

Invasive Physiology in ACS Patient: Can We Believe It?

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Disclosure

- Institutional Research Grant
 - St. Jude Medical (Abbott Vascular)
 - Philips Volcano
- Consulting Fee
 - RainMed Medical Imaging

Domain of Invasive Physiologic Evaluation

Epicardial Coronary Stenosis



FFR
NHPRs (iFR/dPR/RFR/DFR)
HSR

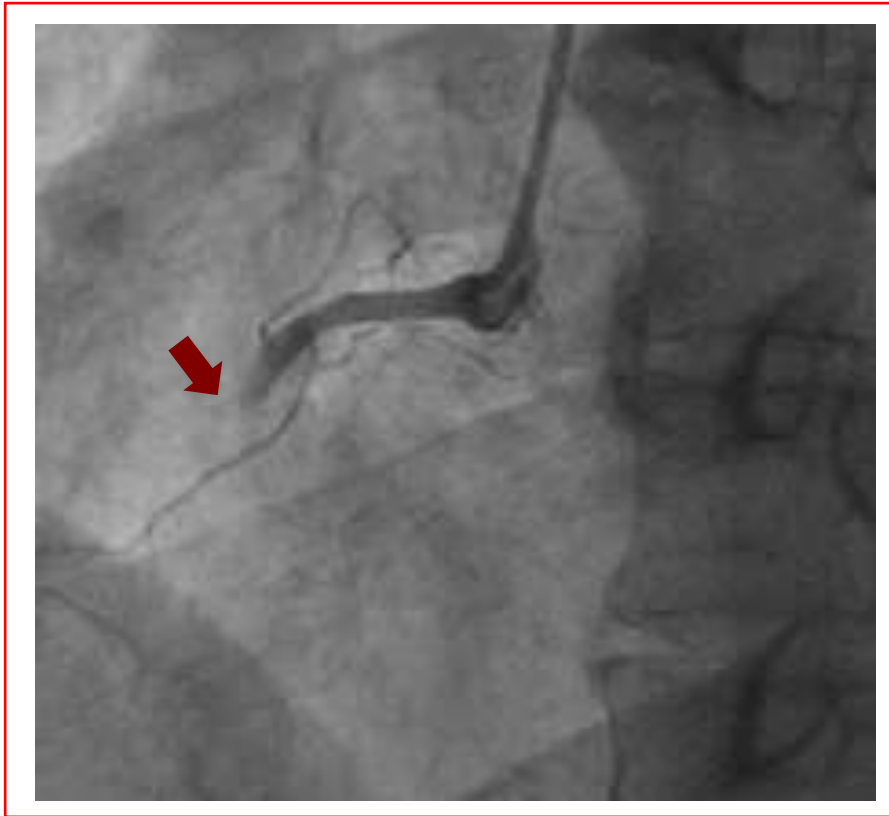
Microcirculation



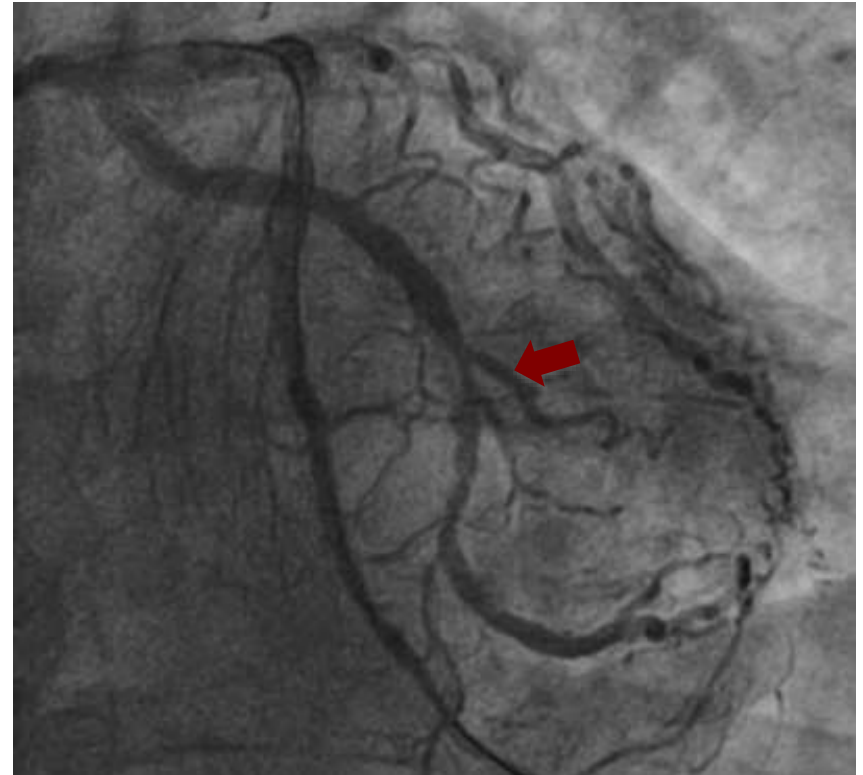
Index of Microcirculatory Resistance
Hyperemic Microcirculatory Resistance

Invasive Physiology in AMI

Culprit



Non culprit

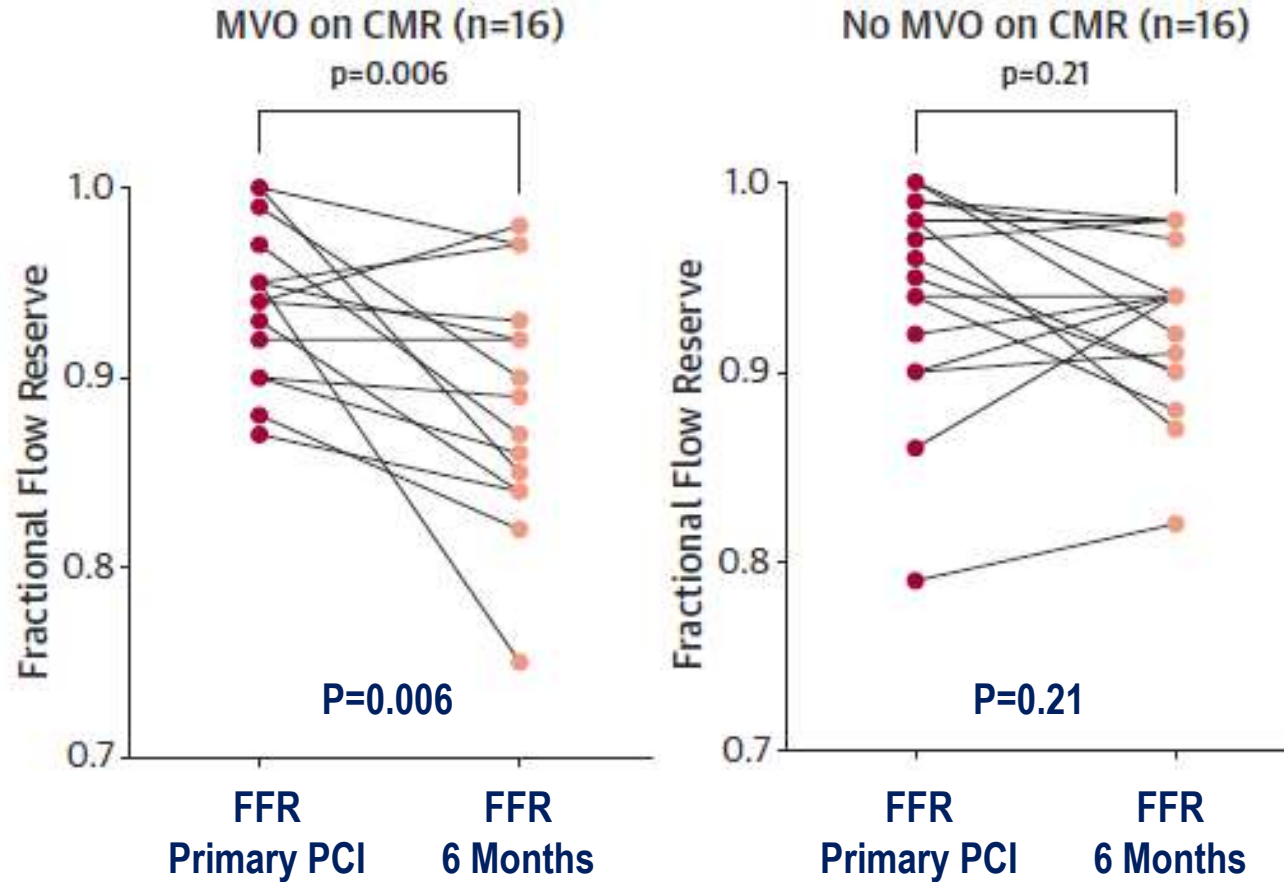


Impact of Acute MV dysfunction to FFR in STEMI (Culprit)

82 Patients with STEMI

CFR/IMR/FFR in Culprit Vessel (Primary PCI, Day 1, and 6 Months)

Changes of the Physiologic Indexes by Presence of MVO in CMR



FFR in culprit vessel underestimates lesion severity in the presence of significant microcirculatory dysfunction

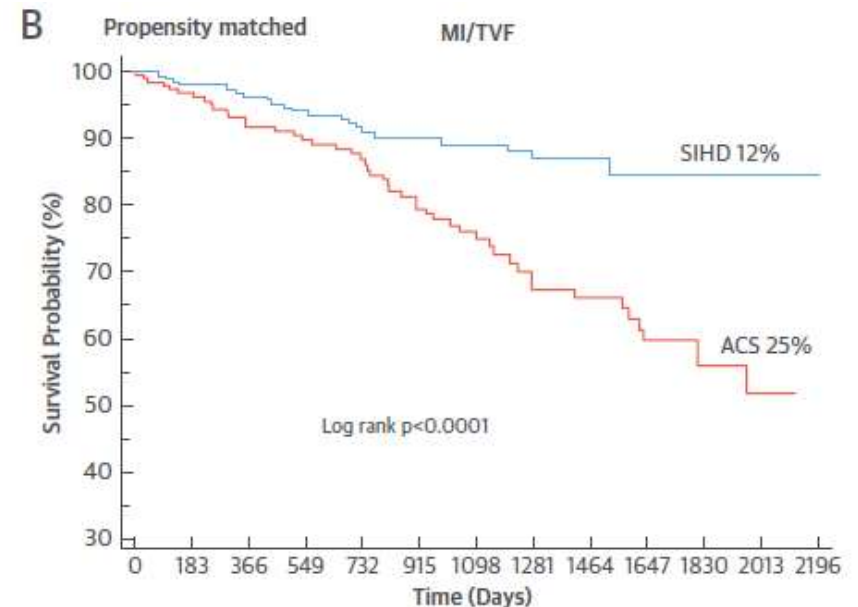
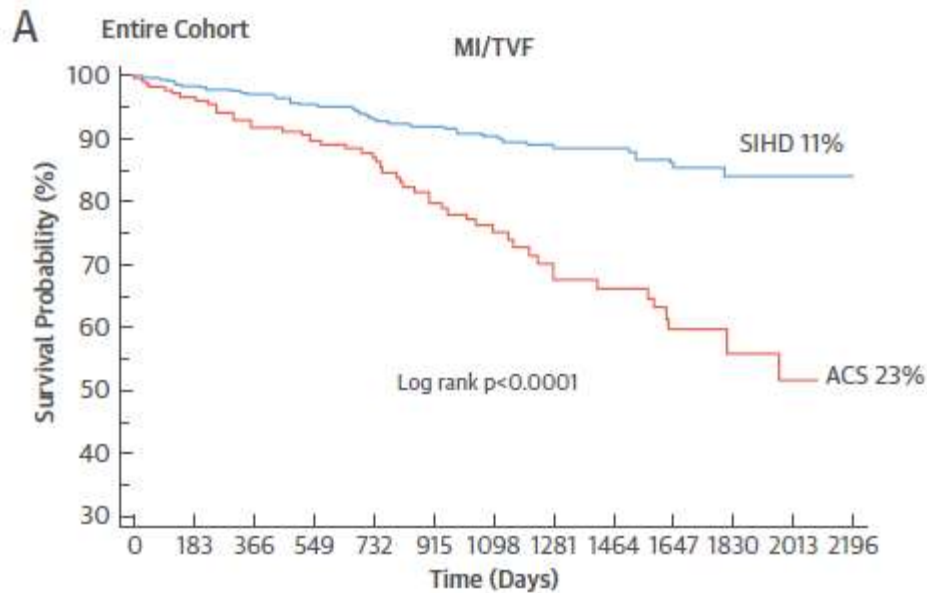
Outcome of FFR-guided Deferred lesion in NSTEMI-ACS (Culprit)

206 NSTEMI-ACS Patients vs. 370 Patient with SIHD

MI and TVF during 3.4 ± 1.6 years follow-up

PS matched pairs (200 patients in ACS vs. SIHD)

NSTEMI-ACS culprit lesion deferred based on FFR >0.75



Deferring PCI based on FFR for **culprit lesion** in NSTEMI-ACS patients is associated with worse clinical outcomes than SIHD

Microcirculation is more important in culprit vessel territory

	Number	Main finding	Cut-off value of index
Association Studies			
Fearon et al	29	IMR correlates with infarct size and less ventricular function recovery at 3 months	IMR >32
Lim et al	40	IMR predicts myocardial viability and 6-month left ventricular recovery	IMR >33
McGoech et al	57	IMR independently predicts left ventricular function and infarct size	IMR 38
Payne et al.	108	IMR inversely correlates with myocardial salvage and predicts MVO and myocardial hemorrhage	-
Prognosis Studies			
Fearon et al	253	IMR predicts death and re-hospitalization at 12 months	IMR >40
Park SD et al	89	Depressed CFR and elevated IMR (Overt microvascular damage) showed significantly higher rates of MACCE at 3-year	CFR \leq 2, IMR>27 (mean value)
Carrick et al	283	IMR>40 is a multivariable associate of LV and clinical outcomes post-STEMI, independent of the size of infarction.	CFR \leq 2, IMR>40

Invasive Physiology in Culprit Vessel of AMI

Epicardial Coronary Circulation



- Culprit lesion requires revascularization based on clear prognostic benefit over MT.
- Evaluating culprit lesion using FFR/NHPRs and deferral of revascularization is inherently limited.

Microcirculation



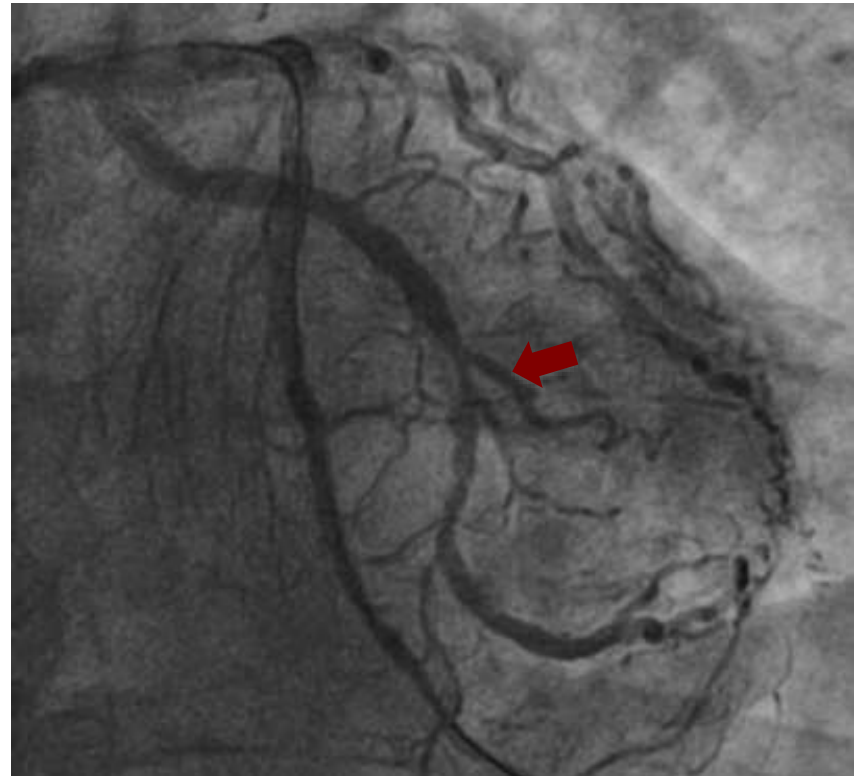
- Microcirculatory dysfunction in culprit vessel territory is more important in AMI patients.
- IMR is the independent prognostic indicator in STEMI patients.

Invasive Physiology in AMI

Culprit



Non culprit



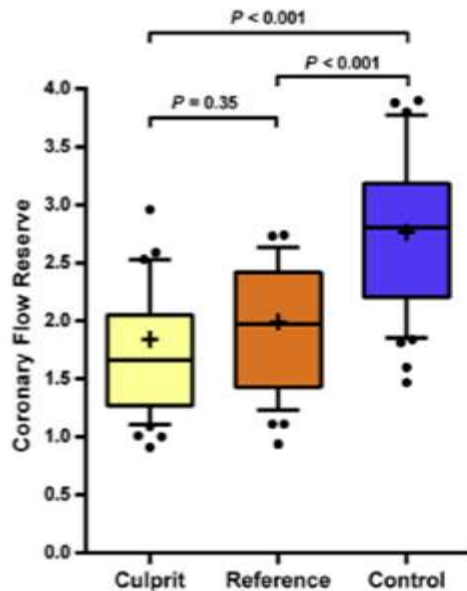
About 40-60% of AMI patients have non-culprit vessel stenosis

Concerns for Reliability of Non-culprit FFR in STEMI

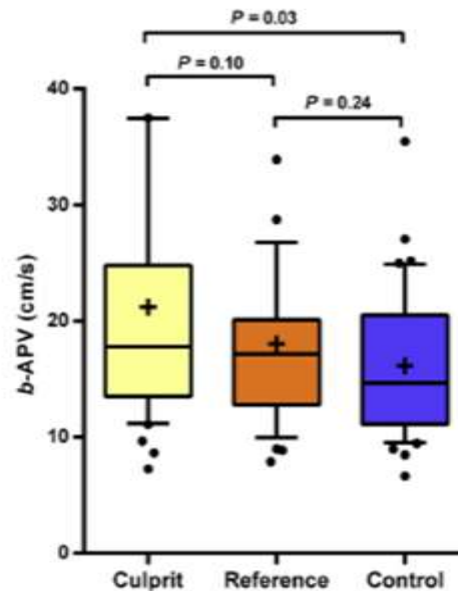
- What is the issue? -

40 STEMI patients,
PS matched with 40 Stable Angina without obstructive lesion

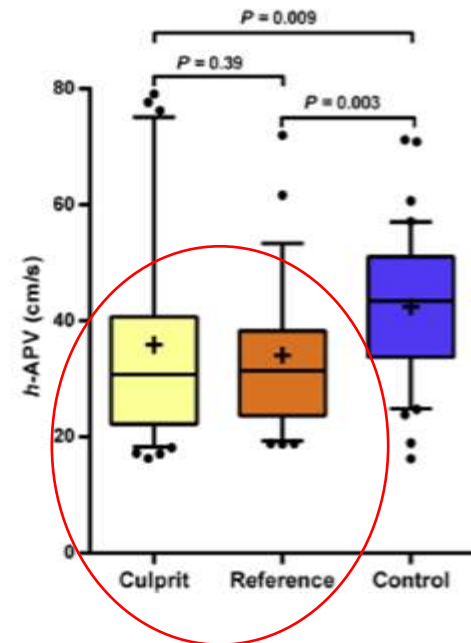
A. CFR (Doppler)



B. Resting APV



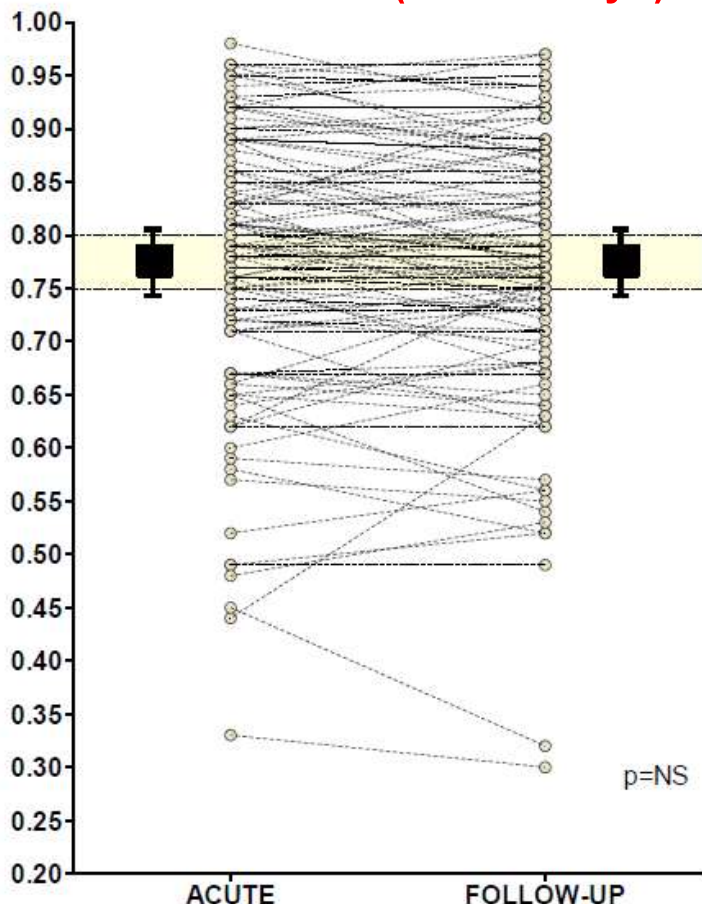
C. Hyperemic APV



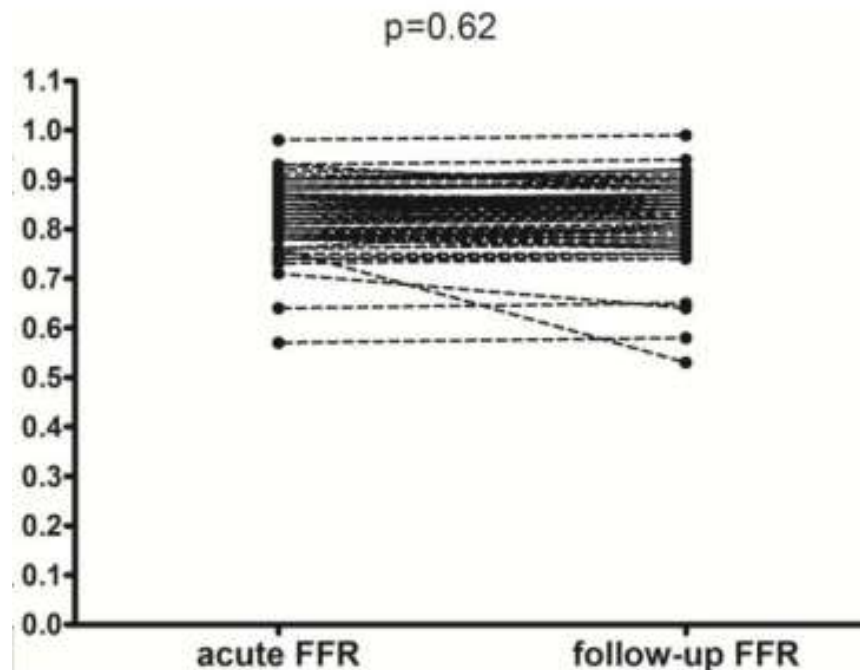
They claimed **blunted hyperemic response** in STEMI setting
Possibility of underestimation of non-culprit stenosis severity by FFR

Actual Comparison Data of Non-culprit FFR (Acute vs. FU)

101 patients with ACS (75 STEMI, 26 NSTEMI)
Acute vs. F/U (35±24 days)



50 STEMI patients
Acute vs. F/U (5-8 days)



Non-culprit FFR did not show significant change between acute vs. F/U phase

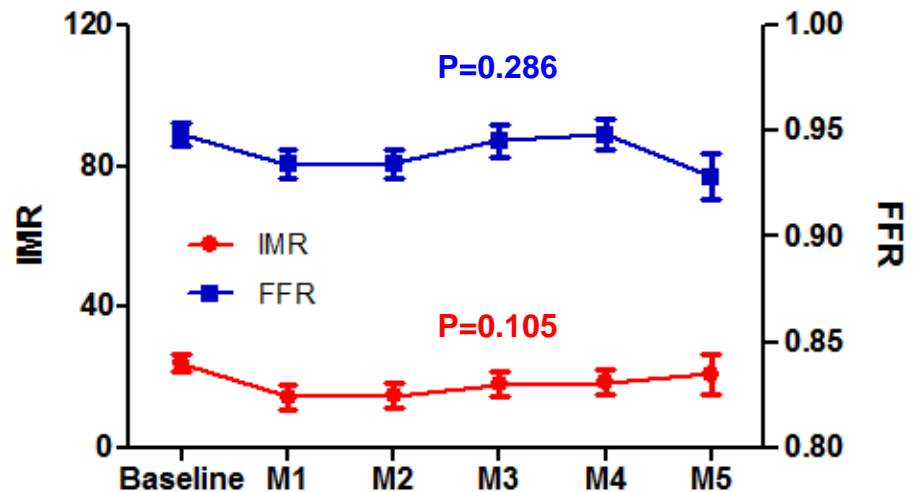
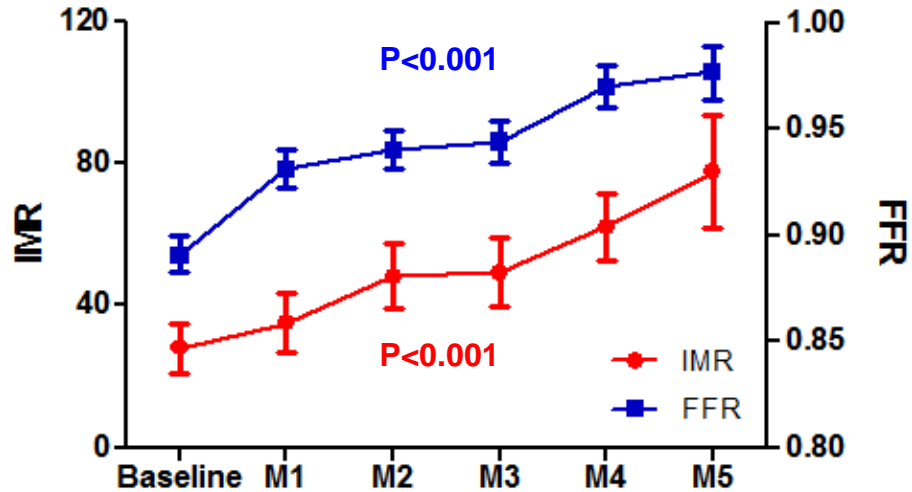
Microcirculatory dysfunction in ACS

- Culprit vs. Non-culprit Vessels -

Inducing significant MV damage in LAD with Repeated IC injection of Microsphere 50um
Artificial intermediate stenoses were created in LAD and LCX using balloon

LAD (Microsphere)
- Simulating Culprit Vessel -

LCX (No Microsphere)
- Non-culprit Vessel -



Microcirculatory dysfunction in culprit vessel is regional problem and did not affect non-culprit vessel territory (FFR and IMR in non-culprit were not changed significantly)

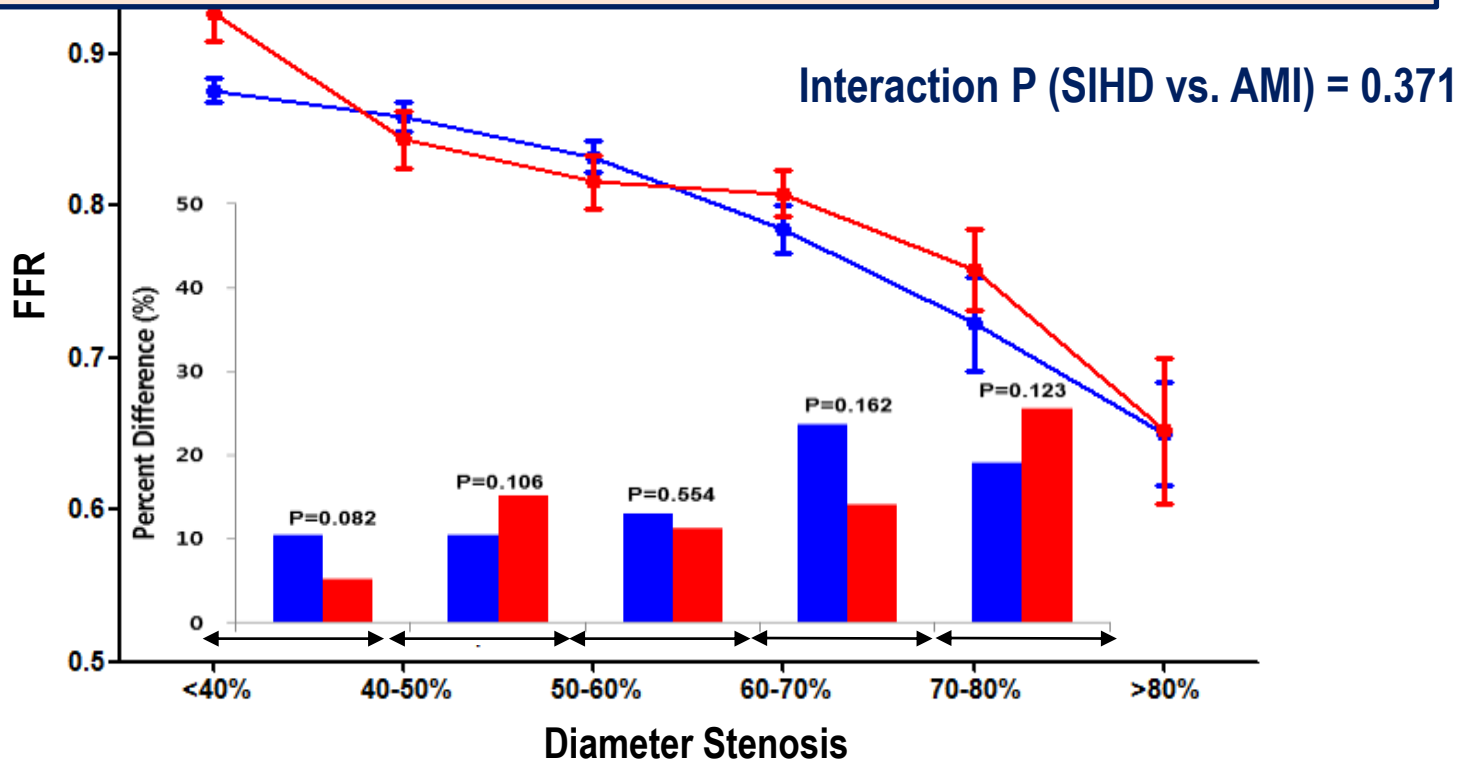
FFR for Non-Culprit Stenosis Evaluation - At the time of Primary PCI -

100 AMI with Multivessel Disease (FFR/CFR/IMR at Acute stage)
vs. 203 Stable IHD Patients

All physiologic indices were measured after Primary PCI during acute stage

Fractional Flow Reserve

Even in the acute stage of MI,
Non-culprit FFR reliably reflect lesion severity.

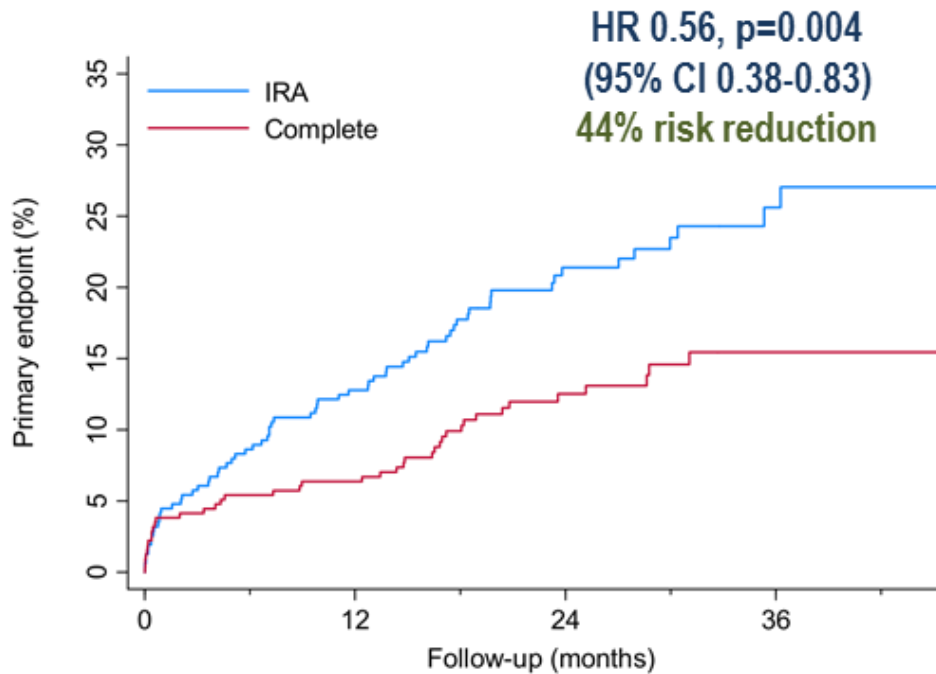


Solid Evidence of FFR-guided Non-culprit PCI

DANAMI-3-PRIMULTI (N=627)

Staged non-culprit FFR PCI: Median 2 days (2-4)

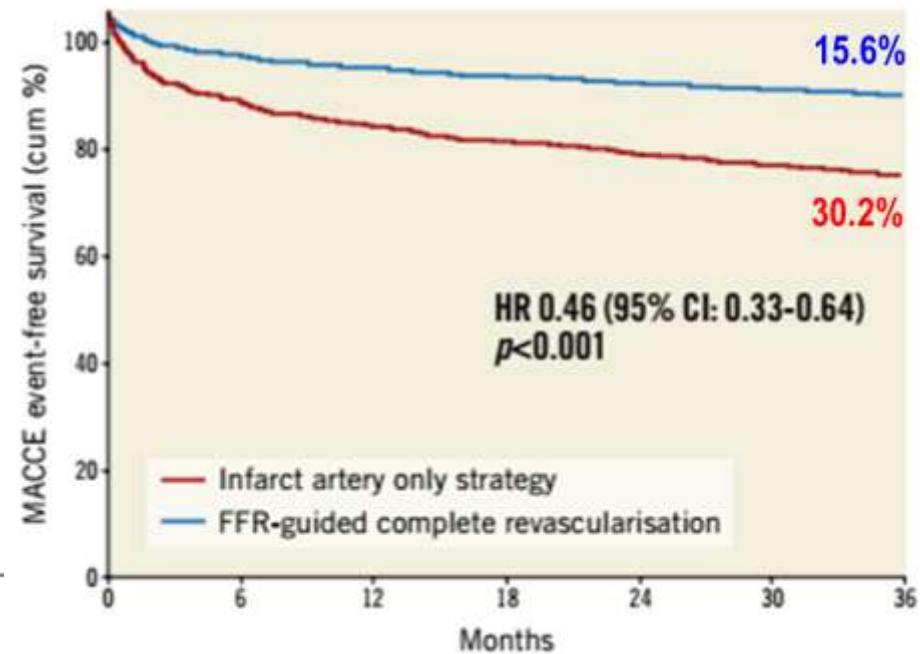
All death, MI, ischemia-driven revascularization
Median follow-up 27 months



COMPARE-ACUTE Trial (N=885)

83% Simultaneous FFR-guided PCI

All death, MI, revascularization, and CVA
At 3 Years



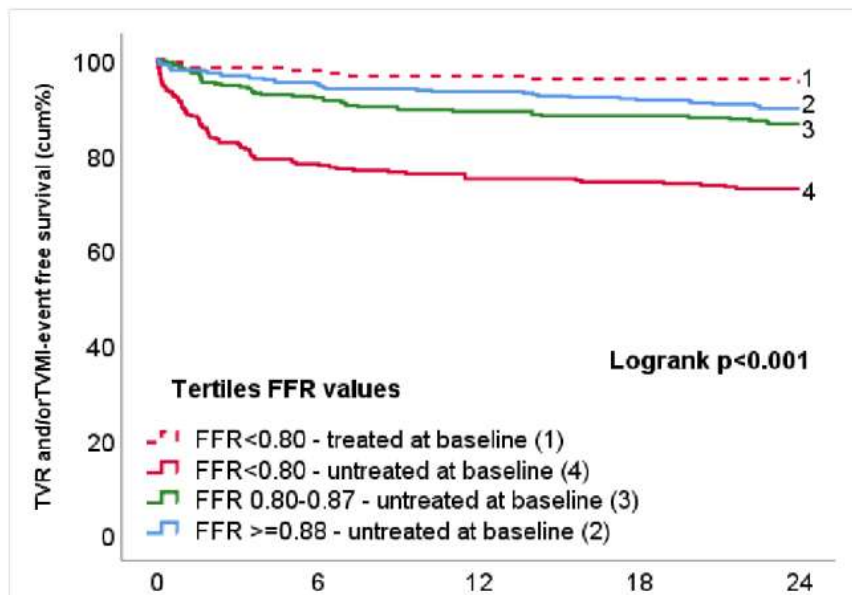
FFR-guided **Staged or Simultaneous** non-culprit vessel PCI showed
Significant benefit in terms of composite endpoints
(Any Death, MI, I-D revascularization)

How to Select Non-Culprit Stenosis for PCI

Angiographic Stenosis Severity (Visual/QCA) in COMPLETE Trial

CV death/MI	Complete no. of events/total no. (%/yr)	Culprit only no. of events/total no. (%/yr)	HR (95% CI)	P value for Interaction
Overall	158/2016 (2.7)	213/2025 (3.7)	0.74 (0.60-0.91)	
<i>Main pre-defined:</i>				
Proximal/mid LAD non-culprit stenosis				0.2
Presence	64/820 (2.7)	78/849 (3.1)	0.86 (0.62-1.20)	
Absence	87/1097 (2.7)	129/1085 (4.2)	0.65 (0.49-0.85)	
Non-culprit stenosis severity \geq 80% visual or \geq 60% core lab				0.033
Presence	127/1668 (2.6)	183/1631 (3.9)	0.67 (0.53-0.84)	
Absence	31/346 (3.2)	29/392 (2.6)	1.23 (0.74-2.04)	

Physiologic Stenosis Severity (FFR) in COMPARE-ACUTE Trial



Both Angio- and FFR- are supported by RCTs

Angiographic stenosis	FFR immediate phase	FFR staged phase
PRAMI	COMPARE-ACUTE	DANAMI-3-PRIMULTI
CvLPRIT		
COMPLETE		

Contemporary Recommendations

How to Treat Non-culprit Stenosis in ACS?

2017 ESC/EACTS Guideline for STEMI

Class IIa, LOE A

Routine Revascularization of non-IRA lesions should be considered in STEMI patients with multivessel disease **before hospital discharge**.

Key Messages

Management of non-IRA lesions: Treatment of severe stenosis (evaluated either by **angiography** or **FFR**) should be considered before hospital discharge (either **immediately** during the index PCI or **staged** at a later time).

2020 ESC/EACTS Guideline for NSTEMI-ACS

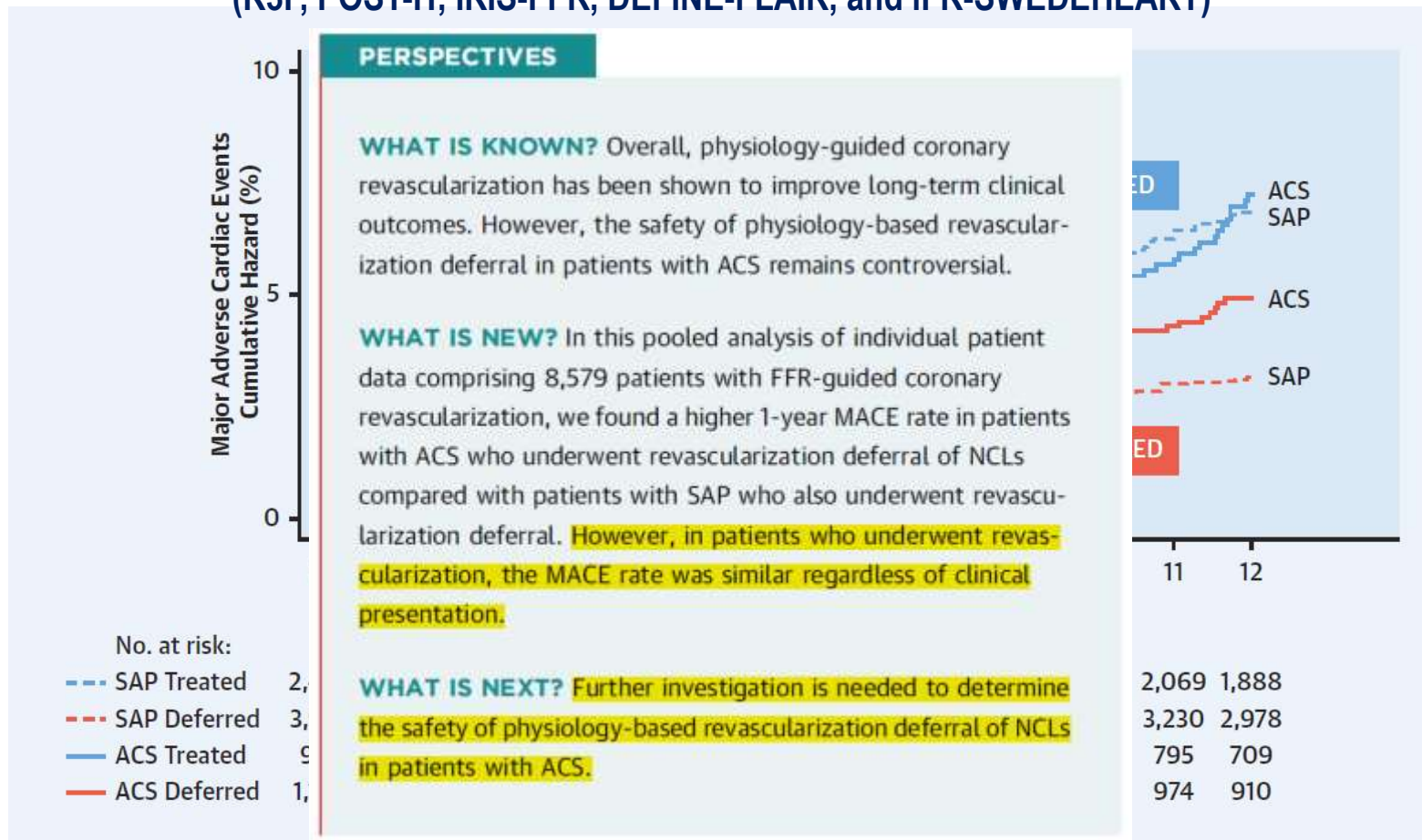
Class IIb, LOE B

FFR-guided revascularization of a non-culprit NSTEMI-ACS lesion may be used during index PCI.

FFR-based Deferral of Non-Culprit Vessel vs. Stable CAD

2,118 ACS (STEMI/NSTEMI/UA) vs. 6,461 Stable CAD

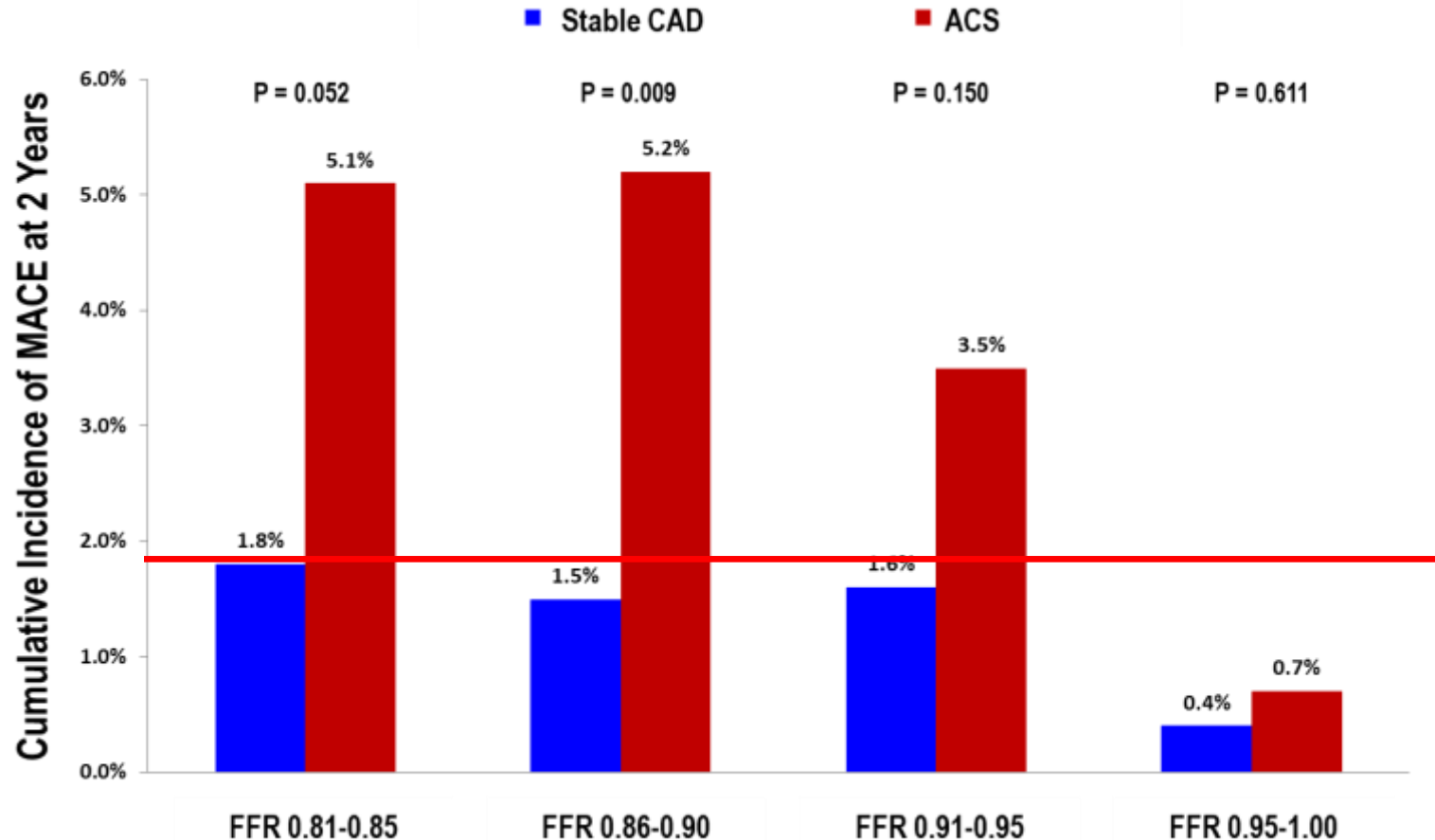
Revascularization was deferred in 5,129 patients based on FFR>0.80 (59.8%)
(R3F, POST-IT, IRIS-FFR, DEFINE-FLAIR, and iFR-SWEDEHEART)



Deferred ACS patients (non-culprit stenosis) had significantly higher risk of clinical events (mainly unplanned revascularization) than Stable CAD

FFR-based Deferral of Non-Culprit Vessel vs. Stable CAD

301 Patients with NSTEMI-ACS vs. 1,295 Patients with Stable CAD
In all patients, revascularization was deferred based on $FFR > 0.80$

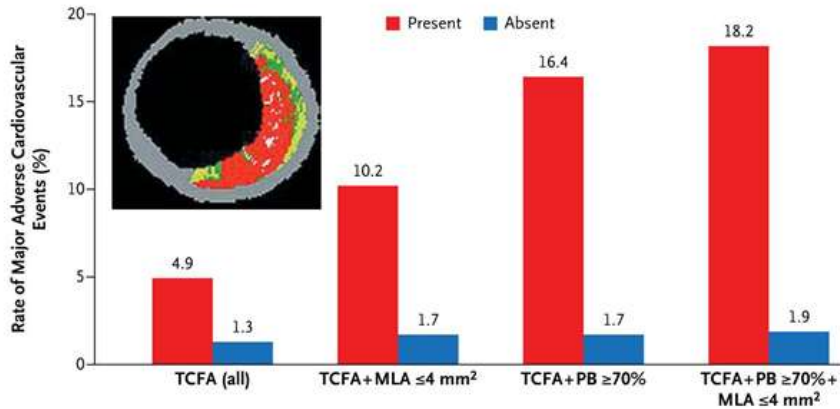


Deferred ACS patients (non-culprit stenosis) had significantly higher risk of clinical events than Stable CAD,

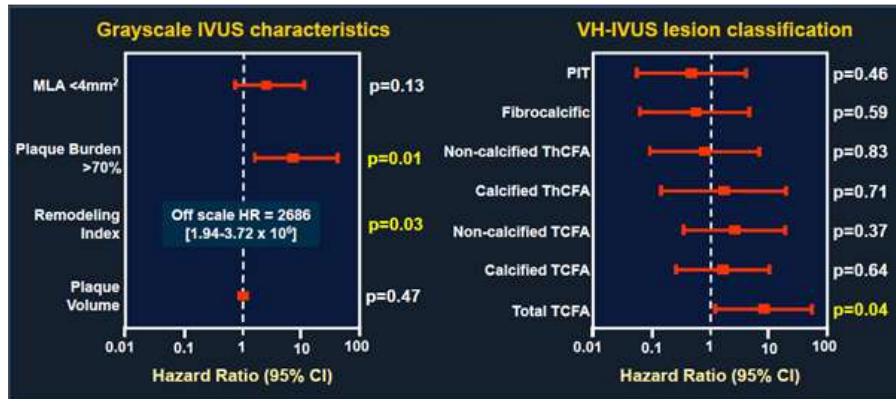
Regardless of FFR values in non-culprit vessel

Prognosis of Non-Culprit Vessel of ACS Patients

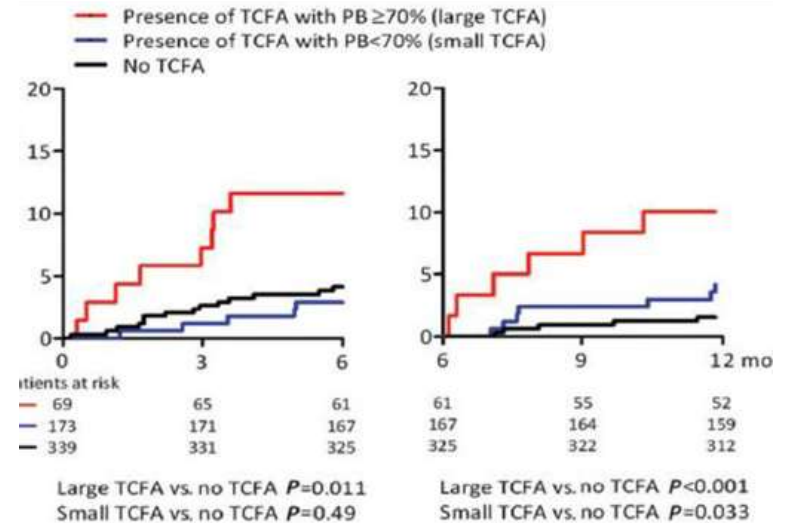
PROSPECT Trial



VIVA



ATHEROREMO



ACS patient with vulnerable plaques in non-culprit vessel consistently show worse clinical outcome

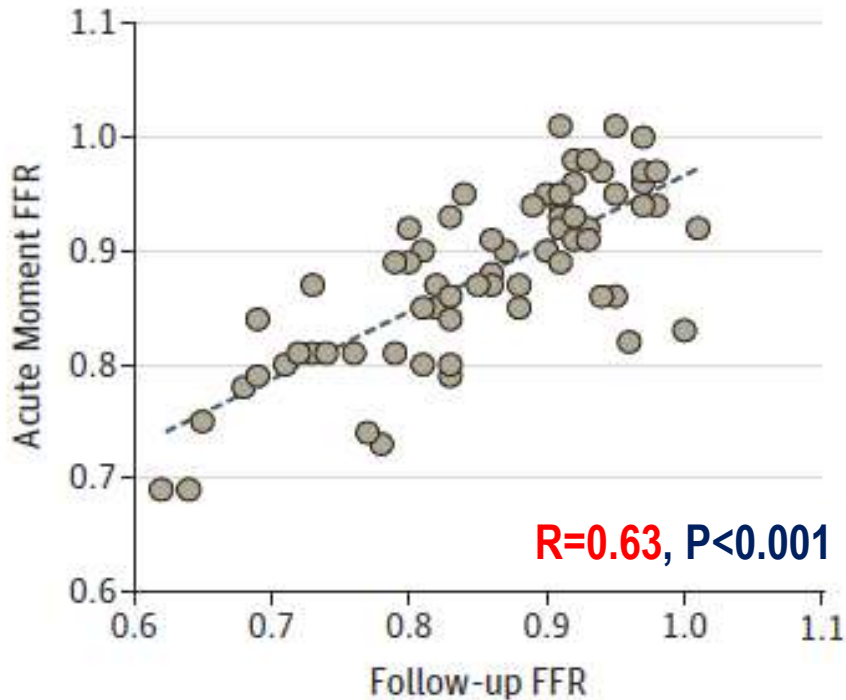
It is not a matter of reliability or cutoff value of FFR.
 It is patient characteristics like DM/CKD/PVD patients

Which Physiologic Index?

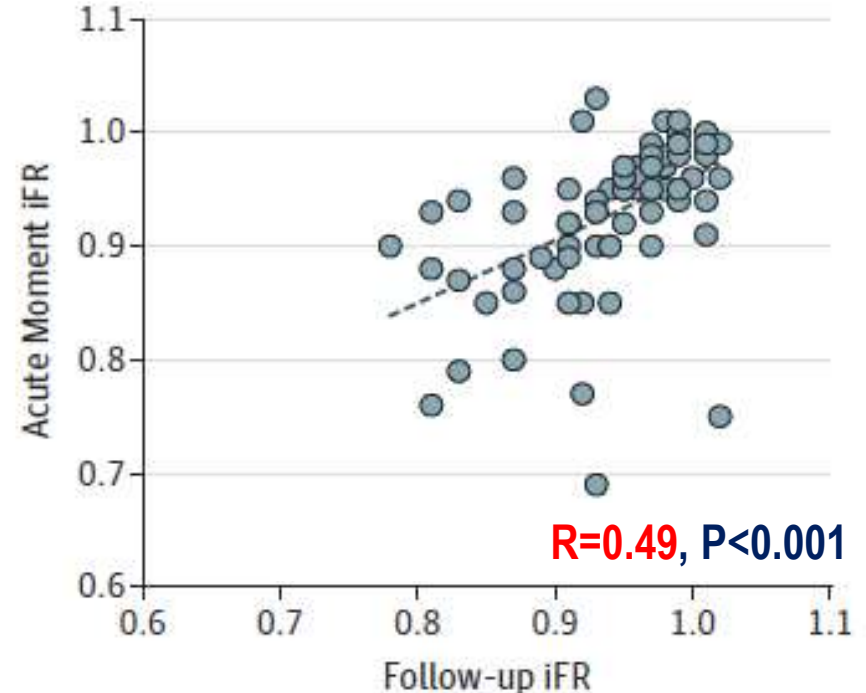
FFR vs. NHPRs in Non-culprit Vessel of STEMI

73 STEMI patients, Acute vs. 1 month Follow-up FFR/iFR in Non-culprit

FFR in Non-culprit



iFR in Non-culprit



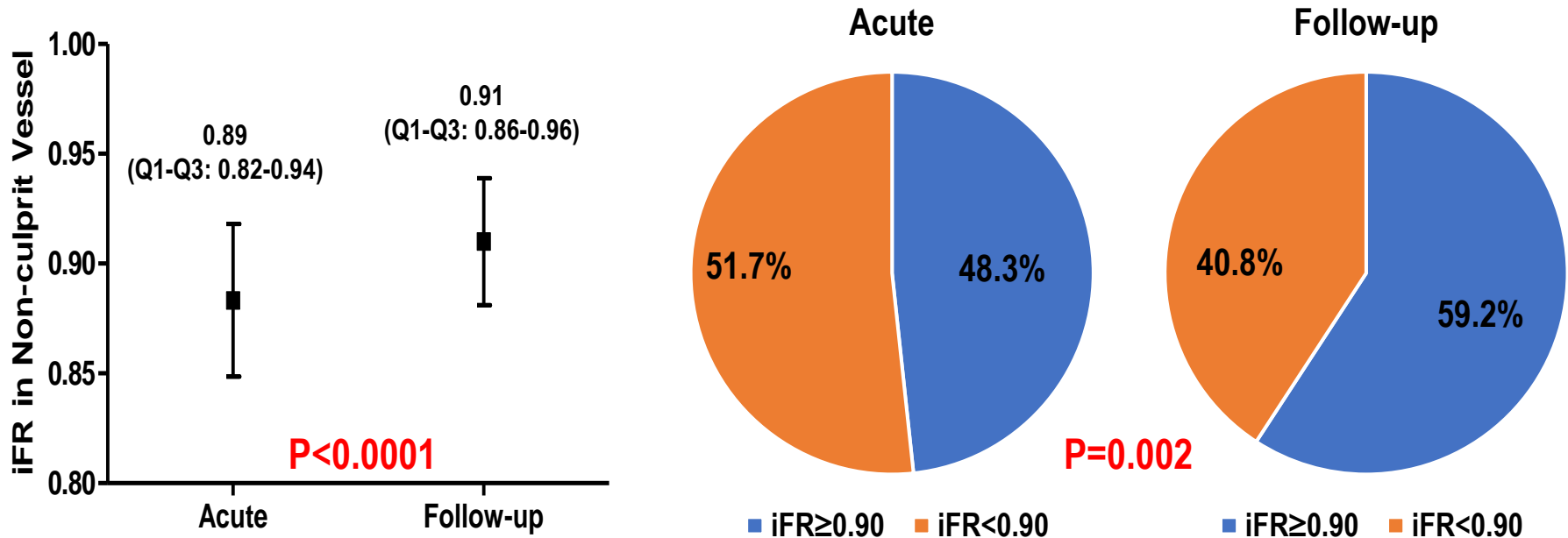
Acute vs. 1 month Follow-up

FFR significantly decreased vs. iFR did not change

But, iFR showed much lower correlation between acute and follow-up values

NHPRs (iFR) in Non-culprit Vessel in STEMI (iSTEMI study)

120 STEMI patients, 147 paired iFR values in non-culprit vessels
Acute vs. Follow-up values (Median 16 days, Q1-Q3: 5-32 days)



**Classification agreement between acute and follow-up
iFR values in Non-culprit vessel was only 78%**

**iFR in non-culprit vessel during acute phase significantly
overestimates stenosis severity.**

Changes of Resting / Hyperemic Indexes in STEMI Non-culprit - Preclinical Validation -

Porcine STEMI Model : Balloon Occlusion of **LCX (STEMI culprit)**

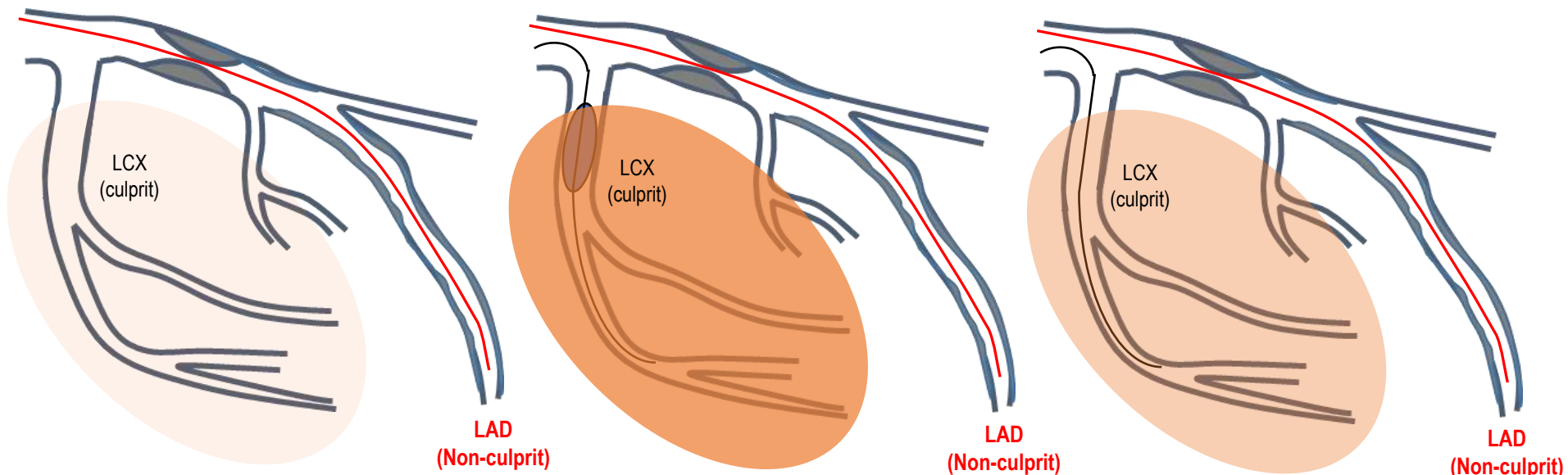
Serial resting/hyperemic physiologic indexes in **LAD (Non-culprit)**

In 3 phases (Before and During LCX occlusion, and After reperfusion of LCX)

[1] Before LCX occlusion

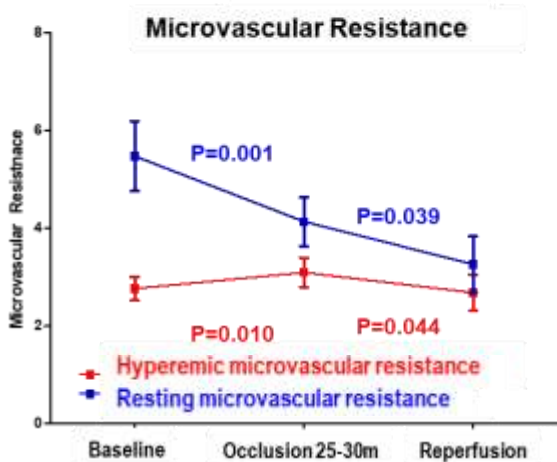
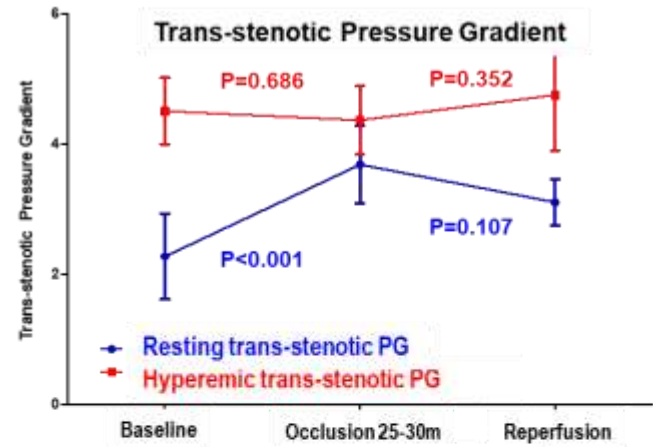
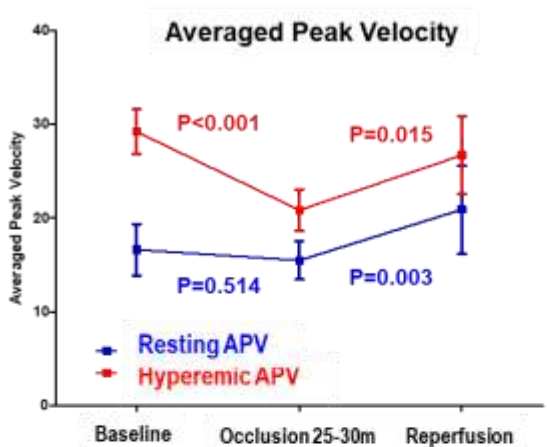
[2] During LCX occlusion

[3] After LCX reperfusion



Changes of Resting / Hyperemic Indexes in STEMI Non-culprit - Preclinical Validation -

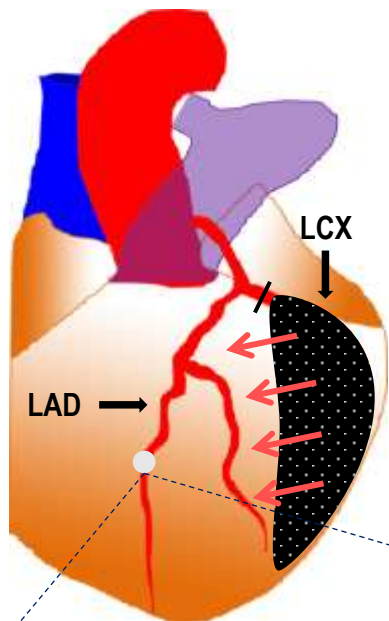
Porcine STEMI Model : Balloon Occlusion of **LCX (STEMI culprit)**
Serial resting/hyperemic physiologic indexes in **LAD (Non-culprit)**
Before LCX occlusion, During LCX occlusion, After LCX reperfusion



Serial Changes of Hemodynamics in STEMI Non-culprit

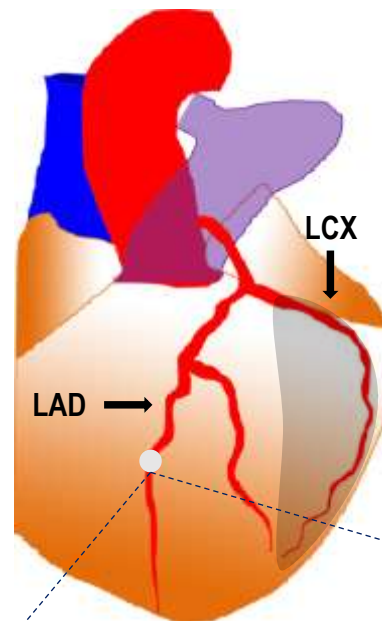
- Preclinical Validation -

During Balloon Occlusion of IRA



Non-IRA	
CFR	↓↓
iFR	↓↓
FFR	↑

After Reperfusion of IRA



Non-IRA	
CFR	↓↓
iFR	↓↓
FFR	↔

Resting

Hyperemia

APV	↔	APV	↓↓
Microvascular Resistance	↓↓	Microvascular Resistance	↑↑
Trans-Stenotic PG	↑↑	Trans-Stenotic PG	↓

Resting

Hyperemia

APV	↑↑	APV	↔
Microvascular Resistance	↓↓	Microvascular Resistance	↔
Trans-Stenotic PG	↑↑	Trans-Stenotic PG	↔

Conclusion

Invasive Physiology in Non-Culprit Vessel of AMI

Yes. It is reliable.

Additional consideration is needed.

- Clinical presentation (STEMI vs. NSTEMI-ACS)
- Target vessel (Culprit vs. Non-culprit)
- Type of Index (Hyperemic vs. NHPRs)
- Timing of measurement (Acute vs. Staged)

In Acute Phase	Culprit of STEMI	Non-Culprit of STEMI	Non-Culprit of NSTEMI-ACS
Resting coronary flow	↑↑	↑↑↑	↑ (Not significant)
Hyperemic coronary flow	↓↓	↔	↔
CFR	↓↓↓	↓↓	↓ (Not significant)
IMR	↑↑↑ (Prognostic indicator)	↔	↔
FFR	Not Recommended	Reliable	Reliable
NHPRs (iFR/FR/dPR/DFR)	Not Recommended	Possible overestimation of non-culprit lesion severity	Reliable