

Debate: Does Morphology Predict Future Events?

Con: No, it is Not Enough

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Disclosure

I have nothing to disclose

High-Risk Non-Invasive Tests (Annual Mortality >3%)

- LVEF < 35%
- High-risk Treadmill score
- Reversible large perfusion defect
- > Moderate sized, multiple defects
- LV dilatation
- RWMA on low-dose dobu-echo

| | | | | | |
|---------------------------|--------------------------------|-------------------------------|----------------------------|------------------------------|-----------------------------|
| Class III or IV Max Rx | A | A | A | A | A |
| Class I or II Max Rx | A | A | A | A | A |
| Asymptomatic Max Rx | U | A | A | A | A |
| Class III or IV No/min Rx | A | A | A | A | A |
| Class I or II No/min Rx | U | A | A | A | A |
| Asymptomatic No/min Rx | U | U | A | A | A |
| | | | | | |
| Coronary Anatomy | CTO of 1 vz.; no other disease | 1-2 vz. disease; no Prox. LAD | 1 vz. disease of Prox. LAD | 2 vz. disease with Prox. LAD | 3 vz. disease; no Left Main |

Low-Risk Non-Invasive Tests (Annual Mortality <1%)

- Low-risk treadmill score
- Normal or small perfusion defect
- Normal stress echo

| | | | | | |
|---------------------------|--------------------------------|-------------------------------|----------------------------|------------------------------|-----------------------------|
| Class III or IV Max Rx | U | A | A | A | A |
| Class I or II Max Rx | U | U | A | A | A |
| Asymptomatic Max Rx | I | I | U | U | U |
| Class III or IV No/min Rx | I | U | A | A | A |
| Class I or II No/min Rx | I | I | U | U | U |
| Asymptomatic No/min Rx | I | I | U | U | U |
| | | | | | |
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Patel et al. Circulation 2009;119:1330-52

Benefit of FFR-guided PCI and safety for deferral of PCI (FFR >0.75-0.80) has been established

7-Year Follow-up Outcomes FFR-Guided vs. Angiography-Guided PCI

Registry of 7,358 patients referred for PCI at the Mayo Clinic (2002-2009), 14.8% received FFR guidance

- Deferred PCI after FFR lowered **MI** risk (HR 0.46; 95% CI 0.26-0.82; p=0.008)
- FFR guided group had a trend for lower **death/MI** (HR 0.85; 95% CI 0.71-1.01; p=0.06)
- After excluding FFR 0.75-0.80 and deferring PCI, FFR led to reduced **death/MI** (HR 0.80; 95% CI 0.66-0.96; p=0.02)

Li J, et al. Eur Heart J 2013;Epub ahead of print

Current Guideline

2010 ESC Class I *Level of Evidence A*

FFR-guided PCI is recommended for detection of ischemia-related lesions when objective evidence of vessel-related ischemia is not available

2009 AHA/ACC Class IIa *Level of Evidence A*

FFR is reasonable to assess intermediate lesion (30-70% DS) and can be useful to guide revascularization in stable IHD

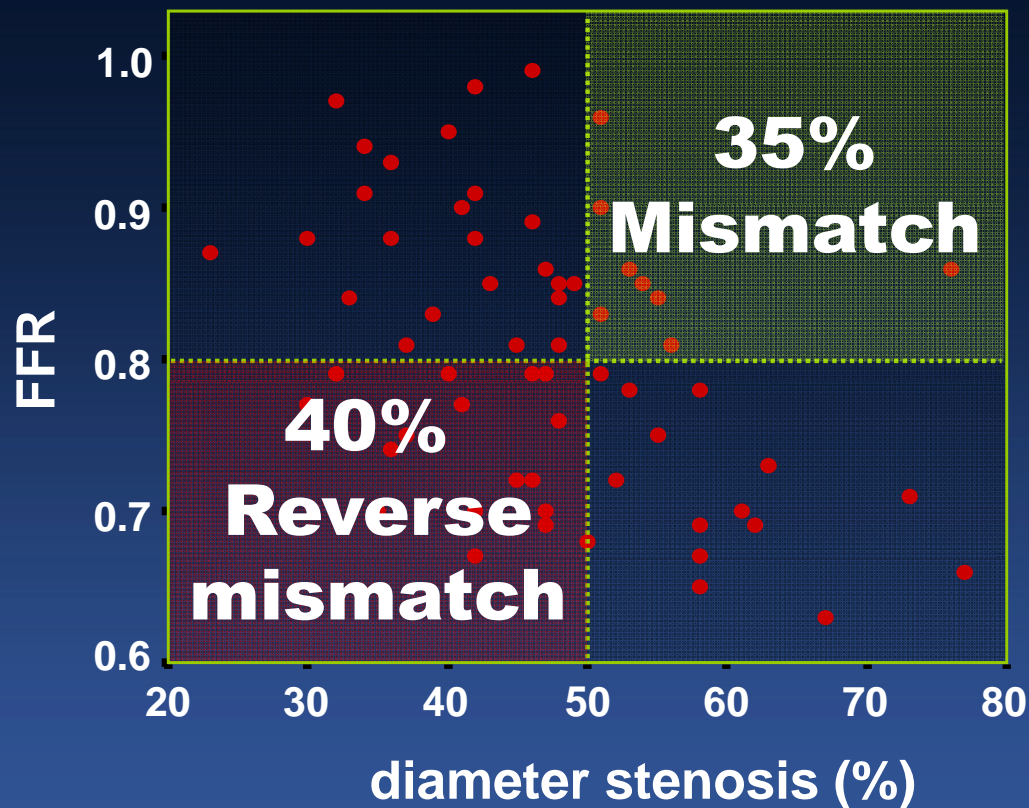
Title: Does Morphology Predict Future Events?

1. Can morphological stenosis severity predict the functional significance?
2. Can morphological characteristics of coronary plaque predict future events?

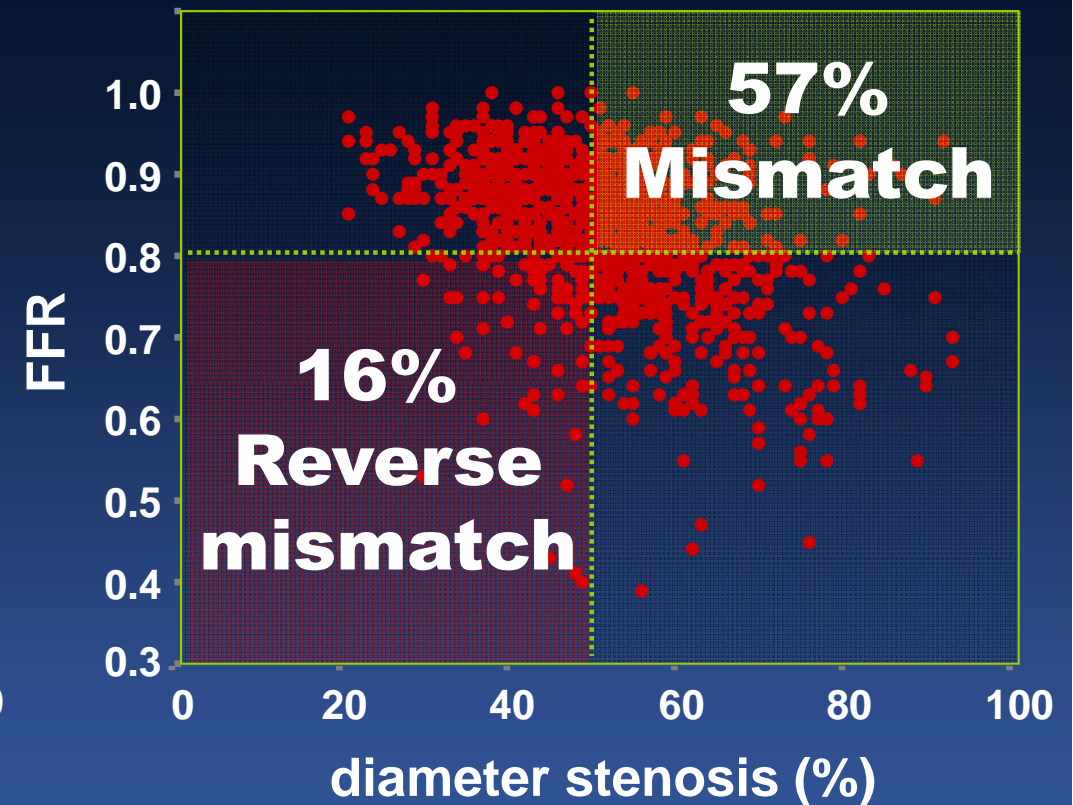
1000 Consecutive Patients

(1129 lesions with DS >30%) who underwent IVUS and FFR

63 LM lesions



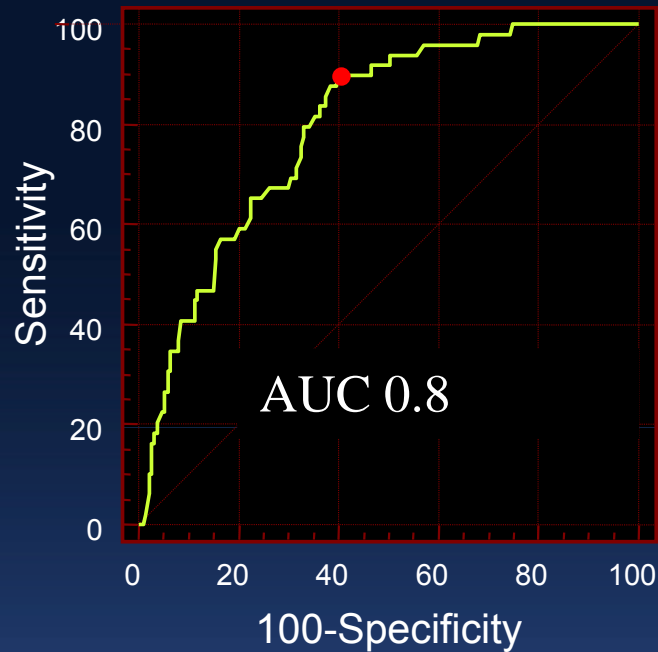
1066 Non-LM lesions



Park et al. JACC interv 2012;5:1029-36

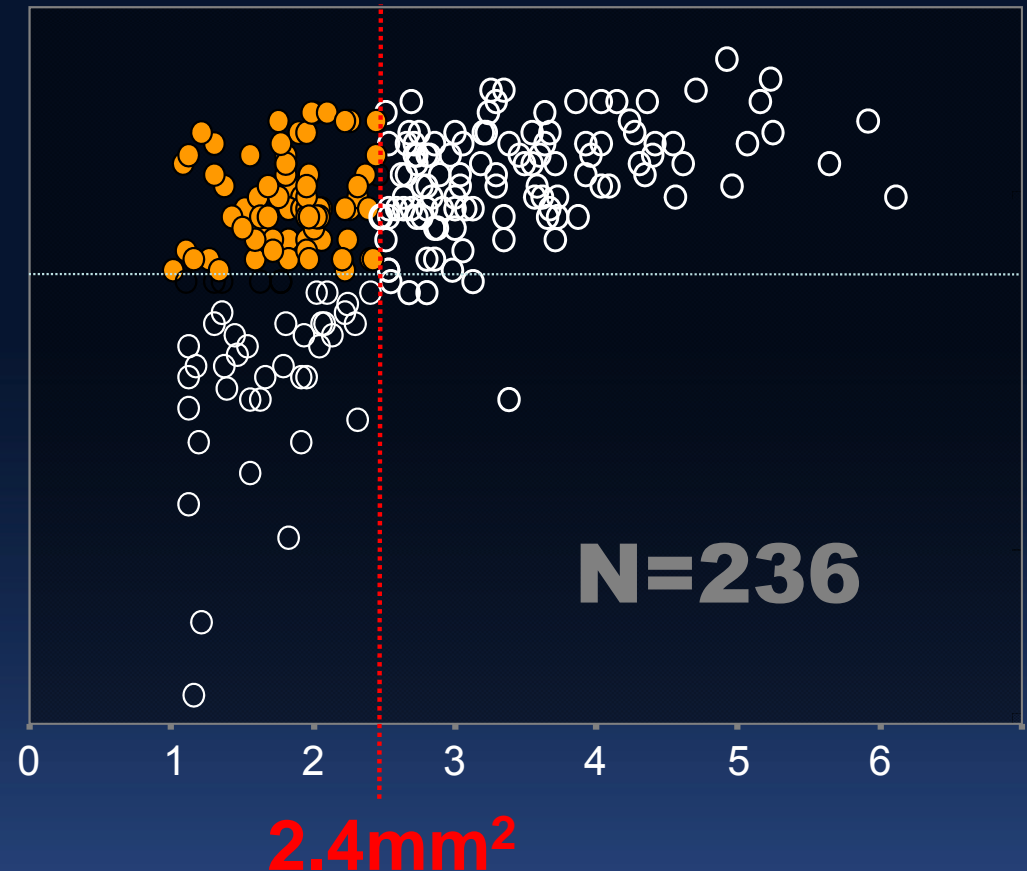
AMC Data, ClinicalTrials.gov NCT01366404

MLA 2.4mm²



Sensitivity 90%
Specificity 60%
PPV 37%
NPV 96%
Accuracy 68%

FFR
0.80



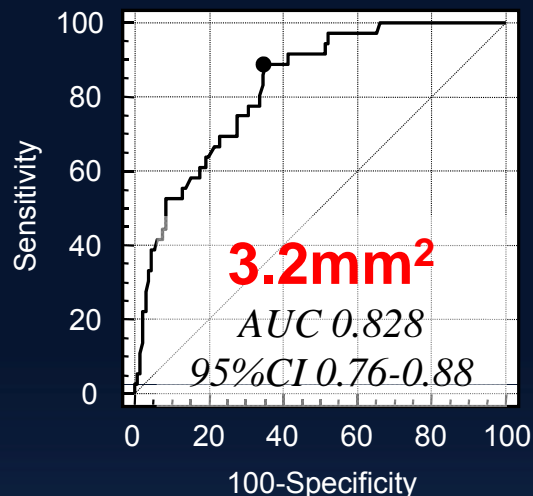
40% of lesions with normal FFR
were targets for unnecessary PCI

Kang et al. Circ Cardiovasc Interv 2011;4:65-71

| | N | FFR | MLA | AUC | Sens | Spec | PPV | NPV | Accura |
|-------------------------------|----|------|------------|-----|------|------|-----|-----|------------|
| Takaki (1999 Circ) | 51 | 0.75 | 3.0 | — | 83% | 92% | — | — | — |
| Briguori (2001 AJC) | 53 | 0.75 | 4.0 | — | 92% | 56% | 38% | 96% | 64% |

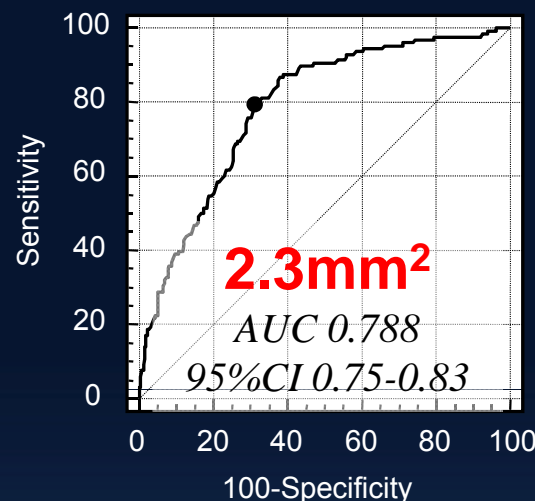
| | | | | | | | | | |
|--------------------------------|-----|------|---------------------|------|-----|-----|-----|-----|------------|
| Ben-Dor (2012 *) | 205 | 0.80 | 3.09 | 0.73 | 69% | 72% | — | — | 70% |
| Kang (2011 Circ int) | 236 | 0.80 | 2.4 | 0.80 | 90% | 60% | 37% | 96% | 68% |
| Kang (2012 AJC) | 784 | 0.80 | 2.4 | 0.77 | 84% | 63% | 48% | 90% | 69% |
| Koo (2011 JACC int) | 267 | 0.80 | 2.75 | 0.81 | 69% | 65% | 27% | 81% | 67% |
| Gonzalo (2012 JACC) | 47 | 0.80 | 2.36 IVUS | 0.63 | 67% | 65% | 67% | 65% | 66% |
| Gonzalo (2012 JACC) | 61 | 0.80 | 1.95 OCT | 0.70 | 82% | 63% | 66% | 80% | 72% |

RLD>3.5mm [161]



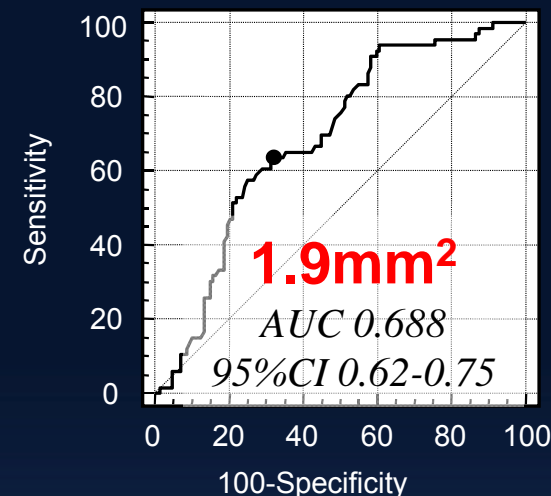
Sens 89% Spec 65%

RLD 2.75–3.5mm [439]



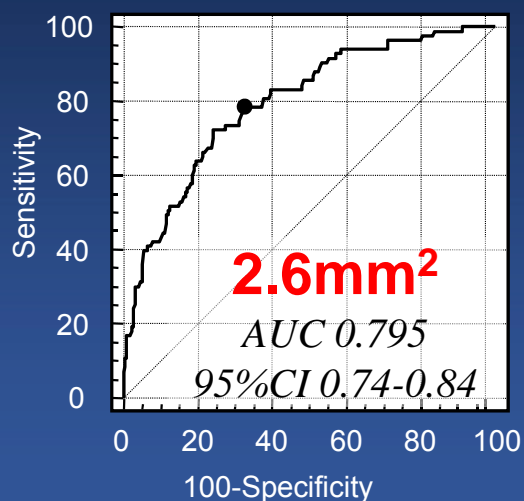
Sens 80% Spec 68%

RLD<2.75mm [184]



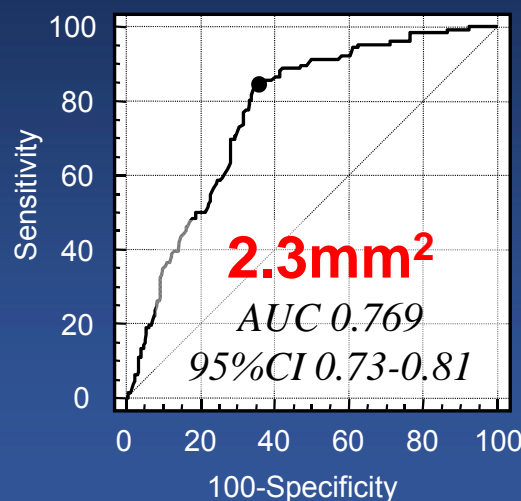
Sens 64% Spec 69%

Proximal [285]



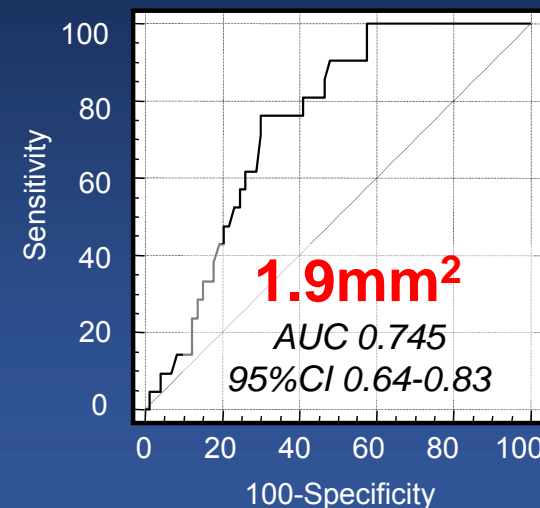
Sens 78% Spec 68%

Mid [405]



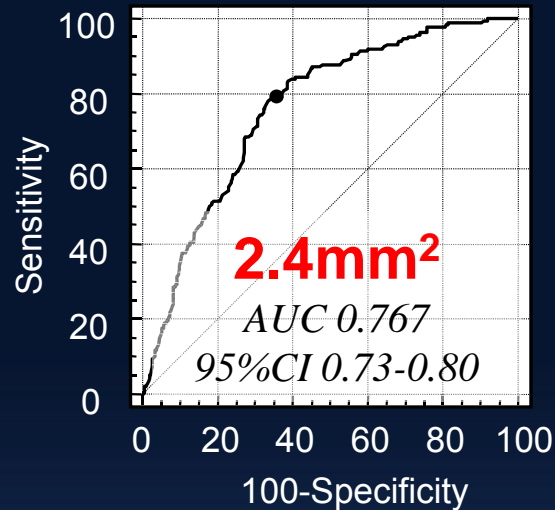
Sens 84% Spec 65%

Distal [94]



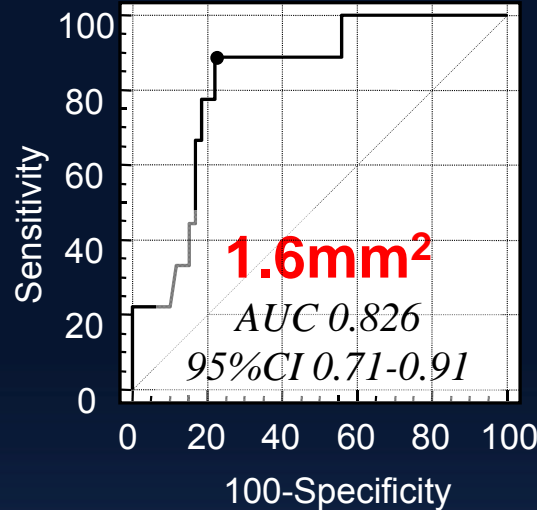
Sens 76% Spec 70%

LAD [528]



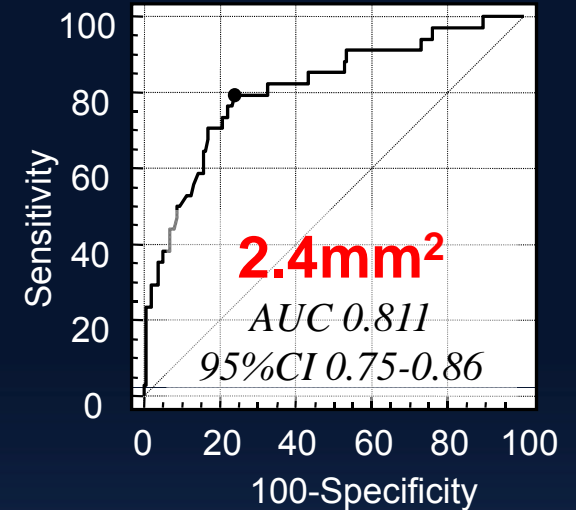
Sens 80% Spec 64%

LCX [68]



Sens 89% Spec 77%

RCA [188]



Sens 79% Spec 77%

All Subgroup-specific MLAs Showed Diagnostic Accuracies <70-75%

Kang et al. Am J Cardiol 2012;109:947-53

Why Mismatch Between MLA-FFR?

| | Beta | p-value | Adjusted OR | 95% CI |
|--|--------|---------|-------------|---------------|
| MLA<2.4 but FFR≥0.8 “Mismatch” | | | | |
| Female gender | 0.371 | 0.048 | 1.450 | 1.003 – 2.095 |
| LAD location | -0.406 | 0.027 | 0.666 | 0.465 – 0.954 |
| Reference lumen ø | -1.209 | <0.001 | 0.298 | 0.204 – 0.437 |
| Distal segment | 0.704 | 0.002 | 2.021 | 1.293 – 3.159 |
| MLA≥2.4 but FFR<0.8 “Rev-mismatch” | | | | |
| Age | -0.062 | <0.001 | 0.940 | 0.909 – 0.972 |
| LAD location | 0.813 | 0.071 | 2.256 | 0.932 – 5.460 |
| Plaque rupture | 2.410 | <0.001 | 11.138 | 4.886 – 25.39 |

Age, female, LAD location, distal segment, plaque rupture, reference lumen ø

AMC Data, ClinicalTrials.gov NCT01366404

Multivariable Analysis Predicting FFR

in 700 LAD lesions of 700 patients

**Including age, female, body surface area, smoking, angiographic DS, minimal lumen diameter, lesion length, IVUS-MLA, plaque burden, averaged reference EEM area and %area stenosis, †addition of left ventricular mass*

| | Total (700 patients)* | | | 608 patients with echo data† | | |
|-----------------|-----------------------|--------------|-----------------------|------------------------------|------------------|-----------------------|
| | β | p value | 95% CI | β | p value | 95% CI |
| Age | 0.119 | 0.001 | 0.000–0.002 | 0.192 | <0.001 | 0.001–0.002 |
| BSA | -0.111 | 0.002 | -0.101– -0.024 | | | |
| LV mass | | | | -0.121 | <0.001 | -0.001 – 0.000 |
| Angiographic DS | -0.185 | <0.001 | -0.002 – -0.001 | -0.190 | <0.001 | -0.002 – -0.002 |
| Lesion length | -0.110 | 0.001 | -0.001 – 0.001 | -0.077 | 0.027 | -0.001 – 0.000 |
| IVUS-MLA | 0.312 | <0.001 | 0.022 – 0.035 | 0.294 | <0.001 | 0.019 – 0.032 |
| Plaque burden | -0.115 | 0.002 | 0.001 – 0.000 | -0.157 | <0.001 | -0.002 – -0.001 |

Kang et al. JACC Cardiovasc Interv 2013 in press

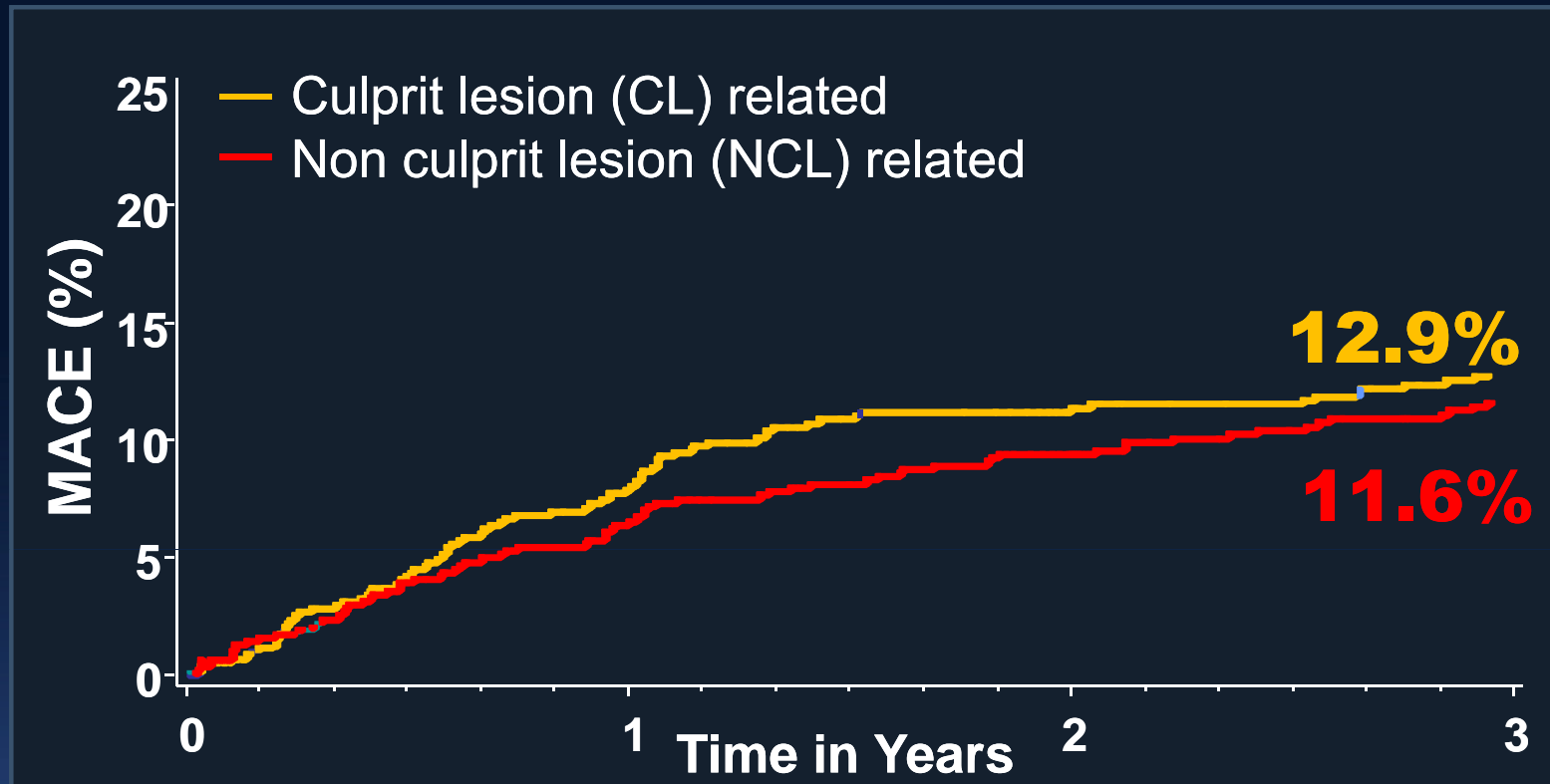
Title: Does Morphology Predict Future Events?

1. Can morphological stenosis severity predict the functional significance?

→ **No!**

2. Can morphological characteristics of coronary plaque predict future events?

PROSPECT 3-year MACE (N=697 ACS pts.)



*MACE = cardiac death, arrest, MI, rehospitalization for unstable/ progressive angina

| | HR [95% CI] | p value |
|--------------------------------|-------------------|---------|
| PB_{MLA} ≥70% | 5.03 [2.51-10.11] | <0.001 |
| VH-TCFA | 3.35 [1.77-6.36] | <0.001 |
| MLA ≤4.0 mm² | 3.21 [1.61-6.42] | 0.001 |

Stone G et al. *N Engl J med* 2011;364:226-35

Cumulative Rates of 3-year MACE

| | Culprit -related | Nonculprit -related | Indeterminate events | All events |
|---|---------------------|------------------------|-------------------------|-------------|
| Composite end point | 12.9% (83) | 11.6% (74) | 2.7% (17) | 20.4% (13) |
| Cardiac death, arrest, MI | 2.2% (14) | 1.0% (6) | 1.9% (12) | 4.9% (31) |
| ▪ Cardiac death | 0.2% (1) | 0 | 1.8% (11) | 1.9% (12) |
| ▪ Cardiac arrest | 0.3% (2) | 0 | 0.2% (1) | 0.5% (3) |
| ▪ Myocardial infarction | 2.0% (13) | 1.0% (6) | 0.3% (2) | 3.3% (21) |
| ▪ Rehospitalization for unstable/ progressive angina | 11.5% (74) | 10.8% (69) | 0.8% (5) | 17.5% (113) |
| Revascularization | 10.9% (70) | 10.5% (67) | 0 | 17.1% (110) |

$143 - 108 = 35$, Thus, 35 (51%) of 69 non-culprit events were overlapped with culprit-related events

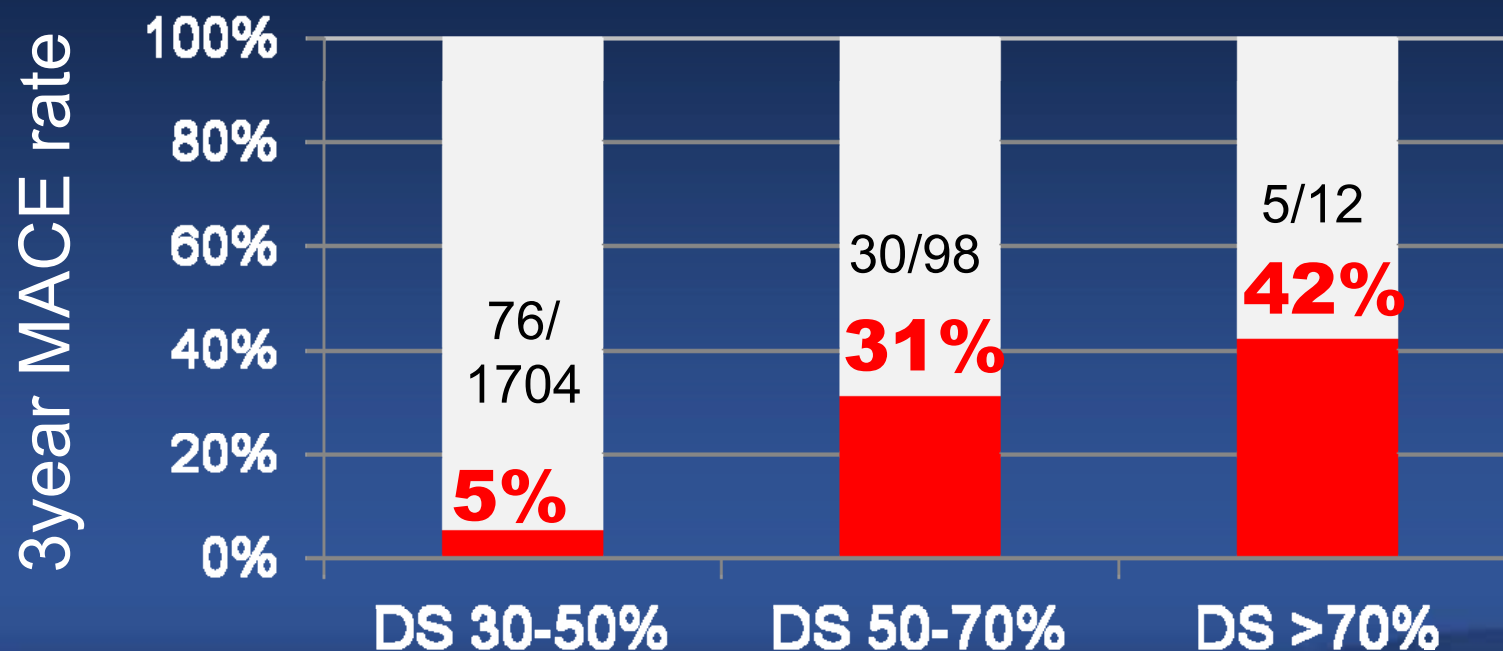
Characteristics of **1814 Non-culprits, 697 patients**

- All ACS patients
- Only 110 (6%) lesions had angiographic DS >50%
- Only 283 (9%) lesions had plaque burden $\geq 70\%$
- Prevalence of TCFA per patient: 46.7%
- Prevalence of TCFA per lesion: 21.6%
- Median IVUS-MLA 5.9 mm² (IQR 4.3–8.1mm²)
- Median lesion length 11.2 mm (IQR 5.8–21.7mm)

In patients with mild coronary stenosis
(***functionally insignificant*** in majority),
cardiac death and MI are ***extremely rare***

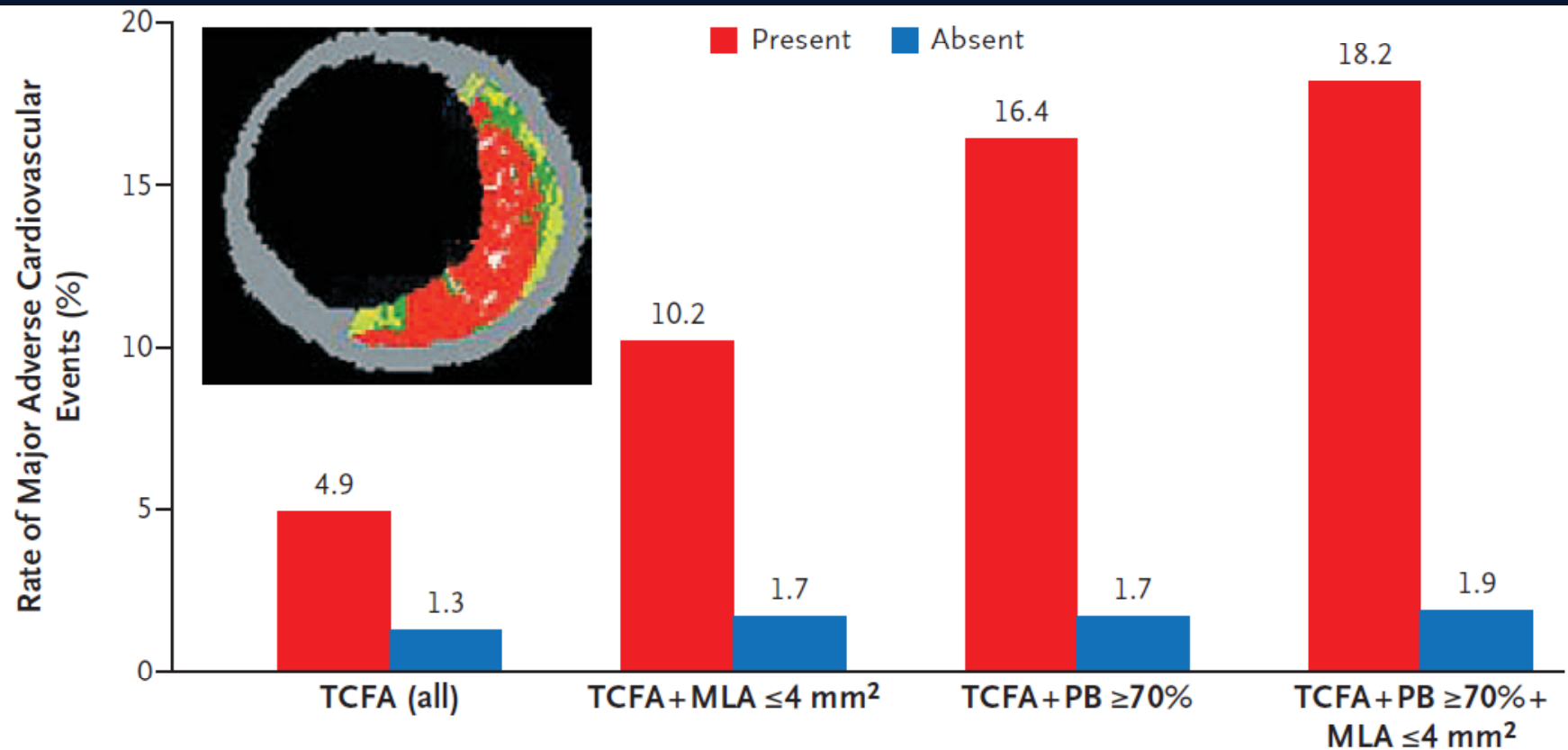
“Although nonculprits responsible for MACE were frequently angiographically mild, most were TCFA, fibroatheromas or characterized by a large plaque burden, a small MLA”

| | N | QCA DS 30-50% | QCA DS 50-70% | QCA DS >70% |
|----------|------|---------------|---------------|-------------|
| MACE (+) | 106 | 76 (72%) | 30 (28%) | 5 (5%) |
| Total | 1814 | 1704 (94%) | 98 (5.5%) | 12 (0.5%) |



TCFAs Predict Future Death or MI?

TCFAs Predict Disease Progression?



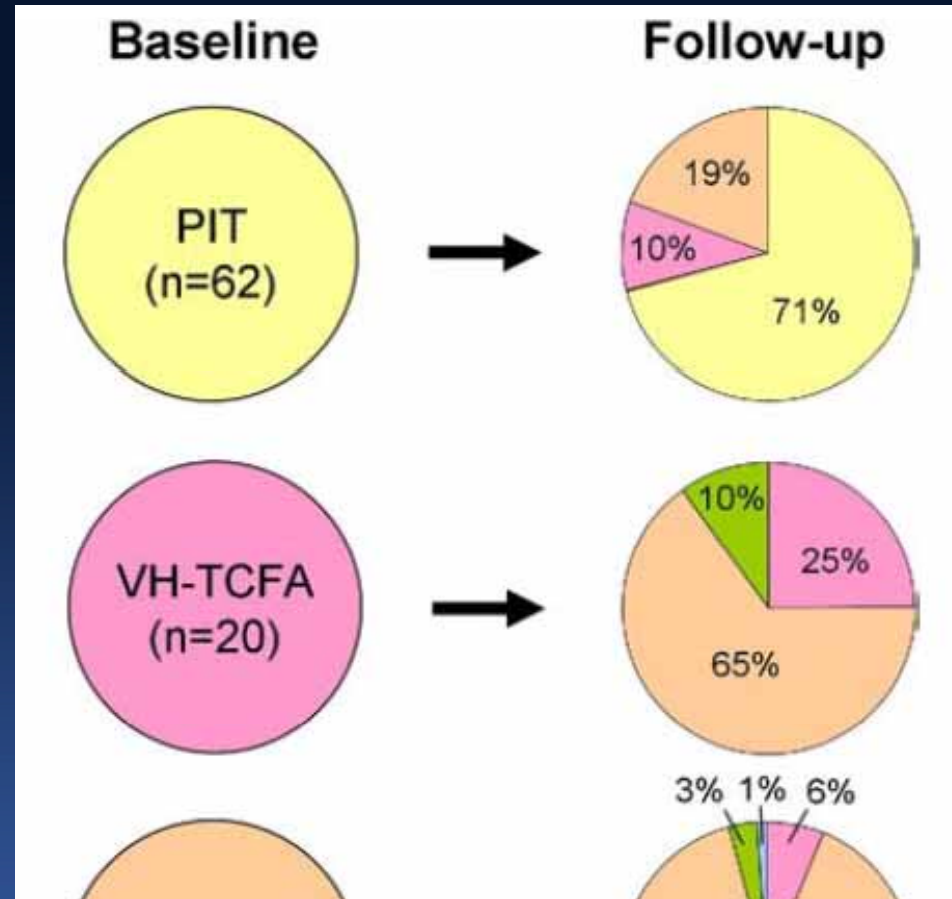
| | | | | |
|------------------------------|------------------|-------------------|--------------------|--------------------|
| Lesion hazard ratio (95% CI) | 3.90 (2.25–6.76) | 6.55 (3.43–12.51) | 10.83 (5.55–21.10) | 11.05 (4.39–27.82) |
| P value | <0.001 | <0.001 | <0.001 | <0.001 |
| Prevalence (%) | 46.7 | 15.9 | 10.1 | 4.2 |

Stone G et al. *N Engl J med* 2011;364:226-35

Current TCFA's Predict Future TCFA?

Dynamic Natural History of Plaque Vulnerability

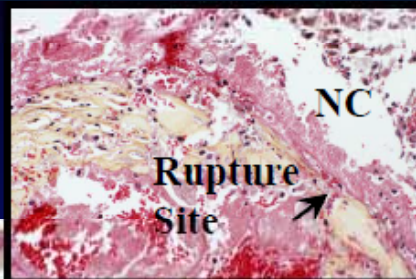
(Global VH-IVUS Registry of CRF, NY)



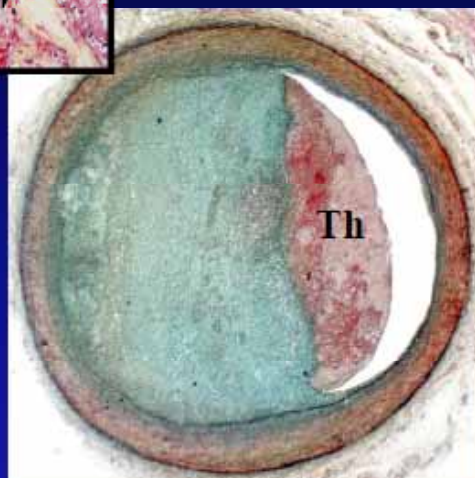
Can the presence of TCFA at a given time point predict the entire clinical course?

Are Patients Without Current TCFA Free From Future Events?

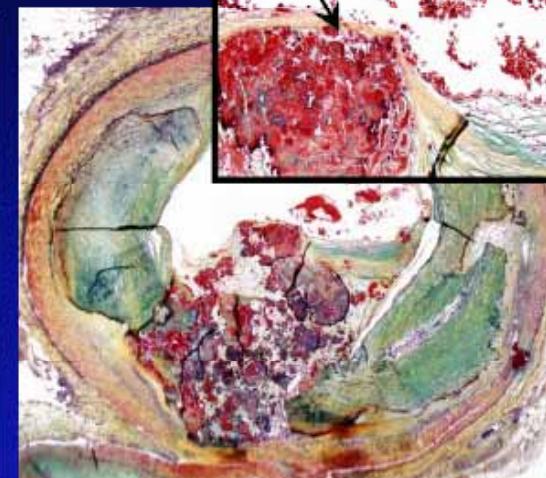
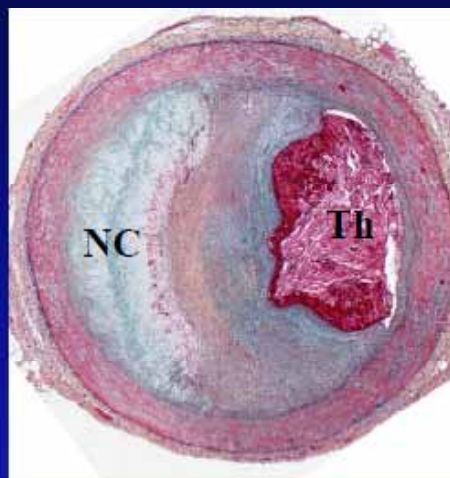
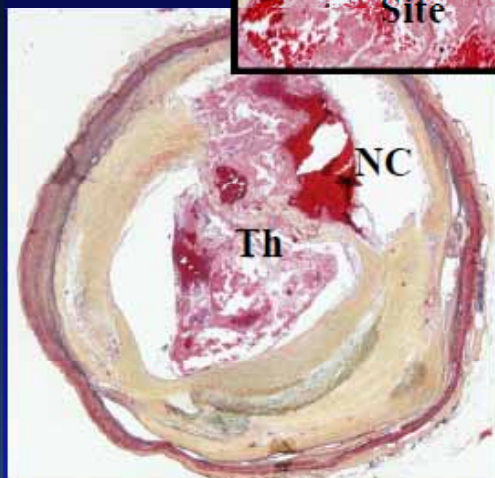
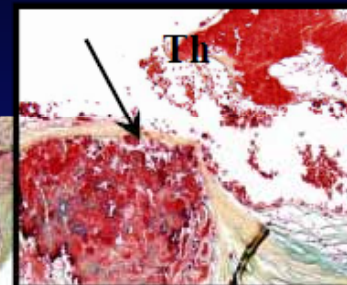
Rupture



Erosion



Calcified nodule



60% thrombi in SCD
M>F, Older, Ca⁺⁺
Eccentric = concentric
Greater % stenosis
Macs, T cells,
HLA-DR

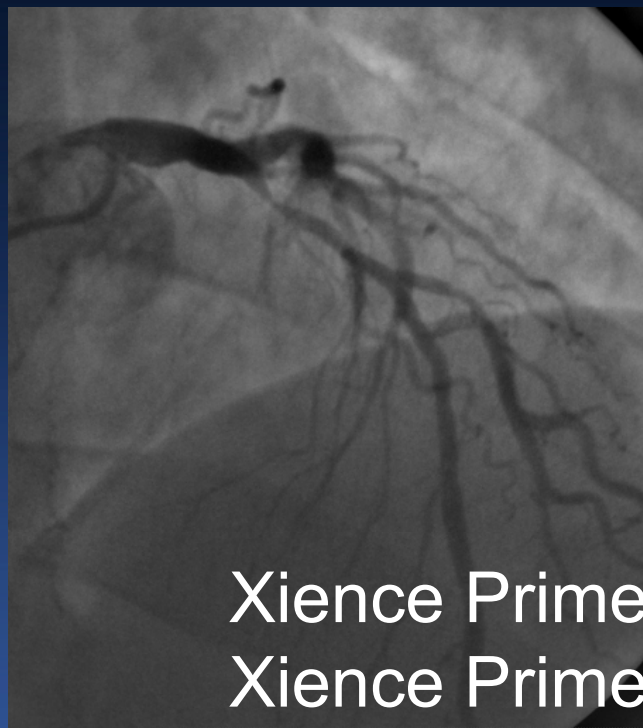
30-35% thrombi in SCD
M=F, younger
Usually eccentric
Lesser % stenosis
SMC rich, proteoglycans

2-7% thrombi in SCD,
calcified plates,
M>F, older,
mid RCA & LAD
Usually eccentric
Stenosis variable

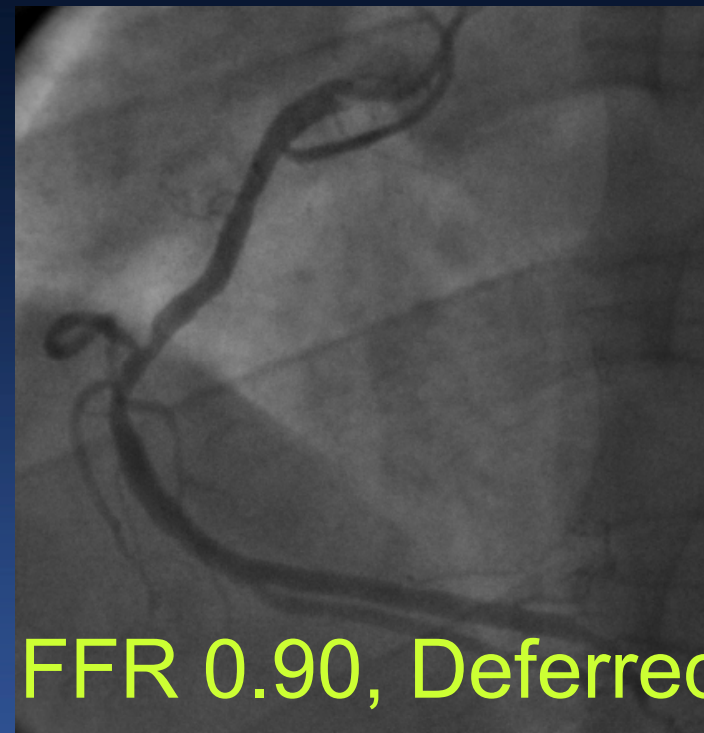
TCFA is a prerequisite for plaque rupture, not for SCD

CASE 42 year-old Male

- Hypertension, hyperlipidemia, smoker, obesity
- Unstable angina



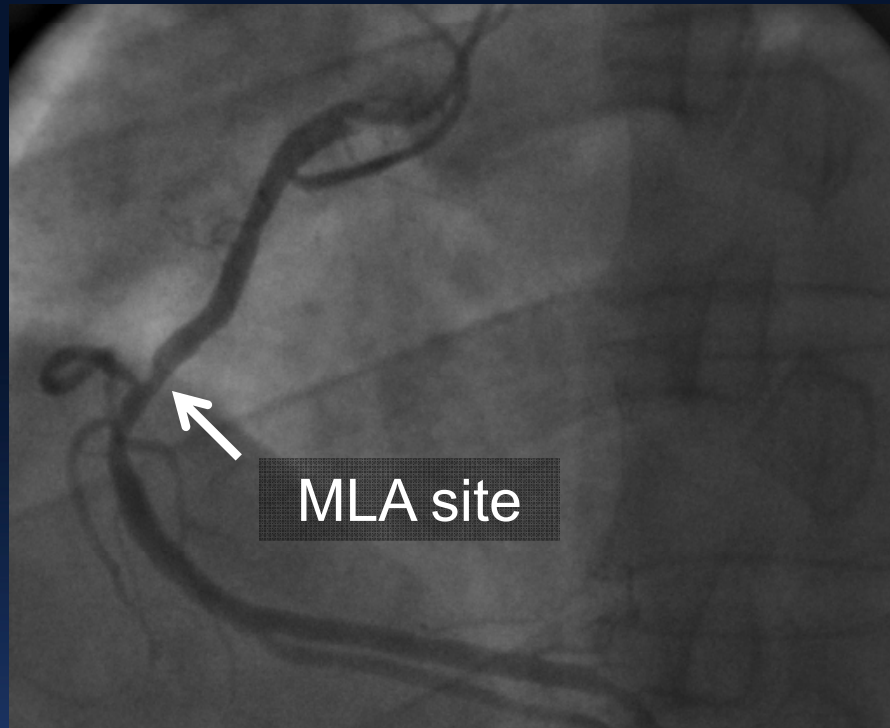
Xience Prime 3.5 x 23mm
Xience Prime 3.0 x 38mm



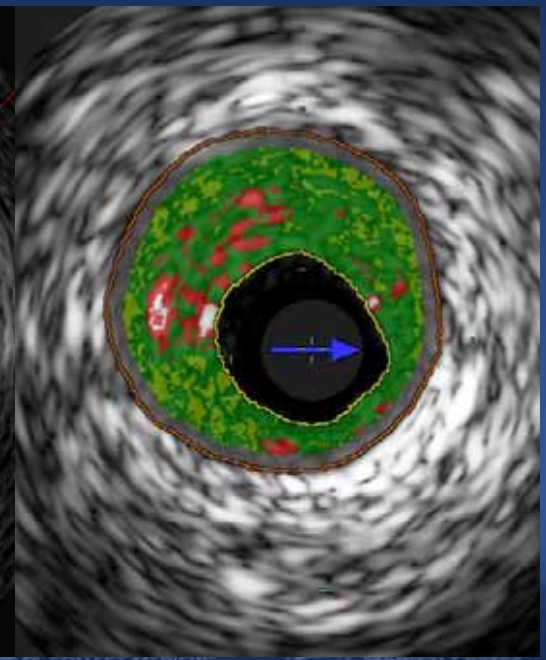
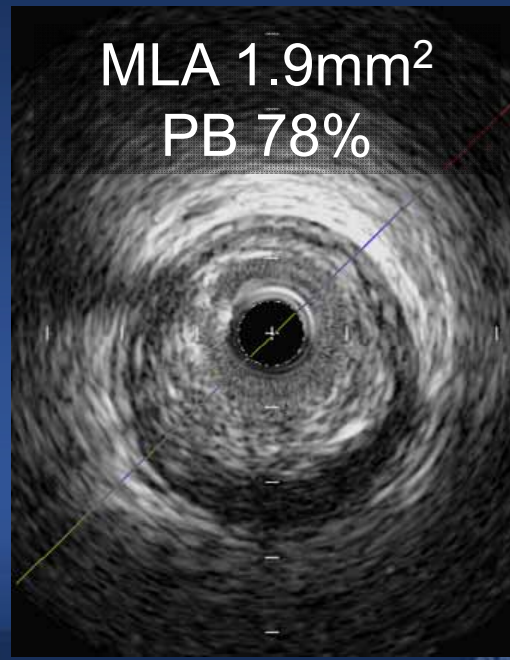
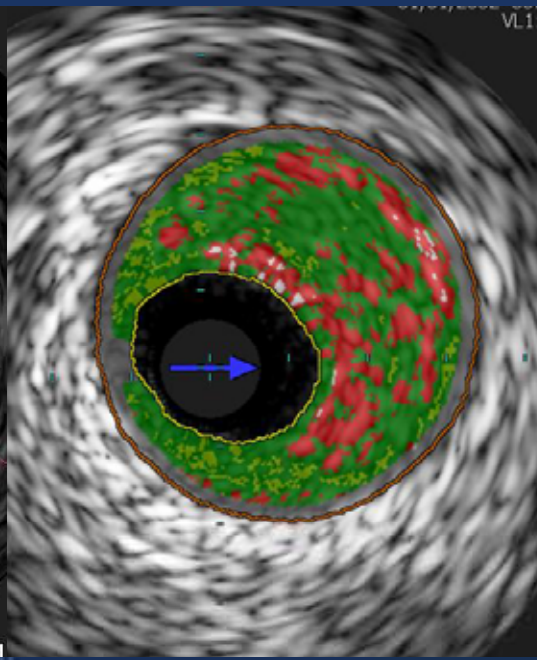
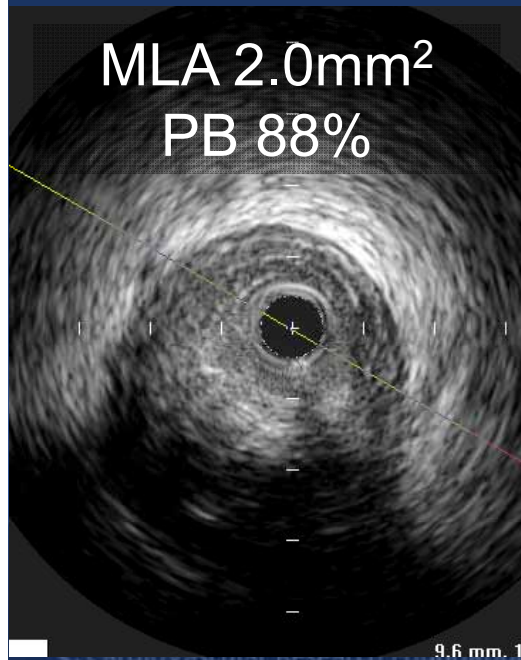
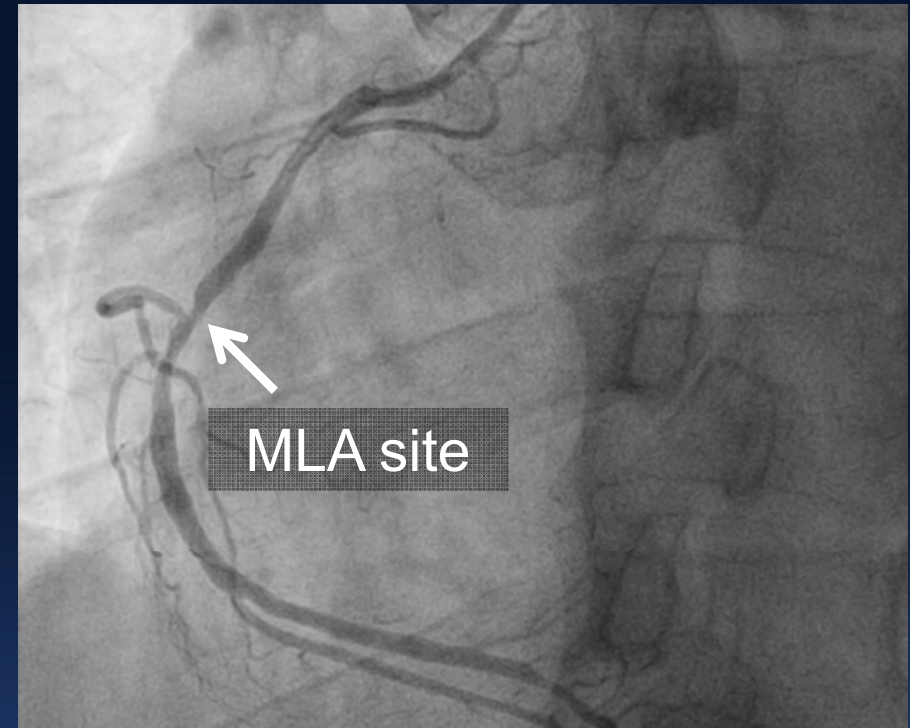
FFR 0.90, Deferred

Rosuvastatin 10mg
Life style modification for 1 year

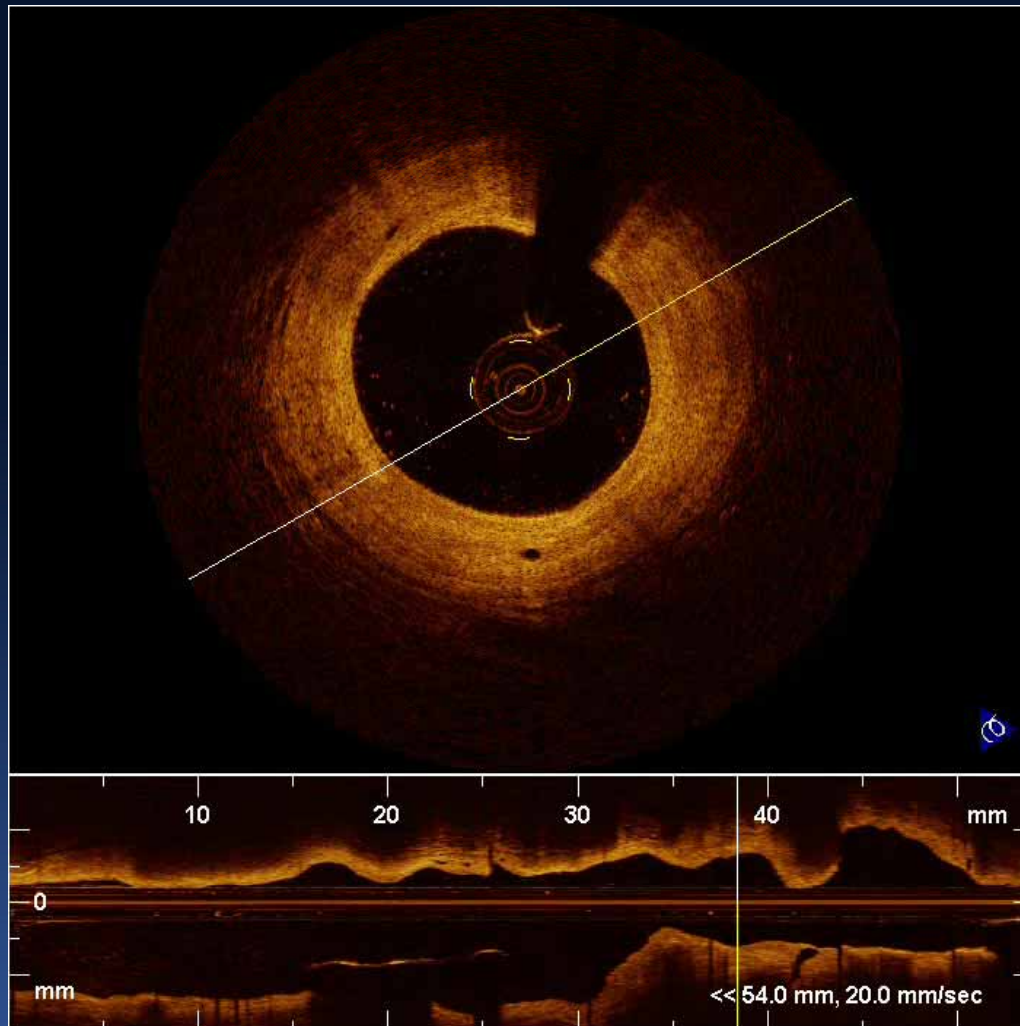
Baseline



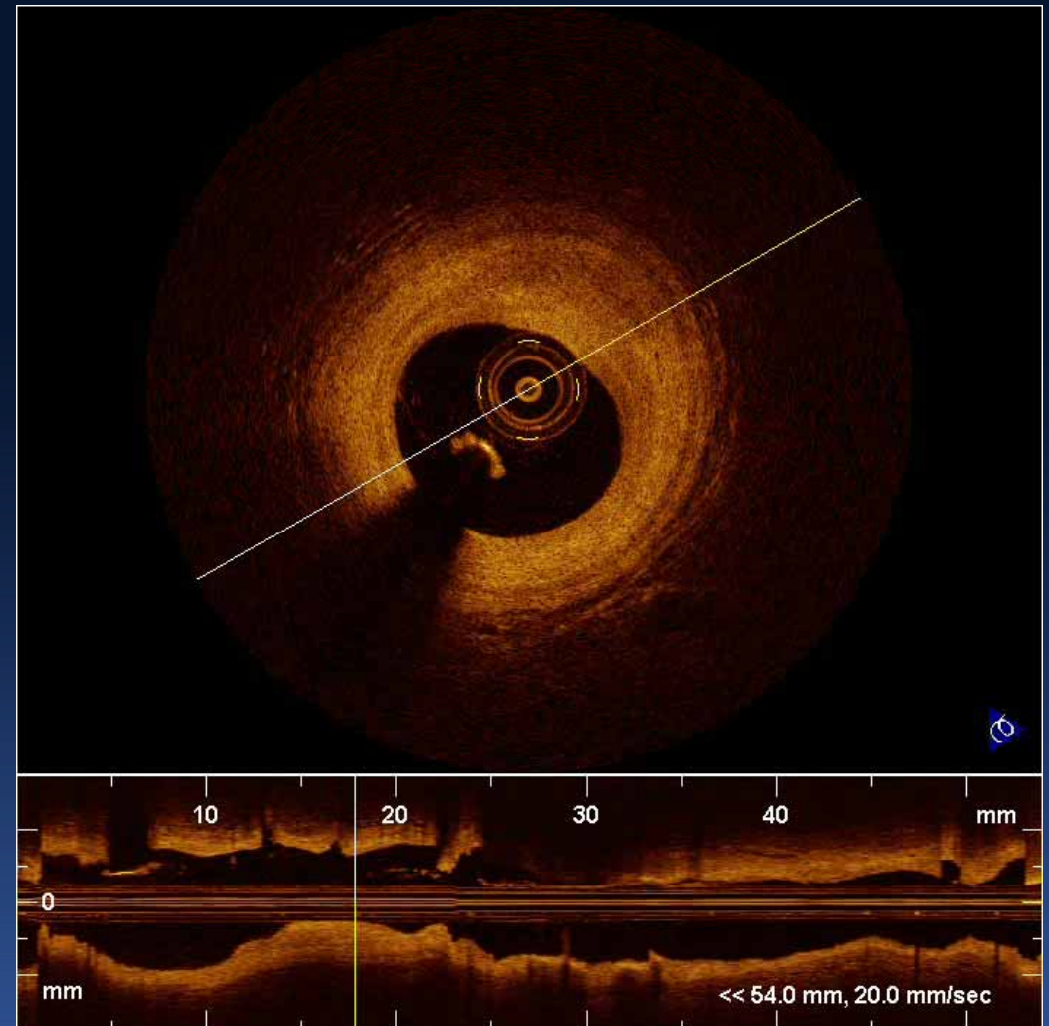
1-year follow-up



Baseline

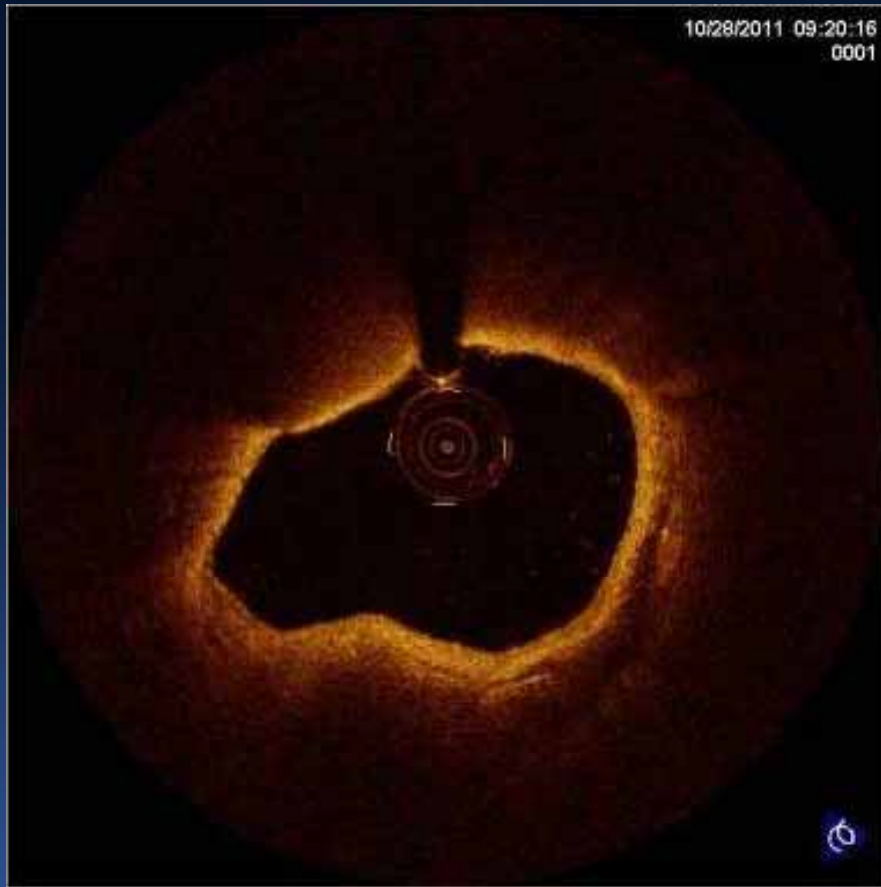


1-year follow-up

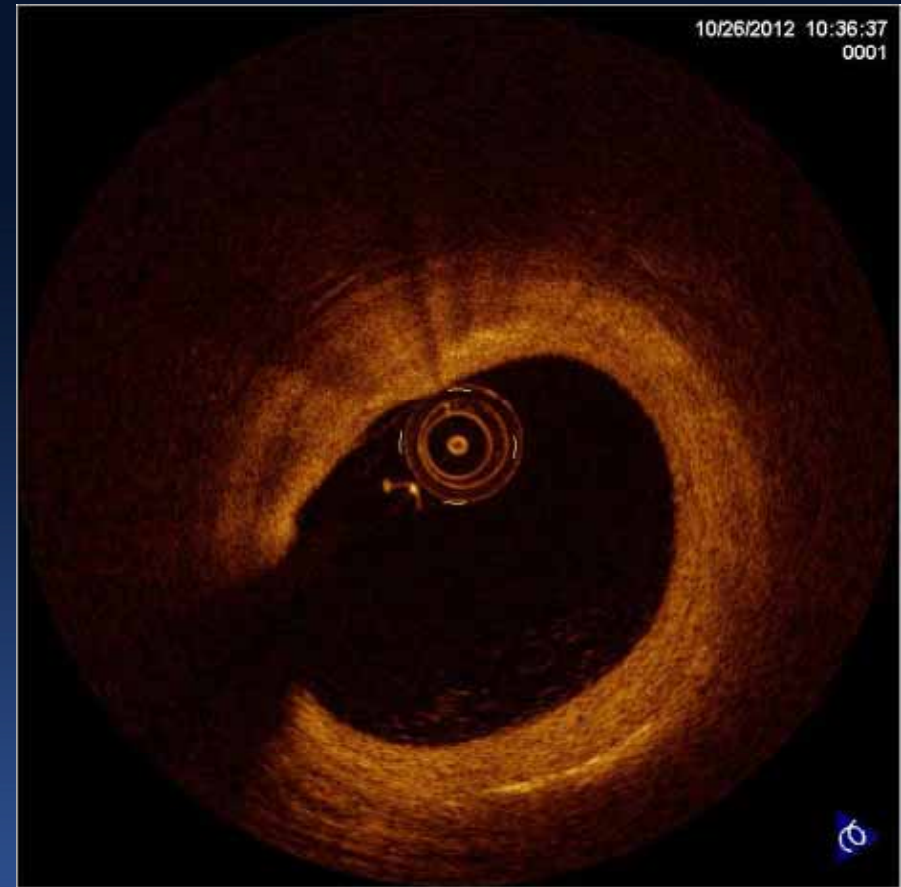


Rosuvastatin 10mg Life style modification

Baseline



1-year follow-up



Rosuvastatin 10mg
Life style modification

Changes in Patient were more remarkable...



| | 2011,10,25 | 2012,10,26 |
|-------------------------|-----------------|--------------|
| Clinical symptom | Unstable angina | Asymptomatic |
| Smoking | Smoker | Quit |
| Body weight (Kg) | 99.5 | 92.7 |
| T. cholesterol (mg/dl) | 244 | 162 |
| HDL-cholesterol (mg/dl) | 46 | 48 |
| LDL-cholesterol (mg/dl) | 172 | 96 |
| hsCRP (mg/dl) | 1.54 | 0.05 |

SUMMARY

- QCA-DS or IVUS-MLA can't predict ischemia
- Appropriateness for PCI should be based on direct functional assessment
- TCFA is a marker of current vulnerability and a prerequisite for plaque rupture. However, the majority do not evolve thrombotic events in the setting of lack of ischemia
- To manage **vulnerable plaque** and **vulnerable patient**, we need more systemic approach