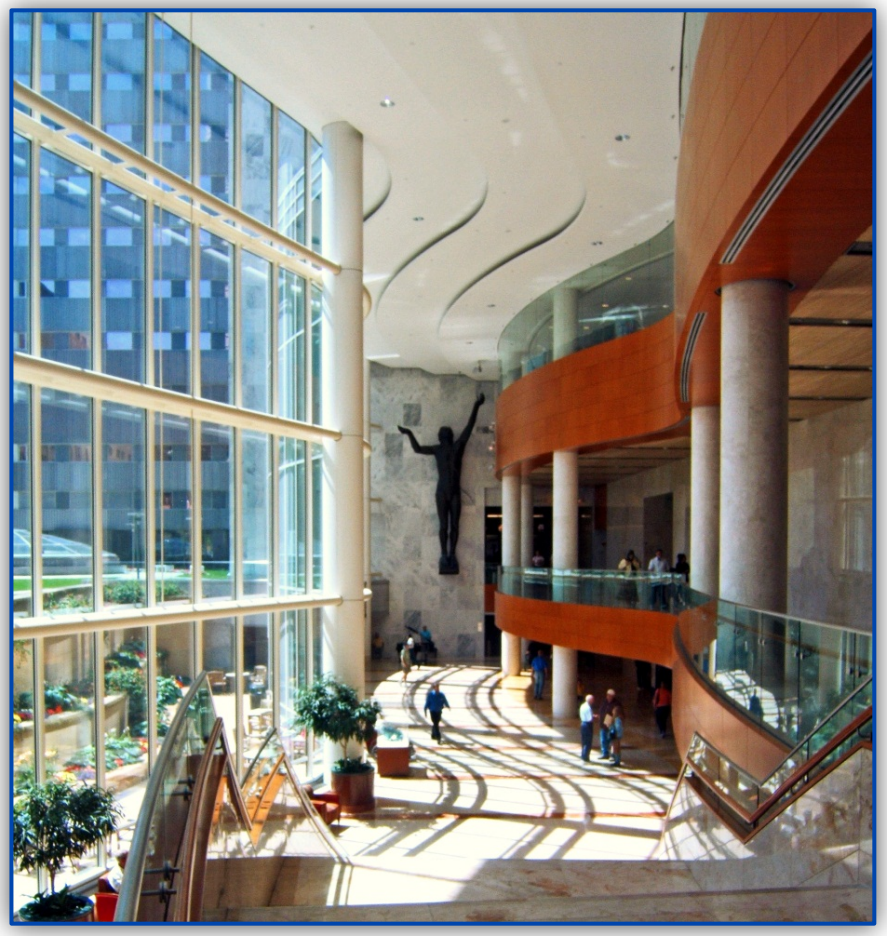

Fractional flow reserve without adenosine: ready for prime time?

Amir Lerman, MD
Professor of Medicine
Chair for Research
Cardiovascular Division

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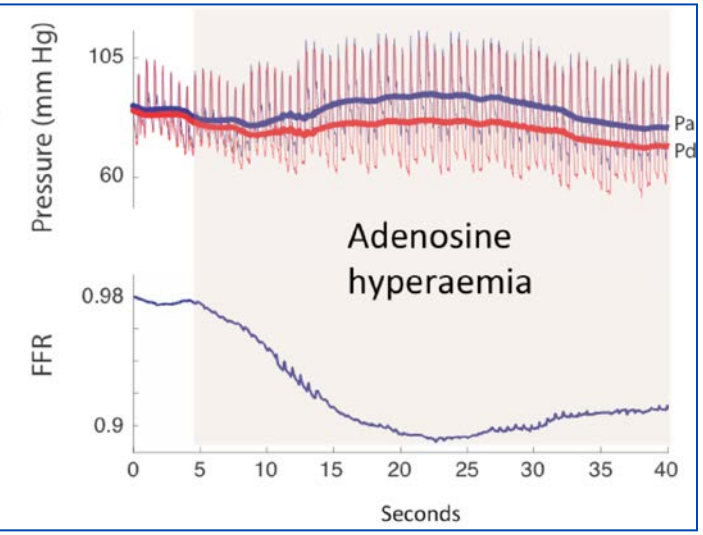
Physiological Assessment of Stenosis

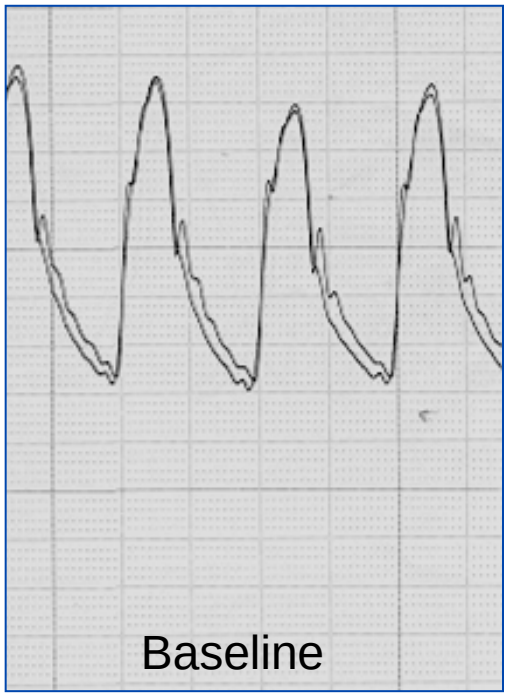
FFR

Hyperemia



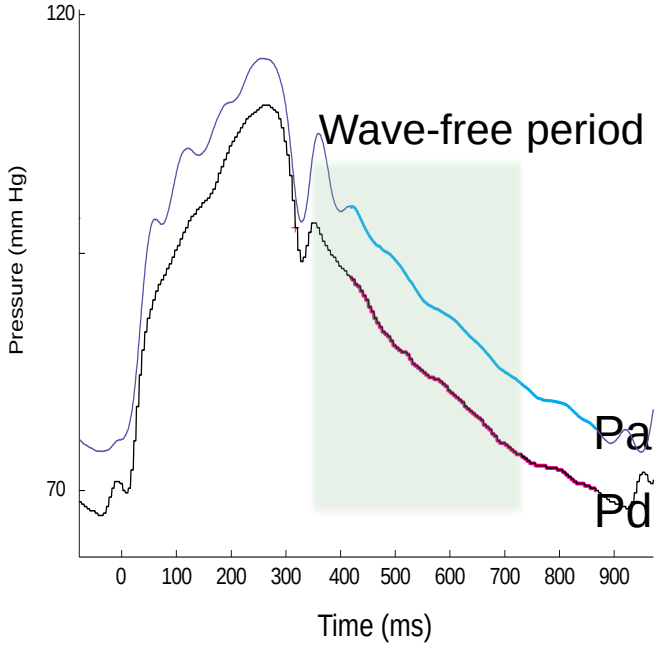
Pressure Gradient

Resting



iFR

Resting



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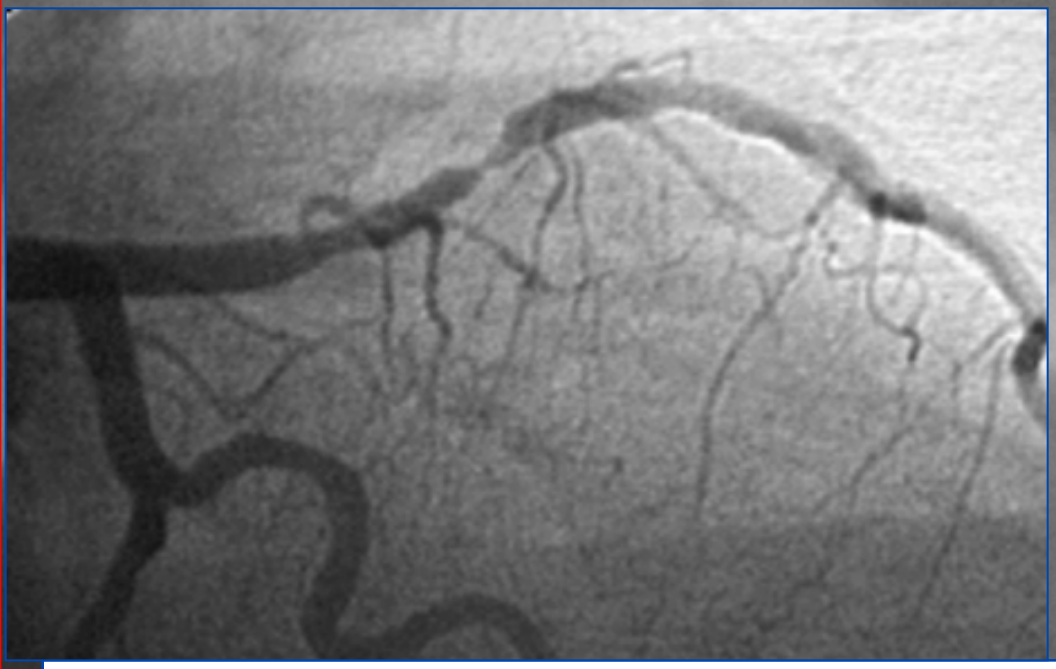
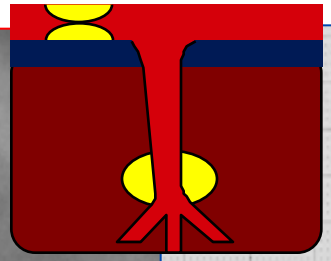
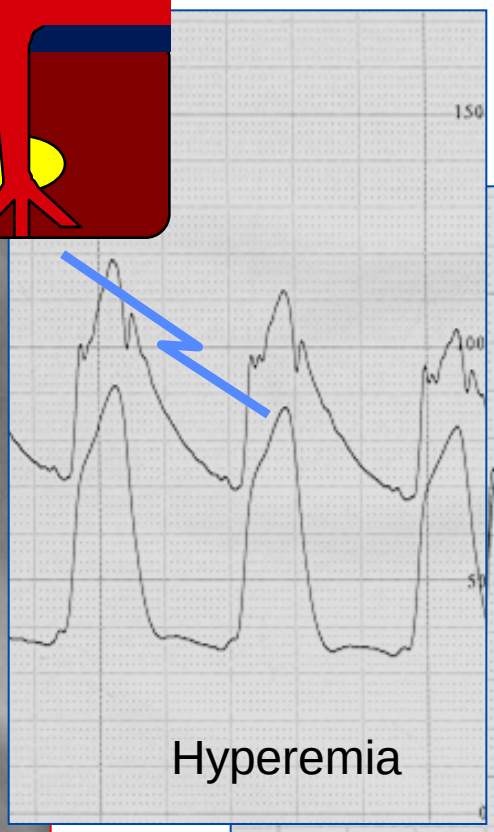
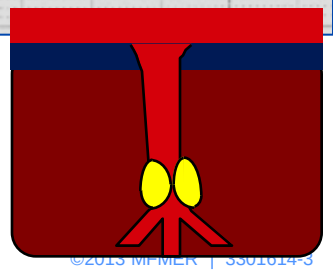
Coronary Stenoses Resting and hyperemic Flow

Hyperemia "uncover" the true gradient across the lesion









- ***Myocardial Fractional Flow Reserve during hyperemia***

$$FFR: = \frac{P_d}{P_A}$$

Fractional Flow Reserve to Determine the Appropriateness of Angioplasty in Moderate Coronary Stenosis

lomized Trial

Bruyne, MD, PhD; Nico H.J. Pijls, MD, PhD;

Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 21, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.01.087

CLINICAL RESEARCH — Interventional Cardiology

Percutaneous Coronary Intervention of Functionally Nonsignificant Stenosis

5-Year Follow-Up of the DEFER Study

Nico H. J. Pijls, MD, PhD,* Pepijn van Schaardenburgh, MD,* Ganesh Man
Eric Boersma, PhD,‡ Jan-Willem Bech, MD, PhD,* Marcel van't Veer, MSc
Jan Hoorntje, MD, PhD,‖ Jacques Koolen, MD, PhD,* William Wijns, MD,
Bernard de Bruyne, MD, PhD†

Eindhoven, Rotterdam, Maastricht, and Zwolle, the Netherlands; and Aalst, Belgi

Objectives The purpose of this study was to investigate the appropriateness of stenting stenosis.

Background Percutaneous coronary intervention (PCI) of an intermediate stenosis withou formed, but its benefit is unproven. Coronary pressure-derived fractional flow used to identify a stenosis responsible for reversible ischemia.

Methods In 325 patients scheduled for PCI of an intermediate stenosis, FFR was mea vention. If FFR was ≥0.75, patients were randomly assigned to deferral (Def (Perform group; n = 90) of PCI. If FFR was <0.75, PCI was performed as pla Clinical follow-up was 5 years.

Results There were no differences in baseline clinical characteristics between the 3 g tained in 98% of the patients. Event-free survival was not different between t and 73%, respectively; p = 0.52), but was significantly worse in the Referen posite rate of cardiac death and acute myocardial infarction in the Defer, Pe 3.3%, 7.9%, and 15.7%, respectively (p = 0.21 for Defer vs. Perform group; both other groups). The percentage of patients free from chest pain at follow Defer and Perform groups.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 15, 2009 VOL. 360 NO. 3

Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention

Pim A.L. Tonino, M.D., Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D.,
ebert, M.D.,
h Manohara
hilip A. Mac

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Fractional Flow Reserve–Guided PCI for Stable Coronary Artery Disease

Bernard De Bruyne, M.D., Ph.D., William F. Fearon, M.D., Nico H.J. Pijls, M.D., Ph.D., Emanuele Barbato, M.D., Ph.D., Pim Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Mobius-Winckler, M.D., Gilles Riouffol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D., Keith Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D., Jane B. Johnson, R.N., B.S.N., Andreas Limacher, Ph.D., Eveline Nüesch, Ph.D., and Peter Jüni, M.D., for the FAME 2 Trial Investigators*

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 13, 2012 VOL. 367 NO. 11

Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, M.D., Ph.D., Nico H.J. Pijls, M.D., Ph.D., Bindu Kalesan, M.P.H., Emanuele Barbato, M.D., Ph.D., Pim A.L. Tonino, M.D., Ph.D., Zsolt Piroth, M.D., Nikola Jagic, M.D., Sven Möbius-Winkler, M.D., Gilles Rioufol, M.D., Ph.D., Nils Witt, M.D., Ph.D., Petr Kala, M.D., Philip MacCarthy, M.D., Thomas Engström, M.D., Keith G. Oldroyd, M.D., Kreton Mavromatis, M.D., Ganesh Manoharan, M.D., Peter Verlee, M.D., Ole Frobert, M.D., Nick Curzen, B.M., Ph.D., Jane B. Johnson, R.N., B.S.N., Peter Jüni, M.D., and William F. Fearon, M.D., for the FAME 2 Trial Investigators*

ABSTRACT

European Heart Journal (2013) **34**, 1375–1383
doi:10.1093/eurheartj/eht005

CLINICAL RESEARCH
Interventional cardiology

Long-term outcomes of fractional flow reserve-guided vs. angiography-guided percutaneous coronary intervention in contemporary practice

Jing Li[1], Muhamad Y. Elrashidi[2], Andreas J. Flammer[3,4], Ryan J. Lennon[5], Malcolm R. Bell[3], David R. Holmes[3], John F. Bresnahan[3], Charanjit S. Rihal[3], Lilach O. Lerman[6], and Amir Lerman[3]*

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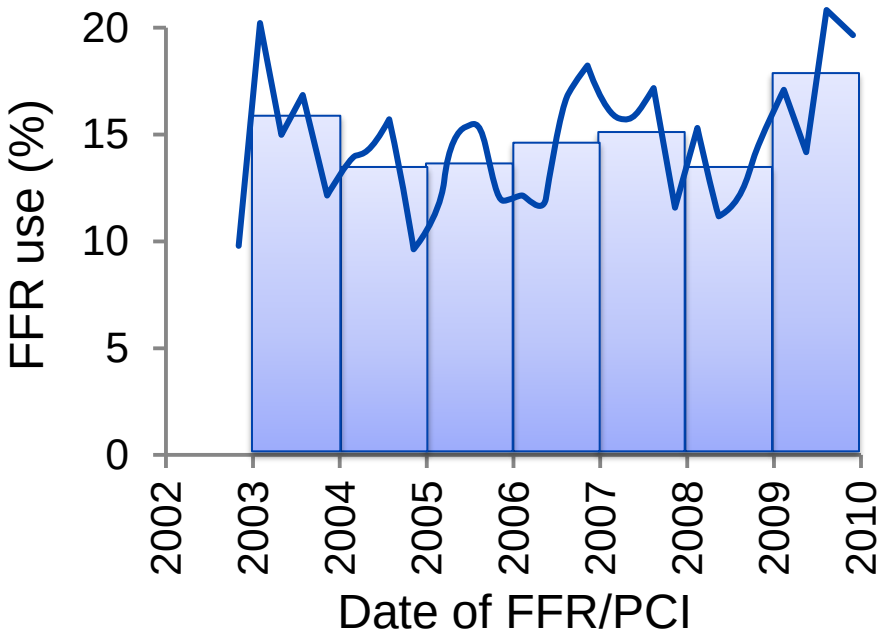
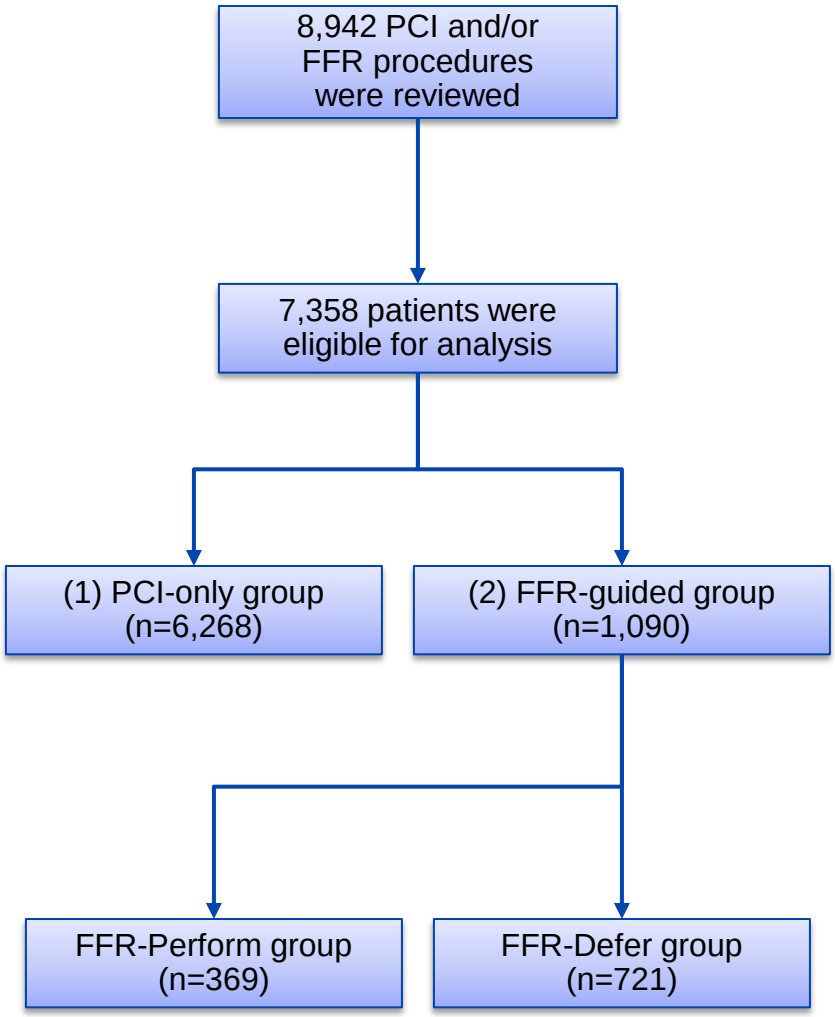
Received 23 July 2012; revised 14 December 2012; accepted 4 January 2013; online publish-ahead-of-print 23 January 2013

Utility Rates of Fractional Flow Reserve Between 2002 and 2009



Study Flow Chart



Li et al: European Heart Journal 34:1375, 2013

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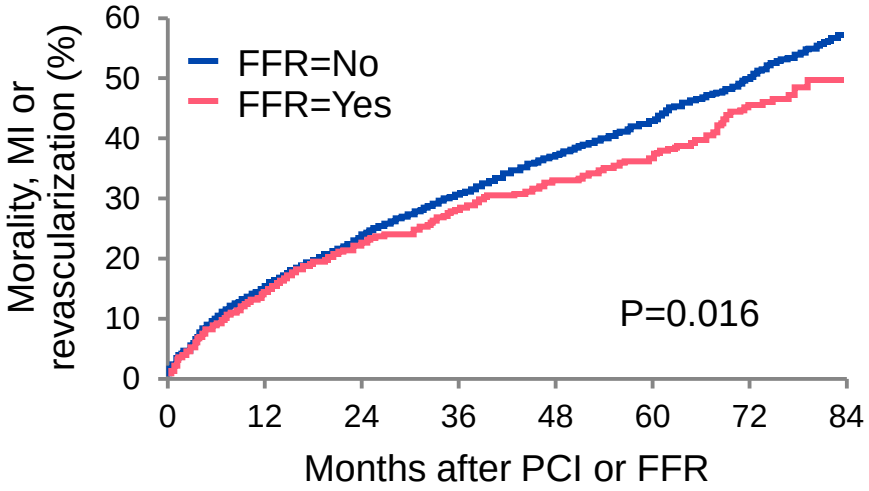
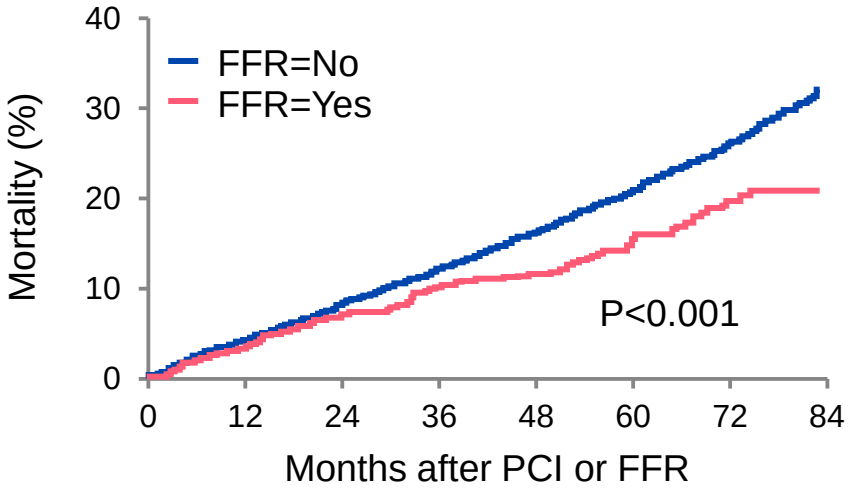
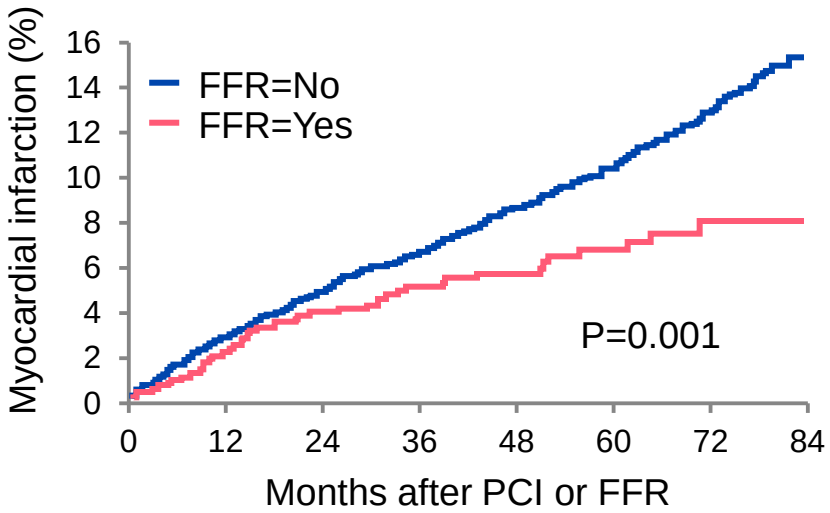
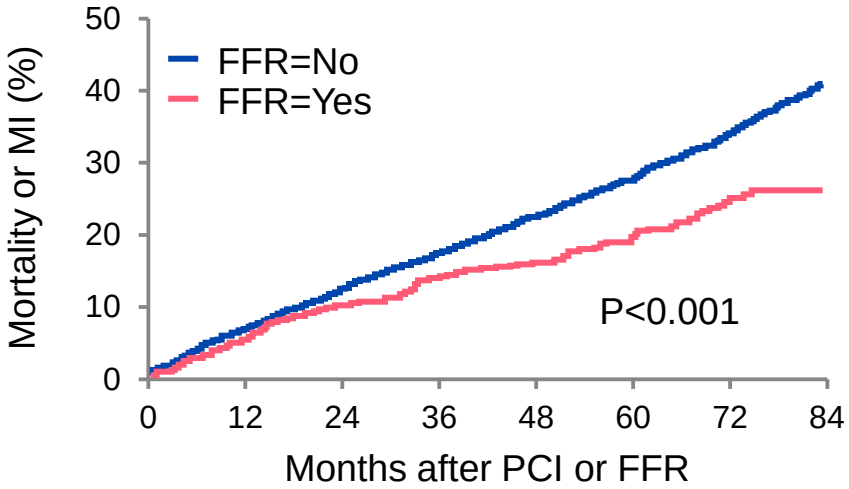
Long-Term Adverse Events in the Percutaneous Coronary Intervention-Only Group and Fractional Flow Reserve-Guided Group









Li et al: European Heart Journal 34:1375, 2013

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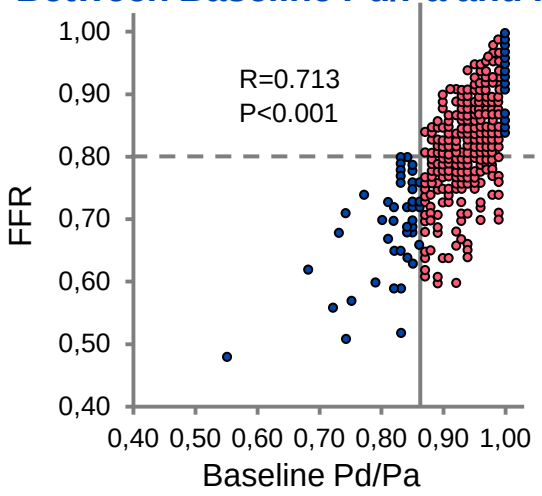
Clinical Usefulness of Nonhyperemic Baseline Pd/Pa as a Hybrid Baseline Pd/Pa – Fractional Flow Reserve Strategy

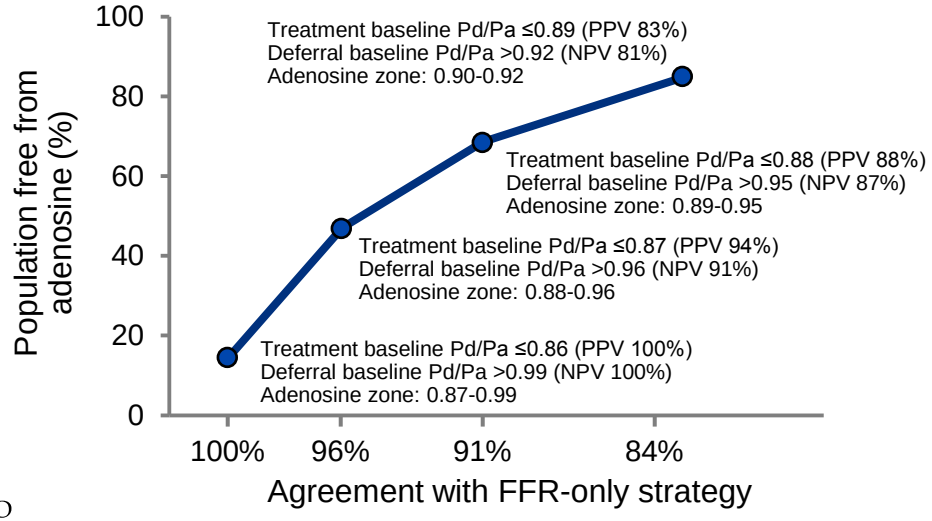
Methods – 570 lesions from 527 consecutive patients who had both baseline Pd/Pa and FFR determined were evaluated

Results – A hybrid strategy using a deferral baseline Pd/Pa value of 1.00 (negative predictive value of 100%) and a treatment baseline of Pd/Pa value of 0.86 or lower (positive predictive value of 100%), and limiting adenosine to a baseline Pd/Pa value between 0.87 and 0.99 would prevent the need for vasodilator drugs in 14.6% of lesions (14.0% patients)

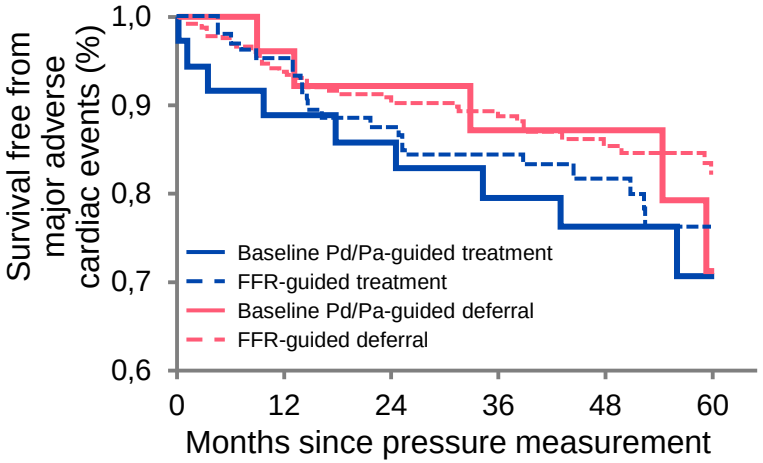
Scatter Plot Showing a Relationship Between Baseline Pd/Pa and FFR



Population of Adenosine-Free Lesions by Desired PPV and NPV



MACE-Free Survival Rate With a Hybrid Baseline Pd/Pa-FFR Strategy



Kwon et al: Coronary Artery Dis, 2014

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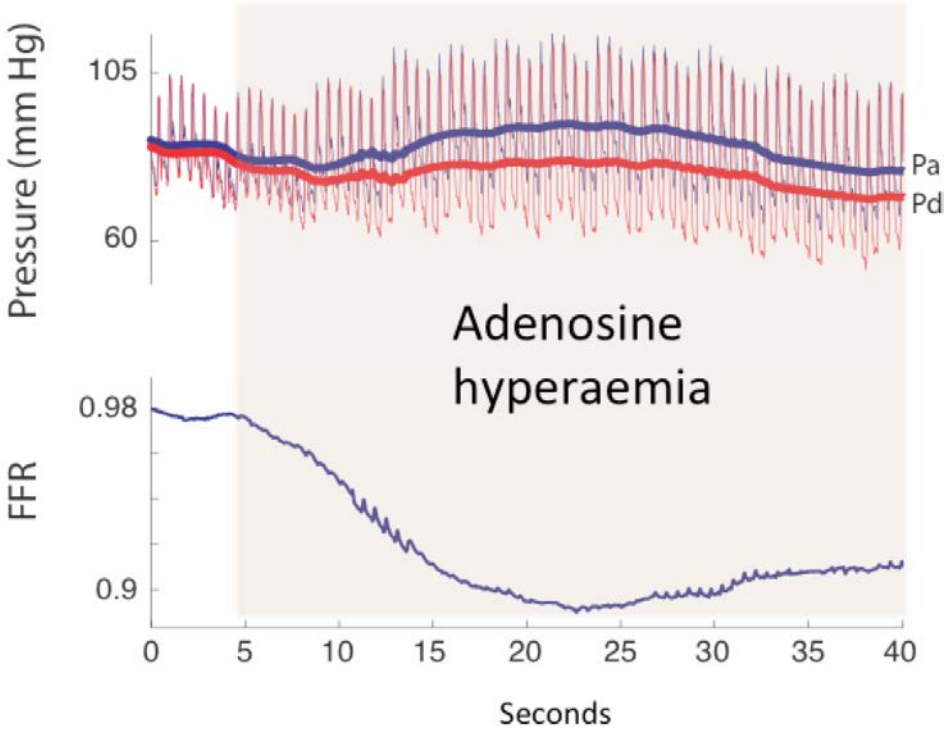
Physiological stenosis assessment

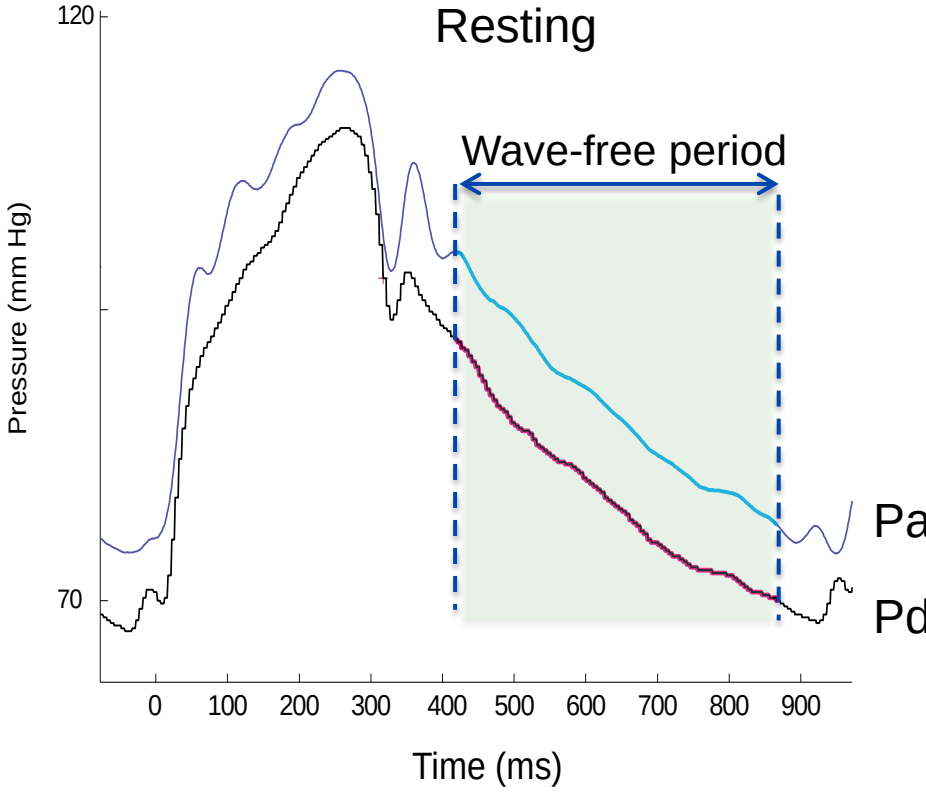
FFR

Hyperaemia



iFR

Resting



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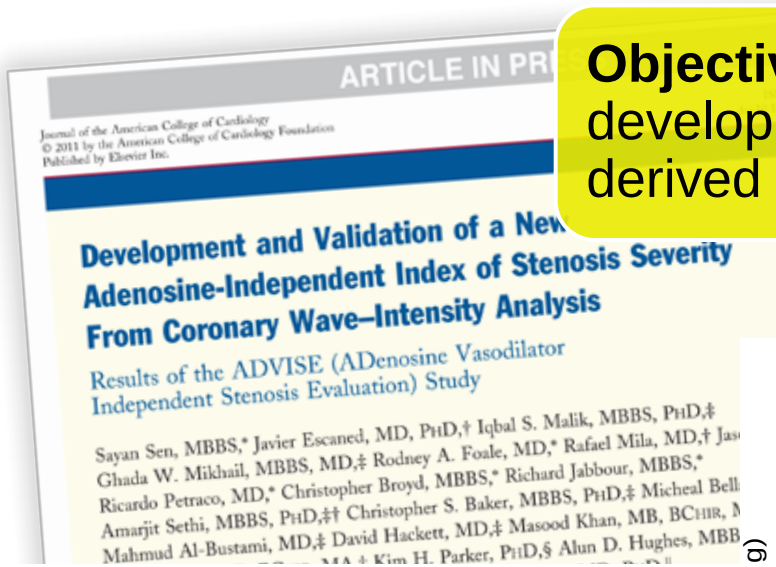
Objectives: The purpose of this study was to develop an adenosine-independent, pressure-derived index of coronary stenosis severity.


ARTICLE IN PR

Journal of the American College of Cardiology
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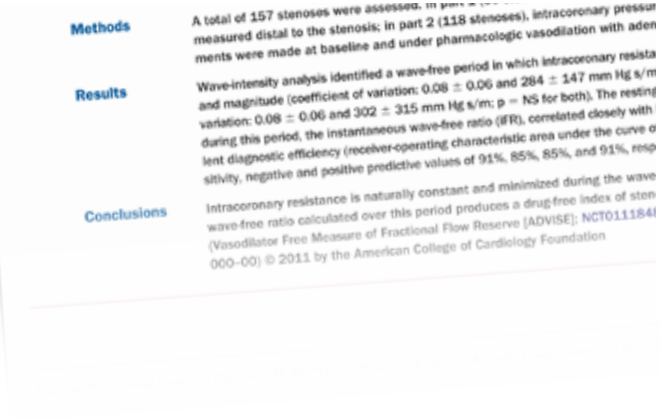
Development and Validation of a New Adenosine-Independent Index of Stenosis Severity From Coronary Wave–Intensity Analysis

Results of the ADVISE (ADenosine Vasodilator Independent Stenosis Evaluation) Study

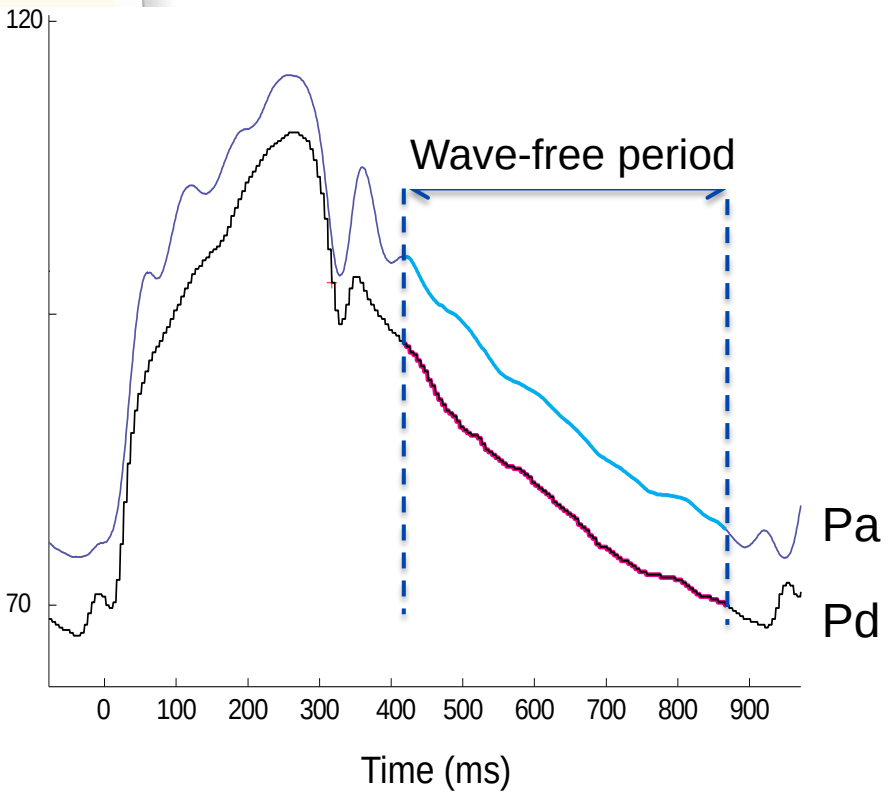
Sayan Sen, MBBS,* Javier Escaned, MD, PHD,† Iqbal S. Malik, MBBS, PHD,‡ Ghada W. Mikhail, MBBS, MD,‡ Rodney A. Foale, MD,* Rafael Mila, MD,† Jas Ricardo Petraco, MD,* Christopher Broyd, MBBS,* Richard Jabbour, MBBS,* Amarjit Sethi, MBBS, PHD,‡† Christopher S. Baker, MBBS, PHD,‡ Micheal Bell Mahmud Al-Bustami, MD,‡ David Hackett, MD,‡ Masood Khan, MB, BCHIR, M


Methods A total of 157 stenoses were assessed. In part 2 (118 stenoses), intracoronary pressur measured distal to the stenosis; in part 2 (118 stenoses), intracoronary pressure ments were made at baseline and under pharmacologic vasodilation with aden

Results Wave-intensity analysis identified a wave-free period in which intracoronary resista and magnitude (coefficient of variation: 0.08 ± 0.06 and 284 ± 147 mm Hg s/m variation: 0.08 ± 0.06 and 302 ± 315 mm Hg s/m; p = NS for both). The resting during this period, the instantaneous wave-free ratio (iFR), correlated closely with lent diagnostic efficiency (receiver-operating characteristic area under the curve o sitivity, negative and positive predictive values of 91%, 85%, 85%, and 91%, resp

Conclusions Intracoronary resistance is naturally constant and minimized during the wave wave-free ratio calculated over this period produces a drug-free index of sten (Vasodilator Free Measure of Fractional Flow Reserve [ADVISE]; NCT011184 000–00) © 2011 by the American College of Cardiology Foundation

- Instantaneous wave-free ratio (**iFR**) is a recently introduced pressure-derived, adenosine-free index for assessment of coronary stenosis relevance.



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Key iFR validation studies

- Correlation
- Resistance
- Non invasive test
- Added value

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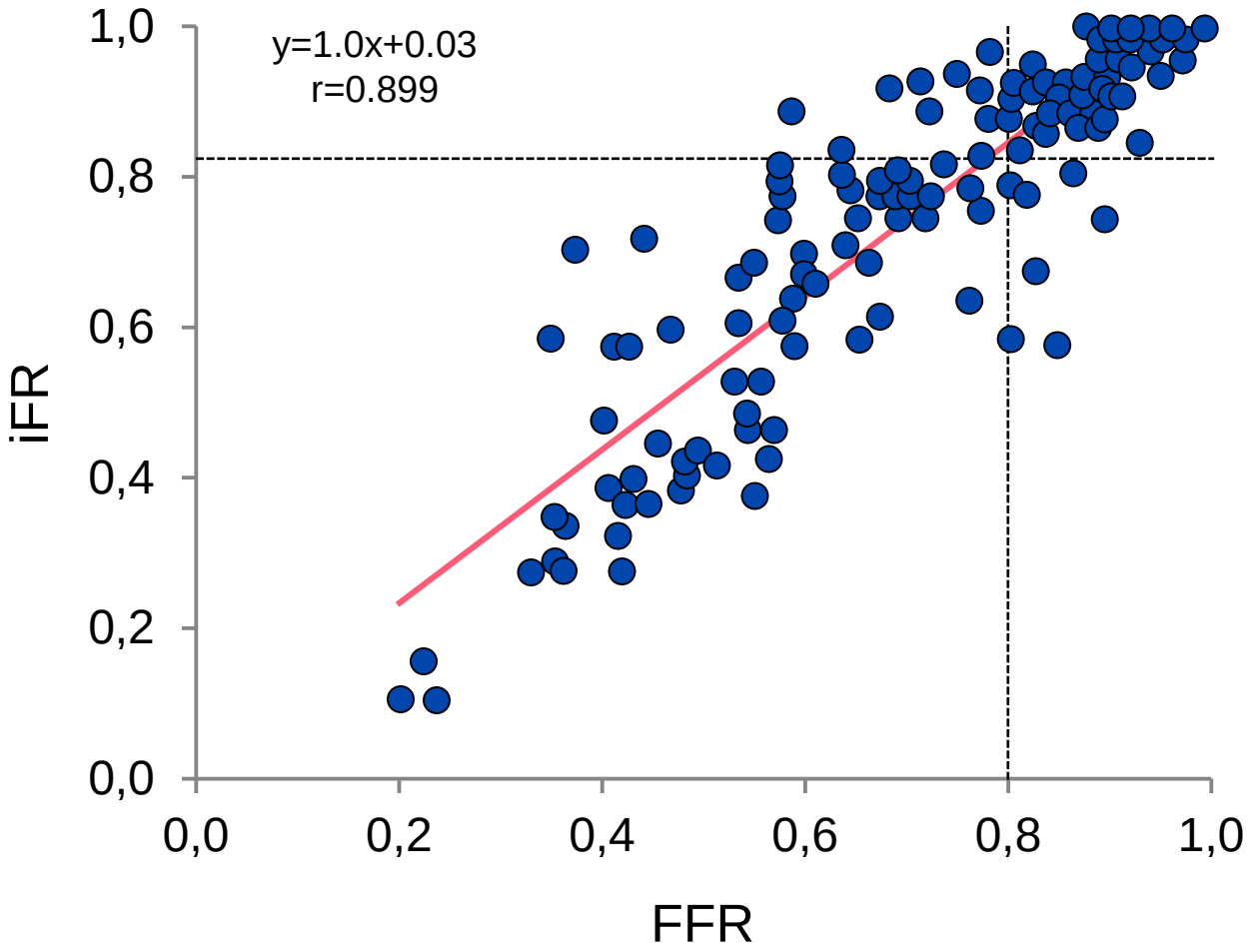
Correlation between iFR and FFR



Sen et al: J Am Coll Cardiol 2012;59:000–00

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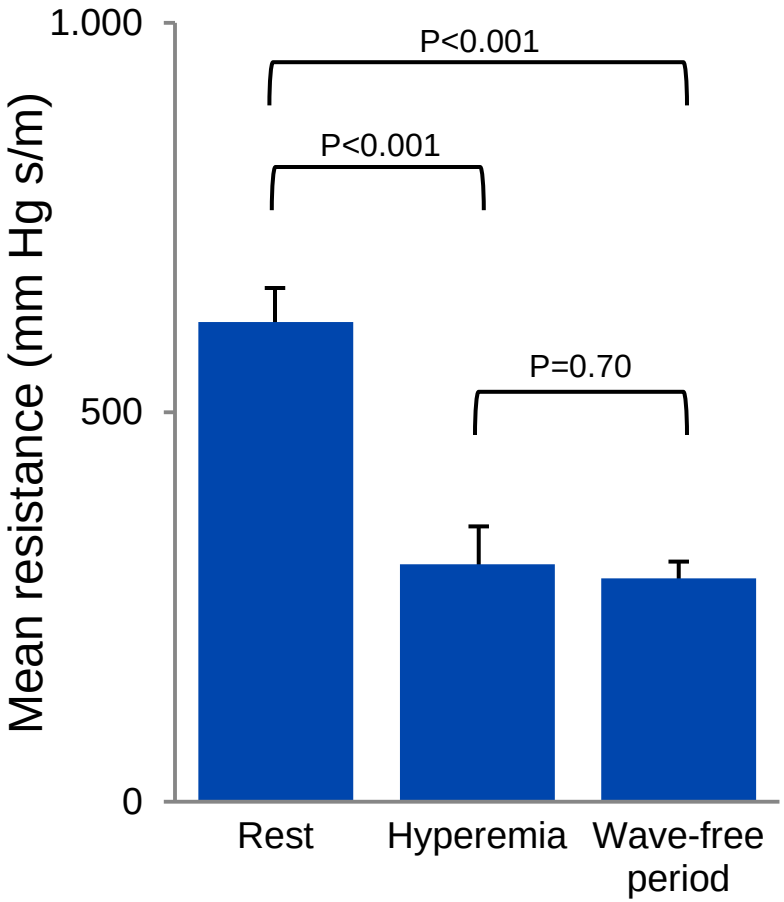
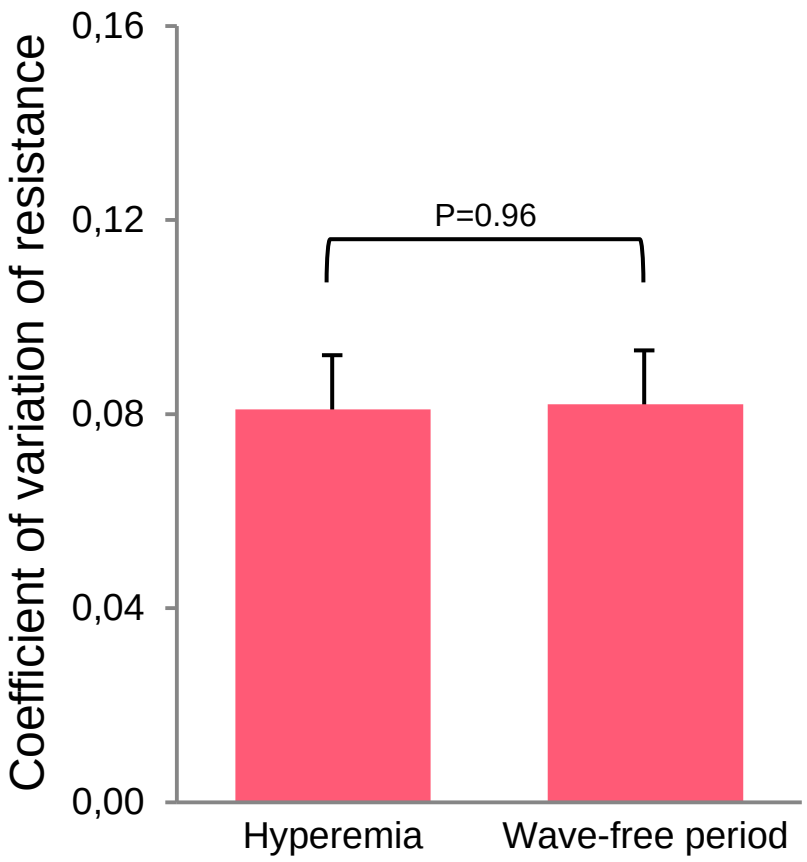
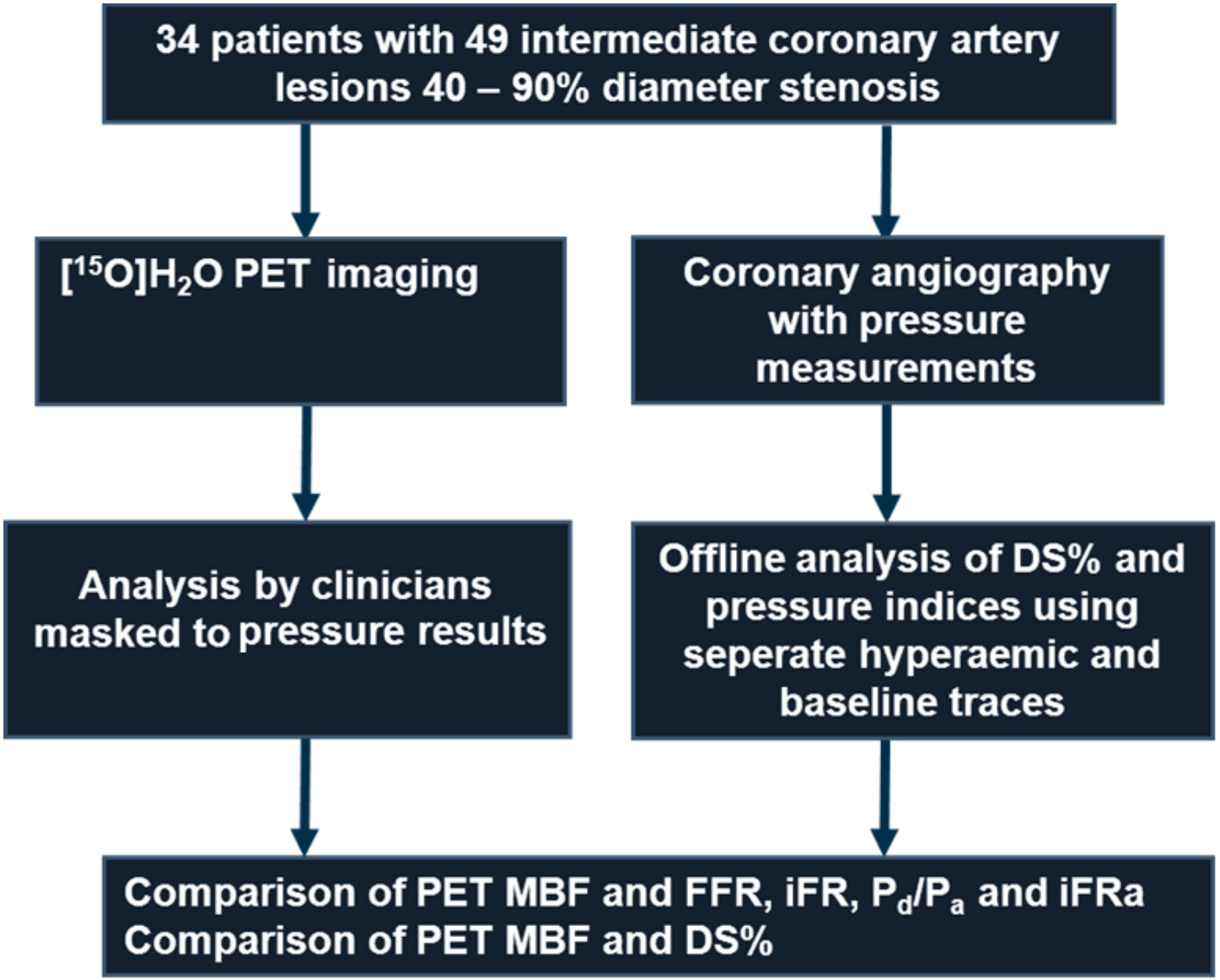
Intracoronary Resistance During Pharmacologic Vasodilation Compared with Resistance During the Wave-Free Period





Sen et al: J Am Coll Cardiol 2012;59:000–00

Study Protocol



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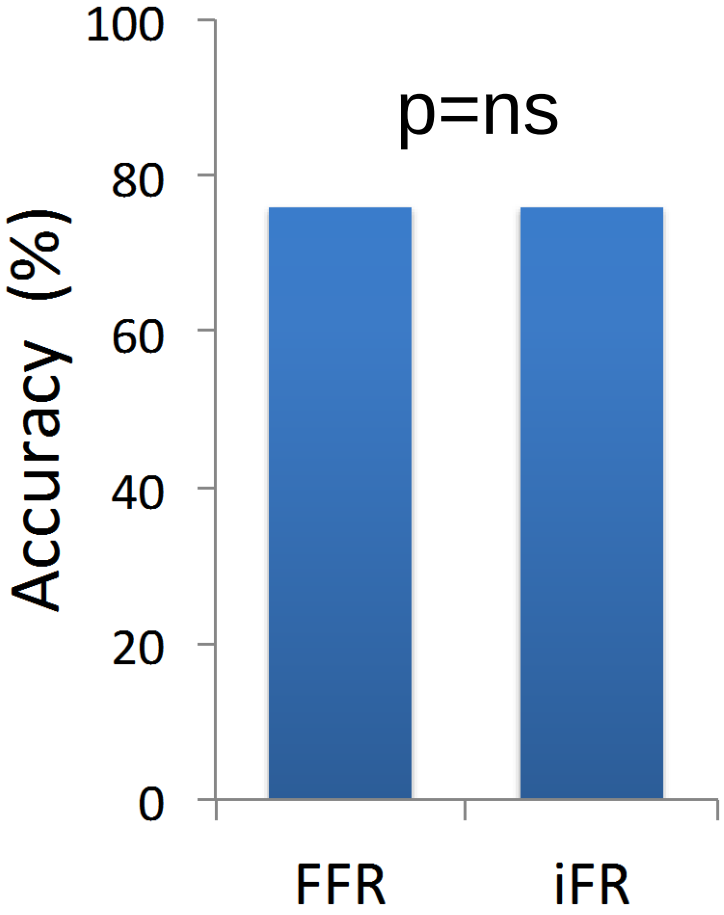
De Waard G et al. ACC 2014

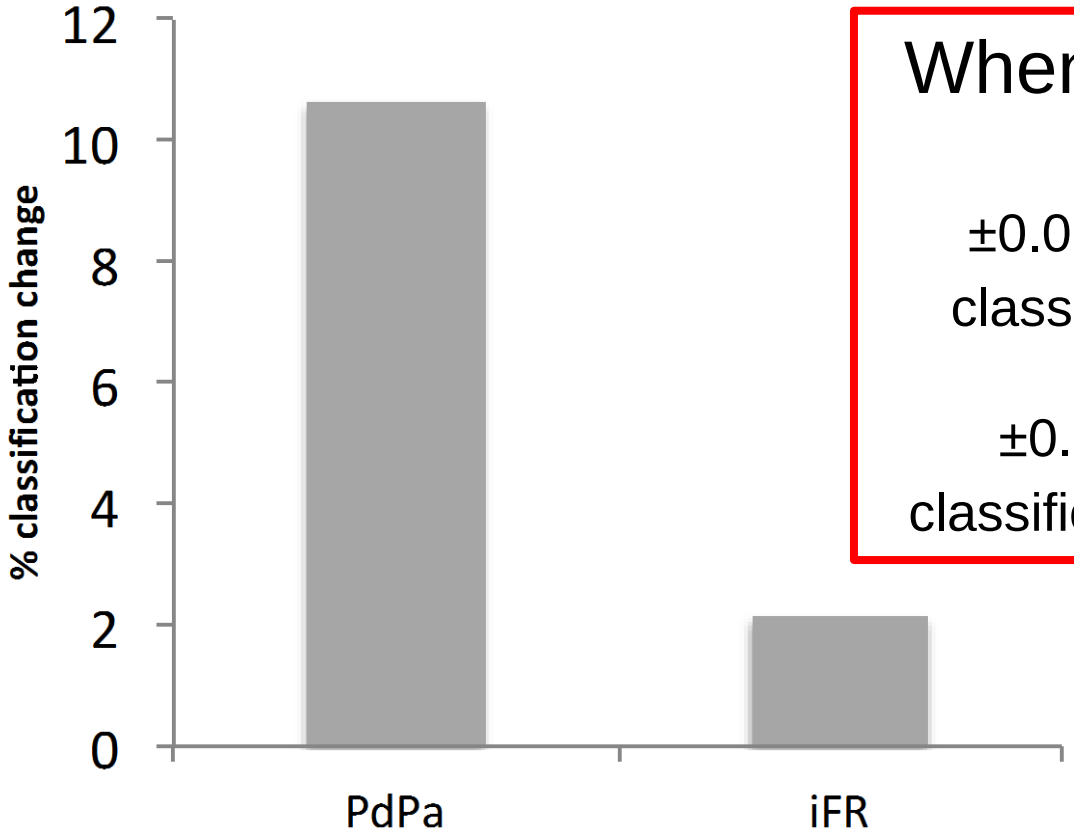
iFR and FFR have *similar diagnostic power* to detect ischemia



MAYO CLINIC

De Waard G et al. ACC 2014

iFR is 5 times more sensitive than Pd/Pa



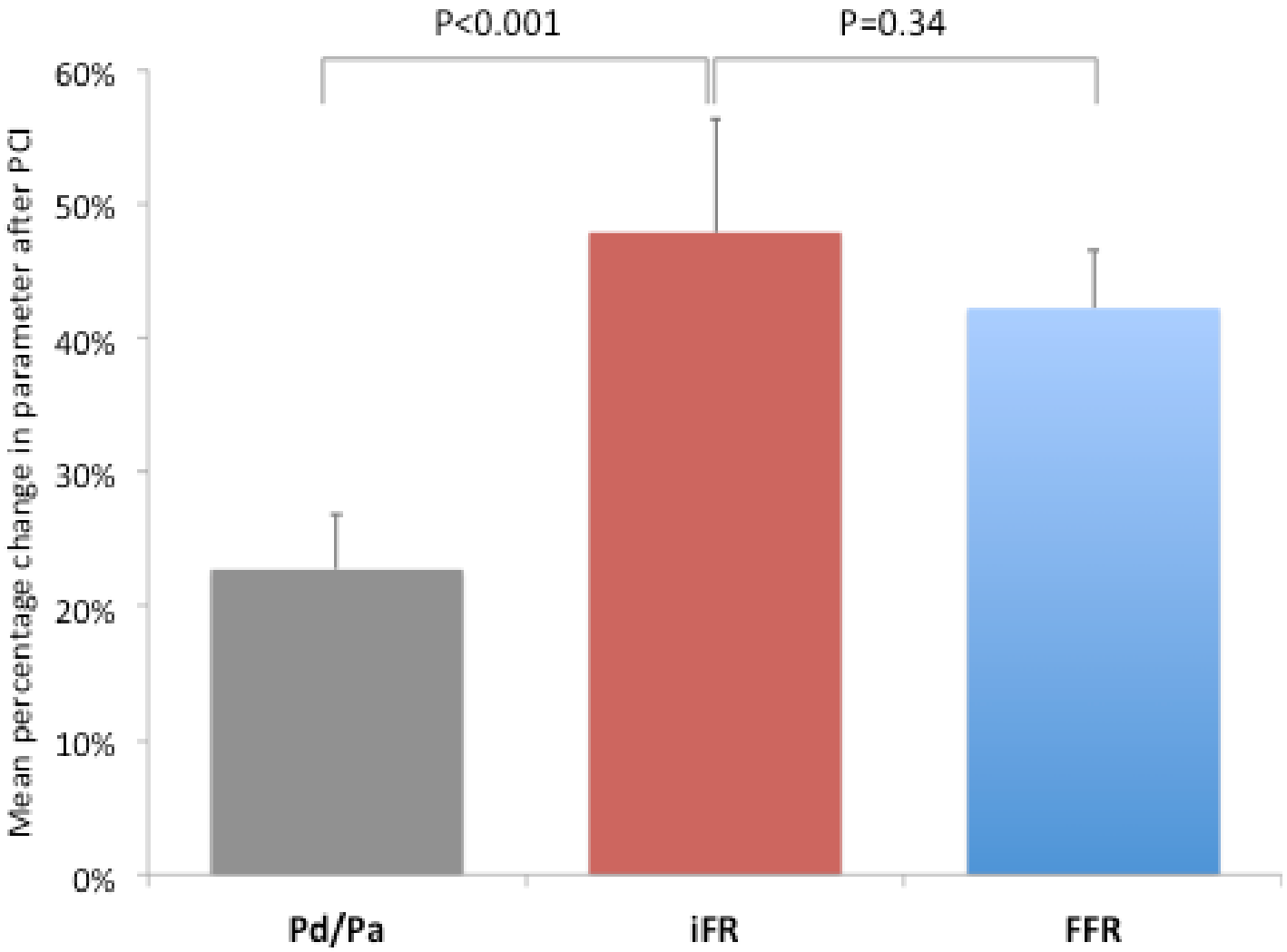
When compared to FFR

±0.02 drift in Pd/Pa changes classification ***11%*** of the time

±0.02 drift in iFR changes classification only ***2%*** of the time

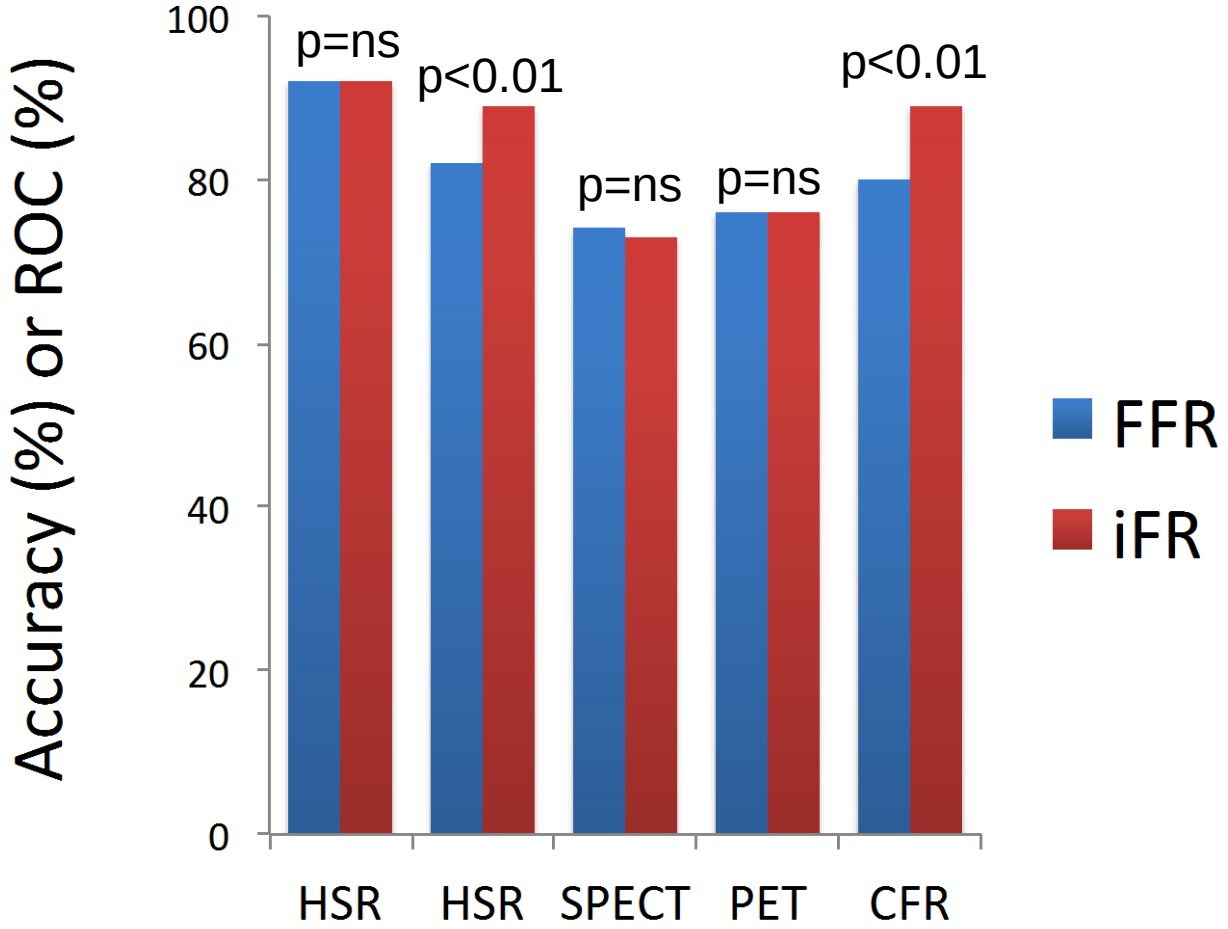
de Waard et al. ACC 2014

Delta of Index after PCI



Nijjer S et al. Heart 2013

Vasodilators ***do not*** improve physiological diagnostic accuracy



1. Van de Hoef et al. Circ Cardiovasc Interv. 2012;5(4):508-14
2. Sen et al. J Am Coll Cardiol. 2013;61(13):1409-20
3. Van de Hoef Euroint. (*in press*)
4. Sen et al. J Am Coll Cardiol. 2013;62(6):566
5. Petraco et al. Circ. Int. (*in press*)
6. de Waard et al. (ACC 2014)

Consistent iFR cut-points

IFR value with best classification for FFR≤0.80

ADVISE-Registry (n= 339)	0.89
South Korean Study(n=238)	0.90
RESOLVE(n=1593)	0.90
ADVISE-*in Practice*(n=392)	0.90
ADVISE 2 (n=689)	0.89

FDA Labeling iFR = 0.89

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ADVISE II

*AD*enosine *V*asodilator *I*ndependent *S*tenosis *E*valuation *II*

A prospective, observational, non-randomized, double blind, global,

multi-center registry with an adaptive design, investigating the diagnostic utility of instantaneous wave-free ratio in assessing

coronary stenosis relevance

Funded by Volcano.

Principal Investigators

Javier Escaned, MD PhD, Amir Lerman, MD

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Background

- Although the reported agreement between iFR and FFR has been good, some discrepancy has been observed, potentially related to:
  - Retrospective designs
  - Heterogeneous FFR technique
  - Differences in iFR detection algorithm
  - Lack of ECG to detect wave-free period
  - Potential artifacts in wave forms have not been ruled out
  - Pressure drift was not ruled out

A prospective study with rigorous methodology was deemed required to establish the clinical value of iFR

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Study Objective and Design

- To prospectively assess the clinical value of iFR to characterize, without concomitant administration of hyperemic agents and outside a specified range of iFR values, coronary stenosis severity as determined with fractional flow reserve (FFR).

- Prospective, observational, non-randomized, double blind, global, multi-center registry with an adaptive design.

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What makes ADVISE II different?

- **Design:** Prospective, global (US, EU, Africa), multi-center (n=40), double blind registry with an adaptive design based on interim analyses.
- **Data collection:** standardized guidewire/console, IV adenosine and pressure pullback were mandatory.
- **iFR algorithm:** iFR calculation software analysis tool (HARVEST) fully consistent with upcoming online commercial system.
- **iFR calculation and data analysis:** performed at an independent core laboratory (CARDIALYSIS, Rotterdam, The Netherlands).
- **Primary endpoint:** focused on the clinical applicability of iFR in the context of a hybrid iFR/FFR strategy[1].

[1]Petraco et al. EuroIntervention 2013;8:1157-1165

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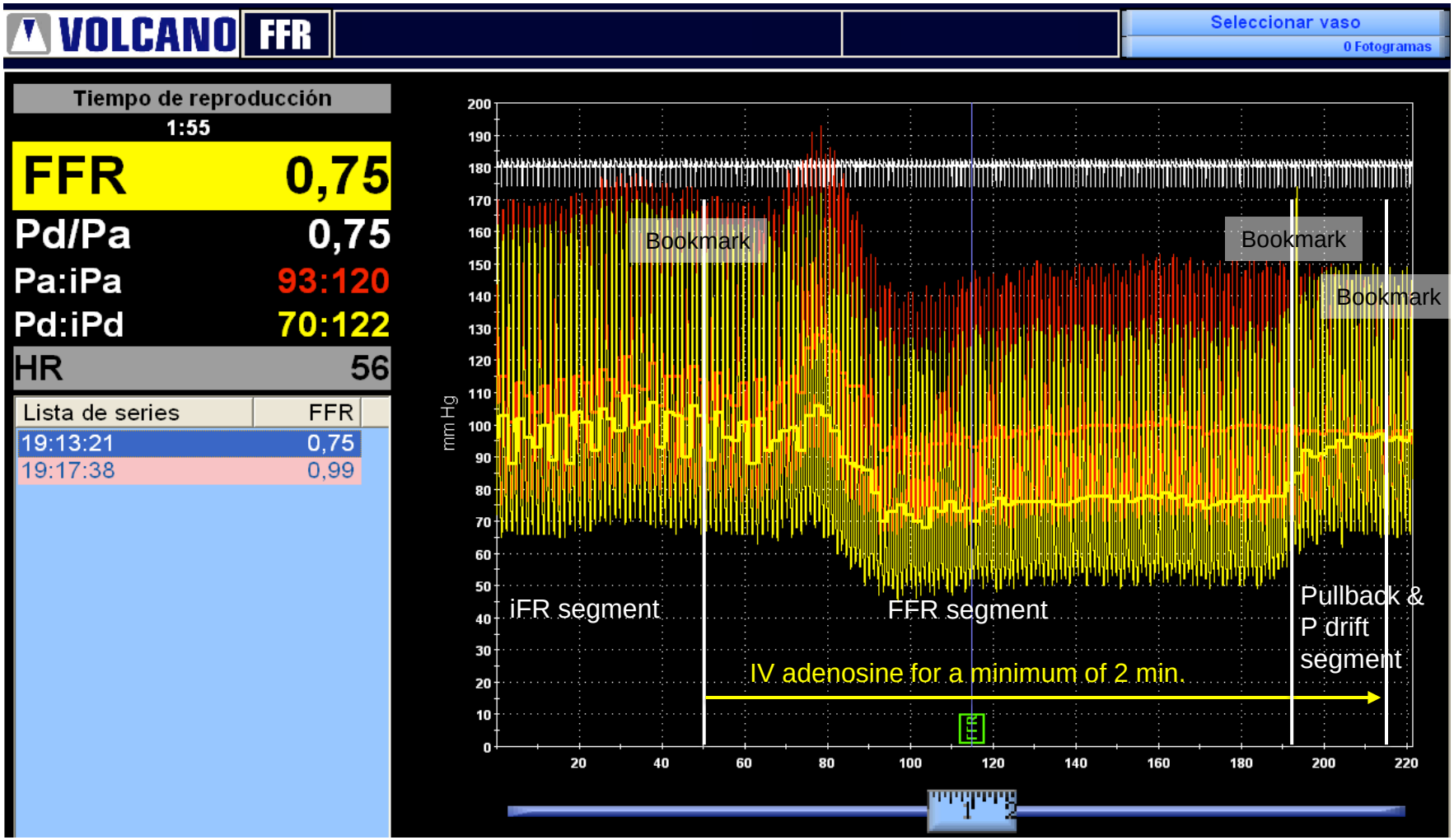
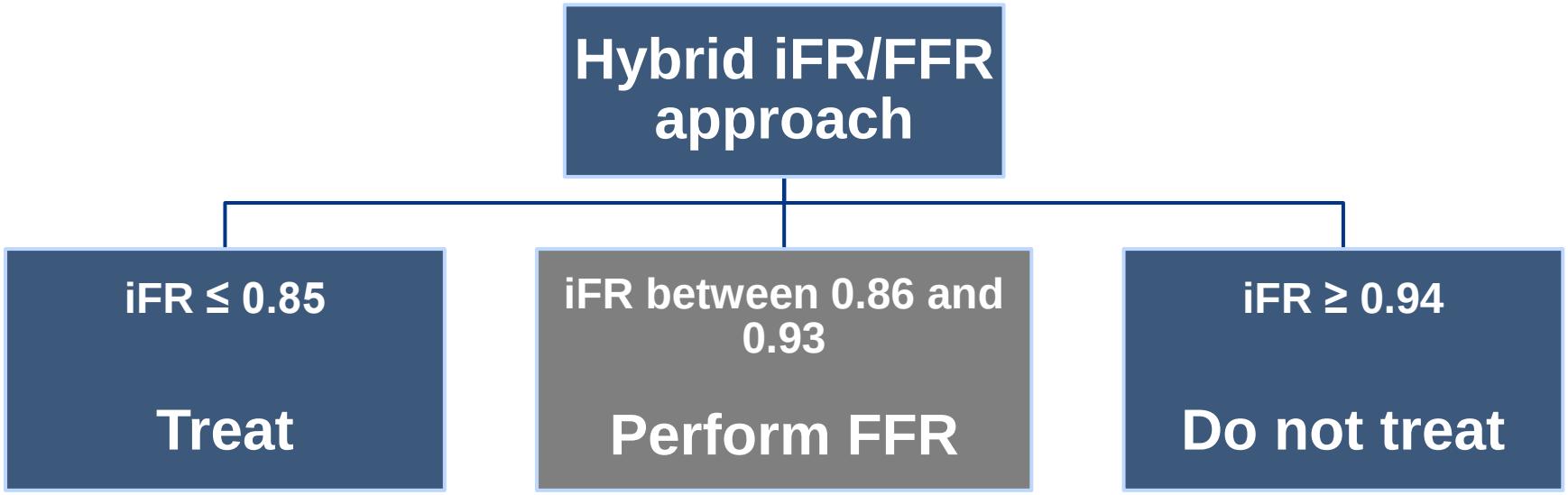
Standardized data collection



Data acquisition was performed in a single tracing, with bookmarks introduced for identification of relevant study segments during core lab analysis.

Hybrid iFR/FFR approach



This hybrid diagnostic strategy aims to increase adoption of physiology-guided PCI, by decreasing the need for adenosine while maintaining a high classification agreement with an FFR-only strategy[1].

[1]Petraco et al. EuroIntervention 2013;8:1157-1165

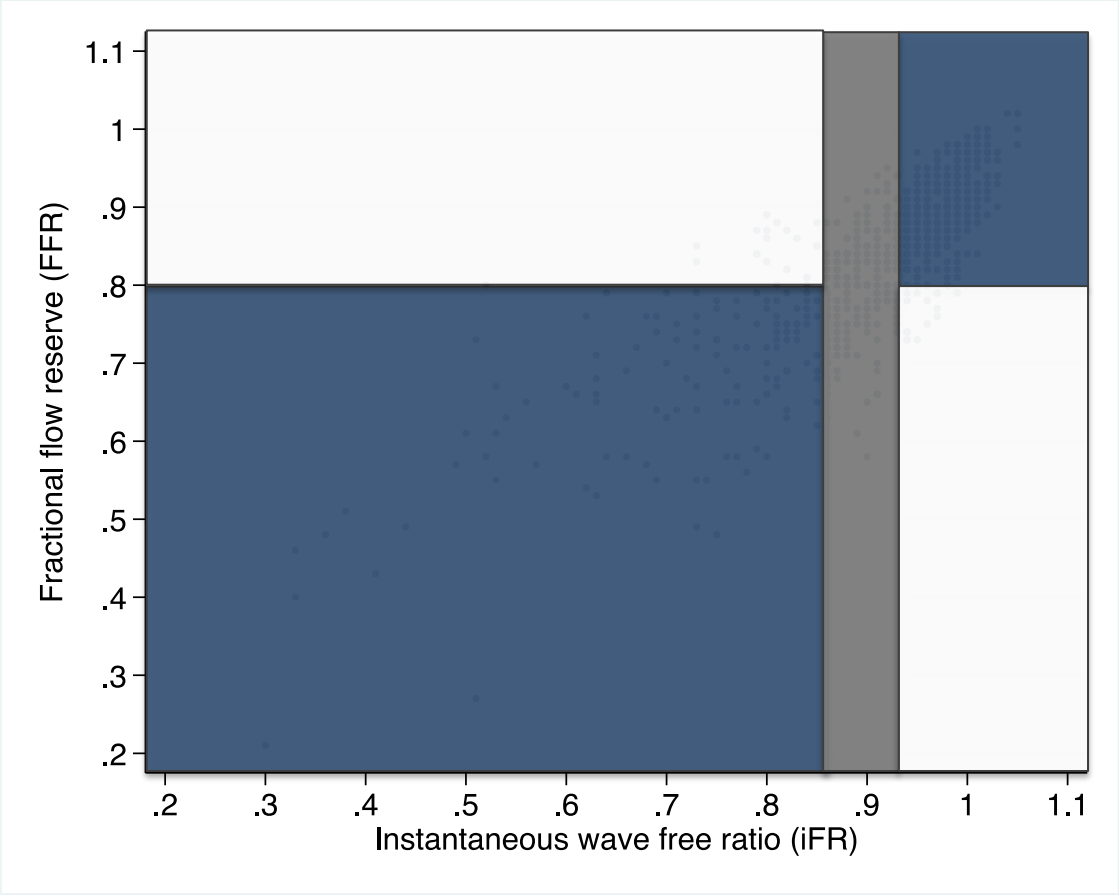
Primary endpoint

- Percentage of stenoses properly classified in terms of hemodynamic severity by iFR (outside ≤ 0.85 iFR ≥ 0.94):

Hemodynamic severity was established with an FFR value ≤ 0.80.

Properly classified

iFR/FFR disagreement



Secondary Endpoints

- Minimum iFR exclusion ranges around iFR=0.89 in which iFR and FFR agreement is equal to or greater than 80 and 90%.
- Sensitivity/specificity as well as positive predictive and negative predictive values of iFR for FFR prediction.
- Diagnostic efficiency of iFR to identify FFR severe stenoses (AUROC).
- Correlation coefficient (r) of the iFR FFR relationship.
- Estimated proportion of patients free from adenosine in a hybrid iFR-FFR approach.
- Estimated cost saving in a hybrid iFR/FFR approach.

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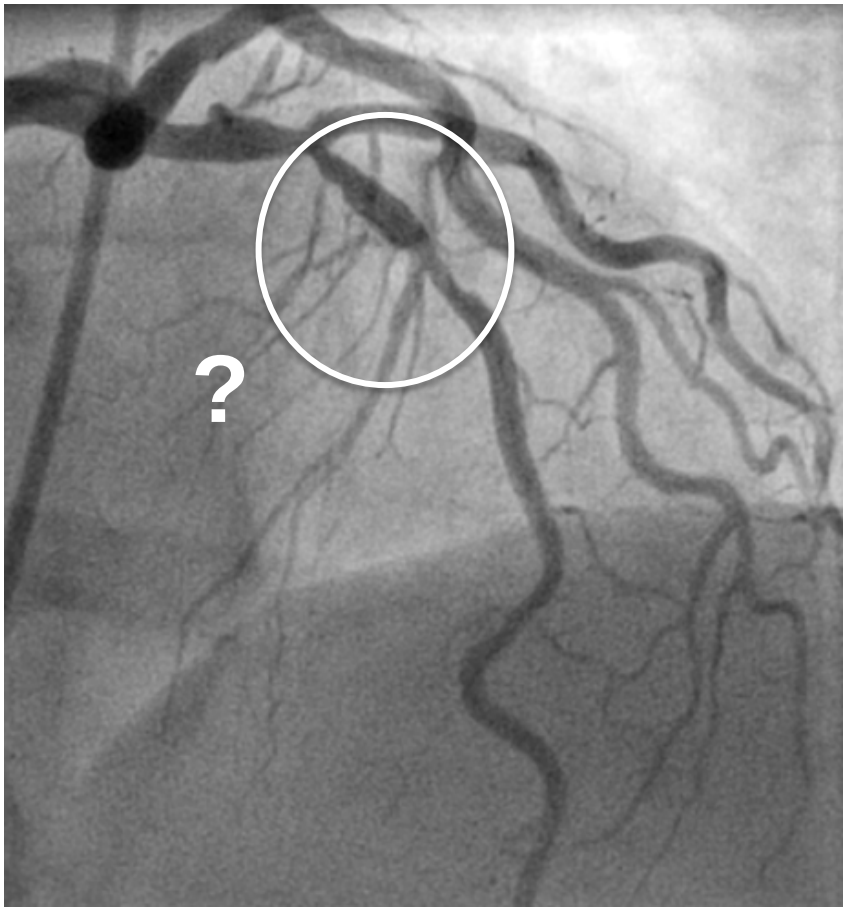
Inclusion criteria

- Age ≥ 18 and ≤ 85 years.
- Willing to participate and able to understand, read and sign the informed consent document before the planned procedure.
- Eligible for coronary angiography and/or percutaneous coronary intervention.
- One or more stenoses DS>40% (visual assessment).
- Stable angina or acute coronary syndromes (non-culprit vessels).



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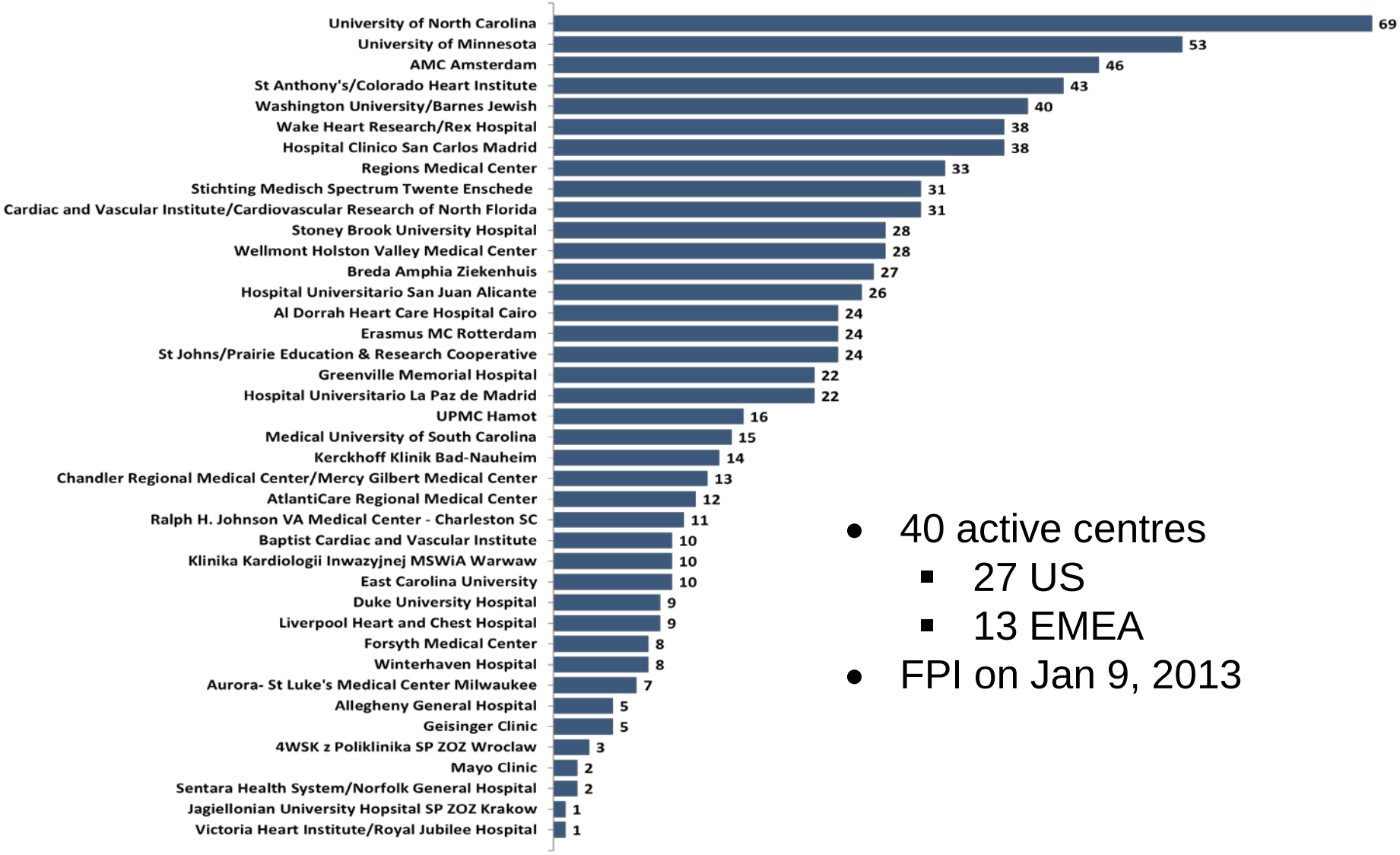
Enrollment and Participating Centres



- 40 active centres
  - 27 US
  - 13 EMEA
- FPI on Jan 9, 2013

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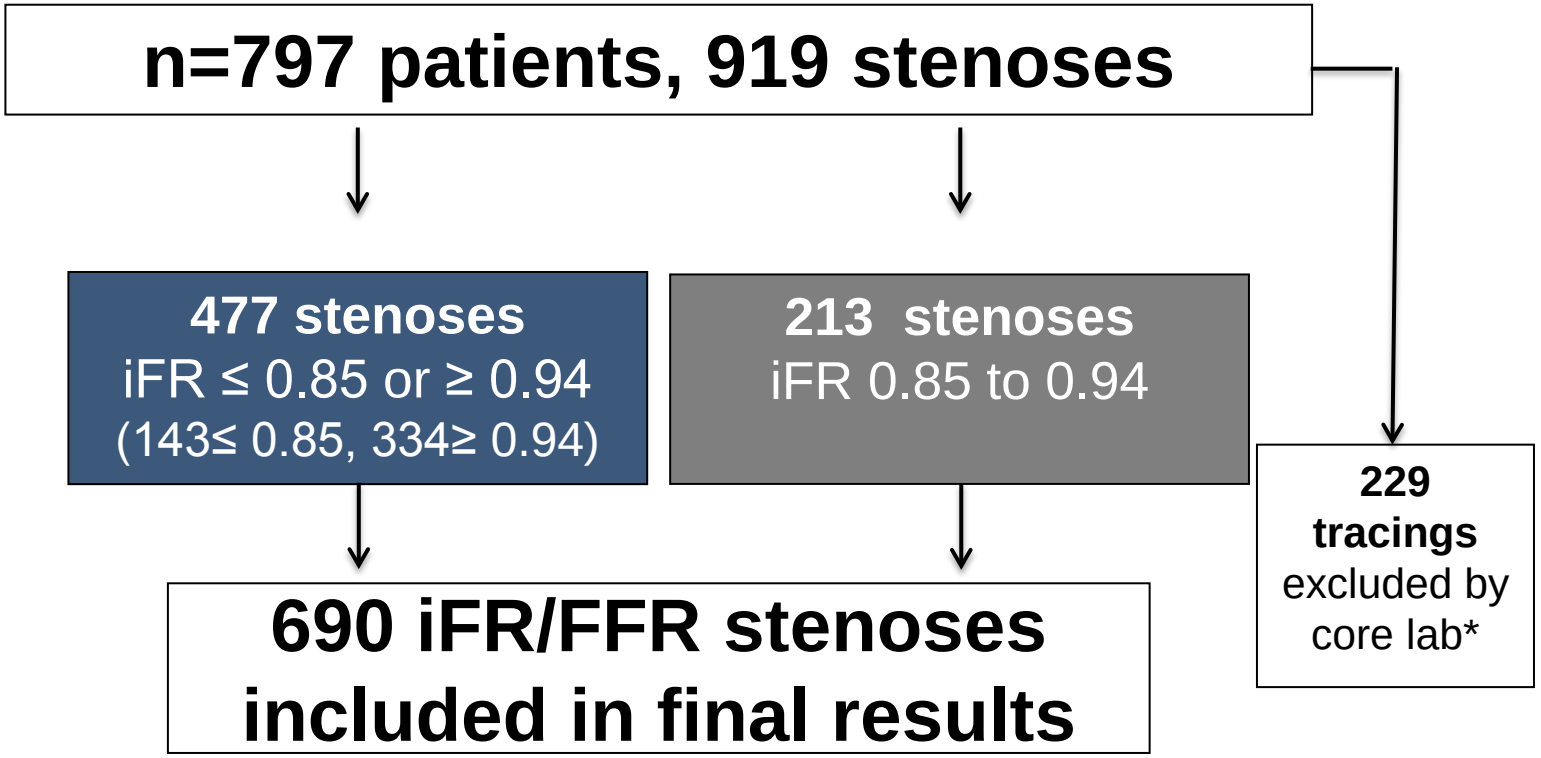
Study Flow Chart

Pre-specified final analyses at n=797



*Artifacts in pressure or ECG recording: 109; pressure drift documented: 70; pullback not recorded: 34; other: 16

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Clinical and angiographic data

Patient characteristics	%
Age (years)	64±11*
Gender (Male)	69
Hypertension	78
Diabetes	35
Smoker	22
Prior MI	34
Clinical presentation:	
- Stable angina	54
- Unstable angina	25
- Silent ischemia	12
- NSTEMI (>48 hr)	6
- STEMI (>48 hr)	3

Stenoses characteristics	%
Diameter stenosis *(visual assessment)*	59.7±13.2*
Lesion Type	
- A	34.9
- B1/B2	52.2
- C	12.9
Vessel	
-LAD	54.4
-LCX	25.7
-RCA	19.9

*mean ± SD

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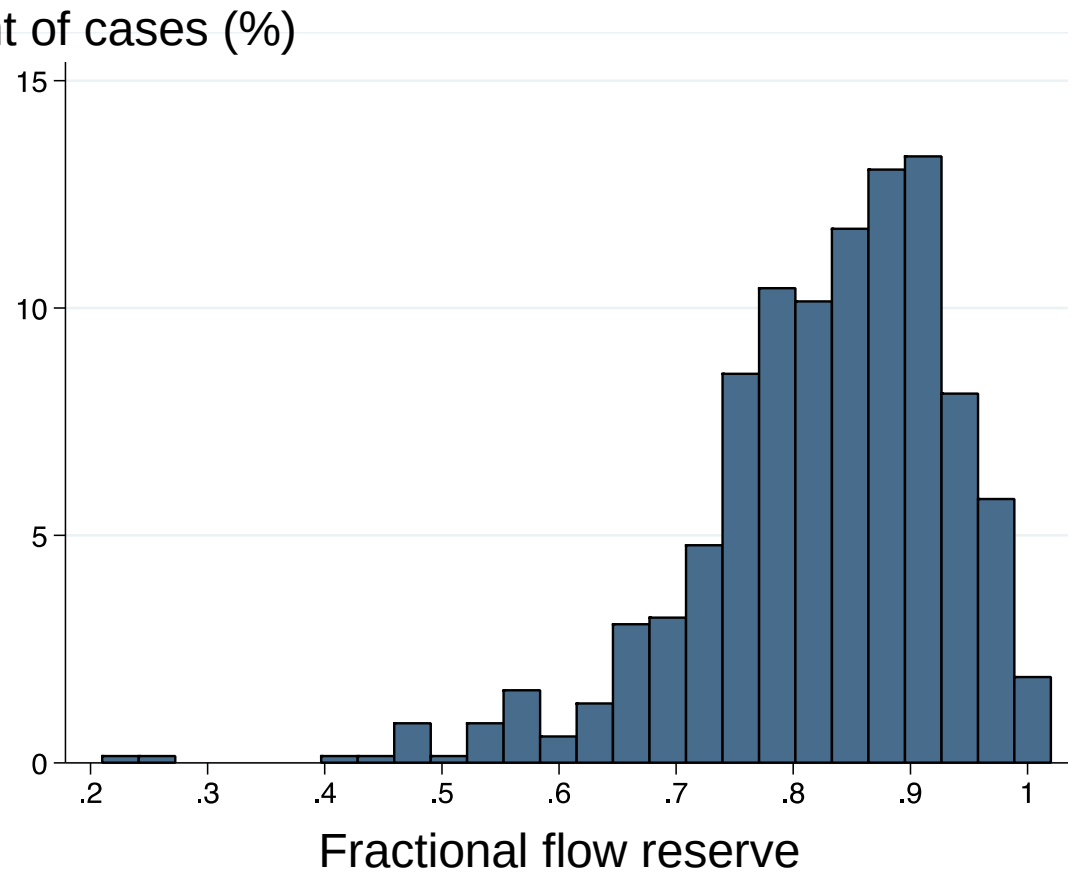
Stenosis severity (FFR)

FFR:

- Mean ± SD = 0.83 ± 0.11
- Median (IQR) = 0.84 (0.77, 0.90)
- FFR ≤ 0.80 = 36%
- FFR < 0.75 = 21%
- FFR 0.60 to 0.90 = 73%



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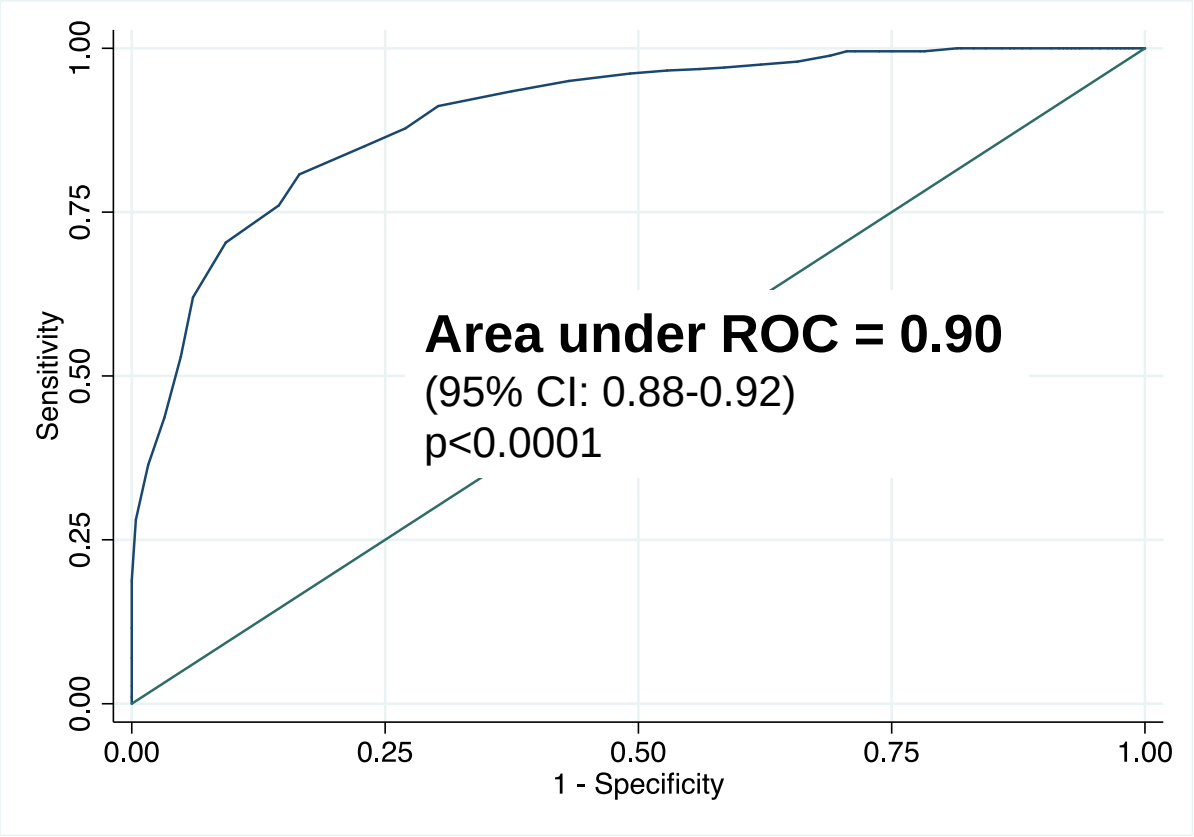
Overall The Diagnostic accuracy of iFR

- 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%



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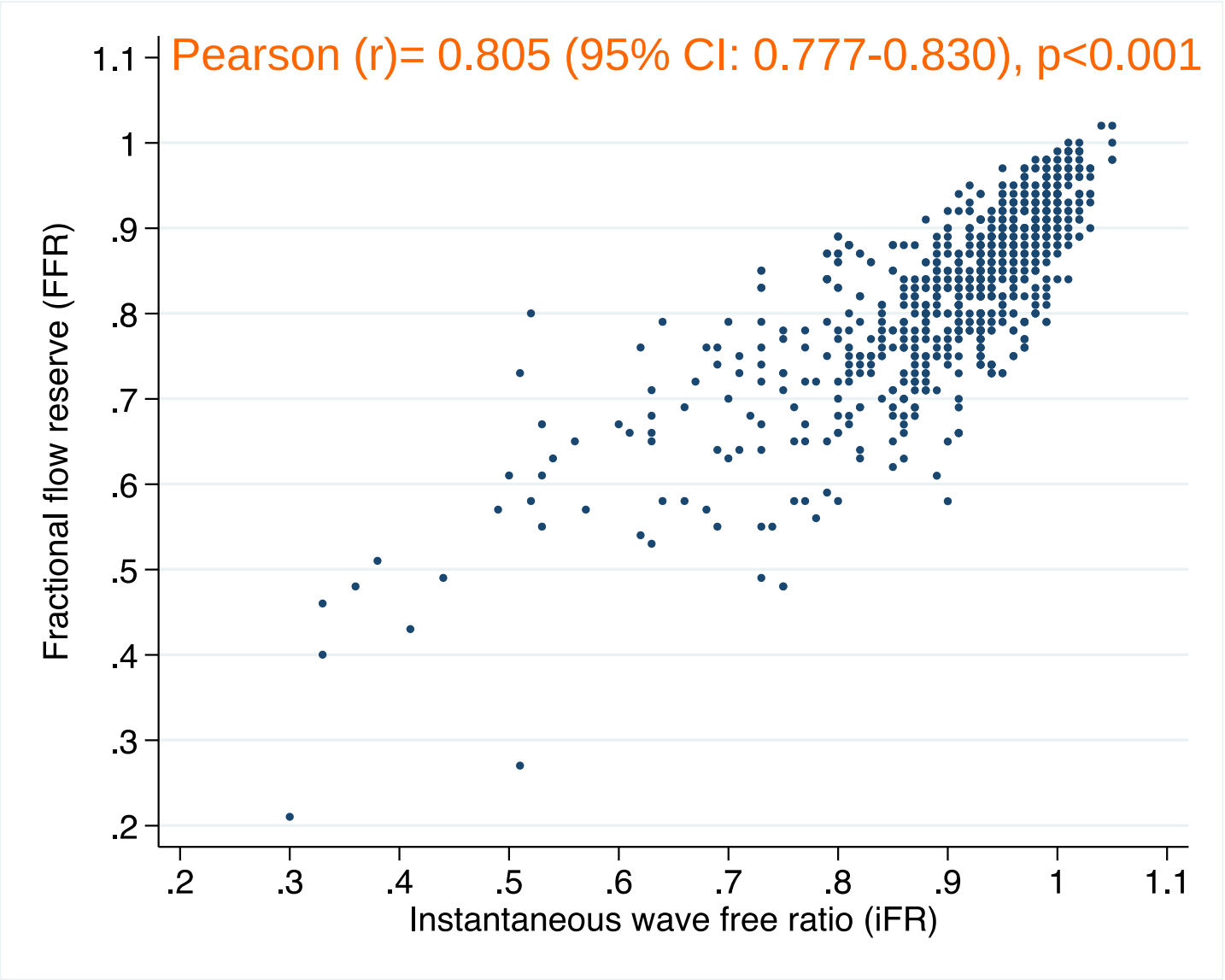
Scatterplot of iFR vs FFR



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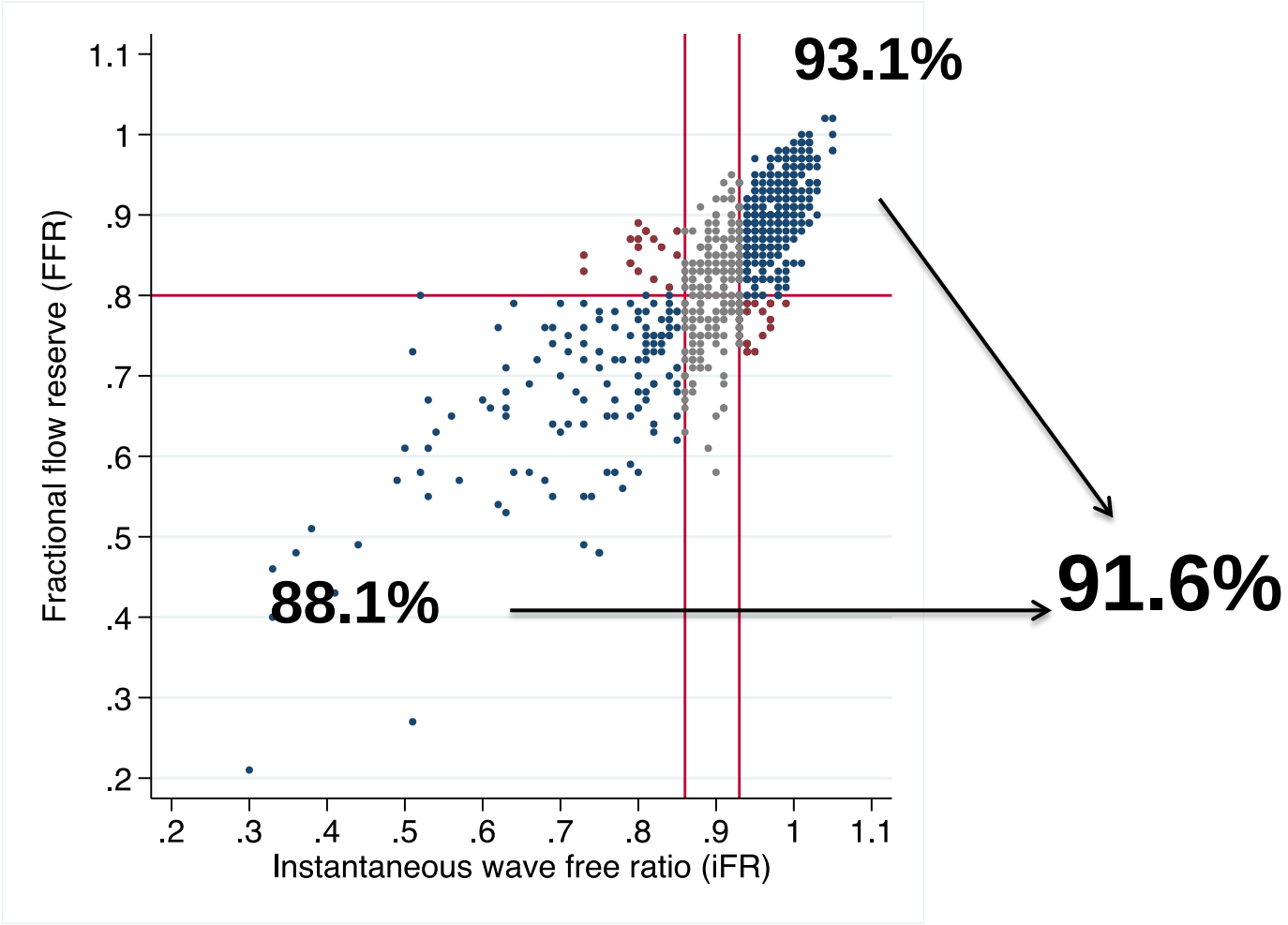
Primary Endpoint

Percentage of stenoses properly classified in terms of hemodynamic severity by iFR (outside ≤ 0.85 iFR ≥ 0.94



The percentage of stenoses properly classified in terms of hemodynamic severity by iFR (outside ≤ 0.85 iFR ≥ 0.94) was 91.6%

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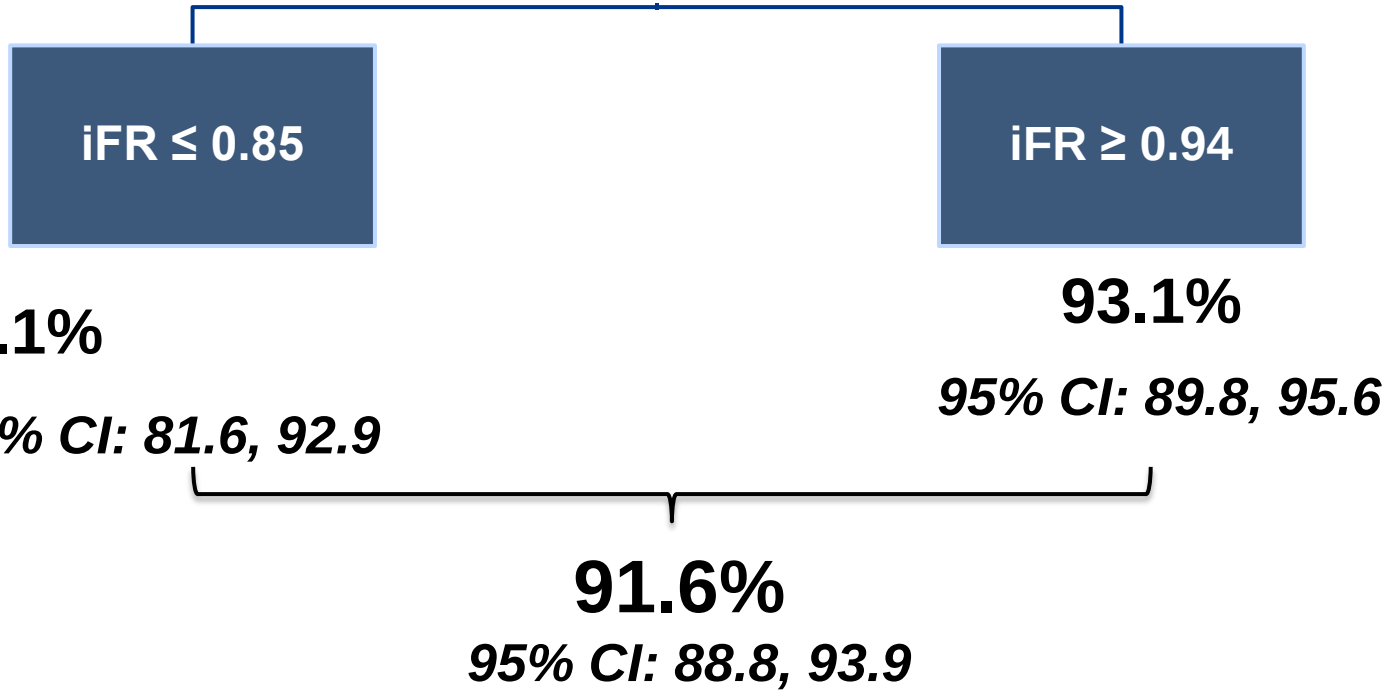
Primary Endpoint

The percentage of stenoses properly classified in terms of hemodynamic severity by iFR (outside ≤ 0.85 iFR ≥ 0.94) was **91.6%**



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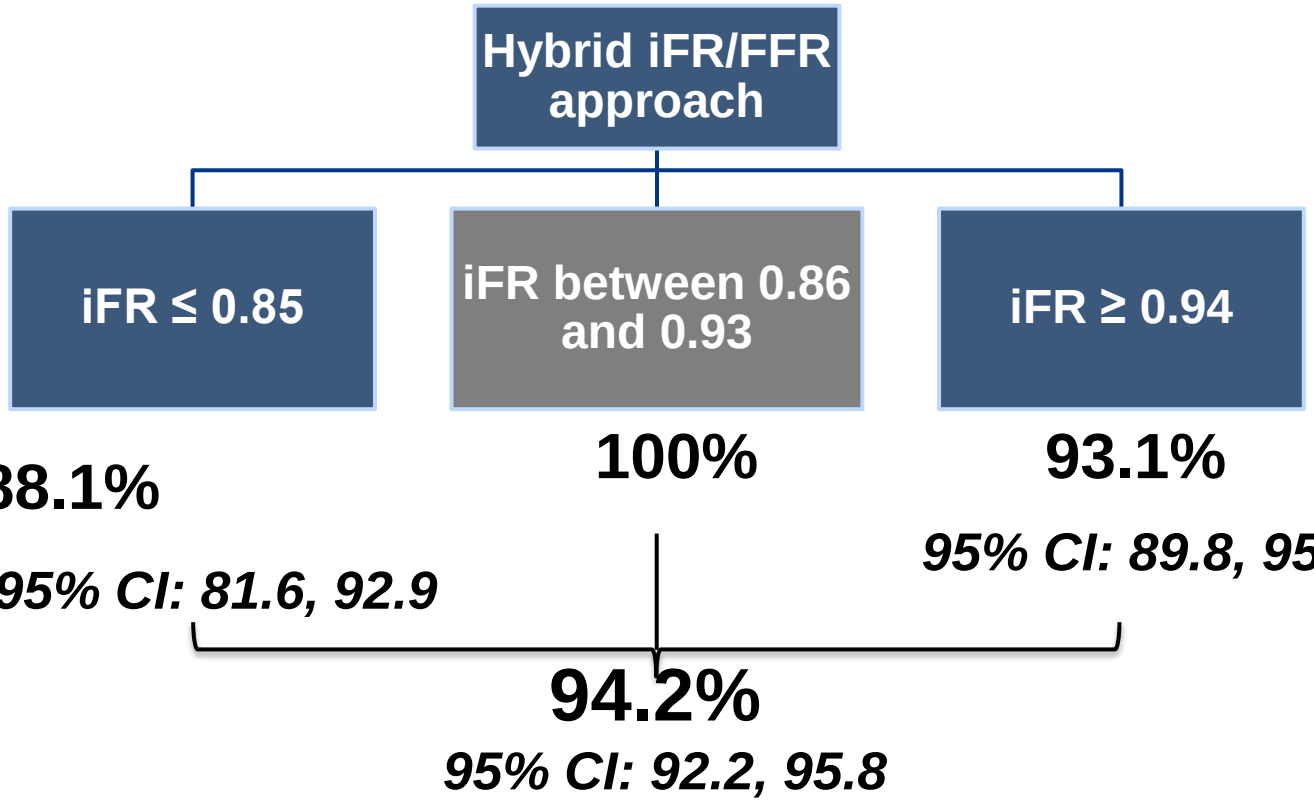
Hybrid iFR/FFR Approach

The percentage of stenoses properly classified by using the hybrid iFR/FFR approach was **94.2%**.



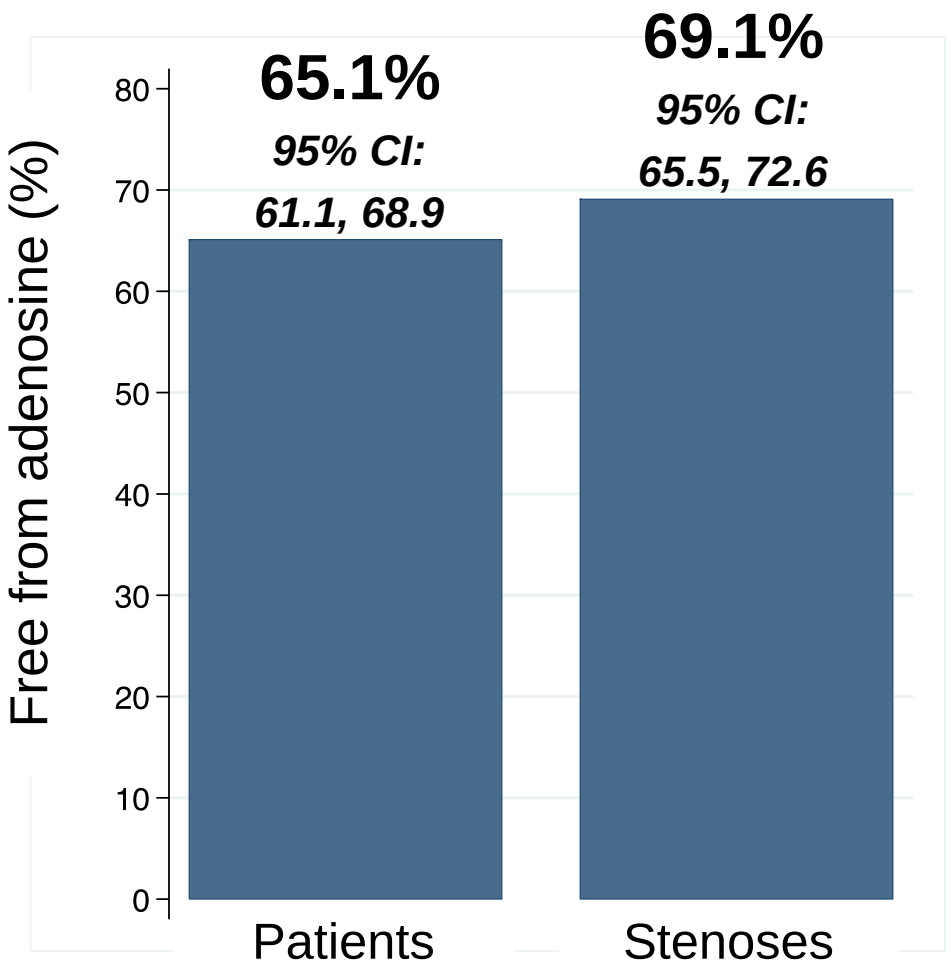
Sensitivity: 90.73%

Specificity: 96.15%

PPV: 92.98%

NPV: 94.87%

Estimated saving from adenosine in a hybrid iFR-FFR approach



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	iFR	FFR
Pressure Wire	✔	✔
Hyperemia free	✔	✗
Typical measurement time	5 seconds	2-10 min
Pressure damping unlikely	✔	✗
Cost saving(add to FAME)	Adenosine / Time Equipment	✗
Side effects	✔	✗
Optimized for pullback	✔	✗
Rapid peri-PCI assessment	✔	✔
Evidence against ischemia	Coming!	✔

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Summary

- iFR is simple to perform, and lowers the barriers for physiological assessment
- iFR and FFR are ***equal*** at significant stenoses
- iFR has **widest dynamic range of any resting index**

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