Can We Prevent Future Events of Deferred Lesions ? *PREVENT Trial ;* Design and Rationale

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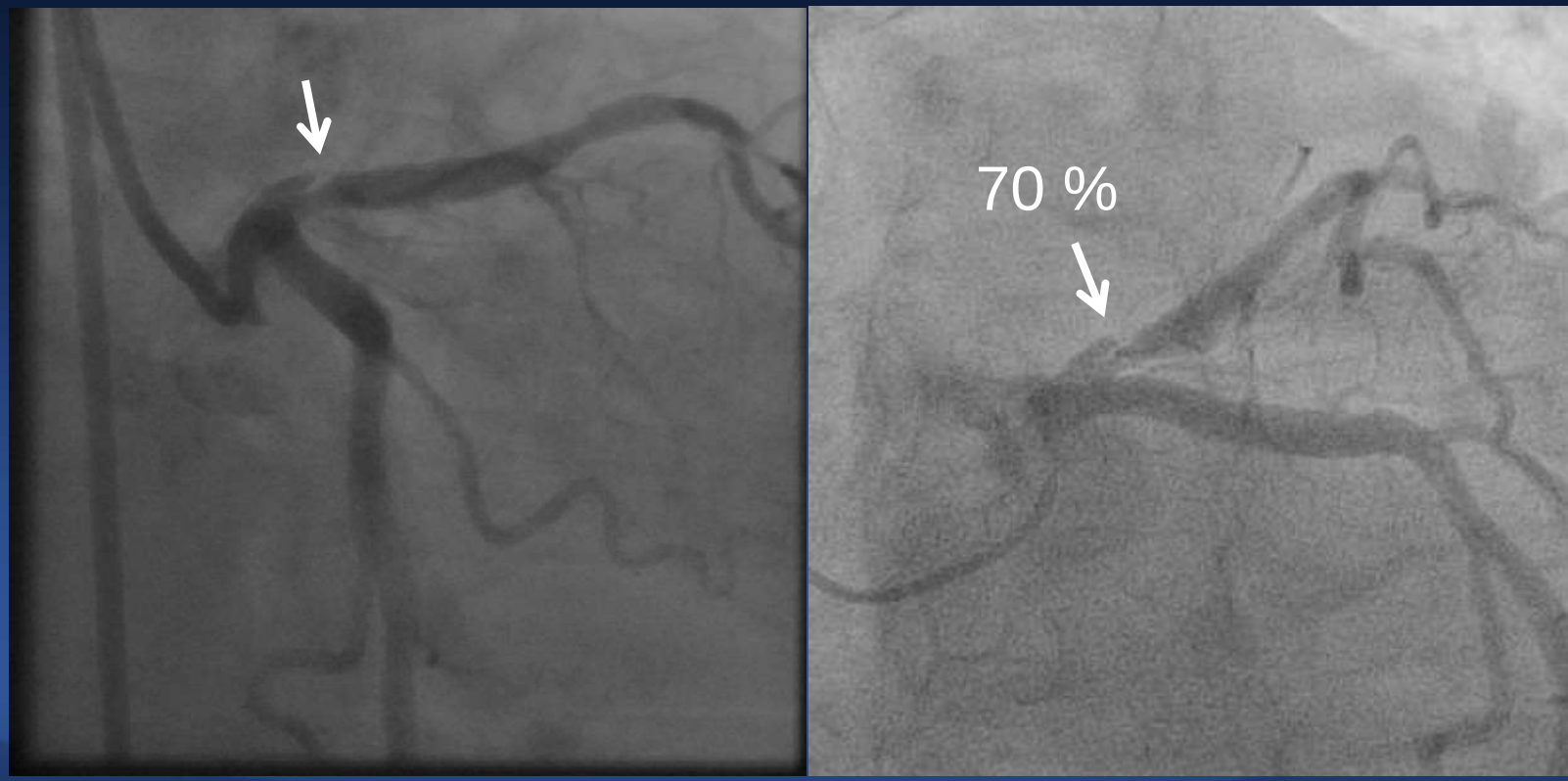
M/74,
Asymptomatic Plaque Rupture

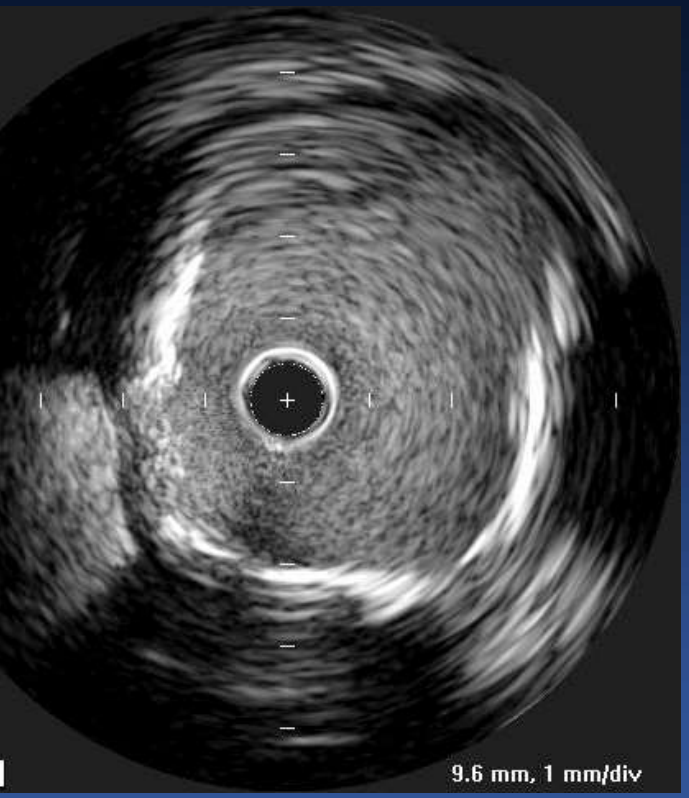
Proximal LAD Stenosis on Coronary CT,
Hypertension, DM, Hyperlipidemia, Ex-smoker

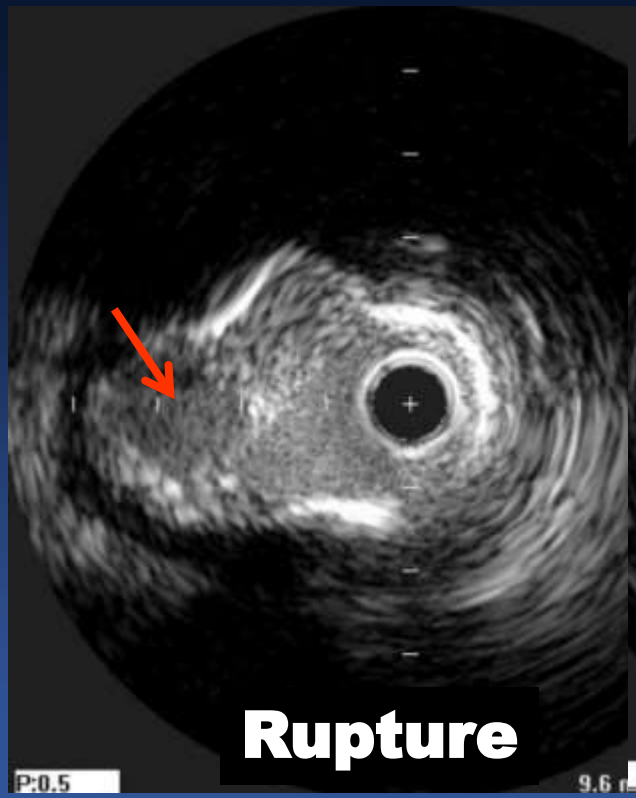


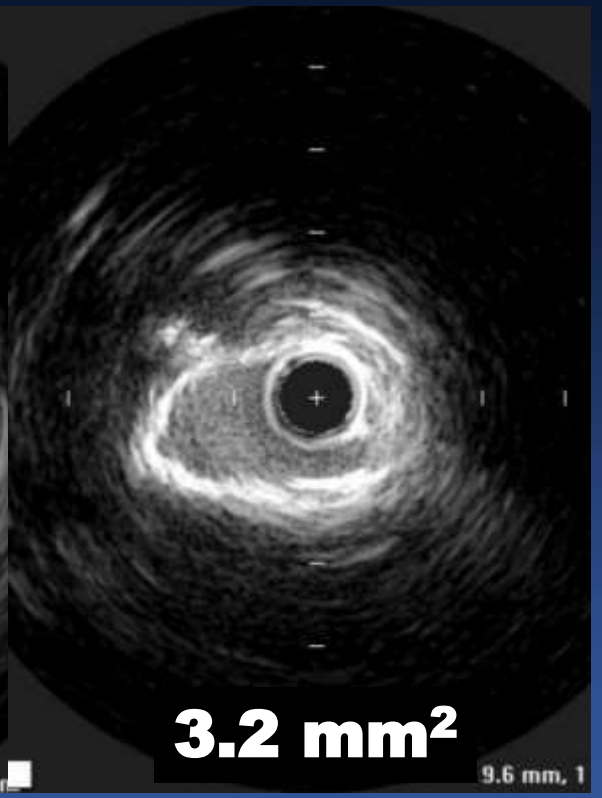
IVUS

LM

LAD, Culprit





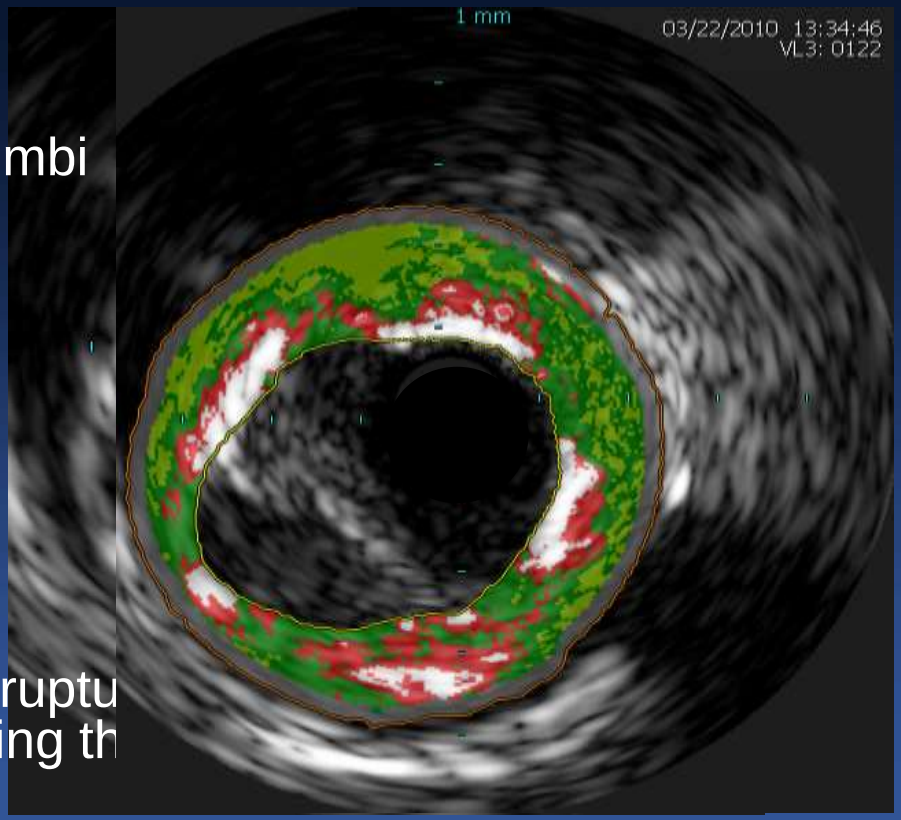


VH-IVUS

LAD, Culprit

Thrombi

Plaque ruptu
organizing th



PB: 71.3%
FI : 41.4%
FF: 20.0%
NC: 23.0%
DC: 15.6%

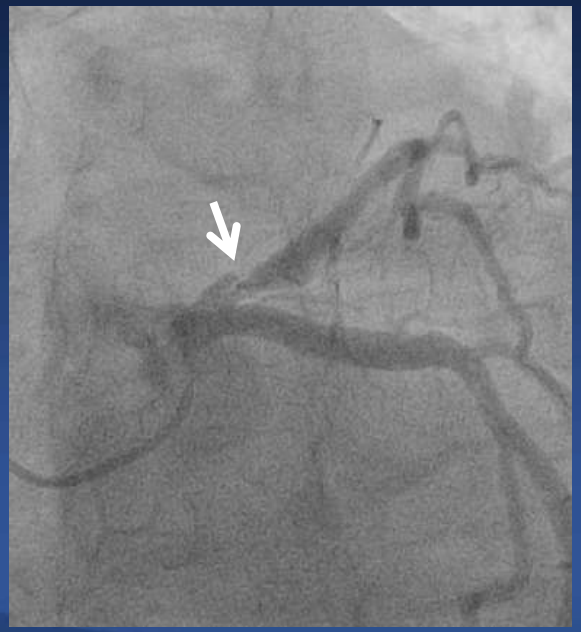
Vulnerable Plaque !

To Treat Based on Vulnerability, Not To Treat Based on FFR >0.80

Visual Functional Mismatches

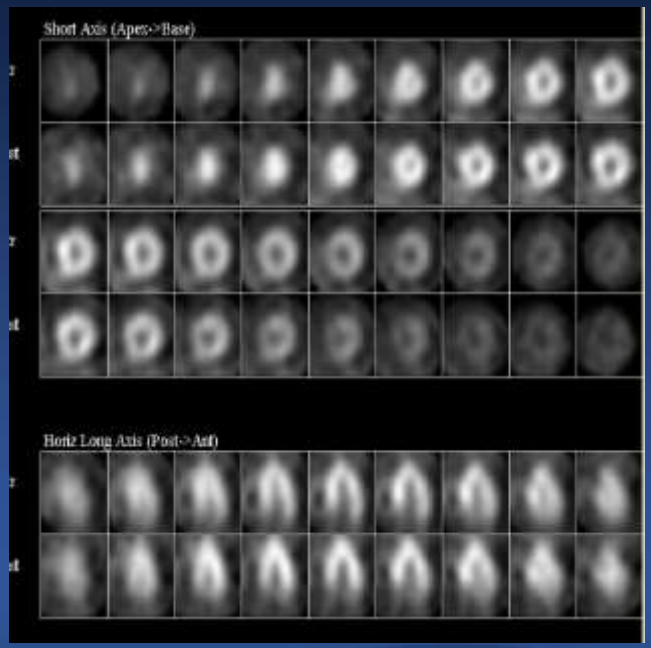
Just Defer

Vulnerable Plaque



Negative FFR 0.89

Normal Thallium Spect



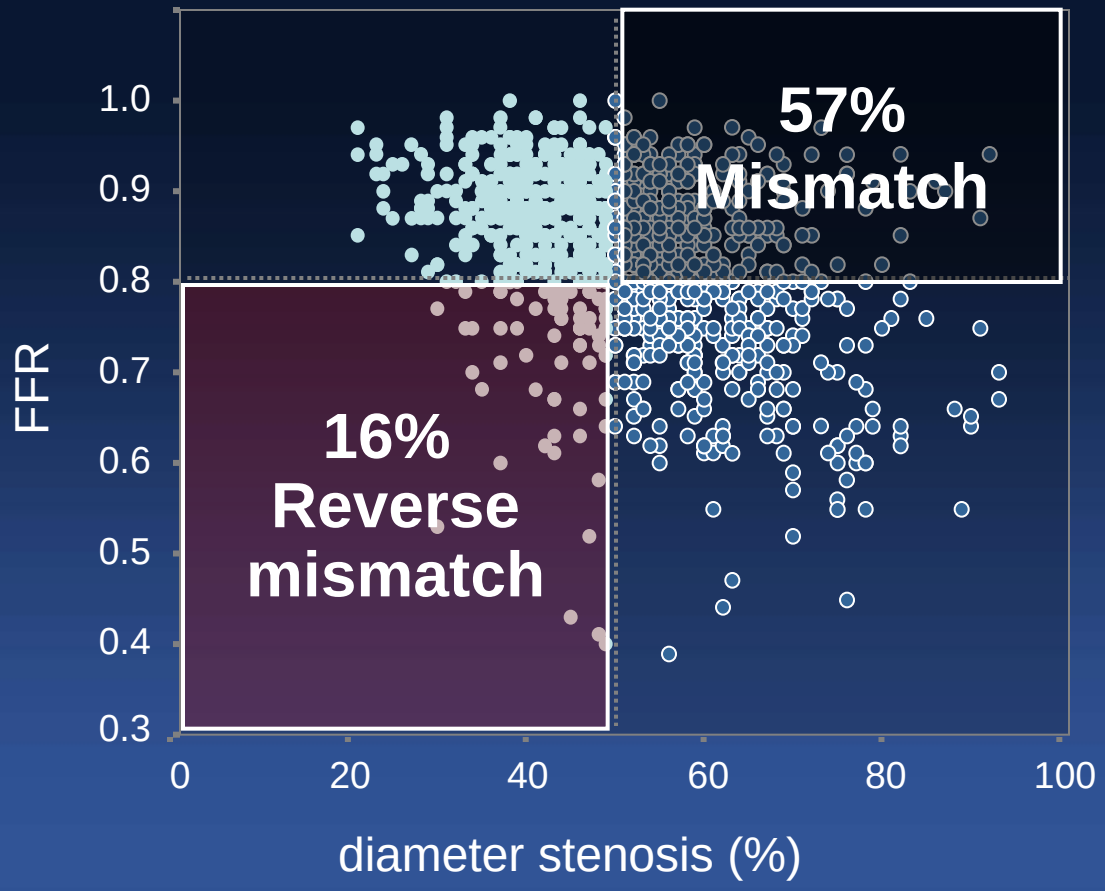
Why I Defer ?

1. I am a FFR believer.
2. FFR is *well matched with non-invasive stress tests.*
3. Negative non-invasive stress tests means *just excellent prognosis (0.6%/year, Cardiac Death and MI),* even in the presence of angiographically proven coronary artery disease.

Shaw LJ, J Nucl Cardiol 2004;11:171-85 ,
Prognostic value of gated myocardial perfusion SPECT.
Very large meta-analysis. (n=39,173 patients)

Many Mismatches

(1066 Non-LM lesions, AMC data)



Tighter stenosis,
Negative FFR

Insignificant
stenosis,
Positive FFR

Park SJ et al, JACC Intv 2012;5:1029 –36

FFR Guided (>0.80) Defer,
Visually Significant Stenosis
(with/without Vulnerable Features)

Is It Really Safe?

< 1% of Death and MI / Year

From NUCLEAR studies, DEFER, FAME

Multicenter, Prospective Registry to Evaluate
The Natural History of FFR-Guided Deferred Coronary Lesions

IRIS FFR DEFER Registry

Patients with ≥1 Deferred Target Lesions
(DS>50% by visual estimation and FFR>0.80)

Deferred Patients
(N=10,000)

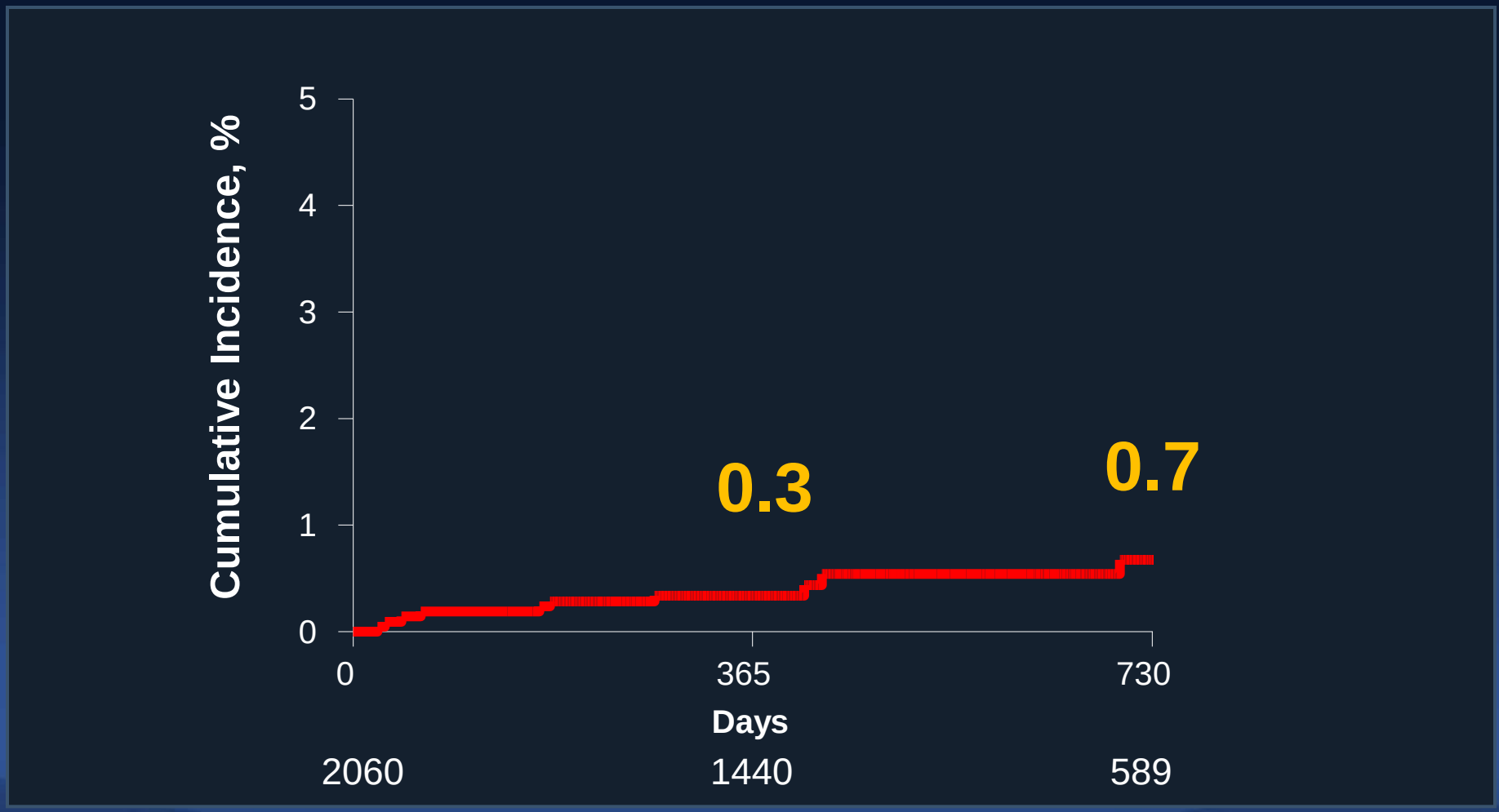
Imaging Sub-Study
(n=1,200)

2 year Clinical F/U

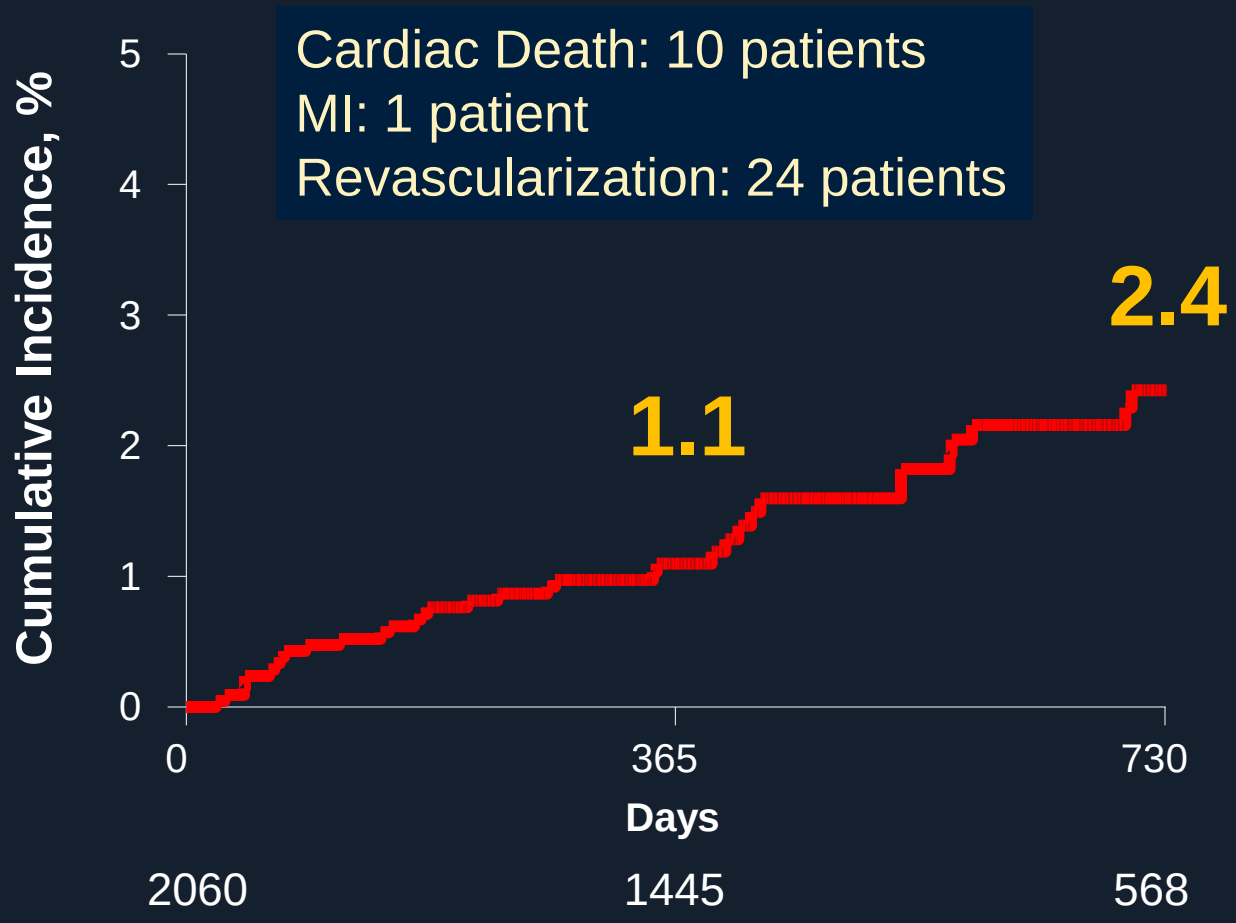
2-year CAG & Imaging FU
- IVUS
- VH-IVUS
- OCT

Primary Endpoint : *Target Vessel Related (TVF)*
Cardiac Death, MI, and Clinical driven TVR at 2 year

Death and MI at 2 Year (per patient, n=2,060)



Death / MI Revascularization at 2 Year (per patient, n=2,060)



FFR Guided Defer *Is*
Safe and Good !

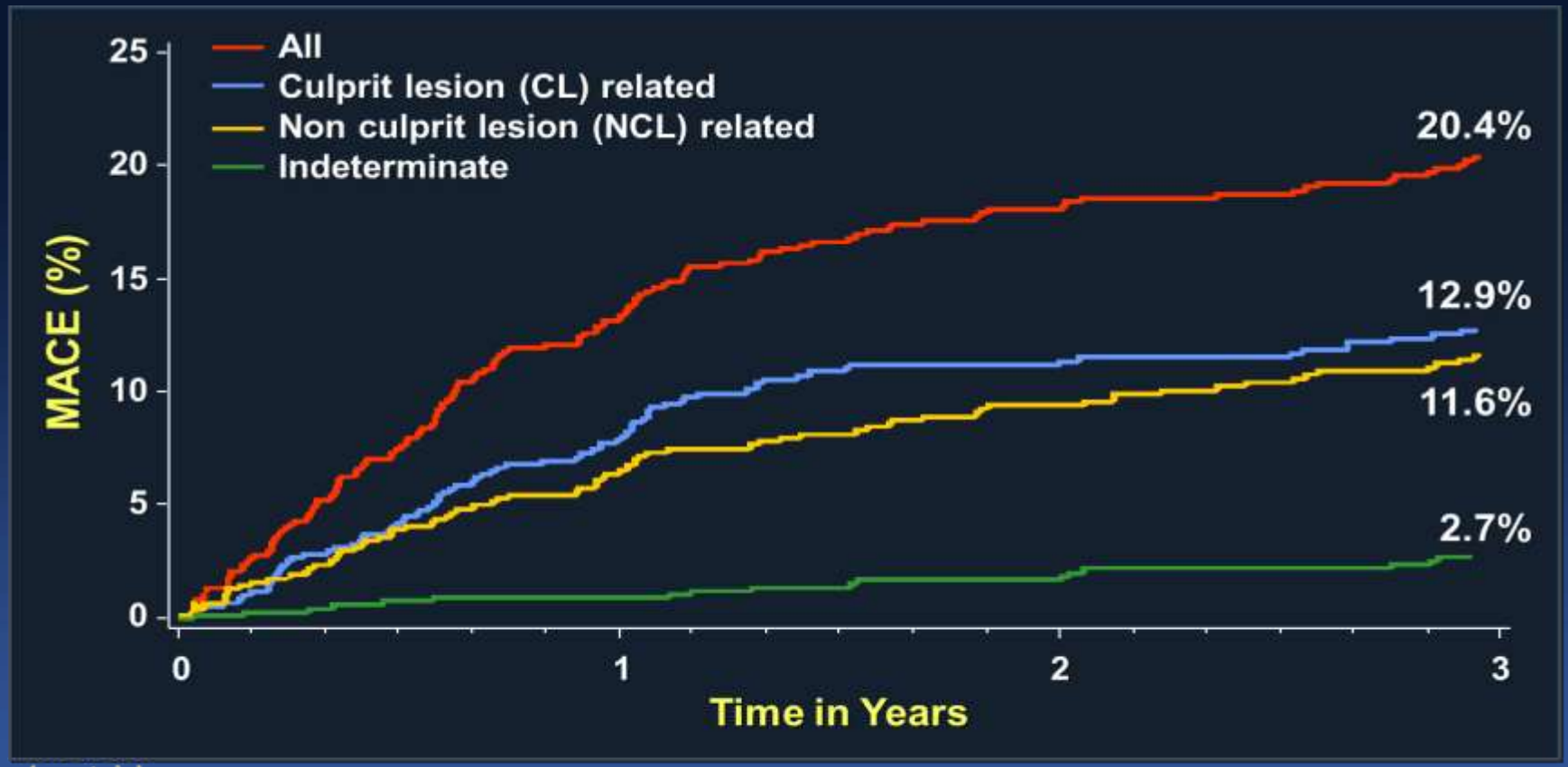
Q1,

Should We Treat

Functionally Insignificant Vulnerable Plaque **?**

PROSPECT: MACE

(N=700, ACS, 3-Vessel Imaging after PCI)



Number at risk

ALL	697	557	506	480
CL related	697	590	543	518
NCL related	697	595	553	521
Indeterminate	697	634	604	583

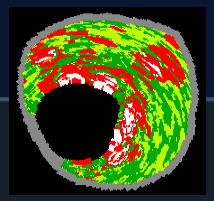
Stone GW et al. NEJM 2011;364:226-35

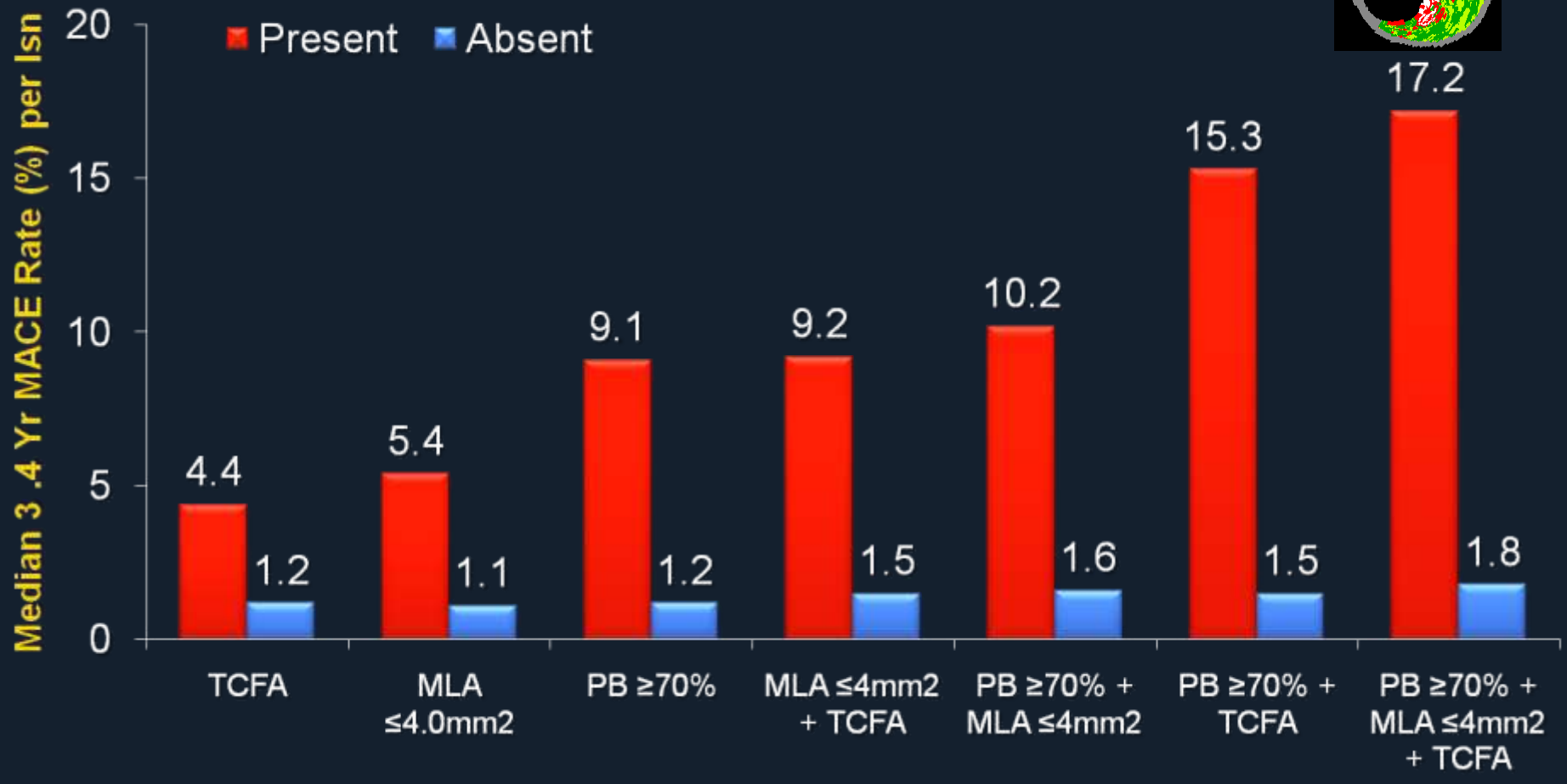
Independent Predictors
of Non-Culprit Lesion Level Events

Variable	HR [95% CI]	P value
PB_{MLA} ≥70%	5.03 [2.51, 10.11]	<0.0001
VH-TCFA	3.35 [1.77, 6.36]	0.0002
MLA ≤4.0 mm^2	3.21 [1.61, 6.42]	0.001

by Cox Proportional Hazards regression

PROSPECT: Correlates of Non Culprit Lesion Related Events





	TCFA	MLA ≤4.0mm2	PB ≥70%	MLA ≤4mm2 + TCFA	PB ≥70% + MLA ≤4mm2	PB ≥70% + TCFA	PB ≥70% + MLA ≤4mm2 + TCFA
Prevalence*	51.2%	49.1%	30.7%	17.4%	15.4%	11.0%	4.6%
Lesion HR	3.8 (2.2, 6.6)	5.0 (2.9, 8.7)	7.9 (4.6, 13.8)	6.4 (3.4, 12.2)	6.7 (3.4, 13.0)	10.8 (5.5, 21.0)	10.8 (4.3, 27.2)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

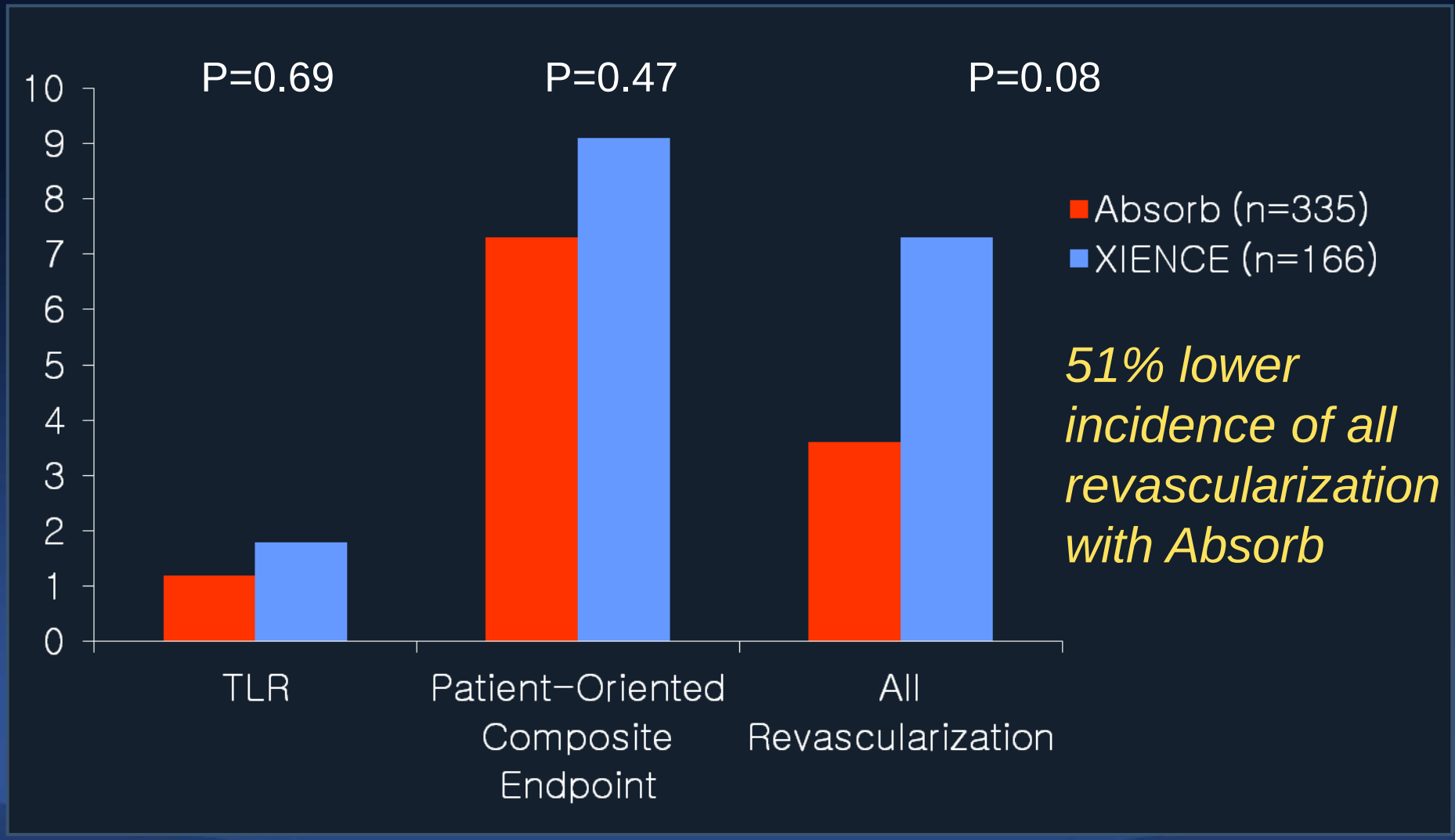
*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

Q2,
Can BVS Implantation Stabilize Plaque Vulnerability ?

Abbott Absorb, Balloon expandable, Bioresorbable Vascular Scaffolds (BVS)

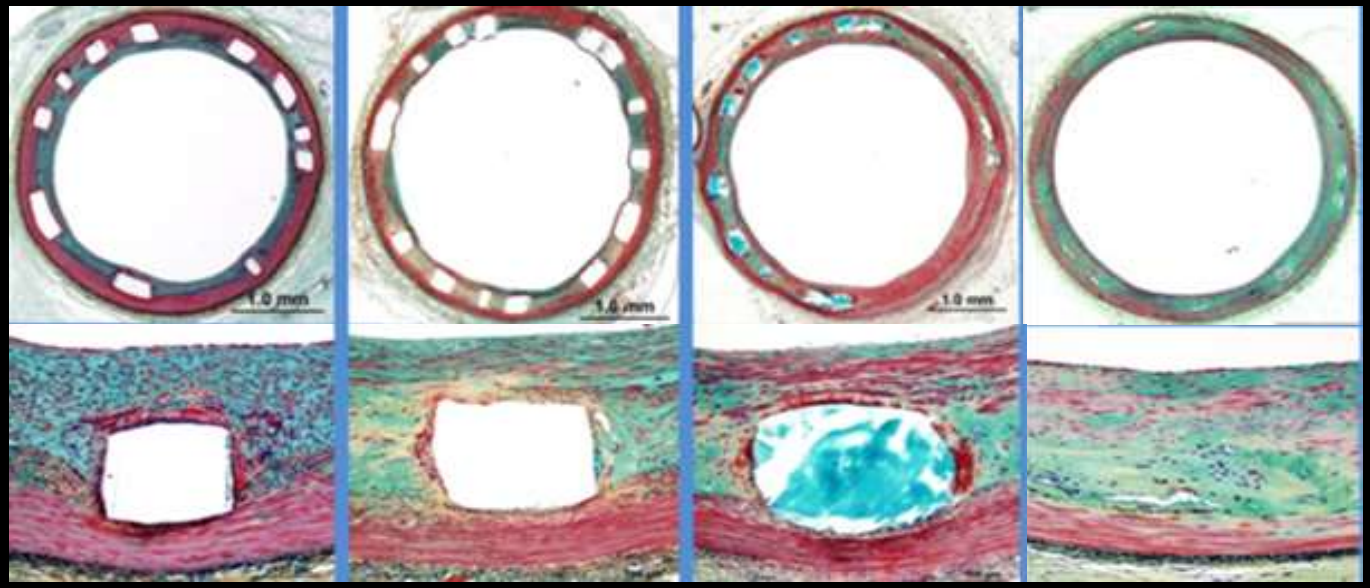
PLLA ; Poly (L-lactide), Everolimus eluting
Multi-link pattern, 150 um

ABSORB II, 1-year Results



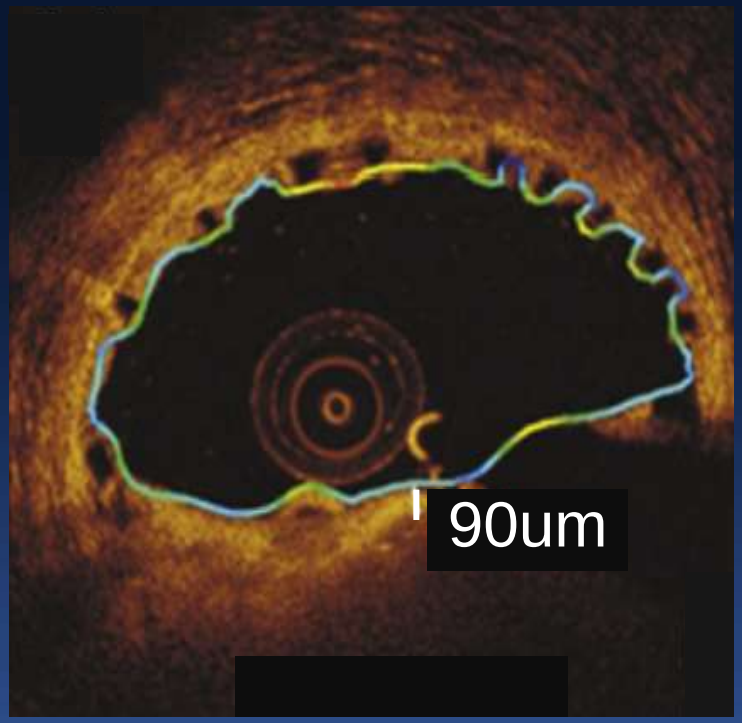
Patrick W Serruys, et al, Lancet Sep 14, 2014

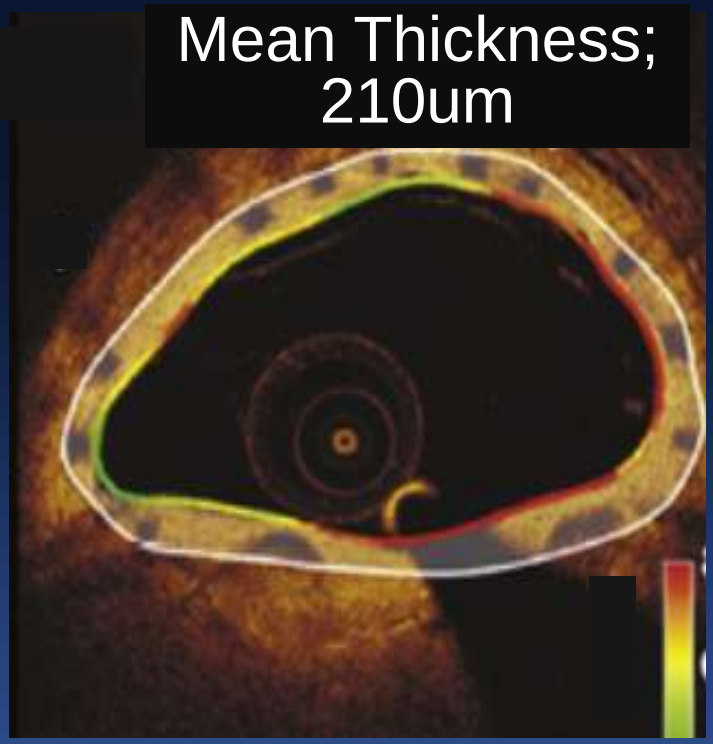
BVS Strut Was Replaced With *Smooth Muscle Cells and Myofibroblasts*



1 month 6 month 2 year 5 year

BVS Deployed on Fibroatheroma

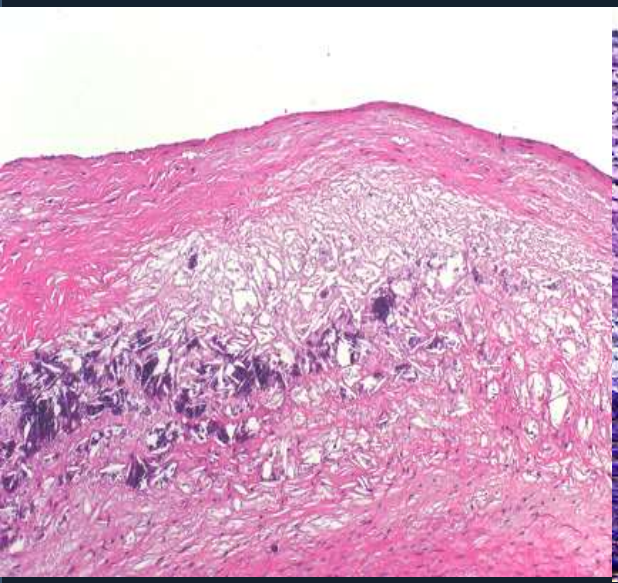




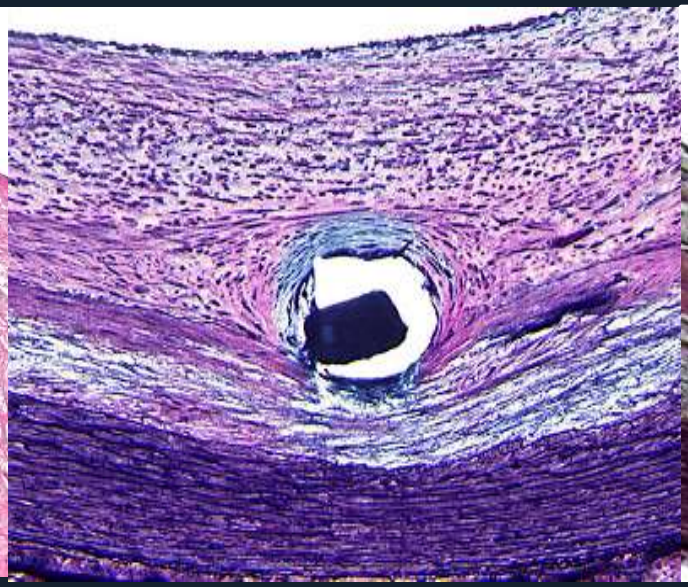
A 210um layer of Neointima at 2 years.

Bourantas CV et al. Am Heart J 2013;165:869-81

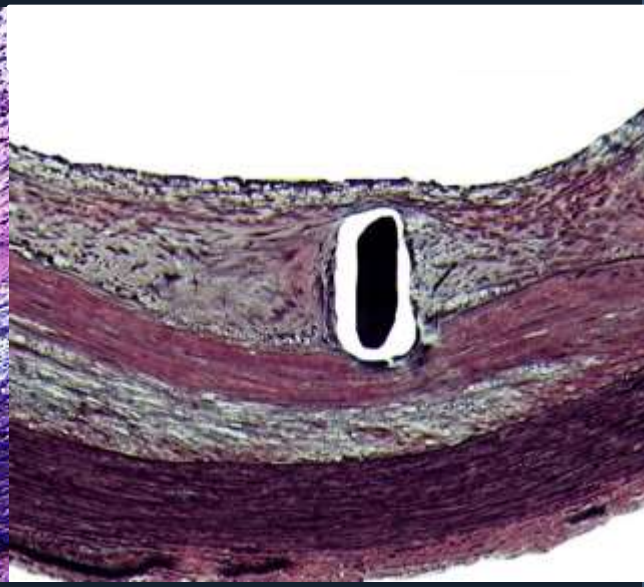
Everolimus Induced
Less Neointimal Hyperplasia on TCFA



TCFA



Metallic &
Polymer Strut

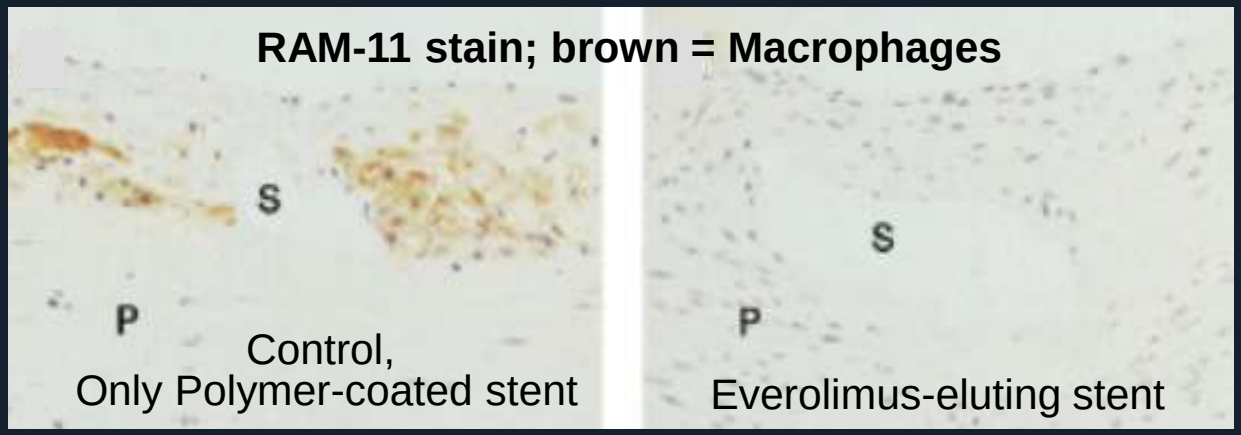


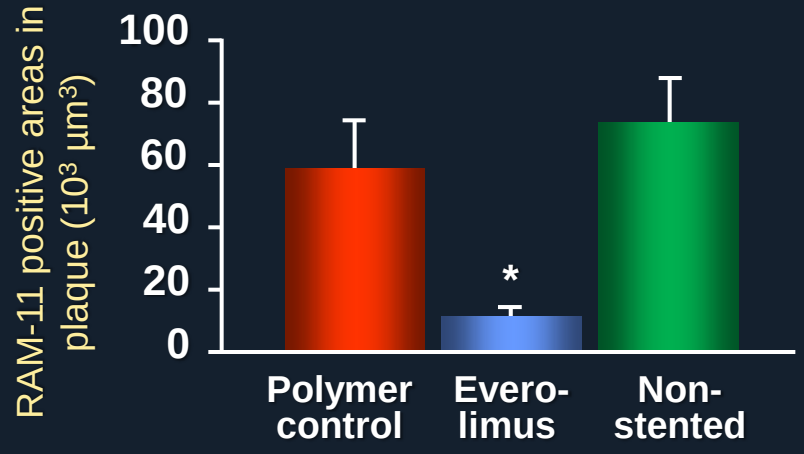
Everolimus Strut

Adapted from Moreno PR.Cardiol Clin 2010;28:1-30

Everolimus Induced Autophagy of Macrophages

Atherosclerotic arteries of cholesterol-fed rabbits

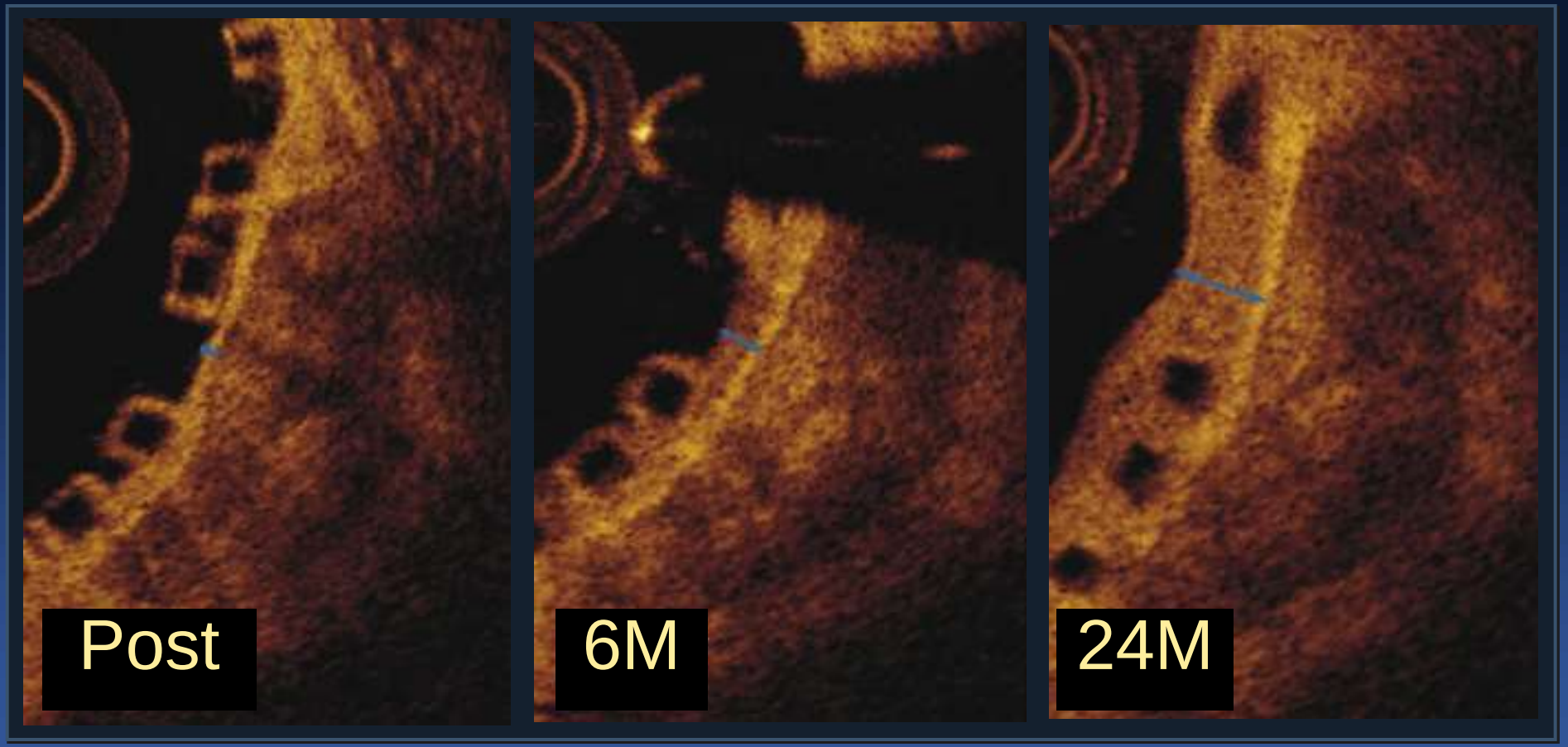




EES resulted in marked reduction of macrophage content, with preservation of SMC, *which can stabilize the plaque vulnerability*

Verheye S et al. JACC 2007;49:706-15

BVS Over A Calcified Plaque, Sealing and Shielding of Plaques

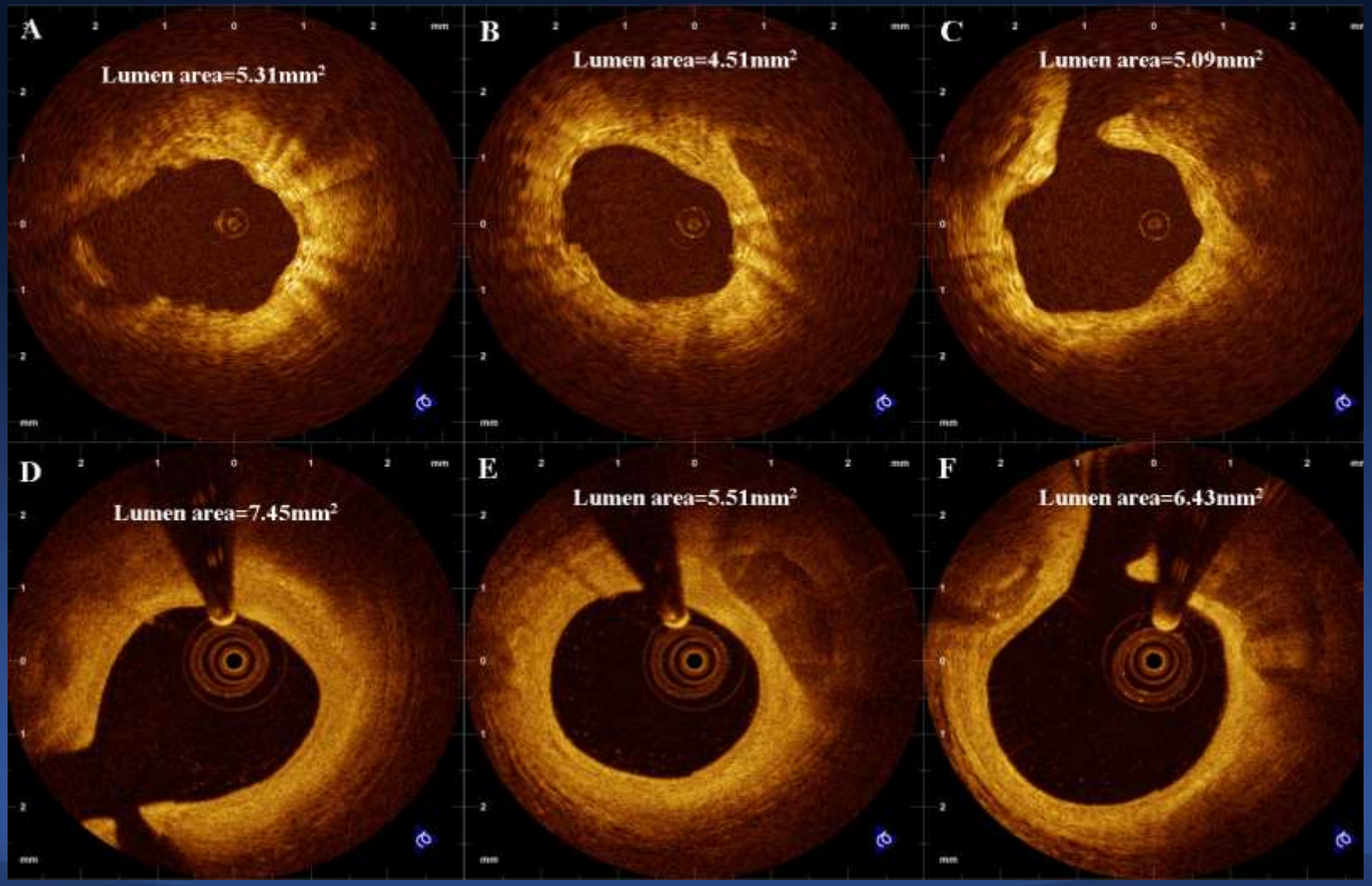


Brugaletta S et al. Atherosclerosis 2012

Overall, BVS Effect on TCFA;
Plaque Stabilization and Lumen Enlargement

6 months

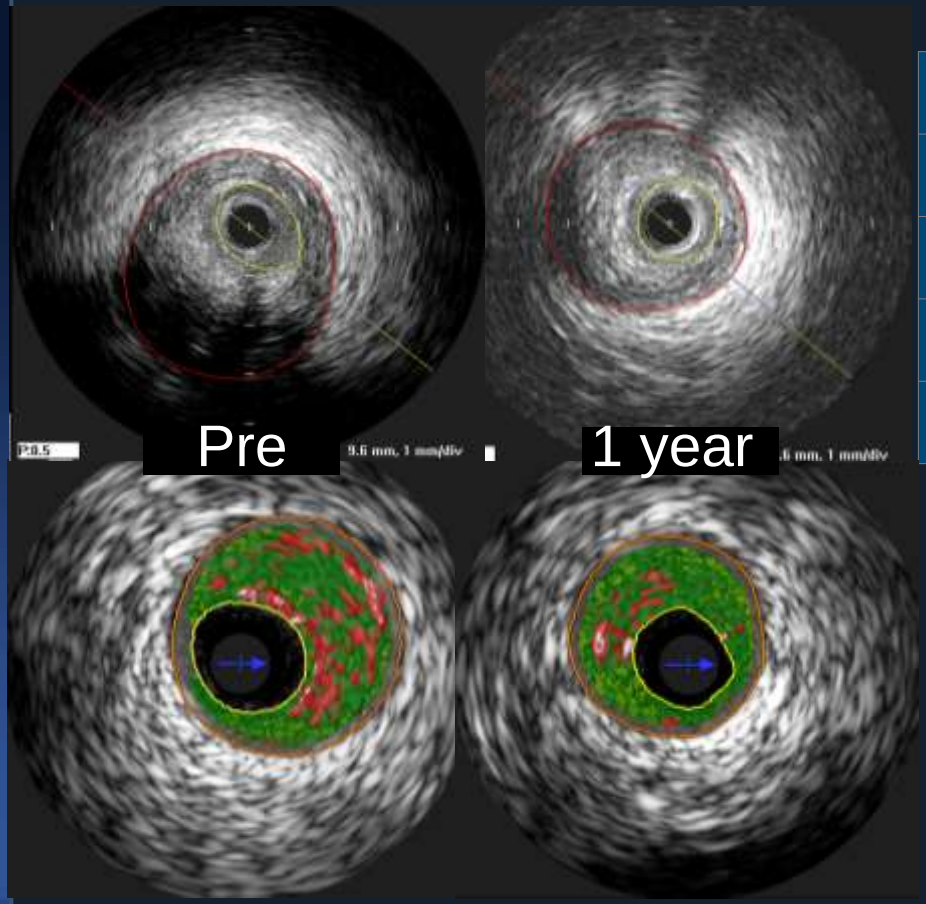
60 months



Karanasos A et al. Circulation. 2012;126:e89-e91

Natural Plaque Changes of Deferred Lesion

Natural Aging, Plaque Changes
After 1 year of Statin Therapy



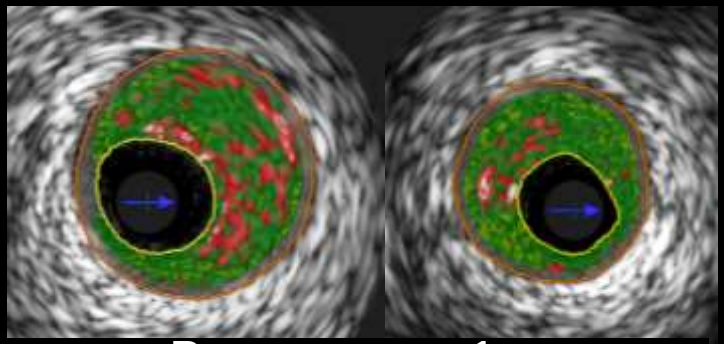
	Pre	1 year
Vessel area (mm^2)	13	12 (8%) ↓
Mean lumen area (mm^2)	3.9	3.6 (8%) ↓
Plaque area (mm^2)	8.6	8.2 (5%) ↓
Necrotic core (%)	22	18 (18%) ↓

Decreased

- *Vessel area,*
- *Plaque area,*
- *MLA, and*
- *% Necrotic core.*

BVS induced Lumen Enlargement due to Significant Plaque Regression

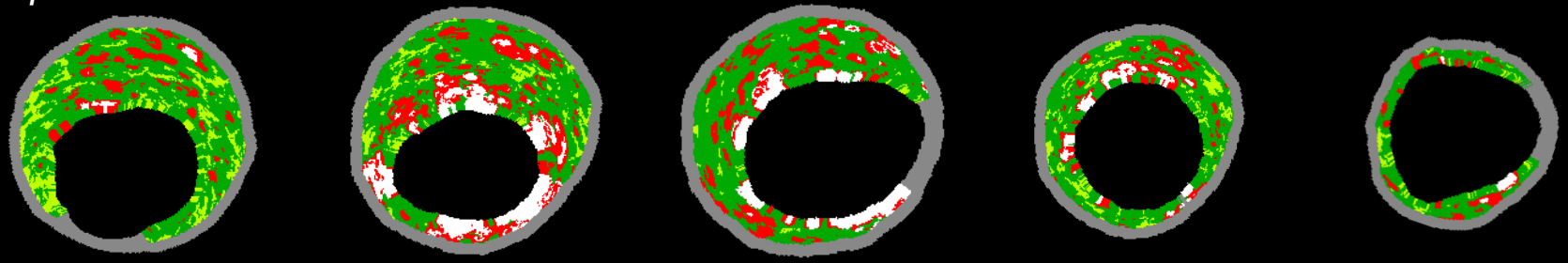
Natural Aging with Statin



Pre 1 year

	Pre	1 year
Vessel Area	13	12 (8%) ↓
MLA	3.9	3.6 (8%) ↓
Plaque Area	8.6	8.2 (5%) ↓

BVS Implantation



	Pre-PCI	Post-PCI	6 months	2 years	5 years
Vessel area (mm^2)	15.72	15.34 (3%) ↓	14.09 (10%) ↓	13.76 (12%) ↓	
MLA (mm^2)	6.95	6.17 (11%) ↓	6.56 (5.6%) ↓	8.09 (16%) ↑	
Plaque area (mm^2)	8.78	9.17 (4%) ↑	7.54 (14%) ↓↓	7.07 (19%) ↓↓	

Hypothesis,

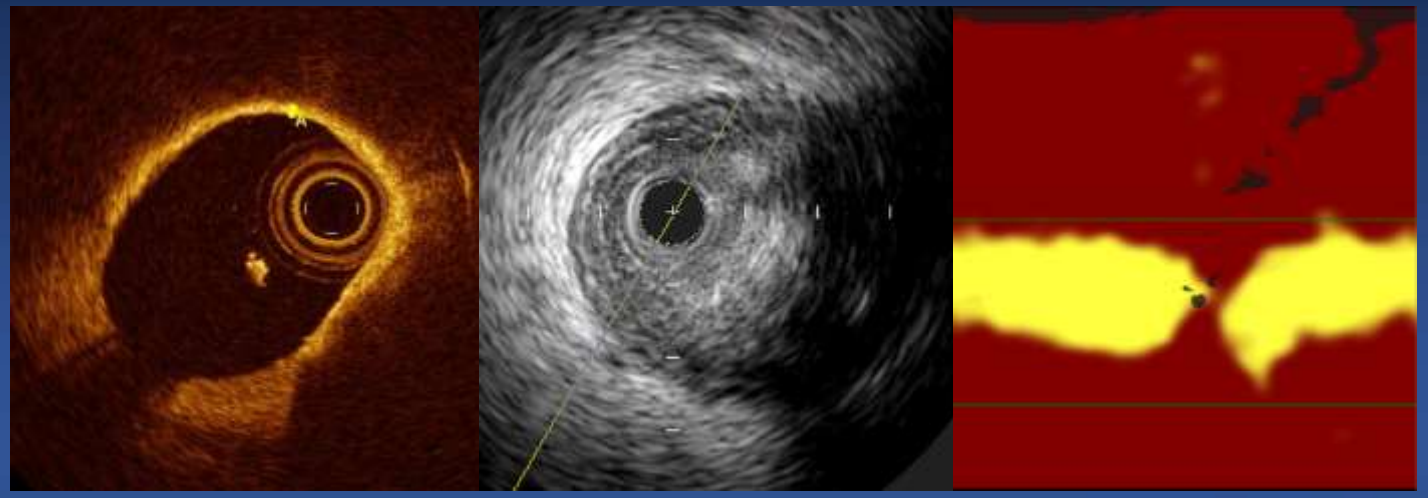
BVS Implantation Can Stabilize Plaque Vulnerability and Induce Plaque Regression, Which May Prevent Future Events of Deferred Lesions.

PREVENT Study,

The ***PREVENT***ive Implantation of BVS on Stenosis With Functionally Insignificant Vulnerable Plaque.

Searching for Vulnerable Plaque,
Functionally Insignificant (FFR >0.80)

1. TCFA
2. PB_{MLA} ≥70%
3. MLA ≤4.0 mm^2
4. LRP on NIRS ($_{max}LCBI_{4mm}$>500)



The ***PREVENT***ive Implantation of Bioresorbable Vascular Scaffold on Stenosis With Functionally Insignificant Vulnerable Plaque

PREVENT Trial

Any Epicardial Coronary Stenosis

with *FFR ≥0.80* and with *Two* of the following

1. IVUS MLA ≤4.0mm^2
2. IVUS Plaque Burden >70%
3. Lipid-Rich Plaque on NIRS ($_{max}$LCBI$_{4mm}$>500)

R

BVS+OMT	OMT
N=1000	N=1000

Primary endpoint *at 2 years*:
CV death, MI, Hospitalization d/t unstable angina

OCT sub-study/ NIRS sub-study, (300 patients in each arm at 2 years)

Objective,

To determine whether BVS implantation on functionally insignificant vulnerable plaque, reduce the incidence of the composite of MACEs compared with optimal medical therapy alone.

A prospective, randomized, multicenter, clinical trial with ‘all comers’ design. Approximately 2,000 patients will be enrolled from international heart centers.

Inclusion Criteria

Age 18 years or older,
Symptomatic or asymptomatic coronary stenosis,
Eligible for PCI, with
FFR >0.80 and met the two of the following

1. IVUS MLA<4mm2
2. IVUS plaque burden>70%
3. Lipid-rich plaque on NIRS ($_{max}LCBI_{4mm}$>500)

Exclusion Criteria

Preferred treatment for CABG, STEMI, Bypass graft lesion, Contraindication to dual antiplatelet therapy Life expectancy <2y, Planned cardiac surgery or planned major non cardiac surgery, Woman who are breastfeeding, pregnant or planning to become pregnant during the course of the study.

Primary and Major Secondary End Point,

The primary endpoint is the 2-year MACE (cardiovascular death, nonfatal MI, unplanned rehospitalization due to unstable angina).

The secondary endpoints include overall MACE, non-urgent revascularization, and rate of cerebrovascular event.

PREVENT Trial,

Will Be Started May, 2015

Principal Investigators
Seung-Jung Park, MD, PhD.
Korea

Co-Principal Investigator
Gregg Stone, MD, PhD.
USA

Active Participants
Major 10 centers more in Korea
Dr. Takashi Akasaka, Japan
3-4 centers more in Japan
Dr. Kao in Taiwan China

Ron Waksman, MD. USA
Alan Young, MD.USA
David Cohen, MD. USA
Antonio Colombo, MD. Italy