Can We Safely Defer PCI Just Based on FFR>0.80?

Yes, already proven

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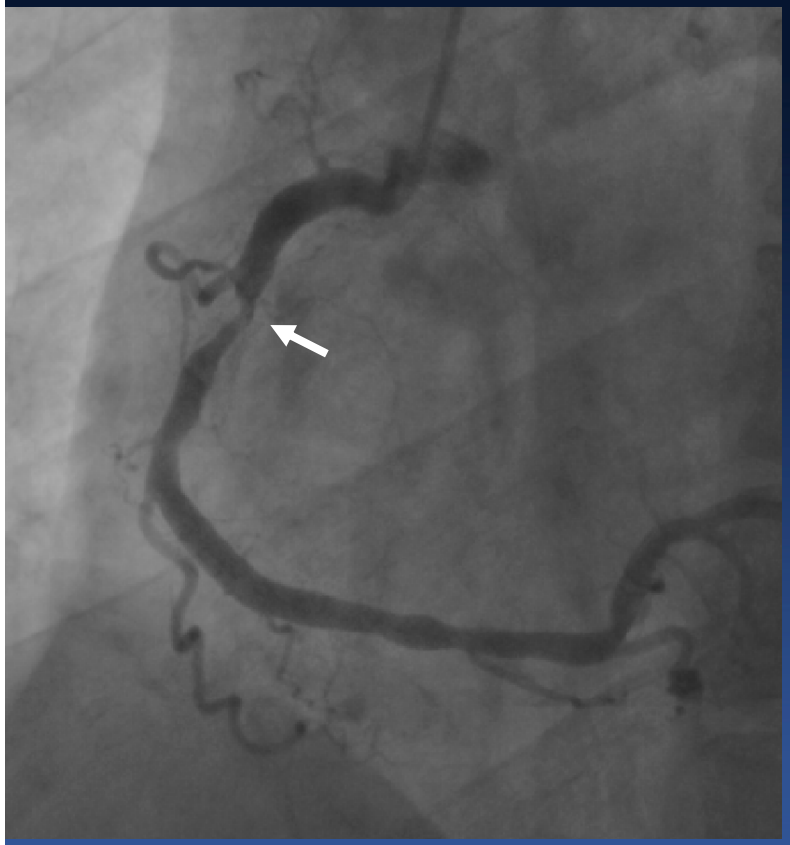
University of Ulsan, College of Medicine
Heart Institute, Asan Medical Center, Seoul, Korea

Why FFR ?

Is Angiography Enough for Diagnosis of Clinical Ischemia ?

Visual Functional Mismatch



Angiographic DS(%) : 85%

IVUS MLA : 2.8 mm^2

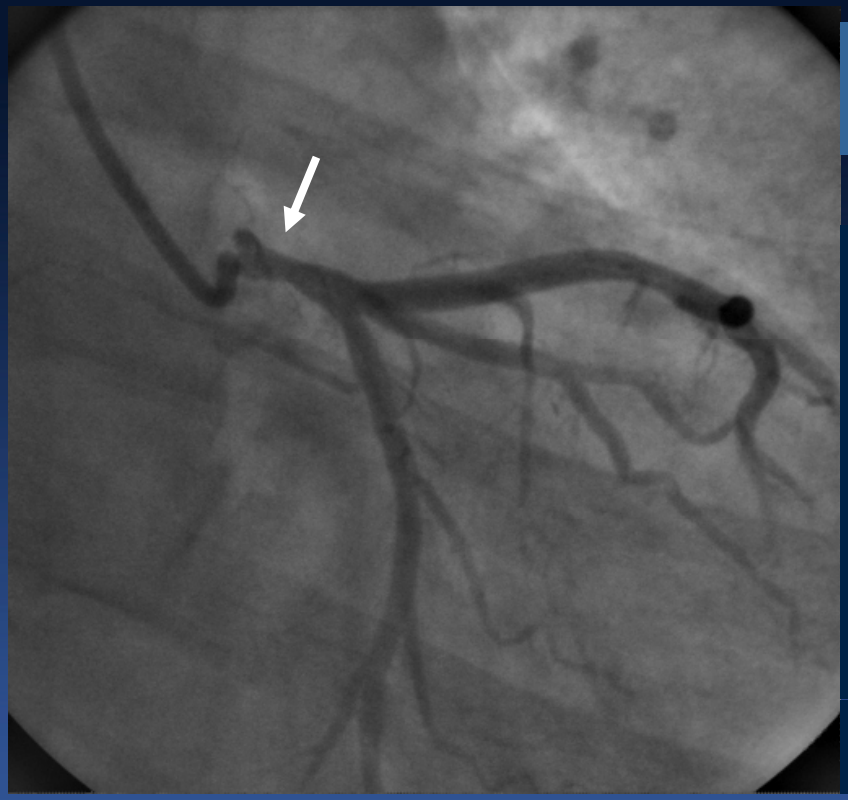
FFR : 0.84

Treadmill test : Negative

Thallium spect : Normal

Stress Echo : Normal

Reverse Mismatch



Visual Estimation : 30%

FFR : 0.70

IVUS MLA: 4.5 mm2

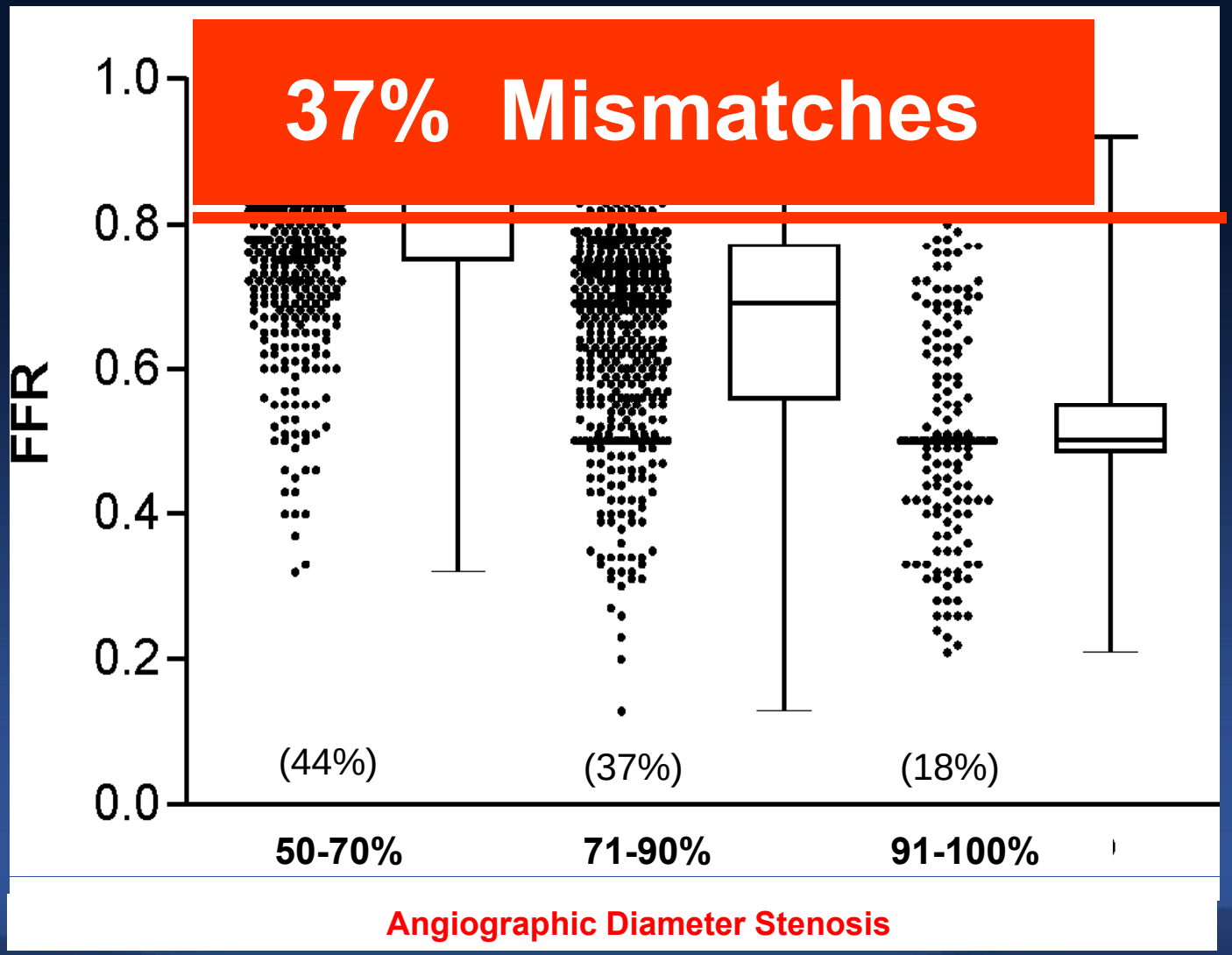
Treadmill test: + stage 2

Thallium spect : + large LAD

Many Mismatches !! Angiography vs. FFR

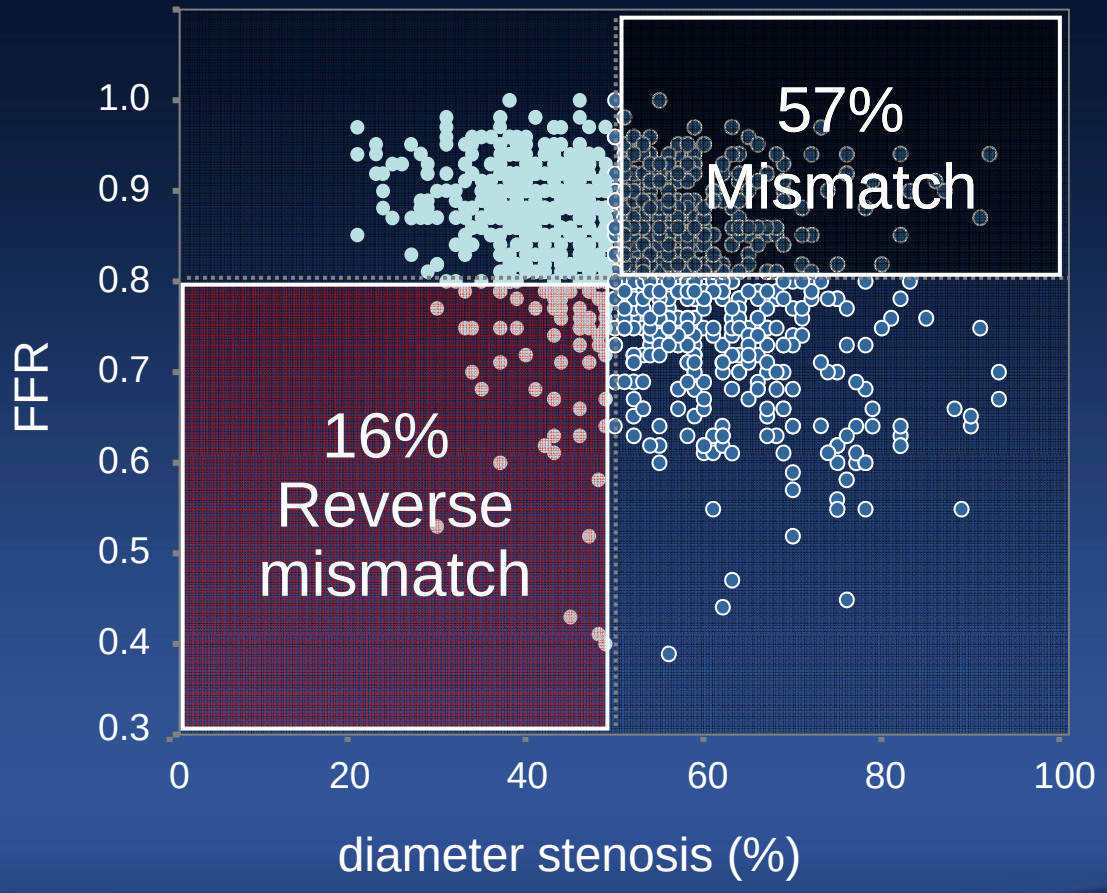
FAME Study

1329 lesions in the FFR-guided arm



Mismatch Disease
in the Cath Lab

1066 Non-LM lesions



AMC data

Validation of
Angiography vs.
non-invasive stress test

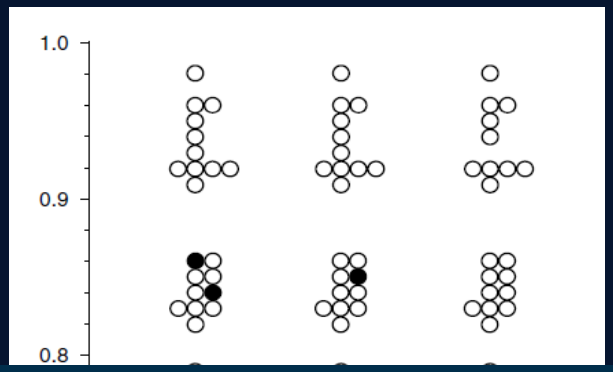
Only Evidences

In patients with normal myocardial perfusion scan (negative non-invasive stress tests) means just excellent prognosis. (0.6%/year, Cardiac Death and MI), even in the presence of angiographically proven CAD.

Shaw LJ, J Nucl Cardiol 2004;11:171-85 ,
Prognostic value of gated myocardial perfusion SPECT.
Very large meta-analysis. (n=39,173 patients)

Validation of
FFR vs.
non-invasive stress test

Clear !

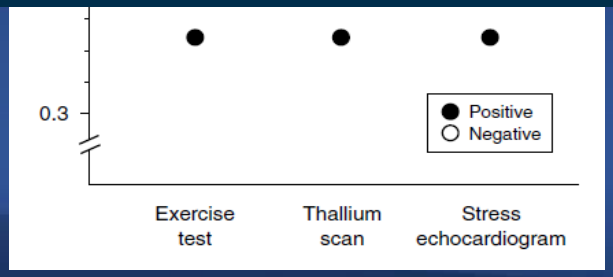


First Validation

with Non-invasive Stress Test Results

(n=45 patients, intravenous adenosine infusion)

FFR <0.75 is well matched with positive stress test (TMT and Thallium SPECT).



Pijls NHJ, NEJM 1996;334:1703-8

Best Cut-off Value of FFR

Author	Number	Stress Test	BCV	Accuracy
Pijls et al.	60	X-ECG	0.74	97
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Cut-off value of 0.72 - 0.78 is extremely reproducible and very solid.

DeBruyne et al.	57	MIBI-SPECT post-MI	0.78	85
Samady et al.	48	MIBI-SPECT post-MI	0.78	85
Ahn JM et al.(2011)	151	SPECT	0.77	89

Validation and Threshold of Ischemia

FFR < 0.80
is a good surrogate
for clinical ischemia.

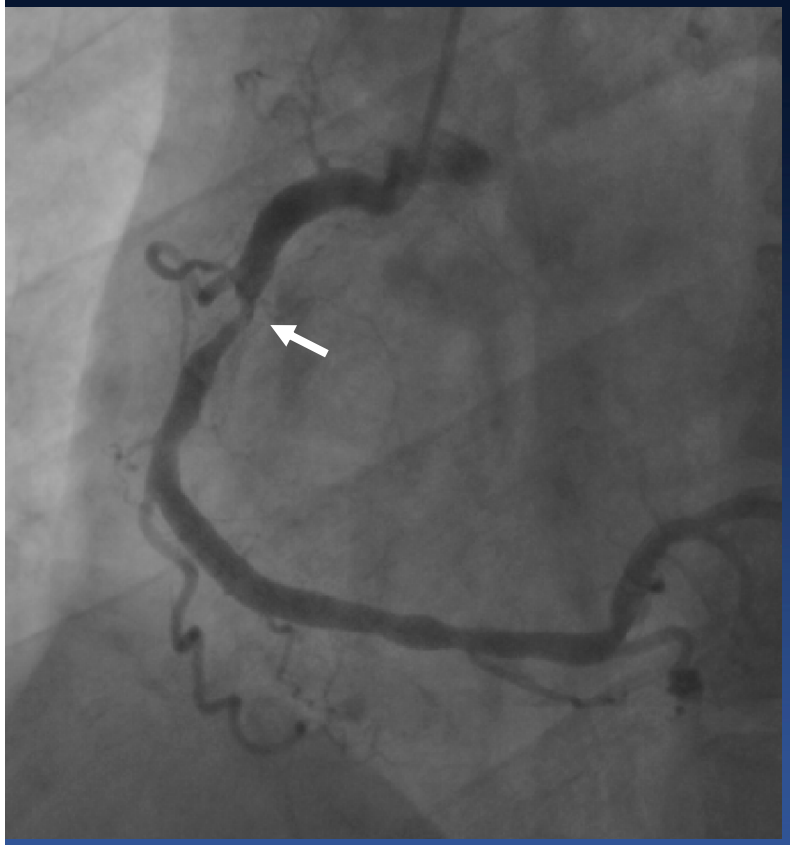
Treat or Not Treat
Operator's discretion

Validation and Threshold of Ischemia

FFR > 0.80
is a perfect surrogate
for absence of ischemia.

Negative FFR Never Lies
100% Specificity

Treat or Not Treat ?



Angiographic DS(%) : 85%

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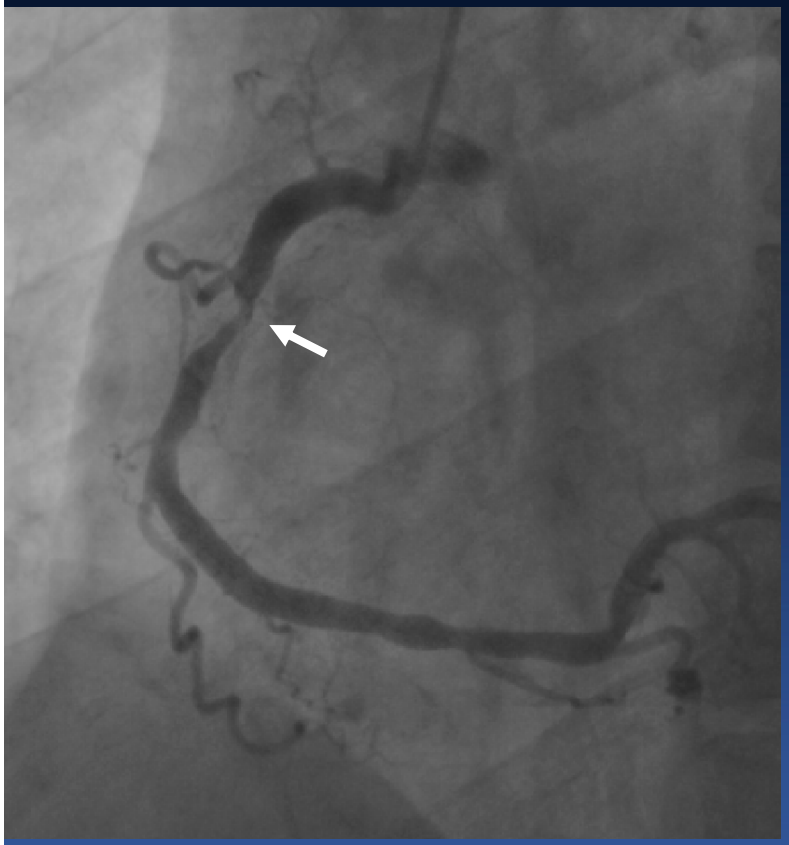
Just Defer !



Angiographic DS(%) : 85%

IVUS MLA : 2.8 mm^2

FFR : 0.84

Treadmill test : Negative

Thallium spect : Normal

Stress Echo : Normal

Negative FFR : 0.84

Means absence of clinical ischemia

The ESC guidelines classify FFR-guided treatment as "Class I, with level of evidence A."

Treat or Not Treat

Evidence Based Medicine

Negative FFR, matched negative non-invasive stress tests, means just excellent prognosis. (0.6%/year, Cardiac Death and MI), even in the presence of angiographically proven CAD.

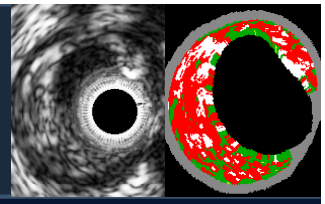
Shaw LJ, J Nucl Cardiol 2004;11:171-85 ,
Prognostic value of gated myocardial perfusion SPECT.
Very large meta-analysis. (n=39,173 patients)

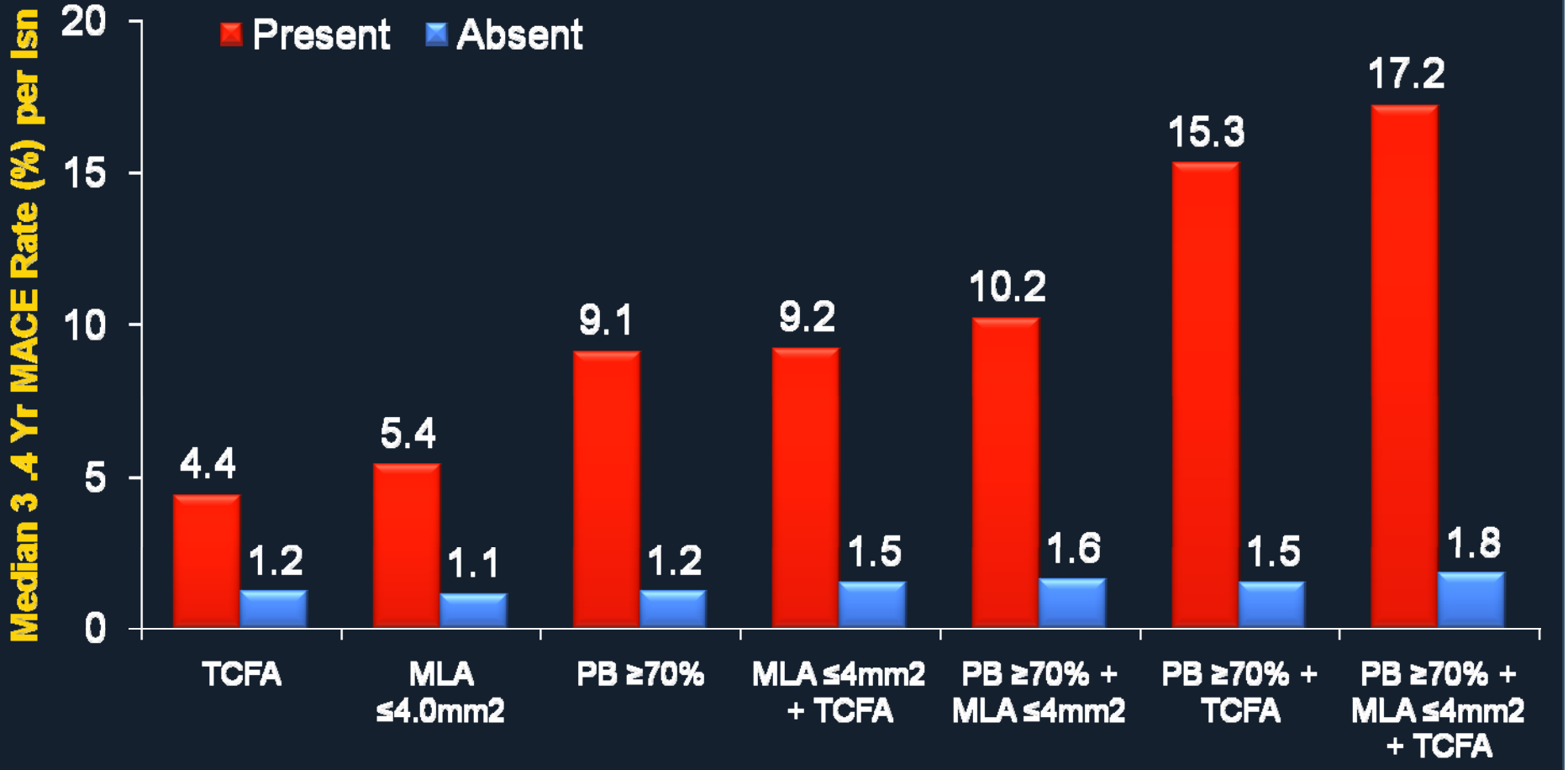
Conflict Concept of

FFR vs. Vulnerable Plaque and Acute Coronary Syndrome

Akiko is Worrying About the Vulnerable Plaque Before and even After Event…

PROSPECT: Correlates of Non Culprit Lesion Related Events





Lesion HR	3.8 (2.2, 6.6)	5.0 (2.9, 8.7)	7.9 (4.6, 13.8)	6.4 (3.4, 12.2)	6.7 (3.4, 13.0)	10.8 (5.5, 21.0)	10.8 (4.3, 27.2)
P value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Prevalence*	51.2%	49.1%	30.7%	17.4%	15.4%	11.0%	4.6%

*Likelihood of one or more such lesions being present per patient. PB = plaque burden at the MLA

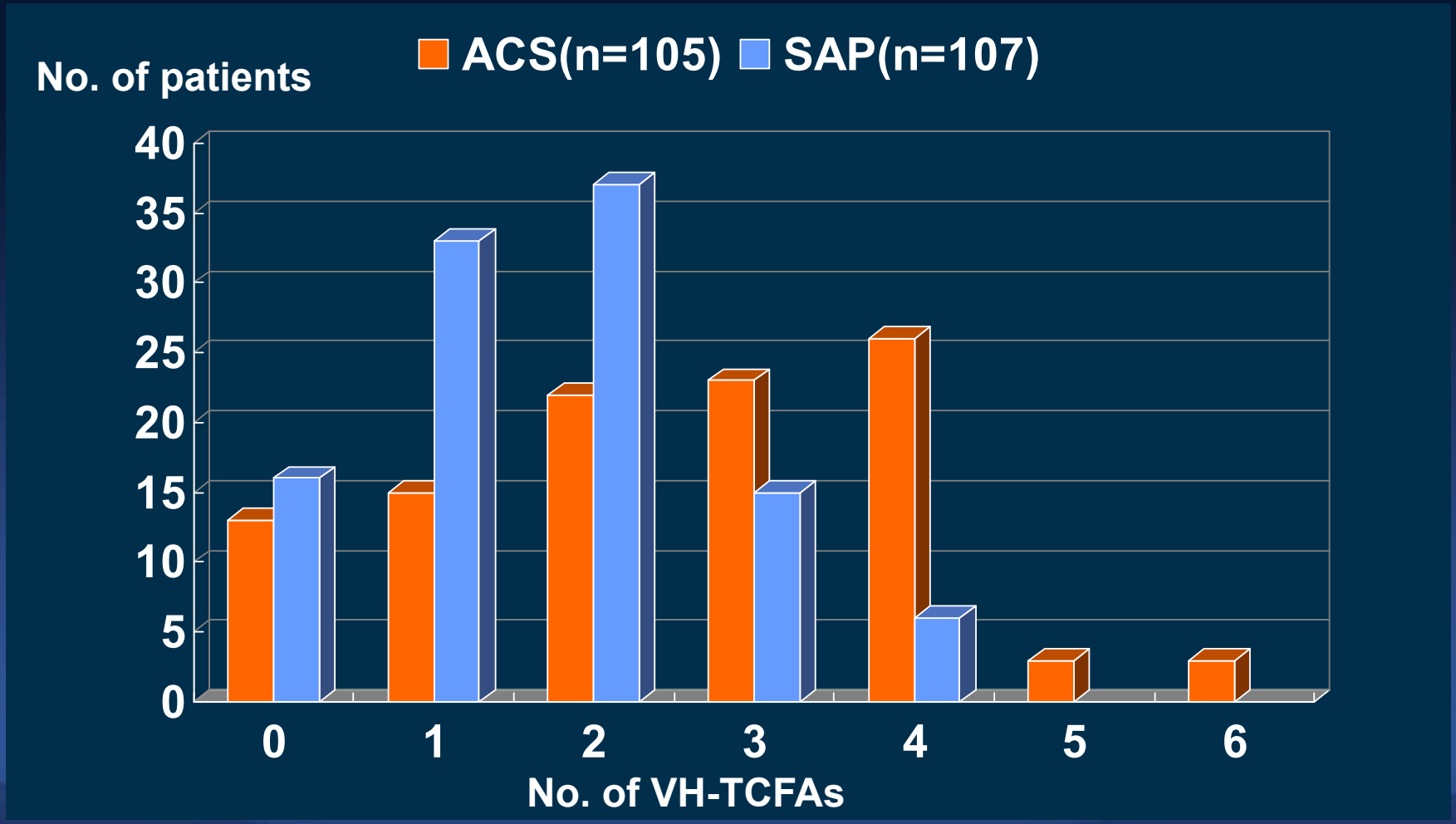
However,

Focal Treatment for the Vulnerable Plaque (before event, and no evidence of clinical ischemia) is Not Validated !!

Before Rupture

VH-TCFA in ACS and Stable Angina

3-Vessel VH-IVUS Study (n=213 pts)



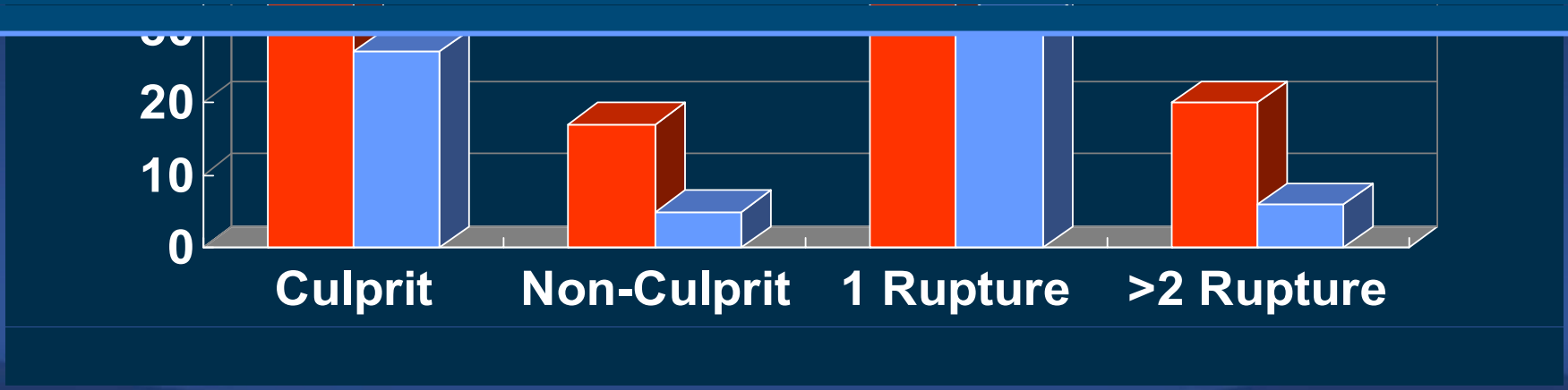
Hong MK et al, AJC. 2008;101:568-572

After Rupture

Plaque Rupture in AMI and Stable Angina

3-Vessel IVUS Study (n=235 pts)

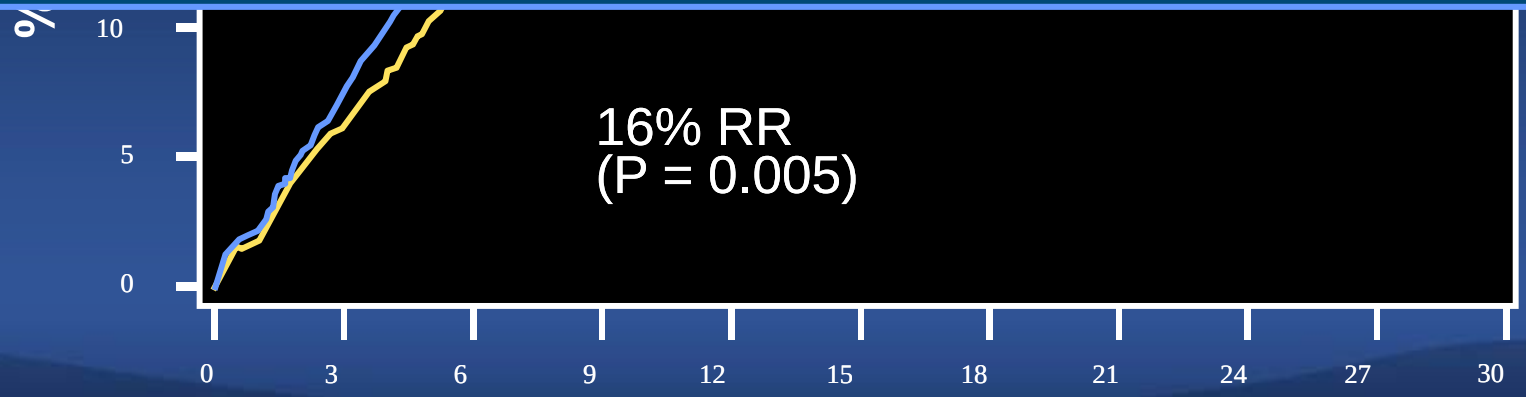
Acute coronary syndrome is a systemic disease, not a focal process. Vulnerability is usually widespread, not focal. It is the patient that is vulnerable, not the plaque !!



Vulnerable Plaque is Good Target for Medical Intervention

PROVE-IT TIMI-22

Currently, no studies demonstrated improved outcomes following focal intervention of “vulnerable plaque” except medical treatment.

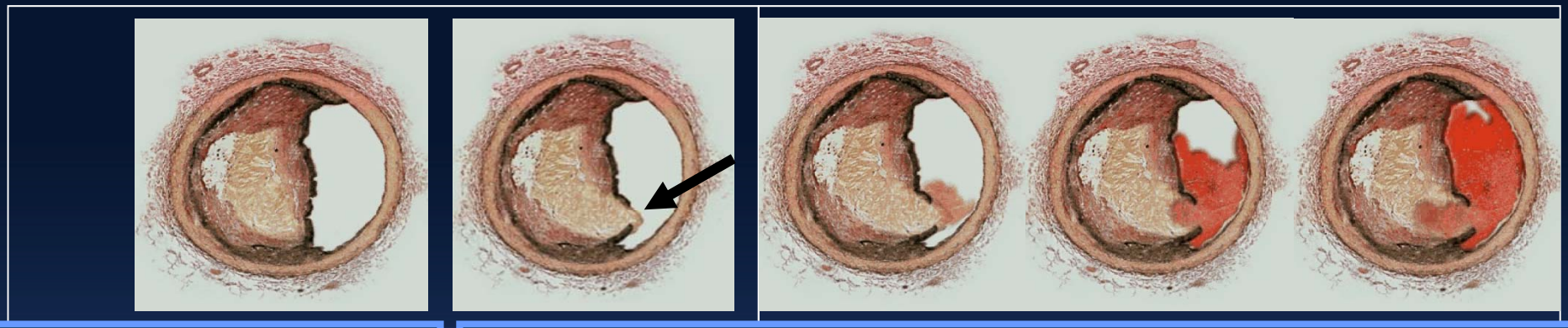


NEJM 2004;350:1495-1504

Concern is,

Does FFR Work for Culprit Lesion Before and After Rupture ?

Pathologic Spectrum of Vulnerable Plaque



Before Event (Rupture)

FFR Works

After Event (Rupture)

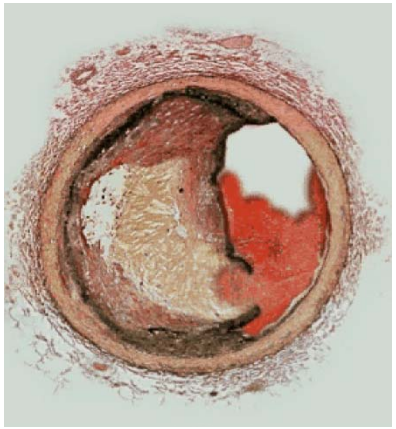
FFR Still Works Except STEMI

Clinical Spectrum

Vulnerable Plaque Morphology

(especially, rupture and thrombus) after event would be just one of the local characteristics to determine the FFR, if there was not serious myocardial damage.

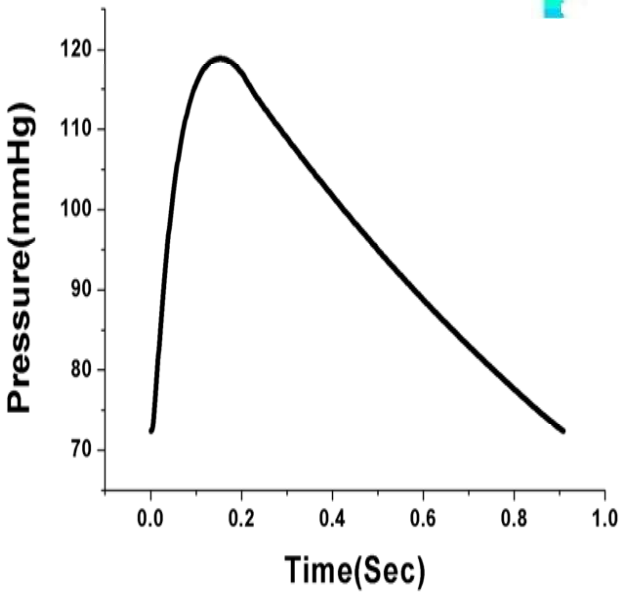
Vulnerable Plaque Simulation

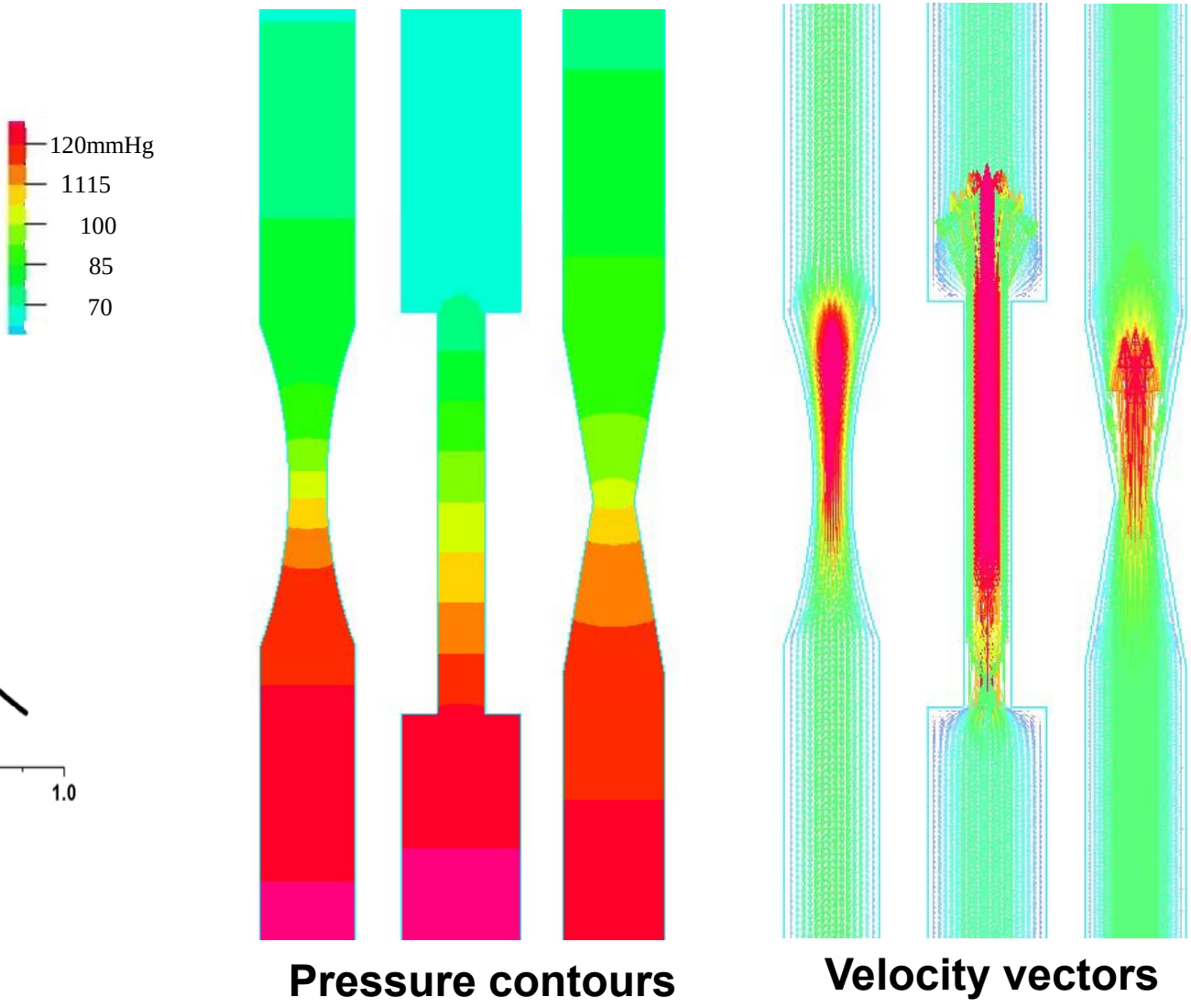


Plaque rupture

Thrombus, surface roughness

Steady-state 3D Simulation under Hyperemic Condition





Pressure contours

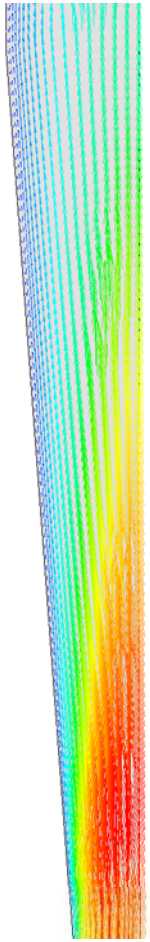
Velocity vectors

Different Surface Roughness

Fixed
Diameter
Stenosis
50%

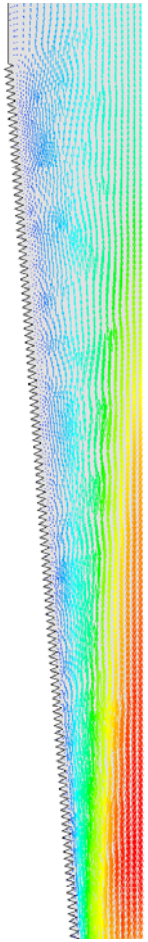
20mm

Smooth
Surface



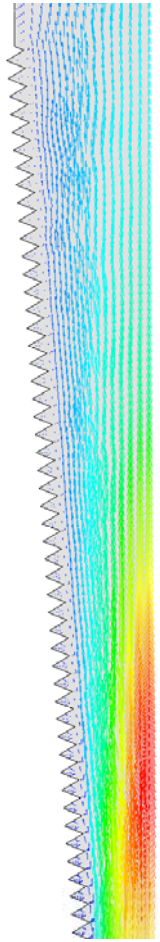
FFR : 0.81

Roughness
0.05 mm



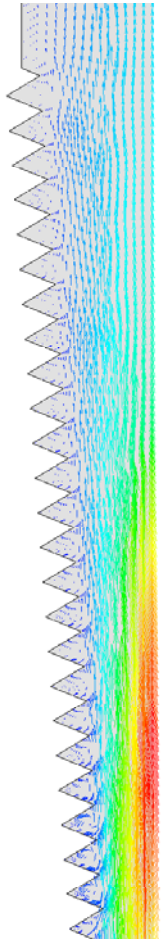
0.72

Roughness
0.1mm



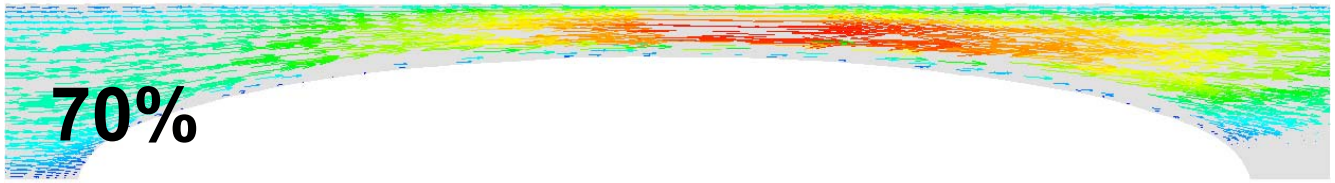
0.60

Roughness
0.2 mm

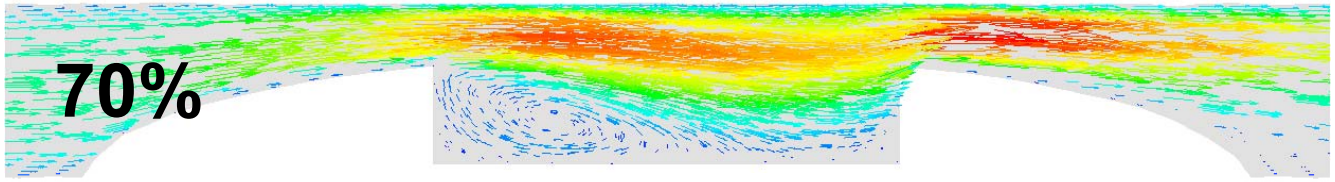


0.54

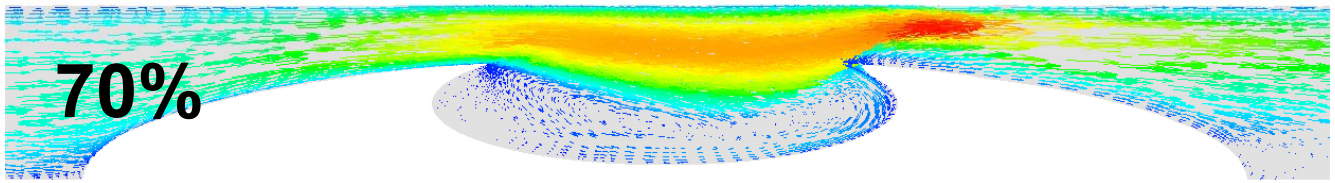
Presence of Plaque Rupture



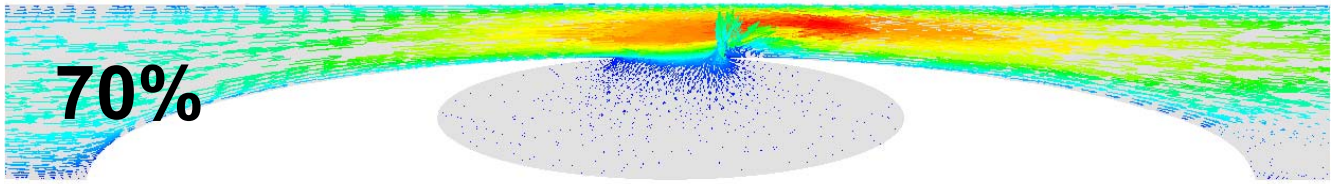
FFR : 0.62



0.68



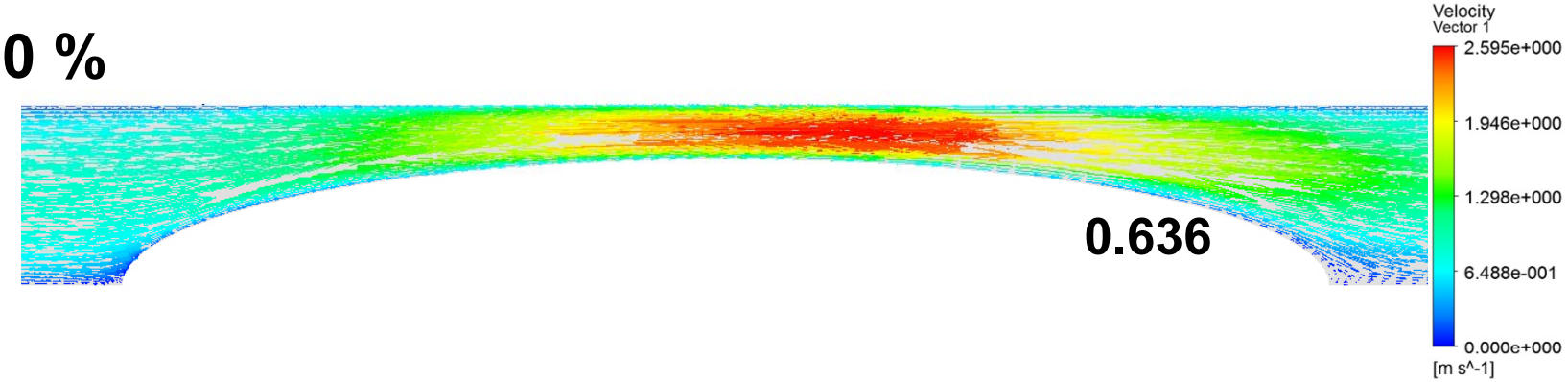
0.66



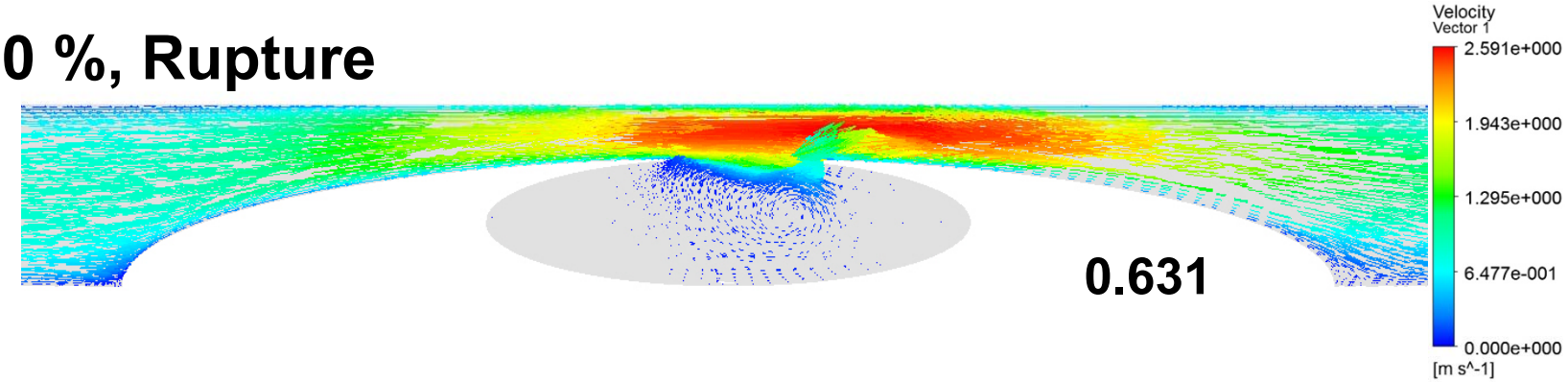
0.58

Rupture and Roughness

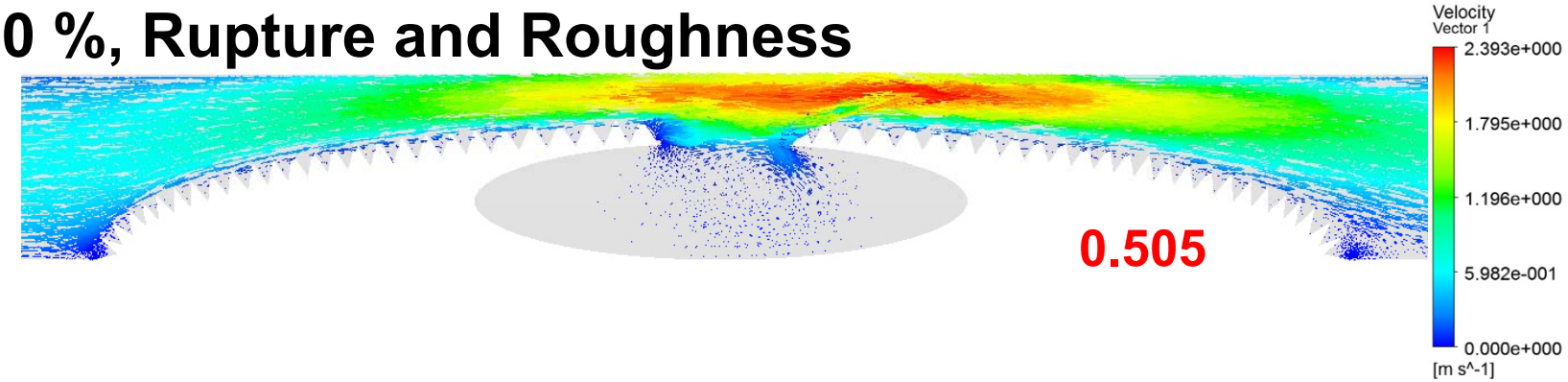
70 %



70 %, Rupture



70 %, Rupture and Roughness



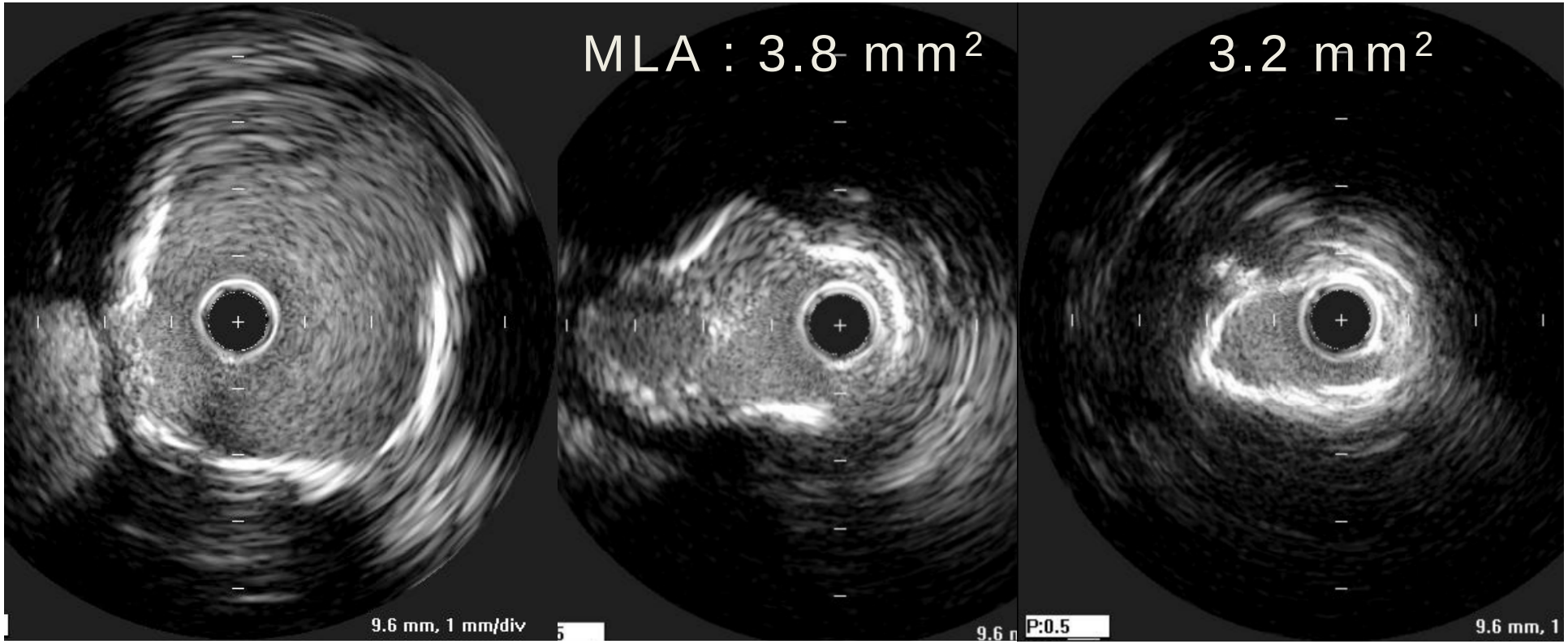
Summary,

FFR have already reflected the plaque vulnerability such as rupture and thrombus burden on the lesion.

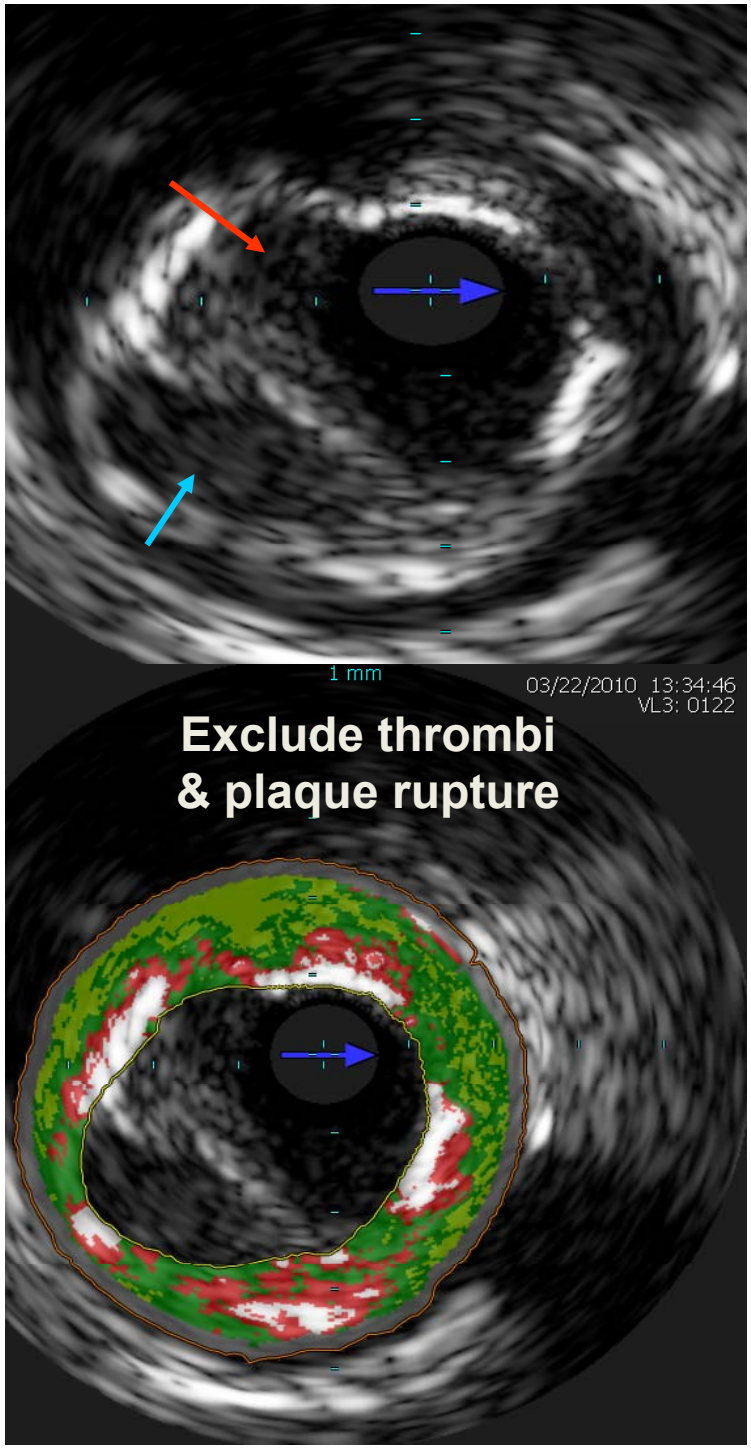
FFR represents integrated summation of total morphology and physiologic significance.

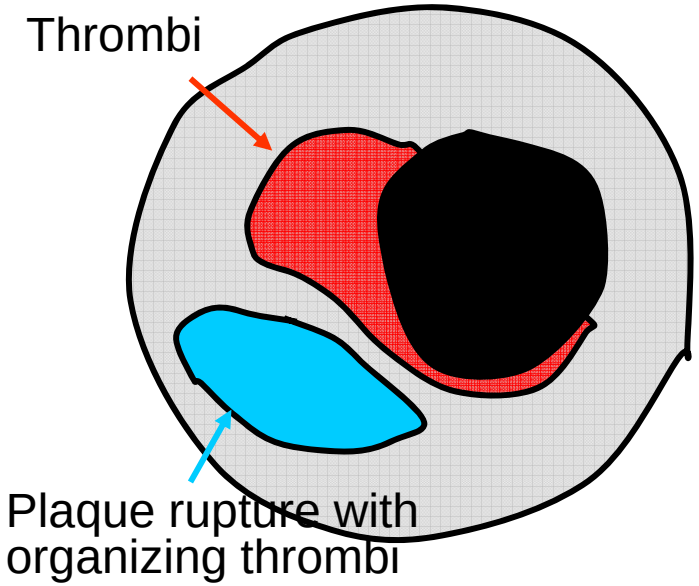
M/74,
Multiple stenosis on Coronary CT, Asymptomatic
Hypertension, DM, Hyperlipidemia, Ex-smoker,

IVUS
(LAD pullback)



LM LAD





Frame Statistics

Plaque Burden: 71.3%

FI : 41.4%
FF: 20.0%
NC: 23.0%
DC: 15.6%

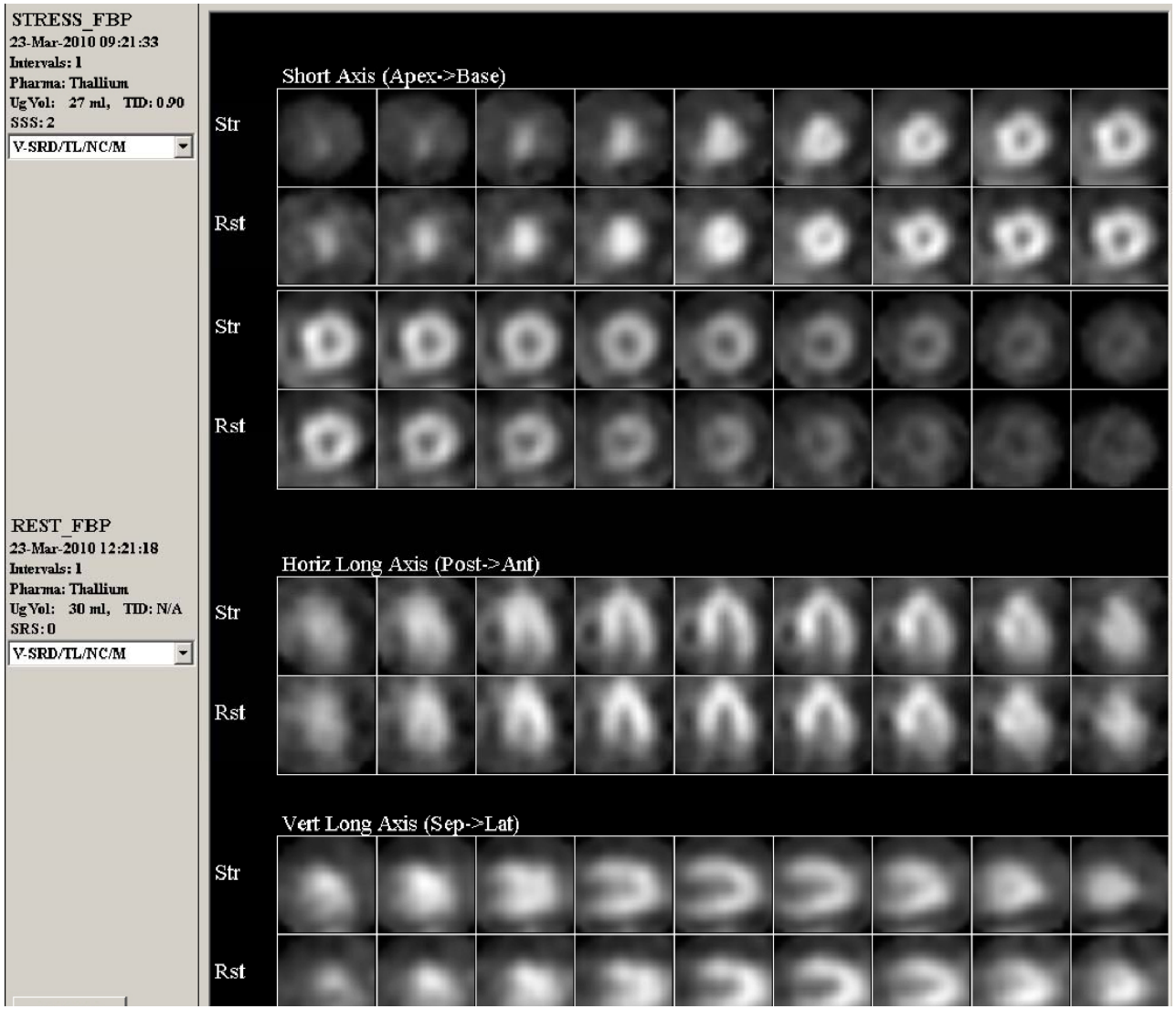
M/74,
Multiple stenosis on Coronary CT, Asymptomatic
Hypertension, DM, Hyperlipidemia, Ex-smoker,

What would you do ?

FFR

(intravenous adenosine, 240 μg/kg/min)

Thallium Spect ; Normal Perfusion



Treat or Not treat

74/M, Asymptomatic,
Ruptured Plaque, pLAD

Visual Estimation: 60%
IVUS MLA : 3.2mm^2
Large PB (72%)
Large necrotic core,
FFR 0.89
Thallium scan : Normal

Old Story

Conservative Strategy : Better !

CAG and Revascularization in selected patients after stress tests

The five-year data are consistent with earlier data reported from the ICTUS trial, which showed no benefits of early invasive management after one and three years of follow-up (de Winter et al, NEJM 2005; Hirsch et al, Lancet 2007,Neth Heart J. 2010)

- FRISC II (Lancet 1999;354:708)
- TACTICS, TIMI-18 (NEJM 2001;344:1879)

Early Invasive Treatment for ACS (after Event),

Validated in the Setting of
- Hemodynamic Instability,
- Electrical Instability,
- Persistent Symptoms,
- Persistent EKG Changes,
- Elevated Troponin T

Should be
Positive FFR
No Doubt !

My Thought is,

If FFR is negative(>0.80), patient has no clinical ischemia, just deferral would be OK even after stabilized ACS with negative FFR (exactly same with selective invasive strategy).

FFR is constantly well matched with patient's symptoms and non-invasive stress tests.

Although we need more data about the natural fate of ruptured plaque (FFR>0.80), we know that majority of plaque disruption is silent.

My Thought,

In Any Lesions with Negative FFR (>0.80),

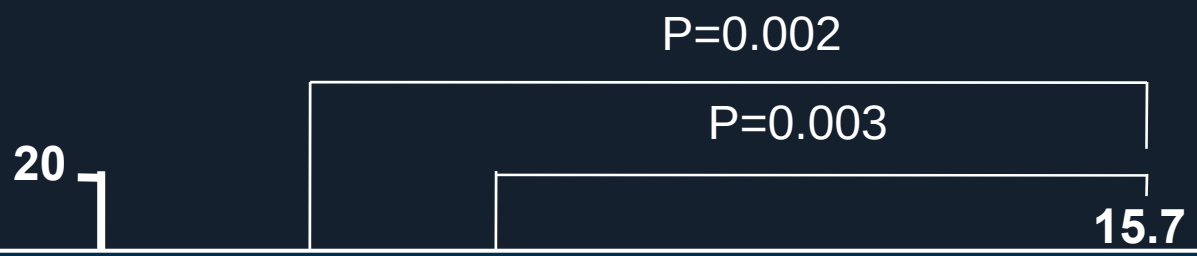
Just Defer !

Concern is,

Deferral,
Is It Really Safe ?

DEFER 5 year

Cardiac Death and MI



3.3 % / 5 years = 0.6 % / year

Pijls et al. J am Coll Cardiol 2007;49:2105-11

FAME Study 2 year FU
Outcomes of Deferred Lesion

FFR-guided group:
509 patients (1329 stenoses)

Event Rate of Deferred Lesion
0.2% MI,
3.2% Repeat Revascularization.

1 d/t a deferred lesion (0.2%)
8 stent related or due to a new lesion (1.6%)

16 d/t a deferred lesion (3.2%)
37 d/t in-stent restenosis or a new lesion (7.2%)

J Am Coll Cardiol 2010;56:177-84

Long Term Prognosis of Deferred Proximal LAD

5 years Event Rate

5.3% Mortality,

0.4% MI,

2.0% Repeat Revascularization.

No at risk						
Aalst	466	410	341	262	173	109
Rotterdam	1868	1839	1803	1772	1725	1675

JACC: Cardiovascular Interventions 2011;4:1175-82

Meta-Analysis

1. **FFR vs. Angio-Guided PCI**
2. **Outcomes Of Deferred PCI**
   - **Non-LM Epicardial Artery**
   - **LM Coronary Artery**

Park SJ, Ahn JM et al. Unpublished data

Meta-Analysis (1)

1. FFR vs. Angio-Guided PCI

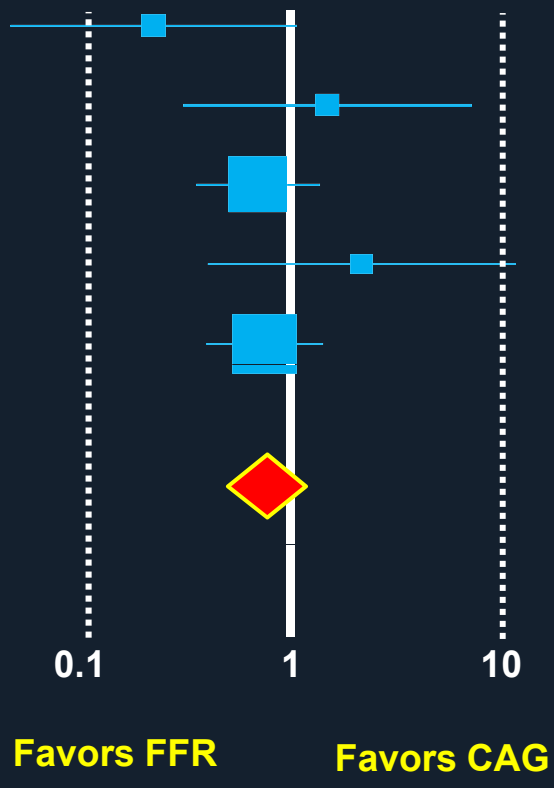
FFR vs. Angio-Guided PCI
(6 Studies, 2584 patients)

Year	Authors	Pt N.	FFR Cutoff	Study Design
2005	Wongpraparute et al.	137	0.75	Retrospective Observational
2005	Legalery et al.	407	0.80	Retrospective Observational
2008	Koo et al.	220	0.75	Retrospective Observational
2010	Pijls et al.	1005	0.80	Prospective Randomized
2011	Angkananard et al.	98	0.75	Retrospective Observational
2012	Puymirat et al.	717	0.80	Retrospective Observational

FFR vs. Angio-Guided PCI

Death

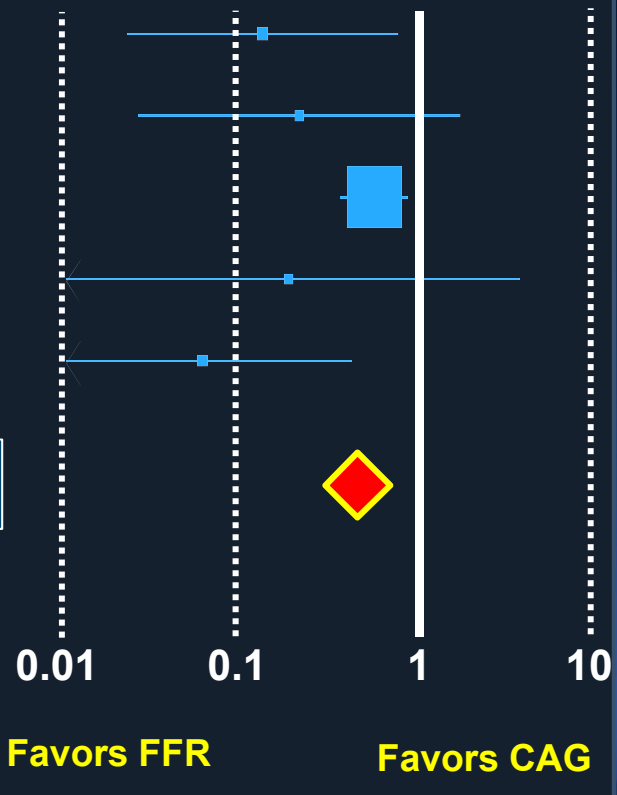
Study	OR (95% CI)		P Value
Wongpraparute et al.	0.20	(0.04-1.03)	0.055
Legalery et al.	1.43	(0.28-7.33)	0.671
Pijls et al.	0.66	(0.32-1.35)	0.252
Angkananard et al.	2.09	(0.36-11.97)	0.408
Puymirat et al.	0.71	(0.36-1.38)	0.312
	0.71	(0.46-1.10)	0.12



FFR vs. Angio-Guided PCI

Nonfatal MI

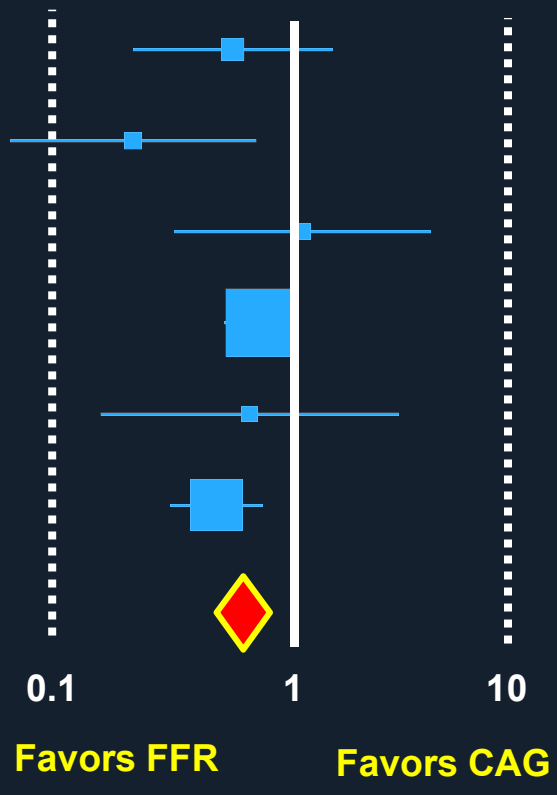
Study	OR (95% CI)		P Value
Wongpraparute et al.	0.14	(0.02-0.83)	0.03
Legalery et al.	0.22	(0.03-1.88)	0.17
Pijls et al.	0.59	(0.37-0.95)	0.03
Angkananard et al.	0.19	(0.01-4.10)	0.29
Puymirat et al.	0.06	(0.01-0.45)	0.01
	0.46	(0.30-0.71)	<0.01



FFR vs. Angio-Guided PCI

TVR

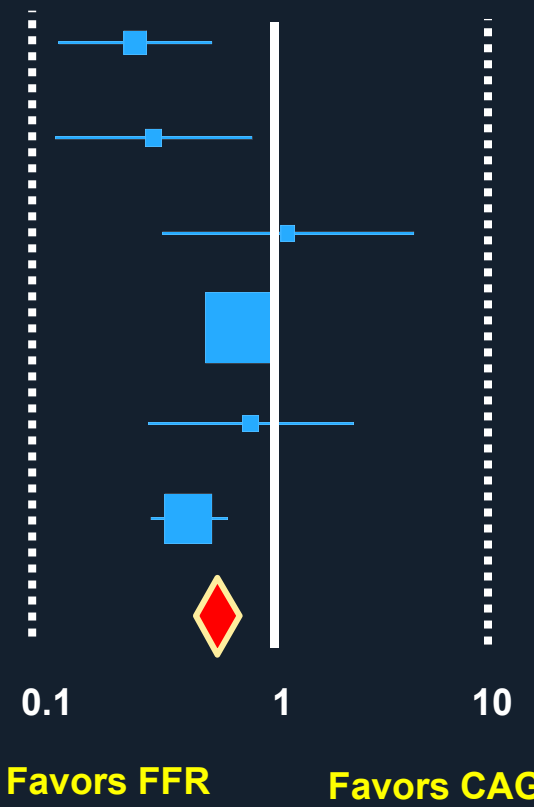
Study	OR (95% CI)		P Value
Wongpraparute et al.	0.62	(0.22-1.76)	0.37
Legalery et al.	0.22	(0.06-0.80)	0.02
Koo et al.	1.26	(0.33-4.83)	0.73
Pijls et al.	0.82	(0.55-1.2)	0.30
Angkananard et al.	0.73	(0.16-3.47)	0.70
Puymirat et al.	0.52	(0.32-0.86)	0.01
	0.67	(0.51-0.88)	<0.01



FFR vs. Angio-Guided PCI

MACE

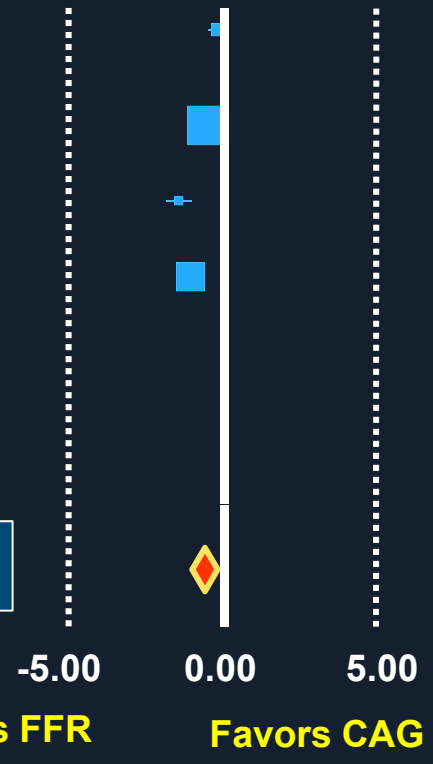
Study	OR (95% CI)		P Value
Wongpraparute et al.	0.26	(0.11-0.58)	0.001
Legalery et al.	0.31	(0.11-0.88)	0.03
Koo et al.	1.26	(0.33-4.83)	0.73
Pijls et al.	0.76	(0.55-1.03)	0.08
Angkananard et al.	0.85	(0.28-2.57)	0.78
Puymirat et al.	0.45	(0.29-0.69)	<0.01
	0.59	(0.47-0.74)	<0.01



FFR vs. Angio-Guided PCI

Number of Stents Used

Study	Standard Difference (Standard Error)		P Value
Wongpraparute et al.	-0.31	(0.17)	0.007
Pijls et al.	-0.64	(0.07)	<0.001
Angkananard et al.	-1.50	(0.23)	<0.001
Puymirat et al.	-1.15	(0.09)	<0.001
	-0.81	(0.05)	<0.001



FFR vs. Angio-Guided PCI

FFR Guided PCI is Better !

Outcomes	Relative Risk Reduction	P value
Death	↓ 29%	0.12
MI	↓ 54%	<0.01
TVR	↓ 33%	<0.01
MACE	↓ 41%	<0.01
Stent Used	↓ 0.8 Stent	<0.01

Park SJ, Ahn JM et al. Unpublished data

Meta-Analysis (2)

1. FFR vs. Angio-Guided PCI

2. Outcomes Of Deferred PCI

- Non-LM Epicardial Artery
- LM Coronary Artery

Park SJ, Ahn JM et al. Unpublished data

Clinical Outcomes After Deferral of Revascularization (32 Studies, 3251 patients)

Year	Authors	N. Of Pts	LM	Title
1998	Bech et al.	100	N	Long-term follow up after deferral of percutaneous transluminal coronary angioplasty of intermediate stenosis on the basis of
2001	Bech et al.	24	Y	Value of fractional flow reserve in making decisions about bypass surgery for equivocal left main coronary artery disease
2002	Chamuleau et al.	92	N	Usefulness of fractional flow reserve for risk stratification of patients with multivessel coronary artery disease and an intermediate
2004	Lopez-Palop et al.	41	N	Utility of the fractional flow reserve in the evaluation of angiographically moderate in-stent restenosis
2004	Reczuch et al	26	N	Fractional flow reserve assessment to determine the indications for myocardial revascularisation in patients with boderline stenosis
2004	Dias et al.	21	N	Long term outcome of conservatively treated patients with borderline coronary lesions – the role of the fractional flow reserve
2005	Legutko et al.	20	Y	Measurement of fractional flow reserve in patients with multi-vessel coronary artery disease and borderline lesions prevents
2005	Reczuch et al.	41	N	Value of fractional flow reserve in the management of patients with moderate coronary stenosis
2005	Kobori et al.	113	N	Usefulness of fractional flow reserve in determining the indication of target lesion revascularization
2005	Mates et al.	85	N	Long-term follow-up after deferral of coronary intervention based on myocardial fractional flow reserve measurement
2005	Sueman et al.	8	Y	Coronary pressure measurement to determine treatment strategy for equivocal left main coronary artery lesions
2005	Beger et al.	127	N	Long-term clinical outcome after fractional flow reserve-guided percutaneous coronary intervention in patients with multivessel
2006	Lindstaedt et al.	24	Y	Clinical outcome in patients with intermediate or equivocal left main coronary artery disease after deferral of surgical revascularization
2006	Potvin et al.	201	N	Usefulness of fractional flow reserve measurement to defer revascularization in patients with stable or unstable angina pectoris
2006	Fischer et al.	111	N	Outcome of patients with acute coronary syndromes and moderate coronary lesions undergoing deferral of revascularization based
2006	Verna et al.	54	N	Performing versus deferring coronary angioplasty based on functional evaluation of vessel stenosis by pressure measurements
2006	Jimenez-navarro et al	12	N	Usefulness of fractional flow reserve in multivessel coronary artery disease with intermediate lesions
2007	Rieber et al	56	N	Five-year follow-up in patients after therapy stratification based on intracoronary pressure measurement
2007	Pijls et al.	91	N	Percutaneous coronary intervention of functionally nonsignificant stenosis 5-year follow-up of the DEFER study
2007	Chamuleau et al.	107	N	Long-term prognostic value of CFVR and FFR versus perfusion scintigraphy in patients with multivessel disease
2008	Meuwissen et al.	29	N	The prognostic value of combined intracoronary pressure and blood flow velocity measurements after deferral of percutaneous
2008	Koo et al.	63	N	Physiological evaluation of the provisional side-branch intervention strategy for bifurcation lesions using fractional flow reserve
2008	Dominguez-Franco	136	N	Long-term prognosis in diabetic patients in whom revasculariozation is deferred following frational flow reserve assessment
2009	Courtis et al.	82	Y	Usefulness of coronary fractional flow reserve measurements in guiding clinical decisions in intermediate or equivocal left main
2009	Hamilos et al.	138	Y	Long-term clinical outcome after fractional flow reserve-guided treatment in patients with angiographically euivocal left main coronary
2010	Esen et al.	162	N	The prognostic value of combined fractional flow reserve and TIMI frame count measurement in patients with stable angina pectoris
2010	Pijls et al.	513	N	Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery
2010	Marques et al.	70	N	Patients with coronary stenosis and a fractional flow reserve of >0.75 measured in daily practice at the VU university medical center
2011	Nam et al.	30	N	Usefulness of coronary pressure measurement for functional evaluation of drug-eluting stent restenosis
2011	Misaka et al.	29	N	Long-term clinical outcomes after deferral of percutaneous coronary intervention of intermediate coronary stenoses based on
2011	Muller et al.	564	N	Long-term follow-up after fractional flow reserve-guided treatment strategy in patients with an isolated proximal left anterior
2011	Lopez-Palop et al.	81	N	Results of fractional flow reserve measurement to evaluate nonculprite coronary artery stenoses in patients with acute coronary

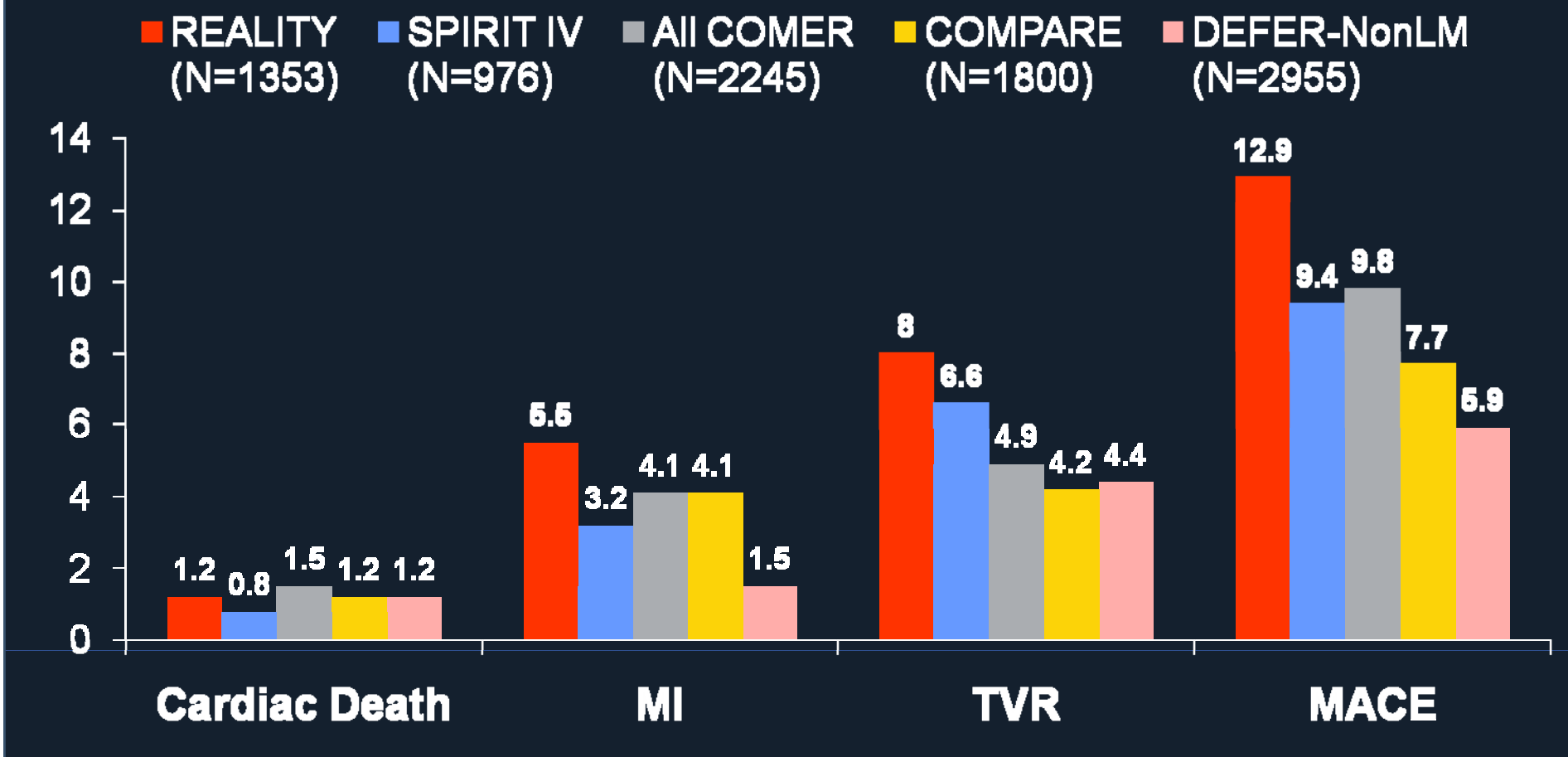
Clinical Outcomes After Deferral of Revascularization

Non-LM Epicardial Artery
(26 studies, 2955 patients)

Outcomes	Incidence (%/year)
All Death	2.2 (1.5-3.2)
Cardiac Death	1.2 (0.8-1.7)
Myocardial Infarction	1.5 (1.0-2.2)
TVR	4.4 (3.1-6.2)
MACE	5.9 (4.3-8.1)

Clinical Outcomes After Deferral of Revascularization

Non-LM Epicardial Artery



Clinical Outcomes After Deferral of Revascularization

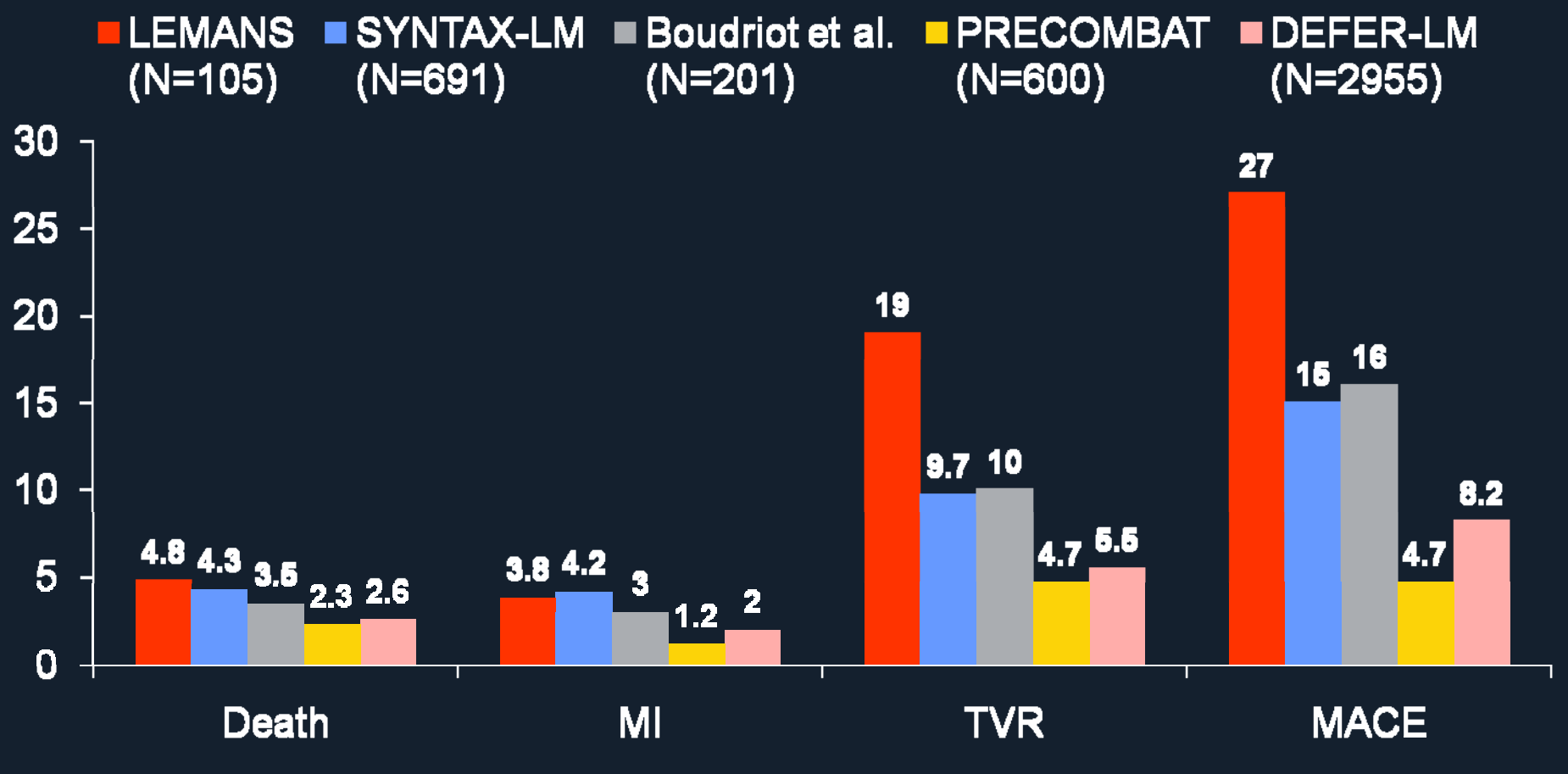
Left Main Coronary Artery

(6 studies, 296 patients)

Outcomes	Incidence (%/year)
All Death	2.6 (1.3-5.2)
Cardiac Death	2.6 (1.3-5.2)
Myocardial Infarction	2.0 (0.7-5.1)
TVR	5.5 (3.3-8.8)
MACE	8.2 (5.5-12.1)

Clinical Outcomes After Deferral of Revascularization

LM Coronary Artery



Summary (2)

FFR guided deferred PCI reduced the frequency of non-fatal MI, TVR, MACE and number of stents used.

Meta-analysis for clinical outcomes of deferred PCI using FFR showed that all cause mortality was 2.2% in non-LM coronary artery and 2.6% in left main disease per year. There was a tendency of lower frequency of MI, TVR and MACE compared to studies using various stents.

FFR >0.80

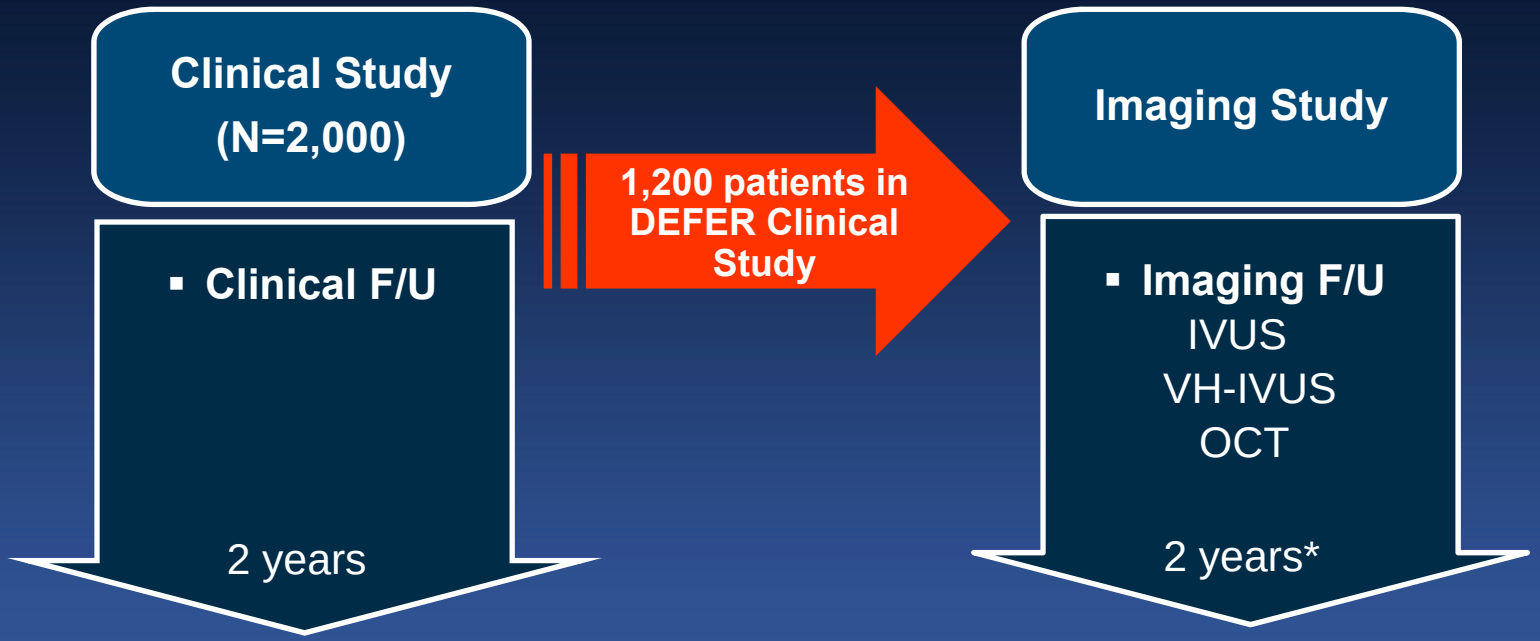
Just Defer !

Do You Still Concern about Defer ?

Multicenter, Prospective Registry to Evaluate The Natural History of FFR-Guided Deferred Coronary Lesions

IRIS FFR DEFER Registry

Patients (N=2,000) with ≥1 Deferred Target Lesions
(DS>30% by visual estimation and FFR>0.80)



Primary Endpoint : 2 year TVF
Target vessel related Cardiac Death, MI, and Clinical driven TVR

*** 2-year CAG & Imaging FU will be conducted after Completion of 2-year Clinical FU**