

The Basics of Coronary Physiology

Measurement: FFR, iFR and other NHPRs

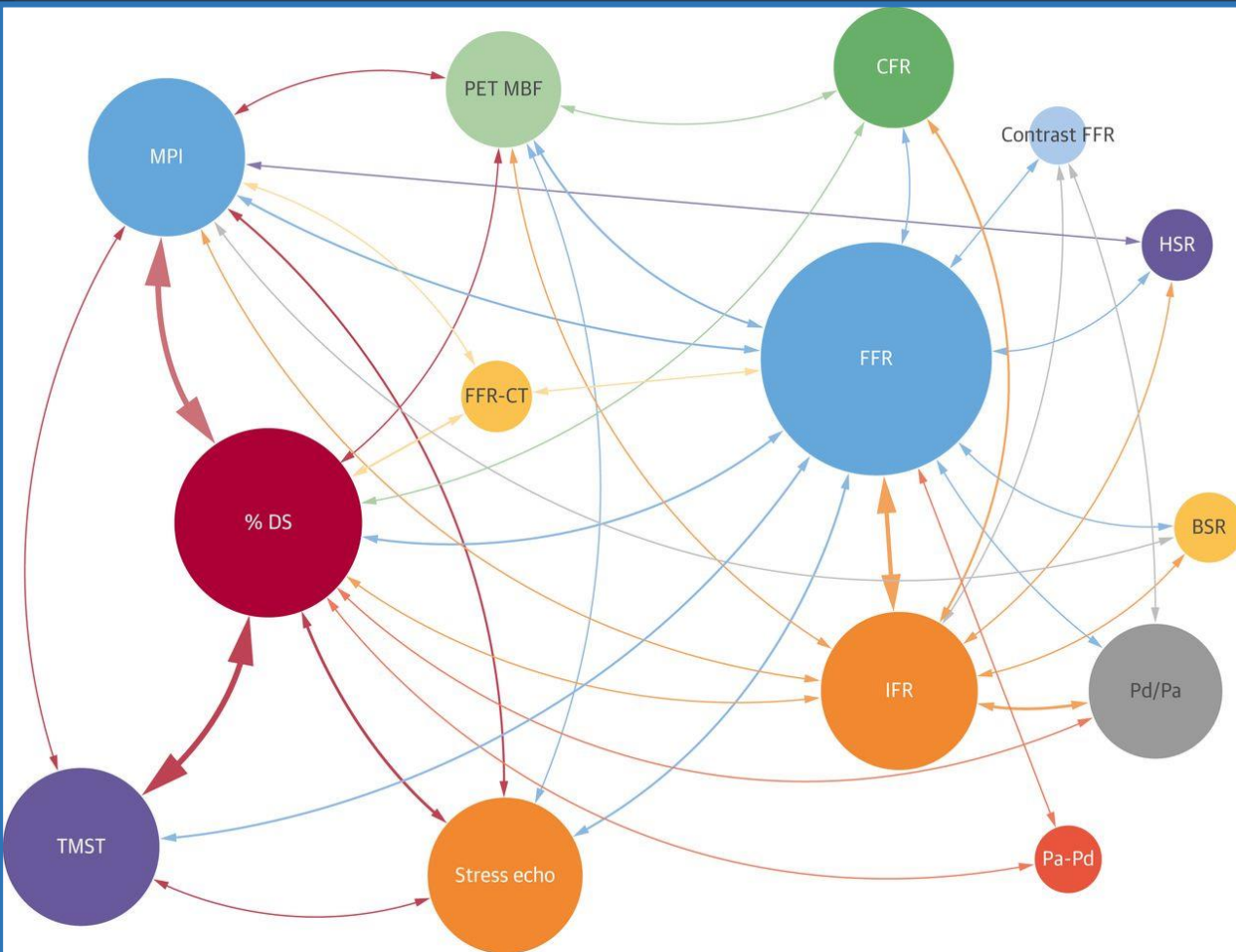
Jung-Min Ahn, MD

Departement of Cardiology, Asan Medical Center, Seoul, Korea

Disclosure

- I, Jung-Min Ahn, have NO conflict of interest related to this presentation.

Many Indices



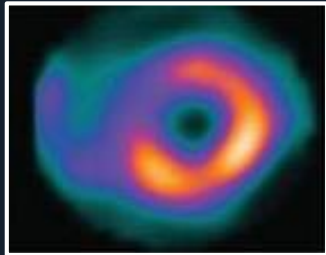
- Non-Invasive Functional Study
 - Treadmill test
 - Stress echocardiography
 - Myocardial perfusion imaging
 - SPECT
 - MRI, CT
- Fractional Flow Reserve (FFR)
- Non-Hyperemic Pressure Ratio (NHPR)
 - iFR
 - Resting Pd/Pa
 - dPR
 - RFR

Morton J. Kern et al. JACC 2017;70(17):2124-7

How To Detect Objective Ischemia

- During **Stress**, Decreased Coronary Blood Flow To Induce

Myocardial
Perfusion
Imaging



Myocardial Perfusion Abnormality

Stress Echo



Contractile Abnormality

Treadmill Test



Electrical Abnormality

Direct Evidence
of Ischemia

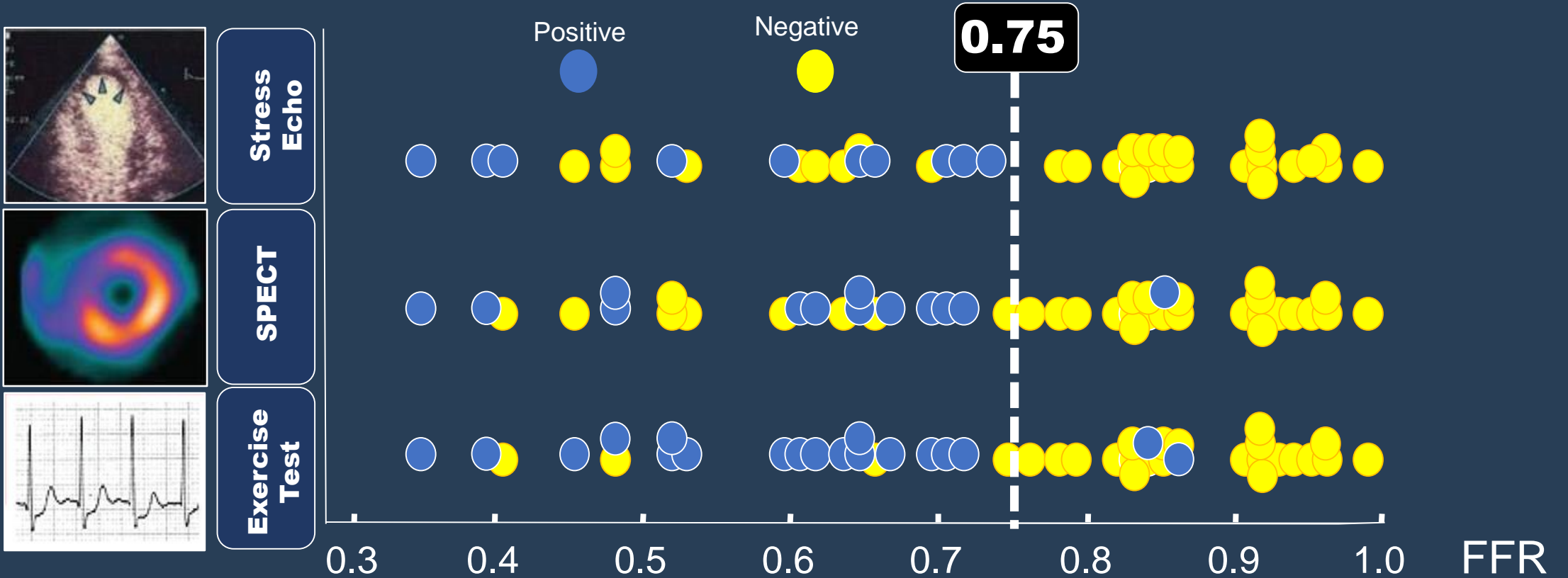


Ischemia Test in Cath Lab ?



FFR as A Non-Invasive Functional Study In Cath Lab

Comparison with 3 Non-Invasive Functional Studies



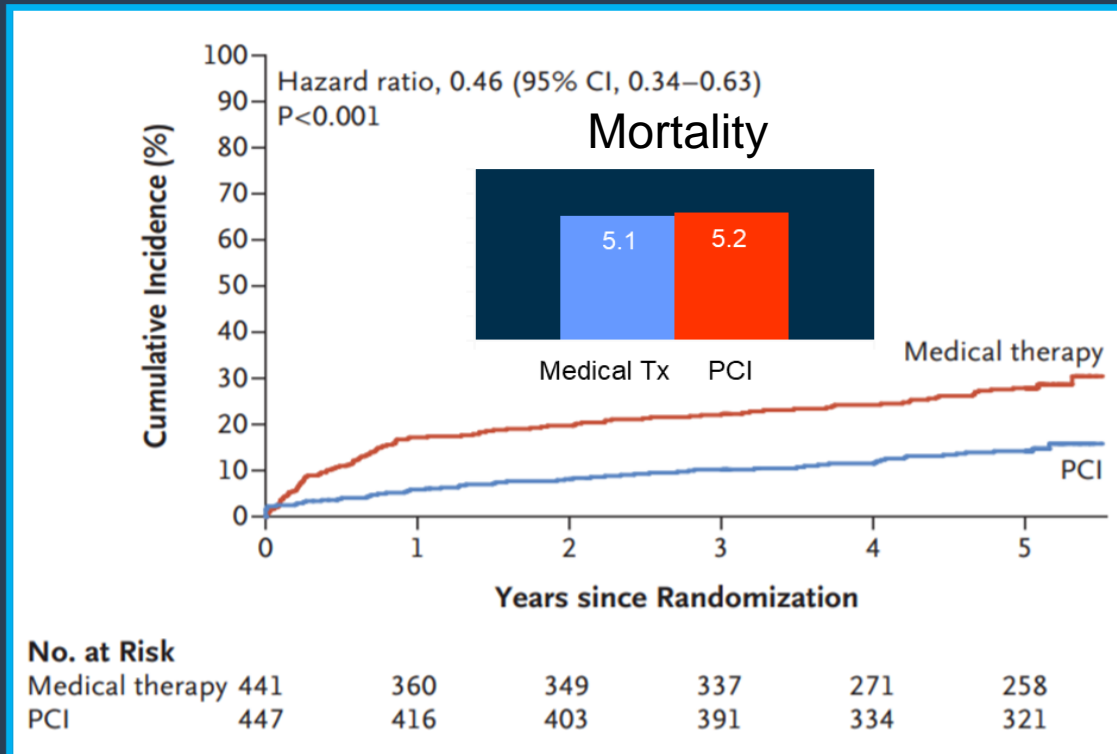
- N = 45 patients
- Sensitivity 88%, Specificity 100%, **PPV 100%**, NPV 88%

Current Cut-off Value of FFR: 0.80

Author	Number	Stress Test	BCV	Accuracy
Pijls et al.	60	X-ECG	0.74	97
DeBruyne et al.	60	X-ECG/SPECT	0.72	85
Pijls et al.	45	X-ECG/SPECT/pacing/DSE	0.75	93
Bartunek et al.	37	DSE	0.68	90
Abe et al.	46	SPECT	0.75	91
Chamuleau et al.	127	SPECT	0.74	77
Caymaz et al.	40	SPECT	0.76	95
Jimenez-Navarro et al.	21	DSE	0.75	90
Usui et al.	167	SPECT	0.75	79
Yanagisawa et al.	167	SPECT	0.75	76
Meuwissen et al.	151	SPECT	0.74	85
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

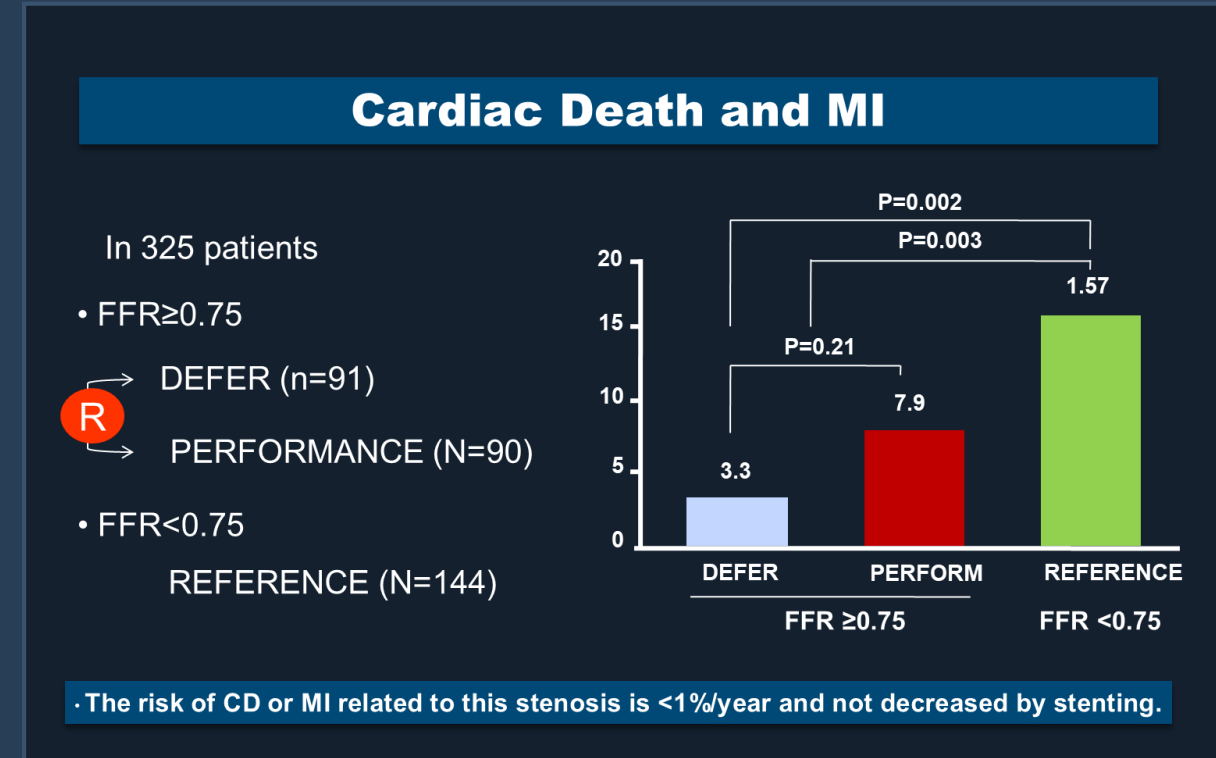
FFR \leq 0.80: Stenting Justified

FAME 2



FFR $>$ 0.80: Defer

DEFER

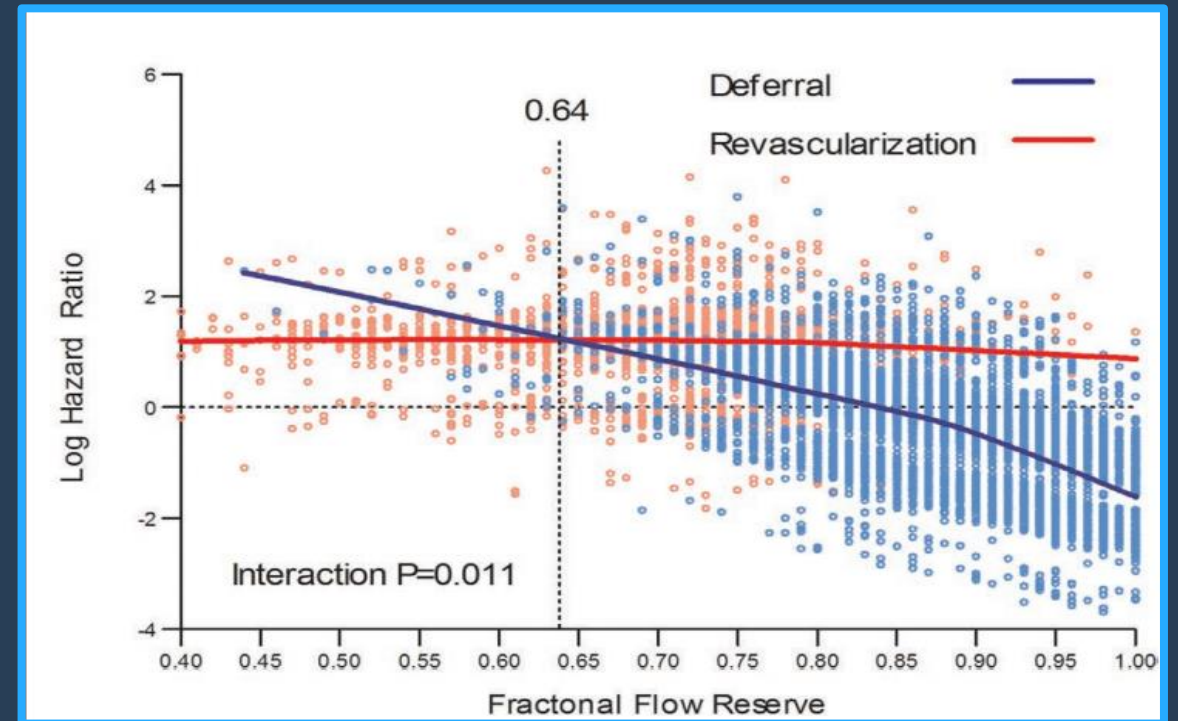
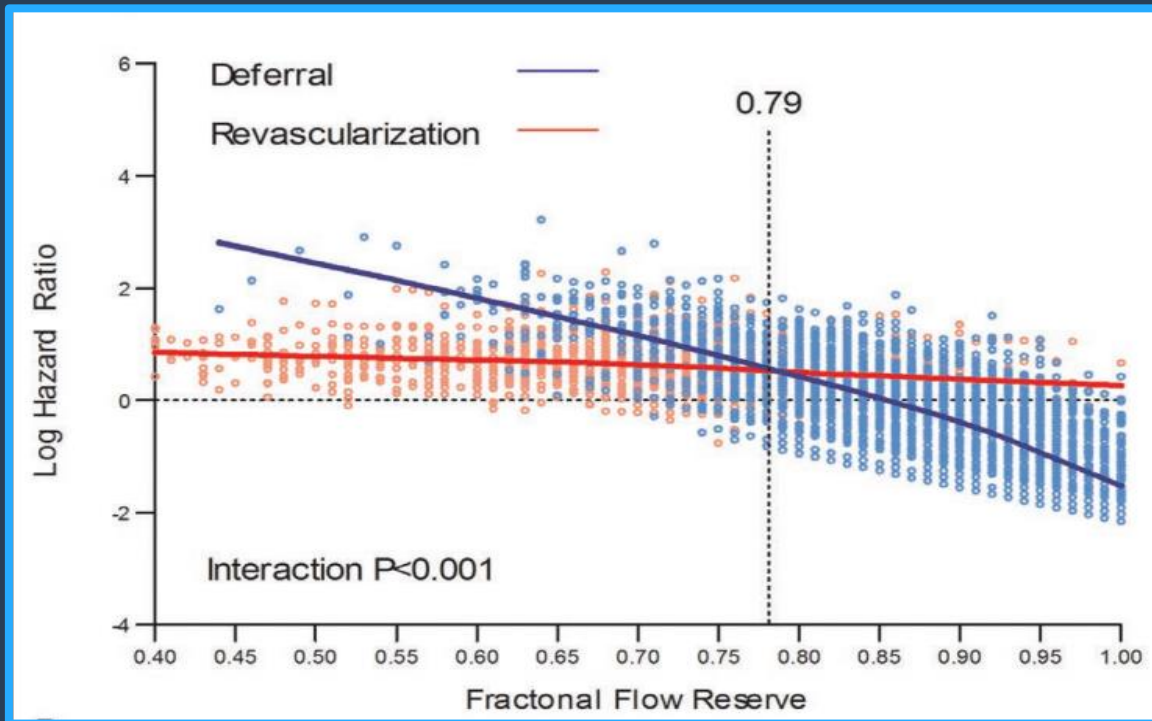


Outcome Derived Revascularization Threshold

FFR: **Clinical Index** To Decide Revascularization

Cardiac Death, MI, and TVR

Cardiac Death, and MI

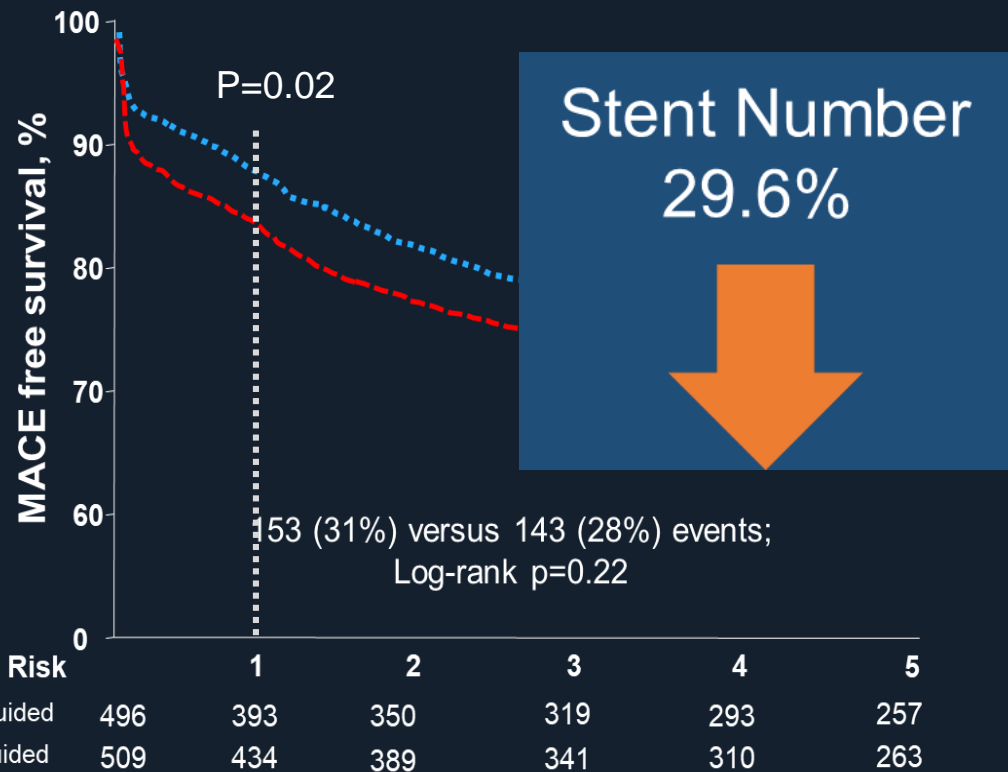


Ahn JM, Park SJ et al. Circulation 2017 Jun 6;135(23):2241-2251

FFR Guided PCI

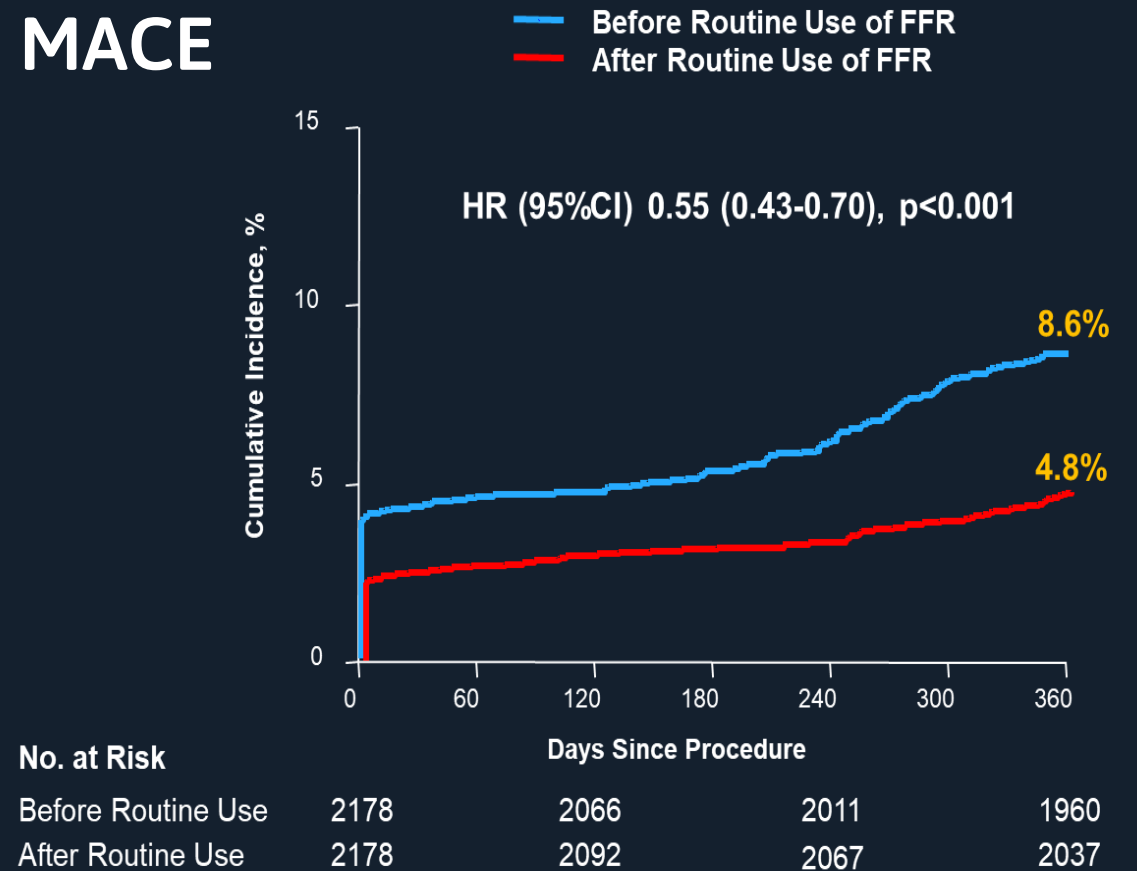
FAME I

MACE



Asan PCI Registry

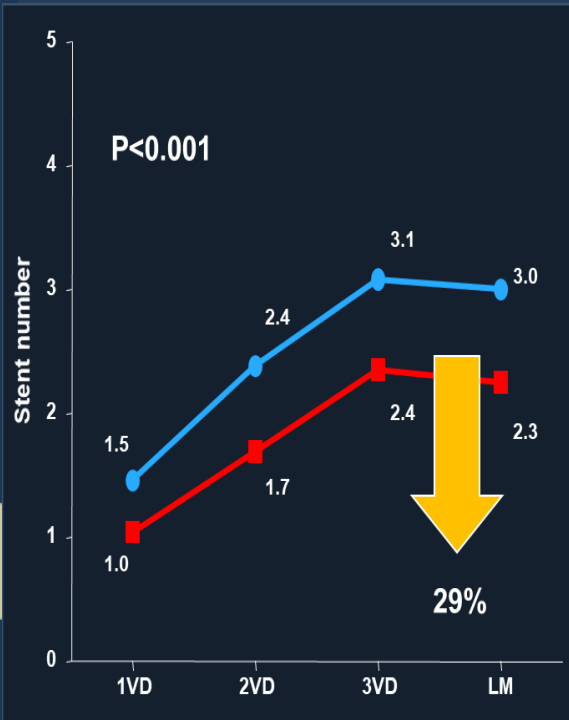
MACE



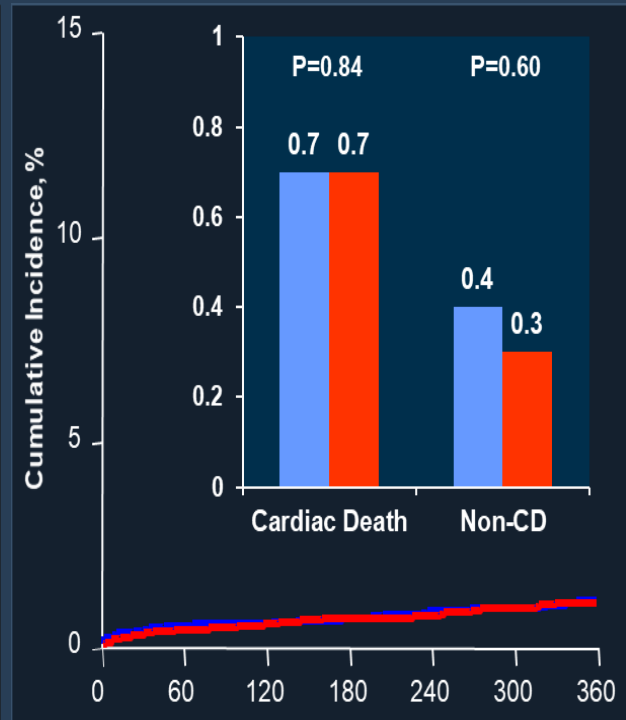
Asan PCI Registry

■ Before Routine Use
■ After Routine Use

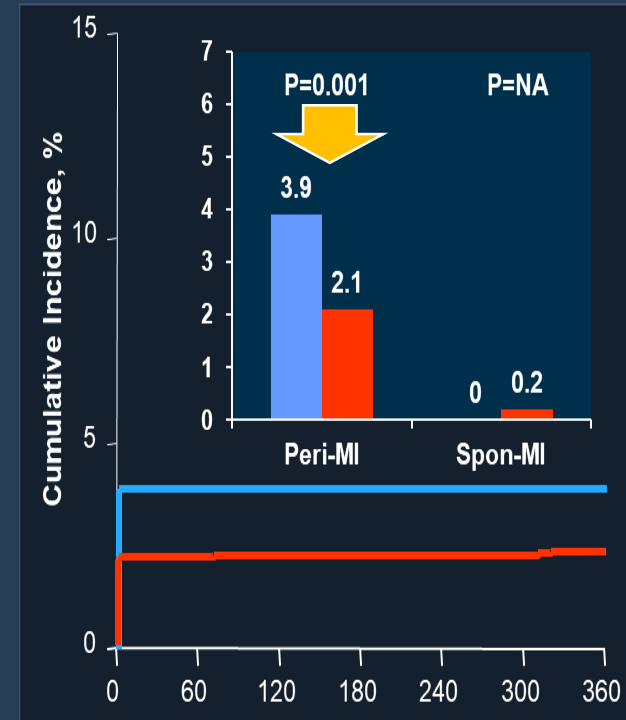
Stent Number



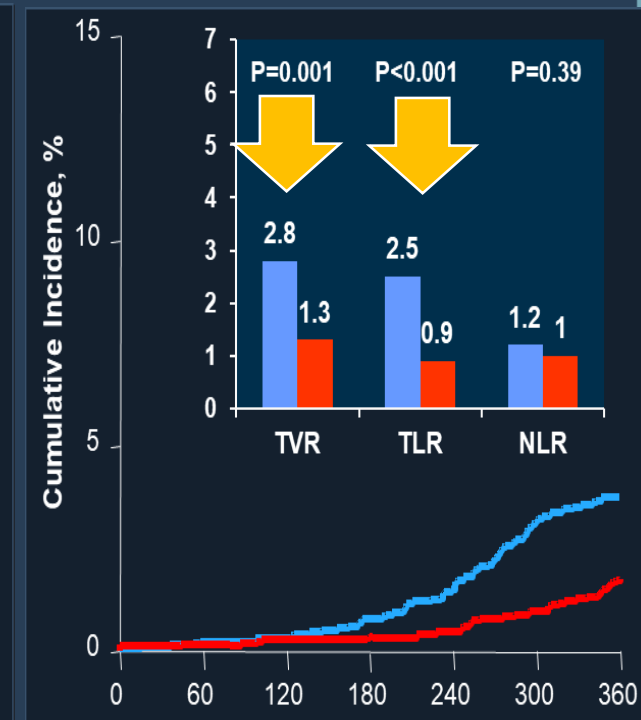
Death



Myocardial Infarction



Repeat Revascularization



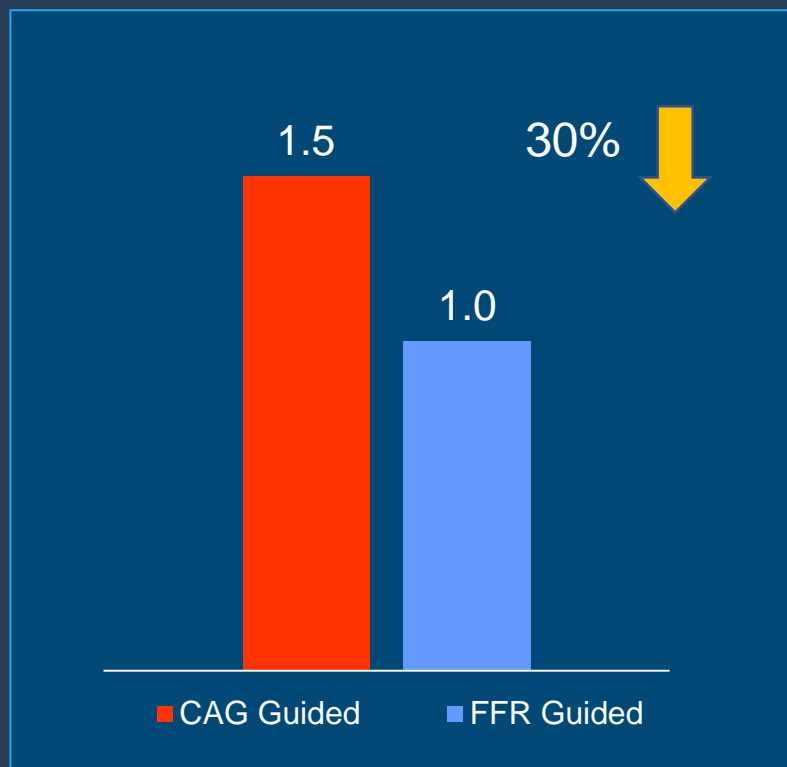
- The benefit of FFR guided PCI is primarily due to
 - 1) The reduced number of stents per patient
 - 2) The subsequent decreased risk of peri-procedural MI and repeat revascularization
 - 3) Favorable outcome with less stenting

Treatment Strategy

Reduced Stent Number and Increased Medical Treatment

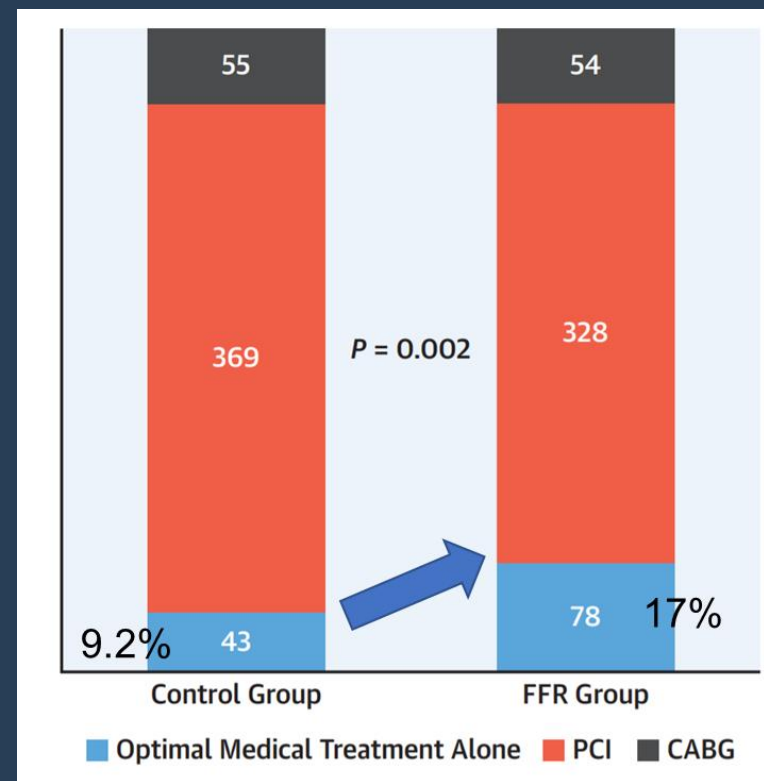
FLOWER-MI

Number of stents per patient



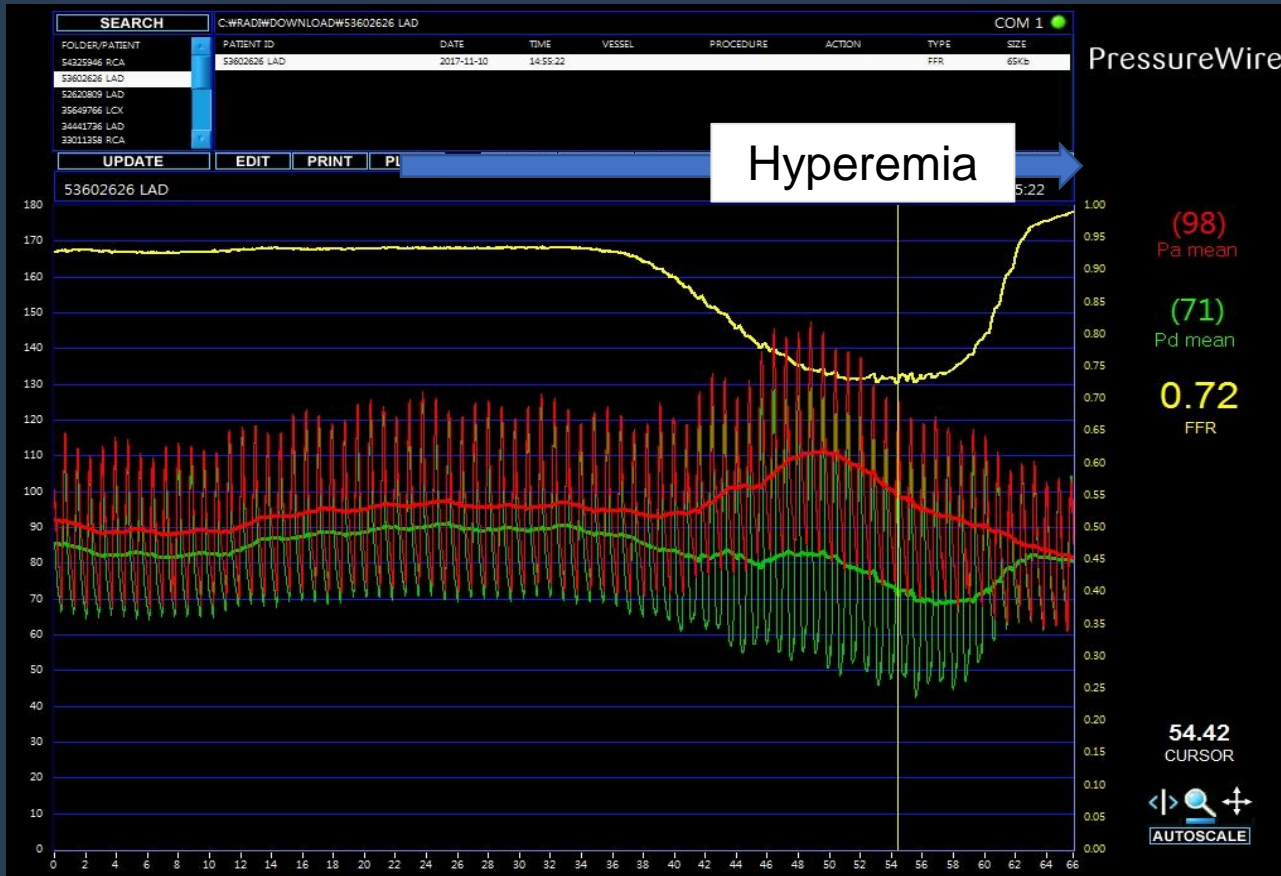
N Engl J Med 2021;385:297-308

FUTURE Trial



J Am Coll Cardiol 2021;78:1875-1885

FFR Requires Hyperemia (Adenosine, ATP, Nicorandil etc.)



- Contraindicated or disliked by patients
- Adds costs and time
- Adds inconvenience and risk

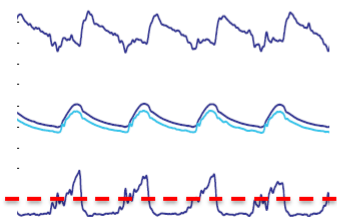
Since TCT 2011,

iFR, Instantaneous wave-free ratio

Hypothesis 1

Resistance measured at rest during wave-free period is similar to mean resistance during **hyperaemia**.

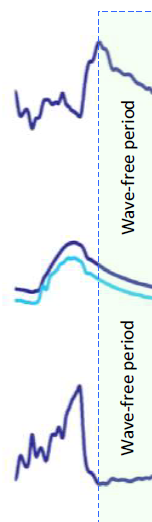
Hyperaemic mean resistance



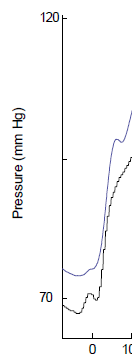
ADVISE study

Hypothesis 2

The Pd/Pa ratio (**iFR**) during the rest period was similar to **FFR**.

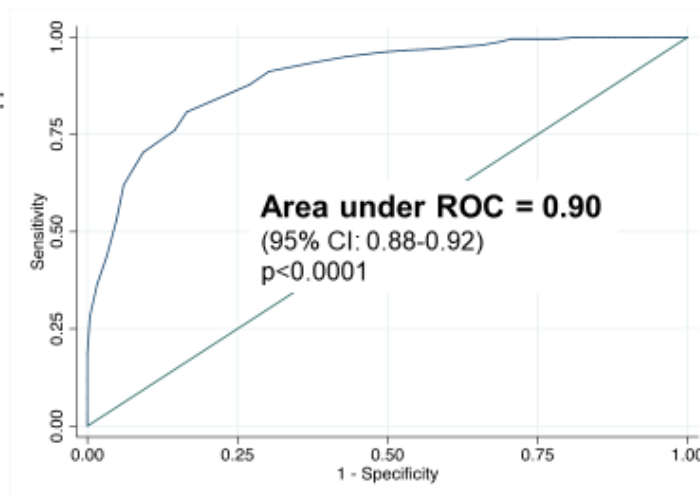


ADVISE study



Diagnostic accuracy of iFR Compared with FFR, 0.80

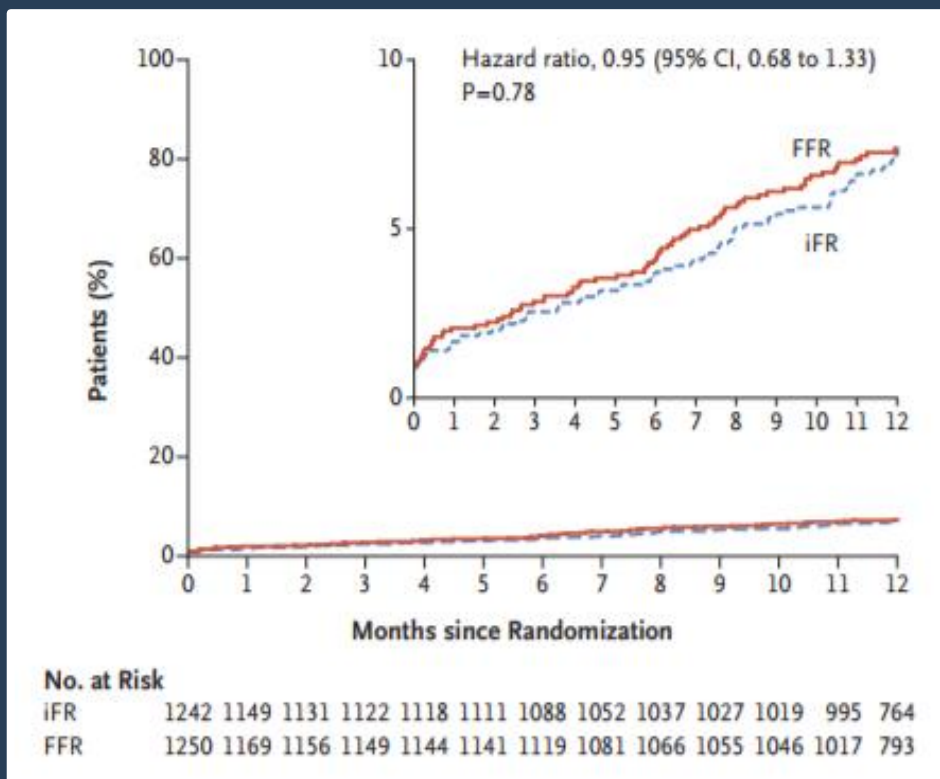
- Best iFR cut-off: **≤0.89**
- Properly classified by iFR: **82.46%**
- Specificity: **87.78%**
- Sensitivity: **72.98%**
- Positive predictive value: **77.02%**
- Negative predictive value: **85.27%**



ACC 2017,

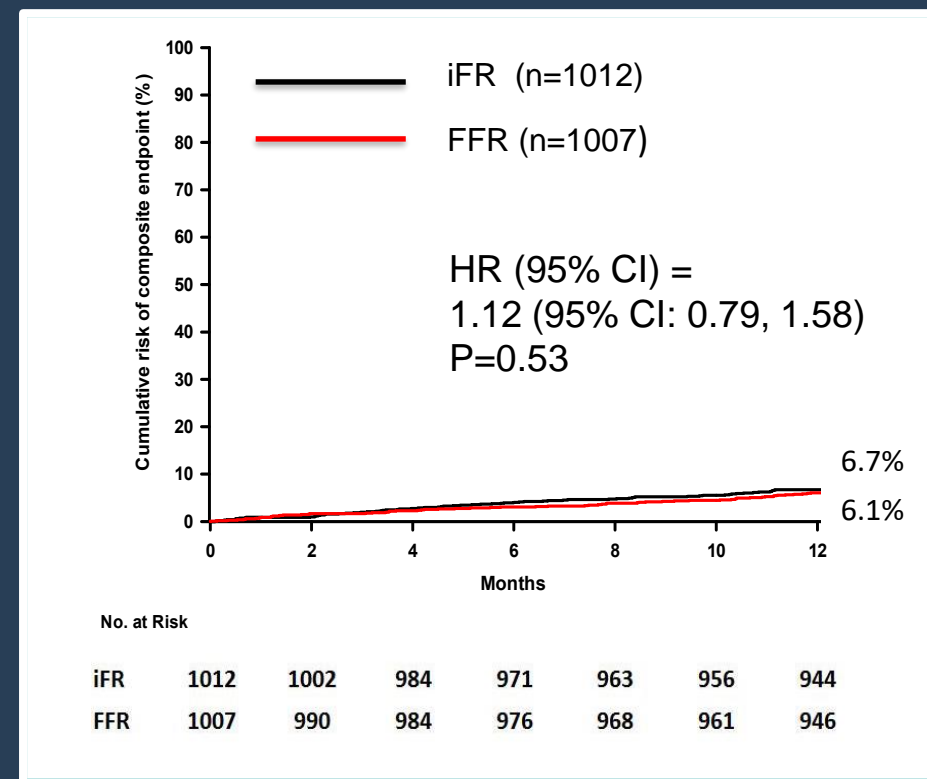
iFR is Non-Inferior to FFR to Guide Revascularization Decision

DEFINE-FLAIR



N Engl J Med. 2017 May 11;376(19):1824-1834

iFR-SWEDEHEART



N Engl J Med. 2017 May 11;376(19):1813-1823

Guidelines

ESC Guideline 2018

Recommendations	Class ^a	Level ^b
When evidence of ischaemia is not available, FFR or iwFR are recommended to assess the haemodynamic relevance of intermediate-grade stenosis. ^{15,17,18,39}	I	A
FFR-guided PCI should be considered in patients with multivessel disease undergoing PCI. ^{29,31}	IIa	B
IVUS should be considered to assess the severity of unprotected left main lesions. ^{35–37}	IIa	B

ACC/AHA Guideline 2021

Recommendations for the Use of Coronary Physiology to Guide Revascularization With PCI		
Referenced studies that support the recommendations are summarized in Online Data Supplement 5 .		
COR	LOE	Recommendations
1	A	1. In patients with angina or an anginal equivalent, undocumented ischemia, and angiographically intermediate stenoses, the use of fractional flow reserve (FFR) or instantaneous wave-free ratio (iFR) is recommended to guide the decision to proceed with PCI. ¹⁻⁶
3: No benefit	B-R	2. In stable patients with angiographically intermediate stenoses and FFR >0.80 or iFR >0.89, PCI should not be performed. ⁷⁻¹⁰

Since 2017, Many Non-Hyperemic Pressure Ratios (NHPR)

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ORIGINAL INVESTIGATION

Agreement of to Aortic Coronary the Instantaneous

Yuhei Kobayashi, MD,^{1,2} Nils P. Johnson,^{3,4} Colin Berry, MBChB, PhD,^{3,4} Allen Jerrett,⁵ Gilles Rioufol, MD, PhD,⁶ Seung-Jung Park,⁷ Keith G. Oldroyd, MBChB, MD,⁸ Ema Bernard De Bruyne, MD, PhD,⁴ William

ABSTRACT

BACKGROUND Recently, 2 randomized resting coronary physiological index, and distal to aortic coronary pressure (Pd/Pa) catheterization laboratory; however, it

OBJECTIVES The goal of this study

METHODS A total of 763 patients were assessed. Using iFR ≤ 0.89 as resting conditions.

RESULTS According to the independence (82.2% vs 96.1%; $p < 0.001$), respectively (interquartile range: 0.88 to 0.95), and according to the receiver-operating characteristic curve: 0.98, 95% confidence interval: accuracy, sensitivity, specificity, positive and 92.7%, respectively. These results

CONCLUSIONS Pd/Pa was analyzable agreement with iFR, suggesting that it Approximate FFR Compared to Pure Re © 2017 by the American College of Card



Listen to this manuscript's audio summary by ACC Editor in Chief Dr. Valentin Fuster.



From the ¹Stanford University School of Medicine, ²McGovern Medical School at UMass Lowell and the Netherlands; ³Navaliska Institute, Södertälje Hospital National Hospital, Uppsala, Sweden; ⁴Cardiovascular and Medical Sciences, University of Bristol, National Institute for Research in Dementia, National University Hospital, Seoul, South Korea; ⁵CARMEN, Lyon, France; ⁶University of Ottawa, ⁷Center Aorta, Aorta, Belgium; and the ⁸Windhover was an investigator-initiated study sponsored by

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Comparison Diastolic Res Are They All Equal

Marcel van't Veer, MSc, PhD,^{1,2} Stuart Watkins, MBChB, MD,^{3,4} Lokien X. van Nunen, MD, PhD,⁵

ABSTRACT

BACKGROUND Pressure measurement during resting-state physiological assess

OBJECTIVES The aim of this study

METHODS In the population of this study, iFR calculated by proprietary compared with the ratio of resting (dPR), 25% to 75% of diastole (dIFR-like indexes shortening the differences, Spearman correlation diagnostic performance with res

RESULTS Median iFR in 197 patients differences (\pm SD) with iFR were 0.009 (FR_{rest}), 0.003 \pm 0.006 > 0.99 ($p < 0.001$ for all). Area accuracy compared with FFR wa

CONCLUSIONS All diastolic measurements agreement with FFR. A numerical guidelines, and clinical relevance Unselected Population Referred © 2017 The Authors. Published access article under the CC BY-NC

From the ¹Department of Cardiology, Card Engineering, Eindhoven University of Technology Research Centre, University of Ghent Golden Jubilee National Hospital, Clydebank, ²Cardiovascular Center Aorta, Aorta, Naples, Italy; ³Dr. van't Veer has received an equity in Philips, GE, HeartFlow, and Jude Medical and Cardiovascular System Boston Scientific, Dr. De Bruyne is Shanghai Omega Pharma; his institution, the Card track, and St. Jude Medical; and his institution, and Boston Scientific outside of his received speaker and consultancy fees of Glasgow hold research and consultant Abbott; and has received research support relevant to the contents of this paper to

Manuscript received September 2, 2017;



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Validation of a novel non-hyperemic artery stenosis severity: the (VALIDATE RFR) study



Johan Svanerud¹, MSc; Jung-Min Ahn, Ankit Gore^{2,3}, BS, MSc; Akiko Maebe, Bernard De Bruyne⁴, MD, PhD; Nils P. Johnson^{3,4}, MD; Colin Berry^{3,4,5,6,7,8,9,10,11}, MD, PhD; Ziad A.

1. Corvenis Research AB, Uppsala, Sweden; 2. Asan Medical Research Foundation, New York, NY, USA; 4. St. Francis Hospital, the Netherlands; 6. Eindhoven University of Technology, Delft, the Netherlands; 7. New York-Presbyterian Hospital/Columbia University Medical Center, New York, NY, USA; 8. Weatherhead PET Center, Division of UHealth and Memorial Hermann Hospital, Houston, TX, USA; 9. Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland, UK; 10. University of Bristol, Bristol, UK; 11. Institute of Cardiovascular and Medical Sciences, Glasgow, Scotland, UK. This paper also includes supplementary data published online at

KEYWORDS

- fractional flow reserve
- innovation
- other imaging modalities

Abstract
Aims: Randomised controlled trial of fractional flow reserve (FFR) for by sensitive landmarking of the resistance occur during a fixed Δ a novel non-hyperemic index of distal coronary pressure to aortic and timing within the cardiac cycle.

Methods and results: VALIDATE RFR. The primary endpoint was in 651 waveforms in which iFR correlated to iFR ($R=0.99$, $p < 0.0001$). The diagnostic performance specificity 96.9%, positive predictive operating characteristic curve of 95% CI: -0.009 to 0.006, $p=0.002$ and 32.4% (167/516) compared to FFR was lowest (4

Conclusions: RFR is diagnostic Pd/Pa during the full cardiac cycle would be missed by assessment

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ESC
European Society of Cardiology
European Heart Journal (2019) 40, 2585–2592
doi:10.1093/eurheartj/ehz230

Diastolic pressure ratio validation vs. the instantaneous wave-free ratio

Nils P. Johnson¹, Wenguang Li², Xi Chen³, Colin Berry^{3,4}, William F. Fearon⁵, and K

¹Weatherhead PET Center, Division of Cardiology, Department of Medicine, McGovern Medical School, Baylor College of Medicine, Houston, TX, USA; ²British Heart Foundation Glasgow Cardiovascular Research Centre, Glasgow, Scotland, UK; ³West of Scotland Heart and Lung Centre, Golden Jubilee National Hospital, Glasgow, Scotland, UK; ⁴University of Bristol, Bristol, UK

Aims

The instantaneous wave-free ratio (iFR) non-hyperaemic conditions. To test for unique coronary pressure measurements, we compared numerical similarity and test/retest repeatability.

Methods and results

Eight hundred and ninety-three lesions from 100 patients. Diastolic pressure ratio and a linear transformation. Mean difference between dPR and iFR [Δ = (ROC) curve (AUC) = 0.997] mirrored that of iFR [Δ = -0.012 \pm 0.031, r^2 = 0.927, AUC = 0.997] matched almost exactly (average Δ = <0.001).

Conclusions

Our dPR offers numerical equivalency to iFR during the period of diastole, the agreement between the two methods further confirm numerical equivalency.

Keywords

Instantaneous wave-free ratio • Coronary

Introduction

Resting coronary physiology to guide revascularization procedures dates to the very advent of percutaneous coronary intervention (PCI). In the first reported series of coronary balloon angioplasties in 1979, Andreas Grüntzig measured the pressure drop across the stenosis (ΔP) at baseline and again after dilation, although biased by the acknowledged retrograde gradient generated by the device itself.¹ Pressure gradient assessment was a routine component of interventional procedures in the initial years, until catheters became too small to obtain reliable signals through the central channel. In some early clinical cases at Emory University, measurement of resting ΔP was

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ORIGINAL ARTICLE

Validation of Resting Diastolic Pressure Ratio Calculated by a Novel Algorithm and Its Correlation With Distal Coronary Artery Pressure to Aortic Pressure, Instantaneous Wave-Free Ratio, and Fractional Flow Reserve

The dPR Study

See Editorial by Kern and Seto

BACKGROUND: Instantaneous wave-free ratio (iFR) offers a reliable non-hyperemic assessment of coronary physiology but requires dedicated proprietary software with a fully automated algorithm. We hypothesized that dPR (diastolic pressure ratio), calculated with novel universal software, has a strong correlation with iFR, similar diagnostic accuracy relative to resting distal coronary artery pressure/aortic pressure and fractional flow reserve (FFR).

METHODS AND RESULTS: The dPR study is an observational, retrospective, single-center cohort study including patients who underwent iFR or FFR. Dedicated software was used to calculate the dPR from Digital Imaging and Communications in Medicine (DICOM) pressure waveforms. The flat period on the pressure difference between sample (dP) to the time difference between the same sample points (dt) signal was used to detect automatically the period, where the resistance is low and constant, and to calculate the dPR, which is an average over 5 consecutive heartbeats. The software was validated by correlating iFR results with dPR. Software validation was done by comparing 78 iFR measurements in 44 patients who underwent iFR. Mean iFR and dPR were 0.91 ± 0.10 and 0.92 ± 0.10 , respectively, with a significant linear correlation ($R=0.997$; $P < 0.001$). Diagnostic accuracy was tested in 100 patients who underwent FFR. Mean FFR, resting distal coronary artery pressure/aortic pressure, and dPR were 0.85 ± 0.09 , 0.94 ± 0.05 , and 0.93 ± 0.07 , respectively. There was a significant linear correlation between dPR and FFR ($R=0.77$; $P < 0.001$). Both distal coronary artery pressure/aortic pressure and dPR had good diagnostic accuracy in the identification of lesions with an FFR ≤ 0.80 (area under the curve, 0.84; 95% CI, 0.76–0.92 and 0.86; 95% CI, 0.78–0.93, respectively).

CONCLUSIONS: dPR, calculated by a novel validated software tool, showed a strong linear correlation with iFR. dPR correlated well with FFR with a good diagnostic accuracy to identify positive FFR.

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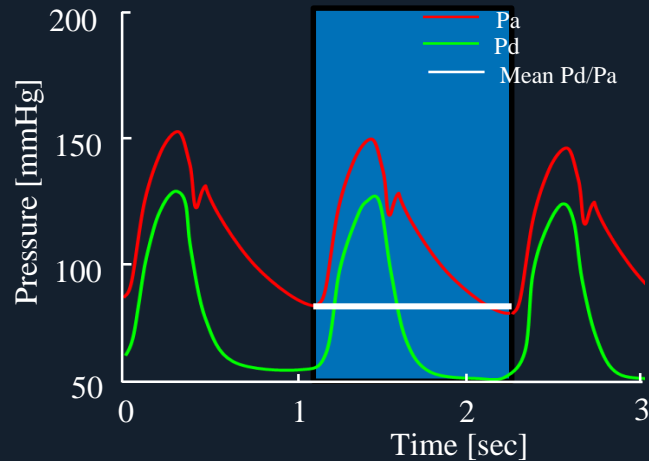
*J. Ligthart and Dr Masjedji contributed equally to this paper.

Key Words: catheter • methods • physiology • software • software validation

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<https://www.ahajournals.org/journal/circinterventions>

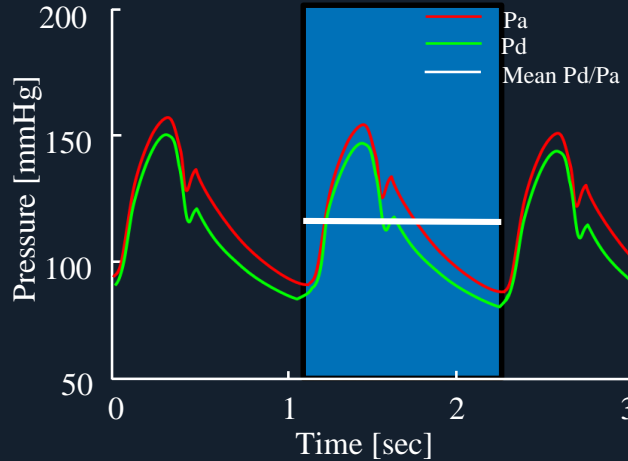
Definition of Physiologic Indices

(A) FFR (≤ 0.80)



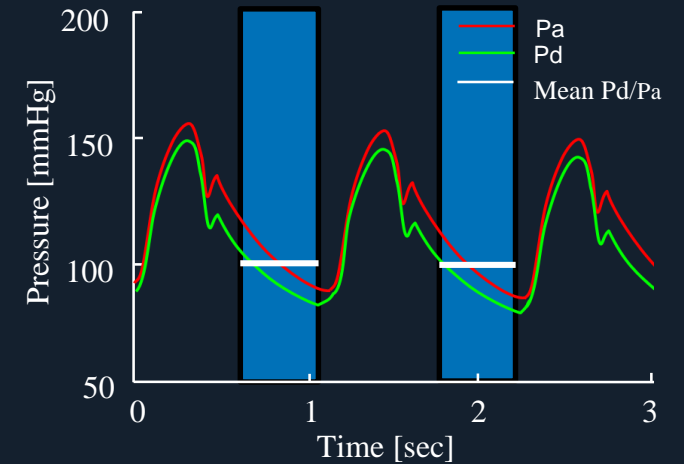
Mean Pd/Pa at hyperemia during the entire cardiac cycle

(B) Resting Pd/Pa ($\leq 0.91/0.92$)



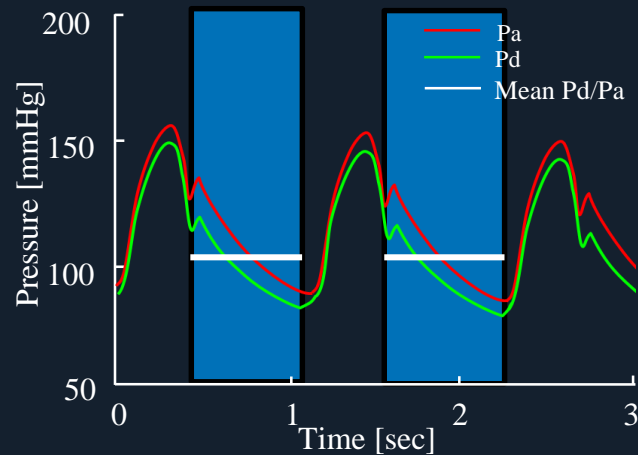
Mean Pd/Pa at rest during the entire cardiac cycle

(C) iFR (≤ 0.89)



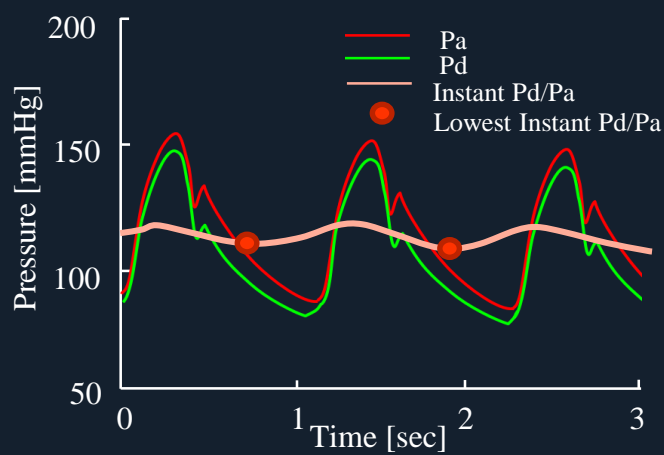
Mean Pd/Pa at rest during wave free period (WFP)

(D) dPR (≤ 0.89)



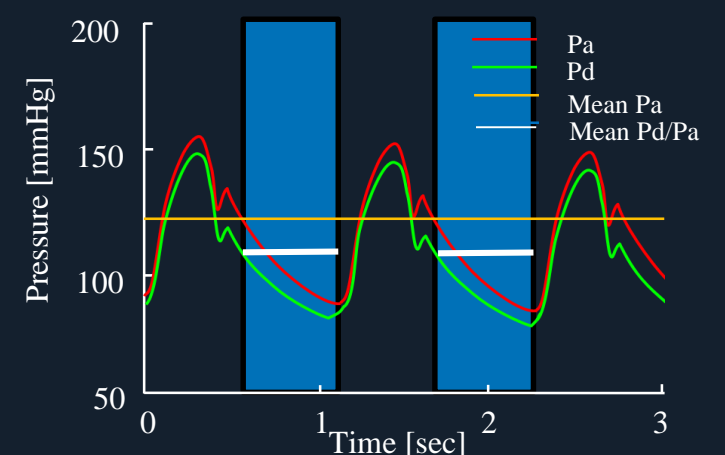
Mean Pd/Pa at rest during the entire diastole

(E) RFR (≤ 0.89)



Lowest Instant Pd/Pa at rest during the entire cardiac cycle

(F) DFR (≤ 0.89)



Mean Pd/Pa at rest during the period Between Pa < mean Pa AND down-sloping Pa

IRIS-FFR Registry

2301 lesions in 1851 patients
With valid resting and hyperemic raw pressure tracing (≥ 5 beats)

1329 lesions were **deferred** after physiologic assessment

FFR

IRIS FFR

**Resting
Pd/Pa***

IRIS FFR*

iFR^{virtual}‡

Nils P. Johnson
Wenguang Li

dPR

Marcel van 't Veer
Johan Svanerud

RFR

Ziad A. Ali
Johan Svanerud

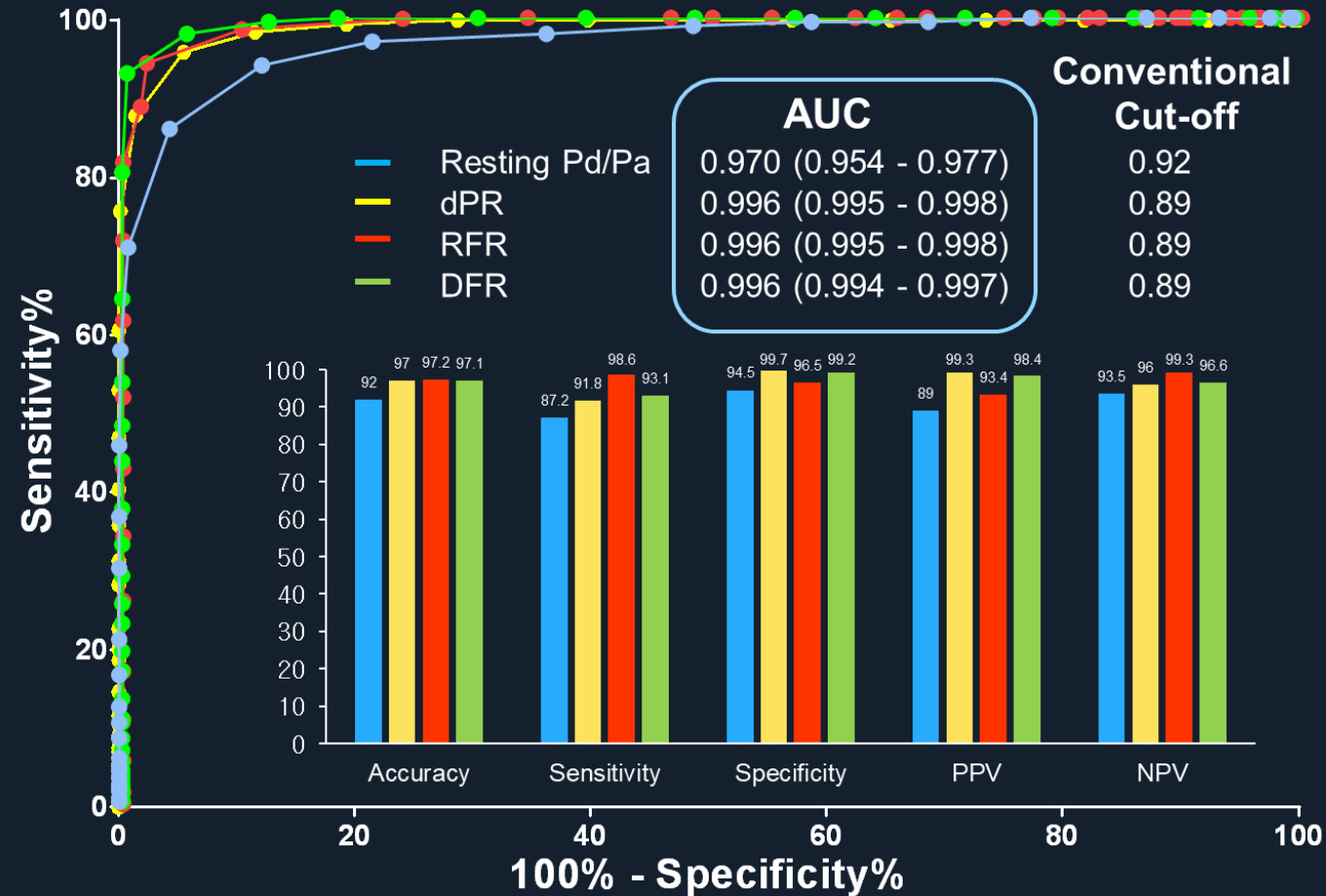
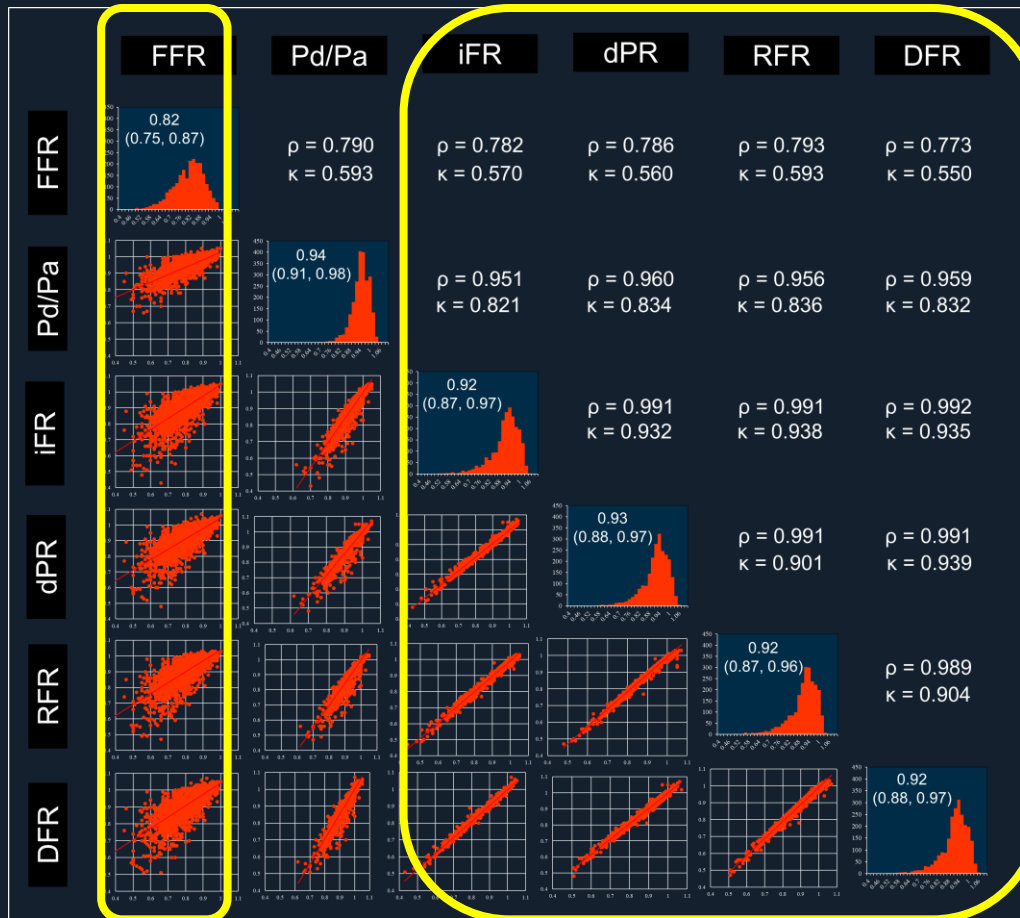
DFR

Nils P. Johnson
Wenguang Li

*All resting tracings were confirmed by Wenguang Li during virtual iFR and DFR calculation
‡calculated using the proprietary software (Volcano Corporation)

NHPR vs. iFR

Prediction of $iFR \leq 0.89$

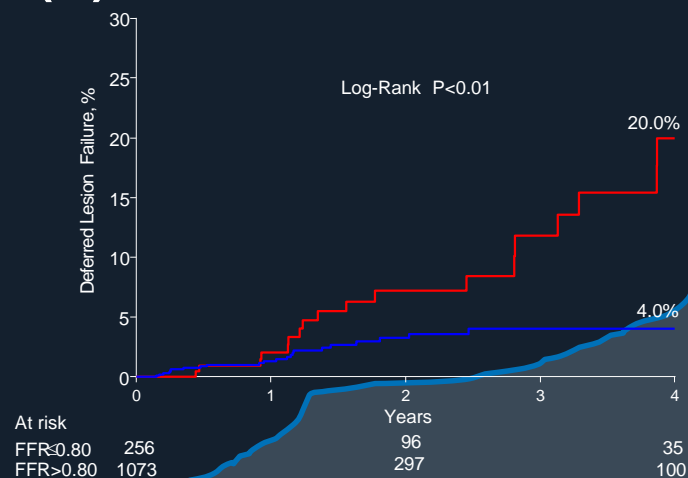


80-85% Accuracy

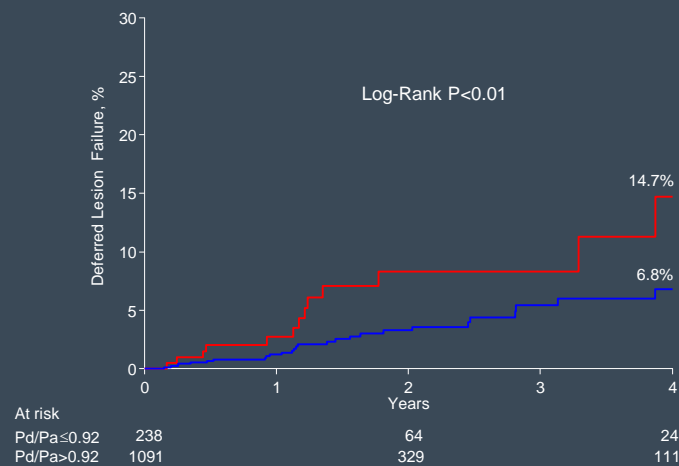
97% Accuracy

Kaplan-Meier Curves

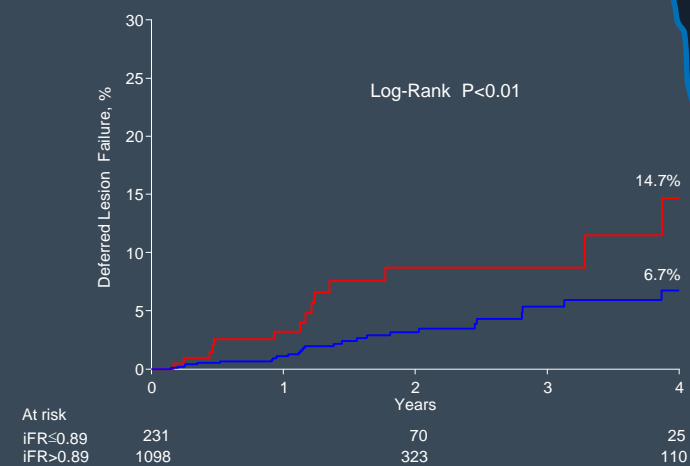
(A) FFR



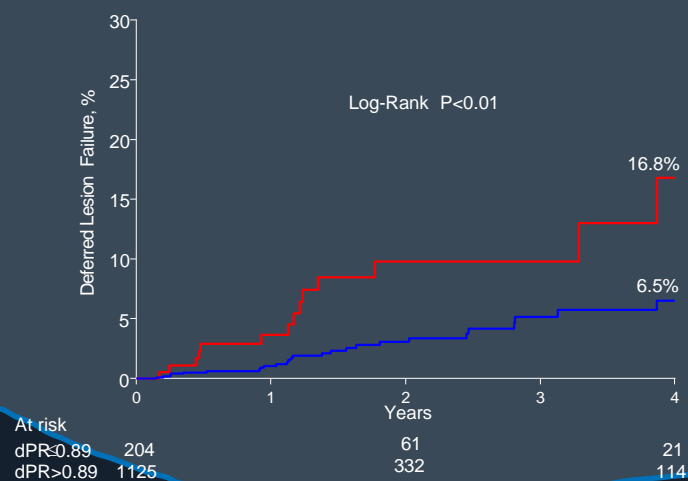
(B) Resting Pd/Pa



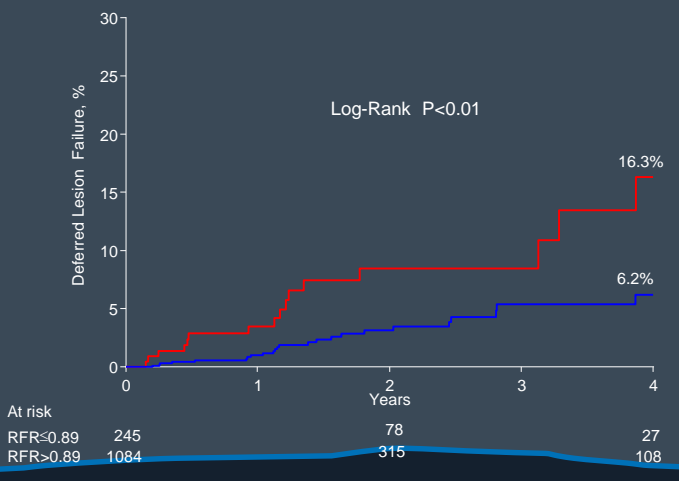
(C) iFR



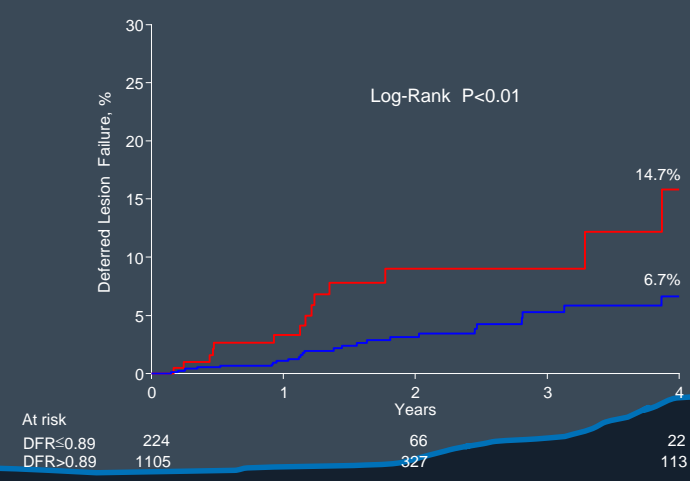
(D) dPR



(E) RFR

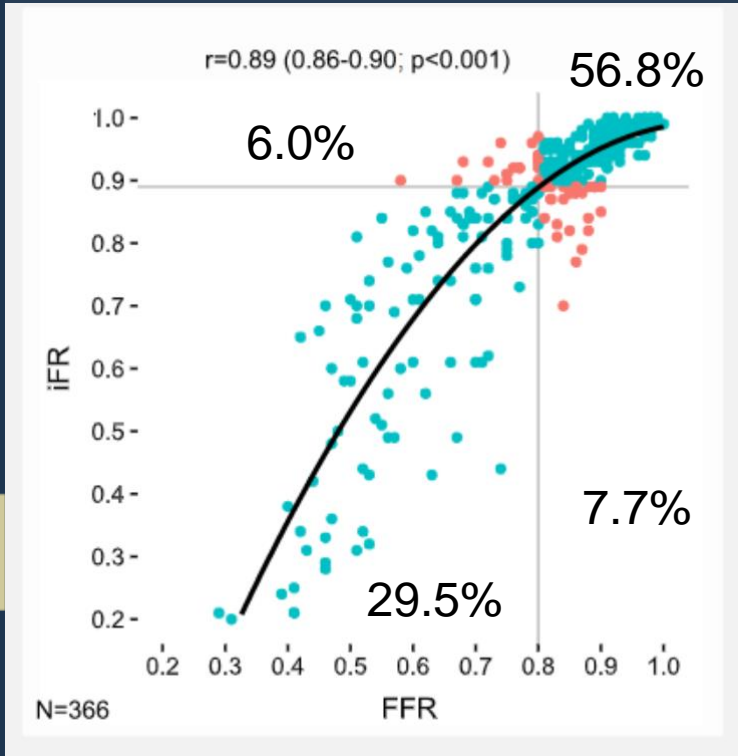


(F) DFR



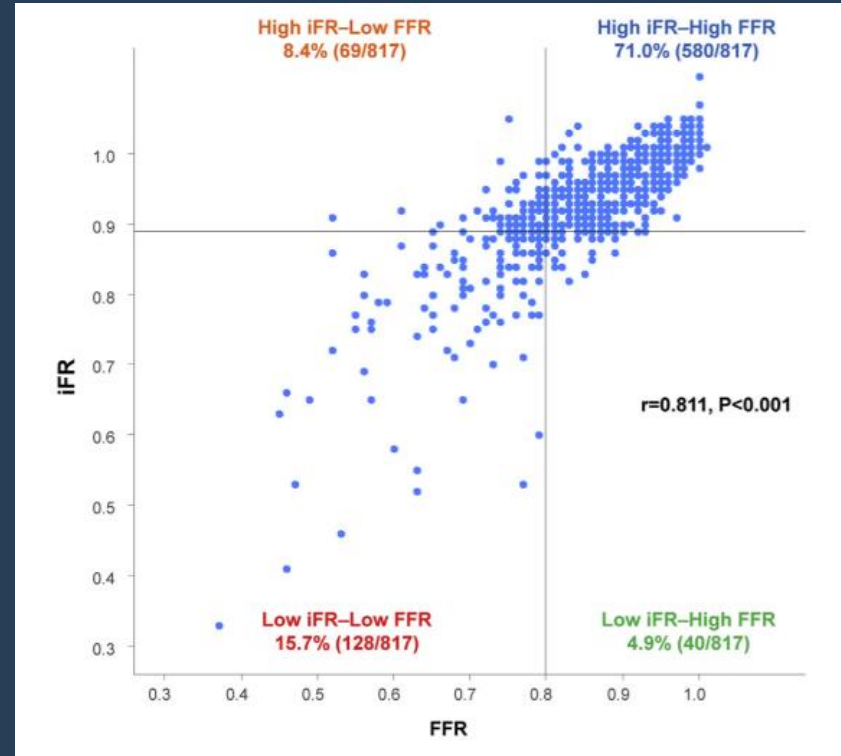
Frequency of FFR/iFR Discordance

13.7 %



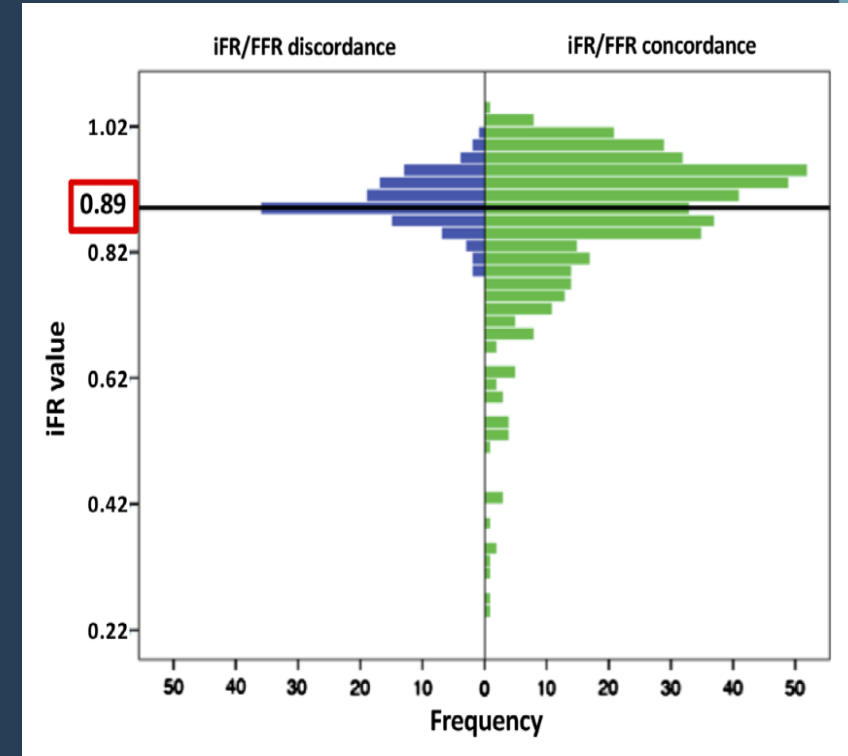
Cook CM et al.
JACC Cardiovasc Interv. 2017;10(24):2514-2524

13.3 %



SH Lee et al.
JACC Cardiovasc Interv. 2019;12(20):2018-2031

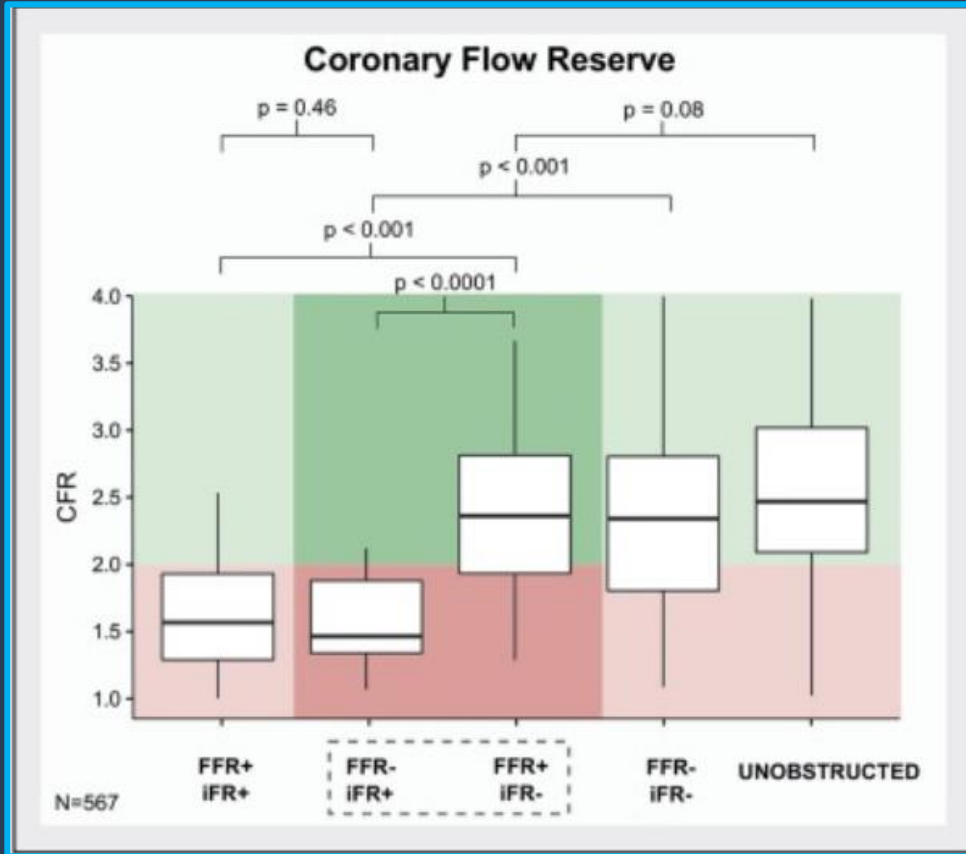
20.6 %



Derimay F et al.
Catheter Cardiovasc Interv. 2019 Sep 1;94(3):356-363

Physiologic and Anatomic Characteristics of Discordant Lesions

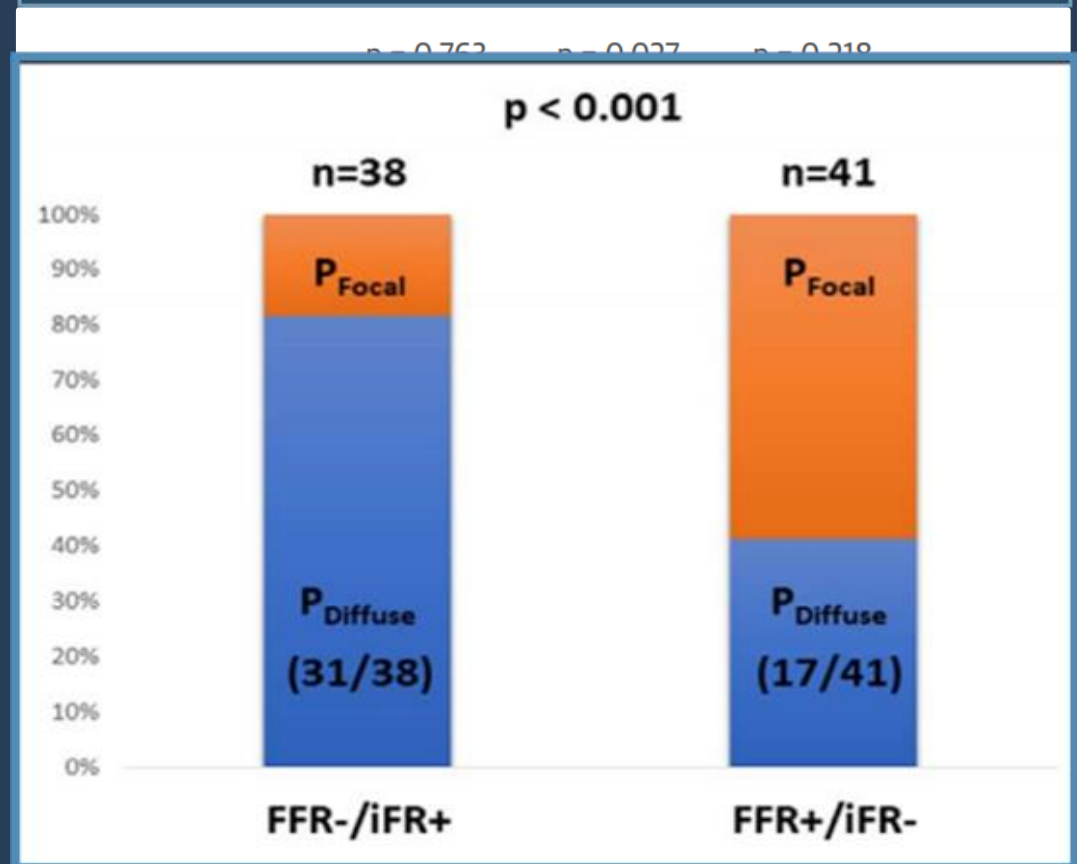
Differences in Coronary Flow Reserve



Cook CM et al.

JACC Cardiovasc Interv. 2017;10(24):2514-2524

FFR+/*i*FR- : Focal Disease
FFR-/*i*FR+ : Diffuse Disease

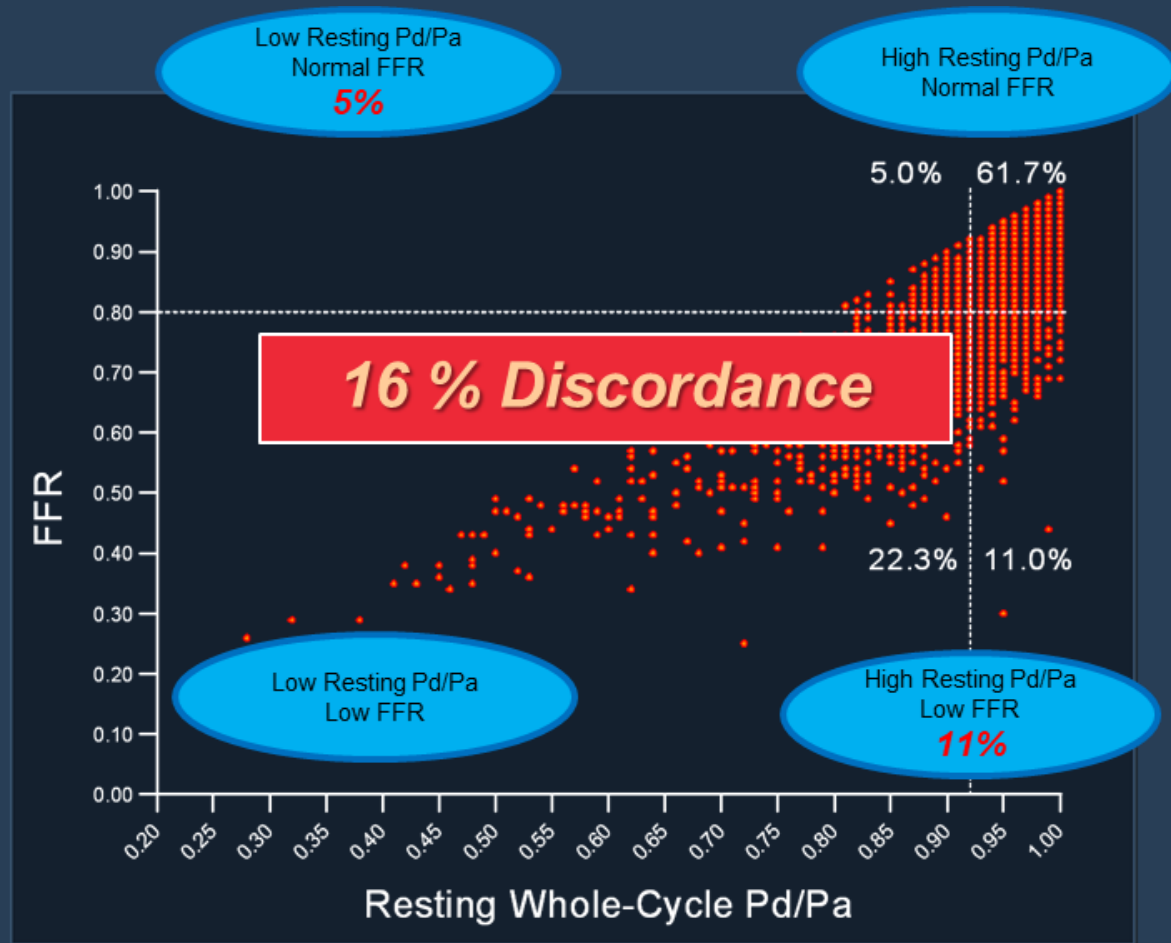


JACC Cardiovasc Imaging. 2020 Mar;13(3):746-756.

Circ Cardiovasc Interv. 2019;12:e007494

*Adverse plaque characteristics include low-attenuation plaque, positive remodeling, spotty calcification, and napkin risk sign

Clinical Characteristics of Discordant Lesions



	Odds Ratio	95% CI	P Value
<i>Resting Pd/Pa ≤ 0.92 and FFR > 0.80</i> <u>Very Small Hyperemic Pressure Drop</u>			
Age	1.02	1.01-1.03	0.004
Gender (Male)	0.74	0.59-0.94	0.012
Diabetes	1.50	1.19-1.89	0.001
Hyperlipidemia	0.72	0.57-0.91	0.005
Proximal location (vs. mid to distal)	0.60	0.49-0.78	<0.001
<i>Resting Pd/Pa > 0.92 and FFR ≤ 0.80</i> <u>Very Big Hyperemic Pressure Drop</u>			
Age	0.98	0.97-0.99	<0.001
Gender (Male)	1.79	1.45-2.22	<0.001
Diabetes	0.68	0.66-0.96	0.016
Family history	0.68	0.50-0.87	0.003
Chronic renal failure	0.32	0.14-0.75	0.008
Diameter stenosis (≥50%)	4.06	3.16-5.21	<0.001
AHA/ACC B2C lesion	1.44	1.20-1.71	<0.001

Low CFR phenotype

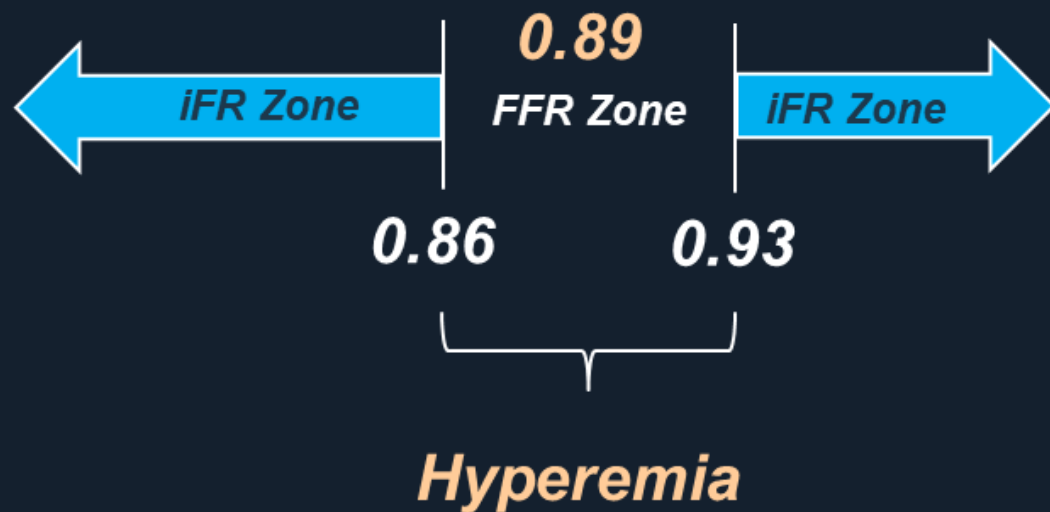
Super normal CFR phenotype

LM/pLAD

Ahn JM, Park SJ et al. *Circ Cardiovasc Interv.* 2020 May;13(5):e007868

How To Compromise the Discordance

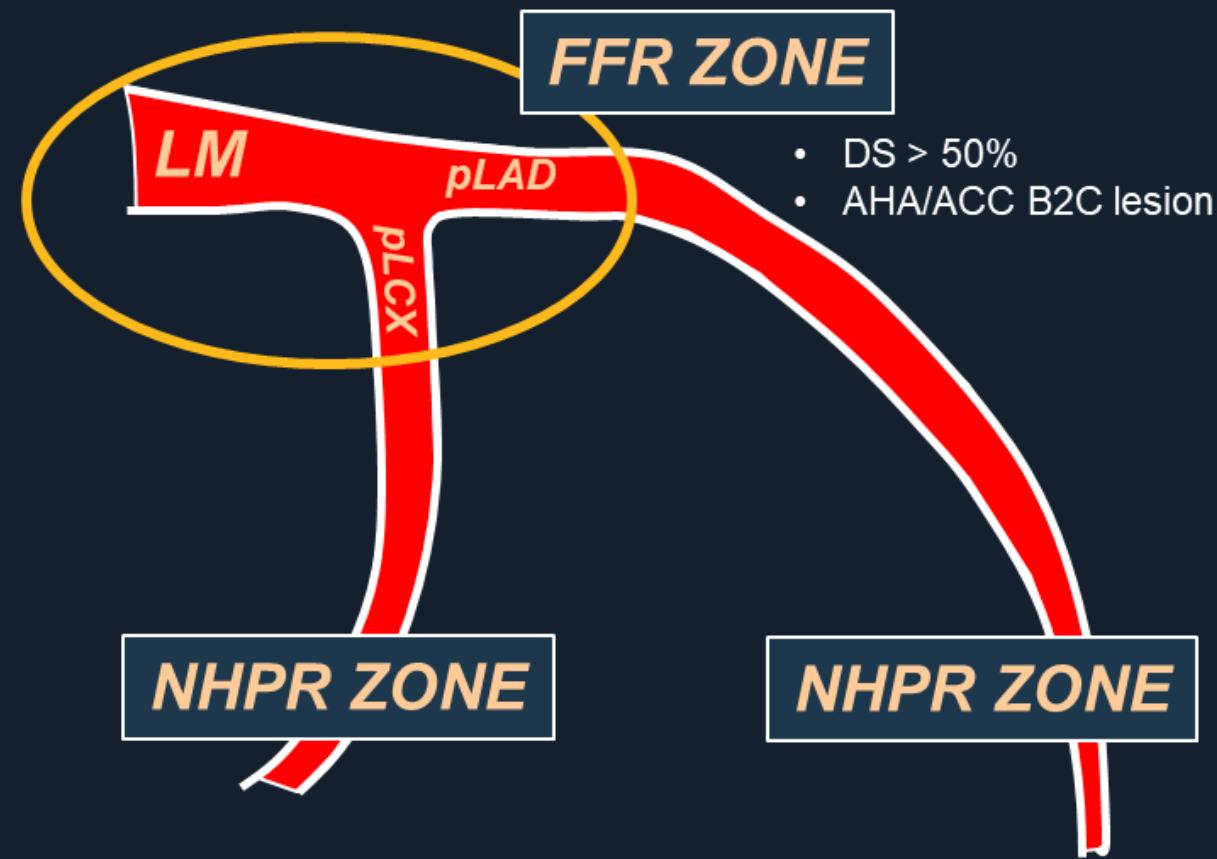
Physiologic Consideration



Clinical Consideration

- Young age
- Male
- Diabetes

Anatomical Consideration



Summary

- Current guideline widely endorsed intracoronary physiology, both FFR and iFR.
- iFR could be used in the revascularization decision-making, particularly when hyperemic agents are not easily available.
- FFR would be preferred in lesions which was proximally located or showed angiographically tight or complex.
- All NHPR (resting Pd/Pa, iFR, dPR, RFR, DFR) are the same. Physicians can apply other NHPRs in daily practice in the same manner as iFR.
- In the post-ISCHEMIA era, $FFR \leq 0.80$ (or $iFR \leq 0.89$) would be a minimum requirement for coronary revascularization and stenting on the stenosis with $FFR > 0.80$ (or $iFR > 0.89$) is never justified. Please defer.