Translational Nuclear Imaging of Plaque Vulnerability

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**CARDIOLOGY
SEOUL ST. MARY'S HOSPITAL
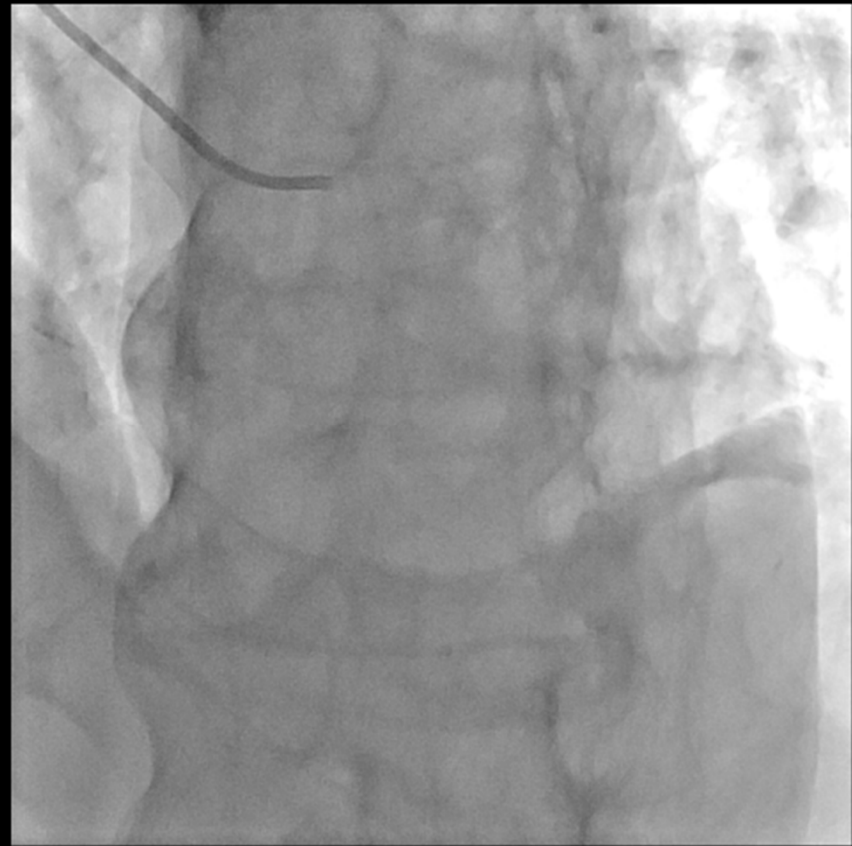CATHOLIC UNIVERSITY OF KOREA**

66/M, routine health examination
On statin and aspirin
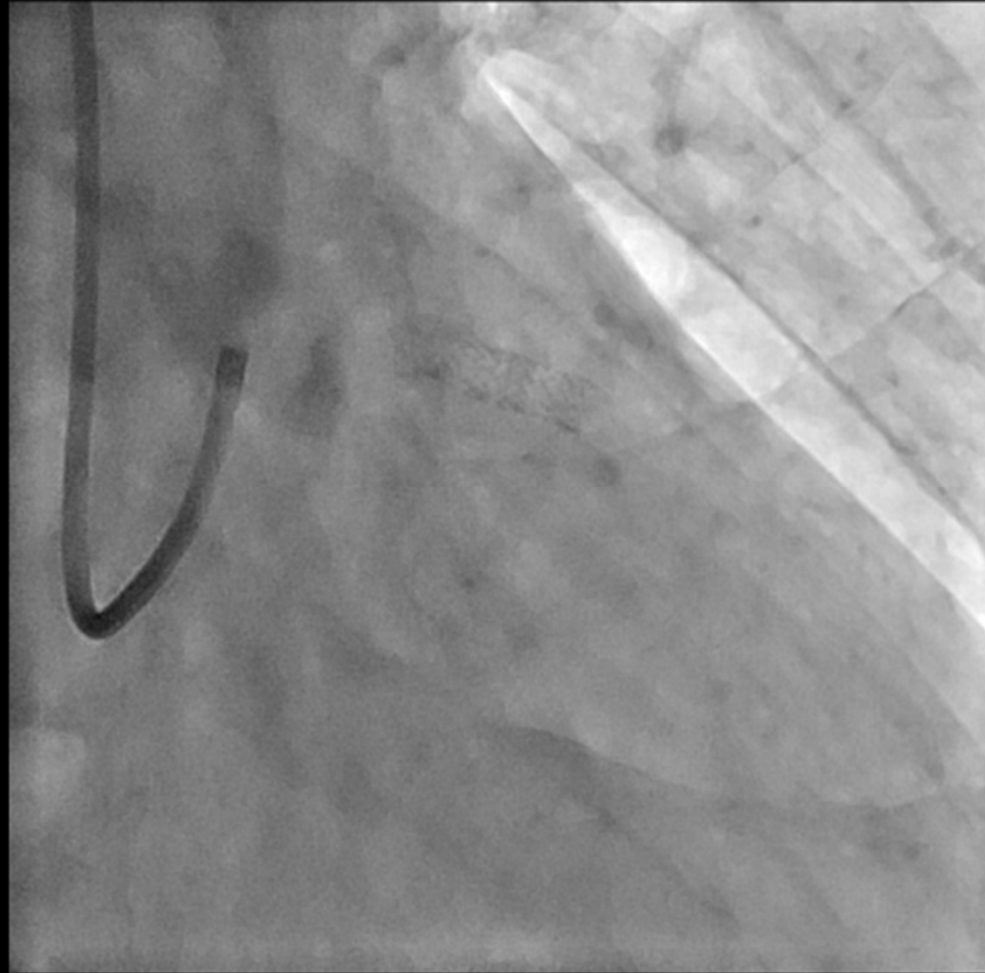FBS 91 mg/dL, TC 158 mg/dL, HDL 69 mg/dL, LDL 67 mg/dL

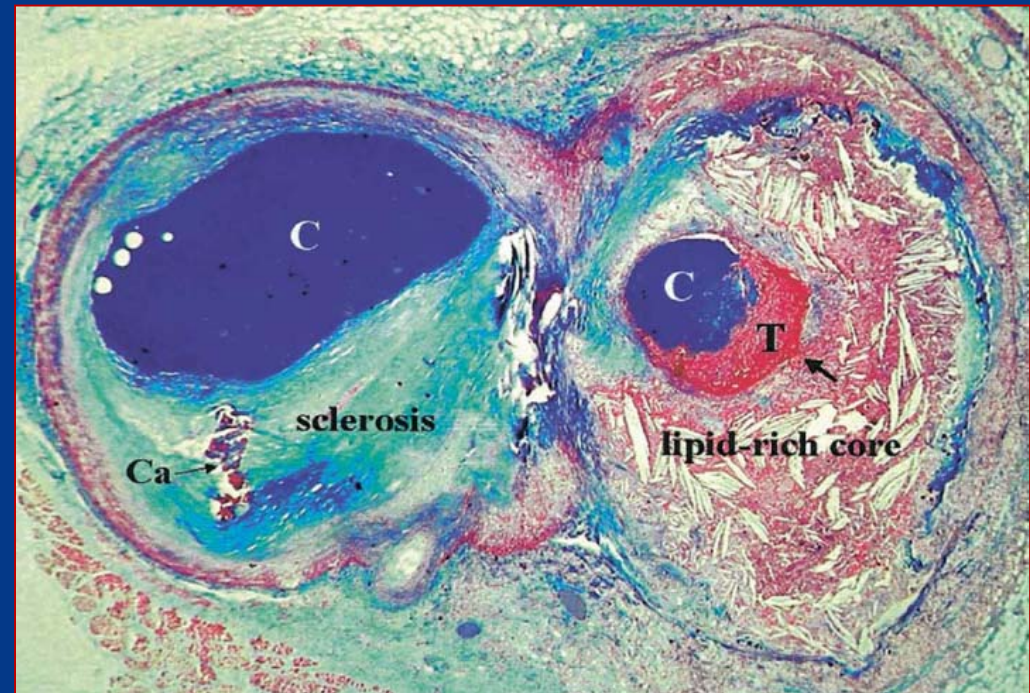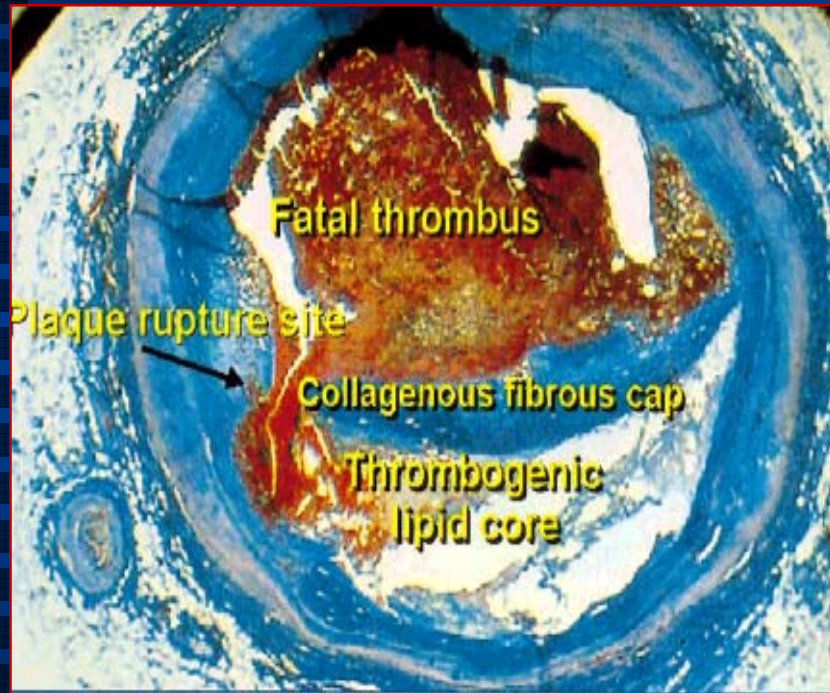# 6 months later, severe resting chest pain at ER
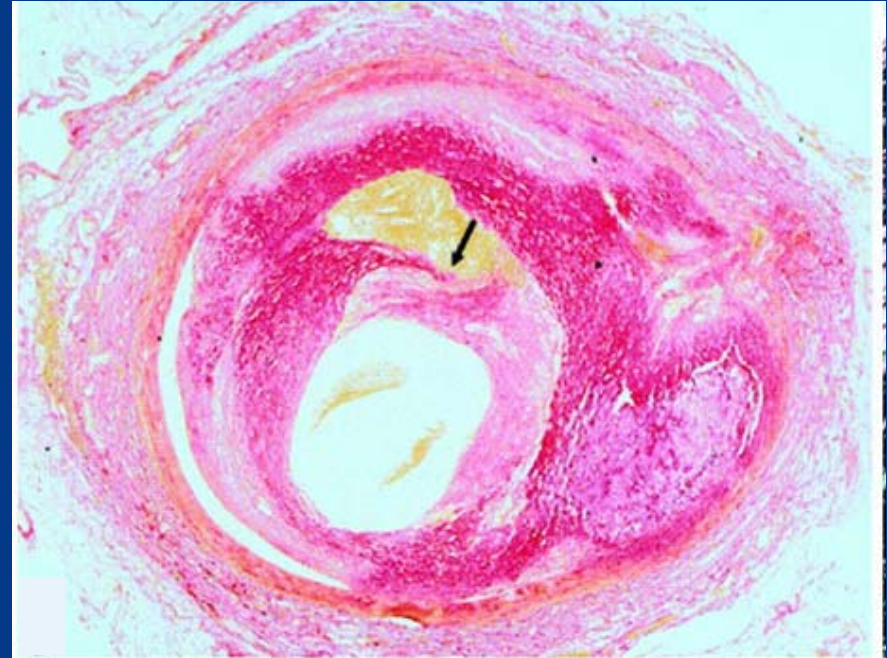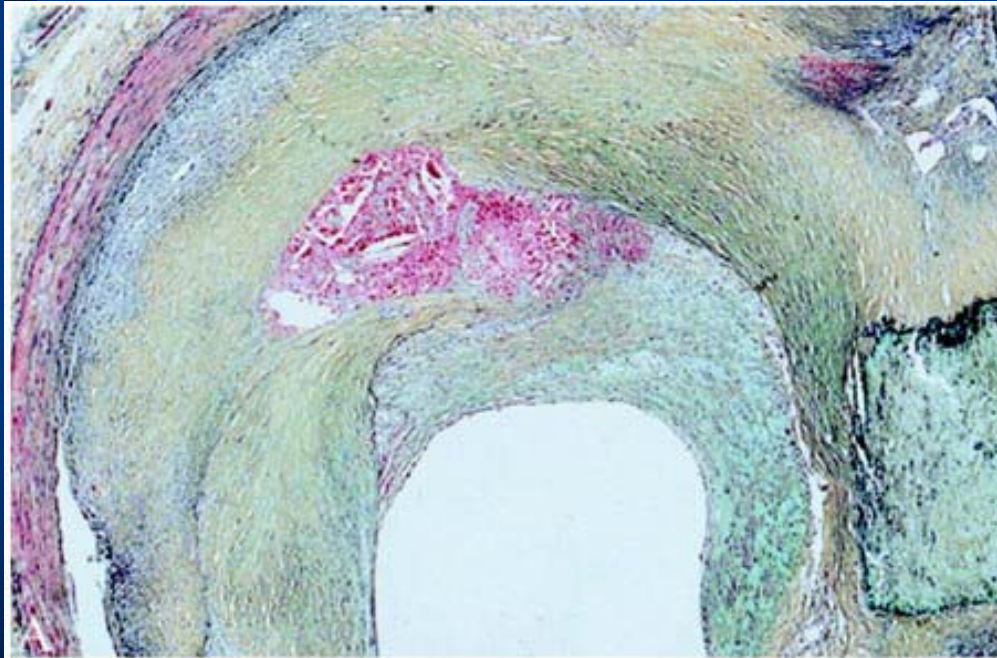## FBS 98 mg/dL, TC 119 mg/dL, HDL 62 mg/dL, LDL 43 mg/dL

Promus Element 4.0*16 mm

Who has vulnerable atherosclerotic plaques?

Plaque rupture & healing frequently occur in our coronary arteries

a. Monocyte
b. Infiltrating monocytes / macrophages
c. RBC's and platelets
d. Extracellular matrix
e. Smooth muscle cell
f. Endothelial cell
g. MMPs

A. THIN FIBROUS CAP

B. LARGE LIPID CORE

h. Ox-LDL
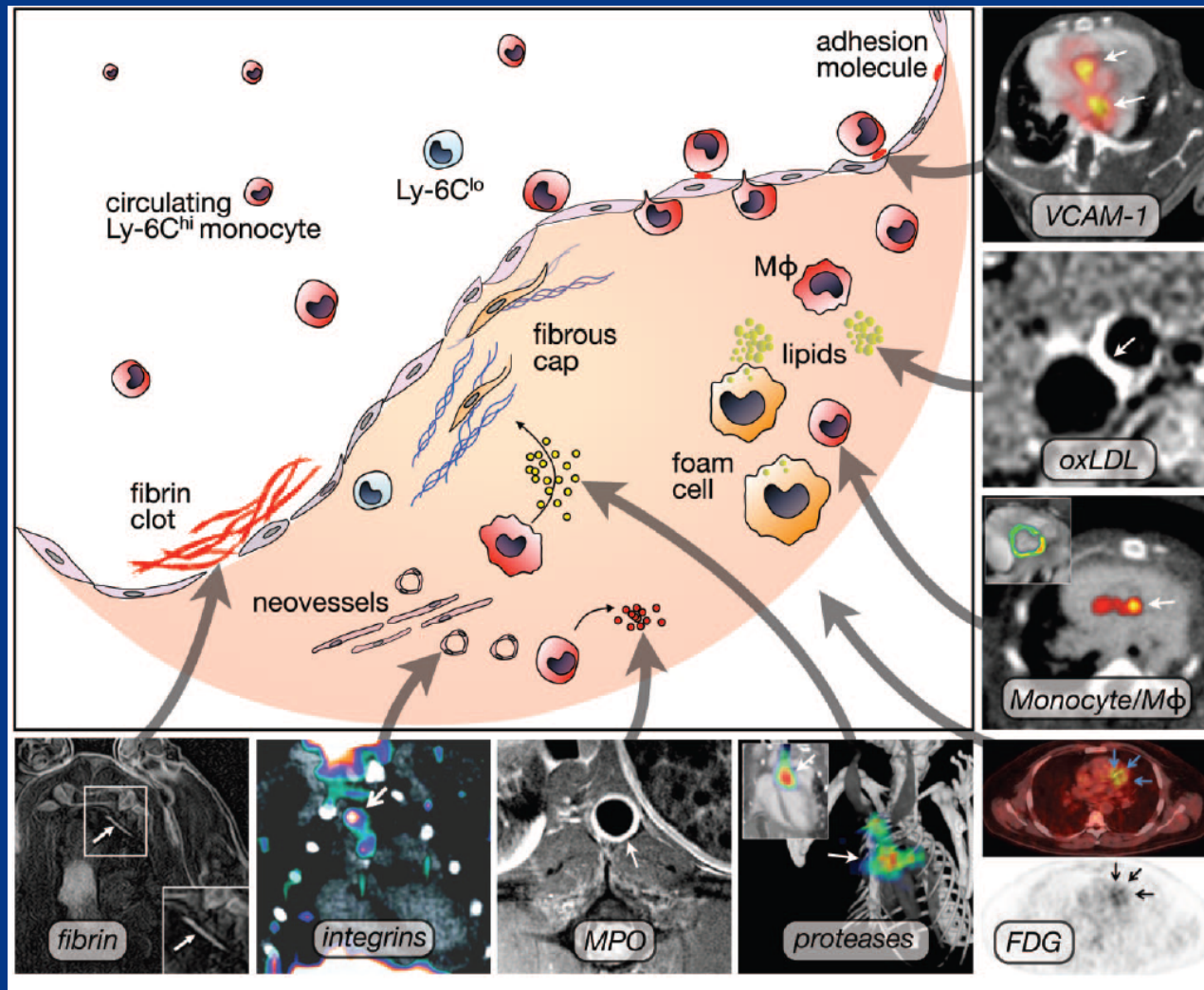i. Apoptotic macrophages
j. T- cell
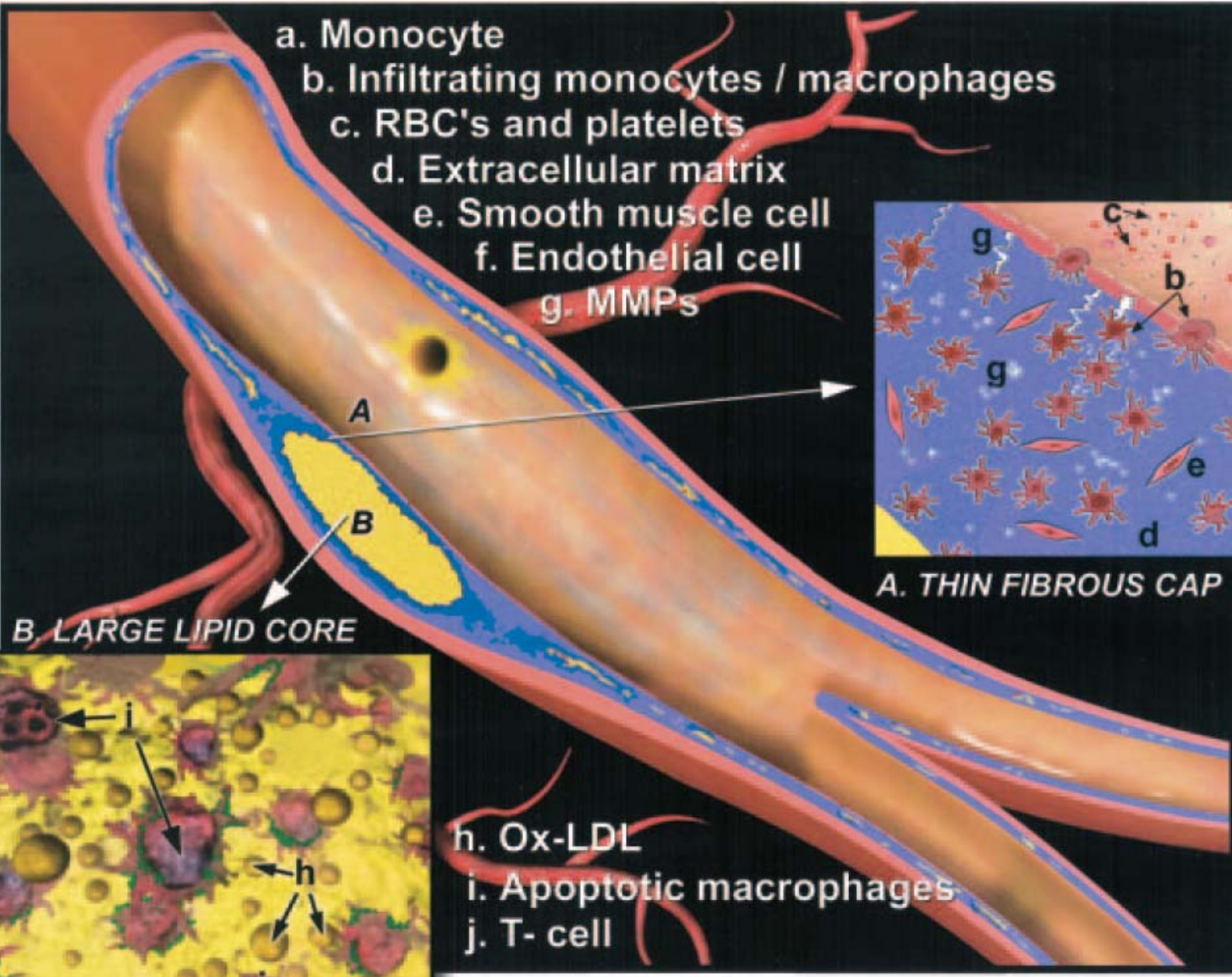
Molecular Imaging of Vulnerable plaques
Advances in small animal imaging systems
Advances in targeted/activatable molecular imaging probes
(MRI, optical imaging, CT, PET, SPECT)

Safety Issue of Nanoparticle

We do not have a complete knowledge of nanoparticle's
- Toxicity
- Biodistribution
- Excretion
- Pharmacokinetics

**FDA applies the same degree
of regulatory oversight on
new imaging agents as new drugs**

Characteristics of Molecular Imaging Modalities

Imaging Modality	Spatial Resolution, mm	Imaging Sensitivity, mol/L probe
Fluorescence Imaging	≤ 1	$10^{-10} - 10^{-12}$
PET	2-4 (clinical PET) 1-2 (microPET)	$10^{-11} - 10^{-12}$
SPECT	7-15 (clinical SPECT) 0.5-2 (microSPECT)	$10^{-10} - 10^{-11}$
MRI	0.5-1.5 (1.5T MRI) 0.01-0.1 (small animal MRI)	$10^{-3} - 10^{-5}$
CT	0.5-2 (clinical CT) 0.02-0.3 (microCT)	$10^{-2} - 10^{-3}$

PET & intravascular fluorescence sensing catheter are the answer for the Clinical Translation of Molecular Imaging of Vulnerable Plaques in terms of safety and spatial resolution within near future.

Present & Future of Vascular PET Imaging

1. ^{18}F-FDG PET/CT of carotid arteries

2. Coronary arterial ^{18}F-FDG PET/coronary CT angiography imaging

3. Hybrid PET/CT of myocardial perfusion PET & coronary CT angiography

4. Novel coronary arterial PET imaging agents other than FDG

FDG PET/CT of carotid arteries

^{18}F-FDG PET/CT
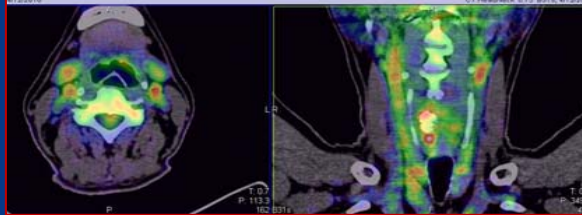
Avid uptake by plaque macrophages
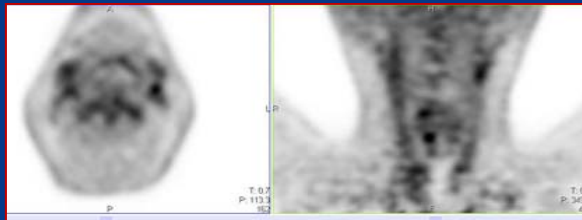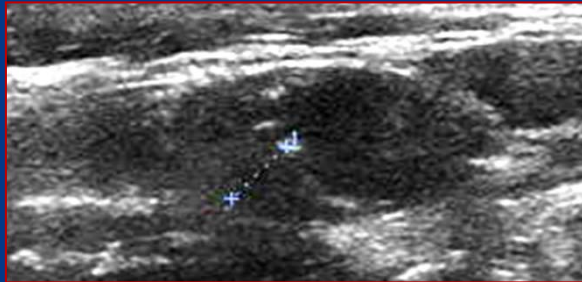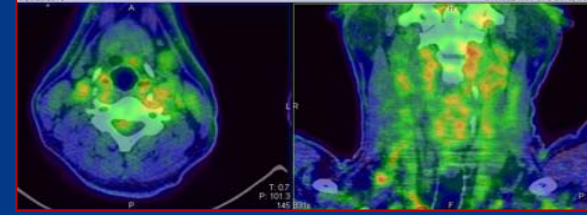## Already used as molecular PET imaging of atherosclerosis
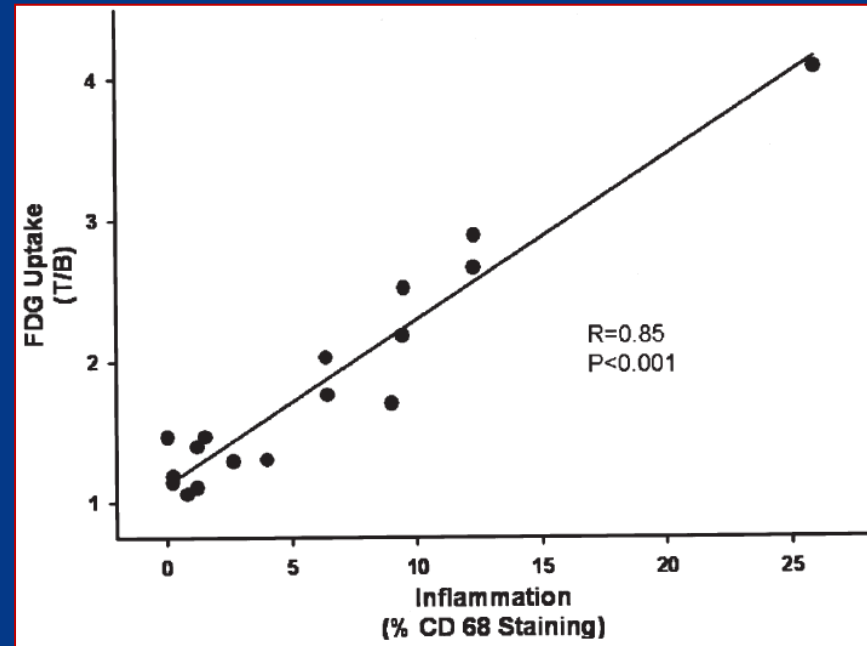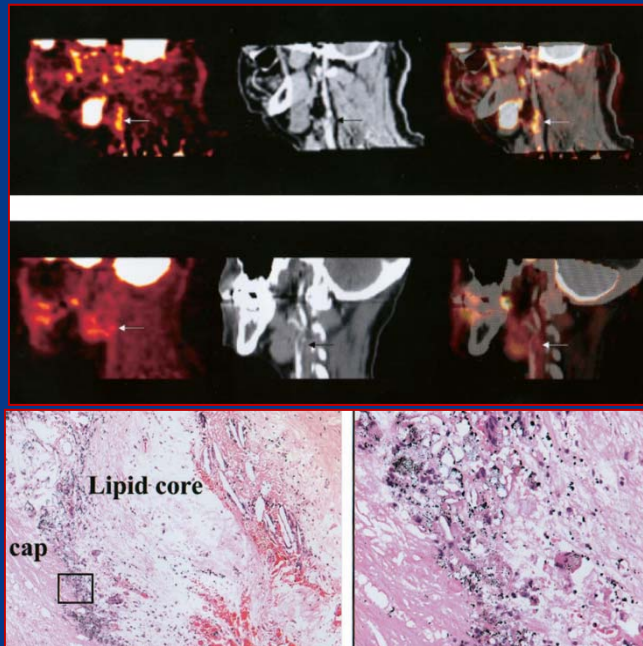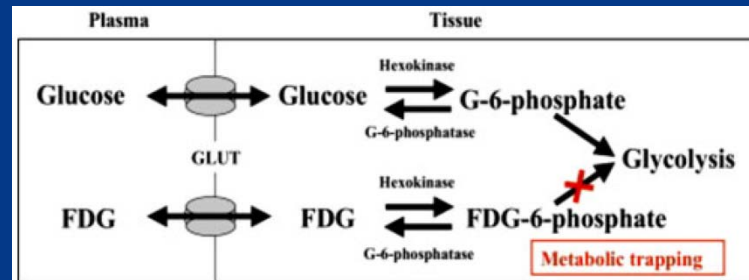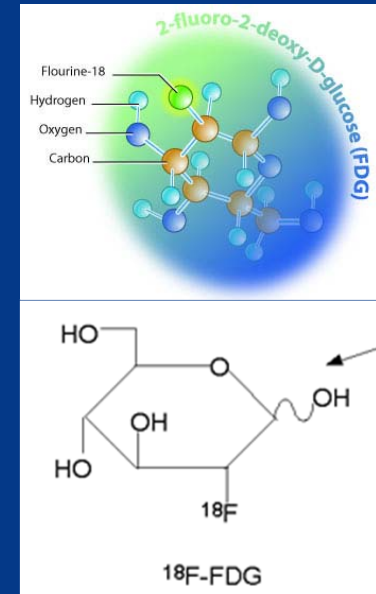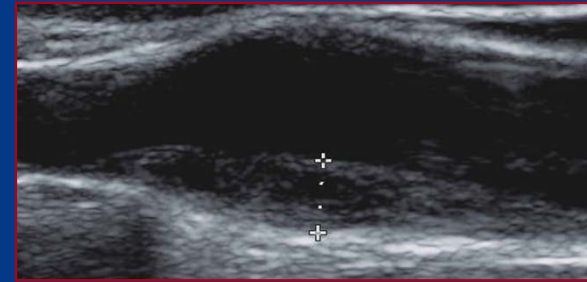
Circulation 2002;105:2708-11

J Am Coll Cardiol 2006;48:1818-24

Discrepancy between structure & inflammation imaging

Highly inflamed plaque
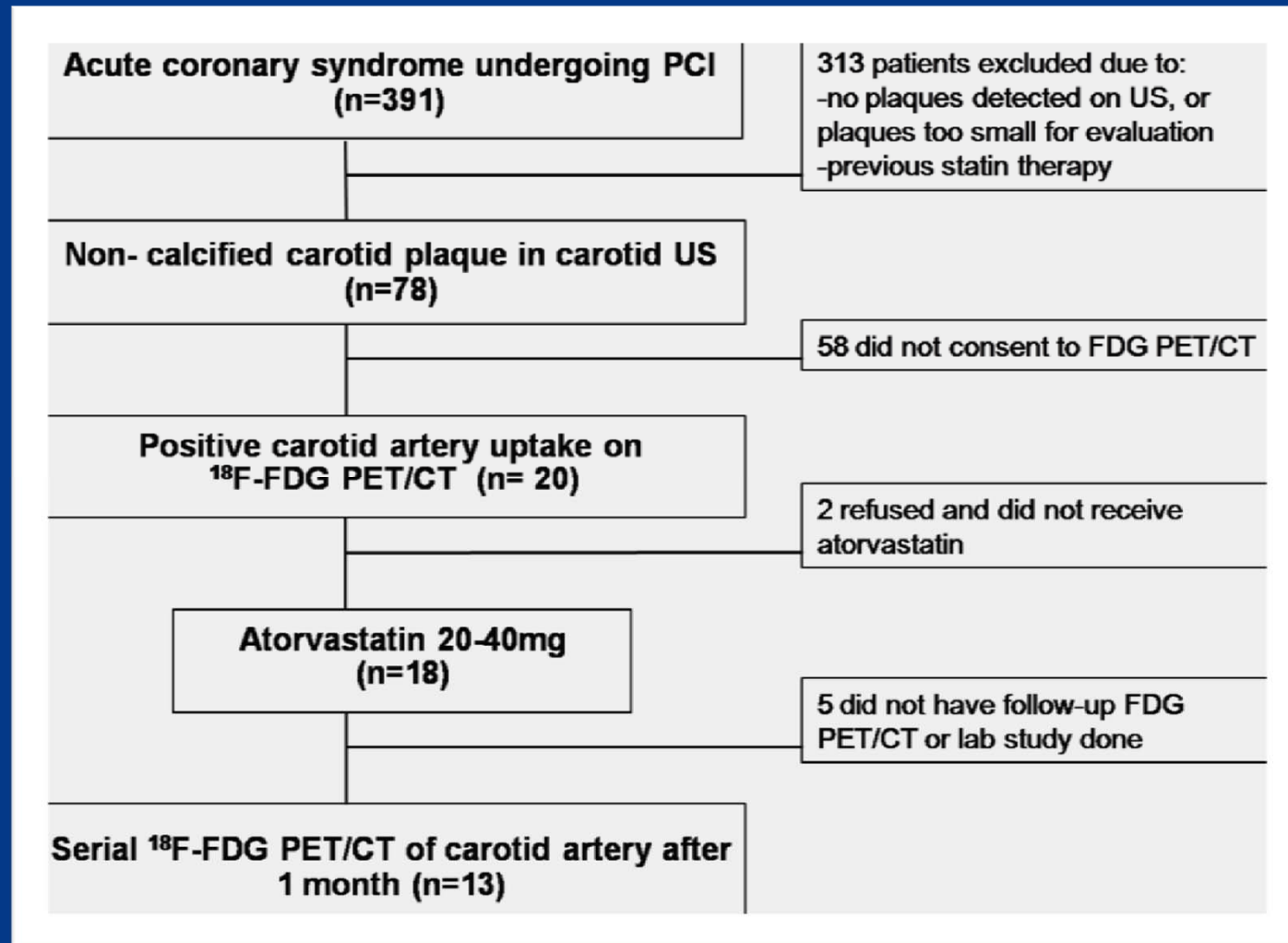

Less inflamed plaque

FDG PET/CT of carotid arteries
## Ready for routine clinical practice?

1. Tool for monitoring the adequacy of anti-
   inflammatory therapy in patients with
   high vascular risk

2. Tool for evaluating novel anti-atherosclerotic
   therapeutics

3. Tool to predict future vascular events
   - regionally
   - globally

Seoul St.Mary's Hospital
Cardiovascular Center

Short-term statin fails to suppress plaque inflammation in ACS (UA+NSTEMI)

Acute coronary syndrome undergoing PCI (n=391)

313 patients excluded due to:
-no plaques detected on US, or plaques too small for evaluation
-previous statin therapy

Non- calcified carotid plaque in carotid US (n=78)

58 did not consent to FDG PET/CT

Positive carotid artery uptake on 18F-FDG PET/CT (n= 20)

2 refused and did not receive atorvastatin

Atorvastatin 20-40mg (n=18)

5 did not have follow-up FDG PET/CT or lab study done

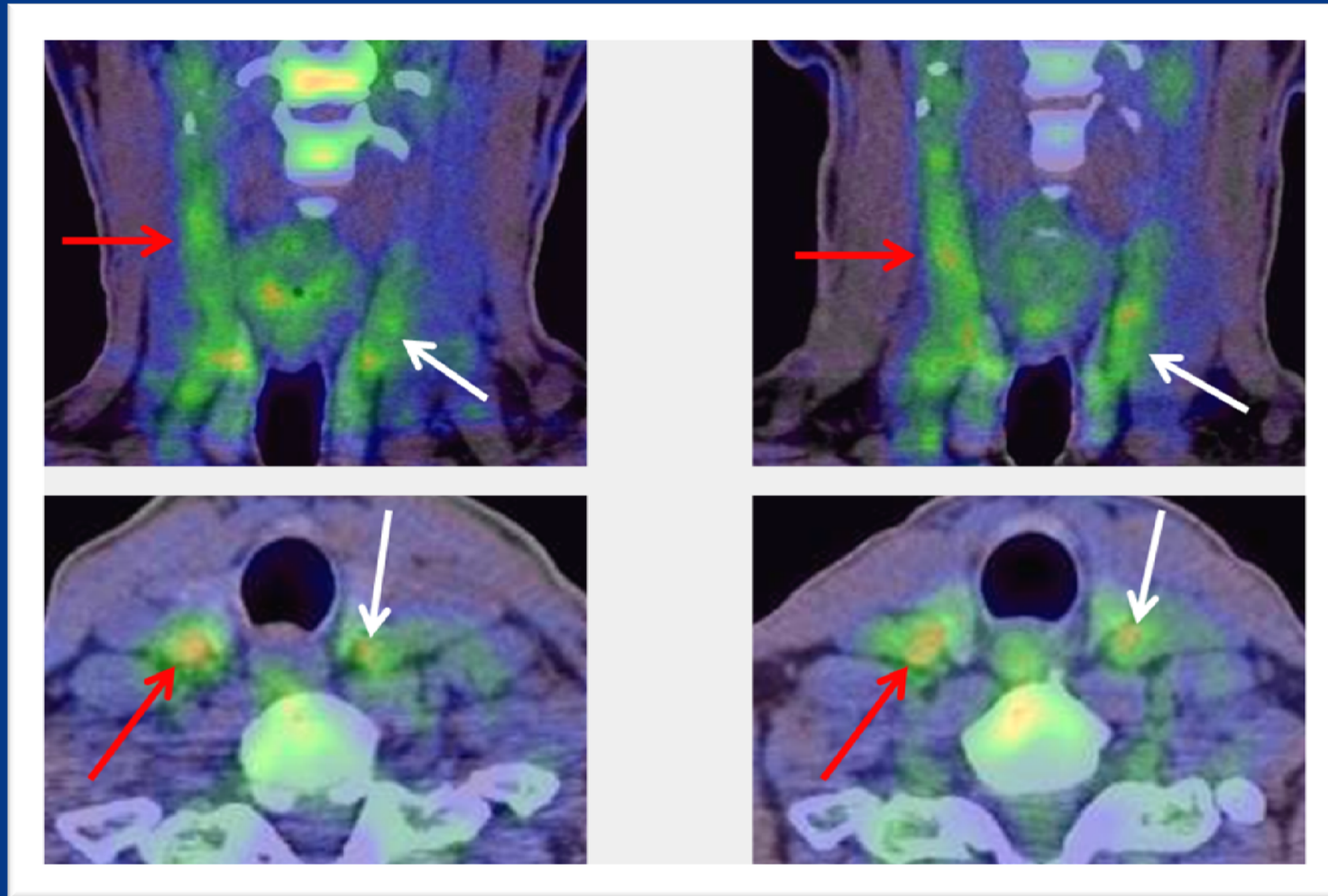Serial 18F-FDG PET/CT of carotid artery after 1 month (n=13)

Short-term statin fails to suppress plaque inflammation in ACS
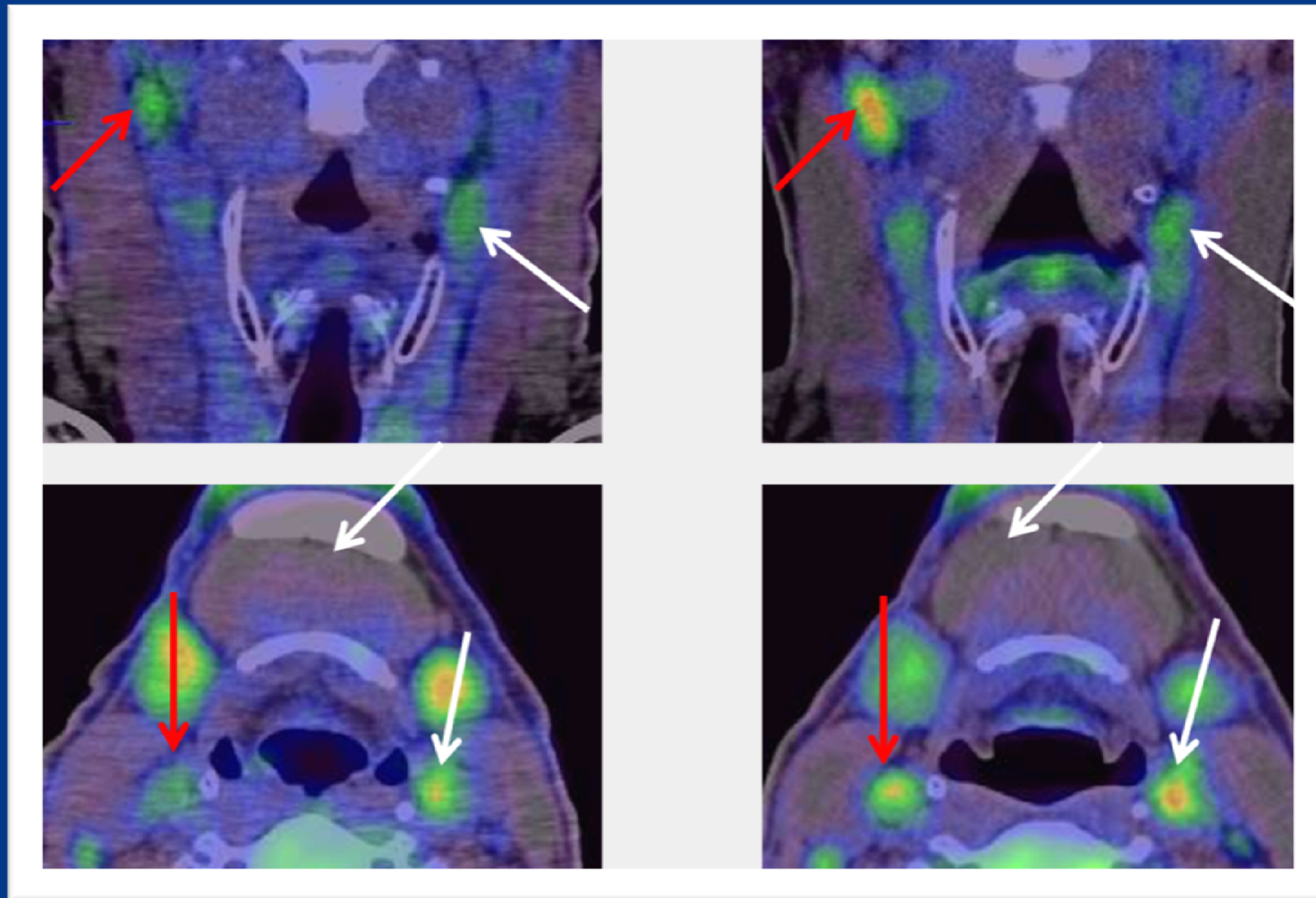## Statin non-responder : LDL-C 86 mg/dL
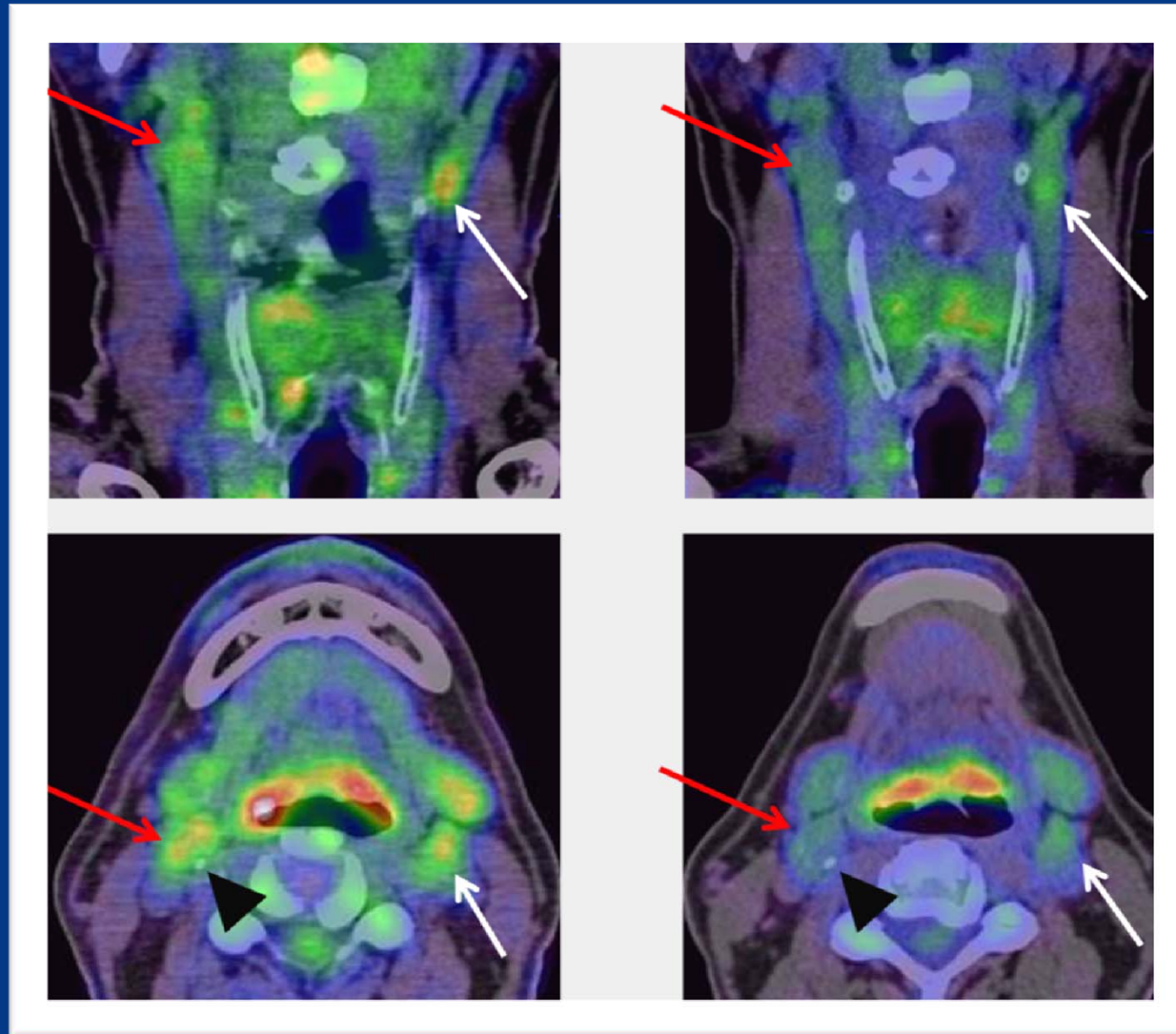
Short-term statin fails to suppress plaque inflammation in ACS
Statin responder : LDL-C 50.6 mg/dL

Short-term statin fails to suppress plaque inflammation in ACS
## Statin responder : LDL-C 61 mg/dL

FDG PET/CT of carotid arteries

1. We found FDG PET/CT is a useful tool to monitor anti-atherosclerosis therapy in patients with high vascular risk

2. Early, intensive statin therapy does not always guarantee the resolution of plaque inflammation at 1 month post-statin.

Seoul St.Mary's Hospital
Cardiovascular Center

Hurdles

Coronary arterial ^{18}F-FDG PET/coronary CT angiography fusion imaging
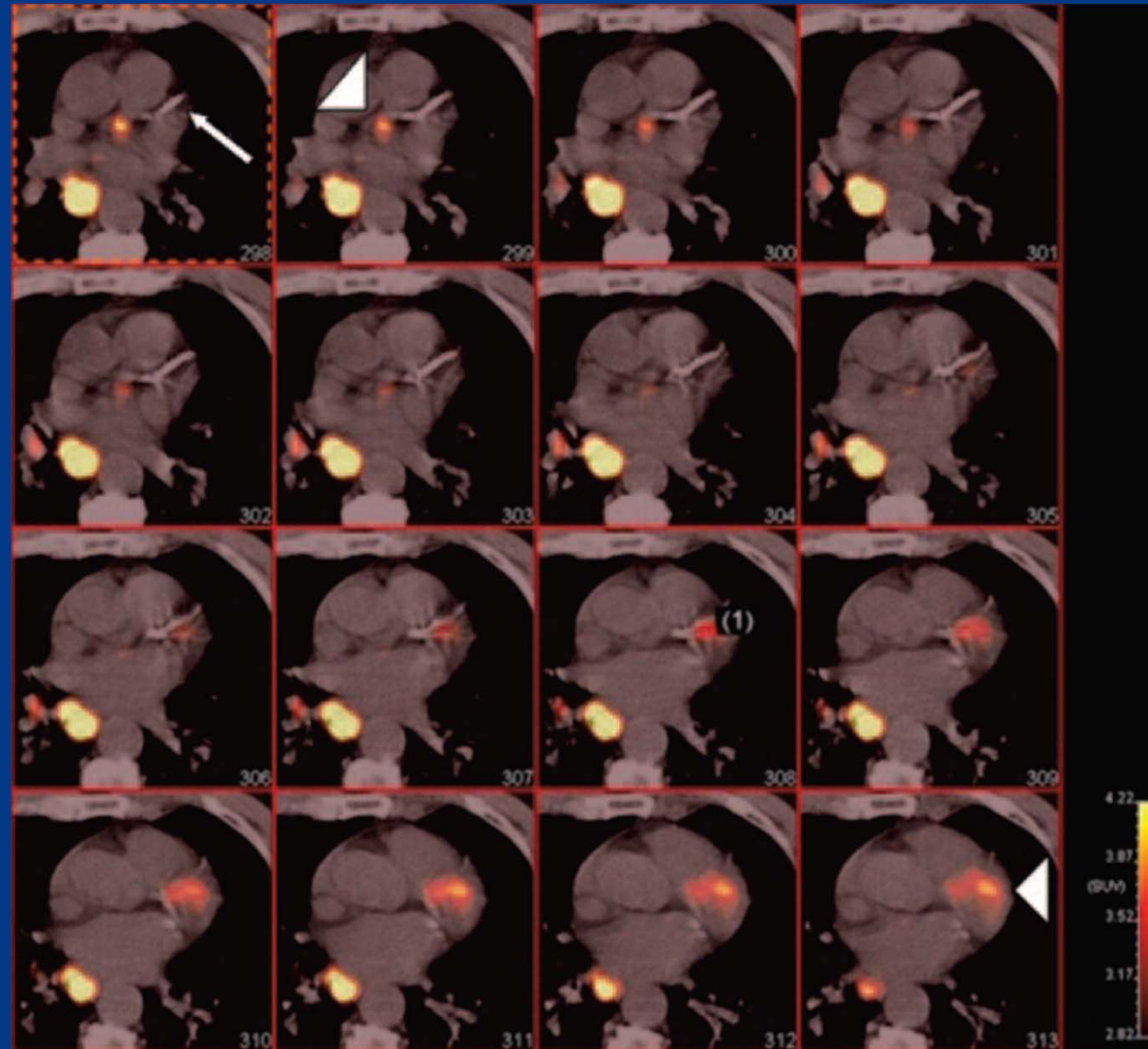
1. Avid myocardial FDG uptake

2. Small size of coronary artery
   - limited spatial resolution of PET
   - lower FDG uptake of small coronary plaque

3. Considerable cardiac motion

If we could fuse coronary arterial FDG PET with coronary CT angiography, then!!!
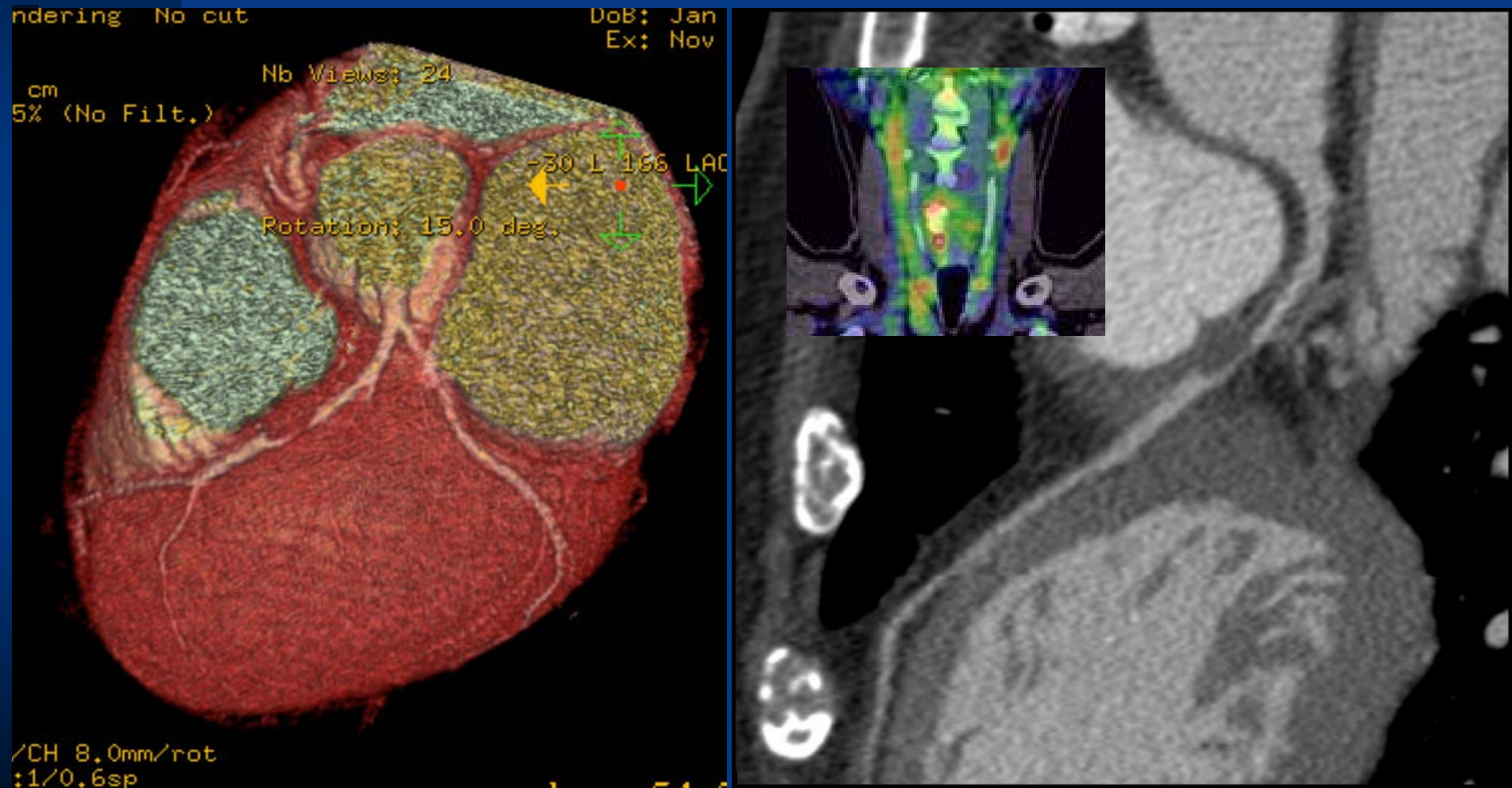
1st report of coronary arterial PET/CT in humans

## Esophageal cancer, Dietary manipulation (low carbohydrate & high fat diet)

Practical Hurdles in widespread use of coronary arterial FDG PET/CT

1. Avid myocardial FDG uptake
    pre-imaging high-fat, low carbohydrate diet
2. Small size of coronary artery
    - limited spatial resolution of PET
   - lower FDG uptake of small coronary plaque

HD•PET → spatial resolution 2 mm
## Point Spread Function Reconstruction
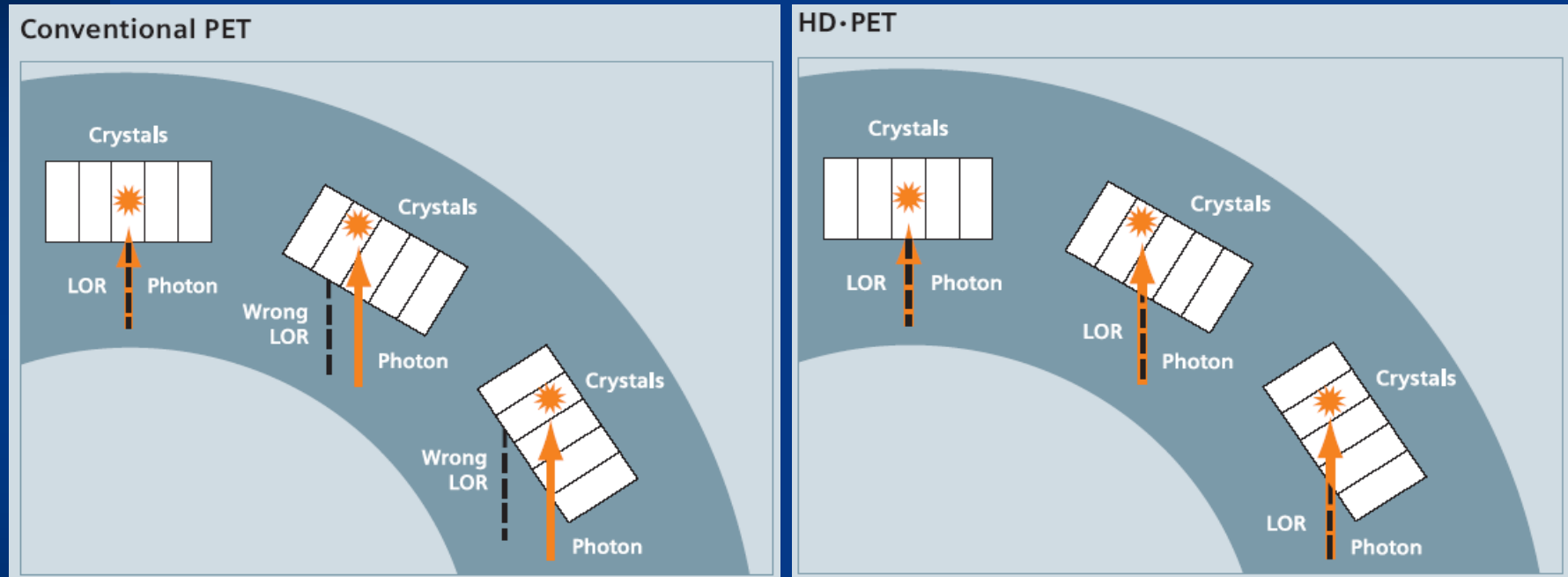
HD•PET incorporates accurately measured point spread functions in the reconstruction algorithms, effectively positioning the LORs in their actual geometric location, which dramatically reduces blurring and distortion in the final image.

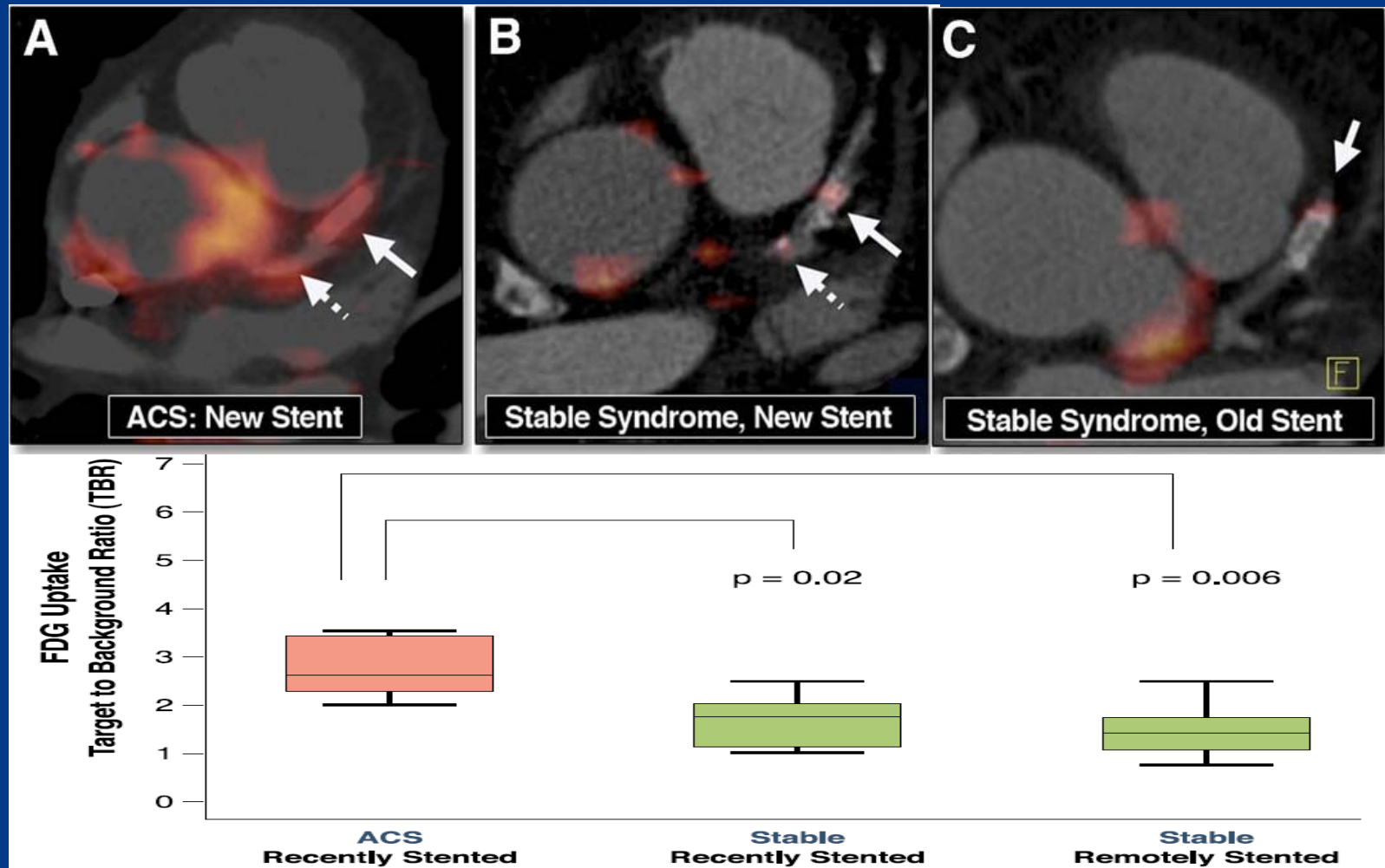# Practical Hurdles in widespread use of
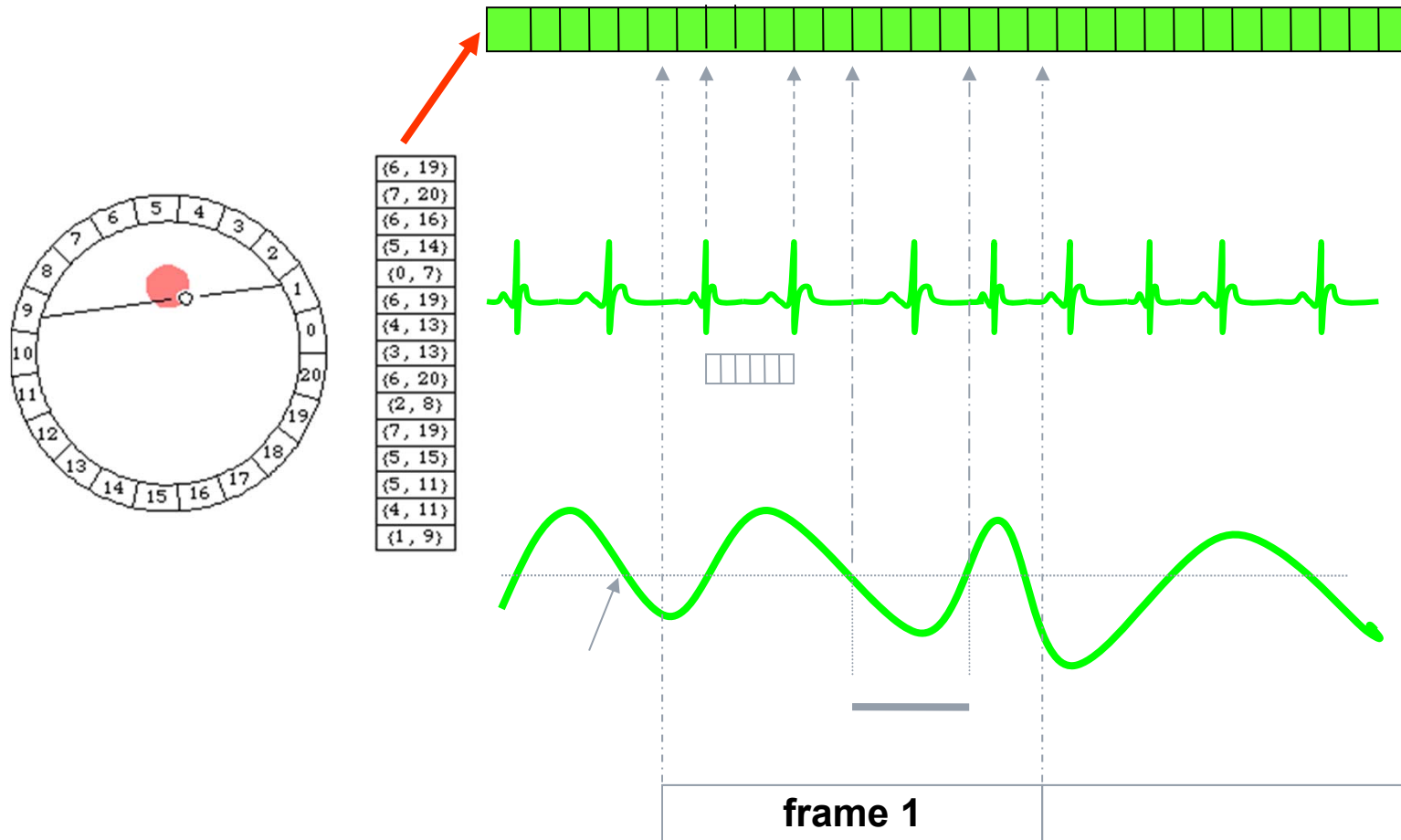
Fusion of Coronary arterial FDG PET/Coronary CT angiography
In stented patients for AMI vs stable angina
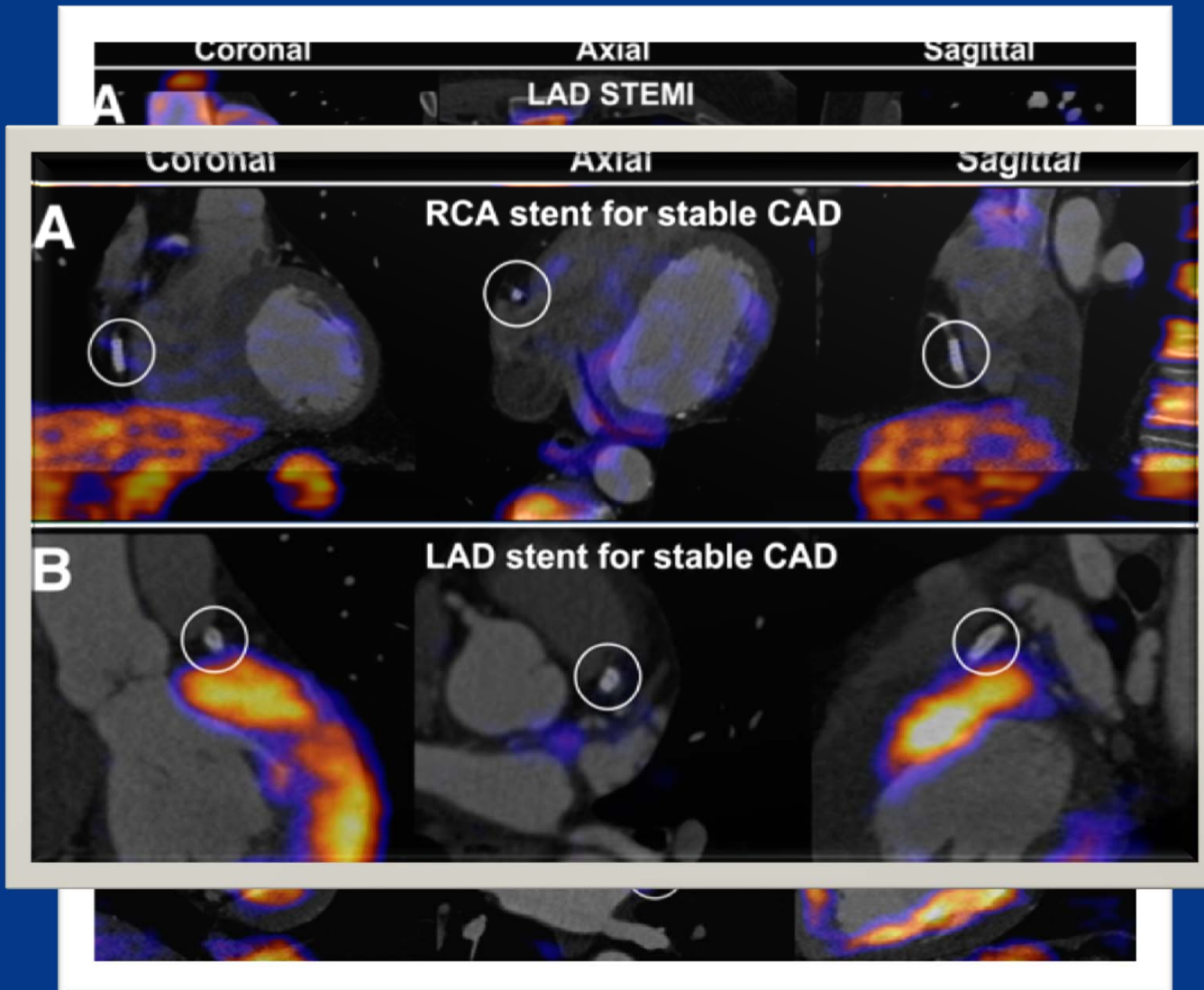

Cheng VY et al, J Nucl Med 2012;53:1-9

Imaging of coronary inflammation with FDG PET/CT CAG in humans

*Rogers IS et al, JACC CV Imaging 2010;3:388-97*

1. **Coronary arterial PET/coronary CT angiography fusion imaging will be available in the near future**

2. **However, some clinical hurdles should be overcome before routine adoption of fusion coronary arterial PET imaging**

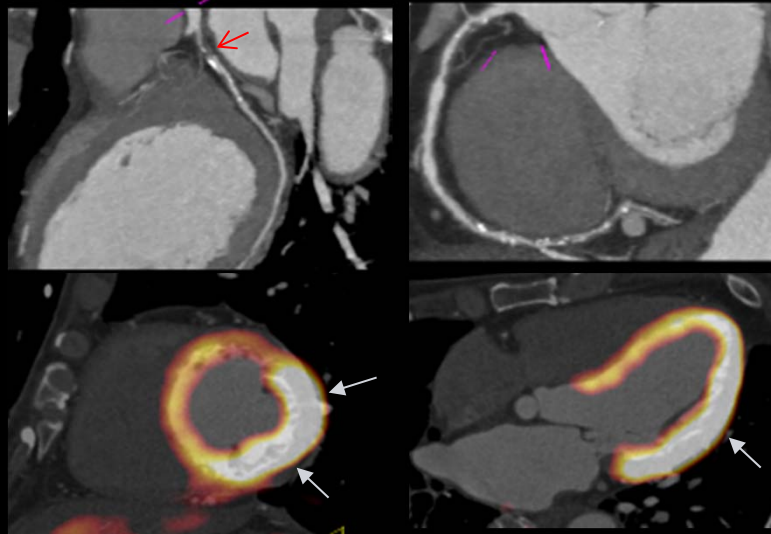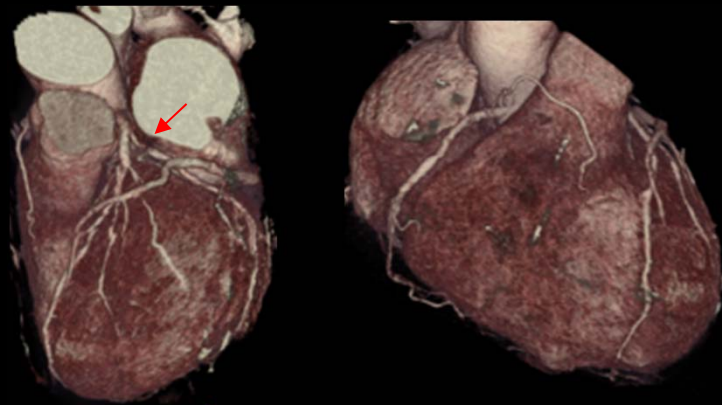# Hybrid PET/CT of myocardial perfusion PET & coronary CT angiography

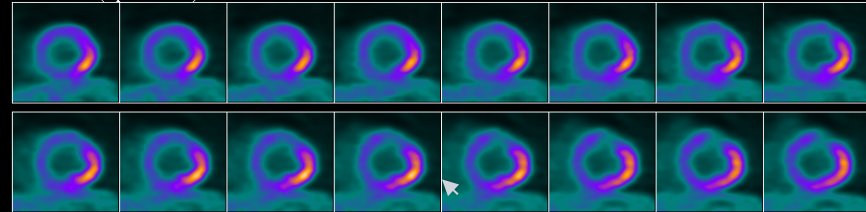# Integrated images of myocardial perfusion PET & coronary CT angiography

Hybrid PET/CT of myocardial perfusion PET & coronary CT angiography

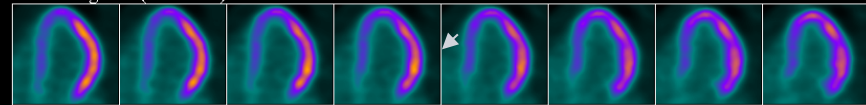*Kajander S et al, Circulation 2010;122:603-13*
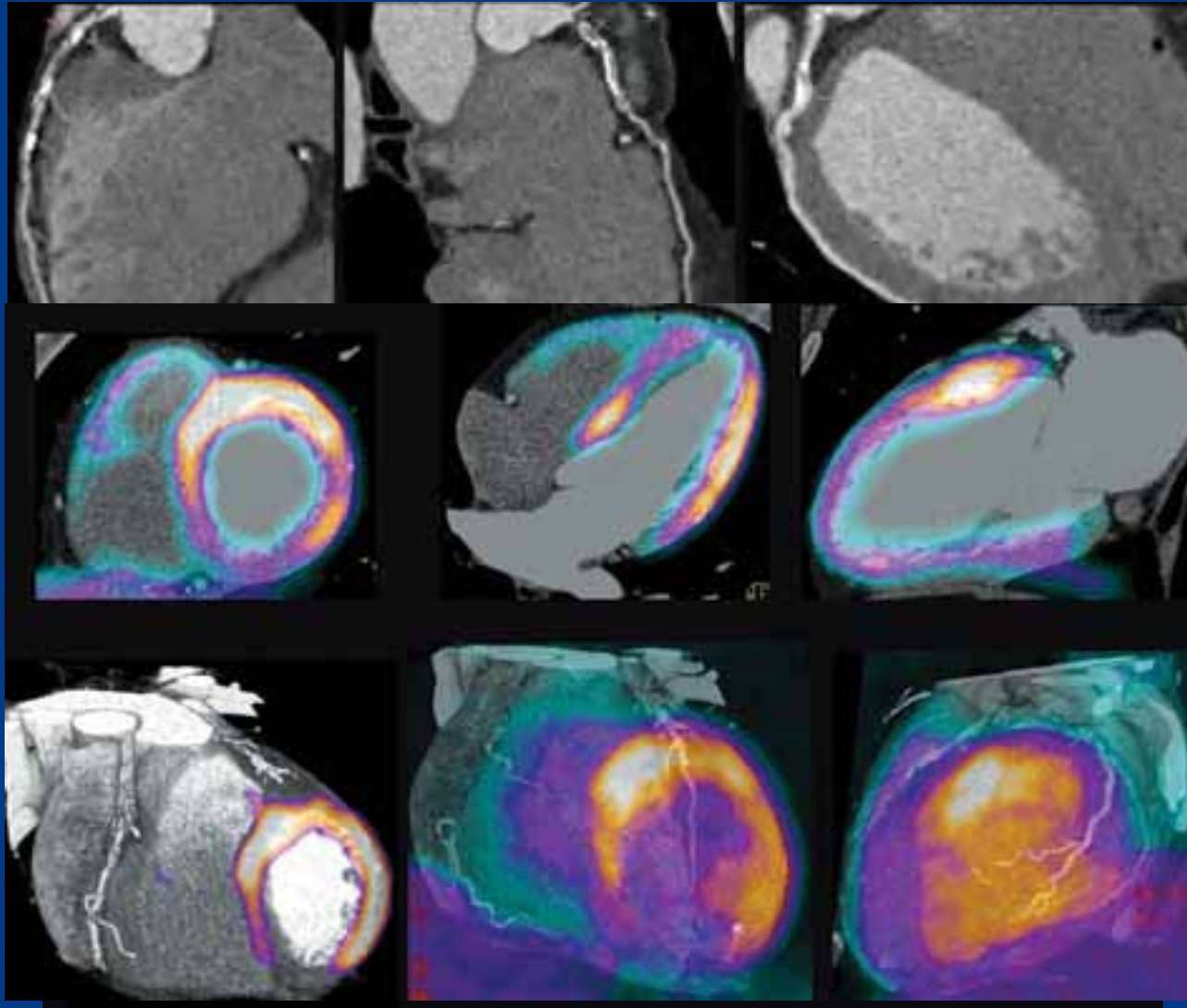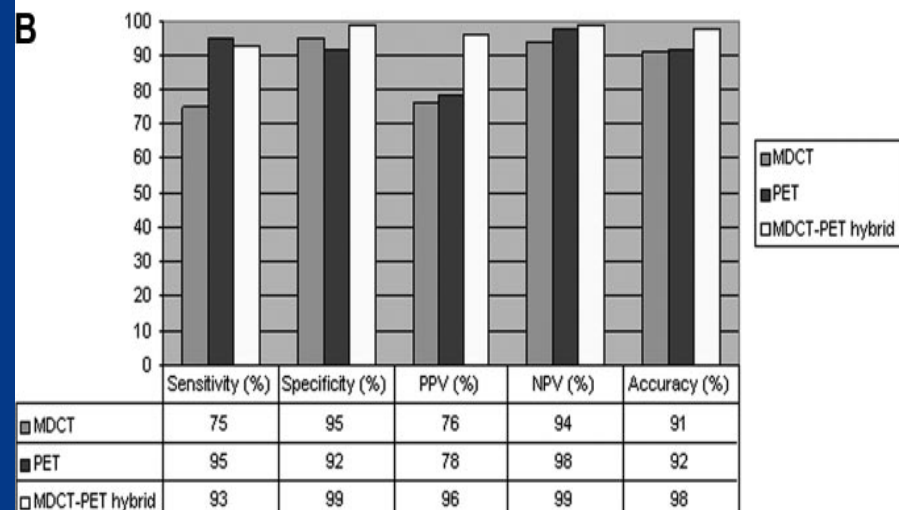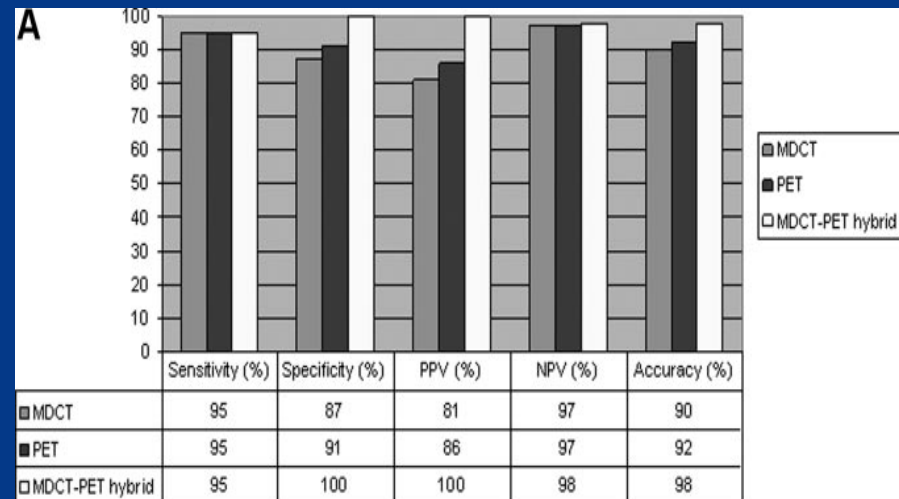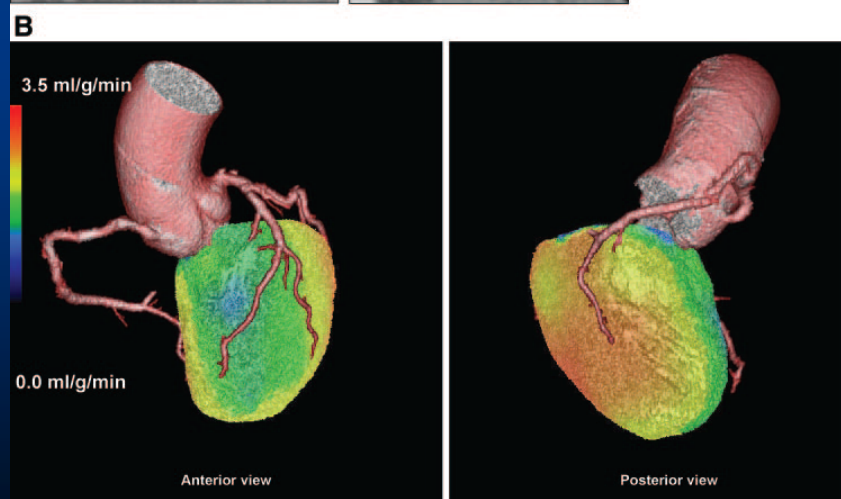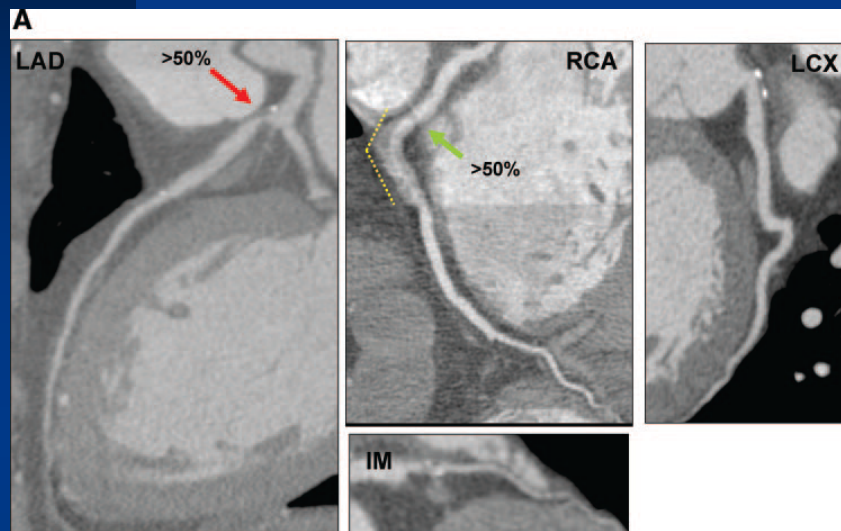
Fusion imaging of coronary CT angiography & FDG PET/CT
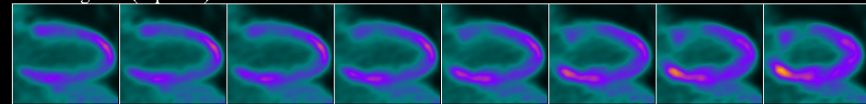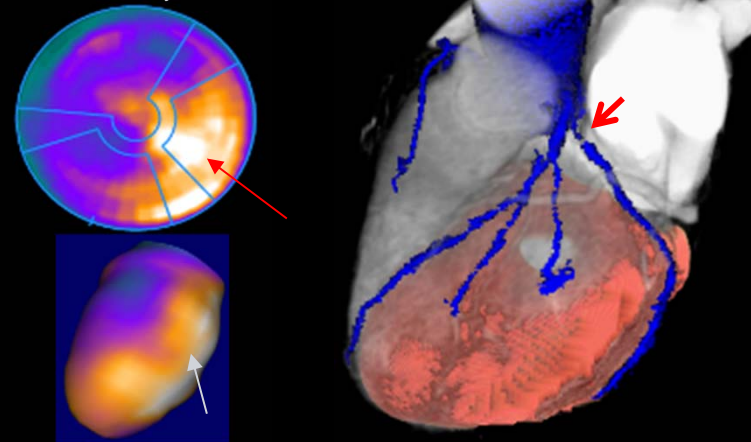
Hybrid imaging of myocardial perfusion PET & coronary CT angiography fusion imaging will be available in the near future.

Automatic alignment of myocardial perfusion PET & coronary CT angiography will make hybrid imaging more promising.

# Novel coronary arterial PET imaging probes other than FDG

Advantages

1. Avoid myocardial uptake
   → Target-to-background ratio↑
2. Highly specific for vulnerable plaques & thus
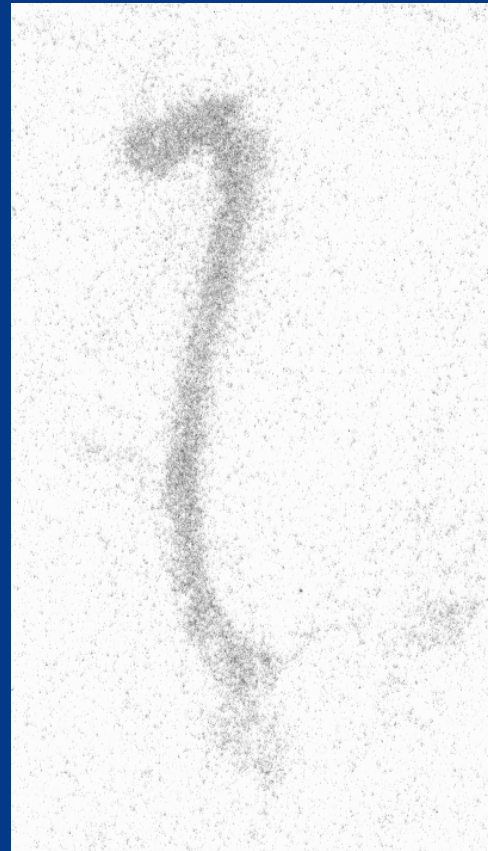   → Positive & negative predictive value↑

Difficulty

Highly specific for vulnerable plaque
→ significant accumulation of PET agent at least within 2-3 hours because of short half-life of ^{18}F

FDG vs novel apoptosis-targeting PET tracer successfully developed for cancer detection
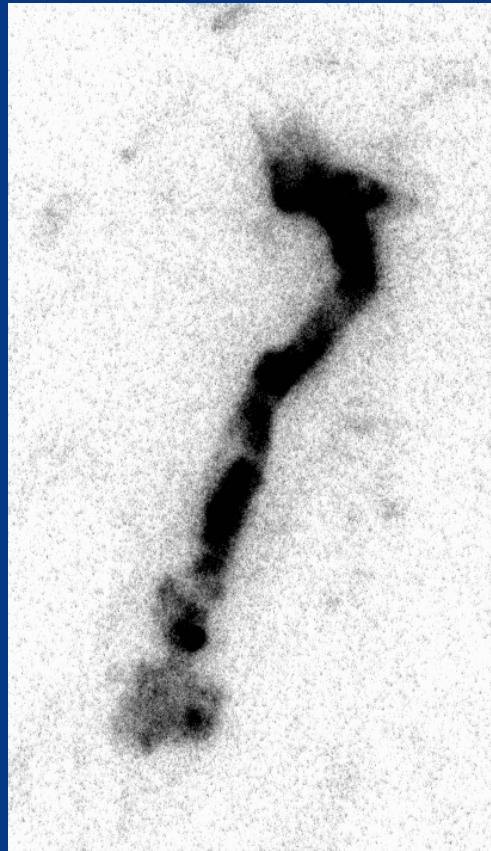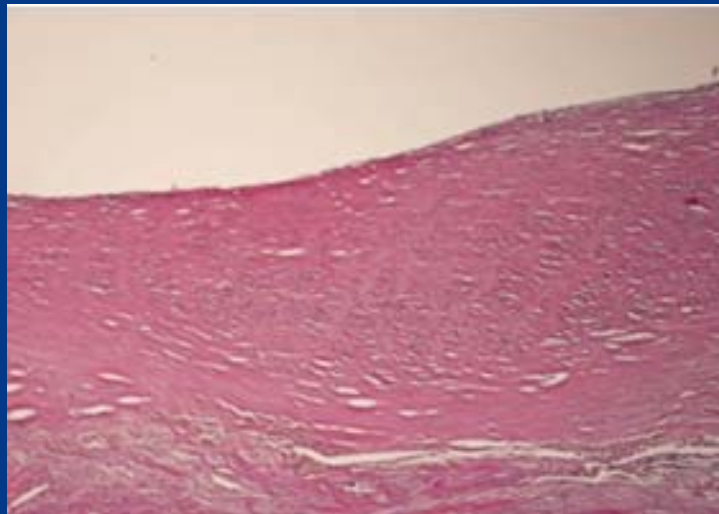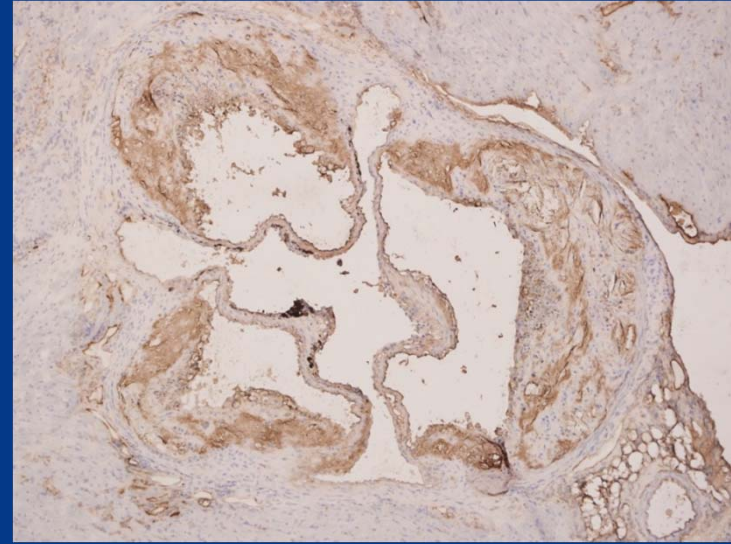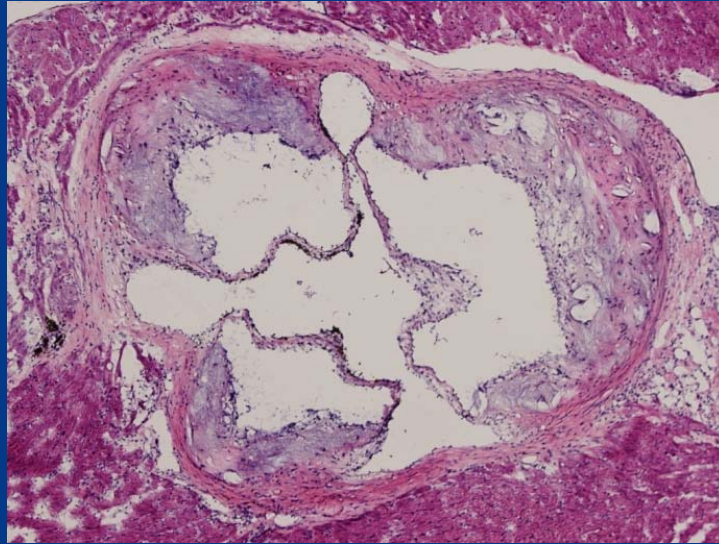

FDG   **Novel tracer**

Atherosclerosis in mice vs humans

- **Inflammation is the most abundant plaque component in mice, whereas in humans it constitutes only 2% to 5% of total lesion volume.**

- **The precise mechanisms of progression from an asymptomatic stable to high-risk plaque are incompletely understood.**

- **The best target to identify vulnerable plaques in humans are not yet known.**

Present & Future of Vascular PET Imaging

1. ^{18}F-FDG PET/CT of carotid arteries is ready for its prime time.

2. Coronary arterial ^{18}F-FDG PET/coronary CT angiography imaging will shift current vascular imaging pardigm.

3. Hybrid PET/CT of myocardial perfusion PET & coronary CT angiography will be a new blueocean.

4. Novel coronary arterial PET imaging agents other than FDG will replace FDG to identify vulnerable plaques in coronary arteries.

Thank you for your attention!