

Meccanismi fisiopatologici e implicazioni cliniche dell'infarto miocardico con coronarie angiograficamente normali

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Myocardial infarction with non-obstructive coronary artery disease

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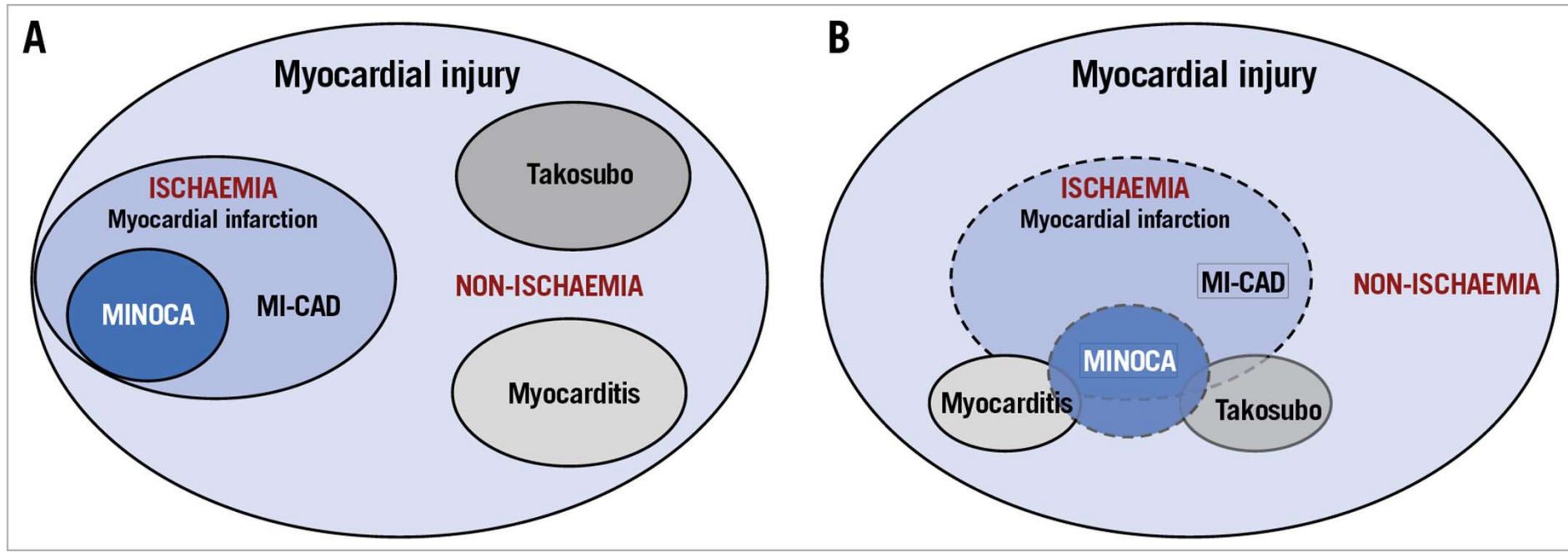
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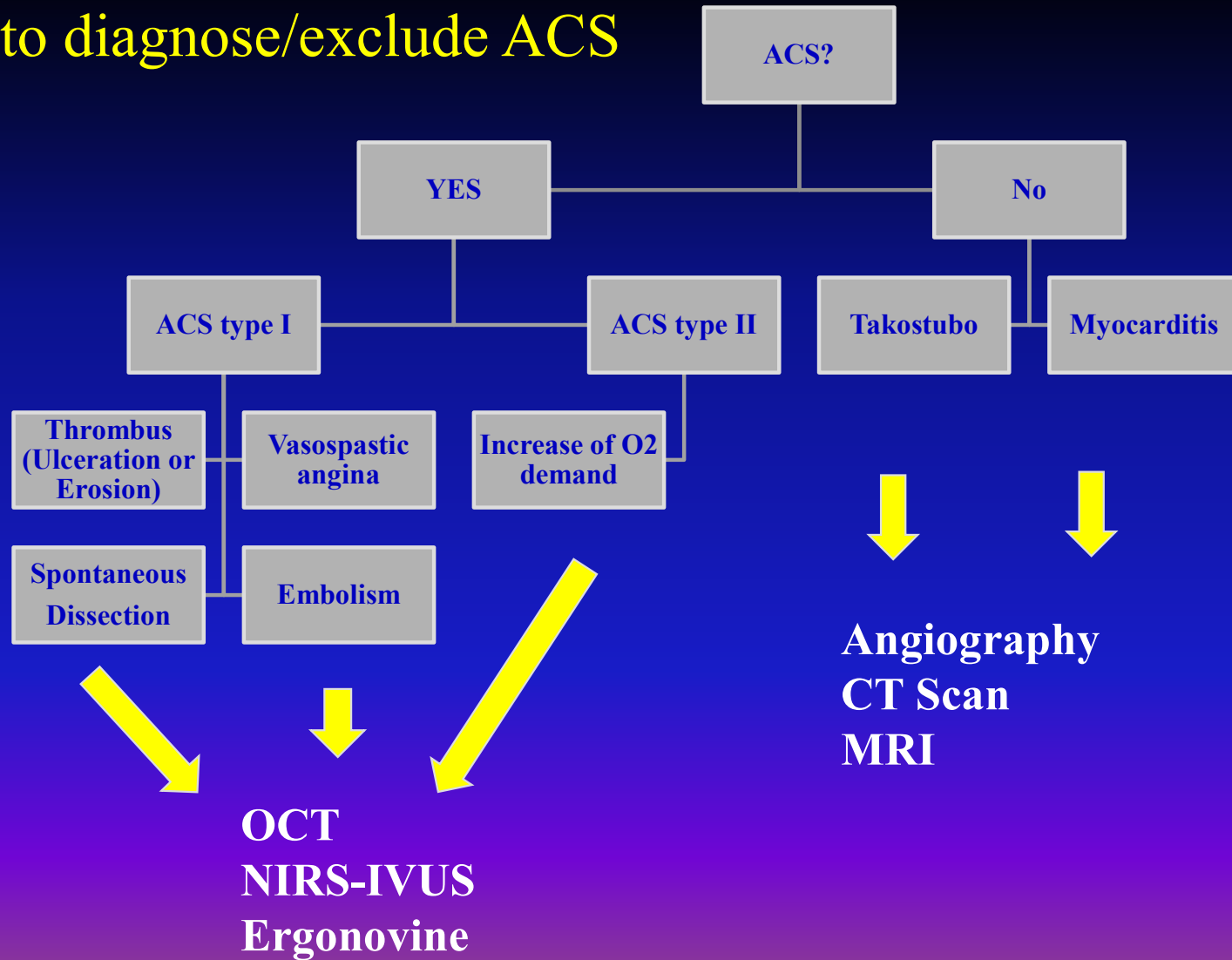


State of the Art
by EuroIntervention

EuroIntervention 2



An algorithm to diagnose/exclude ACS



Angio leaves doubts in *about 10-20% of cases of ACS*

- **Ambiguous single lesion**
- **Multiple non significant lesions**
- ***Uncertainty whether to diagnose an ACS and or to treat the lesion***

First of all look carefully at the coronary angiogram

.....Absence of significant narrowing does not mean much !

..... Smooth contour means no CAD

..... Smooth contour means no CAD



Consider

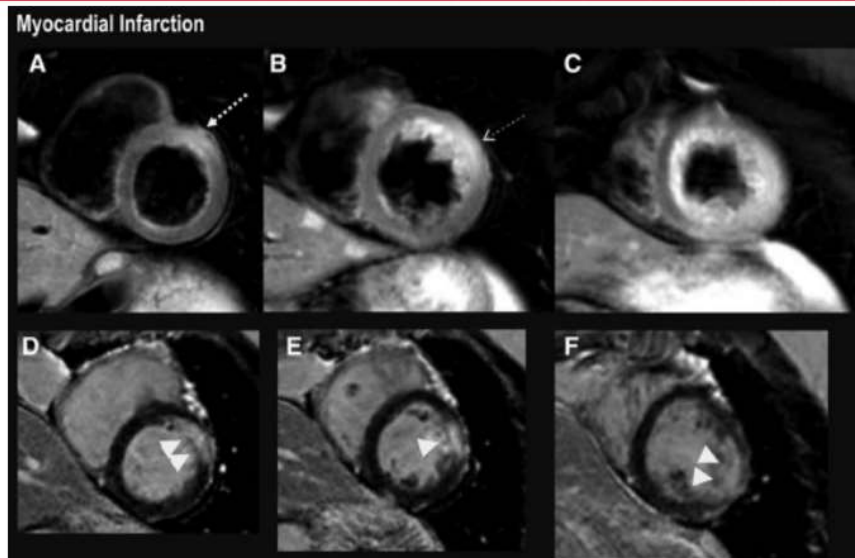
- Non ACS
- Takotsubo especially in presence of ST elev.
- Myocarditis
- ACS (less likely)
 - Spasm
 - Resolved thrombus in absence of atherosclerosis
 - Resolved coronary embolism

HARP-MINOCA: CMR

T2-weighted images

MINOCA in LAD territory

Late gadolinium enhanced images



OCT culprit
CMR evidence of
infarction or regional
ischemic injury in 69%

Ischemic CMR findings
(LGE or regional injury)
44% no OCT culprit

(suspect culprit
coronary spasm,
thromboembolism, or missed
culprit lesion)

MRI very useful for a
differential diagnosis
(ACS vs Myocarditis,
or Stress
Cardiomyopathy)

CMR in Women with Chest Pain and No Obstructive CAD

Women's Ischemia Syndrome Evaluation – Coronary Vascular Dysfunction

Myocardial infarction with non-obstructive coronary artery disease

Bertil Lindahl^{1*}, MD, PhD; Tomasz Baron¹, MD, PhD; Mario Albertucci², MD; Francesco Prati^{2,3}, MD

1. Department of Medical Sciences, Uppsala University, Uppsala, Sweden; 2. Centro per la Lotta contro l'Infarto (CLI) Foundation, Rome, Italy; 3. Uni-Camillus, Saint Camillus International University of Health Sciences, Rome, Italy

“Angiographically, culprit plaques may seem normal, although there may be findings compatible with MINOCA. These include mild narrowing (less than 50%), lesions with asymmetry, narrow neck, irregular borders, haziness or radiolucent flap”.

**Mild vessel irregularities
= Atherosclerosis**



**Marked vessel irregularities
= advanced stage atherosclerosis**



Marked vessel irregularities = Advanced stage atherosclerosis



Risk ratios for yearly rate of overall mortality in patients with MINOCA vs patients with myocardial infarction associated with coronary artery disease.

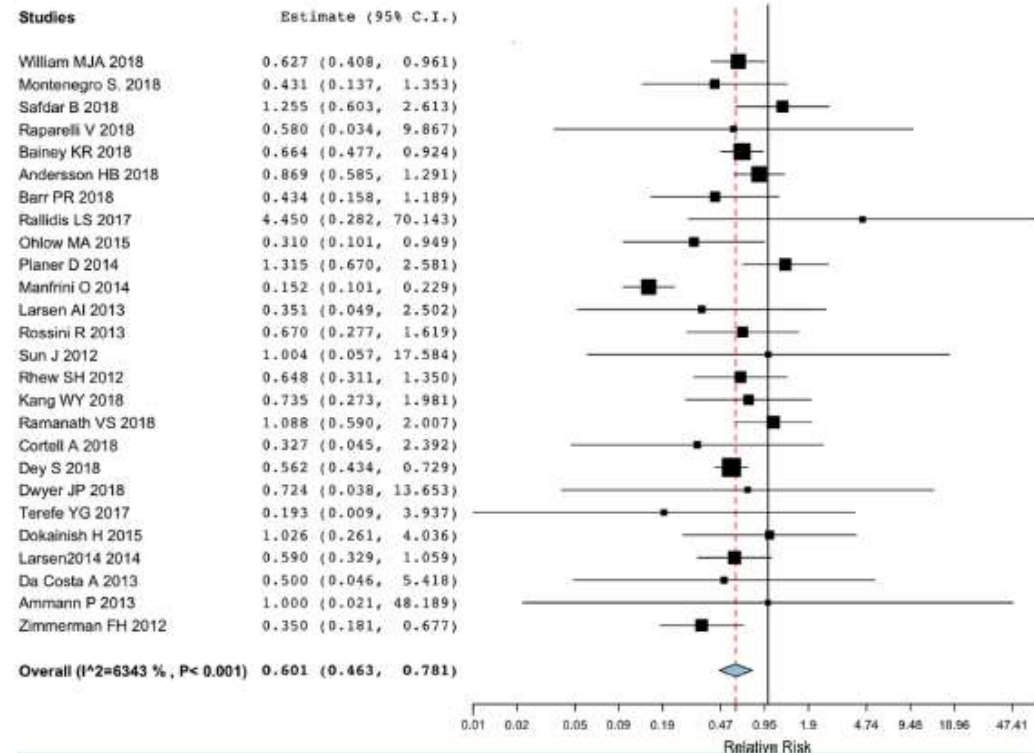


Figure 3 Forest plot of risk ratios for yearly rate of overall mortality in patients with MINOCA vs patients with myocardial infarction associated with coronary artery disease. Markers represent point estimates of risk ratios, and marker size represents study weight. Horizontal bars indicate 95% confidence intervals (CIs).

Pelliccia et al. Am J Med. 2017

Long-term survival and causes of death in patients with ST-elevation acute coronary syndrome without obstructive coronary artery disease.

Anderrson et al.

Eur Heart Journal 2017

Table 2 Risk of death in patients with ST-elevation acute coronary syndrome

	Hazard ratio (95% confidence interval)	P-value
Short-term mortality (<=30 days)		
Model 1		
Obstructive CAD	1.0 (reference)	—
Non-obstructive CAD	0.49 (0.27–0.89)	0.018
Normal coronary arteries	0.31 (0.11–0.83)	0.021
Model 2		
Obstructive CAD	1.0 (reference)	—
Non-obstructive CAD and elevated TnT	0.74 (0.40–1.36)	0.333
Non-obstructive CAD and normal TnT	0.14 (0.02–1.02)	0.052
Normal coronary arteries and elevated TnT	0.40 (0.13–1.25)	0.116
Normal coronary arteries and normal TnT	0.25 (0.04–1.75)	0.162
Long-term mortality (>30 days)		
Model 1		
Obstructive CAD	1.0 (reference)	—
Non-obstructive CAD	1.15 (0.77–1.72)	0.487
Normal coronary arteries	2.44 (1.58–3.76)	<0.001
Model 2		
Obstructive CAD	1.0 (reference)	—
Non-obstructive CAD and elevated TnT	1.21 (0.73–1.98)	0.463
Non-obstructive CAD and normal TnT	1.07 (0.54–2.09)	0.856
Normal coronary arteries and elevated TnT	2.65 (1.52–4.61)	0.001
Normal coronary arteries and normal TnT	2.67 (1.39–5.14)	0.003

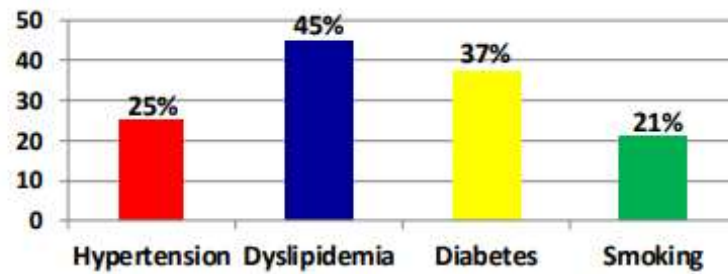
Long-term survival and causes of death in patients with ST-elevation acute coronary syndrome without obstructive coronary artery disease. Andersson et al. Eur Heart Journal 2017

	Obstructive CAD, n = 4239	Non-obstructive CAD, n = 298	Normal coronary arteries, n = 256	P-value
Age, median (range)	63 (24–101)	65 (32–91)	55 (17–96)	<0.001
Male sex, n (%)	3138 (74)	182 (61)	160 (63)	<0.001
Body mass index (kg/m ²), median (IQR)	26 (24–29)	25 (22–28)	25 (22–29)	<0.001
Hypertension, n (%)	1582 (40)	126 (44)	60 (24)	<0.001
Hyperlipidaemia, n (%)	1091 (30)	96 (37)	36 (16)	<0.001
Active or previous smoker, n (%)	2814 (75)	179 (69)	121 (54)	<0.001
Diabetes type 1 or 2, n (%)	514 (13)	33 (12)	22 (9)	0.167
Previous myocardial infarction, n (%)	389 (10)	33 (12)	2 (1)	<.001
Previous stroke, n (%)	200 (5)	19 (7)	4 (2)	0.023
Family history of ischaemic heart disease, n (%)	1239 (35)	72 (29)	43 (20)	<0.001
History of heart failure, n (%)	146 (4)	16 (6)	7 (3)	0.159
Killip class, n (%)	—	—	—	<0.001
I	3709 (91)	243 (95)	216 (98)	—
II	230 (6)	8 (3)	3 (1)	—
III	46 (1)	3 (1)	2 (1)	—
IV	79 (2)	3 (1)	0 (0)	—
Admission to cardiac invasive centre, n (%)	—	—	—	<0.001
By ambulance	2839 (69)	170 (58)	133 (54)	—
Referred from local hospital	1272 (31)	122 (42)	114 (46)	—
Cardiac arrest before procedure, n (%)	307 (7)	9 (3)	3 (1)	<0.001
Cardiogenic shock before procedure, n (%)	122 (3)	2 (1)	0 (0)	0.003

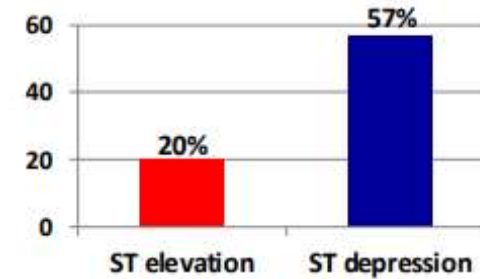
Pelliccia et al. Am J Med. 2017

Presenting features of 36,932 MINOCA patients

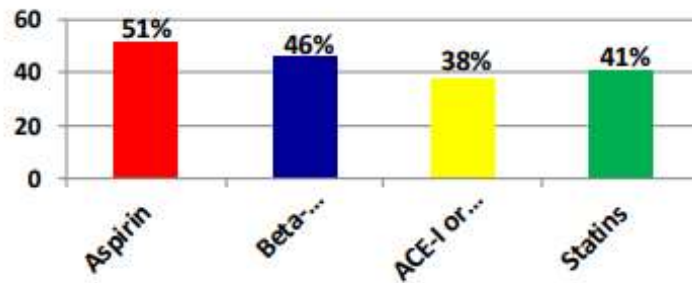
CARDIOVASCULAR RISK FACTORS



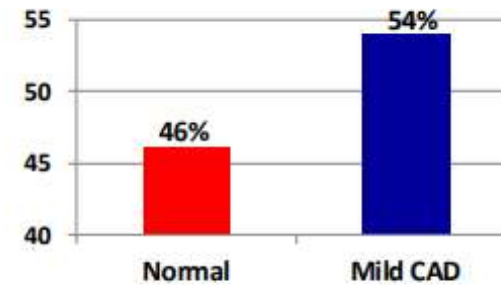
ECG FINDINGS



TREATMENT



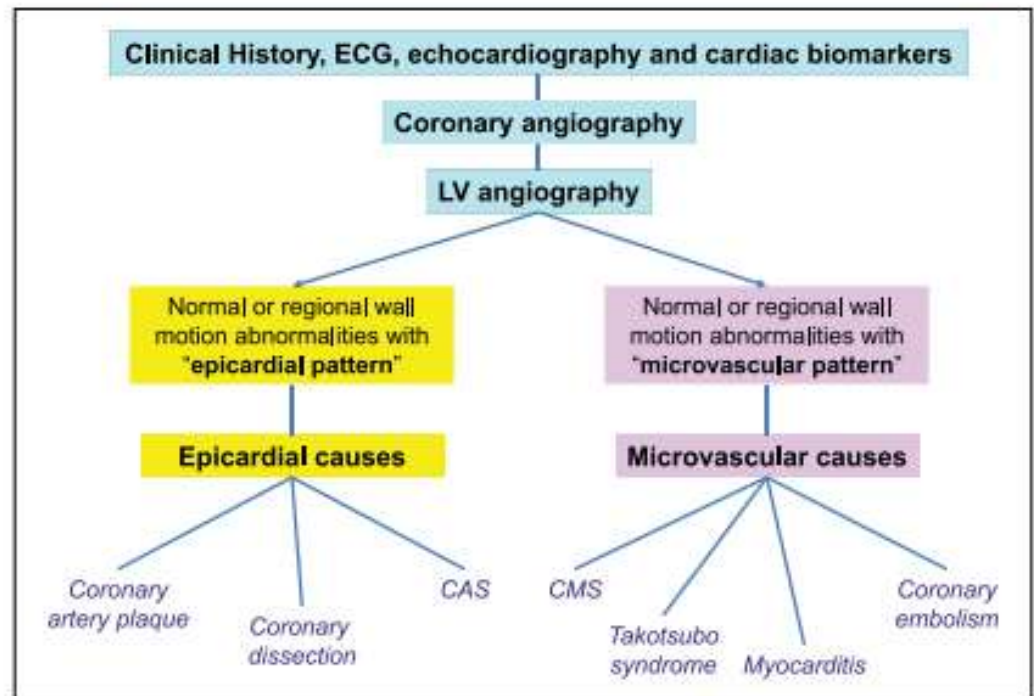
CORONARY ARTERIES



Editor's Choice- Pathophysiology, diagnosis and management of MINOCA: an update

Giancarla Scalone, Giampaolo Niccoli and Filippo Crea

European Heart Journal: Acute Cardiovascular Care
2019, Vol. 8(1) 54–62
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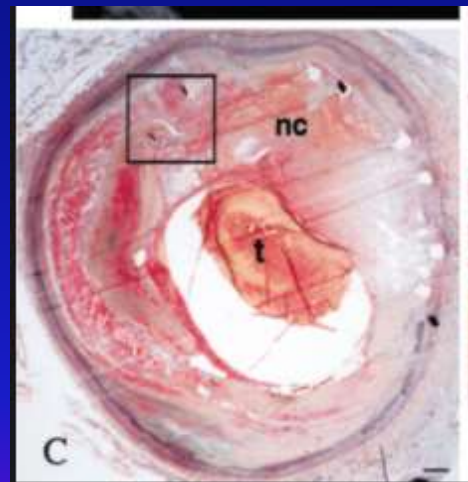


**Angiographic identification of
culprit lesions in patients with
ACS is usually a simple task**

Thrombus is the ultimate event of the coronary pathway leading to ACS

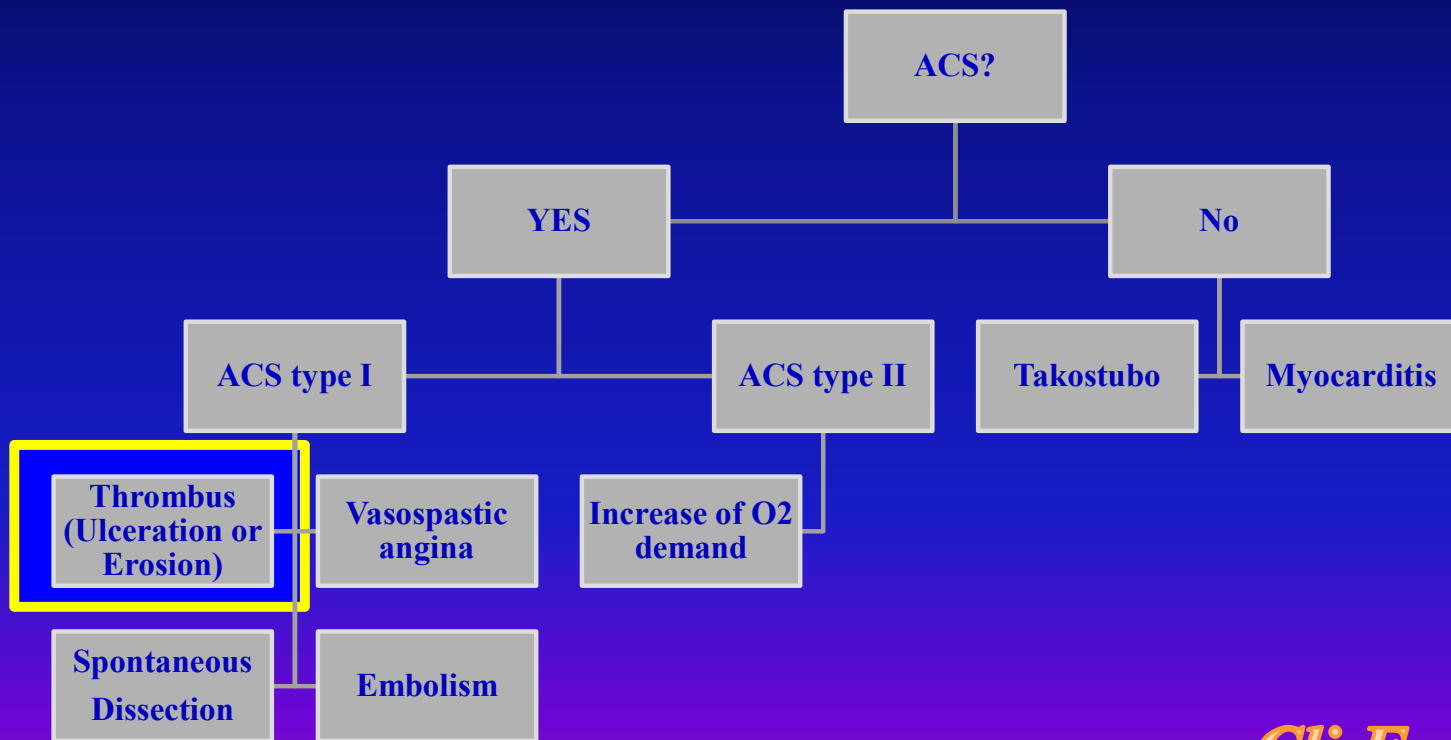


Occlusive thrombus



Non occlusive thrombus

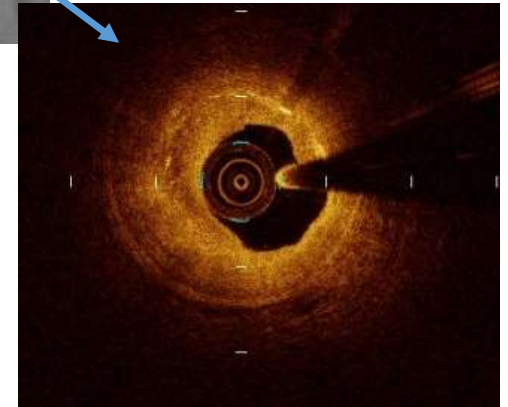
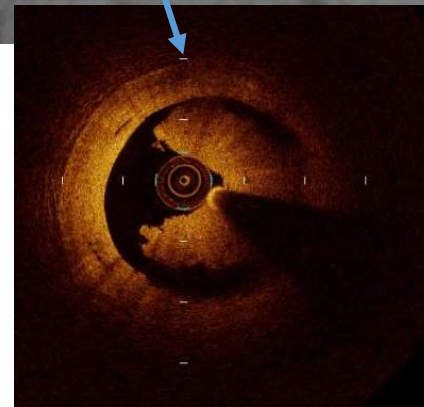
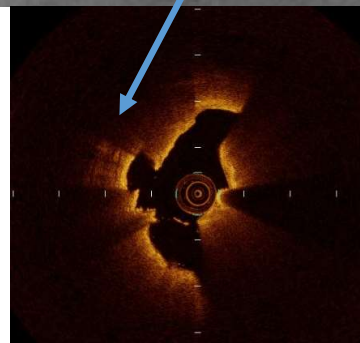
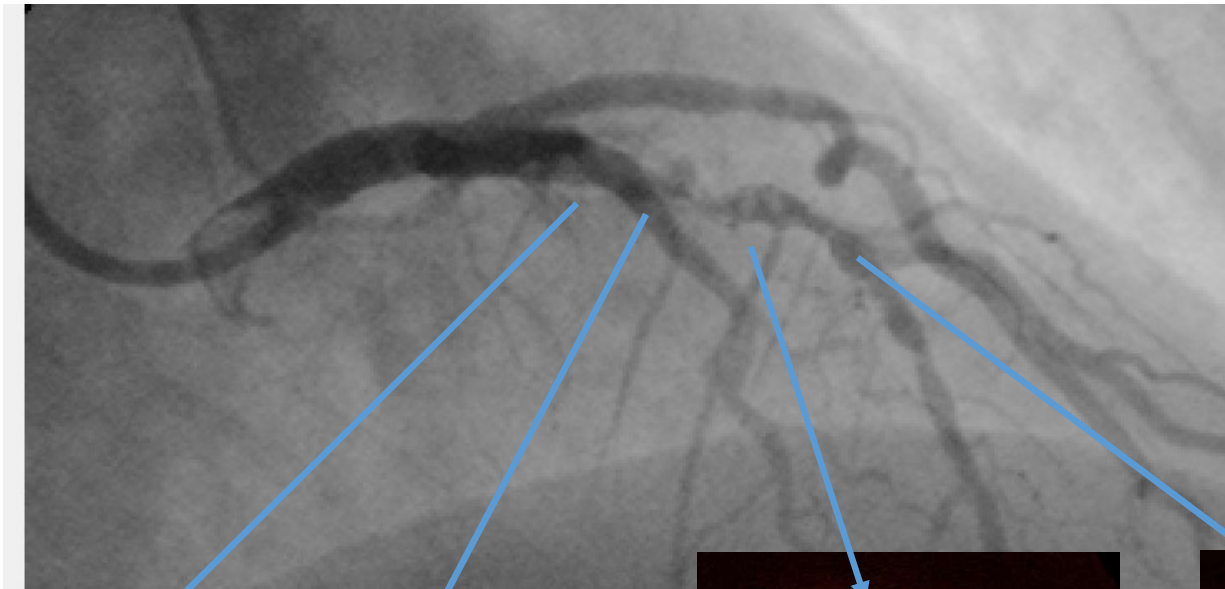
An algorithm to diagnose/exclude ACS



- Plaque rupture/ endothelial erosion are common causes of MINOCA

**ACS pt with severe LAD narrowing.
Typical OCT aspect. Plaque ulceration with large thrombus**

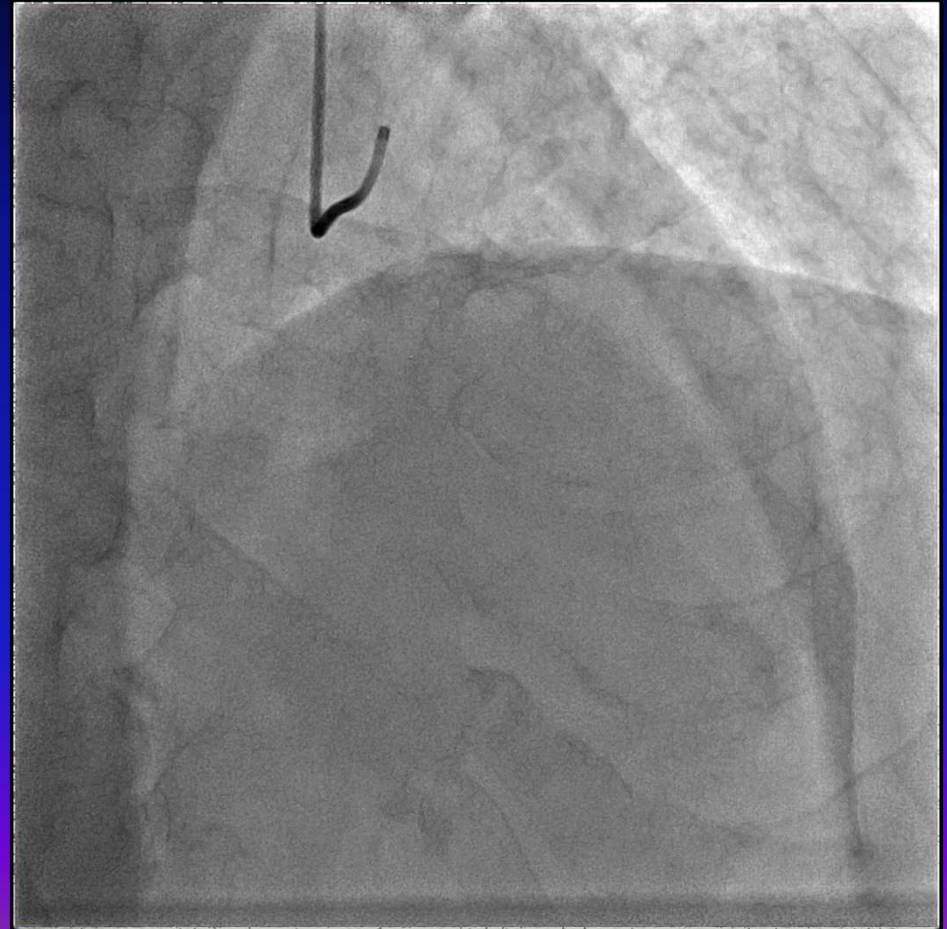
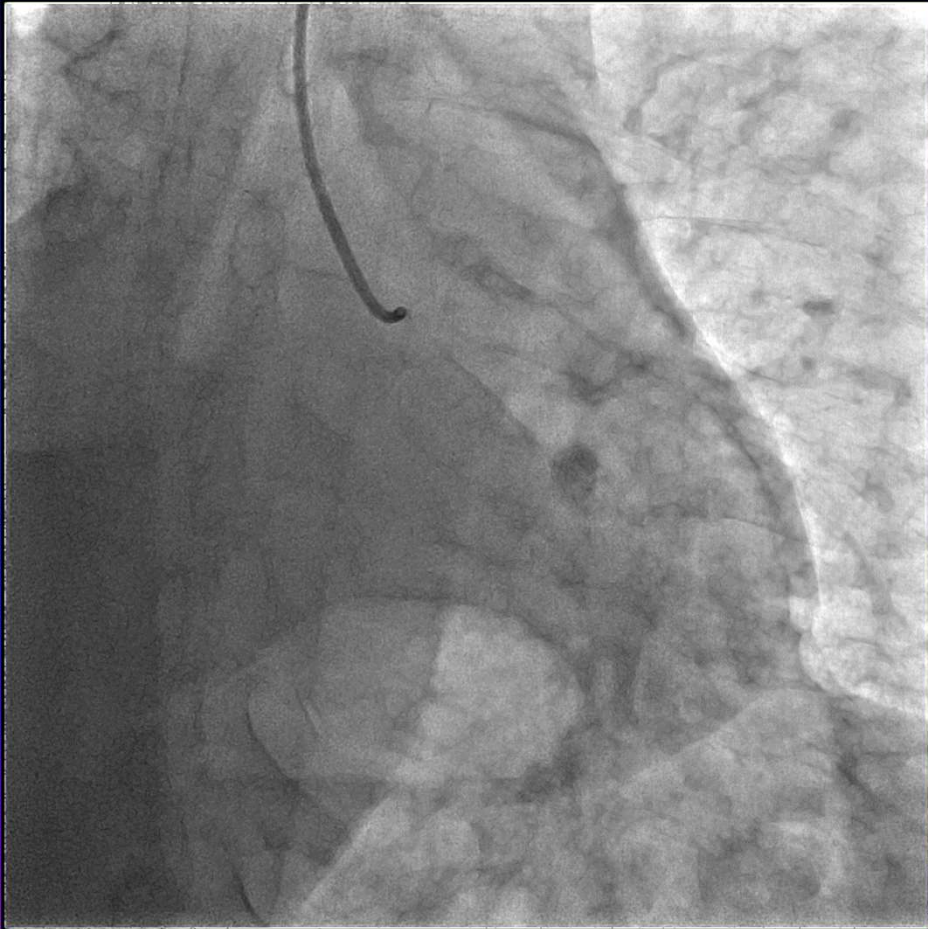
FR. Male 55 Y

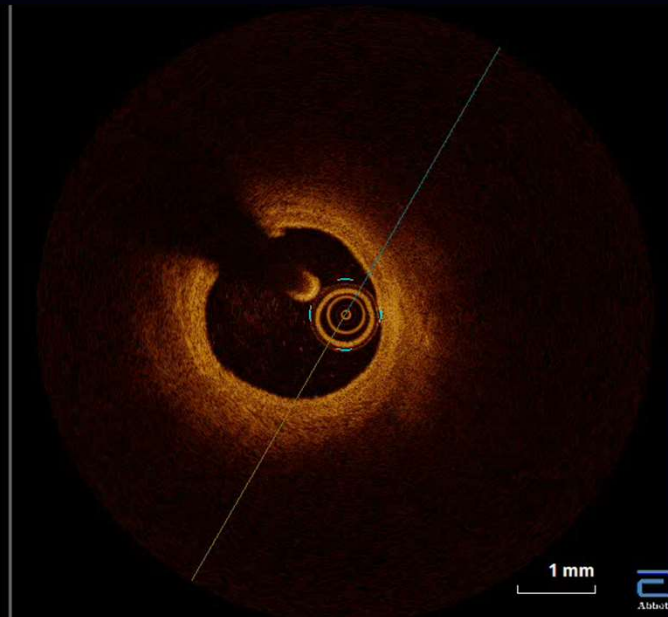
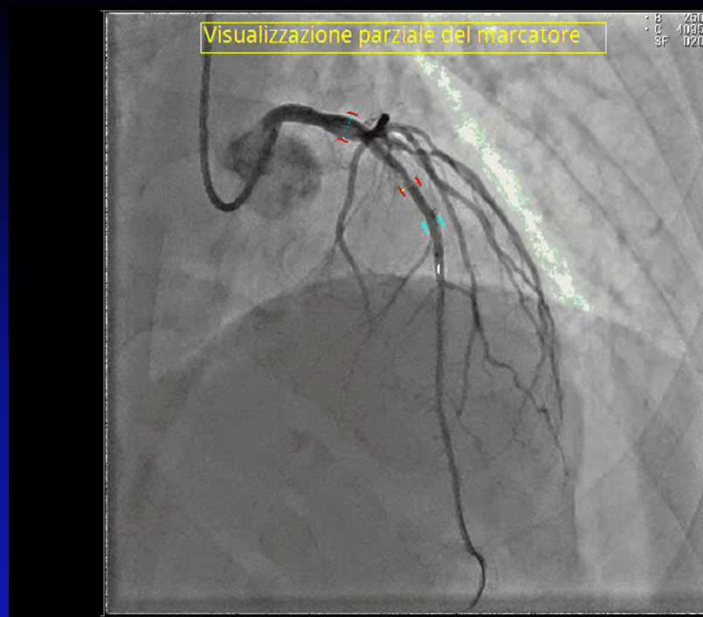


TA, Male, 70 Y/o

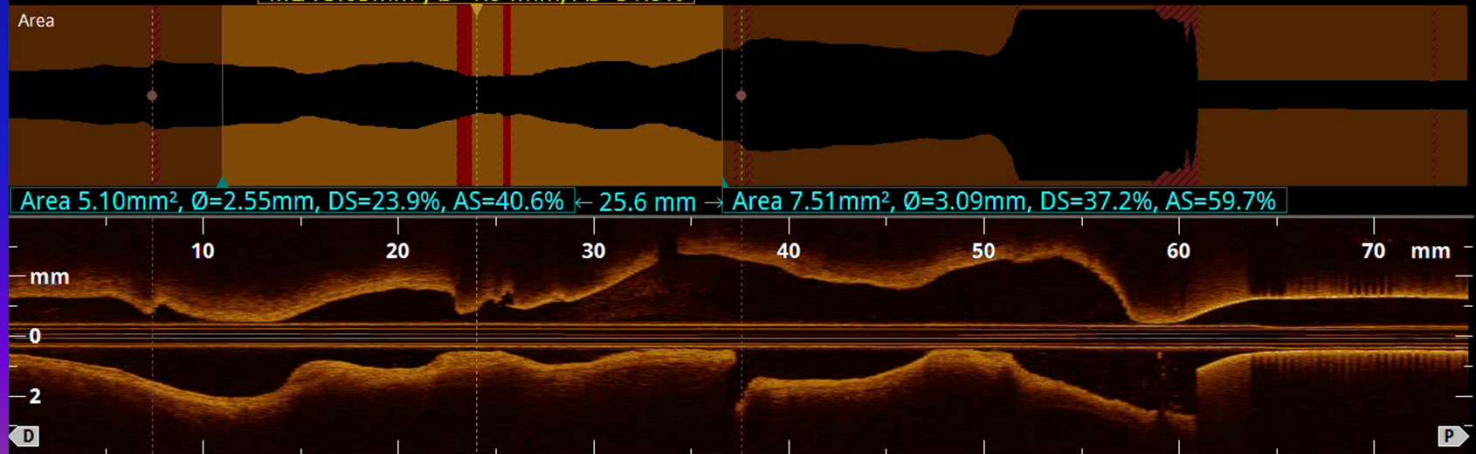
- Hypertension, Hypercholesterolemia and Family History
- Mild symptoms: Shortness of breath in the last 15 days.
Palpitations, No chest discomfort
- Ventricular tachycardia at Holter monitoring
- Emergency department: Significant increase of HS troponin

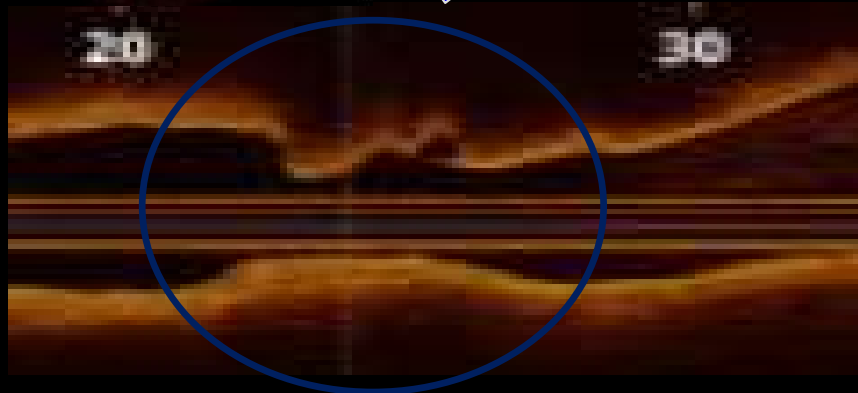
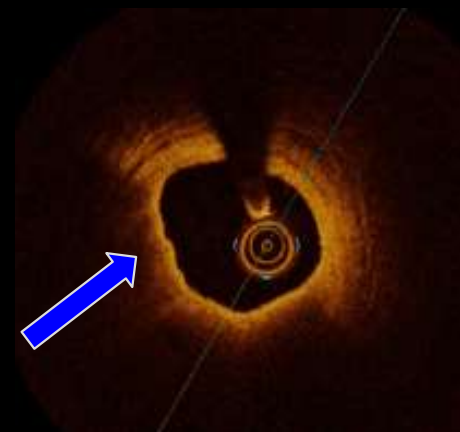
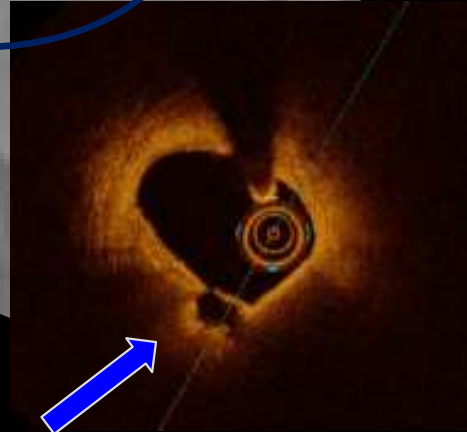
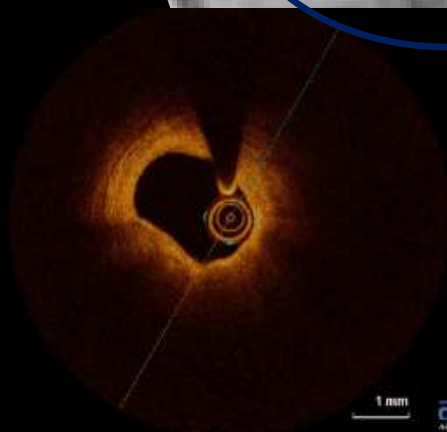
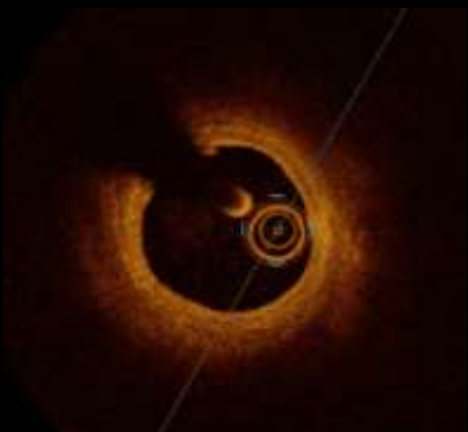
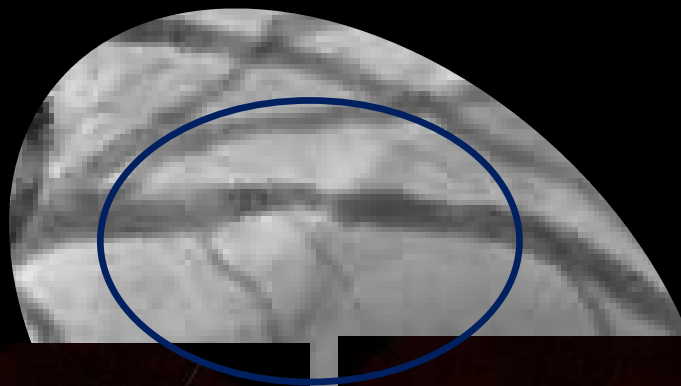
Angiogram: 30% stenosis. FFR: Negative (0,98)



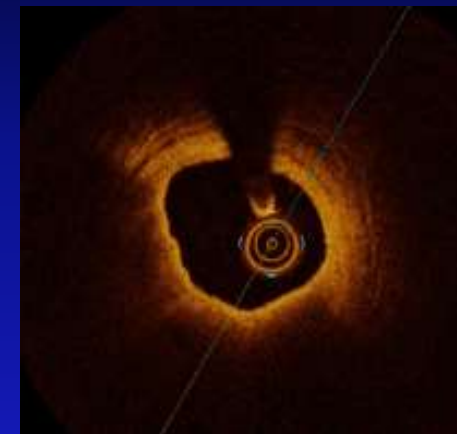
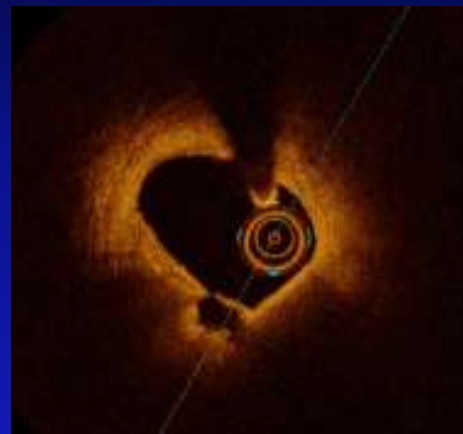
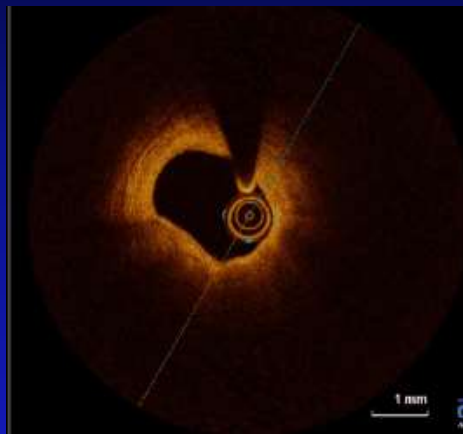
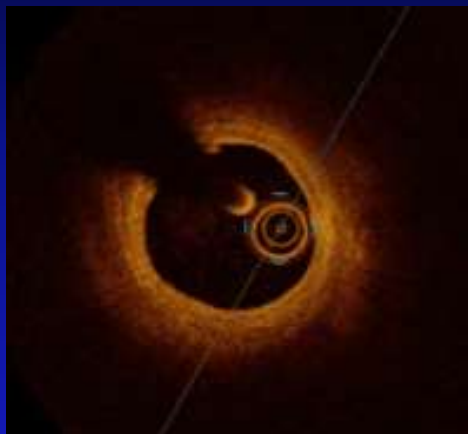


MLA 3.03mm², Ø=1.94mm, AS=51.9%





Subacute plaque rupture



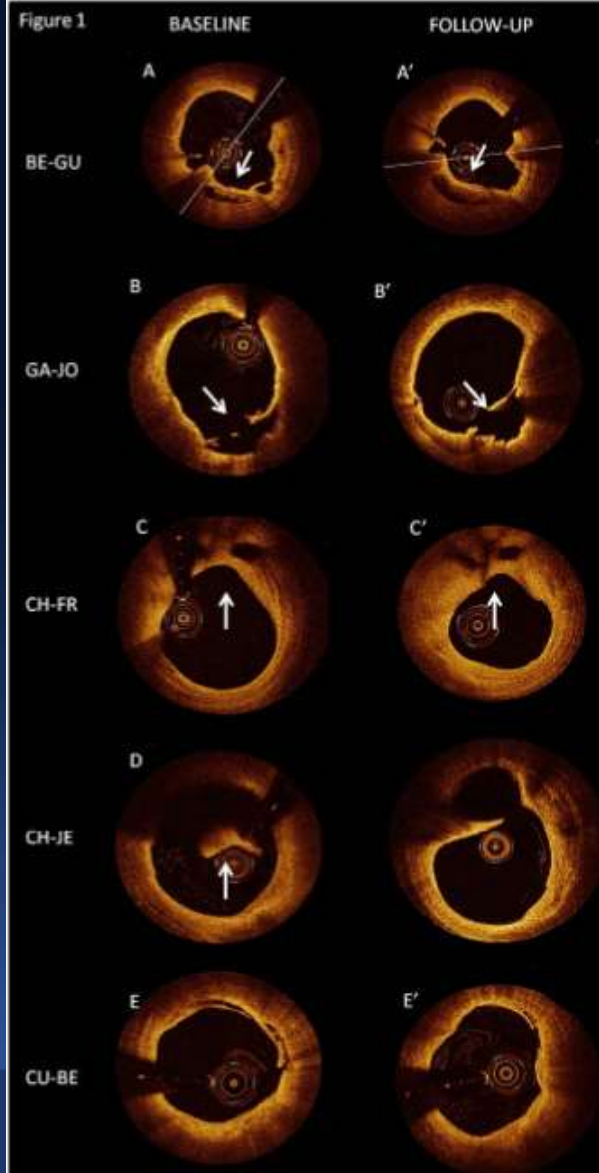
.....MINOCA

Therapy : DES positioning plus ACS therapy

**Post intervention and FU
assessment with OCT**

**Culprit lesions with
Ulceration**

Eurointervention 2015

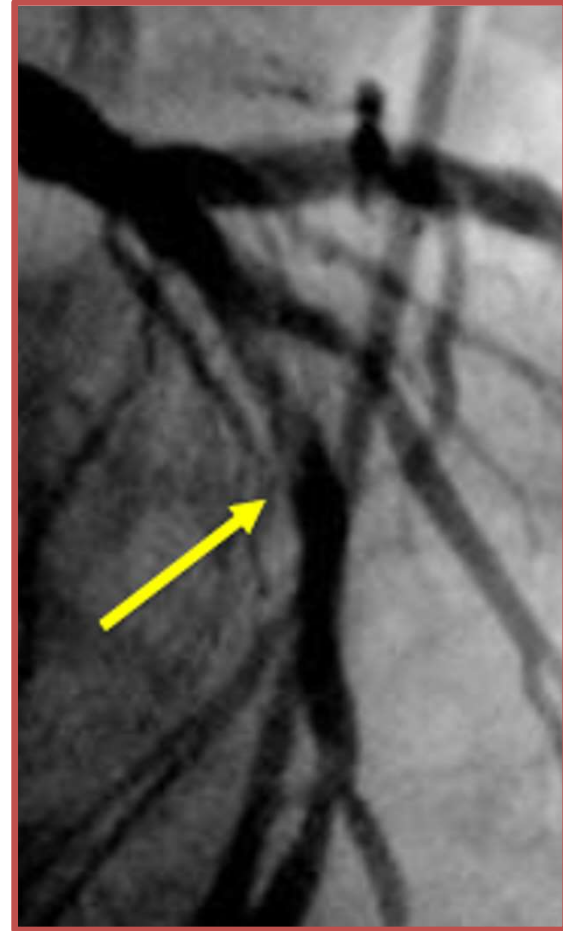


- Man 66 Y
- FR: Smoker,
- **Symtoms:** Rest angina. 15 min. of lenght.

Two epsisodes

Ecg: T wave inversion

UTIC: Throponin increased

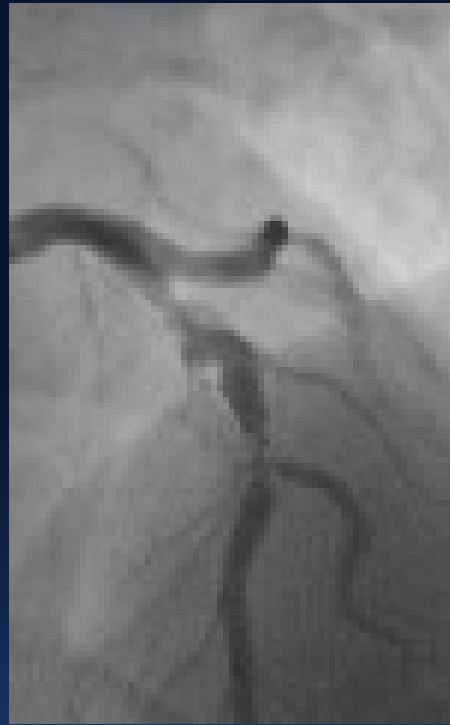
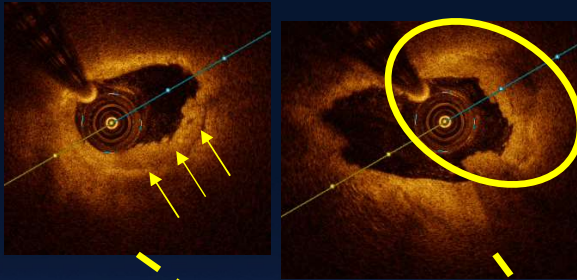


Lesion identification/interpretation

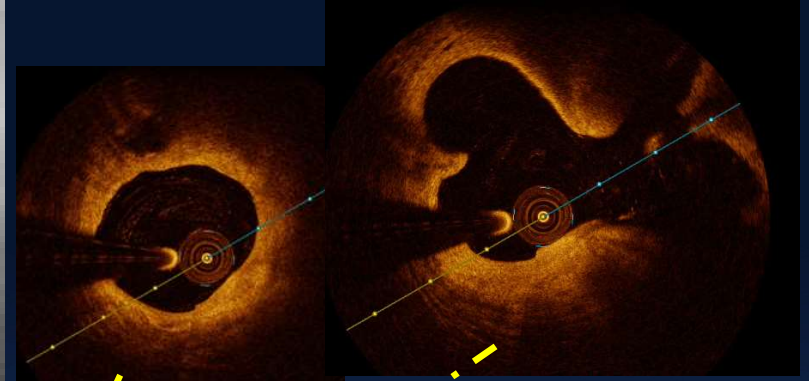
ACS: Ulceration
With Small Thrombus



PLAQUE EROSION

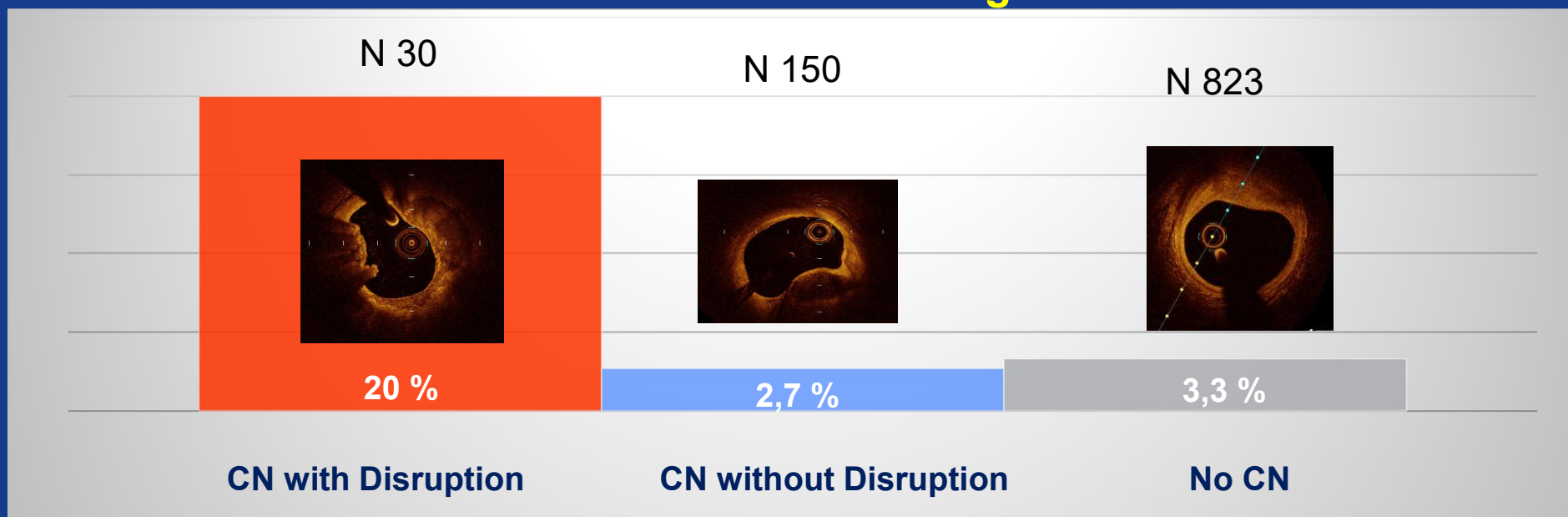


Mild angio Narrowing



OCT CHARACTERIZATION OF CALCIFIED NODULES WITH AND WITHOUT DISRUPTION OF INTIMAL FIBROUS RHYME AND LONG TERM CLINICAL OUTCOME: A SUBANALYSIS OF THE CLIMA STUDY

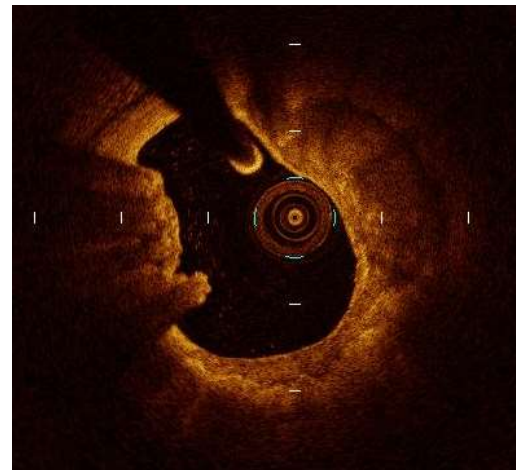
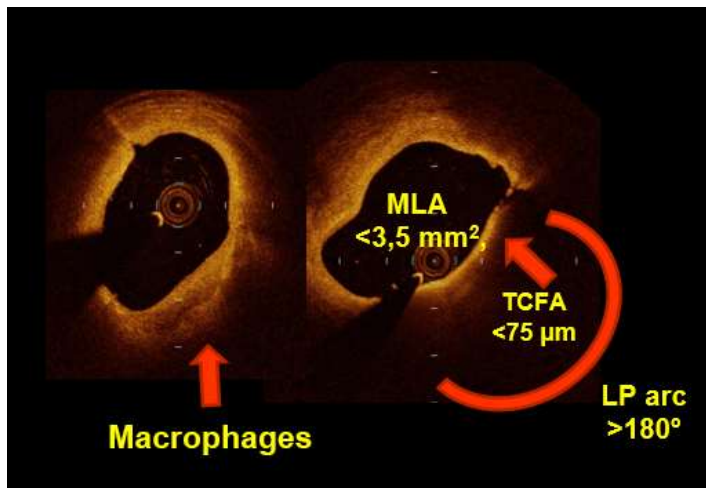
Cardiac death and or target MI



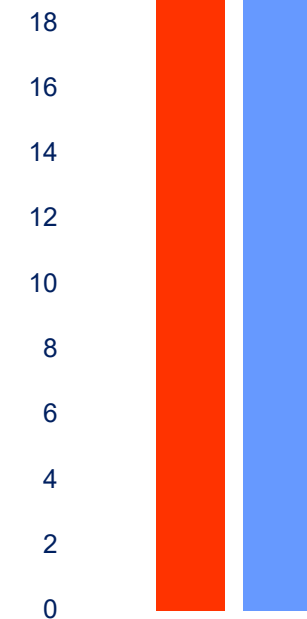
Prati et al. Eurointervention 2020

Cardiac death and or target MI in the CLIMA Study

1003 pts with CAD



20 % **Event rate**

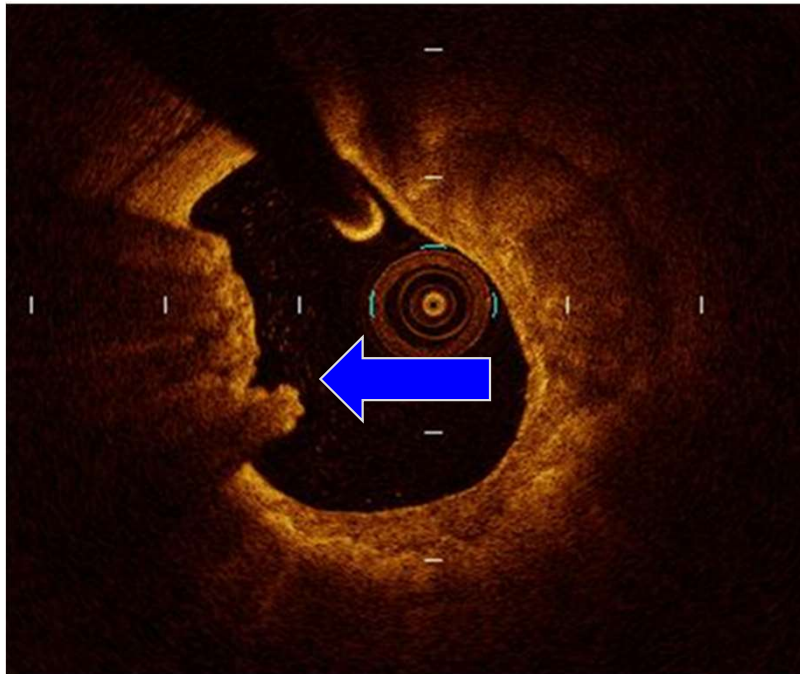


Vulnerable plaque with TFC, large lipid and Inflammation

CN with Disruption

Disrupted calcific Nodule
Thin FC plus large lipid and infl.

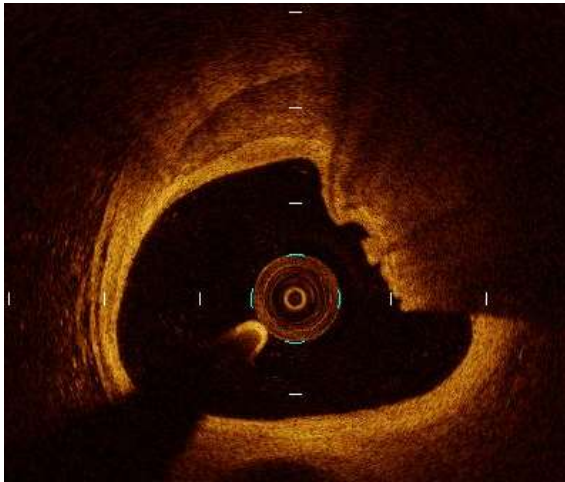
“Calcified nodules are an infrequent cause of acute thrombosis in ACS (about 5-6% of ACS). They typically occur in aged atherosclerosis and seem unlikely to be involved in MINOCA”.



Still a valid assumption?

Lindhal e Prati Eurointervention 2022

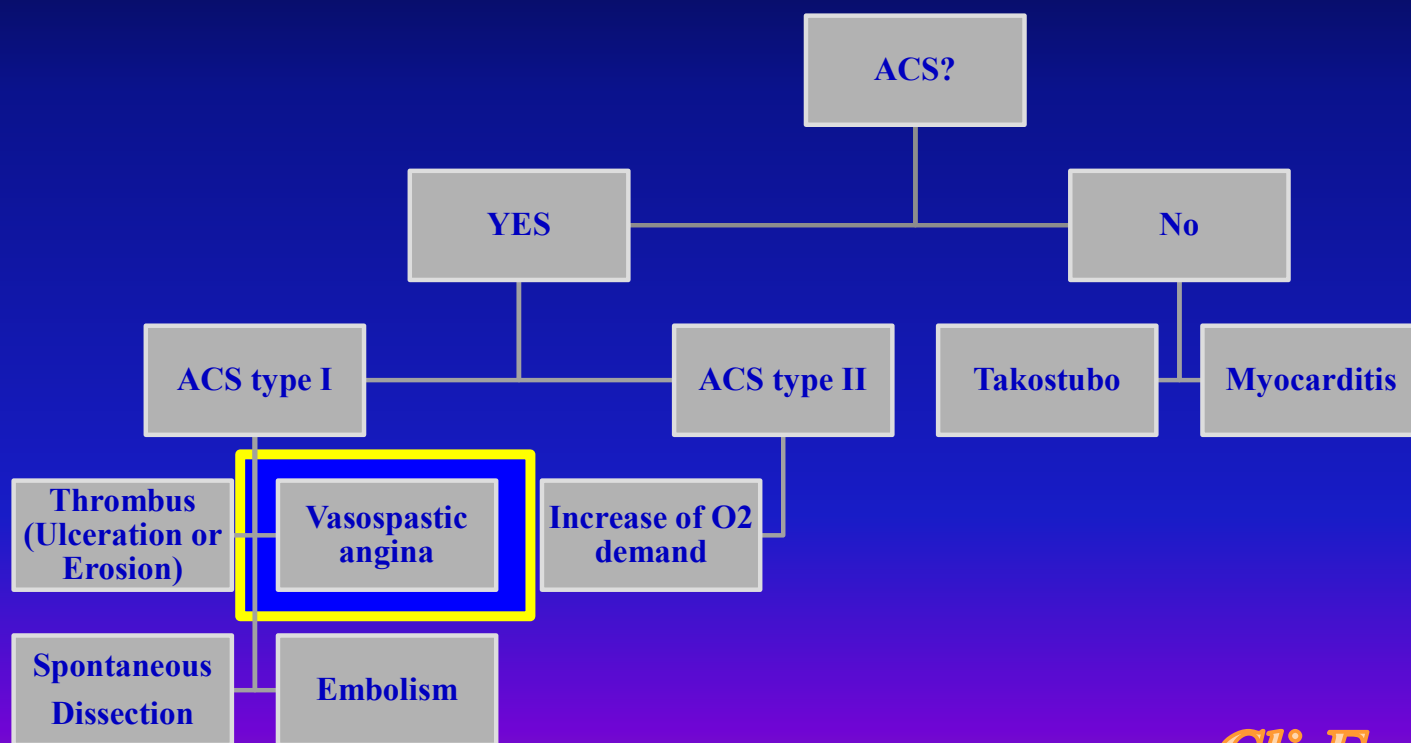
Calcific nodules with disruption



Room for dual antiplatelet therapies ?

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

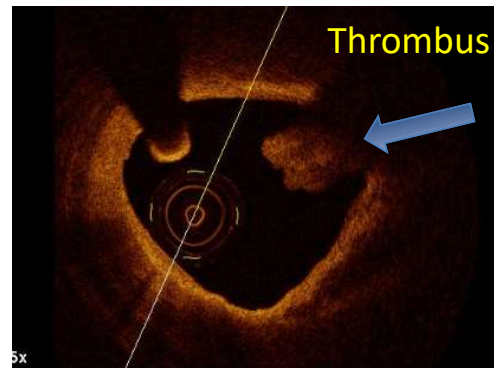
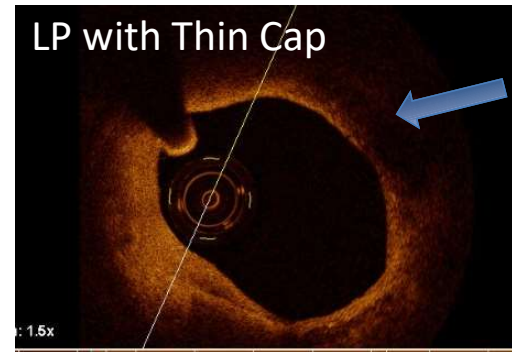
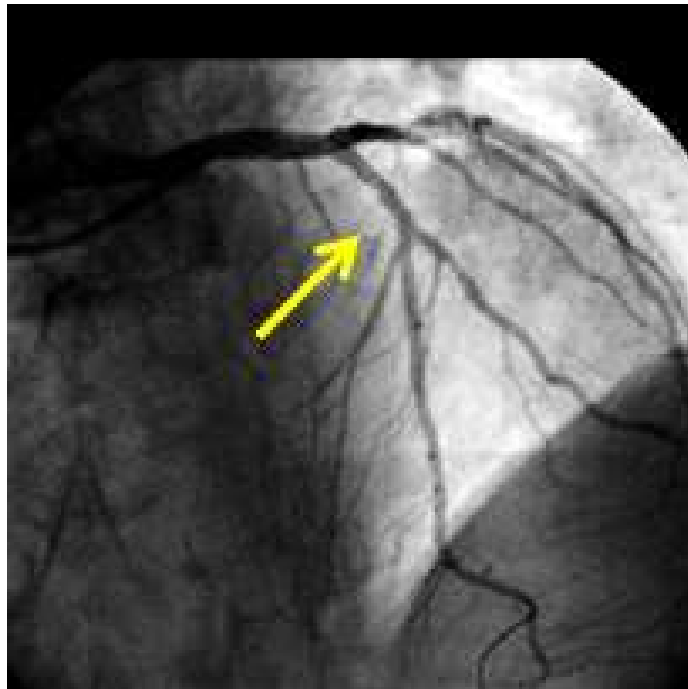
An algorithm to diagnose/exclude ACS



- 61 years old male without a previous history of CAD
- RF: Smoke
- Unstable angina with a single rest episode.
- The ECG showed a transient ST elevation in the anterior leads lasting 5-10 minutes.

Variant Angina ? or Plaque Rupture ?

FD-OCT: Ruptured plaque with mild thrombus



- OCT was diagnostic.
- In absence of sign of fresh thrombosis consider Acethylcoline or Ergonovin test

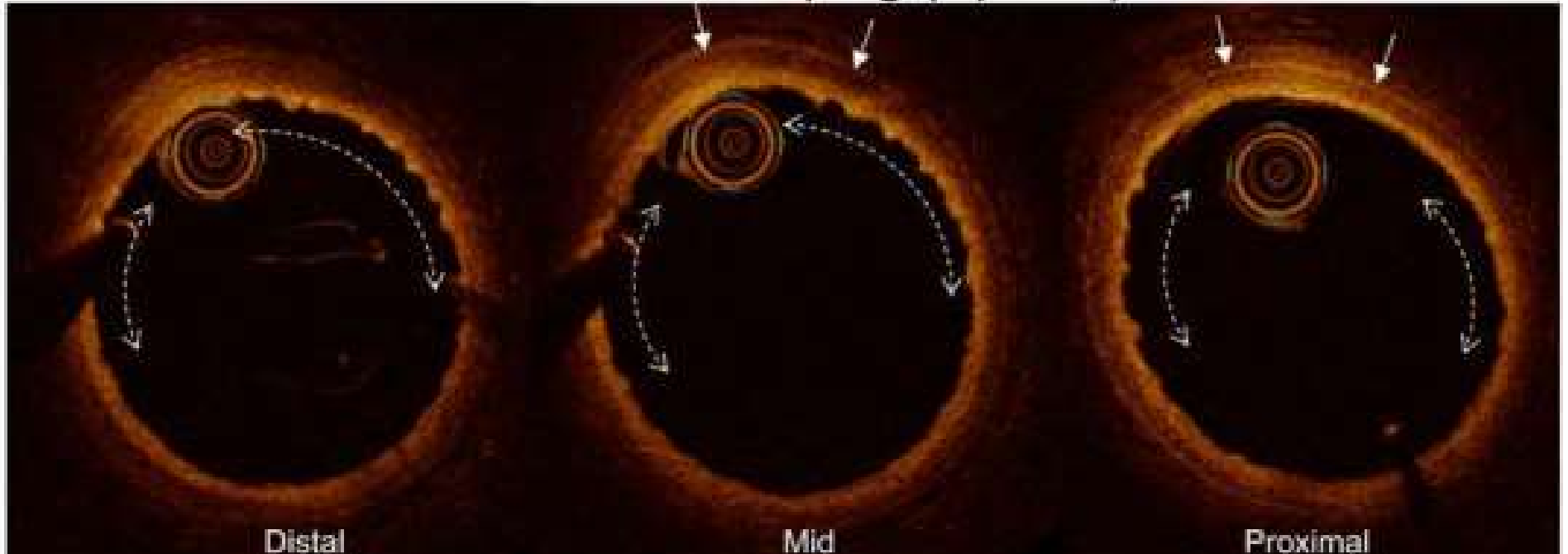
**Use ACS therapy : Dual antiplatelet therapy plus lipid lowering
No need to use calcium-antagonist**

MINOCA due to coronary spasm

Intimal Bumping and Media Thickening

E

Intimal Bumping (Spasm)

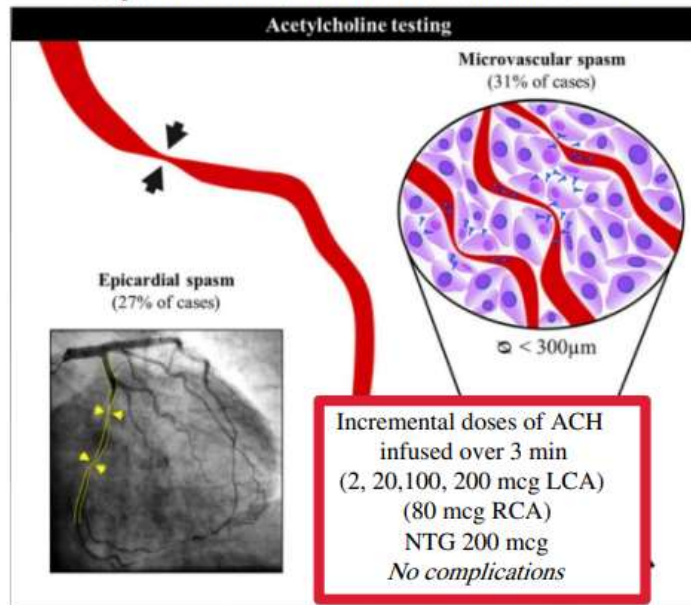


Reynolds HR et al. Circulation 2021

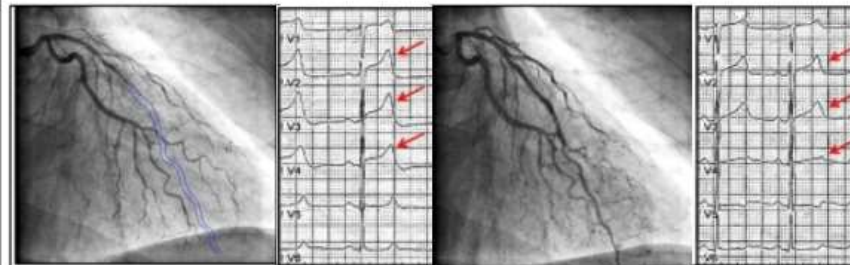
- The frequency of epicardial vasospasm as the cause of MINOCA is dependent on the used definition. It varies very widely in different studies, ranging from 3% to 95%.
- Provocative tests for spasm are seldom used in clinical practice in most countries; however, some recent studies have shown the procedure to be safe.

Coronary Epicardial and Microvascular Spasm in MINOCA Pts with NSTEMI

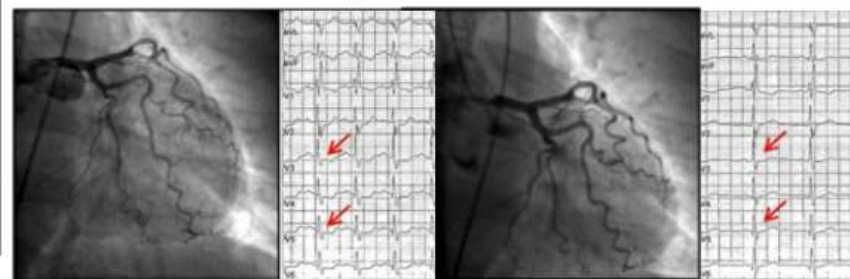
N=96 patients with NSTEMI and no obstructive CAD



Epicardial Vasospasm



Microvascular Vasospasm



Safety of Acetylcholine Testing in MINOCA

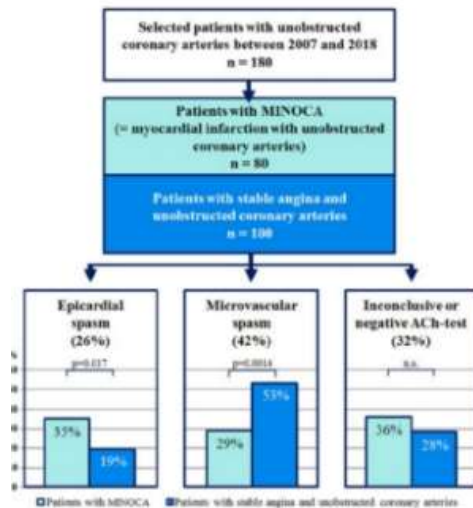
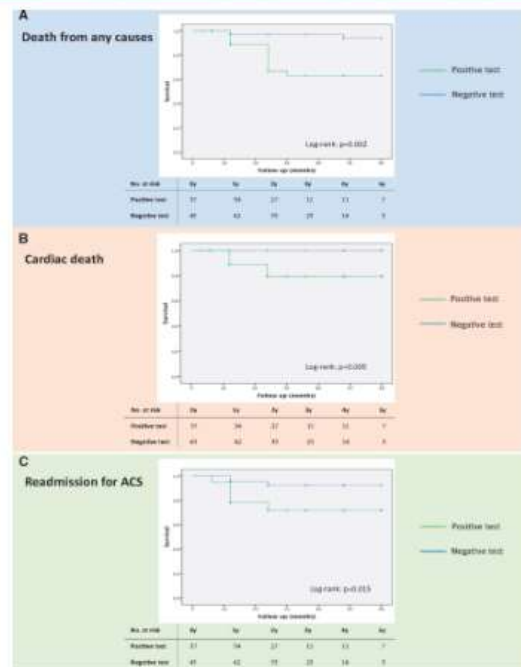
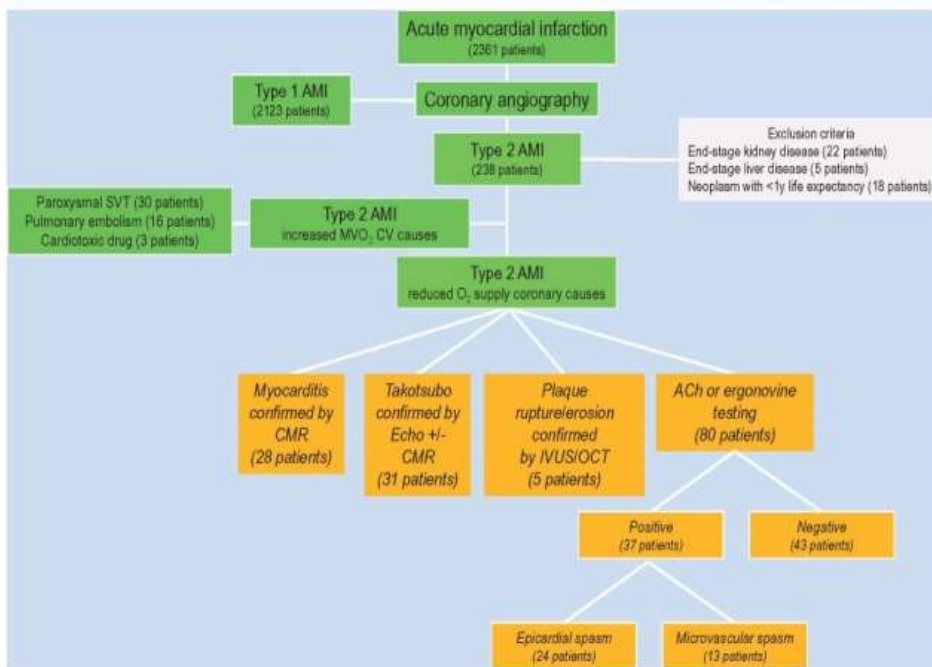


Table 1 Demographic data, risk factor data and assessment of complications during acetylcholine (ACh) test.

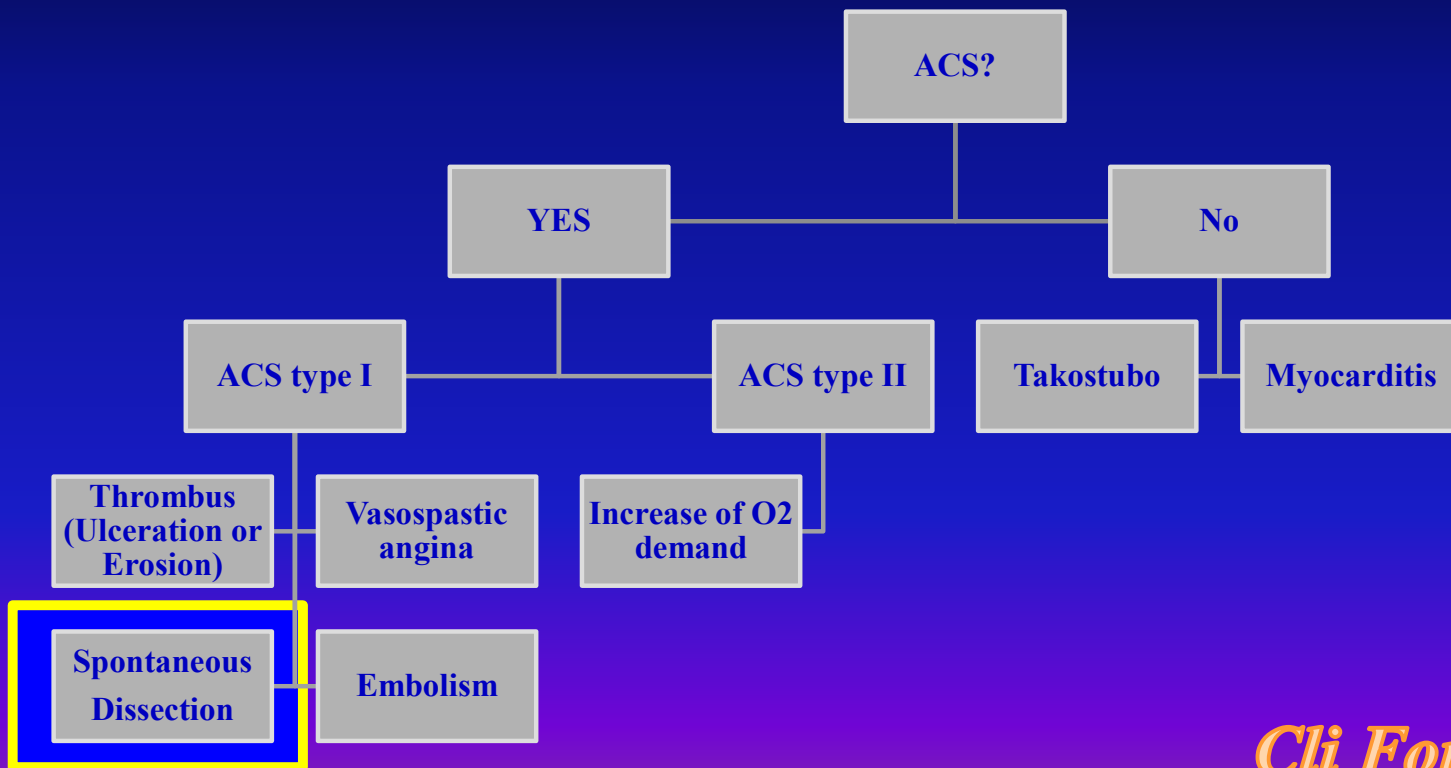
n	Patients with MINOCA	Patients with stable angina and unobstructed arteries	p-Value
	80	100	
Sex (female, %)	32 (40%)	61 (61%)	0.005
Age (mean, SD)	63±15	62±12	0.614
Hypertension	50 (62%)	56 (56%)	0.381
Smoking >5 years	17 (21%)	24 (24%)	0.664
Hypercholesterolaemia	28 (35%)	51 (51%)	0.032
Diabetes mellitus	15 (19%)	21 (21%)	0.710
Transient side effects during ACh test	11 (14%)	16 (16%)	0.674
AV-block or sinus bradycardia <50 bpm	10 (12.5%)	13 (13%)	0.999
Ventricular ectopic beats	1 (1%)	1 (1%)	0.875
Hypotension <90 mm Hg systolic	0 (0%)	2 (2%)	0.206
Transient complication during ACh test	2 (2.5%)	1 (1%)	0.438
Paroxysmal atrial fibrillation	2 (2.5%)	1 (1%)	0.438

Coronary Vasospasm Predicts MACE post MINOCA

Coronary Vasospasm Predicts MACE post MINOCA



An algorithm to diagnose/exclude ACS

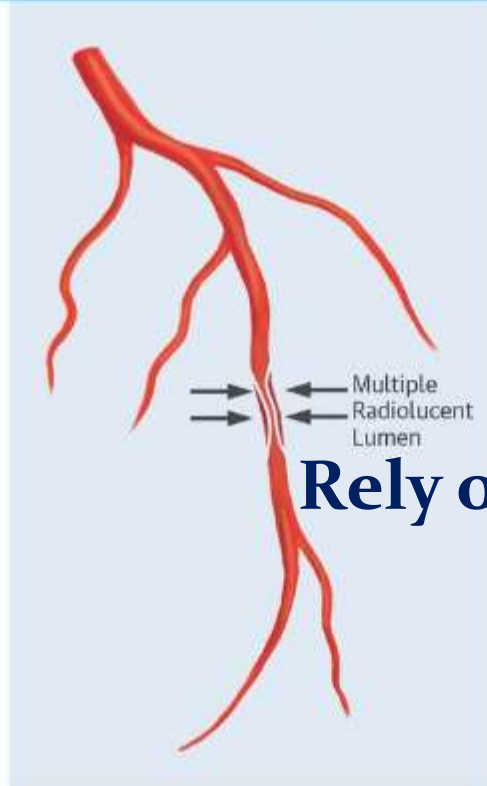


SCAD

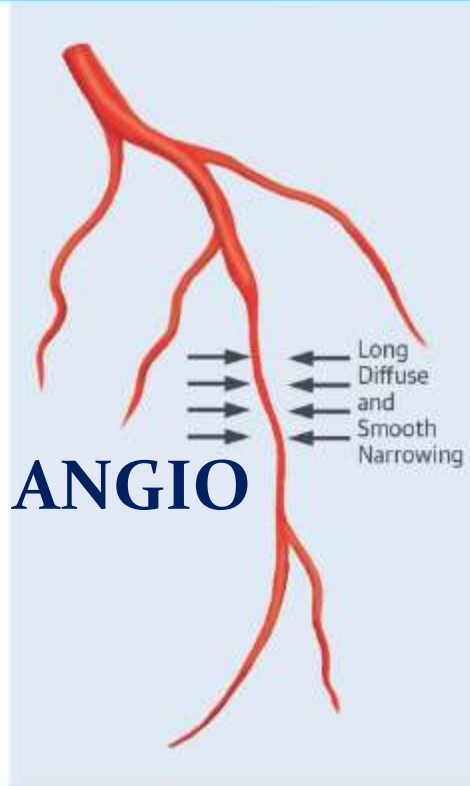
- False lumen within the coronary artery wall that may compress the true lumen and cause ischaemia
- Mechanisms of intramural haematoma.
 - “inside-out” hypothesis; disruption of the endothelial-intimal layer, blood from the lumen to the vessel wall
 - “outside-in” hypothesis, bleeding of the vasa vasorum
- SCADs often heal spontaneously (between 70% and 97%). Healing tends to occur in an early phase (within days) and is a common finding after the first month
- In general, coronary angiography is the key diagnostic tool.
- CTCA sensitivity is suboptimal because of its pdoes not have a sufficient spatial resolution.

CENTRAL ILLUSTRATION: SCAD Classification

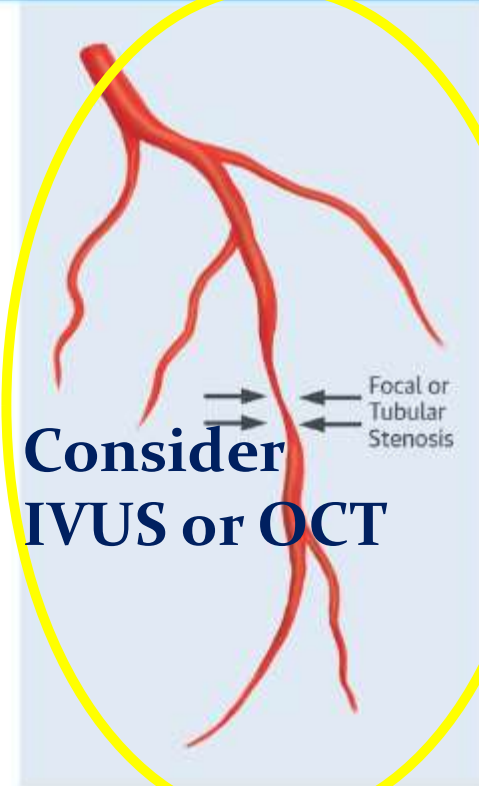
Type 1



Type 2



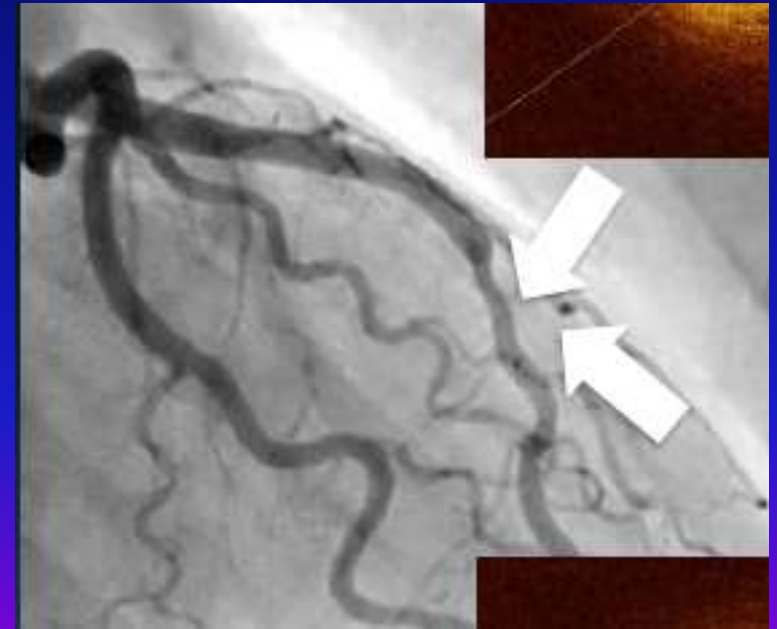
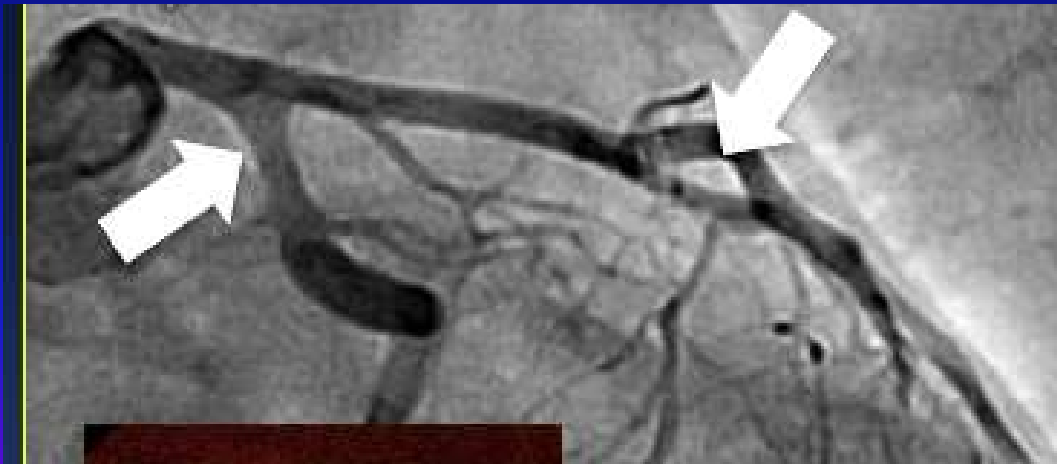
Type 3



Rely on ANGIO

**Consider
IVUS or OCT**

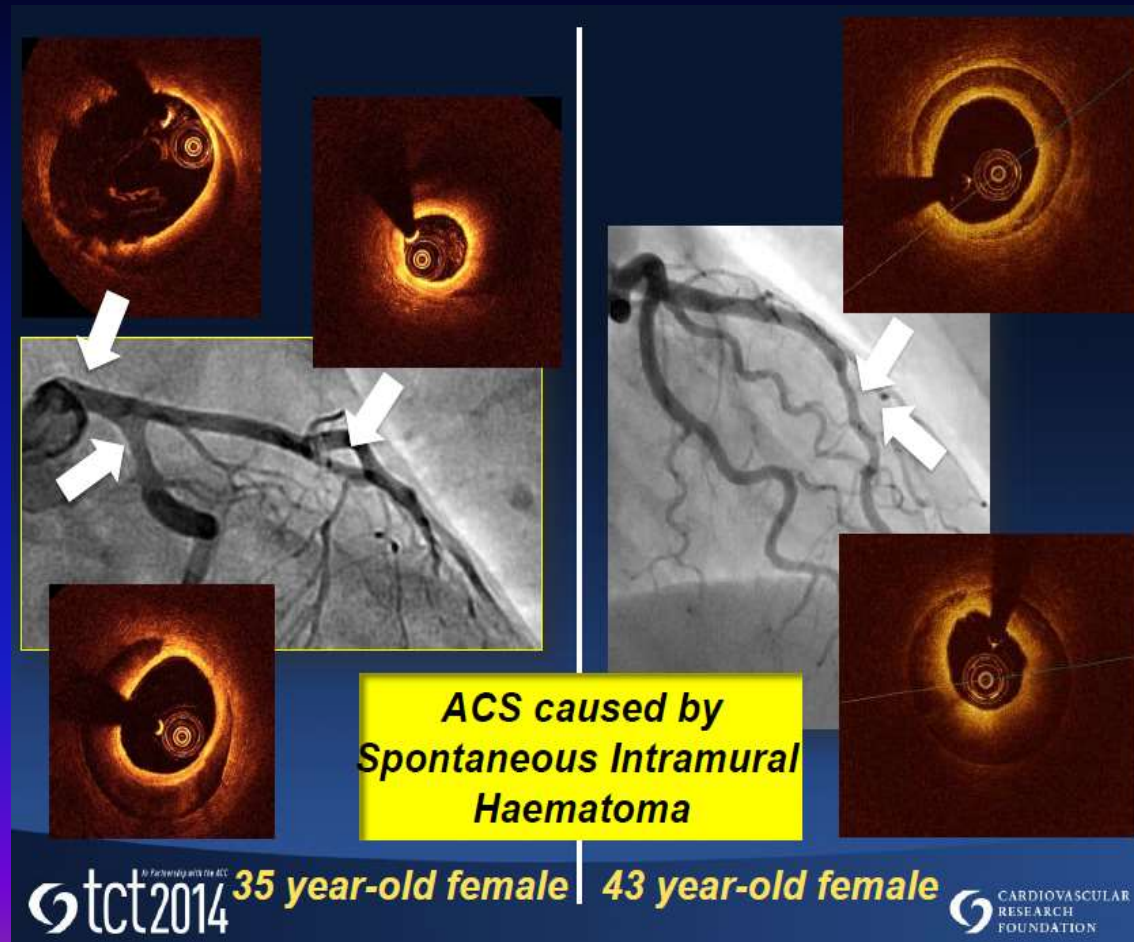
- Female 43Y/o
- No risk factors
- Chest pain lasting 30 minutes
- Admission ecg: anterior ST depression



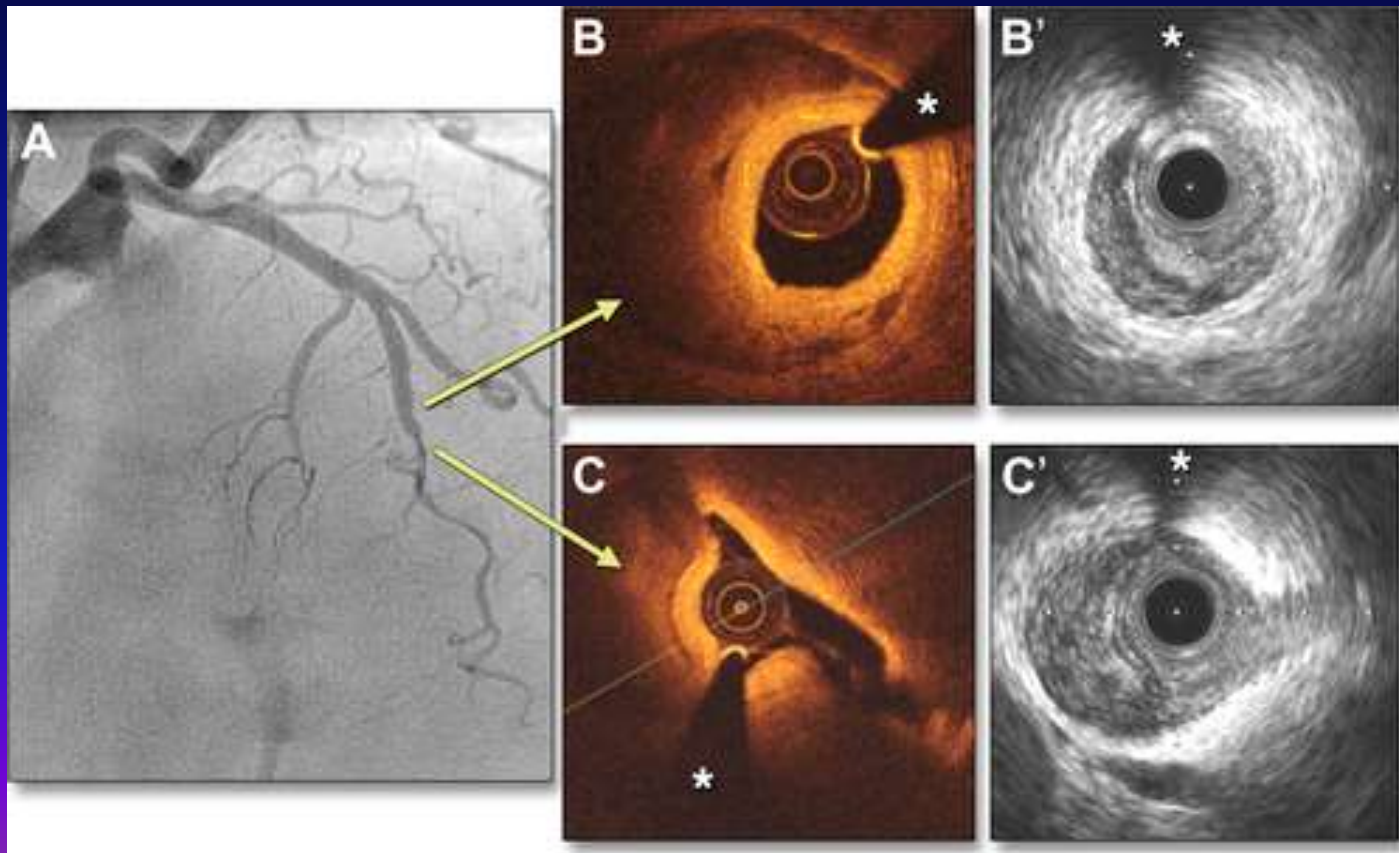
Type 3 dissection

Type 3 dissection

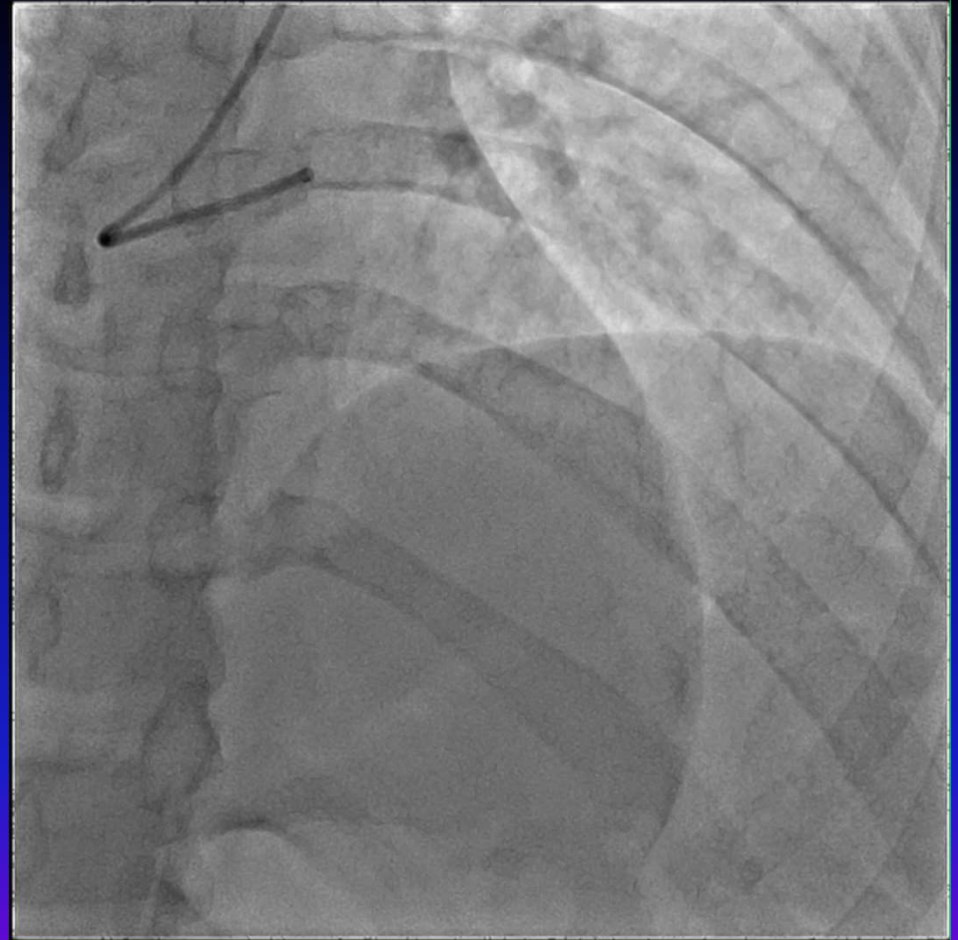
- PTCA: Avoid if possible
- Antiplatelets: ???
- Lipid lowering: no



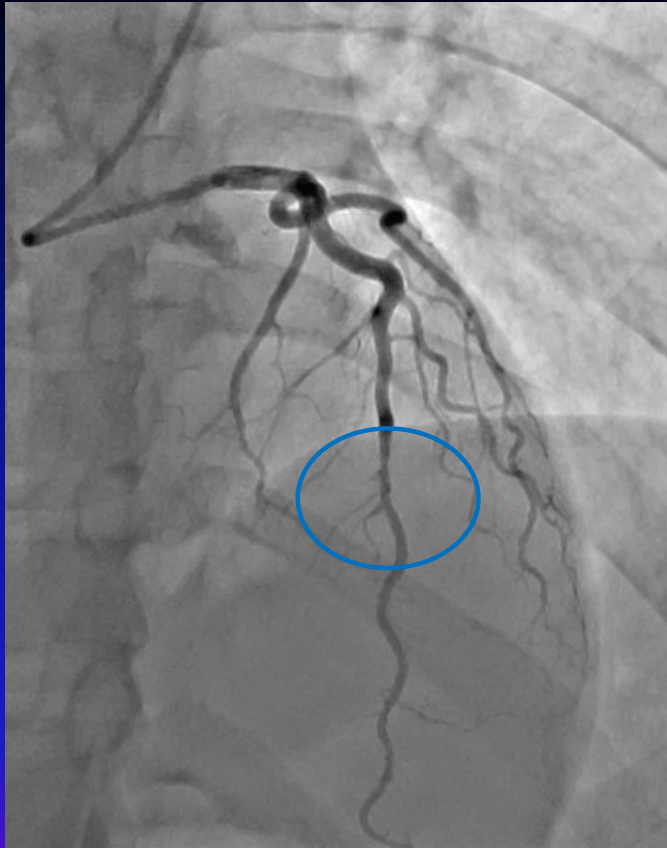
SCAD: IVUS and OCT detection



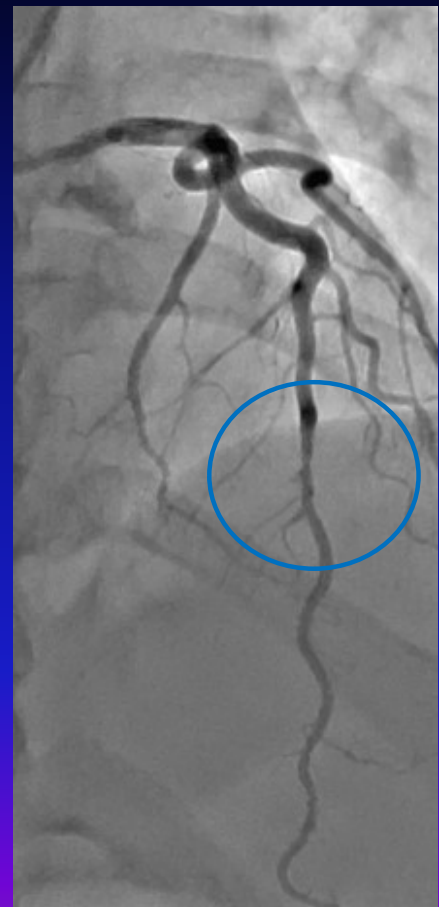
- E C Female , 38 y
- Rest Angina
- Ecg: Anterior ST depression
- HS Tropin increased



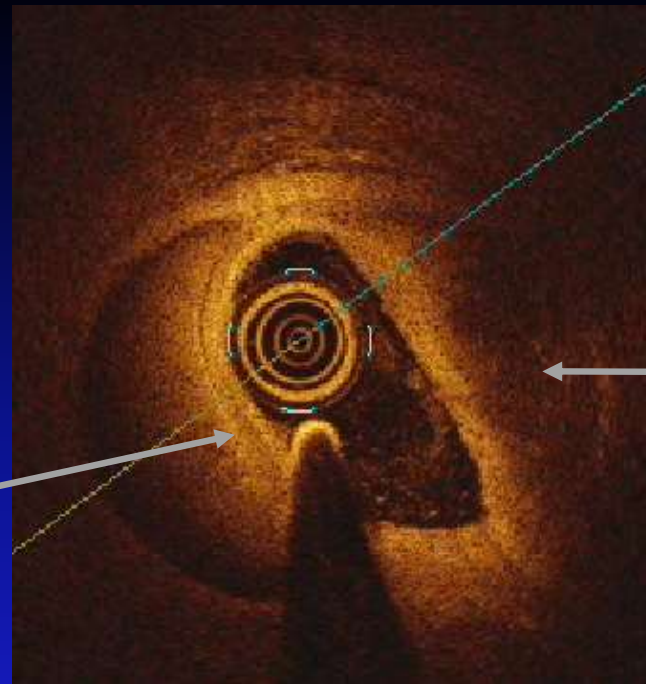
Type 3 dissection



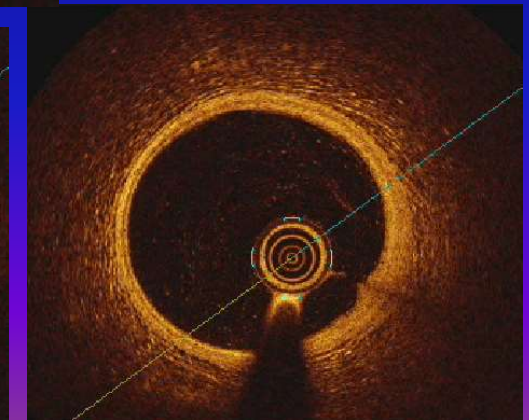
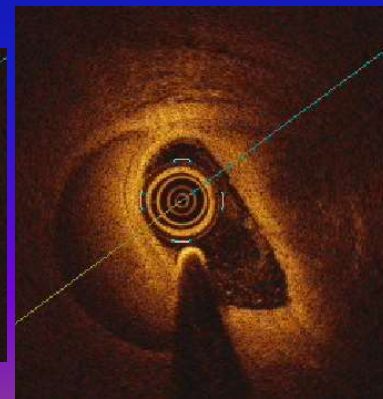
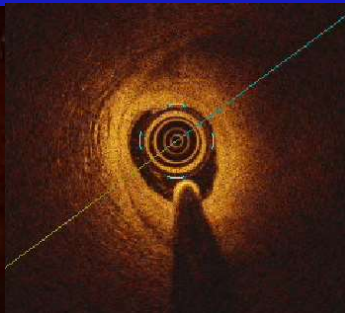
The lesion was NOT treated



Media



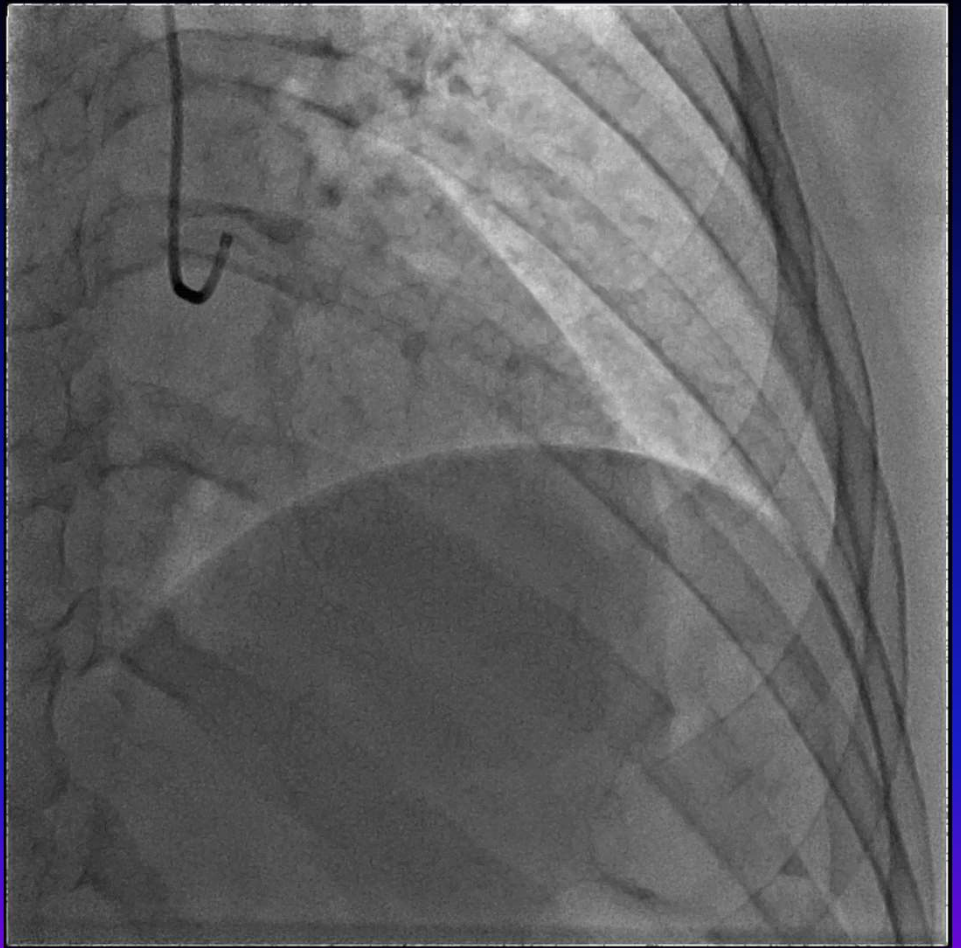
Hematoma



CL 59 y/o

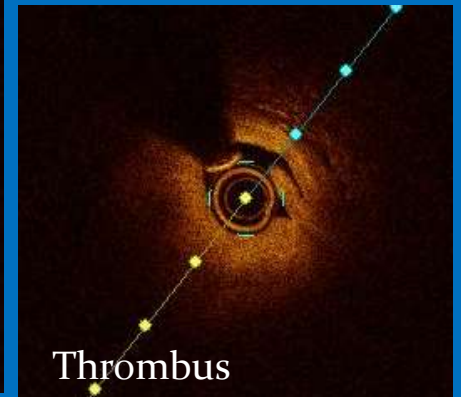
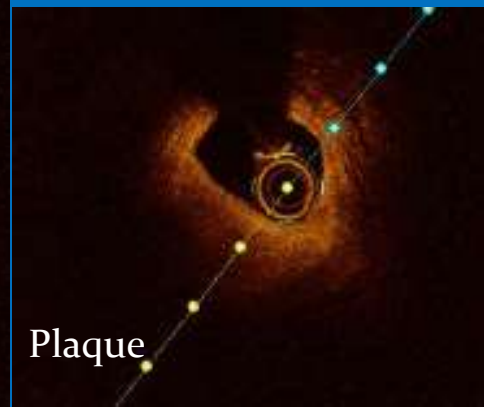
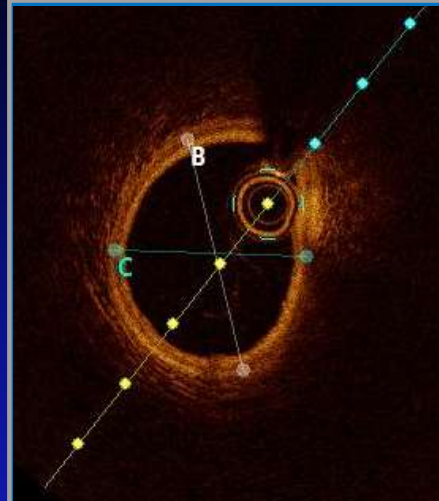
- Rest Chest pain episode
- ECG: ST depression in the ant. Leads
- Troponin increase

Type 3 dissection ?



Visualizzazione parziale del marcatore

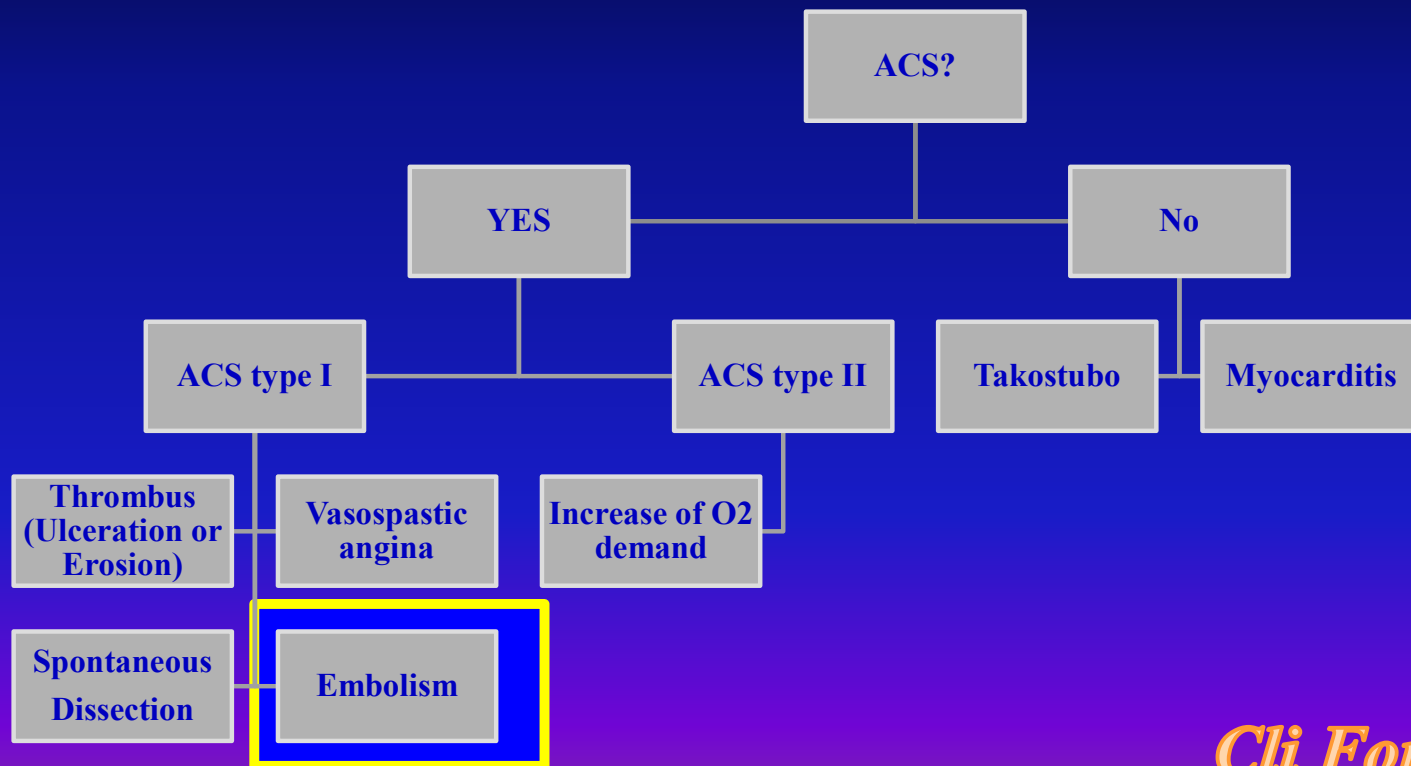
218
2300
RE36



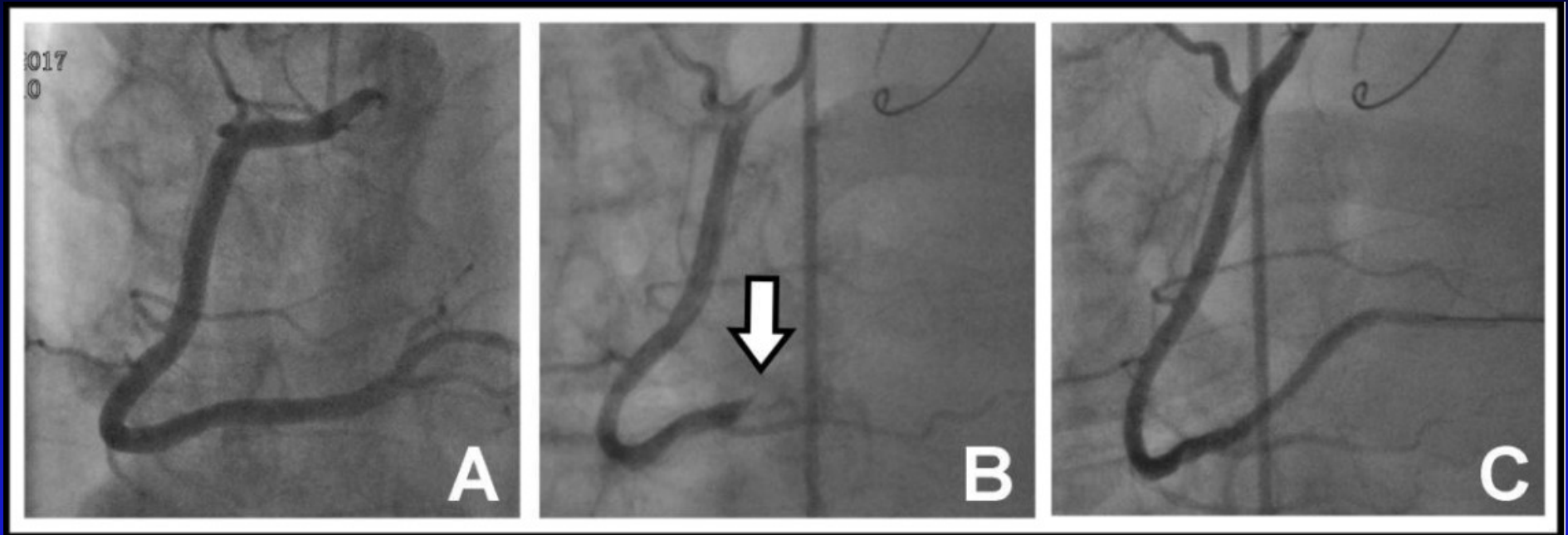
Plaque Erosion

**DES positioning plus dual antiplatelet
therapy plus lipid lowering**

An algorithm to diagnose/exclude ACS

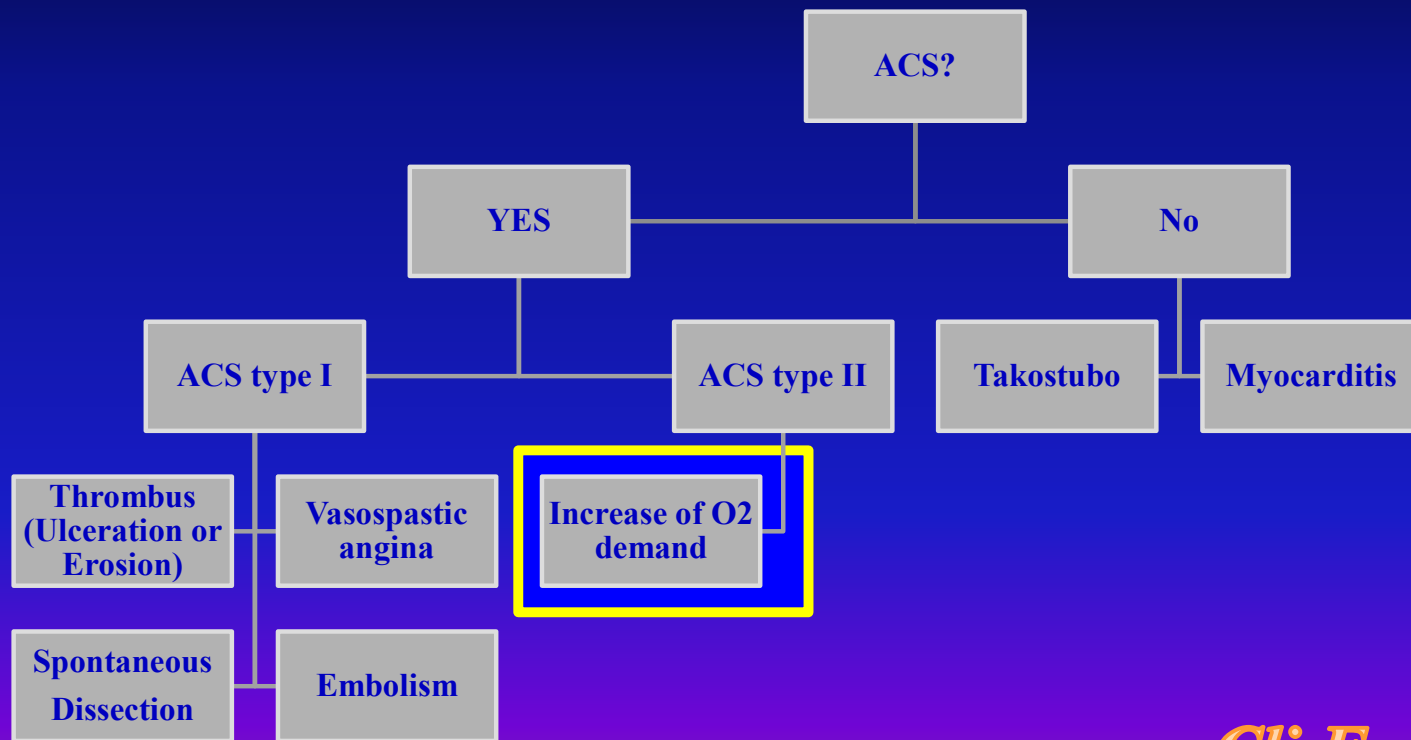


Coronary Embolism



- Thrombus stump totally occluding a coronary artery without atherosclerosis
- The diagnosis poses on clinical aspects and angiographic pattern

An algorithm to diagnose/exclude ACS



□ Woman 64 Y

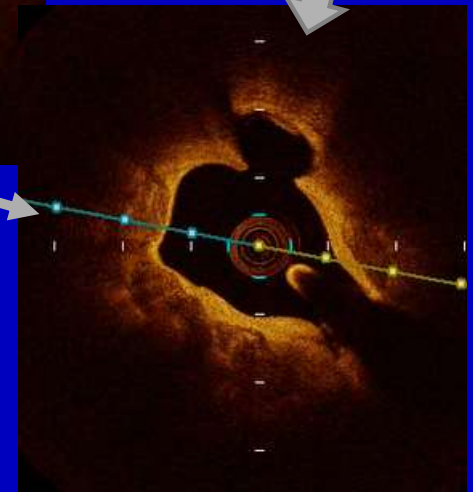
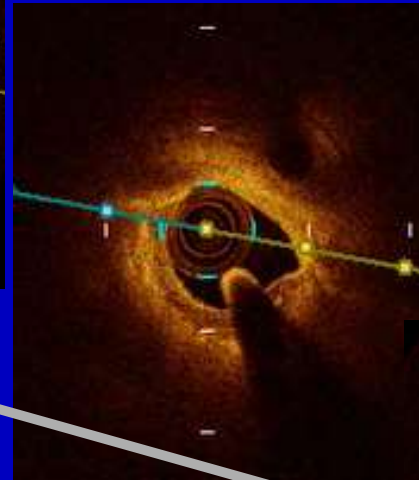
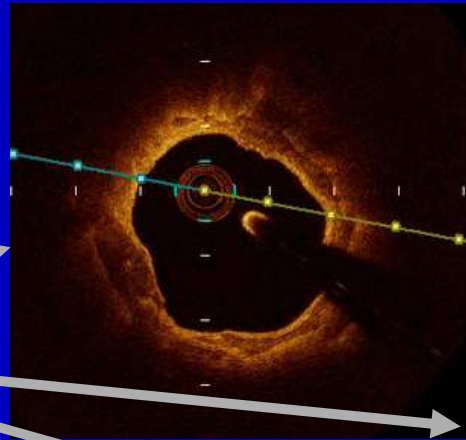
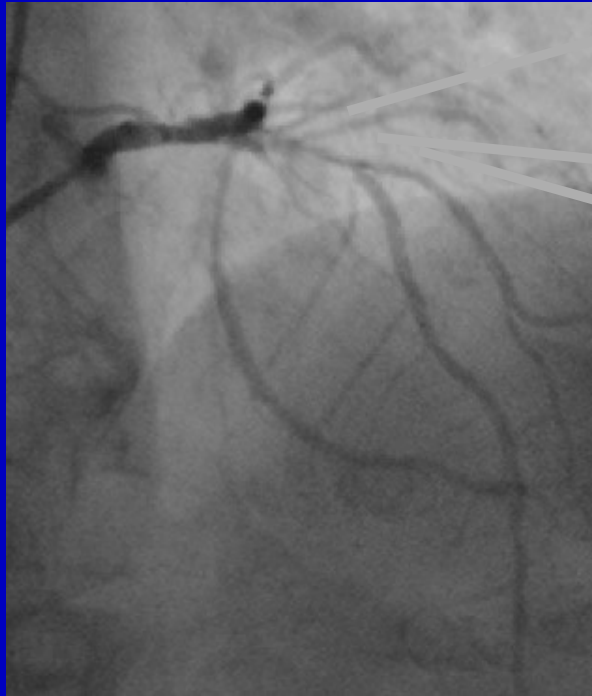
□ FR: Smoker, Familiarity for CAD

Sintomi: Rest angina. 20 min. of lenght

Ecg: ST depression

UTIC: Throponin increased

AS. 72 y. Hypertension and dyslipidemia
Anterior NSTEMI during a high pressure episode



No fresh thrombus
Type II MI

Therapy of Type II NSTEMI?

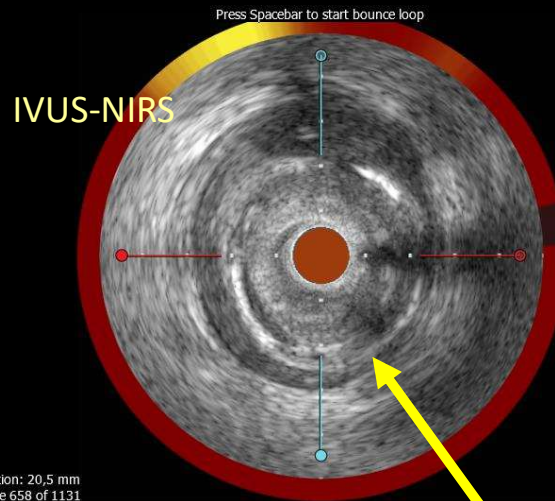
Choose the Ideal Imaging Tool

- **Use OCT to study plaque anatomy with acute thrombosis**
- IVUS is not ideal
- FFR does not seem useful
- CT resolution is not adequate
- **Use Cardiac MR for differential diagnosis**

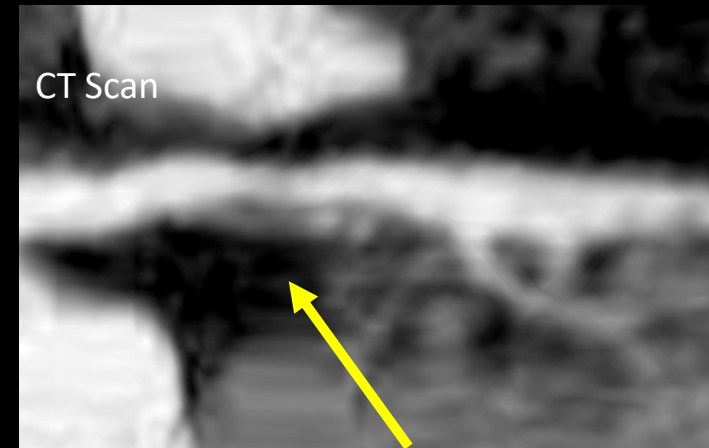


Fresh Thrombus

Location: 20,5 mm
Frame 658 of 1131

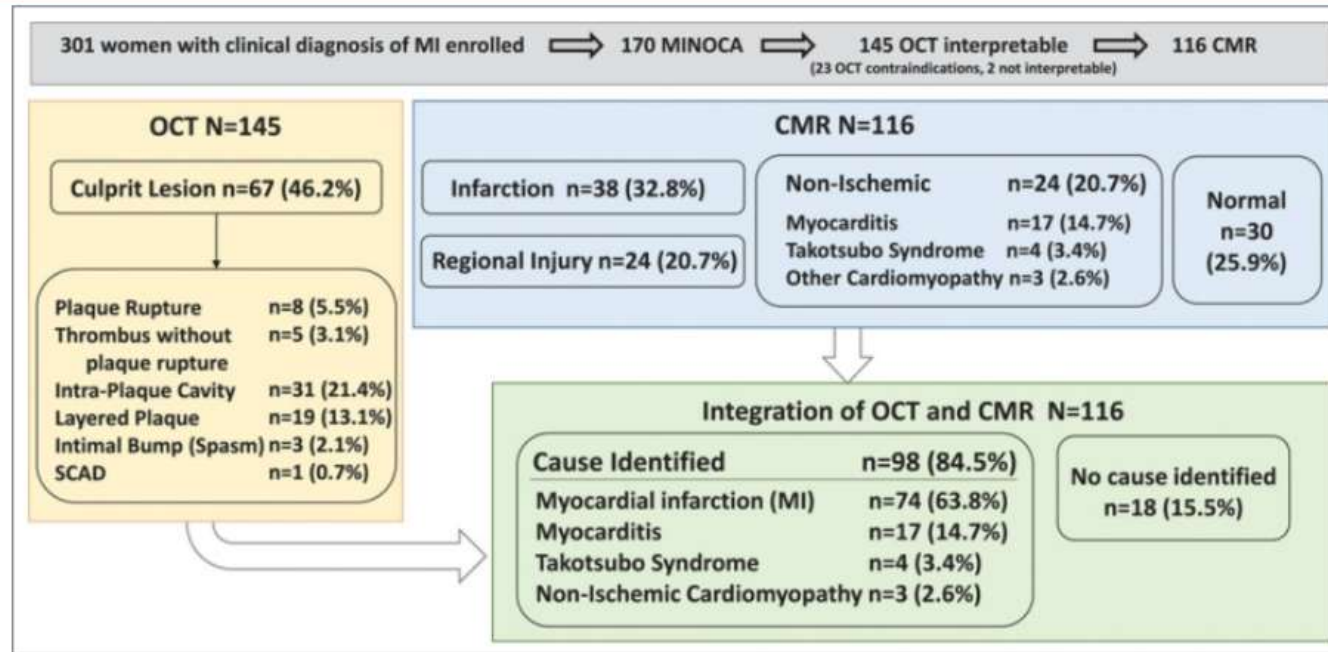


Plaque Burden plus lipids



Suboptimal Resolution

Optical Coherence Tomography (OCT) & Cardiac Magnetic Resonance (CMR) HARP-MINOCA



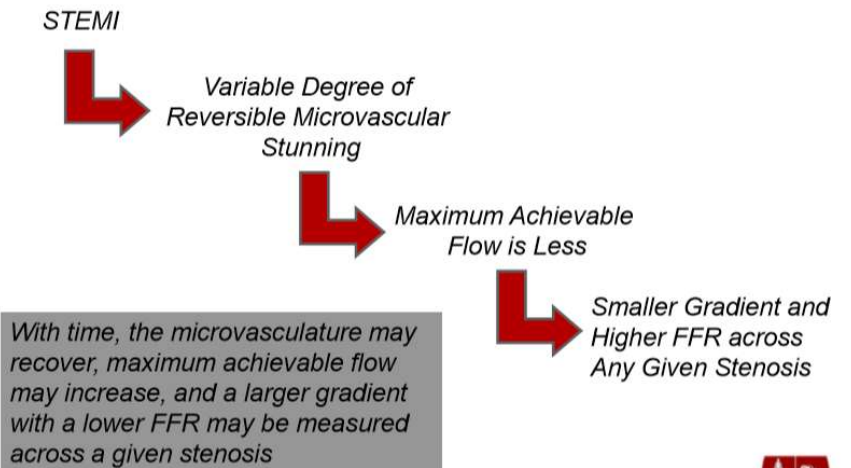
- In the acute setting FFR is unable to identify the presence of the culprit site (can't show anatomical features)
- **FFR measurement of culprit site is not reliable because the myocardial bed supplied by the STEMI vessel is injured and infarcted with significantly, albeit transiently, reduced coronary and microvascular flow.**

In the culprit-only approach, the non-target vessel has little contribution to the immediate clinical decisions.

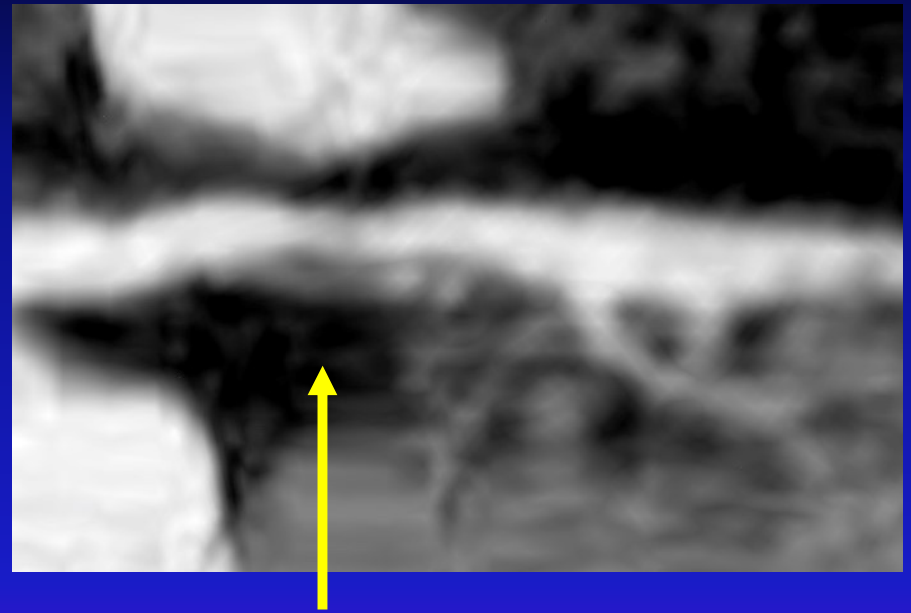
De Bruyne B et al. *Circulation*. 2001; 104(2):157-162.

Samady H et al. . *J Am Coll Cardiol*. 2006; 47(11): 2187-2193.

Acute Microvascular Damage and FFR



- AL, 24 y/o
- Premature ventr. beats plus a single episode of rest chest pain lasting 20 minutes
- RF: Hypercholesterolemia
- Negative treadmill testing
- **Positive CT Scan**



Diagnosed as prox LAD ulceration

- AL, 24 y/o
- Premature ventr. beats plus a single episode of rest chest pain lasting 20 minutes
- RF: Hyperchlesterolemia
- Angio: Atherosclerosis
 - 50% Prox LAD Narrowing
- OCT:
 - Lipid plaque with thick FC
 - Stable plaque without thrombus



NOT a MINOCA



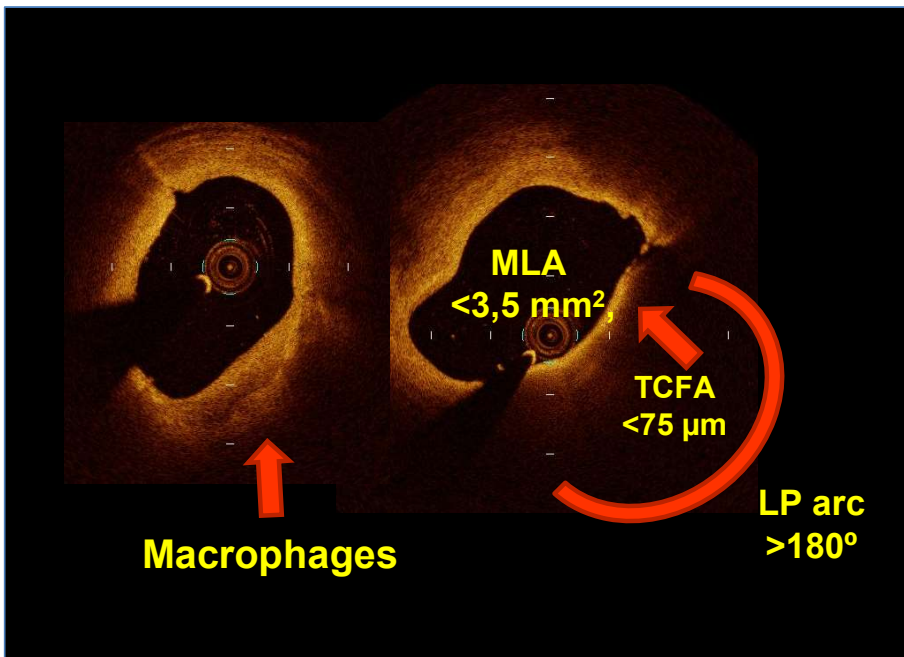
The ACS can be excluded.

The chest pain episode is very likely unrelated to ischemia

AL has an early atherosclerosis and he needs an intensive statin treatment

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 can be modified by
PCSK9 Inhib.*

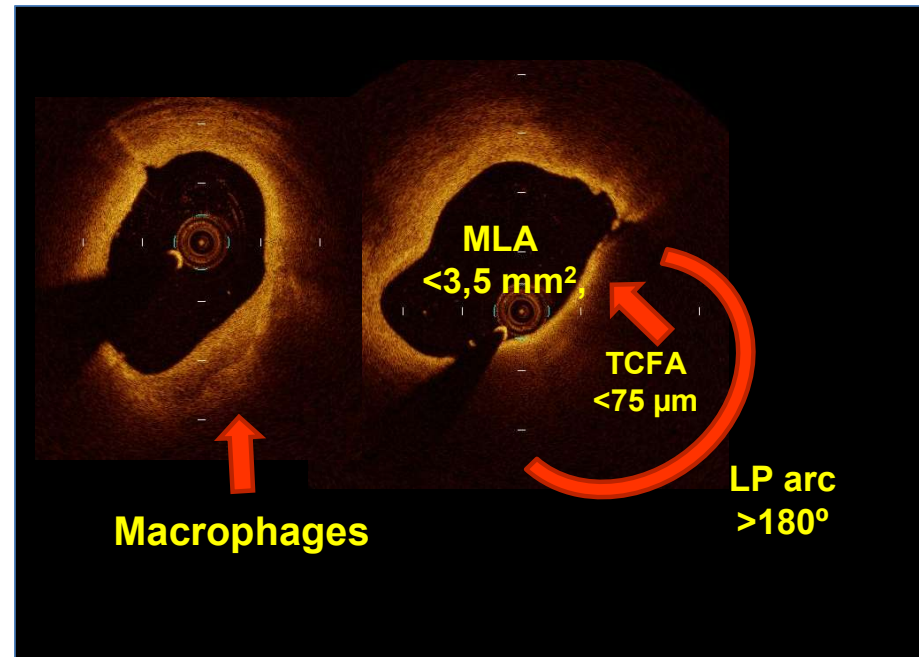
The CLIMA study

1003 patients enrolled. Prox. LAD interrogation with OCT
1 year clinical FU

Primary endpoint.

Correlation between the **simultaneous** presence of the following four OCT criteria of plaque vulnerability in the explored lesions **and hard clinical outcome**

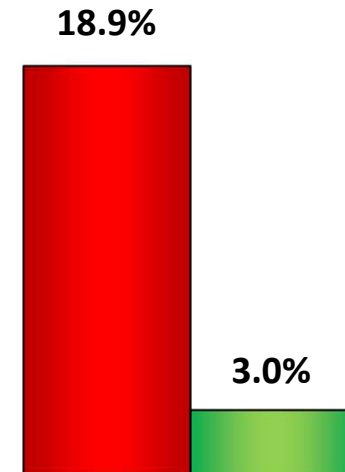
(cardiac death + target vessel myocardial infarction either STEMI or NSTEMI)



1003 patients enrolled,
Prox. LAD interrogation with OCT
1 year clinical FU

OCT criteria	HR	p
<u>MLA</u>		
Minimum lumen area <3.5mm ²	HR 2.07 (1.1-4.0)	0.032
<u>TCFA</u>		
TCFA <75 μm (%)	HR 4.65 (2.4-9.0)	<0.001
<u>Maximum lipid arc</u>		
Maximum lipid arc >180°	HR 2.40 (1.2-4.8)	0.013
<u>Presence of macrophages (%)</u>	HR 2.66 (1.2-6.1)	0.021
Cholesterol crystal (%)	HR 1.66 (0.8-3.4)	0.160
Layered tissue (%)	HR 0.91 (0.4-2.2)	0.841
Calcified nodules (%)	HR 1.73 (0.8-3.7)	0.147
Ulcerated plaque (%)	HR 2.03 (0.8-5.4)	0.154
Vasa vasorum (%)	HR 1.24 (0.6-2.4)	0.527
MLA <3.5mm², TCFA <75 μm, LP arc >180°, MØ (%)	HR 7.54 (3.1-18.6)	<0.001

■ Event* ■ no event



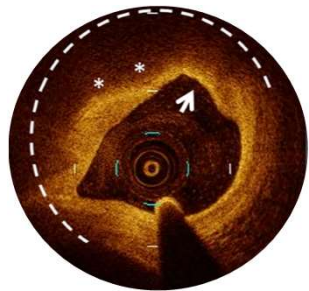
plaque vulnerability

(with MLA <3.5mm², TCFA <75μm,
LP arc >180° Macrophages)

*composite of cardiac death and
target-vessel myocardial infarction

study flow chart

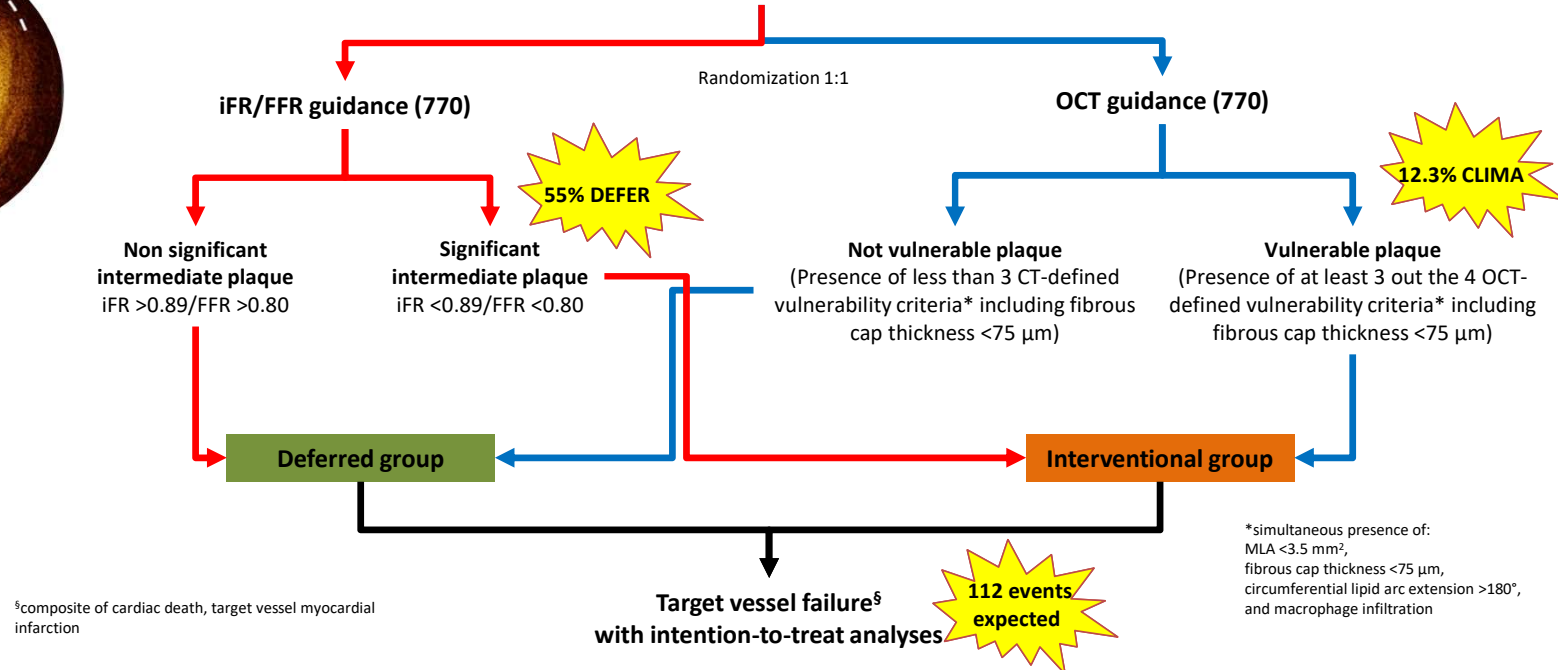
- Inclusion criteria:**
- Single intermediate lesion in non culprit vessels of patients with acute coronary syndrome diagnosis
 - Life expectancy >3 years
 - Age >18 years



Intermediate lesion in a naïve major coronary segment ($\varnothing \geq 2.5$ mm) determining stenosis between 40-70%

- Exclusion criteria:**
- incomplete imaging of the segment of interest (including at least 5 mm at both stenosis edges);
 - diffusely segment diseased with more than one lesion (preventing correct adverse event attribution) or significant (>70%) lesion in the same coronary vessel;
 - ostial left main or graft conduits involvement;
 - prior myocardial infarction or revascularization in the same coronary vessel;
 - non-cardiac co-morbid conditions that may result in protocol noncompliance.

QCA validation and randomization to (stratified by LAD localization and center)



[§]composite of cardiac death, target vessel myocardial infarction

Conclusions

- In presence of MINOCA identify ischemic and non ischemic diseases (Takotsubo and Myocarditis)
- In pts with ischemia identify the ACS pathophysiology. This has important clinical implications and is a guidance for optimal treatment
- Accurate reading of Coronary Angiography and use of IC Imaging modalities, particularly OCT, permit to identify a correct pathophysiology.
- Cardiac MRI useful for a proper differential diagnosis