TCT Asia 2006

Biolimus A9 Drug-Eluting Stents: Technical Aspects and a Comprehensive Review of the EU, Asia-Pacific, and US Clinical Trial Program

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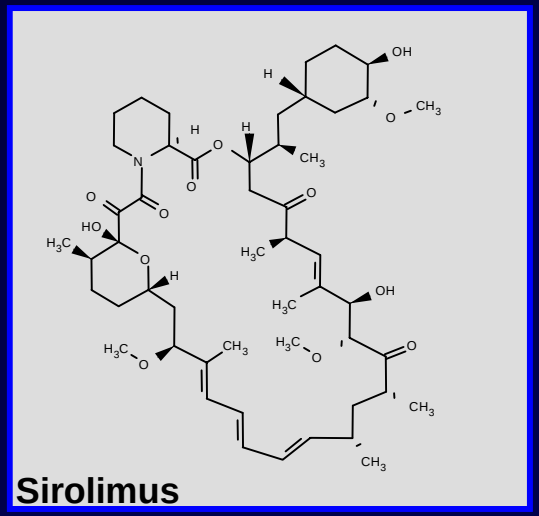
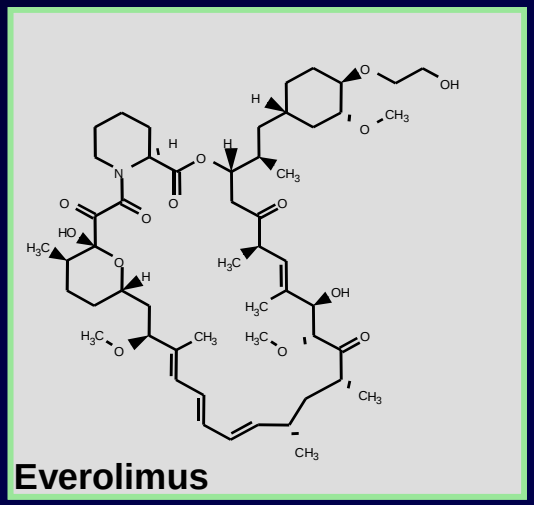
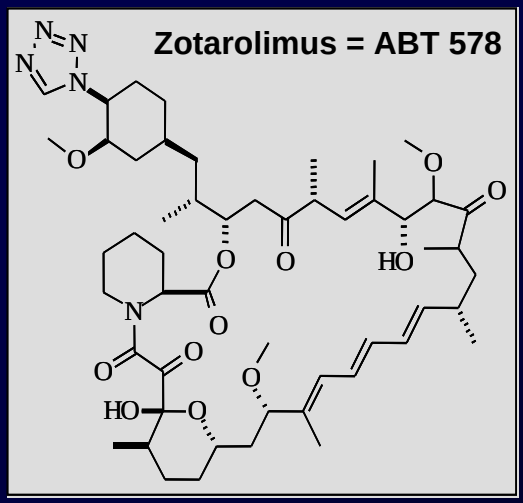
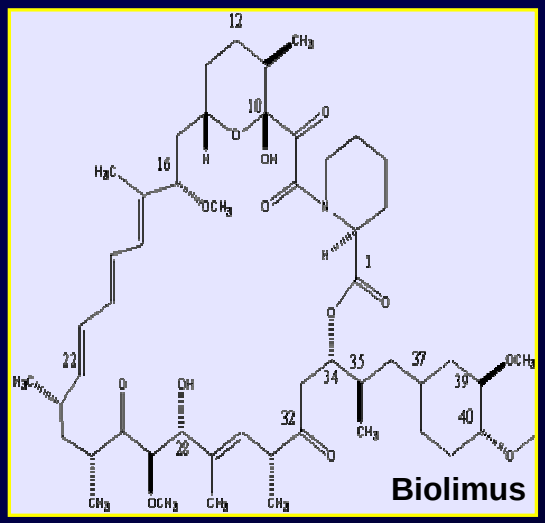
Several New DES are based on Limus-Family drugs









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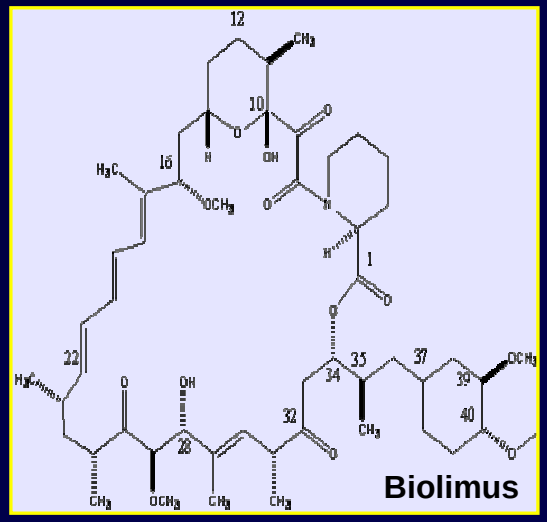
Several New DES are based on Biolimus



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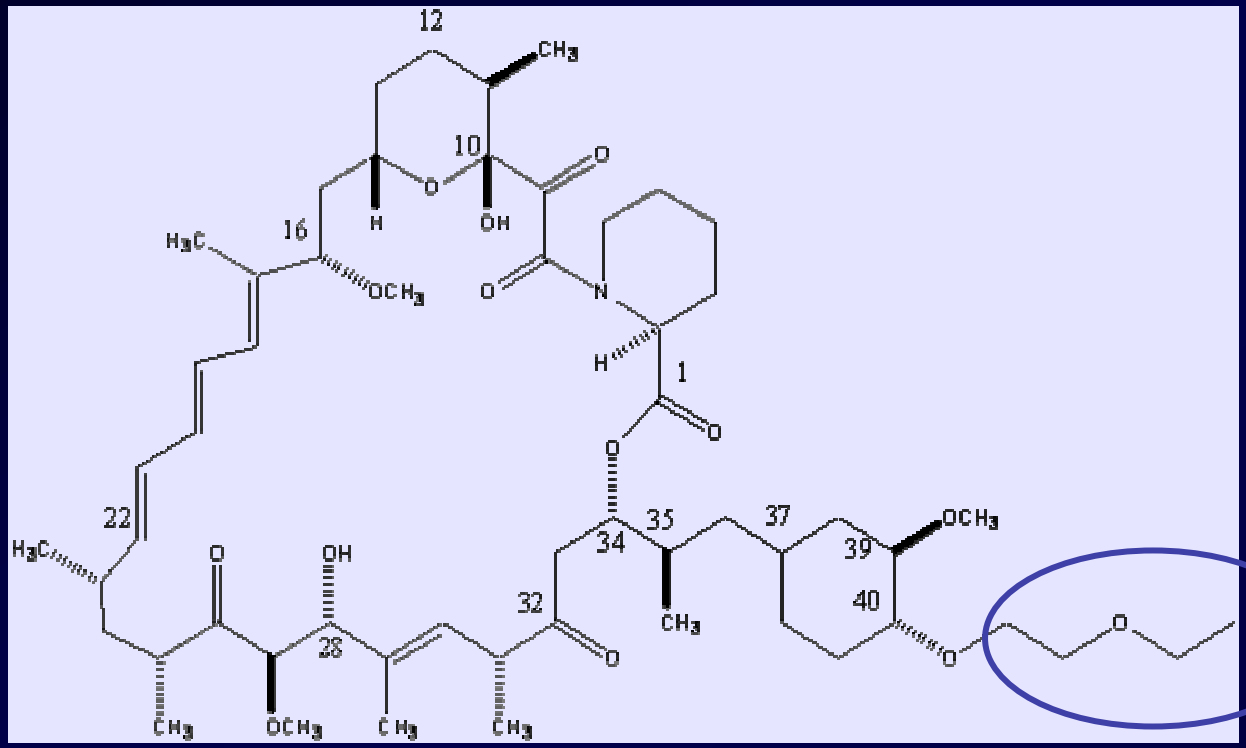
Biolimus A9



40-O-(2-ethoxyethyl) modification:

- ***Most preferred position for stent-based applications***
- ***Does not affect FKBP binding properties***

New Molecular Entity ($C_{55}H_{87}NO_{14}$)

- More lipophilic than sirolimus/everolimus
- Immunosuppressant

Mechanism of Action

- Anti-proliferative agent
- Binds to FKBP-12
- Inhibits mTOR activity

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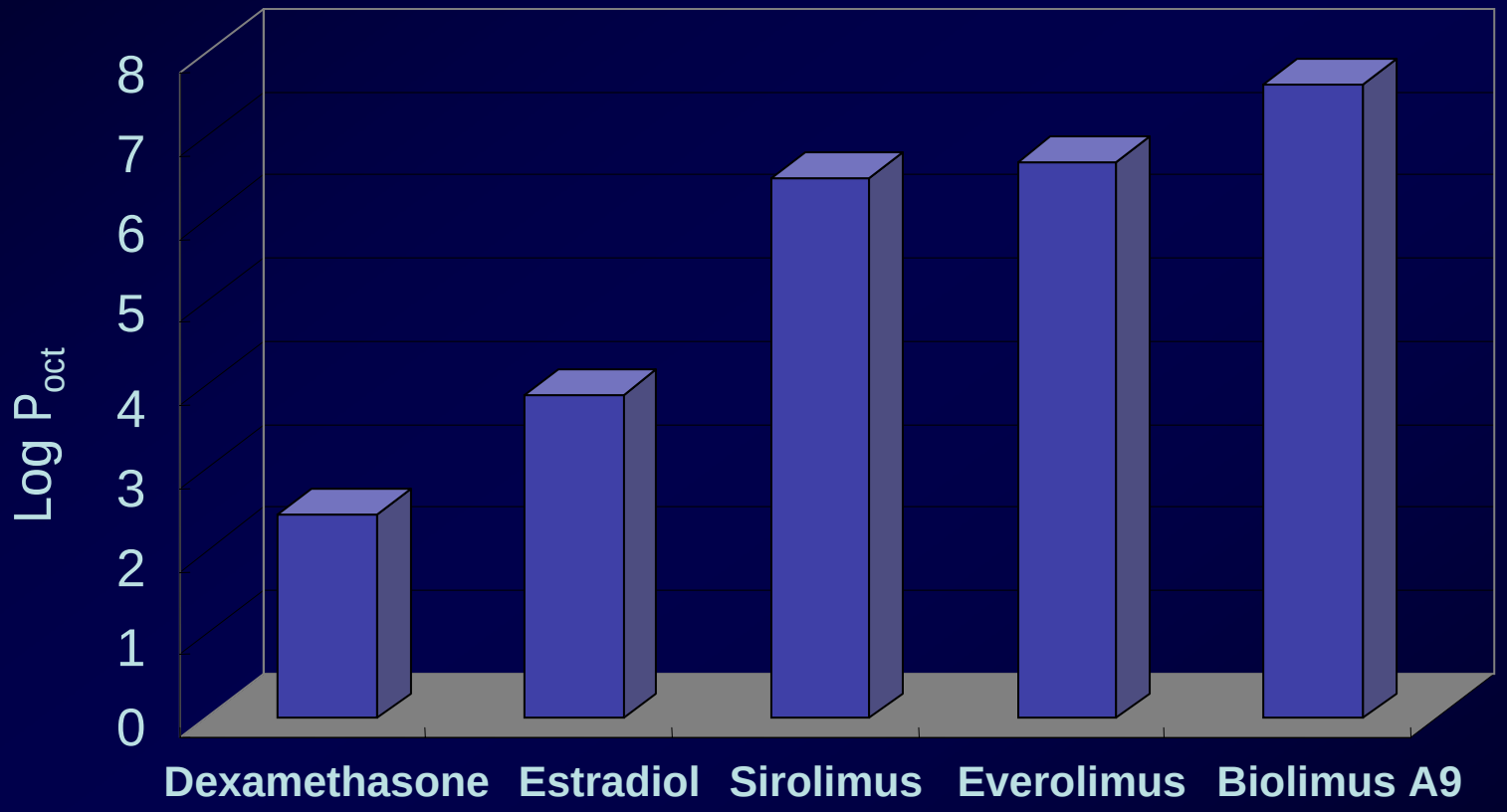
Lipophilicity of Biolimus A9 and Other Limus Drugs



Test Method: Lombardo F.; Shalaeva M.; Tupper K.; Gao F.; Abraham M. ELogPoct: A Tool for Lipophilicity Determination in Drug Discovery. *J. Med. Chem*. 2000, 43, 2922-2928.

Biolimus A9 Pharmacokinetics

- With a 10X higher lipophilicity, BA9 partitions with higher affinity into fatty tissues and is less available in blood compared to Sirolimus
- Animal studies suggest comparable potency and safety
- Readily attaches to and enters smooth muscle cell membranes
- Binds to immunophillins inside the cell, causing cell cycle arrest at G_0
- Powerful immunosuppressant

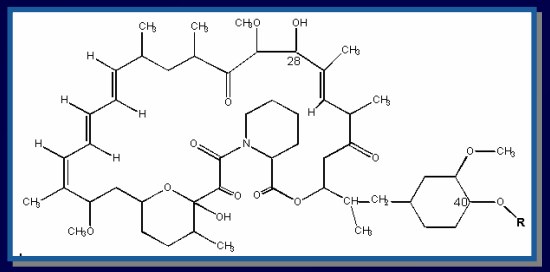
BioMatrix™ Stent Components

S-Stent™ (316L stainless steel)

- Quadrature-link design; increased flexibility
- Reduced turbulence and wall injury

PLA Polymer

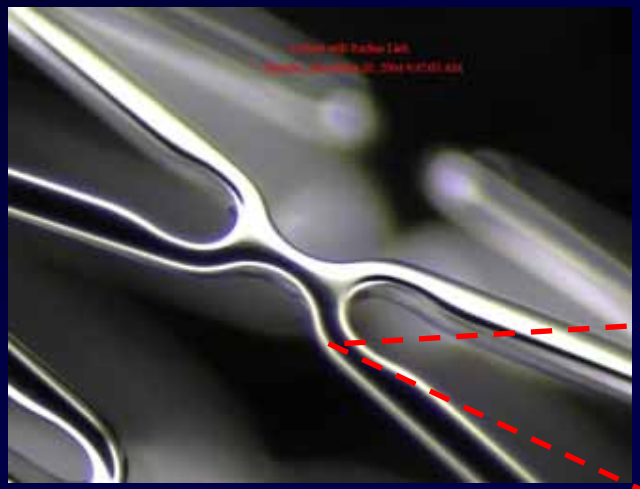
- Asymmetrical abluminal coating with a biodegradable polymer
- Simultaneously releases drug and polymer
- Controlled biodegradability
- High drug-carrying capacity



Biolimus A9™ (rapamycin derivative)

- Powerful immunosuppressant, anti-inflammatory
- Prevents smooth muscle cell proliferation
- More lipophilic; faster cellular absorption

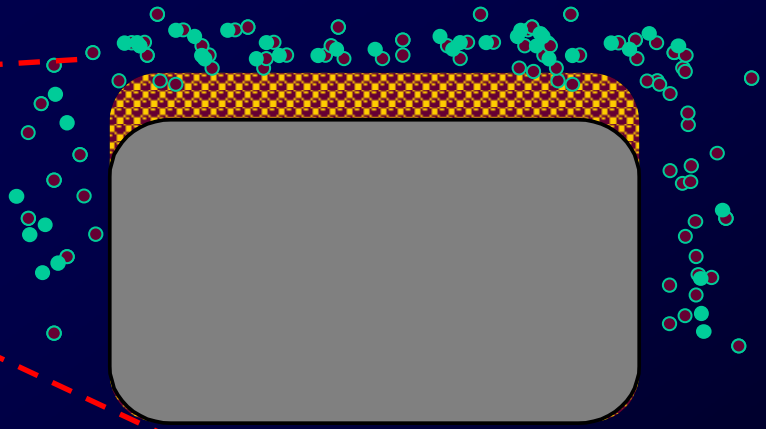
New Stent Platform: BioMatrix II™



Improved stainless steel Bioflex Stent™ platform with abluminal-only ***biodegradable*** polymer coating, improved flexural ruggedness

Drug: Biolimus A9
15.6 mg/mm-stent length

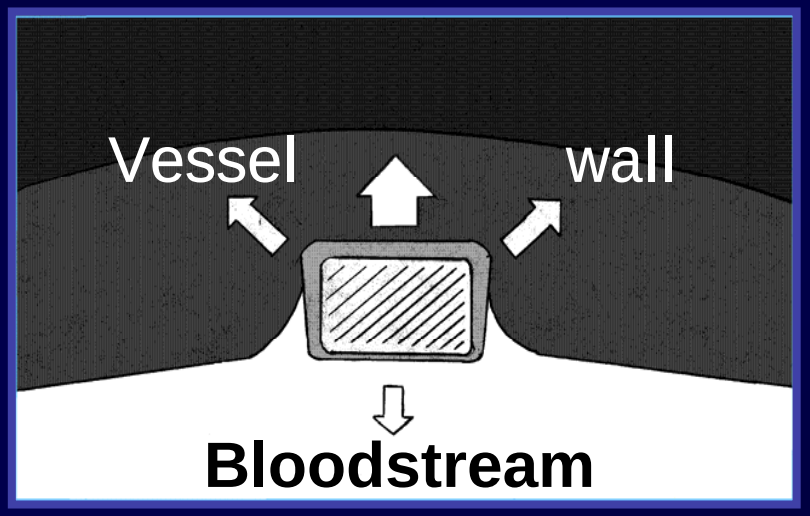
Drug carrier: **P**oly(**L**actic **A**cid)
PLA:BA9=50:50



Cross-section sketch
of Biolimus A9-eluting stent

Biodegradable PLA Coating Method

- Asymetric thin films of PLA degrade by surface erosion
- Drug occupies >50% of the drug/polymer matrix
- Physical contact and drug delivery to vessel wall only, not bloodstream



Drug targets blood vessel walls and only a minimal amount is released into circulation

STEALTH I FIM

Randomized (2:1), Double-Blind, Multi-Center Clinical Trial

Single De Novo Native Coronary Artery Lesions (Type A-B2)
Vessel Diameters: 2.75 - 4.0 mm
Stent Diameters: 2.5 - 4.0 mm
Lesion Length: ≤24 mm
Stent Lengths: 12 - 28 mm
Pre-Dilatation Required/Post-Dilatation at physician discretion
Anti-Platelet Therapy for 3 months

BioMatrix™ n=80

S-Stent Control n=40

Sites: Germany (2) and Brazil (1)

Clinical Follow-Up

30d 3mo 6mo 12 mo

(Single Center Subset)

Angiographic / IVUS Follow-Up

Primary Endpoint:	In-Segment Late Loss at 6 months (QCA)
Key Secondary Endpoints:	MACE (death, MI, or TLR) at 30 days, 6 and 12 months Device and Procedure (Clinical) Success Clinically driven TLR and TVF at 6 and 12 months Pharmacokinetics of Biolimus ABR, LL and % volume obstruction at 6 and 12 months

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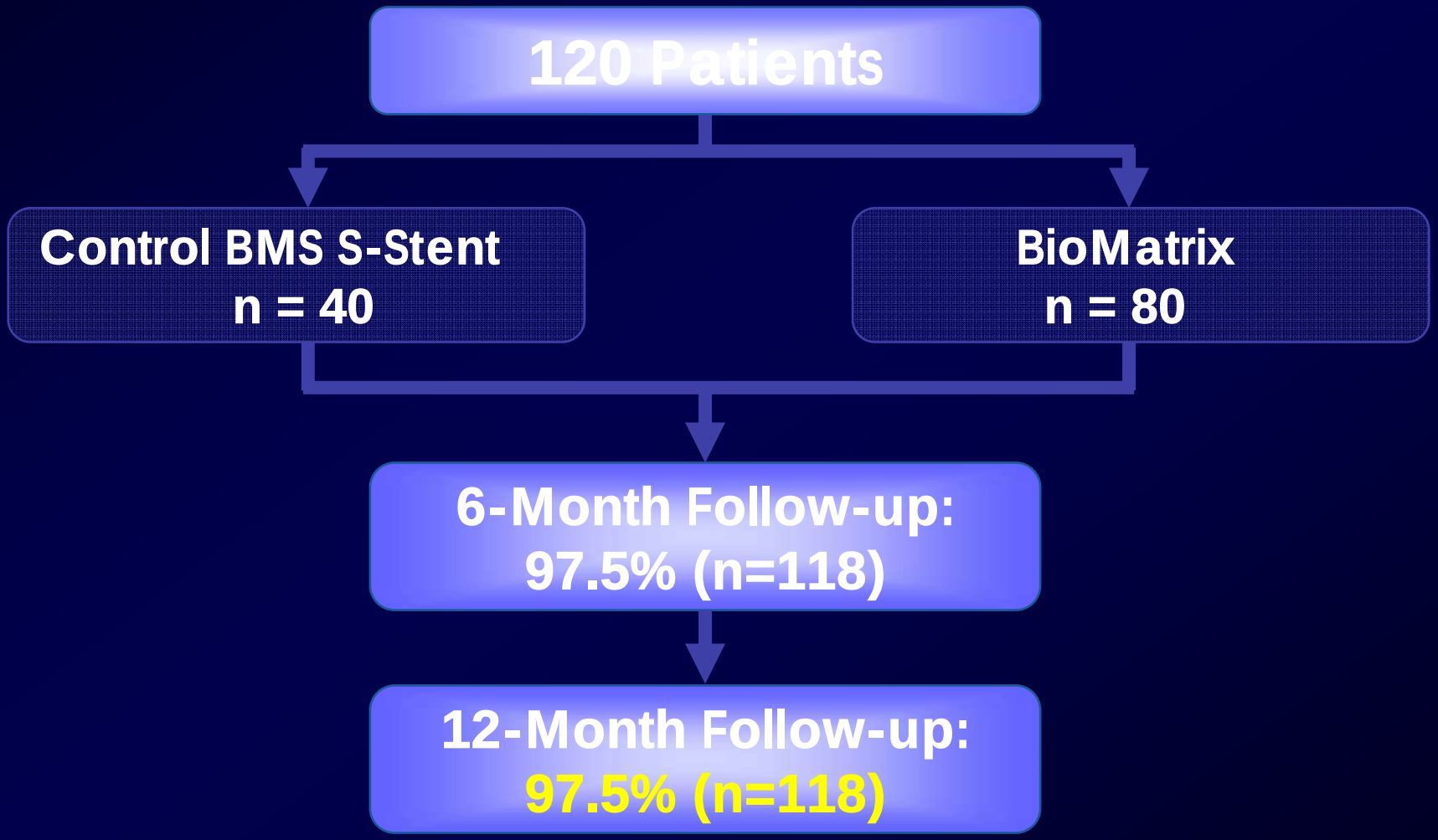
STEALTH I Clinical Trial



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Cumulative Hierarchical MACE

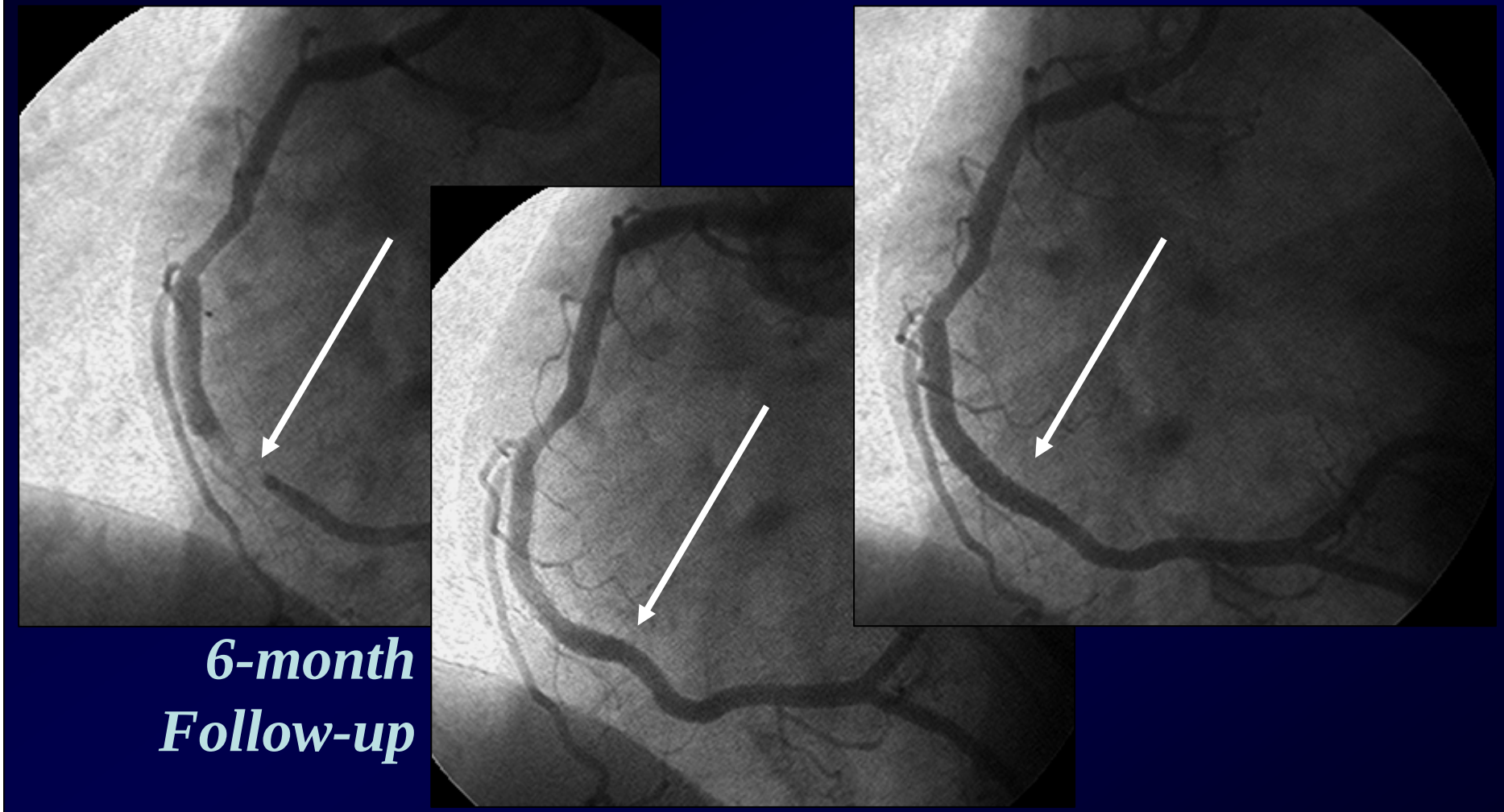
RESULTS	6 Months		12 Months	
	S-Stent	BioMatrix	S-Stent	BioMatrix
MACE	2.5%	3.8%	5.0%	5.1%
Death*	0.0%	0.0%	2.5%	1.3%
Q Wave MI	0.0%	1.3%	0.0%	1.3%
Non-Q Wave MI	2.5%	1.3%	2.5%	1.3%
TLR-CABG	0.0%	0.0%	0.0%	0.0%
TLR-PTCA	0.0%	1.3%	0.0%	1.3%

*Death events were noncardiac: 1 diabetic foot syndrome (S-Stent) and 1 acute leukemia (BioMatrix)

BioMatrix Case Example

pre

post



6-month Follow-up

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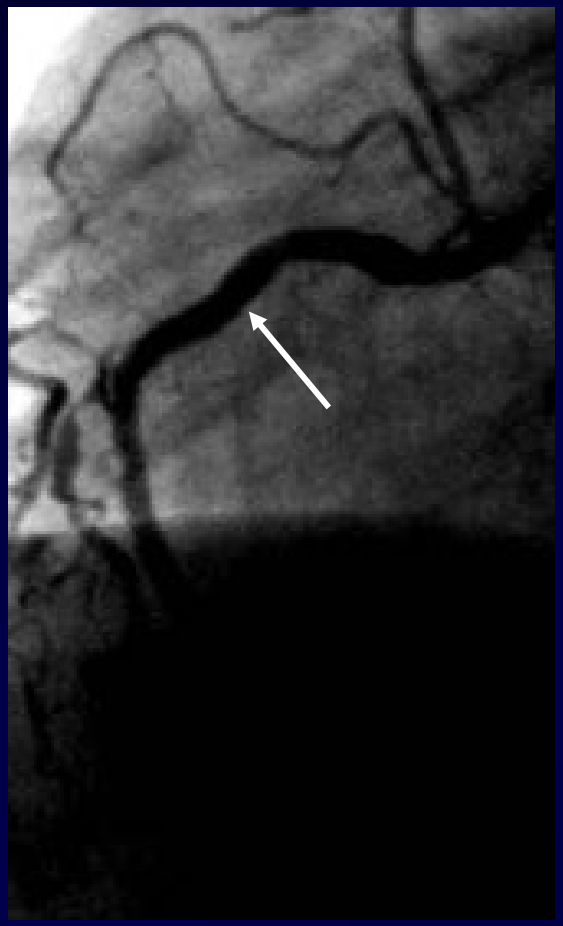
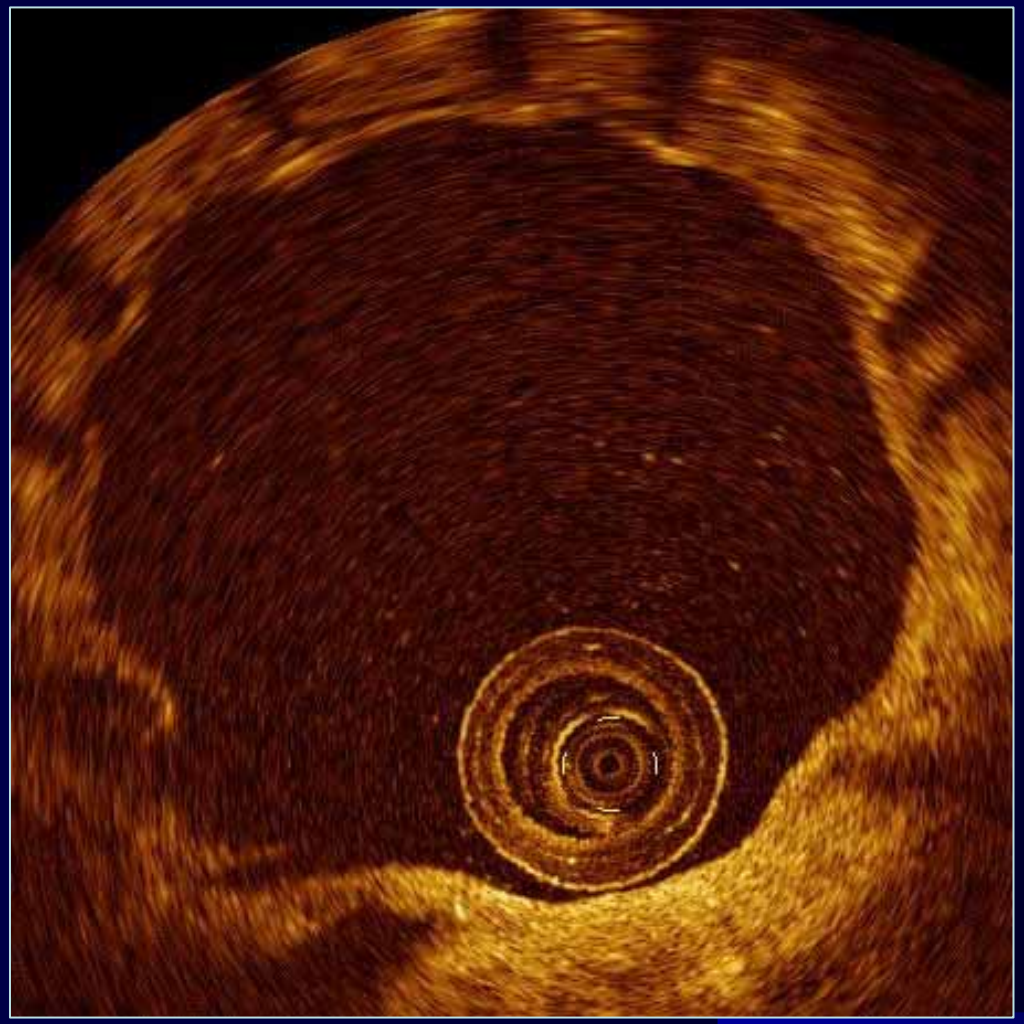
BioMatrix Case Example

STEALTH-1 12 mths follow-up





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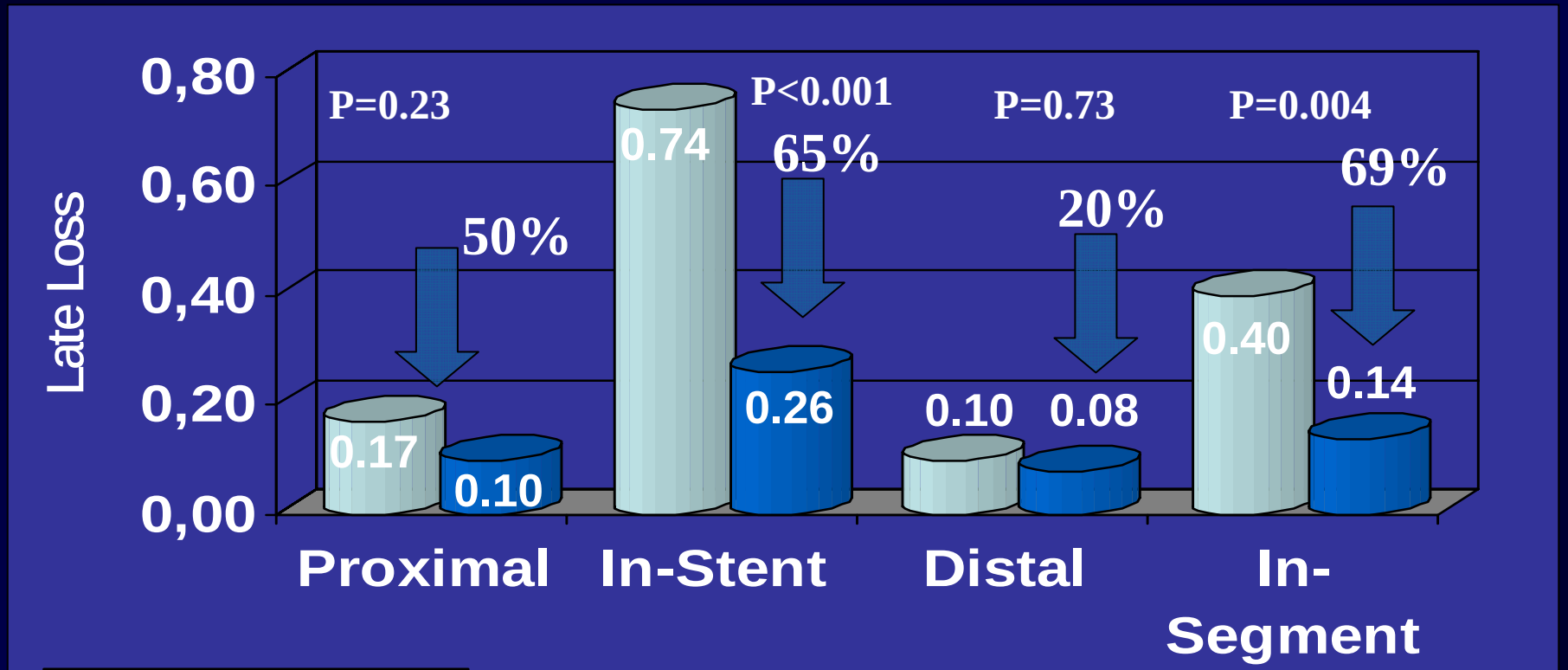
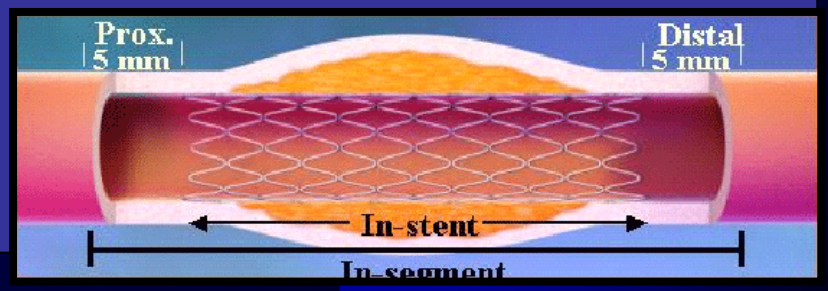
STEALTH I: Late Loss—Edge Results





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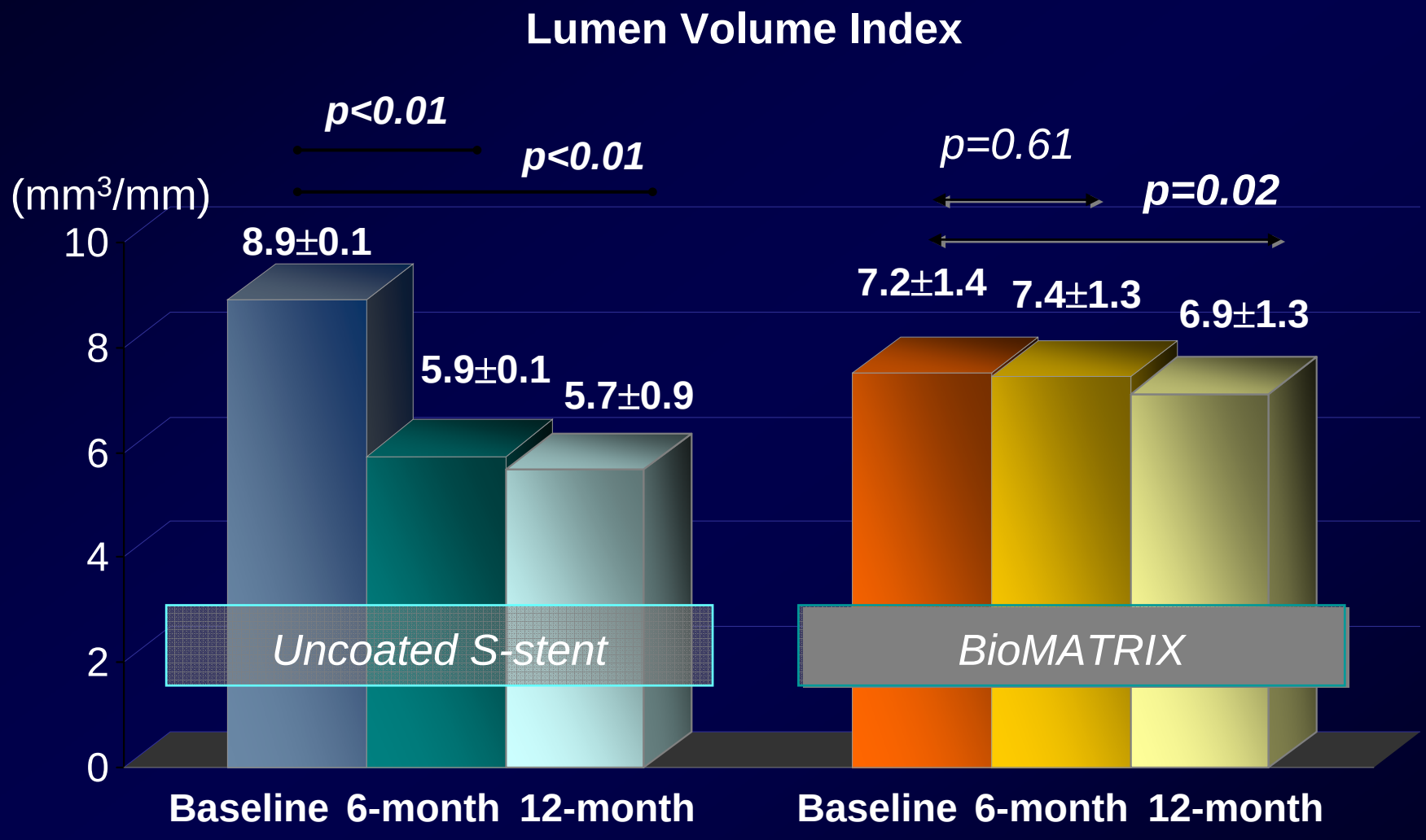
Serial Volume Index Changes in-stent



*Complete 14 Serial Volumetric Analysis cases (BMS 3, DES 11)

*Nonparametric Wilcoxon Signed Rank Test

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STEALTH I: Subgroup analysis

Diabetics

(oral or insulin dep)

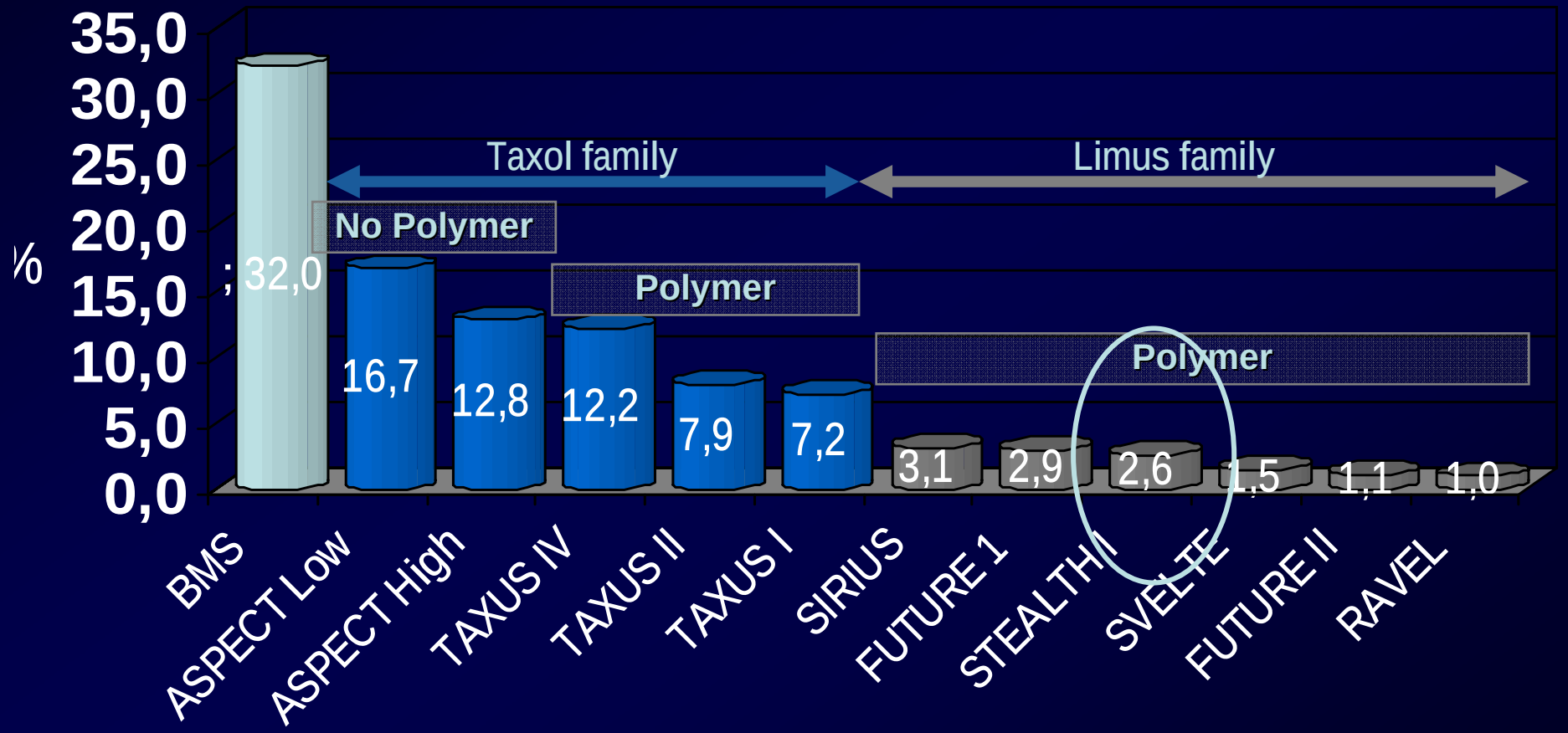
	BioMatrix™ (n=19)	S-Stent™ (n=8)	*p* value
Late Loss (mm)	0.25 ±0.33	0.77 ±0.31	0.001
% DS	9.6 ±10.6	28.4 ±12.2	<0.001
MLD (mm)	2.5 ±0.5	2.1 ±0.5	0.027

Small vessel

(<2.75mm)

	BioMatrix™ (n=35)	S-Stent™ (n=13)	*p* value
Late Loss (mm)	0.15 ±0.32	0.87 ±0.37	<0.001
% DS	5.9 ±11.9	33.6 ±12.8	<0.001
MLD (mm)	2.4 ±0.4	1.6 ±0.4	<0.001

Comparison of Neointimal Volume



Courtesy Shimada, Honda, Hassan, Fitzgerald

Stealth 1 Clinical results – in comparison

	STEALTH I		JNJ	BSX	Medtronic
	BioMatrix	Control	Sirius	Taxus IV	Endeavor II
Late Loss (in-stent) mm	0.26	0.74	0.17	0.39	0.62
Binary Restenosis rate (%)					
In-stent	3.90	7.70	3.20	9.10	9.50
In-segment	3.90	7.70	8.90	12.40	13.30
Target Lesion Revascularization (%)	1.30	0.00	4.90	3.20	8.1*
Major Adverse Cardiac Event (%)	5.00	7.50	8.30	8.50	7.40

*TVF

Biosenor's Study Program

STEALTH I	**FIM**	**Completed**
BEACON	**Web-based Registry**	**Ongoing**
LEADERS	**OUS- Efficacy Study**	**1Q 2006**
STEALTH II	**US - Efficacy Study**	**1H 2006**

Ongoing Trials

Asia

Aim: The BEACON Registry has been designed to evaluate continued safety and efficacy of the BioMatrix Biolimus A9-eluting stent in a broader patient population

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BEACON Registry

- **Description:**
  - Prospective, multinational, multicenter, observational Web-based registry
- **Objective:**
  - Assessment of clinical outcomes in patients receiving the BioMatrix™ Stent
- **Enrollment:**
  - 800 patients from 9 sites in Asia
  - Patient data collected at 1, 3, 6, and 12 months following stent implant
- **Primary Endpoint:**
  - Target vessel revascularization (TVR) rates
- **Secondary Endpoints:**
  - MACE rate
  - Correlation TVR, lesion characteristics and patient comorbidities

LEADERS Trial

Limus Eluted from A Durable vs. ERodible Stent Coating

- **Trial:**
  - Randomized, multi-center, comparison of BioMatrix™ Stent (Biolimus A9™) with Cypher™ Stent (Sirolimus)
- **Enrollment:**
  - 1,000 patients from ~3 sites in Europe. Data collection at 1, 6, 8, 9, and 12 months following stent implant, and annually thereafter for 5 years
- **Endpoints:**
  - MACE at 9 months
  - TVR rates at 9 months
  - In-lesion and in-stent restenosis
  - In-lesion and in-stent MLD
- **Timing:**
  - 3Q 2005

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STEALTH II US Pivotal

Randomized (1:1), Double-Blind, Multi-Center Study

Single De Novo Native Coronary Artery Lesions (Type A-B2)
Vessel Diameters: ≥2.5 – ≤3.5 mm
Stent Diameters: 2.5 – 3.5 mm
Lesion Length: ≥10 mm - ≤24 mm
Stent Lengths: 8 - 28 mm
8 and 12 mm Lengths for Bailout Only
Pre-Dilatation and Post-Dilatation at physician discretion
Anti-Platelet Therapy for 6 months

BioMatrix™ II
n= ~720
Evaluable

TAXUS Control
n= ~720
Evaluable

~70 Sites: US and Canada

Clinical Follow-Up

30 d | 6 mo | 9 mo | 12 mo | 2-5 yrs

Angiographic / IVUS Follow-Up

Primary Endpoint:	Ischemia Driven TVF at 9 months
Key Secondary Endpoints:	MACE (death, MI, or TLR) at 30 days, 6, and 9 months Device, Lesion and Procedure Success Clinically driven TLR, TVR at 6 and 9 months MLD, Binary Restenosis and Late Loss at 9 months Volumetric Obstruction at 9 months

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STEALTH II: US PIVOTAL

- Trial:
  - Prospective, multi-center, 1:1 randomized comparison of BioMatrix™ stent with Taxus™ stent
- Enrollment:
  - 1,584 patients from ~70 sites. Data collection at 1, 6, 9, and 12 months, and annually thereafter for 5 years
- Endpoints:
  - Ischemia-driven target vessel failure (TVF) rates at 9 months
  - Late loss, binary restenosis, MLD, TLR, and TVR
  - MACE
  - Device/Lesion/Procedural Success
- Timing:
  - Enrollment 1H 2006

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NOBORI Clinical Program

	Type of study
– STEALTH	Randomized (vs. BMS)
– NOBORI 1	Randomized (vs. Taxus)
– NOBORI PK	Registry
– NOBORI SV/LL	Registry
– NOBORI 2	Registry
– NOBORI Japan	Randomized

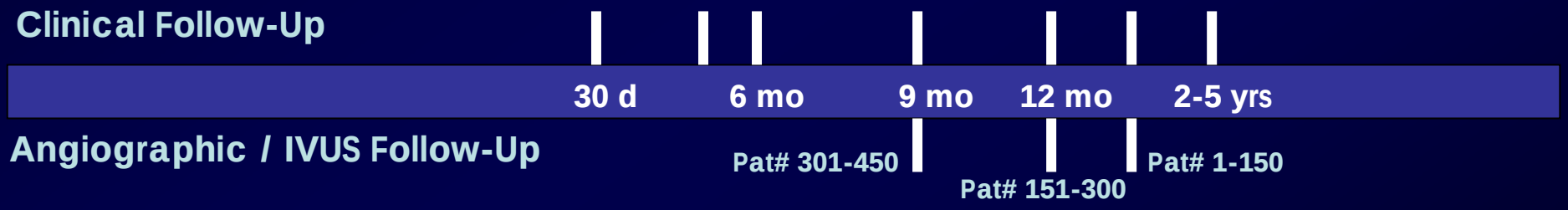
NOBORI II EU/Asia

Registry

Patients with Ischemic Heart Disease due to stenotic lesions of native coronary arteries with reference vessel diameter ≥ 2.5mm and ≤ 3.5mm.

Nobori Stent
n= ~ 1200

~70 Sites: EU and Asia



Primary Endpoint: MACE free survival at 12 months

IVUS Follow-up in subgroups of 50 pts each

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Summary

- Extensive preclinical studies confirm safety and efficacy of Biolimus A9™ and the BioMatrix™ Stent
- The STEALTH I trial demonstrated that Biolimus A9™ is an effective drug for use in DES
- Larger clinical trials are now underway, to test the durability of these results in larger populations and a wider range of more complex lesions