

How Should I treat: Vulnerable plaque

Diagnostic and therapeutic options

Salvatore Brugaletta

Disclosures/Conflicts of interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

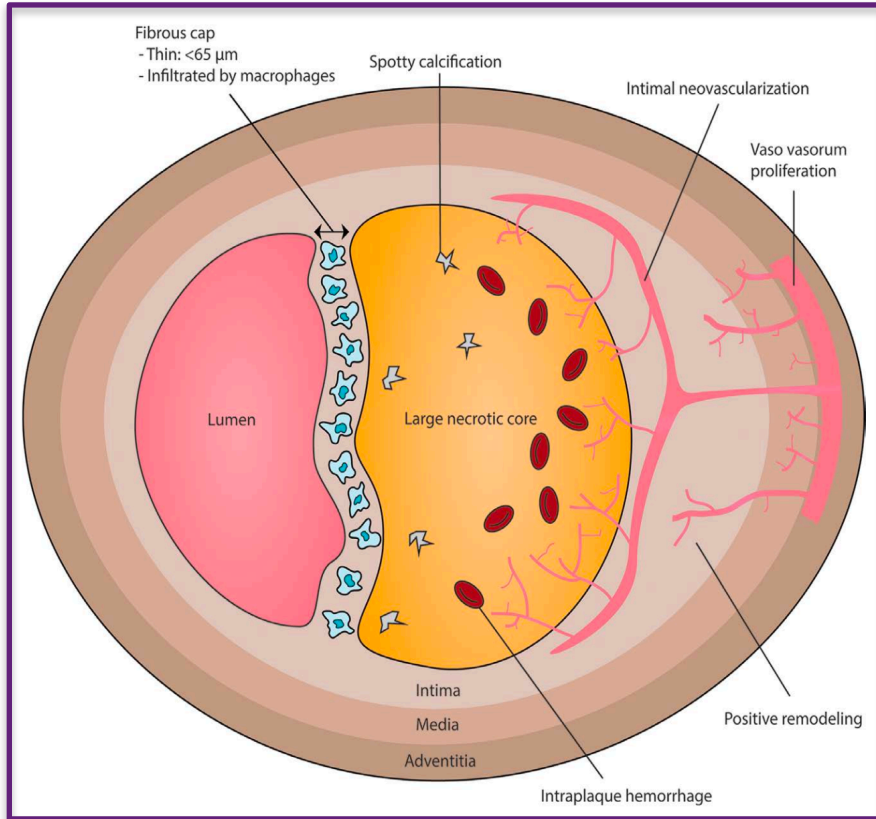
Affiliation/Financial Relationship

- Consulting Fees/Honoraria

Company

- Bayer, Boston Scientific, Novonordisk

Anatomical definition of vulnerable plaque



✓ ***THIN cap***

✓ ***Macrophages***

✓ ***Intraplaque hemorrhage***

✓ ***Angioneogenesis***

✓ ***Spotty Ca^{2+}***

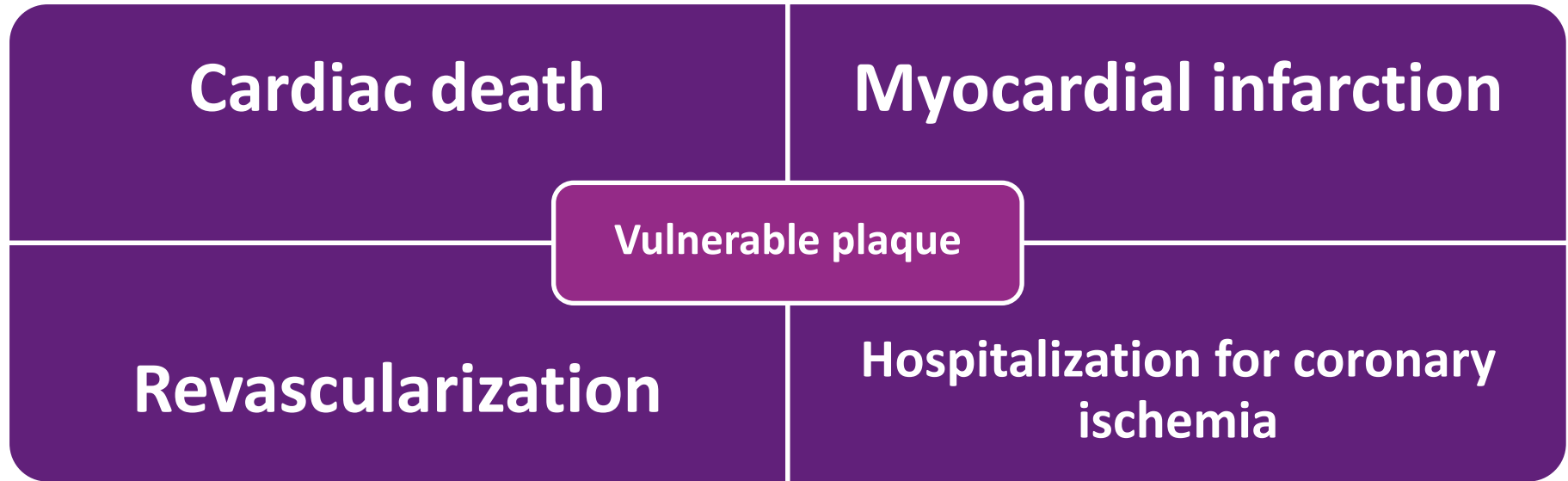
✓ ***Large lipid pool/necrotic core***

Clinical definition of vulnerable plaque

Coronary plaque with high likelihood of thrombotic complications and rapid progression

Clinical definition of vulnerable plaque

Coronary plaque with high likelihood of thrombotic complications and rapid progression



Circulation. 2003 Oct 7;108(14):1664-72.

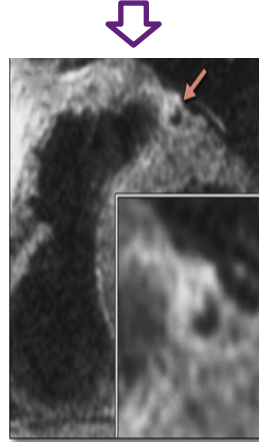
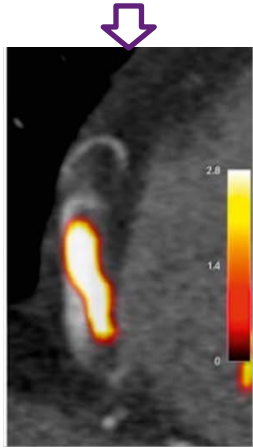
HOW to identify vulnerable plaque

NON INVASIVE

CT scan

PET-CT

MRI

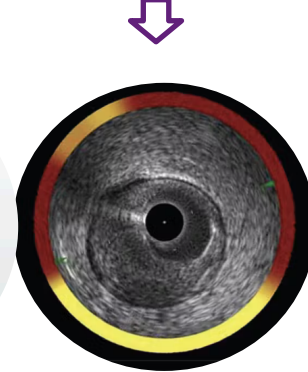
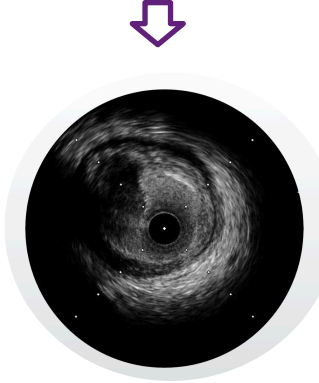


INVASIVE I.C. IMAGING

IVUS

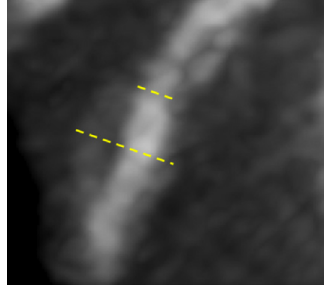
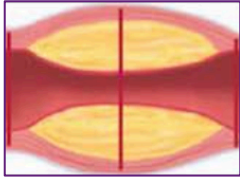
IVUS-NIRS

OCT

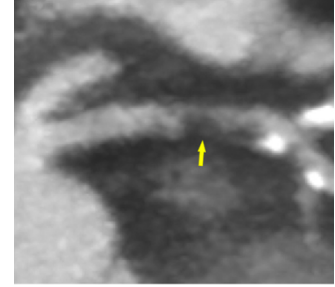
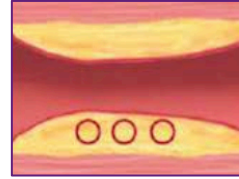


CT Scan

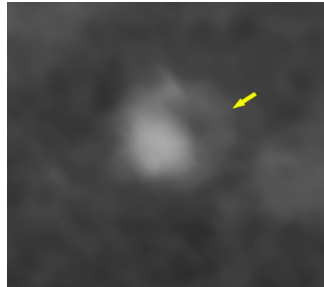
Positive remodelling



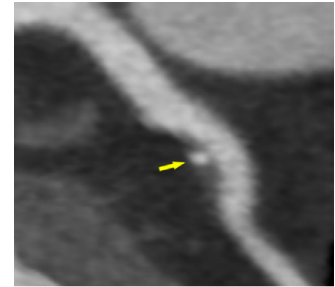
Low-attenuation plaque (HU<30)



Napkin-ring sign

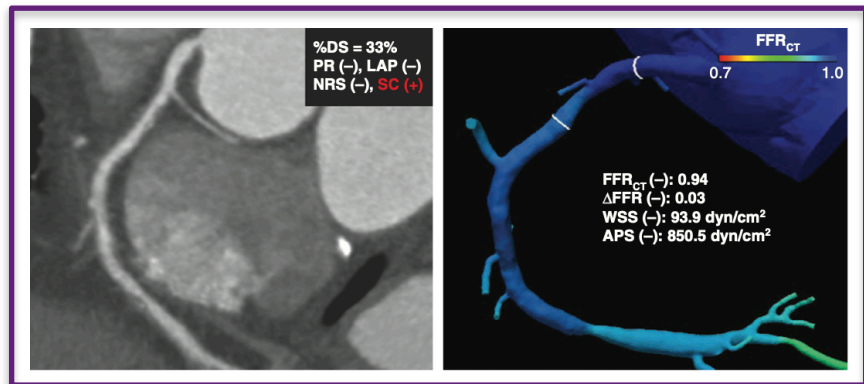


Spotty calcium

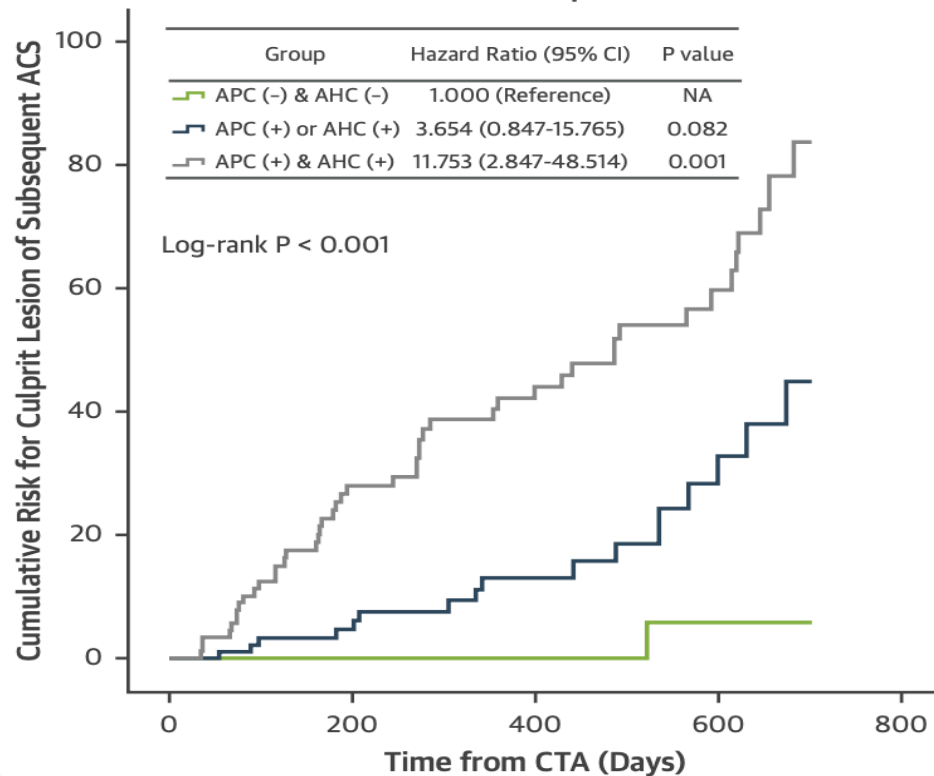


CT Scan

Identification of High-Risk Plaques Destined to Cause Acute Coronary Syndrome Using Coronary Computed Tomographic Angiography and Computational Fluid Dynamics



Cumulative Risk for Culprit Lesion on ACS



	MRI	PET/CT
Spatial resolution	0.2-1 mm ³	4 mm
Cost	++	+++
Lipid/necrotic core	+++	-
Spotty calcification	+	++
Fibrous cap	++	-
Plaque inflammation	+	+++
Availability	+	-

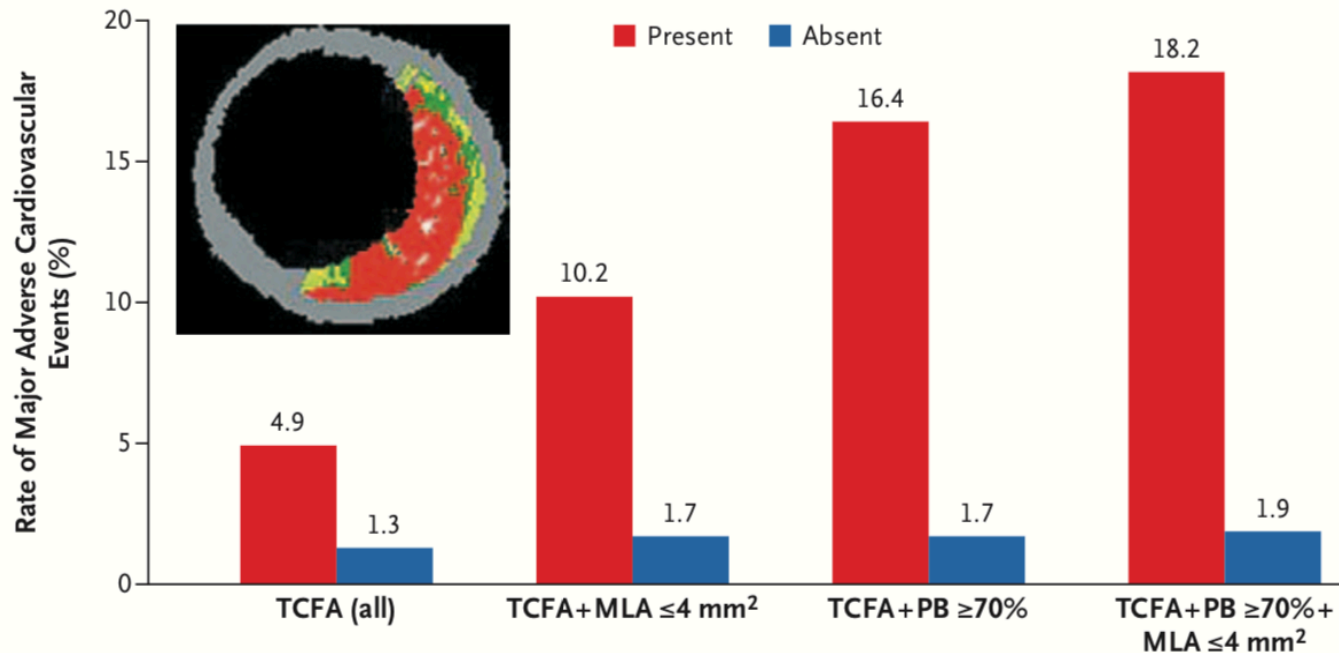
	MRI	PET/CT
Spatial resolution	0.2-1 mm ³	4 mm
Cost	++	+++
Lipid/necrotic core	+++	-
Spotty calcification	+	++
Fibrous cap	++	-
Plaque inflammation	+	+++
Availability	+	-

Promising but still on the way

Bom et al. Circ Cardiovasc Imaging. 2017;10:e005973.

Marc R. Dweck. et al. J Am Coll Cardiol Img 2016;9:306-16.

IVUS-VH: when it all began. . .

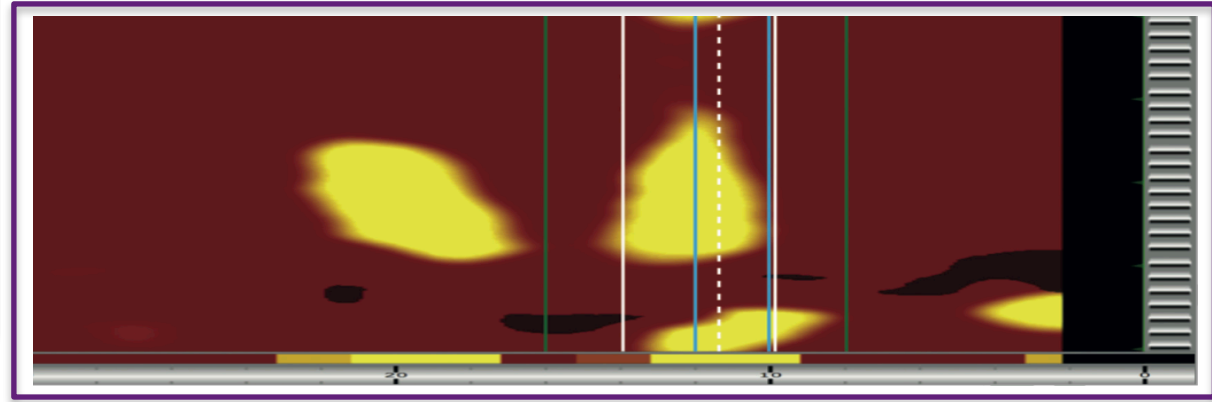
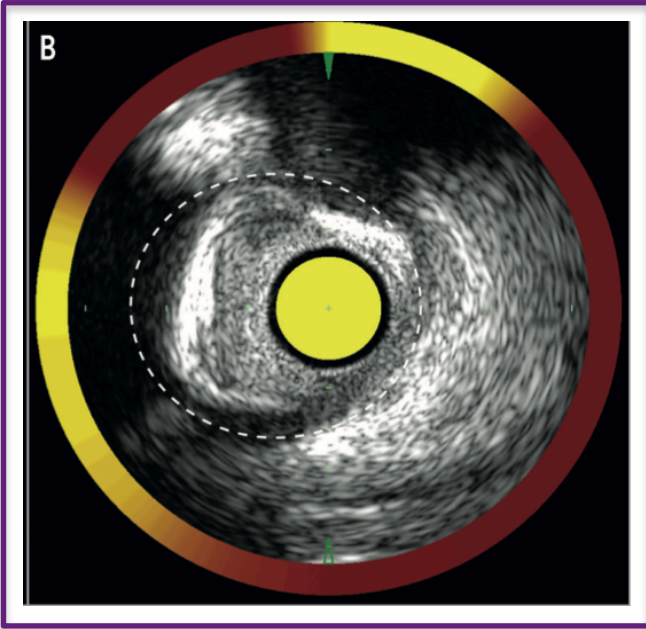


Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

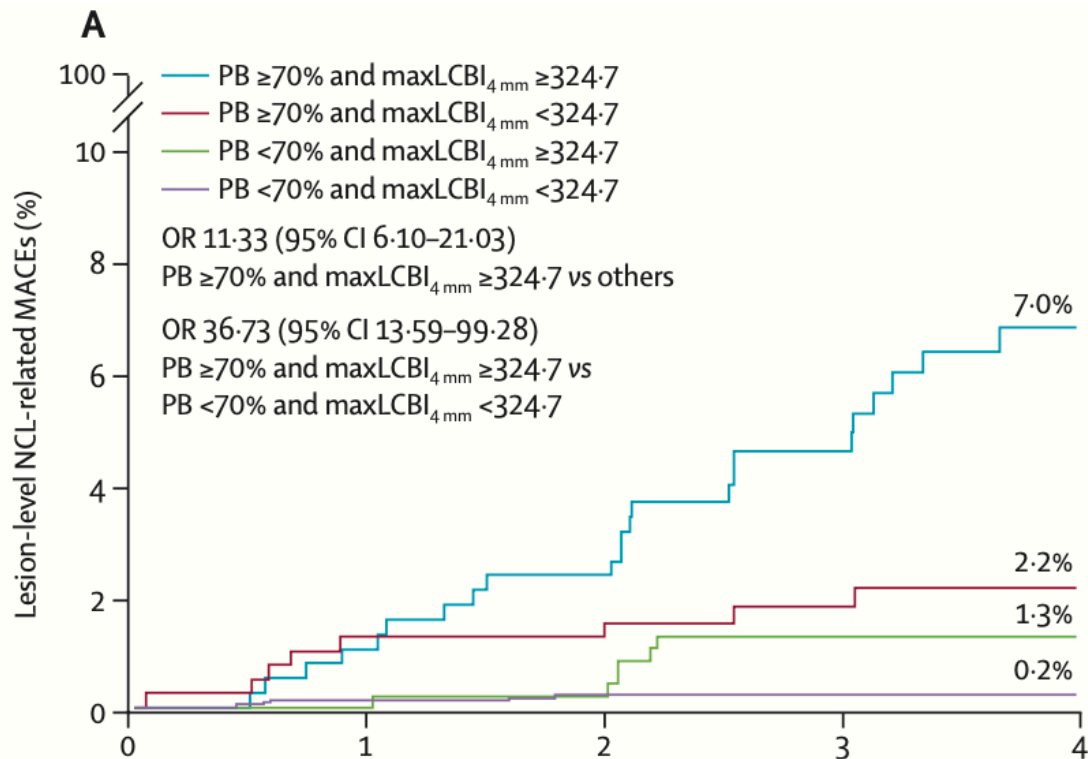
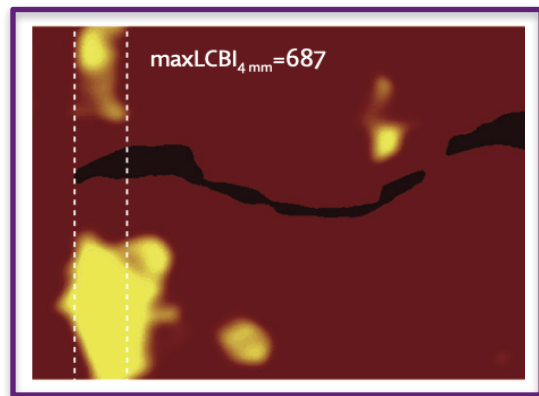
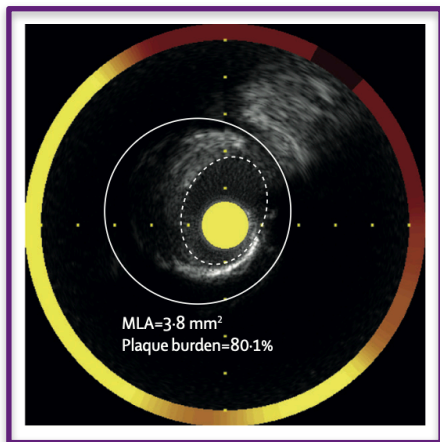
IVUS-Near Infrared spectroscopy (NIRS)

Lipid core burden index [LCBI]

$\text{Max LCBI}_{4\text{mm}} > 400$



IVUS-NIRS



OCT: The *THIN CAP* Fibroatheroma

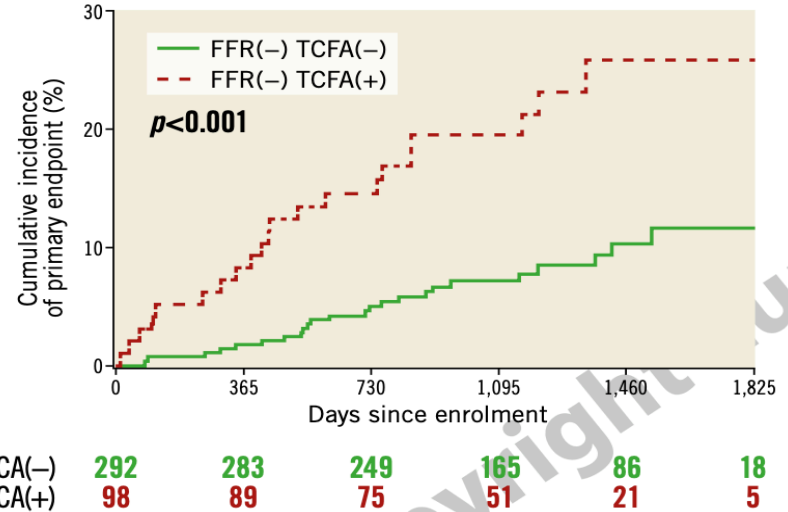
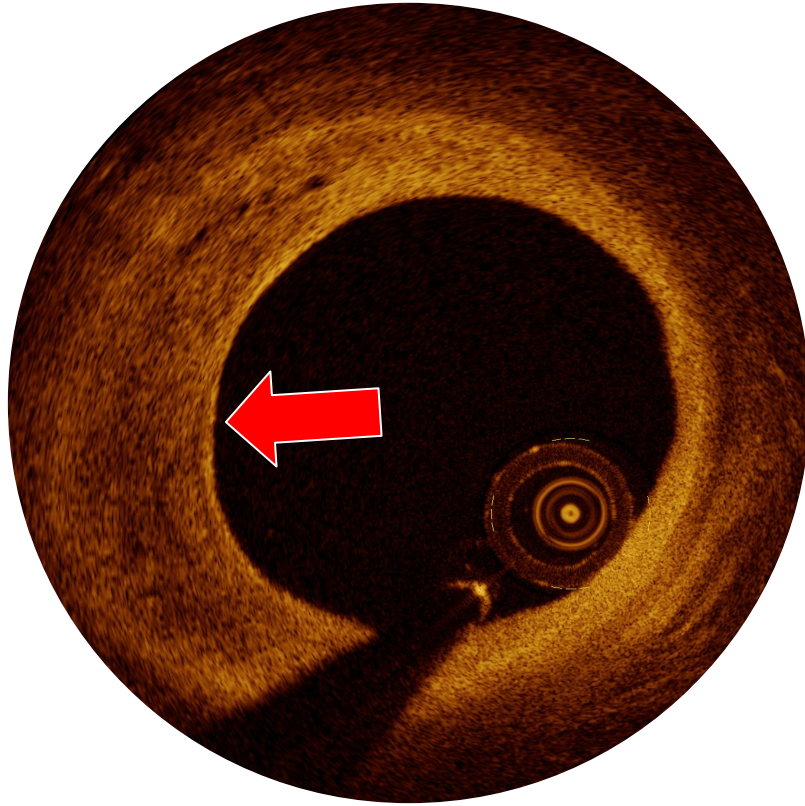


Figure 1. Kaplan-Meier curves for primary endpoint of FFR(-) TCFA(-) vs FFR(-) TCFA(+) groups. FFR: fractional flow reserve; TCFA: thin-cap fibroatheroma

When the plaque is VULNERABLE?

Study	I.C. imaging	Sample size	Population	FU (y)	Predictors	Primary endpoint
PROSPECT, 2011.	IVUS-VH	697	ACS	3.4	MLA (<4 mm ²), TCFA VH Plaque burden (PB) >70%	CD, cardiac arrest, MI or hospitalized angina
VIVA, 2011	IVUS-VH	170	CCS	1.7	MLA (<4 mm ²), TCFA VH Plaque burden (PB) >70%	CD, MI, unplanned revascularization
ATHEROREMO-IVUS, 2013	IVUS-VH	581	CCS	1	TCFA, PLAQUE BURDEN ≥70%	Death, ACS or unplanned revascularization
ATHEROREMO-IVUS, 2014	IVUS-NIRS	203	CCS	1	LCBI≥43.0	Death, nonfatal ACS, stroke, unplanned revascularization
LRP, 2019	IVUS-NIRS	1563	ACS	2	Max LCBI _{4mm} ≥ 400	Death, cardiac arrest, MI, ACS, revascularization, hospitalized angina
CLIMA, 2020.	OCT	1003	Only LAD	1	TCFA (65 µm) + MLA (<3.5 mm ²) + Macrophages + LA>180°	CD, target segment MI
PROSPECT II, 2021	IVUS-NIRS	898	ACS	3.7	MAXLCBI ≥ 324.7, PBI ≥ 70%, MLA ≤ 4 mm ²	CD, MI; UA, angina requiring revascularization or with rapid lesion progression
COMBINE OCT-FFR, 2021.	OCT	550	DM	1.5	TCFA (<65 µm) & LA>90°	CD, target-vessel MI, clinically driven TLR or hospitalized angina
Wakayama registry, 2021.	OCT	1378	ACS	6	TCFA (65 µm) + LA>180°	ACS
PECTUS, 2023.	OCT	420	ACS	4	2 of LA>90°, TCFA (<65 µm), plaque rupture/thrombus	CD, NCL nonfatal MI, unplanned revascularization

When the plaque is VULNERABLE?

Study	I.C. imaging	Sample size	Population	FU (y)	Predictors	Primary endpoint
PROSPECT, 2011.	IVUS-VH	697	ACS	3.4	MLA (<4 mm ²), TCFA VH Plaque burden (PB) >70%	CD, cardiac arrest, MI or hospitalized angina
VIVA, 2011	IVUS-VH	170	CCS	1.7	MLA (<4 mm ²), TCFA VH Plaque burden (PB) >70%	CD, MI, unplanned revascularization
ATHEROREMO-IVUS, 2013	IVUS-VH	581	CCS	1	TCFA, PLAQUE BURDEN ≥70%	Death, ACS or unplanned revascularization
ATHEROREMO-IVUS, 2014	IVUS-NIRS	203	CCS	1	LCBI≥43.0	Death, nonfatal ACS, stroke, unplanned revascularization
LRP, 2019	IVUS-NIRS	1563	ACS	2	Max LCBI _{4mm} ≥ 400	Death, cardiac arrest, MI, ACS, revascularization, hospitalized angina
CLIMA, 2020.	OCT	1003	Only LAD	1	TCFA (65 µm) + MLA (<3.5 mm ²) + Macrophages + LA>180°	CD, target segment MI
PROSPECT II, 2021	IVUS-NIRS	898	ACS	3.7	MAXLCBI ≥ 324.7, PBI ≥ 70%, MLA ≤ 4 mm ²	CD, MI; UA, angina requiring revascularization or with rapid lesion progression
COMBINE OCT-FFR, 2021.	OCT	550	DM	1.5	TCFA (<65 µm) & LA>90°	CD, target-vessel MI, clinically driven TLR or hospitalized angina
Wakayama registry, 2021.	OCT	1378	ACS	6	TCFA (65 µm) + LA>180°	ACS
PECTUS, 2023.	OCT	420	ACS	4	2 of LA>90°, TCFA (<65 µm), plaque rupture/thrombus	CD, NCL nonfatal MI, unplanned revascularization

Vulnerable plaque treatment: how and why?

Medical treatment



Mechanical treatment



Fibrous Cap Thickening

Increasing cap thickness ($>65\mu\text{m}$) to reduce susceptibility to rupture.



Necrotic Core Regression

Reducing lipid pool size and inflammatory cell infiltration.



Reducing Thrombogenicity

Passivating the plaque surface to prevent luminal thrombosis.

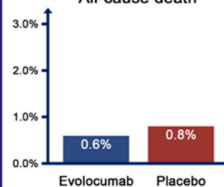


Systemic management

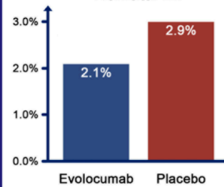
GLAGOV

968 pts with non-obstructive CAD

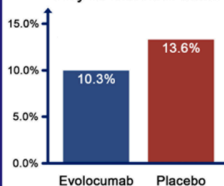
All-cause death



Nonfatal MI



Any revascularization

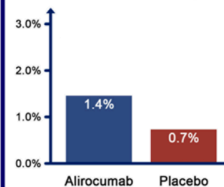


Follow-up: 78 weeks

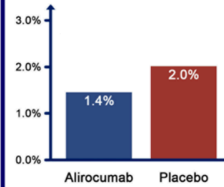
PACMAN-AMI

300 ACS pts with residual non-obstructive CAD

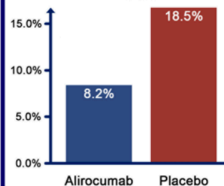
All-cause death



MI



IDR

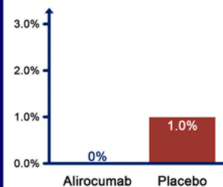


Follow-up: 52 weeks

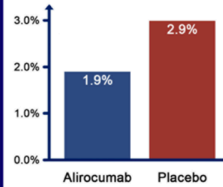
ODYSSEY J-IVUS

206 ACS pts with uncontrolled dyslipidemia

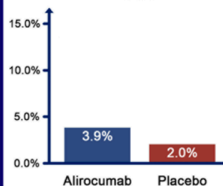
All-cause death



MI



IDR



Follow-up: 36 weeks

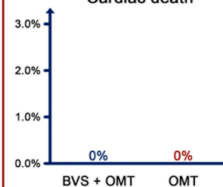
Focal management



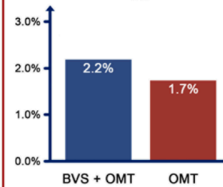
PROSPECT ABSORB

182 ACS pts with residual non-obstructive CAD

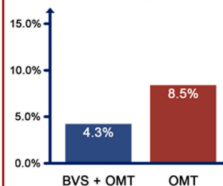
Cardiac death



MI



IDR

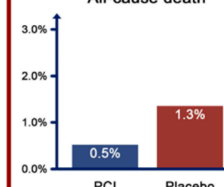


Follow-up: 104 weeks

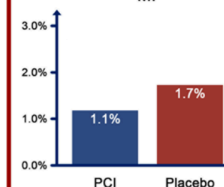
PREVENT

1,606 pts with non-obstructive CAD

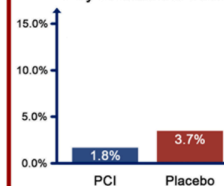
All-cause death



MI



Any revascularization



Follow-up: 104 weeks

PREVENT TRIAL



POPULATION

(IVUS or OCT)

Patients with imaging-identified “vulnerable” plaques. (83% CCS)

These are high-risk, lipid-rich plaques that are not yet restricting blood flow (FFR > 0.80).



FFR > 0.80



OUTCOME

Major Event Rate:

Preventive PCI resulted in a massive reduction in cardiac death, heart attacks, and emergency hospitalizations.

0.4%



2 Years

3.4%



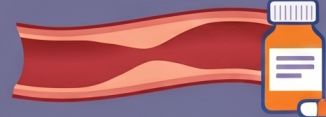
INTERVENTION & COMPARISON

Preventive PCI + Medication vs. Medication Alone.

803 patients received stents plus optimal medical therapy (OMT), while 803 received OMT only.



Preventive PCI (803)



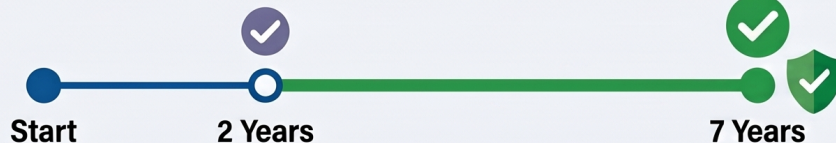
Medication Alone (803)



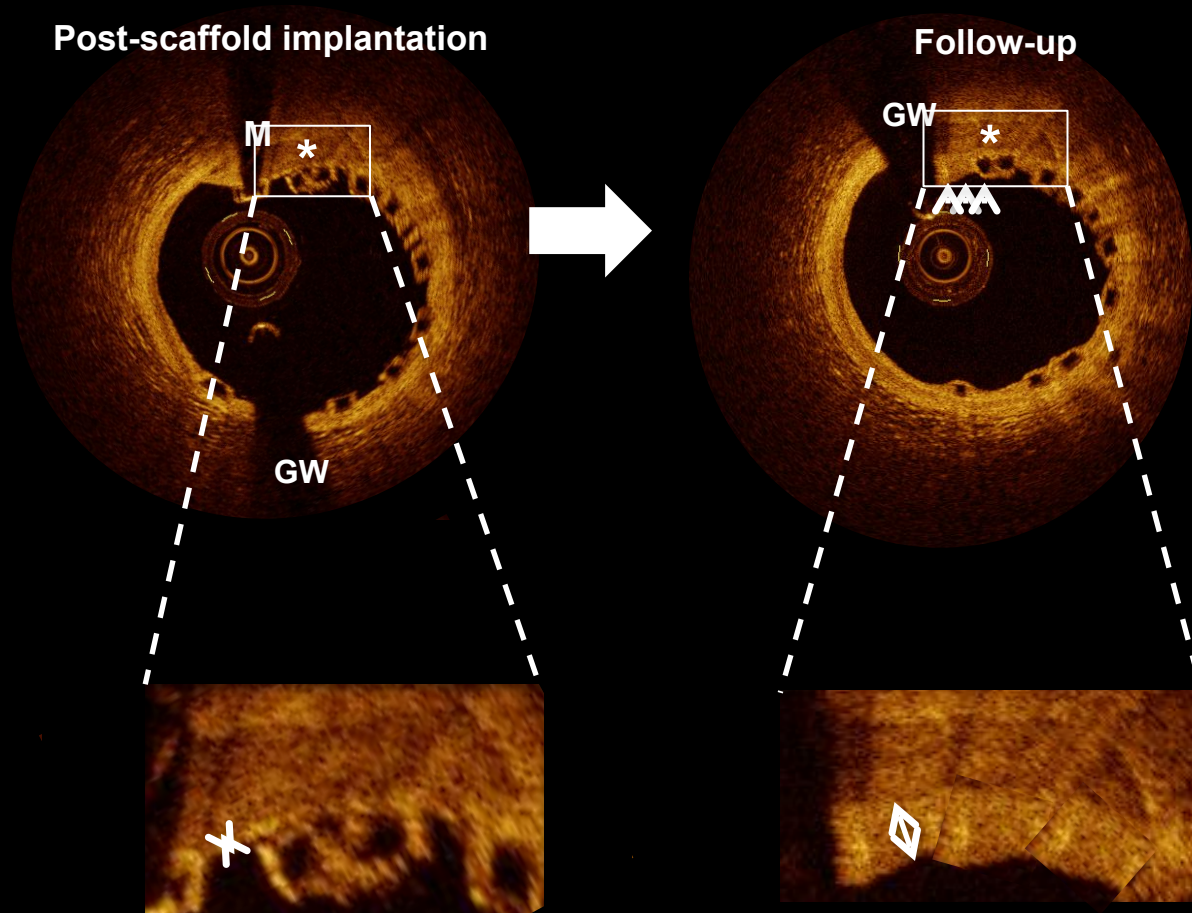
TIME

Immediate benefits sustained for 7 years.

The primary results were measured at 2 years, but the protective effect remained significant throughout the long-term follow-up.



Can the scaffold cap the plaque?

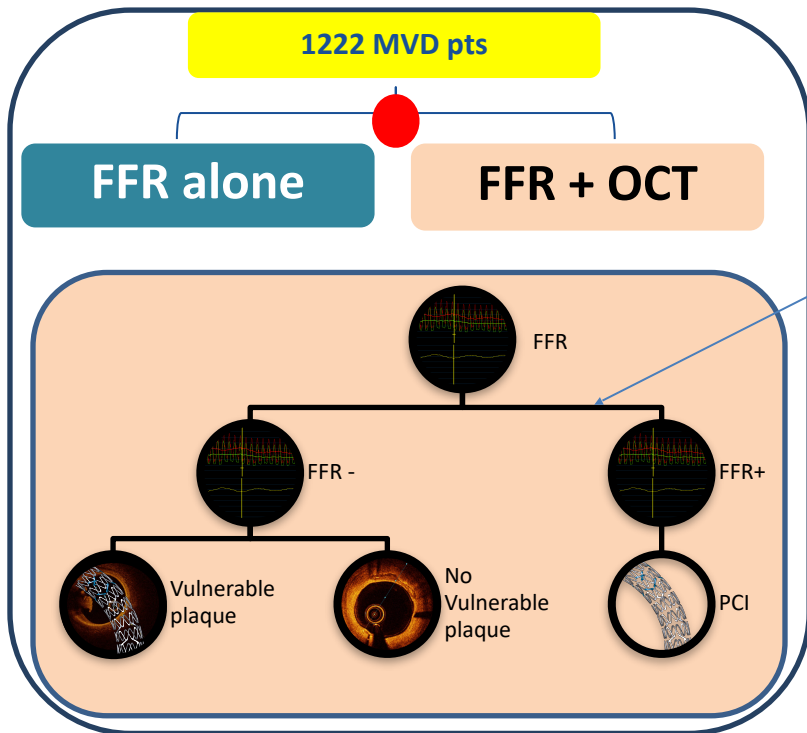


Trial (Clinicaltrials.gov identifier)	VULNERABLE (NCT05599061)	NCT06855537	COMBINE-INTERVENE (NCT05333068)	INTERCLIMA (NCT05027984)
Design	Randomized, open-label	Randomized, open-label	Randomized, single-blind	Randomized, single-blind
Expected sample	N=600	N=2190	N=1222	N=1420
Population	STEMI patients with multivessel disease and 40–70% nonculprit lesions in different vessels than the culprit lesion, with FFR >0.80 and OCT features of VP	ACS patients with ≥1 non-flow-limiting OCT-defined VP in a vessel with FFR/ QFR > 0.80	Patients with multivessel coronary artery disease	ACS patients with a 40–70% diameter stenosis at QCA with no other significant stenosis in the same vessel
Intervention	PCI plus optimal medical therapy	PCI of vulnerable plaques using DES or DCB + optimal medical therapy (high-intensity lipid-lowering + colchicine)	Revascularization based on combined OCT and FFR	OCT (fibrous cap thickness <75 µm plus at least 2 other criteria of plaque vulnerability)
Control	Optimal medical therapy	Optimal medical therapy alone (high-intensity lipid-lowering + colchicine)	Revascularization based on FFR and sham OCT	iFR or RFR ≤0.89 or FFR ≤0.80
Primary outcomes	Composite of cardiovascular death, target-vessel myocardial infarction, or clinically and physiologically oriented target-vessel revascularization	Composite of cardiac death, target-vessel myocardial infarction, ischemia-driven target-vessel revascularization, or hospitalization for unstable angina	Composite of cardiac death, any myocardial infarction, or any clinically driven revascularization	Composite of cardiac death or nonfatal spontaneous target-vessel myocardial infarction
Follow-up	4 y	2 y	2 y	2 y
Anticipated completion date	December 2028	September 2027	March 2026	July 2025

STUDIES COMBINING FFR and OCT for treatment of coronary lesions

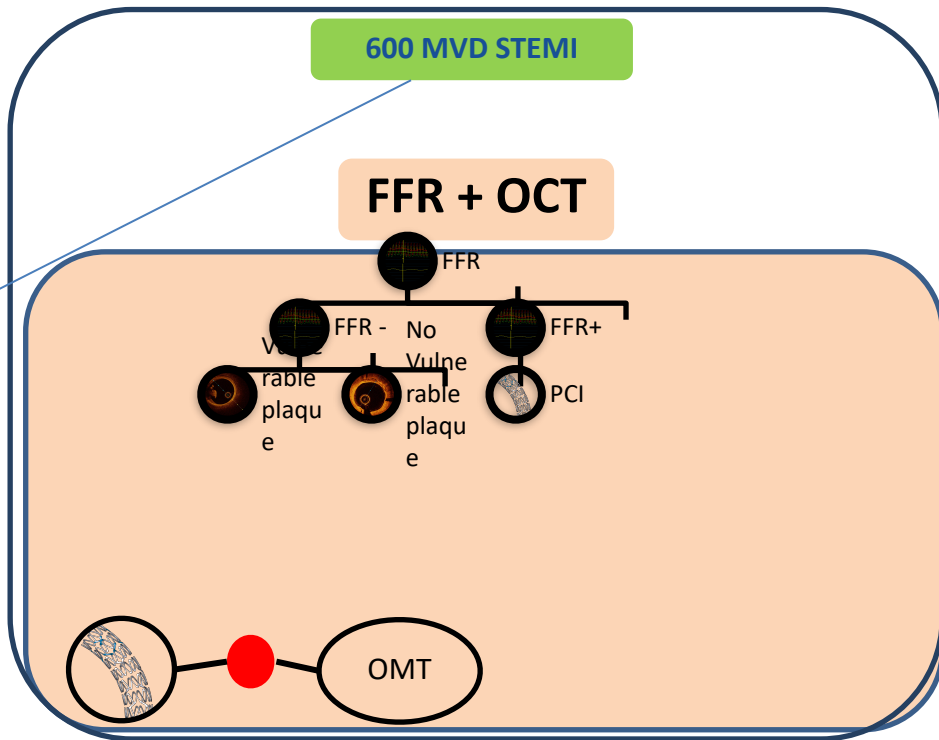
COMBINE INTERVENE

Prospective, randomized, multicentre study



VULNERABLE TRIAL

Prospective, randomized, multicentre study

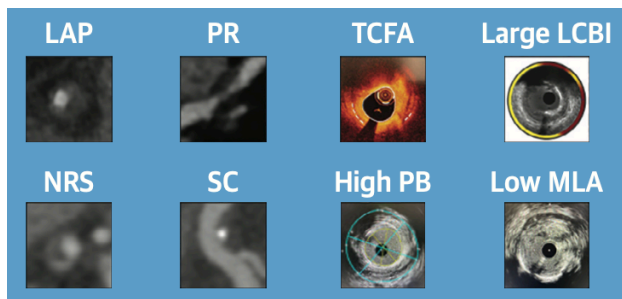


Value of VP diagnosis and treatment

**Pts analyzed
ACS or stable**



Definition of VP



FU Length



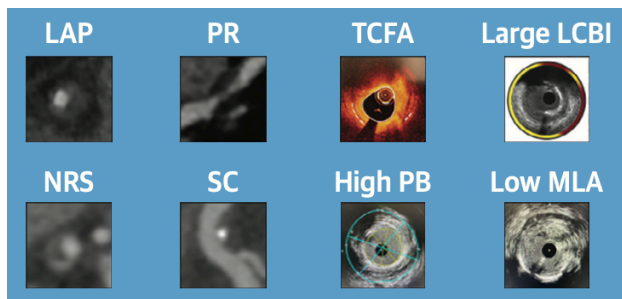
**Event rate should not be too low to see a signal of
focal/systemic therapy**

Value of VP diagnosis and treatment

Pts analyzed
ACS or stable



Definition of VP



FU Length



COMBINE-INTERVENE & VULNERABLE will give us more data about the value of preventive mechanical treatment

Thank you!



@sbrugaletta

sabrugaletta@gmail.com