FACULTY OF HEALTH SCIENCES
AARHUS UNIVERSITY

Non-invasive functional testing in 2014

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Disclosures: *Research grants:*
Edwards and Siemens

Non-invasive functional testing in 2014

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European Heart Journal
doi:10.1093/eurheartj/eht296

ESC GUIDELINES

2013 ESC guidelines on the management of stable coronary artery disease

The Task Force on the management of stable coronary artery disease of the European Society of Cardiology

Task Force Members: Gilles Montalescot* (Chairperson) (France), Udo Sechtem* (Chairperson) (Germany), Stephan Achenbach (Germany), Felicita Andreotti (Italy), Chris Arden (UK), Andrzej Budaj (Poland), Raffaele Bugiardini (Italy), Filippo Crea (Italy), Thomas Cuisset (France), Carlo Di Mario (UK), J. Rafael Ferreira (Portugal), Bernard J. Gersh (USA), Anselm K. Gitt (Germany), Jean-Sebastien Hulot (France), Nikolaus Marx (Germany), Lionel H. Opie (South Africa), Matthias Pfisterer (Switzerland), Eva Prescott (Denmark), Frank Ruschitzka (Switzerland), Manel Sabaté (Spain), Roxy Senior (UK), David Paul Taggart (UK), Ernst E. van der Wall (Netherlands), Christiaan J.M. Vrints (Belgium).

Non-invasive functional testing in 2014

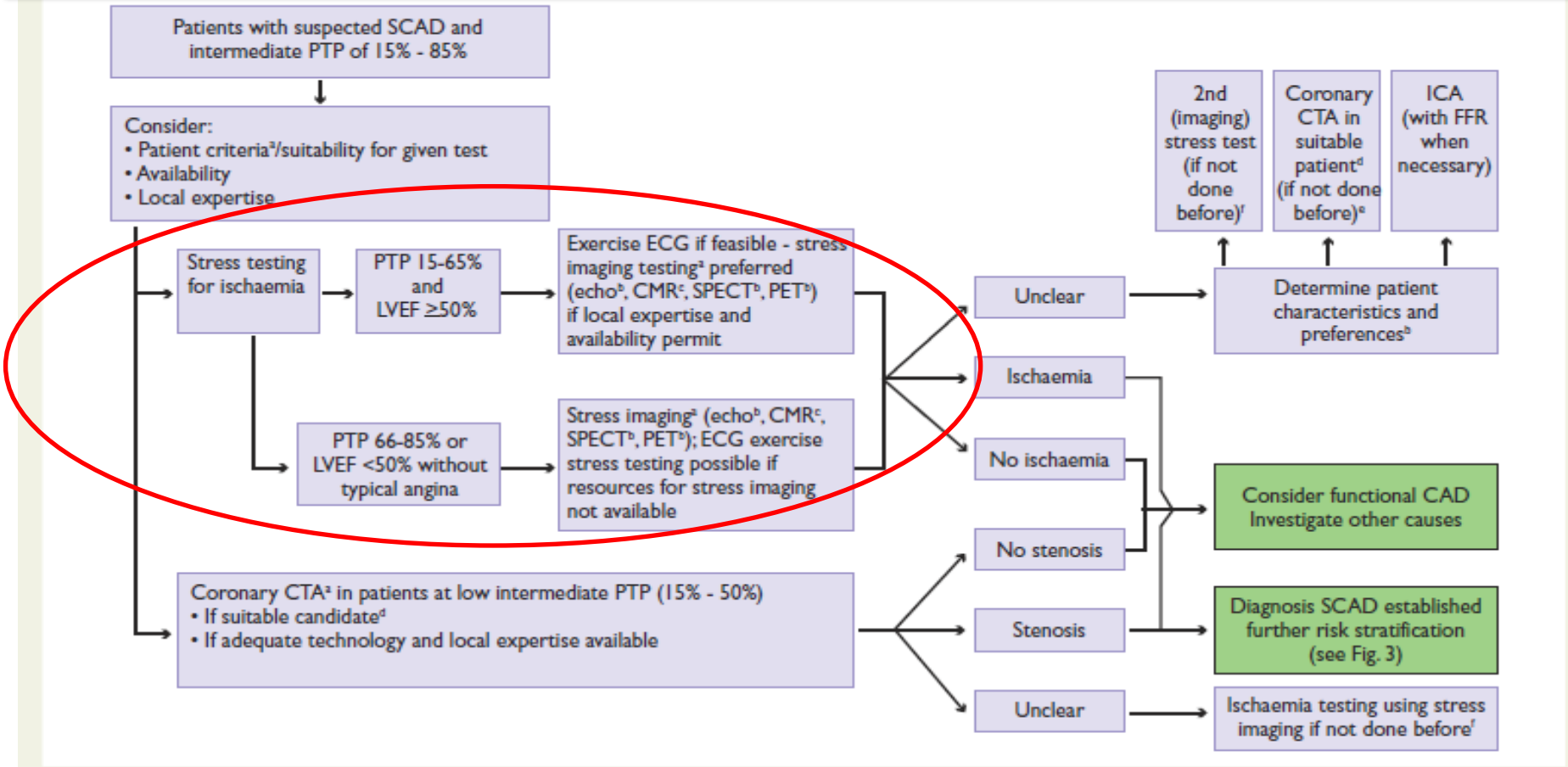


Figure 2 Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability. CAD = coronary artery disease; CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PET = positron emission tomography; PTP = pre-test probability; SCAD = stable coronary artery disease; SPECT = single photon emission computed tomography.

[a]Consider age of patient versus radiation exposure.

[b]In patients unable to exercise use echo or SPECT/PET with pharmacologic stress instead.

[c]CMR is only performed using pharmacologic stress.

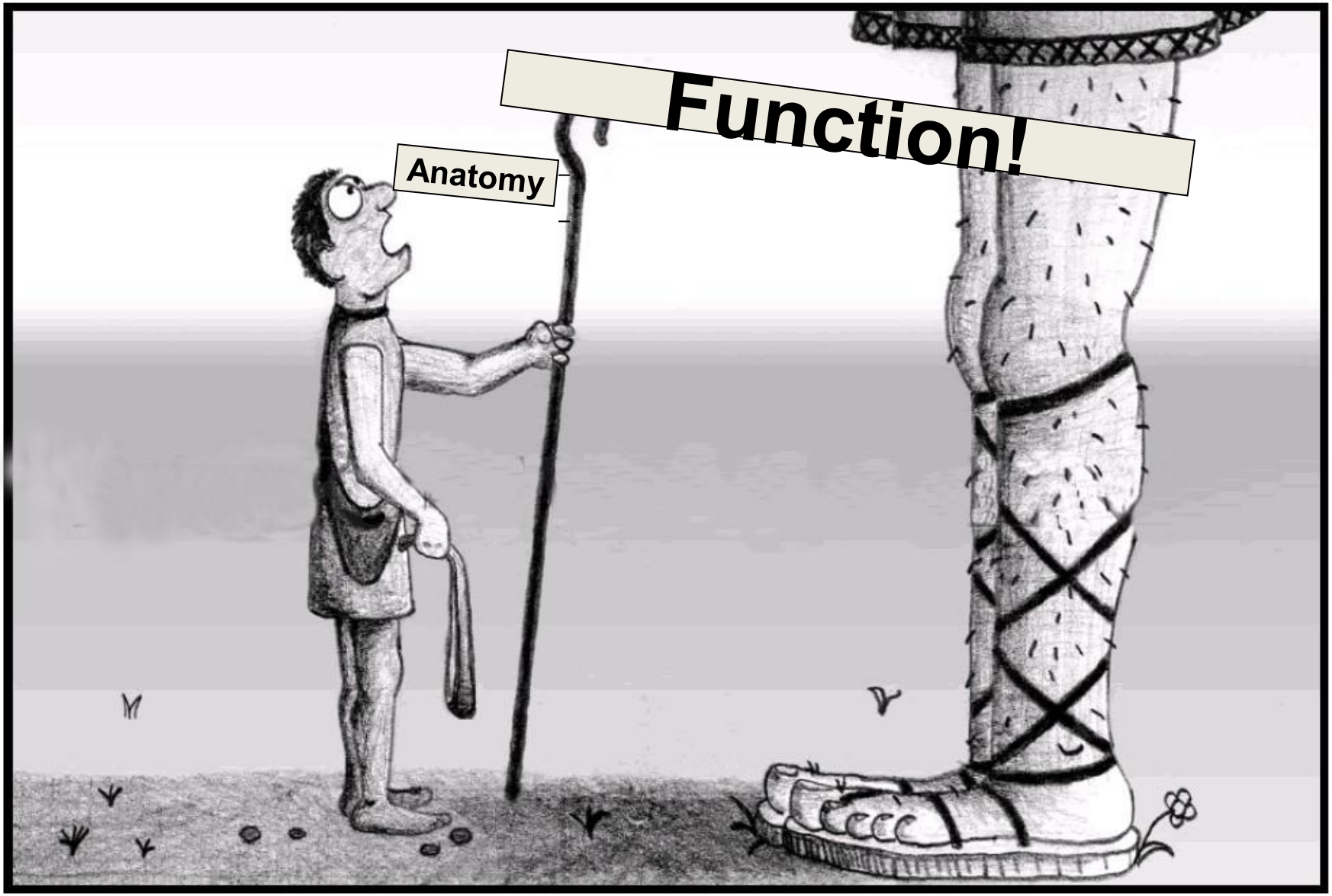
[d]Patient characteristics should make a fully diagnostic coronary CTA scan highly probable (see section 6.2.5.1.2) consider result to be unclear in patients with severe diffuse or focal calcification.

[e]Proceed as in lower left coronary CTA box.

[f]Proceed as in stress testing for ischaemia box.

Montalescot G, EHJ 2013

Non-invasive functional testing in 2014



- **Is non-invasive functional testing diagnostic accurate?**

Non-invasive functional testing in 2014, *CAD diagnosis*

Table 12 Characteristics of tests commonly used to diagnose the presence of coronary artery disease

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG [a, 91, 94, 95]	45–50	85–90
Exercise stress echocardiography[96]	80–85	80–88
Exercise stress SPECT[96-99]	73–92	63–87
Dobutamine stress echocardiography[96]	79–83	82–86
Dobutamine stress MRI[b,100]	79–88	81–91
Vasodilator stress echocardiography[96]	72–79	92–95
Vasodilator stress SPECT[96, 99]	90–91	75–84
Vasodilator stress MRI[b,98, 100-102]	67–94	61–85
Coronary CTA[c,103-105]	95–99	64–83
Vasodilator stress PET[97, 99, 106]	81–97	74–91

CAD = coronary artery disease; CTA = computed tomography angiography; ECG = electrocardiogram; MRI = magnetic resonance imaging; PET = positron emission tomography; SPECT = single photon emission computed tomography.
[a] Results without/with minimal referral bias.
[b] Results obtained in populations with medium-to-high prevalence of disease without compensation for referral bias.
[c] Results obtained in populations with low-to-medium prevalence of disease.

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Montalescot G, EHJ 2013

Non-invasive functional testing in 2014, *CAD diagnosis*

Sensitivity (%) and specificity (%) for hard events over the course of 6 years

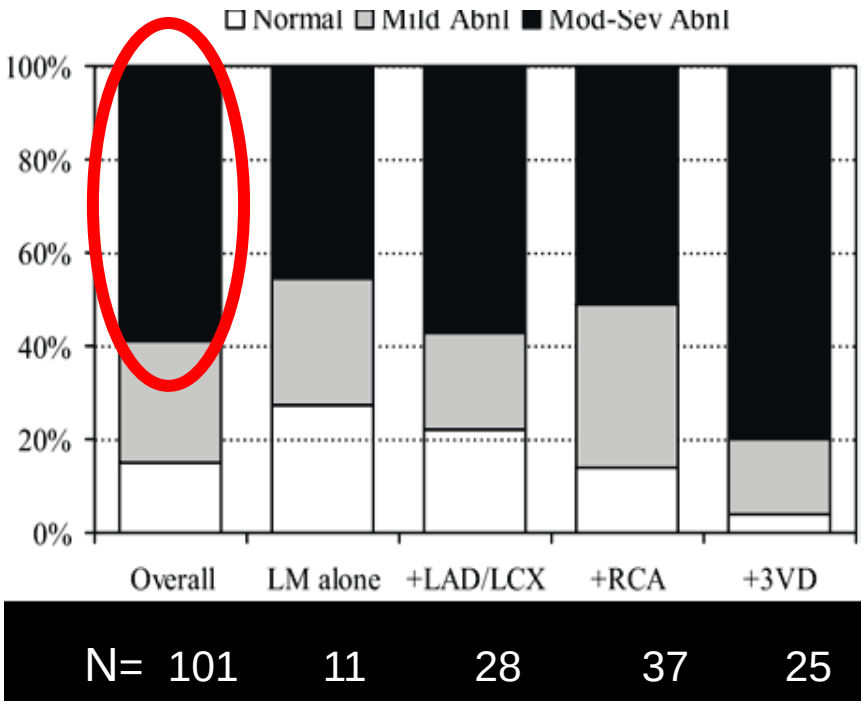
	Total cohort		Pat. with known CAD		Pat. without known CAD	
	ECG	SE	ECG	SE	ECG	SE
1 year						
Sensitivity	27.4	81.1	21.9	86.6	35.3	73.0
Specificity	87.0	92.8	84.8	74.8	87.4	96.3
2 years						
Sensitivity	25.5	74.7	20.0	80.1	33.3	66.7
Specificity	87.0	93.5	84.4	76.5	87.5	96.6
3 years						
Sensitivity	25.0	68.5	20.6	76.0	30.7	58.1
Specificity	87.2	93.9	84.9	77.6	87.6	96.7
4 years						
Sensitivity	25.8	65.1	21.0	72.1	32.1	55.3
Specificity	87.0	93.7	82.9	75.9	87.6	96.7
5 years						
Sensitivity	23.8	61.9	19.8	69.8	28.9	51.4
Specificity	86.7	93.6	83.8	76.5	87.1	96.4
6 years						
Sensitivity	22.8	59.6	19.0	67.9	27.7	48.7
Specificity	85.5	91.3	80.0	75.3	86.5	94.4

2684 patients suspected of CAD
6 y fu

Hard event:
- Cardiac death (1%),
- AMI (0.6%)
- Coronary revasc or coronary stenosis >75% (6%

Leischick R, Int J Cardiol 2007

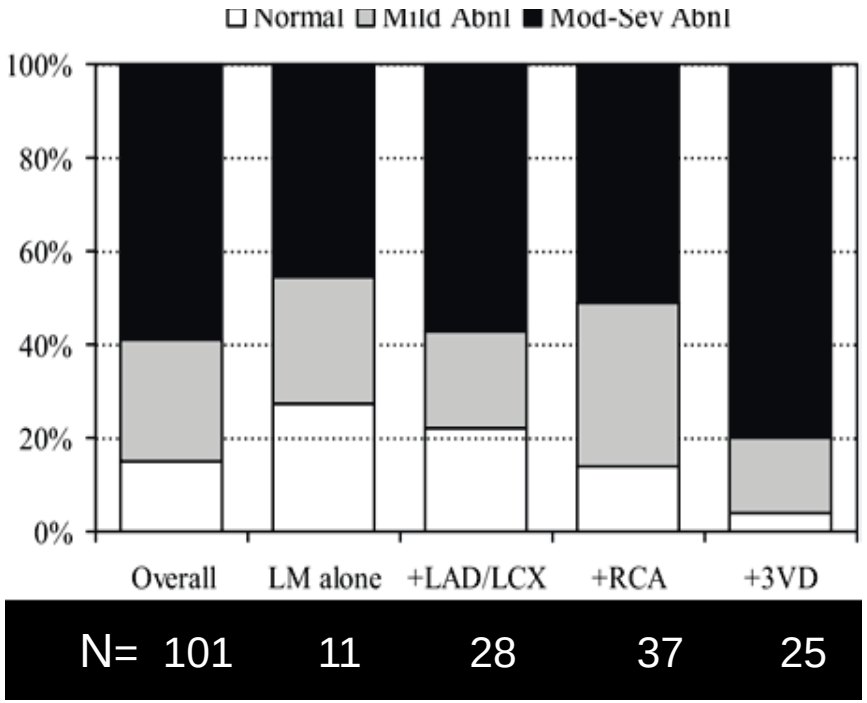
Non-invasive functional testing in 2014, *CAD diagnosis*



- 101 patients with left main CAD (>50%), RCA/LAD/Cx >70%
- No prior MI or revasc.
- Exercise or adenosine gated sestambi SPECT

Berman DS , J Nucl Cardiol 2007

Non-invasive functional testing in 2014, *CAD diagnosis*



- 101 patients with left main CAD (>50%), RCA/LAD/Cx >70%
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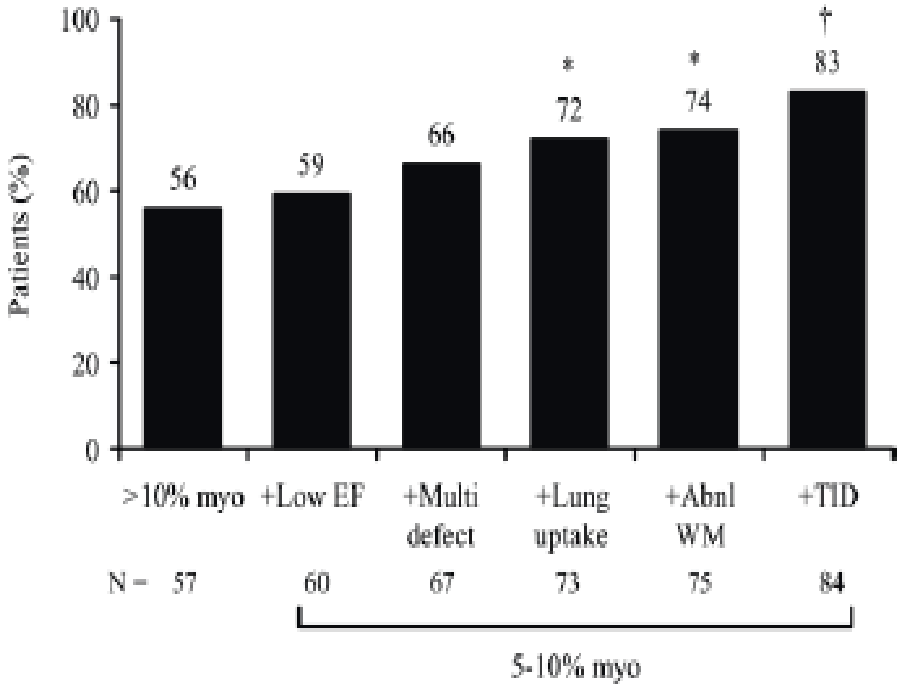
- **MPI high risk: myocardium stress >10% or 5-10% + >1 non-perfusion abnormalities**



Berman DS , J Nucl Cardiol 2007

Non-invasive functional testing in 2014, *ICA gatekeeper*

Low Diagnostic Yield of Elective Coronary Angiography

Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S., J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D., Ralph G. Brindis, M.D., and Pamela S. Douglas, M.D.

ABSTRACT

BACKGROUND

Guidelines for triaging patients for cardiac catheterization recommend a risk assessment and noninvasive testing. We determined patterns of noninvasive testing and the diagnostic yield of catheterization among patients with suspected coronary artery disease in a contemporary national sample.

METHODS

From January 2004 through April 2008, at 663 hospitals in the American College of Cardiology National Cardiovascular Data Registry, we identified patients without known coronary artery disease who were undergoing elective catheterization. The patients' demographic characteristics, risk factors, and symptoms and the results of noninvasive testing were correlated with the presence of obstructive coronary artery disease, which was defined as stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial vessel.

RESULTS

A total of 398,978 patients were included in the study. The median age was 61 years; 52.7% of the patients were men, 26.0% had diabetes, and 69.6% had hypertension. Noninvasive testing was performed in 83.9% of the patients. At catheterization, 149,739 patients (37.6%) had obstructive coronary artery disease. No coronary artery disease (defined as <20% stenosis in all vessels) was reported in 39.2% of the patients. Independent predictors of obstructive coronary artery disease included male sex (odds ratio, 2.70; 95% confidence interval [CI], 2.64 to 2.76), older age (odds ratio per 5-year increment, 1.29; 95% CI, 1.28 to 1.30), presence of insulin-dependent diabetes (odds ratio, 2.14; 95% CI, 2.07 to 2.21), and presence of dyslipidemia (odds ratio, 1.62; 95% CI, 1.57 to 1.67). Patients with a positive result on a noninvasive test were moderately more likely to have obstructive coronary artery disease than those who did not undergo any testing (41.0% vs. 35.0%; P<0.001; adjusted odds ratio, 1.28; 95% CI, 1.19 to 1.37).

CONCLUSIONS

In this study, slightly more than one third of patients without known disease who underwent elective cardiac catheterization had obstructive coronary artery disease. Better strategies for risk stratification are needed to inform decisions and to increase the diagnostic yield of cardiac catheterization in routine clinical practice.

Almost 400.000 subjects suspected of SAP

- **82% with prior non-invasive testing**

Non-invasive functional testing in 2014, *ICA gatekeeper*

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39% without disease!!

63% without obstructive disease!!!

Non-invasive functional testing in 2014, *ICA gatekeeper*

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Manesh R. Pate
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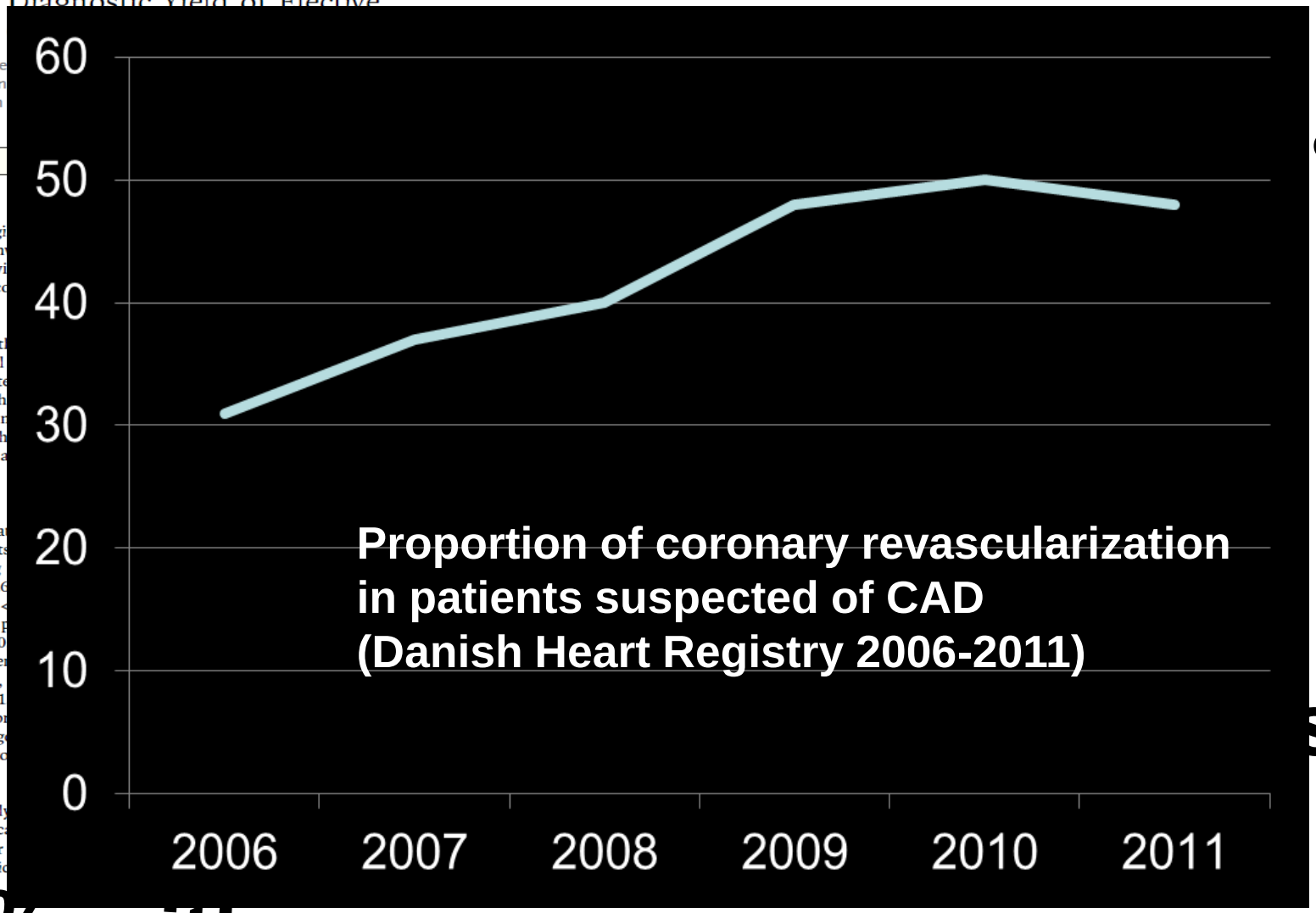

of SAP

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63% without obstructive disease!!!

- **Selection bias**

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- **The diagnostic specificity of a test declines with time**

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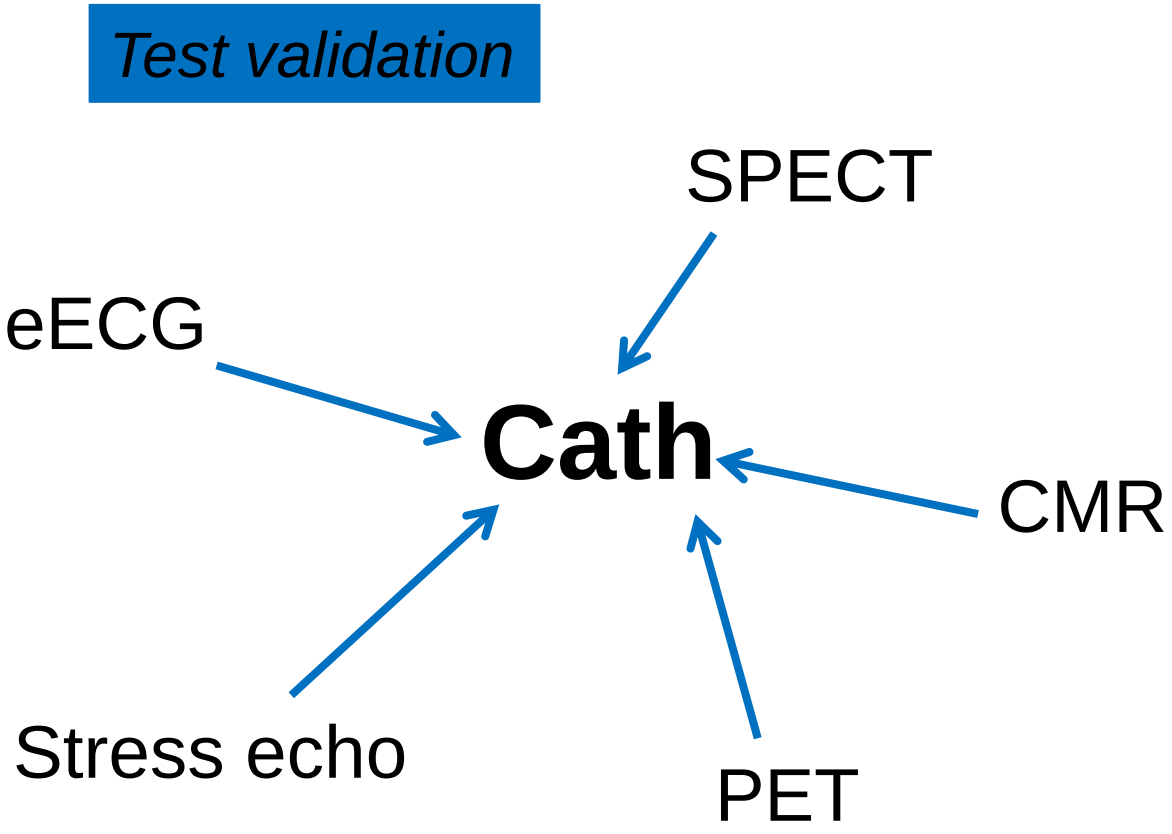
- The diagnostic specificity of a test declines with time

- **Publication bias / ”File cabinet” phenomenon**

Validation paradox



Hecht HS, JCCT, 2009

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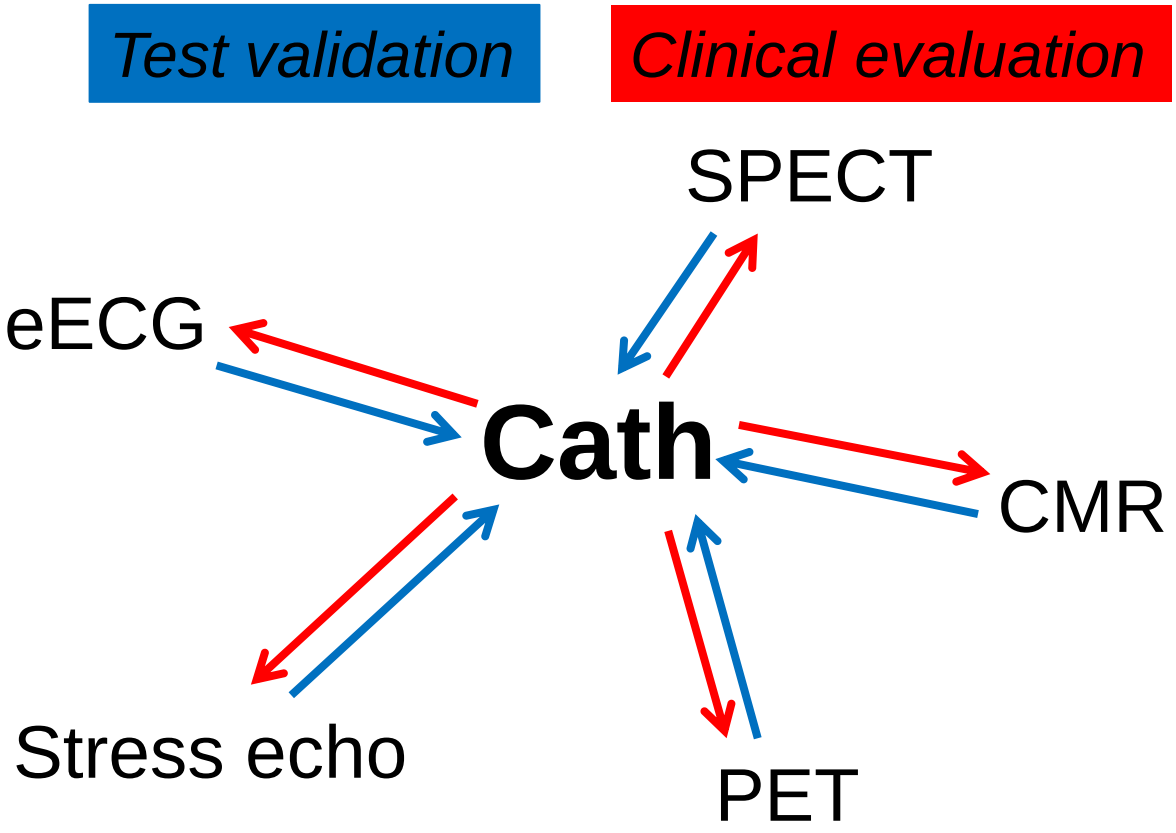

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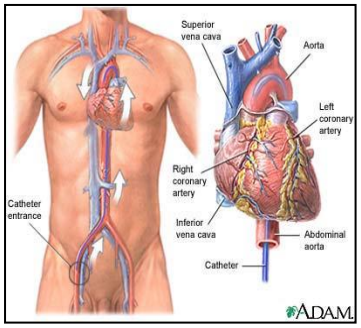
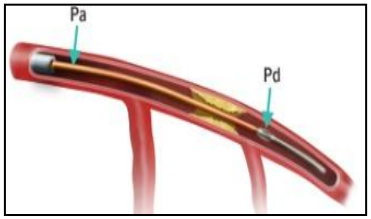
Non-invasive functional testing in 2014





$$FFR = \frac{Distal\ Coronary\ Pressure\ (Pd)}{Proximal\ Coronary\ Pressure\ (Pa)}$$

(During Maximum Hyperemia)

Using FFR to guide therapy resulted in 33% reduction in the risk of death or major cardiac events and reduced cost[1,2]

*

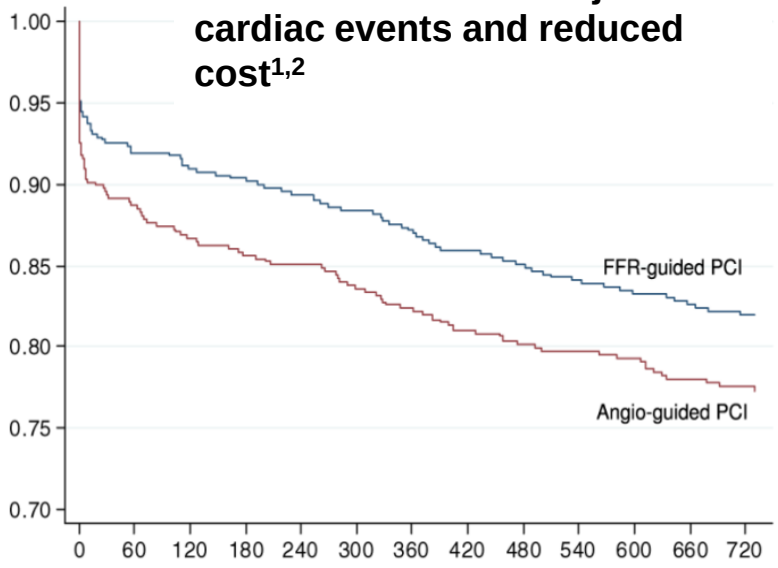
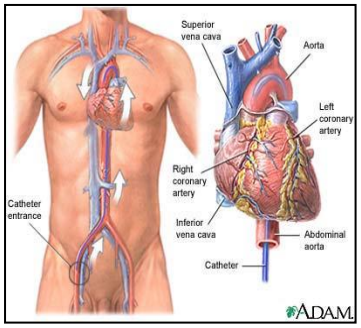
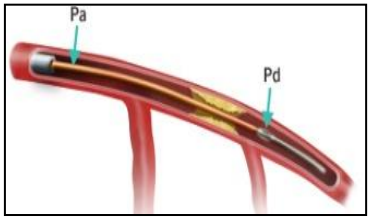


Image source:
http://www.ptca.org/news/2010/0623_FFR.html

1. Hamm et al., EHJ, 2011
2. Tonino et al. N Engl J Med. 2009 Jan 15;360(3):213-24.
3. Pijls, NH et al. J Am Coll Cardiol. 2007 May 29;49(21):2105-11.

Non-invasive functional testing in 2014





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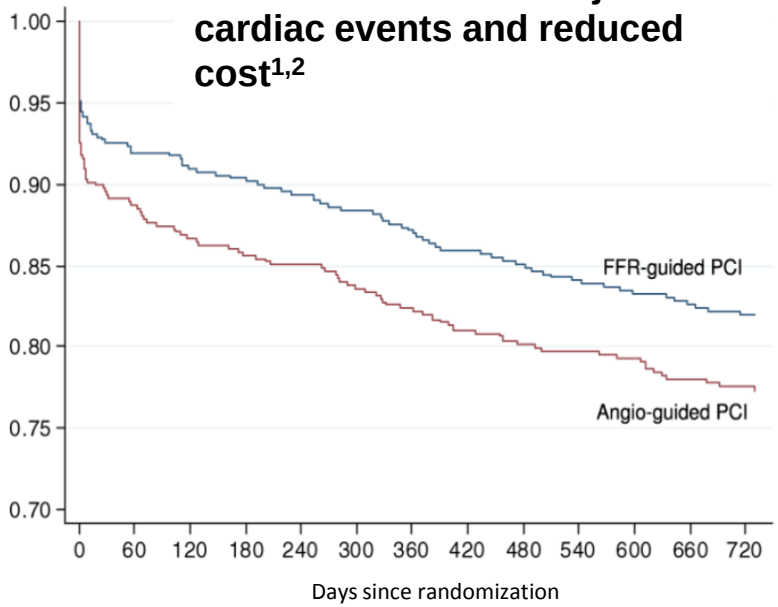

Invasive Fractional Flow Reserve (FFR) has emerged as the gold standard “bridge” test to determine optimal (medical vs. PCI) artery-specific therapy

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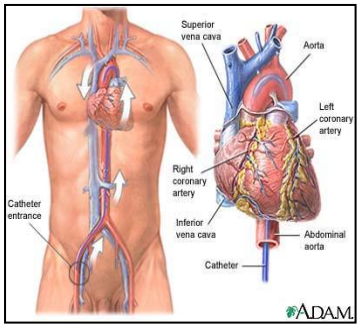

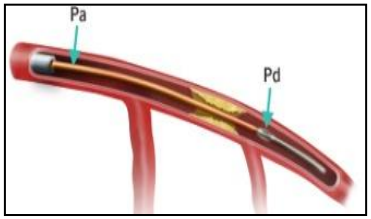

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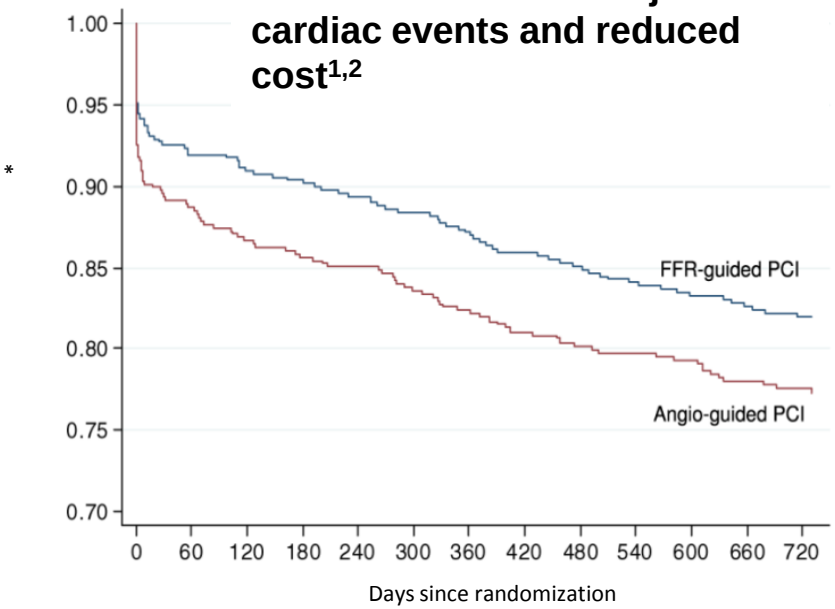

Invasive Fractional Flow Reserve (FFR) has emerged as the gold standard "bridge" test to determine optimal (medical vs. PCI) artery-specific therapy

The diagnostic performance of non-invasive testing modalities should be tested using FFR as the gold standard

Image source:
http://ww

1. Hamm et a
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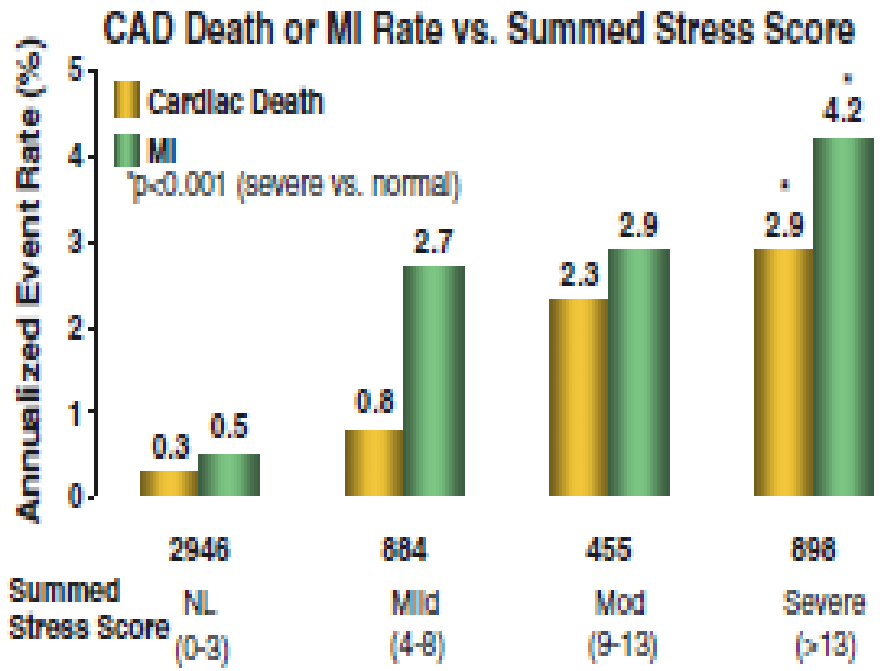
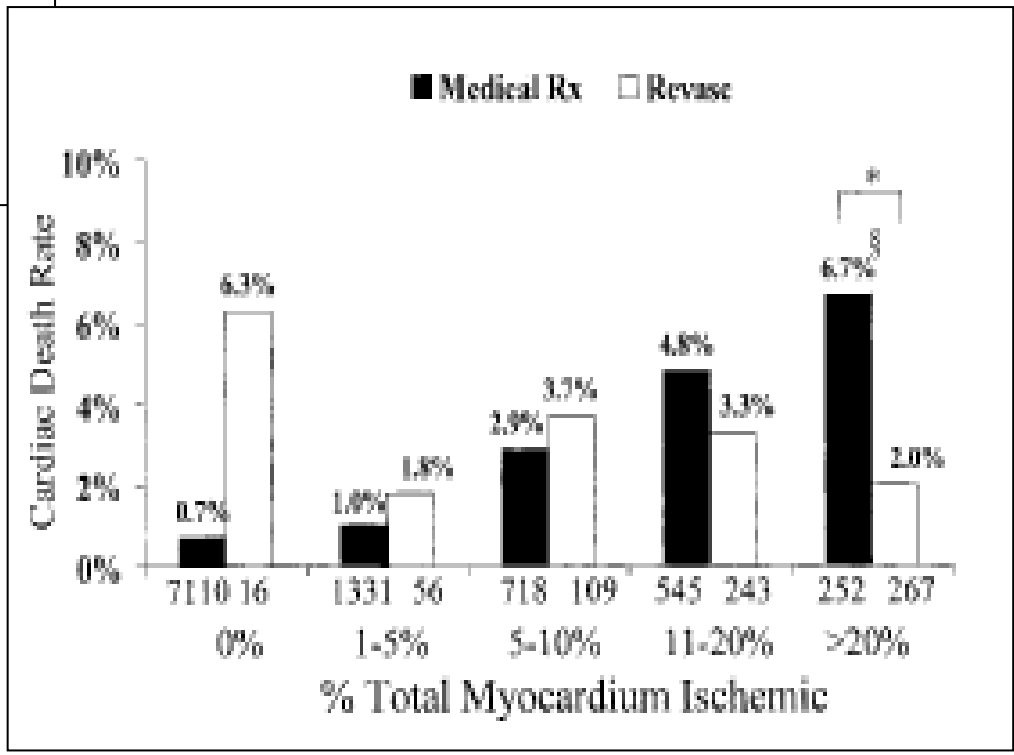
Non-invasive functional testing in 2014

- Is non-invasive functional testing diagnostic accurate?
- **Does the information from non-invasive functional testing change outcomes?**

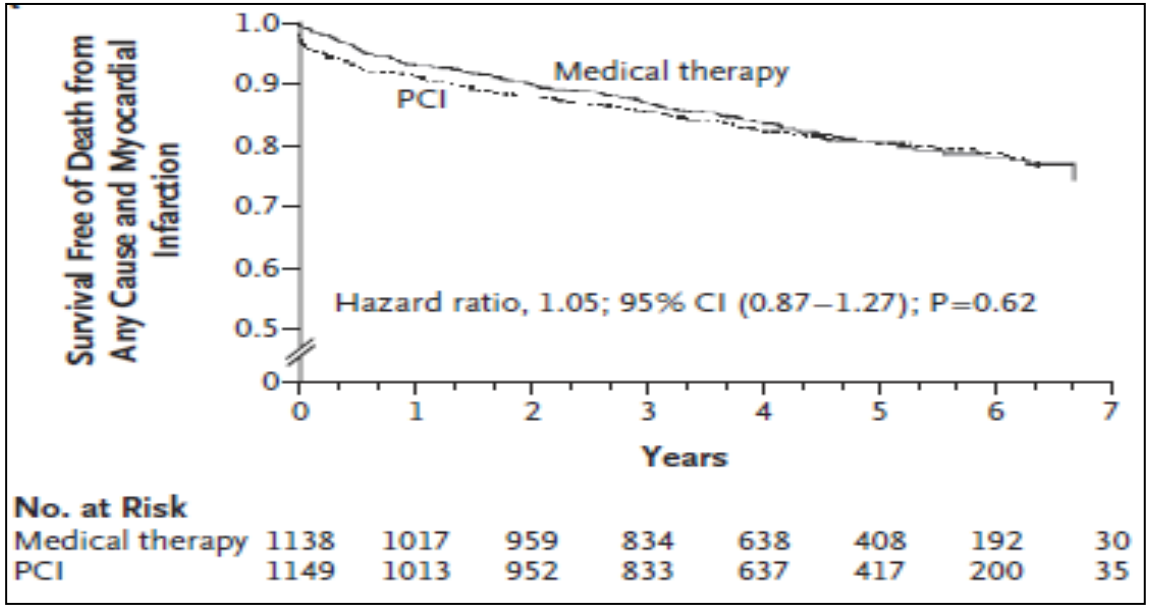
Non-invasive functional testing in 2014, *Myocardial ischemia and prognosis*





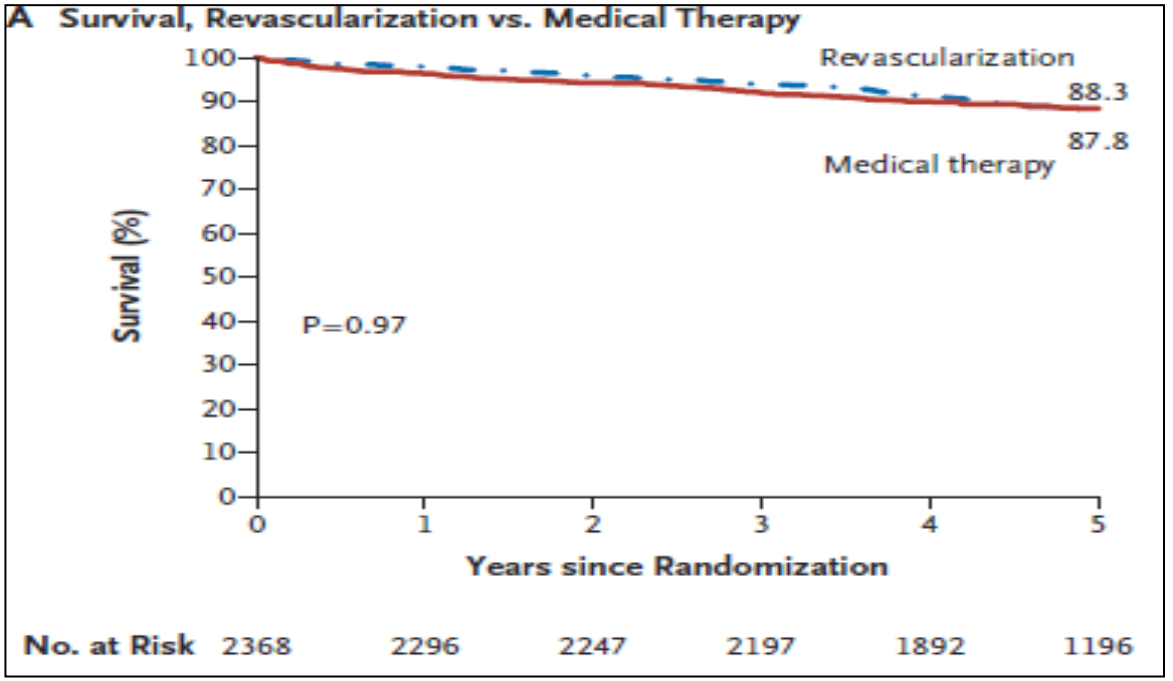
Hachamovitch R, Circulation 2003

Non-invasive functional testing in 2014, *Myocardial ischemia and treatment decision*



COURAGE study

BARI-2D study



Boden WE, NEJM 2007

Frye RL, NEJM 2009

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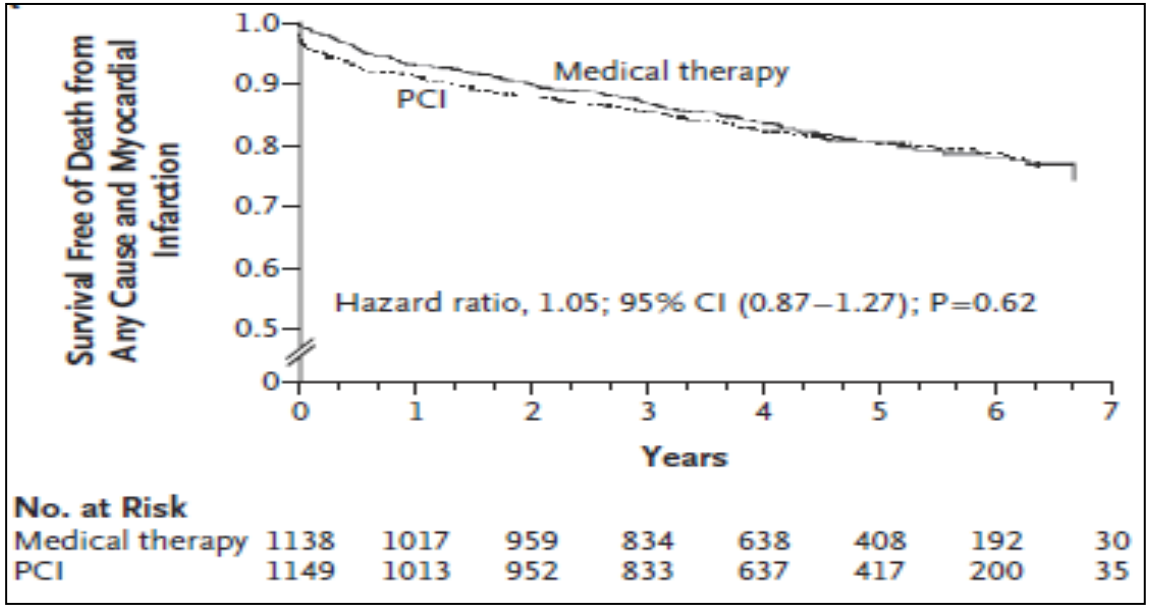
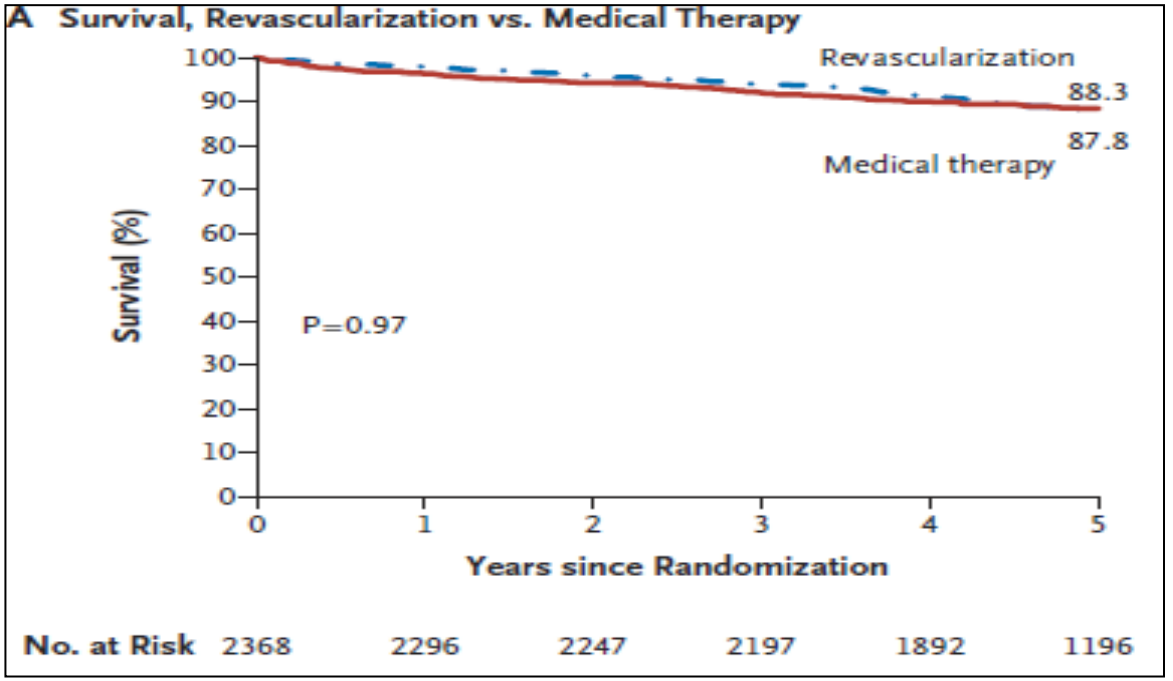


”**COURAGE**-ischemia”:
Proximal 70% stenosis and *ST↓ or T-wave↓ in resting ECG or ischemia in stress ECG or imaging test or at least one proximal 80% stenosis*

”**BARI-2D** ischemia”:
Proximal 50% stenosis and
positive stress test or >70% stenosis and classical angina



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Non-invasive functional testing in 2014, -*Conclusion*

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Non-invasive functional testing in 2014, -*Conclusion*

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8000 patients, randomized to interventional or conservative treatment, moderate-severe ischemia (PET, SPECT,CMR,Echo) at cor-lab reads.

Non-invasive functional testing in 2014

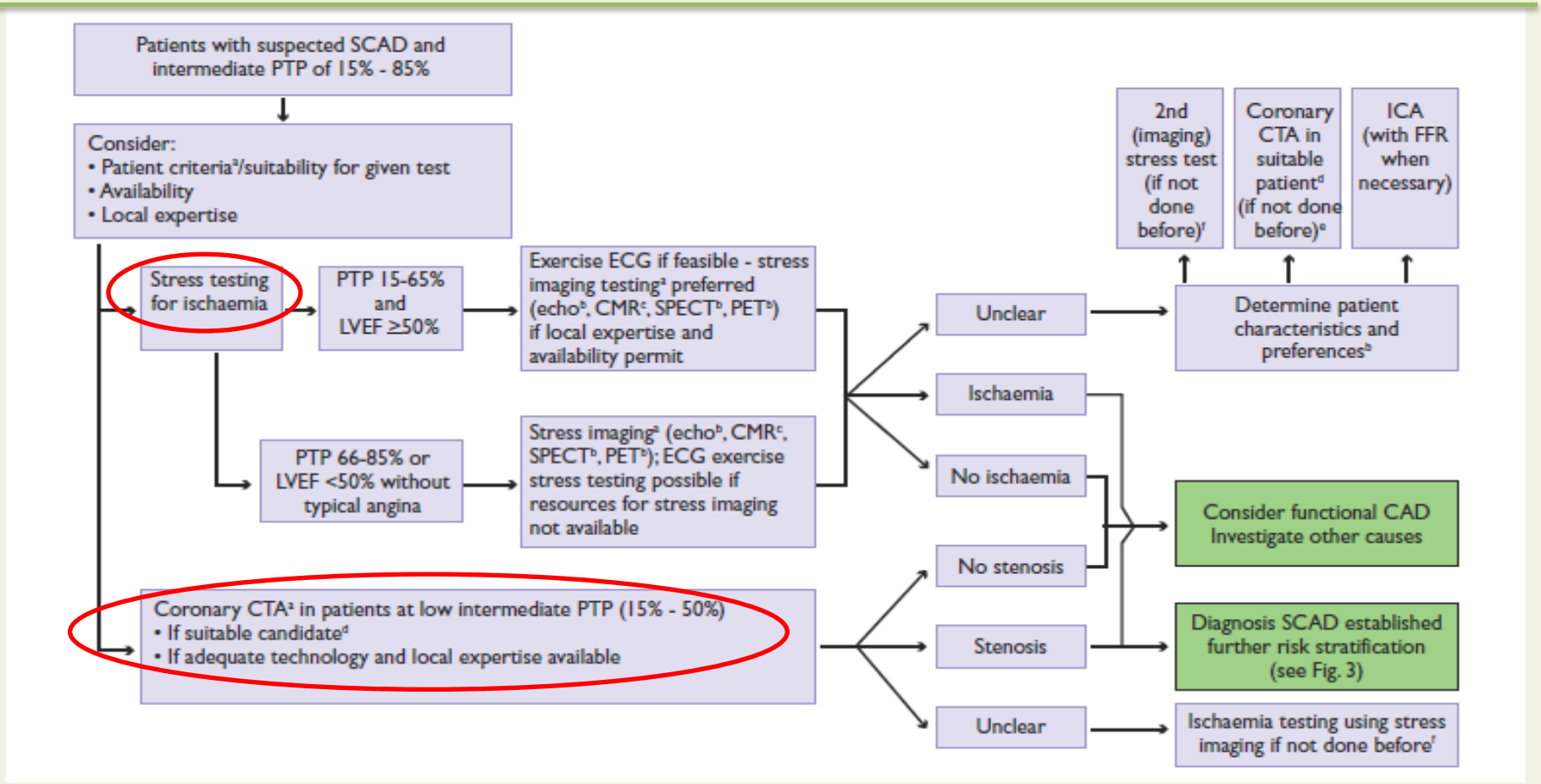

Figure 2 Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability. CAD = coronary artery disease; CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PET = positron emission tomography; PTP = pre-test probability; SCAD = stable coronary artery disease; SPECT = single photon emission computed tomography.

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Non-invasive functional testing in 2014

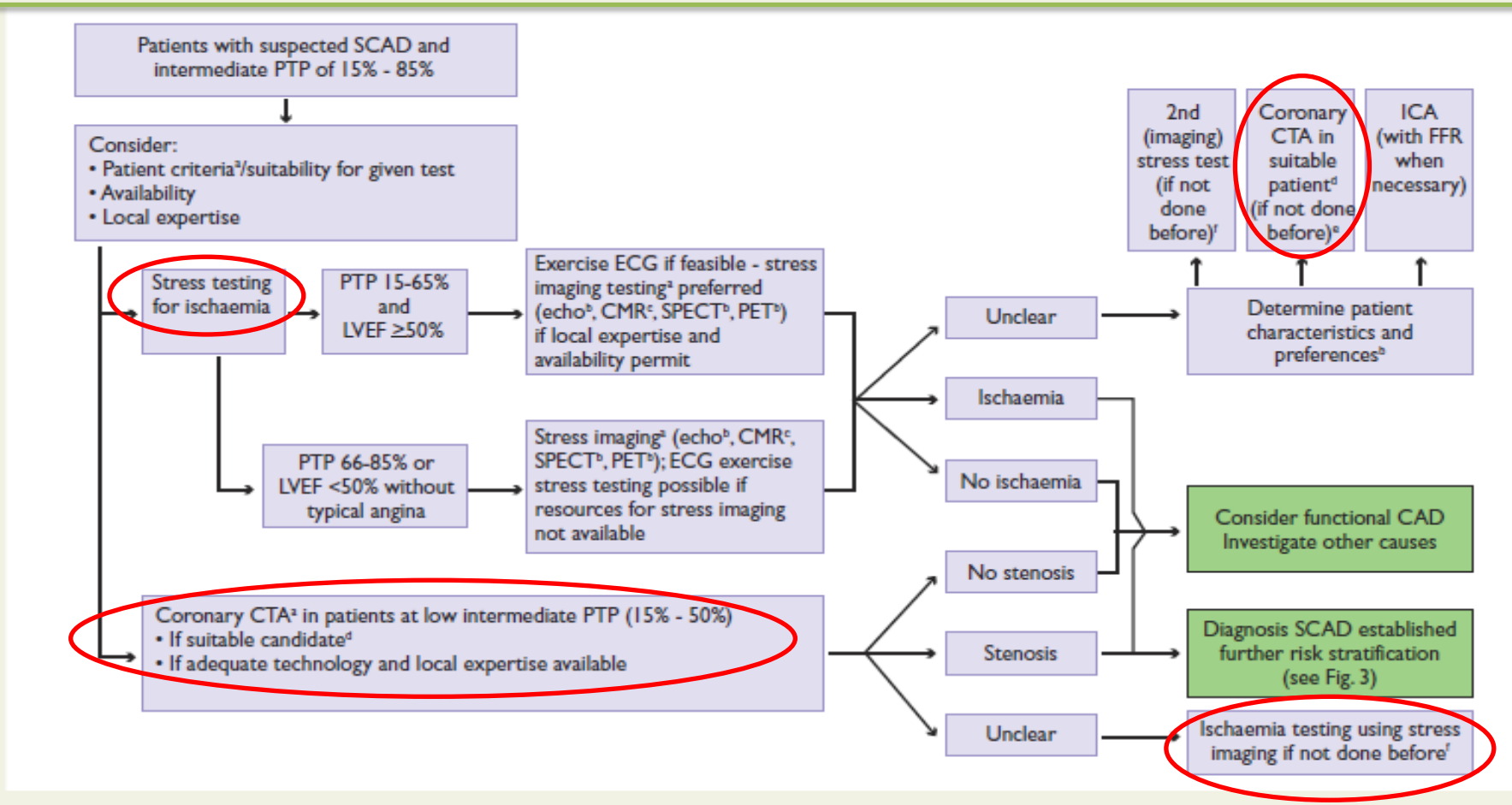

Figure 2 Non-invasive testing in patients with suspected SCAD and an intermediate pre-test probability. CAD = coronary artery disease; CTA = computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; ICA = invasive coronary angiography; LVEF = left ventricular ejection fraction; PET = positron emission tomography; PTP = pre-test probability; SCAD = stable coronary artery disease; SPECT = single photon emission computed tomography.

[a]Consider age of patient versus radiation exposure.

[b]In patients unable to exercise use echo or SPECT/PET with pharmacologic stress instead.

[c]CMR is only performed using pharmacologic stress.

[d]Patient characteristics should make a fully diagnostic coronary CTA scan highly probable (see section 6.2.5.1.2) consider result to be unclear in patients with severe diffuse or focal calcification.

[e]Proceed as in lower left coronary CTA box.

[f]Proceed as in stress testing for ischaemia box.

Montalescot G, EHJ 2013

Non-invasive CAD diagnosis and management requires understanding of two fundamental questions

Non-invasive CAD diagnosis and management requires understanding of two fundamental questions

FUNCTION: Is coronary ischemia causing my patient's symptoms?

Regional differences in

- myocardial blood flow (e.g. SPECT, PET, CMR) or
- left ventricular wall motion (e.g. stress echocardiography)

ANATOMY: Are there narrowings in the coronary arteries?

- Coronary CT Angiography

Non-invasive functional testing in 2014, - *the future!*

Incremental value of combining 64-slice computed tomography angiography with stress nuclear myocardial perfusion imaging to improve noninvasive detection of coronary artery disease

Akira Sato, MD,[a] Toshihiro Nozato, MD,[b] Hiroyuki Hikita, MD,[b] Shinsuke Miyazaki, MD,[b] Yoshihide Takahashi, MD,[b] Taishi Kuwahara, MD,[b] Atsushi Takahashi, MD,[b] Michiaki Hiroe, MD,[c] and Kazutaka Aonuma, MD[a]

Table 3. Per-patients analysis of 64-slice CTA and combined stress nuclear MPI for the detection of coronary stenoses

	All patients for analysis with nonevaluable patients considered positive (n = 130)	Combined stress MPI results to all nonevaluable patients (n = 130)
Sensitivity	99% (76/77)	99% (76/77)
Specificity	70% (37/53)	87% (46/53)*
PPV	82% (76/92)	91% (76/83)*
NPV	97% (37/38)	98% (46/47)
Accuracy	87% (113/130)	94% (122/130)*

*$P < 0.001$ vs all patients for analysis with nonevaluable patients considered positive. Abbreviation as in Table 2.

Sato A, J Nucl Cardiol 2010

Non-invasive functional testing in 2014, - *the future!*

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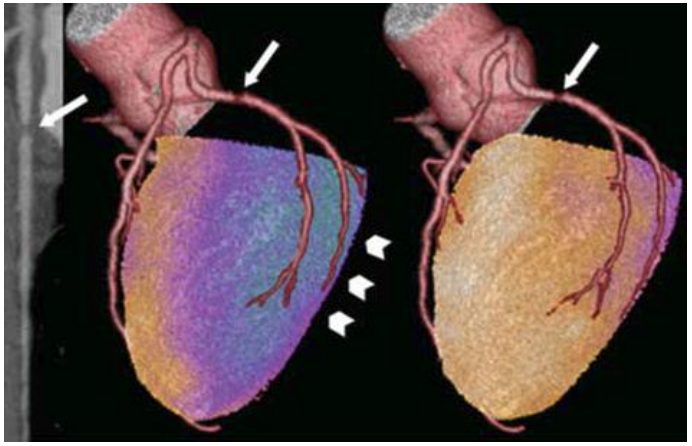
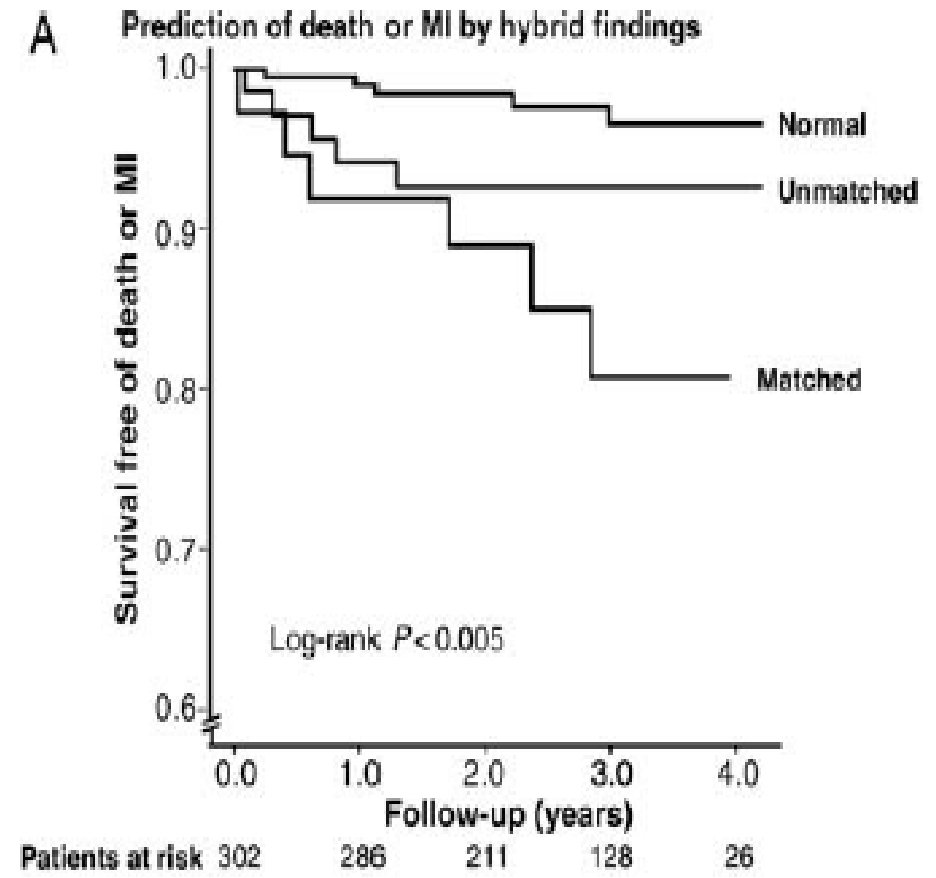
Sato A, J Nucl Cardiol 2010

Non-invasive functional testing in 2014, - *the future!*



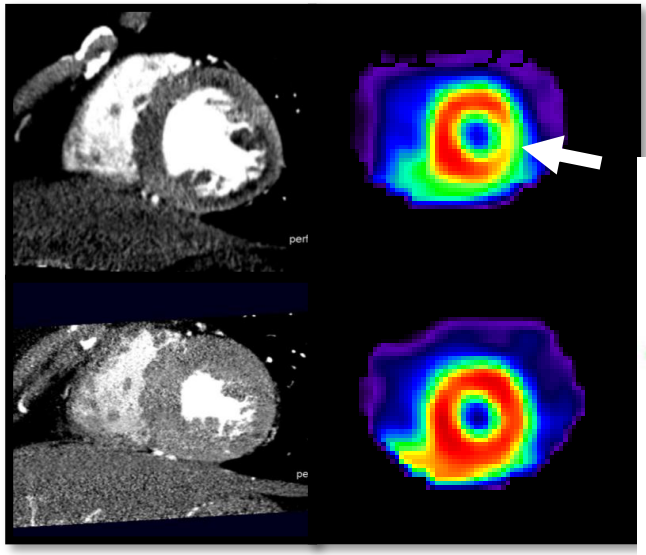
Prognostic value of cardiac hybrid imaging integrating single-photon emission computed tomography with coronary computed tomography angiography

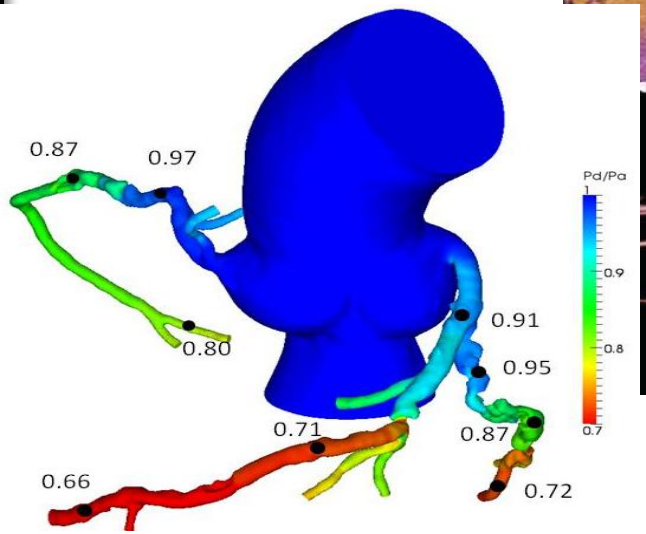
Aju P. Pazhenkottil[1], René N. Nkoulou[1], Jelena-Rima Ghadri[1], Bernhard A. Herzog[1], Ronny R. Buechel[1], Silke M. Küest[1], Mathias Wolfrum[1], Michael Fiechter[1], Lars Husmann[1], Oliver Gaemperli[1], and Philipp A. Kaufmann[1,2]*

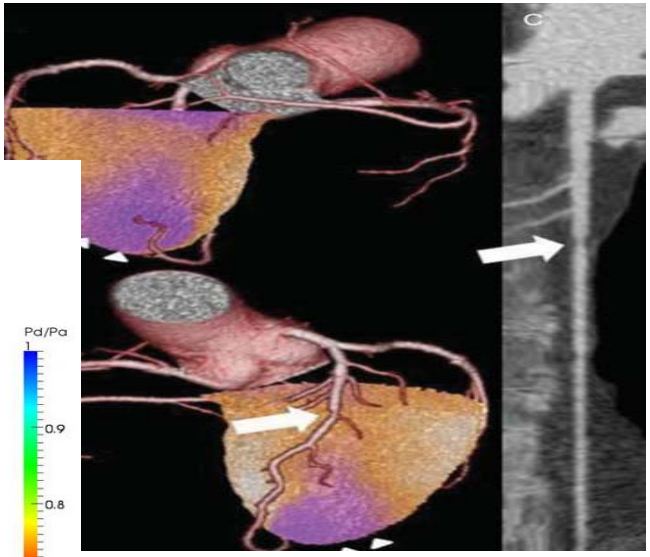


Pazhenkottil AP, EHJ 2011

- Function AND anatomy
- FFR as the reference standard







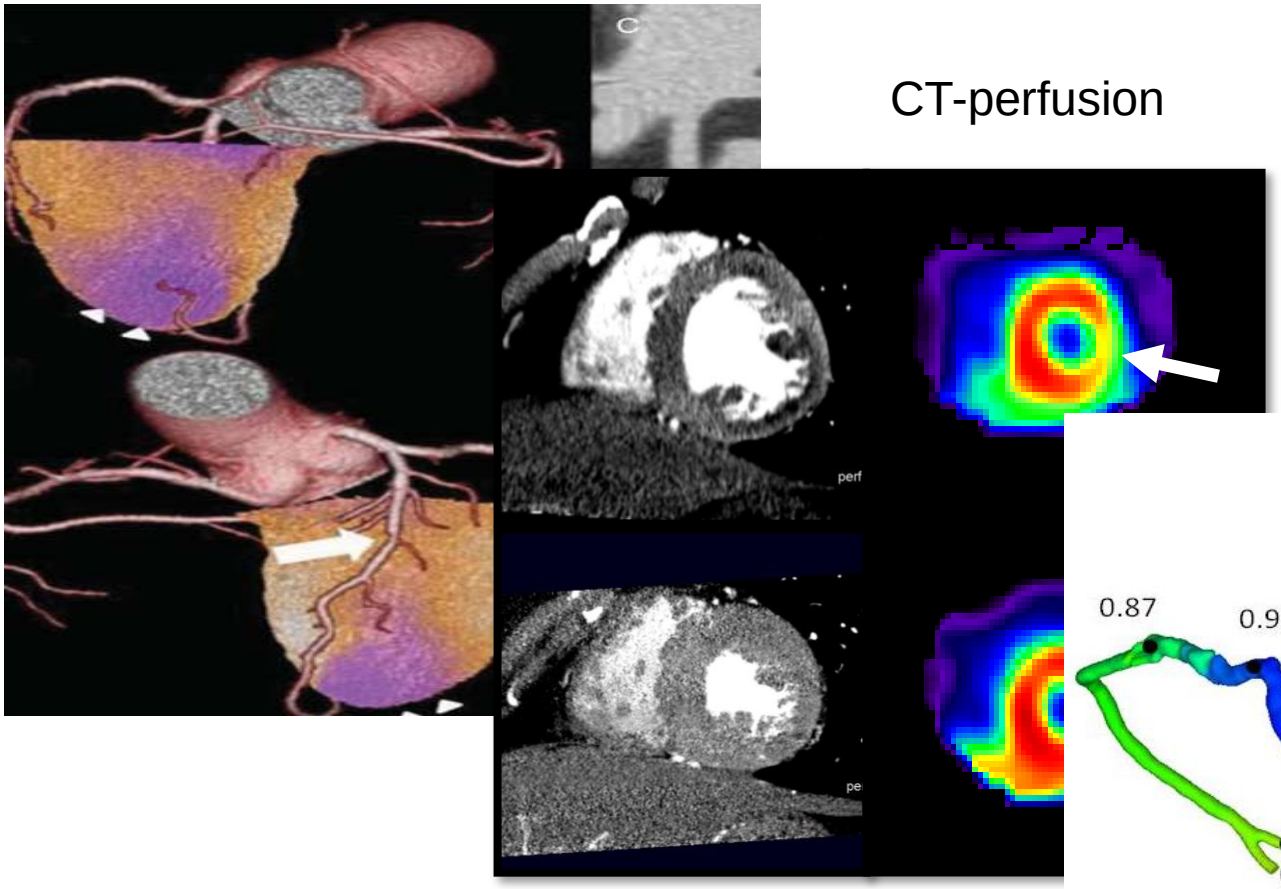
Thank you

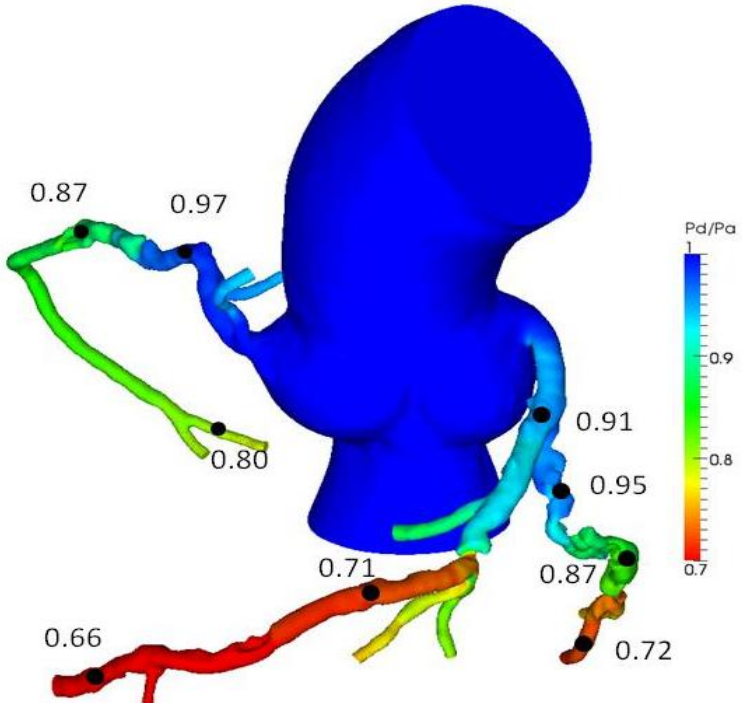
Non-invasive functional testing in 2014, *-assessment of anatomy and function in one single test*

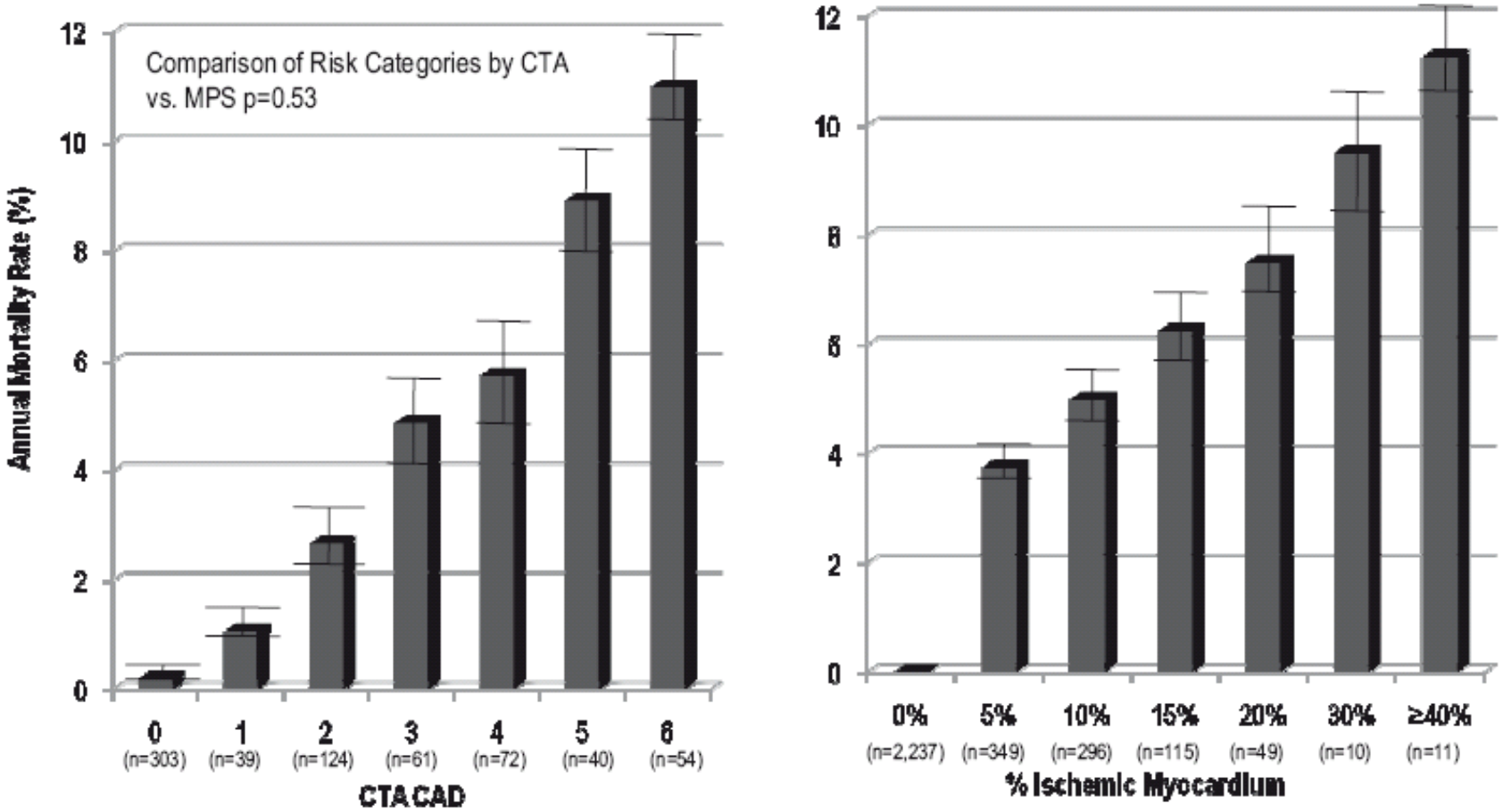
PET-CT

CT-perfusion

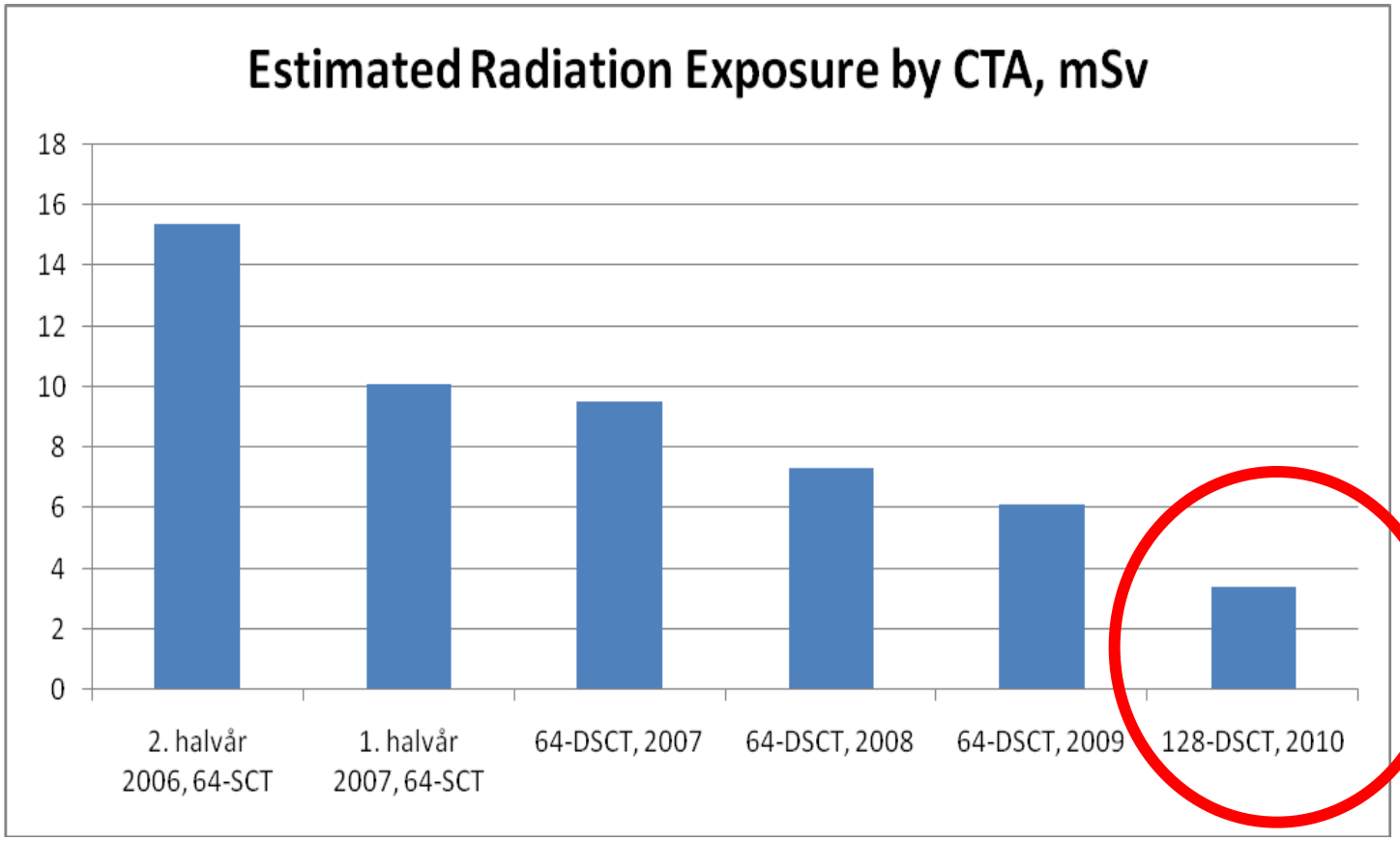
FFR_{CT}

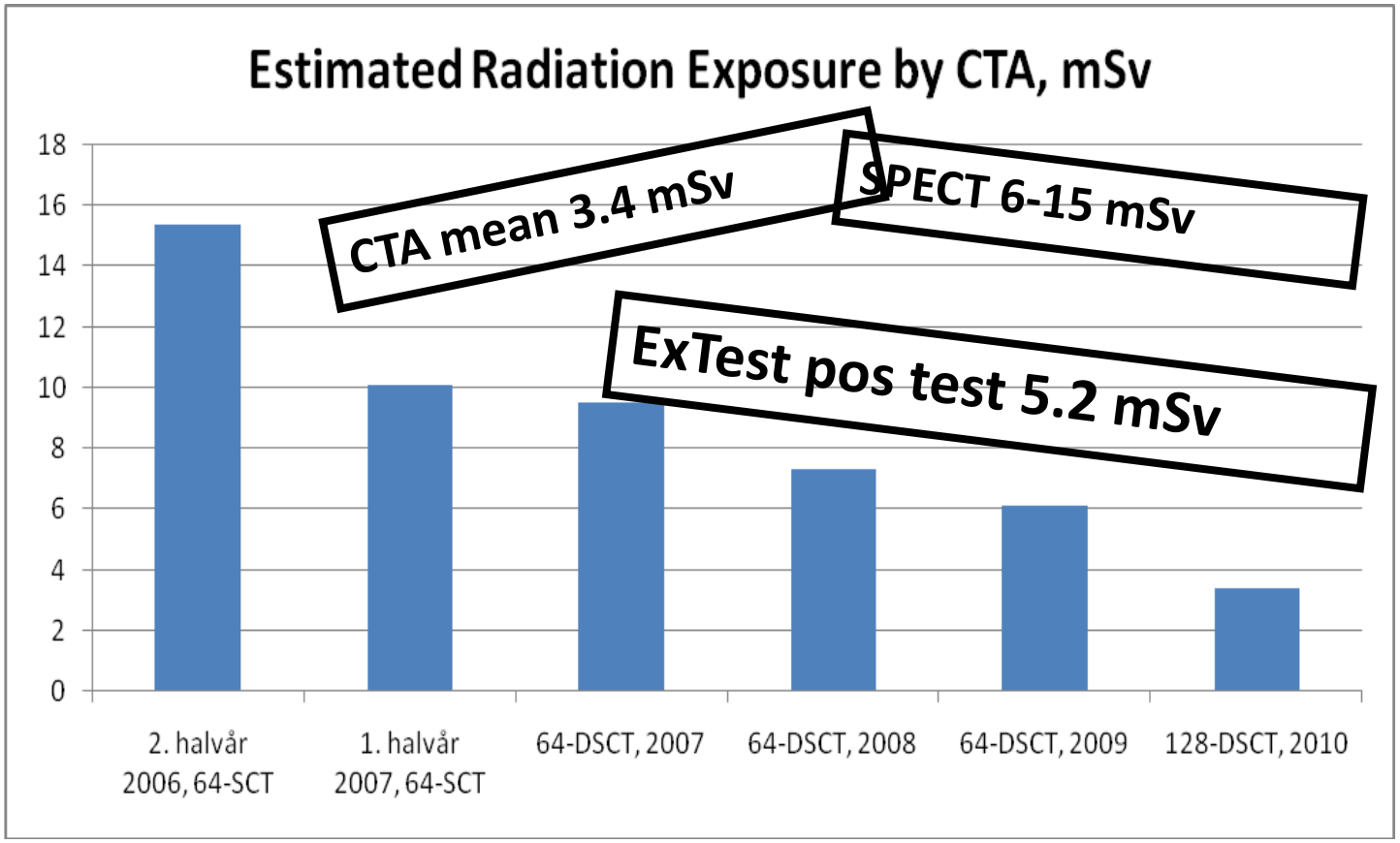


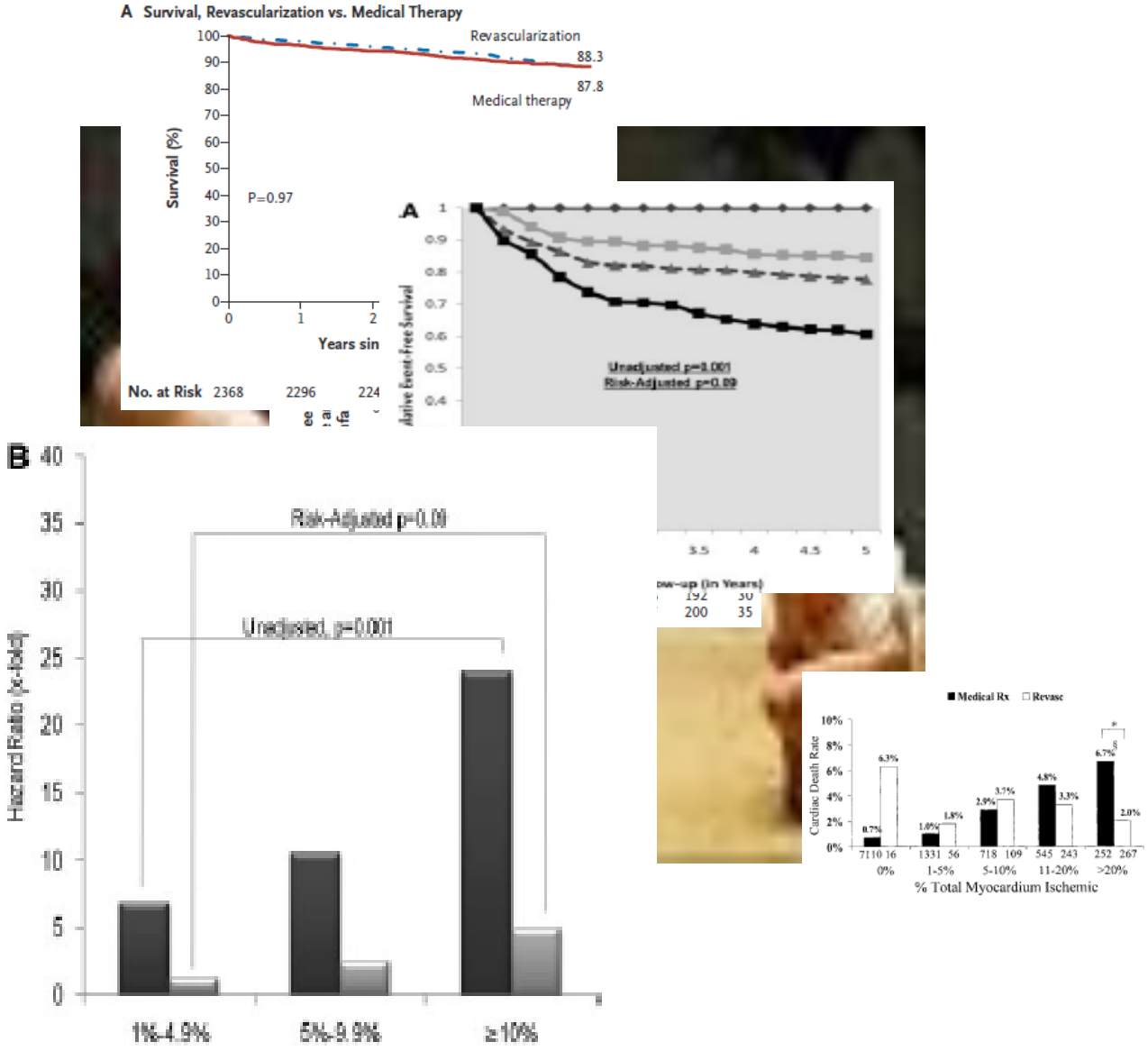


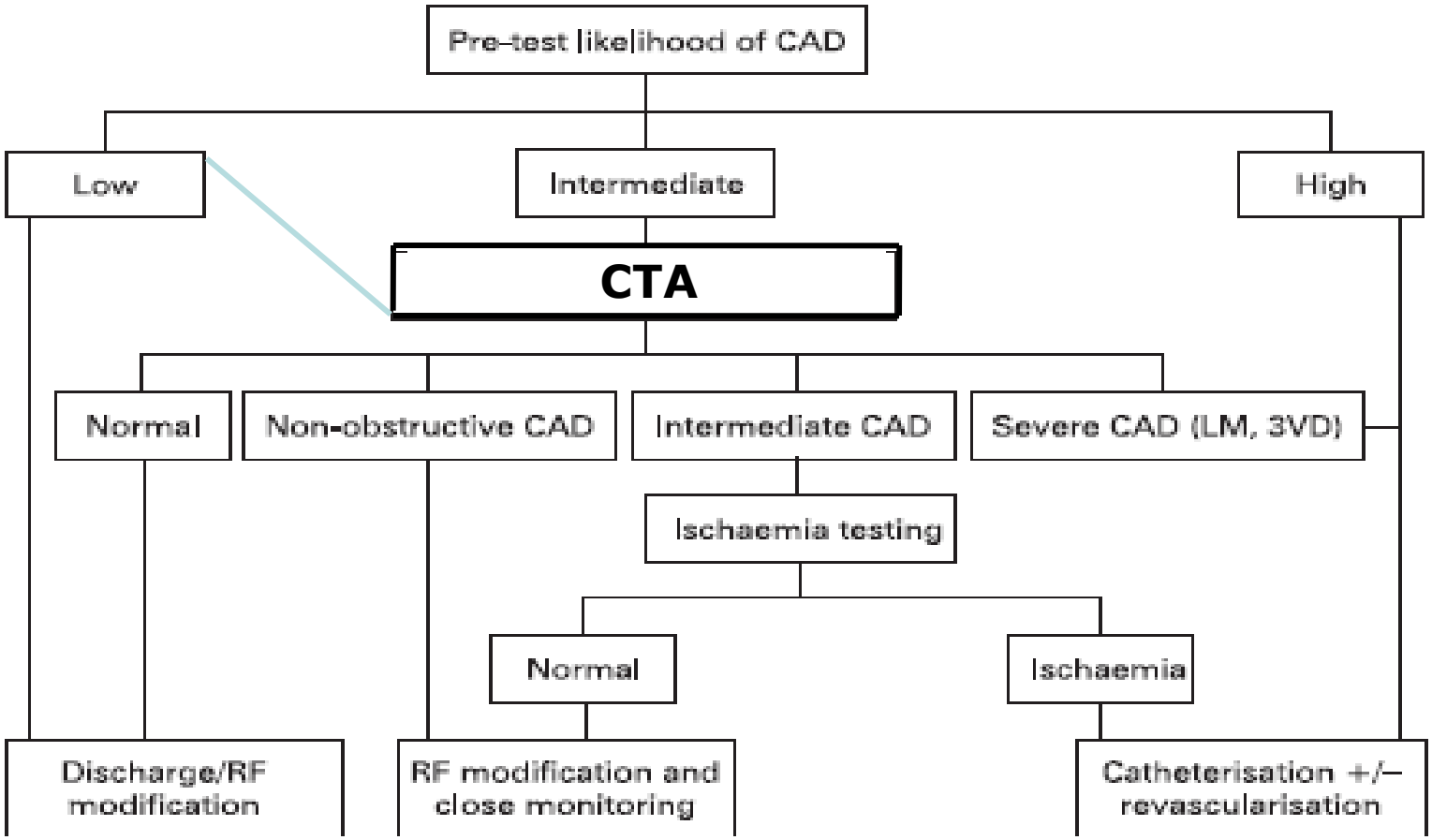


Prognosis by coronary computed tomographic angiography: Matched comparison with myocardial perfusion single-photon emission computed tomography

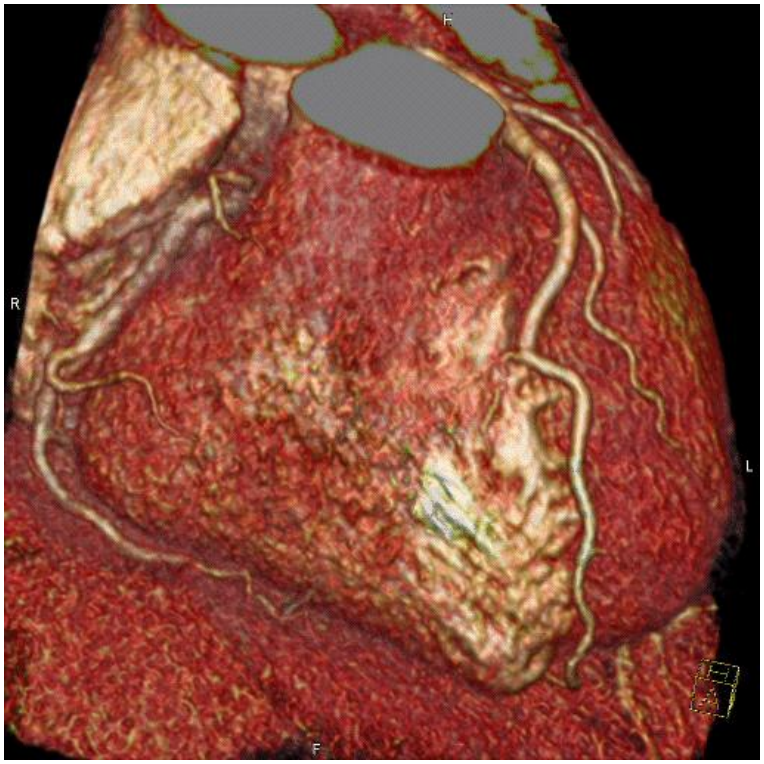

Estimated Radiation Exposure by CTA, mSv
18
16
14
12
10
8
6
4
2
0
2. halvår 2006, 64-SCT
1. halvår 2007, 64-SCT
64-DSCT, 2007
64-DSCT, 2008
64-DSCT, 2009
128-DSCT, 2010

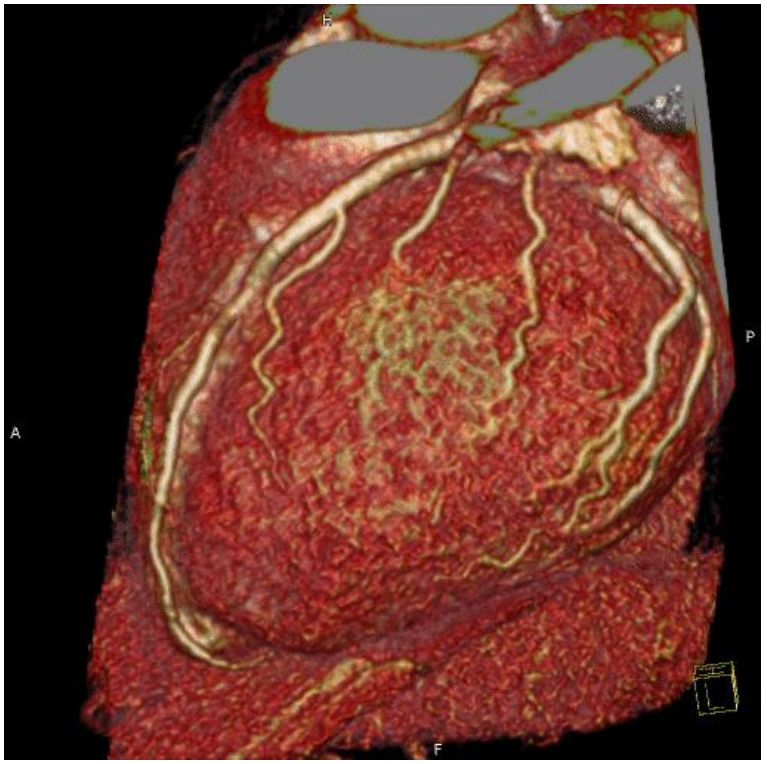

Estimated Radiation Exposure by CTA, mSv
CTA mean 3.4 mSv
SPECT 6-15 mSv
ExTest pos test 5.2 mSv
18
16
14
12
10
8
6
4
2
0
2. halvår 2006, 64-SCT
1. halvår 2007, 64-SCT
64-DSCT, 2007
64-DSCT, 2008
64-DSCT, 2009
128-DSCT, 2010

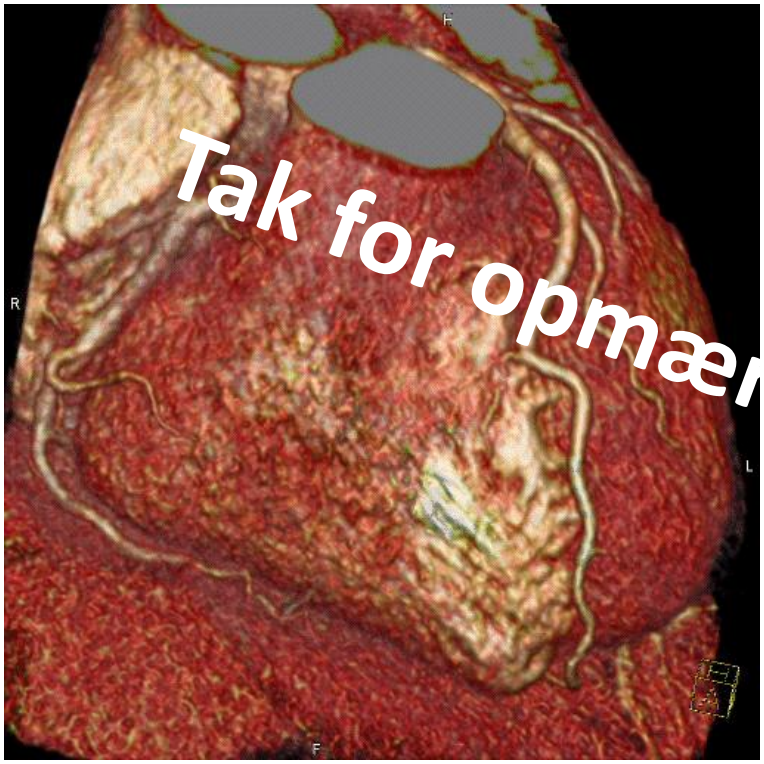

A Survival, Revascularization vs. Medical Therapy
Revascularization
88.3
87.8
Medical therapy
Survival (%)
P=0.97
Years sin
No. at Risk 2368 2296 224
A
Unadjusted p=0.001
Risk-Adjusted p=0.09
B
Risk-Adjusted p=0.09
Unadjusted, p=0.001
Hazard Ratio (x-fold)
1%-4.9%
5%-9.9%
≥10%
Medical Rx
Revasc
Cardiac Death Rate
6.3%
0.7%
1.8%
1.0%
3.7%
2.9%
4.8%
3.3%
6.7%
2.0%
7110 16
1331 56
718 109
545 243
252 267
0%
1-5%
5-10%
11-20%
>20%
% Total Myocardium Ischemic

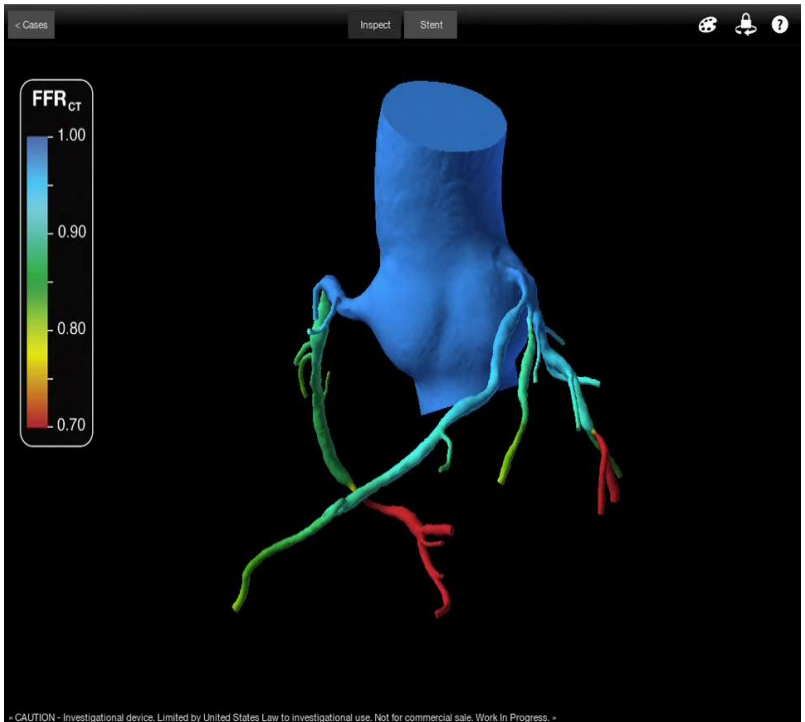

Pre-test likelihood of CAD
Low
Intermediate
High
CTA
Normal
Non-obstructive CAD
Intermediate CAD
Severe CAD (LM, 3VD)
Ischaemia testing
Normal
Ischaemia
Discharge/RF modification
RF modification and close monitoring
Catheterisation +/– revascularisation

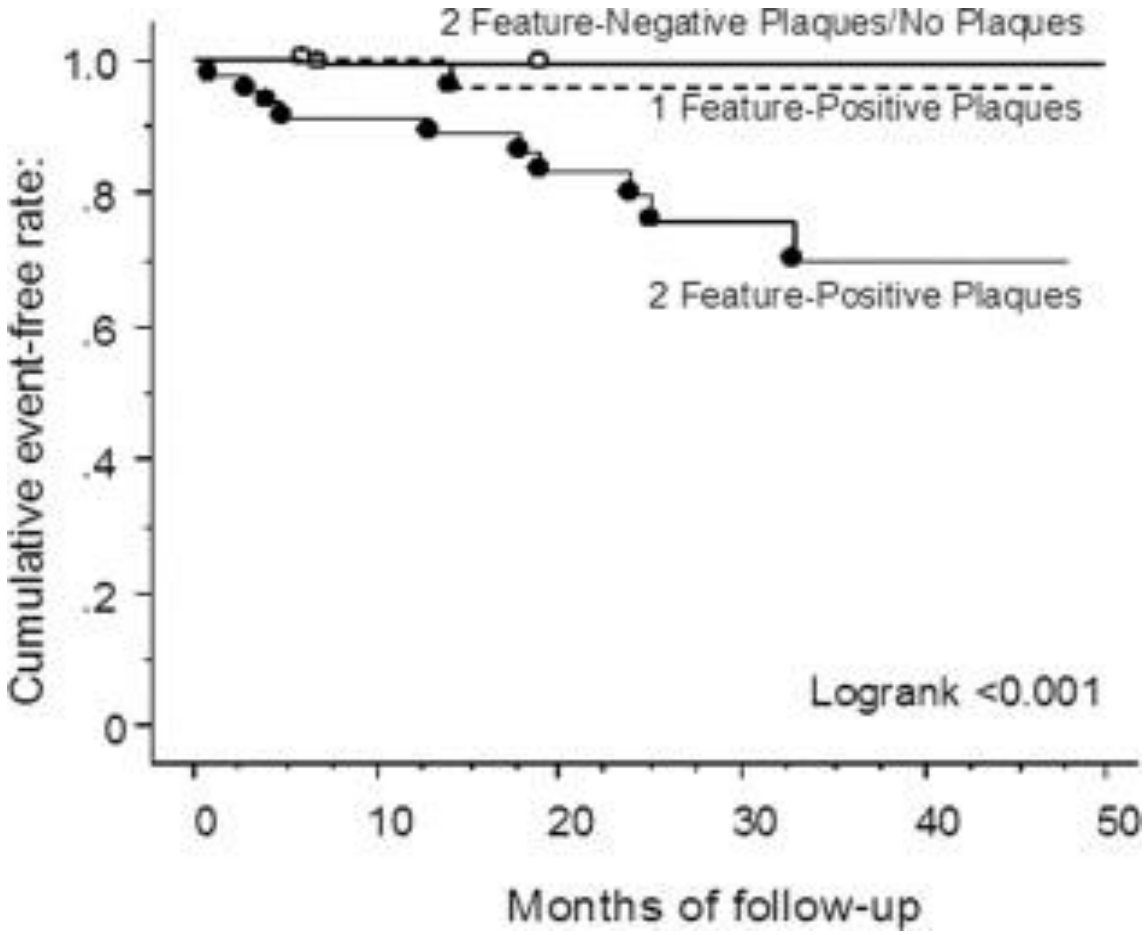
Teknik	Varighed	Røntgen, mSv	Spatiale opløselighed	Temporale opløselighed	Fordele	Ulemper
Ekko	15-30 min	0	~ 1mm	< 33 msek	Let tilgængelig Non-invasiv -røntgen -kontrast	2-D info Operatør afhængig Afhængig af anatomi /akustiske forhold
CT	< 10 sek	0.5-10	0.4 – 0.5 mm	83-170 msek	Non-invasiv Høj spatial opløselighed	Kun anatomi Røntgen, Kontrast Afhængig af lav og regelmæssig puls
MR	20-45 min	0	0.7 – 3.0 mm	120-150 msek	Non-invasiv -røntgen -kontrast	Lav tilgængelighed Omstændelig Lav opløselighed Risiko for HR og respirations artefakt
KAG	10-15 min	2-10	0.2 mm	< 10 msek	Høj opløselighed	2-D info, Kun ”luminologi” Invasiv, -sjældne men alvorlige komplikatio Operatør afhængig Røntgen, Kontrast


H
R
L
F


H
A
P
F

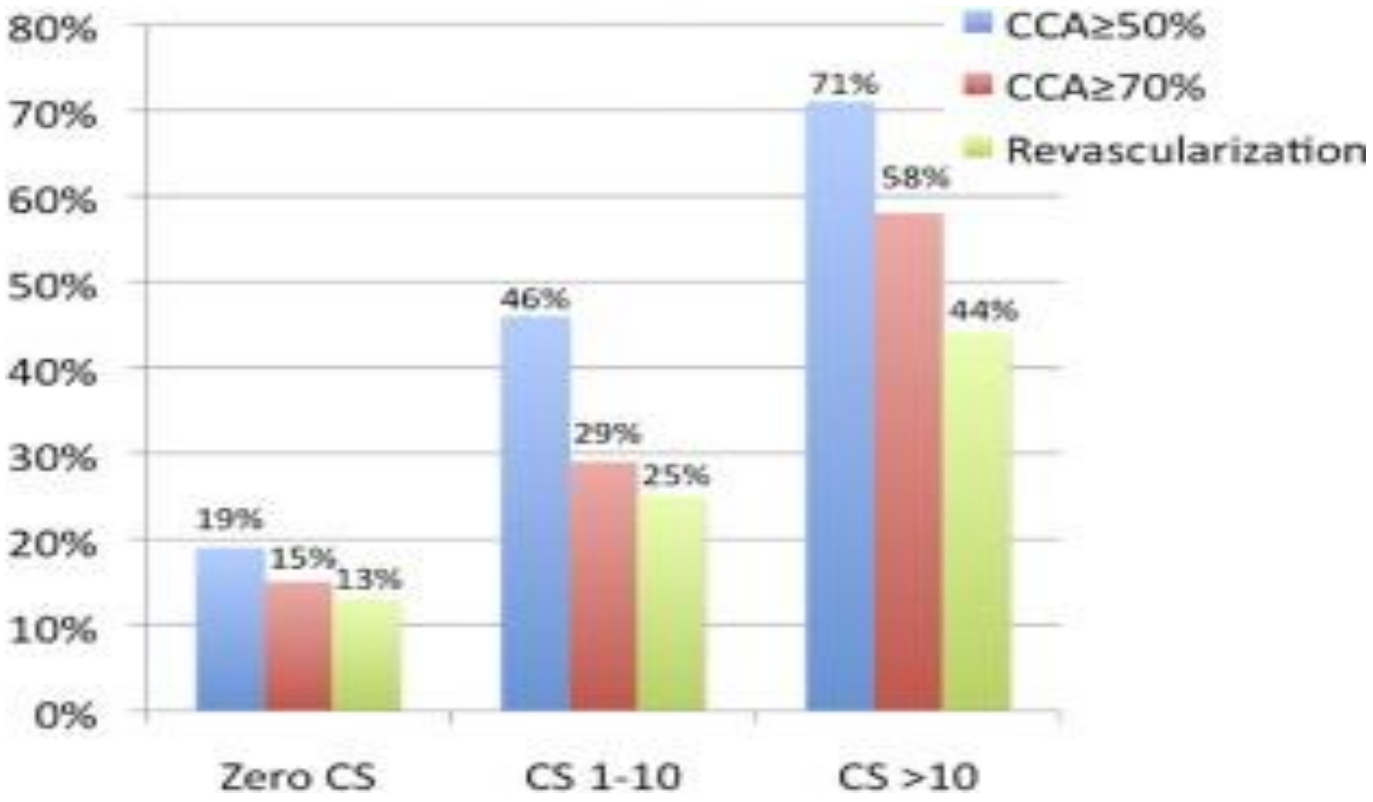

Tak for opmærksomheden!


< Cases
Inspect
Stent
FFR CT
1.00
0.90
0.80
0.70
« CAUTION - Investigational device. Limited by United States Law to investigational use. Not for commercial sale. Work In Progress. »

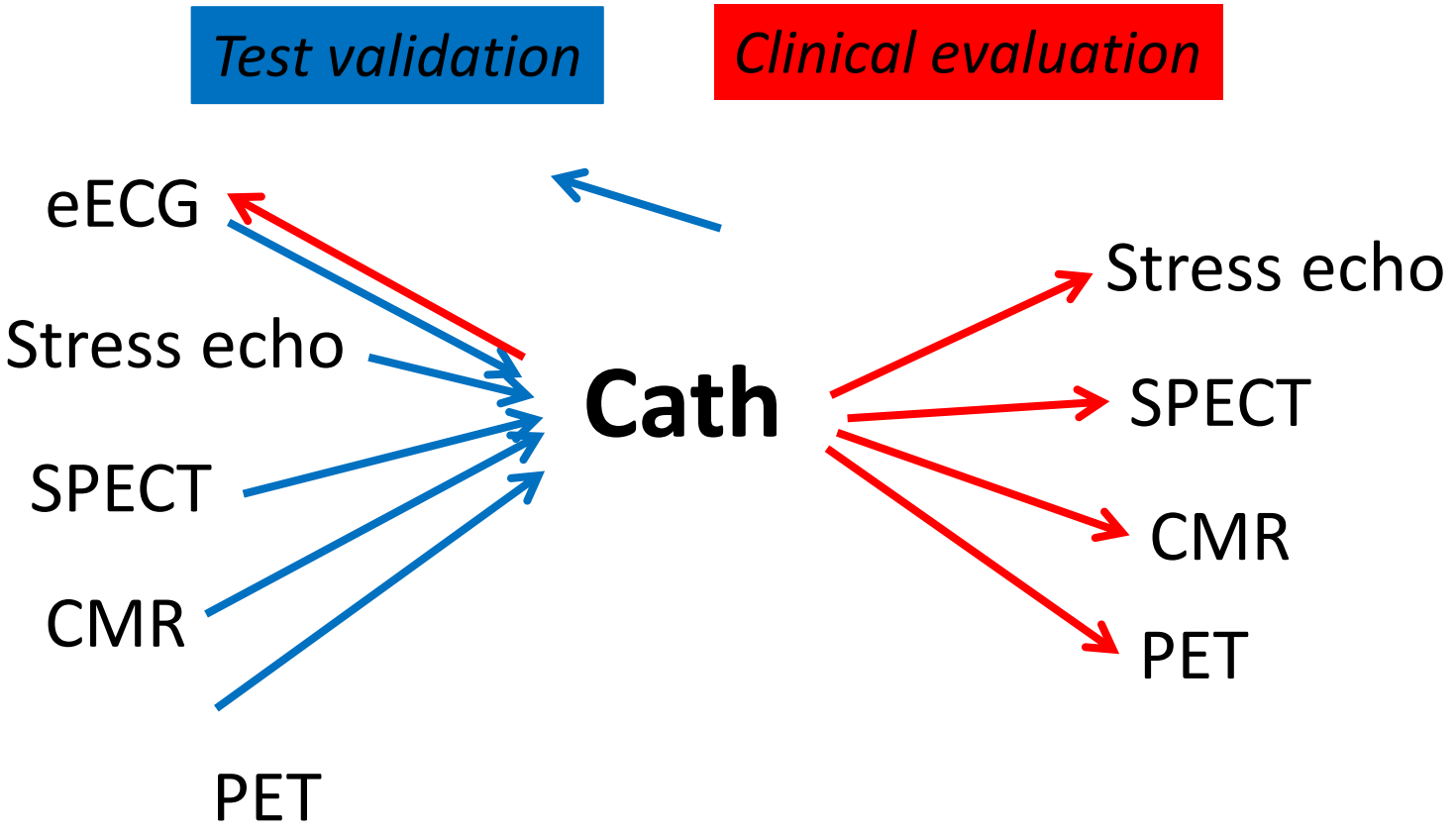


N =1059, suspected of CAD
F/u 27 months, Reg.: ACS

Plaquefeatures:
- Low attenuation
- Positive remodelling


80%
70%
60%
50%
40%
30%
20%
10%
0%
CCA≥50%
CCA≥70%
Revascularization
19%
15%
13%
46%
29%
25%
71%
58%
44%
Zero CS
CS 1-10
CS >10

Validation paradox



Hecht HS, JCCT, 2009

Non-invasive functional testing in 2014

Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Möbius-Winkler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D., Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D., Jane B. Johnson, R.N., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D., for the FAME 2 Trial Investigators*

ABSTRACT

BACKGROUND

The preferred initial treatment for patients with stable coronary artery disease is the best available medical therapy. We hypothesized that in patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), percutaneous coronary intervention (PCI) plus the best available medical therapy would be superior to the best available medical therapy alone.

METHODS

In patients with stable coronary artery disease for whom PCI was being considered, we assessed all stenoses by measuring FFR. Patients in whom at least one stenosis was functionally significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Patients in whom all stenoses had an FFR of more than 0.80 were entered into a registry and received the best available medical therapy. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

RESULTS

Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical-therapy group (hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% vs. 11.1%; hazard ratio, 0.13; 95% CI, 0.06 to 0.30; P<0.001); in particular, in the PCI group, fewer urgent revascularizations were triggered by a myocardial infarction or evidence of ischemia on electrocardiography (hazard ratio, 0.13; 95% CI, 0.04 to 0.43; P<0.001). Among patients in the registry, 3.0% had a primary end-point event.

CONCLUSIONS

In patients with stable coronary artery disease and functionally significant stenoses, FFR-guided PCI plus the best available medical therapy, as compared with the best available medical therapy alone, decreased the need for urgent revascularization. In patients without ischemia, the outcome appeared to be favorable with the best available medical therapy alone. (Funded by St. Jude Medical; ClinicalTrials.gov number, NCT01132495.)

From the Cardiovascular Center Aalst, Onze-Lieve-Vrouw Clinic, Aalst, Belgium (B.D.B., E.B.); Department of Cardiology, Catharina Hospital, and Department of Biomedical Engineering, Eindhoven University of Technology — both in Eindhoven, the Netherlands (N.H.J.P., P.A.L.T.); Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine, and Clinical Trials Unit Bern, University of Bern, Bern, Switzerland (B.K., P.J.); Hungarian Institute of Cardiology, Budapest (Z.P.); Clinical Center Kragujevac, Kragujevac, Serbia (N.J.); Heart Center Leipzig, Leipzig, Germany (S.M.-W.); Cardiovascular Hospital, Lyon, France (G.R.); Karolinska Institutet at Södersjukhuset, Stockholm (N.W.), and Örebro University Hospital, Örebro (O.F.) — both in Sweden; Department of Internal Medicine and Cardiology, University Hospital Brno, Brno, Czech Republic (P.K.); King's College Hospital, London (P.M.), Golden Jubilee National Hospital, Glasgow (K.G.O.), Royal Victoria Hospital, Belfast (G.M.), and Department of Cardiology, Southampton University Hospital Trust, Southampton (N.C.) — all in the United Kingdom; Department of Cardiology, Rigshospitalet University Hospital, Copenhagen (T.E.); Atlanta Veterans Affairs Medical Center, Atlanta (K.M.); Northeast Cardiology Associates, Bangor, ME (P.V.); St. Jude Medical, Plymouth, MN (J.B.J.); and Stanford University Medical Center, Stanford, CA (W.F.F.). Address reprint requests to Dr. De Bruyne at the Cardiovascular Centre Aalst, OLV-Clinic, Moorselbaan 164, B-9300 Aalst, Belgium, or at bernard.de.bruyne@olvz-aalst.be.

*The investigators in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on August 28, 2012, and updated on October 18, 2012, at NEJM.org.

N Engl J Med 2012;367:991-1001.
DOI: 10.1056/NEJMoa1205361

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

Pim A.L. Tonino, M.D., Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Uwe Siebert, M.D., M.P.H., Sc.D., Fumiaki Ikeno, M.D., Marcel van 't Veer, M.Sc., Volker Klauss, M.D., Ph.D., Ganesh Manoharan, M.D., Thomas Engstrøm, M.D., Ph.D., Keith G. Oldroyd, M.D., Peter N. Ver Lee, M.D., Philip A. MacCarthy, M.D., Ph.D., and William F. Fearon, M.D., for the FAME Study Investigators*

ABSTRACT

BACKGROUND

In patients with multivessel coronary artery disease who are undergoing percutaneous coronary intervention (PCI), coronary angiography is the standard method for guiding the placement of the stent. It is unclear whether routine measurement of fractional flow reserve (FFR; the ratio of maximal blood flow in a stenotic artery to normal maximal flow), in addition to angiography, improves outcomes.

METHODS

In 20 medical centers in the United States and Europe, we randomly assigned 1005 patients with multivessel coronary artery disease to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography. Before randomization, lesions requiring PCI were identified on the basis of their angiographic appearance. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was 0.80 or less. The primary end point was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year.

RESULTS

The mean (±SD) number of indicated lesions per patient was 2.7±0.9 in the angiography group and 2.8±1.0 in the FFR group (P=0.34). The number of stents used per patient was 2.7±1.2 and 1.9±1.3, respectively (P<0.001). The 1-year event rate was 18.3% (91 patients) in the angiography group and 13.2% (67 patients) in the FFR group (P=0.02). Seventy-eight percent of the patients in the angiography group were free from angina at 1 year, as compared with 81% of patients in the FFR group (P=0.20).

CONCLUSIONS

Routine measurement of FFR in patients with multivessel coronary artery disease who are undergoing PCI with drug-eluting stents significantly reduces the rate of the composite end point of death, nonfatal myocardial infarction, and repeat revascularization at 1 year. (ClinicalTrials.gov number, NCT00267774.)

From the Catharina Hospital, Eindhoven, the Netherlands (P.A.L.T., N.H.J.P., M.V.); Cardiovascular Center Aalst, Aalst, Belgium (B.D.B.); University of Health Sciences, Medical Informatics, and Technology, Hall in Tirol, Austria, and Massachusetts General Hospital, Harvard Medical School, Boston (U.S.); Stanford University Medical Center and Palo Alto Veterans Affairs Health Care Systems, Stanford, CA (F.I., W.F.F.); Medizinische Poliklinik, Campus-Innenstadt, University Hospital, Munich, Germany (V.K.); the Heart Centre, Royal Victoria Hospital, Belfast, United Kingdom (G.M.); Rigshopitalet, Copenhagen (T.E.); Western Infirmary, Glasgow, United Kingdom (K.G.O.); Northeast Cardiology Associates, Bangor, ME (P.N.V.L.); and King's College Hospital, London (P.A.M.). Address reprint requests to Dr. Pijls at the Department of Cardiology, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands, or at nico.pijls@inter.nl.net.

*The investigators participating in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study are listed in the Appendix.

N Engl J Med 2009;360:213-24.

Non-invasive functional testing in 2014

Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Möbius-Winkler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D., Ole Frobert, M.D., Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Verlee, M.D., Nick Curzen, B.M., Ph.D., Jane B. Johnson, R.N., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D., for the FAME 2 Trial Investigators*

ABSTRACT

BACKGROUND

The preferred initial treatment for patients with stable coronary artery disease is the best available medical therapy. We hypothesized that in patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), percutaneous coronary intervention (PCI) plus the best available medical therapy would be superior to the best available medical therapy alone.

METHODS

In patients with stable coronary artery disease for whom PCI was being considered, we assessed all stenoses by measuring FFR. Patients in whom at least one stenosis was functionally significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Patients in whom all stenoses had an FFR of more than 0.80 were entered into a registry and received the best available medical therapy. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

RESULTS

Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical-therapy group (hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% vs. 11.1%; hazard ratio, 0.13; 95% CI, 0.06 to 0.30; P<0.001); in particular, in the PCI group, fewer urgent revascularizations were triggered by a myocardial infarction or evidence of ischemia on electrocardiography (hazard ratio, 0.13; 95% CI, 0.04 to 0.43; P<0.001). Among patients in the registry, 3.0% had a primary end-point ev

CONCLUSIONS

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From the Cardiovascular Center Aalst, Onze-Lieve-Vrouw Clinic Aalst, Belgium (B.D.B., E.B.); Department of Cardiology, Catharina Hospital, Eindhoven, Biomedical Engineering — both in Eindhoven, University of Technology, Eindhoven, the Netherlands (N.H.J.P., P.A.L.T.); Division of Clinical Epidemiology and Biostatistics, Institute of Social and Preventive Medicine and Clinical Trials Unit, University of Bern, Bern, Switzerland (B.K., P.J.); Hungarian Institute of Cardiology, Budapest (Z.P.); Clinical Center Kragujevac, Kragujevac, Serbia (N.J.); Heart Center Leipzig, Leipzig, Germany (G.M.-W.); Cardiovascular Hospital, Lyon, France (G.R.); Södersjukhuset, Stockholm (N.W.), and Örebro University Hospital, Örebro (O.F.) — both in Sweden; Department of Internal Medicine and Cardiology, University Hospital Brno, Brno, Czech Republic (P.K.); King's College Hospital, London (P.M.); Golden Jubilee National Hospital, Glasgow (K.G.O.); Royal Victoria Hospital, Belfast (G.M.), and Department of Cardiology, Southampton University Hospital Trust, Southampton (N.C.) — all in the United Kingdom; Department of Cardiology, Rigshospitalet, Copenhagen (T.E.); Atlanta Veterans Affairs Medical Center, Atlanta (K.M.); Northeast Cardiology Associates, Bangor, ME (P.V.); St. Jude Medical, Plymouth, MN (J.B.J.); and Stanford University Medical Center, Stanford, CA (W.F.F.). Address reprint requests to Dr. De Bruyne at the Cardiovascular Centre Aalst, OLV Clinic, Moorselbaan 164, B-9300 Aalst, Belgium, or at bernard.de.bruyne@olvz-aalst.be.

*The investigators in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME 2) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Economic Evaluation of Fractional Flow Reserve–Guided Percutaneous Coronary Intervention in Patients With Multivessel Disease

William F. Fearon, MD; Bernhard Bornschein, MD, MPH; Pim A.L. Tonino, MD, PhD; Raffaella M. Gothe, BS; Bernard De Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD; Uwe Siebert, MD, MPH, MSc, ScD; for the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) Study Investigators

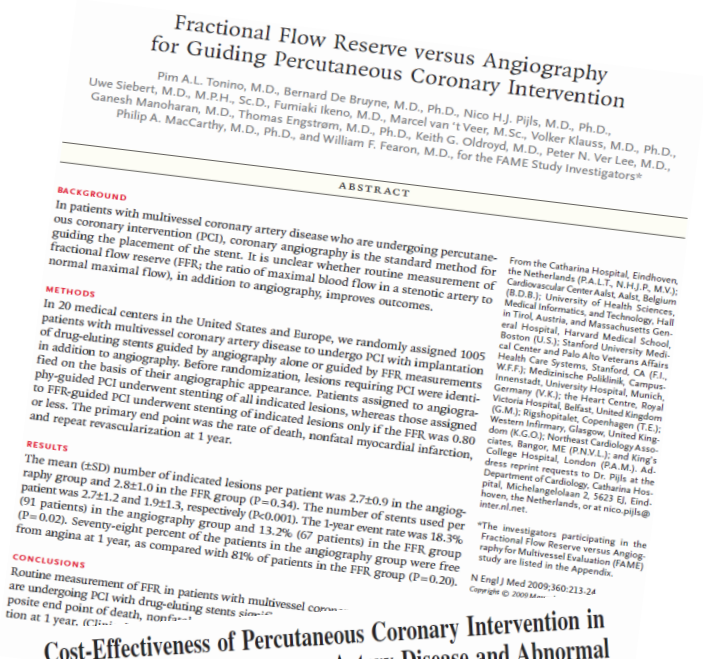
Background—The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) study demonstrated significantly improved health outcomes at 1 year in patients randomized to multivessel percutaneous coronary intervention guided by fractional flow reserve (FFR) compared with percutaneous coronary intervention guided by angiography alone. The economic impact of routine measurement of FFR in this setting is not known.

Methods and Results—In this study, 1005 patients were randomly assigned to FFR-guided or angiography-guided percutaneous coronary intervention and followed up for 1 year. A prospective cost-utility analysis comparing costs and quality-adjusted life-years was performed with a time horizon of 1 year. Quality-adjusted life-years were calculated with the use of utilities determined by the EuroQol 5 dimension health survey with US weights. Direct medical costs included those of the index procedure and hospitalization and costs for major adverse cardiac events during follow-up. Confidence intervals for both quality-adjusted life-years and costs were estimated by the bootstrap percentile method. Major adverse cardiac events at 1 year occurred in 13.2% of those in the FFR-guided arm and 18.3% of those in the angiography-guided arm ($P=0.02$). Quality-adjusted life-years were slightly greater in the FFR-guided arm (0.853 versus 0.838; $P=0.2$). Mean overall costs at 1 year were significantly less in the FFR-guided arm ($14 315 versus $16 700; $P<0.001$). Bootstrap simulation indicated that the FFR-guided strategy was cost-saving in 90.74% and cost-effective at a threshold of US $50 000 per quality-adjusted life-years in 99.96%. Sensitivity analyses demonstrated robust results.

Conclusion—Economic evaluation of the FAME study reveals that FFR-guided percutaneous coronary intervention in patients with multivessel coronary disease is one of those rare situations in which a new technology not only improves outcomes but also saves resources.

Clinical Trial Registration—URL: http://ClinicalTrials.gov. Unique identifier: NCT00267774. (***Circulation***. **2010;122:2545-2550.**)

Key Words: angiography ■ coronary disease ■ cost-benefit analysis ■ fractional flow reserve, myocardial ■ physiology ■ stents



Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

Pim A.L. Tonino, M.D., Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Uwe Siebert, M.D., M.P.H., Sc.D., Fumiaki Ikeno, M.D., Marcel van 't Veer, M.Sc., Volker Klauss, M.D., Ph.D., Ganesh Manoharan, M.D., Thomas Engstrøm, M.D., Ph.D., Keith G. Oldroyd, M.D., Peter N. Ver Lee, M.D., Philip A. MacCarthy, M.D., Ph.D., and William F. Fearon, M.D., for the FAME Study Investigators*

ABSTRACT

BACKGROUND

In patients with multivessel coronary artery disease who are undergoing percutaneous coronary intervention (PCI), coronary angiography is the standard method for guiding the placement of the stent. It is unclear whether routine measurement of fractional flow reserve (FFR; the ratio of maximal blood flow in a stenotic artery to normal maximal flow), in addition to angiography, improves outcomes.

METHODS

In 20 medical centers in the United States and Europe, we randomly assigned 1005 patients with multivessel coronary artery disease to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography. Before randomization, lesions requiring PCI were identified on the basis of their angiographic appearance. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was 0.80 or less. The primary end point was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year.

RESULTS

The mean (±SD) number of indicated lesions per patient was 2.7±0.9 in the angiography group and 2.8±1.0 in the FFR group ($P=0.34$). The number of stents used per patient was 2.7±1.2 and 1.9±1.3, respectively ($P<0.001$). The 1-year event rate was 18.3% (91 patients) in the angiography group and 13.2% (67 patients) in the FFR group ($P=0.02$). Seventy-eight percent of the patients in the angiography group were free from angina at 1 year, as compared with 81% of patients in the FFR group ($P=0.20$).

CONCLUSIONS

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From the Catharina Hospital, Eindhoven, the Netherlands (P.A.L.T., N.H.J.P., M.V.); Cardiovascular Center Aalst, Aalst, Belgium (B.D.B.); University of Health Sciences, Medical Informatics, and Technology, Hall in Tirol, Austria, and Massachusetts General Hospital, Harvard Medical School, Boston (U.S.); Stanford University Medical Center and Palo Alto Veterans Affairs Health Care Systems, Stanford, CA (F.I., W.F.F.); Medizinische Poliklinik, Campus-Innenstadt, University Hospital, Munich, Germany (V.K.); the Heart Centre, Royal Victoria Hospital, Belfast, United Kingdom (G.M.); Rigshospitalet, Copenhagen (T.E.); Western Infirmary, Glasgow, United Kingdom (K.G.O.); Northeast Cardiology Associates, Bangor, ME (P.N.V.L.); and King's College Hospital, London (P.A.M.). Address reprint requests to Dr. Pijls at the Department of Cardiology, Catharina Hospital, Michelangelolaan 2, 5623 EJ, Eindhoven, the Netherlands, or at nico.pijls@inter.nl.net.

*The investigators participating in the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study are listed in the Appendix.

N Engl J Med 2009;360:213-24

Cost-Effectiveness of Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease and Abnormal Fractional Flow Reserve

William F. Fearon, MD; David Shilane, PhD; Nico H.J. Pijls, MD, PhD; Derek B. Boothroyd, PhD; Pim A.L. Tonino, MD, PhD; Emanuele Barbato, MD, PhD; Peter Jüni, MD; Bernard De Bruyne, MD, PhD; Mark A. Hlatky, MD; on behalf of the Fractional Flow Reserve Versus Angiography for Multivessel Evaluation 2 (FAME 2) Investigators

Background—The Fractional Flow Reserve Versus Angiography for Multivessel Evaluation (FAME) 2 trial demonstrated a significant reduction in subsequent coronary revascularization among patients with stable angina and at least 1 coronary lesion with a fractional flow reserve ≤0.80 who were randomized to percutaneous coronary intervention (PCI) compared with best medical therapy. The economic and quality-of-life implications of PCI in the setting of an abnormal fractional flow reserve are unknown.

Methods and Results—We calculated the cost of the index hospitalization based on initial resource use and follow-up costs based on Medicare reimbursements. We assessed patient utility using the EQ-5D health survey with US weights at baseline and 1 month and projected quality-adjusted life-years assuming a linear decline over 3 years in the 1-month utility improvements. We calculated the incremental cost-effectiveness ratio based on cumulative costs over 12 months. Initial costs were significantly higher for PCI in the setting of an abnormal fractional flow reserve than with medical therapy ($9927 versus $3900, $P<0.001$), but the $6027 difference narrowed over 1-year follow-up to $2883 ($P<0.001$), mostly because of the cost of subsequent revascularization procedures. Patient utility was improved more at 1 month with PCI than with medical therapy (0.054 versus 0.001 units, $P<0.001$). The incremental cost-effectiveness ratio of PCI was $36 000 per quality-adjusted life-year, which was robust in bootstrap replications and in sensitivity analyses.

Conclusions—PCI of coronary lesions with reduced fractional flow reserve improves outcomes and appears economically attractive compared with best medical therapy among patients with stable angina.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01132495. (***Circulation***. **2013;128:1335-1340.**)

Non-invasive functional testing in 2014

Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Möbius-Winkler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D., Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D., Jane B. Johnson, R.N., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D., for the FAME 2 Trial Investigators*

ABSTRACT

BACKGROUND
The preferred initial treatment for patients with stable coronary artery disease is the best available medical therapy. We hypothesized that in patients with functionally significant stenoses, as determined by measurement of fractional flow reserve (FFR), percutaneous coronary intervention (PCI) plus the best available medical therapy would be superior to the best available medical therapy alone.

METHODS
In patients with stable coronary artery disease for whom PCI was being considered, we assessed all stenoses by measuring FFR. Patients in whom at least one stenosis was functionally significant (FFR, ≤0.80) were randomly assigned to FFR-guided PCI plus the best available medical therapy (PCI group) or the best available medical therapy alone (medical-therapy group). Patients in whom all stenoses had an FFR of more than 0.80 were entered into a registry and received the best available medical therapy. The primary end point was a composite of death, myocardial infarction, or urgent revascularization.

RESULTS
Recruitment was halted prematurely after enrollment of 1220 patients (888 who underwent randomization and 332 enrolled in the registry) because of a significant between-group difference in the percentage of patients who had a primary end-point event: 4.3% in the PCI group and 12.7% in the medical-therapy group (hazard ratio with PCI, 0.32; 95% confidence interval [CI], 0.19 to 0.53; P<0.001). The difference was driven by a lower rate of urgent revascularization in the PCI group than in the medical-therapy group (1.6% vs. 11.1%; hazard ratio, 0.13; 95% CI, 0.06 to 0.30; P<0.001); in particular, in the PCI group, fewer urgent revascularizations were triggered by a myocardial infarction or evidence of ischemia on electrocardiography (hazard ratio, 0.13; 95% CI, 0.04 to 0.43; P<0.001). Among patients in the registry, 3.0% had a primary end-point ev

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This article was published on August 28, 2012, at

Economic Evaluation of Fractional Flow Reserve–Guided Percutaneous Coronary Intervention in Patients With Multivessel Disease

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Conclusion—Economic evaluation of the FAME study reveals that FFR-guided percutaneous coronary intervention in patients with multivessel coronary disease is one of those rare situations in which a new technology not only improves outcomes but also saves resources.

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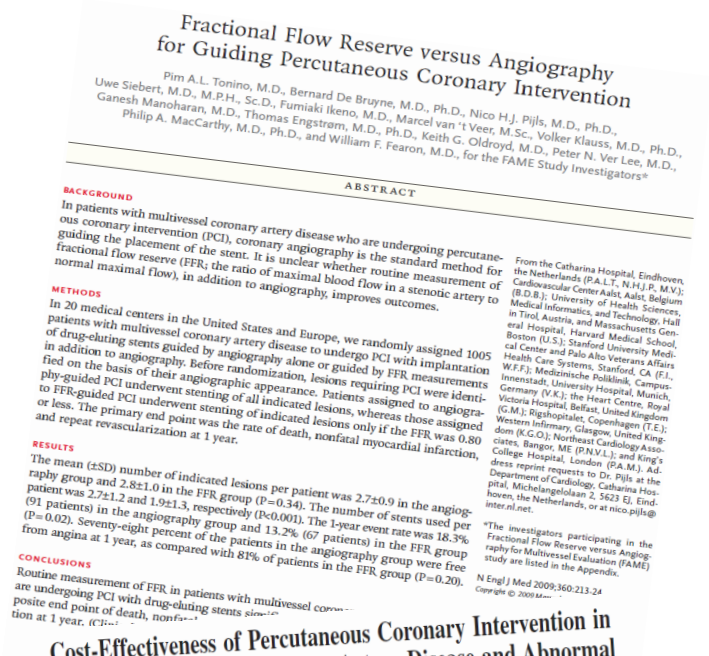

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In patients with multivessel coronary artery disease who are undergoing percutaneous coronary intervention (PCI), coronary angiography is the standard method for guiding the placement of the stent. It is unclear whether routine measurement of fractional flow reserve (FFR; the ratio of maximal blood flow in a stenotic artery to normal maximal flow), in addition to angiography, improves outcomes.

METHODS
In 20 medical centers in the United States and Europe, we randomly assigned 1005 patients with multivessel coronary artery disease to undergo PCI with implantation of drug-eluting stents guided by angiography alone or guided by FFR measurements in addition to angiography. Before randomization, lesions requiring PCI were identified on the basis of their angiographic appearance. Patients assigned to angiography-guided PCI underwent stenting of all indicated lesions, whereas those assigned to FFR-guided PCI underwent stenting of indicated lesions only if the FFR was 0.80 or less. The primary end point was the rate of death, nonfatal myocardial infarction, and repeat revascularization at 1 year.

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N Engl J Med 2009;360:213-24

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Invasive Fractional Flow Reserve (FFR) has emerged as the gold standard "bridge" test to determine optimal (medical vs. PCI) artery-specific therapy

Non-invasive functional testing in 2014

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Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

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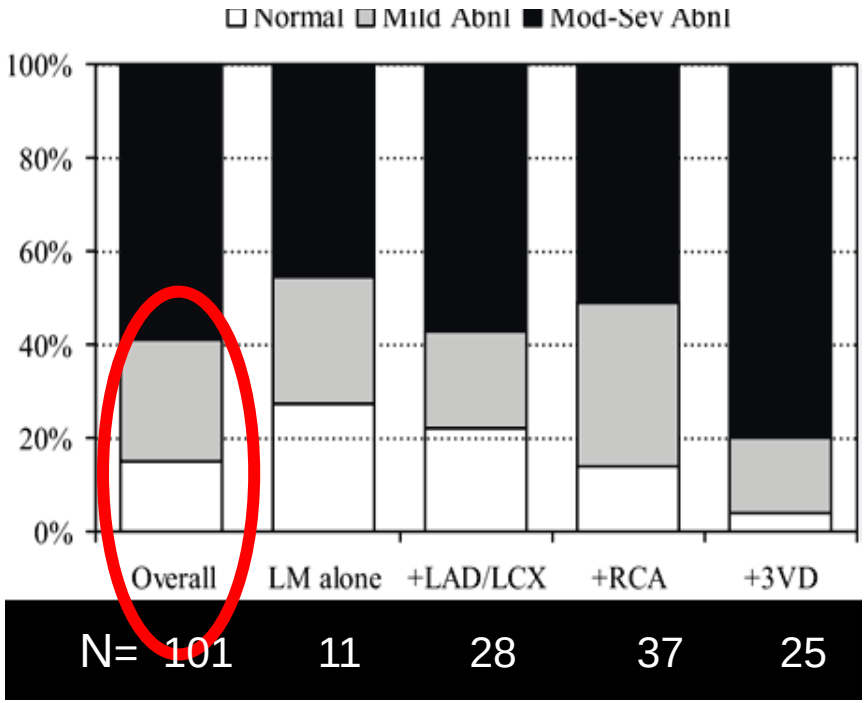
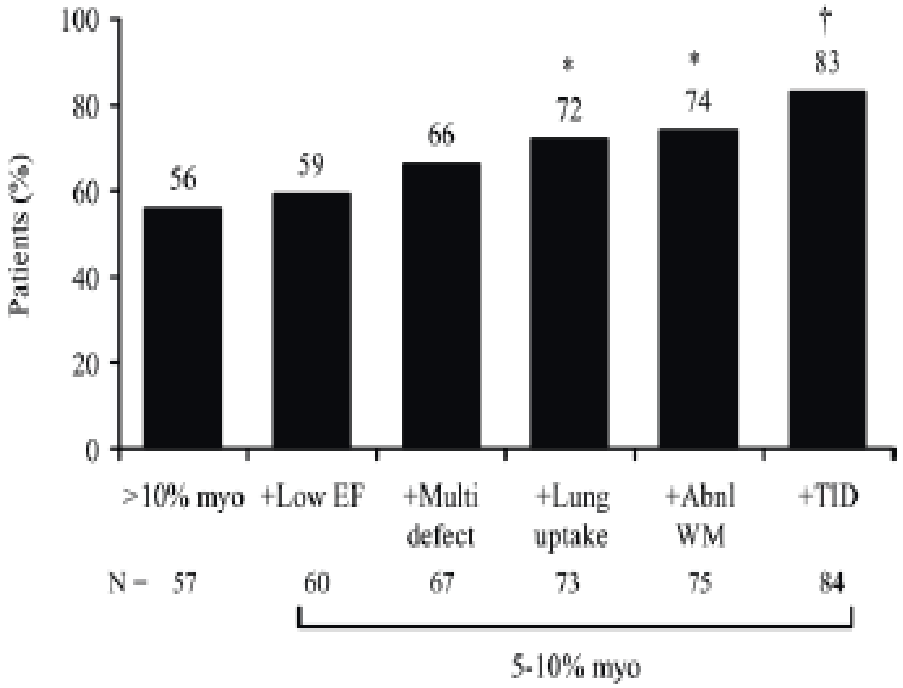
The diagnostic performance of non-invasive testing modalities should be tested using FFR as the gold standard

Non-invasive functional testing in 2014, *CAD diagnosis*



- 101 patients with left main CAD (>50%), RCA/LAD/Cx >70%
- No prior MI or revasc.
- Exercise or adenosine gated sestambi SPECT
- **MPI high risk: myocardium stress >10% or 5-10% + >1 non-perfusion abnormalities**



Berman DS , J Nucl Cardiol 2007