The Future PROSPECT for the Role of Antiplatelet Therapy

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Conflict of interest

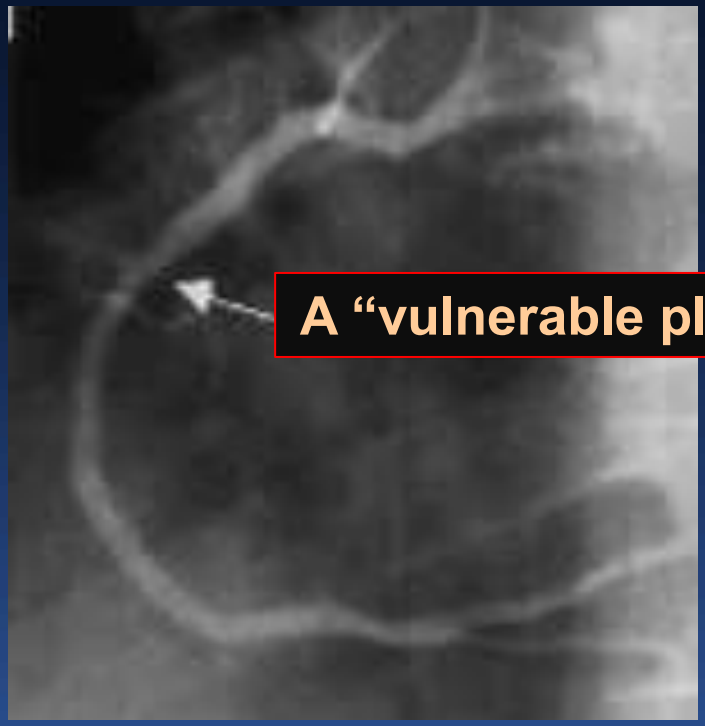
- None

Focus on Non-Culprit Lesions

NHLBI Dynamic Registry 1997 – 1999

5.8% of 3,747 pts undergoing PCI developed clinical plaque progression within 1 yr requiring unplanned PCI (62% w/ACS)

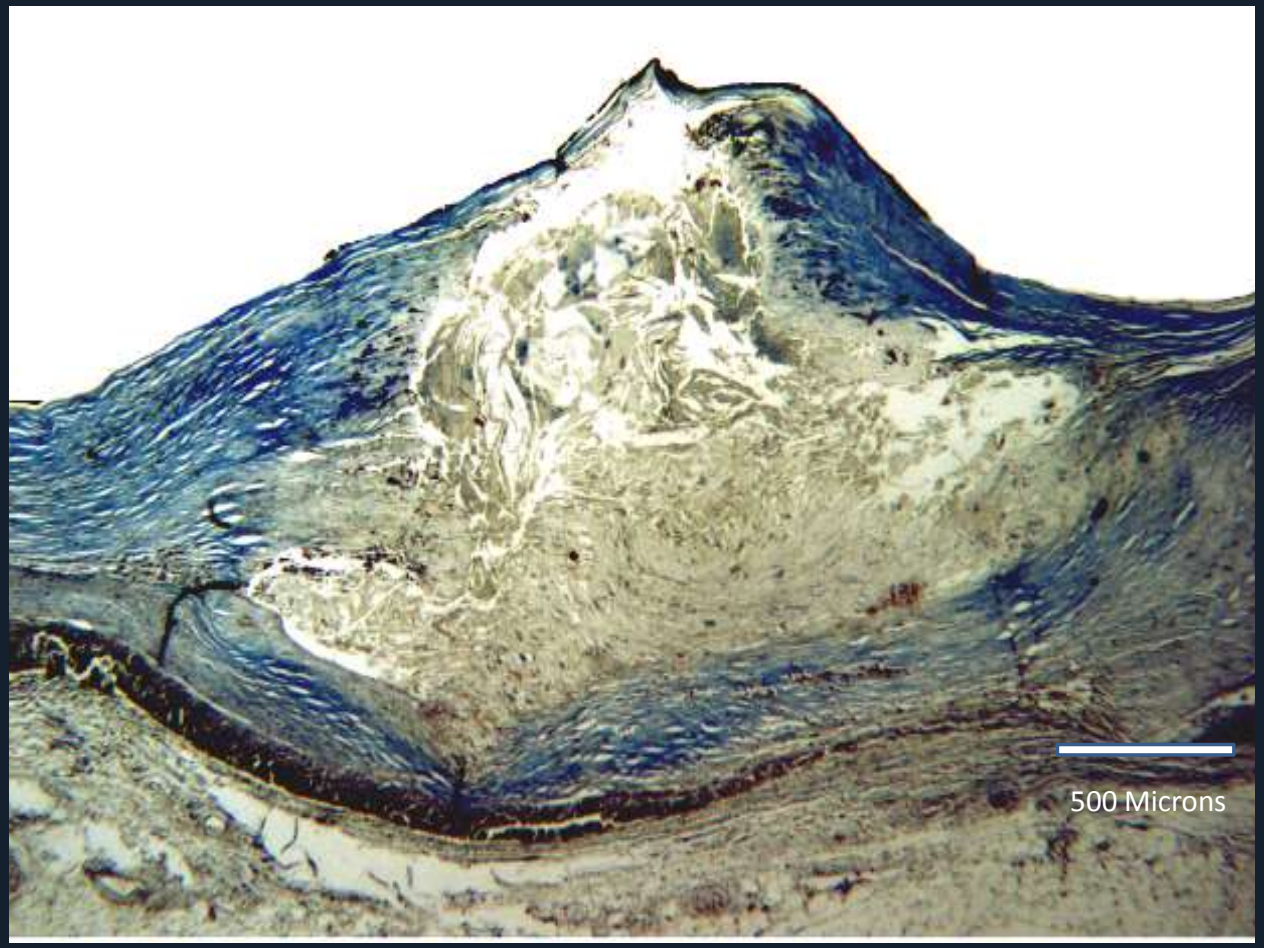
Plaque progr. from 42 ± 21% to 84 ± 14% @ mean of 5.2 mos



RCA at the time of LAD PCI **Unstable angina 133 days later**

Glaser R et al. Circ 2005;111:152-158

Thin Cap Fibroatheroma (TCFA) is the Precursor Lesion of Plaque Rupture

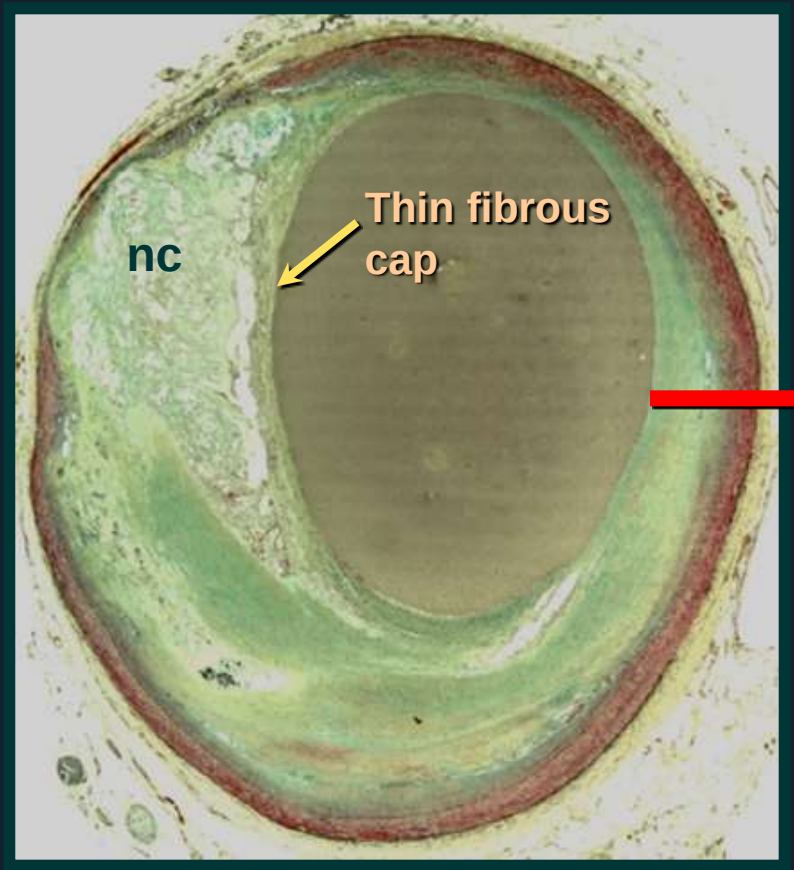


TCFA =

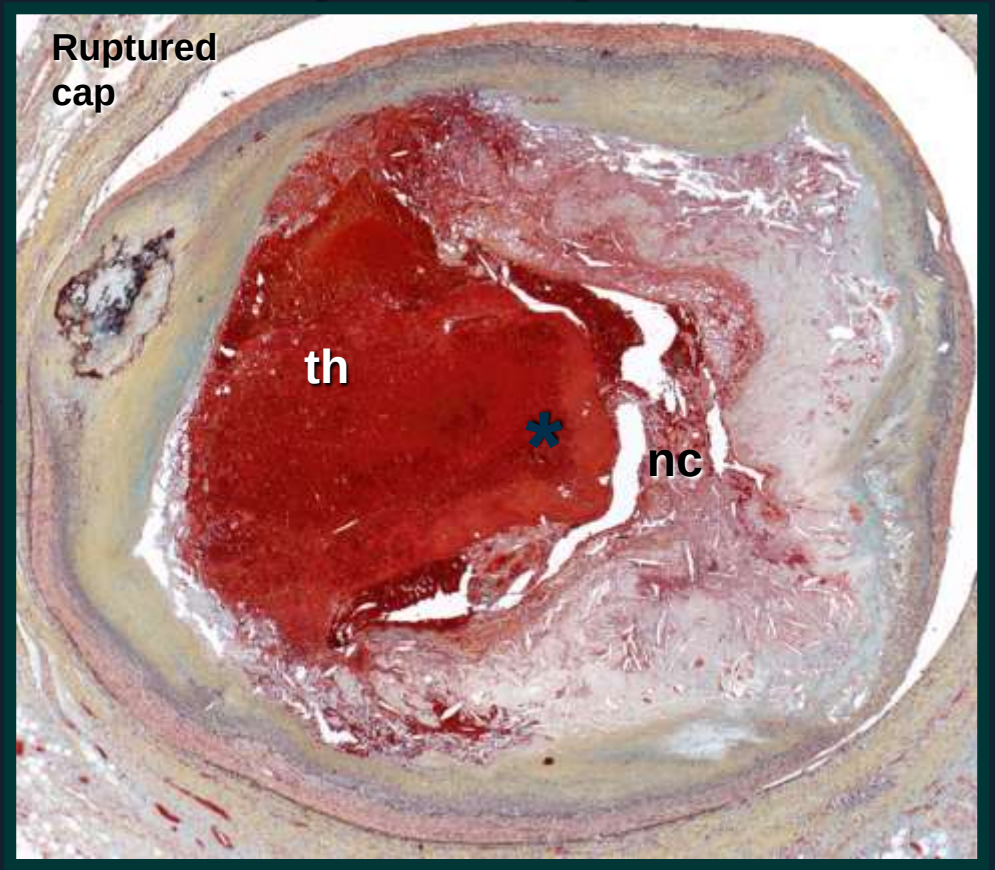
- Lipid rich necrotic core
- Thin fibrous cap (<65 um)
- Cap = type 1 coll with few SMC
- Cap infiltrated by mp and lym

Thin Cap Fibroatheroma (TCFA) is the Precursor Lesion of Plaque Rupture

TCFA



Plaque Rupture



TCFA =

- Lipid rich necrotic core
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- Cap = type 1 coll with few SMC
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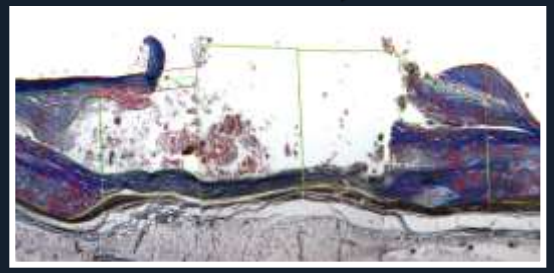
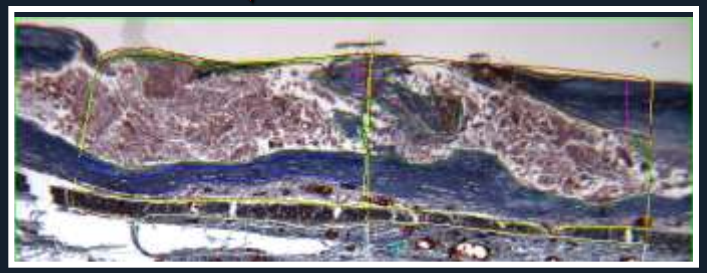
Symptomatic Vulnerable Plaque:
A Focal Manifestation of a Systemic Disease

Longitudinal sections from 50 autopsy hearts
10.9 meters examined from 148 coronary arteries



Plaque rupture



Thin cap fibroatheroma

Pathologic intimal thickening

Cheruvu P et al. JACC 2007

Longitudinal sections from 50 autopsy pts

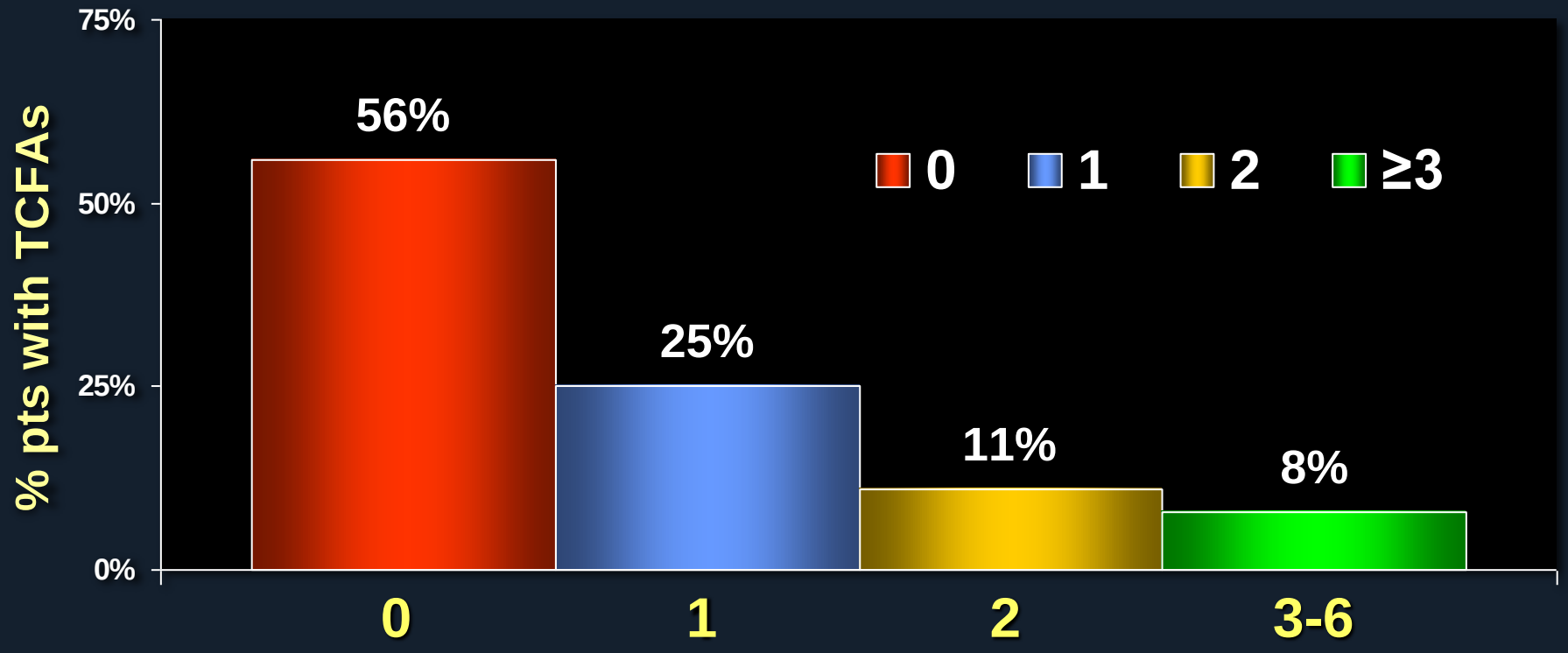
10.9 meters examined from 148 coronary arteries

44% of pts had ≥1 TCFA (range 0 - 6)

Mean 0.46 TCFAs/pt

(0.55 vs. 0.38 in pts with MI/CV death vs. other)

- 1.21/pt in hearts with ruptured plaques -

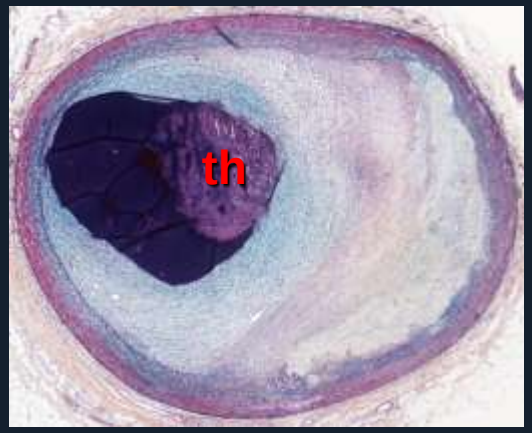


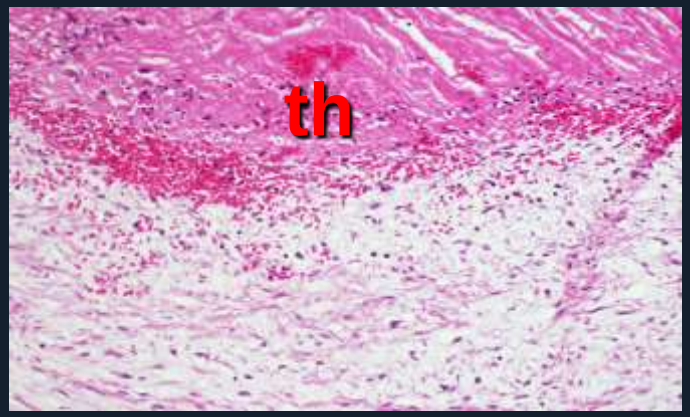
Cheruvu P et al. JACC 2007

Plaque Morphology of AMI/SCD w/Thrombi

Plaque Rupture
60%(f) – 80%(m)

Plaque Erosion
20%(m) - 40%(f)

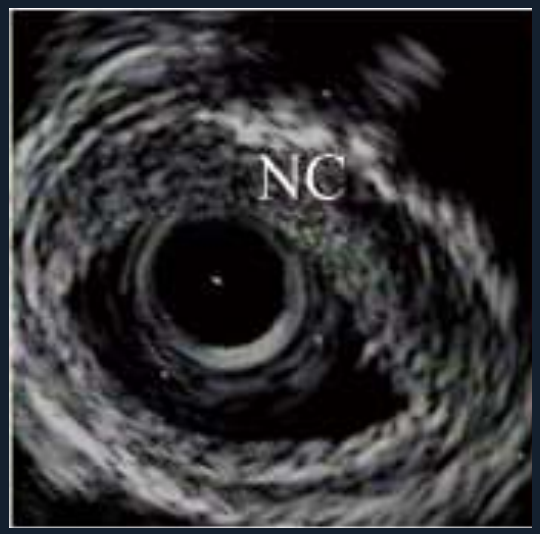


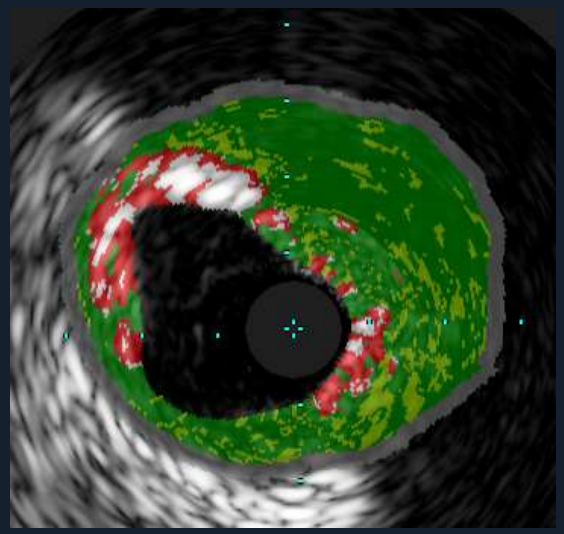


Calcified Nodule
2% - 7%

IVUS/VH vs. OCT vs. NIRS

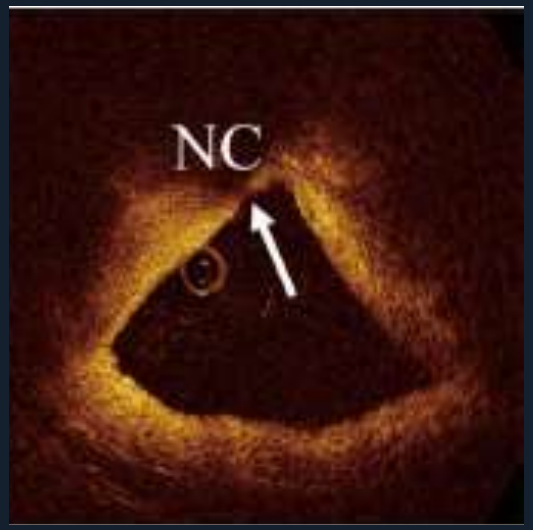
Grayscale IVUS

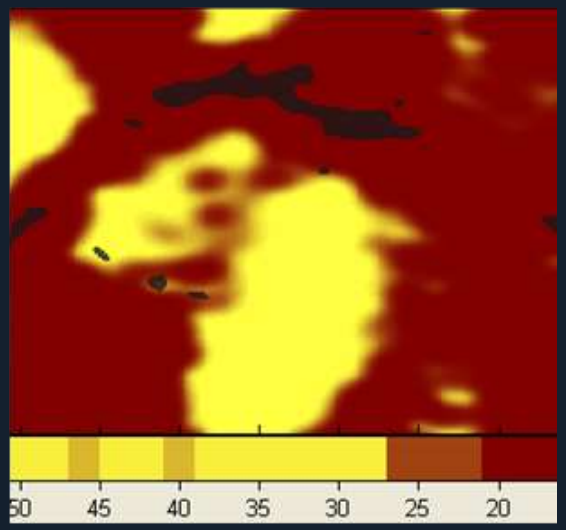




RF-IVUS (VH)

OCT (OFDI)

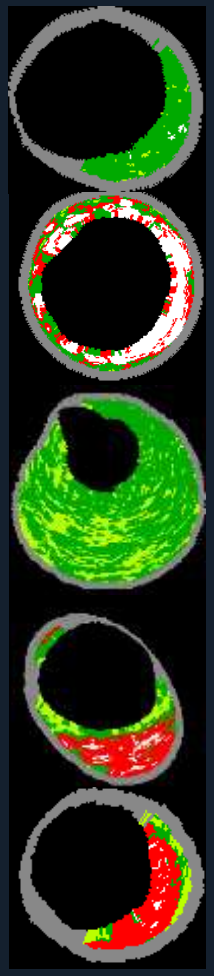




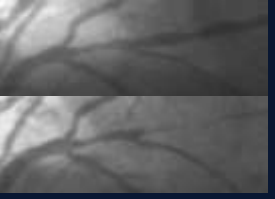
NIR Spectroscopy

Virtual histology lesion classification

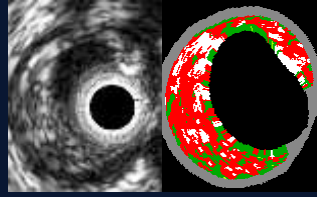
Lesions are classified into 5 main types



1. Fibrotic
2. Fibrocalcific
3. Pathological intimal thickening (PIT)
4. Thick cap fibroatheroma (ThCFA)
5. VH-thin cap fibroatheroma (VH-TCFA)
   (presumed high risk)



PROSPECT Study



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

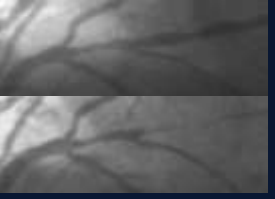
PCI of culprit lesion(s)

Successful and uncomplicated

Formally enrolled

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

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



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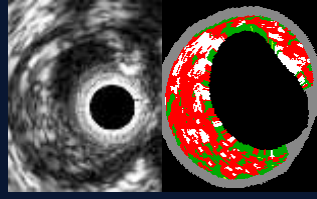


3-vessel imaging post PCI

Angiography (QCA of entire coronary tree)

IVUS

Virtual histology

Palpography (n=~350)

Proximal 6-8 cm of each coronary artery

Meds rec
Aspirin
Plavix 1yr
Statin
Repeat biomarkers
@ 30 days, 6 months

F/U: 1 mo, 6 mo, 1 yr, 2 yr, ±3-5 yrs

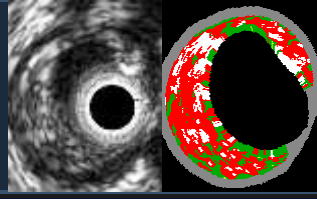
MSCT Substudy
N=50-100

Repeat imaging in pts with events

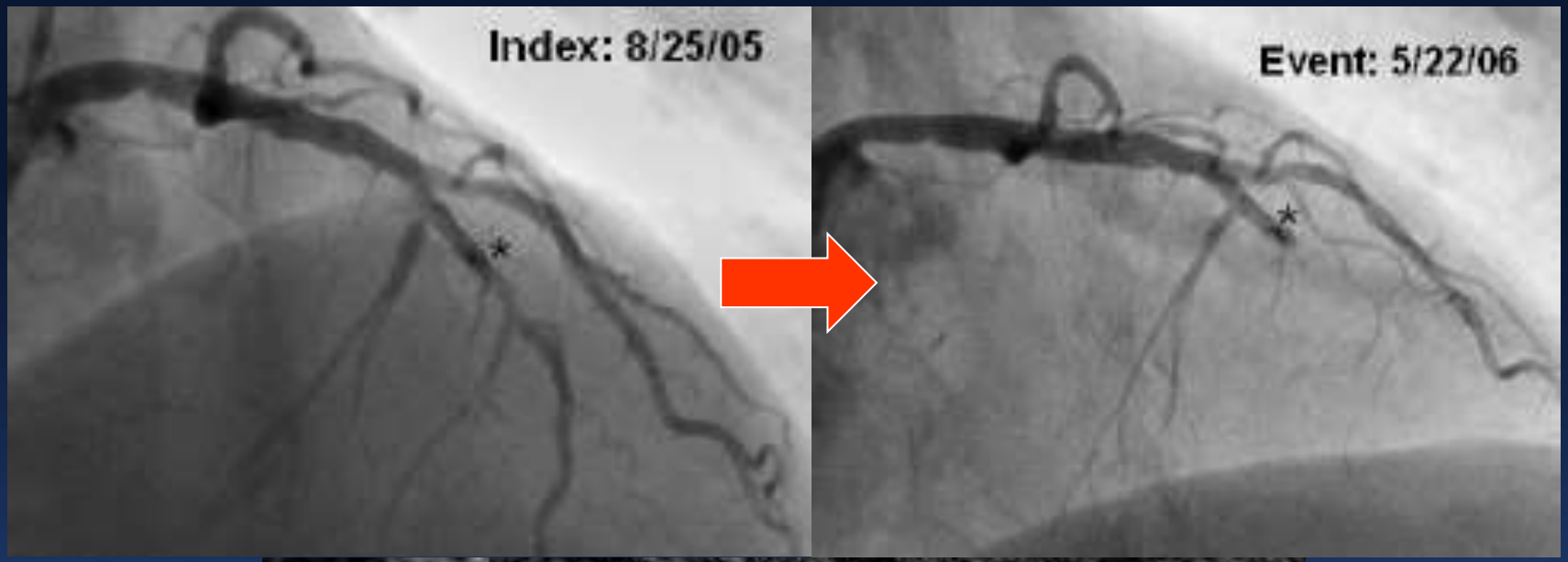
Stone GW et al. NEJM 2011;364:226-35

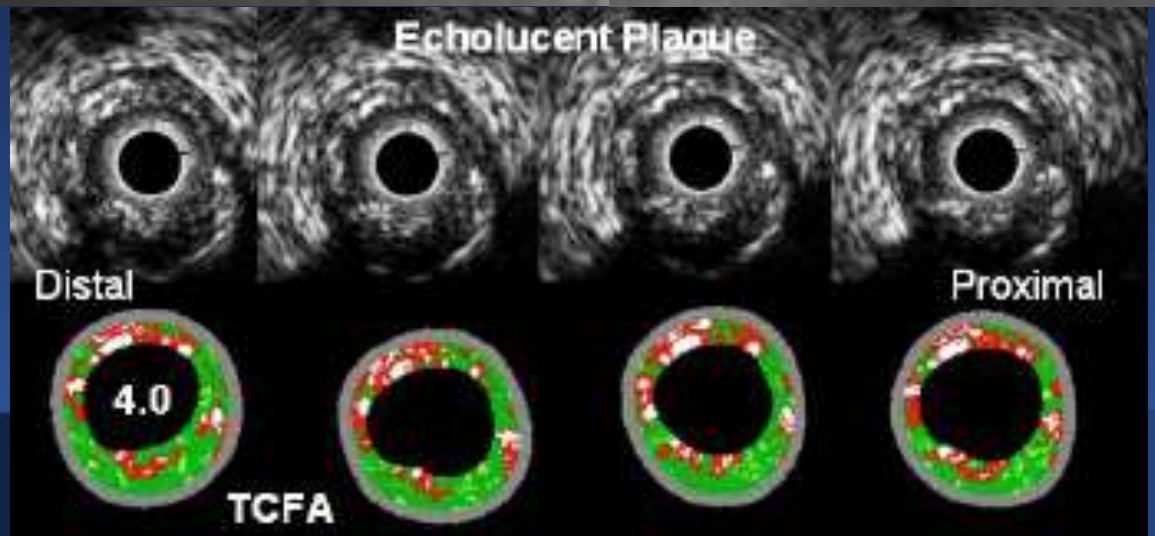
PROSPECT case example

PROSPECT case example



MLA 4.0 mm^2; plaque burden 72%; TCFA





STEMI

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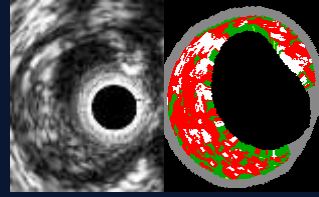
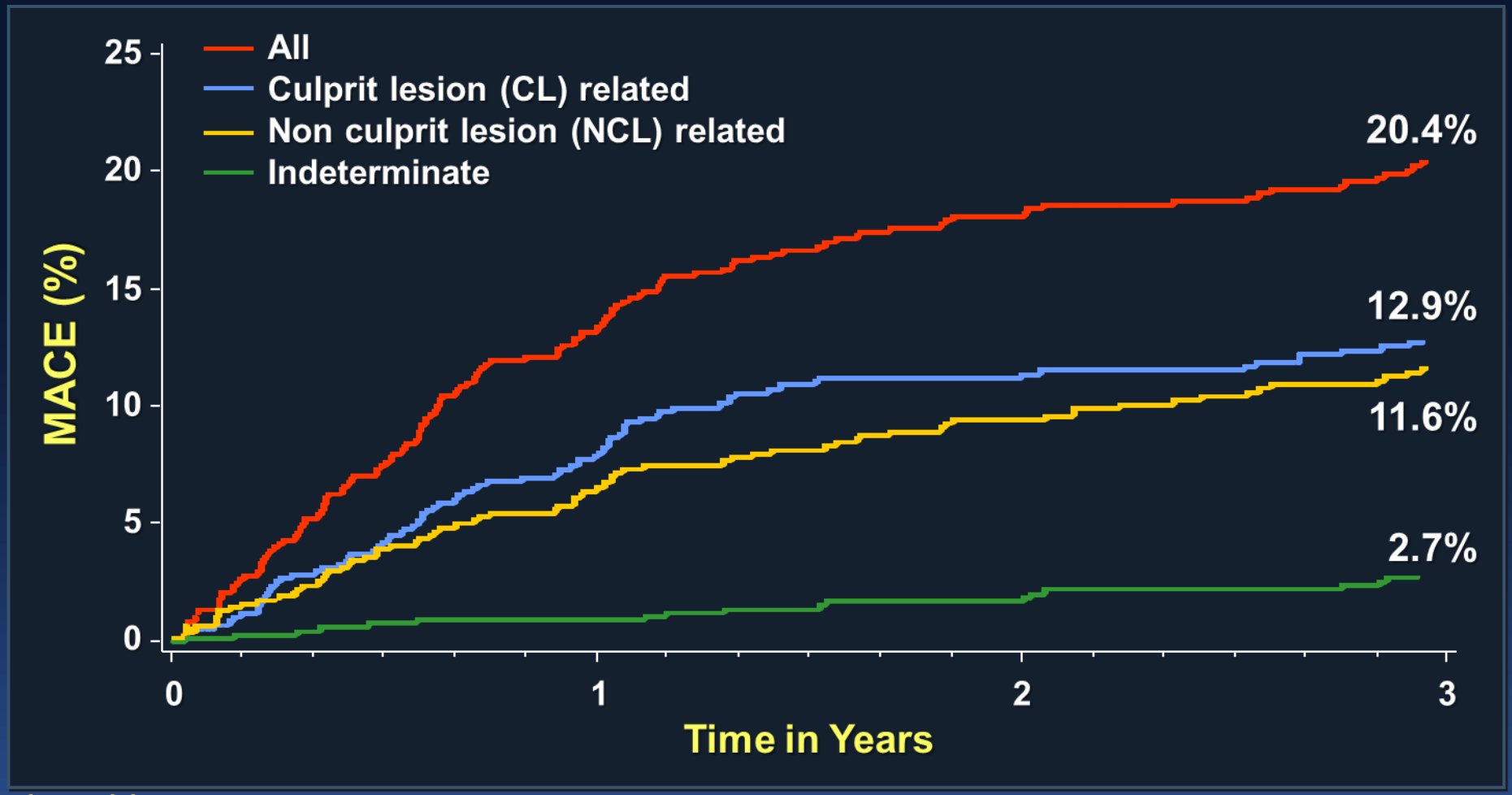
PROSPECT: MACE (N=697)





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

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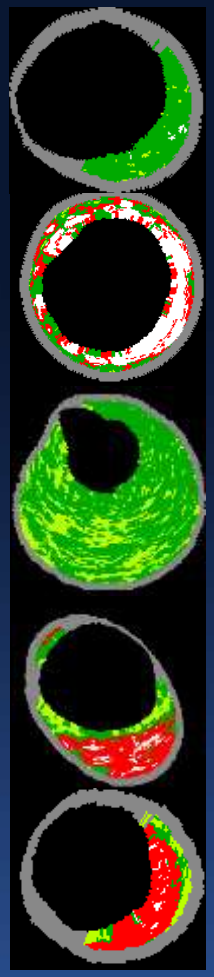
PROSPECT: VH-IVUS Imaging



1. Fibrotic
2. Fibrocalcific
3. Pathological intimal thickening (PIT)
4. Thick cap fibroatheroma
5. VH-thin cap fibroatheroma (presumed high-risk)

Plaque subtype	N=2811
Fibrotic	2.5%
Fibrocalcific	1.2%
PIT	35.9%
Fibroatheroma	57.4%
- Thick cap	36.2%
- VH-TCFA	18.9%
- Single, - Ca	5.2%
- Single, + Ca	0.5%
- Multiple, - Ca	9.5%
- Multiple, + Ca	6.1%

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

PROSPECT: Multivariable Correlates of Non-Culprit Lesion Related Events

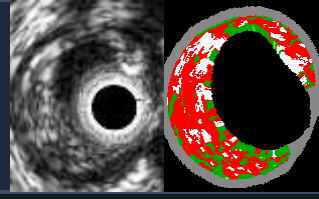
Independent predictors of lesion level events by Cox Proportional Hazards regression

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

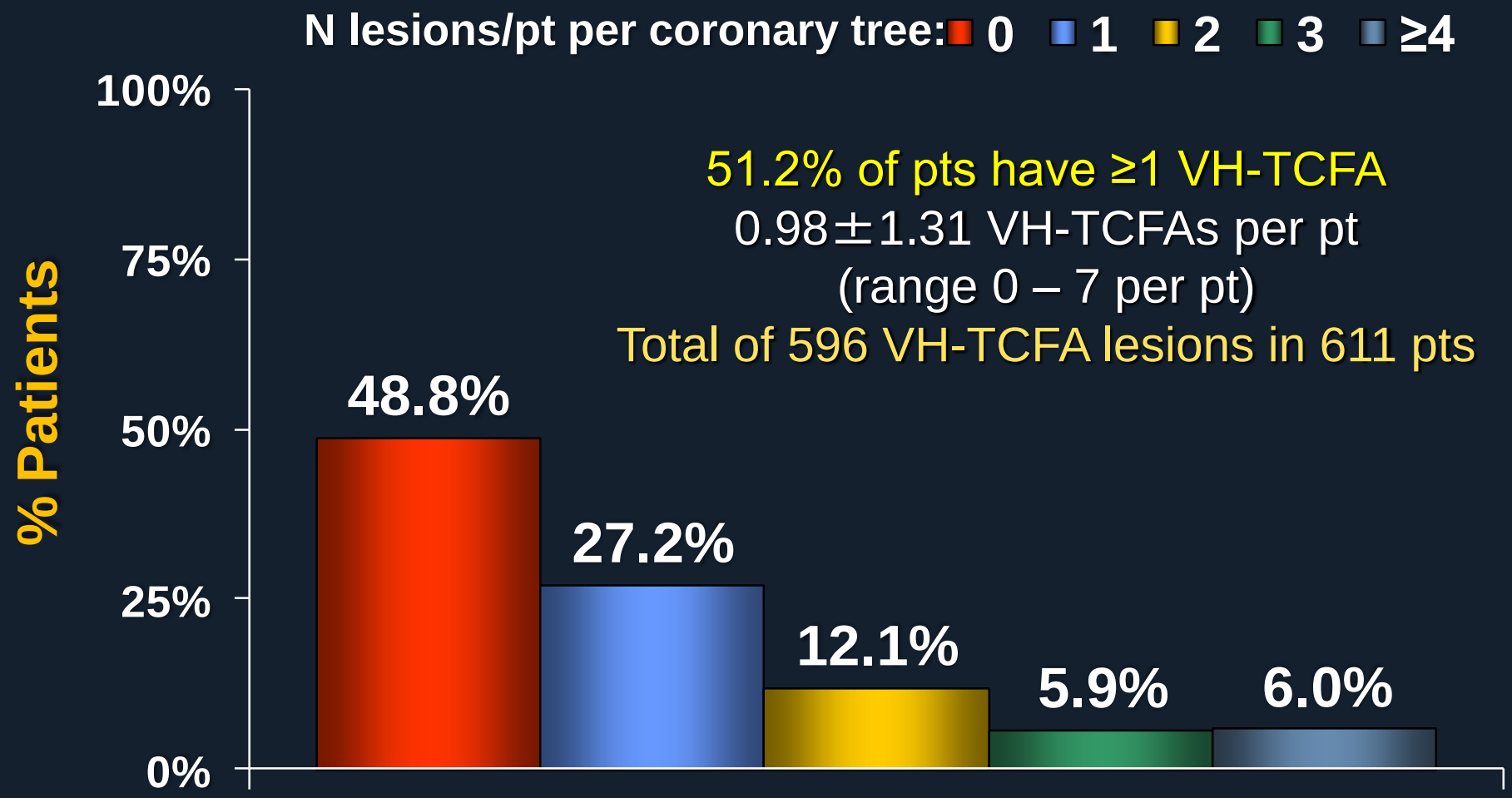
Variables entered: minimal lumen area (MLA), plaque burden at the MLA, external elastic membrane at the MLA, lesion length, distance from the coronary ostium to the MLA, remodeling index, thin-cap fibroatheroma, insulin-requiring diabetes and prior percutaneous coronary intervention

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

PROSPECT: Imaging Summary



Per patient incidence of VH-TCFAs

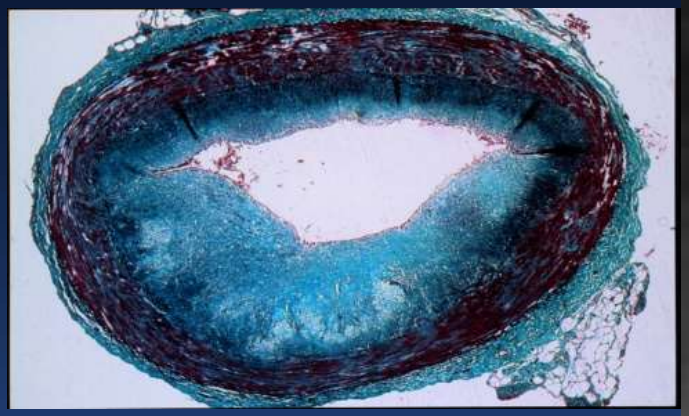


51.2% of pts have ≥1 VH-TCFA
0.98±1.31 VH-TCFAs per pt
(range 0 – 7 per pt)
Total of 596 VH-TCFA lesions in 611 pts

Diagnosis of Vulnerable Plaque

Requires seeing beyond the angiogram

The "stable" atherosclerotic plaque

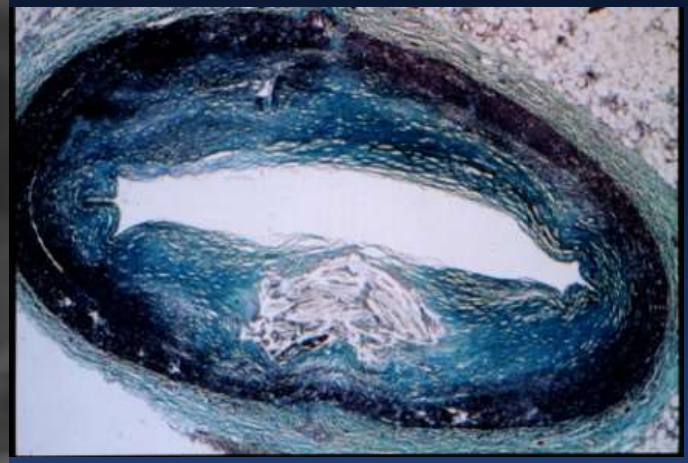


Inactive and non-inflamed plaque

Pathologic intimal thickening

vs.

The "vulnerable" atherosclerotic plaque



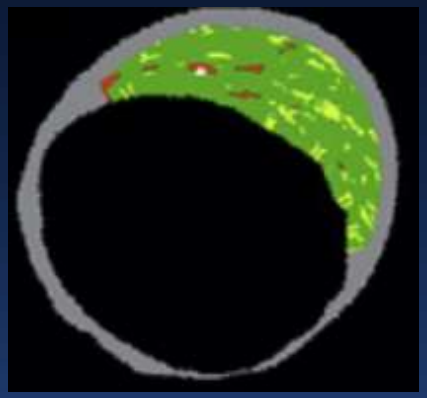
Active and inflamed plaque

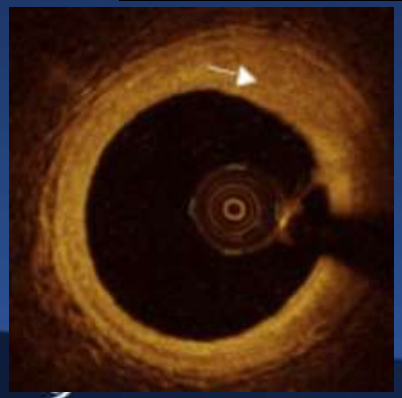
Thin-cap fibroatheroma

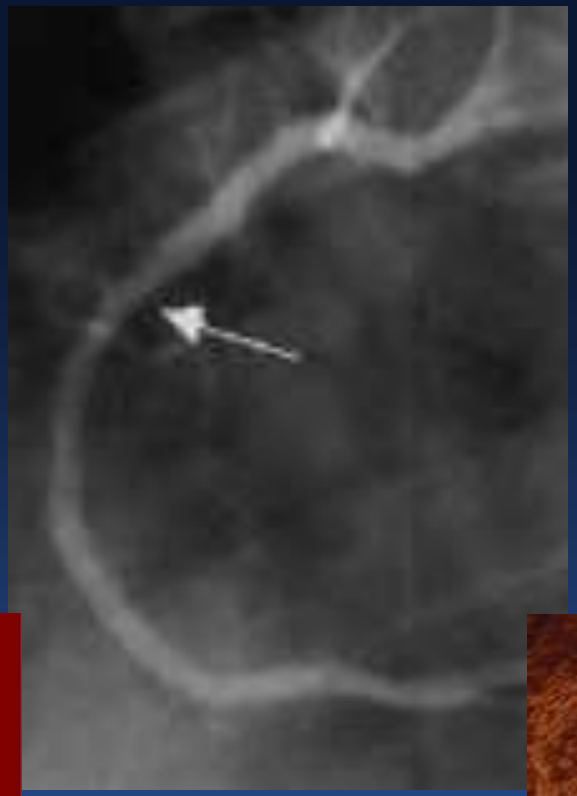
Diagnosis of Vulnerable Plaque

Requires seeing beyond the angiogram

The "stable" atherosclerotic plaque

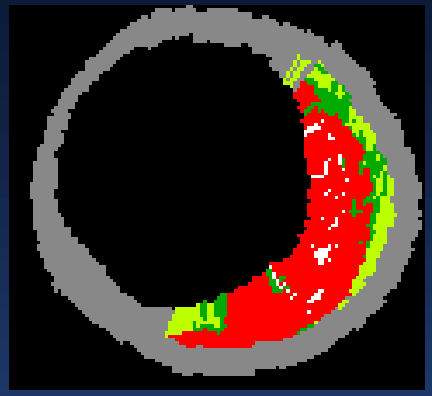


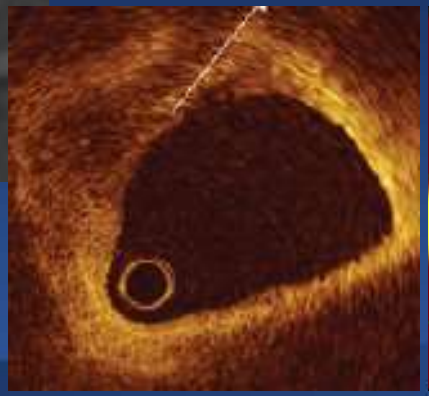


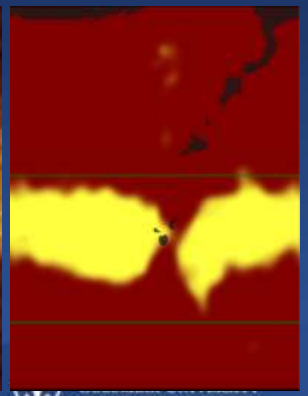


VS.

The "vulnerable" atherosclerotic plaque



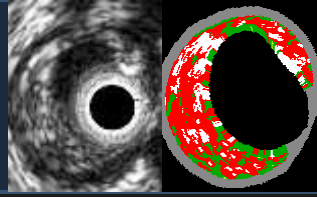




But: No one images mild atherosclerosis!

You can assume that 50% of pts with MI have untreated TCFAs!

PROSPECT: MACE

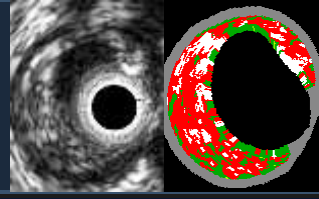


3-year follow-up, non hierarchical

	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)

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

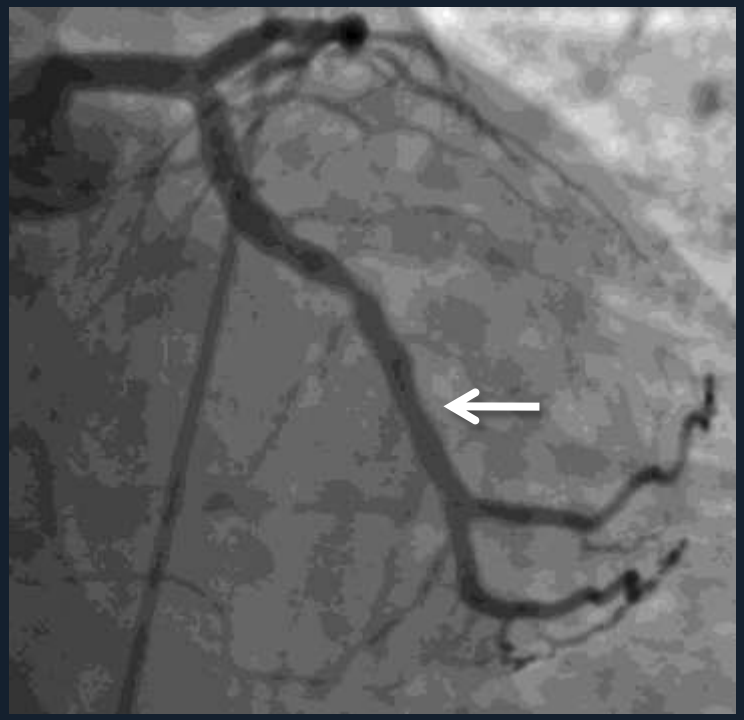
PROSPECT 82910-012: 52 yo♂



2/13/06: NSTEMI, PCI of MLAD

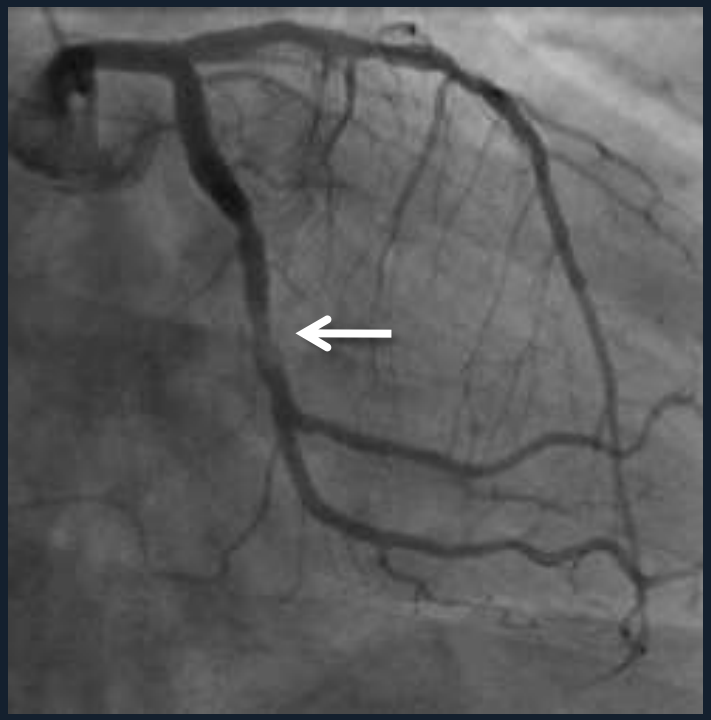
2/6/07 (51 weeks later): NSTEMI attributed to LCX

Index 2/13/06



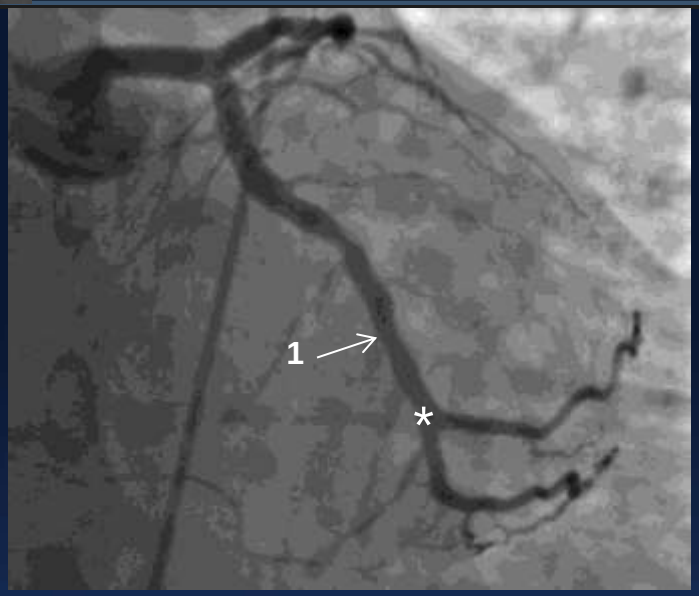
QCA DS 28.6%

Event 2/6/07



QCA DS 71.3%

PROSPECT 82910-012: Index 2/13/06



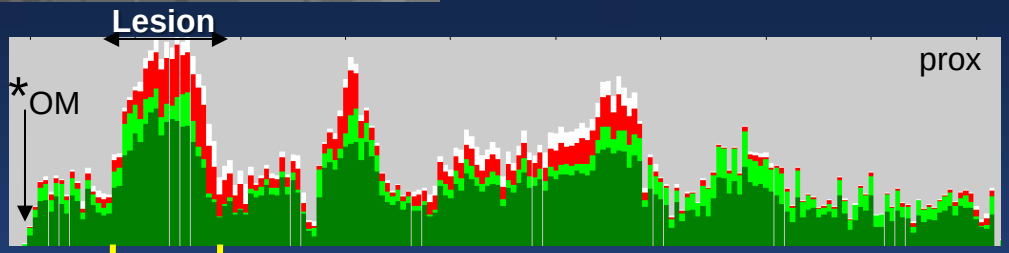
Baseline PLCX

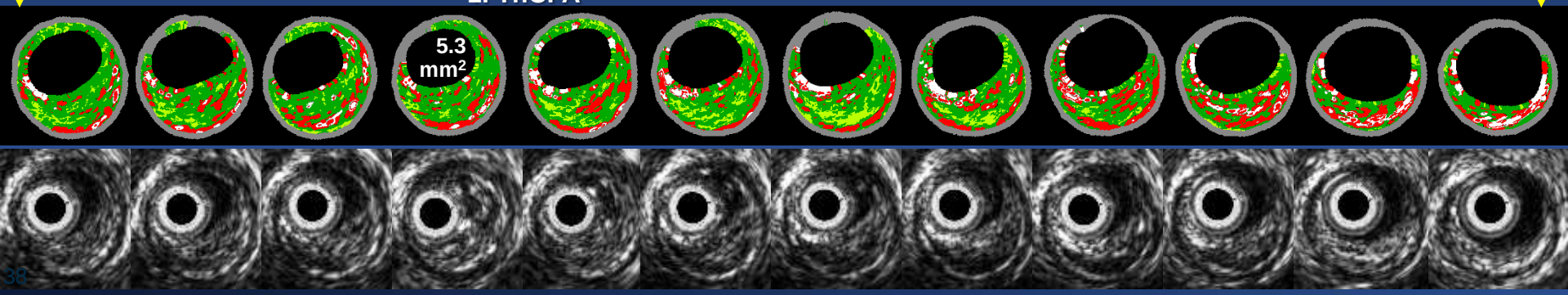
QCA: RVD 2.82 mm,

DS 28.6%, length 6.8 mm

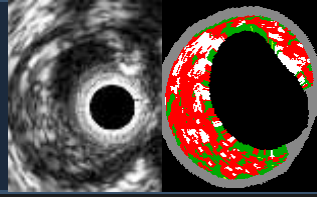
IVUS: MLA 5.3 mm^2

VH: ThCFA





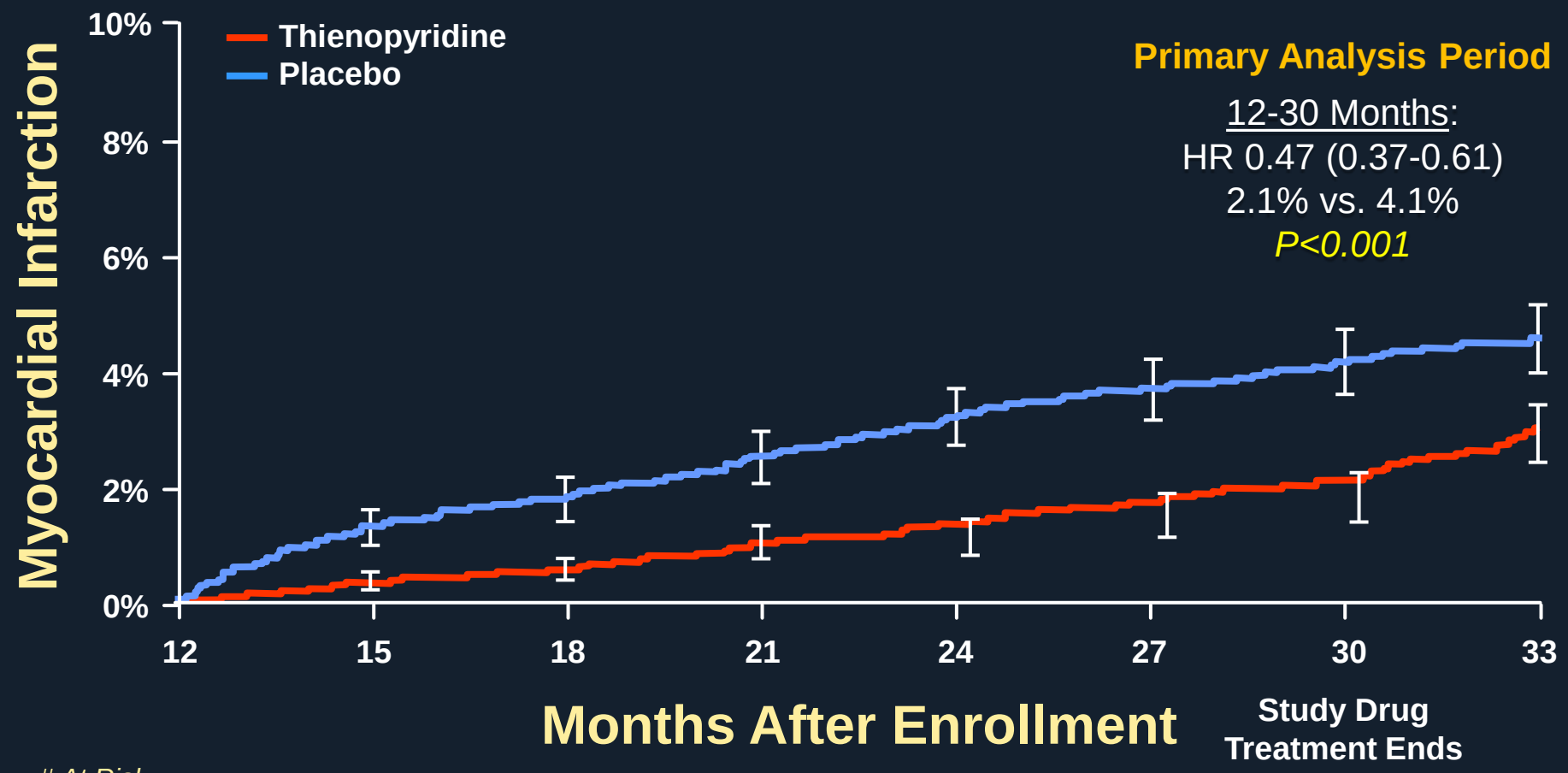
Medication Use



	Discharge	1 year	3 years
Aspirin	96.8%	94.7%	91.7%
Clopidogrel	97.1%	71.1%	35.1%
Statin	85.5%	84.0%	84.5%
Beta-blocker	90.7%	85.9%	81.0%
ACEI/ARB	69.1%	69.3%	70.6%

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

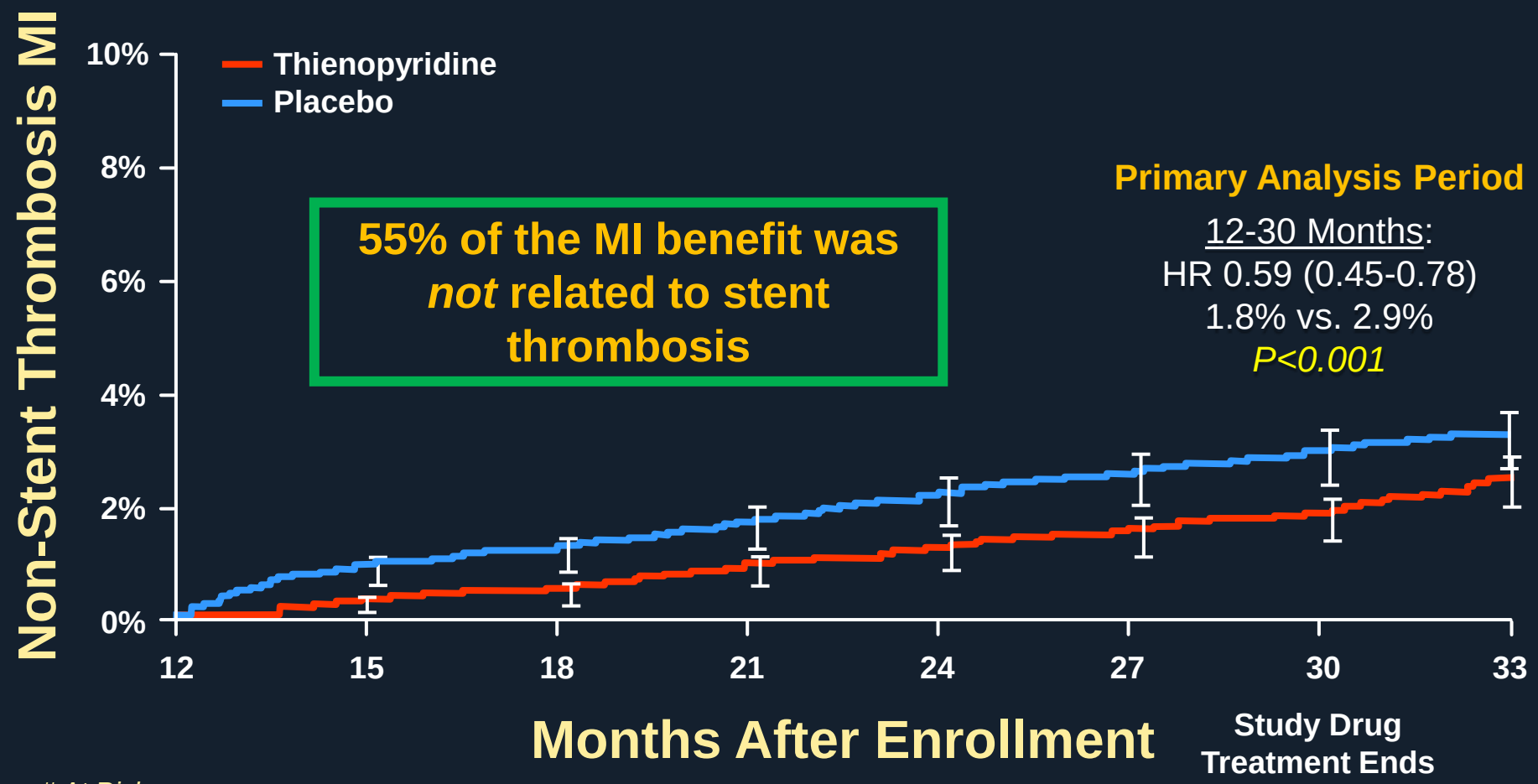
Myocardial Infarction



# At Risk								
Thienopyridine	5020	4920	4849	4789	4717	4634	4580	3051
Placebo	4941	4804	4727	4653	4565	4501	4440	3012

Mauri L et al. NEJM 2014

Non-Stent Thrombosis MI



# At Risk								
Thienopyridine	5020	4920	4851	4792	4721	4611	4588	3066
Placebo	4941	4820	4751	4686	4607	4547	4491	3052

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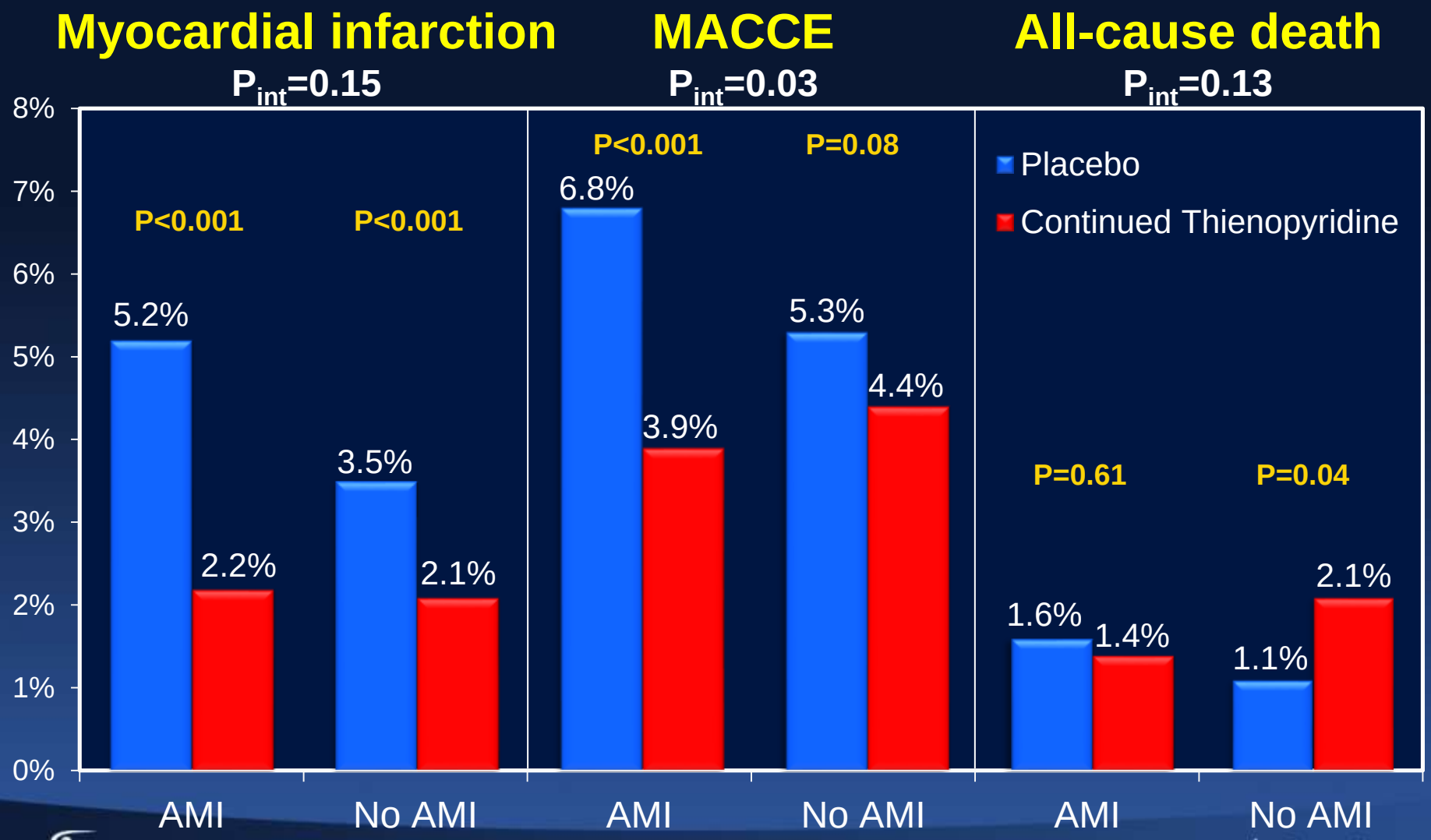
Treatment Effect According to AMI Presentation Status at 12-30 Months: All Randomized Pts (N=11,648)

3,576 (30.7%) presented with MI (47% STEMI, 53% NSTEMI)



Yeh R et al. JACC 2015:on-line

Conclusions

1. Rapid lesion progression of vulnerable plaques, with coronary thrombosis, is the cause of most ACS
2. Most non-ruptured vulnerable plaques are TCFAs with high plaque burden, and are especially likely to be present in pts with MI
3. In high-risk pts with untreated vulnerable plaques, effective secondary prevention (DAPT, statins and more) may prevent coronary occlusion and convert a likely MI into unstable angina or lesser clinical syndromes