Fractional Flow Reserve is the Gold Standard Index for Assessing Coronary Artery Disease

William F. Fearon, MD
Professor of Medicine
Director, Interventional Cardiology
Stanford University

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

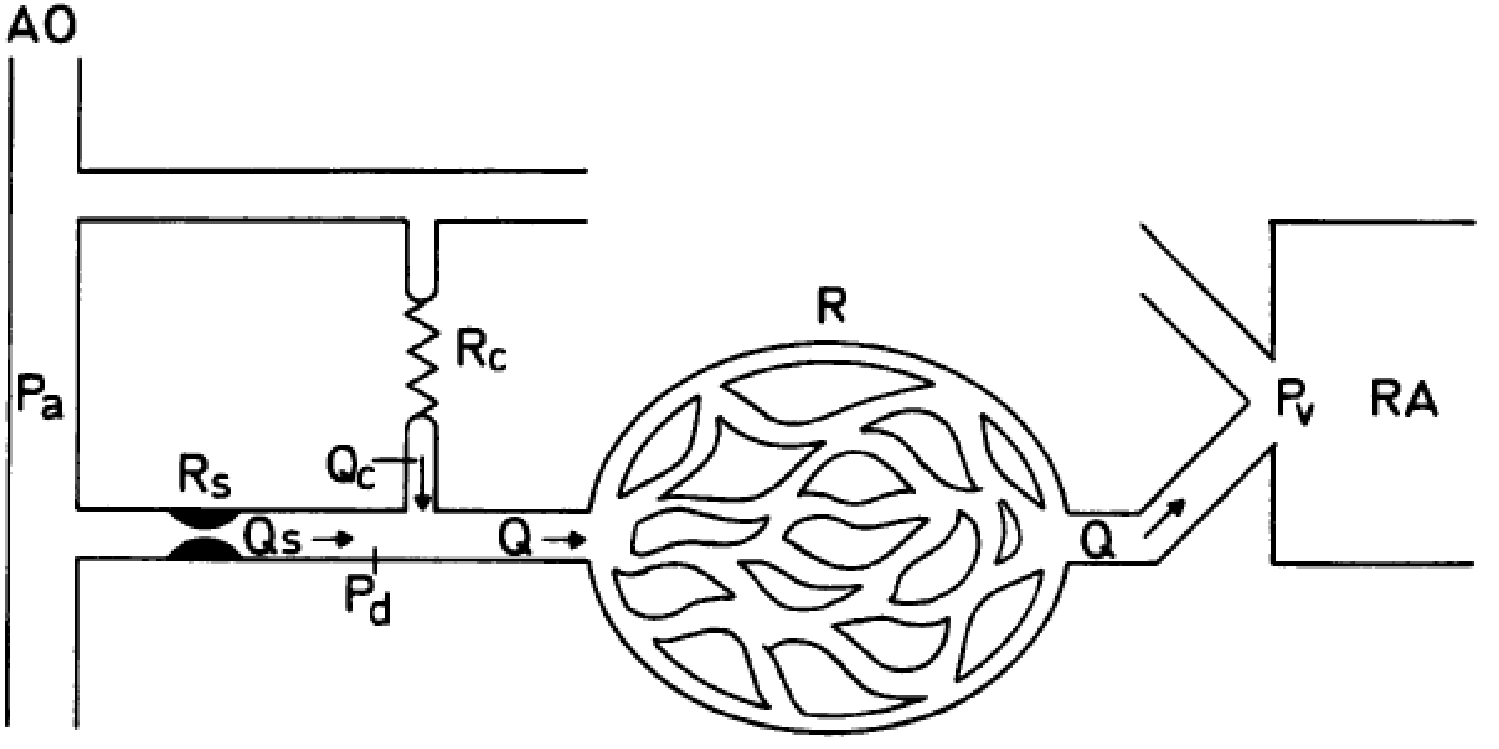
Affiliation/Financial Relationship	Company
Grant/ Research Support:	Abbott
Grant/ Research Support:	Medtronic
Grant/ Research Support:	ACIST Medical
Grant/ Research Support:	CathWorks
Consulting Fees/Honoraria:	Boston Scientific
Major Stock Shareholder/Equity Interest:	
Royalty Income:	
Ownership/Founder:	
Salary:	
Intellectual Property Rights:	
Other Financial Benefit (minor stock options):	HeartFlow

Why is FFR the Gold Standard?

- Well-founded scientific basis
- Validated in an animal model
- Well-validated against non-invasive tests for ischemia
- Highly reproducible
- Predicts clinical outcomes
- Most widely studied index

Scientific Basis of FFR

Schematic model of the coronary circulation



Pijls, et al. Circulation 1993;86:1354-67.

Scientific Basis of FFR

Equations to derive FFR_{myo}, FFR_{cor}, and FFR_{coll}

$$\frac{P_a - P_v}{P_w - P_v} = 1 + \frac{R_c}{R} = \text{constant} \qquad (1)$$

As explained later, Equation 1 is used in connection with Equation 2 in case P_a is not constant.

$$\text{FFR}_{cor} = \frac{Q_s}{Q_s^N} = \frac{P_d - P_w}{P_a - P_w} \qquad (2a)$$

$$= 1 - \frac{\Delta P}{P_a - P_w} \qquad (2b)$$

$$\text{FFR}_{myo} = \frac{Q}{Q^N} = \frac{P_d - P_v}{P_a - P_v} \qquad (3a)$$

$$= 1 - \frac{\Delta P}{P_a - P_v} \qquad (3b)$$

$$Q = Q_s + Q_c \qquad (4a)$$

or

$$Q_c = (\text{FFR}_{myo} - \text{FFR}_{cor}) \cdot Q^N \qquad (4b)$$

$$\frac{Q_s^{(2)}}{Q_s^{(1)}} = \frac{P_d^{(2)} - P_w^{(2)}}{P_d^{(1)} - P_w^{(1)}} \qquad (5a)$$

or

$$\frac{\text{FFR}_{cor}^{(2)}}{\text{FFR}_{cor}^{(1)}} = \left(1 - \frac{\Delta^{(2)}P}{P_a^{(2)} - P_w^{(2)}}\right) : \left(1 - \frac{\Delta^{(1)}P}{P_a^{(1)} - P_w^{(1)}}\right) \qquad (5b)$$

$$\frac{Q^{(2)}}{Q^{(1)}} = \frac{P_d^{(2)} - P_v^{(2)}}{P_d^{(1)} - P_v^{(1)}} \qquad (6a)$$

or

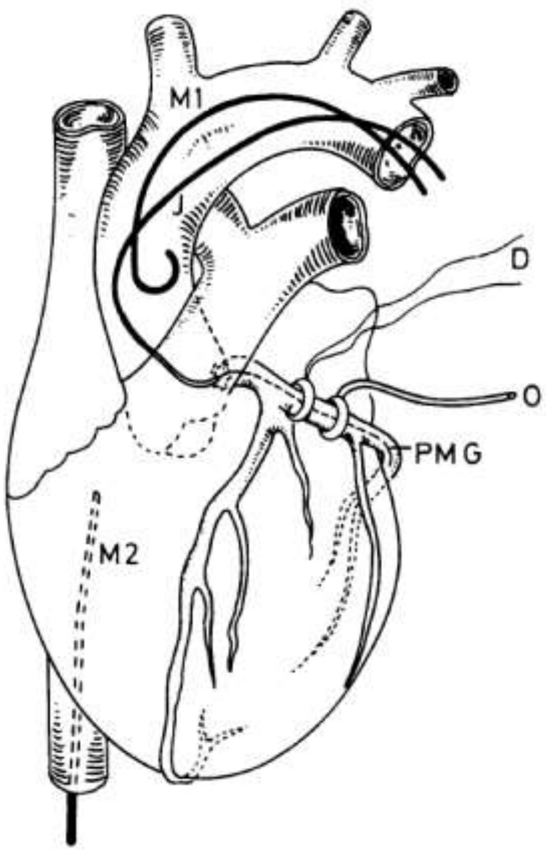
$$\frac{\text{FFR}_{myo}^{(2)}}{\text{FFR}_{myo}^{(1)}} = \left(1 - \frac{\Delta^{(2)}P}{P_a^{(2)} - P_v^{(2)}}\right) : \left(1 - \frac{\Delta^{(1)}P}{P_a^{(1)} - P_v^{(1)}}\right) \qquad (6b)$$

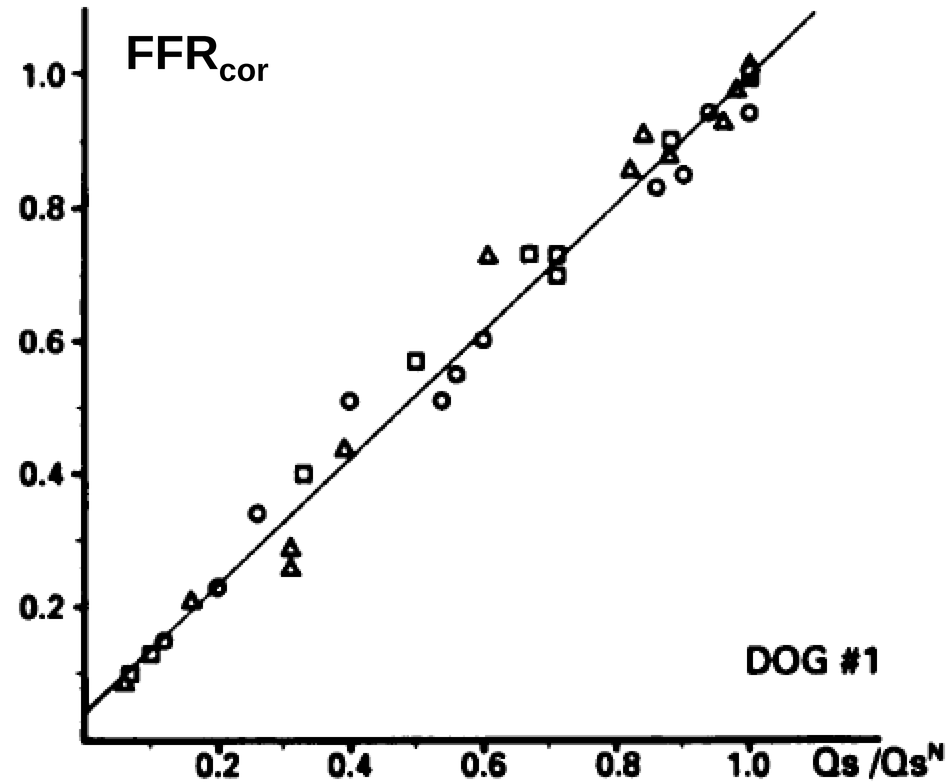
$$\frac{Q_c^{(2)}}{Q_c^{(1)}} = \frac{\Delta^{(2)}P}{\Delta^{(1)}P} \qquad (7a)$$

Pijls, et al. Circulation 1993;86:1354-67.

Animal Validation of FFR

FFR compared to invasive gold standard of absolute flow in 5 dogs at 3 different arterial pressure levels and 12 different stenoses (r=0.98)

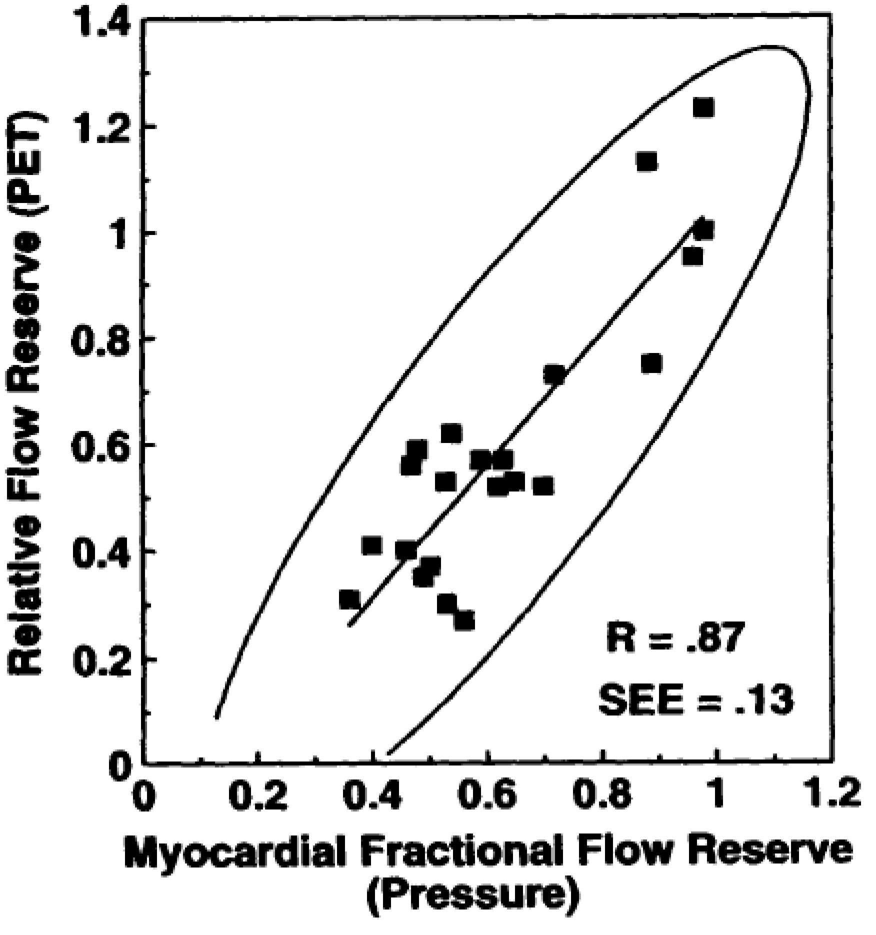




Pijls, et al. Circulation 1993;86:1354-67.

Validation of FFR

FFR compared to noninvasive gold standard of relative flow reserve using PET in 22 patients with LAD stenosis



De Bruyne, et al. Circulation 1994;89:1013-22.

Validation of FFR

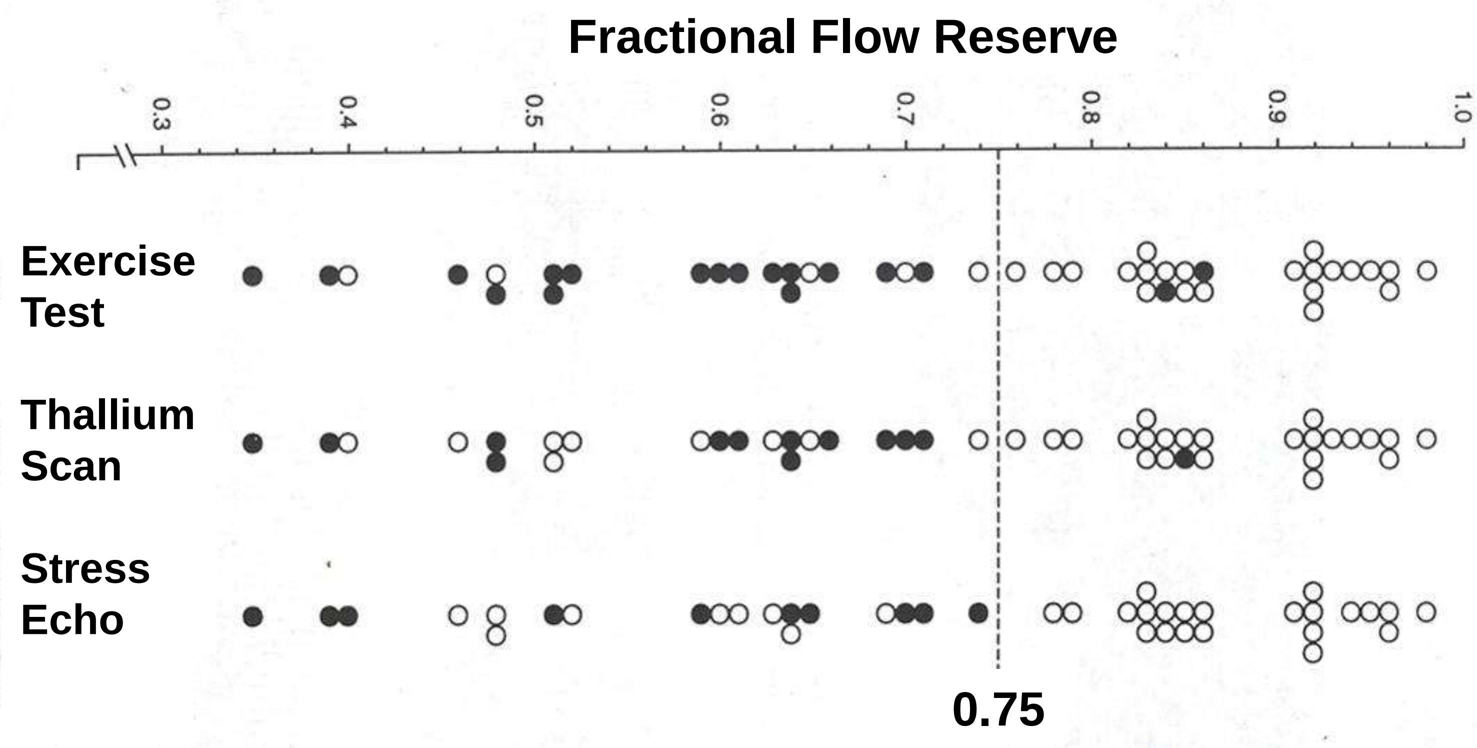
FFR compared to noninvasive gold standard of relative flow reserve using PET in 22 patients with LAD stenosis

	Correlation Coefficient
Myocardial fractional flow reserve	.87
Resting transstenotic pressure gradient	−.61

De Bruyne, et al. Circulation 1994;89:1013-22.

Human 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 vasodilatation					
De Bruyne (1995)[38] (Intracoronary papaverine or adenosine)	60 (60)	X-ECG, MPS	0.66	87	SVD
Bartunek (1996)[132] (Intracoronary papaverine or adeno	75 (75)	DSE	0.75	81	SVD
Abe (2000)[133] (Intravenous ATP)				91	SVD
De Bruyne (2001)[134] (Intravenous or intracoronary adenc or intravenous ATP)				85	Previous MI
Yanagisawa (2002)[135] (Intracoronary papaverine)				76	Previous MI
Ziaee (2004)[136‡] (Intravenous or intracoronary adenosine)	55 (55)	MPS, X-ECG, DSE	0.75	88	Ostial
Morishima (2004)[137] (Intracoronary papaverine)	20 (20)	MPS	0.75	85	SVD
Kobori (2005)[138§] (Intracoronary papaverine)	147 (155)	MPS	0.75	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

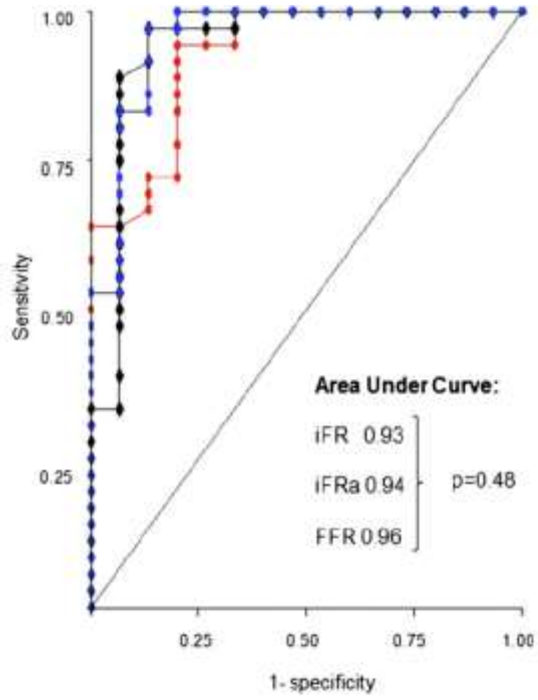
> 1,500 Patients

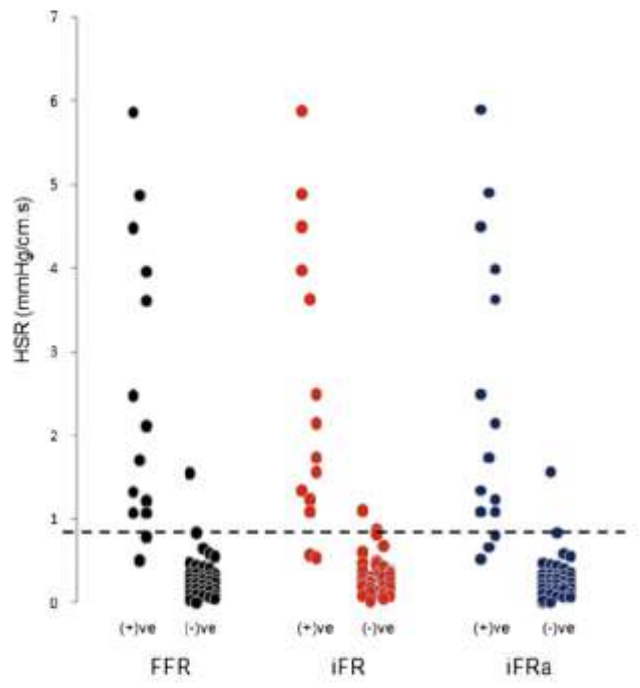
24 Studies

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

More Recent "Validation" Studies

FFR and iFR compared with "hyperemic stenosis resistance" (HSR)



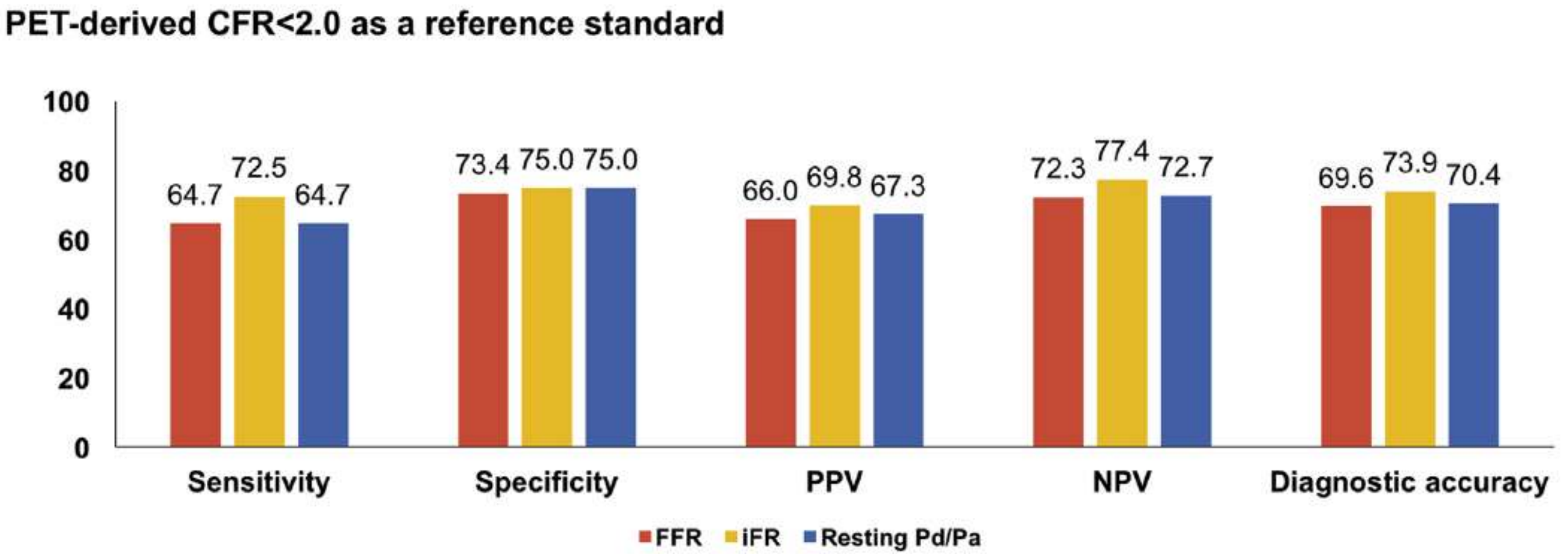


Hyperemic stenosis resistance is not a gold standard. There are no validation studies or clinical outcome studies with HSR.

Sen, et al. J Am Coll Cardiol 2013;61:1409-20.

More Recent "Validation" Studies

FFR, iFR, Resting Pd/Pa measured in 115 patients and compared with PET



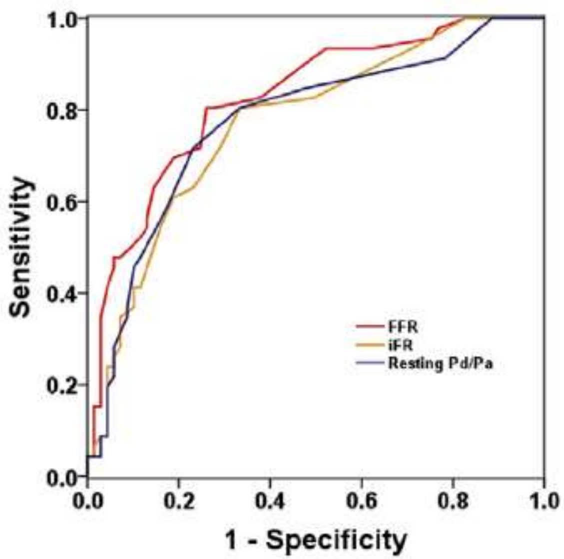
CFR is not a gold standard for assessing epicardial disease! CFR interrogates the entire coronary circulation. We do not expect FFR to correlate with CFR!

Hwang, et al. J Am Coll Cardiol Intv 2017;10:751-60.

More Recent Validation Study

FFR, iFR, Resting Pd/Pa measured in 115 patients and compared with PET

PET-derived RFR<0.75 as a reference standard



	AUC	95% CI	p value
FFR	0.826	0.749-0.903	<0.001
iFR	0.771	0.684-0.858	<0.001
Resting Pd/Pa	0.774	0.684-0.864	<0.001

Reference	Testing	Difference between areas	p value
iFR	FFR	0.055	0.047
Resting Pd/Pa		0.052	0.093
Resting Pd/Pa	iFR	0.003	0.836

When compared with relative flow reserve (RFR), which is more epicardial specific, FFR is significantly more accurate than iFR.

Hwang, et al. J Am Coll Cardiol Intv 2017;10:751-60.

Most Recent Validation Study

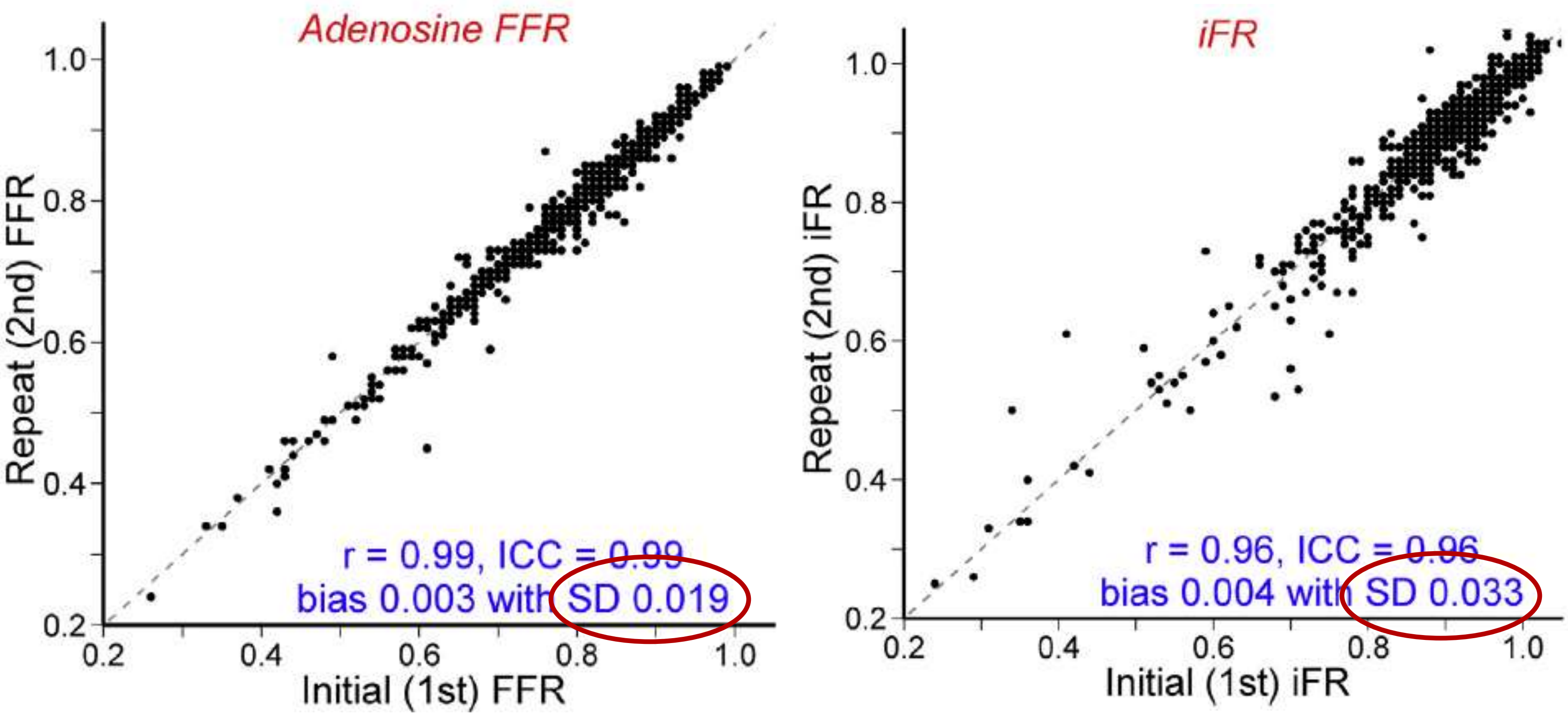
FFR and iFR compared with dobutamine stress echo in 62 stable CAD patients

DSE as gold standard					
	Sensitivity	Specificity	NPV	PPV	Accuracy
iFR	55.6	75.7	87.5	35.7	71.7
FFR	100	83.8	100	60	87

Panoulas, et al. EuroIntervention 2018;13:1959-66.

FFR is Highly Reproducible

Repeated measurement of FFR in 763 patients in the CONTRAST study

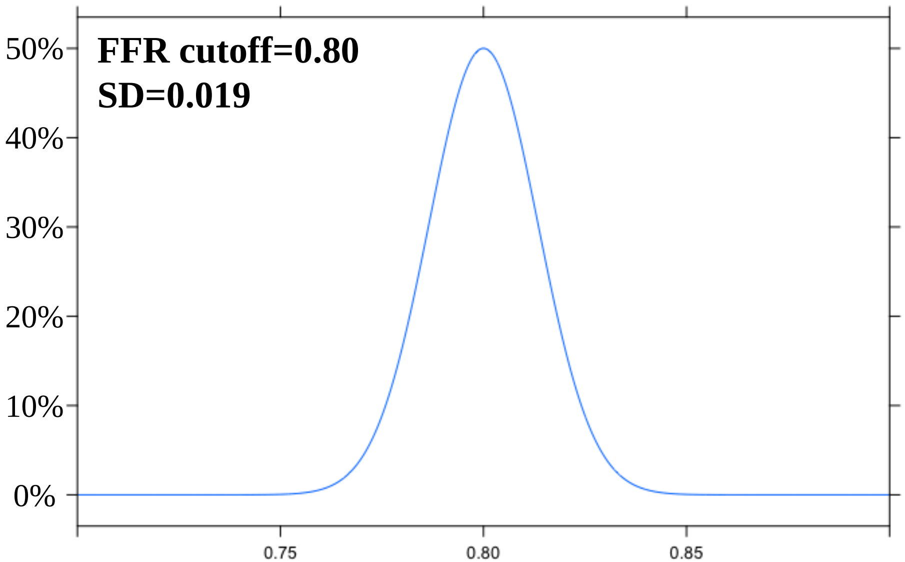


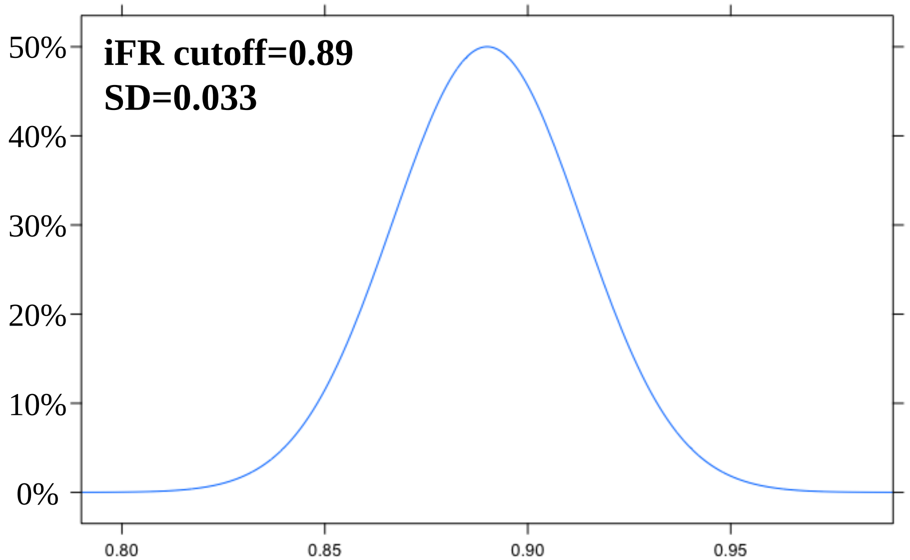
Johnson, et al. J Am Coll Cardiol Intv 2016;9:757-67.

FFR is Highly Reproducible

Repeated measurement of FFR in 763 patients in the CONTRAST study

Probability that revascularization decision will change if measurement is repeated

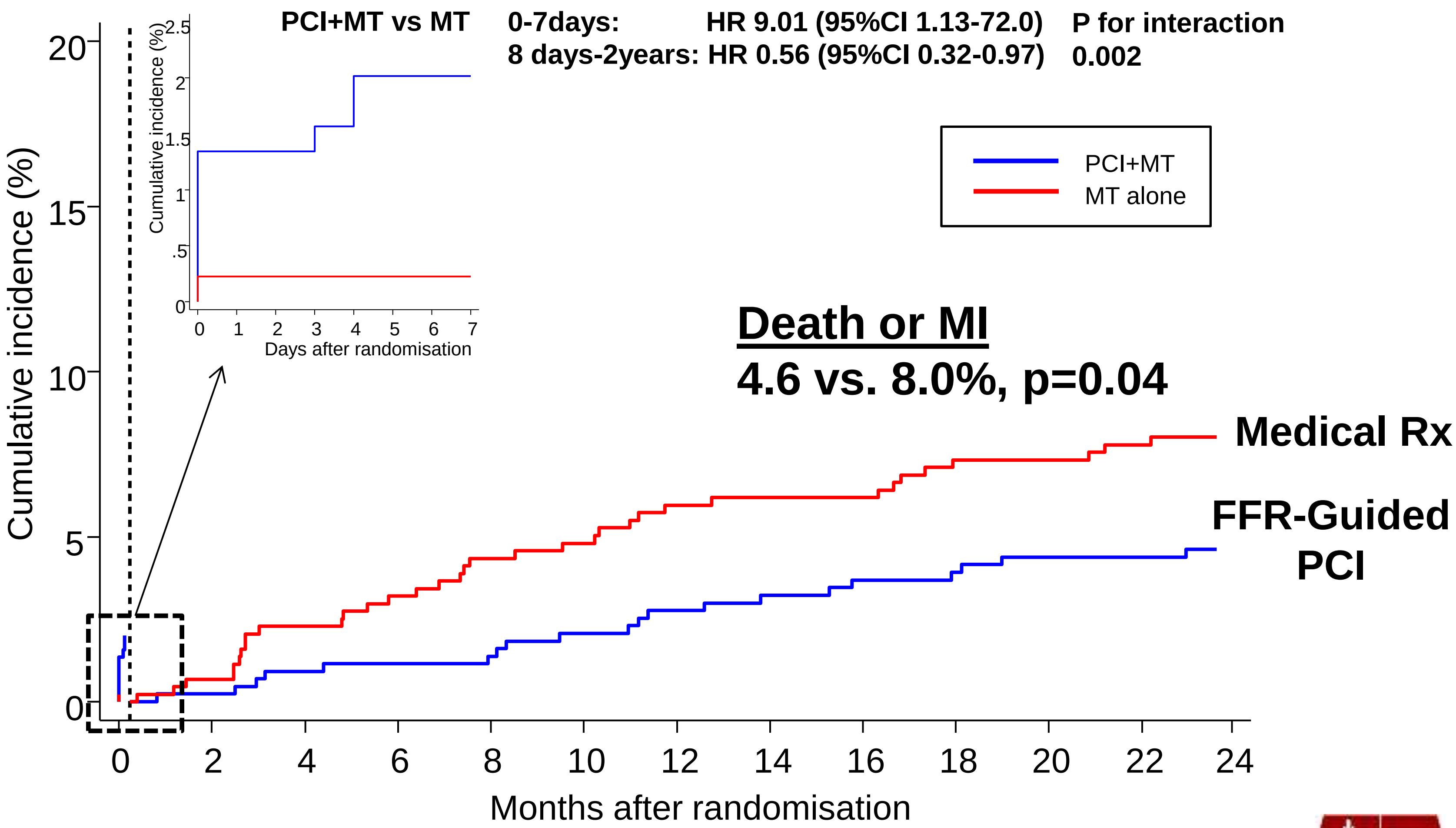




Johnson, et al. J Am Coll Cardiol Intv 2016;9:757-67.

FFR Predicts Adverse Events

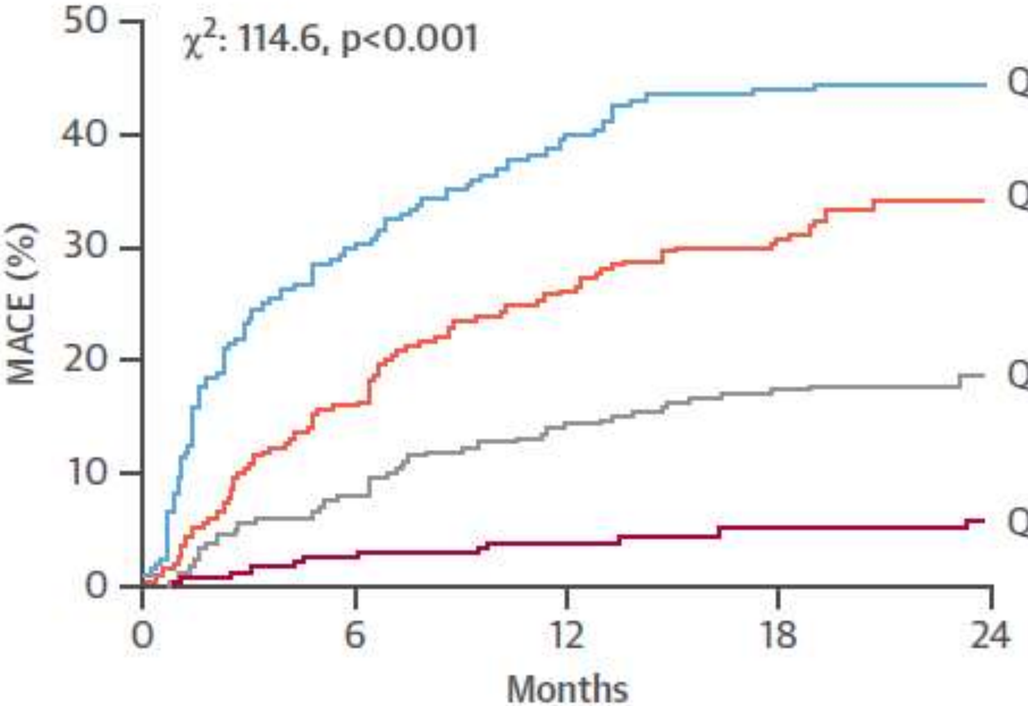
Landmark Analysis of Death/MI after 7 days in FAME 2 Trial



De Bruyne, et al. New Engl J Med 2014;371:1208-17.

FFR Predicts Adverse Events

1,029 lesions from 607 medically treated patients in FAME 2



FFR≤0.63

FFR=0.64-0.77

FFR=0.78-0.86

FFR=0.87-1.0

	0	6	12	18	24
Q1	234	227	223	220	185
Q2	263	239	220	211	178
Q3	270	225	196	184	152
Q4	233	162	140	125	111

Barbato, et al. J Am Coll Cardiol 2016;68:2247-55.

FFR Predicts Adverse Events

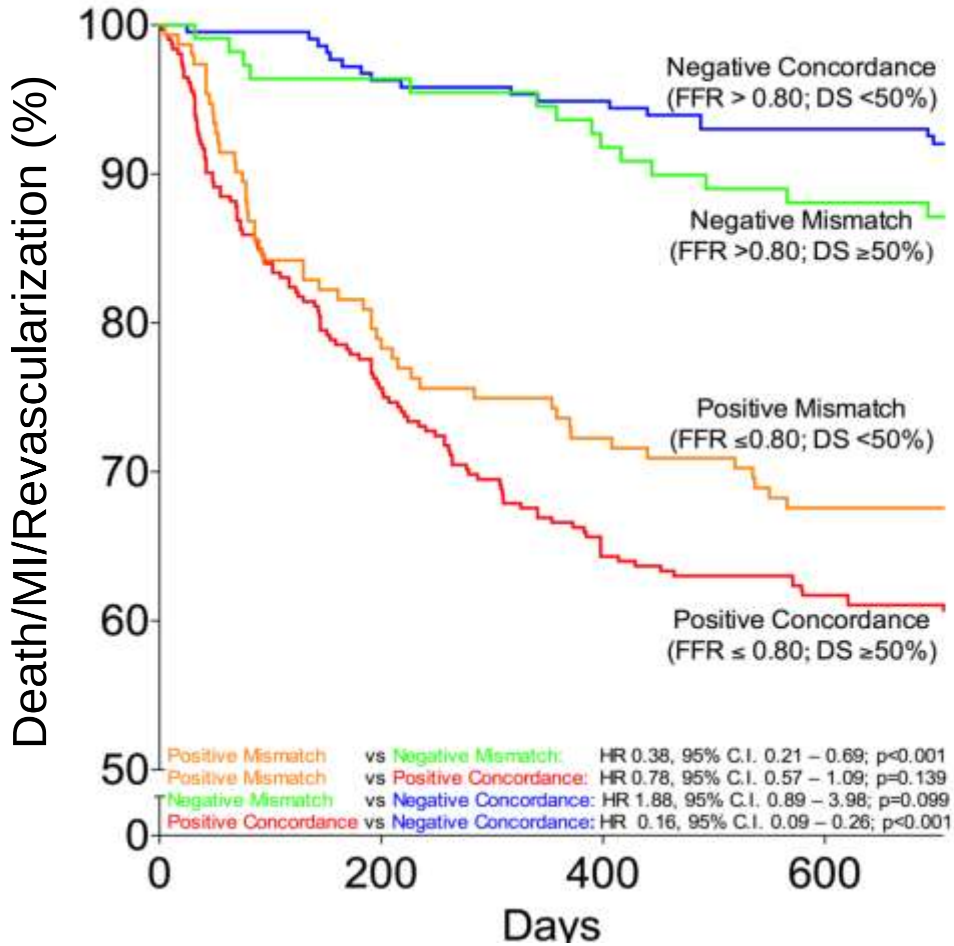
1,029 lesions from 607 medically treated patients in FAME 2

Quartile	n (%)	HR (95% CI)	p Value
MACE			
Q1 (0.87-1.00)	14 (5.4)	Ref.	–
Q2 (0.78-0.86)	50 (19.2)	3.44 (1.90-6.23)	<0.001
Q3 (0.64-0.77)	91 (35.0)	6.71 (3.82-11.78)	<0.001
Q4 (≤0.63)	105 (40.4)	9.84 (5.63-17.20)	<0.001
Death or MI			
Q1 (0.87-1.00)	6 (14.0)	Ref.	–
Q2 (0.78-0.86)	8 (18.6)	1.20 (0.41-3.45)	0.74
Q3 (0.64-0.77)	17 (39.5)	2.52 (0.99-6.39)	0.05
Q4 (≤0.63)	12 (27.9)	2.04 (0.76-5.43)	0.15
Urgent revascularization			
Q1 (0.87-1.00)	2 (2.9)	Ref.	–
Q2 (0.78-0.86)	8 (11.4)	3.61 (0.77-16.99)	0.10
Q3 (0.64-0.77)	31 (44.3)	14.29 (3.42-59.73)	<0.001
Q4 (≤0.63)	29 (41.4)	15.56 (3.71-65.20)	<0.001

Barbato, et al. J Am Coll Cardiol 2016;68:2247-55.

FFR Predicts Adverse Events

1,029 lesions from 607 medically treated patients in FAME 2

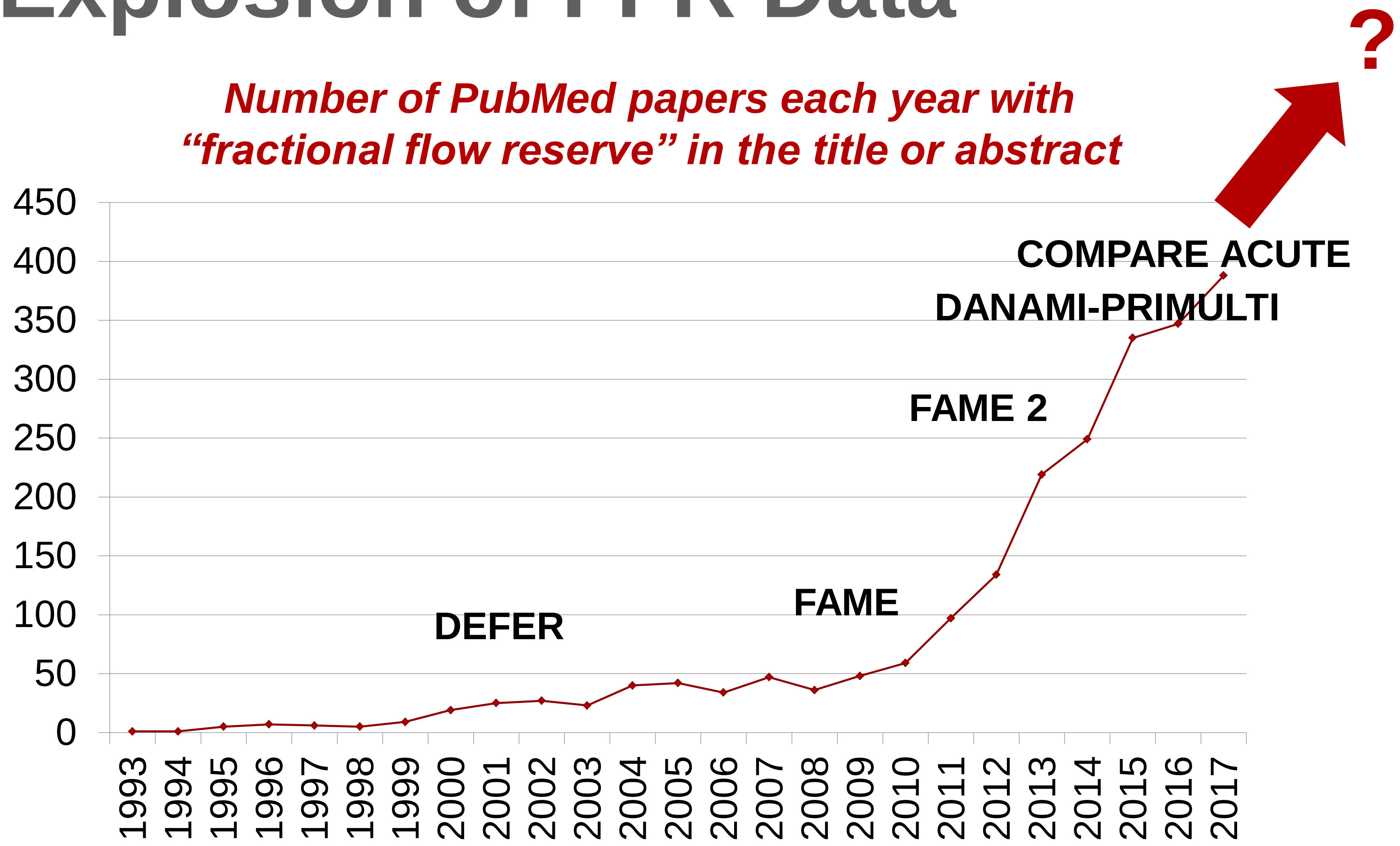


Negative Concordance : FFR >0.80; DS <50%
Negative Mismatch : FFR >0.80; DS ≥50%
Positive Mismatch : FFR ≤0.80; DS <50%
Positive Concordance : FFR ≤0.80; DS ≥50%

Ciccarelli, et al. Circulation 2018;137:1475-85.

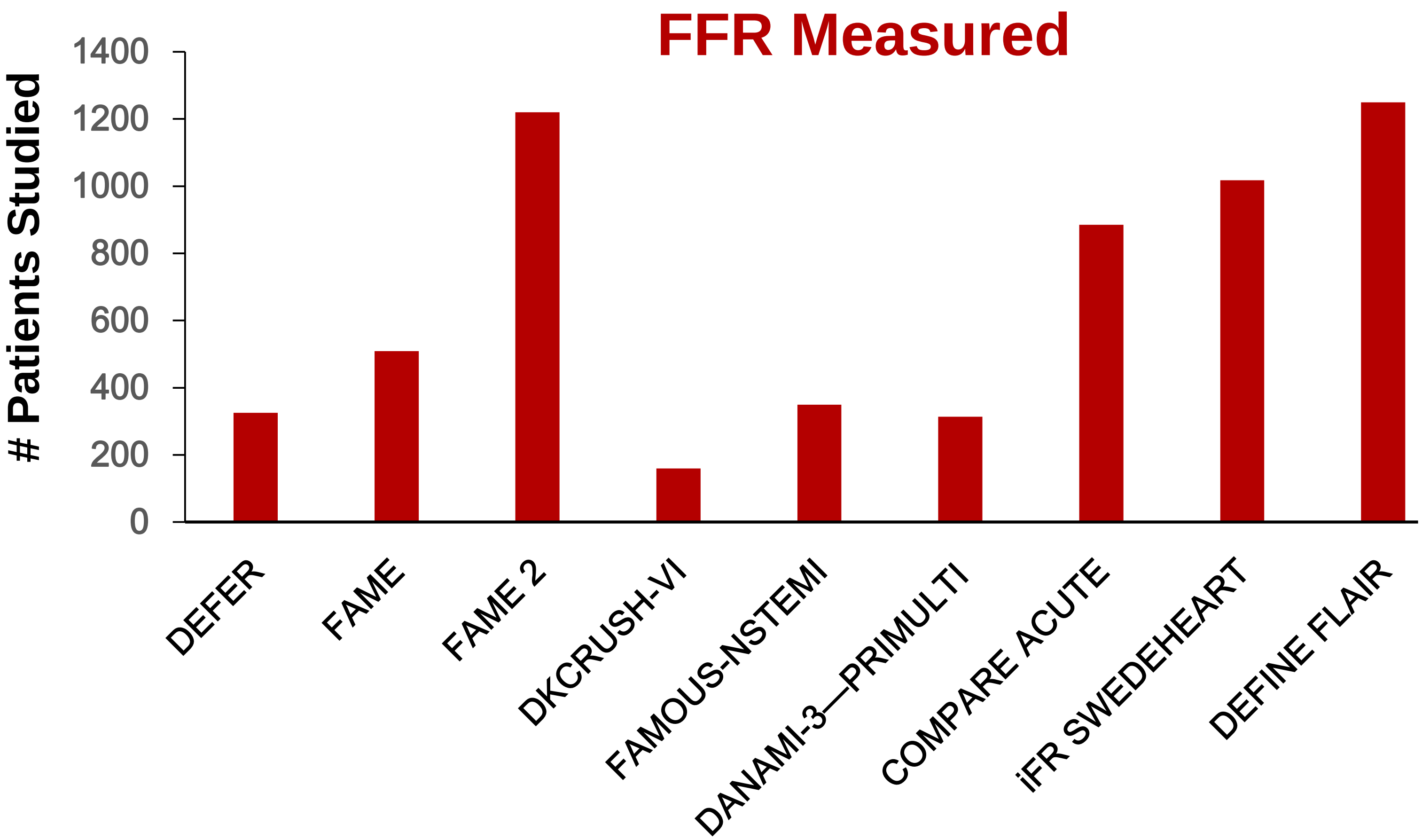
Explosion of FFR Data

Number of PubMed papers each year with "fractional flow reserve" in the title or abstract



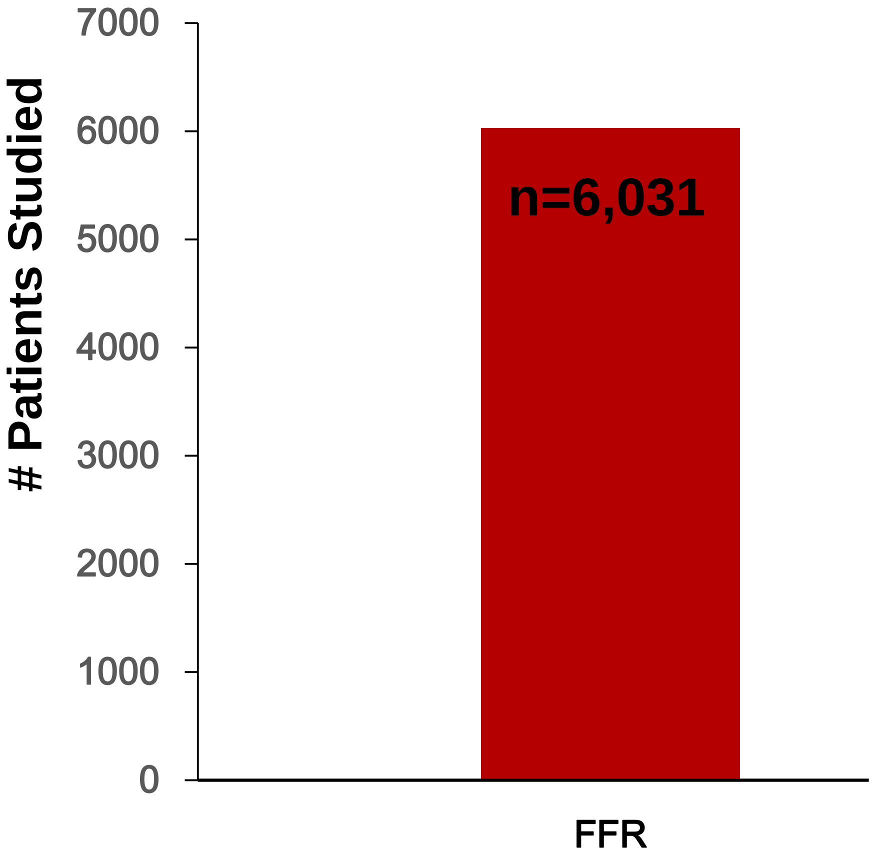
FFR and Outcomes Trials

Randomized, multicenter outcomes trials with FFR



FFR and Outcomes Trials

Randomized, multicenter outcomes trials with FFR or iFR



FFR Remains the Gold Standard

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- Validated in an animal model
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- Predicts clinical outcomes
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