

# How to find ischemia?

*FFR is the gold standard*

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# Disclosure Statement of Financial Interest

Within the past 12+ months, Nils Johnson has had a financial interest/arrangement or affiliation with the organization(s) listed below.

## Affiliation/Financial Relationship

- Grant/research support  
(to *institution*)
- Licensing and associated consulting  
(to *institution*)
- Support for educational meetings/training  
(honoraria/fees donated to *institution*)

## Organizations (alphabetical)

- St Jude Medical (for CONTRAST study)
- Volcano/Philips (for DEFINE-FLOW study)
- Boston Scientific  
(for smart-minimum FFR algorithm)
- Various, including academic and industry

# FFR = diagnostic test



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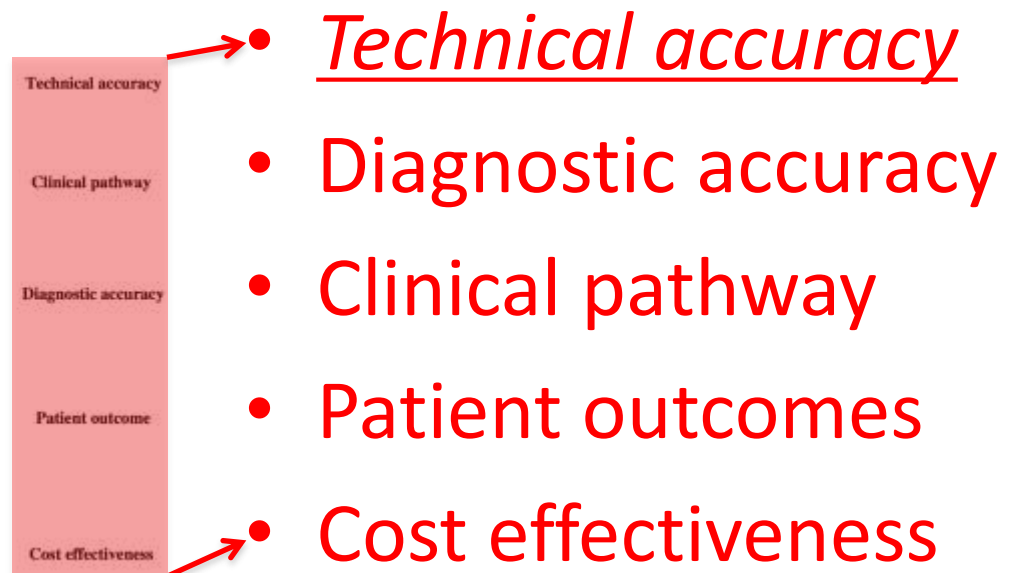
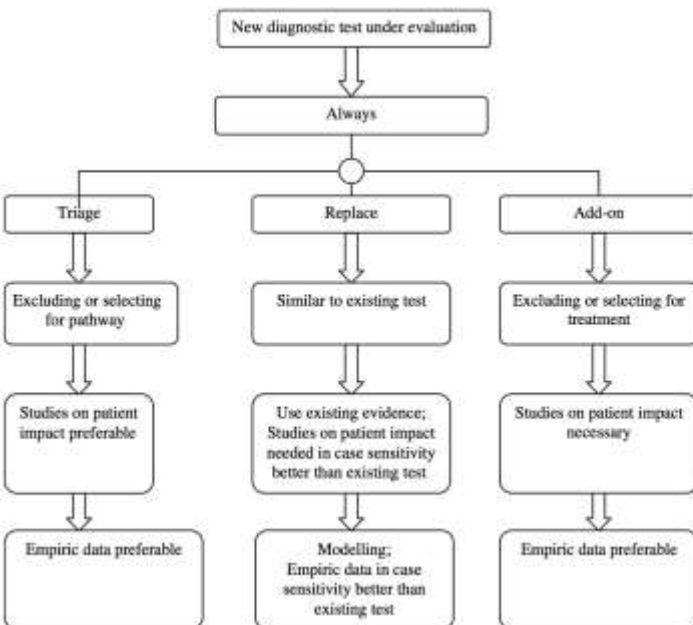
Journal of Clinical Epidemiology 60 (2007) 1116–1122

Journal of  
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## REVIEW ARTICLE

The **evaluation of diagnostic tests**: evidence on technical and diagnostic accuracy, impact on patient outcome and cost-effectiveness is needed

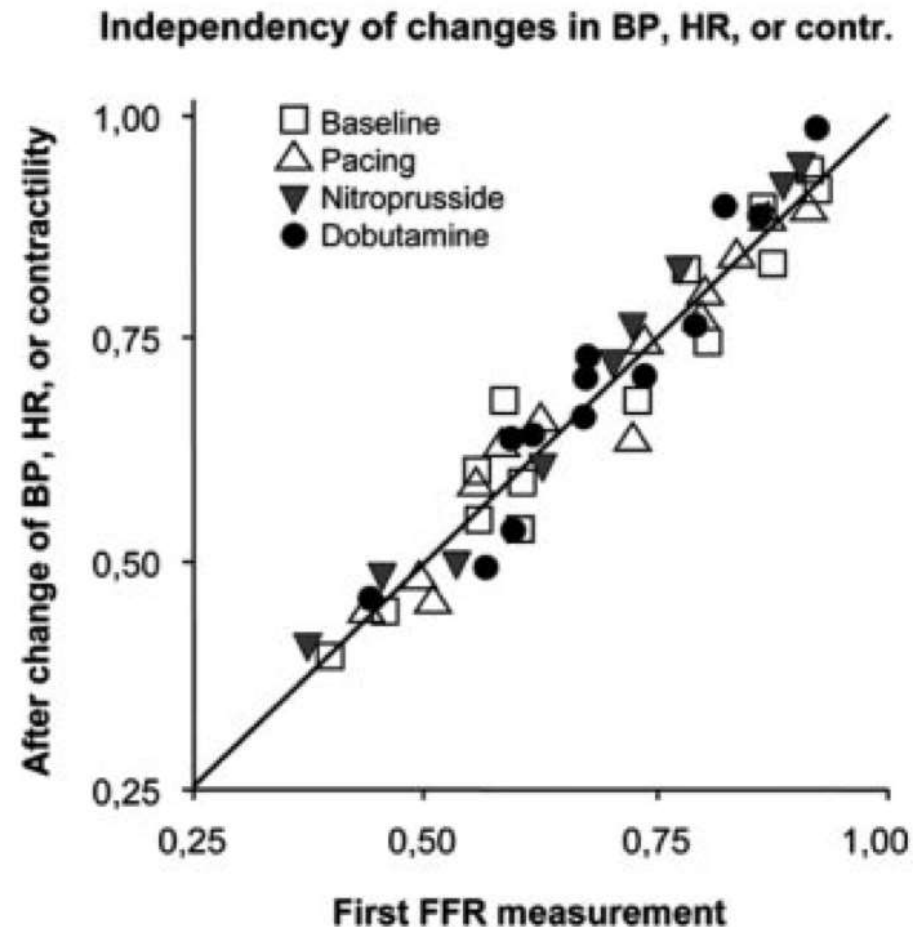
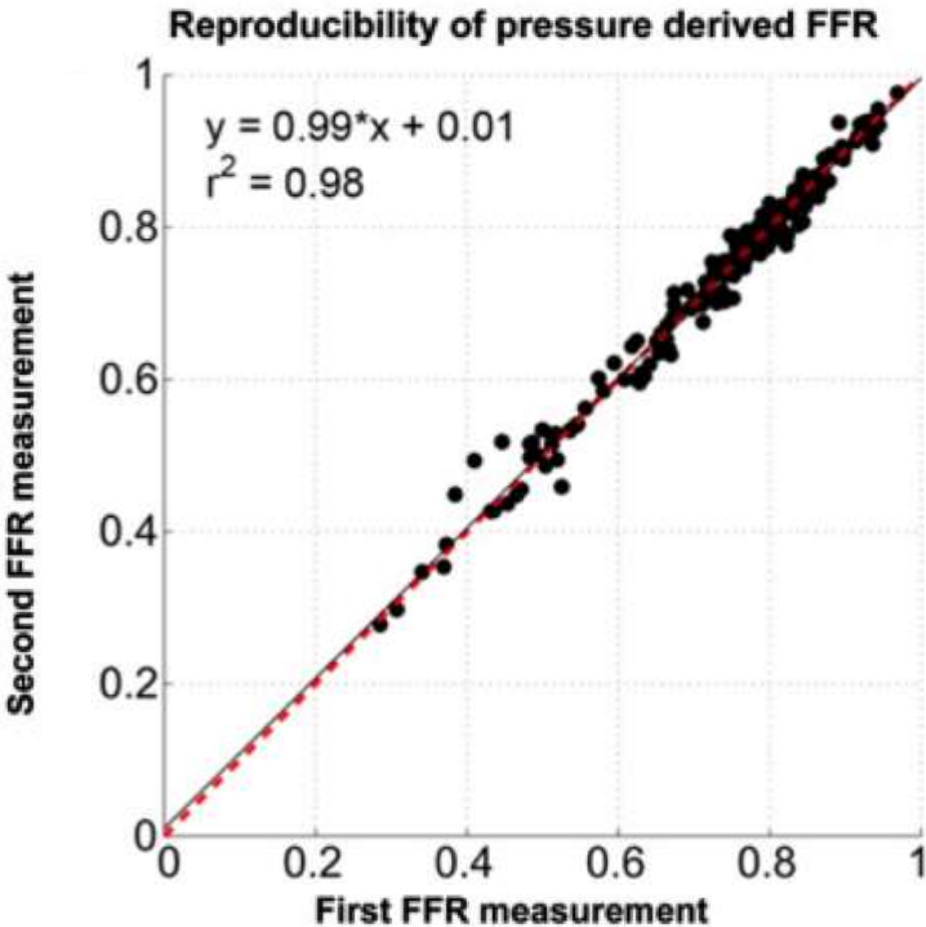
A. Van den Bruel<sup>a,b,d,\*</sup>, I. Cleemput<sup>b</sup>, B. Aertgeerts<sup>a,d</sup>, D. Ramaekers<sup>b,d</sup>, F. Buntinx<sup>a,c,d</sup>



# Technical accuracy

- **Analytical sensitivity**
  - Ability to detect a specified quantity of substance
  - Can the pressure wire *measure pressure* correctly?
- **Reproducibility**
  - Obtain the same result on repeated testing
  - *Stability of FFR* when measured twice

# Technical accuracy: Reproducibility



2<sup>nd</sup> measurement = 1<sup>st</sup> measurement

unaffected by hemodynamics

left inset = Berry C, *JACC*. 2013 Apr 2;61(13):1421-7. (Figure 5A)

right and frame = Kern MJ, *Circulation*. 2006 Sep 19;114(12):1321-41. (Figure 5)

# Technical accuracy: Reproducibility

**Table 1. Coefficients of Variation in Cardiology Practice**

Measurement	First Author (Ref. #)	Coefficient of Variation
FFR	Berry et al. (4)	3%
Fasting plasma glucose	Mooy et al. (6)	9%
Ambulatory systolic blood pressure	Eguchi et al. (7)	11%
LDL	Miller et al. (8)	6%–14%
Ejection fraction by echocardiography	Grothues et al. (9)	12%
Percent diameter stenosis by QCA	Reiber et al. (10)	17%–18%
CRP	Bower et al. (11)	46%

CRP = C-reactive protein; FFR = fractional-flow reserve; LDL = low-density lipoprotein; MRI = magnetic resonance imaging; QCA = quantitative coronary angiography.

# FFR = diagnostic test



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Technical accuracy  
Clinical pathway  
Diagnostic accuracy  
Patient outcome  
Cost effectiveness

- Technical accuracy
- Diagnostic accuracy
- Clinical pathway
- Patient outcomes
- Cost effectiveness

# Diagnostic accuracy

- Definition

- “test’s ability to correctly detect or exclude a target condition or disease in patients”

- Study design

- “*optimal design* is that of the *cross-sectional study* in which the index test is compared to a reference standard in a cohort of patients that are selected from a *clinically relevant population*”

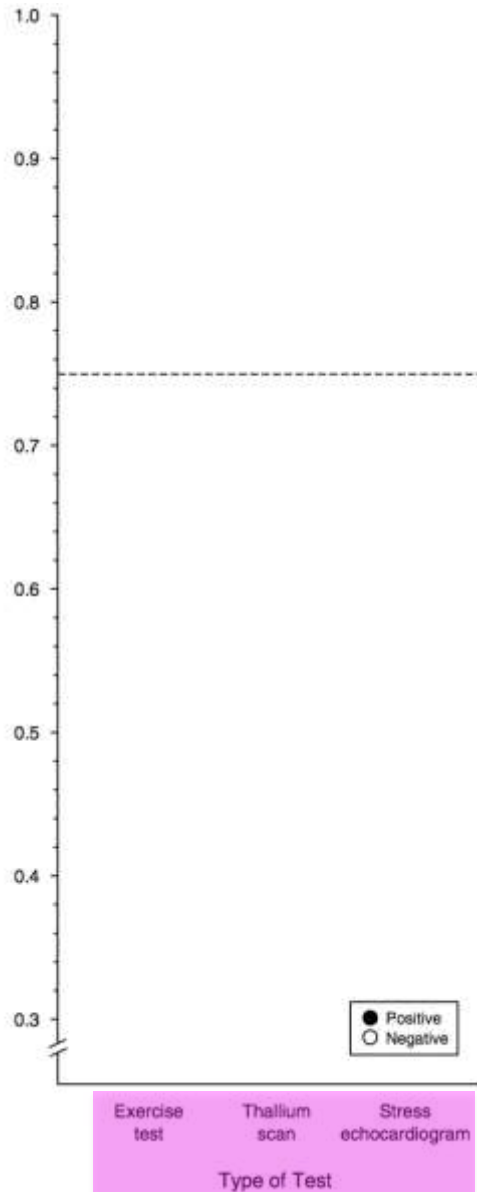


# Optimal design

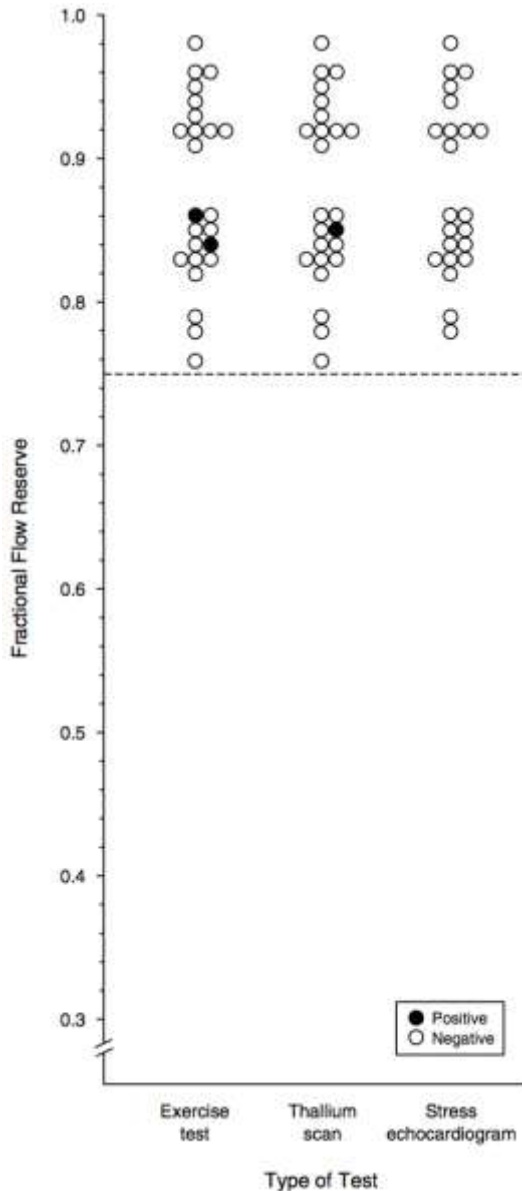
- 45 *consecutive* patients
  - *chest pain*
  - moderate ( $\approx 50\%$ ) *stenosis*
  - *uncertainty* on relationship between chest pain and stenosis
  - lesion located proximally in a *major coronary artery*

# Optimal design

- Exercise ECG
  - “*electrical* ischemia”
- Exercise SPECT
  - “*perfusion* ischemia”
- Dobutamine echocardiography
  - “*contractile* ischemia”
- FFR
  - new diagnostic test

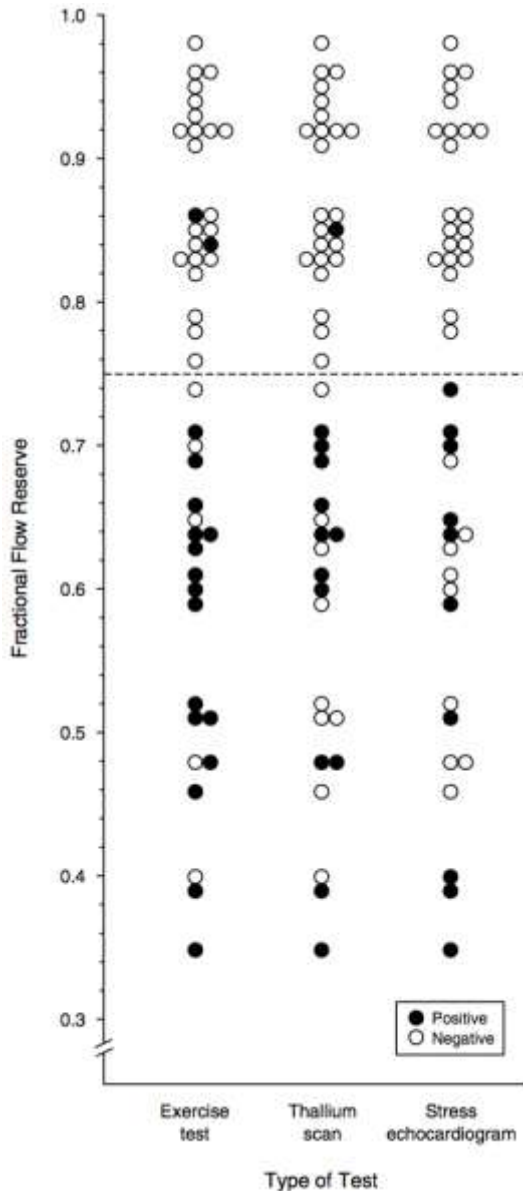


# Optimal design



- FFR > 0.75
  - 21 had all 3 tests negative
  - only 3 had only 1/3 tests positive
  - no events during 14 months with medical therapy

# Optimal design



- FFR < 0.75

- all 21 had 1+ test positive (often 2)
- 13 PCI, 7 CABG, 1 refused
- all *positive tests return to normal*
- all *FFR increased to >0.75* after PCI

# FFR = diagnostic test



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Technical accuracy  
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- Technical accuracy
- Diagnostic accuracy
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- Patient outcomes
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# Clinical pathway

- **Replace**
  - More accurate, cheaper, faster, and/or less invasive
  - (venous Doppler instead of invasive venography)
- **Triage**
  - Typically exclude patients from further evaluation
  - (D-dimer for PE, but if positive then need more testing)
- **Add-on**
  - Occurs after existing clinical pathway
  - (FFR after non-invasive testing and invasive angiography)

# Clinical pathway: FFR trials

- **Add-on**

- Occurs after existing clinical pathway
- Major outcome trials enrolled patients with
  - angina despite medical therapy
  - often non-invasive testing
  - significant angiographic lesion(s) in major vessel
- *Only then was FFR added*

# Clinical pathway: DEFER

- **Clinical symptoms despite medical therapy**
  - 86% taking at least 1 anti-anginal
  - all patients had angina, 89% significant symptoms
    - CCS class II – 52%
    - CCS class III – 29%
    - CCS class IV – 8%
- **Non-invasive testing**
  - negative, equivocal, or not done
- **Invasive angiography**
  - one lesion  $>50\%$ DS with RVD $>2.5$ mm
- *Only then add-on FFR*



# Clinical pathway: FAME 1

- **Clinical symptoms despite medical therapy**
  - 77%  $\beta$ -blocker, 34% nitrates, 22% calcium blocker
  - all patients had angina, 75% significant symptoms
    - CCS class II – 33%
    - CCS class III – 25%
    - CCS class IV – 17%
- **Non-invasive testing and invasive angiography**
  - two lesions >50%DS in a major vessel
  - “... thought to require PCI on the basis of angiographic appearance and clinical data”
- *Only then add-on FFR*

# Clinical pathway: FAME 2

- **Clinical symptoms despite medical therapy**
  - 76%  $\beta$ -blocker, 24% calcium blocker
  - 2/3 of patients had significant baseline angina
    - CCS class II – 45%
    - CCS class III – 16%
    - CCS class IV – 7%
- **Non-invasive testing and invasive angiography**
  - at least one lesion  $>50\%$ DS with RVD $>2.5$ mm
  - “... thought to require stenting on the basis of the clinical and angiographic data”
- *Only then add-on FFR*

# Clinical pathway: FFR trials

- **Add-on**

- Occurs after existing clinical pathway
- Major outcome trials enrolled patients with
  - angina despite medical therapy
  - often non-invasive testing
  - significant angiographic lesion(s) in major vessel
- *Only then was FFR added*
- Thus *FFR augments, not replaces, clinical judgment*

# FFR = diagnostic test



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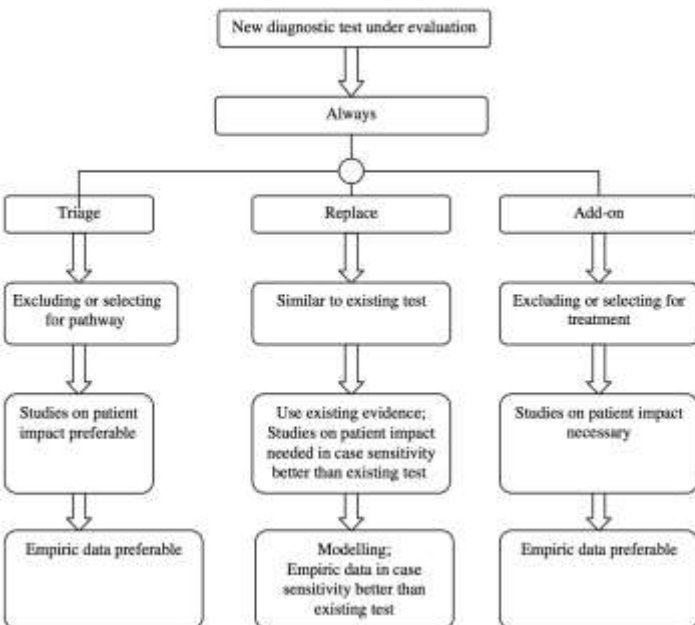
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# Patient outcomes

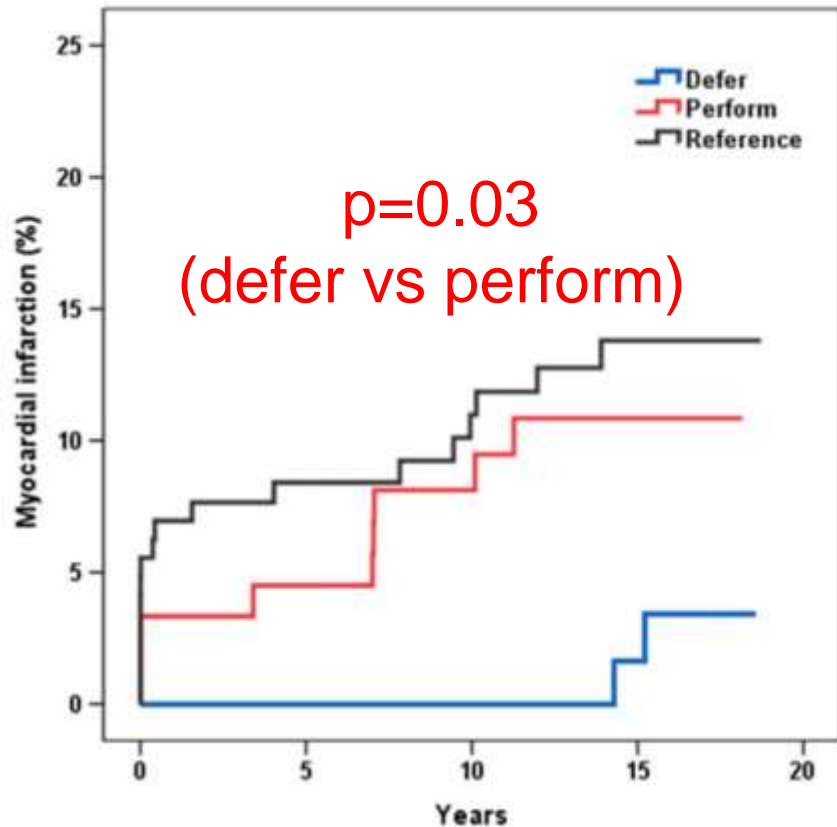
- Definition

- “ultimate goal of health care is to improve patient **outcome**: expected harm, such as burden, pain, risk, or costs, should be weighed against expected benefit, such as improved life expectancy, quality of life, avoidance of other test procedures, etc.”

- Study design

- “the *randomized controlled trial (RCT)* is the study design the *least prone to bias* to estimate these risks and benefits”

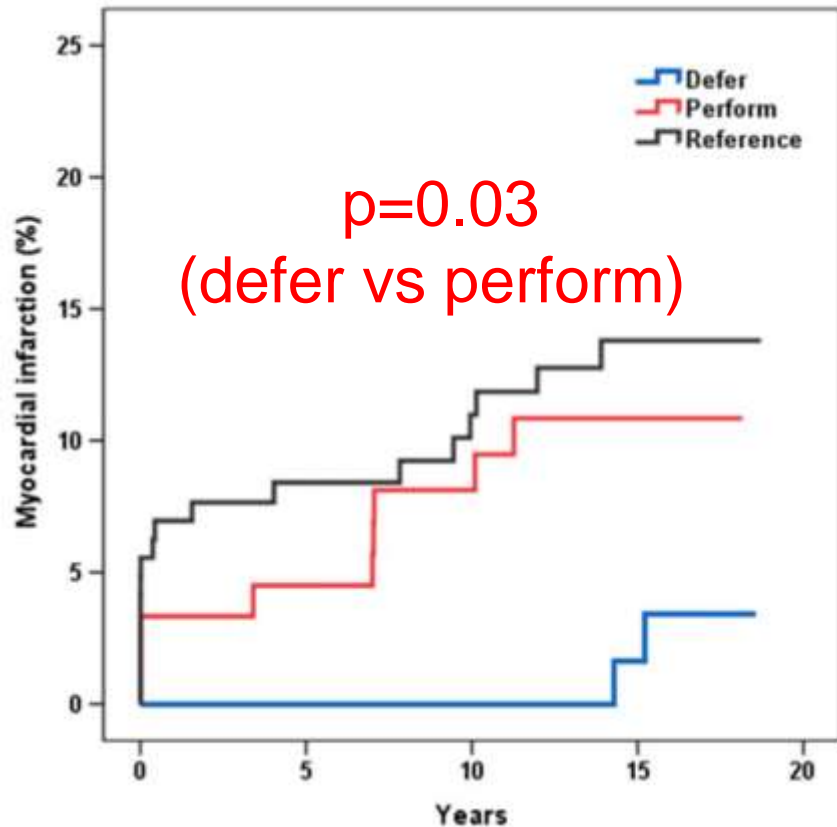
# Patient outcomes: RCT – DEFER



*significant*

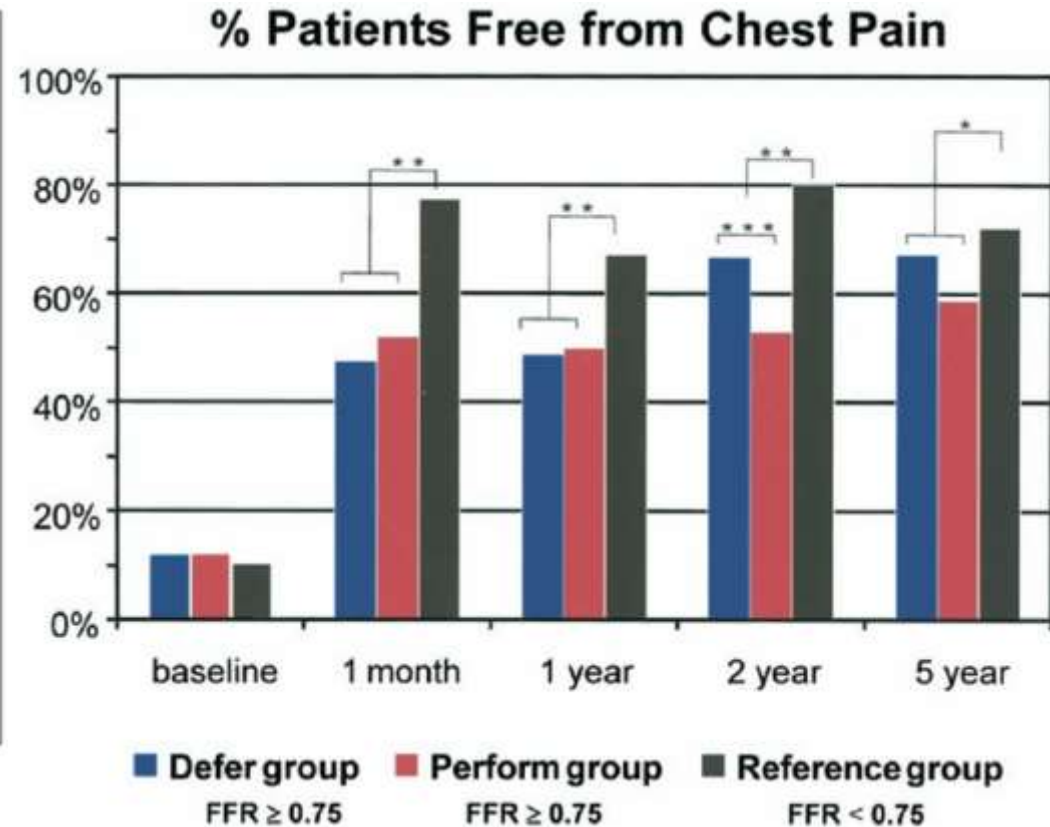
decrease in MI

# Patient outcomes: RCT – DEFER



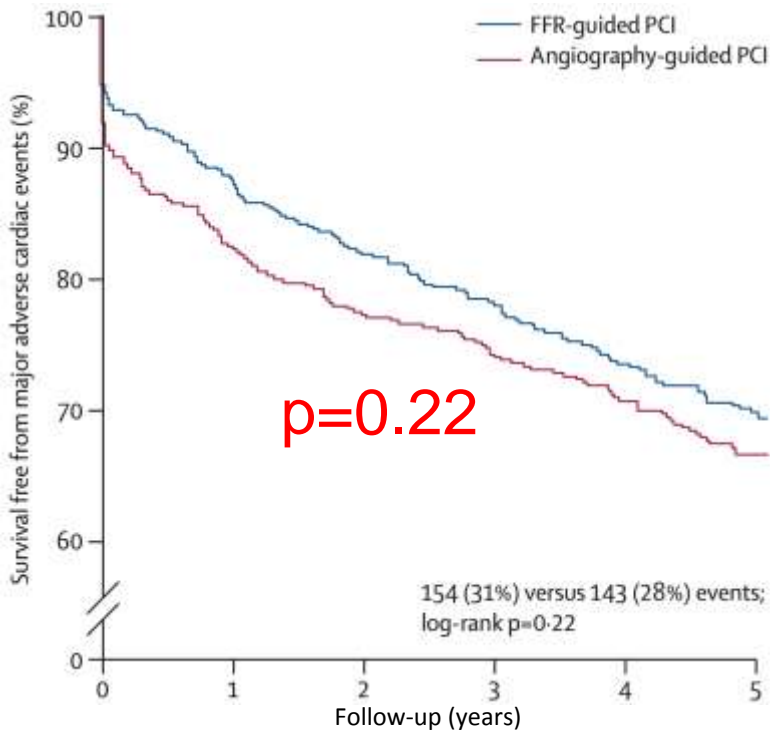
*significant*

decrease in MI



If  $FFR \geq 0.75$ , then defer PCI offers *same* angina relief *without* more medication

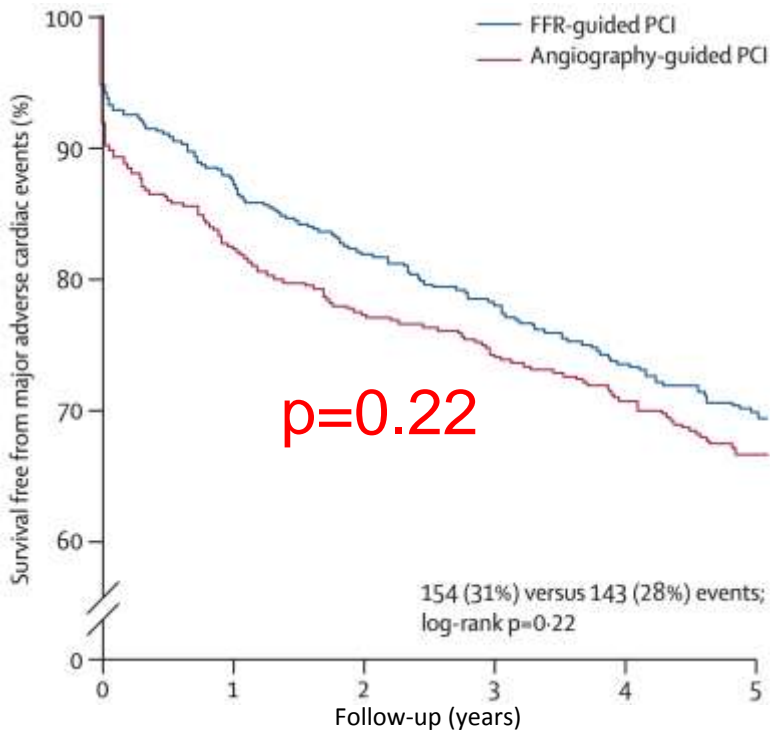
# Patient outcomes: RCT – FAME 1



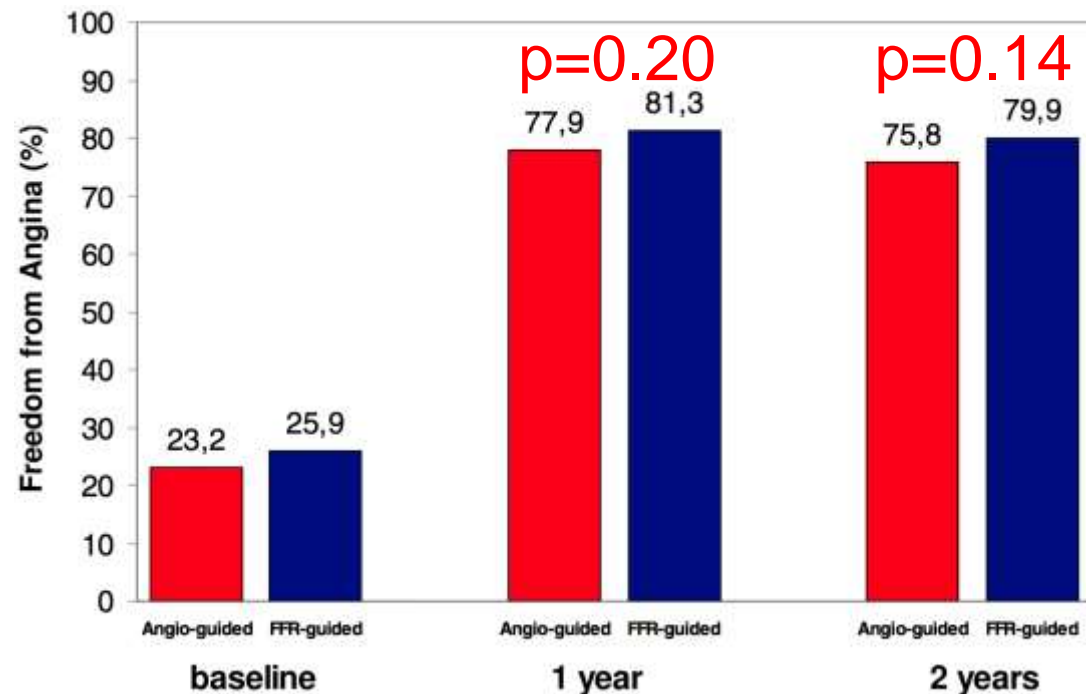
*trend* towards  
decreased death/MI



# Patient outcomes: RCT – FAME 1

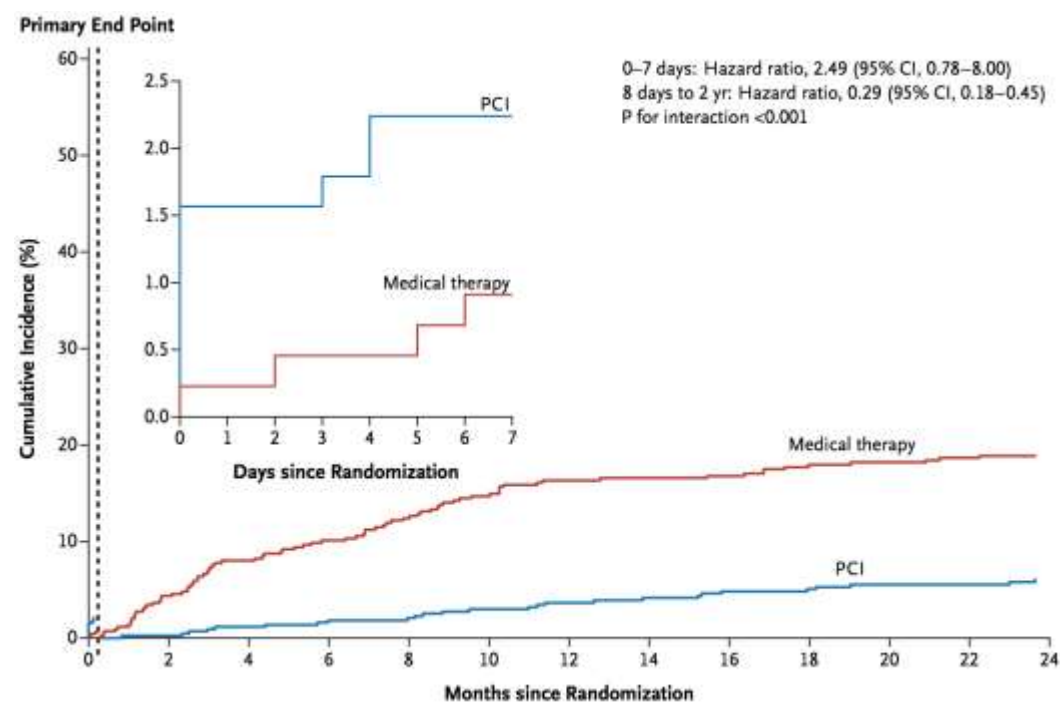


*trend* towards  
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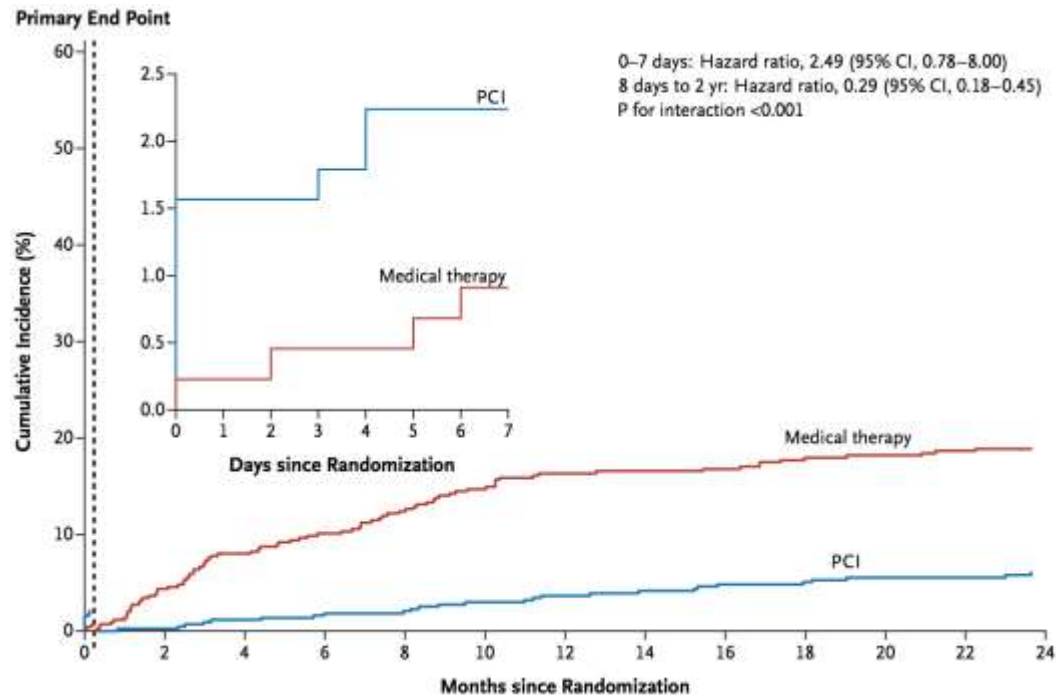
If  $FFR > 0.80$ , then defer PCI  
offers *same* angina relief  
*without* more medication

# Patient outcomes: RCT – FAME 2

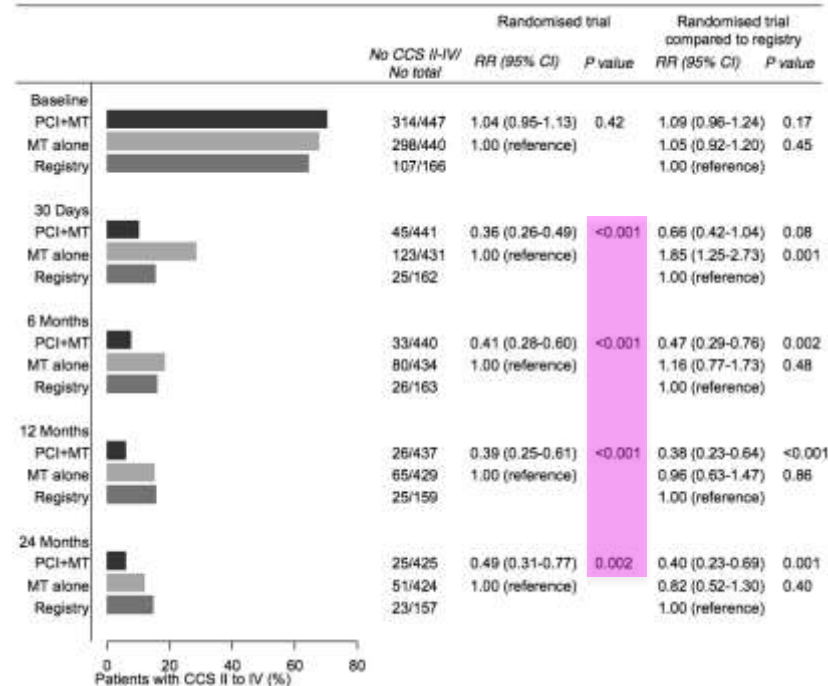


*trend* towards  
decreased death/MI  
especially after 7 days

# Patient outcomes: RCT – FAME 2

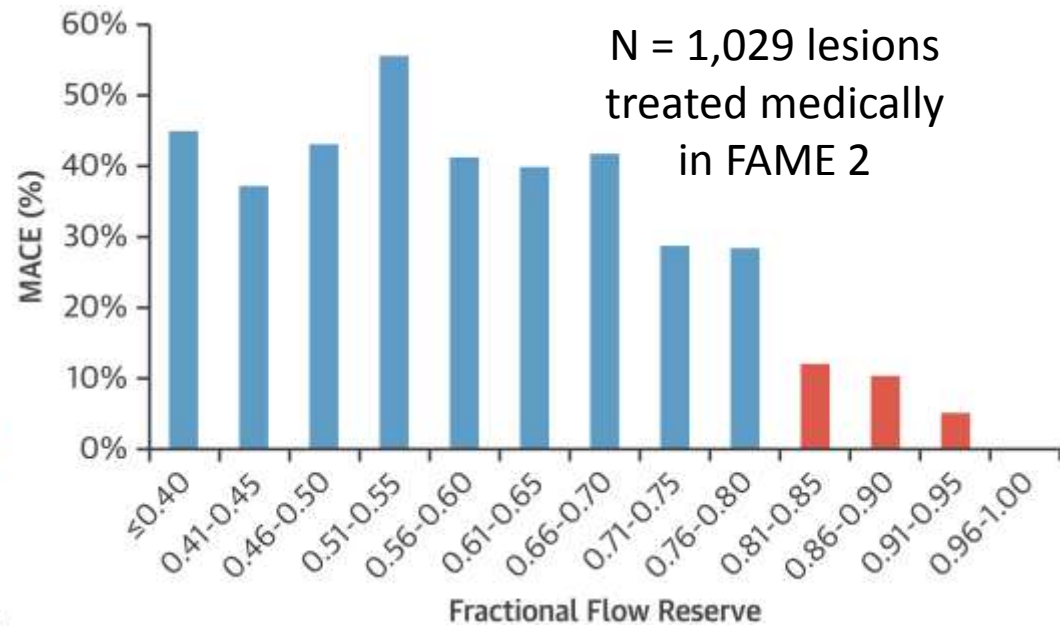
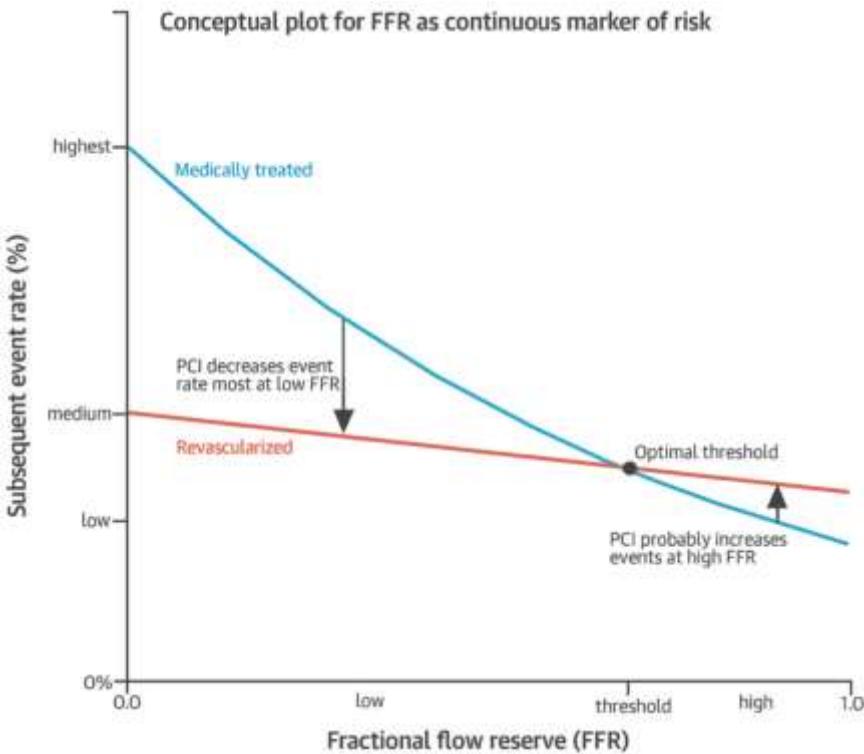


*trend* towards  
 decreased death/MI  
 especially after 7 days



If  $FFR \leq 0.80$ , then PCI  
 offers *better* angina relief  
 compared to *medical therapy*

# FFR risk continuum



Allows for “personalized” treatment

left = Johnson NP, *JACC*. 2014 Oct 21;64(16):1641-54. (Central Illustration)

right = Barbato E, *JACC*. 2016 Nov 29;68(21):2247-2255. (Figure 3 with annotation)

# FFR = diagnostic test



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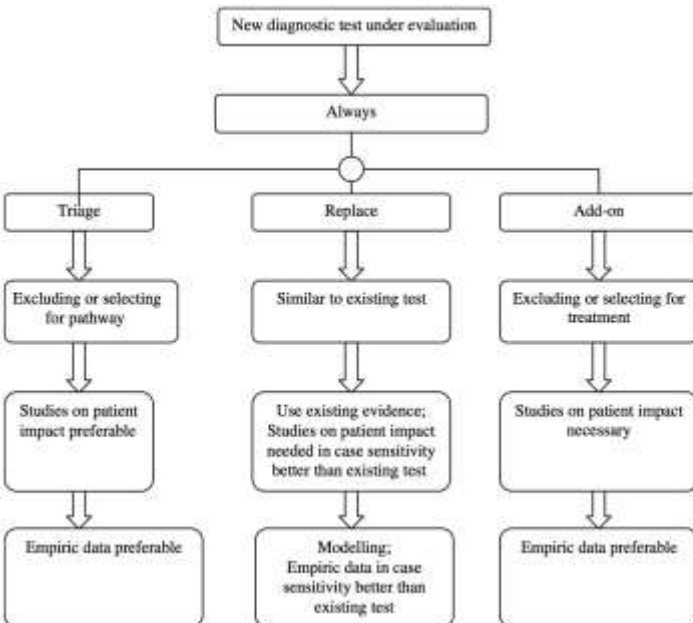
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# Cost effectiveness

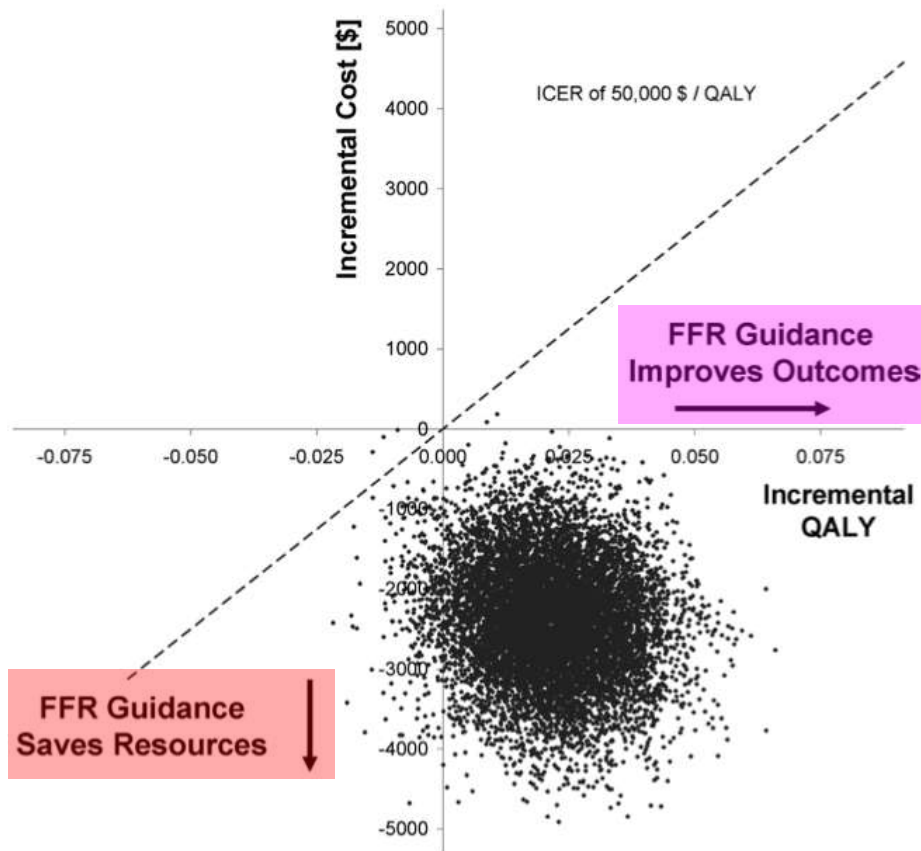
- Definition

- “goes beyond the individual risks and benefits, but assesses whether the *cost of using a given test is acceptable to society*”

- Study design

- “cost-effectiveness of diagnostic tests is often assessed by means of economic models ... the values of all *input variables must be based on solid evidence* from literature or observations”

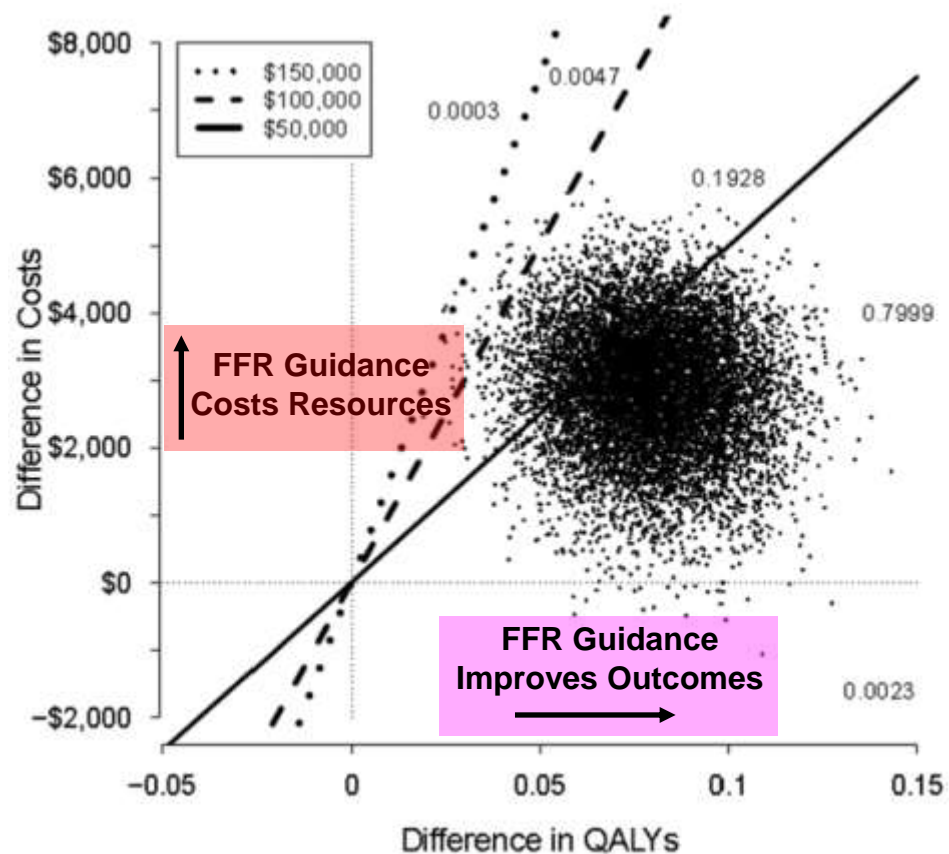
# Cost effectiveness: FAME 1&2



In FAME 1, FFR

improved outcomes (QALY)

and reduced cost



In FAME 2, FFR

improved outcomes (QALY)

but increased cost

Tradeoff: \$36,000/QALY

FAME 1 = Fearon WF, *Circulation*. 2010 Dec 14;122(24):2545-50. (Figure 1)

FAME 2 = Fearon WF, *Circulation*. 2013 Sep 17;128(12):1335-40. (Figure 2)

# FFR = gold standard

- Technical accuracy
  - FFR offers *superior repeatability* to most clinical tests



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- Patient outcome
  - FFR improved outcomes in *DEFER, FAME 1, FAME 2*
  - FFR has *continuous relationship with prognosis*

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  - FFR improved outcomes in *DEFER, FAME 1, FAME 2*
  - FFR has *continuous relationship with prognosis*
- Cost effectiveness
  - FFR *dominant in FAME 1, cost effective in FAME 2*