# Experimental Basis and Clinical Validation of FFR

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# Disclosure Statement of Financial Interest

***Within the past 12 months, I or my spouse/partner have had a financial interest /arrangement or affiliation with the organization(s) listed below***

| Affiliation/Financial Relationship | Company |
|---|---|
| Grant/ Research Support: | St. Jude Medical |
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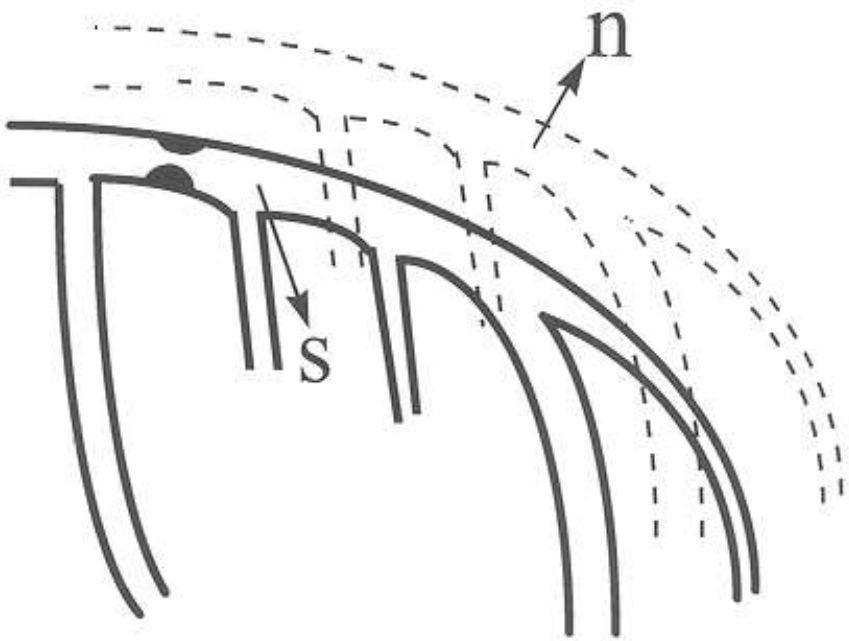
| Consulting Fees/Honoraria: | Medtronic |
| Major Stock Shareholder/Equity Interest: | |
| Royalty Income: | |
| Ownership/Founder: | |
| Salary: | NIH-R01 HL093475 (PI) |
| Intellectual Property Rights: | |
| Other Financial Benefit (minor stock options): | HeartFlow |

# Fractional Flow Reserve (FFR)

**Maximum flow down a vessel in the presence of a stenosis…**

**…compared to the maximum flow in the hypothetical absence of the stenosis**




Pijls and De Bruyne, Coronary Pressure
Kluwer Academic Publishers, 2000

# Derivation of FFR

- $$\text{FFR} = \frac{\text{Coronary Flow (Stenosis)}}{\text{Coronary Flow (Normal)}}$$

- $$\text{Coronary Flow} = \frac{\text{Pressure}}{\cancel{\text{Resistance}}}$$

- ***at maximal hyperemia*** $\text{Coronary Flow} \approx \text{Pressure}$

# Derivation of FFR

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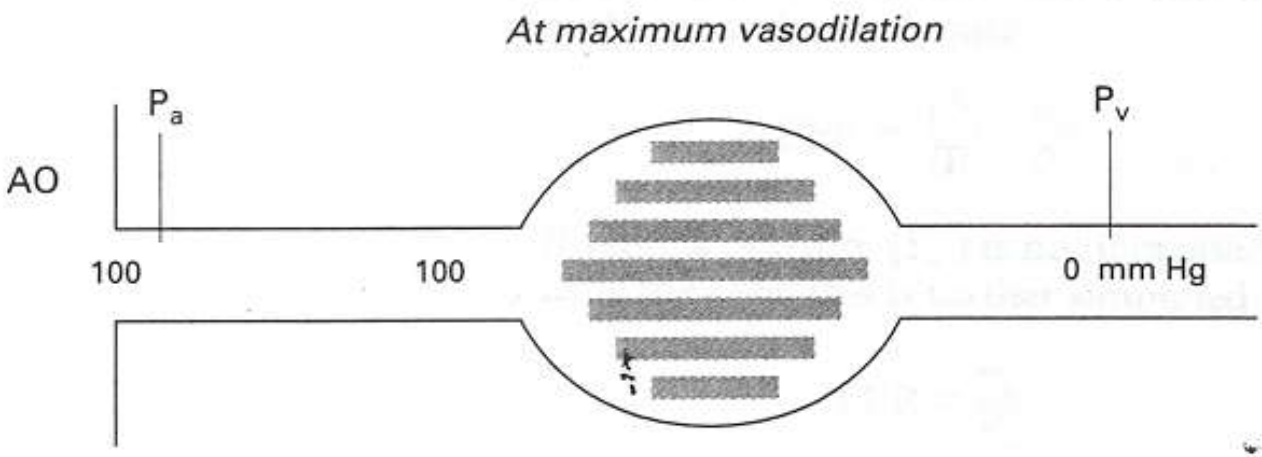
- $$\text{Coronary Flow} = \frac{\text{Pressure}}{\cancel{\text{Resistance}}}$$

- ***at maximal hyperemia*** Coronary Flow ≈ Pressure




Adapted from: Pijls and De Bruyne, Coronary Pressure
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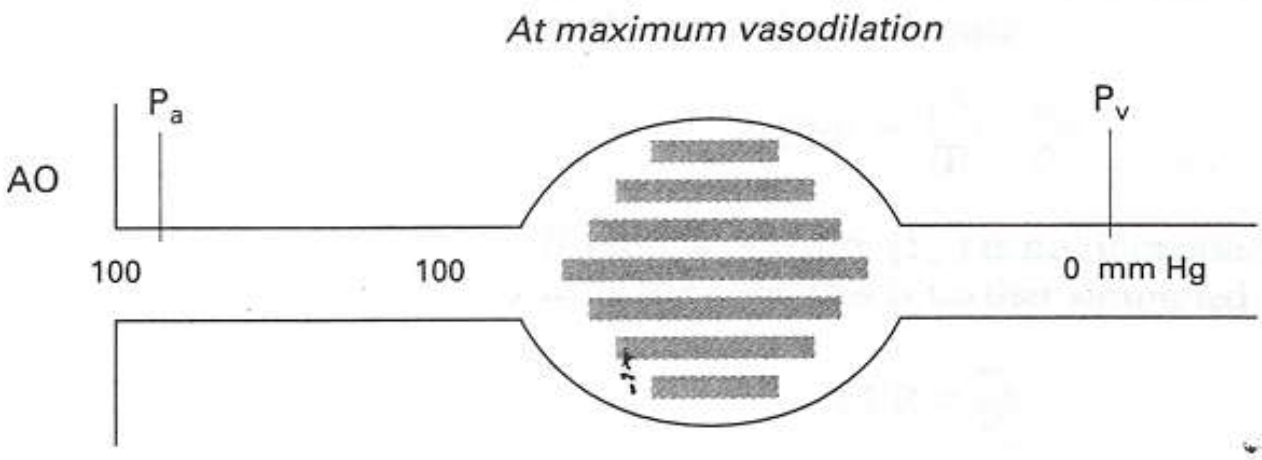
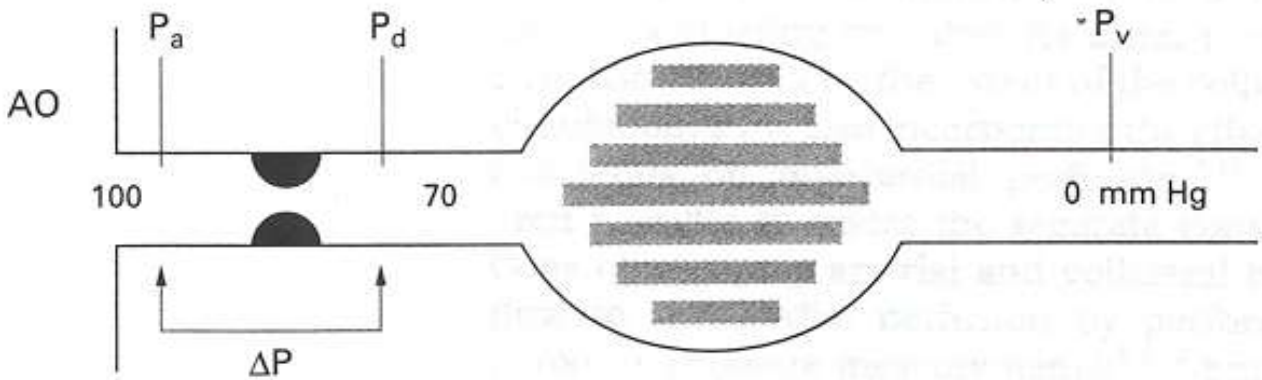



**FFR = $P_d$ / $P_a$**

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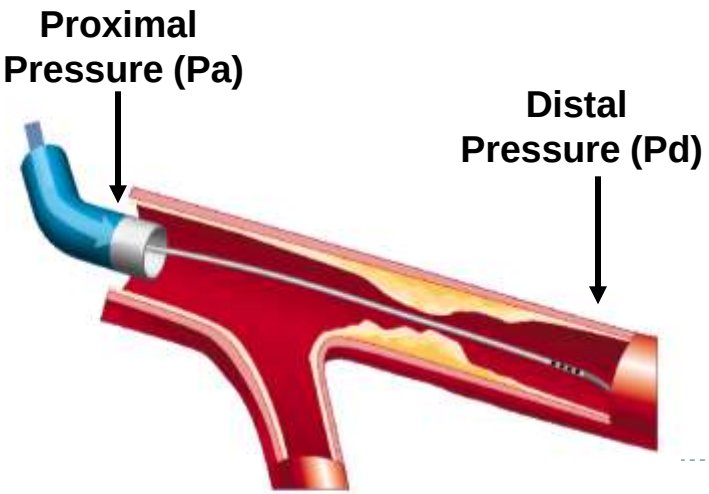
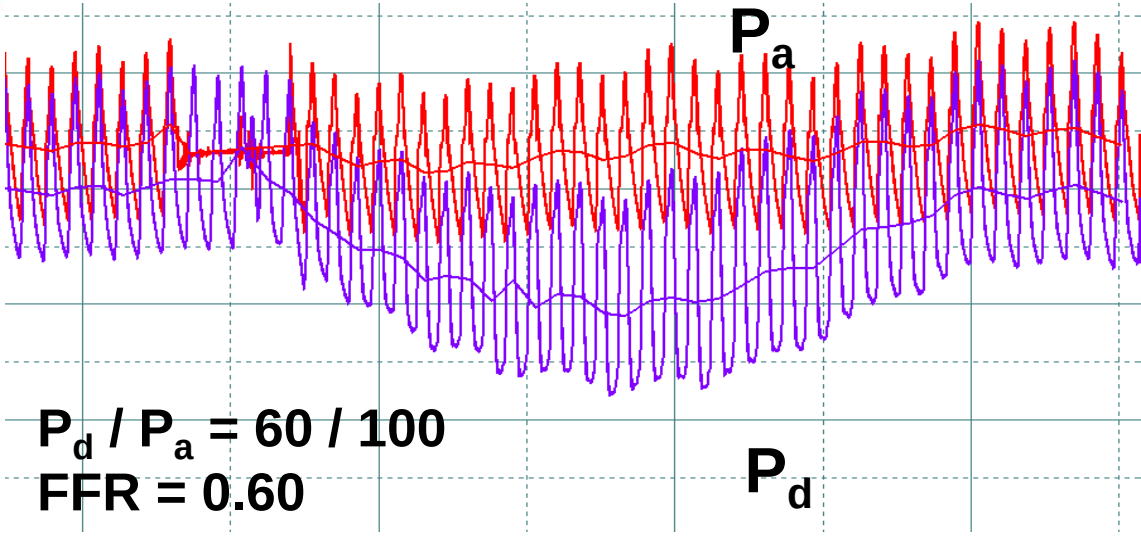
# Fractional Flow Reserve




**FFR = $P_d$ / $P_a$**

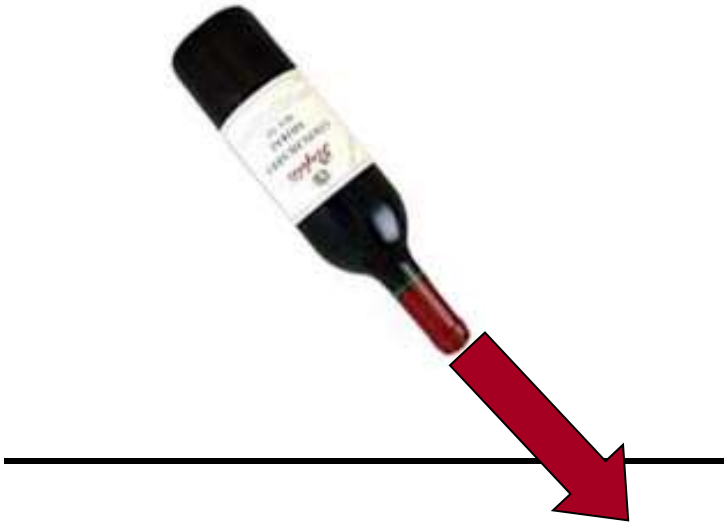
***during maximal flow***




**$P_d$ / $P_a$ = 60 / 100**
**FFR = 0.60**

# CFR

*Hyperemic Flow*



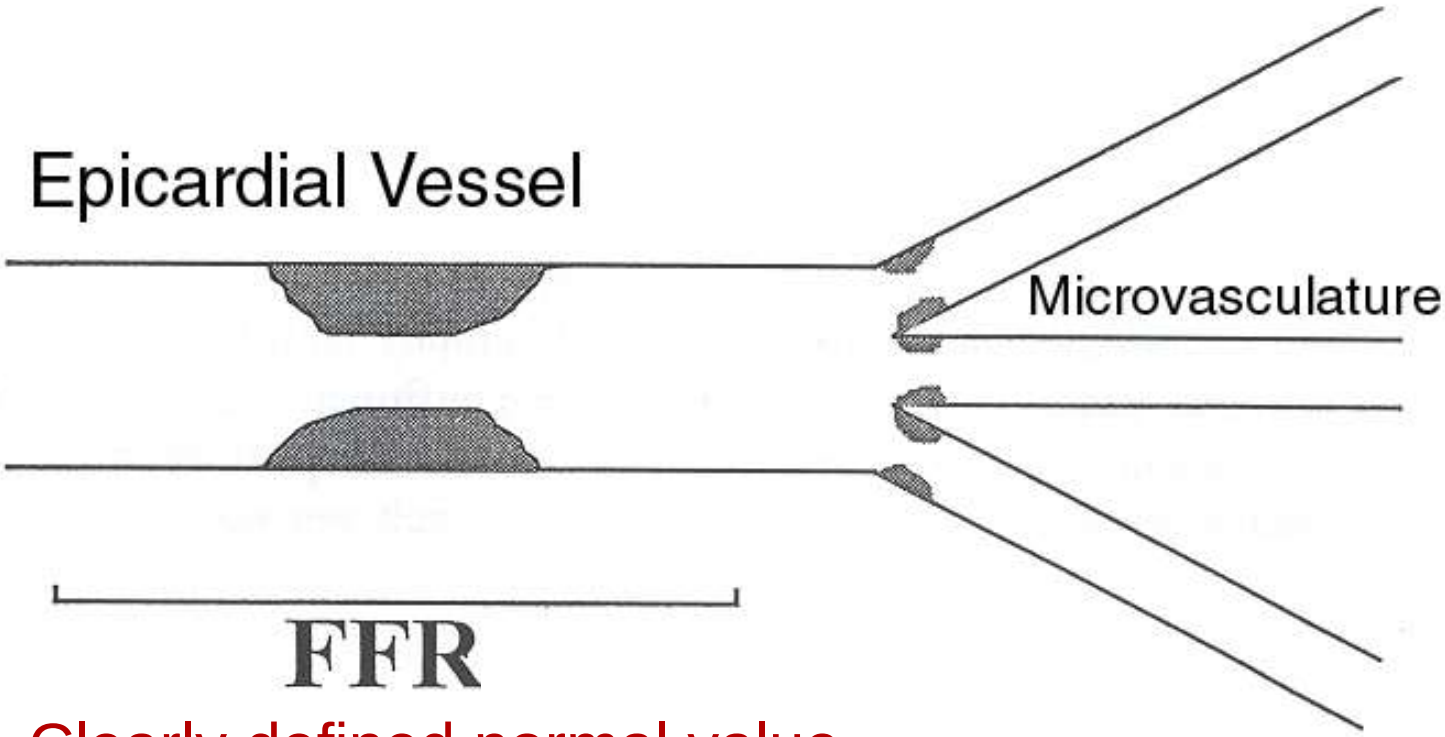
*Resting Flow*

# FFR

*Hyperemic Flow with Stenosis*

*Hyperemic Flow without Stenosis*

# Unique Aspects of FFR

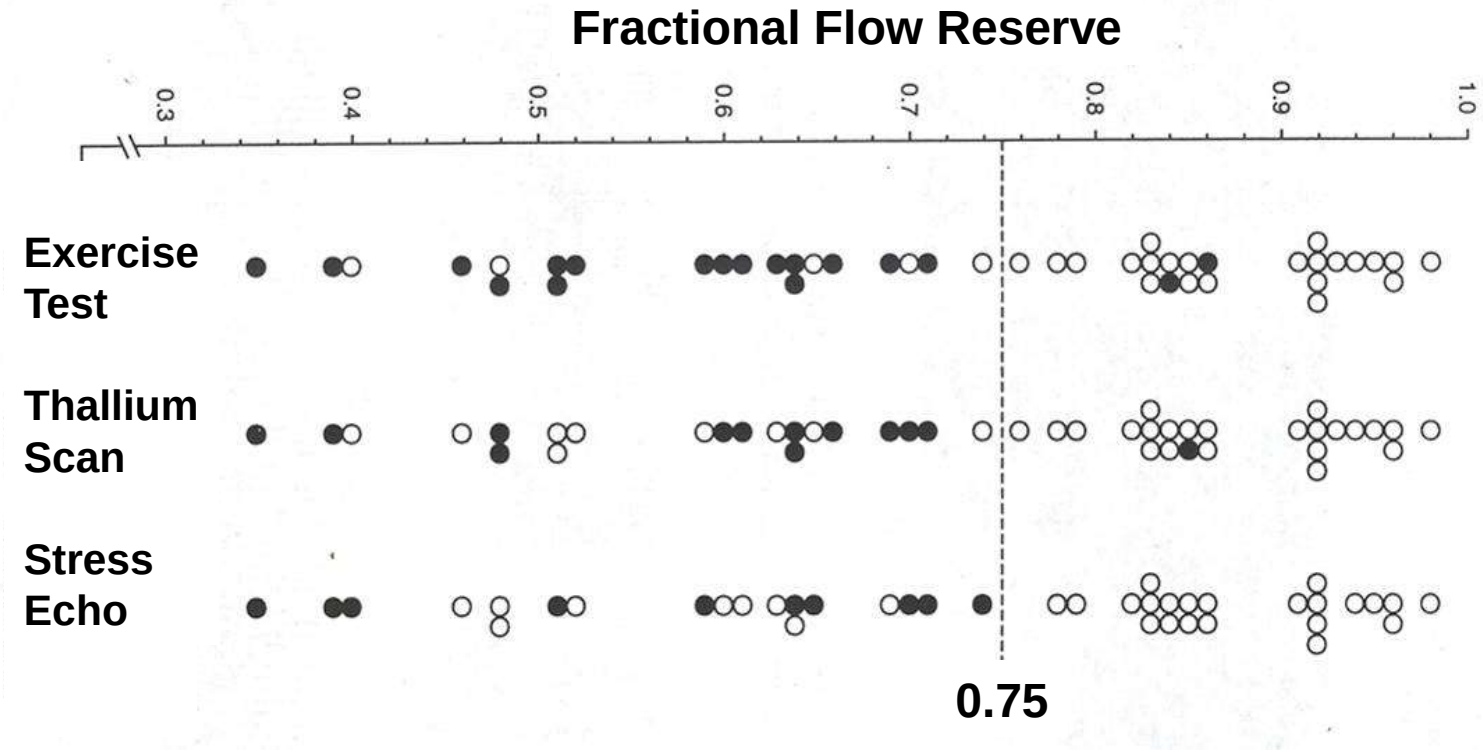



- Clearly defined normal value
- Not affected by resting hemodynamics
- Relatively easy to perform

Adapted from: Pijls and De Bruyne, Coronary Pressure
Kluwer Academic Publishers, 2000

# Validation of FFR

***FFR compared to noninvasive "gold" standard of 3 stress tests (accuracy > 95%)***




***FFR < 0.75*** **: Sensitivity = 88%**
**Specificity = 100%**

Pijls, et al. New Engl J Med 1996;334:1703

# FFR Validation Studies

## *Noninvasive Imaging*

| Study | Number of patients (lesions) | Ischaemic test | Best cut-off value | Accuracy (%) | Clinical setting |
|---|---|---|---|---|---|
| *Intravenous adenosine infusion (140 μg/kg/min)* | | | | | |
| Pijls (1995)[34] | 60 (60) | X-ECG | 0.74 | 97 | SVD |
| Pijls (1996)[33] | 45 (45) | X-ECG, MPS, DSE | 0.75 | 93 | SVD |
| Jimenez-Navarro (2001)[120] | 21 (21) | DSE | 0.75 | 90 | SVD |
| Rieber (2004)[121] | 48 (48) | MPS, DSE | 0.75 | 76–81 | MVD |
| Erhard (2005)[122] | 47 (47) | MPS, DSE | 0.75 | 77 | MVD |
| Hacker (2005)[123] | 50 (50) | MPS | 0.75 | 86 | SVD |
| **Total or average (as applicable)** | **271 (271)** | **NA** | **0.75** | **87** | **NA** |
| *Intracoronary adenosine bolus (maximum 40–60 μg)* | | | | | |
| Tron (1995)[124] | 62 (70) | MPS | 0.69 | 67 | 1, 2, and 3-VD |
| Bartunek (1997)[125] | 37 (37) | DSE | 0.67 | 90 | SVD |
| Caymaz (2000)[126] | 30 (40) | MPS | 0.75 | 95 | SVD |
| Fearon (2000)[127] | 10 (10) | MPS | 0.75 | 95 | SVD |
| Chamuleau (2001)[128] | 127 (161) | MPS | 0.74 | 77 | MVD |
| Seo (2002)[129] | 25 (25) | MPS | 0.75 | 60 | Previous MI |
| Kruger (2005)[130] | 42 (42) | MPS | 0.75 | 88 | ISR |
| Samady (2006)[131] | 48 (48) | MPS, DSE | 0.78 | 92 | Previous MI |

# FFR Validation Studies

## *Noninvasive Imaging*

| | | | | | |
|---|---|---|---|---|---|
| van de Hoef (2012)[66]* | 232 (299) | MPS | 0.76 | 74 | MVD |
| **Total or average (as applicable)** | **613 (732)** | **NA** | **0.74** | **83** | **NA** |
| *Other method of vasc* | | | | | |
| De Bruyne (1995)[38] (Intracoronary papave | | | | 87 | SVD |
| Bartunek (1996)[132] (Intracoronary papave | | | | 81 | SVD |
| Abe (2000)[133] (Intravenous ATP) | | | | 91 | SVD |
| De Bruyne (2001)[134] (Intravenous or intrac or intravenous ATP) | | | | 85 | Previous MI |
| Yanagisawa (2002)[135] (Intracoronary papave | | | | 76 | Previous MI |
| Ziaee (2004)[136‡] (Intravenous or intrac | | | | 88 | Ostial |
| Morishima (2004)[137] (Intracoronary papave | | | | 85 | SVD |
| Kobori (2005)[138§] (Intracoronary papaverine) | | | | 70 | Restenosis |
| Ragosta (2007)[139] (Intracoronary adenosine, 30–40 μg in the RCA, 80–100 μg in the LCA) | 36 (36) | MPS | 0.75 | 69 | MVD |

***> 1,500 Patients***

***24 Studies***

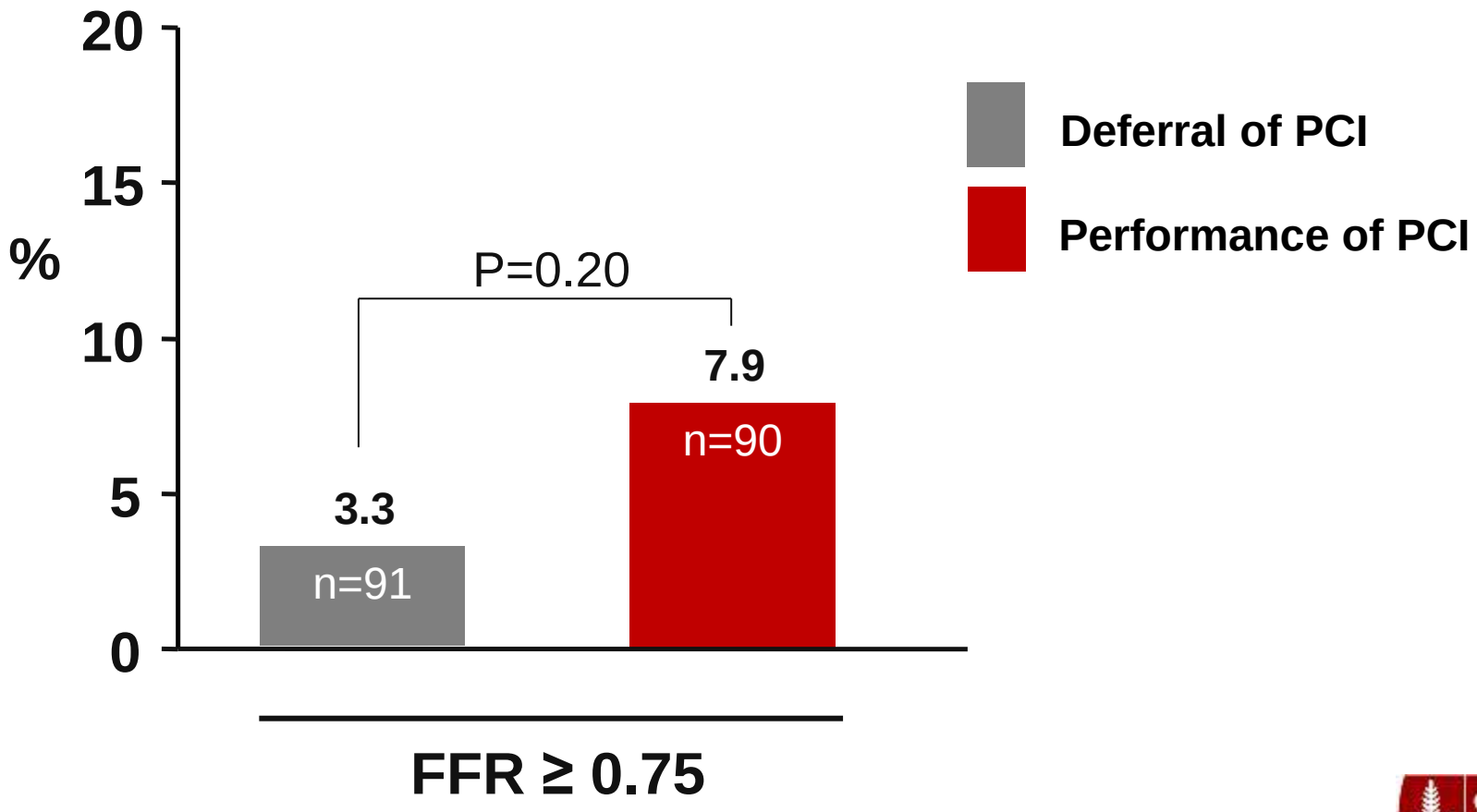
***Best Cut-Off Value?***

***< 0.75***

van de Hoef, et al. Nat Rev Cardiol 2013;10:439-52.

# Safety of Deferring PCI Based on FFR

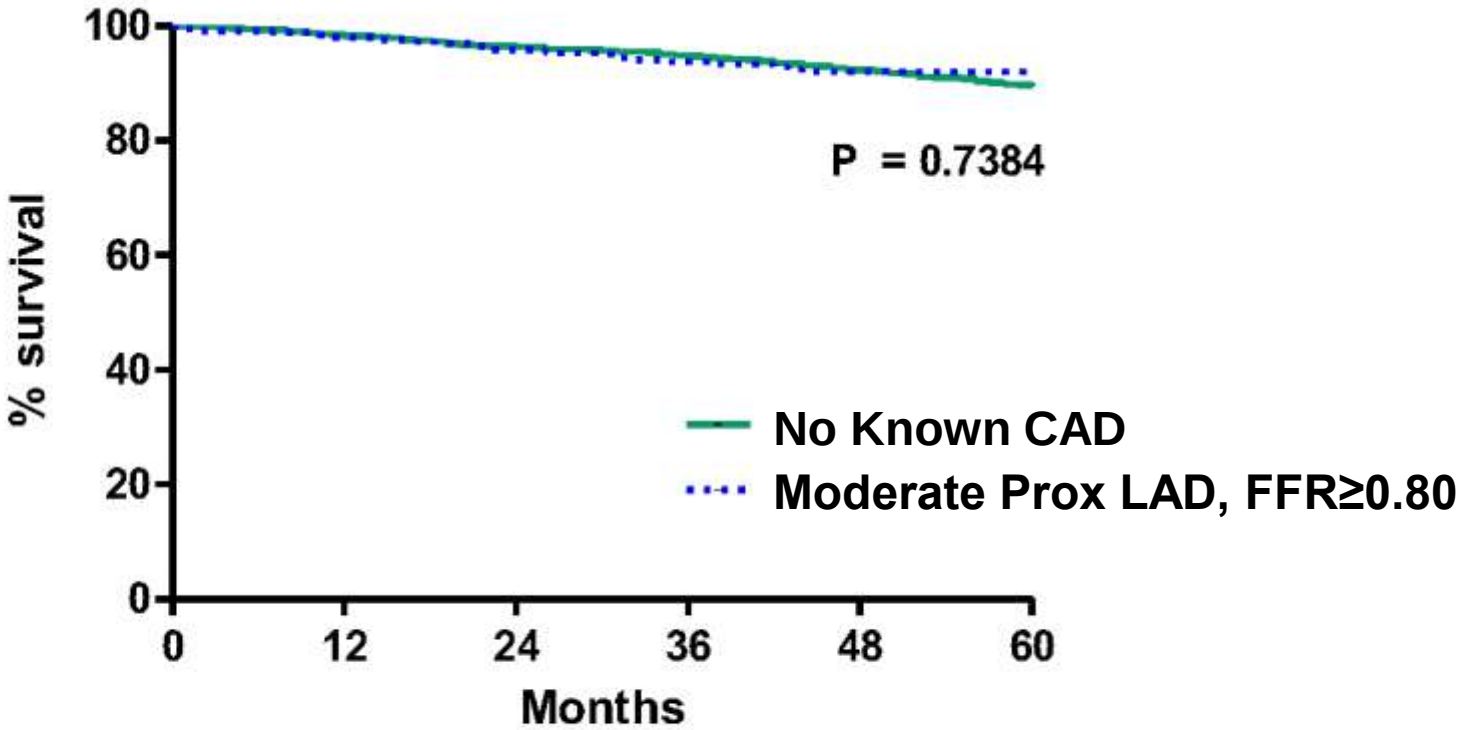
## *5 Year Cardiac Death and MI rate in DEFER trial*




Pijls, et al. J Am Coll Cardiol 2007;49:2105-11.

# Safety of Deferring PCI Based on FFR

***5 year follow-up of 564 intermediate proximal LAD lesions deferred because FFR≥0.80***




| No at risk | | | | | | |
|---|---|---|---|---|---|---|
| - - - - | 466 | 410 | 341 | 262 | 173 | 109 |
| ——— | 1868 | 1839 | 1803 | 1772 | 1725 | 1675 |

Adapted from: Muller, et al. JACC Cardiovasc Interv 2011;4:1175-82

# What happens to deferred lesions?

**513 Deferred Lesions in 509 FFR-Guided Patients**

↓ *2 Years*

**9**
**Late Myocardial Infarctions**

→ **8**
**Stent-Related or due to a New Lesion**

↓

**1**
**Myocardial Infarction due to an Originally Deferred Lesion**

***Two Year Follow-up of Lesions Deferred in FAME***

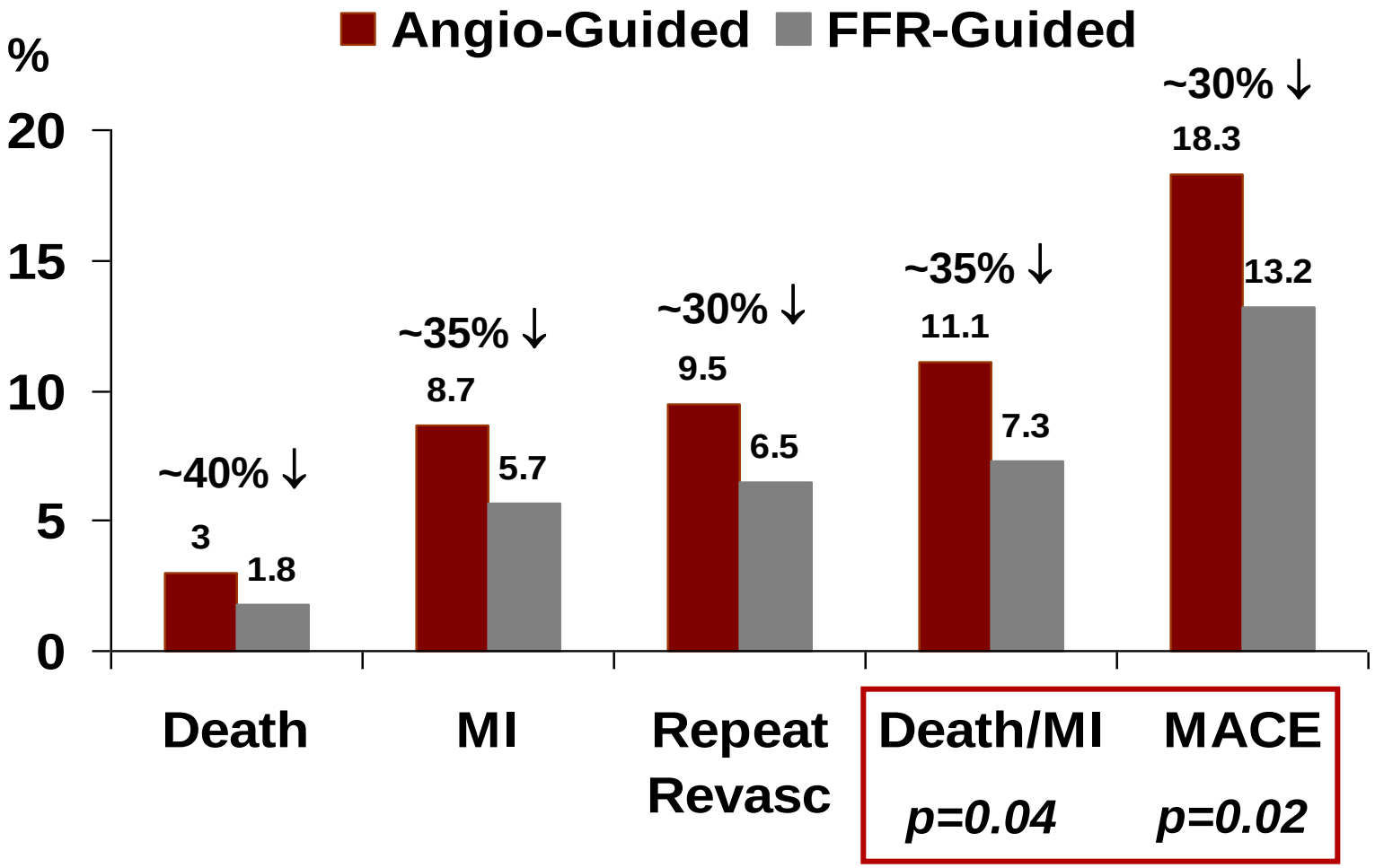
**Deferred Lesion Events**

- ***Only 0.2% caused an MI***
- ***Only 3.2% required revascularization***

Pijls, et al. J Am Coll Cardiol 2010;56:177-84

# FAME Study: One Year Outcomes

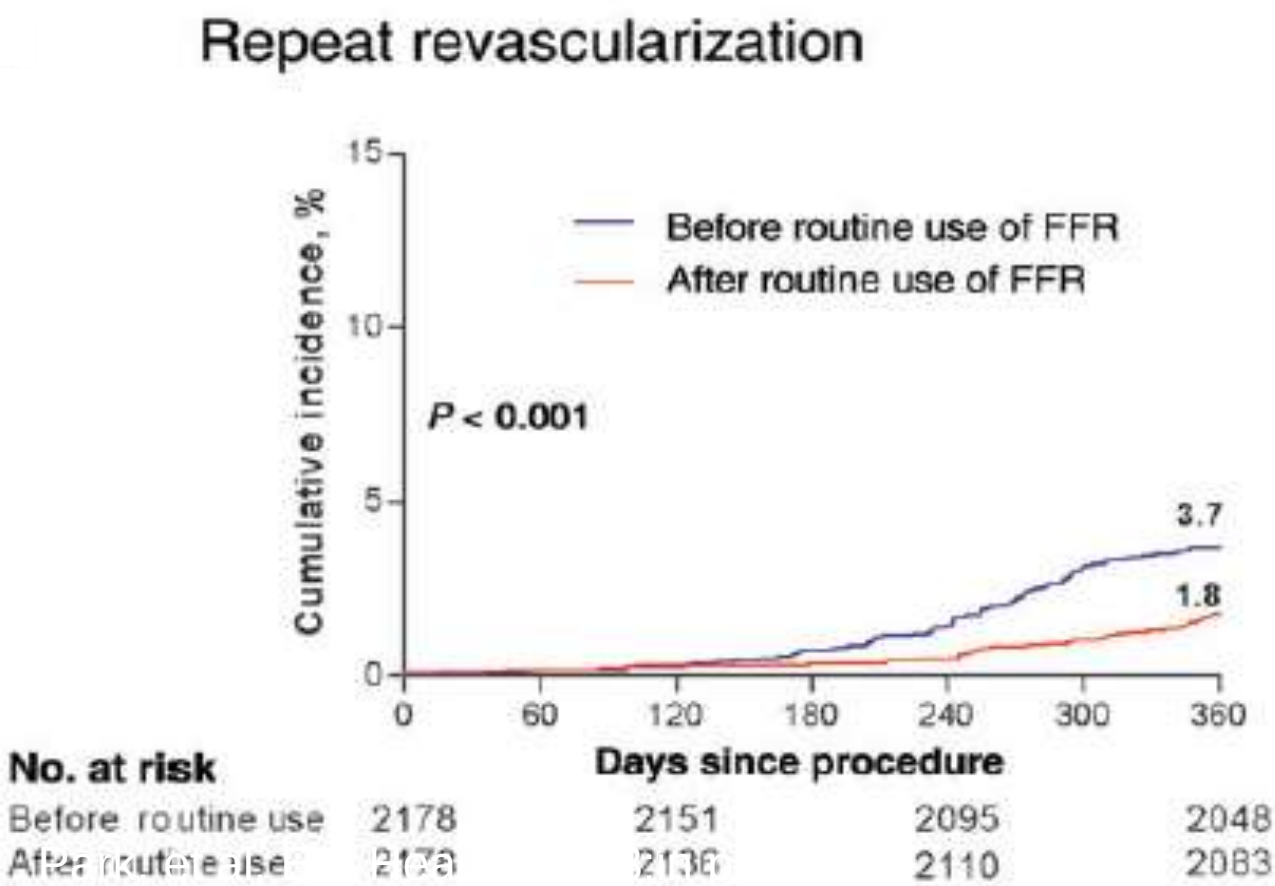
***1,005 patients with multivessel CAD randomized to FFR or Angio-guided PCI***




Tonino, et al. New Engl J Med 2009;360:213-24.

# Real World FFR Use

***2,178 pairs of propensity matched patients before and after routine FFR use***




Park SJ, et al. Eur Heart J 2013;34:3353-61.

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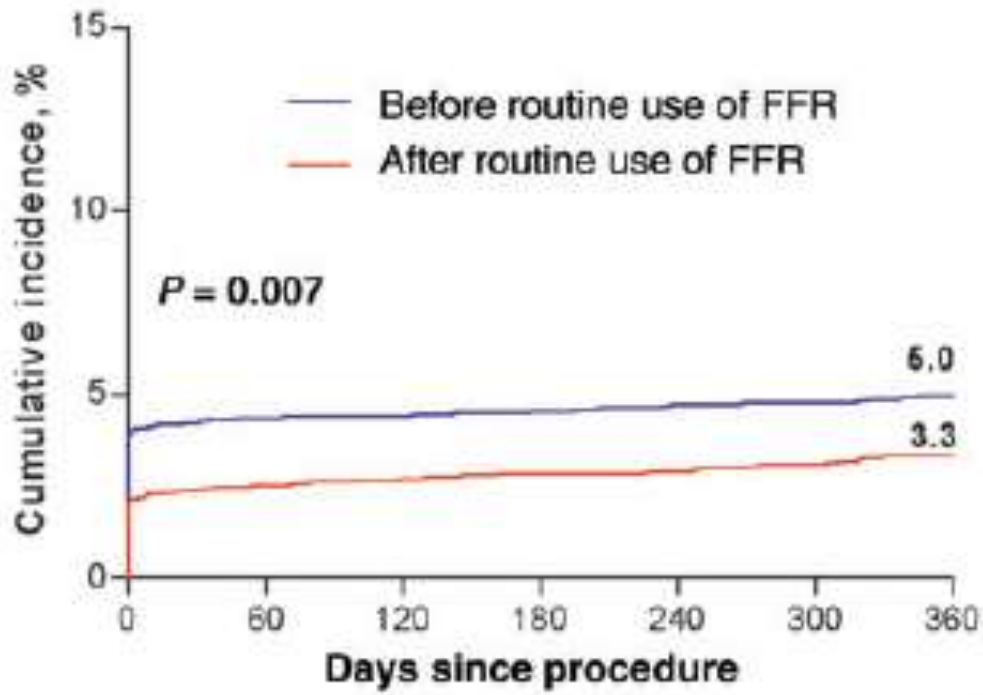


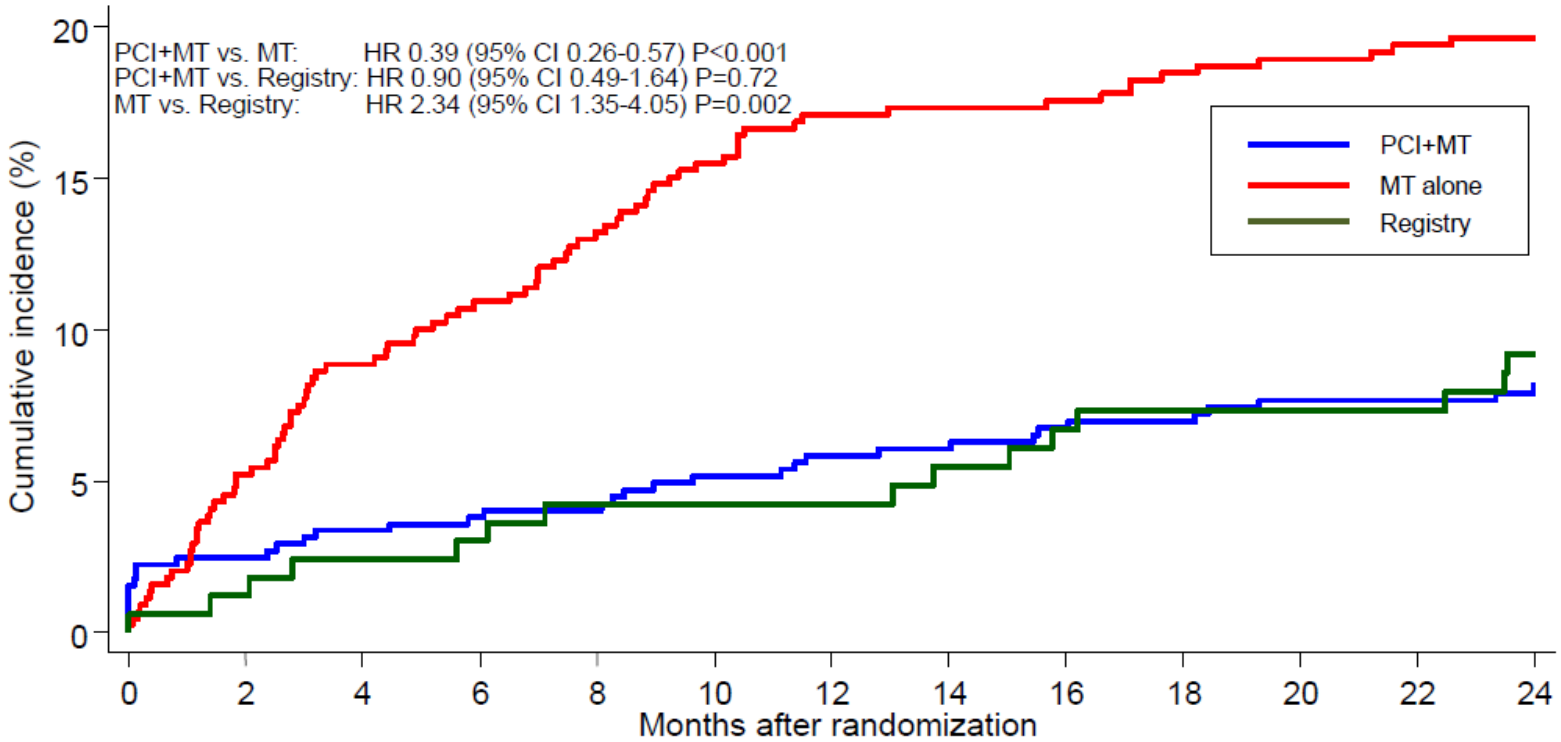

| No. at risk | | | | |
|---|---|---|---|---|
| Before routine use | 2178 | 2071 | 2041 | 2036 |
| After routine use | 2178 | 2098 | 2075 | 2066 |

Park SJ, et al. Eur Heart J 2013;34:3353-61.

# If the FFR is ≤ 0.80, is it unsafe to defer PCI?

# FAME 2: Two Year Follow-Up

***Two year rate of primary endpoint: Death, MI, Urgent Revascularization***



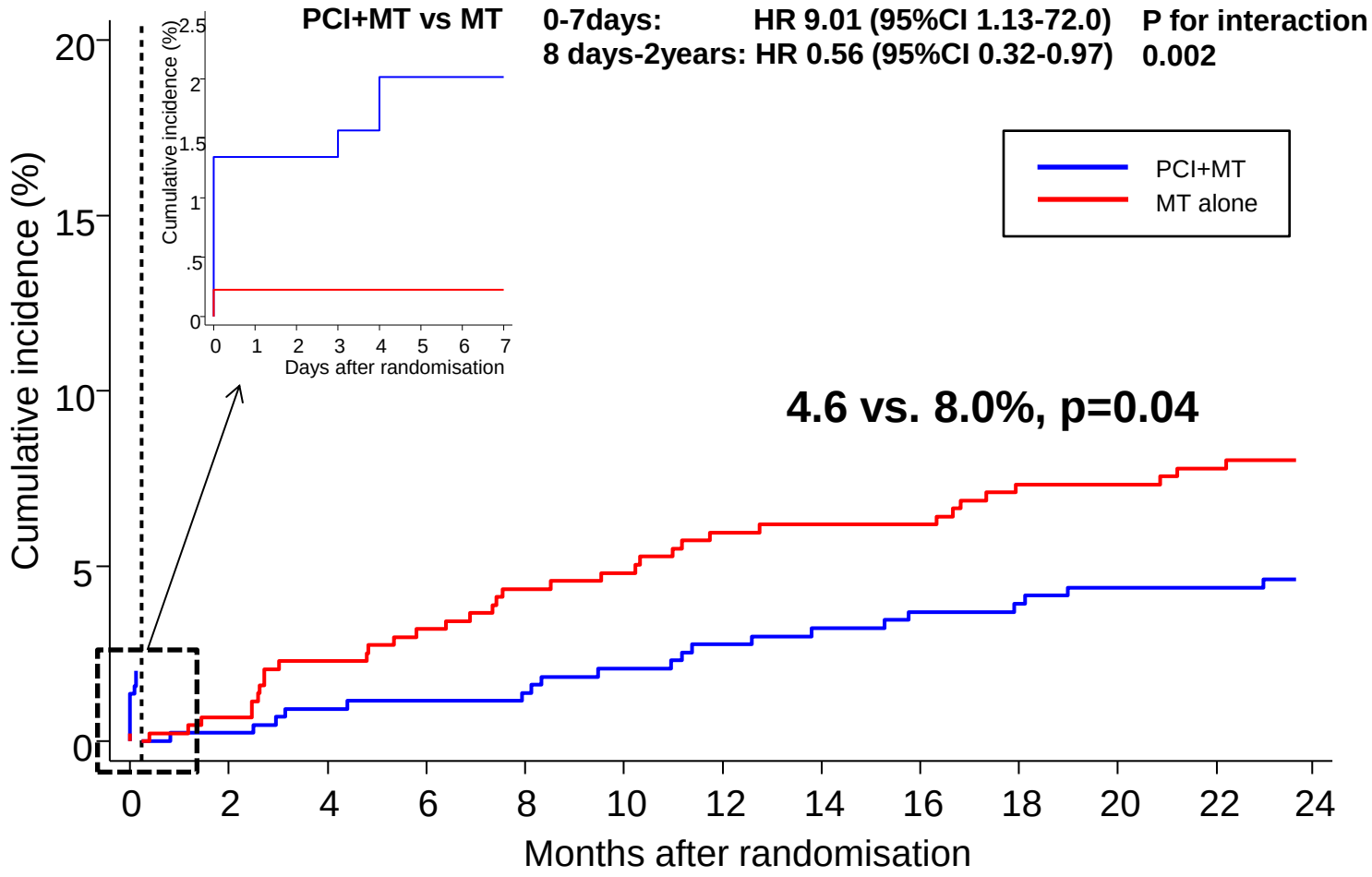

No. at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| MT | 441 | 417 | 398 | 389 | 379 | 369 | 362 | 360 | 359 | 355 | 353 | 351 | 297 |
| PCI+MT | 447 | 434 | 429 | 426 | 425 | 420 | 416 | 414 | 410 | 408 | 405 | 403 | 344 |
| Registry | 166 | 164 | 162 | 160 | 157 | 157 | 156 | 153 | 151 | 150 | 150 | 150 | 122 |

De Bruyne, et al. NEJM 2014;371:1208-17.

# FAME 2: Two Year Follow-Up

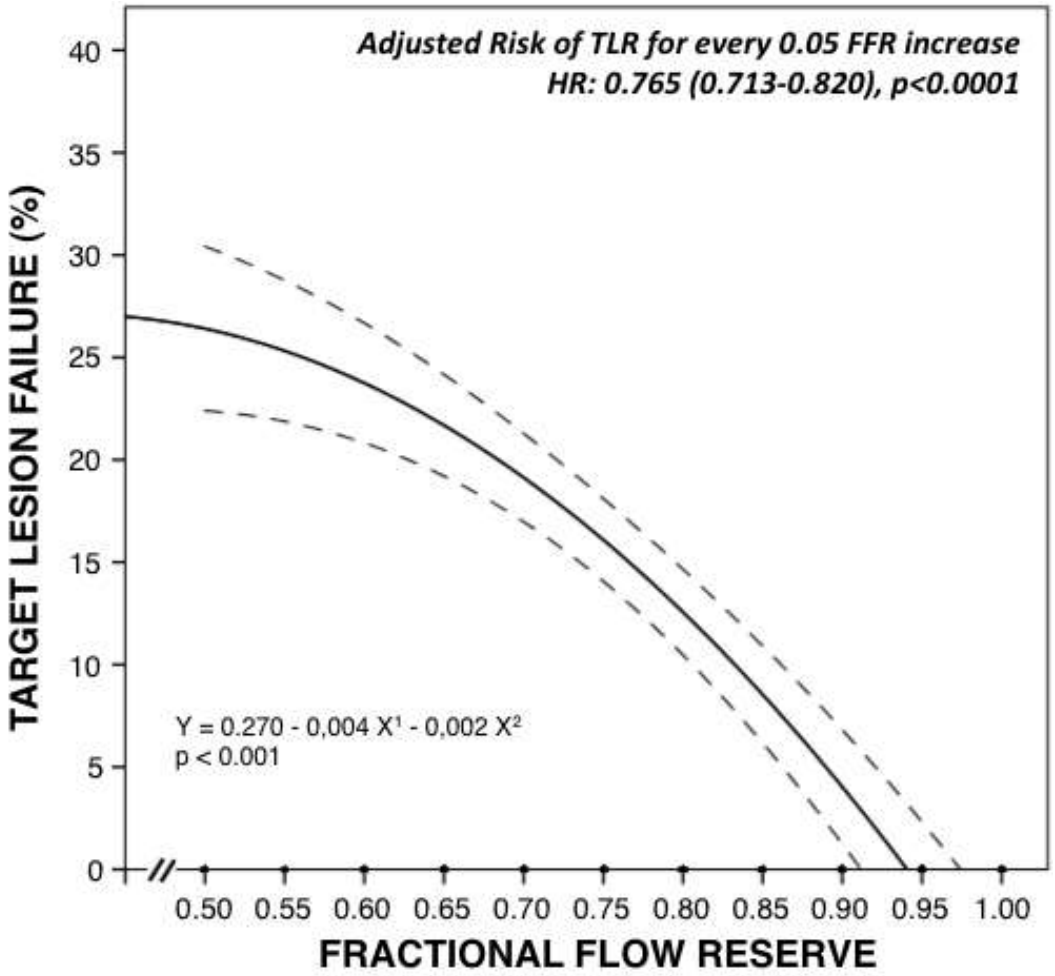
***Landmark Analysis of Death/MI after 7 days***




De Bruyne, et al. NEJM 2014;371:1208-17.

# Relationship between FFR and MACE

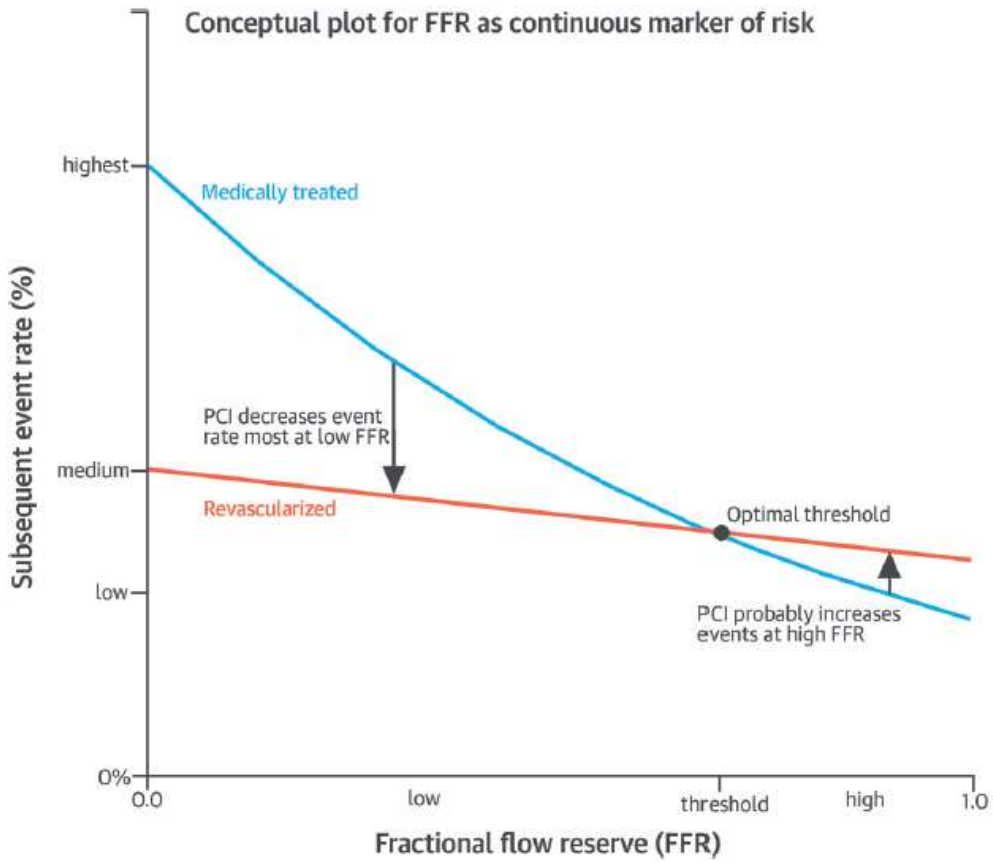
***607 medically treated patients in FAME 2***




Barbato, et al. ESC 2013

# FFR Meta-Analysis

***Meta-analysis of a total of 9,173 (study-level) and 6,961 (patient-level) lesions in which FFR was measured and average follow-up of 16 and 14 months***




Johnson, et al. J Am Coll Cardiol 2014;64:1641-54

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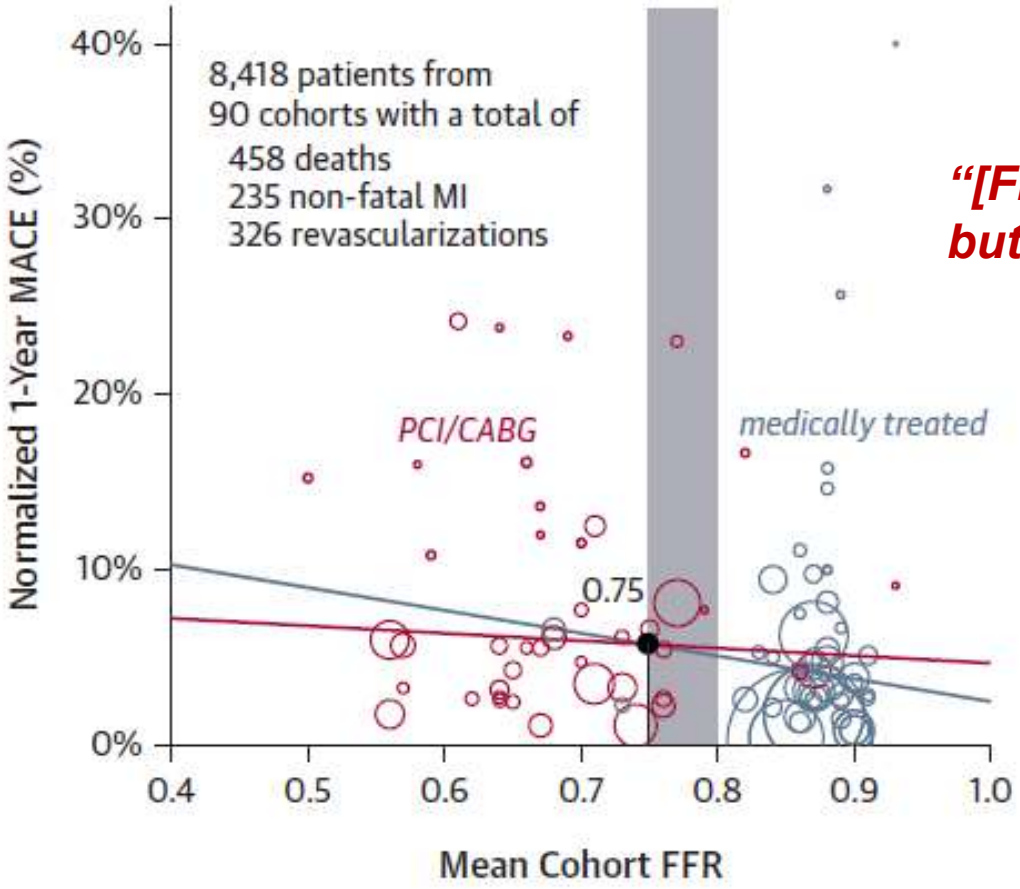
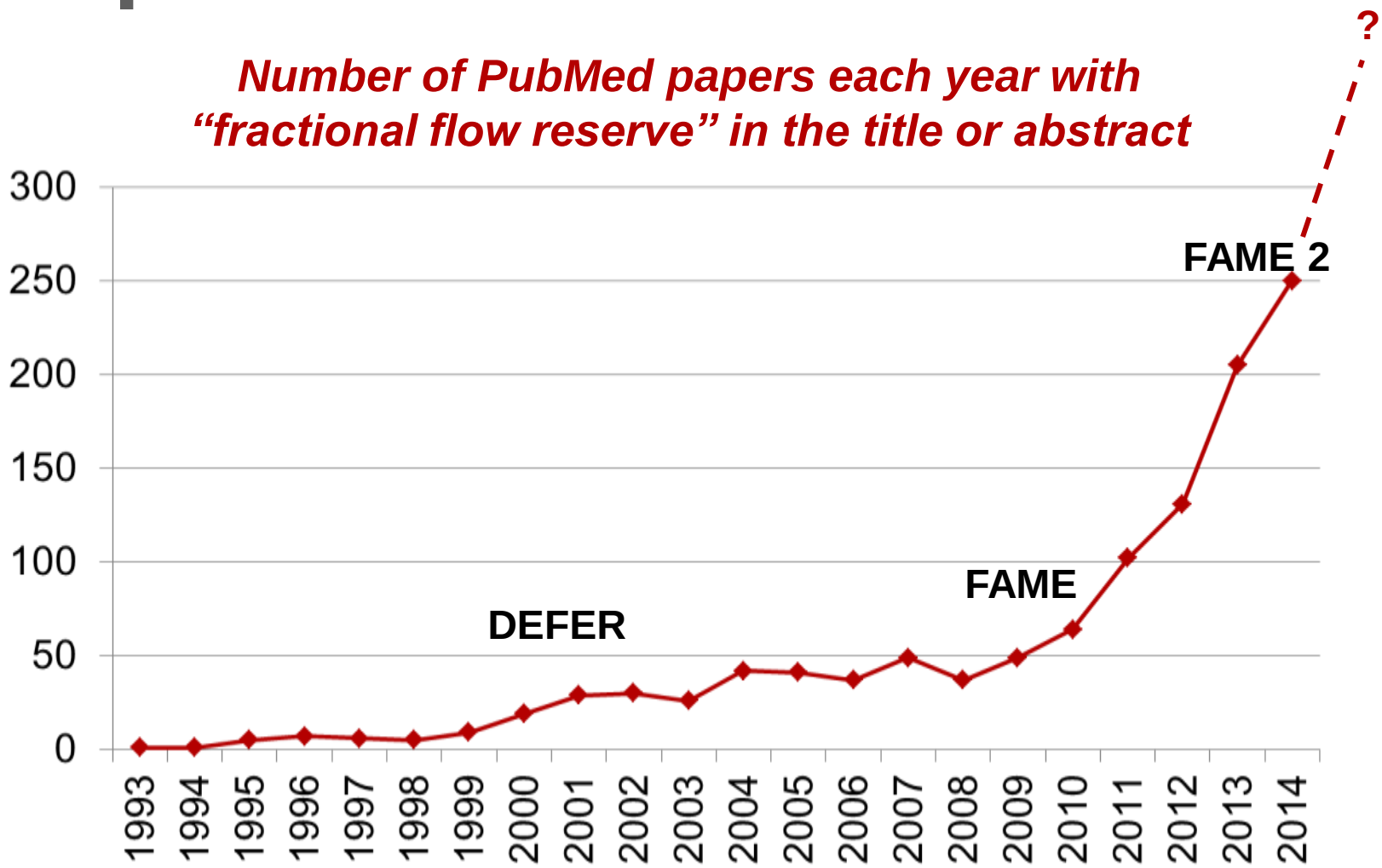



***"[FFR] is not a dichotomous state, but a graded continuum"***

Johnson, et al. J Am Coll Cardiol 2014;64:1641-54

# Explosion of FFR Data



# Conclusion:

- FFR is based on sound coronary physiologic principles.
- FFR is the only invasive index validated against a true noninvasive gold standard.
- FFR has a wealth of data validating it against clinical outcomes.