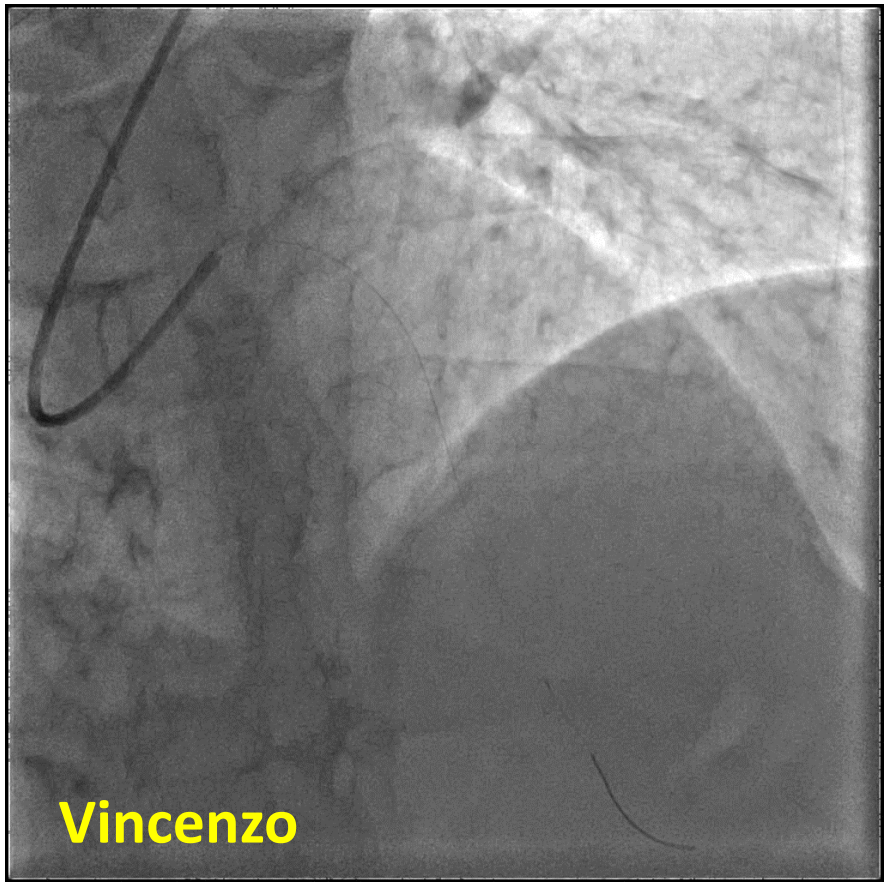
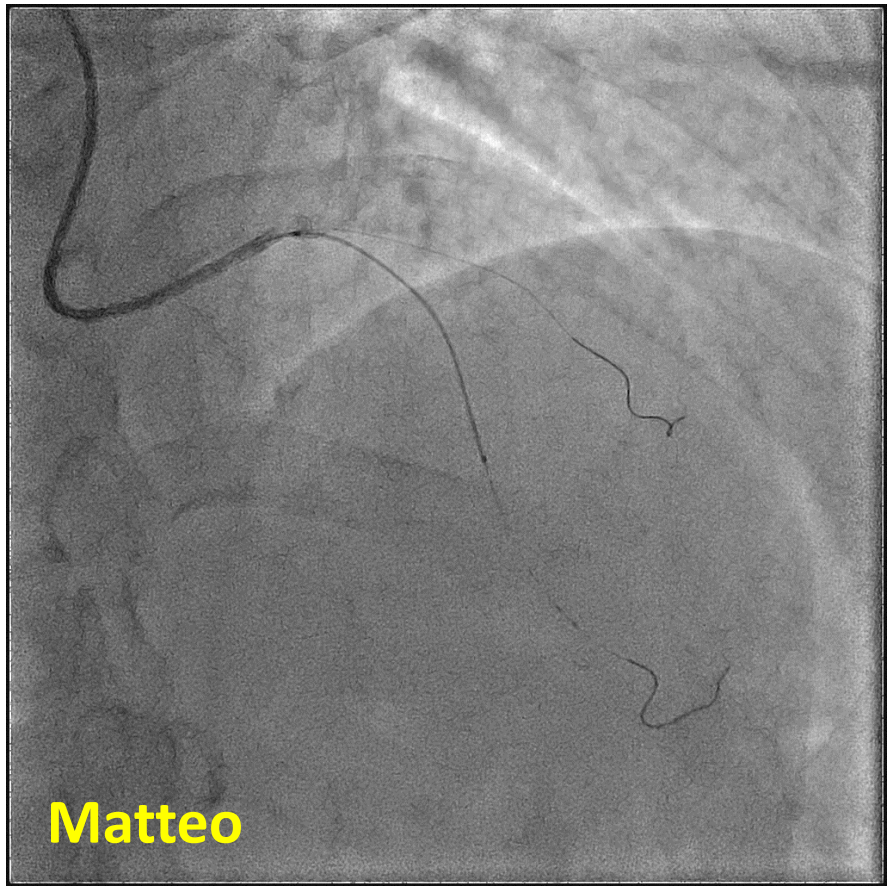
# Ruolo dell'imaging nel paziente multivasale complesso: esistono davvero le lesioni vulnerabili?

***Cuore e non solo***
***Genova Aprile 2023***

**F Prati**
**San Giovanni Hospital, Rome**
**and Cli Foundation**

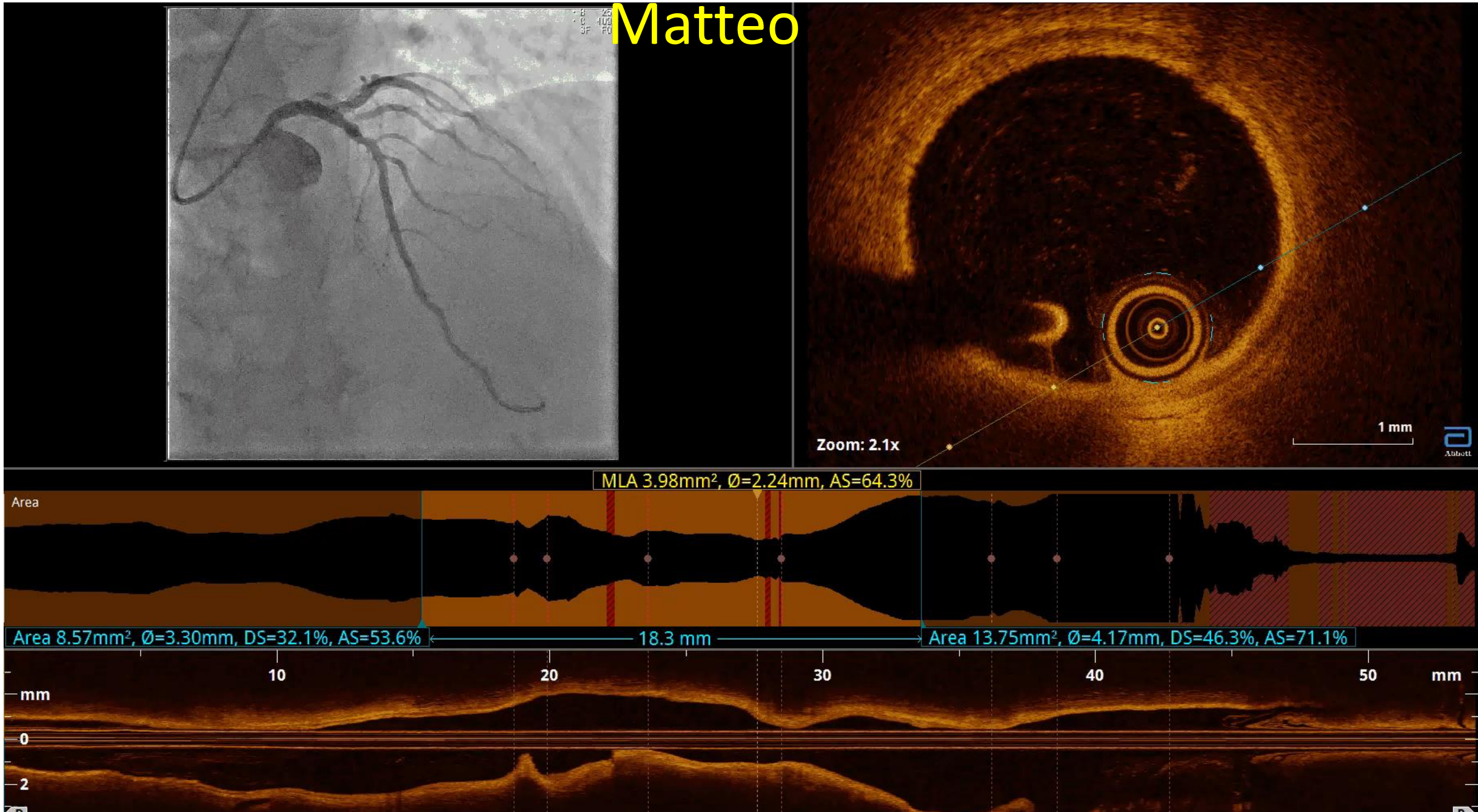
- Acute Inferior STEMI
- Mild LAD stenosis in single vessel disease
- RF: Ipercholesterolemia (LDL  Chol 150-165 mg/dl)



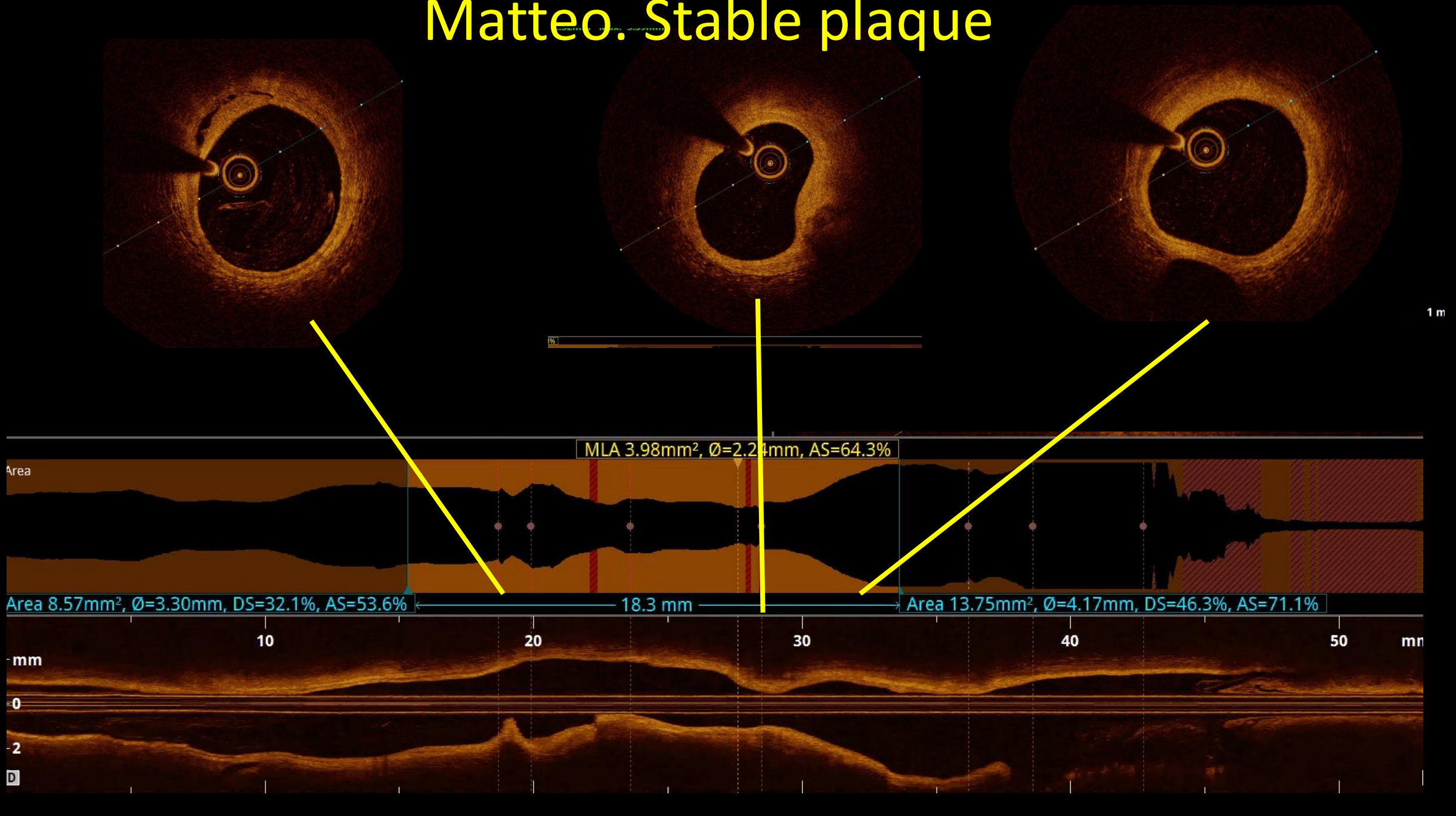



- The two are like peas in a pod?
- ……Not really

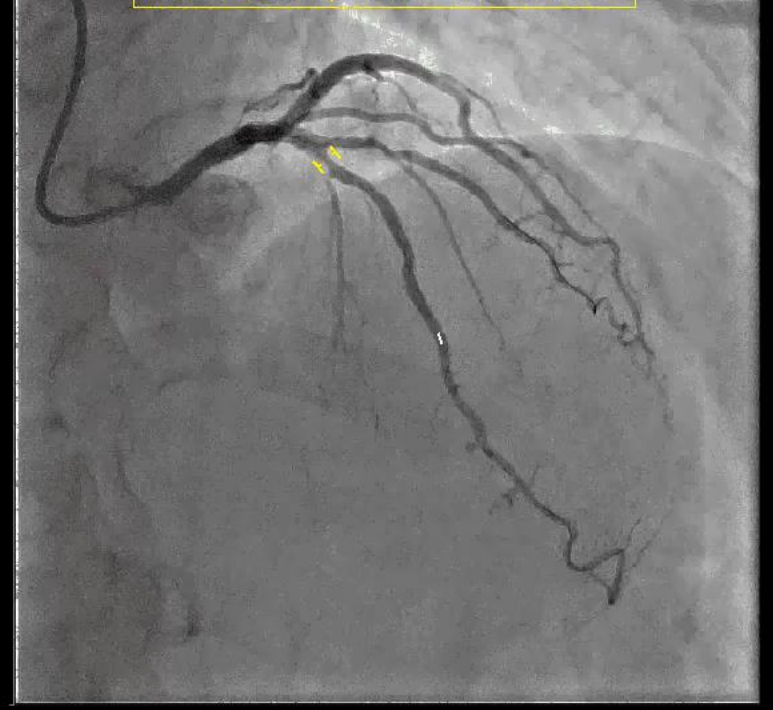
# Matteo

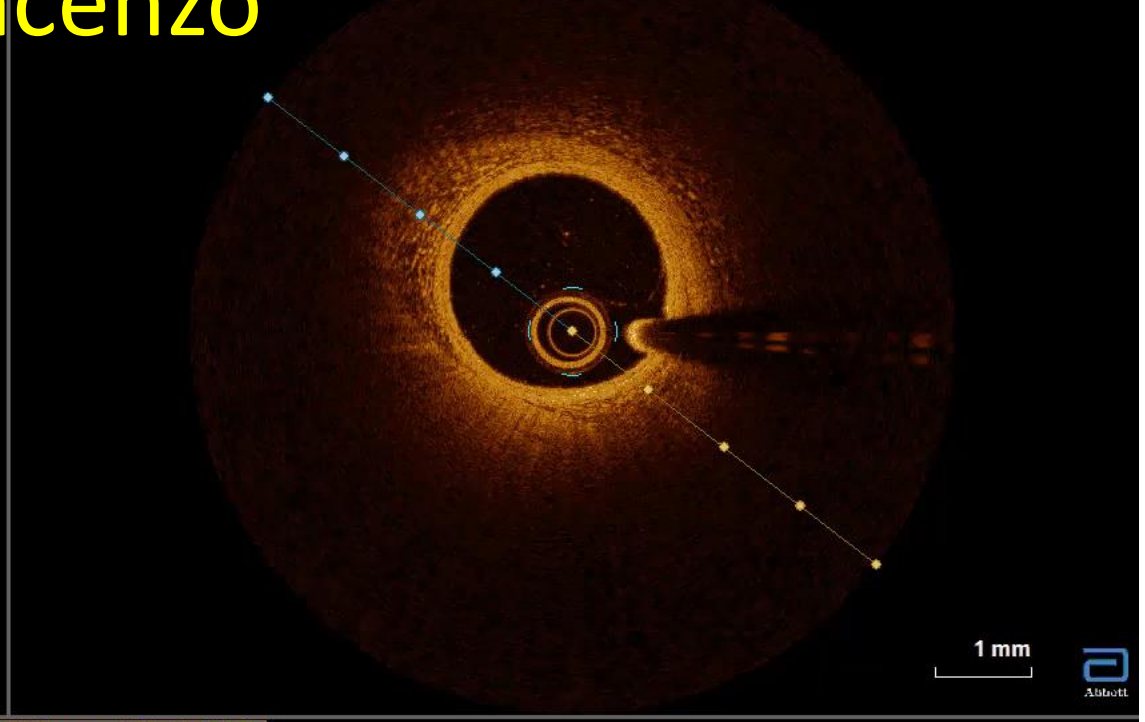

Zoom: 2.1x
1 mm
Abbott
MLA 3.98mm², Ø=2.24mm, AS=64.3%
Area
Area 8.57mm², Ø=3.30mm, DS=32.1%, AS=53.6%
18.3 mm
Area 13.75mm², Ø=4.17mm, DS=46.3%, AS=71.1%
10
20
30
40
50
mm
mm
0
2

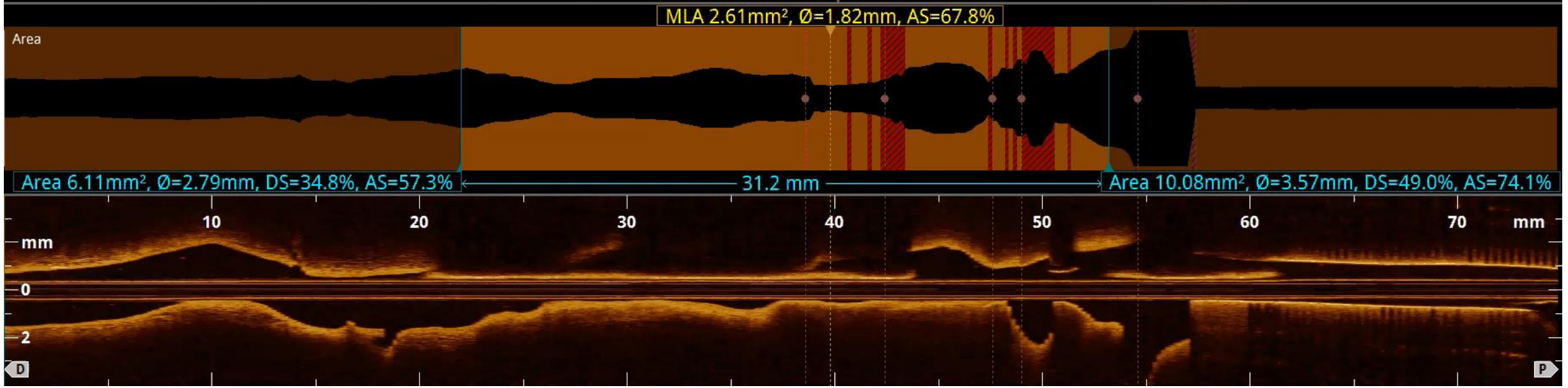
# Matteo. Stable plaque

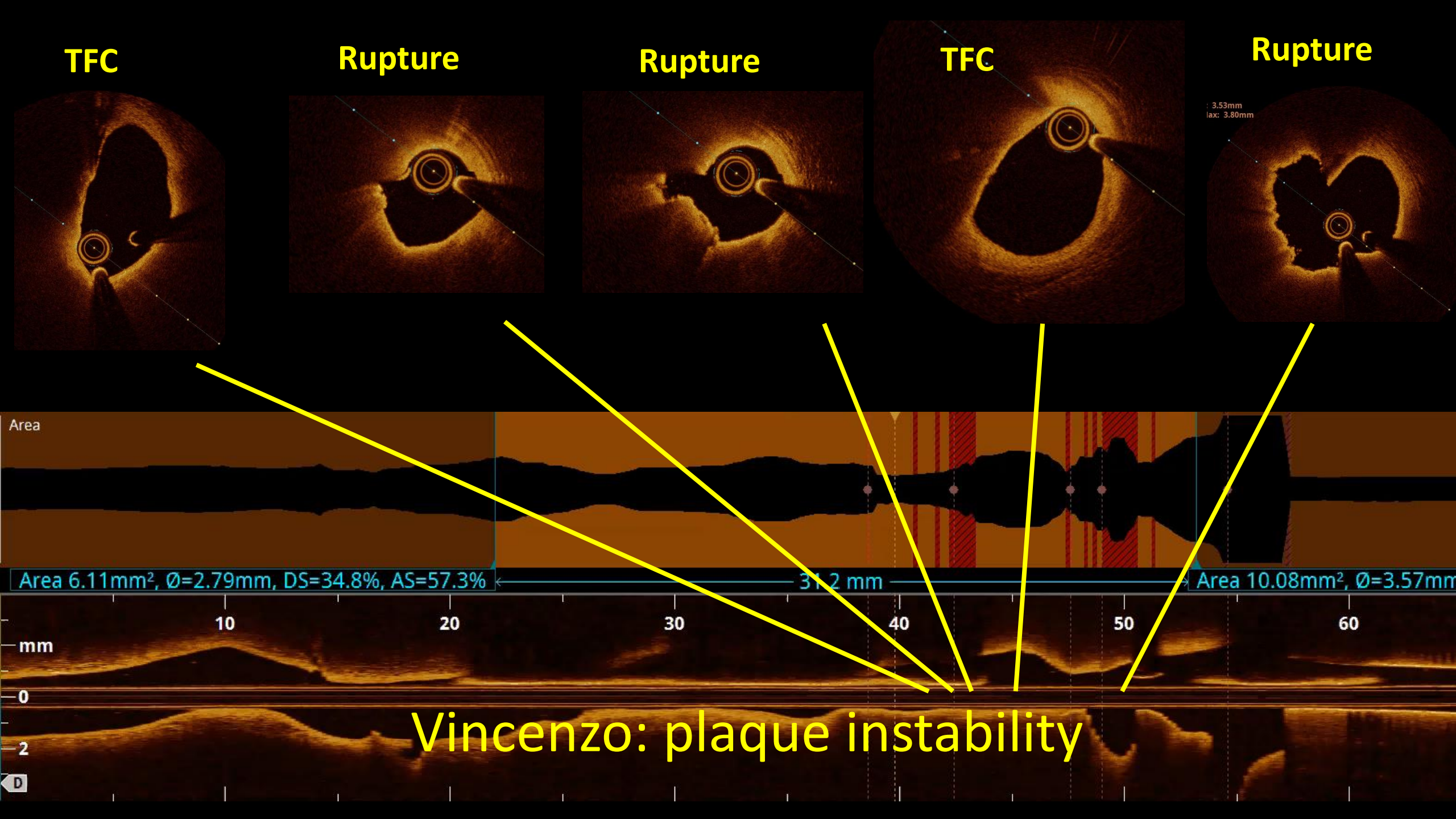


Vincenzo




1 mm
Abbott


MLA 2.61mm², Ø=1.82mm, AS=67.8%
Area
Area 6.11mm², Ø=2.79mm, DS=34.8%, AS=57.3%
31.2 mm
Area 10.08mm², Ø=3.57mm, DS=49.0%, AS=74.1%
10
20
30
40
50
60
70
mm
mm
0
2
D
P


TFC
Rupture
Rupture
TFC
Rupture
3.53mm
lax: 3.80mm
Area
Area 6.11mm², Ø=2.79mm, DS=34.8%, AS=57.3%
Area 10.08mm², Ø=3.57mm
10
20
30
40
50
60
mm
0
2
D
Vincenzo: plaque instability

- **THE CRITICAL VIEW OF THE CONCEPT OF PLAQUE VULNERABILITY:**

**THE KEY ISSUES**

*Studies on plaque vulnerability were not sufficiently encouraging*

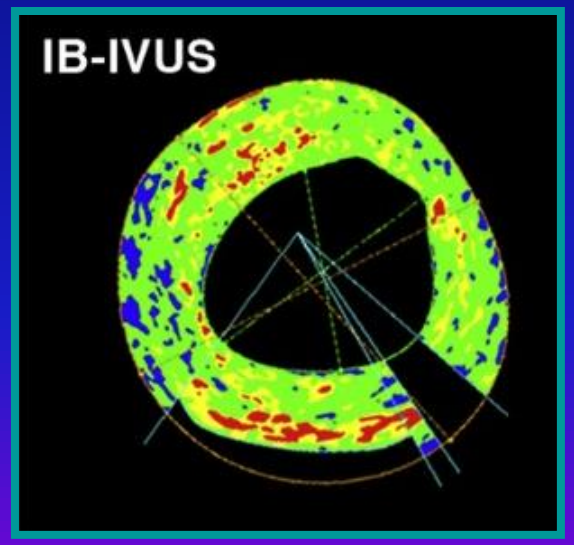
# Natural history of non-culprit vulnerable plaques

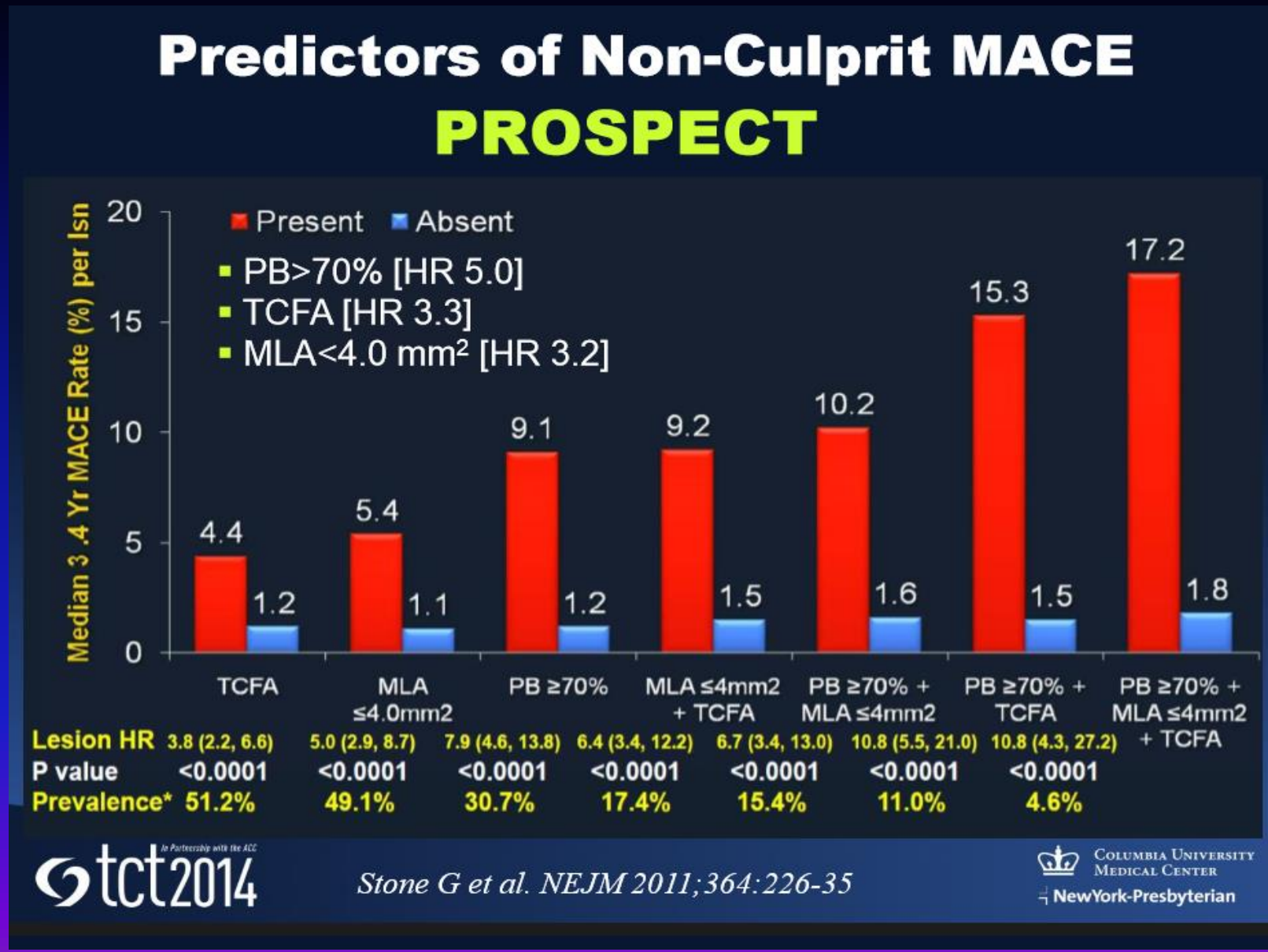
CCC 2022


| Study | ICI | N | PV criteria | Risk of events | CV death | Target vessel MI |
|---|---|---|---|---|---|---|
| PROSPECT | IVUS VH | 697 | MLA/PB/ VH-TFC | ↑* | N/A | N/A |
| Xing et al. | OCT | 1474 | LP>192.8° | ↑* | NS | NS |
| Lipid Rich Study | IVUS NIRS | 1271 | MaxLCBI 4mm | ↑* | N/A | N/A |
| Hoshino et al. | OCT | 510 | LRP in IFC | ↑* | NS | NS |
| CLIMA | OCT | 1003 | TFC +MLA+Mø +LP>180° | ↑ CD+tv MI | ↑ | ↑ |
| COMBINE | OCT | 390 | TCFA | ↑* CD+tv MI | NA | ↑ |
| PROSPECT II | IVUS NIRS | 898 | PB/MLA/ MaxLCBI4mm | ↑* | ↑ | ↑ |
| Kubo et al. (retrosp) | OCT | 1378 | TFC/LRP/ MLA/Mø | ↑(ACS) | NA | ↑ |

*cardiac death, MI and revascularization and /or angina

697 patients with ACS and three-vessel coronary angiography and IVUS – VH after PTCA

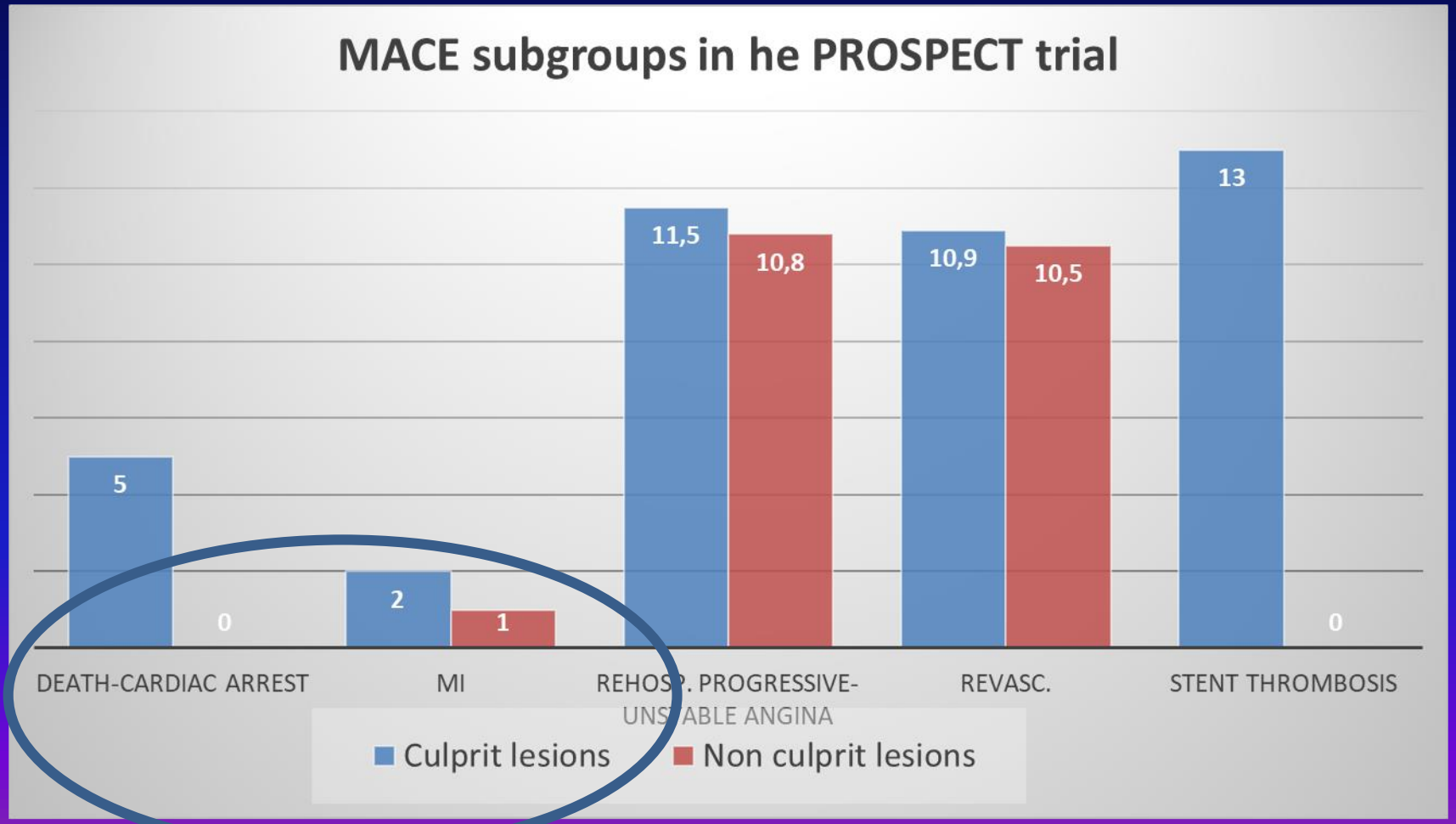



N Engl J med 2011

# PROSPECT. New Engl J Med 2010

3-year cumulative rate of MACE in 697 patients with ACS and gray-scale plus radiofrequency intravascular three-vessel coronary assessment



EDITORIAL COMMENT

# Vulnerable Plaque and Einstein's Definition of Insanity*

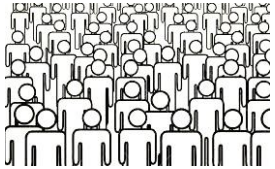
Steven E. Nissen, MD

A quote often attributed to Albert Einstein defines insanity as "doing the same thing over and over again and expecting different results." That's exactly what has happened with efforts to identify the elusive entity of "vulnerable plaque" using various coronary imaging modalities. Proponents of this concept have tried for decades to

abnormal temperature readings in the coronary arteries of patients with unstable syndromes. Then, almost inexplicably, silence.

The rise and fall of coronary thermography is emblematic of a pattern that has recurred repeatedly during the last 2 decades. The list of failed techniques for vulnerable plaque detection seems almost

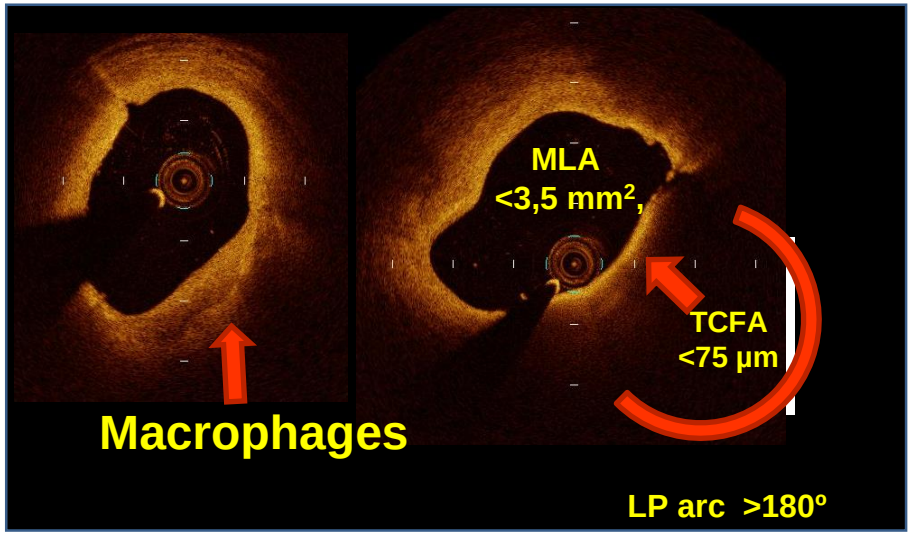
Nissen SE. JACC. 2020;75:1383-1385.



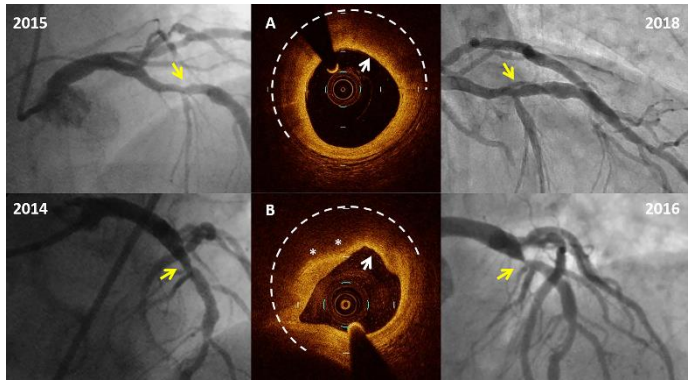
# CLIMA Study

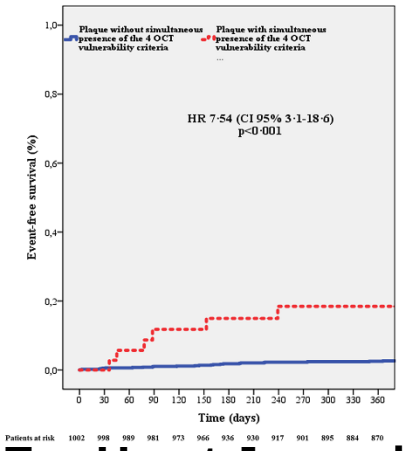
OCT LAD in 1003 patients with clinically indicated coronary angiogram from 11 independent centres enrolled from January 2013 to December 2016

MLA $<3.5mm^2$ + FCT <75µm + Lipid arc circ. extension >180° + OCT defined macrophages

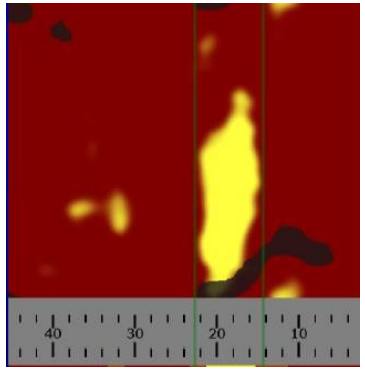



In 19.4% of patients who experienced the primary end-point the combination of the 4 findings was an independent predictor of events (HR 7.54, CI 95% 3.1-18.6).



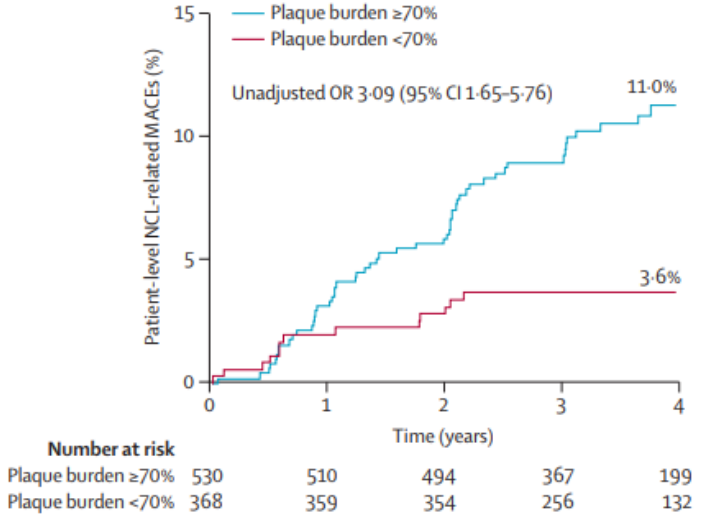

Eur Heart Journal 2020



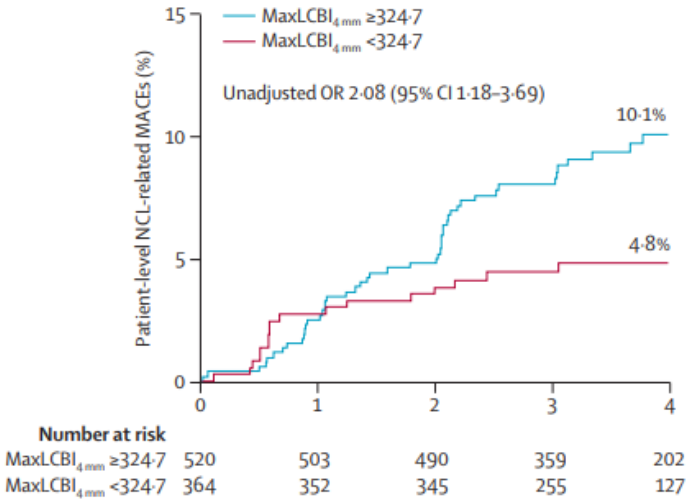
# Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study

David Erlinge, Akiko Maehara, Ori Ben-Yehuda, Hans Erik Bøtker, Michael Maeng, Lars Kjøller-Hansen, Thomas Engstrøm, Mitsuaki Matsumura, Aaron Crowley, Ovidiu Dressler, Gary S Mintz, Ole Fröbert, Jonas Persson, Rune Wiseth, Alf Inge Larsen, Lisette Okkels Jensen, Jan Erik Nordrehaug, Øyvind Bleie, Elmir Omerovic, Claes Held, Stefan K James, Ziad A Ali, James E Muller, Gregg W Stone, for the PROSPECT II Investigators*

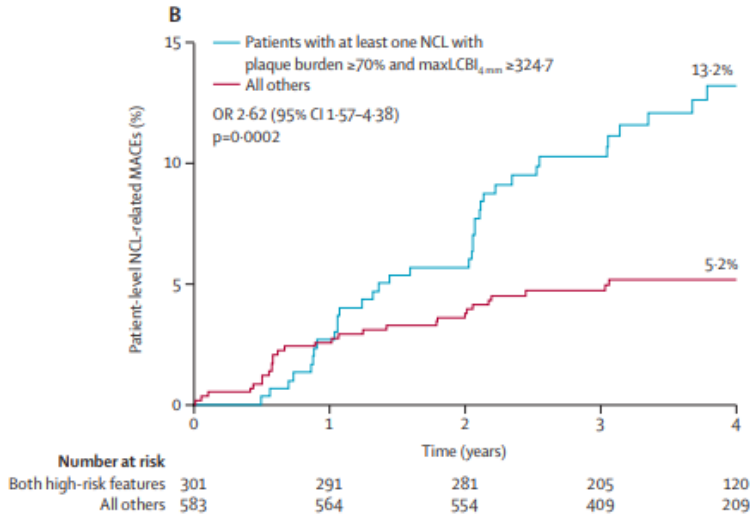
## Plaque Burden >70%




## Max LCBI > 324




## Max LCBI > 324 + Plaque Burden >70%




**MACEs (the composite of cardiac death, myocardial infarction, unstable angina, or progressive angina)**

Lancet 2020

# Identification of vulnerable plaques and patients by intracoronary near-infrared spectroscopy and ultrasound (PROSPECT II): a prospective natural history study

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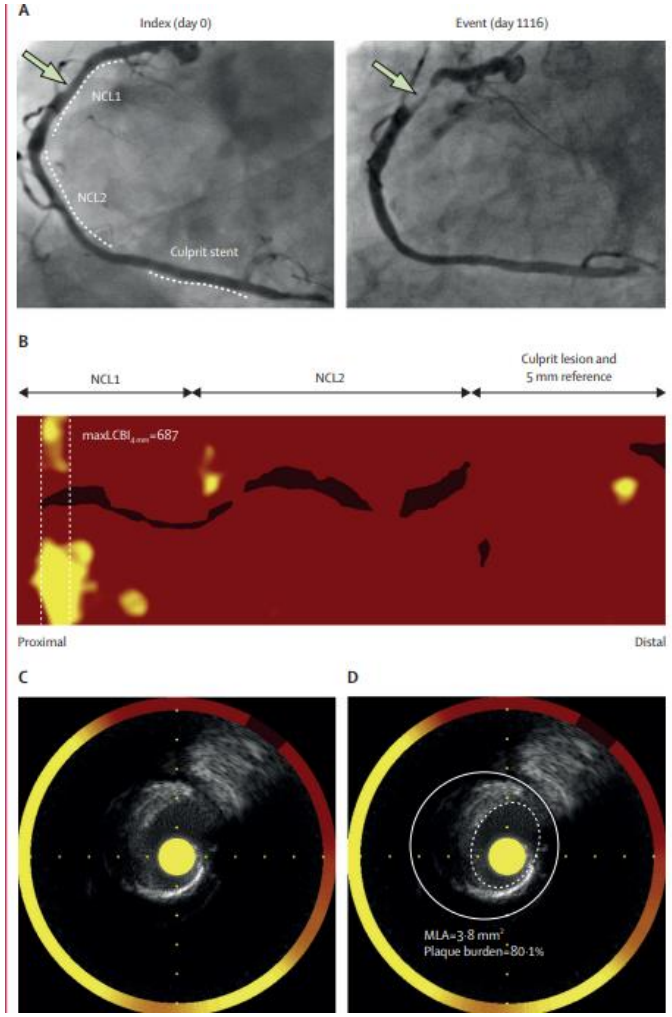



Lancet 2020

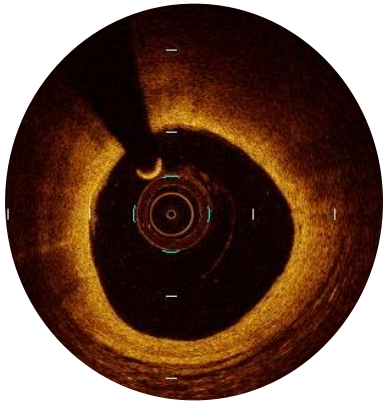
# PROSPECT II

| | Event rate in patients with at least one NCL with high-risk plaque characteristics | Event rate in patients without NCLs with high-risk plaque characteristics | Unadjusted odds ratio (95% CI) |
|---|---|---|---|
| **MaxLCBI$_{4mm}$ ≥324·7** | | | |
| Number of patients | 520 | 364 | -- |
| Non-culprit MACEs | 48 (10%) | 17 (5%) | 2·08 (1·18–3·69) |
| Myocardial infarction | 18 (4%) | 4 (1%) | 3·20 (1·07–9·55) |
| Unstable angina | 4 (1%) | 5 (1%) | 0·54 (0·14–2·04) |
| Progressive angina | 30 (6%) | 8 (2%) | 2·73 (1·24–6·03) |
| **Plaque burden ≥70%** | | | |
| Number of patients | 530 | 368 | -- |
| Non-culprit MACEs | 53 (11%) | 13 (4%) | 3·09 (1·65–5·76) |
| Myocardial infarction | 20 (5%) | 3 (1%) | 4·72 (1·39–16·01) |
| Unstable angina | 5 (1%) | 4 (1%) | 0·85 (0·23–3·17) |
| Progressive angina | 32 (6%) | 6 (2%) | 3·89 (1·61–9·42) |
| **Minimal lumen area ≤4·0 mm²** | | | |
| Number of patients | 679 | 219 | -- |
| Non-culprit MACEs | 62 (10%) | 4 (2%) | 5·49 (1·97–15·28) |
| Myocardial infarction | 22 (4%) | 1 (<1%) | 7·16 (0·96–53·41) |
| Unstable angina | 7 (1%) | 2 (1%) | 1·09 (0·23–5·31) |
| Progressive angina | 37 (6%) | 1 (<1%) | 12·55 (1·71–92·08) |

Data are n (%) unless otherwise stated. No cardiac deaths were attributed to NCLs. MACE=major adverse cardiac event. MaxLCBI$_{4mm}$=maximum lipid core burden index within any 4 mm segment across the entire lesion. NCL=non-culprit lesion.

*Table 1:* **NCL-related MACEs during follow-up in patients with versus without lesions with high-risk plaque characteristics**

Circulation



EDITORIAL

# Forget Ischemia: It's All About the Plaque

David E. Newby, DM, PhD; Michelle C. Williams, MBChB, PhD; Marc R. Dweck, MD, PhD

The introduction of invasive coronary angiography in the 1960s was a major step forward in the understanding and treatment of coronary artery disease. However, high initial complication rates and limited availability led to the widespread development of ischemia testing techniques as safer, noninvasive surrogate methods of identifying obstructive coronary

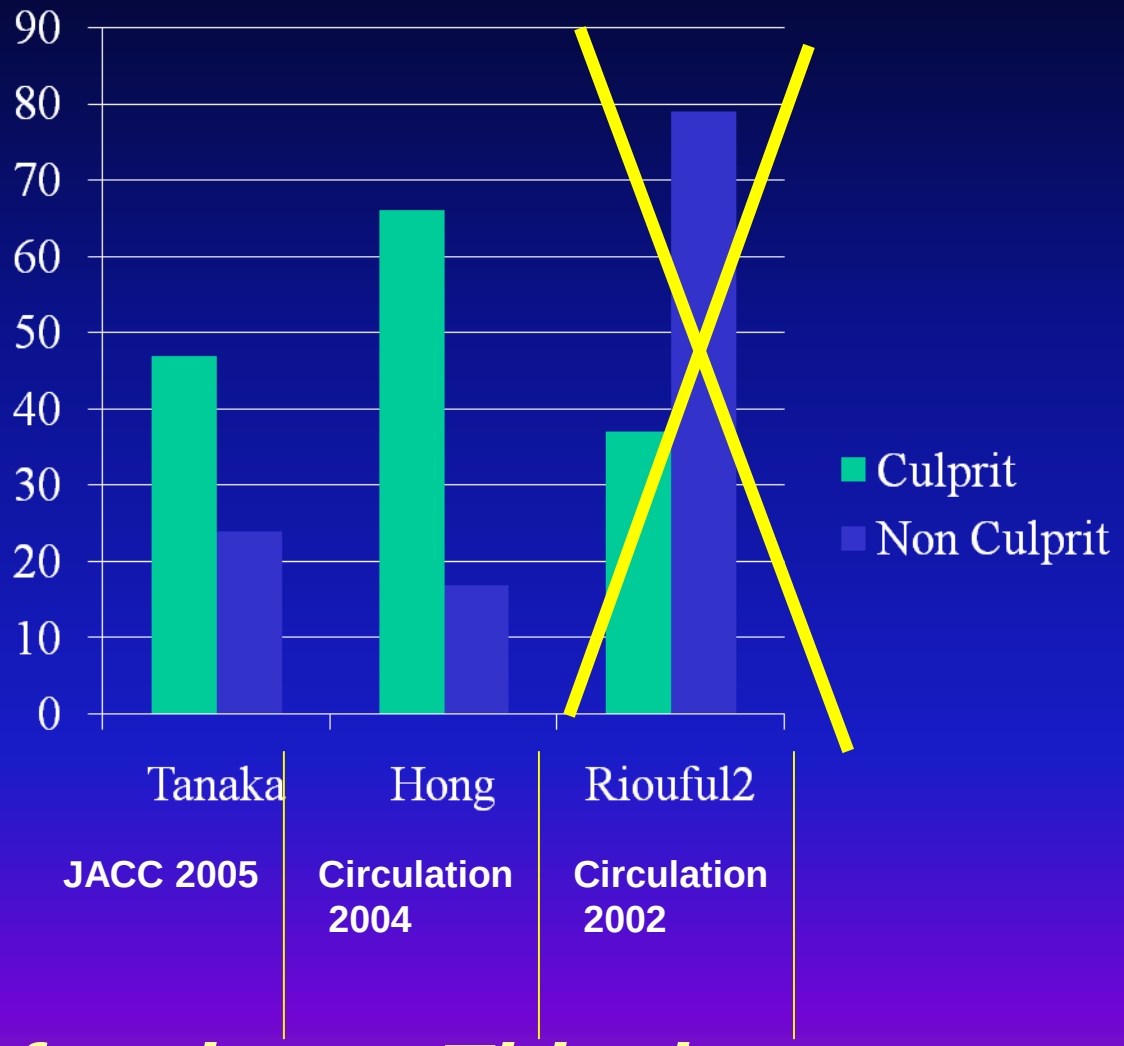
nostic benefit was found from coronary revascularization in patients with stable coronary artery disease and myocardial ischemia after a median of 3 years of follow-up.[3]

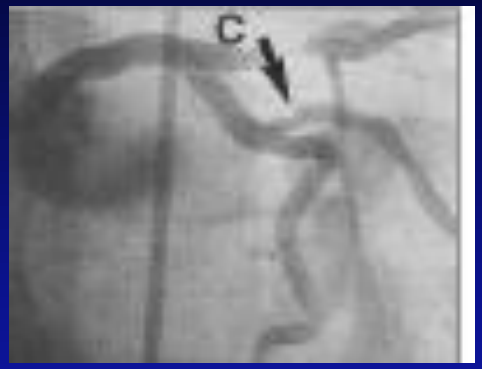
In this issue of *Circulation*, 2 important substudies of ISCHEMIA are presented by Reynolds et al.[4,5] In one analysis,[4] ISCHEMIA investigators examined both the prognostic predictive power and the potential trial

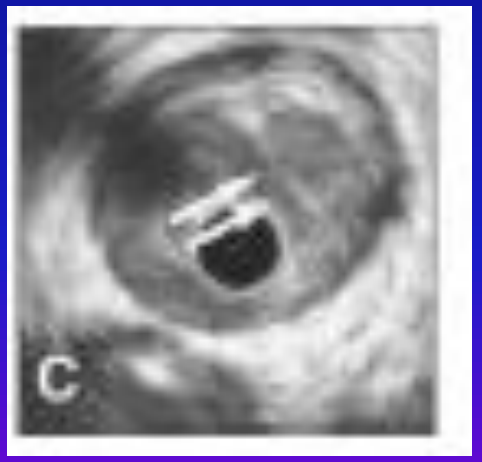
*Circulation*. 2021;144:1039–1041. DOI: 10.1161/CIRCULATIONAHA.121.054102

*It seems worthless any attempt to stabilize plaques if silent ruptures occur often and plaque phenotypes are too dynamic to become a reliable* target .

# Plaque rupture without trhrombus in culprit e non culprit lesions in pts with ACS. IVUS imaging of the 3 main vessels



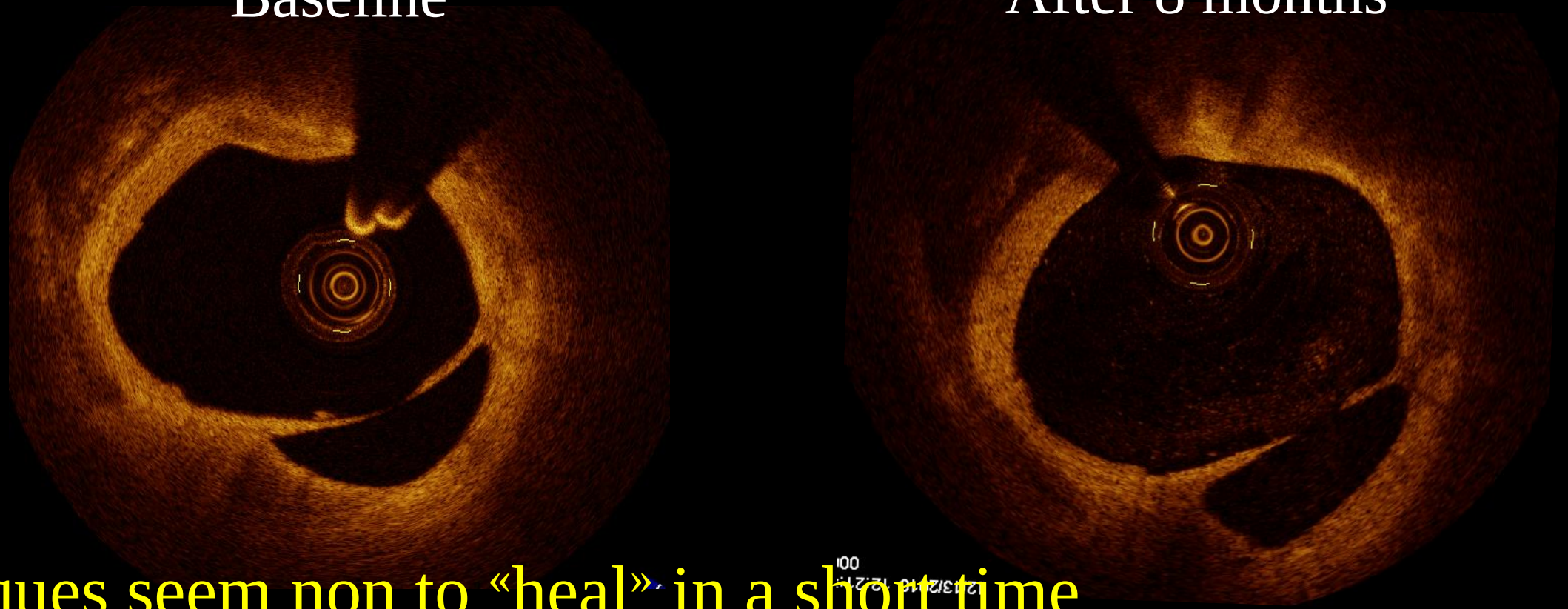




***30% of patients. This does not seem a trivial number.***

*Anectodal cases, based on sequential imaging studies, showed that plaque ulcers can remain stable for months or years.*

Baseline

After 8 months



Plaques seem non to «heal» in a short time

Di. Vito et al. JACC Imaging 2013

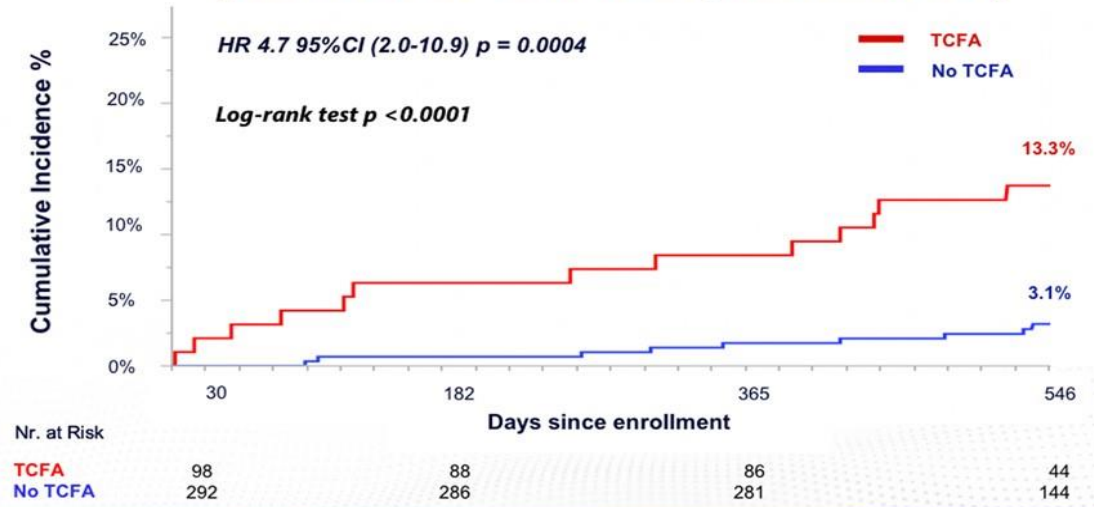
- *Does a snapshot of plaque characteristics at a certain point make sense?*

- *Plaques can lose their "vulnerability" characteristics in response to therapy or, vice versa, get worse over a few months in untreated patients.*

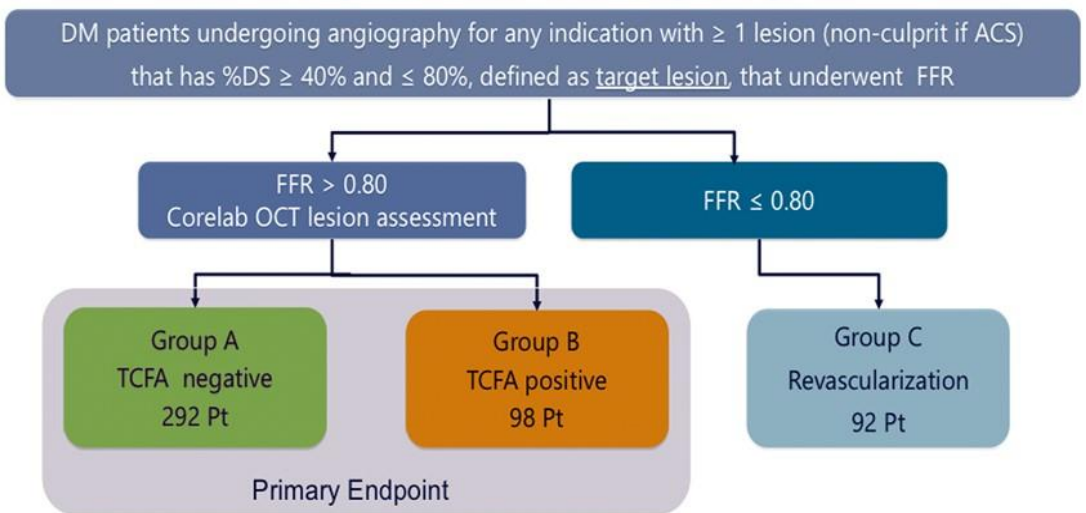
# Combined *Optical Coherence Tomography* and *Fractional Flow Reserve* Assessment to Better Predict Adverse Event Outcomes in DM Patients COMBINE (FFR–OCT) Trial

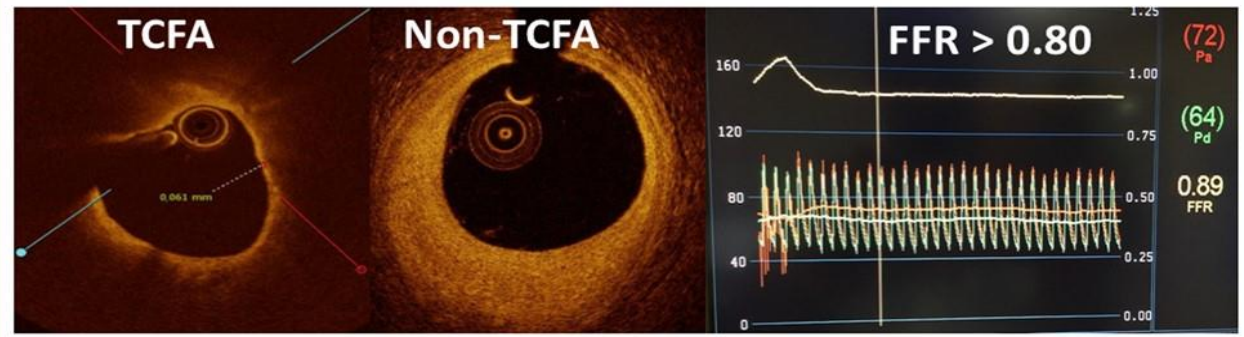
***Aim:*** **to explore the hypothesis that in patients with fast progressing atherosclerosis like DM patients, identification of TCFAs may be more important than ruling out the presence of flow-limiting lesions in predicting future MACE**

## Primary Endpoint
### (CD, TVMI, CD-TLR, or Hospitalization UAP)



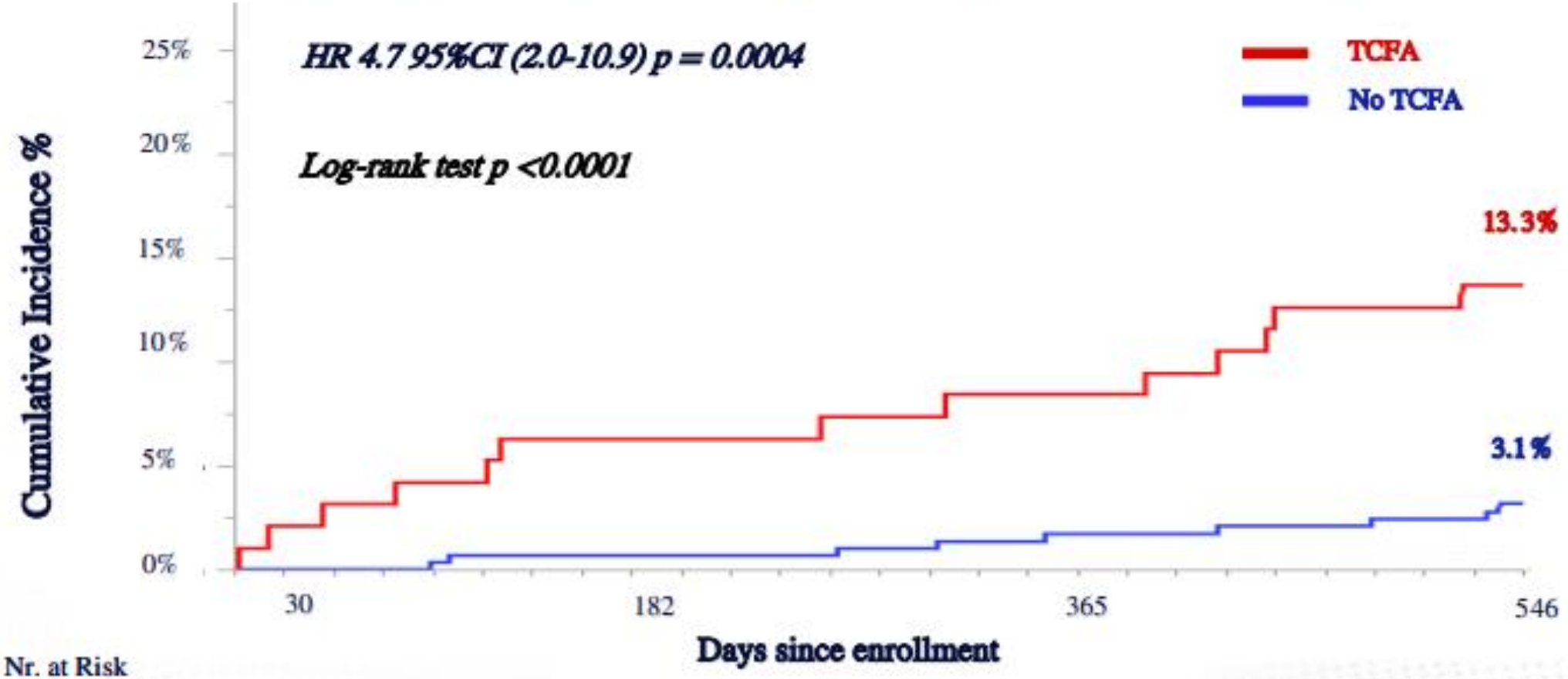

## COMBINE (FFR-OCT) Design
### Prospective Natural History Study




***Conclusions:*** **In DM patients, TCFA represents 25% of FFR-negative lesions and OCT-detected TCFA is associated with a 5-fold higher rate of adverse events despite the absence of ischemia**

# Primary Endpoint
## (CD, TVMI, CD-TLR, or Hospitalization UAP)



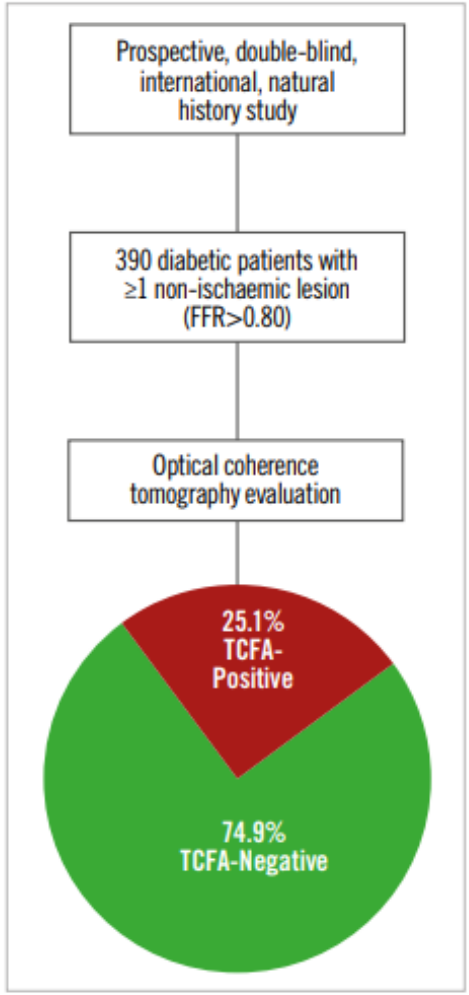

Nr. at Risk

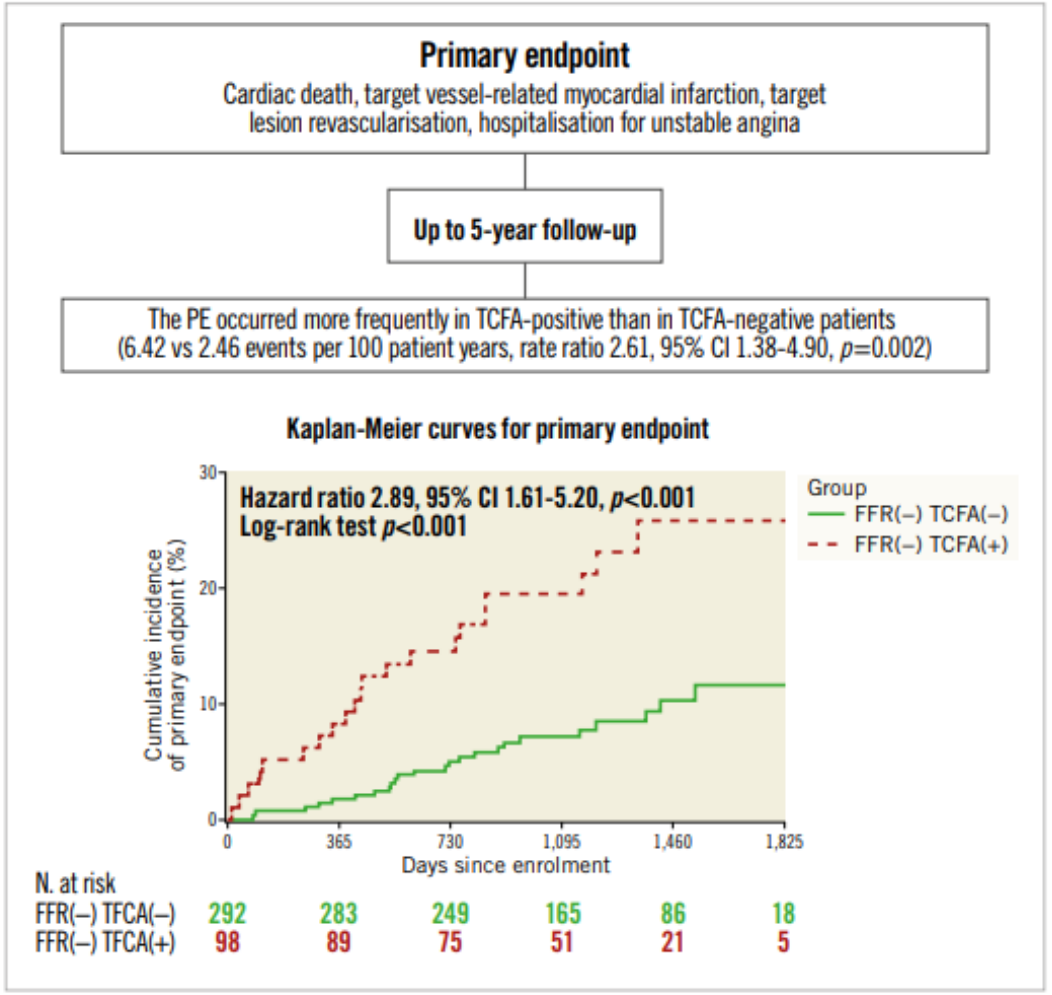
| | | | | |
|---|---|---|---|---|
| TCFA | 98 | 88 | 86 | 44 |
| No TCFA | 292 | 286 | 281 | 144 |

Circulation 2021

# Long-term outcomes of patients with normal fractional flow reserve and thin-cap fibroatheroma

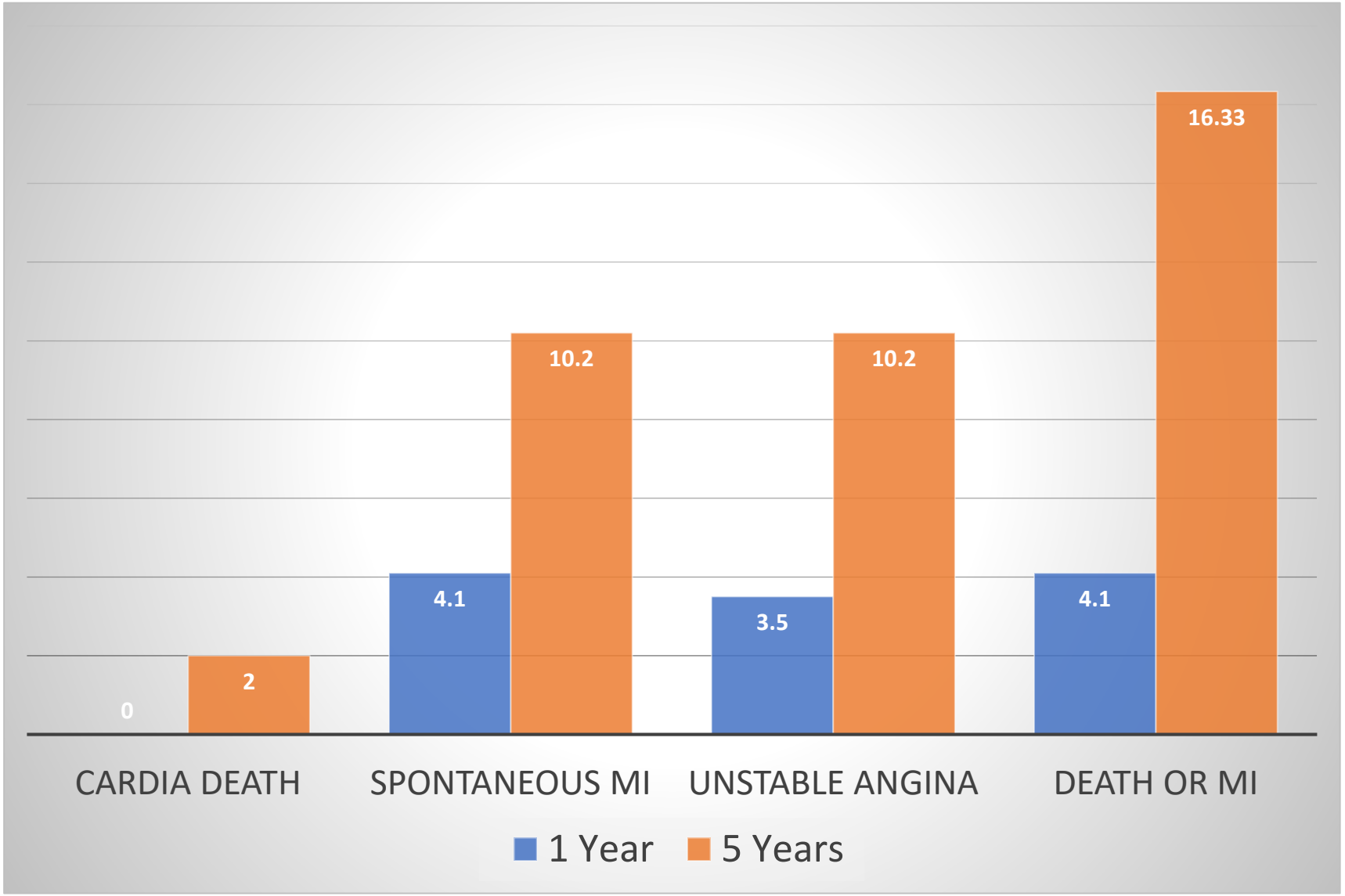
## Fabris et al. Eurointervention. In press

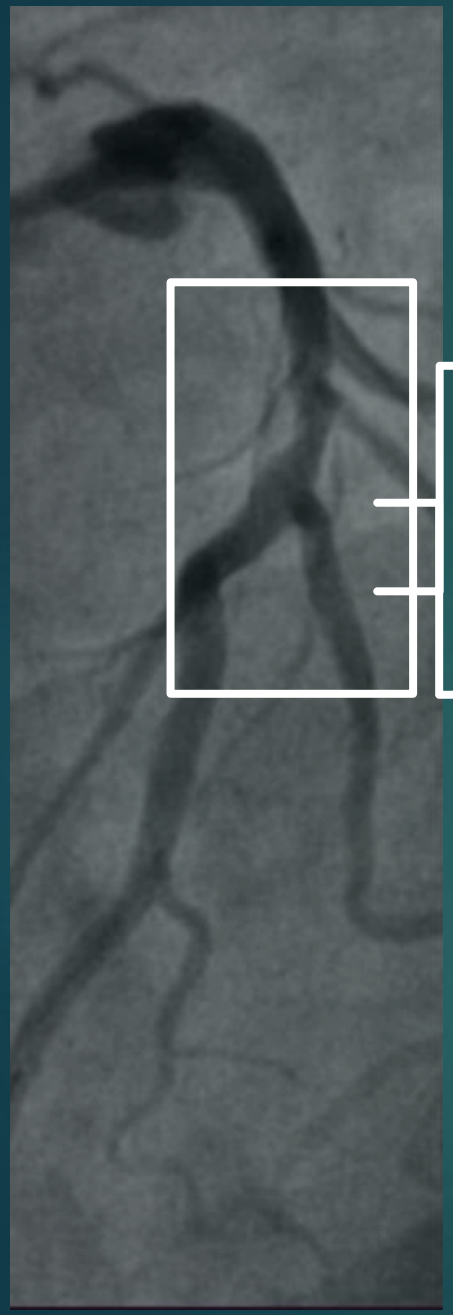



*Among patients with diabetes mellitus and fractional flow reserve (FFR)-negative non-culprit lesions enrolled in the COMBINE OCT-FFR study, patients with thin-cap fibroatheroma (TCFA) had a higher rate of the composite primary endpoint (cardiac death, target vessel-related myocardial infarction, target lesion revascularisation, hospitalisation for unstable angina) than those who were TCFA-negative, up to 5 years of follow-up. CI: confidence interval; FFR: fractional flow reserve; OCT: optical coherence tomography; PE: primary endpoint; TCFA: thin-cap fibroatheroma*

# COMBINE Study. Clinical end-point at 1 year and 5 years





# Is functional assessment so good for predicting hard events?

CCC 2022

Angiography guidance

Physiology guidance

## Angio vs Functional-guided PCI

| Study acronym | Year | N | Enrolled lesions | ↓CV death | Non fatal MI | Repeat revascularization |
|---|---|---|---|---|---|---|
| FAME II | 2014 | 465 | >50% | X | X | ↓ |
| CVLPRIT | 2015 | 296 | >50% 2 v<br>>70% 1 v | X | X | X |
| DANAMI-3-PRIMULTI | 2015 | 627 | >50%<br>FFR | X | X | ↓ |
| COMPARE ACUTE | 2017 | 885 | >50%<br>FFR | X | X | ↓ |
| FLOWER-MI | 2021 | 1171 | ≥70% (98% cases) | X | X | X |

*SHOULD WE TARGET AND TREAT VULNERABLE PLAQUES ?*

- **Identify vulnerable plaques**

**Interventional Treatment**

**Drug Treatment**

- Treat with drugs

# Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes

## The MIRACL Study: A Randomized Controlled

**Figure 4.** Risk Ratio Plot

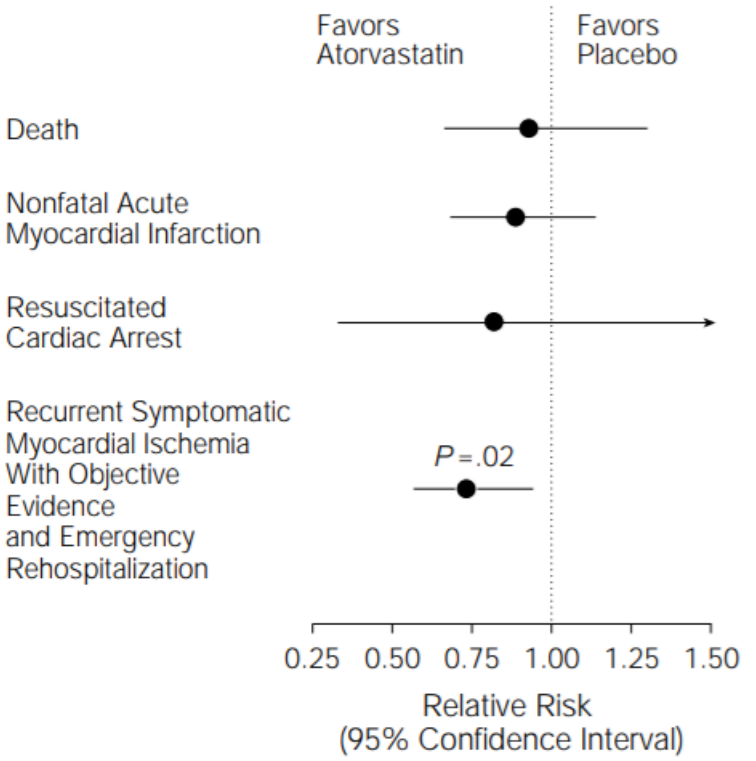
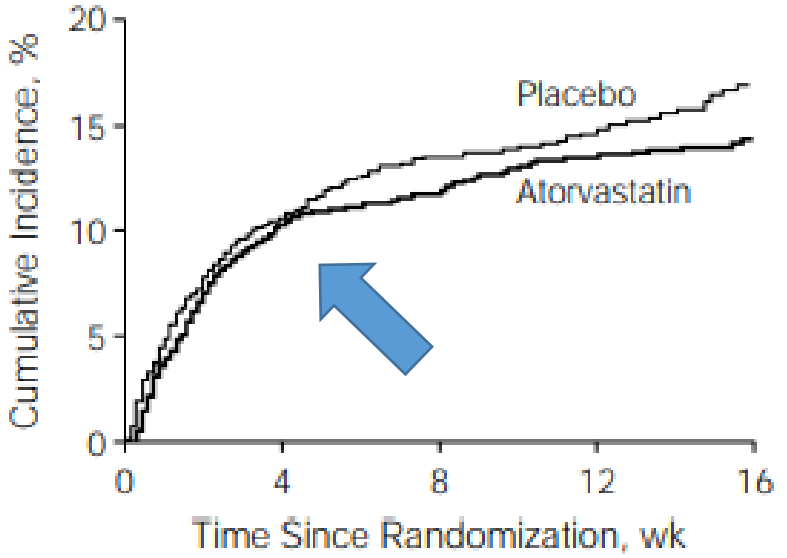


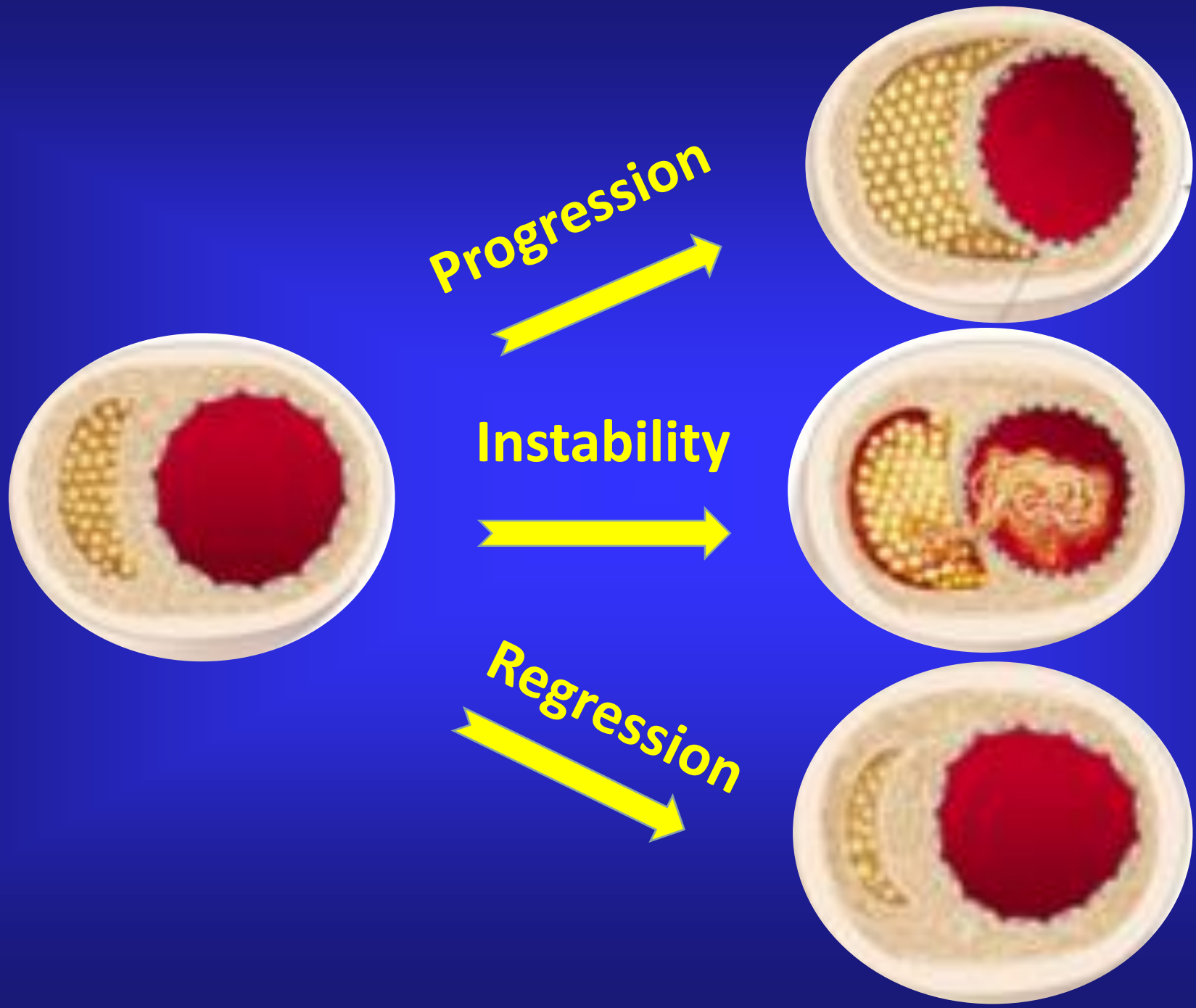

**Figure 3.** Kaplan-Meier Estimates of Primary Outcomes




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Atorvastatin | 1538 | 1381 | 1351 | 1323 | 518 |
| Placebo | 1548 | 1384 | 1338 | 1318 | 473 |

The relative risk of the composite outcome in the atorvastatin group compared with the placebo group was 0.84 (95% confidence interval, 0.70-1.00; $P=.048$), based on a Cox proportional hazards analysis. The decrease in number at risk at 16 weeks reflects the fact that many patients completed the study within the days immediately preceding 16 weeks.

**JAMA 2001**


Progression
Instability
Regression

Original Article

# Assessing the impact of PCSK9 inhibition on coronary plaque phenotype with optical coherence tomography: rationale and design of the randomized, placebo-controlled HUYGENS study

Stephen J. Nicholls, Steven E. Nissen, Francesco Prati, Stephan Windecker, Yu Kataoka, Rishi Puri, Thomas Hucko, Helina Kassahun, Jason Liao, Ransi Somaratne, Julie Butters, Giuseppe Di Giovanni, Stephen Jones, Peter J. Psaltis

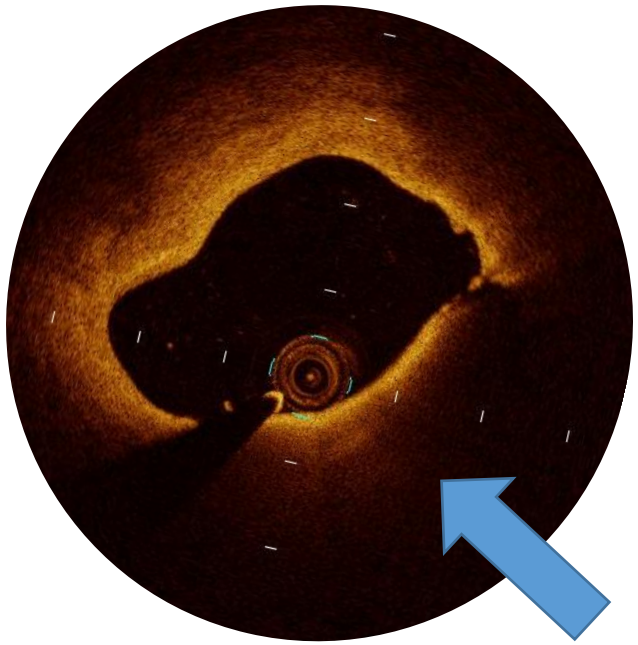
Cardiovascular Diagnosis and Therapy 2021

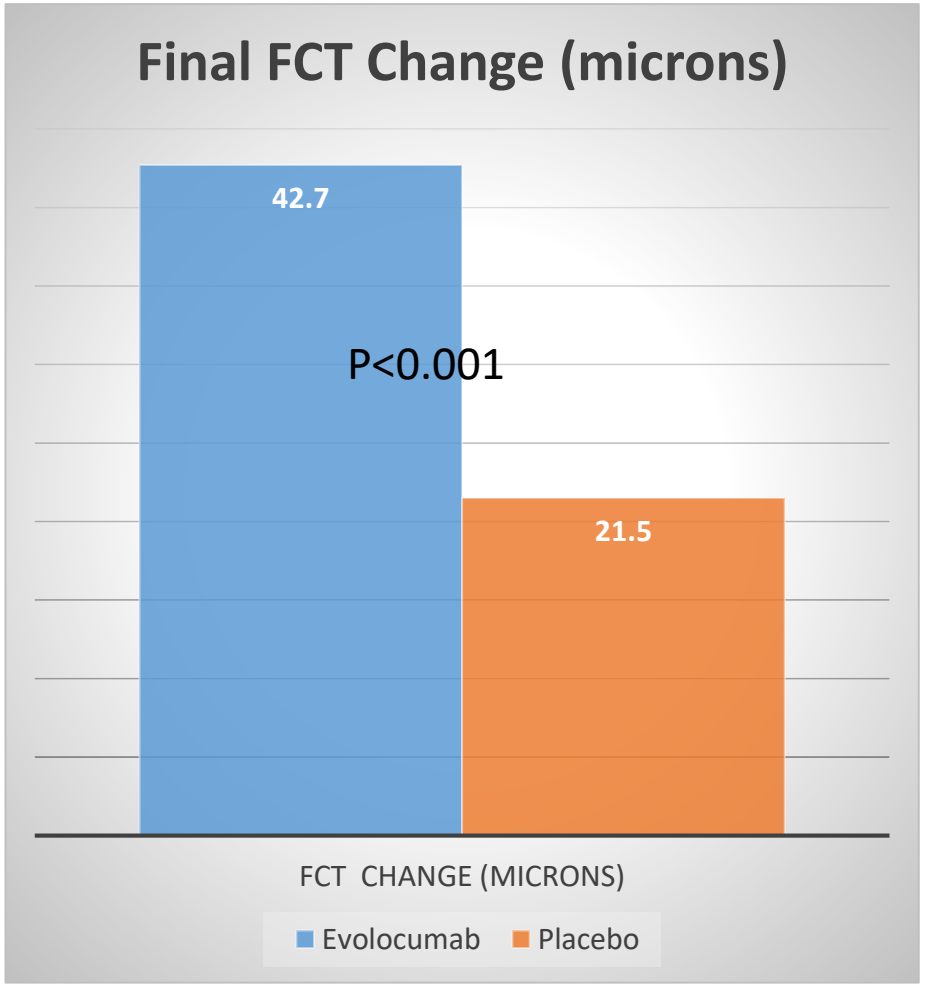
# High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)

## Main study end-point: increase in FCT

**Evolocumab group: FCT increased from 56,6 µ to 100,6 m (+ 82%)**

**Placebo group: FCT increased from 54,6 µ to 81,7 (+ 44%)**





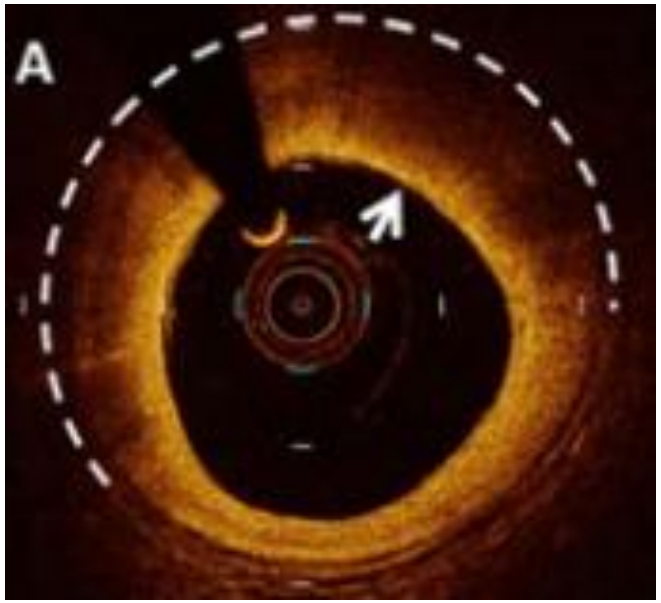

***JACC IMAGING 2020***

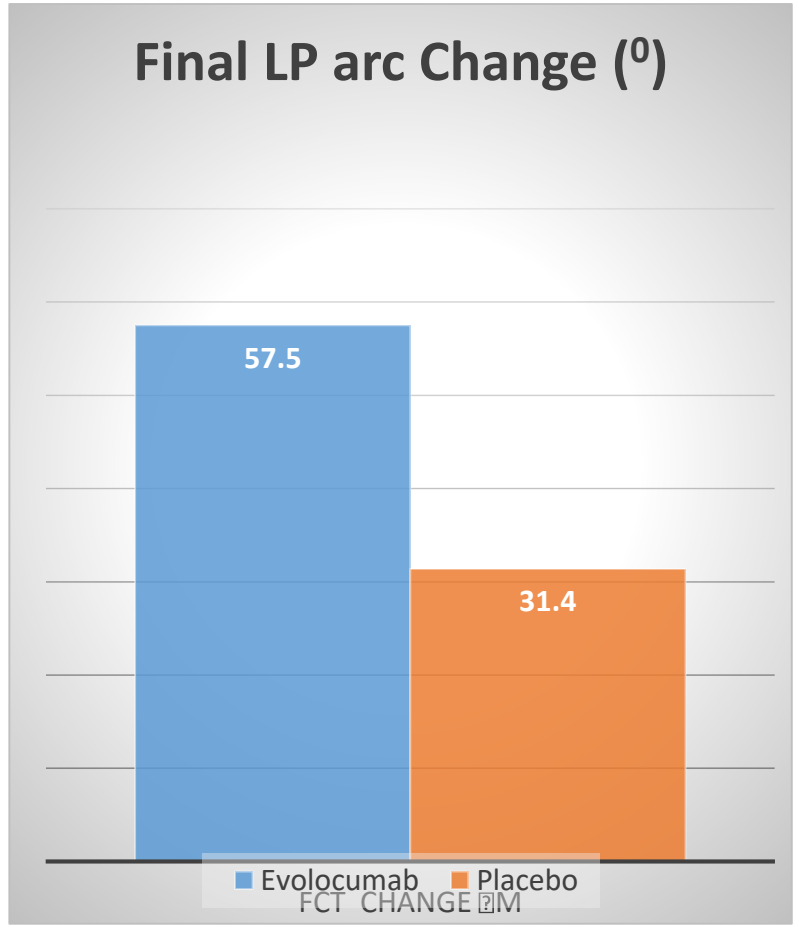
# High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)

## Secondary study end-point: reduction in max lipid arc

**Evolocumab group: LP arc decrease from 230,2$^0$ to 171,9$^0$ (-57.5$^0$)**

**Placebo group: LP arc decrease from from 224,8$^0$ to 193,6$^0$ (- 31.4$^0$)**



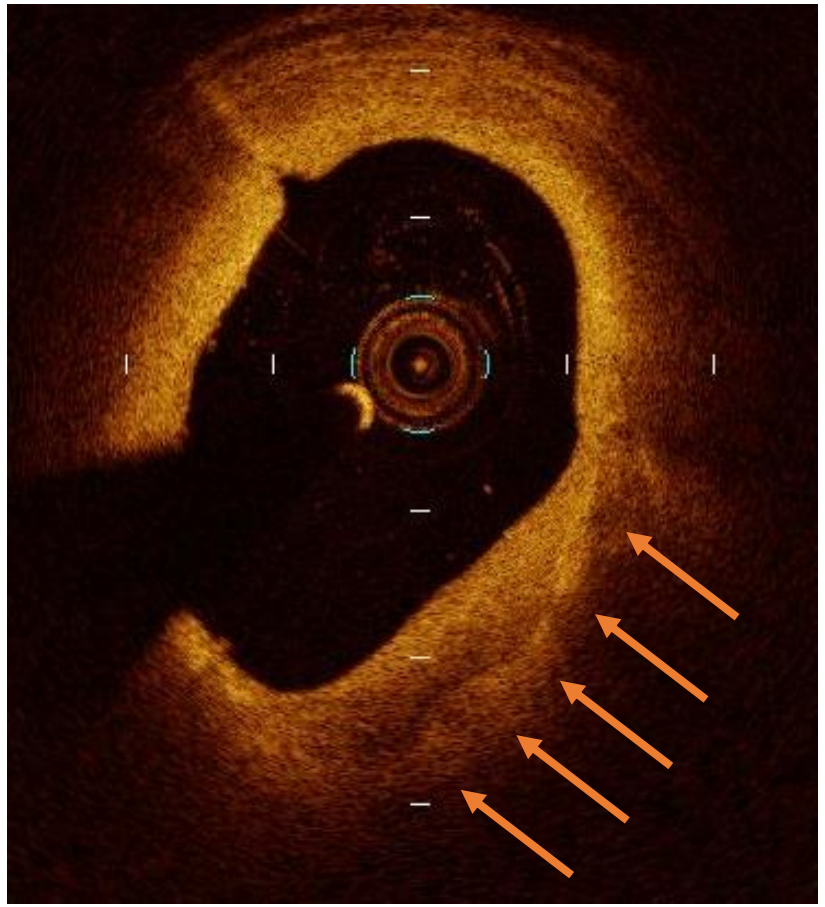




***JACC IMAGING 2020***

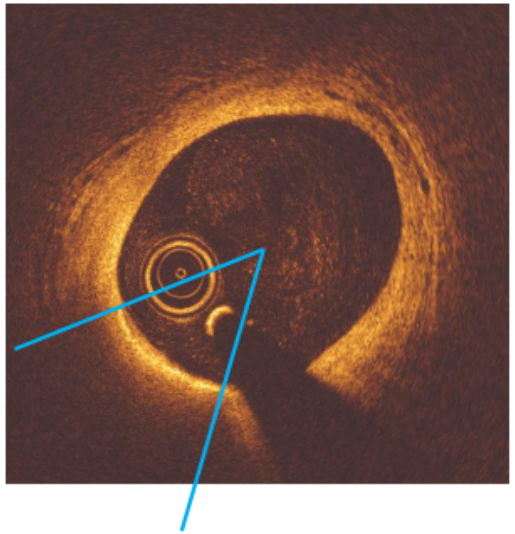
# High-Resolution Assessment of Coronary Plaques in a Global Evolocumab Randomized Study (HUYGENS)

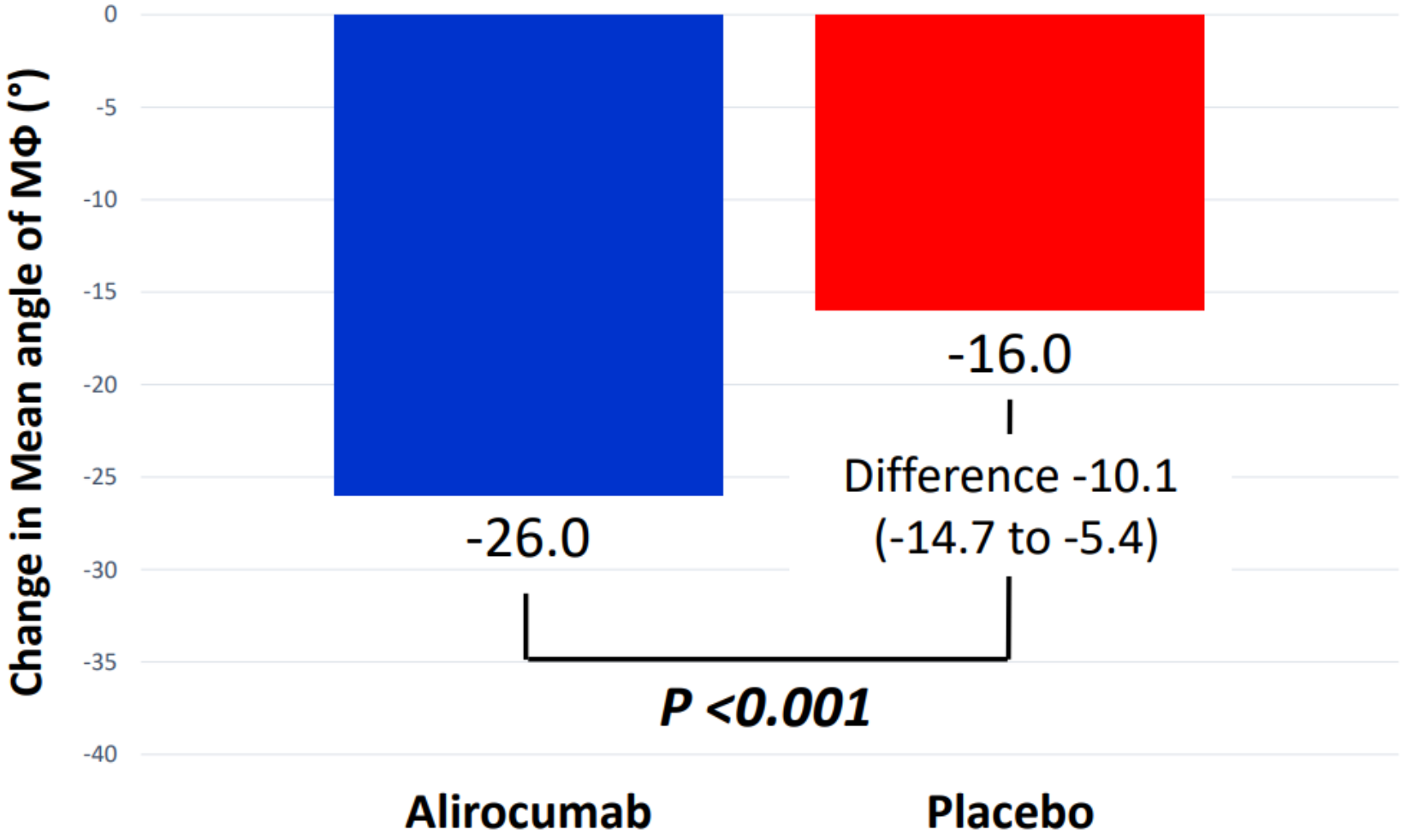
**How about OCT detected macrophages ?**

***Is it possible to reduce inflammatory components with evolocumab?***



# Prespecified Secondary EP:
## Change in Macrophage Angle (OCT)

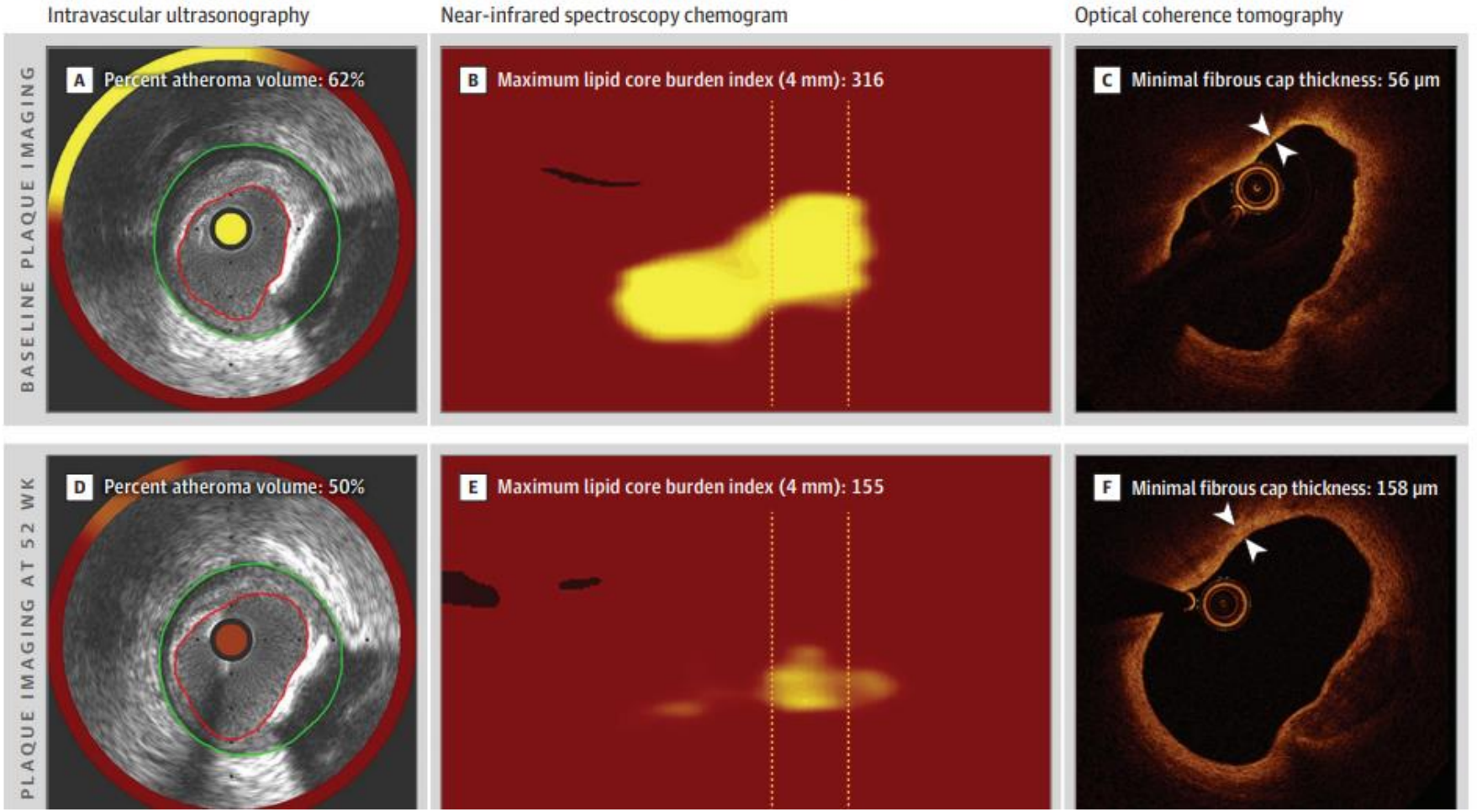





JAMA 2022

# PACMAN

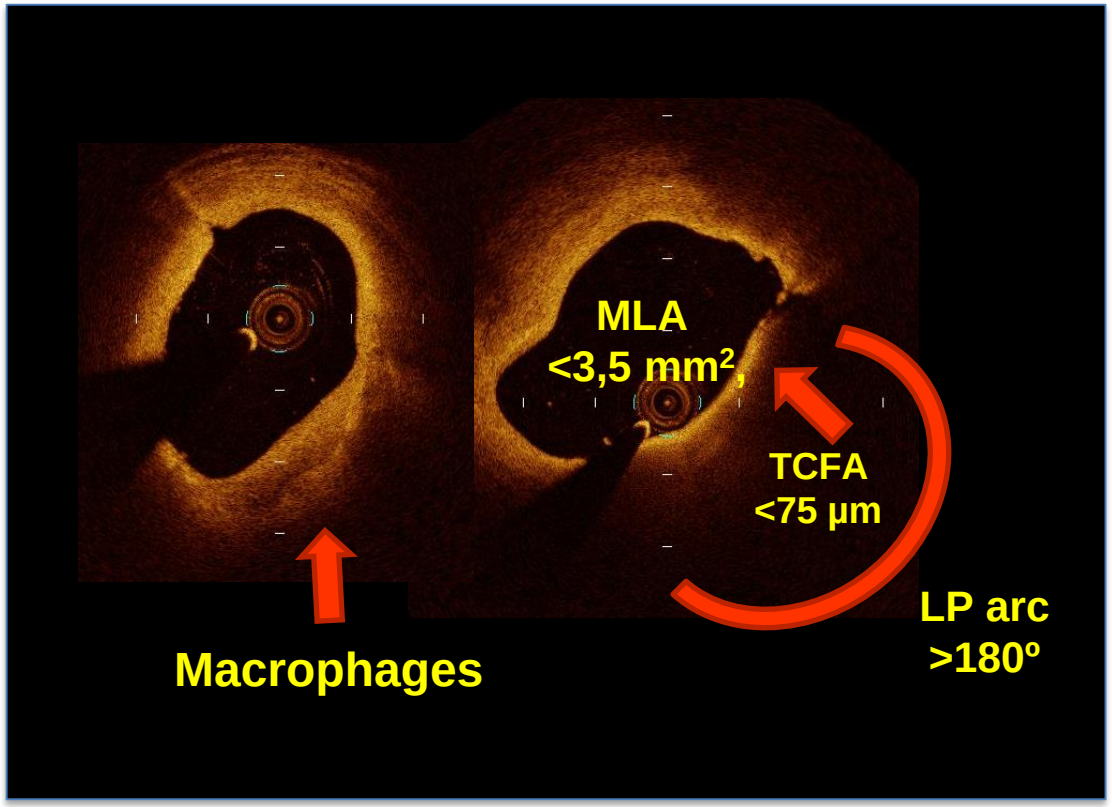
Figure 3. Example of Plaque Regression, Lipid Regression, and Fibrous Cap Thickening in a Trial Patient




JAMA 2022

# The CLIMA study. Eur Heart Journal 2020

**1003** patients enrolled. Prox. LAD interrogation with OCT. 1 Y FU

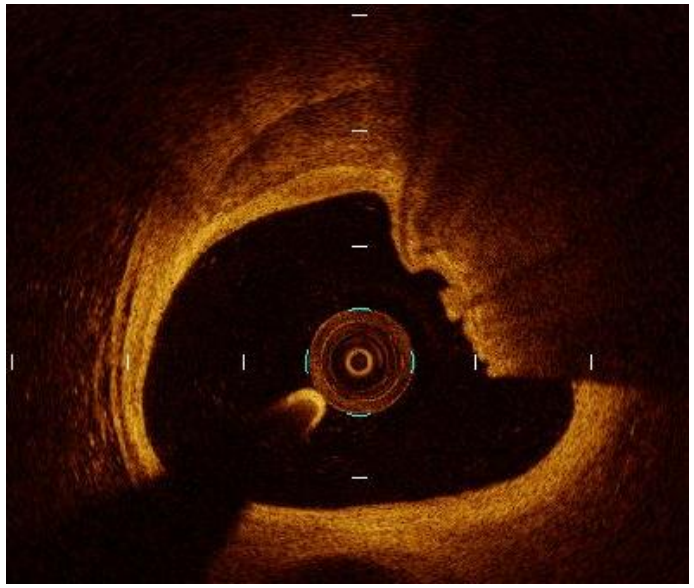



**4 OCT criteria related to hard cardiac end-points (Cardiac Death and target vessel MI)**

**Macrophages**
**LP arc**
**Thin FC**

***All modified by Evolocumab And Alirocumab***

# *Calcific nodules with disruption*

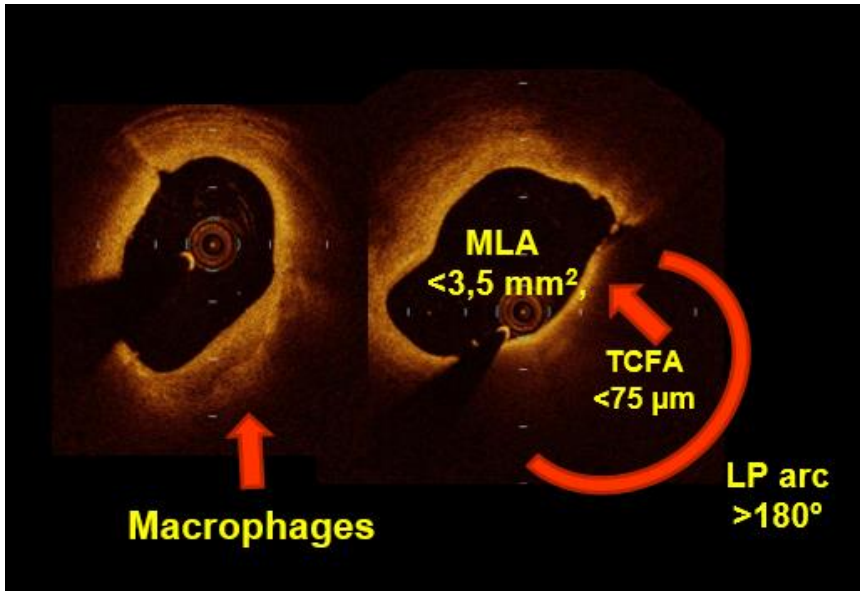


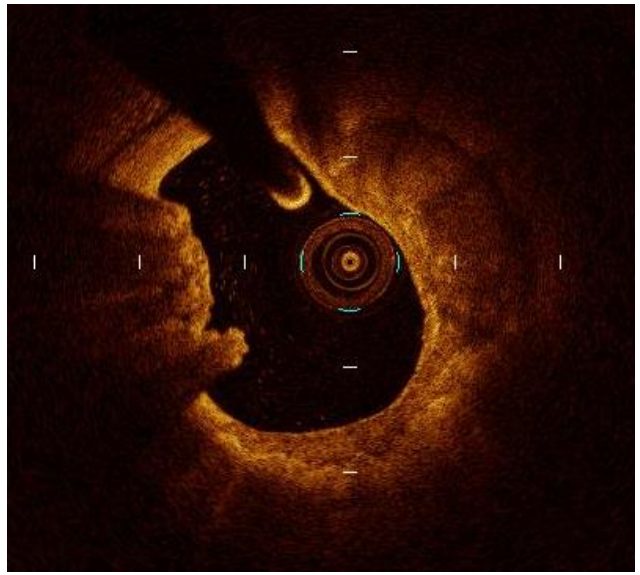
**Room for dual antiplatelet theraphies ?**

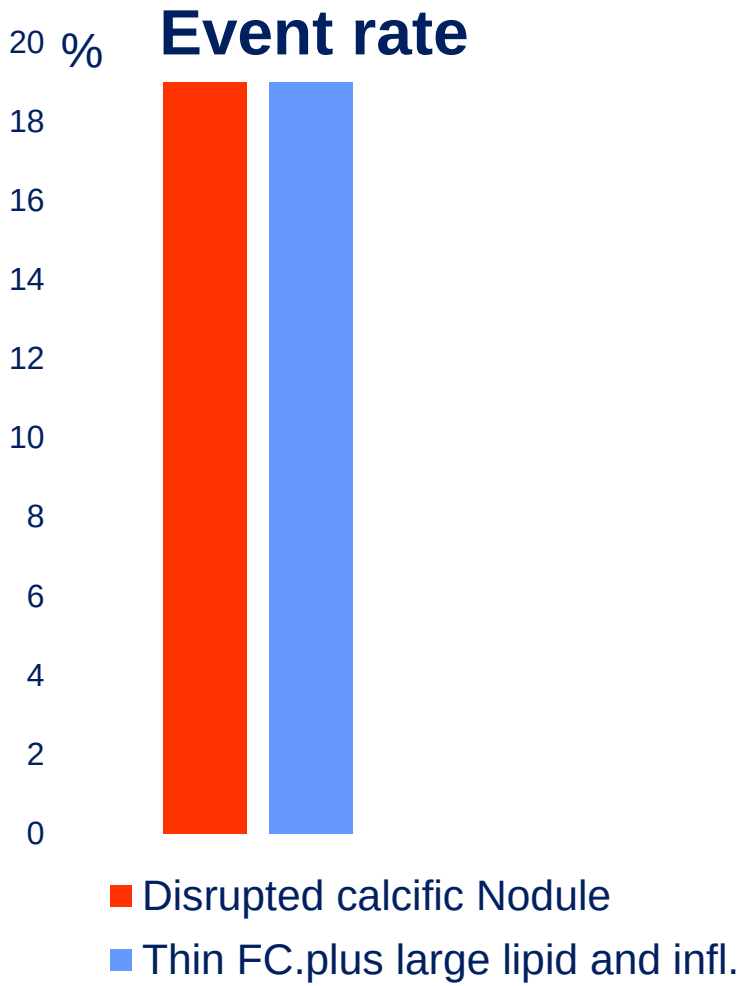
- Kobayashi N, Takano M, Tsurumi M et al. Cardiology 2018; 269:356-361
- Prati et al. Eurointervention 2020.

# Cardiac death and or target MI in the CLIMA Study

## 1003 pts with CAD



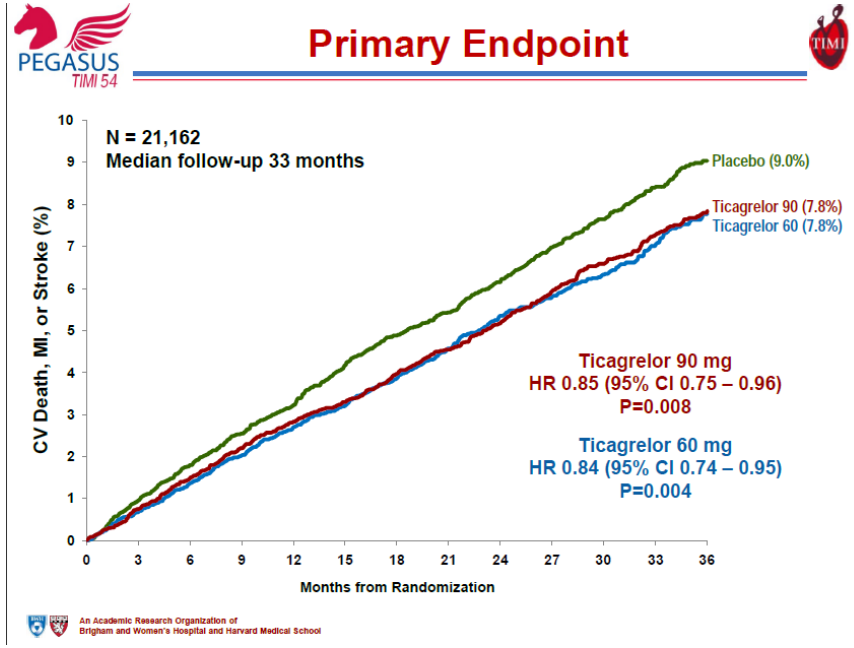






**Vulnerable plaque with TFC, large lipid and Inflammation**

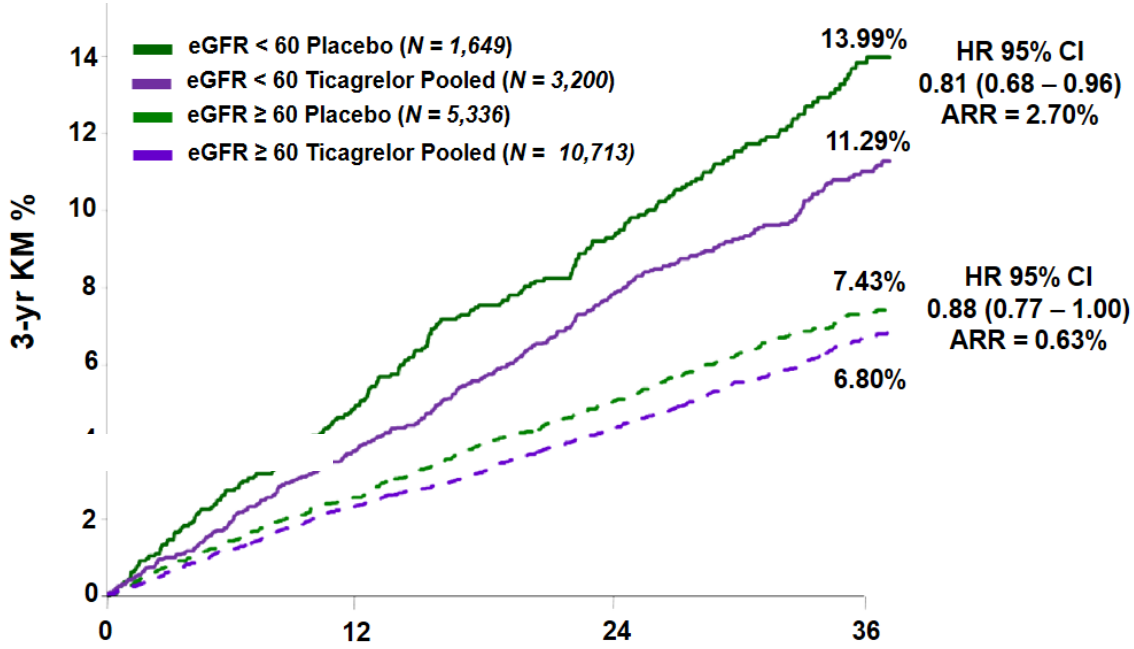
**CN with Disruption**

**European Heart Journal 2020**

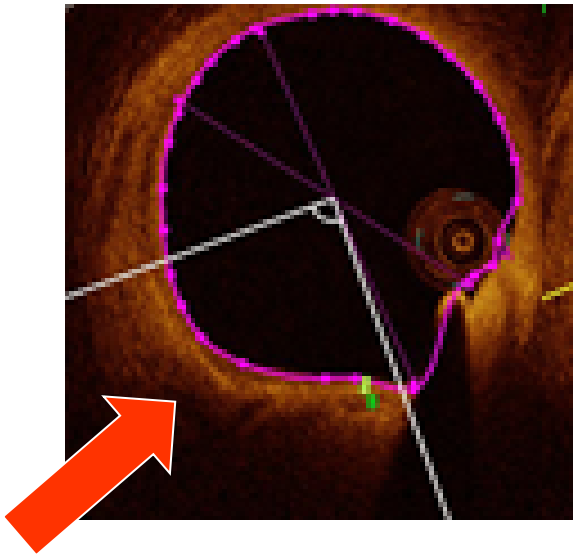



- ✓ Age ≥ 65
- ✓ DM
- ✓ CKD
- ✓ MVD
- ✓ > 1 prior MI

# Long term FU with ticagrelor plus aspirin in pts with renal insuff.



# *Plaques with high inflammation*

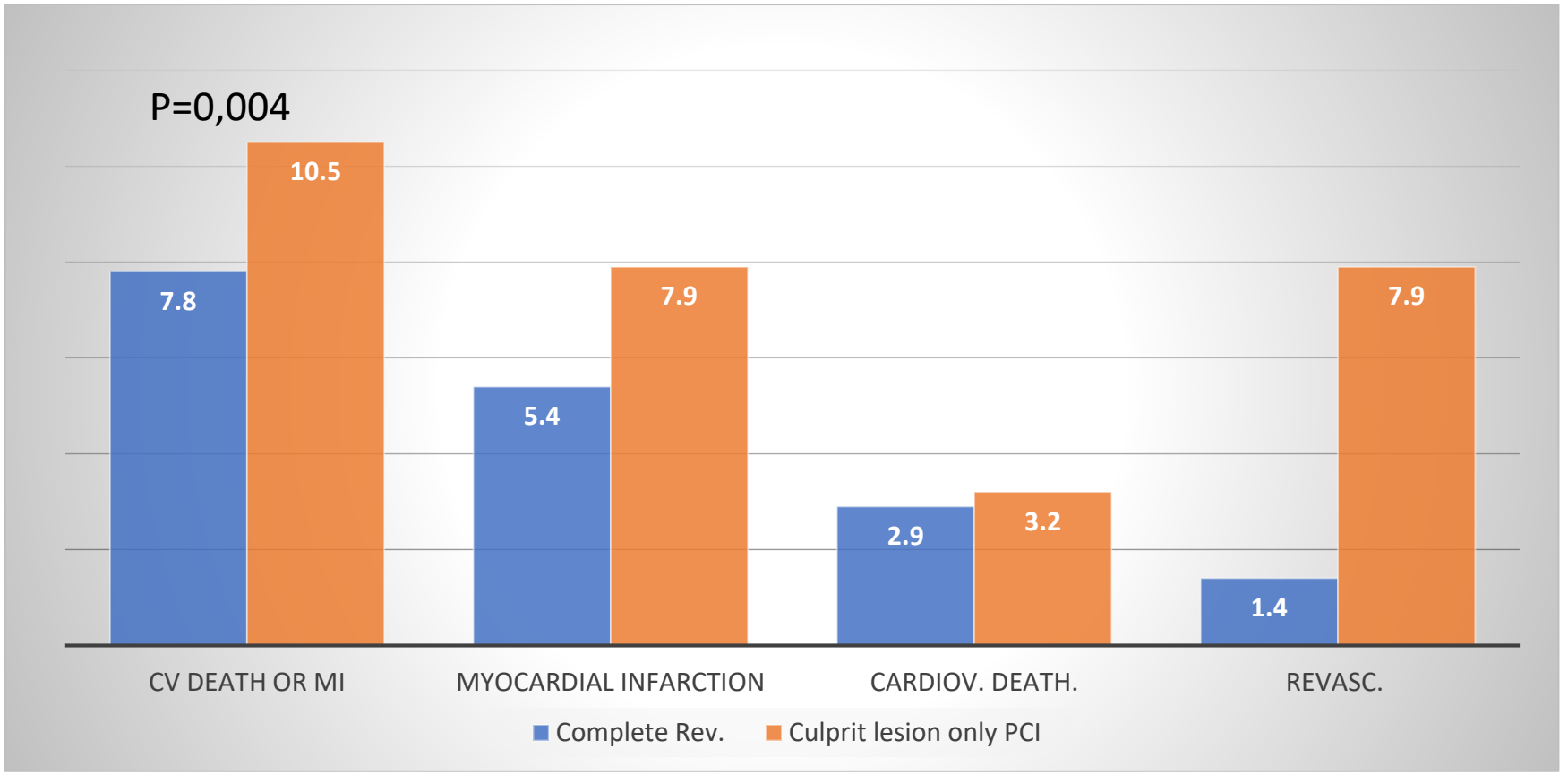


**Room for**
**anti-inflammatory drugs?**

- Treat with coronary intervention

# COMPLETE

- 4041 pts with STEMI and multivessel CAD with successful culprit-lesion PCI
- Complete revascularization with PCI of  significant nonculprit lesions or no further revascularization.




**New Engl J Med 2019**

# The INTERCLIMA trial
## DESIGN

CCC 2022

### Objective


Treatment of non-culprit intermediate coronary lesions in patients with ACS.

### Study population

ACS patients with intermediate coronary lesions (i.e., 40% to 70% diameter stenosis) in non-culprit vessels.

### Sample size

1420 pts (710 per group) randomized participants to provide over 90% power to detect non inferiority of OCT vs iFR/FFR/RFR for the primary composite event rate

### Primary Endpoint

2-year

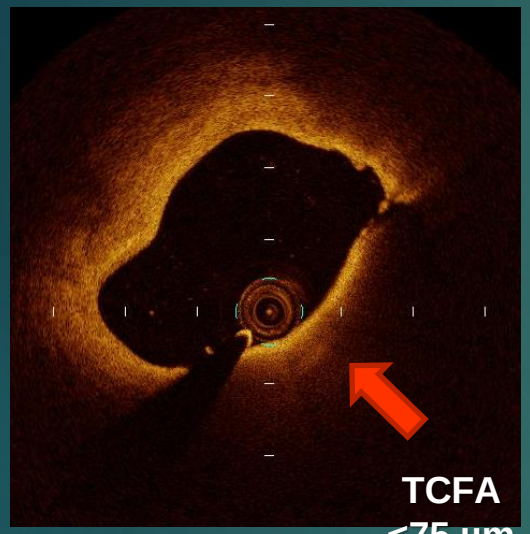
Composite of cardiac death and non-fatal spontaneous target-vessel myocardial infarction

**Clinicaltrial.gov ID: NCT050227984**

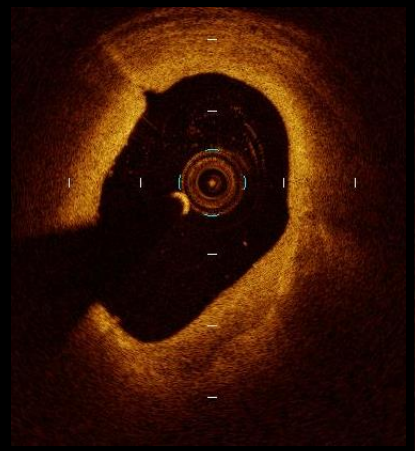
# Vulnerability criterion applied

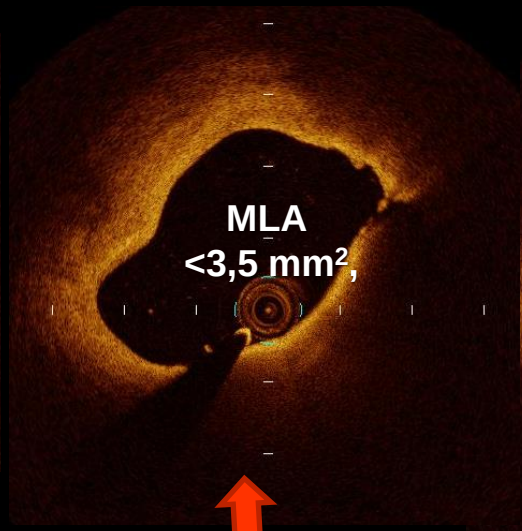
CCC 2022

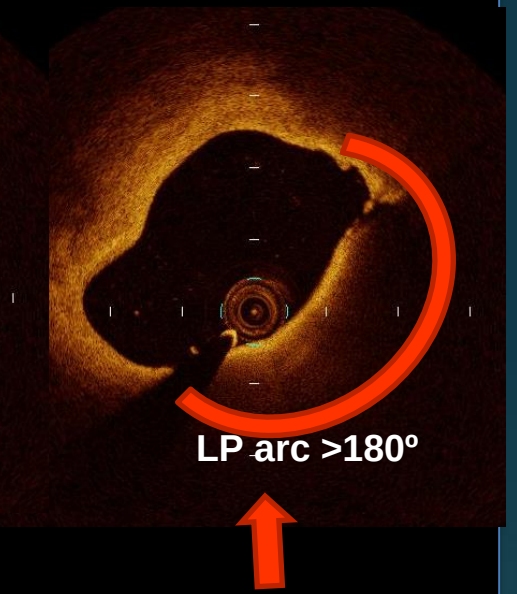
## Presence of thin FC thickness plus two of the other three vulnerable variables




At least 2



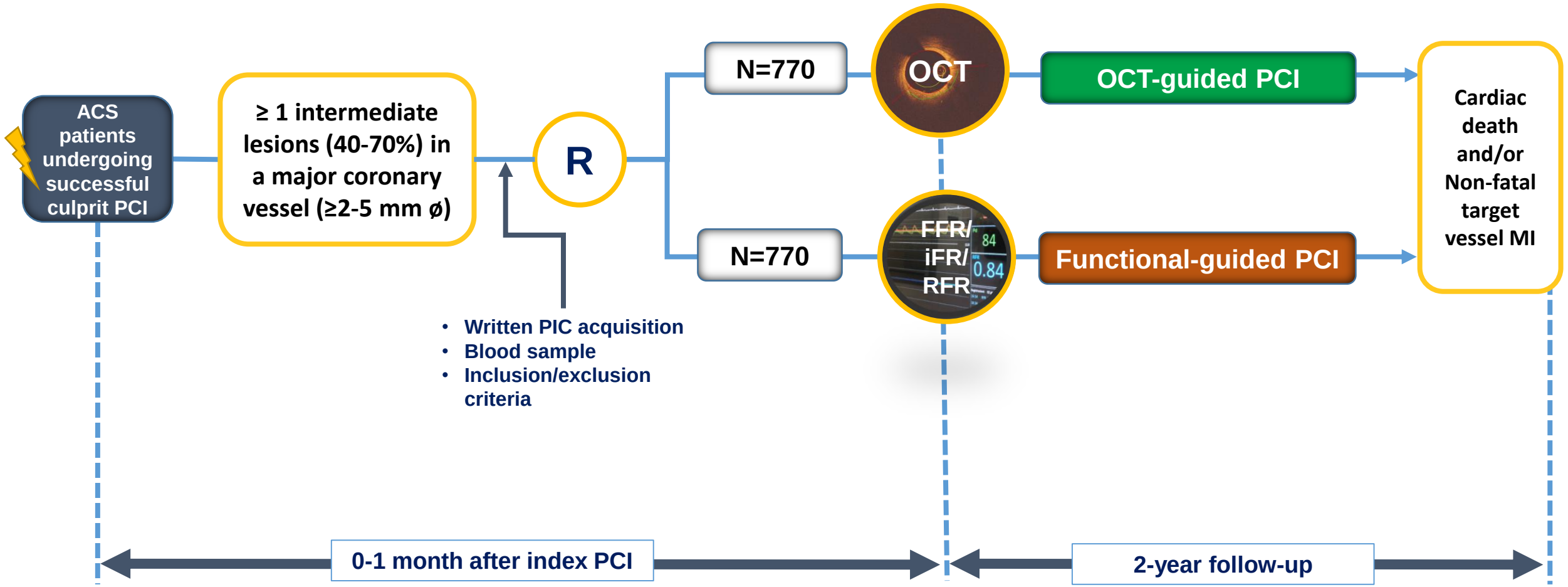



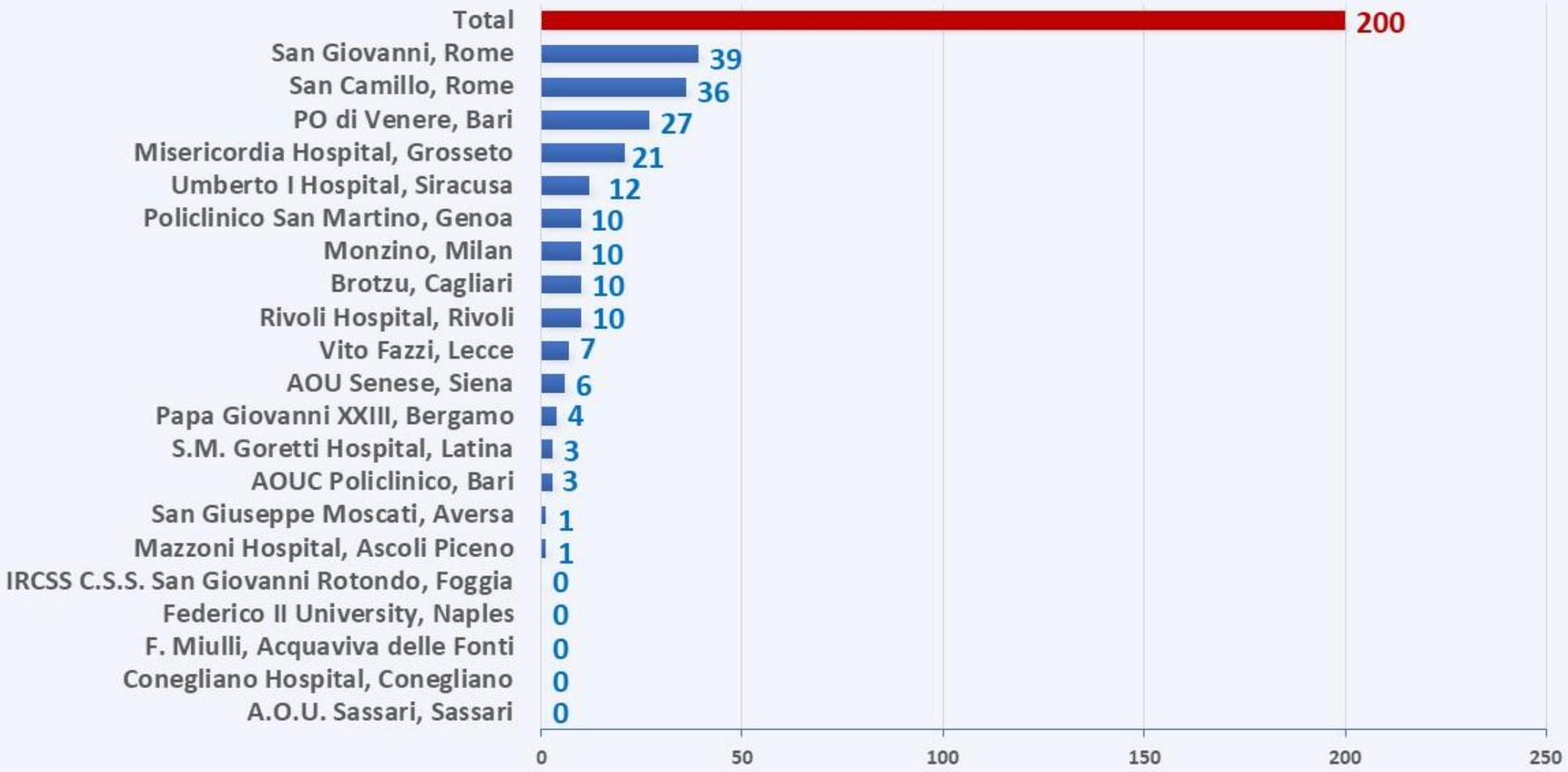

| | | | |
|---|---|---|---|
| Hazard ratio | 4.65 (2.4-9.0) | 2.66 (1.2-6.1) | 2.07 (1.1-4.0) | 2.40 (1.2-4.8) |
| p value | <0.001 | 0.021 | 0.032 | 0.013 |

CLIMA study. Prati et al. Eur Heart J. 2020;41:383-391.

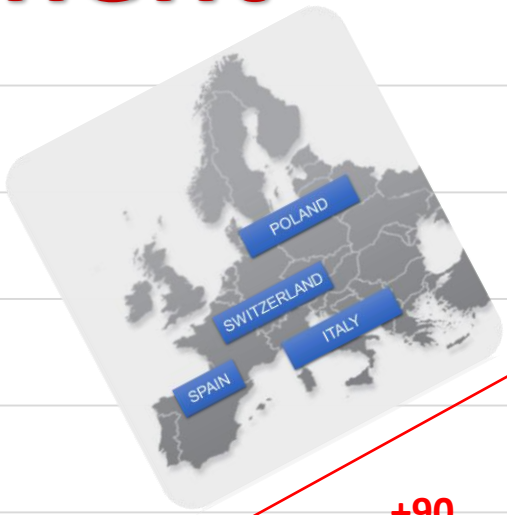
# INTERCLIMA study design
## multicenter, international, randomized controlled trial



# INTERCLIMA trial



# Enrollment




1600
1400
1200
1000
800
600
400
200
0

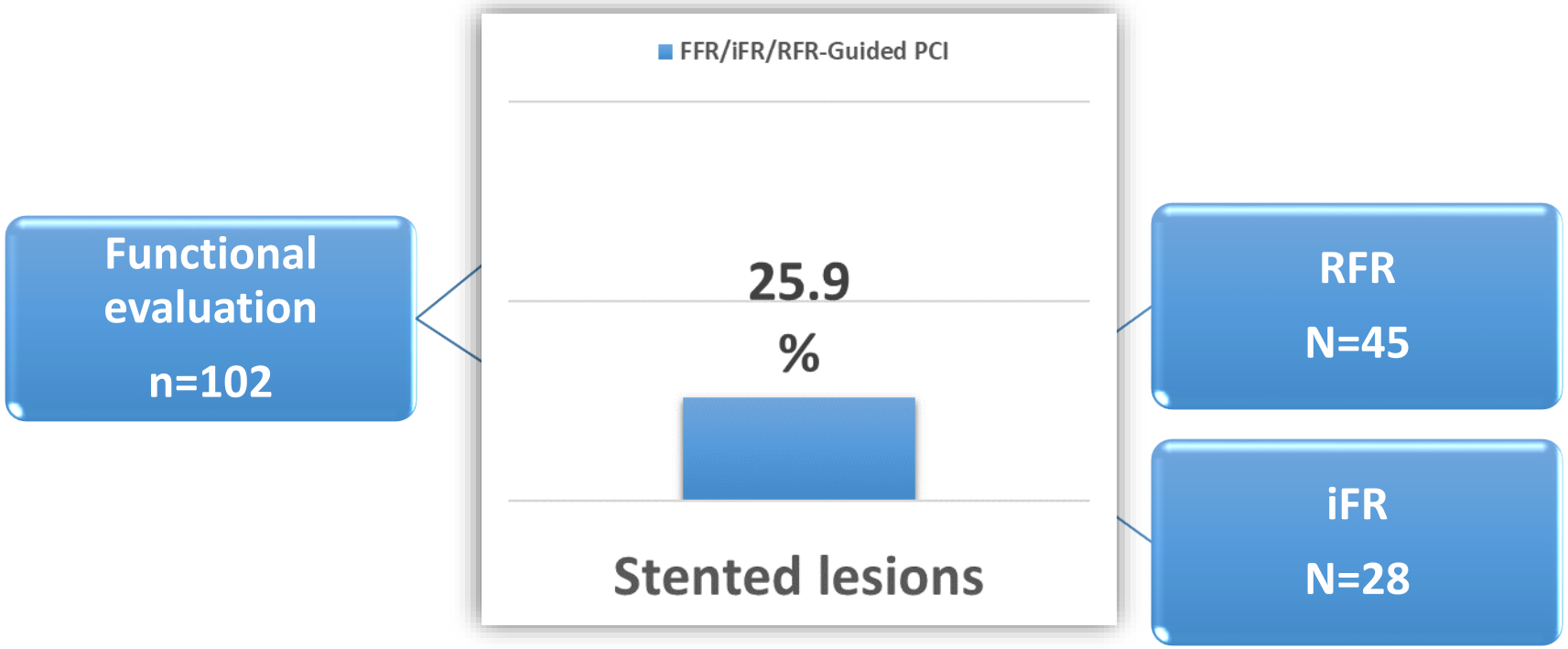
Oct-21 Nov-21 Dec-21 Jan-22 Feb-22 Mar-22 Apr-22 May-22 Jun-22 Jul-22 Aug-22 Sep-22 Oct-22 Nov-22 Dec-22 Jan-23 Feb-23 Mar-23 Apr-23 May-23 Jun-23 Jul-23 Aug-23 Sep-23 Oct-23 Nov-23 Dec-23 Jan-24

9 10 13 25 37 51 62 84 93 102 115 132 152 200 250 330 410 500 590 680 770 860 950 1040 1130 1230 1420

+9 +13 +17 +30 +50 +50 +80 +90 +90 +90 +90 +90 +90 +90

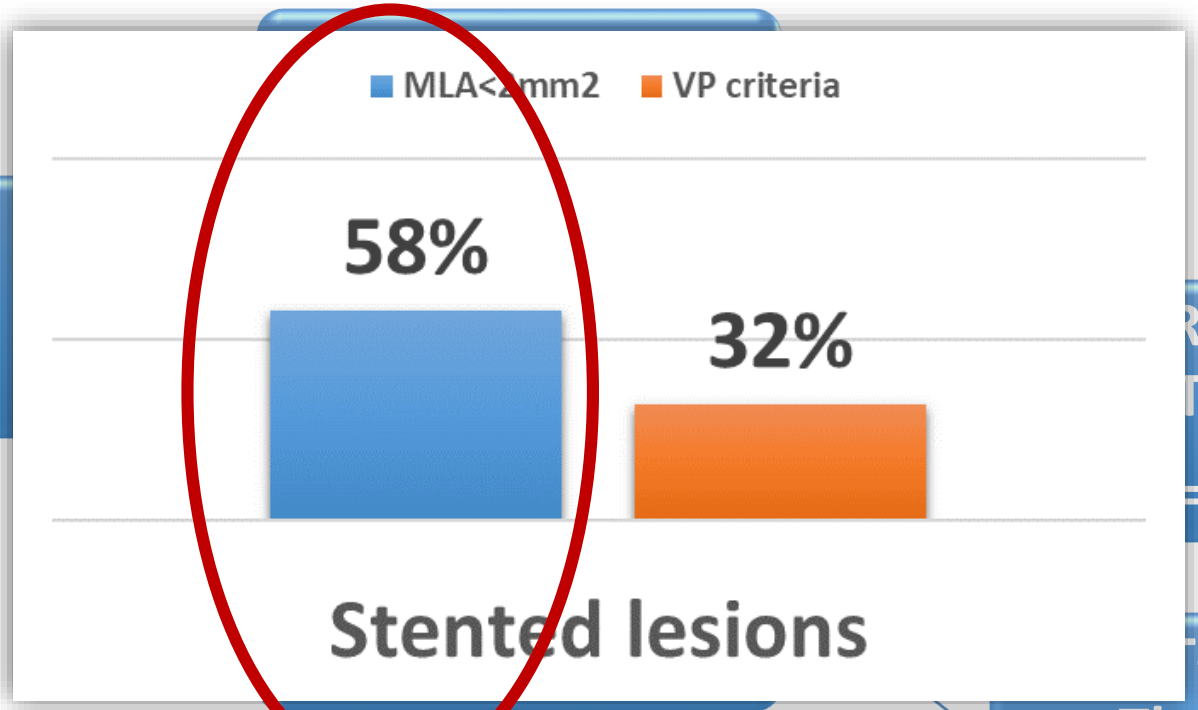
The INTERCLIMA trial
NCT05027984

# Functional evaluation



# OCT-guided lesion assessment/PCI

OCT
n=92




RCLIMA VP
T criteria
=18/60

T-defined
Thrombus
N=3/60

# Take Home Messages

- *Studies on plaque vulnerability are very encouraging*
- *Assessment of plaque morphology by meands of OCT and NIRS-IVUS predict the risk of hard events better than physiology.*
- *A snapshot of plaque characteristics at a certain point identify long term clinical risk*
- *On going studies on plaque vulnerability will telle us whether vulnerable plaques should be treated*

# Conclusions

- **Imaging modalities to detect atherosclerosis permit a precision medicine approach based on fenotype evaluation**
- **Non invasive assessment of atherosclerosis (Calcium score, TC, femoral and carotid echodoppler) should be encouraged**
- **Qualitative assessment of atherosclerosis with invasive imaging modalities identifies pts at high risk of coronary events.**
- **CT scan is an alternative approach to coronary angiography**