# What Is a Vulnerable Plaque?
## Insights from Invasive Intravascular Imaging

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# DISCLOSURE

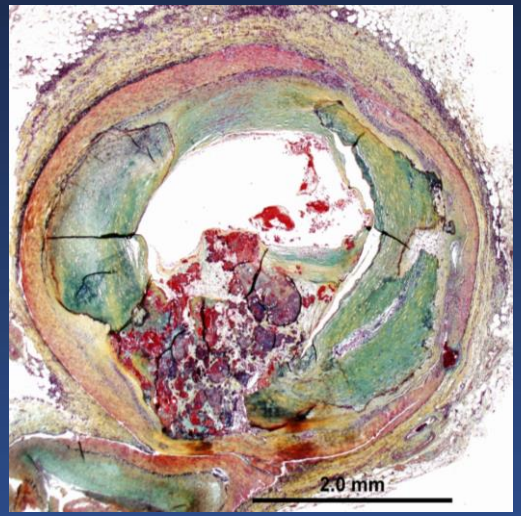
- Consultant: Boston Scientific, Abbott Vascular, Philips, CANON
- Advisory Board: SpectraWave
- Speaker Honoraria: Nipro

# “Vulnerable Plaque” which causes thrombotic event or rapid lesion progression (silent thrombosis & healing)

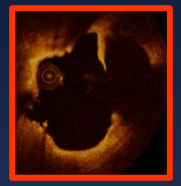
## Plaque Rupture


## Plaque Erosion

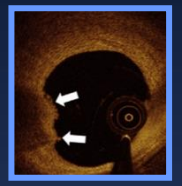

## Calcified Nodule



# OCT Defined Underlying Plaque in ACS

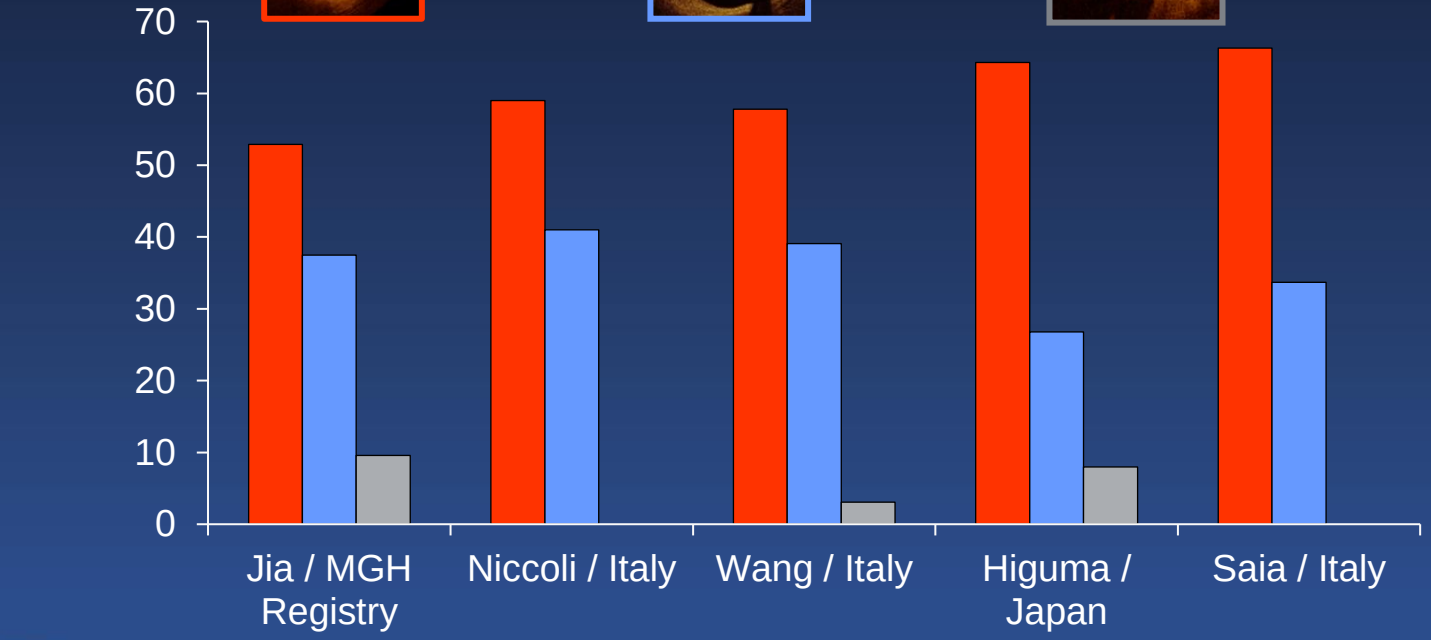


**Plaque Rupture**



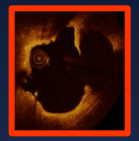
**Plaque Erosion**

**Calcified Nodule**

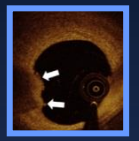



Jia H, et al. JACC 2013;62:1748-58. Niccoli G et al. EHJ 2015; 36:1377-84.Wang L et al. EHJI 2015 doi:10.1093/ehjc.jev105 Higuma T et al. JACC Interv 2015;8:1166-76. Saia JACC Img 2015; 8: 566-75.

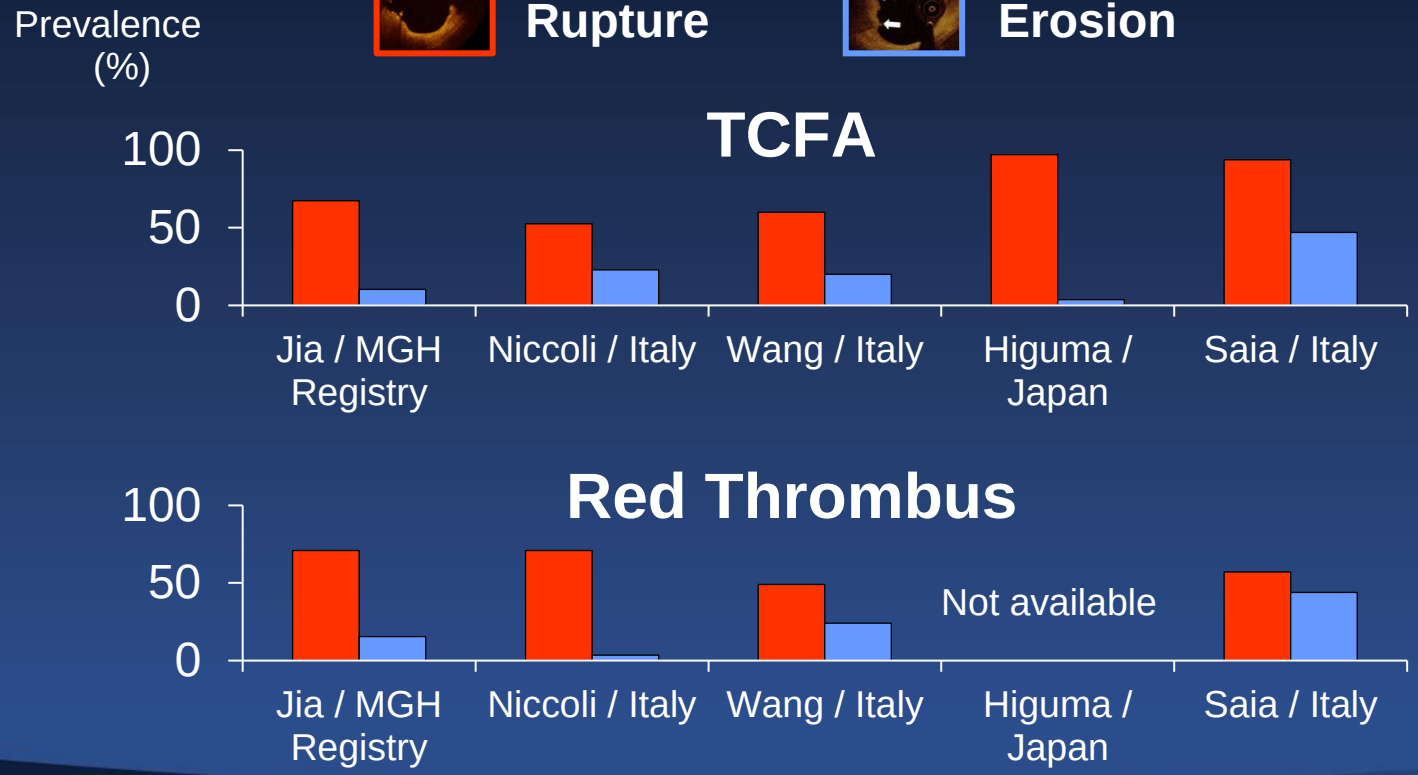
# Difference of Underlying Morphology



**Plaque Rupture**



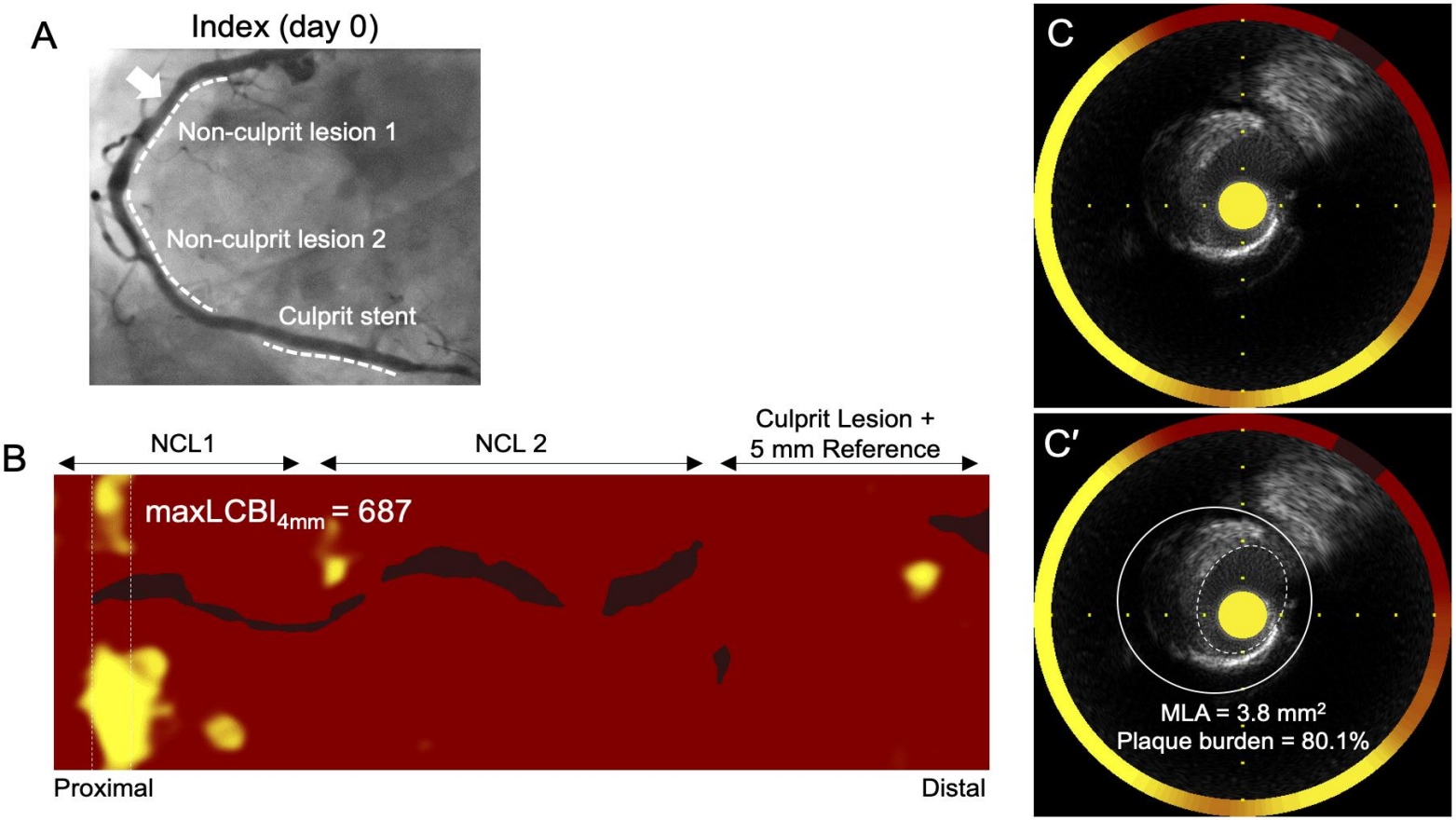
**Plaque Erosion**




Jia H, et al. JACC 2013;62:1748-58. Niccoli G et al. EHJ 2015; 36:1377-84.Wang L et al. EHJI 2015 doi:10.1093/ehjc.jev105 Higuma T et al. JACC Interv 2015;8:1166-76. Saia JACC Img 2015; 8: 566-75.

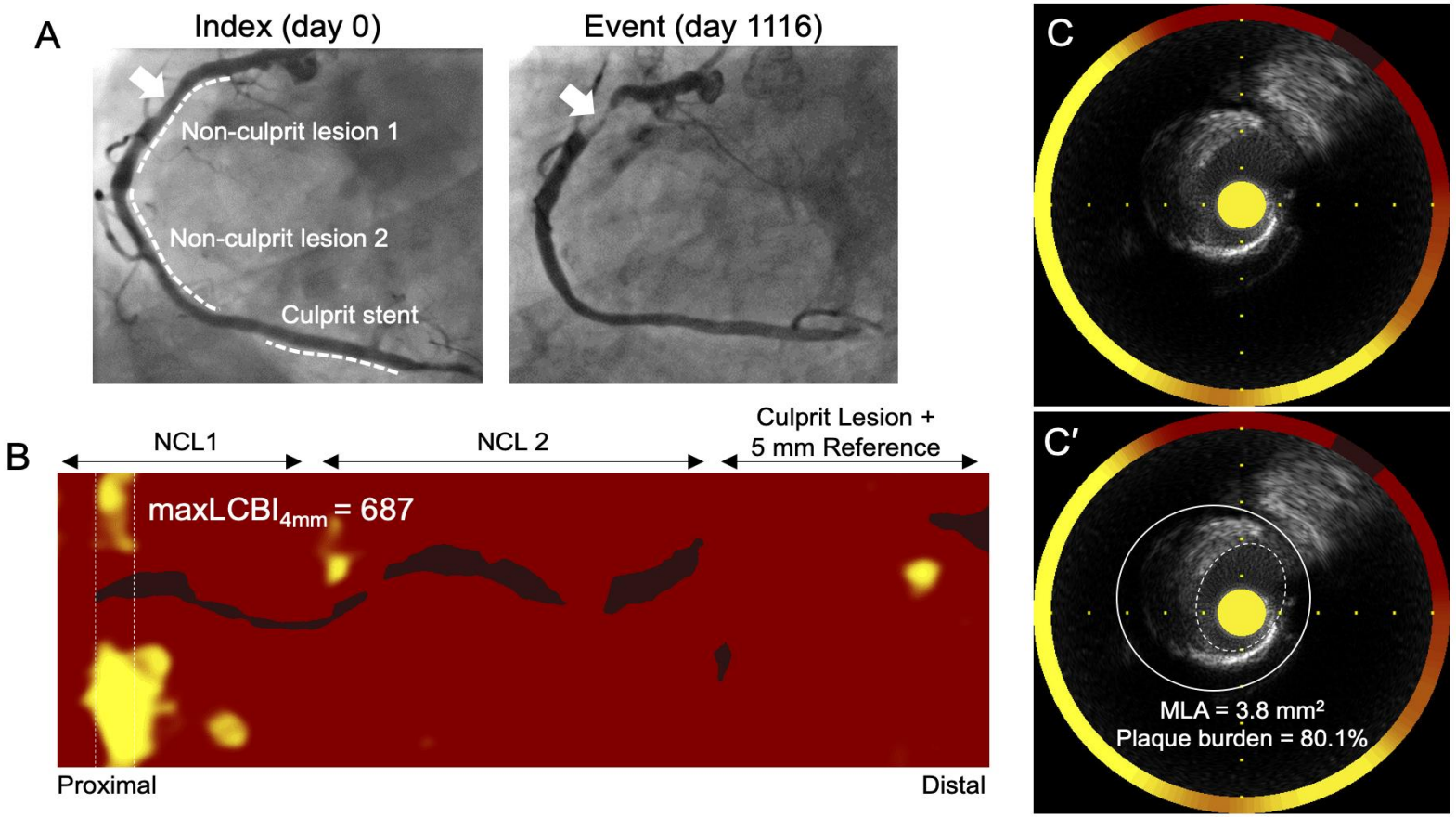
# Representative case

## An adverse event attributed to an untreated NCL



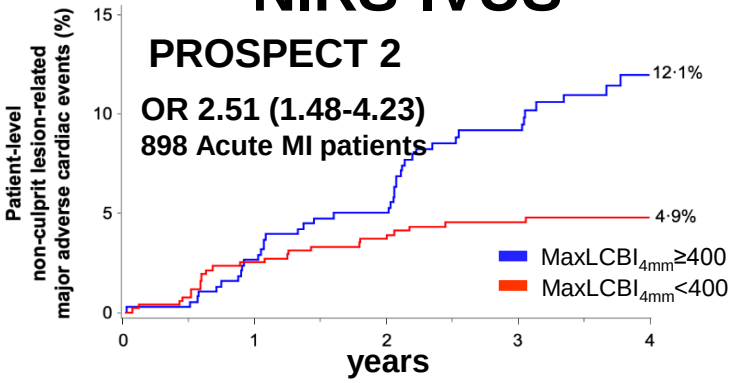
# Representative case

## An adverse event attributed to an untreated NCL

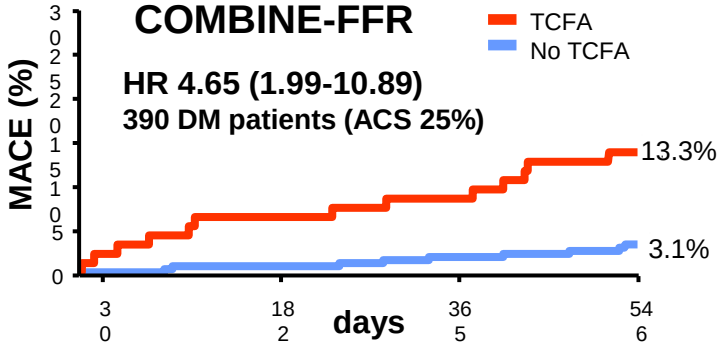


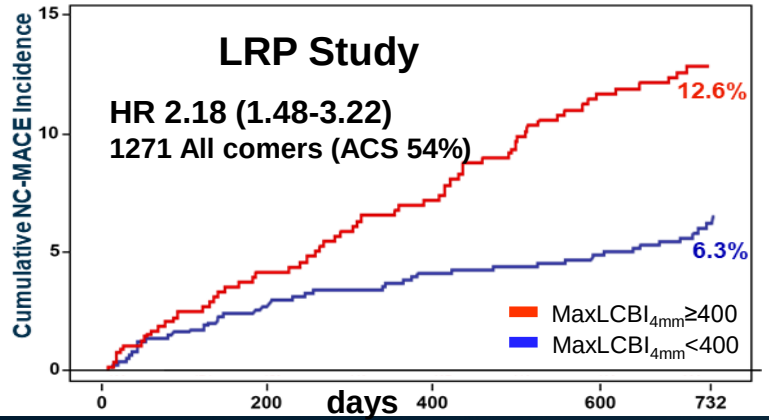
# The Importance of NIRS/IVUS or OCT High-Risk Plaque in the Secondary Prevention Cohort

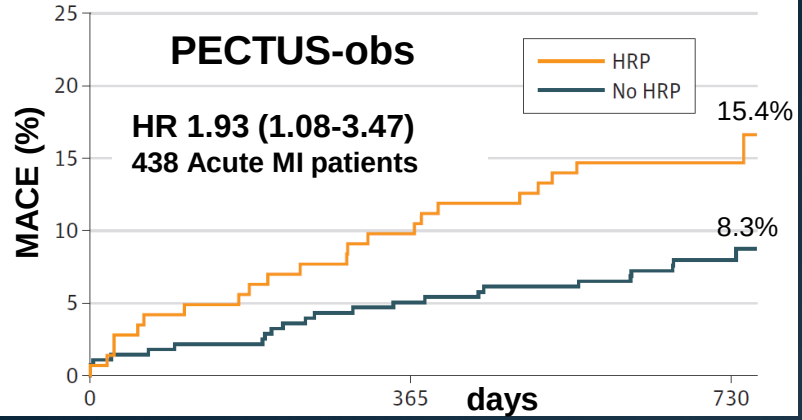
## NIRS-IVUS




## OCT




Waksman R, Lancet 2019;394:1629-1637; Erlinge D, Lancet 2021;397:985-95; Kedhi E, EHJ 2021 42:4671-4679; Mole JQ , JAMA Cardiol 2023: e232910

# Lesion Level Predictors for Non-Culprit Lesion Related MACE - adjusted -

| | PROSPECT | PROSPECT II | Jiang et al. |
|---|---|---|---|
| VH-TCFA | 3.35 (1.77-6.36) | | |
| OCT-TCFA | | | 7.64 (3.42-9.82) |
| MaxLCBI4mm≥325 | | 3.80 (1.87-7.70) | |
| Plaque burden≥70% | 5.03 (2.51-10.11) | 5.37 (2.42-11.89) | |
| MLA4mm$^2$ (IVUS) or ≤3.5mm$^2$ (OCT) | 3.21 (1.61-6.42) | 1.85 (0.95-3.61) | 4.11 (1.72-9.82) |

Jiang E, et al. JACC 2023:81 1217-30; Stone GW et al. NEJM 2011: 364, 226-235; Erlinge D, et al. Lancet 2021: 397, 985-5.

# Vulnerable Plaque - Meta Analysis -

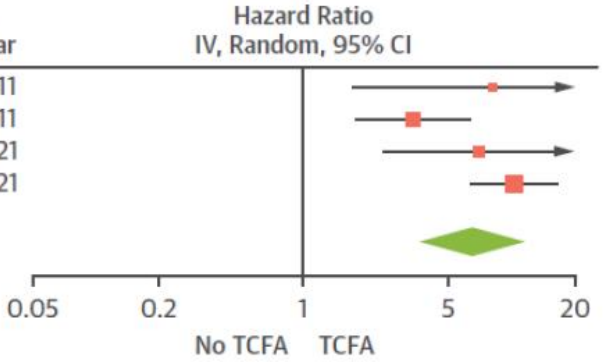
9 prospective, 21 retrospective; 4 OCTs 3 VH-IVUS, 2 NIRS-IVUS, 21 CT, 30369 pts

Lesion-Level

## Thin Cap Fibroatheroma

| Study or Subgroup | Log [Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Calvert, 2011 | 2.0992 | 0.7769 | 13.0% | 8.16 [1.78, 37.41] | 2011 |
| Stone, 2011 | 1.209 | 0.3255 | 30.9% | 3.35 [1.77, 6.34] | 2011 |
| Kedhi, 2021 | 1.9459 | 0.5398 | 20.4% | 7.00 [2.43, 20.16] | 2021 |
| Kubo, 2021 | 2.3428 | 0.2419 | 35.6% | 10.41 [6.48, 16.73] | 2021 |
| Total (95% CI) | | | 100.0% | 6.55 [3.40, 12.60] | |

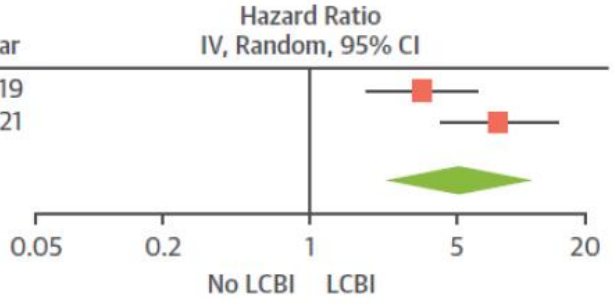
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 7.86$, df = 3 ($P = 0.05$); $I^2 = 62\%$
Test for overall effect: Z = 5.63 ($P < 0.00001$)




## Large Lipid Core Burden Index

| Study or Subgroup | Log [Hazard Ratio] | SE | Weight | Hazard Ratio IV, Random, 95% CI | Year |
|---|---|---|---|---|---|
| Waksman, 2019 | 1.2208 | 0.309 | 50.8% | 3.39 [1.85, 6.21] | 2019 |
| Erlinge, 2021 | 2.058 | 0.3276 | 49.2% | 7.83 [4.12, 14.88] | 2021 |
| Total (95% CI) | | | 100.0% | 5.12 [2.25, 11.62] | |

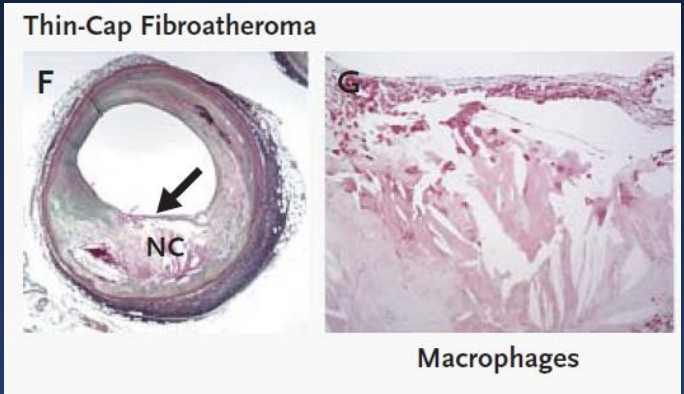
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 3.46$, df = 1 ($P = 0.06$); $I^2 = 71\%$
Test for overall effect: Z = 3.90 ($P < 0.0001$)




Gallone G. et al. JACC Img 2023; 16: 1584-1604.

# 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

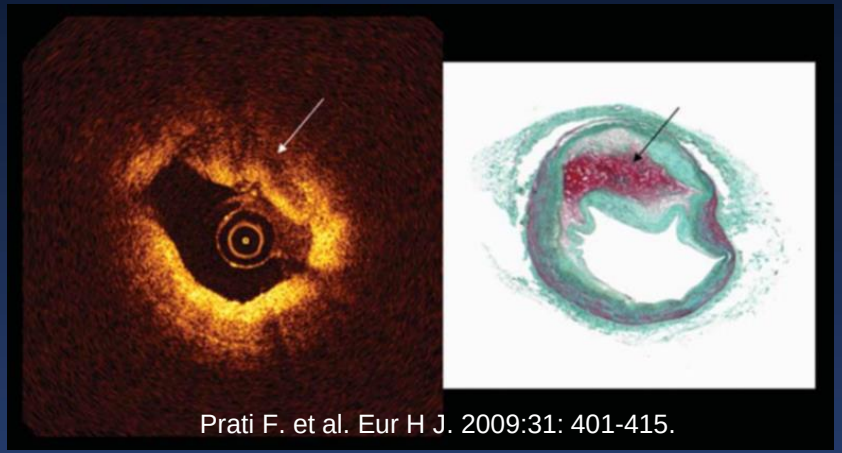



Among all of the cells in the body, the erythrocyte membrane has the greatest amount of free cholesterol; therefore, free cholesterol from the destroyed erythrocytes in IPH becomes a localized source of cholesterol crystals.

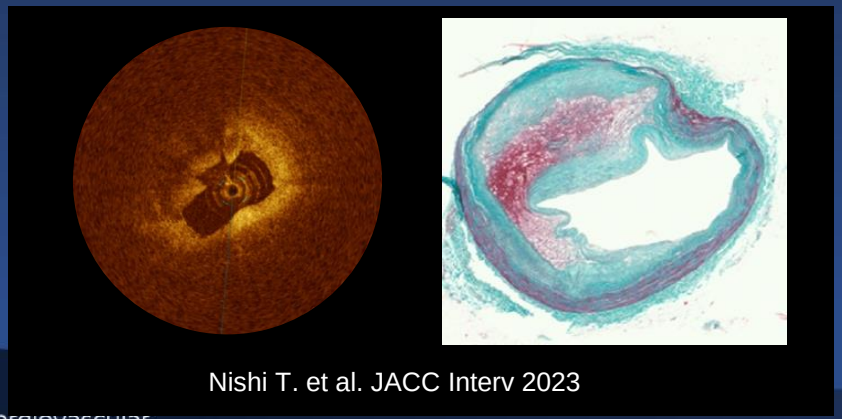
| | # of plaques | Glycophorin A Score | Iron Score | Size of NC |
|---|---|---|---|---|
| PIT | 129 | 0.09 ± 0.04 | 0.07 ± 0.05 | - |
| Early fibroatheroma | 79 | 0.23 ± 0.07 | 0.17 ± 0.08 | 0.06 ± 0.02 |
| Late fibroatheroma | 105 | 0.94 ± 0.11 | 0.41 ± 0.09 | 0.84 ± 0.08 |
| TCFA | 52 | 1.60 ± 0.20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

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

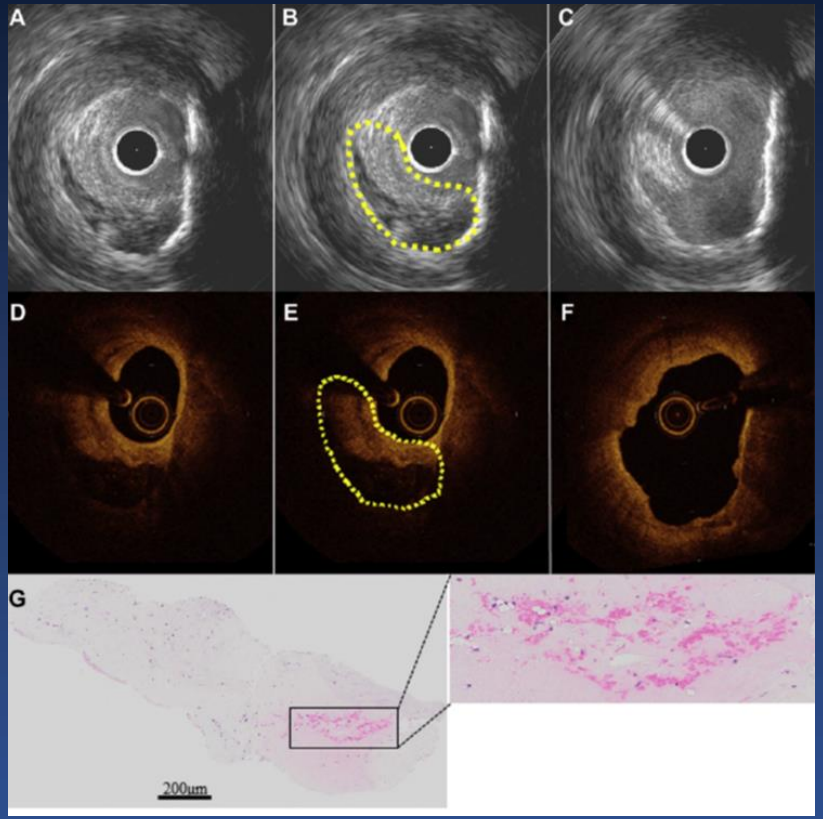
# Intraplaque Hemorrhage



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



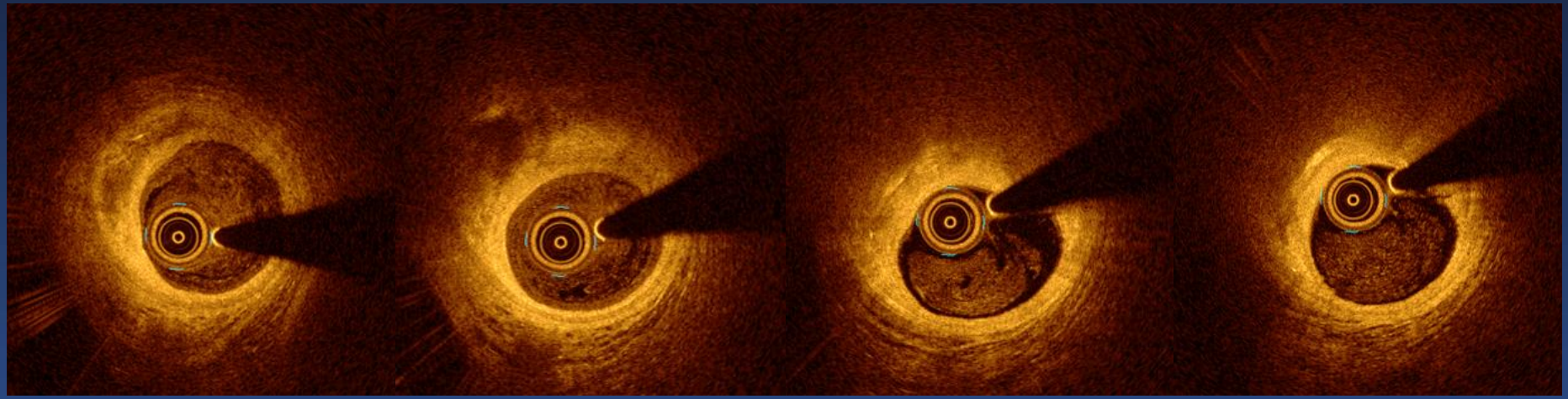
Nishi T. et al. JACC Interv 2023




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.

# Independently Associated Morphology with Non-culprit Related Long-trem Events

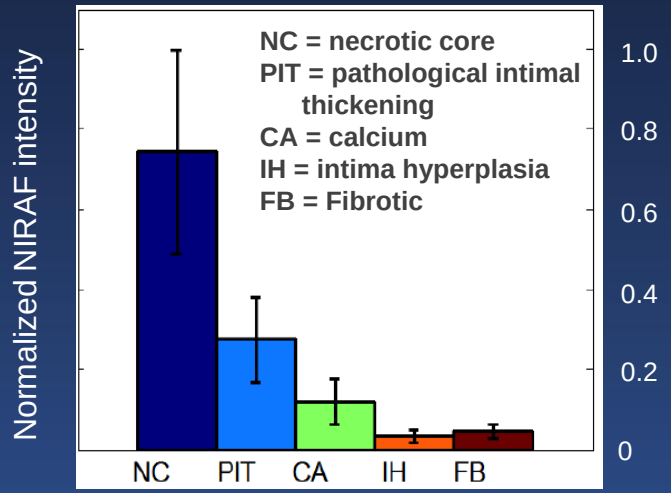
## - Lesion level model 20 events in 735 non-culprit lesions -

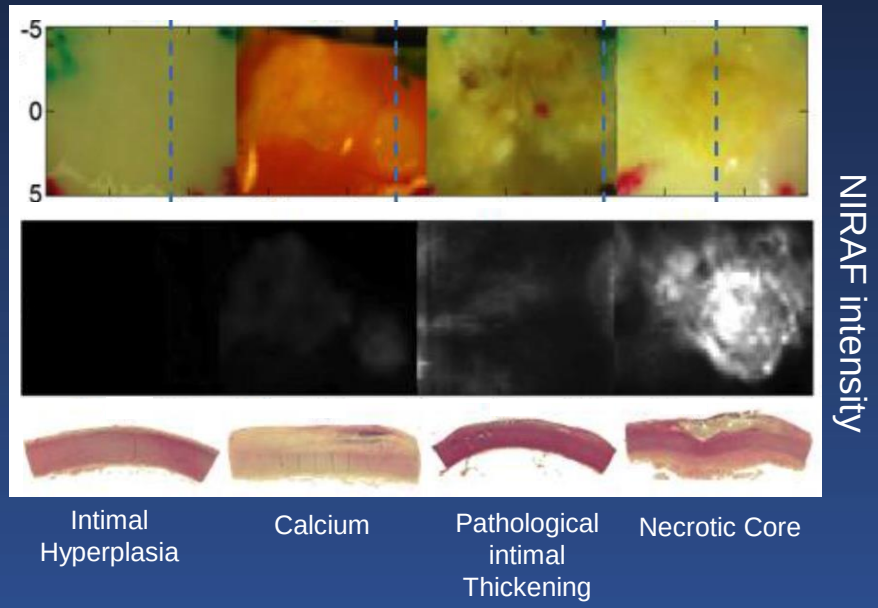
| | Hazard Ratio (95% CI) | P-value |
|---|---|---|
| LIA+CC | 3.09 (1.27, 7.50) | 0.01 |
| Thin-cap fibroatheroma | 4.38 (1.44, 13.30) | <0.01 |
| Minimum lumen area<3.5mm$^2$ | 5.33 (1.94, 14.62) | <0.01 |

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

# OCT-NIRAF
# Near Infrared Auto-Fluorescence Molecular Imaging

NIRAF study on ex-vivo human plaques (n=50)




**NIRAF signal was elevated in some necrotic cores**

Wang et al., Biomed Optics Express, 2015;6:1363-1375.

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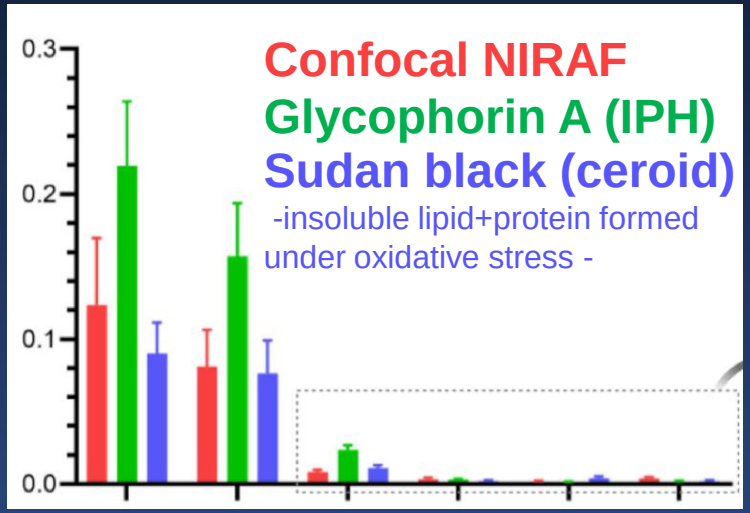
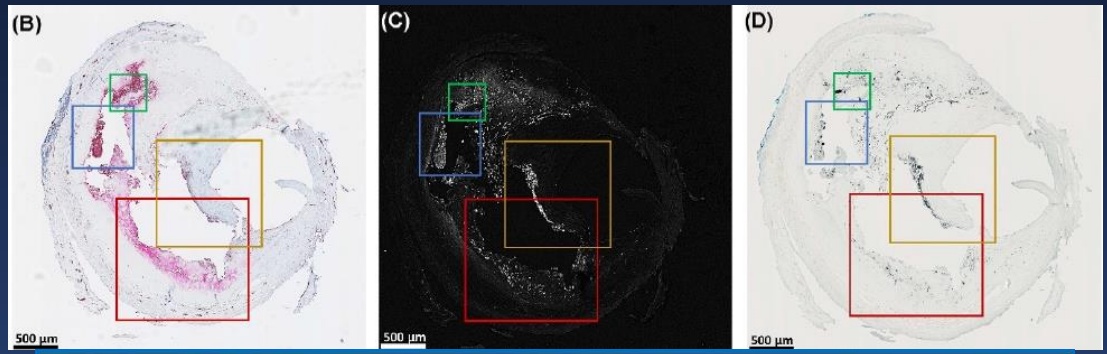
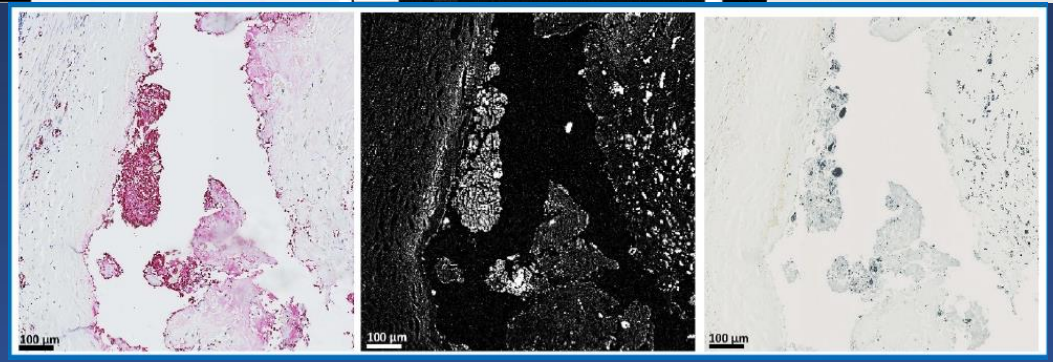
# Histological Correlation of NIRAF




Glycophorin A Confocal NIRAF Sudan black




Kunio M, Tearney GJ. et al. Atherosclerosis 2022:344, 31-39

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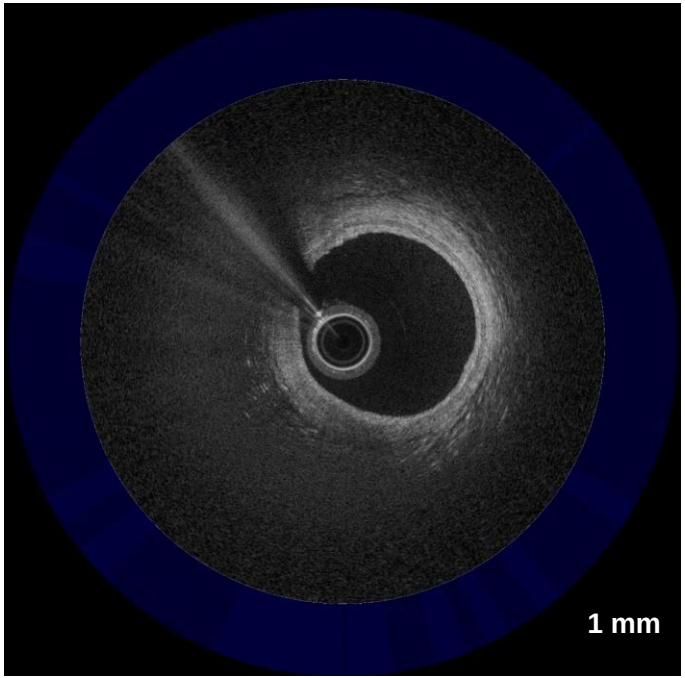
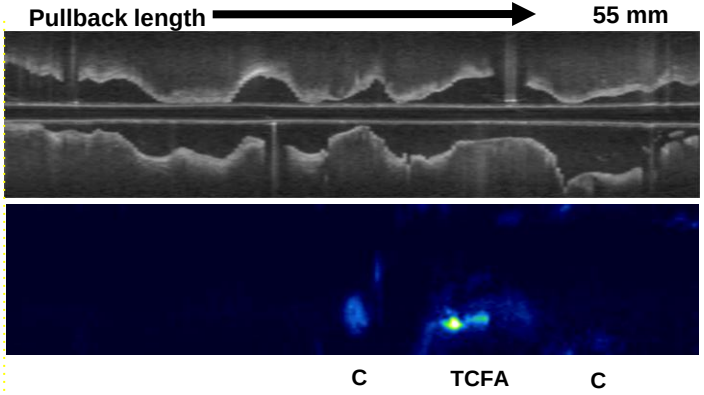
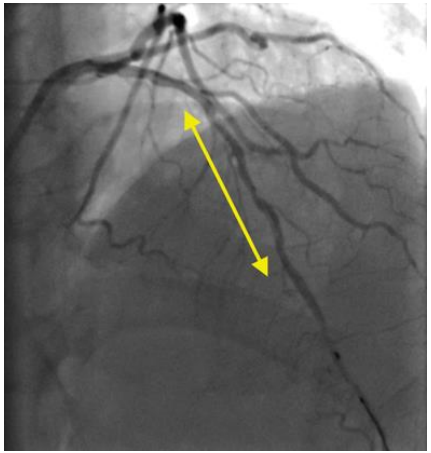
# NIR autofluorescence (NIRAF)-OCT: first-in-human study



***Ughi….Jaffer, Tearney. JACC CV Imaging 2016***

***Slide, Courtesy of Dr.Jaffer F***

***-- NIR-autofluorescence (NIRAF)***
***-- NIRAF present in some complex plaques***

***Giovanni Ughi***

***Gary Tearney***

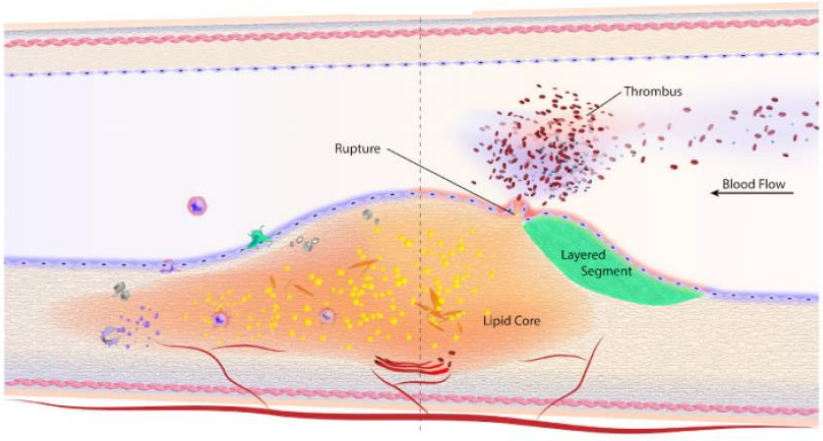
MASSACHUSETTS GENERAL HOSPITAL
CORRIGAN MINEHAN HEART CENTER

# Flow Dynamics to Predict Plaque Erosion

EES: Endothelial share stress, force due to tangential friction of blood flow on the endothelium
EESG: EES gradient
OSI: Oscillatory shear index, change of EES vector indicating flow recirculation

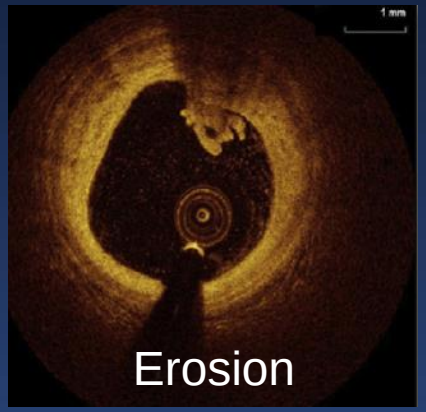
- Thondapu V et al. Cardiovas Research 2021:117 1974-85.
- 18 plaque erosion compared with non-erosion site
- High EES, EESG, OSI

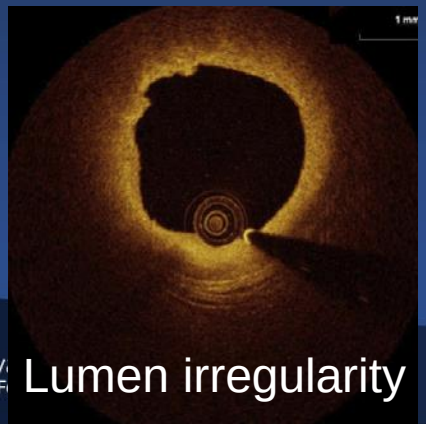
- Hakim D et al. Atherosc 2023:376 11-8.
- 24 plaque erosion compared with matched plaque (same MLA, ref)
- High EES, EESG

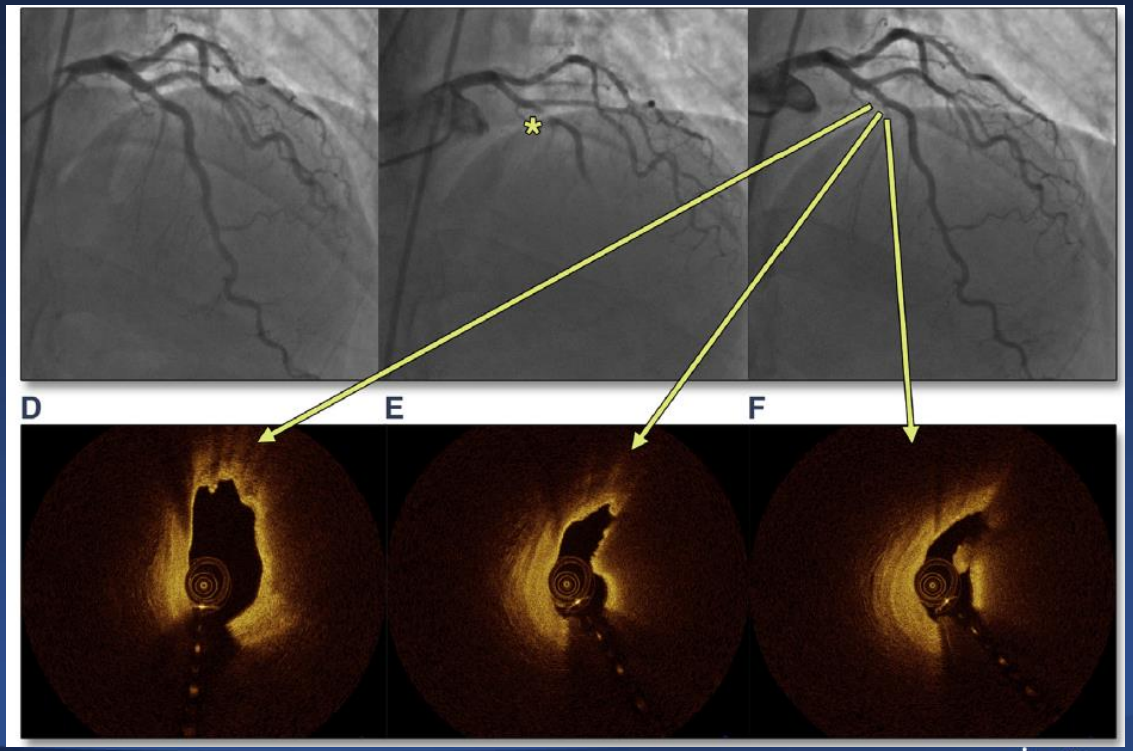


# Association between Spasm and Plaque Erosion

- 80 patients with coronary spasm
- 26% (21/80) plaque erosion, 61% (49/80)



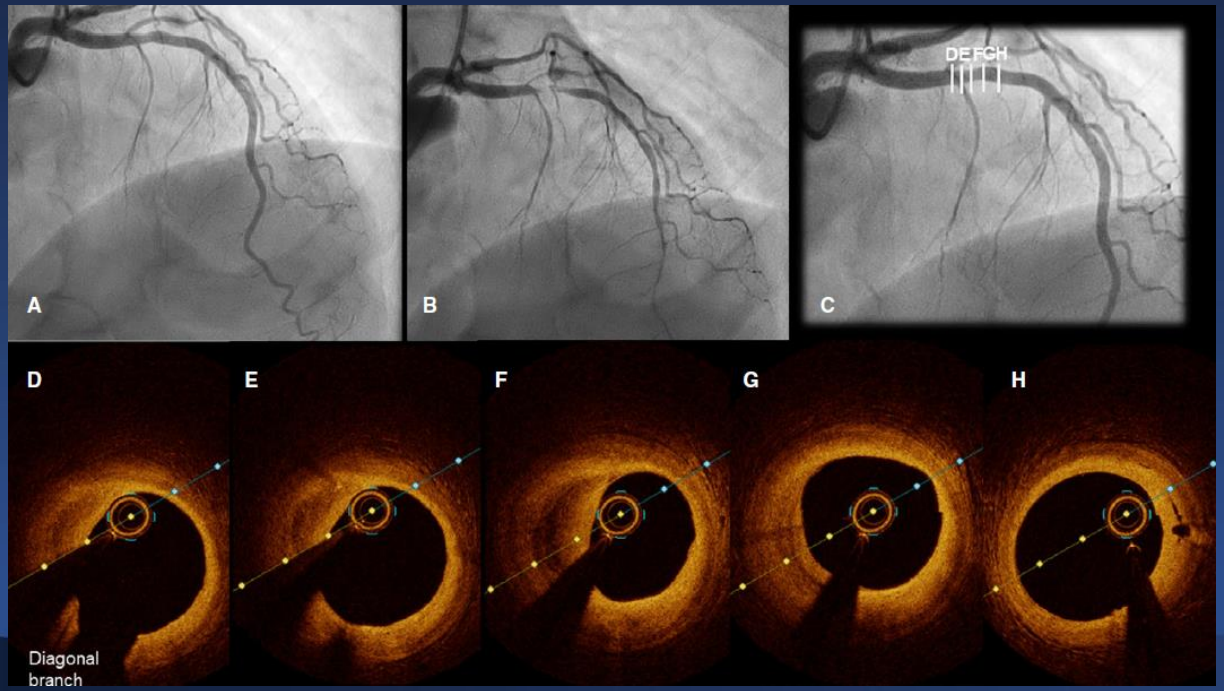




Shin ES, et al. JACC Img 2015;8 1059-67.

# Association between Spasm and Plaque Erosion

- 51 vessels in 39 pts with coronary spasm
- Spasm segment had more layered plaque (93% vs 38%), micro-vessel (73% vs 24%), and macrophage (80% vs 43%) compared with vessels without spasm.

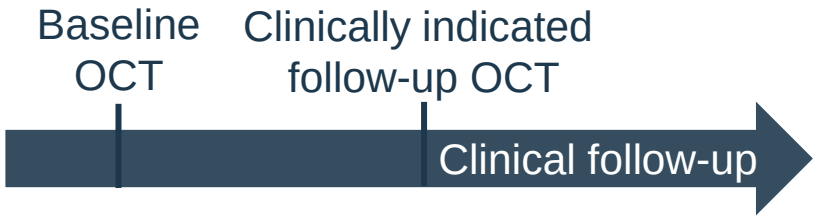



Nishi T, et al. JAHA 2022;11 e024880.

# Newly Developed Calcified Nodule

## Design

- **DESIGN:**
  Retrospective, single-center, observational study using serial OCTs
- **OUTCOMES:**
  OCT-imaged untreated lesion-related target lesion failure




737 patients with 2 times OCT for the same vessel from January 2012 - December 2022

378 patients were excluded
- 259 no detection of calcium by OCT
- 17 graft lesions
- 34 presence of calcified nodule at the 1st OCT
- 32 insufficient image quality
- 36 no OCT image for the same calcified lesion

**372 lesions in 359 patients with 2 times OCT for the same calcified lesion in native coronary arteries**

**Lesions with a new calcified nodule at follow-up**

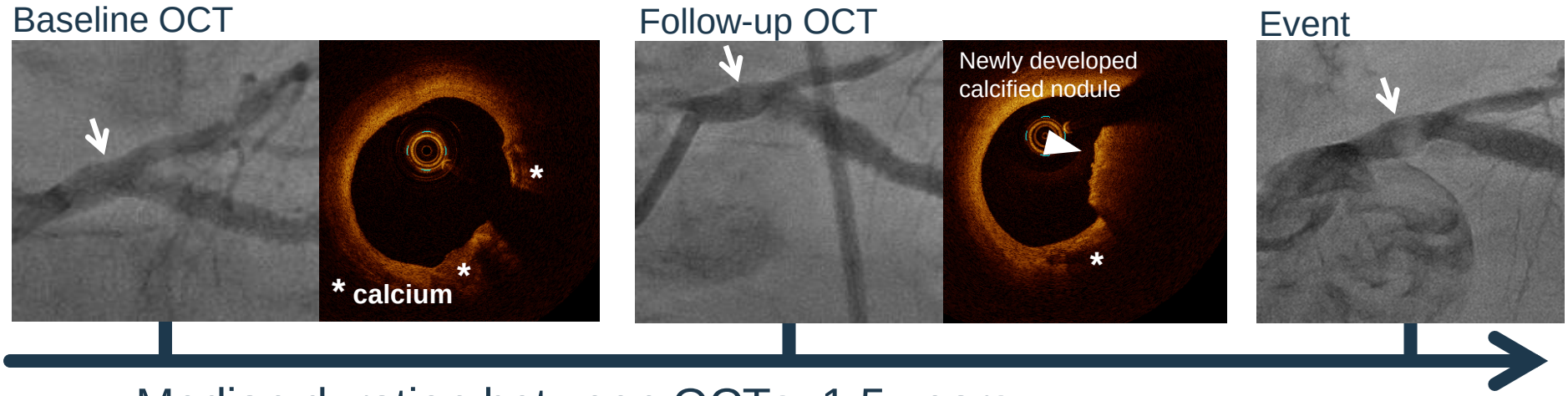
**Lesions without a new calcified nodule at follow-up**



Sugizaki Y, et al. TCT 2023

# The Natural History of CNs

**The prevalence of a new CN development** **7.0**% (26/372 lesions)




Median duration between OCTs: 1.5 years

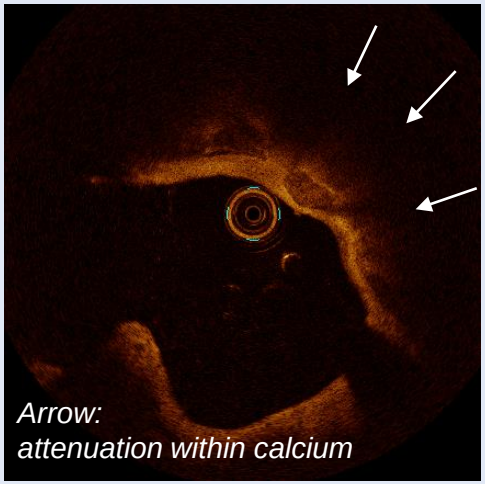
(first and third quartile: 0.7-2.9)



Sugizaki Y, et al. TCT 2023

# Factors Associated with a New CN Development

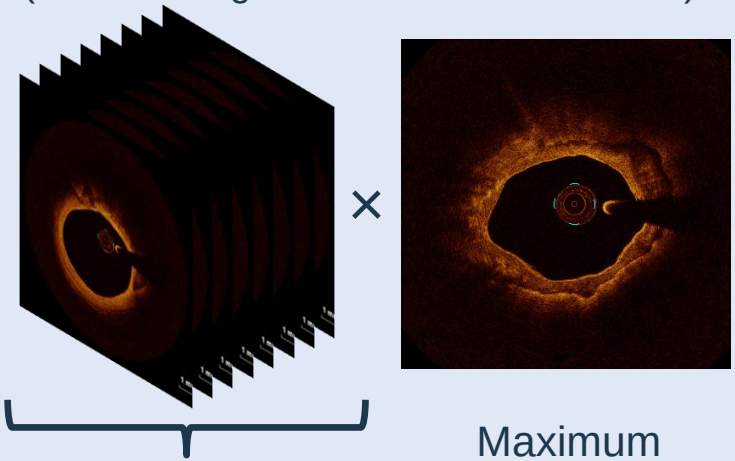
## Calcium with attenuation




**OR 3.13**
**(95%CI 1.04-9.41)**

## Calcium volume index

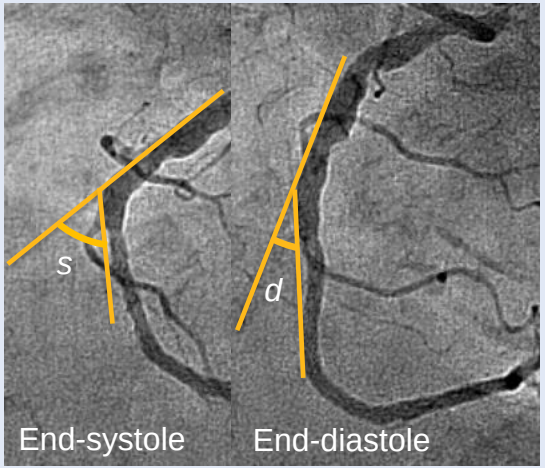
(Calcium length × Maximum calcium arc)




**OR 3.35**
**(95%CI 1.22-9.23)**

## In-lesion Δangle, per10˚

(Δangle = s-d)

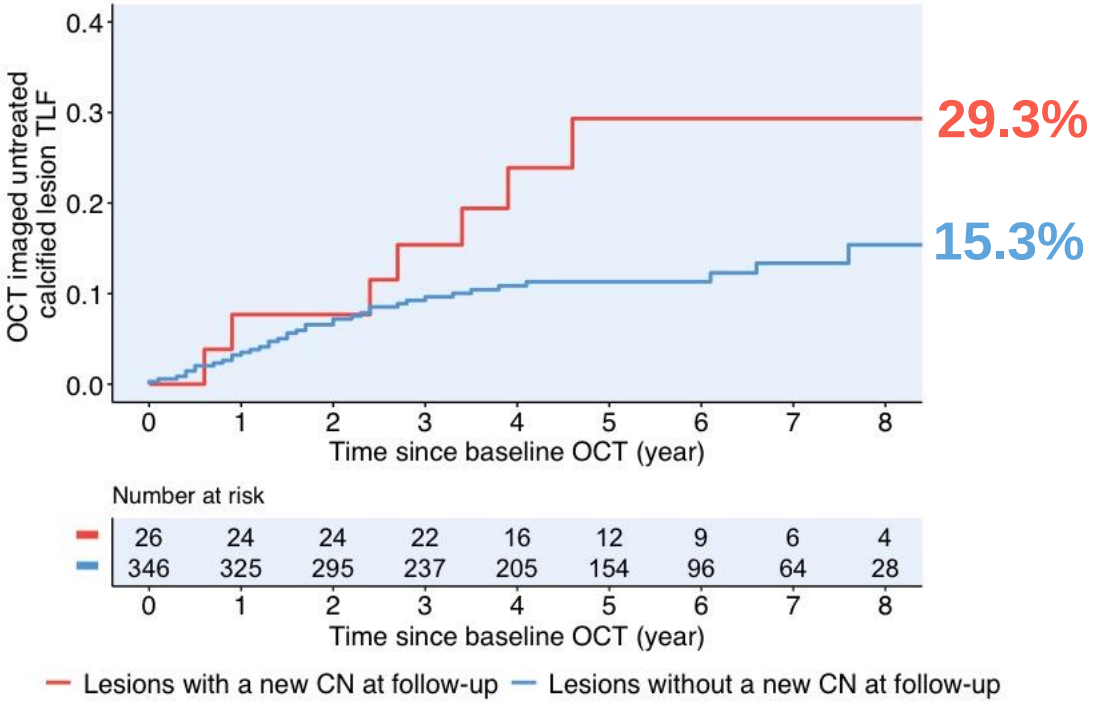



**OR 2.32**
**(95%CI 1.26-4.27)**



Sugizaki Y, et al. TCT 2023

# Cumulative incidence of OCT-imaged untreated calcified lesion-related TLF after baseline OCT



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# Take Home Message

- Vulnerable plaque (prone to thrombosis) were
  - Plaque rupture: Lipid rich plaque, thin-fibrous cap, inflammation
  - Plaque erosion: Share stress and coronary spasm?
  - Calcified nodule: Severely calcified plaque and hinge motion.