FAME 2 and COURAGE:
Going Functional is the Solution!

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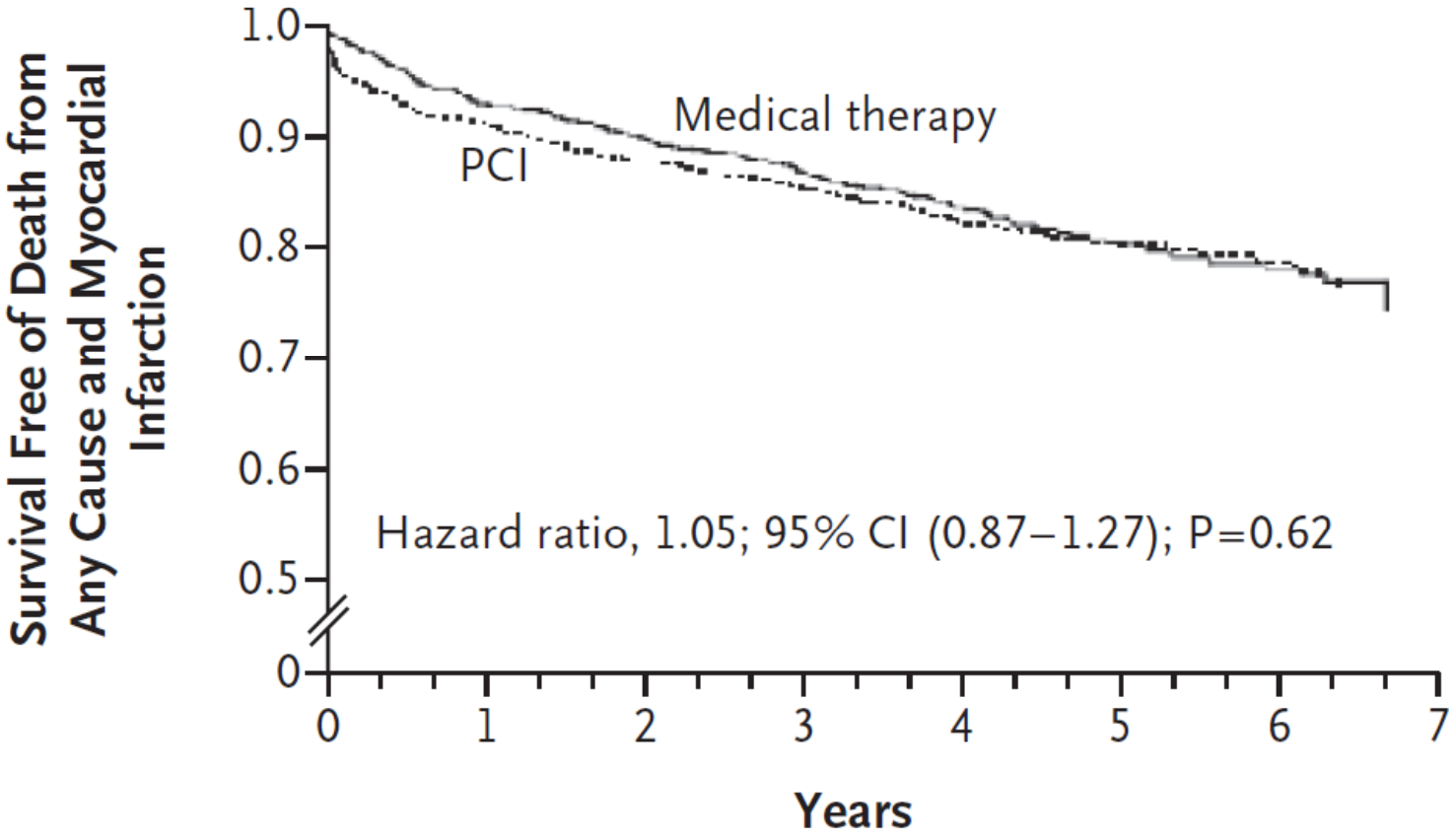
Conflict of Interest

- Advisory Board for HeartFlow
- Research grant from St. Jude Medical
- Research and salary support from National Institutes of Health: 1 R01 HL093475 (PI)

COURAGE Trial:

2,287 stable patients with 1, 2, or 3 vessel CAD randomized to optimal medical therapy or PCI



Boden, et al. New Engl J Med 2007;356:1503-16.

What was the population?

Who was included?

- Inclusion Criteria:

  Ischemia and >70% stenosis (visually)…

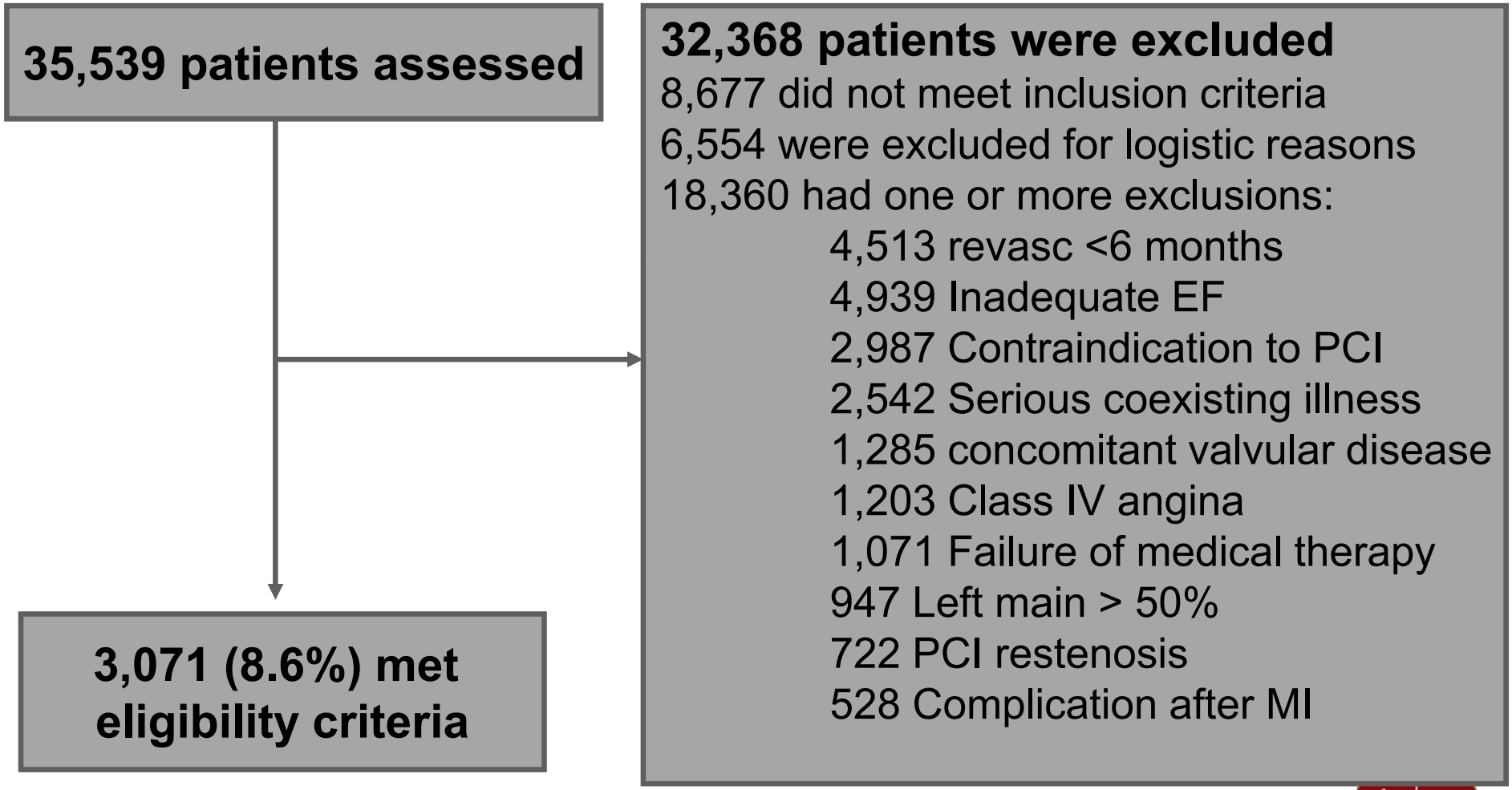
  or…

  >80% stenosis and typical symptoms

…*fairly broad inclusion criteria*

What was the population?

Who was included?



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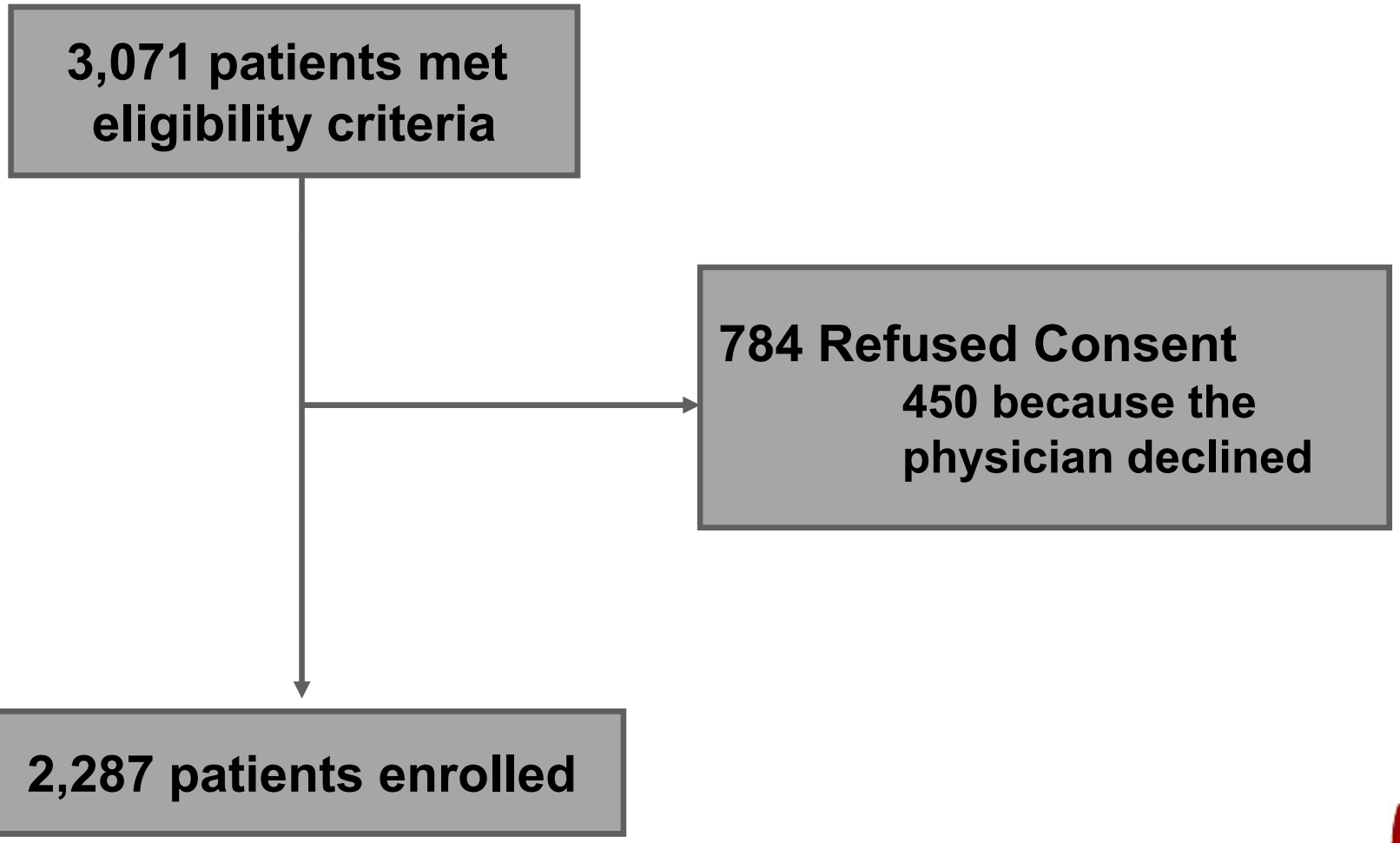


Was PCI Optimal?

→ 787 patients (69%) had multivessel CAD

→ Only 416 (41%) received ≥ 2 stents

→ 371 / 787 (47%) of multivessel CAD patients received only 1 stent

PCI was guided by the angiogram and NPS!

Limitation of Noninvasive Imaging

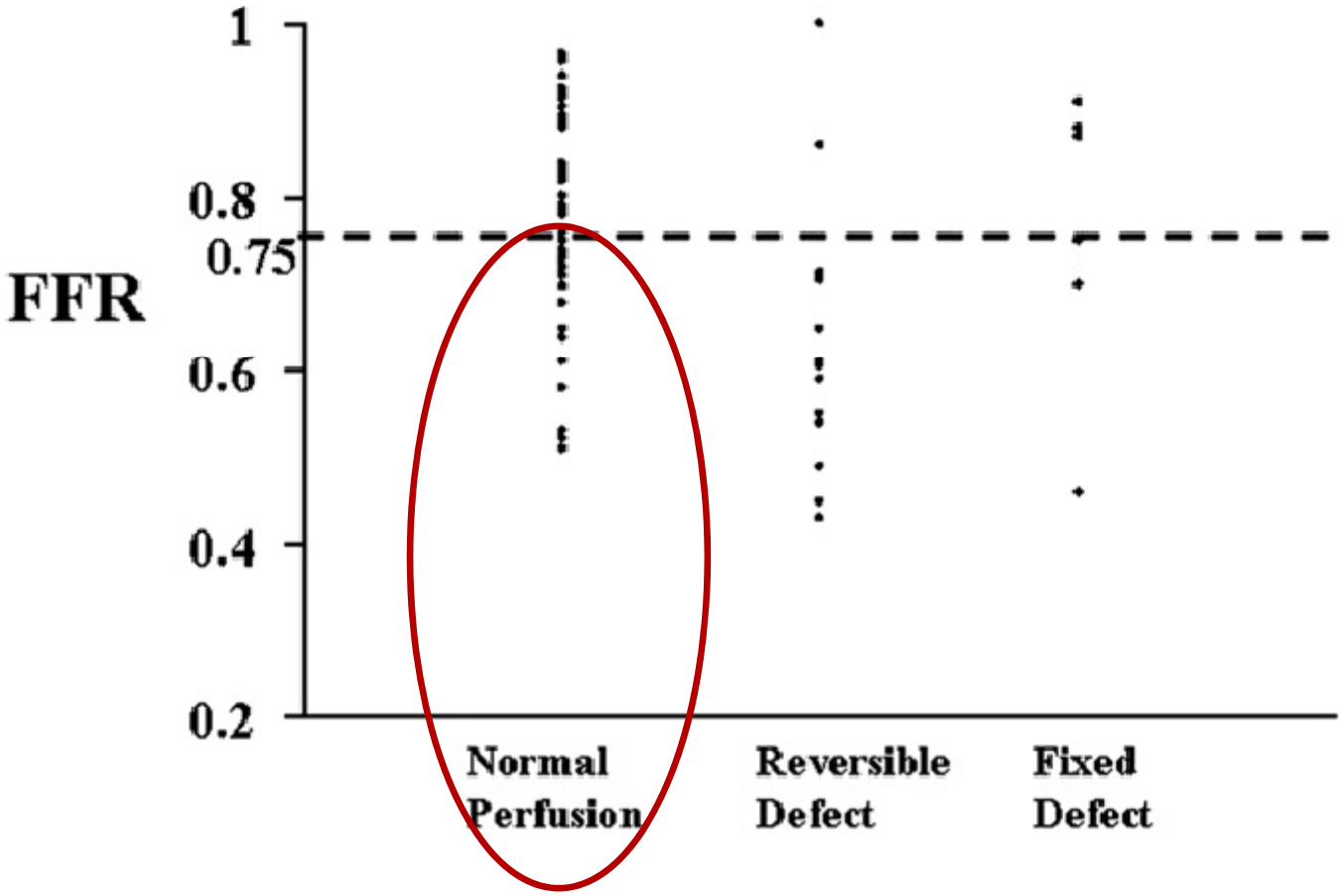
143 Patients with angiographically significant 3 vessel disease (> 70% diameter stenosis)

Thallium Scan Finding	% Patients
No Defect	18%
Single Vessel Pattern	36%
Two Vessel Pattern	36%
Three Vessel Pattern	10%

Lima et al. J Am Coll Cardiol 2003;42:63-70

Inaccuracy of Radionuclide Imaging

36 patients with multivessel CAD

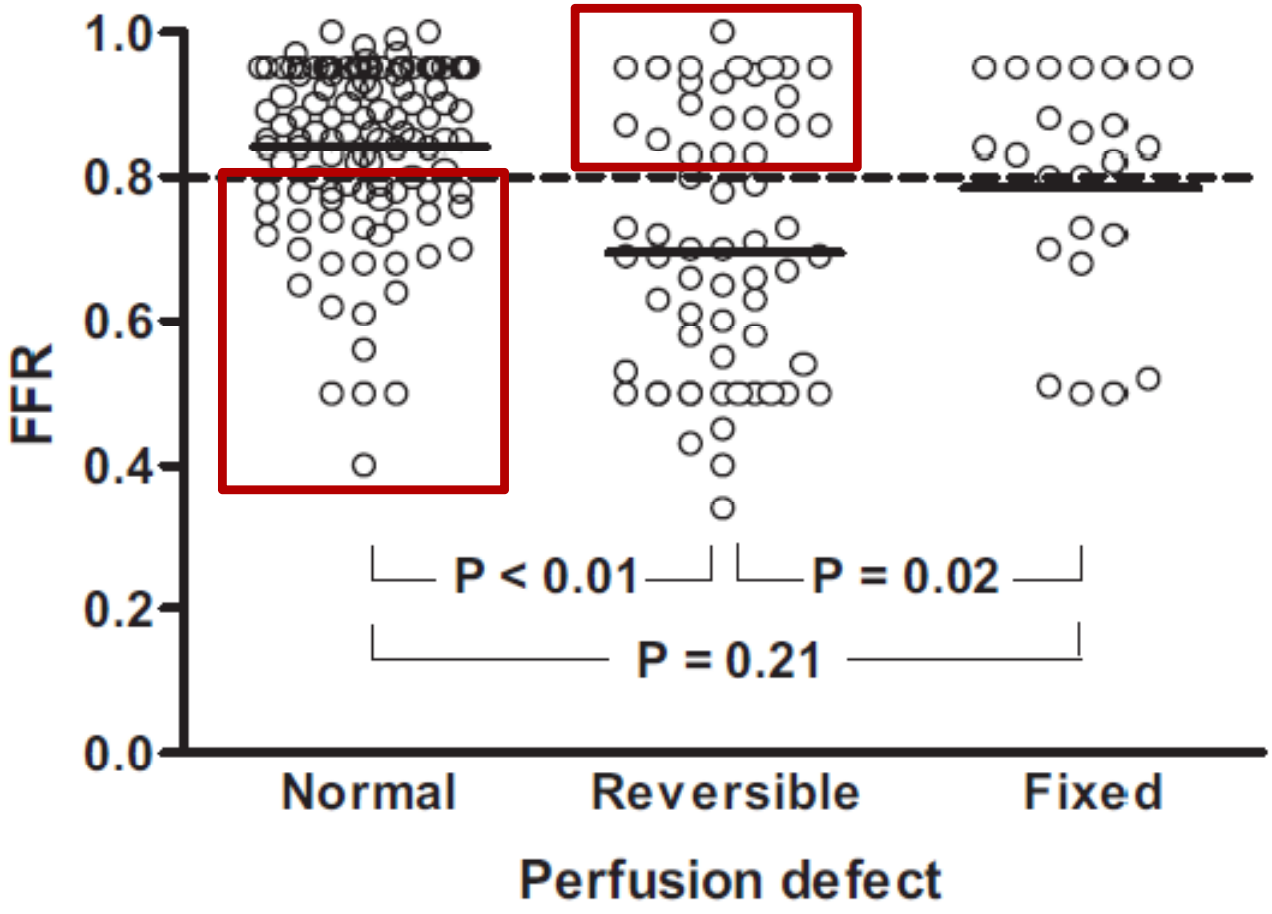


Discordance occurred in 31% of vessels / territories, predominantly because of a low FFR and normal nuclear result

Ragosta, et al. Am J Cardiol 2007;99:896-902

Inaccuracy of Radionuclide Imaging

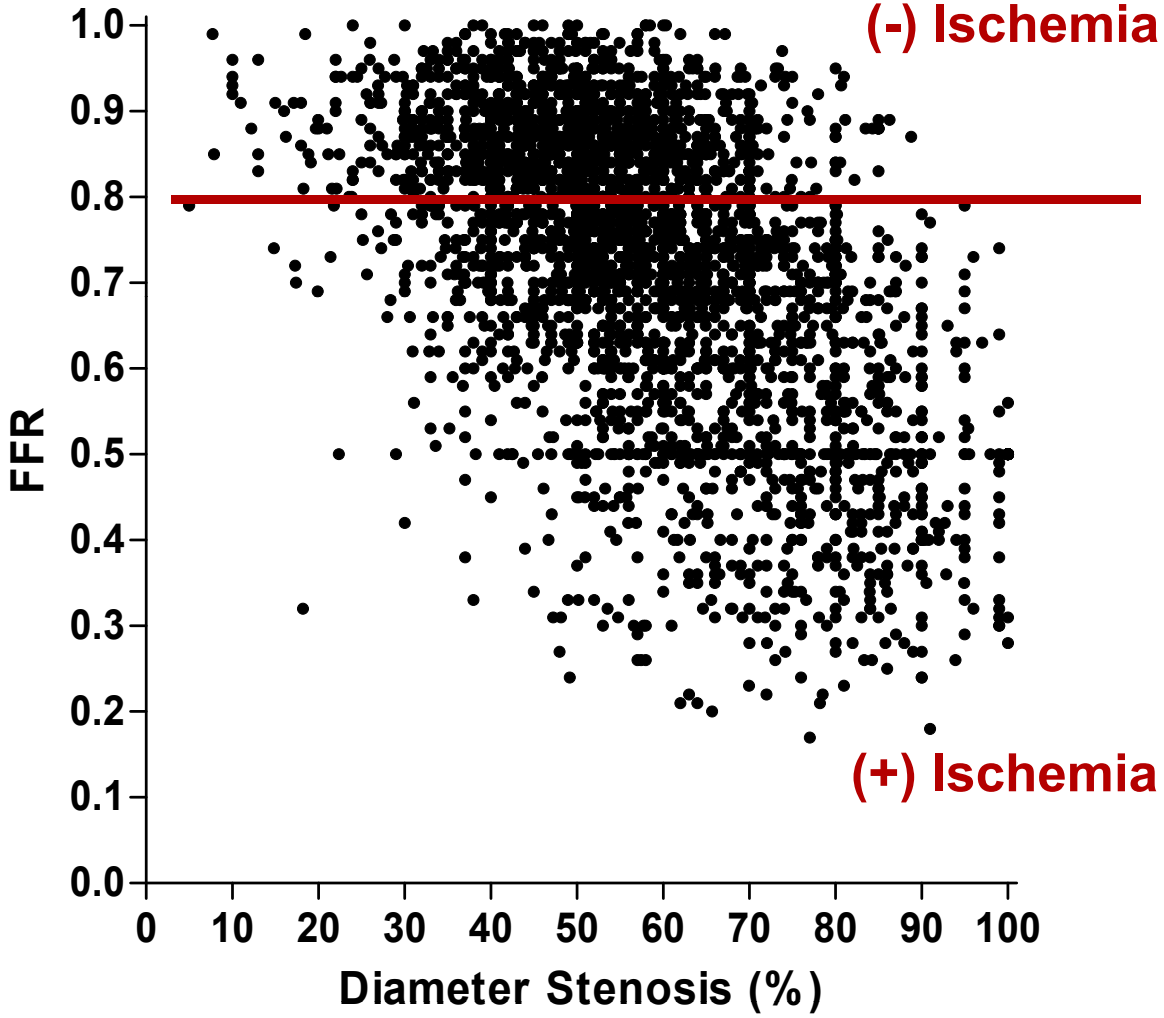
67 patients with angiographic 2 or 3 vessel CAD



Melikian, et al. J Am Coll Cardiol Intv 2010;3:307-14

Limitation of Angiography

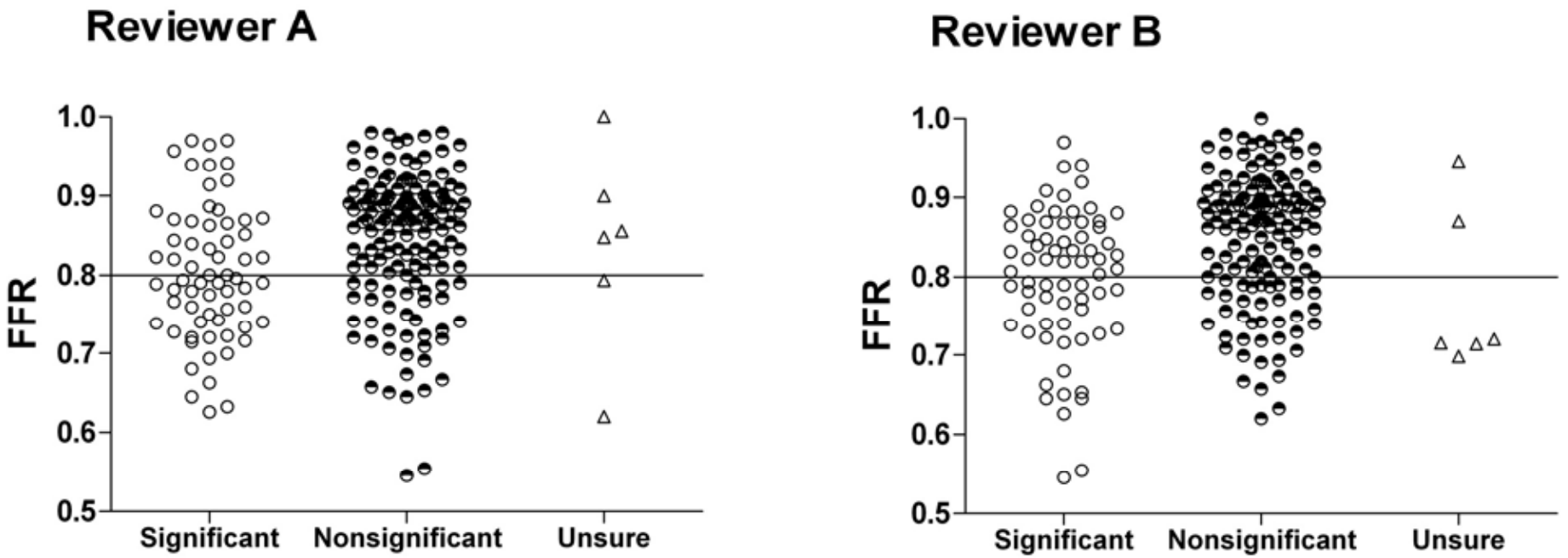
Comparison of QCA to FFR in over 3,000 lesions



Courtesy of Bernard De Bruyne, MD, PhD

Limitation of Angiography

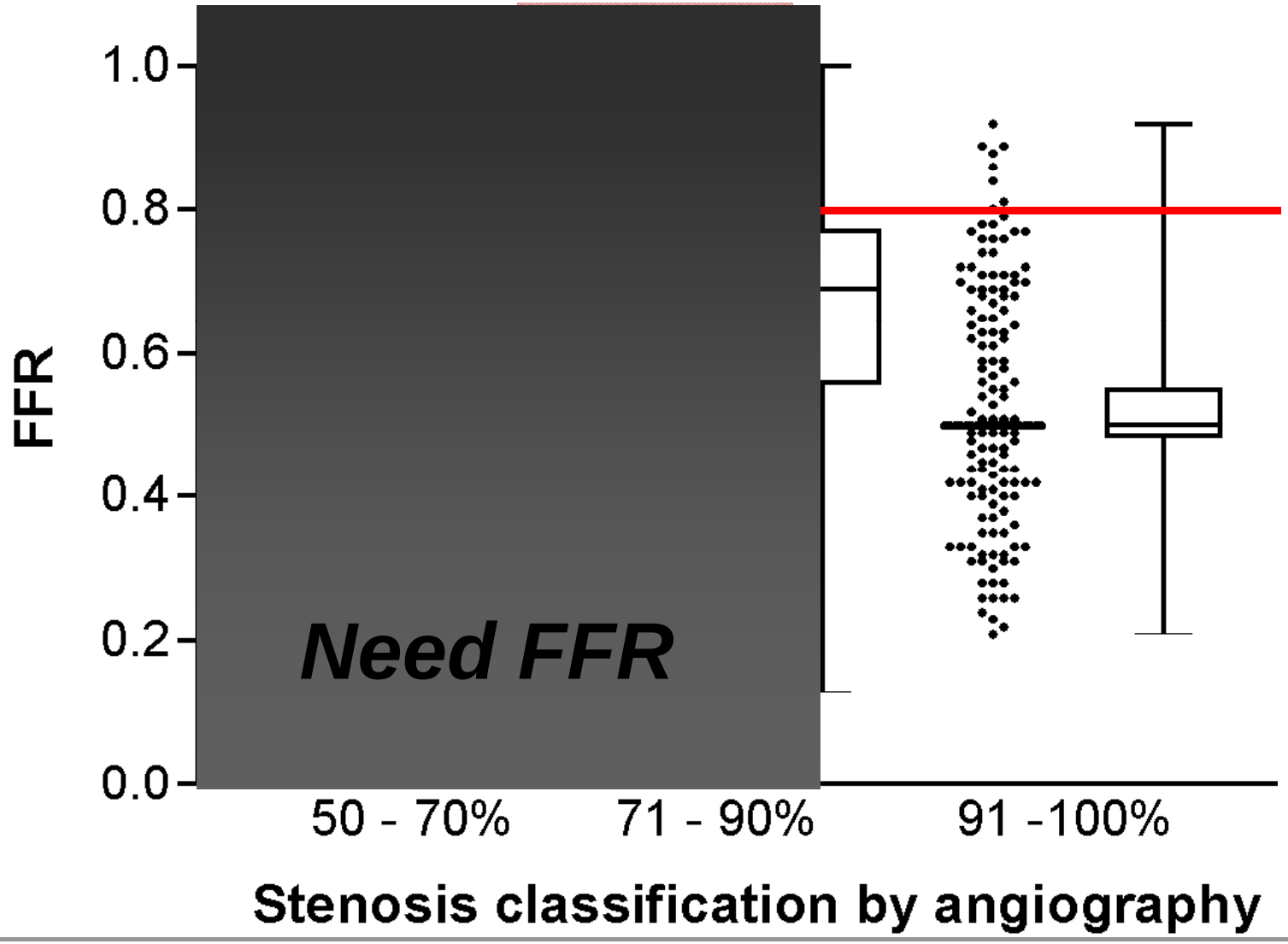
Relation between visual interpretation of equivocal LM disease and FFR



Hamilos, et al. Circulation 2009;120:1505-1512

When should we use FFR?

1329 lesions in the FFR-guided arm of FAME

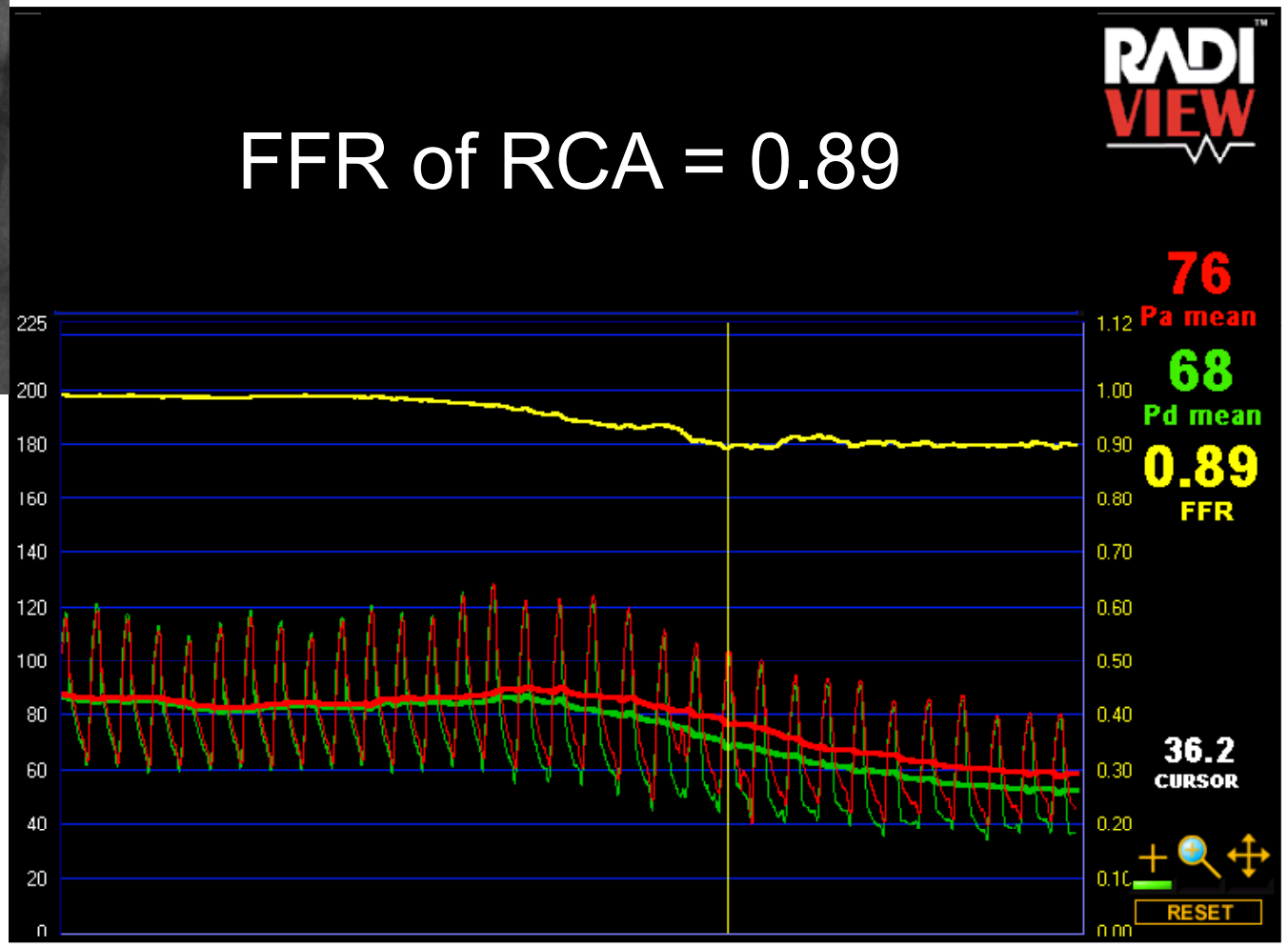


Tonino, et al.J Am Coll Cardiol 2010;55:2816-21.

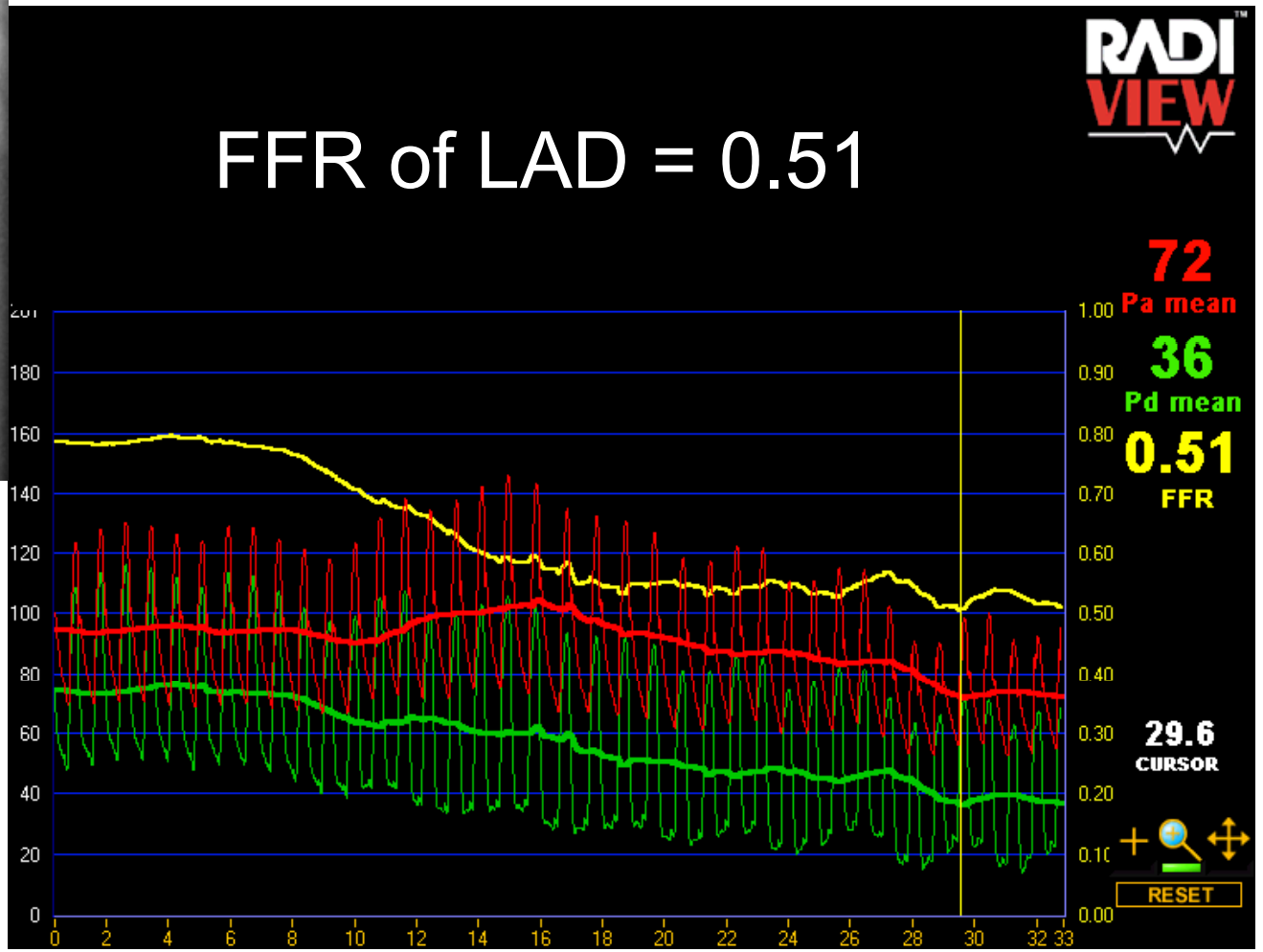
FFR in Multivessel CAD

69 yo man with chest pain and apical ischemia on NPS

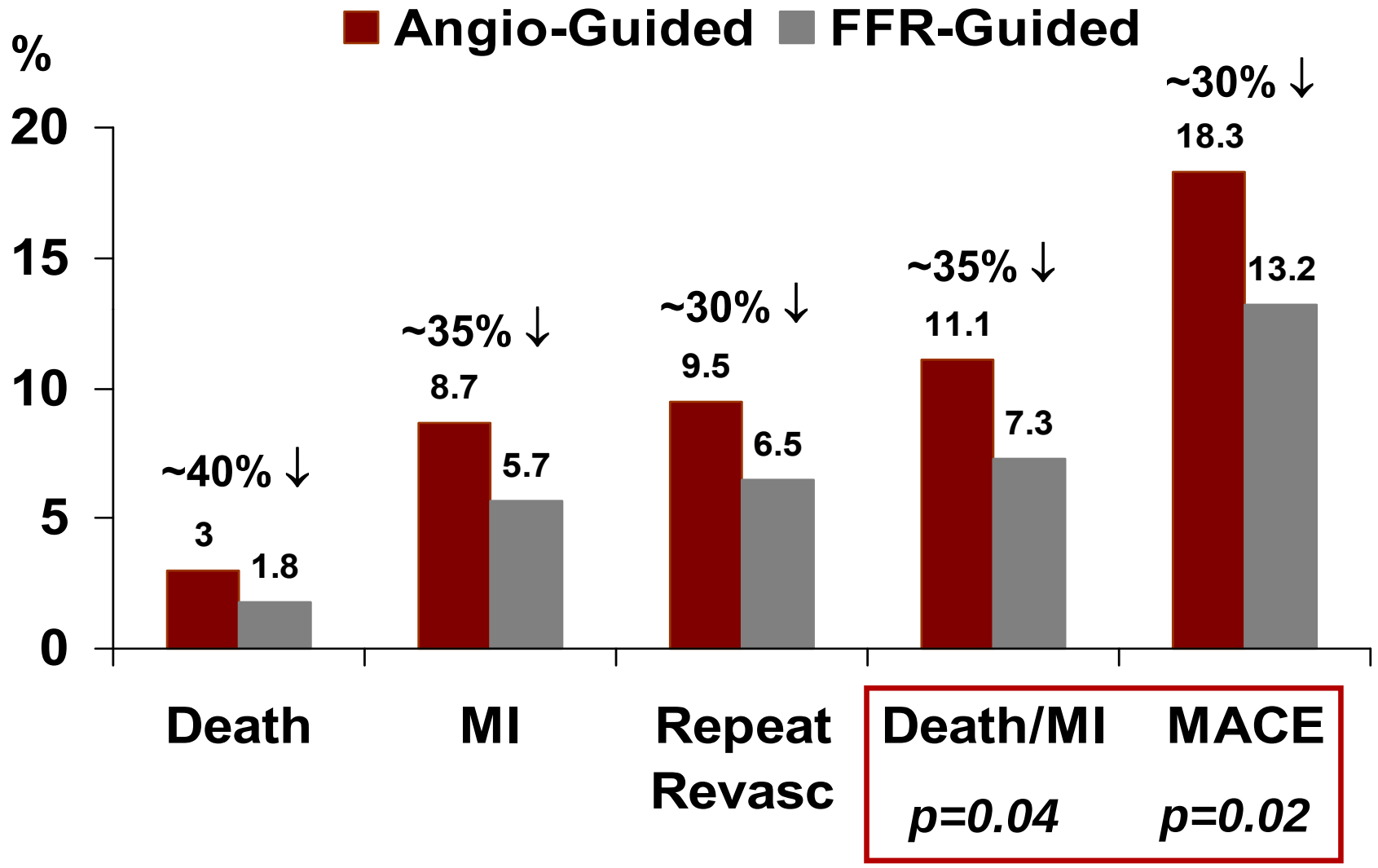
FFR of RCA = 0.89




Filter: Enhance 3


FFR of LAD = 0.51
RADI VIEW
72
Pa mean
36
Pd mean
0.51
FFR
29.6
CURSOR
RESET
180
160
140
120
100
80
60
40
20
0
1.00
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.00
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 33

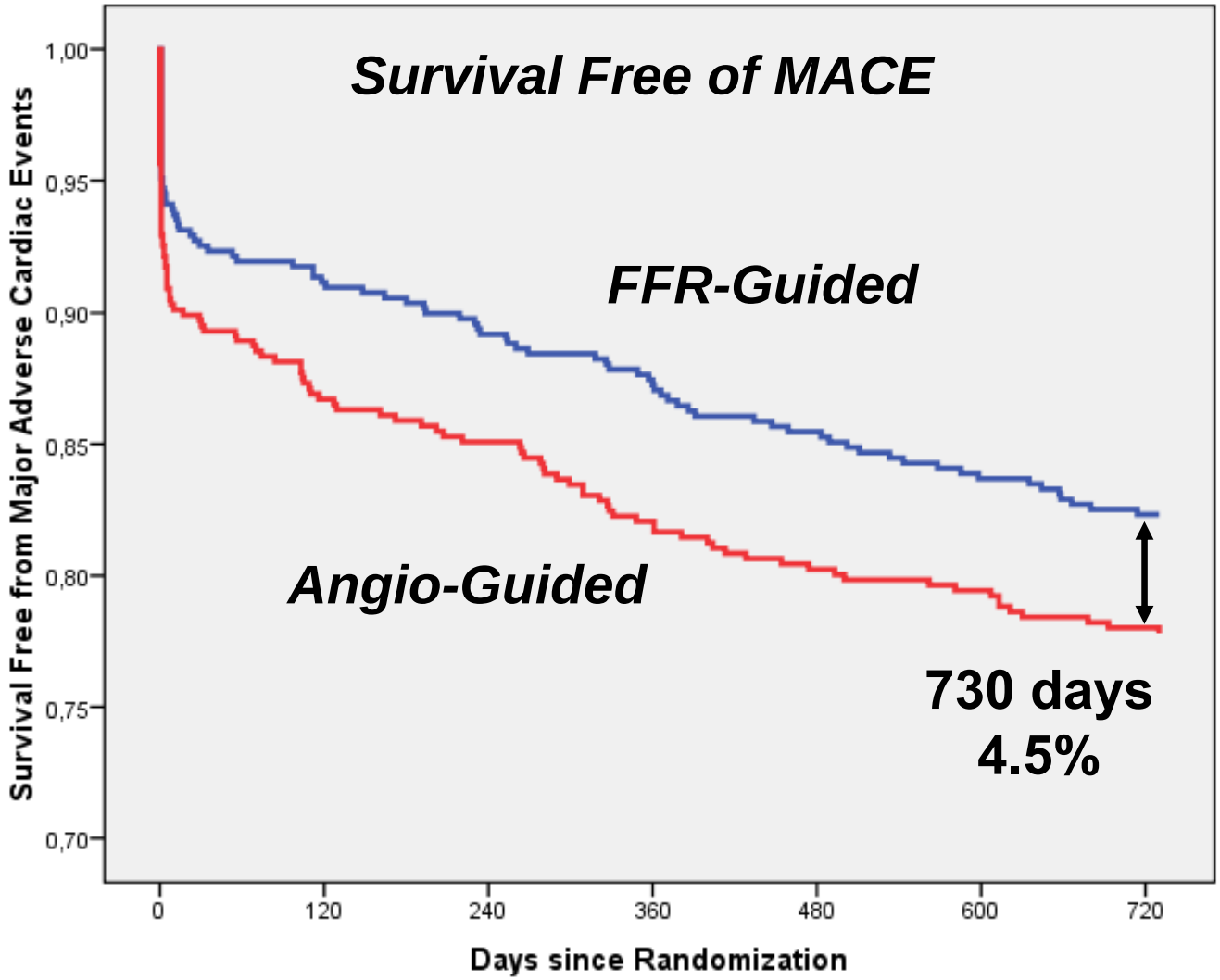
FAME 1 Study: One Year Outcomes



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

FAME Study: Two Year Outcomes

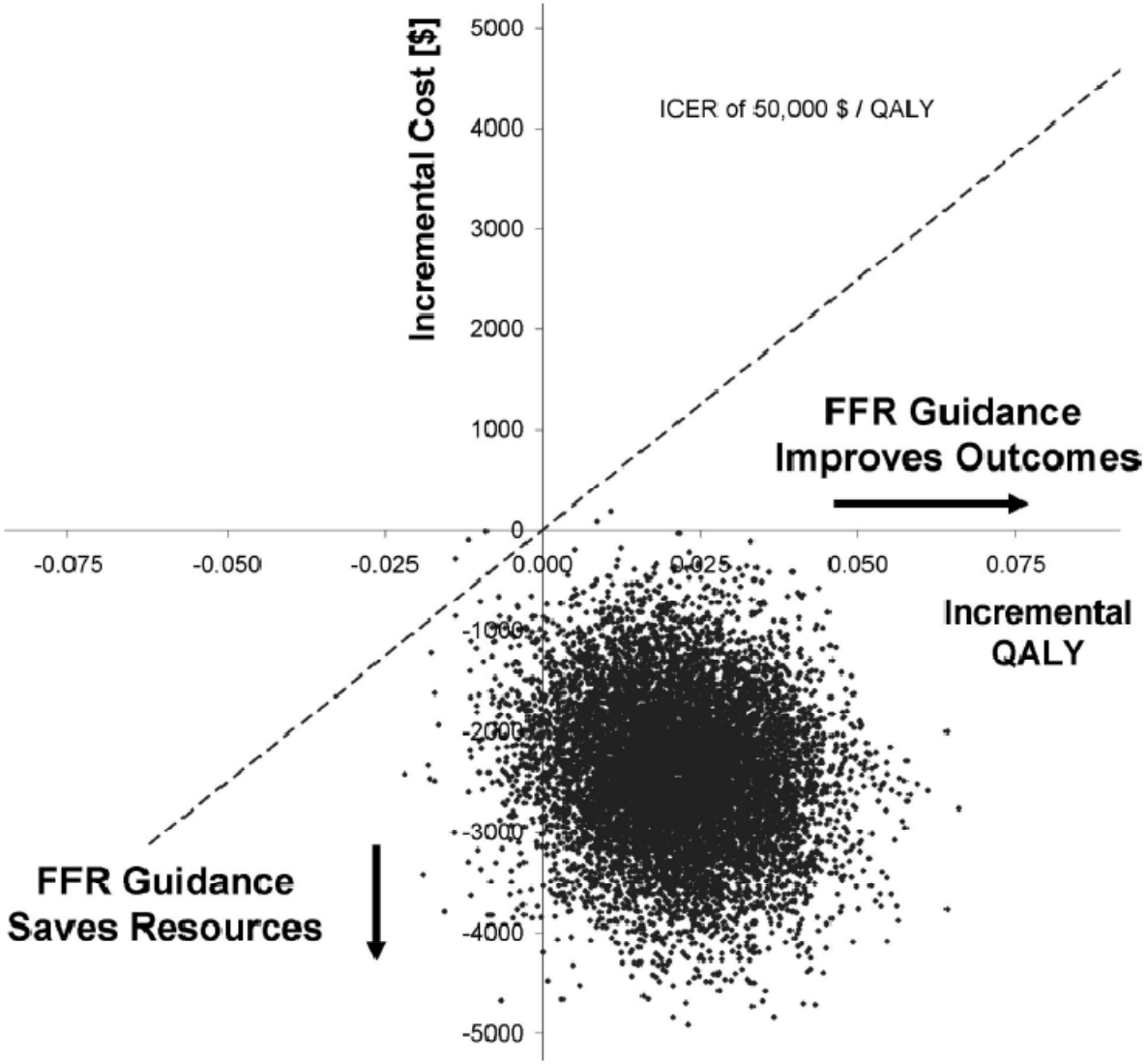
Death/MI was significantly reduced from 12.9% to 8.4% (p=0.02)



Pijls, et al. J Am Coll Cardiol 2010;56:177-184

FAME: Economic Evaluation

Bootstrap Analysis

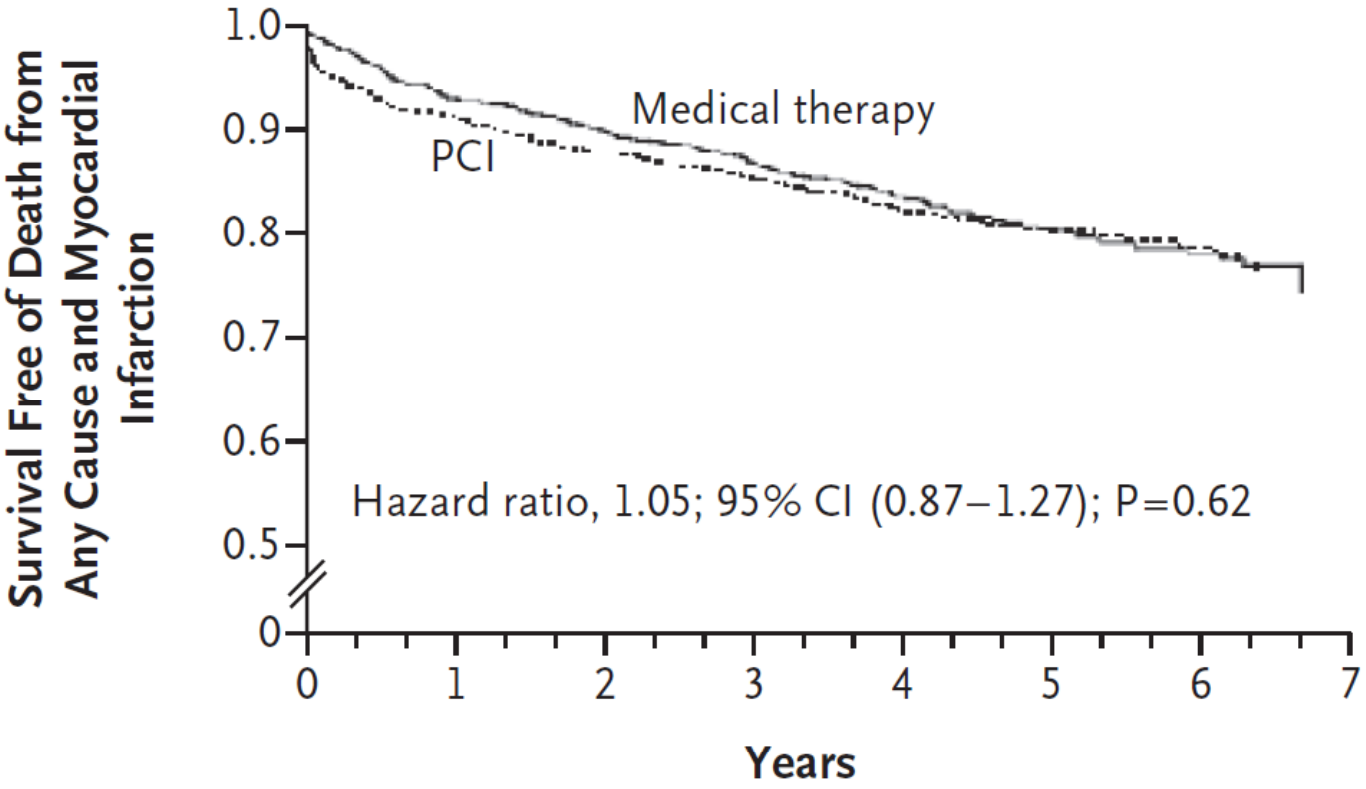


FFR-guided PCI saved >$2,000 per patient at one year compared to Angio-guided PCI

Circulation 2010;122:2545-50.

COURAGE Trial:

2,287 stable patients with 1, 2, or 3 vessel CAD
Randomized to optimal medical therapy or PCI



Hospitalization for ACS was ~12% at 4.6 years and similar between groups

Boden, et al. New Engl J Med 2007;356:1503-16.

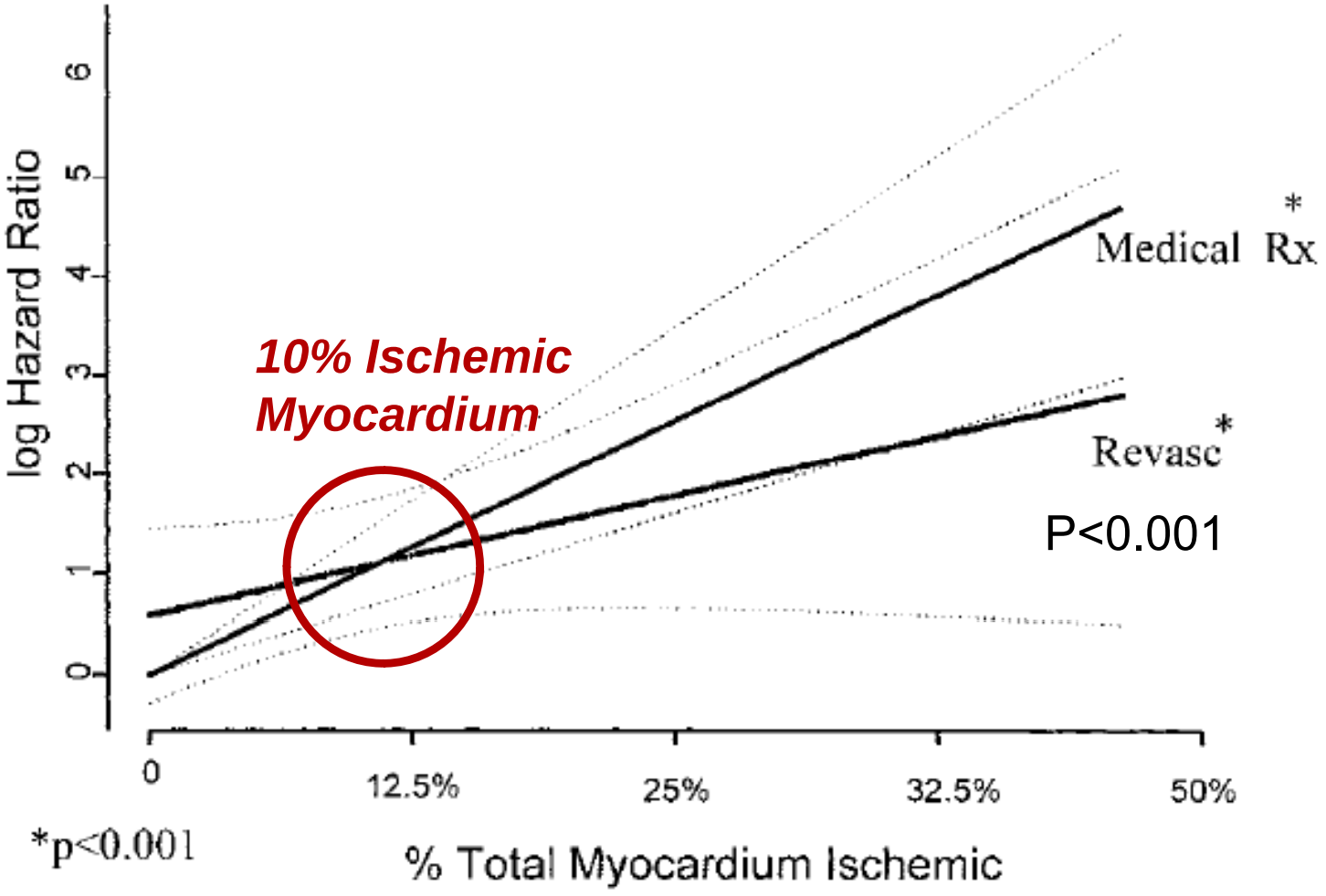
Degree of Ischemia in COURAGE

	PCI+OMT (n=159)			OMT (n=155)			Difference by Treatment	
	Pretreatment	6 to 18 Months	*P*	Pretreatment	6 to 18 Months	*P*	*P*	*P*
Rest TPD	6.4±7	3.4±6	<0.0001	6.1±7	3.3±6	<0.0001	0.70	0.83
Stress TPD	14.6±10	8.9±8	<0.0001	14.7±11	11.4±10	<0.0001	0.87	0.018
Territory								
Right coronary artery	2.5±3	1.4±2	<0.0001	2.7±4	2.1±3	<0.0001	0.60	0.012
Left anterior descending artery	5.8±5	3.6±4	<0.0001	5.9±5	4.8±5	<0.0001	0.97	0.021
Left circumflex artery	5.3±4	3.6±4	<0.0001	5.3±5	4.2±4	<0.0001	0.96	0.26
% Ischemia			<0.0001			<0.0001	0.40	0.019
0 to 4.9%	43.0%	53.4%		37.9%	46.0%			
5% to 9.9%	26.0%	30.9%		29.1%	27.0%			
≥10%	31.0%	15.8%		33.0%	27.0%			
Left ventricular ejection fraction								
Rest	57.0±11	57.0±9	0.97	57.0±9	57.7±6	0.30	0.97	0.14
Poststress	51.0±11	54.8±10	0.001	53.4±10	54.2±12	0.38	0.09	0.49
End-diastolic volume								
Rest	103.2±40	105.2±38	0.41	100.0±30	102.6±32	0.43	0.26	0.30
Poststress	112.7±40	111.0±38	0.44	102.3±33	105.9±35	0.21	0.13	0.33
End-systolic volume								
Rest	47.6±29	47.9±28	0.84	45.2±23	45.0±25	0.88	0.13	0.30
Poststress	57.2±29	52.5±29	0.02	49.5±23	49.8±24	0.88	0.33	0.49

Shaw, et al. Circulation 2008;117:1283-91.

Importance of Myocardial Ischemia

With greater degrees of ischemia, there is a survival benefit for PCI



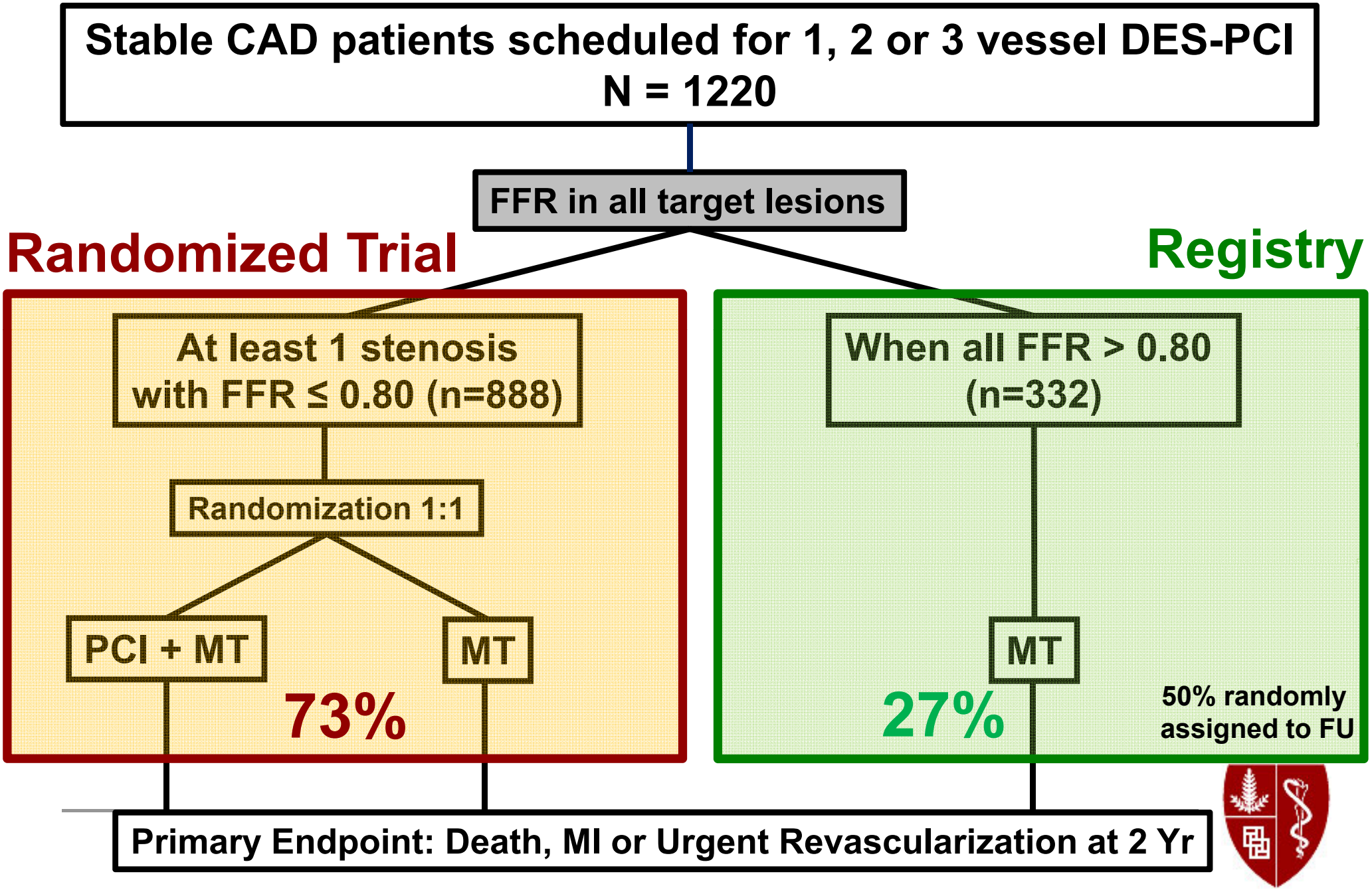
Hachamovitch, et al. Circulation 2003;107:2900-06.

FAME 2: Design

- Hypothesis:
  - Optimal medical therapy plus FFR-guided PCI improves outcomes compared to optimal medical therapy alone in patients with stable coronary artery disease.

De Bruyne, et al. New Engl J Med 2012;367:991-1001

FAME 2

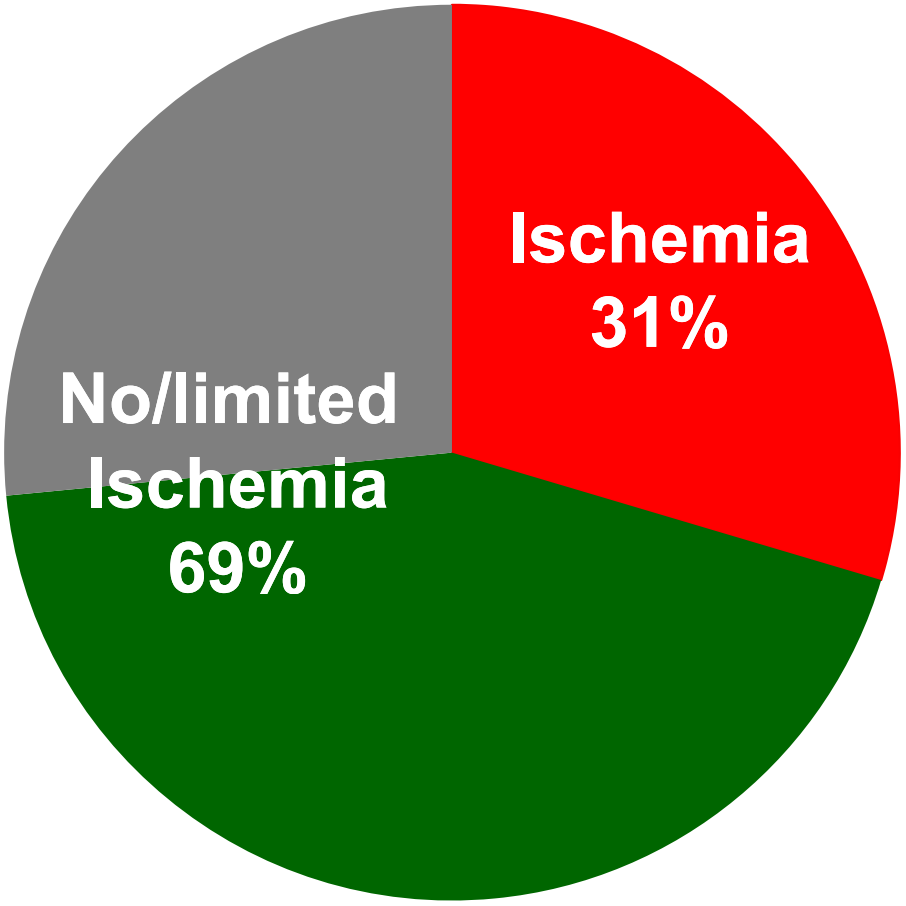

Stable CAD patients scheduled for 1, 2 or 3 vessel DES-PCI
N = 1220
FFR in all target lesions
Randomized Trial
Registry
At least 1 stenosis with FFR ≤ 0.80 (n=888)
Randomization 1:1
PCI + MT
MT
73%
When all FFR > 0.80 (n=332)
MT
27%
50% randomly assigned to FU
Primary Endpoint: Death, MI or Urgent Revascularization at 2 Yr

Degree of Ischemia in COURAGE

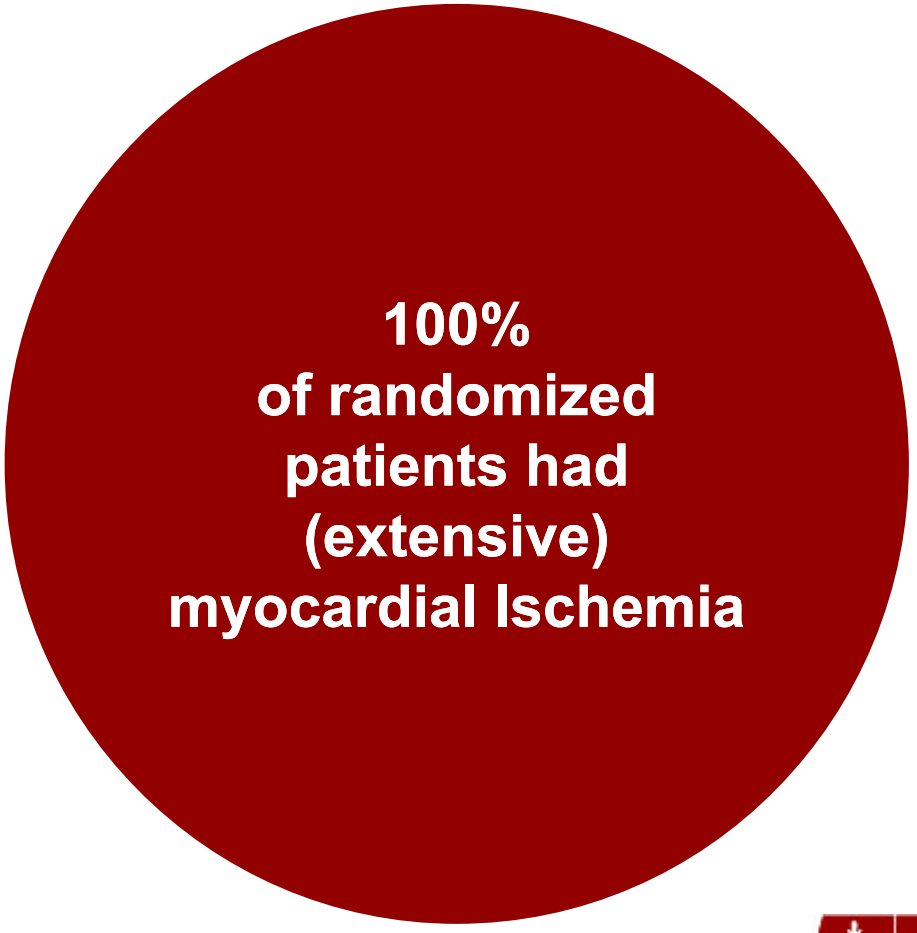
Adapted from LJ Shaw et al Circulation, 2008; Courtesy B De Bruyne, MD, PhD

Importance of Ischemia

COURAGE



FAME 2



Courtesy of: Bernard De Bruyne, MD, PhD

Importance of Patient Selection

Inclusion rates

COURAGE

↓

0.8

pt./mo./center

FAME 2

↓

3.4

pt./mo./center

Courtesy of: Bernard De Bruyne, MD, PhD

Baseline Characteristics

	Randomized Trial		Registry	p
Patients, N	PCI+MT=447	MT=441	with FU=166	
Demographic				
Age (y)	63.5±9.3	63.9±9.6	63.6±9.8	0.90
Male sex - (%)	79.6	76.6	68.1	0.005
BMI	28.3±4.3	28.4±4.6	27.8±3.9	0.14
Risk factors for CAD				
Positive family history CAD - (%)	48.3	46.9	45.8	0.65
Smoking - (%)	19.9	20.4	21.1	0.79
Hypertension - (%)	77.6	77.8	81.9	0.23
Hypercholesterolemia - (%)	73.9	78.9	71.1	0.15
Diabetes mellitus - (%)	27.5	26.5	25.3	0.65
Insulin requiring diabetes - (%)	8.7	8.8	6.0	0.24

De Bruyne, et al. New Engl J Med 2012;367:991-1001

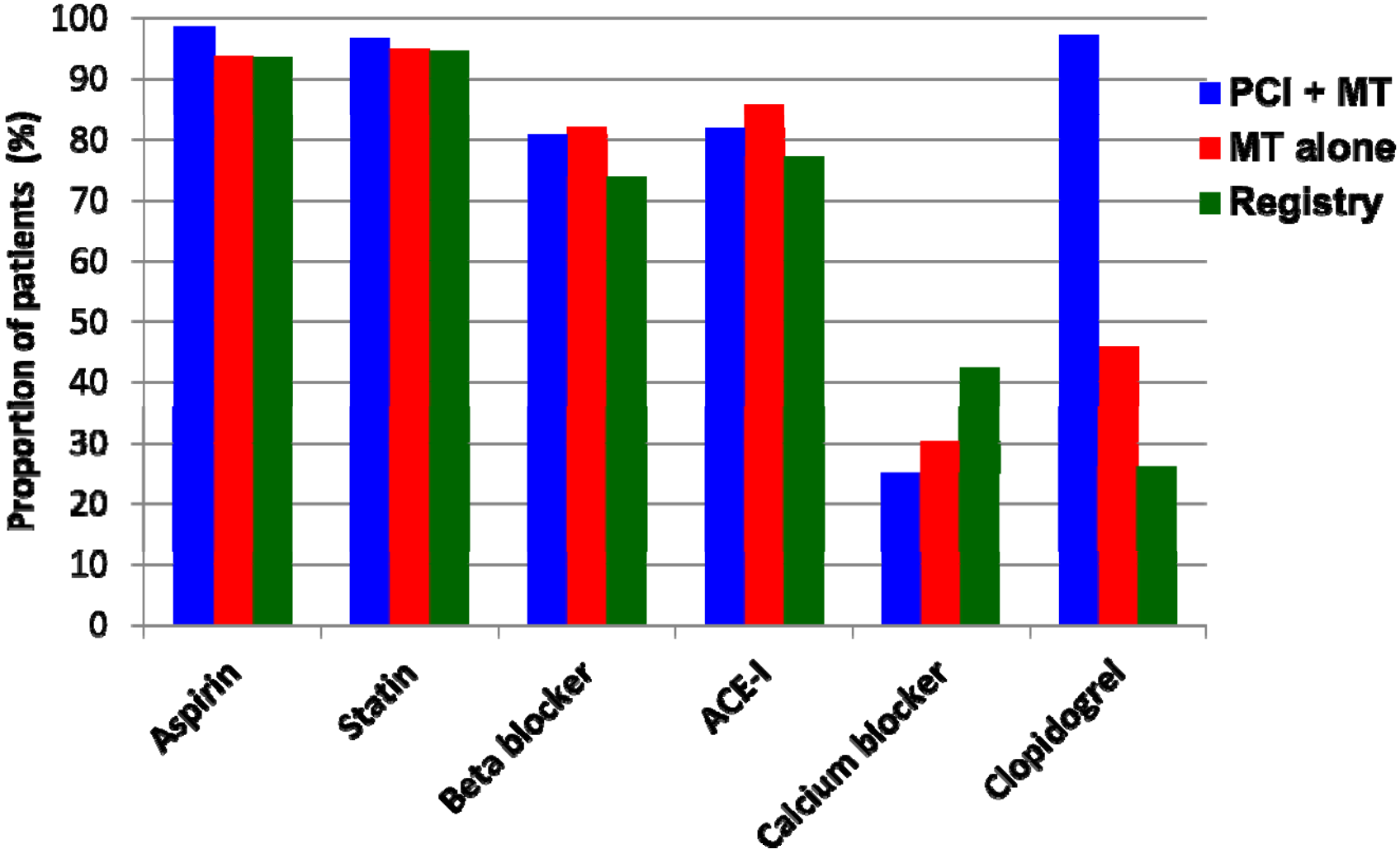
Angiographic Characteristics

	Randomized trial N=888		Registry N=322	P*
Patients, N	**PCI+MT=447**	**MT=441**	**with FU=166**	
Angiographically significant stenoses - no. per patient	**1.87±1.05**	**1.73±0.94**	**1.32±0.59**	**<0.001**
No of vessels with ≥ 1 significant stenoses - (%)				**<0.001**
1	**56.2**	**59.2**	**81.9**	
2	**34.9**	**33.1**	**15.7**	
3	**8.9**	**7.7**	**2.4**	
Prox- or mid- LAD stenoses - (%)	**65.1**	**62.6**	**44.6**	**<0.001**

De Bruyne, et al. New Engl J Med 2012;367:991-1001

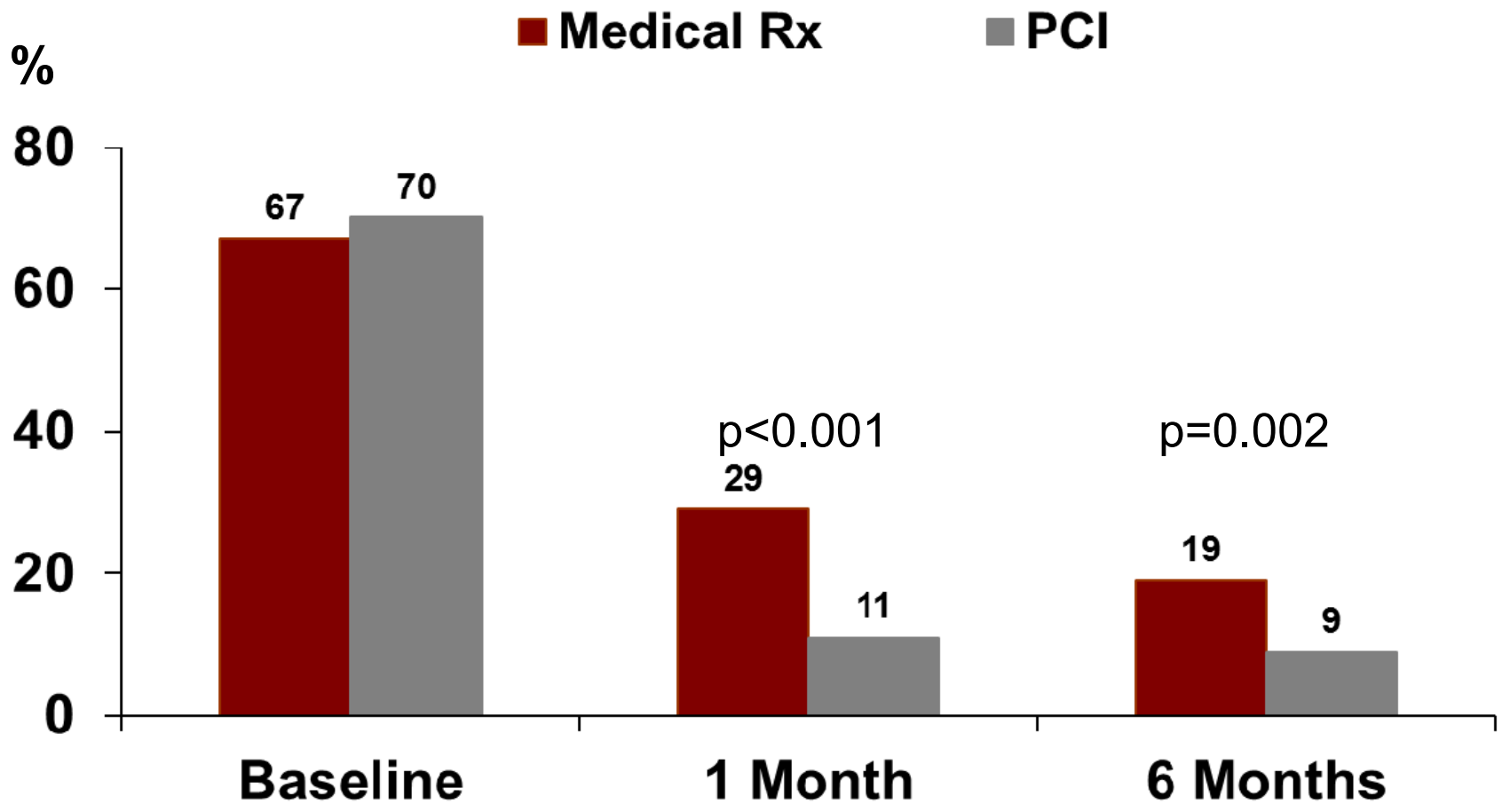
FAME 2 Trial

Medications at 6 Month Follow-Up



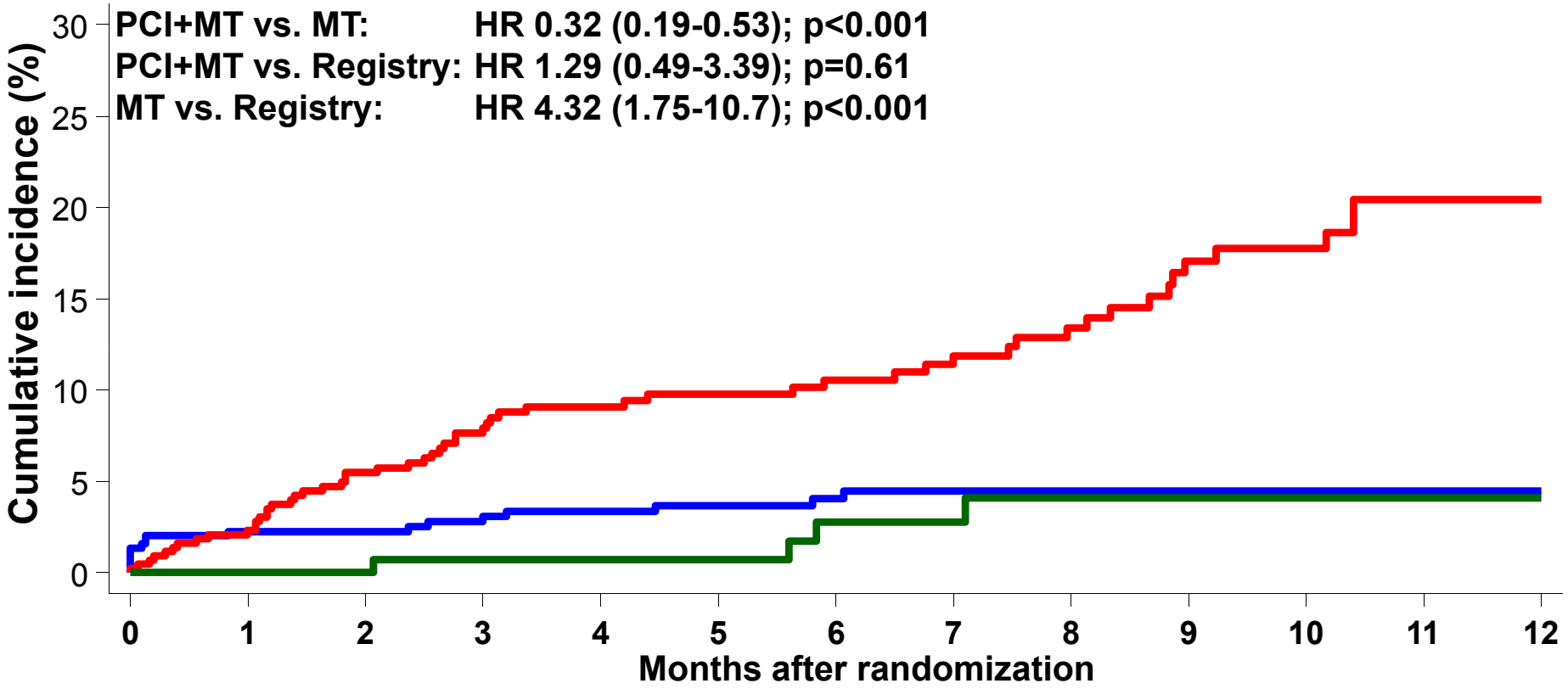
De Bruyne, et al. New Engl J Med 2012;367:991-1001

Patients with Angina Class II to IV



De Bruyne, et al. New Engl J Med 2012;367:991-1001

Primary Endpoint: *Death, MI, Urgent Revasc*



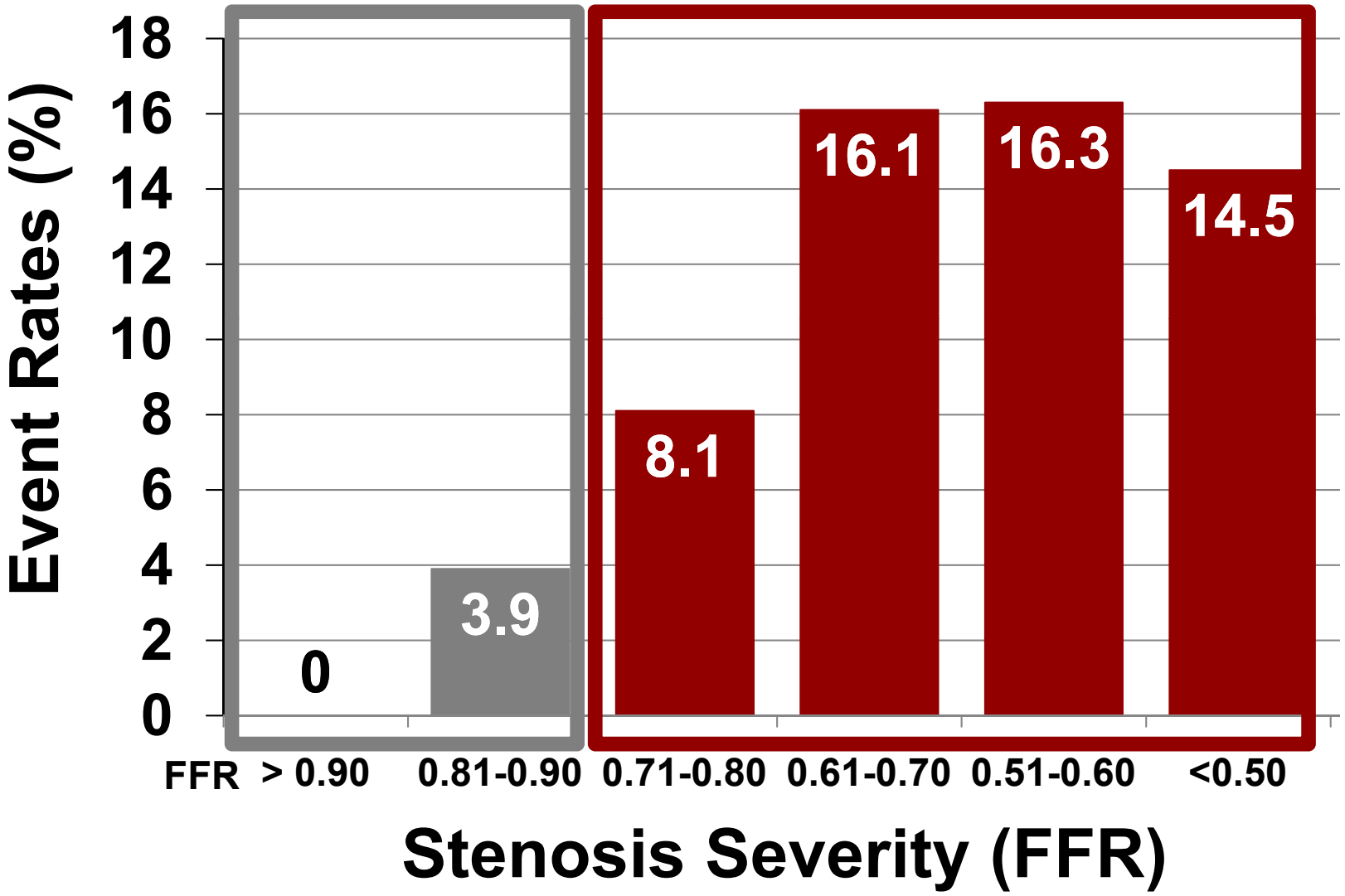
No. at risk

MT	441	414	370	322	283	253	220	192	162	127	100	70	37
PCI+MT	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

De Bruyne, et al. New Engl J Med 2012;367:991-1001

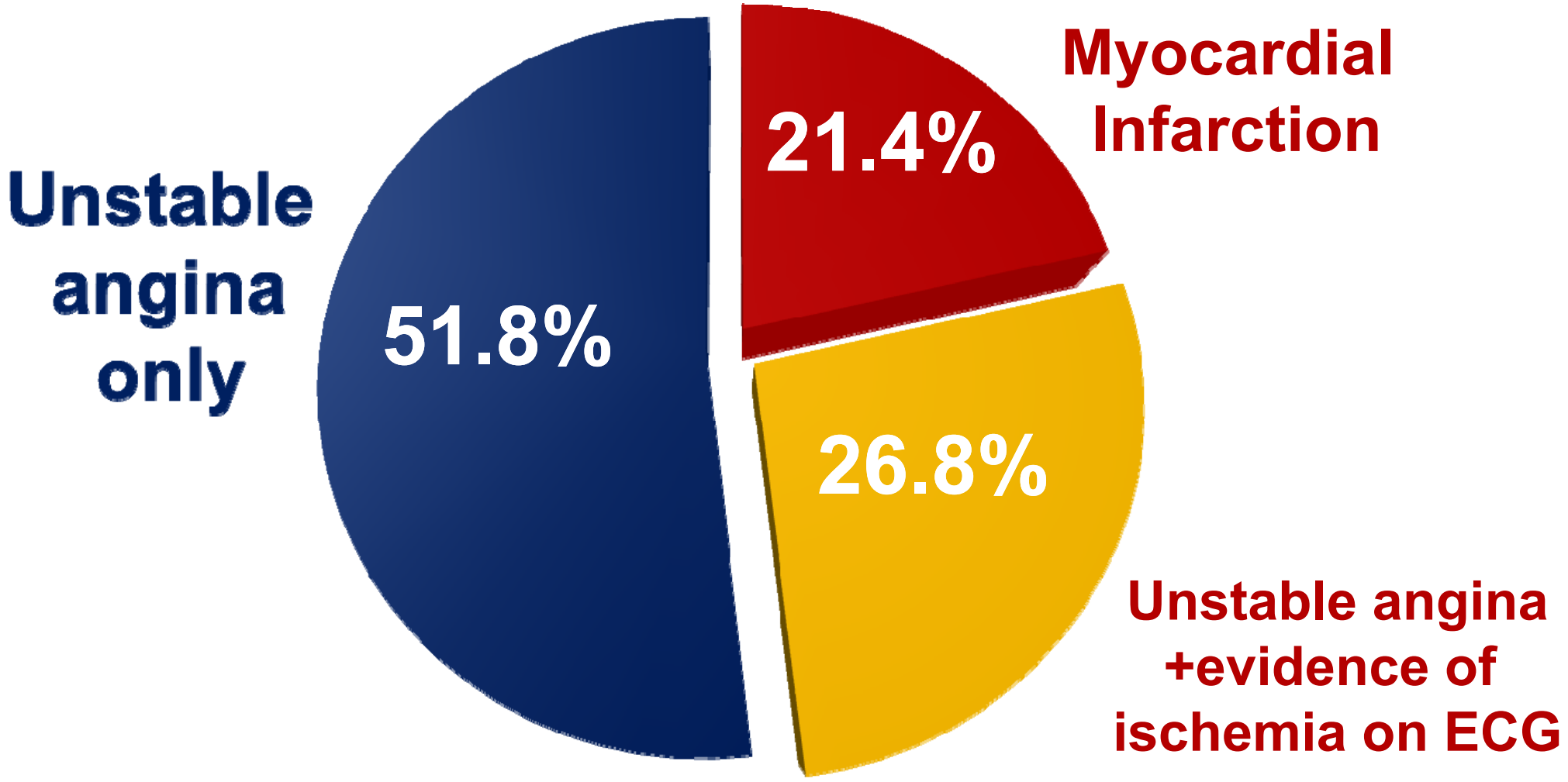
Relationship Between FFR and Outcomes

FAME 2: Patients with angiographically significant stenoses treated with OMT



Courtesy of: Bernard De Bruyne, MD, PhD

Patients with urgent revascularization

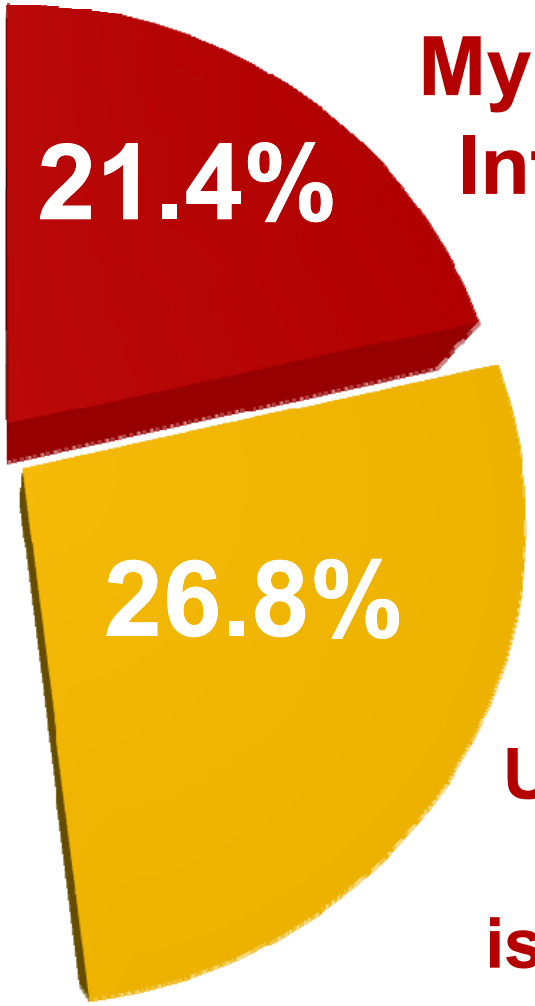


Patients with urgent revascularization

Urgent revascularization driven by MI or unstable angina with ECG changes

FFR-Guided PCI + MT		MT
0.9%	vs.	5.2%

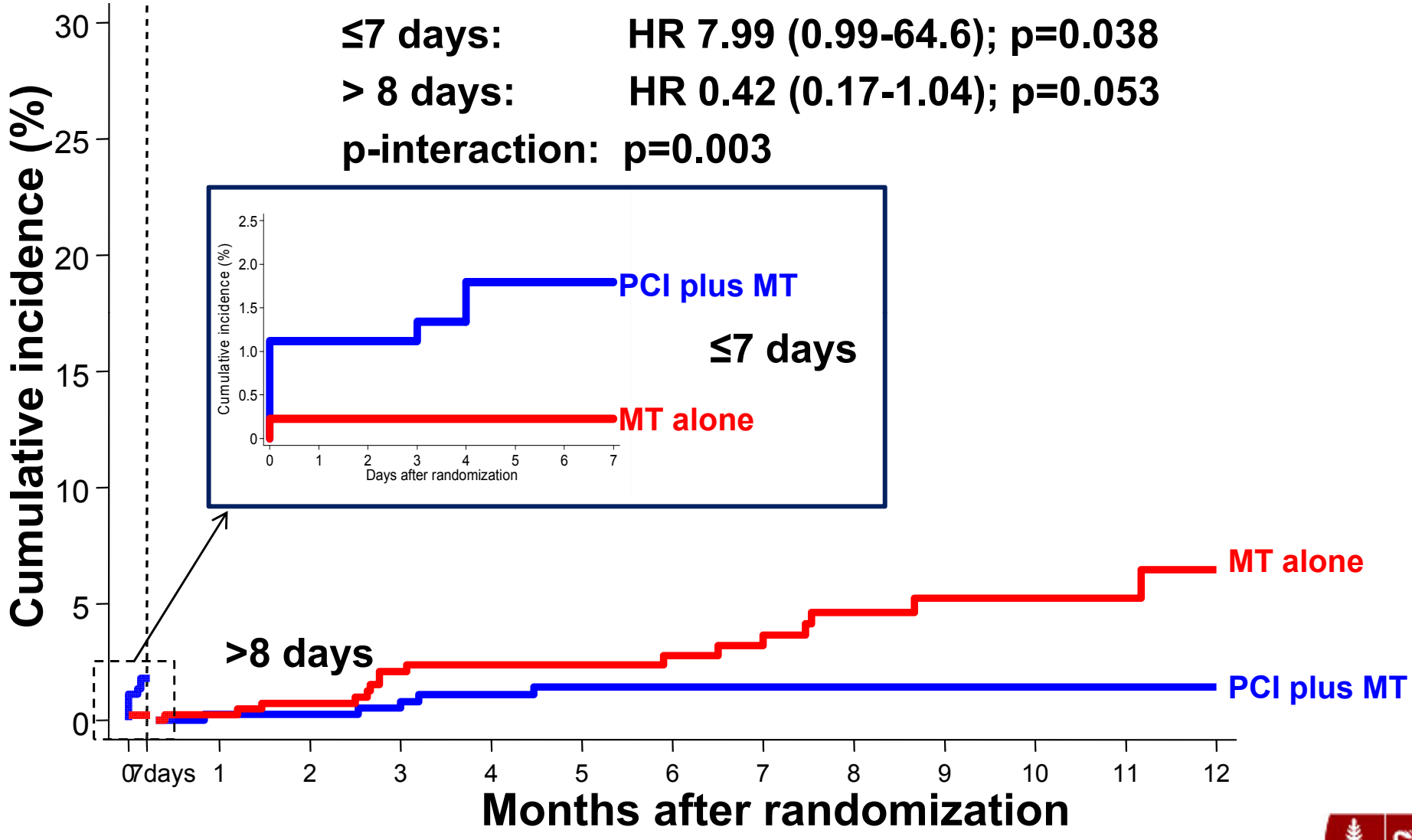
p<0.001
83% Relative Risk Reduction



Myocardial Infarction

Unstable angina +evidence of ischemia on ECG

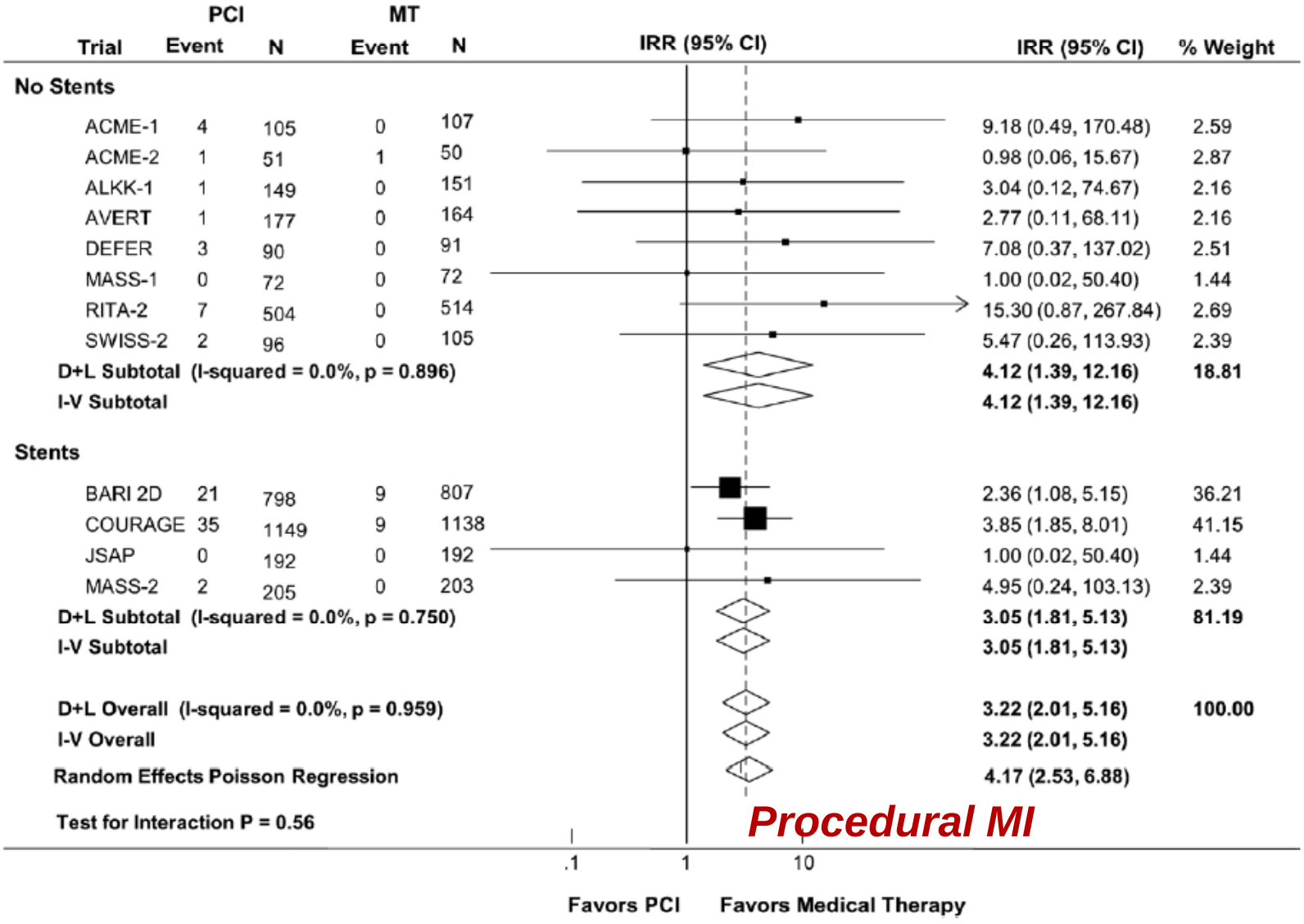
Landmark Analysis for Death/MI



De Bruyne, et al. New Engl J Med 2012;367:991-1001

Spontaneous vs. Procedural MI

Meta-analysis of 12 randomized trials comparing PCI to OMT



Bangalore, et al. Circulation 2013;127:769-781

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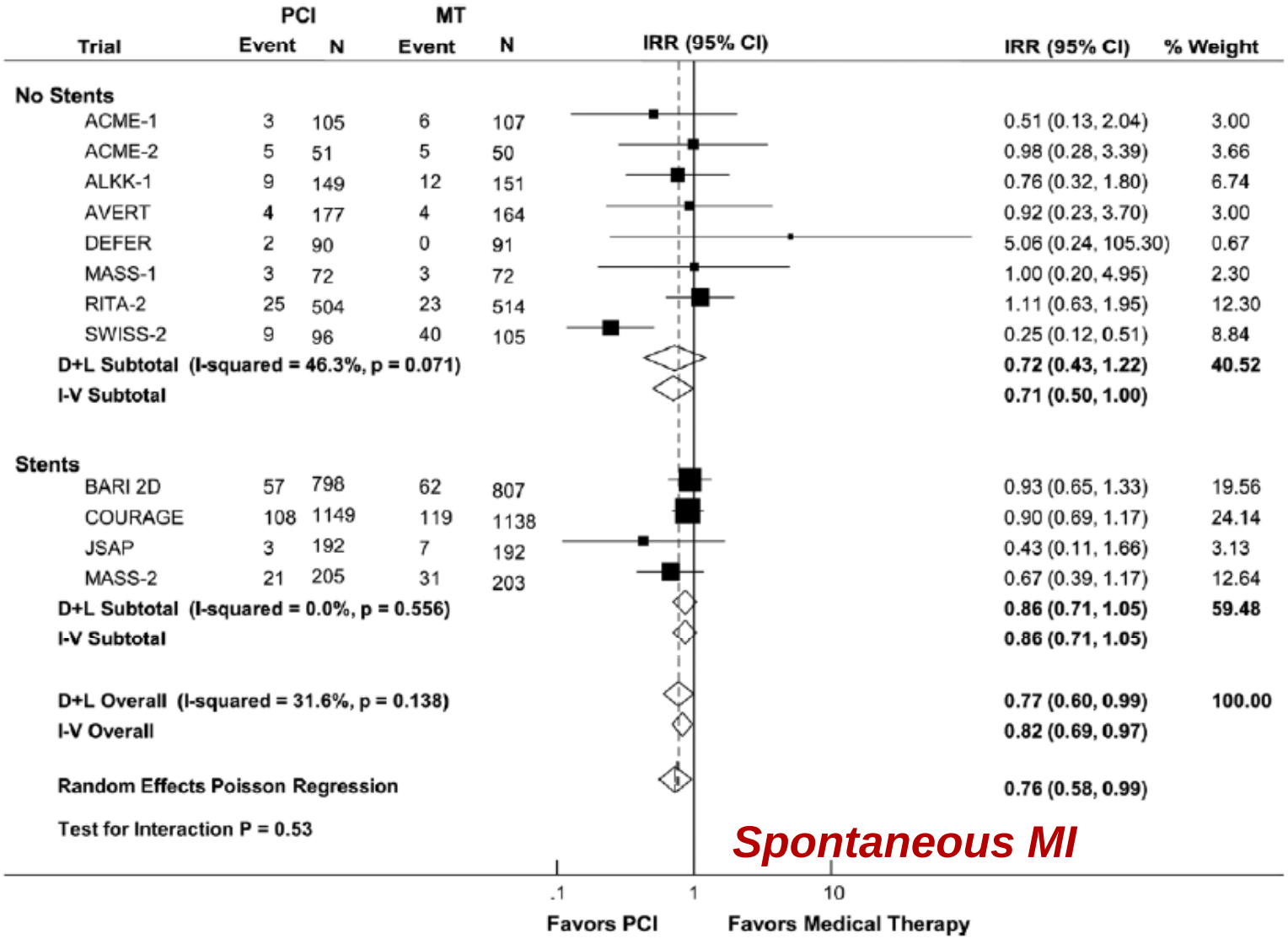

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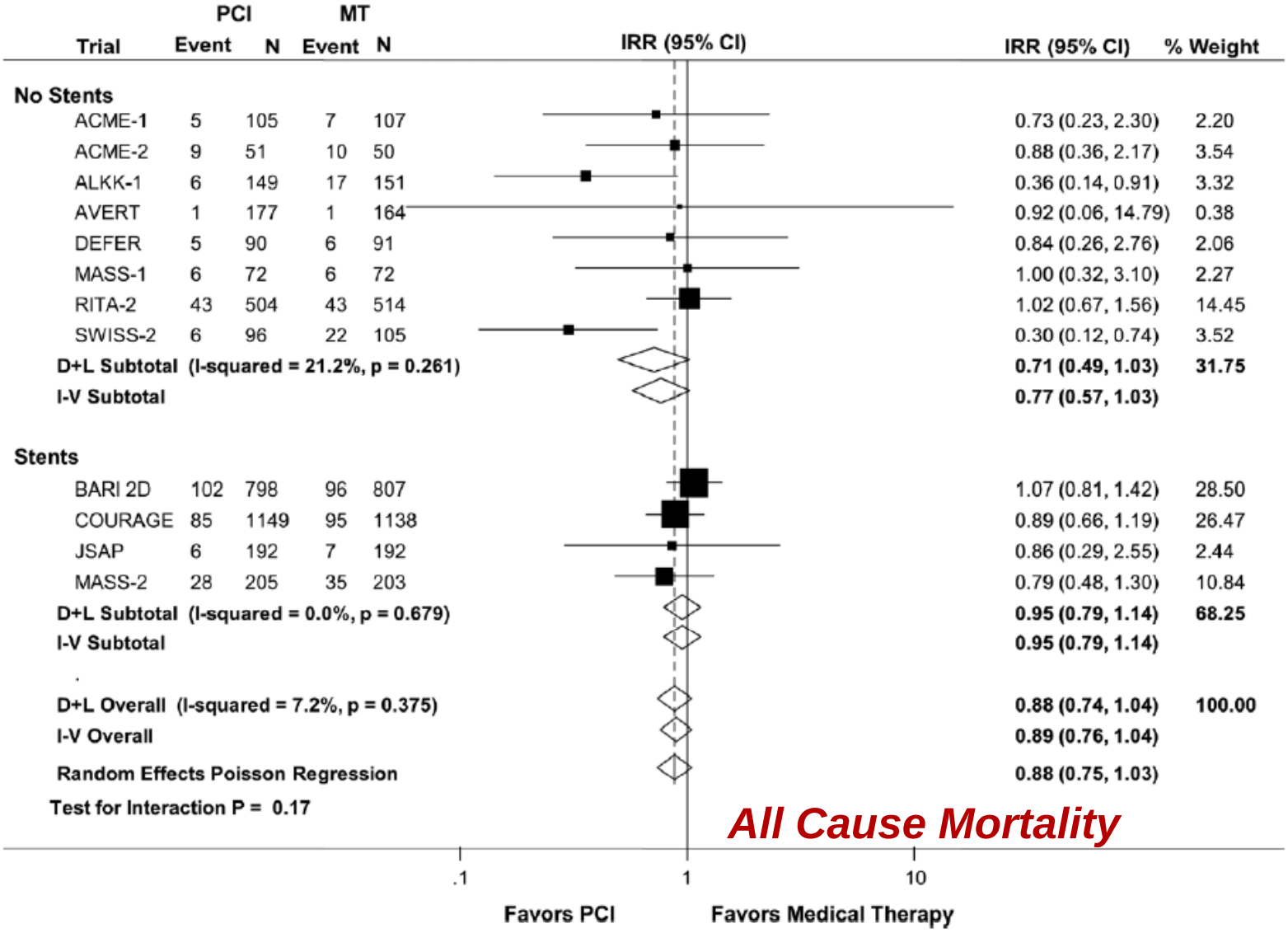
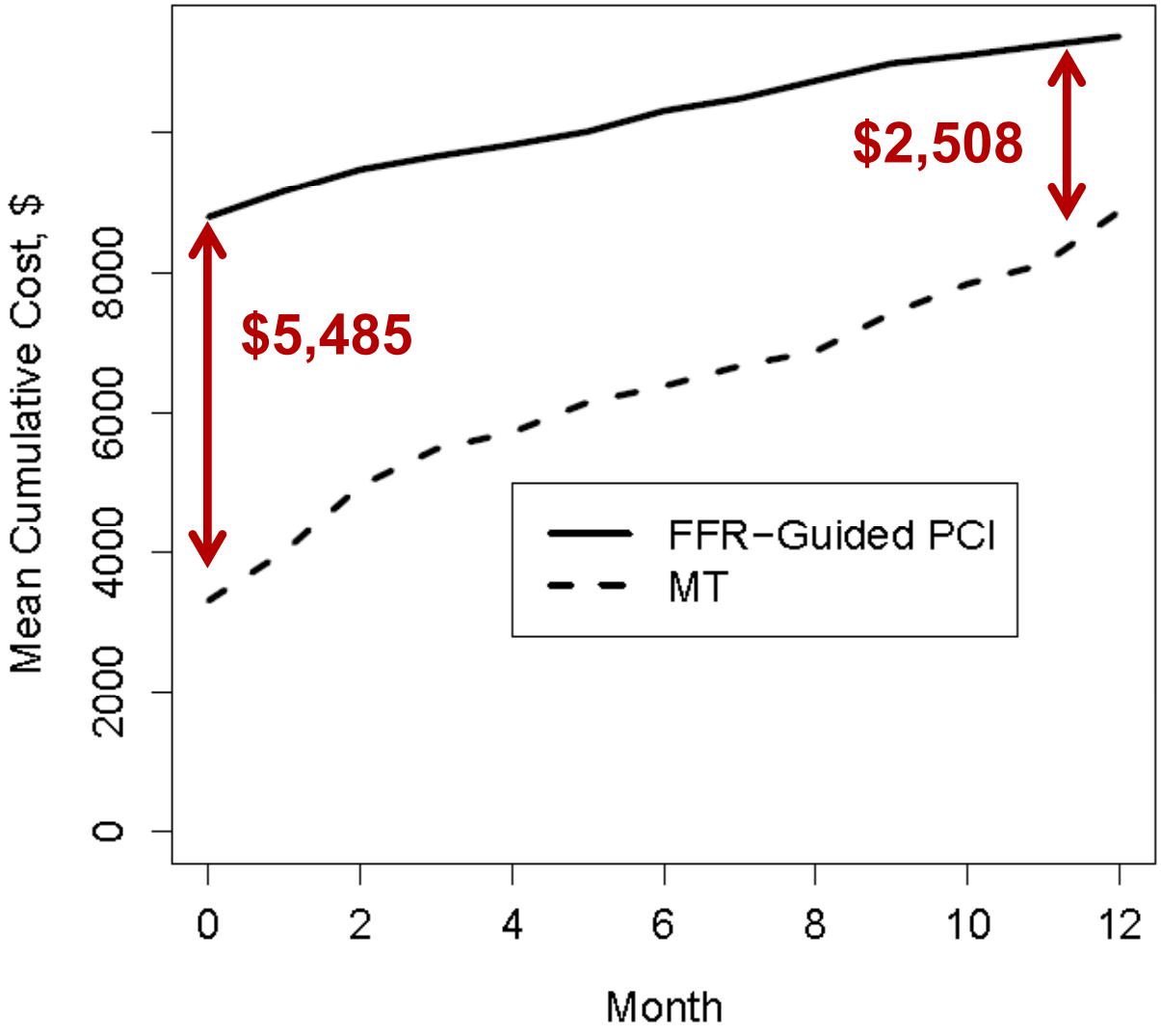


Bangalore, et al. Circulation 2013;127:769-781

FAME 2: *Cost Effectiveness*

Cumulative costs over 12 months



Late Breaking Trial: TCT 2012

FAME 2: *Cost Effectiveness*

Quality of Life at 1 Month

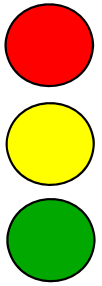
	FFR-Guided PCI	MT	p-value
Angina (%)			
Class 0-1	89	71	<0.001
Class 2-4	11	29	<0.001
Utility Change	**0.054**	**0.003**	**<0.001**

FAME 2: *Cost Effectiveness*

CE Benchmarks:

Hemodialysis ≈ $50,000 / QALY

WHO GDP std ≈ $150,000 / QALY



>$150,000 / QALY

$50K-150K / QALY

<$50,000 / QALY

Study	Comparators	CE Ratio
COURAGE	Angio-Guided PCI vs Medical Therapy	≥ $168,000 / QALY
FAME 1	Angio-Guided PCI vs FFR-Guided PCI	FFR-Guided PCI is Dominant (↓$ / ↑QALY)
FAME 2	FFR-Guided PCI vs Medical Therapy	$32,000 / QALY

Late Breaking Trial: TCT 2012

FAME 2 Trial

Take Home Messages:

- **In patients with stable coronary artery disease, FFR-guided PCI improves patient outcome and is cost-effective when compared to medical therapy alone.**

- **This improvement is driven by a dramatic decrease in the need for urgent revascularization for ACS.**

- **In patients with functionally non-significant stenoses, medical therapy alone resulted in an excellent outcome, regardless of the angiographic appearance of the stenoses.**