Nuclear Imaging Approach to Plaque Characterization

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COI Disclosure

Name of First Author: Joon Young Choi

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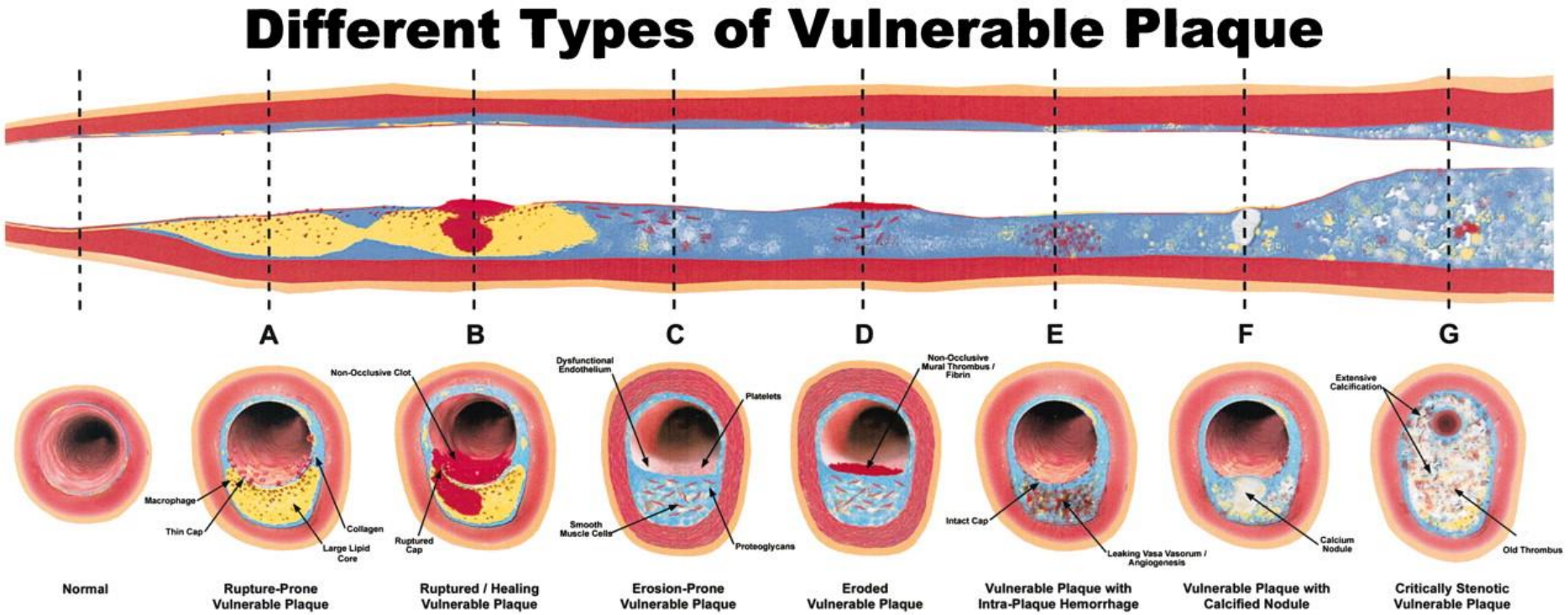
Contents

- Overview of plaque nuclear imaging
- ^{18}F-FDG PET/CT in plaque characterization
- ^{18}F-sodium fluoride PET/CT in plaque characterization
- ^{18}F-GP1 PET/CT in plaque characterization
- Other tracers

Cardiovascular Atherosclerotic Disease

- Leading cause of death in western countries
- Korea: cause of death in 35%
- Preventing acute coronary events and their sequelae
- Identifying patients at increased risk → intensive care
- Various kinds of risk stratification systems: low hazard rate

Vulnerable Plaque Concept



- Future Culprit Plaque, high-risk plaque, unstable plaque
- All thrombosis-prone plaques and plaques with a high probability of undergoing rapid progression, thus becoming culprit plaques

Naghavi M, et al. Circulation. 2003;108:1664-1672

Vulnerable Plaque - Major Criteria

- Active Inflammation
- A thin cap with a large lipid core
- Endothelial denudation with superficial platelet aggregation
- Fissured/injured plaque
- Severe stenosis

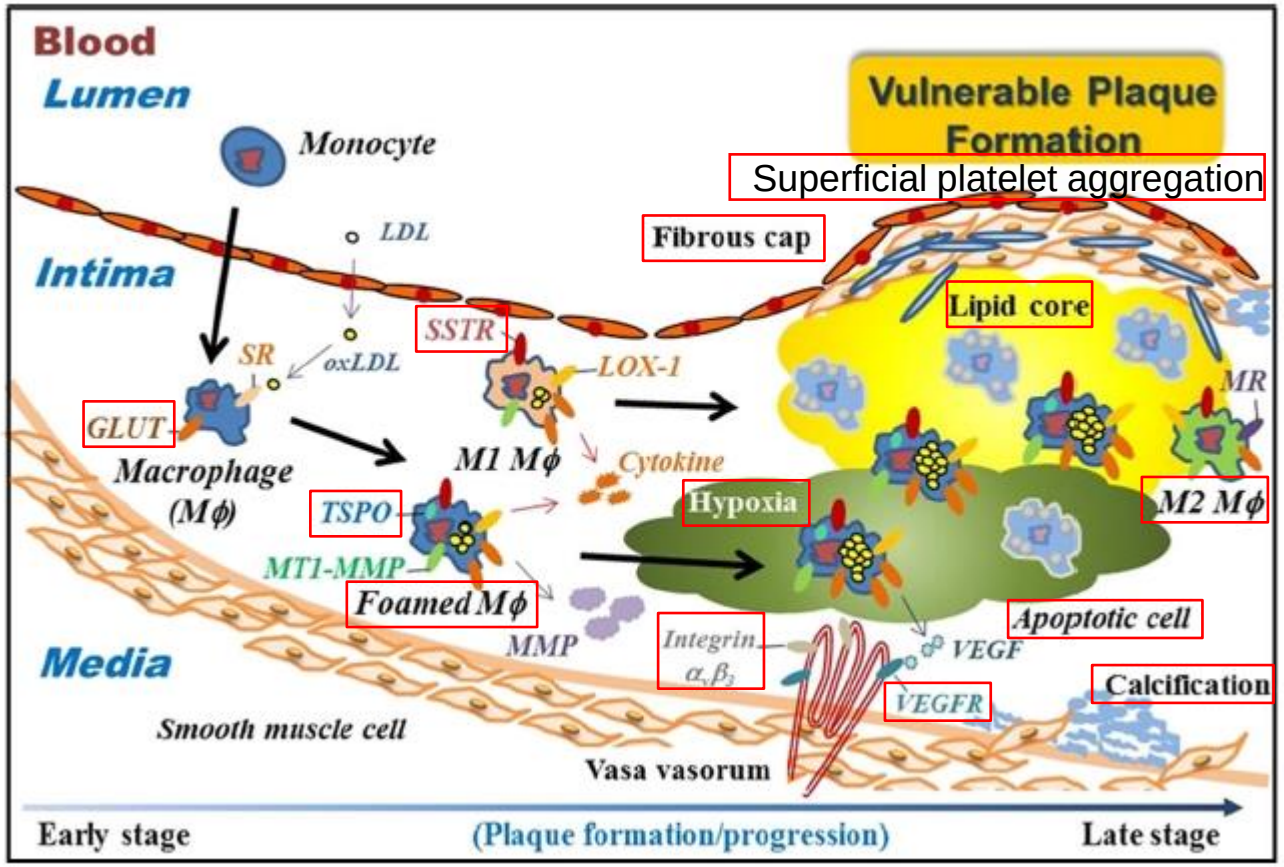
Naghavi M, et al. Circulation. 2003;108:1664-1672

Vulnerable Plaque - Minor Criteria

- Superficial calcified nodules
- Yellow color
- Intraplaque hemorrhage
- Endothelial dysfunction
- Expansive (positive) remodeling

Naghavi M, et al. Circulation. 2003;108:1664-1672

Molecular Targets for Nuclear Imaging



Shimizu Y, et al. Nucl Med Mol Imaging. 2016;50:284–91

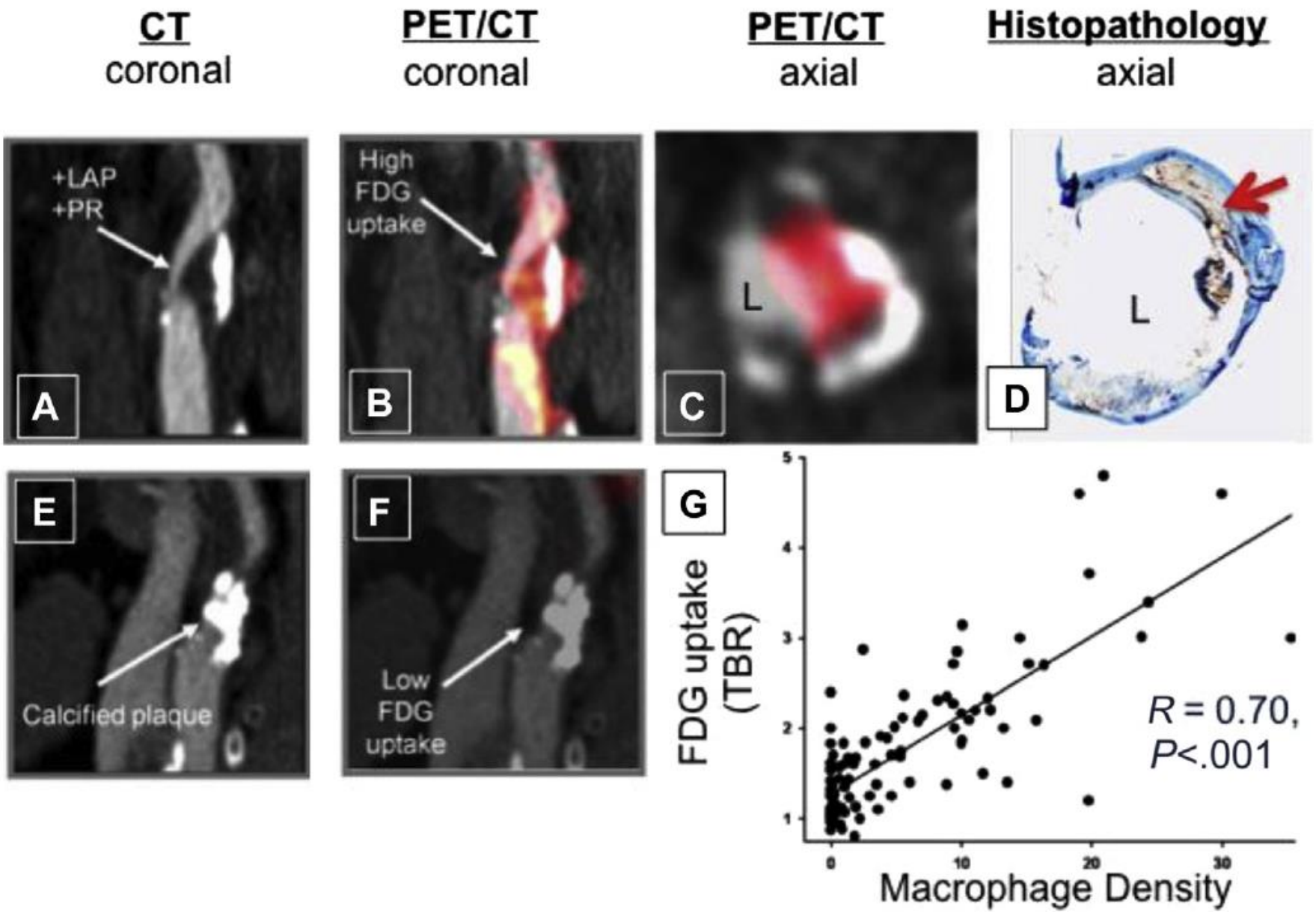
Nuclear Imaging

Process	Target	Probe
Inflammation	Macrophages	^{99m}Tc-MCP-1 [1]
	Chemokine (C-C motif) receptor 2 (Ccr2)	^{11}C-choline [2]
	Choline metabolic activity	^{18}F-fluorocholine [3]
	Translocator protein (TSPO)	^{123}I-DPA-713 [4]
	Somatostatin receptor subtype 2	^{11}C-PK11195 [5]
	Phosphatidyl serine receptor	^{64}Cu-DOTATATE [6, 7] ^{68}Ga-DOTATATE [8]
	Foam cell, M1 macrophage	^{111}In-PS200 [9]
	Glucose metabolic activity	^{18}F-FDG [10]
	M2 macrophage	^{18}F-FDM [11]
	Mannose receptor	^{99m}Tc-/^{123}I-IL-2 [12]
	Lymphocyte	
Lipid core and fibrous cap formation	Lipoprotein(OxLDL)	^{123}I-AHP [13]
	LOX-1 (scavenger receptor)	^{99m}Tc-LOX-1-mAb [14]
	Fatty acid synthesis	^{11}C-Acetate [15]
Apoptosis	Phosphatidyl serine	^{99m}Tc-annexin A5 [16]
	Caspase-3	^{18}F-isatin derivatives [17]
	Membrane alteration	^{18}F-ML-10 [18]
Angiogenesis	VEGF receptor	^{89}Zr-VEGF-mAb [19]
	Integrin-$\alpha_v\beta_3$	^{18}F-galacto-RGD [20]
		^{18}F-RGD-k5 [21]
Hypoxia	Hypoxia	^{18}F-FMISO [22]
Proteolysis	MMPs	^{99m}Tc-/^{111}In-/^{123}I-/^{18}F-MMP inhibitors [23]
		^{99m}Tc-MT1-MMP-mAb [24]
Thrombosis	Platelets	^{111}In-platelets [25] ^{18}F-GP1
	Tissue factor (TF)	^{99m}Tc-TF-mAb [26]
Calcification	Mineral deposition/active calcification	^{18}F-NaF [27, 28]

Shimizu Y, et al. Nucl Med Mol Imaging. 2016;50:284–91

^{18}F-FDG PET/CT

- Glucose analogue
- High uptake in active inflammatory cells such as macrophage
- Whole body hybrid imaging
- Quantification
- Clinically available

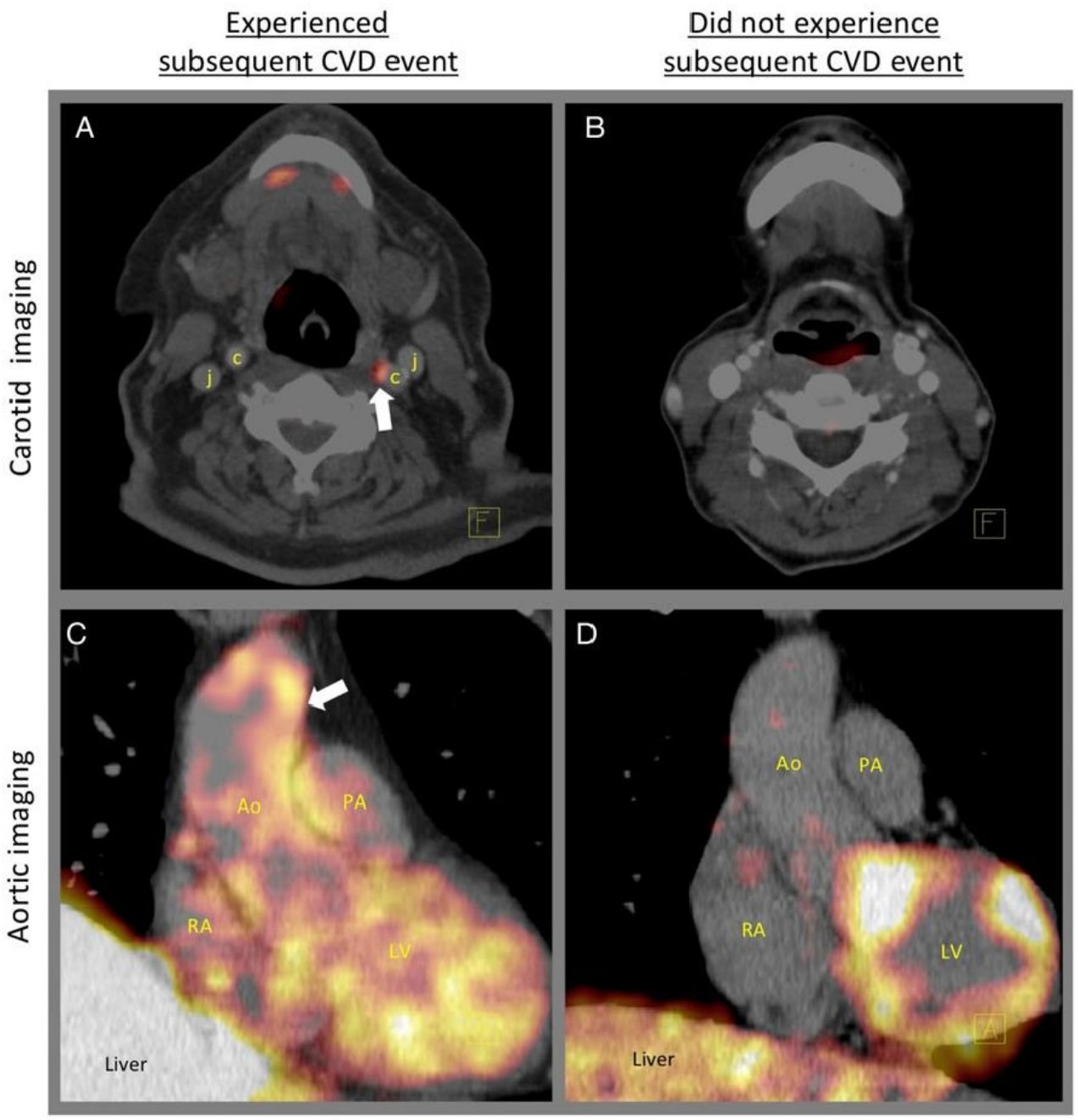


Ali A, et al. Neuroimag Clin N Am. 2016;:45–54

Clinical Results

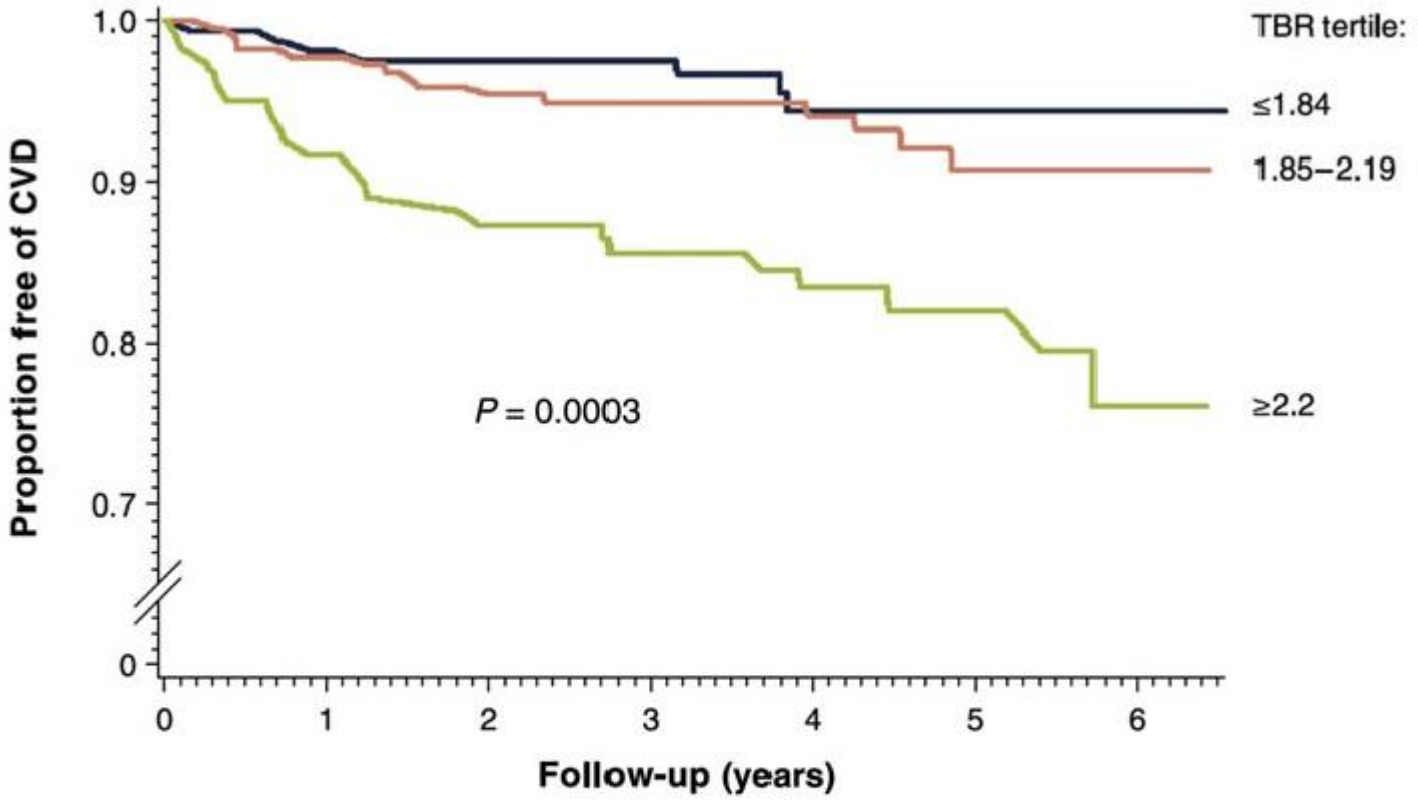
- Aortic FDG uptake: predictor for future CVD events, incremental predictive value above the coronary artery calcium and Framingham Risk Score
- Carotid FDG uptake: predictor for recurrent ipsilateral cerebrovascular events
- FDG PET in drug clinical trial

Rominger A, et al. J Nucl Med 2009;50:1611–20
Figueroa AL, et al. JACC Cardiovasc Imaging 2013;6:1250–9
Marnane M, et al. Ann Neurol 2012;71:709–18
LaRosa JC, et al. N Engl J Med 2005;352(14):1431



Joseph P, et al. Eur Heart J. 2016;37:2974–80

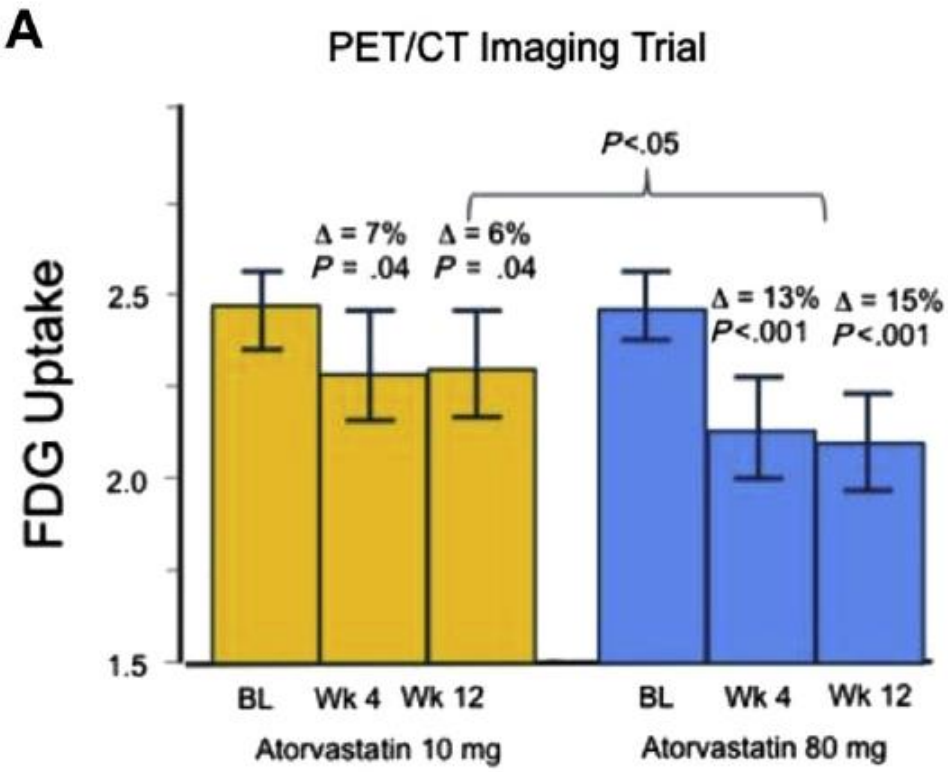
Clinical Outcome Study

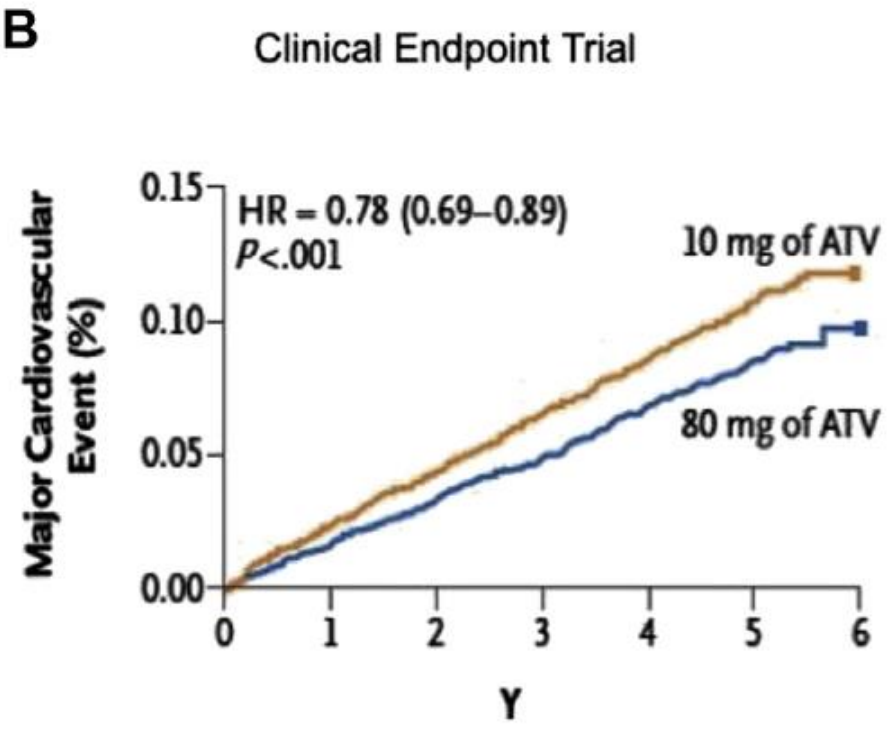


Number at risk:								Adjusted HR:
TBR Tertile 1:	167	160	149	120	75	36	10	1.0 (Referent)
TBR Tertile 2:	224	216	199	170	112	58	14	1.36 (0.55, 3.35)
TBR Tertile 3:	122	108	101	92	74	40	14	4.71 (1.98, 11.2)

Figueroa AL, et al. JACC Cardiovasc Imaging 2013;6:1250–9

FDG PET/CT in Drug Trial





LaRosa JC, et al. N Engl J Med 2005;352(14):1431

Limitations

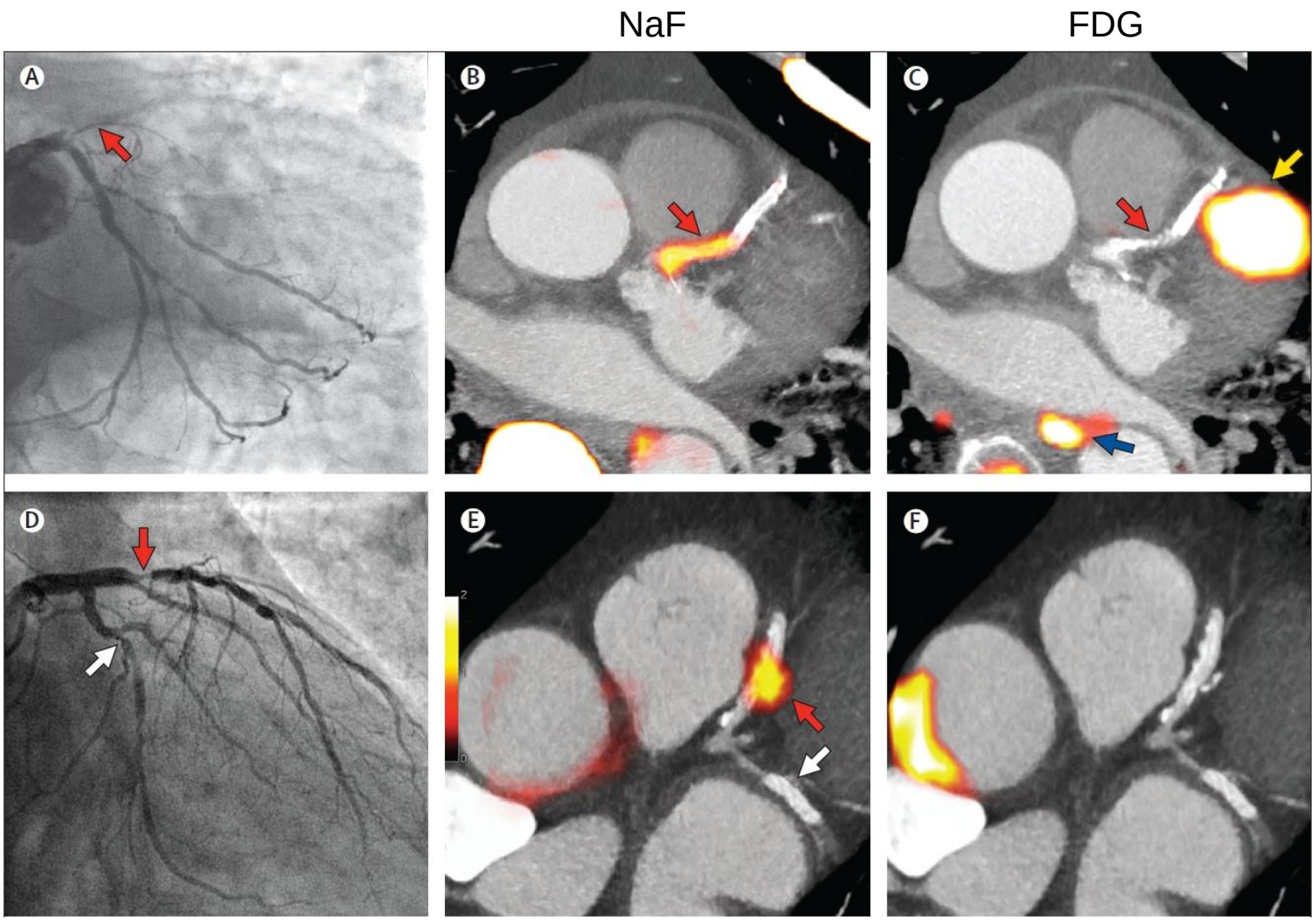
- Lack of large prospective clinical trials
- Various kinds of quantitation methods
- Significant overlap in values
- Low spatial resolution of PET: coronary plaque
- Myocardial physiological uptake
- Motion artifact: respiration, cardiac motion

^{18}F-Sodium Fluoride PET/CT

- To identify areas of calcification, active calcification and micro-calcification of vulnerable plaque
- Low myocardial background uptake, clinically available
- Clinical results
  - High uptake in culprit coronary plaques
  - High uptake associated with high-risk features on IVUS
  - High correlation with clinical CV risk, coronary artery calcium score
- Limitations: lack of good clinical outcome studies

Joshi NV, et al. Lancet 2014;383:705–13
Dweck MR, et al. J Am Coll Cardiol 2012;59:1539–48

^{18}F-Sodium Fluoride PET/CT



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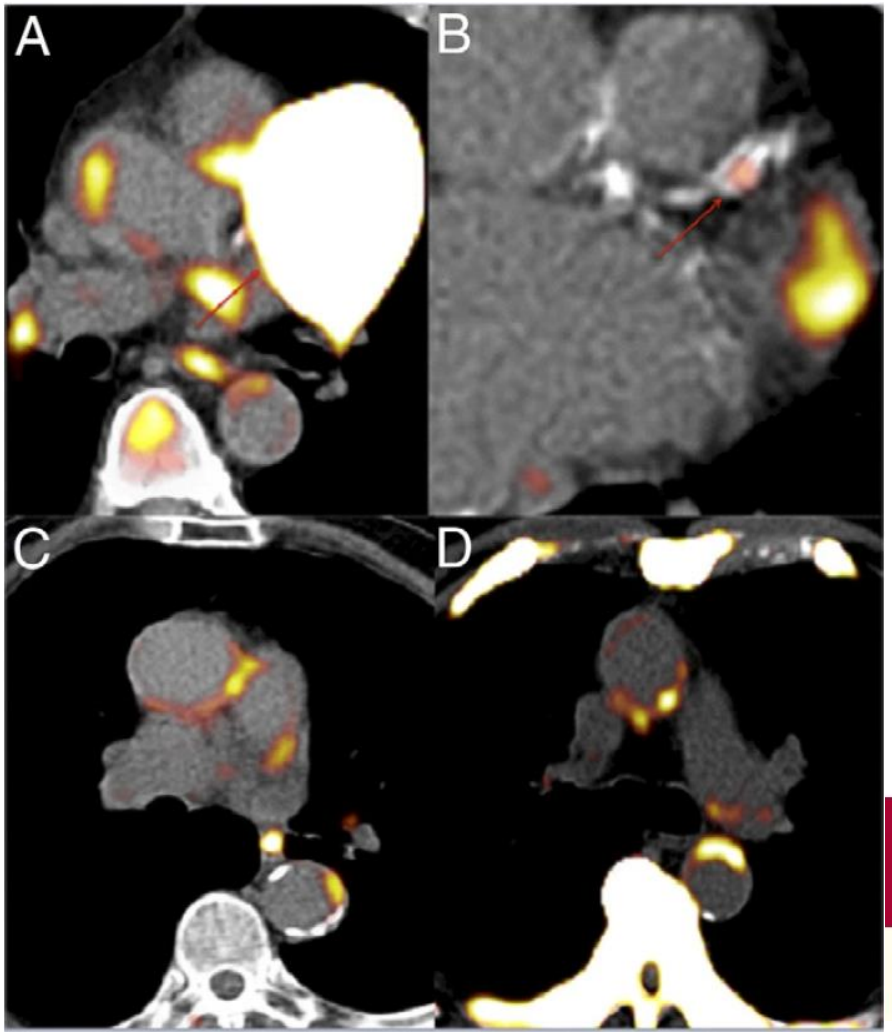
^{18}F-Sodium Fluoride PET/CT



FDG NaF

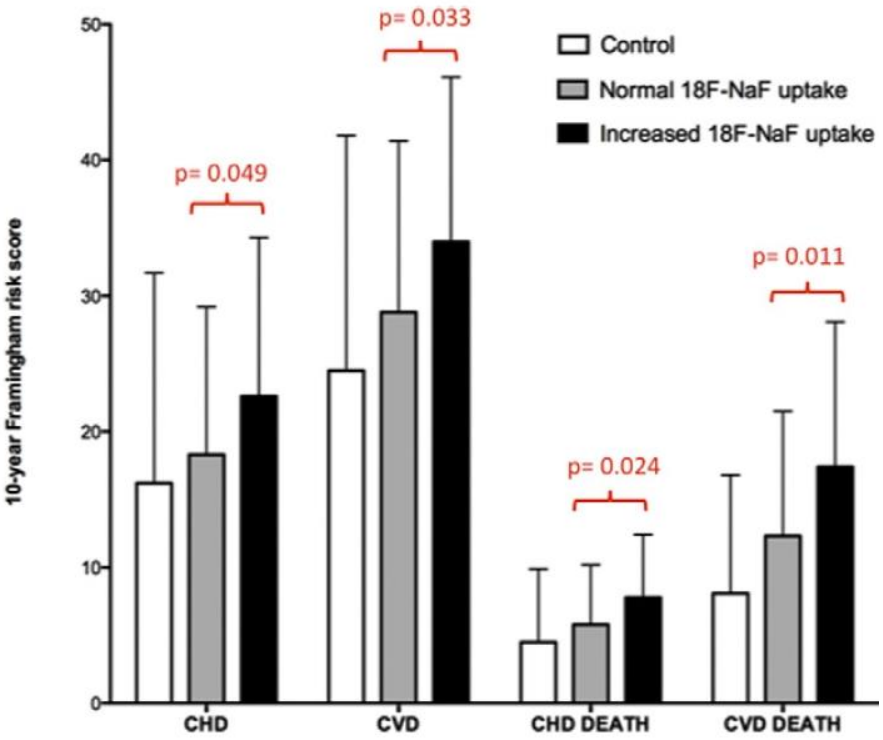


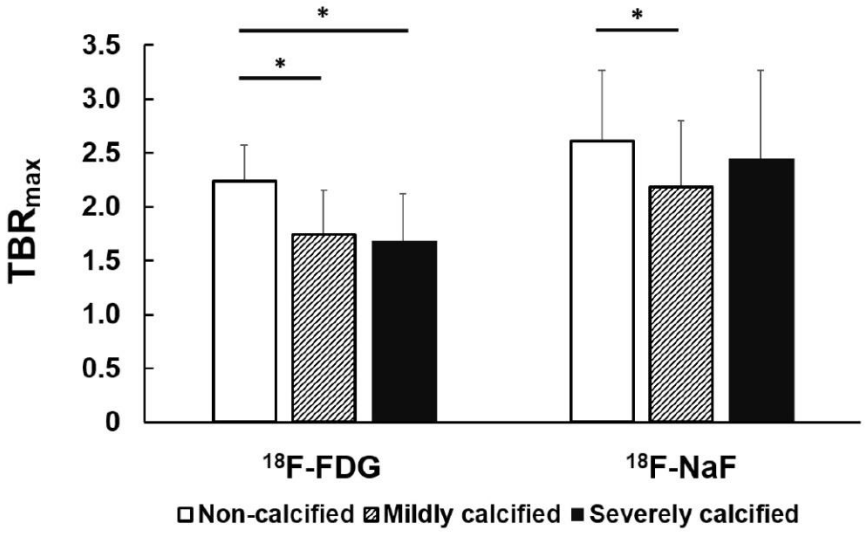
Figure 3 **10-Year Framingham Risk Scores for Control Subjects and Patients With Atherosclerosis Who Did and Did Not Have Increased 18F-NaF Uptake**

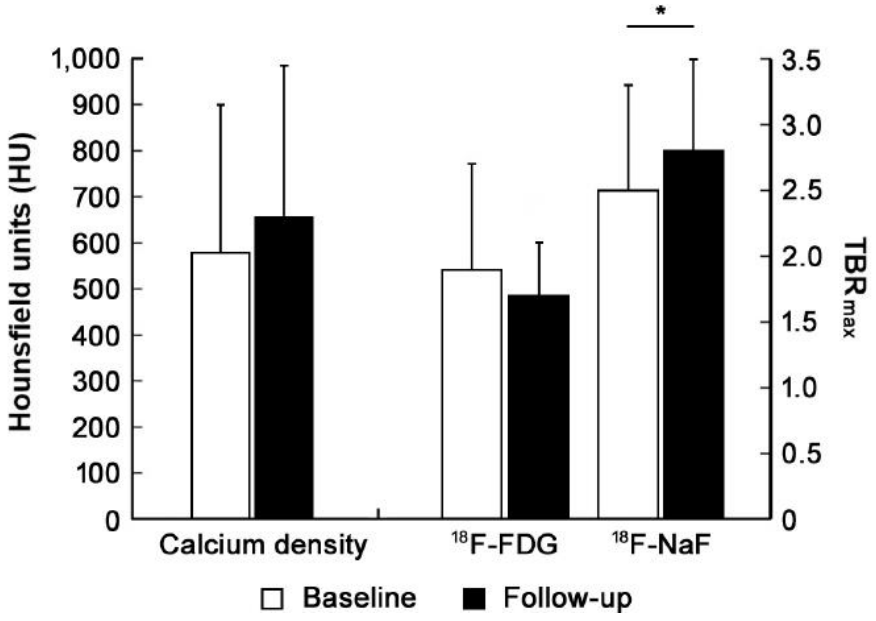
Error bars denote the SD of the mean. 18F-NaF = 18F-sodium fluoride; CHD = coronary heart disease; CVD = cardiovascular disease.

Dweck MR, et al. J Am Coll Cardiol 2012;59:1539–48

FDG vs. NaF PET/CT

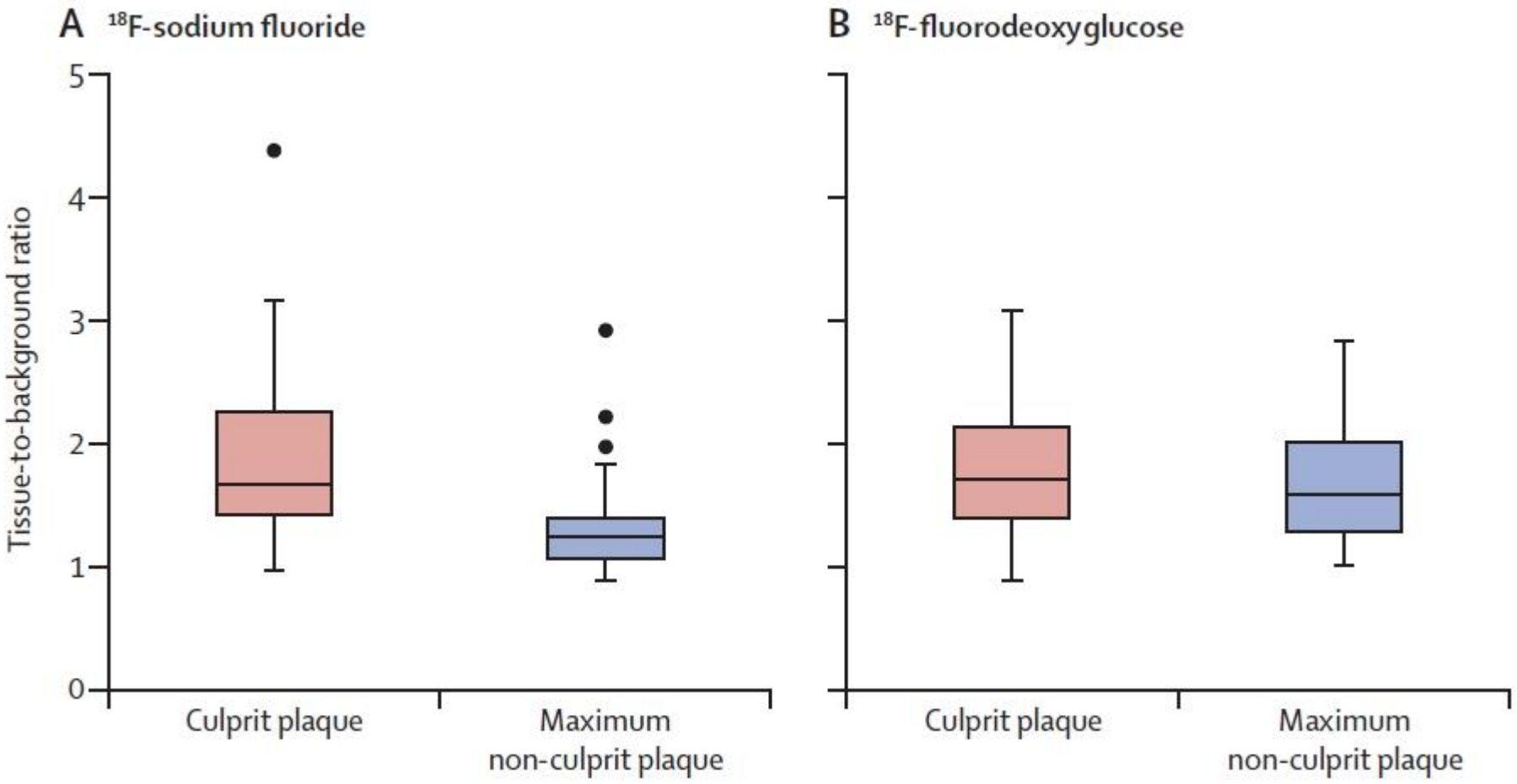
^{18}F-Fluoride uptake (n = 27)	^{18}F-FDG uptake (n = 34)	Arterial calcification (n = 34)	Total no. of patients (n = 45)
PET-positive	PET-positive	CT-positive	25
PET-positive	PET-positive	CT-negative	1
PET-positive	PET-negative	CT-positive	1
PET-negative	PET-positive	CT-positive	7
PET-negative	PET-positive	CT-negative	1
PET-negative	PET-negative	CT-positive	1
PET-negative	PET-negative	CT-negative	9





Derlin T, et al. J Nucl Med. 2011;52(7):1020-7
Li X, et al. J Nucl Med. 2017 Feb 23 (e-pub)

FDG vs. NaF PET/CT



Joshi NV, et al. Lancet 2014;383:705–13

Novel PET Imaging

- ^{68}Ga-DOTATATE: somatostatin receptor on inflammatory cells, associated with coronary calcium score, CV risk
- ^{11}C-PK11195 (targeting translocator protein receptors), ^{18}F-fluoromethylcholine (FMCH), ^{18}F-fluorodeoxymannose (FDM): activated macrophage, preclinical results on stroke, carotid, aorta
- ^{68}Ga-NOTA-RGD and ^{18}F-Galacto-RGD: neoangiogenesis
- ^{18}F-fluoromisonidazole (^{18}F-FMISO): hypoxia
- ^{18}F-GP1: activated platelet

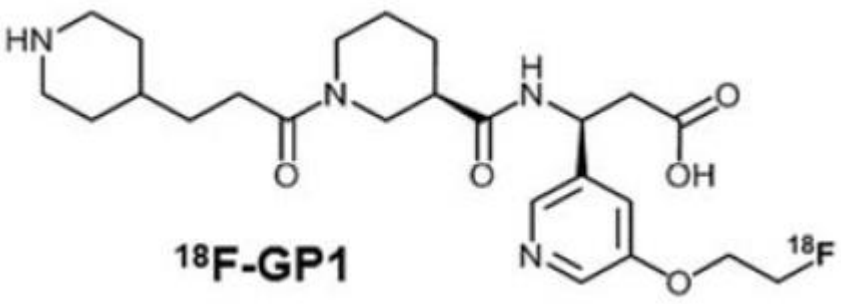
Rominger A, et al. J Nucl Med. 2010;51:193–7
Gaemperli O, et al. Eur Heart J. 2012;33:1902–10
Bucerius J, et al. Eur J Nucl Med Mol Imaging. 2008;35:815–20
Tahara N, et al. Nat Med. 2014;20:215–9
Mateo J, et al. Circ Cardiovasc Imaging. 2014;7:312–20

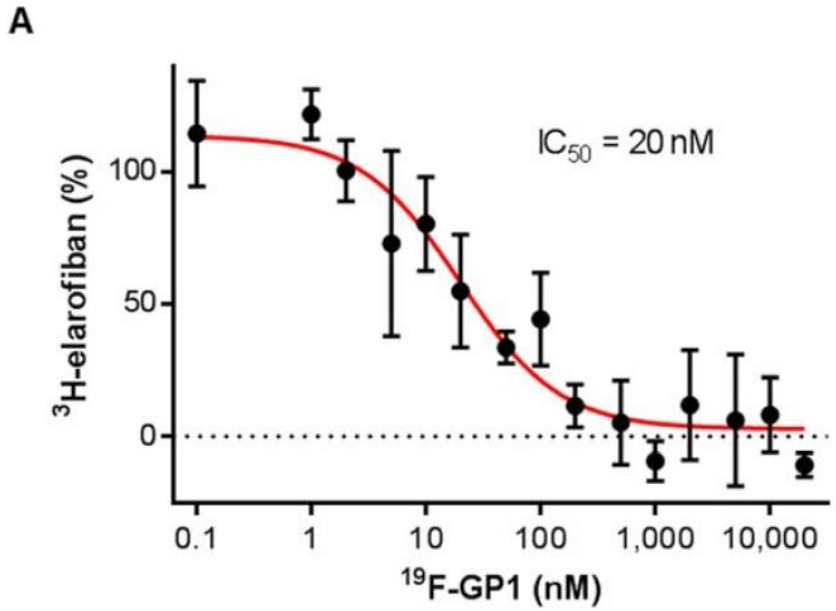
^{18}F-GP1 PET/CT

- High affinity for glycoprotein IIb/IIIa (GPIIb/IIIa) receptor of activated platelet
- Vulnerable plaque in atherosclerosis: endothelial denudation with superficial platelet aggregation
- Originally developed for venous thrombosis imaging
- Promising imaging modality for vulnerable plaque imaging
- Available in Korea
  - Cooperation between Bayer and AMC
  - Ongoing phase I clinical trial
  - Planned phase II-III clinical trial

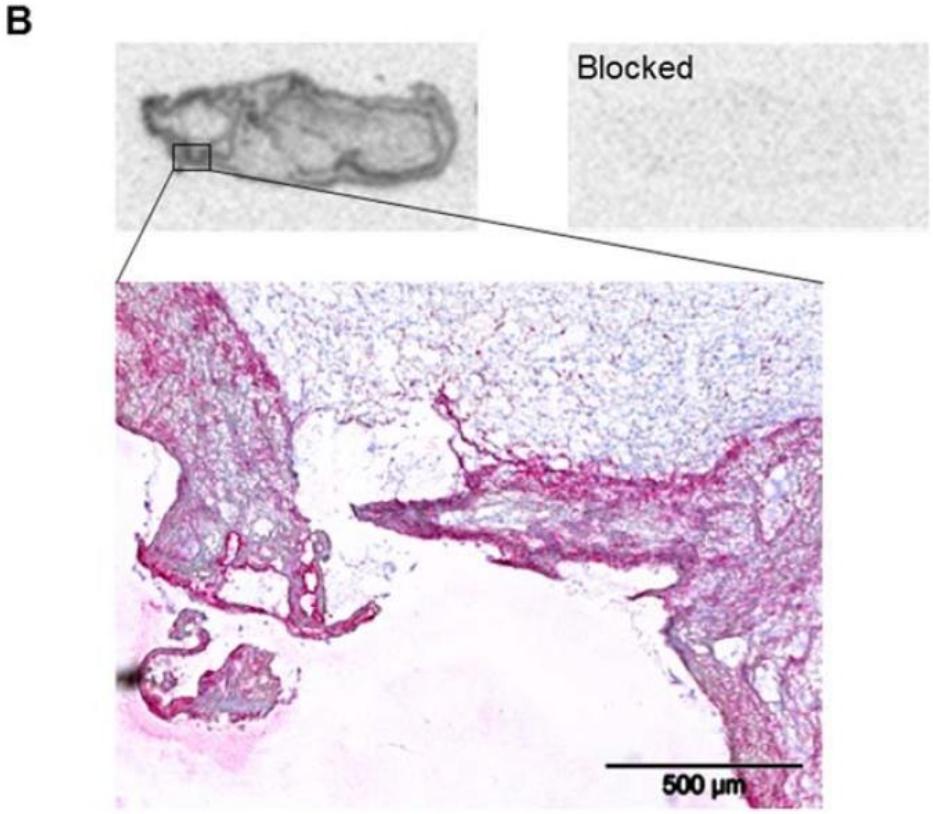
Lohrke J, et al. J Nucl Med. 2017 (e-pub)
Jin S, et al. J Nucl Med. 2017 (abstract)

Pre-clinical Study





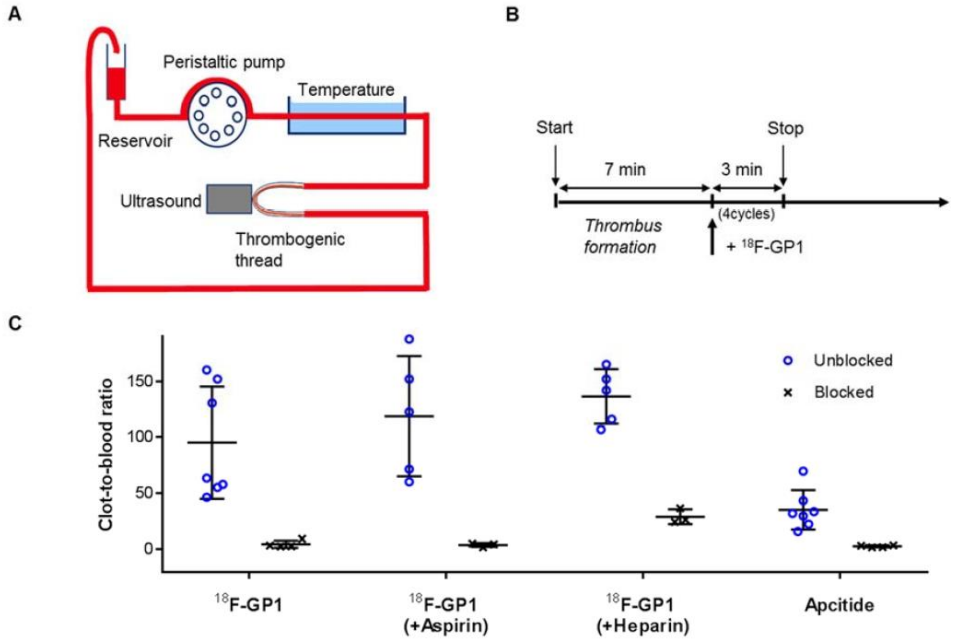
Microtiter plates coated with human GPIIa/IIIb



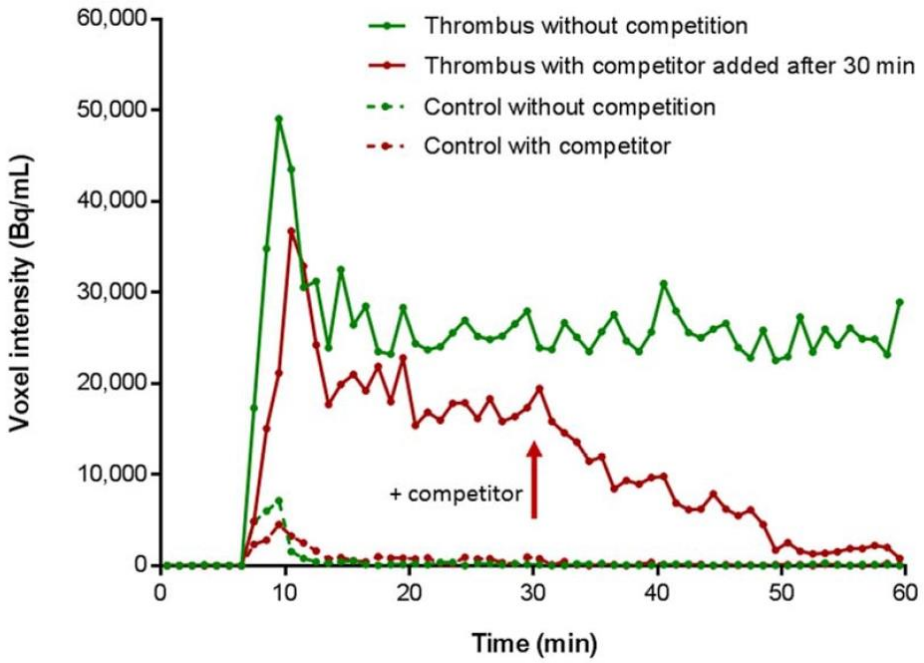
Autoradiography of human left ventricular thrombus

Lohrke J, et al. J Nucl Med. 2017 (e-pub)

Pre-clinical Study



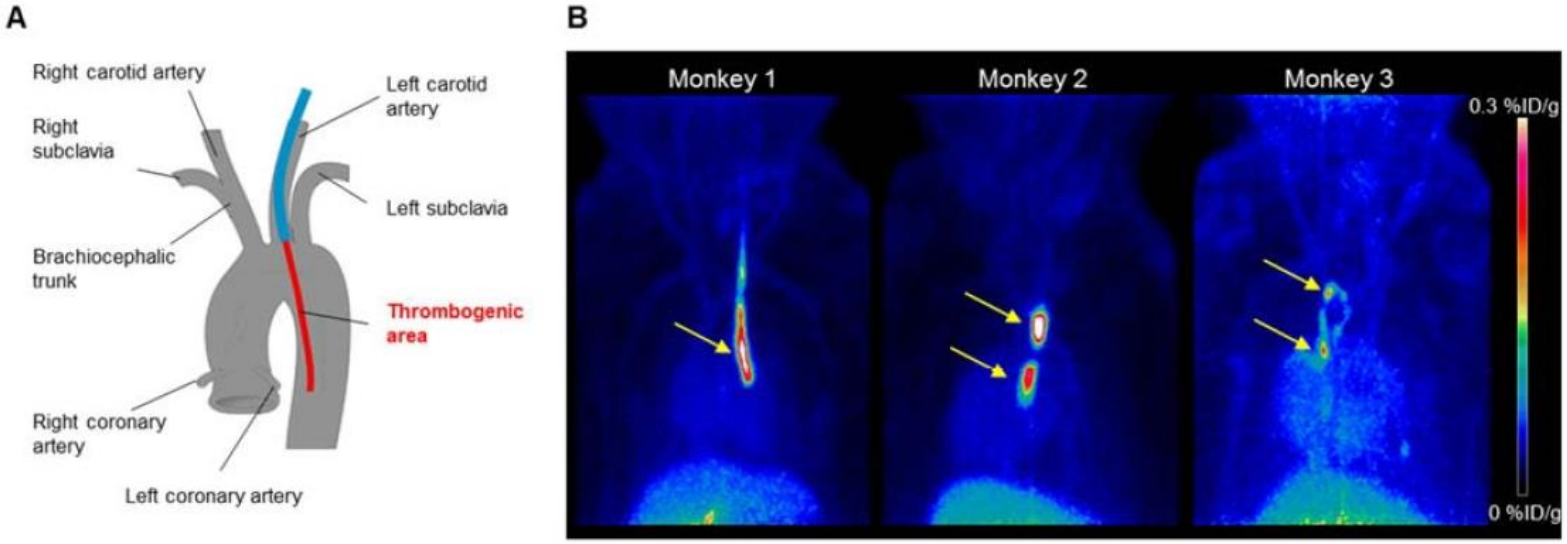
In vitro blood flow model



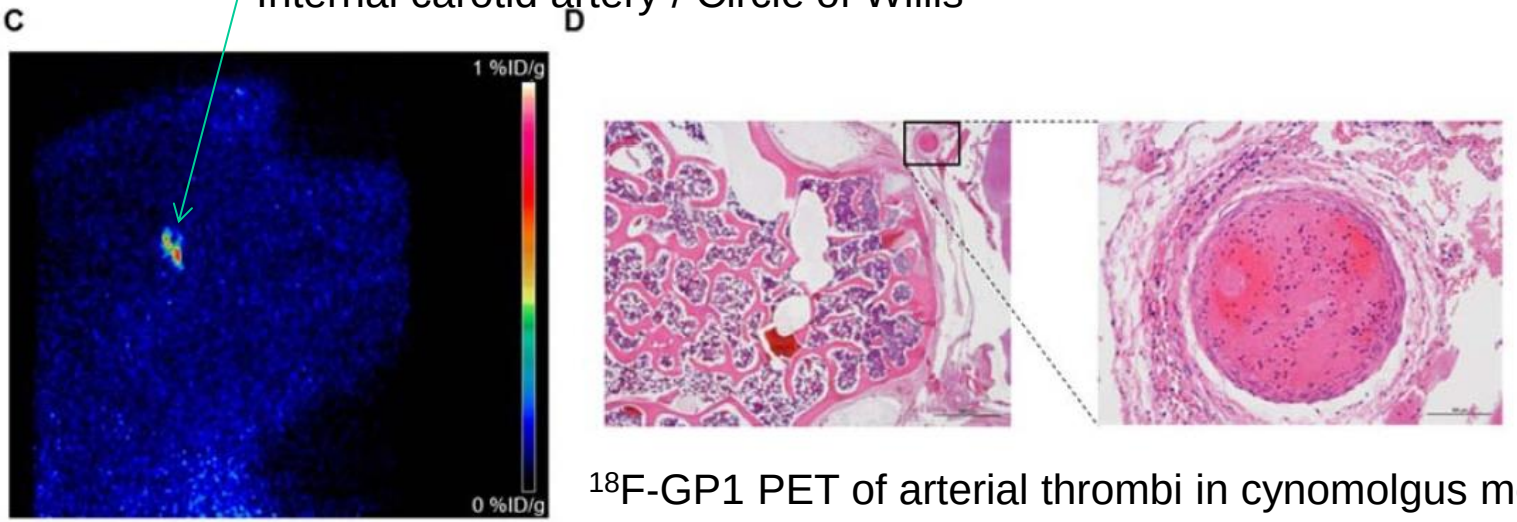
PET imaging of ^{18}F-GP1 thrombus binding in the in vitro blood flow model

Lohrke J, et al. J Nucl Med. 2017 (e-pub)

Pre-clinical Study



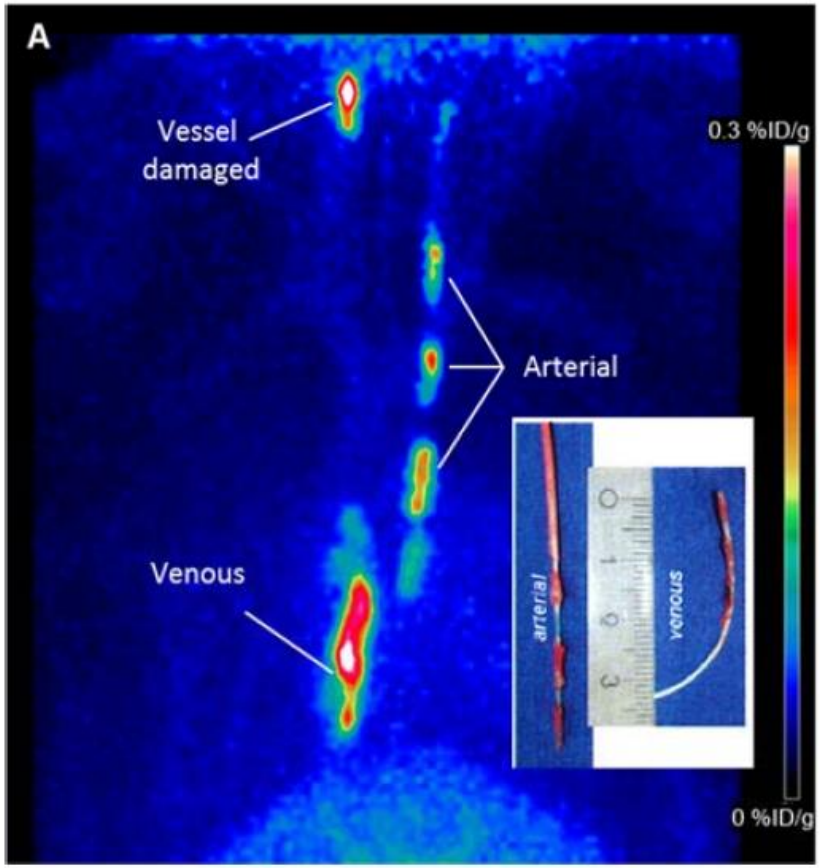
Internal carotid artery / Circle of Willis

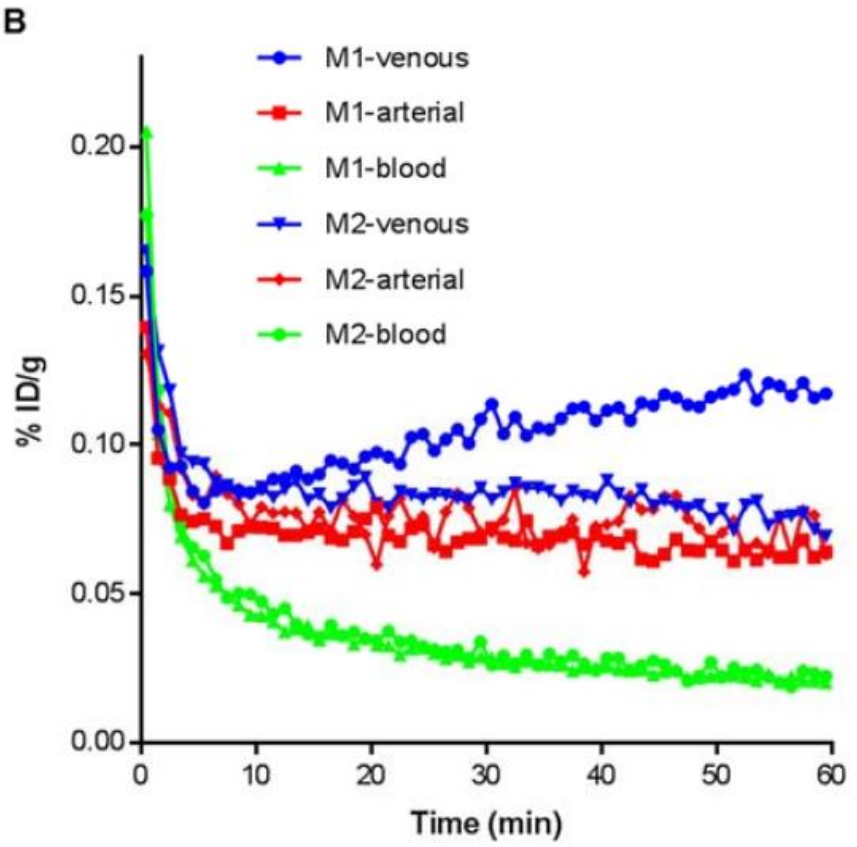


^{18}F-GP1 PET of arterial thrombi in cynomolgus monkeys.

Lohrke J, et al. J Nucl Med. 2017 (e-pub)

Pre-clinical Study





^{18}F-GP1 PET of both arterial and venous thrombi in cynomolgus monkeys.

Lohrke J, et al. J Nucl Med. 2017 (e-pub)

Clinical Study

- Interim analysis of an open-label, single center phase I study

- Patients with deep vein thrombosis (DVT, n=4), pulmonary embolism (PE, n=5) or arterial thromboembolism (ATE, n=6: one cerebral infarction, and 5 subjects after endovascular abdominal aortic aneurysm repair) who had acute thromboembolic focus/foci confirmed by standard imaging modalities

- ^{18}F-GP1 dynamic PET/CT, no drug-related adverse events

Jin S, et al. Annual SNM meeting. 2017 (abstract)

Clinical Study

- Results by visual assessment
  - Patient-based sensitivity: 100% (15/15)
  - Lesion-based sensitivity: 100% in DVT (18/18), 75% in PE (18/24), 86% in ATE (6/7)

- Quantitative results
  - SUV ratio (SUVR): lesion vs. reference tissue
  - DVT: 5.89 ± 2.71 (SUV_{max}), 4.97 ± 1.85 (SUVR)
  - PE: 4.99±2.35 (SUV_{max}), 4.24±2.01 (SUVR)
  - ATE: 5.07±1.95 (SUV_{max}), 5.34±2.17 (SUVR)
  - Clinically unexpected additional thromboembolic lesions: 47% (7/15)

Jin S, et al. Annual SNM meeting. 2017 (abstract)

Summary

- Carotid and aortic FDG uptake is associated with future cardiovascular and cerebrovascular events. However, further large prospective clinical trial is necessary.
- Coronary NaF uptake is associated with vulnerable coronary plaque. However, further clinical outcome study is necessary.
- FDG and NaF uptakes reflect different pathology of atherosclerotic plaque.
- ^{18}F-GP1 PET/CT may be a promising imaging modality for DVT, PE or ATE with a high sensitivity, which deserves further study for plaque characterization.


Thank you for your attention!