Microvascular Dysfunction:
Physiologic Evaluation and Its Clinical Implication
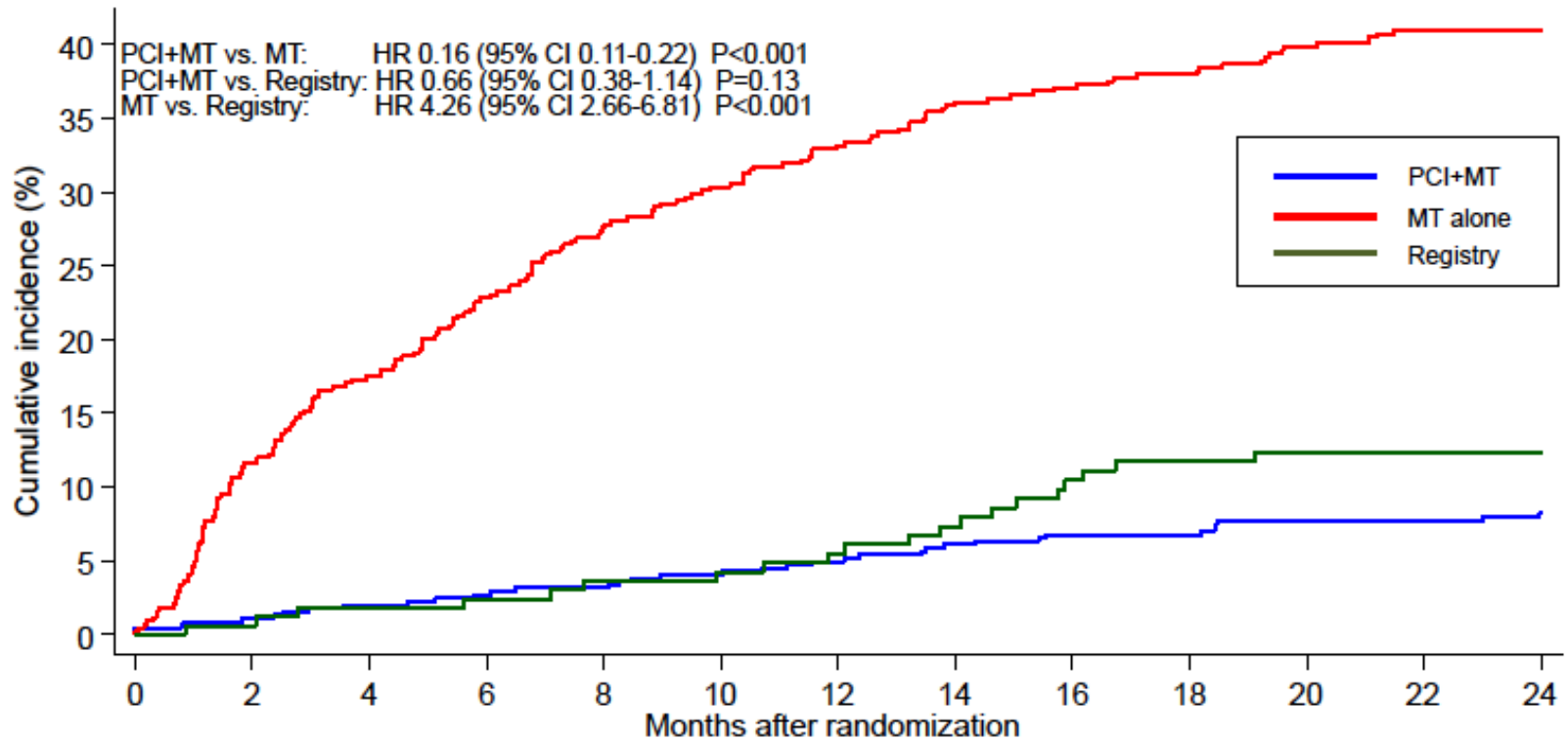
Joo Myung Lee, MD, MPH, PhD

Heart Vascular Stroke Institute,

Samsung Medical Center, Seoul, Republic of Korea

SAMSUNG MEDICAL CENTER   SAMSUNG

SAMSUNG   SAMSUNG MEDICAL CENTER

Introduction
FFR > 0.80 did not mean no ischemia

PCI+MT vs. MT: HR 0.16 (95% CI 0.11-0.22) P<0.001
PCI+MT vs. Registry: HR 0.66 (95% CI 0.38-1.14) P=0.13
MT vs. Registry: HR 4.26 (95% CI 2.66-6.81) P<0.001

Legend:
- PCI+MT
- MT alone
- Registry

Y-axis: Cumulative incidence (%)
X-axis: Months after randomization

In patients with FFR>0.80 (registry arm in FAME II)
9.0 % experienced all-cause death, MI, and urgent revasc.
14.6% showed persistent CCS II-IV angina at 2-years

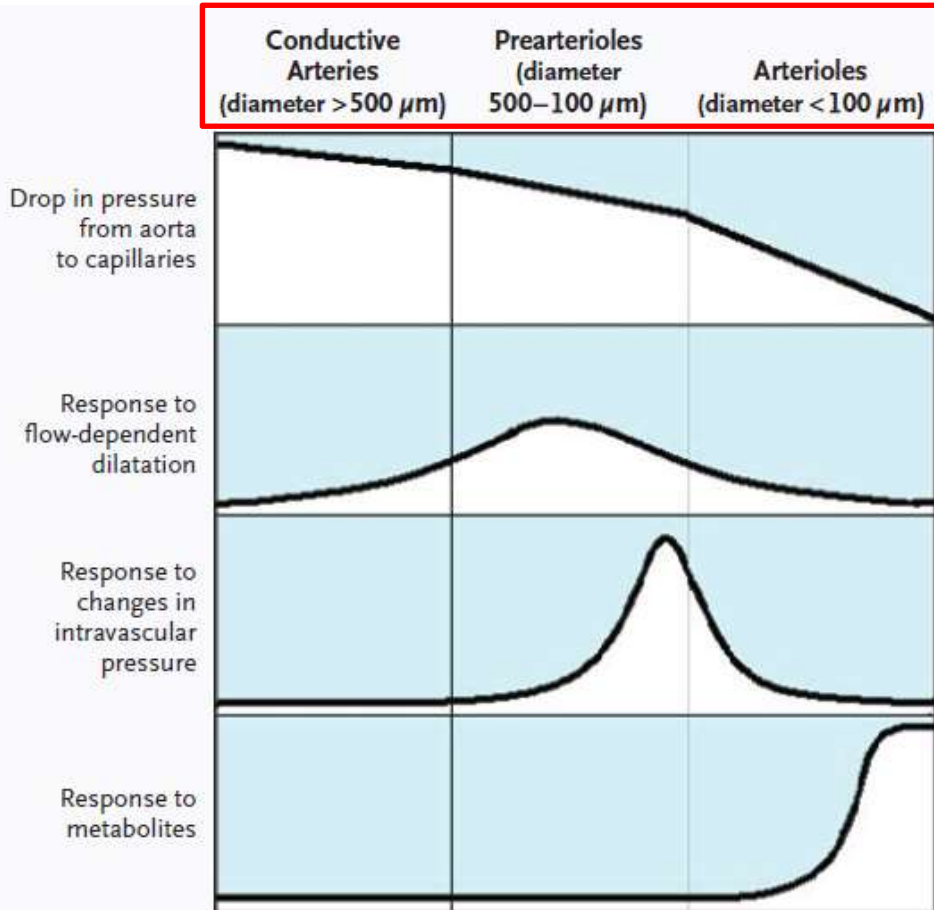# Potential Causes of Cardiac Events/ Chest Pain in Deferred Patients

- **Progression of atherosclerosis**
- **Pain or event due to non-atherosclerotic coronary disease**
- **Vulnerability**
- **Hidden disease, diffuse atherosclerosis**
- **<u>Microvascular disease</u>**

<5% of the total coronary tree

Courtesy to My Mentor, Prof. Koo BK

Ischemic Heart Disease

Figure 1. Functional Anatomy of the Coronary Arterial System.

- Coronary Arterial System is composed of three compartments

- Any of these compartments fail to maintain sufficient O2, myocardial ischemia can occur.

- **Therefore, the presence of epicardial coronary stenosis is not always a "prerequisite" for the IHD.**

Typical Angina, TMT (+)

LAD FFR 0.85
CFR 1.5
IMR 53

LCX FFR 0.99
CFR 1.7
IMR 45

Diagnosis of Micro-Vascular Disease

Exercise Duration : 9 min 58 sec, 12.8 METS
Chest pain during Stage 3 and 4
Horizontal ST depression in II, III, aVF, V3, V4, V5
Duke score : -5 (moderate risk)

Unsolved Issues for Microvascular Disease

[Primary Microvascular disease]

① Distribution and Abnormal value of IMR values in non-MI patients

② Whether Macro- and Micro- disease has independent disease process?

③ Predictors of High IMR and Low FFR

④ Clinical Prognosis of Patients with Microvascular disease

⑤ Mechanism of Clinical Events in Patients with Microvascular disease

⑥ Effective Treatment of Microvascular Disease

[Secondary Microvascular Damage after AMI or Procedure-related]

① Is it "Regional Problem" or "Globalization will be occurred?"

② Non-Culprit stenosis evaluation with FFR

③ How can we reduce MV damage after successful revascularization

Primary Microvascular Disease

International IMR registry
- 1,096 patients with 1,452 coronary arteries -

To explore clinical relevance of microvascular assessment using IMR in addition to the current FFR guided strategy in non-MI patients

[Primary Microvascular disease]

① **Distribution and Abnormal value of IMR values in non-MI patients**

② **Whether Macro- and Micro- disease has independent disease process?**

③ **Predictors of High IMR and Low FFR**

④ Clinical Prognosis of Patients with Microvascular disease

⑤ Mechanism of Clinical Events in Patients with Microvascular disease
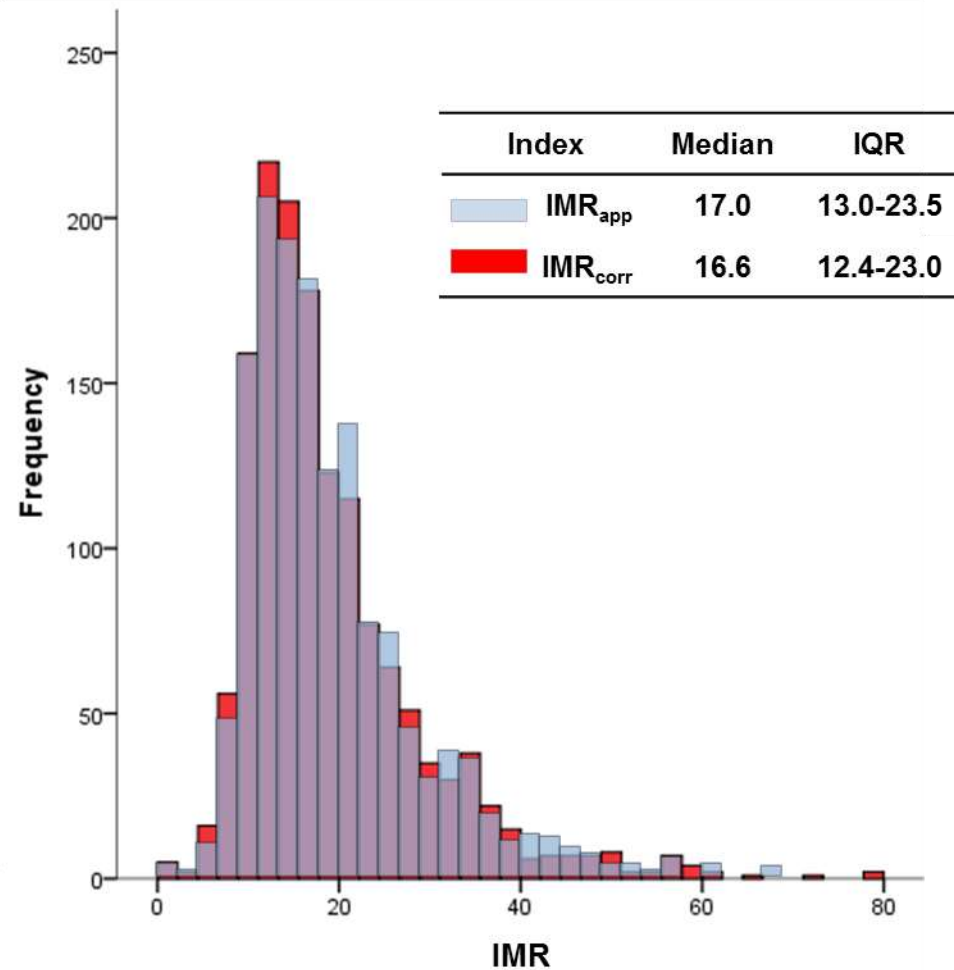
⑥ Effective Treatment of Microvascular Disease

Distribution of FFR and IMR in 1,452 Lesions
International IMR registry (Non-MI Population)
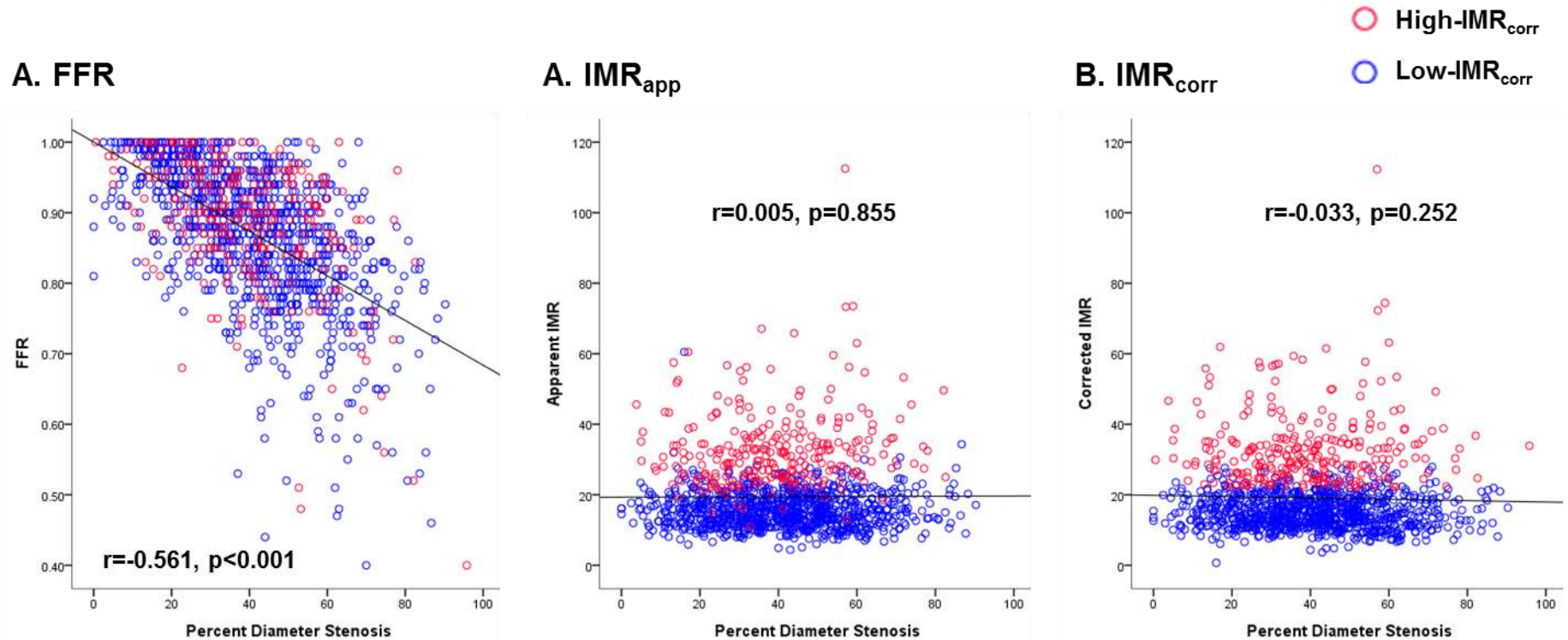
A. Fractional Flow Reserve
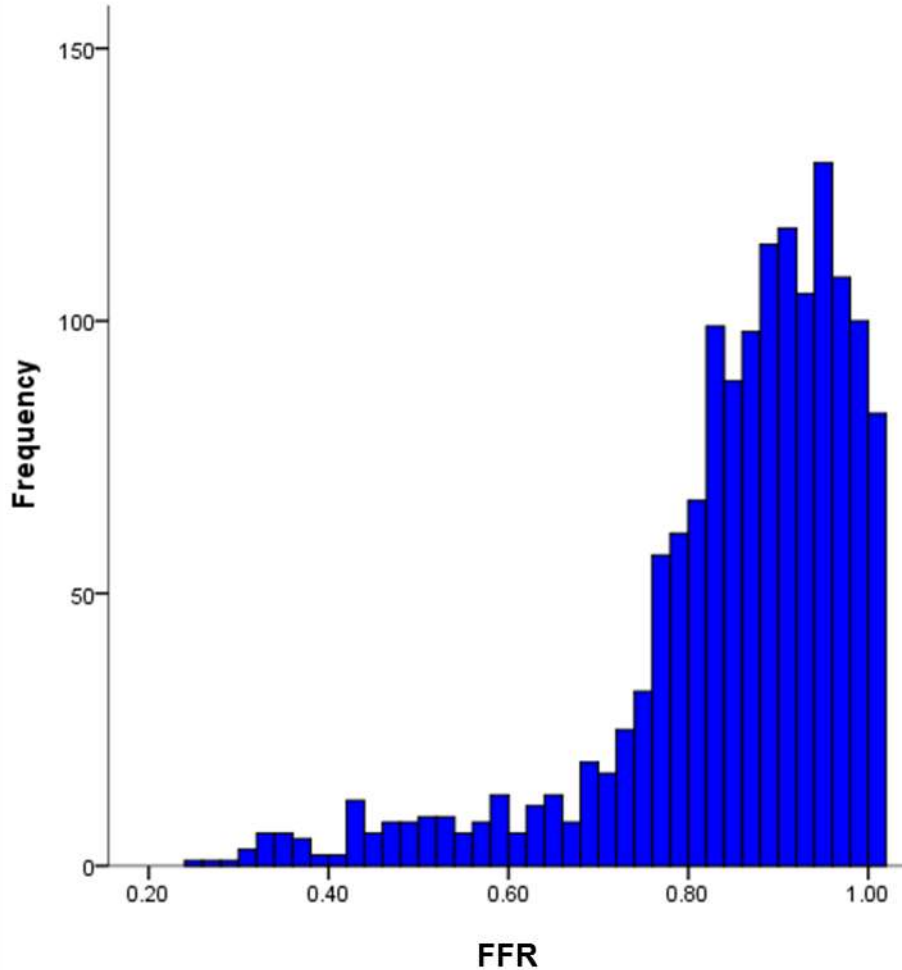
B. Index of Microvascular Resistance

Index	Median	IQR
IMR$_{app}$	17.0	13.0-23.5
IMR$_{corr}$	16.6	12.4-23.0

An *IMR≤25* is considered normal in non-MI population

Association between Angio, FFR, IMR in 1,452 Lesions
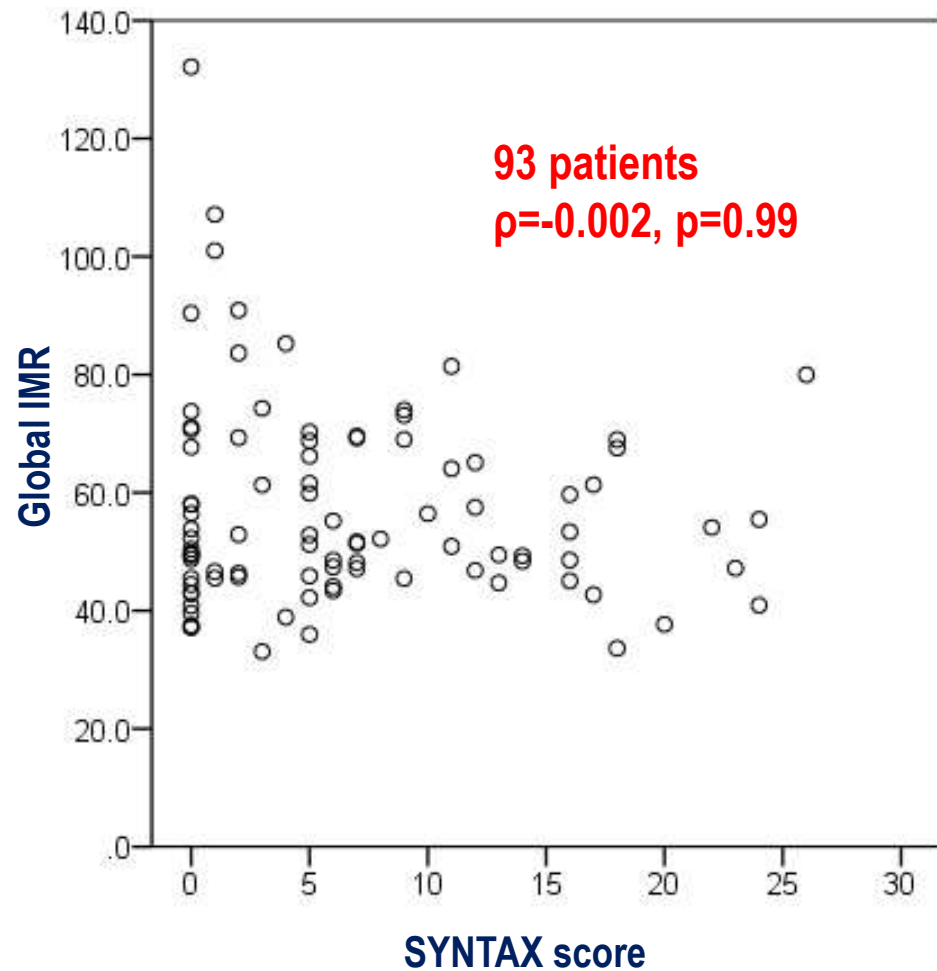## International IMR registry (Non-MI Population)

- ○ High-IMR$_{corr}$
- ○ Low-IMR$_{corr}$

A. FFR

FFR vs Percent Diameter Stenosis

r=-0.561, p<0.001

A. IMR$_{app}$

Apparent IMR vs Percent Diameter Stenosis

r=0.005, p=0.855

B. IMR$_{corr}$

Corrected IMR vs Percent Diameter Stenosis

r=-0.033, p=0.252

- **FFR showed significant correlation with angiographic %DS**

- **IMR did not show any correlation with angiographic %DS**

Correlations between SYNTAX Score and IMR
3-vessel FFR/IMR measure subgroups

A. SYNTAX score (Patient)

93 patients
$\rho=-0.002$, $p=0.99$

B. Vessel-specific SYNTAX score

279 vessels
$\rho=-0.06$, $p=0.36$

Kobayashi Y, Fearon WF, Lee JM, Koo BK et al. Circulation Intervention 2017
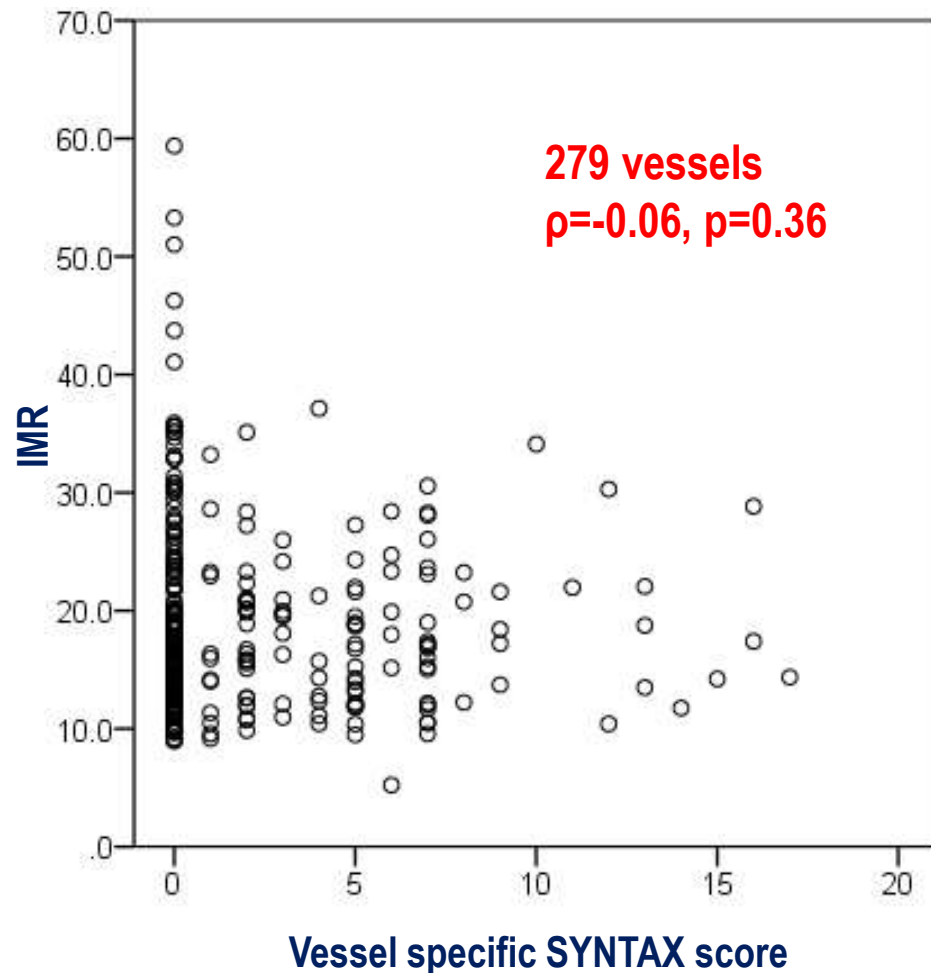
Different Independent Predictor for High-IMR or Low-FFR
International IMR registry

Independent Predictor for High-IMR or Low-FFR in Target Vessels

High-IMR (≥75th percentile)				Low-FFR (≤0.80)			
	OR	95% CI	P value		OR	95% CI	P value
Previous MI	2.16	1.24-3.74	0.006	**LAD**	5.92	3.73-9.41	<0.001
RCA	2.09	1.54-2.84	<0.001	**%DS ≥50%**	5.84	3.98-8.56	<0.001
Female	1.67	1.18-2.38	0.004	**Male**	2.25	1.38-3.66	0.001
Obesity	1.8	1.31-2.49	<0.001	**Age**	1.02	1.00-1.04	0.046

- **Completely different predictors between High-IMR and Low-FFR**

Korean Registry for
Comprehensive Physiologic Evaluation
- 313 patients with 663 coronary arteries -

- **To evaluate the prognostic implications of abnormal CFR and IMR in high-FFR patients.**

[Primary Microvascular disease]

① Distribution and Abnormal value of IMR values in non-MI patients

② Whether Macro- and Micro- disease has independent disease process?

③ Predictors of High IMR and Low FFR

④ Clinical Prognosis of Patients with Microvascular disease

⑤ Mechanism of Clinical Events in Patients with Microvascular disease

⑥ Effective Treatment of Microvascular Disease

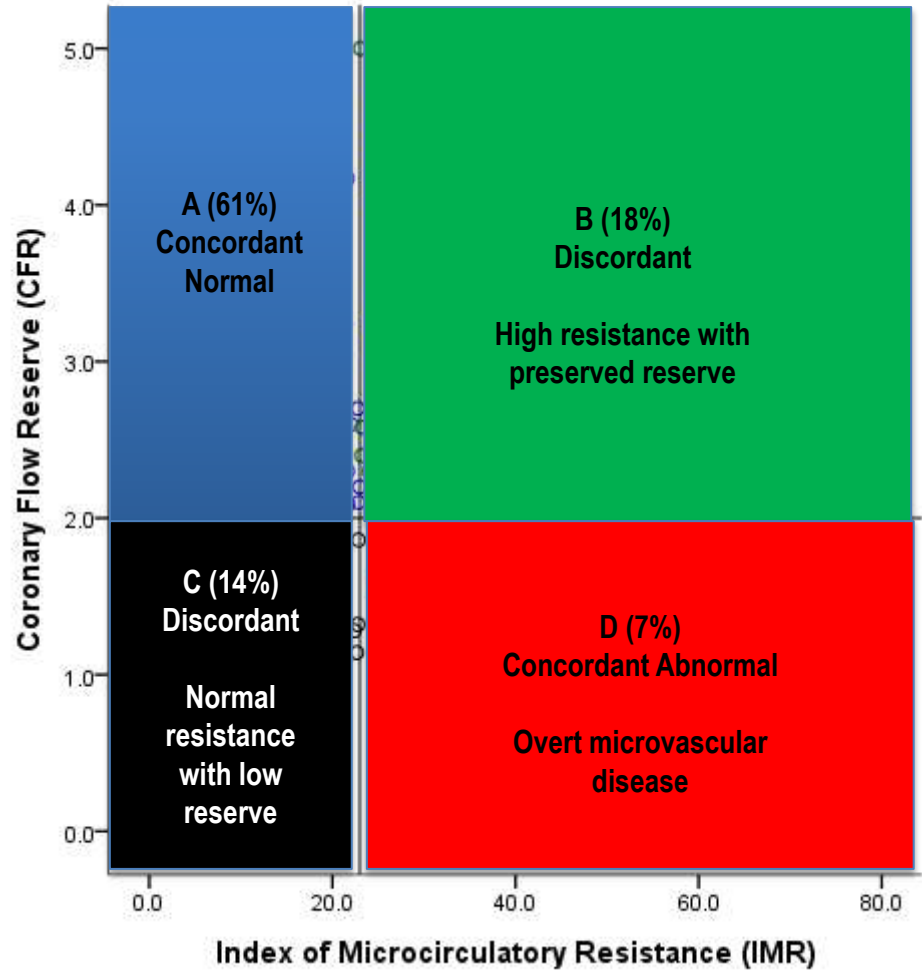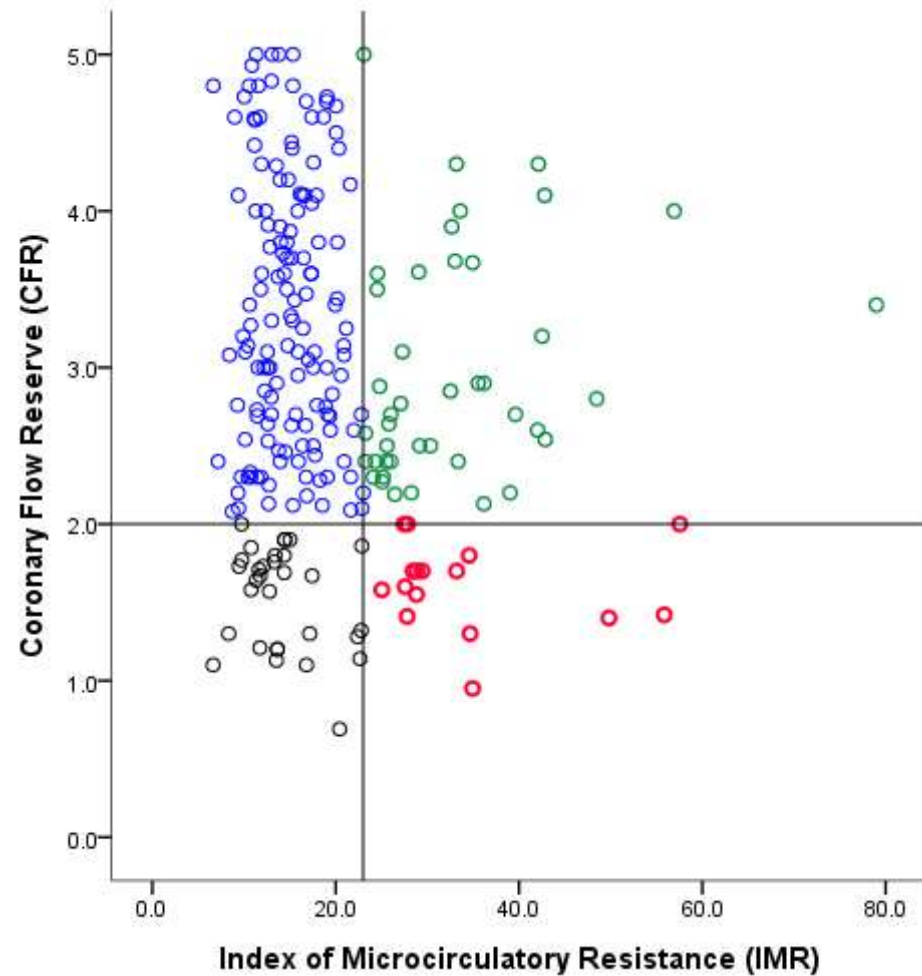# Distribution of patients according to FFR and CFR
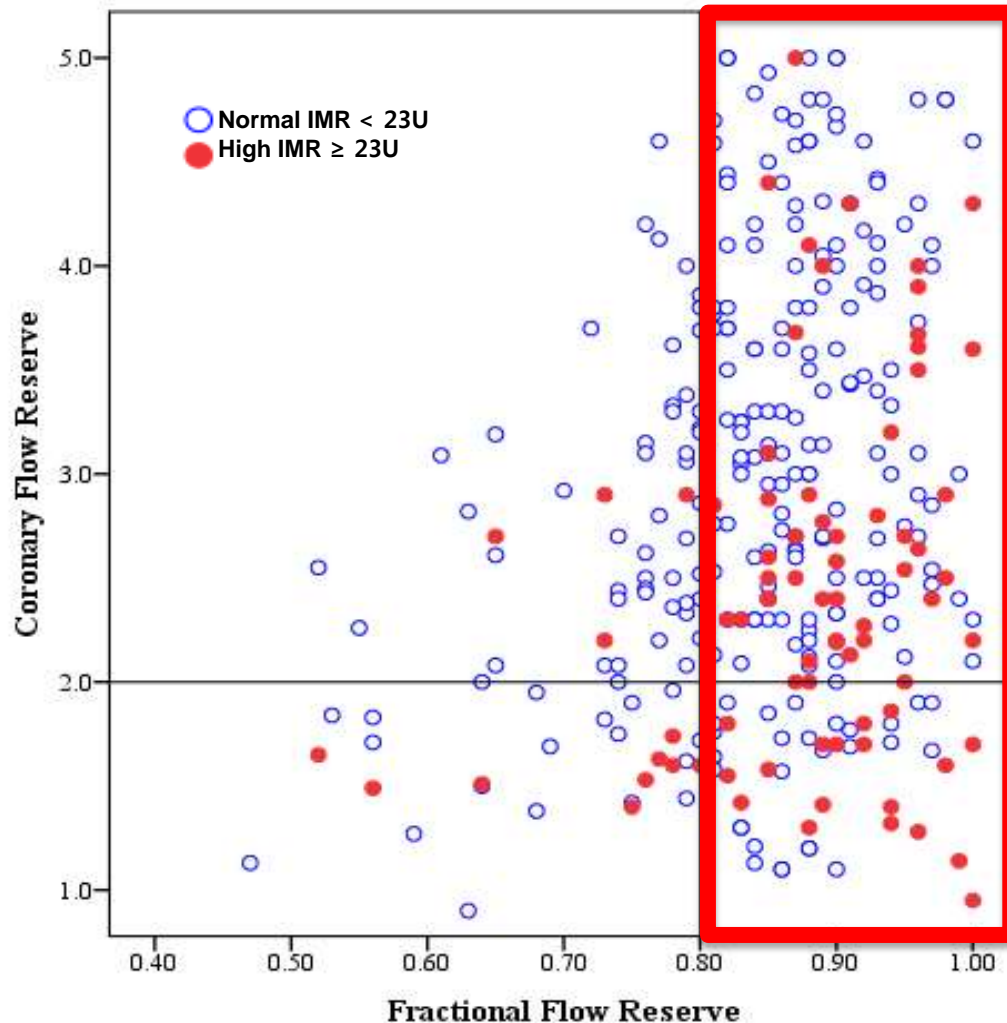
Angiographic % DS: 36.8% (32.4-38.2)

FFR 0.91 (0.90-0.91)

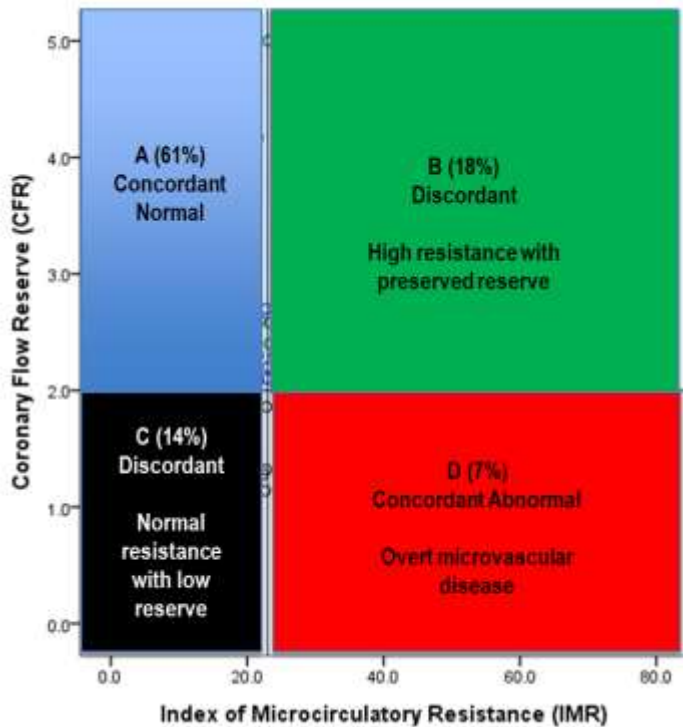CFR 2.88 (2.78-2.97)

IMR 20.2U (19.3-21.1)

Distribution of High-FFR patients according to CFR and IMR

# Comparison of Clinical, Angiographic Findings Among 4 Group of High-FFR population

	Group A (CFR>2 and IMR<23U)	Group B (CFR>2 and IMR≥23U)	Group C (CFR≤2 and IMR<23U)	Group D (CFR≤2 and IMR≥23U)	p value
Age, years	60.2 ± 9.9	63.9 ± 7.1	65.6 ± 9.7	62.6 ± 9.9	0.017
Male					91
BMI, k					51
Hyper					47
Diabet					84
Hypercholesterolemia	88 (62.4%)	23 (54.8%)	17 (54.8%)	7 (43.8%)	0.434
Current smoker	25 (17.7%)	6 (14.3%)	3 (9.7%)	2 (12.5%)	0.687
Family history	23 (16.3%)	7 (16.7%)	3 (9.7%)	1 (6.3%)	0.548
Previous MI	6 (4.3%)	2 (4.8%)	0 (0.0%)	0 (0.0%)	0.541
Previous PCI	40 (28.4%)	7 (16.7%)	9 (29.0%)	2 (12.5%)	0.263
Multivessel disease	57 (40.4%)	12 (28.6%)	14 (45.2%)	3 (18.8%)	0.163
Gensini score	12.0 (6.5-25.5)	11.3 (5.0-18.8)	20.5 (9.0-37.0)	9.3 (4.8-19.5)	0.114
Angiographic characteristics					
Reference diameter	3.02 (2.95-3.09)	3.18 (3.03-3.34)§	2.91 (2.80-3.01)‡	3.12 (2.92-3.32)	0.017

Those patients can be only discriminated by multiple physiologic criteria (FFR, CFR, IMR).

Comparison of Clinical Outcomes Among 4 Group of High-FFR population

Group	CFR	IMR	Hazard Ratio (95% CI)	P value
A	High	Low	1.000 (Reference)	NA
B	High	High	NA	NA
C	Low	Low	2.116 (0.386-11.589)	0.388
D	Low	High	5.623 (1.234-25.620)	0.026

Breslow P for overall comparison = 0.002

Overt Microvascular Disease

POCO, Patient-oriented Composite Outcomes
➔ a Composite of any Death, any MI, and any Revascularization
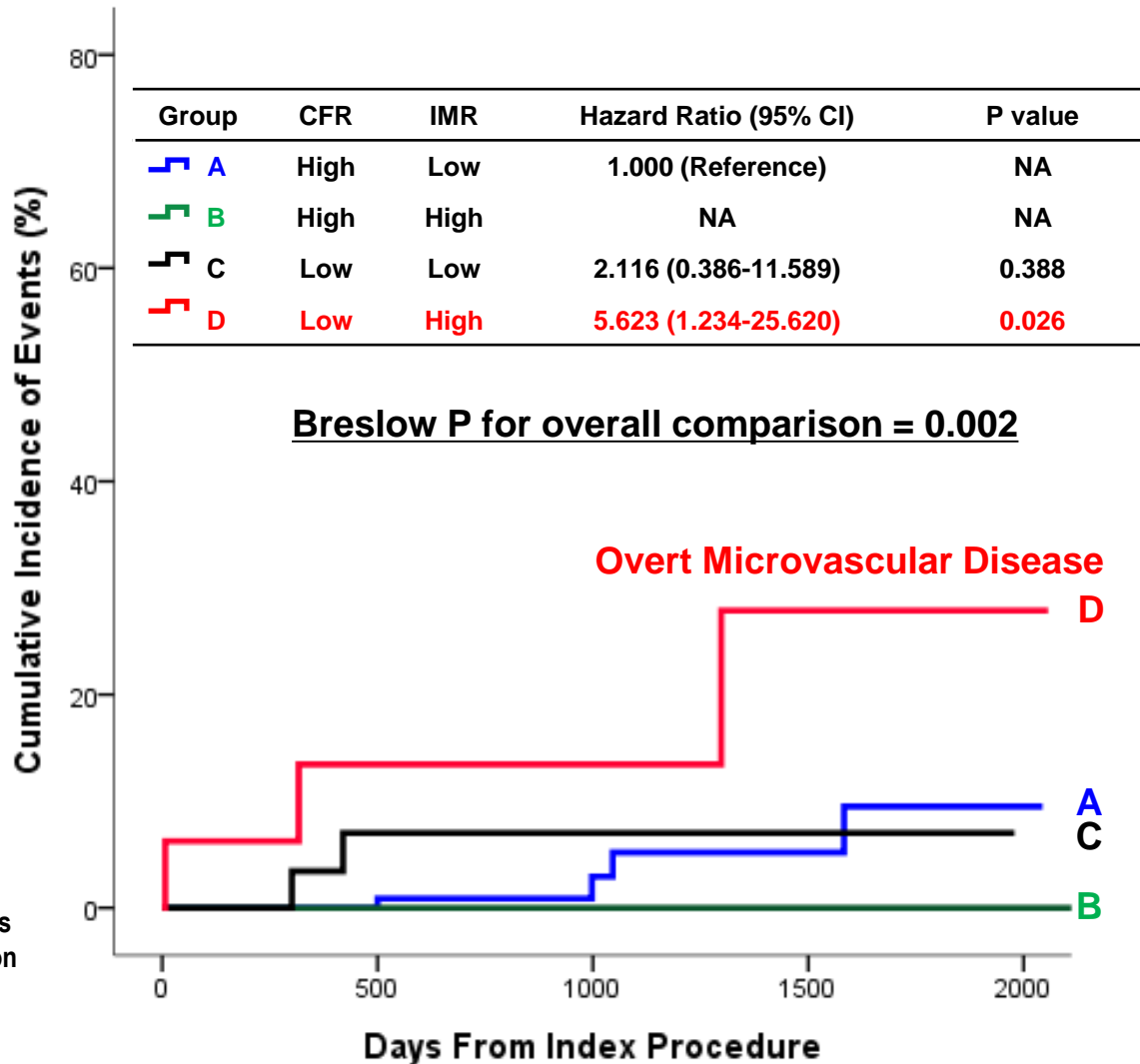
Independent Predictors of POCO Among High-FFR population

Clinical/Angiographic Variables Only

Model 1	HR	95% CI	P
Multivessel disease	3.254	1.082-9.787	0.033
Diabetes mellitus	2.828	1.088-7.349	0.033

Model with Physiologic Index

Model 2	HR	95% CI	P
Low-CFR and high-IMR	4.914	1.541-15.66	0.007
Multivessel disease	3.639	1.238-10.669	0.019
Diabetes mellitus	2.714	1.050-7.016	0.039

Improved discriminant function (Model2)

- **Relative IDI: 0.467, p=0.037**
- **Category-free NRI: 0.648, p=0.007**

Summary

- Macro- and micro-vascular diseases seems to possess "independent disease process" with "different predictors for its development", although complex interaction could be presented.

- Among the high-FFR patients (functionally insignificant macrovascular disease), about 7.0% of patient showed overt microvascular disease (low-CFR and high-IMR).

- Presence of overt microvascular disease was associated with poor prognosis in high FFR population.

- Comprehensive physiologic evaluation is essential to stratify those patients with overt microvascular disease.

SAMSUNG MEDICAL CENTER   SAMSUNG