AARHUS UNIVERSITY

FAVOR II E-J

Diagnostic Accuracy of On-line Quantitative Flow Ratio Functional Assessment by Virtual Online Reconstruction:

FAVOR II Europe-Japan

On behalf of the **FAVOR II** study group

Jelmer Westra

PCI Research
Aarhus University Hospital, Skejby ● Denmark

Aarhus University Hospital

Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Medis medical imaging bv.
• Consulting Fees/Honoraria	• Medis medical imaging bv.

Funding

The study was funded by Aarhus University Hospital, Skejby and participating institutions.

Medis Medical Imaging bv. provided no funding for the study except limited travel arrangements for initiation and monitoring visits.

The QFR solution was made available for free during the study period.

Background

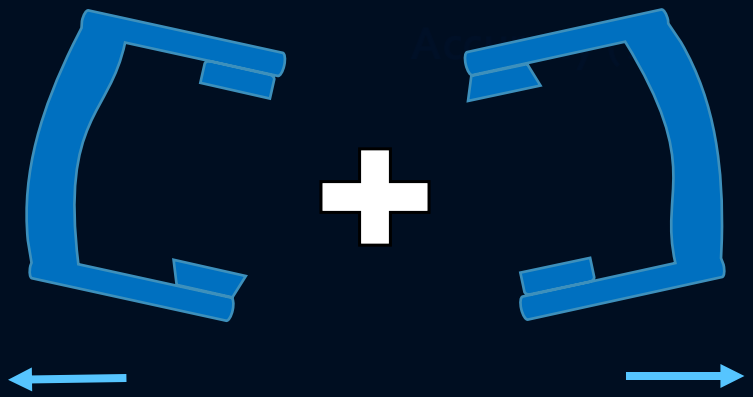
Angiographic based functional lesion evaluation may appear as a cost saving alternative to pressure wire based assessment

Off-line QFR computation has good diagnostic performance and agreement with FFR as reference standard*

In-procedure feasibility and diagnostic performance of QFR is unknown

*Tu et al.; JACC Cardiovasc Interv 2016
Westra et al.; WIFI II, TCT 2016

QFR analysis



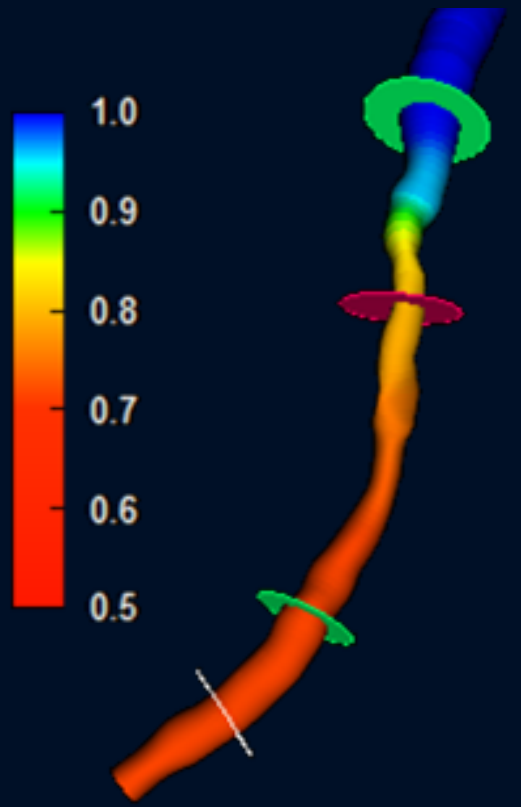
> 25 ° apart

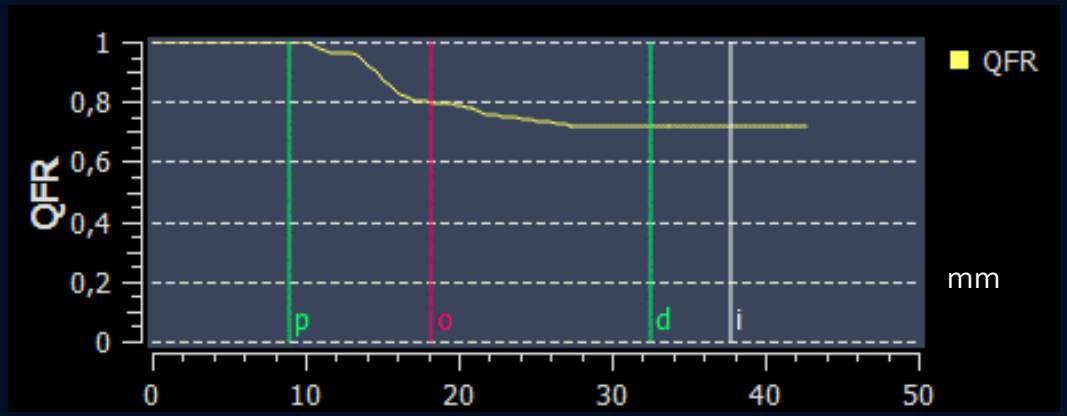
QFR is computed from:

- lumen contours in two standard angiographic projections
- contrast flow velocity estimated by frame count during baseline conditions

QFR by Medis Suite, Medis medical imaging. CE-marked. Not approved for clinical use in the US.

QFR analysis





QFR is an estimate of FFR based on:

- fluid dynamic equations
- emulated hyperaemic flow velocity

QFR by Medis Suite, Medis medical imaging. CE-marked. Not approved for clinical use in the US.

Hypothesis

QFR has superior sensitivity and specificity for detection of functional significant lesions in comparison to 2D-QCA with FFR as gold standard

Design

- Investigator initiated study
- Observational
  - Paired acquisition of FFR and computation of QFR
  - Site specific protocol for effective blinding
  - Strict protocol for QFR analysis
  - More than one study vessel pr. patient allowed
- Planned enrolment of 310 patients
- 11 hospitals in Europe and Japan
- Enrolment period: March 2017 to October 2017

Participating sites

1. Department of Cardiology, Aarhus University Hospital, Skejby, Denmark
   Dr. Niels R. Holm, Jelmer Westra, Omeed Neghabat, Prof. Hans Erik Bøtker, Dr. Evald Høj Christiansen
2. Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy
   Dr. Gianluca Campo, Dr. Matteo Tebaldi
3. The Department of Cardiovascular Medicine; Gifu Heart Center, Gifu City, Japan
   Dr. Hitoshi Matsuo, Dr. Toru Tanigaki
4. Department of Cardiology, Medical University of Warsaw, Warszawa, Poland
   Dr. Lukasz Koltowski, Dr. Janusz Kochman
5. Department of Cardiology, Hagaziekenhuis, The Hague, The Netherlands
   Dr. Tommy Liu, Dr. Samer Somi
6. Federico II University of Naples, Naples, Italy
   Dr. Luigi Di Serafino, Dr. Giovanni Esposito
7. Azienda Ospedaliera Sant'Anna e San Sebastiano, Caserta, Italy
   Dr. Domenico Di Girolamo, Dr. Guseppe Mercone
8. Department of Cardiology, Hospital Clinico San Carlos, Madrid, Spain
   Prof. Javier Escaned, Dr. Hernán Mejía-Rentería
9. Department of Cardiology, University Clinic Giessen & Marburg, Giessen, Germany
   Prof. Holger Nef
10. Klinik für Kardiologie und Angiologie, Essen, Germany
    Dr. Christoph Naber
11. Cardiovascular Department, Ospedale dell'Angelo, Mestre-Venezia, Italy
    Dr. Marco Barbierato, Dr. Federico Ronco

Study organisation

Study chair: Niels Ramsing Holm, Aarhus University Hospital
Co-chair: Evald Høj Christiansen, Aarhus University Hospital
Co-chair: William Wijns, Lamb institute, Ireland

Steering committee: Study chairs. Site primary investigators

Statistics committee: Morten Madsen, Dep. of Clinical Epidemiology, Aarhus University Hospital

QFR tech committee: Jelmer Westra Aarhus University Hospital

FFR core lab: Ashkan Eftekhari, Institute of Clinical Medicine, Aarhus University

QCA core lab: ClinFact, The Netherlands

Trial database: Jakob Hjort, Institute of Clinical Medicine, Aarhus University

Academic study preparation: Birgitte Krogsgaard Andersen, Aarhus University Hospital

Academic research organization: PCI Research, Aarhus University Hospital

Primary endpoint

Sensitivity and specificity of :

QFR compared to two-dimensional QCA

- in assessing functional stenosis relevance

with FFR as reference standard

Sample size

- FAVOR pilot study showed **sensitivity 0.74** and **specificity 0.91***
- Null hypothesis
  - Specificity (QFR) = Specificity (50% DS 2D-QCA)
  - Sensitivity (QFR) = Sensitivity (50% DS 2D-QCA)
- Beta 0.80, alpha 0.05 and estimated FFR≤0.80 prevalence of 30 %
- 274 patients with paired QFR and FFR were needed

*Tu et al.; JACC Cardiovasc Interv 2016

Secondary endpoints

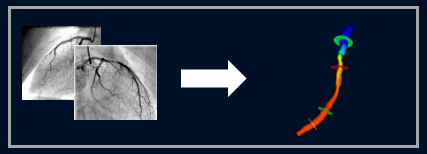
Diagnostic grey zone estimation

- QFR limits to yield 95% sensitivity and specifity with FFR as reference standard
- Feasibility of QFR in FFR assessed lesions
- Positive and negative predictive value of QFR with FFR as reference standard

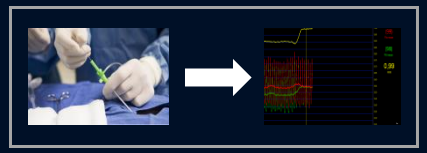
Secondary endpoints

Time to FFR vs. time to QFR

- Time to FFR: from introduction of pressure wire to final drift check conforming drift within limits



- Time to QFR: from start of image evaluation to completed QFR computation



Methods

Inclusion criteria

- Stable angina pectoris
- Evaluation of non-culprit stenosis after acute myocardial infarction

Exclusion criteria

- Myocardial infarction within 72 hours
- Severe asthma or severe chronic obstructive pulmonary disease
- Severe heart failure (NYHA≥III)
- S-creatinine>150µmol/L or GFR<45 ml/kg/1.73m2
- Allergy to contrast media or adenosine
- Atrial fibrillation at time of catheterization

Methods

Angiographic inclusion criteria

- Diameter stenosis of 30%-90% by visual estimate
- Reference vessel size > 2.0 mm in stenotic segment by visual estimate

Angiographic exclusion criteria

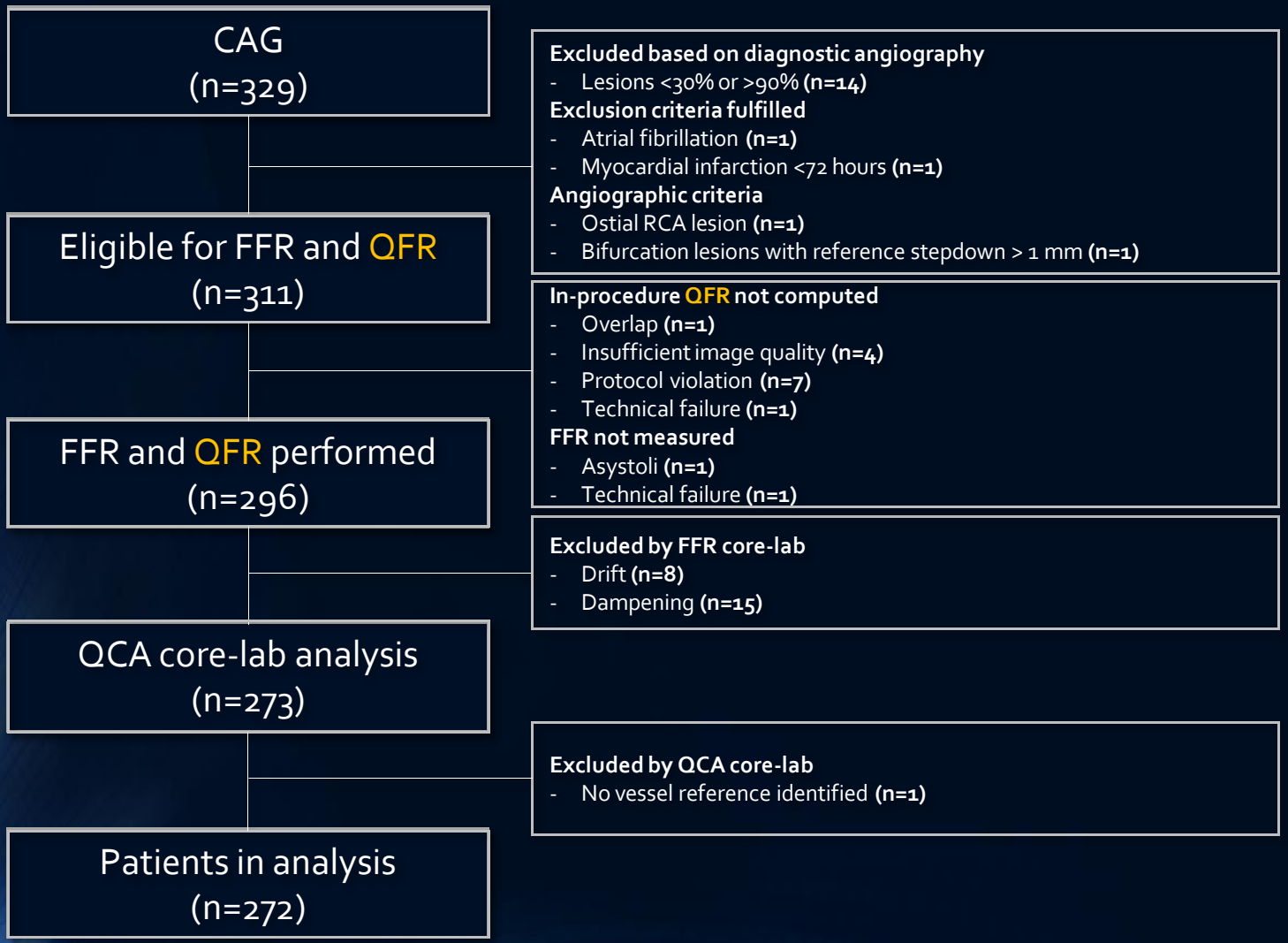
Lesion specific

- Below 30% and above 90% diameter stenosis by visual estimate
- Reference size of vessel below 2.0 mm by visual estimation
- Aorto-ostial lesions
- Bifurcation stenosis with lesions on both sides of a major shift (>1mm) in reference diameter

Angiographic quality

- Poor image quality precluding contour detection
- Good contrast filling not possible
- Severe overlap of stenosed segments
- Severe tortuosity of target vessel

Results - Flowchart



Results

Baseline characteristics	
Age (years)	67 ± 10
Male	196 (72%)
Smoking (current or past)	156 (57%)
BMI (kg/m²)	27 ± 5
Hypertension	201 (74 %)
Hyperlipidemia	186 (68%)
Diabetes	78 (29%)
Family history of CAD	73 (27%)
Ejection fraction (%)	56±10
Previous PCI	109 (40%)
Previous CABG	11 (4%)

Values are n(%) and mean ±SD

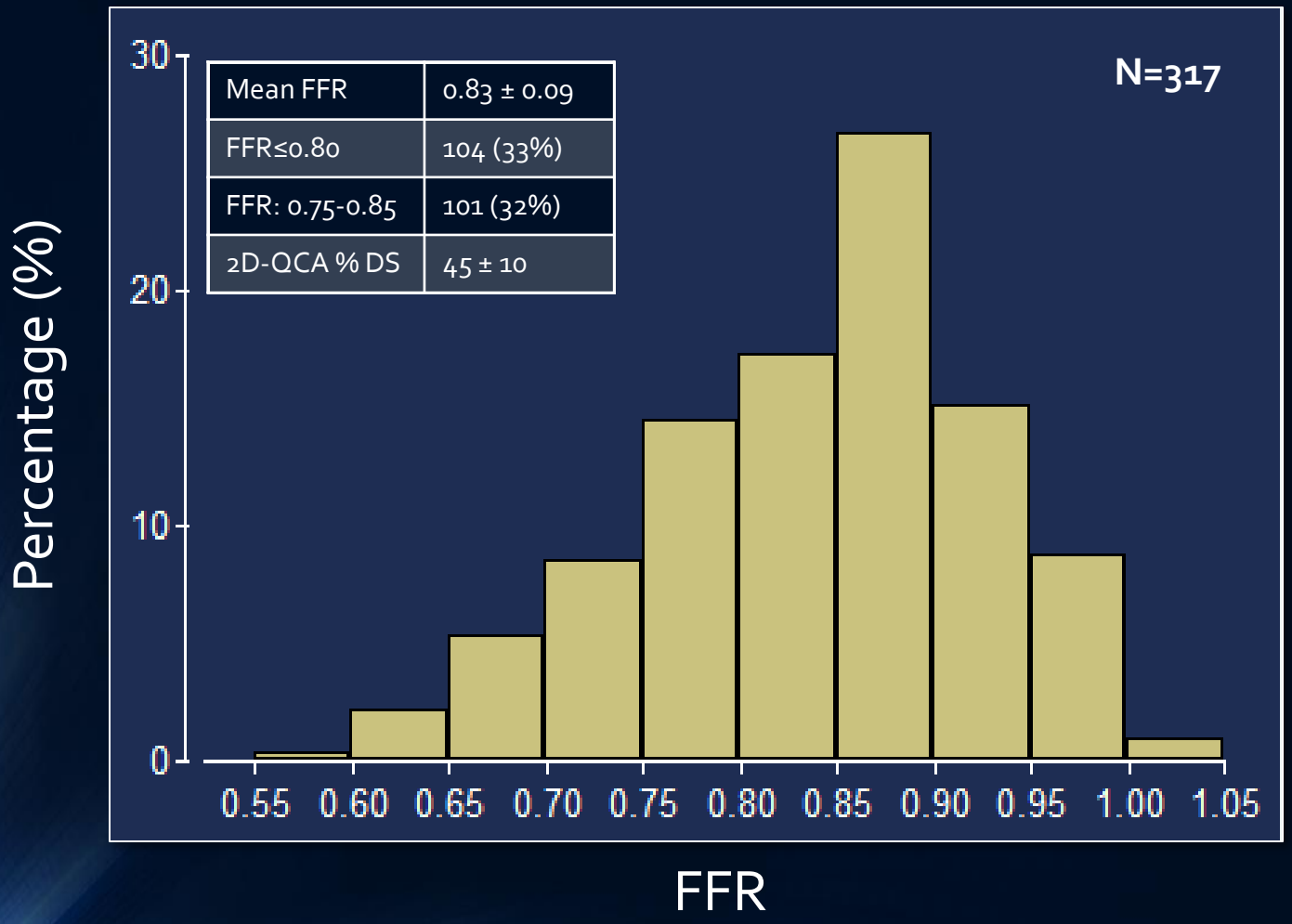
Results

Clinical presentation	
CCS 0	54 (20%)
CCS I	67 (25%)
CCS II	122 (45%)
CCS III	14 (5%)
CCS IV	1 (0%)
Secondary evaluation of NCPL	6 (2%)
Other (dyspnea, arythmia)	8 (3%)

Values are n(%)

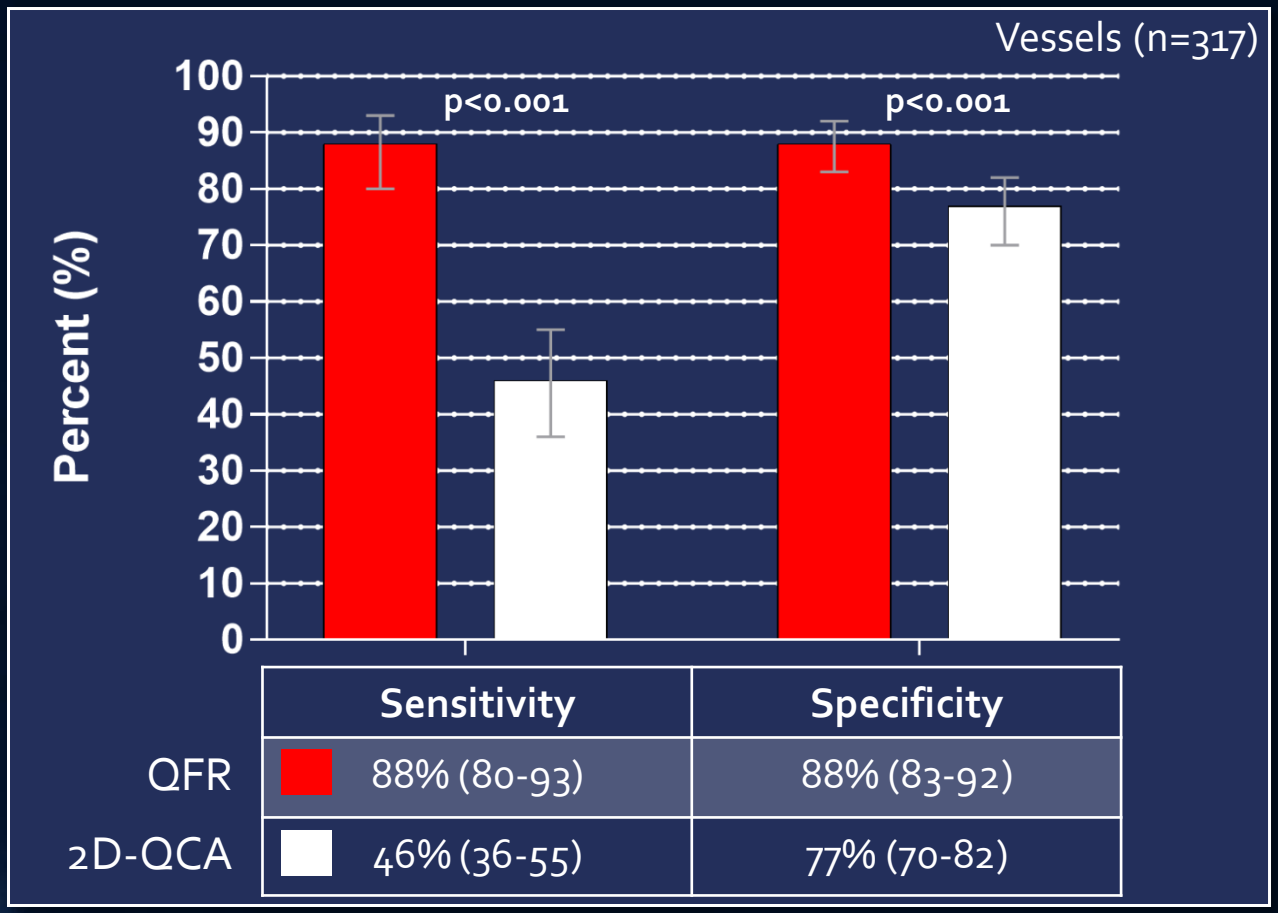
CCS: Canadian Cardiovascular Society grading of angina pectoris; NCPL: Non-culprit lesions

Results – FFR distribution



Primary endpoint

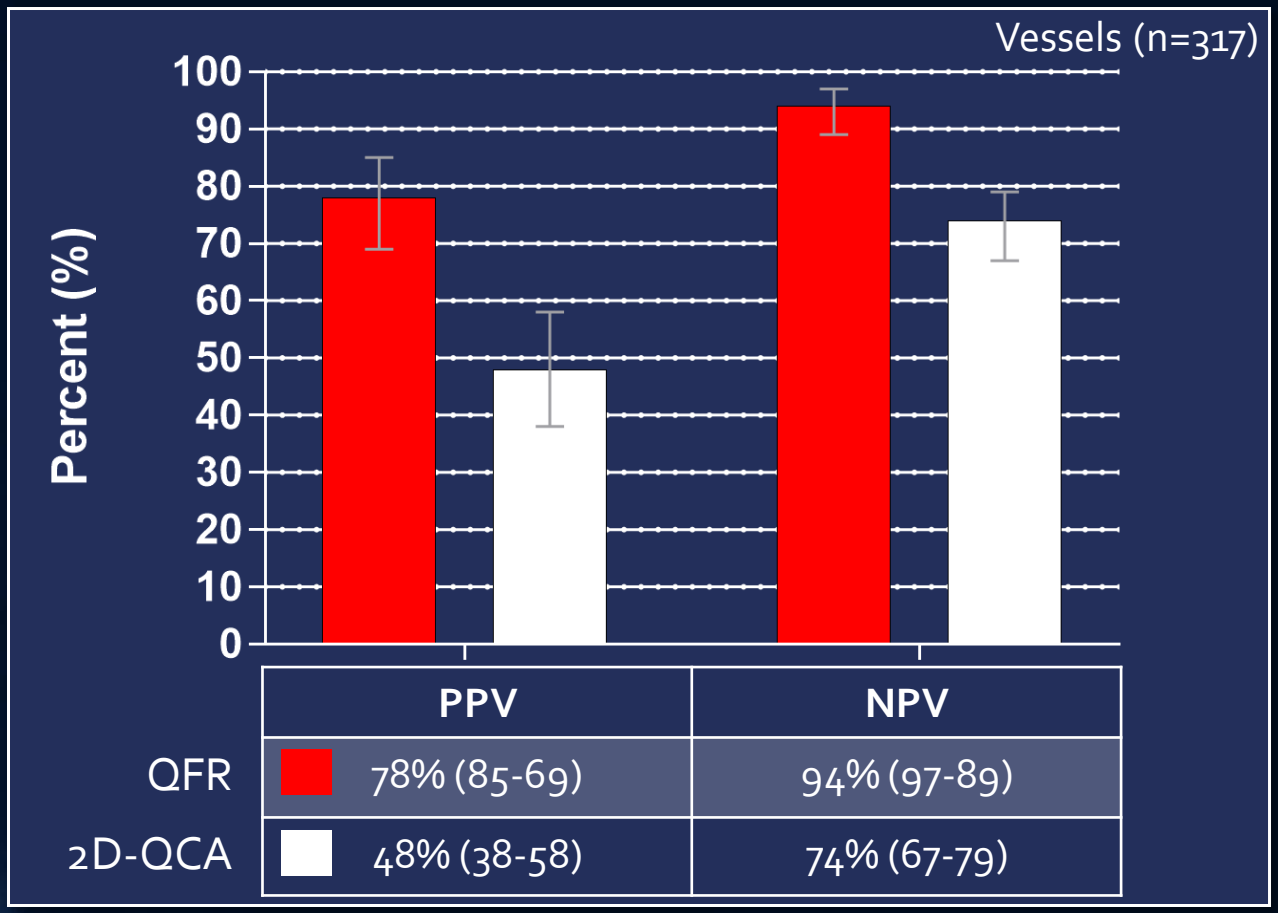
Primary endpoint



	Sensitivity	Specificity
QFR	88% (80-93)	88% (83-92)
2D-QCA	46% (36-55)	77% (70-82)

Comparisons by McNemar's test

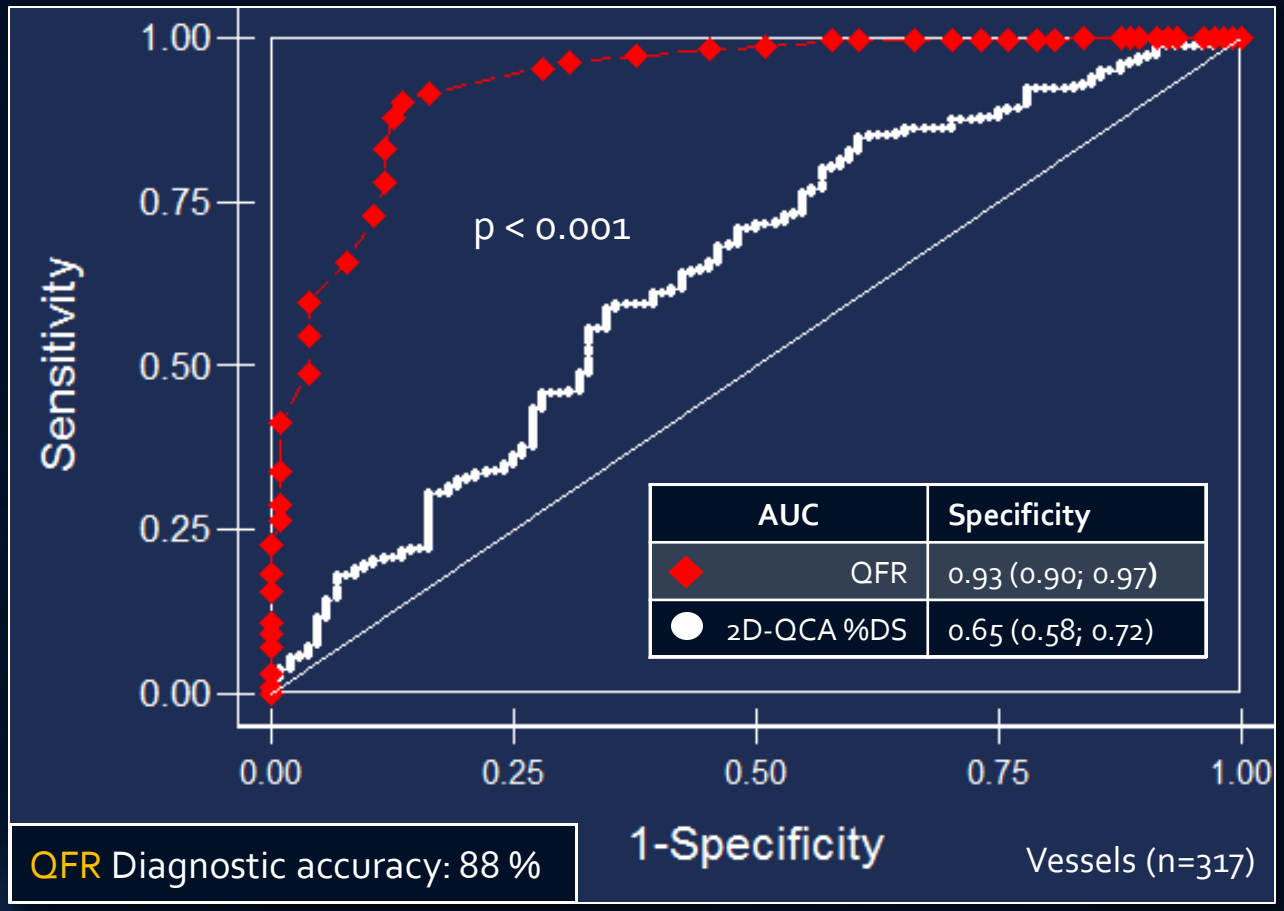
Results – QFR vs. 2D-QCA with FFR as reference



	PPV	NPV
QFR	78% (85-69)	94% (97-89)
2D-QCA	48% (38-58)	74% (67-79)

PPV: Positive predictive value; NPV: Negative predictive value

Results – QFR vs. 2D-QCA with FFR as reference



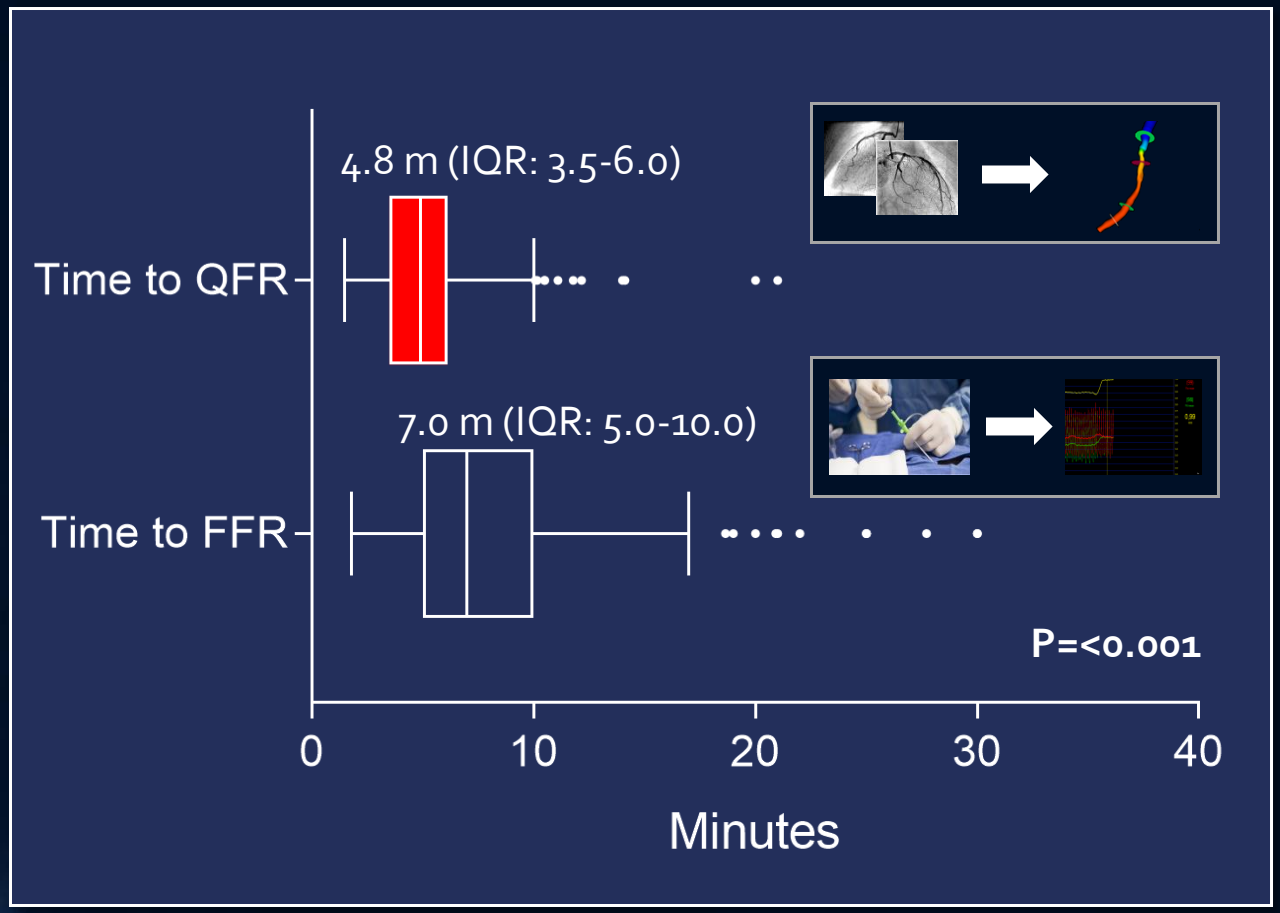
Results – Feasibility

Per vessel*

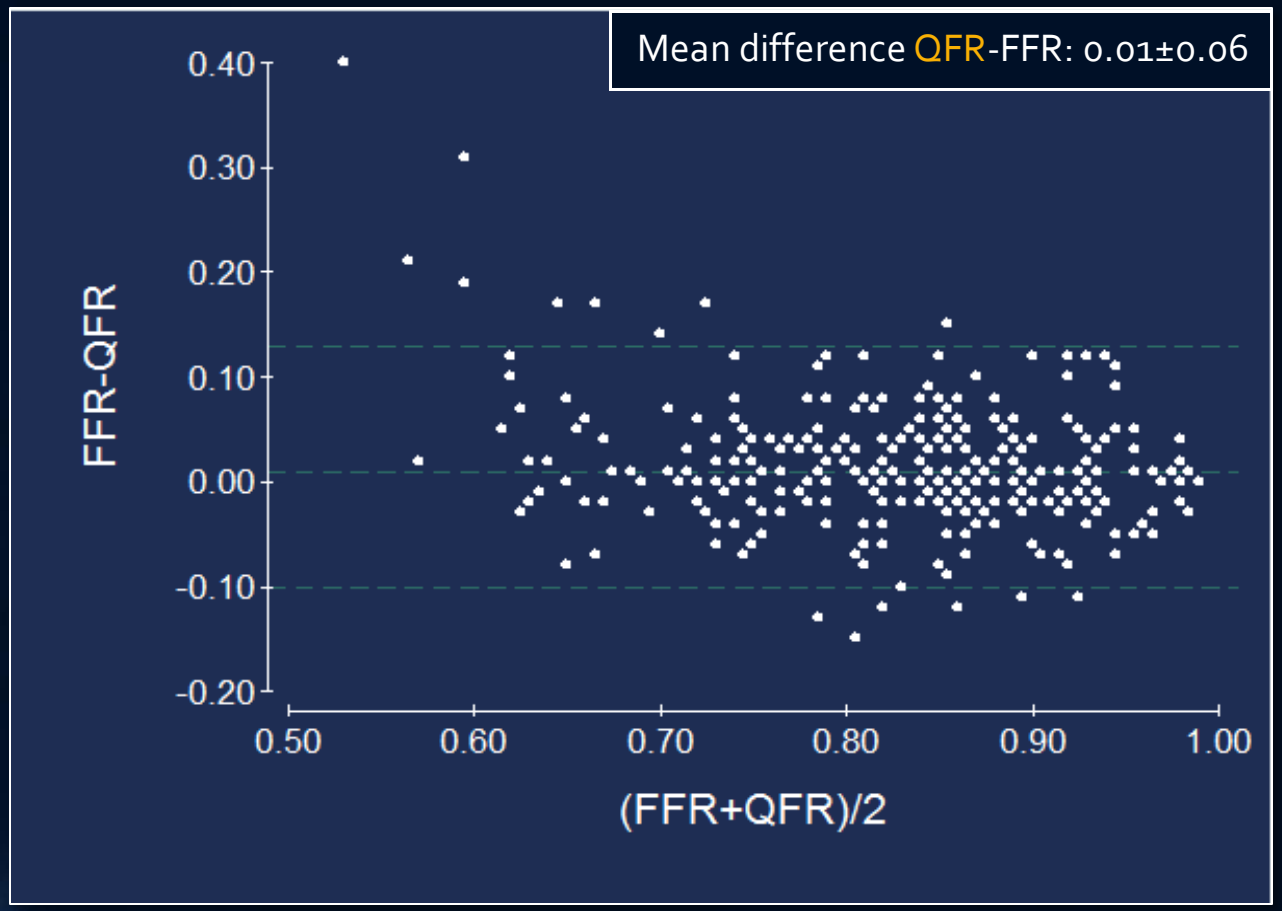
Feasibility	n=373
Successful QFR computations in attempted cases	361 (97%)
Unsuccessful QFR (n=12)	
Overlap	1 (0 %)
Insufficient image quality	6 (2%)
Foreshortening	2 (0.5%)
Technical failure	3 (1%)

*Number of vessels where FFR was measured and QFR attempted but excluding 2 cases with ostial RCA lesions and 4 cases with major bifurcation lesions (exclusion criteria)

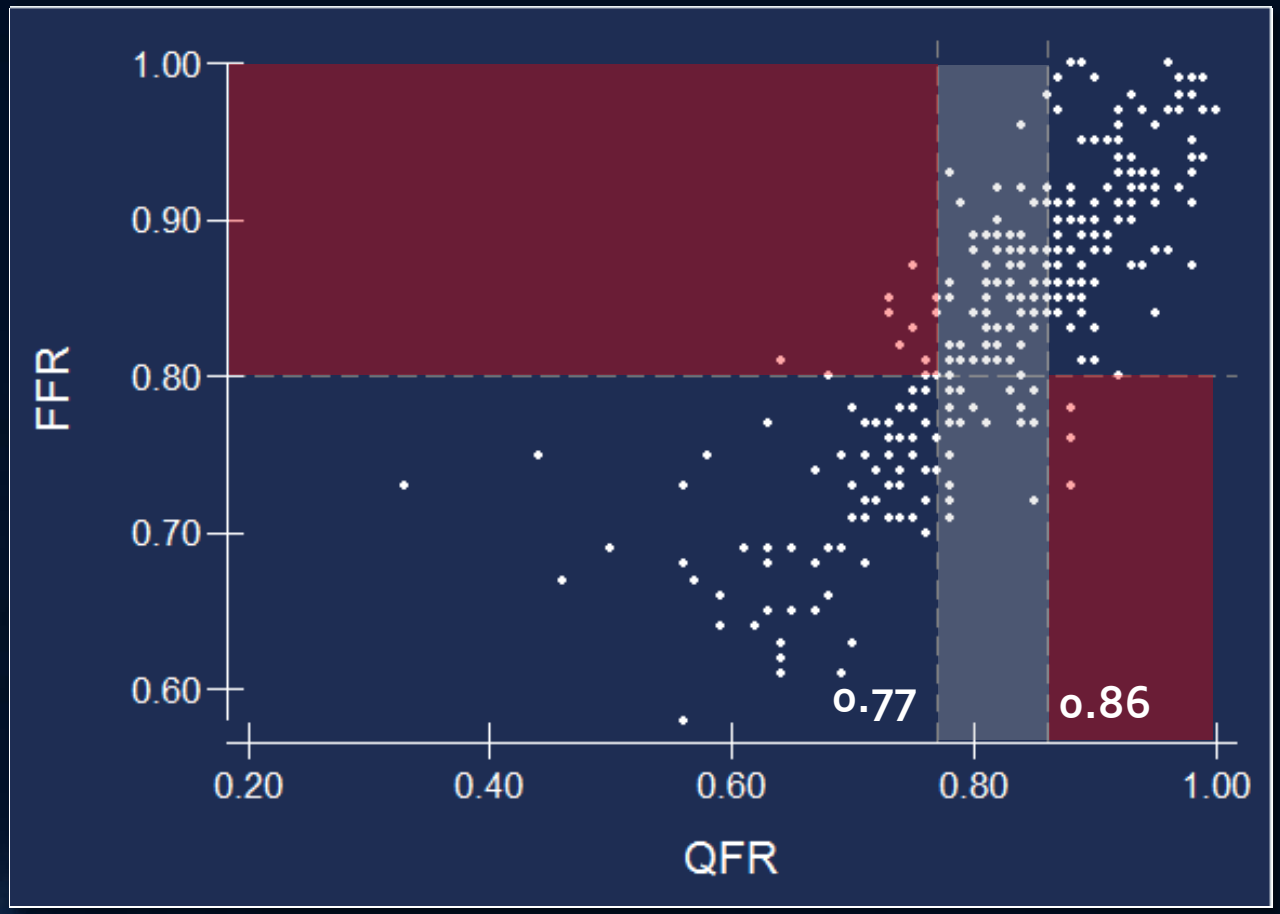
Results – Time to QFR and FFR



Results – Precision

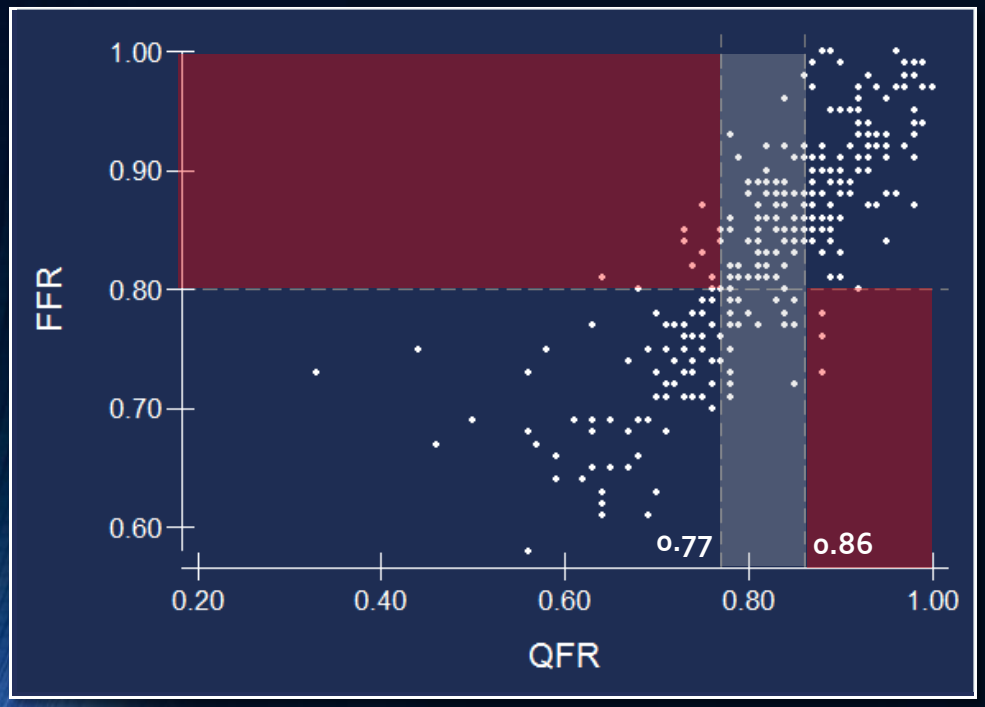


Results – QFR-FFR hybrid approach



QFR limits to yield specificity and sensitivity >95% with FFR as reference

Results – QFR-FFR hybrid approach



- Assuming that FFR is required in the diagnostic grey-zone of QFR, pressure-wire free assesment is possible in potentially 68 % of all lesions while ensuring >95% accuracy

Conclusion

- QFR showed superior sensitivity and specificity for detection of functional significant lesions in comparison with 2D-QCA using FFR as reference standard
- In-procedure QFR computation was feasible and was computed within the time of standard FFR measurements
- Randomized trials are required to determine if a QFR based diagnostic strategy provides non-inferior clinical outcome compared to pressure wire based strategies