
# Molecular and Hybrid Imaging : Ready for clinical use?

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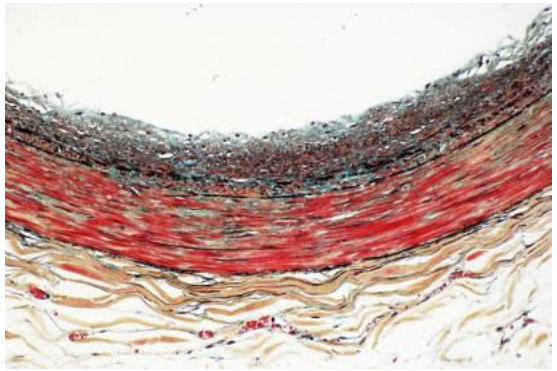
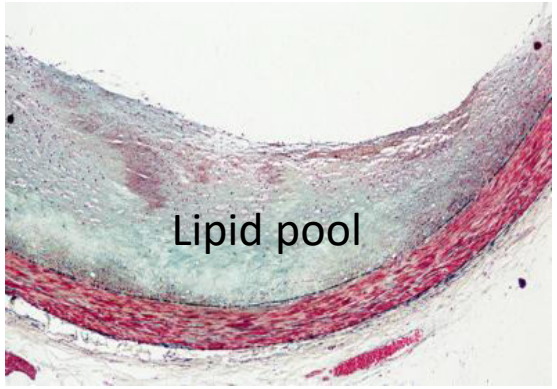
Maasstad Hospital-

PhD candidate Erasmus Medical Centre

EAPCI Chair Gender and Disparities Committee

# Pathology of the Vulnerable Plaque-1






**Adaptive Intimal Thickening**

**Pathologic Intimal Thickening**

Smooth muscle cells and proteoglycans

*Extracellular lipid (lipid pool)* +/- luminal macrophages

SMC muscle cell death (apoptosis)

Microcalcifications

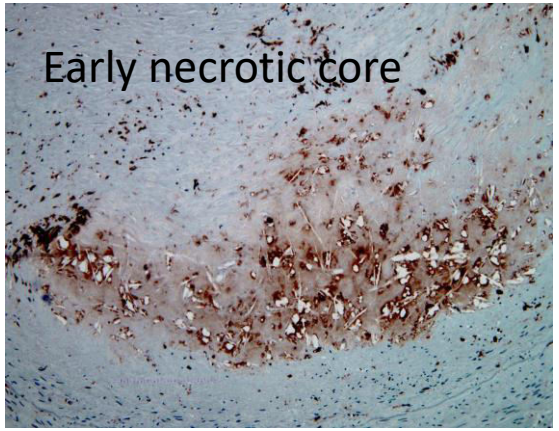
Macrophages

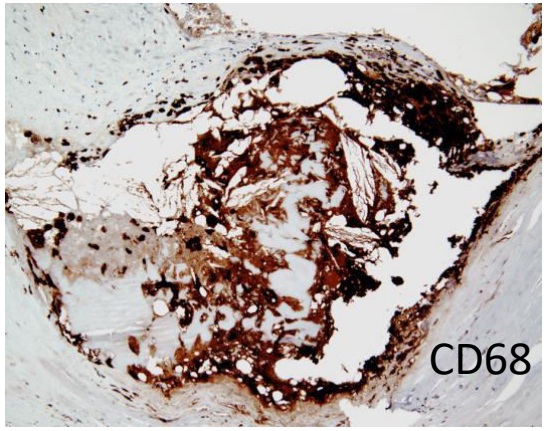
**"Fatty Streak"**

Potential for regression

"***Early Stages of Atherosclerosis Development***"

# Pathology of the Vulnerable Plaque-2




**Early Necrotic Core**

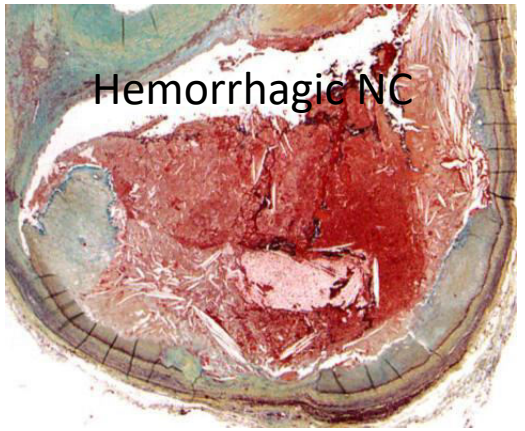
*Macrophages (CD 68+) within the lipidic pool*

*Inflammation T cell*

**Fibroatheroma**

Necrotic core +/- calcification

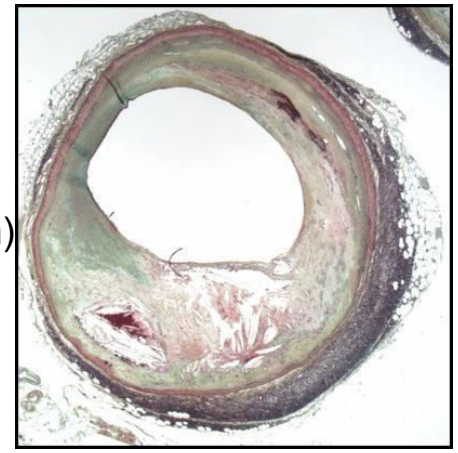
Hemorrhage (red cell membrane)



# Pathology of the Vulnerable Plaque-3

Lipid rich necrotic core

Thin fibrous cap (<65 um)

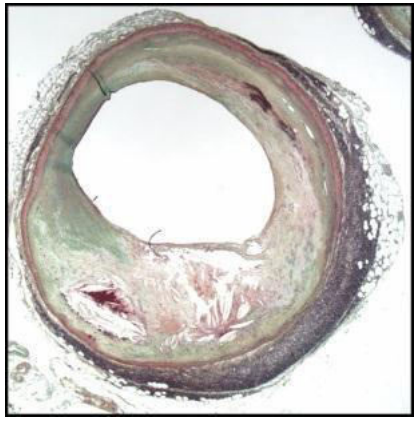


**Thin Cap Fibroatheroma**

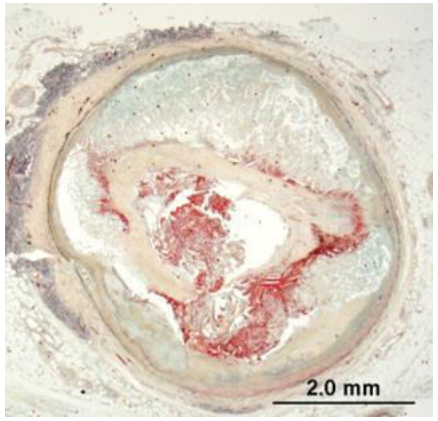
↑Macrophages
↓Phagocytosis
Flow disturbances

**Plaque Rupture**

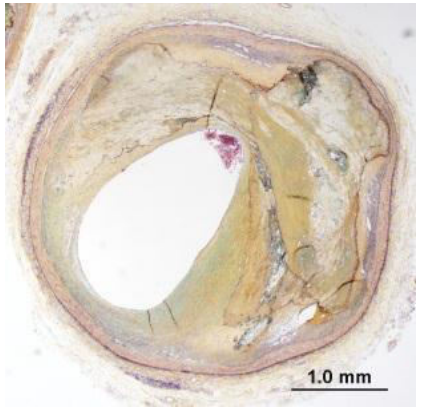
**Healing**



**ACS**




**Accelerated Plaque Progression**



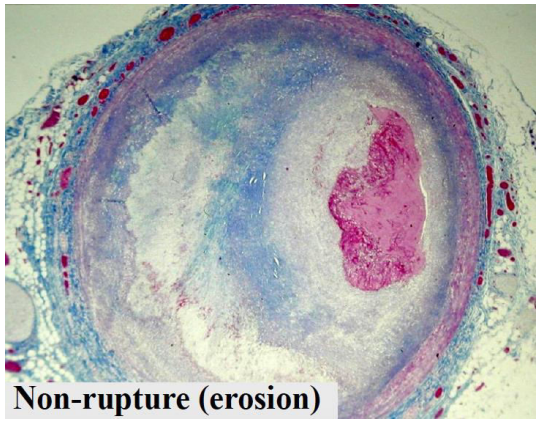
# Pathology of the Vulnerable Plaque-4

**TCFA**

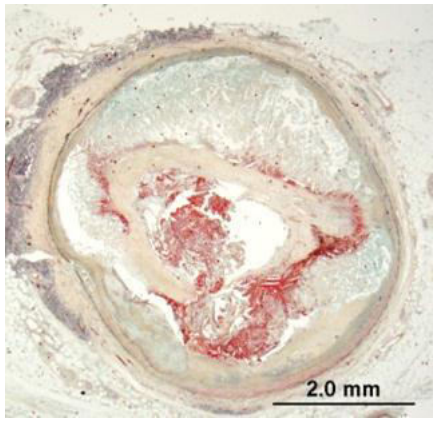

75%

**Pathological Intimal Thickening**

**Fibroatheroma**

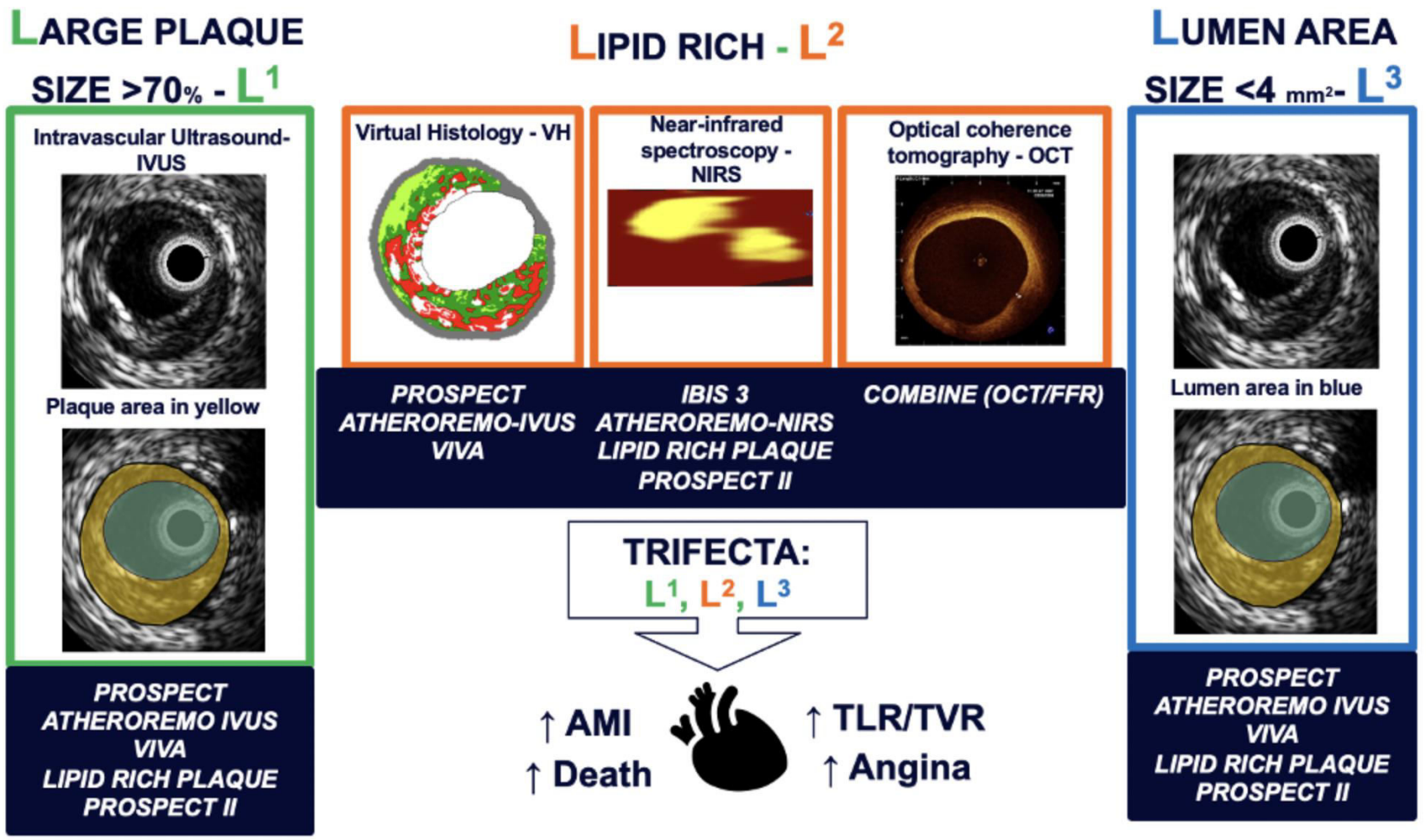



25%




**ACS**

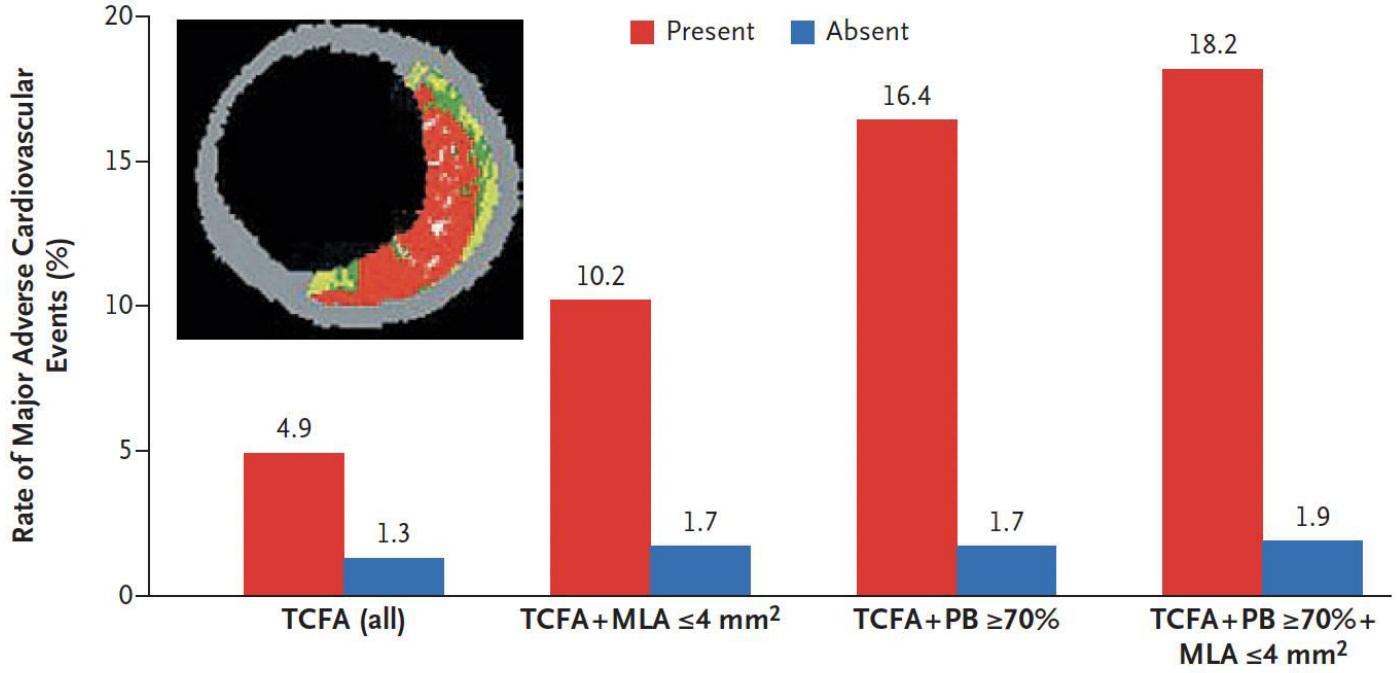
# Can We Identify Vulnerable Plaque?



# Vulnerable Plaque and risk of Events??

# PROSPECT- VH-TFCA and Non Culprit Lesion Related Events

NCLs in ACS patients with ≥30% DS and ≥40% plaque burden
MACE occurred in 20% of pts at median 3.4-year FU

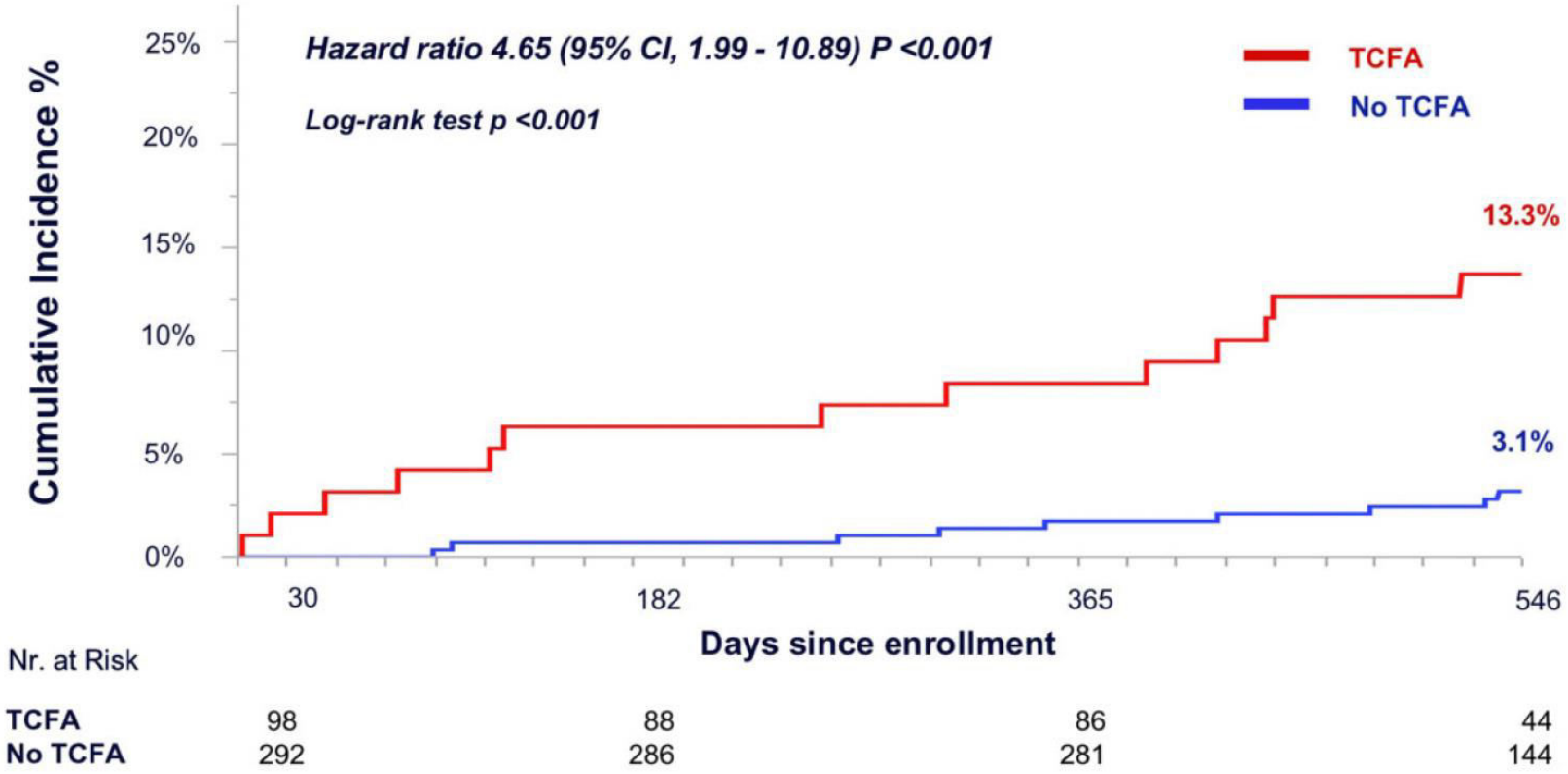


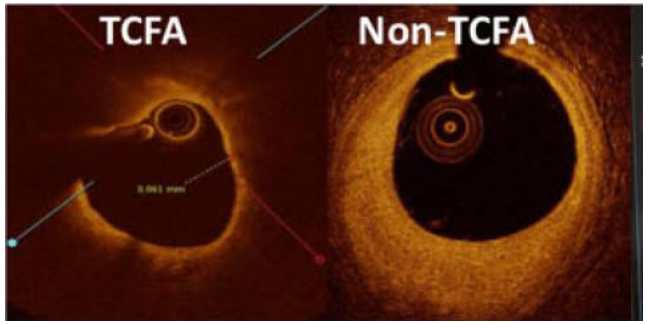

| | | | | |
|---|---|---|---|---|
| Lesion hazard ratio (95% CI) | 3.90 (2.25–6.76) | 6.55 (3.43–12.51) | 10.83 (5.55–21.10) | 11.05 (4.39–27.82) |
| P value | <0.001 | <0.001 | <0.001 | <0.001 |
| Prevalence (%) | 46.7 | 15.9 | 10.1 | 4.2 |

Stone et al. NEJM 2011

# COMBINE: TFCA and adverse events in FFR negative lesion

In diabetic patients, TCFA-represents 25% of FFR negative lesions and is associated with a five-fold higher rate of MACE despite the absence of ischaemia

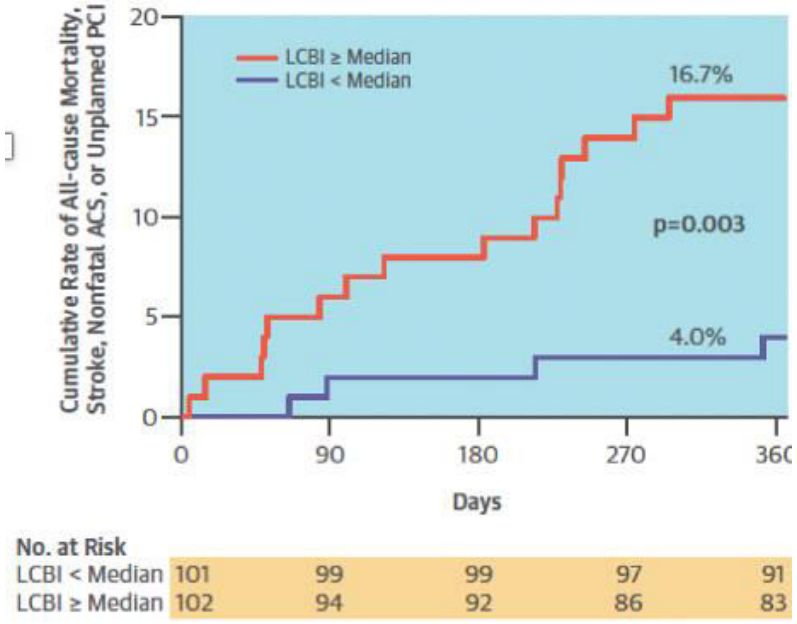



Kedhi et al. EHJ 2021

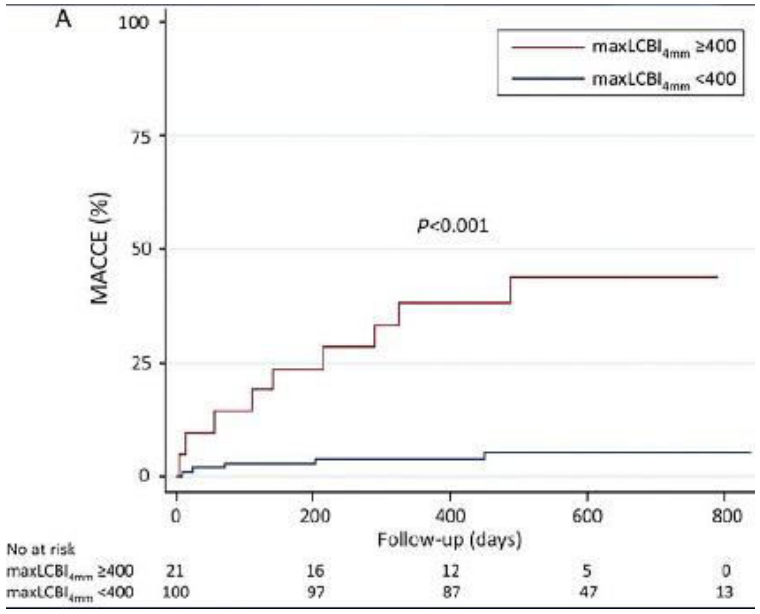
# Lipid rich lesions detected by NIRS and adverse events

Total lipid content assessed by LCBI

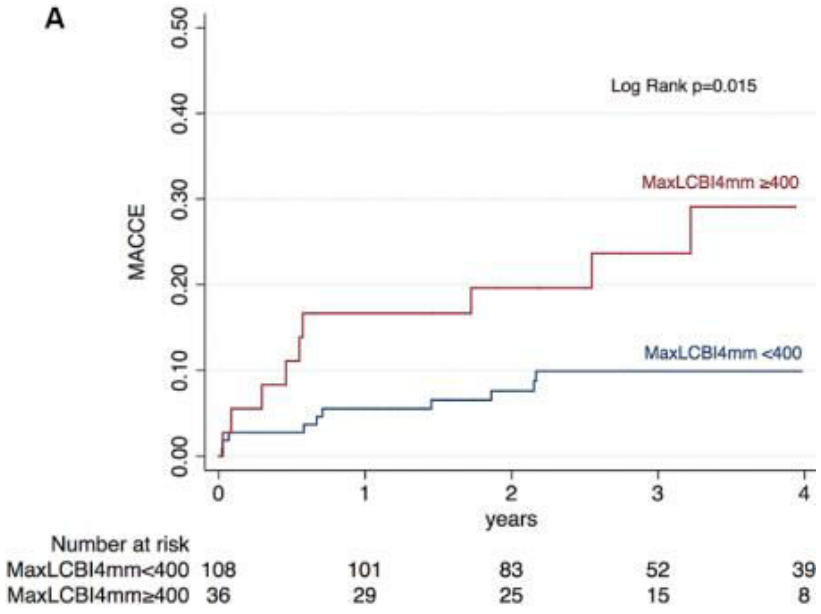



Oemrawsingh et al. JACC 2014

Single non culprit lesion with max LCBI 4mm≥400




Madder et al. EHJ Cardiovasc Imaging 2016

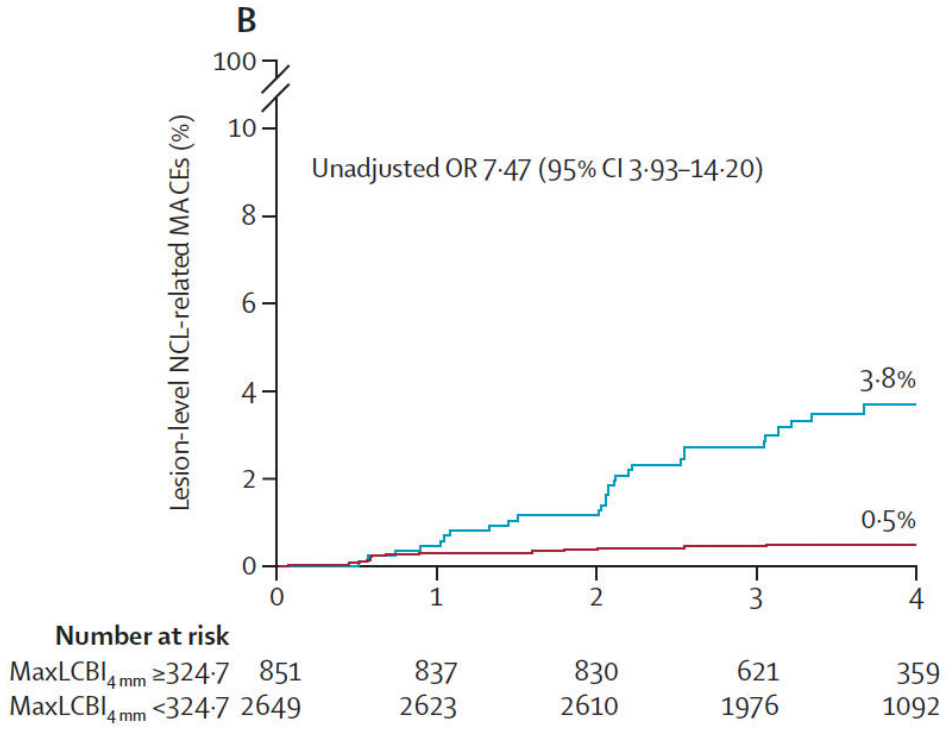



Karlsson et al. Open Heart 2019

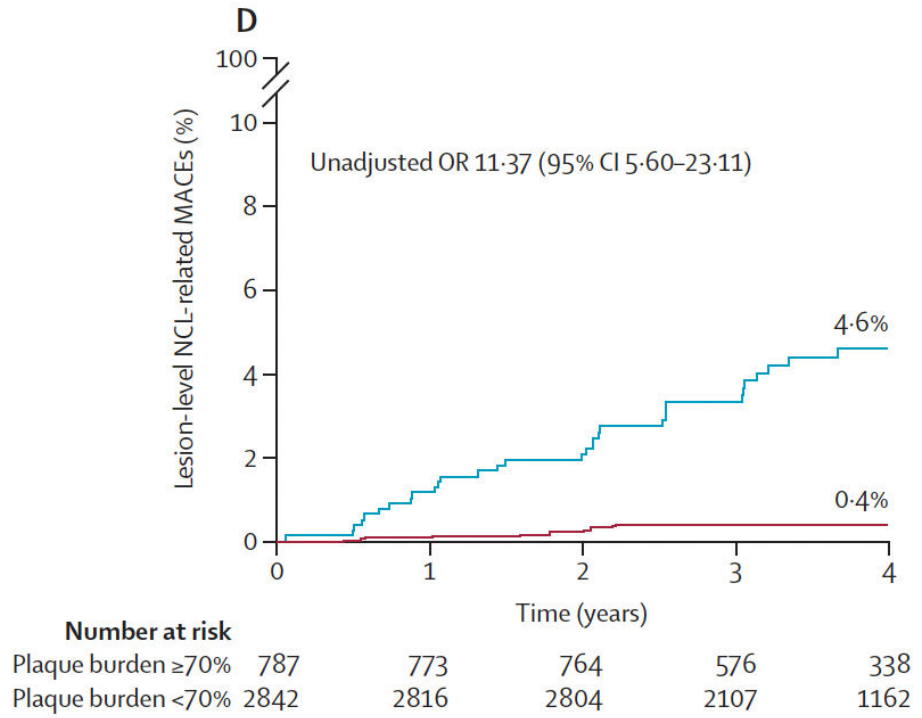
# PROSPECT II-Lipid rich lesions detected by NIRS and adverse events

NCLs in ACS patients with ≥30% DS and ≥40% plaque burden
MACE occurred in 14.4% of pts at median 3.7-year FU

MaxLCBI 4mm ≥324.7




Plaque burden ≥70%




Erlinge al Lancet 2021

# PROSPECT- Modest prognostic value for Vulnerable Plaque

**Table 1. Predictive Performance of Plaque Characteristics**

| | Endpoint | Event Rate, % (n/N)* + Lesion Variable | Event Rate, % (n/N)* − Lesion Variable | OR* | Sn | Sp | PPV | NPV | LR+ | LR− | AUC (95% CI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Lesion-specific | | | | | | | | | | | |
| PB ≥70% | NCL MACE | 8.7% (25/288) | 1.0% (30/2941) | 9.55 | 0.46 | 0.92 | 9% | 99% | 5.59 | 0.59 | 0.82 (0.76–0.87) |
| MLA ≤4.0 $mm^2$ | NCL MACE | 4.9% (30/616) | 1.0% (25/2522) | 5.11 | 0.55 | 0.81 | 5% | 99% | 2.87 | 0.56 | 0.75 (0.67–0.82) |
| TCFA | NCL MACE | 4.4% (26/595) | 1.2% (25/2114) | 3.82 | 0.51 | 0.79 | 4% | 99% | 2.38 | 0.62 | 0.71 (0.62–0.79) |
| PB ≥70% + MLA ≤4.0 $mm^2$ + TCFA | NCL MACE | 18.2% (8/44) | 1.6% (43/2665) | 13.55 | 0.16 | 0.99 | 18% | 98% | 11.58 | 0.85 | 0.86 (0.76–0.92) |
| DS ≥50% (by QCA) | NCL MACE | 10.7% (36/336) | 2.5% (37/1488) | 4.71 | 0.49 | 0.83 | 11% | 98% | 2.88 | 0.61 | 0.74 (0.67–0.80) |
| Patient-specific | | | | | | | | | | | |
| NCL (DS ≥30% by visual estimation) | CL + NCL MACE | 20.7% (125/604) | 7.5% (7/93) | 3.2 | 0.95 | 0.15 | 21% | 92% | 1.12 | 0.35 | 0.69 (0.56–0.79) |
| | NCL MACE | 12.3% (74/604) | 0% (0/93) | NR | 1.00 | 0.15 | 12% | 100% | 1.18 | 0.00 | NR |
| PB ≥70% | NCL MACE | 19.1% (42/220) | 7.0% (31/440) | 3.11 | 0.58 | 0.70 | 19% | 93% | 1.90 | 0.61 | 0.68 (0.60–0.75) |

Data to evaluate lesion-specific risk estimates for SLP and NCL, and patient-specific risk estimates for MLA, TCFA, and DS ≥50% were not available. *Event rates and odds ratios are not based on Kaplan-Meier estimates.

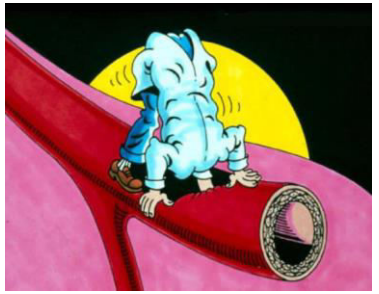
AUC = area under the receiver-operator curve; CI = confidence interval; CL = culprit lesion; DS = diameter stenosis; LR− = negative likelihood ratio; LR+ = positive likelihood ratio; MACE = major adverse cardiac events; MLA = minimum luminal area; NCL = nonculprit lesion; NPV = negative predictive value; NR = not reportable; OR = odds ratio; PB = plaque burden; PPV = positive predictive value; Sn = sensitivity; Sp = specificity; SLP = substantial lesion progression; TCFA = thin-cap fibroatheroma.

Kaul et al. JACC Cardiovasc Imaging 2012

# PROSPECT-Modest prognostic value for Vulnerable Plaque Potential explanations

- IVUS resolution inadequate for plaque characteristics
- No repeat IVUS evaluation: plaque evolves
- TFCA does not necessarily cause ACS and 25% of ACS are caused by erosion
- Inflammatory infiltrate cannot be detected by structural imaging nor by NIRS

# The case for molecular imaging?



- Inflammation drives atherogenesis and plaque rupture
- Structural imaging not yet robust enough for prediction
- Molecular imaging of inflammation will improve risk prediction beyond structural imaging

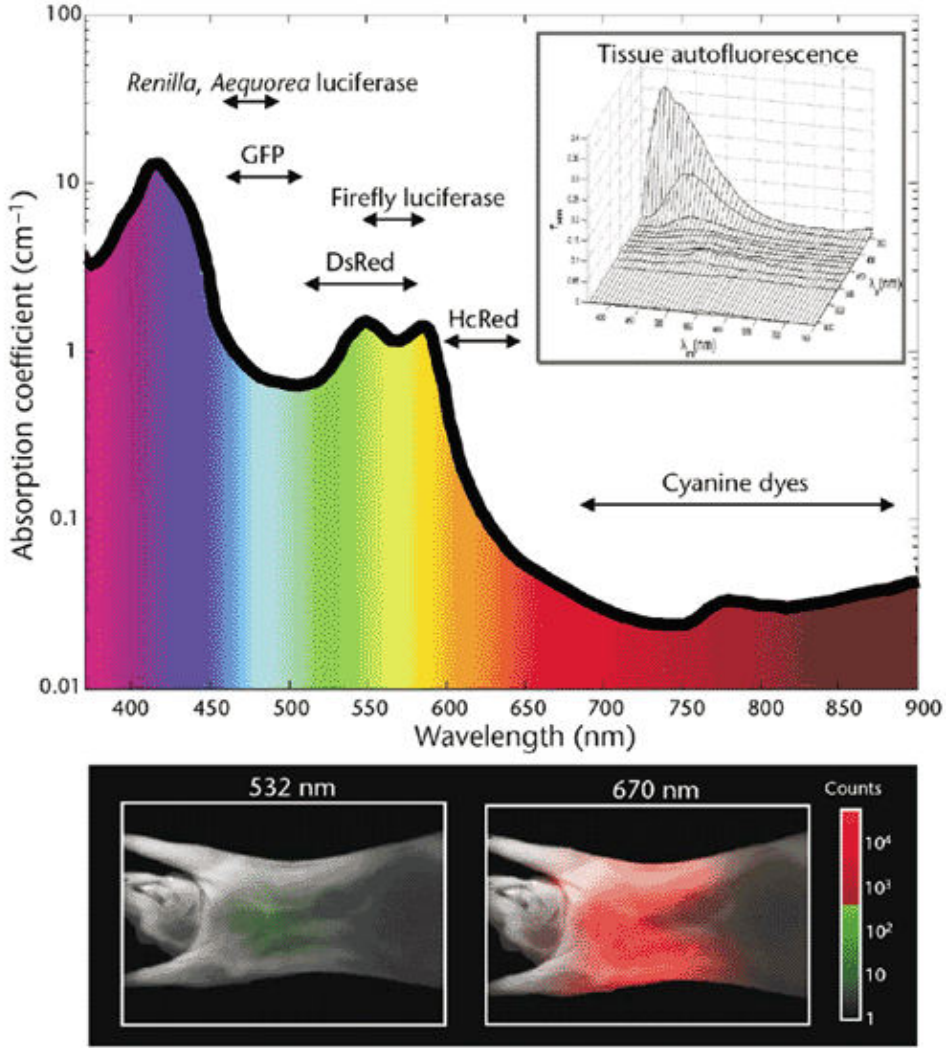
# Near-Infrared Fluorescence (NIRF) Imaging:

## Shedding light onto live molecular targets

↓photon attenuation (more light penetration)

↓autofluorescence enables in vivo imaging

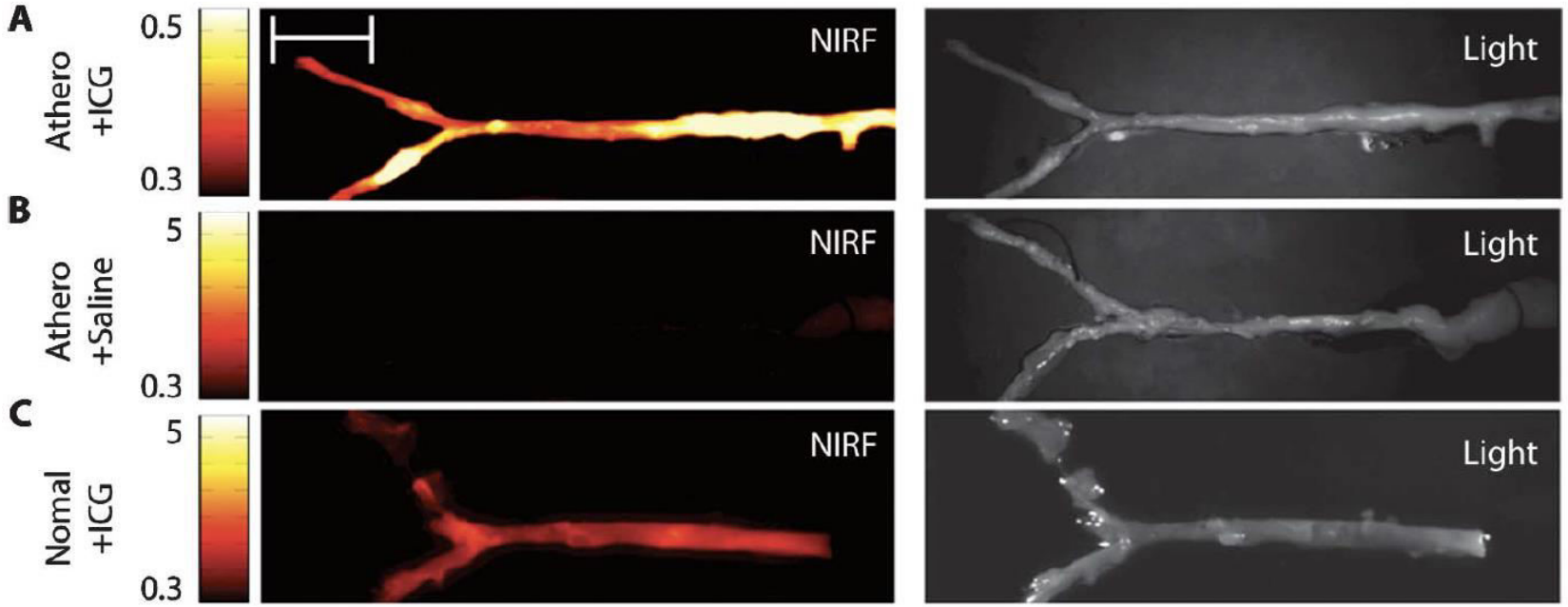
→Visualize in vivo atheroma inflammation

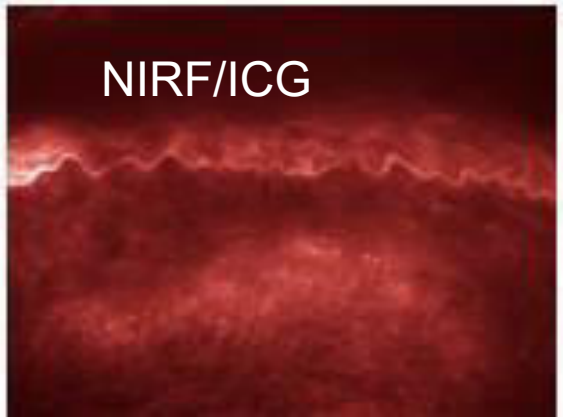


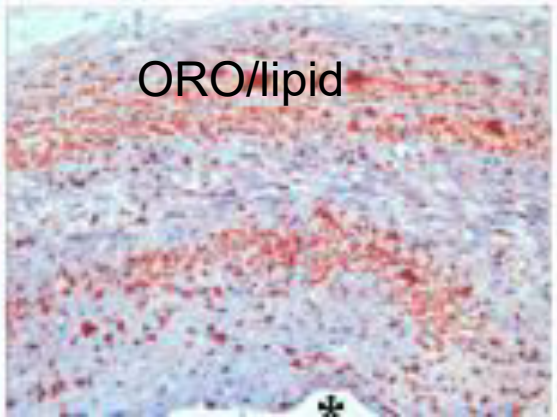

Weissleder, Ntziachristos *Nat Med* 2003

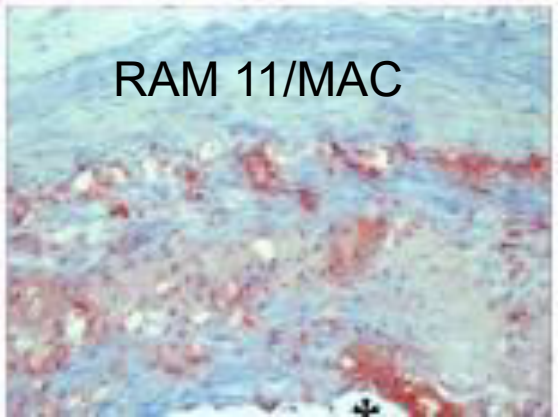
# NIRF for Lipid-Rich, Inflamed Atherosclerotic Plaques

## Indocyanine Green



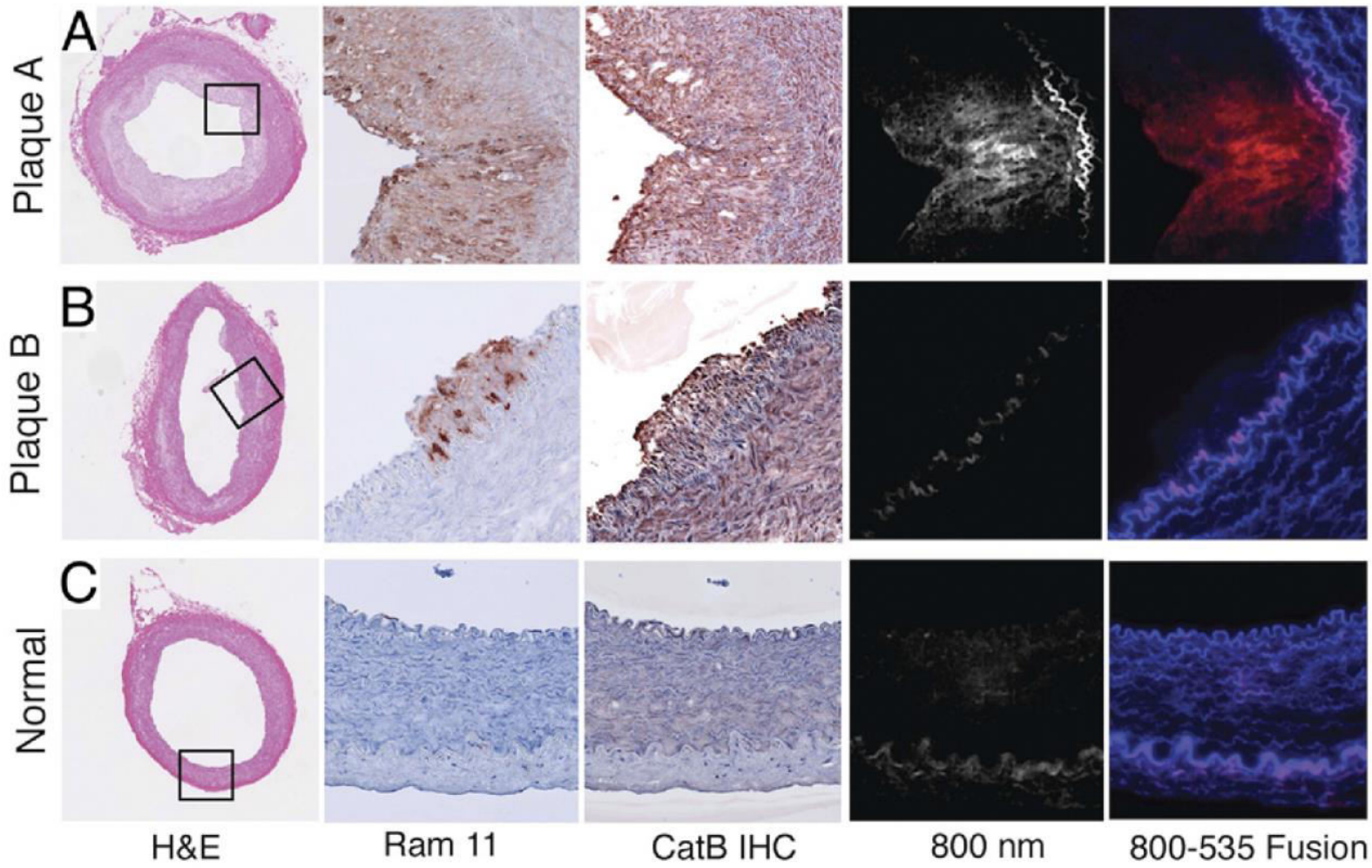




Vinegoni et al. at Med 2003

# NIRF for Lipid-Rich, Inflamed Atherosclerotic Plaques

## Prosense VM110




Jaffer et at JACC 2011

# 2D NIRF-IVUS

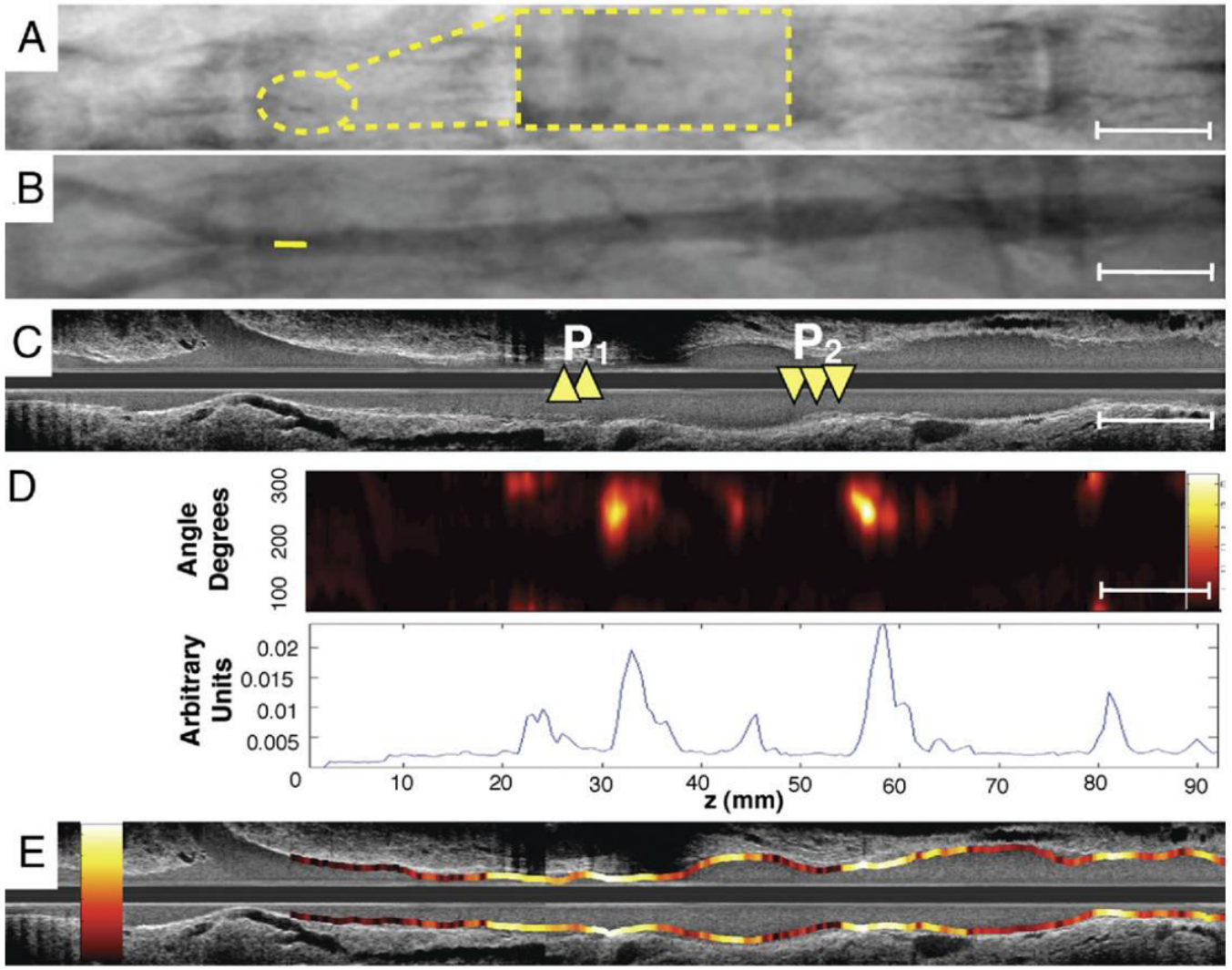
X-RAY

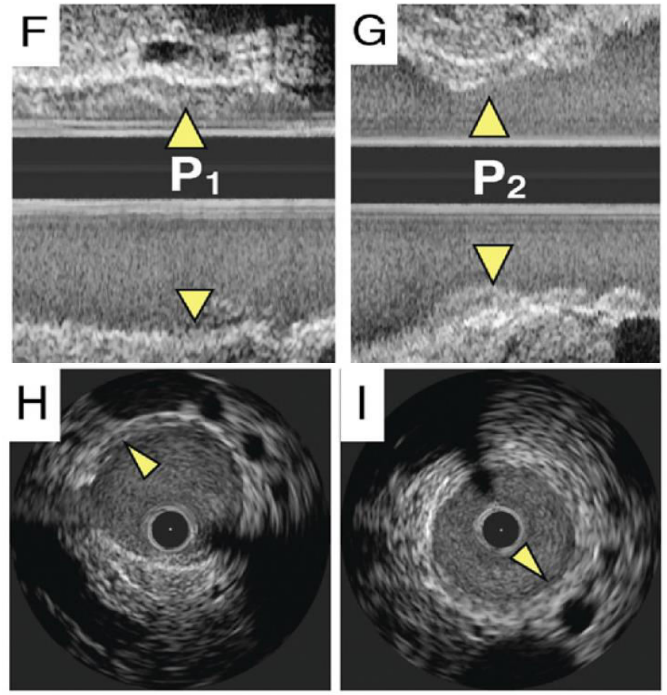
Angiogram

IVUS image

2D NIRF

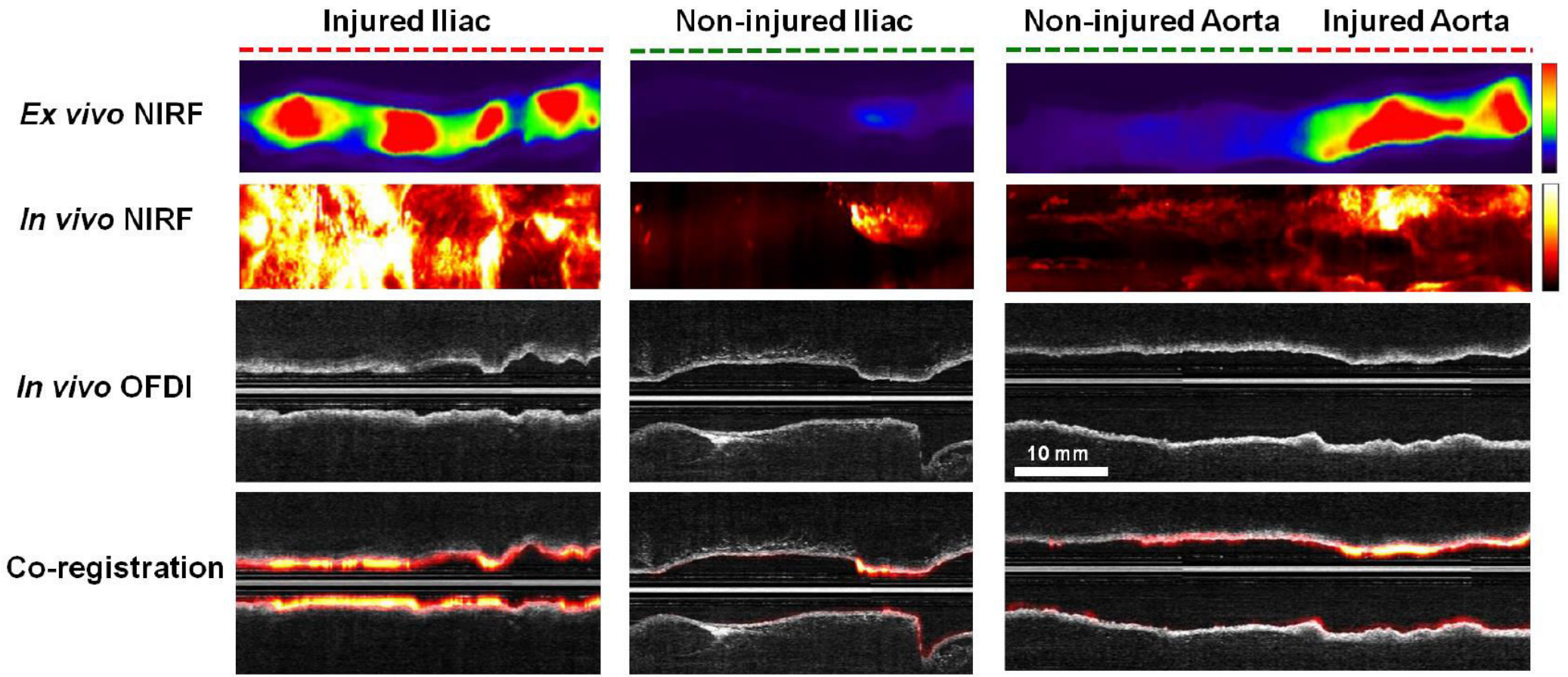
NIRF-IVUS fusion images




Jaffer et at JACC 2011

# 2D NIRF-OCT


Injured Iliac
Non-injured Iliac
Non-injured Aorta
Injured Aorta
Ex vivo NIRF
In vivo NIRF
In vivo OFDI
Co-registration
10 mm

# Conclusions-The case for molecular imaging

- NIRF imaging provides high-resolution quantification of plaque inflammation
- NIRF is ready to translate and synergize with structural imaging for risk prediction
- High resolution imaging of coronary vulnerable plaque: ready to translate into clinical practice?


# Thank you

**Valeria Paradies, MD, MSc**

Interventional Cardiologist and Director of Research Department

Maasstad Hospital-

PhD candidate Erasmus Medical Centre

EAPCI Chair Gender and Disparities Committee

# PROSPECT- VH-TFCA and Non Culprit Lesion Related Events

# PROSPECT: VH-TCFA and Non Culprit Lesion Related Events




| | TCFA | TCFA + MLA ≤4.0mm2 | TCFA + PB ≥70% | TCFA + PB ≥70% + MLA ≤4mm2 |
|---|---|---|---|---|
| Lesion HR | 3.84 (2.22, 6.65) | 6.41 (3.35, 12.24) | 10.77 (5.53, 21.00) | 10.81 (4.30, 27.22) |
| P value | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Prevalence* | 51.2% | 17.4% | 11.0% | 4.6% |

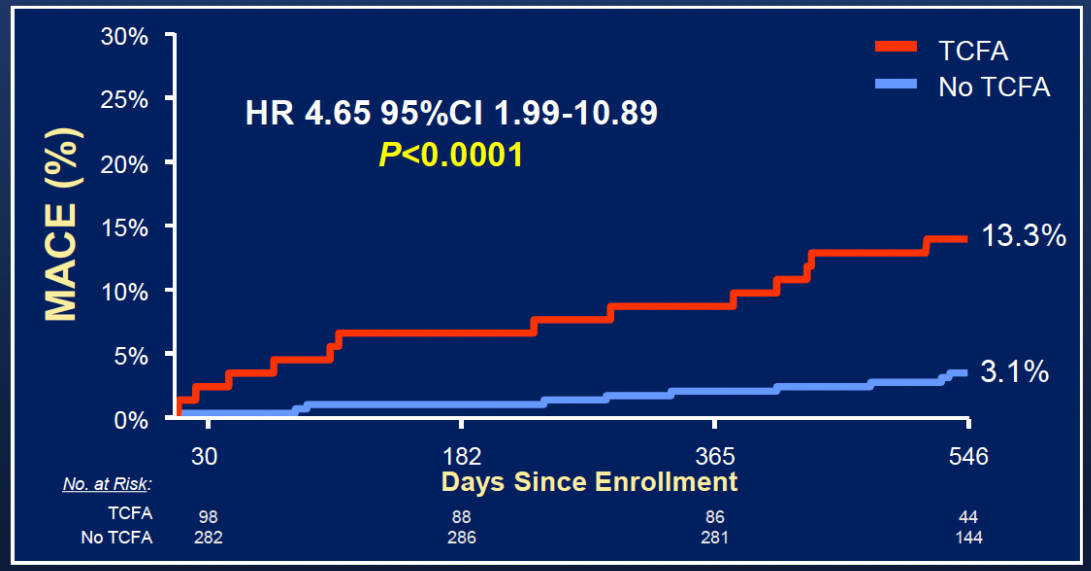
*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

# COMBINE (OCT–FFR) Trial

OCT was performed in 390 pts with diabetes and an intermediate lesion with a visually estimated DS ≥40% - ≤80% with FFR >0.80 (mean 0.88). 24% ACS, 76% SIHD.

**98 (25.1%) lsns were a TCFA* with median FC thickness of 60 (56, 63) µm.** Rx'd w/GDMT.

**Primary MACE Endpoint = CD, TVMI, CD-TLR, or hospitalization for UA at 18 mo.**




| | TCFA+ (n=98) | TCFA- (n=292) |
|---|---|---|
| C. death | 0% | 0.3% |
| TVMI | 4.1% | 0% |
| Spont. MI | 8.2% | 1.0% |
| CD-TLR | 11.2% | 1.4% |
| Hosp for UA | 6.1% | 1.7% |

***TCFA = FCT ≤65 µm and lipid arc >90°**

Mount Sinai Heart

Kedhi E et al. Eur Heart J. 2021;42:4671-9

# PROPSECT: Modest Prognostic Value for VP

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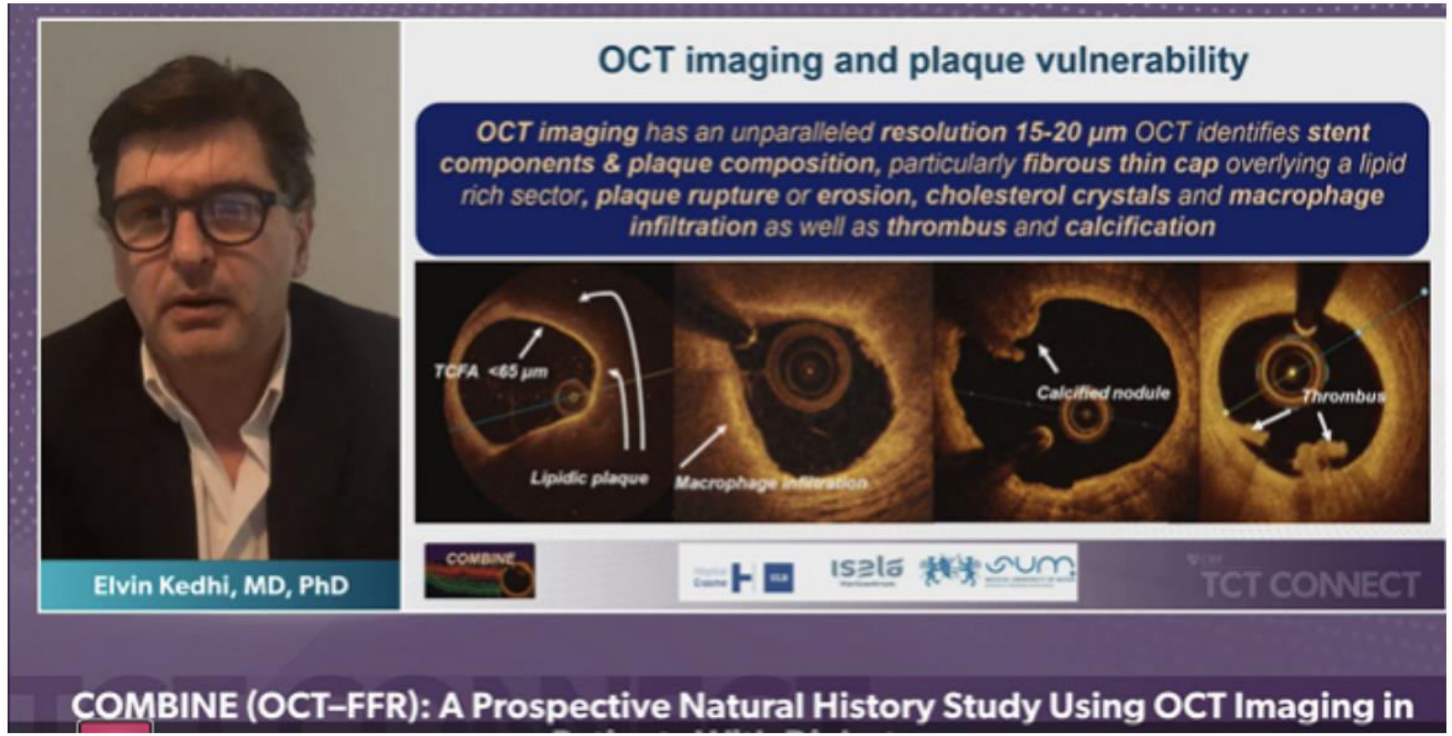
**--GW Stone et al. *N Engl J Med* 2011; 364:226-235**

- IVUS-VH predictive -- but sensitivity and positive predictive values are limited. Even with all 3 parameters present: PPV is only 18%.

**--S Kaul and G Diamond, *JACC CV Imaging* 2012; 5:S106-S110**


OCT imaging and plaque vulnerability
OCT imaging has an unparalleled resolution 15-20 µm OCT identifies stent components & plaque composition, particularly fibrous thin cap overlying a lipid rich sector, plaque rupture or erosion, cholesterol crystals and macrophage infiltration as well as thrombus and calcification
TCFA <65 µm
Lipidic plaque
Macrophage infiltration
Calcified nodule
Thrombus
Elvin Kedhi, MD, PhD
COMBINE
TCT CONNECT
COMBINE (OCT–FFR): A Prospective Natural History Study Using OCT Imaging in

# The Case for Molecular Imaging

- Inflammation drives atherogenesis and plaque rupture
  -Libby et al. *Nature* 2011 473:317-25; Tabas, Glass *Science* 2013;339:166-172
- Structural imaging not yet robust enough for prediction
- To improve risk prediction (ROC/NRI): Uncorrelated biomarkers, or new dimensions of information needed
  --TJ Wang. *Circulation* 2011;123:551-565
- *We hypothesize that molecular imaging of inflammation will improve risk prediction beyond structural imaging*.

*molecular imaging of inflammation will improve risk prediction beyond structural imaging*.

# Targeted Molecular Imaging: Closer to Clinical

- NIRF imaging provides high-resolution quantification of plaque inflammation
- NIRF ready to translate and synergize with structural imaging for risk prediction
- High-resolution imaging of coronary VP: Intravascular NIRF-OFDI, and soon NIRF-IVUS ready to translate
- ICG and new clinical NIRF agents will accelerate intravascular NIRF imaging trials

# Basis for Coronary Molecular Imaging

- Coronary plaque and stent complications remain leading causes of morbidity and mortality worldwide
- Pathobiology drives arterial disease and the design of molecular therapeutics, but is not visible to clinical structural imaging
- Structural imaging of high-risk plaques (e.g. PROSPECT IVUS-VH) currently do not predict risk well enough to enable clinical action (PPV of only 18% to predict ACS by 3 yrs).[1]
- Molecular imaging of coronary plaque biology offers a new approach to understand drivers of plaque and stent complications[2]

[1]Stone GW et al. *NEJM* 2011;364:226-35 [2]Mulder WJ, Jaffer FA, Fayad ZA, Nahrendorf M. *Sci Transl Med* 2014

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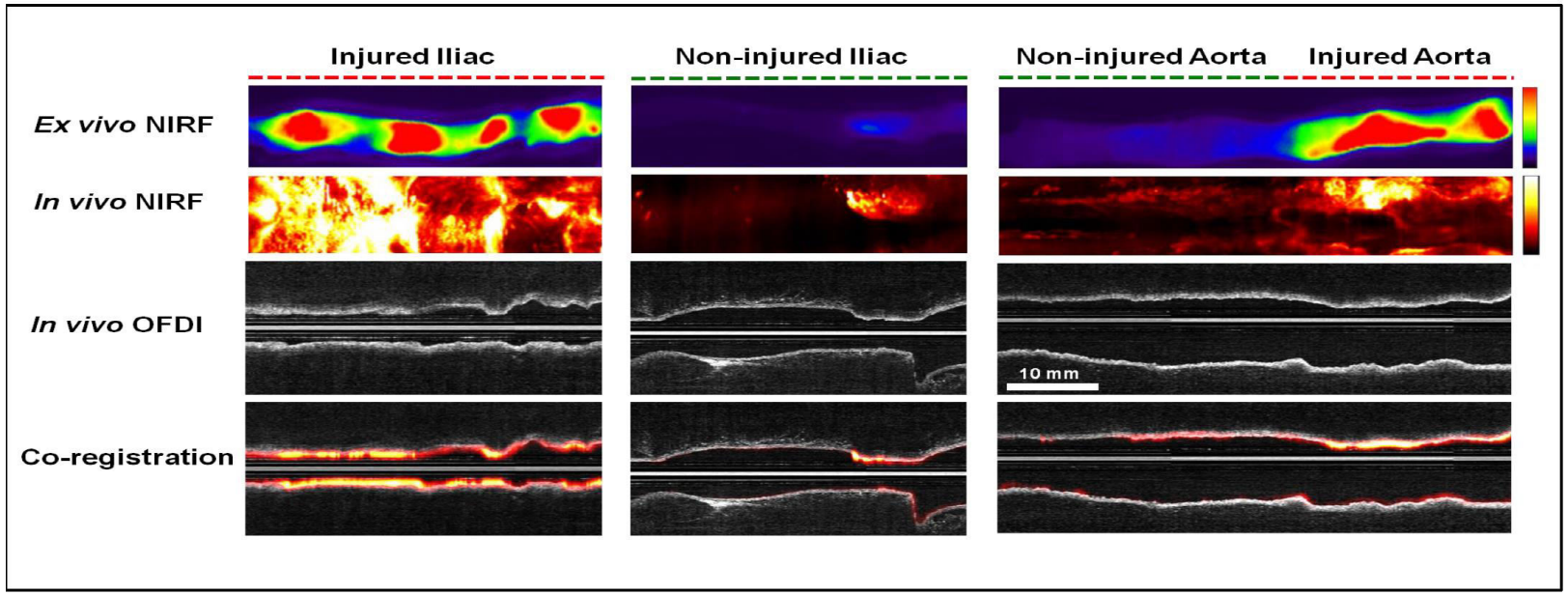
# Dual-modal NIRF-optical coherence tomography single catheter imaging of atheroma inflammation




- Rabbit atherosclerosis: injury + diet
- Saline-flush; 5 mm/second pullback
- Prosense VM110 injected 24h before

-- Yoo, Kim, Jaffer, Tearney et al. *Nature Medicine* 2011

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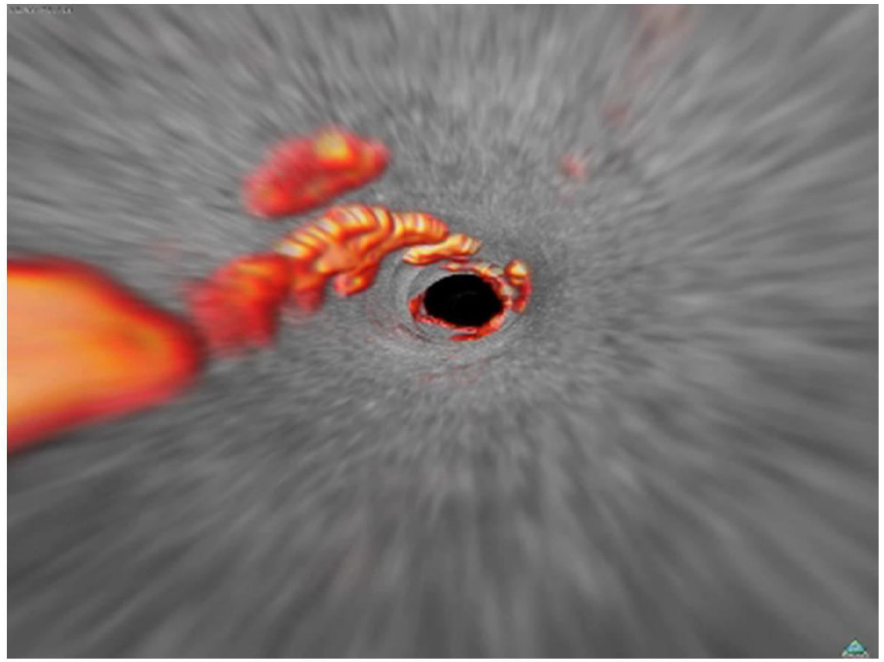
# NIRF-OCT molecular-structural imaging reveals heterogeneous plaque inflammatory protease activity



-- Yoo, Kim, Jaffer, Tearney et al. *Nature Medicine* 2011

- OCT = optical coherence tomography, FDA-approved
- Rabbit aortic atheroma
- Prosense VM110 i.v. 1 day before
- 3D OCT rendered
- NIRF signal surface rendered (nM NIR fluorescence)

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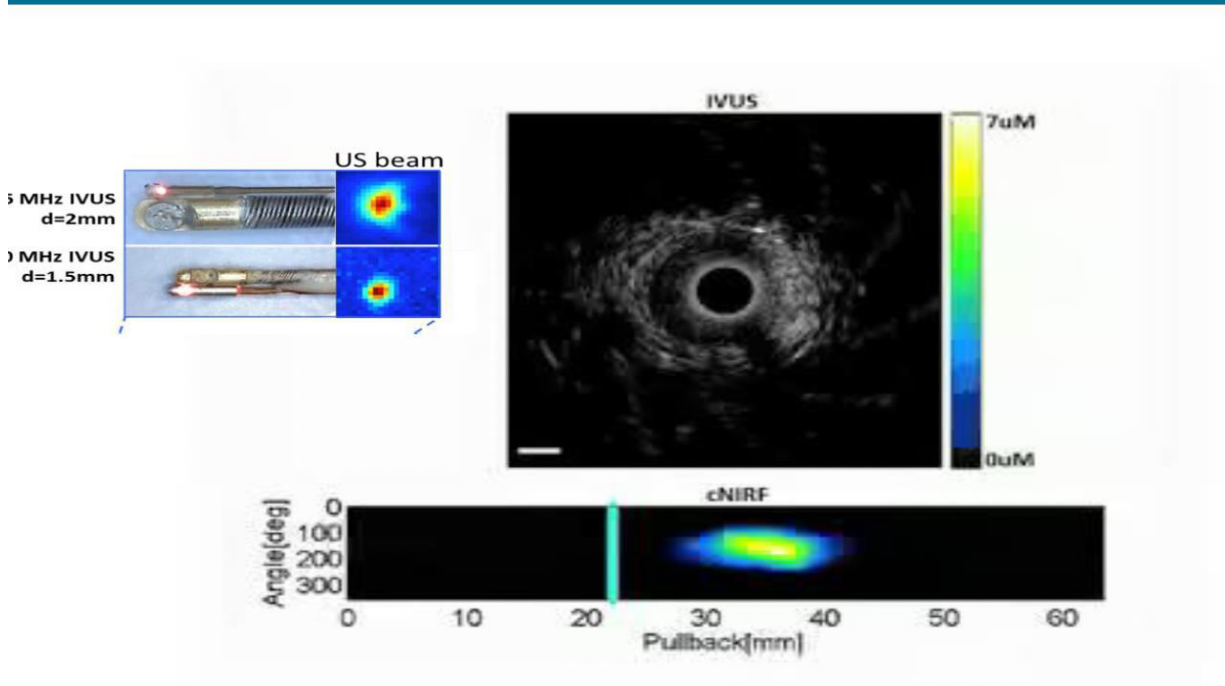
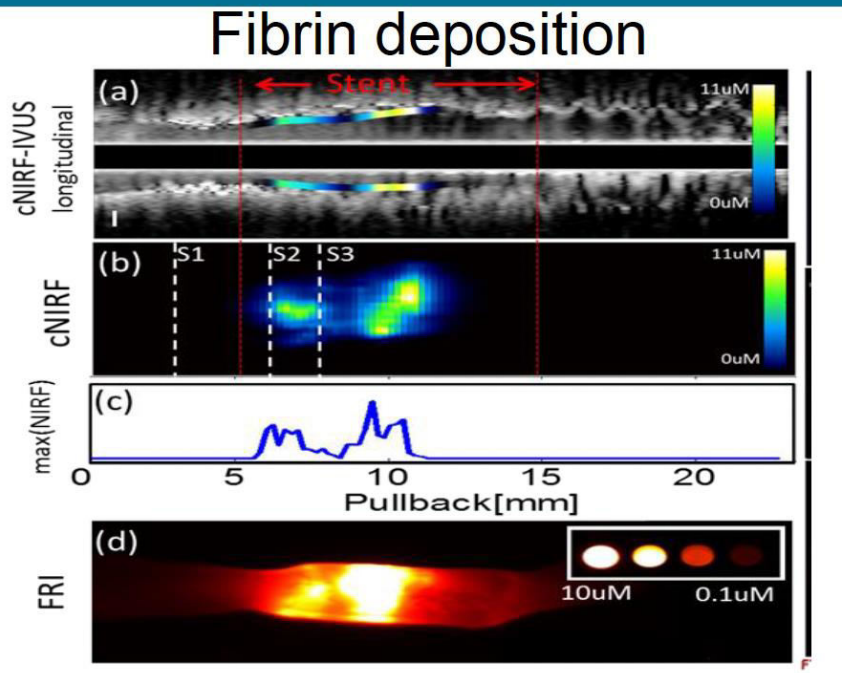
# IVUS-NIRF Structural-Molecular Imaging



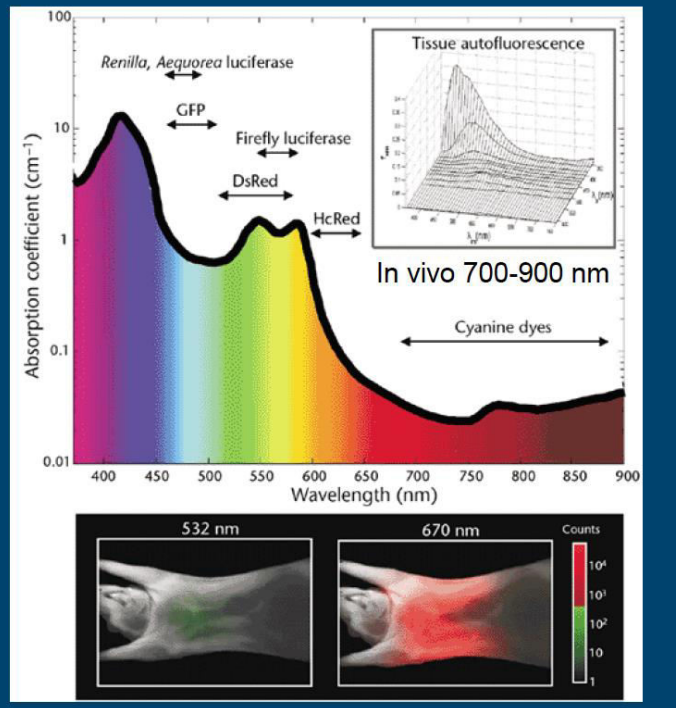




- NIRF+IVUS, the most prevalent intracoronary imaging approach
- Through-blood imaging, no flushing required
- Requires correction of NIRF signal attenuation through blood

-- Bozhko, Osborn..Jaffer, Ntziachristos, EHJ CV imaging 2017

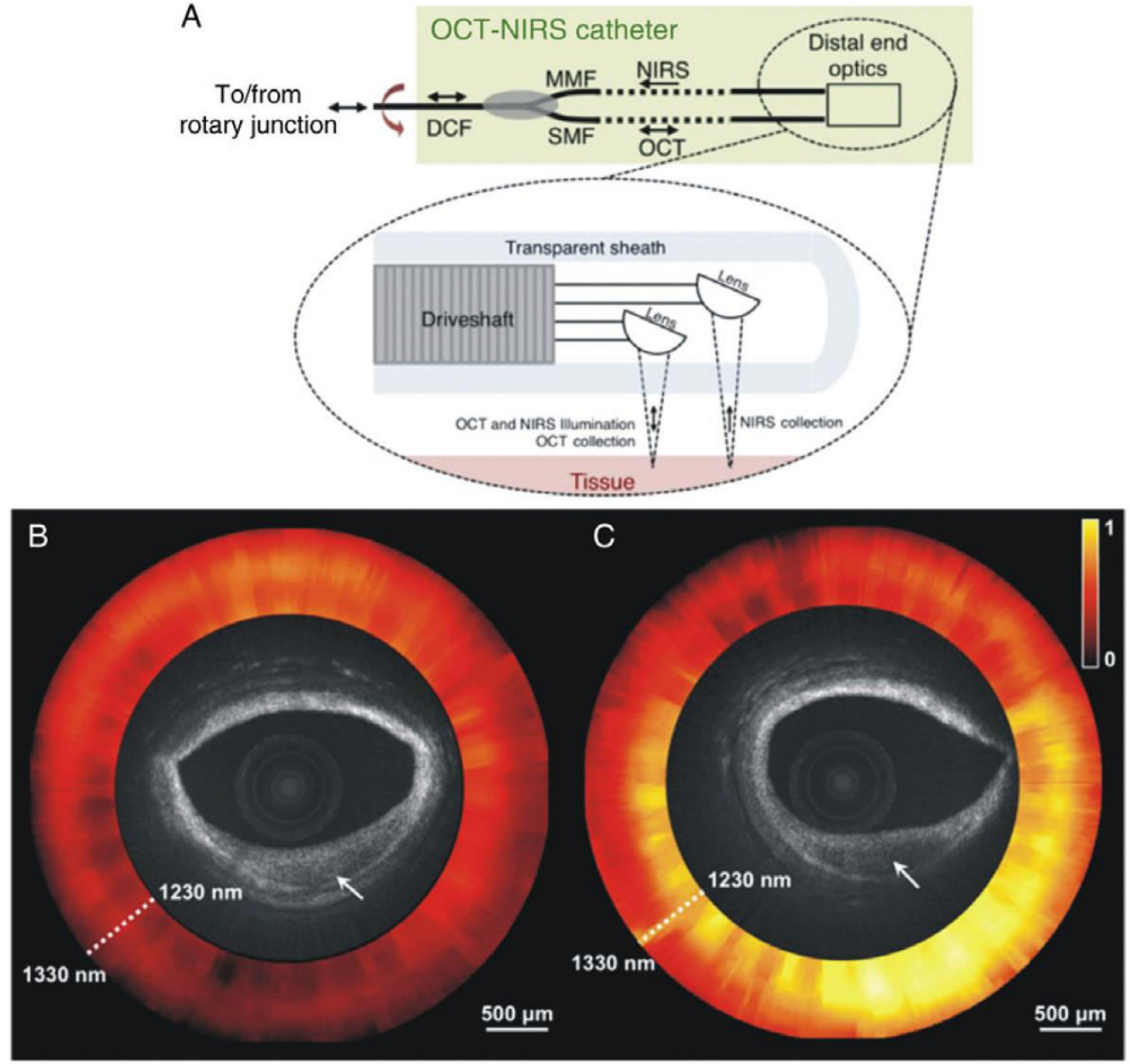
# Near-Infrared Fluorescence (NIRF) Imaging: High-Resolution Pathway To The Coronary Arteries

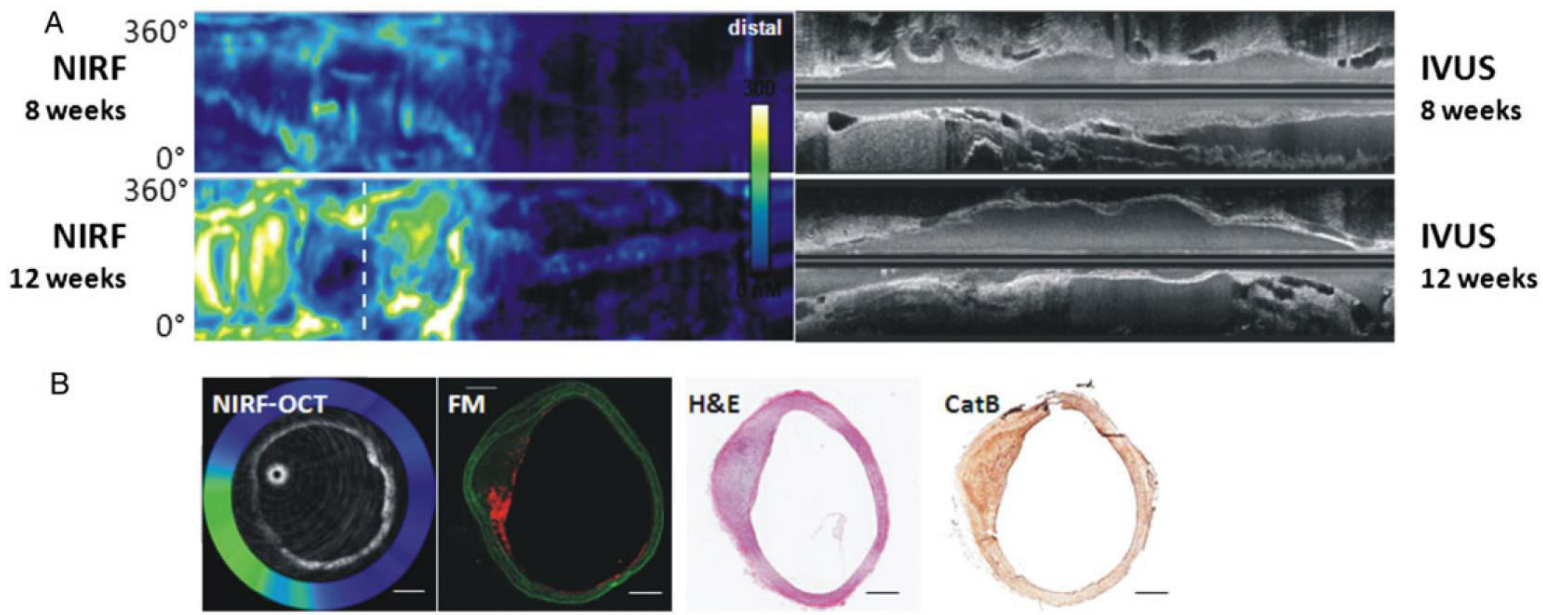
- *Optical imaging is Clinical*: OCT/OFDI, NIRS, Angioscopy
- *NIR window for fluorescence*: ↓photon attenuation (more light penetration); and ↓autofluorescence enables *in vivo* imaging
- *NIRF Molecular Agents*: Clinical emerging: *ICG*, Prosense VM110, IR800-based



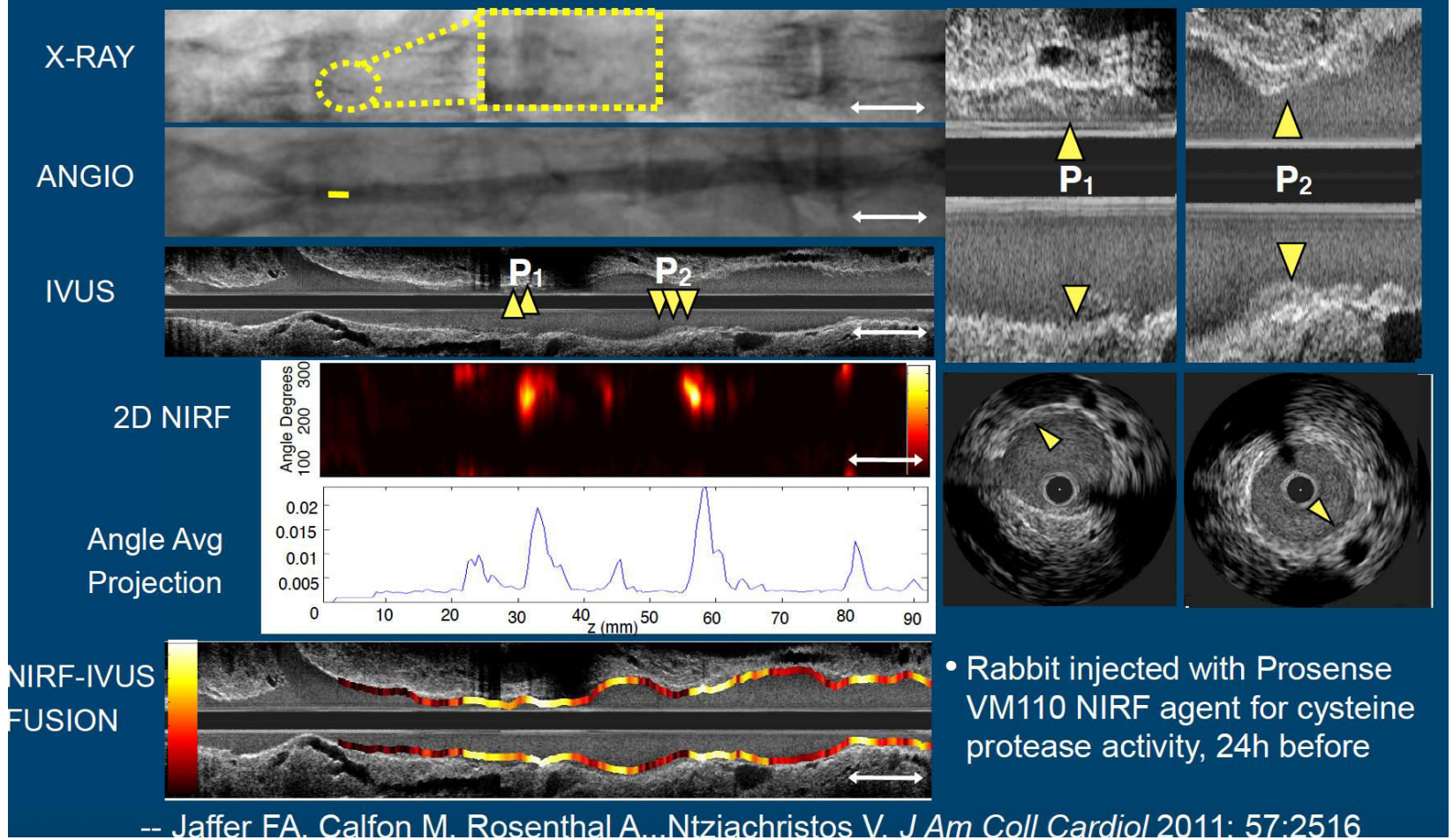

--Weissleder, Ntziachristos *Nat Med* 2003

-*Circulation* 2007; *ATVB* 2009; *Sci Trans Med* 2011; *Nat Med* 2011; *JACC CV imaging* (in press)


A
OCT-NIRS catheter
To/from
rotary junction
DCF
MMF
SMF
NIRS
OCT
Distal end
optics
Transparent sheath
Driveshaft
Lens
Lens
OCT and NIRS Illumination
OCT collection
NIRS collection
Tissue
B
1230 nm
1330 nm
500 µm
C
1230 nm
1330 nm
500 µm
1
0


A
360°
NIRF
8 weeks
0°
distal
300
0
360°
NIRF
12 weeks
0°
IVUS
8 weeks
IVUS
12 weeks
B
NIRF-OCT
FM
H&E
CatB

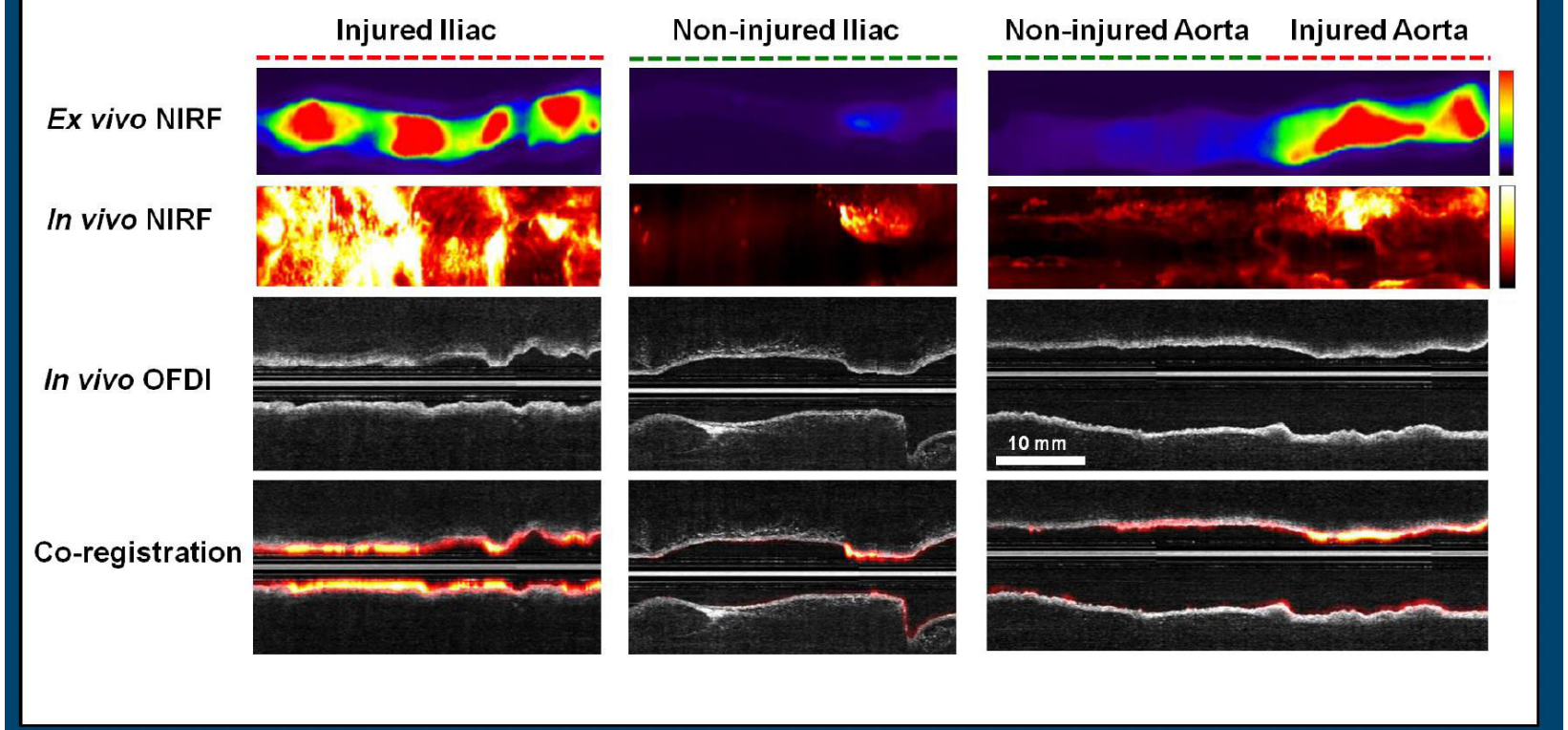
# Standalone NIRF 2D and IVUS of Plaque Inflammatory Protease Activity, Through Blood




- Rabbit injected with Prosense VM110 NIRF agent for cysteine protease activity, 24h before

-- Jaffer FA, Calfon M, Rosenthal A...Ntziachristos V. *J Am Coll Cardiol* 2011; 57:2516

# Dual-modal NIRF-OFDI single catheter quantitative imaging of atheroma inflammation




- NZW rabbit +PTCA +HL
- Saline-flush; 5 mm/second pullback
- Prosense VM110 injected 24h before

--Yoo, Kim....Jaffer, Tearny *Nature Medicine* 2011
-- Jin Won Kim, Hongki Yoo et al. AHA 2011

# Conclusion

- NIRS-IVUS is an easy to use way to identify a vulnerable plaque
- On a patient level four studies have shown prospective validity
- Prospective segment level studies are ongoing