PET/MR and PET/CT for Coronary Artery Disease: Prime Time or Not?

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- PET Imaging in Coronary Artery Disease
  - FDG PET
  - Myocardial Perfusion PET
- Recent Advances in PET for Coronary Artery Disease
  - Instrument (hybrid imaging of PET/MR and PET/CT)
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  - Radiopharmaceuticals
  - Clinical needs
- The Question: Is It Prime Time or Not?

PET Imaging in CAD

FDG PET

Perfusion PET

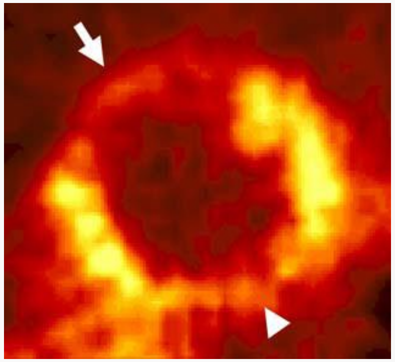
FDG PET for Viability Assessment

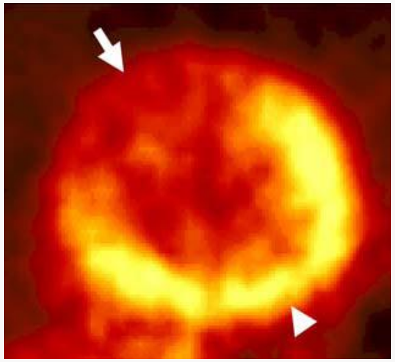
- Energy Metabolism
  - Preserved glucose (anaerobic) metabolism
  - Perfusion-metabolism mismatch

- Current Reimbursement by K-NHIS
  (Since 2006)

1.「본인일부부담금 산정특례에 관한 기준(보건복지부 고시)」
[별표 3(중증질환)]의 구분 1~3과 [별표 4(희귀난치성 질환)]
으로 분류된 질환범주(암, 뇌혈관, 심장, 희귀난치성 질환)
의 경우에는 아래의 범위 내에서 요양급여를 인정함.

나. **허혈성 심질환에서 심근의 생존능 평가** : 치료 전, 치료
후 각각 1회로 인정함


NH_3


FDG

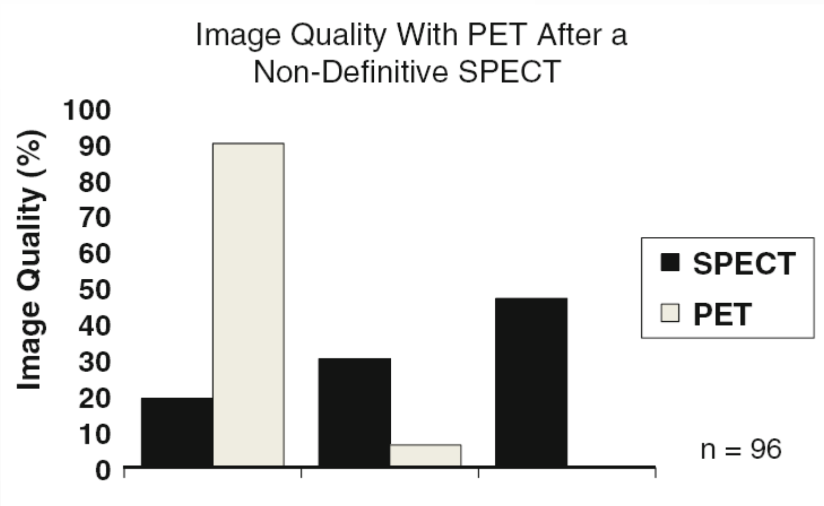
Perfusion PET (in comparison with SPECT)

Why PET ?

- Better image quality
  - CT attenuation correction
  - Localization
  - Sensitive for mild change
- Low radiation dose: 1.5 to 5 mSv
- Patients' convenience
- Absolute flow measurement with ease
  - Tracers: ^{15}O-water, ^{13}N-ammonia, ^{82}Rb, ^{18}F-flurpiridaz
  - Higher extraction fraction of PET tracers
  - Easy dynamic scan for kinetic analysis

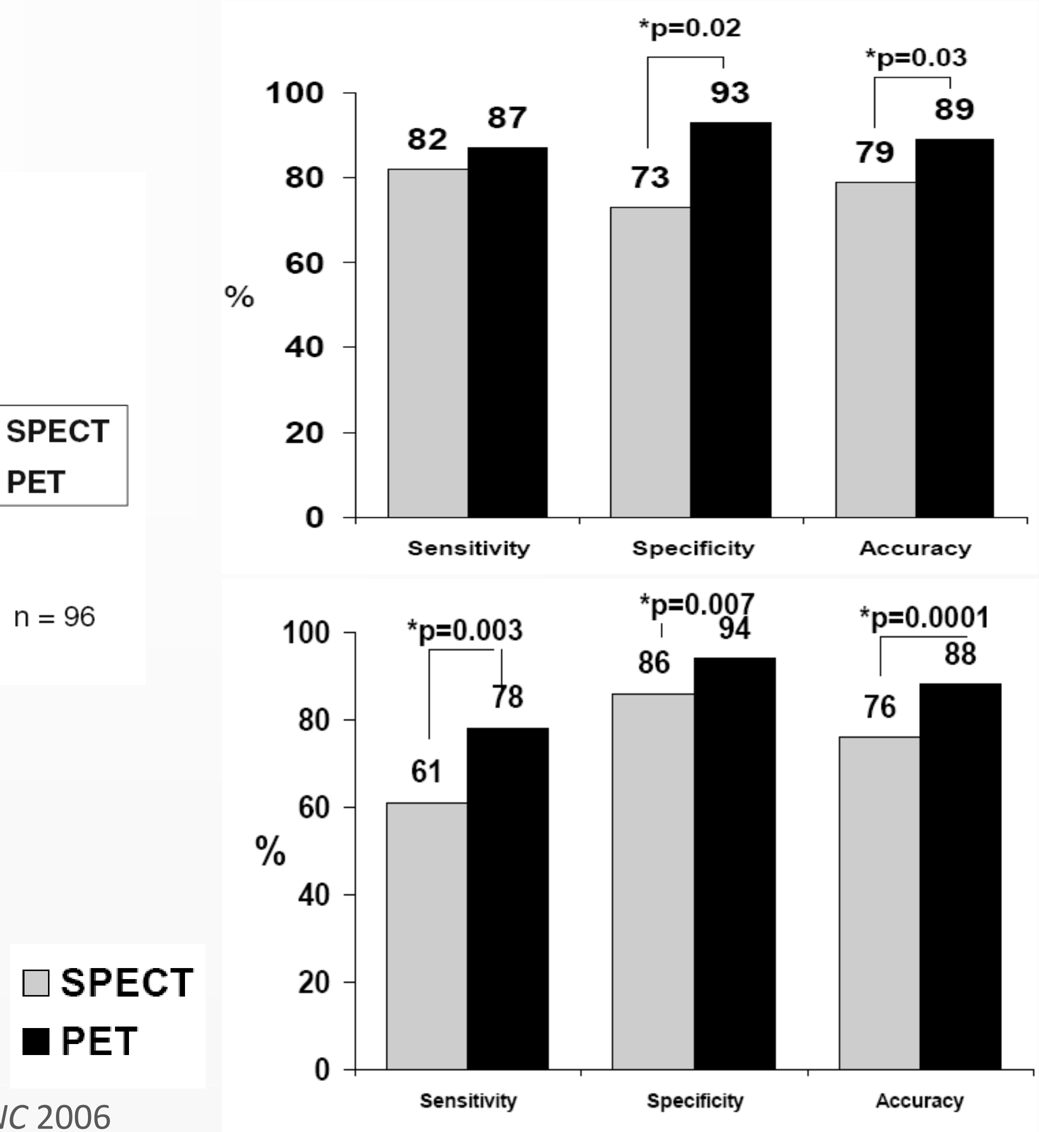
Perfusion PET Quality & Accuracy

Rb-82 PET

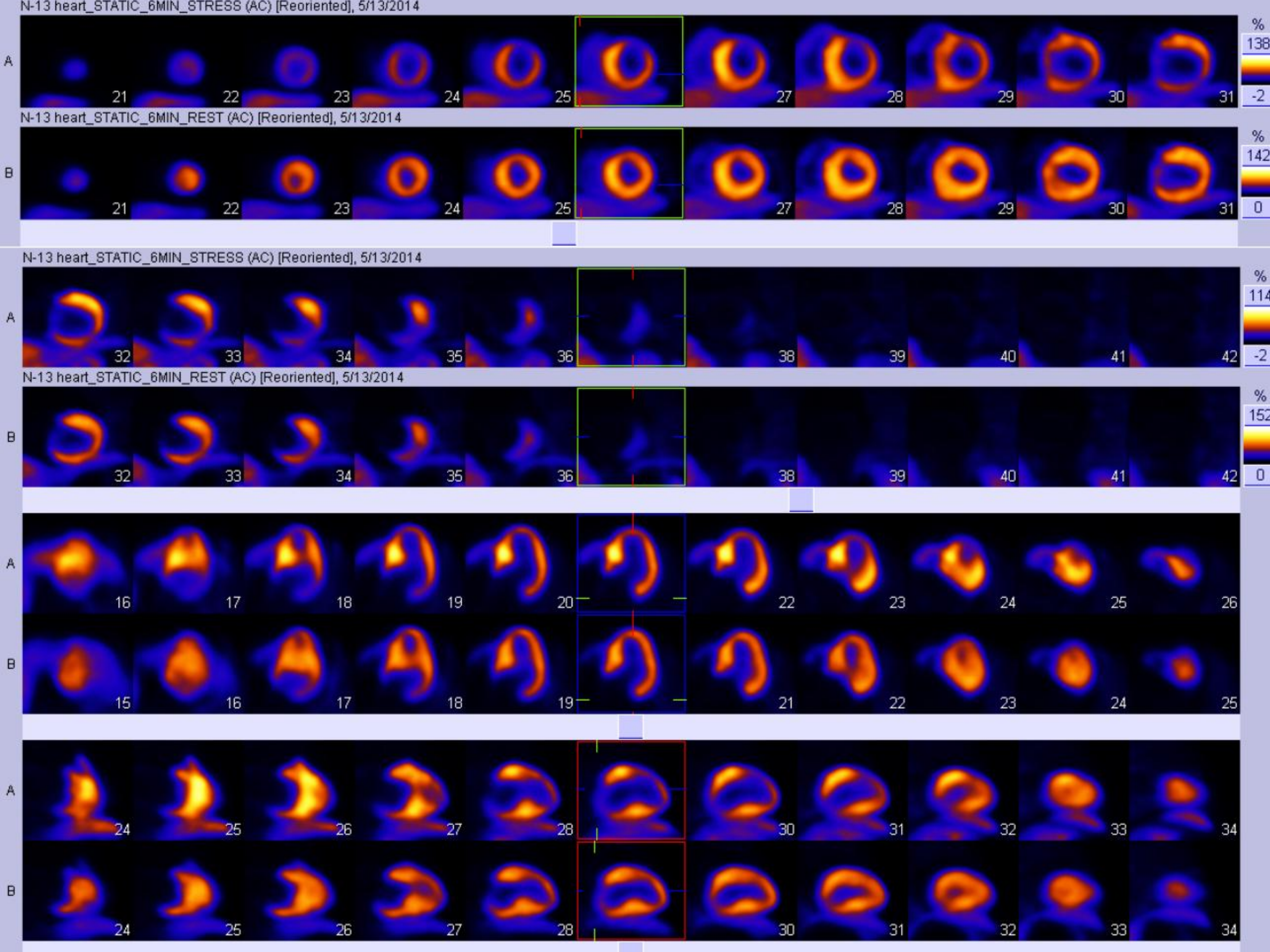


Heller et al. *JNC* 2009

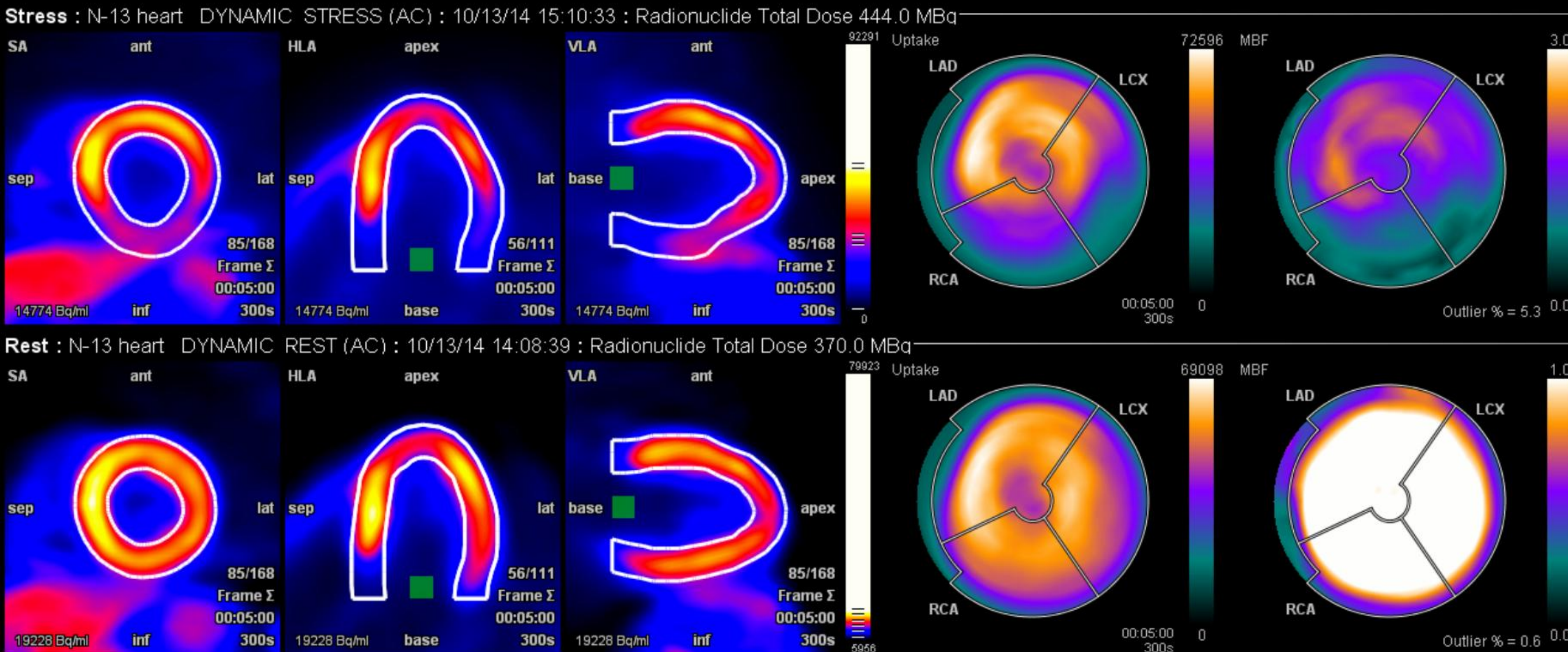
(Modified from Yoshinaga et al. *Circulation* 2006)



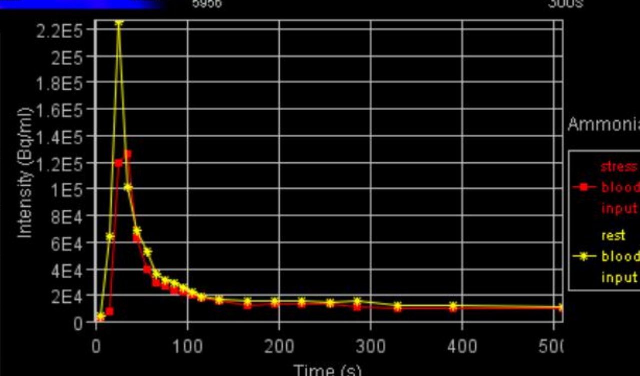
Bateman et al. *JNC* 2006

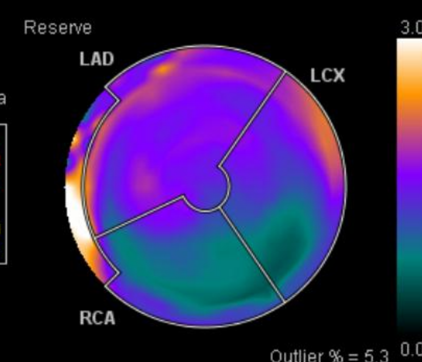

N-13 heart_STATIC_6MIN_STRESS (AC) [Reoriented], 5/13/2014
A
21 22 23 24 25 27 28 29 30 31
%
138
-2
N-13 heart_STATIC_6MIN_REST (AC) [Reoriented], 5/13/2014
B
21 22 23 24 25 27 28 29 30 31
%
142
0
N-13 heart_STATIC_6MIN_STRESS (AC) [Reoriented], 5/13/2014
A
32 33 34 35 36 38 39 40 41 42
%
-2
N-13 heart_STATIC_6MIN_REST (AC) [Reoriented], 5/13/2014
B
32 33 34 35 36 38 39 40 41 42
%
0
A
16 17 18 19 20 22 23 24 25 26
B
15 16 17 18 19 21 22 23 24 25
A
24 25 26 27 28 30 31 32 33 34
B
24 25 26 27 28 30 31 32 33 34

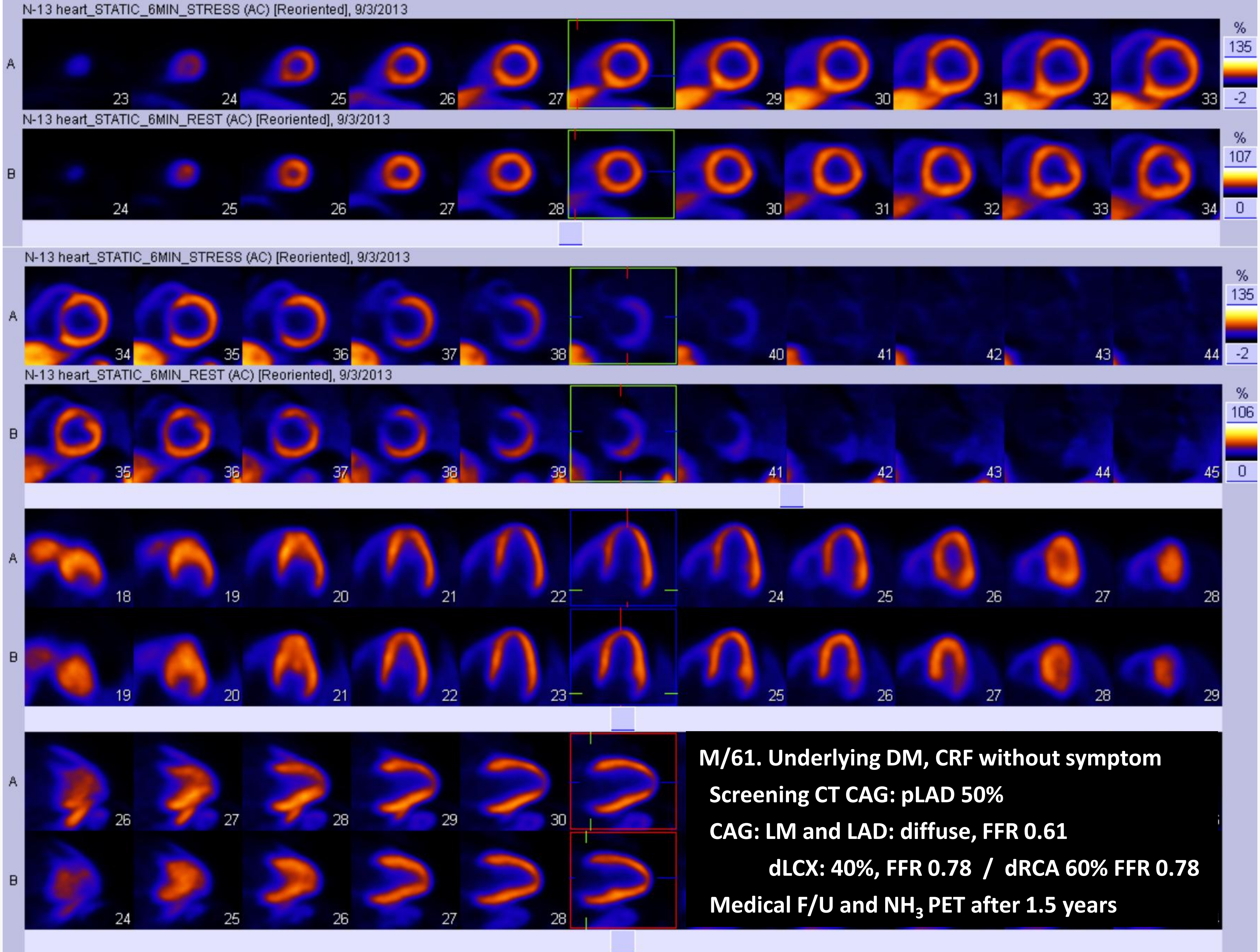
Flow Quantification



	Flow (ml/g/min)				Reserve	
	Stress		Rest			
	mean	std dev.	mean	std dev.	mean	std dev.
LAD	1.70	0.28	1.08	0.19	1.58	0.21
LCX	1.39	0.37	1.08	0.24	1.31	0.41
RCA	1.18	0.43	1.08	0.25	1.04	0.31
Global	1.50	0.40	1.08	0.22	1.38	0.37







M/61. Underlying DM, CRF without symptom

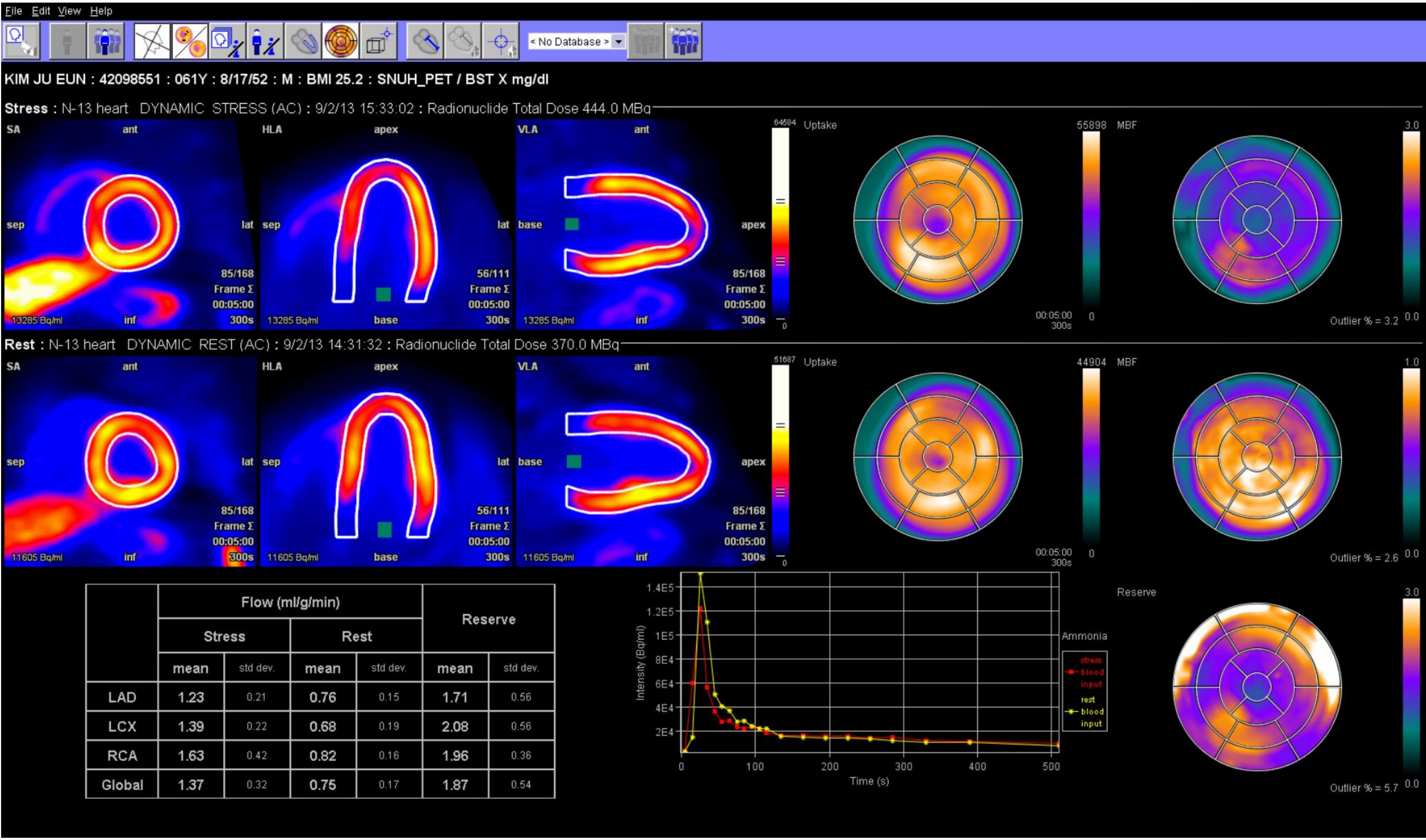
Screening CT CAG: pLAD 50%

CAG: LM and LAD: diffuse, FFR 0.61

dLCX: 40%, FFR 0.78 / dRCA 60% FFR 0.78

Medical F/U and NH_3 PET after 1.5 years

Flow Quantification

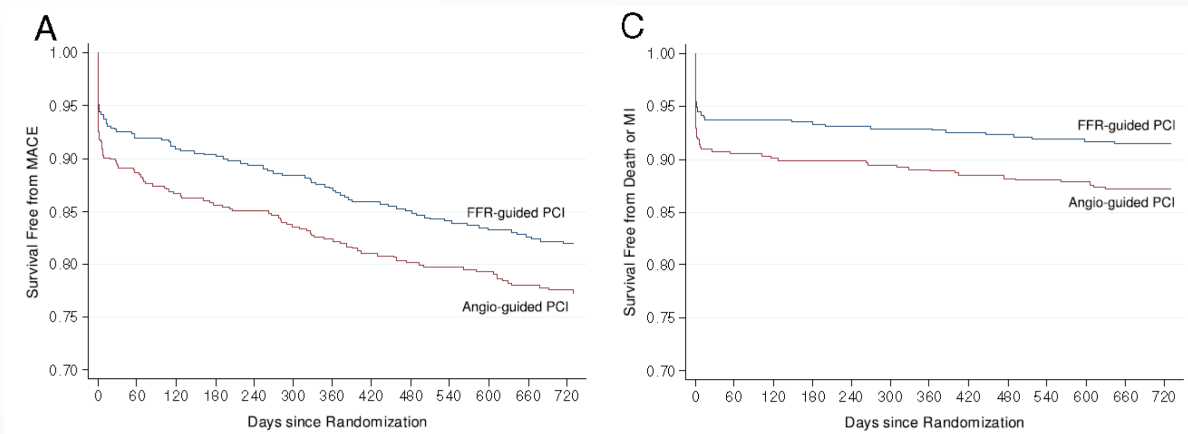


	Flow (ml/g/min)				Reserve	
	Stress		Rest			
	mean	std dev.	mean	std dev.	mean	std dev.
LAD	1.23	0.21	0.76	0.15	1.71	0.56
LCX	1.39	0.22	0.68	0.19	2.08	0.56
RCA	1.63	0.42	0.82	0.16	1.96	0.36
Global	1.37	0.32	0.75	0.17	1.87	0.54

→ Referred for CABG

Needs for Functional Study: FAME I

- **FAME** (*F*ractional Flow Reserve vs. *A*ngiography for *M*ultivessel *E*valuation)
  - FFR-guidance deferred 37% of PCI with better outcomes.

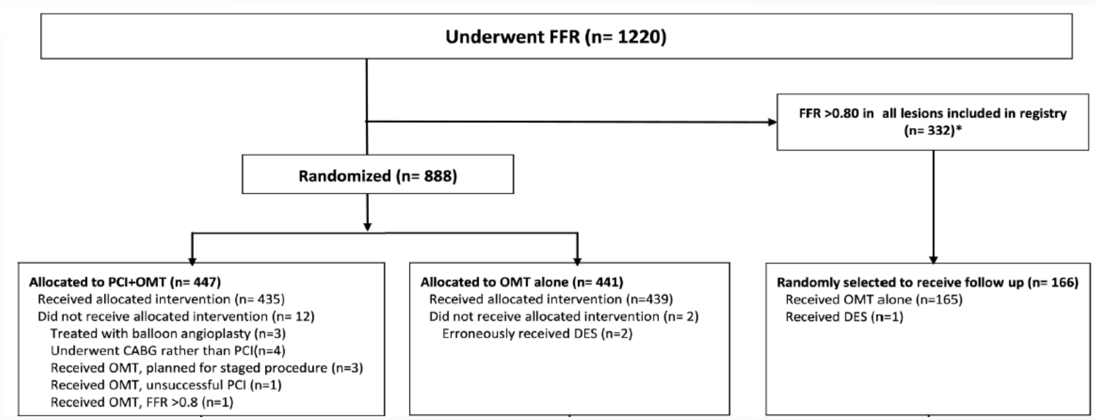


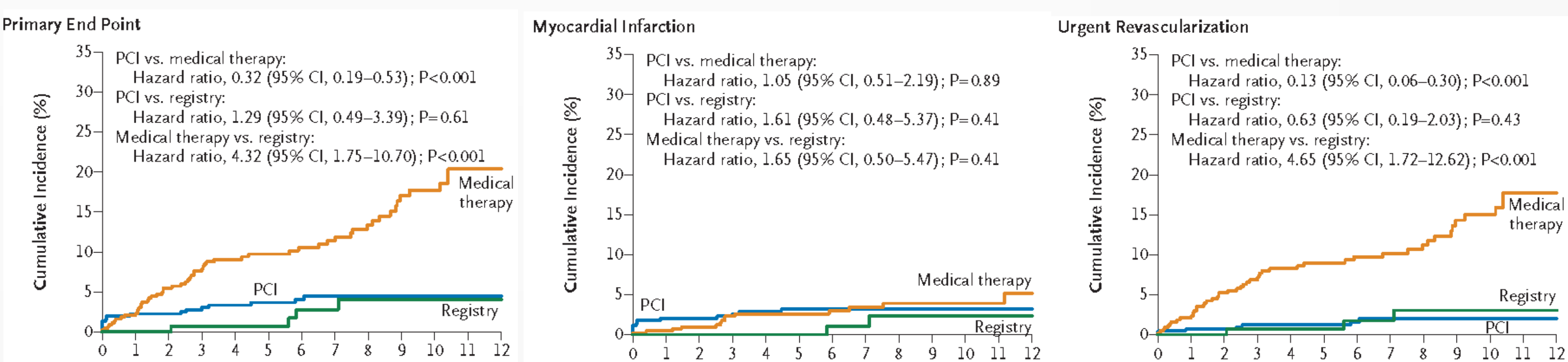
Pijls et al.
J Am Coll Cardiol 2010;56:177

	Angiography Group (n = 496)		FFR Group (n = 509)	p Value*
Procedural and 1-yr costs				
Materials, U.S.$‖	6,007 ± 2,819		5,332 ± 3,261	<0.001
Hospital stay at baseline admission, days	3.7 ± 3.5	>	3.4 ± 3.3	0.05
Incremental health care costs at 1 year, U.S.$¶	14,357		12,291	<0.001
Myocardial infarction	49 (9.9)		31 (6.1)	0.03
CABG or repeat PCI	63 (12.7)	>	54 (10.6)	0.30
Death or myocardial infarction	64 (12.9)		43 (8.4)	0.02
Death, myocardial infarction, CABG, or repeat PCI	111 (22.4)		91 (17.9)	0.08

FAME II

- **Angiographically Proven Stenosis**
  - **In 25%, FFR was not significantly low.**
  - **Regarding FFR <0.80, significantly different outcome**





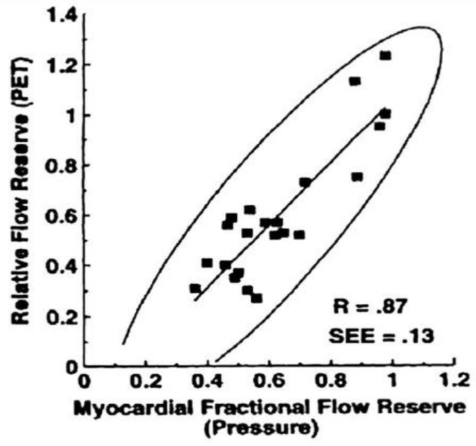
De Bruyne et al. *New Engl J Med* 2012;367:991

FFR vs. CFR

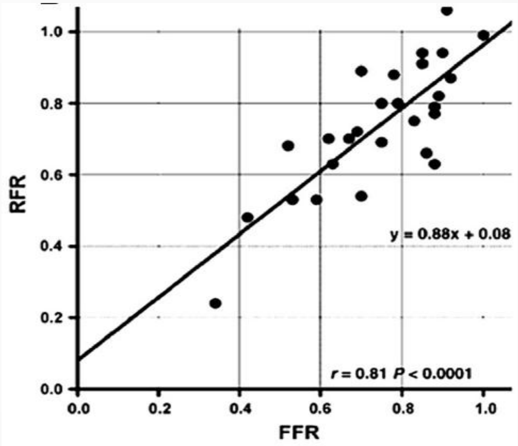
- CFR (Coronary Flow Reserve)
  - **Absolute CFR**: ratio of maximum stress flow to rest flow
  - **Relative CFR**: ratio of maximum stress flow in the diseased artery to maximum stress flow in the absence of disease in either the same or adjacent arterial distribution

Gould et al. *J Am Coll Cardiol 2013*;62:1639

- CFR on Perfusion Imaging vs. FFR
  - FFR: Q_s/Q_n (= relative CFR)



De Bruyne et al. *Circulation* 1994;89:1013

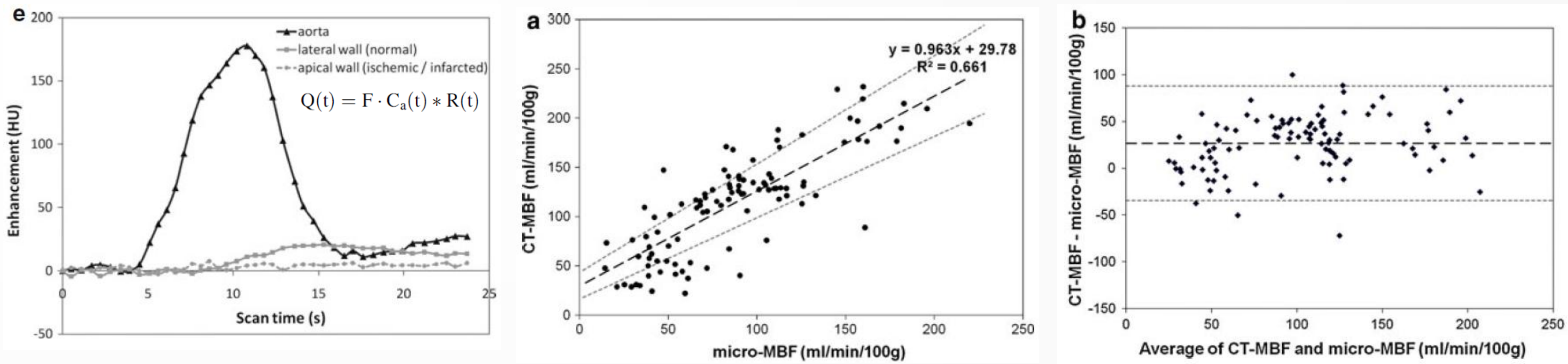


Marques et al. *J Nucl Med 2007*;48:1987

Functional Imaging Studies

Modality	Methods	Pro	Con
CT Perfusion	Dynamic enhancement Semi-kinetic analysis	Easy	Radiation (dynamic) Need for validation
MR Perfusion	Dynamic enhancement Semi-kinetic analysis	No radiation	Need for validation Cost
CT FFR	Hydraulic assumption with 3D CTA	Accessibility	Radiation Need for validation
SPECT	Difference in uptake Kinetic analysis	Accessibility Validation	Radiation Image quality (vs. PET)
PET	Difference in uptake Kinetic analysis	Validation Absolute value	Cost Accessibility

Absolute Perfusion from Perfusion CT



So et al. *Int J Cardiovasc Imaging* 2012;28:1237

linear fit. In addition, the regional MBF was determined by using the following equation: $(US_{MC}/PE_{LVC}) \cdot k$, where US_{MC} is the upslope in the myocardium, PE_{LVC} is the peak enhancement in the left ventricular cavity, and k is a correction factor of 1.5 mL/g/min used to calculate the MBF. The prospectively defined correction factor was higher than that used in previous studies (13,14),

Huber et al. *Radiology* 2013;269:378

$$MBF = \frac{\text{MaxSlope(TissueTAC)}}{\text{Maximum(AIF)}}$$

TABLE 1. Parameter Values for the Total Left Ventricular (LV) Myocardium of the Control Group

	No Adenosine	Adenosine	Adenosine vs. No Adenosine
MBF (mL/100 mL/min)	98.2 ± 18.6 (75.0–119.0)	134.0 ± 40.1 (85.0–191.0)	P = 0.0153
FPDV (mL/100 mL)	13.3 ± 1.8 (11.0–15.8)	16.6 ± 3.2 (11.9–19.6)	P = 0.0078
BV_{iv} (mL/100 mL)	6.2 ± 1.5 (4.1–7.6)	9.4 ± 3.3 (5.5–13.5)	P = 0.0213

All values are presented as mean ± SD with the range given in brackets.
MBF, Myocardial Blood Flow; FPDV, first pass distribution volume; BV_{iv}, intravascular blood volume.

Mahnken et al. *Invest Radiol* 2010;45:298

Absolute Perfusion from Perfusion MR

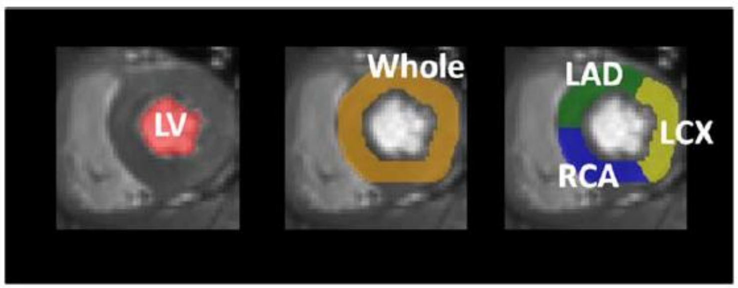
Patlak Plot Method

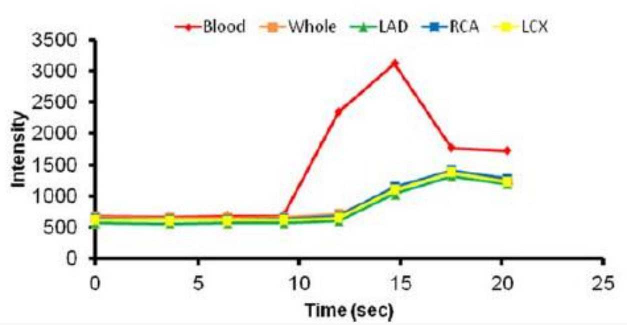
Kurita et al.
Eur Heart J
2009;30:444

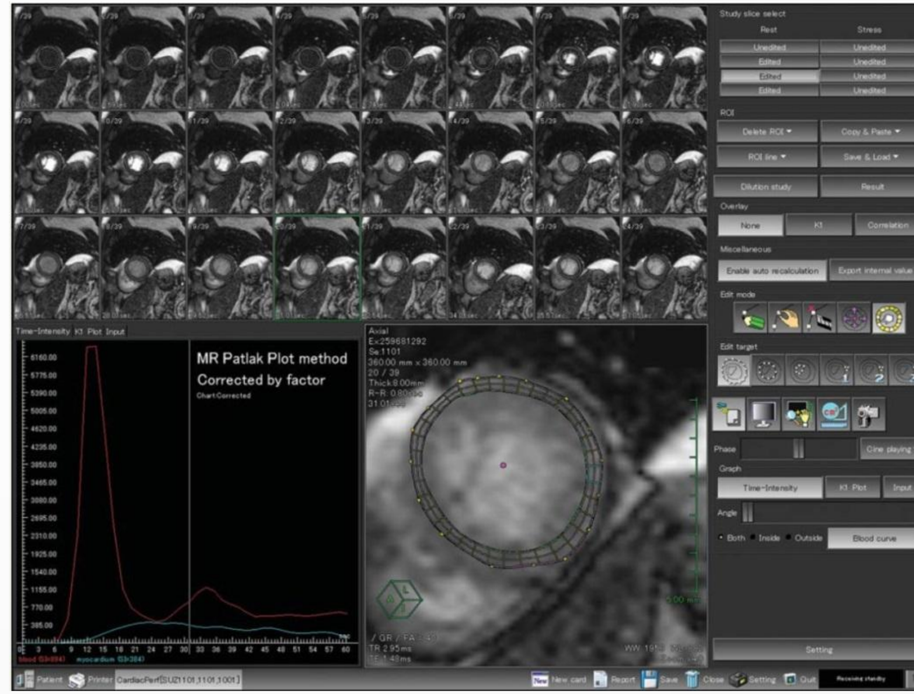
$$\frac{dC_{myo}(t)}{dt} = K_1C_a(t) - k_2C_{myo}(t)$$

$$\frac{dC_{myo}(t)}{dt} \cong K_1C_a(t).$$

$$K_1 = C_{myo}(T) / \int_0^T C_a(t)dt.$$







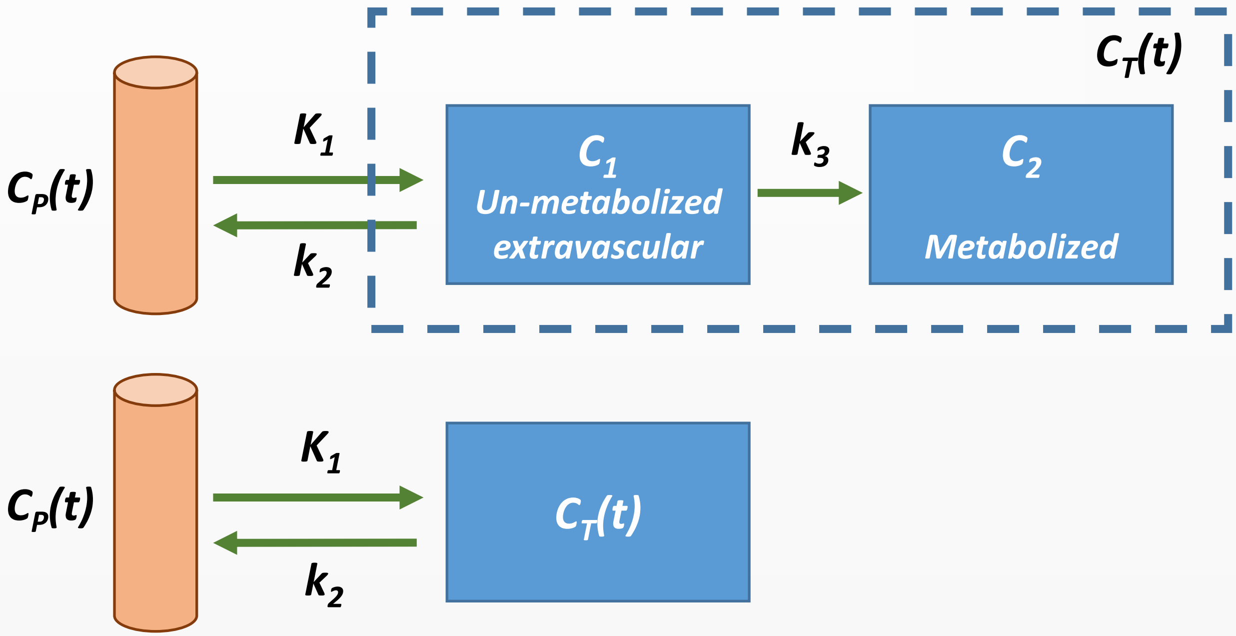
$$dCt(t)/dt = K1 \times Ca(t) - k2 \times Ct(t)$$

$$K1Patlak = \frac{R(t)}{\int_0^T LV(t)dt}$$

Tomiyama et al. *J Mag Res Imaging* 2015;42:754

Absolute Flow Measurement: $^{13}N\text{-}NH_3$

- **Two-tissue compartment model (Michigan/UCLA)**
  - Hutchins et al. *JACC* 1990;15:1032 /Choi et al. *JNM* 1999;40:1045
- **One-tissue compartment model (Duke)**
  - De Grado et al. *JNC* 1996;3:494



$$\frac{dC_1(t)}{dt} = K_1 C_P(t) - (k_2 + k_3) C_1(t)$$

$$\frac{dC_2(t)}{dt} = k_3 C_1(t)$$

$$\frac{dC_{myo}(t)}{dt} = K_1 C_P(t) - k_2 C_{myo}(t)$$

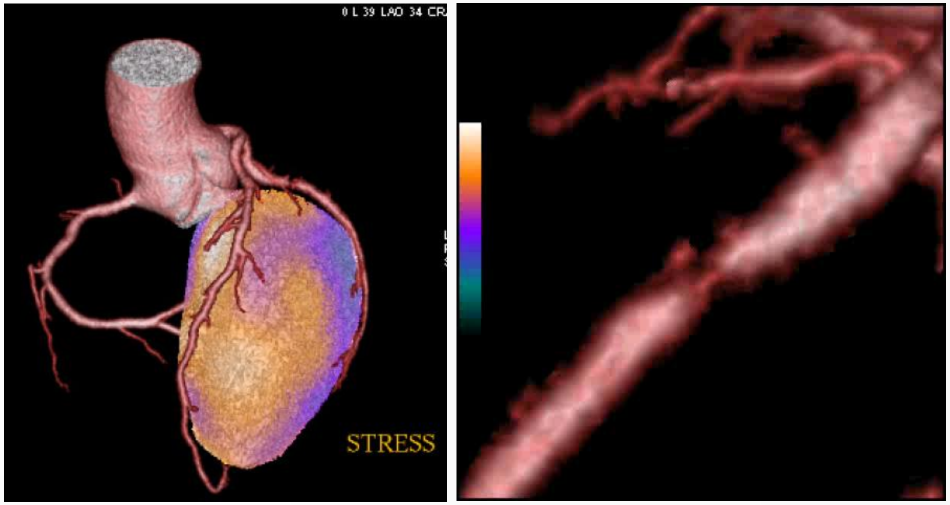
K_1 equals the perfusion

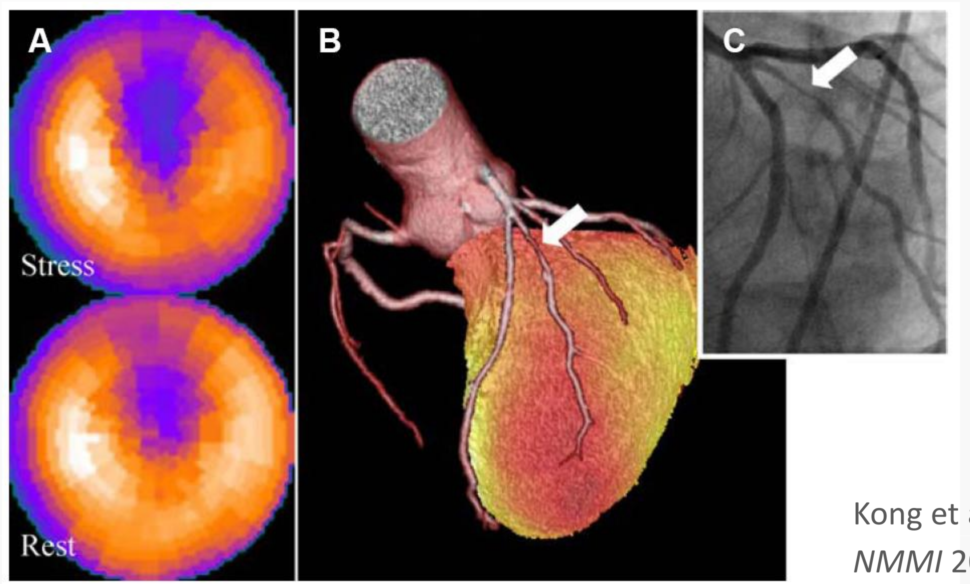
Recent Advances of PET Imaging in CAD

Instrument / Analysis

Radiopharmaceuticals

Hybrid Imaging: SPECT/CT and PET/CT

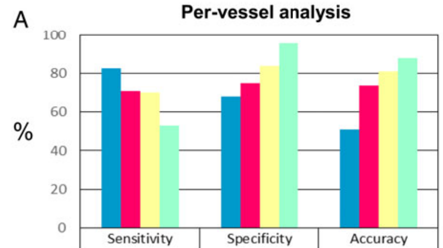




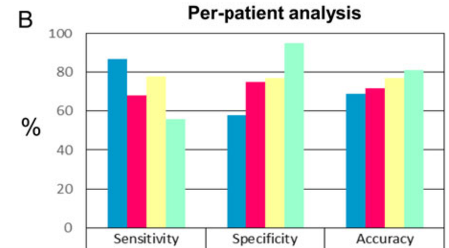
Kong et al.
NMMI 2009

Multicenter Clinical Trial: EVINCI

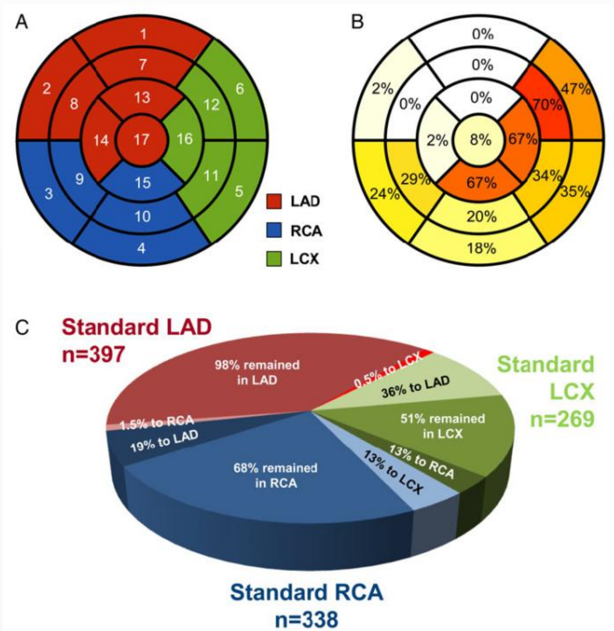
- **Software-based Fusion**
  - **MPS and CTCA**
  - **F/U by CAG and FFR**

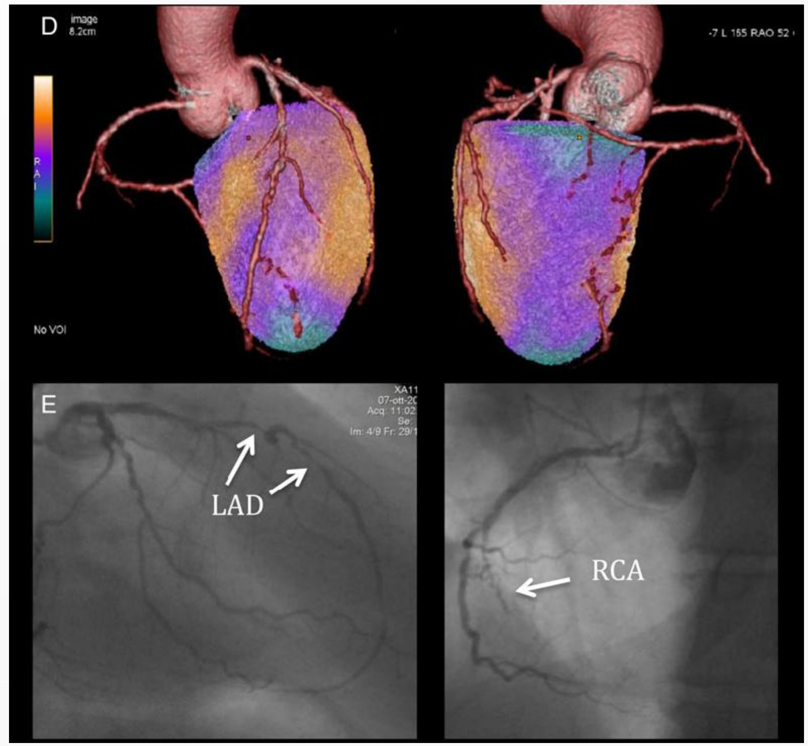


	Sensitivity	Specificity	Accuracy
Hybrid (CT & MPI Match + Mismatch)	83	68	51
MPI	71	75	74
CT-angiography	70	84	81
Hybrid (CT & MPI Match)	53	96	88



	Sensitivity	Specificity	Accuracy
Hybrid (CT & MPI Match + Mismatch)	87	58	69
MPI	68	75	72
CT-angiography	78	77	77
Hybrid (CT & MPI Match)	56	95	81





Liga et al. *Eur Heart J Cardiovasc Imaging* Epub 2016

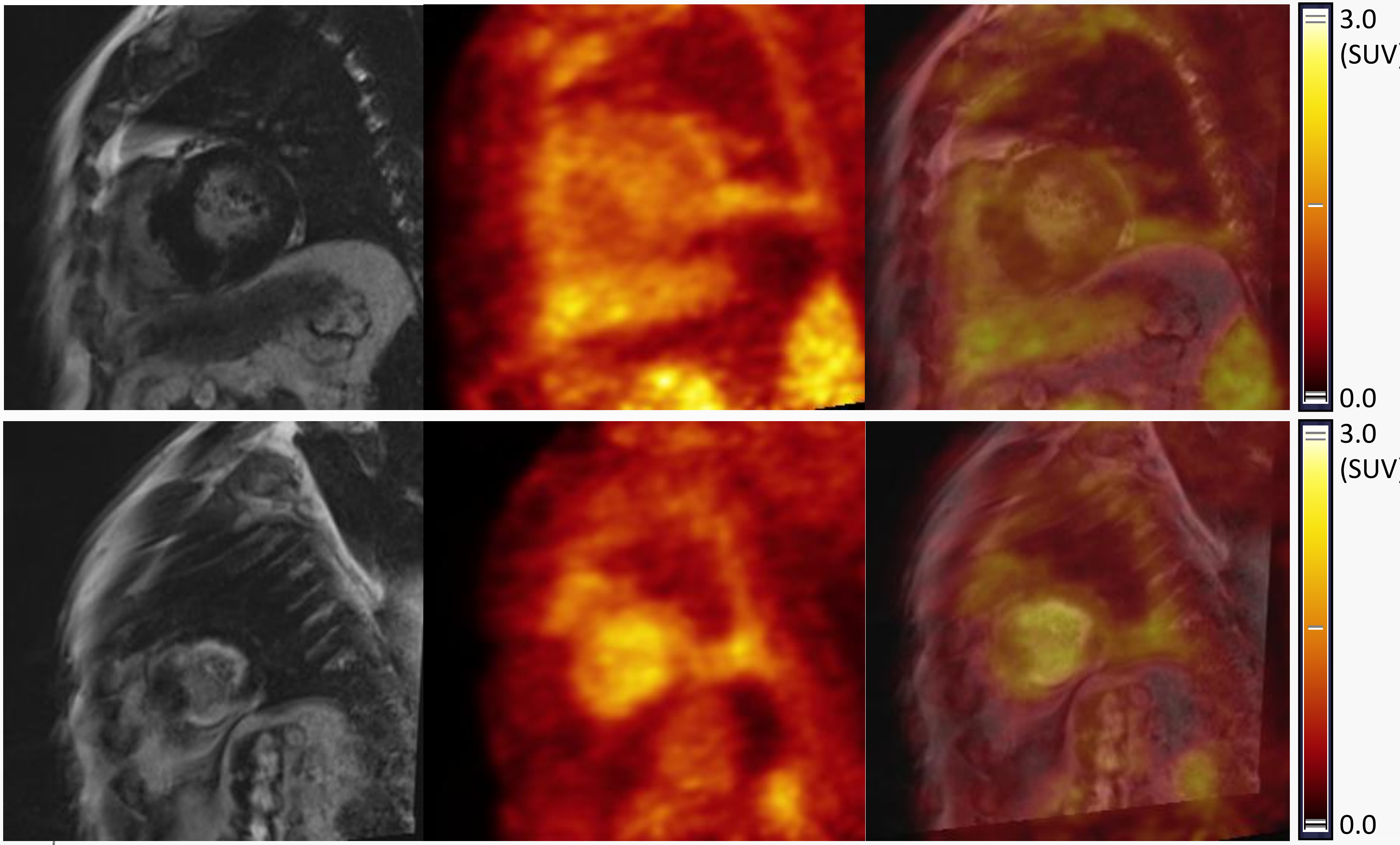
PET/MRI

Philips Ingenuity TF PET/MR

GE Signa PET/MR
(Vendor image)

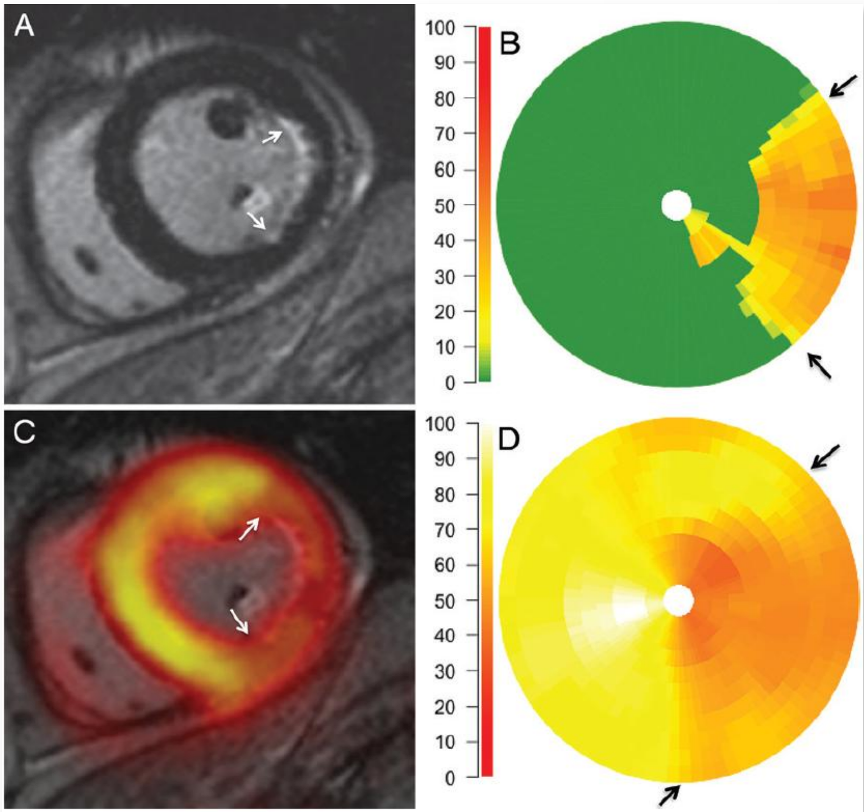
Siemens mMR in SNUH

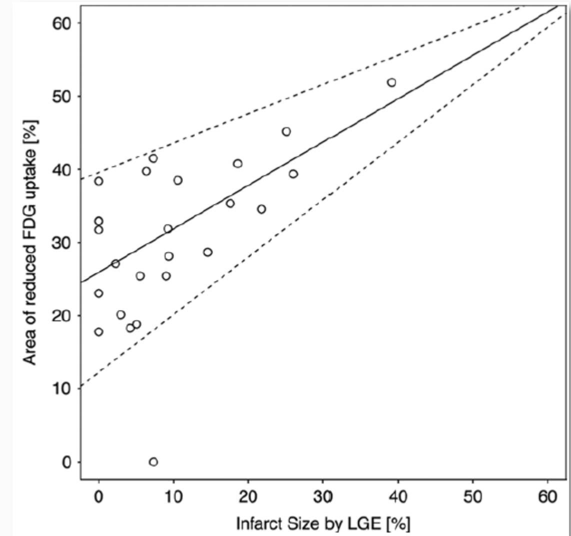
FDG PET/MRI in H-CMP

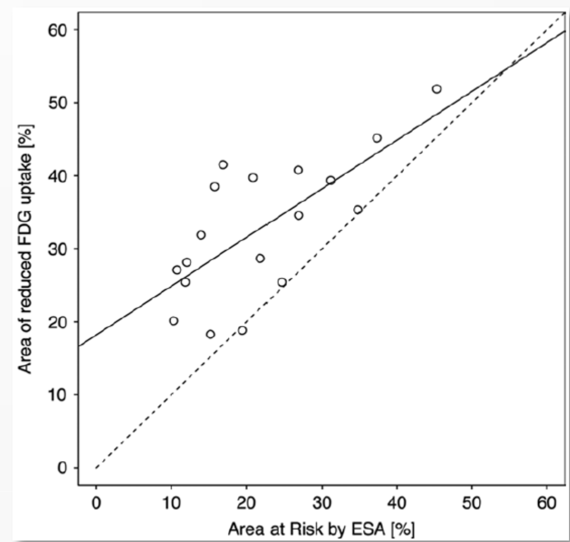


Kim KJ et al. *Presented at KSC 2015*

FDG PET/MRI for Viability Assessment



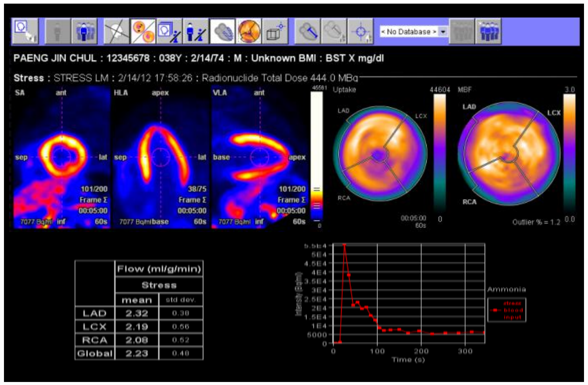




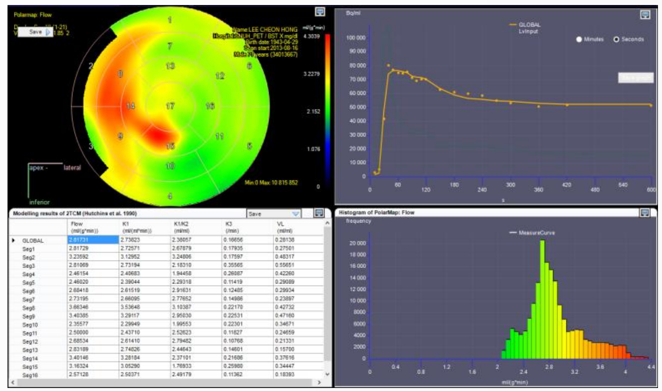
Nensa et al. *Radiology* 2015;276:400

Analysis Tools for Perfusion

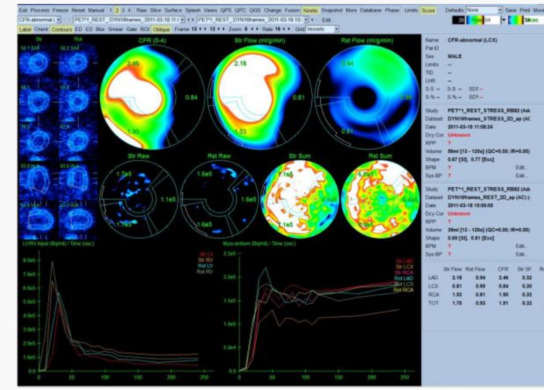
MBF module (Siemens)



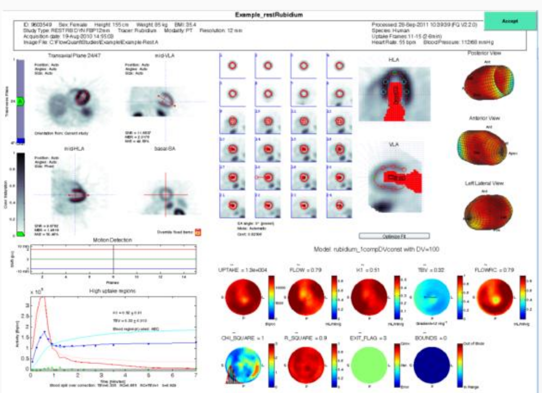
Carimas® (Turku PET Centre)



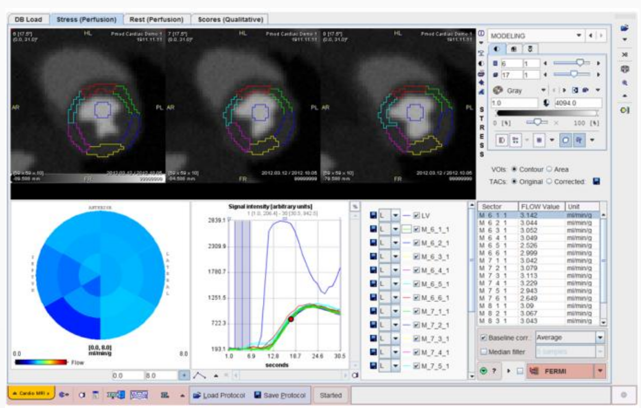
QPS® (Cedars-Sinai)



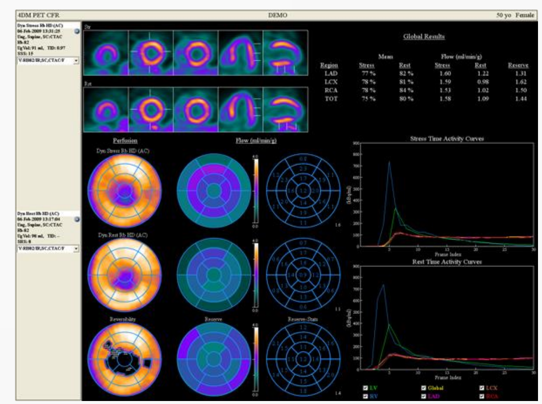
FlowQuant® (U.O.)



PMOD® (PMOD Tech.)



Corridor4DM® (U.M./INVIA)



Myocardial Perfusion Tracers

	^{201}Tl	^{99m}Tc Agents	^{15}O-H_2O	^{13}N-NH_3	^{82}Rb	^{18}F-Flurpiridaz
$T_{1/2}$	73 h	6.01 h	122 sec	9.96 min	76 sec	110 min
Photon Energy	70 keV	140 keV	Positron	Positron	Positron	Positron
Uptake Mechanism	Na/K Channel	Diffusion – Mitochondria	Free Diffusion	Diffusion - Glutamine Syn.	Na/K Channel	Diffusion – Mitochondria
Supply	Pre-order	Labeling	Cyclotron	Cyclotron	Generator (^{82}Sr/^{82}Rb) ($T_{1/2}$ = 25 d)	Cyclotron - Delivery (?)
Dose (MBq)	55 – 111	370 – 925	1,000 – 2,000	370	1,000 – 2,000	185
Exposure (mSv)	12 mSv (6 mSv/mCi)	MIBI: 8 mSv (0.4 mSv/mCi) TF: 5.6 mSv (0.28 mSv/mCi)	2.4 mSv (0.04 mSv/mCi)	1.5 mSv (0.08 mSv/mCi)	3.8 mSv (0.13 mSv/mCi)	< 3
Current Status	30,600/mCi	68,000/0.25v	조제실 제제	품목허가 / 조제실제제	FDA 승인 국내 미도입	해외 임상 3상

^{13}N-NH_3 ⇩ 인정비급여(2015)

^{82}Rb ⇩ 도입 추진 중

Differences in Quantification

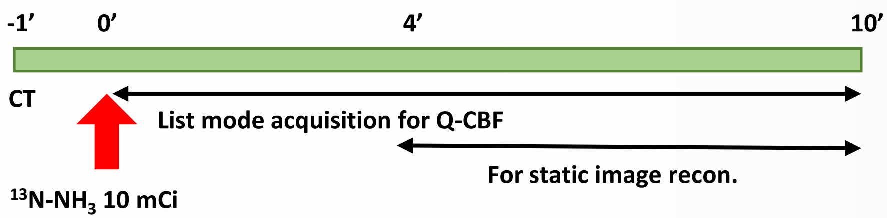
Table 1 Comparison of the available tracers for quantitative perfusion PET

	Advantages	Disadvantages	Threshold values for CAD detection
^{15}O-Water	1. Freely diffusible (linear relationship with MBF) 2. Robust and reliable compartmental modelling 3. Intrinsically quantitative 4. Tight time schedule 5. Wide experience, particularly with hybrid imaging	1. Cyclotron product 2. Very short half-life (complex tracer handling) 3. Absence of morphological myocardial images 4. Complex VOI definition 5. Conventional gated PET impossible	Maximal MBF <2.3 mL/min/g, CFR <2.5
^{13}N-Ammonia	1. Short positron range 2. Reliable compartmental modelling 3. High-quality myocardial images 4. High-quality gated PET 5. Wide experience	1. Cyclotron product 2. Nonlinear extraction fraction 3. Metabolic interferences 4. Prolonged patient schedule	Maximal MBF <1.85 mL/min/g, CFR <2
^{82}Rb	1. Generator product 2. Very tight time schedule 3. Gated PET possible 4. Wide experience, but largely with qualitative imaging	1. Wide positron range 2. Dose-related dead-time losses (3-D imaging) 3. Prompt gamma interference (3-D imaging) 4. Suboptimal extraction fraction 5. Complex compartmental modelling 6. Higher variability of estimated parameters	Maximal MBF <1.4 mL/min/g, CFR <1.7

Sciagra et al. *Eur J Nucl Med Mol Imaging* 2016 EPub

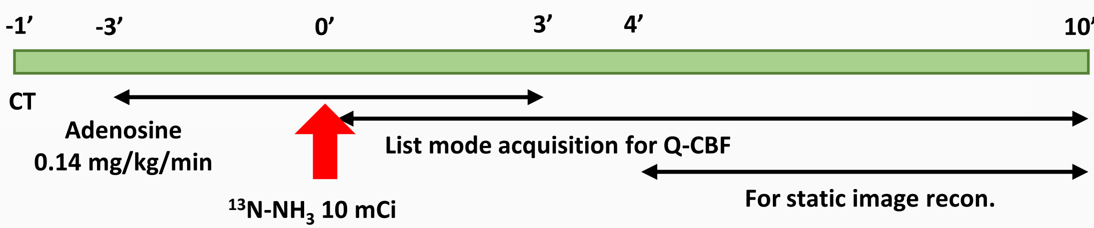
Study Protocol of $^{13}N\text{-}NH_3$ PET

1. Rest : 10 min list-mode dynamic



2. Interval : > 30 min

3. Stress : 10 min list-mode dynamic



- **Dynamic Image Frame**
  - 12×10 s
  - 6×30 s
  - 2×60 s
  - 1×180

A total of 1.6 mSv from PET

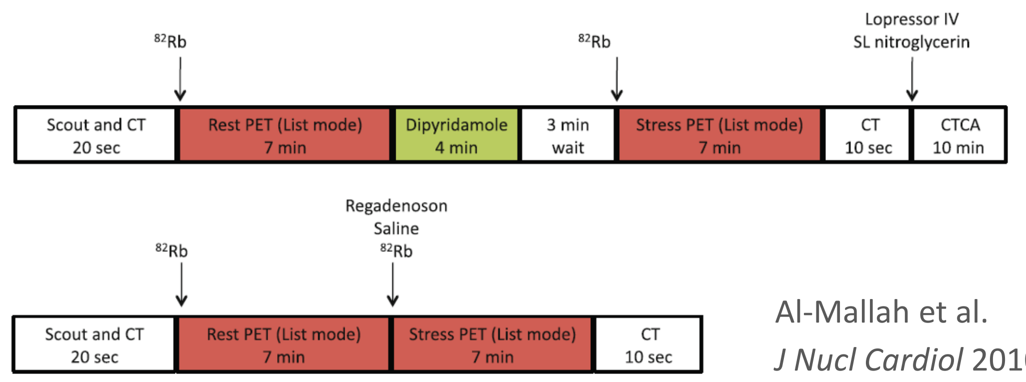
(Tl 2 mCi + MIBI 15 mCi: 15 mSv)

- **Protocol Summary**
  - Room occupying time: 30 min (2회 합계)
  - Scanner occupying time: 25 min
  - Administered radioactivity: 20 mCi of $^{13}N\text{-}NH_3$
  - Radiation dose: < 2 mSv

- **Scheduling & Cyclotron:**
  1일 2회 생산 / 최대 4명 / 평균 2명 검사

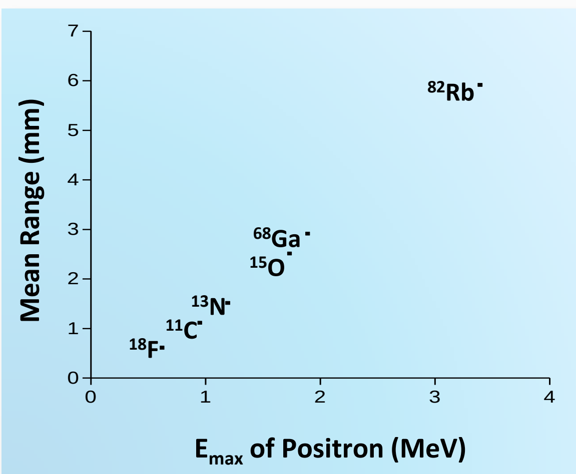
^{82}Rb Perfusion PET Protocols

An Example of Imaging Protocol (^{82}Rb)



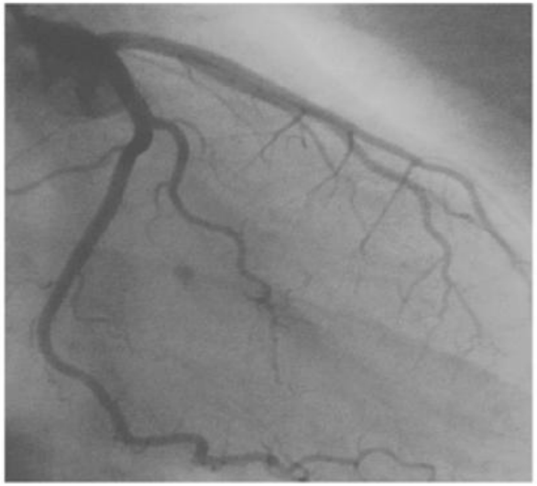
Al-Mallah et al.
J Nucl Cardiol 2010;17:498

^{82}Rb Injection System



Absolute Perfusion Measurement

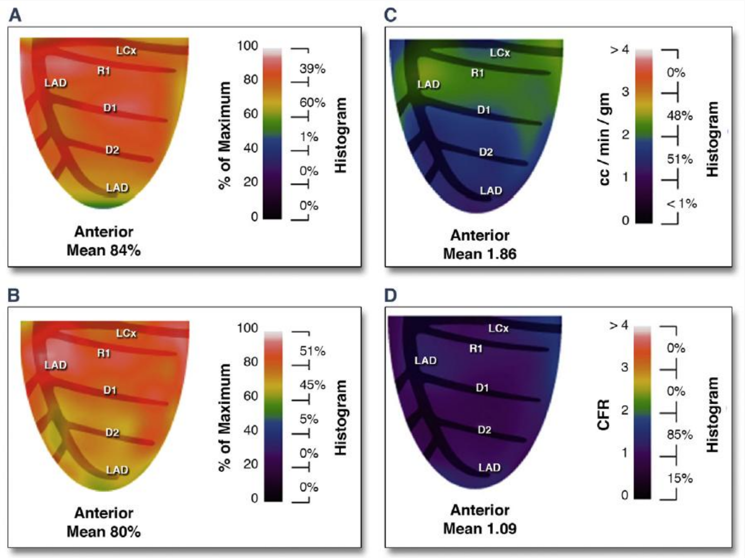
- Need for Quantification of Absolute Myocardial Perfusion
  - 'Balanced ischemia'
  - General microvascular disorders, DM
  - Absolute CFR
- Microvasculature of Myocardium

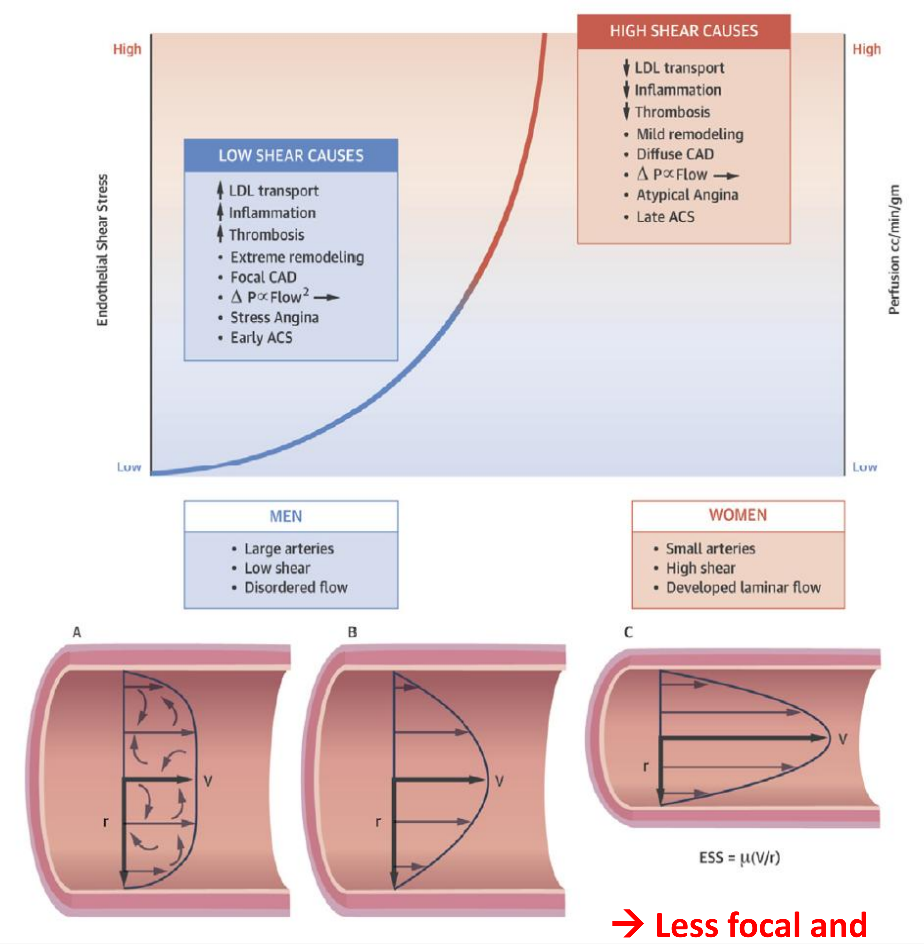



Camici & Rimoldi. *J Nucl Med* 2009;50:1076

Microvascular Dysfunction in Women

- **CAD in Women**
  - **Atypical non-exertional angina with diffuse CAD**
  - **High mortality in aged women when focal stenosis occurs**
  - **Related to diffuse CAD/MVD**

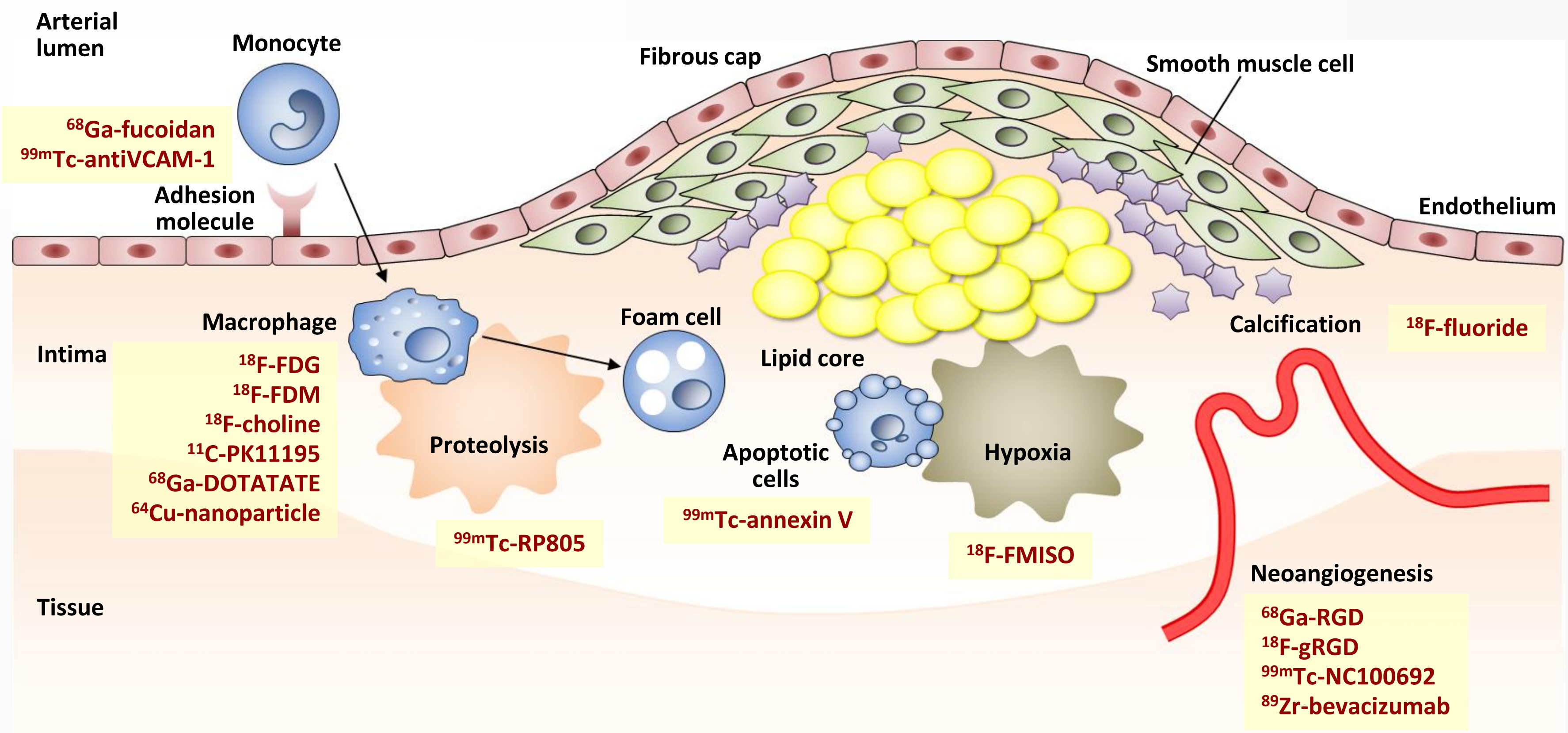




→ **Less focal and more diffuse/MVD**

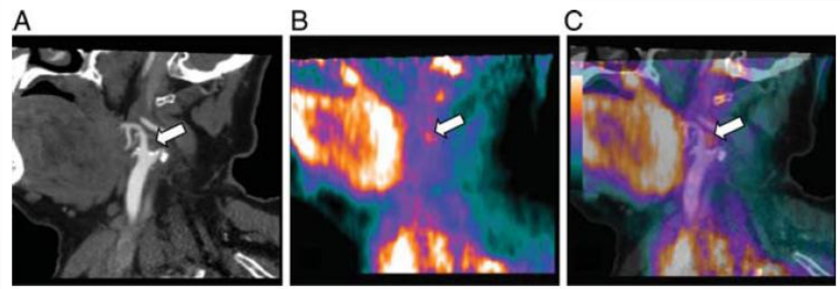
Patel et al. *JACC Cardiovasc Imag* 2016;9:465

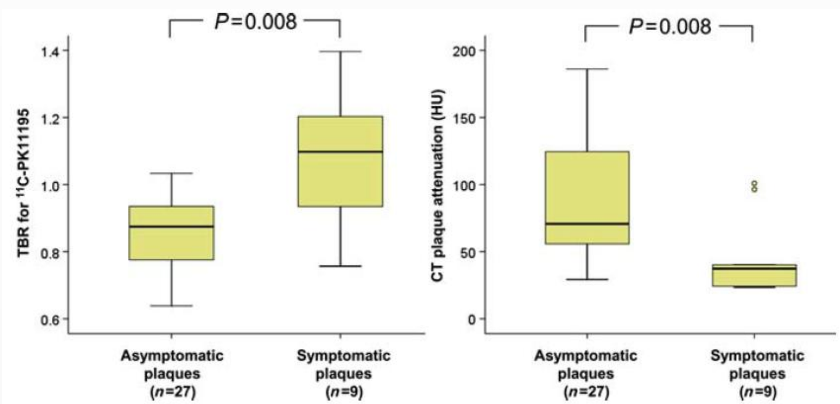
Imaging Targets of Vulnerable Plaque

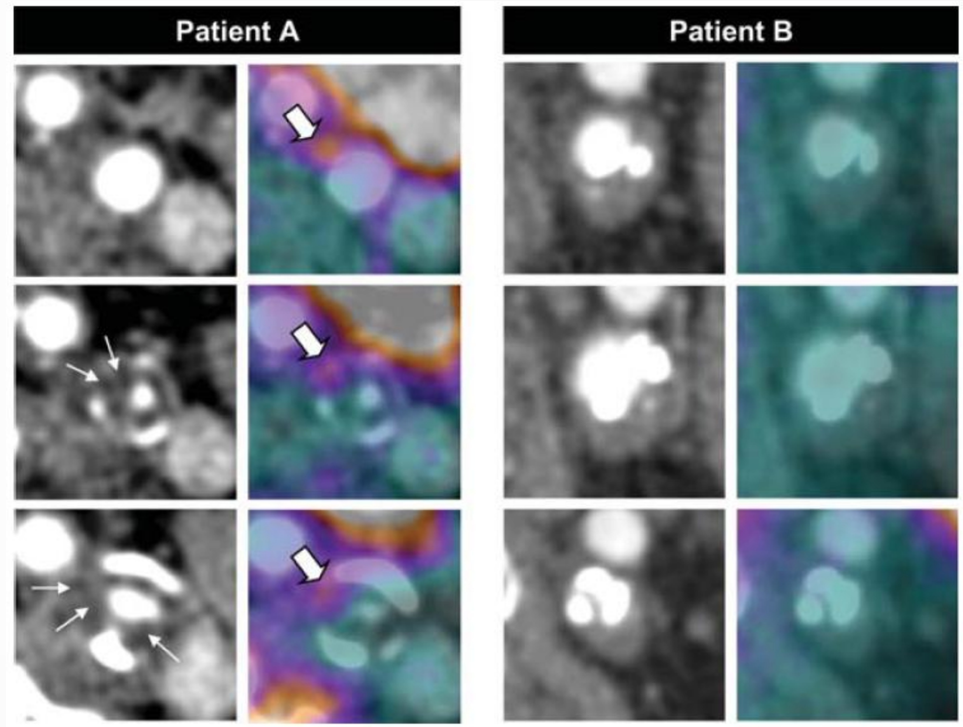


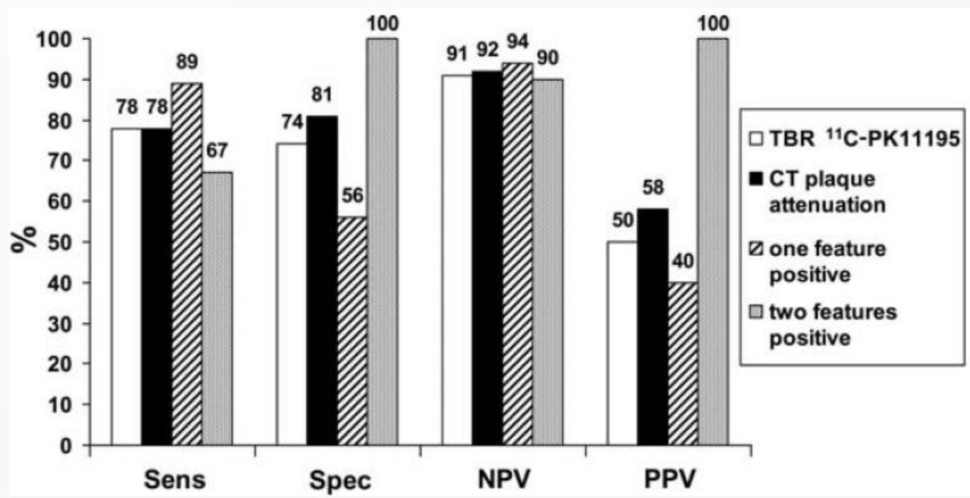
Lee SJ and Paeng JC
Kor J Radiol 2015;16:955

^{11}C-PK11195 PET in Human





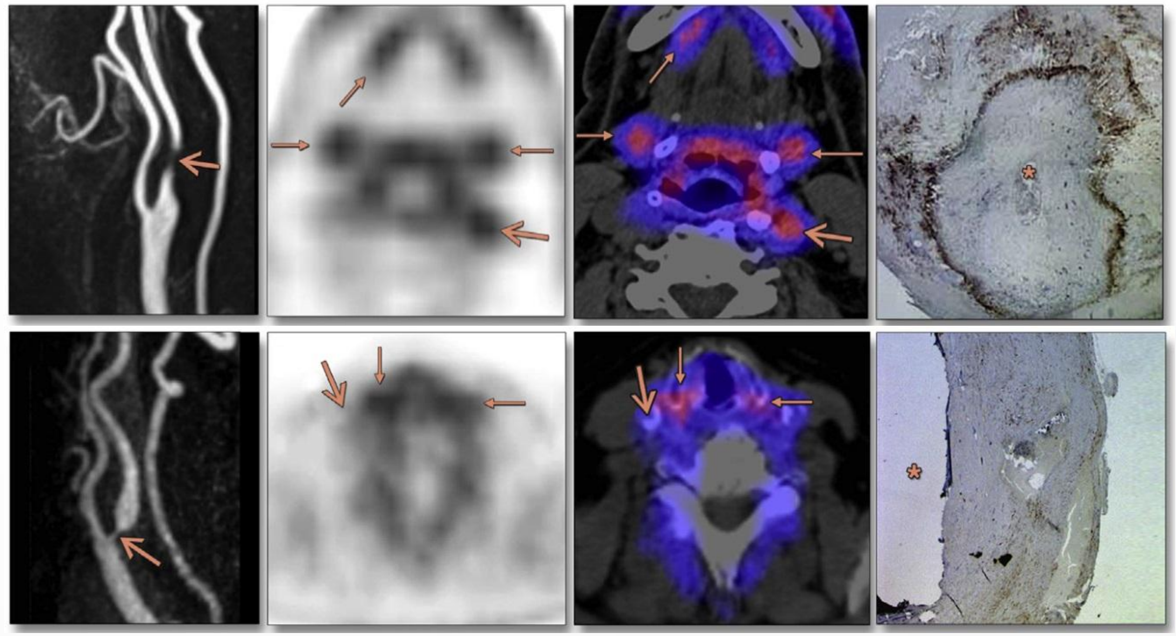


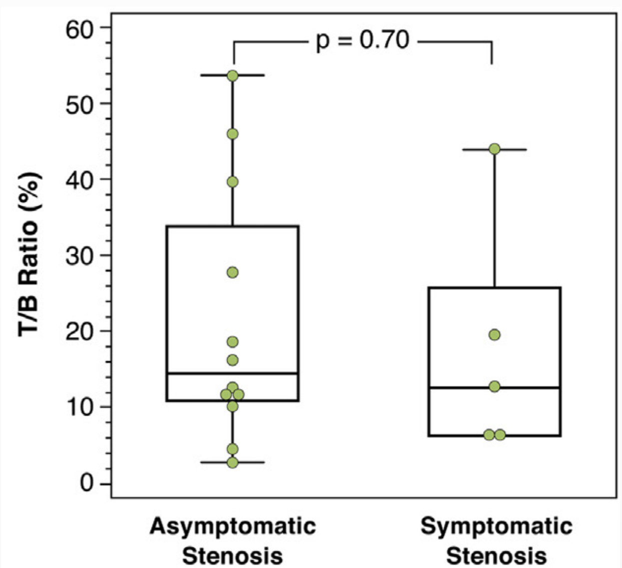


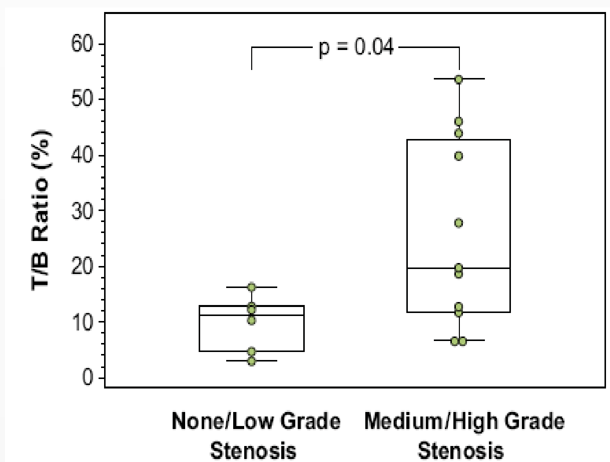
Imaging mechanism:
TSPO (PBR; peripheral benzodiazepine receptor)
expression on macrophages

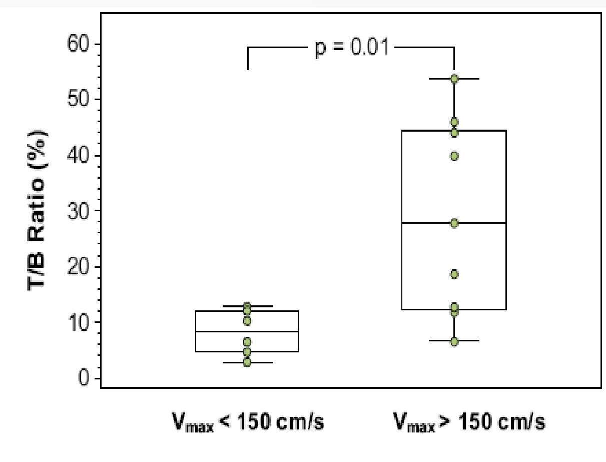
Gaemperli et al. *Eur Heart J* 2012;33:1902

^{18}F-gRGD PET in Human



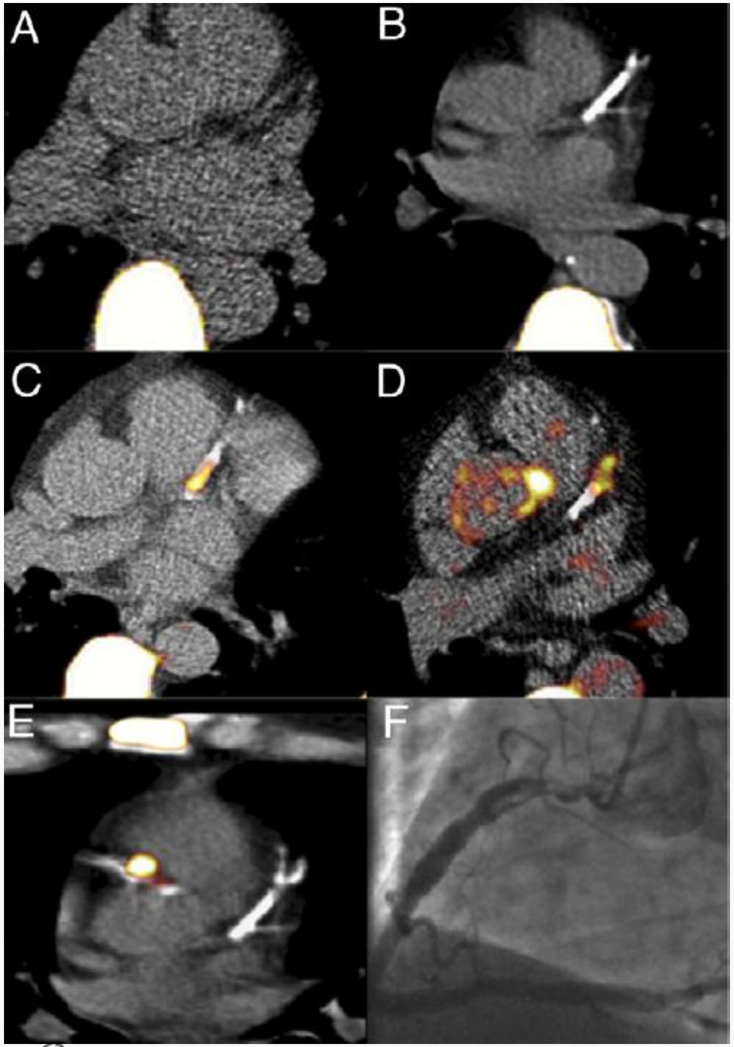




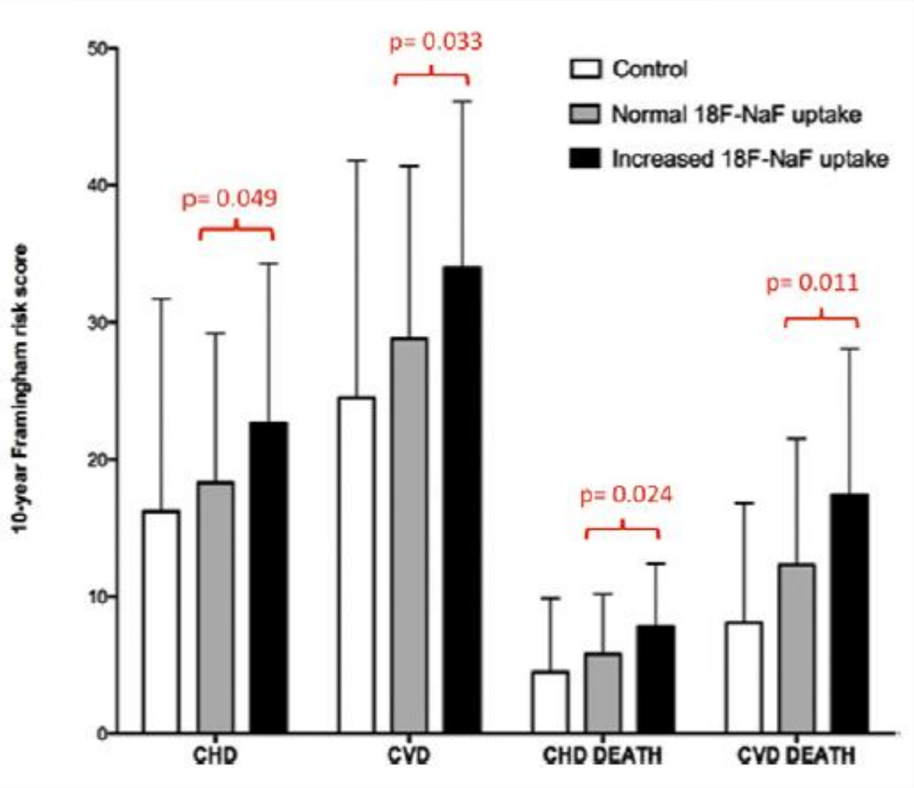


Beer et al. *JACC Cardiovasc Imaging* 2014;7:178

Calcification F-18 Fluoride PET

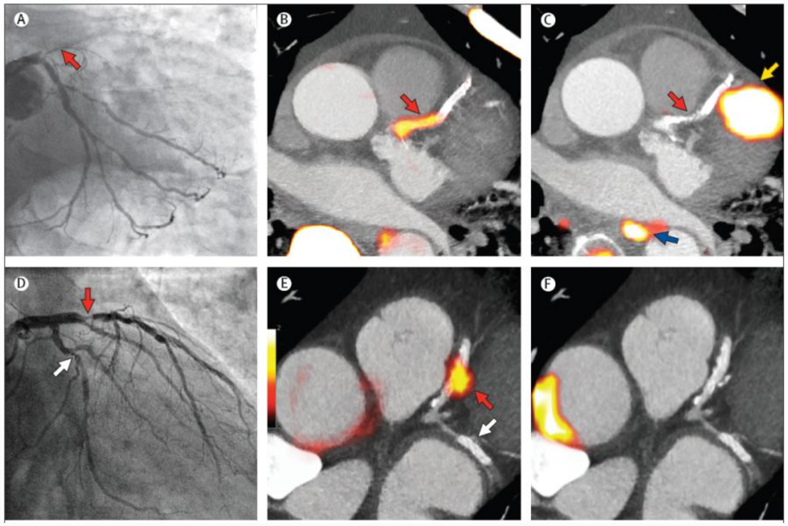


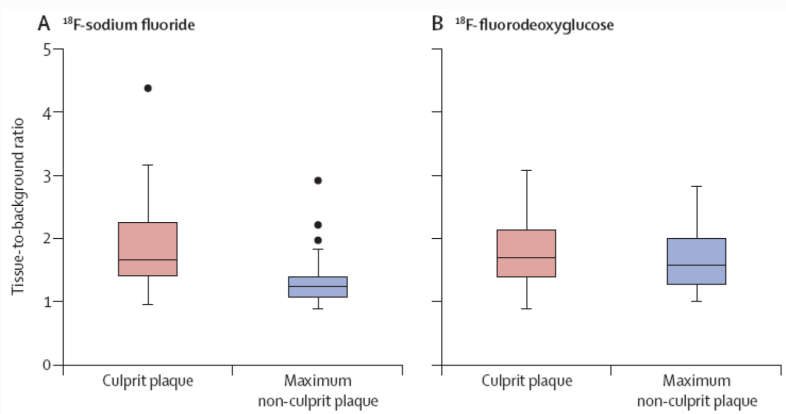
Active calcification in coronary artery



Dweck et al. *JACC* 2012;59:1539

^{18}F-Fluoride PET in Human





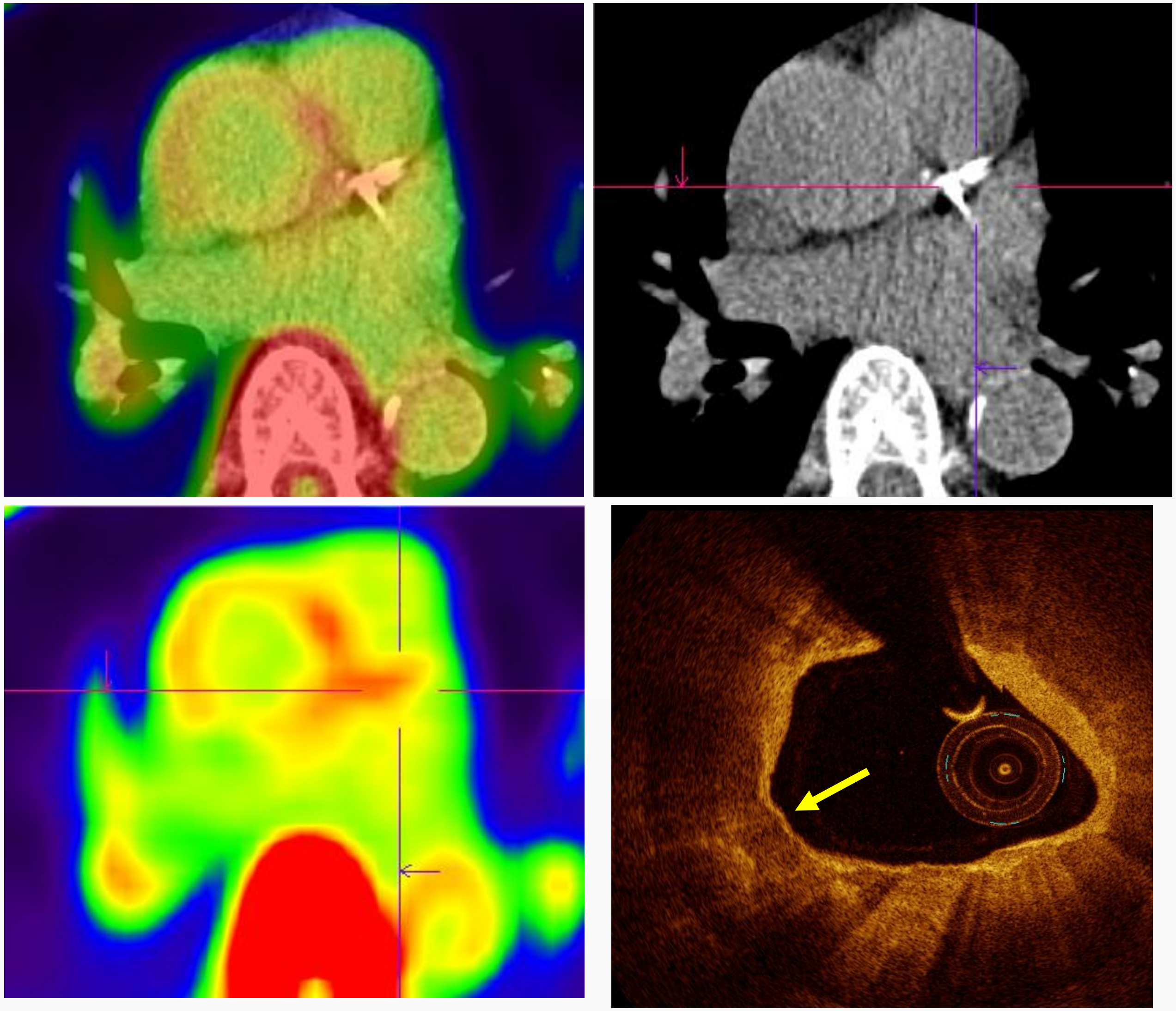
	^{18}F-fluoride positive plaques (n=15)	^{18}F-fluoride negative plaques (n=24)	p
Lumen			
Area (mm^2)	9·0 (5·7–13·5)	6·7 (4·7–9·7)	0·078
Minimal diameter (mm)	2·6 (1·7–3·1)	1·9 (1·7–2·6)	0·165
Maximum diameter (mm)	4·9 (4·1–5·3)	3·6 (3·1–4·6)	0·006
Vessel			
Area (mm^2)	24·1 (17·2–27·1)	14·5 (11·9–18·1)	0·002
Minimal diameter (mm)	4·4 (3·4–5·2)	3·6 (3·0–4·1)	0·057
Maximum diameter (mm)	6·5 (6·0–7·1)	5·2 (4·7–5·9)	0·0001
Plaque			
Length (mm)	14·2 (6·2–23·5)	15·2 (6·7–25·0)	0·941
Volume (mm^3)	152·9 (99·6–289·7)	91·0 (45·8–158·2)	0·032
Burden (%)*	55·6 (48·6–64·4)	54·2 (46·3–57·3)	0·174
Remodelling index	1·12 (1·09–1·19)	1·01 (0·94–1·06)	0·0004
Plaque composition			
Fibrous tissue (%)	51·0 (46·3–56·6)	58·1 (51·6–65·5)	0·015
Fibro-fatty (%)	10·9 (6·0–13·8)	12·6 (9·3–17·8)	0·092
Necrotic core (%)	24·6 (20·5–28·8)	18·0 (14·0–22·4)	0·001
Maximum frame necrotic core (%)†	35·5 (34·2–40·5)	29·2 (23·9–42·1)	0·009
Dense calcium (%)	12·6 (9·1–18·1)	10·2 (4·0–14·9)	0·092
Microcalcification, n (%)	11 (73%)	5 (21%)	0·002
Plaque classification, n (%)			
Thin-cap fibroatheroma	7 (47%)	4 (16%)	0·068
Thick-cap fibroatheroma	5 (33%)	9 (38%)	1·0
Pathological intimal thickening	0	7 (29%)	0·003
Fibrocalcific plaque	3 (20%)	4 (16%)	1·0

Joshi et al. *Lancet* 2014;383:705

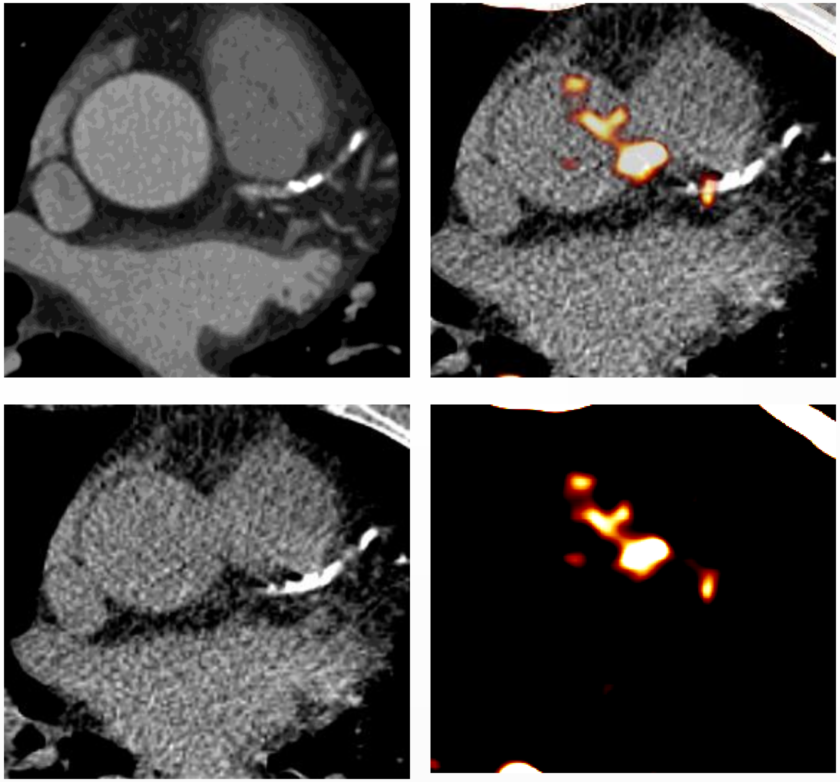
Approved Healthcare Technology in NM

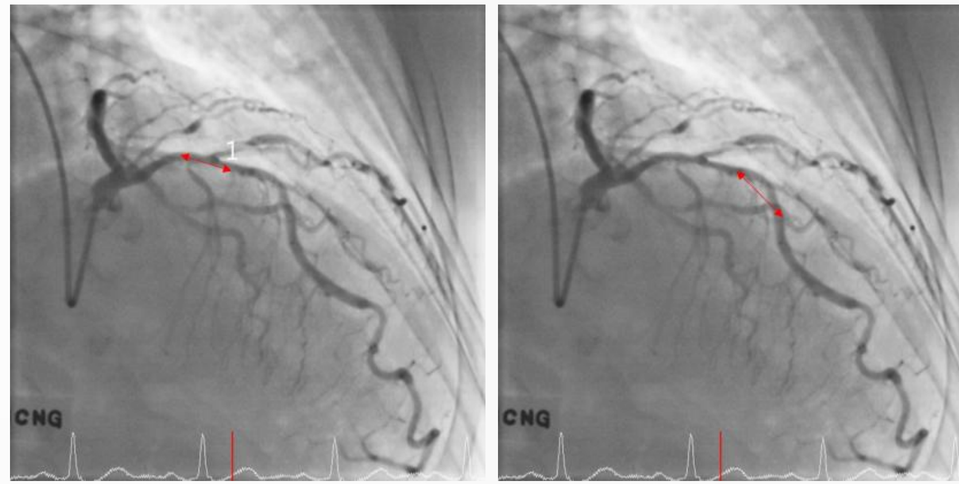
	신의료기술/약품품목허가 내역	보험급여
2009년 이전	(약품 품목허가) ^{18}F-FDG, ^{18}F-FLT, ^{18}F-FPCIT	^{18}F-FDG PET (2006년)
2010년	(2010-15호) 동맥경유방사선색전술 (2010-105호) ^{18}F-NaF PET, ^{11}C-acetate PET	
2011년		
2012년	(2012-92호) ^{18}F-FLT PET, ^{18}F- FPCIT PET (2012-112호) ^{123}I-FPCIT SPECT, ^{13}N-NH_3 PET (2012-131호) Radioiodine SPECT/CT	
2013년	(2013-114호) ^{11}C-methionine PET	
2014년	(약품 품목허가) ^{223}Ra-chloride (Xofigo®) (2014-89호) ^{18}F-FDOPA PET (2014-198호) ^{68}Ga-DOTATATE PET	(제한적 급여) ^{18}F-NaF PET, ^{18}F-FPCIT PET, ^{123}I-FPCIT SPECT
심의 중	^{18}F-FMISO PET 등	

Fluoride PET for Coronary Artery

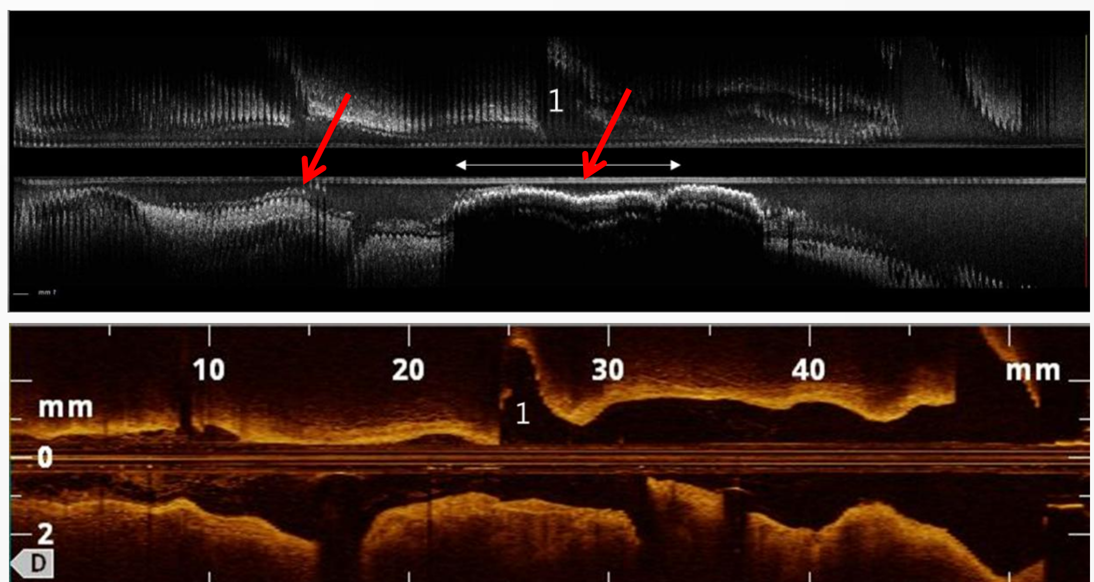


Lee JM, Koo BK, et al. In Preparation





pLAD mLAD



Summary: Prime Time or Not?

- **Position of Perfusion PET in CAD**
  - Absolute flow measurement
  - Lower radiation, shorter imaging time, and higher image quality
- **Recent Changes in PET Imaging**
  - Enabling of clinical perfusion PET / prospect for more RP
  - New technology: hybrid imaging and easy analysis tools
  - Clinical evidences for needs of perfusion measurement
  - However, still limited clinical availability and appropriate niche
- **Future Direction**
  - Improvement in clinical availability
  - Molecular imaging for risk stratification of CAD (?)