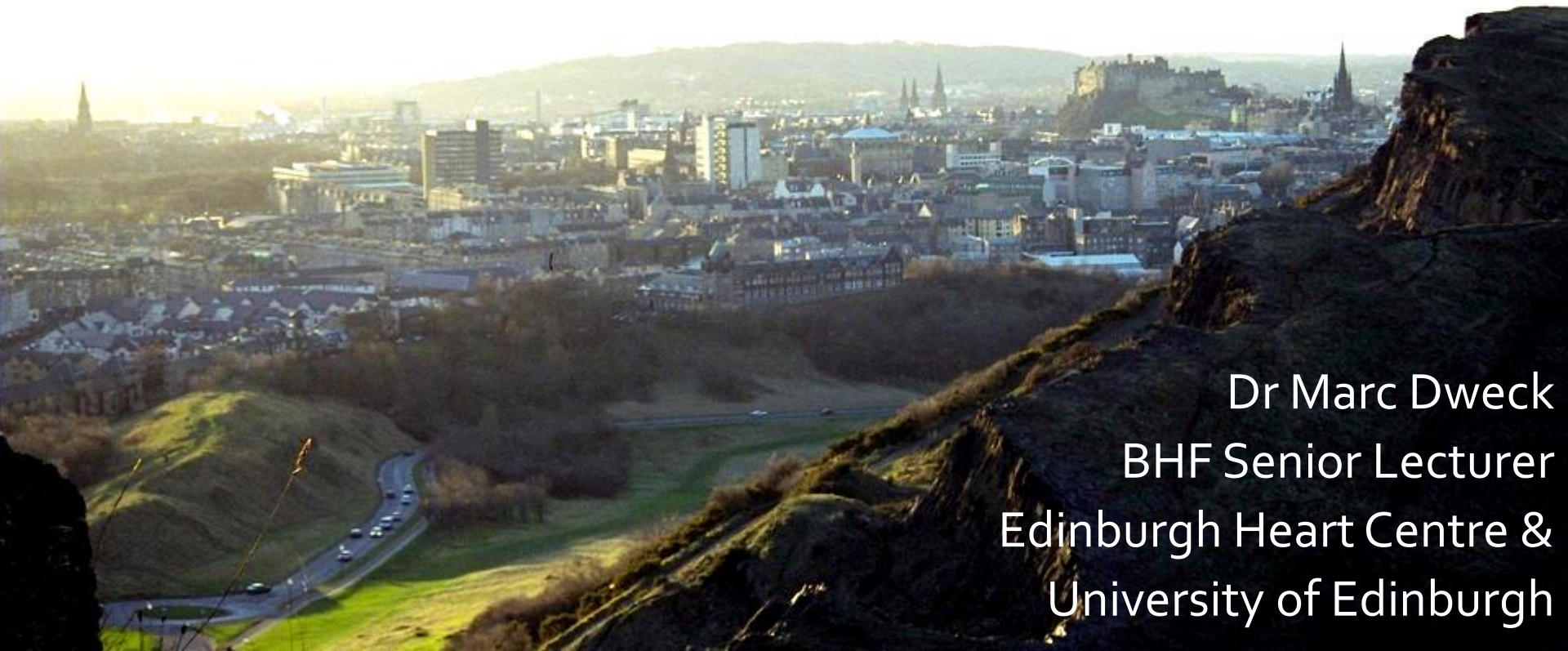




**Edinburgh
Heart Centre**

Imaging Vulnerable Plaque to Stratify Individual Patient Risk



Dr Marc Dweck
BHF Senior Lecturer
Edinburgh Heart Centre &
University of Edinburgh



Objectives

1. Rationale for detecting vulnerable plaque
2. Methods for detecting vulnerable plaque





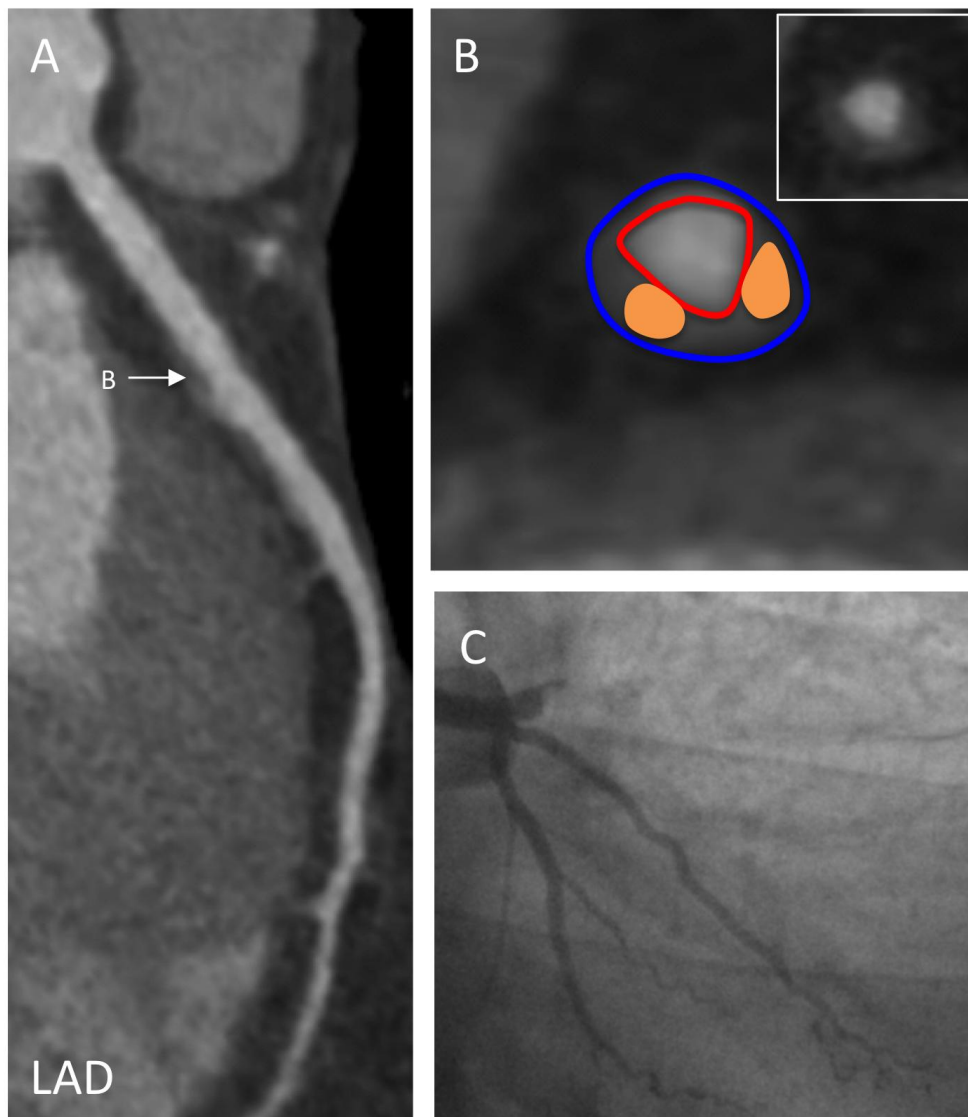


Luminal Stenosis



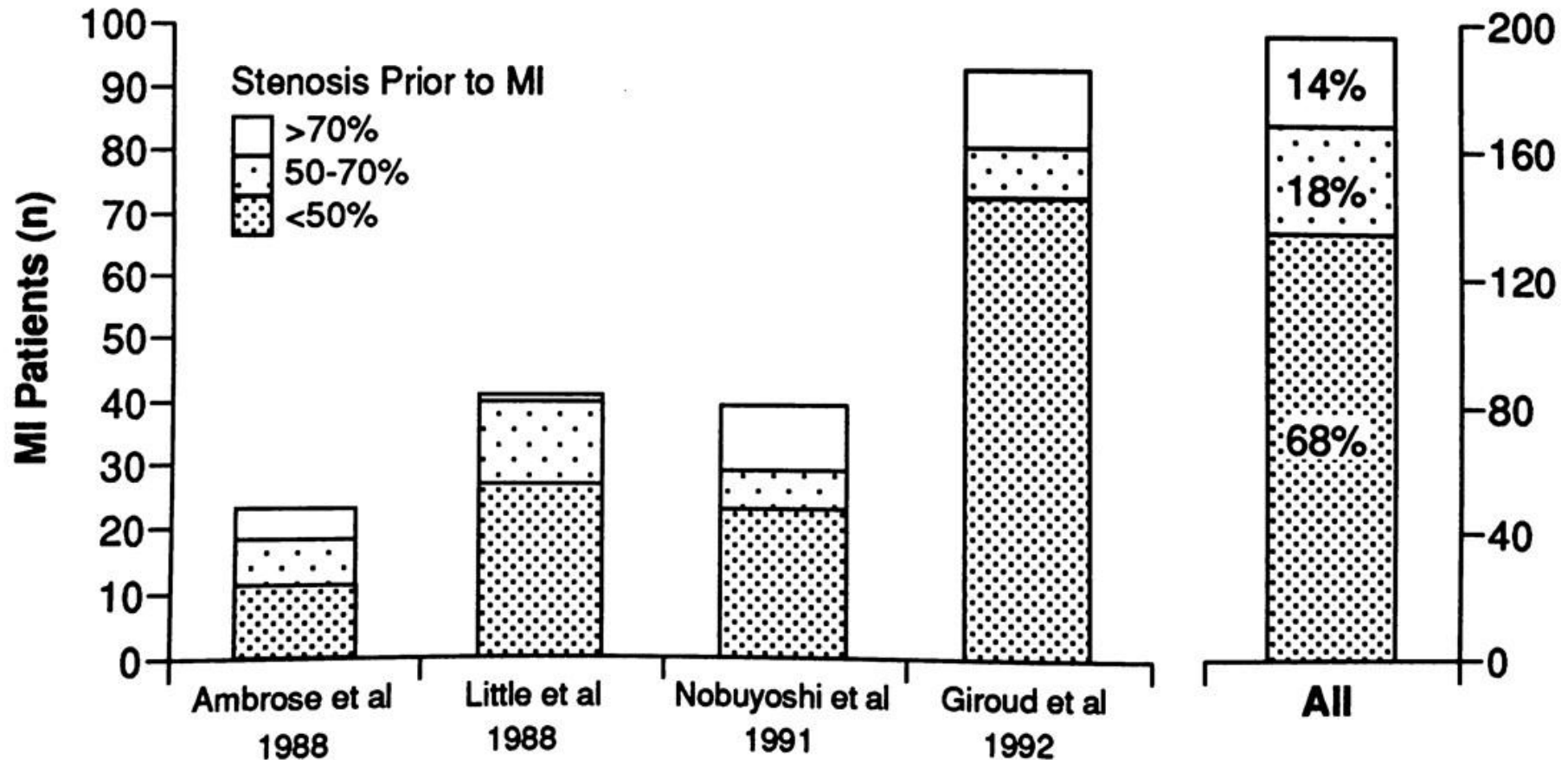


MI arising from a non-obstructive plaque



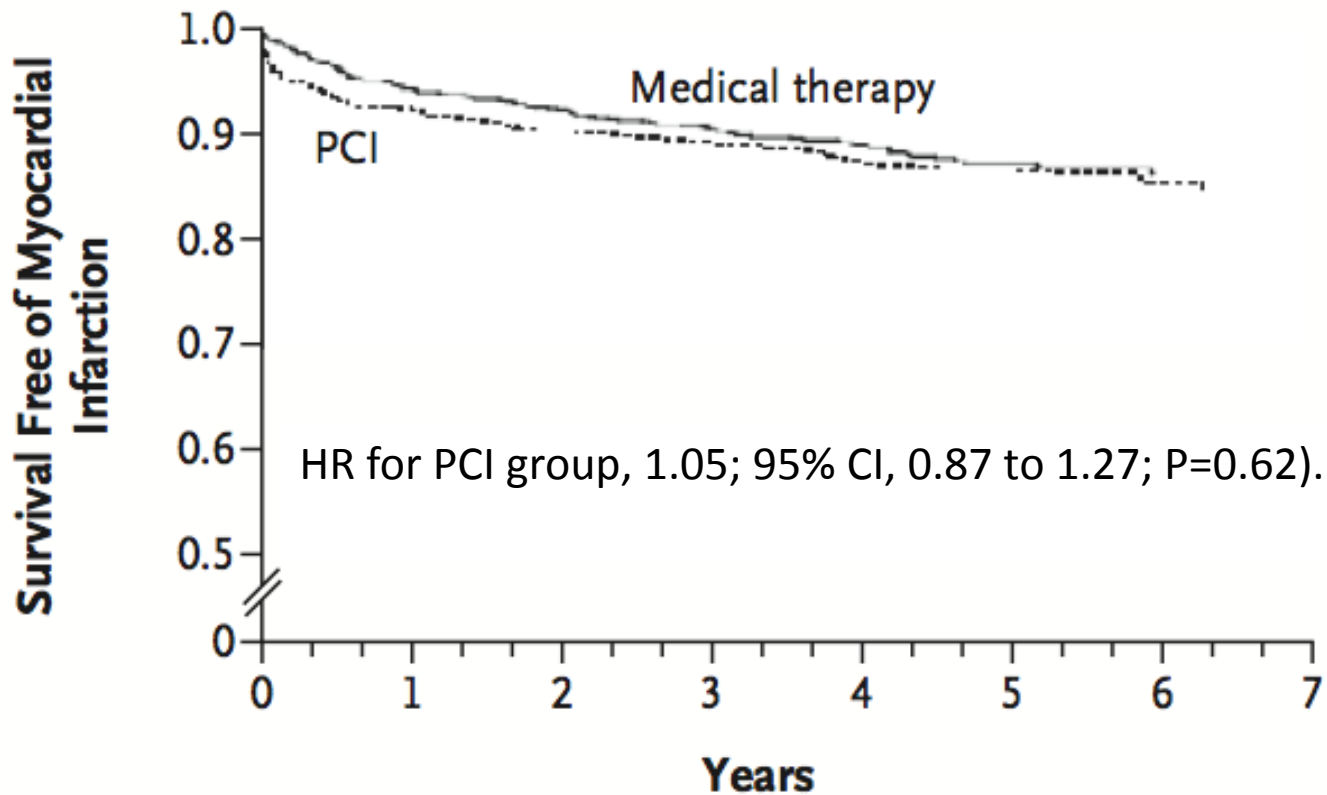


Majority of MI Arise from Mild or Moderate Lesions on Antecedent Angiography





COURAGE

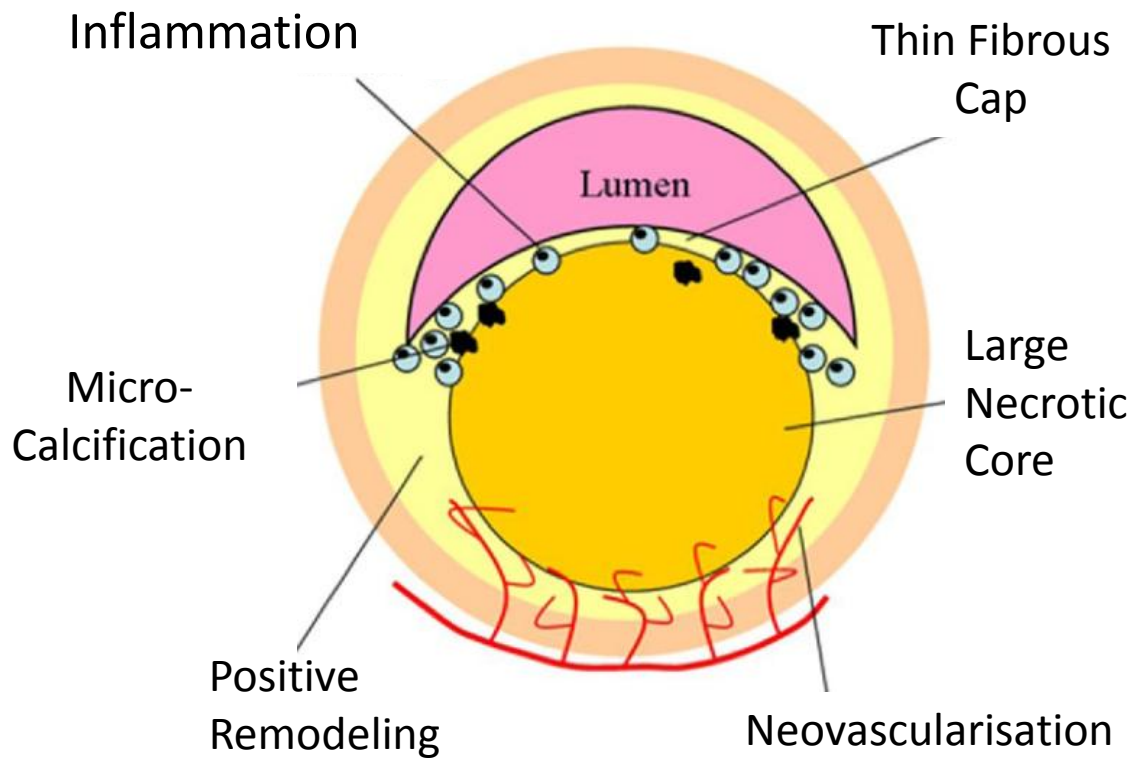


No. at Risk

Medical therapy	1138	1019	962	834	638	409	192	120
PCI	1149	1015	954	833	637	418	200	134



Histological Characteristics of the Vulnerable Plaque



All Potential
Imaging Targets



Potential Imaging Targets

18F-FDG →
11C-PK11195
18F-FMCH
68Ga-Dotate
USPIO MRI

Inflammation

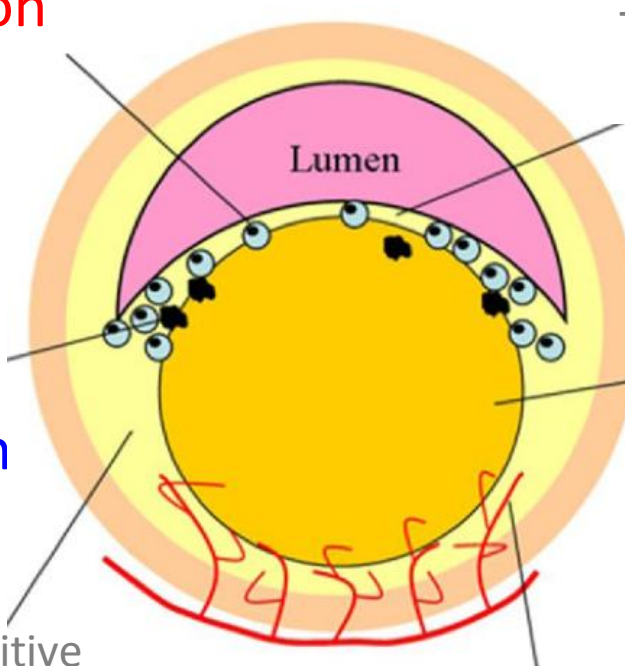
Micro-Calcification

18F-Fluoride

Positive Remodeling
↑
CT

Angiogenesis & Plaque Haemorrhage

↑
18F-Fluciclatide PET
T1 weighted MRI



Thin Fibrous Cap

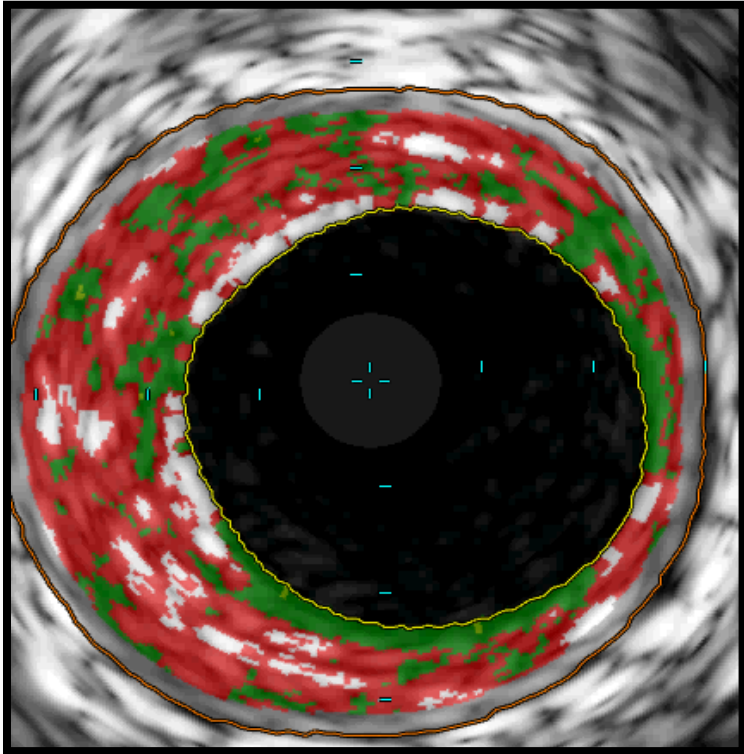
Lumen

Large Necrotic Core ←

CT
18F-FMISO (hypoxia)



PROSPECT



- 697 patients
- 595 VH-IVUS TcFA identified
- Median follow up 3.4 years
- Only 6 resulted in myocardial infarction

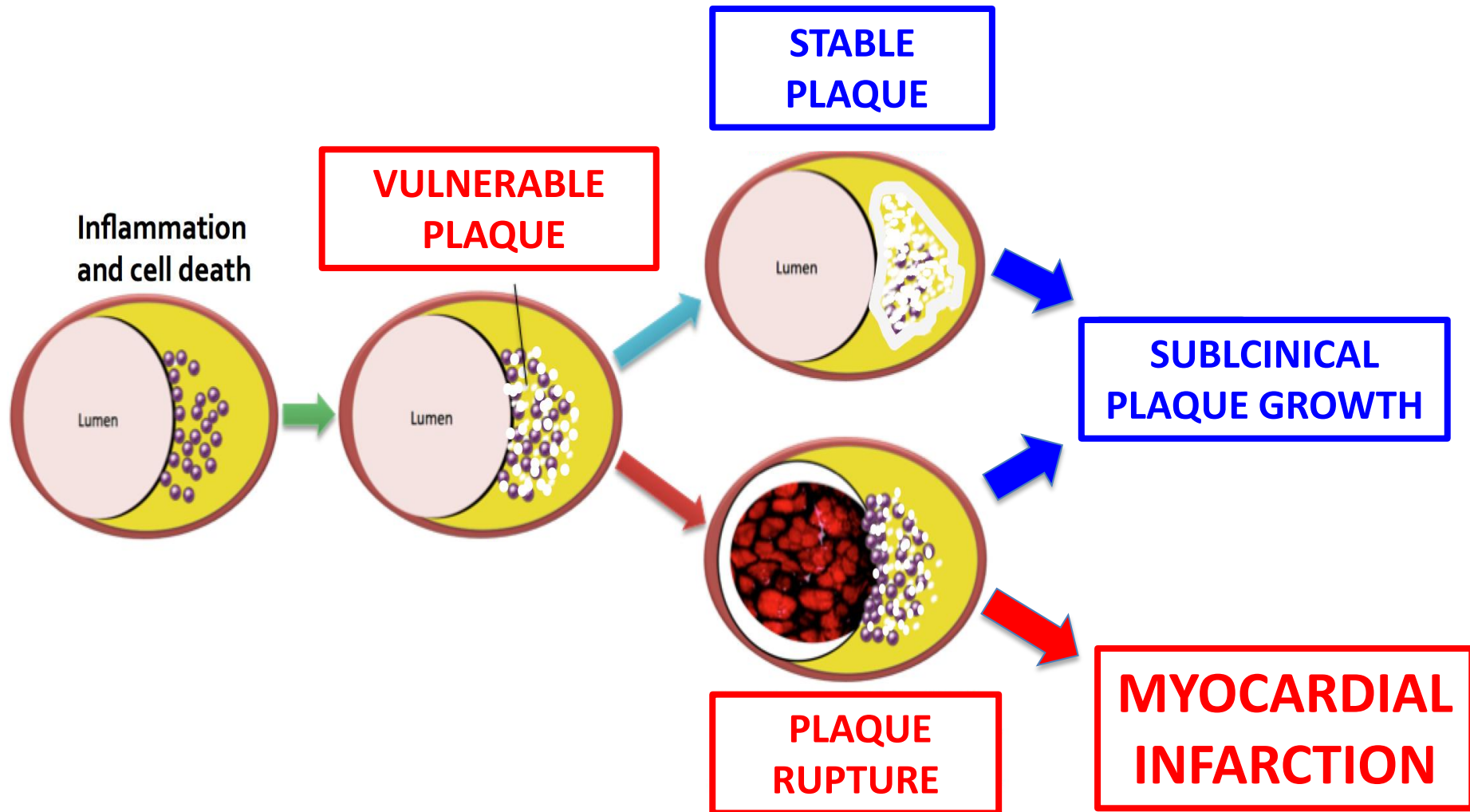


Major Limitation of Vulnerable Plaque Strategy

- In retrospective studies vulnerable plaque consistently associated with rupture and MI
- However prospective studies suggest they are relatively common and go on to cause myocardial infarction in only a minority of cases



Why do Vulnerable Plaques Outnumber Cardiac Events?





Why do Vulnerable Plaques Outnumber Cardiac Events?

1) Vulnerable plaques heal and stabilise

2) Even if they do rupture most plaque rupture events are sub-clinical





The Myth of the Vulnerable Plaque?

- If the majority of vulnerable plaques do not themselves go on to cause events how can we justify going on to treat individual lesions?
- We should focus more on identifying the vulnerable patient.....



Identification of vulnerable plaque
may still be useful at the patient
level





Pan Coronary Vulnerability





Vulnerable Plaques to Identify Vulnerable Patients

- **Vulnerable plaques** do not exist in isolation.
- However patients with active disease tend to develop multiple high risk plaques, increasing that subject's probability of a clinical rupture event: the **vulnerable patient**





Methods for Detecting Vulnerable Plaque





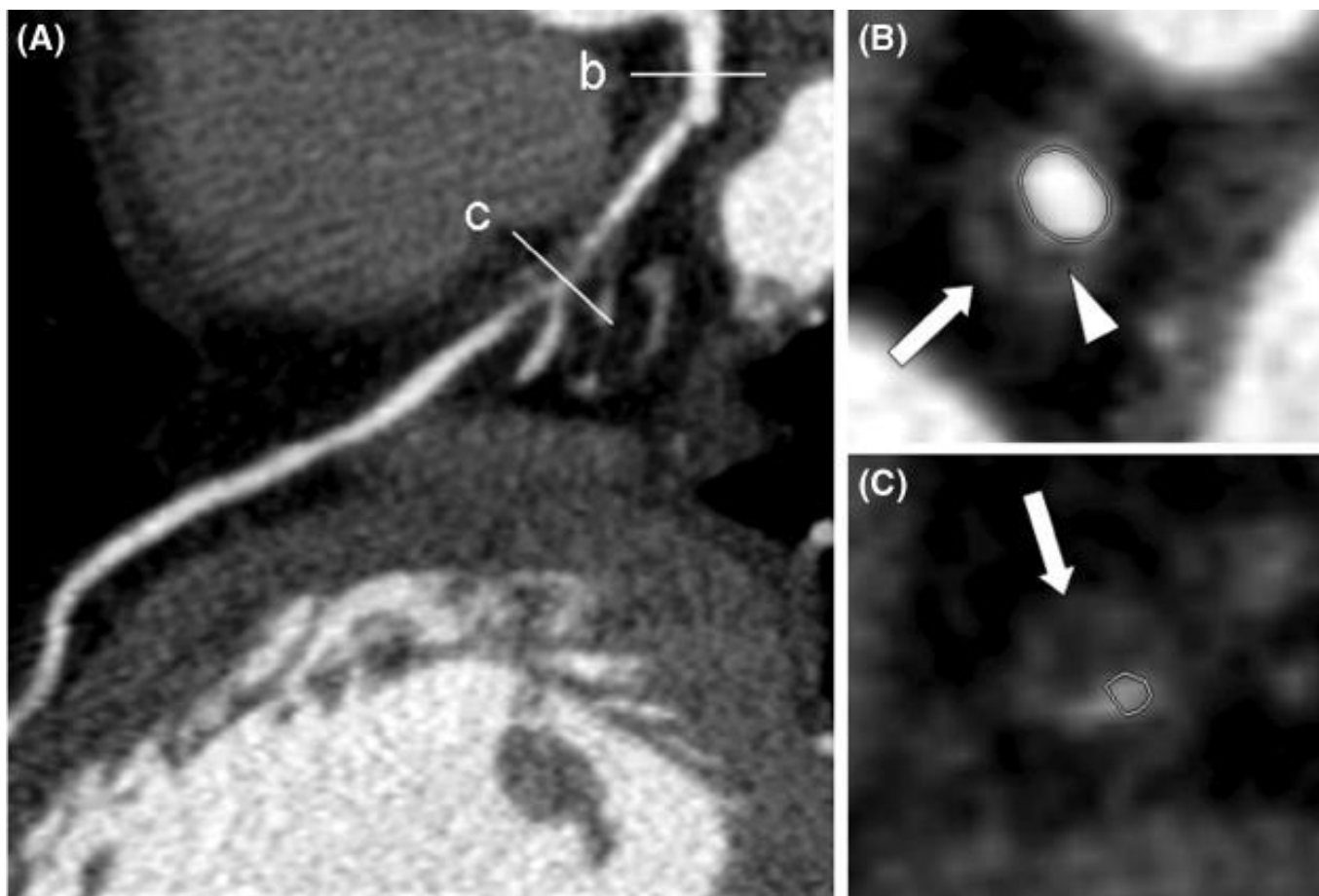
Imaging Methods to Identify Vulnerable Plaque

- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Positron Emission Tomography (PET)





Vulnerable Plaques on CT

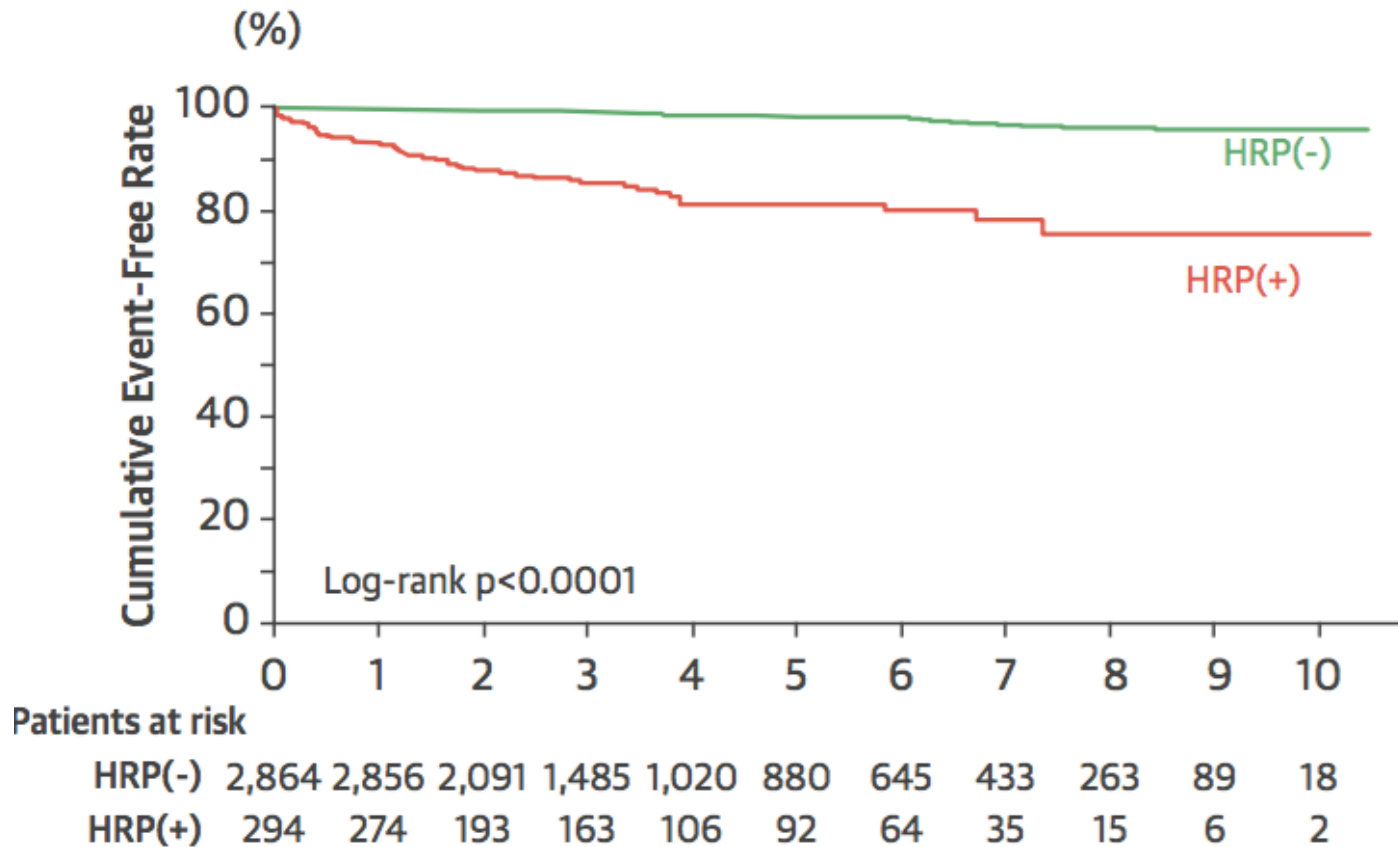


Positive remodelling and low attenuation plaque (necrotic core)



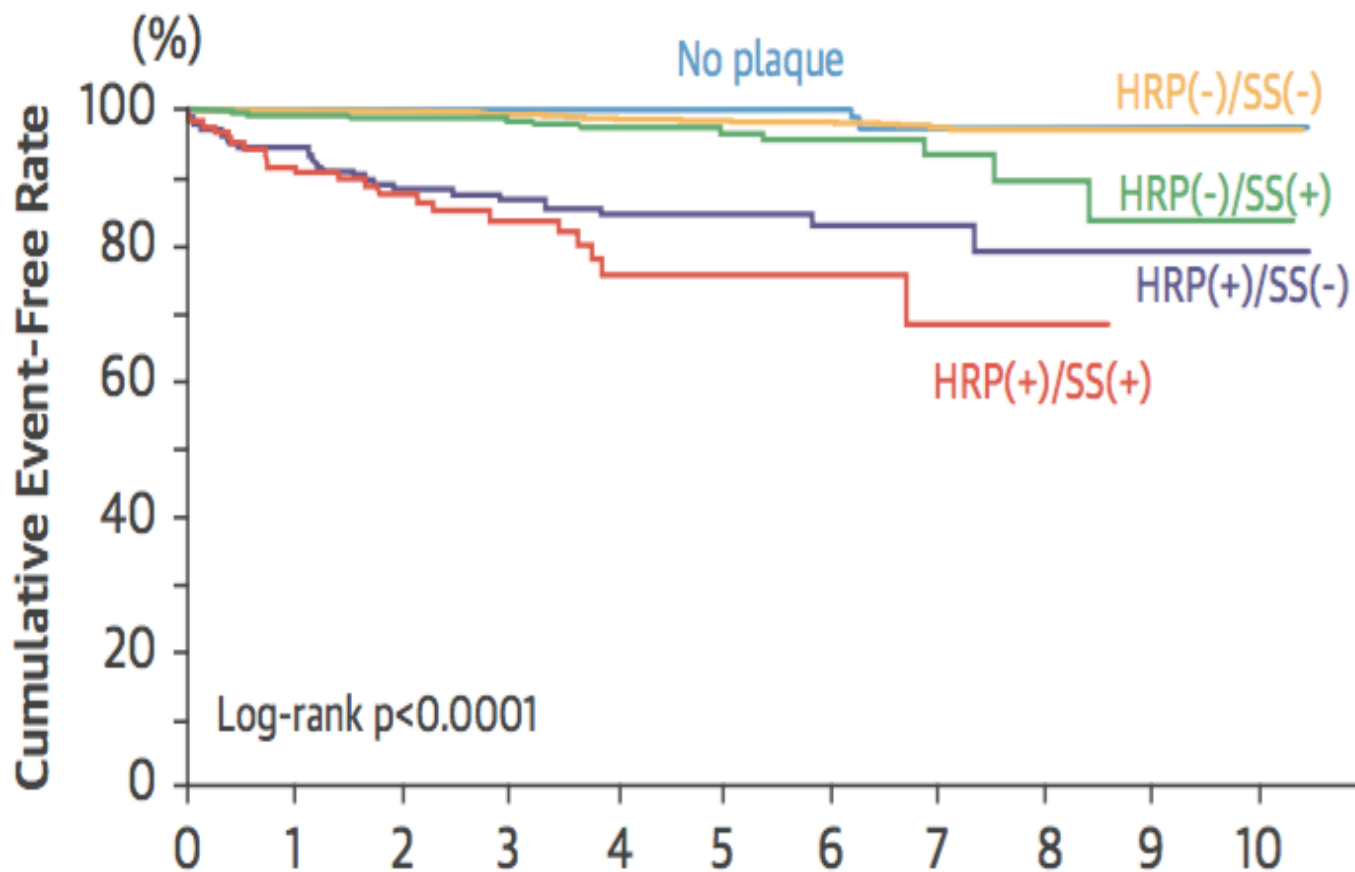
CT Vulnerable Plaques Identify High Risk Patients

N=3158 patients: 294 had high risk plaques ACS 16% patients (n=48)
 2864 did not ACS 1.4% (N=40)



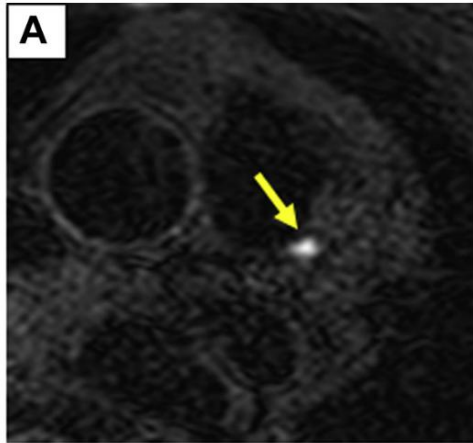


CT Vulnerable Plaques Identify High Risk Patients

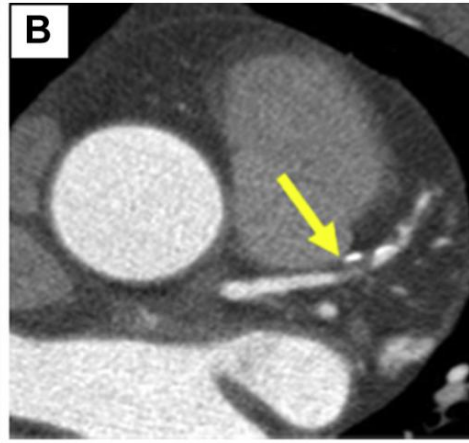




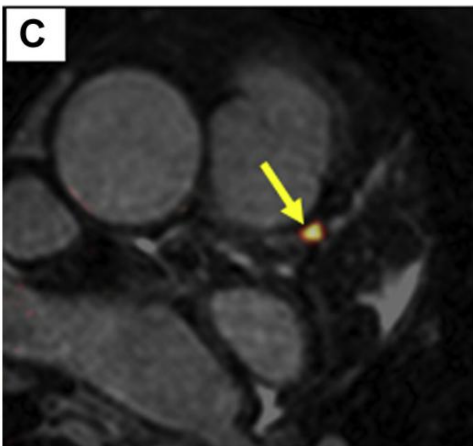
Vulnerable Plaques on MRI



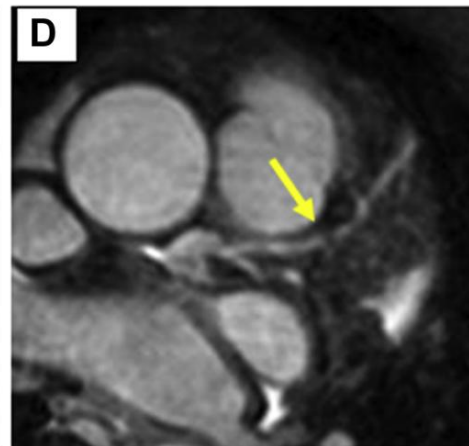
Non-contrast T1WI



CTA

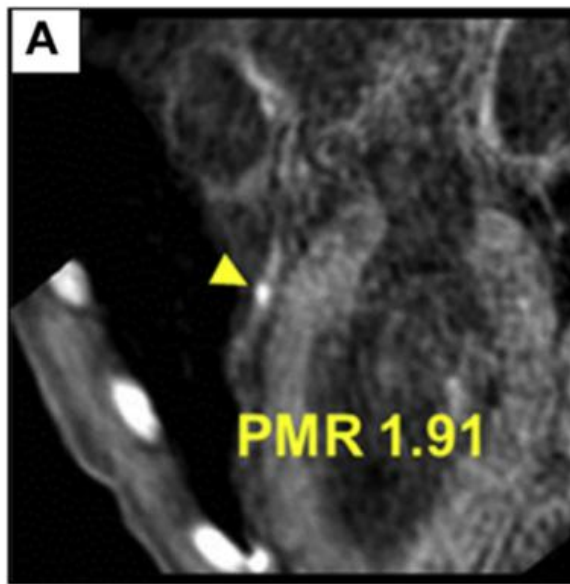


Co-registration image

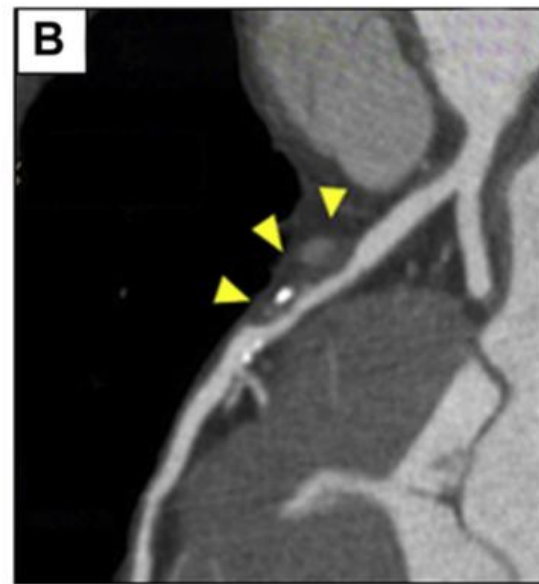


MRA

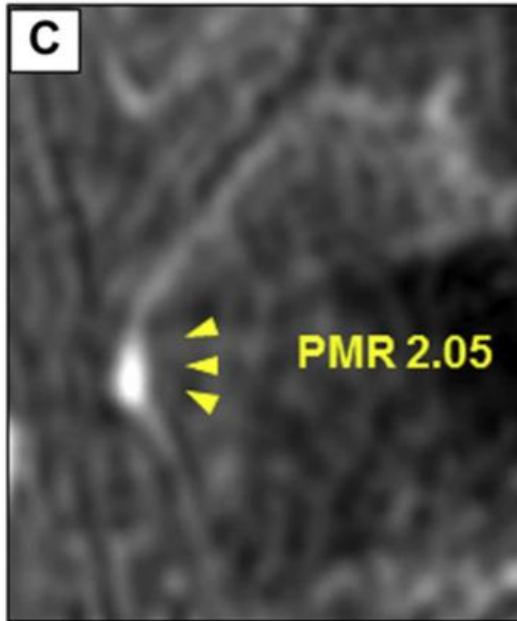
- T1-weighted MRI
- High signal due to methaemoglobin
- Marker of acute luminal thrombus or intraplaque haemorrhage



Non-contrast T1WI



CTA



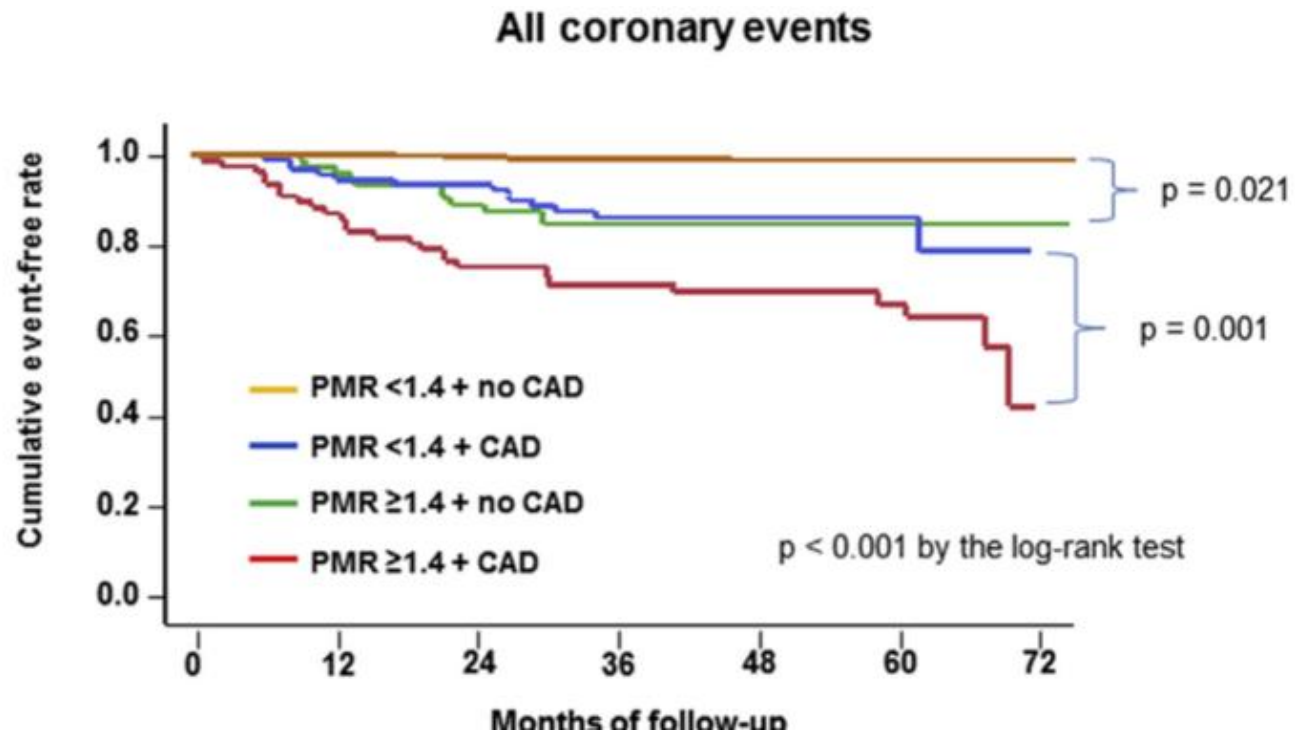
Non-contrast T1WI



CTA



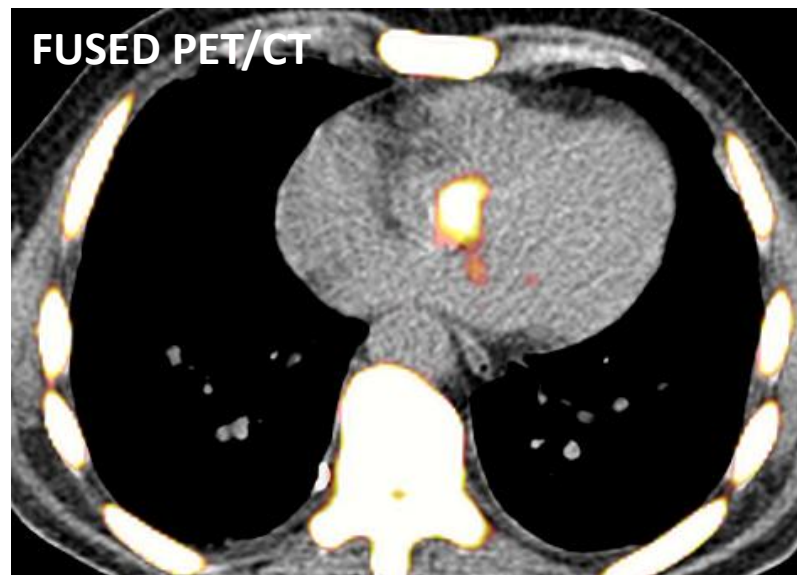
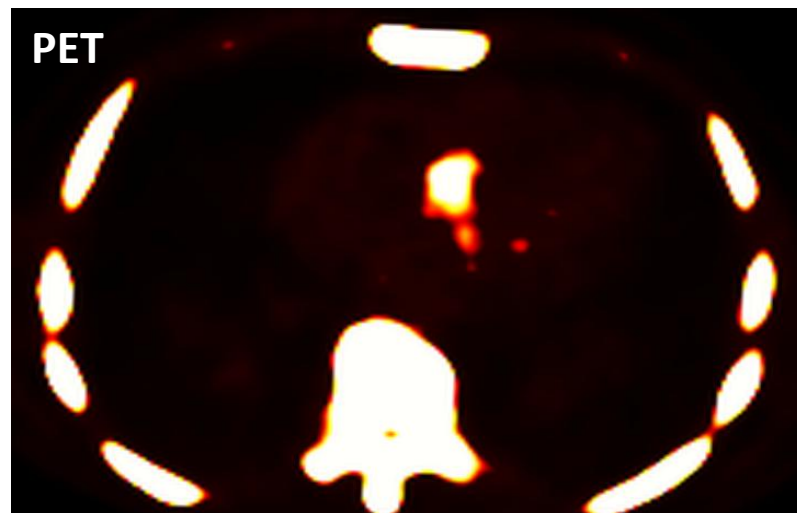
MRI Vulnerable Plaque Identify High Risk Patients



- Single Centre study of 568 patients
- 55 patients had high intensity plaque
- Patients with these plaques had a 9-fold increased risk of future coronary events (HR: 8.93; 95% CI: 3.23 to 24.7; p < 0.001)



Positron Emission Tomography





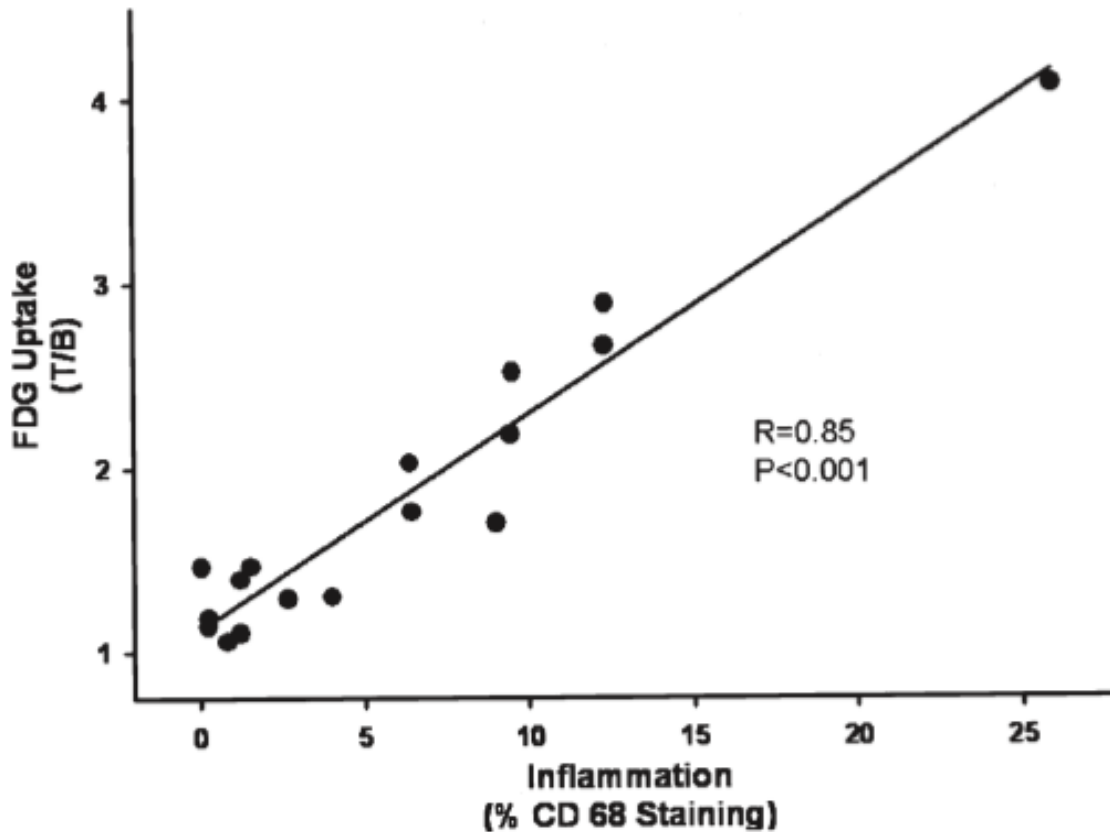
18F-FDG

Glucose analogue

Marker of vascular inflammation



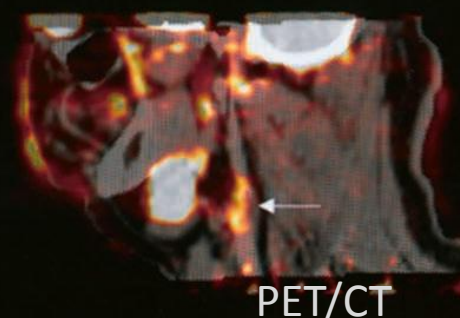
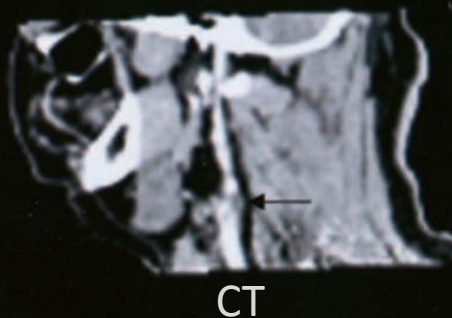
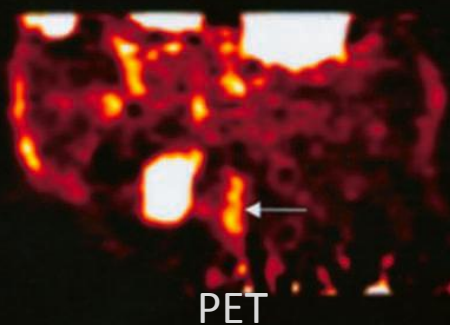
FDG Uptake Reflects Macrophage Infiltration In Carotid Atheroma



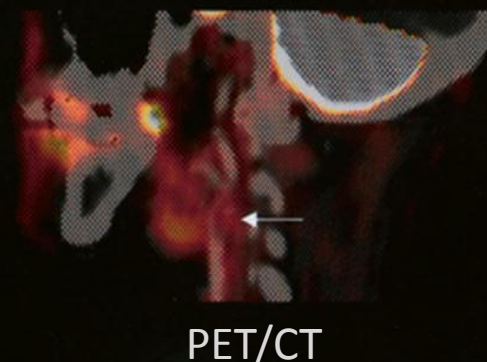
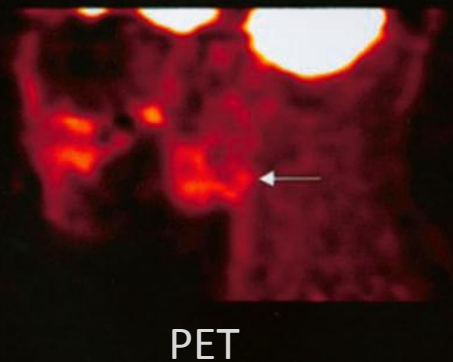


^{18}F Fluoro-Deoxy Glucose *Atherosclerosis*

Culprit Carotid Plaque Post Stroke /TIA



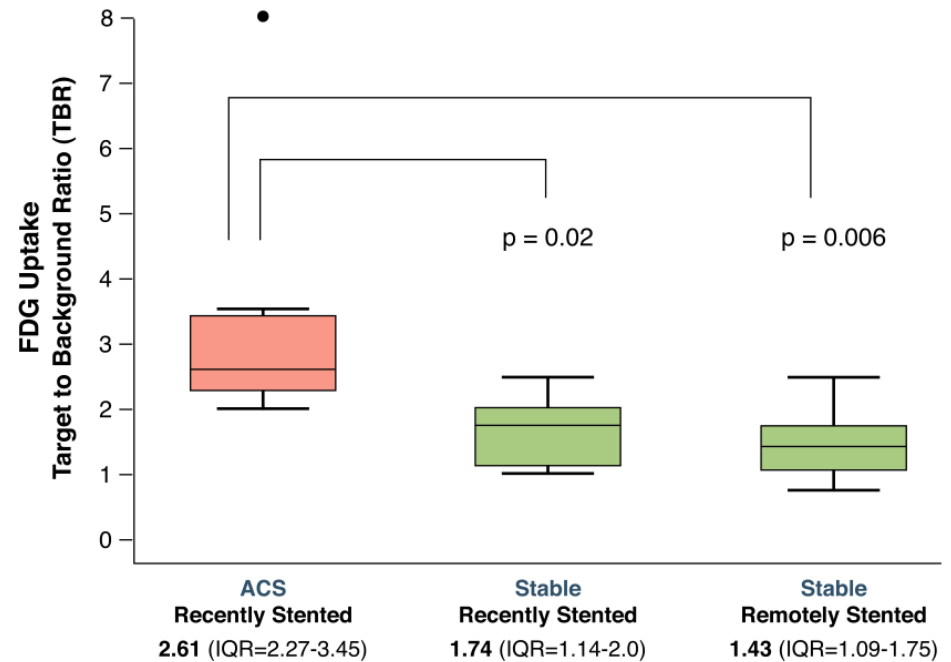
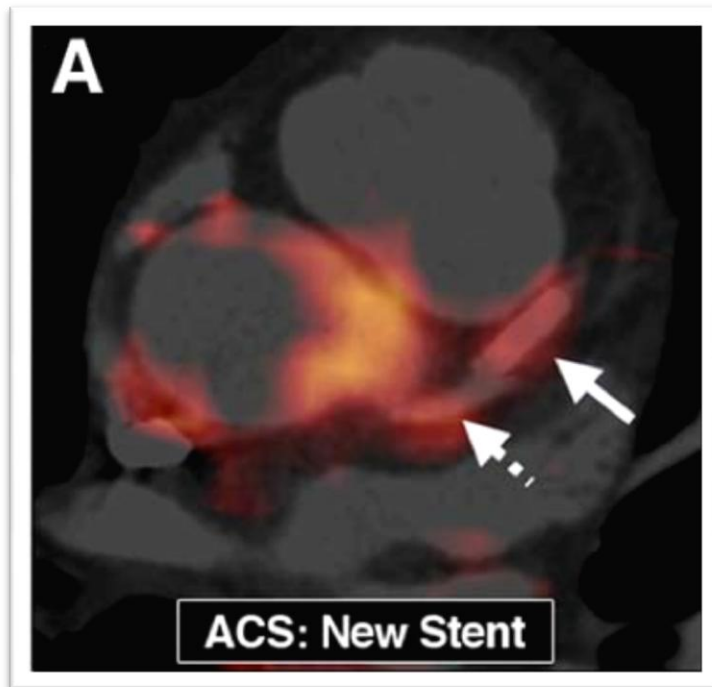
Contralateral Plaque





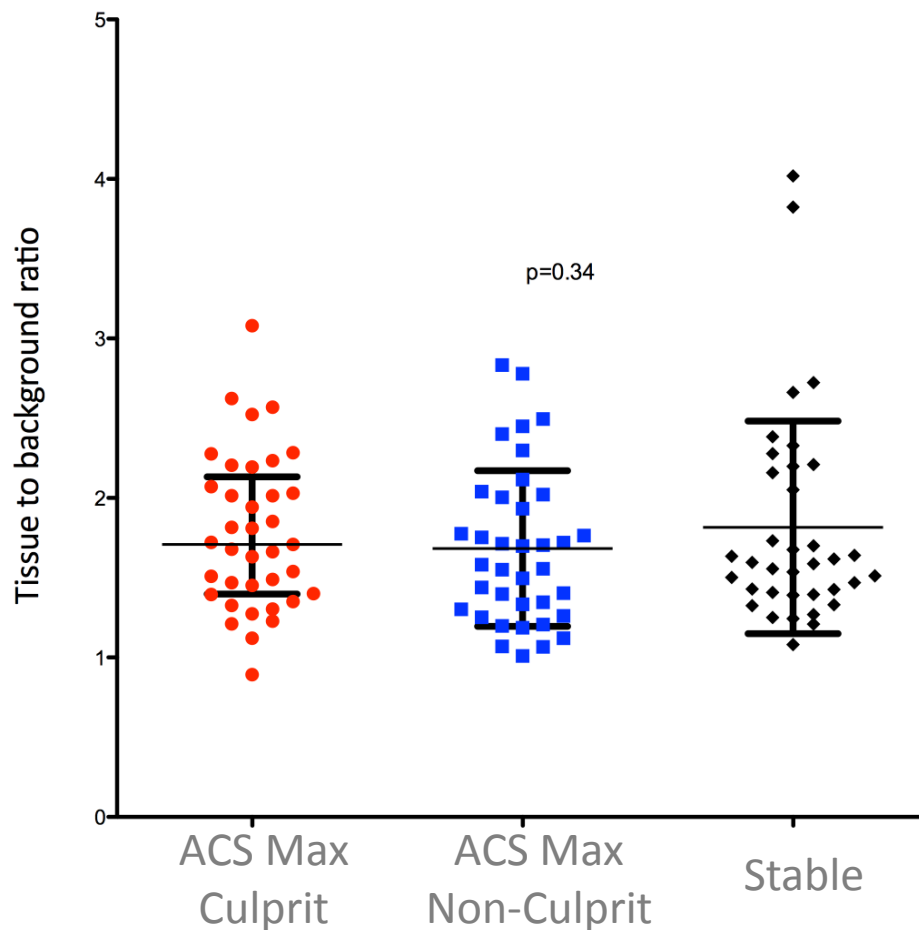
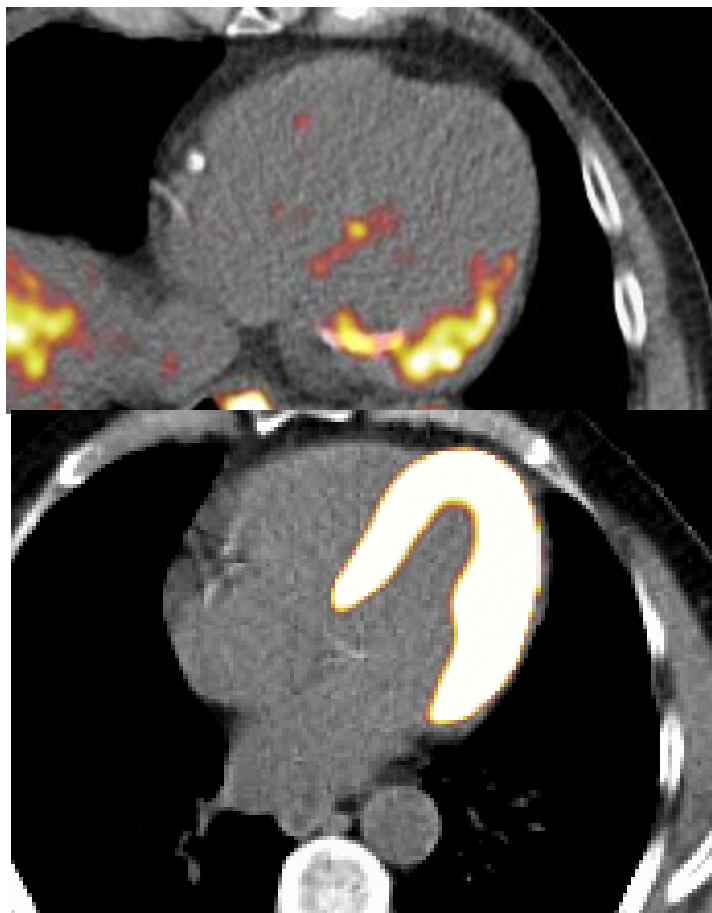
Feasibility of FDG Imaging of the Coronary Arteries

Comparison Between Acute Coronary Syndrome and Stable Angina





Measurement of Coronary 18F-FDG Activity was Difficult

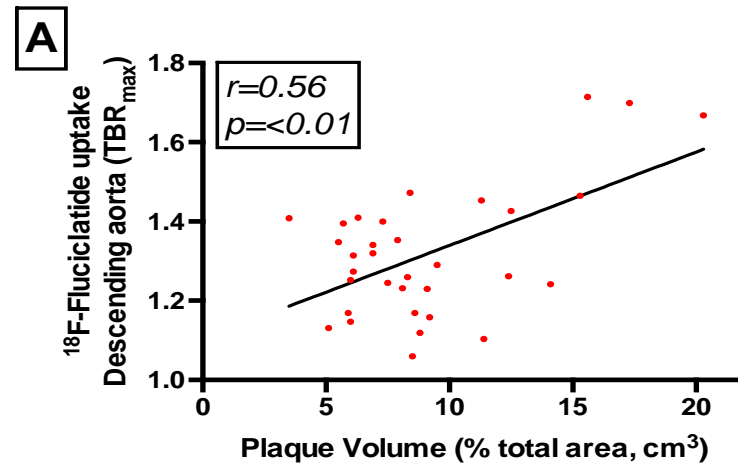
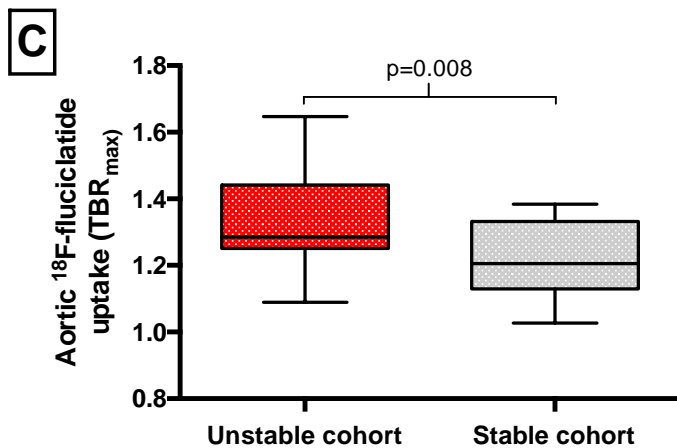
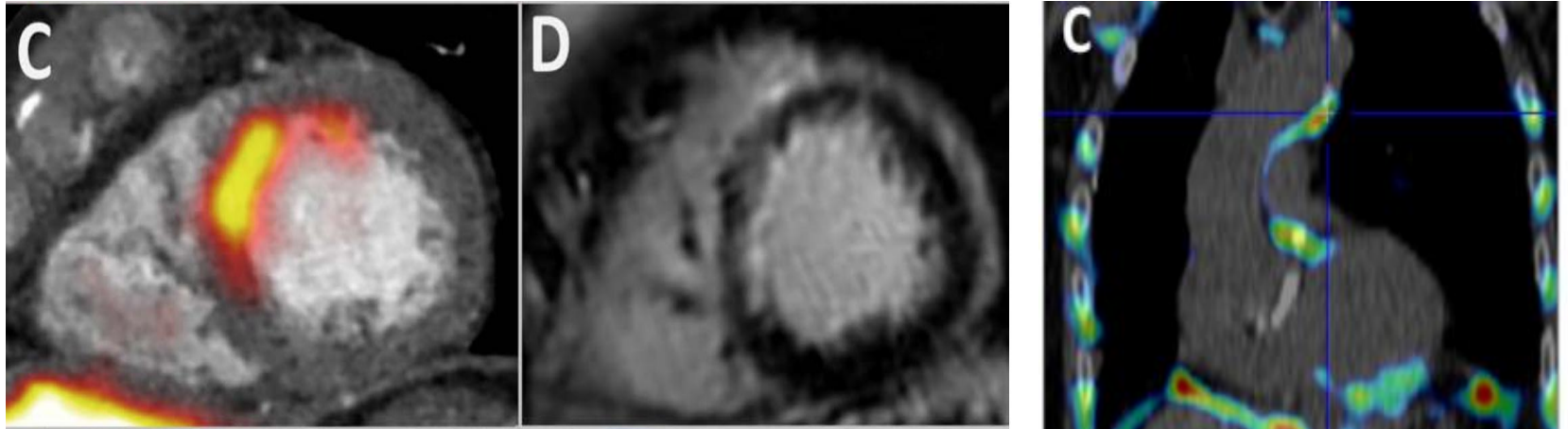


- Not possible in >50% of the coronary vessel territories examined
- No important differences observed between our populations



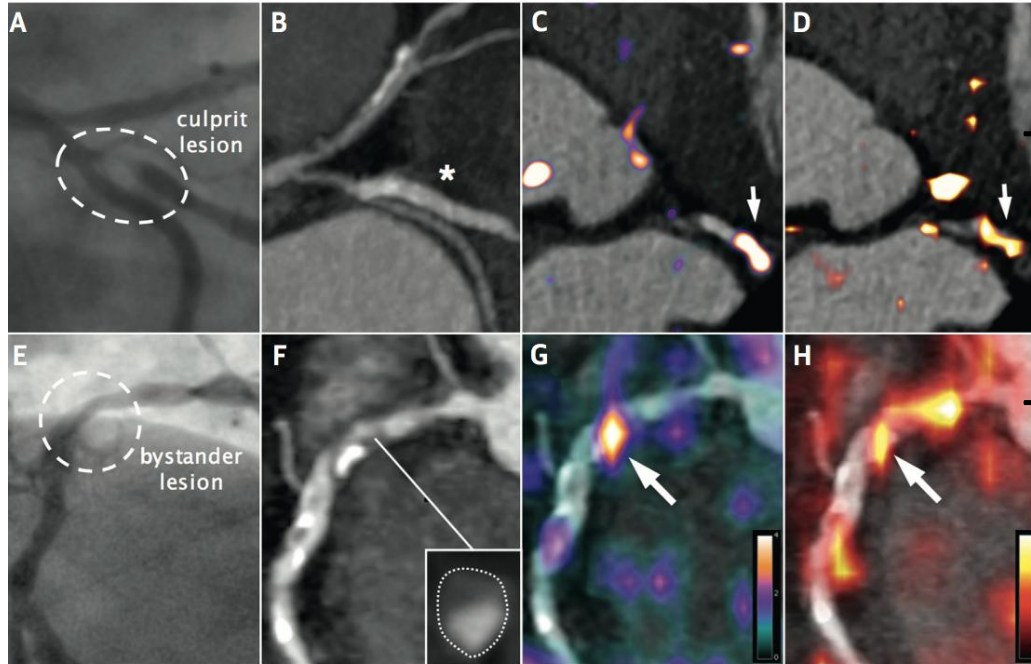
18F-Fluciclatide Angiogenesis

- RGD tracer targeting $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrin receptors



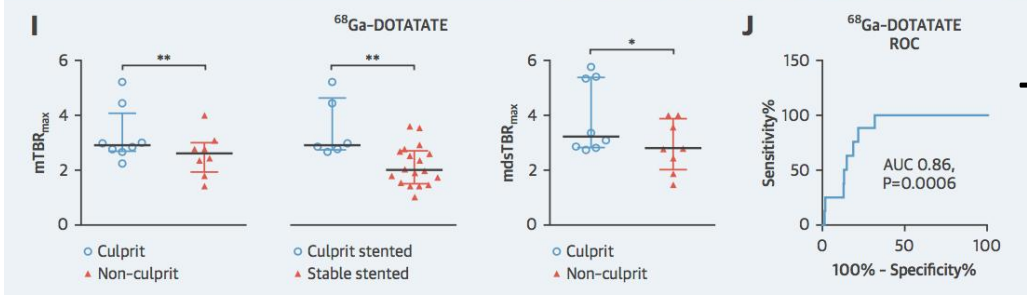


Coronary ^{68}Ga -Dotatate



Somatostatin receptor sub-type 2

Upregulated on the surface of activated macrophages



Localises to culprit and high-risk plaque



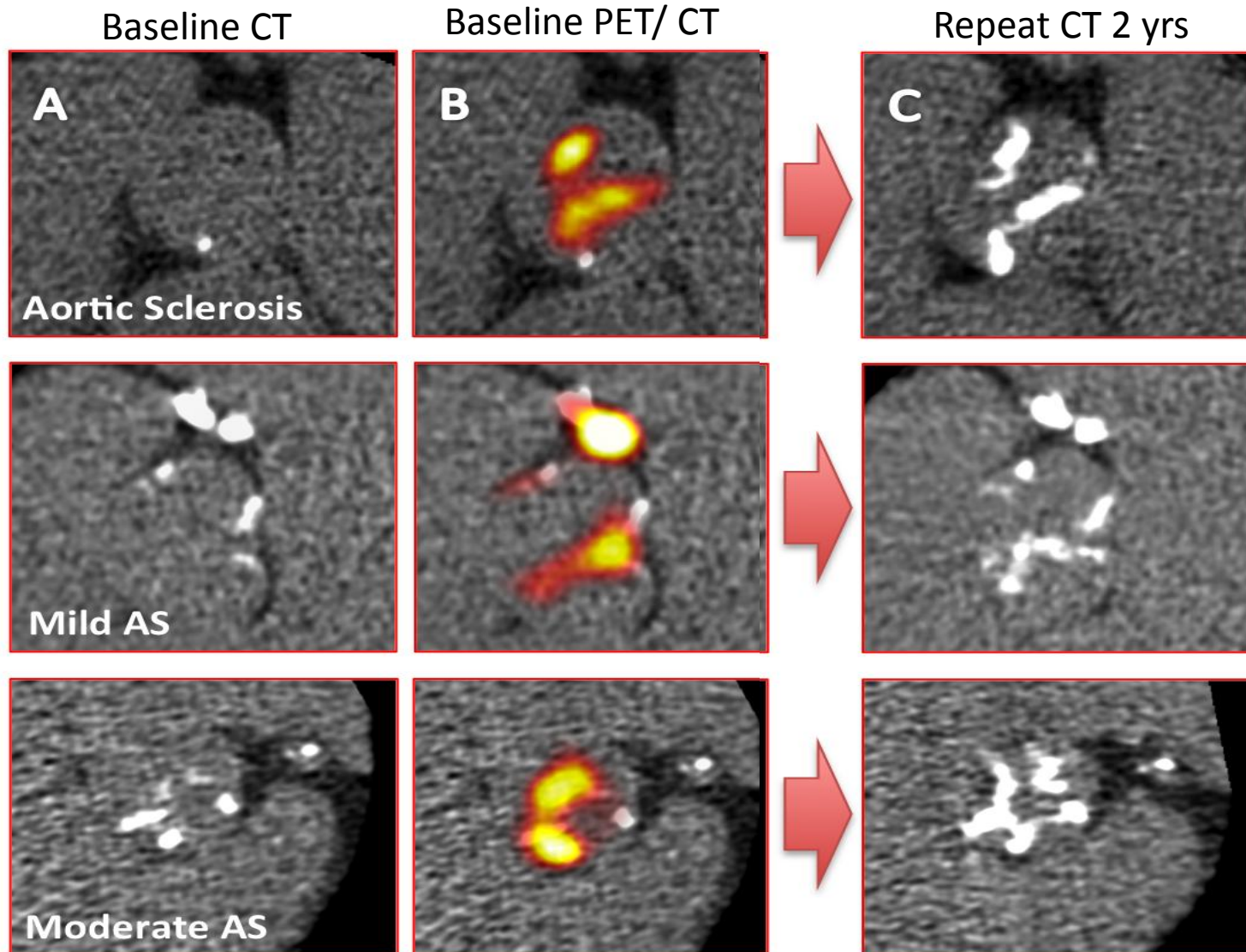
18F-Fluoride

Binds preferentially to newly developing microcalcification





^{18}F -Fluoride Predicts Where New Calcium Will Develop





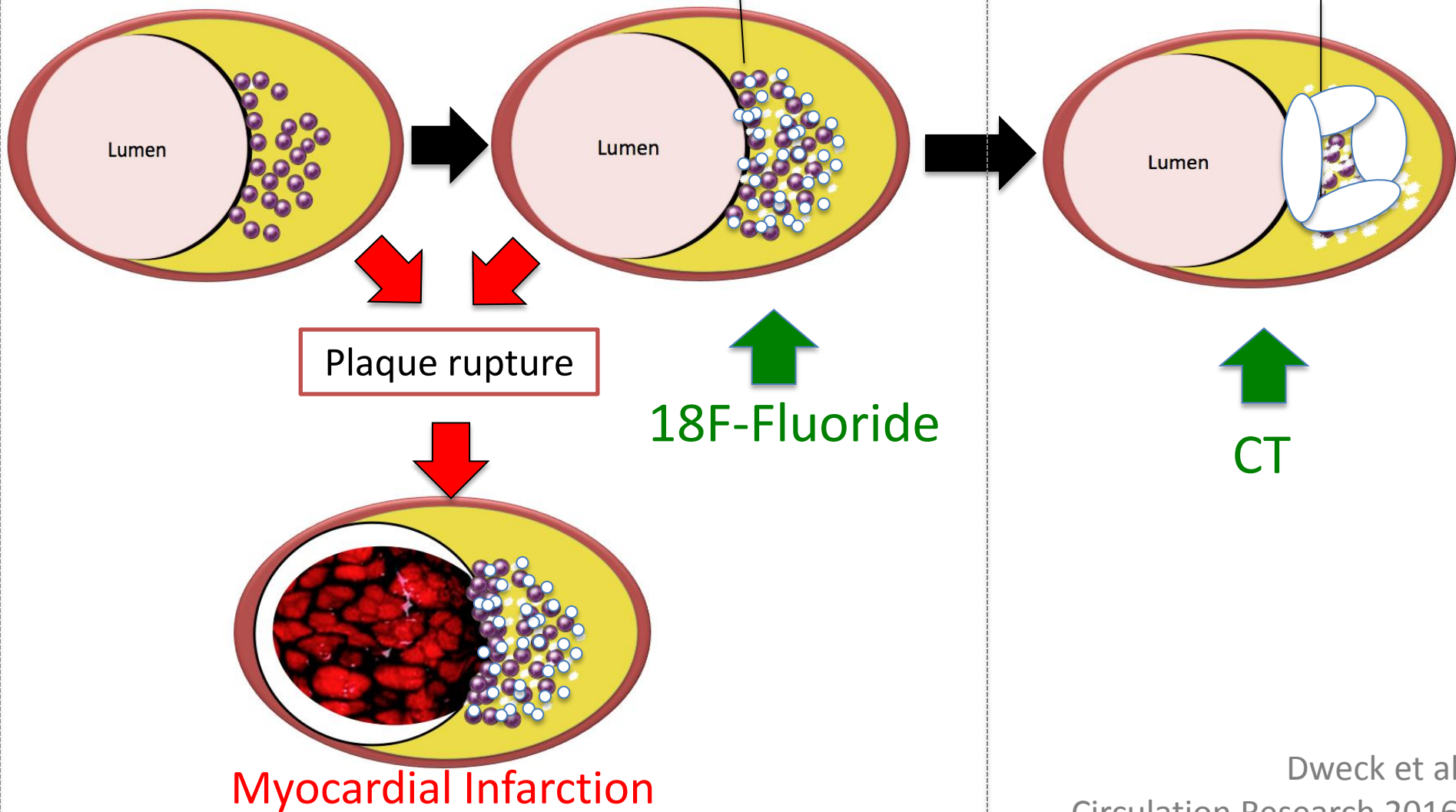
INFLAMMED HIGH RISK PLAQUE

STABILISED PLAQUE

Inflammation

Micro-calcification

Macro-calcification



18F-Fluoride & Coronary Artery Disease





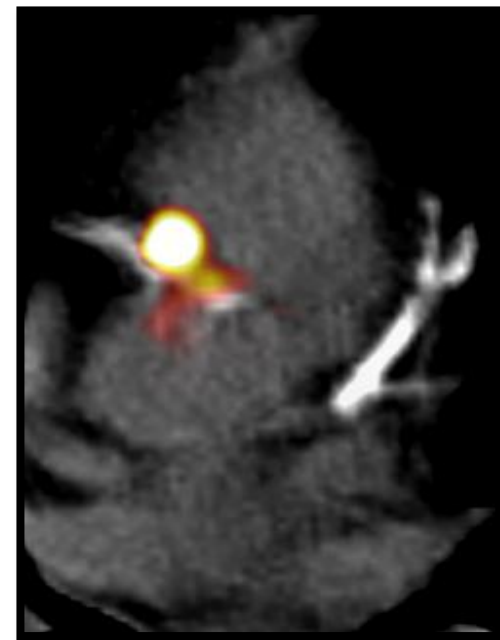
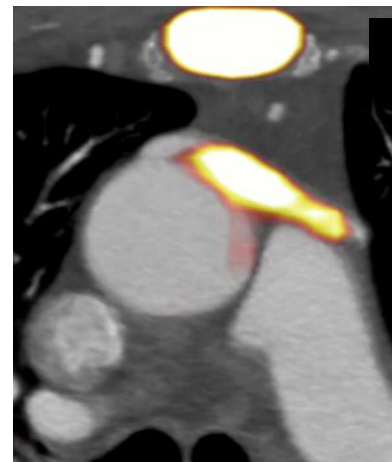
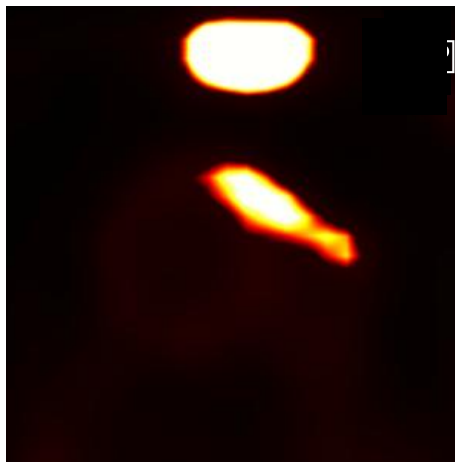
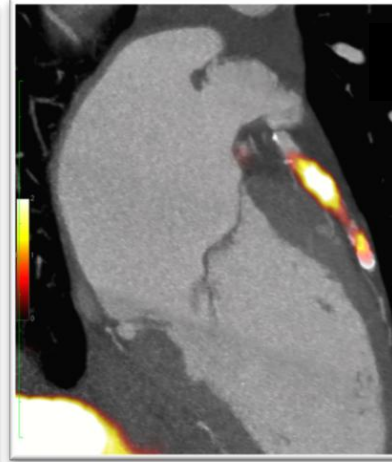
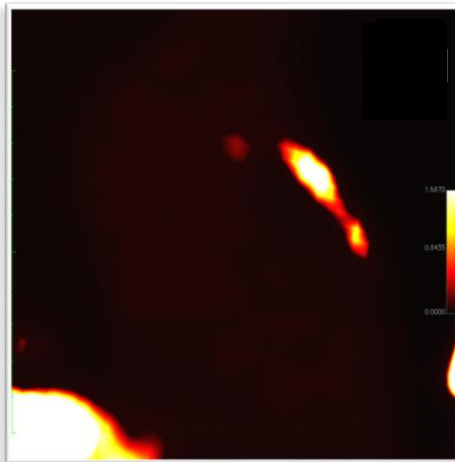
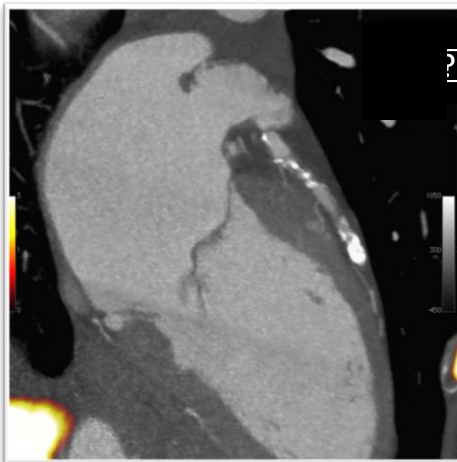
Different Information from CT

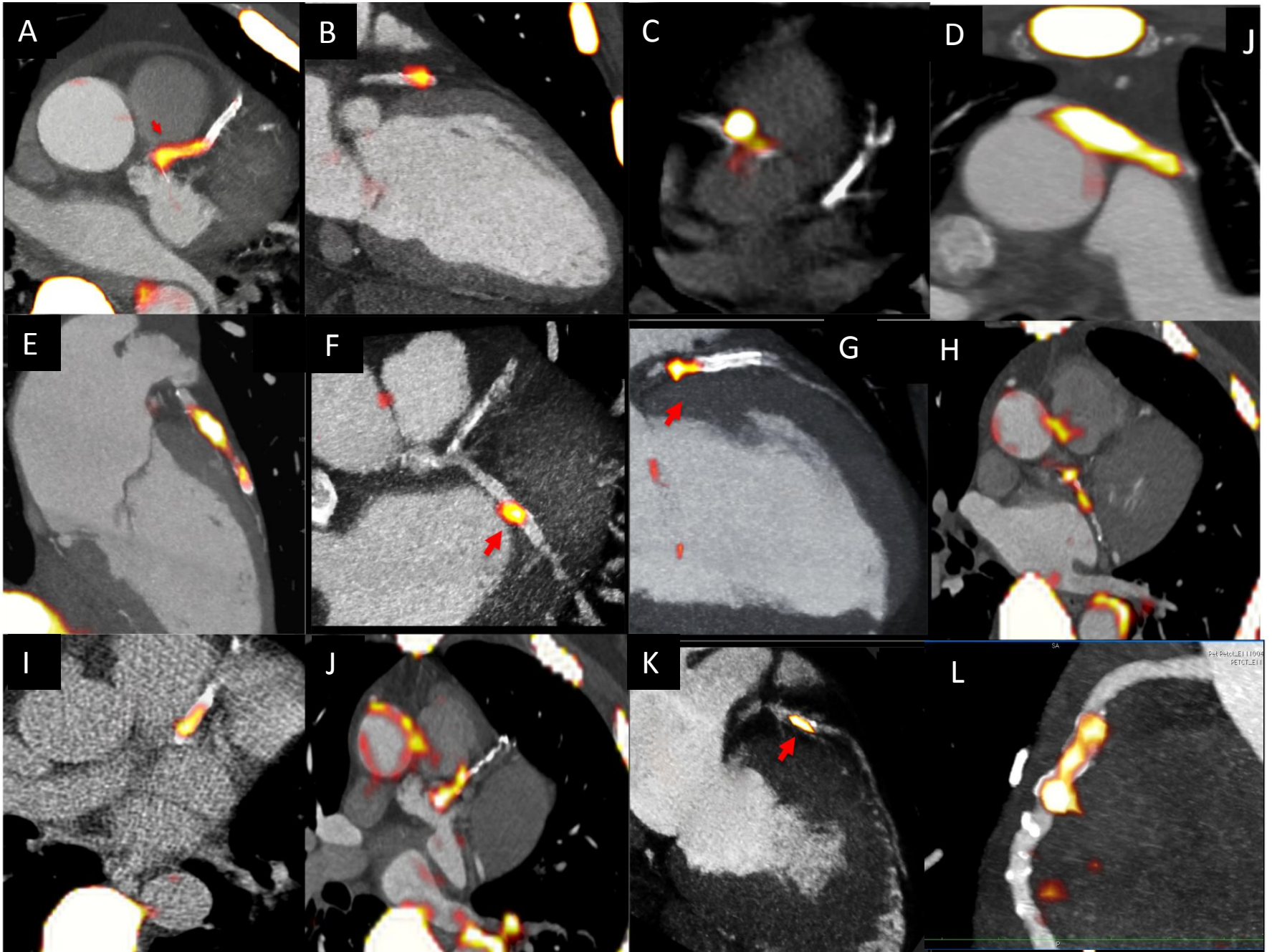
Computed Tomography

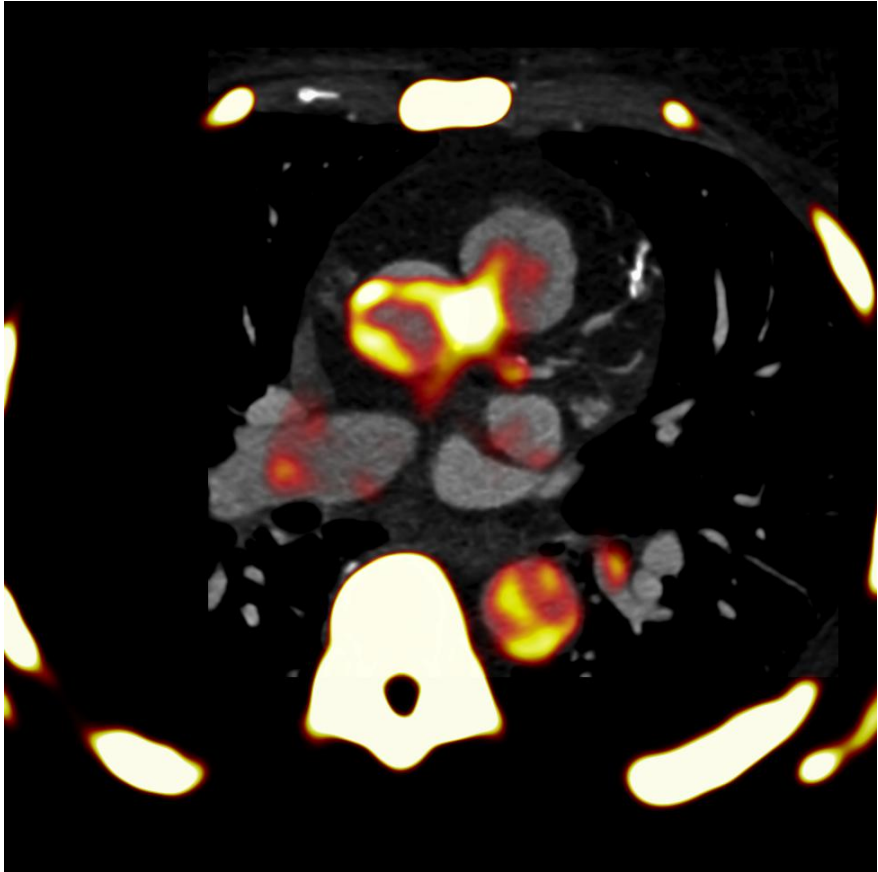
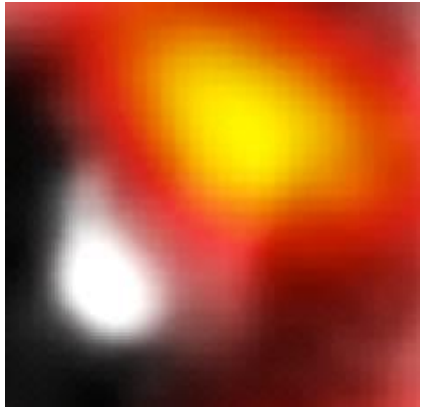
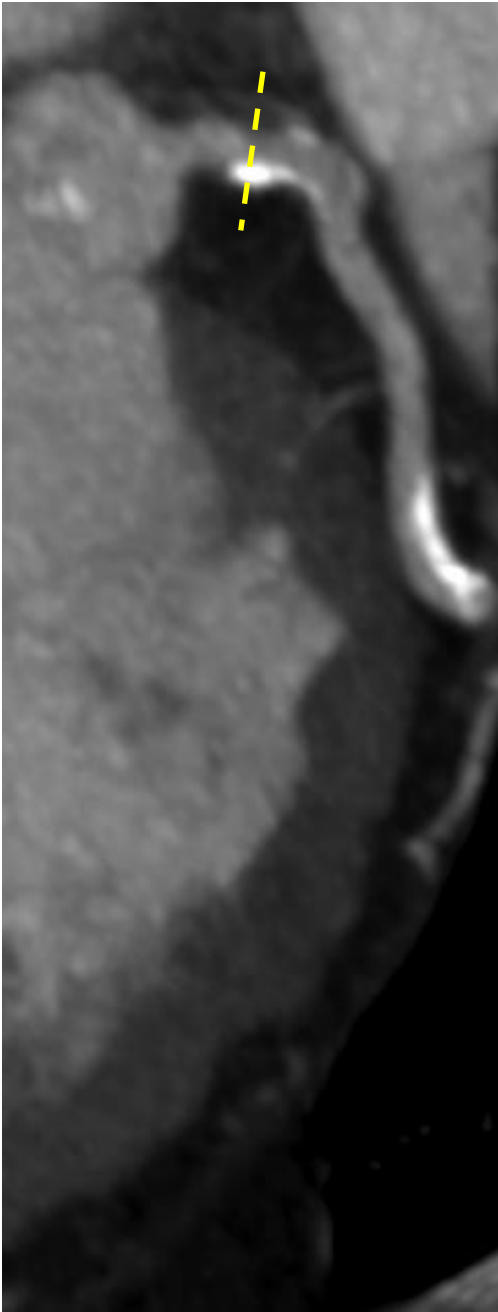
Positron Emission Tomography

Fused PET-CT

Fused PET-CT

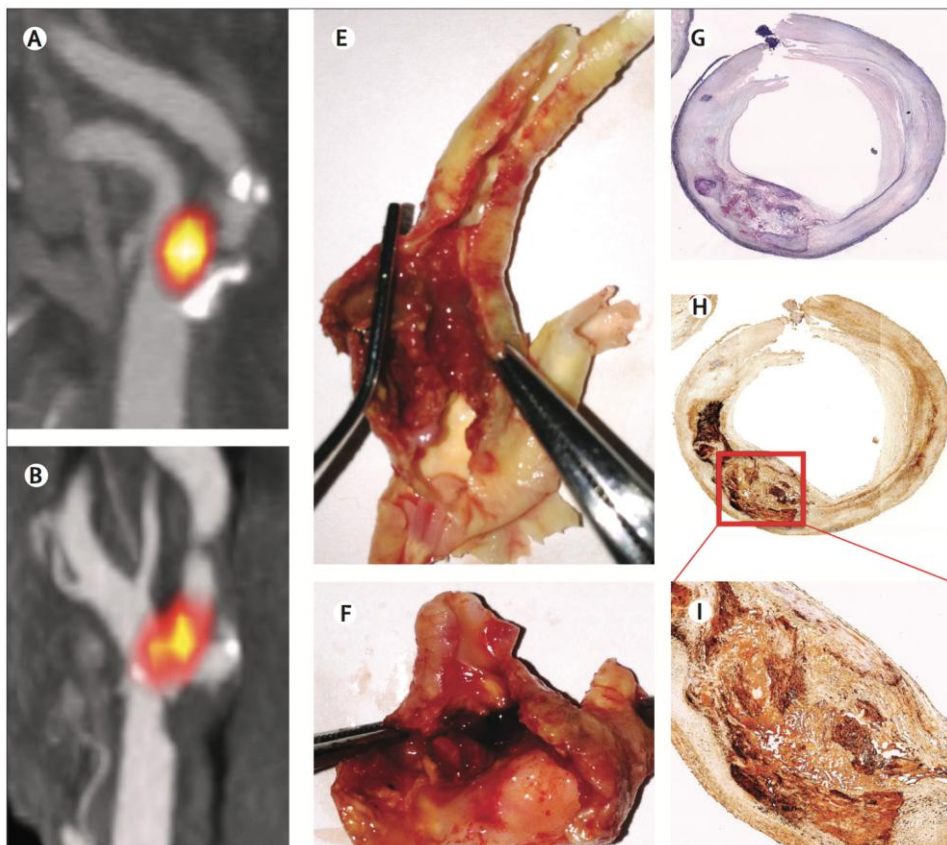




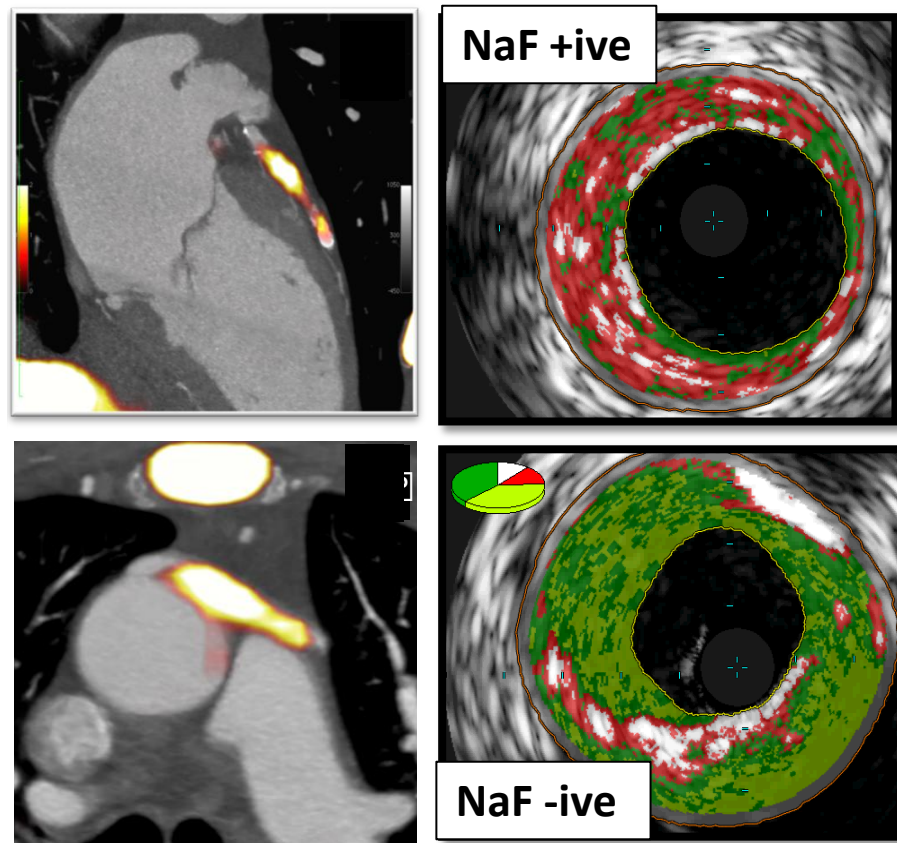


^{18}F -Fluoride vs. VH-IVUS & Histology

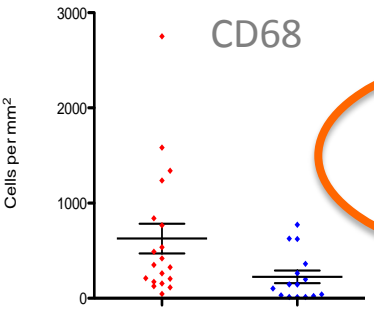
HISTOLOGY



VH-IVUS

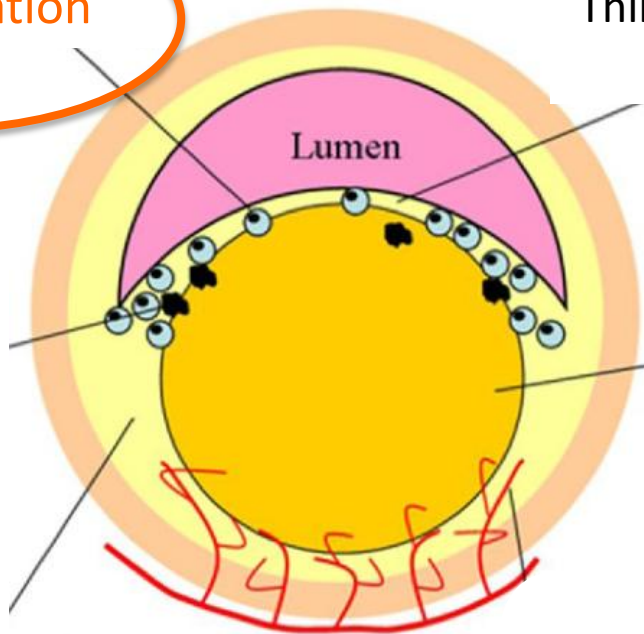


18F-Fluoride Identifies Adverse Plaques

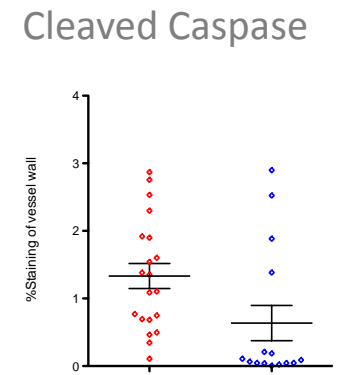


Inflammation

Micro Calcification



Large Necrotic Core



NaF Positive: 73%
NaF Negative: 21%
P<0.001

NaF Positive: 25% (21-29)
NaF Negative: 18% (14-22)
P<0.001

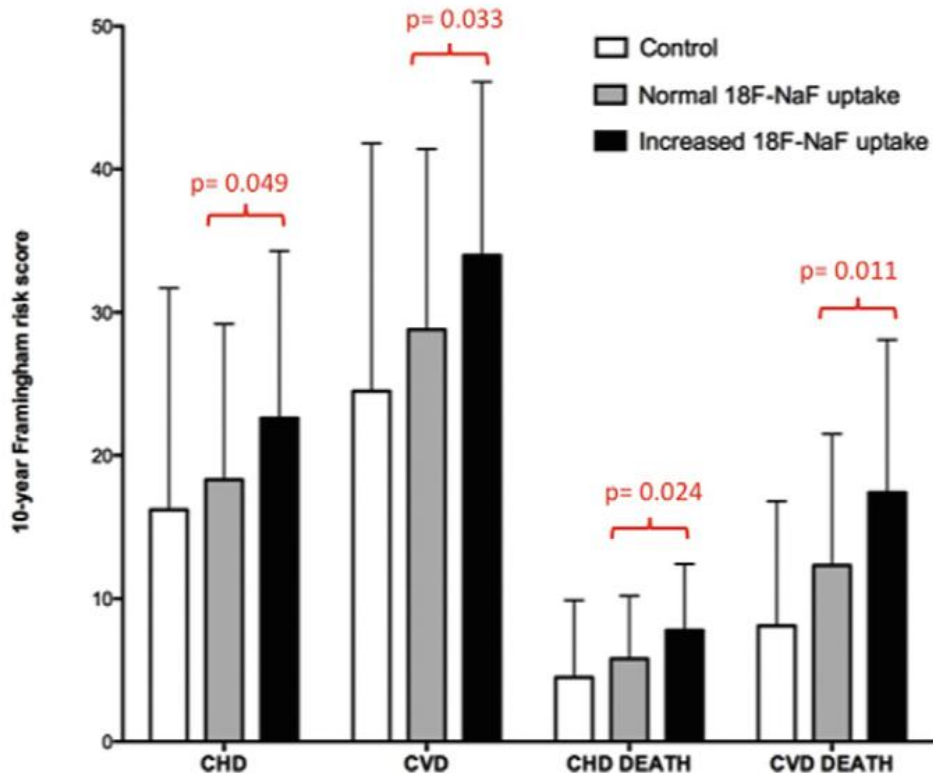
Positive Remodeling

	NaF Positive	NaF Negative	P-value
Minimal Luminal Area mm ² :	9 (6-14)	7 (5-10)	P<0.001
Plaque Area mm ² :	24(21-29)	14 (12-18)	



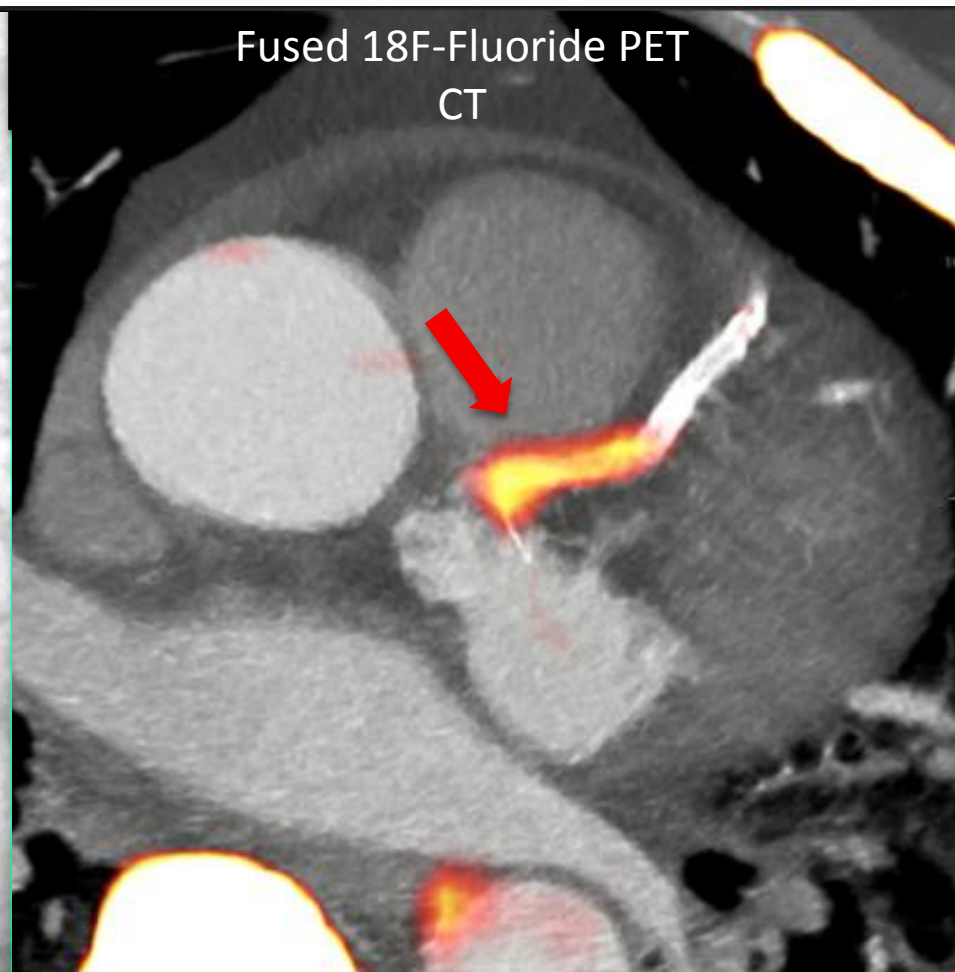
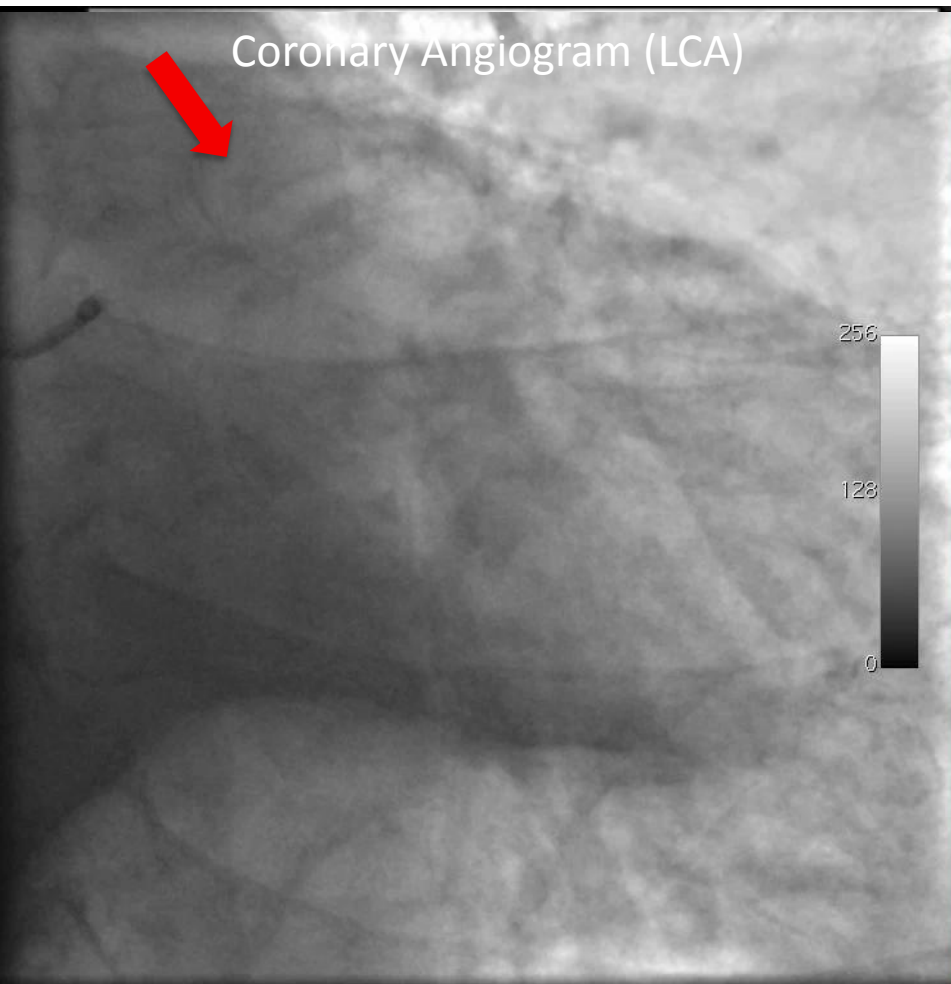
Identifies High Risk Patients

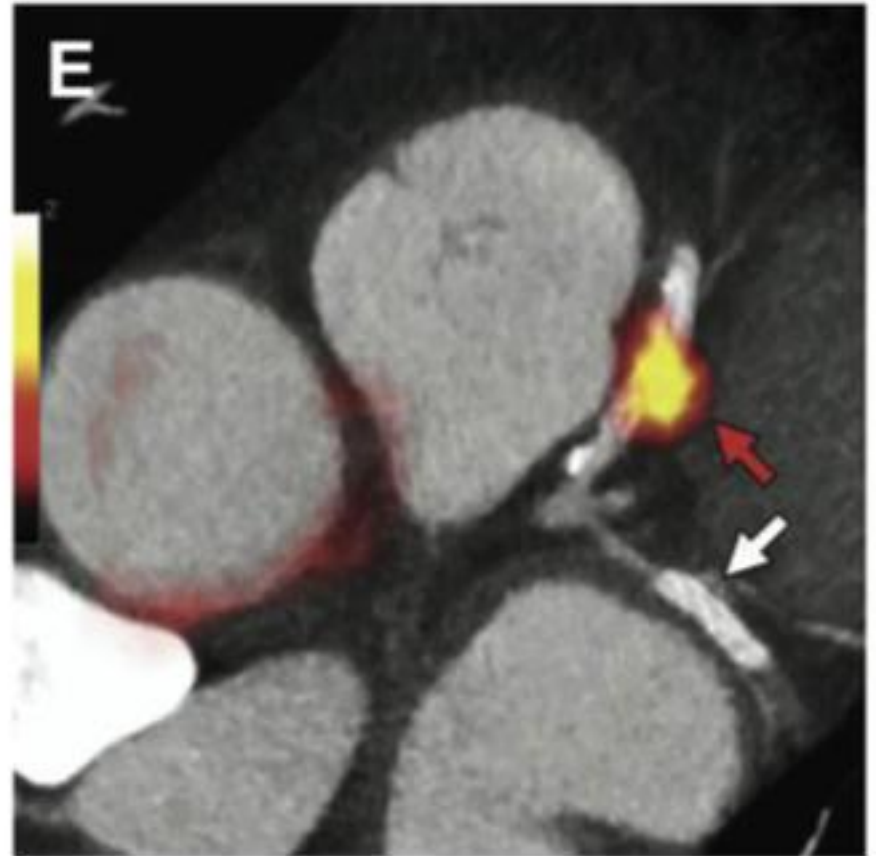
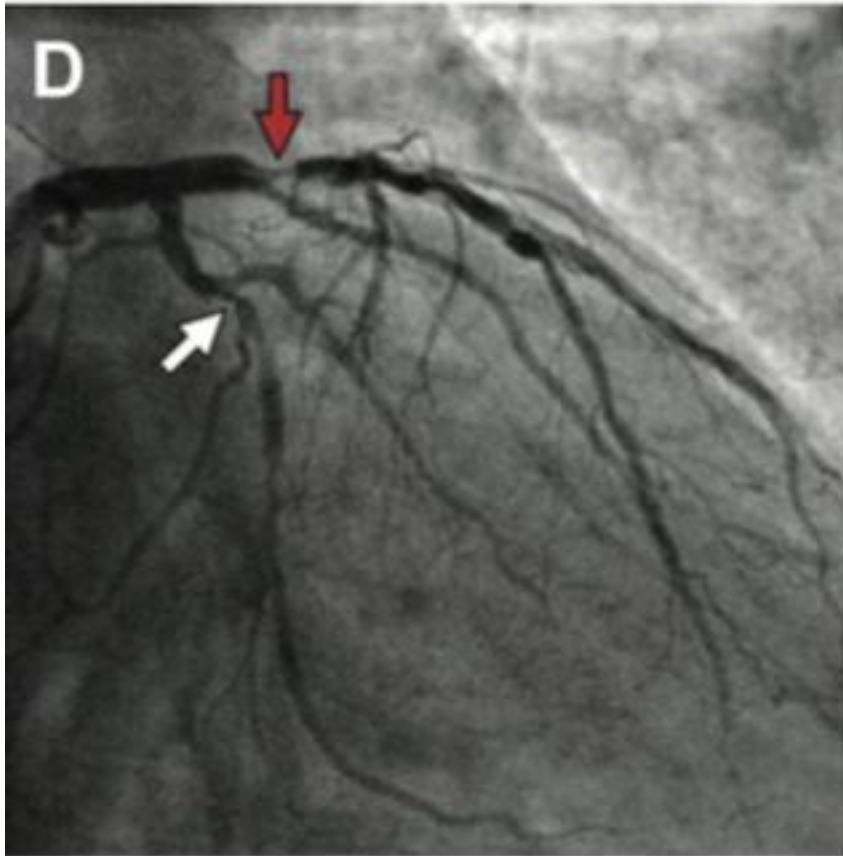
Framingham Risk Scores

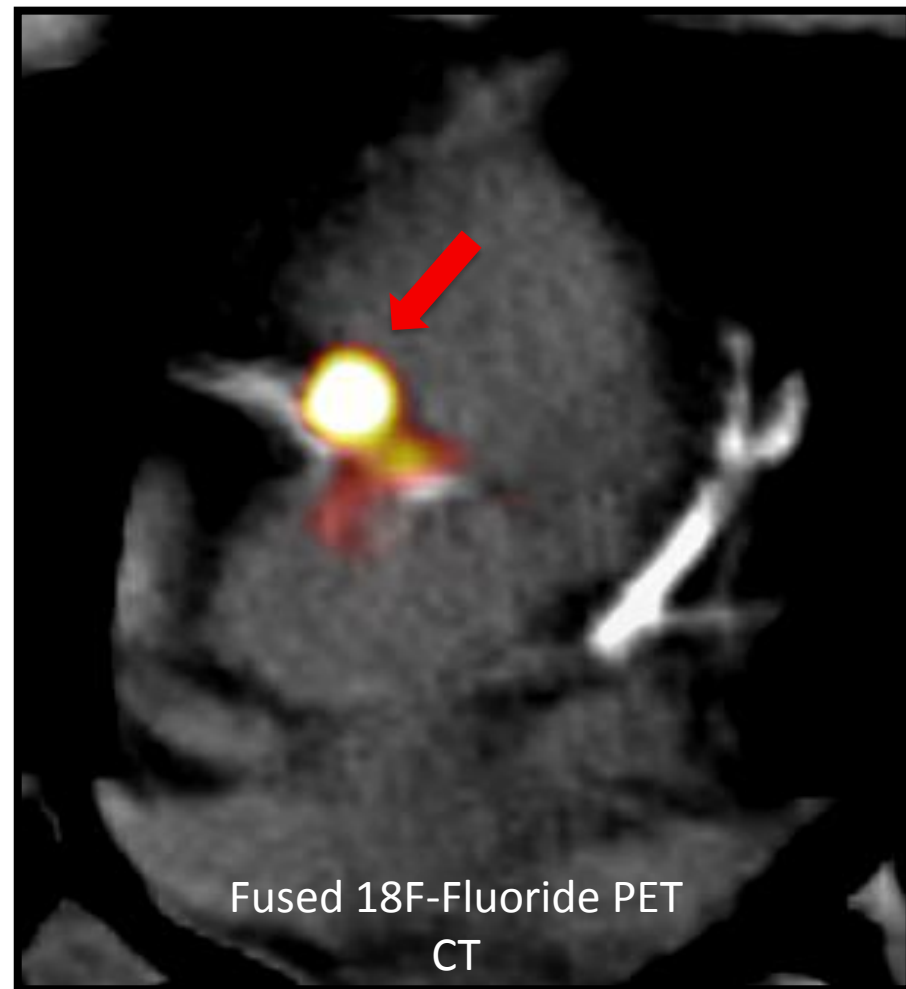
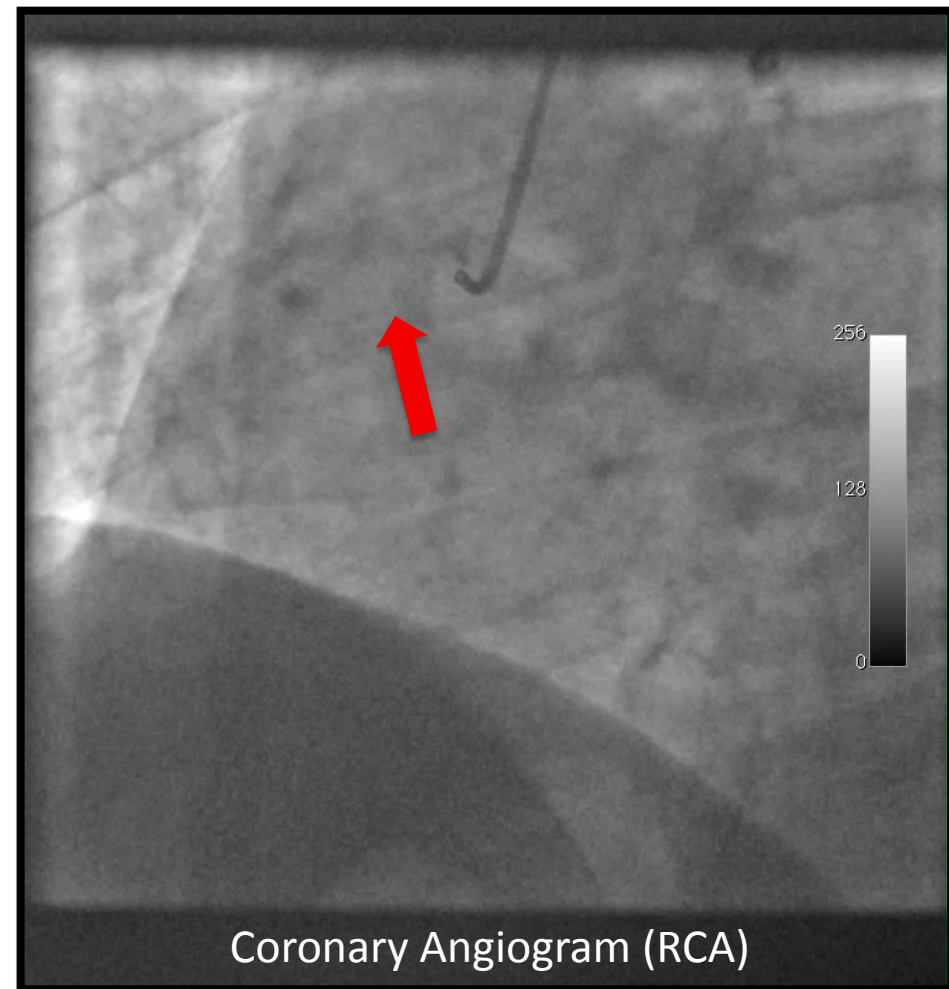




18F-Fluoride post STEMI

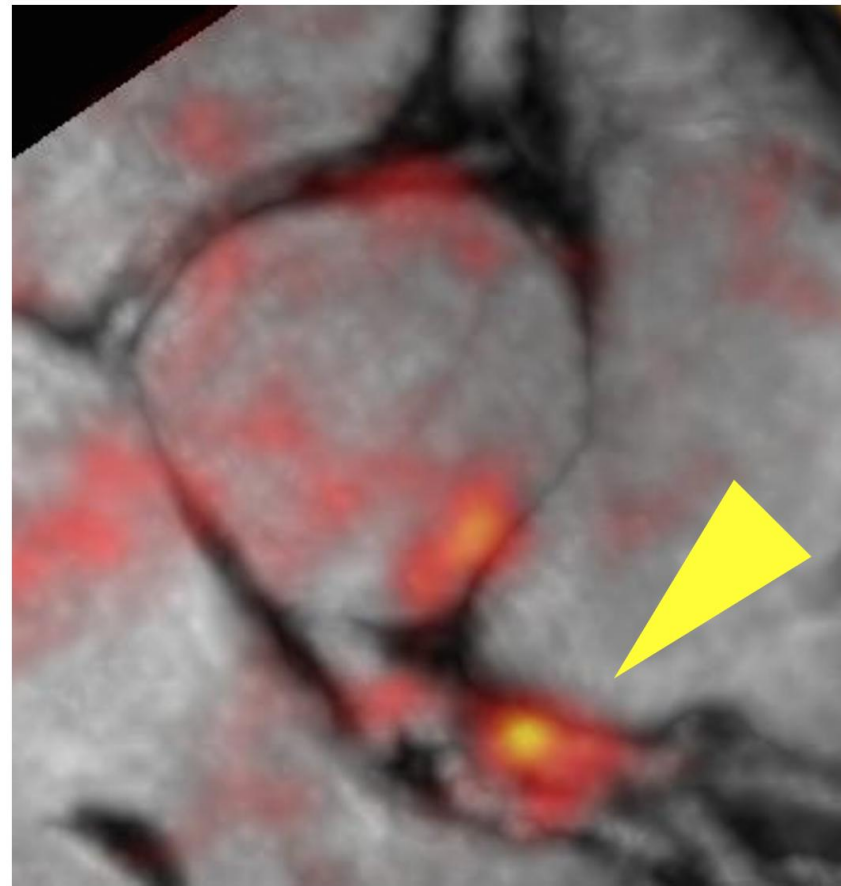




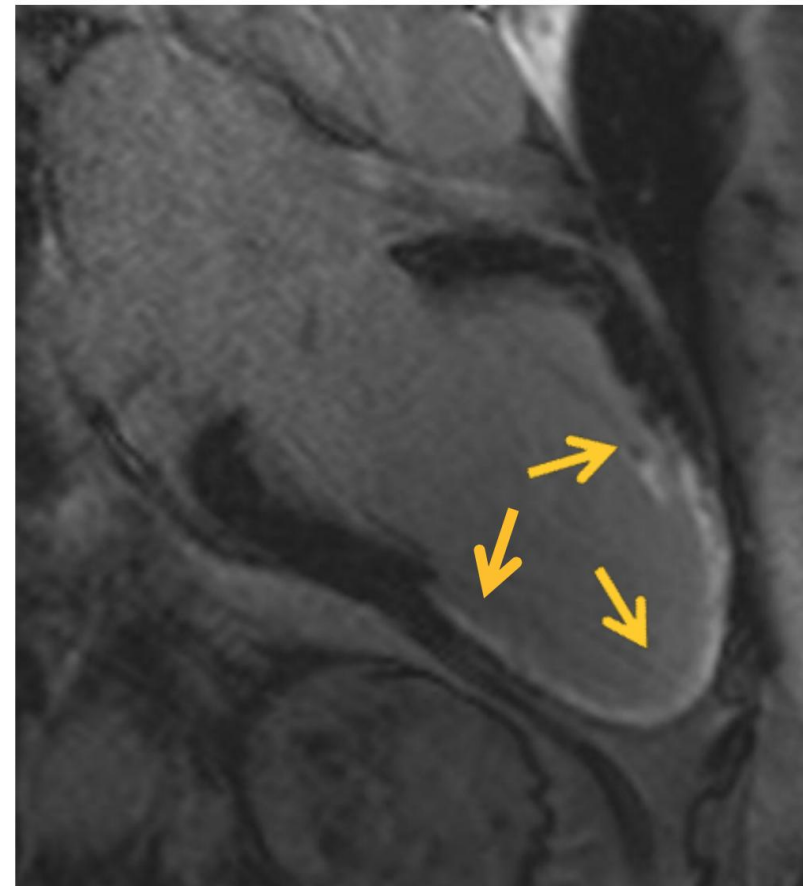




PET/MR Imaging

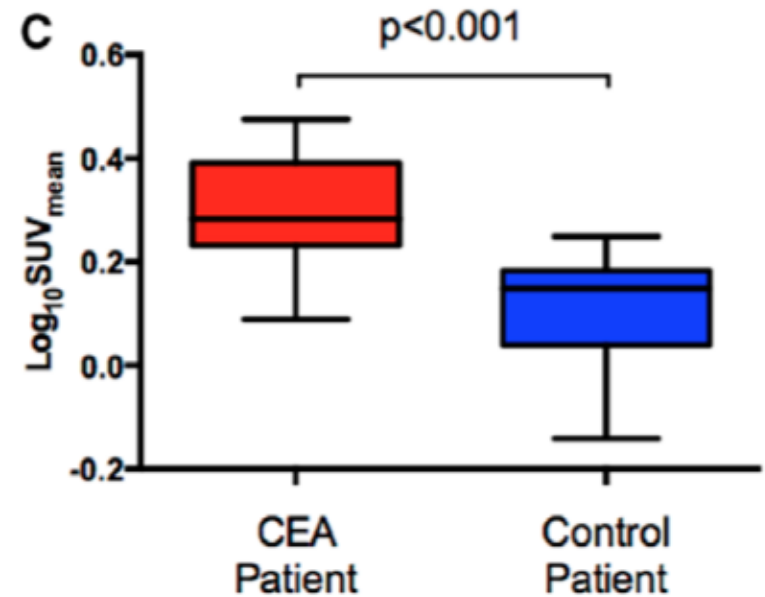
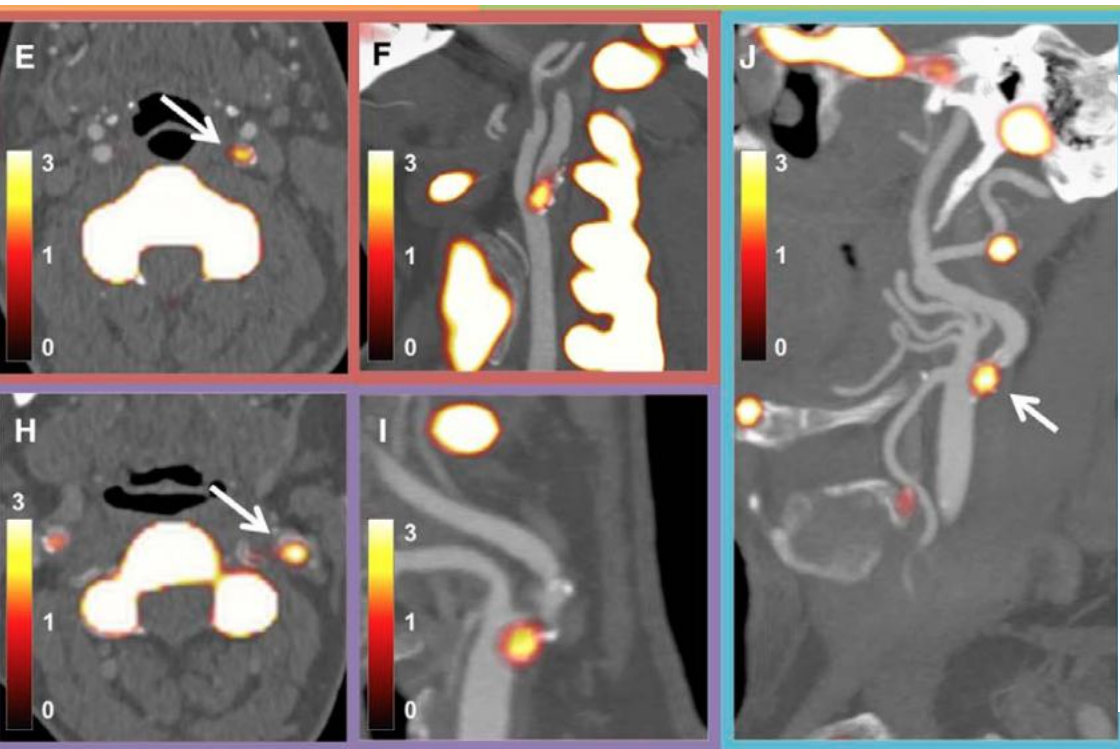


<5mSv



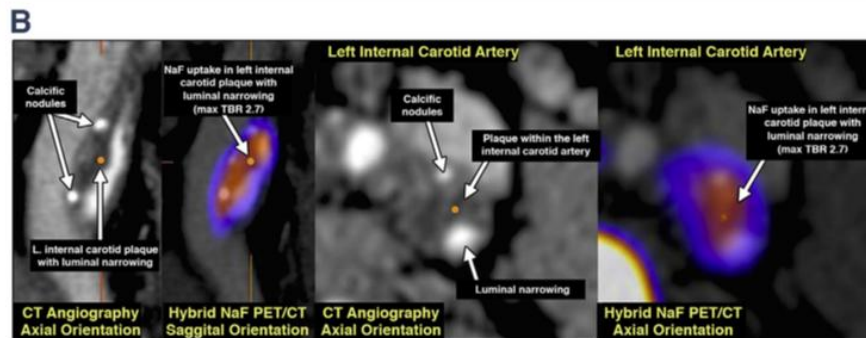
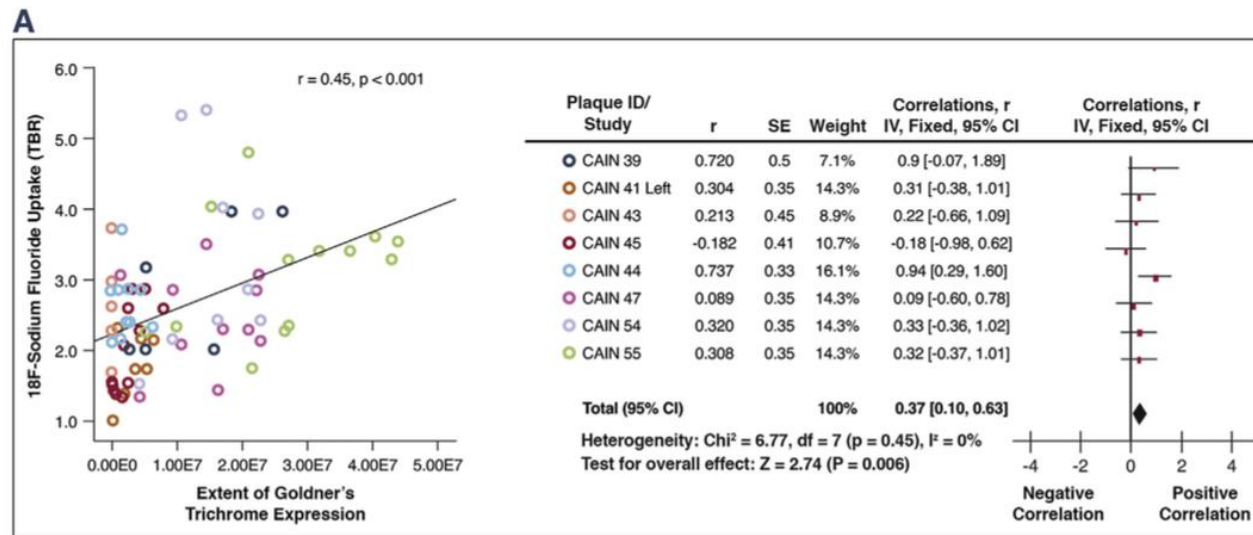
Robson, Dweck, Fayad JACC Imaging 2017

Carotid 18F-Fluoride



Carotid ^{18}F -Fluoride

FIGURE 1 ^{18}F -NaF is a Surrogate Marker of Active Calcification in Carotid Plaque



(A) [^{18}F]-sodium fluoride (^{18}F -NaF) uptake correlation with hydroxyapatite expression; intraplaque clustering is noted (**left**); fixed-effects model for individual lesion correlations ($r = 0.37$, $p = 0.006$) (**right**). **(B)** ^{18}F -NaF uptake encompasses a greater region than calcific nodules within plaque (**left**). CAIN = Canadian Atherosclerosis Imaging Network; CI = confidence interval; CT = computed tomography; df = degrees of freedom; IV = inverse variance; L = left; PET = positron emission tomography; TBR = tissue-to-blood ratio.



Edinburgh
Heart Centre

The PRE¹⁸FIR Study

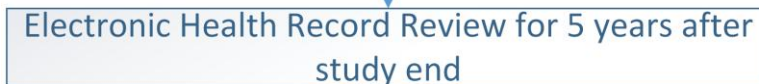
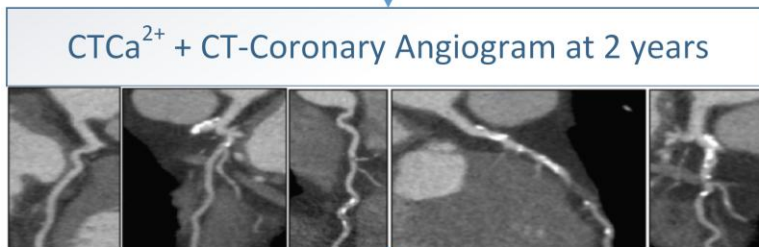
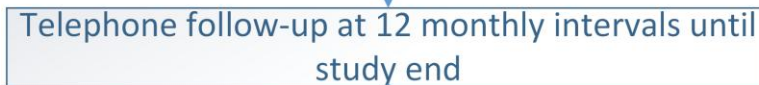
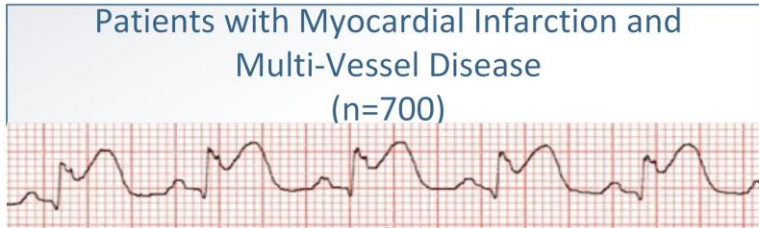


Prediction of Recurrent Events with ^{18}F -Fluoride to Identify Ruptured and High-risk Coronary Artery Plaques in Patients with Myocardial Infarction

welcometrust



Will ^{18}F -Fluoride Predict Events?

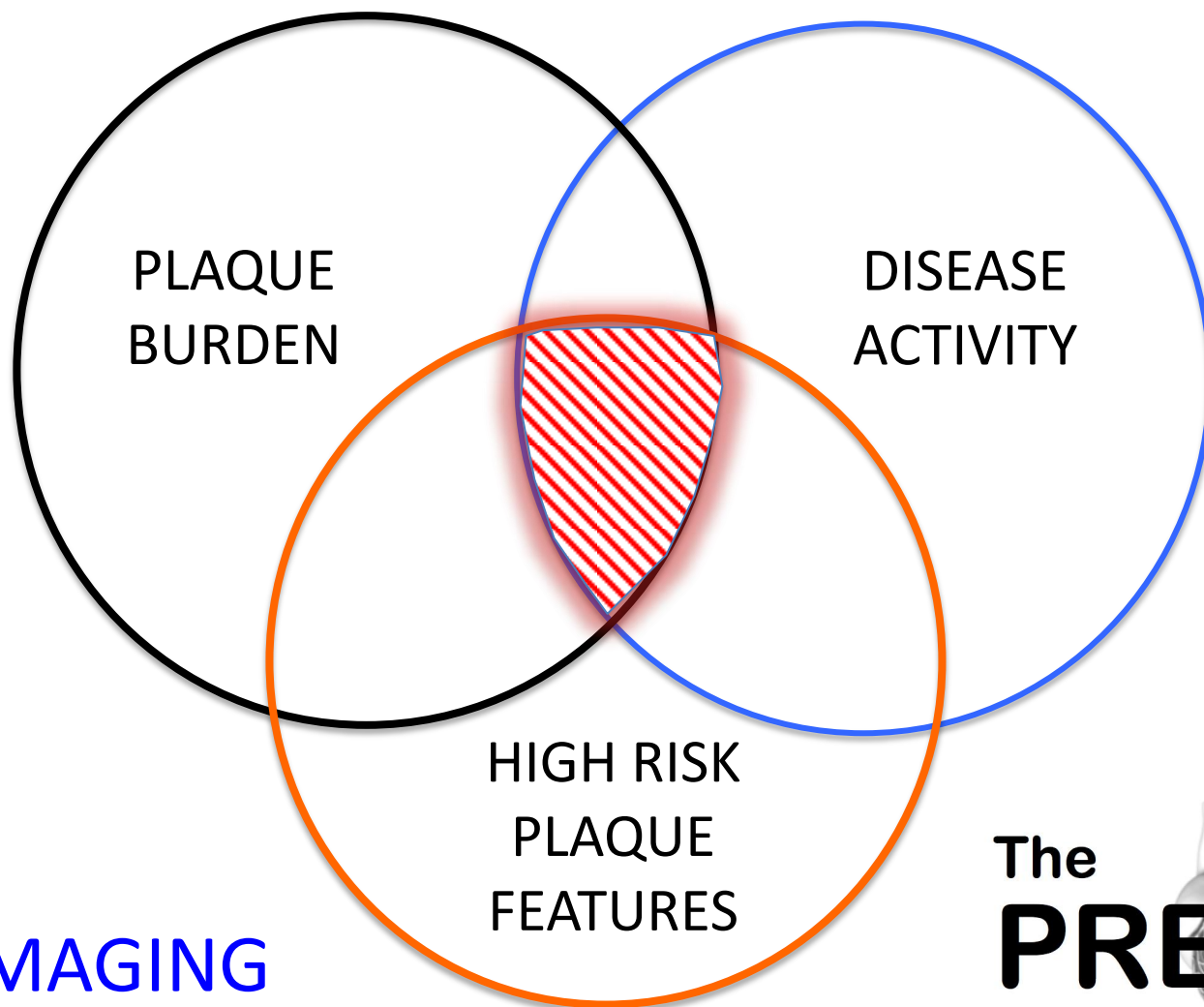


➔ Disease Progression

➔ Clinical Events (Cardiac Death or MI)



MULTI-MODALITY IMAGING



PET/CT IMAGING





Conclusions



- Plaques that rupture and cause myocardial infarction have certain characteristics that can be identified on imaging “**the vulnerable plaque**”
- These are actually relatively common and often heal without clinical consequence. Predicting individual lesions that will cause events is unlikely to be successful
- However identifying vulnerable plaques can help identify patients with active disease and an increased risk of events.
- These **vulnerable patients** could then be targeted with aggressive systemic therapies to prevent events



Acknowledgements



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Prof David Newby
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Dr Anoop Shah
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Dr Jack Andrews
Dr Tim Cartlidge
Dr Alastair Moss
Dr Phil Adamson

University of Cambridge

Dr James Rudd
Dr Anthony Davenport
Dr Agnese Irkle
Prof Martin Bennet

The British Heart Foundation

- BHF Clinical Research Training Fellowship (FS/10/026)
- Extension to Clinical Research Training Fellowship (FS-10/026)
- BHF Clinical Research Training Fellowship (FS/12/84/29814)
- BHF Project Grant (PG/12/8/29371)
- BHF Intermediate Clinical Research Fellowship (FS/14/78/31020)
- BHF Programme Grant (RG/16/10/32375).
- BHF Centre of Research Excellence Award.
- BHF Outstanding Researcher Award 2015

The Chief Scientist Office

Wellcome Trust

Cedars Sinai Hospital LA

Prof Dan Berman
Prof Piotr Slomka
Dr Damini Dey

Mount Sinai Hospital, NY

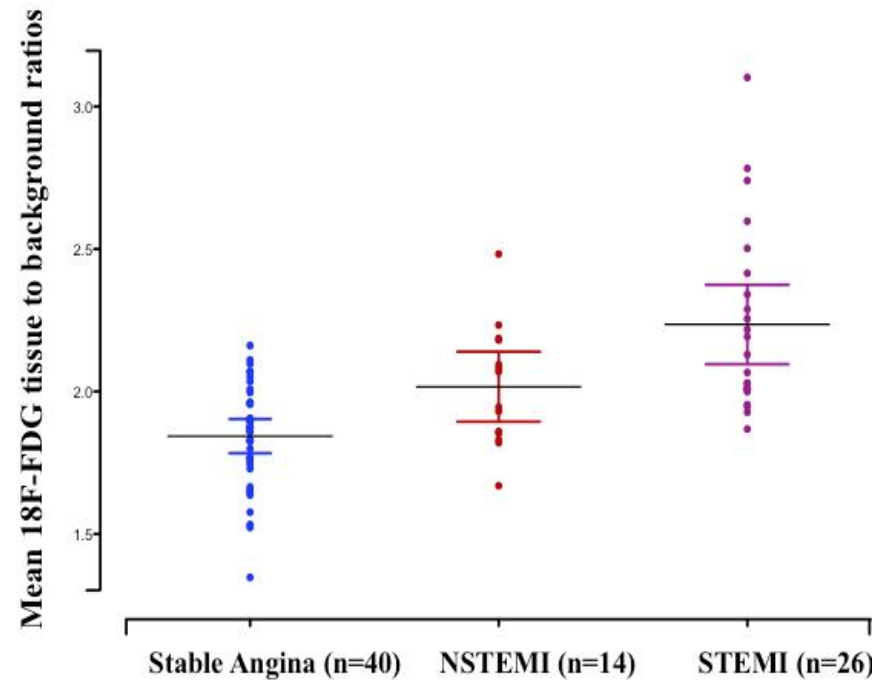
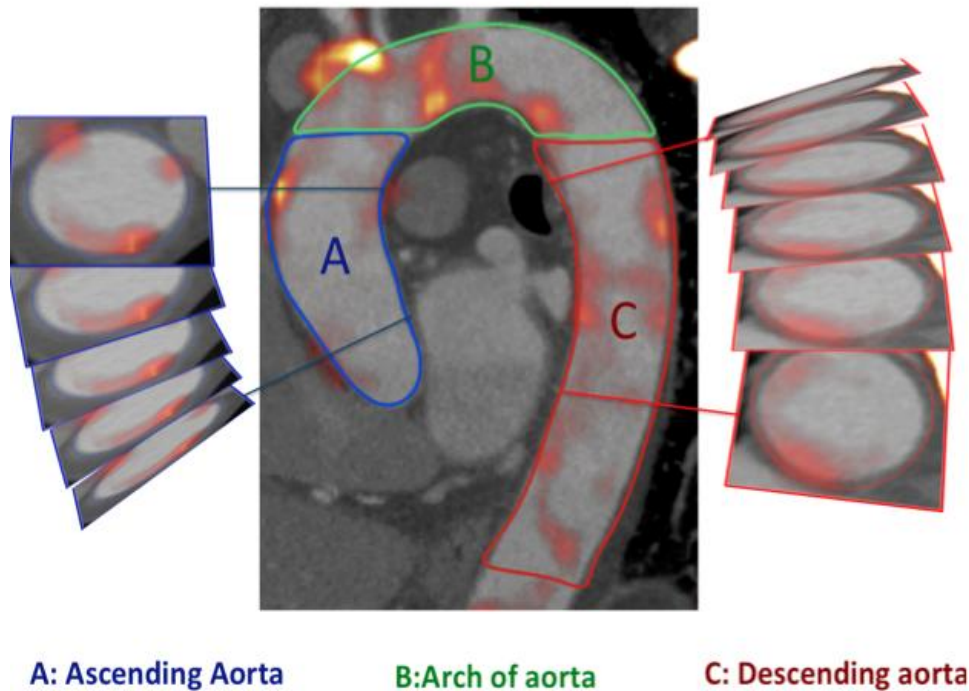
Prof Zahi Fayad
Prof Valentin Fuster
Prof Jagat Narula



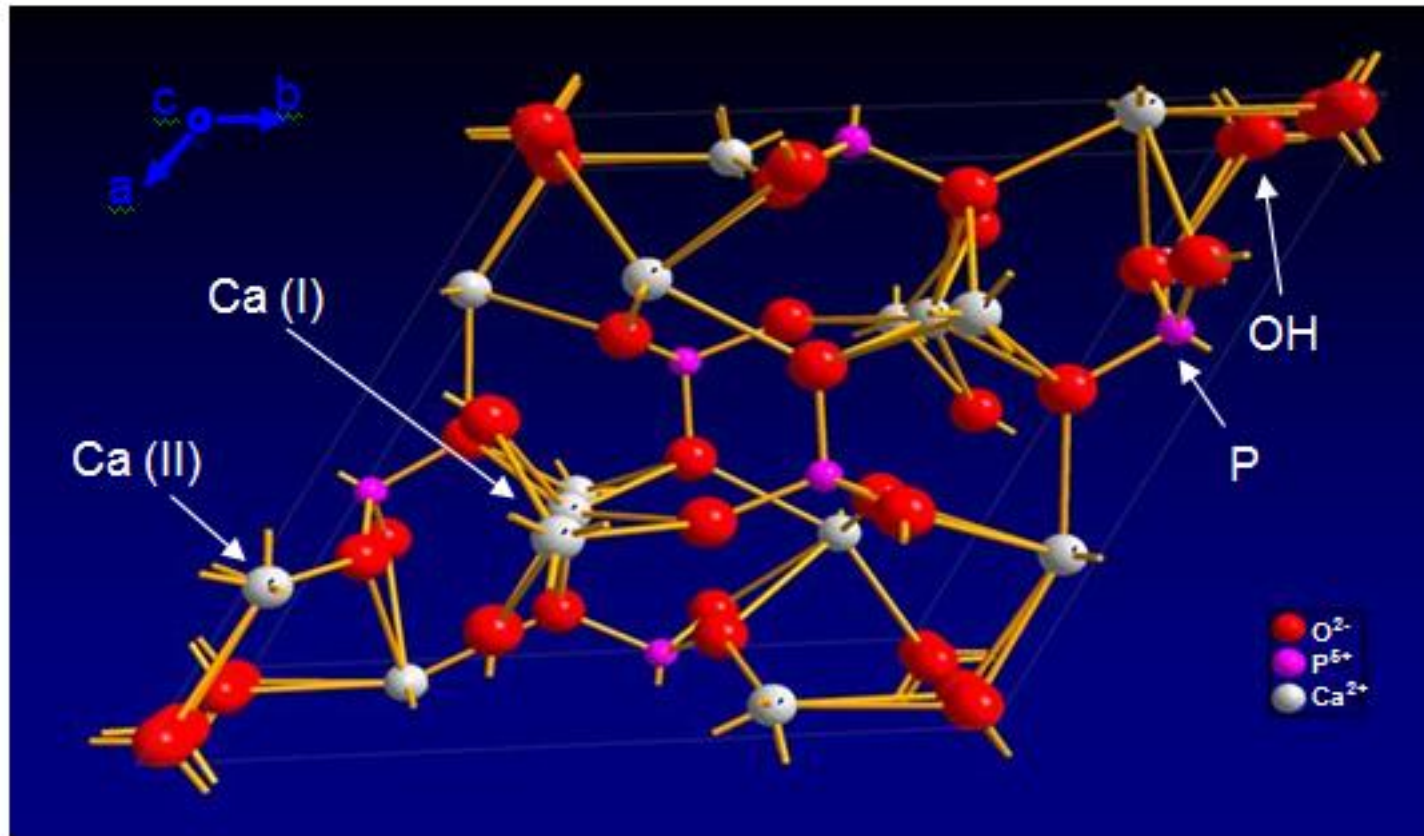
Increased Inflammation in Remote Atheroma Post-MI



¹⁸F-FDG of the Aortae



Binds to Hydroxyapatite Crystal



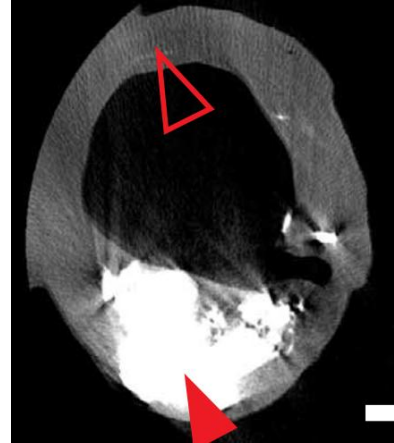
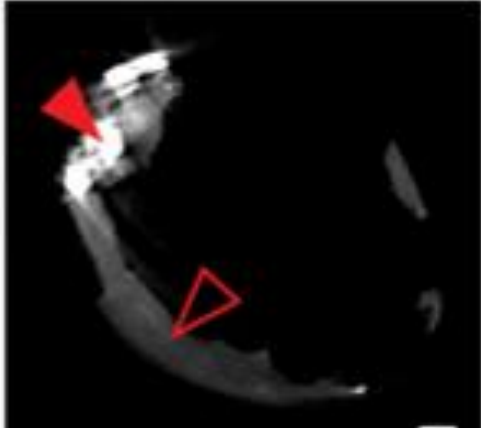
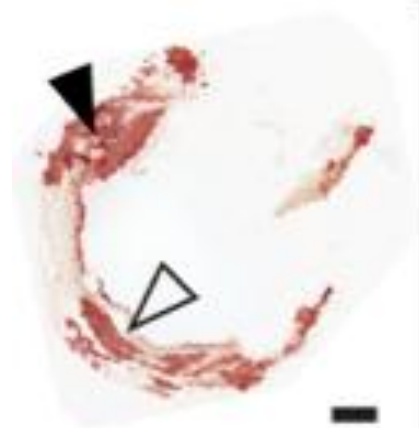
Detects newly developing calcium beyond resolution of CT



Calcium on histology

Micro CT

Micro CT



Autoradiography

Micro PET

Autoradiography

