ZoMaxx
Zotarolimus - Eluting Coronary Stent

Technical Aspects and an Update on the EU and US Zomaxx Trials

Drug Eluting Summit I

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Conflict of Interest

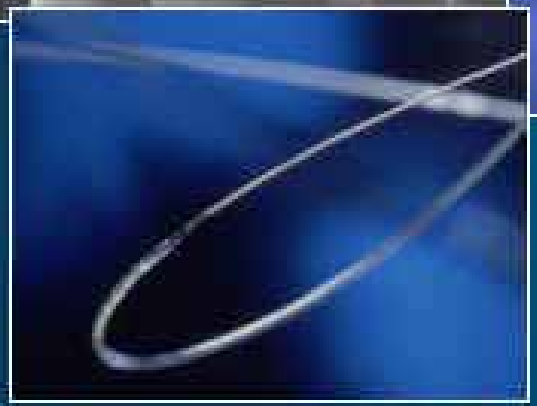
- Member of SAB to Abbott Vascular
- PI of Zomaxx II

ZoMaxx
Zotarolimus-Eluting Coronary Stent

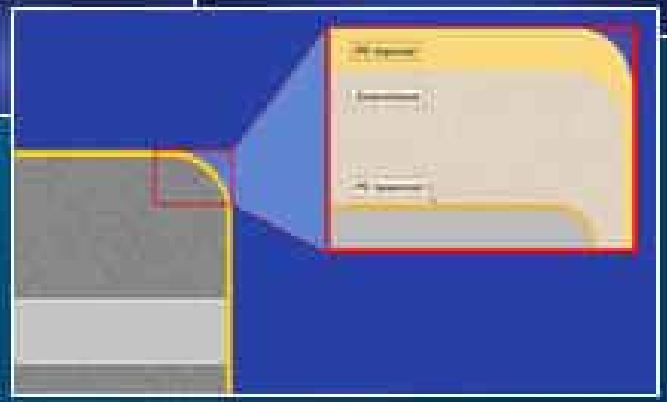
Triplex Material*

O.C.C. Technology

Zotarolimus



Stent Delivery Catheter



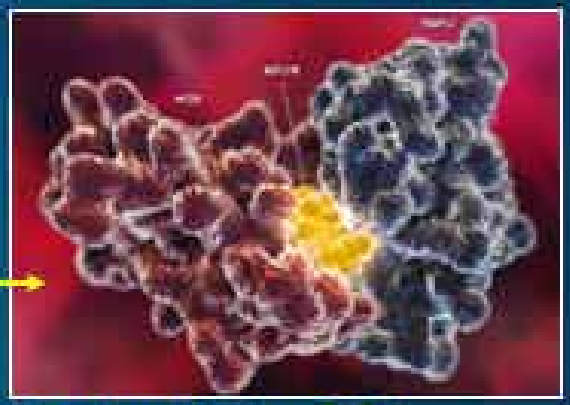
Pharmacoat

*Triplex is a trademark of Uniform Tubing, Inc.

Zotarolimus
Mode of Action

Zotarolimus

Zotarolimus binds with FKBP-12 protein



Complex blocks mTOR signal transduction

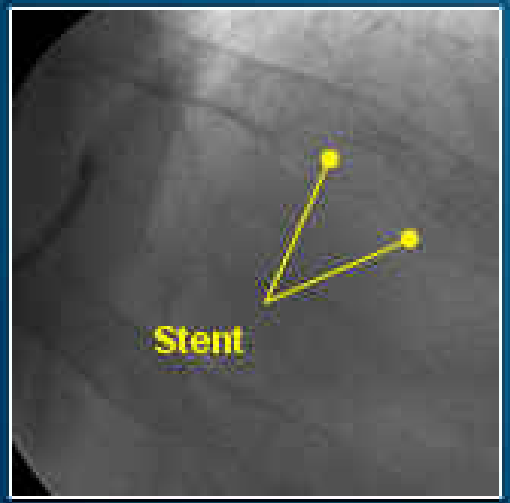
- Zotarolimus binds to the intracellular protein FKBP-12
- Zotarolimus and FKBP-12 form a trimeric complex with the protein kinase termed mammalian target of rapamycin (mTOR)
- Zotarolimus inhibits mTOR's activity, blocking cell cycle progression
- Primary mode of action is anti-proliferative
  - Secondary mode of action is anti-inflammatory

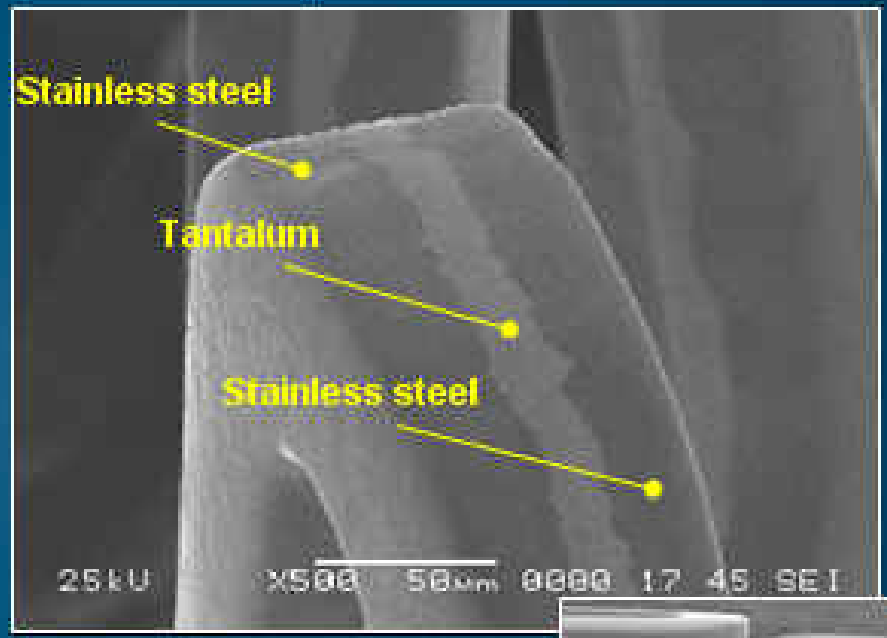
All graphics are artist's impressions only.

Triplex Stent Material

- Stainless steel/Tantalum/Stainless steel composite
  - 0.0007" Tantalum layer
  - 0.0029" strut thickness

= 0.074mm

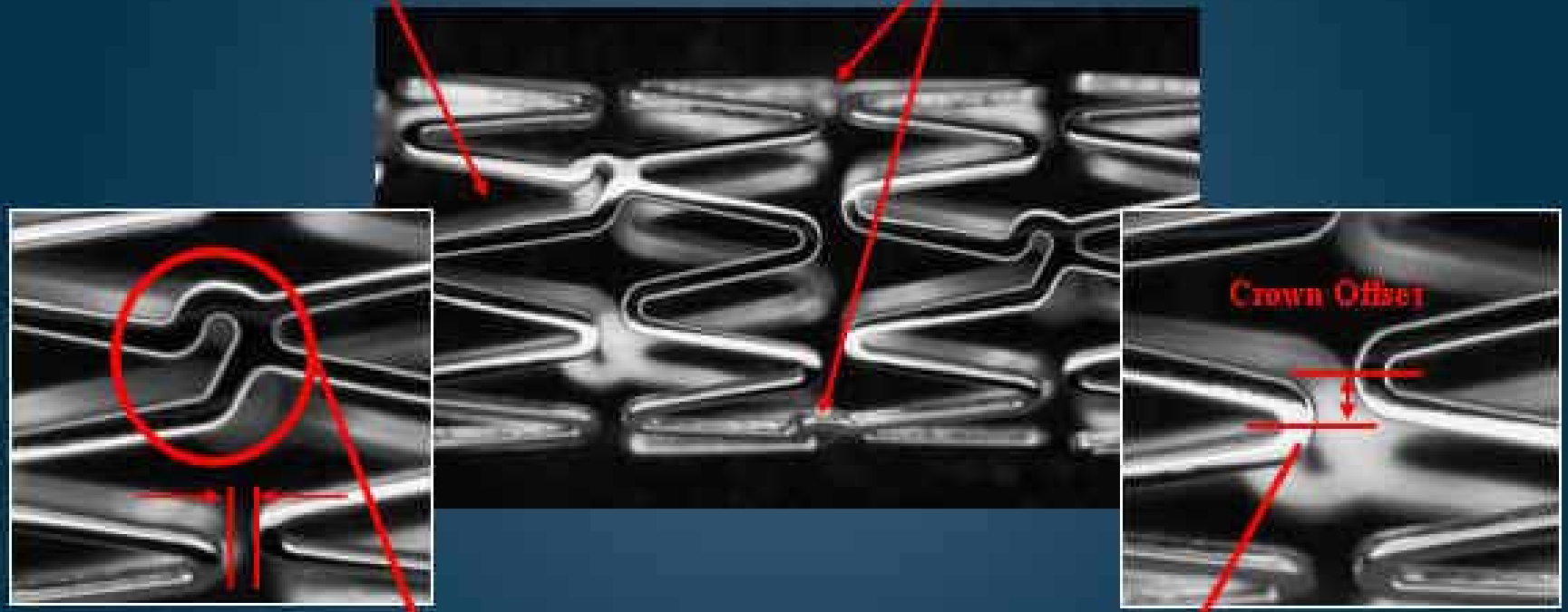




TriMaxx Stent Pattern

8 or 10 cells around perimeter for optimum scaffolding

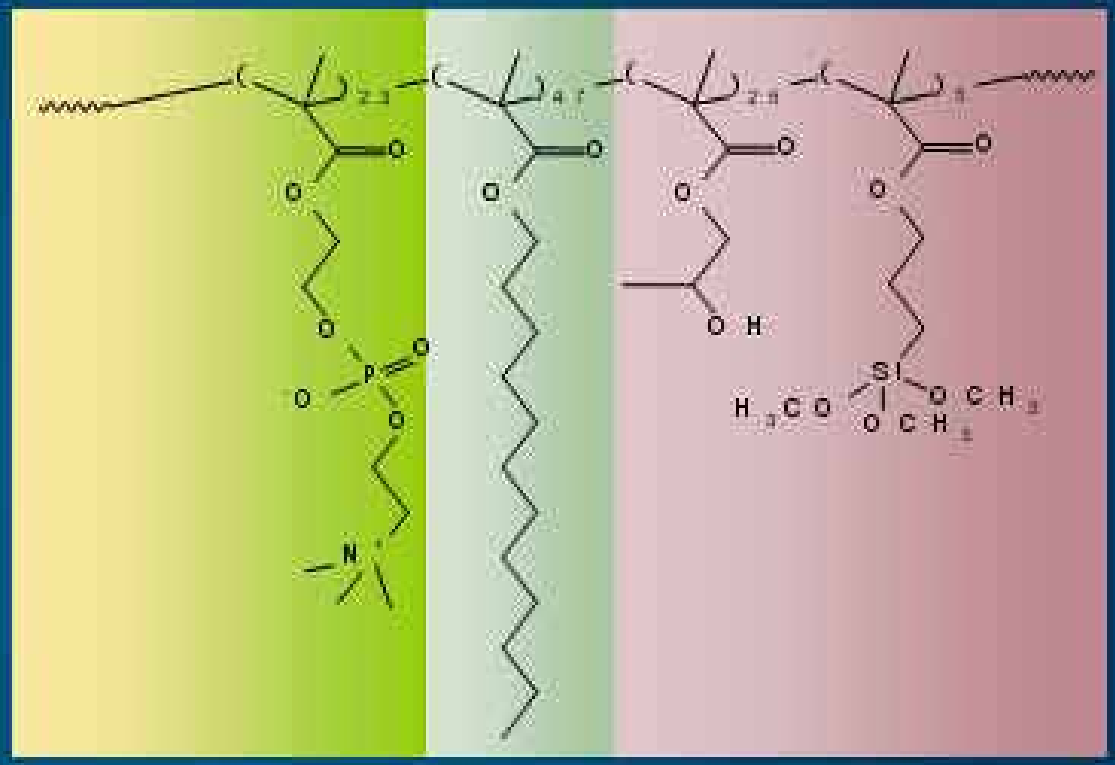
2 connections between rings for optimum flexibility



O.C.C. (Offset Crown Connection): proprietary connection pulls the rings closer together and offsets the apexes of the crowns for improved scaffolding

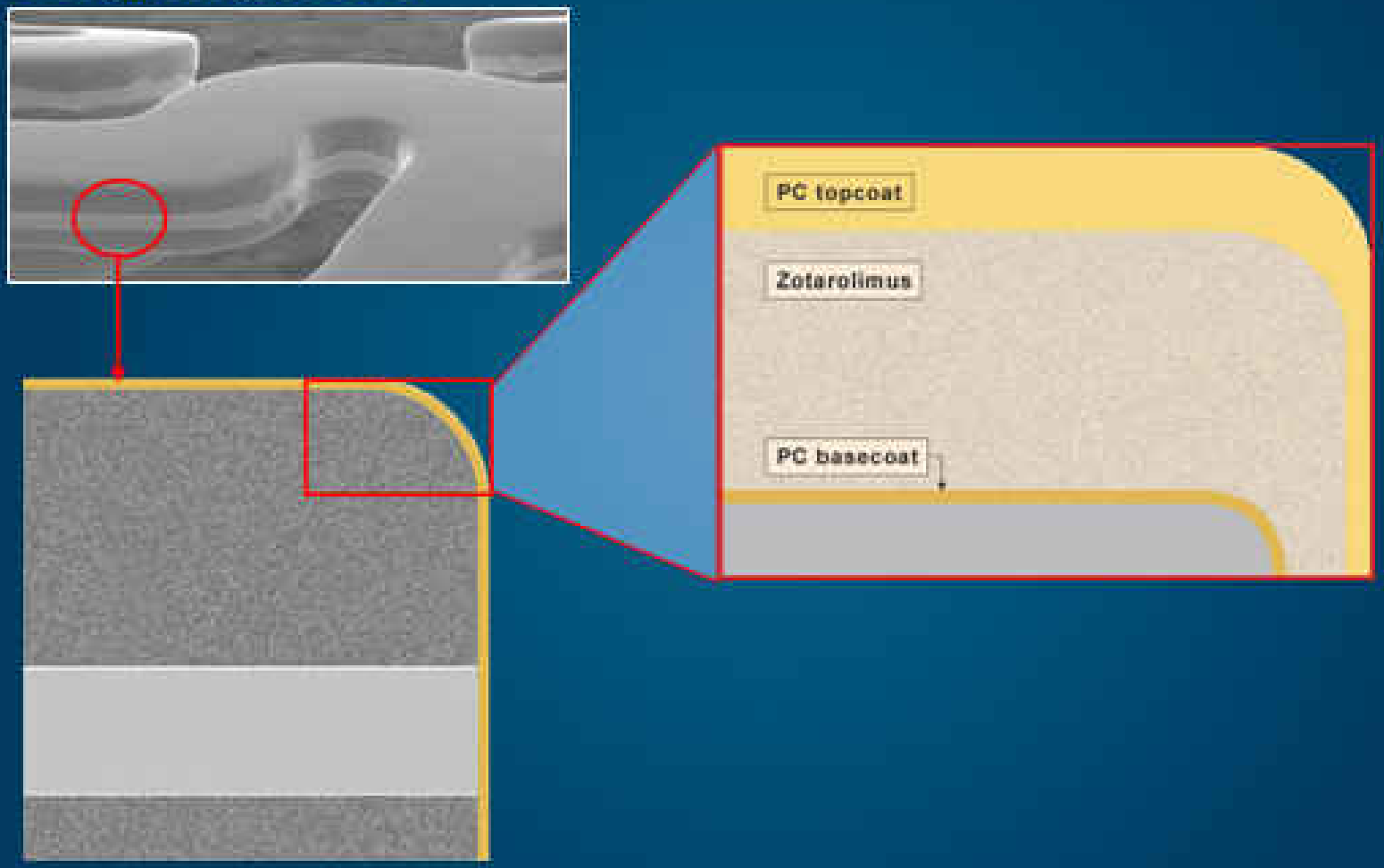
Phosphorylcholine (PC)

- PC coating mimics body's own chemistry
  - Hema-PC: mimics outer membrane of red blood cell for **biocompatibility**
  - Lauryl: hydrophobic for adhesion and **stability with the stent surface**
  - HPMA & TSMA: **cross-linking for robustness**



Lewis AL, Cumming ZL, Goreki HH, Kirkwood LC, Tolhurst LA, Stratford PW. Cross linkable coatings from phosphorylcholine-based polymers. Biomaterials 2001; 22:99–111.

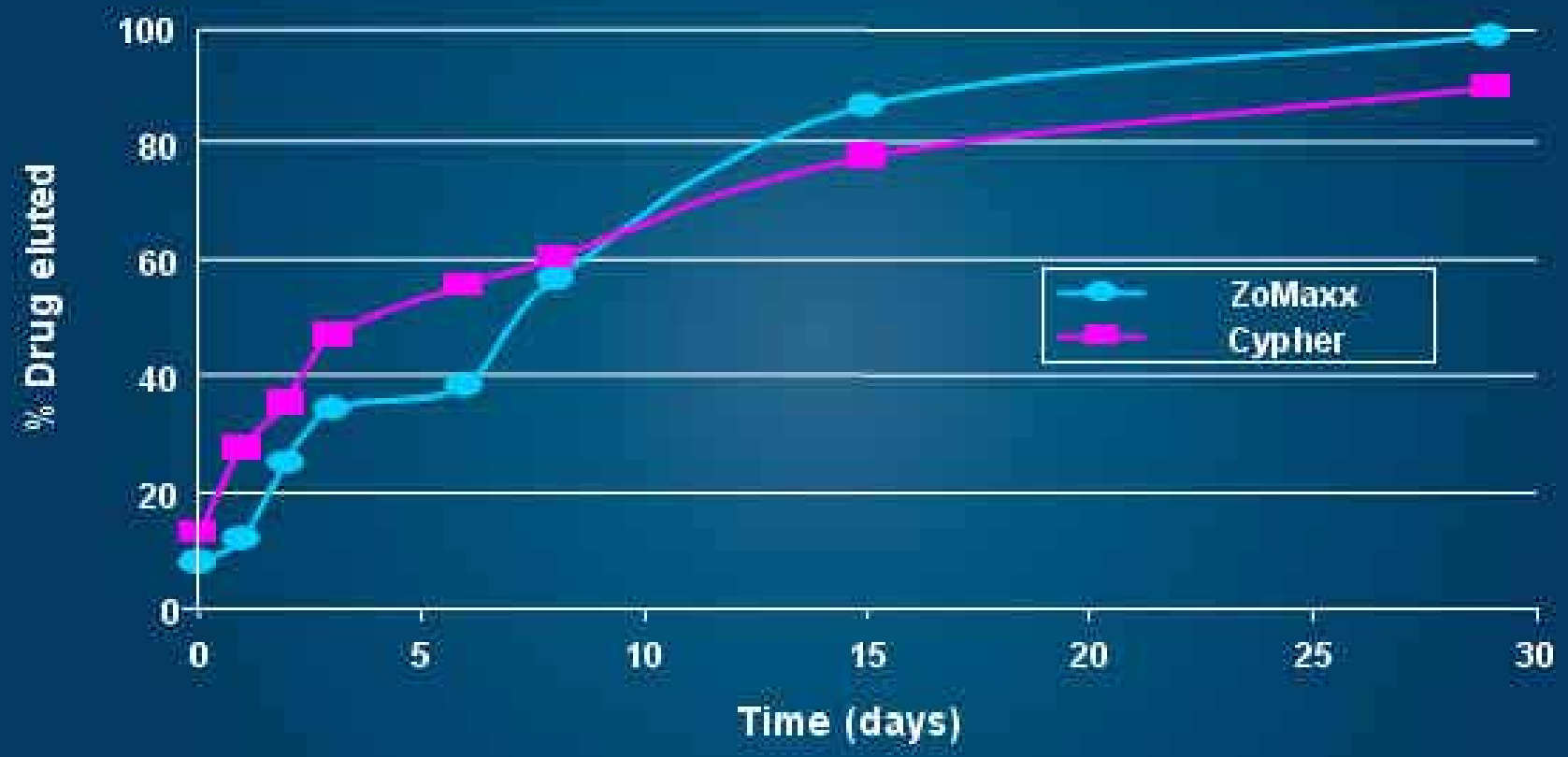
The ZoMaxx Stent
Pharmacoat



All graphics are artist's impressions only.

ZoMaxx
Tetrahelimus - Eluting Coronary Stent

ZoMaxx Stent vs. Cypher Stent
Drug Elution Rates



DeVall M, JIQ, Clifford A, Barry CM, Nowak SA, Sabaj KM, Zielinski DA, Smith G, Zhang J, Cromack K, Dube H, Schwartz LB, Krasnla RW. ABT-578 elution profile and arterial penetration using the ZoMaxx drug-eluting stent (abstract). Am J Cardiol. 2004; 94:223E.; n=4 stents/timepoint; mean ± SEM; Cypher is a trademark of Johnson & Johnson; results not indicative of clinical effectiveness.

ZoMaxx Clinical Program

TRIMAXX study	FIM study 100 patients, single arm, clinical endpoint
ZOMAXX IVUS	FIM study 40 patients, single arm, IVUS endpoint
ZOMAXX I	International pivotal study 400 patients, RCT, angiographic endpoint
ZOMAXX II	US pivotal study 1670 patients, RCT, clinical endpoint
ZOMAXX EUROPE	European single/double vessel 900 patients, single arm, clinical endpoint

ZoMaxx
Zotarolimus-Eluting Coronary Stent

TriMaxx Trial

PI: Alex Abizaid

Single-vessel, *de novo* coronary lesions (Type A-B), length ≥ 10 mm and ≤ 15 mm; RVD ≥ 3.0 ≤ 3.75 mm

Stent diameters	Stent lengths
3.0 mm	18 mm
3.5 mm	18 mm

100 Subjects

Up to 5 sites
- Brazil
- Germany

Clinical follow-up

30d **6mo**

QCA follow-up

Primary endpoint	MACE at 30 days
Secondary endpoints	MACE, TLR, TVR, binary restenosis, late loss at 6 months
Platelet inhibition	Clopidogrel/Ticlid (30 days), ASA 100 mg cont.

TriMaxx Trial
Patient Demographics (n=50)

	% (n) or mean ± SD
Age (years)	59.0 ± 10.4
Male gender	68% (34/50)
Prior MI	58% (29/50)
Prior PCI	18% (9/50)
Diabetes Mellitus	22% (11/50)
Unstable angina	24% (12/50)
Hyperlipidemia	76% (38/50)
Current Smoker	20% (10/50)
History of CHF	2% (1/50)
Mean LVEF (%) (n = 45)	52.2% ± 6.0%

TriMaxx Trial
Procedural Results (n=50)

	% (n) or mean ± SD
Lesion success	100% (50/50)
Device success	98% (49/50)
Procedure success	100% (50/50)
Post-procedure	
In-stent MLD (mm)	2.71 ±0.32
In-stent acute gain (mm)	1.83 ±0.45
In-stent DS (%)	5.1% ±7.0%
In-segment MLD (mm)	2.31 ±0.37
In-segment DS (%)	19.6% ±5.9%

Lesion success <30% residual in-stent diameter stenosis
Device success <30% residual in-stent diameter stenosis with assigned stent
Procedure success <30% residual in-stent diameter stenosis without in-hospital MACE

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TriMaxx Trial
Angiographic Results at 6 Months (n=45)

	% (n) or mean ± SD
In-stent	
MLD (mm)	1.83 ±0.59
Diameter stenosis (%)	35% ±18%
Late Loss (mm)	0.89 ±0.48
Restenosis (%)	22%
In-segment	
MLD (mm)	1.75 ±0.57
Diameter stenosis (%)	38% ±17%
Late Loss (mm)	0.56 ±0.51
Restenosis (%)	22%

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ZOMAXX IVUS Trial

PI: Alex Abizaid

Single-vessel, *de novo* coronary lesions (Type A-B), length ≥ 10 mm and ≤ 15 mm; RVD ≥ 2.75 ≤ 3.25 mm

Stent diameters	Stent lengths
3.0 mm	18 mm

40 Subjects

1 Site – Brazil

Enrollment completed July 2005

Clinical follow-up

30d 4mo 6mo 12mo

QCA/IVUS follow-up

Primary endpoint	Percent in-stent net volume obstruction at 4 months (IVUS)
Secondary endpoints	MACE, TVF, TLR, TVR, binary restenosis, in-stent late loss, neointimal volume, device, lesion and procedure success
Platelet inhibition	Clopidogrel/Ticlid (180 days), ASA 100 mg cont.

ZOMAXX IVUS
Enrollment and Follow-up

Enrollment	April – July 2005
Total patients enrolled	40
Duration of follow-up	3.8 ± 0.3 months
Clinical follow-up	100% (40/40)
Angiographic follow-up	92.5% (37/40)
IVUS follow-up	90% (36/40)

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ZOMAXX IVUS
Patient Demographics (n=40)

	n (%) or mean ± SD
Age (years)	**59** ± 9
Male gender	**22** (55%)
Prior MI	**17** (43%)
Prior PCI	**10** (25%)
Diabetes mellitus	**16** (40%)
Diet-controlled	**4** (10%)
Oral hypoglycemic-controlled	**10** (25%)
Insulin-dependent	**2** (5%)
Hyperlipidemia	**32** (80%)
Current smoker	**9** (23%)
LVEF	**53**% ± 6%

ZOMAXX IVUS
Baseline Vessel and Lesion Characteristics (n=40)

	n (%) or mean ± SD
LAD	**18** (45%)
RCA	**12** (30%)
LCX	**10** (25%)
Moderate/severe tortuosity	**2** (5%)
Moderate/severe calcification	**7** (18%)
B2/C lesions	**24** (60%)
Lesion length (mm)	**14.4** ± 3.3
RVD (mm)	**2.77** ± 0.29
MLD (mm)	**0.84** ± 0.28
Diameter stenosis (%)	**70** ± 10%

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ZOMAXX IVUS
Post-Procedural Results (n=40)

	n (%) or mean ± SD
Lesion success	**40** (100%)
Device success	**40** (100%)
Procedure success	**40** (100%)
In-stent MLD (mm)	**2.69** ± 0.25
In-stent DS (%)	**5.1** ± 5.3%
In-stent acute gain (mm)	**1.87** ± 0.35
In-segment MLD (mm)	**2.32** ± 0.34
In-segment DS (%)	**19** ± 7%
In-segment acute gain (mm)	**1.49** ± 0.38
Total stent length (mm)	**17.7** ± 2.1

Lesion success defined as <30% residual in-stent diameter stenosis; Device success defined as <30% residual in-stent diameter stenosis with assigned stent
Procedure success defined as <30% residual in-stent diameter stenosis without in-hospital MACE.

ZOMAXX IVUS
MACE (n=40)

	In-hospital	30-days	4-months
Q-wave MI	0	0	0
Non Q-wave MI	0	0	0
TVR (ischemia-driven)	0	0	0
CABG	0	0	0
Cardiac death	0	0	0
MACE	**0% (0)**	**0% (0)**	**0% (0)**

No acute, sub-acute or late stent thrombosis through 4 months

1 asymptomatic patient with QCA of 66% at a proximal segment had non-ischemia driven TLR

ZOMAXX IVUS Results
Angiographic Results (n=37)

	% (n) or mean ± SD
In-stent	
MLD (mm)	2.51 ± 0.43
Diameter stenosis	10% ± 14%
Late loss (mm)	**0.20 ± 0.35**
Restenosis	2.7% (1)
In-segment	
MLD (mm)	2.16 ± 0.46
Diameter stenosis	23% ± 13%
Late loss (mm)	**0.17 ± 0.35**
Restenosis	5.4% (2)

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ZOMAXX IVUS
Angiographic Results Stratified by Diabetes

	Non-diabetic (n=24)	Diabetic (n=16)
RVD (mm)	2.74 ± 0.33	2.81 ± 0.22
Lesion length (mm)	14.0 ± 2.4	14.9 ± 4.4
Angiographic follow-up	23 (96%)	14 (88%)
In-stent		
MLD (mm)	2.56 ± 0.46	2.43 ± 0.39
Diameter stenosis	8 ± 14%	14 ± 14%
Late loss (mm)	**0.14 ± 0.34**	**0.31 ± 0.37**
In-segment		
MLD (mm)	2.18 ± 0.51	2.14 ± 0.38
Diameter stenosis	22 ± 15%	25 ± 10%
Late loss (mm)	0.18 ± 0.36	0.17 ± 0.35

ZOMAXX IVUS
IVUS results (n=36)

	mean ± SD or n
Stent volume (mm^3)	136 ± 28
Lumen volume (mm^3)	127 ± 26
Neointimal volume (mm^3)	9.1 ± 10.2
Neointimal volume obstruction (%)	**6.5% ± 6.2%**
Neointimal volume index (mm^3/mm)	0.4 ± 0.4
Stent incomplete apposition (SIA)	4*
Persistent	4
Resolved	1
New (late acquired)	0

No late acquired malapposition

* Two separate sites of SIA observed in one patient

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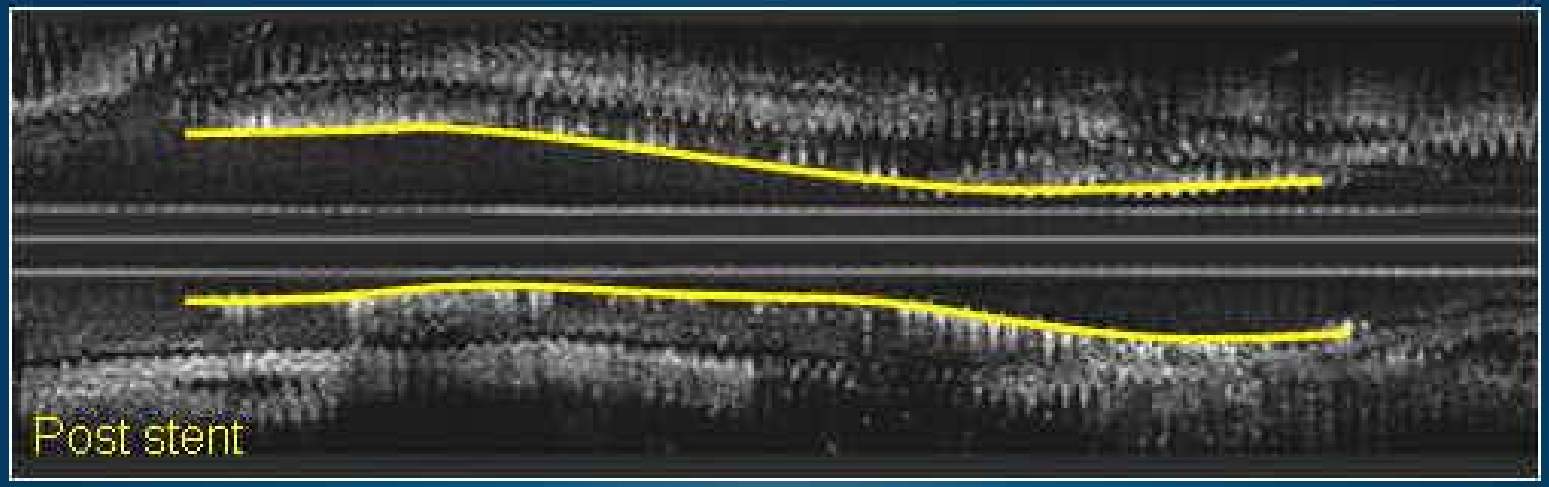
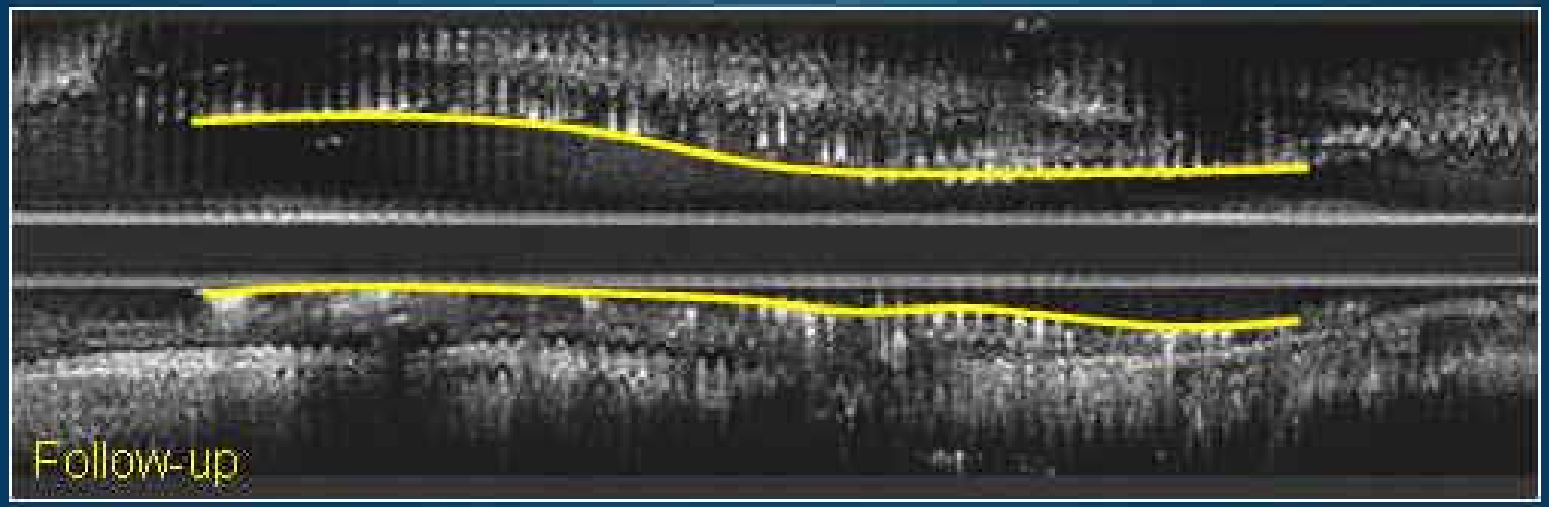
ZOMAXX IVUS – 3D Reconstruction





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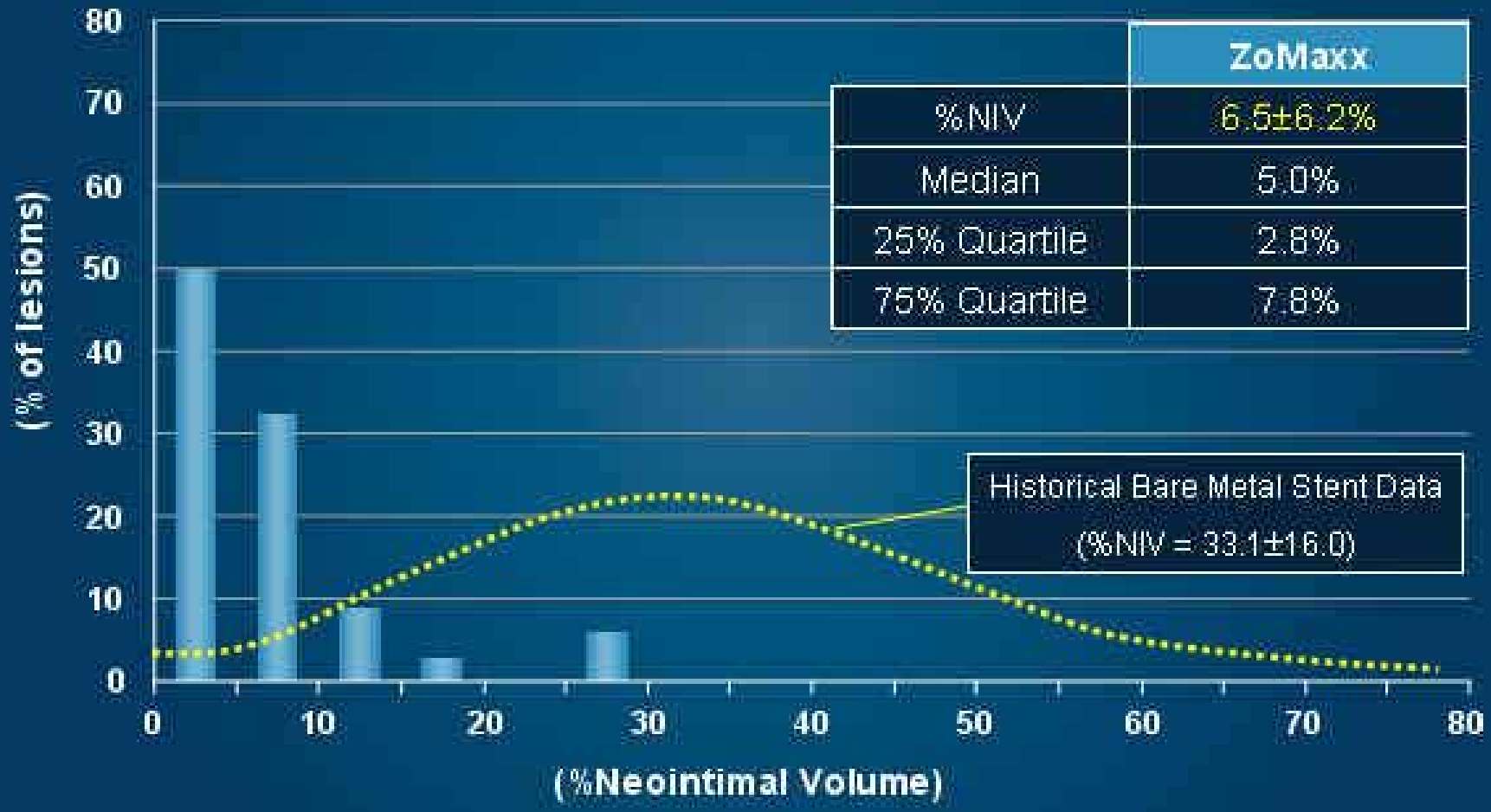
ZOMAXX IVUS
Distribution of %Neointimal Volume



	ZoMaxx
%NIV	6.5±6.2%
Median	5.0%
25% Quartile	2.8%
75% Quartile	7.8%

Slide courtesy of Peter Fitzgerald, Stanford University

ZOMAXX IVUS
Comparison to other DES 4-month results

	Cypher FIM[1]	PISCES (Formulation D5)[2]	ENDEAVOR I[3]	ZOMAXX IVUS
Sample size	15	39	100	**40**
Diabetics	**27%**	**10%**	**16%**	**40%**
RVD (mm)	2.98 ± 0.4	2.73 ± 0.41	2.96 ± 0.47	**2.77 ± 0.29**
Lesion length (mm)	**12.9 ± 2.0**	**9.4 ± 3.2**	**10.9 ± 3.1**	**14.4 ± 3.3**
MACE	0%	2.6%	2.0%	**0%**
Angiographic F/U	100%	95%	97%	**95%**
In-stent late loss (mm)	0.09 ± 0.30	0.38 ± 0.34	0.33 ± 0.36	**0.20 ± 0.35**
In-segment late loss (mm)	0.16 ± 0.30	0.21 ± 0.29	0.21 ± 0.40	**0.17 ± 0.35**

Clinical trial data is not directly comparable

1 Sousa JE et al. Lack of neointimal proliferation after implantation of sirolimus-coated stents in human coronary arteries: A quantitative coronary angiography and three-dimensional intravascular ultrasound study. Circ. 2001; 103:192-195.
2 D5 represents 10 µg paxitaxel release over "30 days"; Aoki J, et al. One-year clinical outcome of various doses and pharmacokinetic release of paclitaxel eluted from an erodable polymer - insights from the Paclitaxel In-stent Controlled Elution Study (PISCES). EuroIntr. 2005; 2:165-172.
3 Meredith IT, et al. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I Trial. EuroIntr. 2005; 2:157-164.

Conclusions

Safe

- No MACE or stent thrombosis at 4 months

Minimizes neointimal hyperplasia

- In-stent late loss of 0.20 ± 0.35mm at 4 months
- Neointimal volume of 9.1 ± 10.2 mm^3

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ZOMAXX I Trial

PI: Bernard Chevalier

Single-vessel, *de novo* coronary lesions (Type A-B), length ≥ 10 mm and ≤ 30 mm; RVD ≥ 2.5 ≤ 3.5 mm
Pre-dilatation required

Stent diameters	Stent lengths
2.5 mm	8, 18, 23, 28 mm
3.0 mm	8, 18, 23, 33 mm
3.5 mm	8, 18, 23, 33 mm

400 Subjects

45 sites
Europe
Australia
New Zealand

ZoMaxx Stent
N = 200

Taxus Stent
N = 200

Randomized, Non-inferiority Trial

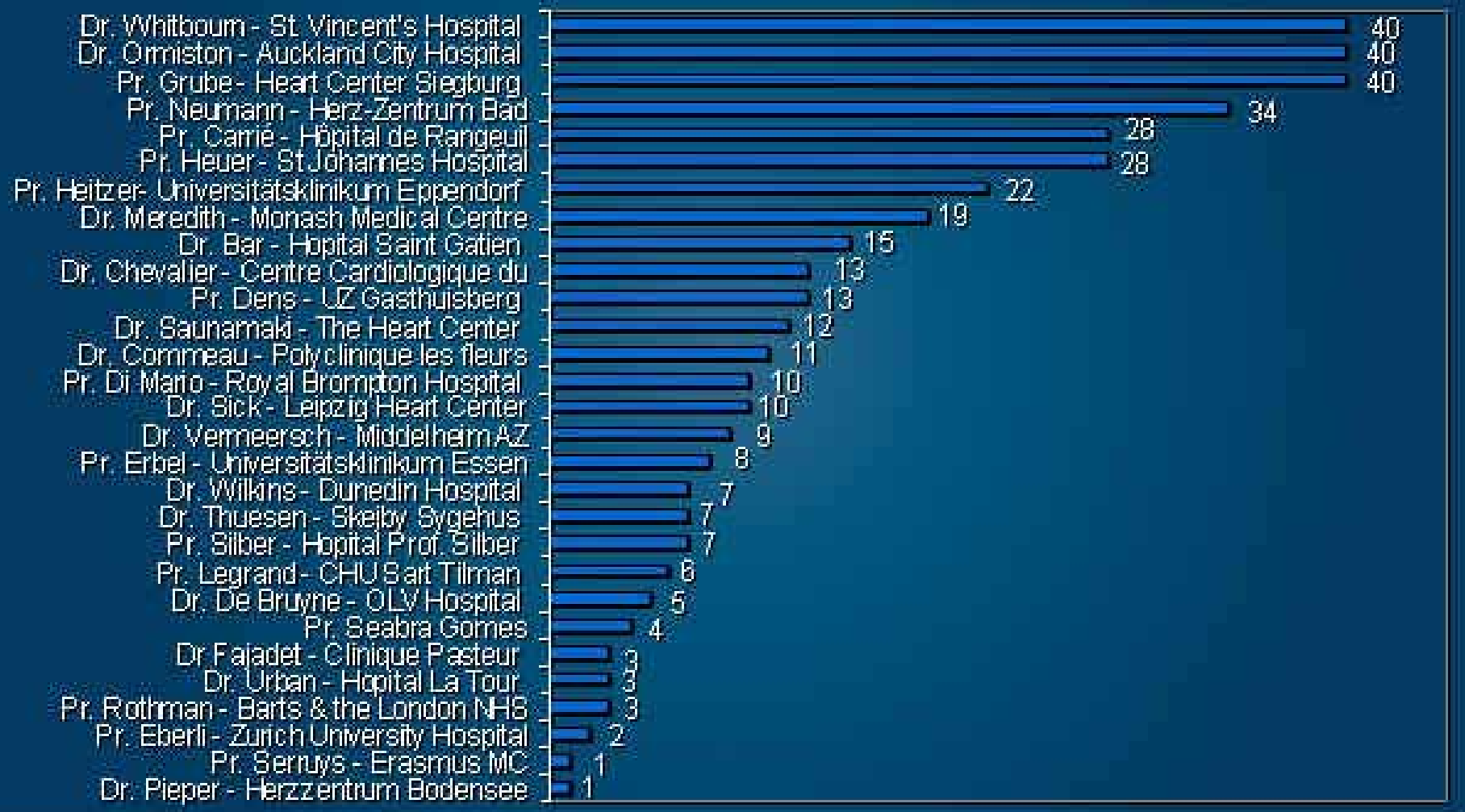
Clinical follow-up: 30d, 6mo, 9mo, 12mo, 2yr, 3yr, 4yr, 5yr

QCA/IVUS follow-up: 9mo

Primary endpoint:	9-mos. In-segment late loss with equivalency limit of 0.25 mm, σ=0.4 mm; >99% power; 1-sided α=0.05
Secondary endpoints:	MACE, TVF, TLR, TVR, binary restenosis, in-stent late loss, neointimal volume, neointimal volume obstruction
Medications:	Clopidogrel 75 mg QD for at least 6 months, ASA 100 mg QD ≥ 12 months
Stratification:	Site

ZoMaxx
Zotarolimus - Eluting Coronary Stent

ZOMAXX I Patient Enrollment



ZoMaxx
Zotarolimus-Eluting Coronary Stent

ZOMAXX II Trial

PIs: Alan Yeung & Bill Gray

Single-vessel, *de novo* coronary lesions (Type A-B), length ≥ 10 mm and ≤ 28 mm; RVD ≥ 2.5 ≤ 3.75 mm
Pre-dilatation required

Stent diameters	Stent lengths
2.5 mm	8, 13, 18, 23, 28 mm
3.0 mm	8, 13, 18, 23, 33 mm
3.5 mm	8, 13, 18, 23, 33 mm

1670 Subjects

75 US sites
Up to 30 OUS

ZoMaxx Stent
N = 835

Randomized, Non-inferiority Trial, Clinical Endpoint

Taxus Stent
N = 835

Clinical follow-up

30d **6mo** **9mo** **12mo** **2yr** **3yr** **4yr** **5yr**

QCA/IVUS follow-up

Primary endpoint:	Non-inferiority to Taxus using 9-mo ischemia driven target vessel revascularization (TVR)
Secondary endpoints:	In-segment late loss at 9-mo. (QCQ)
Additional Analyses:	MACE, TLR, TVR, binary restenosis, in-stent late loss, neointimal volume, clinical outcomes by vessel diameter and lesion lengths
Medications:	Clopidogrel 75 mg QD for 6 months, ASA 325 mg QD for at least 12 months

ZOMAXX II Trial Update

- We have enrolled over 350 patients
- Currently operational in 24 sites
- Recently received FDA approval to expand to all 75 US sites
- Next steps: initiate all sites, initiate ZOMAXX PK Study

ZOMAXX Europe

Up to two *de novo* coronary lesions (Type A-B),
length ≥ 10 mm and ≤ 25 mm (for 2.5 mm stents), ≥ 10 mm and ≤ 30 mm (for 2.75, 3.0 and 3.5 mm stents); RVD ≥ 2.5 ≤ 3.75 mm
Pre-dilatation required

900 Stents

Stent diameters	Stent lengths
2.5 mm	8, 18, 23, 28 mm
2.75 mm	8, 18, 23, 33 mm
3.0 mm	8, 18, 23, 33 mm
3.5 mm	8, 18, 23, 33 mm

Single-arm prospective trial with clinical endpoint

Clinical follow-up

30d | 6mo* | 9mo | 12mo* | 2yr* | 3yr* | 4yr* | 5yr*

*Telephone contact

Primary endpoint	Target lesion revascularization (TLR) at 9-mos.
Secondary endpoints	Device, lesion and procedural success; major adverse cardiac events (MACE) defined as cardiac death, myocardial infarction (Q wave and non-Q wave) at 30-days and 9-mos, target vessel revascularization (TVR) at 9-mos, target vessel failure (TVF) at 9-mos.
Platelet inhibition	Clopidogrel ≥ 75 mg QD for ≥ 6 months, ASA ≥ 75 mg QD for ≥ 12 months

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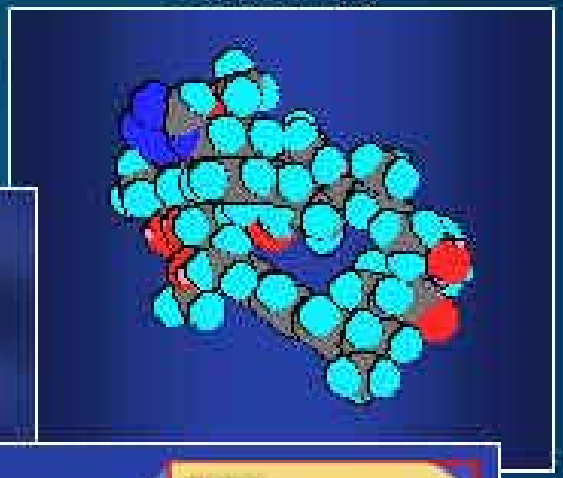
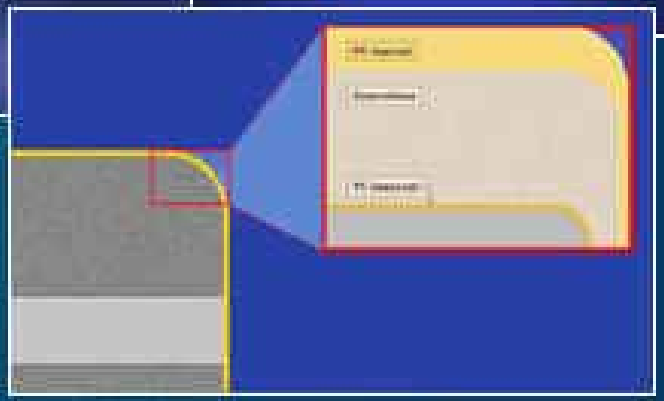
Triplex Material*

O.C.C. Technology

Zotarolimus



Stent Delivery Catheter



Pharmacoat

*Triplex is a trademark of Uniform Tubing, Inc

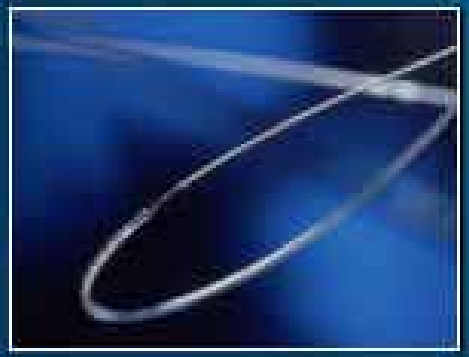
ZOMAXX IVUS

Does Elution Rate Matter?

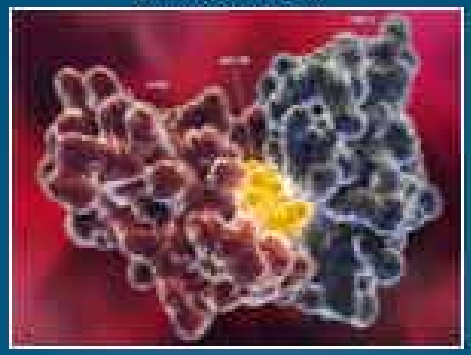
ZoMaxx

TriMaxx Stent

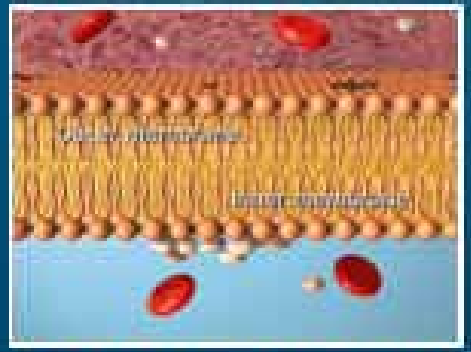
Stent Delivery System



Zotarolimus

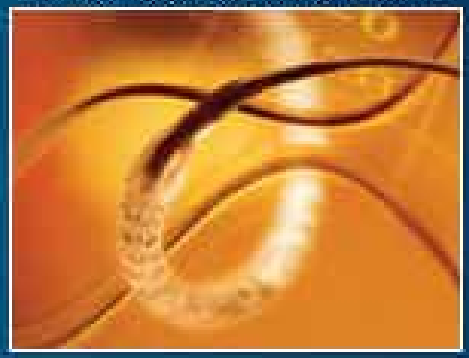


PC Technology



Endeavor

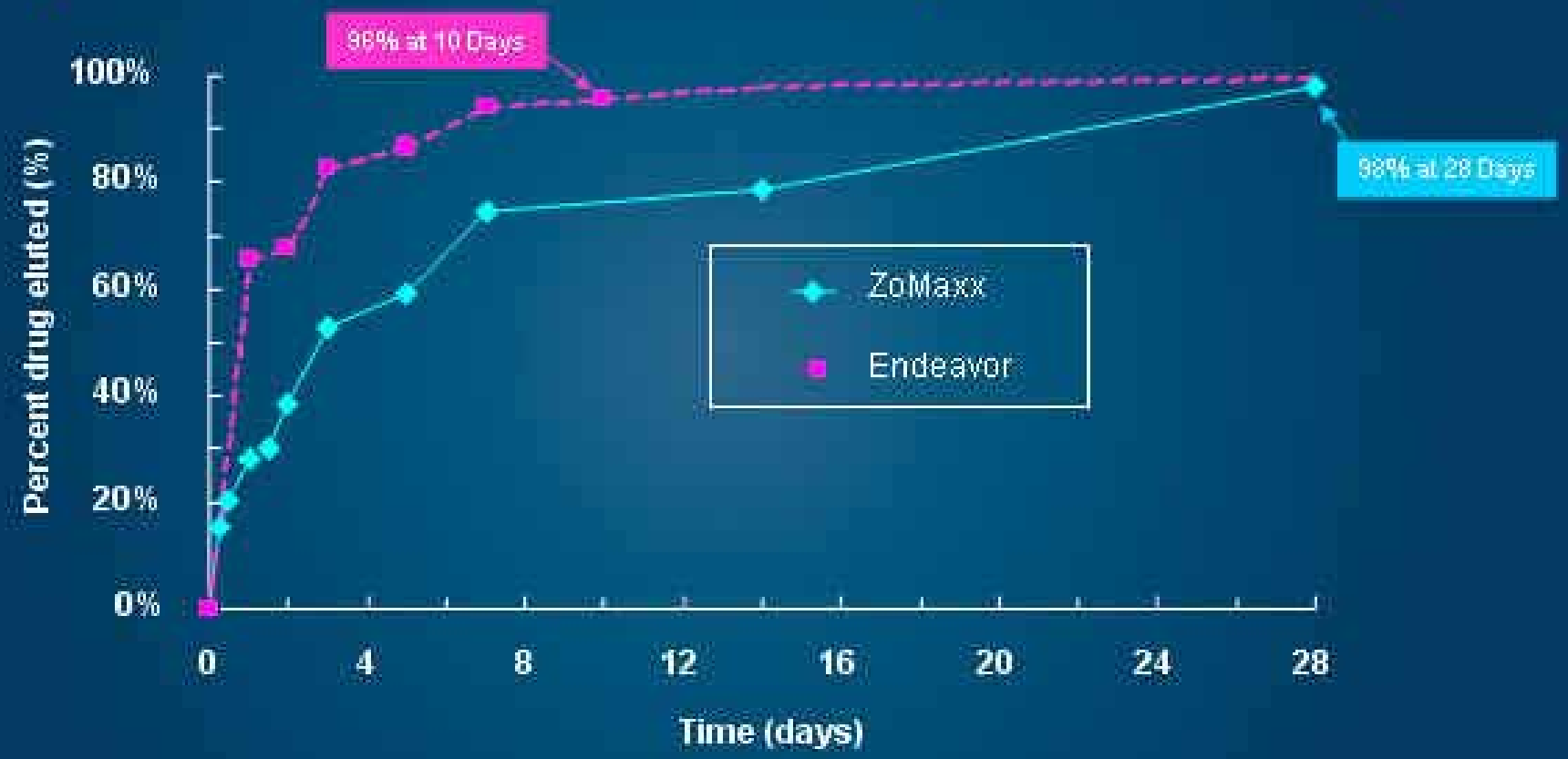
Driver Cobalt Alloy Stent



Stent Delivery System (MX²)

ZoMaxx
Zotarolimus-Eluting Coronary Stent

ZoMaxx Stent versus Endeavor Stent
Experimental Elution Rates (swine model)



ZoMaxx data from Abbott Study TJ03-114 In-vivo Elution of ABT-578 from ZoMaxx Stents. Endeavor data from Kandzari DE. ENDEAVOR Overview of ABT-578/PC Cobalt Technology and Clinical Trial Program. www.TCTMD.com, 2005; n= 6 stents/time point; mean ± SEM. Endeavor is a trademark of Medtronic, Inc.; results not indicative of clinical effectiveness.

ZOMAXX IVUS
Comparison to Endeavor I (4-months follow-up)

	ZoMaxx IVUS	Endeavor I*
Sample size	40	100
Diabetics	16 (40%)	16 (16%)
RVD (mm)	2.77 ± 0.29	2.96 ± 0.47
Lesion length (mm)	14.4 ± 3.3	10.9 ± 3.1
F/U Stent Volume (mm^3)	136	149
F/U Lumen Volume (mm^3)	127	143
Neointimal Volume (mm^3)	9.1 ± 10.2	6.1
% Neointimal Volume	6.5 ± 6.2	4.5

Clinical trial data is not directly comparable

*Meredith IT, Ormiston J, Whitbourn R, Kay IP, Muller D, Bonan R, Popma JJ, Outlip DE, Fitzgerald P, Prpic R, Kuntz RE. First-in-human study of the Endeavor ABT-578-eluting phosphorylcholine-encapsulated stent system in de novo native coronary artery lesions: Endeavor I Trial. EuroInt. 2005; 2:157-164.

ZoMaxx
Zotarolimus - Eluting Coronary Stent

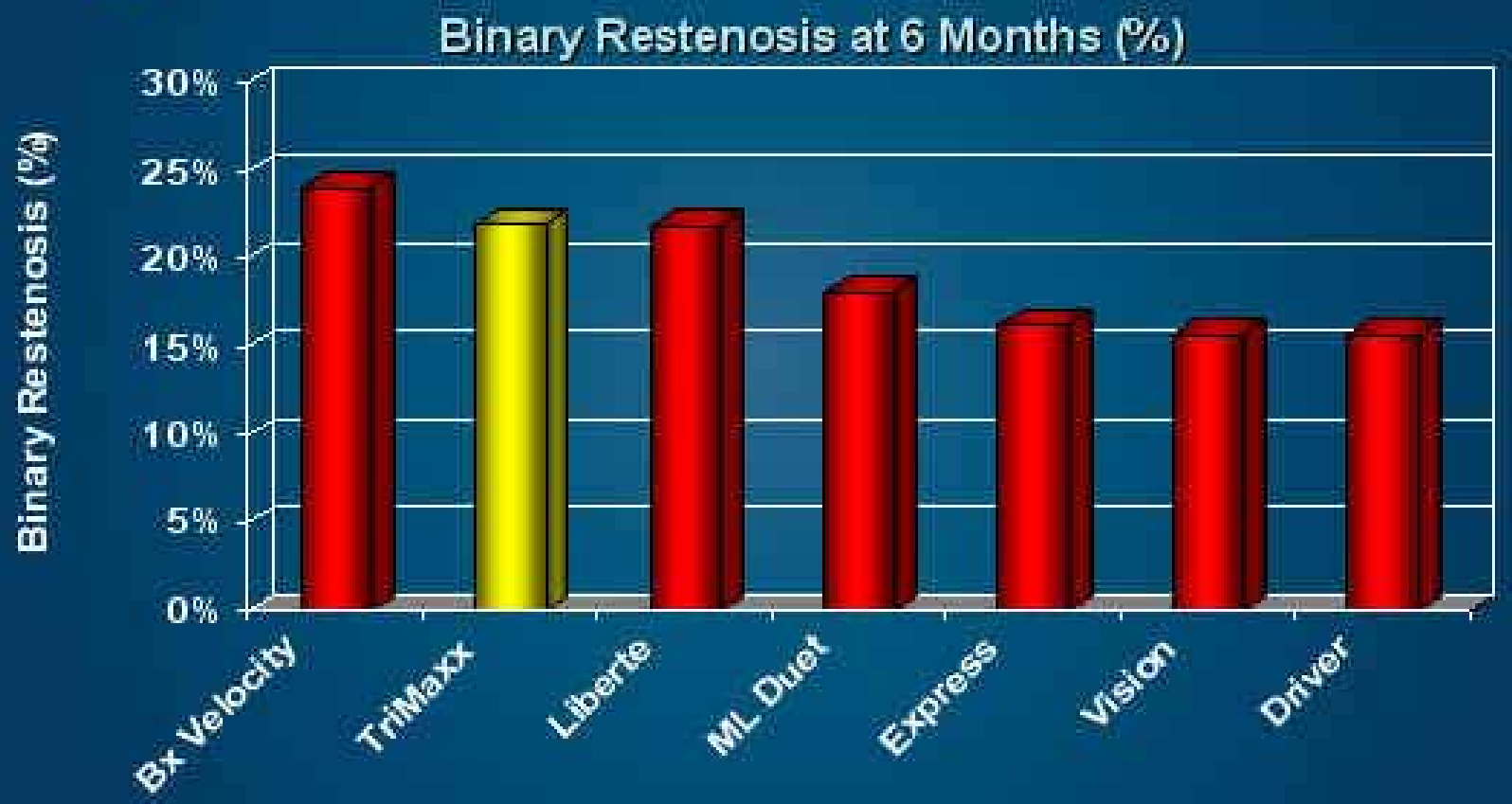
TriMaxx Trial
Comparison of BMS Registries

Bx Velocity: VENUS Registry; Sidar J. TCT 2000.
Driver: Sketbi MH. Am J Cardiol 2006; 86:8-12.
ML Duet: Foley DP. Catheter Cardiovasc Interventi 2001; 54:26-38.
Vision: Kereiakes D. Am J Cardiol 2003; 92:483-488.
Express & Liberte: Derived from Hermiller J. TCT 2004.

Clinical trials not directly comparable.

ZoMaxx
Zotarolimus - Eluting Coronary Stent

TriMaxx Trial
Comparison of BMS Registries



Bx Velocity: VENUS Registry; Eldar J. TCT 2006.
Driver: Sketch MH. Am J Cardiol 2006; 86:8-12.
ML Duet: Foley DP. Catheter Cardiovasc Interv 2001; 64:26-33.
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Express & Liberte: Hermiller J. TCT 2004.

Clinical Trials not directly comparable.

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TriMaxx Trial
Clinical Results (n=50)

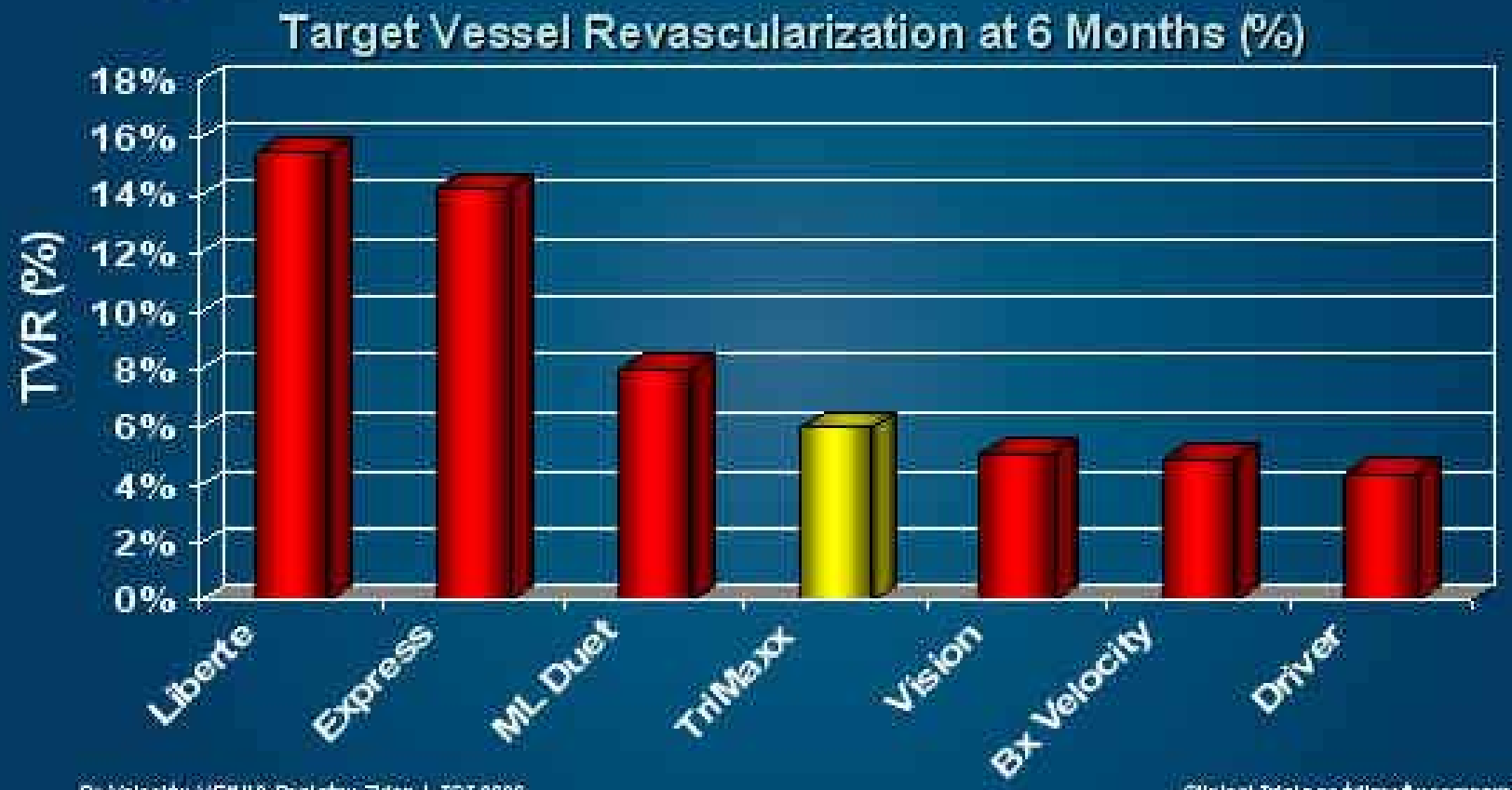
MACE*	In-Hospital	30-days	6 months
Q-wave MI	0% (0/50)	0% (0/50)	2% (1/50)
Non Q-wave MI	0% (0/50)	0% (0/50)	0% (0/50)
TVR	0% (0/50)	0% (0/50)	6% (3/50)
CABG	0% (0/50)	0% (0/50)	0% (0/50)
Cardiac Death	0% (0/50)	0% (0/50)	2% (1/50)
Total MACE	**0% (0/50)**	**2% (1/50)**	**10% (5/50)**

*Patients with multiple MACE events counted only once for most severe event (*i.e.*, hierarchical).

ZoMaxx
Zotarolimus-Eluting Coronary Stent

TriMaxx Trial

Comparison of BMS Registries



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ML Duet: Foley DP. Catheter Cardiovasc Interventi 2001; 54:26-38.
Vision: Kereiakes D. Am J Cardiol 2003; 92:483-486.
Express & Liberte: Hermiller J. TCT 2004.

Clinical Trials not directly comparable.

TriMaxx Trial
Conclusion

Based on this initial clinical experience at a single site:

- Very low profile (strut thickness of 0.0029")
- Ideal radiopacity
- Excellent flexibility and conformability
- Proven safe and biocompatible PC coating
- High procedural success
- Acceptable 6-mos. clinical (6% TVR) and angiographic (22% restenosis) results