Physiology versus Imaging Guided PCI

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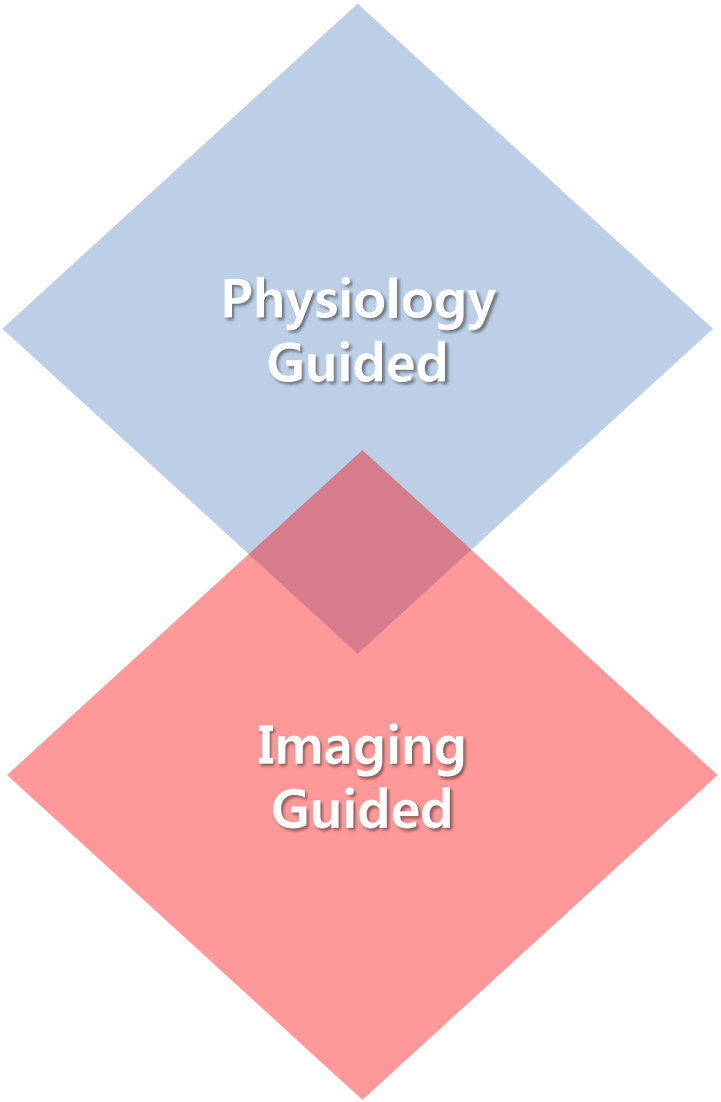
Complex PCI TCTAP 2016

What is Guided PCI…?

Is simply using the imaging or physiologic tool be the guided PCI?

3 Key Components of Guided PCI

1. Specify culprit lesion which induce myocardial ischemia
2. Guide the procedural strategy, technique and devices
3. Evaluate the PCI results and predict the clinical outcome or prognosis



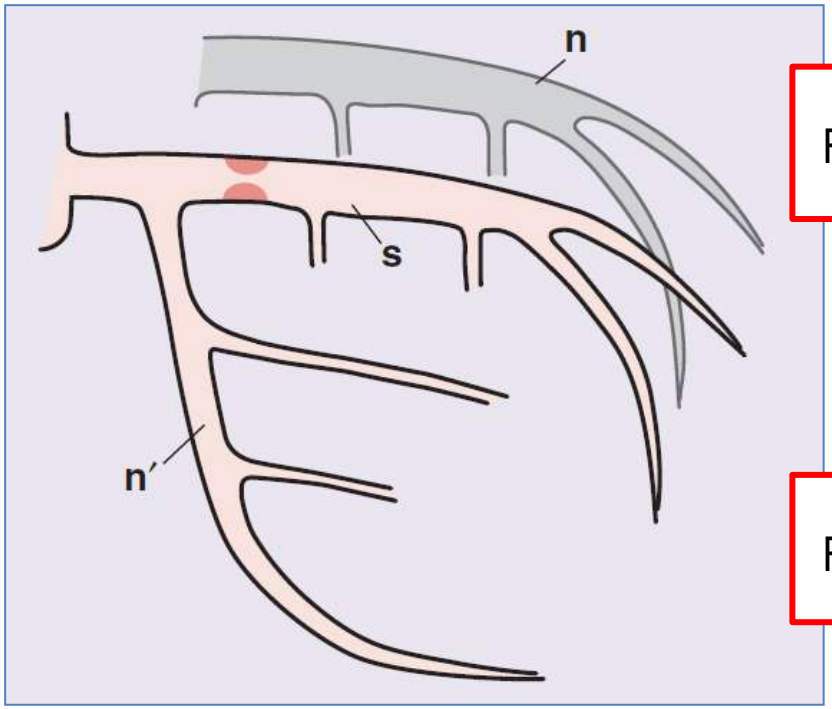
What I think is .. Why versus?

- Is it right to ask a lecture to me "Physiology versus Imaging guided PCI" ?
- Imaging and Physiology are in complementary relationship not in confrontational relationship.
- If you are stuck in one thing too and stubborn, you will lose many good things you already have.

Physiology and Imaging Guided PCI

Specify Culprit Lesion which induce ischemia
Fractional Flow Reserve

FFR in real clinical setting



$$FFR = \frac{\text{Maximal Flow of Stenosed Artery}}{\text{Maximal Flow of } \mathbf{Normal\ Artery}}$$

$$FFR = \frac{\text{Maximal Flow of Stenosed Artery}}{\text{Maximal Flow of } \mathbf{Non\text{-}stenosed\ Artery}}$$

In real clinical setting, FFR indicates,

- **to what extent maximal blood flow could be increased by relieving the specific epicardial obstruction, on a given vasoreactivity and myocardial bed.**

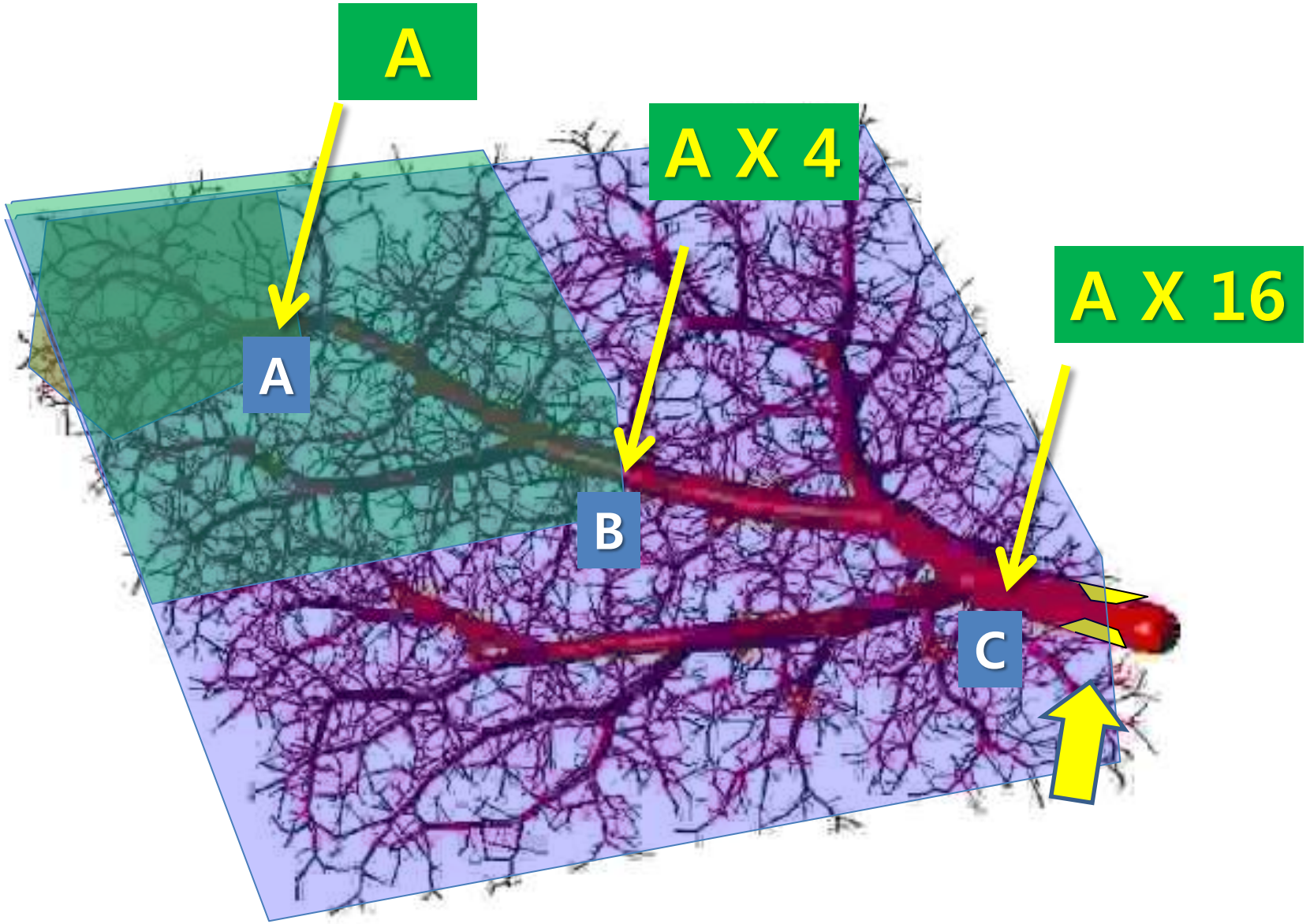
FFR Threshold for Reversible Myocardial Ischemia

Authors	Ref	Patients	#	Test	Threshold
De Bruyne et al.	Circ 1995	1-VD	60	Bicycle ECG	0.72*
Pijls et al.	Circ 1995	1-VD Pre+Post PCI	60	Bicycle ECG	0.74*
Pijls & De Bruyne	NEJM 1996	1-VD, Intermediate Stenosis	45	Bicycle ECG +TL +Dobut Echo	0.75*
Bartunek et al.	JACC 1996	1-VD	75	Dobutamine Echo	0.78*
Chamuleau et al.	JACC 2000	2-VD	127	MIBI-Spect	0.74**
Abe et al.	Circ 2000	1-VD	46	Thallium	0.75*
De Bruyne et al.	Circ 2001	Post MI	57	MIBI-Spect	0.80*
					0.75

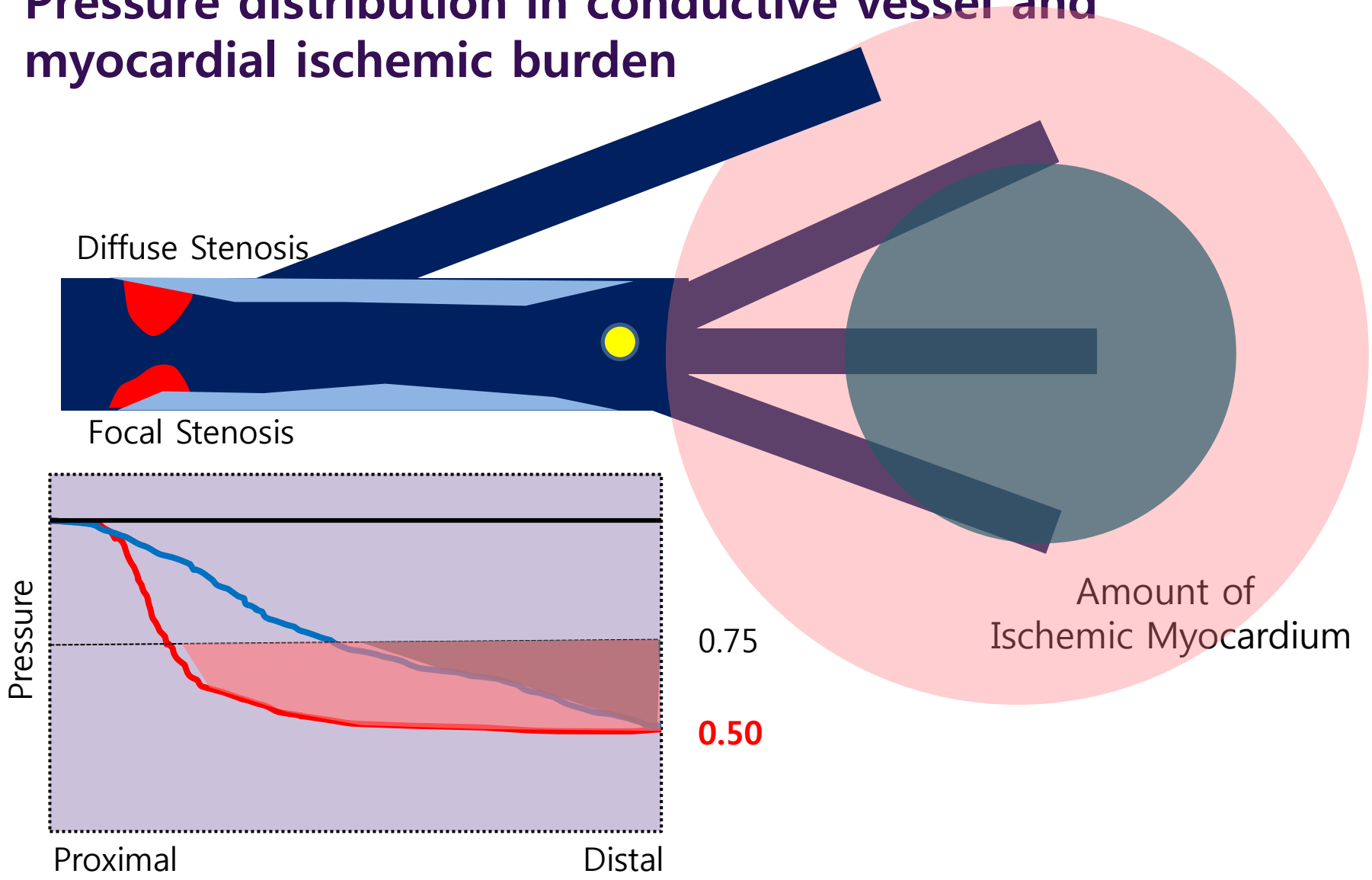
* 100% Specificity , ** Optimal Cutoff Value

Does FFR represent the extent of ischemic burden?

Where do you measure FFR?



Pressure distribution in conductive vessel and myocardial ischemic burden



Complete pullback pressure-tracing with sustained hyperemia is mandatory to know the exact amount of myocardial ischemic burden.

Specify Culprit Lesion which induce ischemia
CT-derived FFR

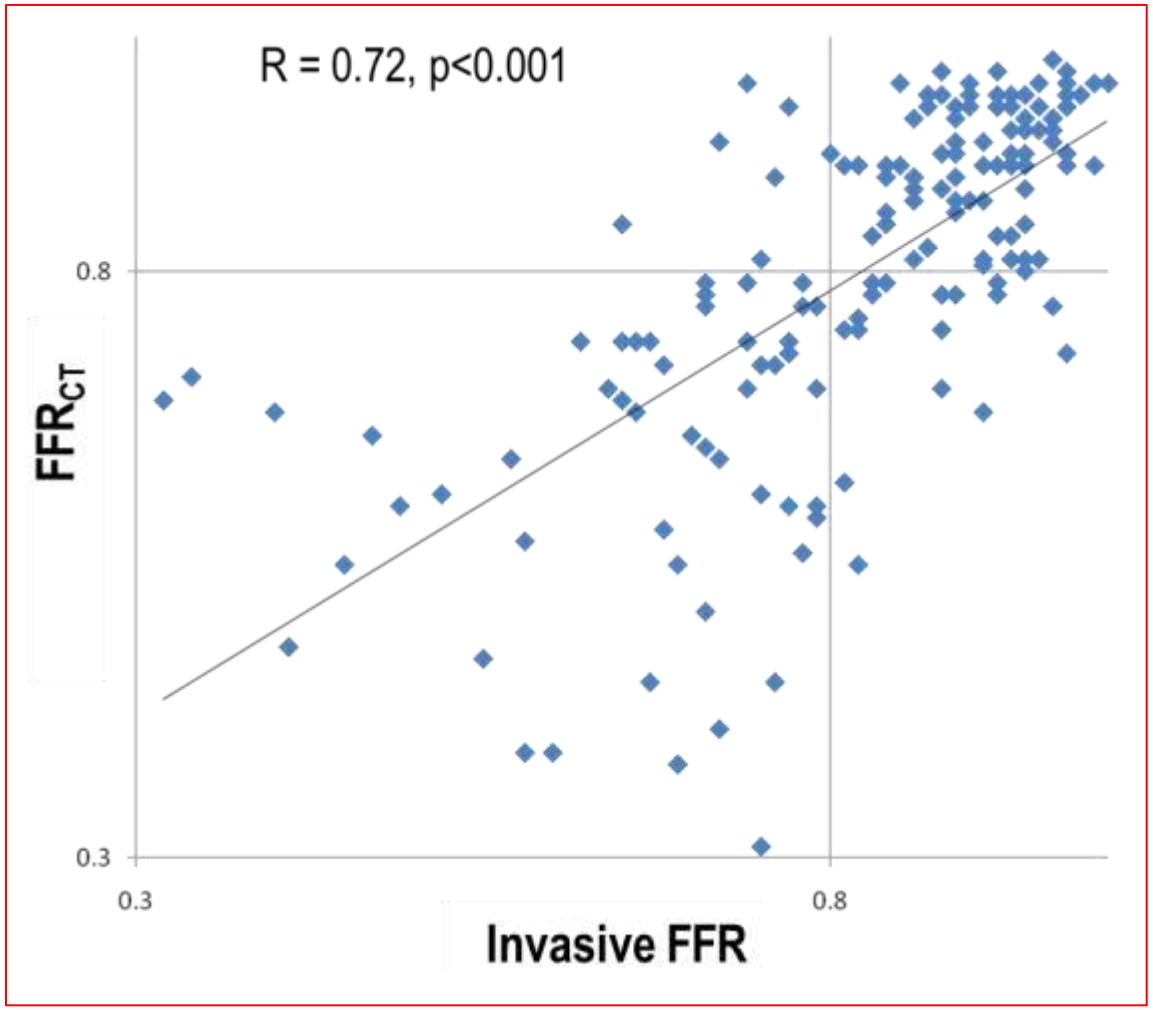
CCT, CTP and CT-FFR: Meta Analysis of Diagnostic Performance versus Invasive FFR

Technique	# Studies	# Patients	Sensitivity	Specificity	PPV	NPV
CCTA	16	1239	0.89 [0.86-0.91]	0.65 [0.62-0.67]	0.48 [0.38-0.58]	0.94 [0.82-0.94]
CTP	5	264	0.83 [0.77-0.88]	0.76 [0.72-0.80]	0.61 [0.46-0.75]	0.91 [0.84-0.99]
CT-FFR	5	714	0.83 [0.79-0.87]	0.77 [0.74-0.80]	0.63 [0.52-0.72]	0.91 [0.79-1.03]

CT-FFR computed tomography fractional flow reserve
CTP computed tomography perfusion
CCTA coronary computed tomography angiography

JA Gonzalez et al, Am J Cardiol 2015;116:1469-1478

Invasive FFR vs. Non-invasive FFR_{CT}

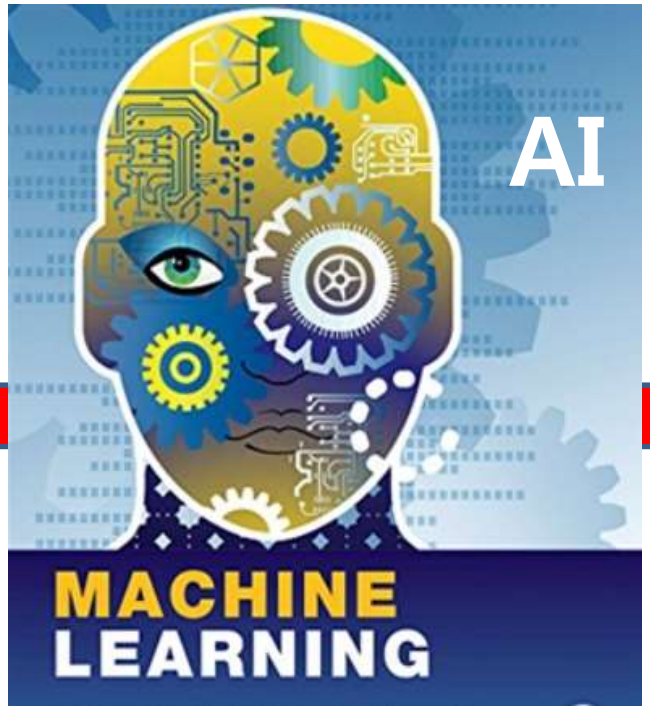


too much scatter....

Koo BK, et al. JACC 2011

CT-derived FFR needs high computational demand

Super Computer



Work Station
3.4GHz, i7 octa-core processor

Physics based computation

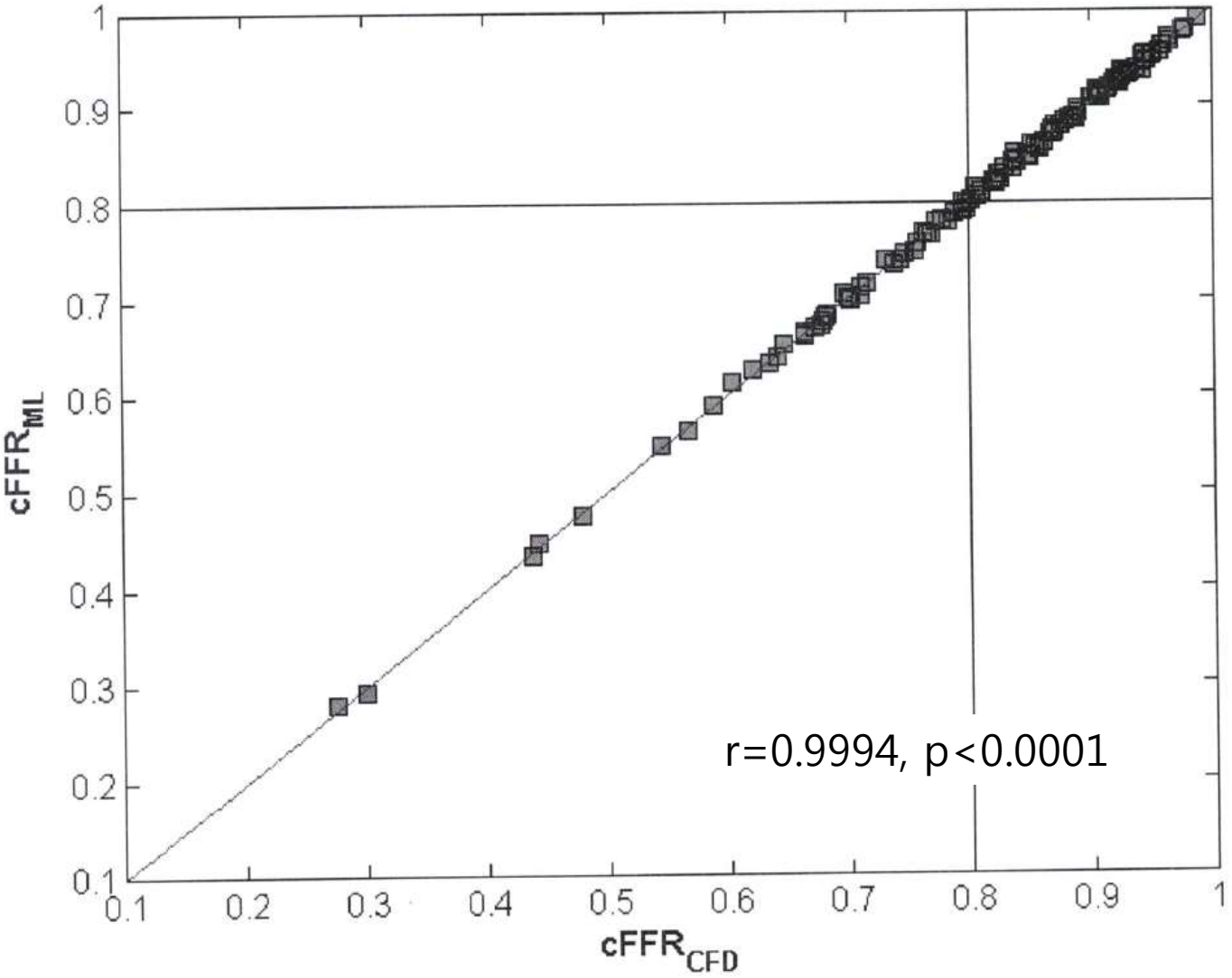
Execution Time **196±78 sec**

Machine learning based model

2.4±0.4 sec

L Itu et al. J Appl Physiol, April 14, 2016

CT-derived FFR: Machine Learned vs. CFD



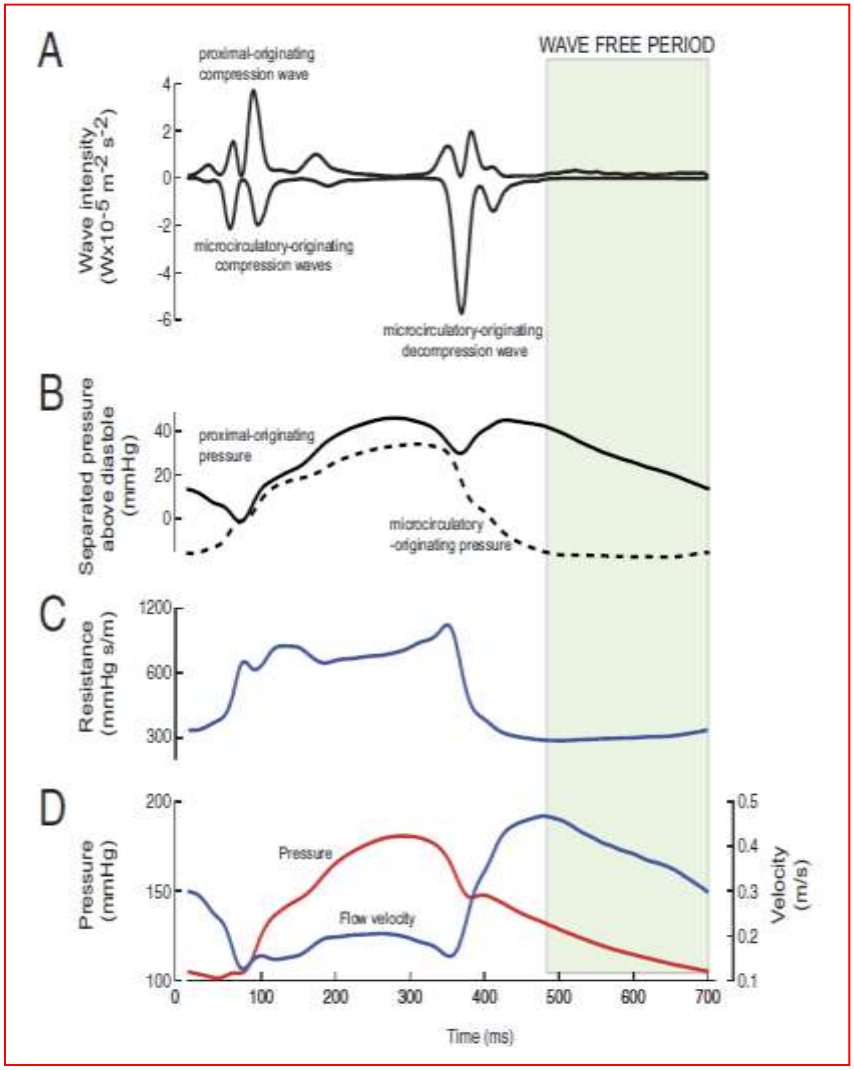
L Itu et al. J Appl Physiol, April 14, 2016

Specify Culprit Lesion which induce ischemia
Instantaneous Wave-Free Ratio (iFR)

Wave Intensity Analysis is Conceptually OK
Instantaneous wave-free ratio (iFR)

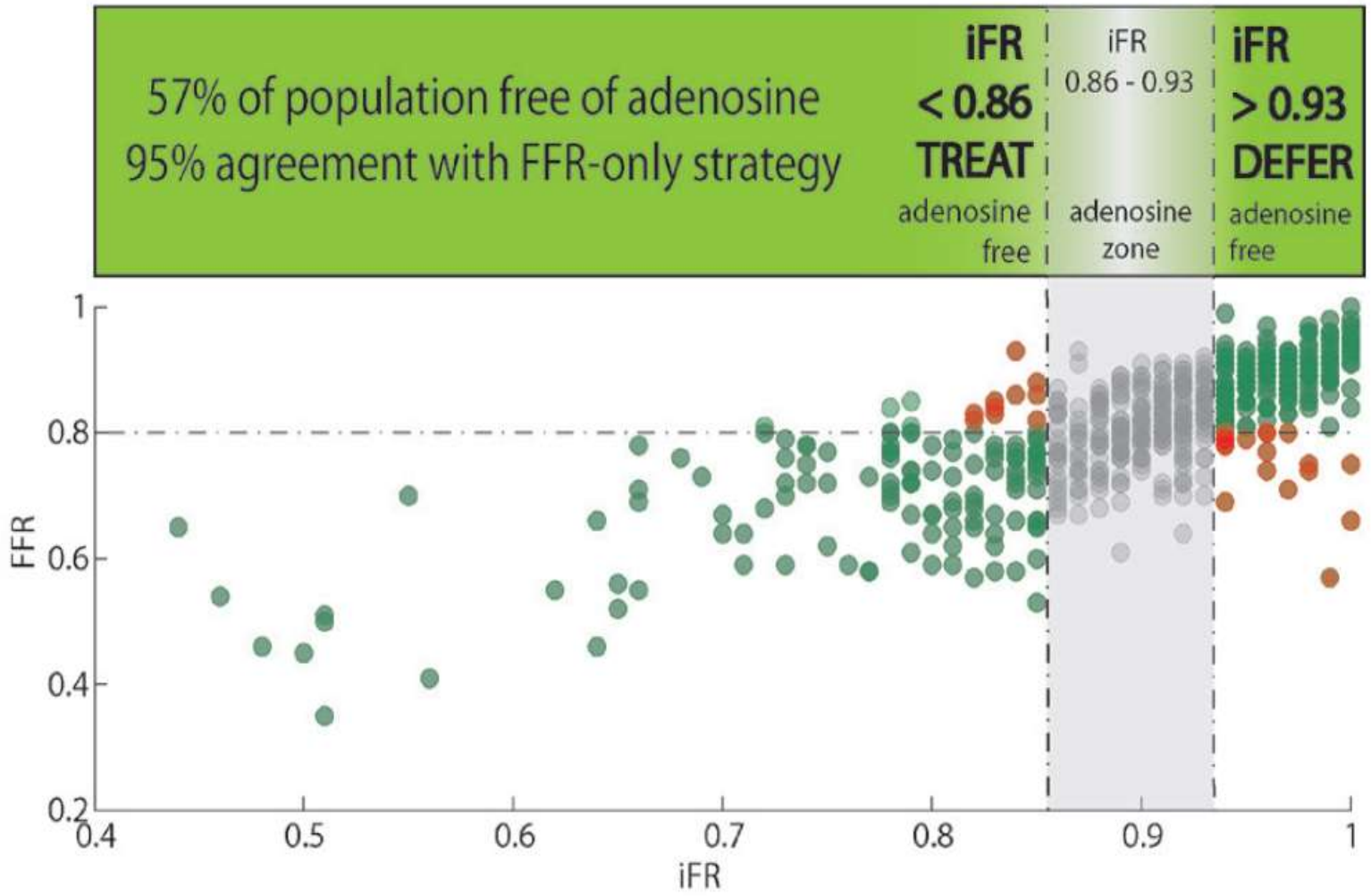
- **Instantaneous wave-free ratio (iFR) proposes that division of reservoir pressure by flow in diastole gives (vasodilated) resistance only.**
- In aorta, as diastolic flow is negligible, the instantaneous pressure/flow ratio implies division by zero, thus physical nonsense (violates Ohm's law). However, in the coronary circulation, errors are mitigated by the fact that flow in diastole is dominant.

- **Therefore, the iFR is assumed to give a measure of minimal (vasodilated) coronary resistance.**
- If true, it could make estimation FFR possible without the need for drugs to obtain maximal dilation.



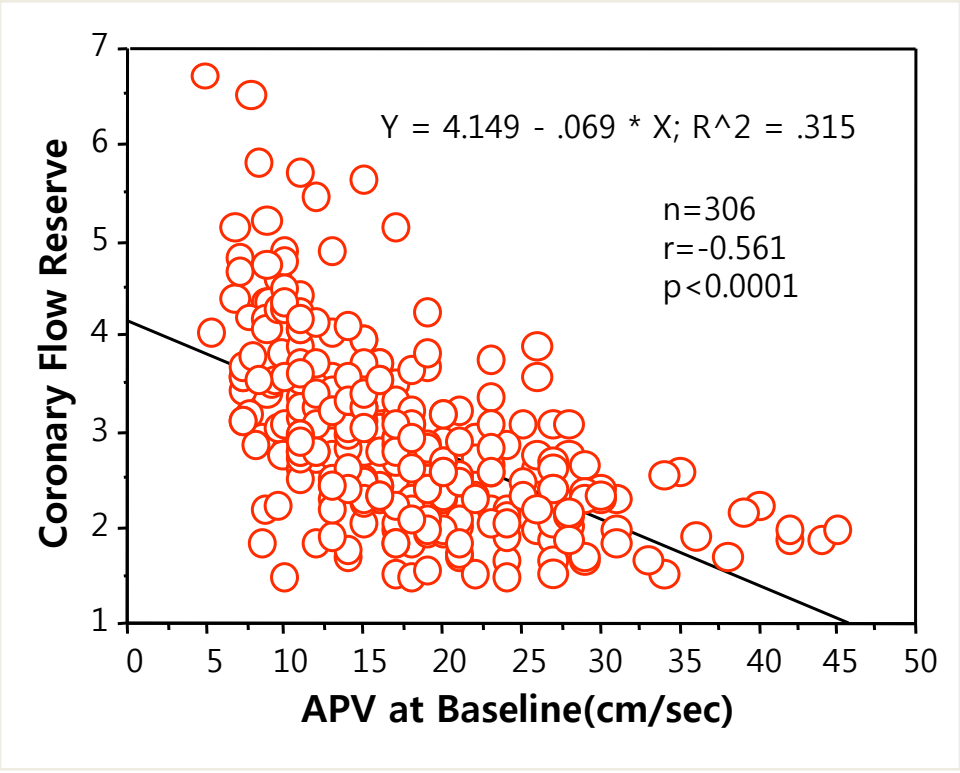
S. Sen et al. J Am Coll Cardiol 2012;59:1392–402
N Westerhof et al. Hypertension. 2015;66:93-98

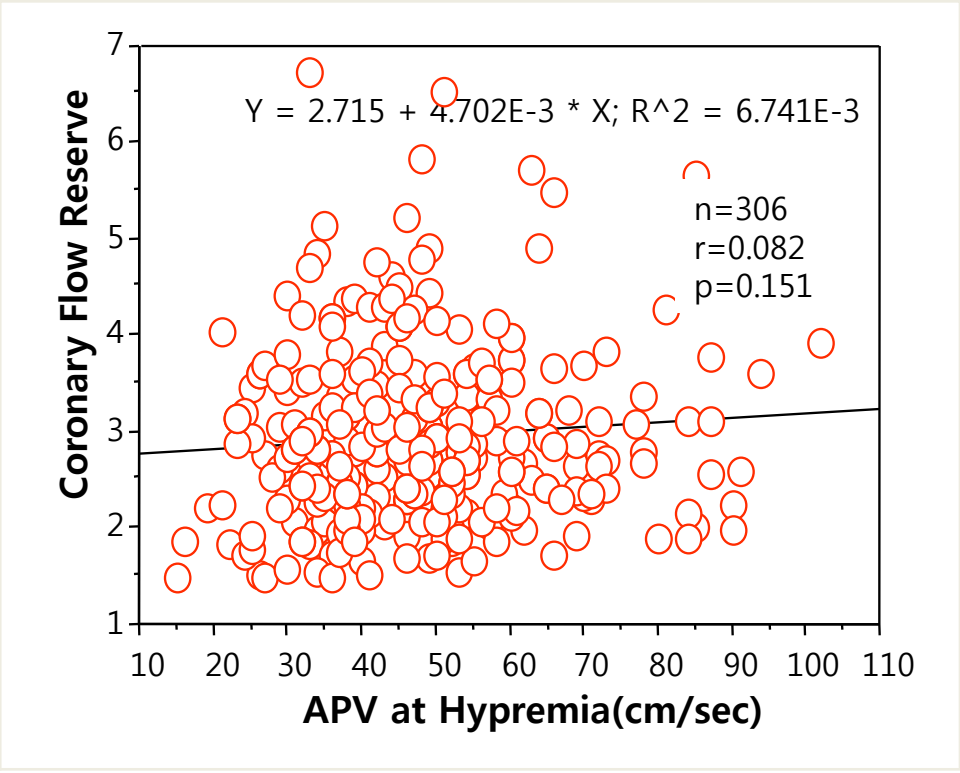
Hybrid iFR-FFR decision-making strategy is needed especially in Gray Zone



R Petraco et al. Eurointervention 2013;8:1157-1165

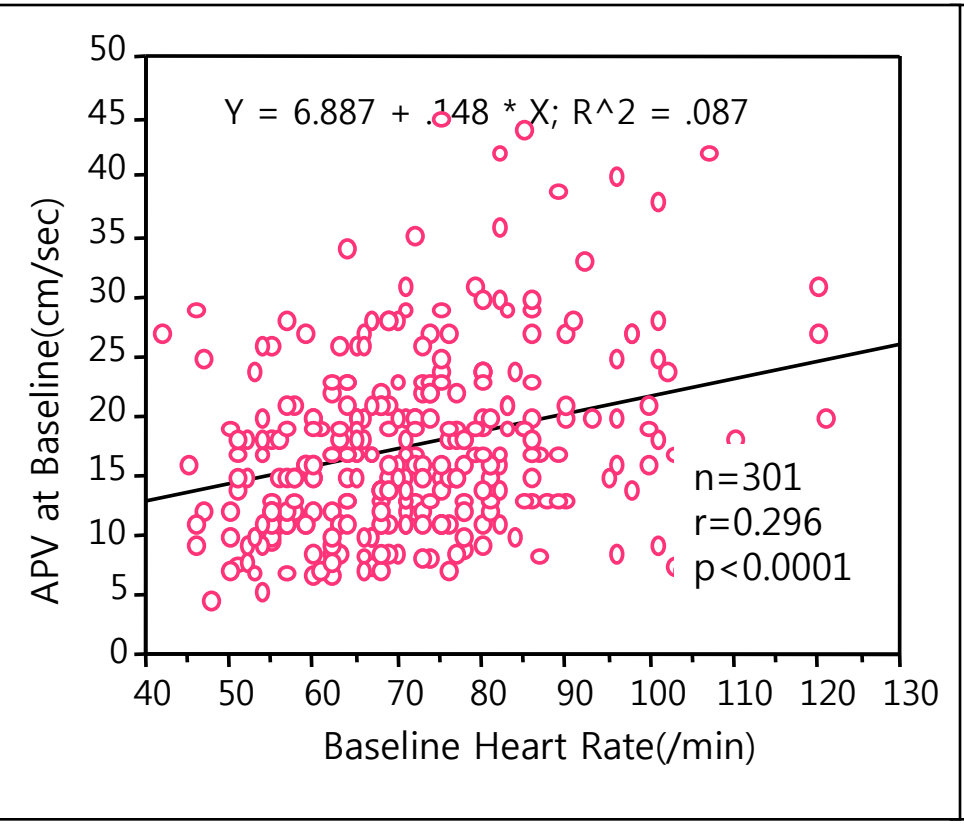
Patients are not in resting condition in Cath Lab. CFR in Angiographic Normal Coronary

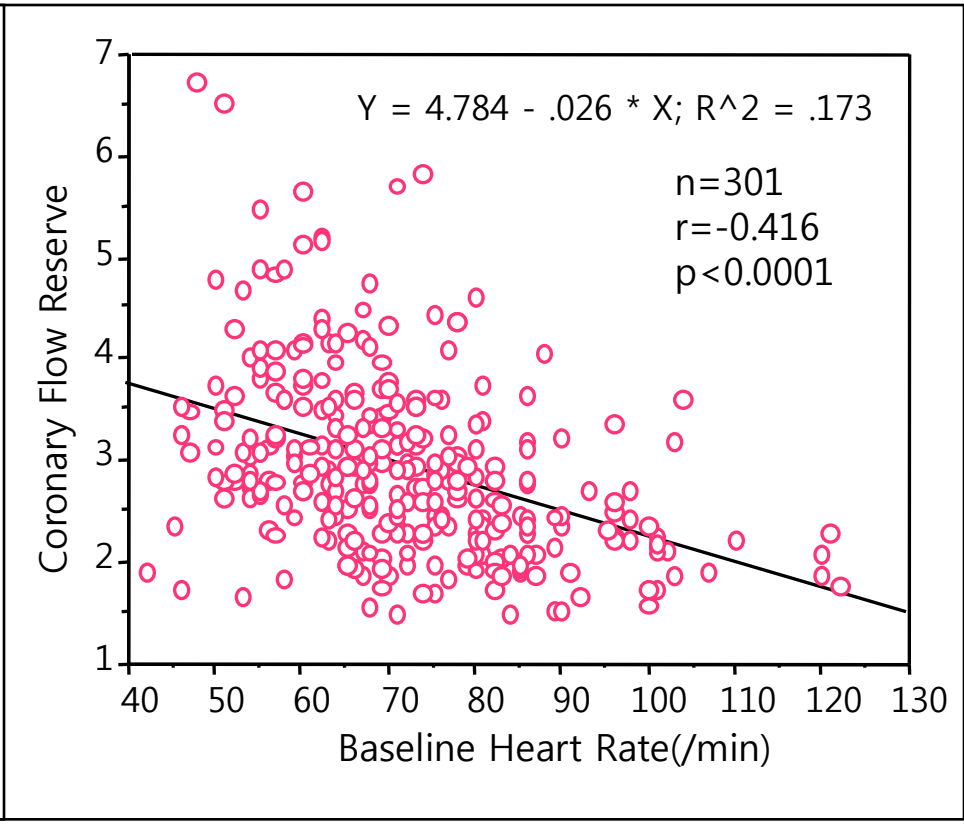




iFR could not be a stand alone index, because it is very hard to get sustained real baseline hemodynamic information in invasive laboratory.

Patients are not in resting condition in Cath Lab. CFR in Angiographic Normal Coronary

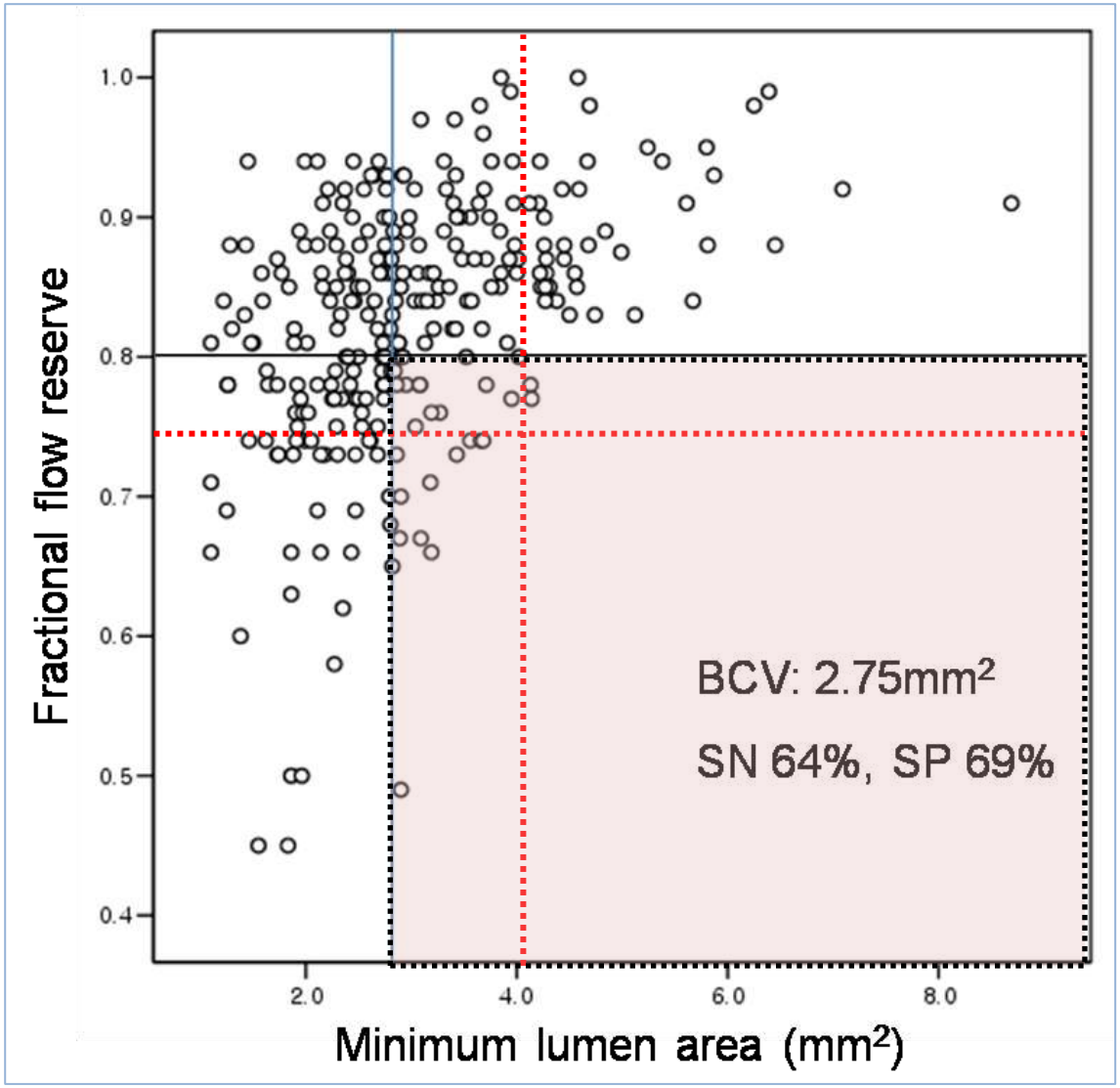




Heart rate is major determinant of coronary flow reserve.

Specify Culprit Lesion which induce ischemia
Intravascular Ultrasound

Physiologic validation of anatomic measurements IVUS MLA and FFR



Koo, Yang et al. J Am Coll Cardiol Intv 2011;4:803–11

Optimal IVUS Criteria and Accuracy for Defining the Functional Significance of Intermediate Coronary Stenoses of Different Locations: BCV of IVUS MLA predicting FFR<0.8 (267 lesions)

	BCV	AUC	95% CI
Lesion Location			
Proximal LAD (n=52)	**3.0 mm^2**	**0.81**	**0.68-0.91**
Mid LAD (n=146)	2.5mm^2	0.64	0.56-0.72
Mid-1 LAD (n=97)	**2.75 mm^2**	0.76	0.66-0.84
Mid-2 LAD (n=49)	NA		
Right coronary artery (n=49)	3.0 mm^2	0.68	0.53-0.81
Left circumflex artery (n=20)	NA		
Vessel Size			
≥ 3.0mm (n=157)	**3.0 mm^2**	**0.70**	**0.61-0.76**
< 3.0mm (n=110)	**2.5 mm^2**	0.61	0.52-0.71

Koo, Yang et al. J Am Coll Cardiol Intv 2011;4:803–11

Determinants of Functionally Significant Coronary Artery Stenosis (FFR <0.8)

	OR	95% CI	p Value
Minimum lumen area	0.35	0.19–0.66	0.001
Proximal segment (vs. mid)	2.97	1.20–7.32	0.02
LAD lesion (vs. non-LAD)	3.40	1.24–9.30	0.02

Other included variables: reference vessel diameter (3.0 mm), diagnosis, multivessel disease, angiographic lesion length(20 mm), percent plaque burden, left ventricular ejection fraction, history of previous myocardial infarction, method of adenosine administration, remodeling index.

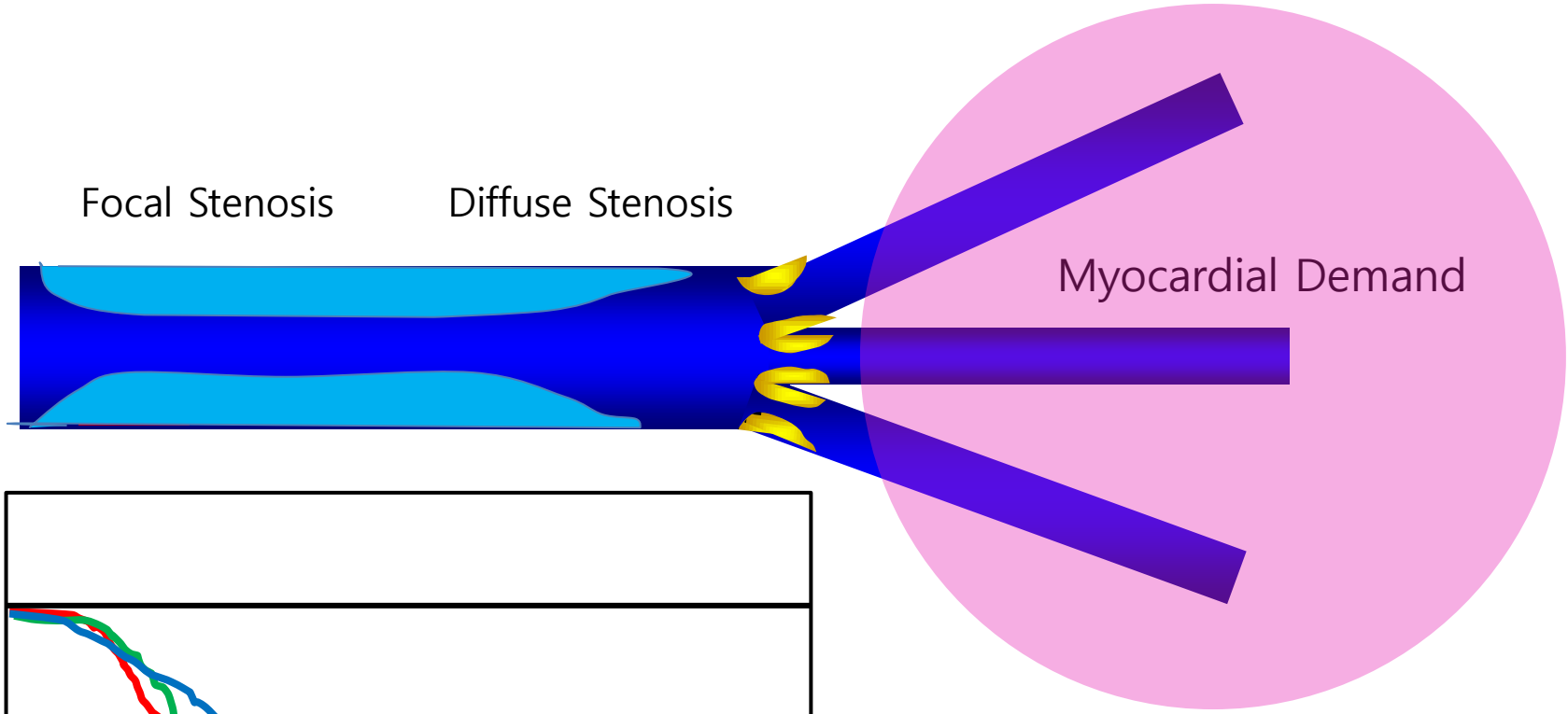
Koo, Yang et al. J Am Coll Cardiol Intv 2011;4:803–11

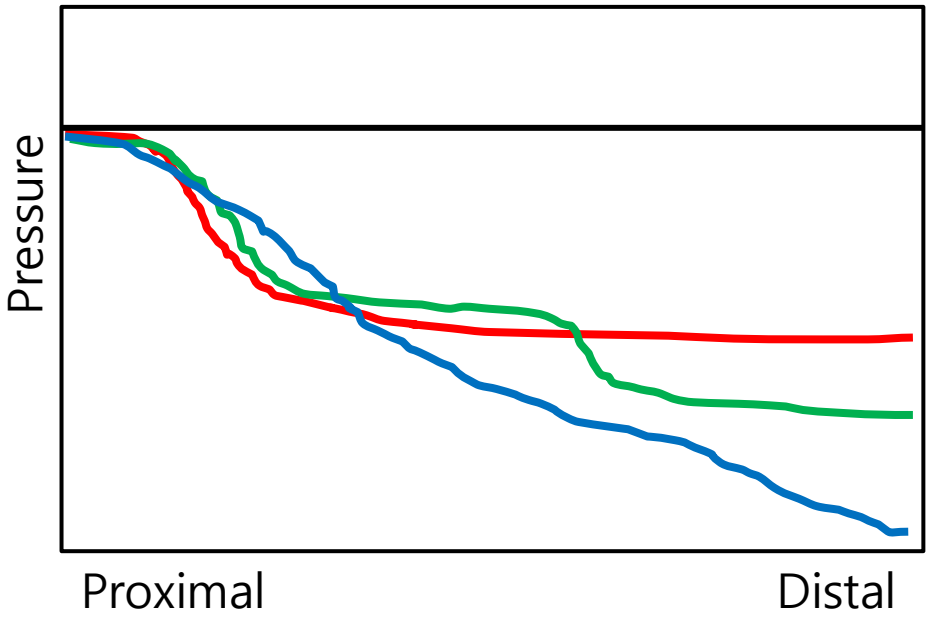
IVUS MLA threshold for ischemic FFR (<0.75 or 0.80) in non-left main intermediate coronary lesions

Reference	No. of lesions	MLA mm^2	Sensitivity %	Specficity %
Takagi †	51	**3.0**	83.0	92.3
Briguori †	53	**4.0**	92.0	56.0
Ben-Dor †	92	**2.8**	79.7	80.3
Ben-Dor	92	**3.2**	69.2	68.3
Ben-Dor	205	**3.09**	69.2	79.5
Koo, Yang	252	**2.75**	69.0	65.0
Han	881	**2.75**	61.0	63.0
Kang	236	**2.4**	90.0	60.0
Kang	784	**2.4**	84.0	63.0
Chen	323	**2.97**	82.9	63.5
Nascimento *	1649	**2.61**	80.0	66.0

† FFR<0.75, * pooled analysis of 9 non-LM trials

Why stick to MLA? Consider Total Plaque Burden



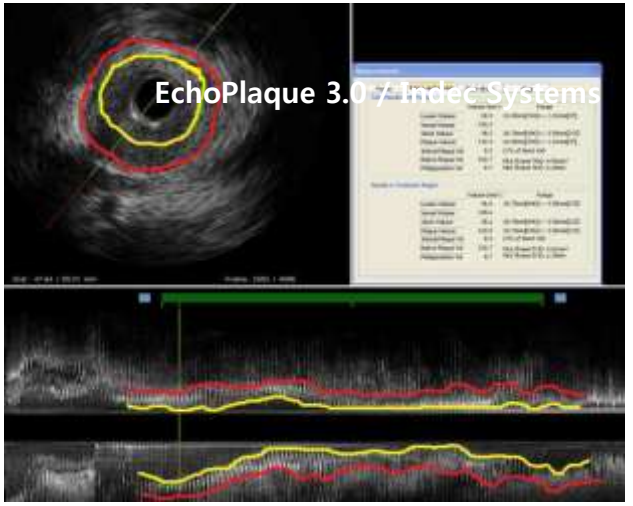


Same MLA, Different FFR
Different Total Plaque Burden
Different Pressure Curve

IVUS Volumetric analysis of Target Vessel
Percent Total Atheroma Volume

- We analyzed IVUS images spaced precisely 1mm apart, with an average of 69.8±14.9 frames per LAD from distal to left main in 130 LAD with intermediate stenosis.
- The leading edge of the lumen and external elastic membrane (EEM) were traced manually using planimetry software (EchoPlaque 3.0) to calculate **total atheroma volume (TAV)** and **total vessel volume (TVV)**.

- TAV (mm^3) = ∑ (EEM area-Lumen area)
- TVV (mm^3) = ∑ EEM area
- **%TAV = TAV / TVV x 100**



XJ Jin, SJ Tahk et al. Int J Cardiol 2015

Diagnostic accuracy of angiographic and IVUS parameters for FFR<0.80

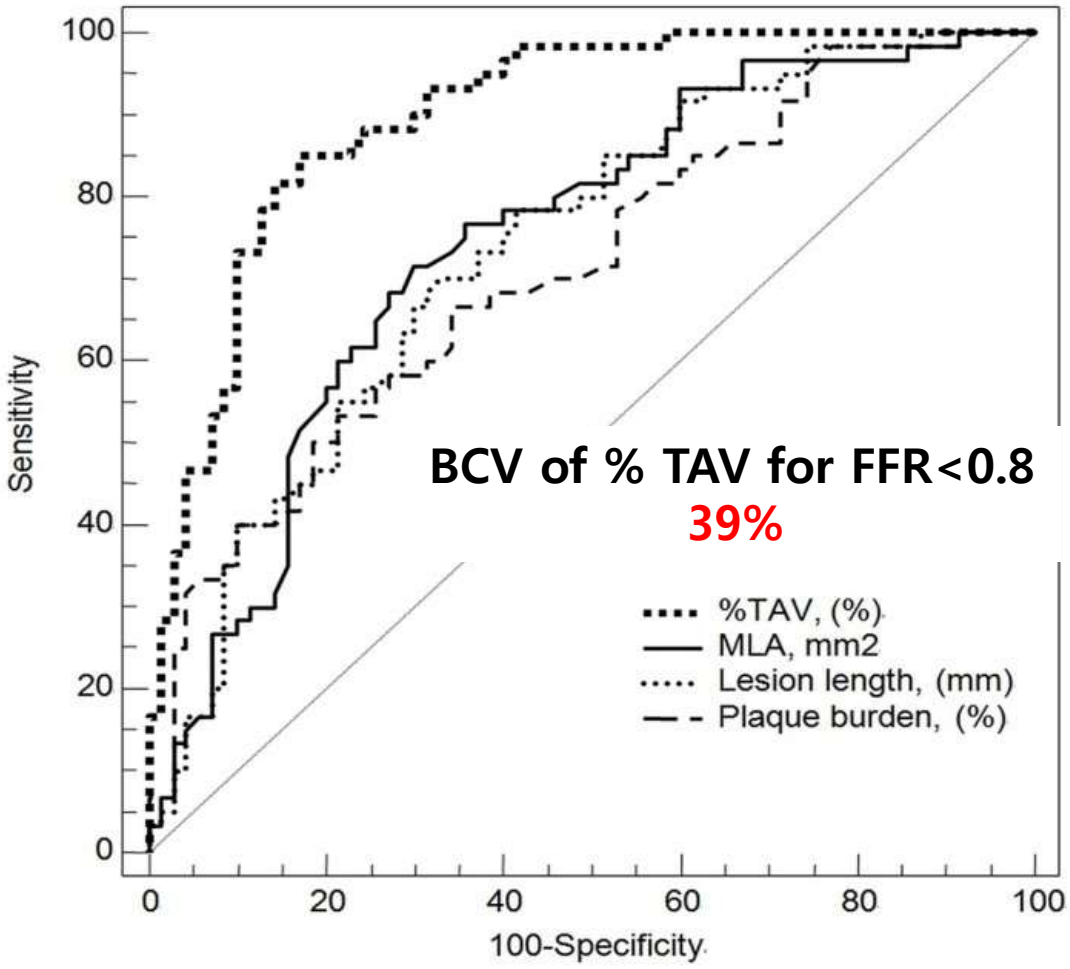
% Total Atheroma Volume

	Sensitivity	Specificity	PPV	NPV	Accuracy
Angiographic parameters					
Minimum lumen diameter, mm	67	64	66	69	65
Diameter stenosis, %	70	69	69	73	70
IVUS parameters					
% total atheroma volume, %	85	83	81	87	84
Minimum lumen area, mm^2	72	70	72	74	71
Plaque burden, %	68	67	68	70	66
Lesion length, mm	70	67	70	72	68

% Total Atheroma Volume = (Total Atheroma Volume)/(Total Vessel Volume) x100

XJ Jin, SJ Tahk et al. Int J Cardiol 2015

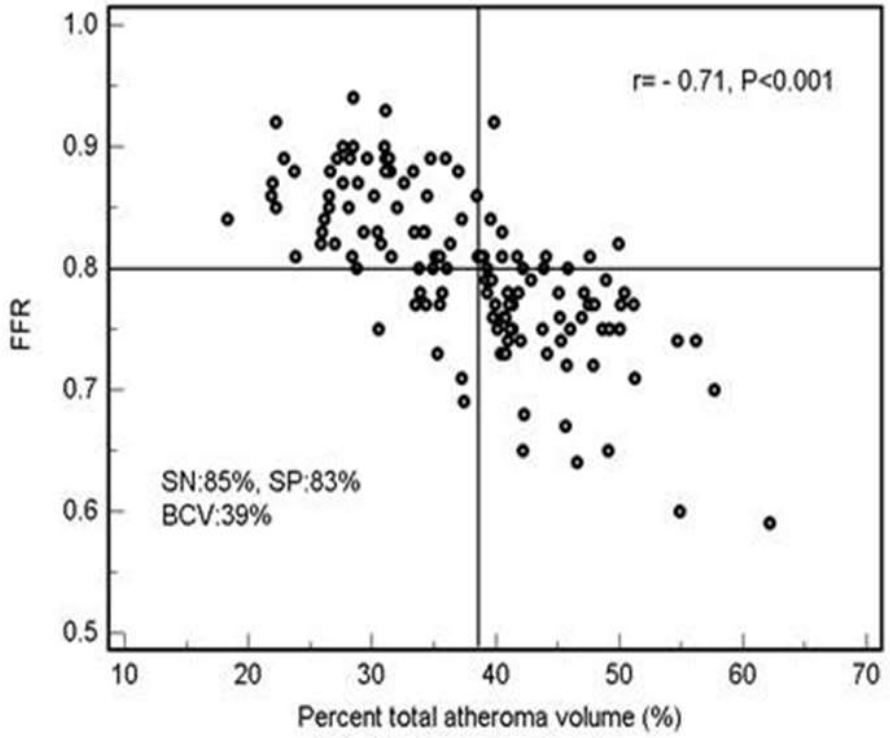
ROC analysis of IVUS parameters
% Total Atheroma Volume

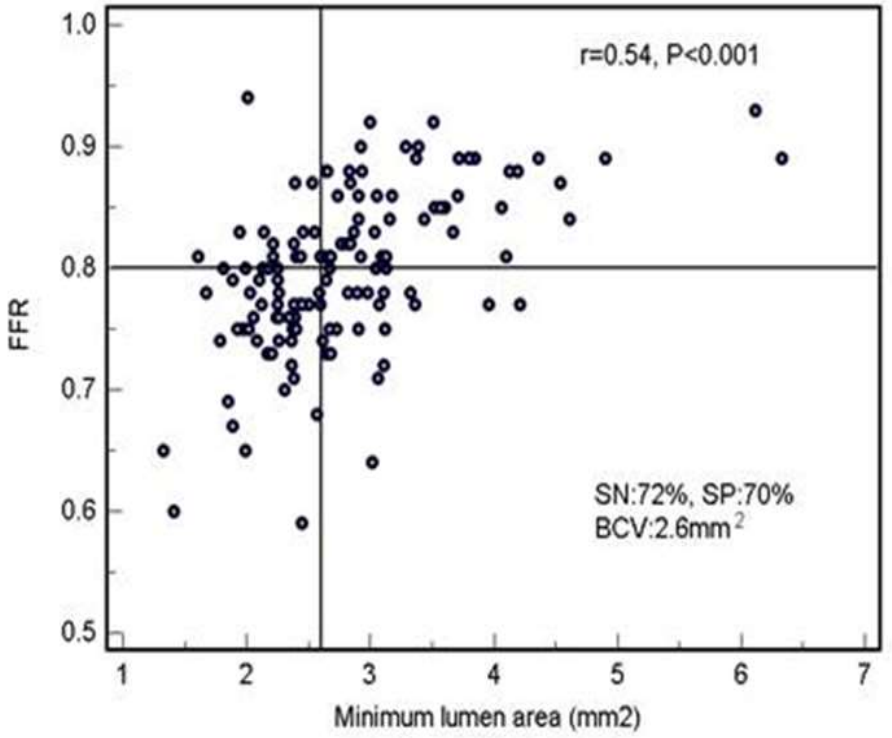


% TAV: % total atheroma volume

XJ Jin, SJ Tahk et al. Int J Cardiol 2015

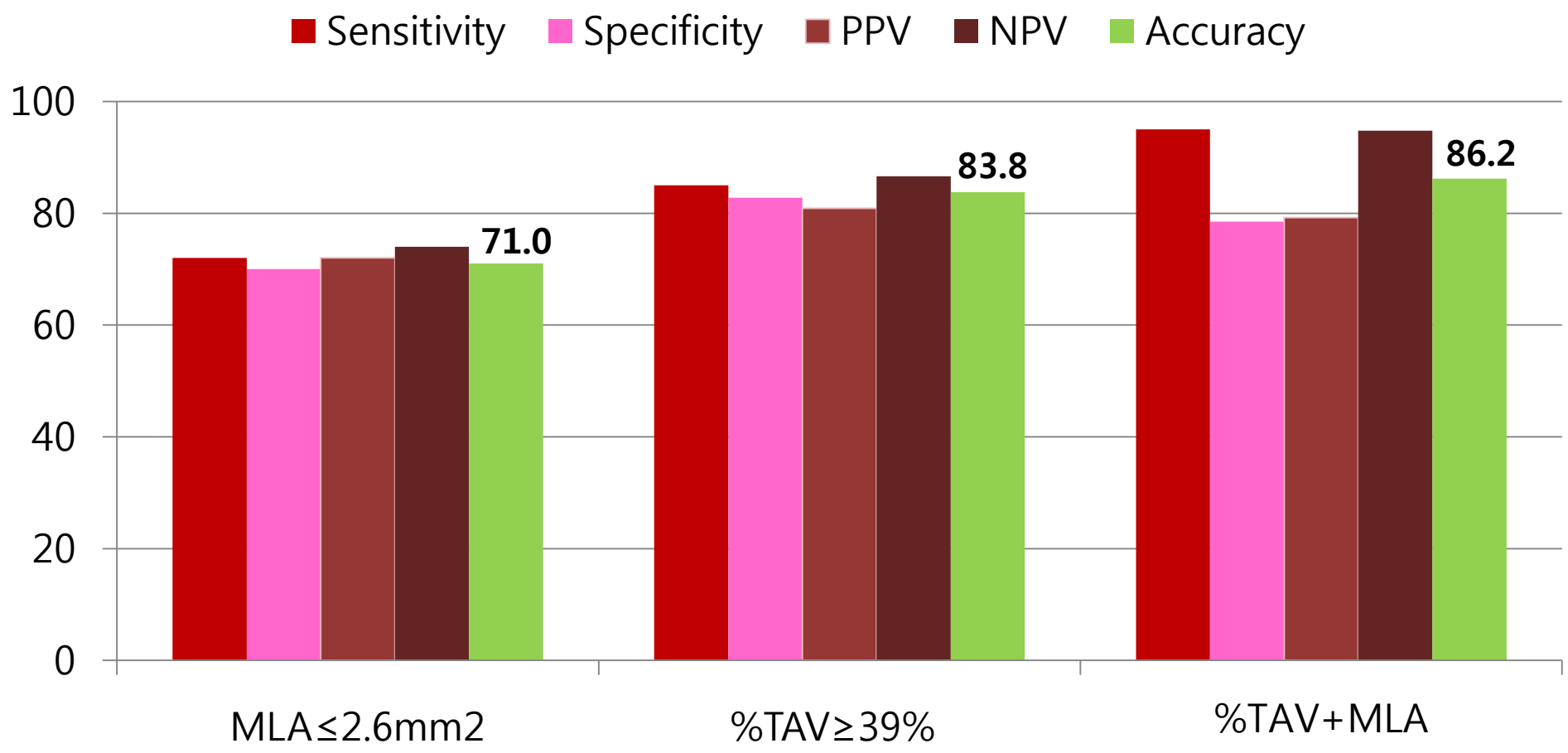
Relationship between FFR and IVUS parameters
% **Total Atheroma Volume and MLA**





XJ Jin, SJ Tahk et al. Int J Cardiol 2015

Diagnostic accuracy of %TAV for FFR<0.80

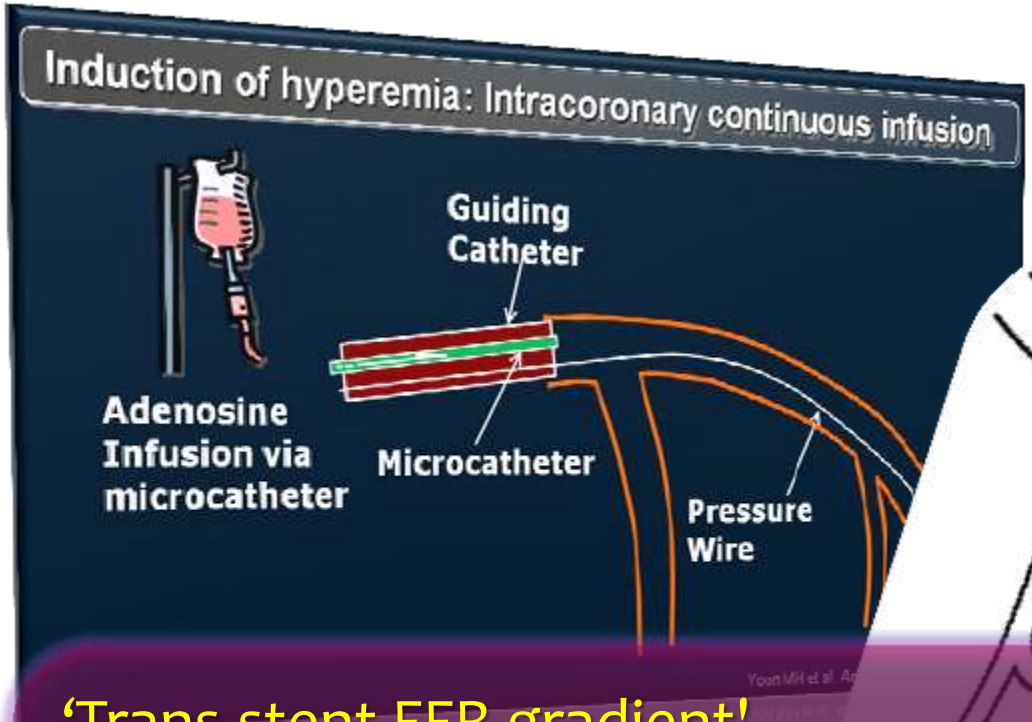


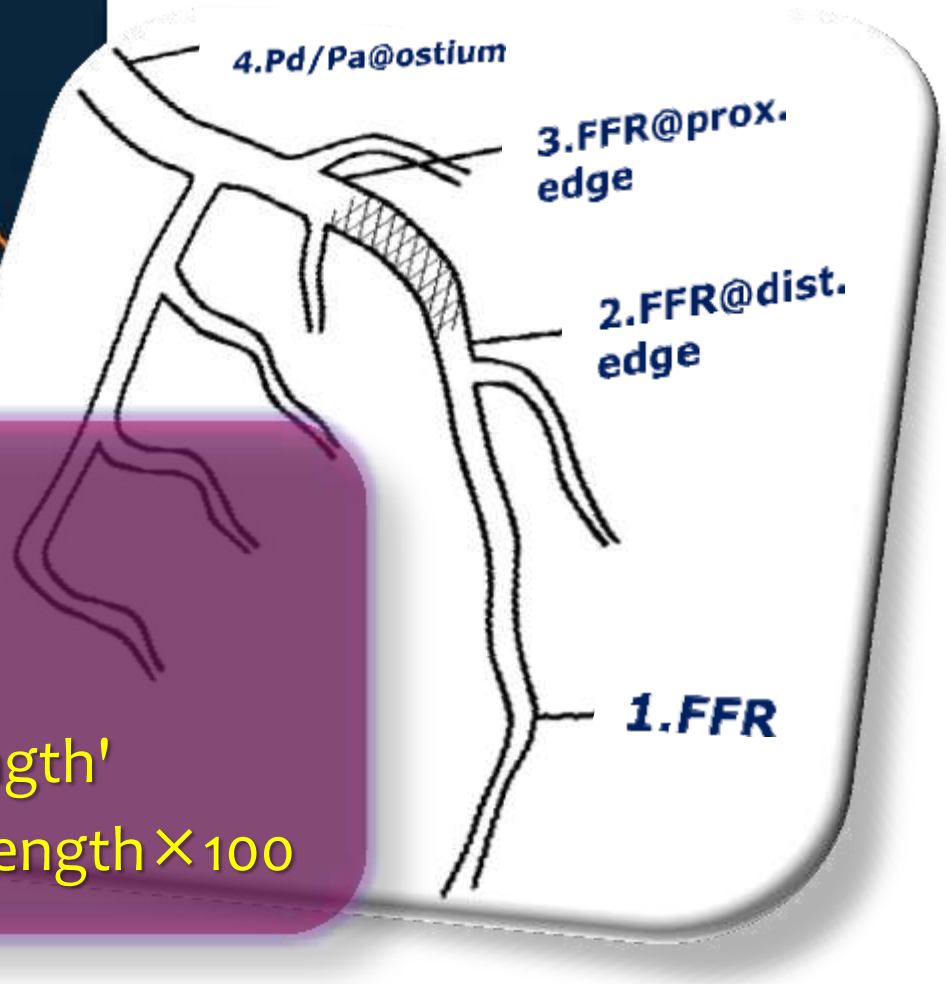
It takes my fellow more than 3 hours for 1 LAD. Advanced software, like a machine, is needed for rapid measurement and calculation.

XJ Jin, SJ Tahk et al. Int J Cardiol 2015

Evaluate PCI Results and Predict Prognosis
Trans-Stent FFR

Post PCI Trans-Stent FFR





'Trans-stent FFR gradient'

$\Delta FFR_{stent} = (3) - (2)$

'Corrected ΔFFR_{stent} by stent length'

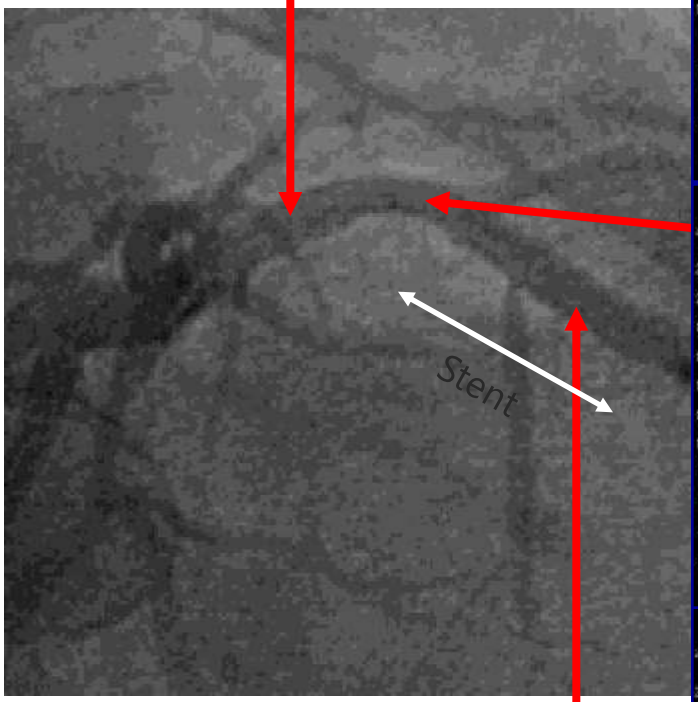
$\Delta FFR_{stent/length} = \Delta FFR_{stent} / \text{stent length} \times 100$

Post PCI Trans-Stent FFR (n=93)

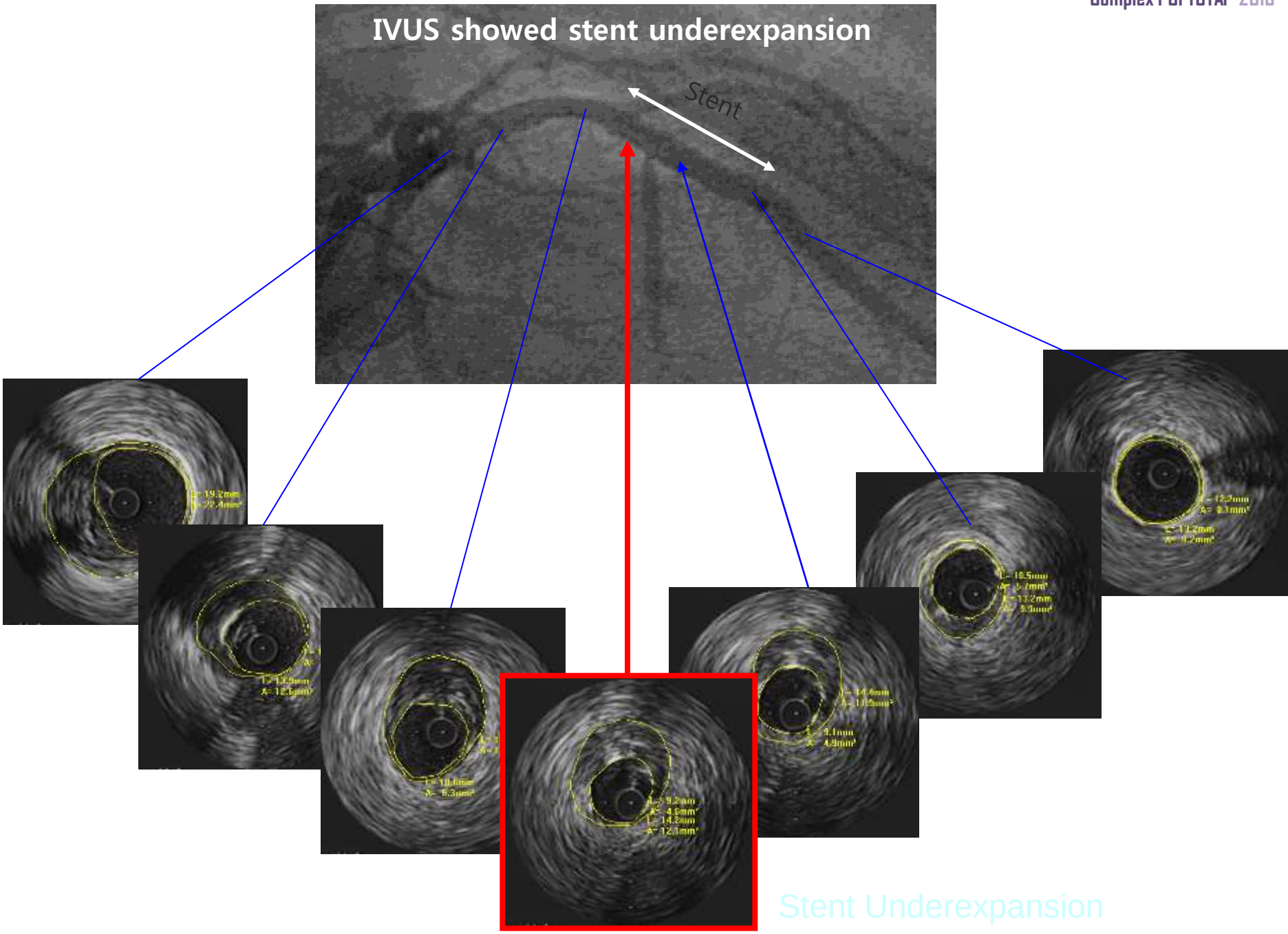
Diagnostic value of $\Delta FFR_{stent/length} \leq 0.140$ to predict optimal IVUS MSA after DES implantation

	Final MSA					
	≥ 5.0 mm^2	< 5.0 mm^2	≥ 5.5 mm^2	< 5.5 mm^2	≥ 6.0 mm^2	< 6.0 mm^2
≤ 0.140	70	4	66	8	57	17
> 0.140	14	5	10	9	12	7
Sensitivity	83 %		87 %		83 %	
Specificity	56 %		53 %		56 %	
PPV	95 %		89 %		77 %	
NPV	26 %		48 %		63 %	

Evaluation of PCI Result
Pullback Tracing with IC adenosine infusion



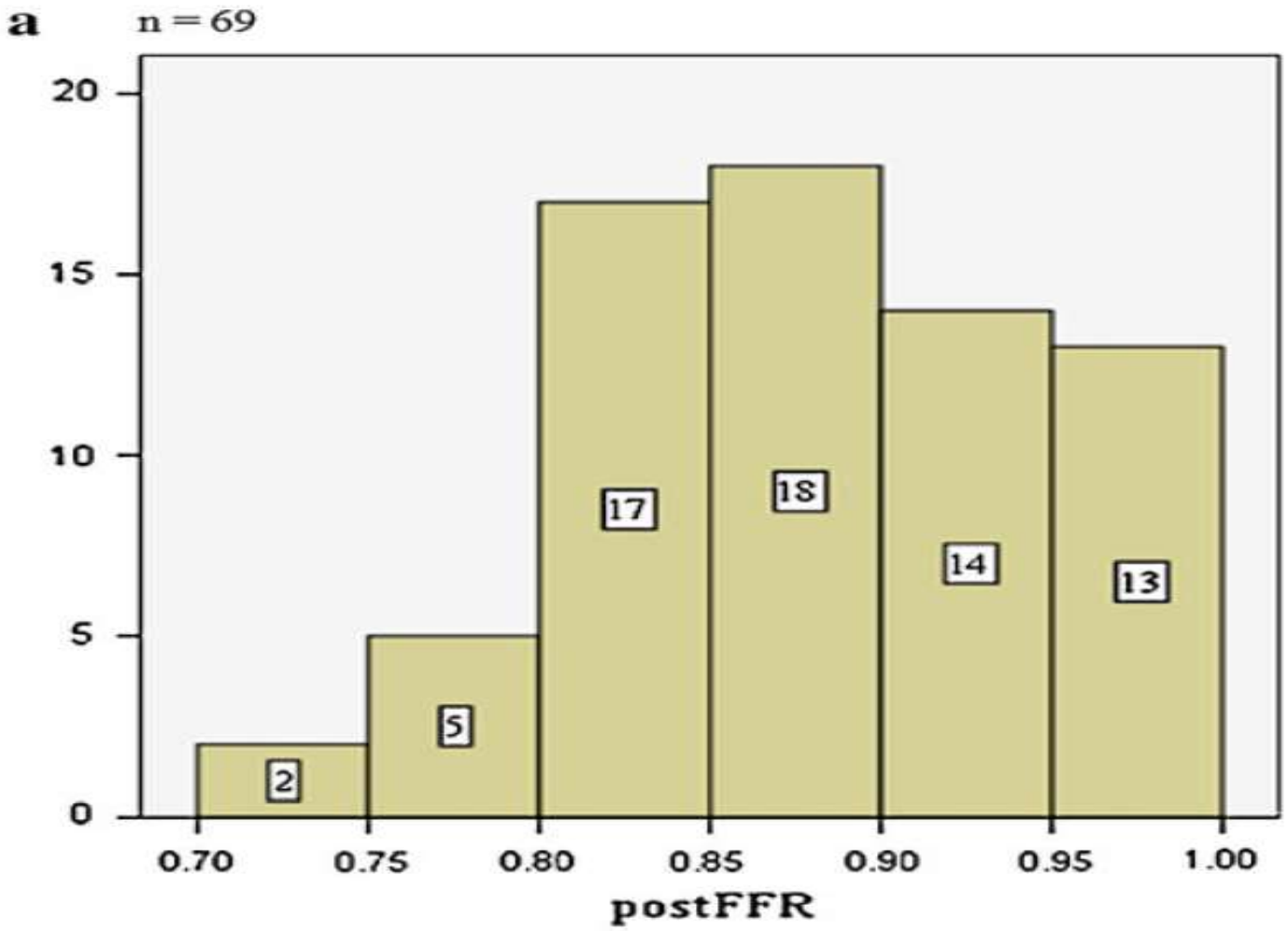
FFR gradient at proximal stent edge of LAD
0.91 →→ 0.99
$\Delta FFR_{stent/length}$ **= 0.44 (>0.14)**


IVUS showed stent underexpansion
Stent
Stent Underexpansion

Evaluate PCI Results and Predict Prognosis

Post PCI FFR: PCI result + Residual Disease

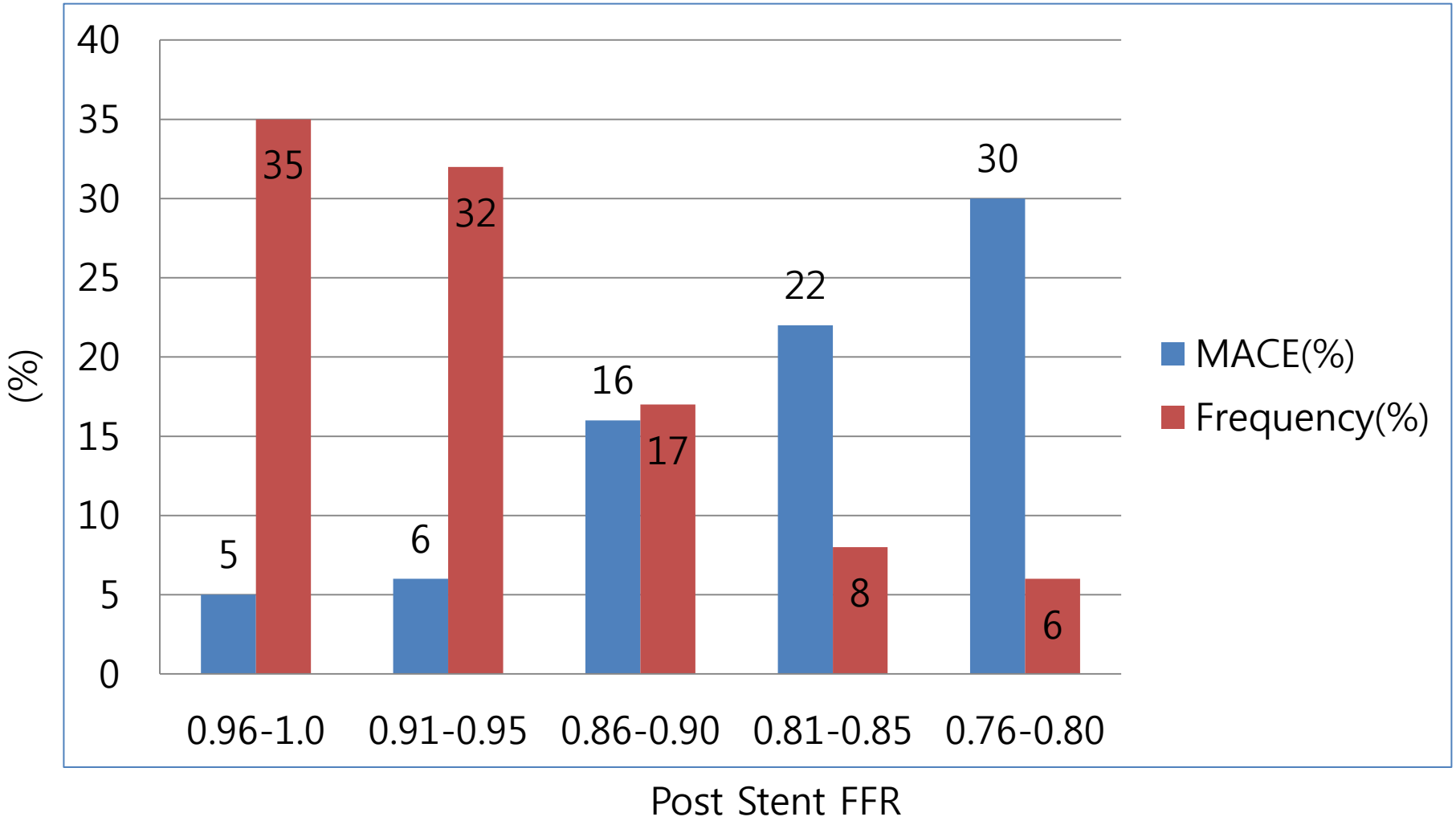
Distribution of Post Stent FFR



It is not easy to achieve post-interventional FFRs of 0.9 or greater.

A Matsuo et al. Cardiovasc Interv Ther (2013) 28:170–177

Post BMS FFR and 6 month MACE



N Pijls et al. Circulation 2002

Post DES FFR and MACE

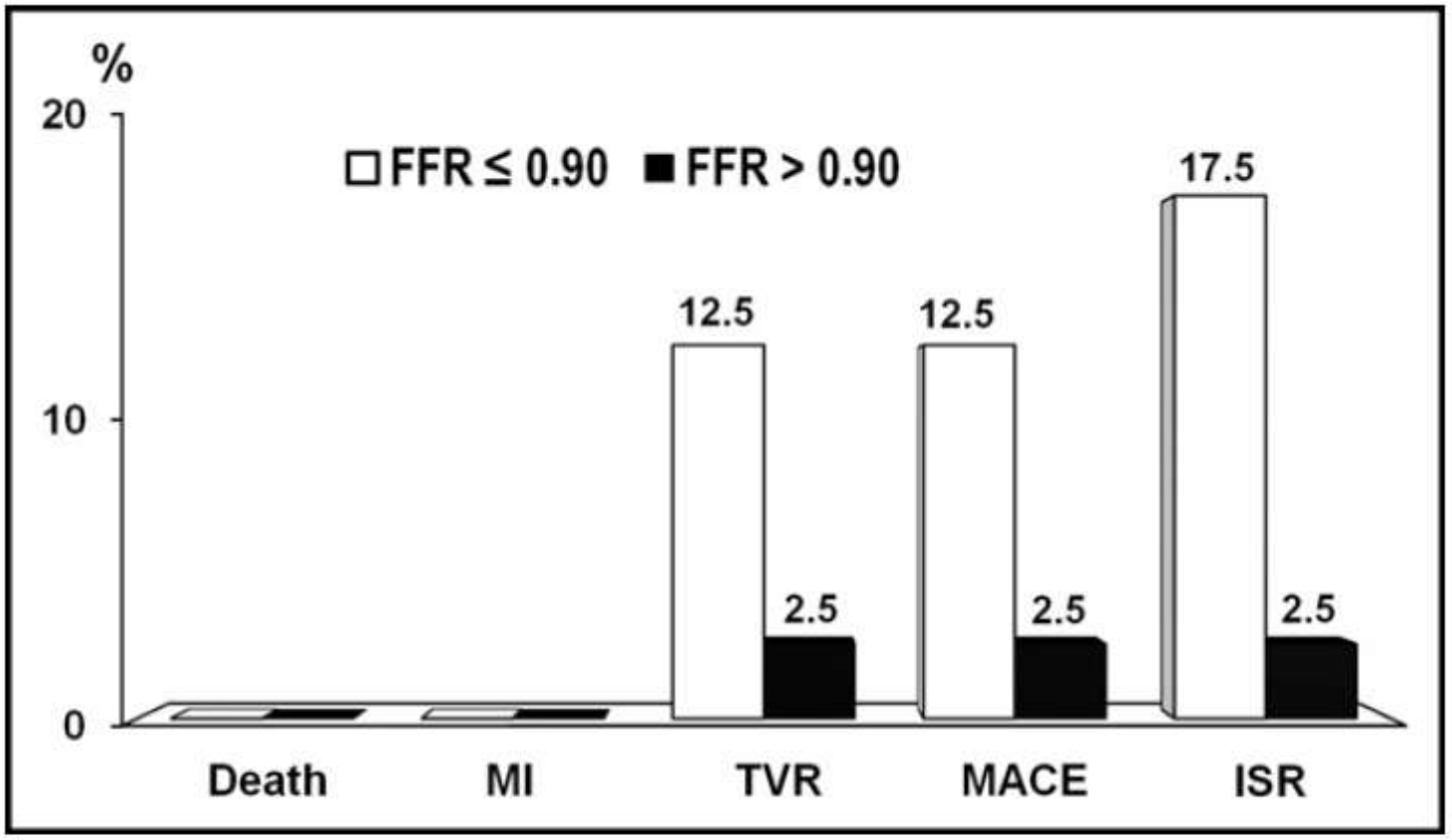
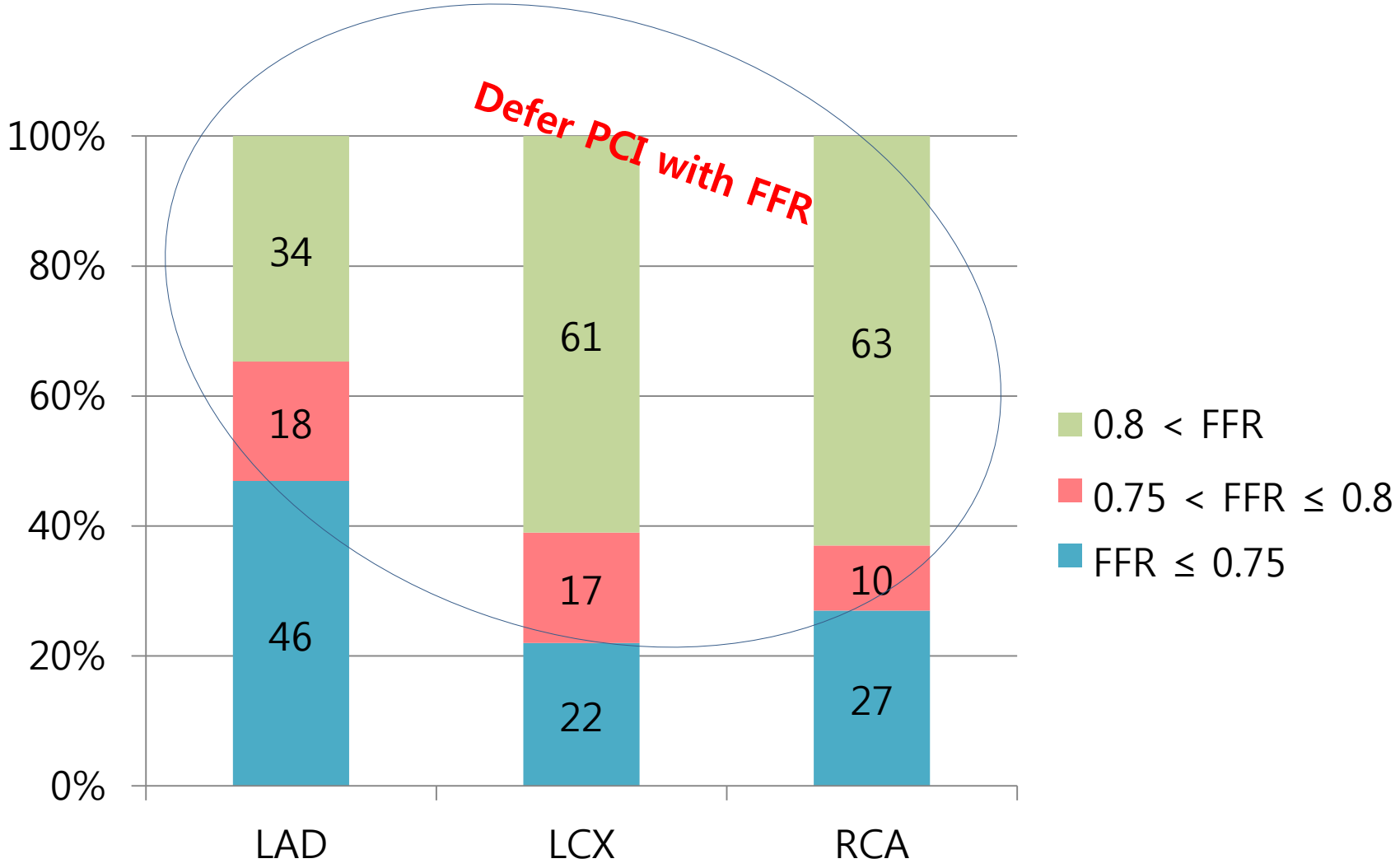


Figure 1. One-year clinical outcomes according to median value of FFR after DES implantation. MI = myocardial infarction; TVR = target-vessel revascularization; ISR = in-stent restenosis. $p < 0.05$.

CW Nam et al. AJC 2011

FFR-guided PCI vs. Angio-guided PCI

FFR in angiographically significant stenosis(%DS>50%)



15-year follow-up of the DEFER trial

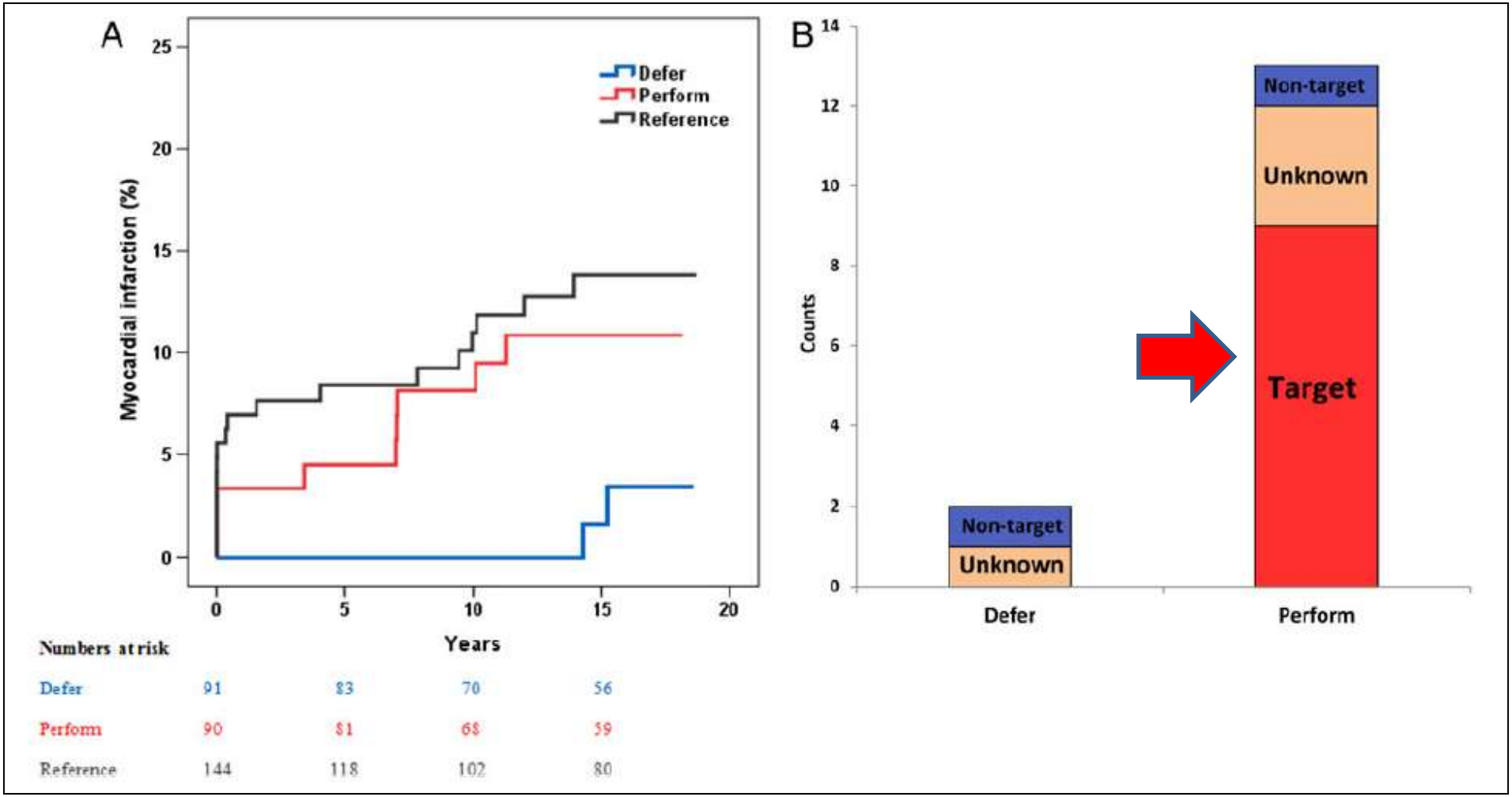
	Defer group (n = 91)	Perform group (n = 90)	Reference group (n = 144)
MI			
All	2	13	19
Target vessel	0	9	13
Unknown vessel	1	3	1
Non-target vessel	1	1	5
PCI			
All	49	47	66
Target vessel	30	28	38
Non-target vessel	19	19	28
CABG			
All	11	7	23
Target vessel	10	7	22
Non-target vessel	1	0	1

Cumulative adverse events after 15 years

Deferral of PCI with FFR (Defer Group: DS>50% and FFR>0.75) is associated with a favorable very long-term follow-up **without signs of late 'catch-up' phenomenon.**

Zimmermann FM, et al. EHJ (2015) 36, 3182–3188

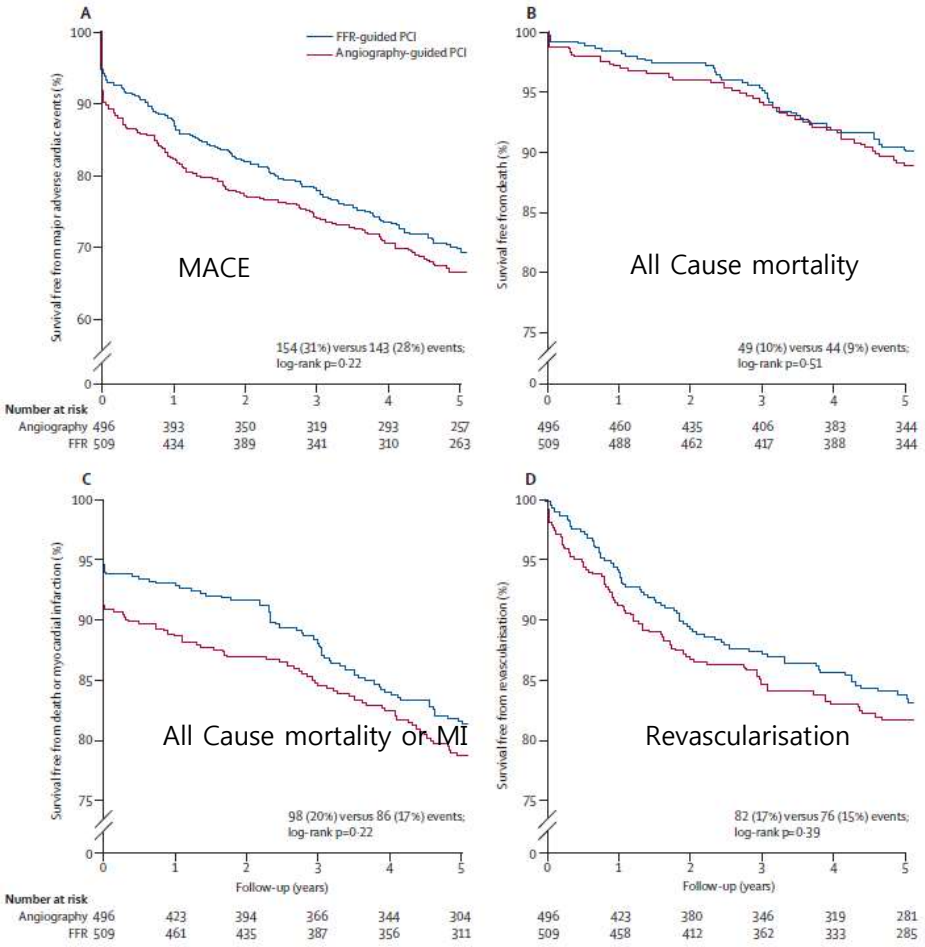
15-year follow-up of the DEFER trial : MI



Kaplan–Meier of myocardial infarction (A) and **relation of myocardial infarction with study vessel territory (B).**

Zimmermann FM, et al. EHJ (2015) 36, 3182–3188

FAME: 5-year follow up



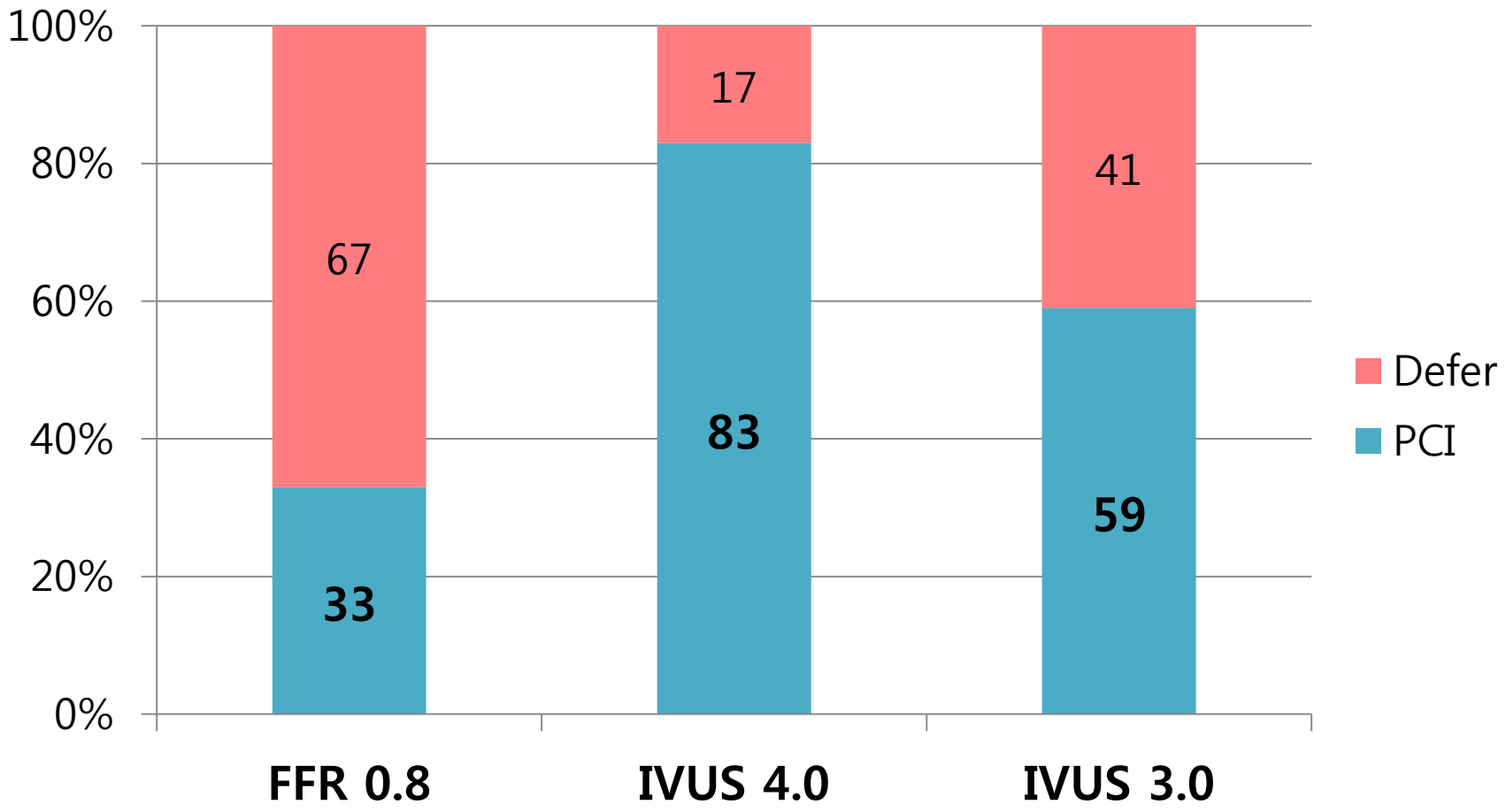
Kaplan-Meier curves for survival free from….

- **FAME confirms the long-term safety of FFR-guided PCI in MVD with significant decrease of MACEs for up to 2 years.** It was achieved with a lower number of stented and less resource use.
- From 2 years to 5 years, the risks for both groups developed similarly.

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

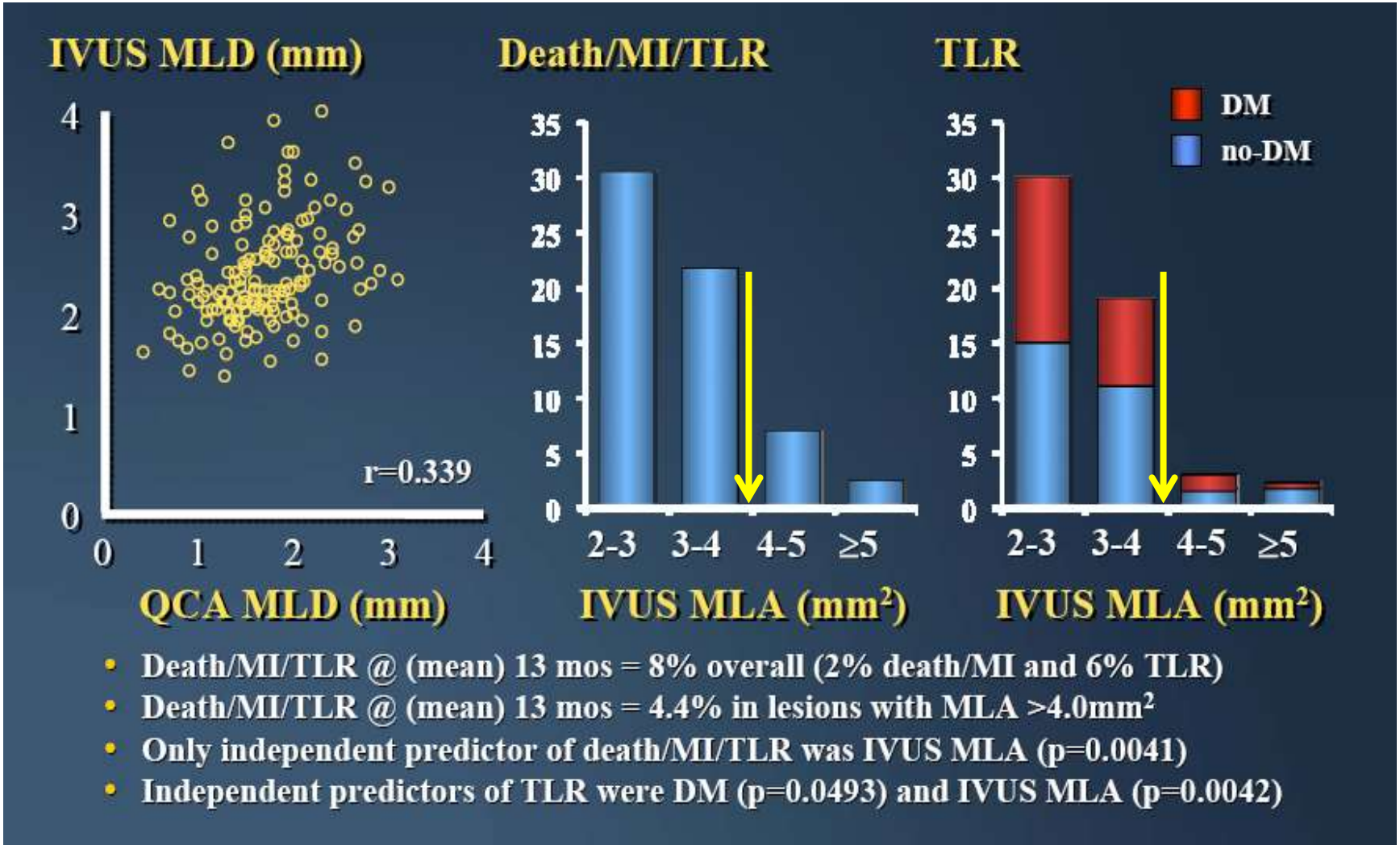
FFR-guided PCI vs. IVUS-guided PCI

Possible Incidence of PCI according to different Cut-Off in intermediate coronary artery stenoses (n=267)



Is it safe to defer PCI in patients with IVUS MLA>4.0mm² ?

Clinical Follow up in 357 Intermediate Lesions in 300 Pts Deferred Intervention After IVUS Imaging

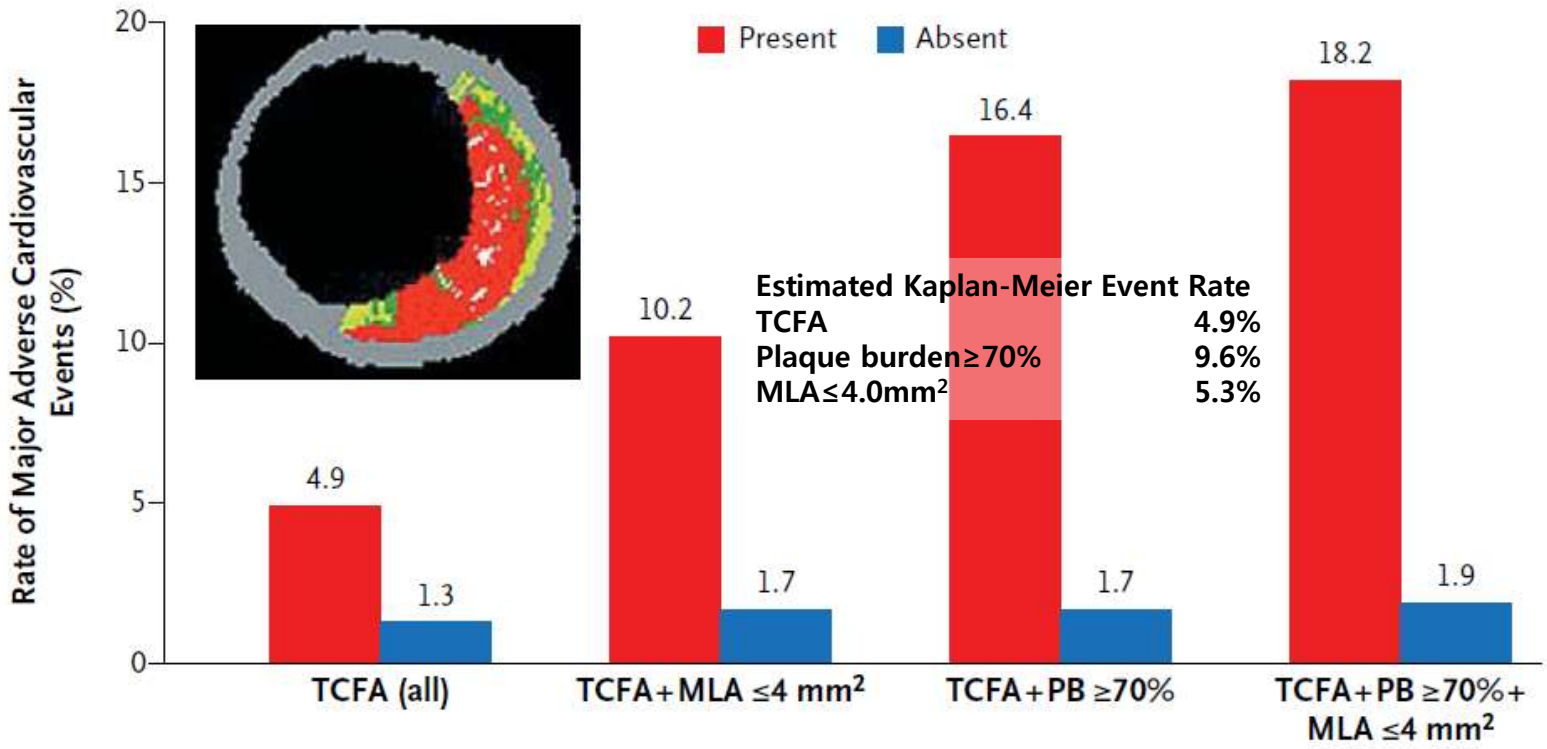


- Death/MI/TLR @ (mean) 13 mos = 8% overall (2% death/MI and 6% TLR)
- Death/MI/TLR @ (mean) 13 mos = 4.4% in lesions with MLA >4.0mm²
- Only independent predictor of death/MI/TLR was IVUS MLA (p=0.0041)
- Independent predictors of TLR were DM (p=0.0493) and IVUS MLA (p=0.0042)

Abizaid, et al. Circulation, 1999

PROSPECT

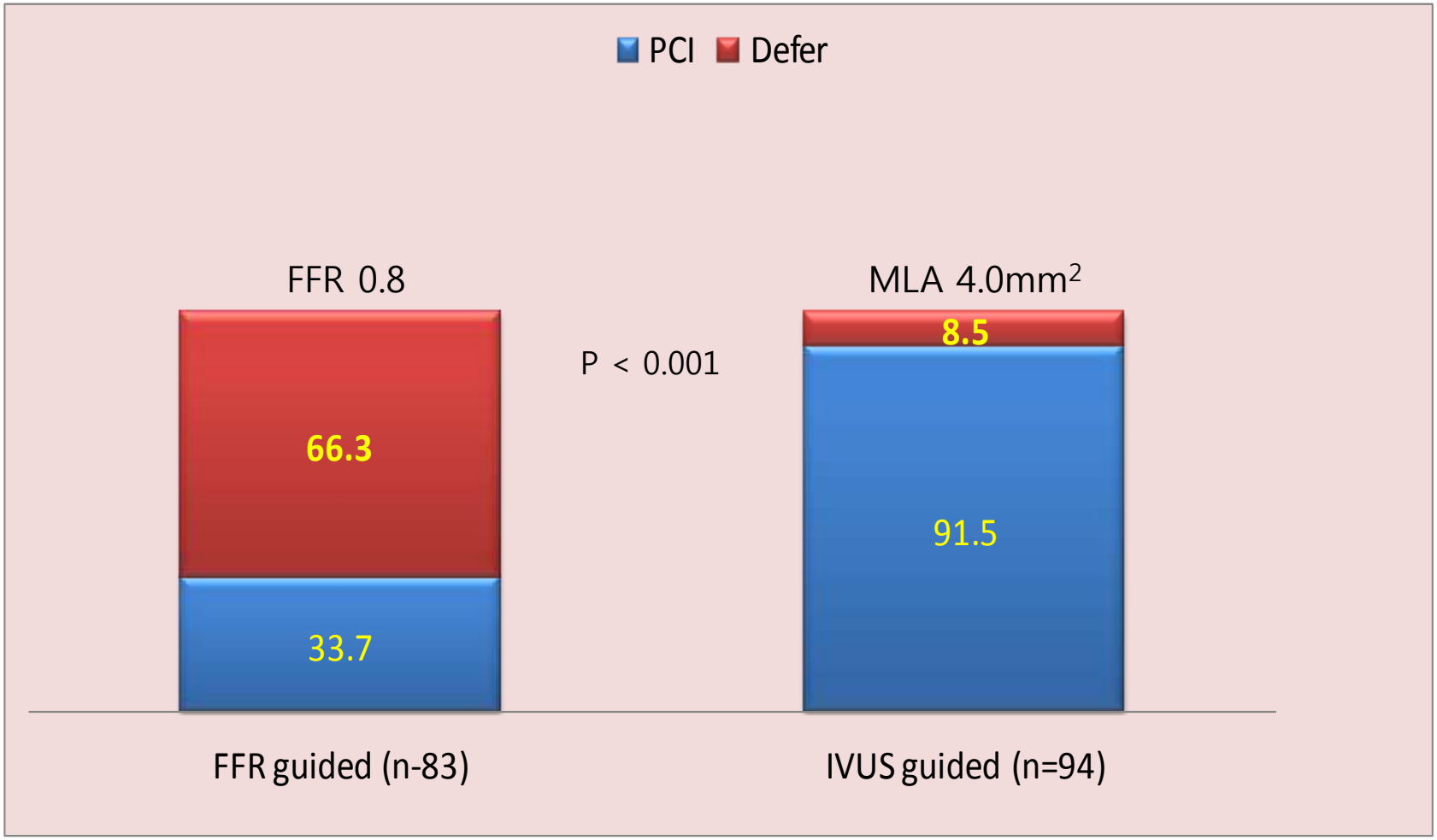
Event Rates for Lesions That Were and Those That Were Not Thin CapFibroatheromas, at a Median Follow-up of 3.4 Years



Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

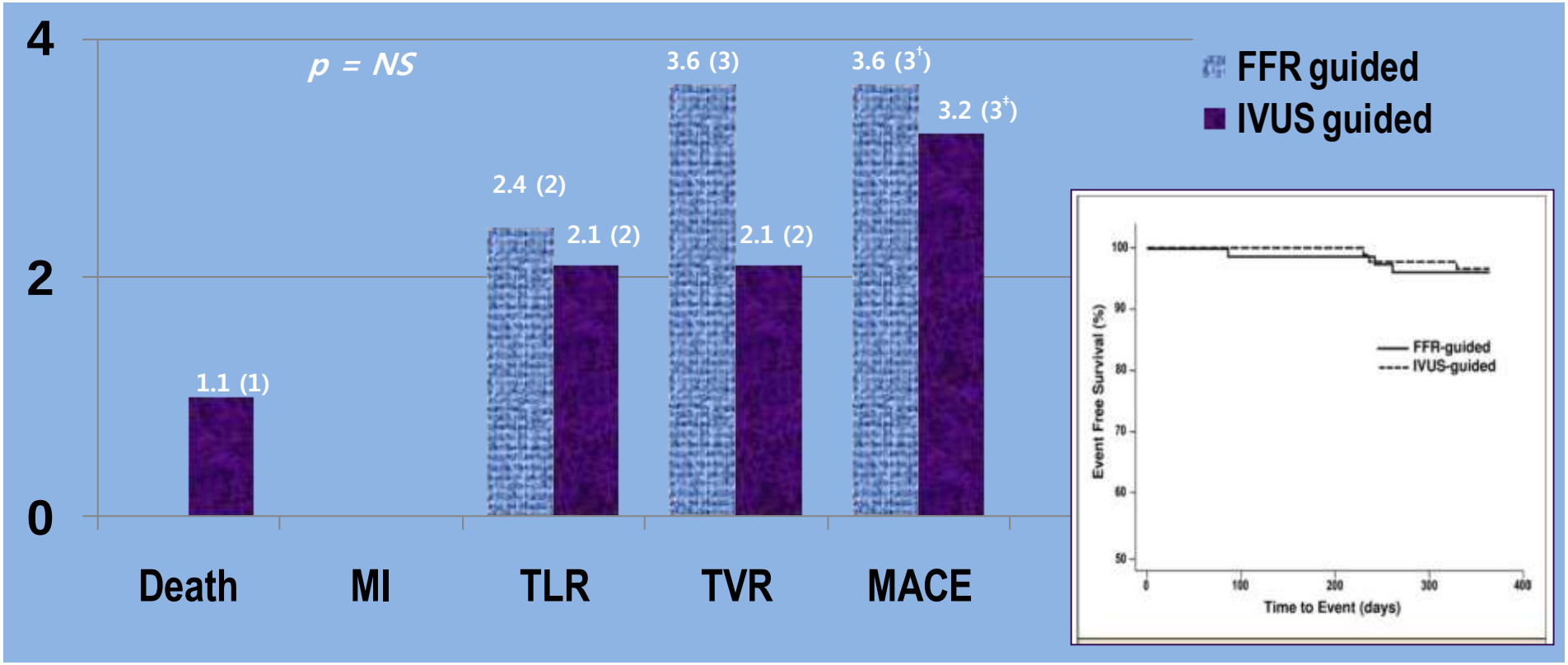
GW Stone et al. PROSPECT, NEJM 2011

IVUS vs. FFR-guided PCI: Korean Registry
Incidence of Deferring PCI



CW Nam et al. JACC Cardiovasc Interv. 2010

IVUS vs. FFR-guided PCI: Korean Registry
One Year Clinical Outcomes and event free survivals



†: one ISR, one de novo in defer lesion, one de novo in non-target lesions

‡: one noncardiac death, two ISR

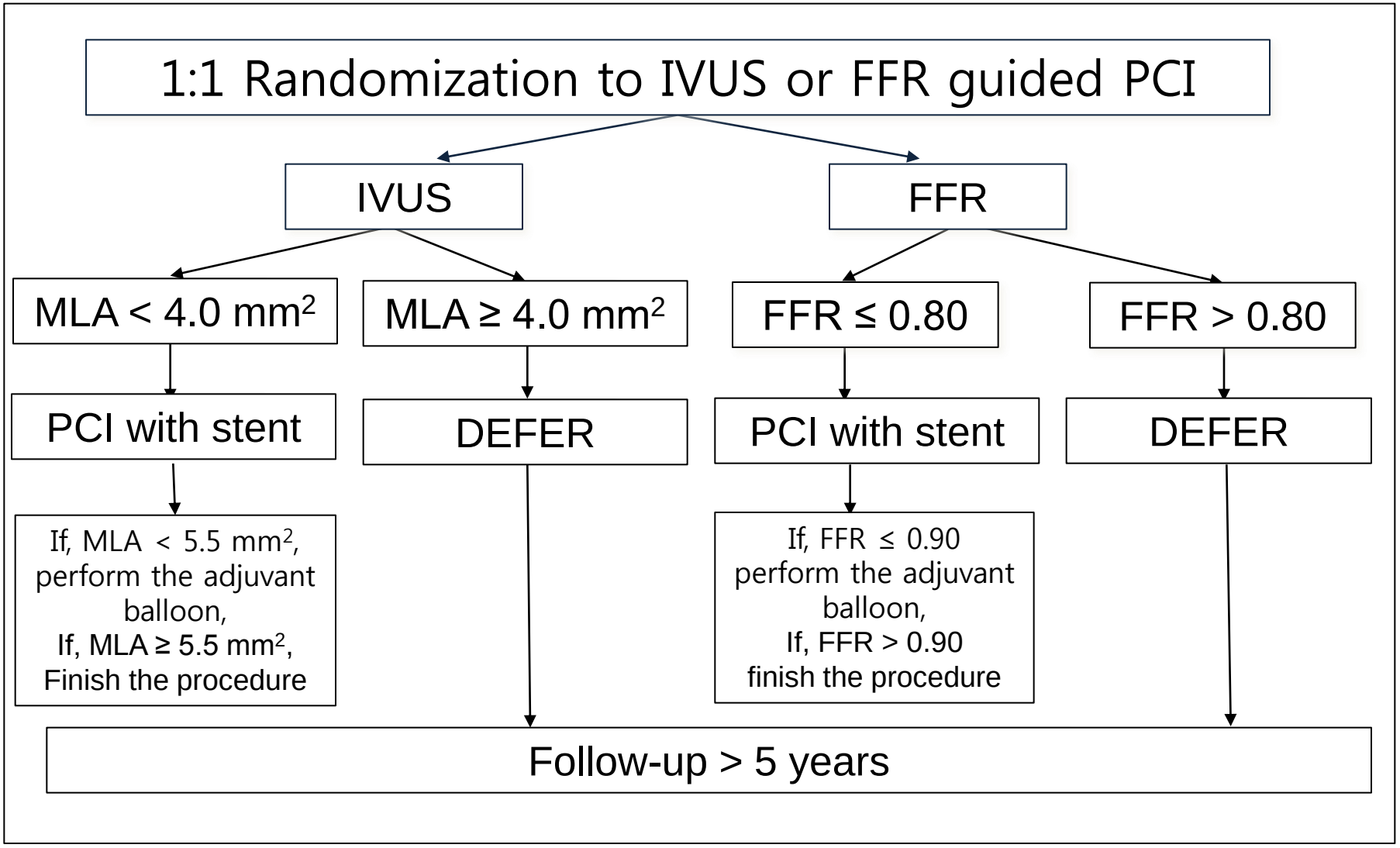
CW Nam et al. JACC Cardiovasc Interv. 2010

Fractional Flow Reserve- And Intra-Vascular Ultrasound-Guided Percutaneous CORonary Intervention with Drug-Eluting Stents in Intermediate Coronary Artery Lesion

FAVOR study

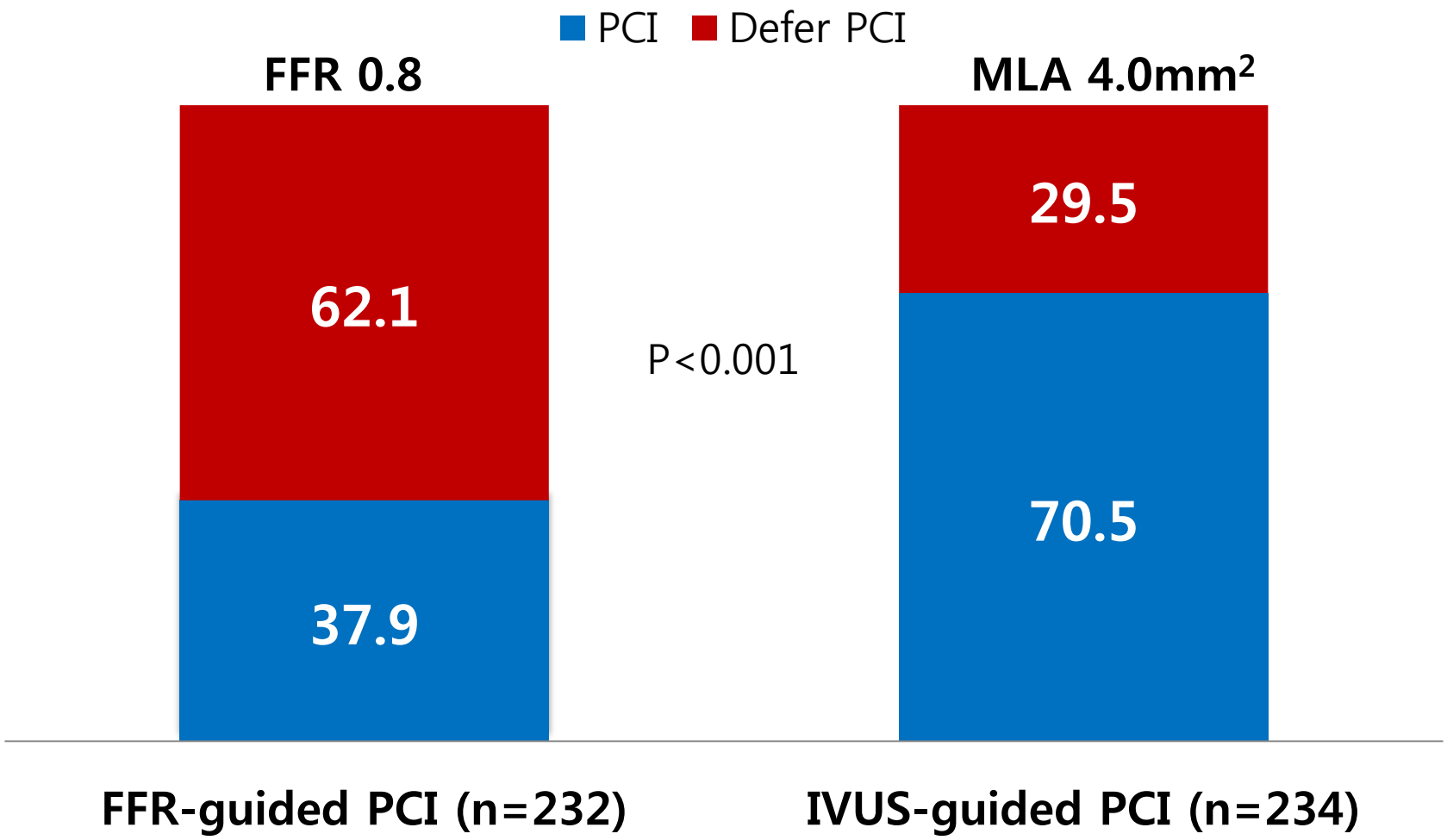
Korean Prospective Randomized Multicenter Trial

FAVOR



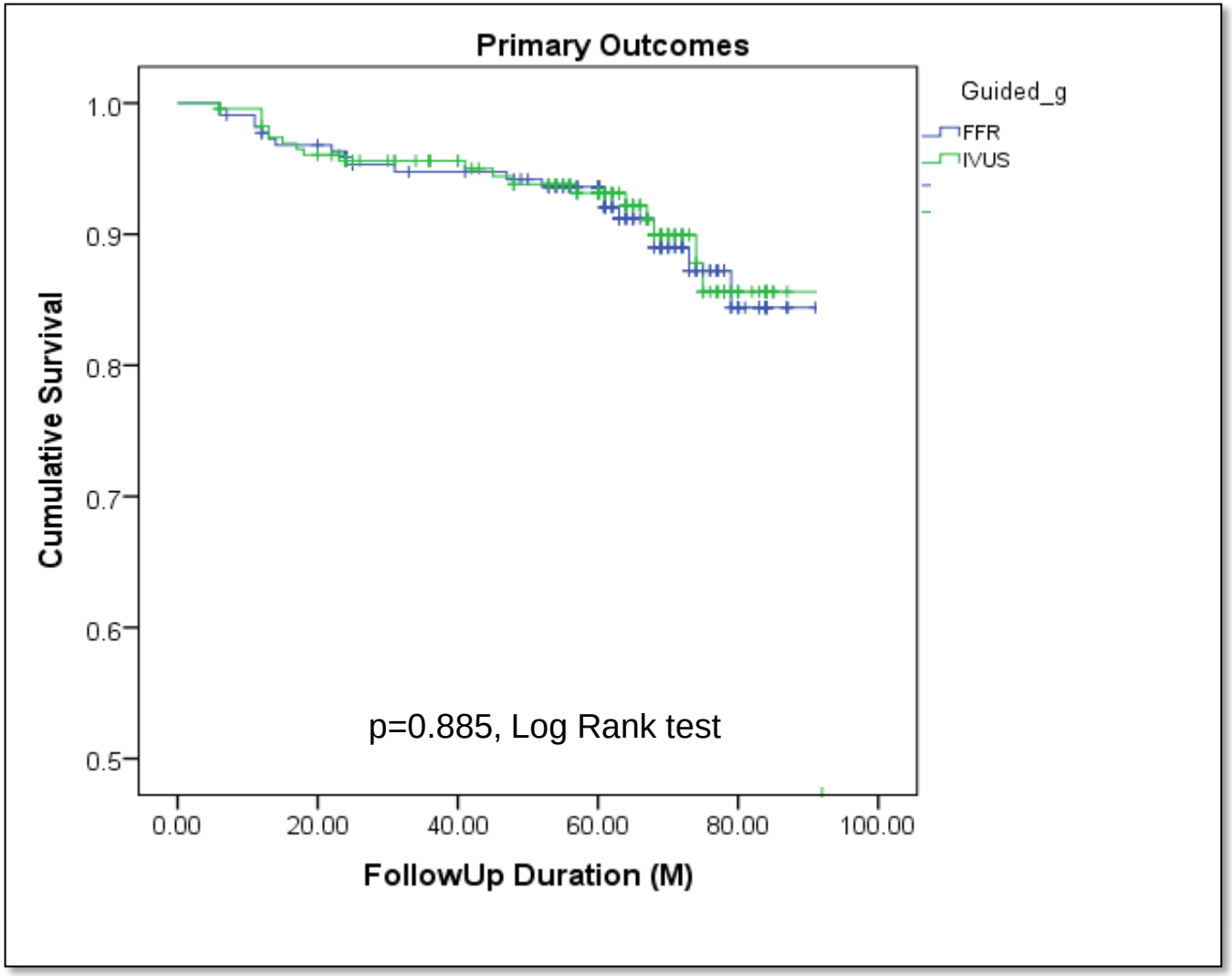
SJ Tahk et al. FAVOR Trial

FAVOR: Incidence of Deferring PCI



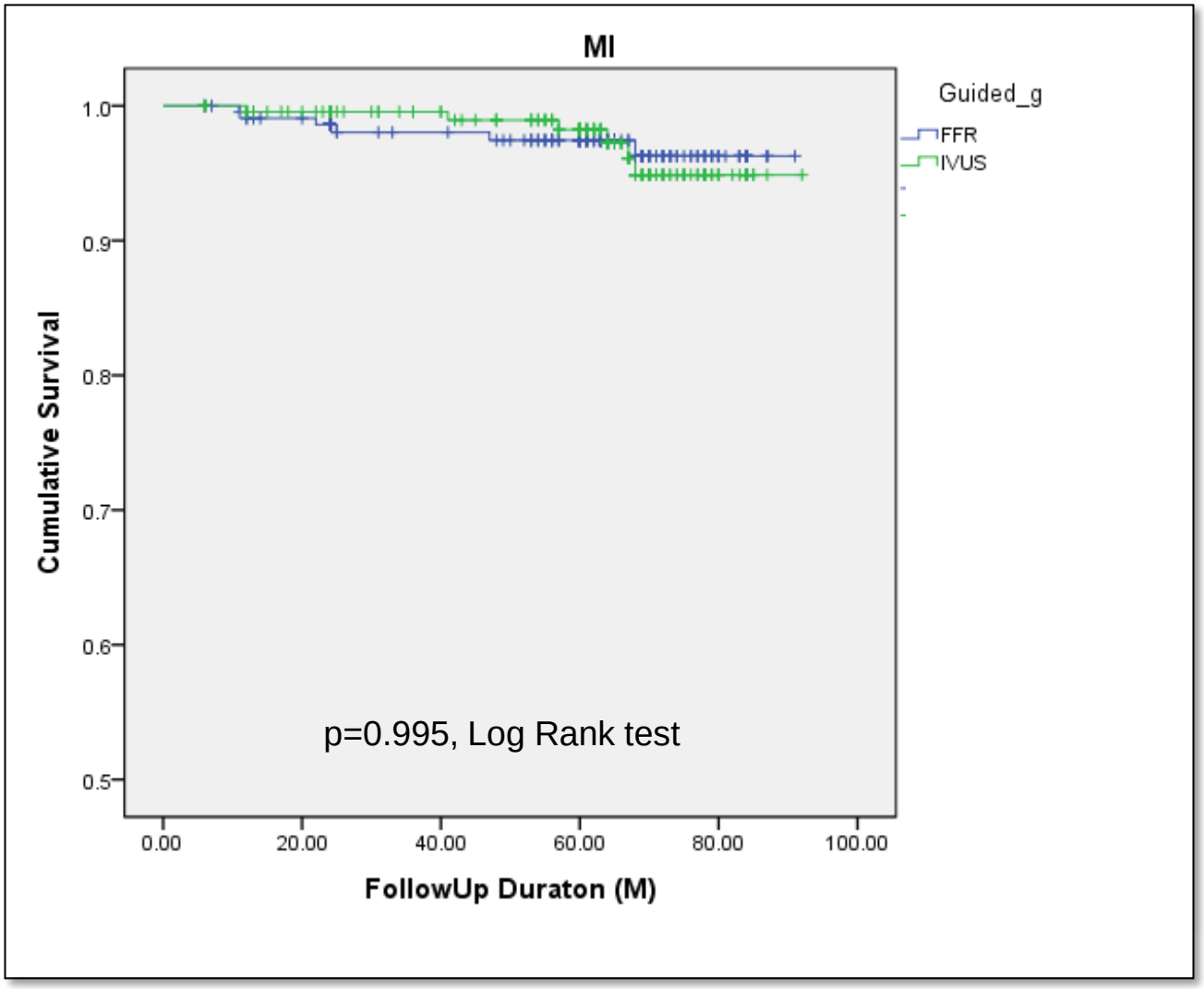
SJ Tahk et al. FAVOR Trial

FAVOR: MACE



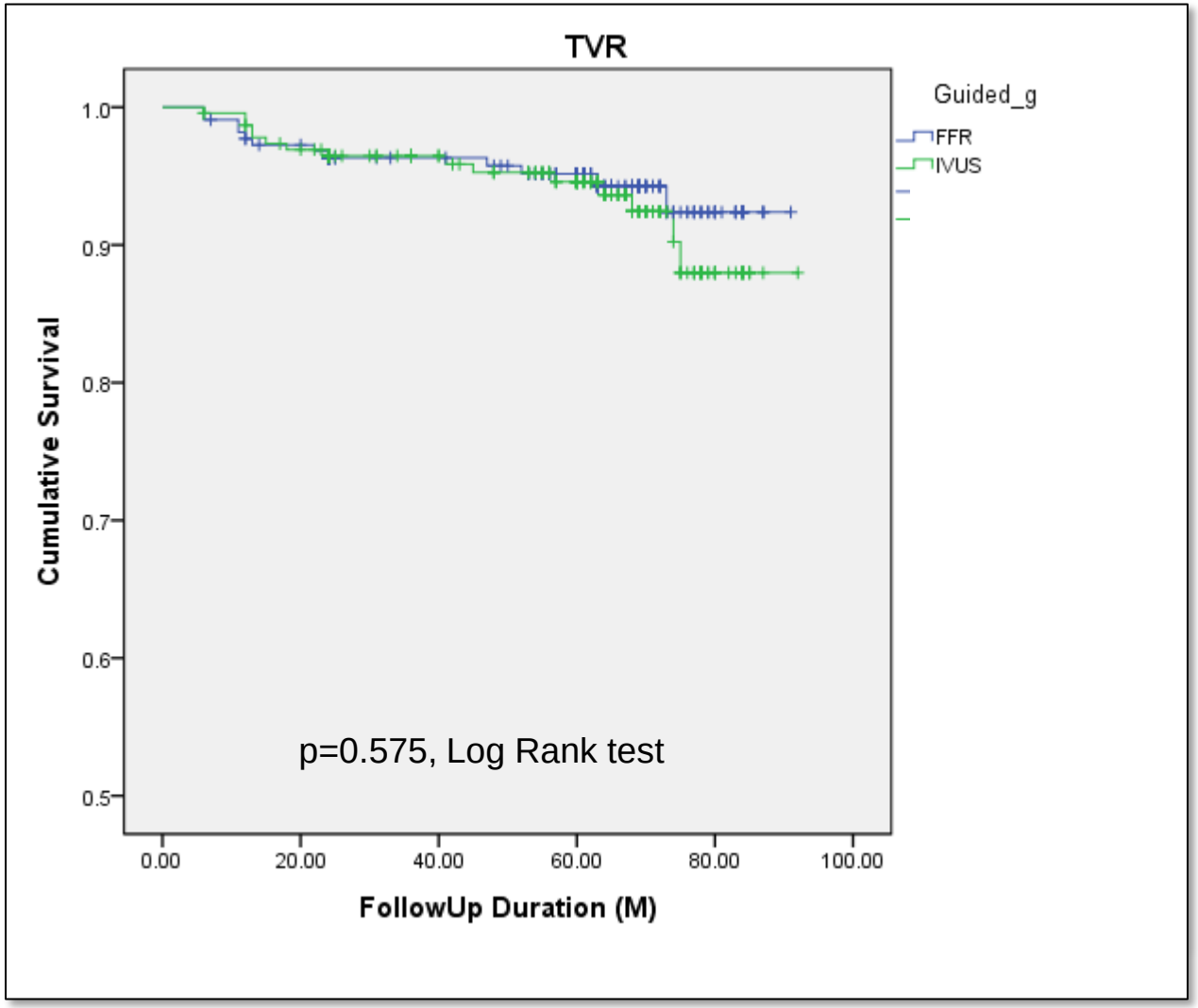
SJ Tahk et al. FAVOR Trial

FAVOR: MI



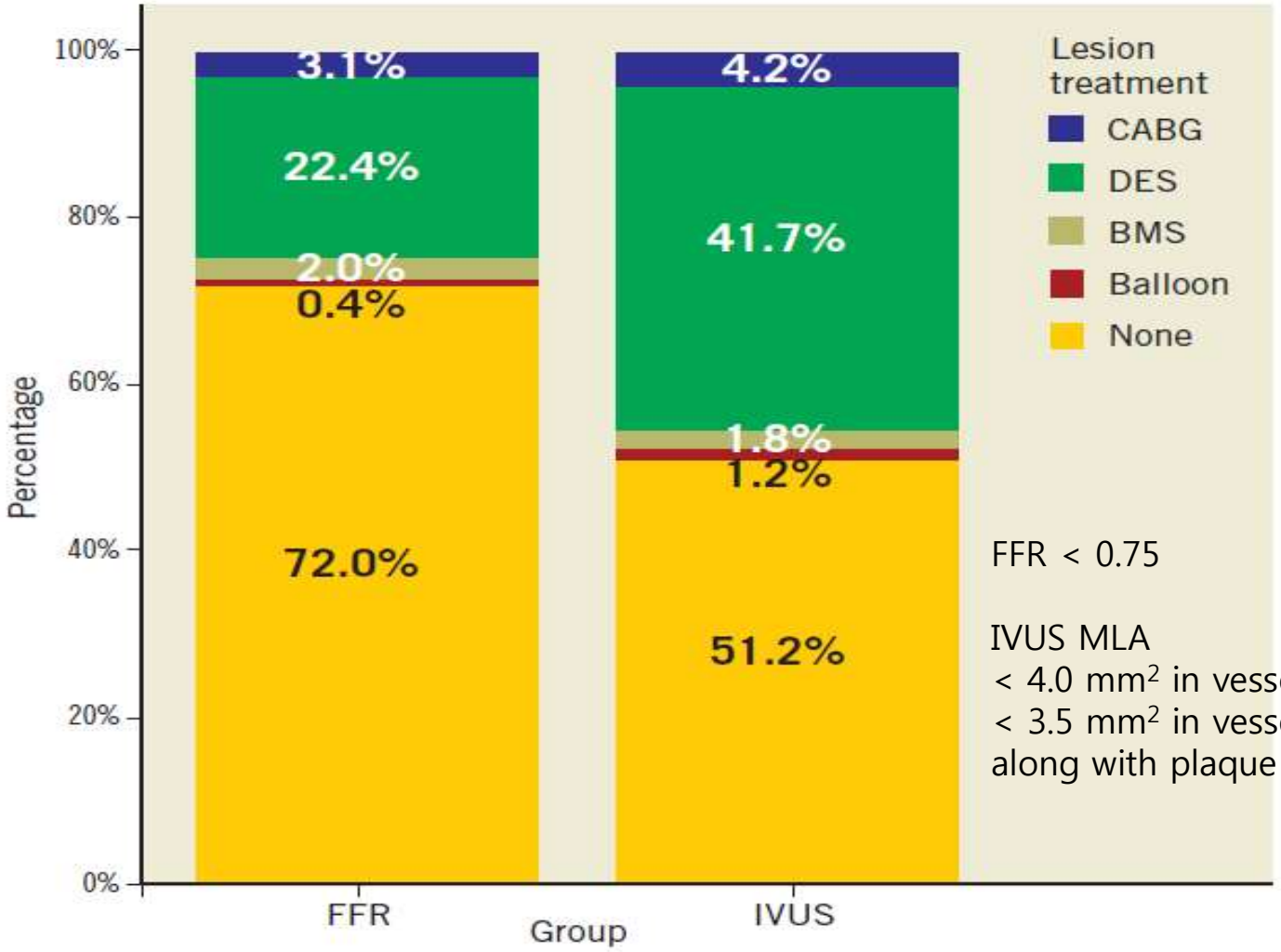
SJ Tahk et al. FAVOR Trial

FAVOR: TVR



SJ Tahk et al. FAVOR Trial

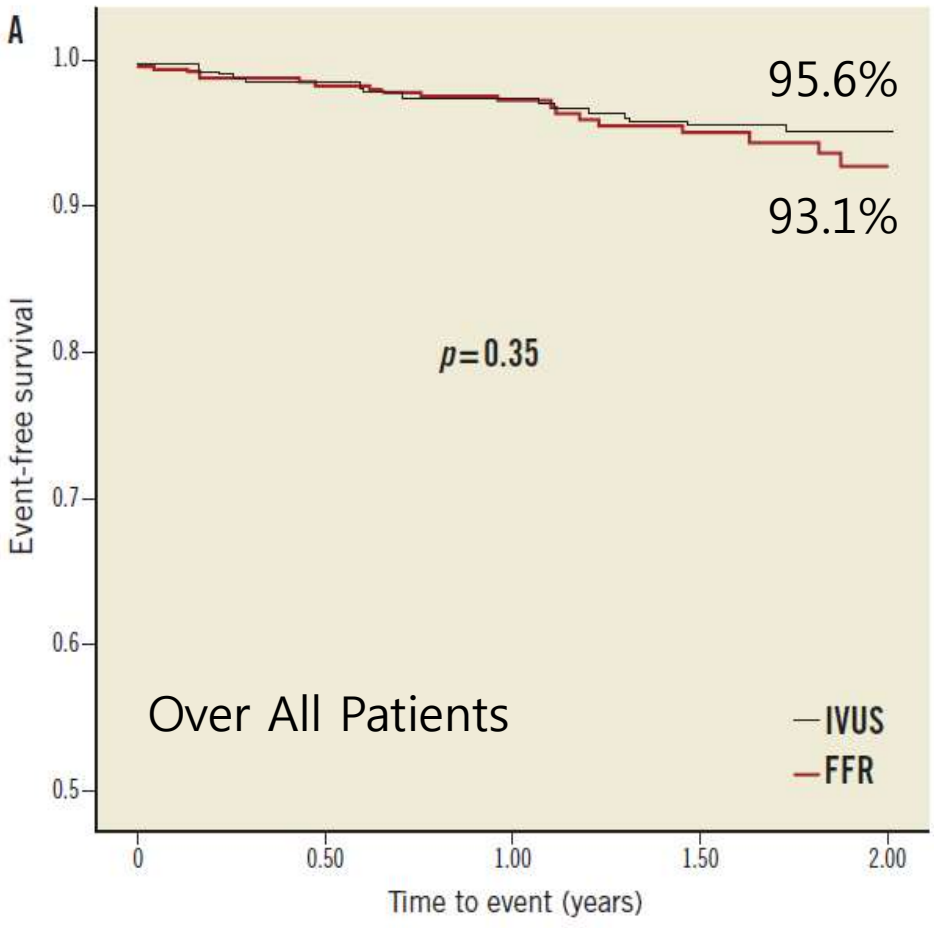
Treatment choice for lesions evaluated in FFR-guided vs. IVUS-guided groups

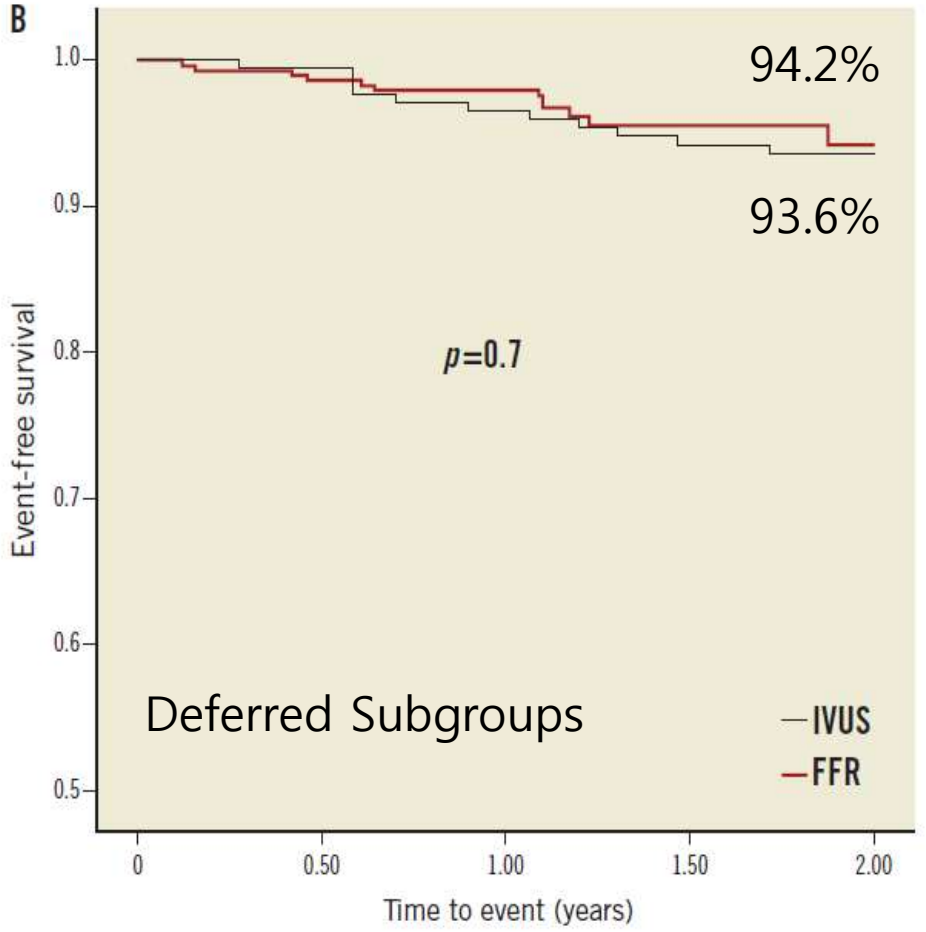


After FFR and IVUS, 72% and 51.2% of lesions, respectively, were left untreated ($p<0.001$)

JM de la Torre Hernandez et al. EuroIntervention 2013;9:824-830

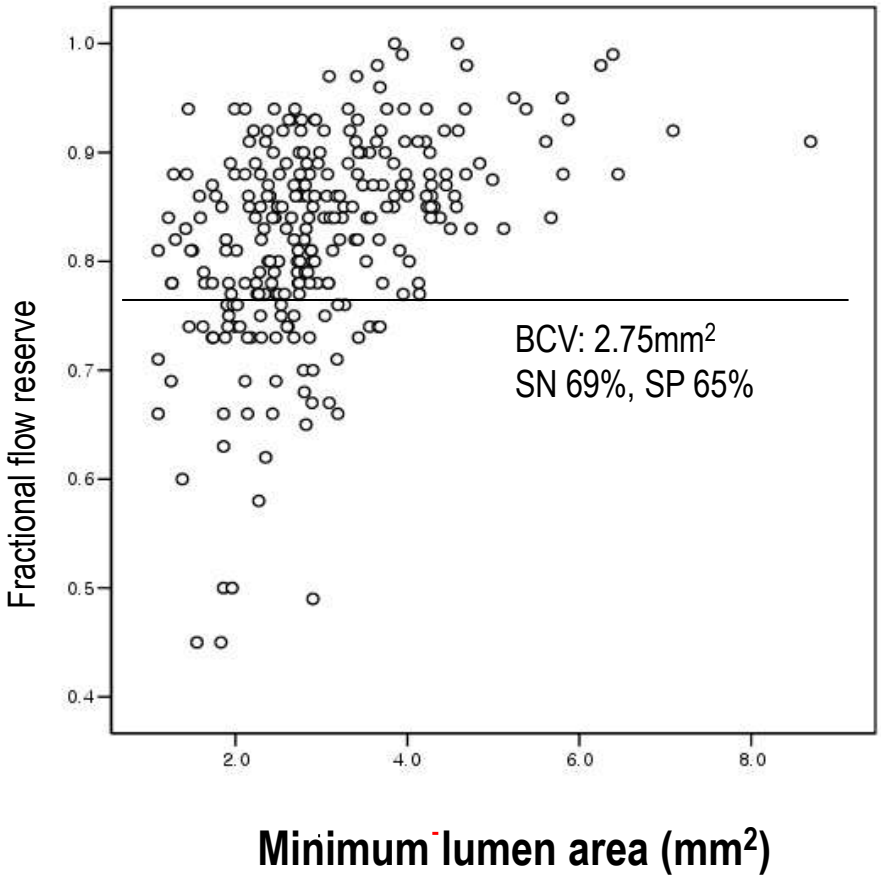
Kaplan-Meier event-free survival curves for the composite endpoint (cardiac death, target lesion MI and TLR)

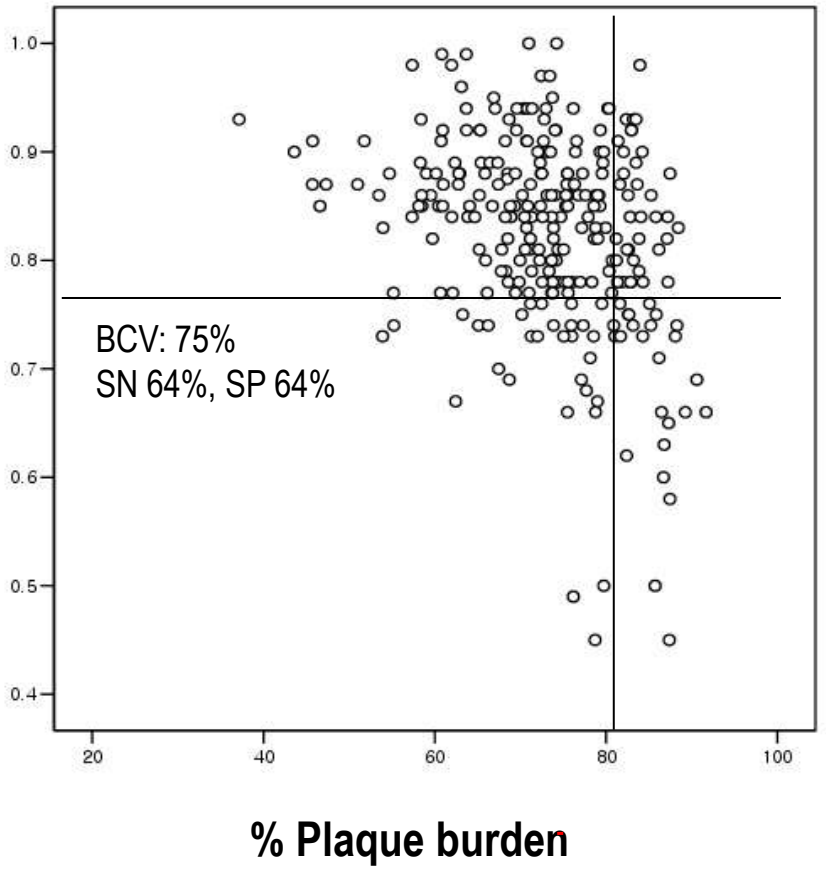




JM de la Torre Hernandez et al. EuroIntervention 2013;9:824-830

Possible explanation why IVUS-guided PCI is not inferior to FFR-guided PCI?





Two of 3 Independent IVUS variable, Correlates of MACE Related to Nonculprit Lesions in PROSPECT, **have relatively good correlation with FFR.**

Korean 4 Centers FFR Registry Data

Possible explanation why IVUS-guided PCI is not inferior to FFR-guided PCI?

MACE of non-culprit coronary stenosis (≈deferred stenosis?) on proper medical treatments from PROSPECT …

- Associated with a large plaque burden, a small luminal area, and thin-cap fibroatheromas.
- **Disease progression rather than plaque rupture. Most events were rehospitalizations for unstable or progressive angina.**
- Death from cardiac causes, cardiac arrest, and myocardial infarction were less common.
- Incidence of MACE is modest.

Y Xie et al. JAmColl Cardiol Img 2014;7:397–405
GW Stone et al. PROSPECT, NEJM 2011

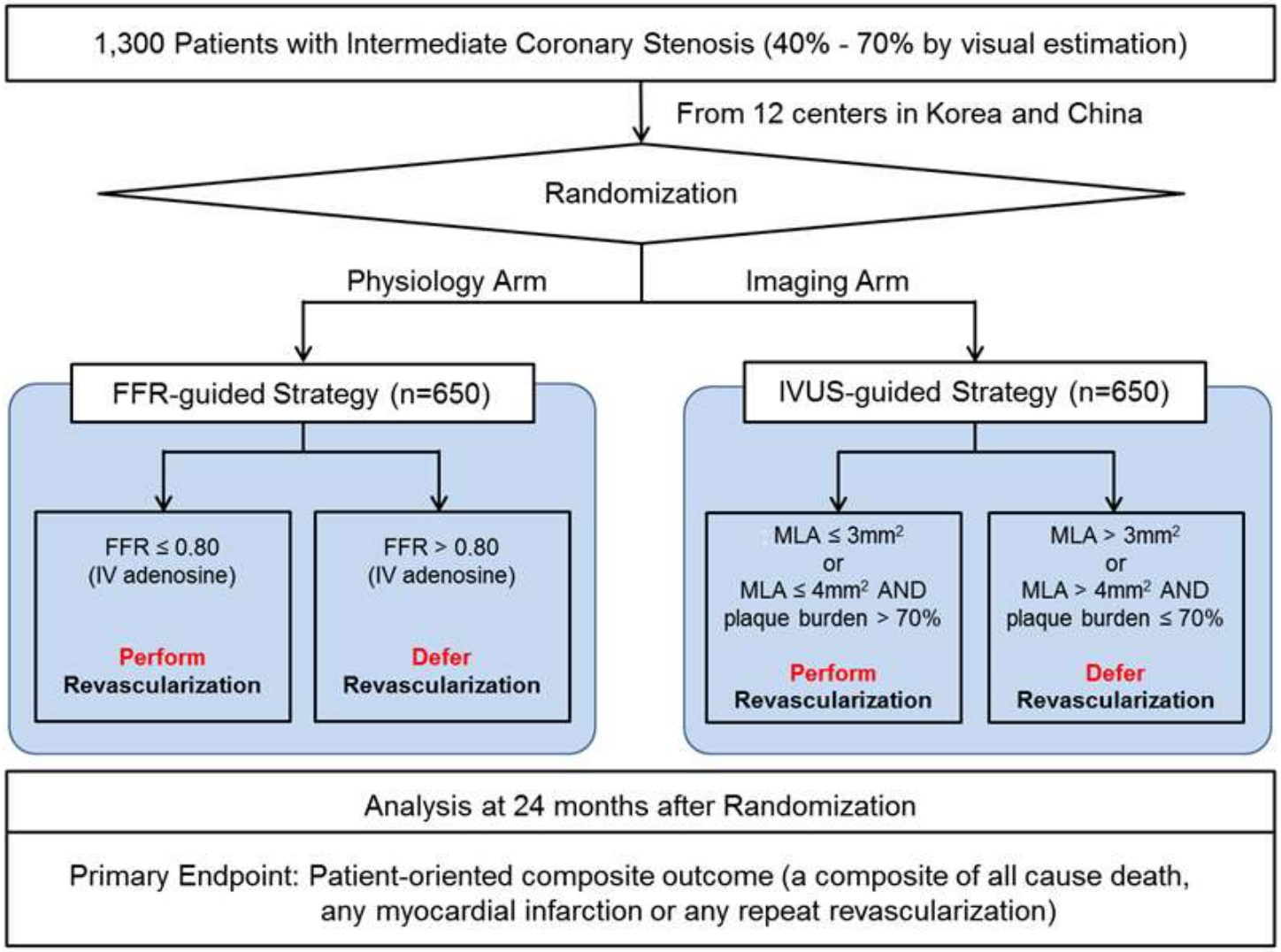
Comparison of Fractional FLow Reserve And IntraVascular ultrasound guided Intervention Strategy for Clinical OUtcomes in Patients with InteRmediate Stenosis

FLAVOUR Study

International

Prospective Randomized Multicenter Trial

Study diagram of the FLAVOUR study

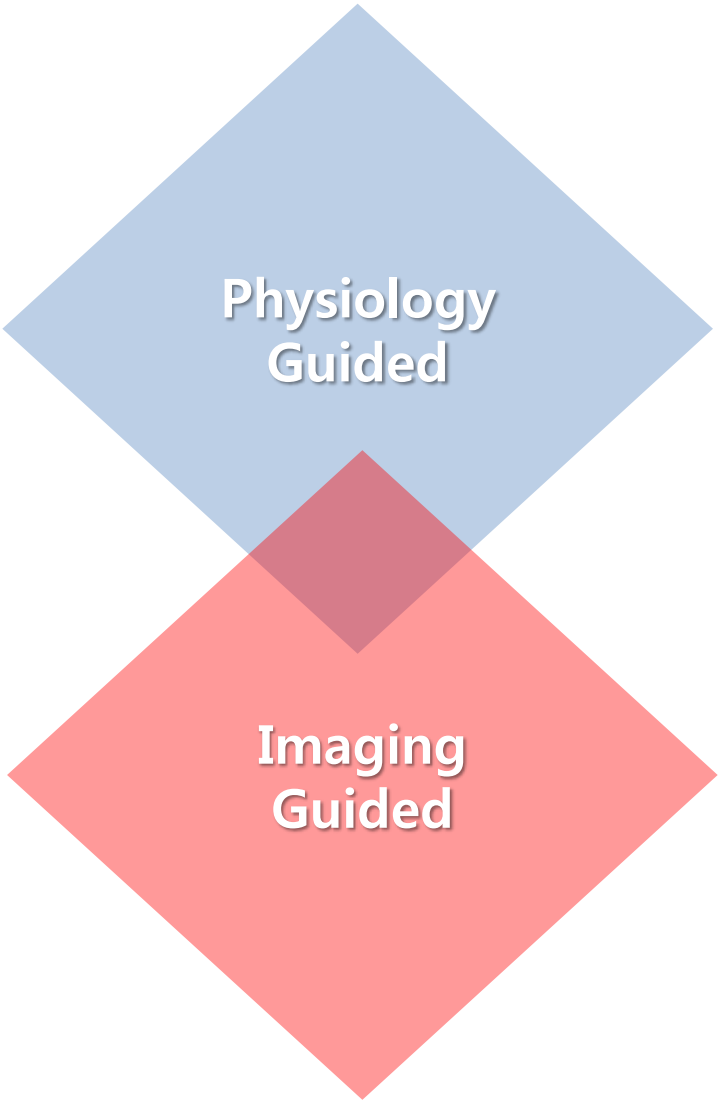


What is optimal guided PCI?

Appropriate using the imaging or physiologic tool alone or together be the optimal guided PCI.

3 Key Components of Guided PCI

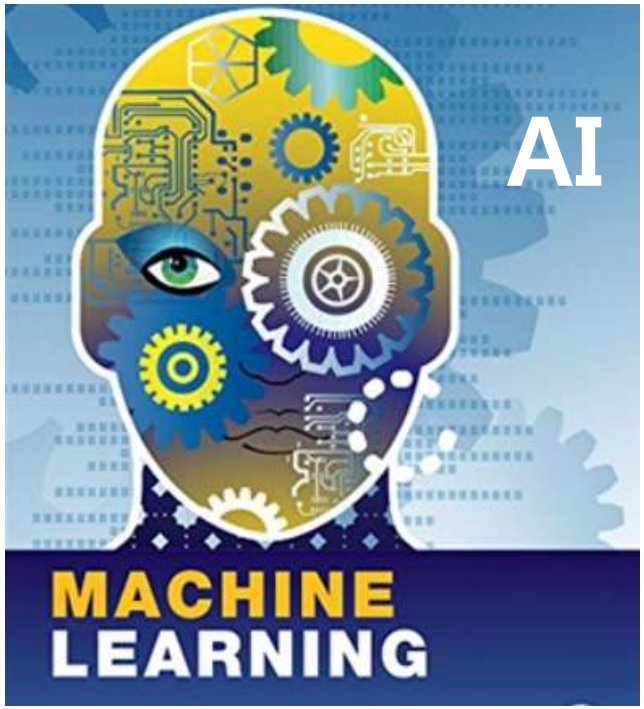
- Specify culprit lesion which induce myocardial ischemia
- Guide the procedural strategy, technique and devices
- Evaluate the PCI results and predict the clinical outcome or prognosis



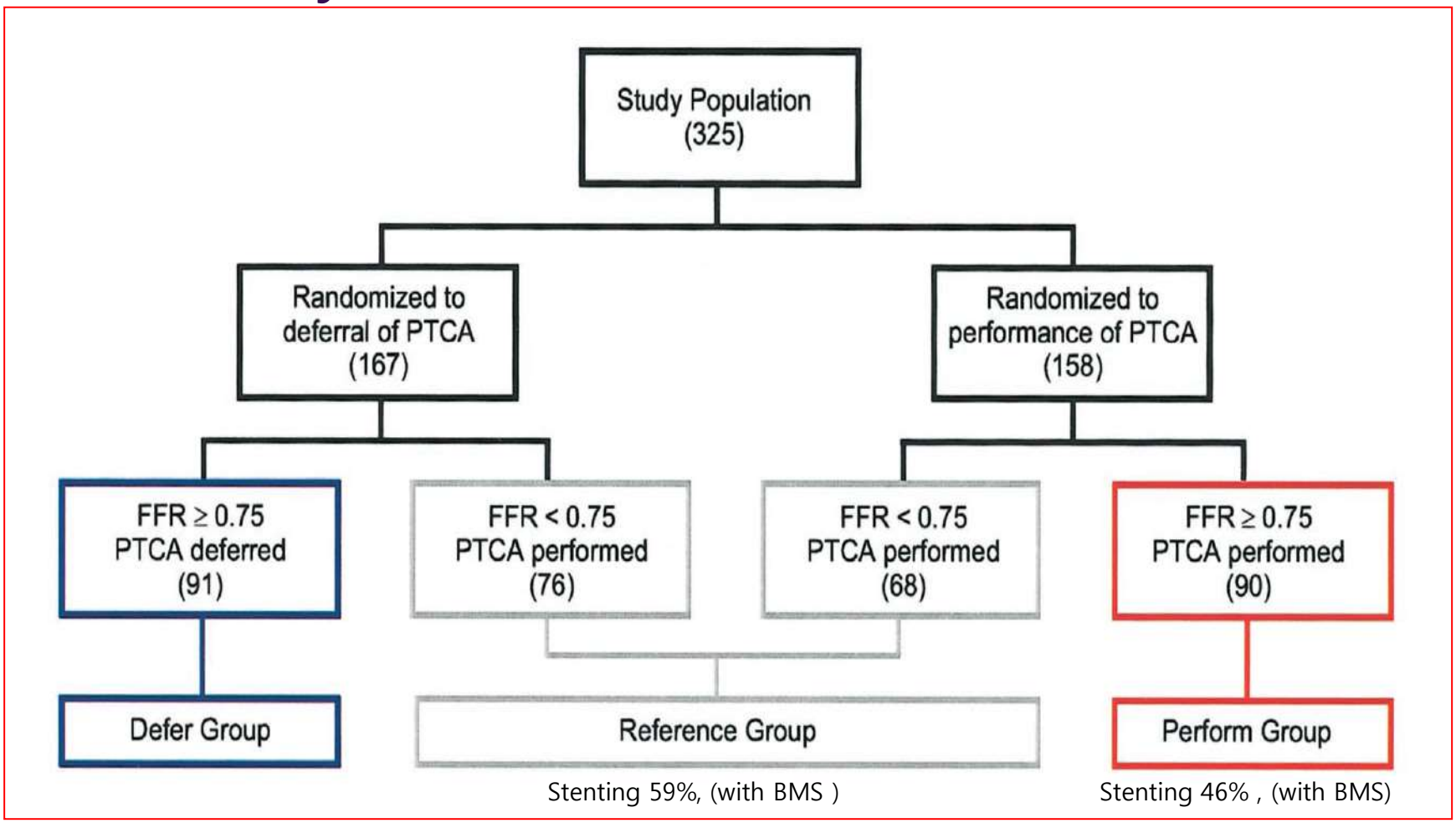
Optimization of PCI comes from Cessation of Cold War Mentality

Hybrid Guided PCI
Right Device
to Right Patient and Lesion
on Right Time

Which one will be Future Interventional Cardiologist



DEFER Study



Patients with stable angina were eligible if they fulfilled the following inclusion criteria: 1) referral for elective PCI of a **single angiographically significant de novo stenosis** (more than 50% diameter stenosis by visual assessment) in a native coronary artery with a reference diameter of more than 2.5 mm; and 2) no evidence of reversible ischemia had been documented by noninvasive testing within the last 2 months.

GJW Bech et al. Circulation. 2001;103:2928-2934
Nico H. J. Pijls et al, JACC 2007;49:2105–11

FFR for prediction of restenosis following SES

Variable	OR	95% CI	*p*
Diabetes mellitus	0.64	0.09–4.53	0.657
Chronic kidney disease	20.99	2.12–207.98	0.009
Pre reference lumen diameter	0.25	0.02–2.64	0.249
Lesion length	1.02	0.92–1.12	0.740
Minimum stent diameter	0.36	0.03–4.04	0.408
Post-percent diameter stenosis	1.05	0.92–1.19	0.497
Pre FFR	0.25	0.00–4.36	0.162
Post FFR	0.01	0.00–0.86	0.019
Minimum stent area	0.91	0.50–1.64	0.754
Minimum lumen area at proximal edge	0.42	0.21–0.87	0.020
Whole minimum lumen area	0.85	0.49–1.49	0.567

H. Ishii et al. Heart Vessels (2011) 26:572–581