Visual-Functional Mismatch: FFR, Not CAG, Has Prognostic Value!!

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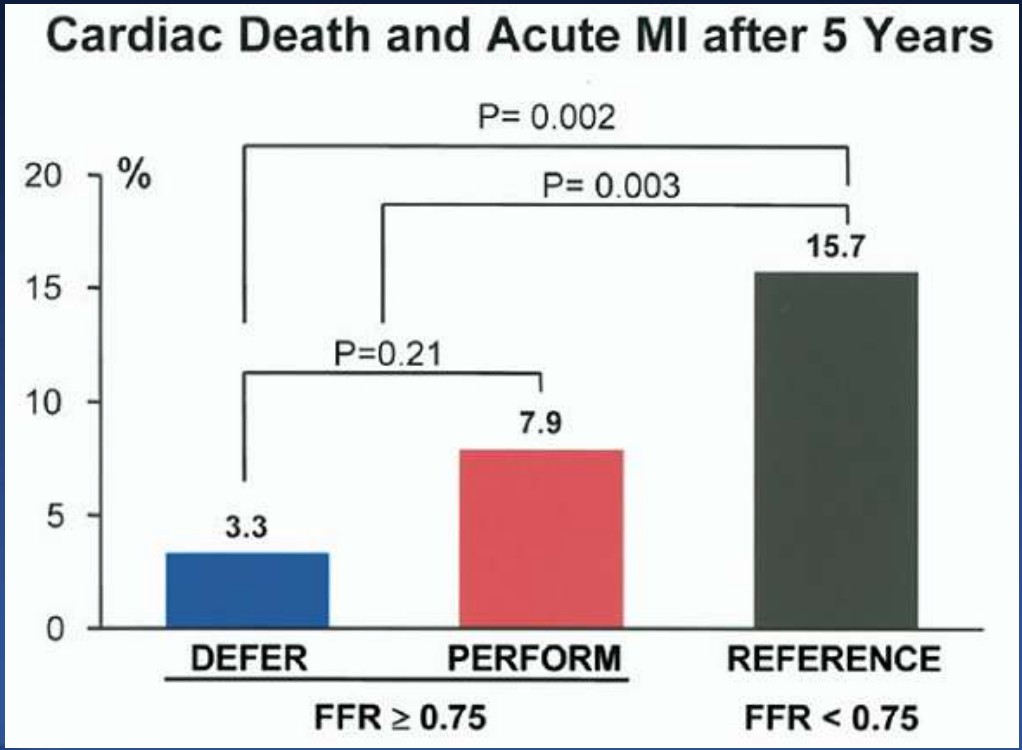
Disclosure Statement of Financial Interest

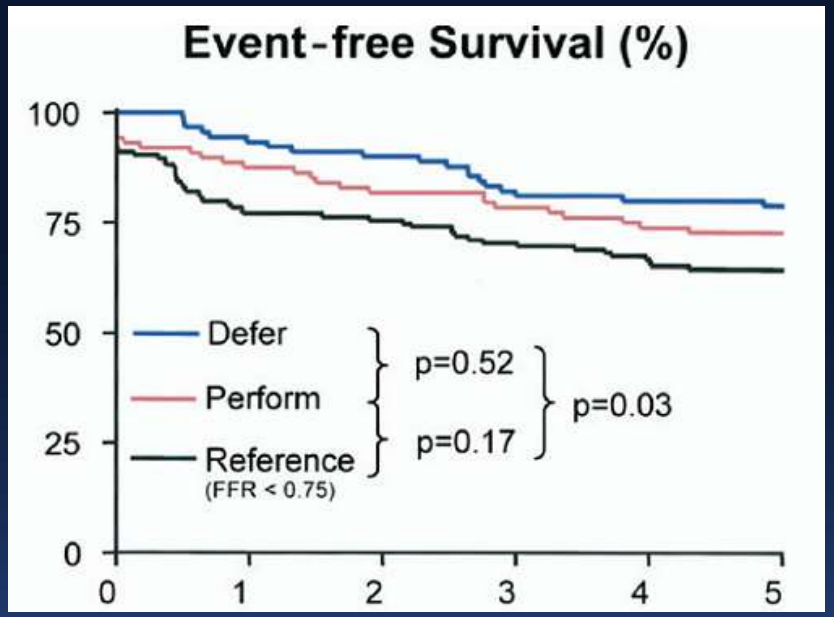
I, Soo-Jin Kang DO NOT have a financial interest /arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

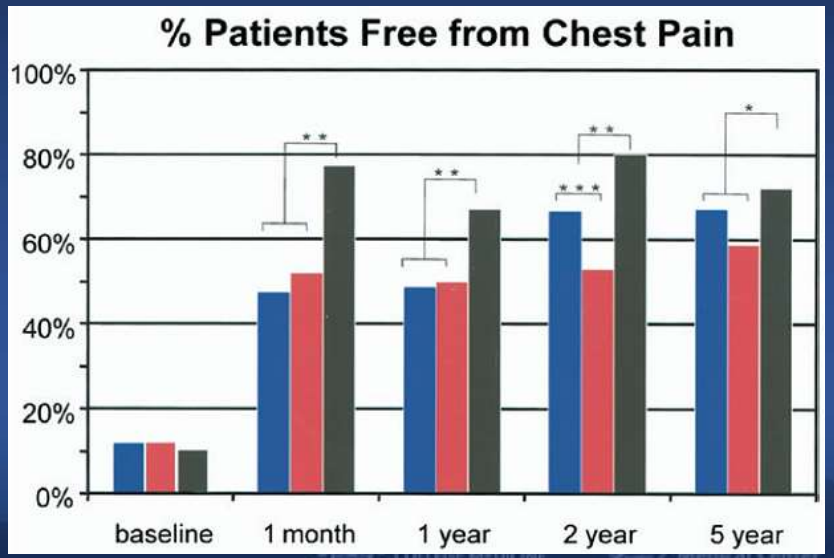
DEFER Trial

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)

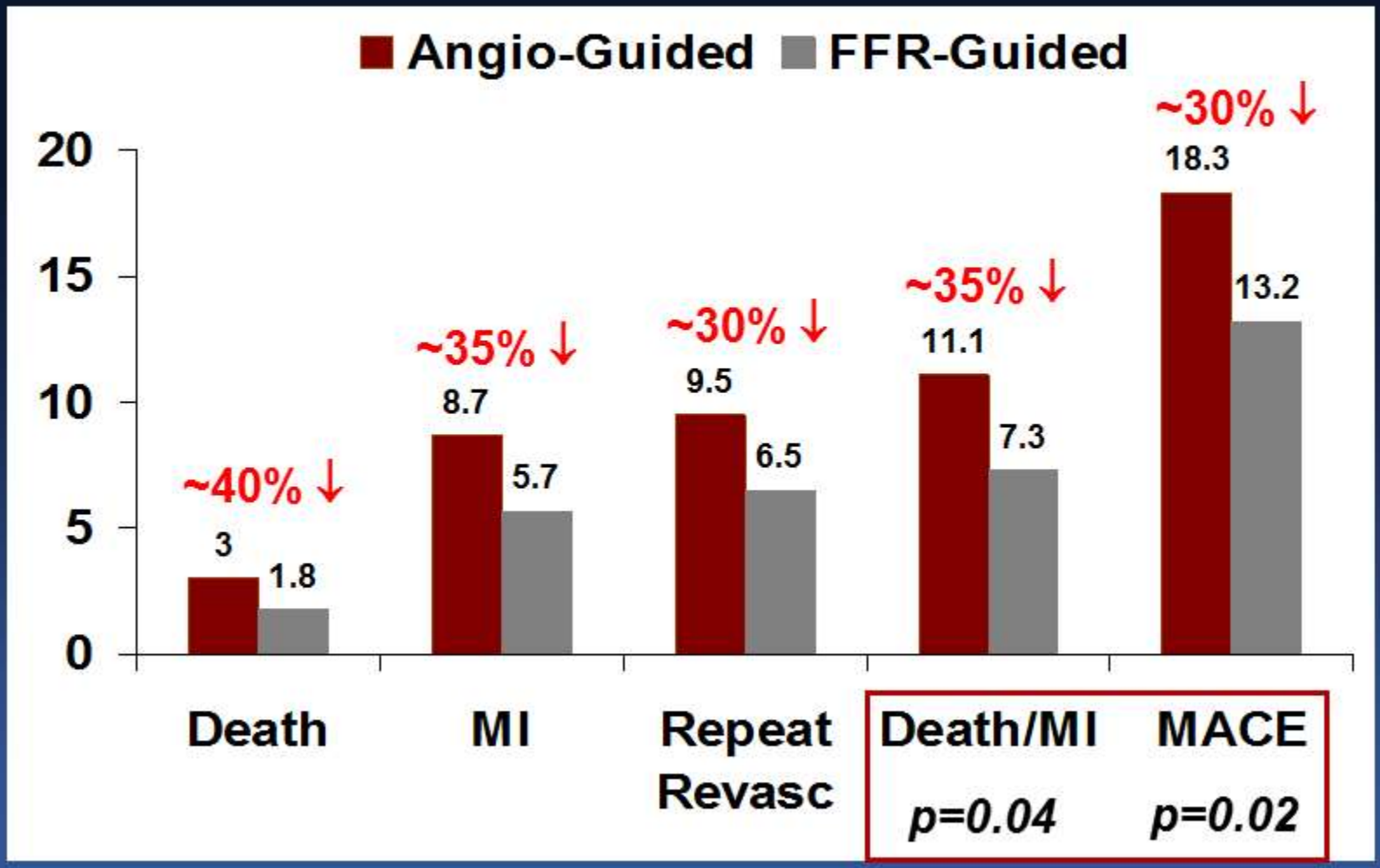






J Am Coll Cardiol 2007;49:2105–11

FAME: One Year Outcomes

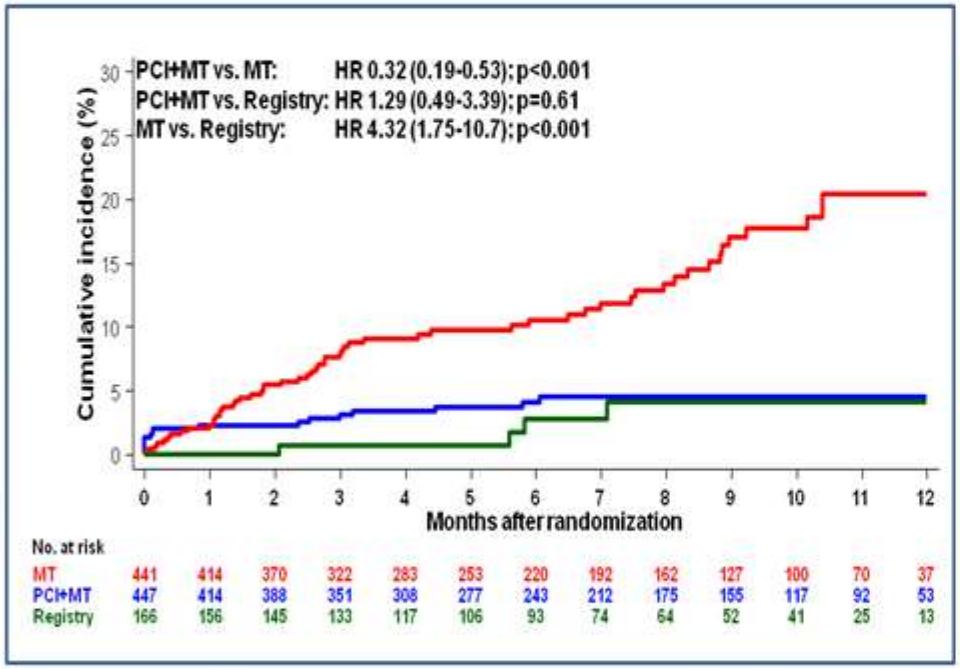


Tonino et al. New Engl J Med 2009;360:213-24

FAME 2

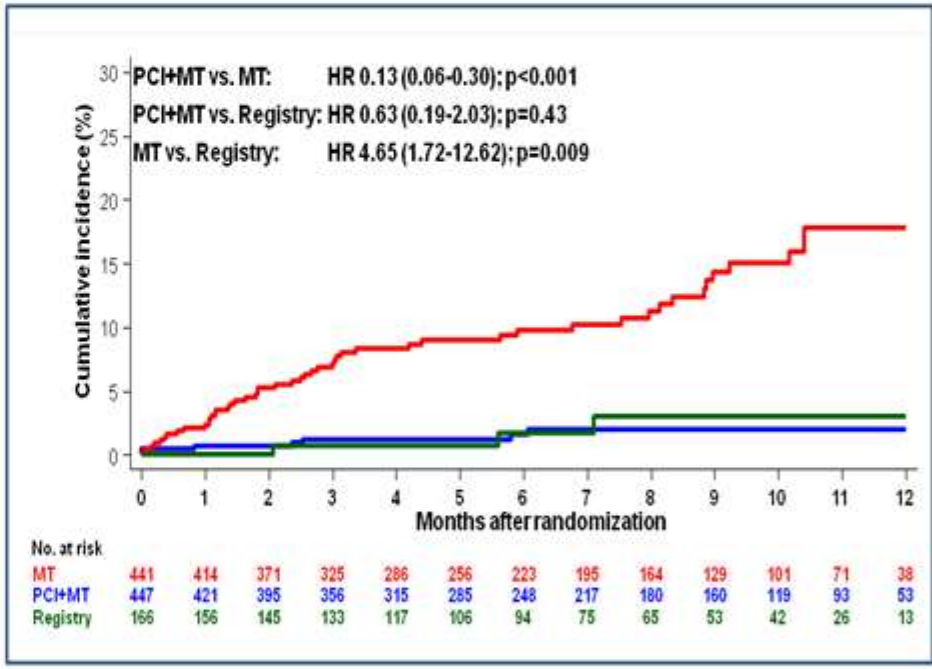
FFR-Guided PCI vs. Medical Therapy in Stable CAD

Primary Outcomes



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

Urgent Revascularization



Deferral vs. performance of percutaneous coronary intervention of functionally non-significant coronary stenosis: 15-year follow-up of the DEFER trial

Frederik M. Zimmermann[1], Angela Ferrara[2], Nils P. Johnson[3], Lokien X. van Nunen[1,4], Javier Escaned[5], Per Albertsson[6], Raimund Erbel[7], Victor Legrand[8], Hyeong-Cheol Gwon[9], Wouter S. Remkes[10], Pieter R. Stella[11], Pepijn van Schaardenburgh[12], G. Jan Willem Bech[13,14], Bernard De Bruyne[2], and Nico H.J. Pijls[1,4*]

	Defer	Perform	Reference	P (Defer vs. Perform)
Death at 15 years	30 (33.0%)	28 (31.1%)	52 (36.1%)	0.78
MI at 15 years	2 (2.2%)	9 (10.0%)	18 (12.5%)	0.033
TVR at 15 years	33 (36.3%)	25 (27.8%)	51 (35.4%)	0.22

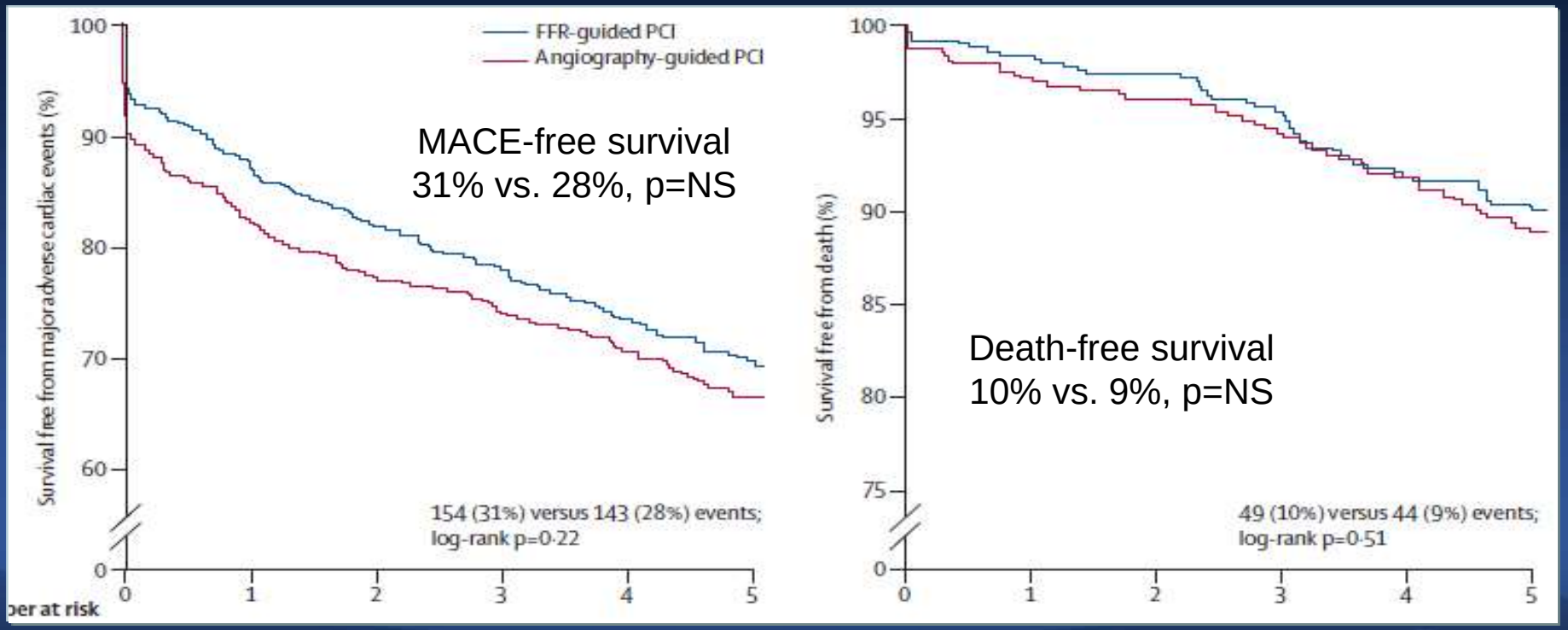
Deferral of PCI of a functionally insignificant lesion is associated with a favorable very long-term outcomes without late ‘catch-up’

Simmermann et al. Eur Heart J 2015 in press

Fractional flow reserve versus angiography for guidance of PCI in patients with multivessel coronary artery disease (FAME): 5-year follow-up of a randomised controlled trial

Lokien X van Nunen, Frederik M Zimmermann*, Pim A L Tonino, Emanuele Barbato, Andreas Baumbach, Thomas Engstrøm, Volker Klauss, Philip A MacCarthy, Ganesh Manoharan, Keith G Oldroyd, Peter N Ver Lee, Marcel van't Veer, William F Fearon, Bernard De Bruyne, Nico H J Pijls, for the FAME Study Investigators*

Long-term safety of FFR-guided PCI that should be the standard of care in multivessel disease



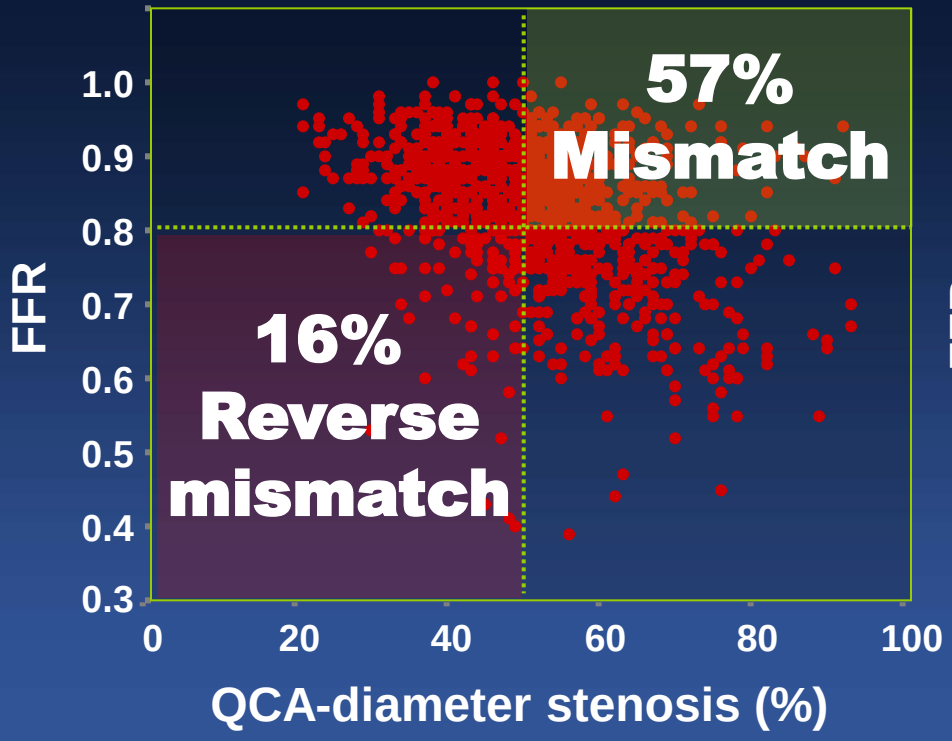
Van Nunen et al. Lancet 2015; 386: 1853–60

Visual-Functional Mismatch

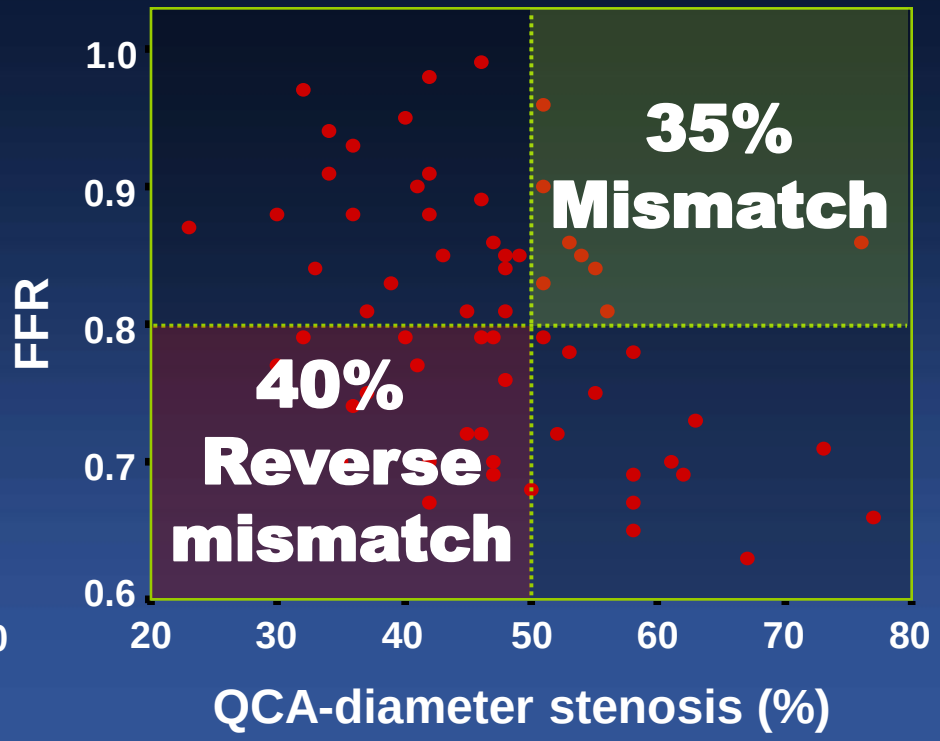
(1129 lesions with DS >30%) who underwent IVUS and FFR

IRIS-FFR ClinicalTrials.gov NCT01366404

1066 Non-LM lesions



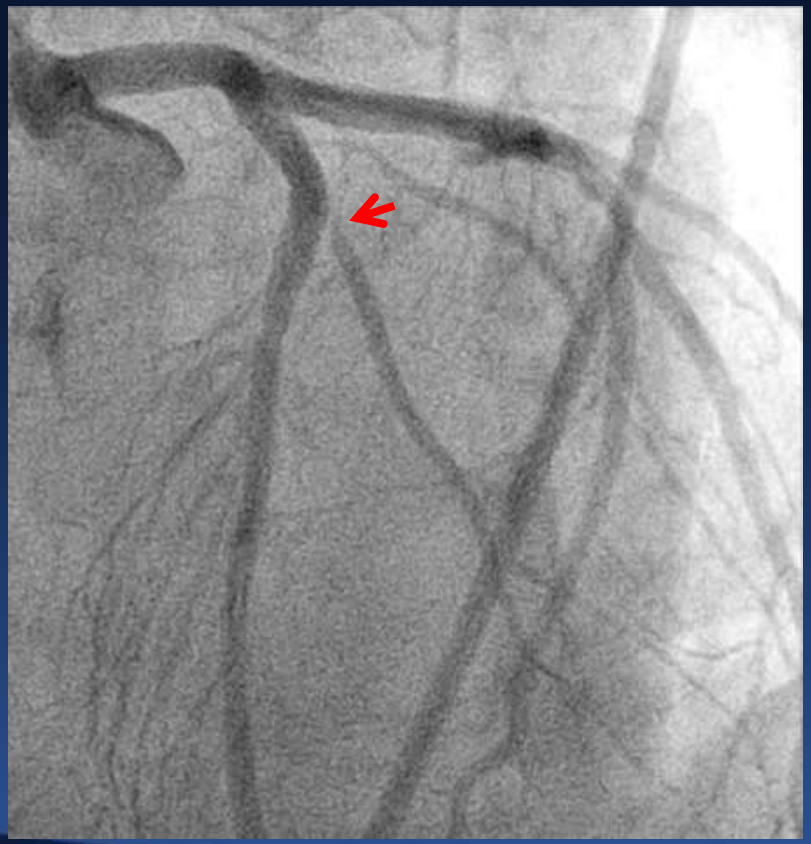
63 LM lesions

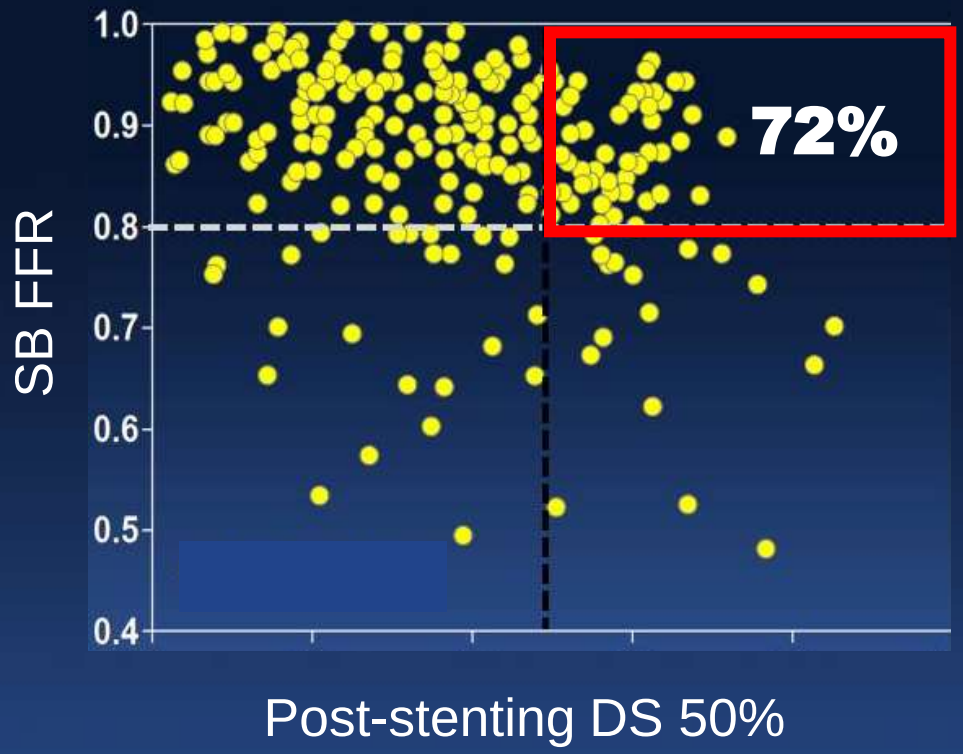


Park et al. JACC interv 2012;5:1029-36

Visual-Functional Mismatch
SB Stenosis

Jailed SB FFR 0.88



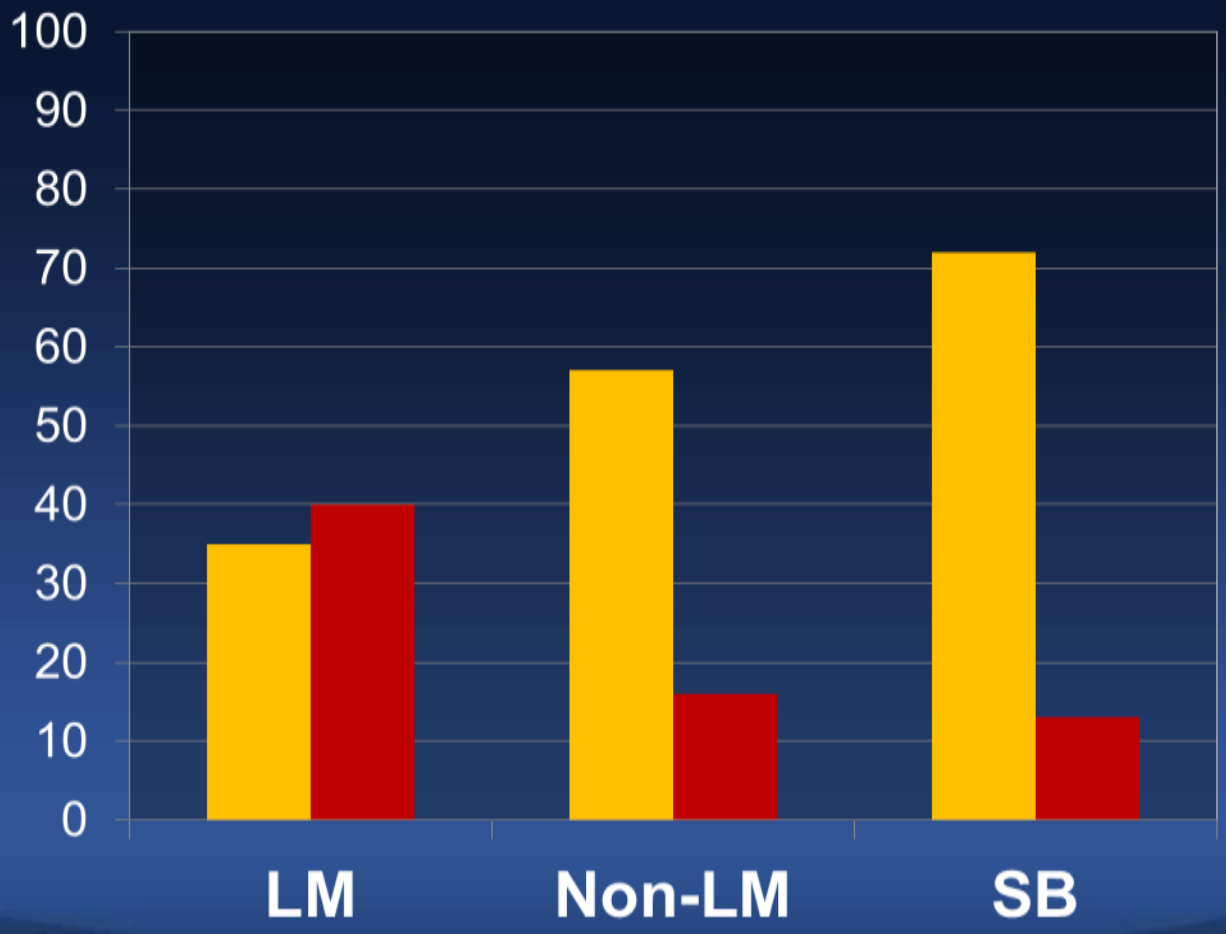


Ahn et al. JACC Interv 2012;5:155-61

Frequency of QCA-FFR Mismatch

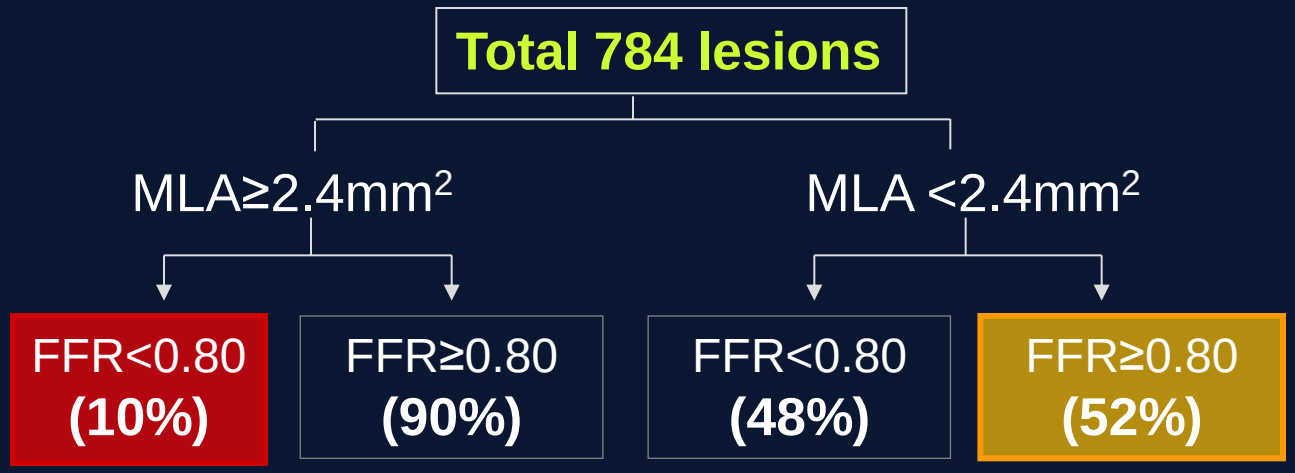
Mismatch: QCA-DS>50%, FFR≥0.80

Reverse-mismatch: QCA-DS≤50%, FFR<0.80



IVUS-FFR Mismatch

	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%**



	p-value	Adjusted OR	95% CI
MLA<2.4 *but* FFR≥0.8 *"Mismatch"*			
Women	0.048	1.450	1.003 – 2.095
LAD location	0.027	0.666	0.465 – 0.954
Reference lumen diameter	<0.001	0.298	0.204 – 0.437
Distal (vs. proximal) segment	0.002	2.021	1.293 – 3.159
MLA≥2.4 *but* FFR<0.8 *"Rev-mismatch"*			
Age	<0.001	0.940	0.909 – 0.972
LAD location	0.071	2.256	0.932 – 5.460
Plaque rupture	<0.001	11.138	4.886 – 25.39

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

Subgroup-specific MLA

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%

Why Mismatch

(1129 lesions with DS >30%) who underwent 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

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

Multivariable Analysis Predicting FFR

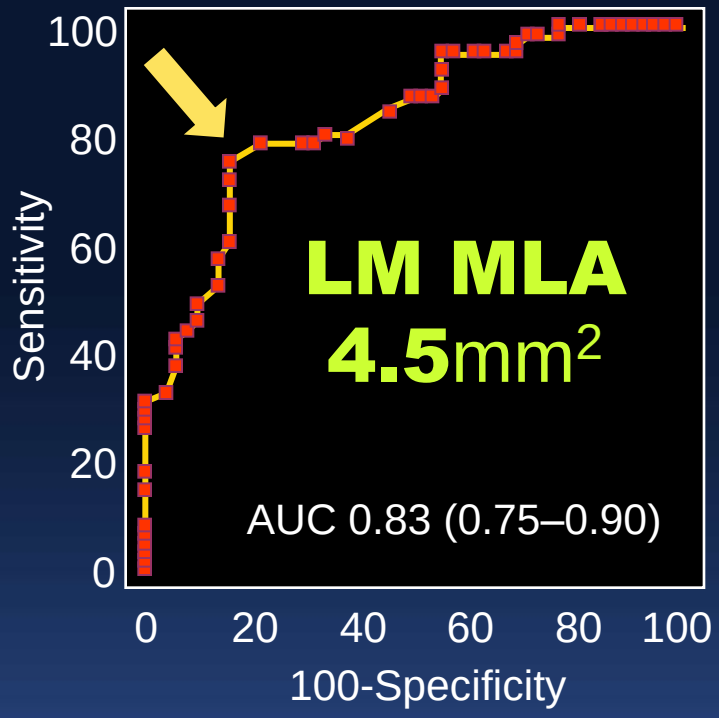
in 700 LAD lesions of 700 patients

**Including age, female, body surface area, smoking, angiographic DS, minimal lumen diameter, lesion length, IVUS-MLA, plaque burden, averaged reference EEM area and %area stenosis, †addition of left ventricular mass*

	Total (700 patients)*			608 patients with echo data†		
	ß	p value	95% CI	ß	p value	95% CI
Age	0.119	0.001	0.000–0.002	0.192	<0.001	0.001–0.002
BSA	**-0.111**	**0.002**	-0.101– -0.024			
LV mass				**-0.121**	**<0.001**	-0.001 – 0.000
Angiographic DS	-0.185	<0.001	-0.002 – -0.001	-0.190	<0.001	-0.002 – -0.002
Lesion length	-0.110	0.001	-0.001 – 0.001	-0.077	0.027	-0.001 – 0.000
IVUS-MLA	0.312	<0.001	0.022 – 0.035	0.294	<0.001	0.019 – 0.032
Plaque burden	-0.115	0.002	0.001 – 0.000	-0.157	<0.001	-0.002 – -0.001

Kang S-J et al. J Am Coll Cardiol Intv 2013;6:562-8

Independent Factors of LM FFR<0.80

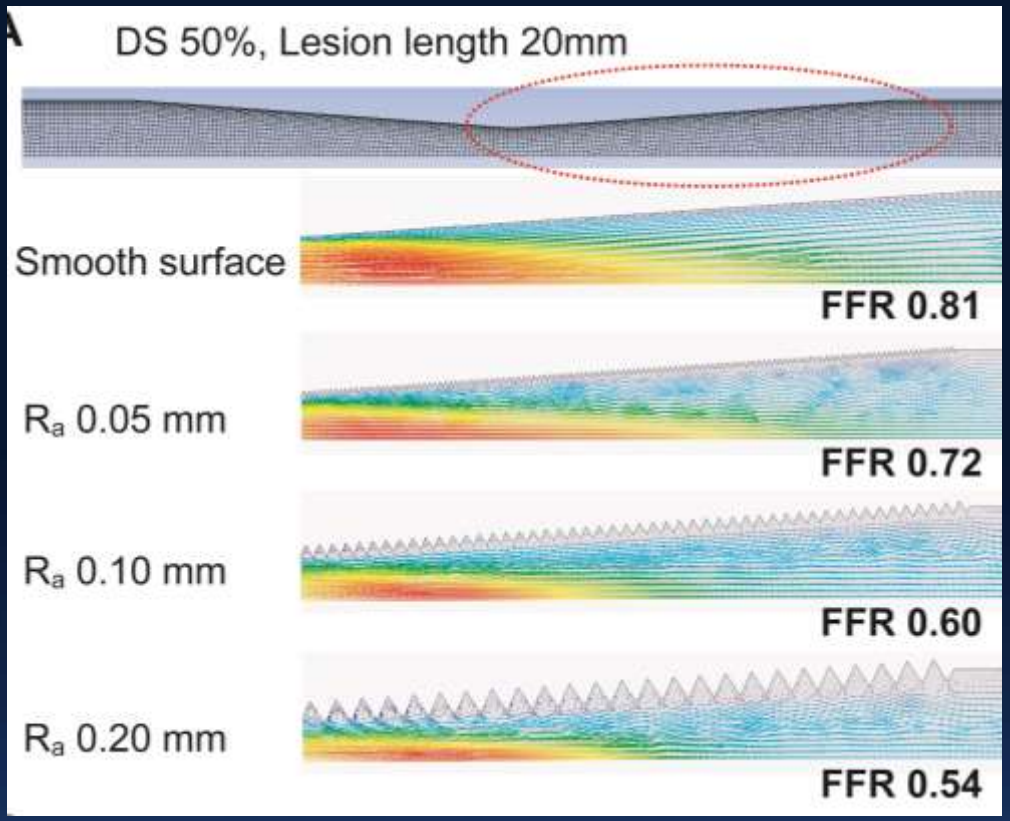


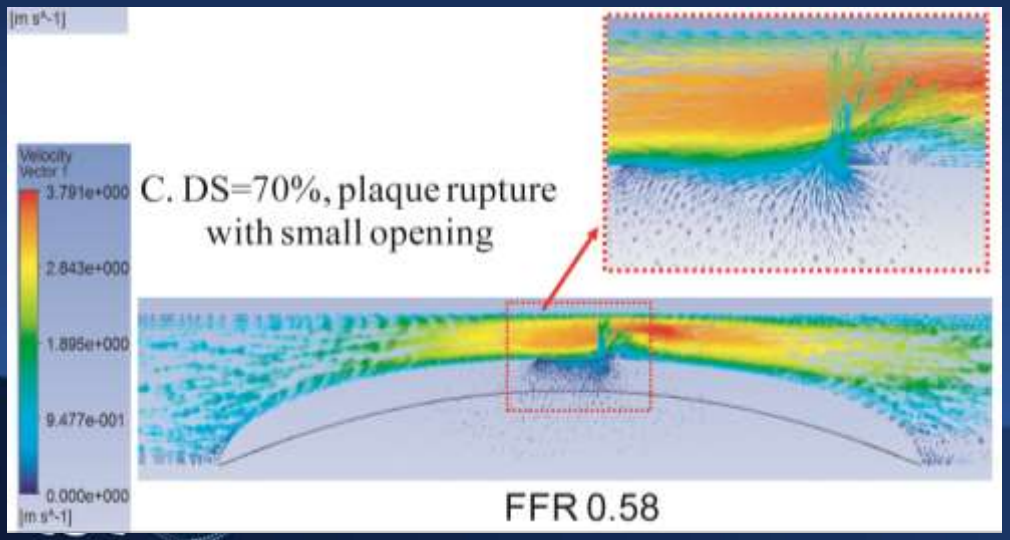
Sensitivity	79%
Specificity	80%
PPV	83%
NPV	76%

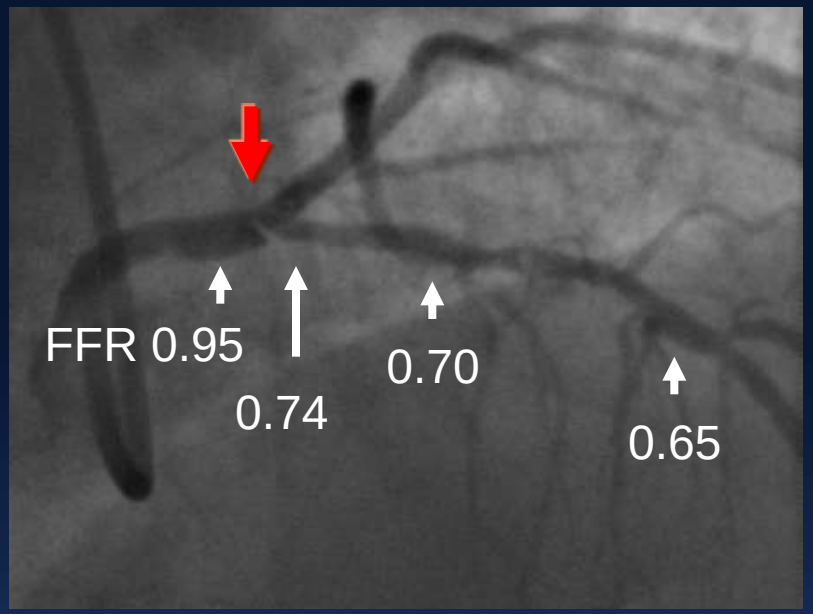
	OR	P
Model 1		
Plaque rupture	4.47	0.014
BMI, kg/m²	1.19	0.05
Age, yrs	0.95	0.031
MLA, mm²	0.37	<0.001
Model 2 *(echo-LV mass)*		
LV mass, g	1.01	0.03
Age, yrs	0.94	0.021
MLA, mm²	0.34	<0.001

Park SJ et al. JACC Interv 2014;7:868–74

Plaque Rupture







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

CARDIOVASCULAR RESEARCH FOUNDATION

Summary

Mechanisms of Visual-Functional Mismatch

Stenosis Severity

- Angiographic DS
- IVUS-MLA
- Plaque burden
- Lesion length

Local Factor

- Plaque rupture

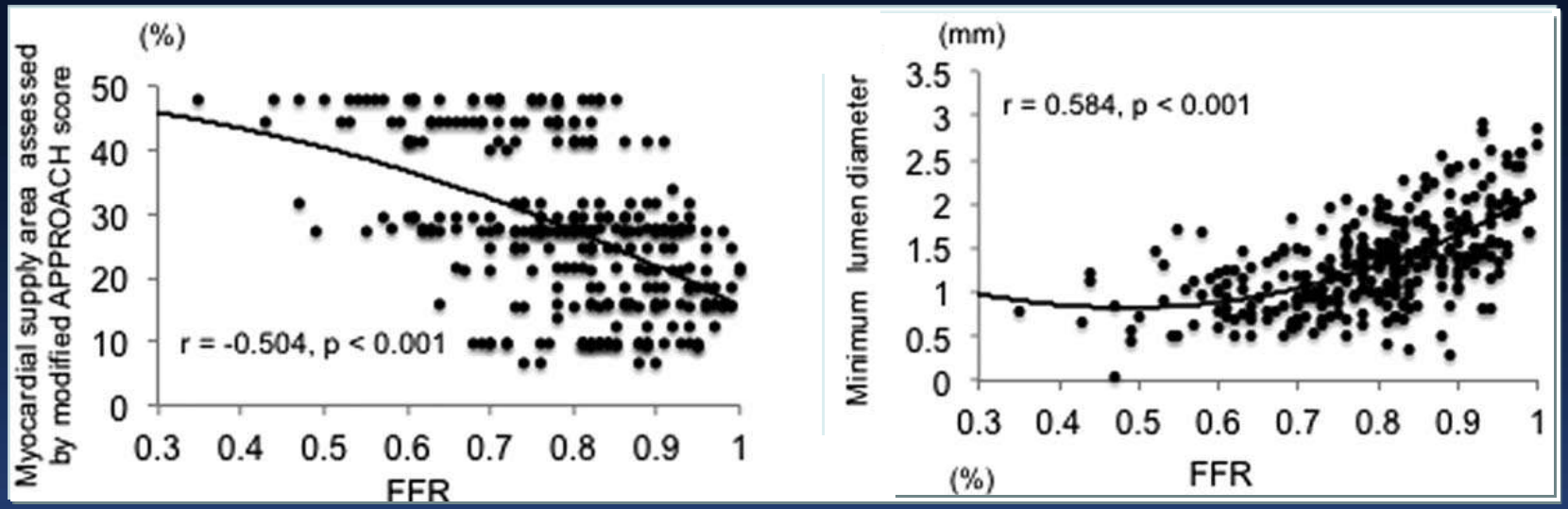
Myocardial Territory

- Age
- Gender
- LAD vs. non-LAD
- Proximal segment
- Ref vessel diameter
- Body surface area
- Body mass index
- LV mass

AMC data

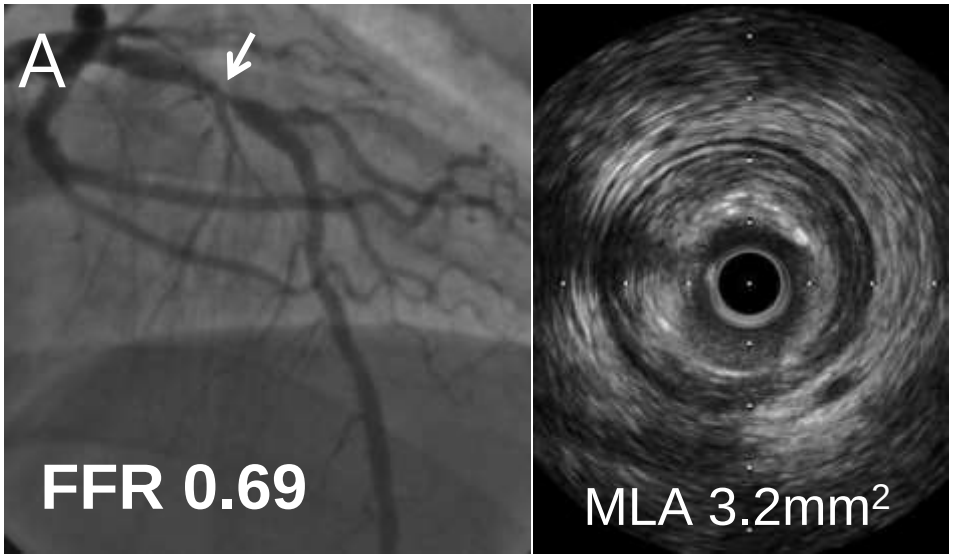
Impact of Myocardial Territory on FFR

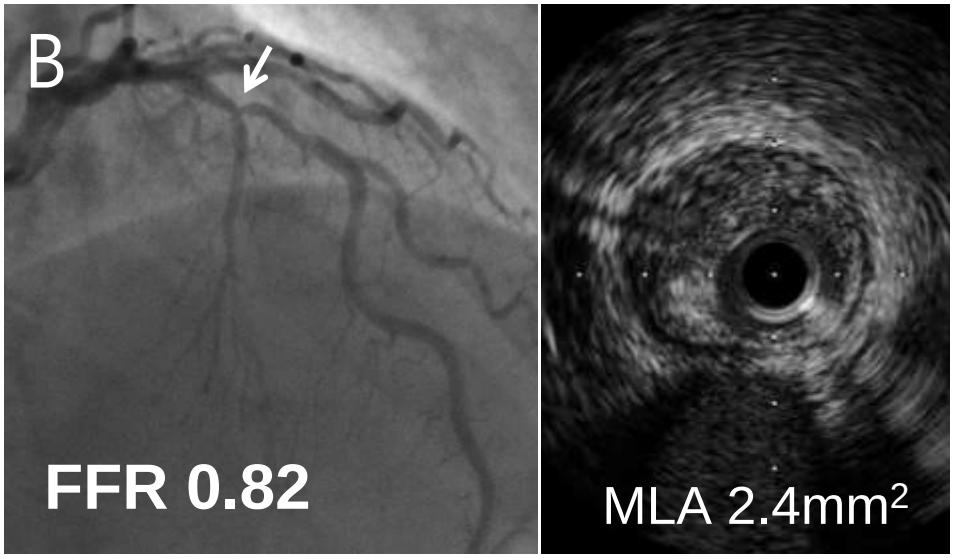
Myocardial area subtended to the artery distal to the stenosis evaluated by angiography using a modified APPROACH score

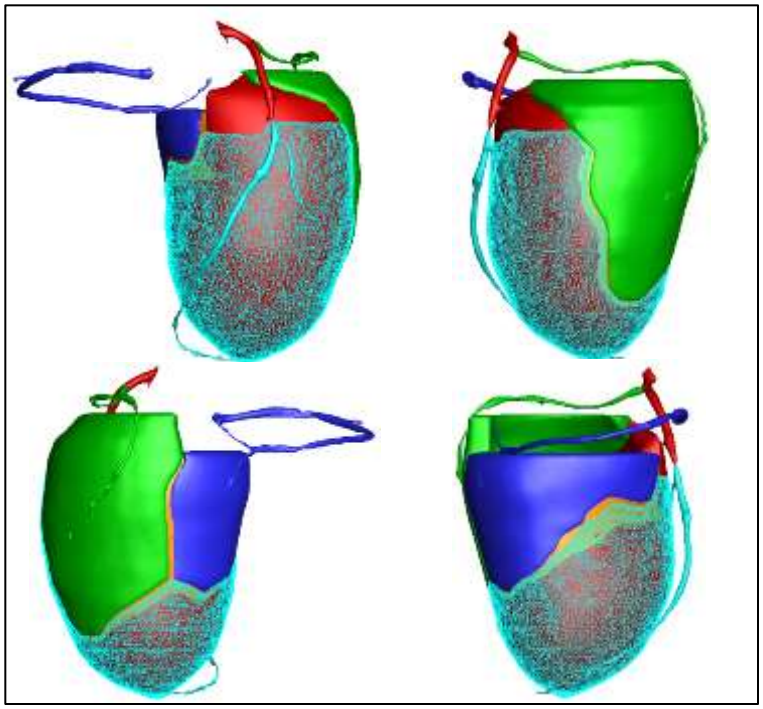


Predictors of FFR<0.80	OR	95% CI	P value
Minimum lumen diameter	0.031	0.013–0.076	< 0.001
Lesion length	1.038	1.009–1.069	0.001
Myocardial size *(modified APPROACH)*	1.113	1.079–1.147	< 0.001

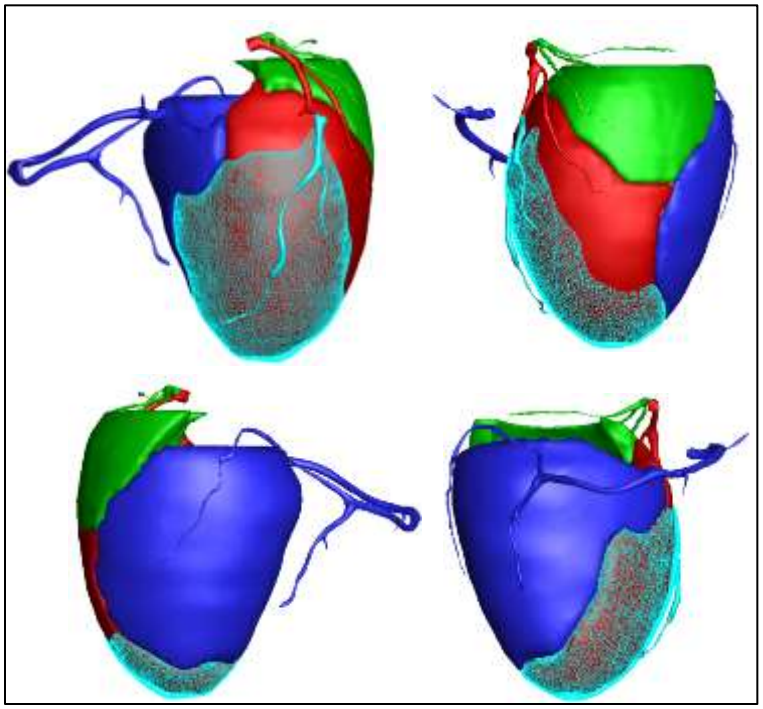
Shiono et al. Catheter Cardiovasc Interv 2014;84:406-13







V_{sub}= 55cc, V_{ratio}= 46%



V_{sub}= 29cc, V_{ratio}= 26%

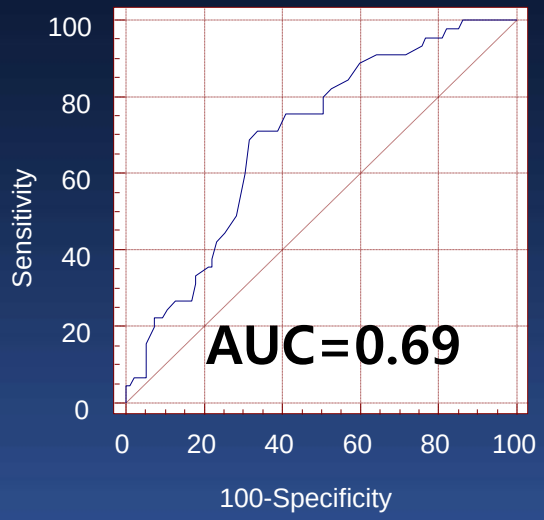
Clinical and CAMS Data

Age, years	62.5±9.2
Men	64 (89%)
Body mass index, kg/m^2	25.1±2.6
CAMS data	
Total LV myocardial volume, cc	120.3±26.1
Myocardial volume of LM territory, cc	79.4±26.9
Myocardial volume of RCA territory, cc	32.1±11.9
Myocardial volume of LAD territory, cc	52.1±14.8
Myocardial volume of LCX territory, cc	34.1±11.5
%Myocardium of RCA territory, %	27.2±8.2
%Myocardium of LAD territory, %	43.9±7.3
%Myocardium of LCX territory, %	28.8±7.9

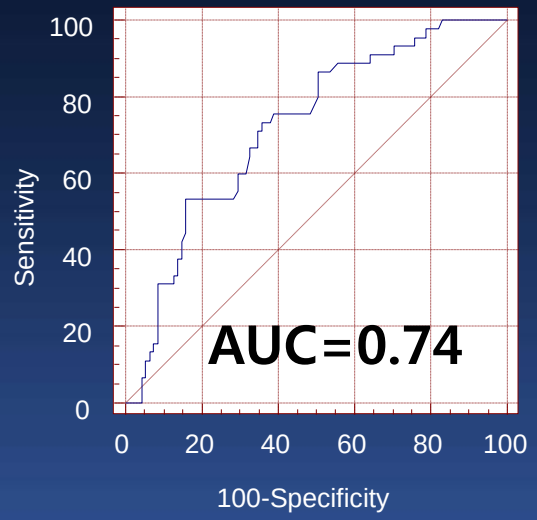
Diagnosis of Ischemia-producing Lesions by Using IVUS-MLA and CAMS

Determinants of FFR ≤0.75

V_{sub} >30.7cc



V_{ratio} >25.4%

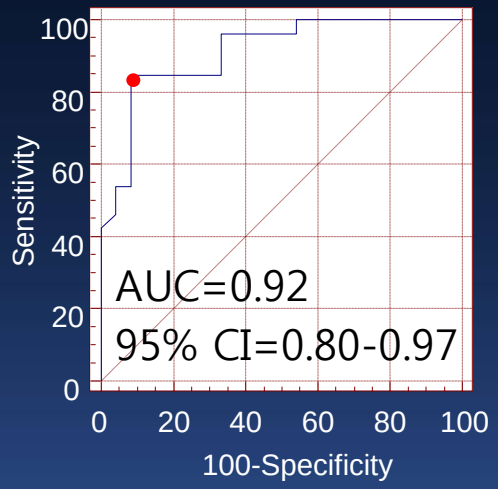


V_{sub} : myocardial volume subtended by stenotic segment
V_{ratio} : Ratio of V_{sub} to total LV myocardial volume

Prediction of FFR ≤0.75

V_{sub} >30.7cc

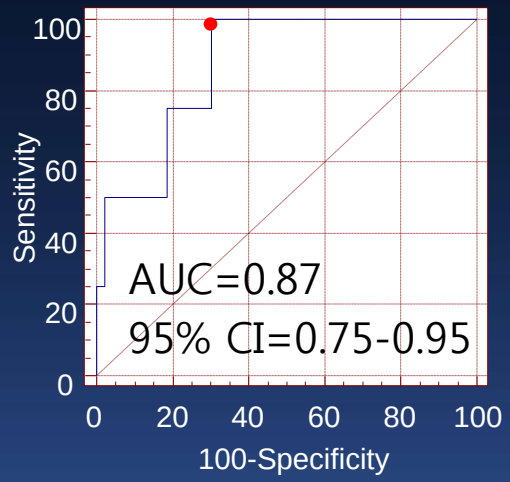
MLA cut-off ≤2.85mm²



Sensitivity 85%
Specificity 92%
PPV 92%
NPV 85%

V_{sub} ≤30.7cc

MLA cut-off ≤2.67mm²



Sensitivity 100%
Specificity 69%
PPV 38%
NPV 100%

In the setting of a larger myocardial territory, IVUS-MLA ≈2.8mm² accurately predicted an FFR ≤0.75, while clinical relevance of the lesions with a smaller myocardium is limited

Summary

- Clinical impact and prognostic value of FFR-guided PCI has been validated even at very long-term
- With a frequent visual-functional mismatch, either angiographic DS or IVUS-MLA poorly predicted FFR
- Functional significance is determined not only by stenosis severity but also by myocardial territories and collaterals
- CAMS-based assessment of myocardial size may improve the accuracy of IVUS prediction for ischemia