# FAME 2 and COURAGE: Going Functional is the Solution!

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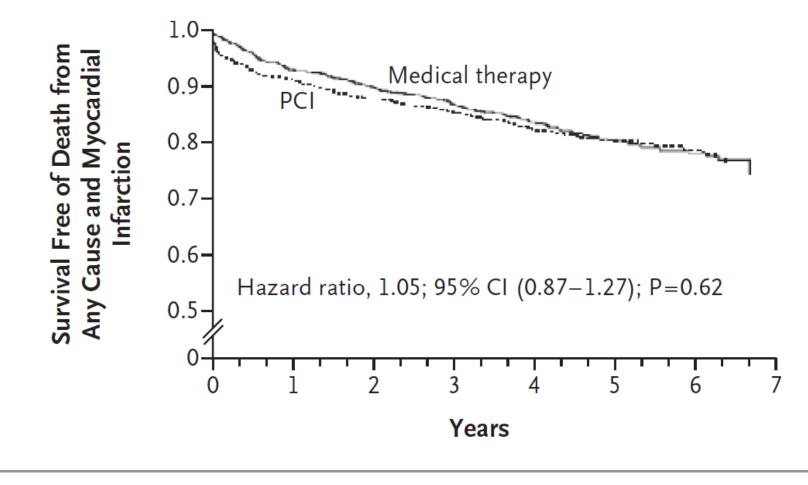
# **Conflict of Interest**

- 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...

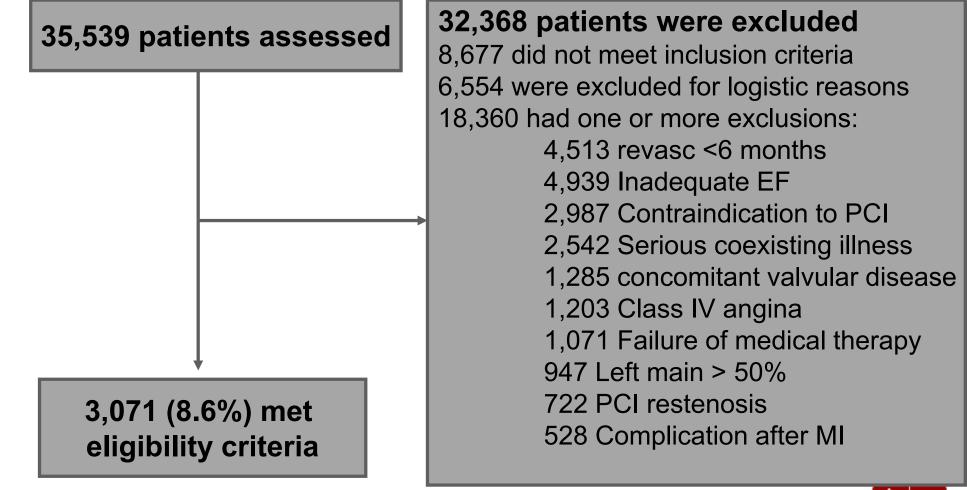
>80% stenosis and typical symptoms

... fairly broad inclusion criteria



# What was the population?

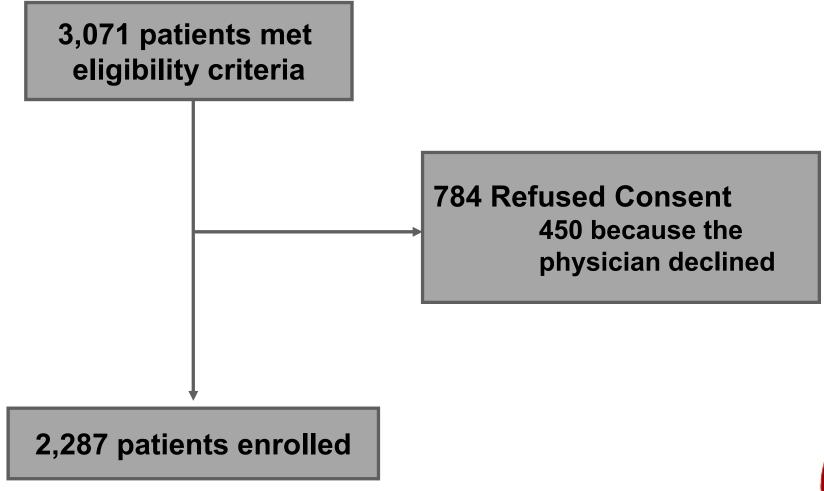
### Who was included?





# What was the population?

### Who was included?





# Was PCI Optimal?

 $\rightarrow$  787 patients (69%) had multivessel CAD

 $\rightarrow$  Only 416 (41%) received  $\geq$  2 stents

 $\rightarrow$  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)

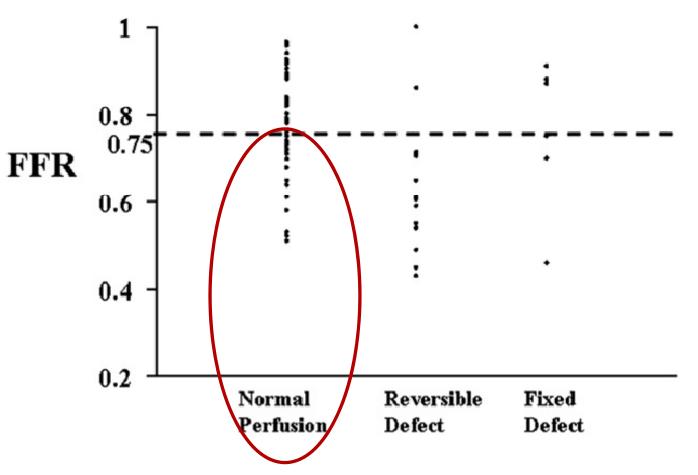
Thallium Scan Finding	% Patients
No Defect	18%
Single Vessel Pattern	36%
Two Vessel Pattern	36%
Three Vessel Pattern	10%



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

## Inaccuracy of Radionuclide Imaging

### 36 patients with multivessel CAD

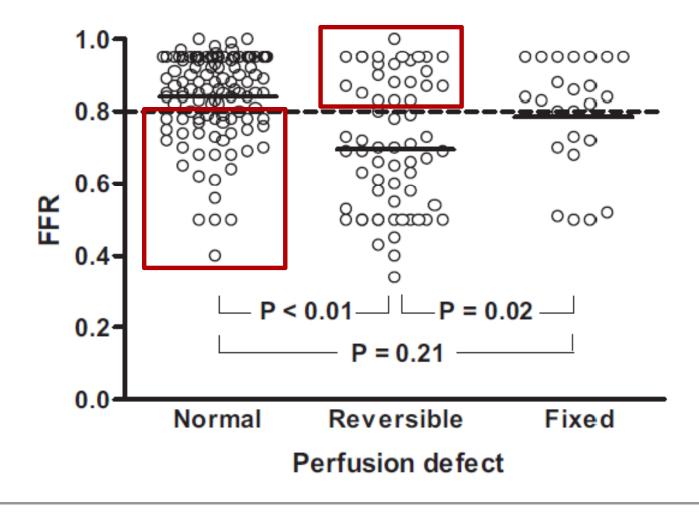


# Discordance occurred in 31% of vessels / territories, predominantly because of a low FFR and normal nuclear result

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

## Inaccuracy of Radionuclide Imaging

### 67 patients with angiographic 2 or 3 vessel CAD

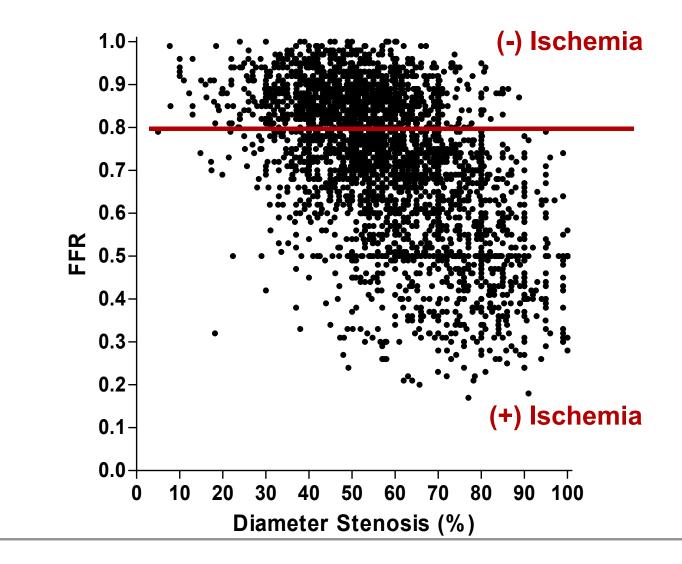




Melikian, et al. J Am Coll Cardiol Intv 2010;3:307-14

# Limitation of Angiography

### **Comparison of QCA to FFR in over 3,000 lesions**

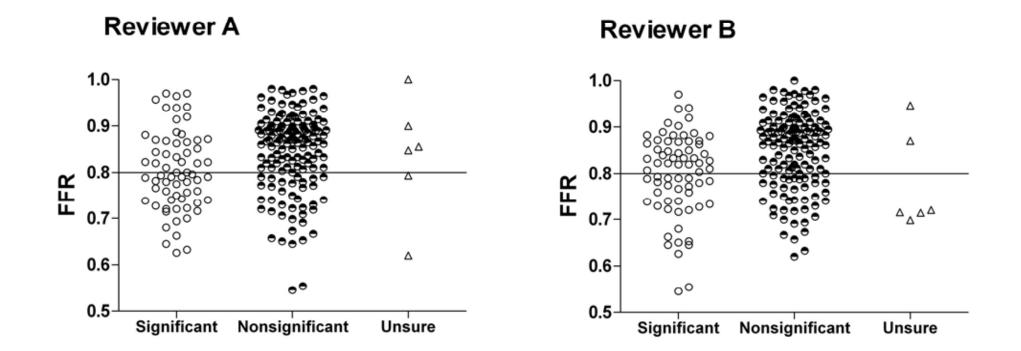




Courtesy of Bernard De Bruyne, MD, PhD

# Limitation of Angiography

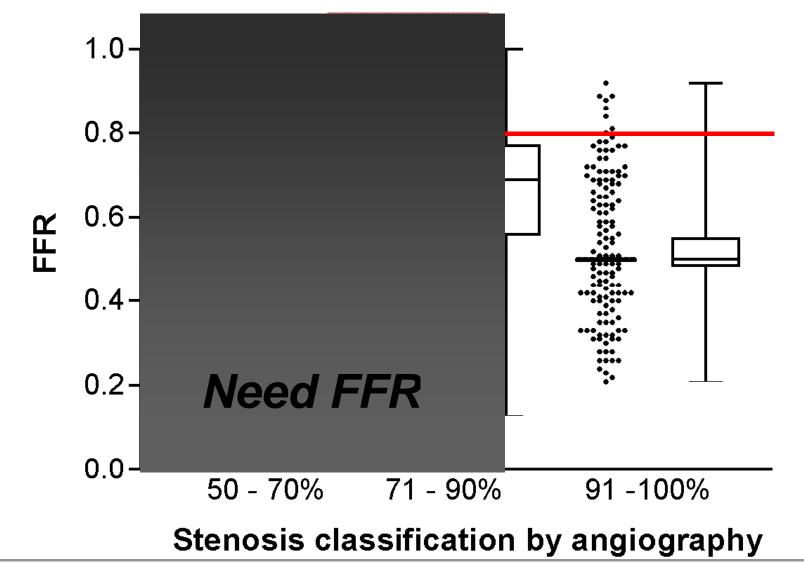
Relation between visual interpretation of equivocal LM disease and FFR





## When should we use FFR?

### 1329 lesions in the FFR-guided arm of FAME

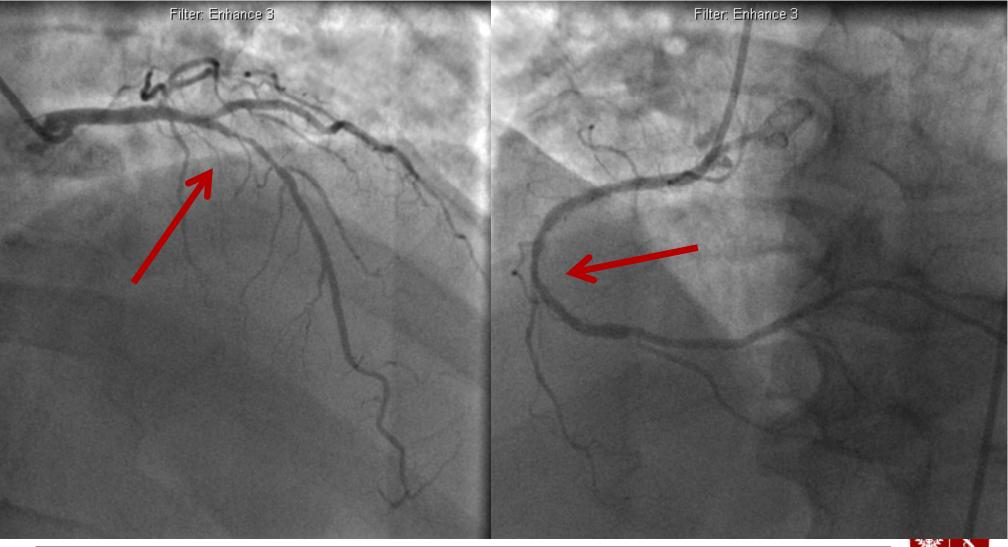


Tonino, et al.J Am Coll Cardiol 2010;55:2816-21.



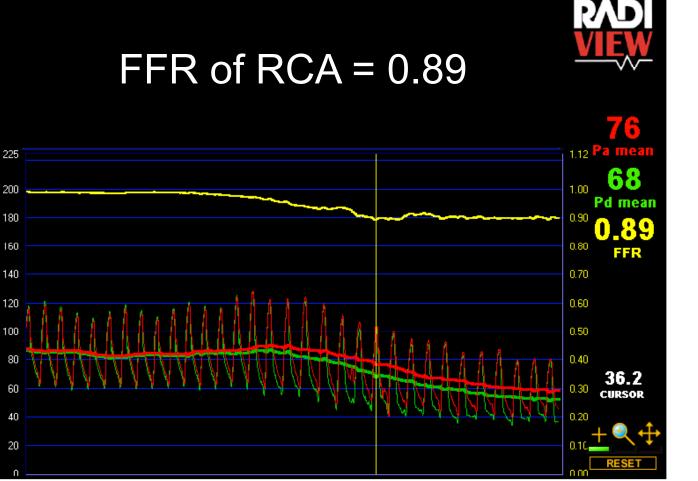
# **FFR in Multivessel CAD**

### 69 yo man with chest pain and apical ischemia on NPS

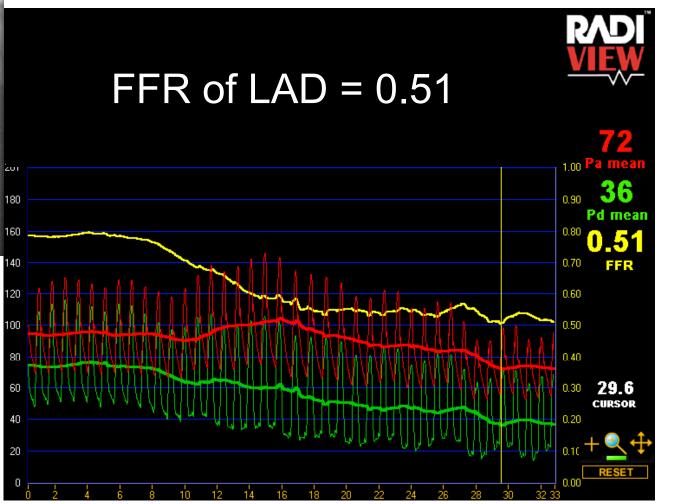








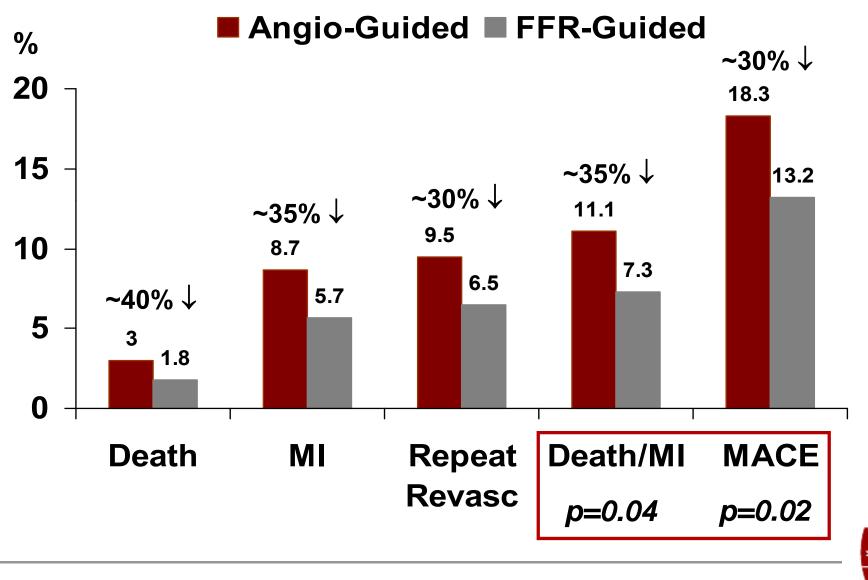




Filter: Enhance 3



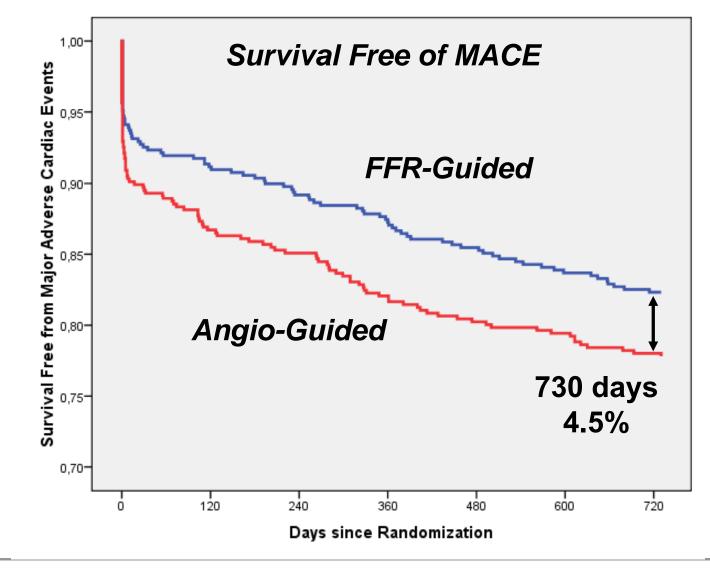
# FAME 1 Study: One Year Outcomes



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)

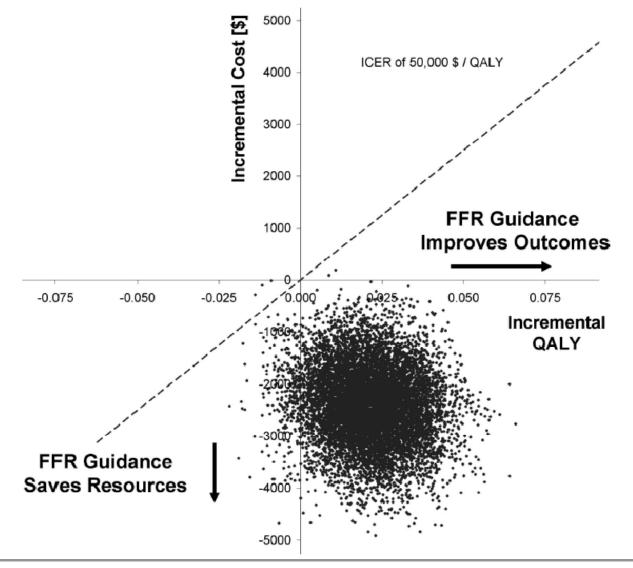




Pijls, et al. J Am Coll Cardiol 2010;56:177-184

## **FAME: Economic Evaluation**

### **Bootstrap Analysis**



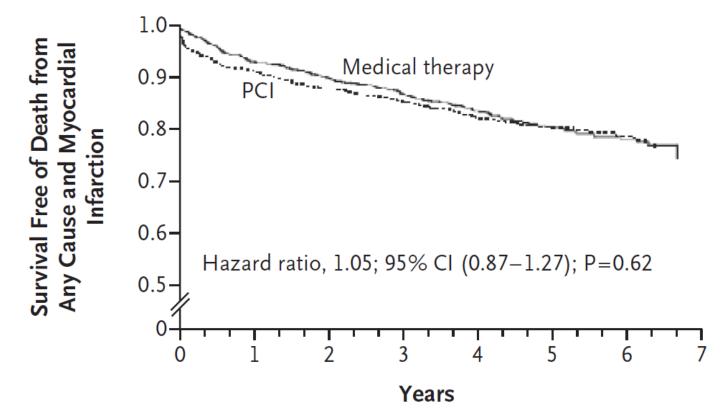
FFR-guided PCI saved >\$2,000 per patient at one year compared to Angioguided PCI

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

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

# **Degree of Ischemia in COURAGE**

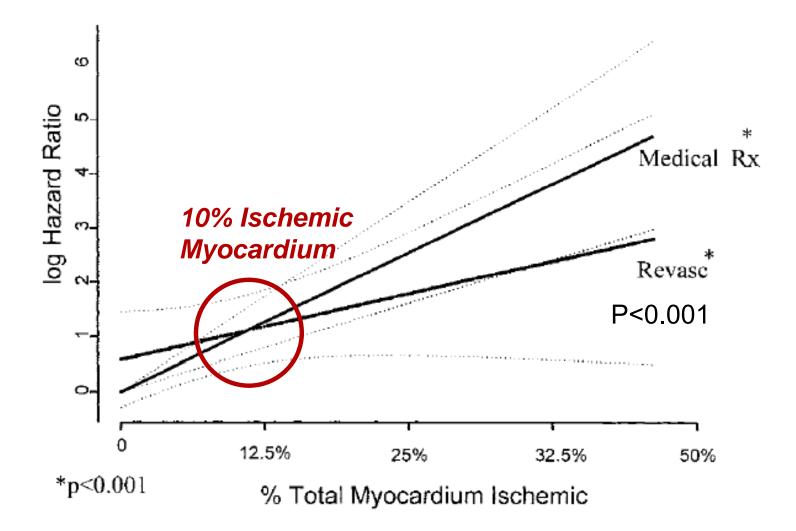
	PCI+OMT (n=159)			OMT (n=155)				ence by atment
	Pretreatment	6 to 18 Months	Р	Pretreatment	6 to 18 Months	Р	Р	Р
Rest TPD	6.4±7	3.4±6	< 0.0001	6.1±7	3.3±6	< 0.0001	0.70	0.83
Stress TPD	14.6±10	8.9±8	< 0.0001	14.7±11	11.4±10	< 0.0001	0.87	0.018
Territory								
Right coronary artery	2.5±3	1.4±2	< 0.0001	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	$100.0 \pm 30$	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





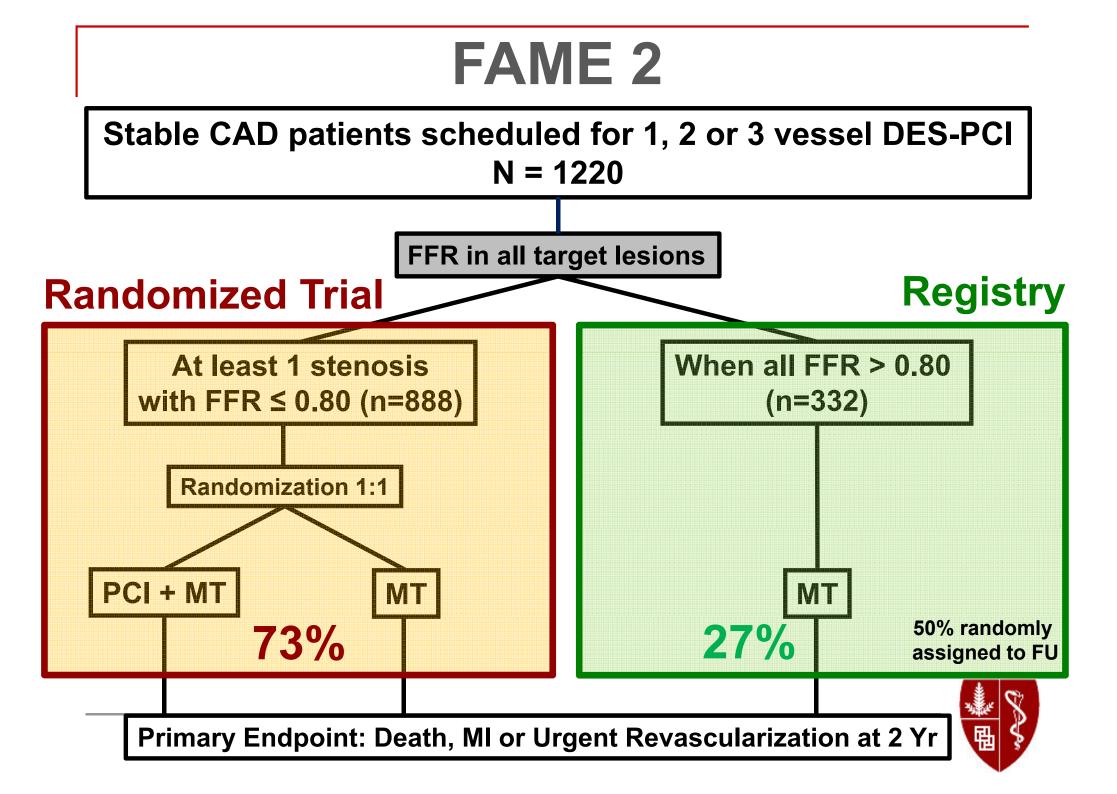
Hachamovitch, et al. Circulation 2003;107:2900-06.

# 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.



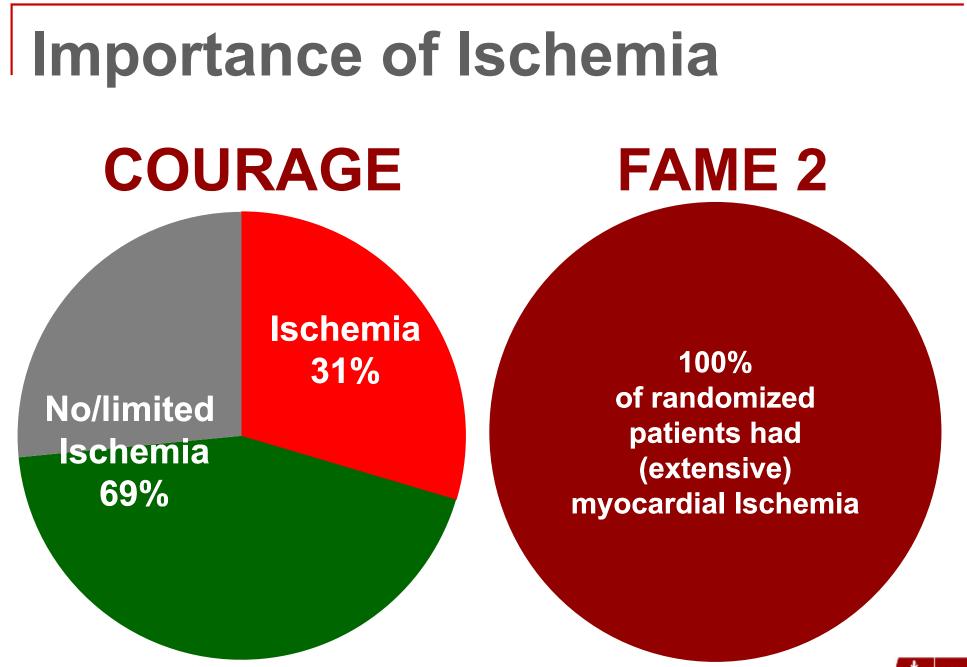


## **Degree of Ischemia in COURAGE**

100% of patients supposed to have Myocardial Ischemia



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





Courtesy of: Bernard De Bruyne, MD, PhD

# **Importance of Patient Selection**

# **Inclusion rates**





Courtesy of: Bernard De Bruyne, MD, PhD

## **Baseline Characteristics**

	Randomiz	ed Trial	Registry	р
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



## **Angiographic Characteristics**

	Randomi: N=8		Registry N=322	<b>P</b> *
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	

65.1

62.6

Prox- or mid- LAD stenoses - (%)

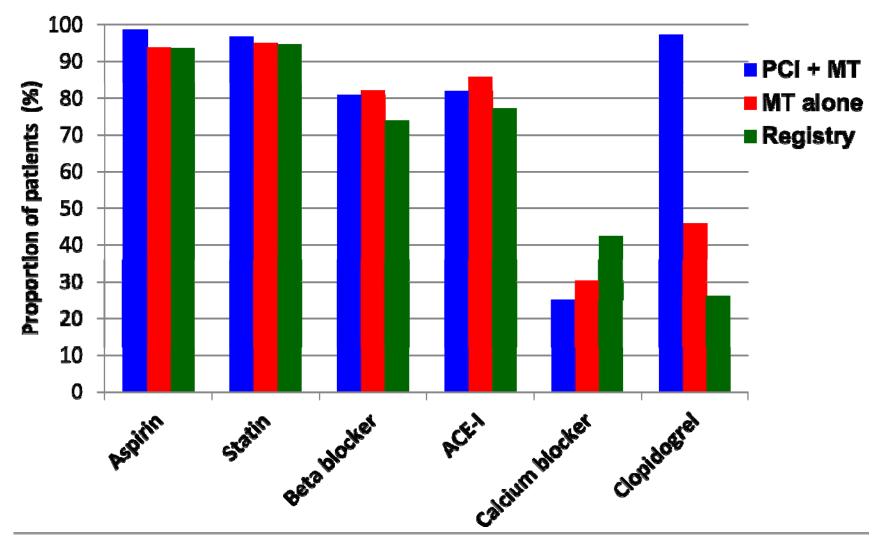
\* 8

< 0.001

44.6

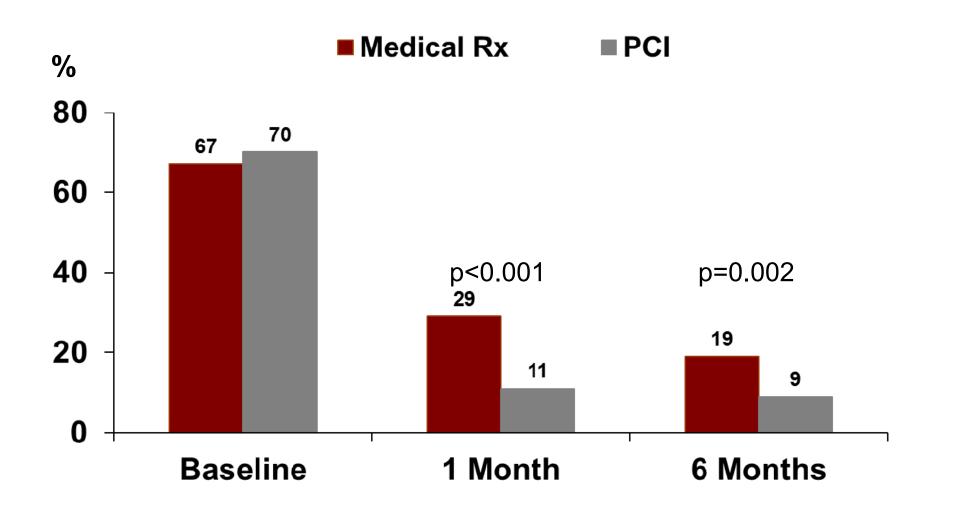
## **FAME 2 Trial**

### Medications at 6 Month Follow-Up



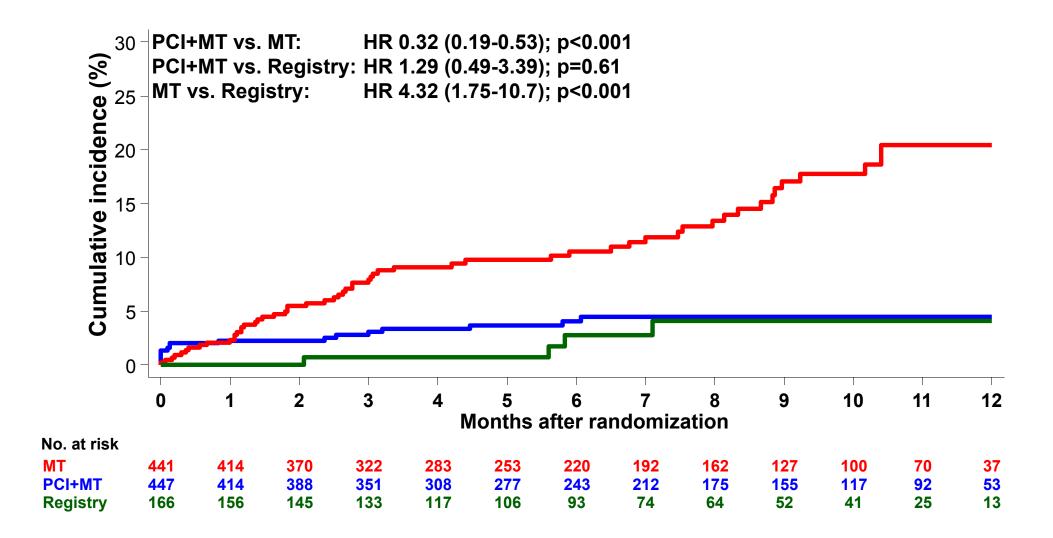


## Patients with Angina Class II to IV





## Primary Endpoint: Death, MI, Urgent Revasc

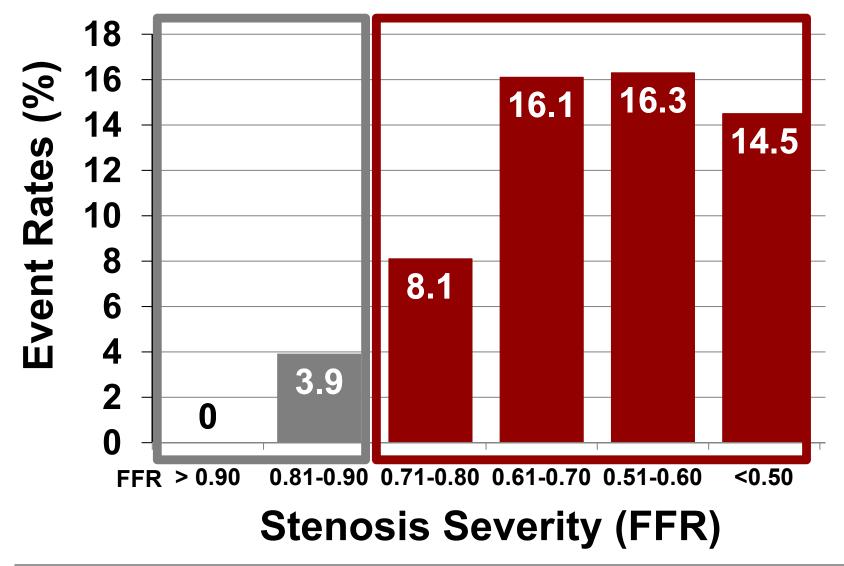






### **Relationship Between FFR and Outcomes**

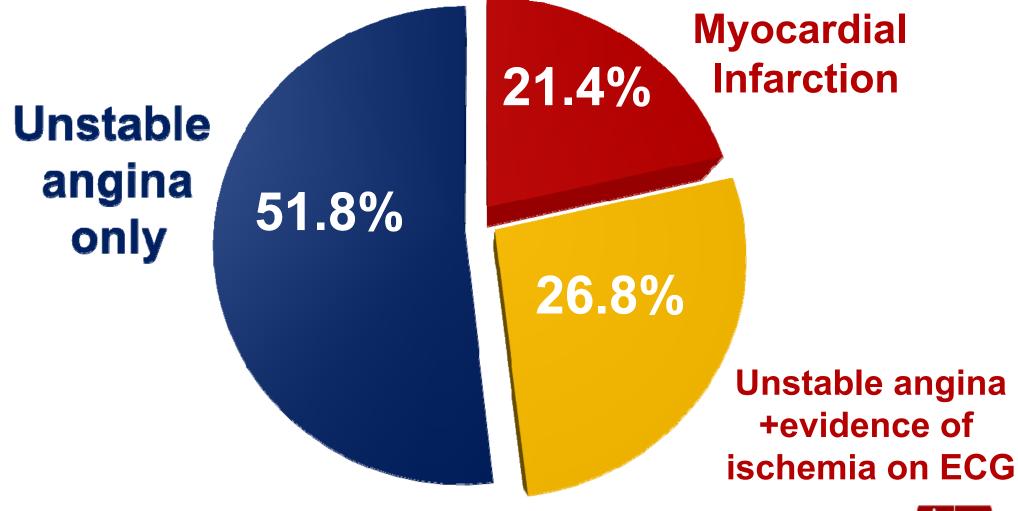
#### FAME 2: Patients with angiographically significant stenoses treated with OMT





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		МТ
0.9%	VS.	5.2%

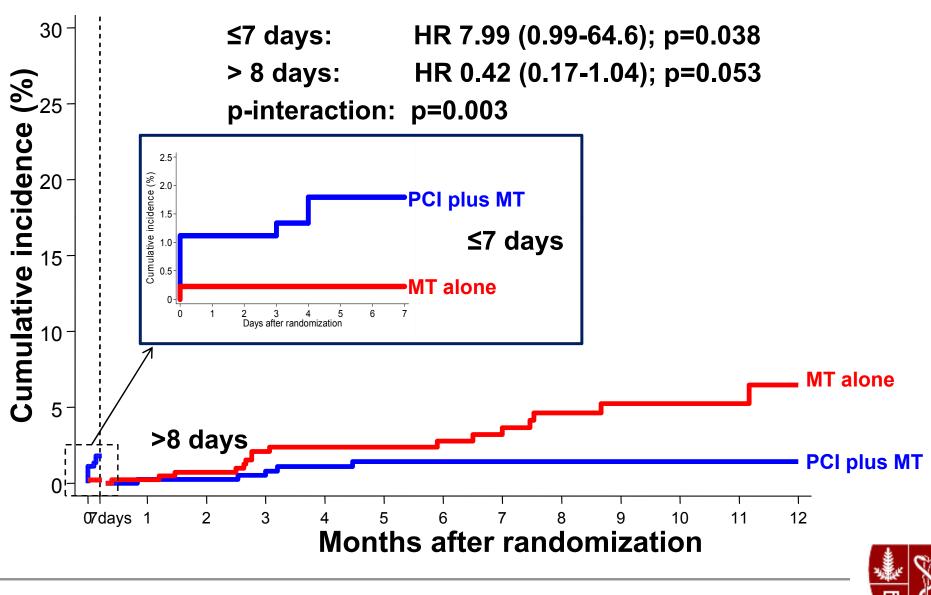
p<0.001 83% Relative Risk Reduction Myocardial 21.4% Infarction

26.8%

### Unstable angina +evidence of ischemia on ECG



# Landmark Analysis for Death/MI



## Spontaneous vs. Procedural MI

#### Meta-analysis of 12 randomized trials comparing PCI to OMT

	PC	I	MT				
Trial	Event	N	Event	N	IRR (95% CI)	IRR (95% CI)	% Weig
ents							
ACME-1	1 4	105	0	107		9.18 (0.49, 170.48)	2.59
ACME-2	2 1	51	1	50		0.98 (0.06, 15.67)	2.87
ALKK-1	1	149	0	151		3.04 (0.12, 74.67)	2.16
AVERT	1	177	0	164		2.77 (0.11, 68.11)	2.16
DEFER	3	90	0	91		7.08 (0.37, 137.02)	2.51
MASS-1	1 0	72	0	72 —		1.00 (0.02, 50.40)	1.44
RITA-2	7	504	0	514		15.30 (0.87, 267.84)	2.69
SWISS	-22	96	0	105		5.47 (0.26, 113.93)	2.39
+L Subto	otal (I-squ		0%, p = 0.8	396)		4.12 (1.39, 12.16)	18.81
/ Subtot	al			-		4.12 (1.39, 12.16)	
BARI 20		798	9	807 1138		2.36 (1.08, 5.15)	36.21 41.15
			-			· · ·	1.44
			-			1	2.39
			-			· · · /	2.59 81.19
		lared – v.	u‰, p = 0.7	50)			01.19
Gubtot						0.00 (1.01, 0.10)	
+L Overa	all (I-squa	ared = 0.0	%, p = 0.95	<b>i9</b> )		3.22 (2.01, 5.16)	100.00
/ Overall						3.22 (2.01, 5.16)	
ndom E	ffects Poi	sson Reg	gression			4.17 (2.53, 6.88)	
st for In	teraction	P = 0.56			Proce	dural MI	
	nts ACME- ACME- ALKK-1 AVERT DEFER MASS- SWISS L Subtot Subtot BARI 20 COURA JSAP MASS- L Subtot Subtot	TrialEventintsACME-1ACME-2ACME-2ALKK-1AVERT1DEFER3MASS-10RITA-27SWISS-22L SubtotalBARI 2D21COURAGE35JSAP0MASS-22L Subtotal(I-square)SubtotalCOURAGE35JSAP0MASS-22L Subtotal(I-square)Overallndom Effects Poi	Trial Event N   ants ACME-1 4 105   ACME-2 1 51   ALKK-1 1 149   AVERT 1 177   DEFER 3 90   MASS-1 0 72   RITA-2 7 504   SWISS-2 2 96   L Subtotal (I-squared = 0.0)   Subtotal 192   MASS-2 2 205   L Subtotal (I-squared = 0.0)   MASS-2 2 205   L Subtotal (I-squared = 0.0)   MASS-2 2 205   L Subtotal (I-squared = 0.0)	Trial Event N Event   ants ACME-1 4 105 0   ACME-2 1 51 1   ALKK-1 1 149 0   AVERT 1 177 0   DEFER 3 90 0   MASS-1 0 72 0   RITA-2 7 504 0   SWISS-2 2 96 0   L Subtotal (I-squared = 0.0%, p = 0.8) 9   COURAGE 35 1149 9   JSAP 0 192 0   MASS-2 2 205 0   L Subtotal (I-squared = 0.0%, p = 0.7) 9   JSAP 0 192 0   MASS-2 2 205 0   L Subtotal (I-squared = 0.0%, p = 0.7) 9   Overall (I-squared = 0.0%, p = 0.95) 10	Trial Event N Event N   ACME-1 4 105 0 107   ACME-2 1 51 1 50   ALKK-1 1 149 0 151   AVERT 1 177 0 164   DEFER 3 90 0 91   MASS-1 0 72 0 72   RITA-2 7 504 0 514   SWISS-2 2 96 0 105   L Subtotal (I-squared = 0.0%, p = 0.896) 105   Subtotal 192 0 192   MASS-2 2 205 0 203   L Subtotal (I-squared = 0.0%, p = 0.959) Subtotal   COURAGE 35 1149 9 1138   JSAP 0 192 0 192   MASS-2 2 205 0 203   L Subtotal (I-squa	Trial Event N Event N IRR (95% Cl)   nts ACME-1 4 105 0 107   ACME-2 1 51 1 50   ALKK-1 1 149 0 151   AVERT 1 177 0 164   DEFER 3 90 0 91   MASS-1 0 72 0 72   RITA-2 7 504 0 514   SWISS-2 2 96 0 105   L Subtotal (I-squared = 0.0%, p = 0.896) Image: Colored and the square in the	Trial Event N Event N IRR (95% Cl) IRR (95% Cl)   nts ACME-1 4 105 0 107 9.18 (0.49, 170.48)   ACME-2 1 51 1 50 0.98 (0.06, 15.67) 3.04 (0.12, 74.67)   ALKK-1 1 149 0 151 3.04 (0.12, 74.67) 2.77 (0.11, 68.11)   AVERT 1 177 0 164 2.77 (0.11, 68.11) 7.08 (0.37, 137.02)   MASS-1 0 72 0 72 1.00 (0.02, 50.40) 15.30 (0.87, 267.84)   SWISS-2 2 96 0 105 4.12 (1.39, 12.16) 4.12 (1.39, 12.16)   L Lsubtotal (I-squared = 0.0%, p = 0.896) 3.85 (1.85, 8.01) 3.85 (1.85, 8.01)   SAP 0 192 0 192 1.00 (0.02, 50.40)   MASS-2 2 205 0 203 4.12 (1.39, 12.16)   MASS-2 2 205 0 203 4.95 (0.24, 103.13)   JSAP 0

Favors PCI Favors Medical Therapy



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

## Spontaneous vs. Procedural MI

#### Meta-analysis of 12 randomized trials comparing PCI to OMT

	P	CI	MT				
Trial	Event	N	Event	N	IRR (95% CI)	IRR (95% CI)	% Weight
No Stents							
ACME-1	3	105	6	107		0.51 (0.13, 2.04)	3.00
ACME-2	5	51	5	50		0.98 (0.28, 3.39)	3.66
ALKK-1	9	149	12	151		0.76 (0.32, 1.80)	6.74
AVERT	4	177	4	164		0.92 (0.23, 3.70)	3.00
DEFER	2	90	0	91		5.06 (0.24, 105.30	) 0.67
MASS-1	3	72	3	72		1.00 (0.20, 4.95)	2.30
RITA-2	25	504	23	514	÷ <b>=</b>	1.11 (0.63, 1.95)	12.30
SWISS-2	9	96	40	105		0.25 (0.12, 0.51)	8.84
D+L Subtotal (I-	squared =	46.3%,	p = 0.071)			0.72 (0.43, 1.22)	40.52
I-V Subtotal					$\langle \rangle$	0.71 (0.50, 1.00)	
Stents							
BARI 2D	57	798	62	807	- <u>-</u>	0.93 (0.65, 1.33)	19.56
COURAGE	108	1149	119	1138	, the second sec	0.90 (0.69, 1.17)	24.14
JSAP	3	192	7	192		0.43 (0.11, 1.66)	3.13
MASS-2	21	205	31	203		0.67 (0.39, 1.17)	12.64
D+L Subtotal (I-	squared =	0.0%, p	= 0.556)		<u>ي</u>	0.86 (0.71, 1.05)	59.48
I-V Subtotal						0.86 (0.71, 1.05)	
D+L Overall (I-se	quared = 3	1.6%, p	= 0.138)		$\diamond$	0.77 (0.60, 0.99)	100.00
I-V Overall						0.82 (0.69, 0.97)	
Random Effects	Poisson F	Regressi	on		$\Rightarrow$	0.76 (0.58, 0.99)	
Test for Interacti	ion P = 0.5	3			Spontane	eous MI	
				F	avors PCI Favors Medical The	rapy	



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

## Spontaneous vs. Procedural MI

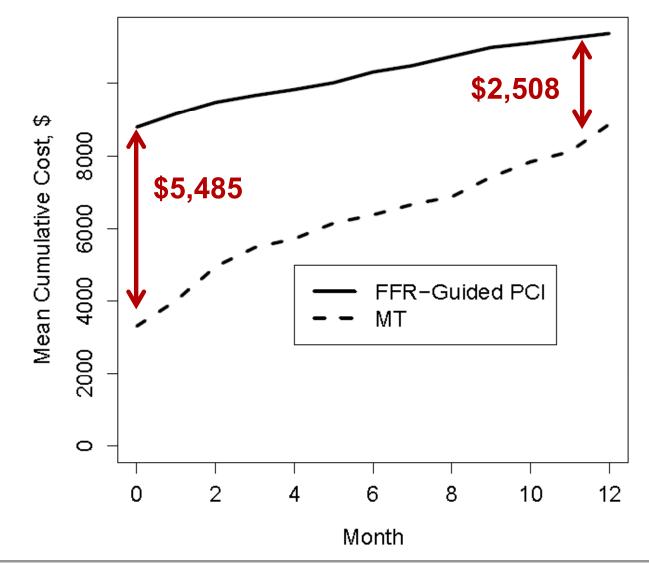
#### Meta-analysis of 12 randomized trials comparing PCI to OMT

	P	CI	M	г			
Trial	Event	Ν	Event	N	IRR (95% CI)	IRR (95% CI)	% Weight
lo Stents							
ACME-1	5	105	7	107		0.73 (0.23, 2.30)	2.20
ACME-2	9	51	10	50	+	0.88 (0.36, 2.17)	3.54
ALKK-1	6	149	17	151		0.36 (0.14, 0.91)	3.32
AVERT	1	177	1	164		0.92 (0.06, 14.79	9) 0.38
DEFER	5	90	6	91		0.84 (0.26, 2.76)	2.06
MASS-1	6	72	6	72	<u>!</u>	1.00 (0.32, 3.10)	2.27
RITA-2	43	504	43	514		1.02 (0.67, 1.56)	14.45
SWISS-2	6	96	22	105		0.30 (0.12, 0.74)	3.52
D+L Subtota	al (I-squ	ared	= 21.2%	, p = 0.261)	$\langle \rangle$	0.71 (0.49, 1.03)	31.75
I-V Subtotal						0.77 (0.57, 1.03)	
Stents							
BARI 2D	102	798	96	807	÷ –	1.07 (0.81, 1.42)	28.50
COURAGE	E 85	1149	95	1138		0.89 (0.66, 1.19)	26.47
JSAP	6	192	7	192		0.86 (0.29, 2.55)	2.44
MASS-2	28	205	35	203		0.79 (0.48, 1.30)	10.84
D+L Subtota	al (I-squ	ared	= 0.0%,	p = 0.679)	$\Diamond$	0.95 (0.79, 1.14)	68.25
I-V Subtotal					$\Rightarrow$	0.95 (0.79, 1.14)	
D+L Overall	(I-squa	ared =	7.2%, p	= 0.375)	$\diamond$	0.88 (0.74, 1.04)	100.00
I-V Overall					$\Diamond$	0.89 (0.76, 1.04)	
Random Eff	ects Po	isson	Regress	sion	$\Leftrightarrow$	0.88 (0.75, 1.03)	
Test for Inter	raction I	P = 0.	17		All Caus	e Mortality	
				.1		10	
					Favors PCI Favors Medical The	erapy	

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**

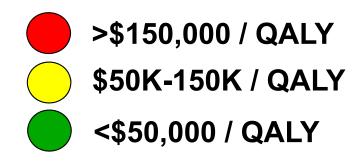
	FFR-Guided PCI	МТ	p-value
Angina (%)			
Class 0-1	89	71	<0.001
Class 2-4	11	29	<0.001
Utility Change	0.054	0.003	<0.001



Late Breaking Trial: TCT 2012

## FAME 2: Cost Effectiveness

<u>CE Benchmarks:</u> Hemodialysis ≈ \$50,000 / QALY WHO GDP std ≈ \$150,000 / 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



# **FAME 2 Trial**

Take Home Messages:

- In patients with stable coronary artery disease, FFRguided PCI improves patient outcome and is costeffective 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.

