FFR and Acute Coronary Syndromes

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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/Medtronic
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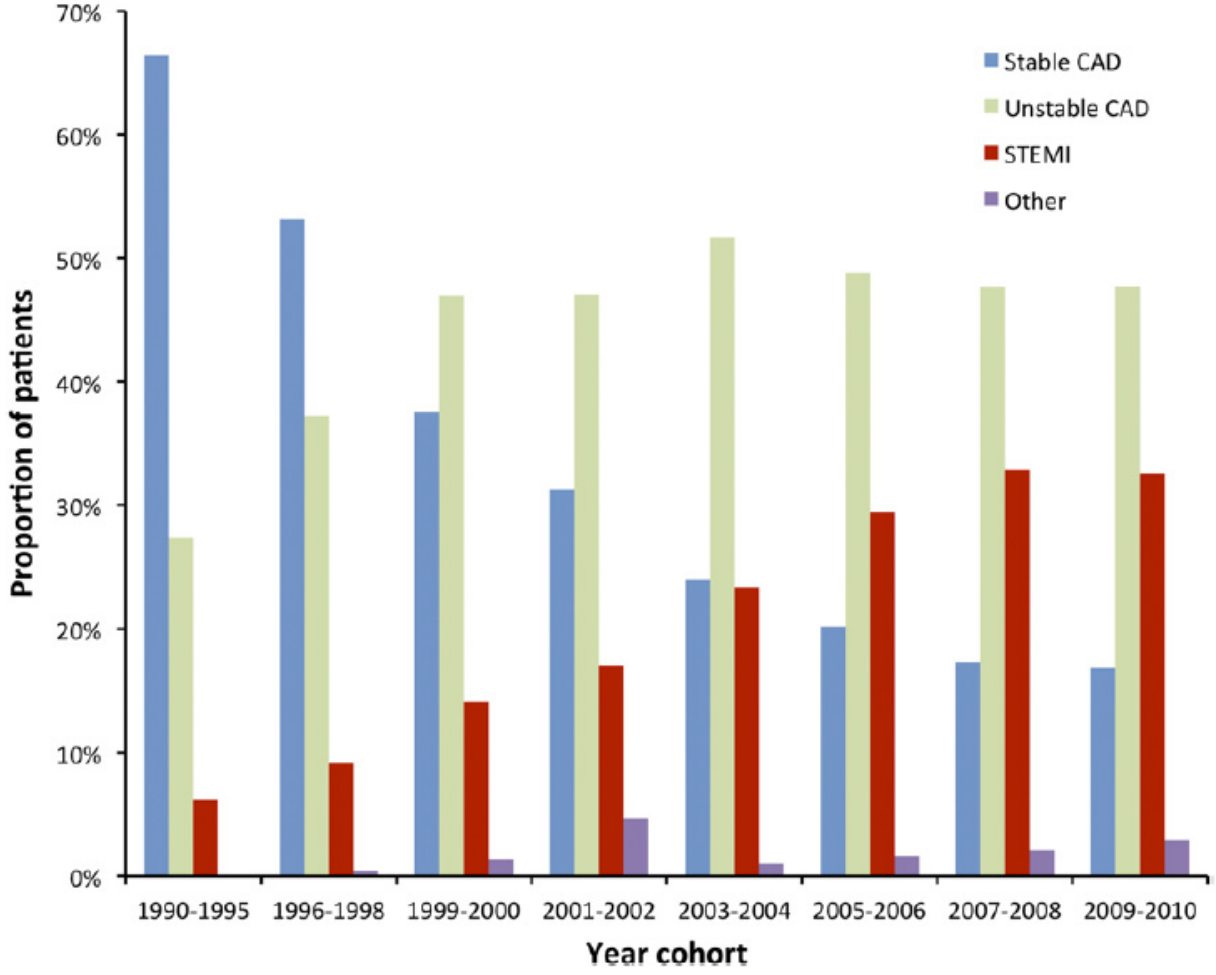
Major Stock Shareholder/Equity Interest:	
Royalty Income:	
Ownership/Founder:	
Salary:	NIH-R01 HL093475 (PI)
Intellectual Property Rights:	
Other Financial Benefit (minor stock options):	HeartFlow

Increasing Prevalence of ACS

144,039 Swedish patients (SCAAR Registry) undergoing PCI between 1990-2010



Fokkema, et al. J Am Coll Cardiol 2013;61:1222-30

Increasing Prevalence of ACS

- 500,154 PCI's performed in the US between 2009-2010 were included in the NCDR
- 71% of these procedures were in patients presenting with an acute coronary syndrome

Chan, et al. JAMA 2011;306:53-61

Overview of FFR in ACS:

- STEMI
  - Acute
  - Chronic
- Non-STEMI
  - Acute
- Culprit vessel
- Non-Culprit vessel

Acute Microvascular Damage and FFR

STEMI

→ *Variable Degree of Reversible Microvascular Stunning*

→ *Maximum Achievable Flow is Less*

→ *Smaller Gradient and Higher FFR across Any Given Stenosis*

With time, the microvasculature may recover, maximum achievable flow may increase, and a larger gradient with a lower FFR may be measured across a given stenosis

Chronic Microvascular Damage and FFR

Old Myocardial Infarction

→ *Irreversible Microvascular Damage*

→ *Maximum Achievable Flow is Less*

→ *Smaller Gradient and Higher FFR across Any Given Stenosis*

In the setting of chronic microvascular dysfunction, the higher FFR is not falsely elevated, but reflects the smaller amount of viable myocardium supplied by the vessel and still provides information about the expected gain in flow after PCI

FFR in Acute STEMI (Culprit Vessel)

FFR after stenting in 33 AMI patients compared to 15 stable angina patients

IVUS Parameters	AMI	Angina	*P*
Ref Lumen Area	7.45 ±2.4	6.49 ±1.6	NS
Min Lumen Area	5.28 ±1.7	5.03 ±1.1	NS
% Area Stenosis	27.3 ±9.3	25.76 ±13.1	NS
Pressure Parameter			
FFR	0.95 ±0.04	0.90 ±0.04	0.003

Cathet Cardiovasc Intervent 2002;57:452-459

FFR in Acute STEMI (Culprit Vessel)

FFR after stenting in 33 AMI patients comparing those with TIMI 3 flow (n=23) to those with TIMI 2 flow (n=10)

IVUS Parameters	TIMI 3	TIMI 2	*P*
Ref Lumen Area	7.69 ±2.6	6.89 ±1.8	NS
Min Lumen Area	5.48 ±1.7	4.86 ±1.7	NS
% Area Stenosis	26.3 ±9.0	30.17 ±9.8	NS
Pressure Parameter			
FFR	0.93 ±0.04	0.98 ±0.02	<0.01

Cathet Cardiovasc Intervent 2002;57:452-459

FFR in Chronic MI (Culprit Vessel)

Changes in flow with and without microvascular dysfunction

	MI	No MI	*P*
Target lesion, n	22	21	
Pre-/postintervention, n	7/15	10/11	0.2
Diameter stenosis, %	43 ± 22	44 ± 16	0.9
MLD, mm	1.7 ± 0.8	1.6 ± 0.6	0.6
Length, mm	9.1 ± 4.0	7.3 ± 3	0.1
Reference diameter, mm	2.9 ± 0.5	2.8 ± 0.6	0.6
Flow velocity measurements			
APV (basal), cm/sec	17 ± 7	17 ± 8	0.8
APV (hyperemic), cm/sec	26 ± 13	36 ± 16	0.03
Coronary flow reserve	1.5 ± 0.3	2.1 ± 0.4	< 0.0001
Flow (hyperemic), ml/min	37 ± 26	48 ± 22	0.03
Pressure measurements			
Gradient (hyperemic), mm Hg	13 ± 11	21 ± 13	0.05
FFR, %	82.6 ± 12.5	79.0 ± 11.7	0.3

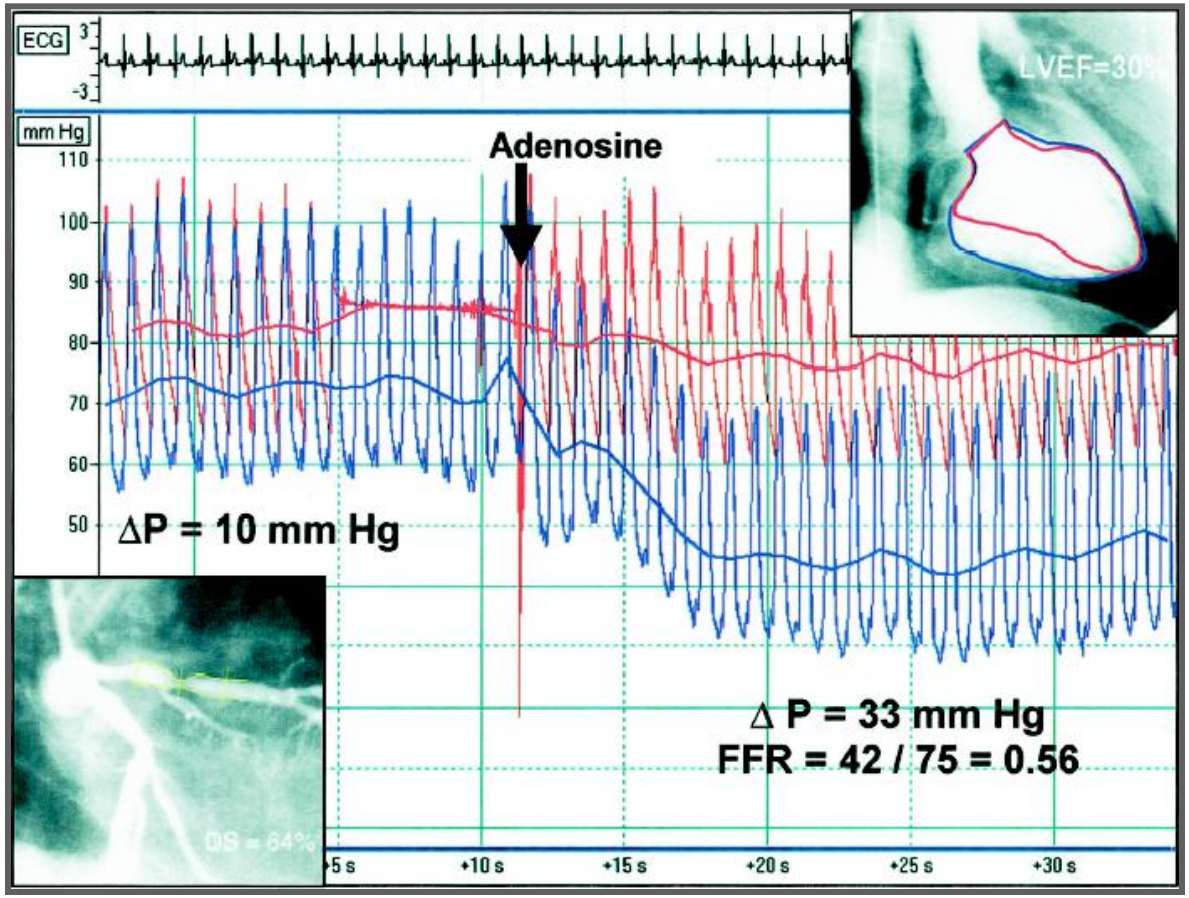
Cathet Cardiovasc Intervent 2001;54:427-434

FFR in ACS

How long do we have to wait after a STEMI before FFR can be reliably measured in the culprit vessel?

FFR after Recent MI (Culprit Vessel)

Comparison of FFR in 57 patients with an MI ≥ 6 days old to SPECT imaging before and after PCI



De Bruyne, et al. Circulation 2001;104:157-162

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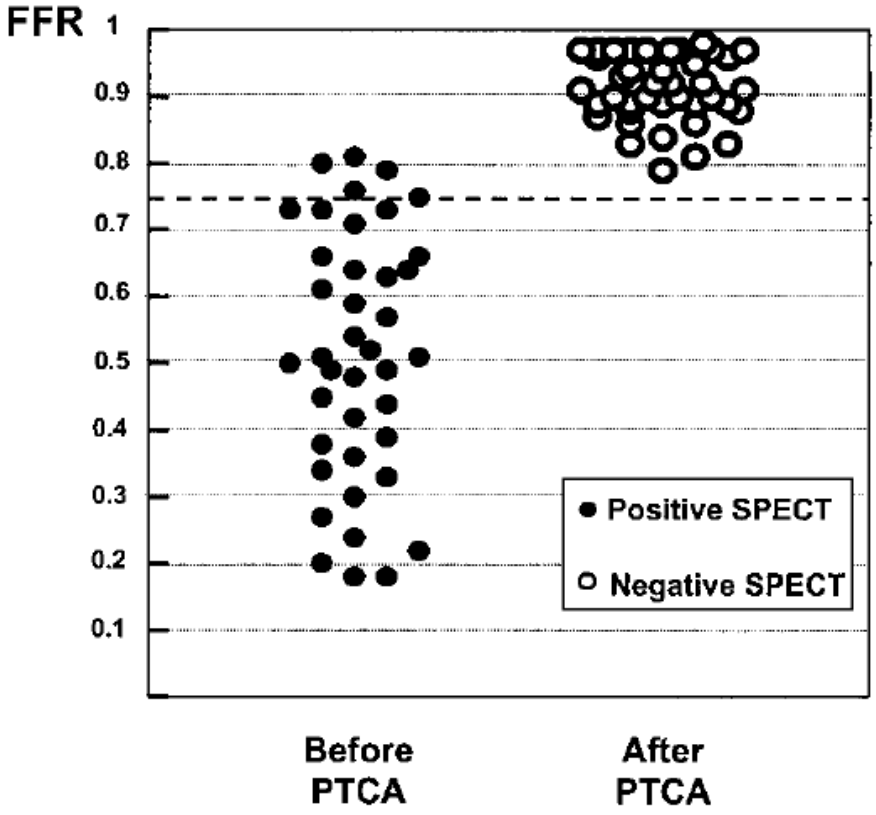


	MIBI + n = 40	MIBI - n = 40
FFR≥0.75 n = 45	5	40
FFR<0.75 n = 35	35	0

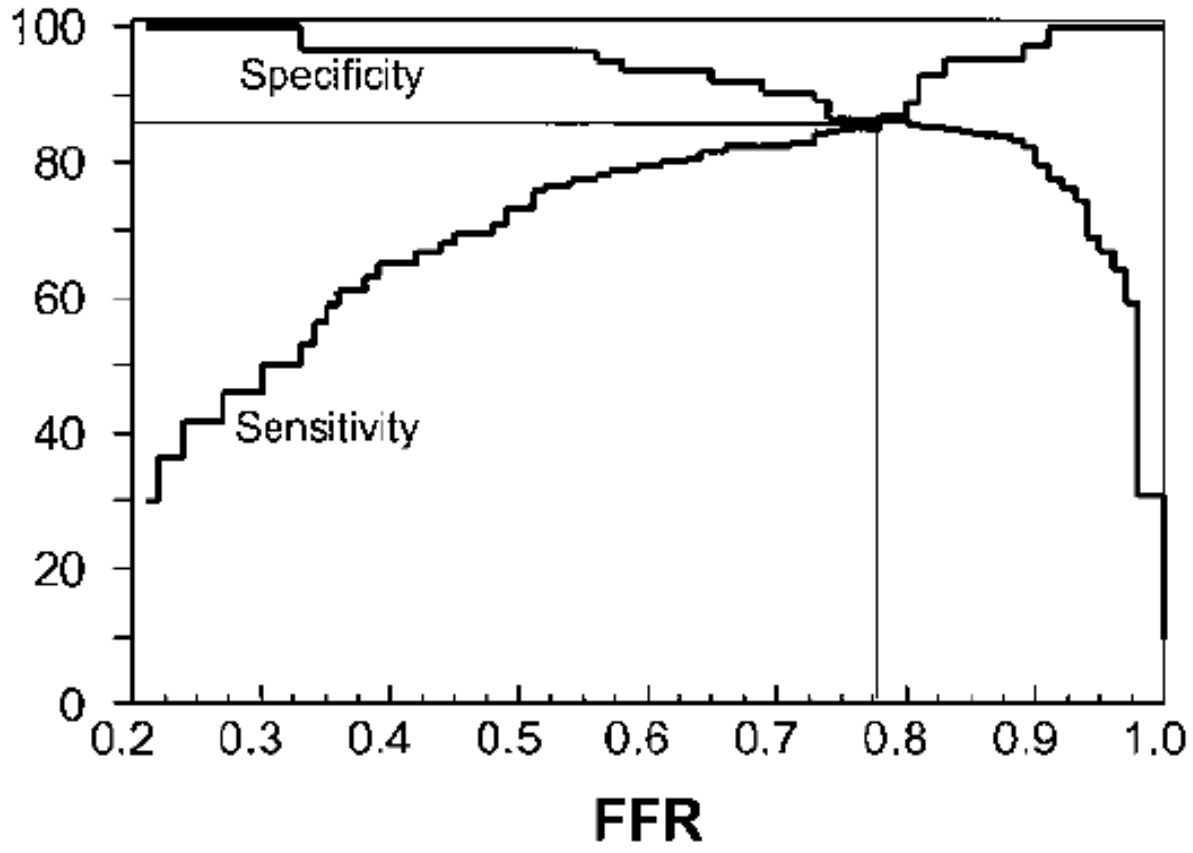
Concordance = 94%

κ = 0.87; P<0.0001

De Bruyne, et al. Circulation 2001;104:157-162

FFR after Recent MI (Culprit Vessel)

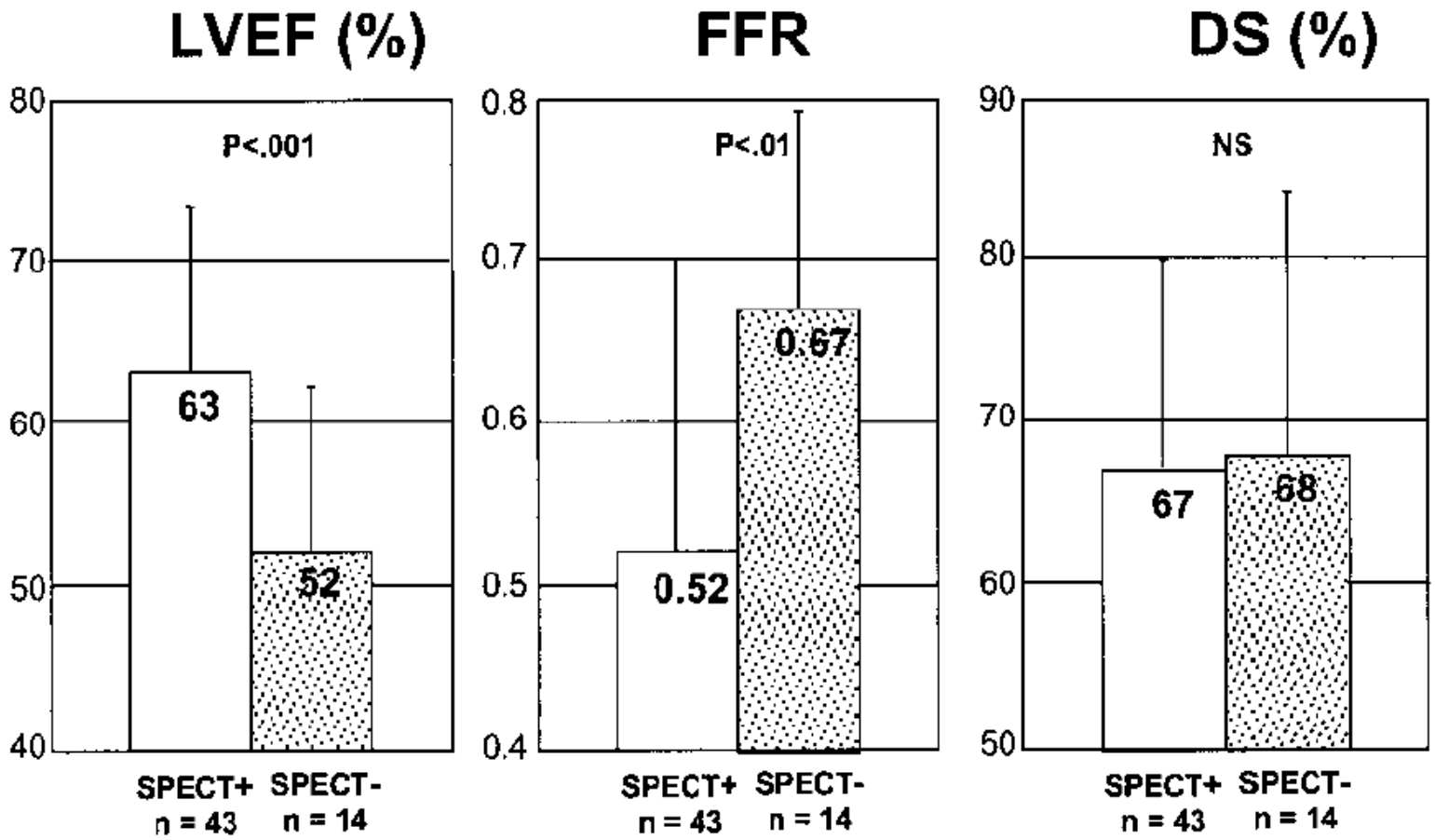
Ideal FFR cutoff in the setting of old MI



De Bruyne, et al. Circulation 2001;104:157-162

FFR after Recent MI (Culprit Vessel)

Relationship between FFR and mass of myocardium at risk



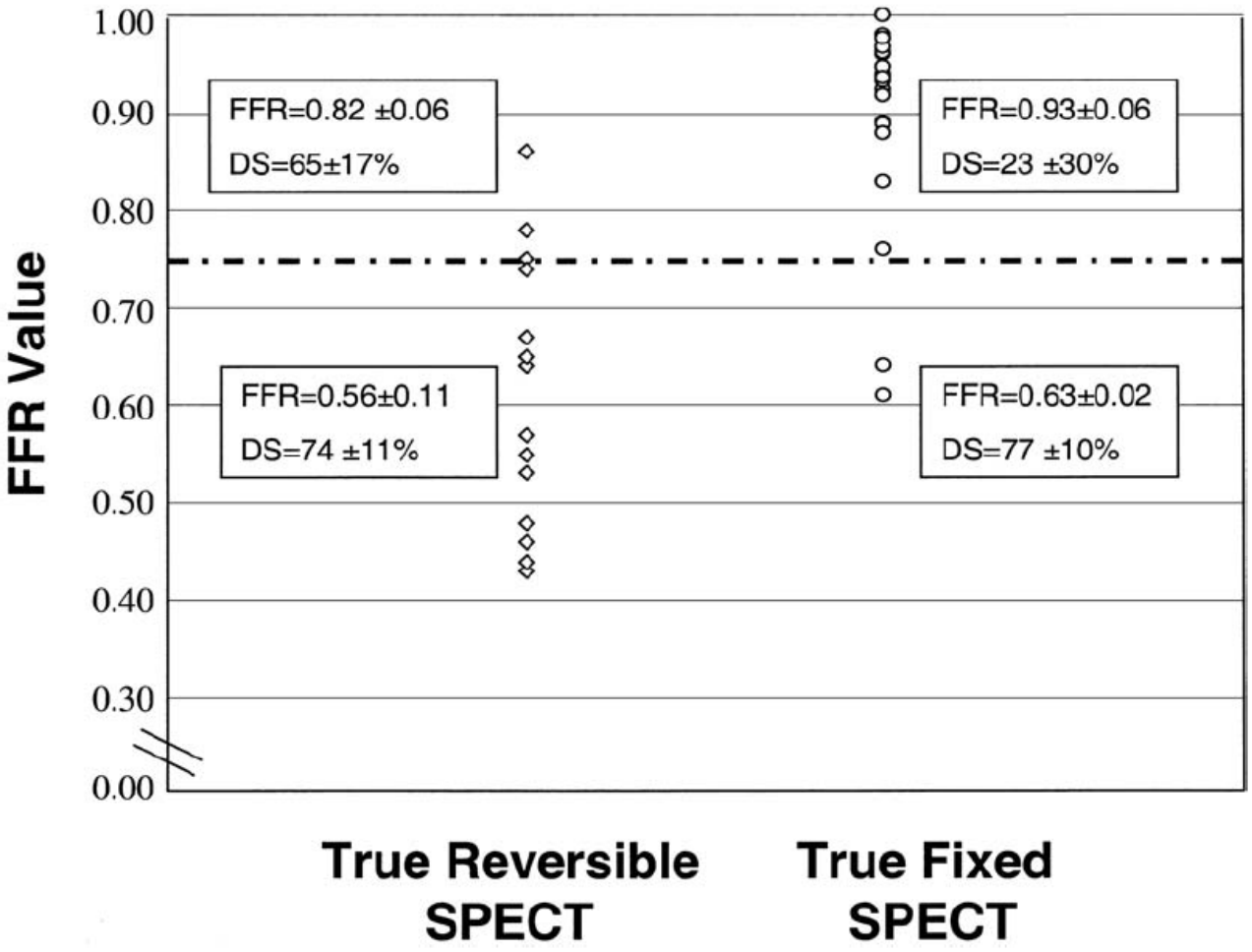
De Bruyne, et al. Circulation 2001;104:157-162

FFR after Recent MI (Culprit Vessel)

- FFR and SPECT performed in 48 patients 3.7 days after MI
  - 73% had STEMI and had to be ≥3 days; ≥2 days for NSTEMI
- 23 patients also had myocardial contrast echo
- Follow-up SPECT was performed 11 weeks later to identify true positive and negatives

Samady, et al. J Am Coll Cardiol 2006;47:2187-2193.

FFR after Recent MI (Culprit Vessel)



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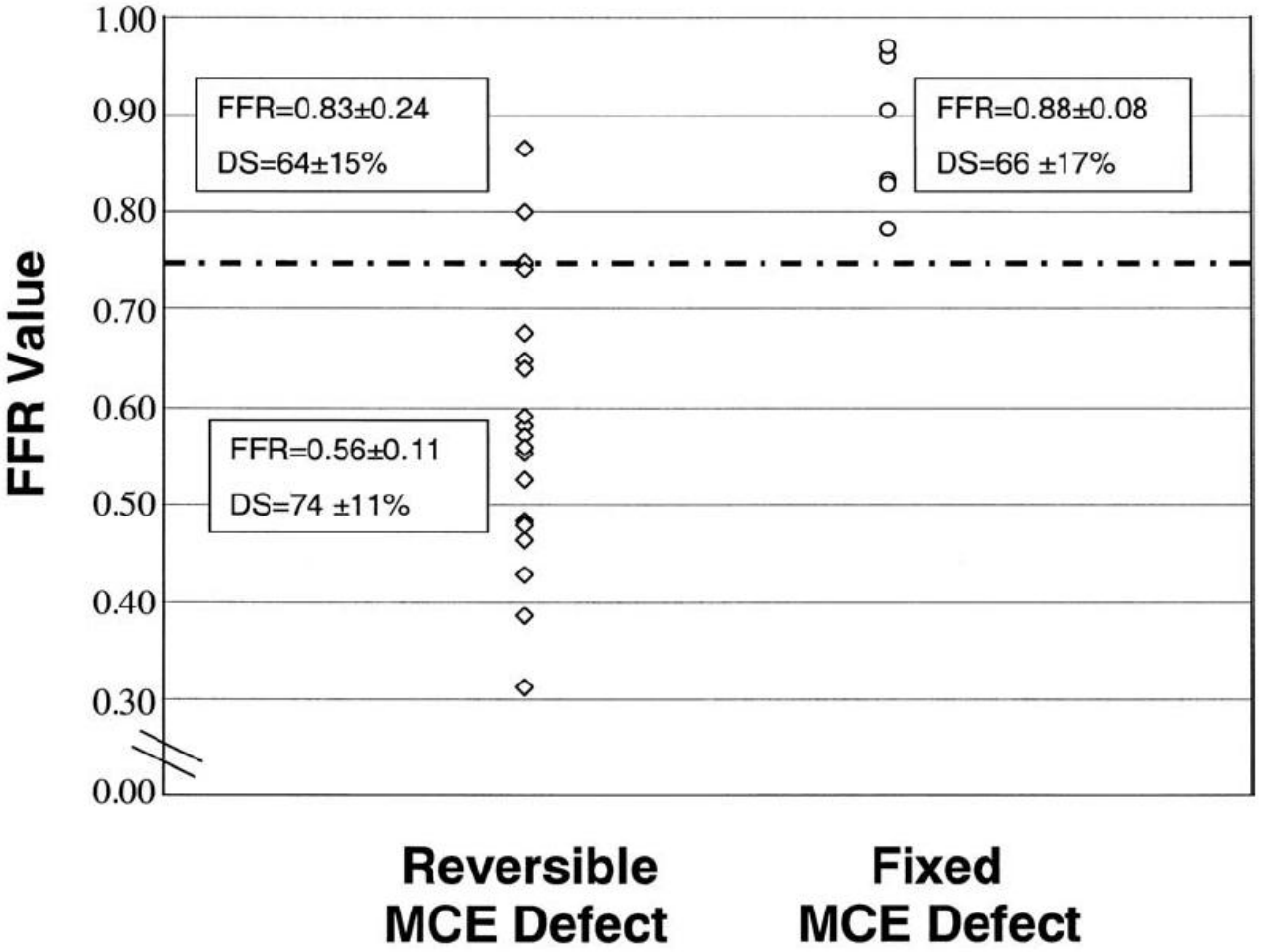

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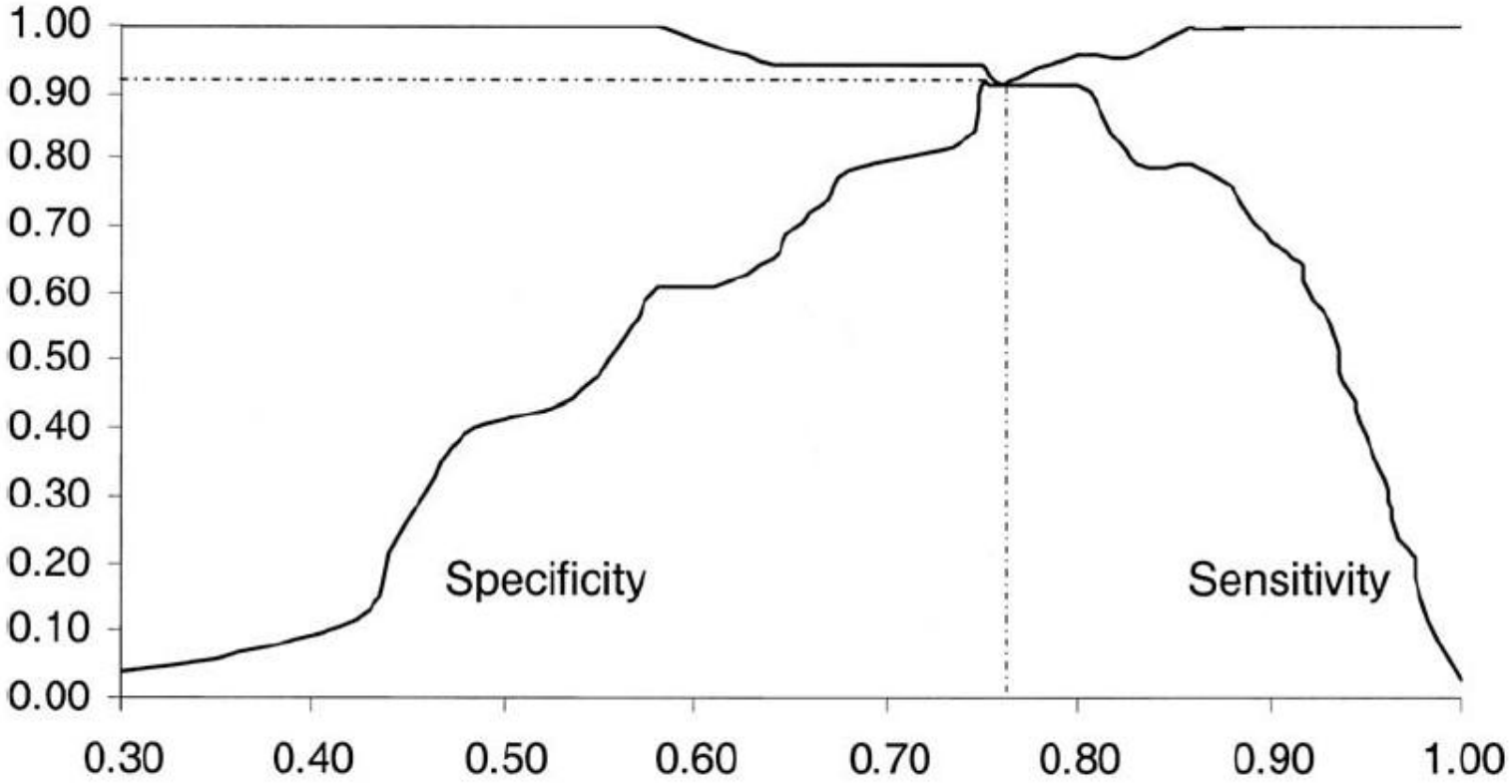
FFR after Recent MI (Culprit Vessel)

Best FFR Cutoff is 0.78



Samady, et al. J Am Coll Cardiol 2006;47:2187-2193.

FFR during/after STEMI (Culprit Vessel)

- How long do you have to wait for "microvascular stunning" to resolve and before you can get a reproducible FFR?

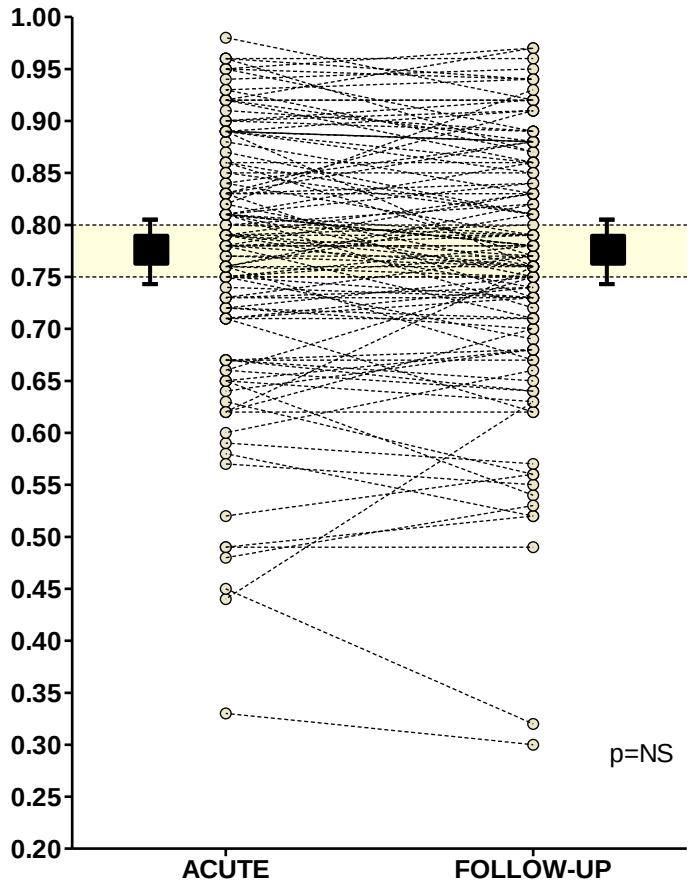
- Likely the time to recovery of the microvasculature is variable, depending on the size of the infarct, and can be as short as days, and as long as a week, or longer…

FFR STEMI (Non-Culprit Vessels)

- During acute STEMI, is FFR measurement of non-culprit vessels reliable?

FFR STEMI (Non-Culprit Vessels)

101 patients with an acute coronary syndrome (75 STEMI, 26 NSTEMI)
112 non culprit stenoses FFR measured acutely and 35±24 days later

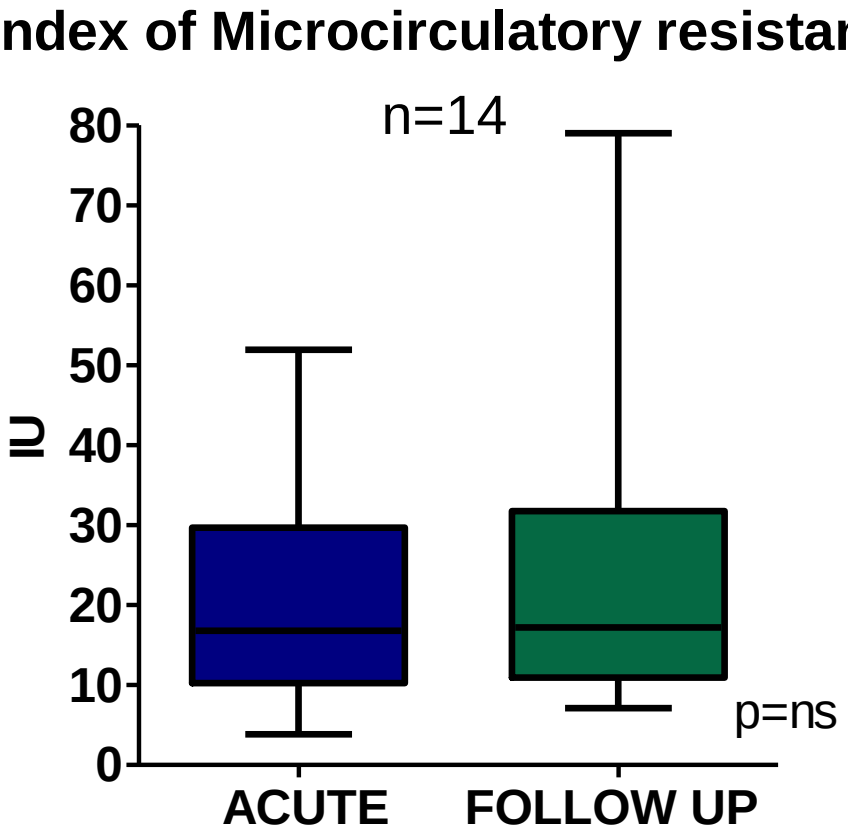


In only 2/112 stenoses was the FFR >0.80 during the ACS and <0.75 at follow-up.

Ntalianis, et al. J Am Coll Cardiol Intv 2010;3:1274

FFR STEMI (Non-Culprit Vessels)

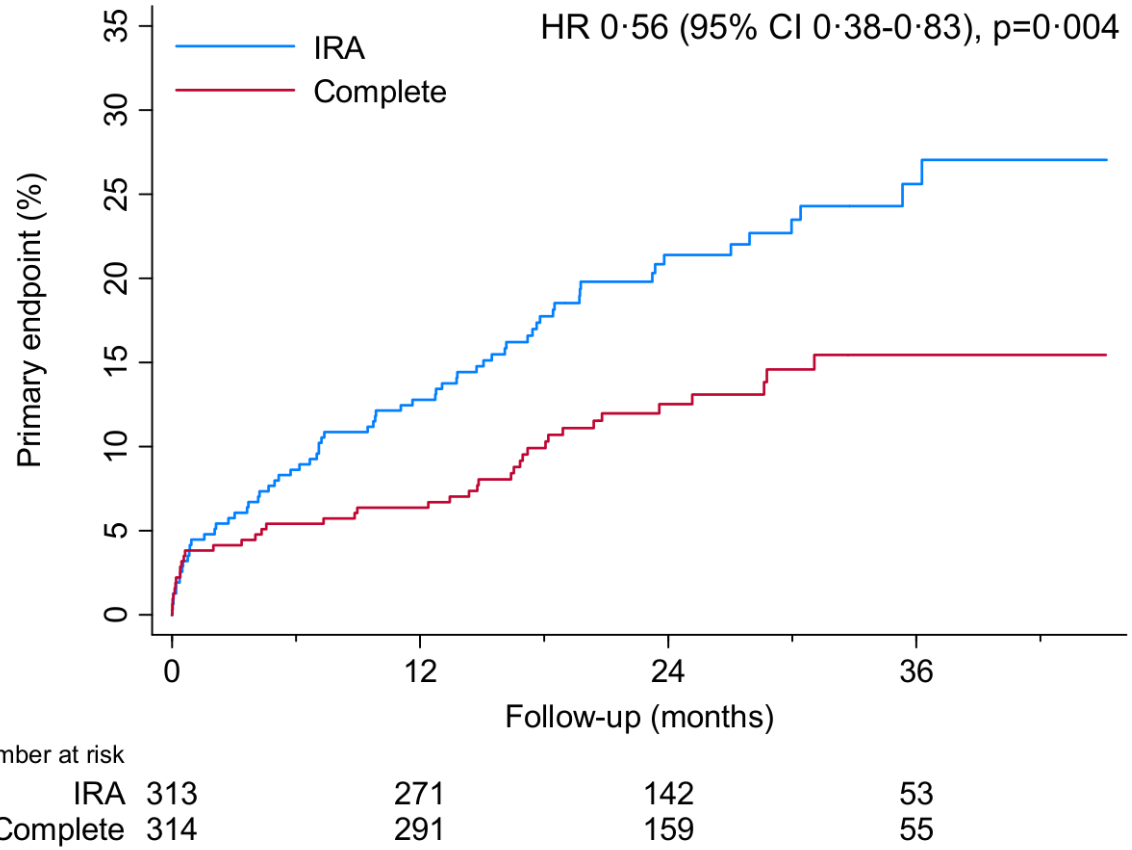
Microvascular resistance did not change from baseline to follow-up



Ntalianis, et al. J Am Coll Cardiol Intv 2010;3:1274

DANAMI3-PRIMULTI Trial:

627 STEMI patients with MVD randomized to culprit only vs. FFR-guided nonculprit PCI



Composite of death, MI, ischemia driven revascularization of non-culprit

Engstrom T, et al. ACC 2015

DANAMI3-PRIMULTI Trial:

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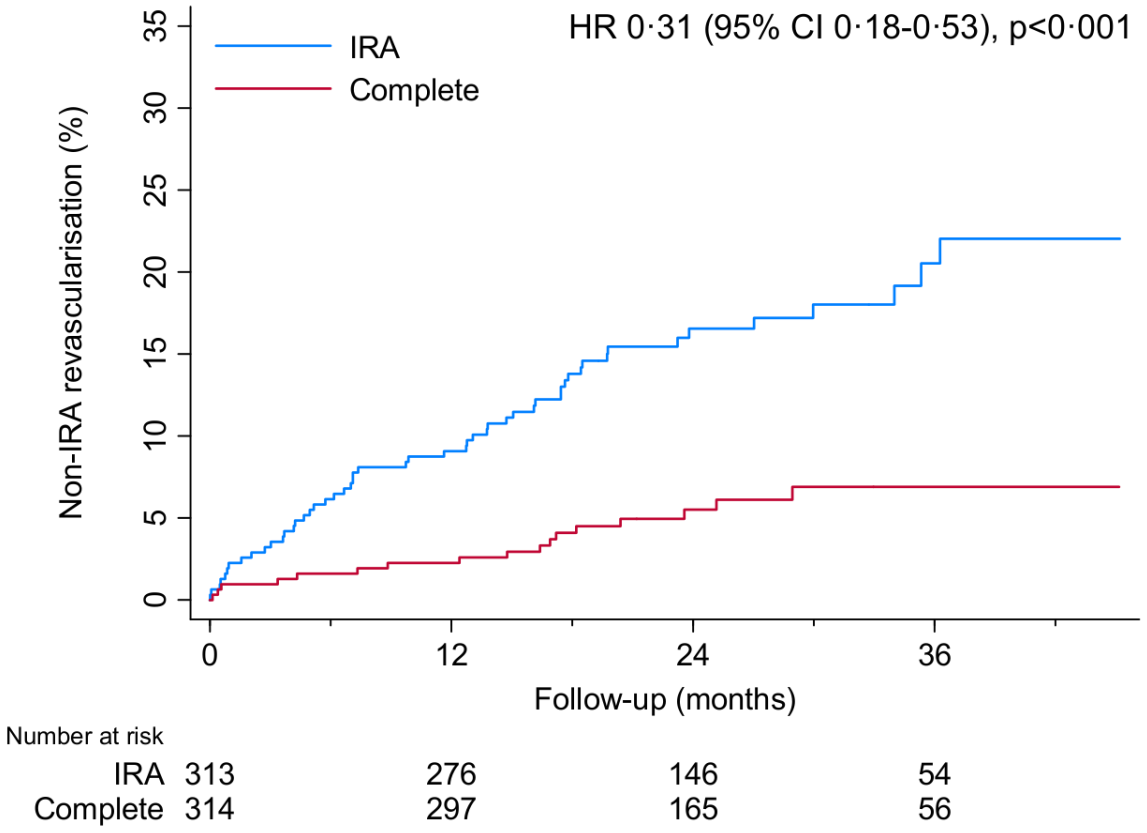


Ischemia driven revascularization of non-culprit

Engstrom T, et al. ACC 2015

FFR during NSTEMI

- Can we measure FFR in non ST elevation acute myocardial infarction?
  - In the culprit vessel?
  - In the non-culprit vessel?

FFR in NSTE ACS (Culprit Vessel)

70 patients with ACS and an intermediate lesion randomized to FFR or stress perfusion scan

	Group 1 (SPS) (n = 35)	Group 2 (FFR) (n = 35)
Age	55 ± 4	59 ± 6
Gender M/F	22/13	24/11
EF	53 ± 4	50 ± 4
MI without ST-segment elevation (n)	24	20
ST-segment changes (n)	16	14
ST-segment changes or T-wave changes (n)	20	18
Prior coronary artery disease	14	9
Hypertension (n)	26	25
Diabetes mellitus (n)	11	13
Hyperlipidemia (n)	22	19
Tobacco abuse (n)	15	20
Lesion		
Left anterior descending (n)	13	15
Circumflex (n)	10	9
Right coronary artery (n)	12	11
Minimal lumen diameter (mm)	1.51 ± 0.1	1.43 ± 0.1
Reference lumen diameter (mm)	3.1 ± 0.2	2.88 ± 0.2
% Diameter stenosis	49 ± 2	48 ± 2

Leesar, et al. J Am Coll Cardiol 2003;41:1115-1121

FFR in NSTE ACS (Culprit Vessel)

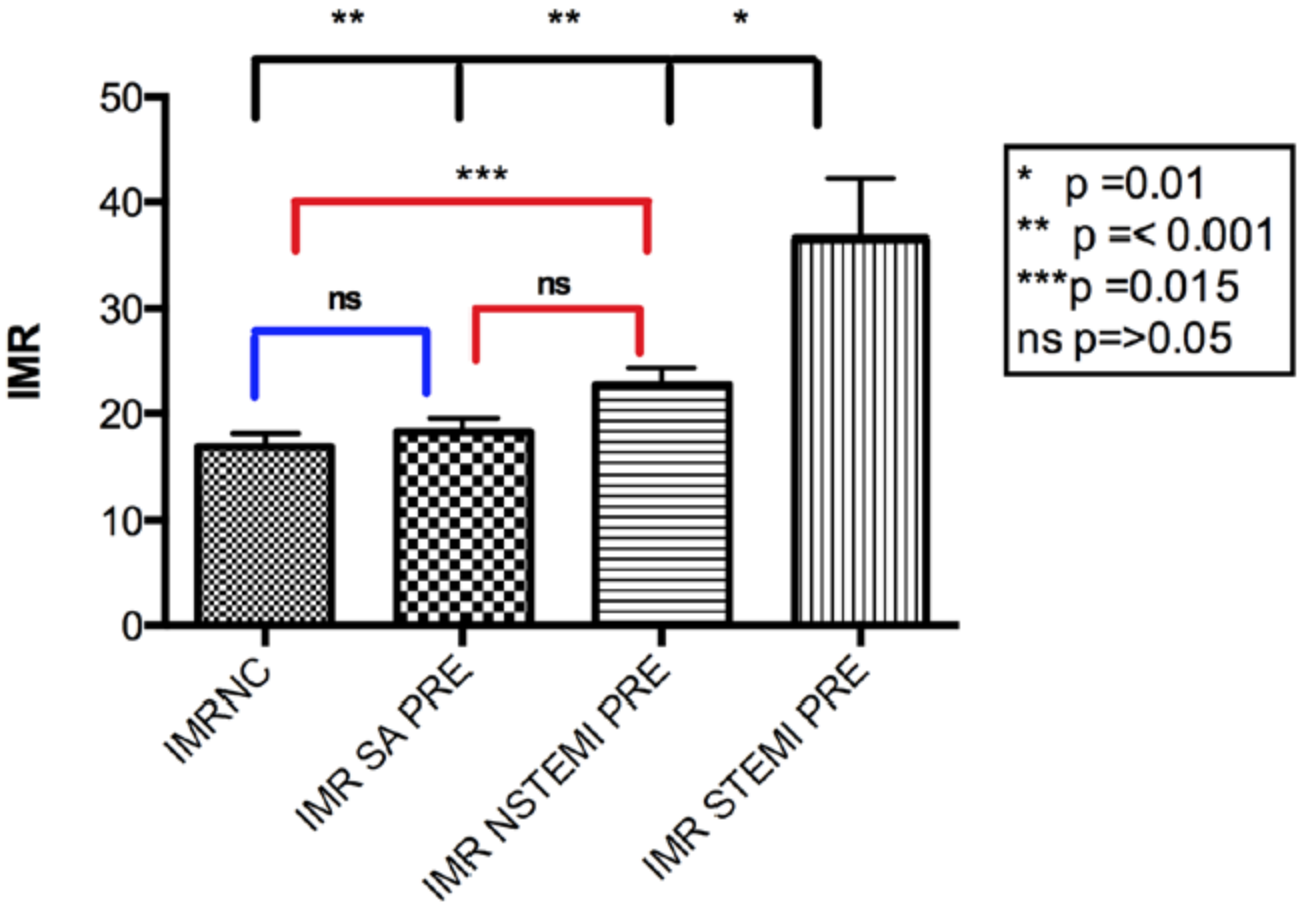
Clinical Events at 1 Year Follow-Up

	Group 1 (SPS) (n = 34)	Group 2 (FFR) (n = 34)
Average follow-up (months)	12.0 ± 0.8	14.0 ± 1.0
Death	0	0
Angina		
No angina (n)	17	24
CCS classification of angina (n)		
1–2	17	10
3–4 (admitted to the hospital)	6	5
Stress perfusion scintigraphy	4	4
Negative (n)	4	4
Cardiac catheterization	2	3
Results (no change)	2	2
Disease progression	0	1
MI	1	1
CABG including target vessel	1	2
PCI	0	0

Leesar, et al. J Am Coll Cardiol 2003;41:1115-1121

IMR in Culprit Vessel (STEMI and NSTEMI)

IMR measured in the culprit vessel of 50 stable, 50 NSTEMI and 40 STEMI patients



Layland, et al. Circ Cardiovasc Interv 2013;6:231-36.

FFR NSTE ACS (Culprit + Non Culprit Vessel)

Fractional Flow Reserve *versus*

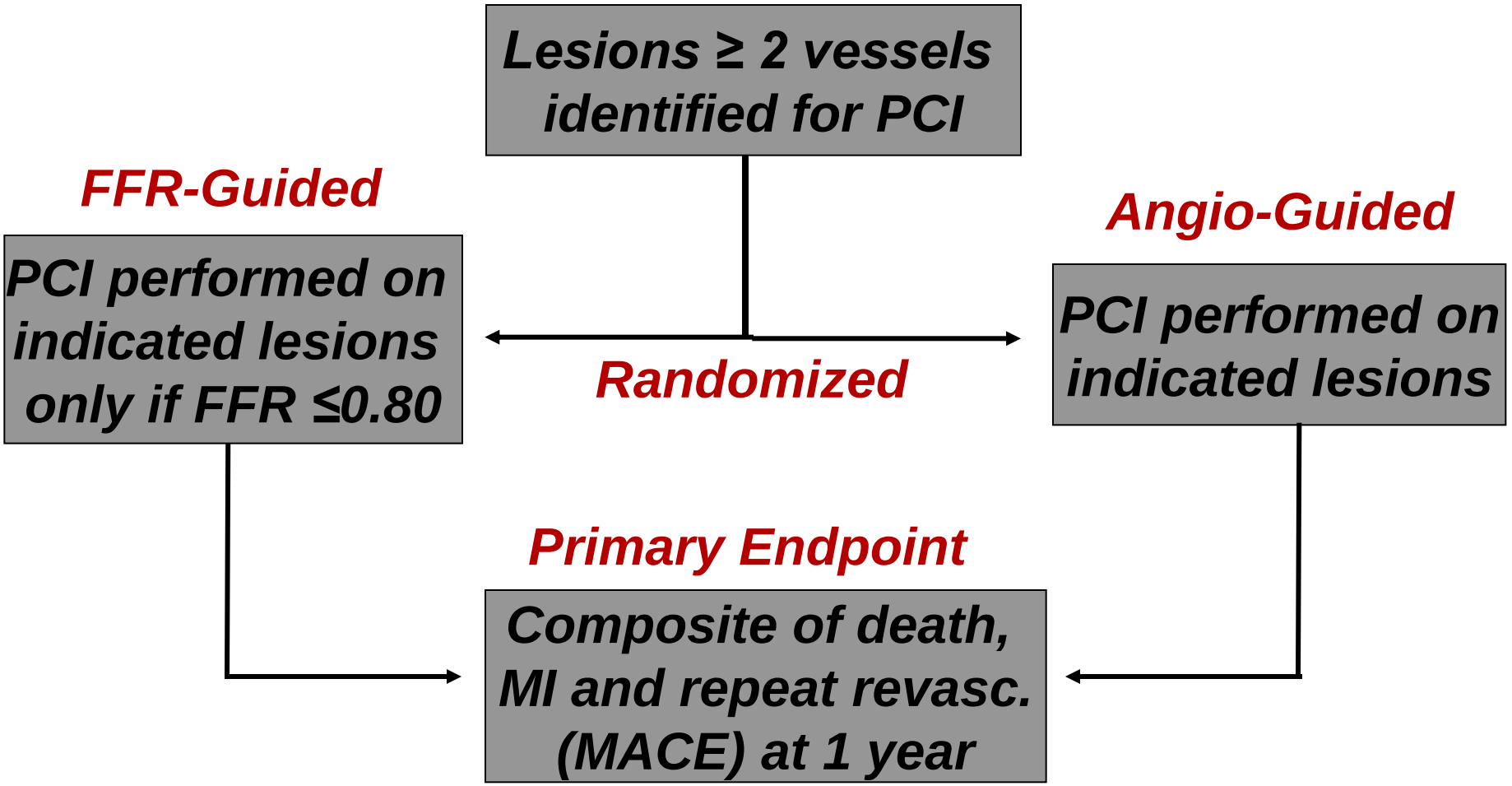
Angiography for

Multivessel

Evaluation

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

FAME Trial:



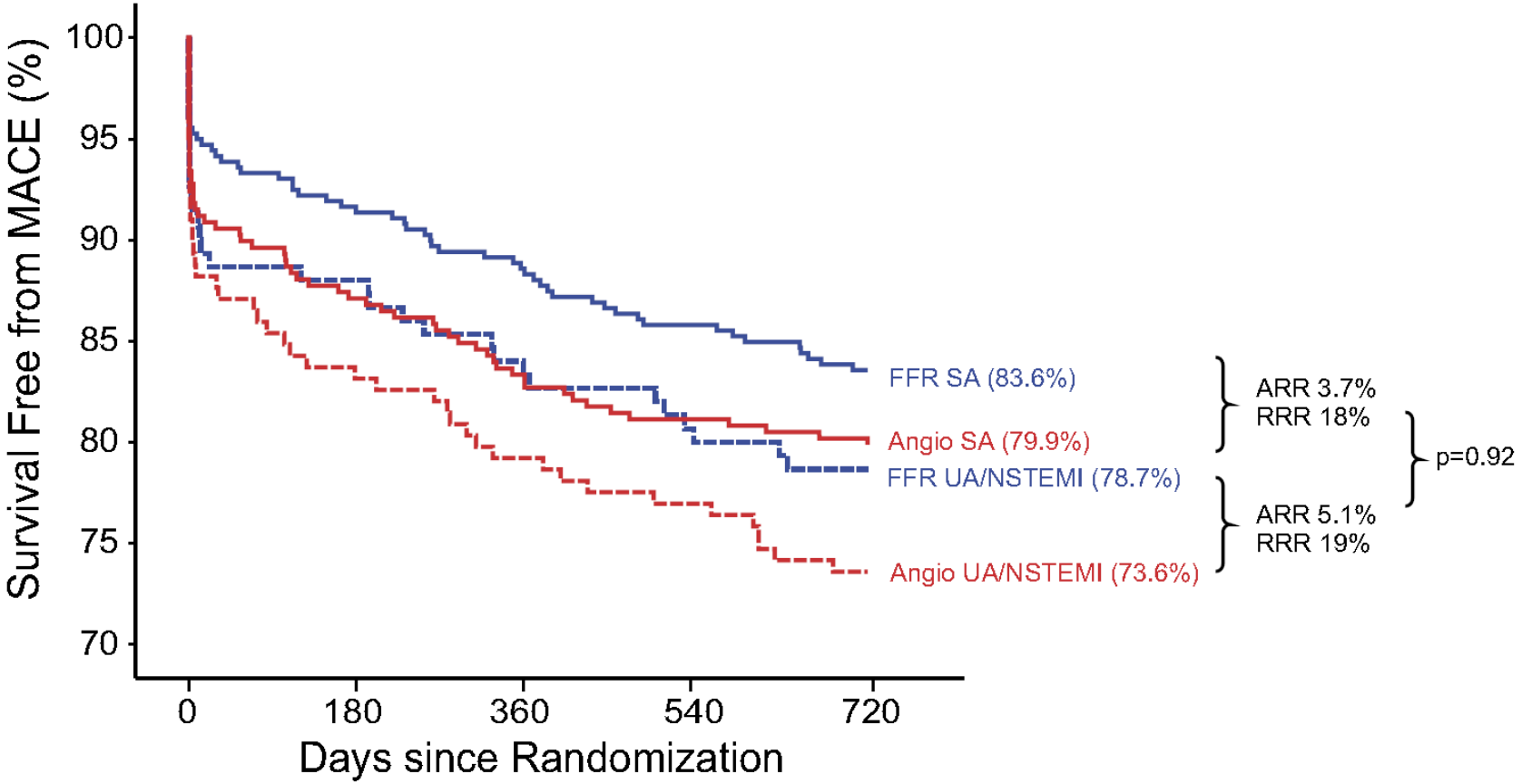
Tonino, et al. New Engl J Med 2009;360:213-24.

Baseline Characteristics

	Angio-Guided n = 496	FFR-Guided n = 509	P Value
Age, mean ±SD	64±10	65±10	0.47
Male, %	73	75	0.30
Diabetes, %	25	24	0.65
Hypertension, %	66	61	0.10
Current smoker, %	32	27	0.12
Hyperlipidemia, %	73	72	0.62
Previous MI, %	36	37	0.84
NSTE ACS, %	**36**	**29**	**0.11**
Previous PCI , %	26	29	0.34
LVEF, mean ±SD	57±12	57±11	0.92
LVEF < 50% , %	27	29	0.47

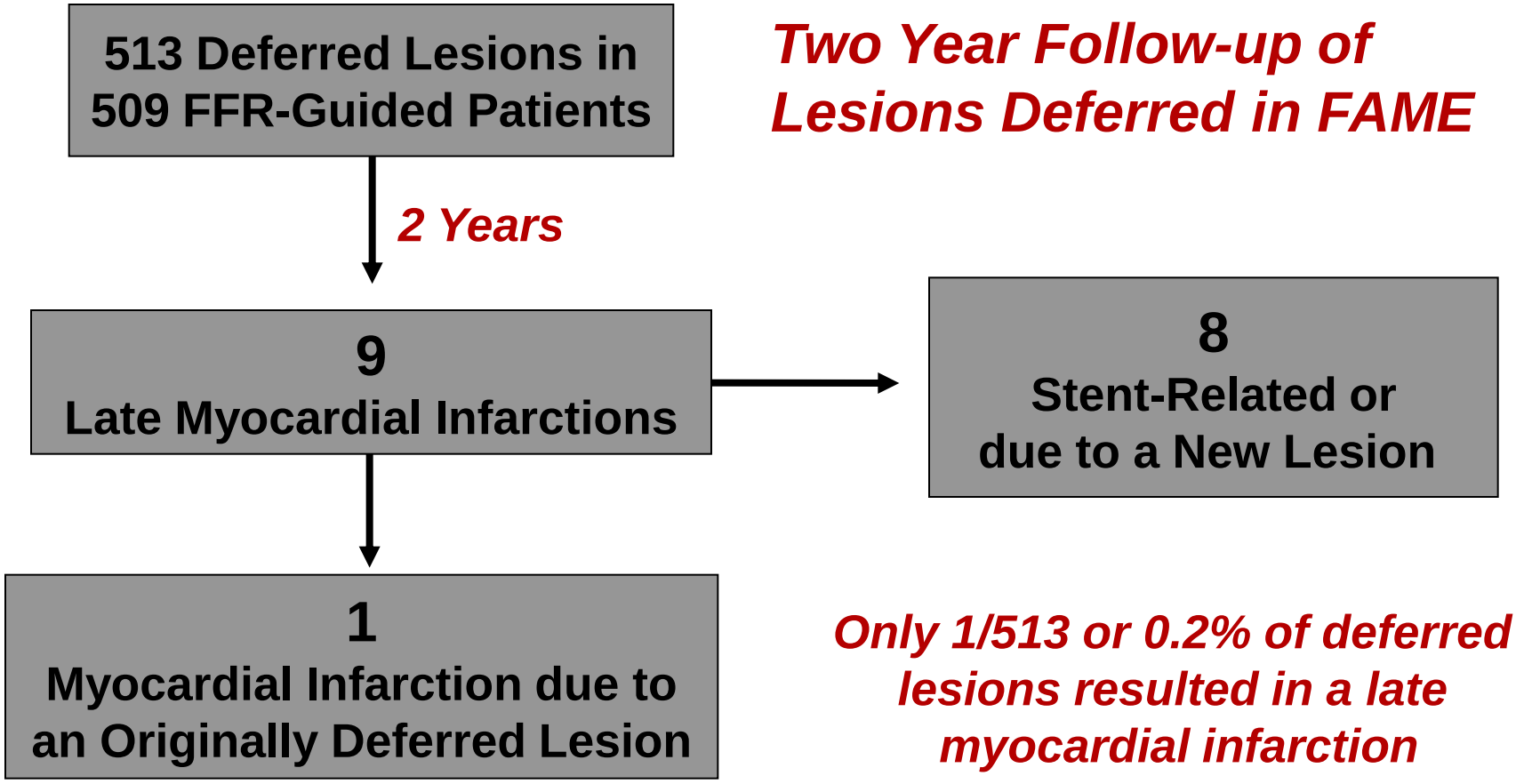
FFR NSTE ACS (Culprit + Non Culprit Vessel)

Comparison of MACE in FAME patients with and without ACS



Tonino, et al. J Am Coll Cardiol Intv 2011;4:1182-9.

What happens to deferred lesions?



Two Year Follow-up of Lesions Deferred in FAME

Only 1/513 or 0.2% of deferred lesions resulted in a late myocardial infarction

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

FAMOUS-NSTEMI

350 NSTEMI patients randomized to FFR-guided or angio-guided PCI

Outcome[a]	Randomly assigned groups		Risk difference (95% CI)	*P*-value[b]
	FFR-disclosure group *n* = 176	Angiography group *n* = 174		
Health outcomes at 12 months, *n* (%)				
Cardiovascular death, non-fatal myocardial infarction, unplanned hospitalization for stroke or transient ischaemic attack (MACCE)	13 (7.4)	16 (9.2)	−1.8% (−7.9, 4.2%)	0.56
Cardiac death, non-fatal myocardial infarction or unplanned hospitalization for heart failure (MACE)	14 (8.0)	15 (8.6)	−0.7% (−6.7, 5.3%)	0.89
MACE, excluding procedure-related myocardial infarction[d]	10 (5.7)	5 (2.9)	2.8% (−1.6, 7.6%)	0.25
All-cause death	5 (2.8)	3 (1.7)	1.1% (−2.4, 5.0%)	0.54
Fatal or non-fatal myocardial infarction[d]	11 (6.2)	15 (8.6)	−2.4% (−8.2, 3.3%)	0.49
Myocardial infarction related to coronary revascularization (Type 4a, Type 4b and Type 5 myocardial infarction)	5 (2.8)	11 (6.3)	−3.5% (−8.5, 1.1%)	0.12
Spontaneous myocardial infarction	7 (4.0)	5 (2.9)	1.1% (−3.1, 5.5%)	0.69

Layland, et al. Eur Heart J 2015;36:100-11.

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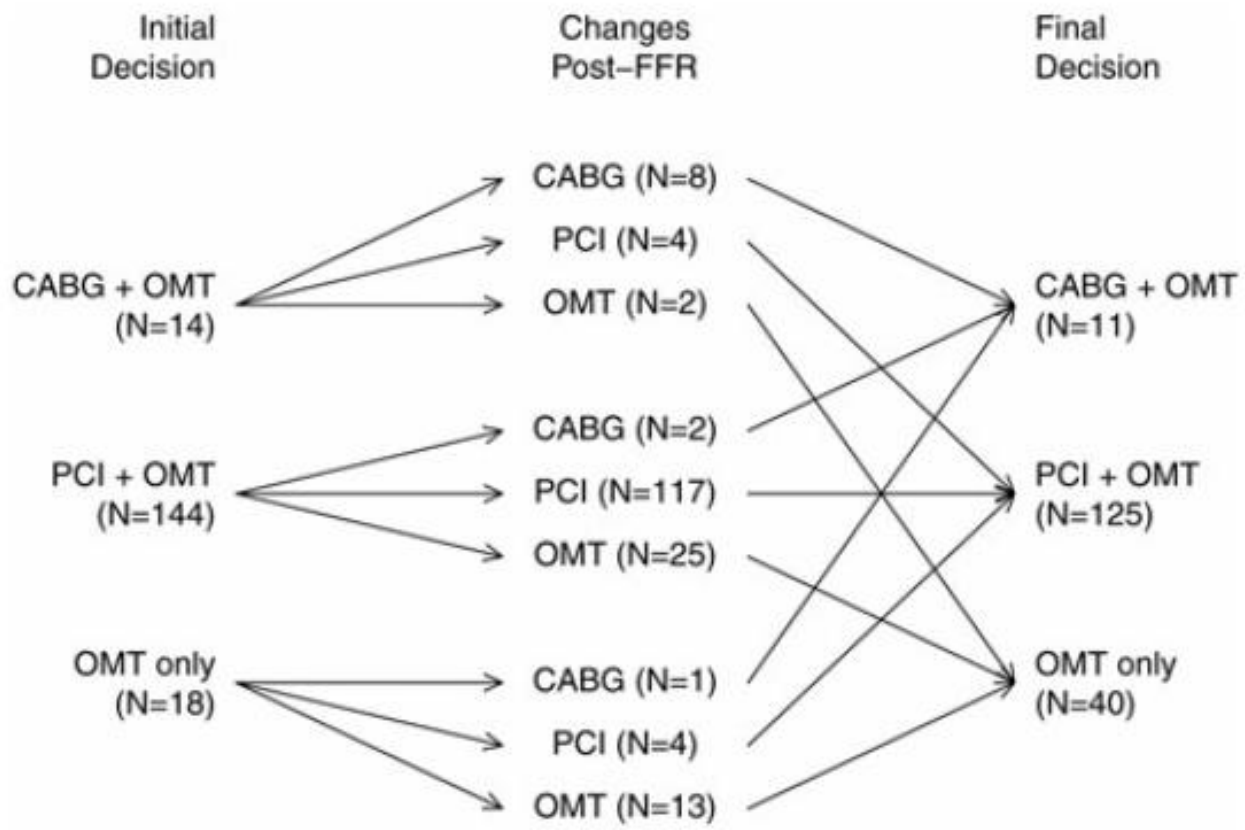

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FFR in Acute Coronary Syndromes

Take Home Messages:

- **FFR of the culprit vessel may be unreliable in the setting of STEMI, but can be accurately measured in the non-culprit vessel**
- **In a less acute MI setting, once microvascular stunning has decreased, FFR at a cut-point of 0.75-0.80 remains accurate**
- **For a given stenosis, FFR correlates inversely with the mass of viable myocardium supplied**
- **FFR appears accurate and safe in the setting of NSTE ACS for both culprit and non-culprit vessels**

Summary

Indications for FFR in Acute Coronary Syndromes

	Culprit Vessel	Non-Culprit Vessel
STEMI (acute)	-	+
STEMI (chronic)	+	+
Non ST Elevation ACS	+	+