ADVISE II

ADenosine ***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.

Javier Escaned MD PhD FESC
on behalf of the ADVISE II Study Team

Potential Conflicts of Interest

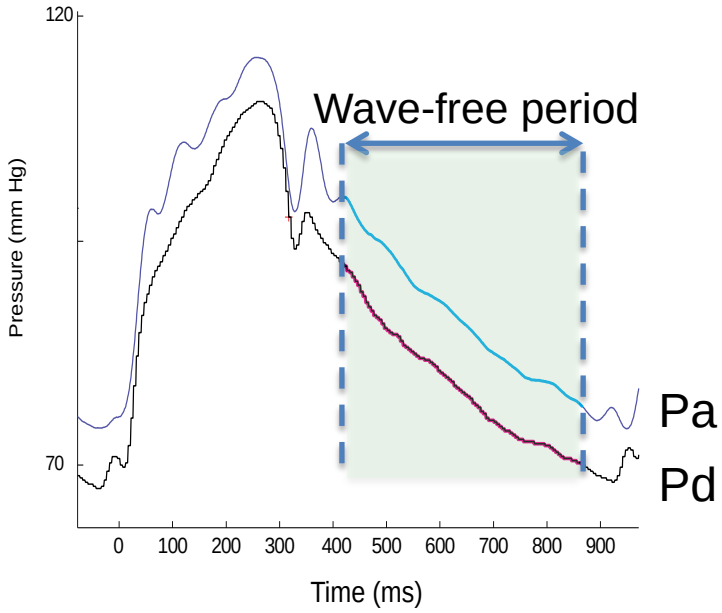
- **ADVISE II** is a study registered at ClinicalTrials.gov (NCT01740895)
- Sponsor of the study: Volcano Corporation
- Speaker's name: Javier Escaned
- Potential conflicts of interest regarding the topics of this presentation:
  - Speaker at educational events: Boston Scientific, St. Jude Medical, Volcano Corporation

Background

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

- iFR has generated considerable interest among cardiologists. Since its introduction in TCT 2011, >1,500 comparisons of **iFR** and fractional flow reserve (**FFR**) have been reported.

- 15 entries on **iFR** made in PubMed in <2 years.



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 EKG 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

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.

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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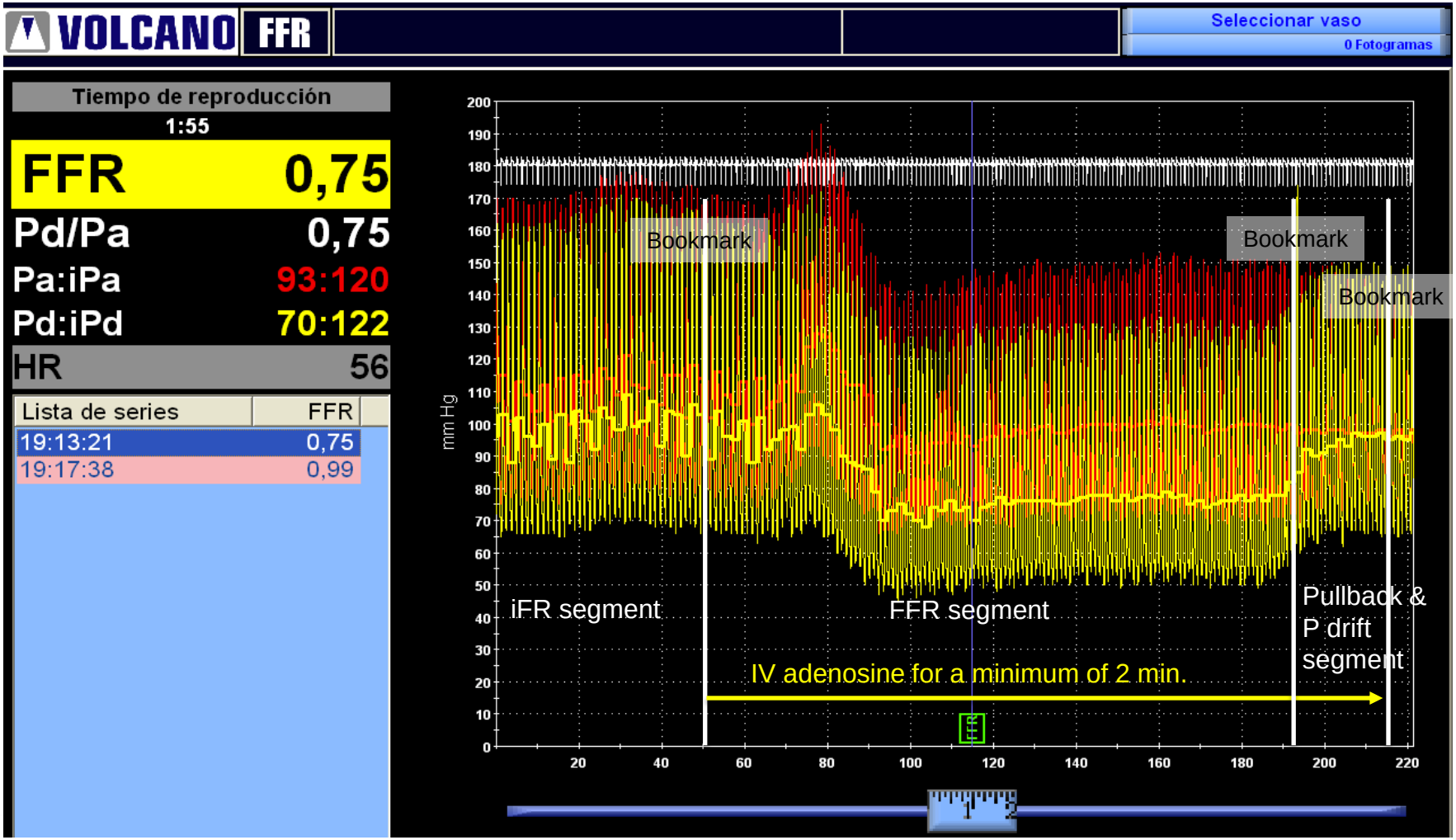
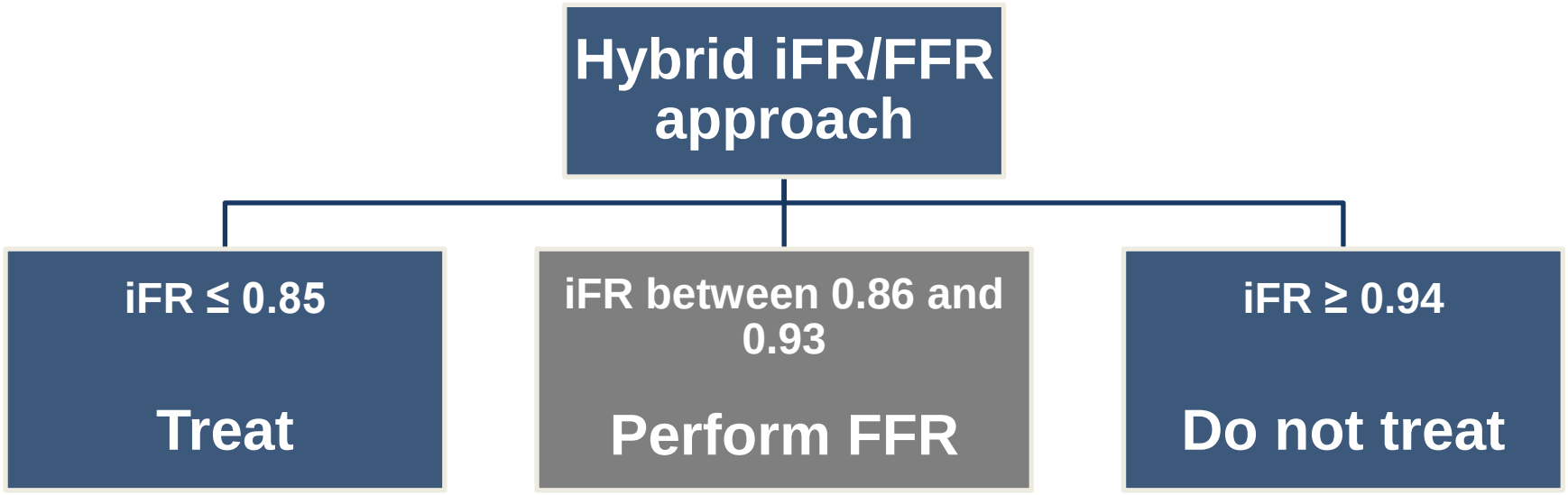
Standardized data collection



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

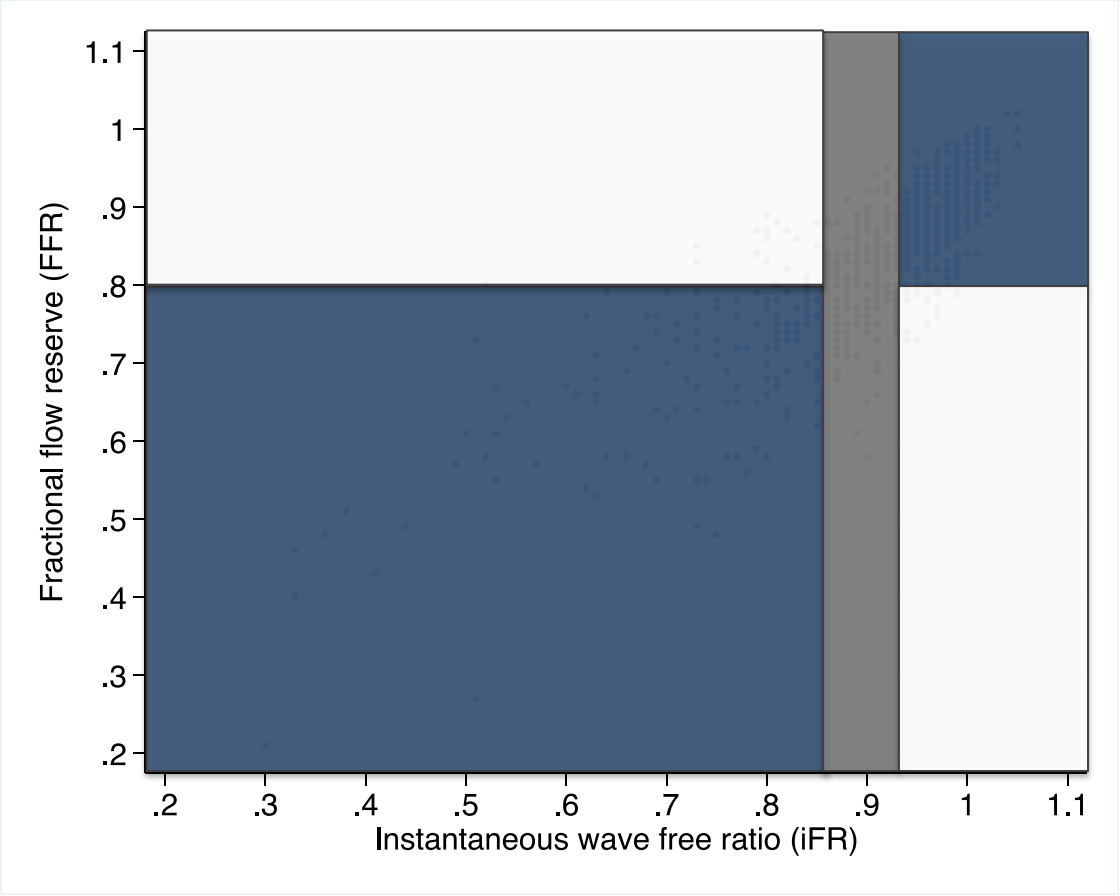
Primary endpoint

- 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

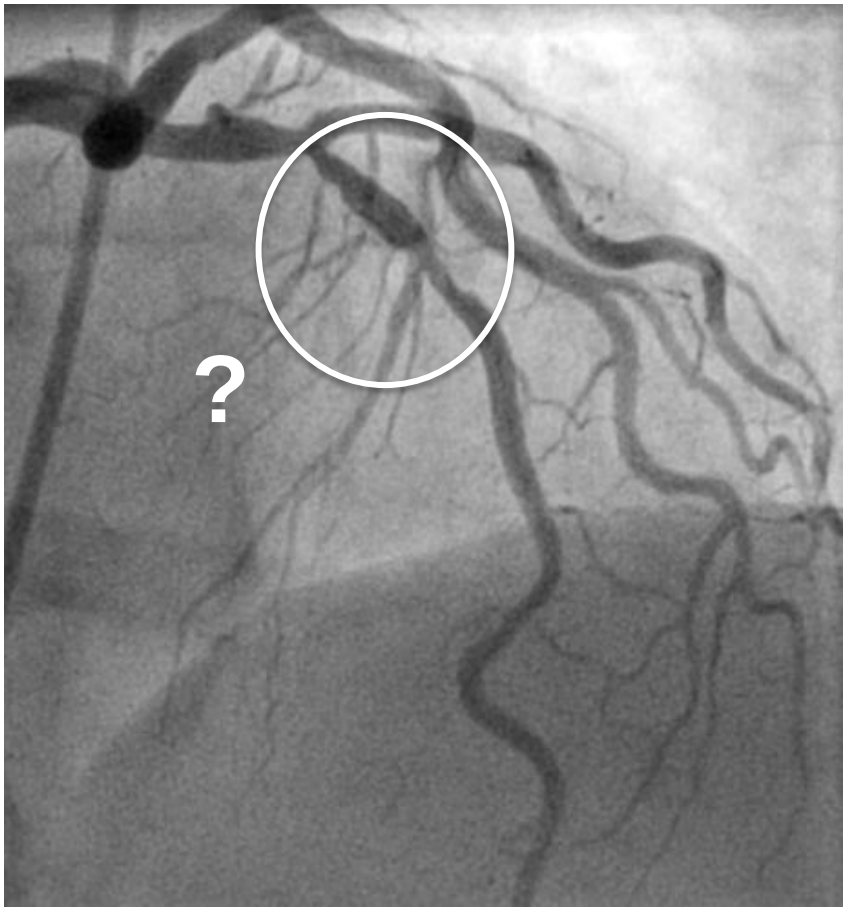


Secondary endpoints

- 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.

Inclusion criteria

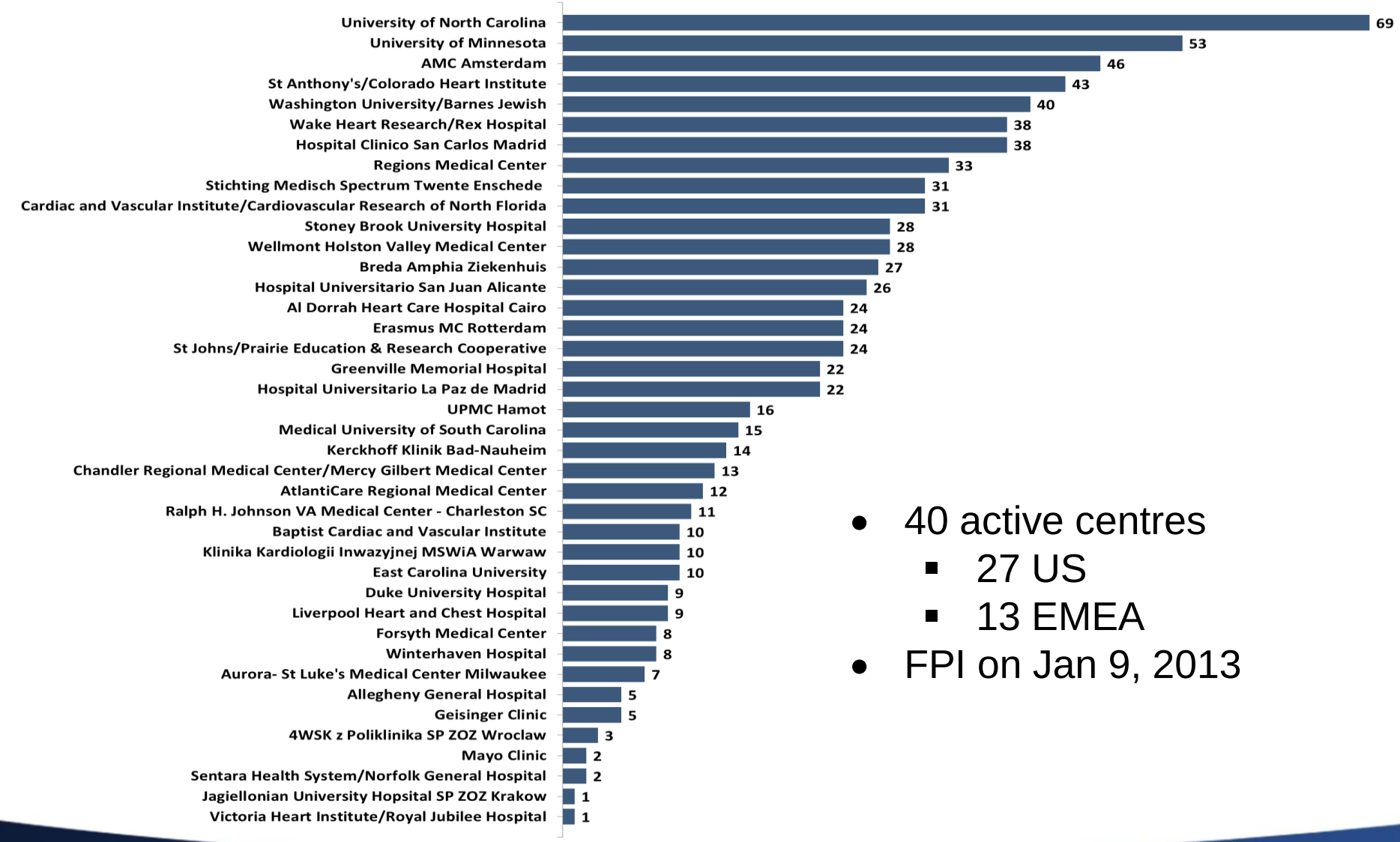
- Age ≥ 18 and ≤ 85 years.
- Willing to participate and able to understand, read and sign the informed consent document before the planned procedure.
- Eligible for coronary angiography and/or percutaneous coronary intervention.
- One or more stenoses DS>40% (visual assessment).
- Stable angina or acute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



Exclusion criteria

- Known contraindication to adenosine administration.
- Contrast allergy.
- Cardiac pacemaker, 1st or 2nd degree AV block, LBBB.
- STEMI or non-STEMI within 48 hours of procedure.
- Severe vessel tortuosity and/or severe calcification by angiogram.
- Significant (moderate or severe) valvular pathology
- Previous CABG with patent grafts to the interrogated vessel.
- Weight >200kg (441 lbs.).
- Hemodynamic instability at the time of intervention.
- Significant hepatic, renal or lung disease / malignancy with poor prognosis.
- Left main stenosis, downstream stenoses, CTOs.
- Known left ventricular ejection fraction (LVEF) ≤ 30.

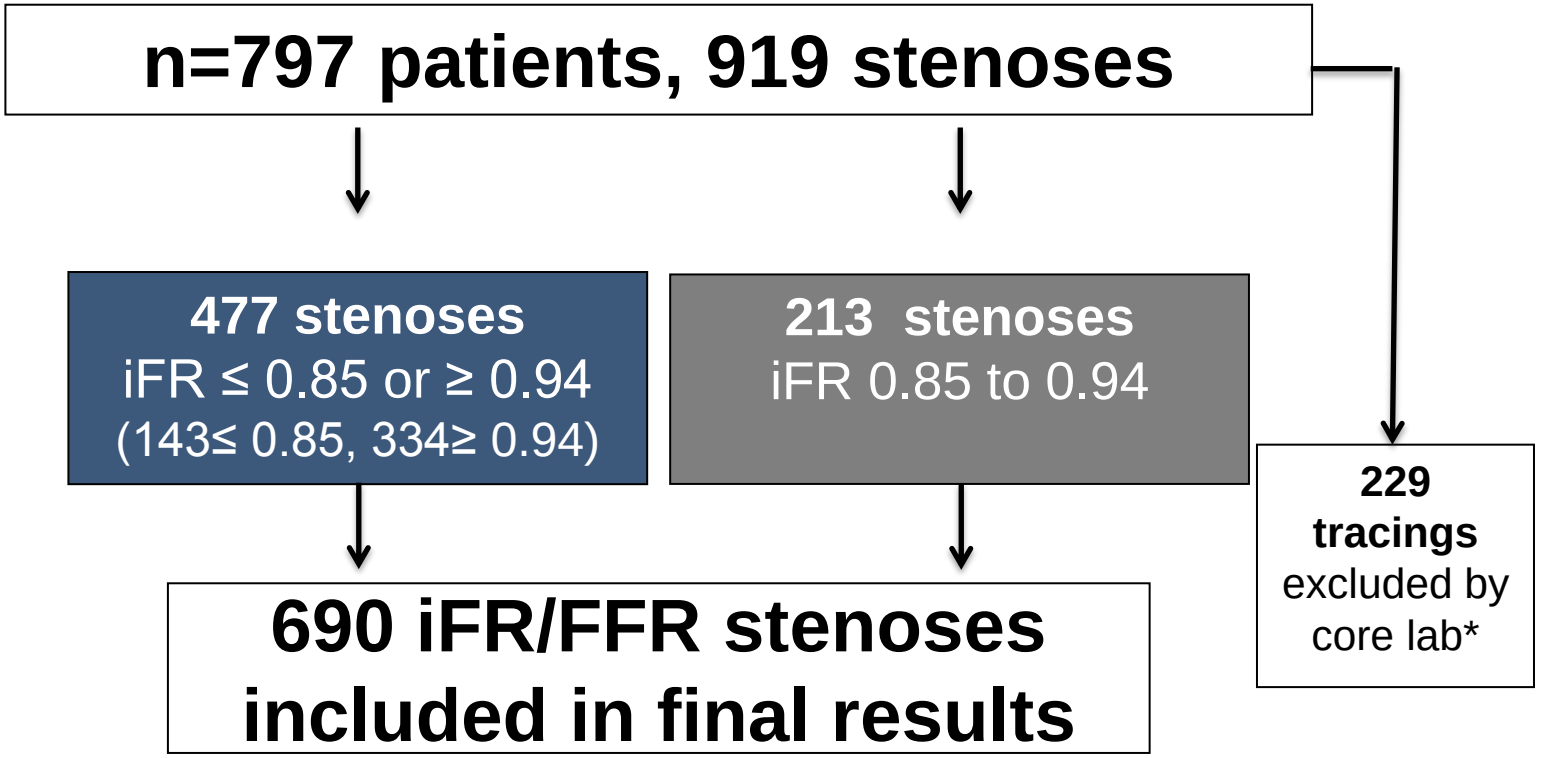
Enrollment and Participating Centres



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

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

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

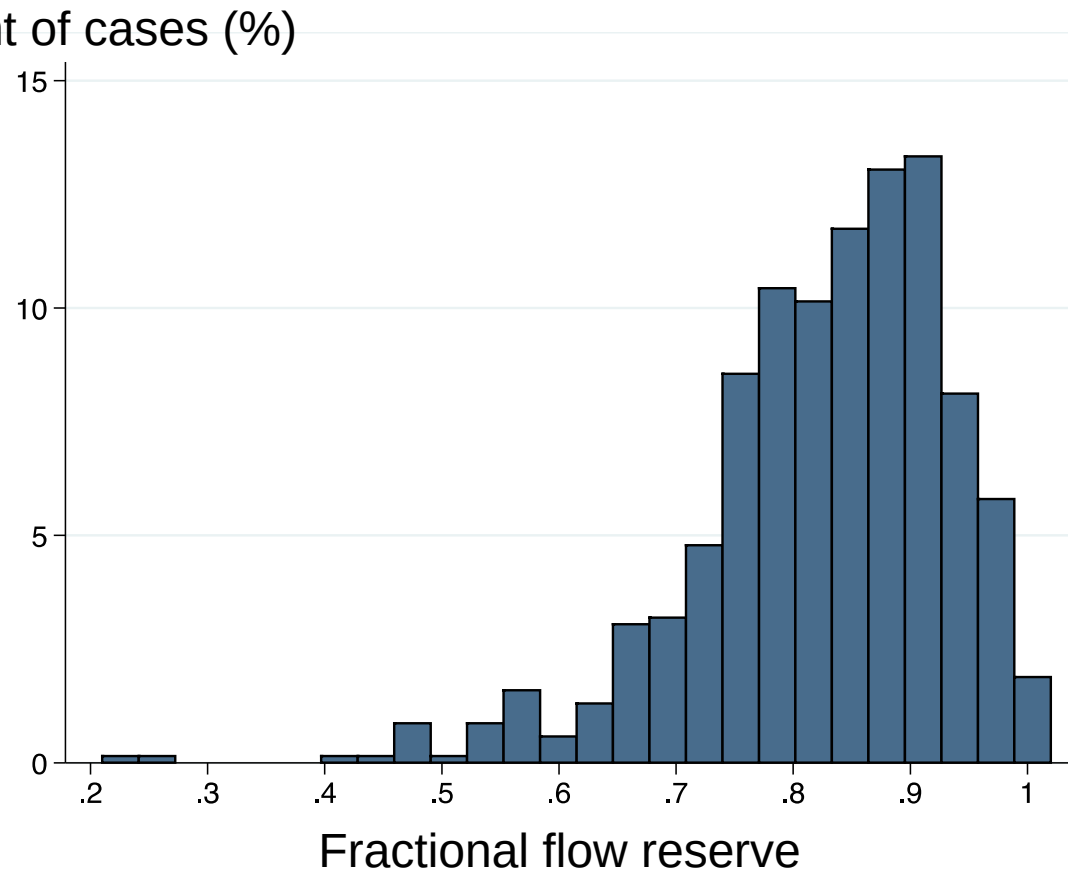
Stenoses characteristics	%
Diameter stenosis *(visual assessment)*	59.7±13.2*
Lesion Type	
- A	34.9
- B1/B2	52.2
- C	12.9
Vessel	
-LAD	54.4
-LCX	25.7
-RCA	19.9

*mean ± SD

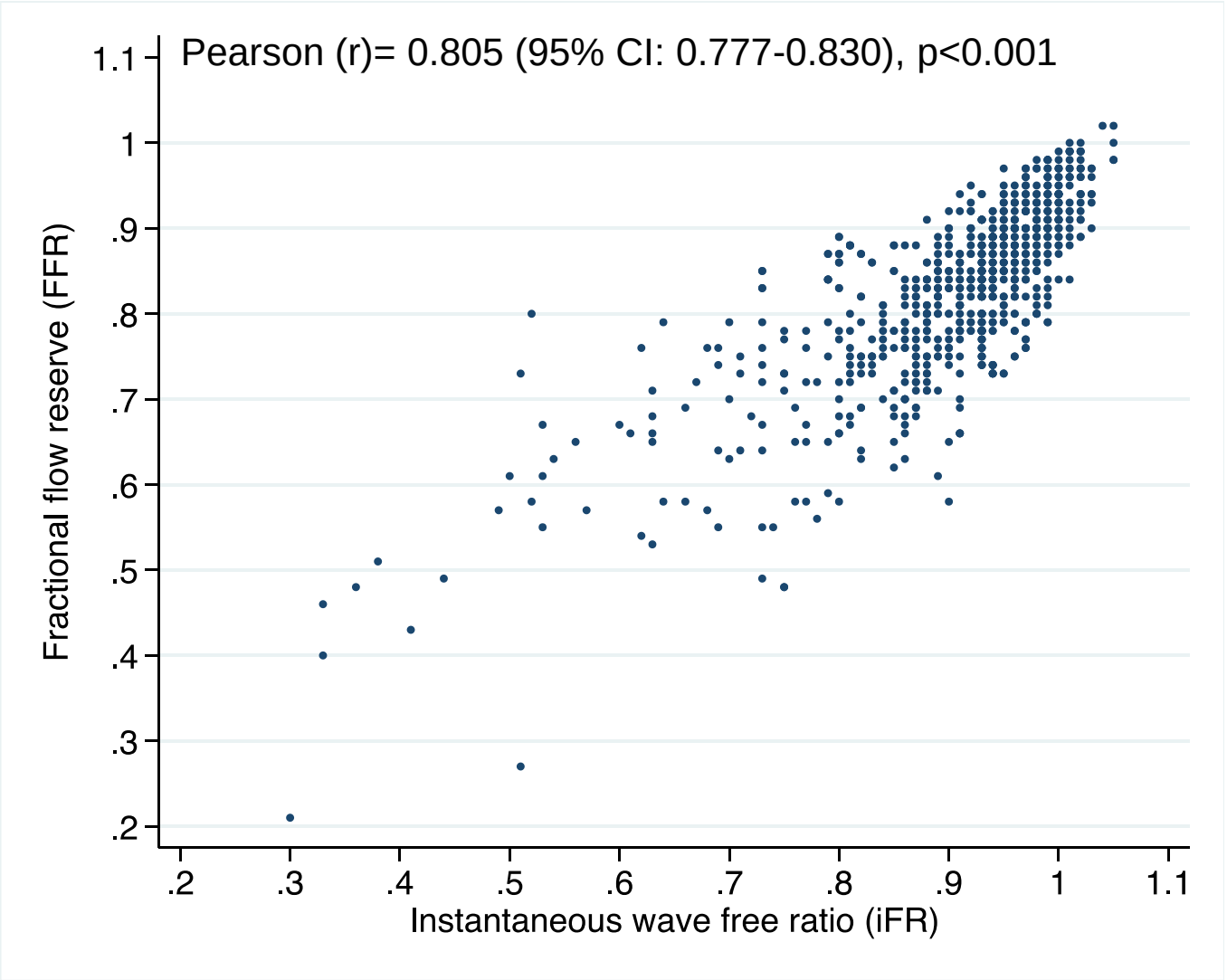
Stenosis severity (FFR)

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%

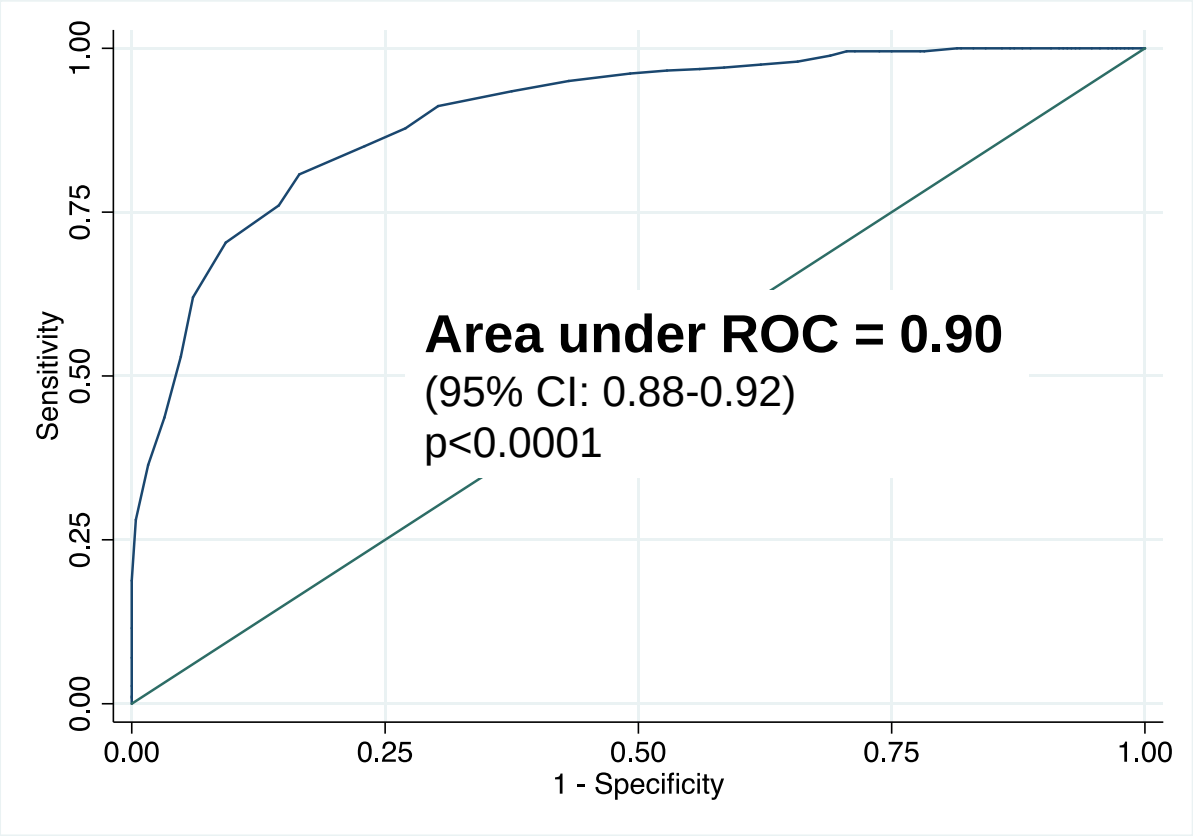


Scatterplot of iFR vs FFR



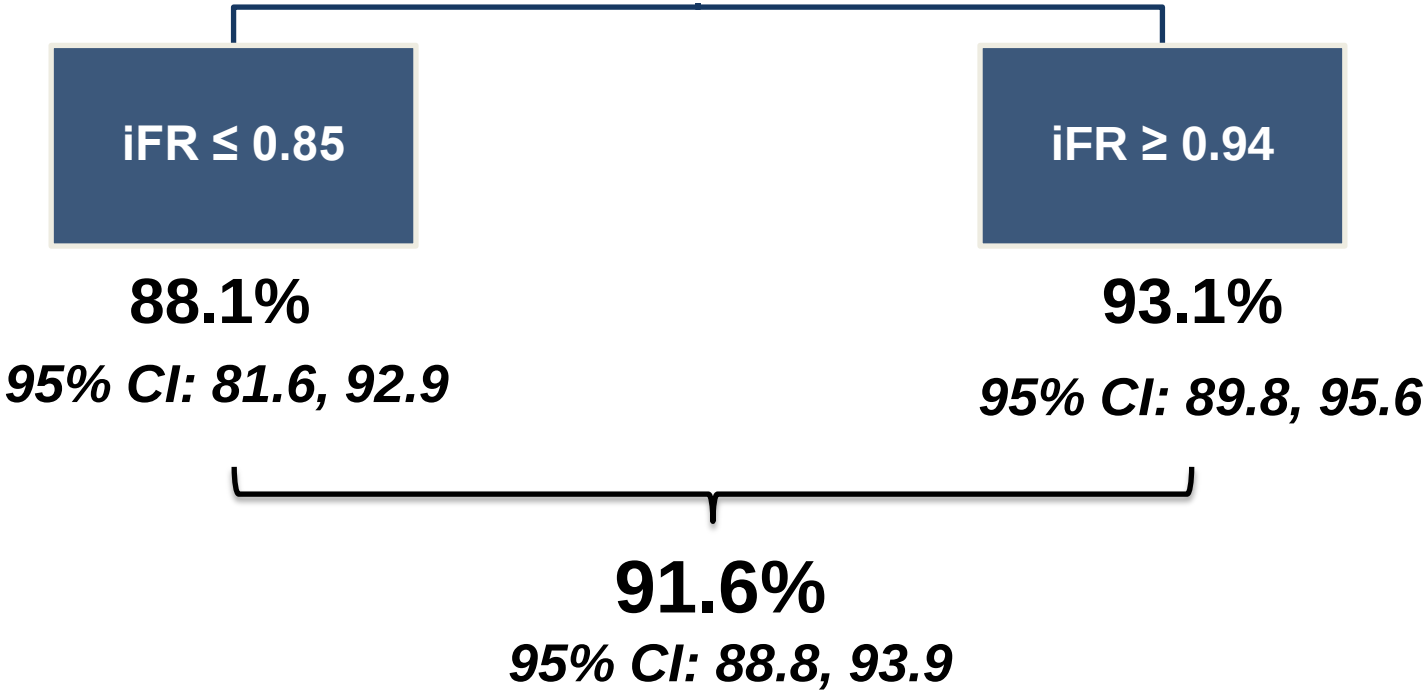
Diagnostic accuracy of iFR

- 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%

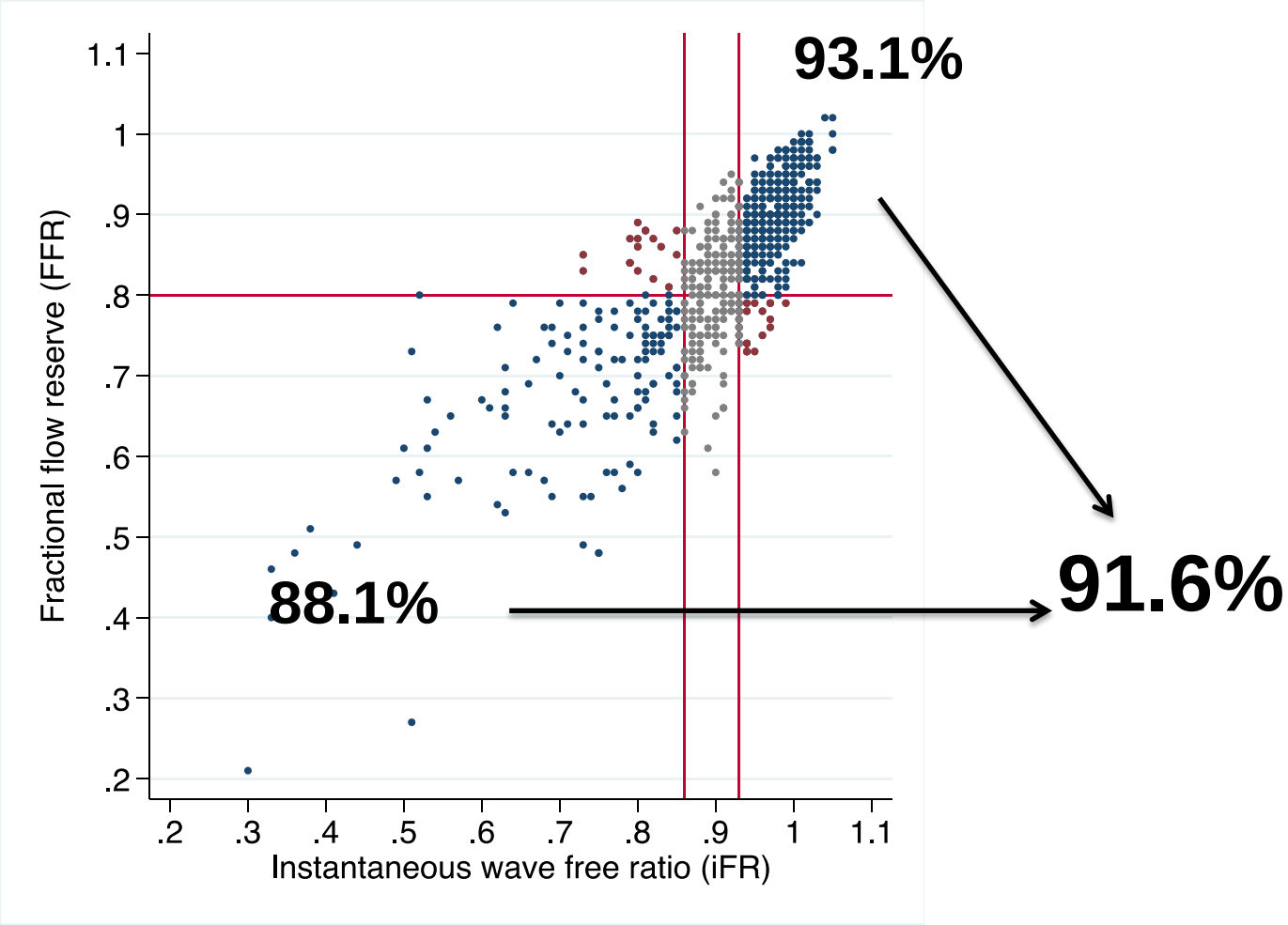


Primary endpoint

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



Primary endpoint



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

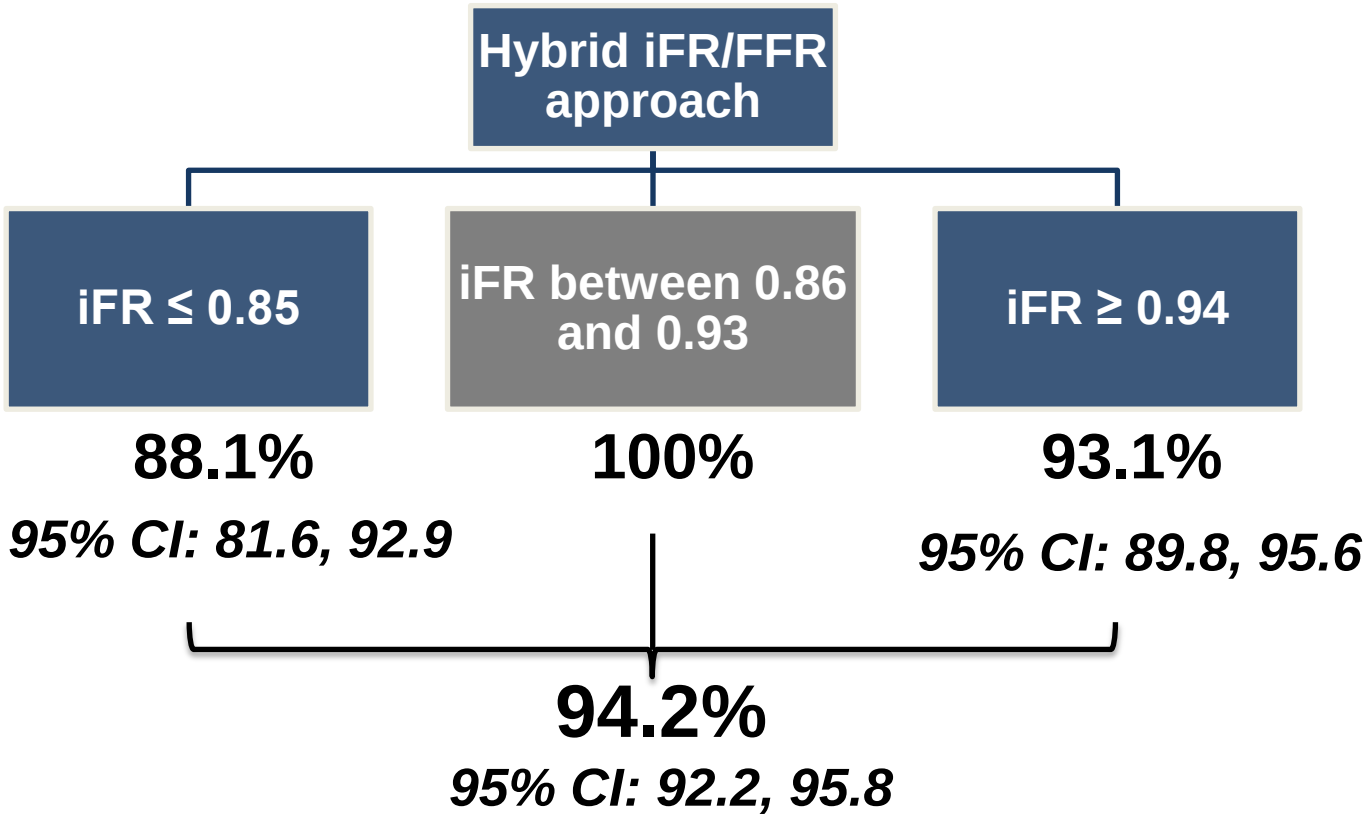
Secondary endpoint

Minimum iFR exclusion ranges around iFR 0.89 in which iFR and FFR agreement is equal to or greater than 80% and 90%.

Minimum required percentage agreement	iFR Exclusion range	Number of iFR stenoses assessed	Number of iFR stenoses with agreement	Percentage agreement
80%	---	690	569	**82.46%**
90%	0.87-0.93	497	452	**90.95%**
95%	0.79-0.94	364	347	**95.33%**

Hybrid iFR/FFR approach

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



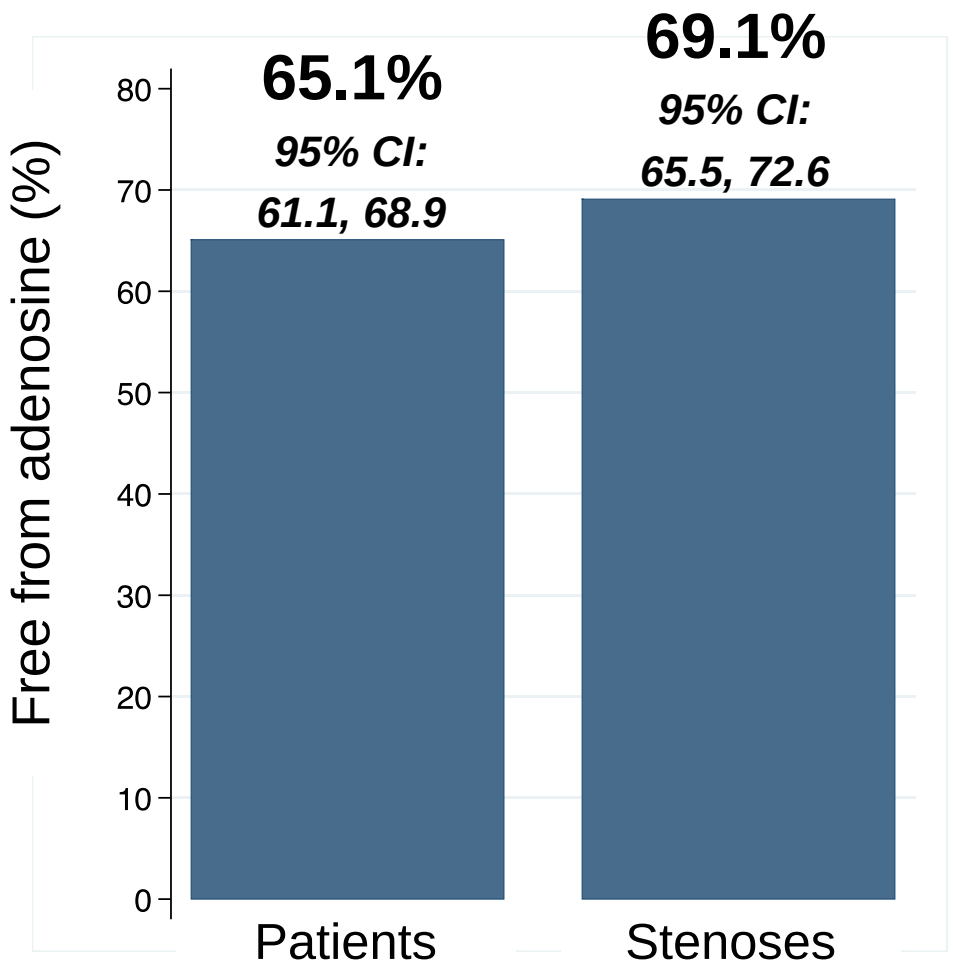
Sensitivity: 90.73%

Specificity: 96.15%

PPV: 92.98%

NPV: 94.87%

Estimated saving from adenosine in a hybrid iFR-FFR approach



Conclusions

- In ADVISE II, **iFR characterized correctly 91.6%** of the stenoses in terms of hemodynamic severity, **outside the pre-specified ≤0.85 and ≥0.94 values**.

- Overall, a **hybrid iFR/FFR approach** would **avoid usage of adenosine in 69.5%** of interrogated stenoses **whilst classifying correctly 94.2%** of them in terms of hemodynamic severity.

ADVISE II Study Team

Participating Centres and Investigators

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