Diagnostic Accuracy of On-line Quantitative Flow Ratio

Functional Assessment by Virtual Online Reconstruction

The FAVOR II study

An academic international multicenter trial by Aarhus University Hospital, Denmark

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Abbreviations

AMI	Acute Myocardial Infarction

AP	Angina Pectoris
AS	Area Stenosis
CABG	Coronary Artery Bypass Grafting
CCS	Canadian Cardiovascular Society Angina Grading System
CK-MB	Creatinine Kinase MB
CRF	Case Report Form
FFR	Fractional Flow Reserve
GCP	Good Clinical Practice
IHD	Ischemic Heart Disease
LBBB	Left bundle branch block
MACE	Cardiac Death, Myocardial Infarction, Stent Thrombosis or Target Vessel Revascularization
MI	Myocardial Infarction
MV	Main Vessel
PCI	Percutaneous Coronary Intervention
QCA	Quantitative Coronary Analysis
QFR	Quantitative Flow Ratio
TNI	Troponin I
TNT	Troponin T
TLR	Target Lesion Revascularization
TVR	Target Vessel Revascularization
TLF	Target Lesion Failure
TVF	Target Vessel Failure

1. Background

Patients in high risk of having one or more coronary stenoses are evaluated routinely by invasive coronary angiography (CAG) and often in combination with measurement of fractional flow reserve (FFR) during the procedure[1]. Stenosis identified by angiography is considered to cause ischemia if the narrowing results in a lumen reduction of more than 90% diameter stenosis by visual estimate. If the lumen reduction is between 30% and 90% it is indicated to measure FFR to assess if the flow is reduced more than 20% by the stenosis. Such a reduction in flow is correlated to ischemia in the downstream myocardium[2,3]. FFR is assessed during CAG by advancing a wire with a pressure transducer towards the stenosis and measuring the ratio in pressure between the two sides of the stenosis during maximum blood flow (hyperaemia). Hyperaemia is induced by adenosine infusion during the measurement.

This strategy of FFR-guided intervention in coronary artery disease is well established by solid clinical evidence and has gained the highest guideline recommendations in Europe[1]. In Denmark FFR is measured in an estimated 4000 patients a year.

Pros and cons of FFR

The solid evidence for FFR evaluation of coronary stenosis and the relative simplicity in performing the measurements have supported wide spread adoption of the technology. However, the need for interrogating the stenosis by a pressure wire carries the risk of dissecting or even perforating the vessel. The wire can also dissect a plaque and cause plaque rupture and thrombus can form around the catheter. These complications are relatively rare but may be detrimental. Another factor is the price where pressure wires and adenosine adds substantially to the procedural costs. Cost-effectiveness analysis has shown that an FFR guided strategy is cost-effective compared to an angiographic guided strategy as fewer stents are implanted per patient[4]. Still, if the cost of doing FFR could be reduced or alleviated it would definitely benefit the economically restrained health care systems.

Wire-free FFR

A new method (QFR by Medis medical imaging) for evaluation of the functional significance of coronary stenosis is based on computer calculation of the FFR value. This calculation is performed by analysing the coronary angiogram and thus reduces or potentially eliminates the need for measuring FFR by pressure wires. The QFR method combines a 3D reconstruction of the target

vessel based on two angiographic projections and the contrast flow velocity to compute the "FFR value". In the presented FAVOR study, QFR was shown to be very promising and results on in-procedure analysis from the WIFI I trial are imminent. Development of similar methods is ongoing in multiple companies and academic groups[5-7] and at present we are not aware that similar methods are tested for in-procedure computation of FFR. The FAVOR study evaluating the QFR technology showed good diagnostic accuracy in comparison to FFR when QFR was based on angiographic views acquired with and without induced hyperaemia.

The available version of the method is capable of assessing QFR during CAG but is not yet CE-marked and has not received FDA approval for clinical decision-making, but it allows evaluation of the feasibility and diagnostic precision of this novel method.

1.1 Purpose

To evaluate the feasibility and diagnostic precision of QFR during CAG in comparison to QCA with FFR as gold standard for physiological lesion evaluation.

1.2 Hypothesis

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

2. Materials and methods

2.1 Design

Prospective, observational, multicenter study with inclusion of 310 patients.

2.2 Patients

Consecutive patients referred for diagnostic angiography are screened for eligibility.

2.2.1 Inclusion criteria

- Stable angina pectoris or secondary evaluation of stenosis after acute MI
- Age > 18 years
- Able to provide signed informed consent

2.2.2 Angiographic inclusion criteria

- Indication for FFR in at least one stenosis:
  - Diameter stenosis of 30%-90% by visual estimate
  - Reference vessel size > 2 mm in stenotic segment by visual estimate

2.2.3 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

2.2.4 Angiographic exclusion criteria

Lesion specific

- Below 30% and above 90% diameter stenosis by visual estimate.
- Reference size of vessel below 2 mm by visual estimation.
- Ostial LMCA lesions
- Ostial RCA lesions
- Distal LMCA lesions in combination with proximal Cx lesions
- Other 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

2.3 Endpoints

2.3.1.1 Primary endpoint

Sensitivity and specificity of QFR in comparison to QCA with FFR as gold standard

2.3.1.2 Secondary endpoints

A) Feasibility of TIMI-flow based QFR in FFR assessed lesions

B) Diagnostic performance of TIMI-flow based QFR in comparison to FFR reported as

1) Sensitivity
2) Specificity

3) Positive predictive value
4) Negative predictive value
5) Positive and negative Likelihood ratio

C) Diagnostic grey zone. QFR limits for achieving 95% sensitivity and specificity in comparison to FFR
D) Diagnostic accuracy of TIMI-flow based QFR in comparison to 2D QCA (>50% diameter stenosis) as area under the curve
E) Diagnostic accuracy of three different methods for computing QFR
1) Fixed hyperemic flow rate (online computed)
2) TIMI flow based without hyperaemia (online computed)
3) TIMI flow based with hyperaemia (core laboratory computed)
F) Reproducibility of QFR
1) Fixed hyperemic flow rate (online computed vs core laboratory computed)
2) TIMI flow based without hyperaemia (online computed vs core laboratory computed)

2.3.2 Procedural endpoints

1) Procedural safety
2) Procedure time to FFR
3) Procedure time to QFR
4) Time to QFR after receiving angiographic images
5) Contrast use
6) Fluoroscopy time

2.4 Study procedure

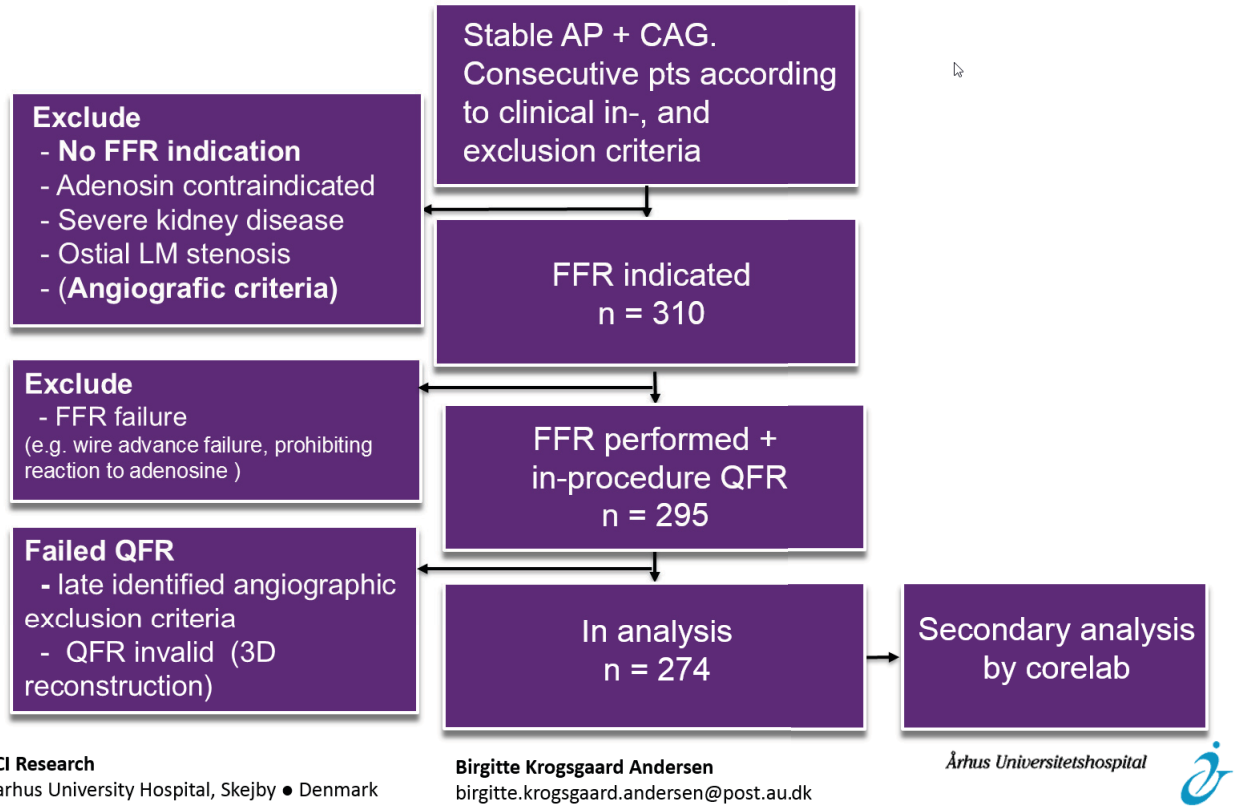
2.4.1 Enrollment and angiographic based exclusion

Patients fulfilling clinical inclusion criteria and fulfills no clinical exclusion criteria are enrolled by providing written informed consent before the procedure (see section 6.3). During angiography patients enters the QFR cohort if fulfilling angiographic inclusion criteria. If patients have angiographic exclusion criteria, they are excluded before attempting QFR. All enrolled patients are entered in the study eCRF. If excluded, reasons are entered in the eCRF.

2.4.2 Study procedure flow

The CAG procedure with FFR assessment is performed as normal best practice. QFR is calculated for all the vessels in which FFR assessment is planned. Angiographic projections are acquired

ensuring minimal overlap of the investigated vessels. Two projections of each vessel to be assessed are obtained at least 25 degrees apart. After initial diagnostic angiography the images are transferred to a workstation for calculation of the QFR-value. Not awaiting the result hereof, the operator continues the procedure by measuring standard FFR during I.V. hyperaemia. The FFR trace is recorded from before inducing hyperaemia to verification of drift not exceeding prespecified limits (section 2.4.3). The procedure is finalized as by normal practice according to the results of angiography and standard FFR. The QFR value is calculated in parallel and the results noted before knowing the measured FFR values. The QFR value may not be used for diagnosing the patient.



2.4.2.1 Coronary angiography, detailed

Two good projections at least 25 degrees apart are required for the 3D vessel reconstruction. Angiographic procedure:

- Inject I.C. nitro-glycerine as early as possible
- Use framerate of at least 12.5/15 frames/sec
- Make sure that the catheter is filled with contrast before the injection (i.e. after administration of nitro-glycerine)
- Use brisk, continuous and fast contrast injections. Aim for full 3 cardiac cycles

- Minimize overlap of target segments
- Avoid foreshortening of the vessel
- Avoid zooming
- Avoid moving the table early after injection
- Aim projections perpendicular to the target vessel
- Make sure that the entire vessel is visible in both projections. Both the proximal end and the potential position of the FFR pressure transducer should be visible in the same frame.

Suggested projections are found in table 1.

Vessel /Bifurcation	1st View	2nd View
LM + LAD/LCX	RAO 20, Caudal 45	AP, Caudal 10
LAD/Diag	AP, Cranial 45	RAO 35, Cranial 20
LCX/OM	LAO 10, Caudal 25	RAO 25, Caudal 25
Proximal+Mid RCA	LAO 45, CAUD 0	AP, CAUD 0
PLA/PDA	LAO 45, CAUD 0	LAO 30, CAUD 30

If only one good projection is identified, consider to use the *Acquisition Guide* tool in the Medis Suite QAngio XA 3D/QFR solution to identify the second projection:

1. Transfer first good projection to QFR computer (see section 2.4.2.2).
2. Right-click on the good projection and start QAngio3D.
3. Choose *Acquisition Guide* (**Figure 1**, red box). The yellow line on the angiography indicates the new projection angle, and should be approximately perpendicular to the target vessel at the lesion site.
    a. If several lesions are located on the same vessel, a compromise must be made to ensure that most and the most severe lesions can be seen in the same projection.
4. Move the projection line by moving the yellow spot (**Figure 1**, arrow) in the Acquisition Guide indicator. Aim to keep the yellow spot inside the green area.
5. Position the C-arm as proposed by the guide.
6. In case of excessive overlap of the target segments and other vessels, rotate the C-arm 5 degrees around the axis of the target vessel.

a. If needed, use the Acquisition guide indicator again by maintaining the angulation of the yellow line and move the yellow spot just outside the green area – away from the red area. Move the C-arm accordingly.

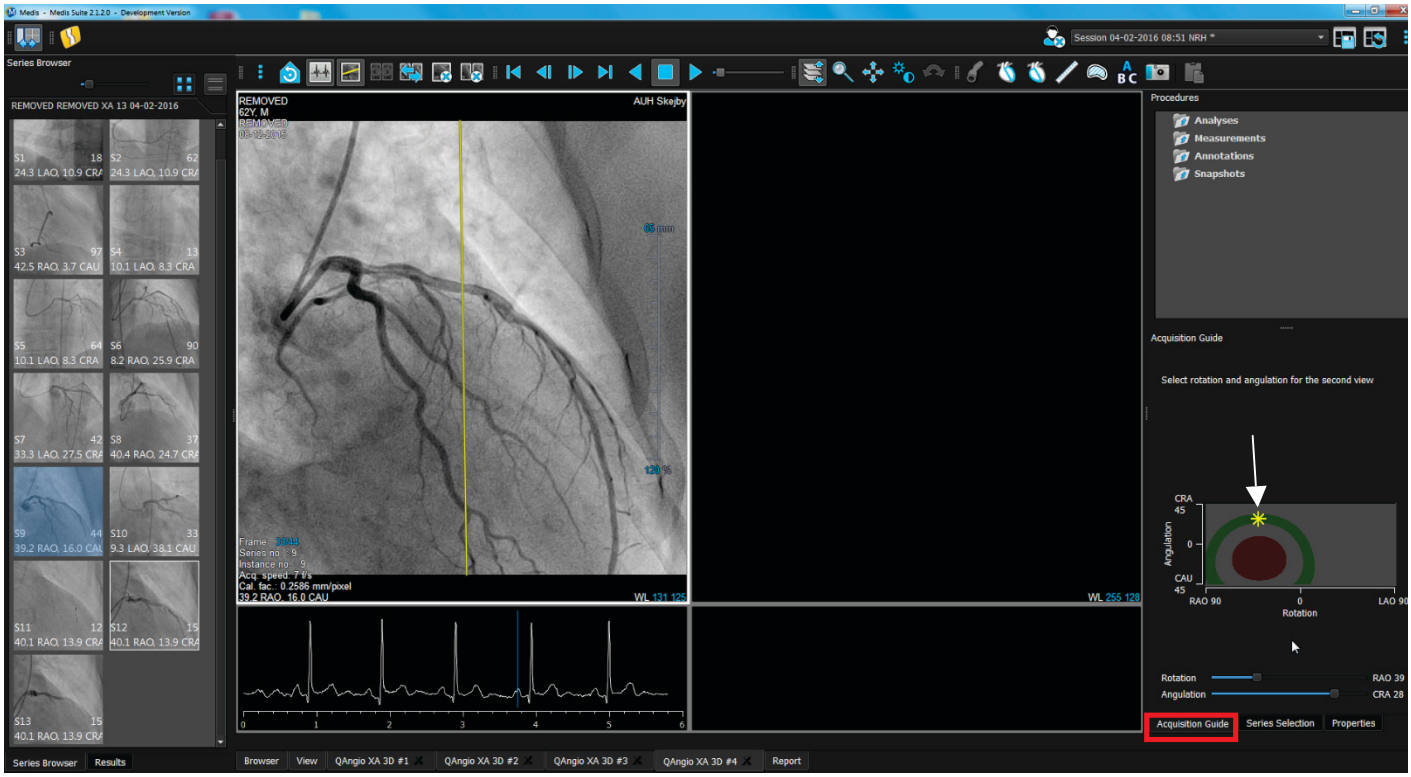


Figure 1 *Acquisition Guide. Red box: Acquisition guide. White arrow: Yellow spot indicating position of C-arm.*

2.4.2.2 Image transfer

The angiographic runs are transferred to the QFR-computer using an angiographic equipment specific protocol.

2.4.2.3 Angiographic run selection

Optimal projections are chosen according to the following criteria:

- Minimal overlap of the target vessel
- Good contrast injection, filling the entire vessel
- Includes both most proximal stenosis and most distal potential location of the pressure transducer of the subsequent FFR assessment

2.4.3 Detailed description of FFR recording:

The pressure wire is prepared and calibrated according to instructions for use. The pressure wire is advanced in the engaged guiding catheter and the pressure transducer positioned just outside the

tip of the catheter and equalized. After equalization, the wire is advanced to a position with the transducer in a stable position distal to the stenosis. In case of long healthy segments distal to the lesion, do not advance the FFR wire to a very distal position as this increases the complexity of acquiring appropriate angiographic views.

I.V. FFR recording: Recording of FFR during I.V. adenosine induced hyperemia is performed by femoral or brachial vein infusion of adenosine at 140 $\mu gL^{-1}min^{-1}$. The infusion rate is increased to 200 $\mu gL^{-1}min^{-1}$ if a stable FFR value is not achieved. At least 20 seconds of the lowest stable value is documented before obtaining an angiographic projection during hyperemia, which should at least be 25 frames/sec.

The entire FFR interrogation is recorded from before equalization and until a potential drift has been checked after retracting the pressure wire.

FFR is calculated as the ratio of distal mean pressure (Pd) measured by the pressure-wire to the proximal mean pressure (Pa) during hyperemia. The FFR cut-off for identification of a flow limiting stenosis is ≤ 0.80 for all lesions. The wire location is documented angiographically for all measurements. A pressure-wire pullback is performed to check for pressure-drift. A drift-value from 0.96-1.04 is accepted; otherwise, the procedure is repeated. For FFR values of 0.76-0.84, a drift with a narrower range of 0.98-1.02 is accepted.

St. Jude FFR systems are recommended, but Volcano FFR systems can be used as well. iFR recordings and Acists FFR system are not allowed. It is mandatory that complete FFR traces can be exported for documentation and core lab analysis. If using the St. Jude Quantien system it is crucial to finalize the recordings and session correctly on the console to avoid loss of FFR data. FFR systems integrated in physiology systems or angiographic equipment are only allowed if a complete trace can be reanalyzed by the FFR core laboratory.

2.4.4 Detailed description of QFR computation

The Medis Suite QAngio XA-3D/QFR solution (Medis medical imaging system bv, Leiden, The Netherlands) is used for computation of QFR. The Medis Suite QAngio XA-3D/QFR solution is installed on a windows based computer. The analysis is performed as described in the manual provided with the software and in a step-by-step study specific standard operating procedure (Appendix A)

2.4.4.1 Documentation of QFR analysis

After finishing the QFR analysis, it is saved by two steps for the study purpose.

1. A screenshot is acquired and saved in a folder named ”Patient X”, X indicating the patient’s study ID.
2. The QFR analysis is saved in the Medis Suite QAngio XA 3D/QFR solution by clicking *Done* in the lower right corner (**Figure 2**, white arrow) and clicking *Save* in the upper panel (**Figure 2**, red arrow).

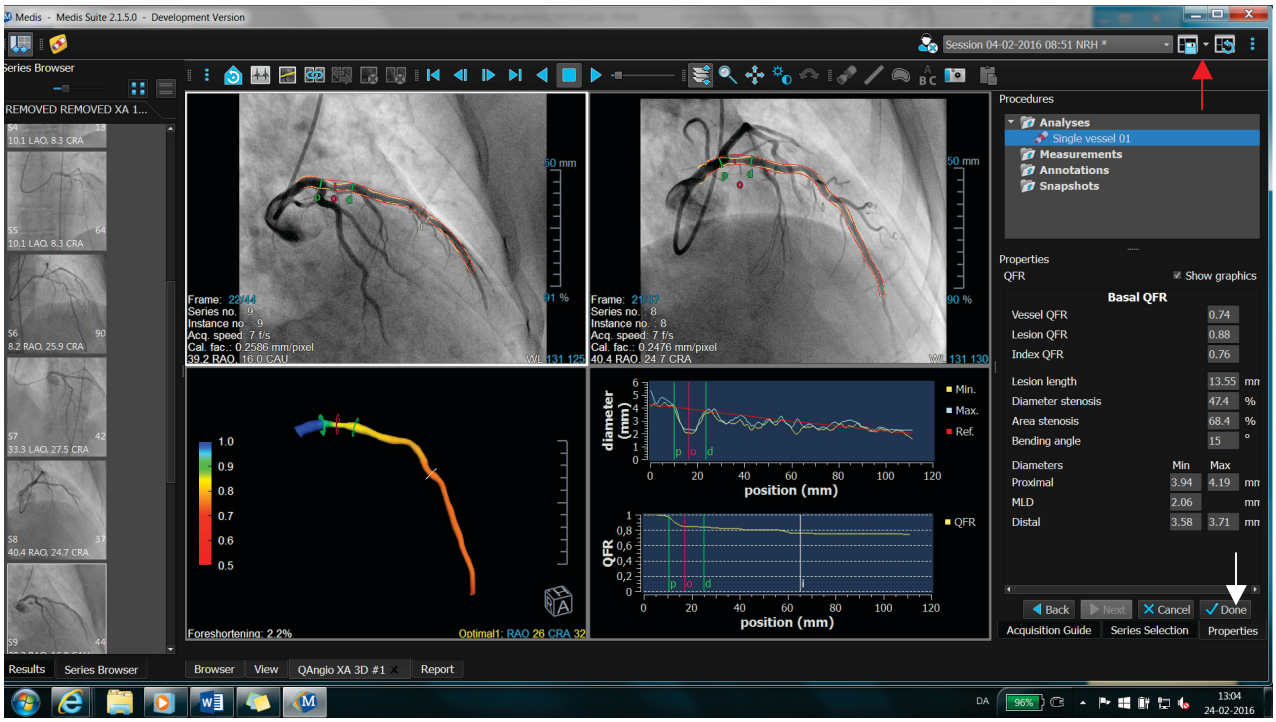


Figure 2 *Documentation. How to save the analysis in the Medis Suite QAngio 3D-/QFR solution.*

After a session is made and saved, Medis Suite QAngio XA 3D/QFR solution will create a Report (summarizing the analysis, including 2D images of the vessel reconstruction, the 3D reconstruction, results etc.). You can easily change which parts of the analysis the report includes by clicking on the different parameters (**Figure 3**, left panel).

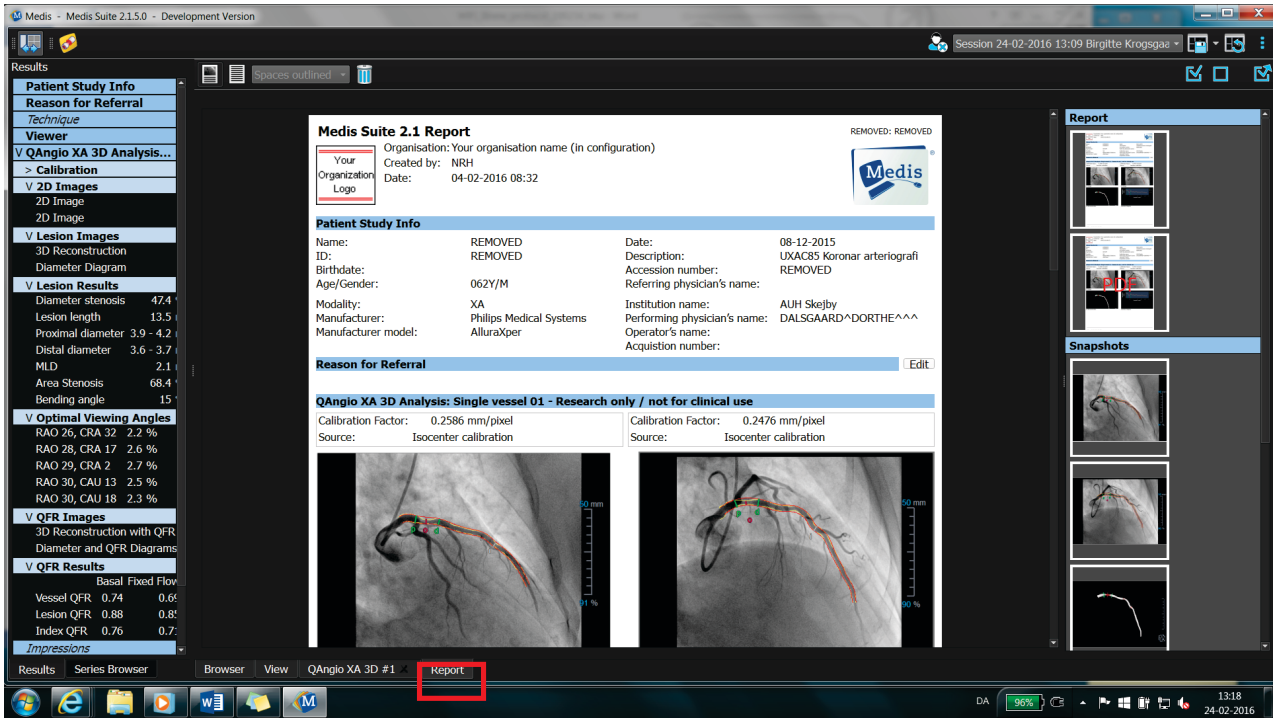


Figure 3 Report

2.4.5 Endpoint definition

2.4.5.1 Feasibility

Fraction of lesions with FFR where QFR was computed

Time to QFR: Time from first image evaluation on QFR computer until TIMI frame count based QFR is obtained.

Time to FFR: Time from starting preparations to do FFR (e.g. ordering assistants to prepare pressure wire, adenosine infusion) FFR value is obtained AND drift has been verified to be within the prespecified limits

2.4.5.2 Endpoint definitions: 3D Quantitative Coronary Angiography (3D-QCA)

- Percentual diameter stenosis: (Reference diameter ÷ minimal luminal diameter)/reference diameter in percent

2.4.6 Definitions of clinical endpoints (procedural)

2.4.6.1 Cardiac death

Encompasses death due to coronary heart disease including fatal myocardial infarction, sudden cardiac death including fatal arrhythmias and cardiac arrest without successful resuscitation, death from heart failure including cardiogenic shock, and death related to a cardiac procedure or surgery within 28 days from the procedure. If death is not clearly attributable to other non-cardiac causes, it will be adjudicated as cardiac death.

2.4.6.2 All-cause mortality (total death)

Total death includes cardiac death and other fatal categories such as cerebrovascular death, death from other cardiovascular disease (i.e. pulmonary embolism, dissection aortic aneurism will be included in this category), death from malignant disease, death from suicide, violence or accident, or death from other reasons.

2.4.6.3 Non-procedure related target lesion myocardial infarction

The term myocardial infarction should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for myocardial infarction:

1) Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following (MI types 1 or 2):

a. Symptoms of ischemia

b. ECG changes indicative of new ischemia (new ST-T changes or new LBBB)

c. Development of pathological Q waves in the ECG

d. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

2) Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood (MI type 3).

3) Pathological findings of an acute myocardial infarction.

2.4.6.4 Procedure related biochemical release of markers (Myocardial infarction related to the index procedure)

The following biomarkers may be used in the study: CK-MB mass and/or Troponin-T/-I. For percutaneous coronary interventions (PCI) in patients with normal baseline biomarker values, elevations of CK-MB greater than 5 X 99th percentile URL are designated as defining PCI-related myocardial infarction (MI type 4a). Similar rise or higher by TnT or TnI will be reported. If cardiac biomarkers are elevated before the procedure and not stable for at least two samples 6 hours apart, there are insufficient data to recommend biomarker criteria for the diagnosis of peri-procedural myocardial infarction. If the values are stable or falling, criteria for re-infarction by further measurement of biomarkers can be applied; that is 20% or more increase of the value in the second sample after the procedure. This value should also exceed the 99th percentile URL.

2.4.6.5 Target lesion revascularization

Coronary artery bypass grafting or PCI of index lesion.

2.4.6.6 Target vessel revascularization

Coronary artery bypass grafting or PCI of index vessel.

2.4.6.7 Target lesion failure

Target lesion failure is defined as objective evidence for in-segment occlusion (symptomatic or asymptomatic) or stenosis causing ischemia.

2.4.6.8 Target vessel failure

Target vessel failure is defined as objective evidence for in-vessel occlusion (symptomatic or asymptomatic) or stenosis causing ischemia.

2.4.6.9 Stent thrombosis

Stent thrombosis is recognized when documented by angiography and/or autopsy and when meeting the criteria for spontaneous myocardial infarction occurring in the territory of the treated vessel. Stent thrombosis is categorized as acute, sub-acute, late and very late and as definite, probable and possible according to the ARC-criteria[8].

2.4.7 FFR core lab analysis

The recorded FFR traces are analyzed by experienced observers at the Coronary Physiology Core Laboratory, Aarhus University, Denmark. The observers are blinded to any other procedural information. FFR recordings are analyzed for achievement of maximal hyperemia, no reversed gradient during hyperemia, no loss of Pa or Pd signal and acceptable drift.

2.4.8 QFR core lab

The angiograms are reanalyzed by two observers blinded to any procedural results and FFR results. Analysis is performed using the three flow models; fixed hyperemic flow rate (HFR), TIMI flow based without hyperaemia and TIMI flow based with hyperaemia. Analysis is performed applying same principles as during on-line computation. Analysis is performed at the core laboratory for interventional imaging at Aarhus University Hospital, Denmark

3. Statistics and sample size

3.1 Statistics

Baseline characteristics and procedural characteristics are presented as count and percentages, or if continuous variables are analyzed by mean and standard deviation if Gaussian distributed, else reported as medians and inter-quartile range. If more than one vessel is assessed pr patient it is analysed on a per vessel level. Feasibility is calculated as the number of successful QFR/number of standard FFR times 100. The primary endpoint is calculated as superiority for sensitivity and specificity of QFR in comparison to QCA. The QCA value in analysis is the lesion site 3D QCA value obtained on-line during QFR analysis. Secondary endpoints include positive predictive value, negative predictive value, together with their 95% confidence intervals (CIs). The area under the curve by receiver-operating characteristic analysis is used to assess the diagnostic accuracy of QFR and QCA with FFR as gold standard. The diagnostic performance of QFR compared to 2D QCA is performed by one-tailed paired comparison of ROC curves (Hanley test). Pearson correlation is used to quantify the correlation between QFR and FFR. Agreement between QFR and FFR is assessed by Bland-Altman plot. Intra- and inter-patient variation in paired QFR and FFR values are compared to detect clustering. Analysis is performed using STATA 13.

3.2 Sample size

The study is an observational study designed to assess the diagnostic accuracy of QFR with FFR as gold standard. Estimates for the sample size calculation are based on the results from the FAVOR study, where a sensitivity of 0.74 and a specificity of 0.91 for QFR was found. The null hypothesis is H0: Sensitivity(QFR) = Sensitivity(DS50). H1: Unequal sensitivities for the two methods.

Calculated with SAS version 9.4 with proc power for paired frequency, to do a sample size analyses for McNemar's test for paired proportions.

We did a normal-approximate McNemar test with the Connor method;

Proportion1=0.48; proportion2=0.74; correlation=-0.1

We did similar for specificity (H0: Specificity(QFR) = Specificity(DS50). H1: Unequal specificities for the two methods.

Proportion1=0.75; proportion2=0.91; correlation=0.4

With power=0.90, alpha=0.05 and a rate of true positives in the population of estimated 30% a total of 274 patients with paired QFR and FFR are required to reject the null hypothesis for sensitivity and 257 for specificity. To accommodate for insufficient angiographic quality or failed FFR a total of 310 patients should be enrolled.

4. Notifications

The study is notified to the Central Denmark Region Committees on Biomedical Research Ethics. Notification to local or national medical ethics committees is performed by the local or national coordinating investigators as required for the individual sites. The study is initiated center wise when full final approval is obtained covering the specific center.

The study does not require notification to the respective National Board of Health as the tested QFR technology is not in contact with the patient (simple file transfer from angiographic equipment to a standard personal computer (PC)) and the obtained measurements are not used for diagnosing the patient during, or at any point after the individual study procedures.

The study is notified to the Danish Data Protection Agency. Data is transferred to the Danish Data Archive before termination of the data controller permission and deletion of all the related study material at Aarhus University Hospital. Data is handled, processed and stored according to the regulations set forth in the "Persondataloven" and published guidelines by the Danish Data Protection Agency. Any additional use or transfer of data is only done pending permission by the Danish Data Protection Agency and by signed data processor agreement if applicable. The notification to the Danish Data Protection Agency covers the handling, processing, storage and transmission for all participating sites in all EC countries. All sites and investigators are required to obey the data protection regulations as referred to in the site contract. Sites outside the EC zone should obtain permission from local or national data protection authorities if required by law.

5. Data management

5.1 Data obtained in the study

Patient data recorded in the study database includes:

Site data entered in eCRF, data entered in the study CRF (CPR no. (only Denmark), patient identifier, hypertension, diabetes, prior PCI or CABG, indication for CAG, creatinine, GFR rate, hemoglobin, blood pressure, pulse, symptoms during adenosine infusion, adenosine infusion rate, FFR-result, time to QFR, time to FFR, QFR result (fixed and TIMI-flow based), clinical decision, treatment.

Site data transferred for documentation and analysis

1. Angiographic runs and documentation for the FFR wire position to be transferred in DICOM format (anonymized but marked with patient id, date, site, study name)

2. FFR traces:
   Volcano systems

   All raw study files are archived on DVD's (not USB memory sticks).

   1) Locate the patient in the Volcano database.

   2) Select the Archive button and then choose storage location (DVD).

   3) Mark "Archive the study anonymously"

   All cases should contain a dir. and SDY. file. Further, all screenshots that may have been acquired should be included.

   St. Jude QUANTIEN systems
   Find the patient in archive and select the export function.
   1) Mark “to USB memory”, “Internal”, “Spreadsheet” and “Bitmap”.
   2) Select “Export all recordings in study”
   3) Click the green export arrow

A typical filename for the raw data file (.DAT) may be:
{7DDB22A7-DEB9-49FA-B420-3AAE68CD870A}.dat
Do not rename the files.

St. Jude OPTIS (ILUMIEN/Integrated) systems
Find the patient and select the specific FFR traces. Click "export".

1) Select native "RAW"
2) Select "anonymize" and "alternate patient ID" to type the patient-identifier
3) Identify export destination (USB/CD/DVD) and click export.

If there prior to export are cases stored on the selected storage device, the QUANTIEN and OPTIS systems asks if the selected case may be added to the existing database.

Transfer all the files from the CD or USB sticks to a separate folder on a hard drive, ZIP it (not by a Mac) and upload it to our trial system (TrialPartner).

3. Screen shot of final screen after each QFR computation

Missing data is verified as missing and indicated by unique coding.

5.2 Monitoring of the study

The study is monitored according to the Good Clinical Practice (GCP) rules by internal professionals at Aarhus University Hospital. During the study period, internal monitors ensures that the trial is conducted in compliance with the protocol, GCP and applicable regulatory requirements.

The site investigator is responsible for accuracy of data submitted for the study organization and for storing source documents for verification of consistency with the data recorded in the e-CRF.

5.3 Data monitoring committee (DMC)

The safety of the study is monitored by the study PI. No data safety monitoring board is formed as the study is observational and participation is not associated with any relevant increased risk.

5.4 Access to source documentation

The investigator(s)/institution(s) will permit study-related monitoring, audits and regulatory inspection(s), to get passed on necessary information from source data/hospital records. The investigator is responsible and verifies that each patient has consented in writing to the outlined information to be passed on from hospital records to the study database. Data to be passed on includes: Patient related data (Weight, Height, Smoker status, Blood pressure), Biochemistry (Creatinine, GFR). Relevant measures for heart disease (Ejection fraction, Angina CCS-class, NYHA class, atrial fibrillation) Relevant disease / former disease (Microvascular disease, Hypertension, Hypercholesterolemia, Diabetes, History of PCI, History of CABG, Severe asthma or COPD); Procedure related data (Access site, Catheter sizes, Lesion description, Procedure time, Fluoroscopy time, Contrast use, Medical treatment during angiography), and descriptions of any complication potentially related to the study investigation.

5.5 Source data verification

During indicated monitoring, the data recorded in the e-CRF by the investigator is controlled for consistency and correctness with the source data/hospital records.

6. Ethical aspects

6.1 Ethical conduct of the study

The study is conducted in accordance with the protocol, applicable regulatory requirements and the ethical principles of the Declaration of Helsinki as adopted by the 18th World Medical Assembly in Helsinki, Finland in 1964 and subsequent versions.

It is the responsibility of the coordinating investigator to obtain approval of the study protocol/protocol amendments, the patient information and the informed consent form from the Ethical Committee for all patients included in the study.

6.2 Risks, side effects, advantages and disadvantages in participating in the study

QFR-computation is performed using the initial angiographic recordings. The recordings need to be of good quality to make sure that the QFR-measurements are carried out properly. In individual cases a need of making 1-2 extra angiographic recordings per vessel interrogated by FFR would be necessary. For each vessel undergoing FFR measurement, and therefore also QFR calculation, the potential extra amount of contrast is estimated to be up to 15mL and the radiation exposure can in total increase by up to 0.1 mSv. This extremely low extra contrast load and radiation exposure is

not supposed to cause any measurable increased risk for the patient. Interventional cardiologists and support staff at the participating sites are well trained to manage and reduce any procedural risks.

The study group finds no reason to believe there should be any ethical problems connected to this study.

There are no firm advantages related to participating in the study.

6.3 Patient information and informed consent

The patient is included in the study after a signed informed consent form is obtained according to the guidelines given by the local scientific medical ethics committee.

Before signing the informed consent form, eligible patients are provided with full and adequate verbal and written information by the professionals responsible for the study. This information is given when a patient is admitted to the department of cardiology or at a visit at the outpatient clinic. Eligible patients will on request be provided with sufficient time for consideration after initial oral information, where the written information is handed out. If the patient wishes so, study participation can be discussed with a third person; as well a third person can be present during the process of information. The investigator and assistants will help arrange that a third person can be present if requested.

It is the responsibility of the investigator to provide each patient with full and adequate verbal and written information about the objectives, procedures and possible risks and benefits from the study. The written patient information must not be changed without prior discussion with the coordinating investigator and notification of the medical ethics committee.

The patients are notified of their voluntary participation and of their right to withdraw from the study at any time and without giving any particular reason. The patients are also informed that withdrawing from the study does not influence their future treatment. The investigator is responsible for obtaining written informed consent from all patients prior to enrolment into the study.

6.4 Withdrawal

A patient can be withdrawn from the study at any time if it is the wish of the patient or if it is medically indicated. In any circumstance, every effort should be made to document patient outcome, if possible.

A patient's participation in the study is discontinued if any of the following criteria applies:

The patient's general condition contraindicates continuing the study, as judged by the investigator.

Non-eligible patient.

Protocol violation.

If the patient decides to withdraw from the study, he/she is contacted in order to, if he/she agrees, obtain information about the reason(s) for discontinuation. The date and reason for the withdrawal is recorded in the CRF.

6.5 Biological material

Biological material will not be drawn or stored in the study.

7. Study plan

7.1 Steering committee

The steering committee consists of Dr. Niels Ramsing Holm, MD (primary investigator), fellow Birgitte Krogsgaard Andersen, professor Hans Erik Bøtker, MD, PhD and senior consultant Evald Høj Christiansen, MD, PhD (Senior supervisor), Aarhus University Hospital, Skejby

All participating site PI are members of the steering committee:

Gianluca Campo, Cardiovascular Institute, Azienda Ospedaliero-Universitaria di Ferrara, Ferrara, Italy

Marco Götte, Department of Cardiology, Haga Teaching Hospital, Leyweg 275, 2545 CH The Hague, Netherlands

Marco Barbierato, Ospidale dell´angelo, Mestre, Italy

Cristoph Naber, Elizabeth Krankenhaus Essen, Essen, Germany

Hitoshi Matsuo Gifu Heart Center, Tokyo, Japan

All steering committee members oversees the safety of the study, and are participating in the interpretation of data.

7.2 Study procedure training

Participating sites are requested to have operators and dedicated staff trained for the QFR computation. The staff receives instructions and training from Medis medical imaging. Only staff that has been trained by Medis can perform the study computation of QFR. Sites are required to have performed at least 20 supervised cases before study enrollment.

7.3 Case by case feedback

Site PI´s receives confidential case by case core lab feedback on QFR computation throughout the study for continuous optimization of operator and QFR observer skills. The feedback relates to the quality of angiographic acquisitions and QFR computation. On-line feedback is provided in special cases or on request.

7.4 Progress of the study

The progress of the study is checked on a monthly basis by the steering committee. They will receive and evaluate data on inclusion rate.

The steering committee receive data by e-mail and answer by e-mail with copy to all members. On basis on comments from the steering committee members, the coordinating investigators draws preliminary conclusions required to be approved by the steering committee members.

8. Economy

The study is an academic conceived investigator study conducted by interventional cardiologists at Aarhus University Hospital. The study is designed, conducted and reported independent of commercial interests. The study is funded by surplus research funding at the Department of Cardiology, Aarhus University Hospital, Skejby. Funding from external sources is applied for. The manufacturer and distributor of the QFR software (Medis Medical Imaging, Leiden, NL) is not involved in design, conduct, or reporting of the study and provides no funding for the study except for making the Medis Suite solution available for free in the study period and provide training for participating sites.

The patients will not receive any remuneration for participating in the study.

8.1 Insurance

Sponsor is liable for the design of the study as outlined in the protocol. Patients are covered by hospital liability insurance or national health insurance as this is an observational academic study.

Sponsor shall approve the insurance coverage as outlined in the signed site contract for all participating centers before enrollment.

9. Publication and ownership of data

9.1 Ownership of data

The source data itself (patient files, imaging data, blood samples) remains the property of the participating centers. All data and information transferred as by protocol and data generated in association with this study will be held in strict confidence and remains the sole property of PCI-Research, Dep. Cardiology, Aarhus University Hospital.

9.2 Publication

Positive, neutral as well as negative or inconclusive result, are published in an international cardiovascular journal without delay. Publication and author issues are decided by the steering committee on basis of general involvement in the study (drafting of protocol, core laboratory function, analysis, drafting of manuscript etc.) and of number of included patients. Subsequent publications of results from the study are coordinated by the steering committee. The steering committee will receive any proposed publication and/or presentation materials prior to submission of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the steering committee.

9.3 Authorship requirements

Requirements for co-authorship on center level includes at least 1) critical appraisal/revision of the protocol 2) inclusion of at least 15 patients and 3) critical revision of the main manuscript.

10. Disputes

In the unlikely event of disputes regarding any study related matter, 1) the study organization will do its outmost to resolve the issue to the satisfaction of all parties, 2) the steering committee will be asked for positions and recommendations, or lastly 3) the PI has the final decision by acting on behalf of the responsible sponsor, Aarhus University, Denmark.

11. Reference list

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