Reclassification of Vulnerable Plaque Including Intraplaque Hemorrhage, Fissure, Healed Plaque and More

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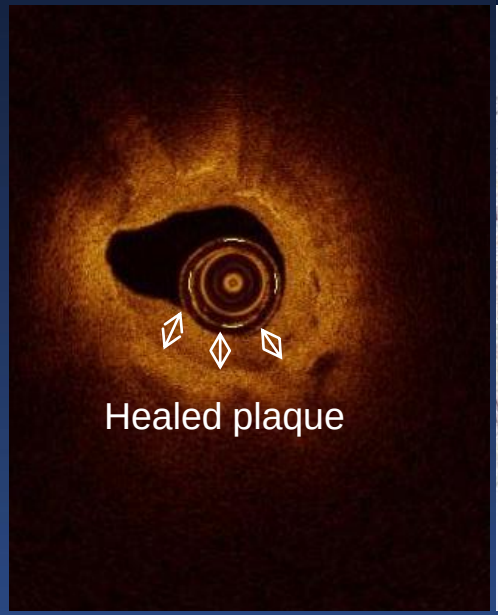
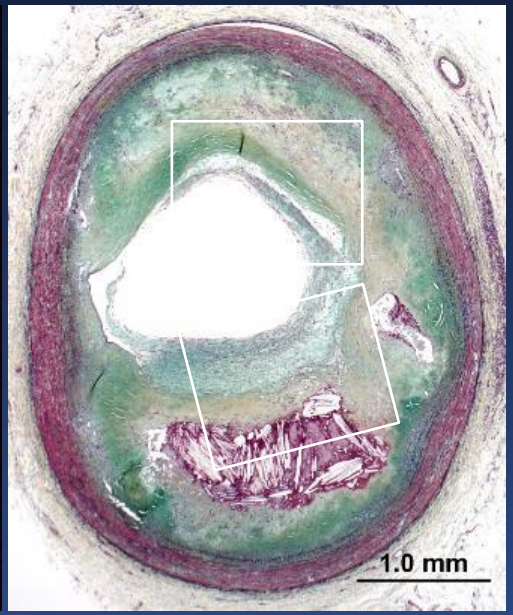
Disclosure Statement of Financial Interest

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

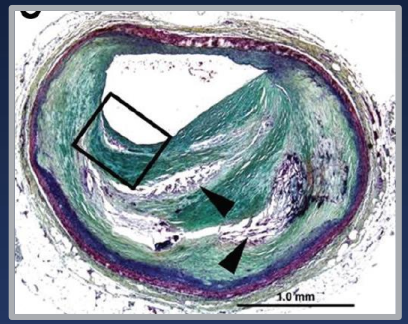
Affiliation/Financial Relationship	Company
• Consultant	Boston Scientific, SpectraWave, Shockwave

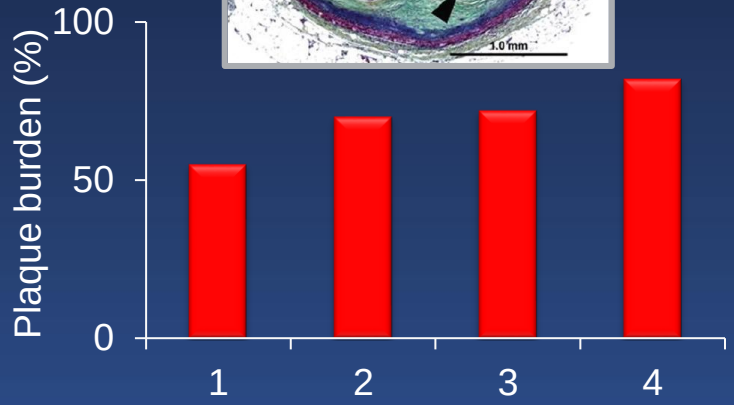
Healed Plaque





OCT to diagnose Healed plaque
Sensitivity=81%, Specificity=98%





# of prior ruptures and healed rupture site

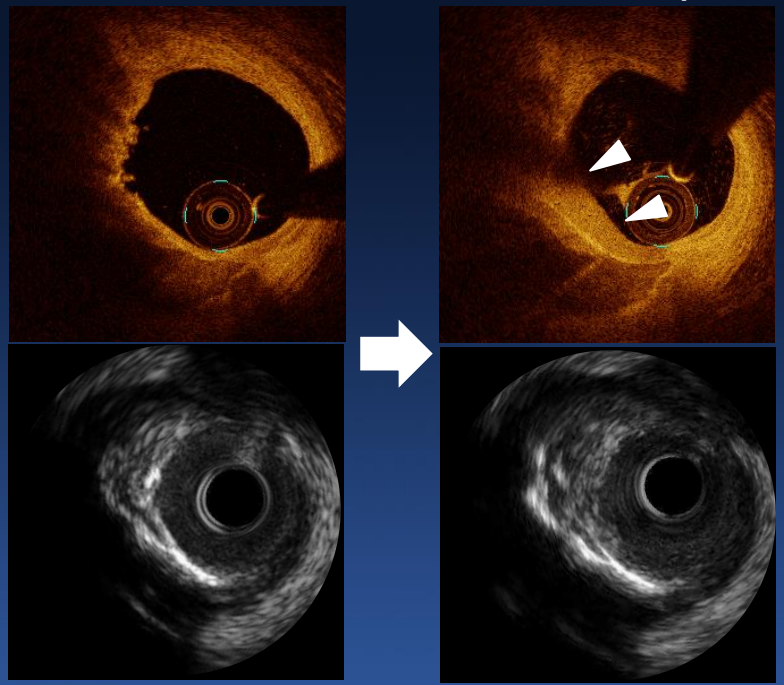
Burk AP et al. Circulation 2001;103:934-940. Mann J et al. Heart 1999;82:265–268.
Shimokado A, Atherosclerosis 2018, 275: 35-42.

Serial OCT in Stable Patients

3 vessel IVUS/OCT in 127 non-culprit lesions in stable 45 pts at 8 months
New healed plaque was found in 38% (9/24) of lesions with progression.

Baseline

Follow-up



Lumen=4.3 mm^2
EEM=13.2 mm^2

Lumen=3.7 mm^2
EEM=14.6 mm^2

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Yamamoto M et al. Circulation Img 2017; doi: 1161/CIRCIMAGING.117.006.347.

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Healed Culprit Plaques in ACS

Prevalence=29% (108/376)

	Healed Plaque Phenotype (n=108)	Non-healed Plaque Phenotype (n=268)	P-value
Clinical Presentation			0.04
STEMI	59.3%	70.1%	
NSTE-ACS	40.7%	29.9%	
hs-CRP, mg/L	4.98 (1.00-11.32)	3.00 (0.30, 10.15)	0.03
Underlying pathology			0.04
Plaque rupture	64.8%	53.0%	
Intact fibrous cap	35.2%	47.0%	
TCFA	56.5%	42.5%	0.02

Fracassi F, et al. JACC 2019;73:2253-63.

Effect of Non-Culprit Healed Plaque on Future ACS

(Screened from 823 pts over 7 yrs, mean age=68 yr)
The rate of recurrent ACS Pt was 3.8% (31/823).

	Recurrent ACS (n=30)	Stable after one MI (n=37)	Stable (n=38)
Criteria	3MI or 4ACS with one MI	>3 yrs stable after one MI	>3 yrs stable without MI
LDL	73 (51, 89)	74 (55, 96)	75 (59, 91)
hs-CRP, mg/L	11.5 (3.2, 38.4)	3.3 (0.8, 7.3)	3.8 (2.9, 14.8)
Gensini angio score	53 (23, 84)	20 (12, 47)	38 (20, 55)
Healed plaque	**3.3% (1/30)**	**29.7% (11/37)**	**28.9% (11/38)**
TCFA	40%	34.2%	8.1%

In PROSPECT, among 668 pts presenting STEMI or NSTEMI, 10.6% (71) pts had prior MI. Subsequent non-culprit MI was 1.0% (6) at 3 yrs. The prevalence of MI 3 times was 0.9% (6/668).

Vergallo R, et al. JAMA Cardiology 2019, doi:10.1001/jamacardio.2019.0275

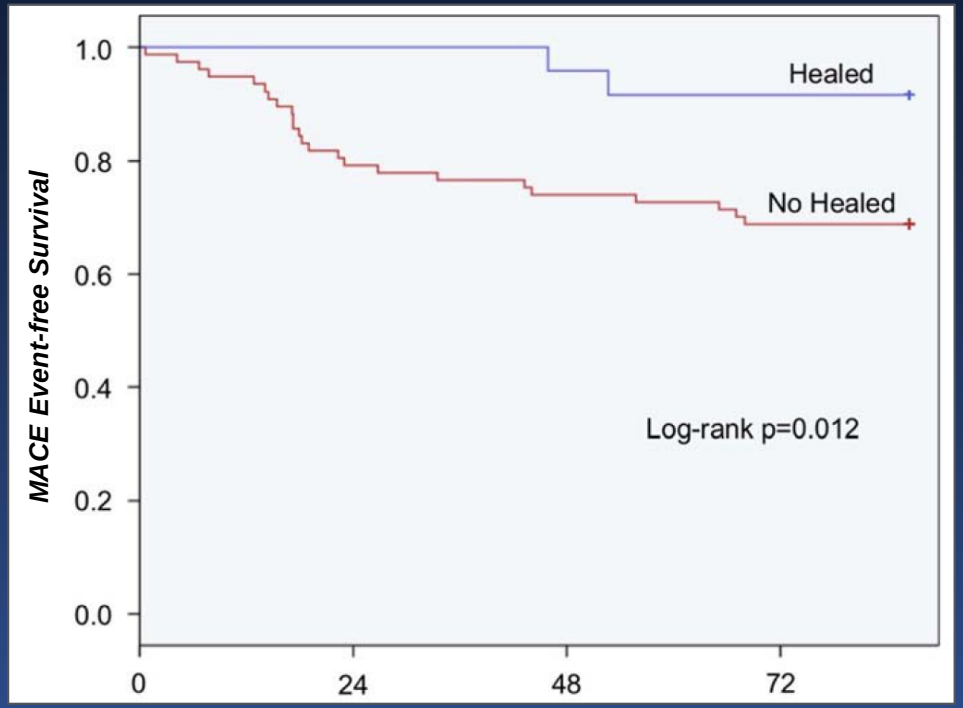
Effect of Non-Culprit Healed Plaque on Subsequent ACS

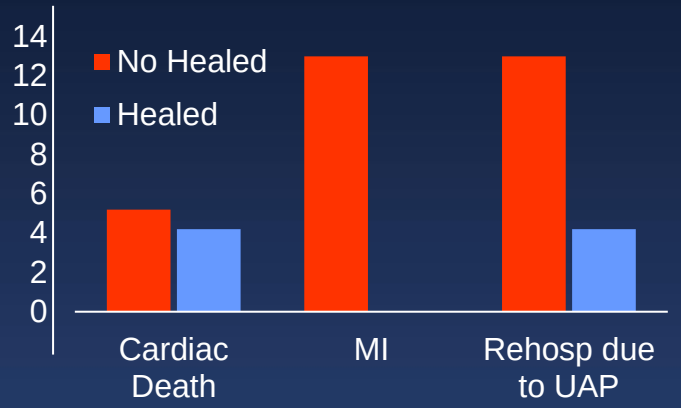
Median FU=3.0 yrs (1.5, 4.7)

	Recurrent ACS (n=29)	Stable after MI (n=36)	Stable (n=36)
Criteria	3MI or 4ACS with one MI	>3 yrs stable after one MI	>3 yrs stable without MI
MACE	51.7% (15)	16.7% (6)	2.8% (1)
Cardiac death	10.3% (3)	2.8% (1)	2.8% (1)
Non-fatal MI	24.1% (7)	5.6% (2)	2.8% (1)
Rehospitalization due to ACS	17.2% (5)	8.3% (3)	8.3% (3)
Non-TVR	31.0% (9)	13.9% (5)	11.1% (4)

Vergallo R, et al. JAMA Cardiology 2019, doi:10.1001/jamacardio.2019.0275

Non-Culprit Related MACE

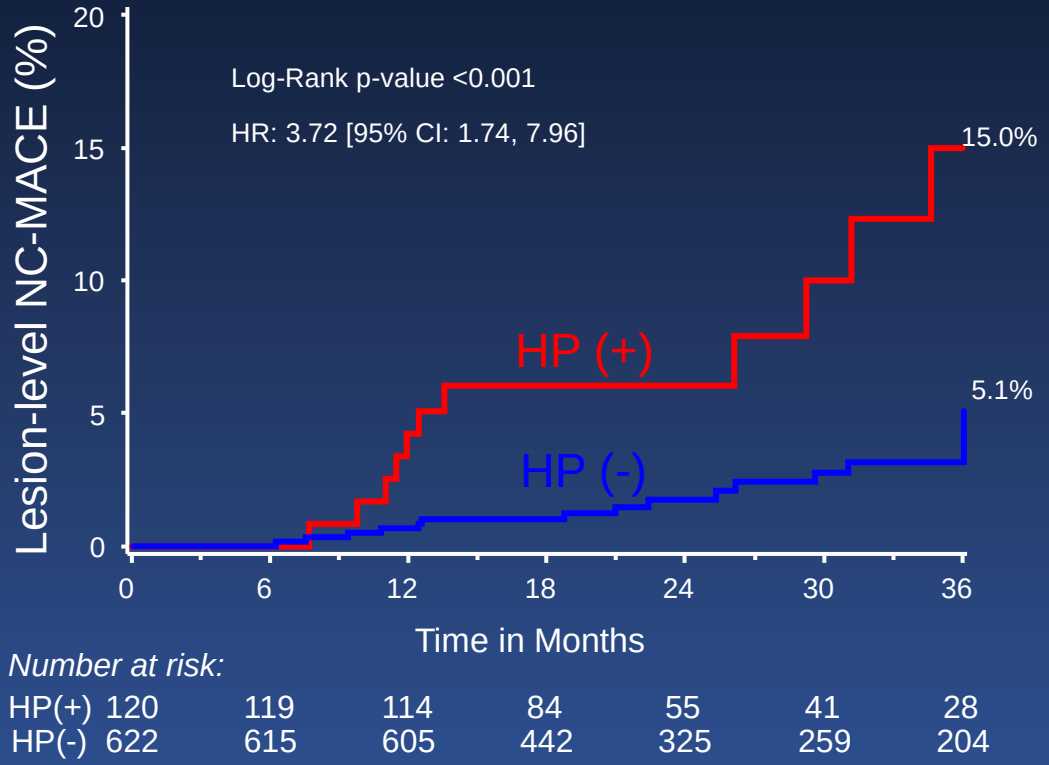




	HR (95% CI)	P-Value
Recurrent ACS	3.09 (1.04, 9.20)	0.04
TCFA	2.80 (1.04, 7.54)	0.04
Macrophage accumulation	2.78 (1.13, 6.86)	0.03
Healed plaque	0.17 (0.03, 0.85)	0.03

Vergallo R, et al. JAMA Cardiology 2019, doi:10.1001/jamacardio.2019.0275

Non-culprit lesion MACE

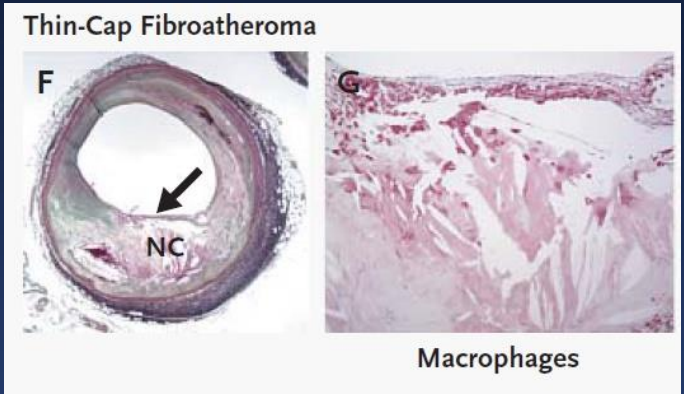


	HR (95% CI)	P-Value
HP	3.56 (1.25, 10.2)	0.02
TCFA	5.89 (1.81, 19.2)	<0.01
MLA<3.5mm^2	6.72 (1.85, 24.4)	<0.01

Usui E. et al. Atherosclerosis. 2021; 332:41-47.

IPH accelerates atherosclerosis progression

Prevalence of IPH 5.0±0.4 in pts with plaque rupture with thrombus, 2.8±0.8 with >75% plaque burden

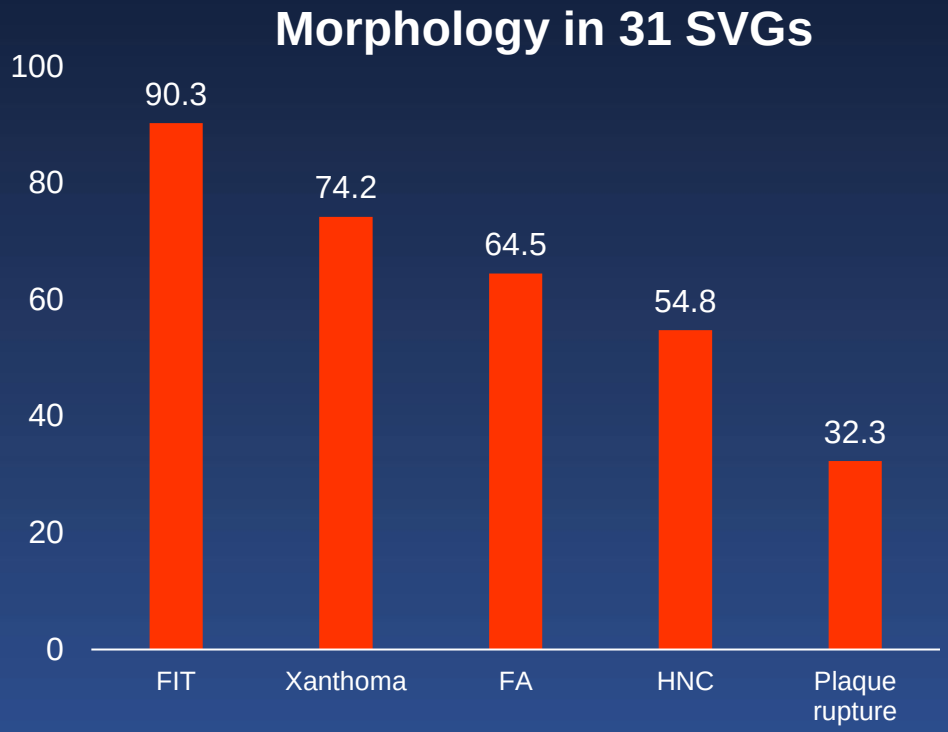


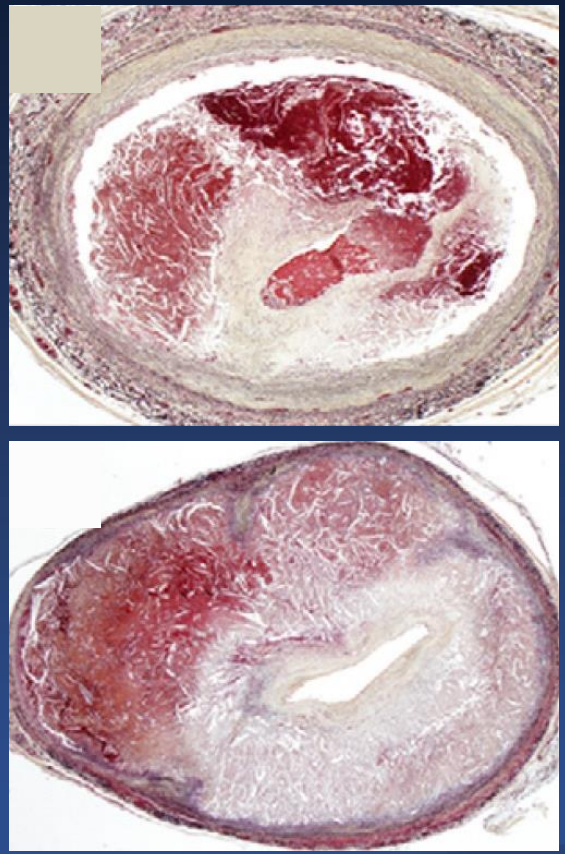
Among all of the cells in the body, the erythrocyte membrane has the greatest amount of free cholesterol; therefore, free cholesterol from the destroyed erythrocytes in IPH becomes a localized source of cholesterol crystals.

	# of plaques	Glycophorin A Score	Iron Score	Size of NC
PIT	129	0.09 ± 0.04	0.07 ± 0.05	-
Early fibroatheroma	79	0.23 ± 0.07	0.17 ± 0.08	0.06 ± 0.02
Late fibroatheroma	105	0.94 ± 0.11	0.41 ± 0.09	0.84 ± 0.08
TCFA	52	1.60 ± 0.20	1.24± 0.24	1.95 ± 0.30

Kolodgie FD, et al. NEJM 2003;349:16-25

Hemorrhagic NC is common in SVG >2 years

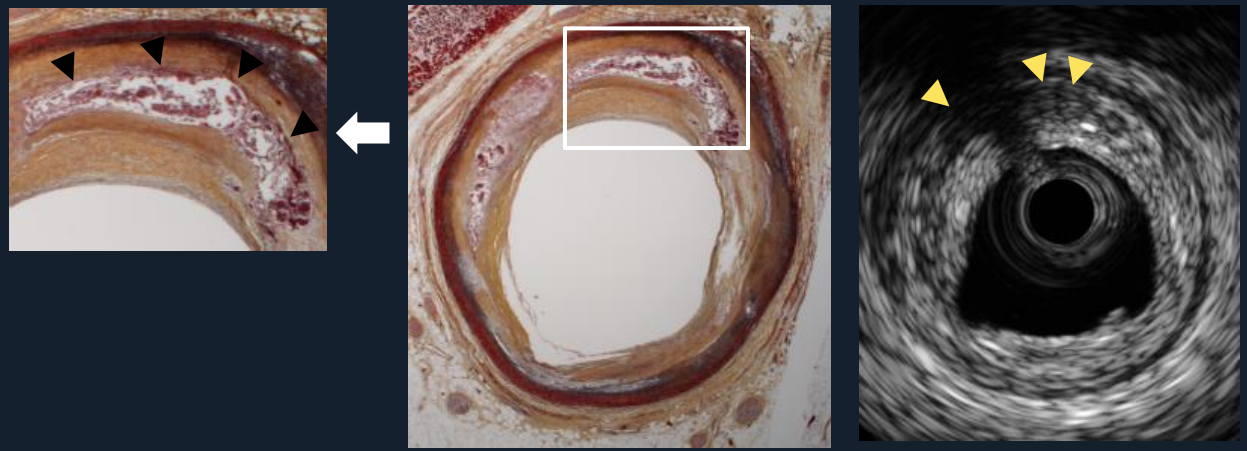




HNC=hemorrhagic necrotic core

Yazdani SK. et al. JACC Interv 2012; 5:666-74. Yazdani SK. et al. Intervent Cardiol Clin 2013; 2:241-249

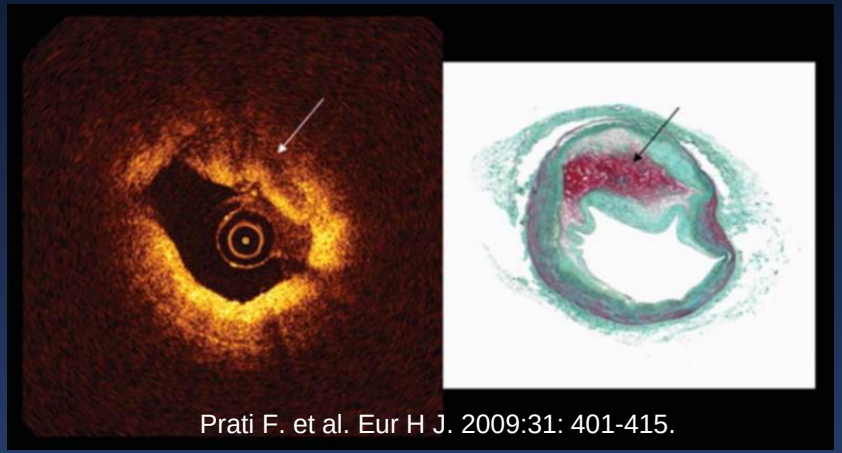
Intraplaque Hemorrhage



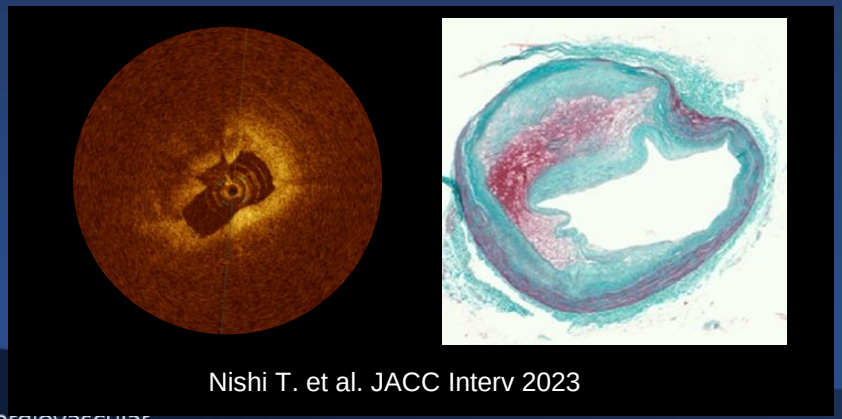
- Pathologic diagnosis : Late fibroatheroma
- IVUS diagnosis : Ecolucent plaque
- Plaque burden = 67.6 %
- Echolucent burden = 17.6 %

Matsumura M, et al. Eur H J Img

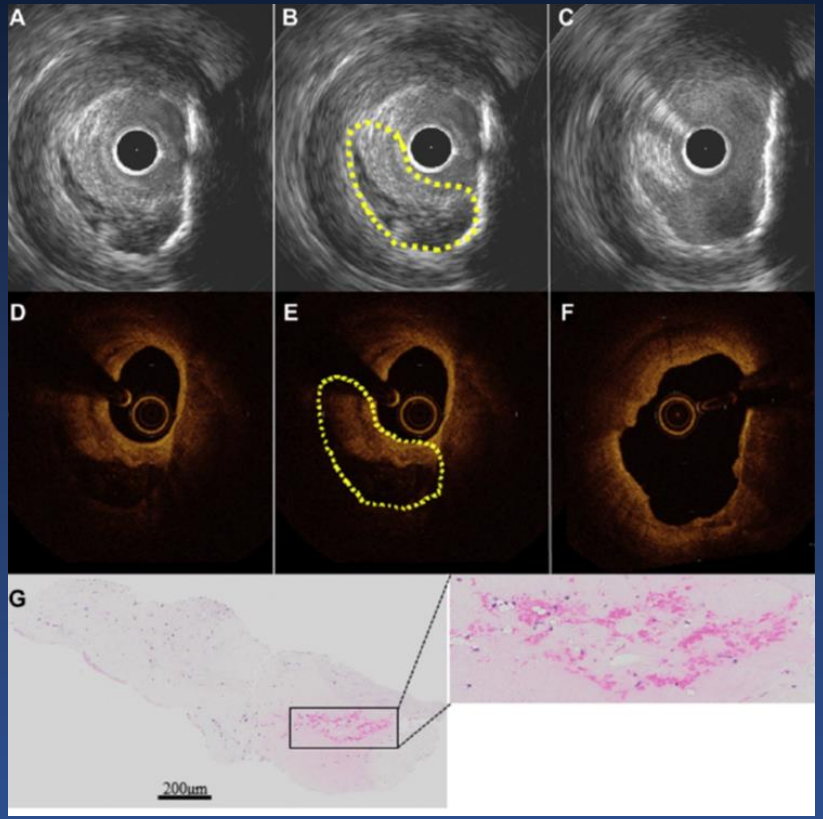
Intraplaque Hemorrhage



Prati F. et al. Eur H J. 2009:31: 401-415.



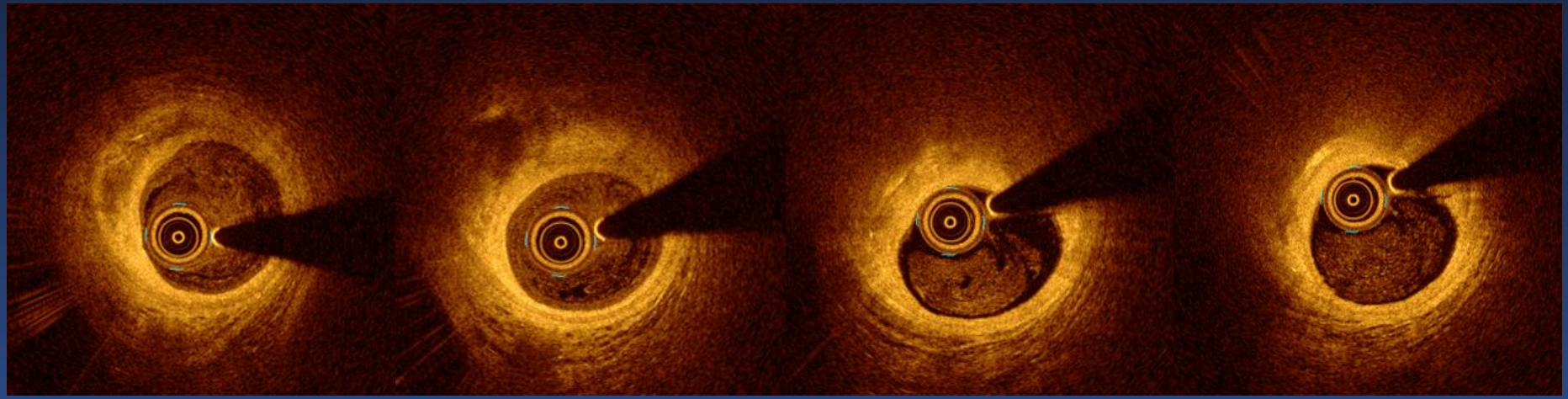
Nishi T. et al. JACC Interv 2023



Hoshino, M. et al. JACC Intv. 2018:11: 1414-1415.

Clinical Representative Case

- In ex vivo study, cholesterol crystal were highly concomitant with IPH.
  Jinnouchi H, et al. EuroIntervention 2020 395-403, Falk E, et al. EHJ 2013 34:719-728.



Usui E. et al. Atherosclerosis. 2021; 332:41-47.

LIA (low intensity area without attenuation) + CC (cholesterol crystal) in 753 non-culprit lesions in 566 patients

- Prevalence: LIA=35.8% (263/735), CC=18.9% (139/735)
- LIA+CC=15.5% (114/753) lesions in 17.8% (101/566) patients.

Key lesion morphology	n of events /N with key morphology	Unadjusted HR (95%CI)	P-value	AUC (95% CI)
LIA+CC	9/114	4.66 (1.94, 11.2)	<0.01	0.65 (0.54, 0.76)
Any LIA	12/263	2.72 (1.12, 6.61)	0.03	0.62 (0.51, 0.74)
Any CC	9/139	3.65 (1.52, 8.73)	<0.01	0.63 (0.52, 0.75)
LIA without CC	3/149	0.68 (0.20, 2.27)	0.53	0.53 (0.45, 0.61)
CC without LIA	0/25	-	-	0.52 (0.51, 0.52)

Usui E. et al. Atherosclerosis. 2021; 332:41-47.

735 Non-culprit lesions in 566 patients

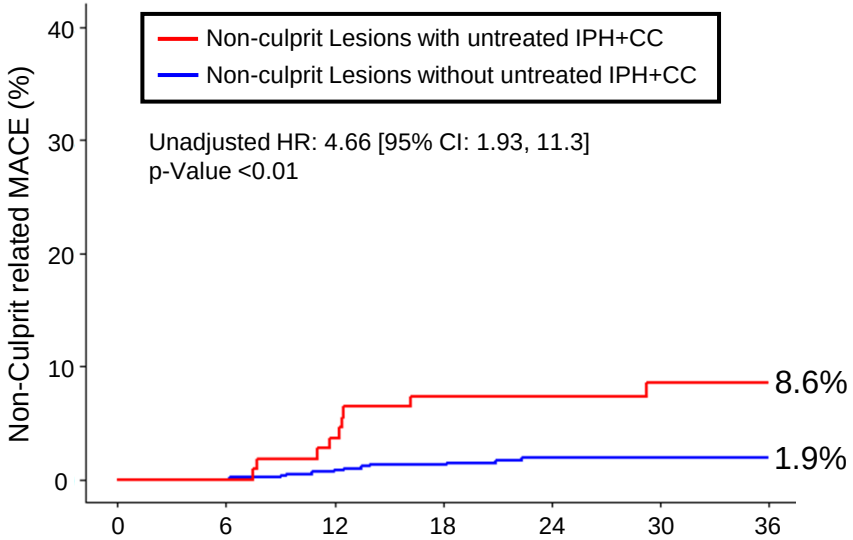
67 (59, 73) years old, 82% male, 36% diabetes mellitus, Clinical presentation: 44% STEMI or NSTEMI (culprit lesion), Japanese

735 total lesions	Non-culprit lesions with LIA+CC (n=114)	Non-culprit lesions without LIA+CC (n=621)	P-value
Minimum lumen area, mm^2	3.8 (2.4, 5.9)	5.1 (3.1, 8.4)	<0.01
Thin-cap fibroatheroma	6%	3%	0.09
Lipid rich plaque	70%	24%	<0.01
Maximum lipidic arc^o	118 (90, 154)	119 (85, 160)	0.69
Healed plaque	38%	16%	<0.01
Macrophage accumulation	100%	81%	0.99

Usui E. et al. Atherosclerosis. 2021; 332:41-47.

LIA+CC were associated with NC events

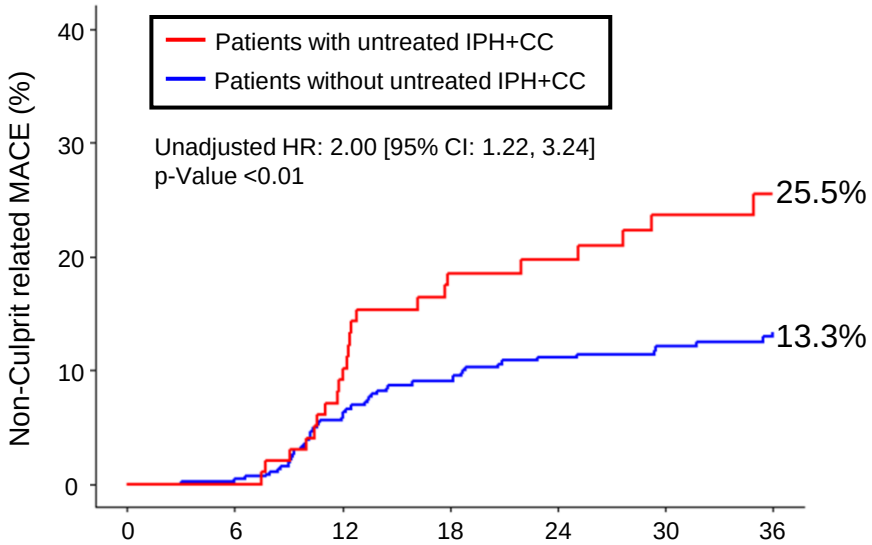
Lesion-level



Number at risk:

IPH+CC (+)	114	110	105	98	85	68	56
IPH+CC (-)	621	614	605	554	462	386	311

Patient-level



Number at risk:

IPH+CC (+)	101	99	89	77	66	51	40
IPH+CC (-)	465	457	428	374	301	252	202

Usui E. et al. Atherosclerosis. 2021; 332:41-47.

Independently Associated Morphology with Non-culprit Related Events

- Lesion level model 20 events in 735 non-culprit lesions -

	Hazard Ratio (95% CI)	P-value
LIA+CC	3.09 (1.27, 7.50)	0.01
Thin-cap fibroatheroma	4.38 (1.44, 13.30)	<0.01
Minimum lumen area<3.5mm^2	5.33 (1.94, 14.62)	<0.01

Usui E. et al. Atherosclerosis. 2021; 332:41-47.

Summary

- Healed plaque is a main mechanism of lesion (stenosis) progression of coronary artery disease. The presence of healed plaque was associated with lesion progression, but not subsequent ACS event.
- Though OCT appearance of intraplaque hemorrhage needs further validation, LIA+CC (low intensity area without attenuation with cholesterol crystal) was associated with future event on top of known high-risk plaque morphology (e.g. TCFA).