SPECT or PET for Cardiovascular Screening in High-Risk Patients

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  - Diagnosis
  - Prognostication
  - Decision Making

Recent Development in Myocardial Perfusion SPECT and PET

Heart-Dedicated SPECT

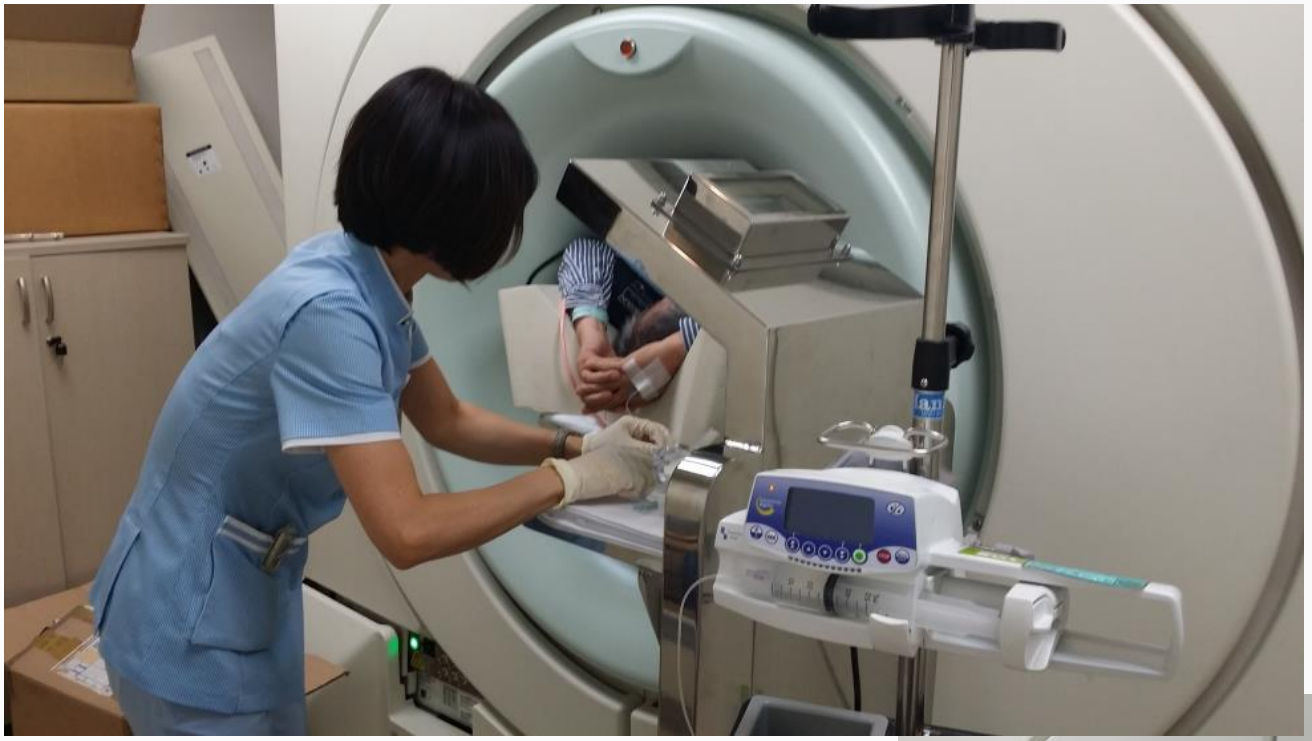
Perfusion PET

Perfusion PET Why PET ?

- **Why PET ?**
  - **Better Image Quality**
    - **CT attenuation correction**
    - **Localization**
    - **Sensitive for mild change**
  - **Absolute quantification**
  - **Low Radiation Dose: 2 to 5 mSv**
  - **Patients' Convenience**

- **PET Agents**
  - **Available in Korea: ^{13}N-ammonia**
  - **North America and EU: ^{82}Rb, ^{18}F-flurpiridaz (phase 3)**

Patient monitoring



Adenosine stress

Tracer injection

^{13}N-NH_3 PET

보건복지부 공고 제2012 - 528호

의료법 제53조제3항 및 신의료기술평가에 관한 규칙 제4조에 의한 신의료기술의 안전성·유효성에 대한 평가결과 고시(보건복지부 고시 제2012 - 92호, 2012. 7. 18)를 다음과 같이 개정 고시합니다.

2012년 9월 3일

보건복지부장관

230. N-13-암모니아 양전자방출단층촬영, N-13-암모니아 양전자방출전산화단층촬영

가. 기술명

- ㅇ 한글명 : N-13-암모니아 양전자방출단층촬영, N-13-암모니아 양전자방출전산화단층촬영
- ㅇ 영문명 : N-13-ammonia positron emission tomography, N-13-ammonia positron emission tomography /computer tomography

나. 사용목적

- ㅇ 심근 관류를 측정함으로써 관상동맥질환의 진단 및 중증도 및 심근 생존능 평가

다. 사용대상

- ㅇ 관상동맥질환 환자 및 의심 환자 또는 심장 재관류술 환자

요양급여행위평가신청서

처리기간: 150일

신청인	기관(단체)명	서울대학교병원	기 관 기 호	11100079
	소재지(주소)	서울시 종로구 대학로 101 (전화 : 02-2072-2114) (E-mail :petpet1@snu.ac.kr)		
	성 명	이 동 수	주민등록번호	5[redacted]
행위명	한 글 명	N-13 암모니아 양전자방출전산화단층촬영 (안정 시) N-13 암모니아 양전자방출전산화단층촬영 (부하 시)		
	영문명(한문명)	N-13-ammonia PET/CT Rest N-13-ammonia PET/CT Stress		
	행위분류에 의한 항목번호	해당사항 없음		
가입자등에게 최초로 실시한 날		2012년 11월 20일		
목적·임상적응증 및 실시방법		첨부자료 참조		
소요장비·소요재료 및 약제		첨부자료 참조		
상대가치점수(추정)		안정 시: 부하 시: (동적영상 시행 및 분석 시 30% 가산)		
년간 실시빈도(추정)		연간 350건		
비 고				

「국민건강보험 요양급여의 기준에 관한 규칙」 제10조제2항에 따라 위 행위에 대한 요양급여대상여부 평가를 신청합니다.

2012 년 11월 20 일

신청인 : 이 동 수 (서명 또는 인)
담당자성 명 : 이 홍 재
전화번호 : 02-2072-3804

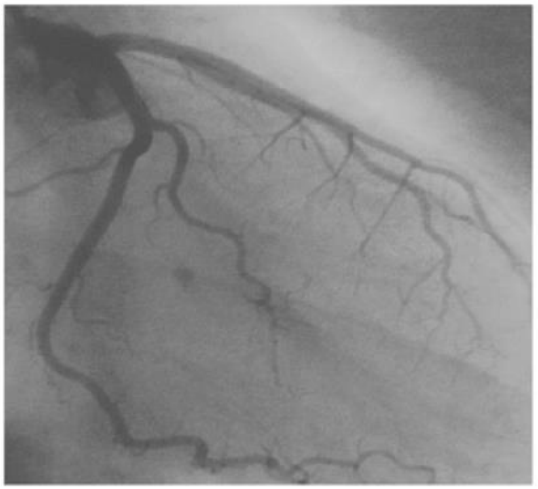
건강보험심사평가원장 귀하

※구비서류
1. 상대가치점수의 산출근거 및 내역에 관한 자료
2. 비용효과에 관한 자료(동일 또는 유사 행위와의 장단점, 상대가치점수 비교 등을 포함합니다)
3. 국내외 실시현황에 관한 자료(최초실시년도, 실시기관명 및 실시건수 등을 포함합니다)
4. 소요장비·소요재료·약제의 제조(수입)허가(신고)관련 자료
5. 국내외의 연구논문 등 기타 참고자료
6. 신의료기술의 안전성·유효성 등의 평가결과통보서

※작성요령
1. 각 항목의 란이 부족한 경우에는 별지를 활용하시기 바랍니다.
2. 소요장비·소요재료 및 약제란에는 소요장비의 명칭·구입가격·구입처 및 내구연한, 소요재료는 명칭·구입가격·구입처 및 1회사용량·반복사용가능횟수, 약제는 명칭·구입가격·구입처 및 1회 사용량 등을 구체적으로 기재하시기 바랍니다.
3. 행위분류에 의한 항목번호란에는 의과·치과 및 한방과 관련협회 또는 관련 학회에서 제정된 행위 분류항목을 기재합니다(해당사항이 없는 경우 "해당사항 없음"으로 기재하시면 됩니다).

Absolute Quantification

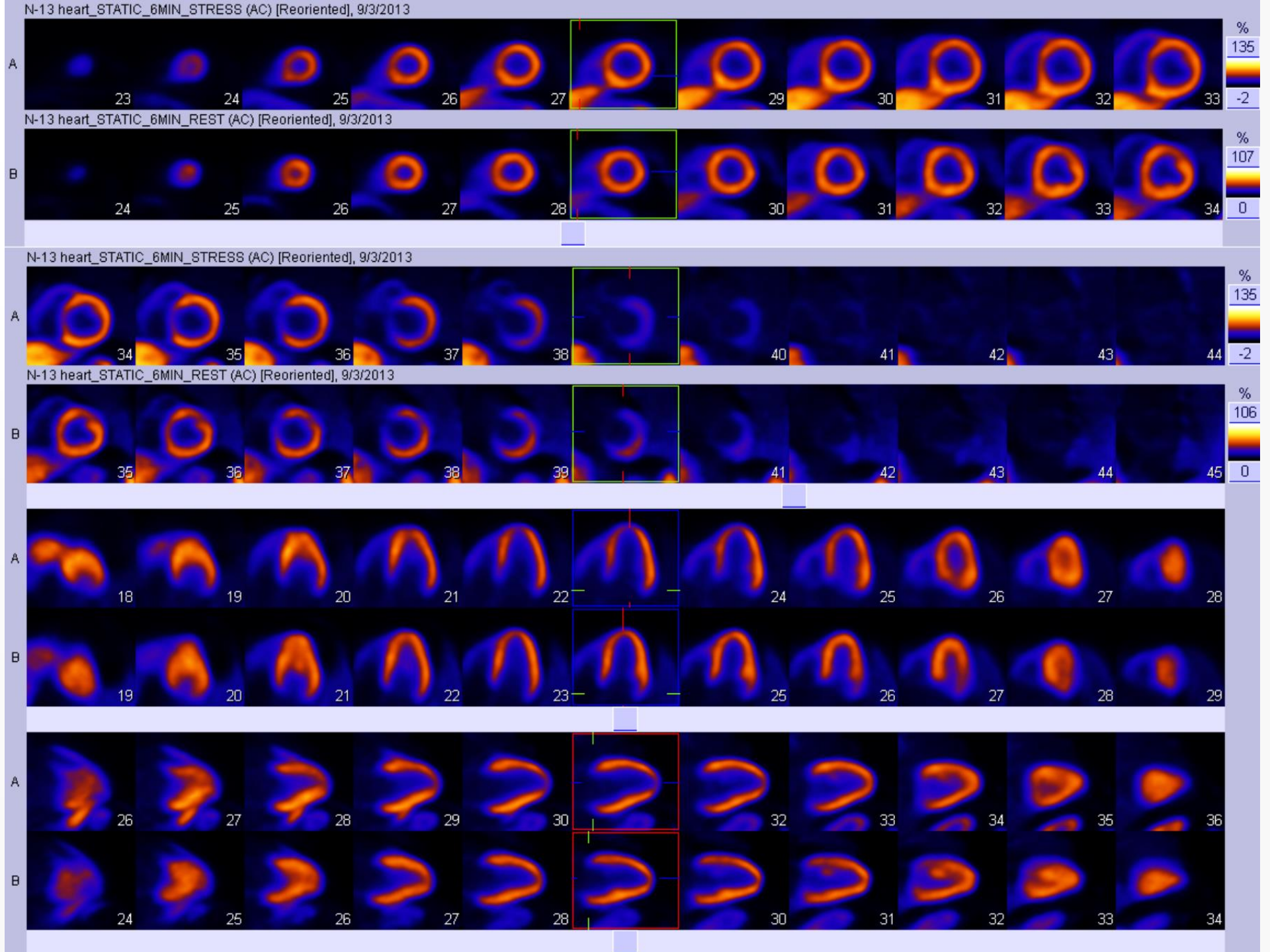
- **Need for Absolute Quantification of Myocardial Perfusion**
  - **‘Balanced ischemia’**
  - **General microvascular disorders**
- **Microvasculature of Myocardium**

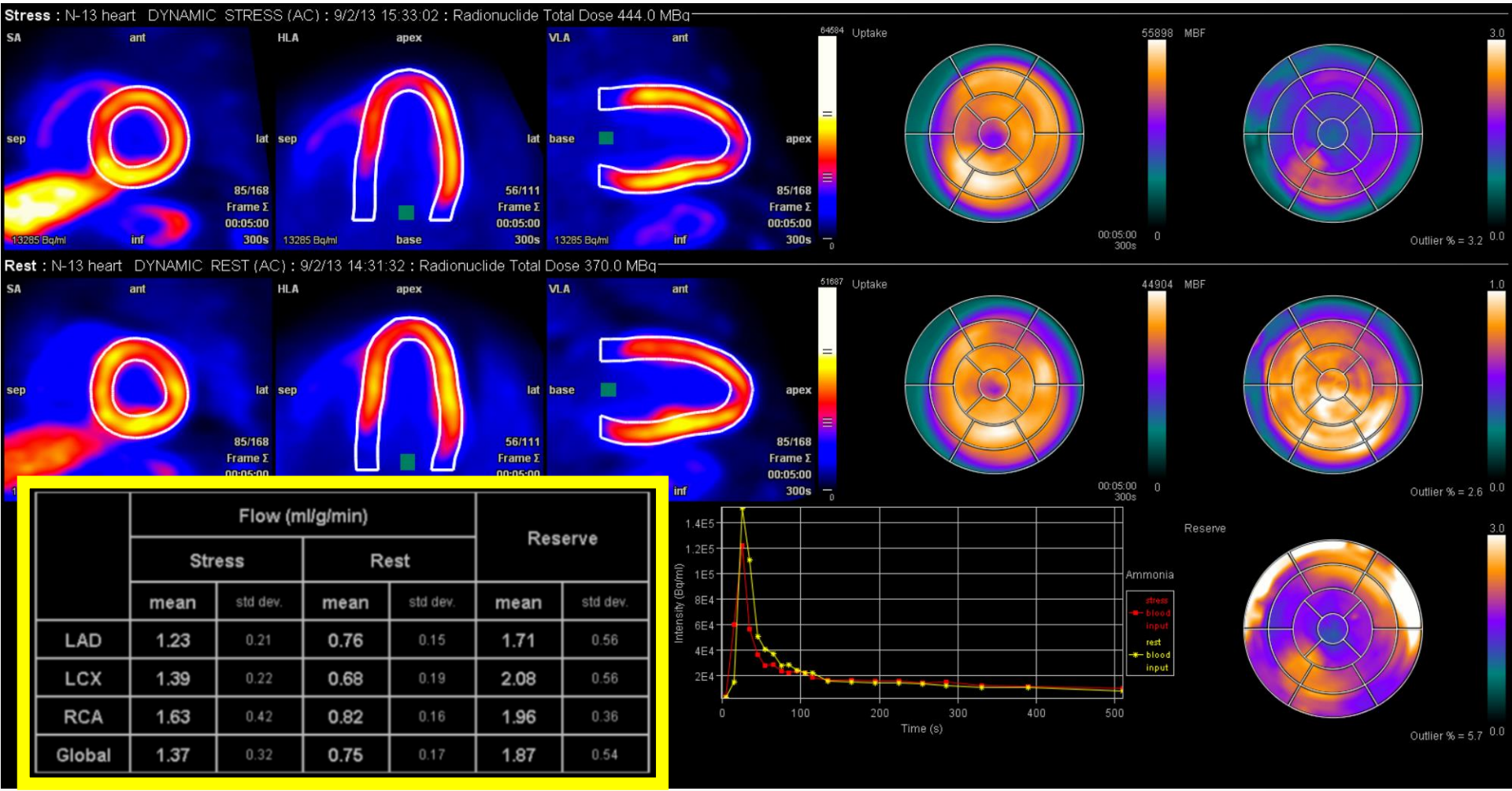


Camici & Rimoldi. *J Nucl Med* 2009

Case

- M/61
  - Underlying DM, CRF without symptom
  - 종합검진으로 시행한 CT CAG 상 pLAD 50%
  - CAG
    - LM and LAD: diffuse
    - dLCX: 40%
    - dRCA: 60%
  - Medical F/U
    - Mild DOE after 1.5-year F/U
  - NH_3 PET


N-13 heart_STATIC_6MIN_STRESS (AC) [Reoriented], 9/3/2013
A
23 24 25 26 27 29 30 31 32 33
%
135
-2
N-13 heart_STATIC_6MIN_REST (AC) [Reoriented], 9/3/2013
B
24 25 26 27 28 30 31 32 33 34
%
107
0
N-13 heart_STATIC_6MIN_STRESS (AC) [Reoriented], 9/3/2013
A
34 35 36 37 38 40 41 42 43 44
%
135
-2
N-13 heart_STATIC_6MIN_REST (AC) [Reoriented], 9/3/2013
B
35 36 37 38 39 41 42 43 44 45
%
106
0
A
18 19 20 21 22 24 25 26 27 28
B
19 20 21 22 23 25 26 27 28 29
A
26 27 28 29 30 32 33 34 35 36
B
24 25 26 27 28 30 31 32 33 34



	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

- NH_3 PET: Decreased vascular reserve in all 3 vessel territories
- CAG: 3-vessel disease, progressed LM
  - Referred for CABG

Gamma Cameras with Specific Designs

CardiArc, CardiArc

Cardius, Digirad

CardioMD, Philips

Ventri, GE

D SPECT, Spectrum Dynamics

Alcyone / NM 530c, GE

NM/CT 570c, GE

Recent Trends in Heart SPECT

- **Hardware**
  - Semiconductor detectors
    - CZT
  - Non-rotating gantry
    - Fixed angles
  - Enhanced sensitivity
    - Fast rotation
- **Software / Protocol**
  - Dynamic SPECT

- Fast scan for patients' convenience
- Low radiation dose for patients' safety
- Dynamic SPECT for absolute flow measurement

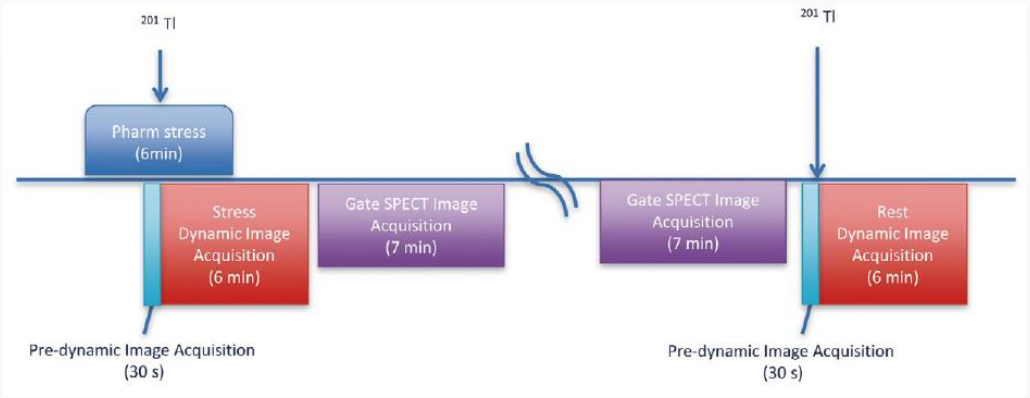
Perfusion Using Dynamic SPECT

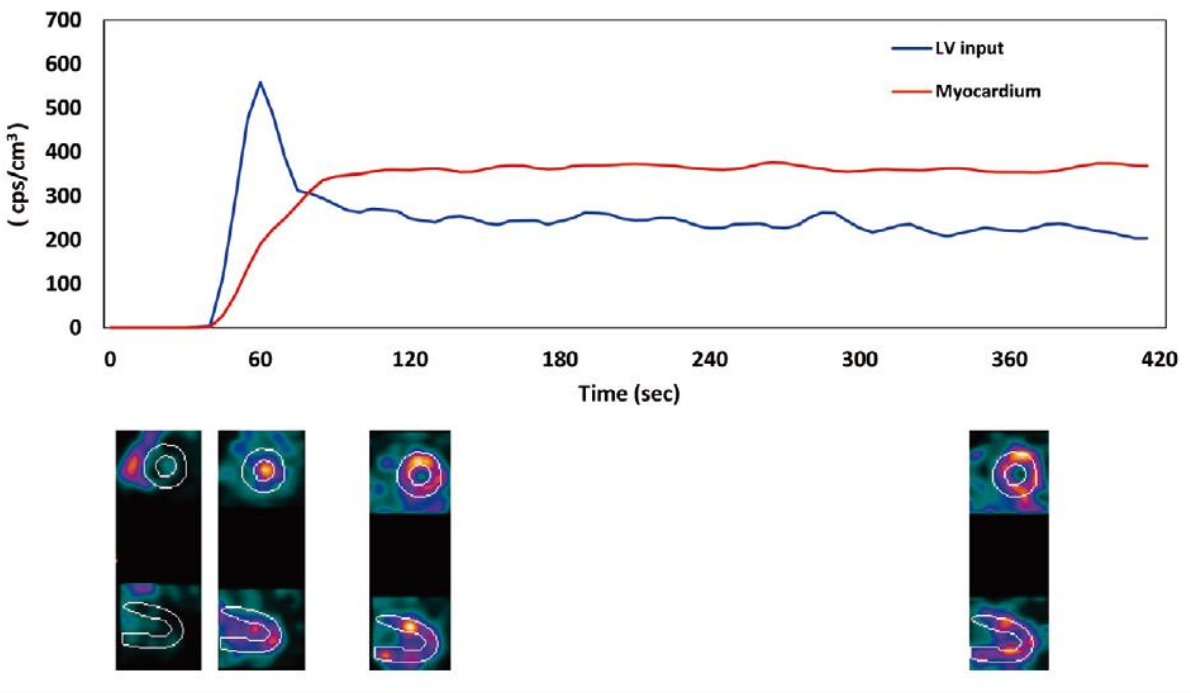
(*Circ J* 2015; **79:** 623–631)

Prediction of Left Main or 3-Vessel Disease Using Myocardial Perfusion Reserve on Dynamic Thallium-201 Single-Photon Emission Computed Tomography With a Semiconductor Gamma Camera

Shinya Shiraishi, MD, PhD; Fumi Sakamoto, MD, PhD; Noriko Tsuda, MD; Morikatsu Yoshida, MD, PhD; Seiji Tomiguchi, MD, PhD; Daisuke Utsunomiya, MD, PhD; Hisao Ogawa, MD, PhD; Yasuyuki Yamashita, MD, PhD

- **Scanner: Discovery 530c**
- **Tracer: ^{201}Tl**
- **Protocol**
  - **111 MBq split for stress / rest**
  - **List-mode dynamic scan for 6 min**
- **Reconstruction**
  - **Frames: 72×5 s**
- **Sampling, segmentation and modeling**
  - **2-compartment model**
  - **MPR index (K1 at stress / K1 at rest)**





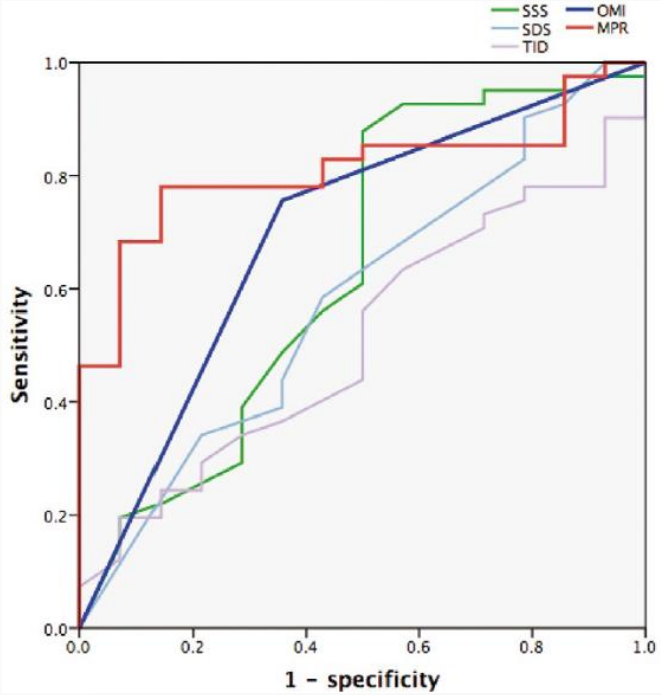


Table 3. Diagnostic Accuracy (n=55)

	Sensitivity	Specificity	PPV	NPV	Accuracy
MPR index	86	78	57	94	80
MPR index and previous MI	50	95	78	85	84
MPR index or previous MI	100	59	45	100	69
Previous MI	64	76	47	86	73

Shiraishi et al. *Circulation J* 2015;79:623

Imaging-Based Screening in High-Risk Patients

Purpose in Clinical Practice

Role of Perfusion Imaging

Discrimination of "High-Risk" Patients

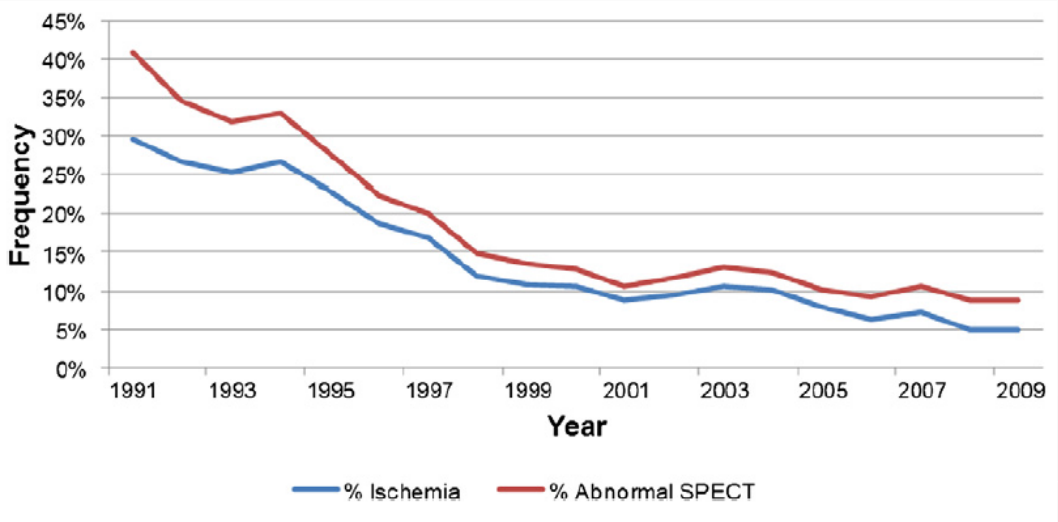
- **Framingham Risk Scores**
  - 1998: age, sex, LDL, HDL, t-chol, HT, smoking, DM
  - 2008: age, sex, HDL, t-chol, SBP (Tx or non-Tx), smoking, DM

Risk Score				Risk Factors/Covariates Included														
Study Group	Study and Region	Data Source	Publication Year	Age	Sex	Total Chol	LDL Chol	HDL Chol	CRP	Systolic BP	BP Rx	Diabetes	HbA1c*	Smoking	Family Hx CVD†	Body Mass Index	Social	Region
Framingham CHD[57]	Framingham MA, USA	EAF, EAM	1998	x	x	x	x	x		x		x		x				
ATP III[24]	Framingham MA, USA	EAF, EAM	2001	x	x	x		x		x	x			x				
Framingham Global[58]	Framingham MA, USA	EAF, EAM	2008	x	x	x		x		x	x	x		x				
PRO-CAM[59]	Muenster, Germany	EM	2002	x			x	x		x		x		x	x			
QRISK[60]	QRESEARCH, United Kingdom	EF, EM	2007	x	x	x		x		x	x			x	x	x	x‡	x
Reynolds Men[61]	Phys Health Study USA	EAF	2008	x		x		x	x	x				x	x			
Reynolds Women[62]	Women's Health Study USA	EAM	2007	x		x		x	x	x			x	x	x			
EURO-SCORE[63]	12 cohorts Europe	EF, EM	2003	x	x	x		x		x				x				x
Pooled Cohort (current)	CARDIA, Framingham, ARIC, CHS,USA	EAF, EAM AAF, AAM		x	x	x		x		x	x	x		x				

Goff et al.
Circulation
2014;129:S49

Data from The Past vs. Risk at Present

Parameters	1991–1995 (n = 6,335)	1996–2000 (n = 10,264)	2001–2005 (n = 14,089)	2006–2009 (n = 8,827)	p Values (Trend)
Pre-test likelihood of CAD					
Mean CAD likelihood	40.1 ± 30.2	44.7 ± 30.8	46.8 ± 30.3	49.2 ± 30.6	0.0001 (<0.001)
Low CAD likelihood, <15%	1,871 (29.5)	2,602 (25.4)	3,181 (22.6)	1,871 (21.2)	
Intermediate likelihood, 15%–84%	3,630 (57.3)	6,035 (58.8)	8,610 (61.1)	5,296 (60.0)	
High CAD likelihood, ≥85%	833 (13.2)	1,627 (15.9)	2,298 (16.3)	1,659 (18.8)	<0.001 (<0.0001)
SPECT results					
Sum stress score ≥5%	2,046 (32.3)	1,666 (16.2)	1,638 (11.6)	829 (9.4)	<0.001 (<0.0001)
Sum difference score ≥5%	1,620 (25.6)	1,372 (13.4)	1,328 (9.4)	530 (6.0)	<0.001 (<0.0001)
Sum stress score ≥10%	1,233 (19.5)	1,013 (9.9)	822 (5.8)	416 (4.7)	<0.001 (<0.0001)
Sum difference score ≥10%	927 (14.6)	775 (7.6)	600 (4.3)	216 (2.5)	<0.001 (<0.0001)
% with TID of the left ventricle	244 (3.9)	276 (2.7)	330 (2.3)	56 (1.6)*	<0.001 (0.008)



Need for revised risk assessment

Rozanski et al.
J Am Coll Cardiol 2013;61:1054

Screening of High-Risk Patients

- **Purpose**
  - Detection of CAD
  - Guidance for management
  - Improvement in outcome

For diagnosis

For outcome

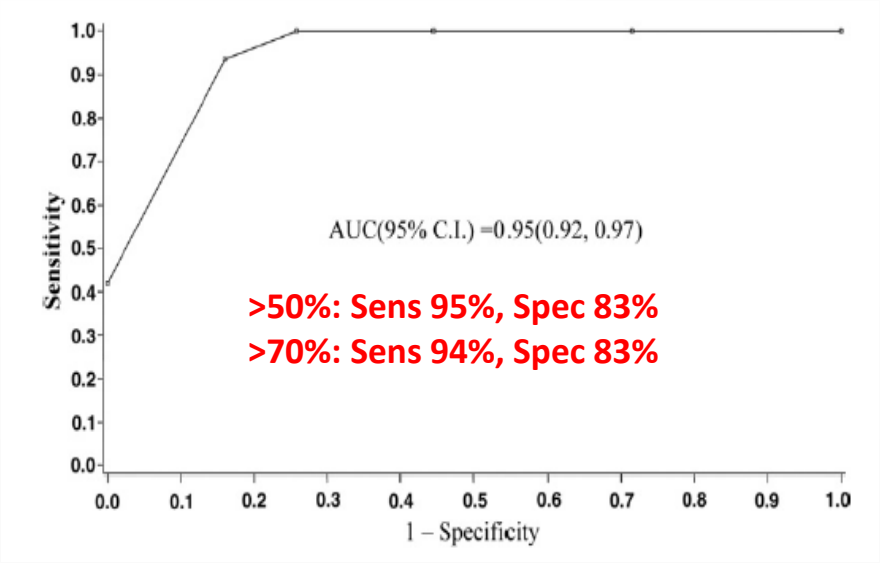
- **Available Non-Invasive Methods**
  - Exercise treadmill test (ETT)
  - CT Coronary angiography (CTCA)
  - CT perfusion, CT FFR
  - MR perfusion
  - Perfusion SPECT, PET

Anatomy-based

Perfusion-based

Diagnostic Value of CTA

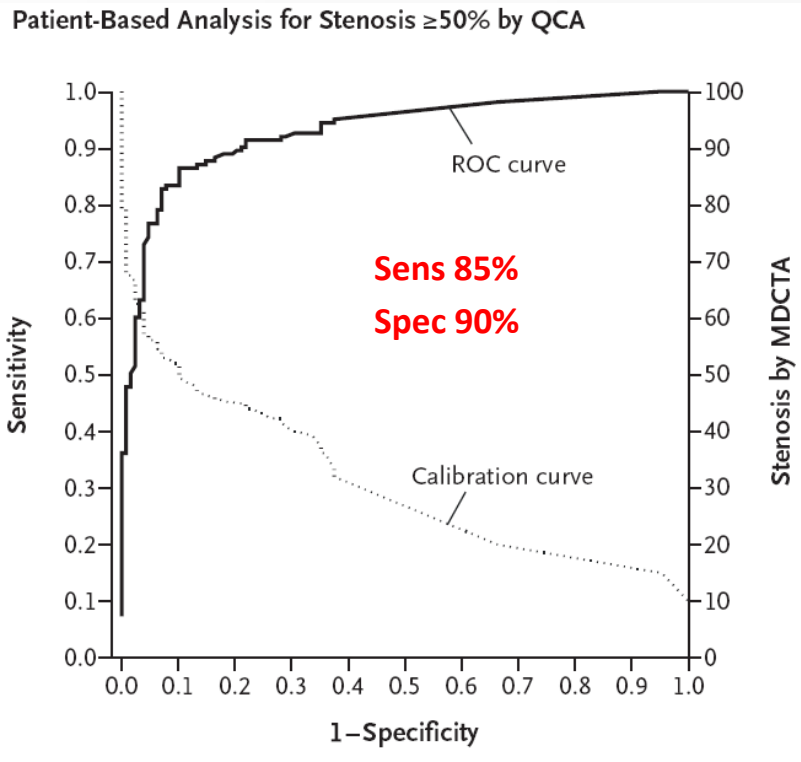
Budoff et al. *J Am Coll Cardiol* 2008;52:1724



ACCURACY Trial

- Prospective, multicenter study
- 64 slice MDCT
- Low likelihood (prevalence 13.9%)

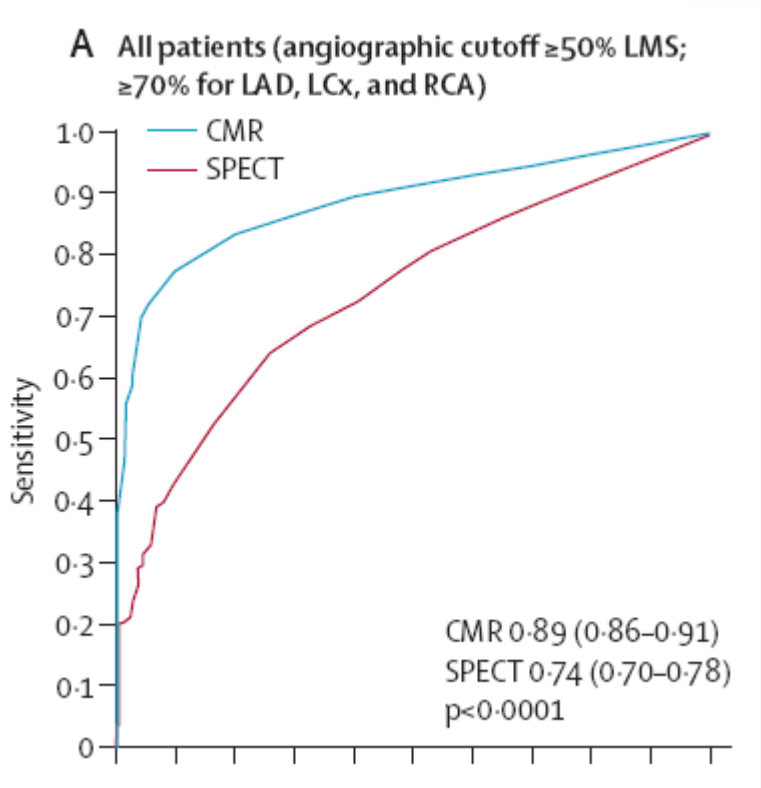
Miller et al. *NEJM* 2008;359:2324



CORE 64 Trial

- Prospective, multinational, multicenter
- 64 slice MDCT in Pre-ICAG patient
- High likelihood (prevalence 56%)

Diagnostic Value of MR Perfusion

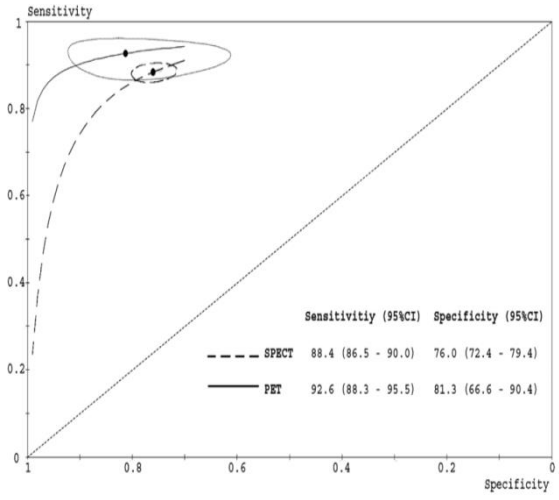


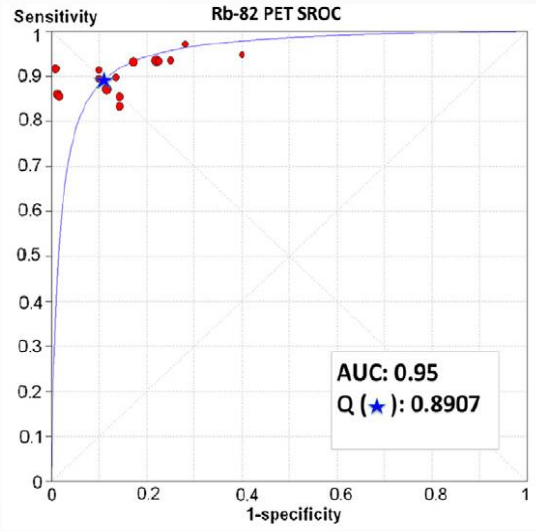
Greenwood et al. *Lancet* 2012;379:453

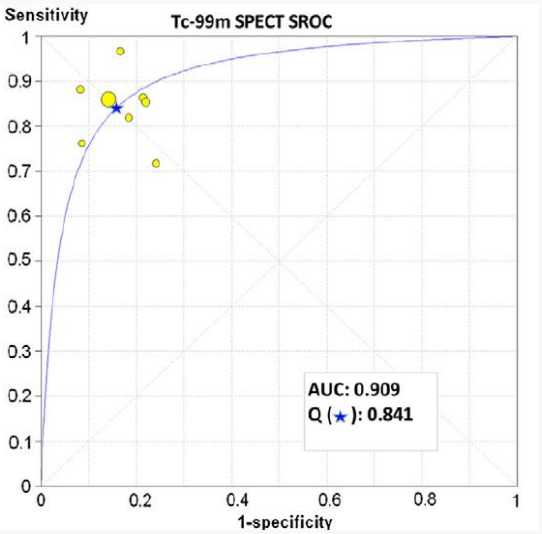
Author and Year*	Criterion for Significant CAD	Sensitivity	Specificity
Schwitter et al, 2001 (48)	Stenosis ≥ 50%	0.86	0.80
Doyle et al, 2003 (55)	Stenosis ≥ 70%	0.58	0.78
Ishida et al, 2003 (56)	Stenosis > 70%	0.90	0.85
Nagel et al, 2003 (57)	Stenosis ≥ 75%	0.88	0.90
Giang et al, 2004 (51)	Stenosis ≥ 50%	0.87	0.86
Kawase et al, 2004 (58)	Stenosis > 70%	0.94	0.94
Paetsch et al, 2004 (59)	Stenosis > 50%	0.91	0.62
Plein et al, 2004 (60)	Stenosis ≥ 70%	0.88	0.83
Takase et al, 2004 (61)	Stenosis > 50%	0.93	0.85
Thiele et al, 2004 (62)	Stenosis ≥ 70%	0.75	0.58
Plein et al, 2005 (63)	Stenosis > 70%	0.88	0.74
Sakuma et al, 2005 (64)	Stenosis > 70%	0.81	0.68
Cury et al, 2006 (65)	Stenosis ≥ 70%	0.93	0.64
Klem et al, 2006 (30)	Stenosis ≥ 70%	0.84	0.58
Pilz et al, 2006 (66)	Stenosis > 70%	0.96	0.83
Merkle et al, 2007 (67)	Stenosis > 70%	0.96	0.72
Cheng et al, 2007 (29)	Stenosis ≥ 50%	0.90	0.67
Greenwood et al, 2007 (68)	Stenosis ≥ 70%	0.72	1.0
Seeger et al, 2007 (69)	Stenosis > 70%	0.92	0.85
Gebker et al, 2008 (37)	Stenosis ≥ 50%	0.90	0.71
Meyer et al, 2008 (70)	Stenosis > 70%	0.89	0.79
Pilz et al, 2008 (71)	Stenosis > 70%	0.92	1.0
Schwitter et al, 2008 (52)	Stenosis ≥ 50%	0.85	0.67
Klein et al, 2008 (72)	Stenosis ≥ 50%	0.87	0.88
Klem et al, 2008 (73)	Stenosis ≥ 70%	0.84	0.88
Thomas et al, 2008 (74)	Stenosis ≥ 50%	0.93	0.84
Burgstahler et al, 2008 (75)	Stenosis ≥ 70%	1.0	0.80
Arnold et al, 2010 (76)	Stenosis ≥ 50%	0.90	0.81
Manka et al, 2010 (77)	Stenosis ≥ 50%	0.92	0.75
Lockie et al, 2011 (78)	Fractional flow reserve < 0.75	0.82	0.94

Coelho-Filho et al. *Radiology* 2013;266:701

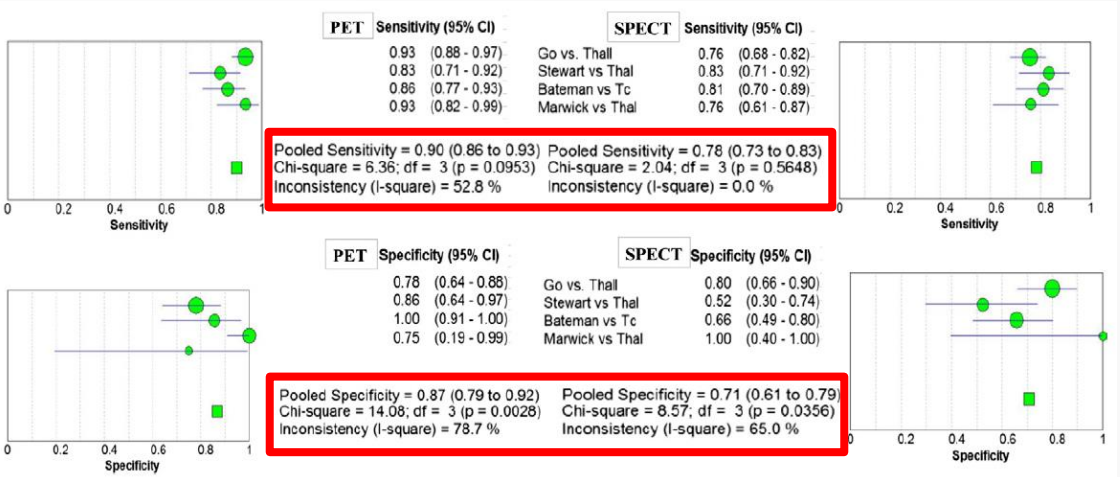
Diagnostic Value of MPI







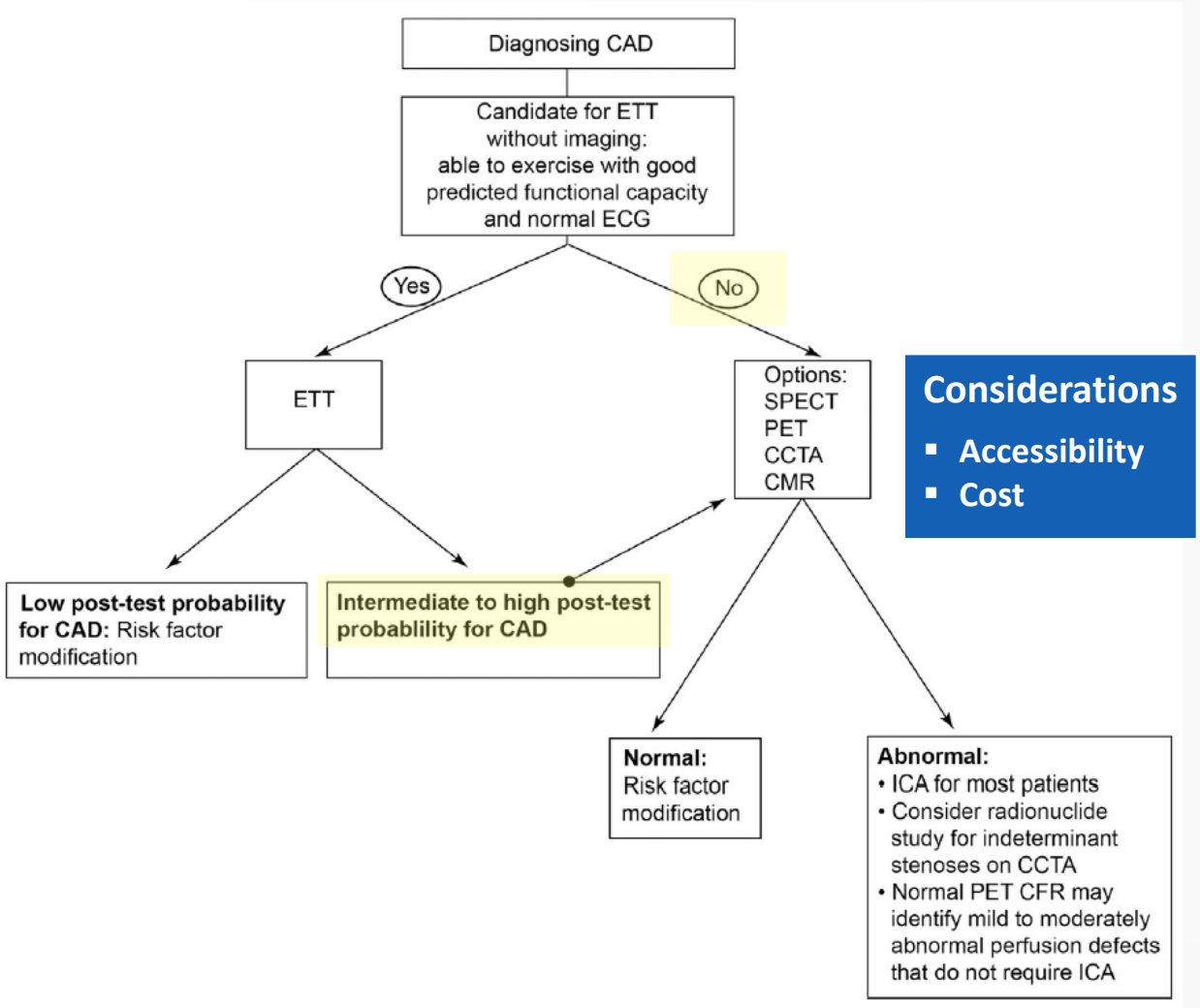
	Sensitivity (95% CI)	Specificity (95% CI)
Base case		
SPECT (n=115)	88.3 (86.5–90.0)	76.0 (72.4–79.4)
PET/PET-CT (n=9)	92.6 (88.3–95.5)*	81.3 (66.6–90.4)
Subgroup analyses SPECT		
Exercise stress (n=41)	89.4 (85.9–92.1)	74.7 (67.9–80.4)
Pharmacologic stress (n=52)	88.4 (85.4–90.8)	79.7 (74.6–84.0)
Technetium-99m (n=60)	90.1 (87.5–92.1)	75.0 (69.6–79.7)
Thalium-201 (n=42)	87.0 (83.6–89.8)	78.2 (72.0–83.3)
Good SPECT studies† (n=54)	87.7 (84.4–90.6)	79.5 (74.9–83.5)
Poor SPECT studies (n=61)	88.9 (86.5–90.9)	72.1 (66.4–77.2)‡
Subgroup analyses PET		
PET only (n=7)	92.9 (85.9–96.6)	85.6 (75.5–92.0)
Good PET/PET-CT studies† (n=7)	95.2 (91.8–97.2)§	80.8 (77.2–84.0)



Parker et al. *Circ Cardiovasc Imaging* 2012;5:700

McArdle et al. *J Am Coll Cardiol* 2012;60:1828

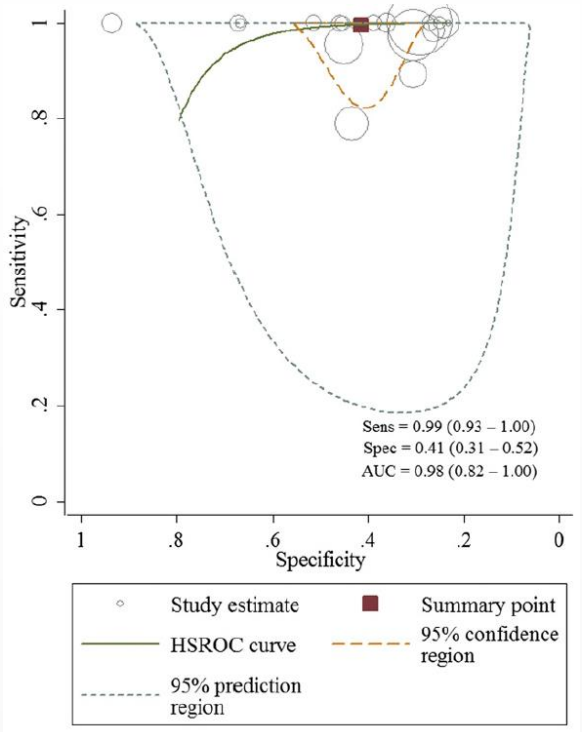
A Scheme for Diagnosis



Cremer et al. *Sem Nucl Med* 2014;44:320

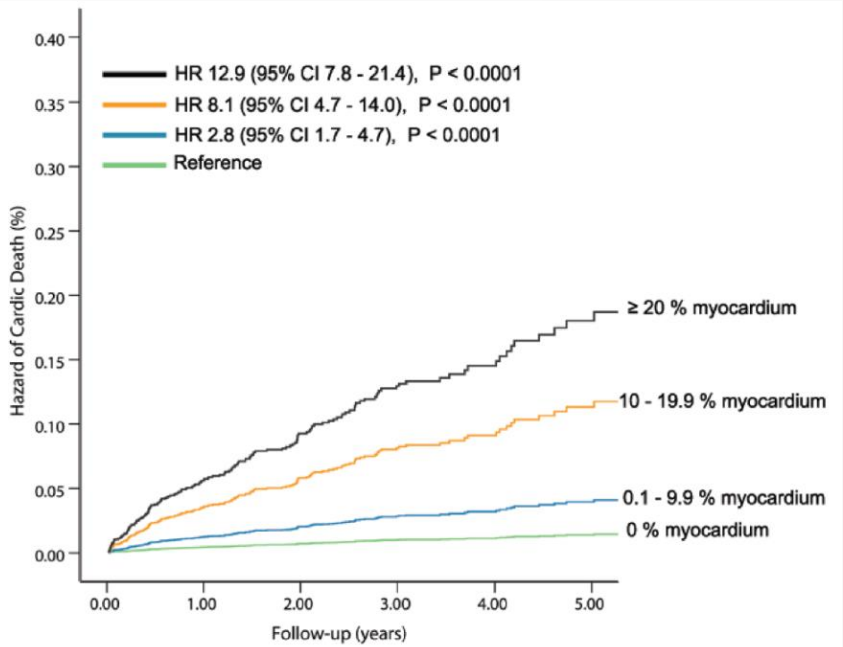
Prognostication

CTCA



Hulten et al. *J Am Coll Cardiol* 2011;57:1237

MPI



Dorbala et al.
J Am Coll Cardiol
2013;61:176

CMR

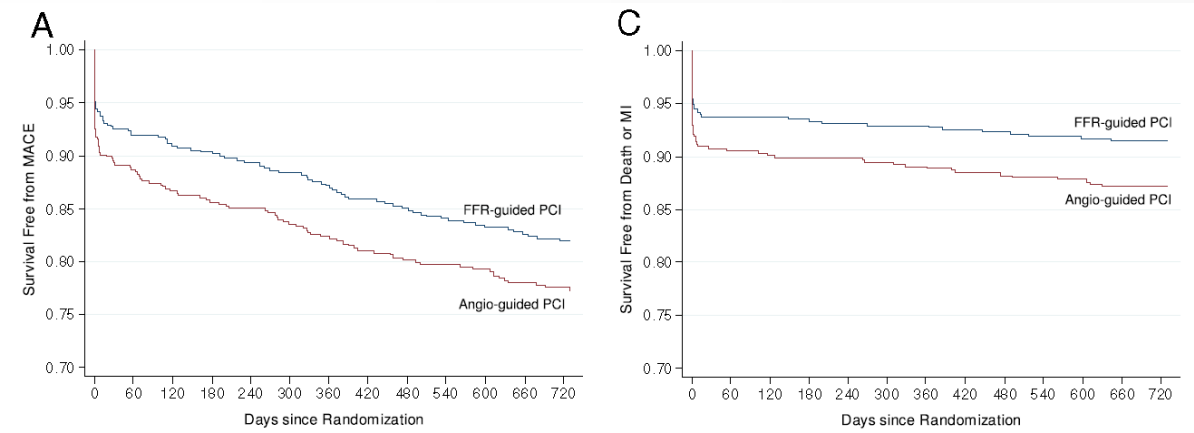
Table 7 Summary CMR findings

	Independent Prognostic CMR Finding (Group 1)	No Independent Prognostic CMR Finding (Group 2)	Not Enough Evidence to Establish the Prognostic Value (Group 3)
Patients with suspected or known CAD			
Hard events	LVEF WMA induced (presence/segments) Perfusion induced (presence/segments) Infarct size (presence/extent/transmurality)	WMA rest (presence/segments)	WMA rest (score) WMA induced (score) Perfusion rest
MACE	Perfusion induced (presence) Infarct size (presence/extent)	LVEF WMA rest (score)	WMA rest (presence/segments) WMA induced Perfusion rest Perfusion induced (segments/score) Infarct size (transmurality)

Aidi et al.
J Am Coll Cardiol
2014;63:1031

Decision Making: FAME I

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

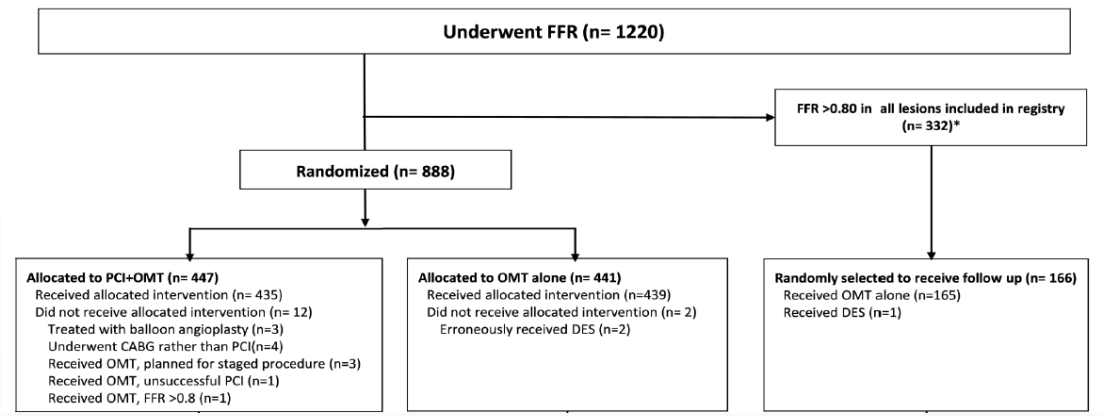


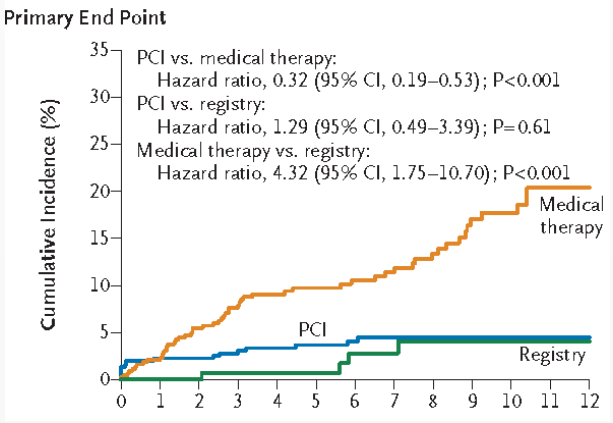
Pijls et al.
J Am Coll Cardiol
2010;56:177

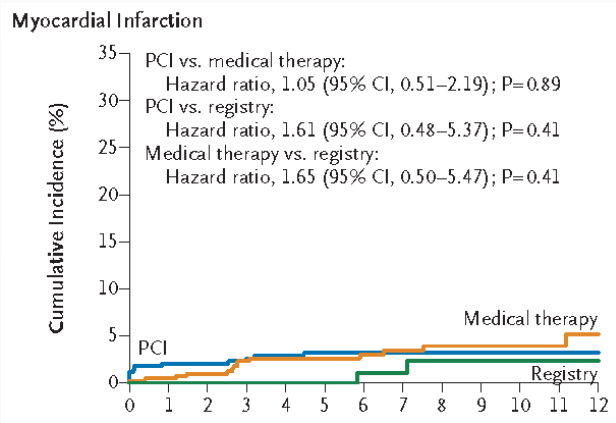
	Angiography Group (n = 496)	FFR Group (n = 509)	p Value*
Procedural and 1-yr costs			
Materials, U.S.$‖	6,007 ± 2,819	5,332 ± 3,261	<0.001
Hospital stay at baseline admission, days	3.7 ± 3.5	3.4 ± 3.3	0.05
Incremental health care costs at 1 year, U.S.$¶	14,357	12,291	<0.001
Myocardial infarction	49 (9.9)	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

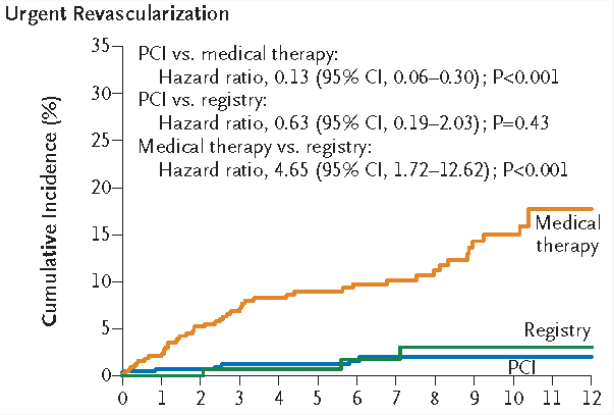
Decision Making: FAME II

- **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

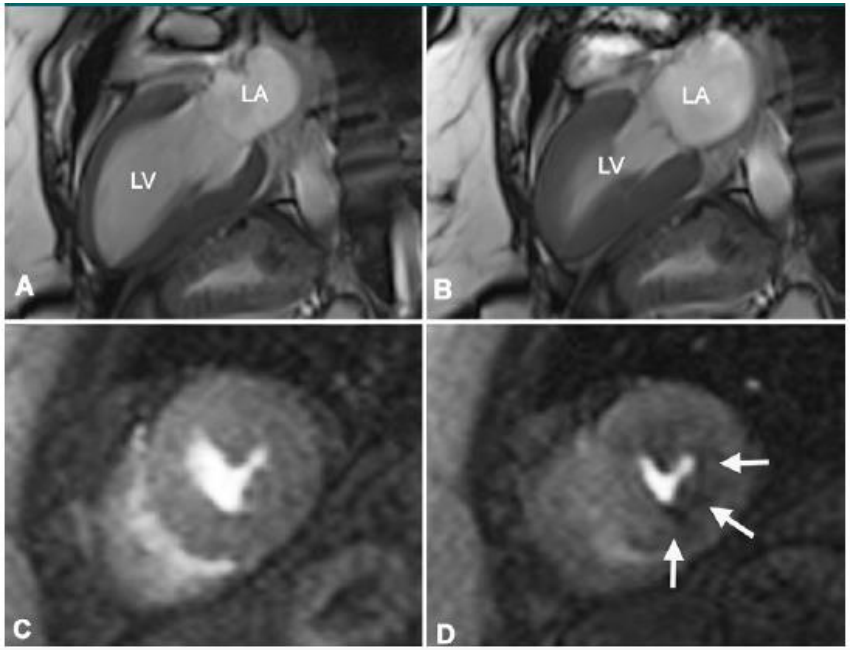
Functional Imaging Studies

Modality	Methods	Pro	Con
CT Perfusion	Phase enhancement Dynamic enhancement	Easy	Radiation (dynamic) Need for validation
MR Perfusion	Dynamic enhancement Kinetic analysis	No radiation	Need for validation Cost
CT FFR	Hydraulic assumption with 3D CTA	Accessibility	Radiation Need for validation
SPECT	Different uptake Kinetic analysis	Accessibility Validation	Radiation Image quality (vs. PET)
PET	Different uptake Kinetic analysis	Validation Quantification	Cost Accessibility

Perfusion Study: CT or MRI

MR Perfusion

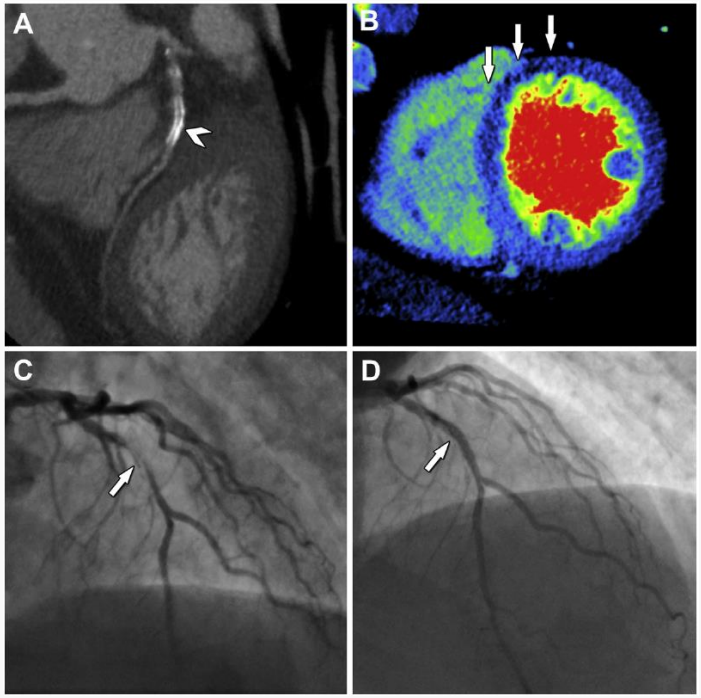
- No radiation
- More clinical data than CTP



Coelho-Filho et al. *Radiology* 2013;266:701

CT Perfusion

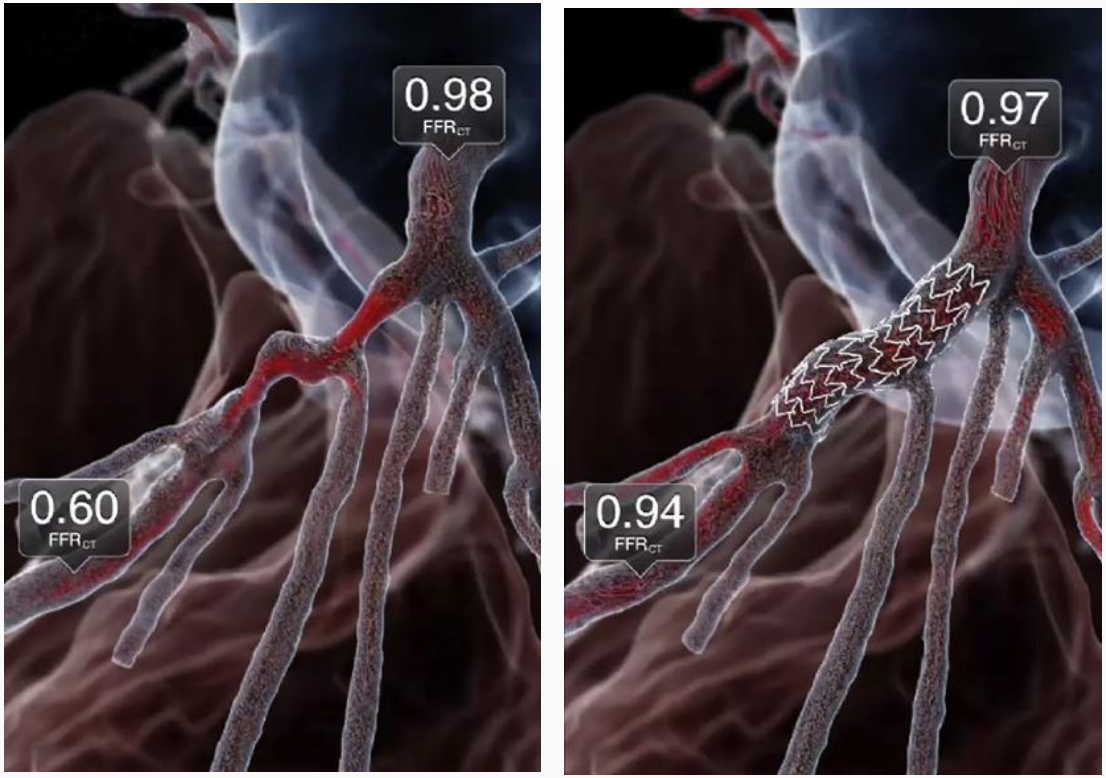
- More radiation dose than CTA
- Insufficient clinical data

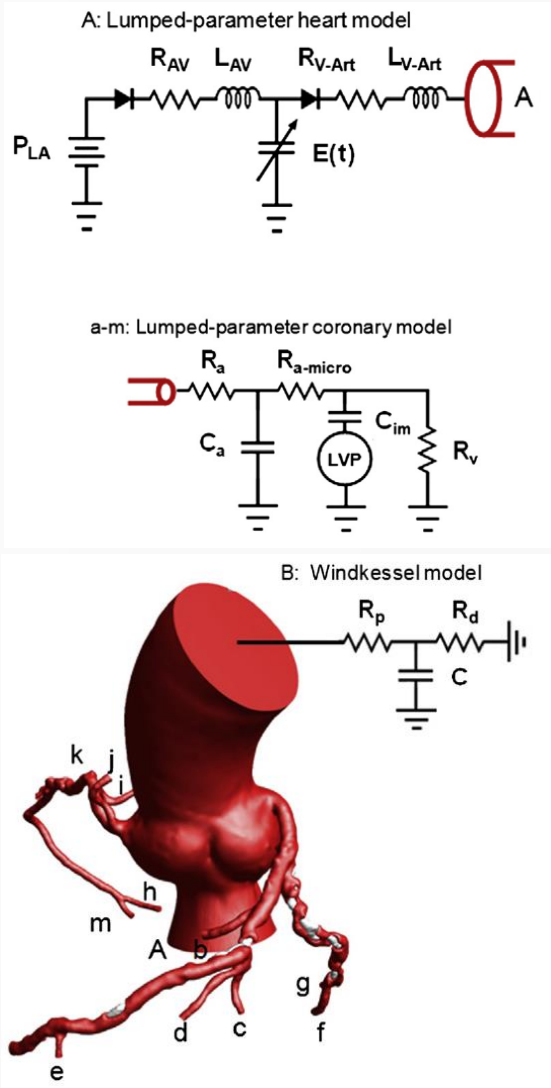


Rief et al. *J Am Coll Cardiol* 2013;62:1476

CT FFR

- **Modeling with Hydraulic Assumption**

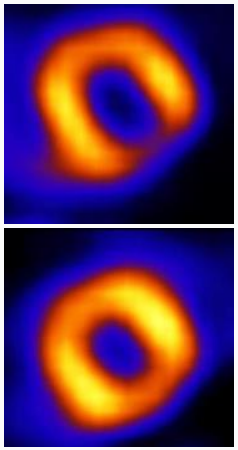


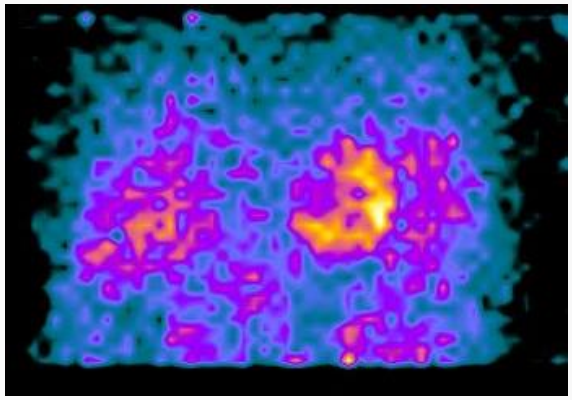


Taylor et al. *J Am Coll Cardiol* 2013;61:2233

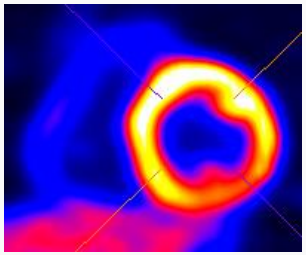
Perfusion Study: SPECT and PET

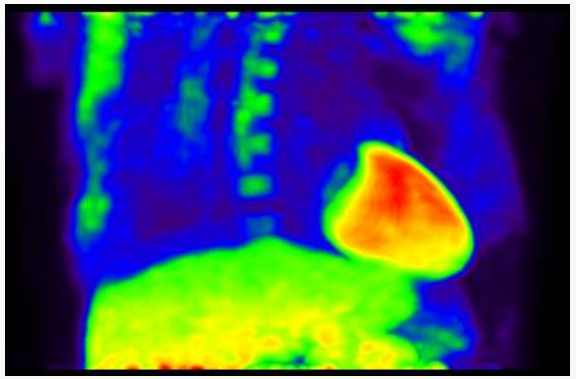
- **SPECT Perfusion**
  - Extensive validation
  - Easy accessibility
  - Radiation & low resolution





- **PET Perfusion**
  - Extensive validation
  - Low radiation
  - Higher resolution
  - Patient's convenience
  - Cost & accessibility



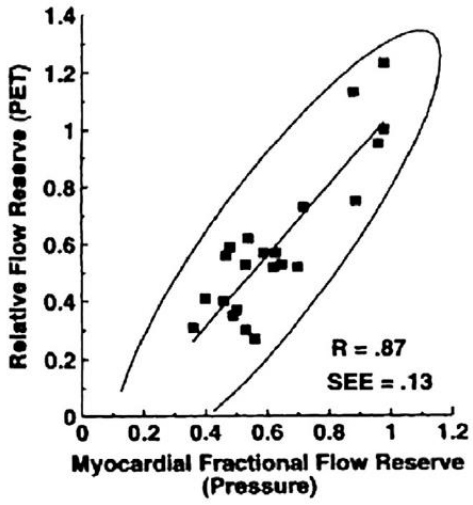


FFR vs. CFR

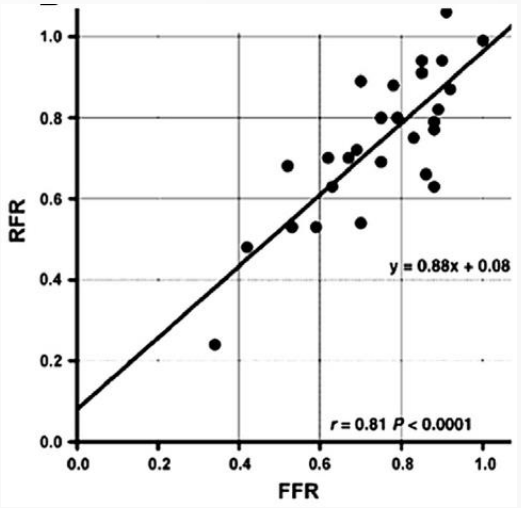
- **CFR (Coronary Flow Reserve)**
  - **Absolute CFR: ratio of maximum stress flow to rest flow**
  - **Relative CFR: ratio of maximum stress flow in the diseased artery to maximum stress flow in the absence of disease in either the same or adjacent arterial distribution**

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

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



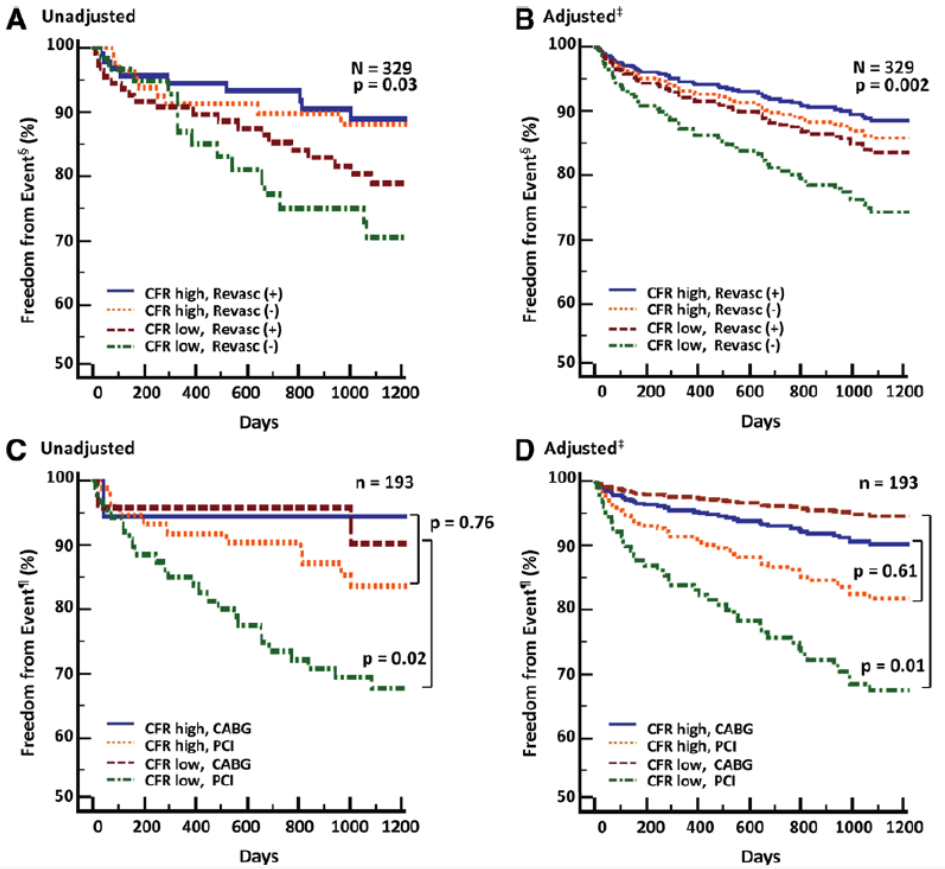
De Bruyne et al. *Circulation* 1994;89:1013

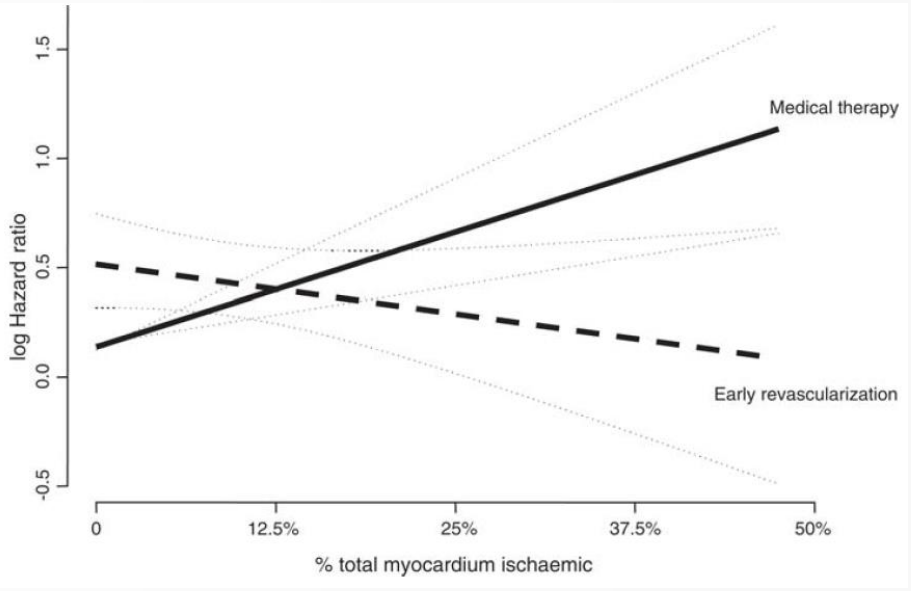


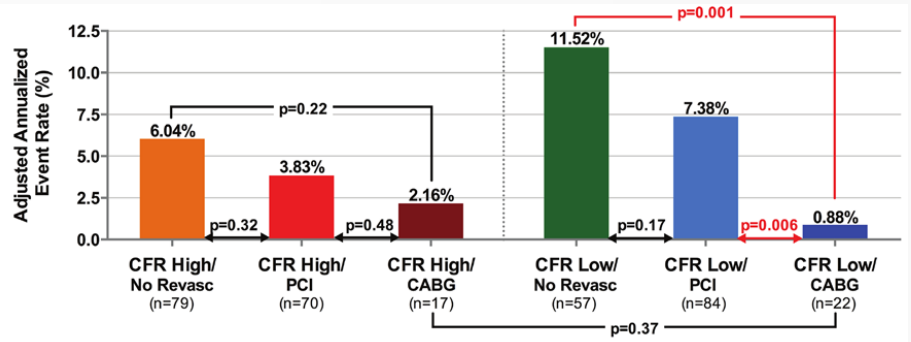
Marques et al. *J Nucl Med 2007*;48:1987

MPI for Decision Making

Hachamovitch et al. *Eur Heart J* 2011;32:1012

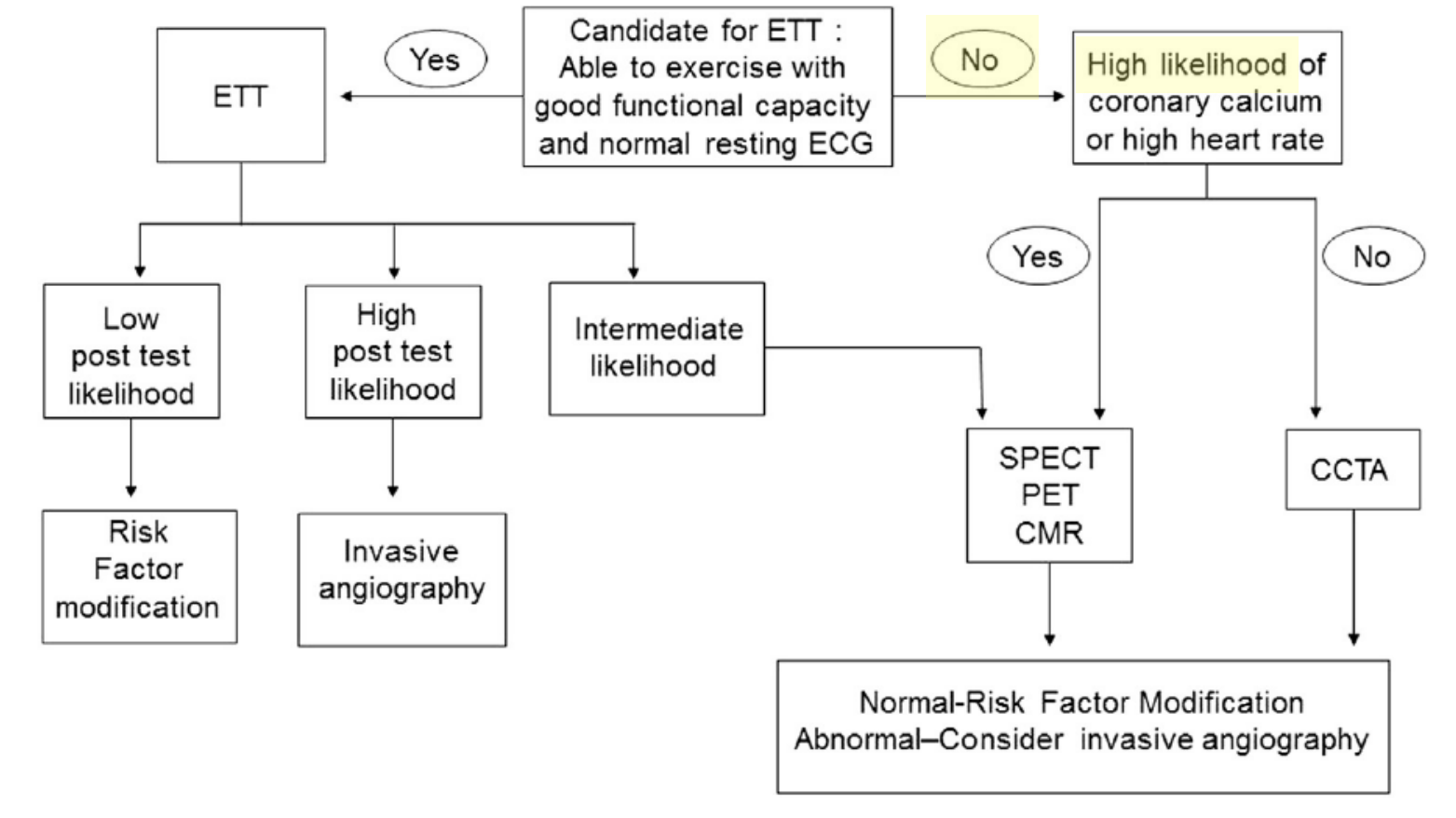






Taqueti et al. *Circulation 2015*;131:19

A Scheme for Management Decision



Cremer et al. *Sem Nucl Med* 2014;44:320

Appropriate Use Criteria for MPI

Table 2. Detection of CAD/Risk Assessment Without Ischemic Equivalent

	Indication	Appropriate Use Score (1–9)
	Asymptomatic	
12.	• Low CHD risk (ATP III risk criteria)	I (1)
13.	• Intermediate CHD risk (ATP III risk criteria) • ECG interpretable	I (3)
14.	• Intermediate CHD risk (ATP III risk criteria) • ECG uninterpretable	U (5)
15.	• High CHD risk (ATP III risk criteria)	A (7)
	New-Onset or Newly Diagnosed Heart Failure With LV Systolic Dysfunction Without Ischemic Equivalent	
16.	• No prior CAD evaluation AND no planned coronary angiography	A (8)
	New-Onset Atrial Fibrillation	
17.	• Part of evaluation when etiology unclear	U (6)
	Ventricular Tachycardia	
18.	• Low CHD risk (ATP III risk criteria)	A (7)
19.	• Intermediate or high CHD risk (ATP III risk criteria)	A (8)
	Syncope	
20.	• Low CHD risk (ATP III risk criteria)	I (3)
21.	• Intermediate or high CHD risk (ATP III risk criteria)	A (7)
	Elevated Troponin	
22.	• Troponin elevation without additional evidence of acute coronary syndrome	A (7)

Hendel et al. *Circulation* 2009;119:e561

Summary

- **Recent Development in SPECT and PET Technology**
  - Heart-dedicated SPECT or SPECT/CT
  - Myocardial perfusion PET
  - Faster, lower-dose, absolute quantification
- **Imaging-Based Screening in High-Risk Patients**
  - Revision of "high-risk" → Needs for new data
  - Diagnosis / prognostication
    - All non-invasive imaging modalities are effective
  - Decision Making
    - Needs for effective functional imaging