An Update on ABT-578 - PC Coated Stent Studies

Abbott Prefer-IVUS
Medtronic Endeavor 1

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Melbourne, Australia

Strategic Alliance

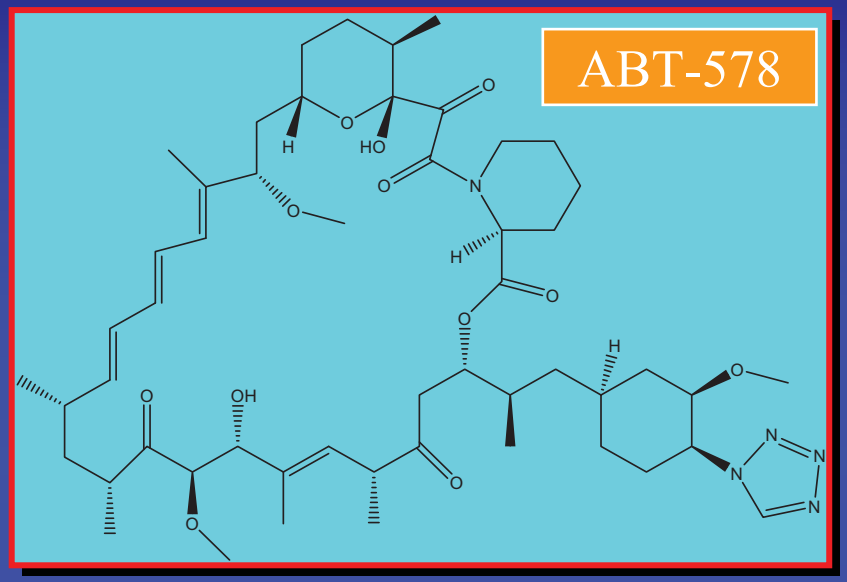
ABT-578 and PC coating on Medtronic AVE stents

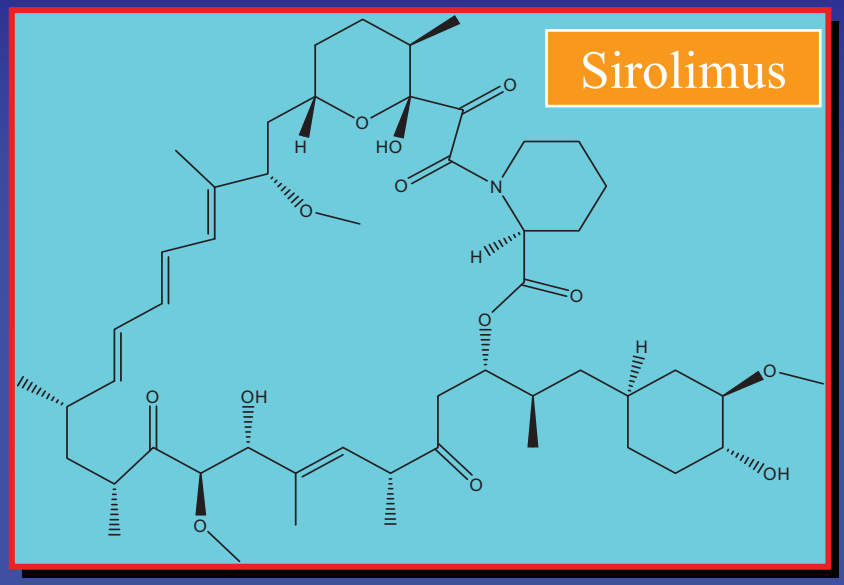
License ABT-578 and PC coating to Medtronic Vascular

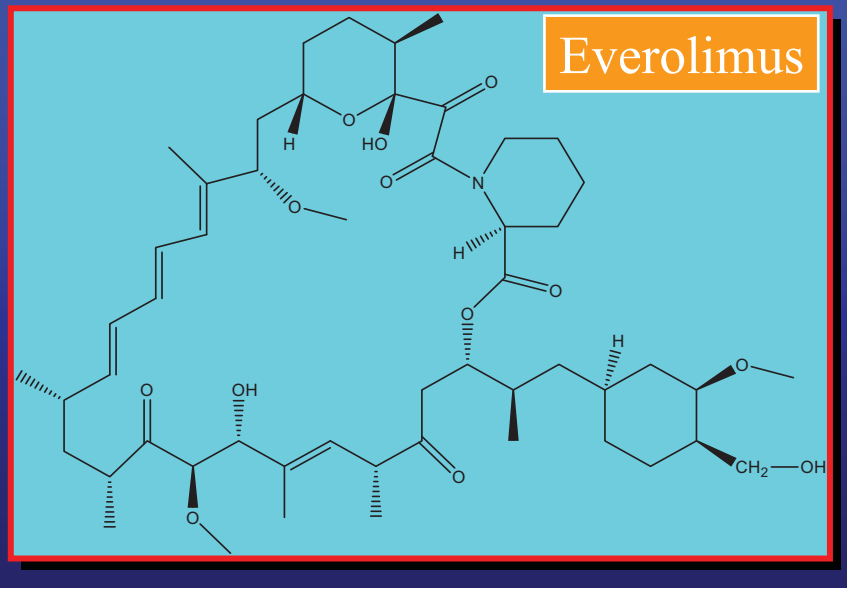
Provide OTW, RX Int'l & new stent delivery system to Abbott

Load Abbott stent on Medtronic delivery system

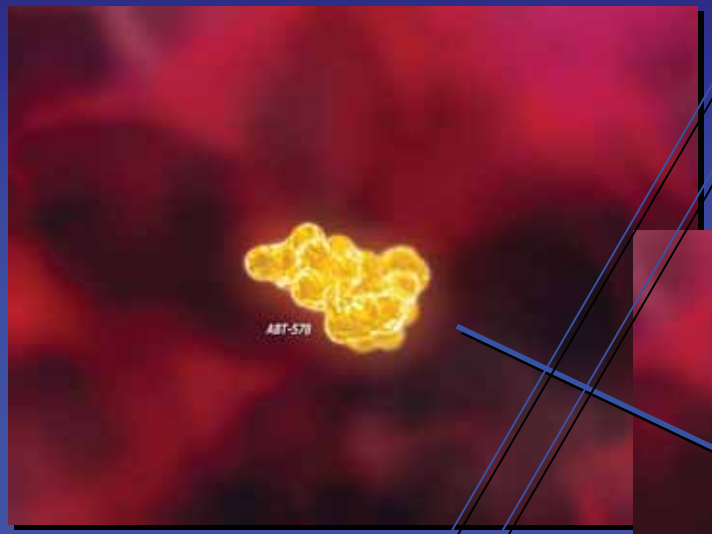
ABT-578 Chemical Structure





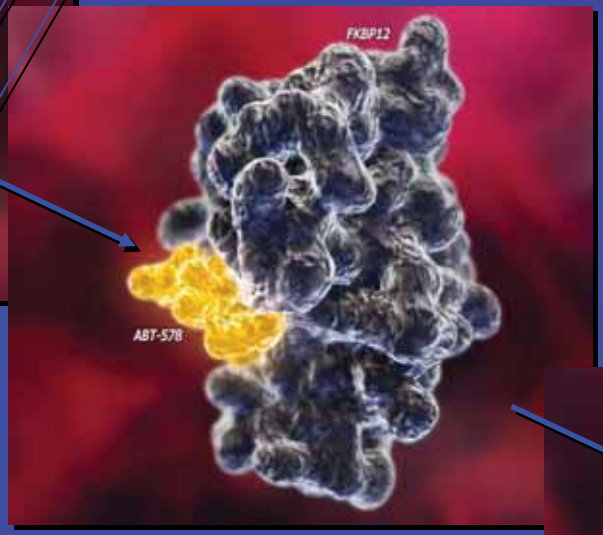


ABT-578 Mechanism of Action

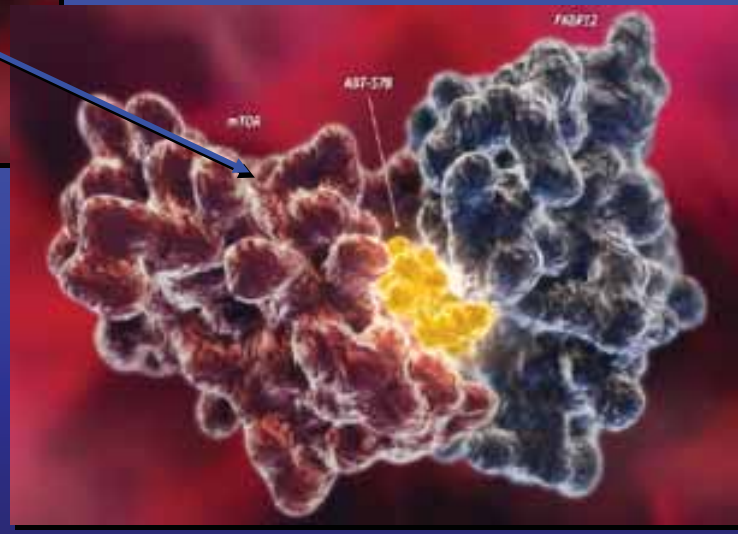


ABT-578

Cell membrane



ABT-578 binds with $FKBP_{12}$ protein



Complex blocks mTOR signal transduction

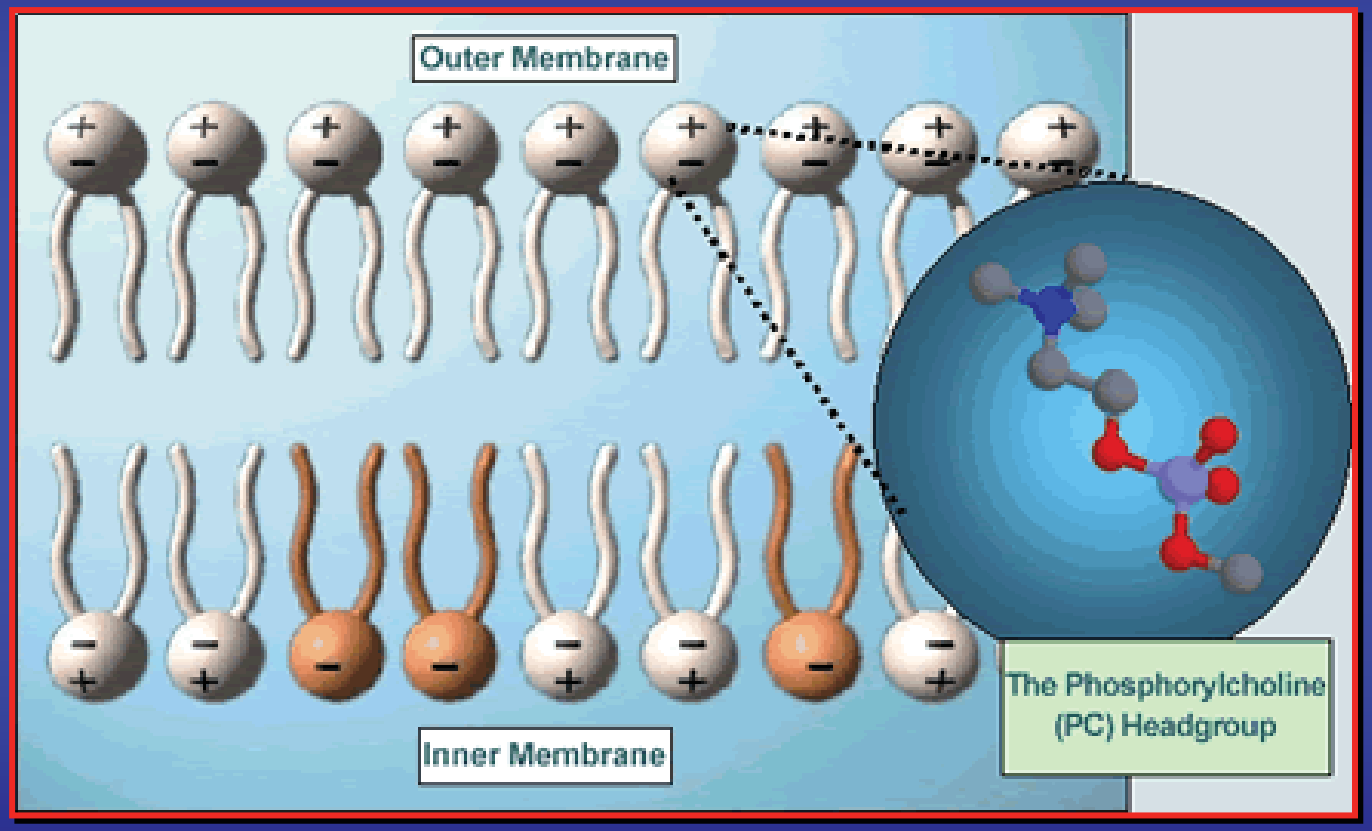
Primary mode of action is anti-proliferative: by inhibiting the function of the cell cycle regulatory protein, mTOR.

Inflammatory response may be limited by blocking local cytokines.

Complex prevents …

- Rb phosphorylation
- p70S6 kinase
- cyclin-dependent kinase (CDK) activation
- p27 down regulation

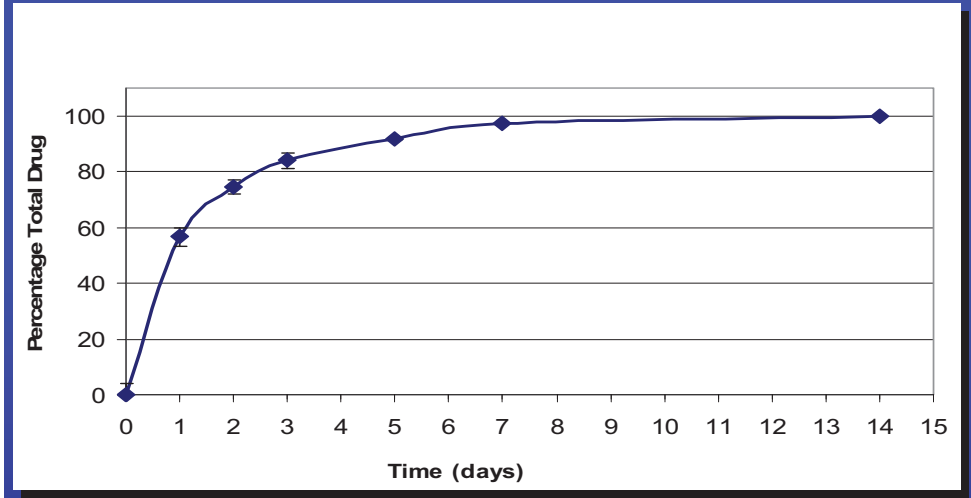
Phosphorylcholine Coating
(PC Technology™)



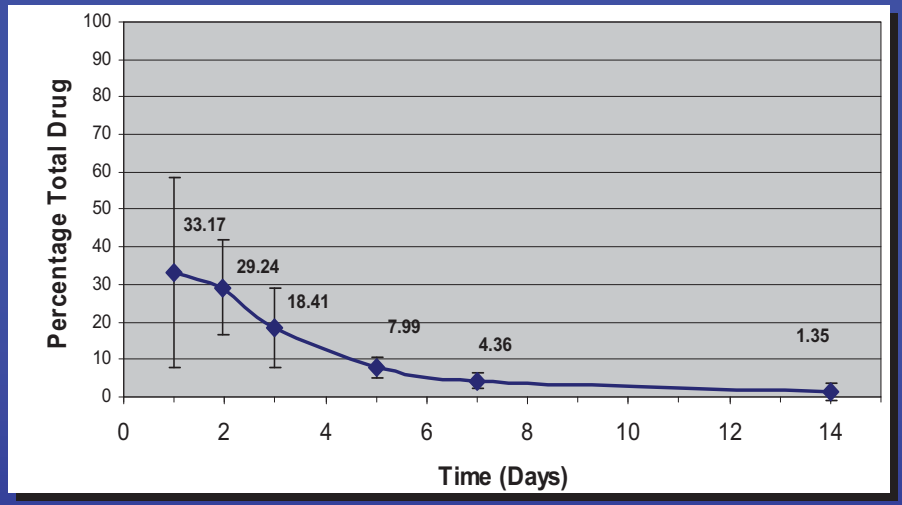
The PC coating is a synthetic copy of the predominant phospholipid of red blood cell membranes.

ABT-578 In vivo Drug Elution Data

% Drug Eluted



% Total Drug Load in Tissue Surrounding Stent



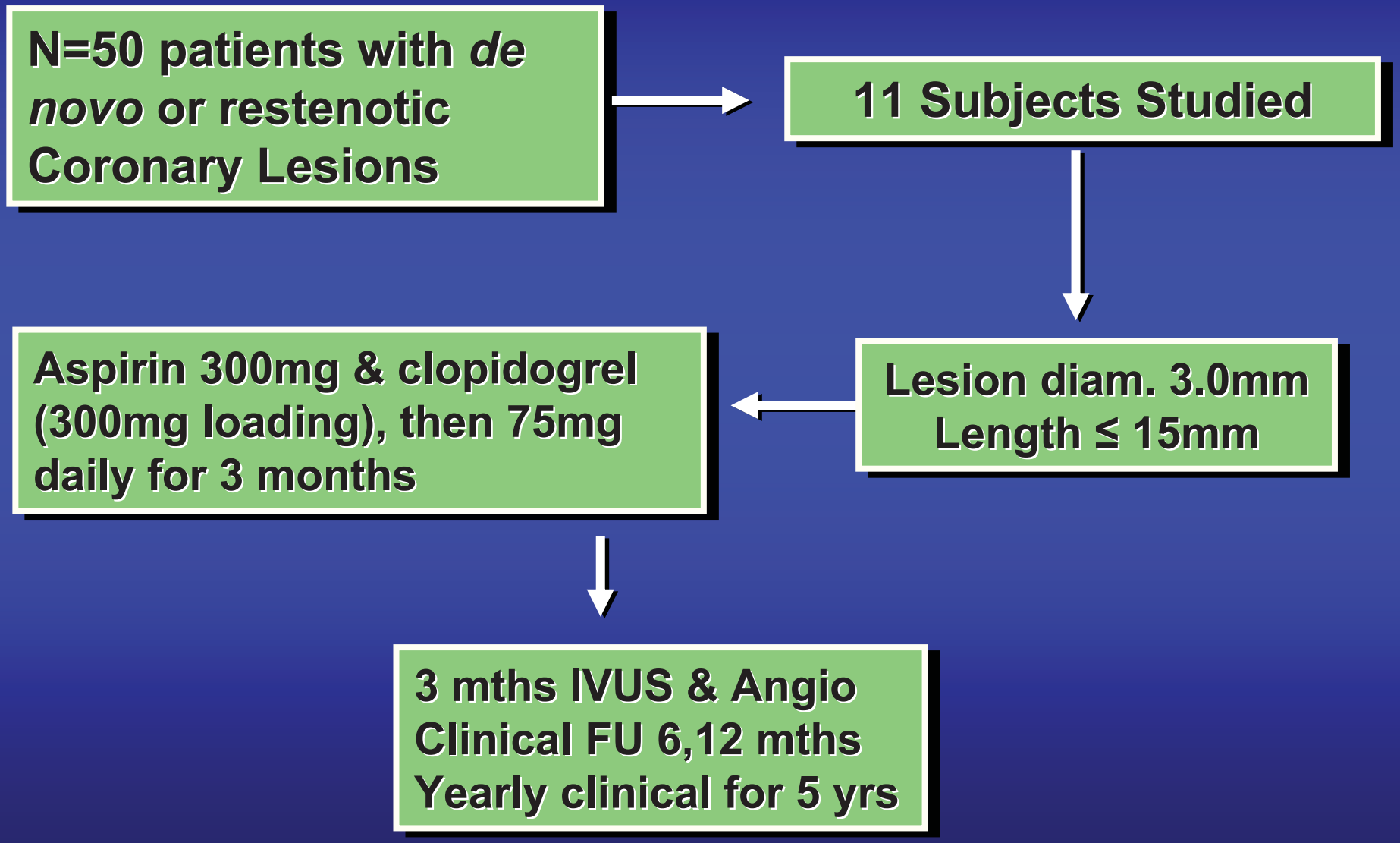
Endeavor Preclinical Study Rabbit Iliac Artery
10μg/mm ABT-578 PC-coated Driver Stent

A. Carter, ACC 2003

PREFER – IVUS

FIM Trial of an ABT-578 eluting stent.

PREFER – IVUS Study Design



PREFER – IVUS Objectives

Primary Objective

- Demonstrate the safety and efficacy of the ABT-578 coated BiodivYsio™ stent

Primary end point

- MACE at 30 days

Secondary Objectives

- Evaluate clinical , angiographic, IVUS and device performance

Secondary Endpoints

- In hospital MACE rate, 6 month MACE rate, TVR rate at 6 mths, 1 year and yearly for 5 years.

Additional Evaluations

- Device, lesion and procedural success

PREFER – IVUS

Investigators

Ian Meredith, Melbourne, Australia 4pts

Robert Whitbourn, Melbourne, Australia 4pts

John Ormiston, Auckland, New Zealand 3pts

Analysis

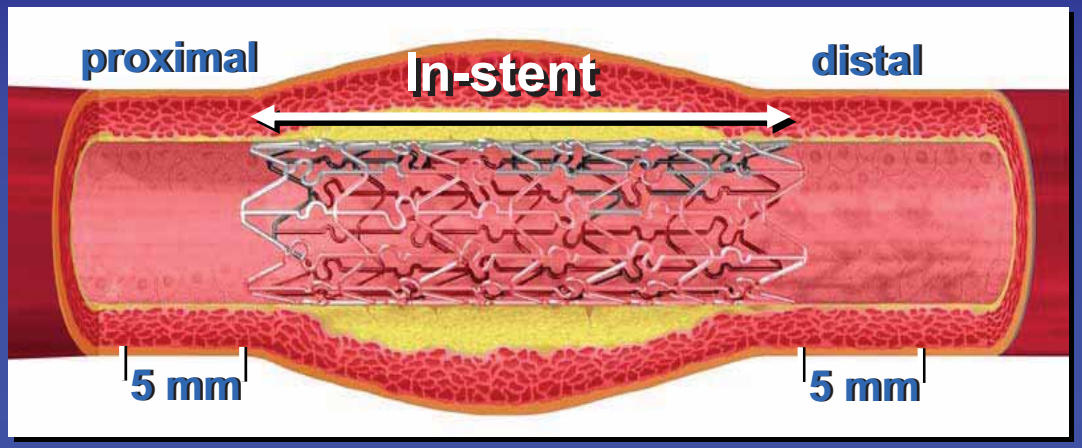
QCA: Brigham and Womens , Boston USA

IVUS: Stanford Interventional Cardiology, California

ECG: Harvard Clinical Research Institute, Boston

PREFER- IVUS

90 day QCA Peri-stent Analysis

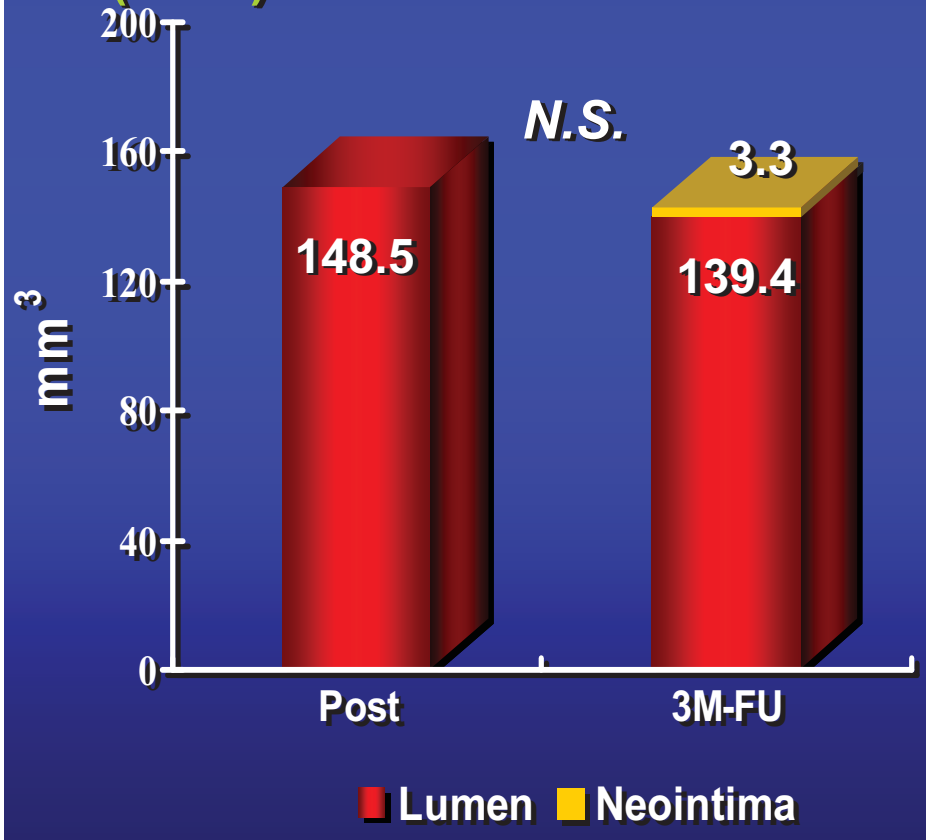


	Late Loss (mm)	Binary Restenosis (%)
In-stent	0.2	0
Proximal margin	0.2	0
Distal margin	0.0	0
In-segment	0.1	0

PREFER- IVUS

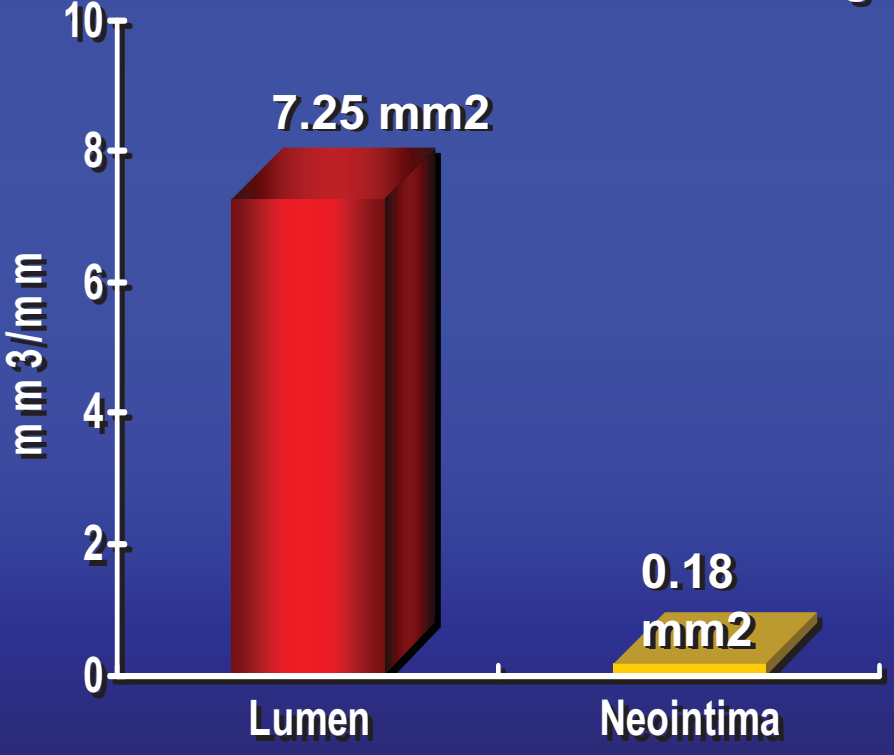
Post PCI & 90 day IVUS Analysis

Lumen & Neointima Volume (n=10)



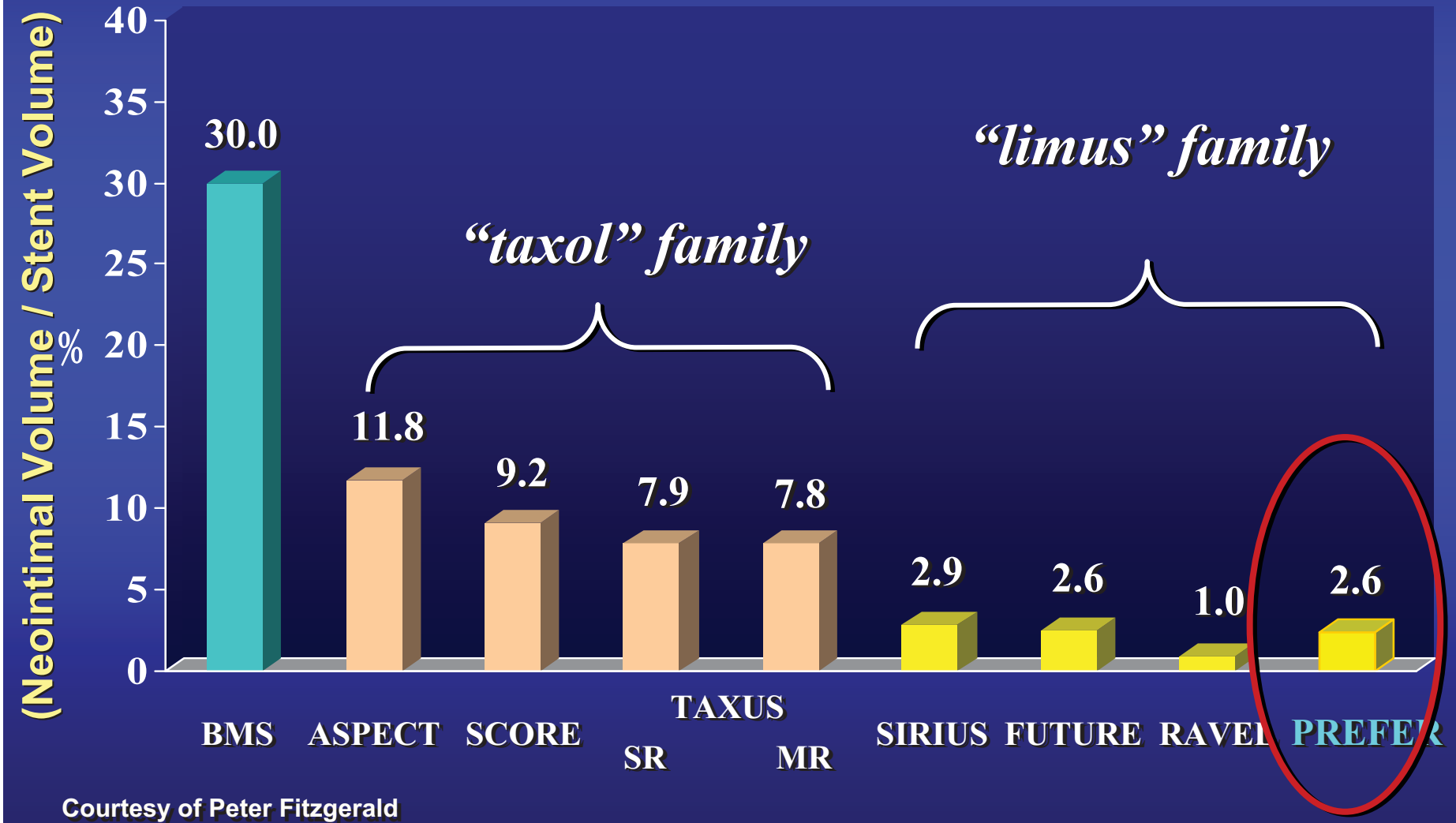
Average Lumen & Neointima Area

Volume index: Volume/Stent Length



Drug eluting stent trials

Comparison of % Neointimal Volume



Courtesy of Peter Fitzgerald

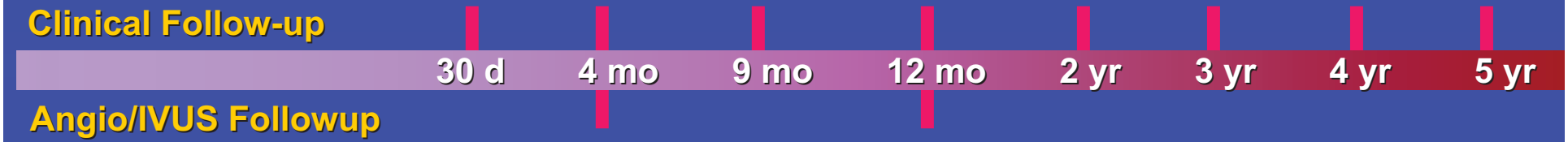
PREFER - IVUS Summary

- No safety concerns associated with the PC coated ABT-578 drug-eluting stent
- Neglible neointimal response both in stent and in segment.
- Zero binary restenosis rate
- No acquired malappositions, aneurysms stent thromboses

Endeavor I

100 patient Treatment and Follow-up Schedule

Single De Novo Native Coronary Lesions (Type A-B2)
Reference Vessel Diameter 3.0 – 3.5 mm
Lesion Length: < 15 mm



Primary Endpoints: MACE at 30 days and late loss (QCA) at 4 mo
Secondary Endpoints: TVF and TLR at 9 months; late loss at 12 mo
IVUS at 4 and 12 months

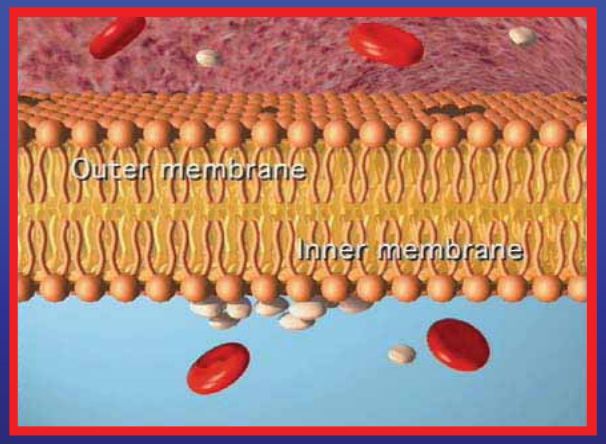
Stent Sizes: 3.0-3.5 mm x 18 mm
Pre- and post-dilatation specified with balloon length < stent length
Antiplatelet therapy for 3 months

Endeavor DES System
Key Components

Driver Cobalt Alloy Stent

Stent Delivery System

PC Technology



Drug: ABT-578

E1 PI & Core Labs

Principal Investigator
Ian T. Meredith, Monash Medical Centre, Melbourne, Aust

QCA Core Lab
Brigham and Women's Hospital, Boston, MA, USA
Jeffrey J. Popma, MD

IVUS Core Lab
Cardiovascular Core Analysis Lab
Stanford Interventional Cardiology, CA, USA
Peter Fitzgerald, MD

Data Coordinating Center
Harvard Clinical Research Institute
Richard E. Kuntz, MD, MSc and Ross Prpic, MBBS

ECG Core Lab
Harvard Clinical Research Institute, Boston, MA, USA
Peter Zimetbaum, MD

Clinical Events Committee/DSMB
Harvard Clinical Research Institute, Boston, MA, USA
Donald Cutlip, MD

E1 Investigational Centers

Investigator	Hospital	# Patients
John Ormiston	Green Lane/Mercy, NZ	32
Robert Whitbourn	St. Vincent's, Melbourne	20
Patrick Kay	Dunedin, NZ	16
Ian Meredith	Monash Medical Centre	14
David Muller	St. Vincent's, Sydney	12
Mark Adams	Royal Prince Alfred Hosp.	3
Con Aroney	The Prince Charles Hosp.	2
Mark Pitney	Eastern Heart Clinic	1

E I Milestones

Milestone	Date
First Ethics Approval	December, 2002
TGA Approval	December, 2002
First Patient Enrolled	January, 2003
Last Patient Enrolled	April, 2003
Last 4 mo Follow up	August, 2003
Database Lock	September, 2003
4 mo Data TCT Presentation	September, 2003
Last 12 mo Follow up	29th April, 2004
12 mo Clinical Data PCR	25th May, 2004
12 mo Angio/ IVUS Data PCR	25th May, 2004

Endeavor I

Patient Demographics

n=100	Baseline
Male	79.0%
Average age (years)	58.8 (35-76)
Prior MI	47.0%
Prior PCI	19.0%
Diabetes Mellitus	16.0%
Unstable Angina	39.0%
Hyperlipidemia	91.8%
Current Smoker	34.0%

Endeavor I

30 day & 4mth Hierarchical MACE

n=100	30 Days	4 Months
MACE	1%	2%
Death	0	0
MI (all)	1%	1%
Q-wave	0	0
Non Q-wave	1%	1%
TLR	0	1%
TVR (non-TL)	0	0

Acute device, lesion and procedural success: 100%
4 mth clinical follow up achieved: 100%

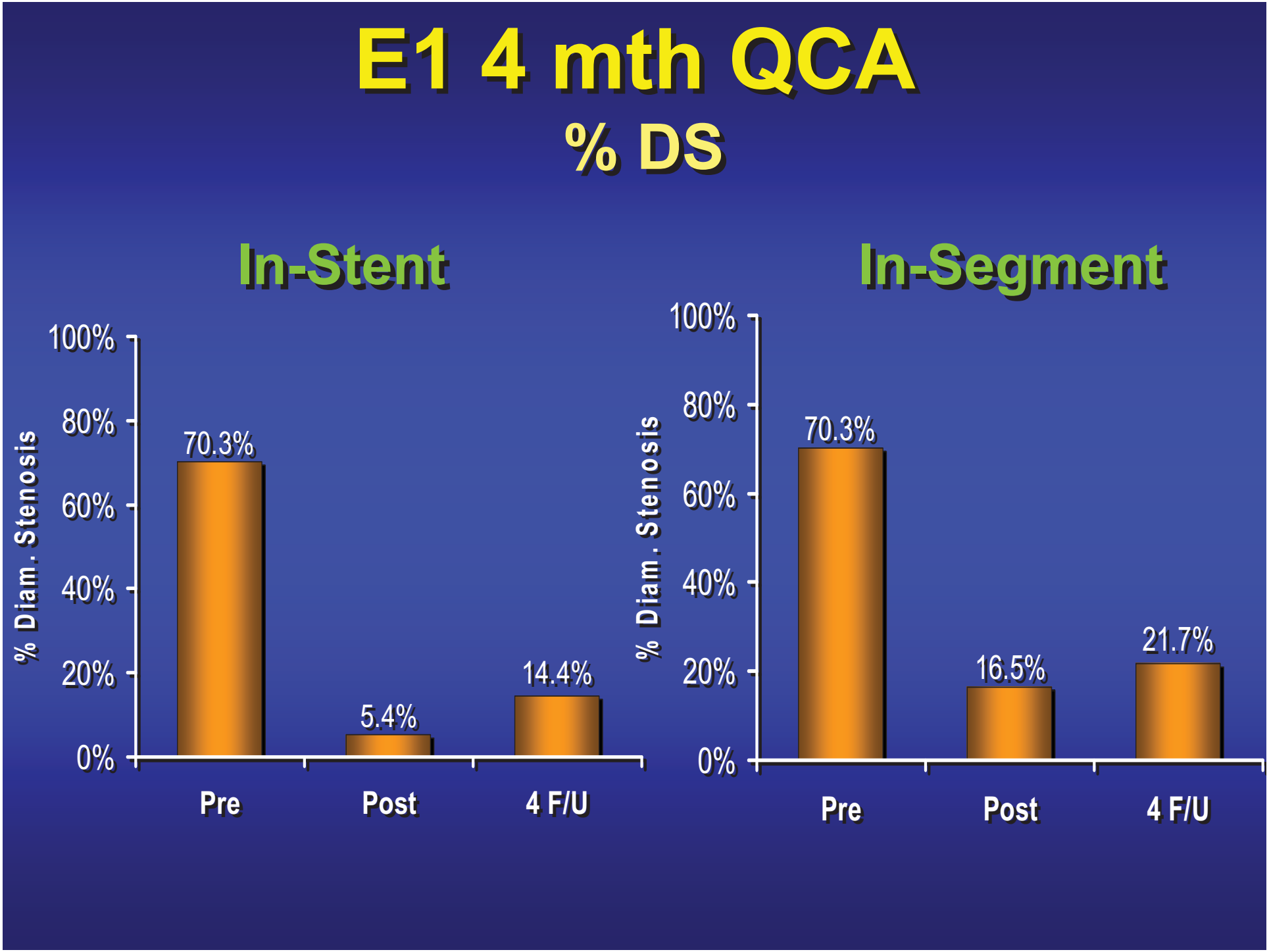
Endeavor I 4 mth QCA

	In-Stent	In-Segment
RVD, mm		2.96 ± 0.47
Lesion Length, mm		10.9 ± 3.1
MLD Pre, mm		0.88 ± 0.33
Post, mm	2.84 ± 0.35	2.52 ± 0.42
4 m follow-up	2.52 ± 0.43	2.31 ± 0.44
Acute Gain, mm	1.96 ± 0.38	1.64 ± 0.42
Late Loss, mm	0.33 ± 0.35	0.20 ± 0.40
Late Loss Index	0.17	0.11

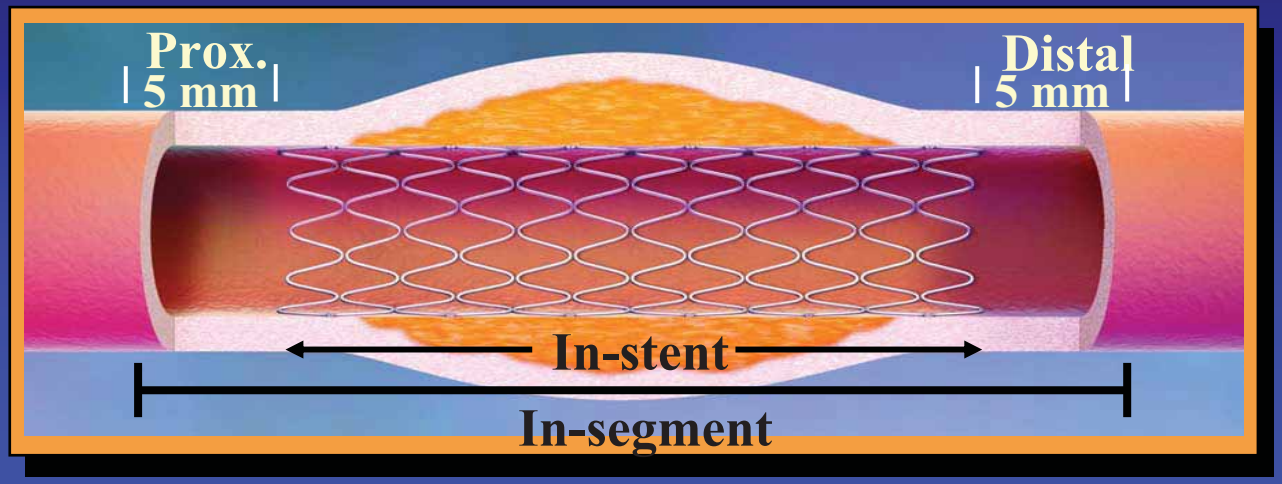
4 mth angio follow up achieved: 99%

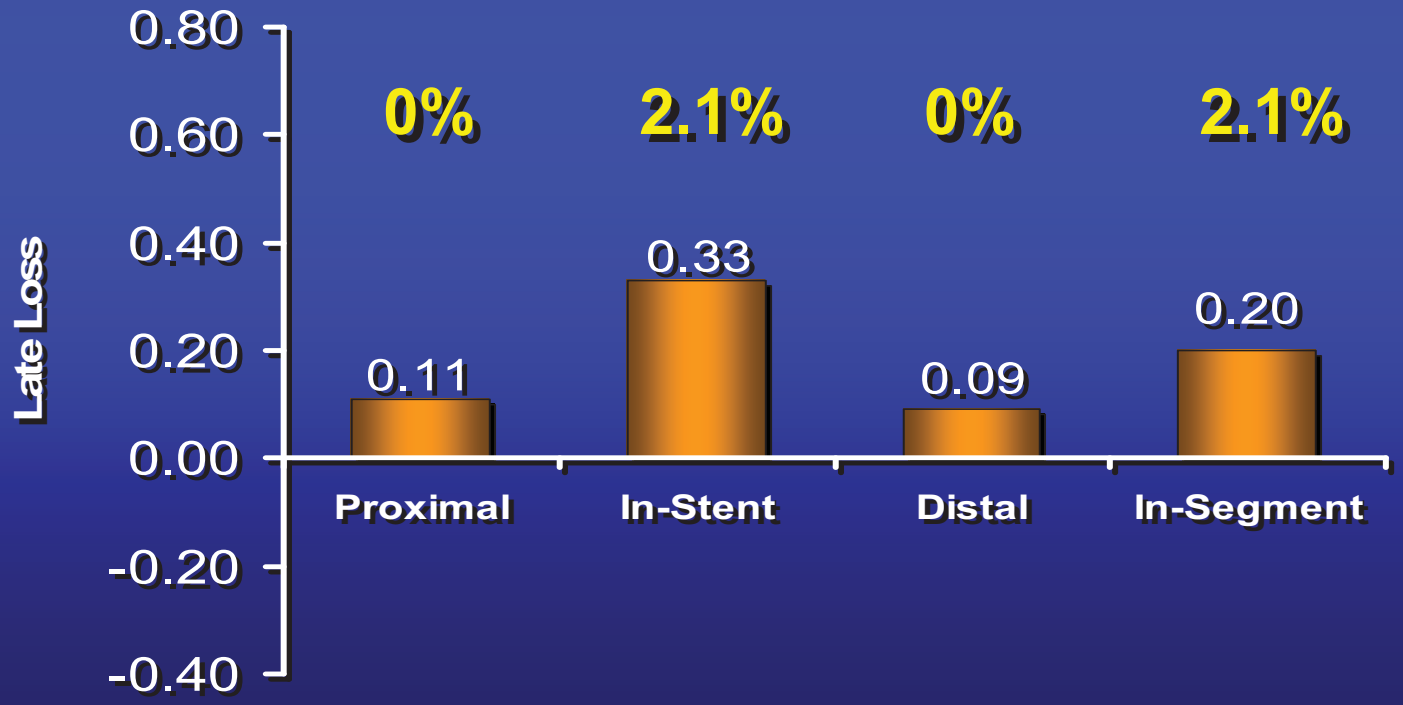
E1 4 mth QCA

% DS



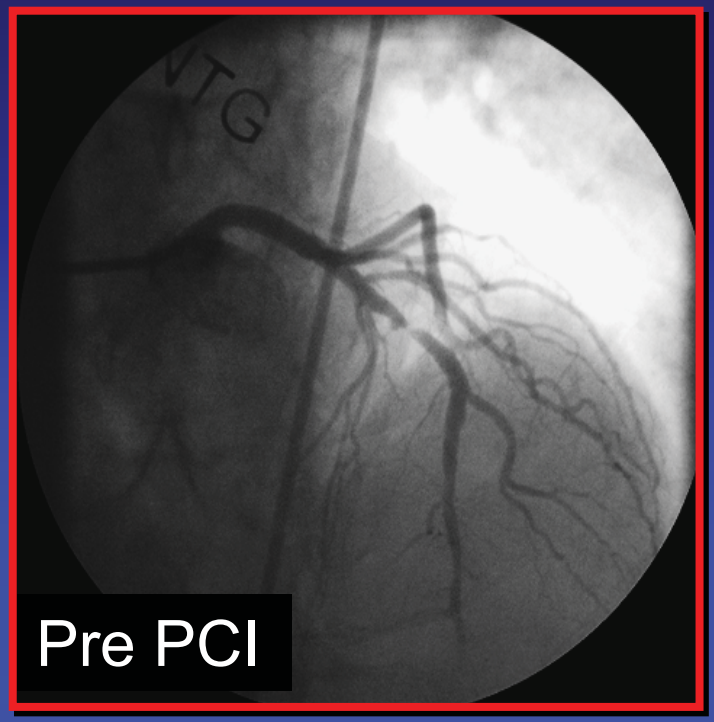
E1 4 mth QCA Edge Data

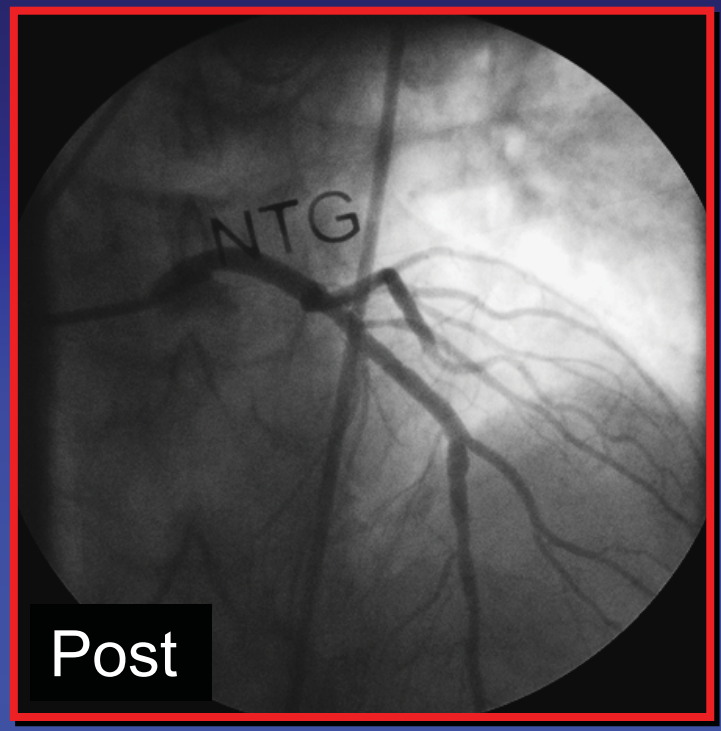


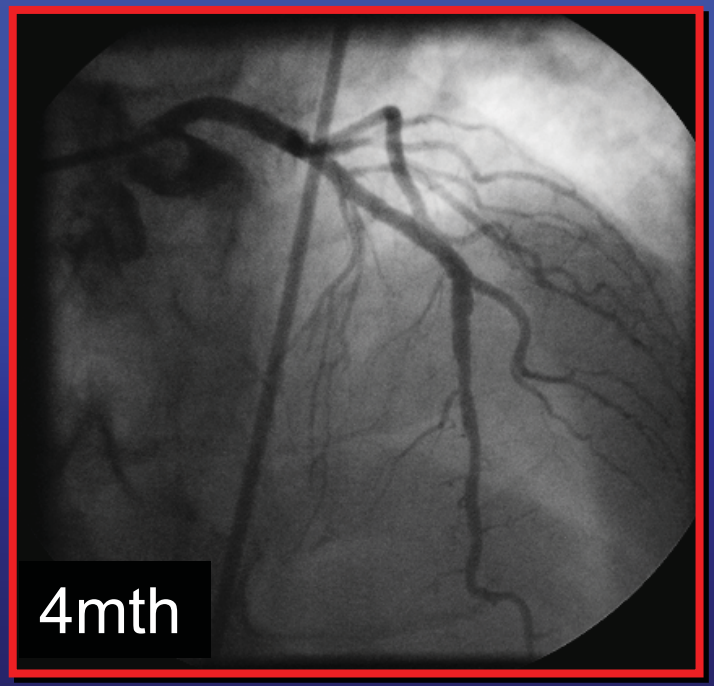


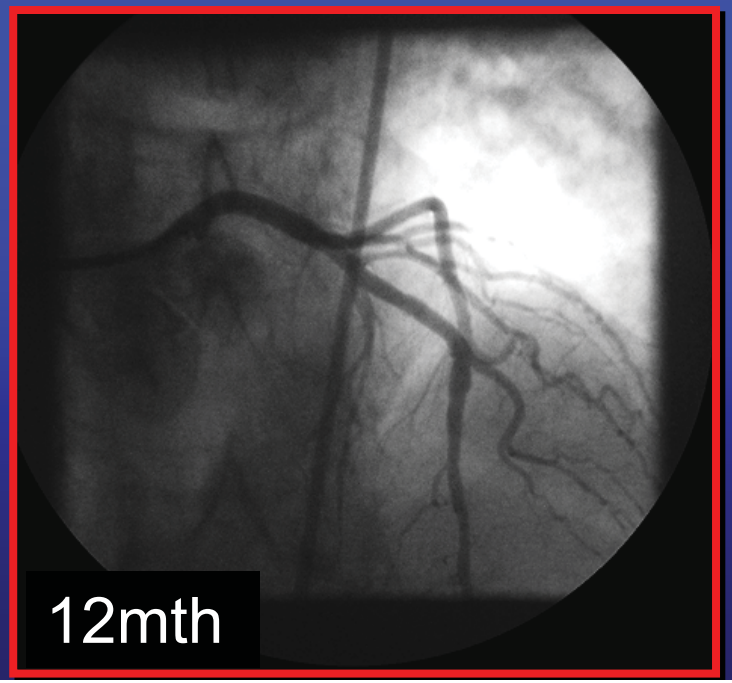
E1

Pt # 006



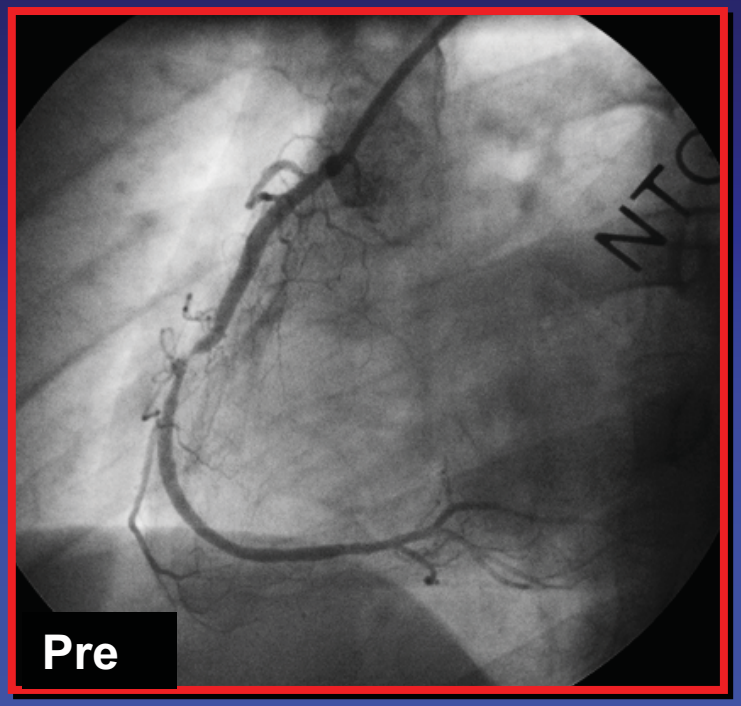


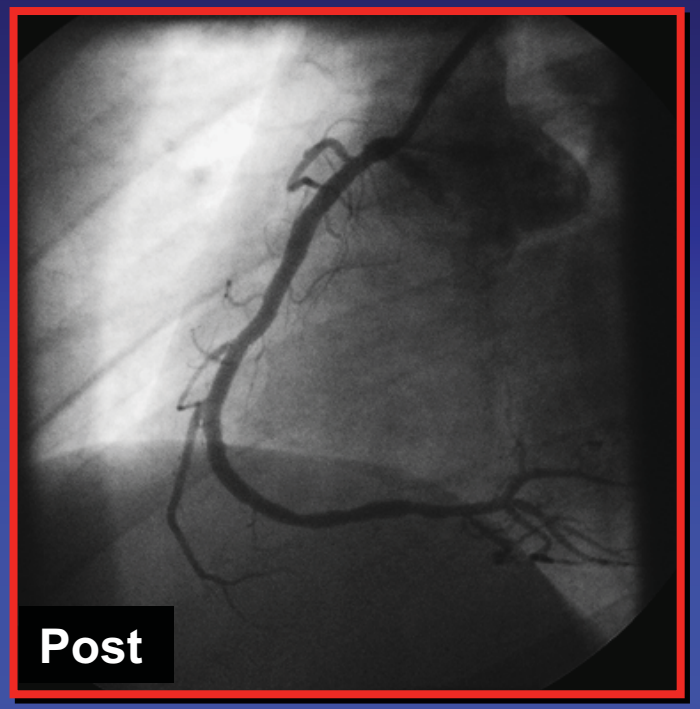


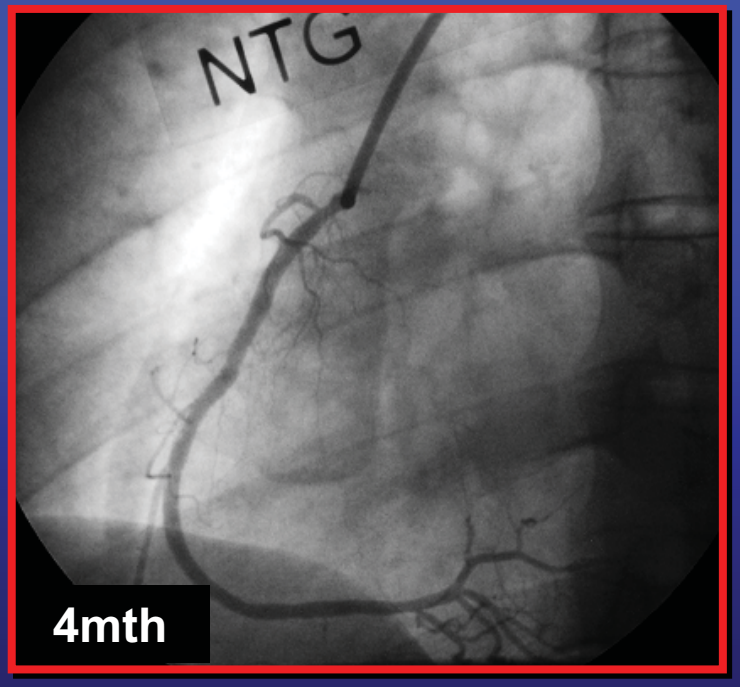


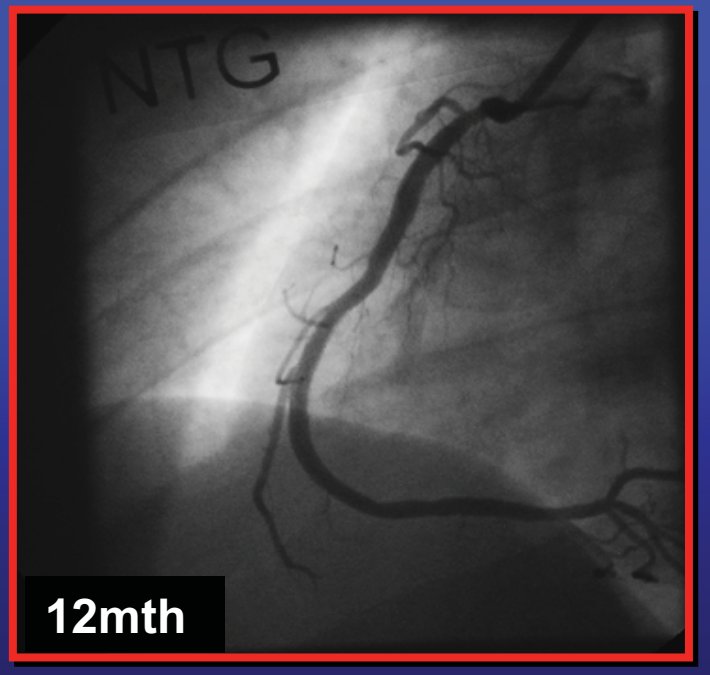
E1

Pt # 0012









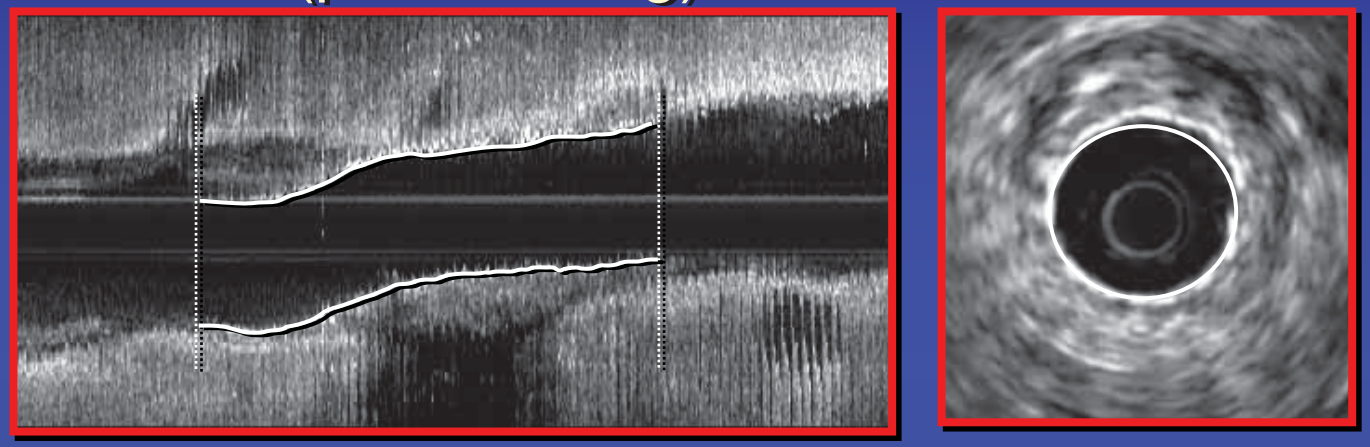
E1 4mth IVUS Data

	Post Mean	Follow up Mean
EEM volume	300 mm^3	321 mm^3
Stent Volume	142 mm^3	149 mm^3
Neointimal Volume	NA	6.1 mm^3
Lumen Volume	142 mm^3	143 mm^3
Percent Volume Obstruction	NA	4.5%
Late Acquired Incomplete Apposition	—	0

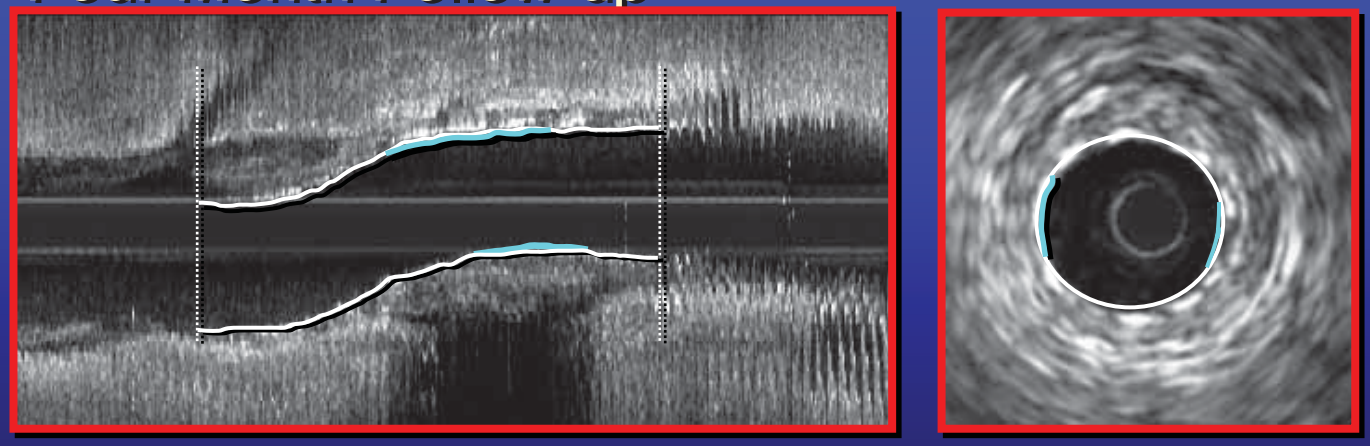
4 mth IVUS follow up achieved: 98%

E1 4 mth IVUS

Baseline (post stenting)



Four Month Follow-up



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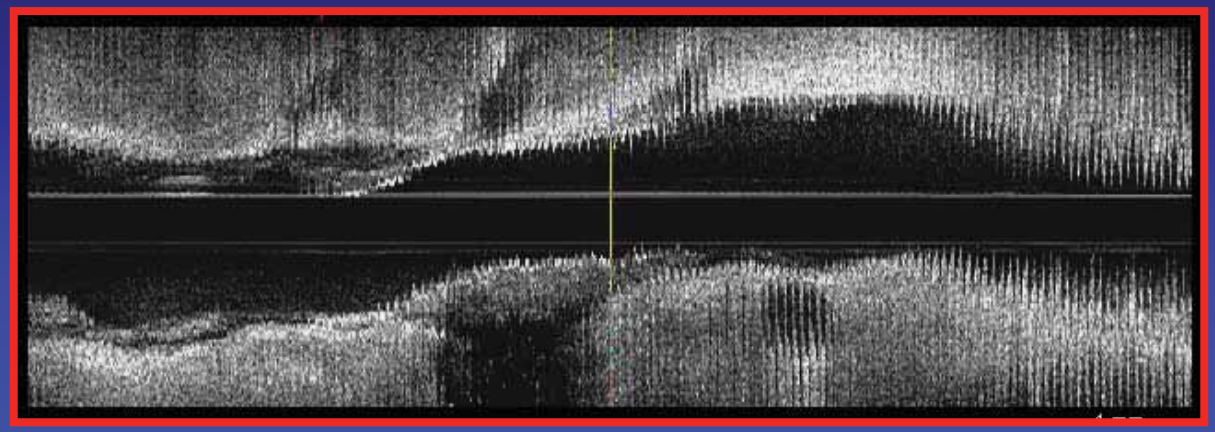
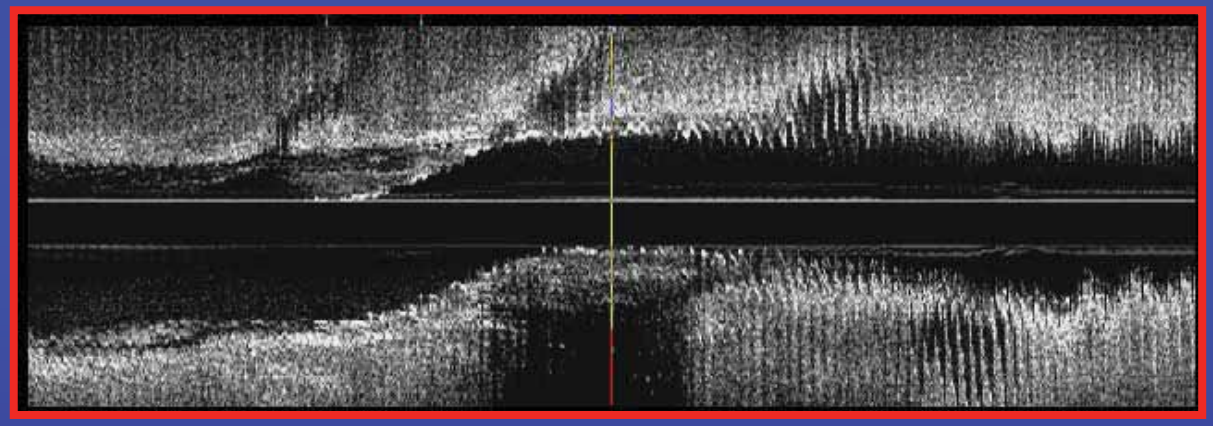
E1 4 &12 mth IVUS F/U

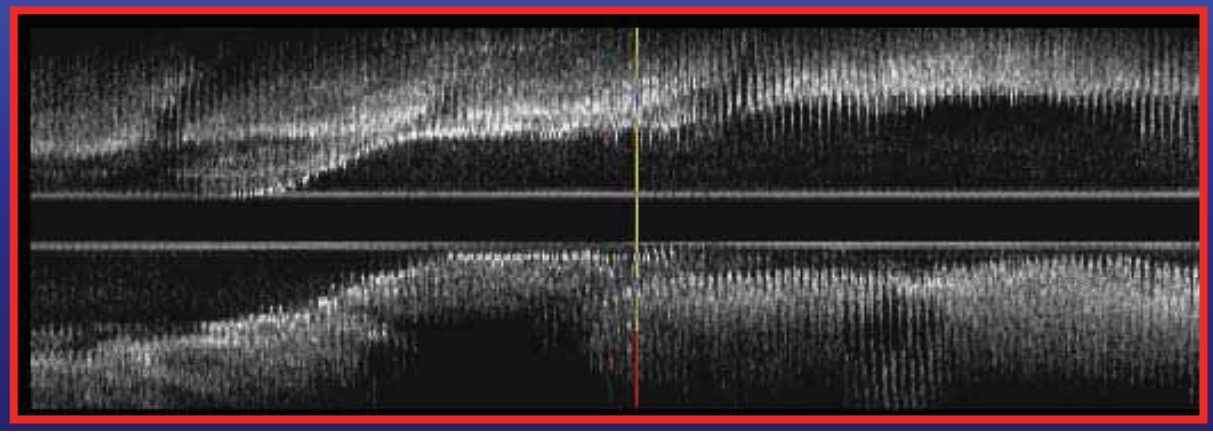


Pt # 0012 RCA

Post Stent

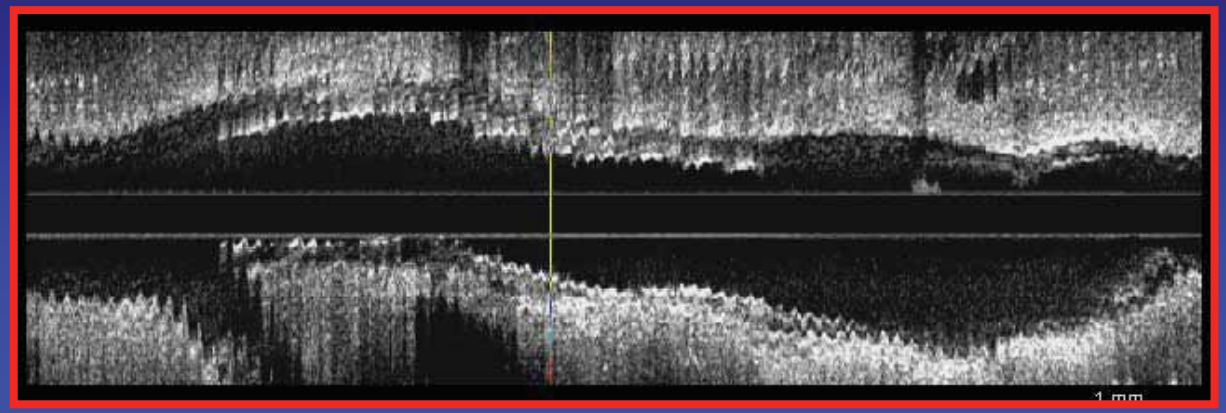


4 mth follow up



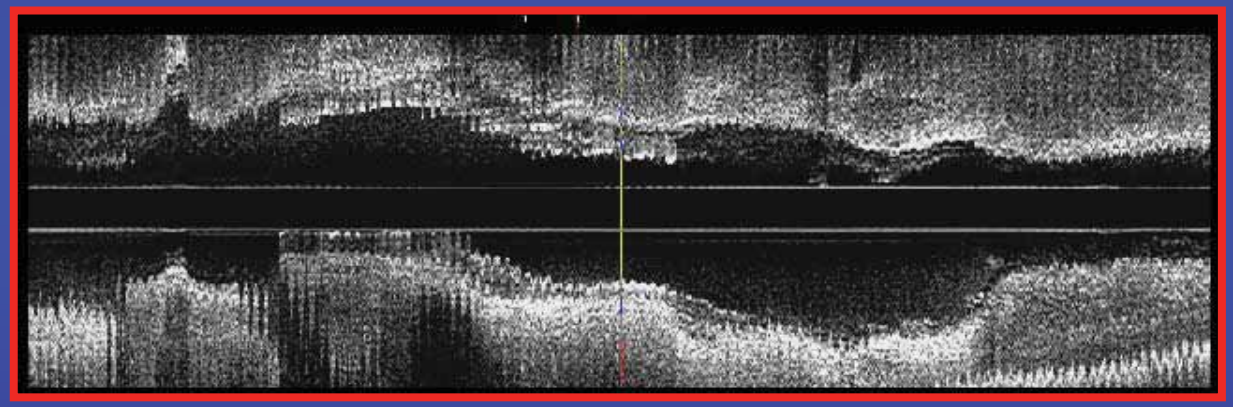
12 mth follow up

E1 4 & 12 mth IVUS F/U

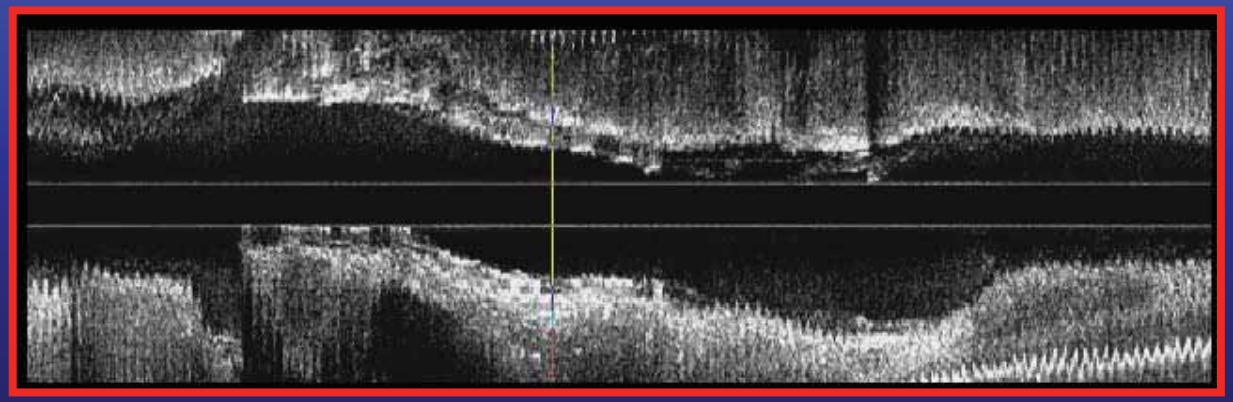


Pt # 006 LAD

Post Stent



4 mth follow up



12 mth follow up

Endeavor II

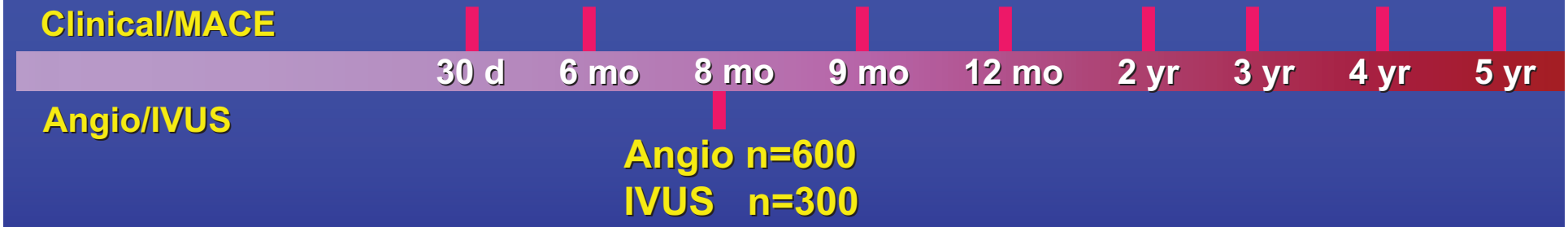
Randomized, Double-blind Trial

Single De Novo Native Coronary Artery Lesions (Type A-C)
Vessel diam: 2.25-3.5mm, Lesion Length: 14-27 mm
N = 1200

90 site Europe, Canada, Israel, South-East Asia, Australia, and New Zealand

Control Driver Stent n=600

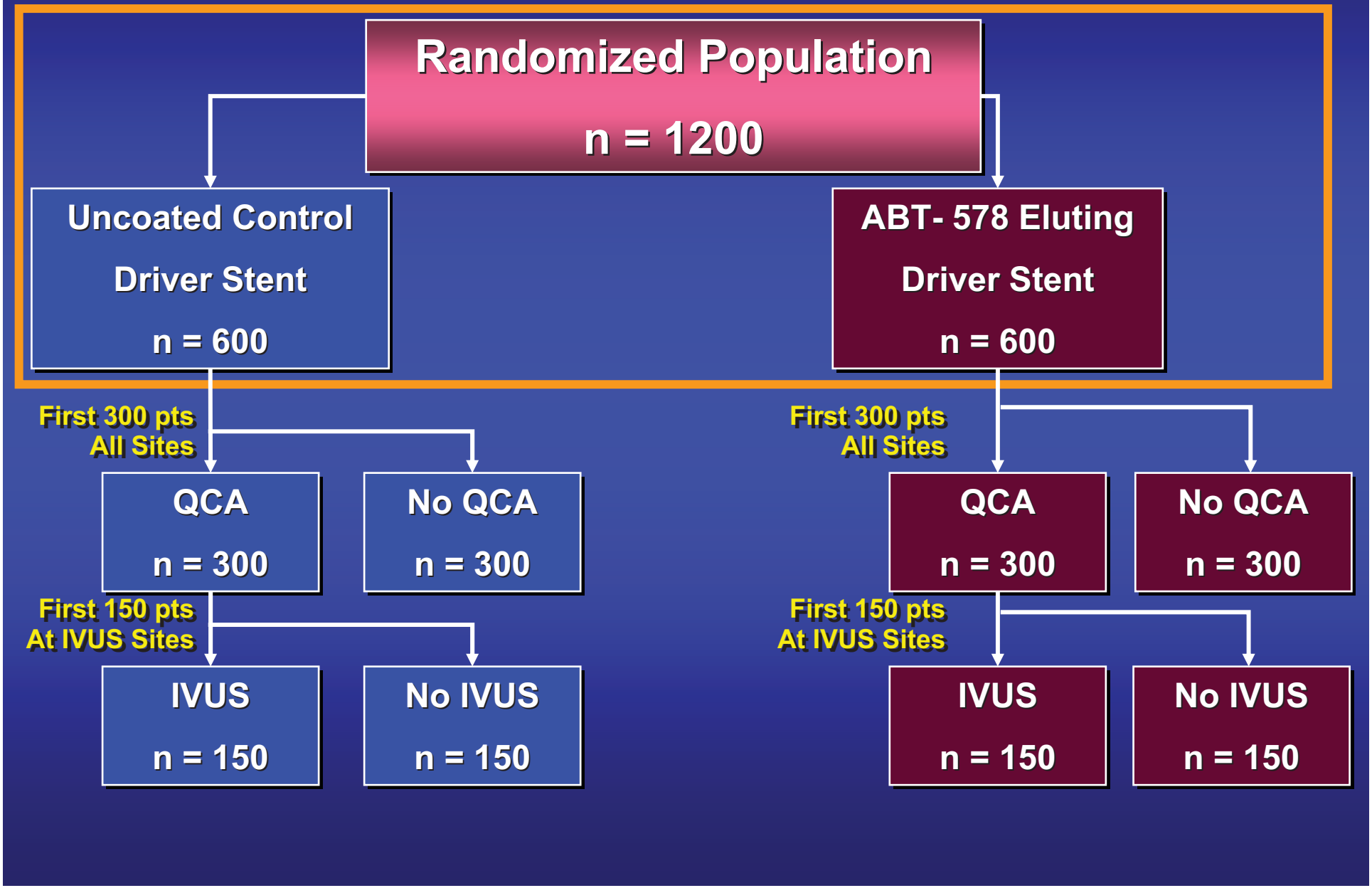
Endeavor Stent n=600



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)

Pre dilatation specified, Antiplatelet therapy for 3 mo, PK sub-study

E II Study Design



Endeavor II

Primary objective

To demonstrate the safety & efficacy of the Endeavor™ Coronary Stent (10 μg/mm ABT-578) compared to the uncoated DRIVER™ Stent for the treatment of single *de novo* lesions in native coronary arteries (2.25-3.5 mm diam).

Primary End-Point

Target Vessel Failure (TVF) rate, defined as a composite of target vessel revascularization, recurrent MI (Q or Non Q-Wave), or cardiac death that could not be clearly attributed to a vessel other than the target vessel at 9 months post procedure.

Endeavor II: Inclusion Criteria

- Age ≥ 18 years
- Evidence of ischemic heart disease or a +ve functional study
- Acceptable for PTCA, stenting and CABG
- SVD or MVD with only moderate stenosis
- Target lesion/ vessel
  - Single de novo, native lesion ≥50% and <100%
  - Lesion length: ≥14 mm and ≤ 27 mm
  - Reference diameter: ≥2.25 mm and ≤ 3.5 mm
- -ve pregnancy test before the procedure if applic
- Subject has provided written informed consent

ENDEAVOR II – Countries & Centers

• Australia	3	• Israel	5
• Austria	2	• New Zealand	2
• Belgium	6	• Poland	4
• Denmark	2	• Portugal	1
• France	11	• Singapore	2
• Germany	15	• Switzerland	3
• Greece	1	• Netherlands	5
• Hong Kong	2	• UK	6

Endeavor II

Investigator	Country	No. of Pts
G Laarman	Netherlands	66
K-H Kuck	Germany	54
T Münzel	Germany	47
E Hauptmann	Germany	42
M Suttorp	Netherlands	41
J Drzewiecki	Poland	40
J Ormiston	New Zealand	37
H-P Schultheiss	Germany	37
M Pieper	Switzerland	37

ENDEAVOR III
Randomized Multi-center Trial

Single *De Novo* Native
Coronary Artery (NCA) Lesion
(Type A-B)
Stent Diameter: 2.5-3.5 mm
Stent Lengths: 18-30 mm (8/9 mm bailout)
Lesion Length: 14 - 24 mm
Pre-dilatation required
Direct Stenting is not allowed

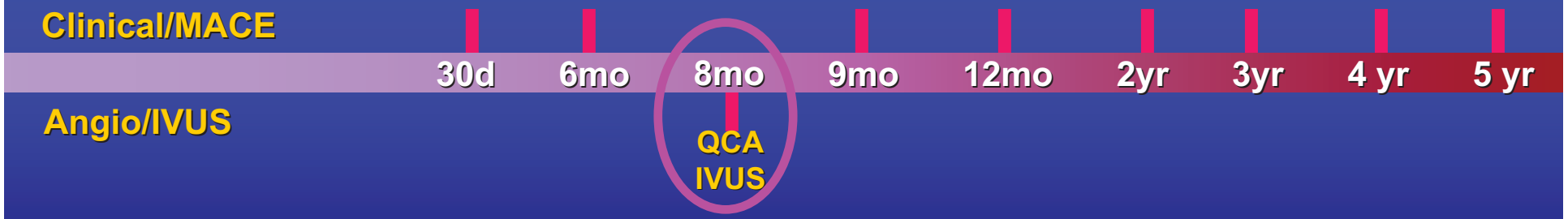
N=436
3:1 Randomization

Single Blind
Single Vessel
No Staging

Control Cypher Stent
n=109

Endeavor Stent
n=327

30 sites
United States



Primary Endpoint: In-segment Late lumen loss by QCA at 8 months
Secondary Endpoints: TLR, TVR, TVF at 9 months & ABR at 8 months
Antiplatelet therapy for ≥ 3 mths

E III PI & Core Labs

Principal Investigators
Martin B. Leon, Lennox Hill Heart Vasc Inst, CRF, NY

QCA Core Lab
Brigham and Women's Hospital, Boston, MA, USA
Jeffrey J. Popma, MD

IVUS Core Lab
Cardiovascular Core Analysis Lab
Stanford Interventional Cardiology, CA, USA
Peter Fitzgerald, MD

Data Coordinating Center
Harvard Clinical Research Institute
Richard E. Kuntz, MD, MSc

ECG Core Lab
Harvard Clinical Research Institute, Boston, MA, USA
Peter Zimetbaum, MD

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Endeavor III

Primary objective

To demonstrate the equivalency of the Endeavor™ Coronary Stent (10 μg/mm ABT-578) with Cordis' Co CYPHER™ Sirolimus-Eluting Coronary Stent System for the treatment of single *de novo* lesions in native coronary arteries 2.5-3.5 mm in diameter.

Primary End-Point

In-segment late loss at 8 months as measured by QCA, defined as the difference between the post-procedure minimal lumen diameter (MLD) and the follow-up angiography MLD.

Endeavor III: Inclusion Criteria

Inclusion criteria (Target lesion):

Same as Endeavor II, except:

- Target vessel must have ≥ TIMI flow 2
- Target lesion length must be ≥ 10 & ≤ 24 mm
- Target vessel ref diam must be ≥ 2.5 & ≤ 3.5 mm

Exclusion criteria (Target lesion):

Same as Endeavor II, except:

- Treatment of one additional (non-target) lesion is permitted

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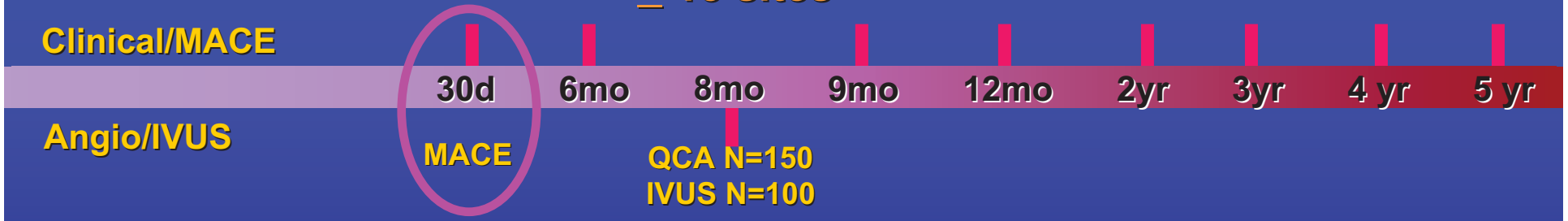
Single-arm Multi-center Registry

Single *De Novo* NCA Lesion
(Type A-B2)
Stent Diameter: 2.25-3.5 mm
Stent Lengths: 8-30 mm (8/9 mm bailout)
Lesion Length: 14 - 27 mm

10 μg ABT-578 per mm stent length
Direct Stenting – Per Investigator Discretion
for lesions ≤ 20mm

N = 300

≤ 15 sites



Primary Endpoint:	MACE at 30 days
Secondary Endpoints:	TLR, TVR, TVF @ 9 mo, QCA & IVUS @ 8 mo
Antiplatelet therapy for ≥ 3 months	

Medtronic Endeavor Update

Endeavor Preclinical

ABT-578 is a synthetic cytostatic agent similar to sirolimus that has been demonstrated to be safe and effective in reducing NIH in animal models.

Endeavor I

First in man trial- 4 mth results suggest that the ABT-578 eluting Endeavor Stent is safe and efficacious in the reduction of in-stent restenosis.

Endeavor II and III

Large scale randomized controlled trials: will provide definitive data regarding the safety and efficacy of the ABT-578 eluting Endeavor Stent.