Functional assessment (invasive) of Coronary Circulation

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www.cardio-aalst.be

Potential conflicts of interest

- Consulting fees and honoraria on my behalf go to the Cardiovascular Research Center Aalst

- Contracted Research between the Cardiovascular Research Center Aalst and the following pharmaceutical and device companies:

  Ablynx, Astra Zeneca, BMS, Eli Lilly, GSK, Therabel, Abbott Vascular, Biotronik, Boston Scientific, Cordis J&J, Edwards, Medtronic, Orbus Neich, St Jude, Terumo

- Ownership Interest: Cardiovascular Research Center Aalst is co-founder of Cardio³BioSciences, a start-up company focusing on cell-based regenerative cardiovascular therapies

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Why do we need functional assessment?

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Event Rates after a Negative Functional Stress Testing

Myocardial Perfusion Imaging or Stress Echocardiography

Table 4 Summary Estimates of Rates After a Negative Test and Negative Predictive Value for Myocardial Infarction or Cardiac Death for Women and Men in Exercise Myocardial Perfusion Imaging and Exercise Echo

Exercise Imaging Modality	n	Mean Follow-Up (Months)	Summary Event Rate After Negative Test (%) (95% CI)	Negative Predictive Value (%) (95% CI)	Annualized Event Rate (%)
MPI			Myocardial Perfusion Imaging		
All	2,900	32	1.03 (0.70–1.48)	99.0 (98.5–99.3)	0.58
Women	1,443	32	0.69 (0.33–1.27)	99.3 (98.7–99.7)	0.33
Men	1,457	20	1.37 (0.84–2.12)	98.6 (97.9–99.2)	0.82
Echo			Stress Echocardiography		
All	5,946	37.6	3.23 (2.70–3.82)	96.8 (96.2–97.3)	1.03
Women	2,547	37.6	2.34 (1.71–3.13)	97.7 (96.9–98.3)	0.75
Men	3,399	37.6	3.90 (3.12–4.81)	96.1 (95.2–96.9)	1.24

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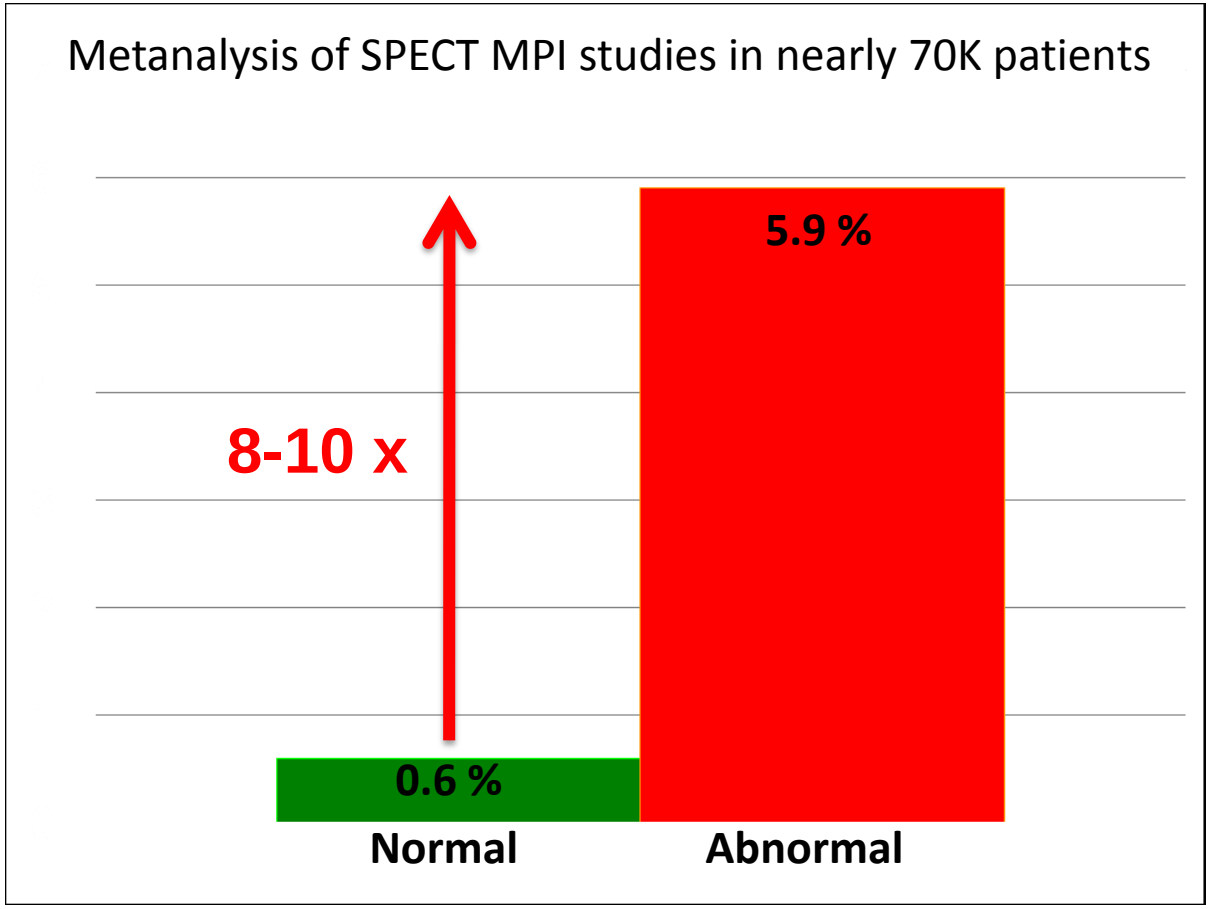
Metz LD et al JACC, 2007

Annual risk of Cardiac Death and Myocardial Infarction



Shaw and Iskandrian J Nucl Cardiol 2004

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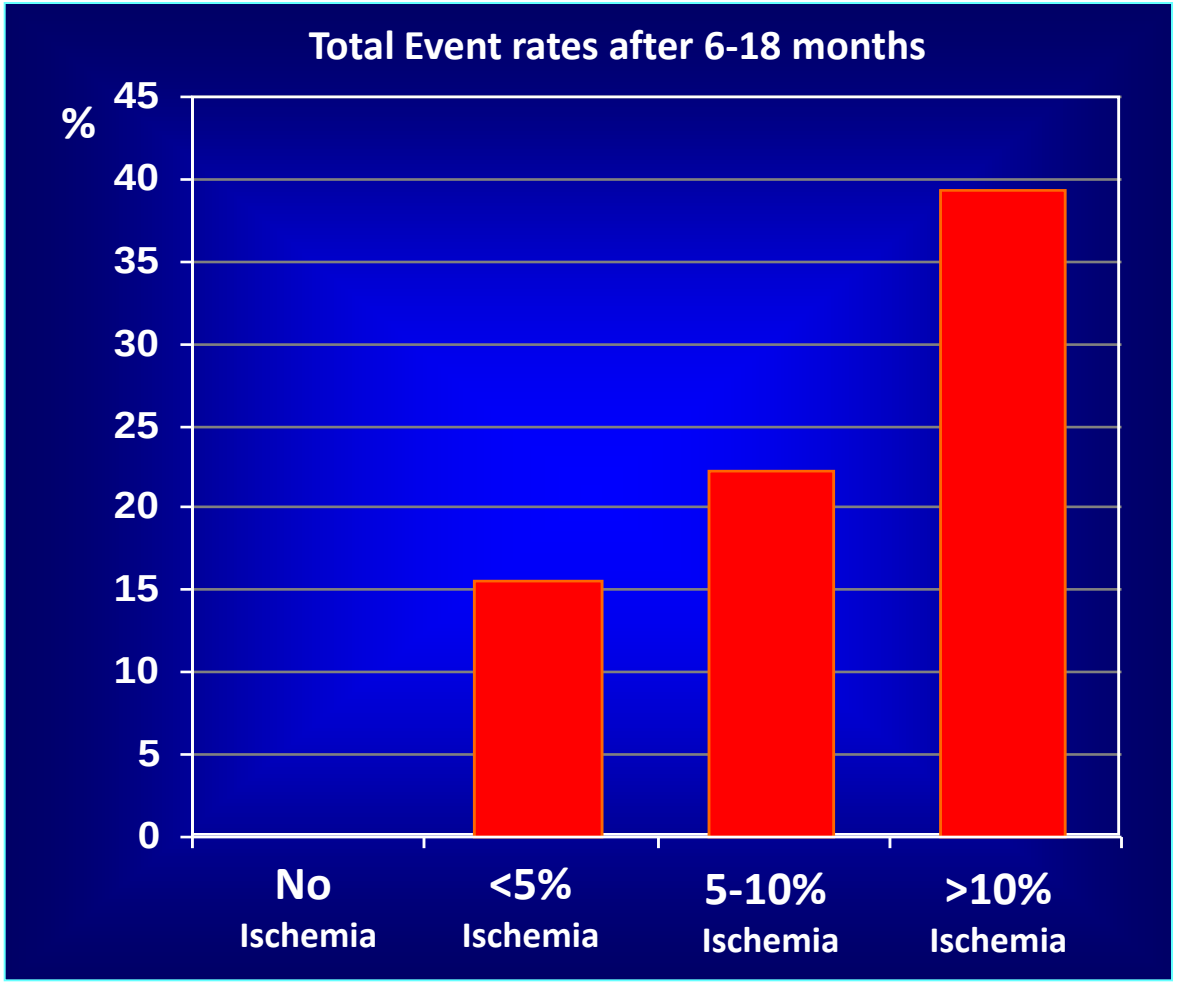
Extent of Functional Assessment abnormality and Cardiovascular Event Rate

- 314 patients with CAD
- After - either PCI+OMT
  - or OMT
- Myocardial perfusion imaging prior and again 6 months after treatment



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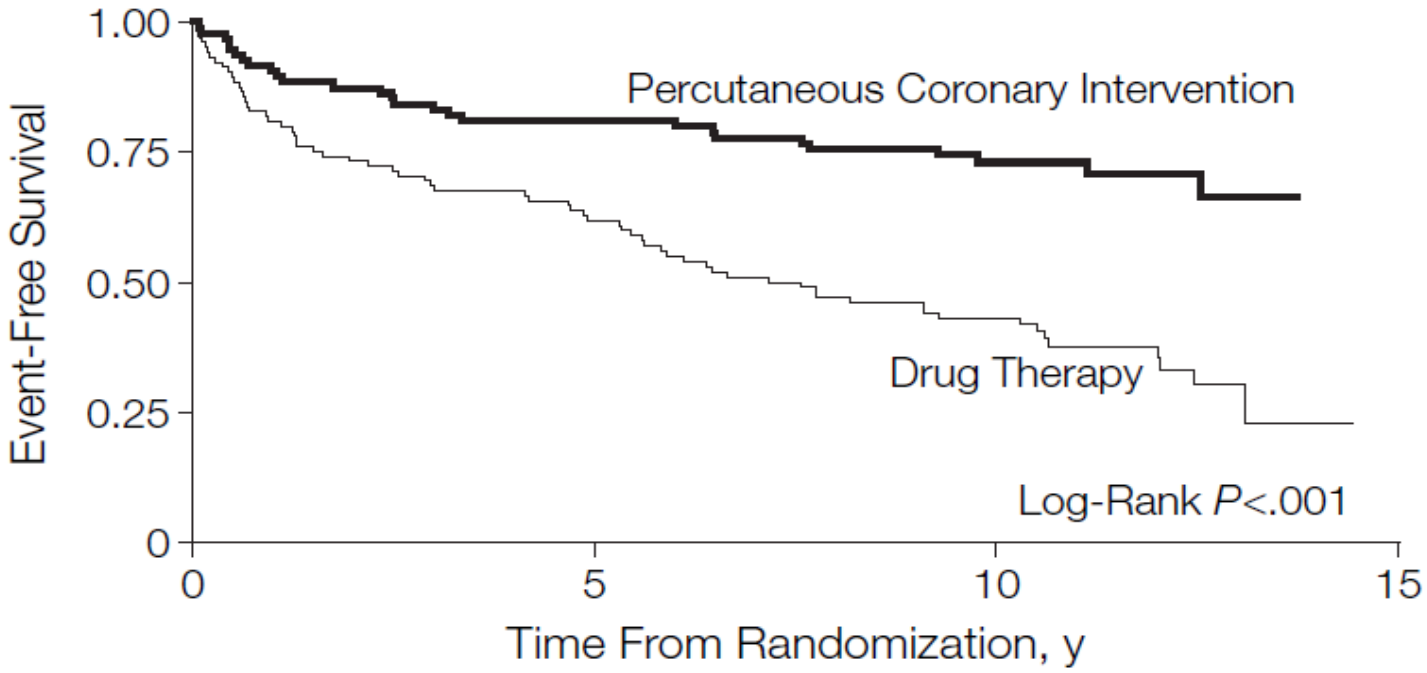
LJ Shaw et al Circulation, 2008

SWISSI II Trial
201 patients with silent ischemia after a myocardial infarction
10 Year-Follow-Up



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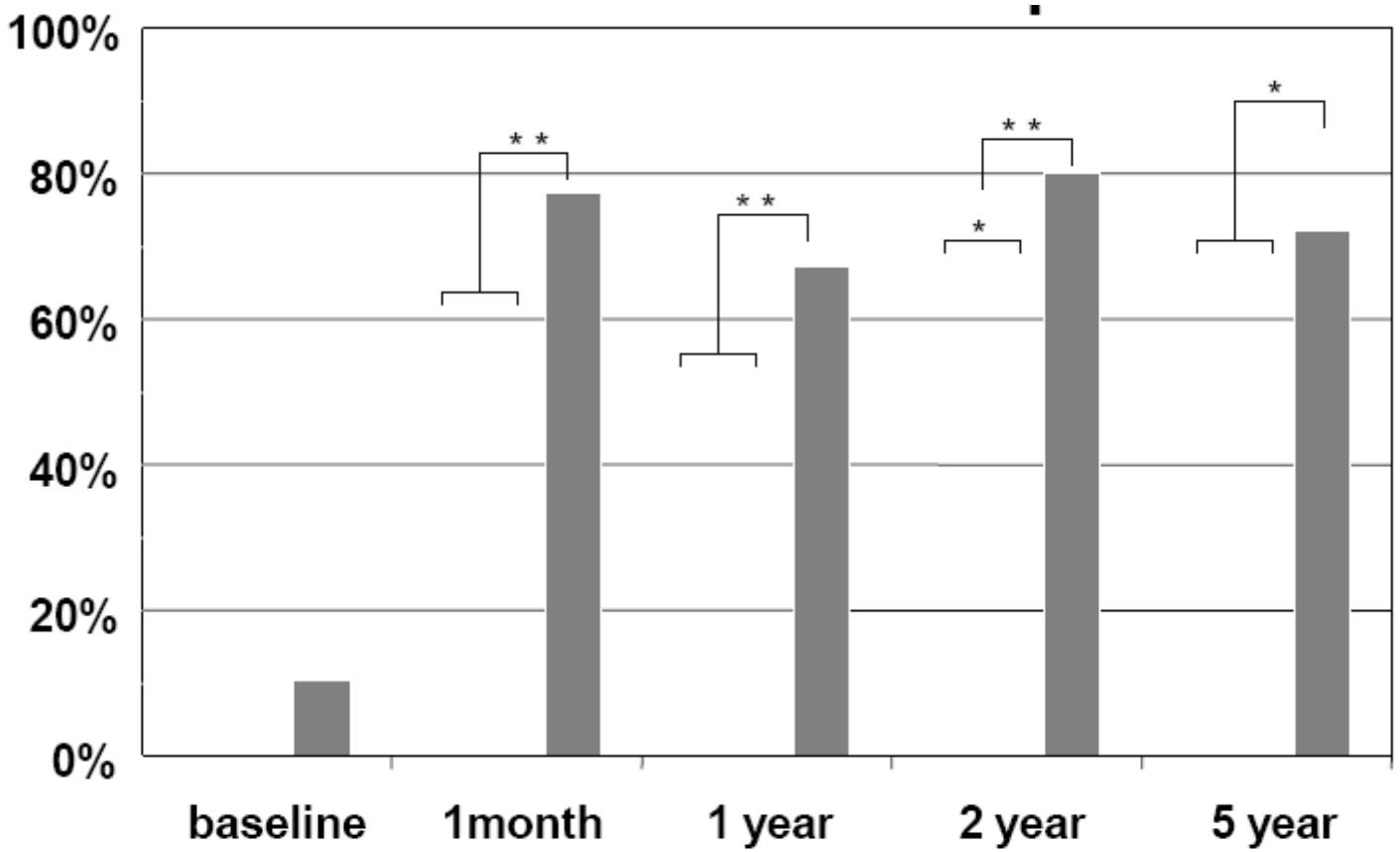
P Erne et al, JAMA 2007

Freedom from Chest-pain



Ischemic lesions (FFR < 0.75)
treated by stenting

Pijls NH et al. JACC 1997

www.cardio-aalst.be

European Heart Journal (2010) 31, 2501–2555
doi:10.1093/eurheartj/ehq277

ESC/EACTS GUIDELINES

Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Developed with the special contribution of the European Association for Percutaneous Cardiovascular Interventions (EAPCI)‡

Authors/Task Force Members: William Wijns (Chairperson) (Belgium)*, Philippe Kolh

... In summary, documentation of ischaemia using functional testing is strongly recommended before elective invasive procedures, preferably using non-invasive testing before invasive angiography

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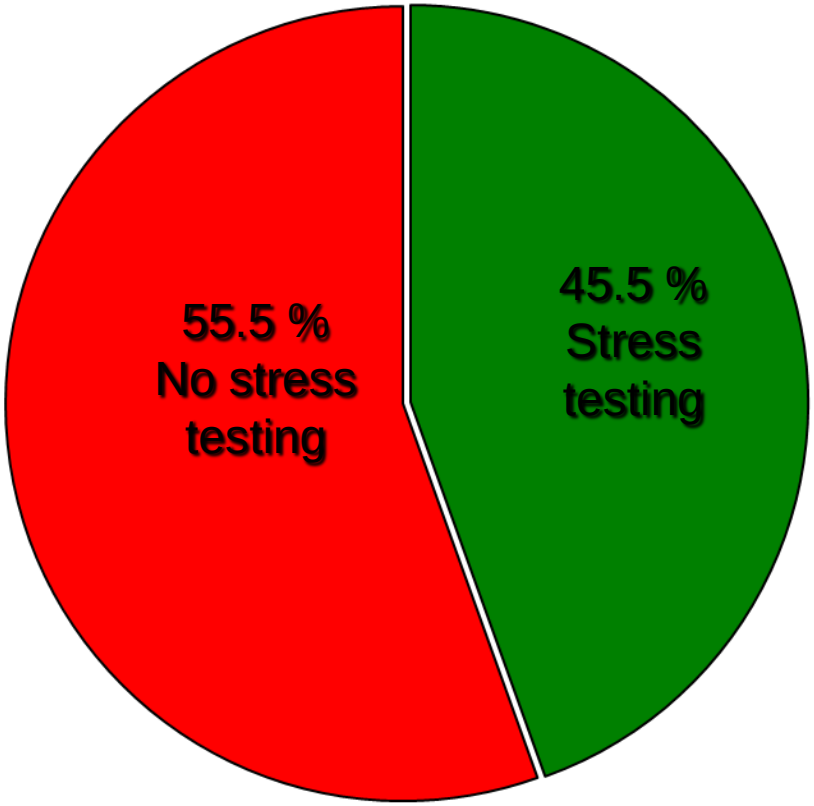
Frequency of stress tests to document ischemia prior to elective CAG+PCI



23887 Medicare patients undergoing *elective* CAG+PCI in 2004

GA Lin et al. JAMA 2008

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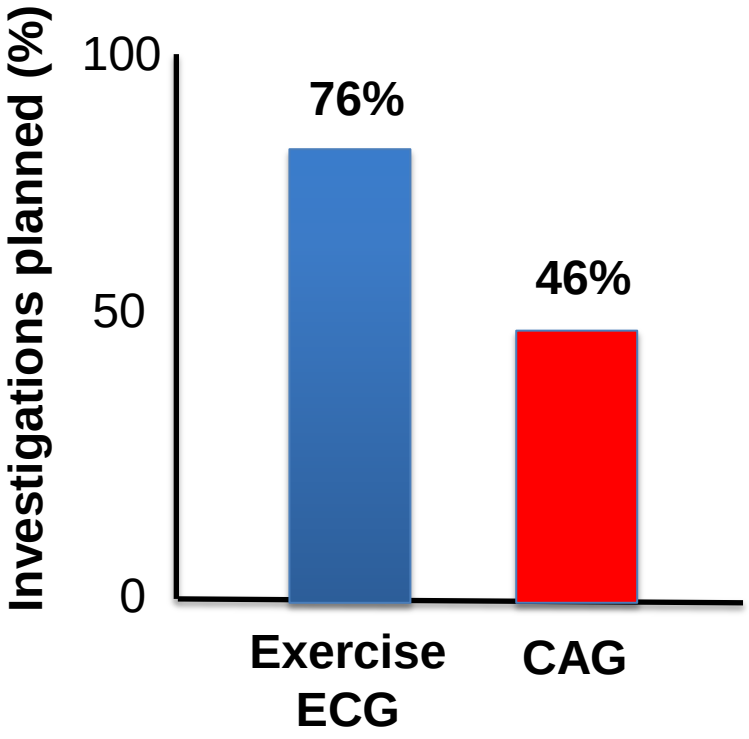
Referral to CAG after the initial consultation



Countries with Low Rate of CAG

- Positive Exercise Test
- Female Gender

Countries with High Rate of CAG

- Positive Exercise Test
- Female Gender
- Invasive Centre
- Symptom duration > 6 months

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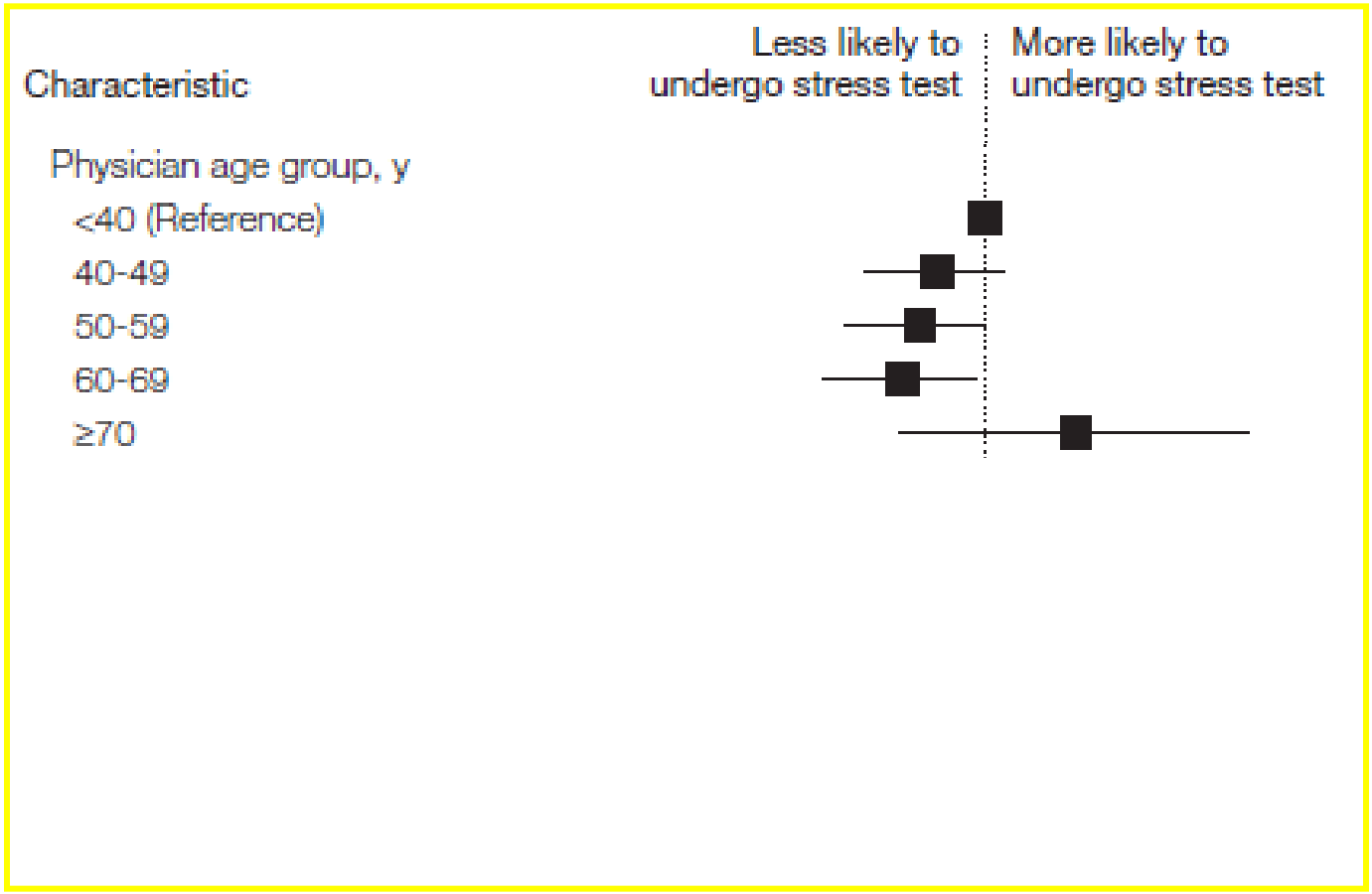
EHS on Stable Angina EHJ 2005

Frequency of Stress Testing to Document Ischemia Prior to Elective CAG+PCI



23887 Medicare patients undergoing *elective* CAG+PCI in 2004

G.A. Lin et al JAMA 2008

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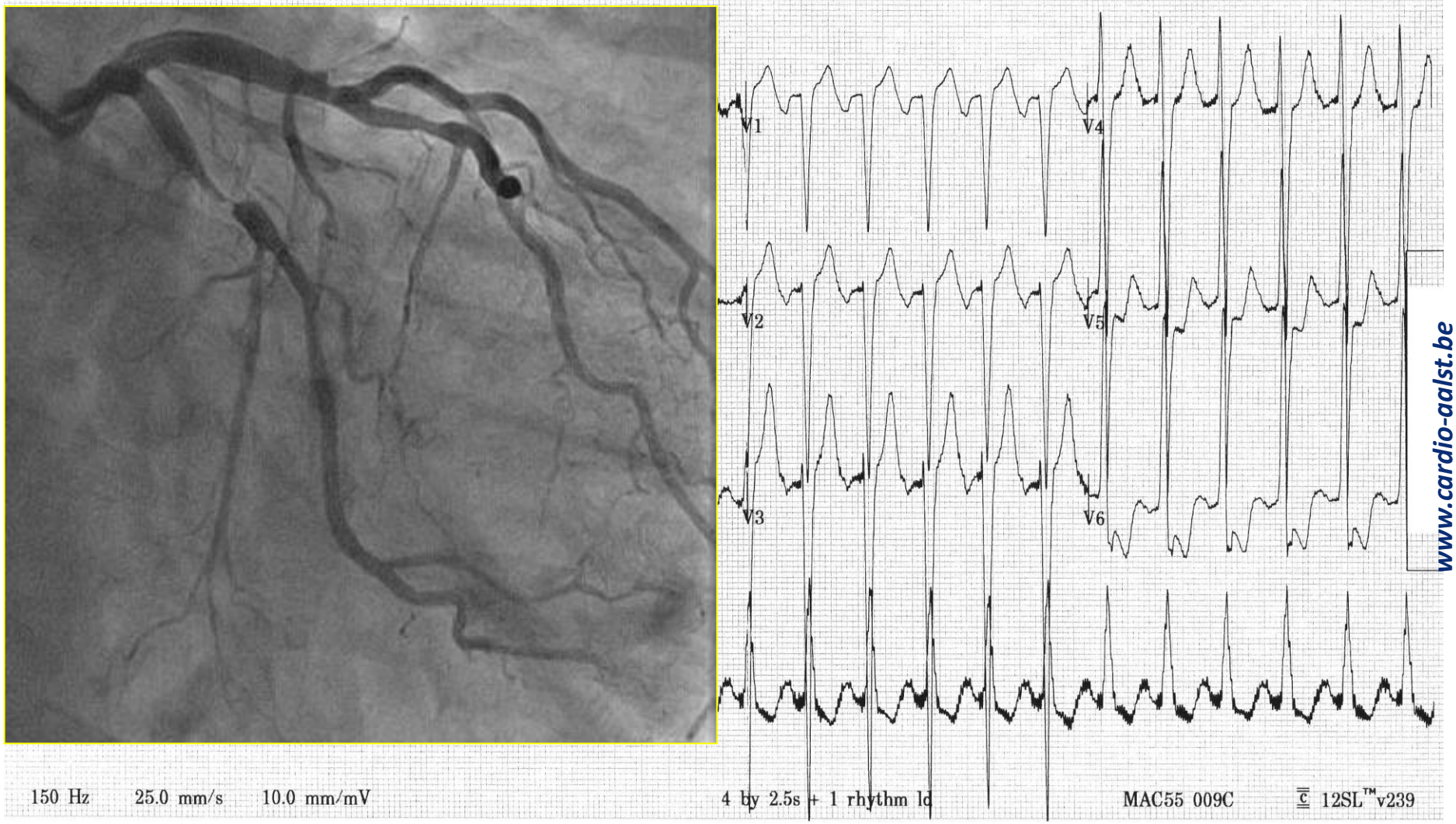

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Clinical conditions in which non-invasive testing Is difficult to interpret

1. During and after acute myocardial infarction
2. Obesity, bundle branch block, …
3. “Intermediate lesion”
4. Left main stenosis
5. Multivessel disease
6. …

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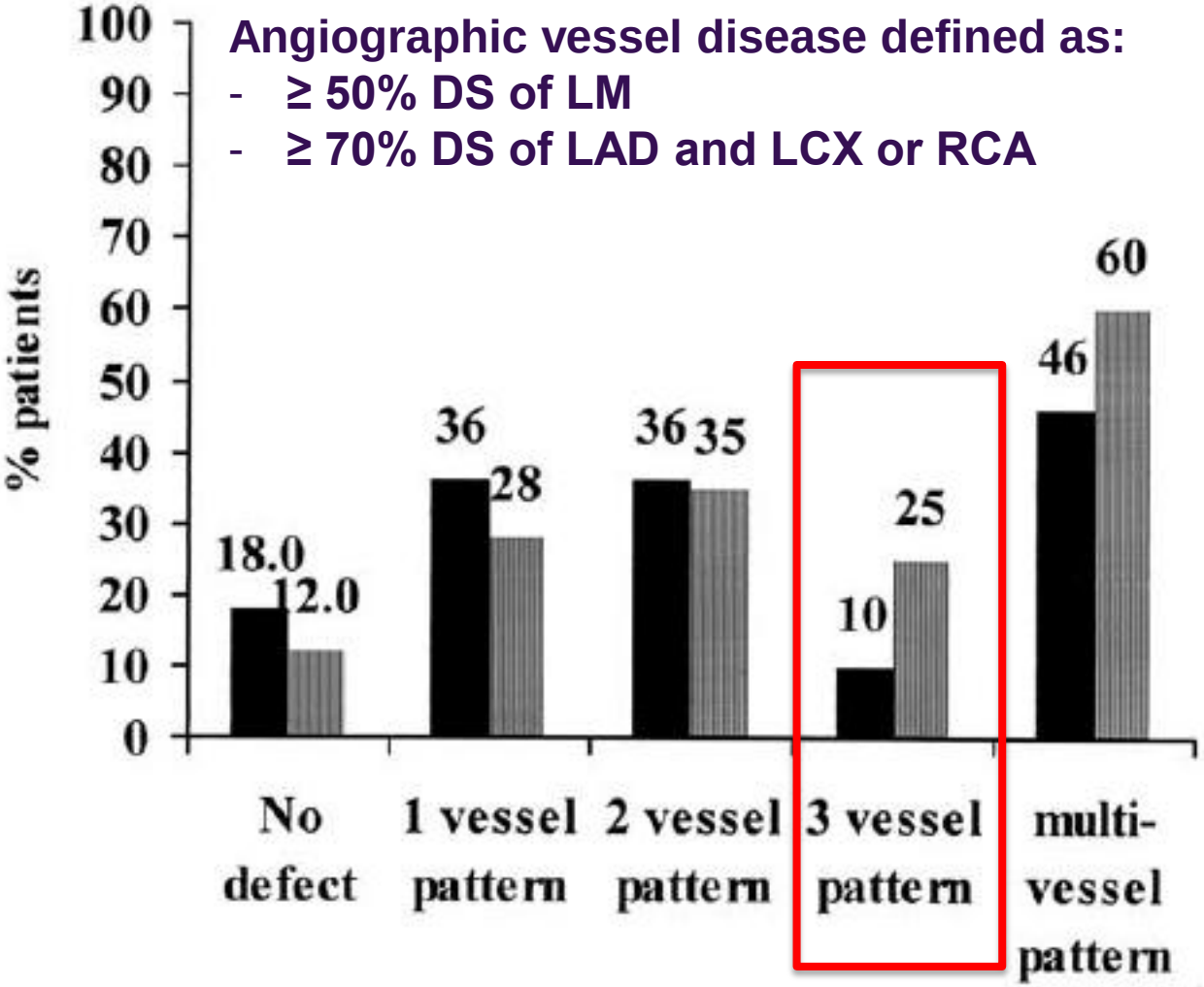
Diagnostic accuracy of ECG-gated SPECT MPI in patients 3-vessel disease



Lima et al. JACC 2003

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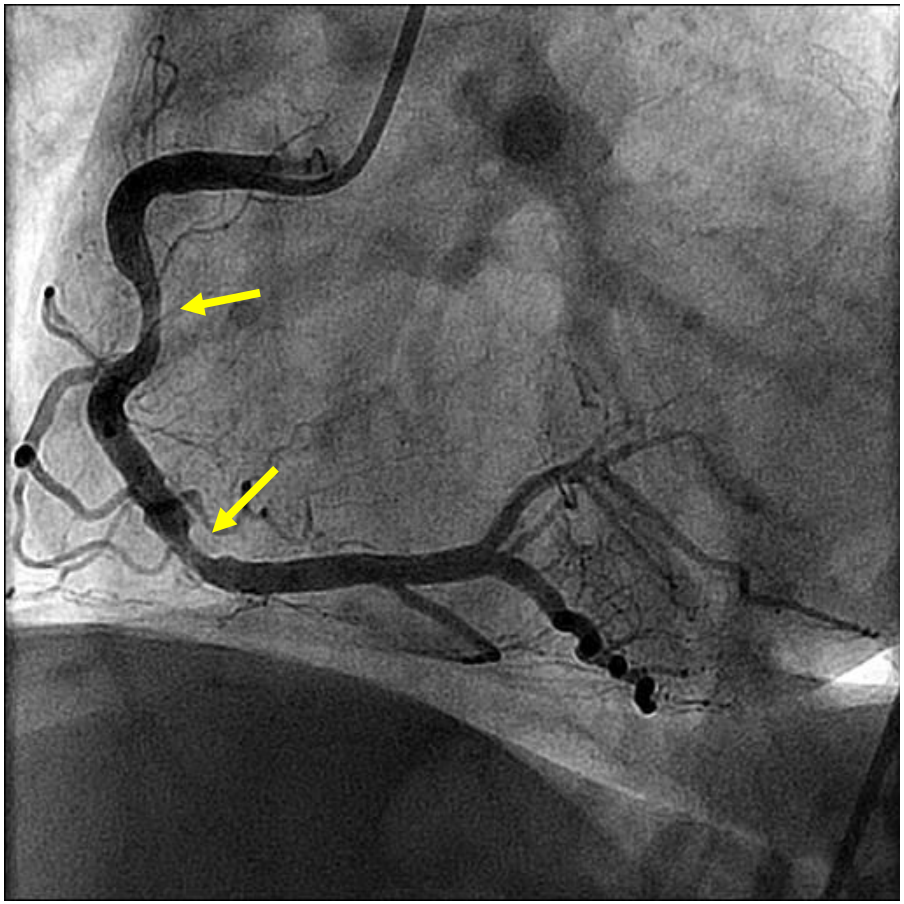

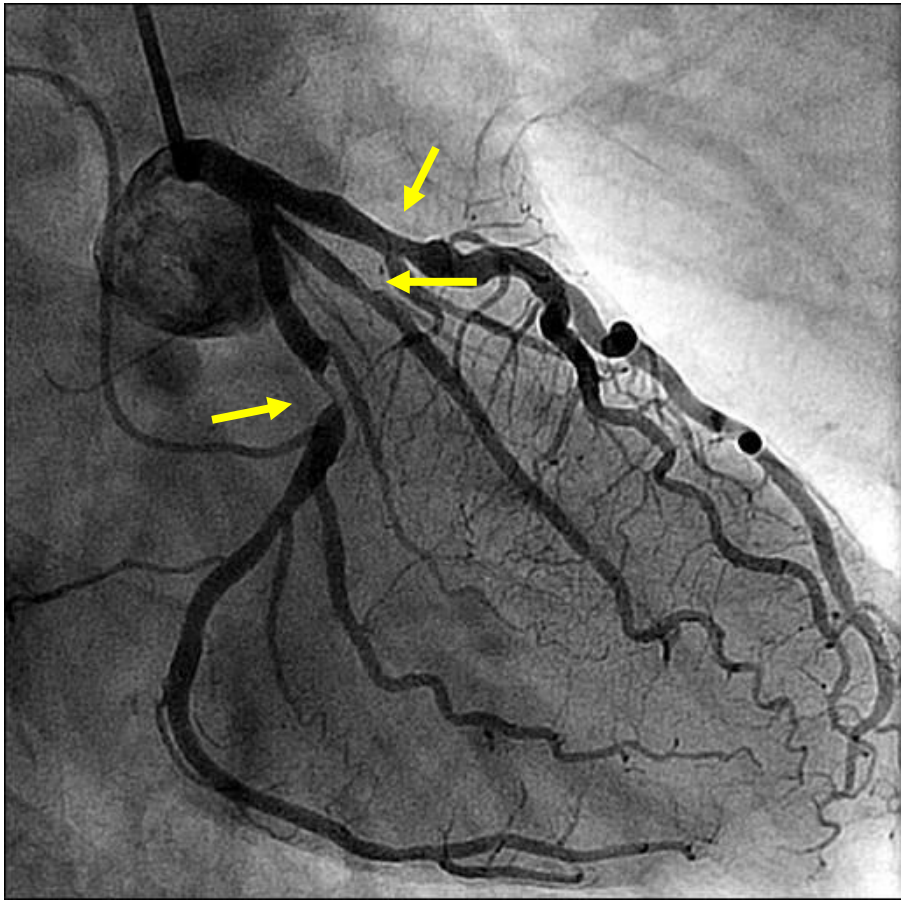

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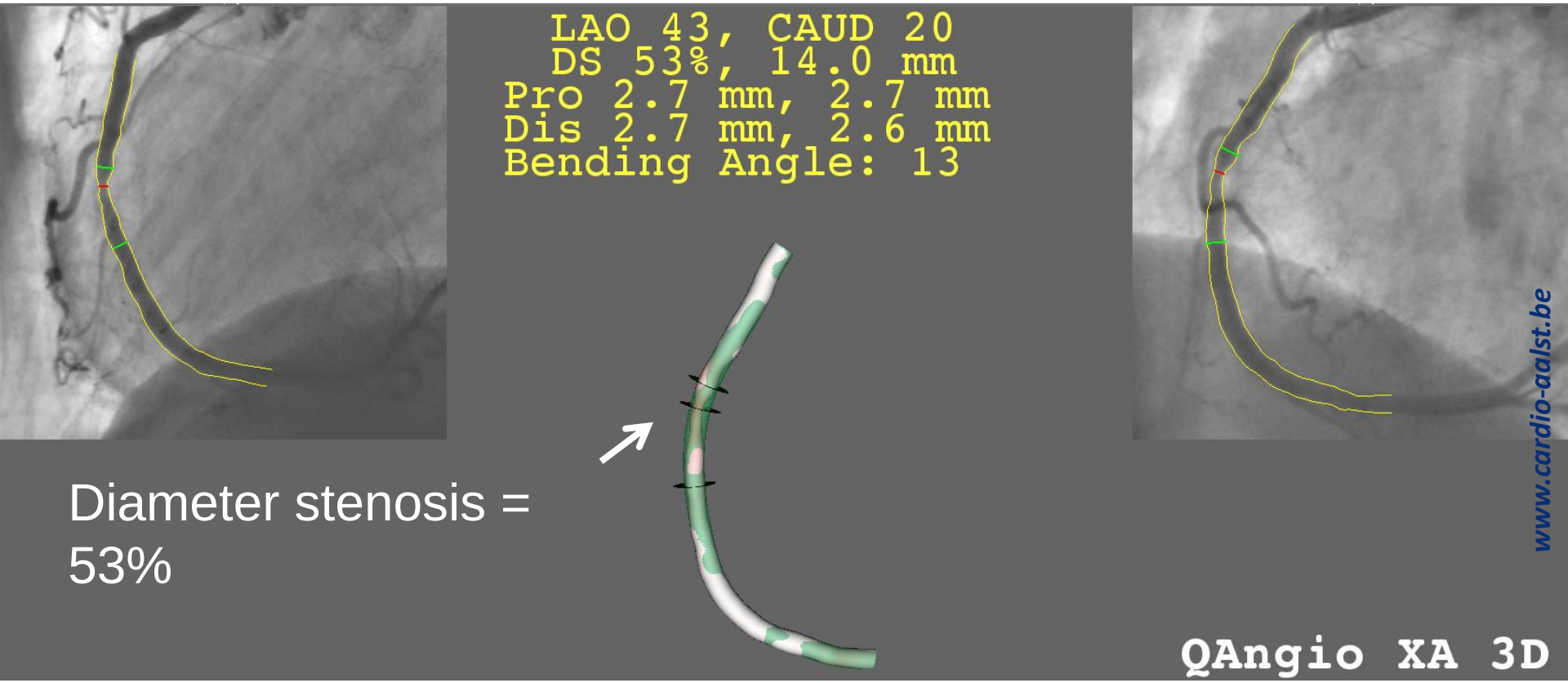
How to proceed?

It is not the question *IF* stenting is indicated, but *WHERE* and *HOW MANY*

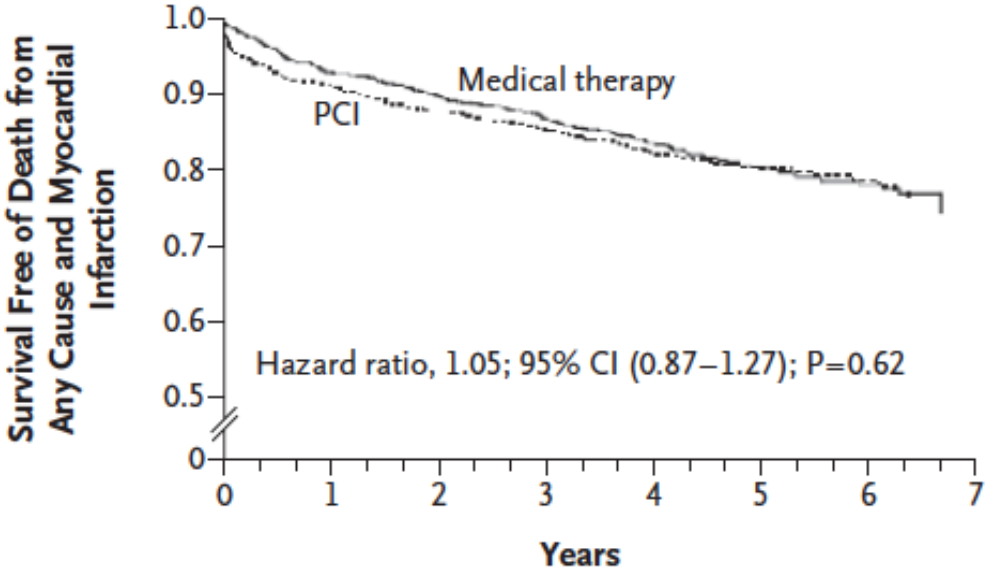
2D and 3D QCA



Diameter stenosis = 53%

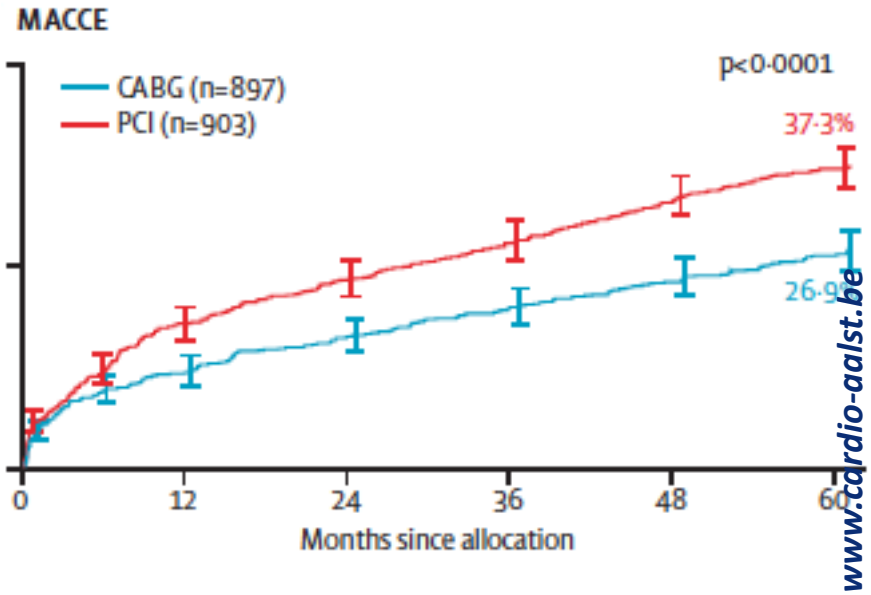
Courtesy of Shengxian Tu

Low-to-intermediate Risk



COURAGE
W.E. Boden et al NEJM 2007

Intermediate-to-high Risk



SYNTAX
F.W. Mohr et al Lancet 2013

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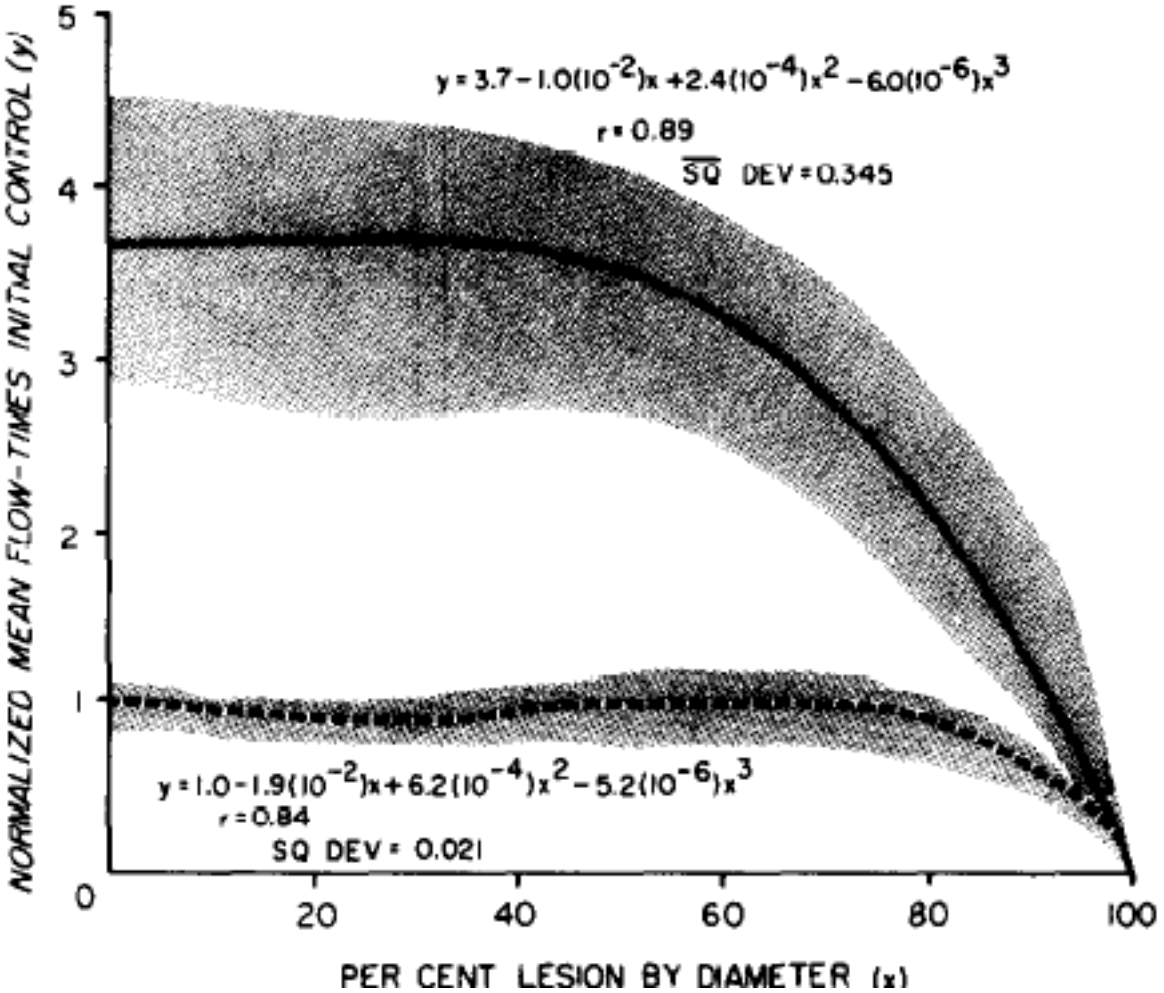
Relationship between %DS and coronary flow



KL Gould et al. Am J Cardiol 1974

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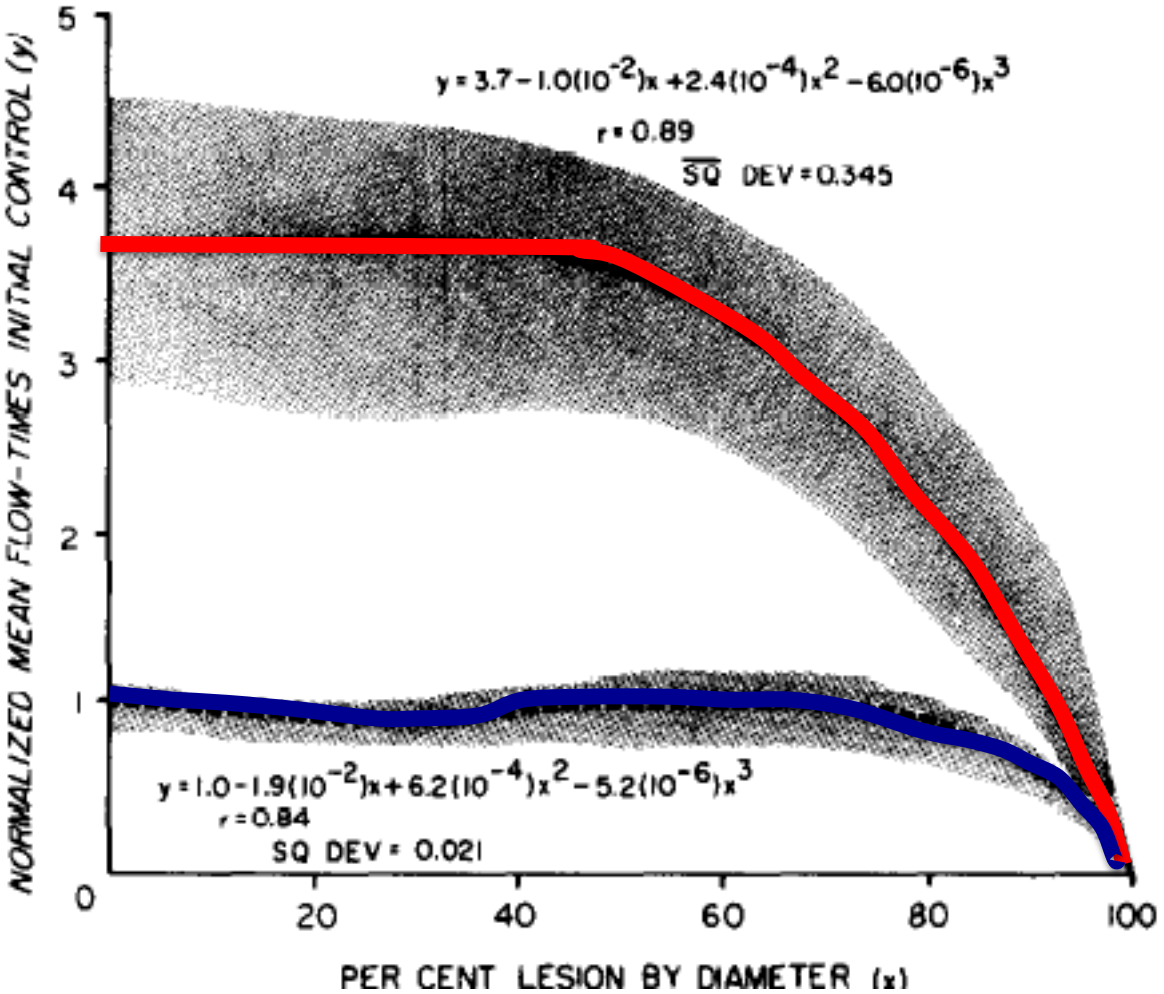
Relationship between %DS and coronary flow



KL Gould et al. Am J Cardiol 1974

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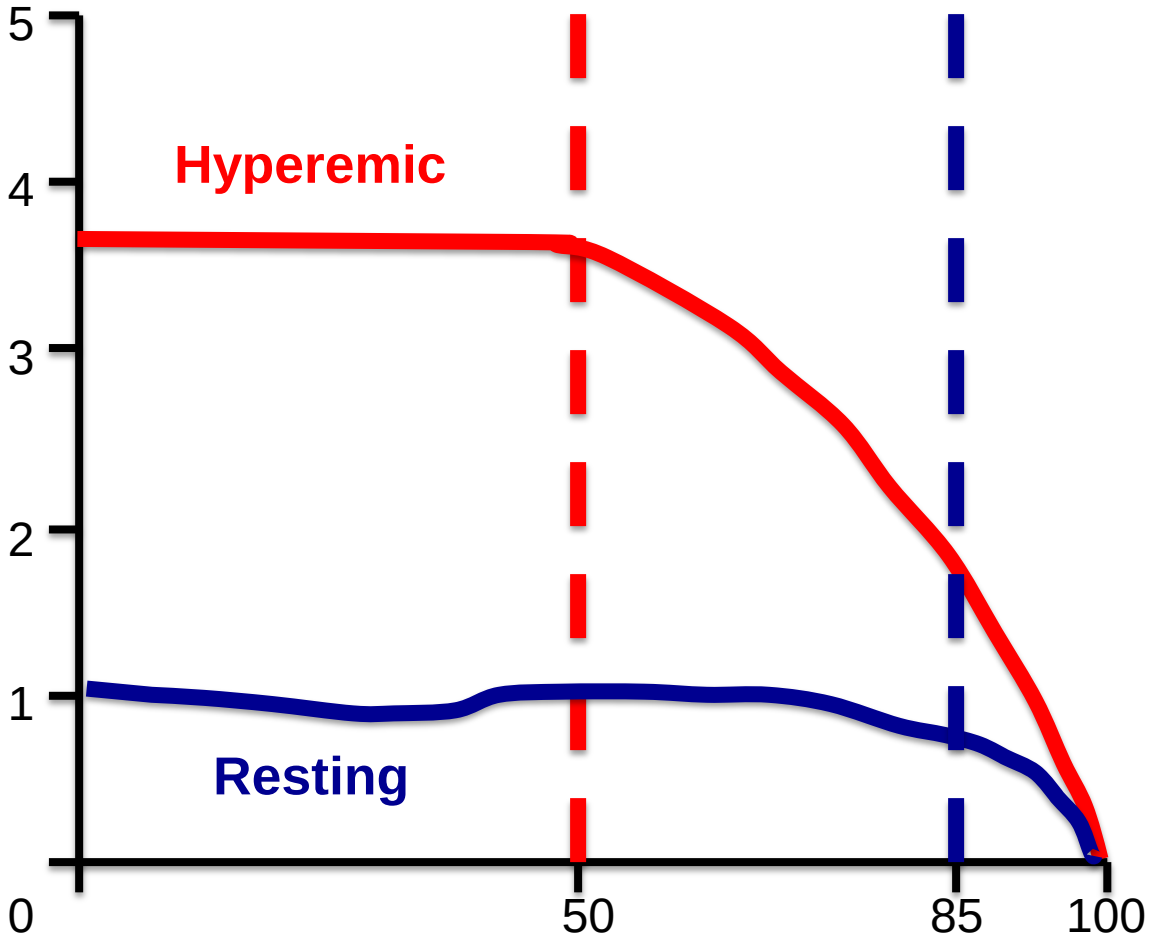

KL Gould et al. Am J Cardiol 1974

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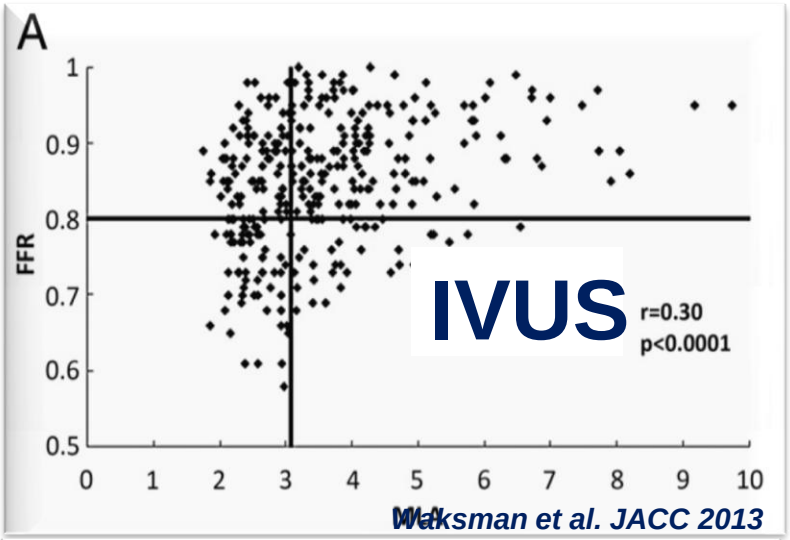
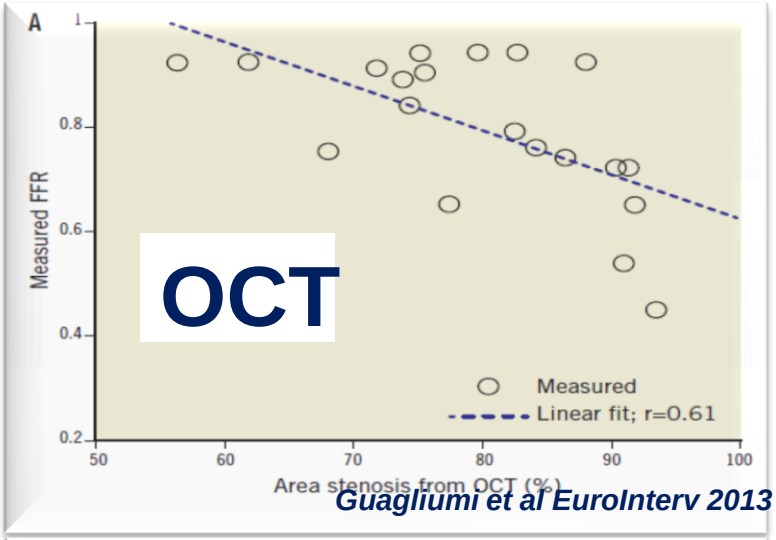
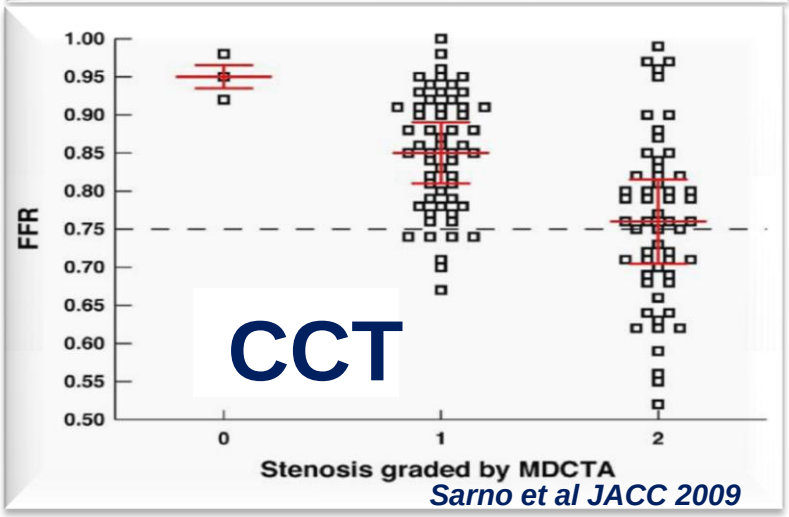
Anatomy vs Physiology: the Chimeric Link



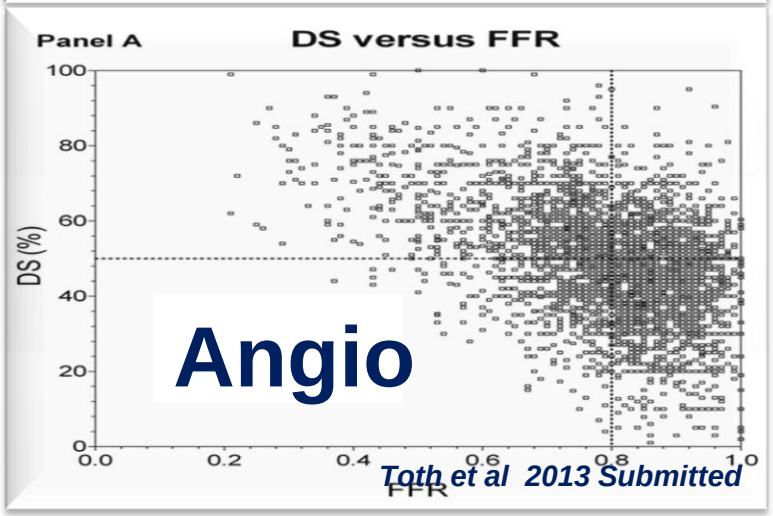
Waksman et al. JACC 2013



Guagliumi et al EuroInterv 2013



Sarno et al JACC 2009



Toth et al 2013 Submitted

Statistical (mechanistic) relation but little clinical relation

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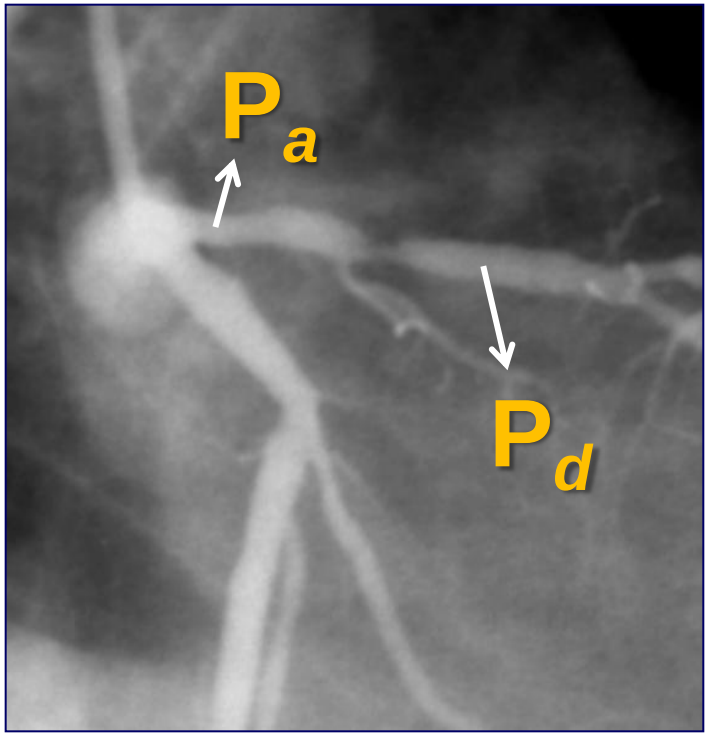
Fractional Flow Reserve

FFR = ratio of hyperemic flow in the stenotic vessel to hyperemic flow in the same vessel but in the absence of the stenosis

FFR = extent to which (%) maximal myocardial flow is limited by the epicardial stenosis



$$FFR = \frac{Q^{S}_{max}}{Q^{N}_{max}} = \frac{P_d}{P_a}$$

During maximal hyperemia

(i.e. during maximal transstenotic flow)

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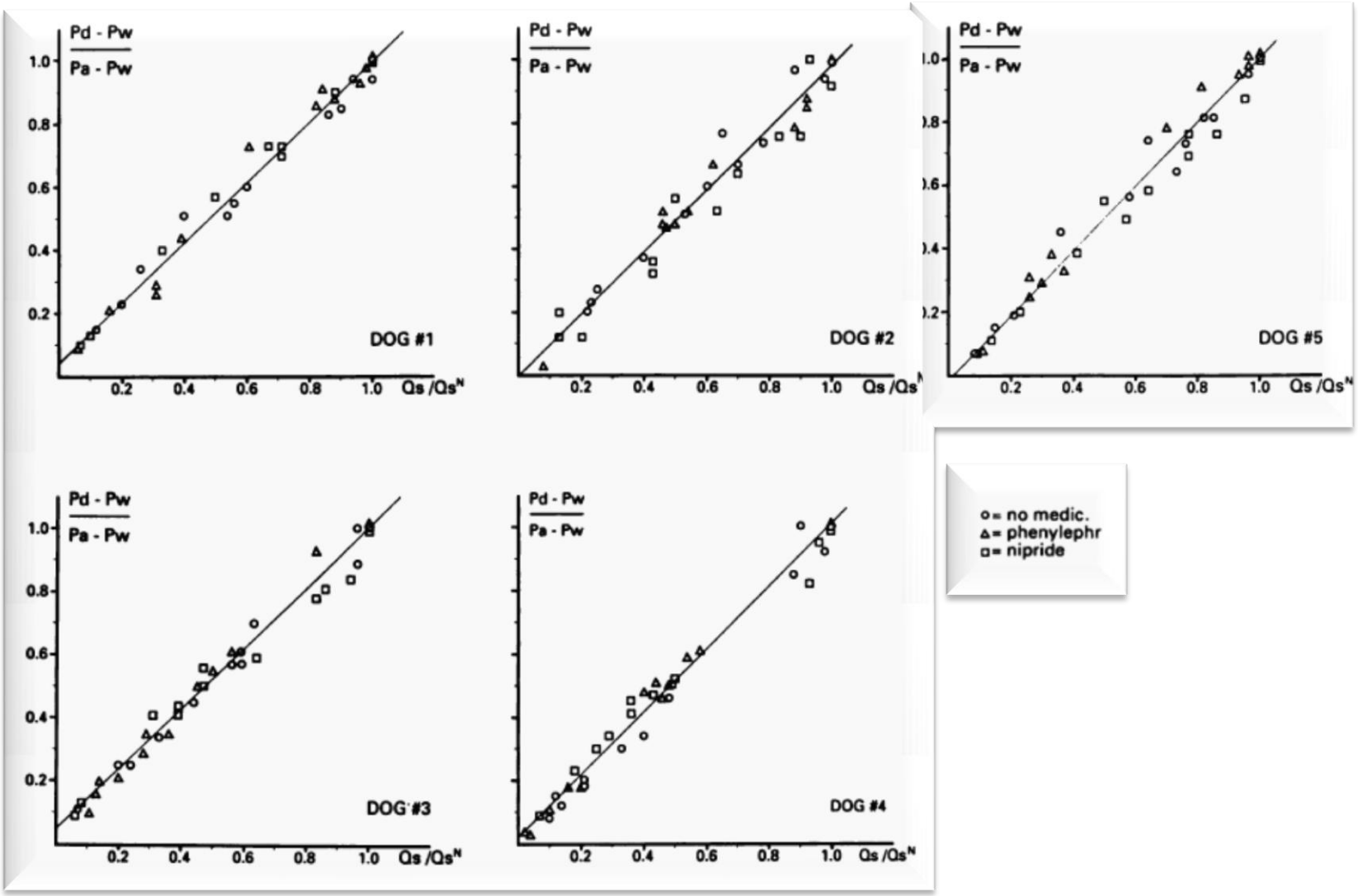
Pijls NHJ et al. Circulation, 1993;86:1354

The relation between P_d/P_a and Q_S/Q_N is LINEAR during HYPEREMIA



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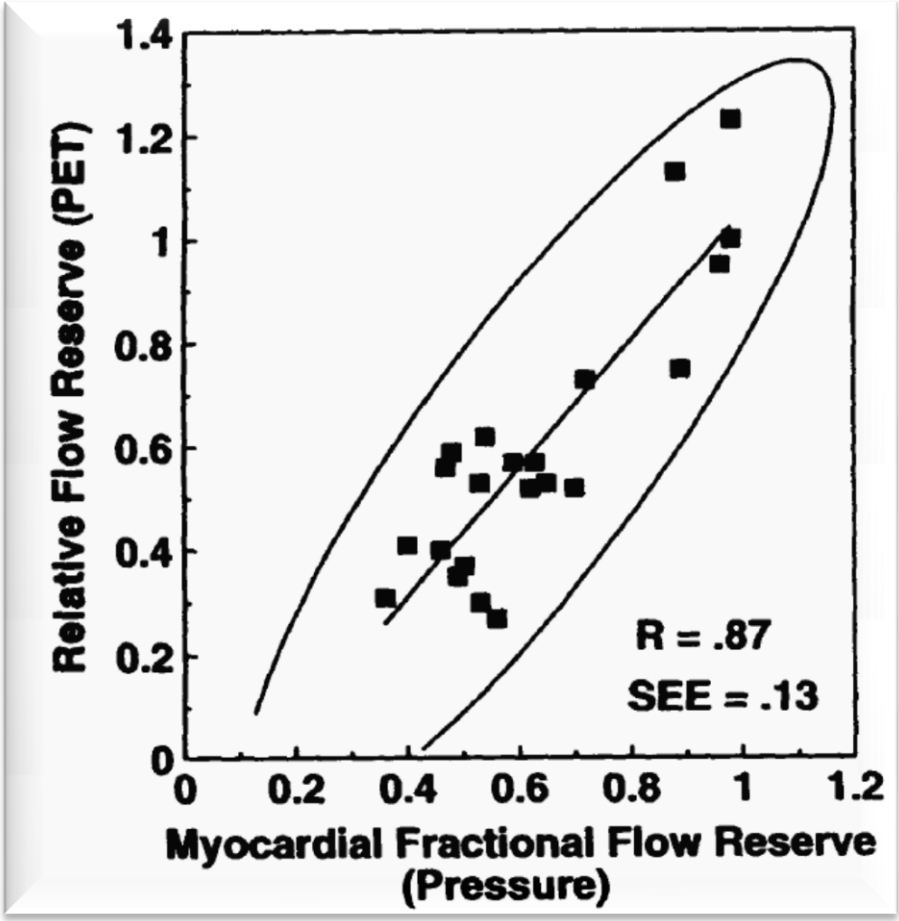
Pijls NHJ et al, Circulation,1993;86:1354

The relation between P_d/P_a and Q_S/Q_N *is LINEAR during HYPEREMIA*

- 22 Patients with an isolated proximal LAD stenosis
- $H_2{}^{15}O$ PET maximal flow in LAD vs normal territories
- FFR within 24 hours



De Bruyne B et al, Circulation,1994;89:1013

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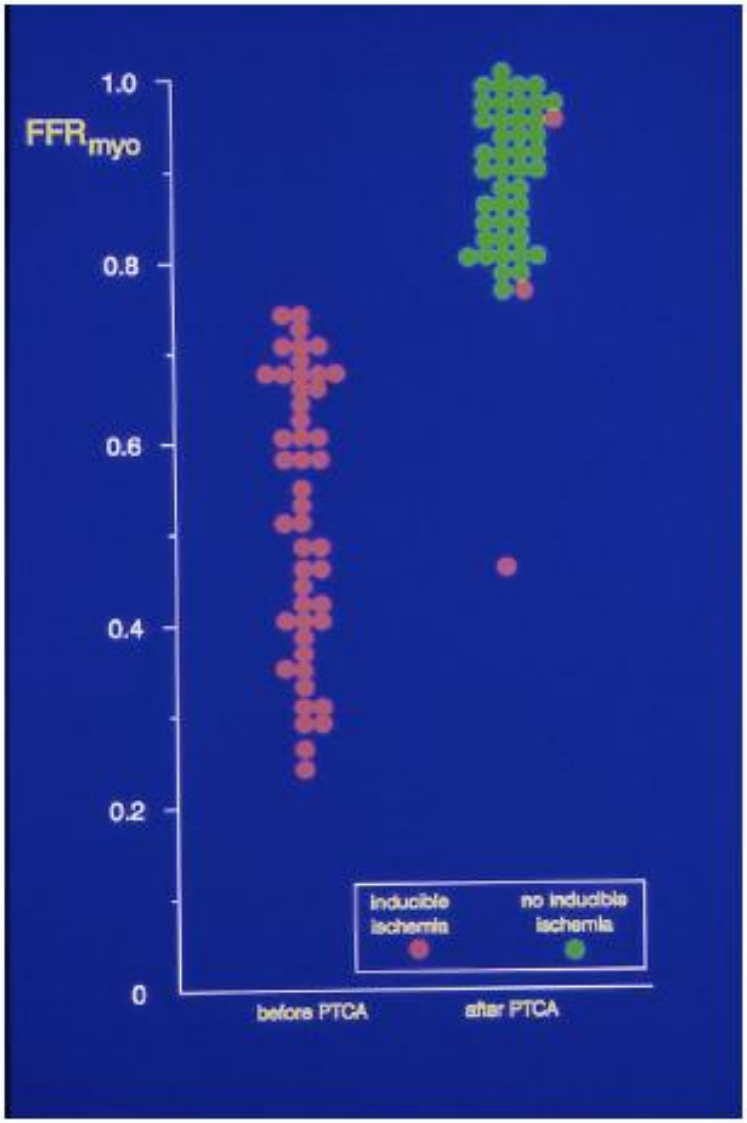
Validation of FFR in Humans (Step 1)



Proper validation of any index needs

2 steps:

1. Searching for the threshold value in a selected population
   (sens, specif, NPV, PPV, ROC analysis)

2. Prospective validation in a population with unknown characteristics

Pijls et al, Circulation 1995
De Bruyne, Circulation 1996

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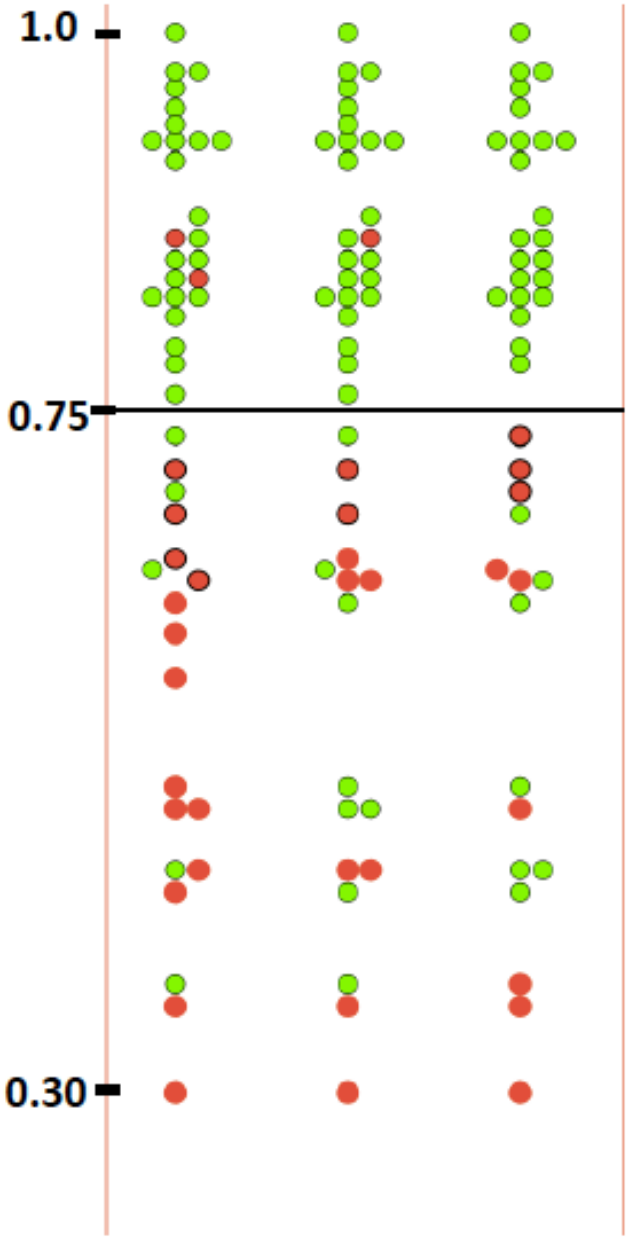

Testing of FFR versus True Gold Standard

Creating a gold standard by ***Prospective Multitesting Sequential Bayesian Approach:***

- Exerc testing = electrical index of ischemia
- MIBISpect = perfusion index of ischemia
- Dobutrex Echo = contractile index of ischemia
- *reversal from positive before to negative after intervention, proves true positivity before and true negativity after test*

Diagnostic accuracy of FFR =

$$\left[(1-0.75) \times (1-0.8) \times (1-0.8)\right]^{-1} = 99\ \%$$

3 unclassifiable patients (no intervention)
→ worst case scenario for FFR → **93 %**

Pijls et al, NEJM 1996

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Threshold value of FFR to detect significant stenosis in humans

FFR is the ***only*** functional index which has ever been validated versus a **true gold standard**.
(Prospective multi-testing Bayesian methodology)

ALL studies ever performed in a wide variety of clinical & angiographic conditions, found threshold between 0.75 and 0.80

Diagnostic accuracy > 93%

Pijls et al, N Engl J Med 1996; 334:1703-1708
Oldroyd et al, Circulation 2010

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Clinical Outcome

- In stable patients with single vessel disease, stenting functionally non-significant stenoses does not improve clinical outcome as compared to deferring these stenoses to optimal medical treatment → → DEFER trial

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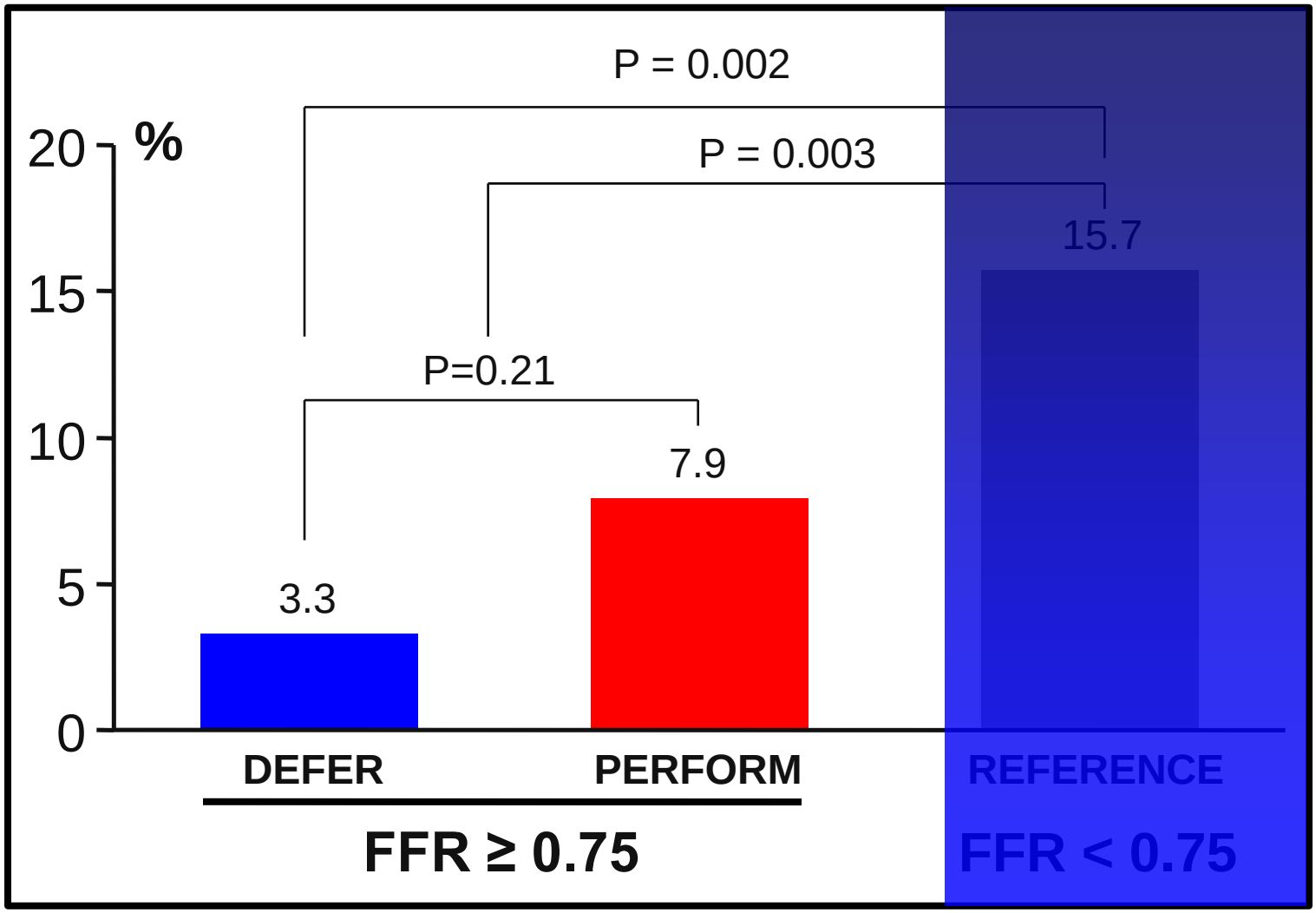
DEFER: Clinical Outcome at 5 Years

Rate of Death/MI after 5 years



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NHJ Pijls et al JACC 2007

Clinical Outcome

- In stable patients with single vessel disease, stenting functionally non-significant stenosis does not improve clinical outcome as compared to deferring these stenoses to optimal medical treatment → → DEFER trial

- In patients with multivessel disease, an FFR-guided PCI strategy improves clinical outcome as compared with an Angio-guided strategy → → FAME trial

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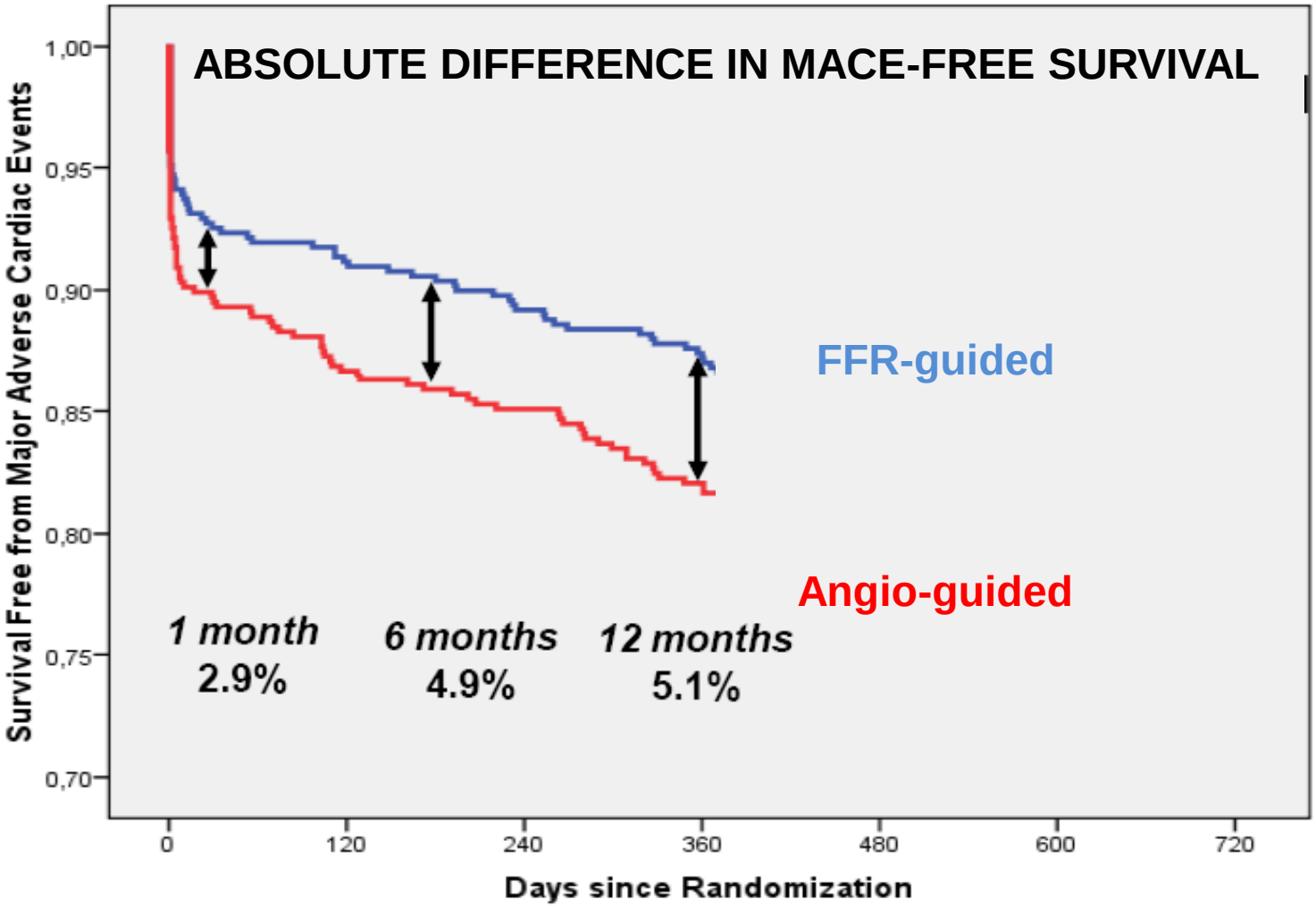
FAME trial



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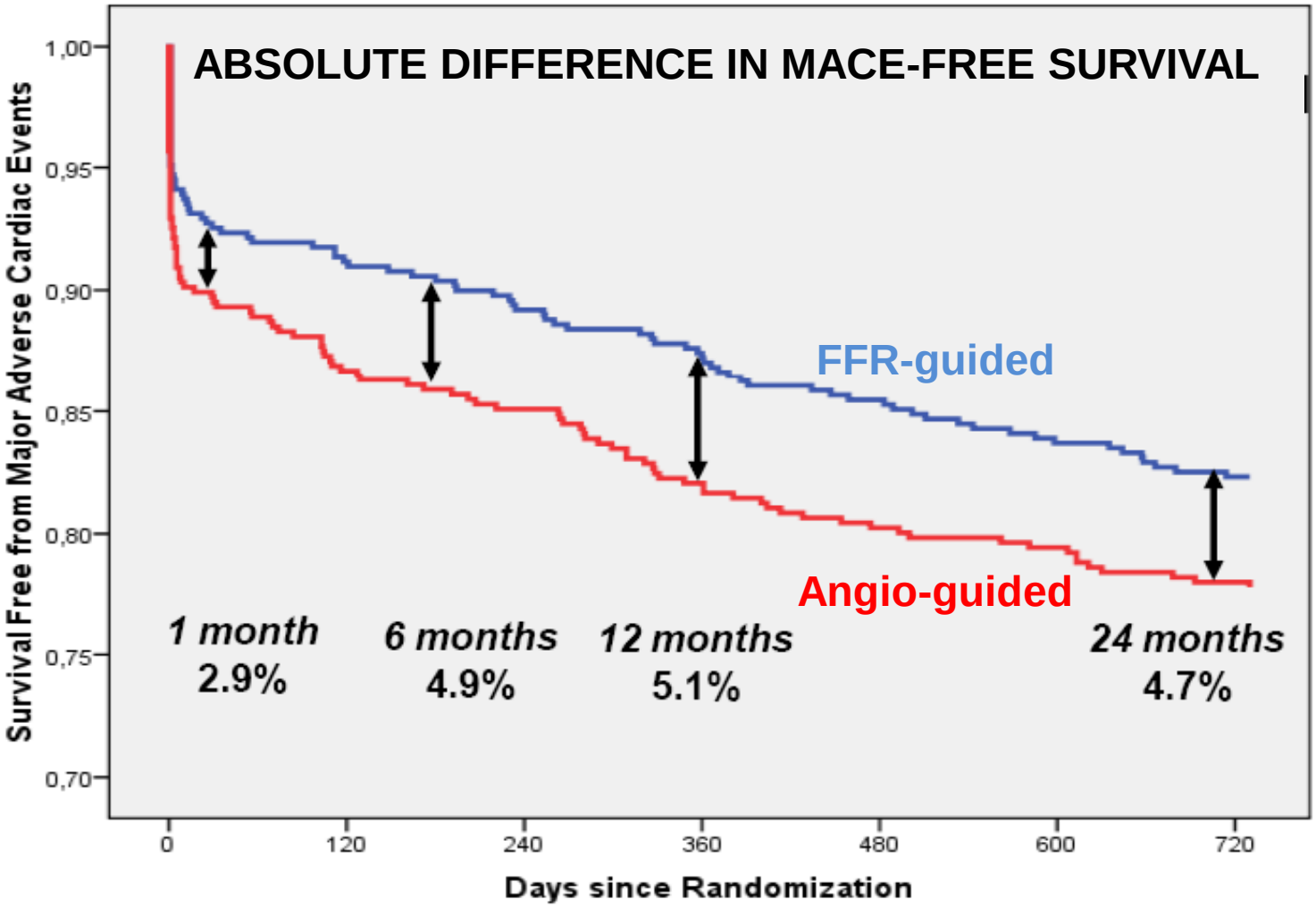
P Tonino et al NEJM 2009

FAME trial



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P Tonino et al NEJM 2009

Clinical Outcome

- In stable patients with single vessel disease, stenting functionally non-significant stenosis does not improve clinical outcome as compared to deferring these stenoses to optimal medical treatment. → → DEFER trial

- In patients with multivessel disease, an FFR-guided PCI strategy improves clinical outcome as compared with an Angio-guided strategy. → → FAME trial

- In stable patients with at least one functional significant stenosis, FFR-guided PCI plus MT is associated with better clinical outcome as compared with MT alone.
  → → FAME 2 trial

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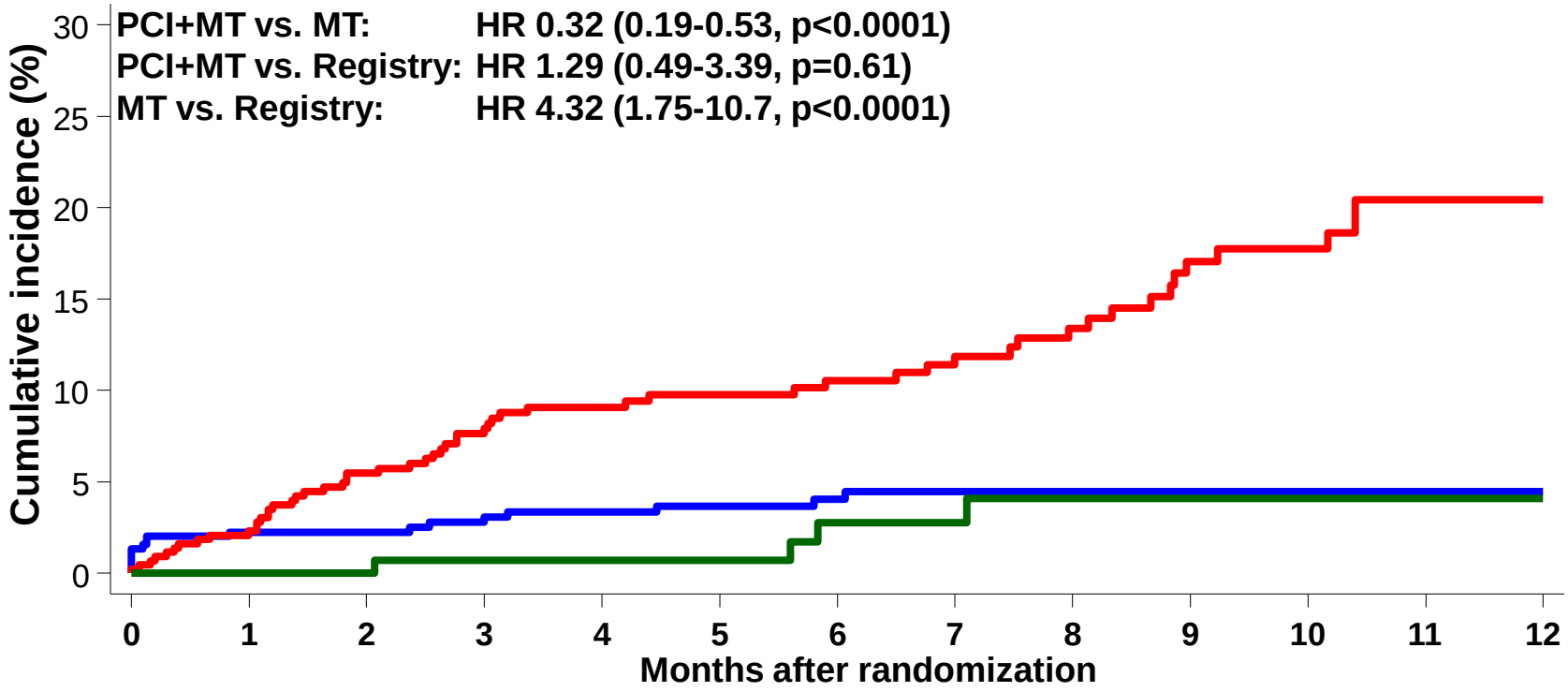
FAME 2 TRIAL
Primary End Point



No. at risk

OMT	441	414	370	322	283	253	220	192	162	127	100	70	37
PCI+OMT	447	414	388	351	308	277	243	212	175	155	117	92	53
Registry	166	156	145	133	117	106	93	74	64	52	41	25	13

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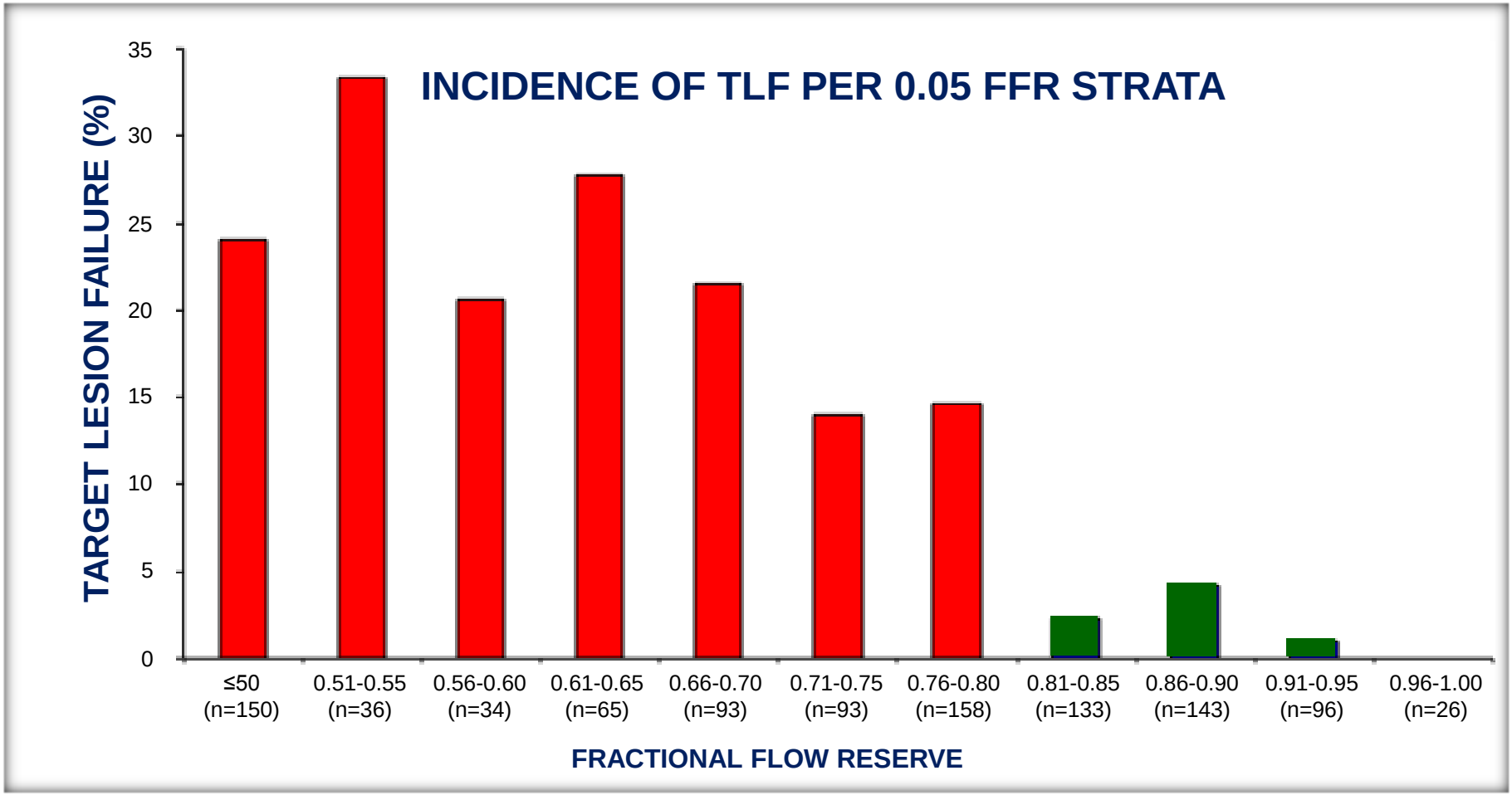
B De Bruyne et al NEJM 2012

FAME 2: 607 Patients on Medical Therapy

(1027 lesions, Median FU= 191 days)



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Actual FFR value predicts the natural history of stenoses in patients with stable coronary disease

Barbato E for the FAME2 investigators ESC 2013

Take-home messages

- Evidences of a beneficial clinical outcome with FFR-guided revascularization strategy in different angiographic settings:
  - Isolated equivocal left main stenosis (n=230+51)
    - ➔ Hamilos, Circ 2009/Lindstaedt, Am Heart J 2006
  - Isolated prox left anterior descending artery (n=72
    - ➔ Muller, JACC Cardiovasc Intv
  - Small vessel disease (n=717)
    - ➔ Puymirat, Circ
  - By-pass grafts (n=22
    - ➔ 013
  - Bifur
    - 008/Kumsars, Eurointv 2012
  - Seria (n=131)
    - ➔ Kim, JACC Cardiovasc Intv 2012
  - Drug Eluting Stent Restenosis (n=49)
    - ➔ Nam, Am J Cardiol 2011
  - Post-stenting (BMS and DES) (n=750+80)
    - ➔ Pijls NHJ, Circ 2002/Nam, Am J Cardiol 2011
  - All comers, contemporary practice (n=7358)
    - ➔ Li J, EHJ 2013

>10000 patients

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Level of Evidence of FFR

- FFR-guided PCI is recommended for detection of ischaemia-related lesion(s) when objective evidence of vessel-related ischaemia is not available

  Class of Recommendation: I

  Level of Evidence: A

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ESC Guidelines on Myocardial Revascularization, EHJ 2010

New Diagnostic Strategies

- RIPCORD study
- French registry
- POST-IT

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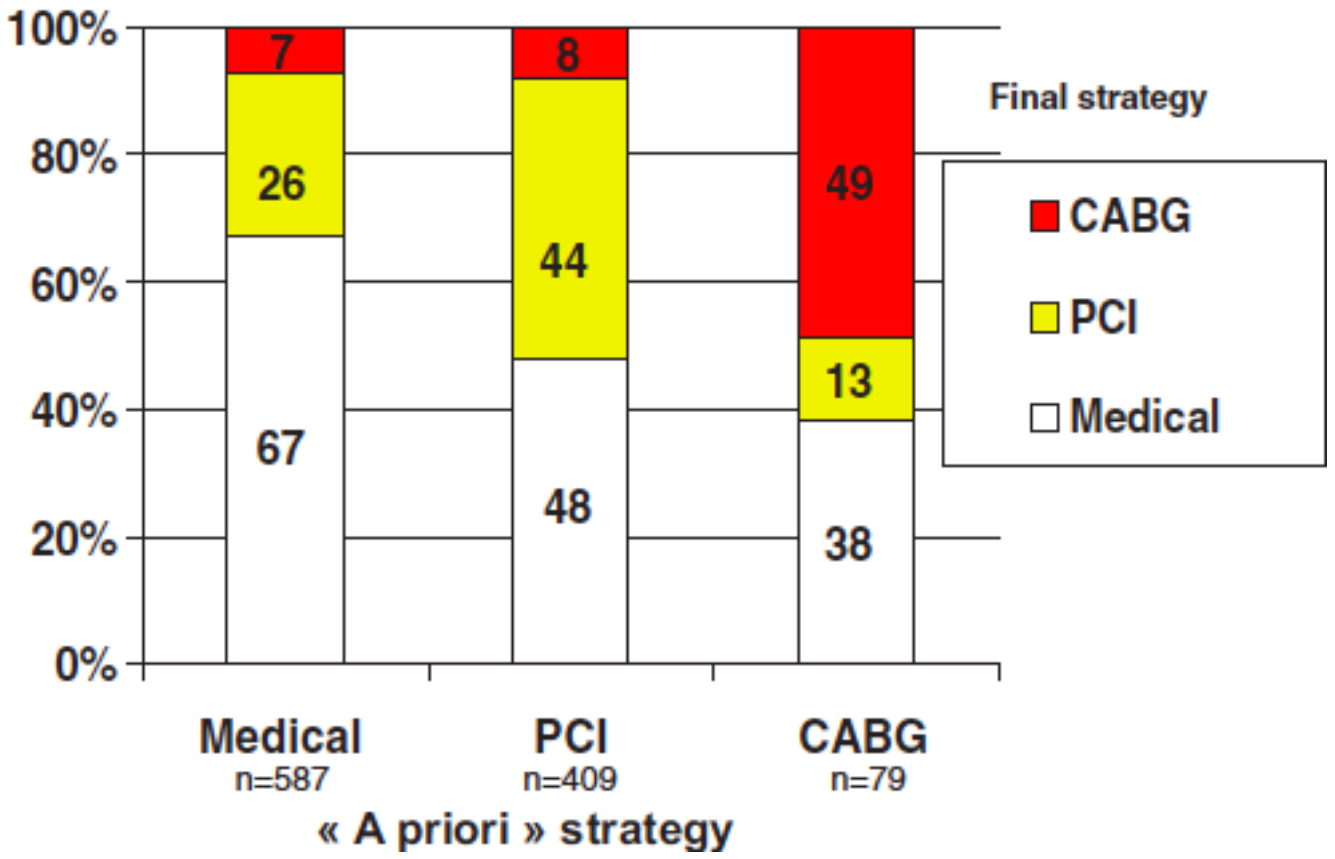
French registry

1075 consecutive patients undergoing diagnostic CAG



Change of Revascularization Strategy in 43% of the patients

E. Van Belle et al Circulation 2013

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New Therapeutic Strategies

- CABG registry
- GRAFFITI trial
- FAME 3 trial

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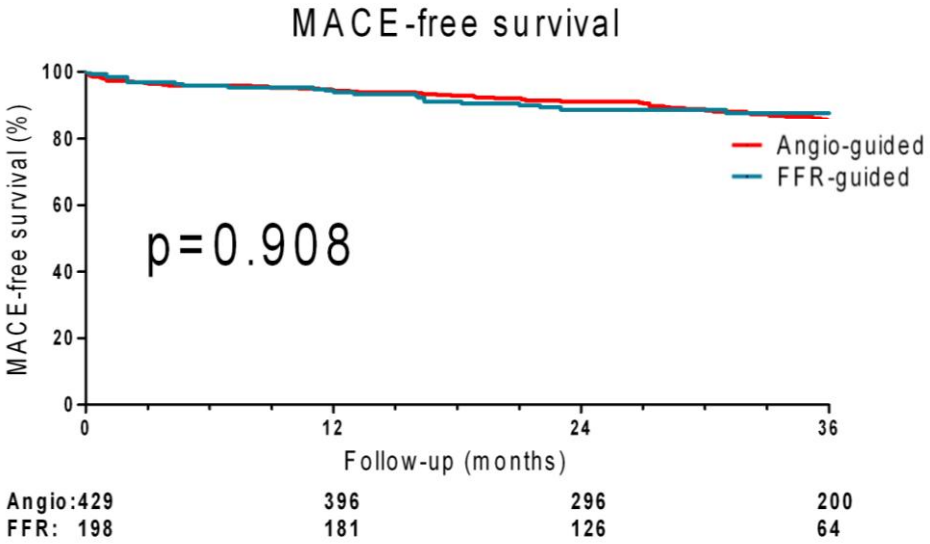
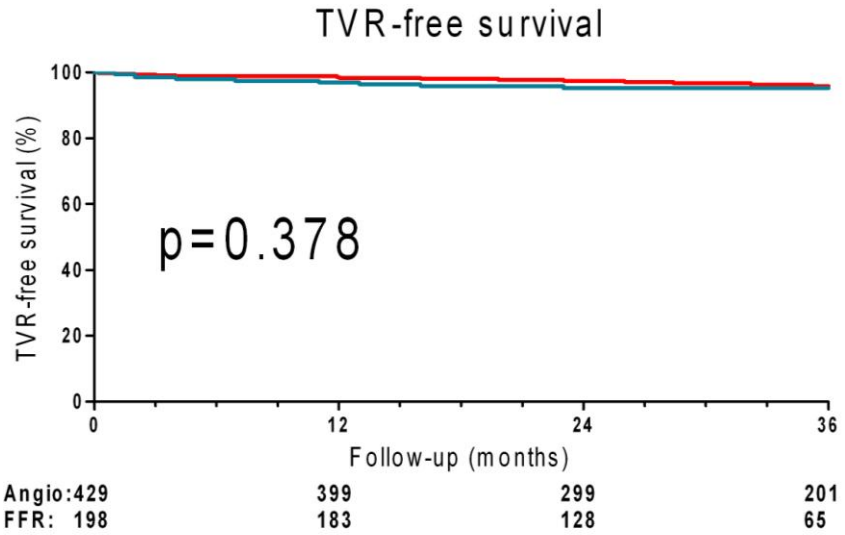
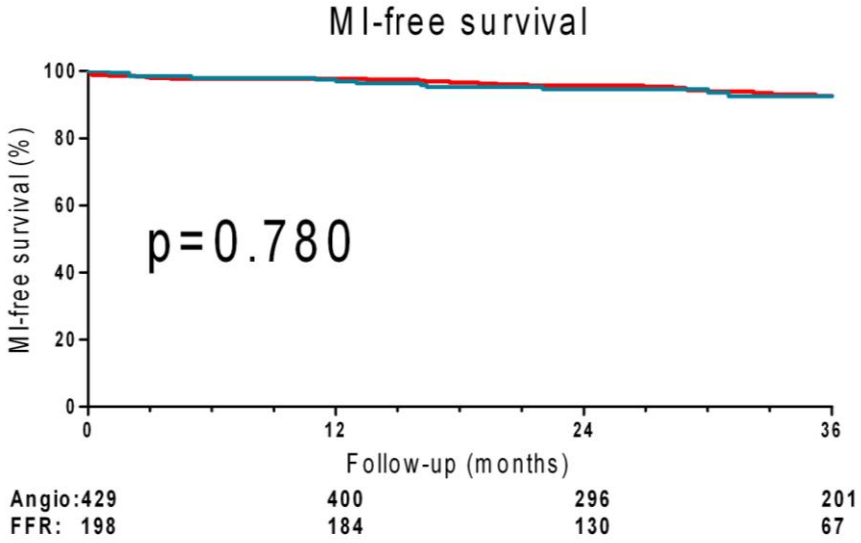
Angio-guided	FFR-guided
n=429	n=198

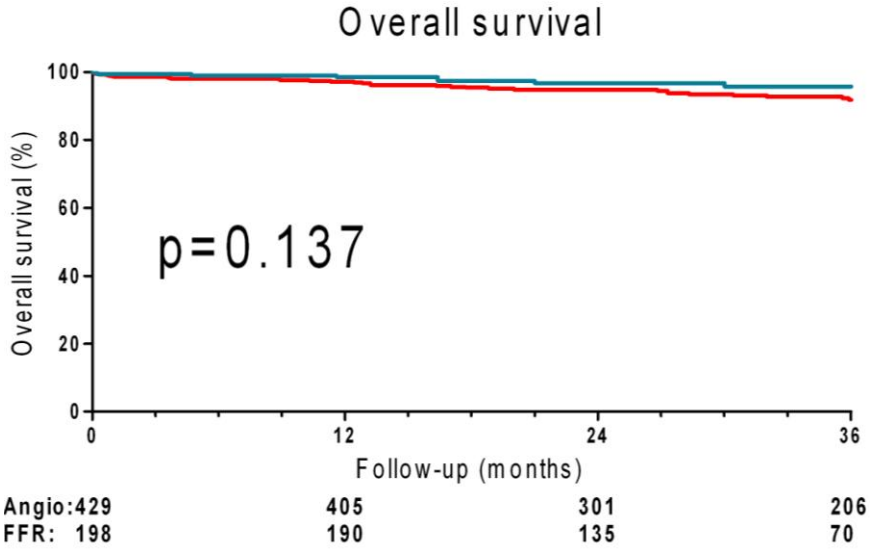
Toth G. et al. Circulation 2013

Clinical endpoints @ 36 months









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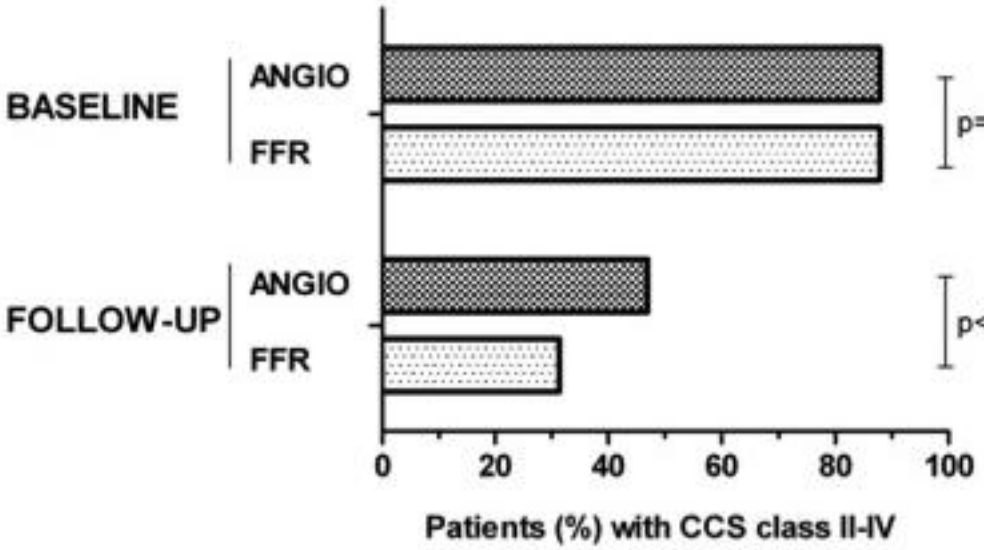
Toth G. et al. Circulation 2013

CCS II-IV @ 36 months



p=1.000 377 [88%] 174 [88%] OR=1.000, 95% C.I. 0.597 to 1.675; p=1.000

p<0.001 201 [47%] 62 [31%] OR=1.948, 95% C.I. 1.362 to 2.786; p<0.001

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Toth G. et al. Circulation 2013

GRAFFITI trial: GRaft Patency After FFR-guided vs Angio-guided CABG: a randomized clinical Trial

PI : Emanuele Barbato MD, PhD
Cardiovascular Center Aalst, Belgium

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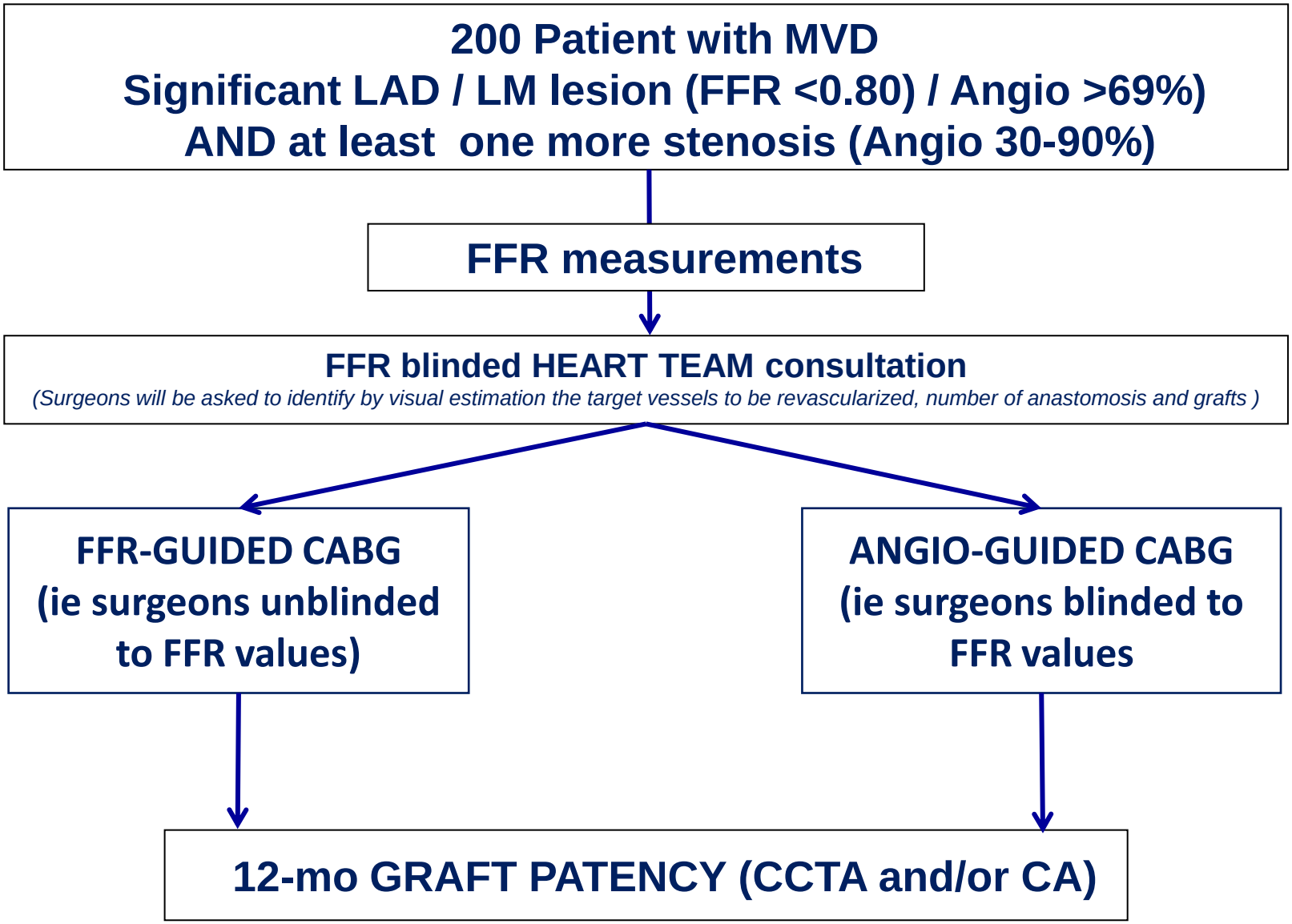
Hypothesis

FFR-guided CABG is associated with a lower rate of 1-year graft occlusion

GRAFFITI trial: GRaft Patency After FFR-guided vs Angio-guided CABG: a randomized clinical Trial



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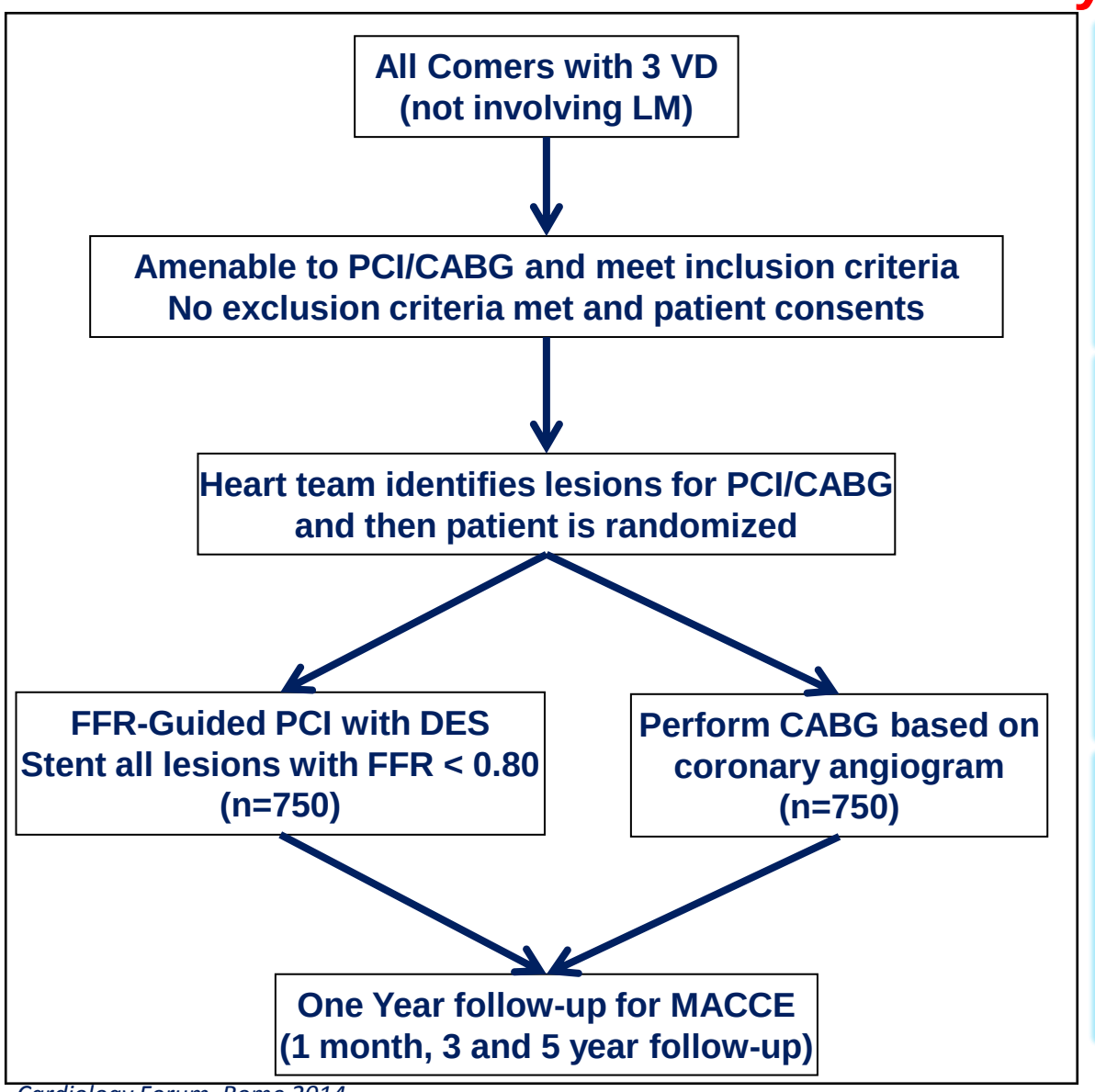
FAME 3: A Comparison of FFR-guided PCI and CABG in Patients with Multivessel Coronary Artery Disease



Hypothesis:

FFR-guided PCI in MVD will result in similar outcomes to CABG

Design:

- Noninferiority design
- Clinically relevant difference of 5%

PI's:

- Fearon WF (PI)
- Pijls NHJ (Co-PI)
- De Bruyne B (Co-PI)

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Can we obtain the same results but simplifying the technique?

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- **Adenosine-free pressure derived coronary functional indexes:**
  - bSR (Piek)
  - iFR (Davies)
  - iFG (Indolfi)
  - Pd/Pa (Mammhas)
- **Non-invasive FFR:**
  - FFR_{CT}

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Accepted Manuscript

Multicenter Core Laboratory Comparison of the Instantaneous Wave-Free Ratio and Resting P_d/P_a with Fractional Flow Reserve: The RESOLVE Study

Allen Jeremias, MD, M
Asrress, MA, BM BCh
Davies, MBBA Javier

Bernard De Bruyne, MD Justin E.

Davies, MBBA Javier Escaned,

Marques,
etraco,
hD Jos

A.E. Spa
MD

MD Jan J. Piek, MD Nico H. Pijls,

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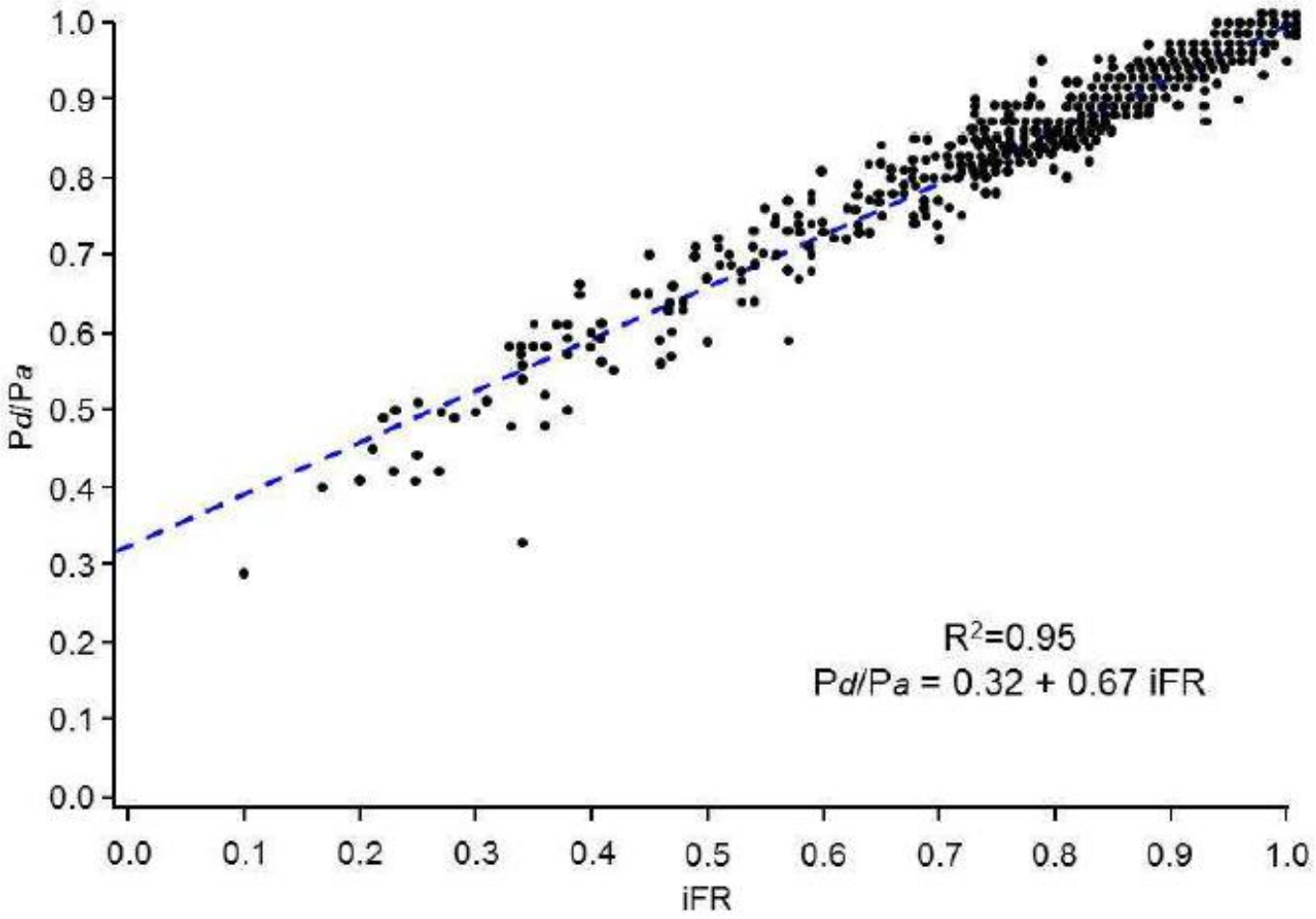
Correlation between Pd/Pa and iFR



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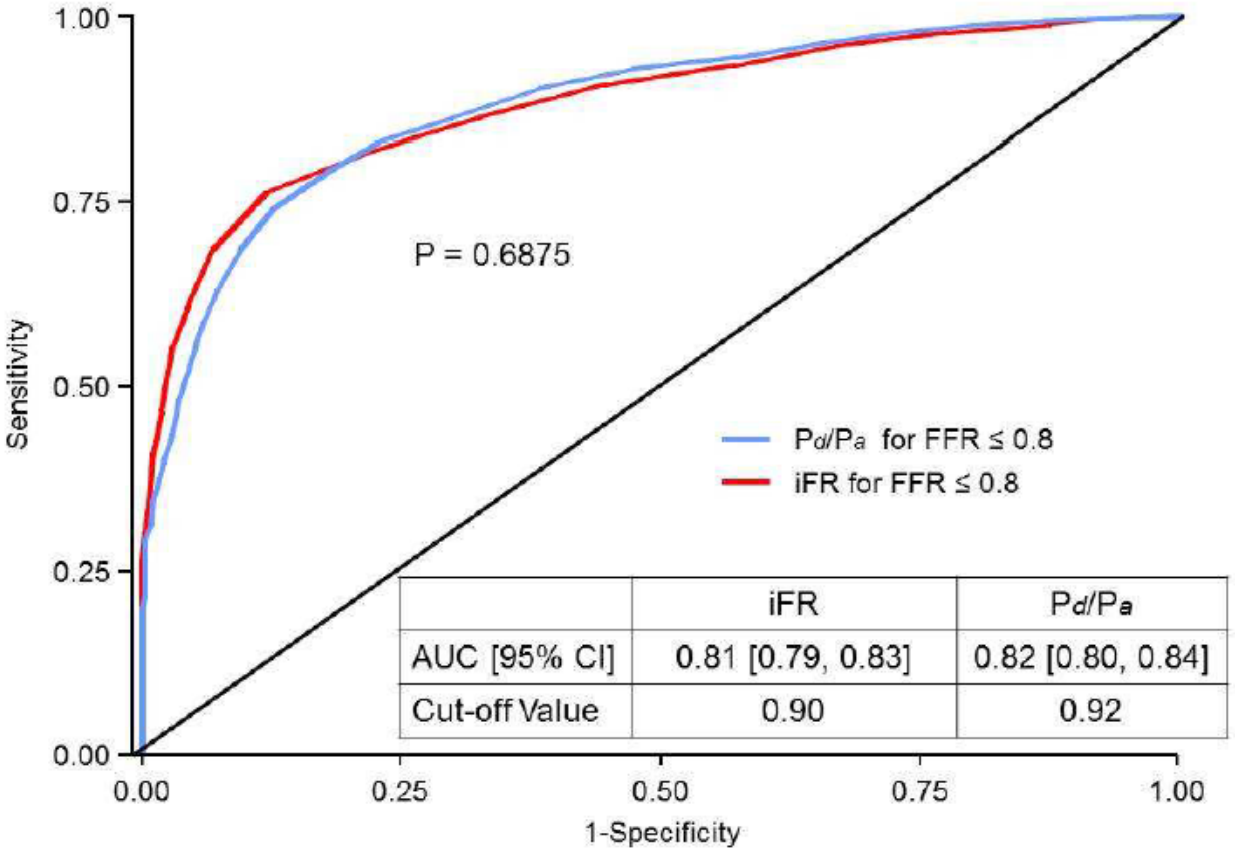
Jeremias A, JACC 2013

Moderate diagnostic accuracy

Figure 2



	iFR	Pd/Pa
AUC [95% CI]	0.81 [0.79, 0.83]	0.82 [0.80, 0.84]
Cut-off Value	0.90	0.92

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Jeremias A, JACC 2013

- **Adenosine-free pressure derived coronary functional indexes:**
  - bSR (Piek)
  - iFR (Davies)
  - iFG (Indolfi)
  - Pd/Pa (Mammhas)
- **Non-invasive FFR:**
  - FFR_{CT}

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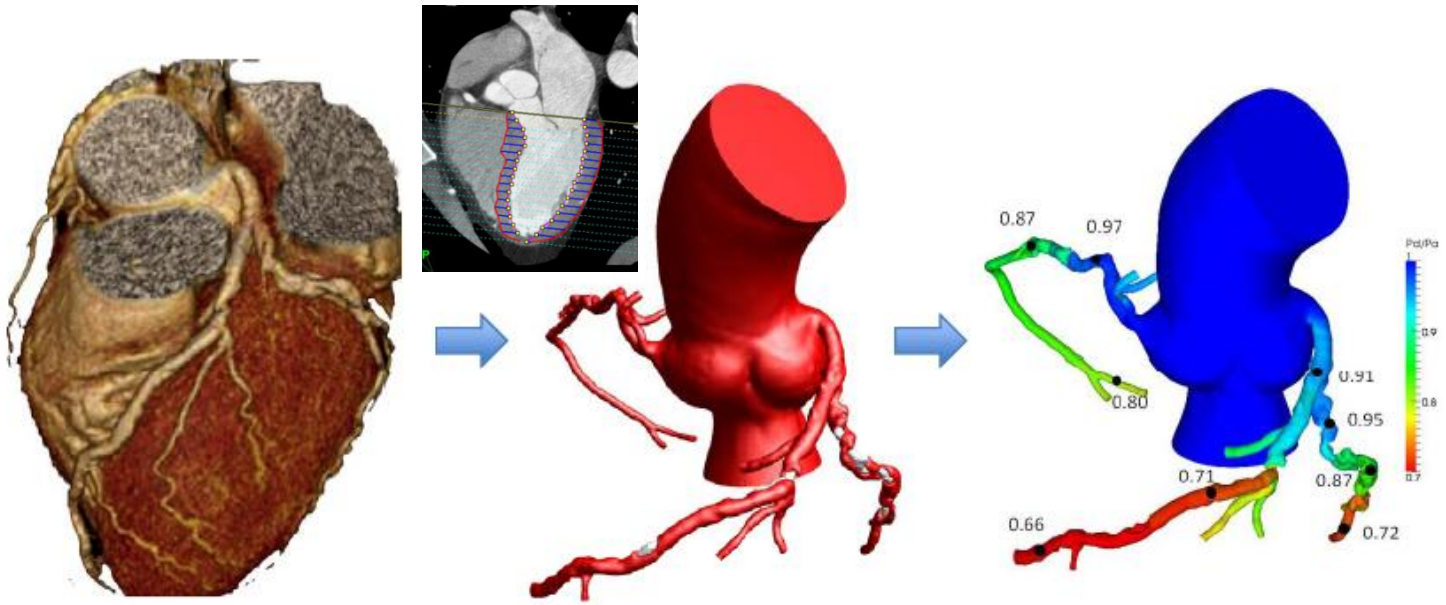
FFR_{CT} From Anatomy to function



64 slice CCTA data

3D Geometric Model

Ratio of coronary to aortic pressure under conditions of simulated hyperemia

1. Coronary flow meets myocardial demand at rest
2. Resistance of microcirculatory vascular bed at rest is inversely proportional to size of feeding vessel
3. Microcirculation has a predictable response to adenosine

Computational Flow Dynamics

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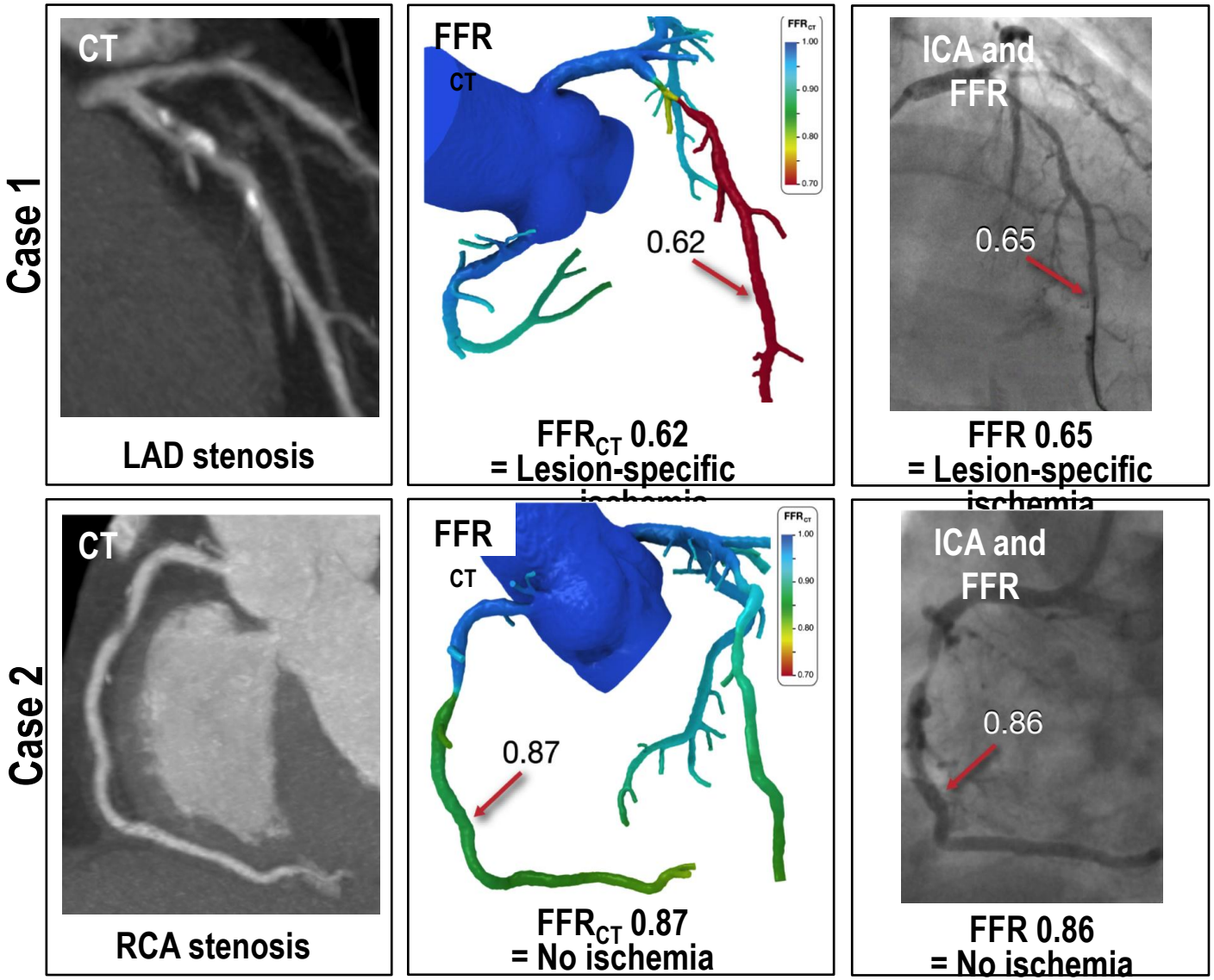

1. Min et al. JAMA 2012;308:1237-1245

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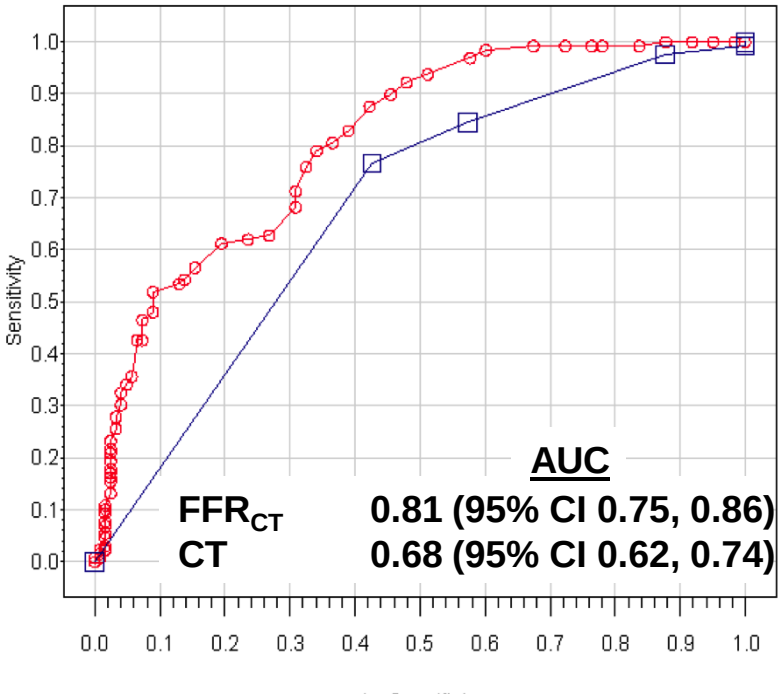
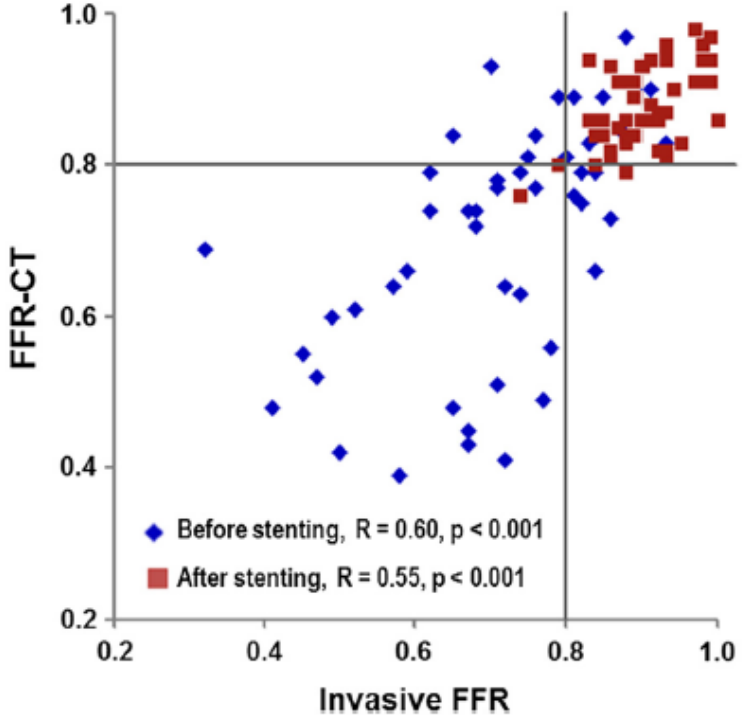
Diagnostic Accuracy of FFR_{CT} : DeFacto

Per-Patient



Before/After Stenting



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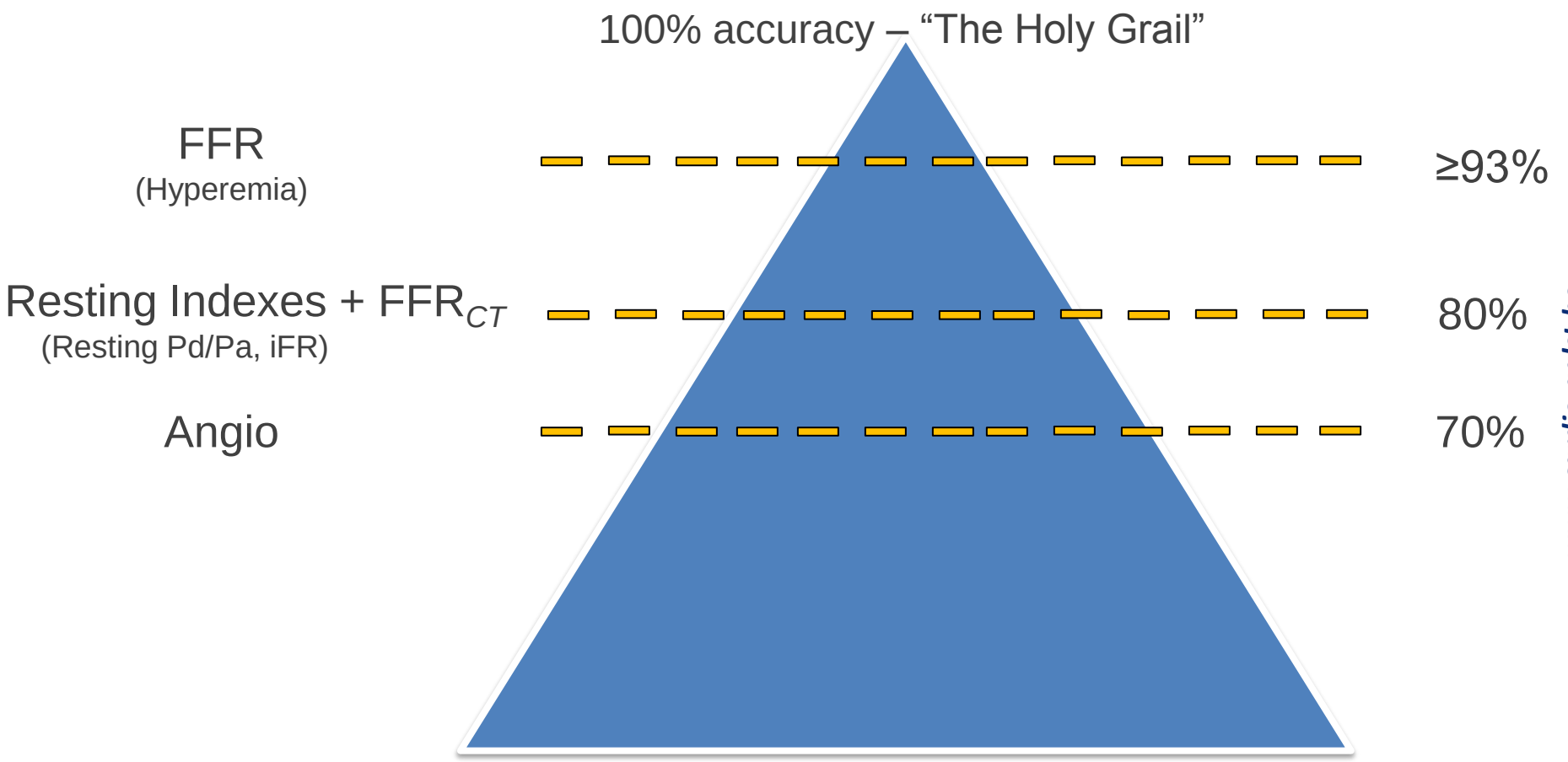
Diagnostic accuracy ≈ 80%

Min JK et al JAMA 2012

Kim KH et al JACC Cv Intv 2014

FFR is the gold standard to assess ischemia



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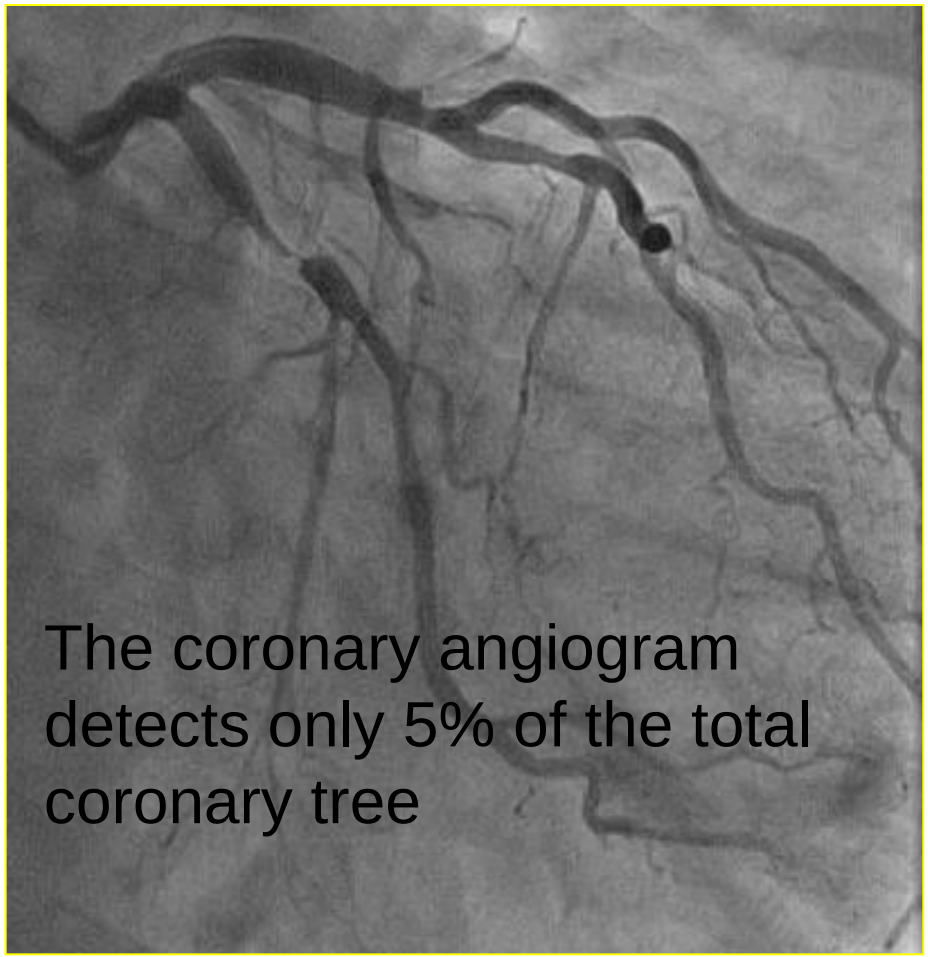
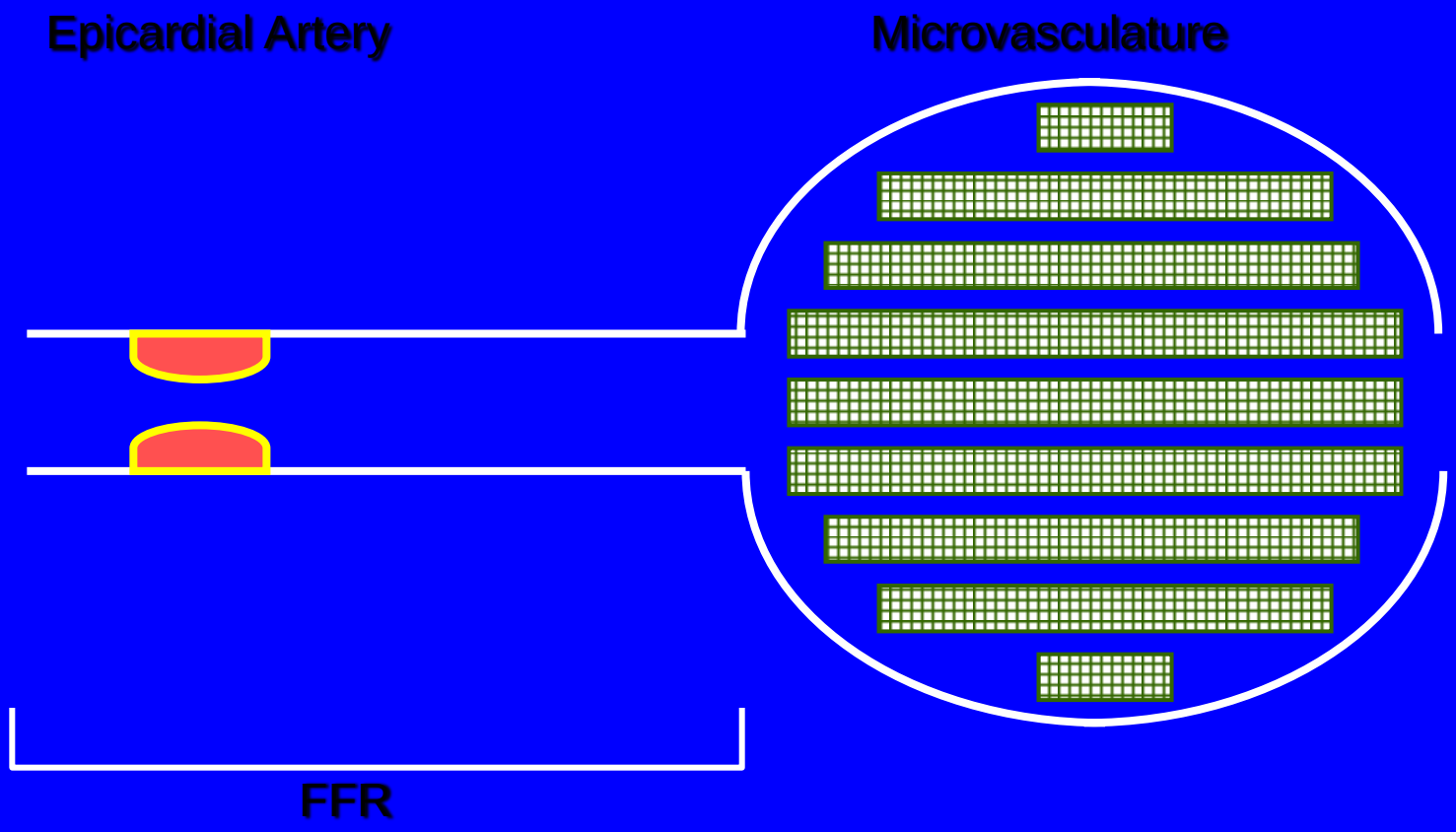
Two-Compartment Model of the Coronary Circulation



Two-Compartment Model of the Coronary Circulation



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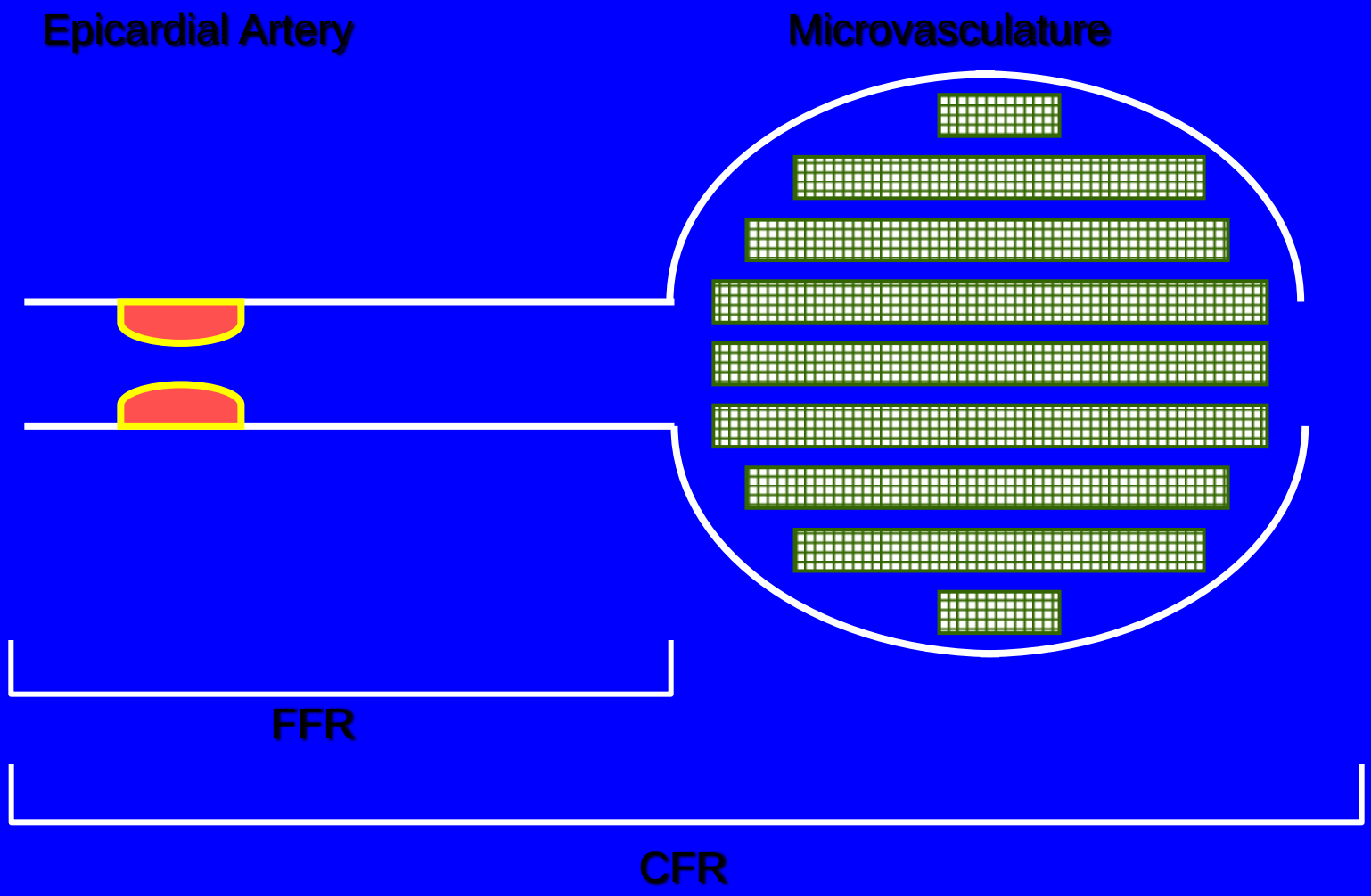
Two-Compartment Model of the Coronary Circulation



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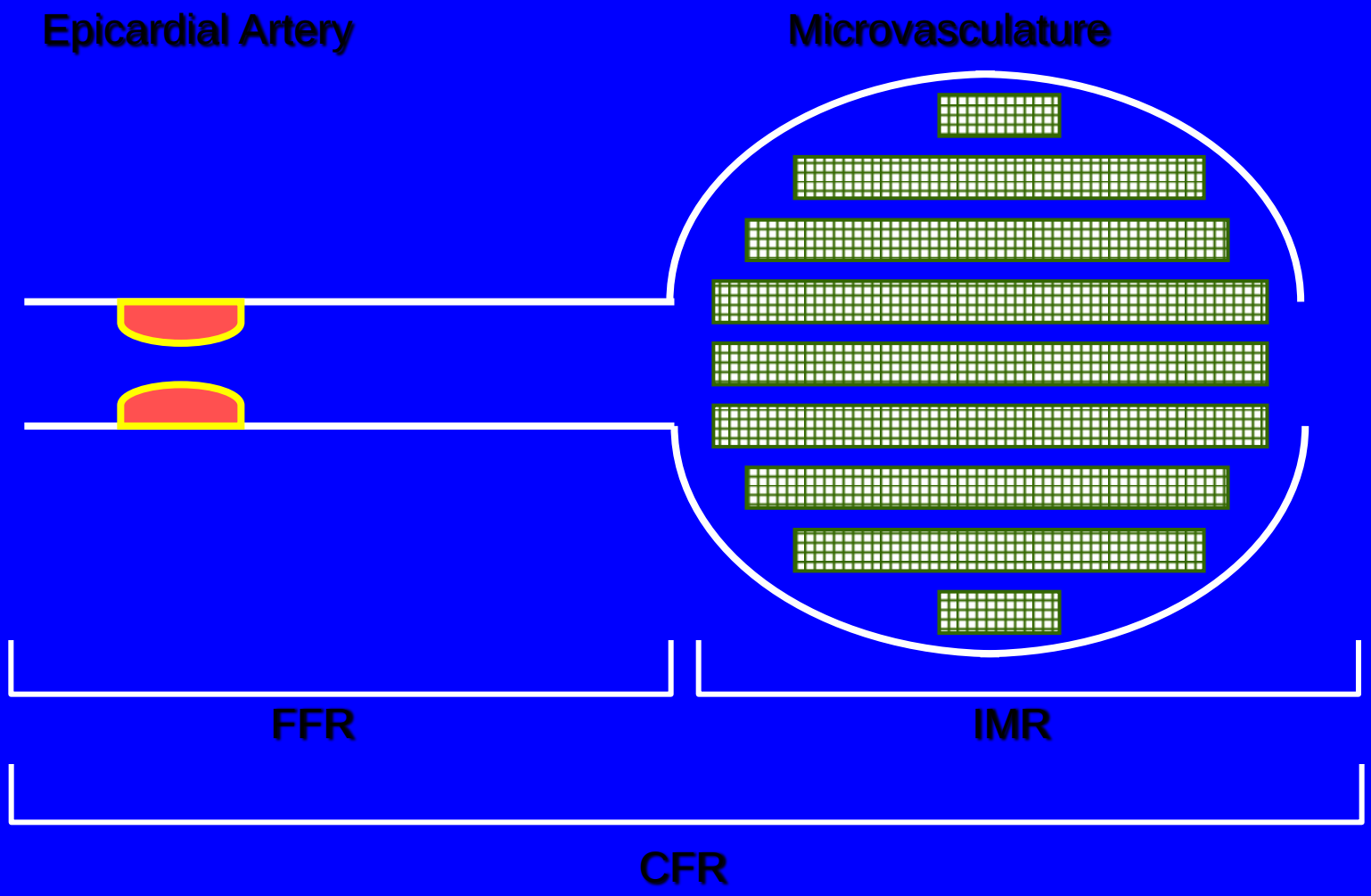
Two-Compartment Model of the Coronary Circulation



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Features of IMR

- Specific for the microvasculature
- Quantitative and reproducible
- Predictive of outcomes
- Independent from changes in heart rate, blood pressure and contractility (Ng, Circulation 2006)

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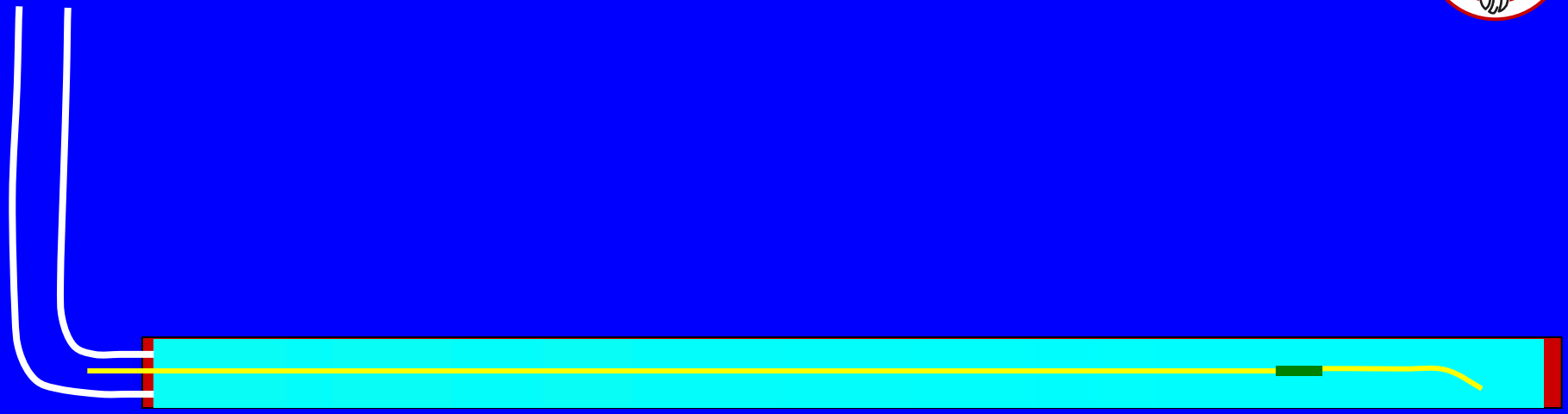
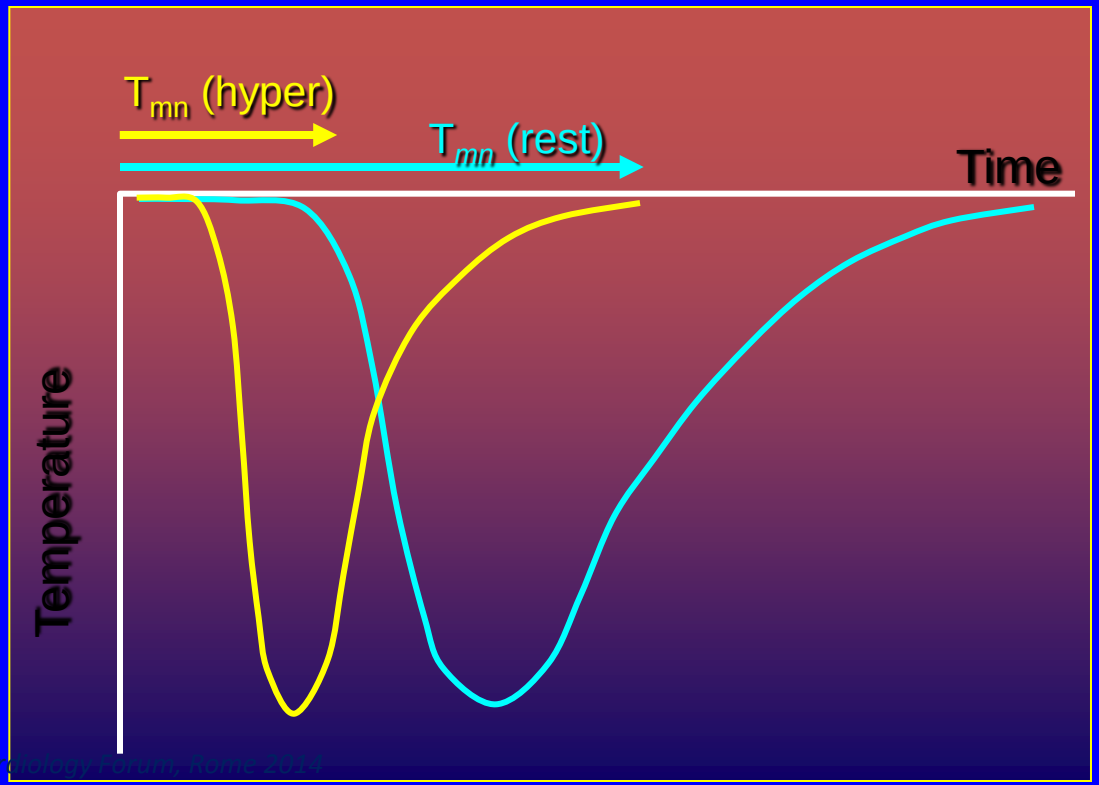
Coronary Thermodilution Principle





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Derivation of IMR

- Resistance = Δ Pressure / Flow
- 1 / Tmn @ Flow
- IMR = Distal Pressure / (1 / Tmn)
- IMR = Distal Pressure x Tmn at maximal hyperemia

Note: Must incorporate coronary wedge pressure to account for collateral flow if significant epicardial stenosis is present

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Clinical use of IMR

- Assessment of myocardial perfusion in STEMI patients
- Predictive of left ventricular remodeling after primary PCI

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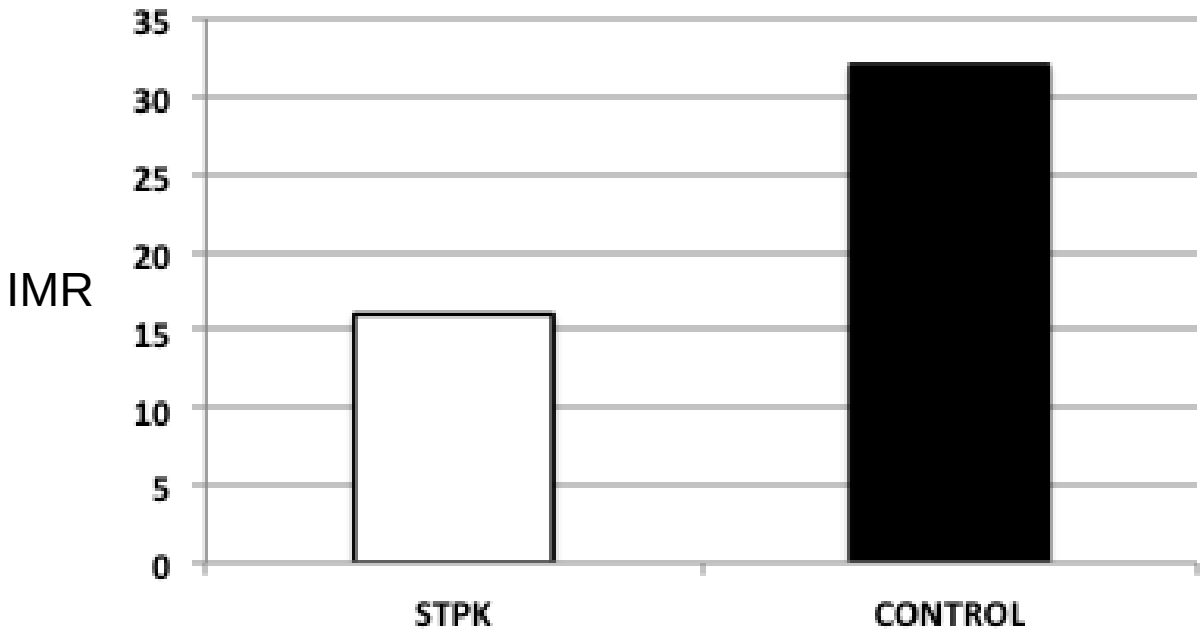
Assessment of myocardial perfusion in STEMI patients

41 STEMI pts randomized either to pPCI plus IC STPK or pPCI alone



Sezer M, NEJM 2007

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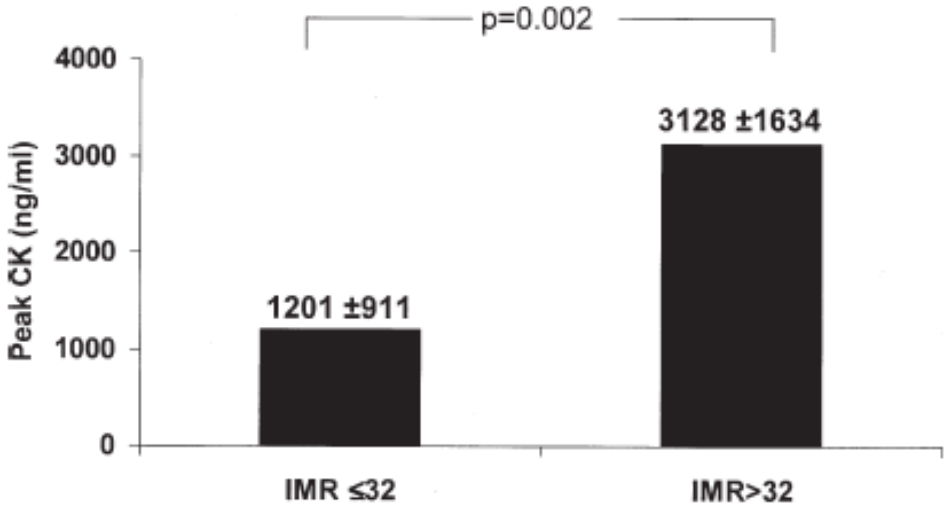
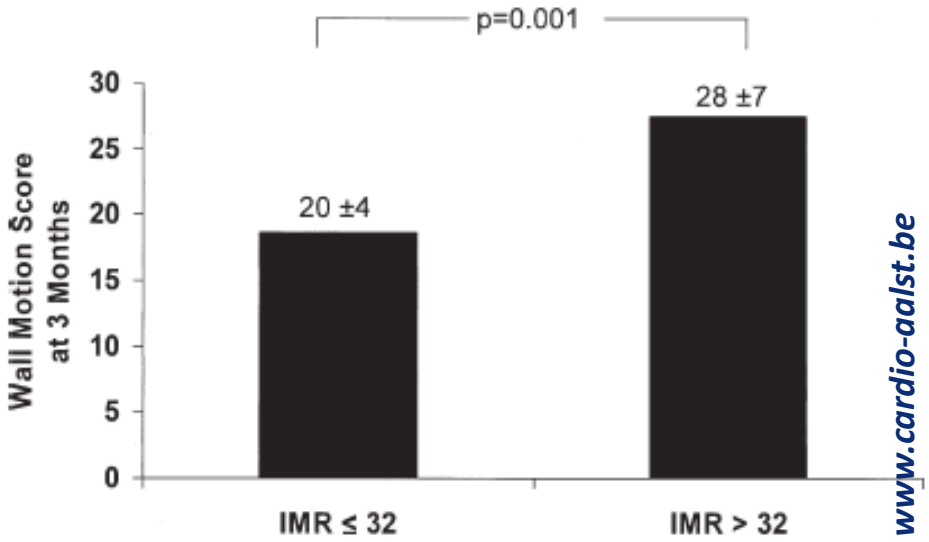
Predictive value after primary PCI

29 STEMI patients undergoing pPCI and IMR assessment



Acute setting



3 months after

Fearon W, JACC 2008

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Clinical use of IMR

- Assessment of myocardial perfusion in STEMI patients
- Predictive value after primary PCI
- Assessment of microvascular damage after elective PCI

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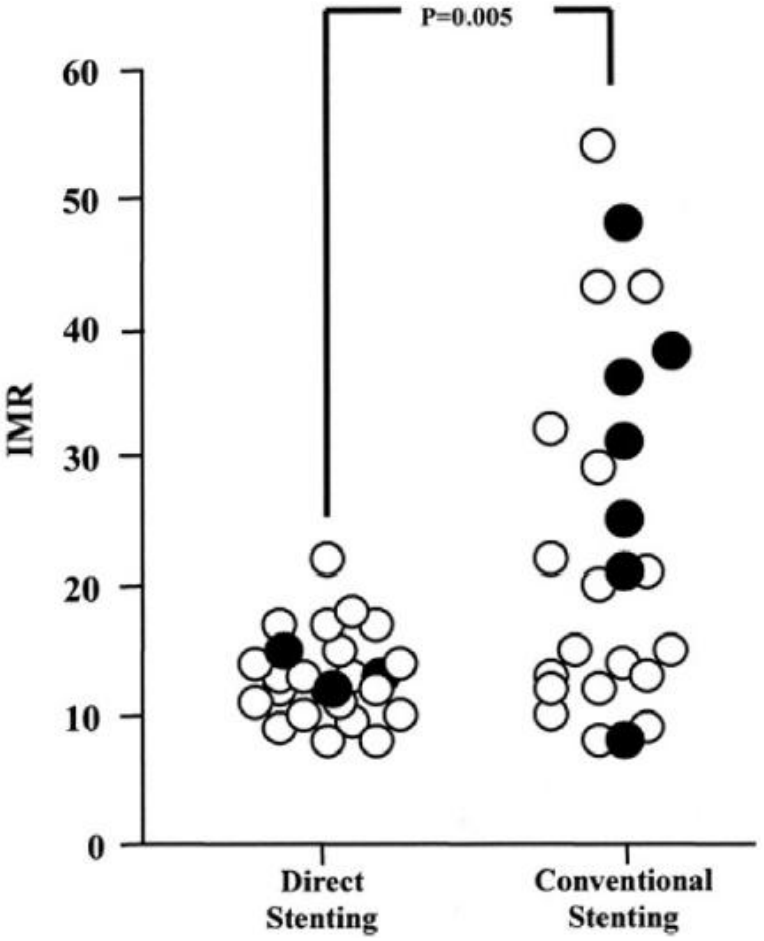
Assessment of microvascular damage after elective PCI

- 50 patients randomized to conventional stenting with predilatation versus direct stenting
- IMR measured after PCI and correlated with troponin release



Cuisset T, JACC 2008

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Clinical use of IMR

- Assessment of myocardial perfusion in STEMI patients
- Predictive value after primary PCI
- Assessment of microvascular damage after elective PCI
- Assessment of pharmacologic strategies to prevent microvascular damage after elective PCI

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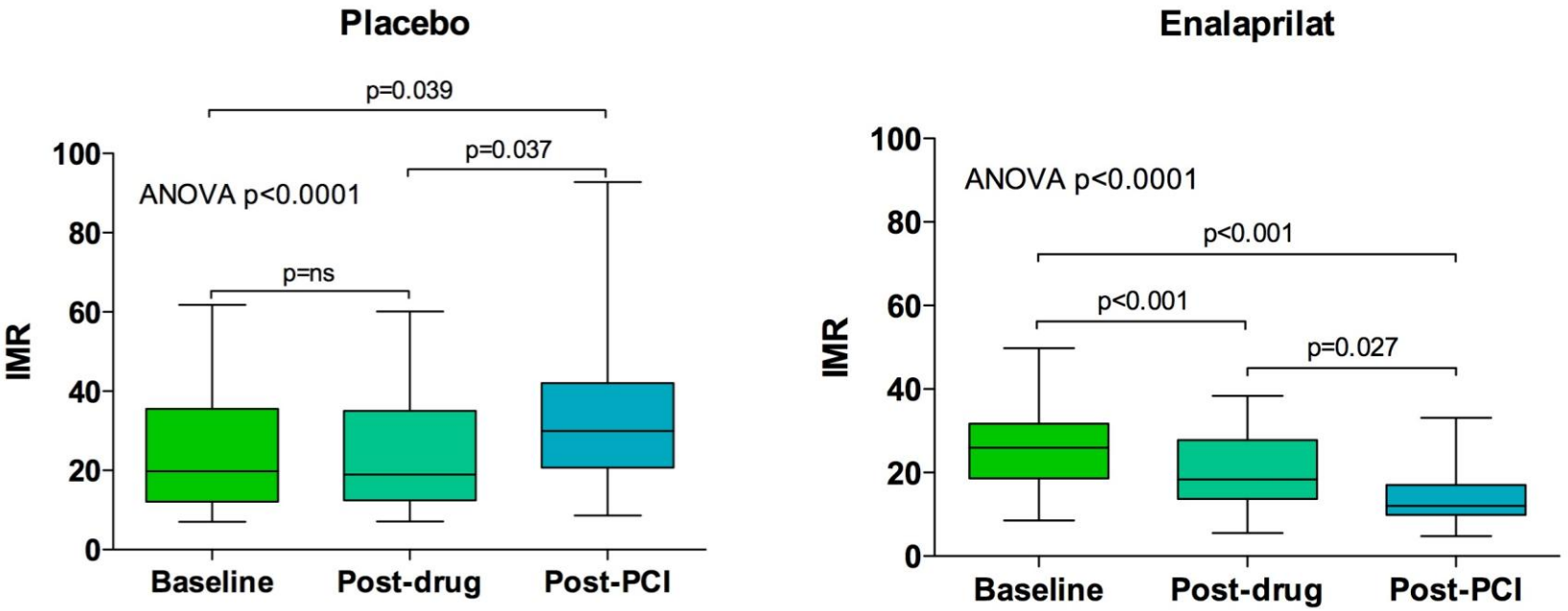
Assessment of pharmacologic strategies to prevent microvascular damage after elective PCI

ProMicro trial



Mangiacapra & Barbato, JACC 2013

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Conclusions

- Functional assessment of the coronary circulation enables the identification of the patients at increased risk of cardiovascular events
- With equivocal or absent objective evidence of vessel-related ischemia, FFR measurement is recommended to guide revascularization
- The latter when adopted eventually translates into an improved clinical outcome of the patients

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