters

Gray WA et al. *Circulation* 2010;121:2672-80

Drug

Paclitaxel is lipophilic, has a high absorption rate (10-15%), and is transferred quickly to the endoluminal surface
-other drugs (i.e. limus) also being tested

Carrier

Governs total drug load, coating durability and uniformity, vessel uptake and downstream drug dose
-i.e. Iopromide

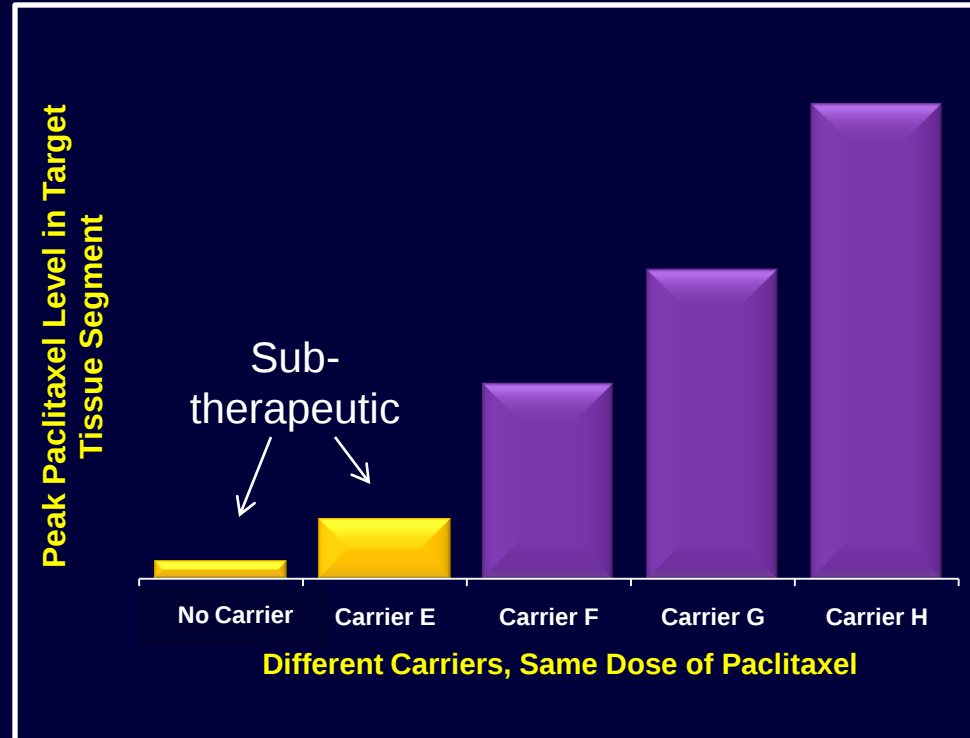
Platforms

Dior (Eurocor)

Moxy (Lutonix, Inc.)

Paccocath (Bayer Schering)

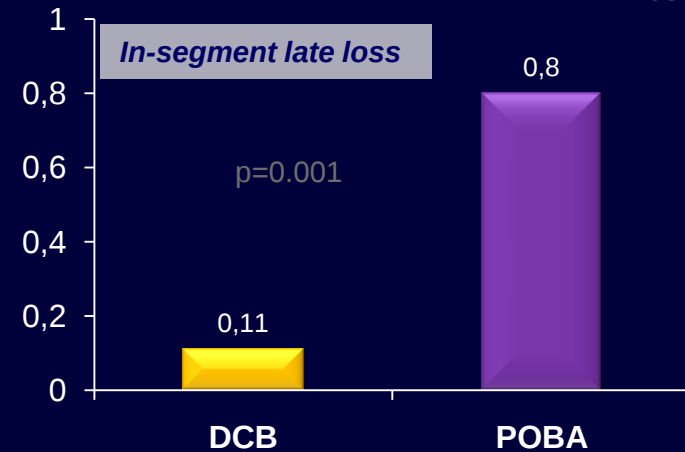
SeQuent Please (B. Braun)



Drug-Coated Balloons for Instant-Restenosis

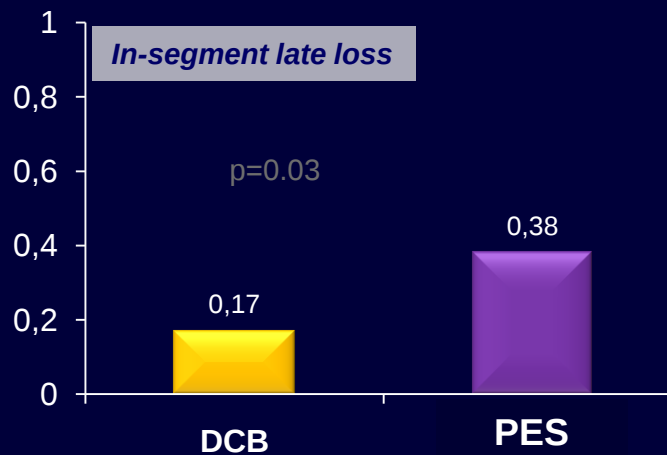
Paccocath ISR I&II

n=108



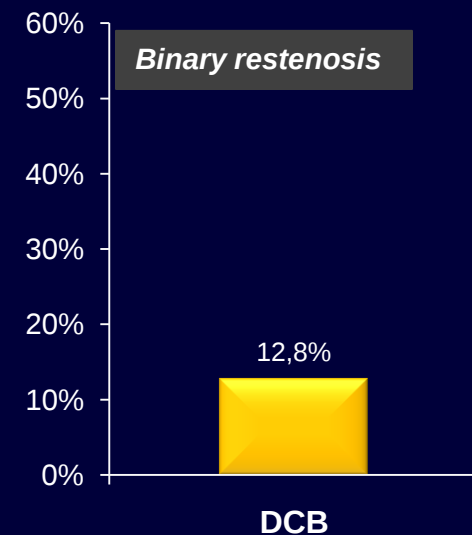
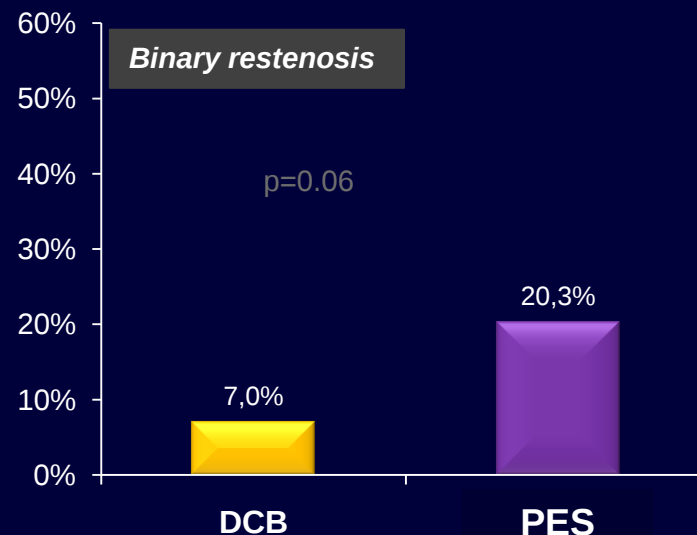
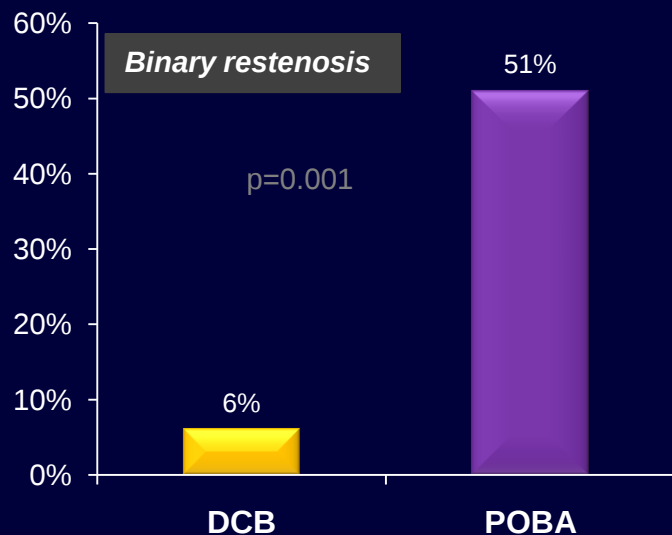
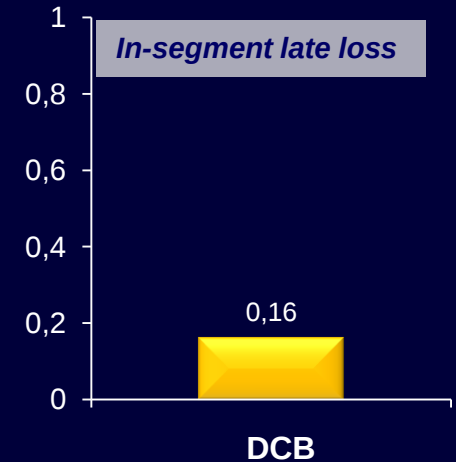
PEPCAD II

n=131



PERVIDEO I

n=41



Scheller B et al. *Clin Res Cardiol* 2008

Unverdorben et al. *Circulation* 2009

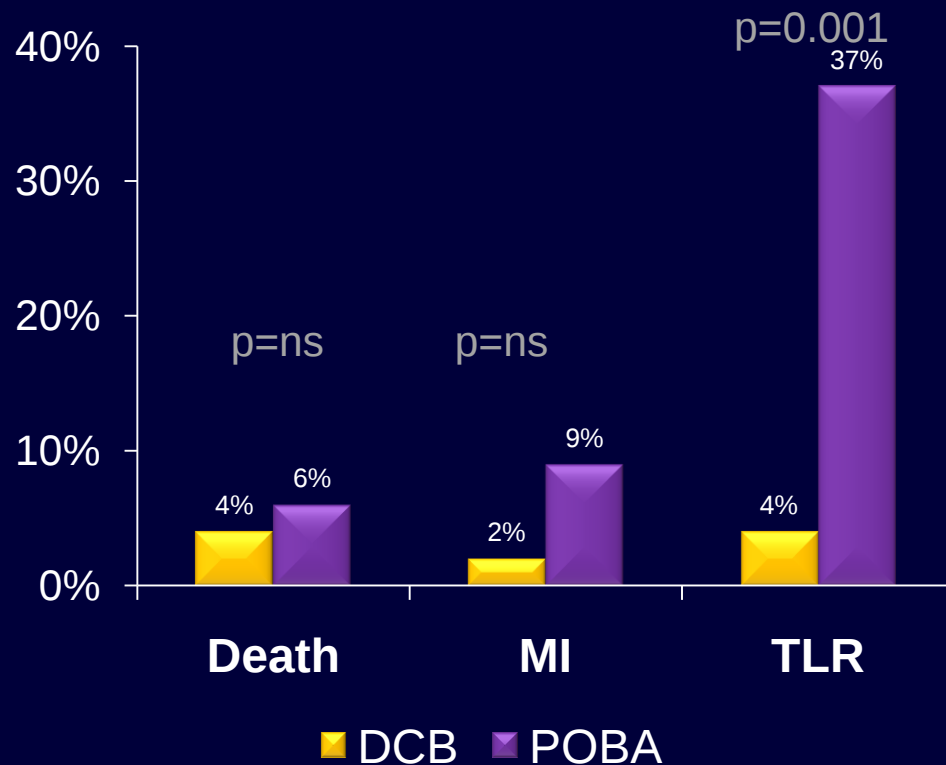
Mauri L, *TCT* 2010

Drug-Coated Balloons for Instent-Restenosis

Clinical follow-up at 12 months

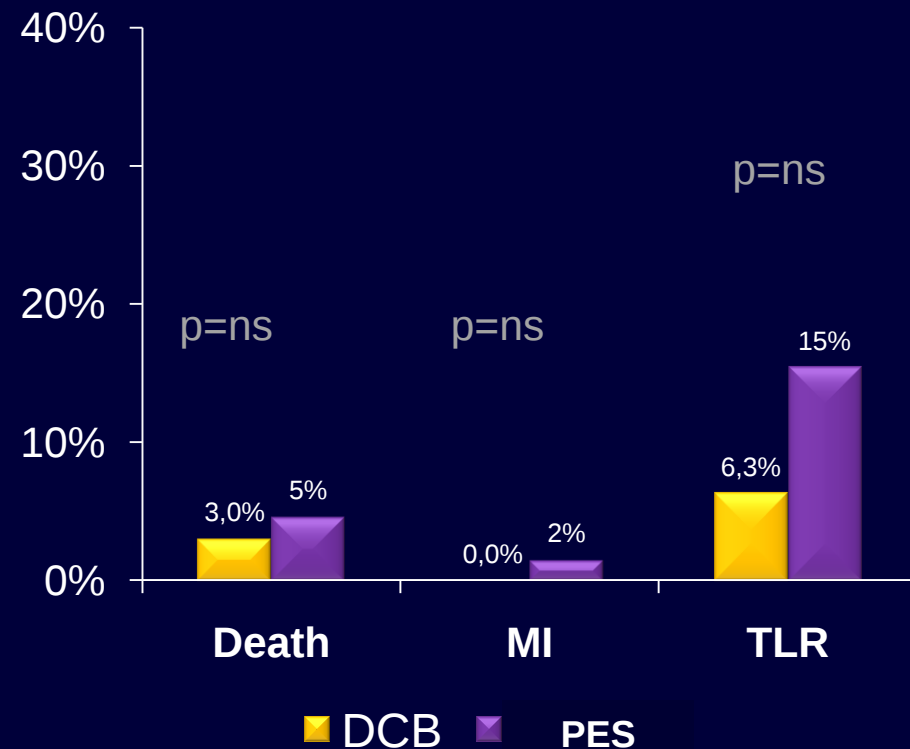
Paccocath ISR I&II

N=108



PEPCAD II

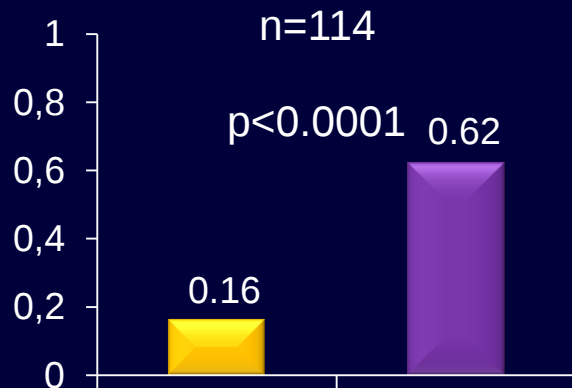
N=131



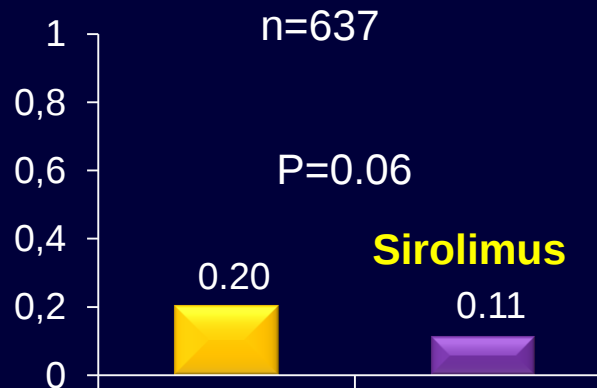
Drug-Coated Balloons for Native, De-Novo Coronary Artery Disease

In-segment late loss

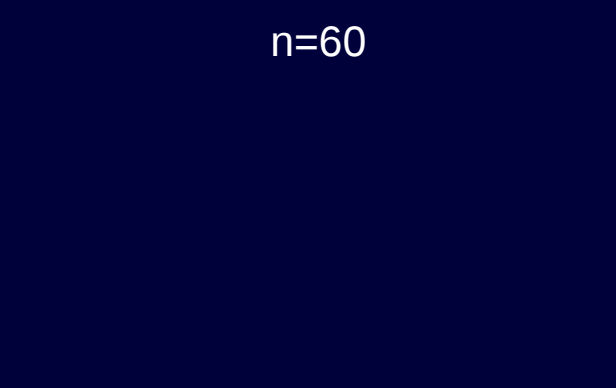
PEPCAD I - SVD



PEPCAD III

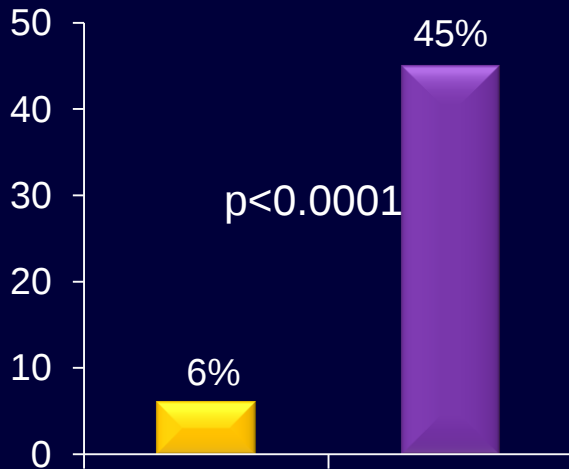


PICCOLETO - SVD

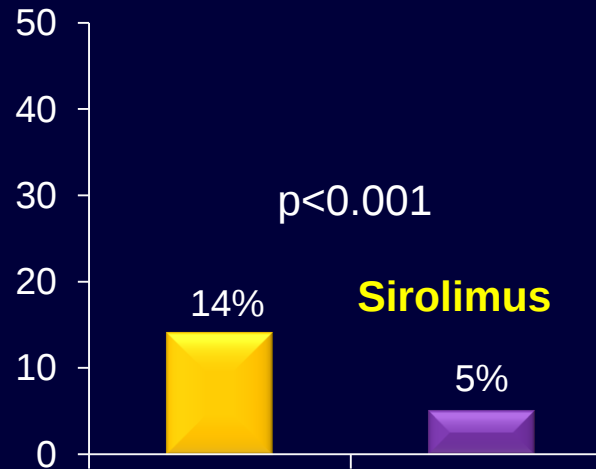


Binary Restenosis

DEB DEB+BMS



DEB+BMS DES



Paclitaxel

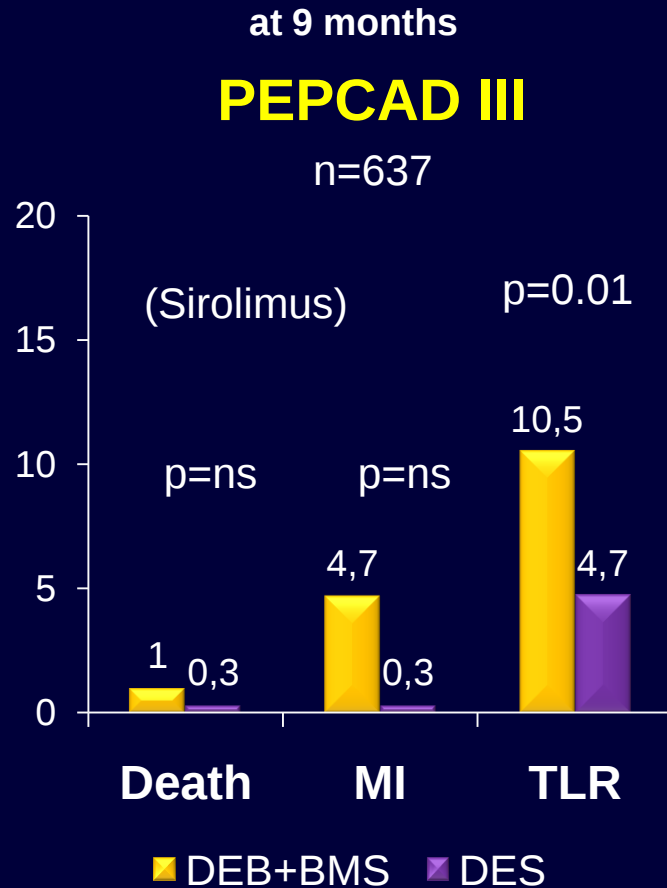
DEB DEB+BMS

DEB+BMS DES

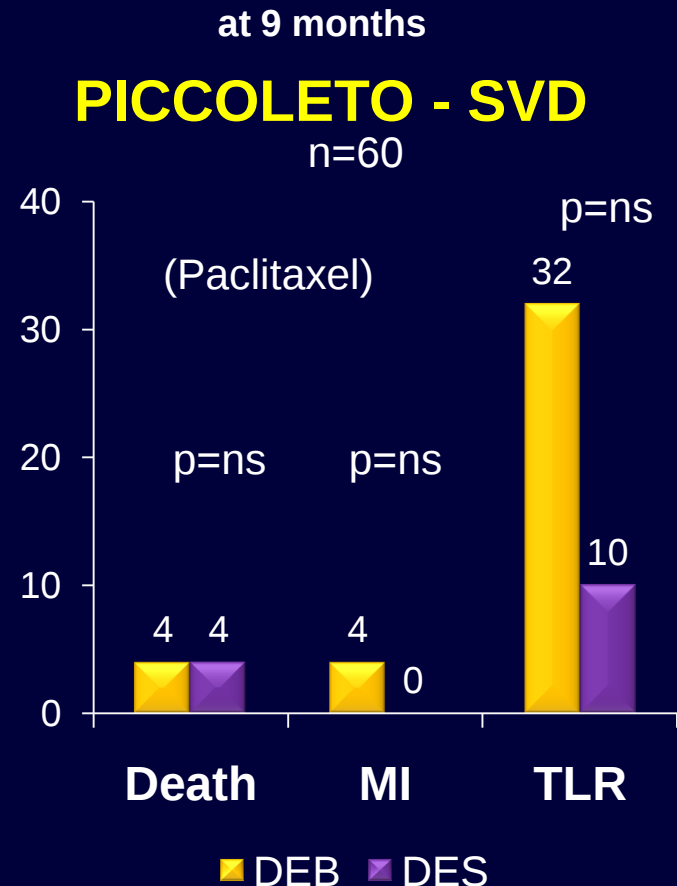
DEB DES

Drug-Coated Balloons for Native, De-Novo Coronary Artery Disease

Clinical follow-up



Hamm et al.
AHA 2009



Cortese et al.
Heart 2010