EVEROLIMUS Eluting Stents

FUTURE - Trial Program

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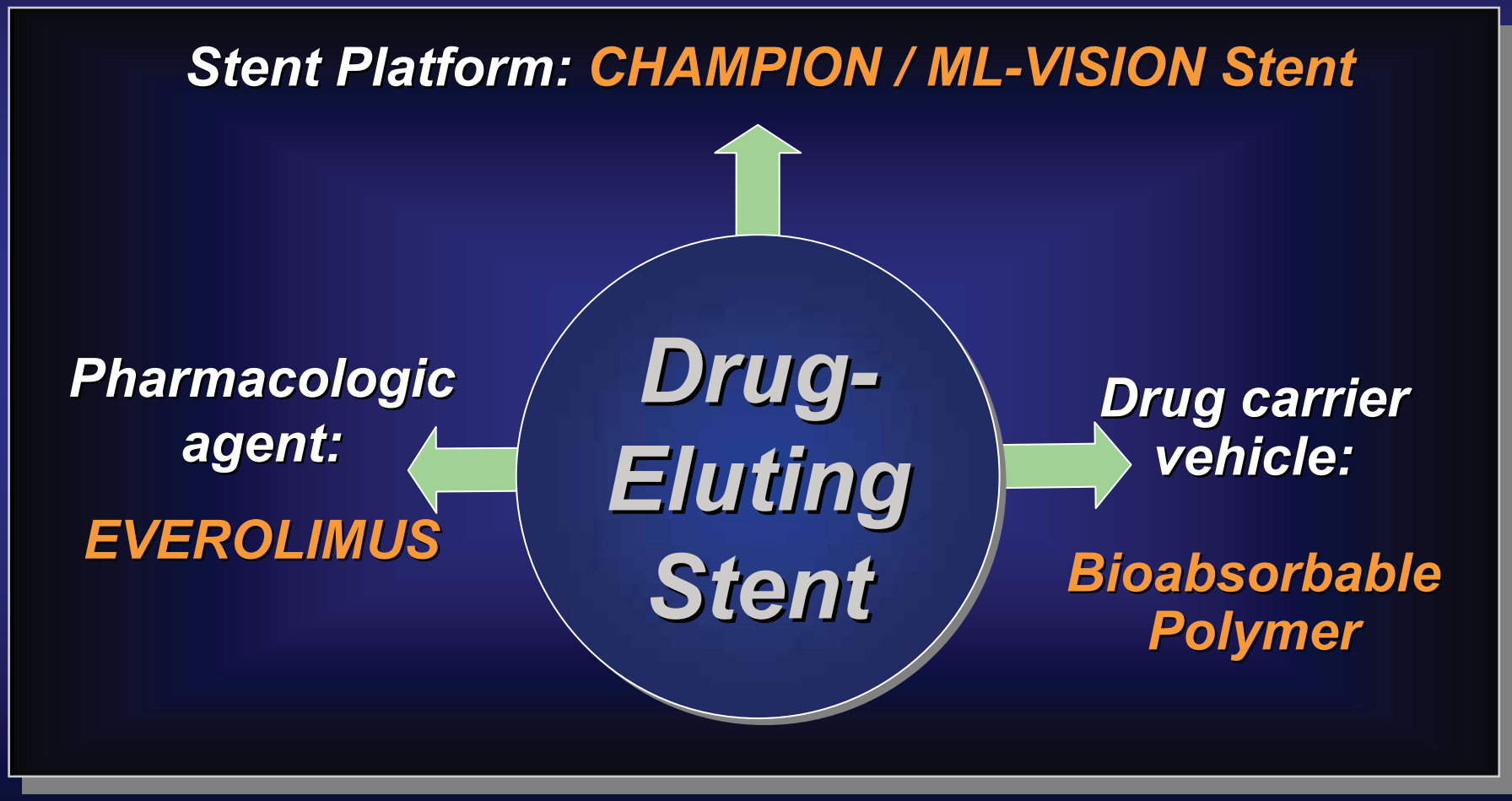
Stanford University, School of Medicine, CA, USA

FUTURE
Everolimus Eluting Stent Program



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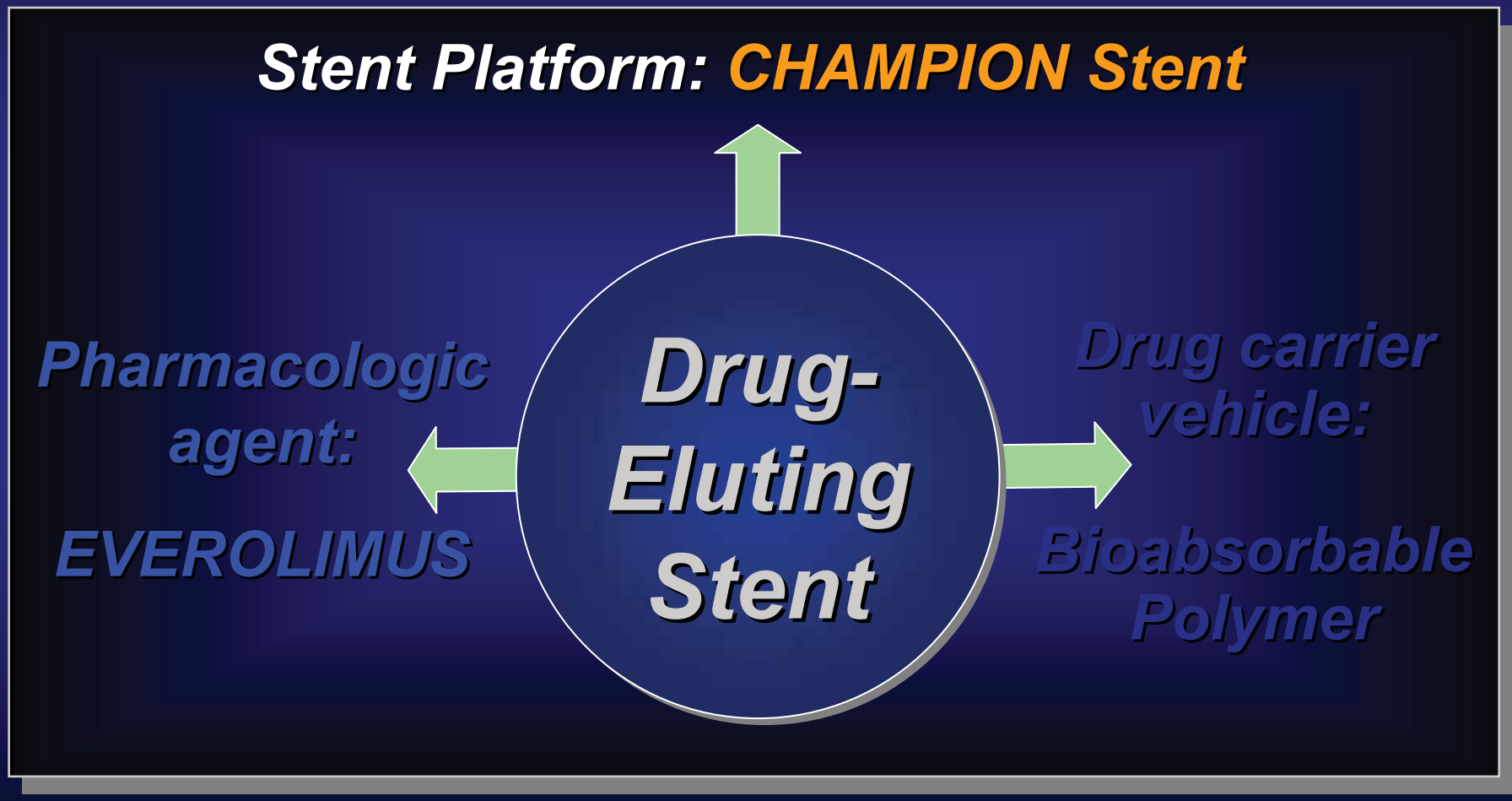
FUTURE
Everolimus Eluting Stent Program



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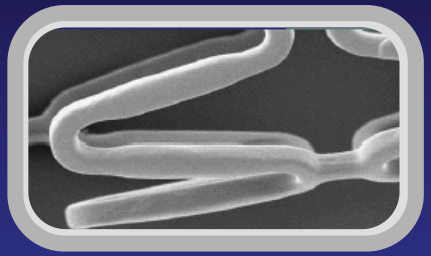
CHAMPION™ Drug Eluting Stent Objectives

Minimize Vessel Injury

- Narrower strut width at crest allows for lower deployment pressures to minimize vessel injury

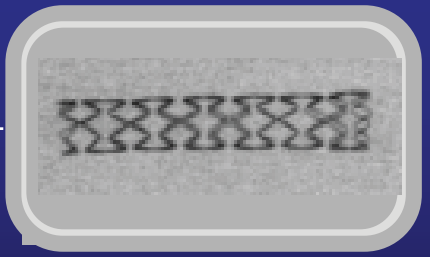


Uniform Strut to Wall Apposition

- Promotes uniform drug delivery in vessel

Precision Placement

- Excellent radiopacity for accuracy of stent placement



Deliverability

- Incorporates same delivery system as ML VISION™ for enhanced deliverability

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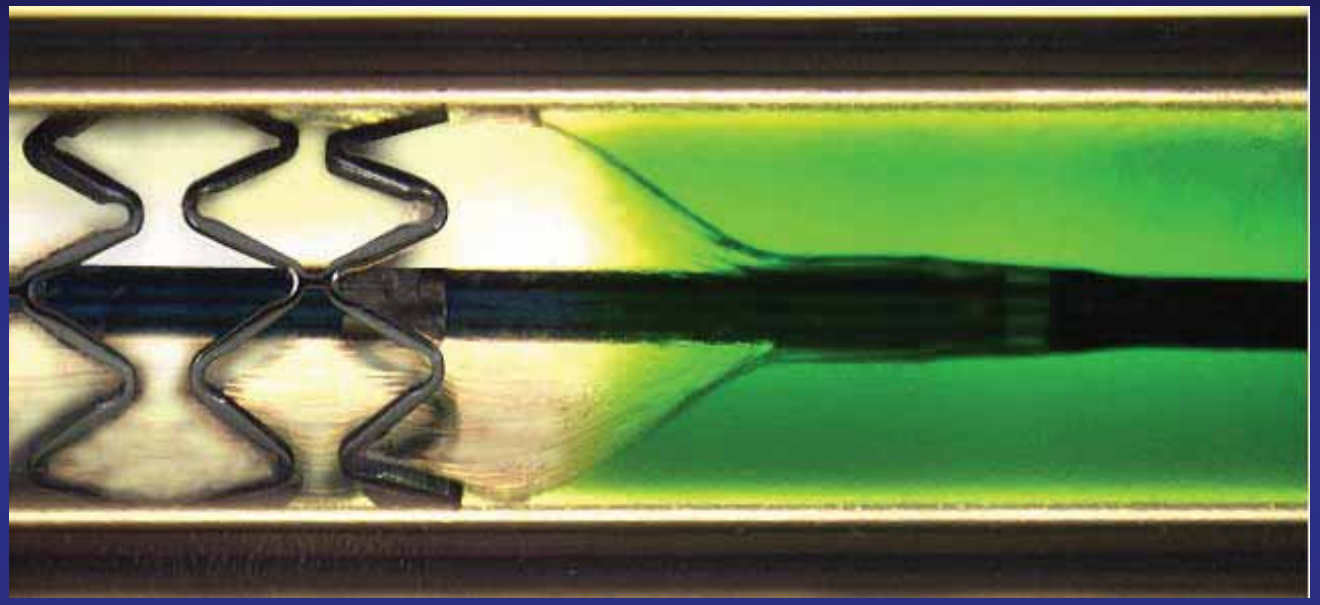
CHAMPION™ Delivery System



- Design objective: Minimize balloon outside the stent to reduce potential for peri-stent injury

CHAMPION™ RX 3.0 x 18 mm

CHAMPION™ Drug Eluting Stent System manufactured entirely by Guidant.

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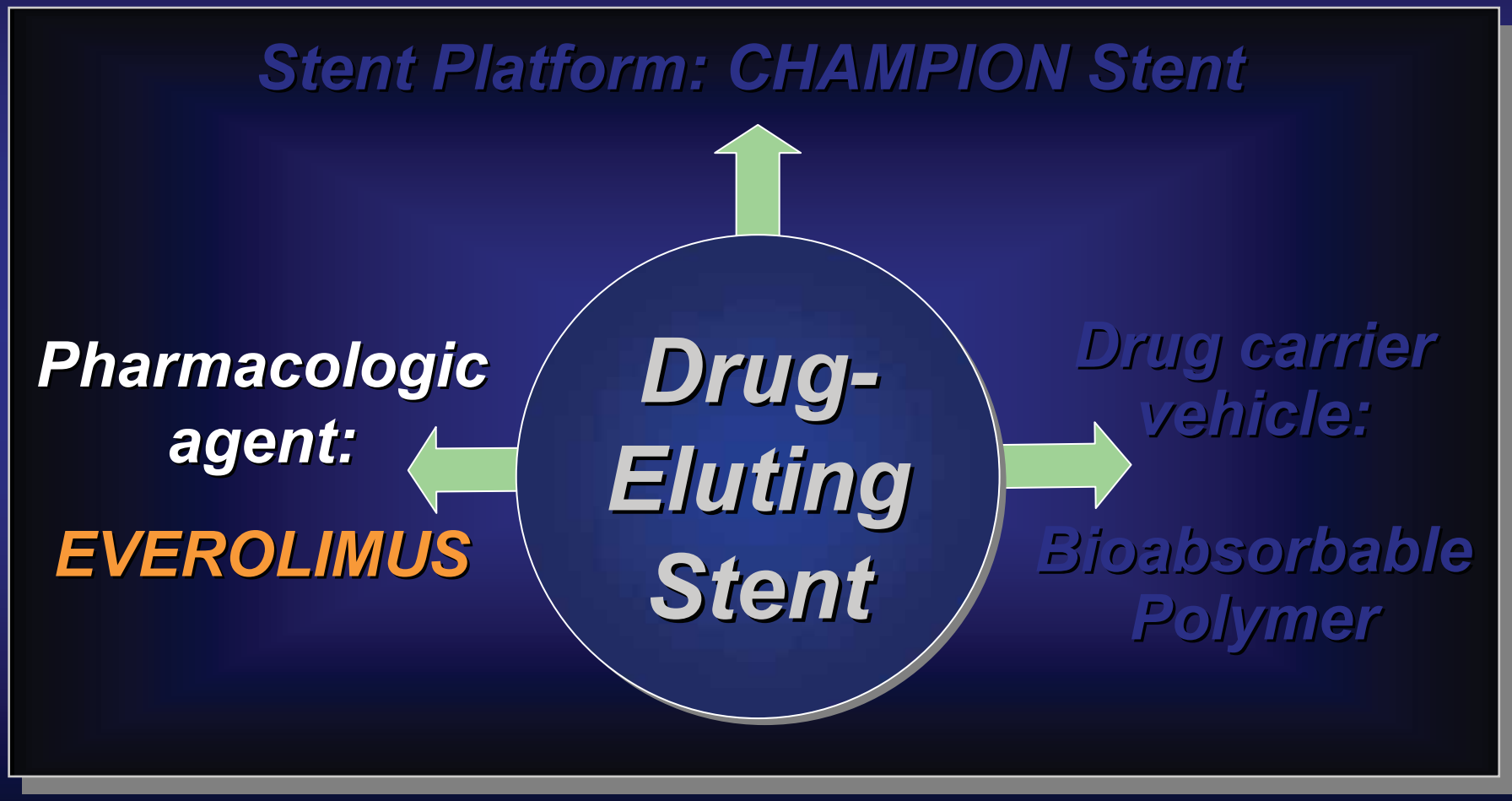
FUTURE
Everolimus Eluting Stent Program



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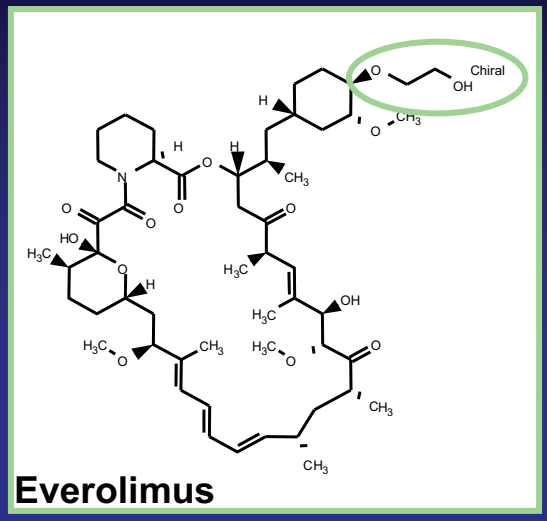
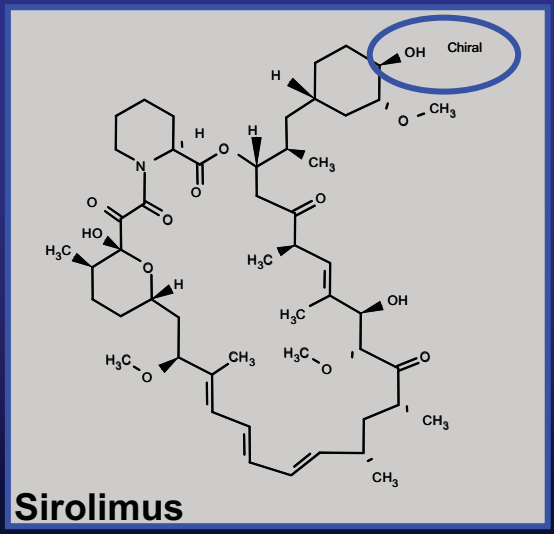
Everolimus

Potential Advantages

- Everolimus designed to have improved pharmacokinetics versus sirolimus for treating organ transplant patients
- Increased lipophilicity and rapid tissue absorption[1]
  - Longer cellular residence time and activity[2]
  - Improved chemical stability[3]
- Reduced intimal thickening in cardiac graft vessels[4] in randomized clinical trial





[1] Crowe and Lemaire. Pharmaceutical Research 1998, 15:11 (1666-1672)
[2] Jacobsen et al. Transplantation Proceedings 2001, 33 (514-515)
[3] Novartis Pharma
[4] Eisen H.J., NEJM, August 28, 2003, 349;9, 847-858

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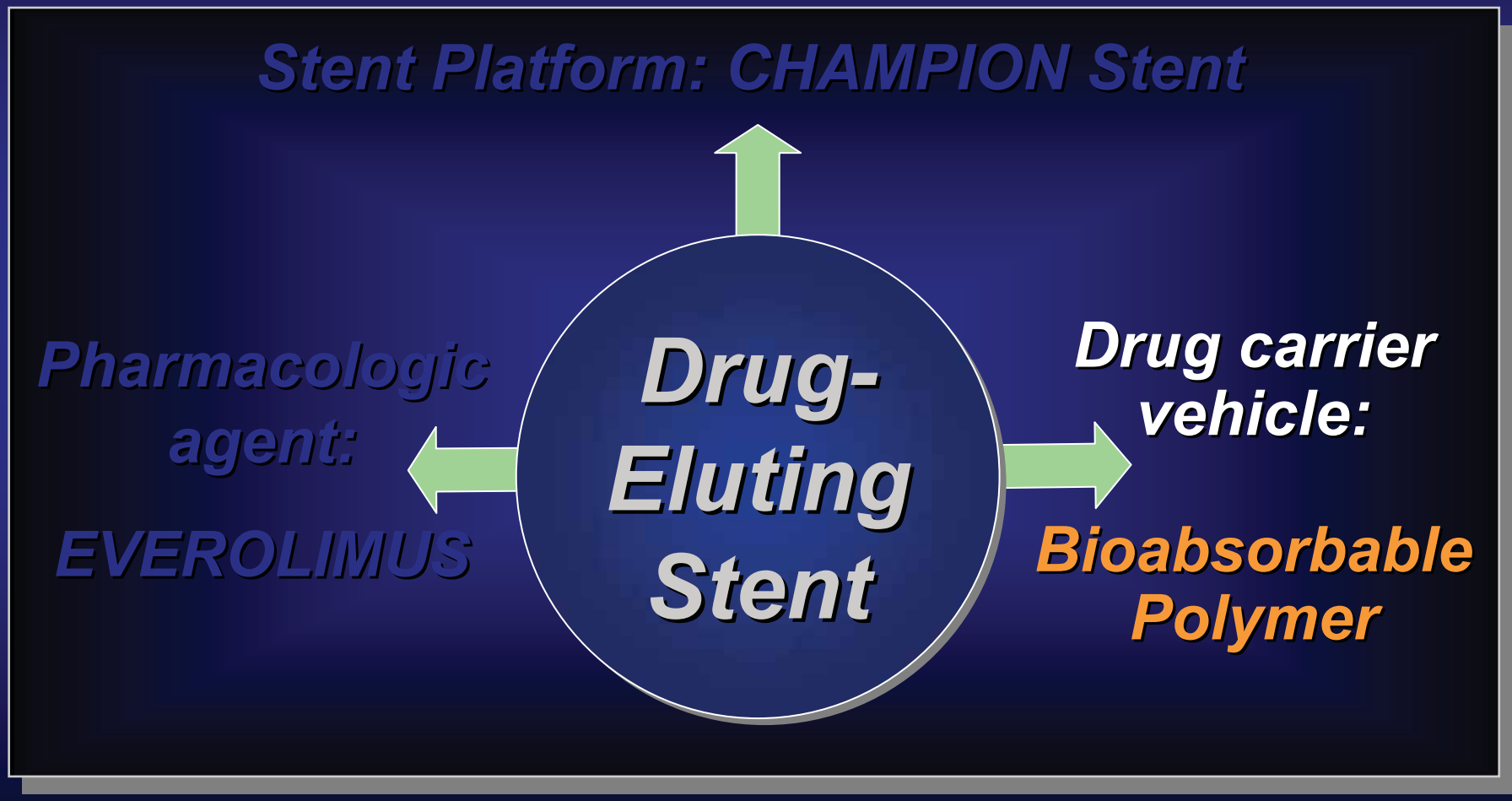
Everolimus Eluting Stent Program



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CHAMPION™ Bioabsorbable Polymer

Thin–film Poly Lactic Acid (PLA)

Safely used in numerous medical applications since the 1980's

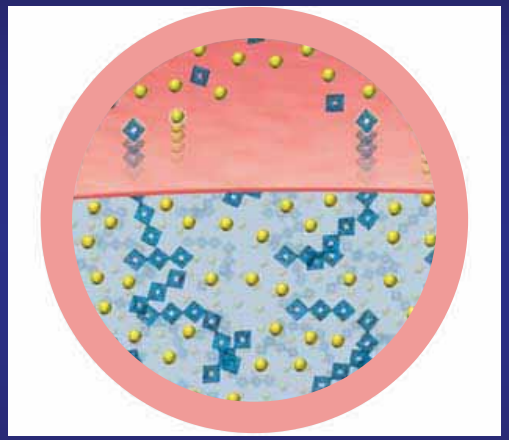
- Vascular, orthopedic, dental

Breaks down to lactic acid, a natural metabolite

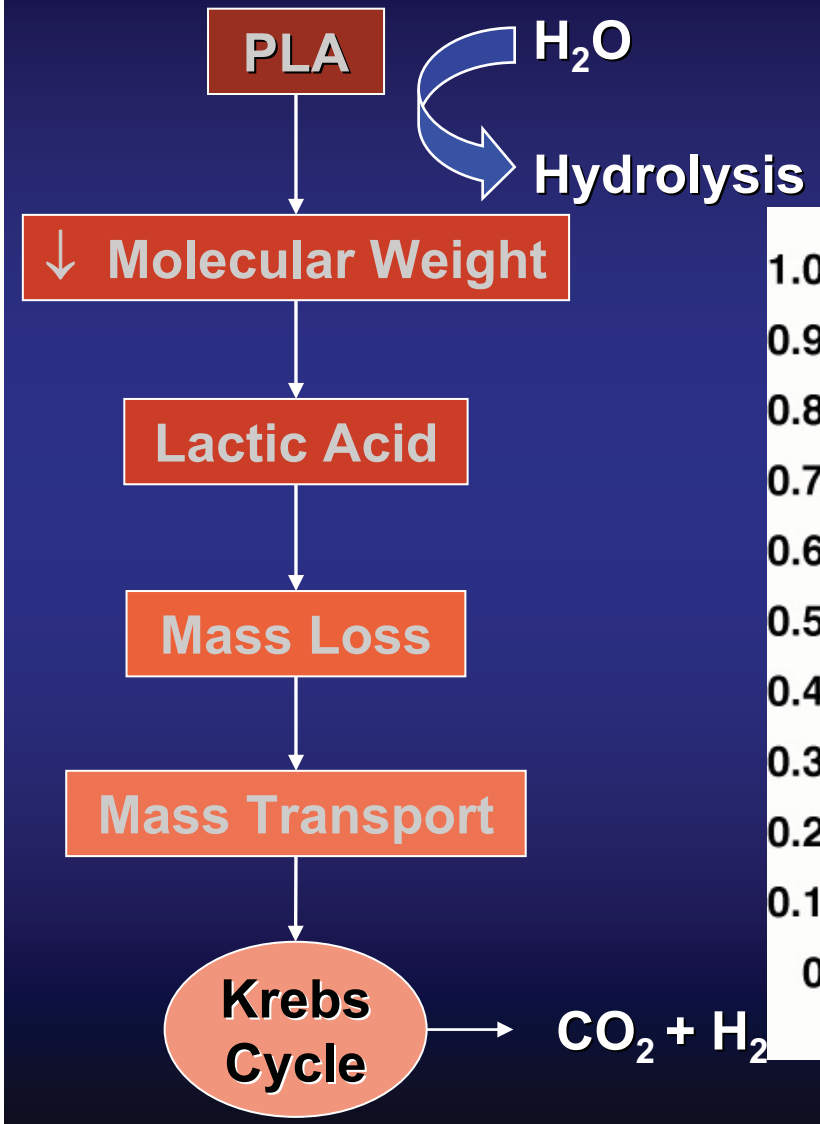
High drug loading capability

- High drug to polymer ratio—ability to load >50% drug

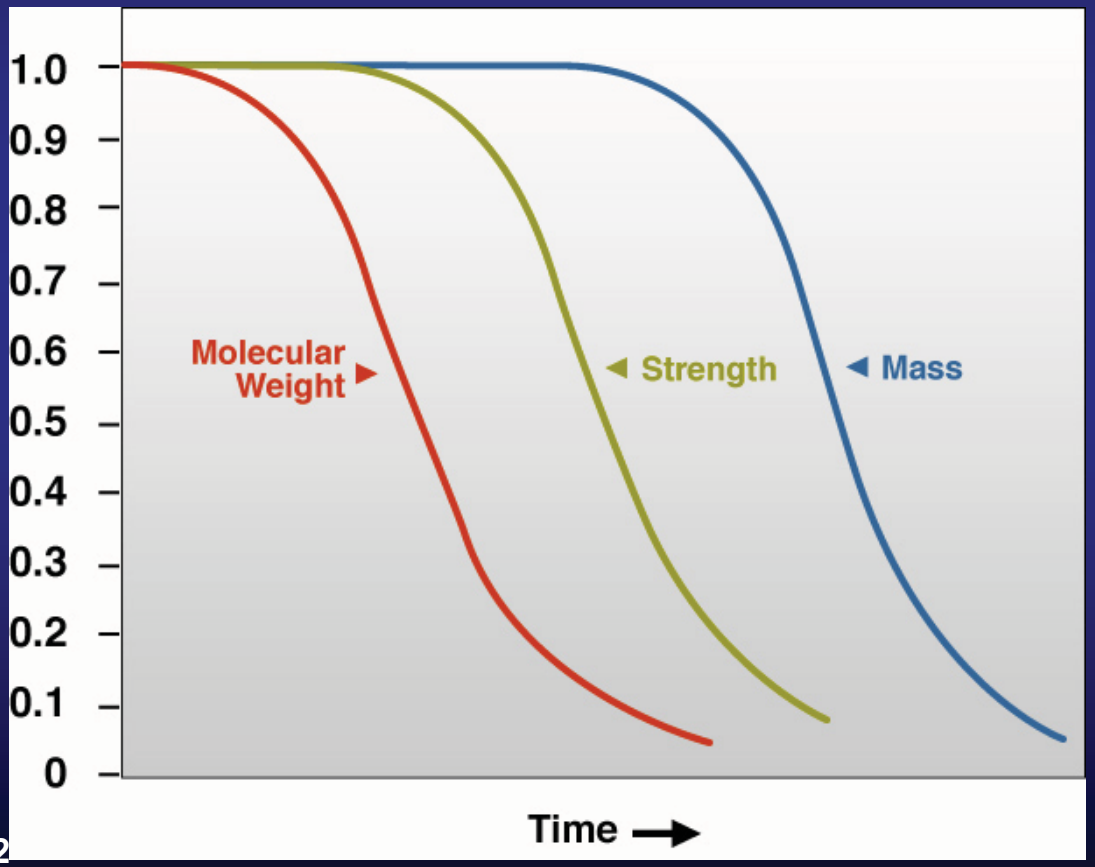
As drug release matrix is absorbed, no residual drug is encapsulated in polymer



PLA Metabolic Pathway



Generalized Degradation Curves[1]



[1]Pietrzak WS, et al. J. Craniofaxial Surg, 1997; 8: 92-96.
Middleton JC, Tipton AJ, Biomaterials, 21 (2000) 2335-2346.

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CHAMPION™ Drug Eluting Stent System

Pre-clinical Experience

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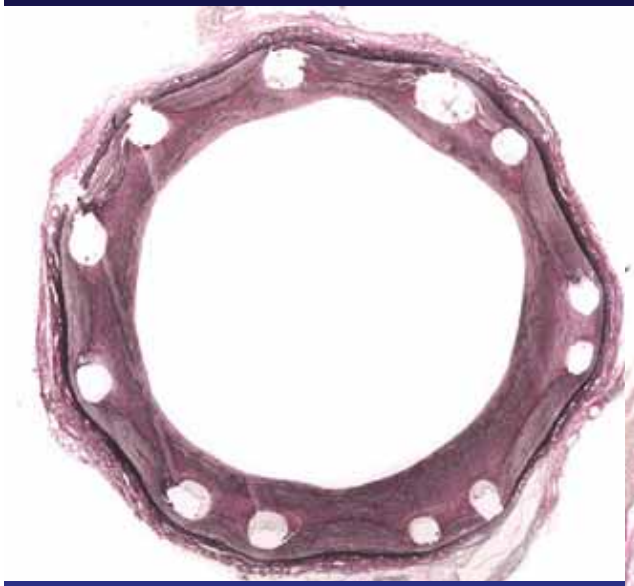
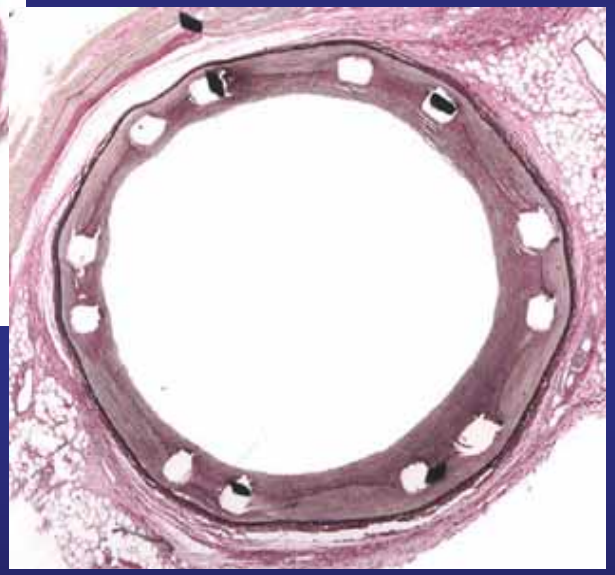
CHAMPION™ 90 Day Safety Study

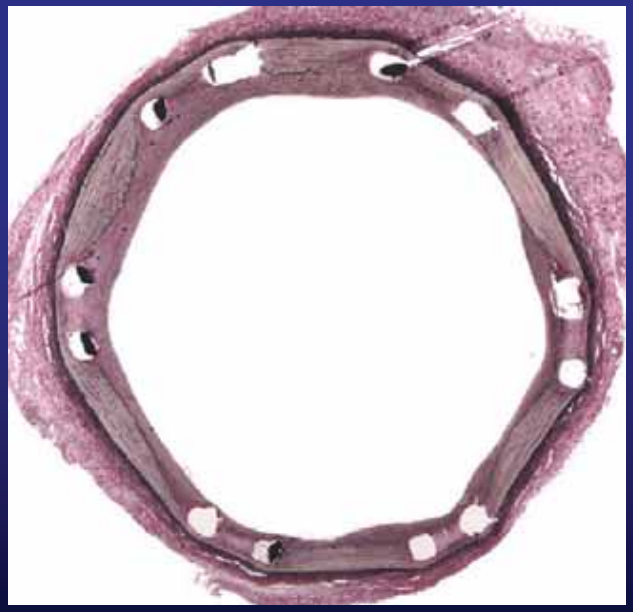
90 Day Porcine Safety Study



Metallic Stent



Polymer Carrier Only



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Balloon: Artery ratio 1.1:1

Images taken at 2x magnification. Photos on file at Guidant

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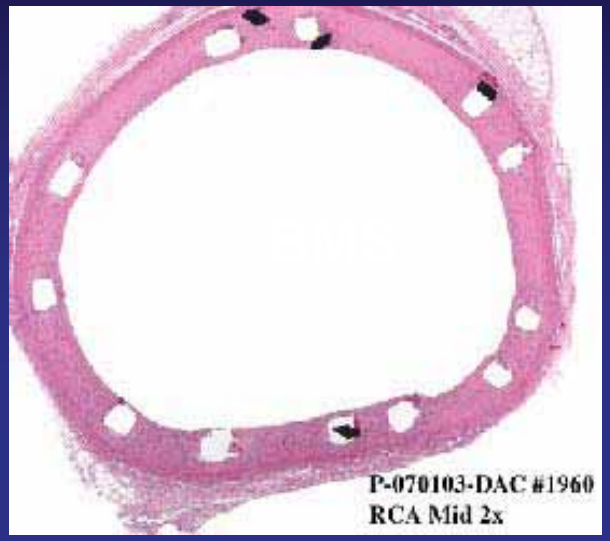
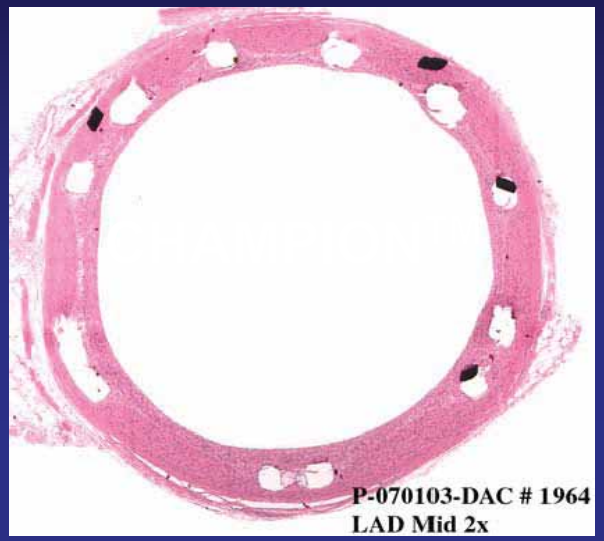
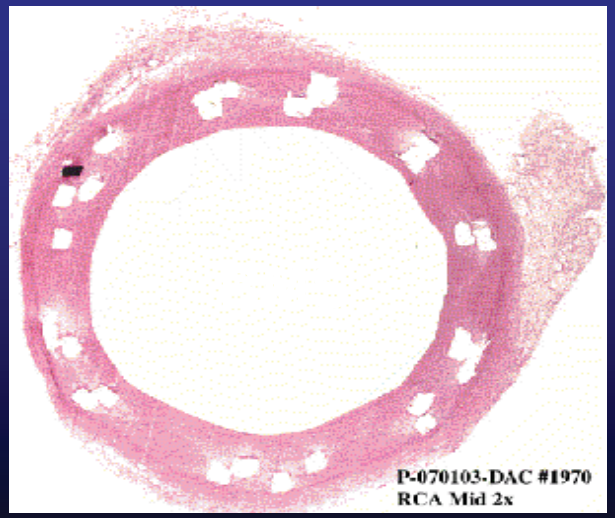
90 Day Overlapping Stent Study

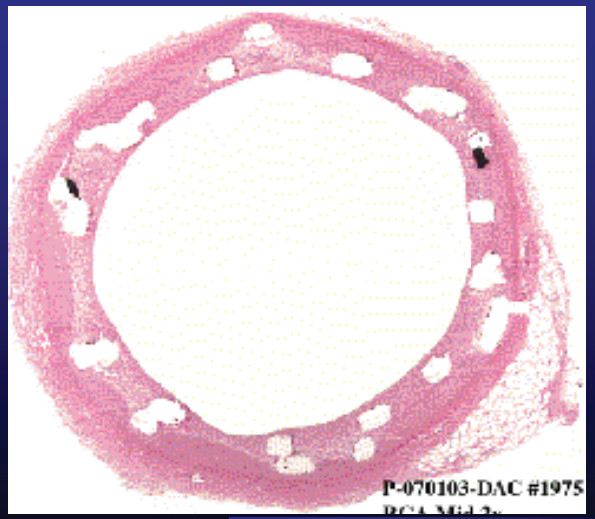


Single stents





Overlapped stents



Photos on file at Guidant

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CHAMPION™ Drug Eluting Stent System

Clinical Experience

and

Clinical Trial Strategy

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Everolimus Eluting Stent Program
CHAMPION™ Clinical Trials

FUTURE I	FUTURE II	FUTURE III	FUTURE IV
Safety and performance	Safety and performance		
Europe	Europe		
n = 42	n = 64		

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Everolimus Eluting Stent Program
FUTURE I and II

Stent sizes: 2.5 – 4.0 mm diameter, 14 and 18 mm lengths

Prospective, randomized

Key Endpoints: Angiographic and IVUS results at 6 months, clinical endpoints at 1, 6 and 12 months

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Everolimus Eluting Stent Program
FUTURE I and II

FUTURE I	FUTURE II

- Assess safety and performance of an Everolimus Eluting Stent
- Single *de novo* lesions, ≤ 18 mm length
- Stent sizes: 2.5 – 4.0 mm diameter, 14 and 18 mm lengths
- Prospective, randomized
- Key Endpoints: Angiographic and IVUS results at 6 months, Clinical endpoints at 1, 6 and 12 months

FUTURE I	FUTURE II
• 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

FUTURE I
6 Month In Stent Angiographic FU

		Everolimus n=25 angio 96% FU	Control n=11 angio 73%FU	P value
MACE		7.7% (2/26)	8.3% (1/12)	NS
Ref Diameter (mm)		3.07	2.94	NS
MLD (mm)	pre	1.12	1.11	NS
	post	3.07	2.94	NS
	F/U	2.97	2.10	<0.0001
% DS	pre	64.09	62.12	NS
	post	1.79	1.73	NS
	F/U	2.63	27.83	0.0010
Acute Gain (mm)		1.95	1.83	NS
Late Loss (mm)		***0.11***	***0.85***	***<0.0001***
Restenosis (%)		***0.0% (0/25)***	***9.1% (1/11)***	***NS***
Lesion Length (mm)		9.17	8.32	NS

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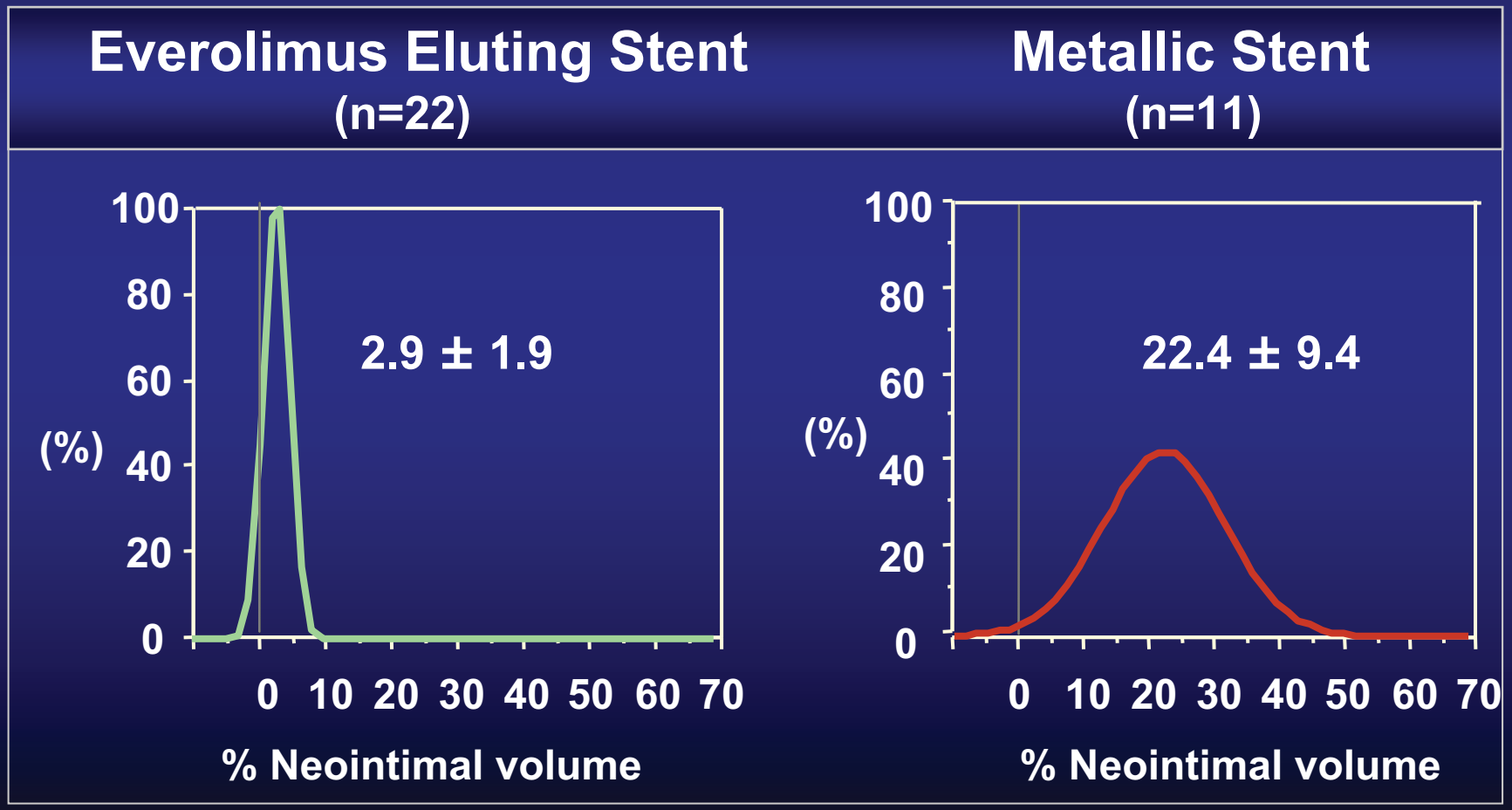
FUTURE I
IVUS 6 Month Follow-Up

Distribution of % Neointimal Volume



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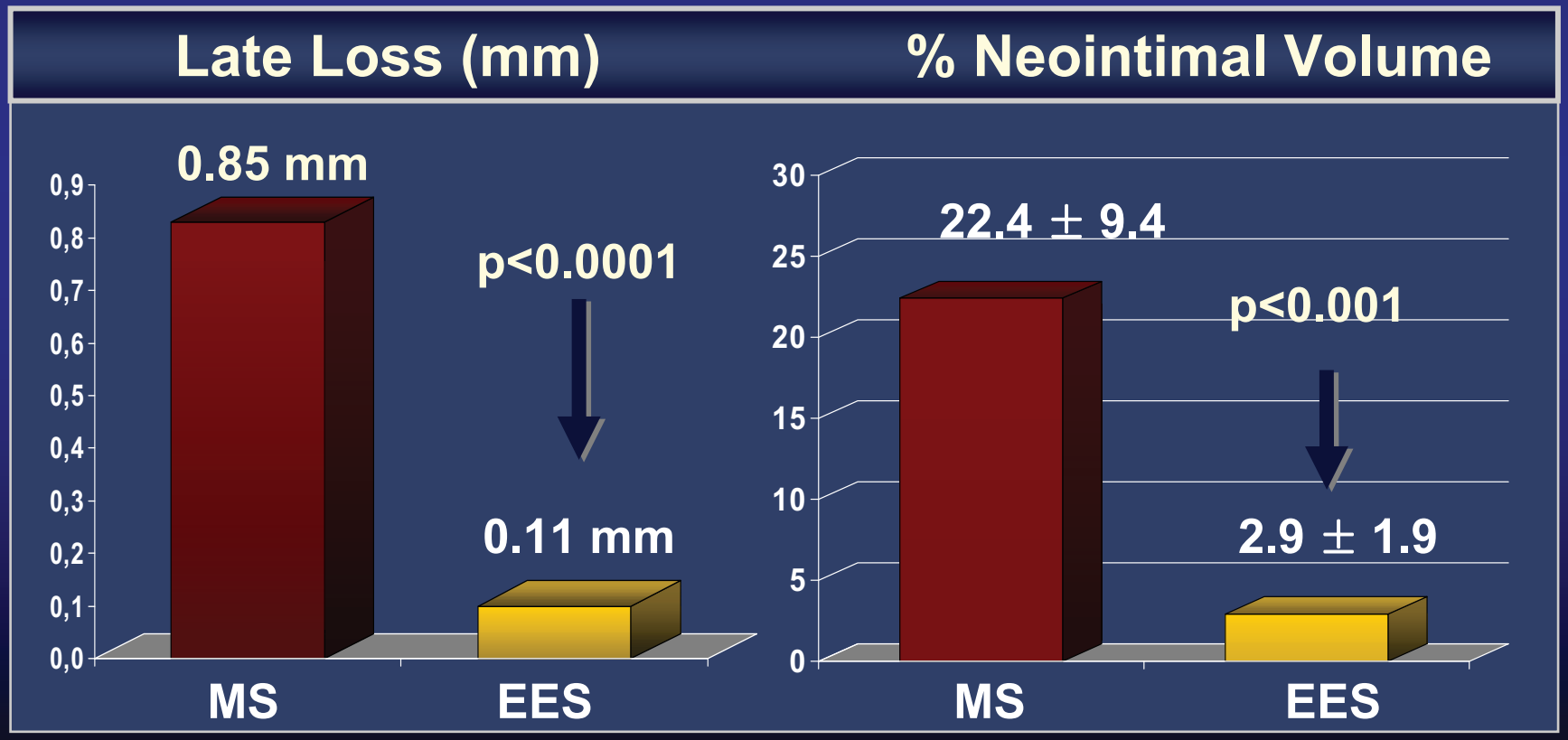
FUTURE I
Key Results

Significant reduction of in-stent tissue proliferation

88% Reduction

87% Reduction



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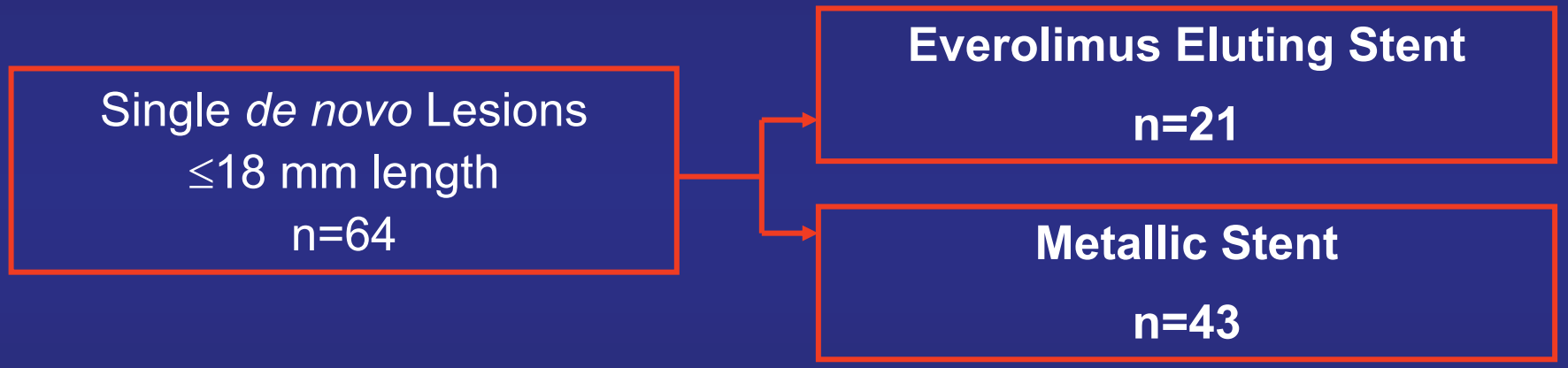
FUTURE II
Study Design

Assess the safety and efficacy of an Everolimus Eluting Stent when compared to a metallic stent



Prospective, Randomized (2:1), Multi-center,
Diabetics Included
Stent sizes: 2.5 – 4.0 mm Diameter , 14 and 18 mm Lengths
Clinical follow-up at 1, 6 and 12 months
Angiographic and IVUS follow-up at 6 months

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FUTURE II
Clinical Follow-Up MACE at 6 months

		Everolimus n=21 # (%)	Control n=40 # (%)	P value
MACE		1 (4.8%)	7 (17.5%)	NS
Death		0 (0.0%)	0 (0.0%)	-
MI	All	0 (0.0%)	1 (2.5%)	NS
	Q-Wave	0 (0.0%)	0 (0.0%)	-
	Non Q-Wave	0 (0.0%)	1 (2.5%)	NS
TLR		**1 (4.8%)**	**6 (15.0%)**	**NS**

Hierarchical

The TLR in the EES group was due to a proximal edge restenosis. Three TLR in the MS group were also due to edge restenosis (1 proximal and 2 distal).

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FUTURE II

6 Month In Stent Angiographic FU

		Everolimus n=21/22* 95% FU	Control n=36/43 83% FU	P value
Ref Diameter (mm)		2.91	2.97	NS
MLD (mm)	pre	1.05	1.03	NS
	post	2.88	2.87	NS
	F/U	**2.74**	**2.02**	**<0.0001**
% DS	pre	64.59	65.56	NS
	post	0.51	3.04	NS
	F/U	**2.94**	**30.35**	**<0.0001**
Acute Gain (mm)		1.83	1.83	NS
Late Loss (mm)		**0.12**	**0.85**	**<0.0001**
Binary Restenosis (%)		**0.0% (0/21)**	**19.4% (7/36)**	**NS**

*One EES patient had 2 lesions treated

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FUTURE II
6 Month In Lesion Angiographic FU

		Everolimus n=21/22* 95% FU	Control n=36/43 83%FU	P value
Ref Diameter (mm)		2.91	2.97	NS
MLD (mm)	pre	1.05	1.03	NS
	post	2.39	2.27	NS
	F/U	**2.19**	**1.75**	**0.003**
% DS	pre	64.59	65.56	NS
	post	18.06	24.06	NS
	F/U	**22.39**	**40.26**	**0.0006**
Acute Gain (mm)		1.34	1.24	NS
Late Loss (mm)		**0.17**	**0.54**	**0.002**
Binary Restenosis (%)		**4.8% (1/21)**	**30.6% (11/36)**	**0.04**

In lesion = in-stent + 5 mm distal and proximal to stent
*One EES patient had 2 lesions treated

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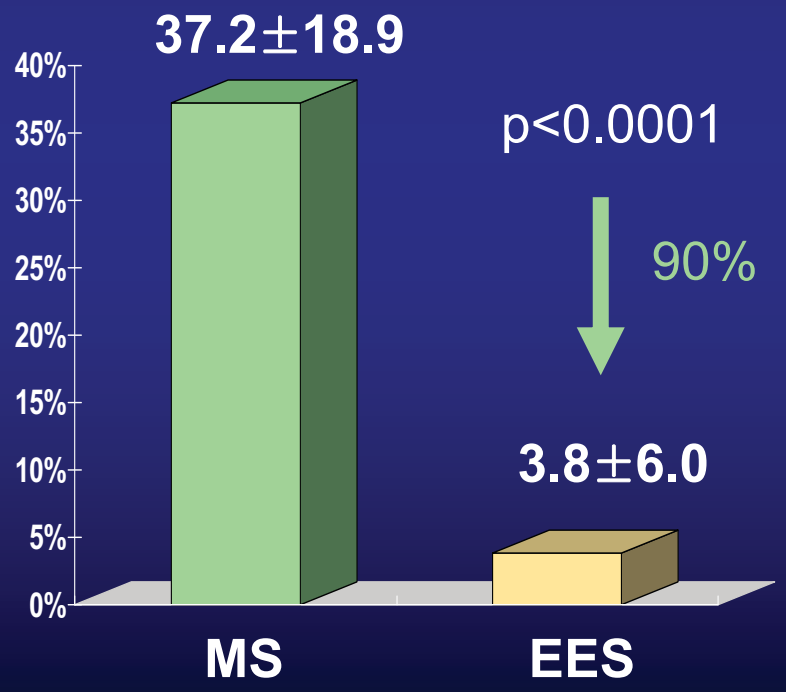
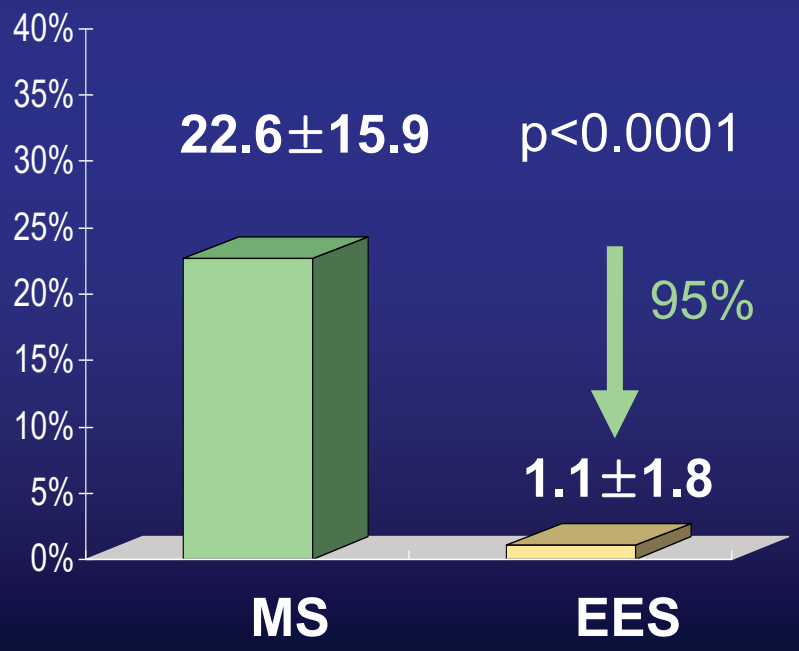
FUTURE II
6 Month IVUS Follow-up

% Cross Sectional Narrowing (NIA/SA)



% Neointimal Volume (NV / SV)



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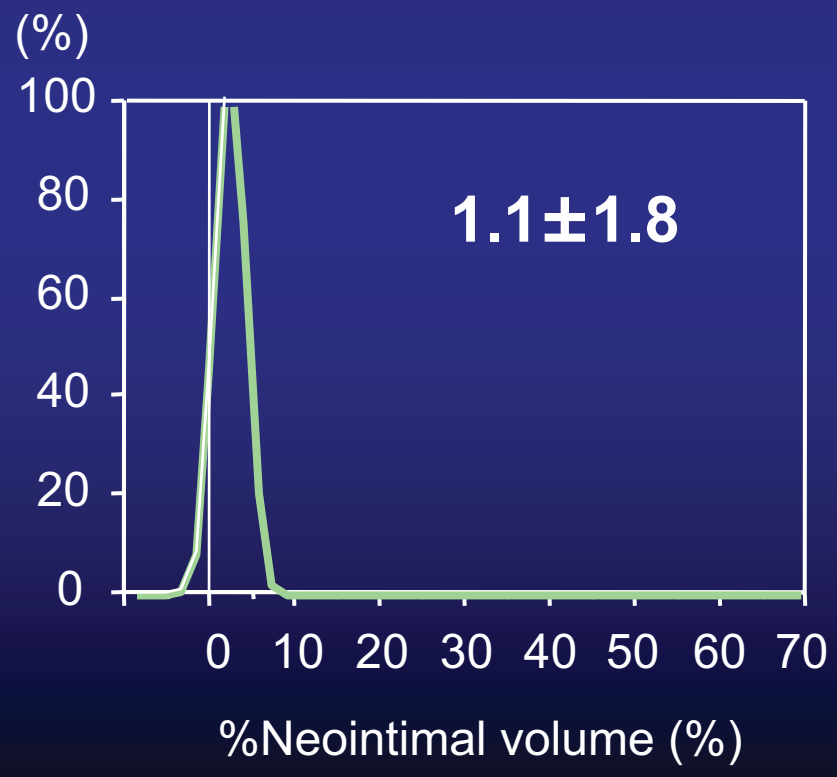
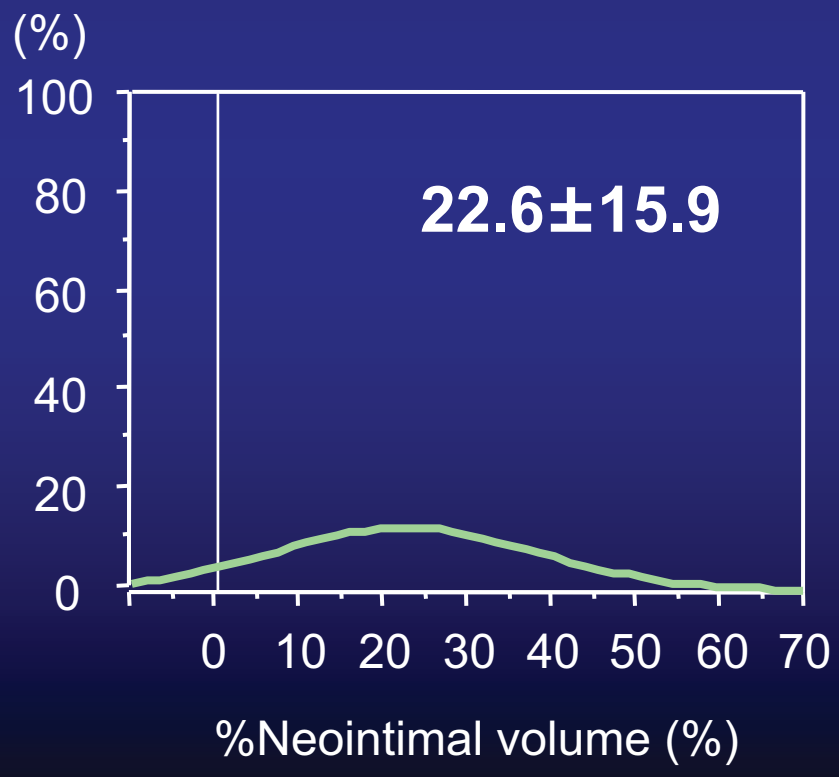
FUTURE II
6 Month IVUS Follow-up

Everolimus Eluting Stent



Metallic Stent



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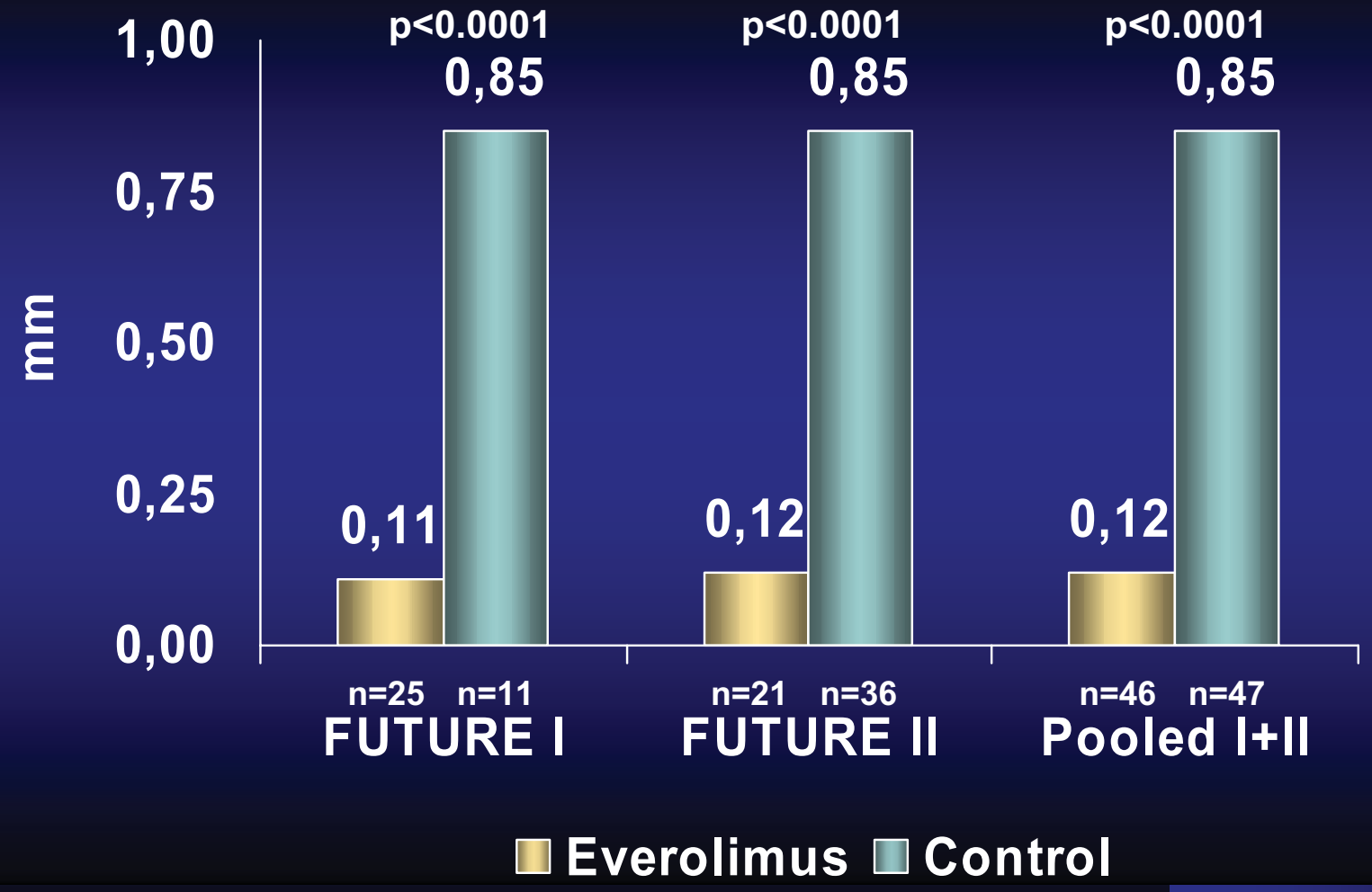
FUTURE I and FUTURE II
In-stent Late Loss at 6MFU



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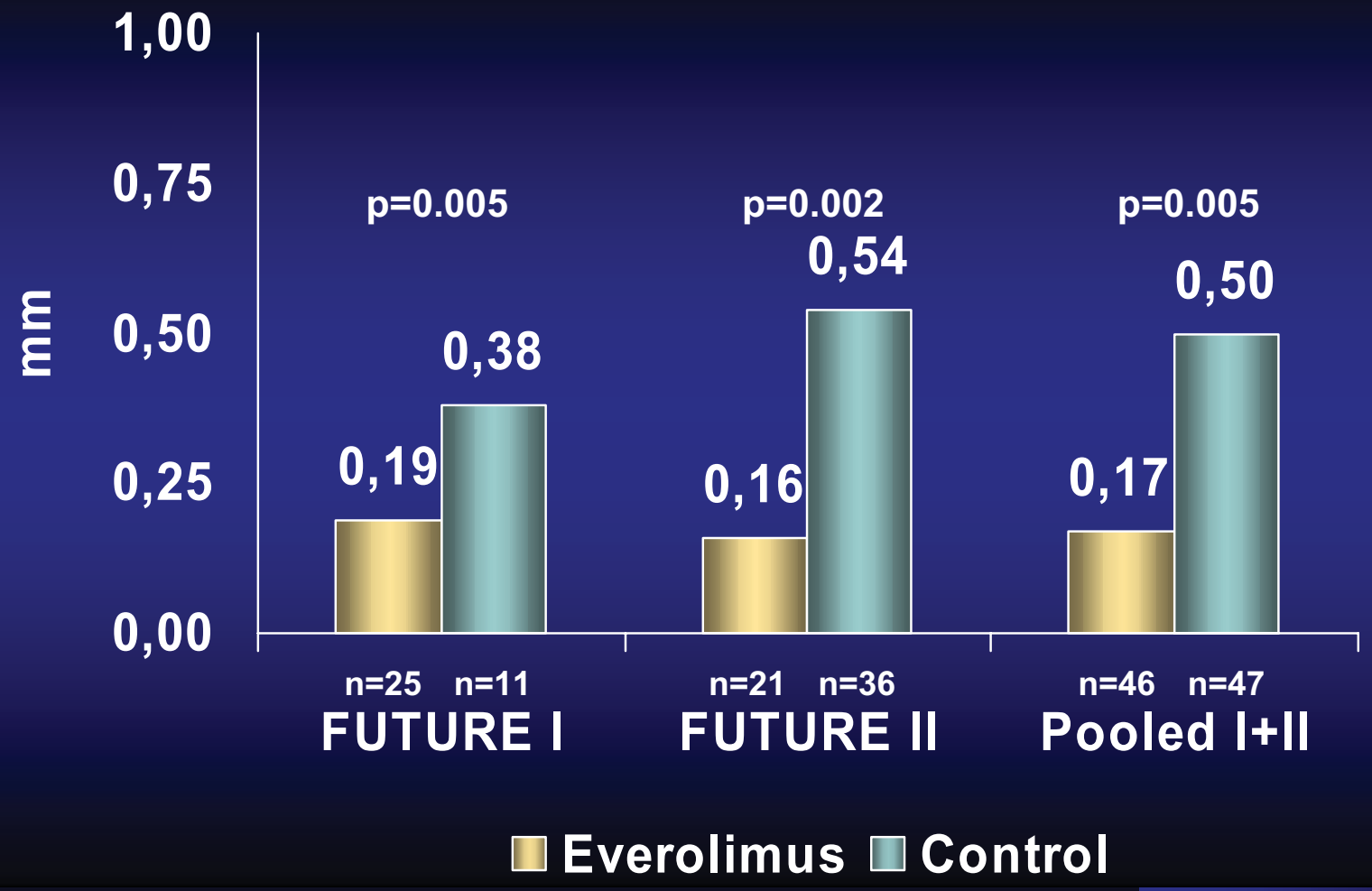
FUTURE I and FUTURE II
In-segment Late Loss at 6MFU



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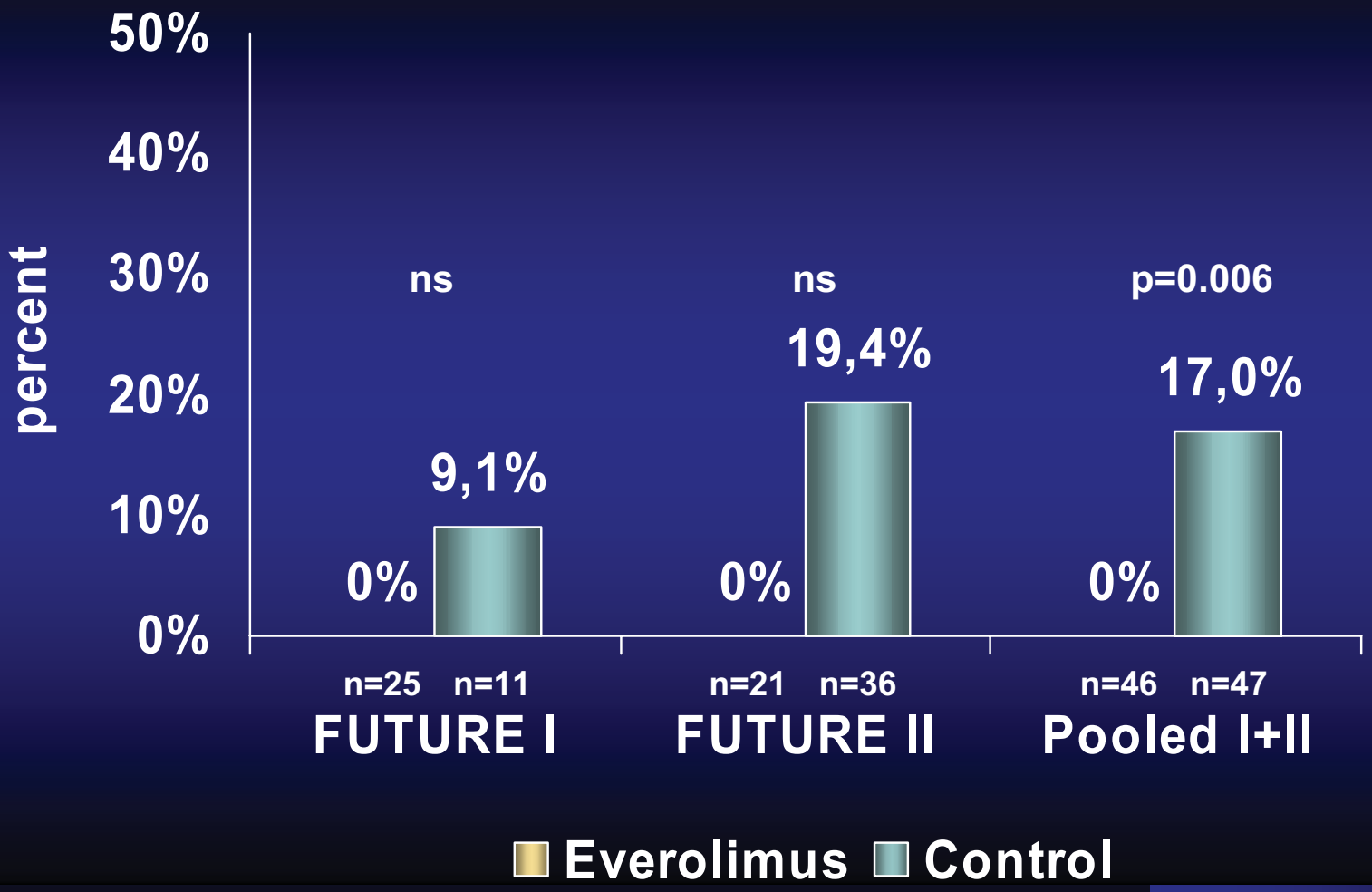
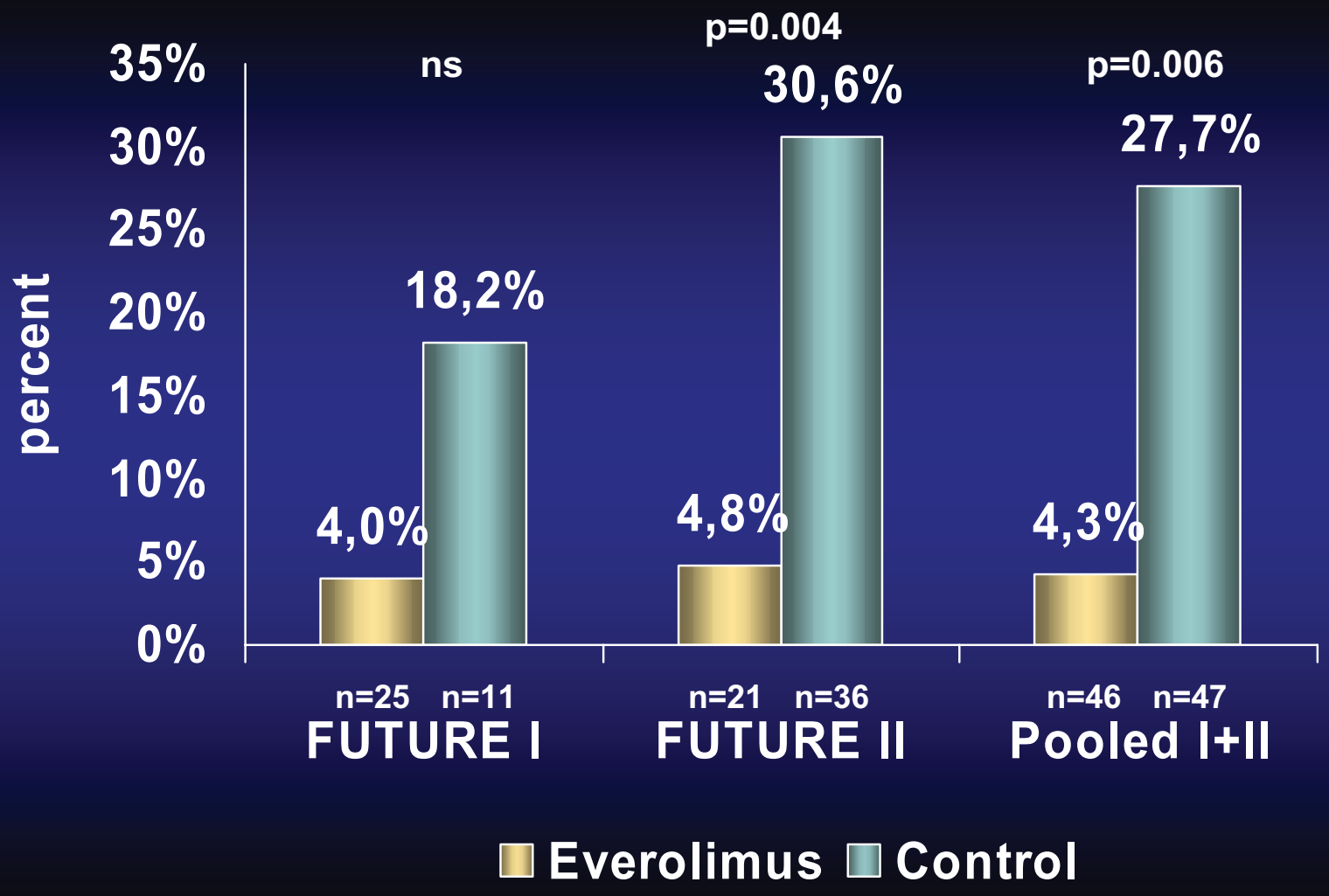
FUTURE I & FUTURE II
In-stent Binary Restenosis at 6MFU



FUTURE I & FUTURE II
In-segment Binary Restenosis at 6MFU



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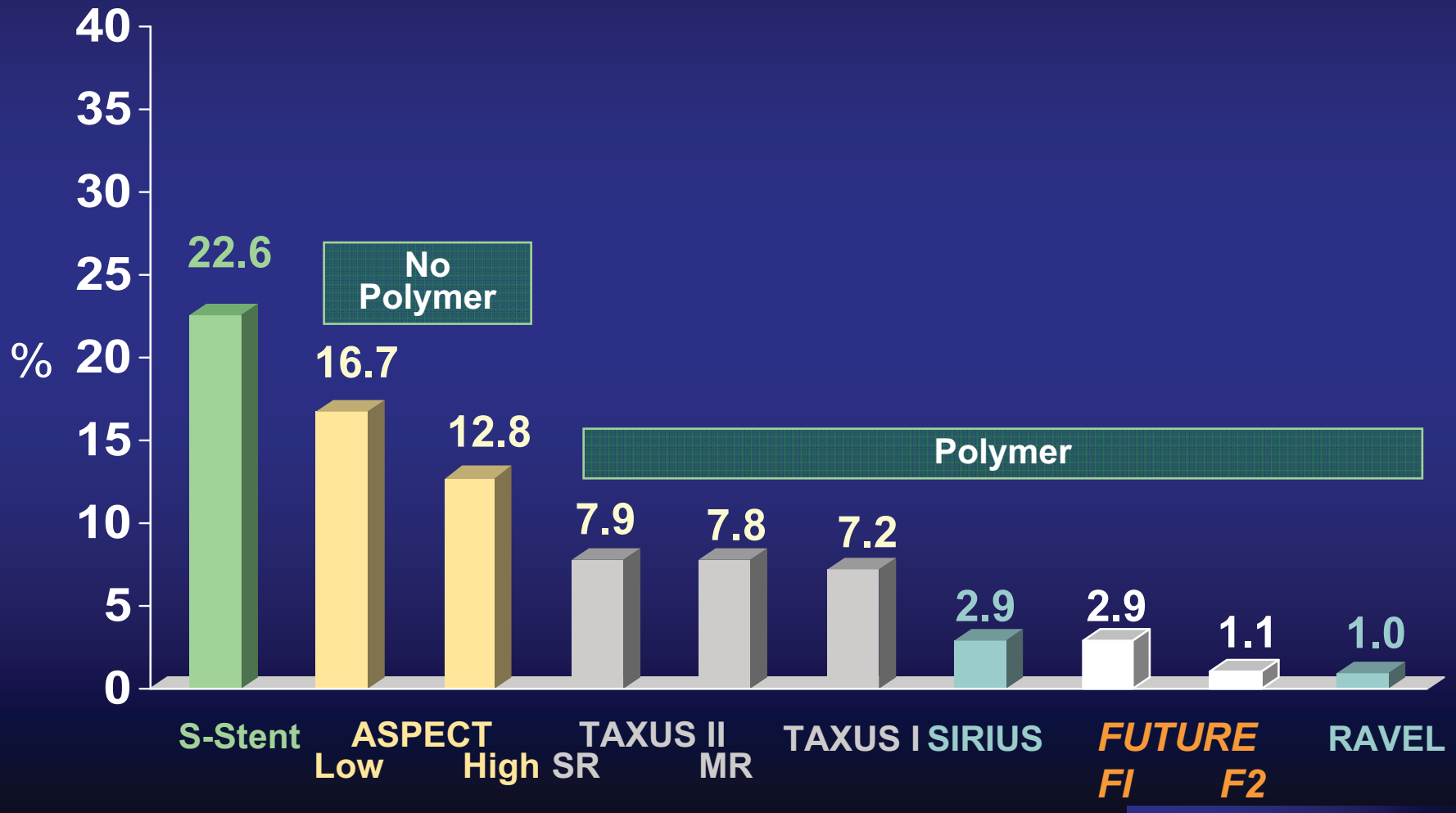
Drug Eluting Stent Trials

Comparison of % Neointimal Volume
(Neointimal Volume / Stent Volume)



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FUTURE I and FUTURE II Follow-Up

6 months

- MACE rates of 7.7 and 4.8%
- No early or late thrombosis
- No late stent malapposition
- Profound decrease of in-stent tissue
- 0% in-stent restenosis
- Less than 5% in-segment restenosis

12 months

- Safety
  - ✓No new MACE events
  - ✓No aneurysms
  - ✓No stent malapposition
- Efficacy
  - ✓Minimal Lumen Area
  - ✓Luminal Volume Index
  - ✓No in-stent binary restenosis

FUTURE I and FUTURE II Conclusions

Clinical data support safety

- MACE rates of 7.7% and 4.8%, respectively at 6 months
- No acute or late thrombosis
- No late stent malapposition

Clinical data show efficacy

- Significant decrease of in-stent tissue proliferation at 6 months
- 0% in-stent restenosis
- Less than 5% in-segment restenosis

The safety and efficacy of everolimus eluting stent appears to be sustained at 12 months

CHAMPION™ Clinical Trials

FUTURE I	FUTURE II	FUTURE III	FUTURE IV
Safety and performance	Safety and performance	Clinical support for OUS launch	
Europe	Europe	International	
n = 42	n = 64	n = 800 PI: E. Grube	

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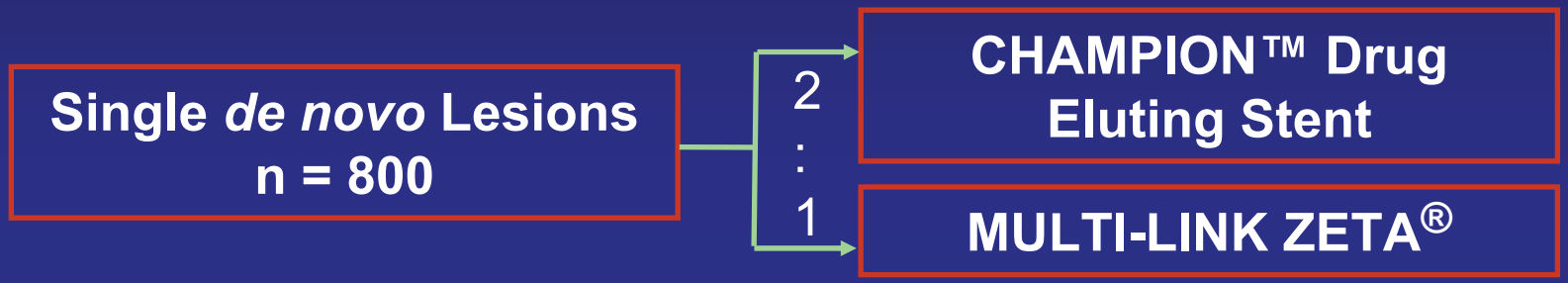
FUTURE III Study Design

FUTURE III



Prospective, randomized 2:1, multi-center, single-blind, superiority trial
International: up to 80 study sites
Stent sizes: 2.5 – 4.0 mm diameter, 8 - 28 mm lengths
Primary endpoint: In-stent late loss at 4/6 months
Clinical follow-up at 1, 4, 6, 9, 12 months, 2 and 3 years
Angiographic and IVUS follow up subsets at 4 & 12 and 6 & 12 months

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CHAMPION™ Clinical Trials

FUTURE I	FUTURE II	FUTURE III	FUTURE IV
Safety and performance	Safety and performance	Clinical support for OUS launch	Pivotal U.S.: Support FDA approval
Europe	Europe	International	U.S.A.
n = 42	n = 64	n = 800	n = 975 PI: C. Rogers

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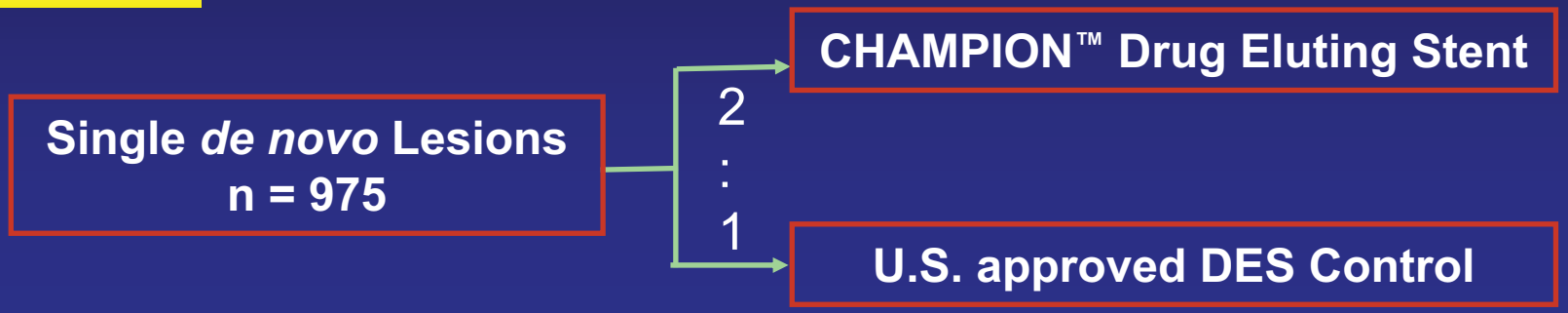
FUTURE IV Study Design

FUTURE IV



Prospective, randomized 2:1, multi-center, single blind, non-inferiority, 975 patients

- Stent Sizes: 2.5 – 3.5 mm diameter, 8 – 28 mm lengths

4.0 mm non-randomized arm: 105 patients

- Stent Sizes: 8 – 28 mm length

Up to 70 study sites

Primary endpoint: Angiographic in-segment late loss at 8 months

Secondary endpoint: Clinically-driven target vessel failure at 9 months

Clinical follow-up at 1, 8, 9, 12 months and 2, 3, 4, 5 years

Angiographic and IVUS subsets at 8 months

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FUTURE
Everolimus Eluting Stent Program
Conclusions

- FUTURE I and FUTURE II data support safety and efficacy of everolimus for DES
- Acute performance tests indicate that the CHAMPION™ Drug Eluting Stent System is competitive
- Future III is expected to begin enrollment in Q1'04
- U.S. Pivotal trial enrollment is expected to begin in Q2'04
- Clinical trial strategy will provide safety and efficacy data and support timely regulatory submissions

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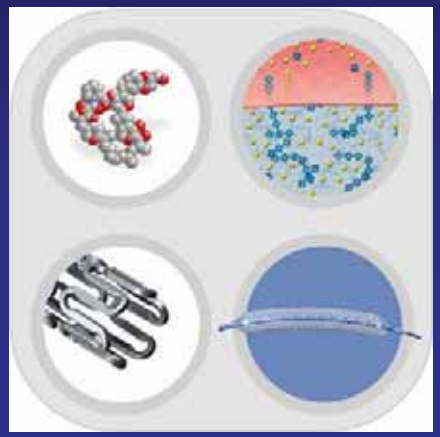
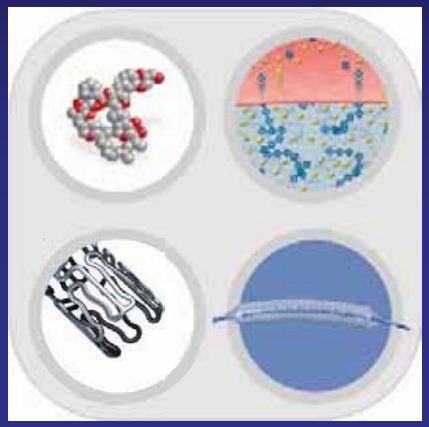
VISION DES Systems

CHAMPION™ Drug Eluting Stent System



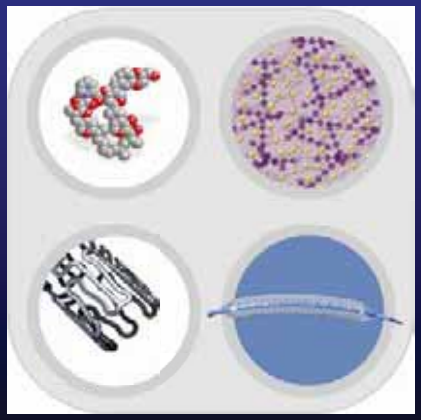
MULTI-LINK VISION™ Platform Drug Eluting Stent System



Bioabsorbable

FUTURE Clinical Trials

MULTI-LINK VISION™ Platform Drug Eluting Stent System

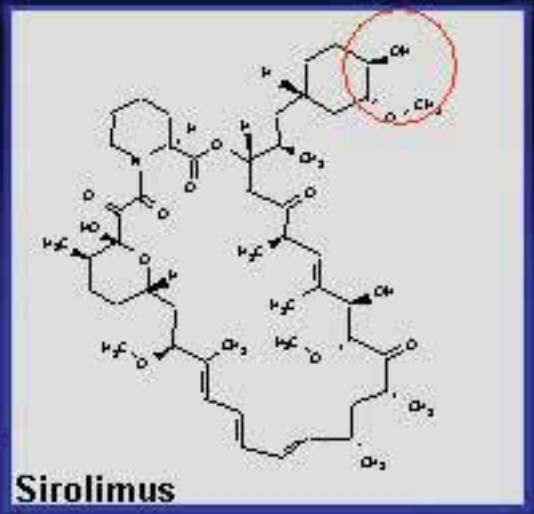


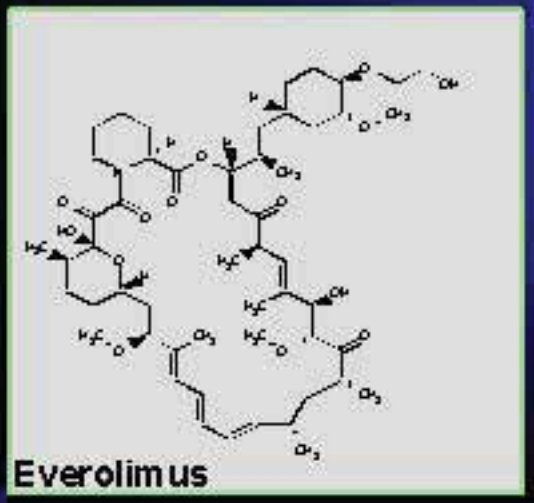
Durable

SPIRIT Clinical Trials

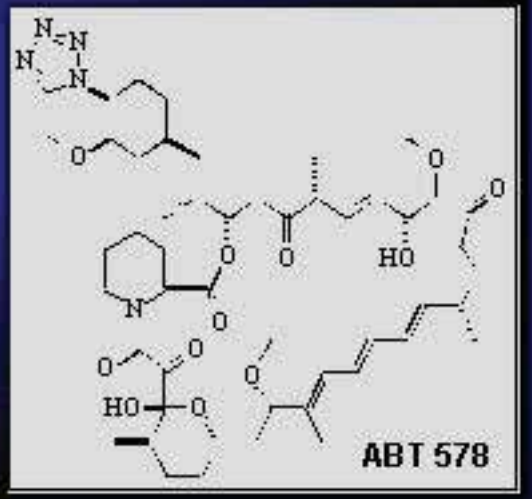
Siegburg / Stanford

Drug Eluting Stents
The Next Generation?


Sirolimus


Everolimus

Biolimus - A9


ABT 578

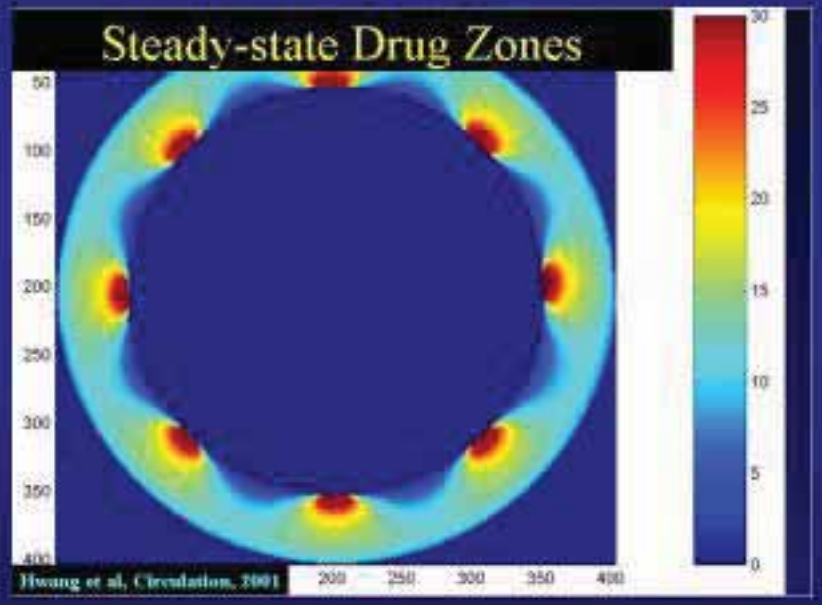
BIOLIMUS A9™: R = new chemical group at 28-O position

Late Loss in Stent vs.Drug Type and Extent of Vessel Injury

- BASED ON PIG EXPERIMENTS AT CEDARS SINAI , LA
- SIROLIMUS CURVE ESTIMATED, BASED ON EARLIER ANIMAL SERIES

Potential Advantages of Biolimus A9

- More bioavailable than Sirolimus; distributes more rapidly into the arterial wall during the initial hours after stent implant.
- Exhibits high potency at injury site and provides extended duration of treatment effect
- Reaches therapeutic concentration in vessel wall in a shorter time after stent implant



STEALTH 1-Trial

- Biolimus First in Man -

(Heart Center Siegburg, Eberhard Grube, PI)

TRIAL DESIGN

- 100-patient, multi-center, single-arm, single dose safety trial (Brazil, Germany)
- De-novo lesions 2.75-4.0 mm diameter X ≤24 mm length
- Biosensors' Challenge stent platform
- First use of Biolimus A9 on a stent

FIRST-IN-MAN TRIAL(CONT)

- IVUS substudy
- Stanford (P Fitzgerald)-IVUS Core Lab
- Lenox Hill (M Leon/A Lansky)-Angiographic Core Lab

- PHARMACOKINETICS SUBSTUDY CONDUCTED ON INVIVO RELEASE OF BIOLIMUS A9 AT:
  - T_0
  - T + 4Hrs
  - T+24Hrs
  - $T_{30\ Days}$

STEALTH-1

Recruitment

Started	Sept, 2003
Completed	March, 2004

Expected completion of study

Expected 6-months f/u completion	Sept, 2004
Expected 12-months f/u completion	March, 2005

Stanford / Siegburg