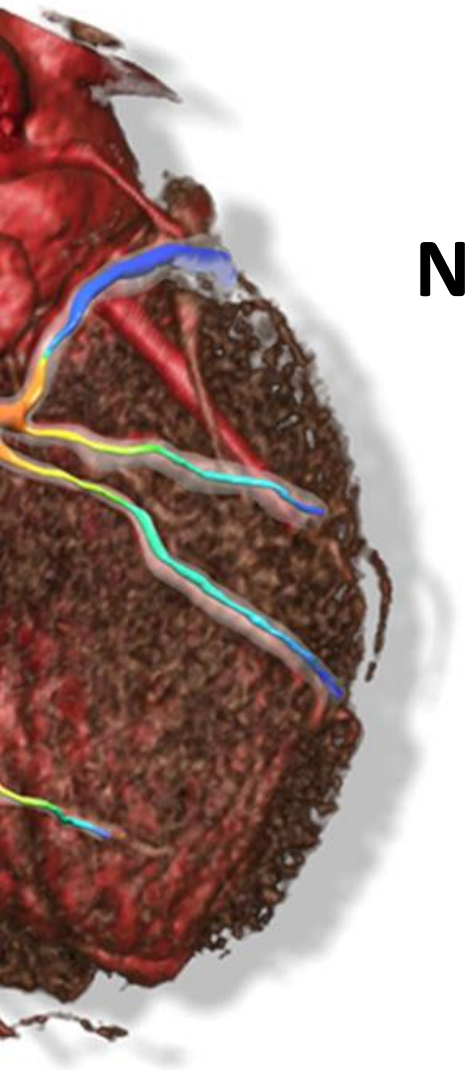
A SMARTool project workshop

CAD RISK PREDICTION AND STRATIFICATION: THE ICT APPROACH



New determinants of coronary artery disease and risk

Antti Saraste, MD, PhD

Turku PET Centre, Turku, Finland

Tuesday 6th November 2018

CNR Research Area Campus
Building A, Room 27
via Moruzzi, 1 Pisa - Italy

Horizon 2020
689068

Symptomatic patients: Likelihood of obstructive CAD according to age, gender and type of chest pain

2013 ESC guidelines on the management of stable coronary artery disease European Heart Journal (2013) **34**, 2949–3003

Pre-test probability

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

- White: pre-test probability: <15% ➔ done
- Blue: pre-test probability: 15-65% ➔ non-invasive testing
- Light red: pre-test probability: 66-85% ➔ non-invasive testing

} ➔ diagnosis+prognosis

- Red: pre-test probability: >85% ➔ non-invasive testing ➔ prognosis

Pre-test probability of CAD according to age, gender and type of chest pain in the ESC 2013 guideline

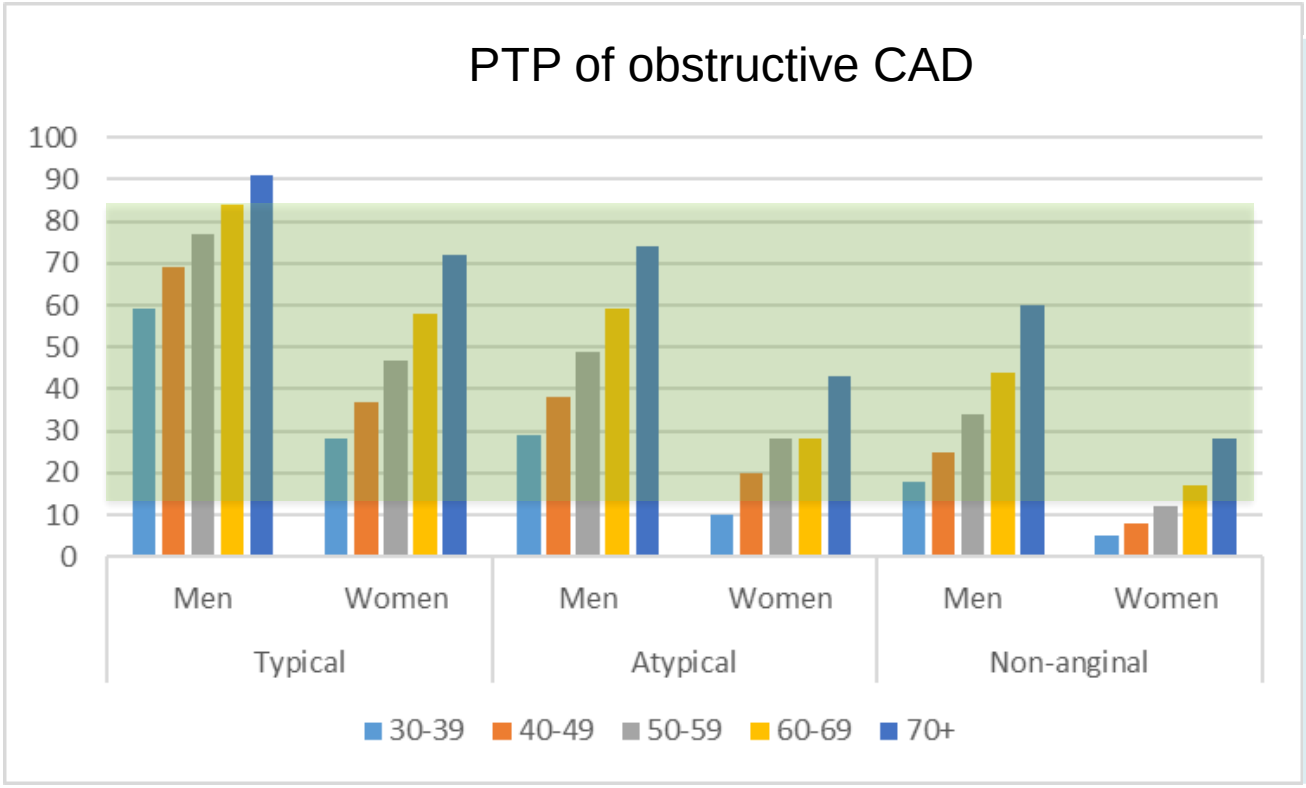


Table 13 Clinical pre-test probabilities[a] in patients with stable chest pain symptoms[108]

	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

ECG = electrocardiogram; PTP = pre-test probability; SCAD = stable coronary artery disease.

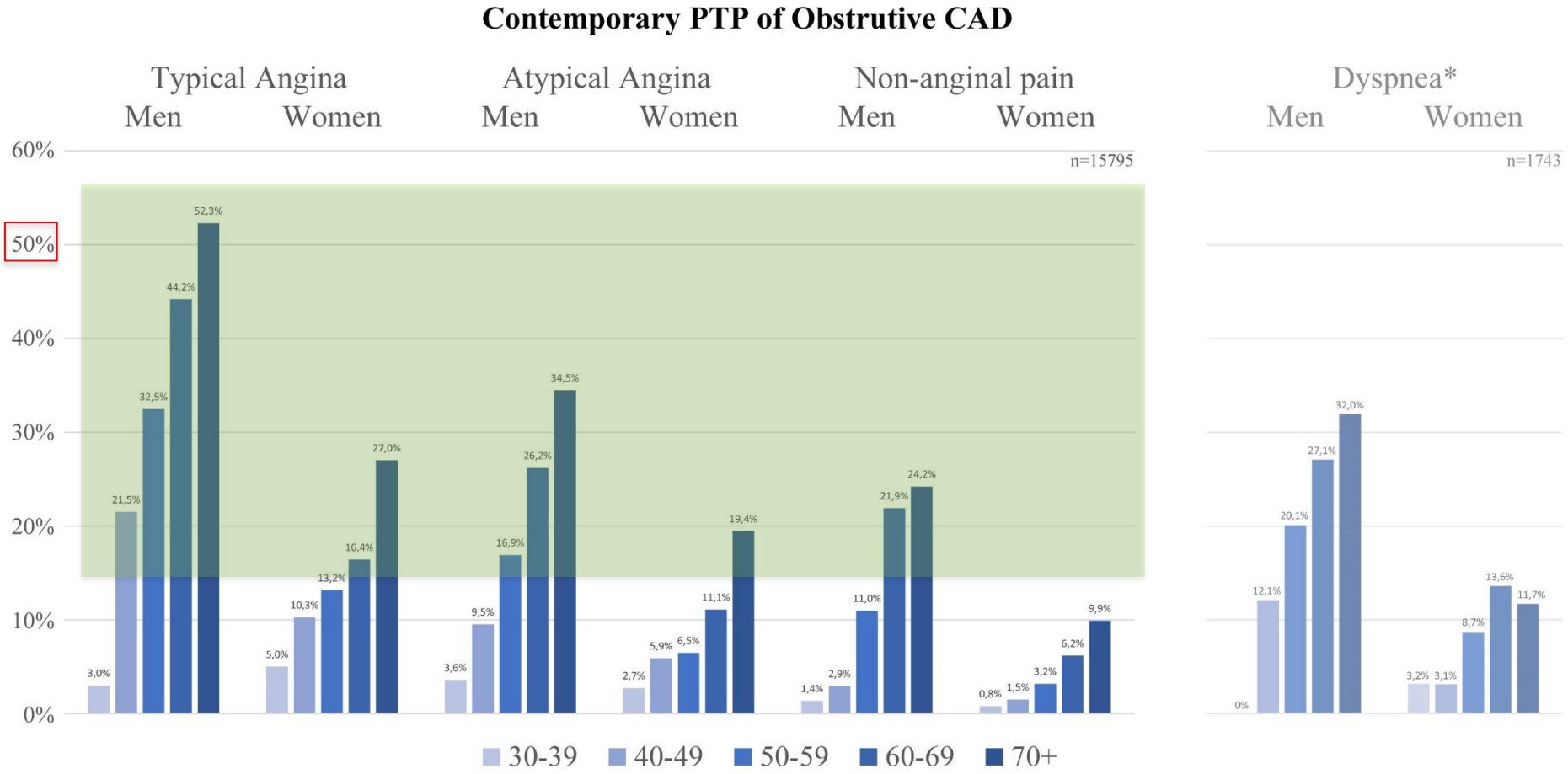
[a] Probabilities of obstructive coronary disease shown reflect the estimates for patients aged 35, 45, 55, 65, 75 and 85 years.

- Groups in white boxes have a PTP <15% and hence can be managed without further testing.
- Groups in blue boxes have a PTP of 15–65%. They could have an exercise ECG if feasible as the initial test. However, if local expertise and availability permit a non-invasive imaging based test for ischaemia this would be preferable given the superior diagnostic capabilities of such tests. In young patients radiation issues should be considered.
- Groups in light red boxes have PTPs between 66–85% and hence should have a non-invasive imaging functional test for making a diagnosis of SCAD.
- In groups in dark red boxes the PTP is >85% and one can assume that SCAD is present. They need risk stratification only.

Diamond and Forrester 1979
Genders Eur Heart J 2011

Prevalence of CAD in contemporary population?

Pre-test probability of CAD based on age, gender and type of symptoms
Pooled analysis of 3 contemporary symptomatic cohorts* with 15,815 patients



** Cheng et al. Circulation 2011,*
Foldyna et al. Eur Heart J Cardiovasc Imaging 2018,
Reeh et al. Eur Heart J 2018 (in press)

Juarez-Orozco et al (submitted)

Prevalence of obstructive CAD according to age, sex and type of chest pain

	Typical Angina		Atypical Angina		Non-anginal	
Age	Men	Women	Men	Women	Men	Women
30-39	3%	5%	4%	3%	1%	1%
40-49	22%	10%	9%	6%	3%	2%
50-59	32%	13%	17%	6%	11%	3%
60-69	44%	16%	26%	11%	22%	6%
≥70	52%	27%	34%	19%	24%	10%

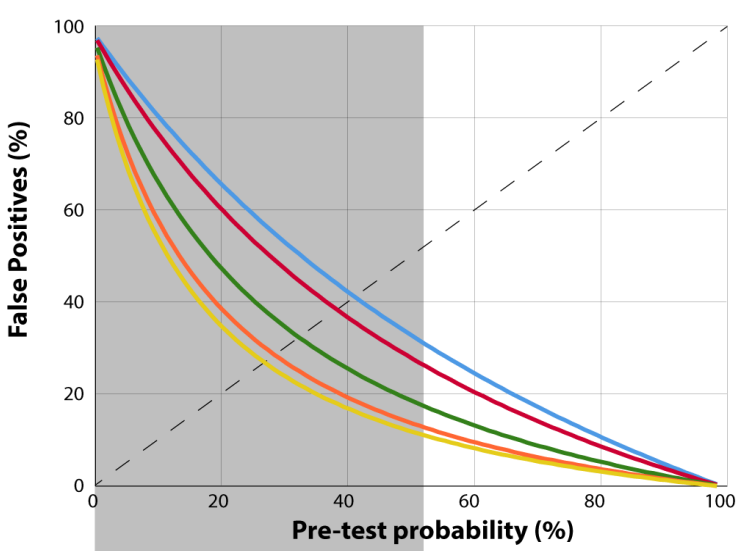
	Typical angina		Atypical angina		Non-anginal pain	
Age	Men	Women	Men	Women	Men	Women
30–39	59	28	29	10	18	5
40–49	69	37	38	14	25	8
50–59	77	47	49	20	34	12
60–69	84	58	59	28	44	17
70–79	89	68	69	37	54	24
>80	93	76	78	47	65	32

	ESC (2013)	
	PTP <15%	PTP ≥15%
SCOT-HEART		
Patients	748	3,022
CAD on CCTA	305	1,314
Normal	198 (64.9)	438 (33.3)
Mild CAD	92 (30.2)	532 (40.5)
Obstructive CAD	15 (4.9)	344 (26.2)

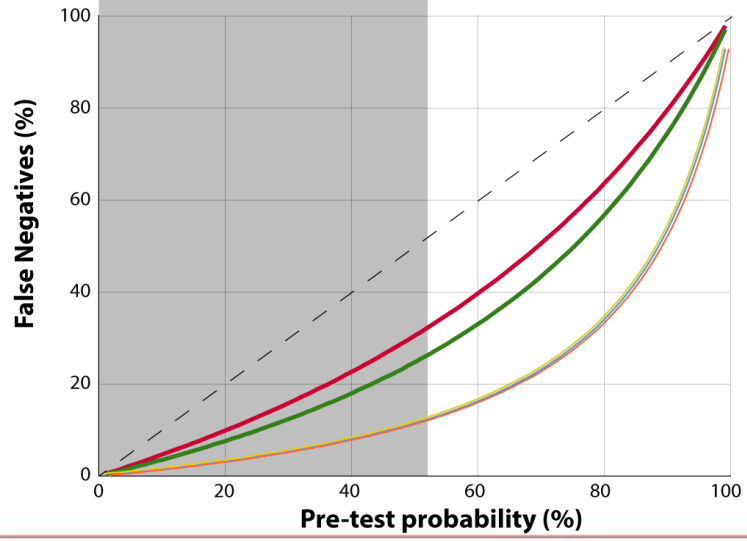
Adamson JACC Cardiovasc Im 2018

The performance of imaging tests to rule-out and rule-in CAD

Rate of diagnostic errors across the possible range of PTPs per technique



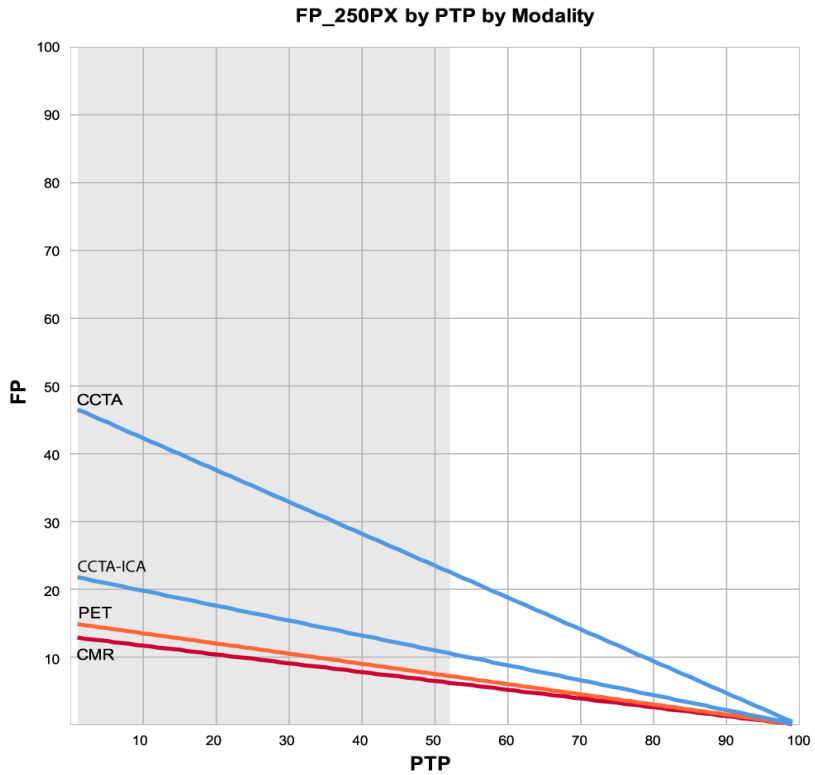
When the Test Result is Positive (ruling-in)



When the Test Result is Negative (ruling-out)

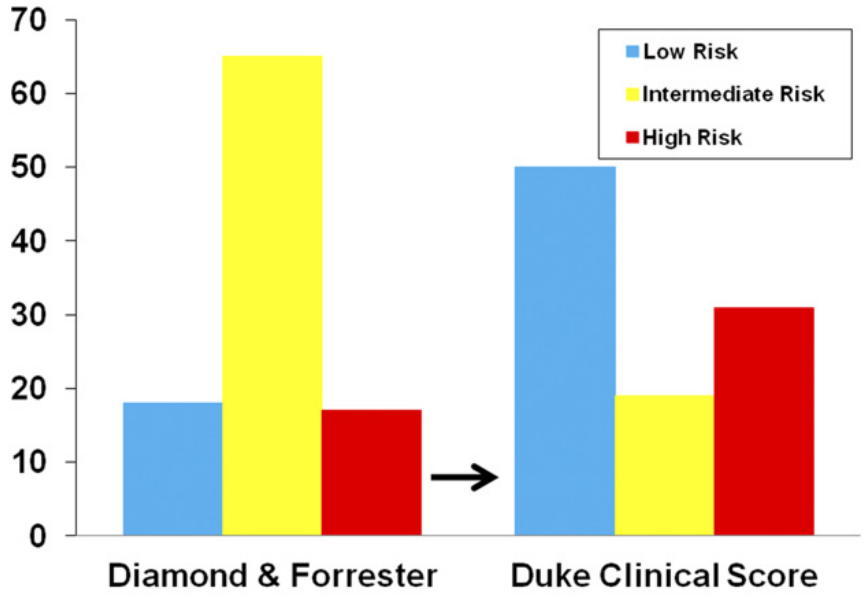
CCTA
ICA
SPECT
PET
CMR

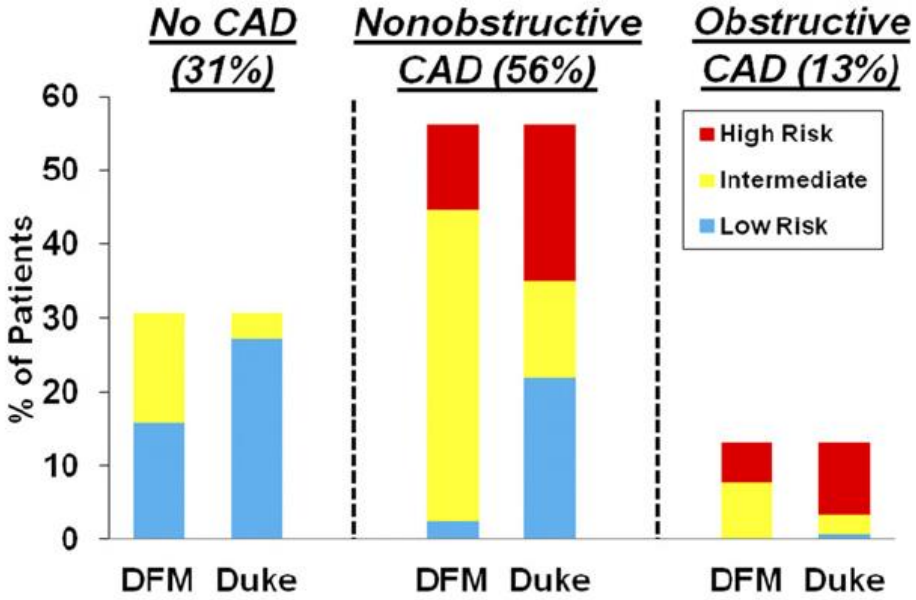
Against FFR



Juarez-Orozco et al (unpublished)

Risk factors improve estimation of pre-test probability of CAD





DFS + previous MI, smoking, hyperlipidemia, diabetes, ST-T wave changes

Wasfy et al. Am J Cardiol 2012

Need for improved tools to estimate risk of obstructive CAD

The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability

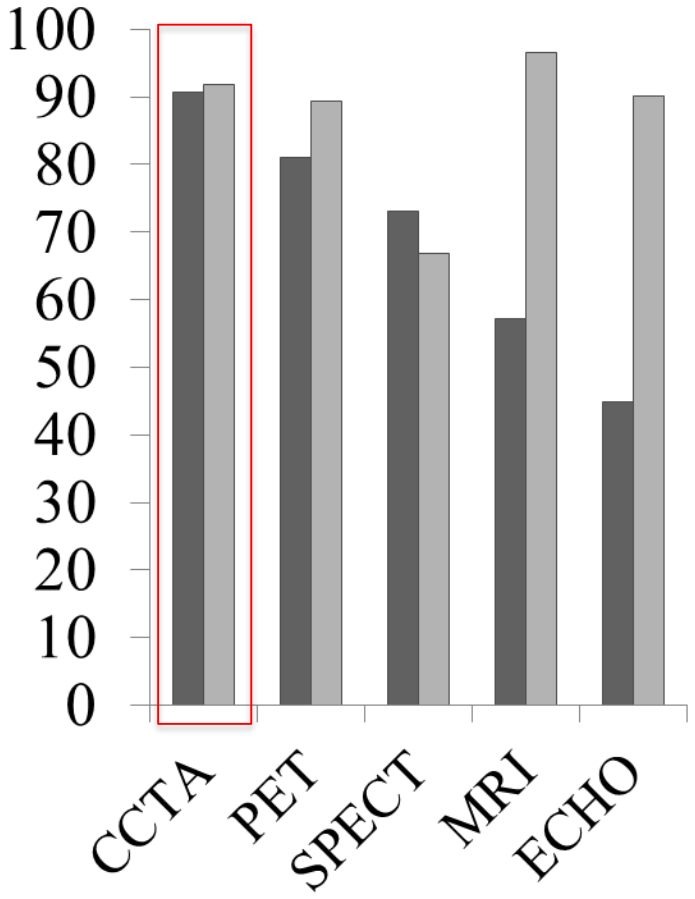
Juhani Knuuti[1]*, Haitham Ballo[1†], Luis Eduardo Juarez-Orozco[1†], Antti Saraste[1], Philippe Kolh[2], Anne Wilhelmina Saskia Rutjes[3], Peter Jüni[4], Stephan Windecker[5], Jeroen J. Bax[6], and William Wijns[7]

European Heart Journal 2018

Anatomically significant CAD (≥50-70% stenosis)

Test	Sensitivity (%), (95% CI)	Specificity (%), (95% CI)
Stress ECG	58 (46–69)	62 (54–69)
Stress echo	85 (80–89)	82 (72–89)
CCTA	97 (93–99)	78 (67–86)
SPECT	87 (83–90)	70 (63–76)
PET	90 (78–96)	85 (78–90)
Stress CMR	90 (83–94)	80 (69–88)

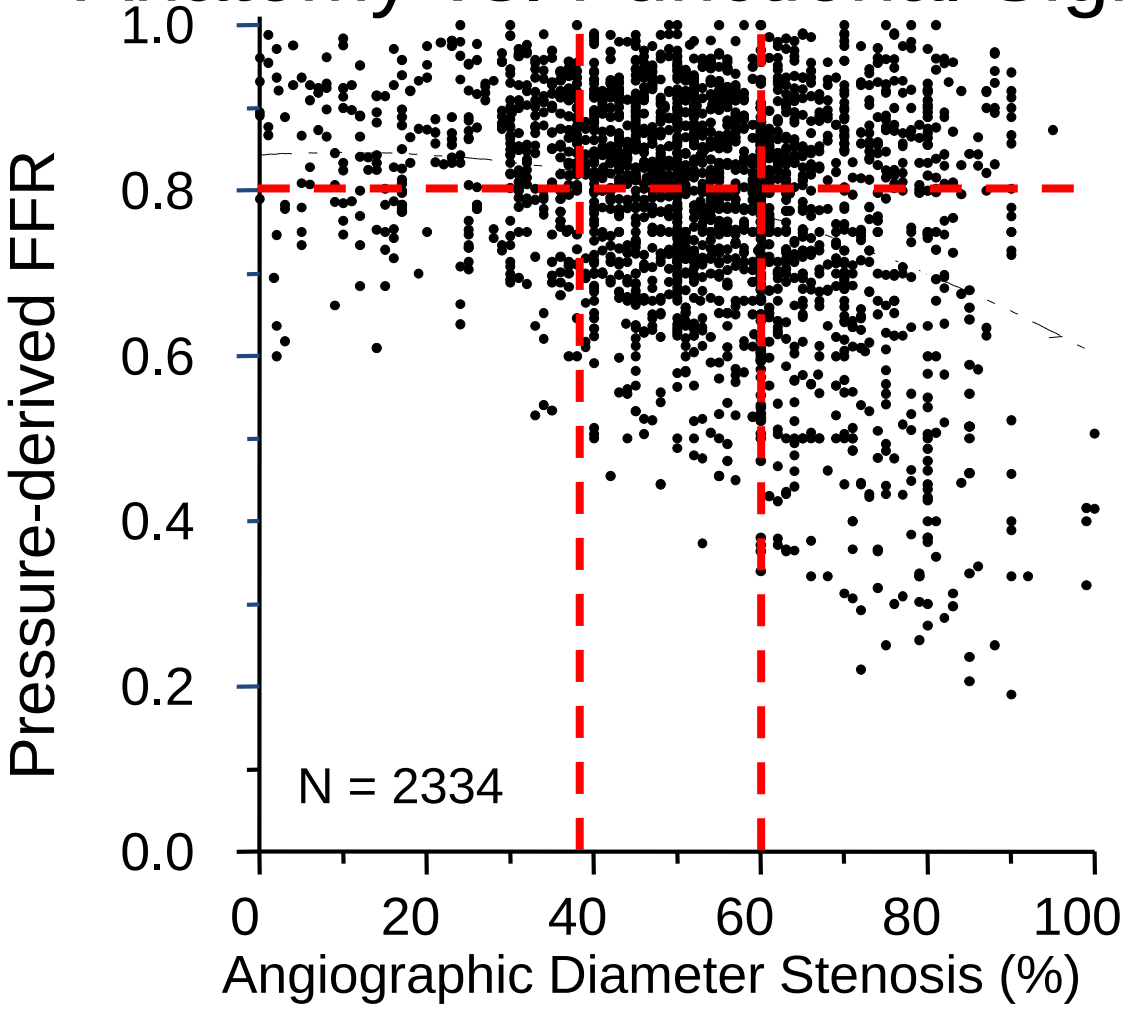
Meta-analysis of 126 studies with >100 pts



CAD prevalence 27%

EVINCI –trial (Neglia et al. Circ imaging 2015)

Challenges for coronary angiography: Anatomy vs. Functional Significance



FFR = Fractional flow reserve – invasive measurement of the pressure gradient during adenosine infusion

FFR ≤ 0.8
→
Symptoms
Prognosis
Revascularization

Wijns, de Bruyne, Vanhoenacker, JNC 2007;93:856-61

The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability

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European Heart Journal 2018

Anatomically significant CAD (≥50% stenosis)			Functionally significant CAD (FFR <0.80)		
Test	**Sensitivity (%), (95% CI)**	**Specificity (%), (95% CI)**	**Test**	**Sensitivity (%), (95% CI)**	**Specificity (%), (95% CI)**
			ICA	68 (60–75)	73 (55–86)
Stress ECG	58 (46–69)	62 (54–69)			
Stress echo	85 (80–89)	82 (72–89)			
CCTA	97 (93–99)	78 (67–86)	CCTA	93 (89–96)	53 (37–68)
SPECT	87 (83–90)	70 (63–76)	SPECT	73 (62–82)	83 (71–90)
PET	90 (78–96)	85 (78–90)	PET	89 (82–93)	85 (81–88)
Stress CMR	90 (83–94)	80 (69–88)	Stress CMR	89 (85–92)	87 (83–91)

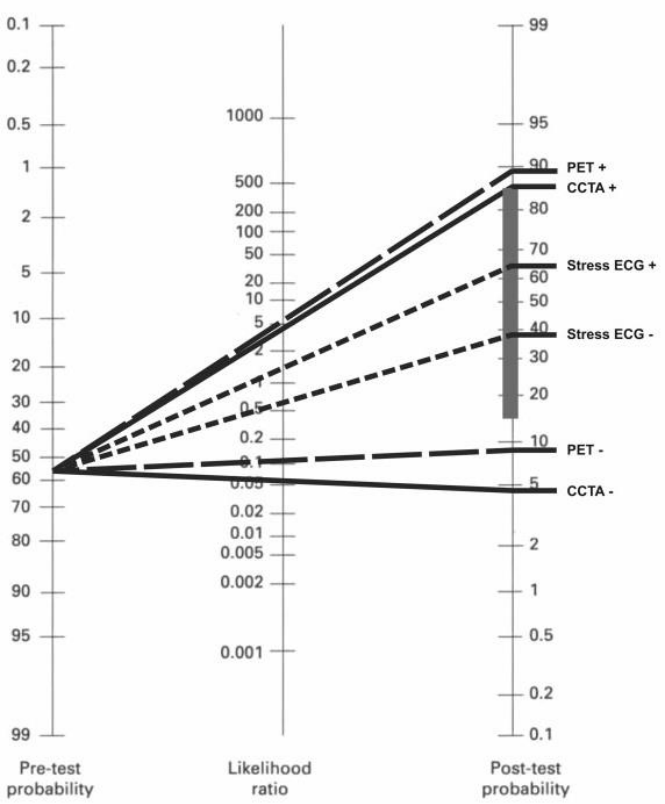
Meta-analysis of 126 studies with >100 pts

Likelihood ratio

$$LR+ = \frac{\Pr(T+|D+)}{\Pr(T+|D-)}$$

$$LR- = \frac{\Pr(T-|D+)}{\Pr(T-|D-)}$$

T+ = Test positive
T- = Test negative
D+ = Disease
D- = No disease



Use the sensitivity and specificity of the test to determine whether a test result usefully changes the probability that a condition exists

The performance of non-invasive tests to rule-in and rule-out significant coronary artery stenosis in patients with stable angina: a meta-analysis focused on post-test disease probability

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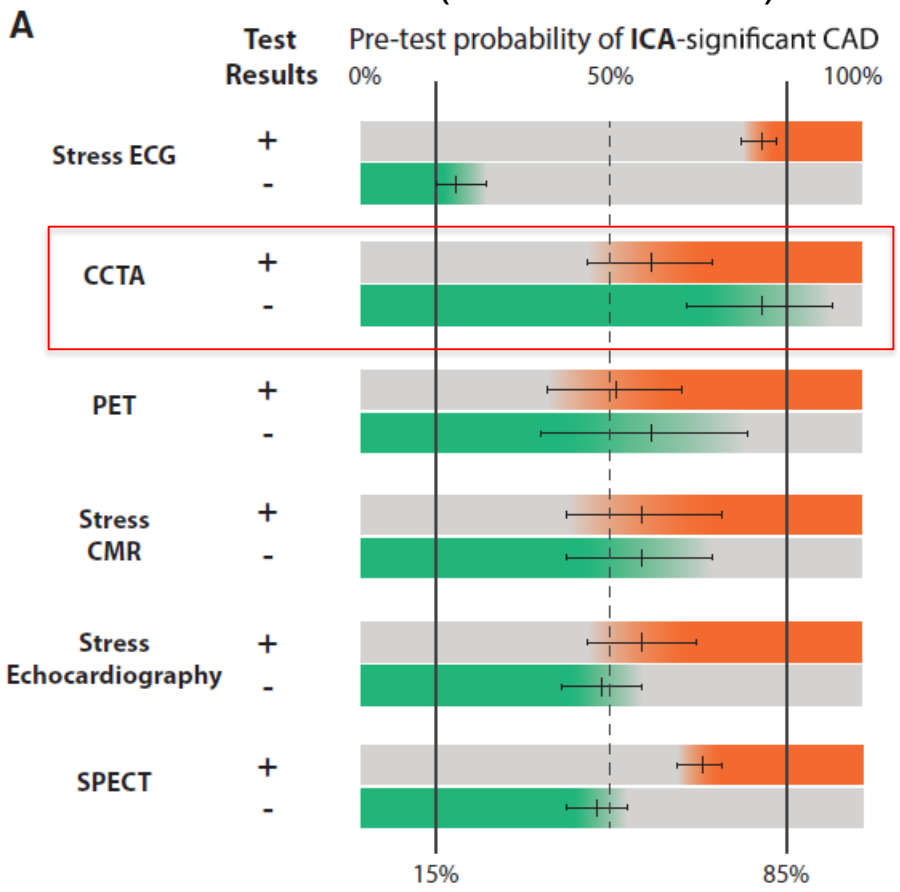
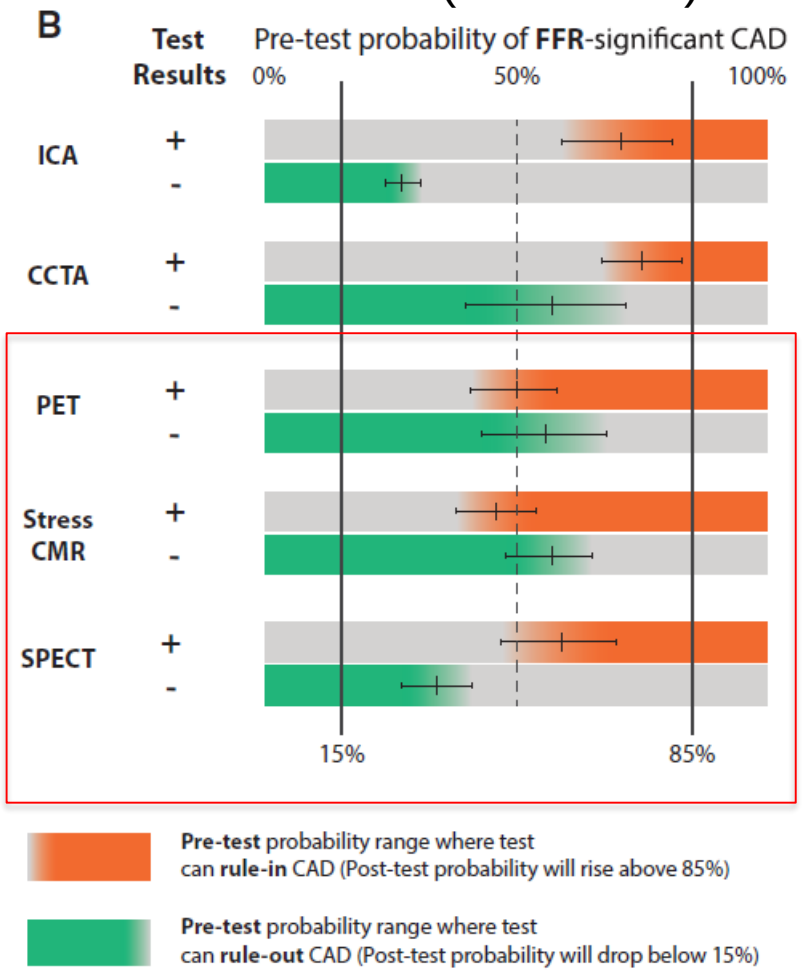
European Heart Journal 2018

Pre-test-probability * LR-/LR+
= Post-test probability

(≥50% stenosis)



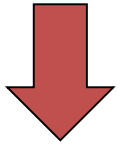
(FFR <0.80)



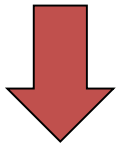
Meta-analysis of 126 studies with >100 pts

The role of imaging in cardiac diseases

- Diagnosis of disease



- Prognosis (low and high risk)



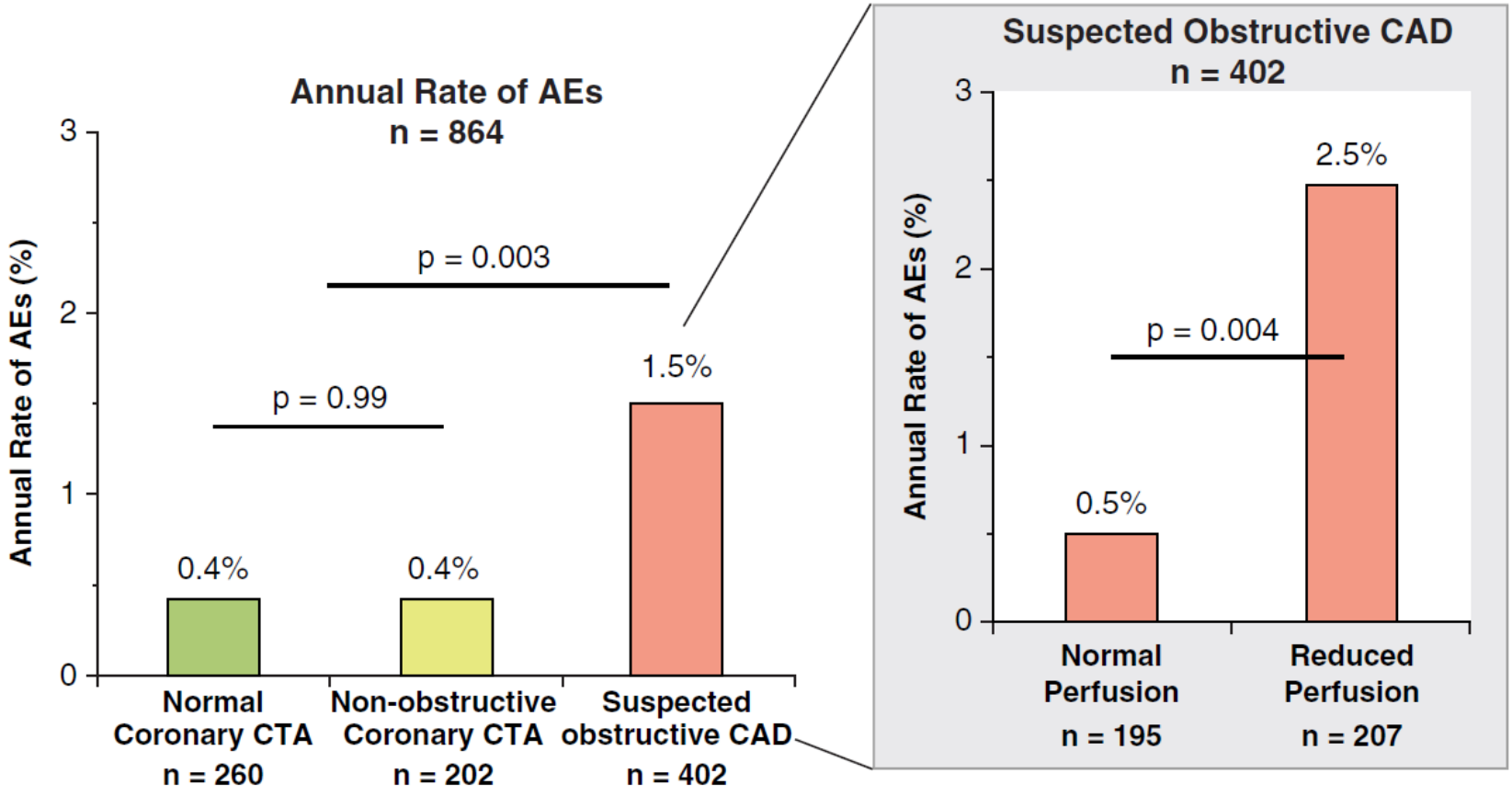
- Guiding therapy → Outcomes

Prognostic Value of Coronary CT Angiography With Selective PET Perfusion Imaging in Coronary Artery Disease

JACC Cardiovasc Imaging 2017

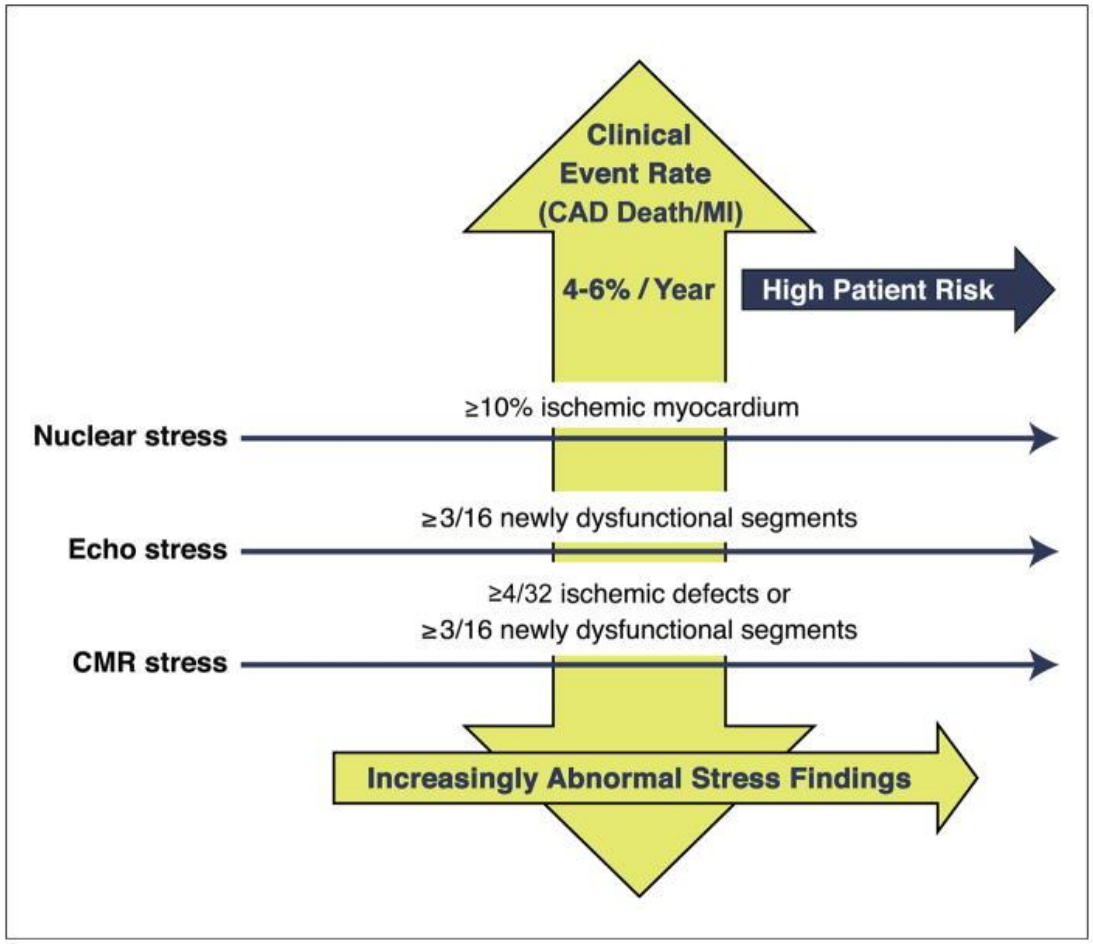
Teemu Maaniitty, MD,[a] Iida Stenström, BM,[a] Jeroen J. Bax, MD, PhD,[b] Valtteri Uusitalo, MD, PhD,[a] Heikki Ukkonen, MD, PhD,[c] Sami Kajander, MD, PhD,[a] Maija Mäki, MD, PhD,[a,d] Antti Saraste, MD, PhD,[a,c] Juhani Knuuti, MD, PhD[a,d]

Myocardial ischemia and annual all-cause mortality, non-fatal MI or UAP



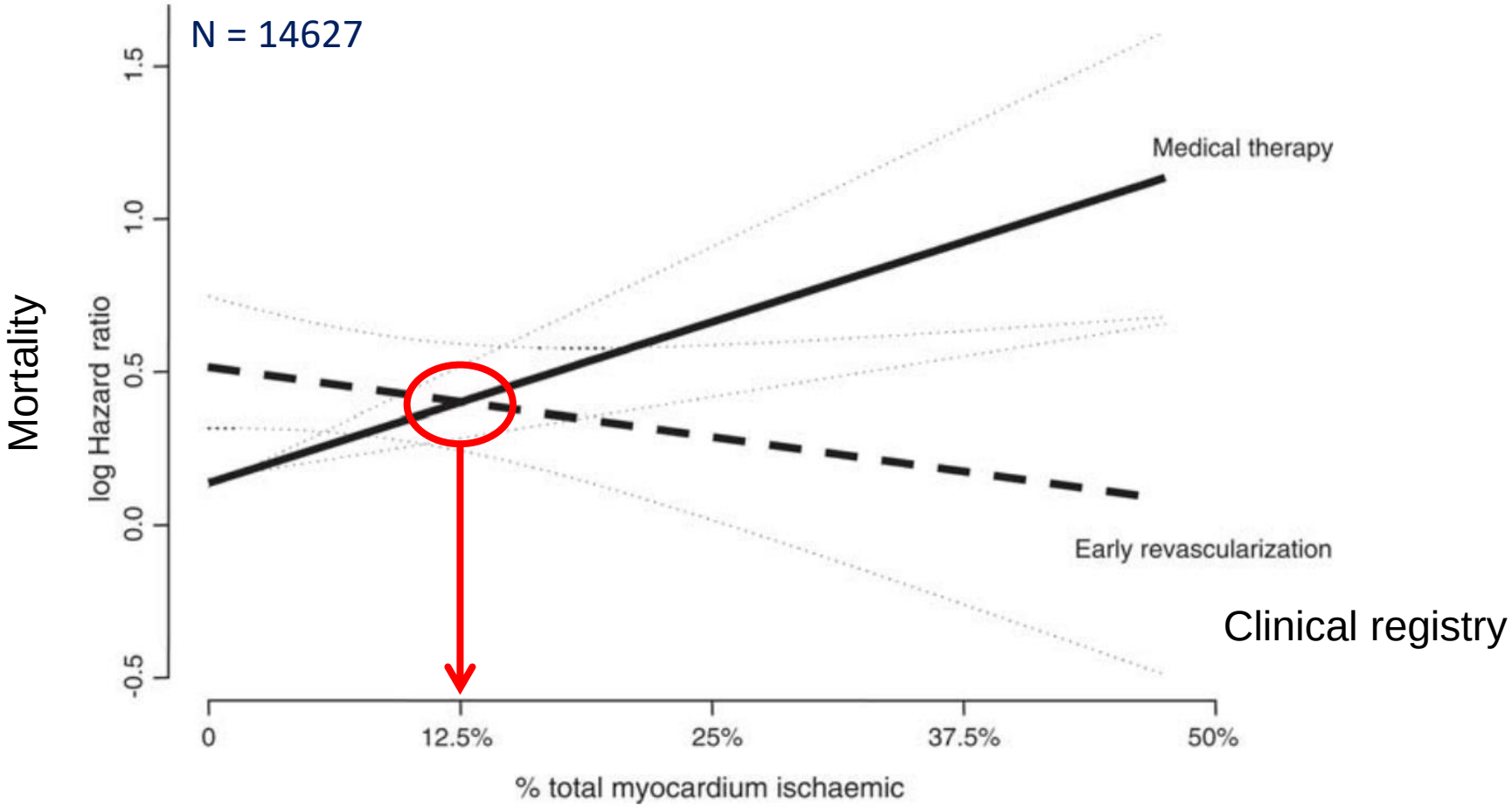
^{15}O-water PET / adenosine stress

Definitions of findings indicating high event risk



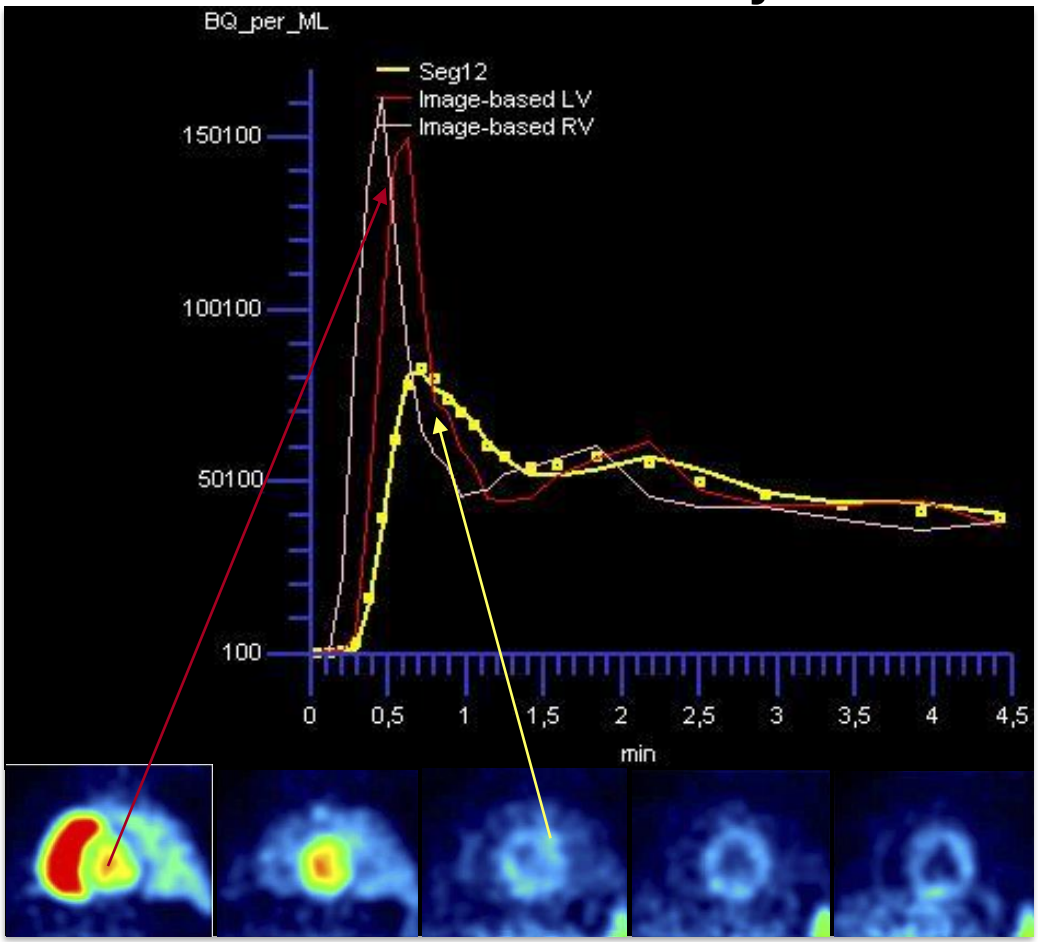
Shaw et al. JACC Cardiovasc Imaging 2014;7:593-604

HR for mortality for pts with stable CAD treated with early revascularization compared with those treated with medical therapy as a function of the percent ischemic myocardium



Hachamovitch R et al. Eur Heart J. 2011 Apr;32(8):1012-24

Flow quantification = absolute myocardial blood flow (MBF) and coronary flow reserve (CFR)



Dynamic imaging
→ Kinetic modeling
→ MBF in ml/g/min
→ CFR

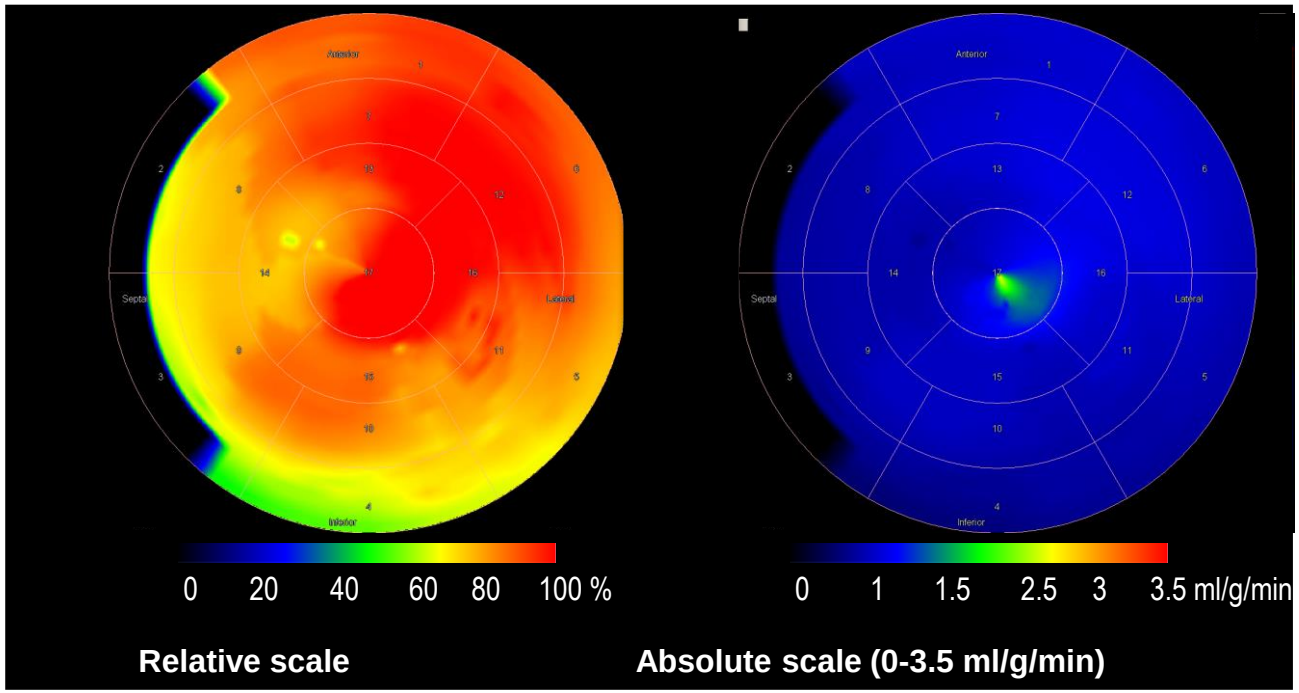
≠ Scores

Technical improvements
- Count rate performance
- Data handling
- Computing power/software

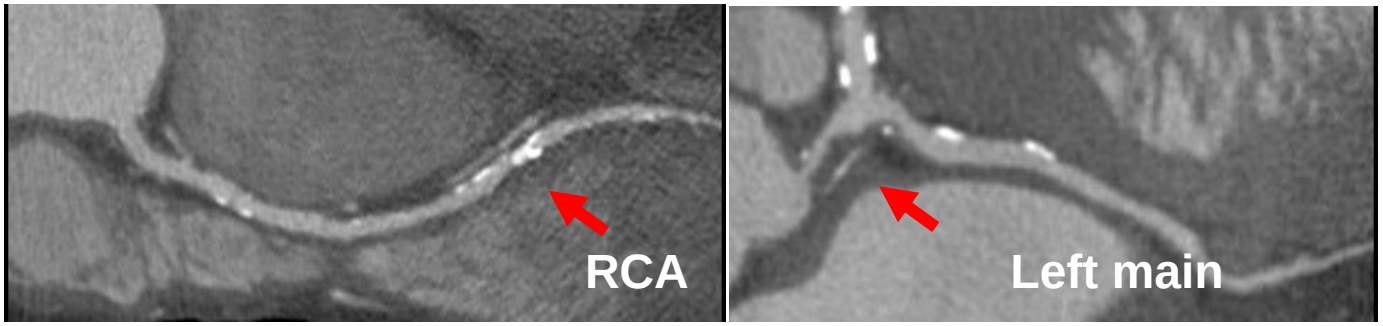
Moody et al J Nucl Cardiol 2015

Combination with clinical protocols

Absolute vs. relative myocardial perfusion with ^{15}O-water PET in LM and 3-vessel CAD



PET perfusion during adenosine stress



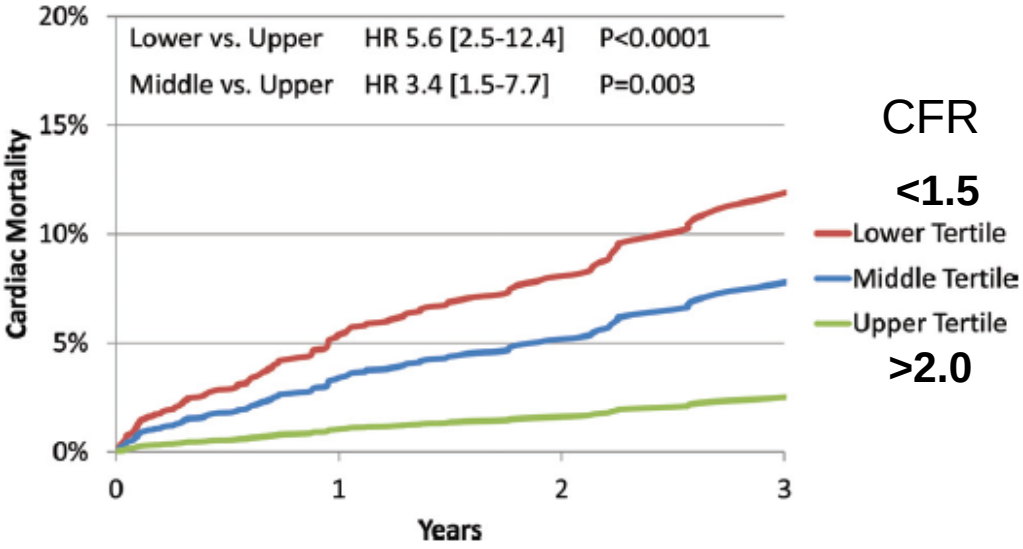
Coronary CTA

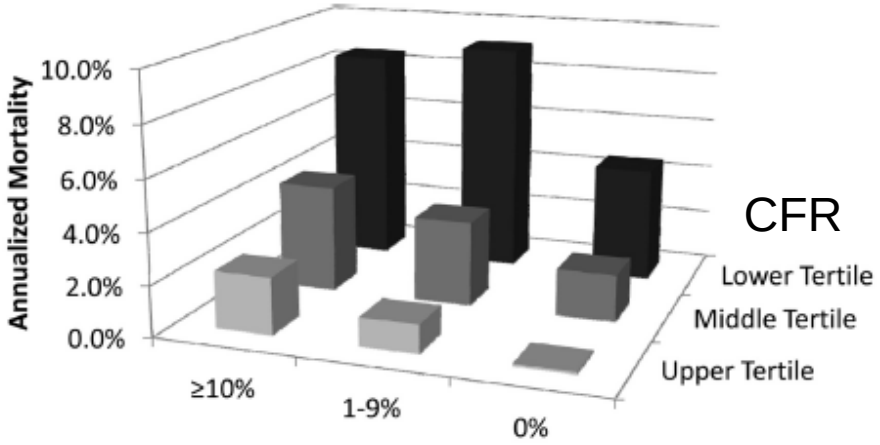
Improved Cardiac Risk Assessment With Noninvasive Measures of Coronary Flow Reserve

Venkatesh L. Murthy, MD, PhD; Masanao Naya, MD, PhD; Courtney R. Foster, RT; Jon Hainer, BS; Mariya Gaber, MS; Gilda Di Carli; Ron Blankstein, MD; Sharmila Dorbala, MD; Arkadiusz Sitek, PhD; Michael J. Pencina, PhD; Marcelo F. Di Carli, MD

Circulation 2011

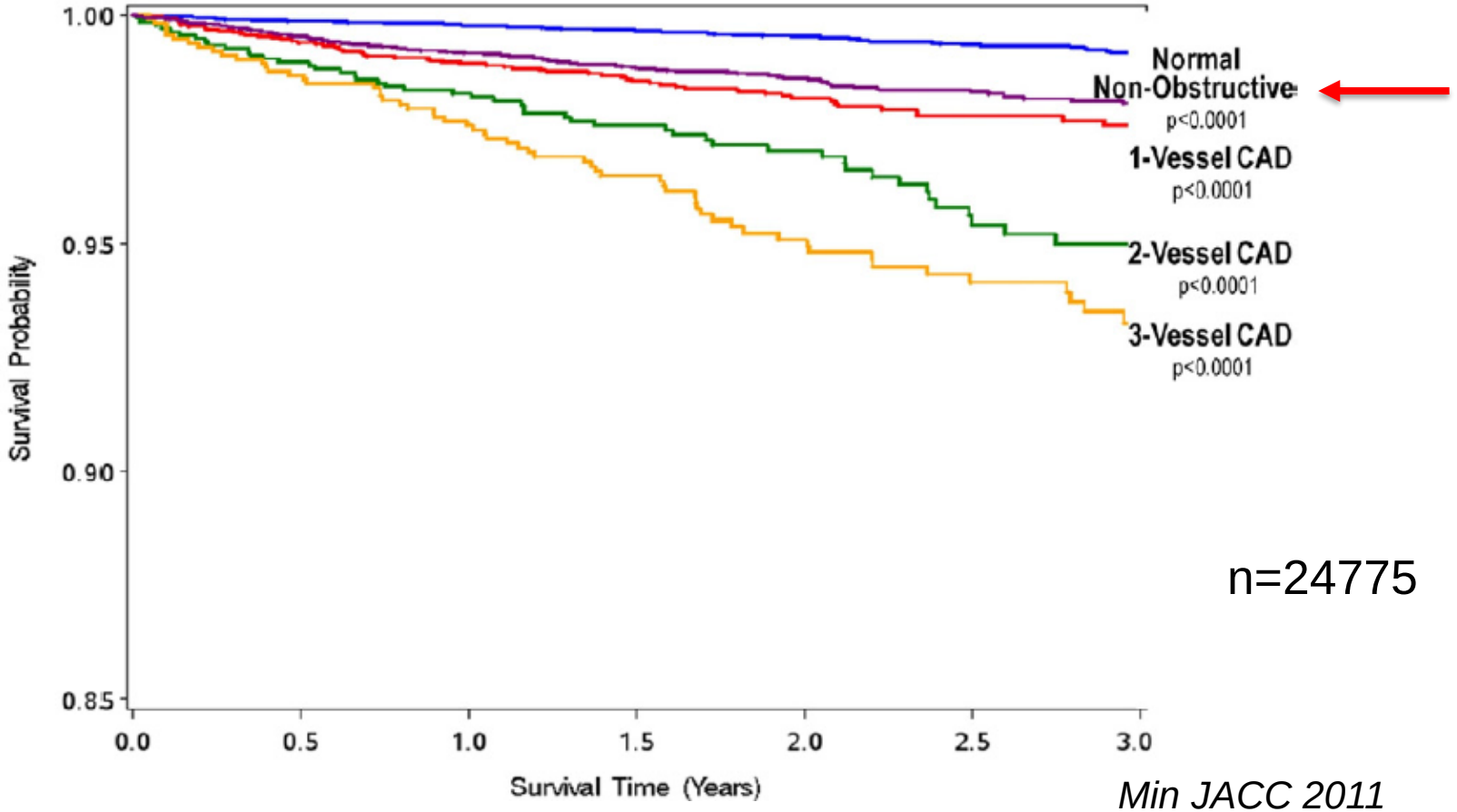
2783 patients with suspected CAD, Rb^{82} rest-stress PET





Prognostic value of CFR

Survival after coronary CT angiography



n=24775

Min JACC 2011

High risk	Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD).
Intermediate rick	Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category.
Low risk	Normal coronary artery or plaques only.

Montalescot EHJ 2013

Risk classification refinement based on coronary calcium score

Prognostic Models Comparative NRIs	
Model #1 FRS + Brachial Flow Mediated Dilation	2.4%
Model #2 FRS + Ankle Brachial Index	3.6%
Model #3 FRS + High Sensitivity CRP	7.9%
Model #4 FRS + Family History	16.0%
Model #5 FRS + Carotid Intima-Media Thickness	10.2%
Model #6 FRS + **Coronary Artery Calcium**	**65.9%**

Risk of CAD in 7.5 years

n=1330 subjects with intermediate CVD risk in the MESA -study

Yeboah et al. JAMA 2012;308:788-95

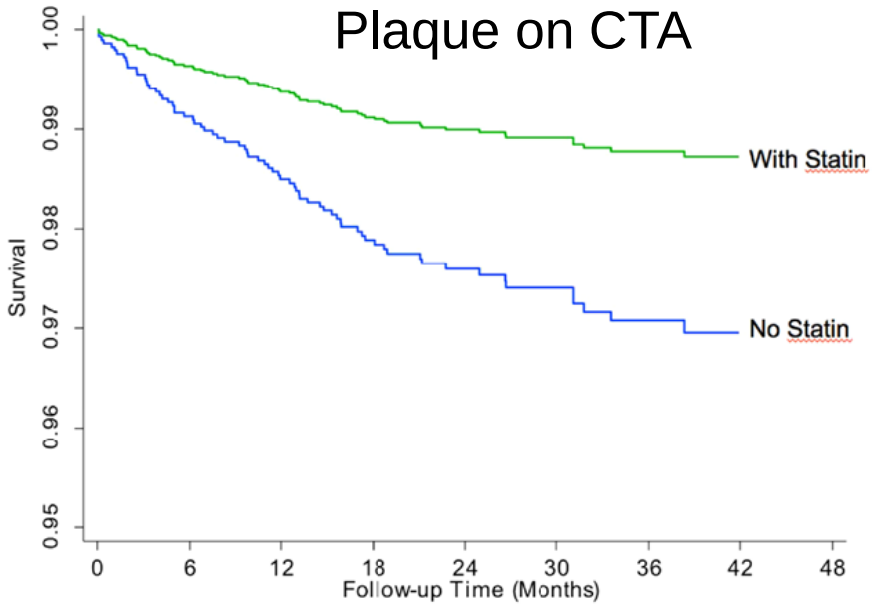
Impact of non-obstructive CAD ?

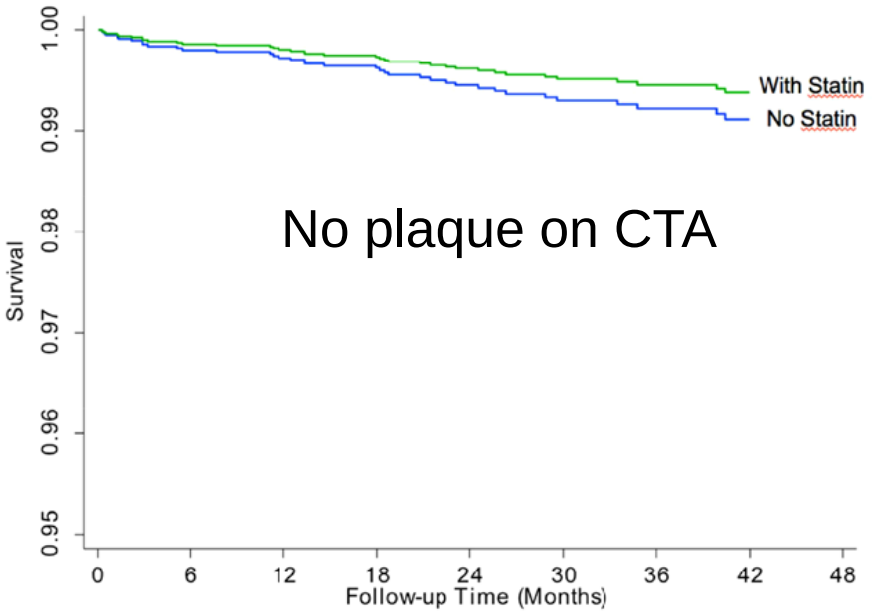
Chow ATVB 2014

n= 10 014

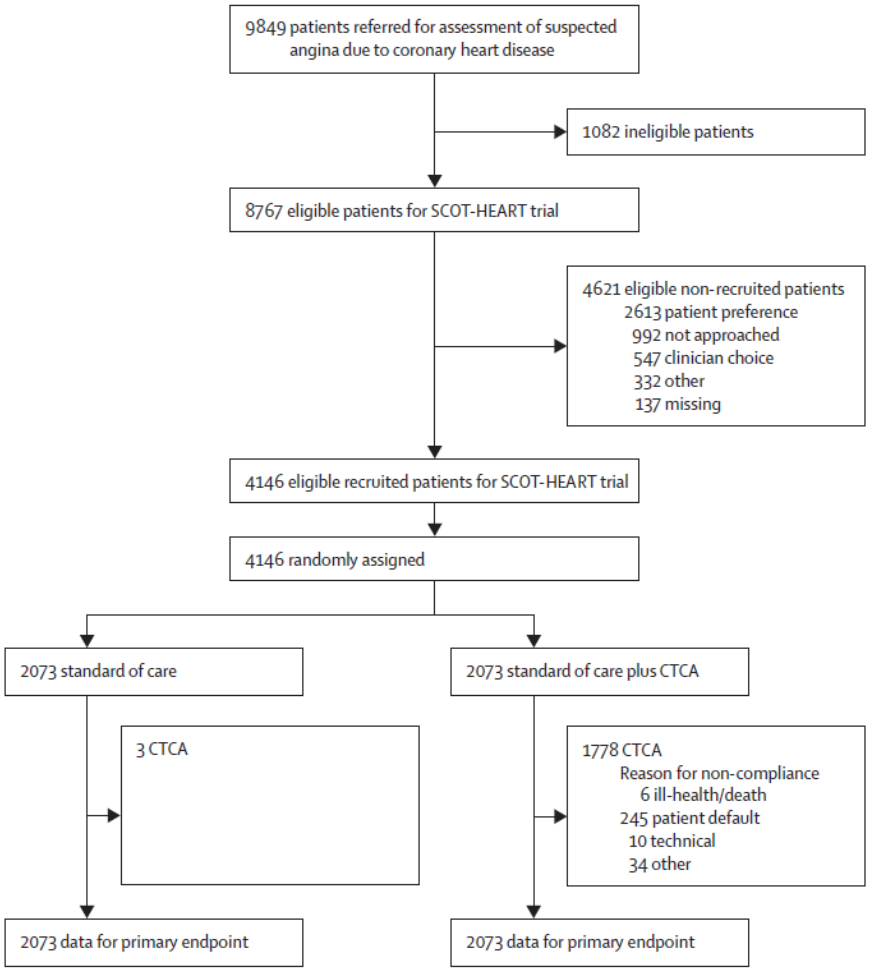
Table 4. Cox Models for All-Cause Mortality in Patients With Nonobstructive CAD

Models	Hazard Ratio* (95% CI)	*P* Value
All patients (n=10 418)		
Statin therapy	0.52 (0.34–0.79)	0.002
ASA therapy	0.77 (0.53–1.12)	0.173
Nonobstructive CAD (n=4706)		
Statin therapy	0.39 (0.23–0.65)	<0.001
ASA therapy	0.66 (0.42–1.04)	0.070
No coronary plaque (n=5712)		
Statin therapy	0.64 (0.30–1.37)	0.252
ASA therapy	0.73 (0.37–1.47)	0.384





Outcomes after noninvasive testing



CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial

Lancet 2015; 385: 2383–91

	Standard care and CTCA		Standard care	
	Cancellation	New	Cancellation	New
Investigations				
Stress imaging	121	5	0	6
Invasive coronary angiography	29	94	1	8
Total	150	99	1	14
Medical treatments				
Preventive treatment	77	293	8	84
Antianginal treatment	112	82	6	11
Total	189	375	14	95

CTCA=CT coronary angiography.

Table 4: **Changes in investigations and treatments at 6 weeks**

-Clarifies diagnosis
-Impacts on investigations and medical treatments

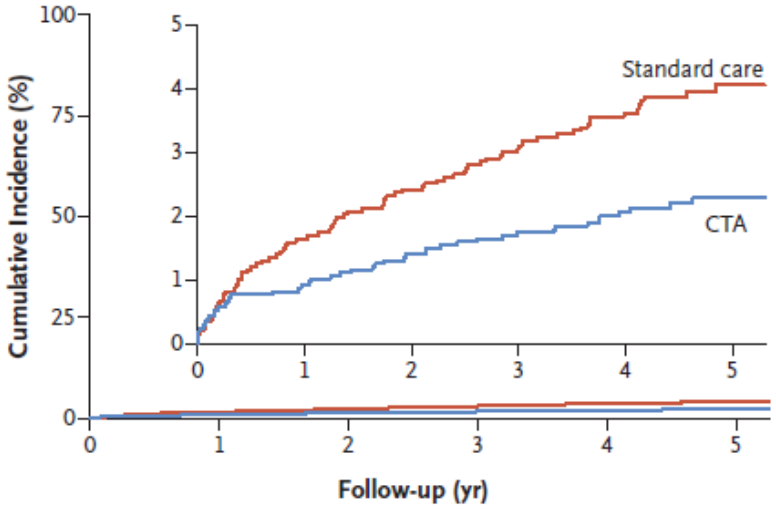
Outcomes after noninvasive testing

Coronary CT Angiography and 5-Year Risk of Myocardial Infarction

DOI: 10.1056/NEJMoa1805971

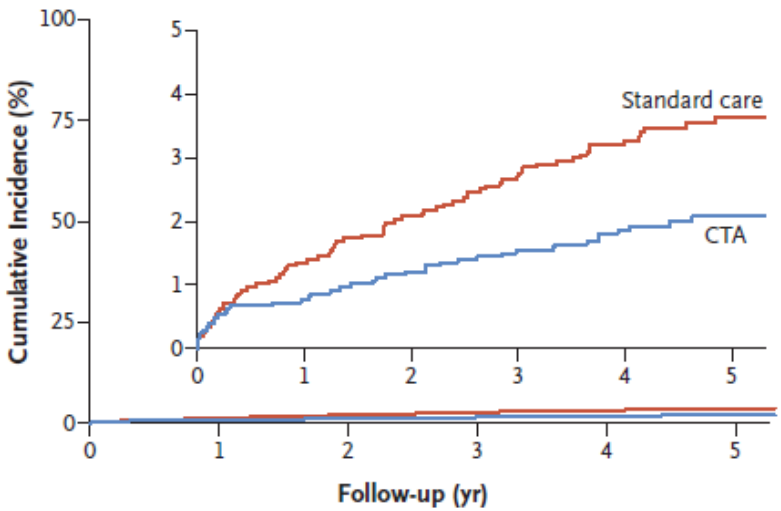
The SCOT-HEART Investigators*

A Death from Coronary Heart Disease or Nonfatal Myocardial Infarction



No. at Risk						
Standard care	2073	2033	2008	1994	1572	856
CTA	2073	2051	2029	2015	1588	872

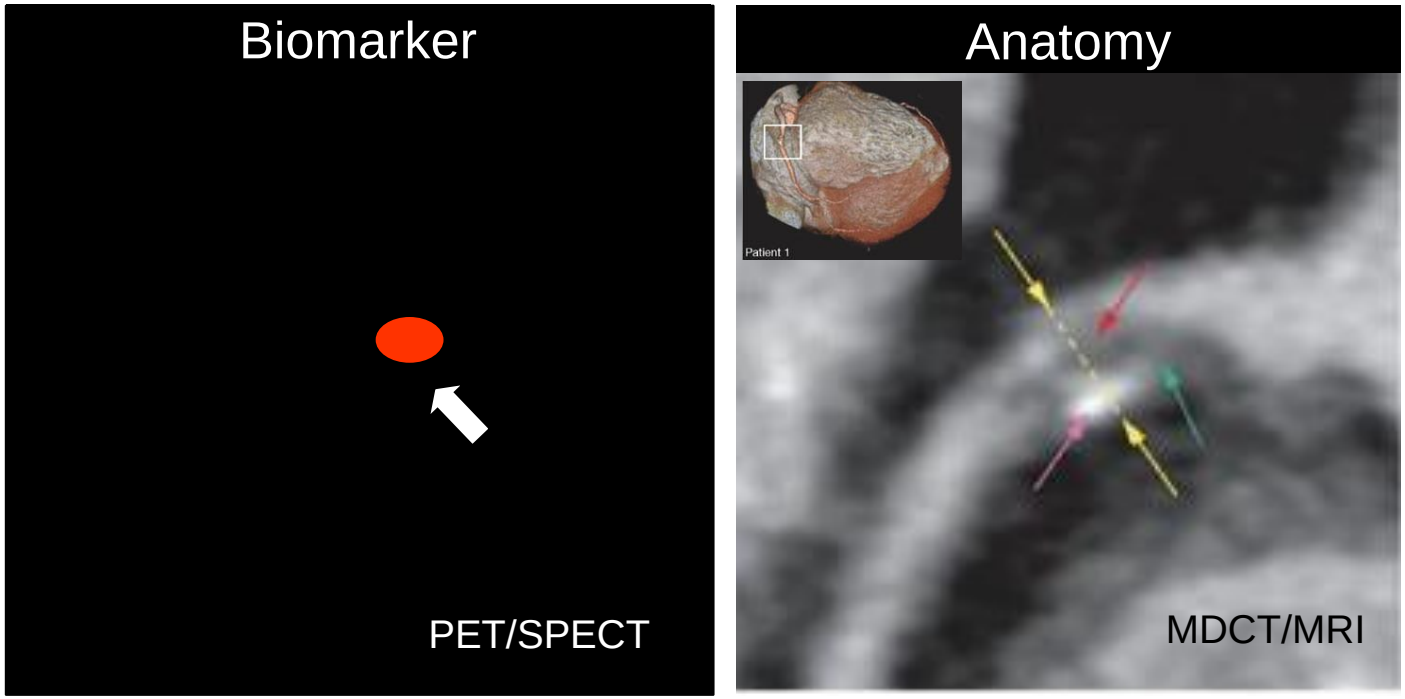
B Nonfatal Myocardial Infarction



No. at Risk						
Standard care	2073	2045	2030	2017	1597	881
CTA	2073	2057	2048	2041	1618	891

PET imaging of inflammation in atherosclerosis?

Turku PET Centre

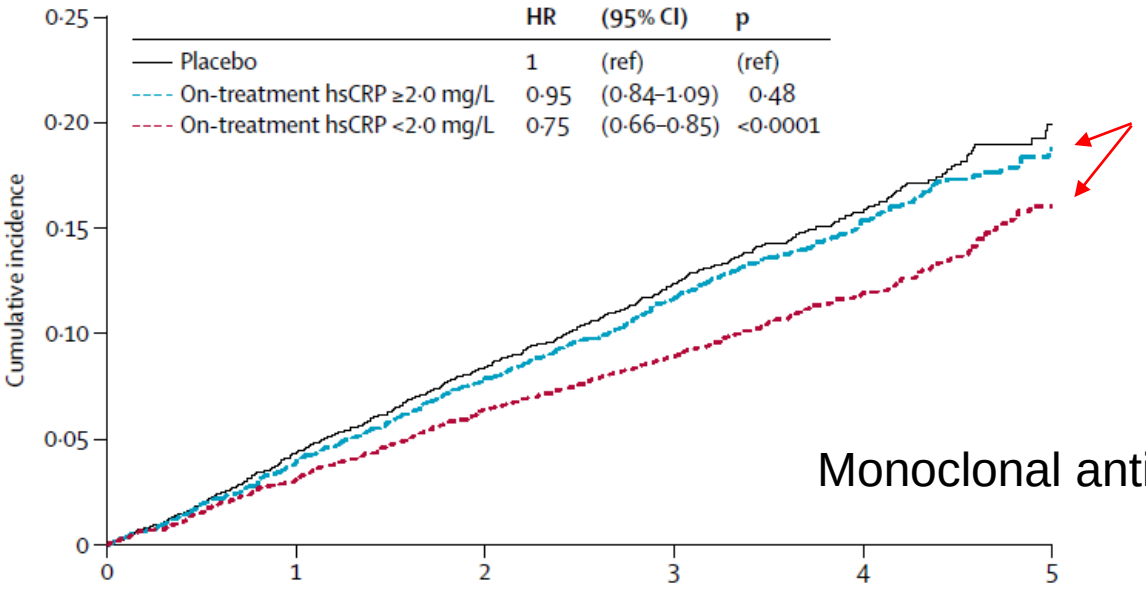


Mechanisms, therapy, progression, event risk

Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial

Paul M Ridker, Jean G MacFadyen, Brendan M Everett, Peter Libby, Tom Thuren, Robert J Glynn, on behalf of the CANTOS Trial Group*

Lancet 2018

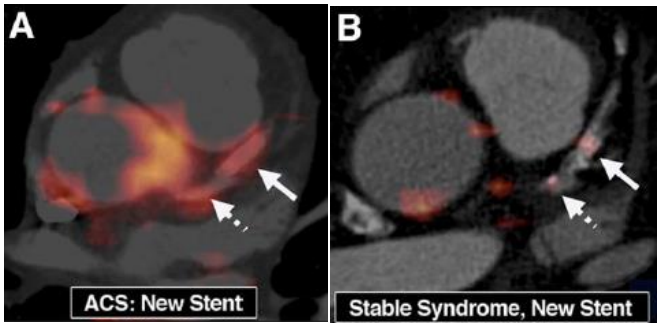


Number at risk						
Placebo	3182	3014	2853	2525	1215	200
Canakinumab:						
hsCRP ≥2·0 mg/L	2868	2724	2574	2258	1087	195
hsCRP <2·0 mg/L	3484	3353	3214	2890	1411	243

Monoclonal antibody targeting IL-1β

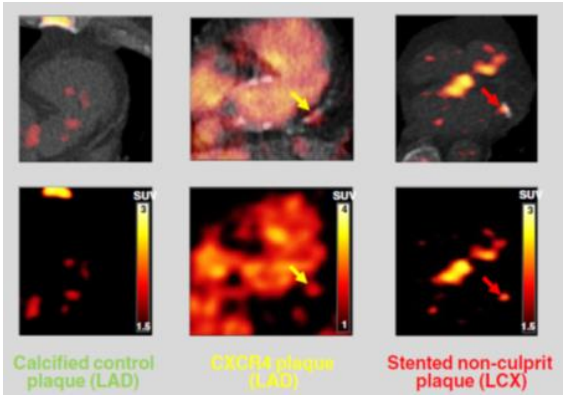
Residual cardiovascular risk → targeting therapies

PET tracers for molecular imaging of coronary atherosclerosis



^{18}F-FDG (macrophages)

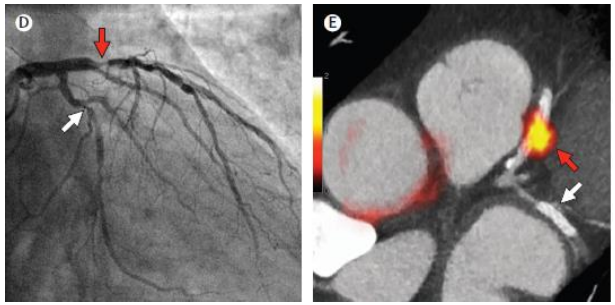
Tawakol JACC Cardiovasc Imaging 2010



^{68}Ga-Pentixafor (CXCR4 receptor/leukocytes)

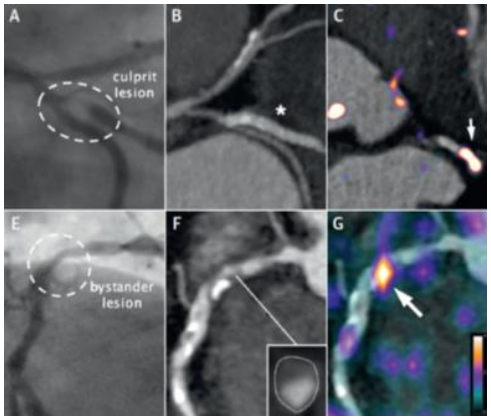
Derlin Eur J Nucl Med Mol Imaging 2018

Signal to noise ratio?



^{18}F-Sodium fluoride (microcalcification)

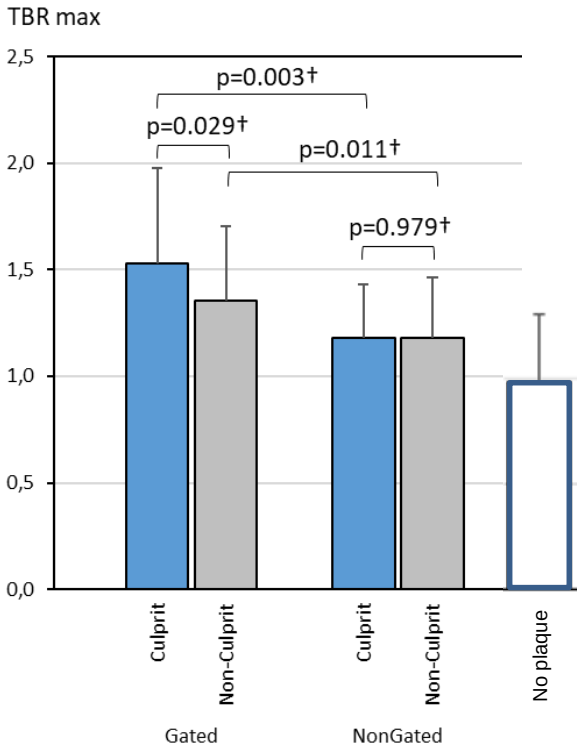
Dweck JACC 2012, Joshi Lancet 2014

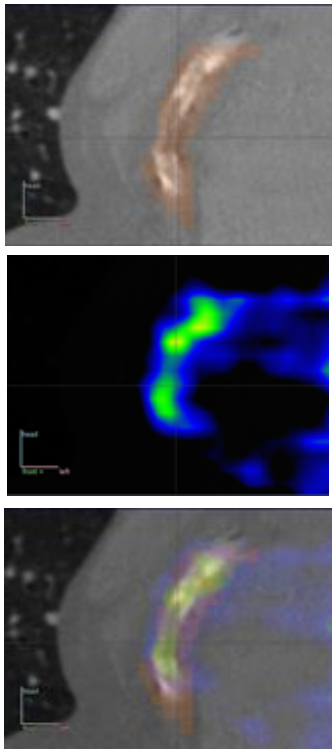


68Ga-DOTATATE (somatostatin receptor/macrophages)

Tarkin J Am Coll Cardiol Imaging 2017

Inflammation in atherosclerosis: Dual gated ^{18}F-FDG PET/CT of in patients with acute coronary syndrome





Myocardial uptake suppressed by low carbohydrate diet + fasting (n=22)

Coronary CT angiography + 18F-FDG PET (dual gating for correction of respiratory and cardiac motion)

Higher TBR in culprit lesions than other plaques

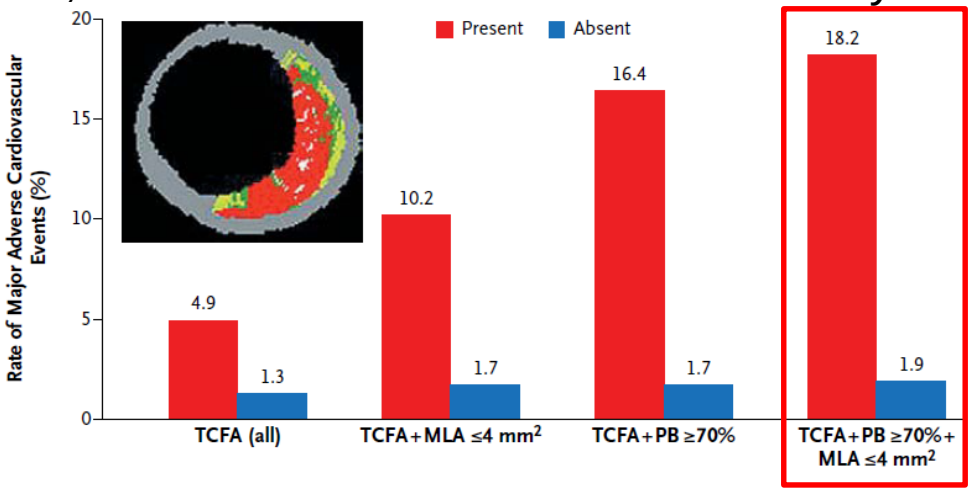
Uotila et al. ESC 2018

Prospective natural-history of coronary atherosclerosis after ACS

Rate of major cardiac events in 3 years = 20.4% (new culprit lesion 11.6%, baseline mean diameter stenosis only 32%)

n=967 patients

IVUS



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Biology and predictive value of vulnerable plaque ?

Stone N Engl J Med 2011

Summary: New determinants of coronary artery disease and risk

- Prevalence of obstructive CAD decreasing
  - Estimation of clinical likelihood ?
  - Impact on diagnostic testing ?
- Imaging powerful risk stratification tool
  - Ischemia
  - Detection of atherosclerosis (symptomatic and asymptomatic individuals)
  - New biomarkers ?