Biological Stent Under Development

가톨릭의과대학 순환기내과
승 기 배

The goals of Any Revascularization Strategy:

Percutaneous Coronary Intervention (PCI)

- **Provide a safe and durable treatment of flow limiting epicardial coronary obstructions**
  - ***stent, +/- radiation, drugs***

- **Prevent future morbidity and mortality arising from ongoing coronary atherosclerosis**
  - ***medical therapy***

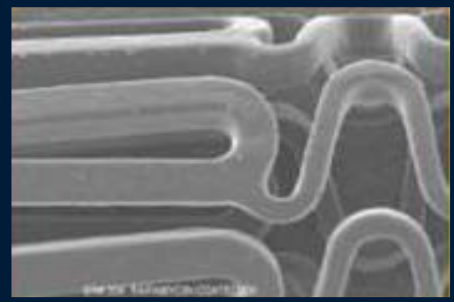
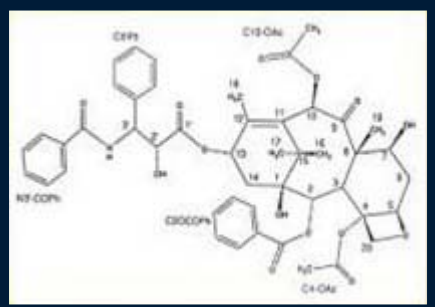
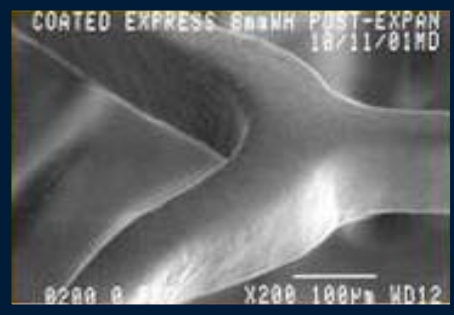
How to provide a safe and durable treatment of atherosclerosis with stent

- Rock bottom binary restenosis
  - low late loss (?)
- Few MACE associated with stent for durable period

What have we learned from datas & experiences ?

- DRUG PROPERTIES
- VASCULAR GEOMETRY
  - Bifurcations
- POLYMER
- CLOT
  - Drugs induce
  - Stent in clot
- STENT DESIGN
- TECHNIGUE
  - Predilation

Drug-eluting Stent in 2004
Safety and Efficacy Proven

	Drug	*Polymer*	*Stent*
Cypher			
	Sirolimus	PEVA+PBMA blend	BX Velocity
TAXUS			
	Paclitaxel	Polyolenfin	Express^2

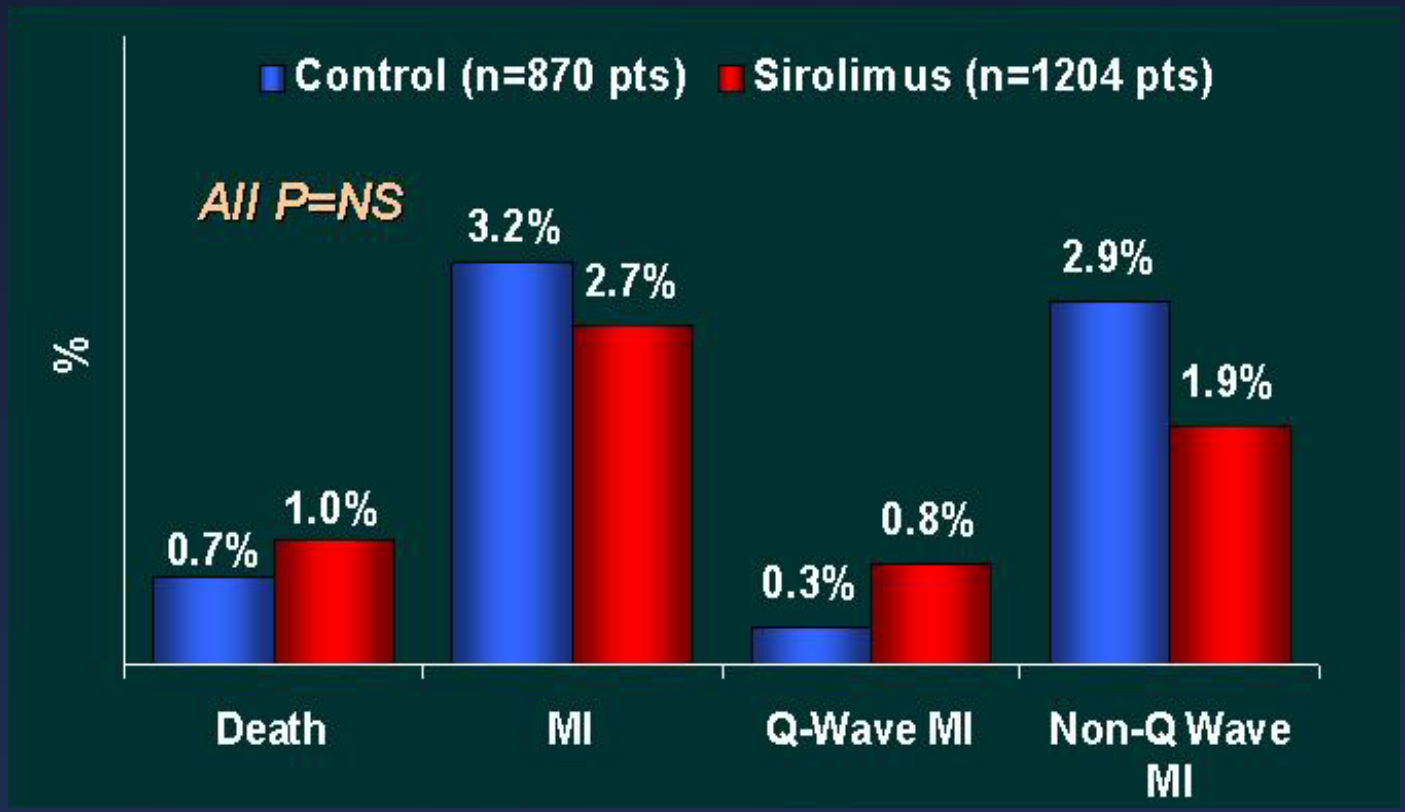
Integrated CYPHER Trials (N=2,074)

Study	RCT vs. BMS	Pts	Study Location		Angio F/U (Mo.)	Clin. F/U (Mo.)	Anti-Coag. Regim. (Mo.)	Core Lab	CEC
SIRIUS	Y	*de novo*	US		8	9,12, 24	3	BW	HCRI
E-SIRIUS	Y	*de novo*	EU		8	9,12, 24	2	BW	HCRI
C-SIRIUS	Y	*de novo*	CA		8	9,12, 24	2	BW	HCRI
DIRECT	N	*de novo*	US		8	9	3	BW	HCRI
SVELTE	N	*de novo & SV*	EU	LA	8	9	2	BW	HCRI
RAVEL	Y	*de novo*	EU	LA	6	6,12,24, 36	2	CS	CS

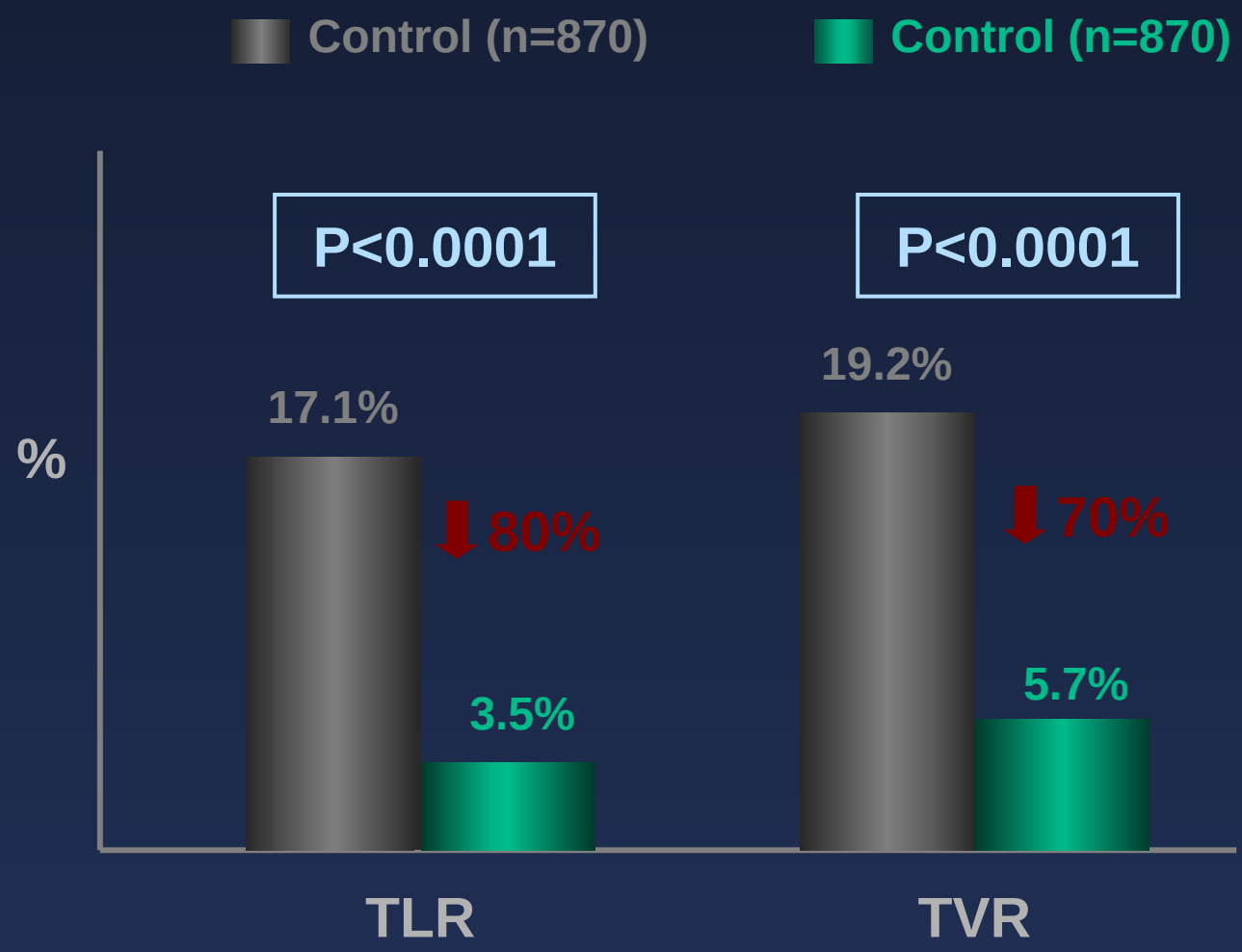
1. *RCT – Randomized Control Trial, BMS – Bare Metal Stent*
2. *SV – Small Vessel*
3. *NA – North America, EU – Europe, US – United States, LA – Latin America*
4. *BW – Brigham and Women's, HCRI – Harvard Clinical Research Institute, CS - Cardialysis*

CYPHER Trials – In-Segment Restenosis

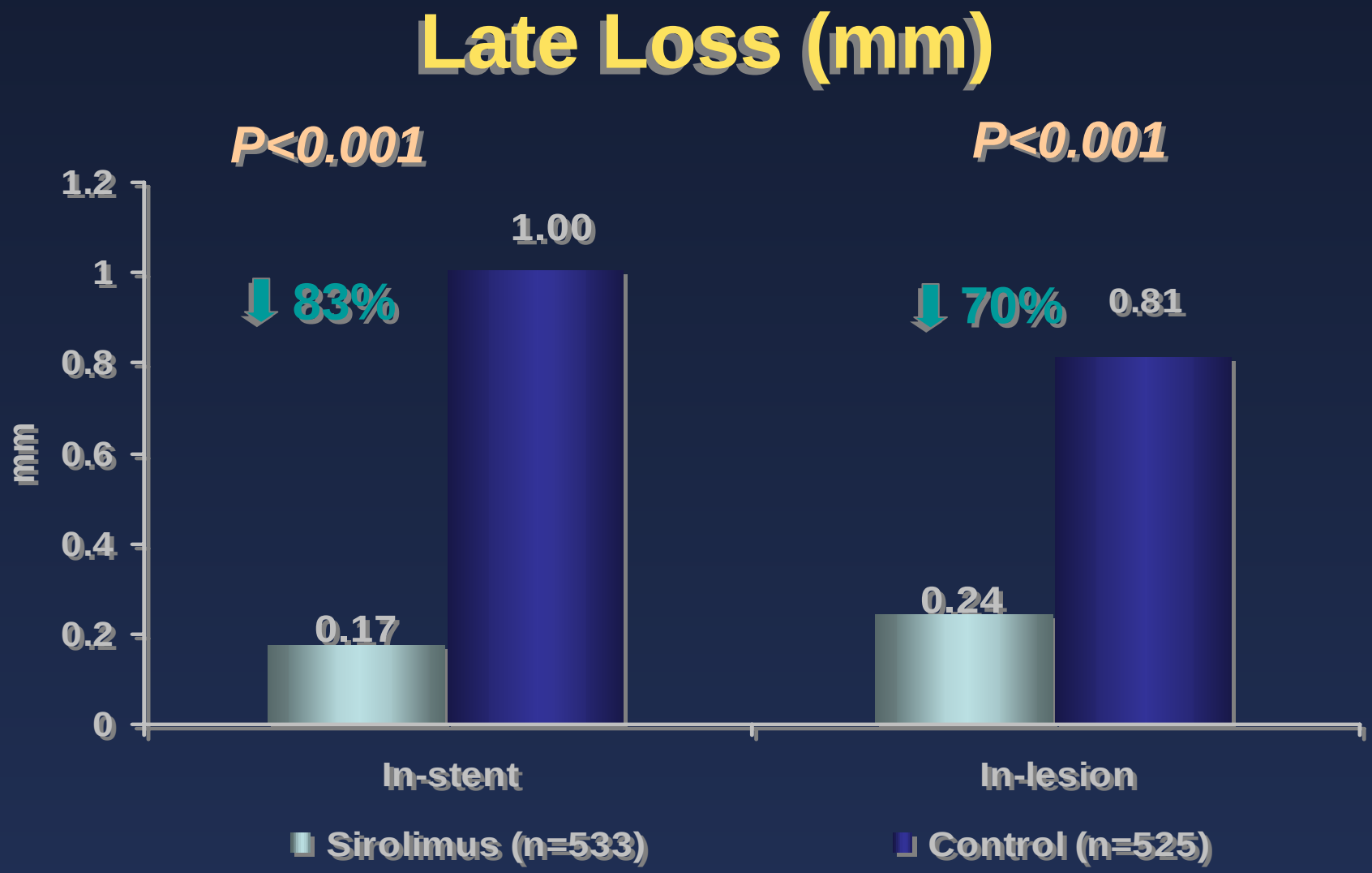
CYPHER Trials
9 Month Outcomes



CYPHER Trials
9 Month Outcomes



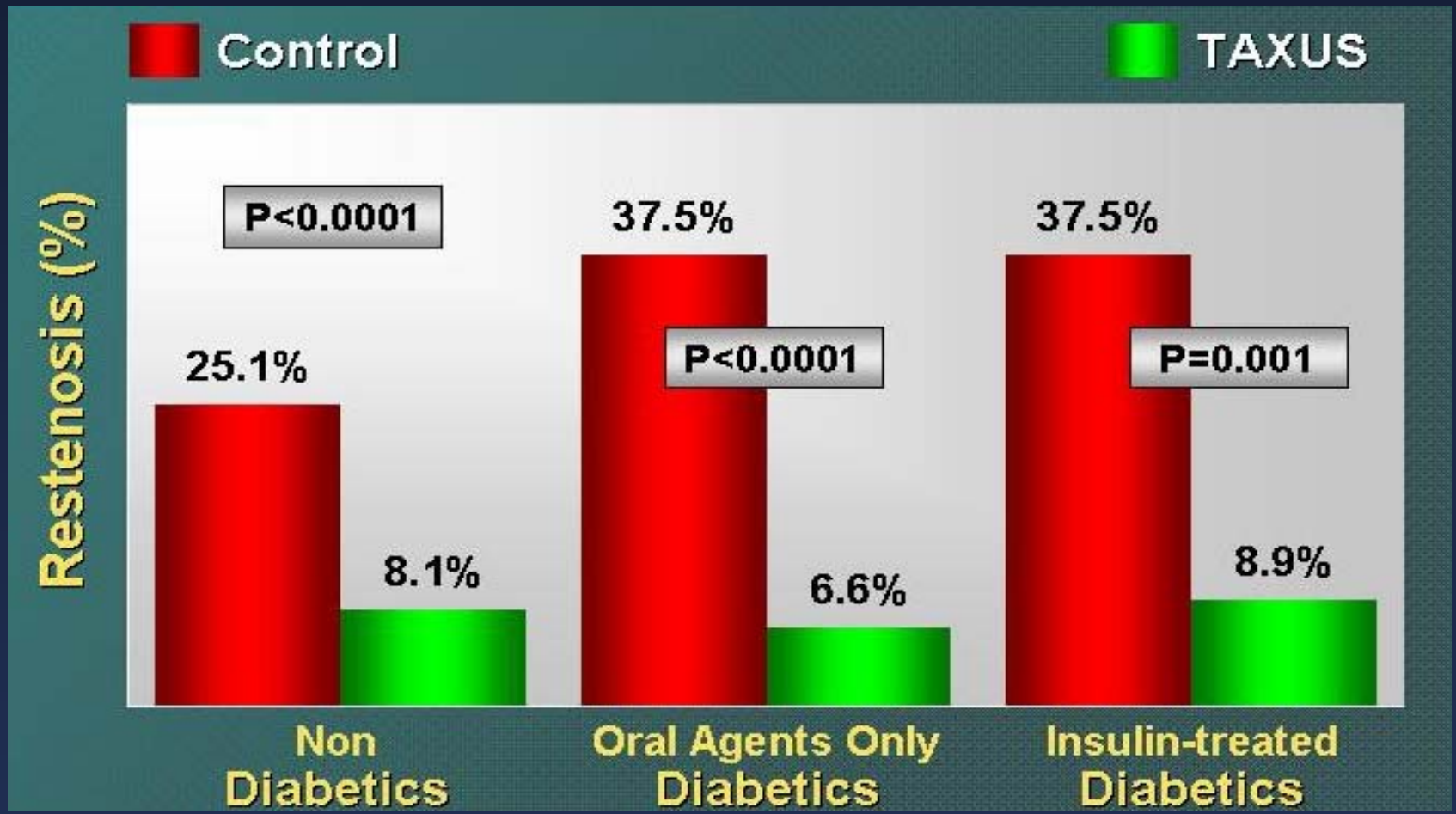
SIRIUS - Late Loss Analysis



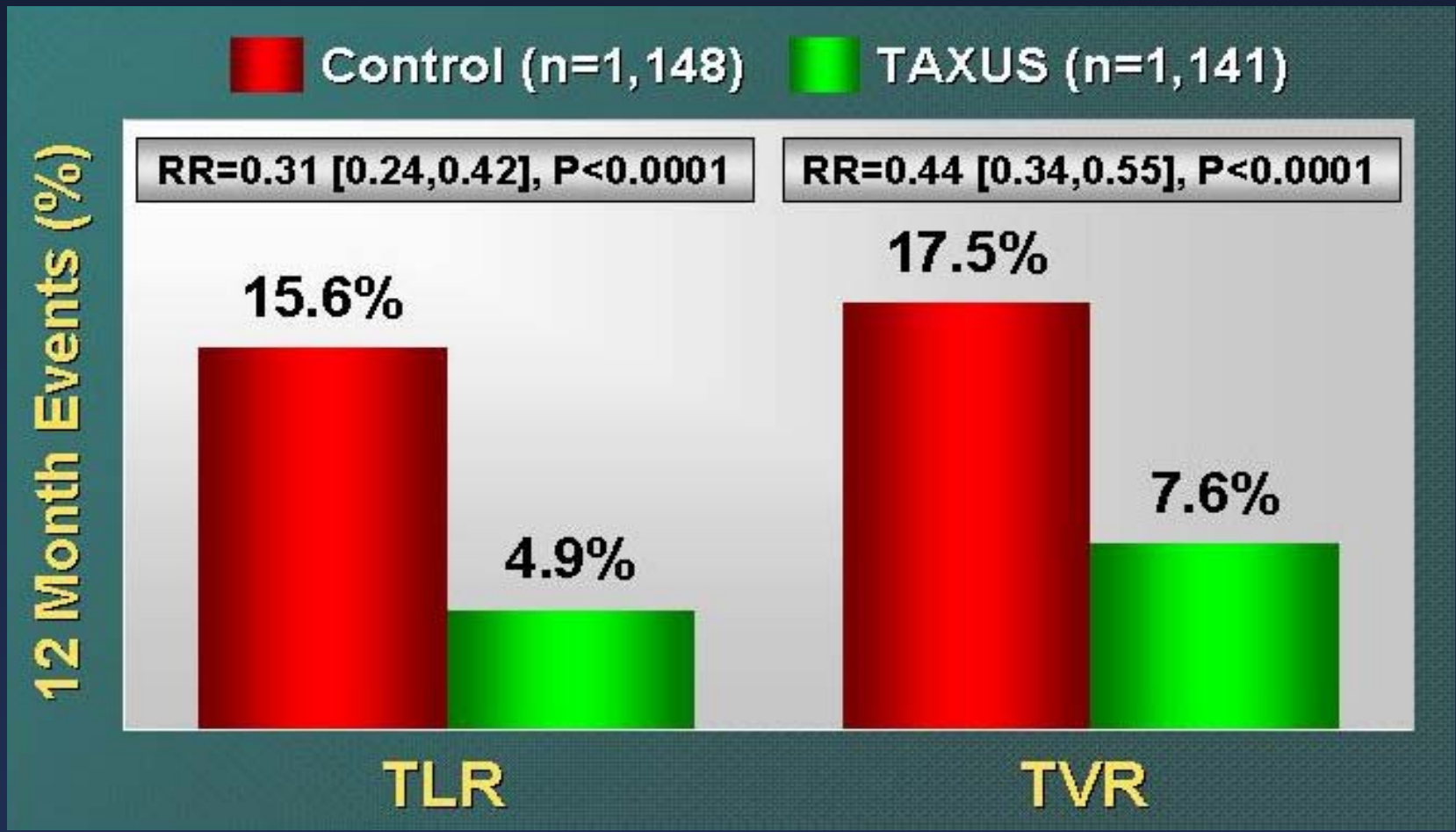
TAXUS II + IV RCT Pooled Data
N = 2,289 randomized pts

	TAXUS DES (n=1,141)	Control BMS (n=1,148)	P value
Age	62.0 ± 10.8	61.8 ± 10.5	0.63
Male	73.0%	74.4%	0.48
Diabetes	18.9%	21.1%	0.20
- insulin req.	6.2%	7.2%	0.34
RVD (mm)	2.76 ± 0.47	2.76 ± 0.48	0.72
Lesion length (mm)	14.1 ± 7.1	14.1 ± 7.0	0.88
Stent length (mm)	22.5 ± 9.6	22.3 ± 9.7	0.67
Stent:lesion length	1.82 ± 0.86	1.80 ± 0.82	0.52
Overlapping stents	28.8%	26.9%	0.67

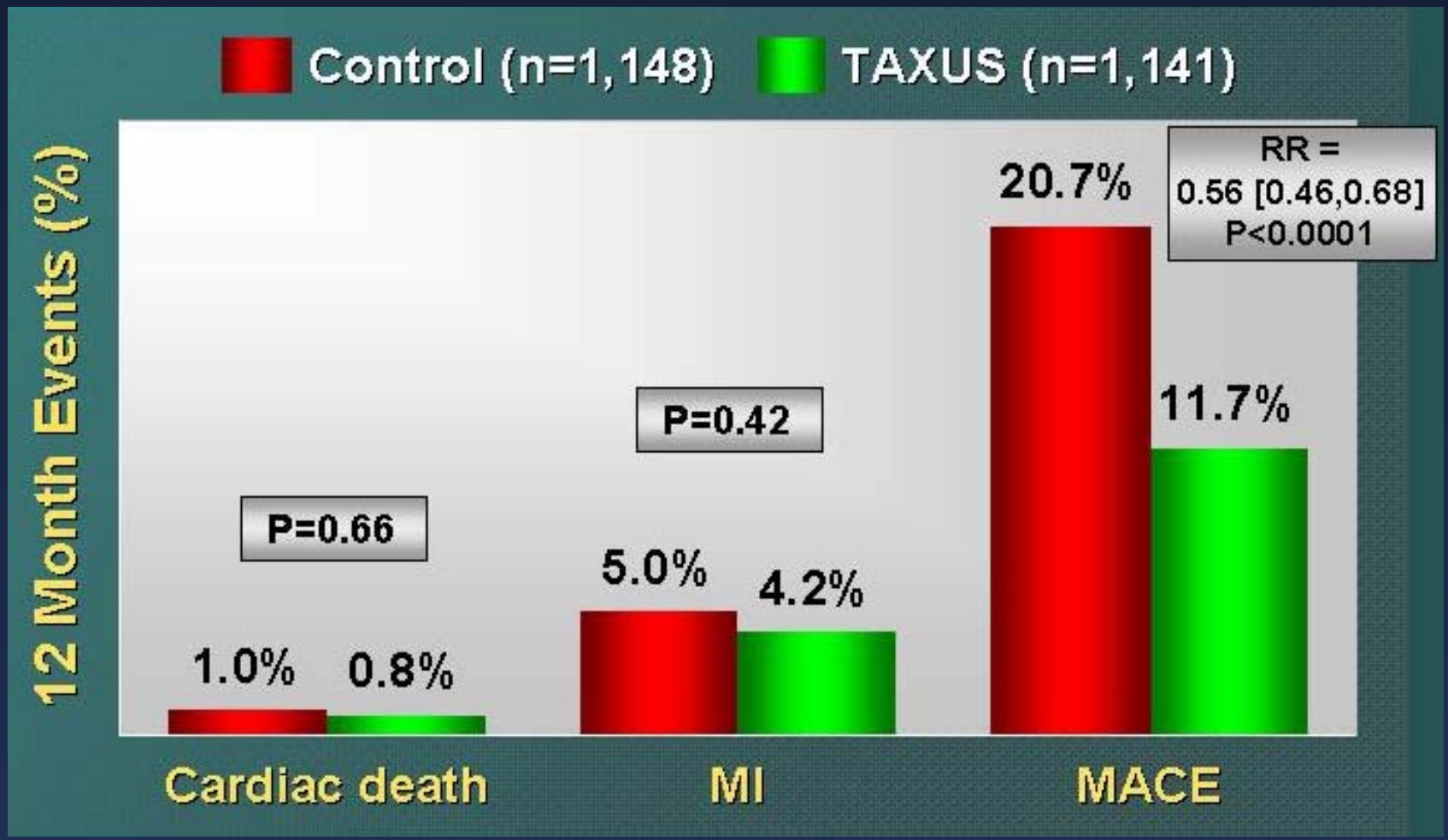
TAXUS II + VI Meta-analysis
Angiographic restenosis



TAXUS II + VI Meta-analysis (n=2,289)
12 Month TLR and TVR



TAXUS II + VI Meta-analysis (n=2,289)
12 Month Cardiac Death, MI and MACE

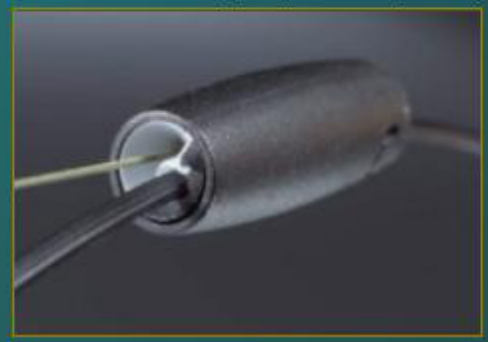


TAXUS II + VI Meta-analysis
In-stent late loss

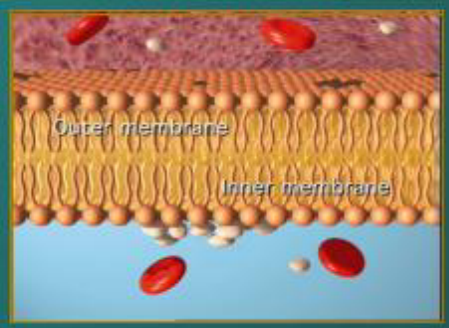
Medtronic Endeavor DES System
Key Components

Driver Cobalt Alloy Stent

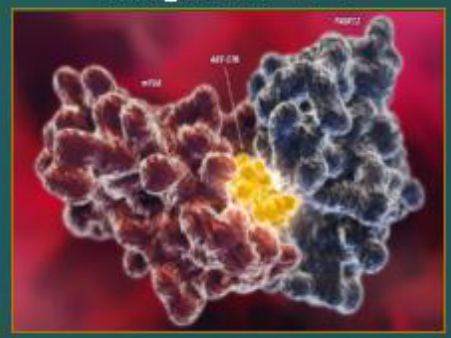
Stent Delivery System (MX^2)



PC Technology



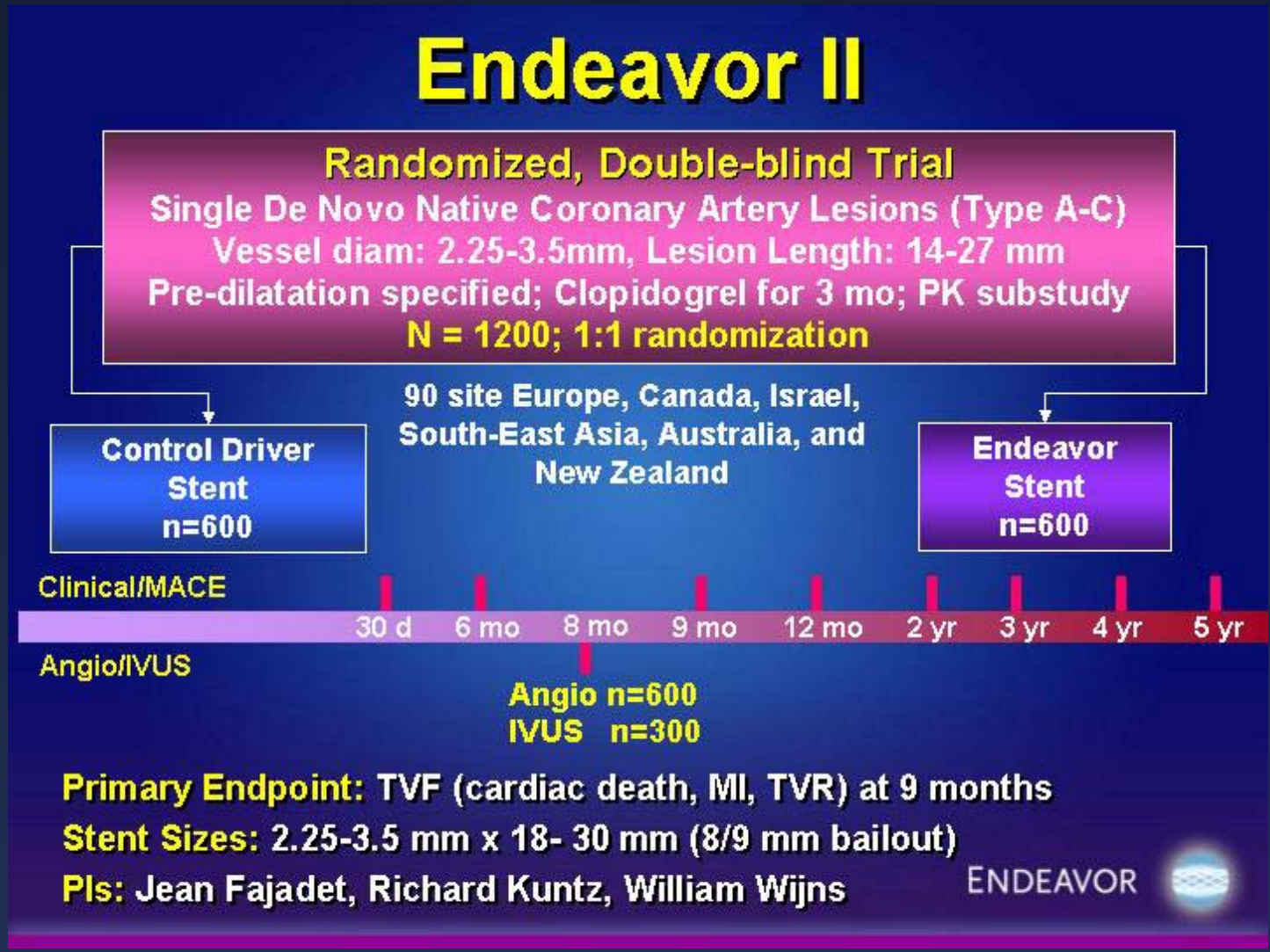
Drug: ABT-578



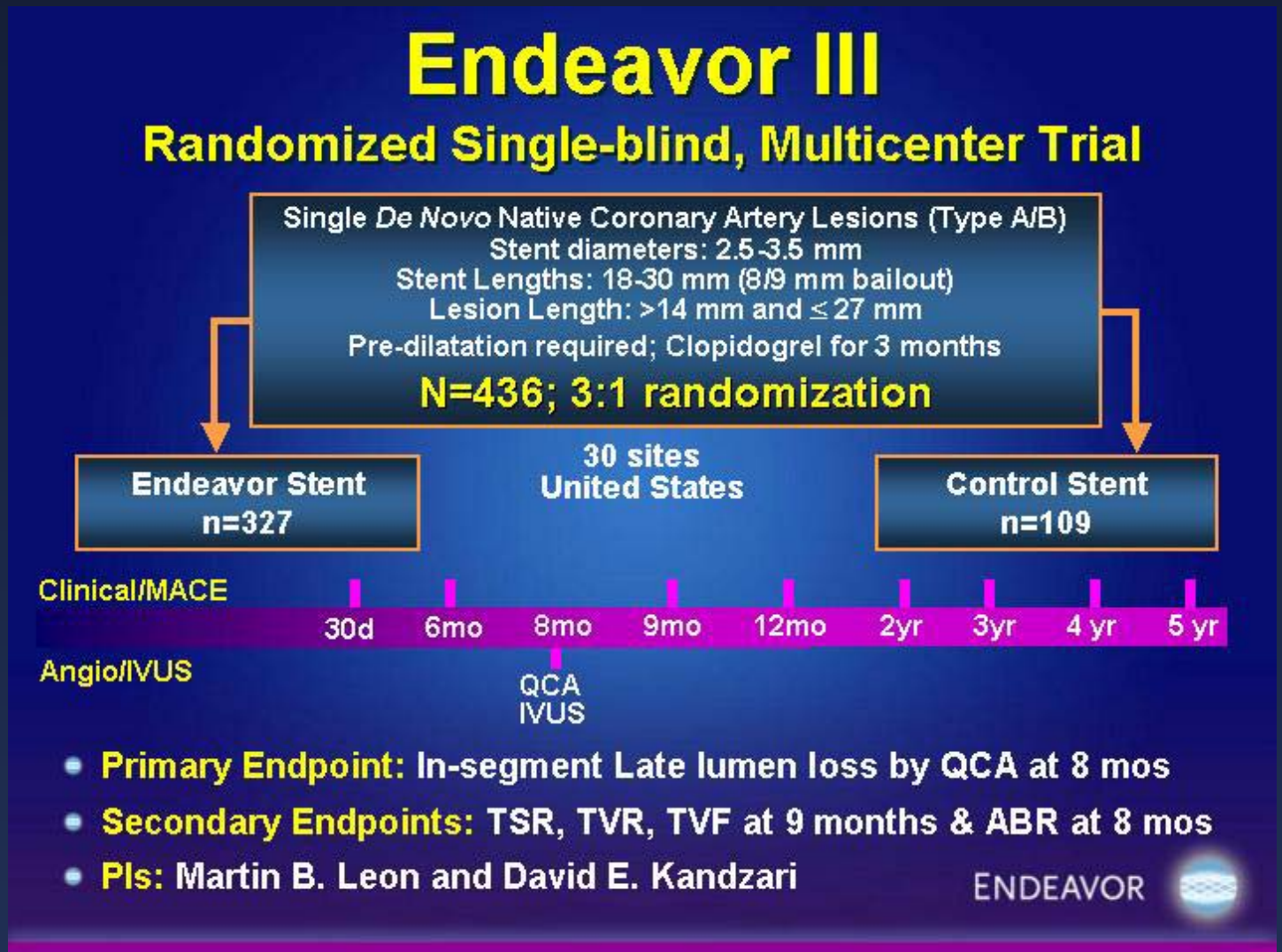
Result of Phase I ENDEAVOR-1 Trial

Measurement	30 Days	4 Months	12 Months
Safety			
MACE	1% *Primary endpoint*	2%	2%
Death	0	0	0
All MI	1%	1%	1%
Q-wave MI	0	0	0
Non-Q-wave MI	1%	1%	1%
TLR	0	1%	1%
TVR (non-TLR)	0	0	0
TVF	---	2%	2% *Secondary endpoint*
Late incomplete apposition	---	0	0
Late Loss			
In-stent	---	0.33	.58
In-segment	---	.21 *Primary endpoint*	.40
Proximal edge	---	.12	.30
Distal edge	---	.09	.23
%DS	---	21.5%	26.8%
Restenosis			
In-stent	---	2.1%	3.3%
Proximal	---	---	0%
Distal	---	---	0%
In-segment	---	2.1%	3.3%

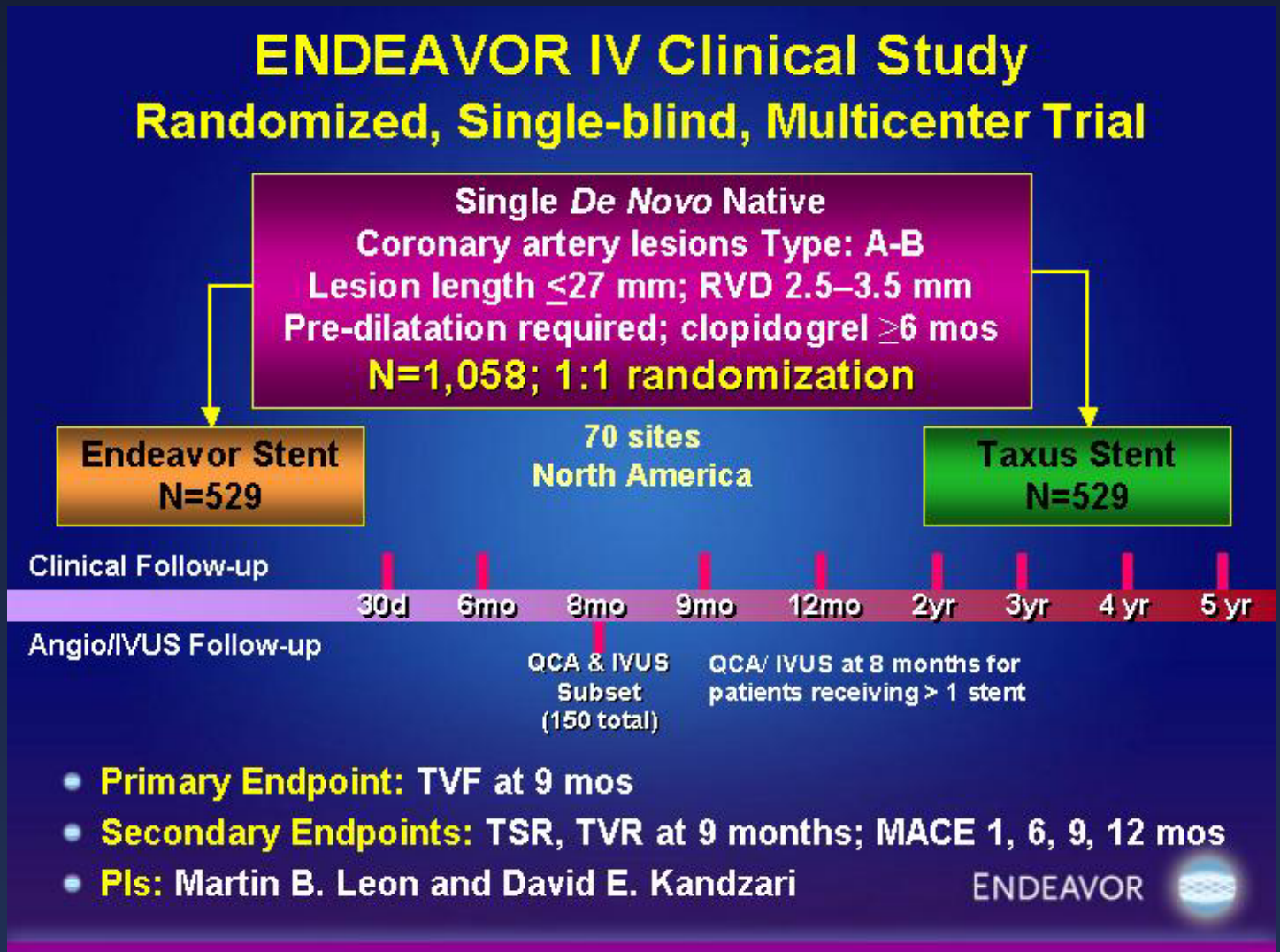
Endeavor II


Endeavor II
Randomized, Double-blind Trial
Single De Novo Native Coronary Artery Lesions (Type A-C)
Vessel diam: 2.25-3.5mm, Lesion Length: 14-27 mm
Pre-dilatation specified; Clopidogrel for 3 mo; PK substudy
N = 1200; 1:1 randomization
90 site Europe, Canada, Israel, South-East Asia, Australia, and New Zealand
Control Driver Stent n=600
Endeavor Stent n=600
Clinical/MACE
30 d
6 mo
8 mo
9 mo
12 mo
2 yr
3 yr
4 yr
5 yr
Angio/IVUS
Angio n=600
IVUS n=300
Primary Endpoint: TVF (cardiac death, MI, TVR) at 9 months
Stent Sizes: 2.25-3.5 mm x 18- 30 mm (8/9 mm bailout)
PIs: Jean Fajadet, Richard Kuntz, William Wijns
ENDEAVOR

Endeavor III



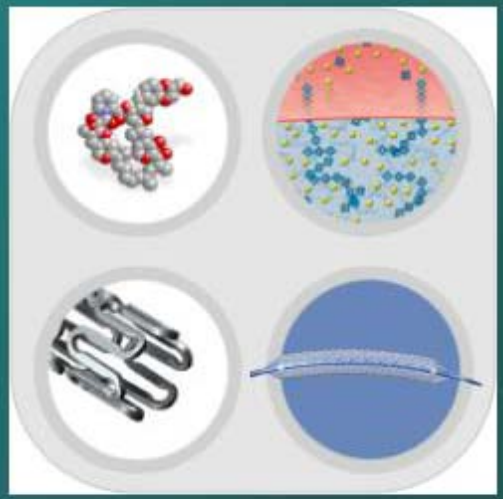
Endeavor IV Clinical Study
Randomized, Single-blind, Multicenter Trial



Guidant CHAMPION™ DES

Everolimus

Bioabsorbable Polymer



CHAMPION™ Stent Platform

ML VISION® Stent Delivery System

FUTURE Clinical Trials

FUTURE I and II: Pilot

FUTURE III and IV: Pivotal

FUTURE I and II Clinical Program

FUTURE I	*FUTURE II*

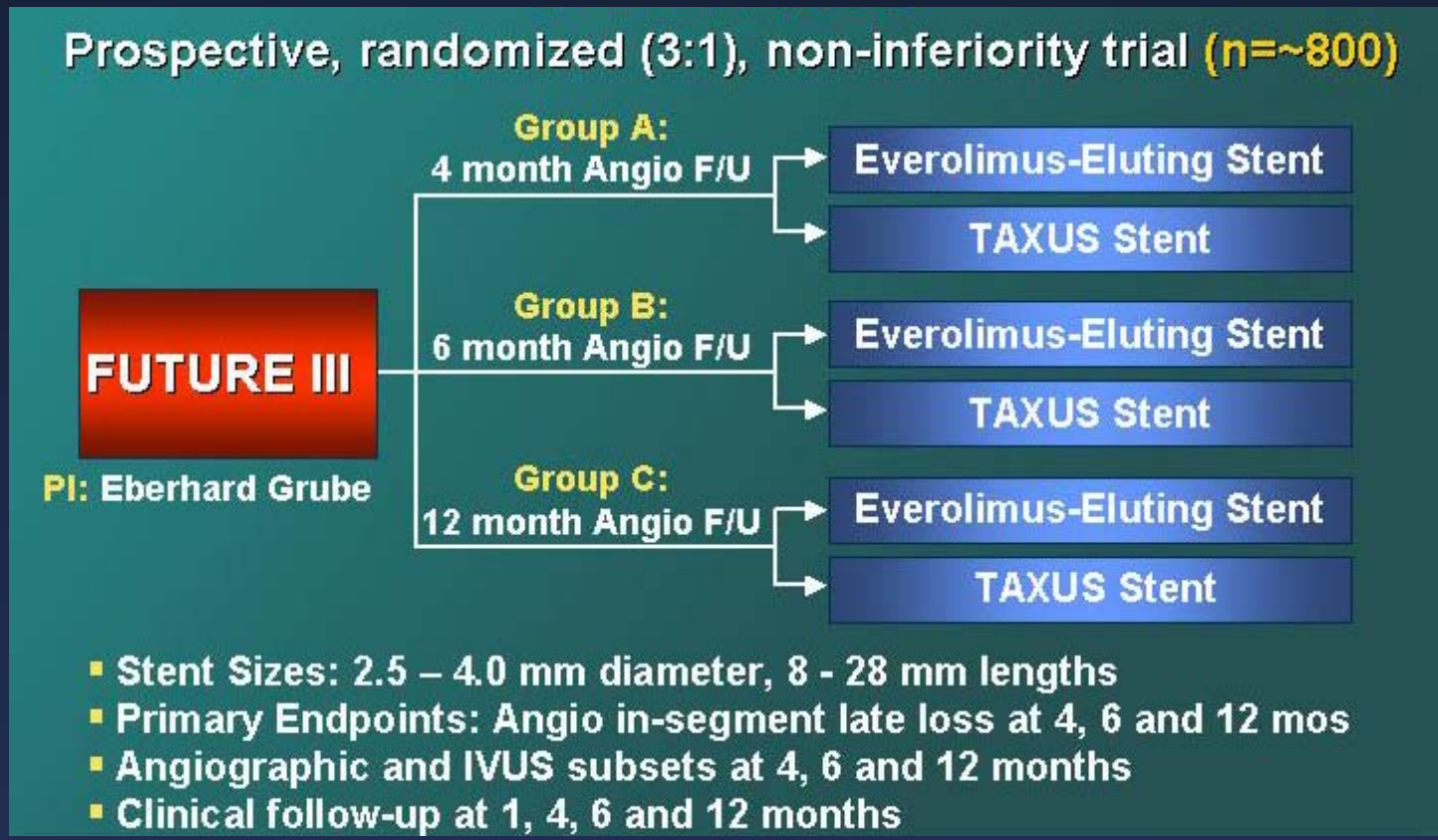
- Asses safety and performance of an Everolimus Eluting Stent
- Single de novo lesion, ≤ 18 mm length
- Stent sizes: 2.5 – 4.0 mm diameter, 14 and 18 mm lenghts
- Prospective, randomized
- Key Endopoint: Angiographic and IVUS result at 6 months, Clinical endpoints at 1. 6 and 12 months

• Diabetic patients excluded (One diabetic included)	• Diabetic patients included
• 42 pts enrolled (27 EES, 15 MS) at one site	• 64 pts enrolled (21 EES, 43 MS) at three sites

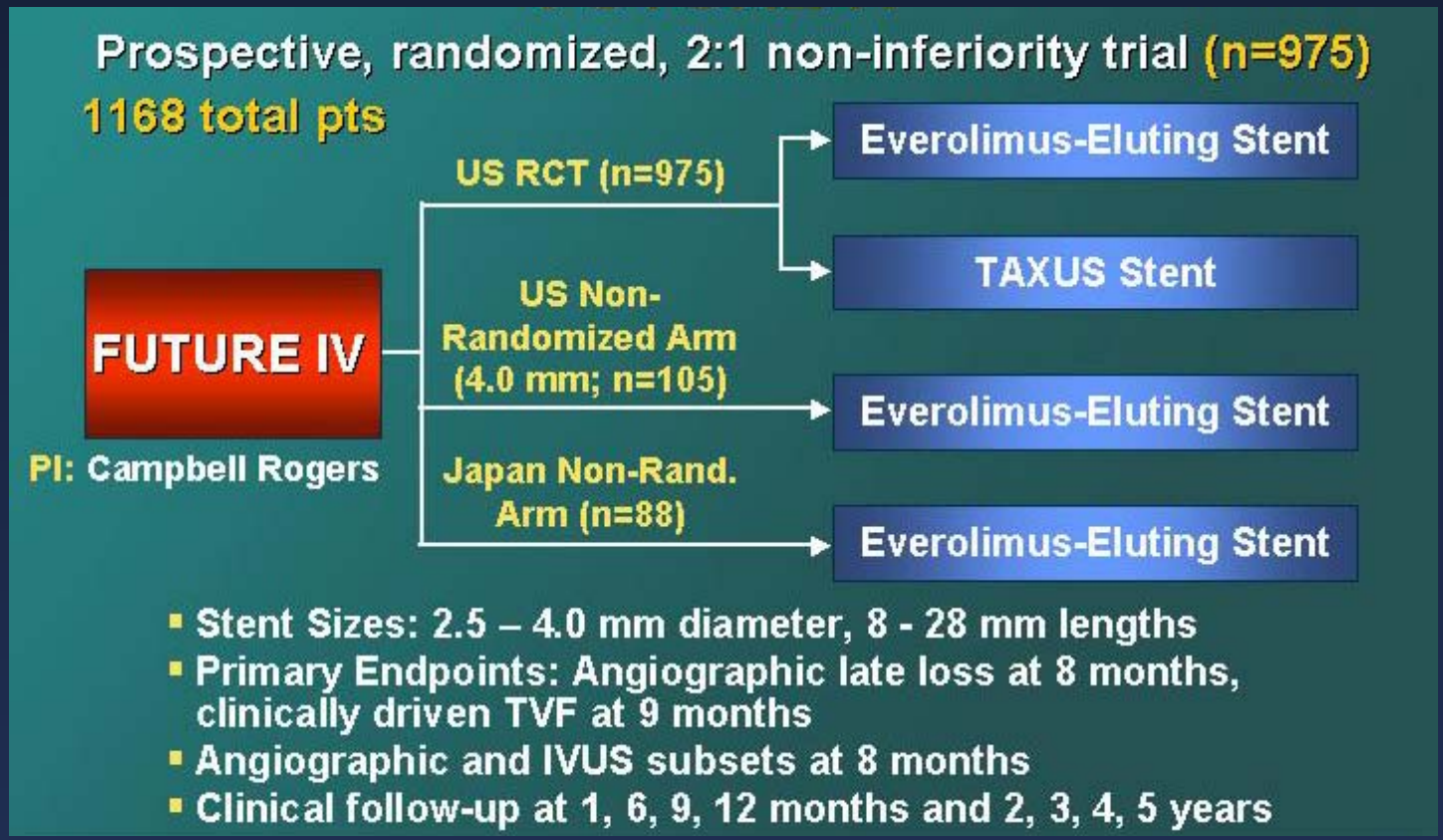
Guidant CHAMPION™ DES system

- Fractures in the stent itself
- Flaring of the balloon at the stent edge
- Flaring of the stent itself at the edges
- Potential polymer problems
- Manufacturing problems

Guidant CHAMPION™ Clinical Trials: FUTURE III



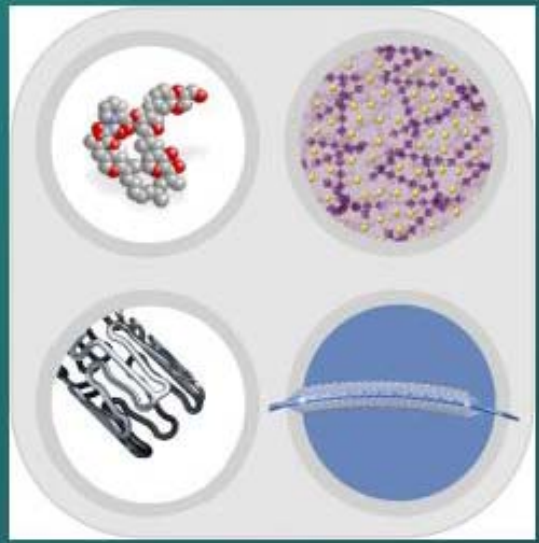
Guidant CHAMPION™ Clinical Trials: FUTURE IV



Guidant ML VISION DES

Everolimus

ML VISION® Stent Platform



Durable Polymer

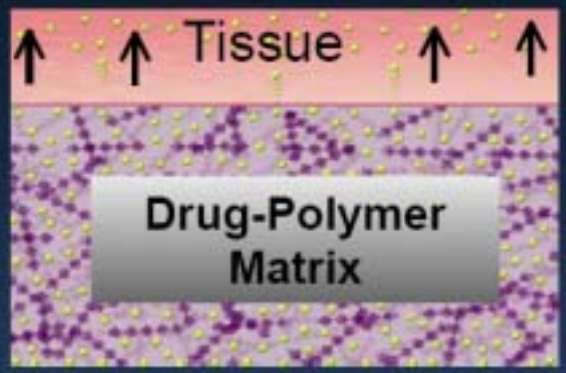
ML VISION® Stent Delivery System

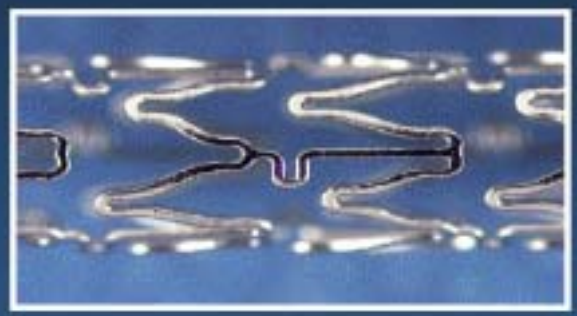
SPIRIT Clinical Trials

SPIRIT First: Pilot

SPIRIT US: Pivotal

Durable Polymer





- Stable polymer matrix affixed to the stent
- No top coat
- Uniform, consistent coating integrity upon deployment
- Hemocompatible
- Polymer allows controlled and sustained release of drug greater than 30 days

ML VISION Stent and Delivery System

- CoCr allows .0032” thin struts for increased stent flexibility
- Maintains radiopacity for precise placement
- Flexible, low profile system
  - 3.0 mm = 0.040“ crossing profile
- Minimal balloon outside the stent for minimizing vessel injury

Study Design

Single *de novo* Lesions
≤ 12 mm length
n = 60

1 : 1

ML VISION® DES
Everolimus Eluting CSS (n=28)

ML VISION™ Control (n=32)

- Prospective, Randomized, Single Blind Trial
- Stent Size: 3.0 x 18 mm
- Clinical follow-up at 1, 6, 9, 12 months, 2, 3, 4, 5 years
- Angiographic and IVUS follow-up at 6 months and 12 months, both arms
- 3 Months Clopidogrel

- PI: Prof.Patrick Serruys, MD, PhD
- Angiographic and IVUS Core Lab:
  - Cardialysis (Rotterdam, The Netherlands)
- Enrollment Complete April 1, 2004
- **Bailout only with bare metal stent -** Only animal data on single stent available at the onset of the study

In-stent 180-day QCA – PRIMARY ENDPOINT

	Everolimus N = 23	Control N = 26	p-value
RVD (mm)	2.61	2.59	ns
MLD (mm)	2.28	1.58	<0.0001
Late loss (mm)*	**0.10**	0.84	**<0.0001**
Late loss index	0.06	0.64	<0.0001
DS (%)	16	39	<0.0001
Binary restenosis rate (%)	0	26.9	0.01

**Primary endpoint*

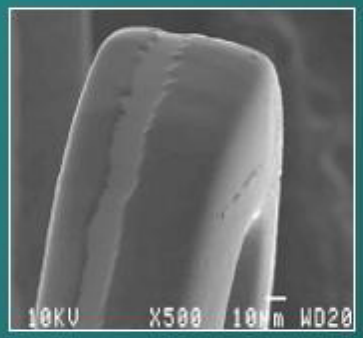
6 months Hierarchical MACE (Per-Protocol)

		Everolimus		Control	
		N =26*	%	N =28*	%
Cardiac death		0	0	0	0
MI	Q-wave**	1	3.8	0	0
	Non Q-wave	0	0	0	0
Clinically driven					
	TLR-CABG	0	0	1	3.6
	TLR-PCI***	1	3.8	5	17.9
Total MACE		**2**	**7.7**	**6**	**21.4**

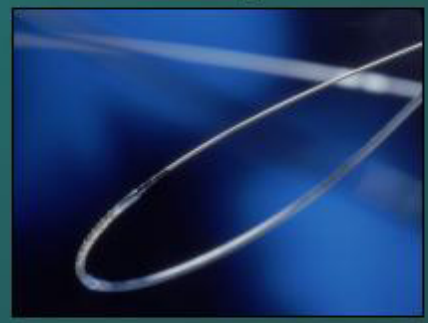
* One patient from each group withdrew consent after 30 days
** Q-wave MI non-target vessel
***PCI at 21 days to treat post procedure dissection.

Abbott ZoMaxx DES System

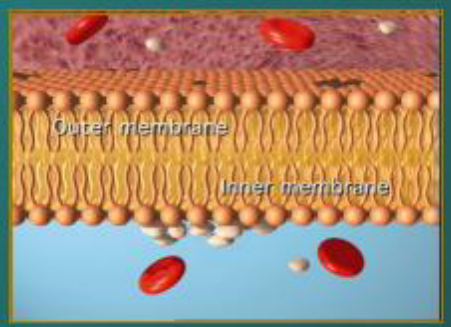
TriMaxx Multi-Alloy Stent



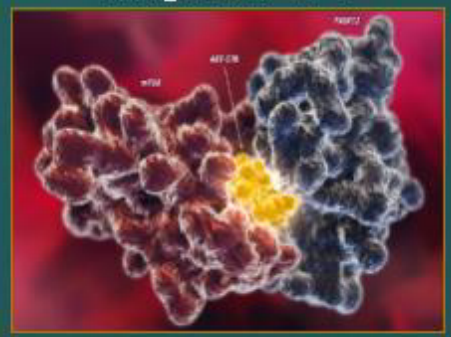
Accel Delivery Catheter



PC Technology



Drug: ABT-578



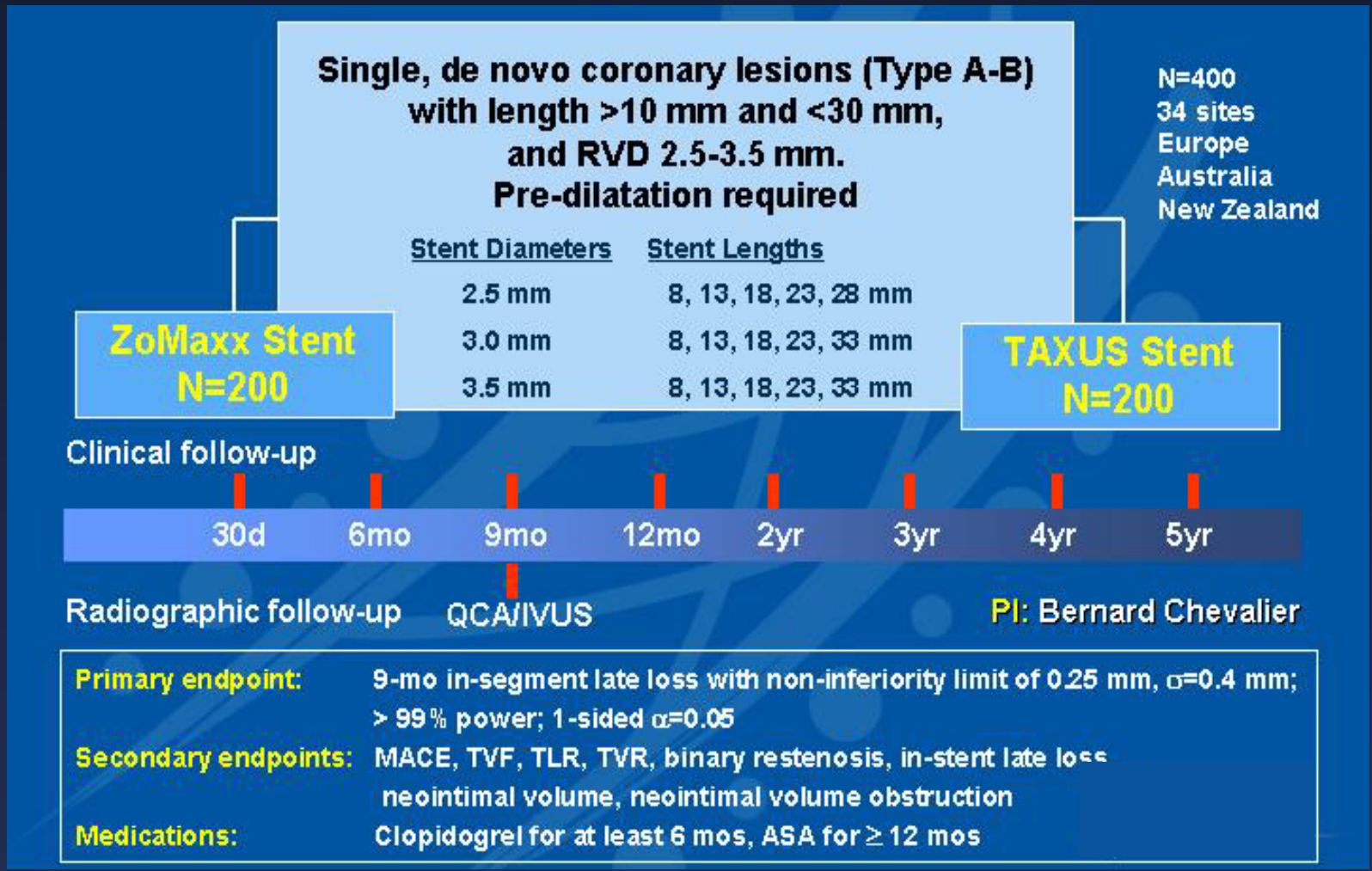
Key Components

Abbott ZoMaxx DES System

- **TriMaxx Multi-Alloy Stent**
  - thinnest layers of stainless steel
  - good radio-opacity
- **Drug**
  - better uptake in the artery
  - lower serum concentration
- **Polymer**
  - different form of phosphorylcholine than Medtronic

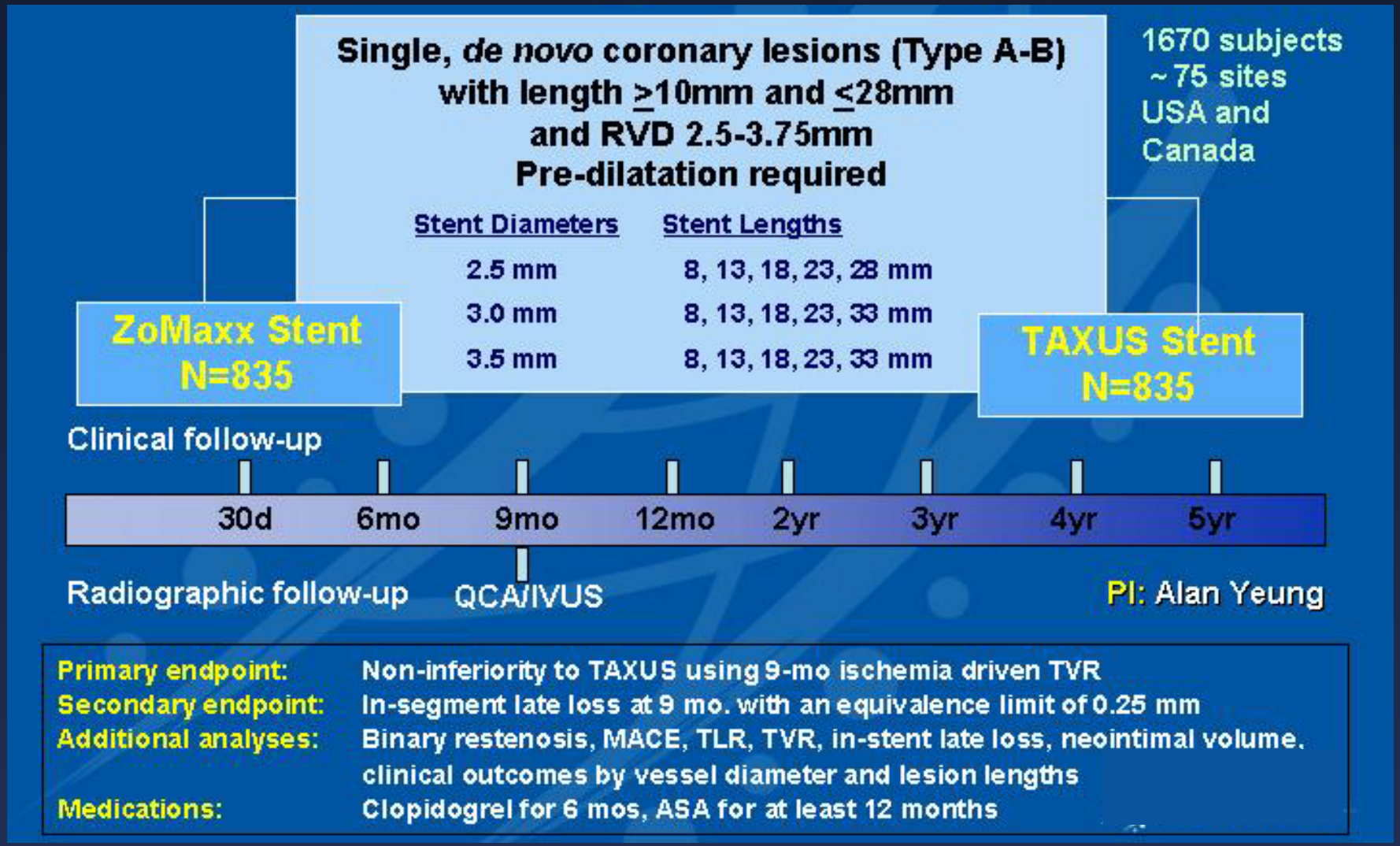
Zomaxx I Trial (n=400)

Randomized, Non-inferiority Trial, Angiographic Endopoint



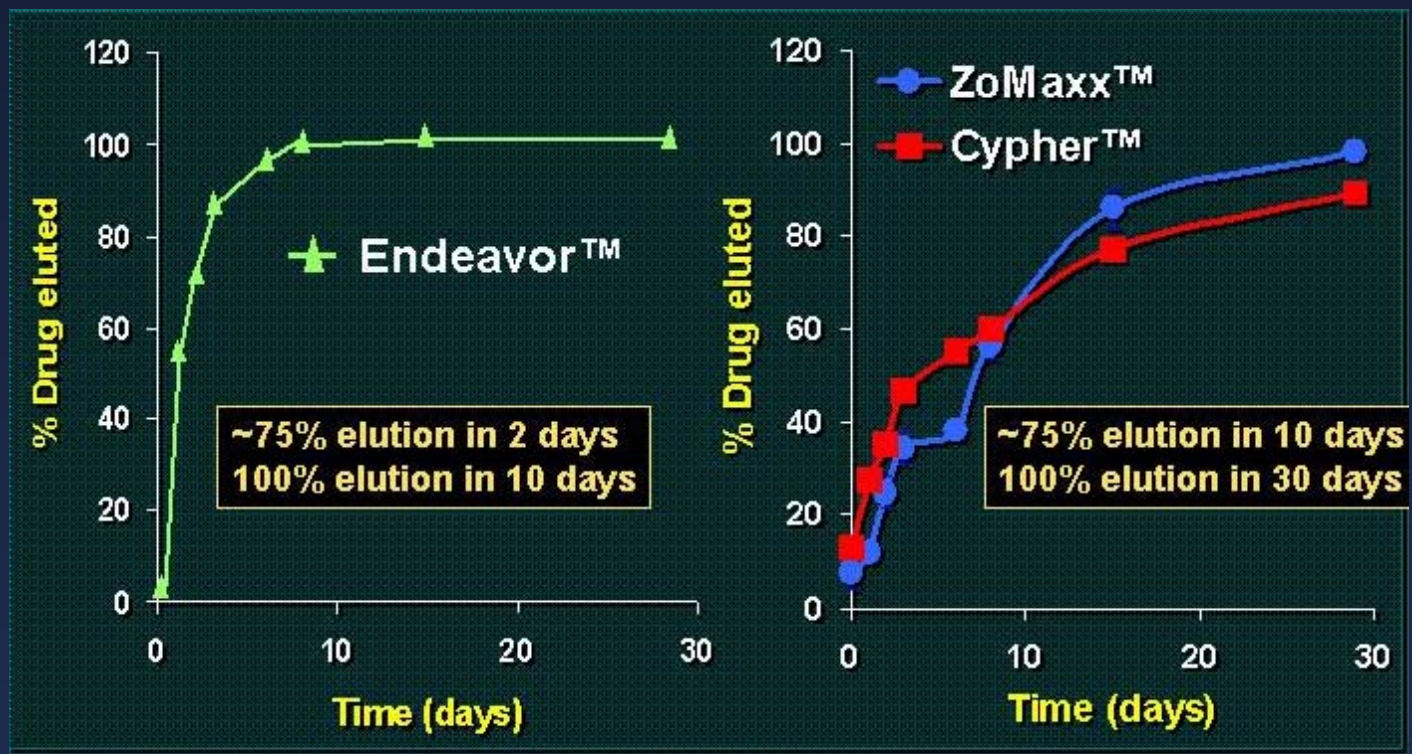
Zomaxx II Trial (n=1,670)

Randomized, Non-inferiority Trial, Angiographic Endopoint



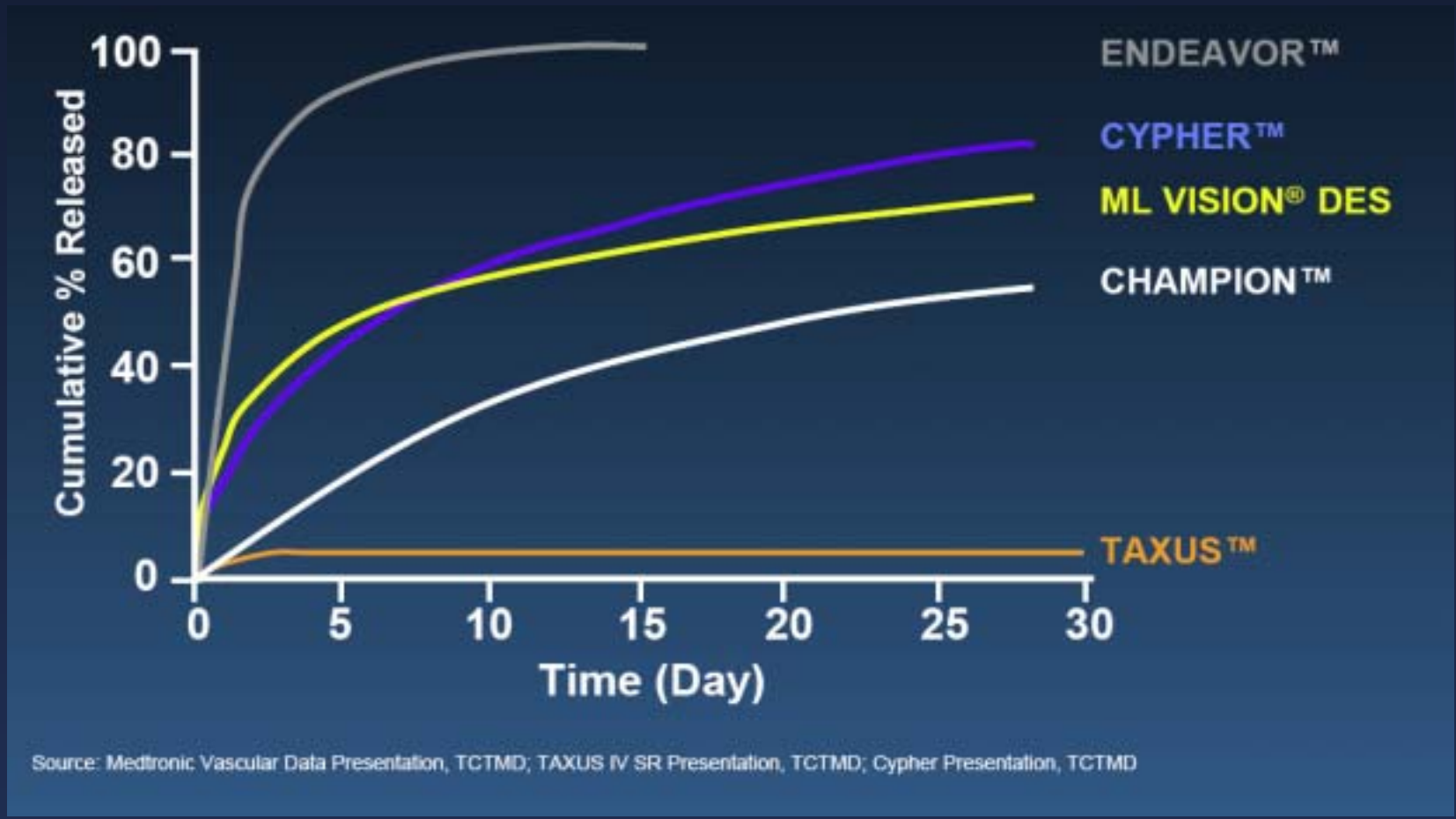
Primary endpoint:	Non-inferiority to TAXUS using 9-mo ischemia driven TVR
Secondary endpoint:	In-segment late loss at 9 mo. with an equivalence limit of 0.25 mm
Additional analyses:	Binary restenosis, MACE, TLR, TVR, in-stent late loss, neointimal volume. clinical outcomes by vessel diameter and lesion lengths
Medications:	Clopidogrel for 6 mos, ASA for at least 12 months

Comparision of in vivo Elution Rates
Rabbit iliac models



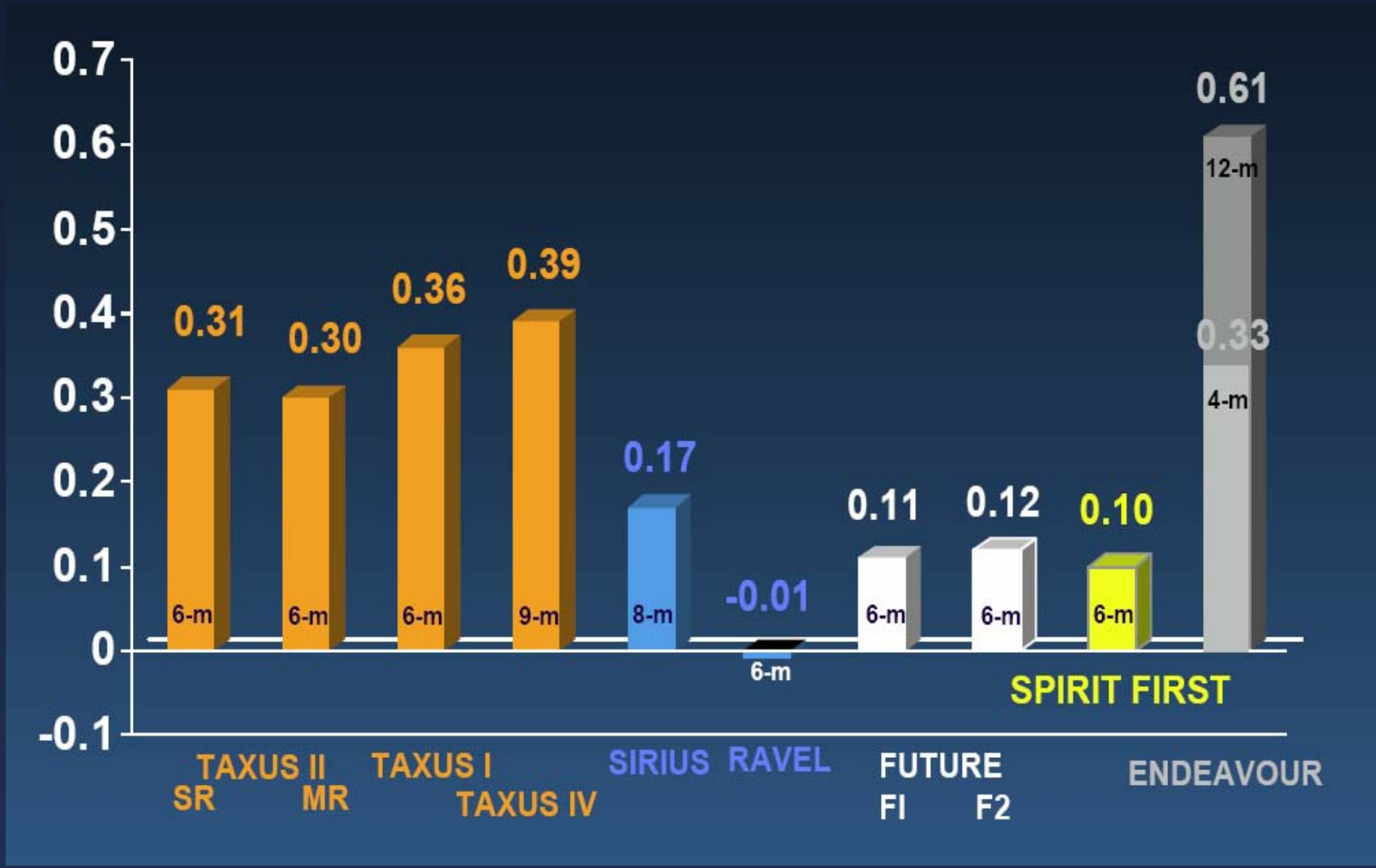
ZoMaxx and Cypher data from B. Chevalier, EuroPCR 2004
Endeavor data from G. Laarman, EuroPCR 2004

DES Release Profiles



Source: Medtronic Vascular Data Presentation, TCTMD; TAXUS IV SR Presentation, TCTMD; Cypher Presentation, TCTMD

Comparision of In-Stent Late-Loss



Other programs are in full swing

- Conor (paclitaxel-elution from a bioabsorbable polymer in laser-drilled wells)
- Biosensors (biolimus A9-elution from a bioabsorbable PLA polymer)
- Sorin (tacrolimus-elution from a carbofilm coated stent)
- Orbus (stent-based endothelial progenitor cell capture technology)

ORBUS Medical Technology

EPC Capture R-Stent Program Changes

Item	HEALING-1	HEALING-2
Device	Wet, hand crimped prototype, supplied in sodium azide preservative and required rinsing before use	Dry formulation that preserves the antibody structure and activity; pre-mounted on Evolution 2SDS
Sterilization	Gamma, 15-25 Gy	Gamma, <15 Gy
Bioactivity	Significant reduction in activity with sterilization	Stable with sterilization, comparable to activity as coupled
TVR	9.1%	N/A
Late loss	0.63 vs. bare 0.8-0.85	N/A
Stent thrombosis	0	0
Patients	16, single center, Netherlands	60 at 10 centers in Belgium, Germany, and the Netherlands
Status	Completed	Enrollment started May 2004
Results	*Primary endpoint:* 30 Day MACE = 0%	Data due at PCR 2005