Angioplasty Summit 2005, Korea

Biolimus A9 Drug-Eluting Stents: The Biosensors STEALTH I Results

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Stanford University, School of Medicine, CA, USA

Study Objective

Demonstrate safety and efficacy of new rapamycin derivative, Biolimus A9, eluted from bioabsorbable PLA-coated stent in *de novo* coronary lesions

Study Sites and Investigators

- Clinical Centers (Eberhard Grube, Principal Investigator):
  - Heart Center Siegburg, Germany
    Eberhard Grube MD
  - Institute Dante Pazzanese of Cardiology São Paulo, Brazil
    Alex Abizaid MD PhD, Eduardo Sousa MD PhD
  - Brüderkrankenhaus Trier, Germany
    Karl-Eugen Hauptmann MD

- Preclinical Animal Studies
  - Cedars-Sinai Medical Center: *S. Kar MD*

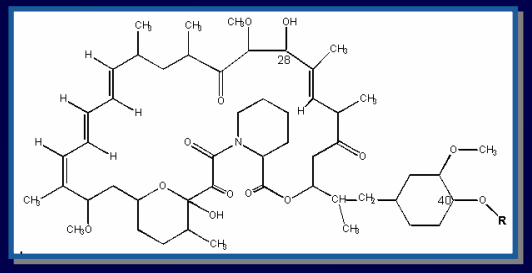
- BA9 Toxicology Studies
  - Terumo Corporation

- BA9 Metabolic Study
  - Univ. of Colorado HSC: *U. Christians MD PhD*

Core Labs

- Angiographic Core Lab
  - Cardiovascular Research Foundation:
    E. Cristea MD, R. Costa MD, A. Lansky MD
- Data Management and Analysis
  - Harvard Clinical Research Institute:
    A. Mercando RN, R. Kuntz MD
  - Cardiovascular Research Foundation:
    M. Negoita MD, R. Mehran MD
- Blood and Tissue Analysis
  - Univ. of Colorado HSC: *U. Christians MD PhD*
- IVUS Core Lab
  - Stanford University:
    Y. Shimada MD, Y. Honda MD, A. Hassan MD, P. Fitzgerald MD PhD
- Clinical Events & DSMB Committees
  - Harvard Clinical Research Institute: *D. Cutlip, MD*

BioMatrix™ Stent Components
(Biosensors International Group)

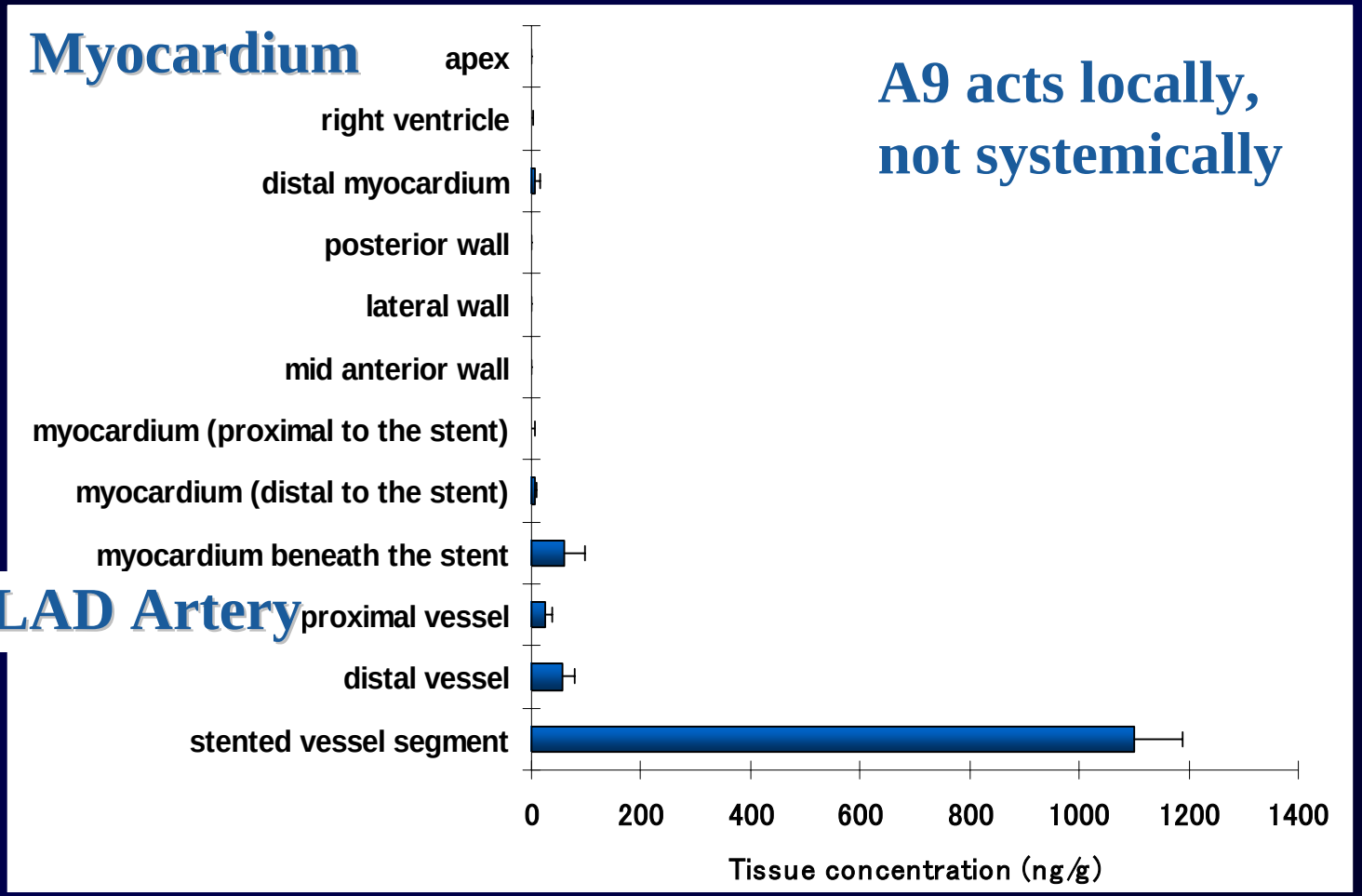


S-Stent™ (stainless steel)
- Quadrature-link design; increased flexibility
- Excellent scaffolding
- Reduced turbulence and wall injury

PLA Polymer
- Uniform thickness; bioresorbable
- Simultaneously releases drug and polymer
- Controlled biodegradability
- High drug-carrying capacity
- Minimizes polymer weight to minimize inflammation; polymer absorbed into tissue

Biolimus A9™ (rapamycin derivative)
- Powerful immunosuppressant, anti-inflammatory
- Prevents smooth muscle cell proliferation
- More lipophilic; elutes faster than rapamycin

Tissue Concentration of Biolimus A9 in Pre-Clinical, 24-hour Porcine Model



A9 acts locally, not systemically

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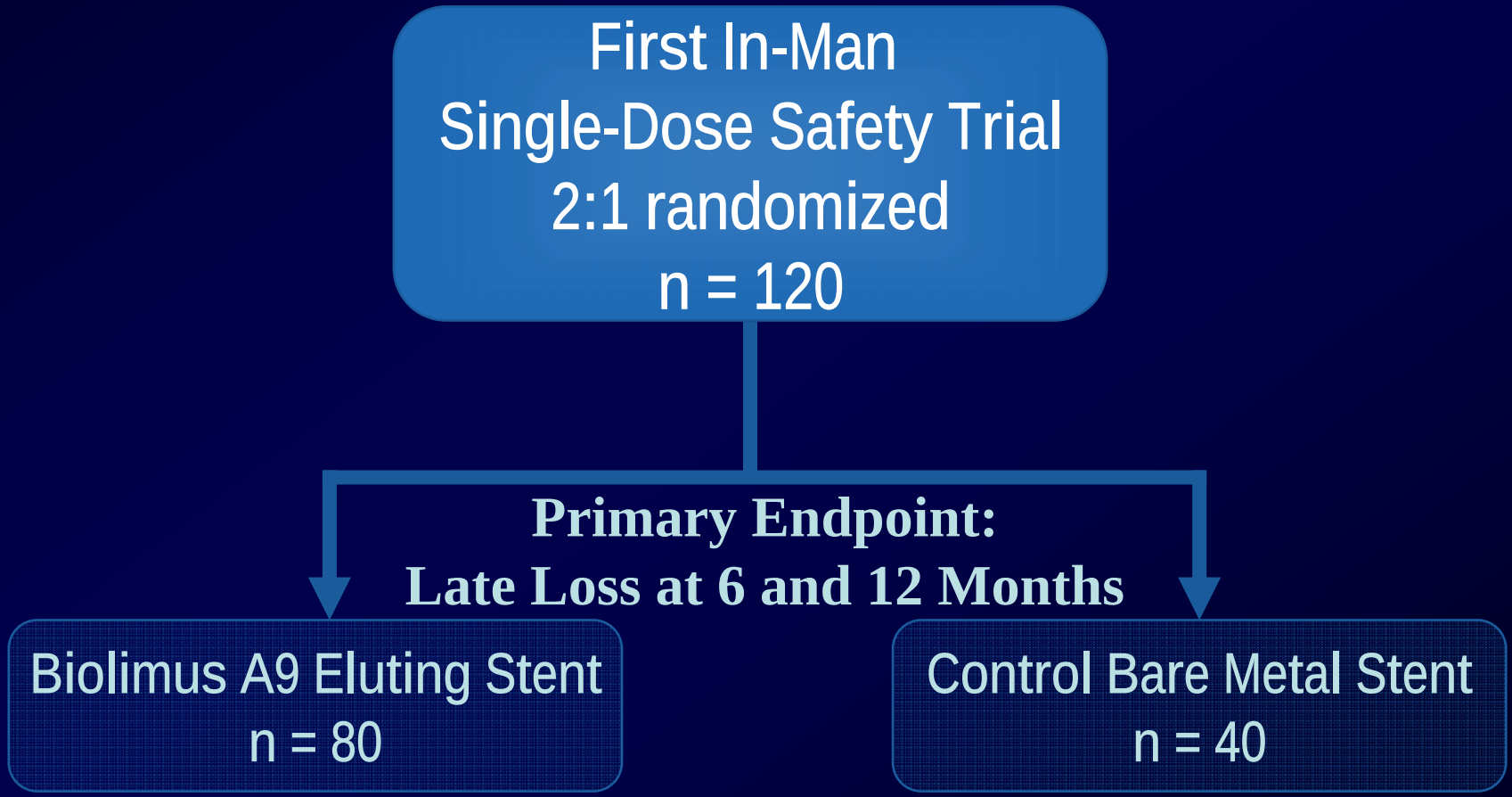
STEALTH Study Design

STent Eluting A9 BioLimus Trial in Humans



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Secondary Endpoints

- Angiographic **in-stent restenosis** (>50% diameter stenosis) at 6 month follow-up
- **MACE**
- **IVUS** changes evaluated at t_0, 6, and 12 months post implant.
- **Biolimus serum levels** measured at t_0, t_{+4}, and before discharge

Inclusion Criteria

- Age > 18 years
- Single *de novo* lesions
- Stenosis > 50%
- **Lesion length ≤ 24 mm**
- Reference diameter (2.7 mm to 4 mm)
- **No direct stenting**

Exclusion Criteria

- LVEF < 30%
- Left main > 50%
- CTO, poor distal flow, thrombus
- Multiple stent (>2) implantation
- 7 days from AMI
- Significant medical comorbidities
- Staged procedures within 3 months
- Side branch > 2 mm
- Coexisting CHD, VHD, CRF
- Contraindication to anticoagulation

Pharmacologic Regimen

- Pre-procedure
  - Aspirin (100–325mg) starting 24 hrs prior to procedure
  - Plavix (loading dose, 300–375 mg within 24 hours pre or post procedure), or
    Ticlid (loading dose, 500mg within 24 hours pre or post procedure)
- During procedure
  - Heparin (boluses to maintain ACT > 250 secs)
  - Plavix 75mg qd or Ticlid 250mg bid
- Post-procedure
  - Aspirin (100–325mg qd) indefinitely
  - Plavix (75mg qd) or Ticlid (250mg bid) for minimum 8 weeks

Patient Demographics and Risk Factors STEALTH

	Control BMS	Biolimus A9	P value
Age (Years)	61.0±9.2	62.0±10.0	0.61
Gender (Male)	82.5%	58.8%	0.01
History of MI	35.0%	37.5%	0.84
Prior PTCA	12.5%	25.0%	0.15
Prior CABG	2.5%	10.0%	0.27
Prior CVA or TIA	7.5%	3.8%	0.40
Diabetes Mellitus	22.5%	26.6%	0.66
Hypertension	85.0%	83.8%	>0.99
Smoking	61.5%	46.3%	0.12

Patient Demographics and Risk Factors

STEALTH

	Control BMS	Biolimus A9	P value
Family History of CAD	30.6%	50.7%	0.06
Congestive Heart Failure	12.8%	3.8%	0.11
LV Ejection Fraction	60.2±13.1%	62.4±11.1%	0.61
Peripheral Vasc. Disease	0.0%	2.5%	0.55
Anginal Status (CCS)			
Class 1	12.9%	10.5%	0.74
Class 2	67.7%	56.1%	0.36
Class 3	16.1%	26.3%	0.42
Class 4	3.2%	7.0%	0.65

Baseline Lesion Characteristics

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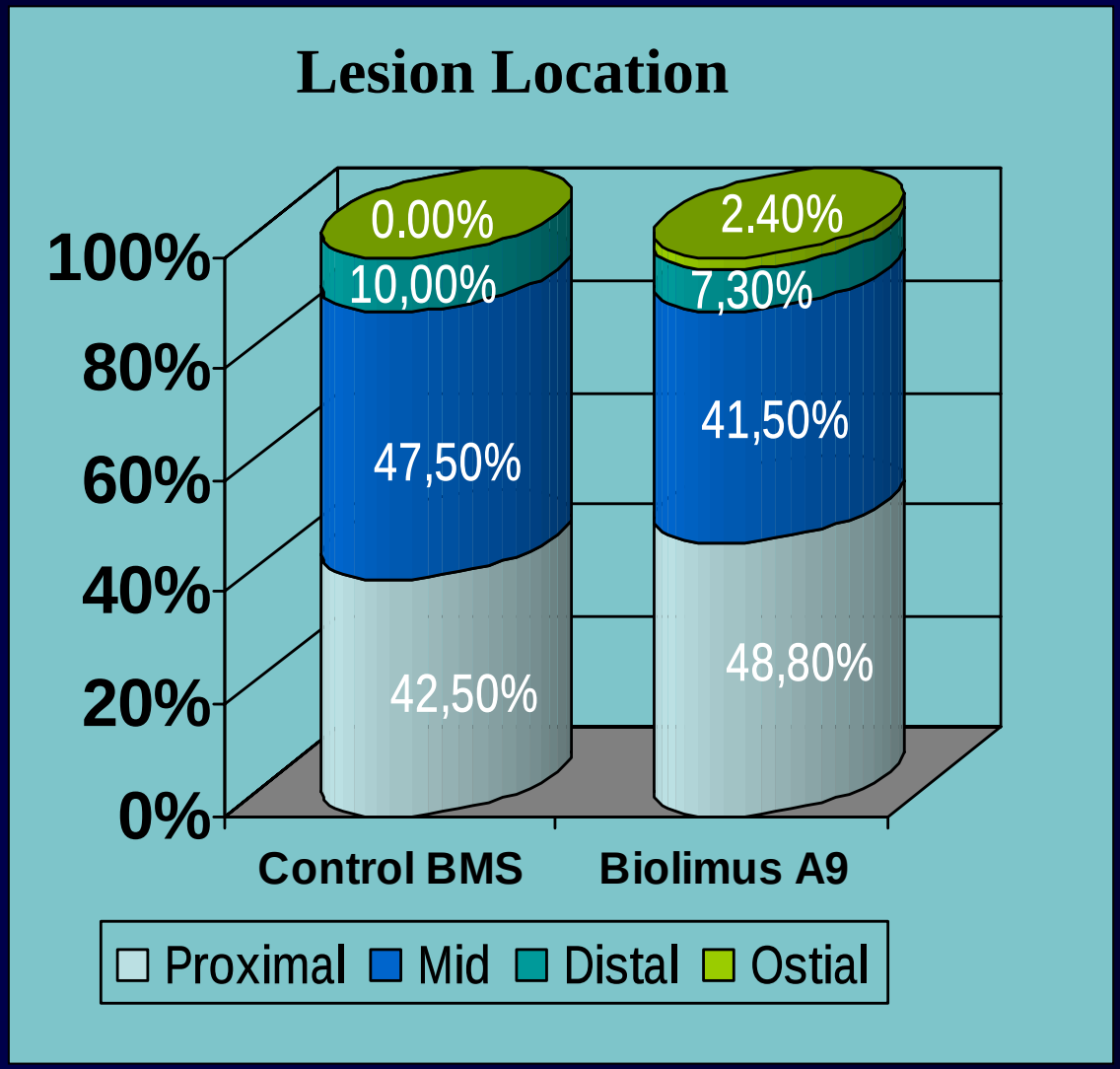

Acute Results

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	Control BMS	Biolimus A9	P value
Ref. Vessel Diam. (mm)	2.97±0.42	2.95±0.40	0.79
Lesion Length (mm)	13.75±3.77	15.37±4.64	0.06
Pre-Procedure			
In-Lesion MLD (mm)	1.07±0.28	1.02±0.27	0.30
In-Lesion DS (%)	64.07±7.72	65.50±7.76	0.34
Post-Procedure			
In-Stent MLD (mm)	2.92±0.33	2.89±0.37	0.68
In-Lesion MLD (mm)	2.48±0.41	2.48±0.38	0.93
In-Stent DS (%)	2.62±8.86	4.61±9.70	0.28
In-Lesion DS (%)	18.08±8.02	18.64±7.74	0.71

Lesion Grade

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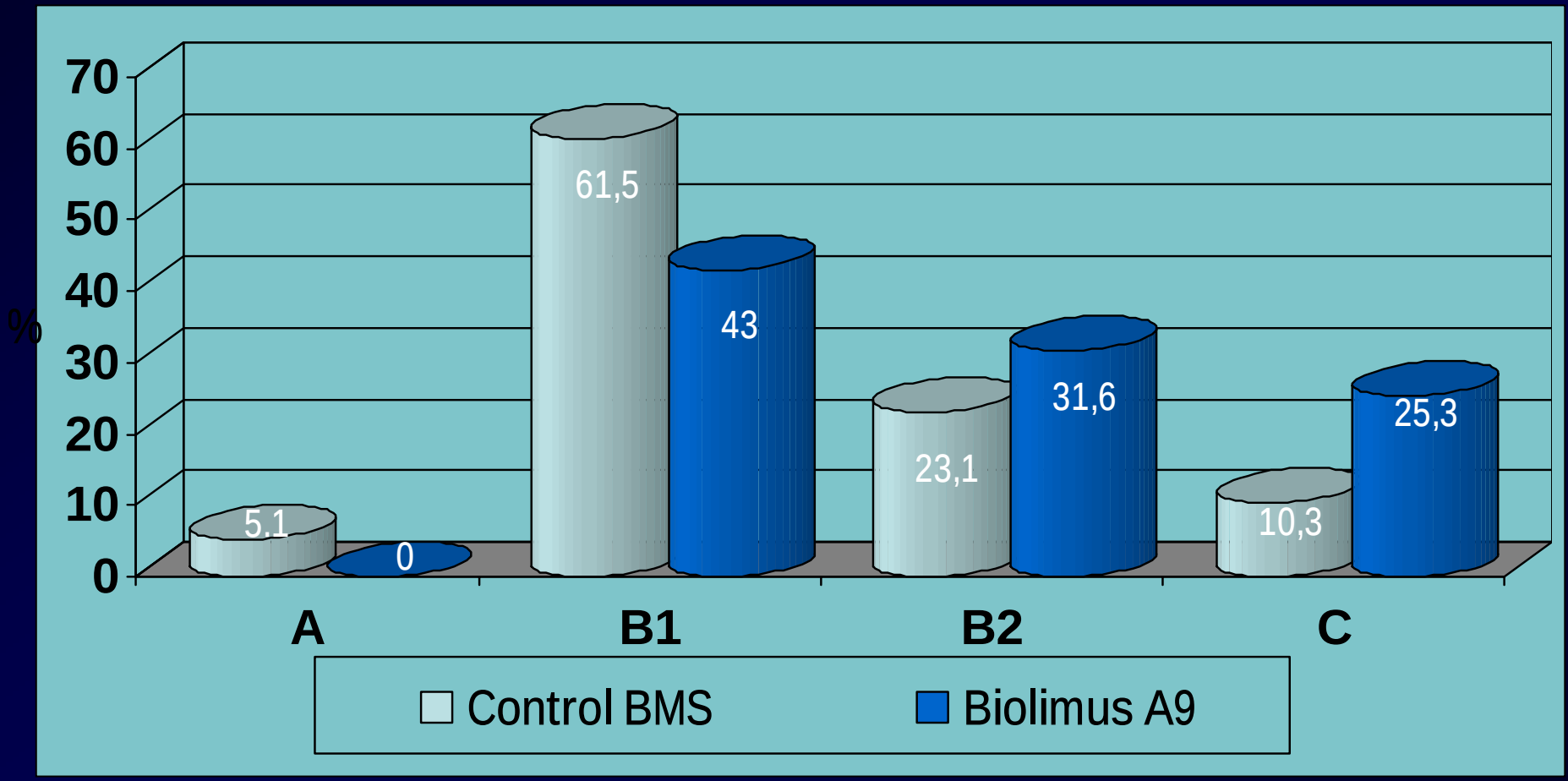

Stent Lengths Implanted

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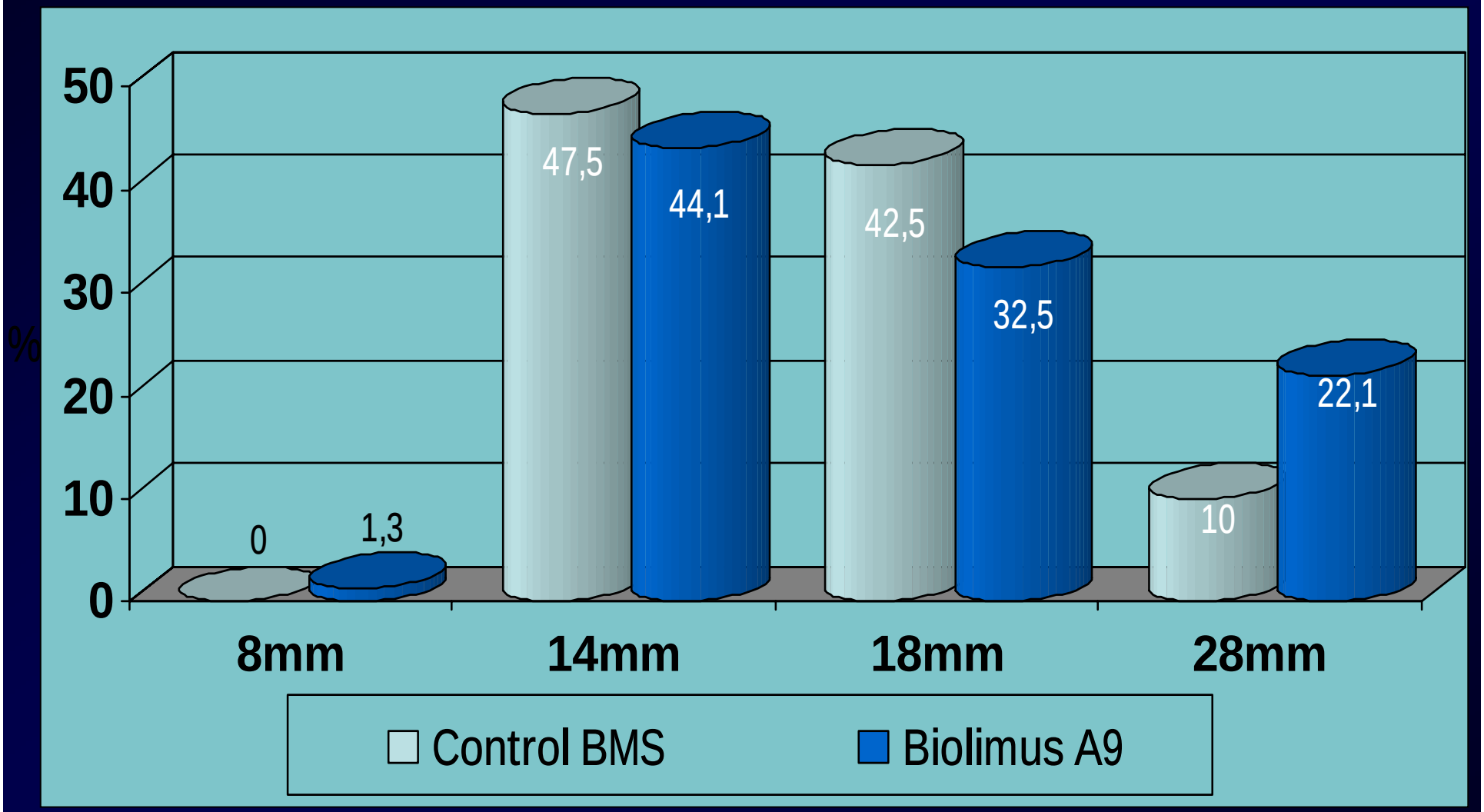

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Stent Diameters Implanted

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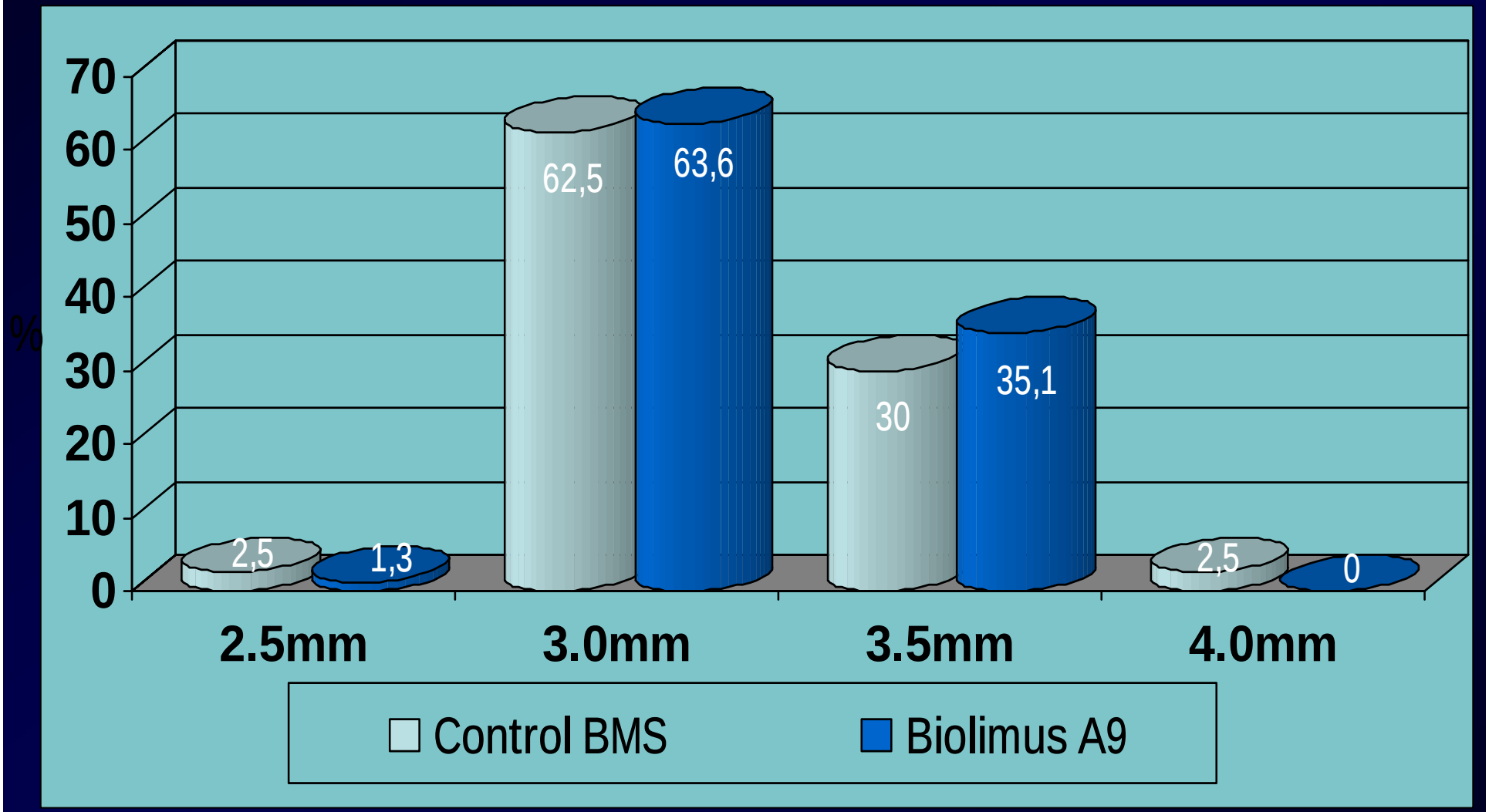

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Follow-up

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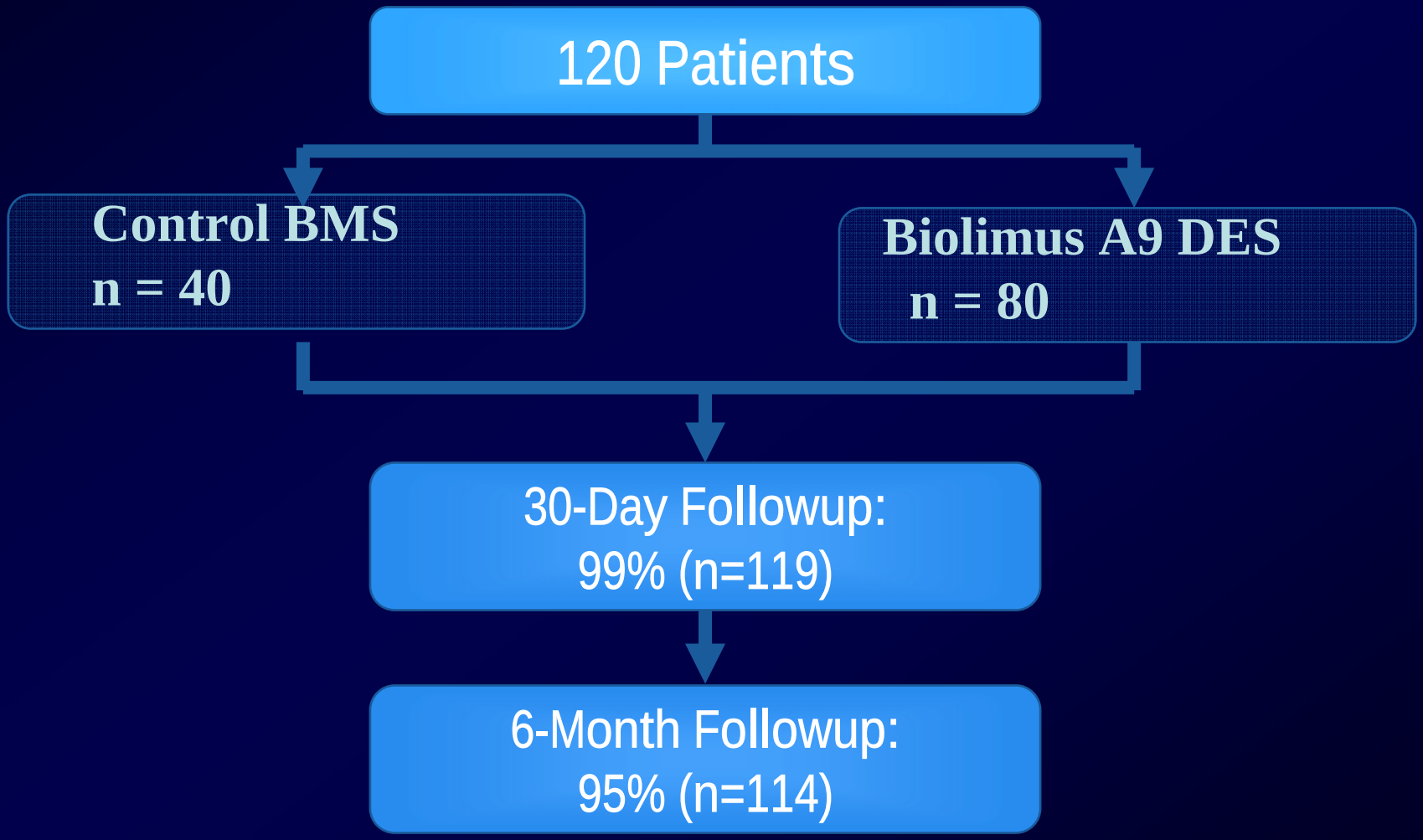

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Cumulative MACE to 6 Months (Hierarchical) STEALTH

	BMS	BioMATRIX	P Value
MACE	**2.5%**	**3.8%**	**>0.99**
Death	0.0%	0.0%	N/A
Q Wave MI	0.0%	0.0%	>0.99
Non-Q Wave MI	2.5%	2.5%	>0.99
Emergent CABG	0.0%	0.0%	N/A
TLR-CABG	0.0%	0.0%	N/A
TLR-PTCA	0.0%	1.3%	>0.99

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In-Stent Angiographic Results—6 Months

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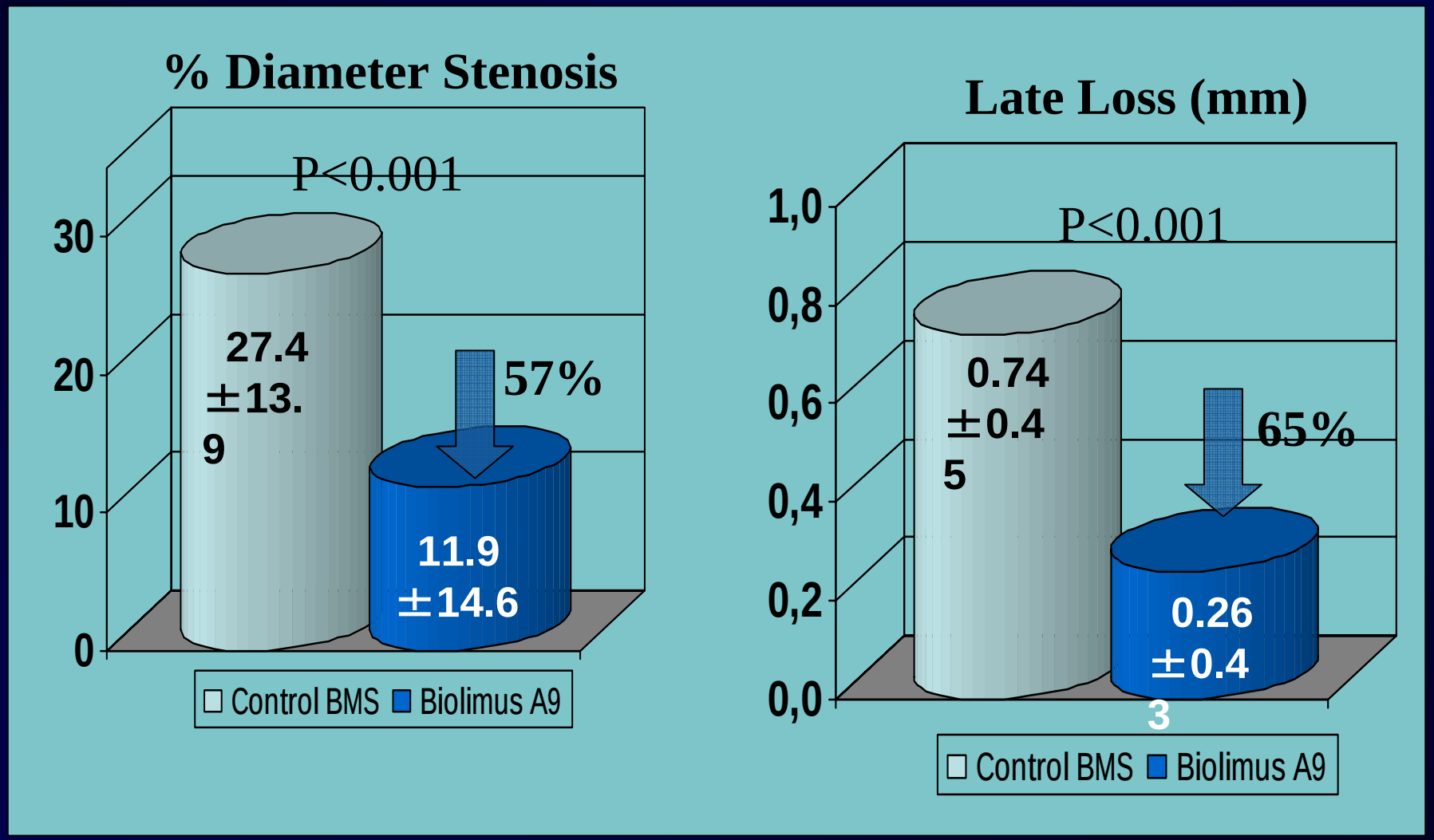

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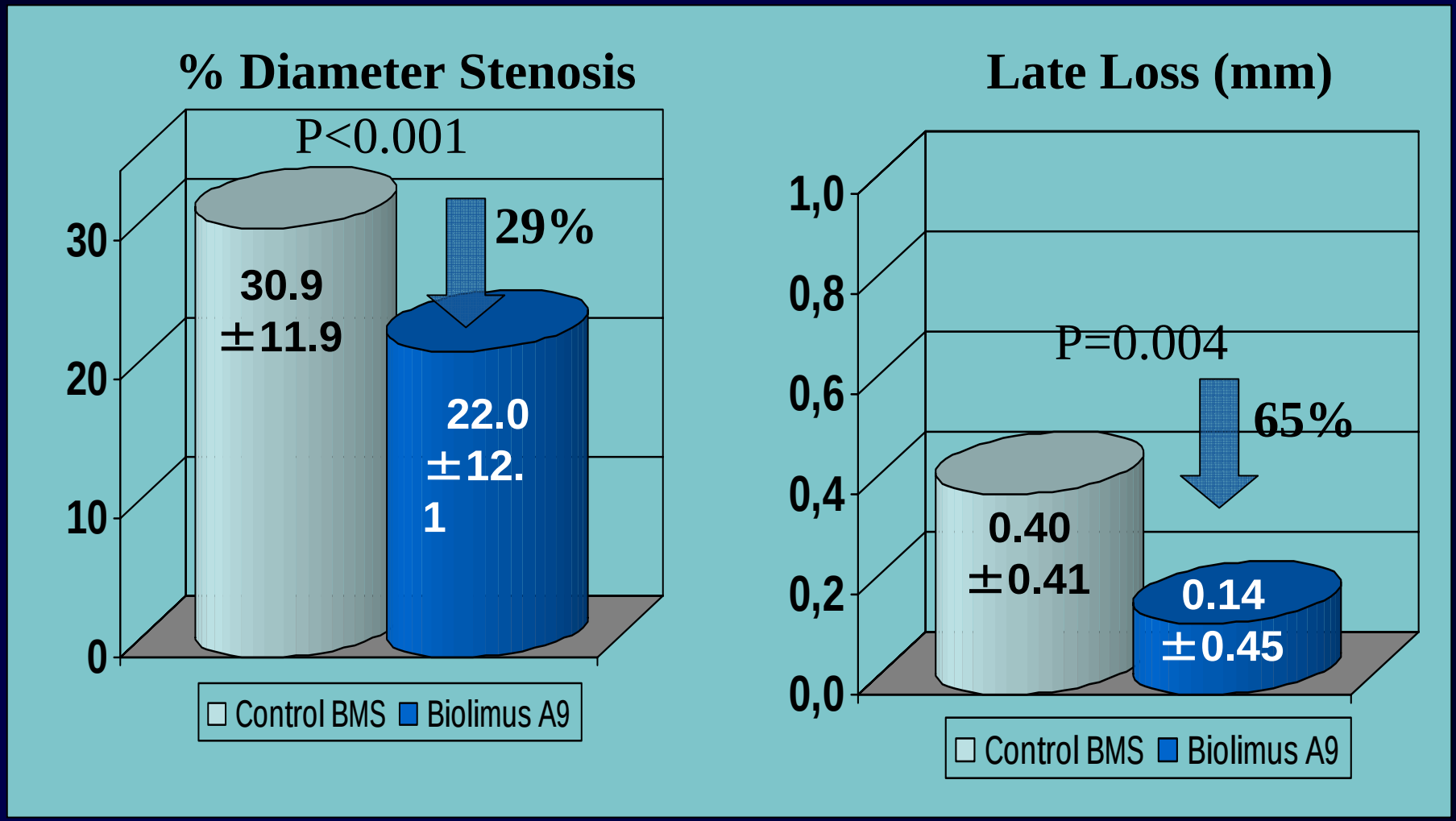
In-Lesion Angiographic Results—6 Months STEALTH



Binary Restenosis—6 Months

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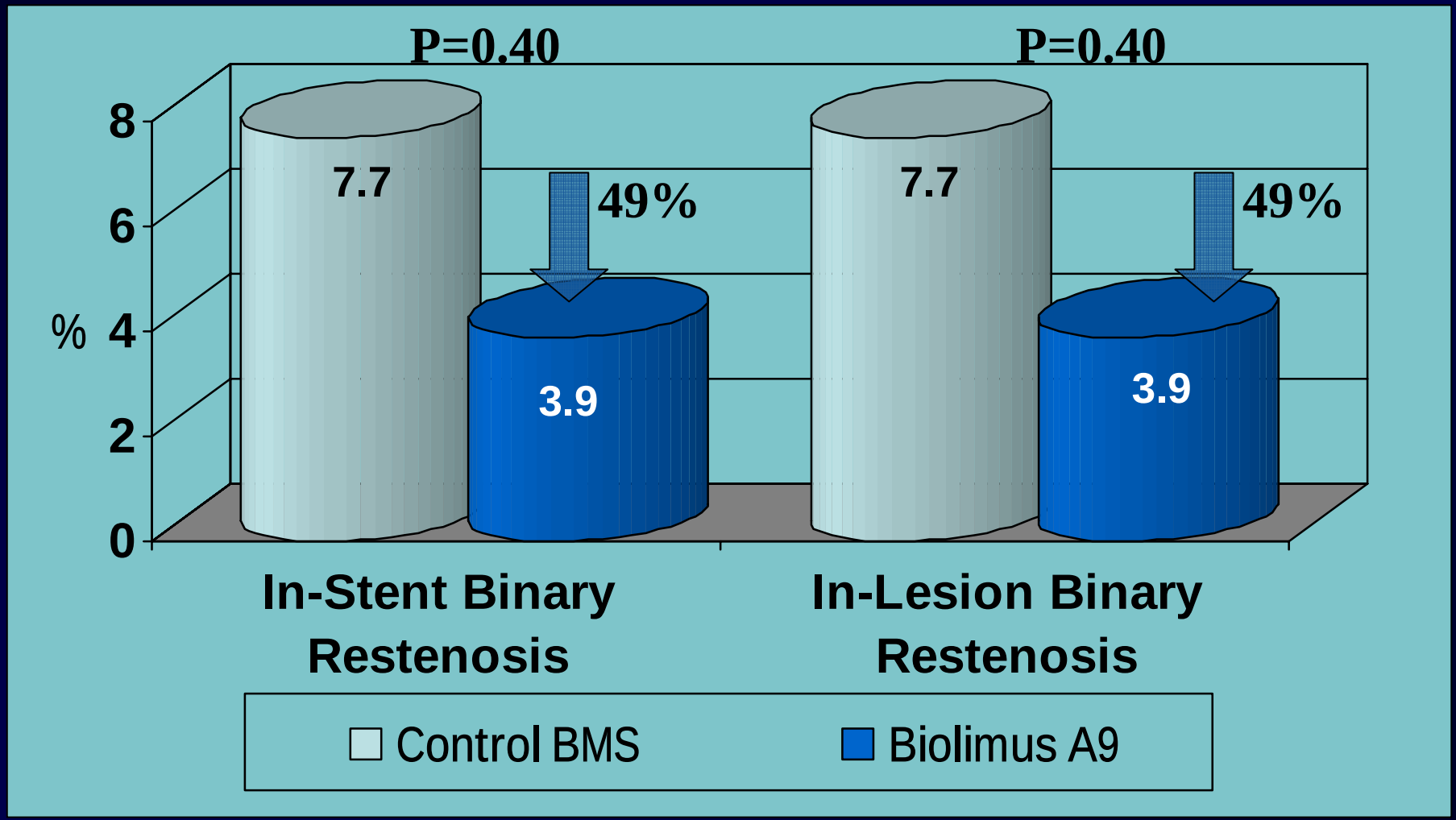

Late Loss—Edge Results

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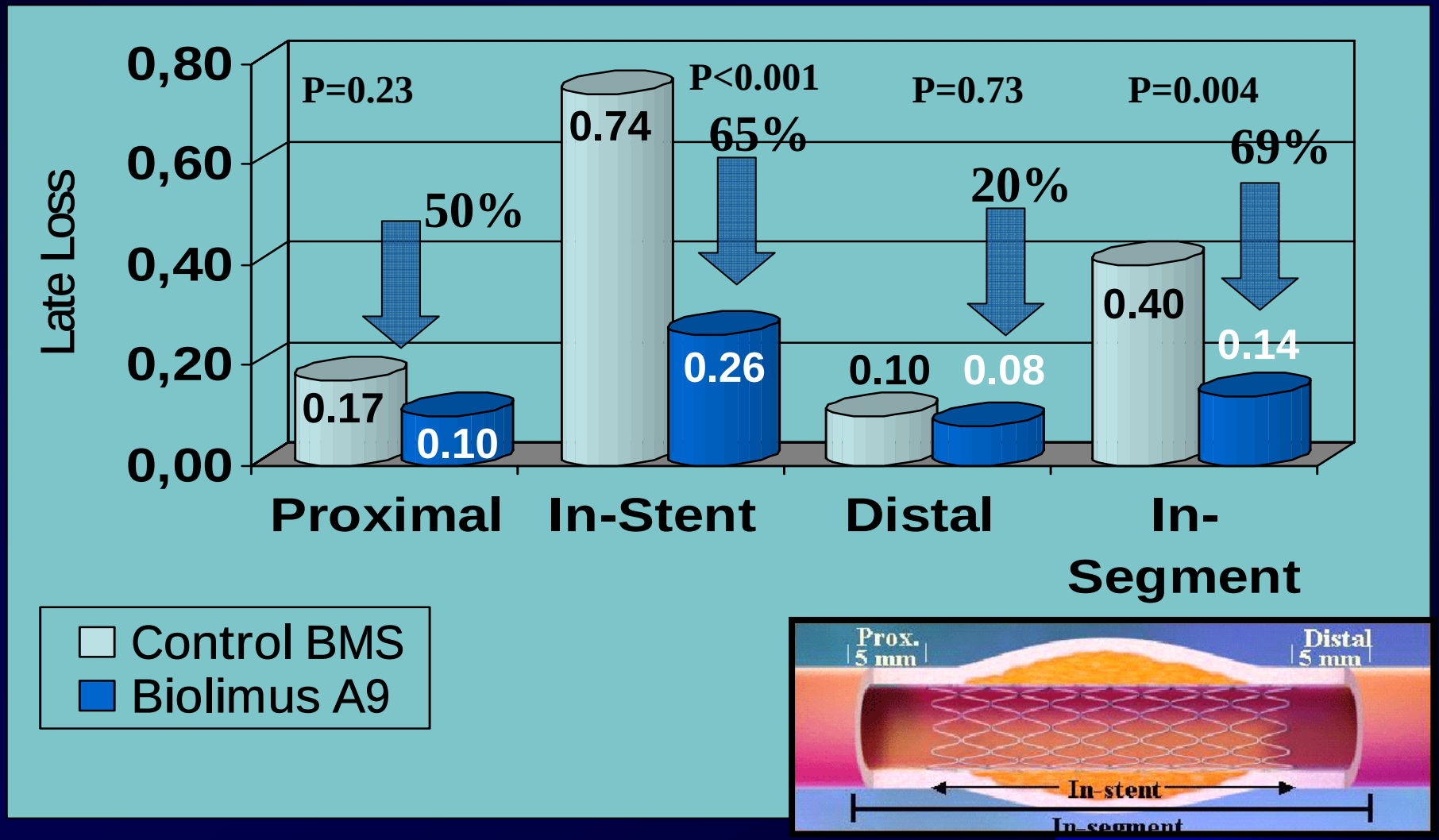

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IVUS Results—6 Months

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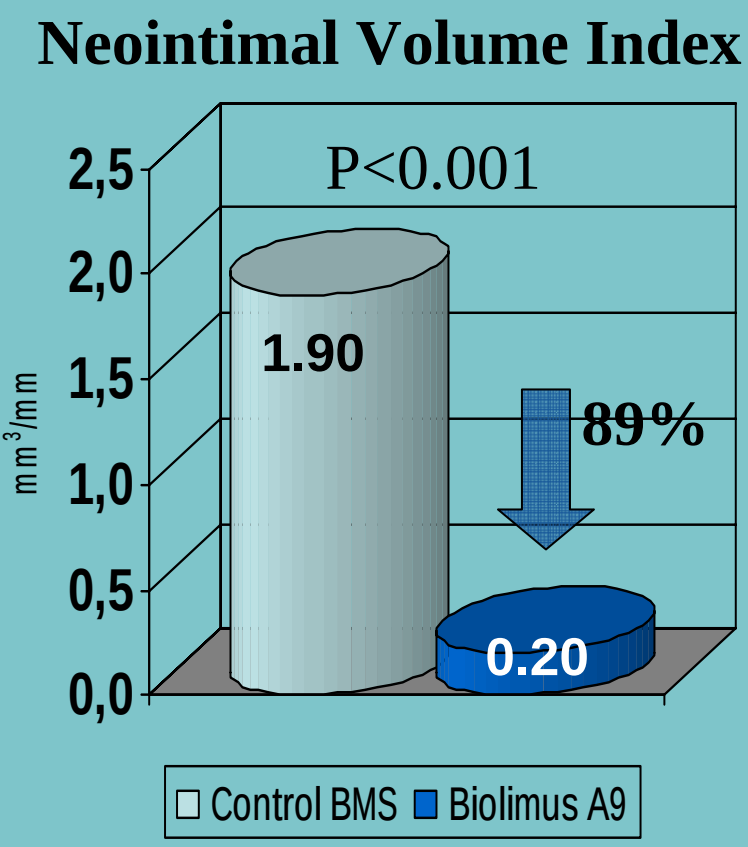
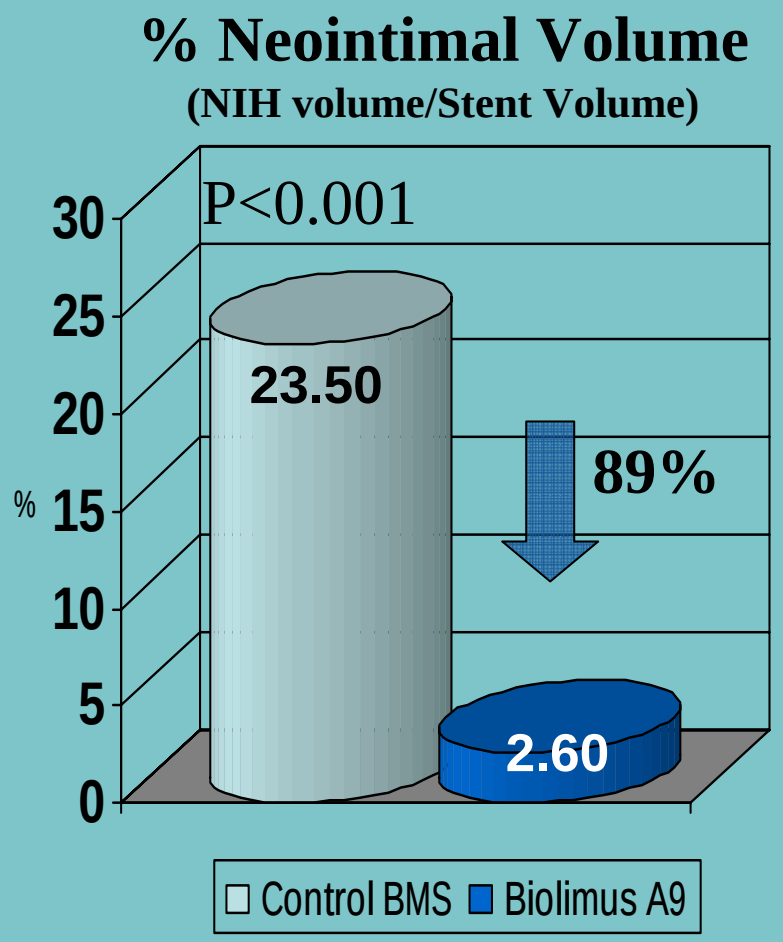
Courtesy Shimada, Honda, Hassan, Fitzgerald, Stanford Core Lab





The incidence of late incomplete apposition was 3% in both groups.

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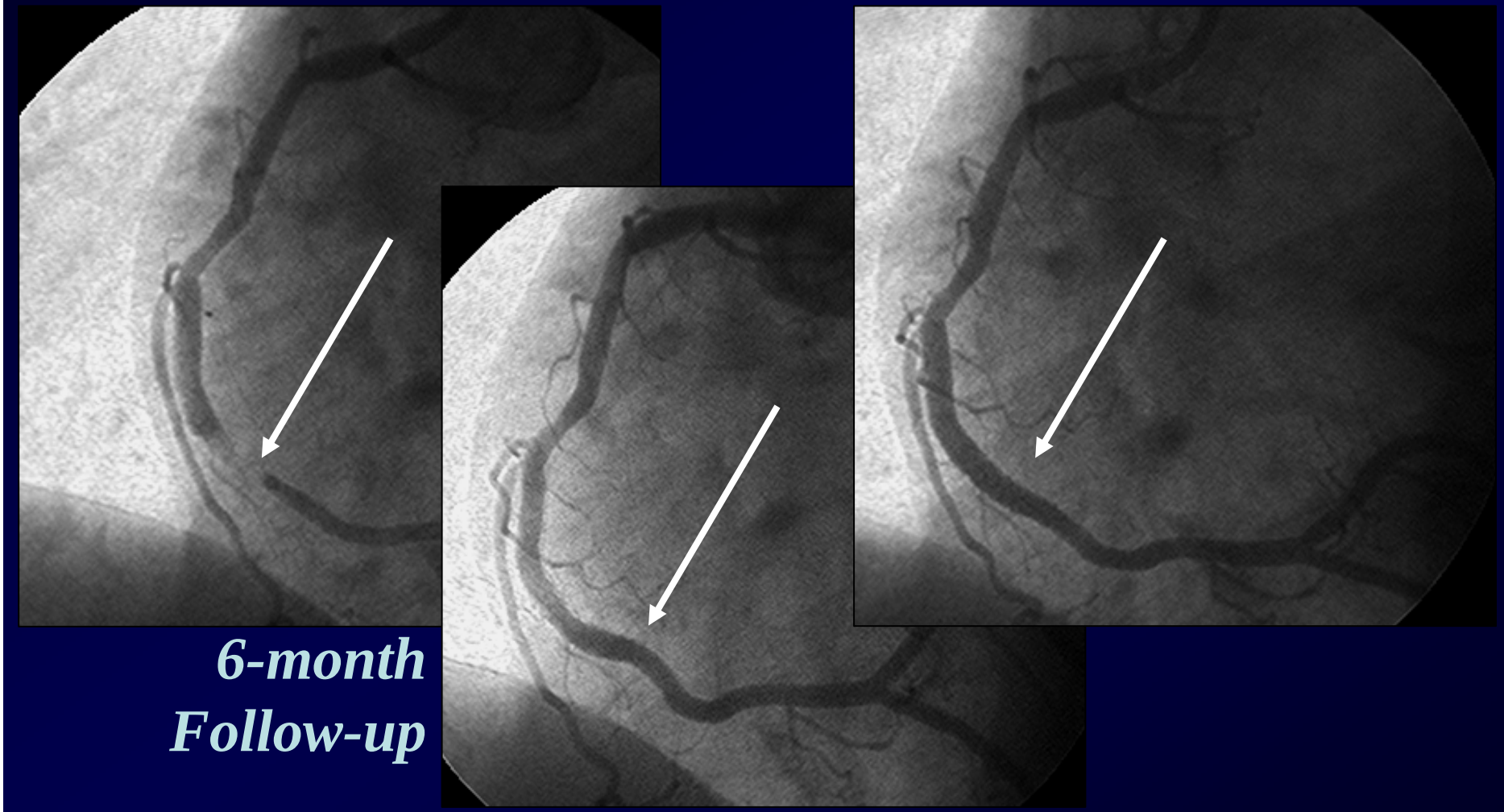
BioMatrix Case Example

preop

postop



6-month Follow-up

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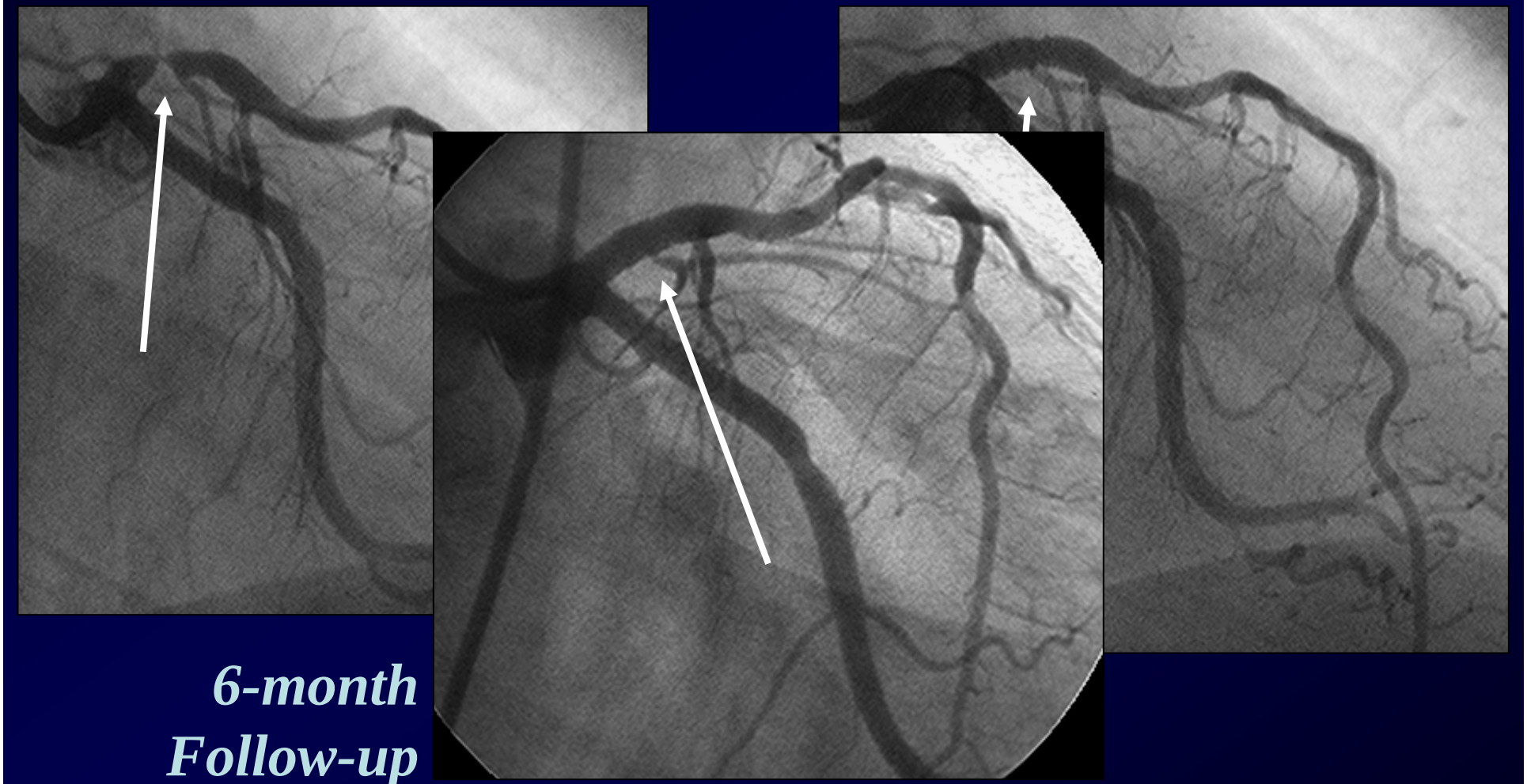
BioMatrix Case Example

preop

postop



6-month Follow-up

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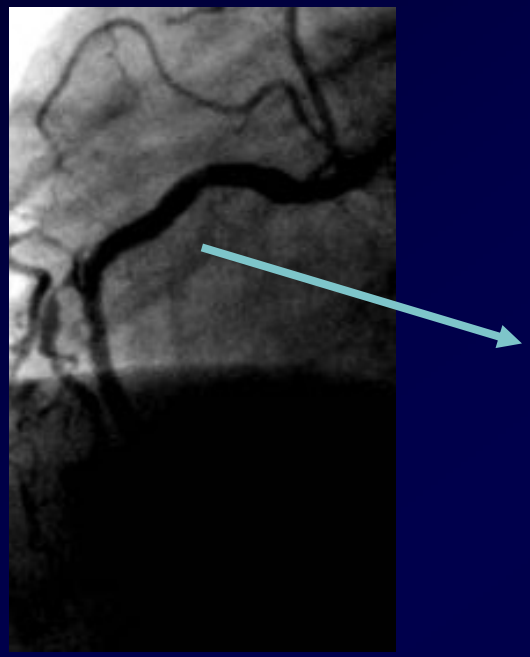
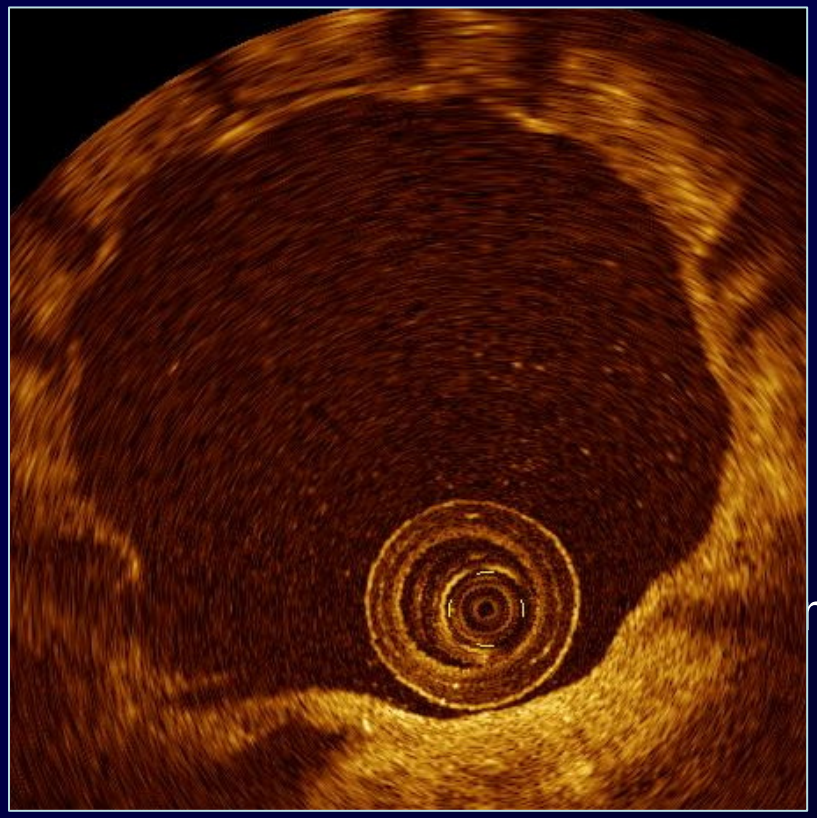
Biolimus-eluting stent

STEALTH-1 12 mths follow-up





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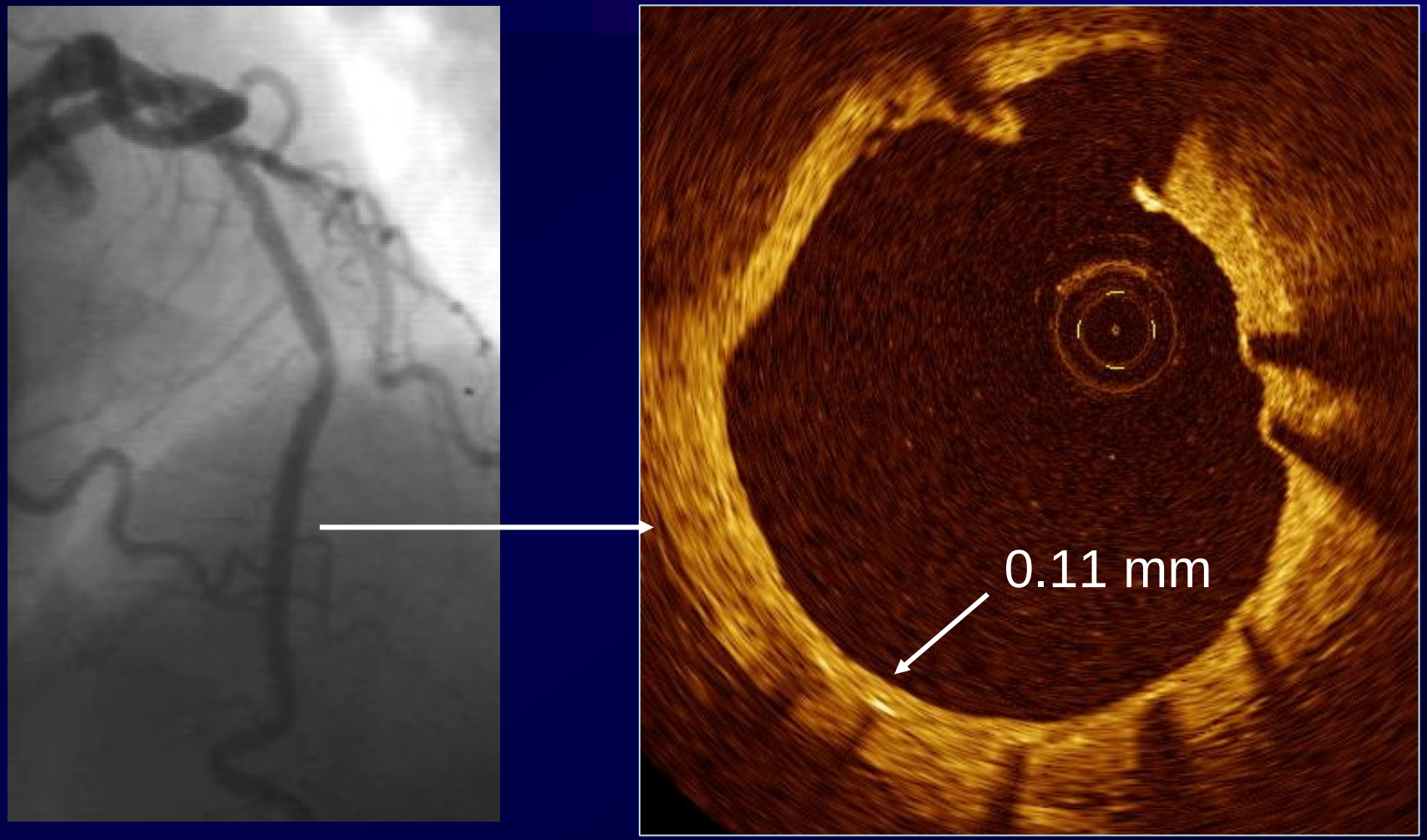
Everolimus-eluting stent



FUTURE-1 29 mths follow-up

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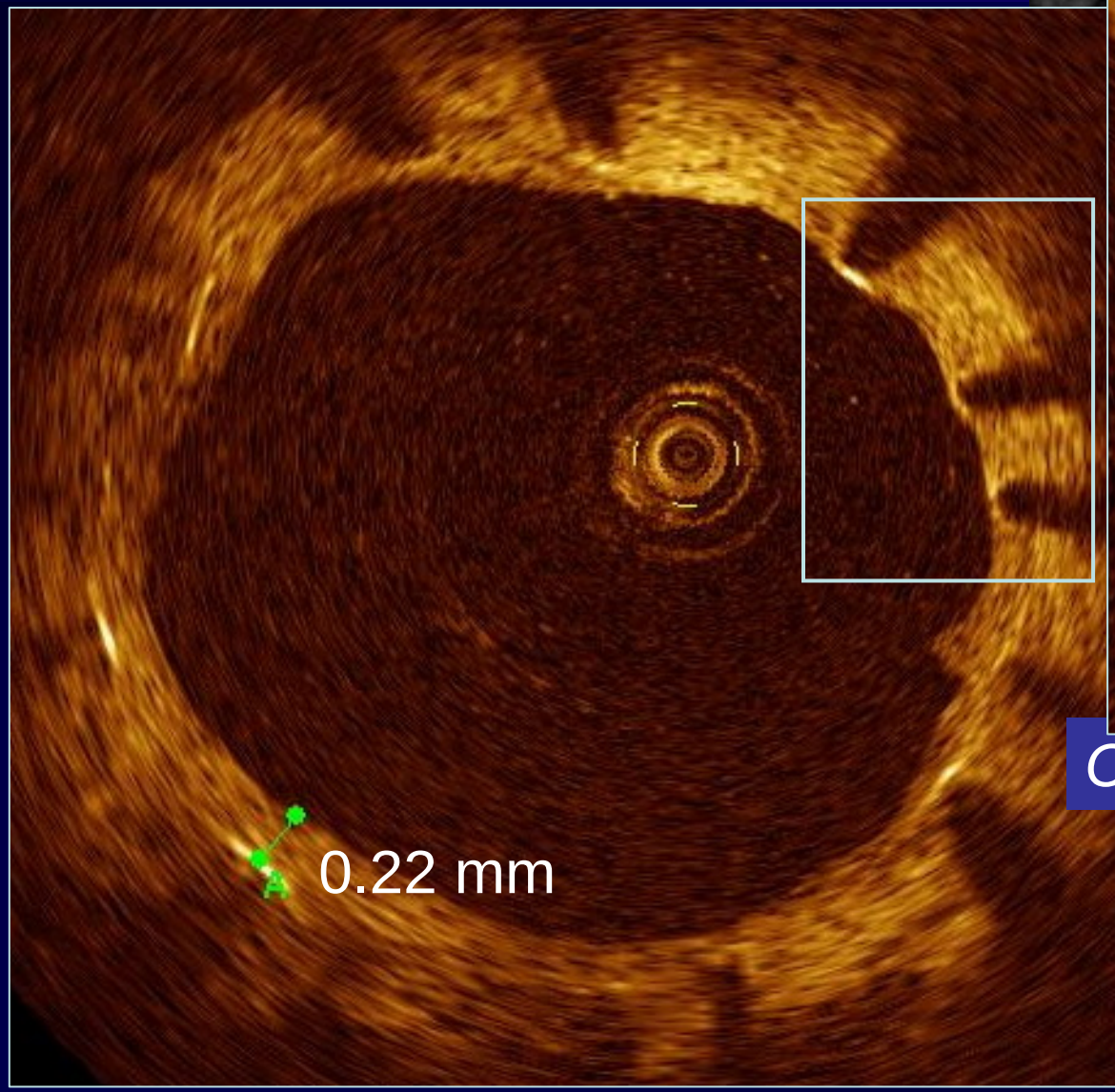
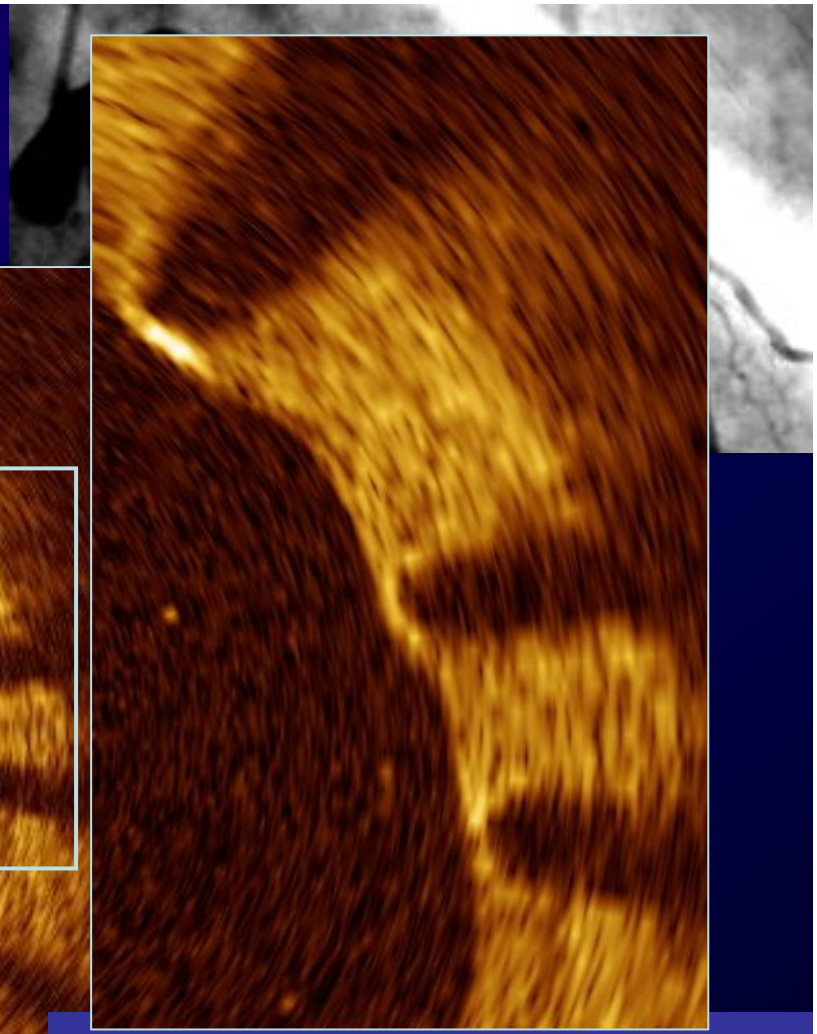
Cypher DES





Cypher 10 mths follow-up

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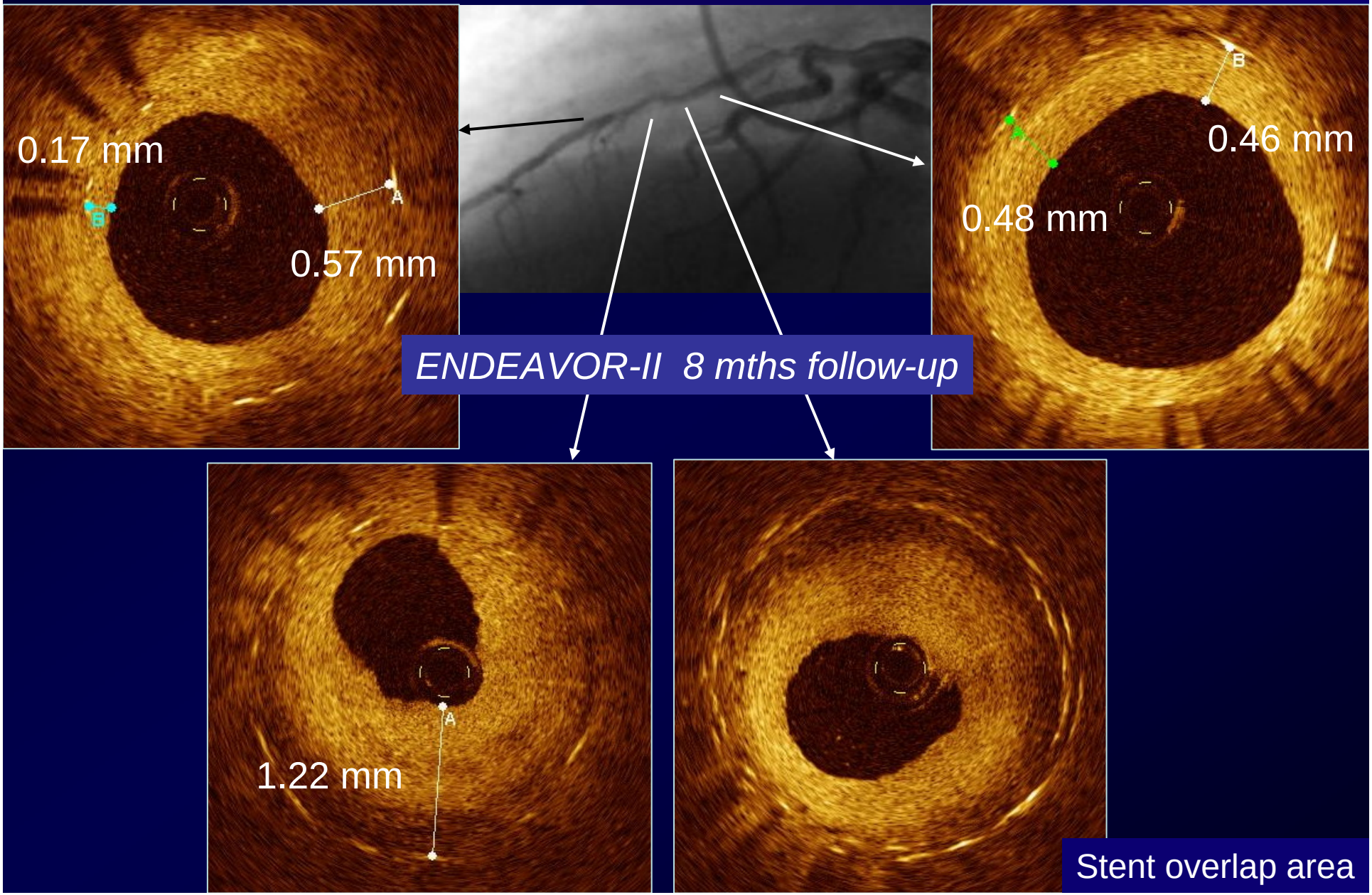
ABT-578-eluting stent



Comparison of Neointimal Volume

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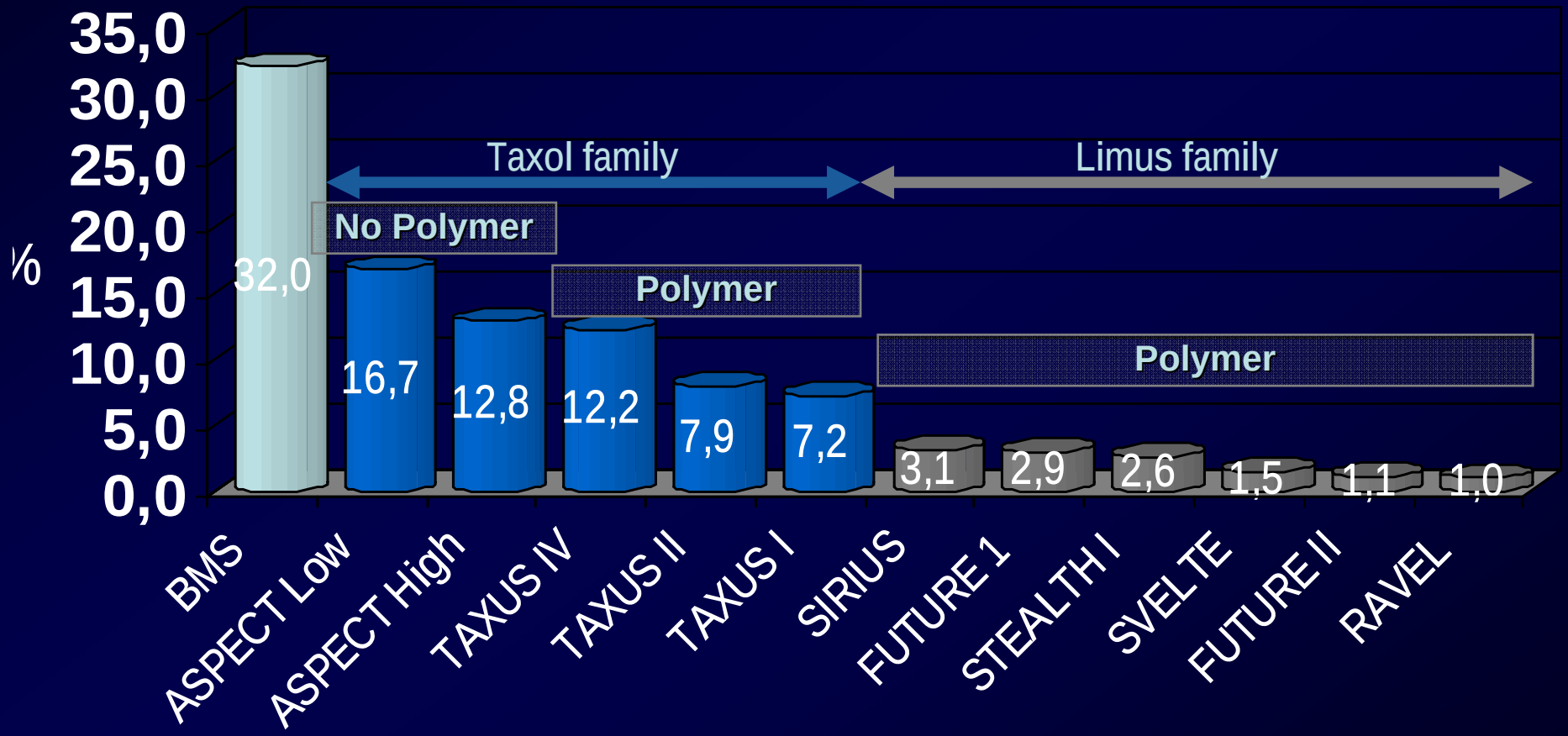

Courtesy Shimada, Honda, Hassan, Fitzgerald

Summary

- **In-stent:** a low restenosis rate (3.9% vs. 7.7%, P=0.4) and decreased late loss (0.26mm vs. 0.74mm, P<0.001) was found in Biolimus A9 DES compared with control.
- Notably, the bare S-Stent (control) restenosis rate and in-stent % DS (23.5%) are lower than rates reported in other stent trials.
- No restenosis occurred at the edges in either cohort.
- By IVUS, % neointimal volume (2.6% vs. 23.5%, P<0.001) was significantly lower in Biolimus A9 DES compared with control.
- Late incomplete apposition was low (3% vs. 3%) in both groups.

Planned Studies

- BIG-SIR Study – 3rd Qtr 2005
  - Randomized, multi-center, comparison trial of BioMATRIX™ Stent with CYPHER™ Stent
- STEALTH US Pivotal Study – 4th Qtr 2005
  - Prospective, multi-center, randomized, non-inferiority trial of BioMATRIX™ Stent compared to TAXUS™ and CYPHER™ stents in the treatment of *de novo* coronary arteries

BIG-SIR STUDY

(**Bi**olimus A-9 vs. **Sir**olimus)

- **Trial:**
  - Randomized, multi-center, comparison trial of BioMATRIX™ Stent with CYPHER™ Stent
- **Objective:**
  - To compare BioMATRIX™ Stent (Biolimus) with CYPHER™ Stent (Sirolimus)
- **Enrollment:**
  - 1,000 patients from ~3 sites in Europe. Patient data collection will occur at 1, 6, 8, 9, and 12 months following stent implant, and at 2, 3, 4, 5 years
- **Primary Endpoint:**
  - Major Adverse Cardiac Events (MACE) at 9 months
  - Target vessel revascularization (TVR) rates at 9 months
- **Secondary Endpoints:**
  - In-lesion and in-stent restenosis
  - In-lesion and in-stent MLD

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STEALTH PIVOTAL

US Pivotal

- **Trial:**
  - Prospective, multi-center, randomized, non-inferiority trial of BioMATRIX™ Stent compared to TAXUS™ and CYPHER™ stents in the treatment of *de novo* coronary arteries
- **Objective:**
  - Demonstrate the safety and efficacy of the BioMATRIX™ Stent as compared to TAXUS™ (Paclitaxel) and CYPHER™ (Sirolimus) stents
- **Enrollment:**
  - 1700 patients from ~70 sites. Patient data collection will occur at 1, 6, 9, and 12 months post stent implant, and annually thereafter for 5 years
- **Primary Endpoint:**
  - Ischemia-driven target vessel revascularization (TVR) rates at 9 months
- **Secondary Endpoints:**
  - Late loss, binary restenosis, MLD, TLR, and TVF
  - Major Adverse Cardiac Events (MACE)
  - Device/Lesion/procedural success

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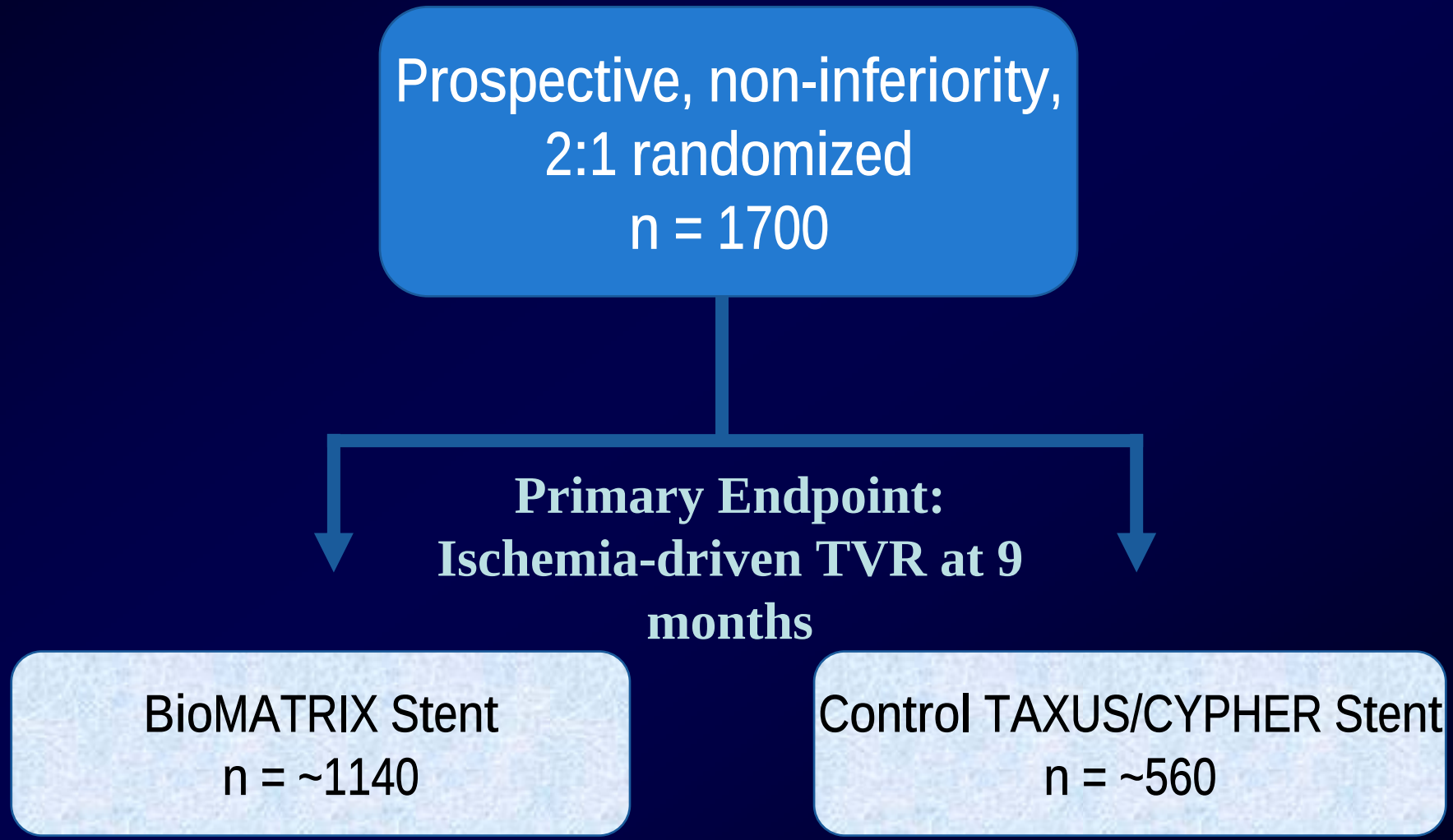
STEALTH PIVOTAL

Study Design



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STEALTH Conclusions

- The BioMatrix stent, eluting the rapamycin derivative Biolimus A9 from a bioabsorbable PLA polymer coating, demonstrates significantly reduced NIH compared to S-Stent controls in this FIM experience.

- A low MACE rate (5%) and the absence of cardiac deaths suggest safety of this new DES.