Do You Want to Treat? Functionally Insignificant Vulnerable Plaque

Yes, I DO!

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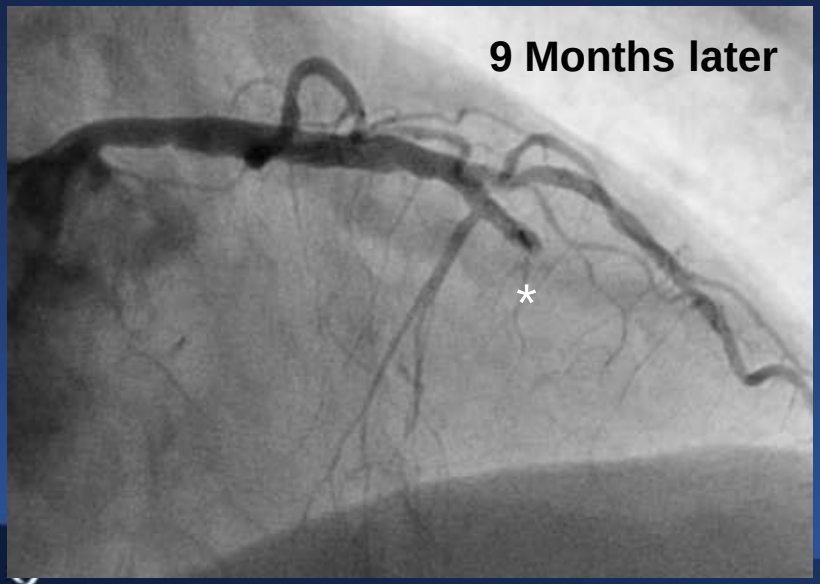
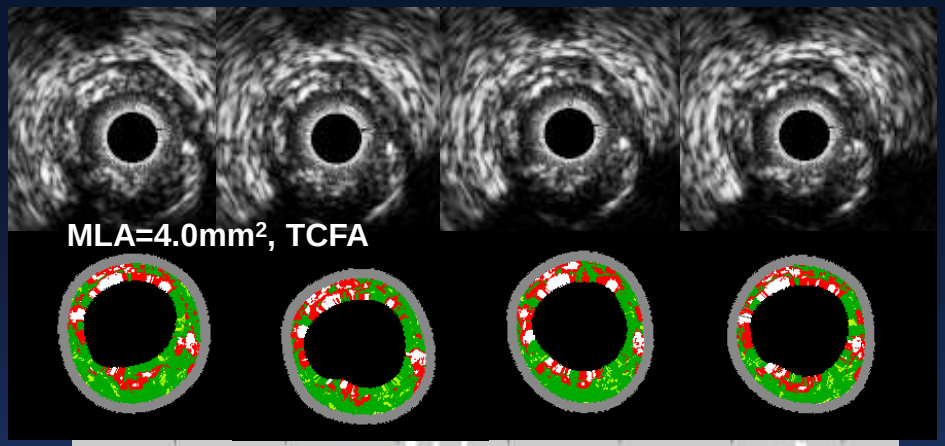
Disclosure Statement of Financial Interest

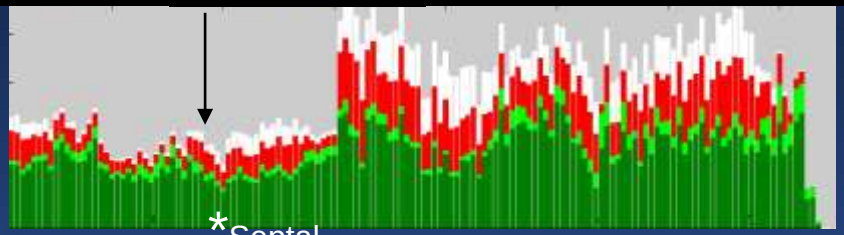
Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Boston Scientific Corporation
• Consulting Fees/Honoraria	• Boston Scientific Corporation, ACIST
• Speaker Fee	• Volcano Corporation, St Jude Medical

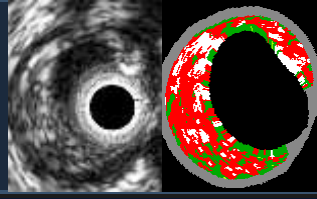
A PROSPECT Case







The PROSPECT Trial



700 pts with ACS

UA (with ECGΔ) or NSTEMI or STEMI >24º
undergoing PCI of 1 or 2 major coronary arteries
at up to 40 sites in the U.S. and Europe

Metabolic S.
- Waist circum
- Fast lipids
- Fast glu
- HgbA1C
- Fast insulin
- Creatinine

PCI of culprit lesion(s)

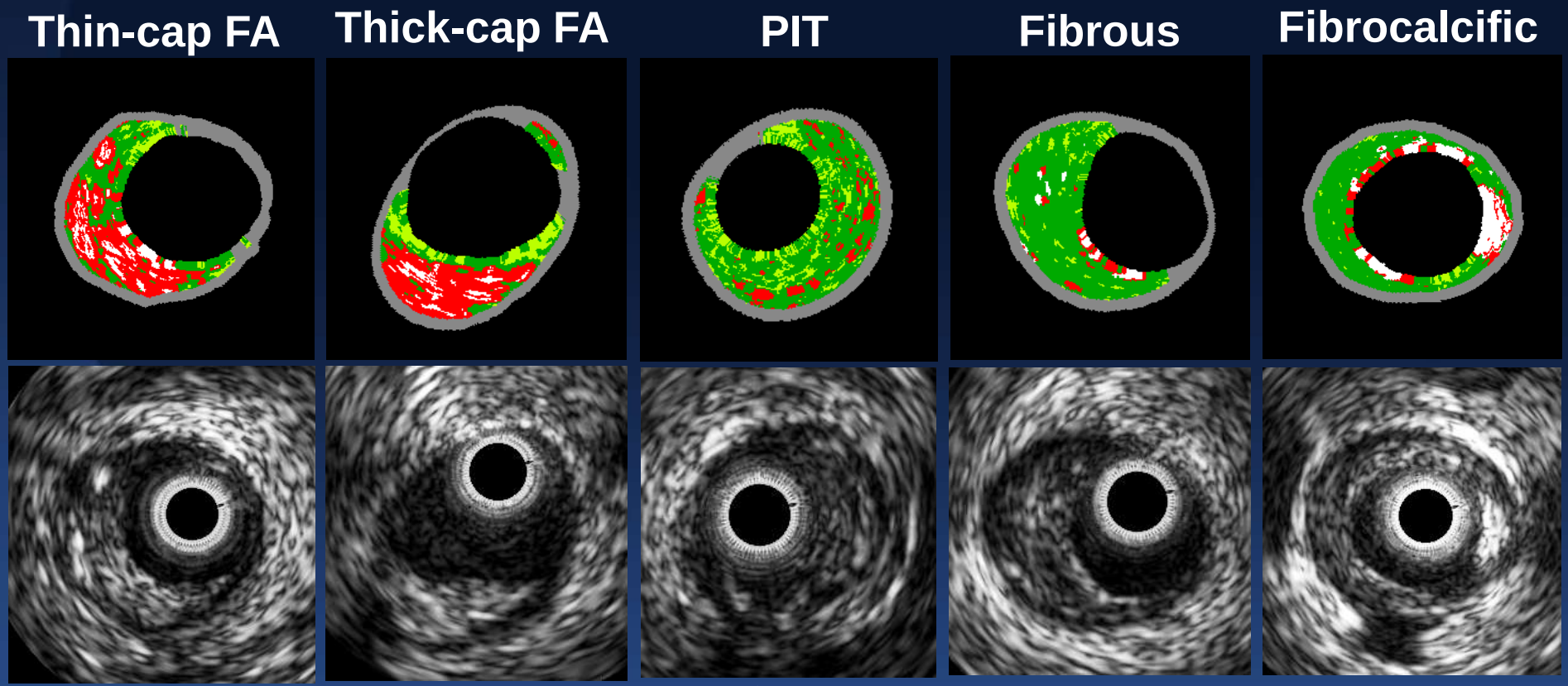
Successful and uncomplicated

Formally enrolled

Biomarkers
- ***Hs CRP***
- ***IL-6***
- ***sCD40L***
- ***MPO***
- ***TNFα***
- ***MMP9***
- ***Lp-PLA2***
- ***others***

PI: Gregg W. Stone
Sponsor: Abbott Vascular; Partner: Volcano

VH-IVUS Classification



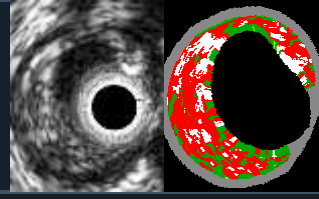
More than 10%
Confluent
Necrotic Core

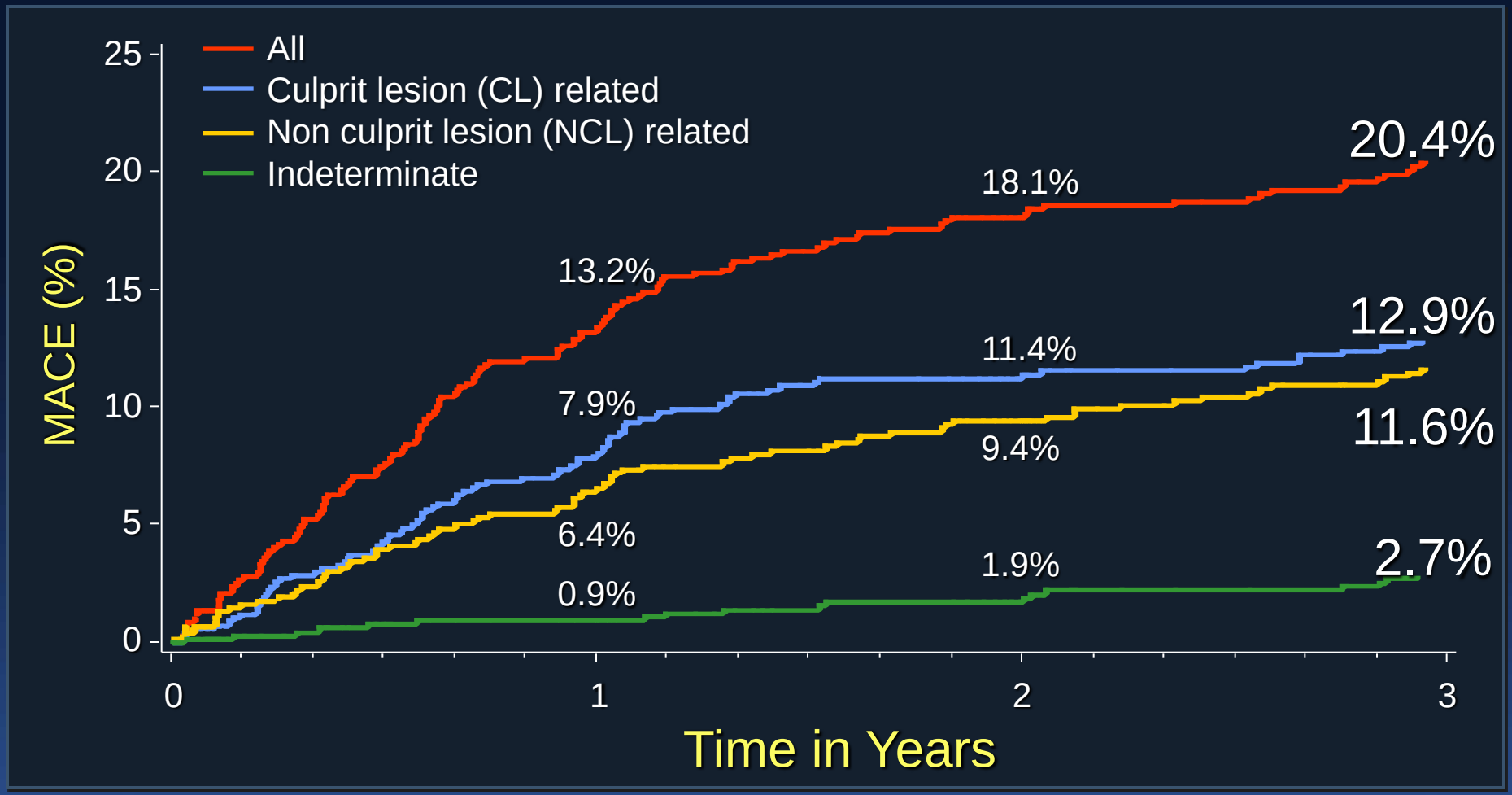
More than 15%
Fibrofatty

NO more than 10%
Confluent Necrotic
Core

More than 10%
confluent
calcium

PROSPECT: MACE





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

PROSPECT: MACE

3-year follow-up, non hierarchical

	All	Culprit lesion related	Non culprit lesion related	Indeter-minate
Cardiac death	1.9% (12)	0.2% (1)	0% (0)	1.8% (11)
Cardiac arrest	0.5% (3)	0.3% (2)	0% (0)	0.2% (1)
MI (STEMI or NSTEMI)	3.3% (21)	2.0% (13)	1.0% (6)	0.3% (2)
Unstable angina	8.0% (51)	4.5% (29)	3.3% (21)	0.5% (3)
Increasing angina	14.5% (93)	9.2% (59)	8.5% (54)	0.3% (2)
Composite MACE	20.4% (132)	12.9% (83)	11.6% (74)	2.7% (17)
Cardiac death, arrest or MI	4.9% (31)	2.2% (14)	1.0% (6)	1.9% (12)

Rates are 3-yr Kaplan-Meier estimates (n of events)

PROSPECT: Multivariable Correlates of Non Culprit Lesion Related Events

Independent predictors of lesion level events by Cox Proportional Hazards regression

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

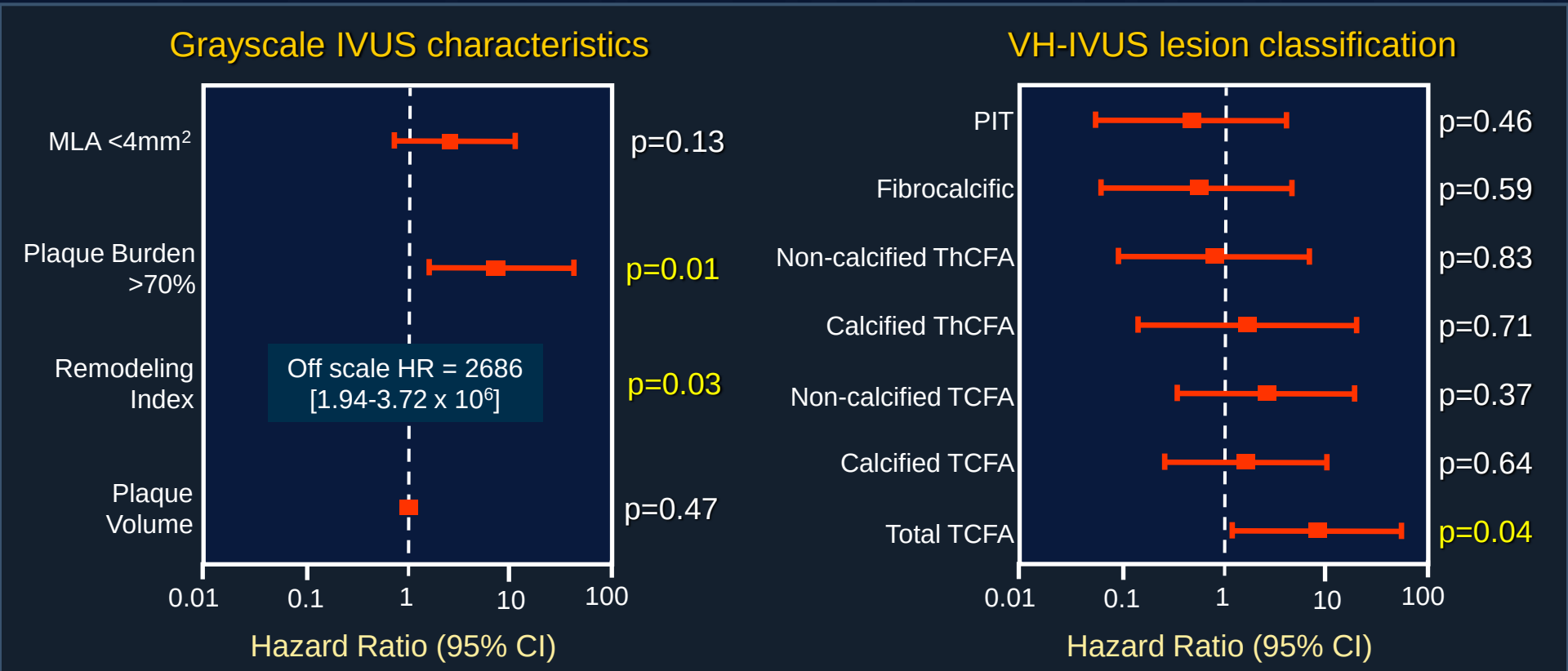
Variables entered into the model: minimal luminal area (MLA) ≤4.0 mm^2; plaque burden at the MLA (PB_{MLA}) ≥70%; external elastic membrane at the MLA (EEM_{MLA}) <median (14.1 mm^2); lesion length ≥median (11.2 mm); distance from ostium to MLA ≥median (30.4 mm); remodeling index ≥median (0.94); VH-TCFA.

VIVA Study (VH-IVUS in Vulnerable Atherosclerosis)

167 pts with stable CAD or ACS underwent 3-vessel VH-IVUS imaging; 1,096 plaques were classified; median follow-up 625 days

18 MACE (death [2], MI [2] or revasc [14]) occurred in 16 pts from 19 lesions (13 nonculprit lesions and 6 culprit lesions)

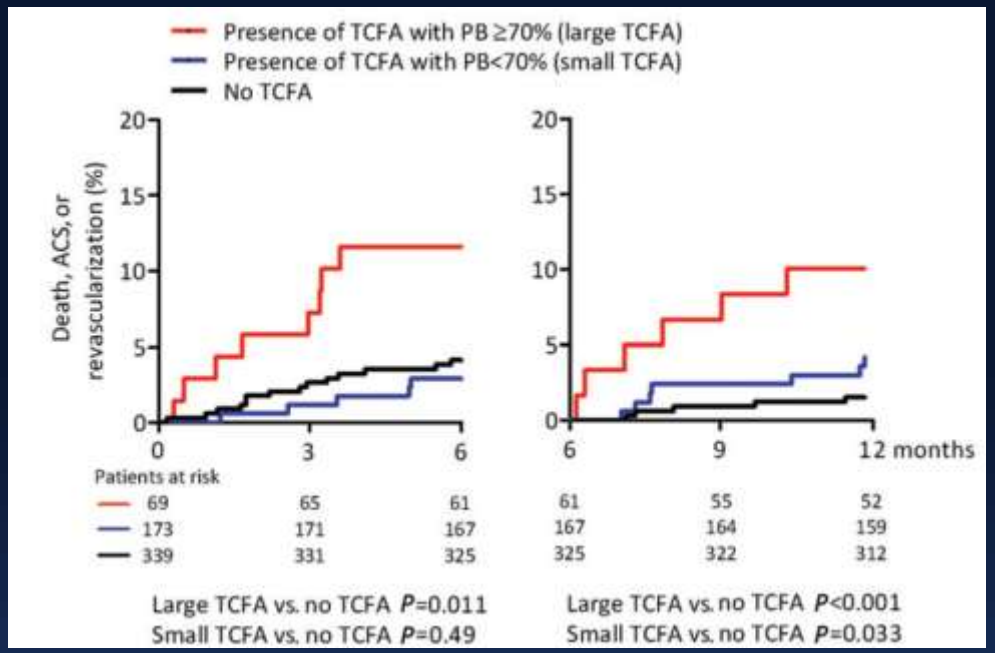
Univariate predictors of non-culprit MACE

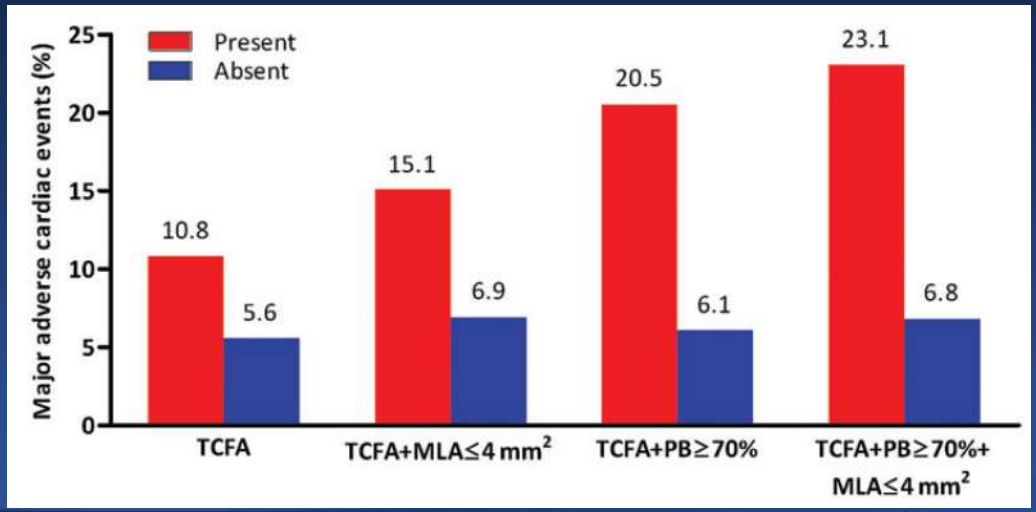


Calvert PA et al. JACC Img 2011;4:894–901

ATHEROREMO-IVUS Study

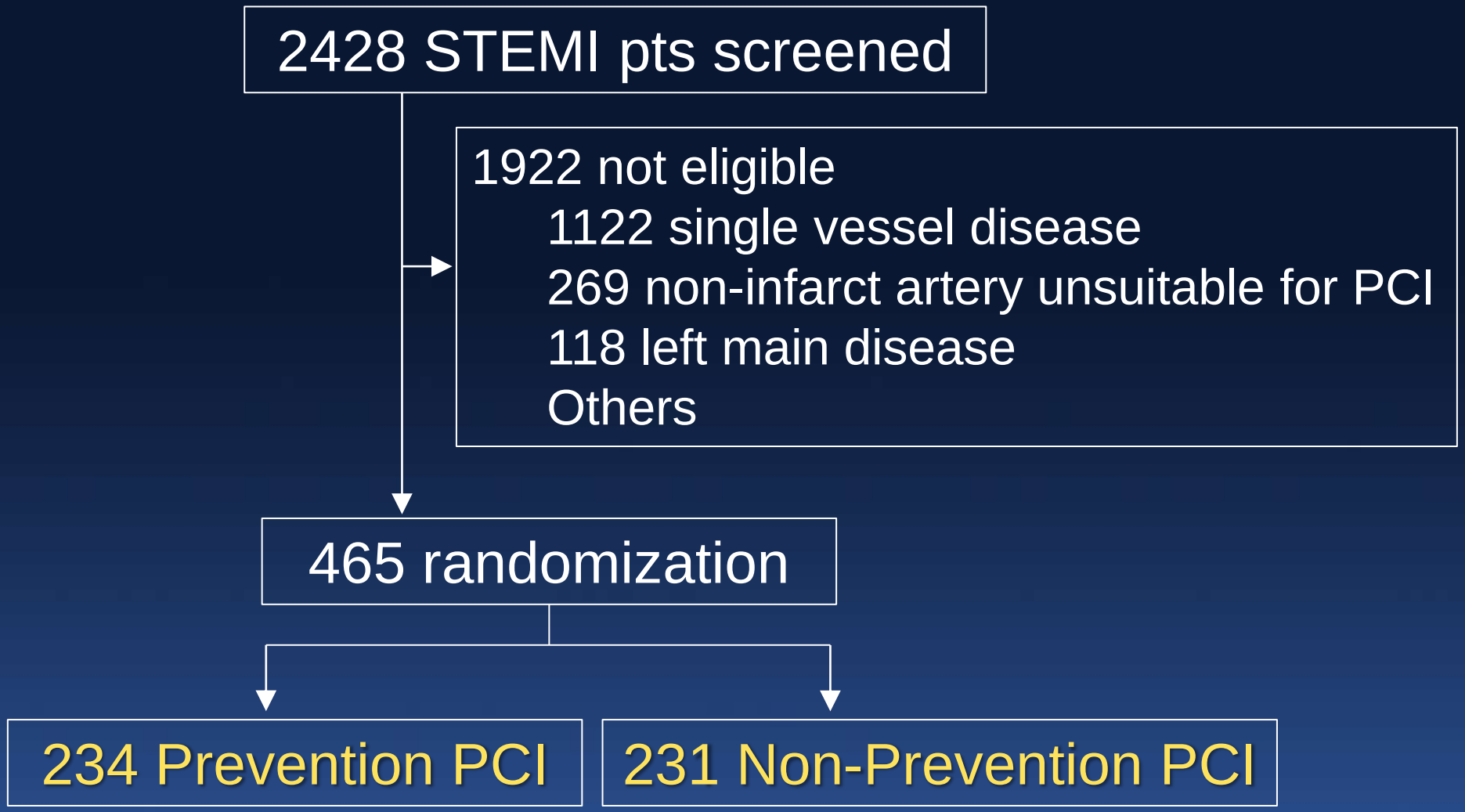
- 581 patients in 2008-2011
- 1 year follow-up
- MACE (non-culprit related ACS, unplanned coronary revascularization or indeterminate mortality)
- Single center, prospective





Cheng JM et al. Eur Heart J 2013, doi:10.1093/eurheartj/eht484

PRAMI - Enrollment -



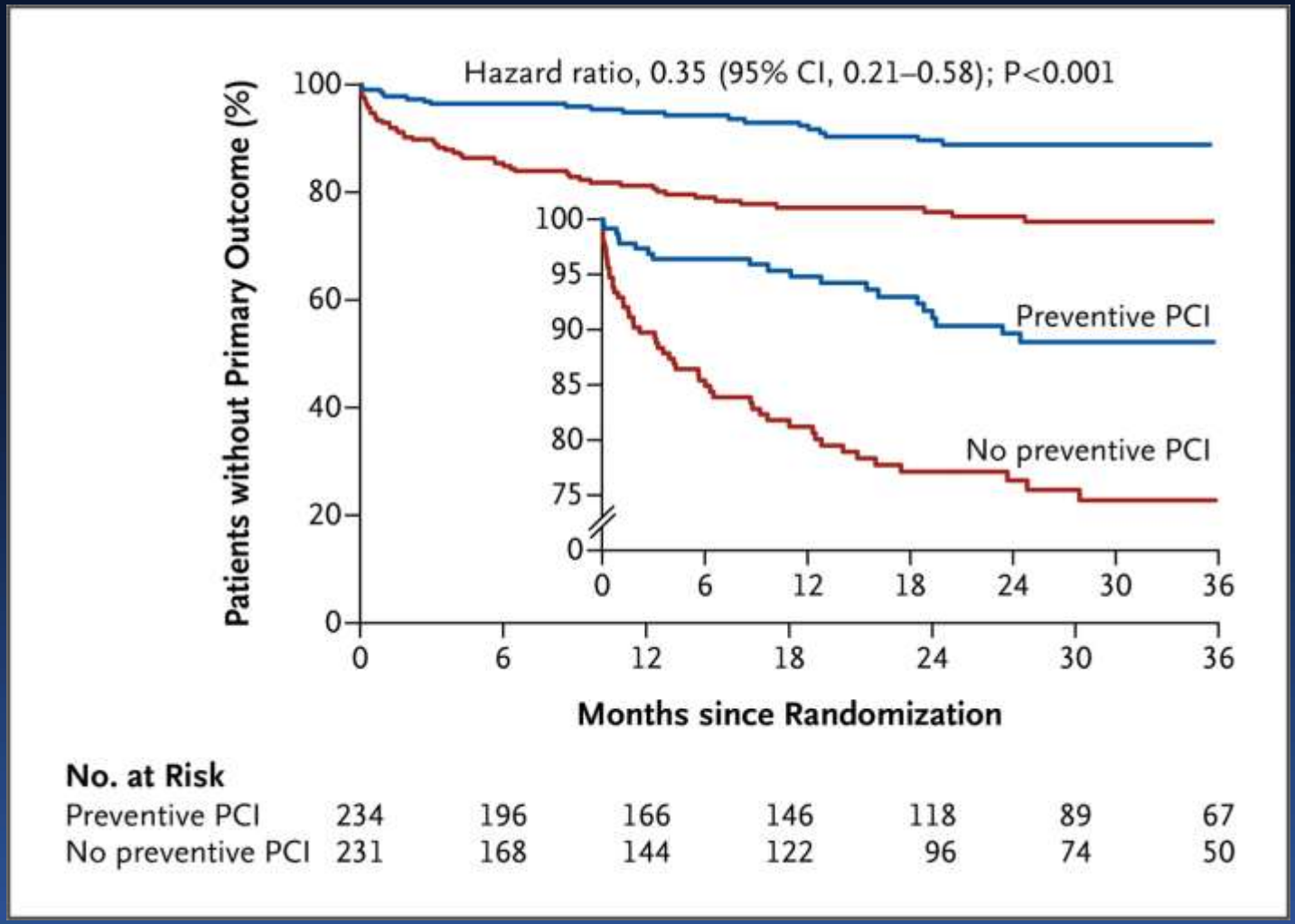
Wald DS et al. N Engl J Med 2013;369:1115-1123.

PRAMI - PCI Procedure -

	Prevention PCI (n=234)	No Prevention PCI (n=231)
Infarct artery		
# of Stent per artery	1.56±0.75	1.42±0.70
Total stent length (mm)	21.8±6.7	21.3±5.6
Non-infarct artery		
# of arteries treated per pt	1.36±0.77	NA
Total stent length (mm)	19.4±5.8	NA

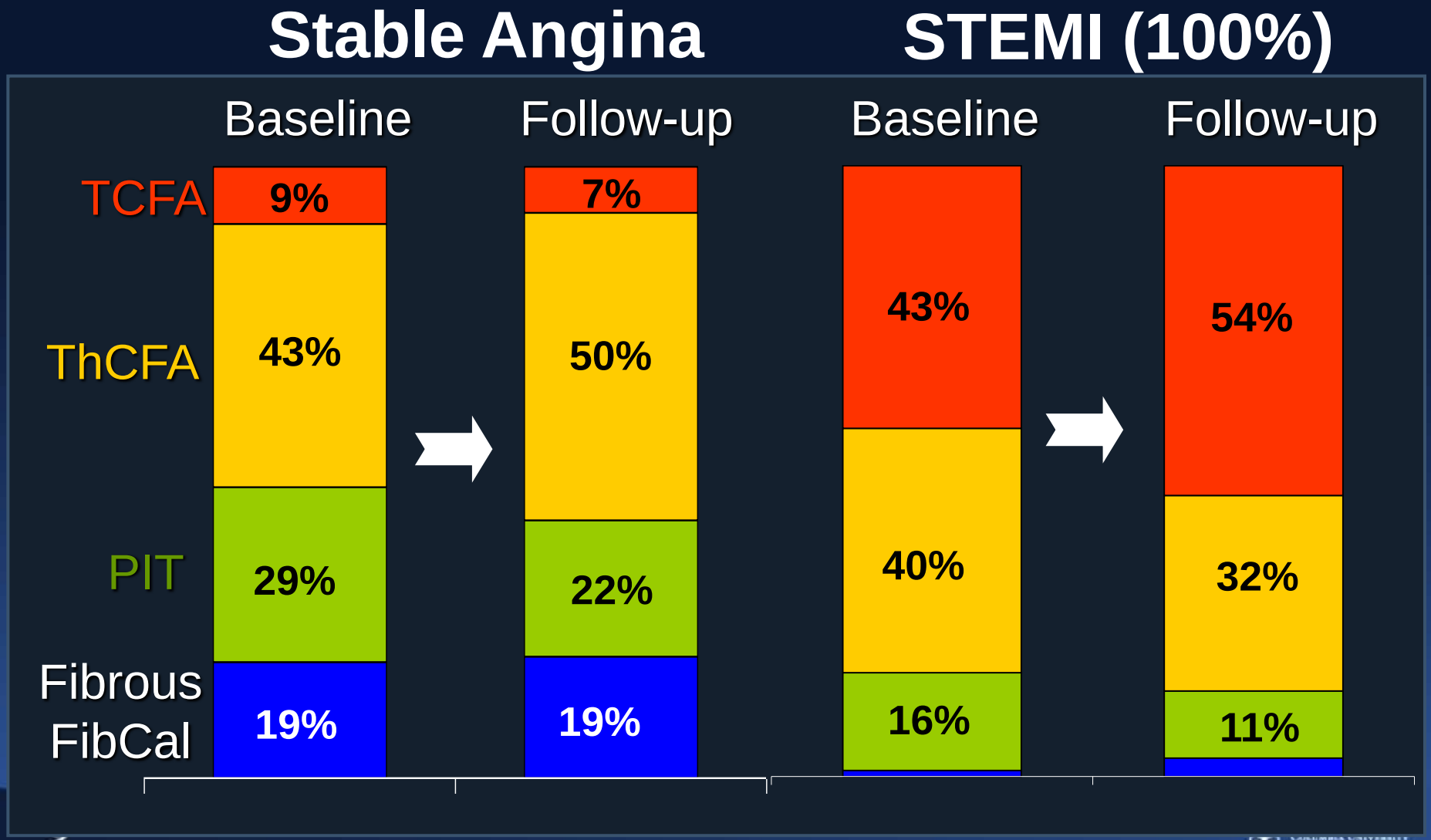
Wald DS et al. N Engl J Med 2013;369:1115-1123.

Kaplan–Meier Curves for the Primary Outcome (Cardiac Death, MI, Refractory Angina)



Wald DS et al. N Engl J Med 2013;369:1115-1123.

Differences in Temporal Changes of Non-Culprit Lesions



OCT Predictor for Progression

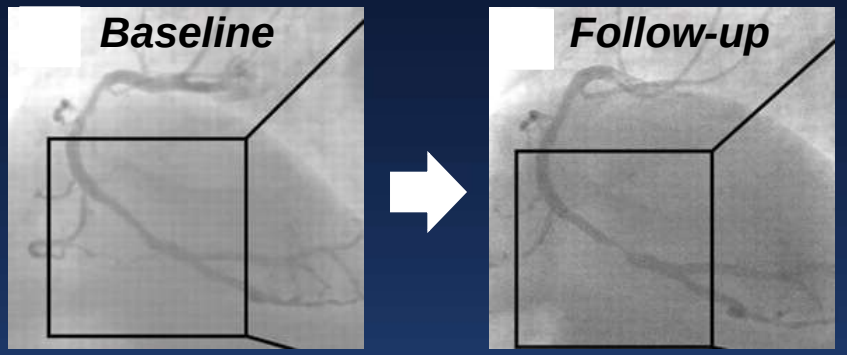
- **DESIGN:** Prospective, Single Center, Observational Study
- **OBJECTIVE:** To evaluate OCT predictor for disease progression in non-culprit lesions
- **METHODS:**

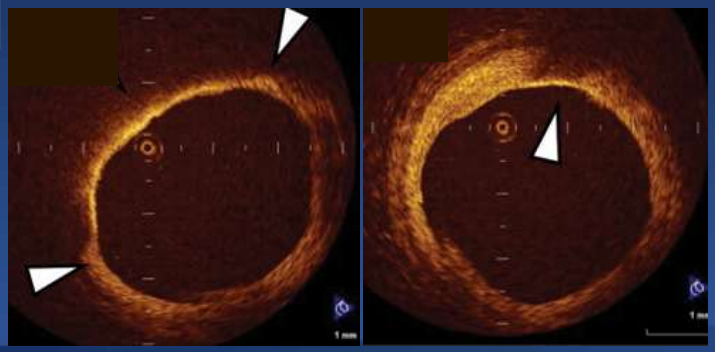
1. 3 vessel OCT after successful PCI of culprit lesions
2. 6-9 month follow-up
3. Progression: Late loss>0.4mm

69 Non-culprit lesion in 69 vessels in 53 pts

- 3 ACS events in 3pts
- 10 progression without event in 10 pts

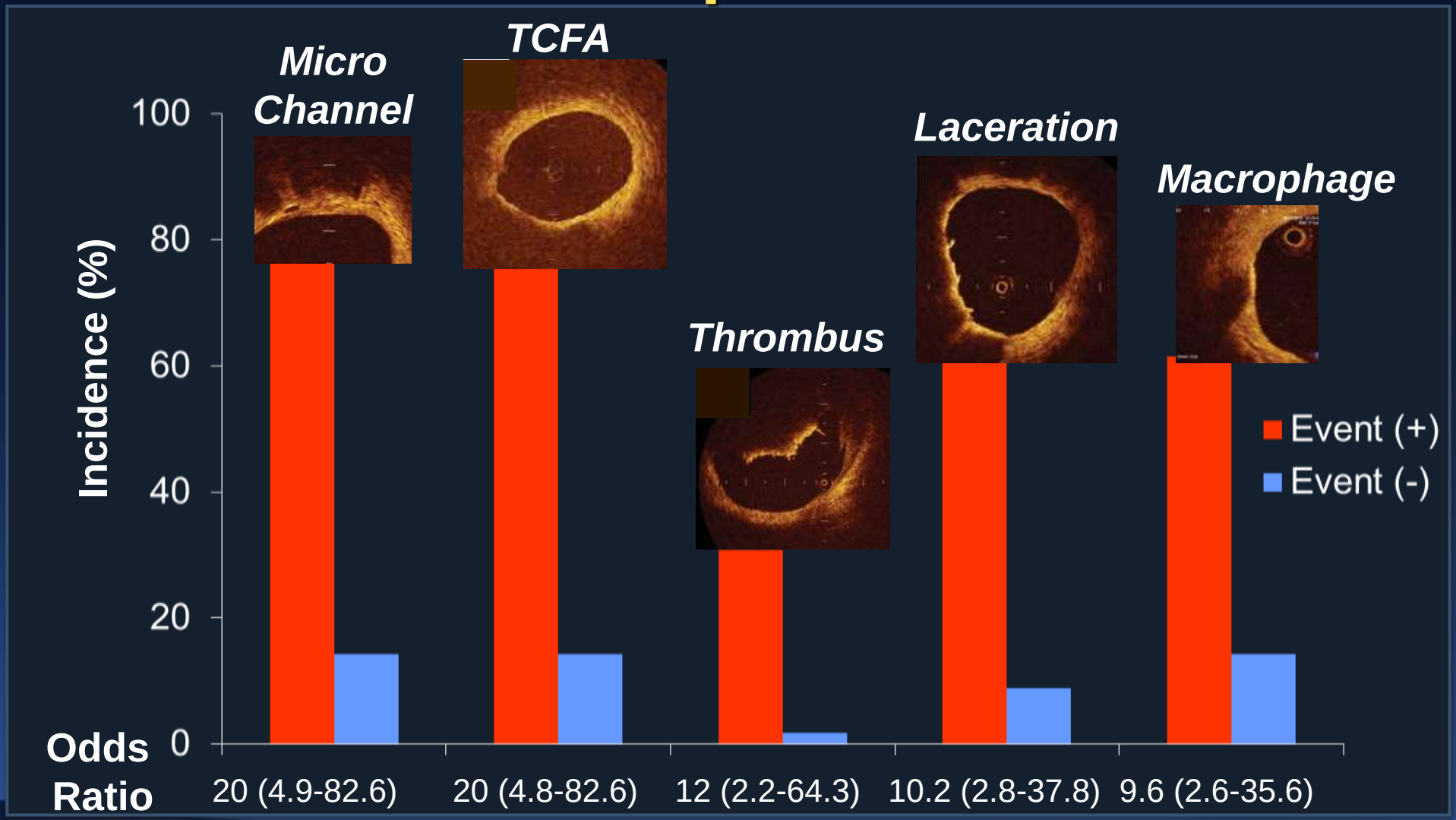
- 56 non-culprit lesion in 40 pts





Uemura et al, *Eur Heart J* 2011 doi:1093/eurheart/ehr284

OCT Predictors for Progression of Non-Culprit Lesions

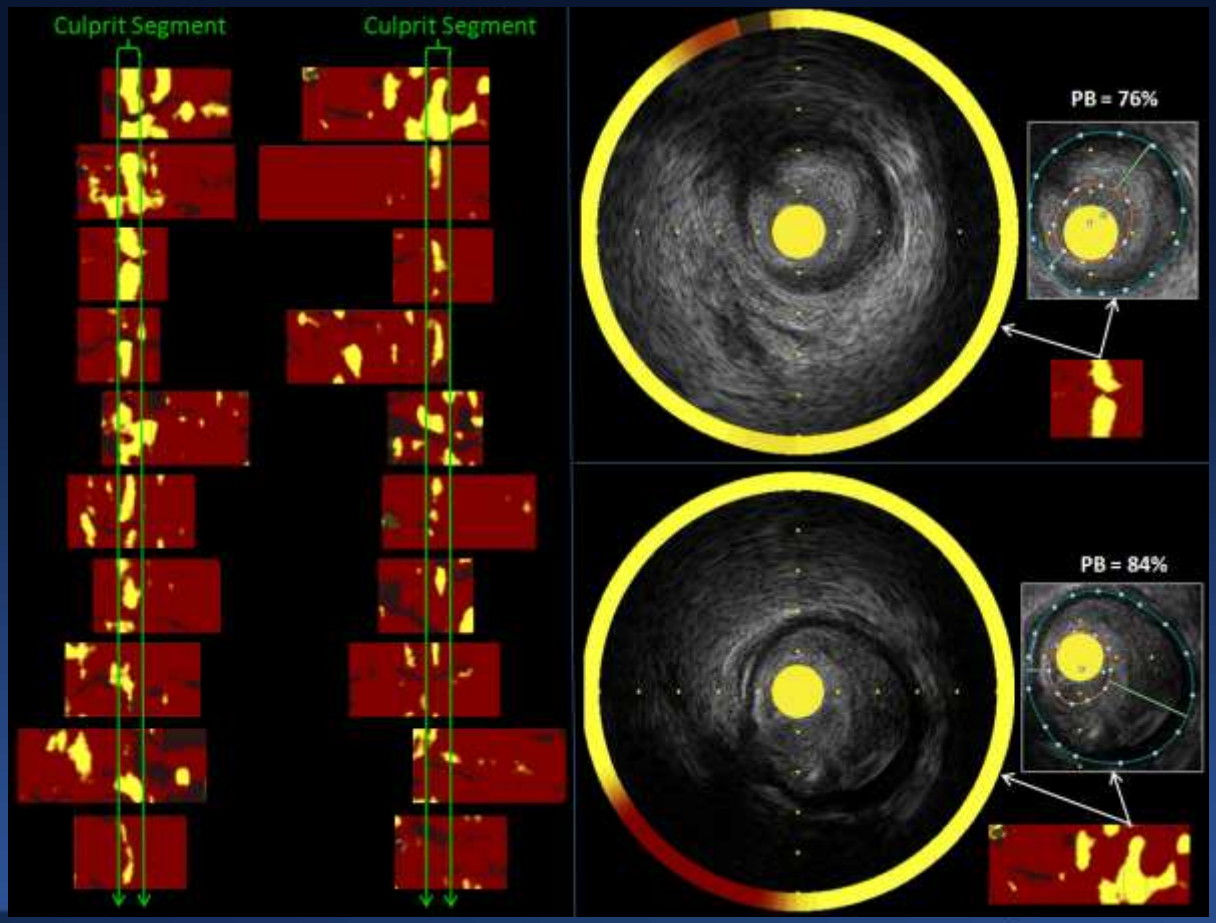


Uemura et al, *Eur Heart J* 2011 doi:1093/eurheart/ehr284

Is there a characteristic signal of lesions that cause STEMI?

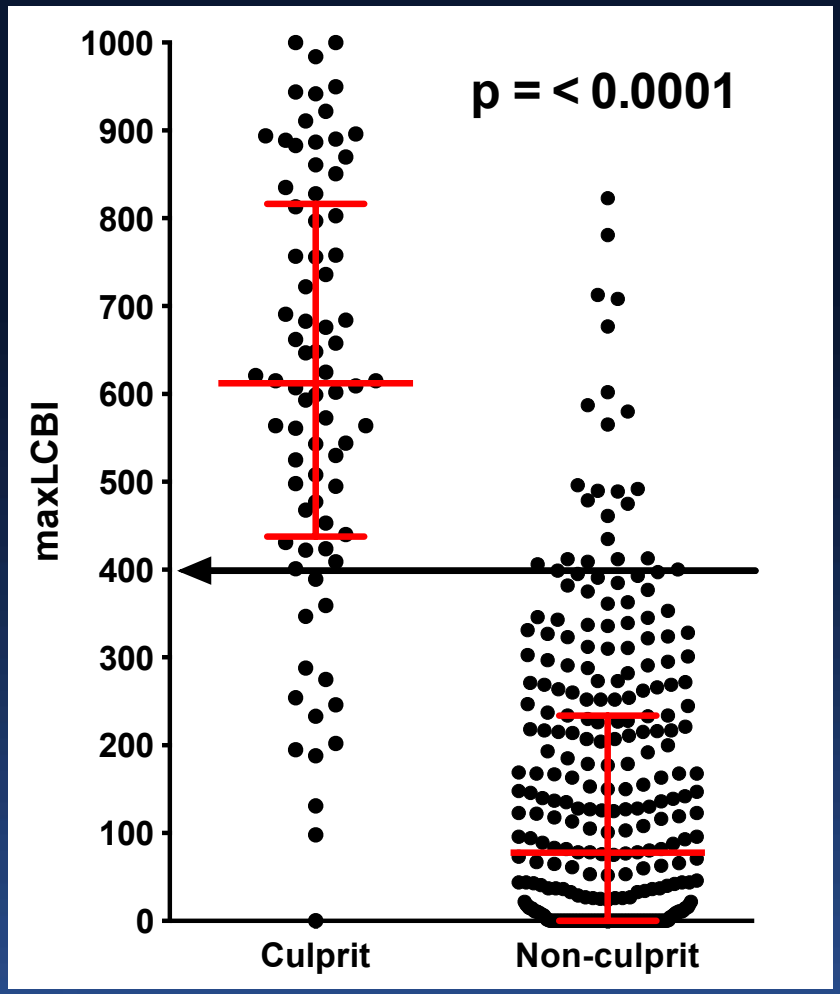
Near infrared spectroscopy (InfraReDx) was performed immediately after infarct artery recanalization in 20 pts with STEMI

The NIRS chemograms of all 20 STEMI pts. The culprit segments contain LCP in 19 cases (95%), all with large plaque burden.



Madder RD. JACC Interv 2013

STEMI culprit vs. non-culprit segments



Mann-Whitney U test
Median ± interquartile range

STEMI culprit lesions:
$maxLCBI_{4mm}$ = 612 (438-817)

Non-culprit lesions:
$maxLCBI_{4mm}$ = 78 (0-234)

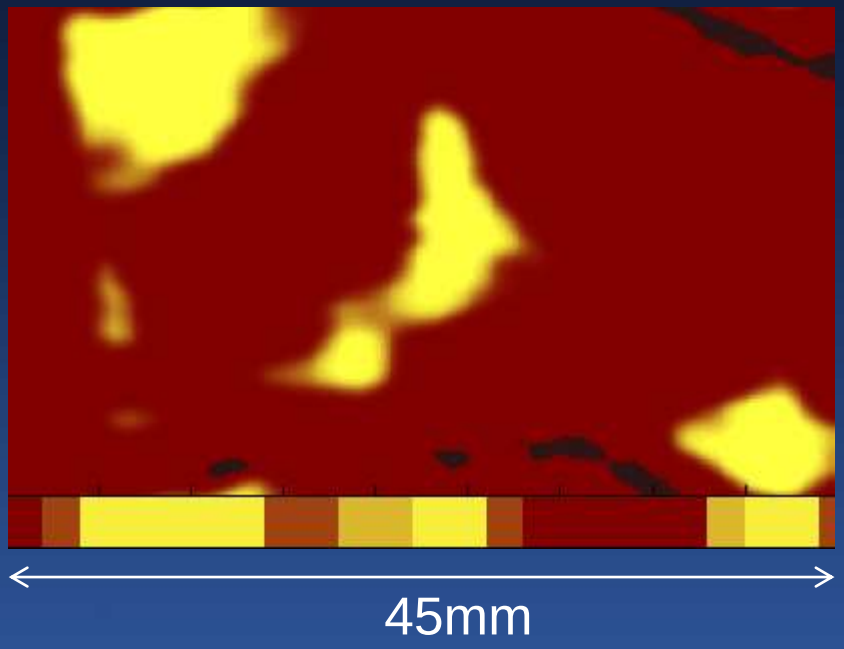
$MaxLCBI_{4mm}$ >400 was present at the STEMI culprit site in 63 of the 78 cases

$MaxLCBI_{4mm}$ >400 was present at the non-culprit site in 22 of the 304 segments

Relationship between Lipid Rich Plaque detected by NIRS and Outcomes

- Prospective Single Center Study, 206 patients (ACS47%)
- Primary Endpoint: Composite of all-cause mortality, non-fatal ACS, stroke and unplanned PCI during one-year FU
- >40mm non culprit segment of NIRS

Lipid Core Burden Index (LCBI)=188

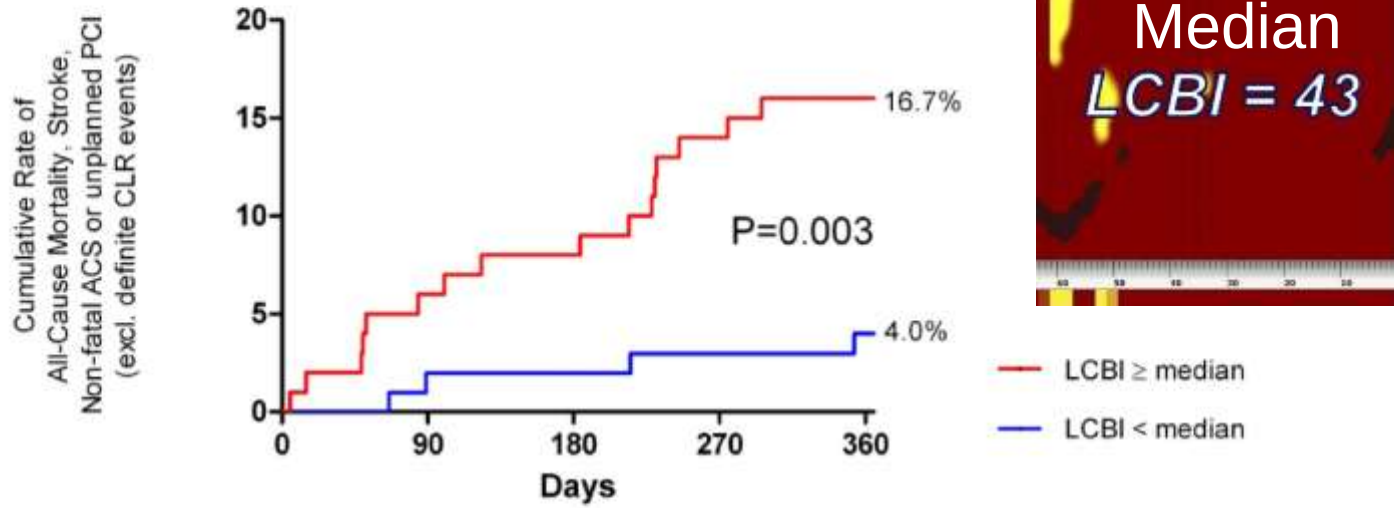


Oemrawsingh RM et al, *ESC2003*

Relationship between Lipidic Plaque detected by NIRS and Outcomes

Primary endpoint

Erasmus MC

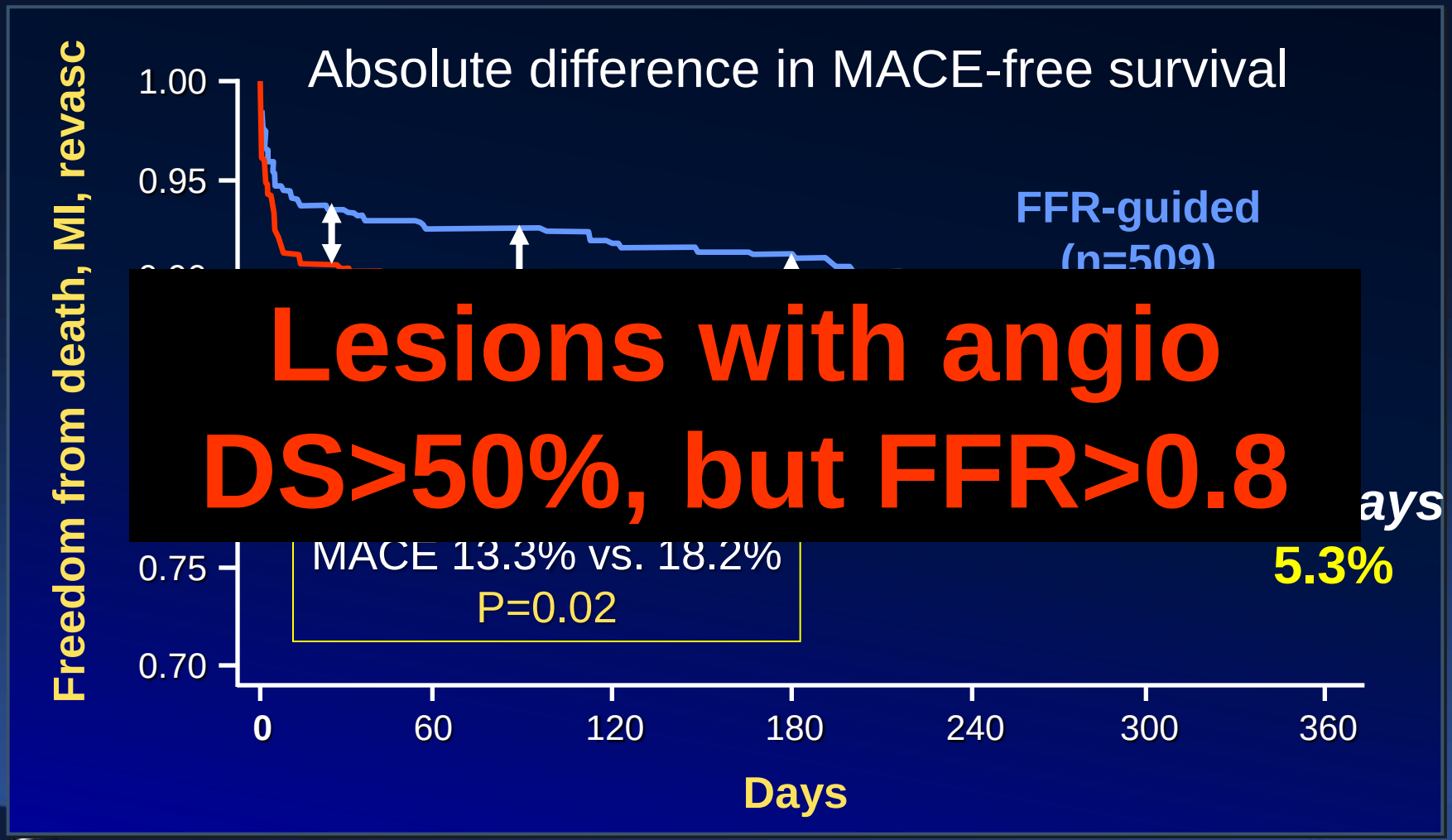


Adjusted HR: **4.04** 95% CI: 1.3-12.3 P=0.01

Oemrawsingh RM et al, *ESC2003*

FAME: Primary Endpoint

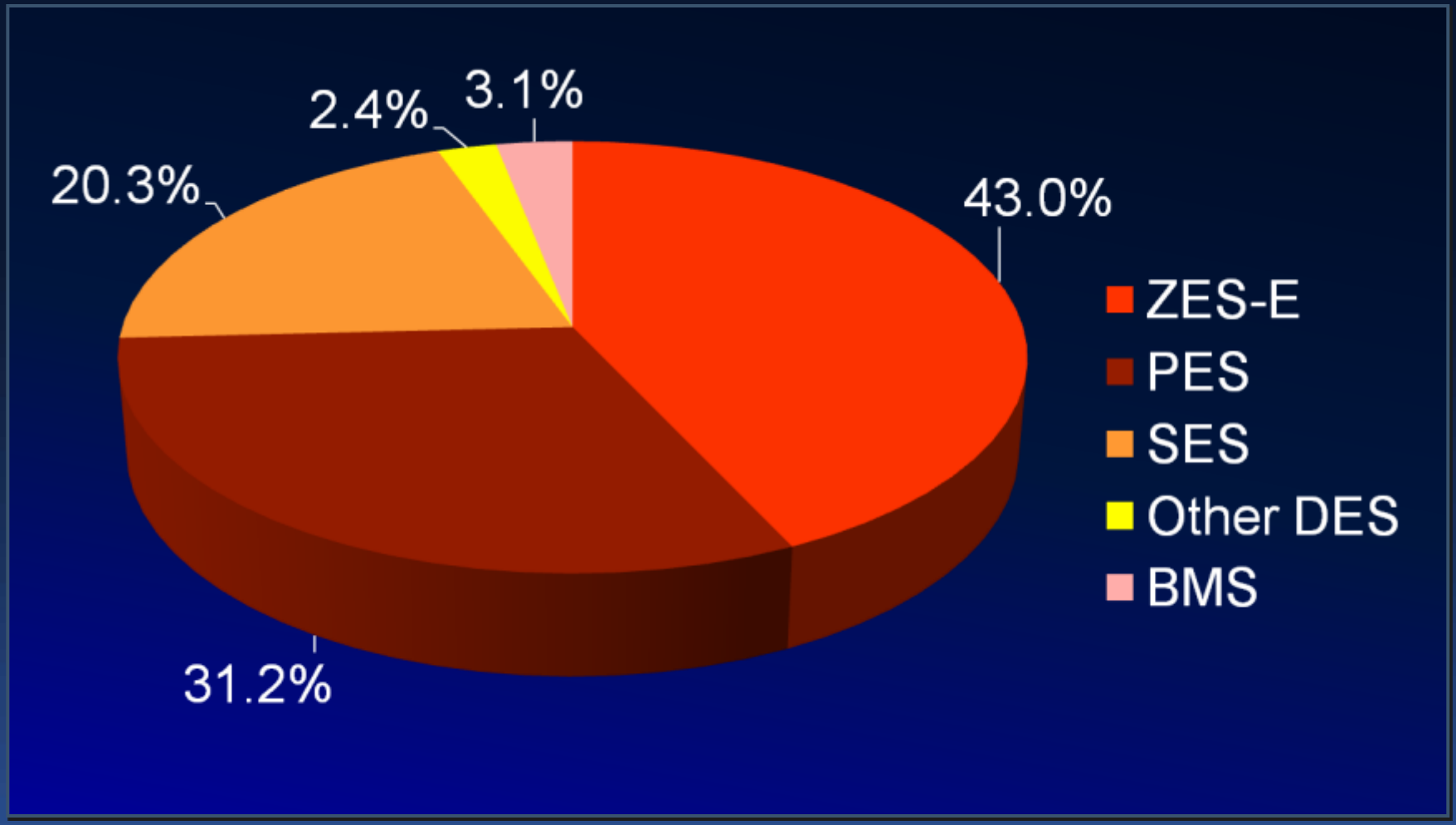
1005 pts with MVD (83% CSA) undergoing PCI with DES were randomized to FFR-guided vs. angio-guided intervention



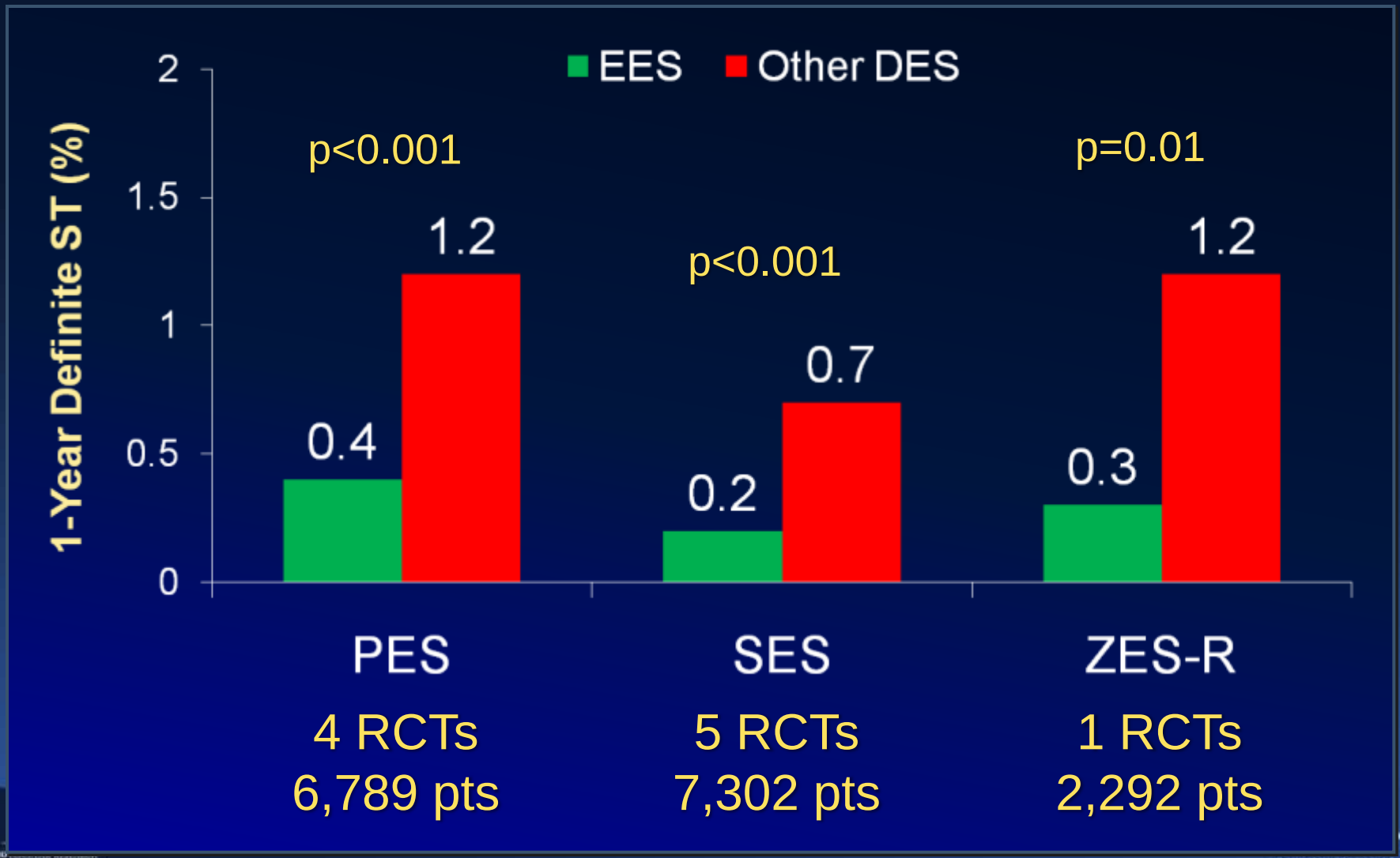
Lesions with angio DS>50%, but FFR>0.8

Tonino PAL et al. NEJM 2009;360:213–24

FAME Trial: Stent Use

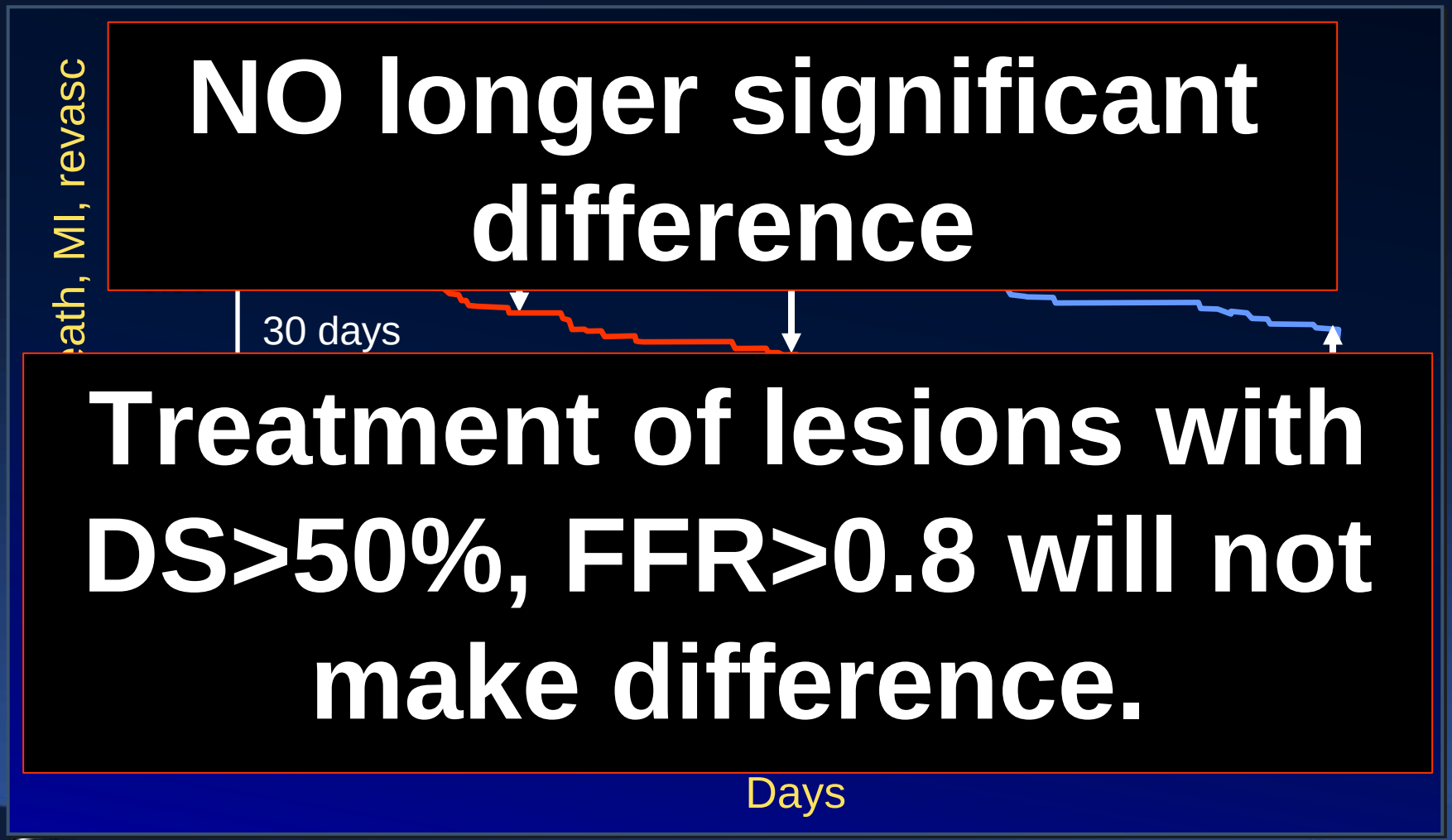


RCTs of EES vs. Other DES (n-16,383): 1-year definite stent thrombosis



FAME: With better stents????

1005 pts with MVD (83% CSA) undergoing PCI with DES were randomized to FFR-guided vs. angio-guided intervention



NO longer significant difference

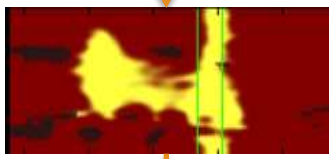
Treatment of lesions with DS>50%, FFR>0.8 will not make difference.

PI: Dr.Ron Waksman

"To evaluate the relationship between non-obstructive lipid-rich plaque and a new coronary events"

Index
N=9000

Suspected Index Culprit Lesion **-or-** Index Culprit Lesion



BLINDED

Index Non Culprit Artery (IVUS is un-blinded)

Send to Core Lab

Core Lab will Un-blind NIRS data

BLINDED

N= 3000
Large LRP
(MaxLCBI4mm ≥ 250)

2yr Follow-Up

BLINDED

N= 6000
Small/No LRP
(MaxLCBI4mm < 250)

N= 3000

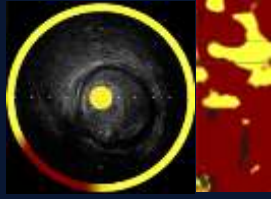
2yr Follow-Up

N= 3000

Terminate upon Discharge

LRP CLINICAL STUDY

PROSPECT II Study



900 pts with ACS at up to 20 hospitals in Sweden, Denmark and Norway (SCAAR)

NSTEMI or STEMI >12º

IVUS + NIRS (blinded) performed in culprit vessel(s)

Successful PCI of all intended lesions (by angio ±FFR/iFR)

↓

Formally enrolled

↓

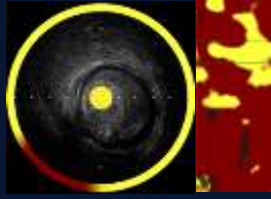
3-vessel imaging post PCI

Culprit artery, followed by non-culprit arteries

Angiography (QCA of entire coronary tree)

IVUS + NIRS (blinded) (prox 6-8 cm of each coronary artery)

↓



PROSPECT II Study
PROSPECT ABSORB RCT

900 pts with ACS after successful PCI

3 vessel IVUS + NIRS (blinded)

≥1 IVUS lesion with ≥70% plaque burden present?

Yes
(N=300)

No
(n=600)

R
1:1

ABSORB BVS + GDMT (N~150)

GDMT
(N=150)

Routine angio/3V IVUS-NIRS FU at 2 years

Clinical FU for ≥3 years

Summary

- Does morphology predict future event?

YES!

- Does physiology predict future event?

YES!

- Should we treat vulnerable plaque in physiologically non-significant lesion?

We will get more answers in PROSPECT2 and LRP Study. But I believe that we need additional predictive parameters to make more strong under the optimal medical therapy.