From FFR to iFR

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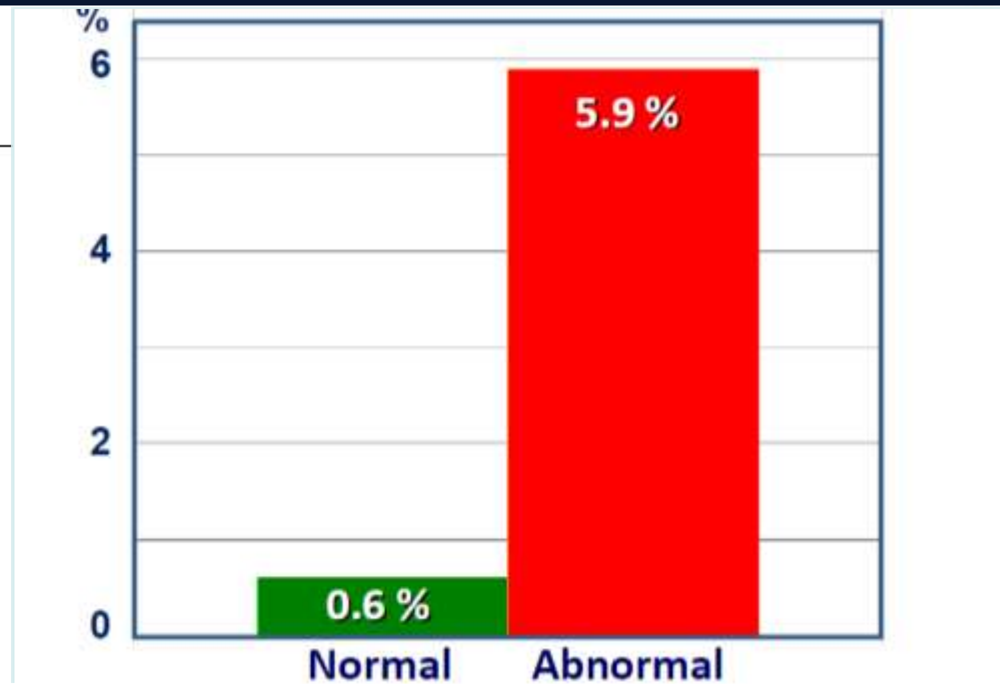
Disclosure Statement of Financial Interest

I, Soo-Jin Kang DO NOT have a financial interest/arrangement or affiliation with one or more organizations that is perceived as a real or apparent conflict of interest in the context of the subject of this presentation

Prognosis of Normal or Low-risk SPECT

Annual risk of cardiac death/ MI: Meta-analysis



Year	Author				
2003	Elhendy[54]				
2003	Hachamovitch[55]				
2003	Shaw[33]				
2002	Gibson[56]				
2001	Galassi[57]				
2000	Groutars[58]				
1999	Soman[59]				
1999	Gibbons[60]				
1999	Vanzetto[61]				
1998	Alkeylani[62]				
1998	Hachamovitch[63]				
1998	Olmos[64]				
1997	Boyne[65]				
1997	Snader[66]	3,400	Tl-201	2.0	1
1996	Geleijnse[67]	392	MIBI	1.8	0.8
1995	Heller[68]	512	MIBI	12.8	1.3
1994	Kamal[69]	177	Tl-201	1.8	0
1994	Machecourt[70]	1,926	Tl-201	2.8	0.5
1994	Stratmann[71]	534	MIBI	1.1	1.6
SPECT experience: 10 years [median (25th–75th percentile)]		39,173*		2.3 (1.8-3.0)	0.6 (0.5-0.9)

Shaw et al. J Nucl Cardiol 2004;11:171-85

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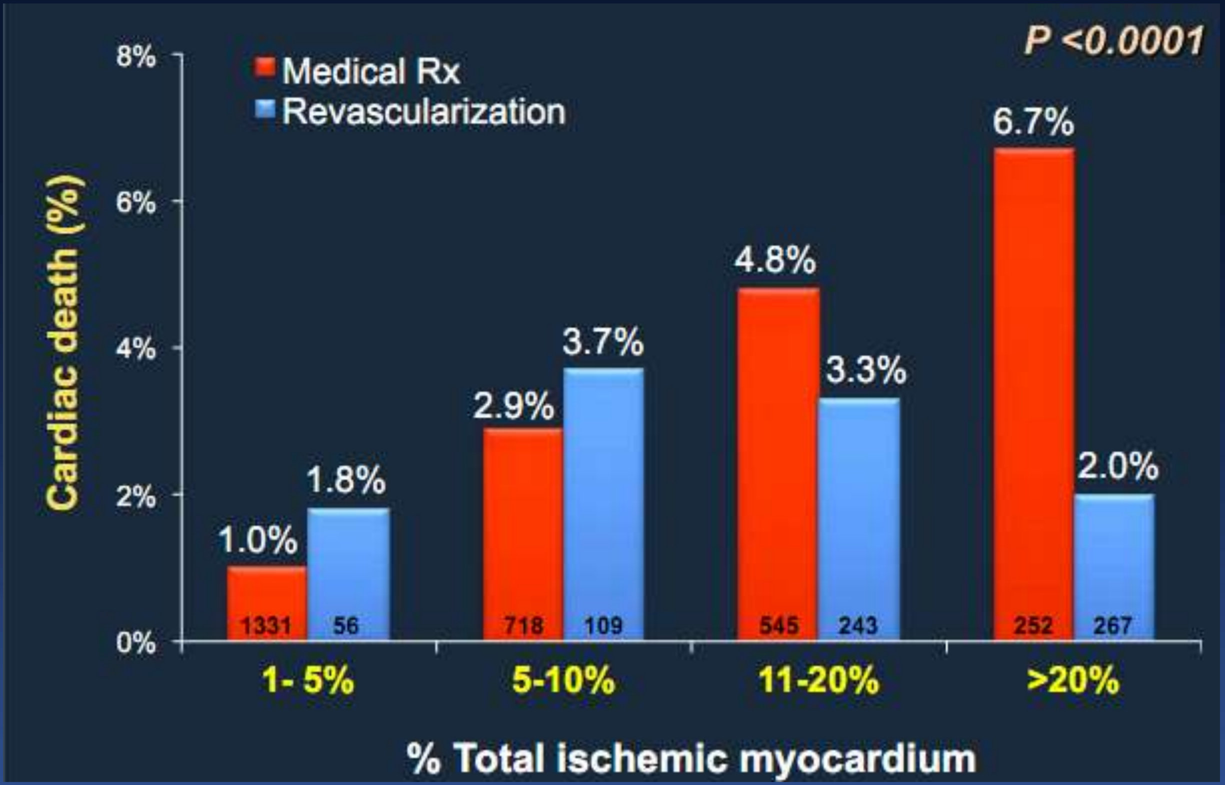
Survival Benefit of Revascularization

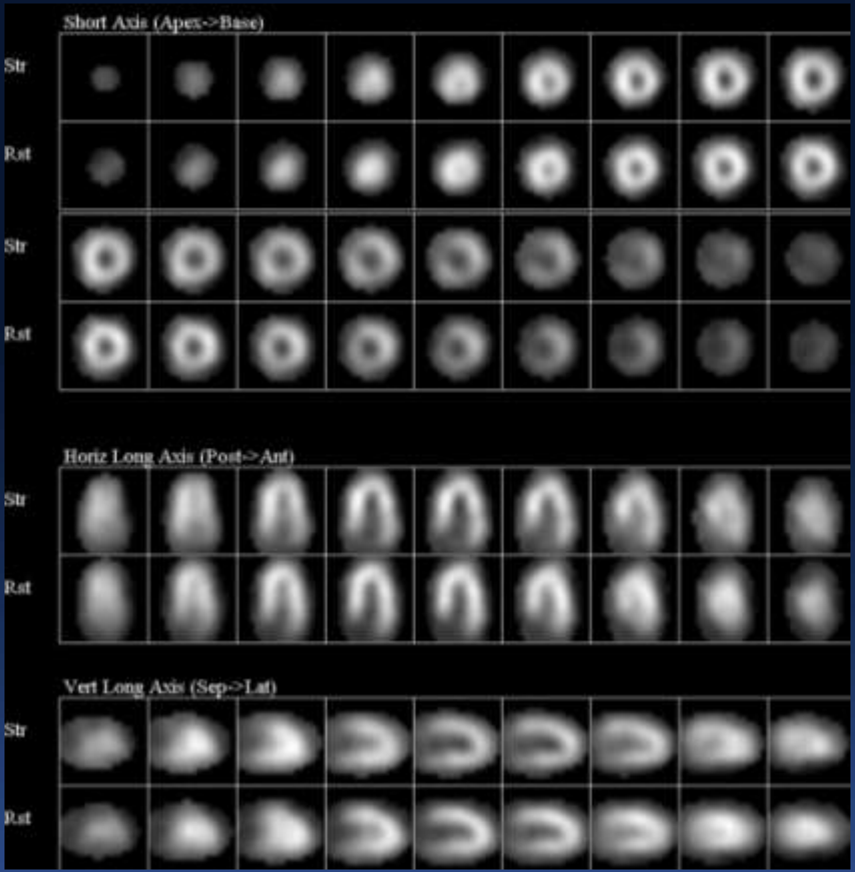
at 1.9-year F/U

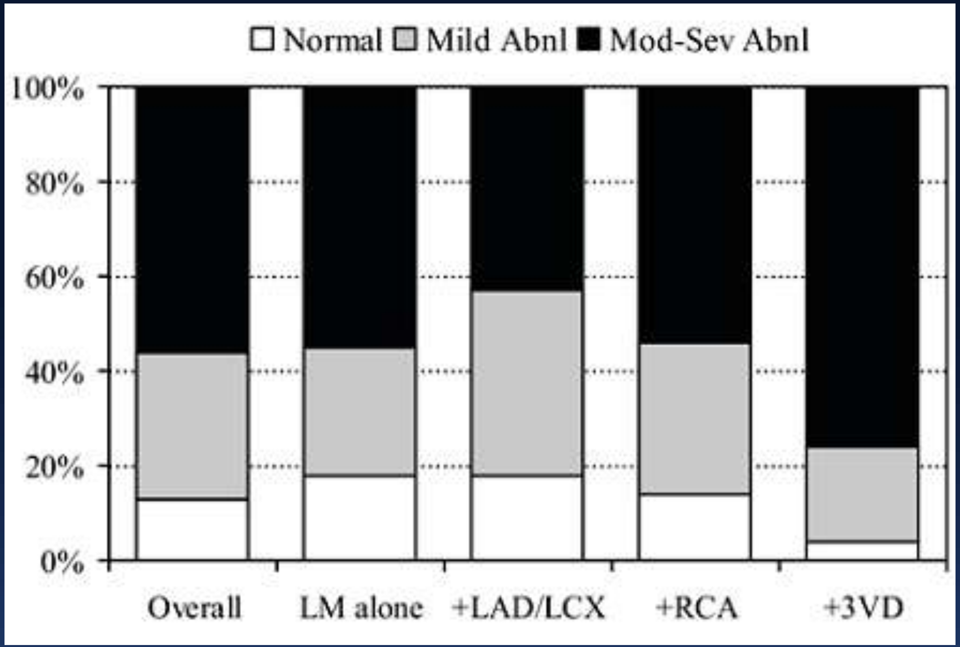


Revascularization had greater survival benefit in patients with moderate to large amounts of ischemia

Hachamovitch et al. Circulation 2003;107:2900-7

Pitfalls of Myocardial Perfusion Scan





False Negative
"Balanced Ischemia"

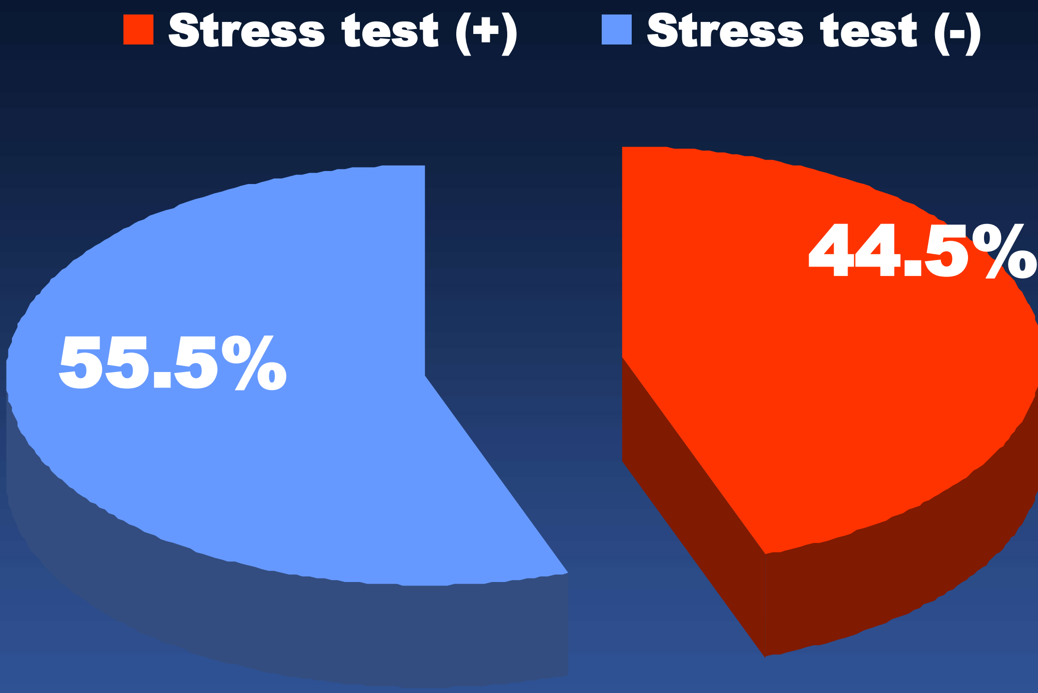
- Underestimation of true severity of multi-vessel dz
- No typical perfusion pattern for LM disease
- Not "Lesion-Specific"

Berman et al. J Nuclear Cardiol 2007;14:521-8

Frequency of Stress Testing

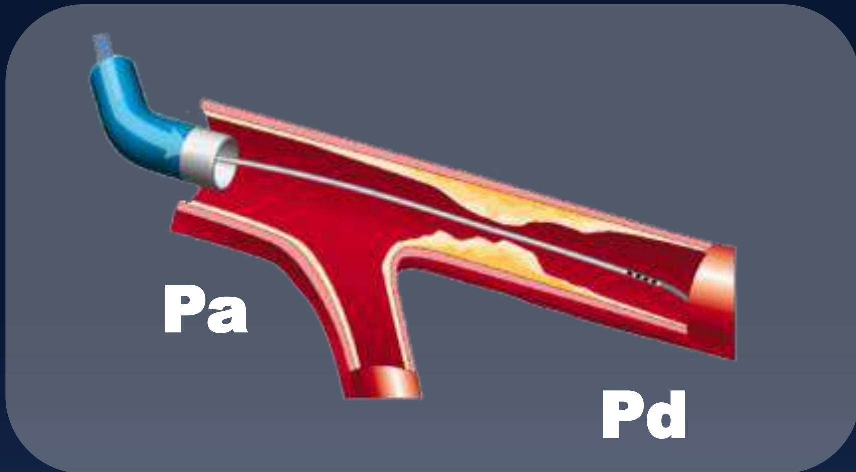
to Document Ischemia Prior to Elective PCI

Stable angina (N=23,837)



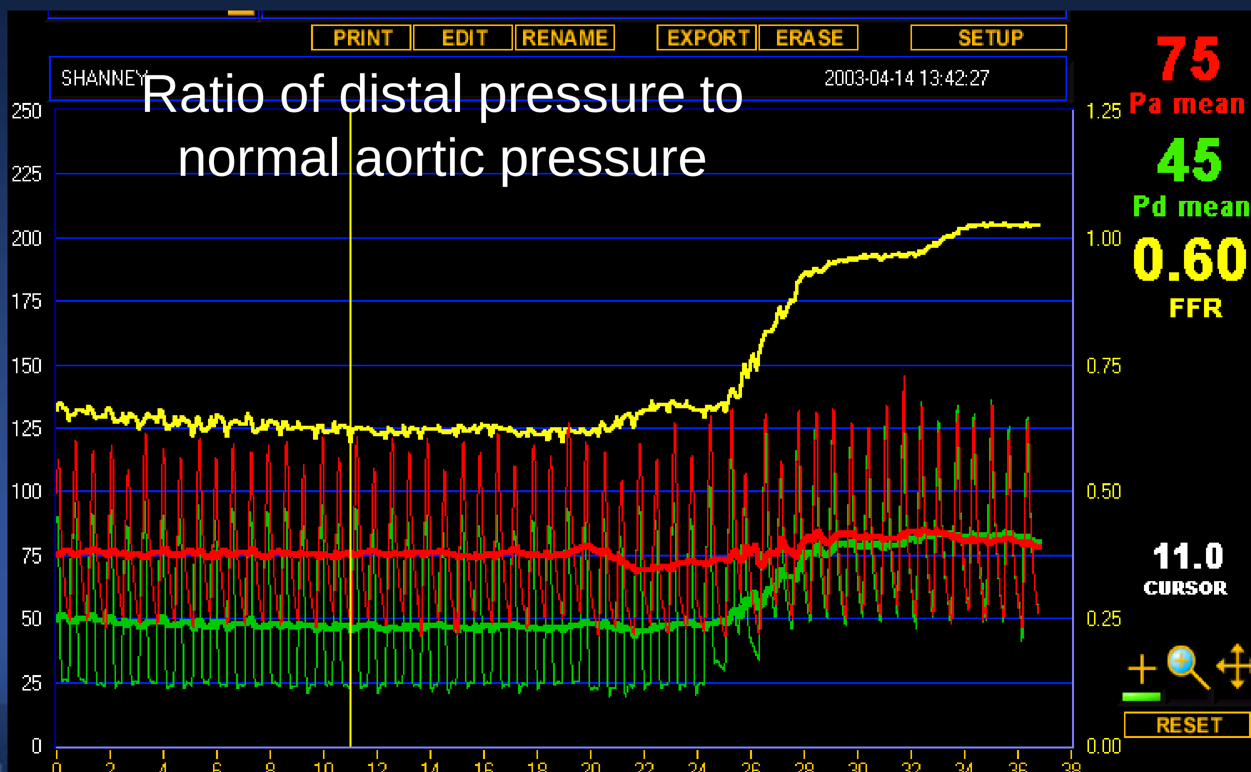
JAMA2008;300:1765-73

Fractional Flow Reserve (FFR)



At Maximal Hyperemia

$$\frac{Q_S^{max}}{Q_N^{max}} = \frac{Pd}{Pa}$$



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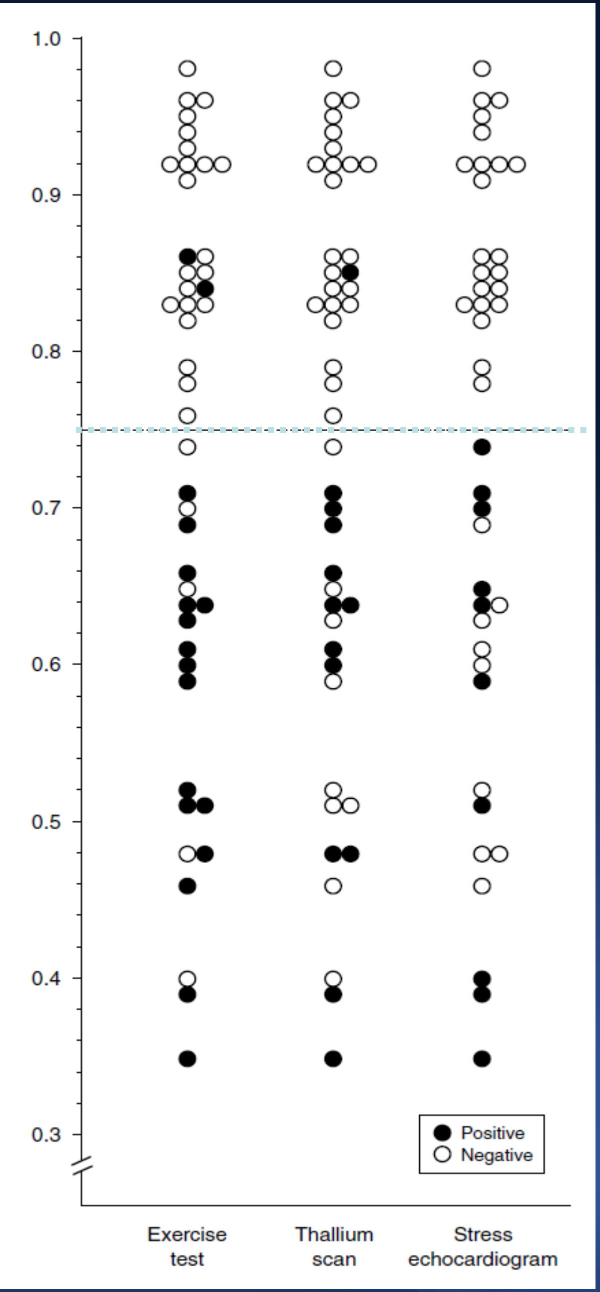
FFR



Validation of FFR

With 3 Non-invasive Stress Tests

FFR <0.75

Sensitivity 88%
Specificity 100%
Positive PV 100%
Negative PV 88%
Accuracy 93%

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

Cut-Offs to Predict Ischemia

0.75 0.80

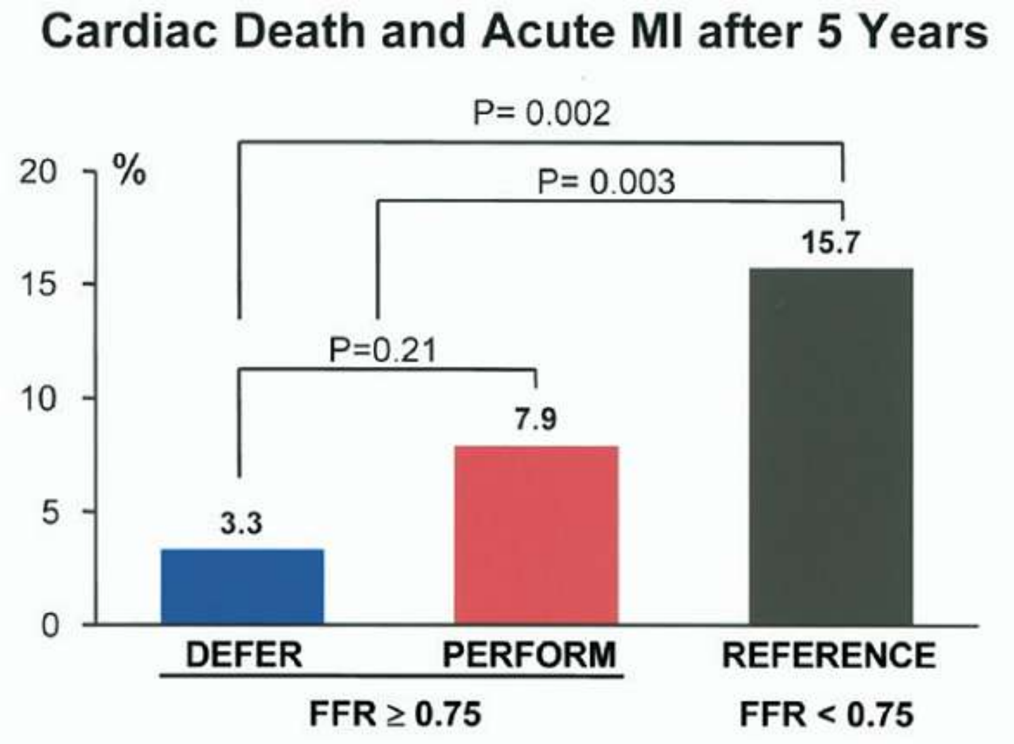
Significant	Grey	Insignificant

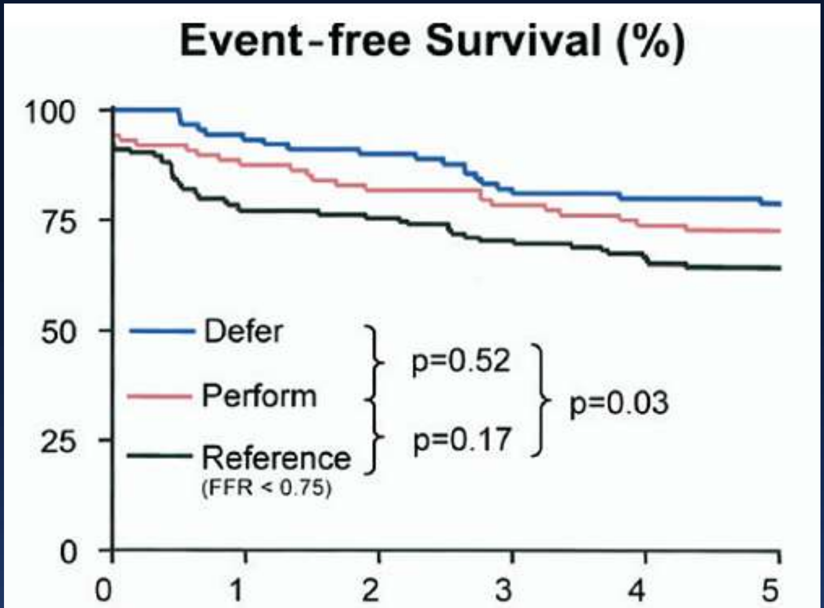
Author	Number	Stress Test	BCV	Accuracy
Pijls et al.	60	X-ECG	0.74	97
DeBruyne et al.	60	X-ECG/SPECT	0.72	85
Pijls et al.	45	X-ECG/SPECT/pacing/DSE	0.75	93
Bartunek et al.	37	DSE	0.68	90
Abe et al.	46	SPECT	0.75	91
Chamuleau et al.	127	SPECT	0.74	77
Caymaz et al.	40	SPECT	0.76	95
Jimenez-Navarro et al.	21	DSE	0.75	90
Usui et al.	167	SPECT	0.75	79
Yanagisawa et al.	167	SPECT	0.75	76
Meuwissen et al.	151	SPECT	0.74	85
DeBruyne et al.	57	MIBI-SPECT post-MI	0.78	85
Samady et al.	48	MIBI-SPECT post-MI	0.78	85
Kang SJ (AMC 2010)	151	SPECT	0.77	89

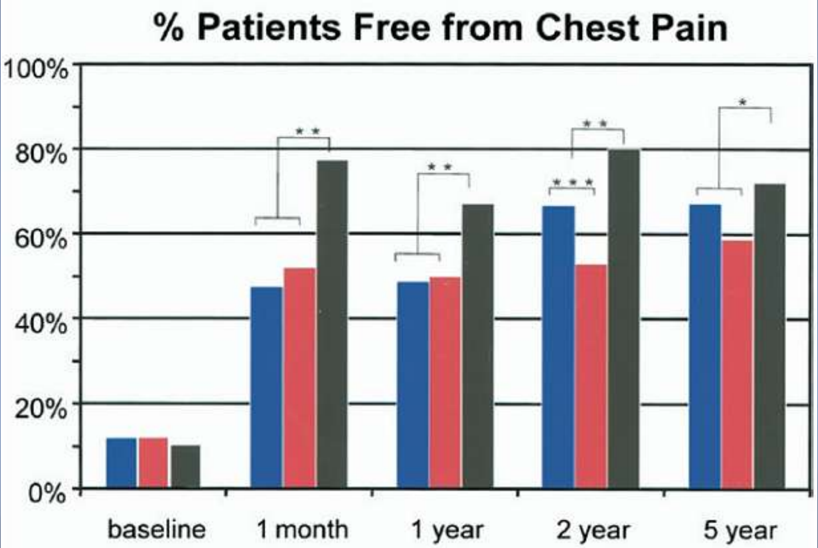
DEFER Trial

325 Patients with Single Vessel Disease

- FFR≥0.75 **DEFER** (91 pts)
- FFR≥0.75 **PERFORM PCI** (90 pts)
- FFR<0.75 **REFERENCE** (144 pts)







J Am Coll Cardiol 2007;49:2105–11

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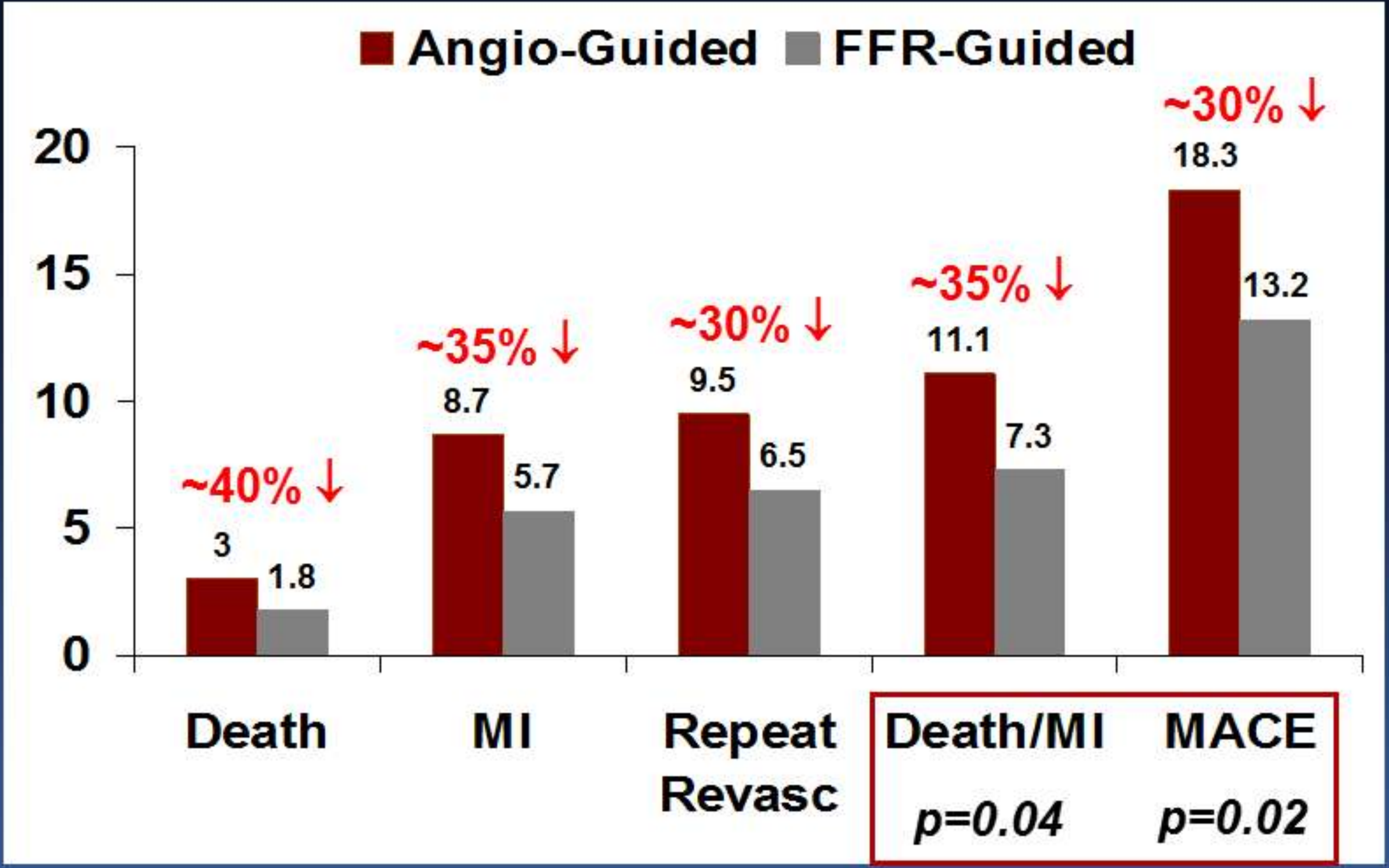
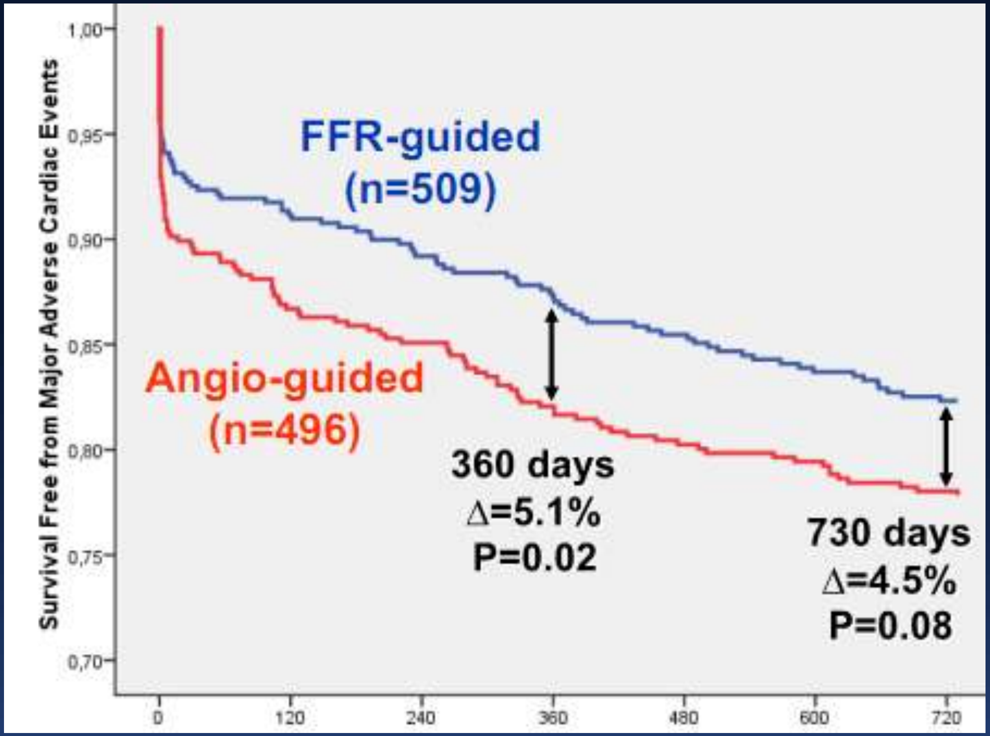
FAME: One Year Outcomes



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

FAME 2-year Outcomes



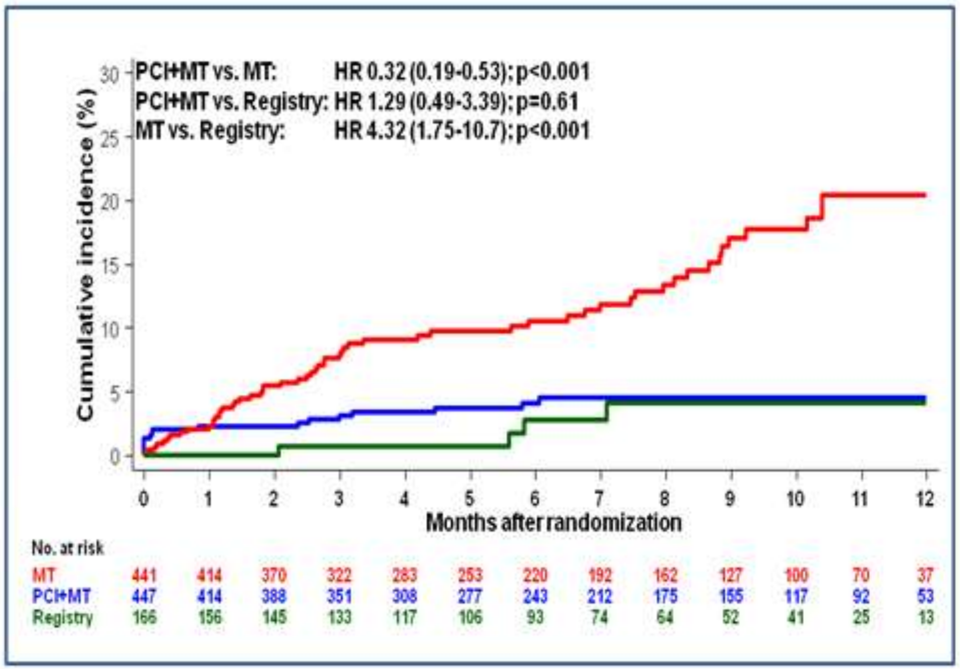
	Angio-guided	FFR-guided	RR	p
MACE at 2 years	**22.4%**	**17.9%**	**0.80**	**0.08**
Death or MI	12.9%	8.4%	0.65	0.02
Revascularization	12.7%	10.6%	0.84	0.30
Angina-free at 2yrs	75.8%	79.9%		0.14

Pijls et al. JACC 2010;56:177-84

FAME 2

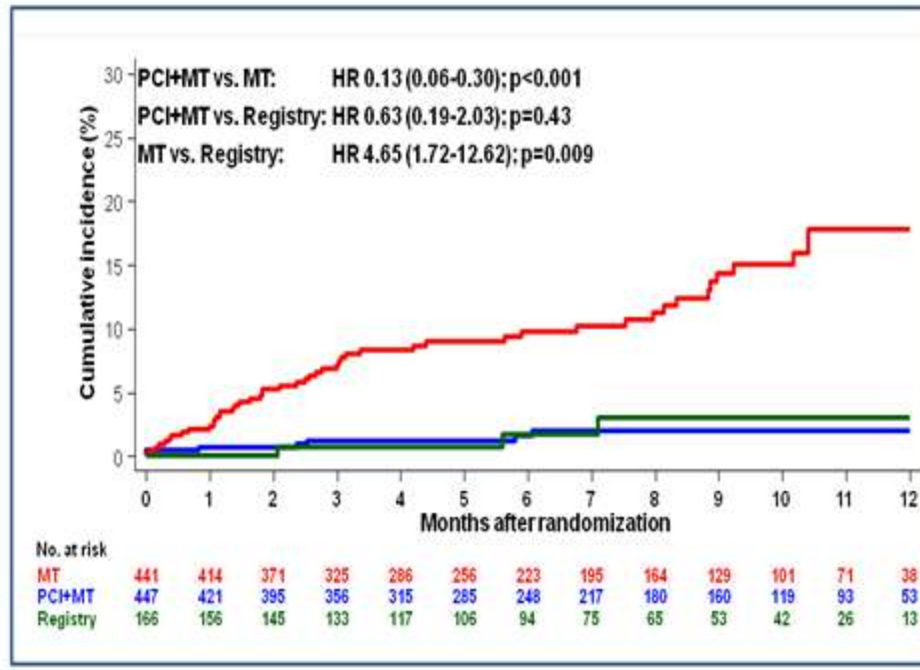
FFR-Guided PCI vs. Medical Therapy in Stable CAD

Primary Outcomes



* Composite of all cause death, myocardial infarction, unplanned hospitalization with urgent revascularization

Urgent Revascularization



▪ FFR >0.75 - 0.80 is useful to identify patients in whom deferral of PCI leads to favorable outcomes

Author	Comparison	Results	p
Lindstaedt[1]	CABG (FFR<0.75) vs. Medical (≥0.80)	4-year Survival 81% vs. 100% MACE-free 66% vs. 69%	NS
Jasti[2]	CABG (FFR<0.75) vs. Medical (≥0.75)	38-month Survival 100% vs. 100% MACE-free 100% vs. 90%	NS
Courtis[3]	Revasc (FFR<0.75) vs. Medical (≥0.80)	14-month MACE 7% vs. 13%	NS
Bech[4]	Revasc (FFR<0.75) vs. Medical (≥0.75)	29-month Survival 100% vs. 97% MACE-free 83% vs.76%	NS
Hamilos[5]	CABG (FFR<0.80) vs. Medical (≥0.80)	5-year Survival 85% vs. 90% MACE-free 74% vs. 82%	NS

[1] Am Heart J 2006;152:156, [2] Circulation 2004;110:2831–6, [3] Am J Cardiol 2009;103:943-9
[4] Heart 2001;86:547-52, [5] Circulation 2009;120:1505-12

Current Guideline

2010 ESC Class I *Level of Evidence A*

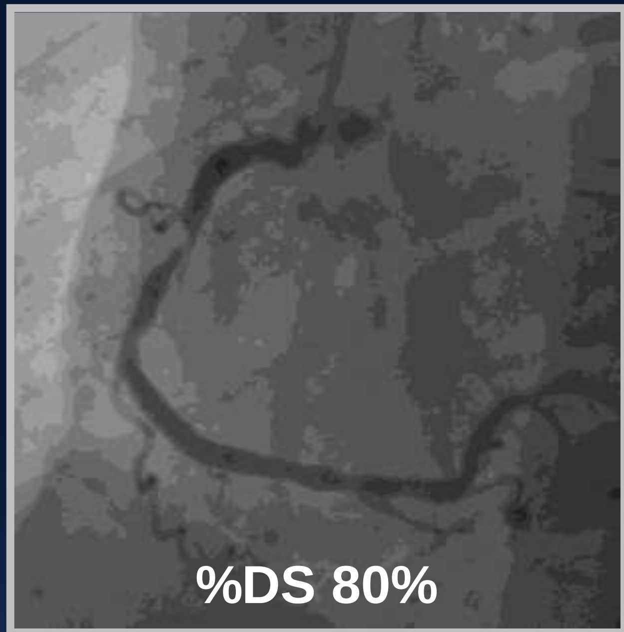
FFR-guided PCI is recommended for detection of ischemia-related lesions when objective evidence of vessel-related ischemia is not available

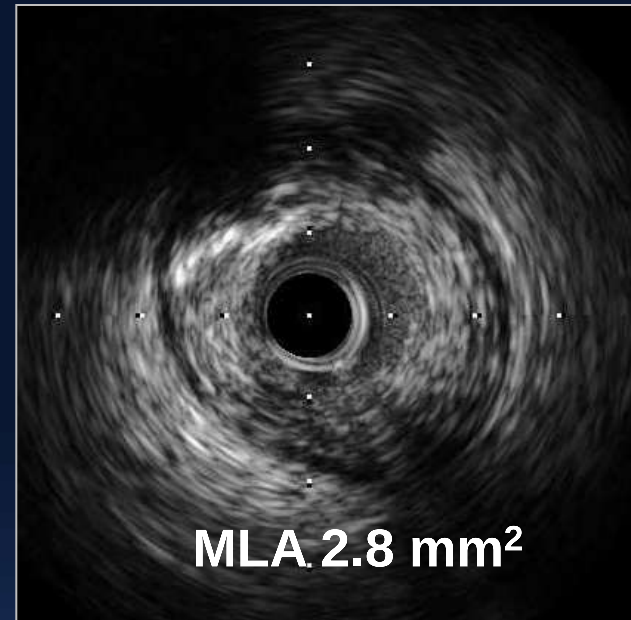
2009 AHA/ACC Class IIa *Level of Evidence A*

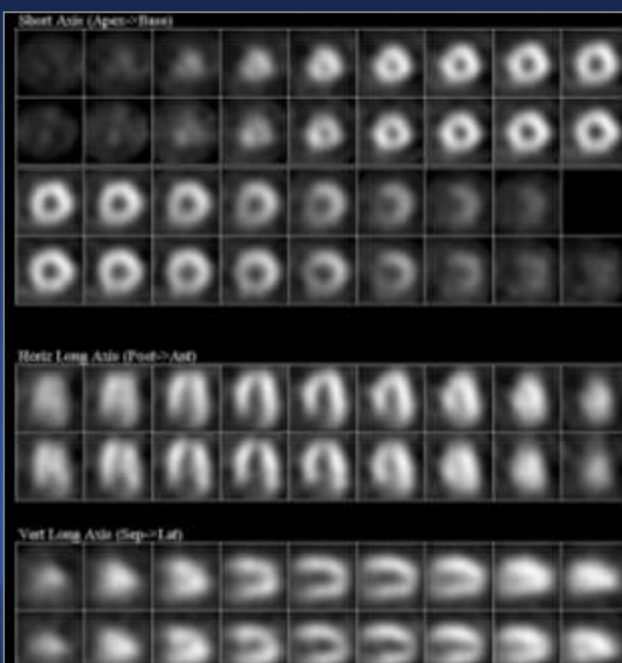
FFR is reasonable to assess intermediate lesion (30-70% DS) and can be useful to guide revascularization in stable IHD

Visual-Functional Mismatch

Frequency and Mechanism


%DS 80%

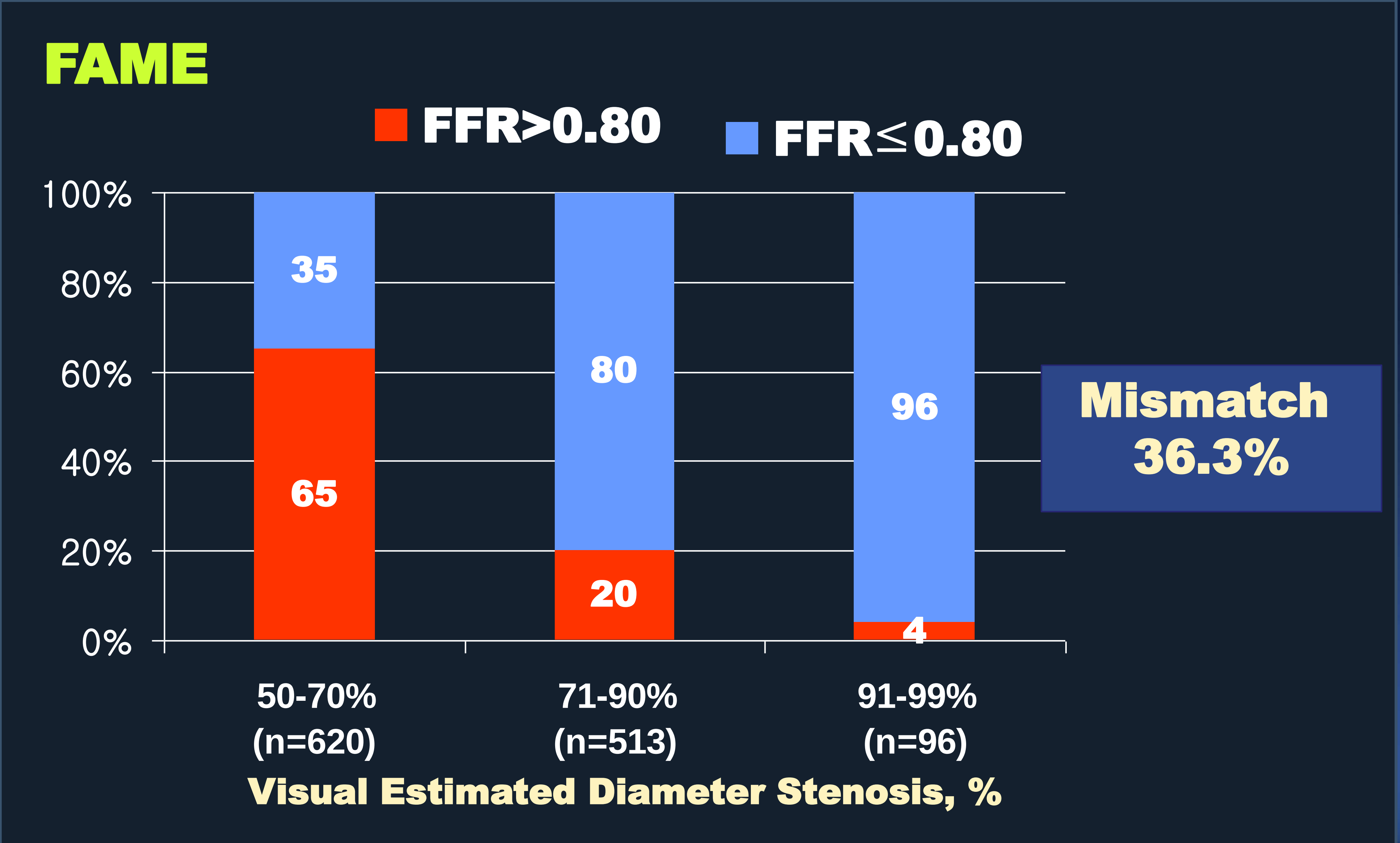

MLA 2.8 mm²


Short Axis (Apex->Base)
Horiz Long Axis (Post->Ant)
Vert Long Axis (Sep->Lat)


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6


PressureWire
(108)
(91)
0.84

Visual-Functional Mismatch



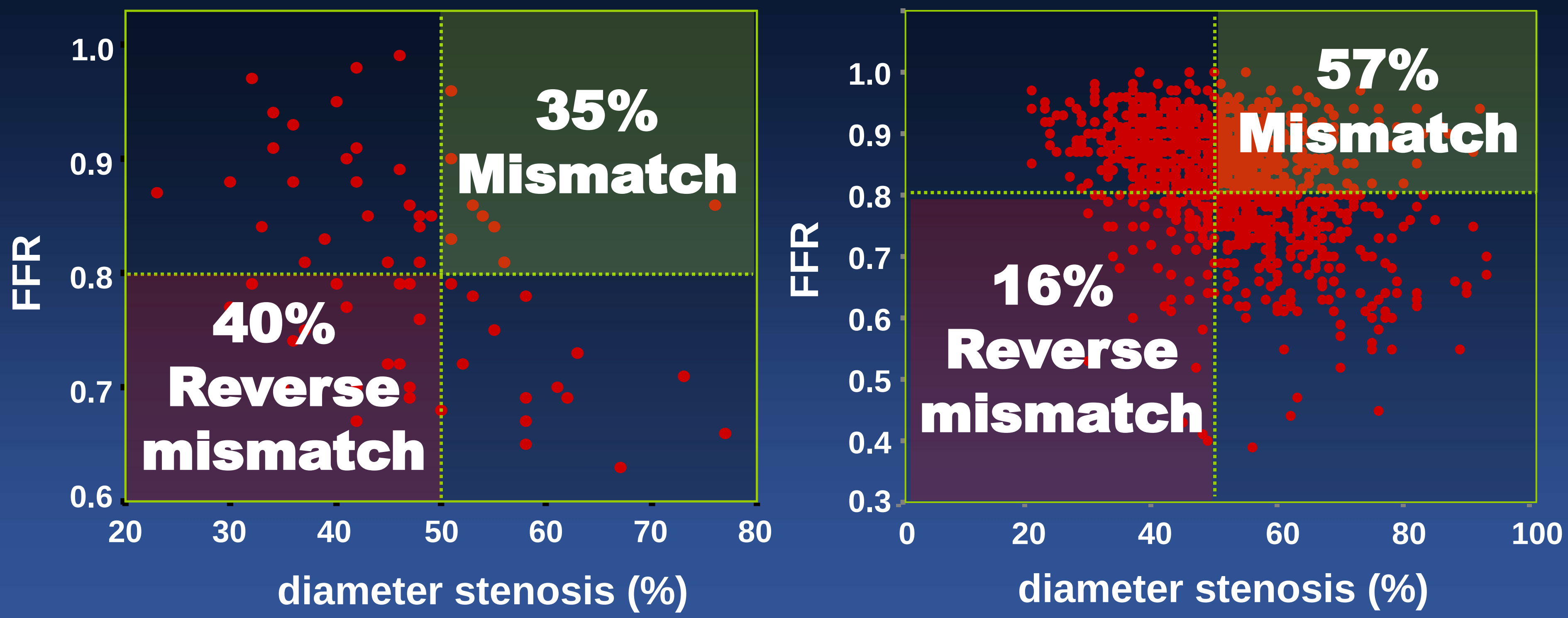
J Am Coll Cardiol 2010;55:2816–21

1000 Consecutive Patients

(1129 lesions with DS >30%) who underwent IVUS and FFR

ClinicalTrials.gov NCT01366404

63 LM lesions   1066 Non-LM lesions



Park et al. JACC interv 2012;5:1029-36

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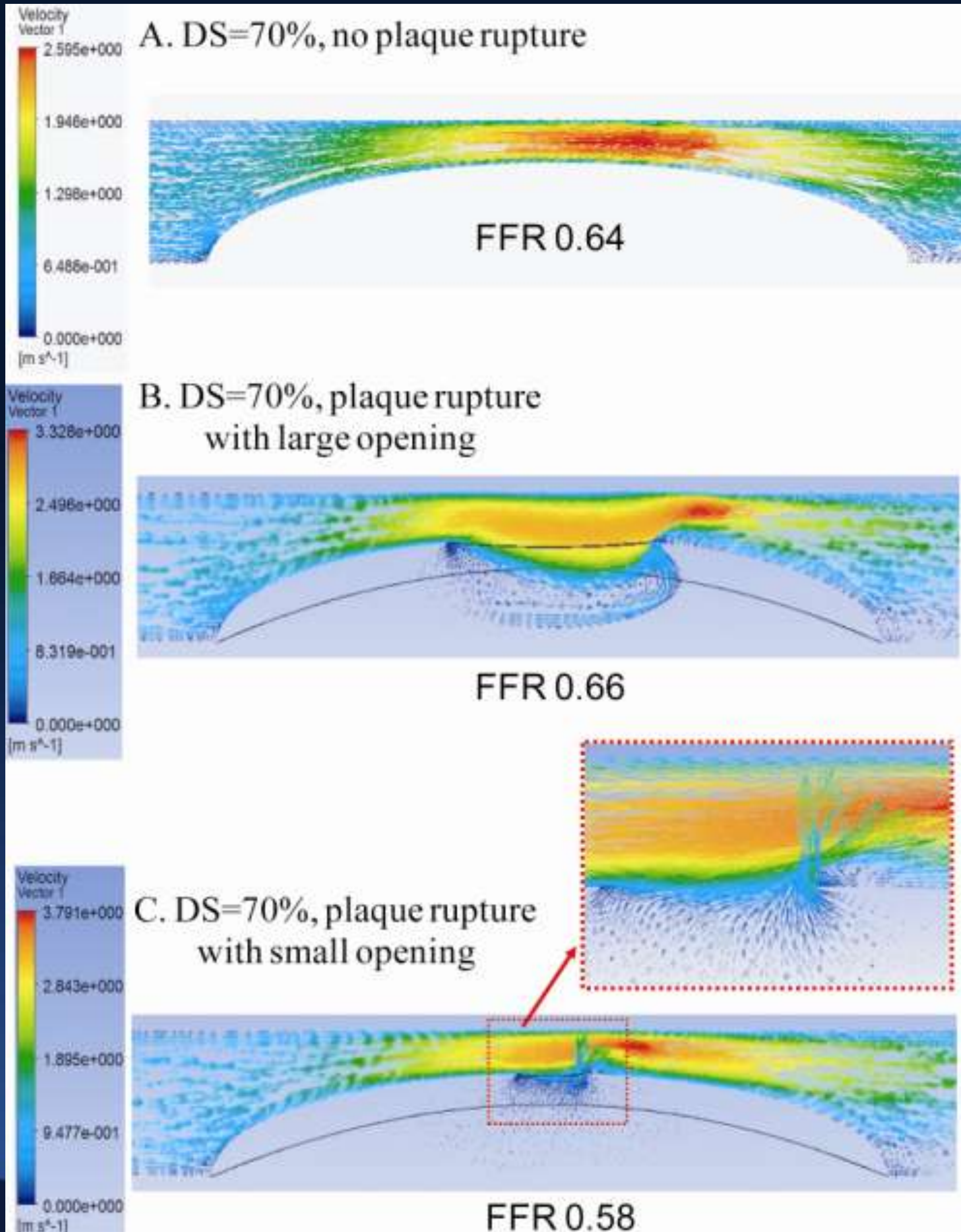
Why Mismatch

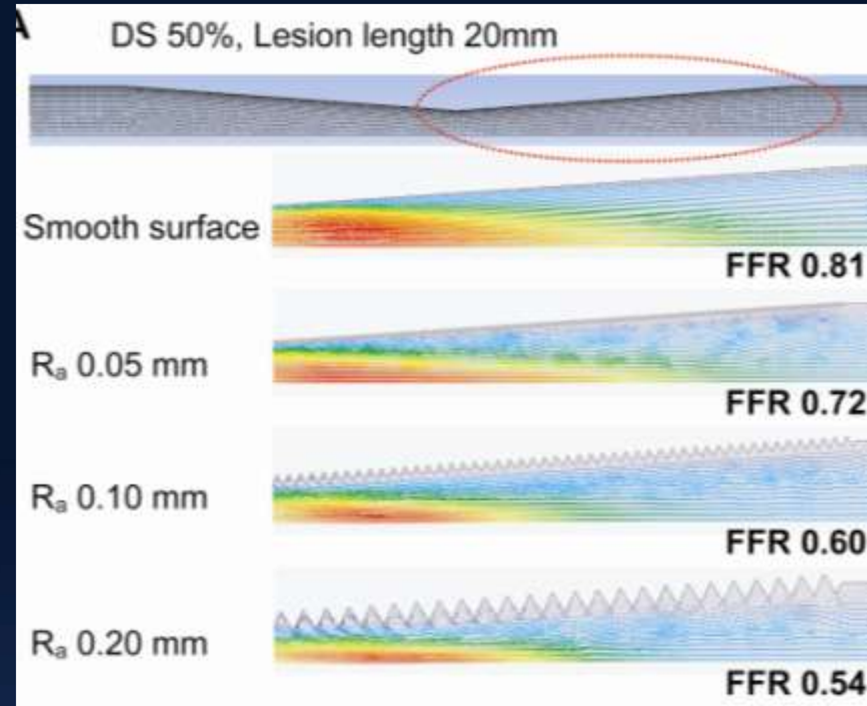
Nov 2009-Jun 2011, 1000 consecutive patients (1129 lesions with DS >30%) who underwent pre-PCI IVUS and FFR
(ClinicalTrials.gov NCT01366404)

Factors Affecting FFR

	Beta	p-value	95% CI
Age	0.008	<0.001	0.004 - 0.011
LAD location	-0.386	<0.001	-0.462 - 0.311
Lesion length	-0.006	<0.001	-0.009 - 0.003
Minimal lumen area	0.185	<0.001	0.149 - 0.222
Plaque burden	-0.006	<0.004	-0.009 - 0.003
Plaque rupture	-0.165	0.020	-0.302 - 0.027

AMC data





Complex or irregular lumen produces greater flow resistance and energy loss of fluid, thus resulting in pressure drop and FFR↓

Park et al. JACC interv 2012;5:1029-36

	N	FFR	RLA	MLA	AUC	Sens	Spec	PPV	NPV	Accu
Takaki (1999 Circ)	51	0.75	9.3	**3.0**	–	83%	92%	–	–	–
Briguori (2001 AJC)	53	0.75	7.8	**4.0**	–	92%	56%	38%	96%	**64%**
Ben-Dor (2012 *)	205	0.80	8.6	**3.09**	0.73	69%	72%	–	–	**70%**
Kang (2011 Circ int)	236	0.80	7.6	**2.4**	0.80	90%	60%	37%	96%	**68%**
Kang (2012 AJC)	784	0.80	8.2	**2.4**	0.77	84%	63%	48%	90%	**69%**
Koo (2011 JACC int)	267	0.80	6.8	**2.75**	0.81	69%	65%	27%	81%	**67%**
Gonzalo (2012 JACC)	47	0.80	7.1	**2.36** IVUS	0.63	67%	65%	67%	65%	**66%**
Gonzalo (2012 JACC)	61	0.80	7.1	**1.95** OCT	0.70	82%	63%	66%	80%	**72%**

Meta-analysis of 11 Clinical Trials

1759 patients with 1953 lesions

Predict FFR<0.80

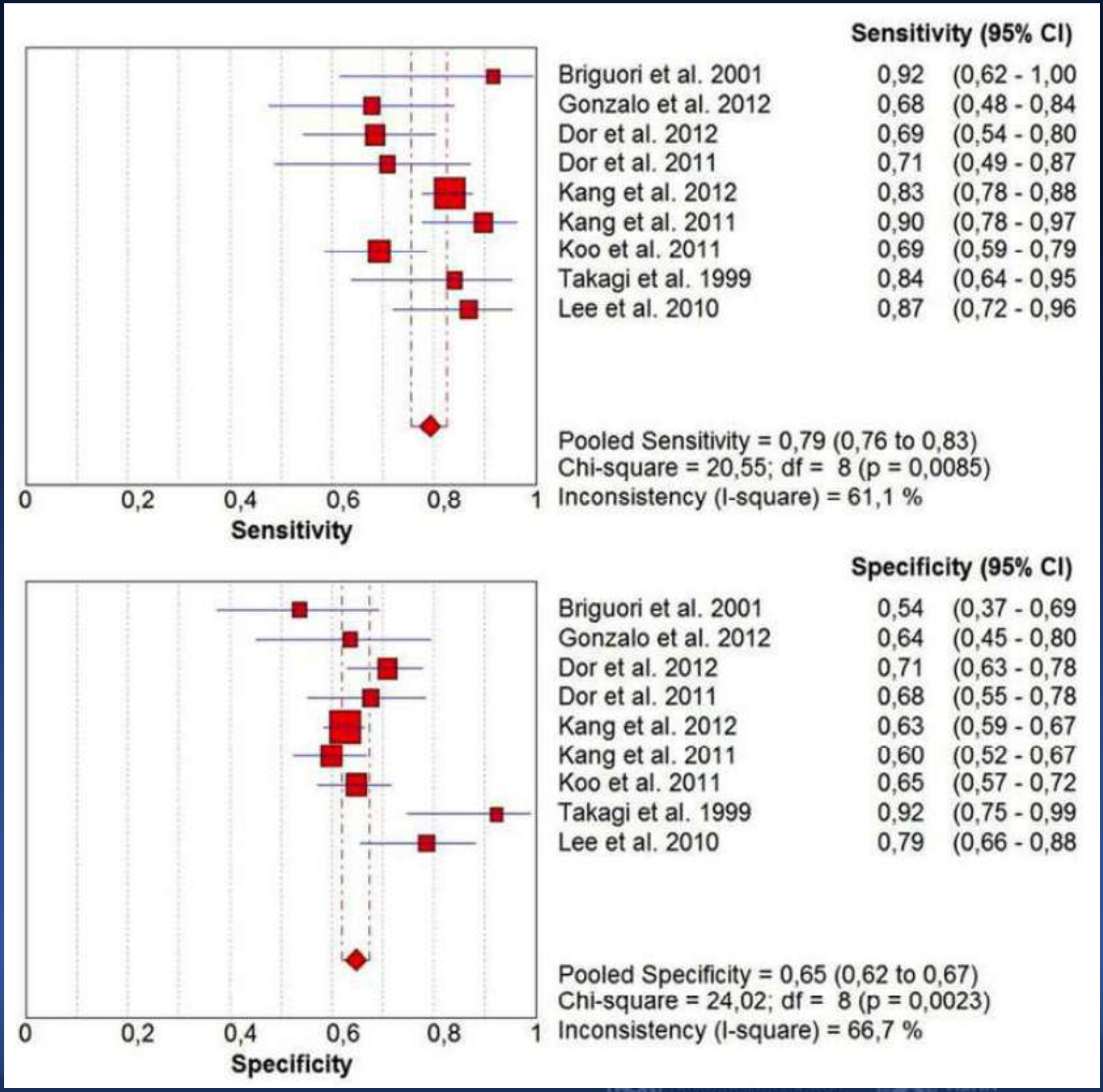
Weighted **MLA 2.61**mm^2

Pooled sensitivity **79%**

Pooled specificity **65%**

Smaller Cut-off than Used

Poor Accuracy



Nascimento et al. Catheter Cardiovasc Interv 2013 (in press)

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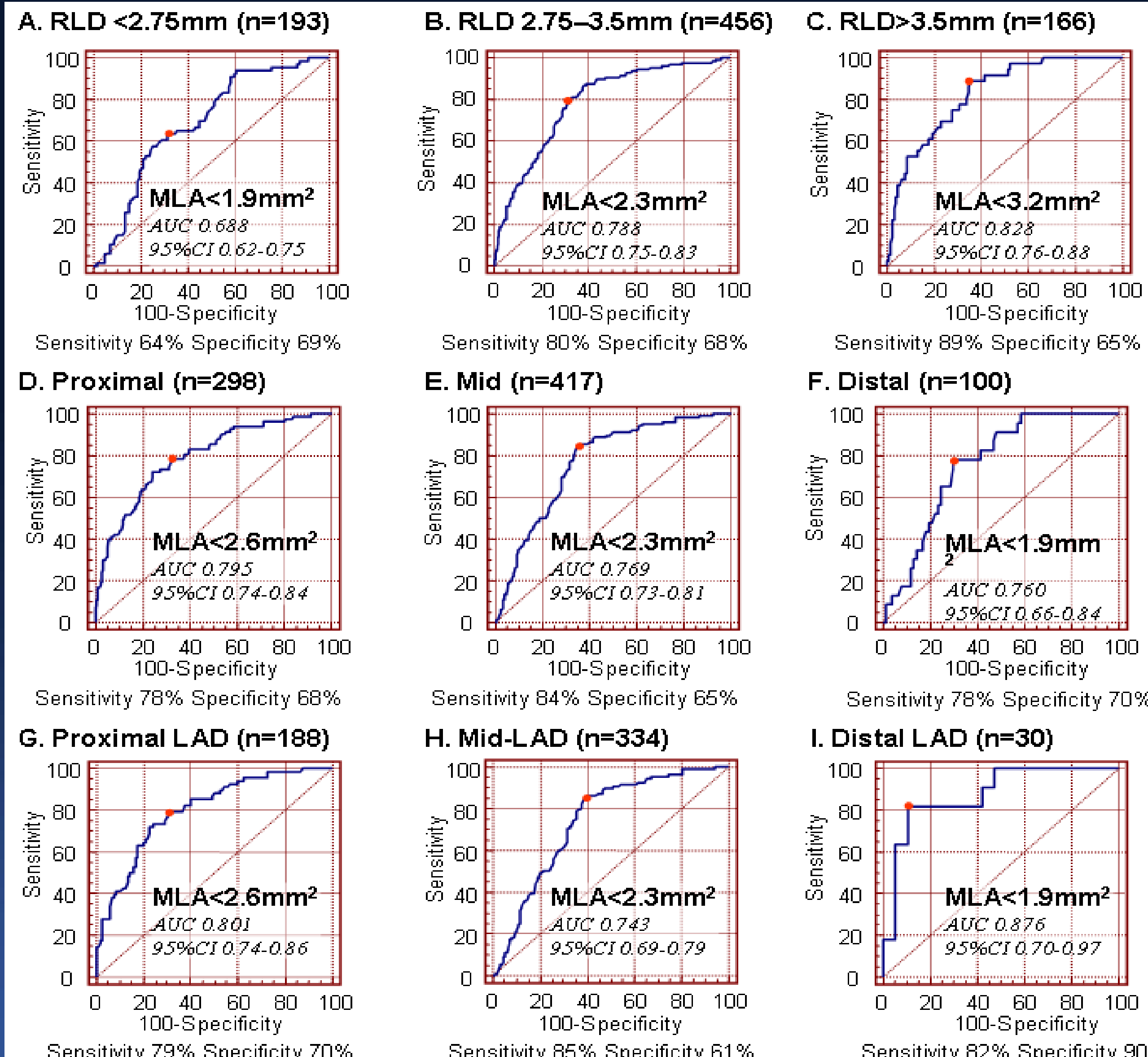

All Subgroup-specific MLA, accuracies <70-75%

Kang et al. Am J Cardiol 2012;109:947-5

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VERDICT F1RST

Optimal MLA Cutoff Values

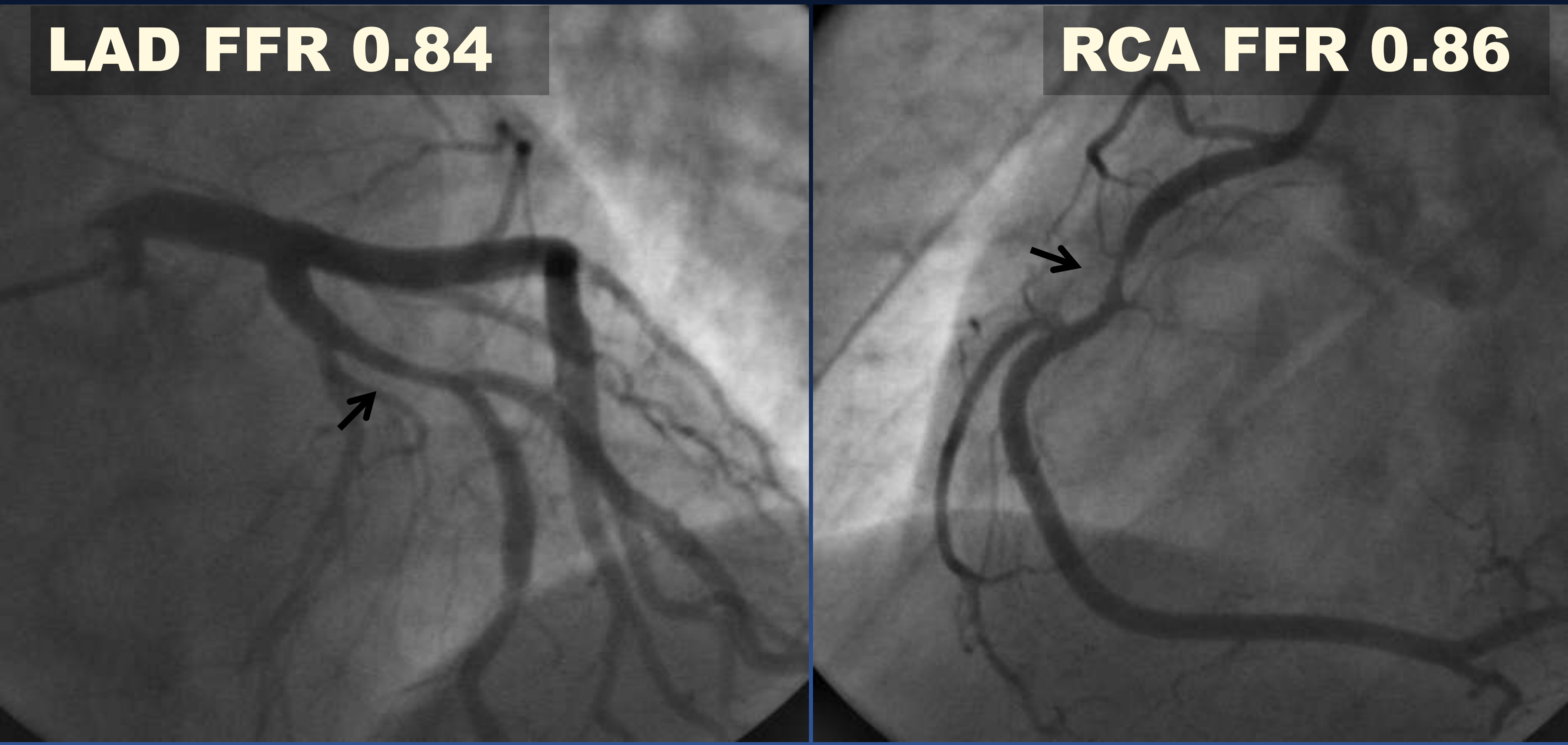
544 intermediate lesions assessed in 516 pts from 24 centers

FFR ≤0.80 in 169/544 lesions (31.1%) and 167/516 pts (32.4%)

	N	MLA cutoff	C-statistic	Accuracy
All lesions	544	2.9 mm^2	0.66	66.0%
LAD	296	2.9 mm^2	0.64	63.5%
LCX	110	2.4 mm^2	0.72	77.3%
RCA	138	2.8 mm^2	0.75	77.5%
Proximal	259	3.0 mm^2	0.76	74.9%
Mid	195	2.6 mm^2	0.63	65.6%
Distal	90	3.0 mm^2	0.63	51.1%
RVD <3.0 mm	322	2.6 mm^2	0.65	66.1%
RVD ≥3.0 mm	219	3.0 mm^2	0.71	72.6%
Length ≤12.3 mm	272	3.0 mm^2	0.67	64.7%
Length >12.3 mm	269	2.8 mm^2	0.69	68.8%

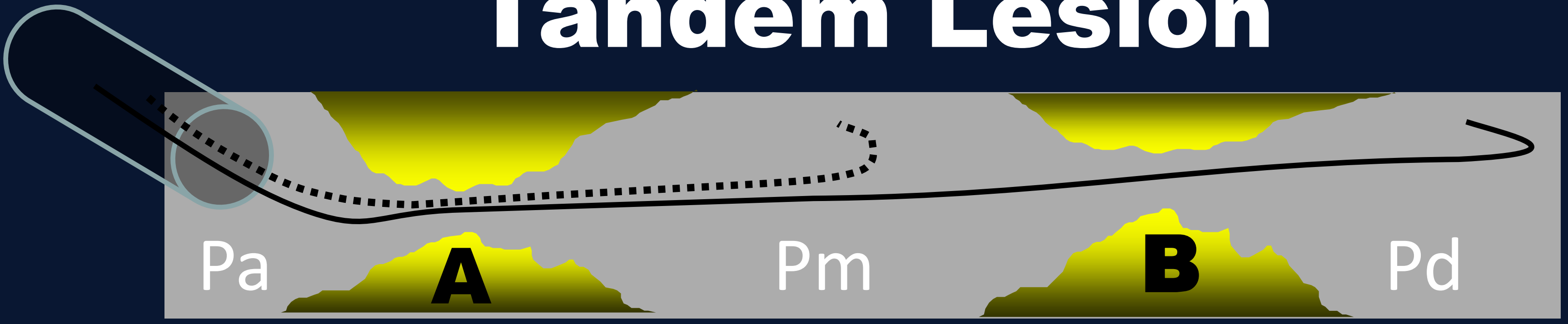
Clinical Utility of FFR

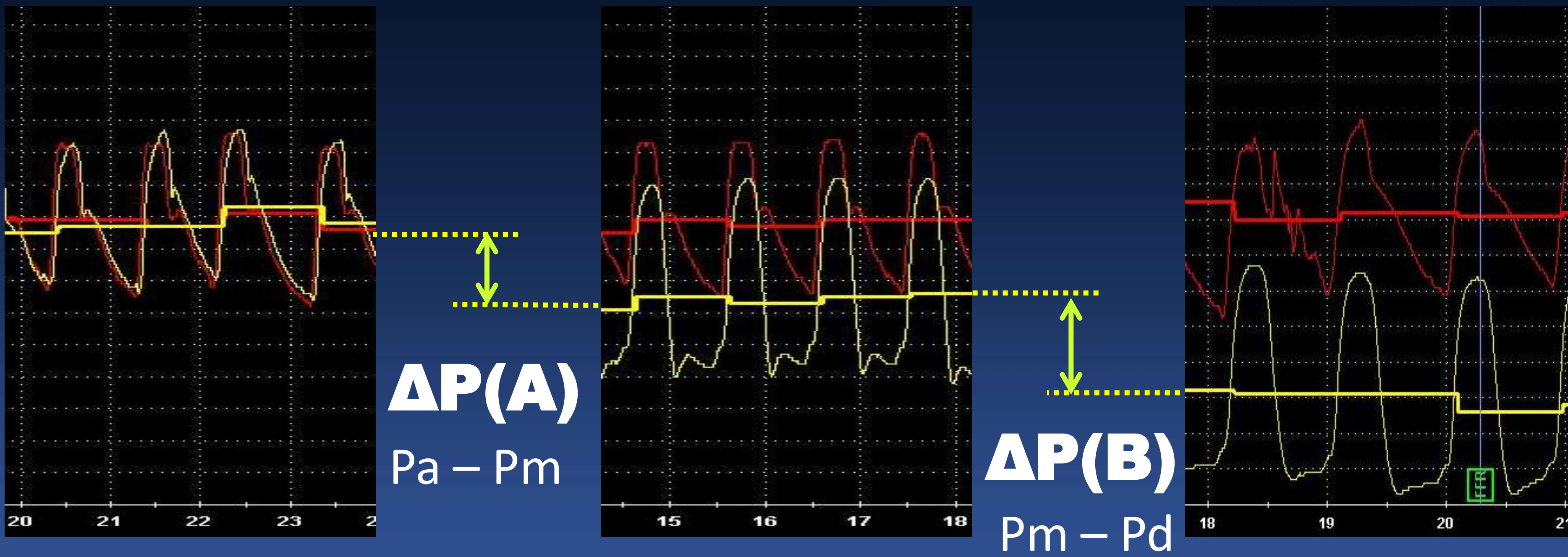
Multi-vessel Disease



Functionally, No Disease!

Tandem Lesion





Treat the lesion with **a larger ΔP** first
Then, repeat FFR across the remaining lesion

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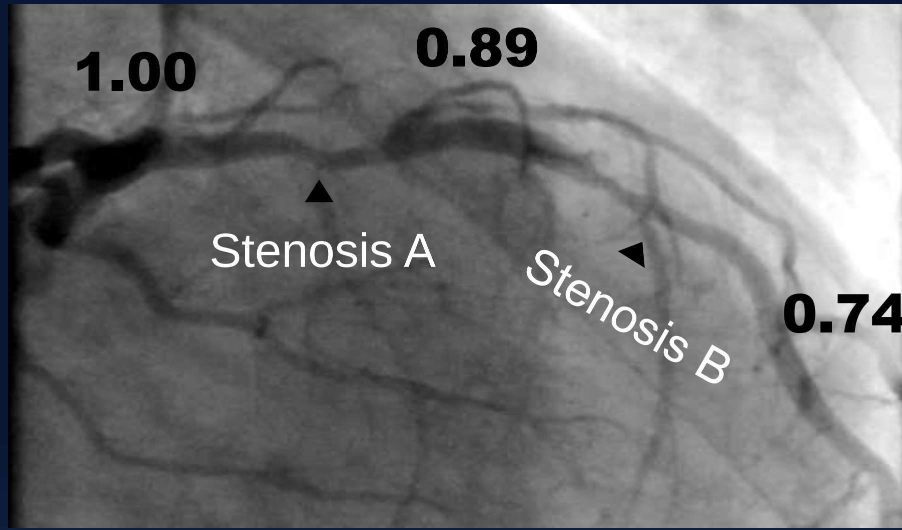
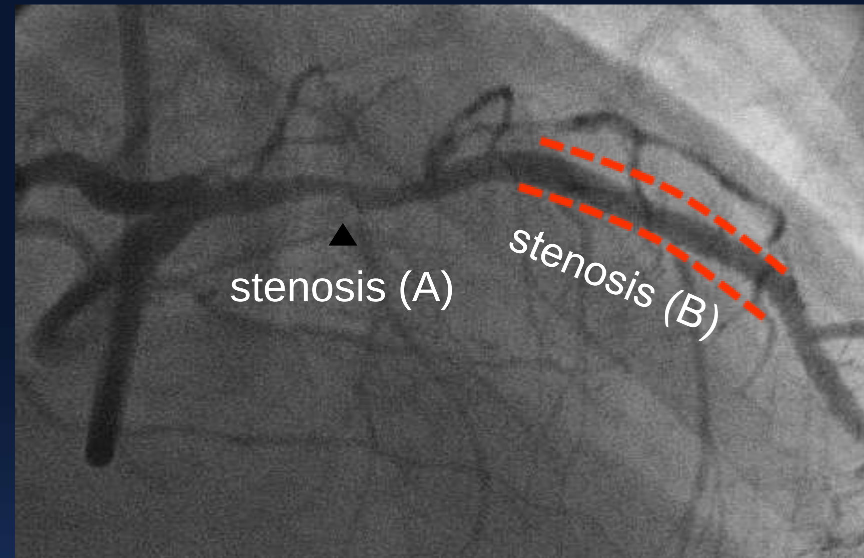


ΔFFR_B 0.15 > ΔFFR_A 0.11

Park et al. Am J Cardiol 2012;110:1578-84

Treat the Distal Stenosis (B) First !



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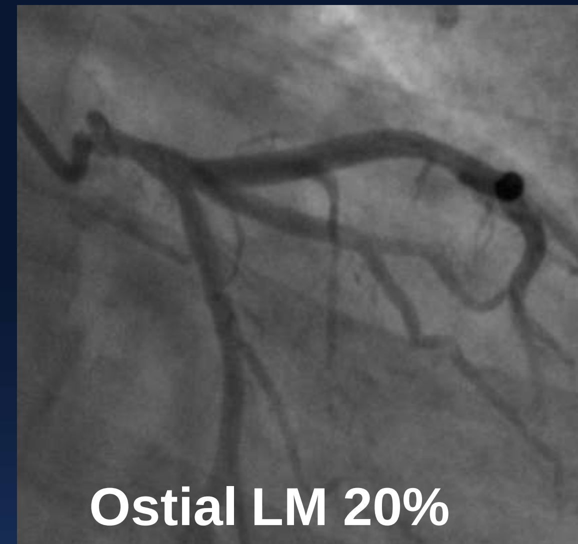
Pure LMCA Disease: Ostial/Shaft



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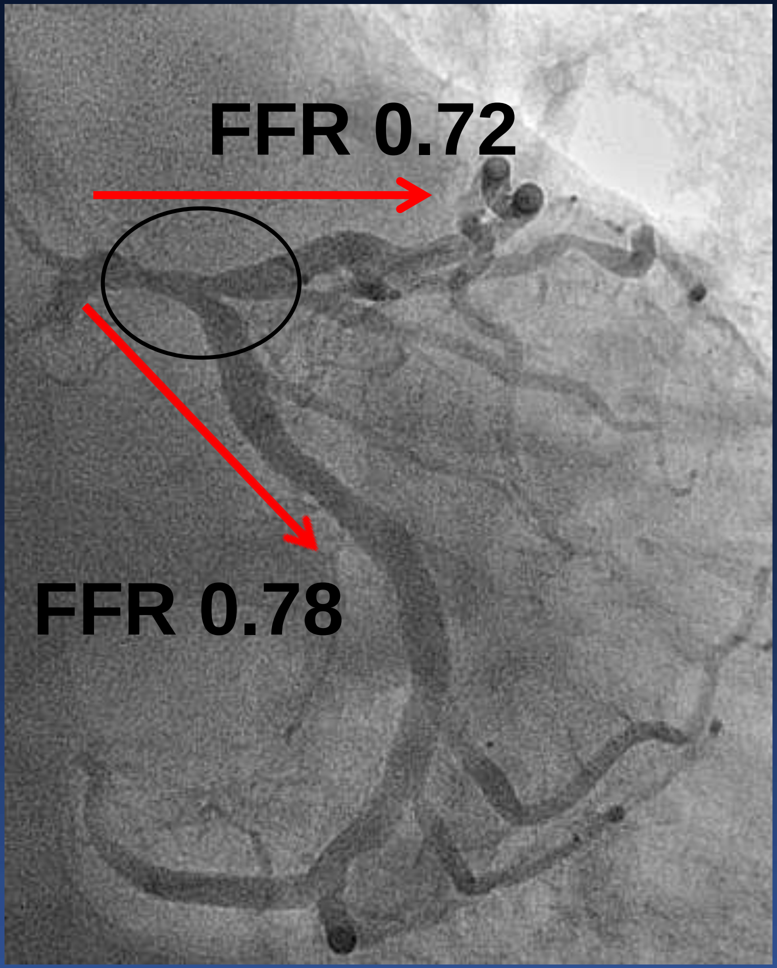
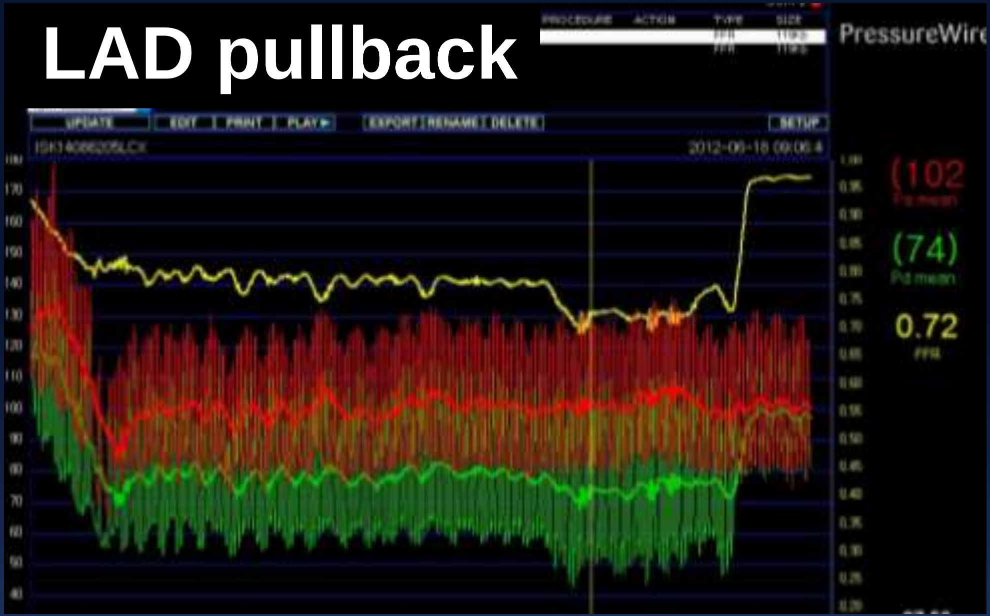
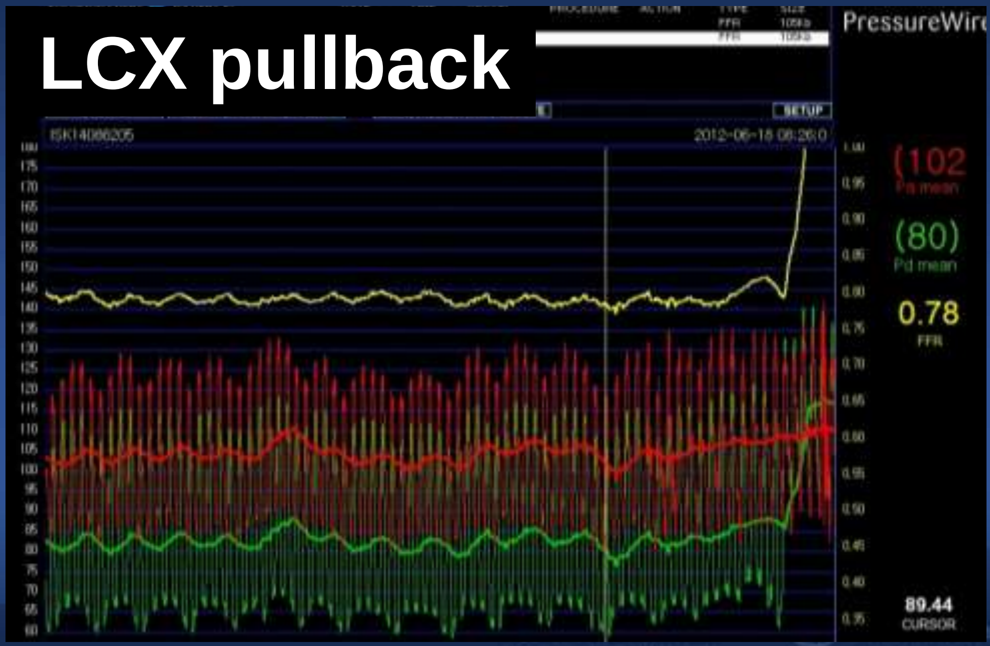
Bifurcation treated as a **'Complex'**







Definitely, Treat!

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Impact of Distal Stentosis on LM FFR

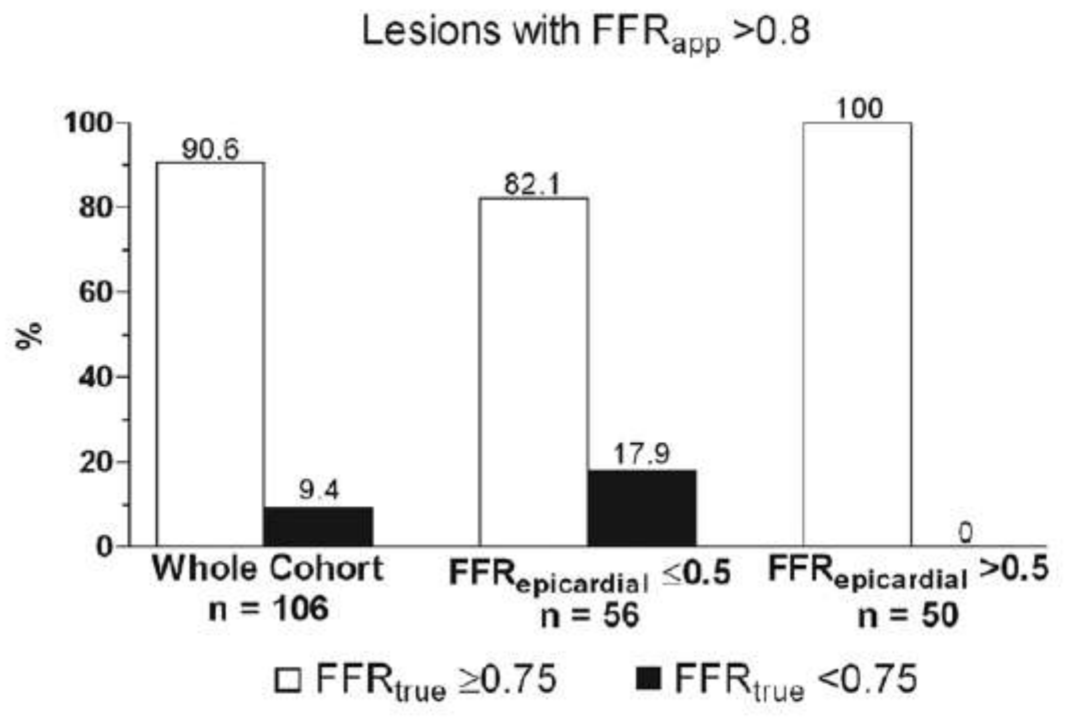


Figure 6. True fractional flow reserve (FFR_{true}) in instances where FFR_{app} >0.8.

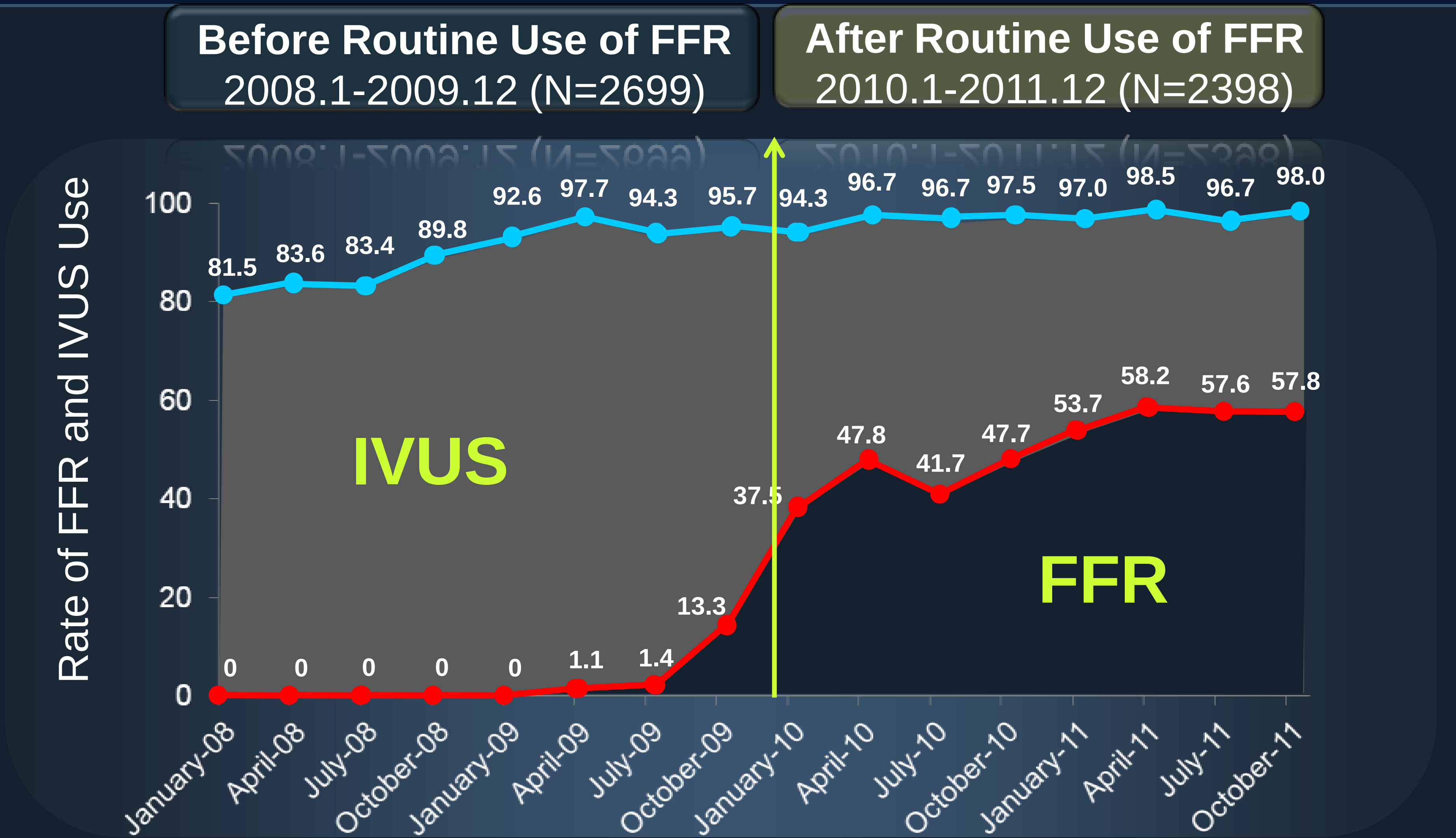
Clinically relevant effect of distal LAD stenosis on LM-FFR occurs only when the stenosis is proximal and very severe (composite FFR of LM and LAD stenosis <0.5)

Yong et al. Circ Cardiovasc Interv 2013;6:161-5

SB Optimization

After Single Stent Cross-Over

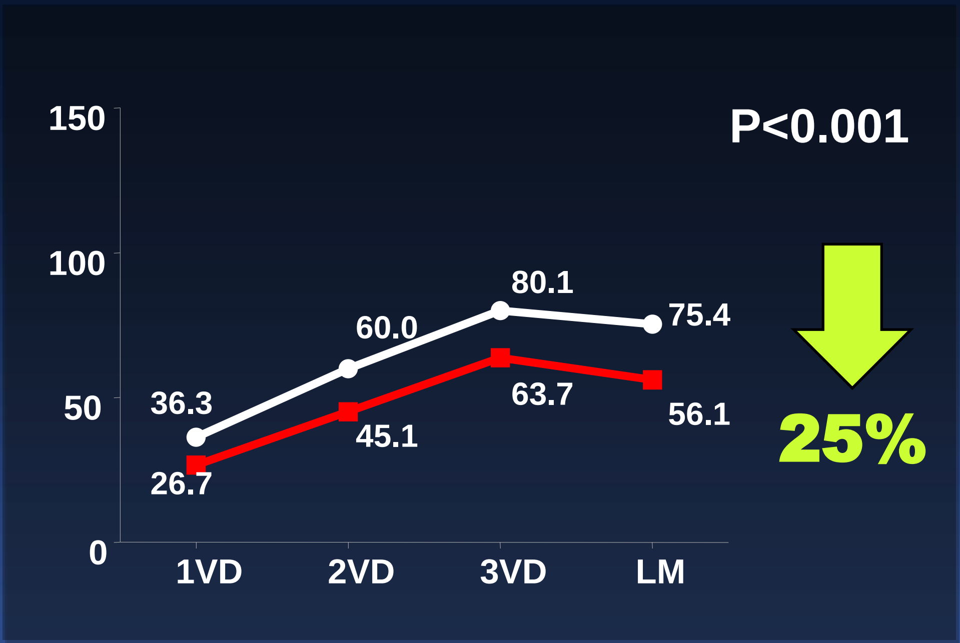
Impact of Routine Use of FFR on PCI Outcomes



Park et al. EHJ 2013;34:3353-61

Impact of Routine Use of FFR on PCI Outcomes

Stent Length (mm)



Stent Number

- Before Routine Use of FFR
- After Routine Use of FFR

Park et al. Eur heart J 2013;34:3353-61

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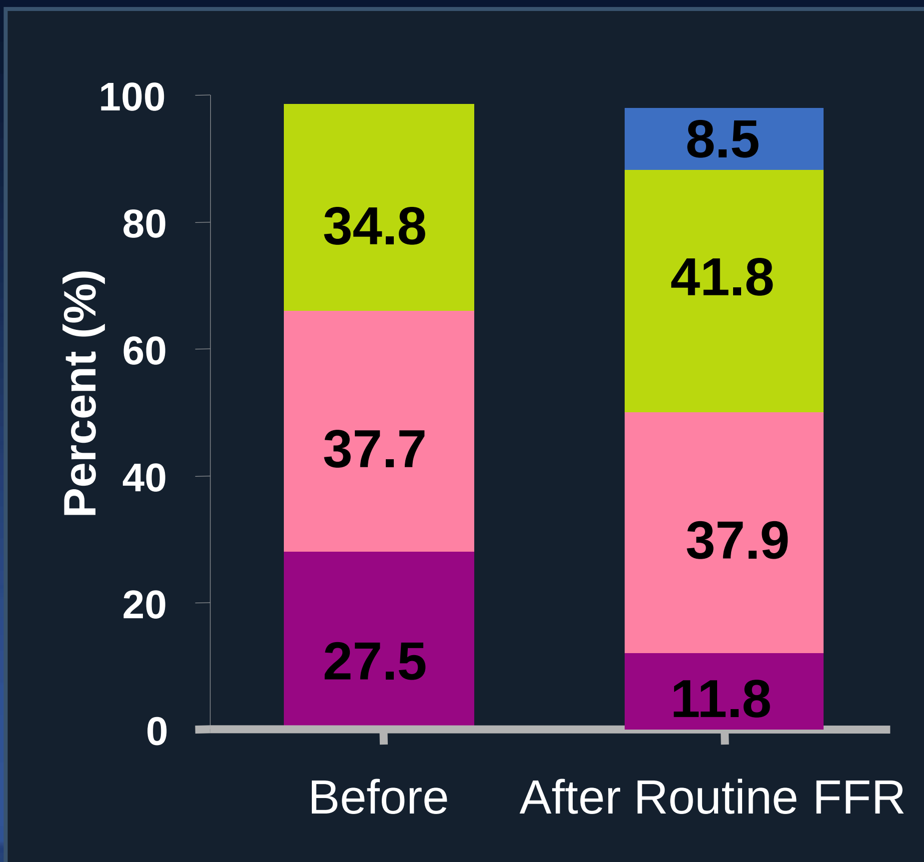
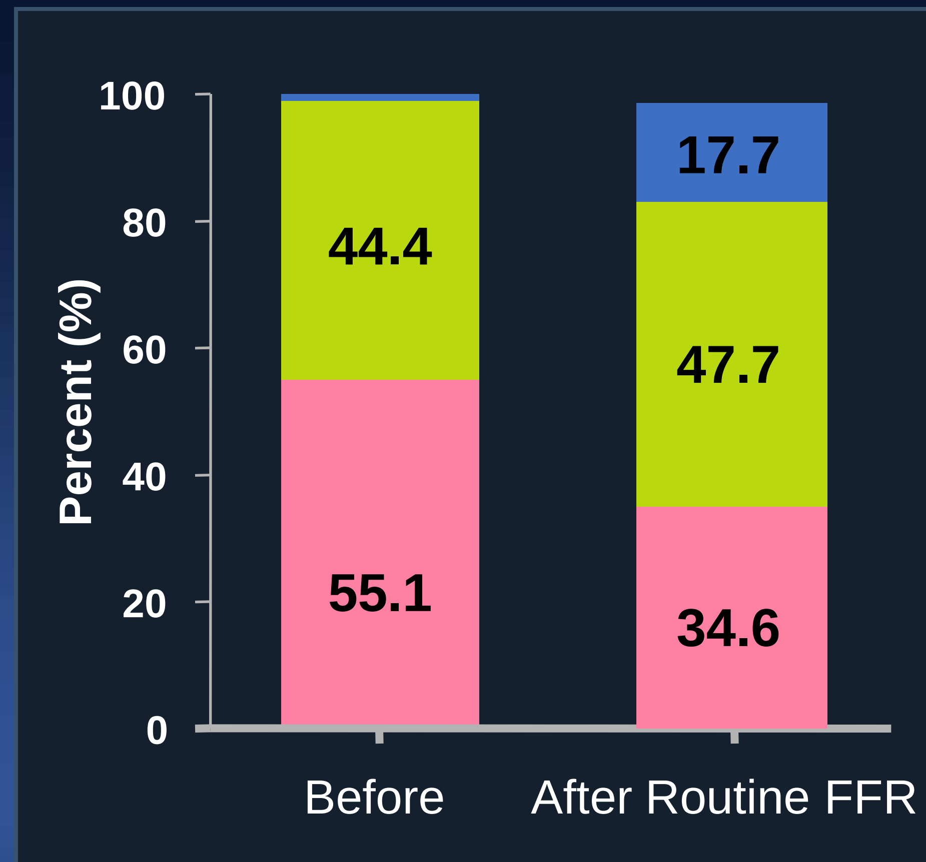
Routine Use of FFR

0 vessel treated
1 vessel treated
2 vessel treated
3 vessel treated

Three Vessel Disease



Two Vessel Disease



Park et al. Eur heart J 2013;34:3353-61

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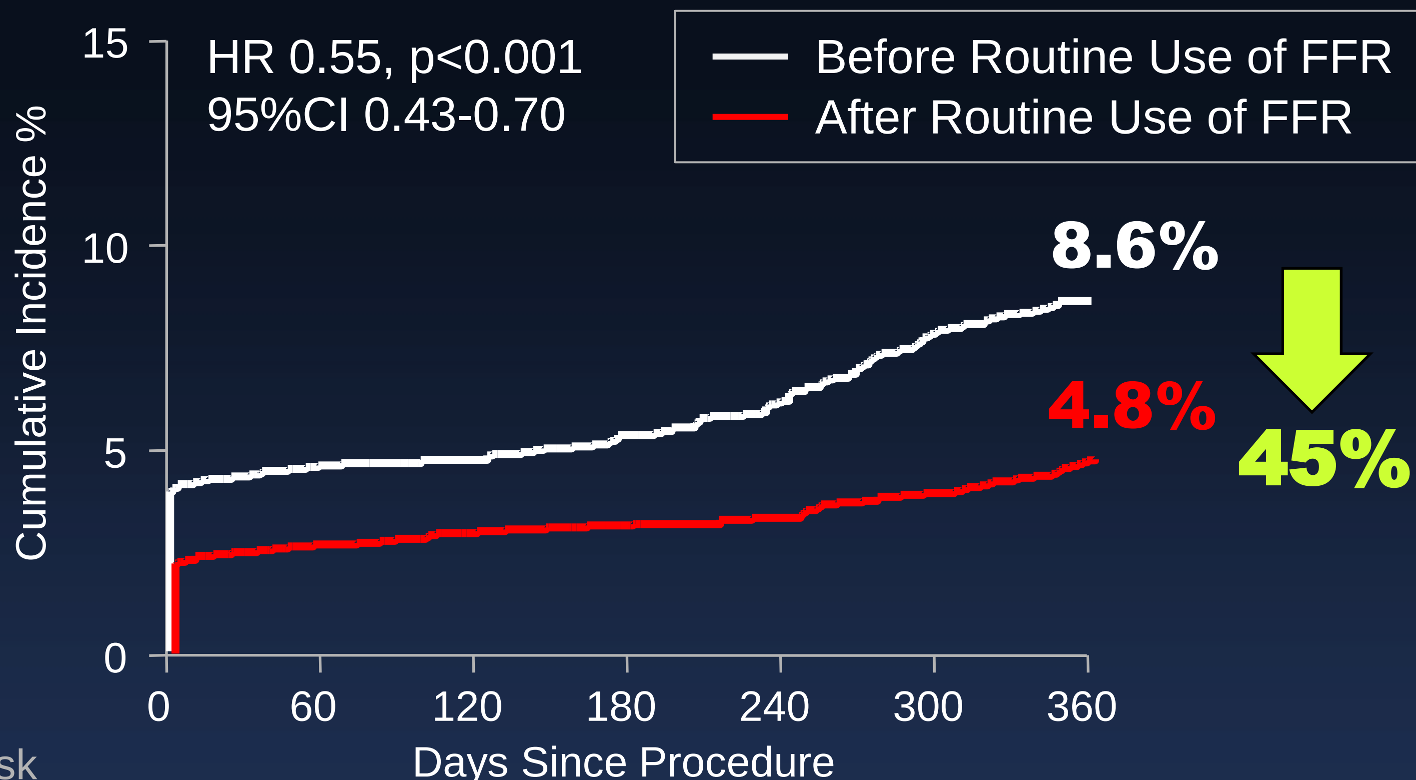
Impact of Routine Use of FFR
Primary Endpoint
(Death, MI, Repeat Revascularization)



No. at Risk				
Before Use	2178	2066	2011	1960
After Use	2178	2092	2067	2037

Park et al. Eur heart J 2013;34:3353-61

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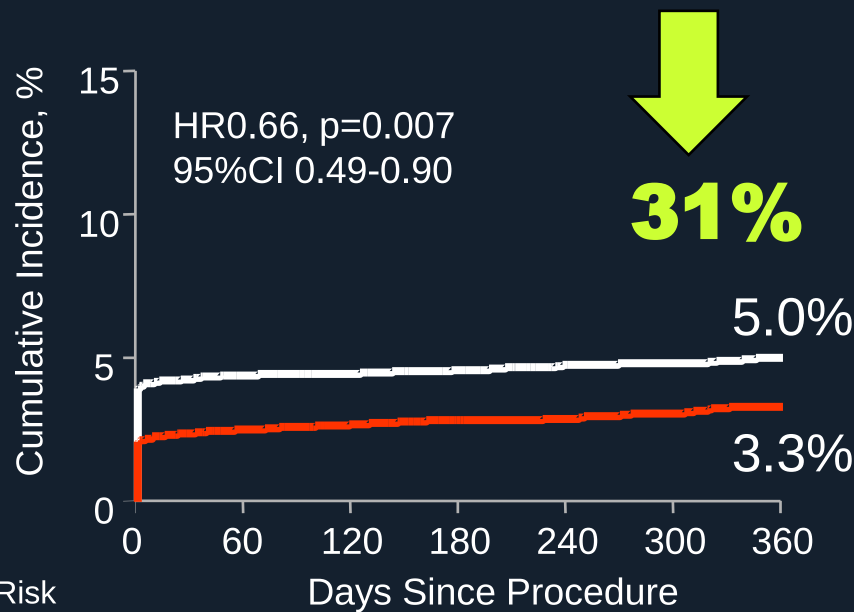
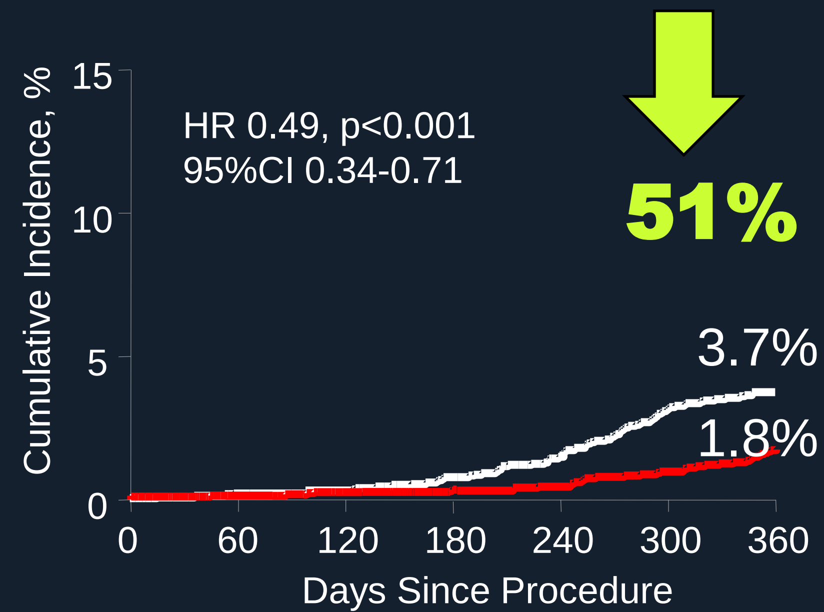
Impact of Routine Use of FFR

Death, MI



No. at Risk				
Before Use	2178	2071	2041	2036
After Use	2178	2098	2075	2066

Repeat Revascularization



Before Use	2178	2151	2095	2048
After Use	2178	2136	2110	2083

— Before Routine Use of FFR
— After Routine Use of FFR

Park et al. Eur heart J 2013;34:3353-61

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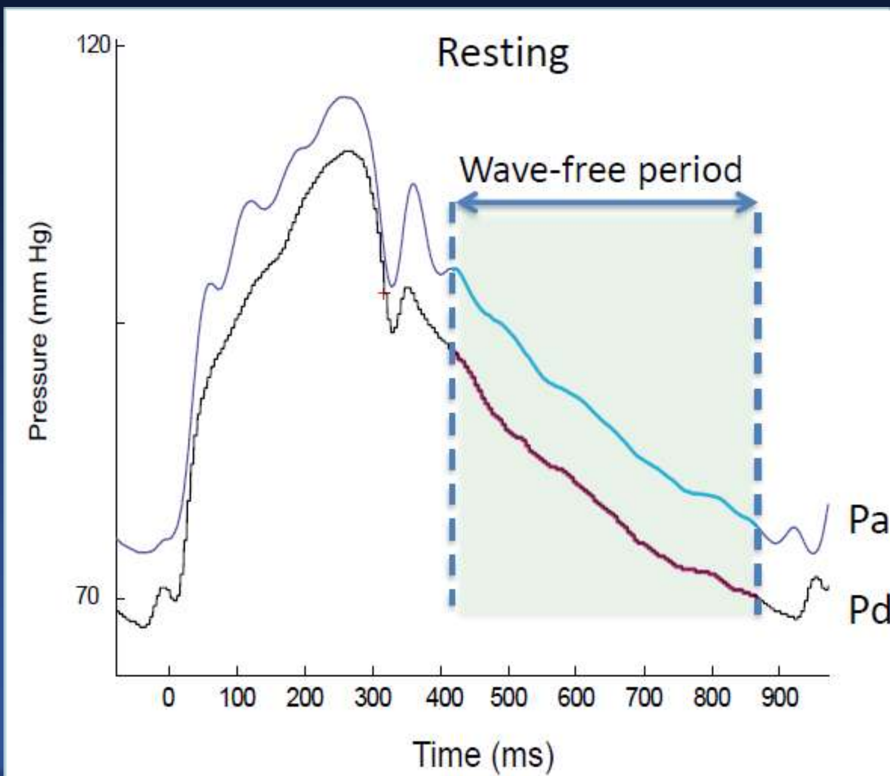
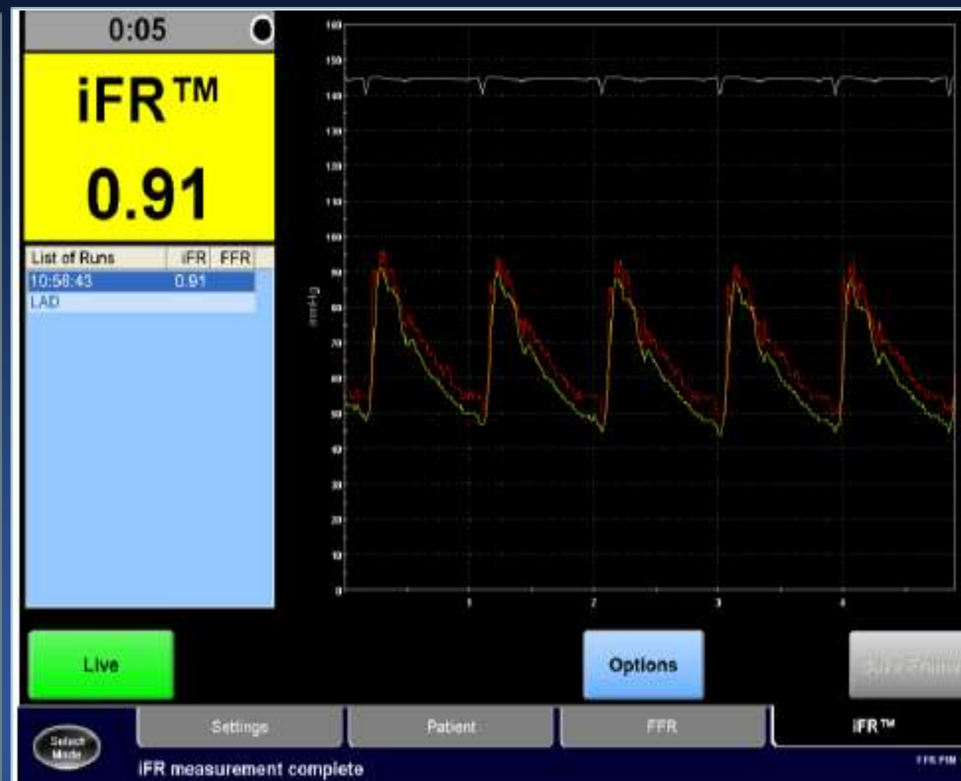
Instantaneous Wave-free Ratio (iFR)

Instantaneous Wave-free Ratio

- Adenosine-free index, the instantaneous PG across stenosis
- By physiologically increased diastolic flow, resting myocardial resistance may equal mean hyperemic resistance





Sen et al. JACC 2012

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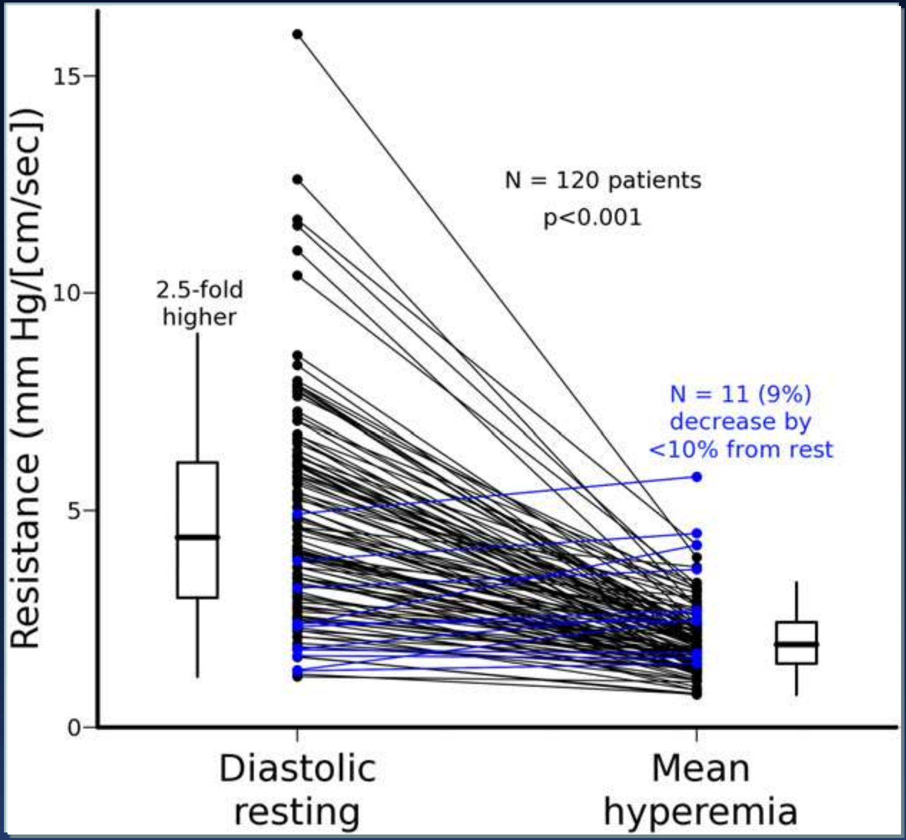
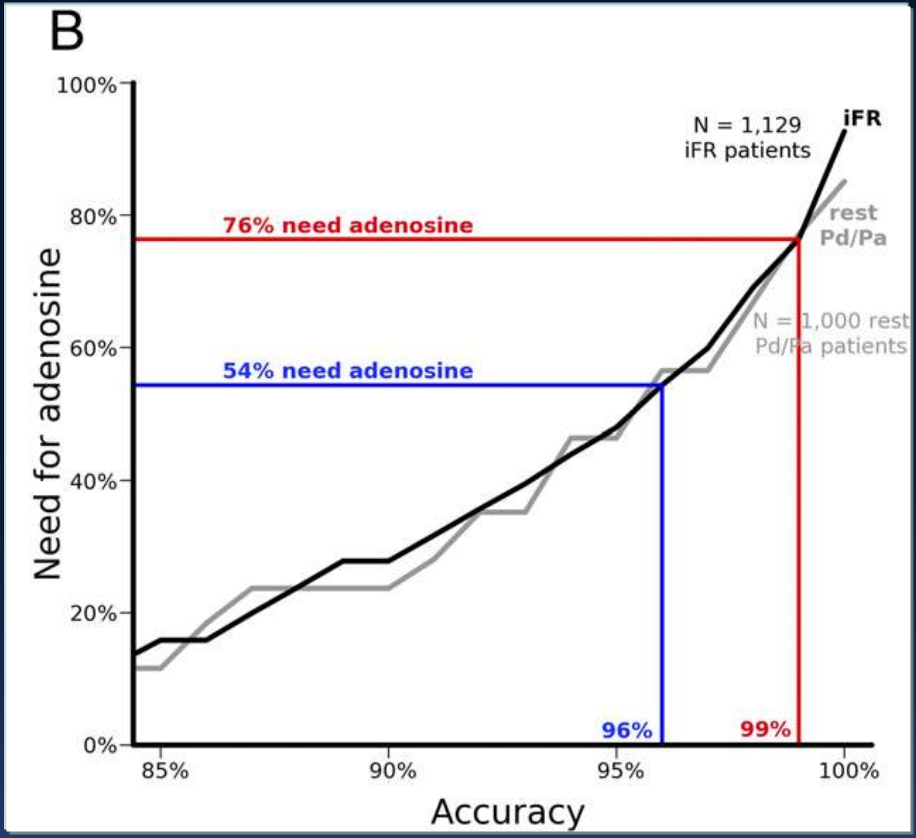
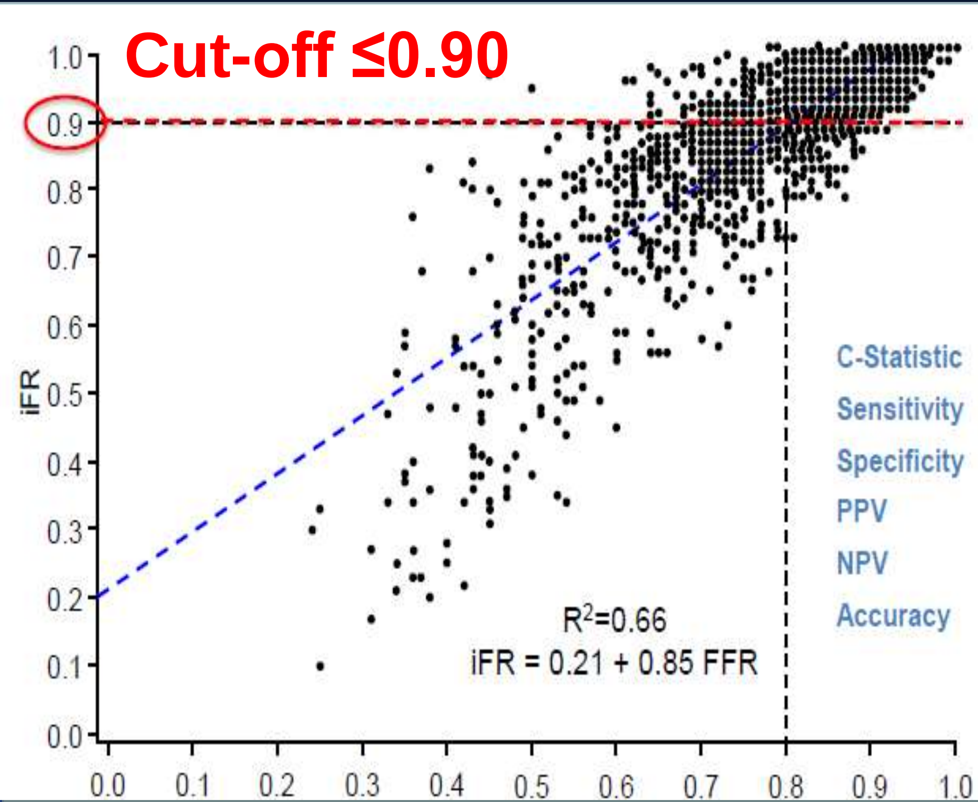




- Diastolic resting resistance consistently exceeds mean hyperemic resistance (on average 2.5 times higher)
- iFR rarely improves the accuracy compared to rest Pd/Pa (relative distal pressure averaged over the whole cycle)
- iFR offers a biased estimate of FFR

Johnson et al. J Am Coll Cardiol 2013;61:1428–35

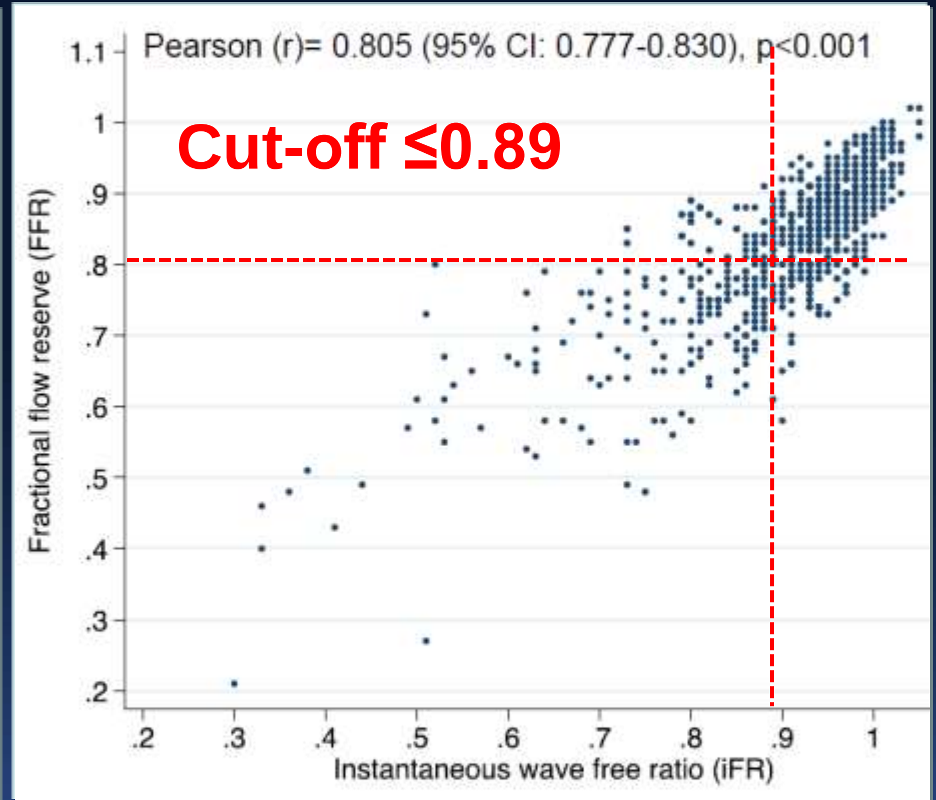
RESOLVE



Sensitivity 78%
Specificity 82%
Positive PV 85%
Negative PV 73%
Accuracy 80%

Jeremias et al. J Am Coll Cardiol 2013 in press

ADVISE II



Sensitivity 73%
Specificity 87%
Positive PV 77%
Negative PV 85%
Accuracy 82%

Escaned et al.
ClinicalTrials.gov NCT01740895

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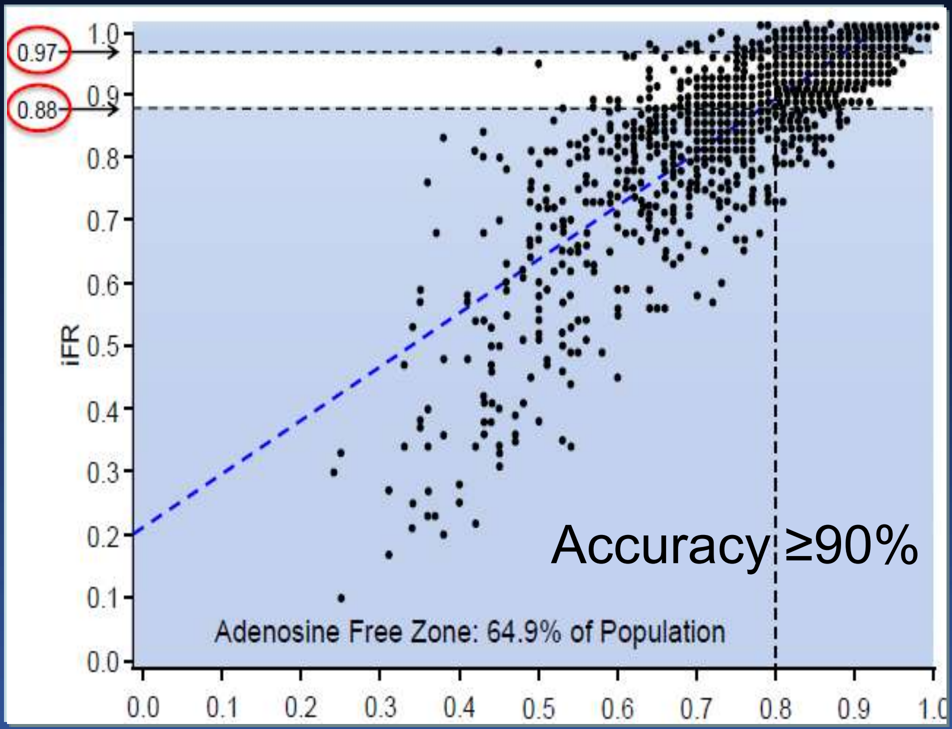
Hybrid iFR/FFR Approach

RESOLVE

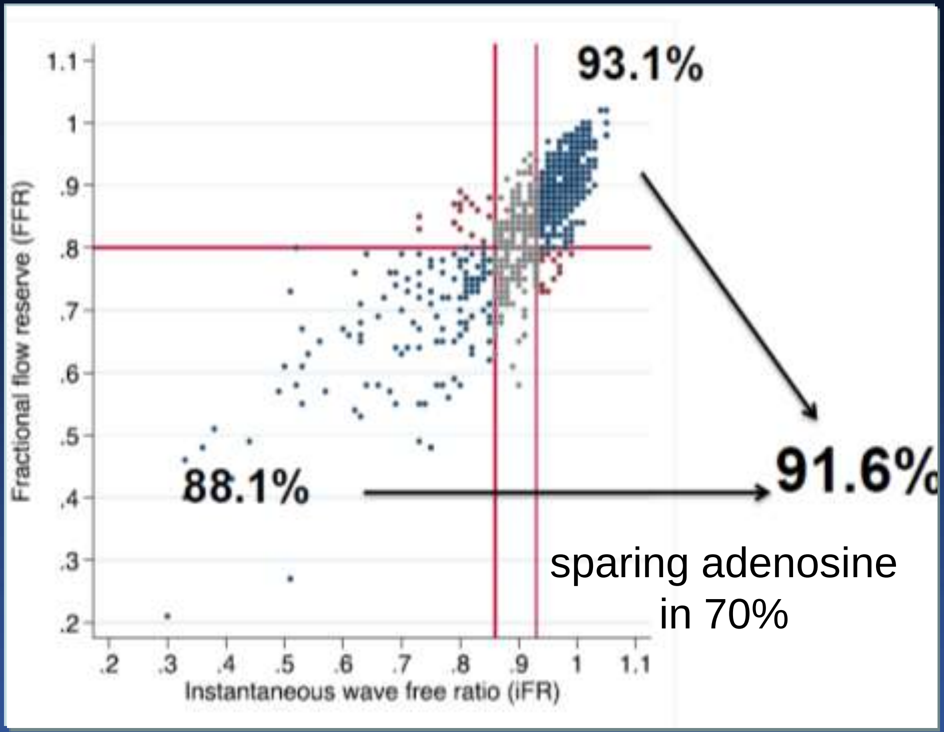
Adenosine requiring range
iFR 0.88-0.97



Jeremias et al. J Am Coll Cardiol 2013 in press

ADVISE II

Adenosine requiring range
iFR 0.86-0.93



Escaned et al.
ClinicalTrials.gov NCT01740895

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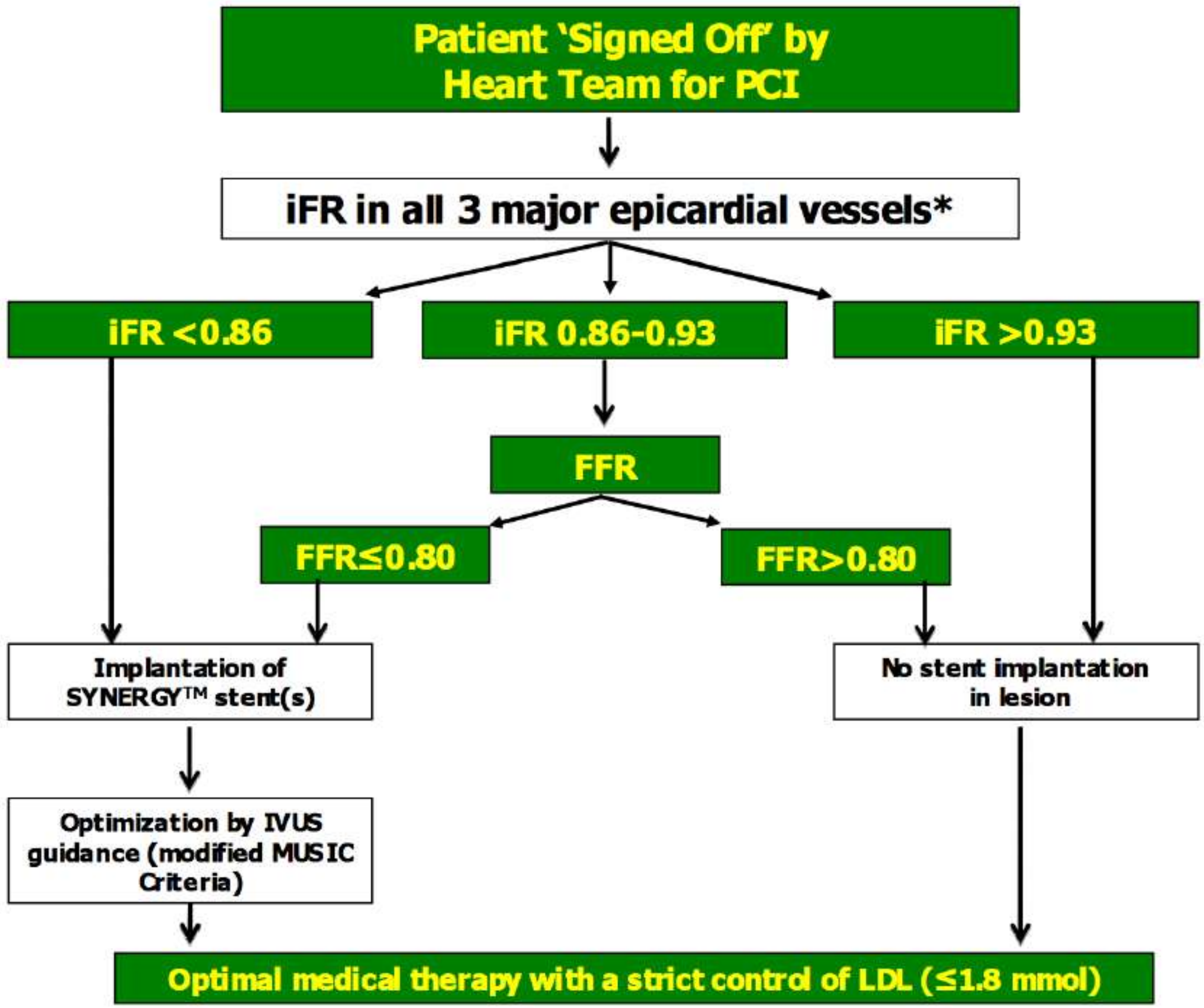
iFR Clinical Implementation SYNTAX II



***FFR with adenosine, iFR/FFR in side branches, all at discretion of the operator**

Serruys P et al. EUROPCR 2013

Summary

- FFR is a gold standard to assess ischemia and cannot be replaced by any single IVUS parameter
- FFR-guided PCI improves clinical outcomes
- Despite the fundamental pitfall of iFR (flow≠ pressure without maximal hyperemia), hybrid iFR /FFR approach increases the accuracy >90%, sparing adenosine use in >60%. Outcome studies will show if the approach is clinically feasible

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