# Vulnerable Plaque 2012

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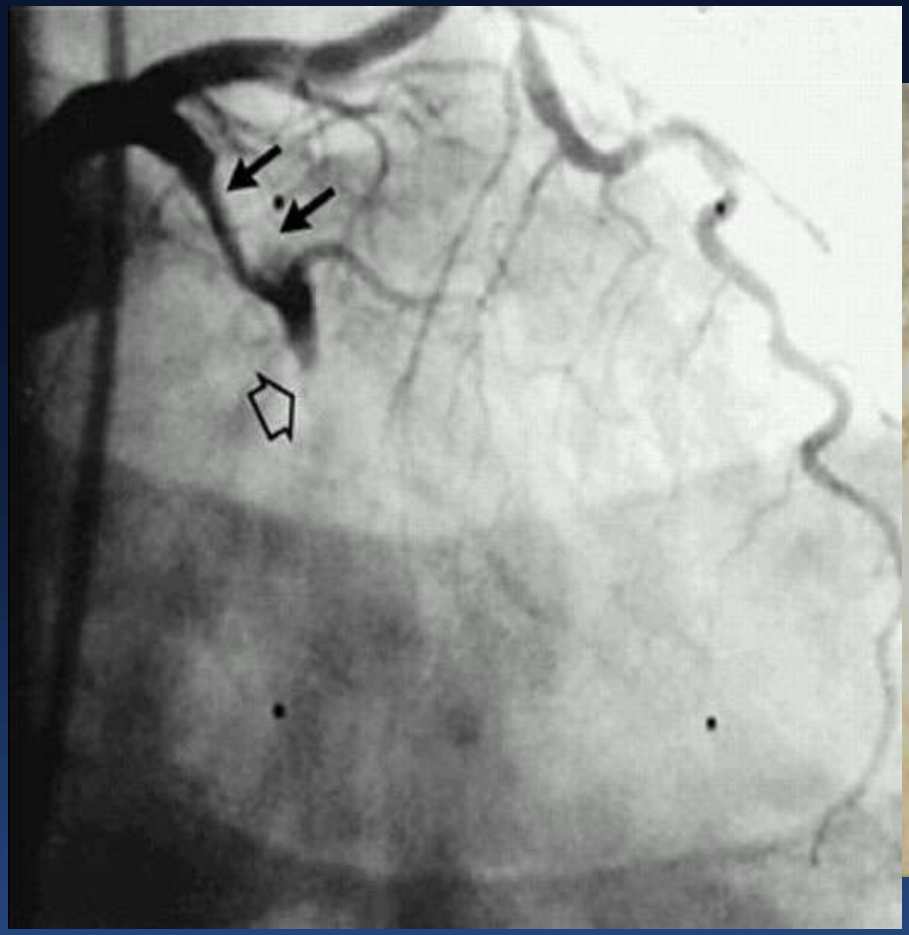
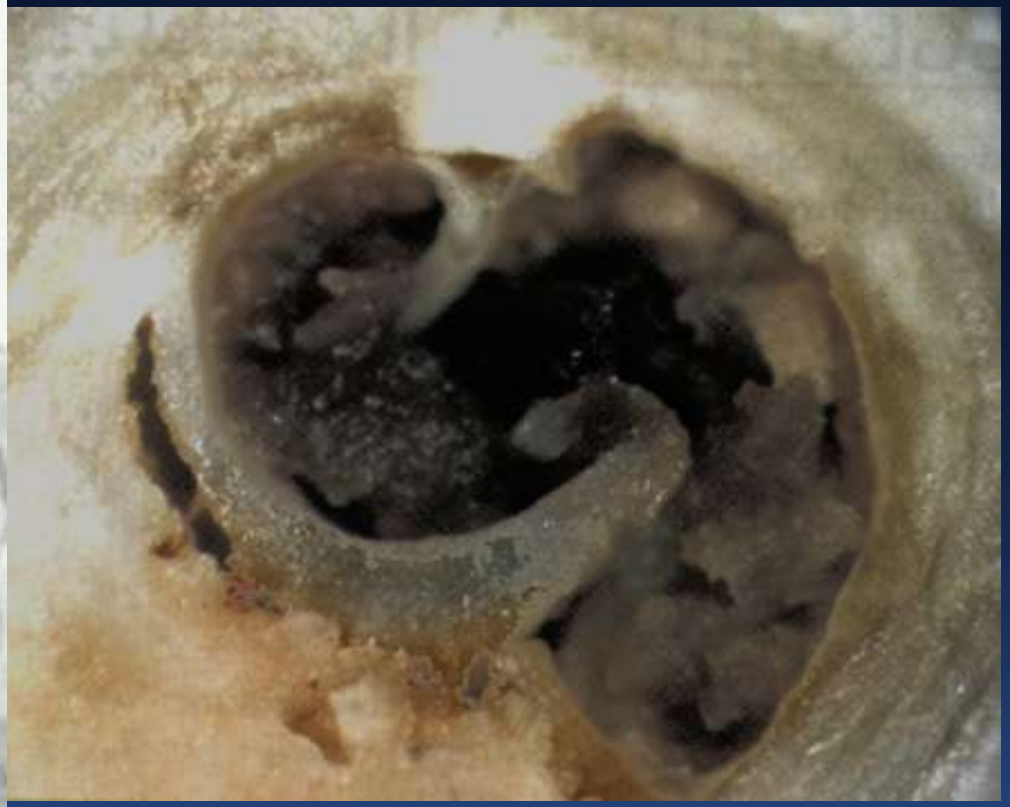
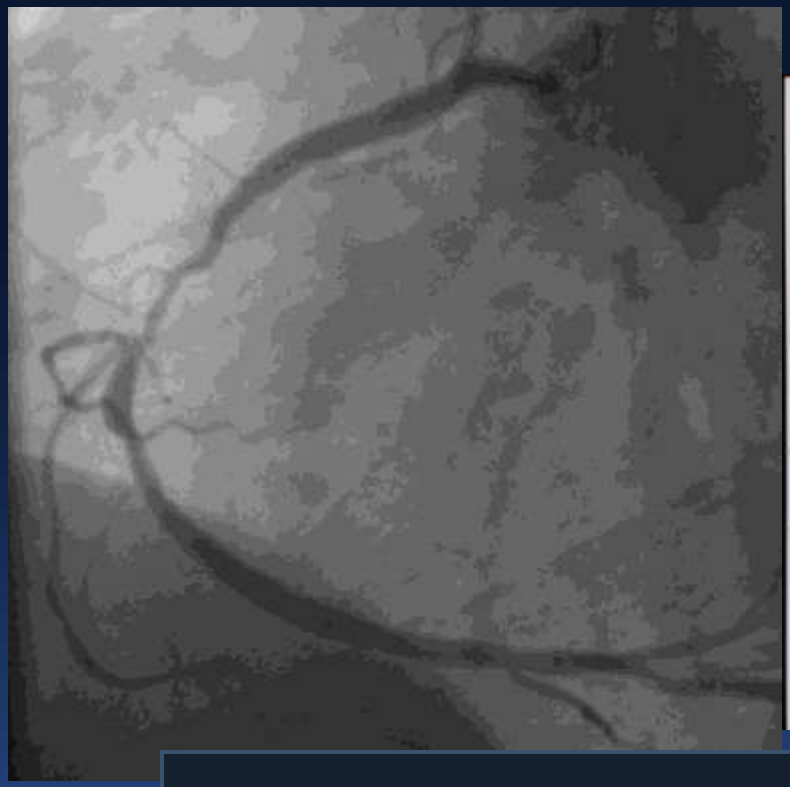
# The Pathophysiology of AMI

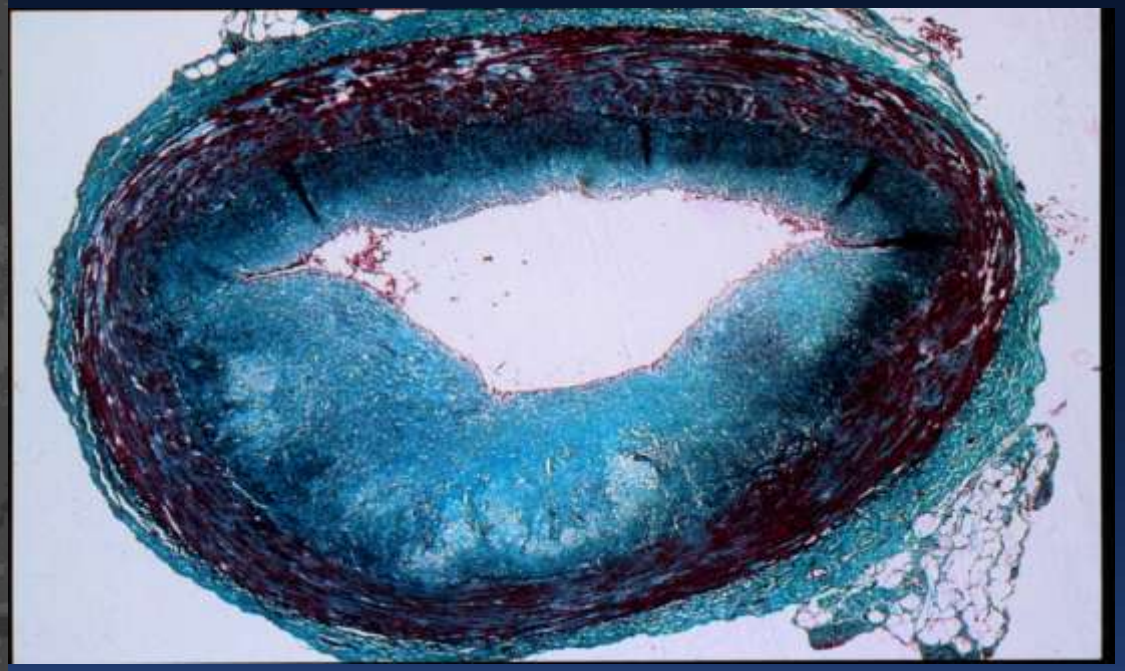




**Ruptured thin capped fibroatheroma with luminal and intraplaque occlusive thrombus**

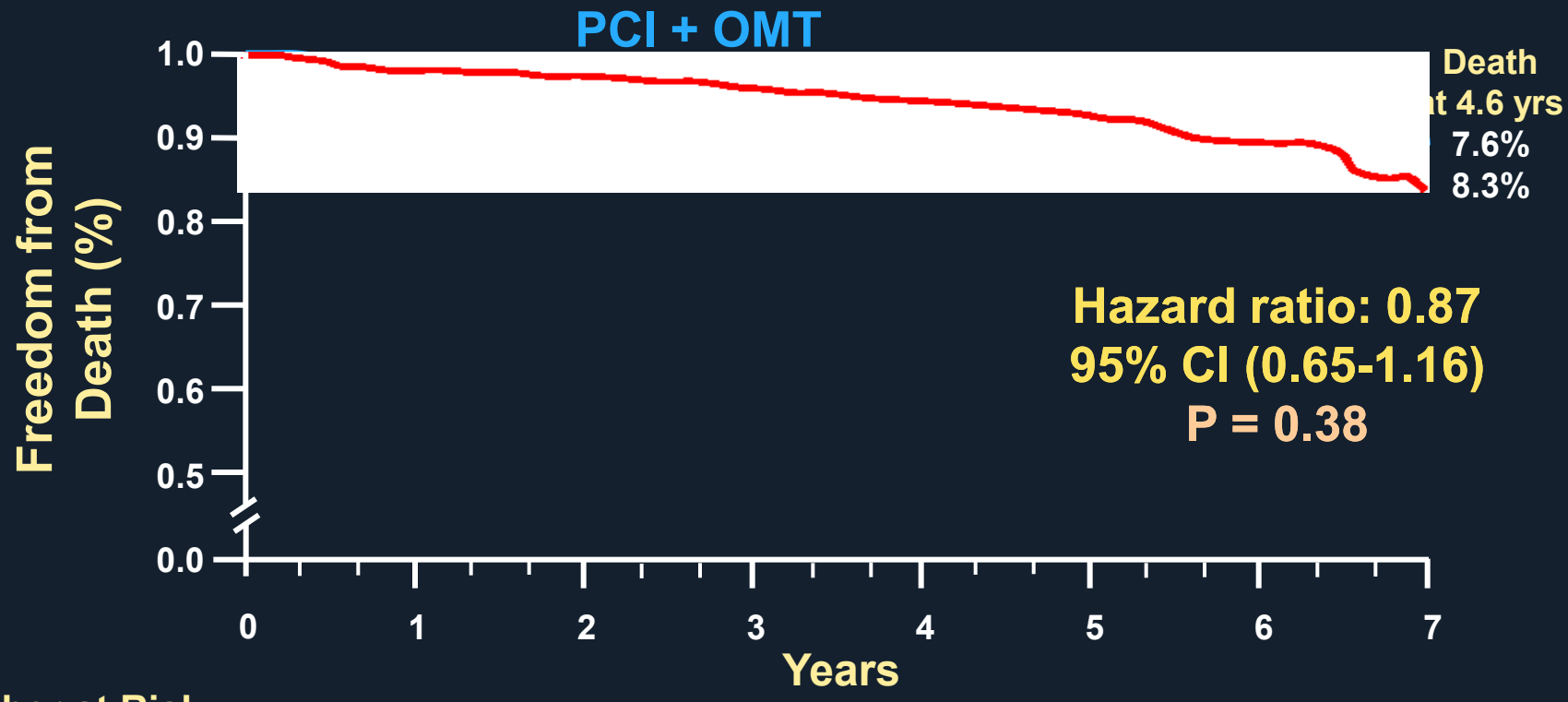
# Stable Coronary Artery Disease
## Fibrotic plaque





- Studies have shown that PCI only decreases the frequency of angina and improves exercise performance

# COURAGE: Survival
## (median FU 4.6 yrs)




**Number at Risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Medical Therapy | 1138 | 1073 | 1029 | 917 | 717 | 468 | 302 | 38 |
| PCI | 1149 | 1094 | 1051 | 929 | 733 | 488 | 312 | 44 |



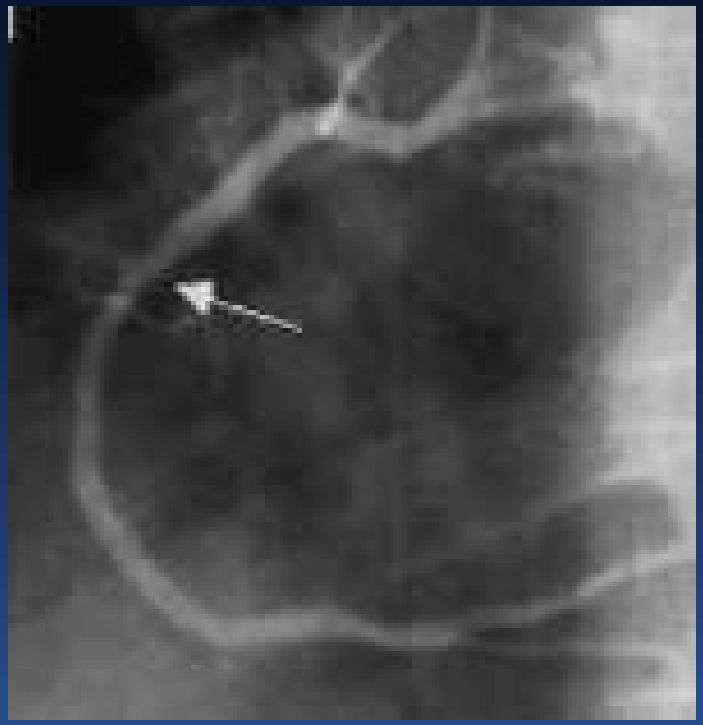
Boden WE et al. NEJM 2007;356:1503-16

# 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**

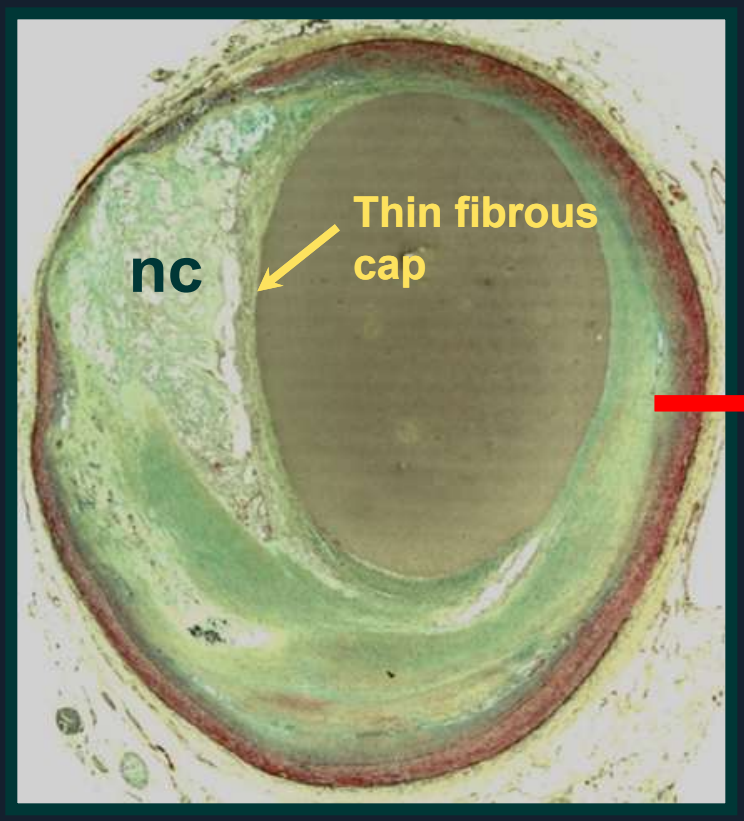
**Unstable angina 133 days later**



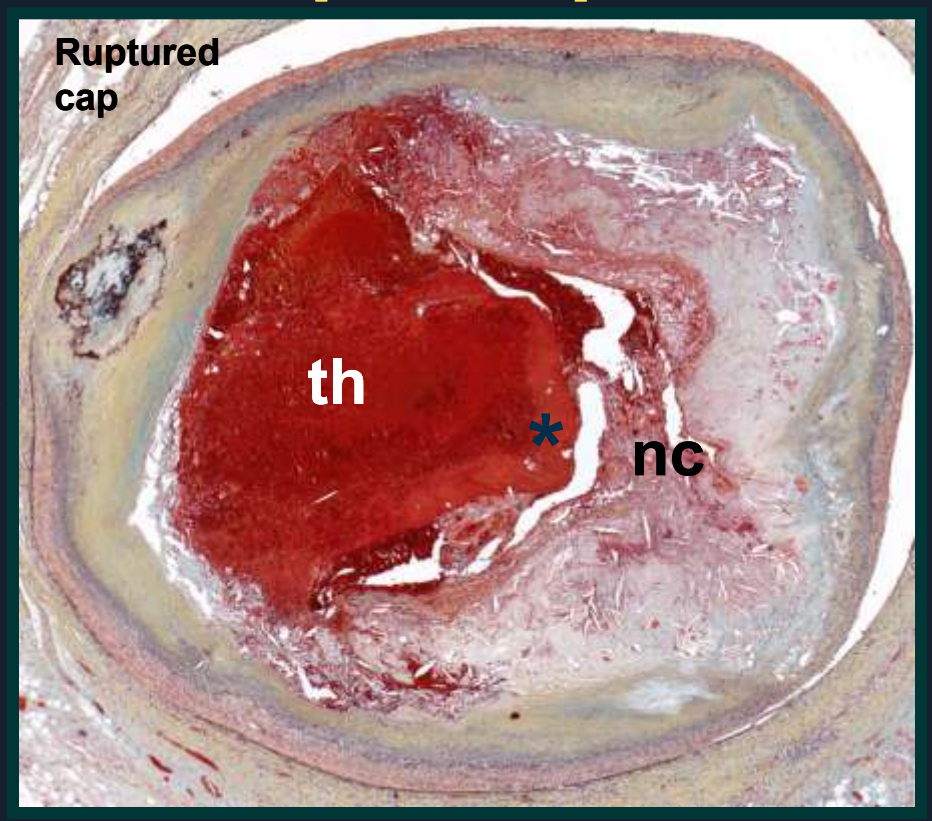
Glaser R et al. Circ 2005;111:152-158

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

## TCFA




## Plaque Rupture

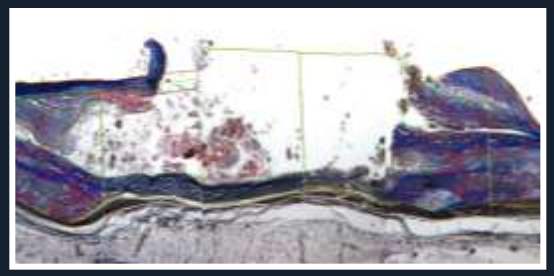



**TCFA =**

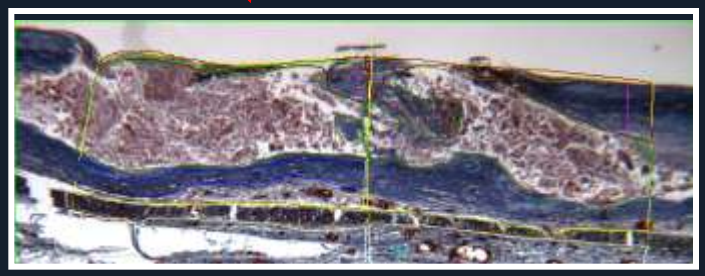
- Lipid rich necrotic core
- Thin fibrous cap (<65 um)
- Cap = type 1 coll with few SMC
- Cap infiltrated by mp and lym

# 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



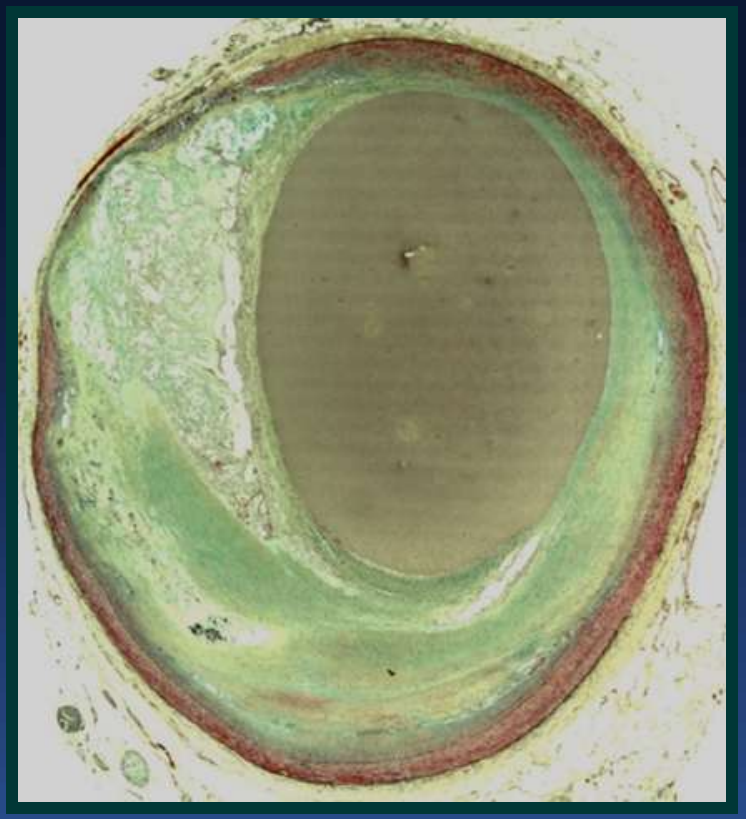
Thin cap fibroatheroma

Pathologic intimal thickening

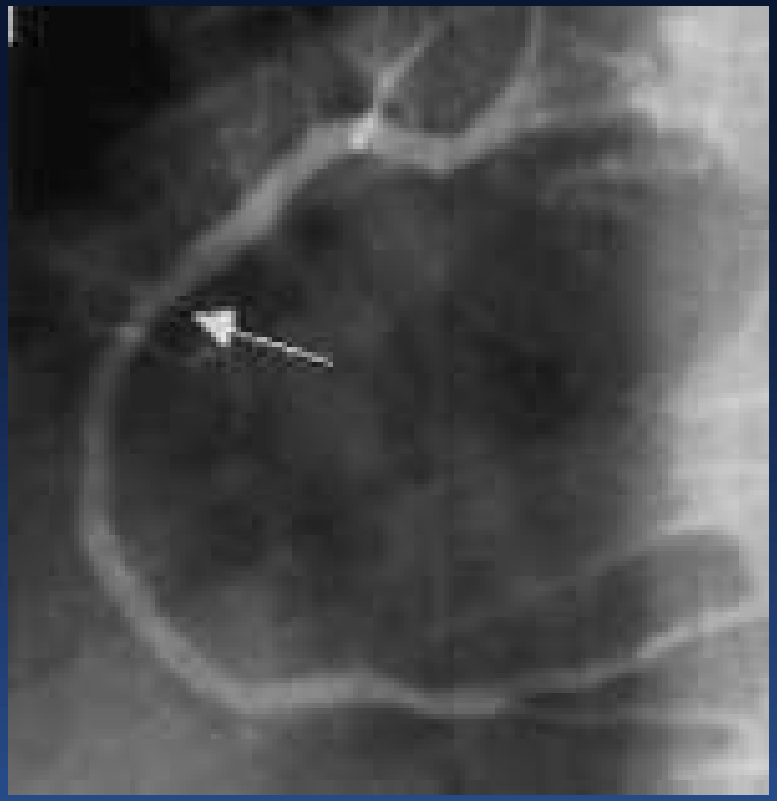
Cheruvu PK et al. JACC 2007;50:940-9

# What is a Vulnerable Plaque?

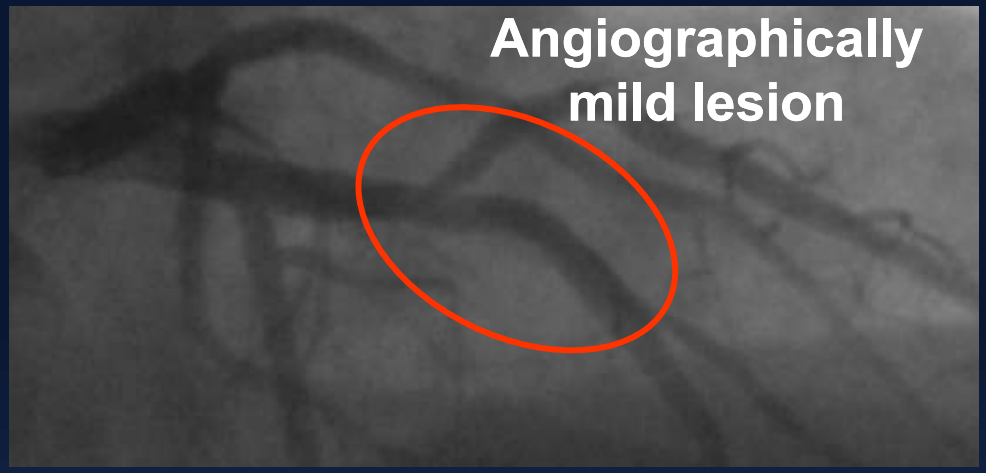
**A thin-cap fibroatheroma?**

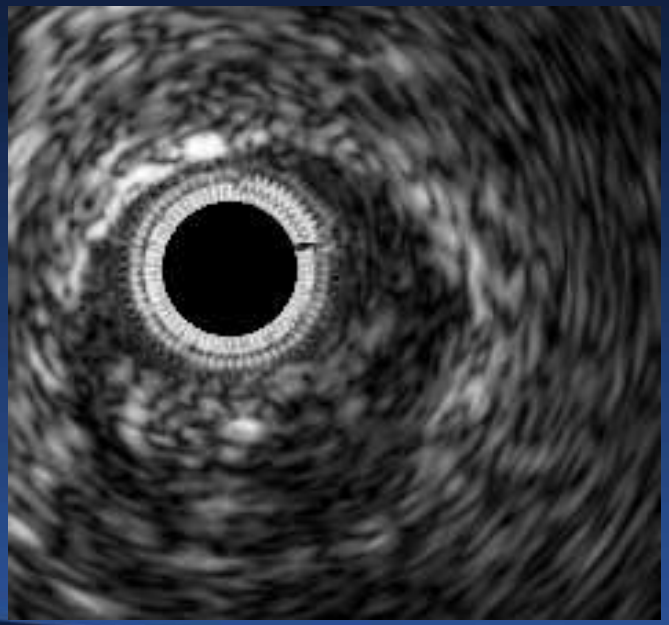


**A lesion that places a pt at risk for future MACE?**



# Angiography underestimates lesion severity



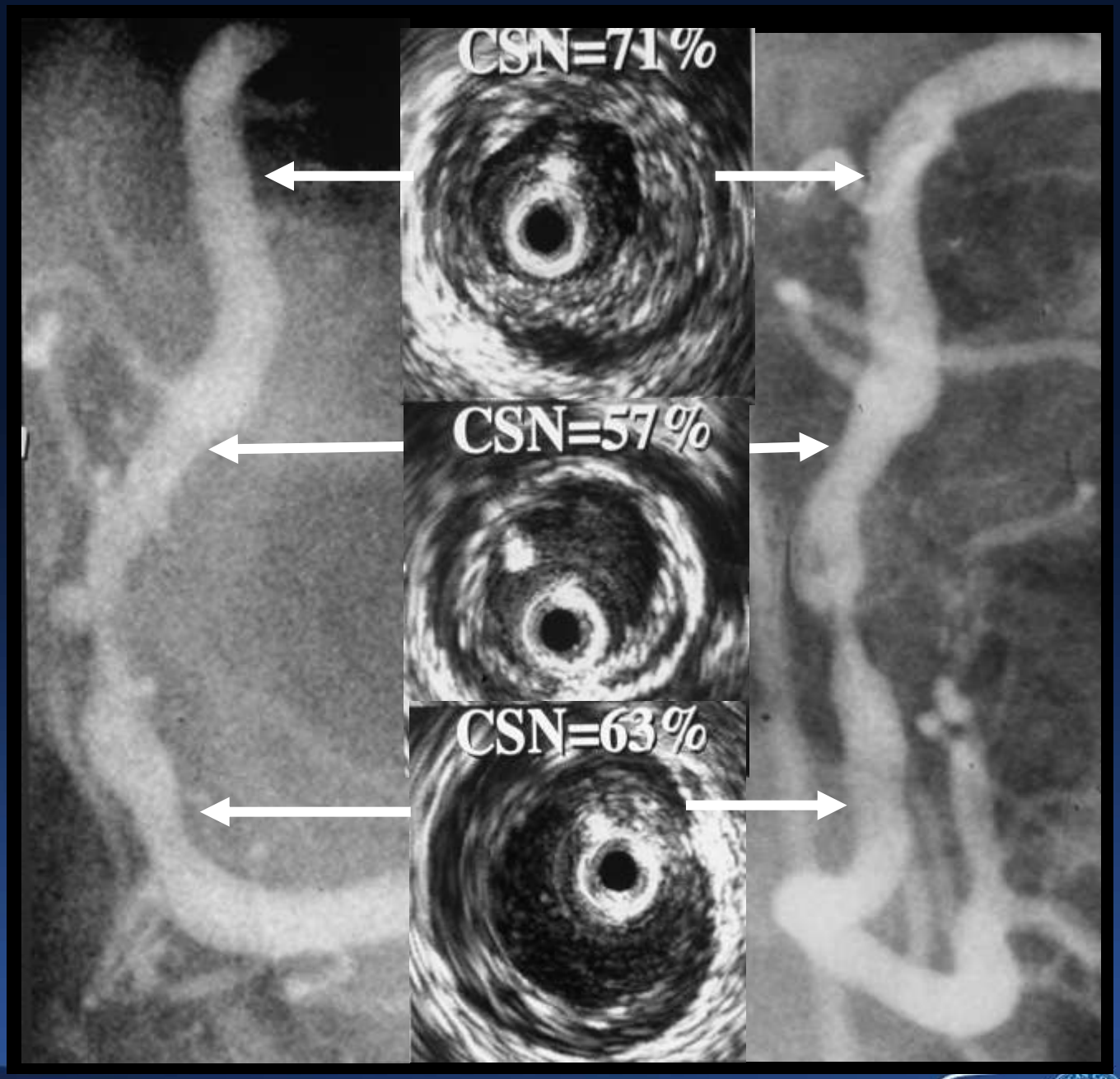



**Grayscale IVUS**
**MLA 3.2 mm²**
**Plaque burden 74%**
**FFR 0.64**

→ Ischemia, angina

→ ? Plaque rupture, ACS

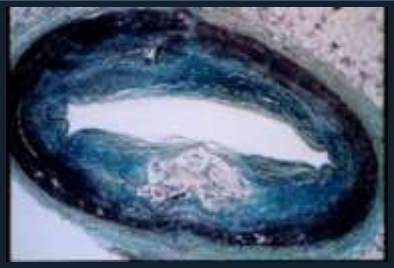
> 90% of "normal" arteries have significant plaque burden by IVUS



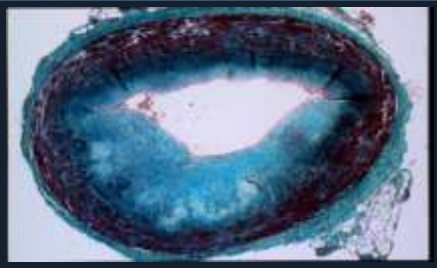



Mintz GS

Active and inflamed plaque

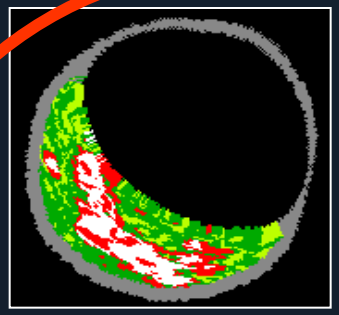


vs.

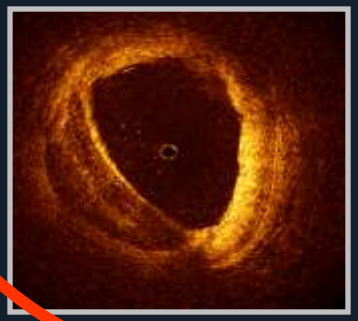


Inactive and non-inflamed plaque

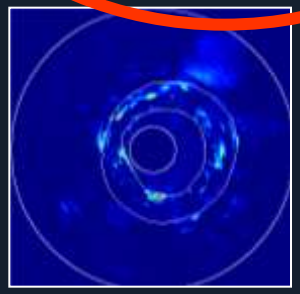
## Morphology



Virtual histology

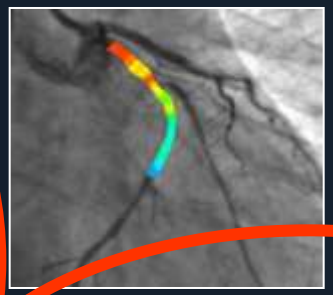


OCT

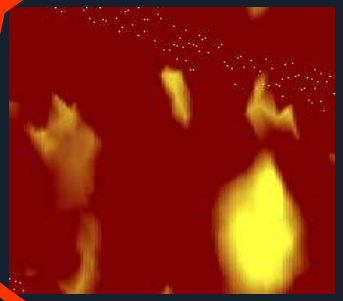


Vasa vasorum imaging

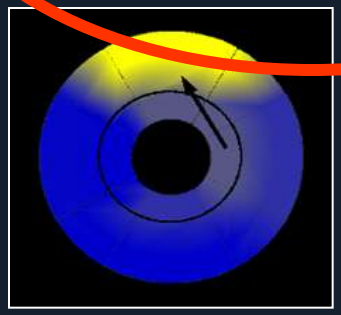
## Activity - Chemistry



Thermography

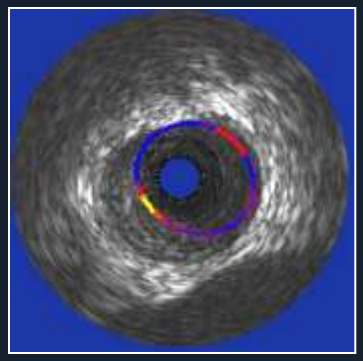


Spectroscopy

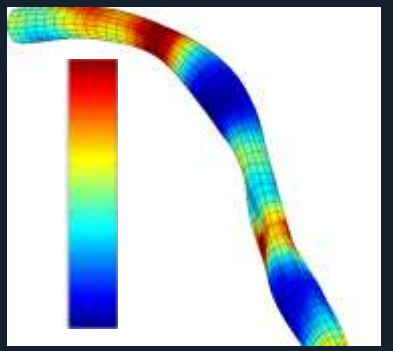


IV MRI

## Physical properties



Palpography

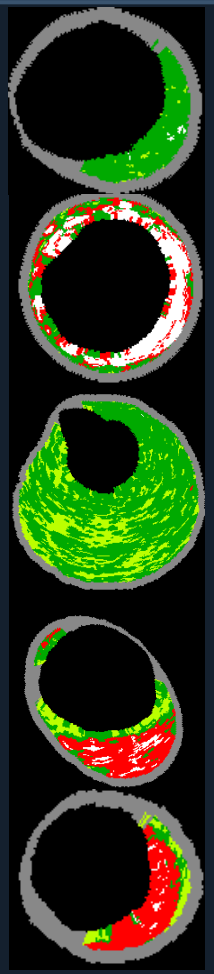


Endothelial shear stress

# PROSPECT: Methodology

## Virtual histology lesion classification

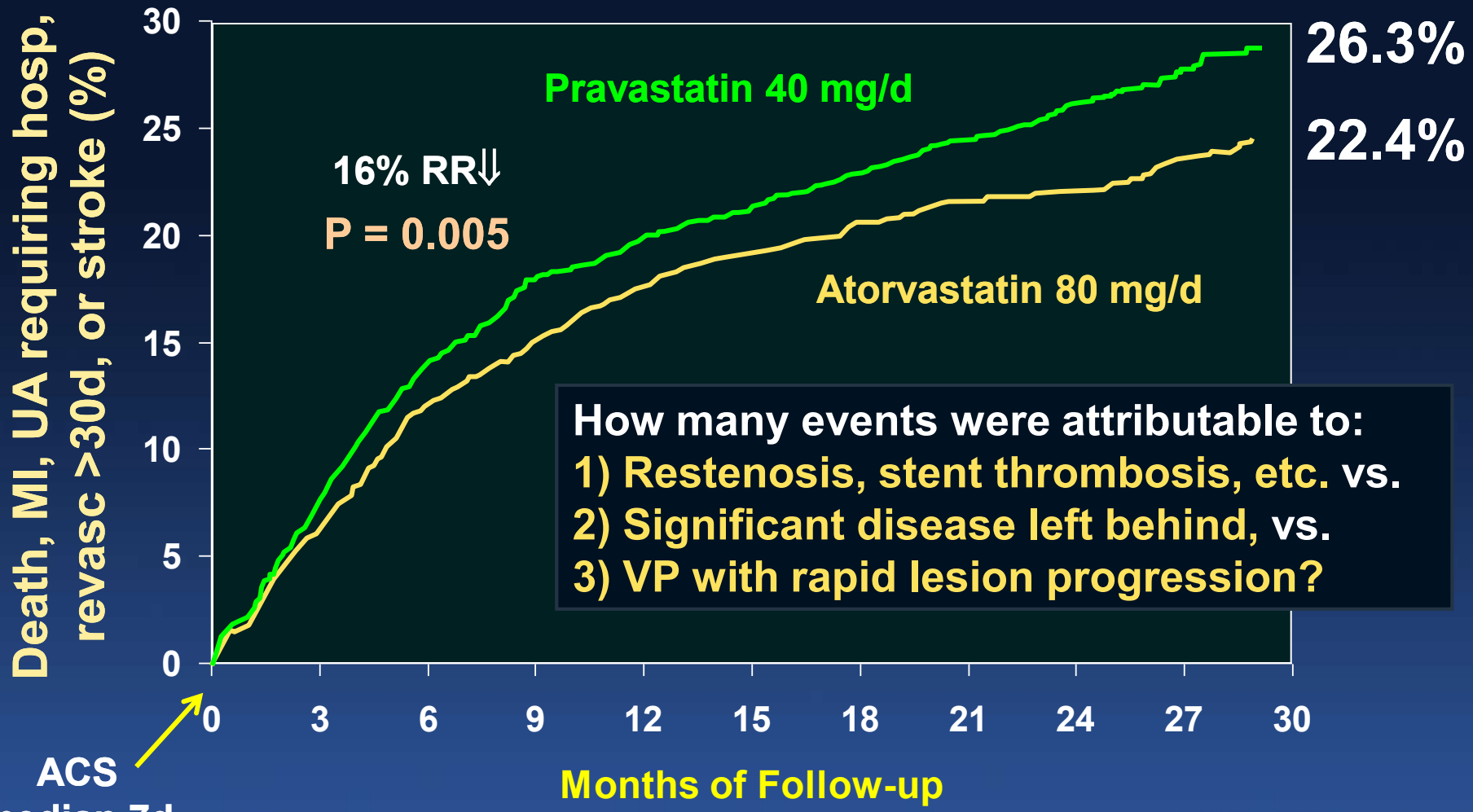
### Lesions are classified into 5 main types



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

# PROVE-IT TIMI-22

## 4,162 Randomized Pts with ACS




Cannon CP et al. NEJM 2004;350:1495-1504

# 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



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

# The PROSPECT Trial

## 3-vessel imaging post PCI

### Culprit artery, followed by non-culprit arteries

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**

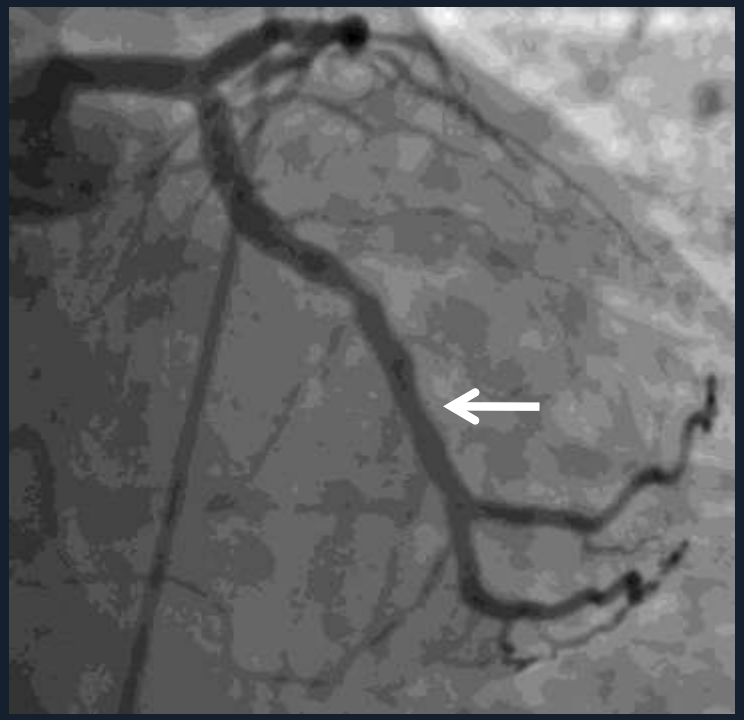
Stone GW et al. NEJM 2011;364:226-35

# PROSPECT 82910-012: 52 yo♂

**2/13/06:** NSTEMI, PCI of MLAD

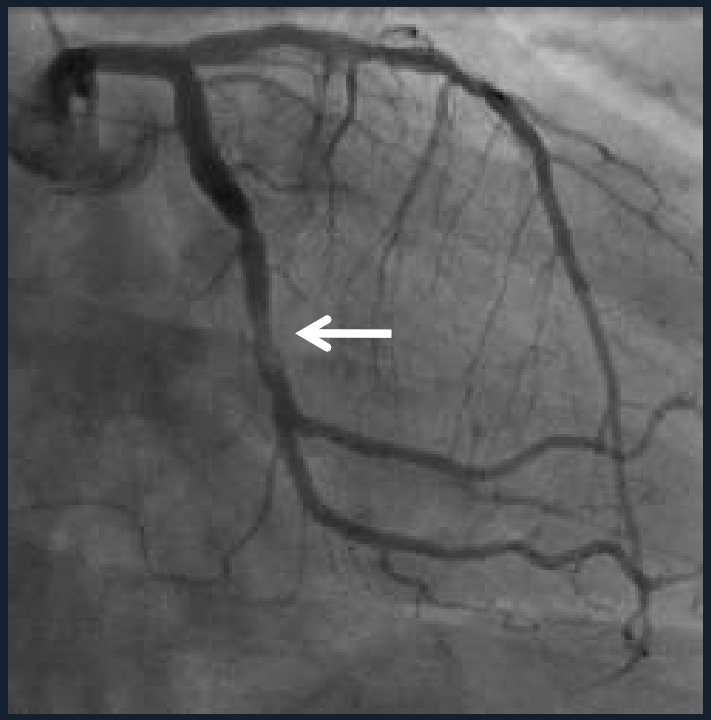
**2/6/07 (51 weeks later):** NSTEMI attributed to LCX

## Index 2/13/06



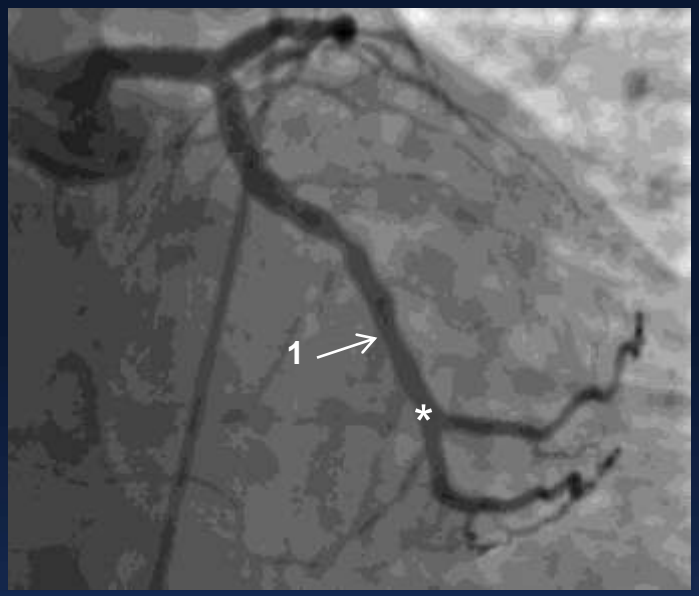
QCA PLCX DS 28.6%

## Event 2/6/07



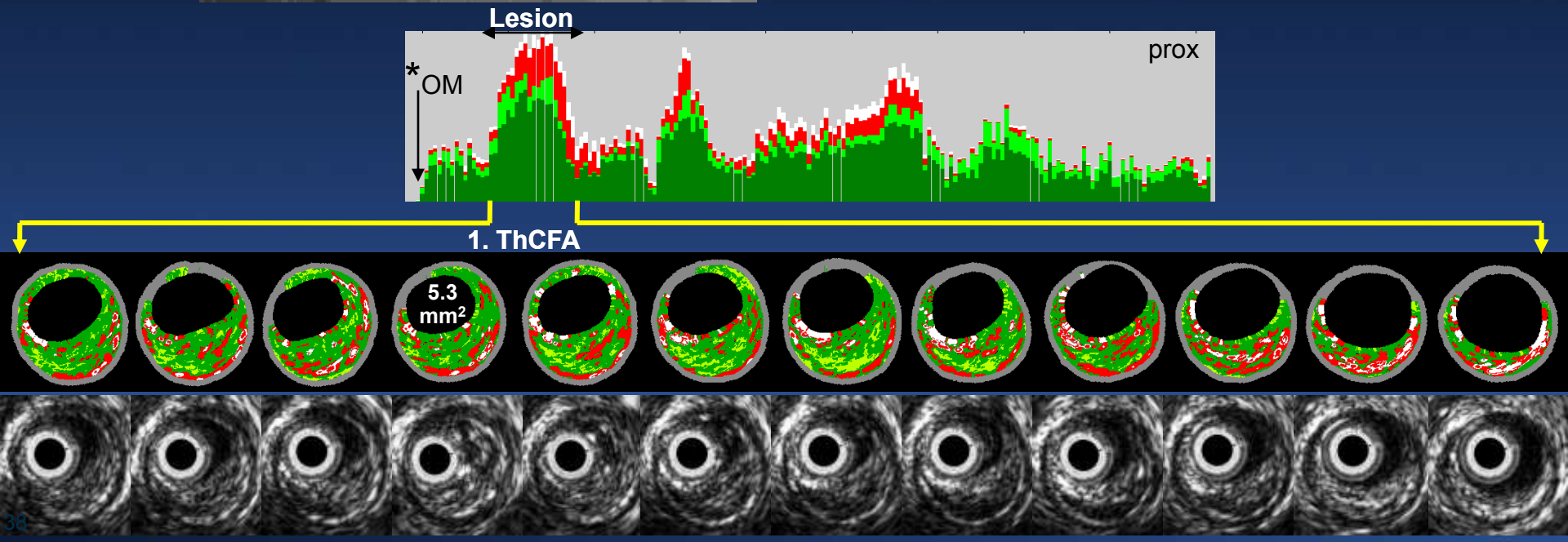
QCA PLCX DS 71.3%

# PROSPECT 82910-012: Index 2/13/06




## Baseline PLCX

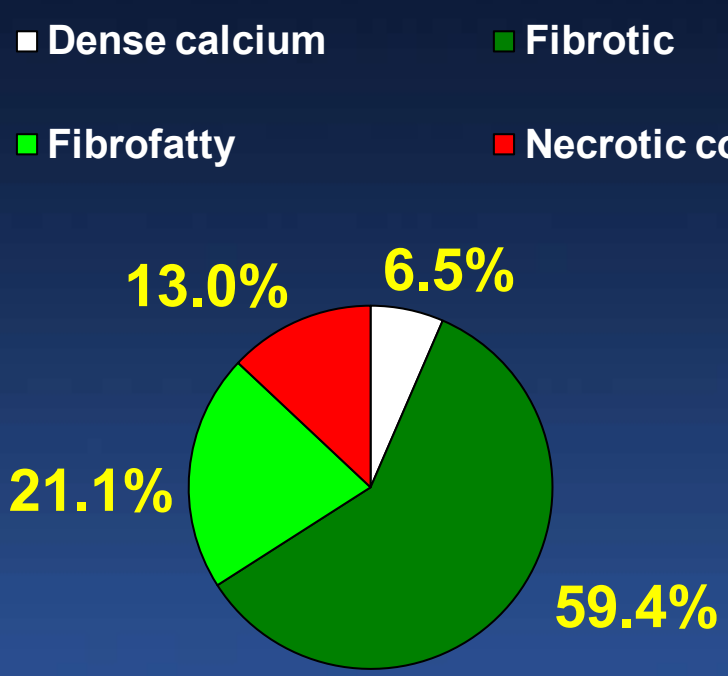
**QCA: RVD 2.82 mm,**
**DS 28.6%, length 6.8 mm**
**IVUS: MLA 5.3 mm²**
**VH: ThCFA**



# PROSPECT: Imaging Summary

## Virtual histology (N=2811 lesions in 611 pts)

### - Mean plaque composition-



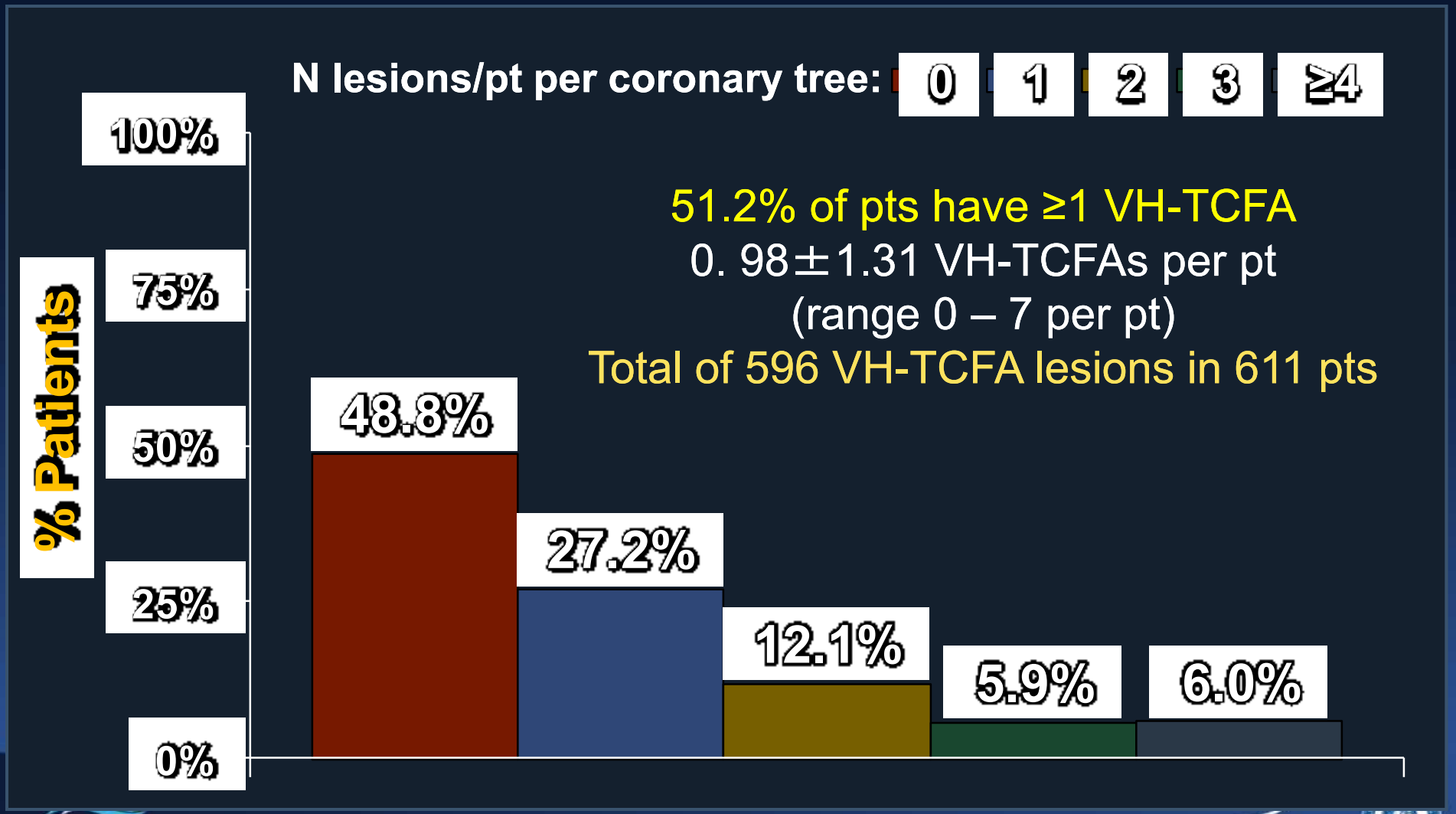

| Plaque subtype | N=2811 |
|---|---|
| Fibrotic | 2.5% |
| Fibrocalcific | 1.2% |
| PIT | 35.9% |
| Fibroatheroma | 57.4% |
| - Thick cap | 36.2% |
| - VH-TCFA | 18.9% |
| - Single, - Ca | 5.2% |
| - Single, + Ca | 0.5% |
| - Multiple, - Ca | 9.5% |
| - Multiple, + Ca | 6.1% |



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

# PROSPECT: Imaging Summary

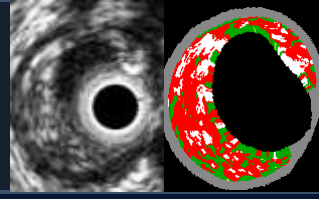
## Per patient incidence of VH-TCFAs

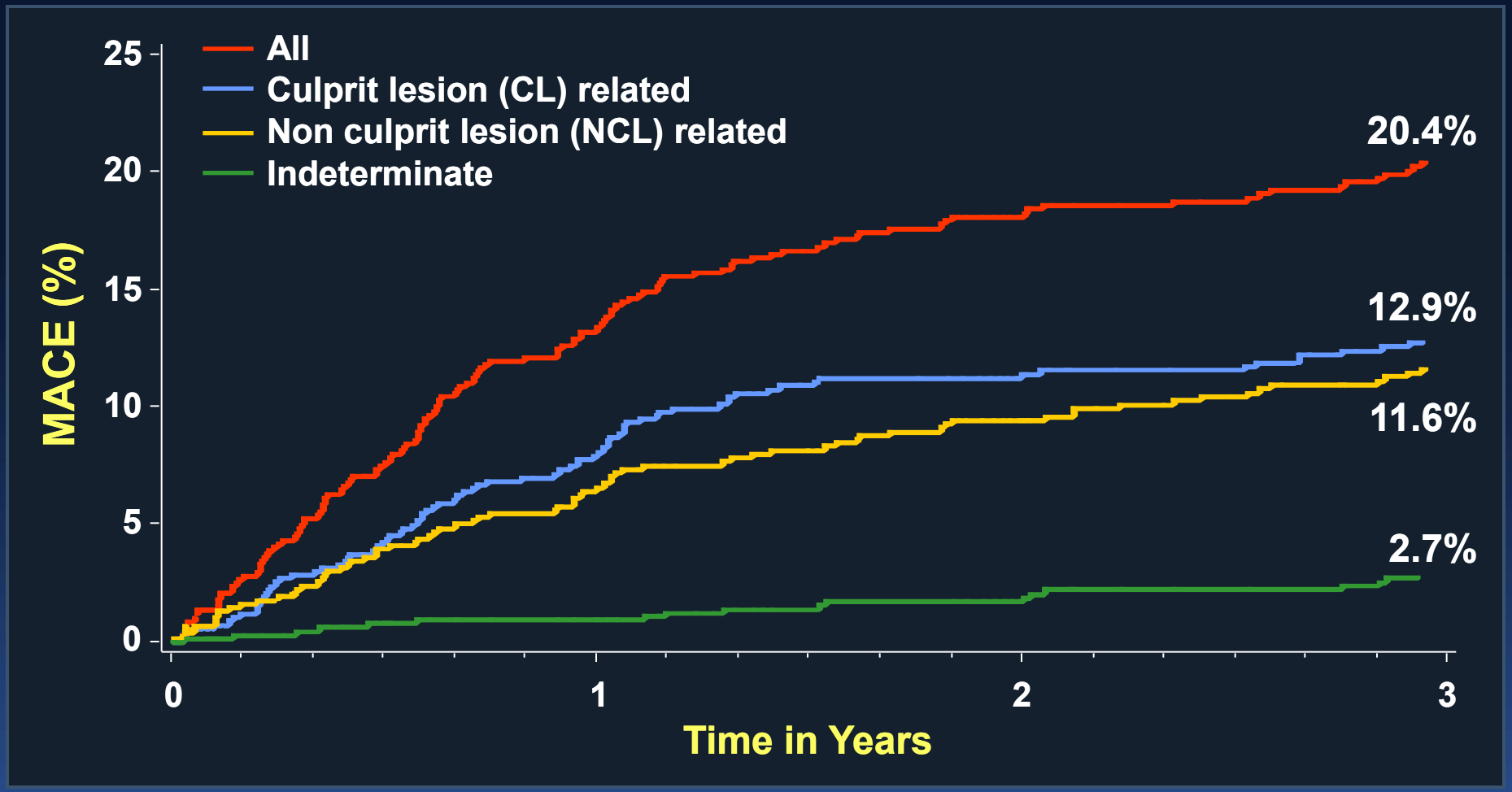





Stone GW et al. NEJM 2011;364:226-35

# 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 |

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

# PROSPECT: MACE

## 3-year follow-up, hierarchical

| | All | Culprit lesion related | Non culprit lesion related | Indeter-minate |
|---|---|---|---|---|
| Cardiac death | 1.9% (12) | 0.2% (1) | 0% (0) | 1.7% (11) |
| Cardiac arrest | 0.3% (2) | 0.3% (2) | 0% (0) | 0% (0) |
| MI (STEMI or NSTEMI) | 2.7% (17) | 1.7% (11) | 1.0% (6) | 0.2% (1) |
| Rehospitalization for unstable or progressive angina | 15.4% (101) | 10.4% (69) | 10.7% (68) | 0.8% (5) |
| 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: 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 |
|---|---|---|
| VH-TCFA | 2.78 [1.52, 5.08] | <0.001 |
| $PB_{MLA}$ (per 10%↑) | 2.39 [1.60, 3.57] | <0.001 |
| MLA (per 1 $mm^2$↓) | 1.44 [1.16, 1.79] | 0.001 |

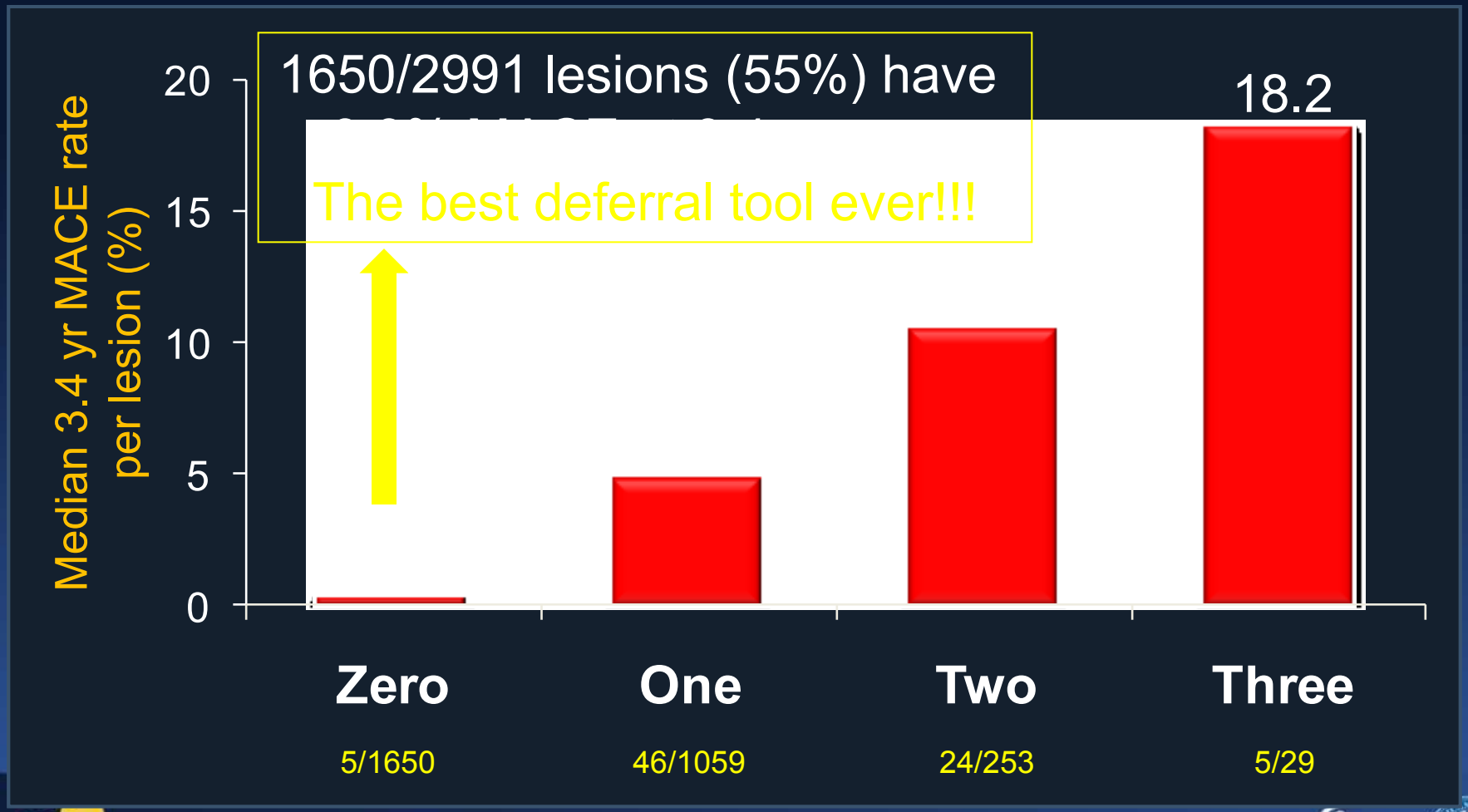
Final variables entered into the model: minimal luminal area (MLA) ≤4.0 $mm^2$; plaque burden at the MLA ($PB_{MLA}$) ≥70%; external elastic membrane at the MLA ($EEM_{MLA}$) <median (14.1 $mm^2$); lesion length ≥median (11.2 mm); distance from ostium to MLA ≥median (30.4 mm); remodeling index ≥median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

C-statistic 0.84

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

# PROSPECT: Correlates of Non-Culprit Lesion Related Events

Number of factors present: $PB_{MLA}$ ≥70%, MLA ≤4.0mm$^2$ or TCFA




PB = plaque burden at the MLA

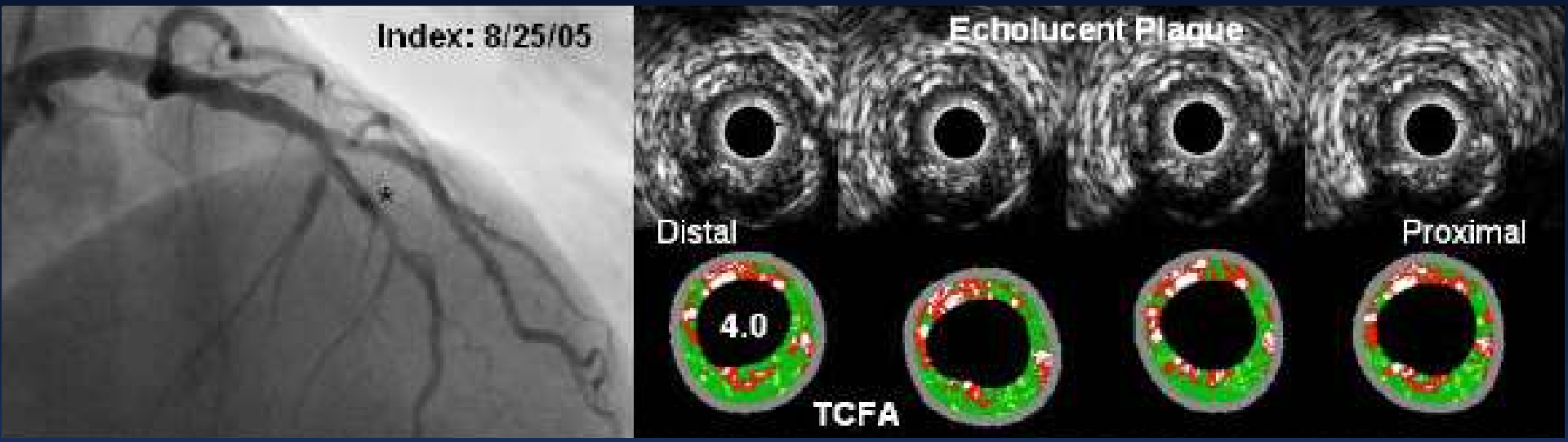
Stone GW et al. NEJM 2011;364:226-35

# PROSPECT Case Example

Would you treat this lesion?

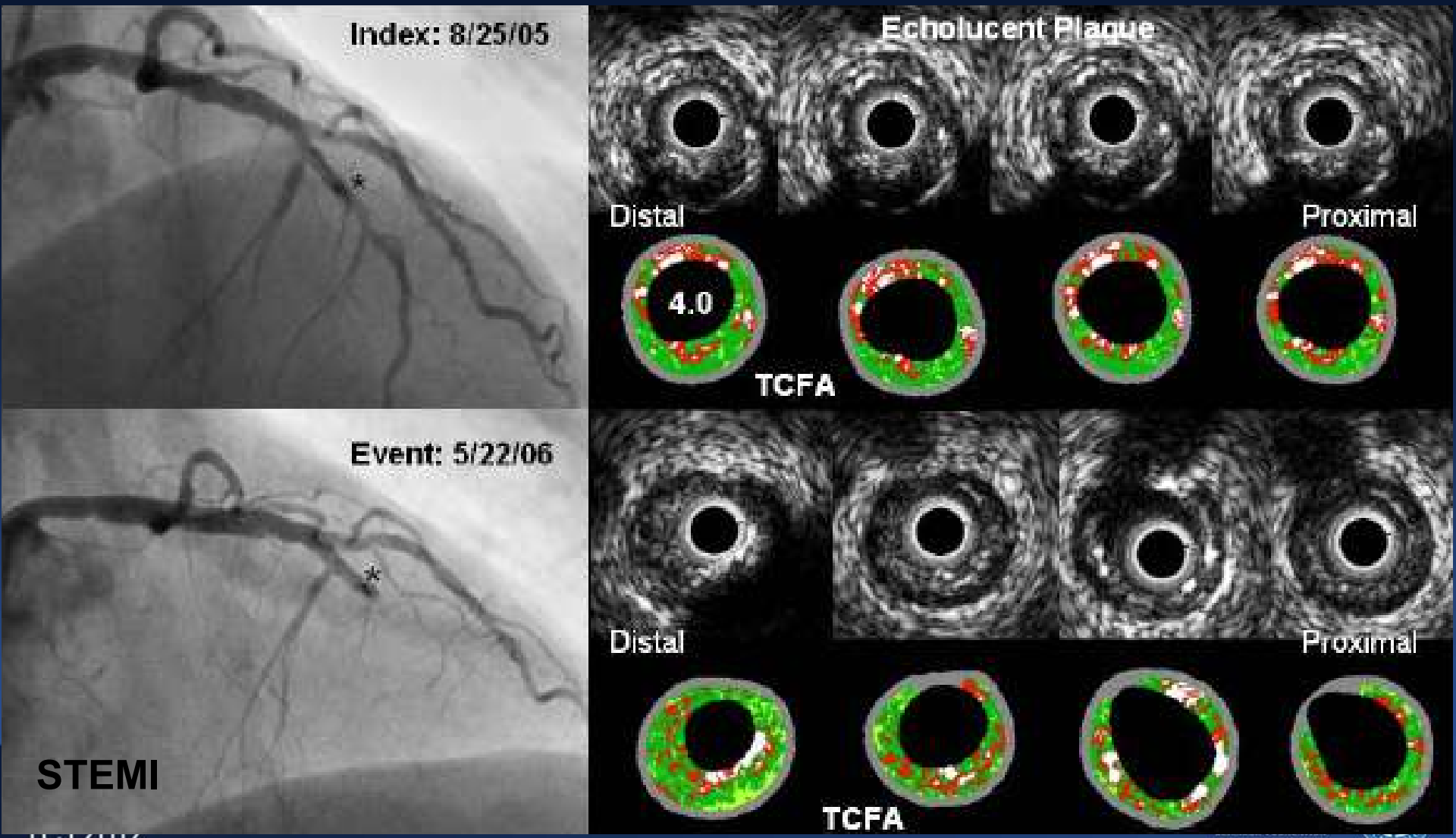
# PROSPECT Case Example

MLA 4.0 $mm^2$; plaque burden 62%; TCFA; FFR ??



# PROSPECT Case Example

## MLA 4.0 $mm^2$; plaque burden 62%; TCFA; FFR ??



# Can We Identify Vulnerable Plaque?

**YES.** Using gray-scale and radiofrequency IVUS, we can identify plaques that place pts at risk for future adverse cardiovascular events, some of which represent severe but angiographically unrecognized disease, and others of which are true atherosclerotic plaques prone to rupture, thrombosis and rapid lesion progression.

# PROSPECT: Implications

- Following successful and uncomplicated PCI in pts with ACS who undergo careful clinical FU, is 3-vessel VH-IVUS to identify and prophylactically stent non-culprit lesions at high risk for future MACE warranted based on PROSPECT?
  - ▸No
    1. The prevalence of high-risk lesions is relatively low (~1 in 4 pts).
    2. 3-vessel imaging is not risk-free (1.6% major complication rate).
    3. When high-risk lesions become symptomatic they usually present with angina and not death or MI.
  - ▸This suggests that absent a randomized trial, optimal medical therapy and close follow-up is more appropriate.

# PROSPECT: Implications

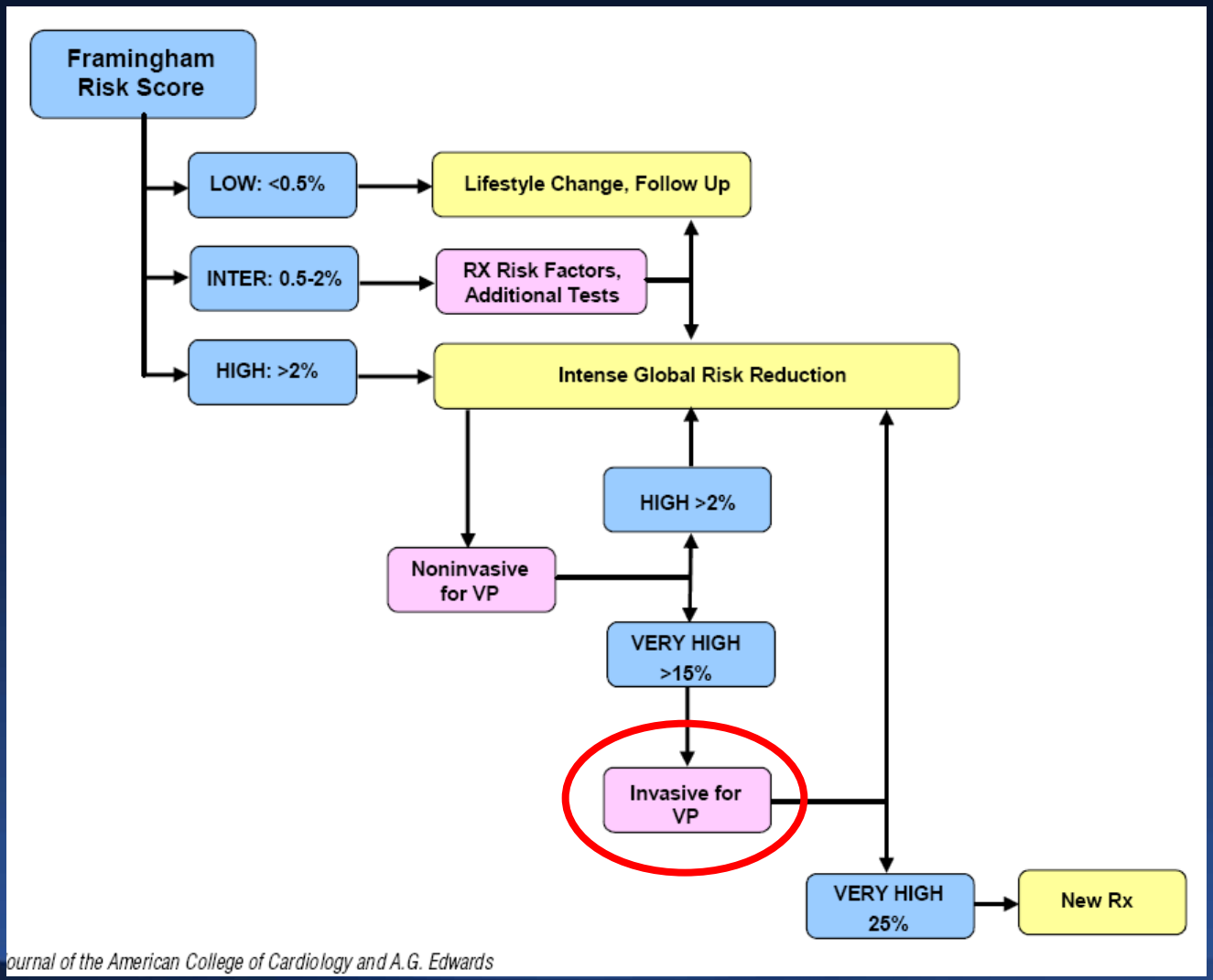
- What if during routine IVUS-guided stenting (e.g. in the MLAD), a high-risk non ischemia-producing lesion happens to be found (e.g. a TCFA with PB of 75% in the PLAD) – is prophylactic stenting justified?
  - No
    1. As long as the patient is medically compliant and is closely followed, when high-risk lesions become symptomatic they usually present with progressive angina and not death or MI.
  - A randomized controlled trial is required to demonstrate the safety and efficacy of prophylactic stenting of non ischemia-producing lesions before this practice can be recommended.

# PROSPECT: Implications

- So where should our efforts for future investigation be focused?
  - The prognosis for pts with ACS after successful PCI who are medically compliant is favorable.
  - However, millions of persons per year who have not been diagnosed with CAD and are not receiving optimal medical therapy die, arrest or develop MI every year.

▸This suggests that future investigation should focus on identifying asymptomatic or minimally symptomatic pts with large plaque burden, small MLA and TCFAs through noninvasive screening (e.g. MSCT), for intensive medical therapy and possibly invasive imaging and Rx.

# Braunwald algorithm for VP screening and Rx remains current




Braunwald E. JACC 2006;47;C101-C103