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Quantitative flow ratio versus fractional flow reserve for guiding percutaneous coronary intervention: design and rationale of the randomised FAVOR III Europe Japan trial

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KEYWORDS

- clinical research
- clinical trials
- fractional flow reserve
- other imaging modalities

Abstract

Quantitative flow ratio (QFR) is a computation of fractional flow reserve (FFR) based on invasive coronary angiographic images. Calculating QFR is less invasive than measuring FFR and may be associated with lower costs. Current evidence supports the call for an adequately powered randomised comparison of QFR and FFR for the evaluation of intermediate coronary stenosis. The aim of the FAVOR III Europe Japan trial is to investigate if a QFR-based diagnostic strategy yields a non-inferior 12-month clinical outcome compared with a standard FFR-guided strategy in the evaluation of patients with intermediary coronary stenosis. FAVOR III Europe Japan is an investigator-initiated, randomised, clinical outcome, non-inferiority trial scheduled to randomise 2,000 patients with either 1) stable angina pectoris and intermediate coronary stenosis, or 2) indications for functional assessment of at least 1 non-culprit lesion after acute myocardial infarction. Up to 40 international centres will randomise patients to either a QFR-based or a standard FFR-based diagnostic strategy. The primary endpoint of major adverse cardiovascular events is a composite of all-cause mortality, any myocardial infarction, and any unplanned coronary revascularisation at 12 months. QFR could emerge as an adenosine- and wire-free alternative to FFR, making the functional evaluation of intermediary coronary stenosis less invasive and more cost-effective.

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Abbreviations

CABG	coronary artery bypass grafting
CTO	chronic total occlusion
FFR	fractional flow reserve
ICA	invasive coronary angiography
LAD	left anterior descending artery
LMCA	left main coronary artery
LVEF	left ventricular ejection fraction
MACE	major adverse cardiovascular events
MI	myocardial infarction
NSTEMI	non-ST-segment elevation myocardial infarction
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
QFR	quantitative flow ratio
RCA	right coronary artery
SOP	standard operating procedure
STEMI	ST-segment elevation myocardial infarction
iFR	instantaneous wave-free ratio

Introduction

Fractional flow reserve (FFR) and the instantaneous wave-free ratio (iFR) are the recommended tests for routine physiological assessment of intermediate coronary stenosis[1]. These pressure wire-based diagnostic methods were shown to provide favourable clinical outcomes in several randomised trials[2-5]. The adoption of FFR has improved following the FAME studies[5,6], but worldwide implementation remains heterogeneous and low. The reasons for this may include physicians' confidence in visual assessment, the incremental and immediate costs, the longer procedure time, the risk related to the advancement of coronary guidewires, and the need for administration of adenosine[7]. To expand the use of physiological guidance for coronary interventions and to overcome the limitations of wire-based methods, invasive coronary angiography (ICA)-based computation methods were developed for less invasive physiological assessments[8-11].

Quantitative flow ratio (QFR) is a method for fast computation of FFR-equivalent measurements based on three-dimensional (3D) reconstructions of coronary arteries and an estimation of contrast flow velocity (eCFV) during ICA. The FAVOR II Europe Japan and FAVOR II China studies[12,13] validated the in-procedure feasibility and diagnostic performance of QFR computation against FFR and showed superiority compared with quantitative angiographic assessment (2D-QCA). The aim of the FAVOR III Europe Japan Study is to determine if a QFR-guided revascularisation strategy provides non-inferior 1-year clinical outcomes as compared to an FFR-guided revascularisation strategy.

Methods

The study is being performed in up to 40 international sites. Enrolment was initiated in November 2018, followed by multicentre enrolment from September 2019. Recruitment is expected to conclude by April 2023, and primary endpoint results will be reported in 2024. A study flowchart is shown in **Figure 1**. The study is listed at ClinicalTrials.gov: NCT03729739. At the point when the manuscript was submitted, 382 patients were enrolled.

STUDY HYPOTHESIS

A QFR-based diagnostic strategy yields a non-inferior clinical outcome as compared to a strategy using pressure wire-based FFR for the assessment of physiological significance and decision-making in patients with intermediate coronary artery stenosis.

PRIMARY ENDPOINTS

The primary endpoint of major adverse cardiovascular events (MACE) is a composite of 1) all-cause mortality, 2) any myocardial infarction, and 3) any unplanned coronary revascularisation at 12 months.

SECONDARY ENDPOINTS

Secondary endpoints are listed in **Supplementary Appendix 1**. Procedural endpoints include performance endpoints on feasibility and procedure time. Lesion-specific documentation for ischaemia is required before repeat revascularisation in patients with angina pectoris. Clinical endpoints are reported for the 30-day, 12-month and 2-year follow-ups. An independent endpoint committee is adjudicating all possible events. Endpoint definitions are provided in **Supplementary Appendix 1**.

PATIENT POPULATION

Patients aged ≥18 with stable angina pectoris or with secondary evaluation of intermediate coronary artery stenosis after acute myocardial infarction and who are able to provide informed consent are eligible for enrolment. Clinical exclusion criteria include ST-segment elevation myocardial infarction (STEMI) within 72 hrs, severe kidney disease, allergy to contrast media or adenosine, atrial fibrillation at the time of ICA, coronary artery bypass graft (CABG) to any target vessel, or left ventricular ejection fraction (LVEF) <30%.

A diagnostic coronary angiography is performed after enrolment and angiographic in- and exclusion criteria have been checked. Patients are eligible for randomisation if they have at least 1 intermediate lesion (diameter stenosis of 40-90% by visual estimate in at least 2 angiographic projections) in a vessel with a reference diameter ≥2.5 mm. Key inclusion and exclusion criteria are provided in **Figure 1**. See **Supplementary Appendix 1** for a full list of the criteria.

The population is described with baseline characteristics, anatomical parameters derived from QCA and the QFR or FFR distribution.

RANDOMISATION

After evaluation of the initial angiographic runs, the patient is randomised in a 1:1 ratio to either QFR or FFR, if all angiographic inclusion criteria and no angiographic exclusion criteria are met **(Supplementary Appendix 1)**.

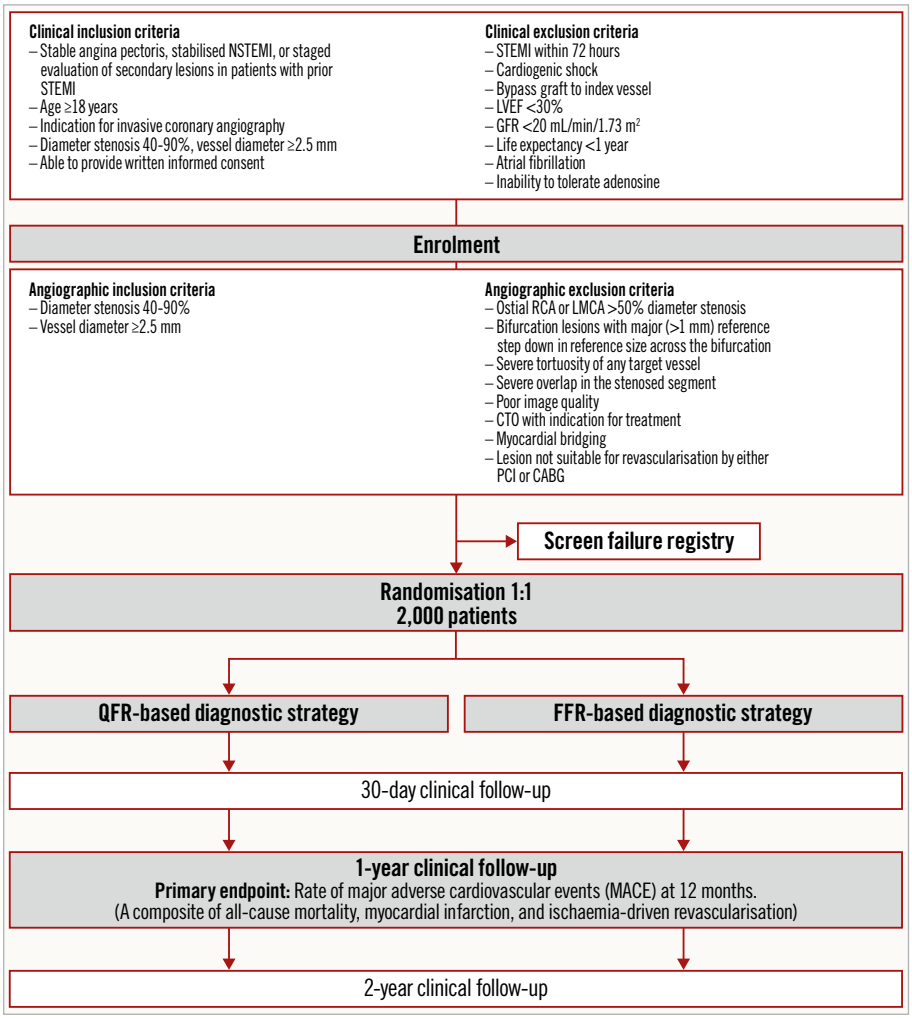

Figure 1. *Study flowchart. CABG: coronary artery bypass graft; CTO: chronic total occlusion; FFR: fractional flow reserve; GFR: glomerular filtration rate; LMCA: left main coronary artery; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-elevation myocardial infarction; PCI: percutaneous coronary intervention; QFR: quantitative flow ratio; RCA: right coronary artery; STEMI: ST-elevation myocardial infarction.*

DIAGNOSTIC STRATEGY

All intermediate lesions in vessel segments with a reference size of at least 2.5 mm are assessed with the allocated method. Non-culprit lesions can be assessed in clinically stable non-ST-segment elevation myocardial infarction (NSTEMI) patients or in a staged evaluation (>72 hours) of patients initially admitted with STEMI.

Randomised patients are subsequently revascularised if indicated by the allocated functional test. Revascularisation is performed by either percutaneous coronary intervention (PCI) or CABG as determined by the clinician or the Heart Team, with the provision that patients with lesions deemed to be significant by the allocated diagnostic strategy undergo immediate or staged (within 60 days) complete coronary revascularisation **(Figure 2)**. The diagnosis by the allocated diagnostic method should be adhered to independent of treatment strategy and whether the treatment is staged.

In cases with failed QFR or FFR evaluations, the patient may be diagnosed with the diagnostic method of the other arm. In the FFR group, any European conformity (CE)-marked resting index may be used as a bailout strategy, if the patient unexpectedly does not tolerate adenosine. Any crossover or use of bailout strategy is reported in measures of feasibility as unsuccessful QFR or FFR measurements.

ETHICS

The study has been notified to the local and regional ethics committees or institutional review boards as appropriate **(Supplementary Appendix 1)**.

STUDY PROCEDURE

INVASIVE CORONARY ANGIOGRAPHY (ICA)

The ICA procedure follows current guidelines and local best practice[14]. The size and type of the catheters are left to the discretion of the treating physician, but the administration of nitroglycerine is mandatory. Two study projections at least 25 degrees apart are acquired for each lesion of interest, at a minimum of 12.5 frames/

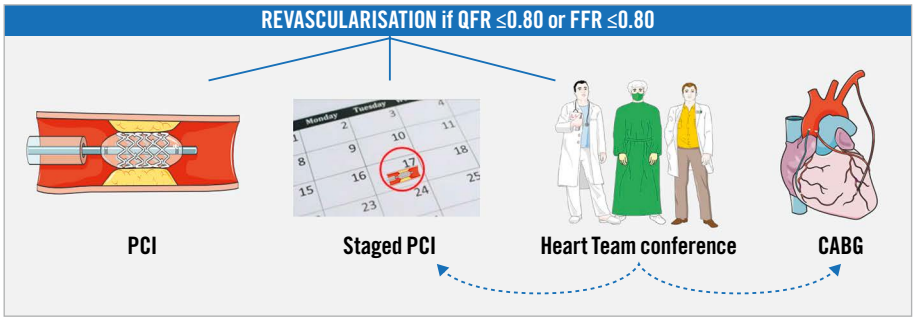

Figure 2. *Coronary revascularisation. All stenoses assessed with either quantitative flow ratio (QFR) or fractional flow reserve (FFR) ≤0.80 should be revascularised. Options for revascularisation: 1) percutaneous coronary intervention (PCI), 2) staged PCI, 3) Heart Team conference leading to either staged PCI or coronary artery bypass grafting (CABG).*

sec, before randomisation. A table of recommended projection angles is provided for all study sites. The study acquisitions should meet the demands for QFR analysis in both arms, i.e., aiming for minimal foreshortening and overlap, avoiding panning and zooming, and ensuring good contrast filling by a long and brisk injection. If the lesion morphology and angiographic quality meet the predefined criteria, the patient is randomised to either the QFR- or the FFR-guided strategy.

QFR ALLOCATION

A description of the QFR computation algorithm is found in **Supplementary Appendix 1**. For extensive review we refer to the existing literature[9].

If a patient is randomised to QFR, the angiographic runs are transferred to the QFR workstation and analysis is performed for all study lesions. QFR **(Figure 3)** is computed on a Windows-based computer (Medis Suite QAngio XA-3D/QFR solution v2.0; Medis Medical Imaging Systems BV). Only trained, certified observers are allowed to perform QFR study procedures. QFR analysis is performed in accordance with the study-specific standard operating procedure (SOP) **(Supplementary Appendix 2)**. Two end-diastolic frames are selected and vessel contours merged for the 3D reconstruction of the segmented vessel. Long segmentations are recommended to make the contrast frame count more reliable. The contrast frame count is performed in an angiographic run with contrast movement clearly visualised. Virtual QFR pullback values may be used to inform about individual contributions in serial stenoses.

The QFR cut-off for the identification of a flow-limiting stenosis is ≤0.80 for all lesions.

FFR ALLOCATION

Standardised FFR measurements are performed according to current clinical recommendations[15]. The FFR cut-off for the identification of a flow-limiting stenosis is ≤0.80 for all lesions. See **Supplementary Appendix 1** for details.

CORONARY REVASCULARISATION

Complete coronary revascularisation is attempted by either PCI or CABG. PCI is performed according to current guidelines using CE-marked permanent drug-eluting stents[1]. Similarly, CABG is performed according to current best practice. QFR should be considered equal to FFR by the surgeon when planning and performing the revascularisation.

PROCEDURE TRAINING

QFR OBSERVERS

The participating sites are requested to allocate staff for training in QFR analysis before performing study procedures. QFR observers are trained and certified by Medis Medical Imaging BV, Leiden, the Netherlands. After the QFR training, all observers are required to submit at least 15 completed QFR analyses for evaluation and feedback from the QFR core laboratory at Aarhus University Hospital. Only fully trained and approved QFR observers can perform study QFR analysis.

TREATING PHYSICIANS

Physicians performing study procedures must complete study-specific training on angiographic quality, as QFR analysis depends on good angiographic quality.

CONTINUOUS FEEDBACK

At the time of conceptualisation, it was unknown whether a learning curve could persist beyond the mandatory training in QFR analysis. To ascertain a high quality QFR analysis, a systematic feedback on image acquisition quality and QFR analysis is provided on a next day basis for all cases analysed by QFR. Feedback is given in interactive online sessions, as recorded feedback or by standardised written feedback formulas.

SAMPLE SIZE CALCULATION

Using the assumptions of a 5% risk of type 1 error, a 15% risk of type 2 error, an estimated 1-year rate of the primary endpoint in both the FFR and the QFR groups of 6.7%, and a non-inferiority limit of 3.4%, sample sizes of 777 patients in each group (1,554 patients in total) are required to be 85% sure that the lower limit of a 1-sided 95% confidence interval (or an equivalent 2-sided 90% confidence interval) will exclude a difference in favour of the FFR group of more than 3.4%. To accommodate for uncertainty of the population risk and patients lost to follow-up, a total of 2,000 patients will be included.

The non-inferiority limit is determined according to the limits applied in the iFR-SWEDEHEART trial (3.2%) and the

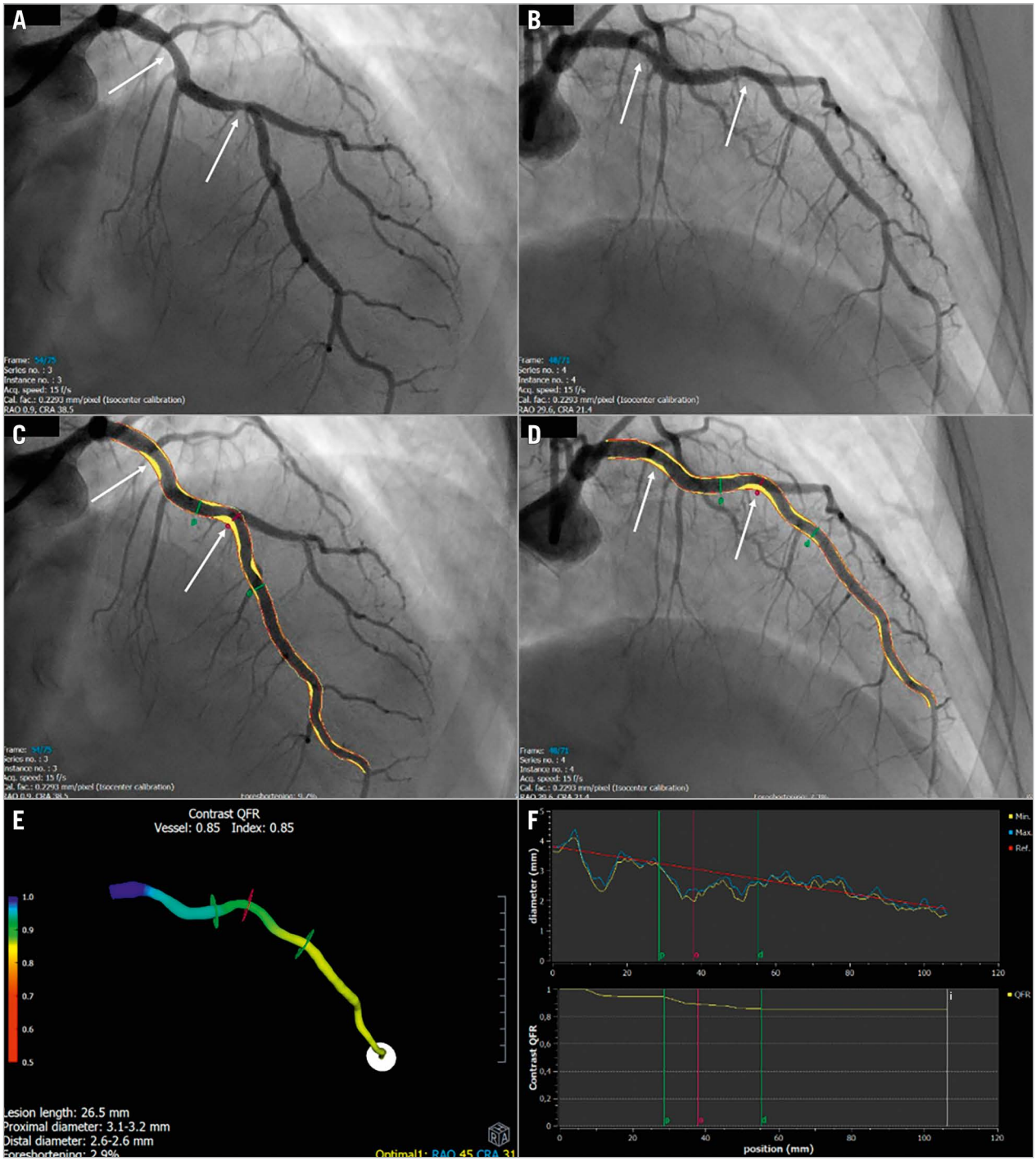

Figure 3. *Representative quantitative flow ratio (QFR) analysis. A,B) Two good angiographic projections of the left anterior descending artery (LAD) at least 25° apart. Two solitary stenoses are identified (white arrows). C,D) Vessel is segmented. Plaque is visualised as yellow areas. Red contours represent the reference vessel function. The red "o" indicates where the lesion is causing the largest drop in QFR value. Proximal (p) and distal (d) lesion delimiters are shown in green. E) 3D model of the vessel with colour-coding of pressure distribution. F) Upper panel: diameter graph. The lesion causing the largest pressure drop is marked with "o" and proximal and distal lesion delimiters "p" and "d". Lower panel: The QFR curve illustrates the decrease in QFR in relation to the two stenoses. The white "i" is an index marker for reading the QFR value at a specific segment allowing for virtual QFR pullbacks.*

DEFINE-FLAIR trial (3.4%), as well as the estimated 1-year rate of the primary endpoint, as a similar population risk is expected. Event rates at 12 months were 6.4% and 6.9% in iFR-SWEDEHEART and DEFINE-FLAIR, respectively[2,3]. An absolute margin is applied, as the population mix is expected to be similar to that in the iFR trials.

STATISTICAL ANALYSIS

All principal analyses are performed in the intention-to-treat population regardless of the actual diagnostic method performed and treatment received. Analyses in the per-protocol population are performed as sensitivity analyses.

Follow-up begins at randomisation. Analysis for the primary endpoint is assessed by 12-month Kaplan-Meier estimates and compared by unadjusted Cox regression analysis. Further information on statistical analysis is found in **Supplementary Appendix 1**.

Discussion

Pressure wire-based functional lesion assessment is the established standard for invasive identification of flow-limiting intermediate coronary artery stenosis[1]. The clinical adoption of FFR is improving but remains low[7,16]. A resting index, iFR, was recently implemented in the revascularisation guidelines of the European Society of Cardiology[1] based on the results of 2 large non-inferiority clinical outcome trials comparing iFR with FFR[2,3]. However, initial data from Italy failed to document an increased use of functional evaluation[7]. A positive evaluation of QFR would allow for the expansion of functional lesion evaluation. Still, physicians' confidence in visual assessment could remain an obstacle to a more widespread introduction of functional lesion evaluation.

QFR was first presented in 2016 and has since been extensively validated in paired analysis with FFR as a reference standard. A good numerical agreement between QFR and FFR was demonstrated in a pooled analysis of prospective studies, while some heterogeneity was observed for binary diagnostic performance estimates[17]. It is anticipated that part of the classification disagreement is an inherent consequence of variability around the diagnostic cut-offs for both tests, as expected for any diagnostic test with a dichotomous cut-off[18]. Classification mismatch is therefore more frequent in studies with a high fraction of cases approaching the diagnostic cut-off[19]. Other factors that may have led to classification mismatches include clinical and procedural characteristics such as microvascular dysfunction, previous myocardial infarction, diabetes, or lesion severity[17,20,21]. However, as feasibility is high and the diagnostic accuracy of QFR appears to be at least as good as iFR with FFR as a reference standard[22], it is justified to proceed with a randomised, clinical outcome trial.

The FAVOR III Europe Japan trial is an open-label, randomised trial aimed to show the non-inferiority of QFR compared with FFR. The design is rather similar to the 2 major trials comparing iFR and FFR[2,3]. The similarity also includes the non-inferiority limit that was accepted with the 2 previous trials.

The primary endpoint of all-cause mortality, any myocardial infarction and any unplanned revascularisation allows for full characterisation of the new QFR strategy. It was important in the selection of this endpoint over target lesion failure to limit the effect of a potential bias in lesion selection and for assessing the feasibility of QFR as a strategy. Physicians are obliged to assess all intermediate lesions in larger vessels to avoid bias in picking lesions most suitable for QFR or FFR. Thus, the primary endpoint implies that it is important to aim for complete revascularisation based on the diagnostic results. Furthermore, the characterisation of QFR as a strategy allows for evaluation of the potential differences in the number of assessed lesions, the number of revascularised lesions and procedure time. As the primary endpoint includes any unplanned revascularisation, documentation for ischaemia, e.g., by FFR, is required in stable patients at re-evaluation to reduce the risk of bias.

It was claimed that the true difference in outcomes between iFR and FFR was only explored when investigating the subgroup of patients where the 2 tests disagreed[23]. The FAVOR III trial aims to evaluate whether a strategy based on QFR is non-inferior to a strategy based on FFR with regard to clinical outcomes. Evaluation of a new diagnostic modality requires evaluation of feasibility in clinical practice, e.g., it is unknown if a QFR strategy inadvertently affects the decision to evaluate a lesion or influences the quality of subsequent revascularisation. Thus, a simple lesion-level randomisation or an evaluation of cases with FFR-QFR mismatch may not provide sufficient evidence to support mainstream clinical use.

The study population risk is expected to reflect the risk in the general European population with symptoms suggestive of obstructive coronary artery disease and at least 1 intermediate stenosis. The risk reported in the iFR trials showed a Northern European population with a low incidence of diabetes and low smoking rates. With almost half of the participating sites located in Southern Europe, the population risk in FAVOR III might be slightly higher. Still, we maintain the same non-inferiority limit as applied in the iFR trials. It is currently unknown whether QFR as a strategy results in more repeat revascularisations, and therefore whether QFR will prove non-inferior is not a pre-given fact.

The use of functional coronary lesion evaluation is limited in most parts of the world. With angiographic evaluation still being the standard in several countries, the parallel FAVOR III China trial (ClinicalTrials.gov: NCT03656848) is aimed to show if QFR guidance provides a superior clinical outcome compared with angiographic guidance. The results of both FAVOR III trials could introduce QFR into general clinical practice and thereby improve the diagnostic approach in centres currently relying on angiography alone or could reduce costs related to pressure wire-based functional evaluation.

Limitations

Several design decisions and limitations are discussed above. Additional limitations include 1) risk of biased case selection, as the angiogram could be known before the study procedure, 2) bias in treatment, e.g., if the choice of modus for revascularisation or optimisation with intravascular imaging differs between the groups, and 3) the evaluation before repeat revascularisation with FFR in both groups could favour FFR.

Conclusions

The FAVOR III Europe Japan randomised trial may determine if QFR-guided coronary artery revascularisation is non-inferior to FFR-guided coronary revascularisation with respect to clinical outcomes.

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Conflict of interest statement

S. Tu has received institutional research grants from Pulse Medical Imaging. J. Escaned has received consultant fees or speaker fees at educational events from Abbott, Boston Scientific, and Philips/Volcano. U. Landmesser has received lecture or advisory honoraria from Abbott, Amgen, Novarti, Bayer, and Sanofi. G. Campo has received an institutional research grant from Medis Medical Imaging BV. W. Wijns has received an institutional research grant and honoraria from MicroPort; is a co-founder of Argonauts; and an innovation facilitator and medical advisor for Rede Optimus. N.R. Holm received speaker fees and institutional research grants from Abbott, Boston Scientific, and Medis Medical Imaging BV. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Methods.

Supplementary Appendix 2. FAVOR III QFR standard operating procedure.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00214

Supplementary data

Supplementary Appendix 1. Methods

Study procedure

Details on FFR recording

Before infusion, the resting distal pressure/proximal pressure (Pd/Pa) is registered.

Intracoronary (i.v.) adenosine

FFR is recorded during hyperemia induced by i.v. adenosine infused at a concentration of 140 $\mu gL^{-1}min^{-1}$. The infusion rate may be increased to 200 $\mu gL^{-1}min^{-1}$ at the operator's discretion in cases with fluctuating hemodynamics. In case of serial stenosis, a pullback trace is recorded during i.v. adenosine infusion to assess the contribution to the pressure drop by each lesion.

Intracoronary (i.c.) adenosine

Recording of FFR with hyperemia induced by i.c. adenosine is allowed if serial lesions are not present. After registration of resting distal pressure/proximal pressure (Pd/Pa), a 100 ug (RCA) or 200 ug (LCA) adenosine bolus is administrated for 1-2 seconds, followed by a brief bolus of saline. The procedure should be repeated if the values are considered unreliable by the treating physician according to standard criteria.

FFR is calculated as the ratio of distal mean pressure measured by the pressure-wire to the proximal mean pressure during hyperemia.

QFR computation

QFR is an estimate of FFR based on stenosis geometry and estimated flow velocity.

Information about stenosis geometry is based on a 3D reconstruction of the vessel. Using two angiographic projections at least 25 degrees apart, the vessel of interest is segmented without its side branches and a 3D model of the anatomy is created. A reference vessel is generated, describing the size of the vessel lumen as expected if the vessel was healthy. The deviation of the segmented, diseased vessel lumen size from the healthy reference size characterizes the stenosis geometry.

Three different flow models have been described for computation of QFR. In the FAVOR III trial, the contrast flow QFR (cQFR) value is used as the final QFR value for clinical decision-making. This computation model uses an estimation of the mean hyperemic flow velocity (HFV) based on frame counting during contrast injection (estimated contrast flow velocity, eCFV), without pharmacologically induced hyperemia. The estimation of HFV from eCFV is calculated based on the equation: $HFV = a0 + a1 * eCFV + a2 * eCFV^2$, where a0, a1 and a2 are constants obtained from training datasets. A detailed description of the methodology can be found in the FAVOR Pilot Study[9].

Statistical analysis

All principal analyses are performed in the intension-to-treat population regardless of actual performed analysis and treatment received. Analyses in the per-protocol population are performed as sensitivity analyses.

The extent of missing data is accessed before the statistical analysis and best-worst and worst-best case sensitivity analyses are applied in case of more than 10% missing data points in one variable. Multiple imputation is applied in case of missing data causing bias or limiting statistical power. Baseline characteristics and procedural characteristics are presented as count and percentages, continuous variables as mean and standard deviation if normal distributed; else reported as medians and interquartile range. Continuous variables are compared with the two-sample t-test or the Mann-Whitney U test, if data follows a non-normal distribution. Categorical variables are analyzed with the $\chi 2$ test or Fisher exact test if cell numbers are small.

Follow-up begins at randomization. Analysis for the primary endpoint is assessed by 12-month Kaplan-Meier estimates and compared by unadjusted Cox regression analysis. Adjusted Cox analysis results are presented.

Both intention-to-treat and per protocol analysis is performed for composite endpoints. All endpoints are assessed until death or loss to follow-up and Kaplan-Meier time-to-event curves are plotted. Patient´s treated by the standard FFR based diagnostic strategy are used as the reference group for the overall and subgroup analyses.

Competing risk analyses will be performed and if it is considered that competing events must be taken into account, the Aalen-Johansen estimates of the cause specific CIF is used instead of Kaplan-Meier. The assumption of proportional hazards in the Cox regression is assessed graphically by plot of observed versus predicted values and by log-log plot.

Kaplan Meier estimates for major adverse cardiac events at 12 months of follow-up are calculated for pre-specified subgroups of patients (classified by baseline demographic and clinical characteristics). Effects of baseline differences between groups are evaluated by Cox proportional hazard regression analysis. A two-sided p value of less than 0.05 indicates significance. Subgroup analyses are prespecified for the following subgroups; single vessel disease, multivessel disease, isolated lesions,

tandem lesions, optimal and sub-optimal angiographic results, stable angina pectoris and acute coronary syndrome (ACS), diabetes, sex, calcified lesions, and SYNTAX score above 11.

Data acquisition

The applied data capture system, Trialpartner (generated by Jakob Hjort, Institute of Clinical Medicine, Aarhus University, Denmark) has integrated modules for enrolment and randomization, eCRF, event reporting, remote and on-site monitoring, study documents library, secure recorded feedback, and a facility for secure upload of source files including anonymized angiographic files, QFR session files, and FFR waveforms. Tech sheets are provided for in-procedure data registration allowing for easy capture of information for the eCRF.

Endpoints

Table I. Primary and secondary endpoints.

	Endpoint	Specification
Primary endpoints	Major adverse cardiovascular events (MACE)	All-cause mortality, any myocardial infarction, and any unplanned revascularization at 12 months
Secondary endpoints	Target vessel failure	A composite of cardiac death, target vessel myocardial infarction and ischemic driven target vessel revascularization
	Individual clinical endpoints assessed at 30 days, 12 months and 2 years	All-cause mortality Cardiac death Any myocardial infarction (MI) All-cause mortality, any myocardial infarction, and any unplanned revascularization (MACE) Stroke Target vessel MI Any unplanned revascularization Any ischemia driven de novo revascularization Ischemia driven target vessel revascularization Ischemia driven treated target lesion revascularization Ischemia driven measured segment revascularization Ischemia driven measured segment de novo revascularization
	Procedural endpoints	Feasibility of QFR Feasibility of FFR Total procedure time

		Contrast volume Fluoroscopy time Number of lesions interrogated Number of stents implanted

MACE; major adverse cardiovascular events, MI; myocardial infarction, QFR; quantitative flow ratio, FFR; fractional flow reserve

Endpoint definitions

Clinical endpoint definitions

All-cause mortality (all deaths)

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.

Any myocardial infarction

As defined in 1.6 or 1.7, in any vessel.

Any revascularization

Coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) of any lesion.

Planned Revascularization:

Revascularization will be considered planned when it is decided at the time of the index procedure, based on the results of angiography and functional testing. Planned revascularization could be performed at the time of the index procedure or within 60 days. Such revascularization will be considered as "primary" revascularization and will not be considered as an endpoint. The "planned" status of the revascularization will be adjudicated.

Unplanned Revascularization:

Revascularization will be considered "unplanned" when not performed as part of standard care during the index procedure or if it was not planned as a staged procedure to occur within 60 days.

Stroke

Stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Death after a stroke that is either a direct consequence of the stroke or a complication of the stroke.

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 the cardiac procedure within 28 days from the procedure. If death is not clearly attributable to other non-cardiac causes, it is adjudicated as cardiac death.

Myocardial infarction (spontaneous)

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 by the third universal definition of myocardial infarction, Thygesen et al. Circulation 2012:

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.

To be classified as a *target vessel MI,* the culprit lesion must be placed in the index vessel.

Procedure related myocardial infarction

Myocardial infarction related to the index procedure (both PCI and CABG) or a staged procedure

Definitions follow the 2013 SCAI criteria by Moussa et al. J Am Coll Cardiol. 2013;62(17):1563-70. In patients with normal baseline CK-MB: The peak CK-MB measured within 48 hours of the procedure rises to ≥10x the local laboratory ULN, or to ≥5x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent left bundle branch block OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 hours of the PCI rises to ≥70x the local laboratory ULN, or ≥35x ULN with new pathologic Q-waves in ≥2 contiguous leads or new persistent left bundle branch block.

2. In patients with elevated baseline CK-MB (or cTn) in whom the biomarker levels are stable or falling: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level.

3. In patients with elevated baseline CK-MB (or cTn) in whom the peak biomarker levels have not been clearly reached, The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above plus new ST-segment elevation or depression plus signs consistent with a clinically relevant MI, such as new onset or worsening heart failure or sustained hypotension.

In addition, either (i) symptoms suggestive of cardiac ischemia or (ii) new ischemic ECG changes or new LBBB, or (iii) angiographic loss of patency of a major coronary artery or a side branch or persistent slow- or no-flow or embolization, or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.

Ischemic driven target vessel revascularization (TVR)

Coronary artery bypass grafting or PCI of index lesion due to ischemia causing lesions.

Procedural endpoint definitions

Feasibility of QFR

Percentage of successful QFR in patients allocated to a QFR based diagnostic strategy

Feasibility of FFR

Percentage of successfully performed FFR measurements in vessels with attempted FFR (vessel level)

Percentages of patients with successful FFR measurements (all attempted)

Procedure time

Time from introduction of the sheet until the sheet for coronary access is removed from the patient

Contrast volume

Total volume of contrast used in the procedure

Fluoroscopy time

Total fluoroscopy time for the procedure

Number of stents implanted

Total number of stents implanted during the procedure. Stents implanted in a staged procedure are included

Randomization process

Informed consent is obtained prior to coronary angiography. Upon evaluation of the initial angiographic runs, the patient is randomized in a 1:1 ratio to either QFR or FFR if all angiographic inclusion criteria and no angiographic exclusion criteria are met. Reasons for exclusion before randomization are recorded in a screen failure registry (Figure 1).

Randomization is performed 1:1 in permuted blocks for site, with block sizes randomly varying between 4, 6 and 8, and with two-level stratification for 1) at least one left anterior descending coronary artery (LAD) study lesion, and 2) diabetes mellitus. Randomization is performed using a proven concealed, end-to-end encrypted, computer-based system (Trialpartner) with randomization sequences created by Jakob Hjort, Institute of Clinical Medicine, Aarhus University, Aarhus, Denmark.

Ethics

Continued. Notifications to local or national medical ethics committees are performed by the national or local coordinating investigators. Medis Suite QFR is CE-marked and FDA 510k listed and is being used within its labeled indication. The centers are initiated when study-specific training

of at least one QFR observer and one investigator are completed, and local EC/IRB approval is granted. During the study period, internal monitors ensure that the trial is conducted in compliance with the protocol, good clinical practice and applicable regulatory requirements by remote monitoring and risk based on-site monitoring.

Study procedures – FFR

Volcano (San Diego, California, USA), Abbott (Illinois, USA) and Boston Scientific pressure wires may be used. After preparation and equalization, the wire is advanced to a position with the transducer in a stable position distal to all lesions in the target vessel. The wire location is documented by angiography for all measurements The entire FFR trace is recorded from before start of adenosine injection/infusion (resting conditions) until verification of drift not exceeding defined limits of 0.96-1.04, or 0.98-1.02 in case of FFR values in the 0.76-0.84 interval.

FFR recording

Before infusion, the resting distal pressure/proximal pressure (Pd/Pa) is registered. Hyperemia is induced by either i.v. or i.c. adenosine. In case of serial stenosis, a pullback trace is recorded during i.v. adenosine infusion to assess the contribution to the pressure drop by each lesion.

Considerations regarding cost effectiveness

As QFR offers a less invasive and presumably more cost-effective diagnostic methodology than FFR and iwFR, QFR is expected to expand the use of functional lesion assessment of coronary stenosis in patients with stable angina and in evaluation of non-culprit lesions.

The cost-effectiveness of QFR still remains to be studied. Eliminating the need for expensive single use equipment and adenosine, QFR is presumed to be more cost-effective than FFR. QFR may allow for full integration in angiographic equipment but such systems are not yet available. In FAVOR III, QFR is analyzed during the ICA using a regular Windows computer connected to the angiographic equipment. Allocation of dedicated staff for training and analysis is necessary. This could have implications for the staffing level, but as QFR is fast and if QFR expands the use of functional evaluation, this might lead to implantation of fewer stents and hence might reduce overall procedure time. A substudy investigating the cost-effectiveness of introducing QFR in full scale clinical practice is planned.

Funding

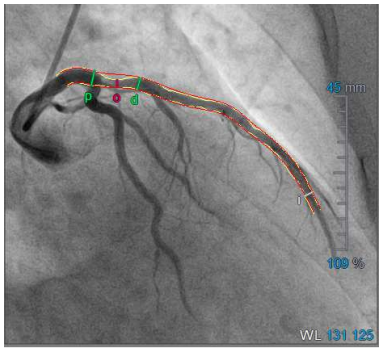
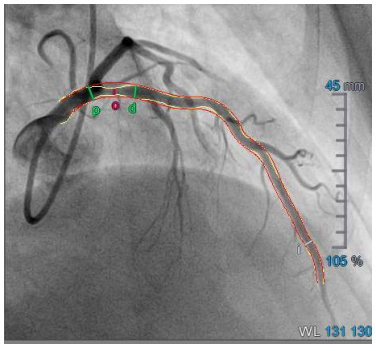
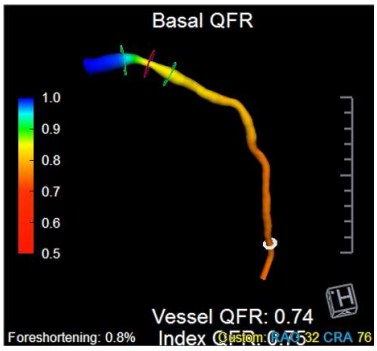
The study is designed, conducted, and reported independent of commercial interests. The study is funded by the manufacturer and distributor of the QFR software (Medis Medical Imaging bv., Leiden, The Netherlands). Medis is making the Medis Suite solution available for free for all participating sites until presentation of the primary endpoint and provides initial training and certification of QFR observers at participating sites.

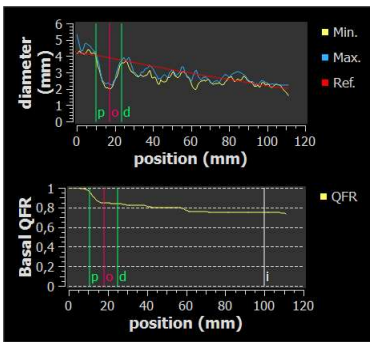
Supplementary Appendix 2

FAVOR III

QFR Standard Operating Procedure

Medis suite QFR version 2.0



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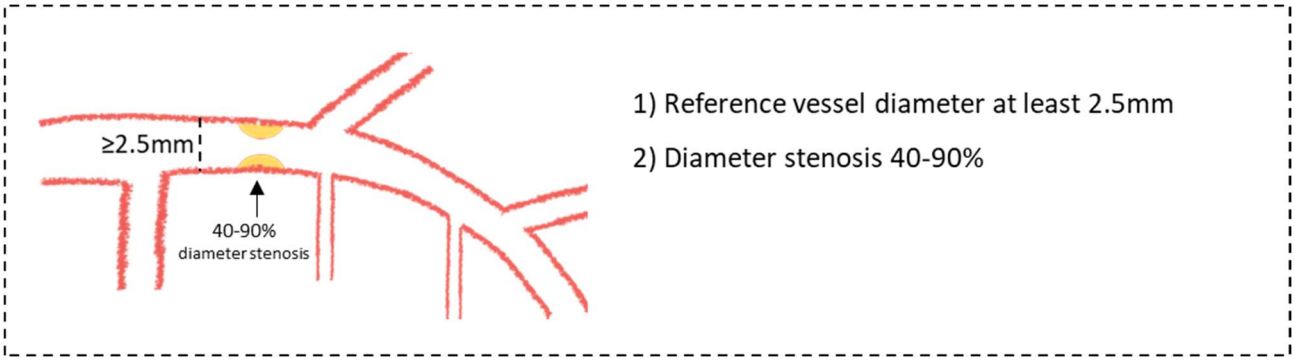
1 Angiographic in- and exclusion criteria

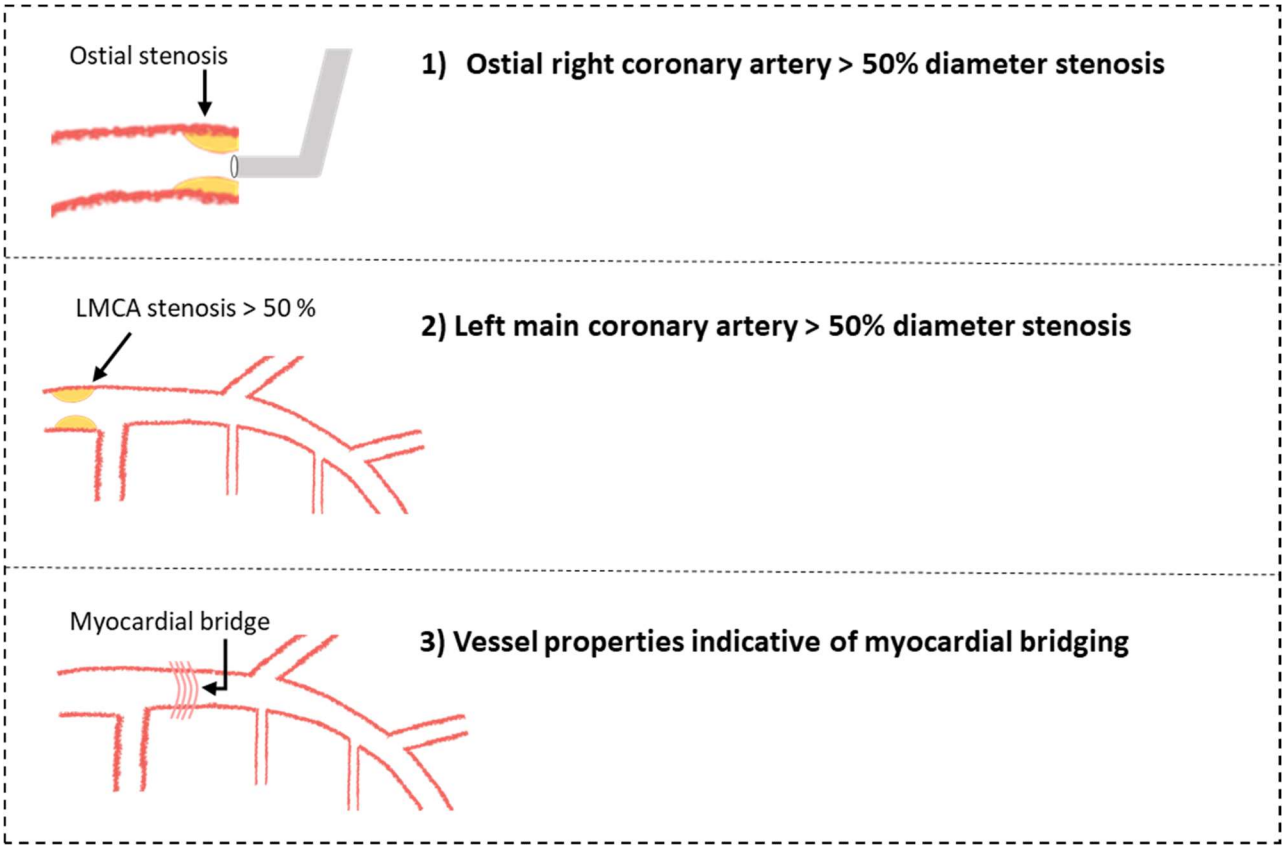
1.1 Inclusion criteria



Supplemental figure 1 *Angiographic inclusion criteria. Both these criteria must apply* to *least one stenosis*

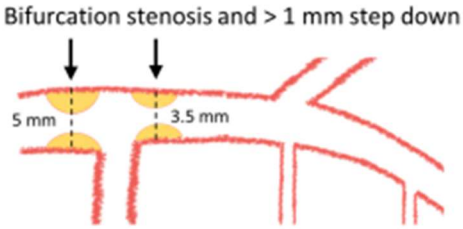
1.2 Exclusion criteria

If one or more of the following criteria apply, the patient is excluded:



Supplemental figure 2 *Angiographic inclusion criteria*

4) Bifurcation stenosis with major (>1 mm) step down in reference size across bifurcation

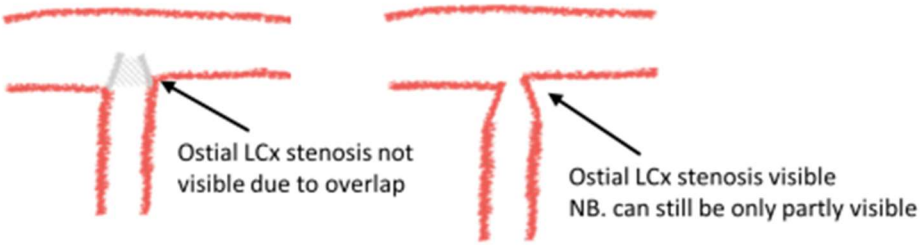


5) Severe tortuosity of any target vessel

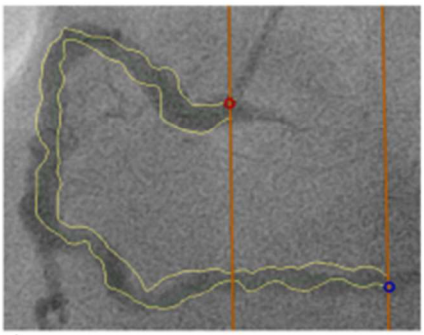
Cases with tortuosity causing overlap or foreshortening involving the stenosis segment may lead to difficulties in corresponding the two projections

6) Severe overlap of the stenosed segment

Look carefully for lesions in the LCx ostium. Ostial LCx stenosis is often difficult to visualize without overlap. Only include if the stenosis is present in its full length in two projections. Look at the diameter function curves to tell whether they correspond.



7) Poor image quality precluding identification of vessel contours



Adjust angiographic equipment settings during initial angiogram if necessary. Exclude patient if image quality is still insufficient for QFR.

After randomization it is no longer possible to exclude a patient due to insufficient image quality. If QFR can not be performed, FFR should be measured.

The application is not able to recognize the vessel contours in cases with excessively low angiographic quality or poor contrast filling

Supplemental figure 3 *Angiographic exclusion criteria*

2 Step-by-step manual

The Medis Suite QAngio XA 3D/QFR solution (Medis medical imaging system bv, Leiden, The Netherlands) is used for computation of QFR in FAVOR III E-J. The Medis Suite QAngio XA 3D/QFR solution requires installation on a Windows-based computer. QFR computation is described in step-by-step below.

2.1 Coronary angiography

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

- Inject I.C. nitroglycerin as early as possible
- Use framerate of at least 12.5 frames/sec
- Make sure that the catheter is filled with contrast before the injection and aim for good catheter alignment (i.e. after administration of nitroglycerin)
- Use brisk, continuous, and fast contrast injections. Aim for full vessel filling during 3 full cardiac cycles
- Minimize overlap of target segments, esp. target lesion
- Avoid foreshortening of the vessel, esp. target lesion
- Avoid zooming but use of other means to increase image quality are encouraged.
- Avoid moving the table early after injection
- Aim for projections perpendicular to the target vessel. It is strongly recommended to use the suggested projection angles (Supplemental Supplemental table **1**)
- Make sure that the entire area of interest is visible in both projections

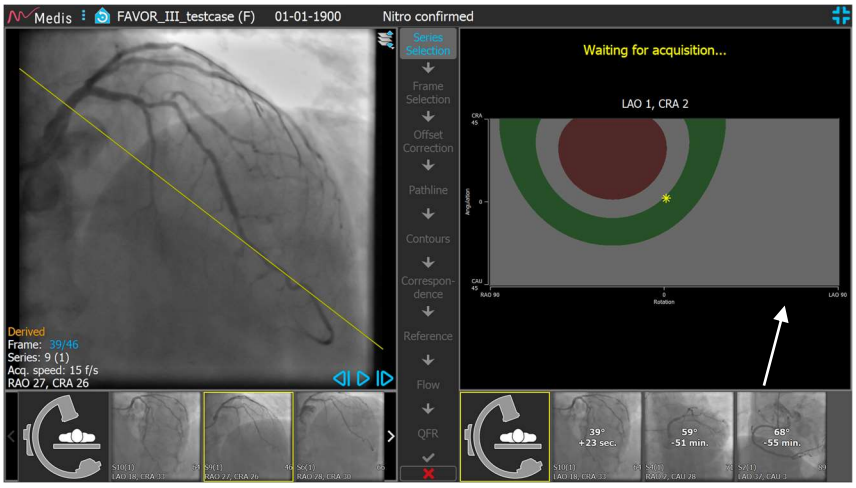
Vessel / bifurcation	1st view	2nd view
LM + LAD/LCx	RAO 20 , CAU 45	AP , CAU 10
LAD/Diag	AP , CRA 45	RAO 30, CRA 20
LCx/OM	LAO 10 , CAU 25	RAO 25 , CAU 35
RCA	LAO 45 , CAU 10	LAO 20, CRA 20

Supplemental table 1 *Recommended projection angles for specific lesion segments. Angulation of more than 25° between projections is required*

2.2 Acquisition Guide (optional)

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

1. Transfer a first good projection to the QFR computer (see 2.3)
2. Left-click on the projection and start the QFR 2.0 application from the upper left corner
3. Choose *Acquisition Guide* (Supplemental Supplemental figure 4, red box). The yellow line indicates the new projection angle, and should be approximately perpendicular to the target vessel at the
   lesion site
   a. If several lesions are located in the same vessel, a compromise must be made to ensure that most of the lesions and the most severe lesions are seen in the same projection
4. Move the projection line by moving the yellow spot (Supplemental Supplemental figure 4, white arrow) in the Acquisition Guide indicator. Aim to 1) keep the yellow dot inside the green area and 2) achieve an angle difference of 35-50 degrees
5. Position the C-arm as proposed by the Guide
6. In case of excessive overlap or foreshortening 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 to the proposed position



Supplemental figure 4 *Acquisition projection angle. Red box: Acquisition Guide. White arrow: Yellow dot indicating position of C-arm. Keep the yellow dot in the green zone.*

2.3 Image transfer

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

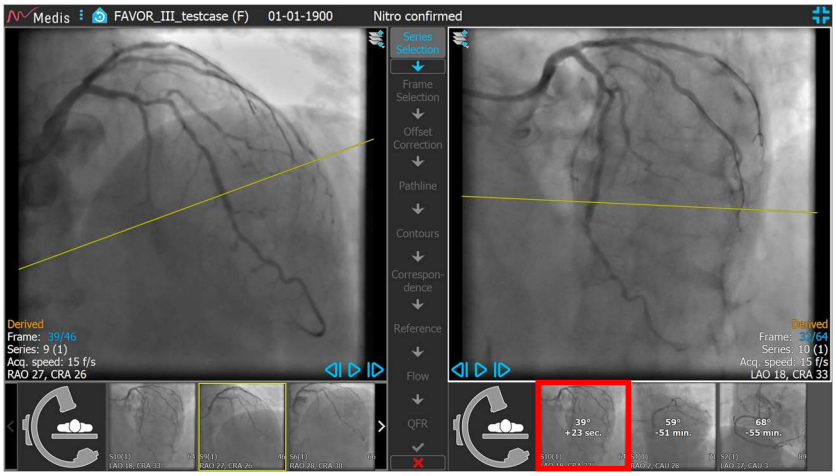
2.4 Angiographic run selection

Optimal projections are chosen according to the following criteria:

- Minimal overlap of the target vessel, esp. target lesion
- Good contrast injection, filling the entire vessel
- Includes both healthy parts of the vessel proximal and distal to all analysed stenoses

1. Identify the optimal projection in the left panel and click the best run.
2. Choose between the other runs in the bottom of the right panel (Supplemental Supplemental figure **5**, red box) to get a presentation of angiographic runs ≥ 25 degrees separated from the selected run
3. Evaluate the potential runs by dragging them into the (empty), right panel (Supplemental Supplemental figure **5***)*
    - If the two projections are not 25 degrees apart, please ask the physician to acquire an additional acquisition. It is *not recommended* to perform a QFR analysis with two projections <25 degrees apart!

4. Keep the best 2nd run in the panel with the yellow projection line perpendicular to the target lesion(s)
    - Make sure both projections are in the same phase looking at the time difference



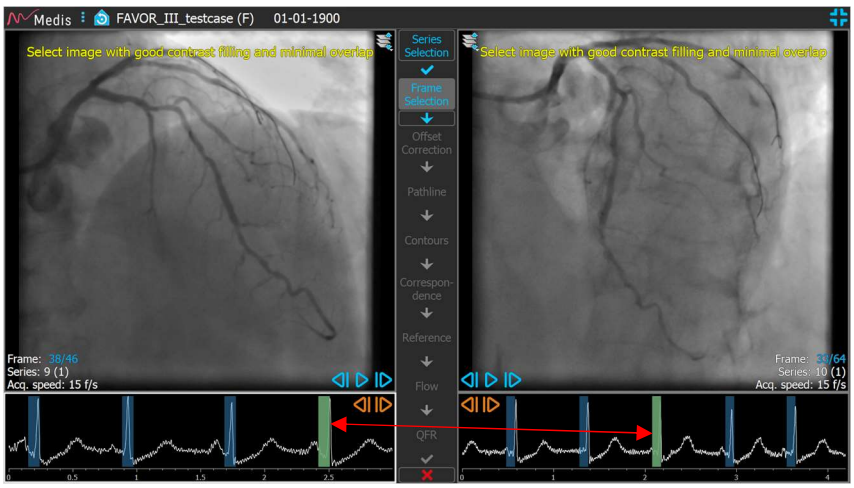
Supplemental figure 5 *Angiographic run selection. Red box: Series Selection*

2.5 Frame selection

The best frames for analysis are selected by ensuring:

- The target lesion site(s) is not overlapped
- The entire vessel is filled with contrast
- Frame includes both healthy parts of the vessel proximal and distal to analysed stenoses
- Frames are end-diastolic (ED) – preferably frames recorded between the P-wave and the QRS-complex (Supplemental Supplemental figure 6).
- The software automatically suggests ED frames (Supplemental figure 6)
- In case of poor image quality in ED frames: scroll through the runs to find a heart beat with better image quality (sharp contours, no overlap of stenosis, etc.)
- Ensure that the two views are selected in the same cardiac phase. If ECG trace is available, at similar ECG positions.

If the ED frame is not optimal for analysis due to bad contrast, poor edges due to vessel movement, overlap, etc., another frame in the ED can be used. The similar ED frame should then be used for both runs, to ensure that they are in the same cardiac phase. A maximum of two frames before the ED can be used conditioned on an acq. speed of 15 frames/second

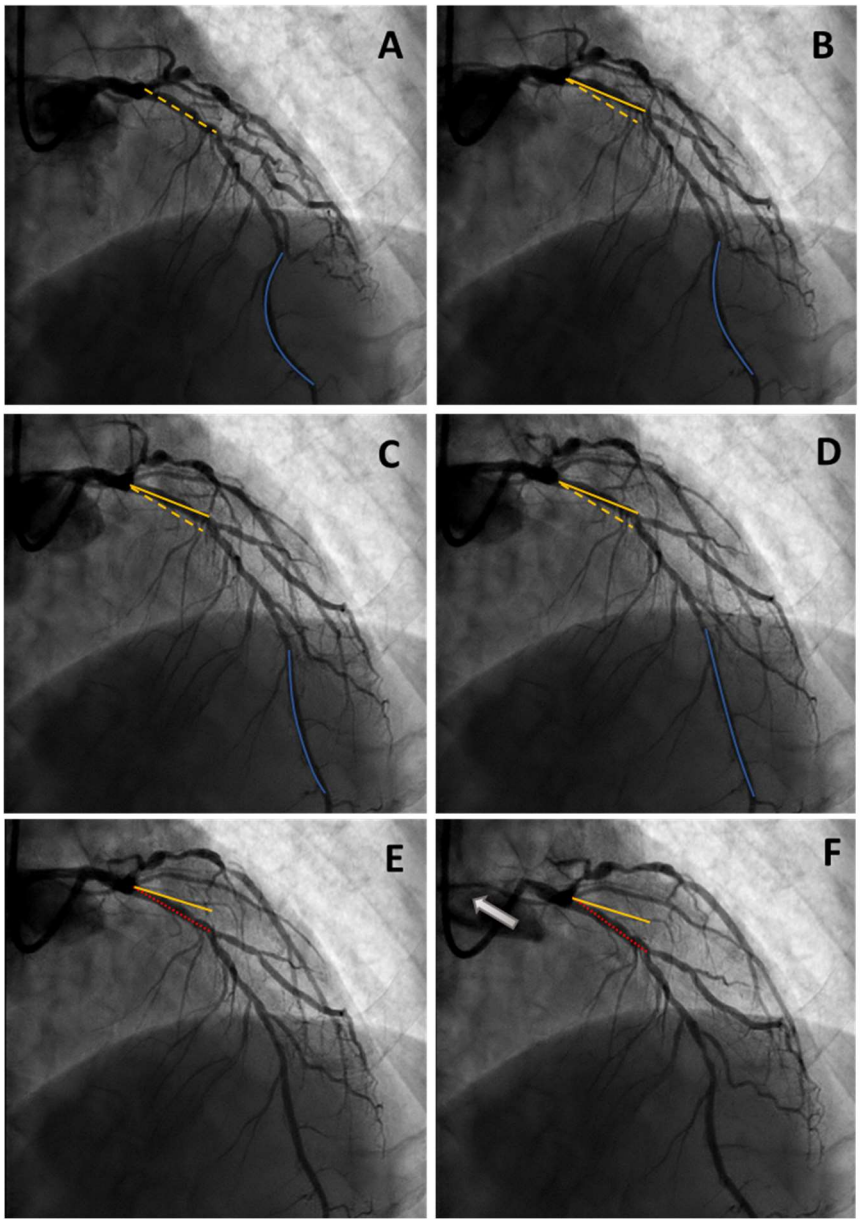


Supplemental figure 6 *Frame selection. Note that both runs are in the same ED phase and the epipolar line is approximately perpendicular to the lesions. Blue highlights are automated indications of end-diastole.*

Selection of ED frame in case of no ECG:

Frame selection for Left coronary artery (LAD) Supplemental figure 7 From frame A to D, LAD moves to upper left position of the image. In frame E, a small downward “tilt” can be seen in LAD. In frame F, the excess contrast in bulbus is flushed away as aortic valve is opening, marking the beginning of the systole. In this case, frame D would be best choice for ED frame. Supplemental figure 7)

- The frame in which the accumulated excess of contrast flushes away into the Aorta is when the aortic valve is opening. The ED frame is 1 or 2 frames (when using 15 f/s) before valve opening (depending on frame rate and heart rate)
- At the end of the diastole;
    - LCA is in the left upper position of the image
    - LCA should be in a stable position just before the “tilt” of LAD
    - LAD is “stretched out”



LAD moves up in the image (from dotted yellow line in image A to plain yellow line in B, C and D)

LAD "stretched out" (blue line in distal LAD is curved in image A and completely stretched out in image D)

Image D is the best choice for an ED frame. In this image, LAD is in the upper part of the image and "stretched out".

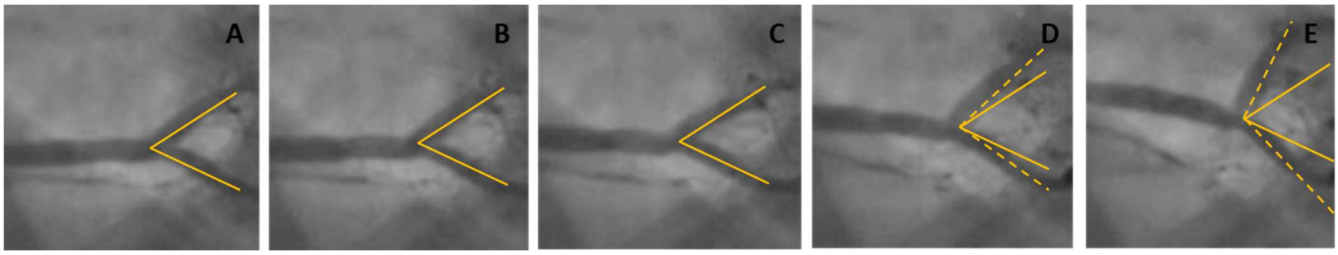
A **downward tilt of LAD** is seen in image E and F (LAD moves from plain yellow line in image D to dotted red line in E and F).
This marks the beginning of the systolic phase. The frame just before this is the ED frame.

The beginning of the systole can furthermore be recognized by outflow of contrast (white arrow in image F) as the aortic valve is opening.

Supplemental figure 7 *From frame A to D, LAD moves to upper left position of the image. In frame E, a small downward "tilt" can be seen in LAD. In frame F, the excess contrast in bulbus is flushed away as aortic valve is opening, marking the beginning of the systole. In this case, frame D would be best choice for ED frame.*

Frame selection for Right coronary artery (RCA)

- 1-2 images before valve opening (when using 15 f/s) (as for LCA)
- RCA should be in a stable position
- The angle between the distal branches (RDP and PLA) is relatively stable in the first part of the diastole but changes at the ED phase. The point for change in angle can be used to identify the ED phase (Supplemental Supplemental figure 8)

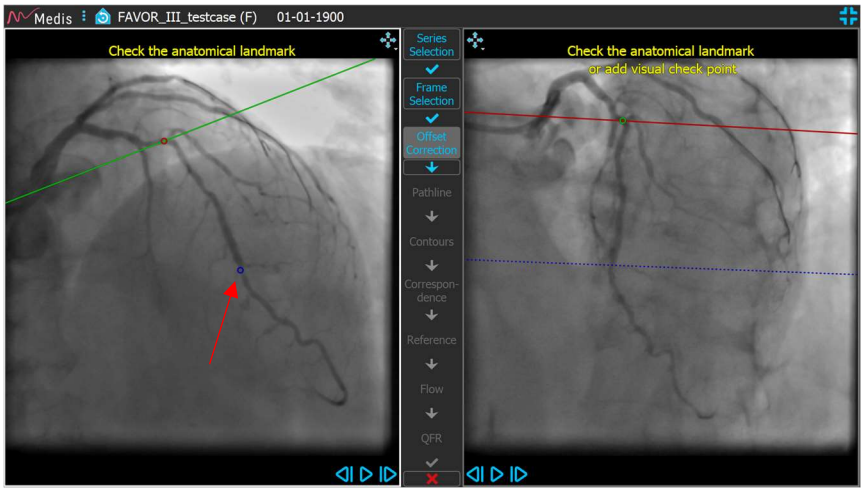


Supplemental figure 8 *Frame A, B, C: relative stable angle between distal branches. Frame D: Angle between RDP and PLA is opening. D is the best choice for ED frame selection. Frame E: Angle increases even more. It is not the size of the angle but the moment of the change after a relative stable angle, that represents the end diastole*

2.6 3D target vessel reconstruction

To link the two projections, corresponding landmarks near the lesion are identified by an "offset point" in each projection (Supplemental Supplemental figure **9**). Make sure to:

- Identify a landmark easily identified in both projections (i.e. a bifurcation, a focal stenosis, or the take-off of a side branch) at, or near, the middle of the vessel
- Place the "offset point" in the middle of the main vessel diameter
- If using a side branch:
    - Select a side branch that departs perpendicularly from the main branch if possible



Supplemental figure 9 *Corresponding point is marked by the red and green spot in the left and right panel, respectively. In this example, the take-off of a side branch/lesion point is easily recognized in both projections and is selected as the point to correspond.*

- Use the *Indicate checkpoints* option, to make sure that the projections are linked together properly. The check is performed as follows;

- Choose another landmark, identifiable in both projections (i.e. a bifurcation, a focal stenosis or the take-off of a side branch) and click on the landmark (Supplemental Supplemental figure 9, red arrow)
- Use the checkpoints to verify positions proximally and distally to the corresponding point

The matching checkpoints are shown as a blue circle in one projection and as a blue dotted line in the other,

- Revise the position of the chosen offset point or select an entirely different location for the offset point if the checkpoints positions are not consistent in the two projections
- A slight mismatch in one of the checkpoints is acceptable and can occur due to minor foreshortening in one of the images. This will be corrected at the next analysis step, if proximal and distal points are placed at clear anatomical landmarks

2.7 Indicating target vessel

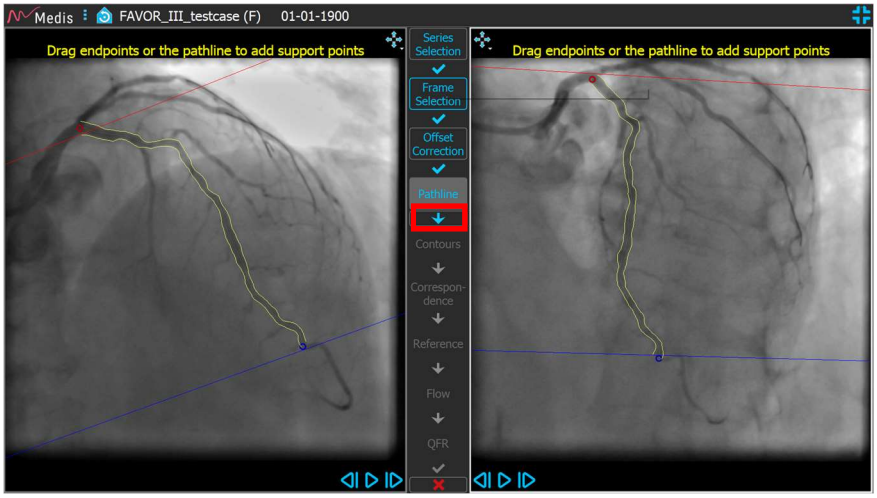
Indication of segment to analyse

1) Ensure that the analysed segment includes reference segments at both ends for optimal reference vessel reconstruction
2) The proximal path line point should be placed in a "most healthy" part of the vessel, proximal to all stenotic segments – preferably at the ostium
3) When the proximal path line point is added in one panel, a corresponding support line is shown in the other panel. The proximal path line point in the second projection is placed on this support line at the supposedly same anatomical location
    a. Positioning the proximal point in relation to an anatomical landmark that can be recognized in both projections is particularly necessary if the support line is parallel to the proximal or distal part of the vessel.
    b. If proximal parts of the vessel correspond poorly, the proximal point in the second projection should not be placed at the indicator line. Instead, landmarks should be used to ensure the same position of the proximal points in the two projections. Later, the projections may need to be "*forced corresponded*" (see 2.9)
4) The distal point is placed distally to the evaluated lesion, at a clear landmark.

NB: It is important to indicate a long segment for analysis to allow for proper frame counting

After indicating proximal and distal points for segmentation in both projections, the vessel path line (Supplemental Supplemental figure **10**) is shown. Verify the path line visually for both projections. If it deviates from the target vessel, it is dragged into position using support points.

When the position of the vessel path line is accepted, continue by clicking the arrow below pathline (Supplemental Supplemental figure **10**, red box)



Supplemental figure 10 *Indicating and segmenting target vessel. The proximal point is marked by red circles while the distal point is marked by blue circles. Proximal and distal points are both placed at anatomical landmarks, at the ostium proximally and at the off-spring of a side branch distally. The path line is fixated by ticking the arrow below pathline (red box)*

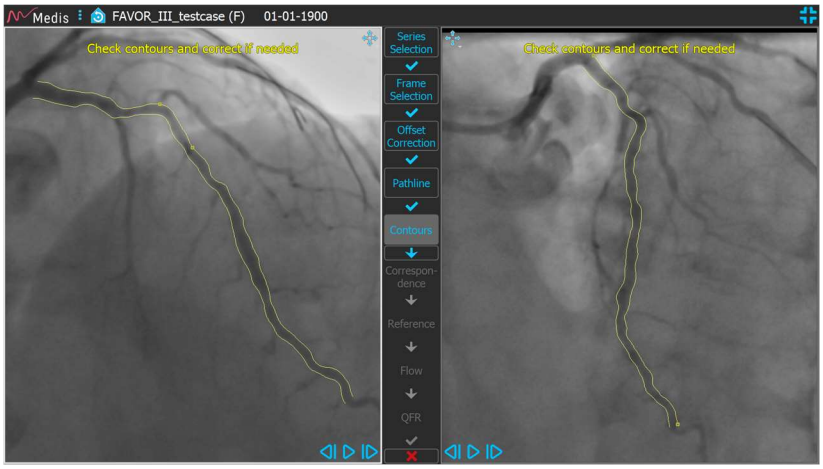
2.8 Lumen contouring

The yellow contour lines (Supplemental Supplemental figure **11**) are adjusted to follow the lumen border.

Pay special attention to:

- Erroneous indication of non-existing narrowing in the proximal and distal ends
- Contouring of the target lesion(s) – correct only when clearly necessary
- Side branches and overlap
- Ensure that contours are correct in all analysed segments – also non-target segments as it influences the reference diameter function and the QFR calculation

The lines are corrected by dragging them into position with correction points. If a correction needs to be reverted, right-click the correction point and it will be deleted.



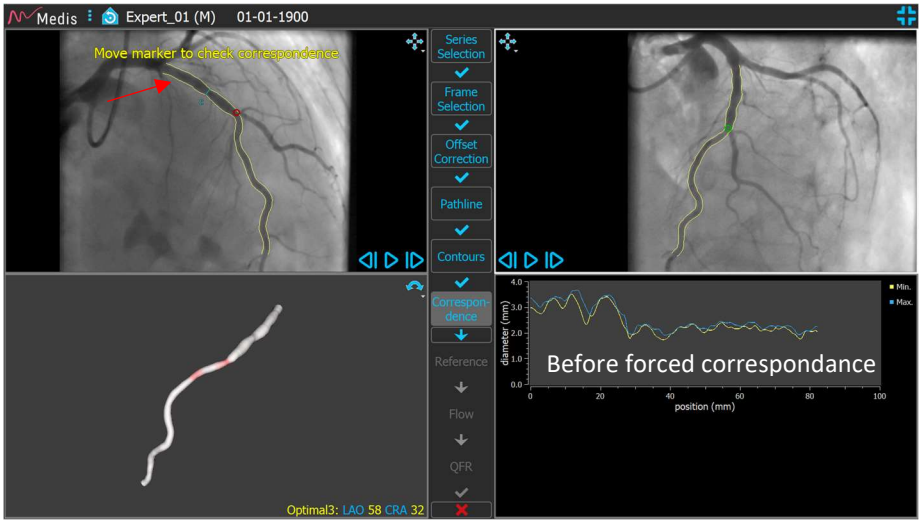
Supplemental figure 11 *Lumen contouring. The yellow lines indicate the lumen border and can be corrected by dragging the lines into position (note the placed correction points; small yellow dots on contour lines). For improved view double click on the panel you want maximize.*

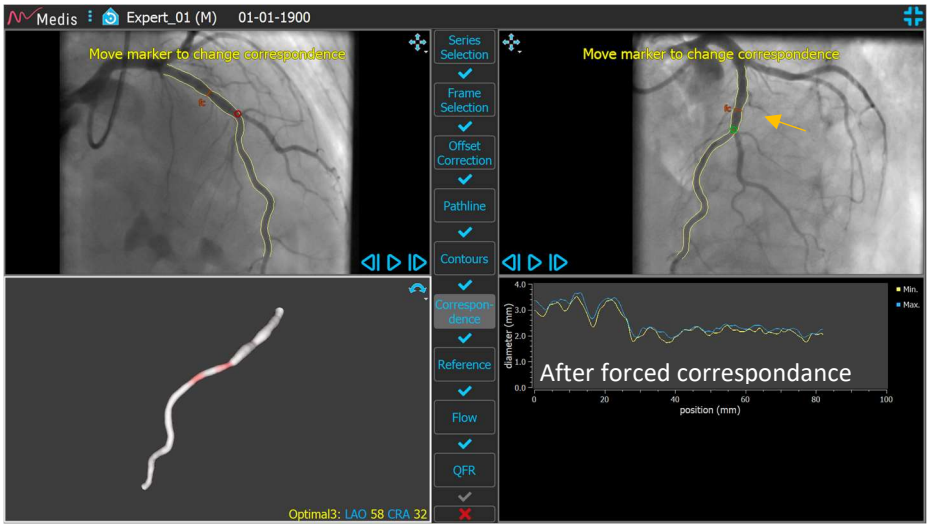
2.9 Forced correspondence

Correspondence of the two projections is performed automatically by making use of the start-, end-, and offset points. Manual “forced corresponding” points can be added to improve analysis if correspondence is suboptimal e.g. due to foreshortening. To evaluate the quality of the correspondence, drag the c-line through the vessel to see if the two contours correspond at the lesion and clear anatomical landmarks. Forced correspondence ensure that the views correspond at the indicated point. Forced correspondence is required when the graphs for the two minimal and maximal diameters in lower right panel are shifted sideways instead of being almost superimposed (Supplemental Supplemental figure 12). Identify an anatomical landmark **easily**

identified in both projections (i.e. the narrowest part of the focal lesion or the off-spring of a side branch)

1) Indicate the landmark in left projection by dragging the correspondence line (c-line)
2) Drag the forced correspondence line (fc-line) on the right projection to the same landmark
3) Check if the curves of maximum and minimum diameters are now more aligned
4) *Adjust the markers until finding the best possible correspondence, with good alignment of the two curves, especially near the lesion(s)*





Supplemental figure 12 *Forced corresponding points. The option is selected by dragging the blue c-line (red arrow) and repositioning the marker in the other panel at a corresponding landmark (yellow arrow). This will initiate forced correspondence. Note the improve alignment around the forced correspondance (fc) line as the graph lines have become almost superimposed*

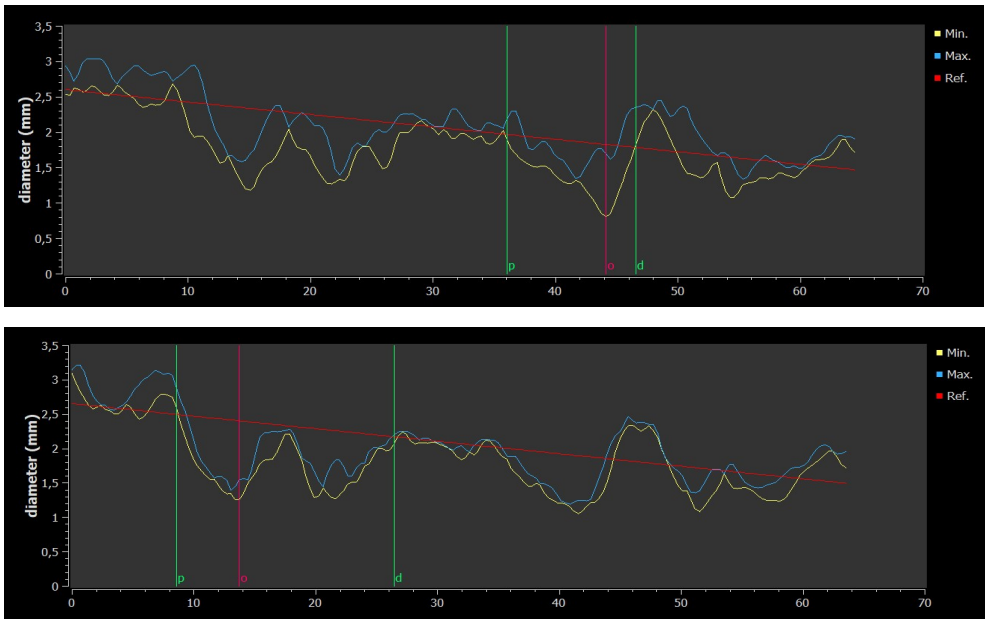
Diameter graph shift

If the diameter graphs are corresponding poorly, please check if former steps are performed correctly.

Poor correspondence of the diameter graphs may be caused by

1. Using two frames that are not in the same phase of the cardiac cycle
2. Error in corresponding the projections / misplaced off-set points
3. Start- or end-point not matching in the two projections. Check if same vessel is analysed
4. Reversed start- and end-point in one of the projections
5. Errors in lumen contouring
6. Foreshortening

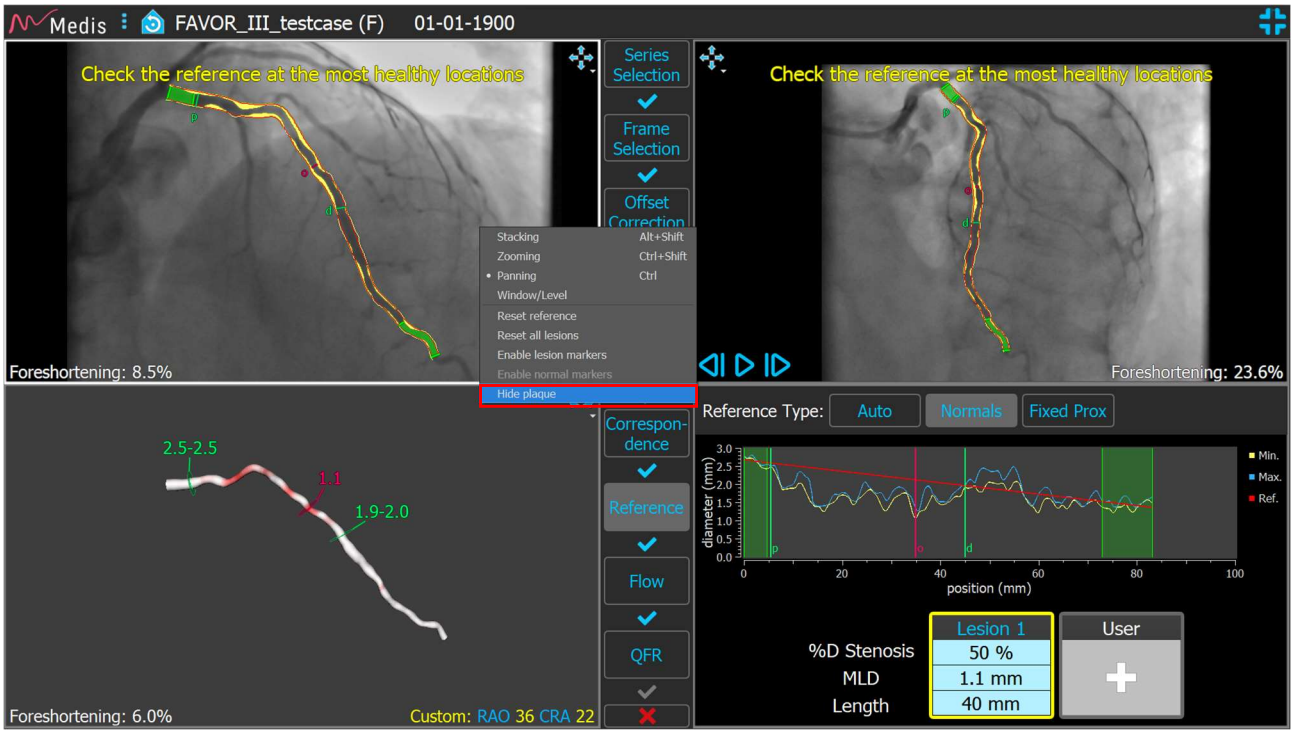
When diameter graphs are not corresponding, consider the abovementioned errors. Return to and evaluate former analysis steps. Please note that some lesions and vessel parts may be elliptical, which will cause the two diameter graphs to differ. Thus, non-corresponding graphs normally have a generalized sideways shift creating a “M or W” effect.



Supplemental figure 13 *A) Poor correspondence of diameter graphs. The stenosis segments are shifted sideways. B) Analysis improved after changes was made in correspondence of the two projections and start-point location. Note that with improved correspondence the MLD and target lesion can change*

2.10 Reference vessel

Parts of the contoured lumen that are narrower than the reference vessel are marked yellow in the angiogram indicating “plaque” (Supplemental Supplemental figure **14**). These yellow markings can be removed by right clicking on the angiogram and then selecting the option *Hide plaque* (Supplemental Supplemental figure **14**, red box).

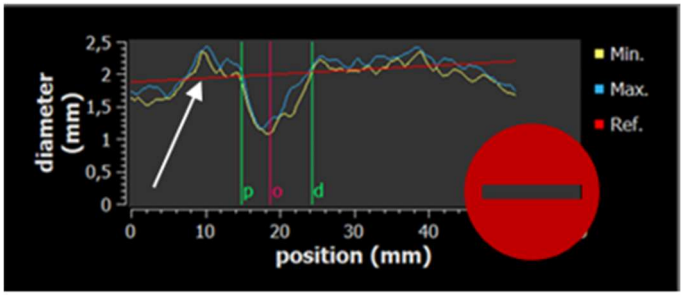


Supplemental figure 14 *Reference vessel (red contours in 2D images). Show/hide yellow plaque (red box)*

2.10.1 Auto

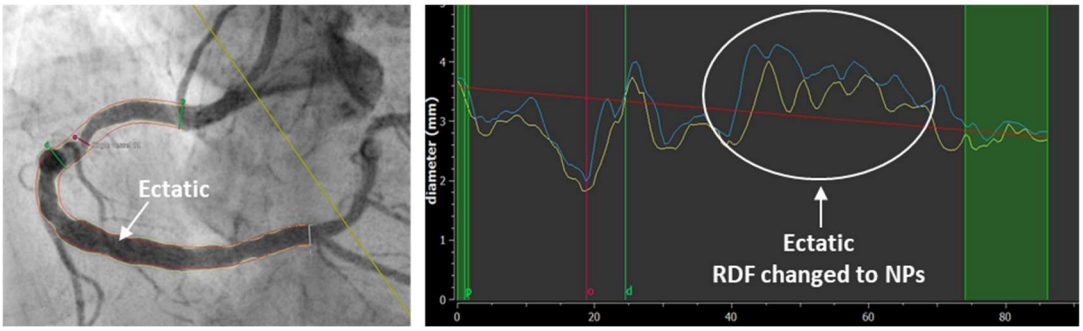
Automatic reference diameter function is used as standard first choice.

The reference function should obey the following:



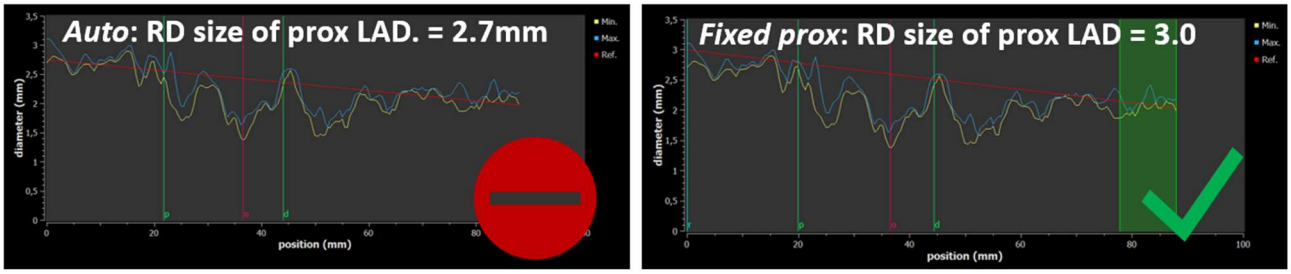
Supplemental figure 15 *The red reference diameter function should always taper. I.e. declining diameter moving to the right. Inverse tapering should always be corrected by adjusting the reference function with “Normals Parts” or “Fixed prox”*

1) **Ensure tapering** of the red diameter reference function in the right direction
2) **Ref. contour should follow healthy parts of the vessel**. Not aneurysmatic or stenotic segments



Supplemental figure 16 *Reference diameter function should not follow ectatic / aneurismatic parts of the vessel.*
RDF = Reference diameter function

3) **Minimal proximal reference diameter size. Gender specific**



Supplemental figure 17 *If the reference size in proximal LAD is small due to diffuse disease(<2.5 mm for women and <3.0 mm for men), a gender specific correction is performed. The fixed proximal diameter in the proximal LAD is set to 3.0-3.5 mm for men and 2.5-3.0 mm for women*

In diffusely diseased vessel, a too small reference size is often generated using the reference function tools. Verify the reference diameter by looking at the diameter graph in the lower right panel. The red line indicates the reference lumen diameter, and the two graphs the minimum and maximum lumen diameters from the 3D reconstruction of the vessel.

The automatic generated reference function is used as the first choice if it follows the criteria.

The reference function should be adjusted with *Normal parts* or *Fixed prox* if the automatic reference function does not fulfil the abovementioned criteria.

2.10.2 Normal parts

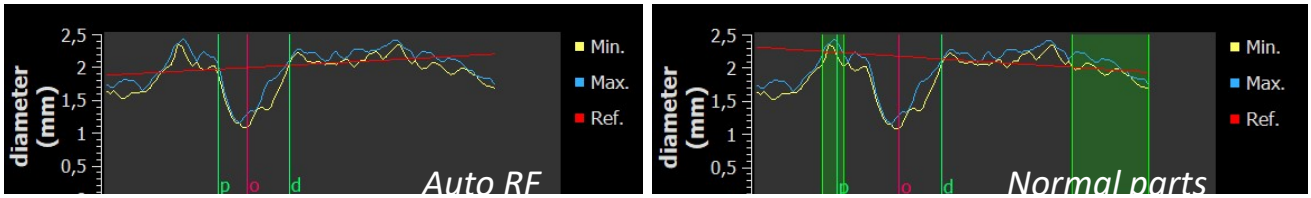
Select “Normals” to edit the reference. Select two healthy areas, using the green “normal parts” areas. The reference function is now calculated as a linear regression based on the two selected “normal parts”. Note the adjusted reference diameter function after using Normal parts as reference strategy (Supplemental Supplemental figure **18**).

When first selecting “Normals”, the default normal parts marked, will be the highest peak before the lesion and the last 10 mm of the analysis – Note that these might not be healthy parts of the vessel and might need to be adjusted.

2.10.3 Selection of normal areas

Selection of normal parts is recommended in vessels with:

- Clearly identifiable healthy segments
- Realistic proximal reference size of the vessel according to gender, body mass index (BMI) and race is not met by the automatic reference diameter function
- In vessels where the automated reference function follows aneurismatic parts of the vessel instead of healthy parts
- Proximal disease with wrongly tapering reference function

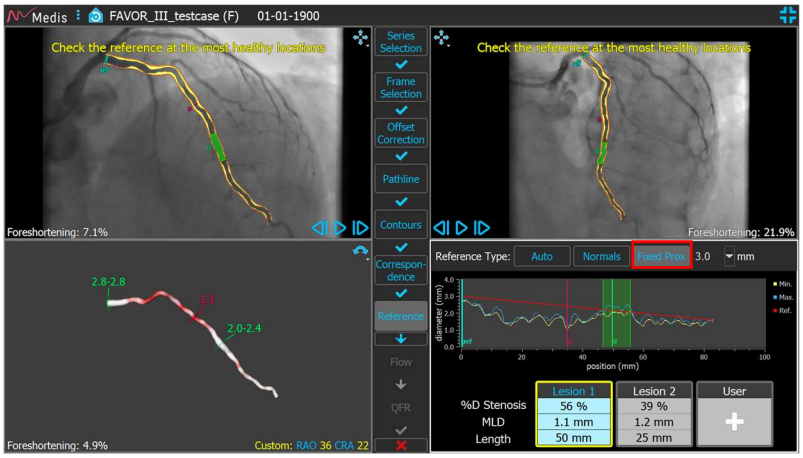


Supplemental figure 18 *Reference diameter function changed from Automatic generated, wrongly tapering reference diameter function (Auto RF) (left panel) to a correct tapering reference diameter function based on Normal parts (right panel)*

2.10.4 Fixed proximal reference

To impute a specific proximal reference size for a segment (give a fixed reference size), use the ”Fixed prox” reference tool. Select “Fixed prox” under “Reference Type” (Supplemental figure 20, red box). A fixed proximal reference size is selected in 0.25 mm intervals from 2 to 5 mm. Place the

proximal reference marker where the vessel should have the indicated value. A healthy distal segment is selected to adjust the slope of the linear function (Supplemental figure 20).



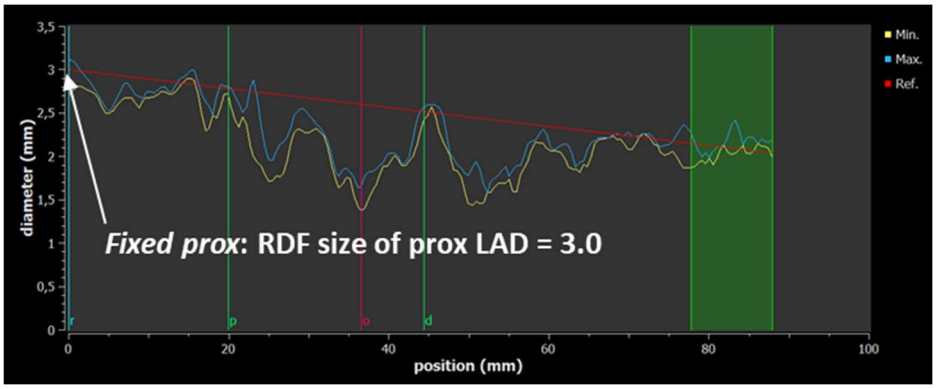
Supplemental figure 19 *Reference diameter function editing using the "Fixed Prox" function (red box). The distal normal area is moved to indicate a healthy distal vessel segment. The "Fixed prox" is placed at the ostium of the vessel.*

A fixed proximal reference is recommended in cases with:

- Proximal LAD reference sizes in Caucasians <2.5 mm for women and <3.0 mm for men if the reference cannot be corrected sufficiently using "Normal parts"
- Diffuse LAD disease with segments in mid/distal vessel parts exceeding the proximal reference size that cannot be corrected by using "Normal parts"

The fixed proximal diameter in the proximal LAD is set to 3.0-3.5 mm for men and 2.5-3.0 mm for women depending on

1. The size of other healthy vessels
2. The patient characteristics (age, BMI, race)



Supplemental figure 20 *Reference diameter function (RDF) based on linear regression from fixed proximal size (in this case 3.0 mm) to distal healthy segment*

NOTE: It is more **important to have a correct reference function by manual adjustments** than preserving a wrongly automatic generated reference function to aim for reduced variability

2.11 Fixed flow QFR computation

1. Enter *Vessel segment*: "Left main/LAD" or "Other" coronary

   A Fixed Flow QFR values will now be calculated

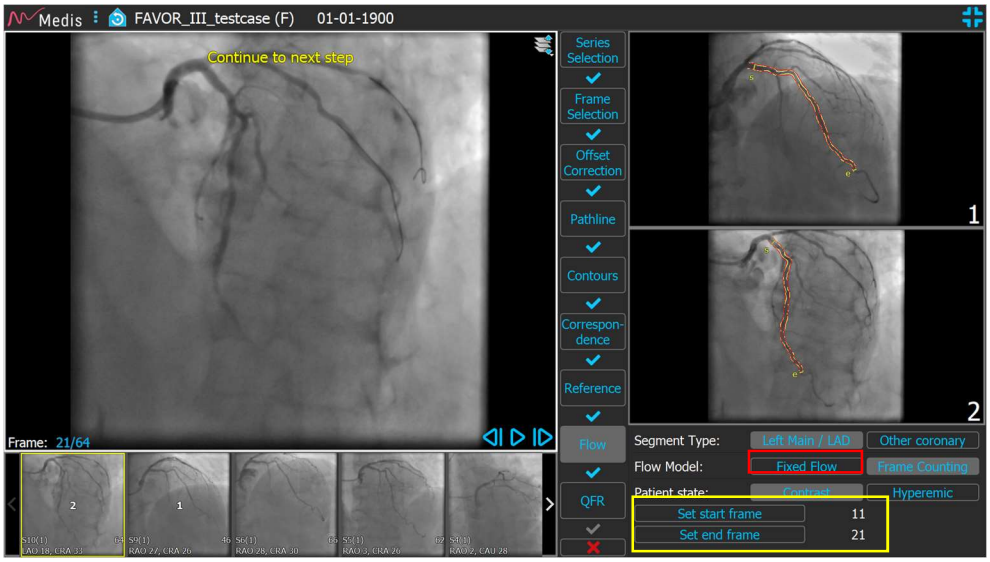
2.12 Frame count based QFR computation

1. Indicate frame count
2. Frame count (Supplemental Supplemental figure **21**, yellow box)
   a. Choose projection for frame count, either
      i. The left panel run
      ii. The right panel run
      iii. Another projection

      Suitable projections for frame count have 1) good contrast filling, 2) a constant contrast flow/speed, 3) a frame rate of at least 12.5 frames/sec, and 4) proximal and distal analysed segments in plane.
   b. *Start frame* is the frame in which the contrast front arrives at the proximal path line point (s-marker)
   c. *End frame* is the frame in which the contrast front arrives at the distal path line point (e-marker). If the proximal or distal point is reached by the contrast between two

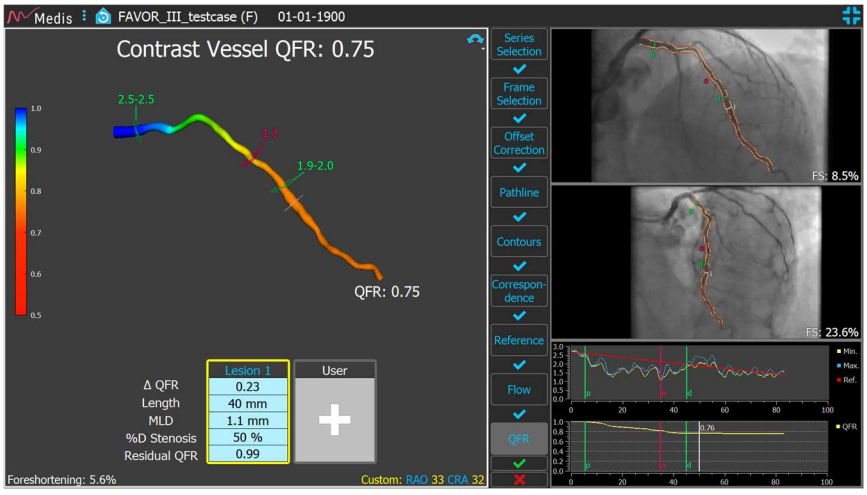
frames, the proximal and the distal vessel delimiters (s- and e- markers) are relocated, to get a better correspondence between the selected start or end frame and the contrast position

PLEASE NOTE that projections where the contrast seems to appear at once in most of the analysed segment are not appropriate for frame count.



Supplemental figure 21 *Red box: indicate vessel for fixed flow QFR computation. Yellow box: Frame count QFR analysis by indicating the start- and end frame for contrast flow through the segmented vessel part. Frames are identified by scrolling through the selected run in lower left image panel.*

After frame count is performed click on the arrow, the Vessel QFR value is presented



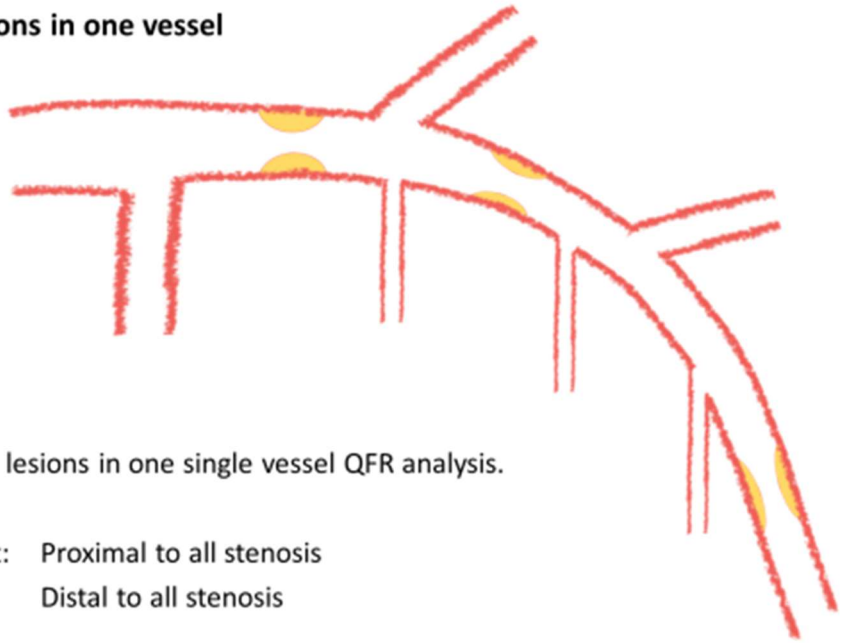
Supplemental figure 22

The following QFR-values are presented in the report after completing the analysis

- Contrast vessel QFR: calculated for the entire contoured segment. Segments proximal to the contoured segment are considered non-stenotic
  Vessel QFR is the value used for clinical decision making in FAVOR III E-J and should be entered in the eCRF
- ΔQFR: Calculated for the percentage pressure drop over the lesion.
- Index QFR: calculated from the proximal end of the contoured segment to the user defined position of the white index line. The index line can be moved everywhere within the contoured vessel segment.

2.13 Serial lesions

Serial lesions in one vessel



Include all lesions in one single vessel QFR analysis.

Start point: Proximal to all stenosis
End point: Distal to all stenosis

NB: Only include patients/vessels if revascularization is possible by either PCI or CABG and the the physician intends to follow the result of QFR or FFR

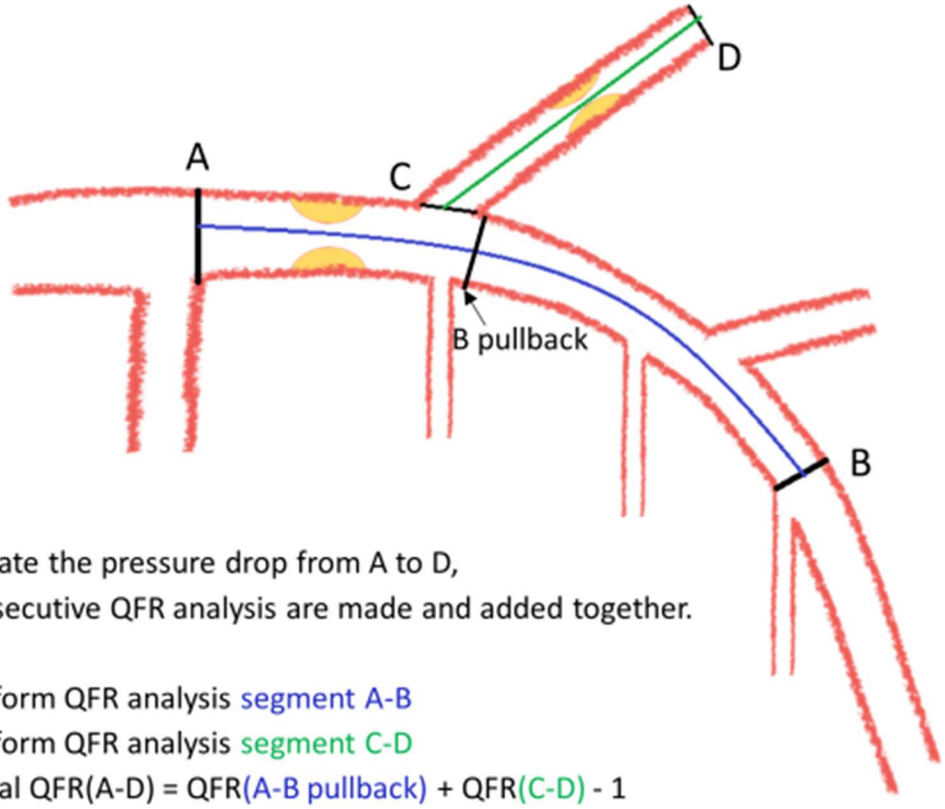
If vessel QFR ≤ 0.80 revascularization is indicated
If vessel QFR > 0.80 revascularization is deferred

Treatment

- Specific treatment decisions are left to the operator's discretion
- Technical aspects of revascularization should always be considered when choosing which lesions to treat
- We suggest the operator to use the QFR pullback in evaluating the severity of the individual lesions

Supplemental figure 23

2.1 Serial lesions in main vessel and side branch



To calculate the pressure drop from A to D,
two consecutive QFR analysis are made and added together.

1) Perform QFR analysis segment A-B
2) Perform QFR analysis segment C-D
3) Serial QFR(A-D) = QFR(A-B pullback) + QFR(C-D) - 1

If serial QFR ≤ 0.80 revascularization is indicated
If serial QFR > 0.80 revascularization is deferred

Example:
QFR prox. LAD (A-B pullback) = 0.85
QFR D1 (C-D) = 0.88
Serial QFR (prox. LAD and D1, A-D) = 0.85 + 0.88 - 1= 0.73 → TREAT

Treatment: See suggestions above (*"Serial lesions in one vessel"*)

Supplemental figure 24

2.14 Left main coronary artery and left anterior descendent stenosis

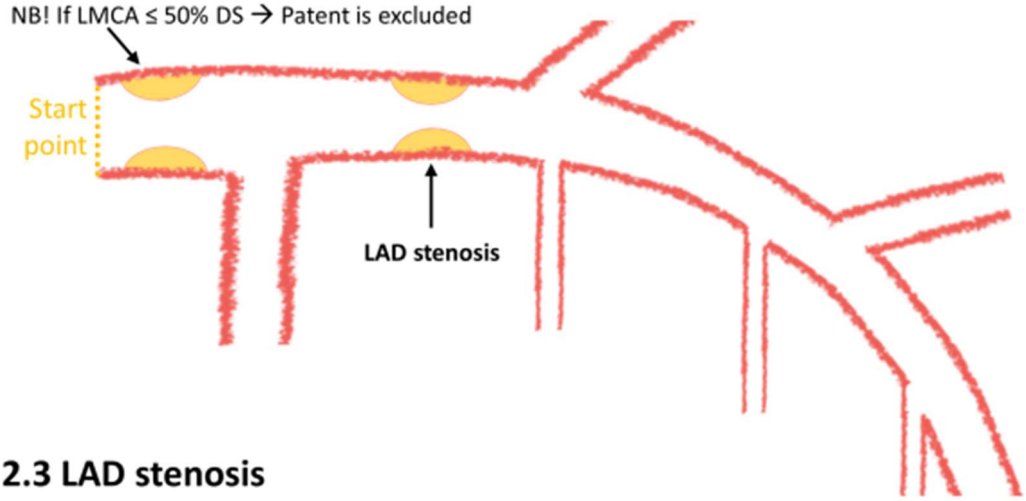
2.2 LMCA and LAD stenosis

If a stenosis is present both in the LM and LAD it is important to start the analysis as proximal as possible to include both stenoses

Be aware of a diameter step down in reference function of >1mm across the LM bifurcation

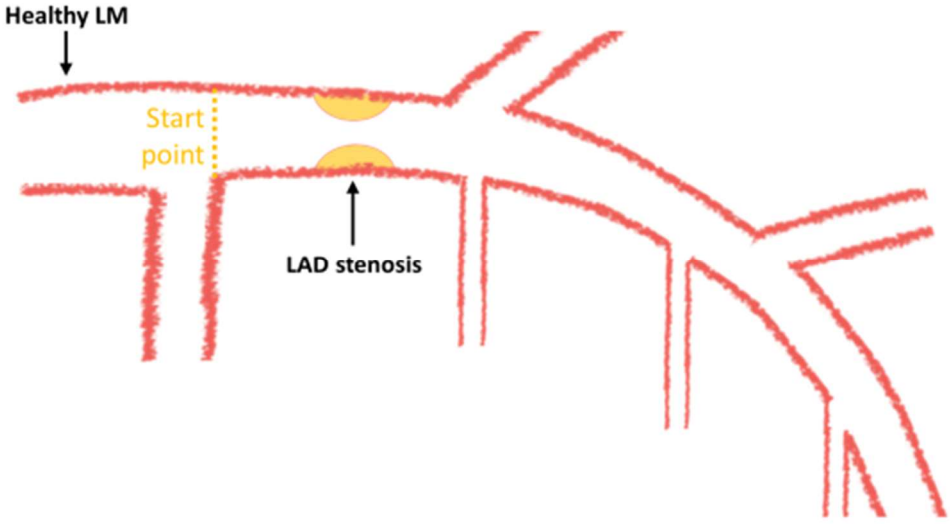
LMCA stenosis < 50 %

NB! If LMCA ≤ 50% DS → Patent is excluded



2.3 LAD stenosis

If a stenosis is present in LAD and LMCA is healthy, the proximal point should be placed in the LAD/CX ostium to exclude the larger diameter in the LMCA



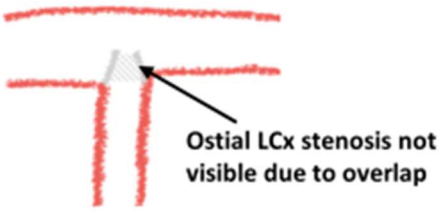
Supplemental figure 25

2.15 Ostial LCx stenosis

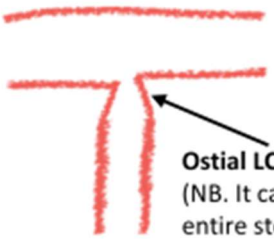
Ostial LCx stenosis is easily missed due to overlap or due to poor contrast filling.

NB: It may be difficult to assess the entire ostial stenosis

To be able to decide if the LCx stenosis is healthy, it is recommended to do a regular spider view to visualize the LAD/LCx bifurcation.



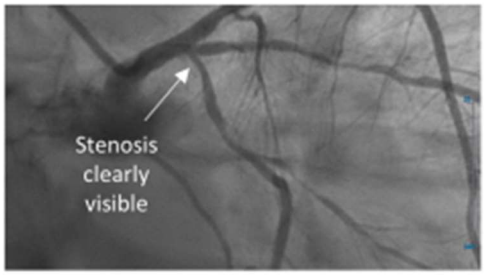
Ostial LCx stenosis not visible due to overlap

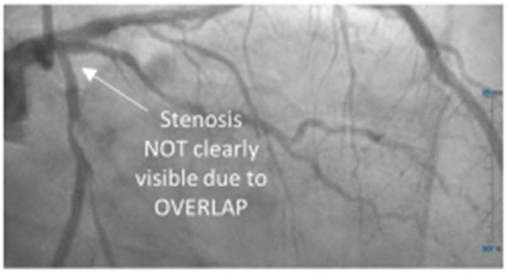


Ostial LCx stenosis visible
(NB. It can be difficult to tell if the entire stenosis length is visible)

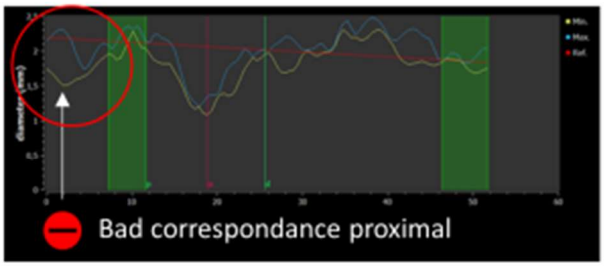
If a stenosis in the Cx ostium is present

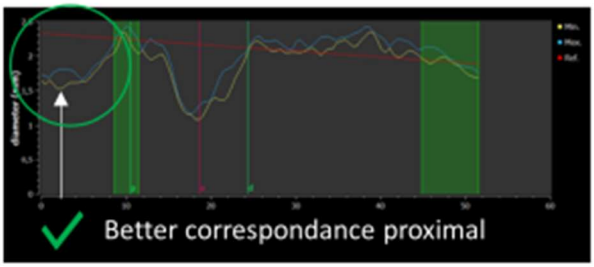
1) Do not randomize until two good projections are obtained, visualizing the stenosis in its entire length





2) Always start QFR analysis at the takeoff of LCx. Look at the diameter graphs to see if the stenosis length and severity in the two views are matching



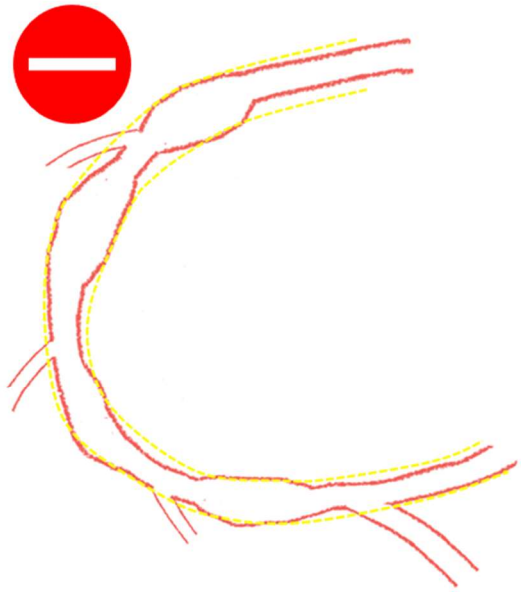


3) If it is not possible to avoid excessive overlap of the stenosis, do not randomize.
If the patient by mistake was already randomized, FFR should be measured (cross over)

Supplemental figure 26

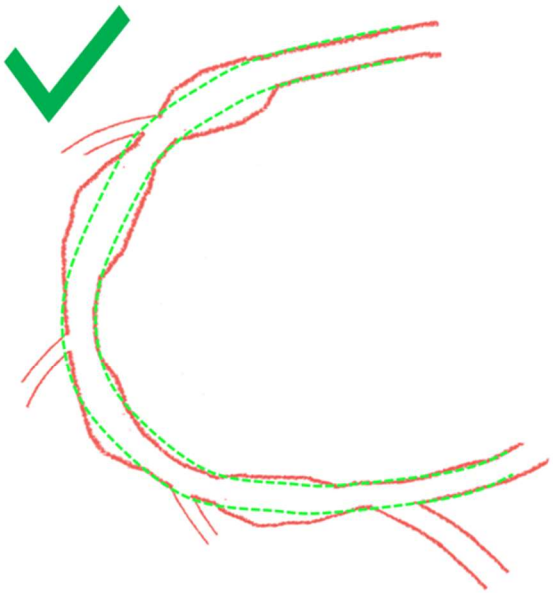
2.16 Aneurysmatic vessels

Aneurismatic vessels can cause problems when creating the reference function
It is often necessary to use *Normal parts* or *Fixed prox* to fit the reference vessel to either apparent normal parts of the vessel or a realistic size according to sex, BMI and race.



Reference function (false)

Do not fit the reference function to aneurismatic / ectatic parts of the vessel as the reference size will be to big and false narrowings are created where the vessel is actually healthy.



Reference function (true)

Clearly visible normal parts:
Use *Normal parts* to create a reference function, fitting it to the healthy parts of the vessel

No visible healthy segments proximally:
Use *Fixed prox* to create a realistic sizing of the vessel proximally.

RCA should normally not exceed 4mm.
Sizing of LAD should be decided on the basis of the size of LM and LCx; sizing of LCx on the basis of the size of LM and LAD.

Supplemental figure 27