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

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PCI Research
Aarhus University Hospital, Skejby • Denmark
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.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
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<tbody>
<tr>
<td>• Grant/Research Support</td>
<td>• Medis medical imaging bv.</td>
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<tr>
<td>• Consulting Fees/Honoraria</td>
<td>• Medis medical imaging bv.</td>
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</tbody>
</table>

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 is an estimate of FFR based on:

- fluid dynamic equations
- emulated hyperaemic flow velocity
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
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   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 specificity 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 ($\text{NYHA} \geq \text{III}$)
- $\text{S-creatinine} > 150 \mu\text{mol/L}$ or $\text{GFR} < 45 \text{ ml/kg/1.73m}^2$
- 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

CAG (n=329)

Excluded based on diagnostic angiography
- Lesions <30% or >90% (n=14)
Exclusion criteria fulfilled
- Atrial fibrillation (n=1)
- Myocardial infarction <72 hours (n=1)

Angiographic criteria
- Ostial RCA lesion (n=1)
- Bifurcation lesions with reference stepdown > 1 mm (n=1)

In-procedure QFR not computed
- Overlap (n=1)
- Insufficient image quality (n=4)
- Protocol violation (n=7)
- Technical failure (n=1)

FFR not measured
- Asystoli (n=1)
- Technical failure (n=1)

Excluded by FFR core-lab
- Drift (n=8)
- Dampening (n=15)

Excluded by QCA core-lab
- No vessel reference identified (n=1)

Patients in analysis (n=272)

Eligible for FFR and QFR (n=311)

QCA core-lab analysis (n=273)

FFR and QFR performed (n=296)

Patients in analysis (n=272)
## Results

### Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>196 (72%)</td>
</tr>
<tr>
<td>Smoking (current or past)</td>
<td>156 (57%)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27 ± 5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>201 (74%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>186 (68%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>78 (29%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>73 (27%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>56 ± 10</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>109 (40%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>11 (4%)</td>
</tr>
</tbody>
</table>

Values are n(%) and mean ±SD
### Clinical presentation

<table>
<thead>
<tr>
<th>CCS Grade</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCS 0</td>
<td>54</td>
<td>20%</td>
</tr>
<tr>
<td>CCS 1</td>
<td>67</td>
<td>25%</td>
</tr>
<tr>
<td>CCS 2</td>
<td>122</td>
<td>45%</td>
</tr>
<tr>
<td>CCS 3</td>
<td>14</td>
<td>5%</td>
</tr>
<tr>
<td>CCS 4</td>
<td>1</td>
<td>0%</td>
</tr>
<tr>
<td>Secondary evaluation of NCPL</td>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>Other (dyspnea, arrhythmia)</td>
<td>8</td>
<td>3%</td>
</tr>
</tbody>
</table>

Values are n(%)
Results – FFR distribution

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFR≤0.80</td>
<td>33%</td>
<td>104</td>
</tr>
<tr>
<td>FFR: 0.75-0.85</td>
<td>32%</td>
<td>101</td>
</tr>
<tr>
<td>2D-QCA % DS</td>
<td>45%</td>
<td>45 ± 10</td>
</tr>
</tbody>
</table>

Mean FFR: 0.83 ± 0.09

N=317
Primary endpoint
Primary endpoint

Comparisons by McNemar’s test

<table>
<thead>
<tr>
<th>Vessels (n=317)</th>
<th>90% (80-93)</th>
<th>88% (83-92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFR</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>2D-QCA</td>
<td>46% (36-55)</td>
<td>77% (70-82)</td>
</tr>
</tbody>
</table>
Results – QFR vs. 2D-QCA with FFR as reference

<table>
<thead>
<tr>
<th></th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFR</td>
<td>78% (85-69)</td>
<td>94% (97-89)</td>
</tr>
<tr>
<td>2D-QCA</td>
<td>48% (38-58)</td>
<td>74% (67-79)</td>
</tr>
</tbody>
</table>

**PPV**: Positive predictive value; **NPV**: Negative predictive value
Results – QFR vs. 2D-QCA with FFR as reference

- QFR Diagnostic accuracy: 88%

AUC and Specificity:
- QFR: AUC = 0.93 (0.90; 0.97), Specificity = 0.93
- 2D-QCA %DS: AUC = 0.65 (0.58; 0.72), Specificity = 0.65

Vessels (n=317)
Results – Feasibility

Per vessel*

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>n=373</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Successful QFR computations in attempted cases</strong></td>
<td>361 (97%)</td>
</tr>
<tr>
<td><strong>Unsuccessful QFR (n=12)</strong></td>
<td></td>
</tr>
<tr>
<td>Overlap</td>
<td>1 (0 %)</td>
</tr>
<tr>
<td>Insufficient image quality</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>Foreshortening</td>
<td>2 (0.5%)</td>
</tr>
<tr>
<td>Technical failure</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

*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

- **Time to QFR**
  - 4.8 m (IQR: 3.5-6.0)

- **Time to FFR**
  - 7.0 m (IQR: 5.0-10.0)

*P* = < 0.001
Results – Precision

Mean difference QFR-FFR: 0.01±0.06
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 assessment 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