



Fractional flow reserve guided percutaneous coronary intervention optimization directed by high-definition intravascular ultrasound versus standard of care: Rationale and study design of the prospective randomized FFR-REACT trial

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Background Post percutaneous coronary intervention (PCI) fractional flow reserve (FFR) is a significant predictor of major adverse cardiac events (MACE). The rationale for low post procedural FFR values often remains elusive based on angiographic findings alone, warranting further assessment using an FFR pullback or additional intravascular imaging. It is currently unknown if additional interventions intended to improve the PCI, decrease MACE rates.

Study design The FFR REACT trial is a prospective, single-center randomized controlled trial in which 290 patients with a post PCI FFR <0.90 will be randomized (1:1) to either standard of care (no additional intervention) or intravascular ultrasound (IVUS)-directed optimization of the FFR (treatment arm). Eligible patients are those treated with angiographically successful PCI for (un)stable angina or non-ST elevation myocardial infarction (MI). Assuming 45% of patients will have a post PCI FFR <0.90, approximately 640 patients undergoing PCI will need to be enrolled. Patients with a post PCI FFR \geq 0.90 will be enrolled in a prospective registry. The primary end point is defined as a composite of cardiac death, target vessel MI and clinically driven target vessel revascularisation (target vessel failure) at 1 year. Secondary end points will consist of individual components of the primary end point, procedural success, stent thrombosis and correlations on clinical outcome, changes in post PCI Pd/Pa and FFR and IVUS derived dimensions. All patients will be followed for 3 years.

Conclusion The FFR-REACT trial is designed to explore the potential benefit of HD-IVUS-guided PCI optimization in patients with a post PCI FFR <0.90 (Dutch trial register: NTR6711). (Am Heart J 2019;213:66-72.)

Background

Accurate angiographic assessment of the severity and hemodynamic importance of coronary artery stenosis can be challenging and proved to be frequently unreliable.^{1,2} Previous studies demonstrated that routine pre-

procedural fractional flow reserve (FFR) in patients with multivessel coronary artery disease undergoing percutaneous coronary intervention (PCI) with drug-eluting stents significantly reduces the rate of the composite end point of death, nonfatal myocardial infarction (MI), and repeat revascularization at 1 year as compared to angiographic guided PCI.³ More recently, FFR after stenting proved to be a strong and independent predictor of major adverse cardiac events (MACE) at 1 year.⁴ A contemporary meta-analysis on the clinical impact of post PCI FFR values showed that an FFR <0.90 is associated with an increased risk of target vessel revascularization (TVR).⁵

A number of factors might cause a post-PCI pressure drop over a treated segment including residual disease in the proximal or distal segment, a geographically

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 RCT# NTR6711.

Submitted December 3, 2018; accepted March 27, 2019.

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0002-8703

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<https://doi.org/10.1016/j.ahj.2019.03.017>

misplaced stent, stent underexpansion, malapposition, plaque protrusion, edge dissection and plaque shift.^{6,7} While these findings are not always readily apparent on coronary angiography alone, high definition (HD) intravascular ultrasound (IVUS) demonstrated to be a powerful tool to detect potential causes for low FFR post stenting. More specifically, these issues proved to be more frequently present in patients with low as compared to high post PCI FFR.⁷ The latter adds to the substantial body of evidence on the benefit of IVUS-guided PCI as compared to angiography-guided PCI in improving long-term outcomes.^{8,9}

While post PCI FFR is at present only rarely performed in routine clinical practice, an FFR after stenting <0.90 proved to be present in approximately 45% of the patients.¹⁰ Additionally, IVUS was able to detect problems of intraluminal obstruction in up to 84% of those cases.⁷ It is currently unknown if additional interventions with the intent to optimize post procedure FFR improve patient outcome.

The rationale and design of the FFR REACT trial was based on a simple and fast way of measuring post PCI FFR using a small microcatheter over the previously used coronary guidewire. Although a substantial body of evidence exists towards a pressure wire based post PCI FFR of 0.90 to predict MACE, at the moment no clear cut-off for post PCI FFR value as measured with a microcatheter to predict events has been established.^{4,5} The potential findings and clinical implications of this study might open the door to a more frequent use of post PCI physiological assessment with the intention to further reduce the risk of future MACE with the help of IVUS.

Study aims

To assess if FFR guided PCI optimization directed by HD-IVUS in patients with an increased risk for MACE (post-PCI FFR below 0.90) will improve clinical outcome and reduce target vessel failure, a composite of cardiac death, target-vessel myocardial infarction and clinically driven TVR at 1 year.

Study design and methods

The FFR REACT trial is a prospective, investigator initiated single-center randomized controlled trial in which 290 patients with a post PCI FFR <0.90 will be randomized (1:1) to either standard of care (no additional intervention, control arm) or IVUS-directed optimization of the FFR (treatment arm). Eligible patients are those treated with angiographically successful PCI for stable or unstable angina or a non-ST elevation myocardial infarction (MI). Patients with a post PCI FFR \geq 0.90 will be enrolled in a prospective registry. All patients will be included in the Erasmus Medical Center (MC), the Netherlands, and followed for up to 3 years after PCI.

The study flowchart is depicted in [Figure 1](#). The study protocol was approved by our local ethical committee on the 26th of October 2017 (MEC-2017-489). Financial support is provided by ACIST Medical Systems, Inc.. The Erasmus Medical Center is totally independent from ACIST Medical Systems, Inc. regarding the conduct of the study and the medical treatment of patients and study subjects. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents. The study is in accordance with Good Clinical Practices (GCP), ISO14155 and with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013). The study is registered at the Dutch trial register: NTR6711.

Study population

With the assumption that post PCI FFR will be <0.90 in 45% of the patients, an estimated number of 640 patients will be enrolled in order to be able to randomize 290 patients. Detailed in- and exclusion criteria are depicted in [Table I](#). Each patient must sign and date the approved informed consent form after the study has been thoroughly explained.

Study endpoints. The primary endpoint will be assessed at 1-year follow-up and is defined as target vessel failure, a composite of cardiac death, target vessel Q-wave or non-Q wave MI and clinically driven TVR.

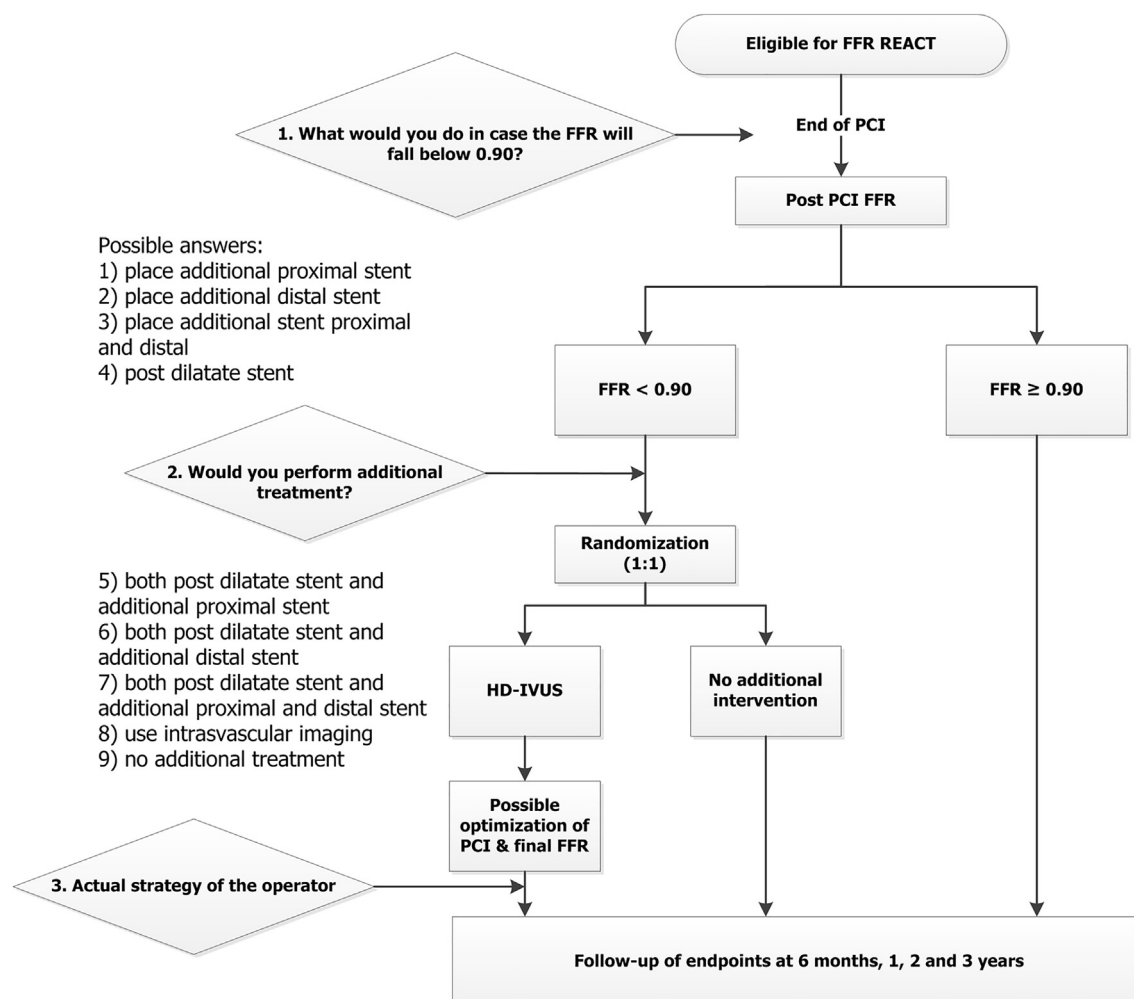
Secondary endpoints consist of the individual components of the primary endpoint at 6 months, 1, 2 and 3 years, along with other clinical endpoints: all-cause death, any coronary revascularization, non-fatal MI, stent thrombosis (according the ARC criteria¹¹), stroke, periprocedural complications and acute kidney injury. Procedural characteristics such as contrast medium usage, number of stents, total stent length and procedural time will be compared between groups. Additionally, correlations between changes in post procedural FFR and Pd/Pa and luminal dimensions on IVUS due to potential optimization will be assessed. [Table II](#) depicts both primary and secondary endpoints.

Finally, operator PCI strategy will be assessed at multiple time points.

Blinding and randomization

Patient randomization will be initiated through a web-based application (ALEA, Formvision, Utrecht, The Netherlands). In order to prevent a disturbed allocation between treatment arms, a block randomization will be used, varying between four and six in size. Subjects will be blinded to the post procedural FFR and subsequent treatment allocation. In order to monitor the level of blinding, the perceived treatment allocation will be inquired at the 1 year clinical follow-up visit. Furthermore, the procedure report will not contain any details

Figure 1



Study flow chart including the operator strategy questionnaire. The first two rhombuses contain the operator questions. The third rhombus is not asked but filled in according to the additional intervention. Nine possible answers are provided. FFR is fractional flow reserve, HD-IVUS is high definition intravascular ultrasound and PCI is percutaneous coronary intervention.

about post procedural FFR and subsequent treatment arm allocation. More specifically, no information will be provided on the measured vessel, post PCI FFR value and potential randomization allocation in the procedure report or discharge letter. Event adjudication at the set time points of 6 months, 1, 2 and 3 years will be performed by an independent critical event committee, not aware of the patients' specific FFR values and/or randomization allocation. Patients will be unblinded at the last follow-up moment (3 years).

Investigational products. Post PCI FFR will be assessed using the Navvus® monorail microcatheter (ACIST Medical Systems, Inc., Eden Prairie, MN) advanced over the previously used coronary guidewire. This monorail microcatheter precludes the need to advance a separate pressure wire along the treatment

segment which will simplify and speed-up post PCI FFR measurements.¹²

Additional imaging in the intervention group will be performed using the multi frequency (40–60 MHz) Kodama® HD-IVUS catheter (ACIST Medical Systems, Inc., Eden Prairie, MN). Both devices are CE marked and are currently used in regular clinical practice.

Study procedures

Routine care. Procedures will be performed according to standard clinical practice: angiography guided PCI and stenting with the use of periprocedural imaging, (either IVUS or OCT) and/or pre-procedural functional assessment (either iFR or FFR) left at the discretion of the operator.¹³ Angiographic success was defined as residual stenosis <30% by visual analysis in the presence of TIMI 3 grade flow. Procedural success will be identified as

Table I. In- and exclusion criteria.

Inclusion criteria

- Age ≥ 18
- Stable- or unstable angina or Non-ST segment elevation myocardial infarction
- Target lesion stenosis $\geq 50\%$ by visual estimation or QCA successfully treated by PCI and stenting
- Written informed consent
- The patient agrees to the follow-up

Exclusion criteria:

- Patients with ST-elevation myocardial infarction within the last 72 hours.
- Target vessel distal reference diameter < 2.25 mm
- Cardiogenic shock or severe hemodynamic instability
- Unsuccessful stenting
- PCI without stenting
- Inability to perform post procedure FFR
- The patient has other medical illnesses (i.e., cancer) that may cause the patient to be non-compliant with the protocol, confound the data interpretation or are associated with limited life expectancy (i.e., less than 1 year)

QCA is quantitative coronary angiography, FFR is fractional flow reserve, PCI is percutaneous coronary intervention.

angiographic success in the absence of periprocedural MI. Dual antiplatelet therapy (including aspirin and a P2Y12 inhibitor) will be prescribed for at least 6 months to all patients consisting of clopidogrel in case of stable angina, or prasugrel/ticagrelor for at least 12 months in case of an acute coronary syndrome.¹⁴

Study measurements and interventions, if applicable, will only be performed after confirmation of angiographic success of the PCI and after administration of intracoronary nitrates.

Post procedural indices: Pd/Pa and FFR

Pd/Pa is defined as a ratio, where Pd is the distal coronary pressure derived from the tip of the Navvus® catheter and Pa stands for proximal coronary pressure (measured at the tip of the guiding system). The two values are recorded simultaneously during resting conditions. FFR is defined as mean distal coronary artery pressure divided by mean aortic pressure during maximum hyperemia achieved by continuous intravenous infusion of adenosine at a rate of 140 $\mu\text{g/kg/min}$ through an antecubital vein.

Both indices will be measured approximately 20 mm from the most distal stent edge. A pullback will be performed to obtain pressure gradients on the distal and proximal stent edges. Drift will be checked at the end of each pullback. Measurements with a drift value above 0.02 will be repeated a second time.¹⁵ All vessels with a drift value above 0.05 during the second attempt will be excluded from the study. All pressure tracing will be stored in a dedicated database for off-line analyses. All tracings will be analyzed for ventricularization, dampening and drift by our academic corelab.

Table II. Primary and secondary endpoints of the FFR-REACT trial.

Primary endpoints

Target vessel failure*

Secondary endpoints

In hospital

- Procedural characteristics e.g. contrast medium usage, no. of stents, total stent length and procedural time
- Major access site bleeding
- Periprocedural MI
- Acute kidney injury
- Periprocedural complications
- Change in post-procedural FFR after optimization therapy
- Change in post-procedural Pd/Pa and FFR after optimization therapy
- Correlation of the IVUS parameters and proximal VS stent VS distal FFR drop in categories of 0.05.
- Correlation of FFR segmental drop and minimum luminal area on IVUS and 3D QCA
- Correlation of Pd/Pa and FFR, both dependent and independent of IVUS findings
- Operators PCI strategy change dependent on the information received from either FFR or IVUS

6 months and longer follow-up

- The individual components of the primary endpoint (cardiac death, target vessel MI, target vessel revascularization)
- All-cause mortality
- Cardiovascular mortality
- Prehospitalization for heart failure
- Target lesion revascularization
- Any coronary revascularization
- Non-fatal myocardial infarction
- Stent thrombosis
- Periprocedural MI
- Stroke
- Kidney injury
- Correlation of Pd/Pa, FFR and the primary endpoints components

*A composite of cardiac death, target-vessel myocardial infarction and clinically driven TVR at 1 year. MI is myocardial infarction, FFR is fractional flow reserve, QCA is quantitative coronary angiography, PCI is percutaneous coronary intervention and IVUS is intravascular ultrasound.

Intravascular ultrasound (Intervention Group)

IVUS-directed FFR optimization will be guided by an automated pullback with a 40–60 MHz HD-IVUS catheter at a speed of 2.5 mm/sec (24 frames/mm) starting approximately 20 mm distal from the most distal stent edge. Images will be analyzed online in order to identify potential reasons for the low post-procedural FFR. Treatment of potential anomalies will be performed through a guidance protocol initiated in order to standardize potential further treatment (Table III) and will be based on the patient's characteristics, angiographic anatomy, distal and interval Pd/Pa and FFR and luminal IVUS dimensions. Final resting Pd/Pa and FFR will be measured at the end of the procedure if additional treatment was performed along with an IVUS pullback assessing the final treatment result.

All IVUS pullbacks will be analyzed offline using QCU-CMS (Leiden University MC, LKEB, Division of Image Processing, version 4.69). Offline analysis will be performed by three independent IVUS experts within our academic corelab. All IVUS pullback will be divided in

Table III. stepwise protocol after high definition IVUS.**Malapposition**

- When malapposition is present in more than 1 frame post dilatation with a balloon ≥ 0.25 mm larger than the stent balloon is recommended. Malapposition due to a non-symmetrical vessel should not be additionally dilated.

Edge dissection

- Additional stenting is recommended in case a distal edge dissection of more than 90 degrees is encountered. In case of a proximal edge dissection additional stenting is left at the discretion of the operator.

Underexpansion

- Underexpansion can be measured with the help of a simple calculating tool, based on the MUSIC criteria.¹⁶ This will be done ad hoc. When the criteria of underexpansion are met, additional dilatation should be performed preferably by using a non-compliant balloon with a diameter ≥ 0.25 mm larger than the largest balloon used.

Residual lesion.¹⁷⁻²¹

- Measure reference vessel diameter (RVD) distally of the potential residual lesion. A residual lesion is present in case:
 - o RVD is 2,5–3,0 mm and lesion MLA is $<2,5$ mm²
 - o RVD is 3,0–3,5 mm and lesion MLA is $<3,0$ mm²
 - o RVD is $>3,5$ mm and lesion MLA is $<3,5$ mm²
 - o In case left main lesion: if MLA is $<6,0$ mm².
- Stent size for additional treatment should be based on lesion length and RVD.

To ensure a homogenous treatment approach post IVUS imaging of the treated segment the following guidelines have been designed.

4 segments, a distal segment, in stent, in segment (stent \pm 5 mm) and a proximal segment. The luminal dimensions for all segments will be separately analyzed, including, but not limited to, minimal lumen area, minimal lumen diameter, minimal stent area, mean lumen diameter, mean lumen diameter and maximum plaque burden. Additionally, malapposition, stent edge dissections, underexpansion and residual lesion will be scored according to Table III.

Conservative treatment (Control Group)

No further treatment or IVUS assessment will be performed. Procedures will be concluded based on the confirmation of angiographic success according to routine clinical practice.

Operator strategy. Operator strategy will be assessed at 3 time points during the procedure based on the available information at that stage: following angiography, following first post-PCI FFR in patients with a FFR <0.90 , and following HD-IVUS in subjects who are randomized to the IVUS-directed FFR optimization. In the first question, the operator will be asked what he/she would do in the hypothetical case the FFR would fall below 0.90. Possible answers are: 1) place additional proximal stent 2) place additional distal stent 3) place additional stent proximal and distal 4) post dilatate stent 5) both post dilatate stent and additional proximal stent 6) both post dilatate stent and additional distal stent 7) both post dilatate stent and additional proximal and distal stent 8) perform intravascular imaging 9) no additional treatment. A similar question will be asked directly after the first FFR measurement in

which the answer may be guided by the information provided by the initial post PCI Pd/Pa and FFR (pullback) analyses. The latter two answers will be compared to the actual treatment strategy based on the IVUS pullback (Figure 1). The operator strategy questions were added with the intent to further assess how the use of post PCI FFR and IVUS impact treatment strategies intended to improve PCI results.

Follow-up at 6 months, 1, 2 and 3 years follow-up

All patients will be contacted by letter and/or telephone contact at 6, 24 and 36 months. Before patient contact, survival status will be ascertained by an automated civil registry check. A clinical follow-up with ECG will be scheduled at 12 months. All possible clinical outcomes, including all-cause mortality, cardiac mortality, myocardial infarction (MI), target lesion revascularization (TLR) and TVR, any revascularization, stent thrombosis, stroke and bleeding. Additional information will be retrieved in case of event triggers from local electronic medical records, referring physicians and general practitioner.

Data management and monitoring

Registry of specific endpoints and other details will be managed through OpenClinica, an electronic, online, case report form (CRF) application. Follow-up contacts will be performed by physicians or study nurses not involved in the index procedure and blinded to the final FFR and assigned treatment arm. All data will be anonymized and handled confidentially. The key to the de-anonymization will be safeguarded by the principal investigator.

Event adjudication will be performed by an independent Clinical Events Committee (CEC) unaware of the post PCI FFR and assigned treatment arm. Specific information in the PCI report on the treatment strategy will be masked when submitting documents to the CEC.

Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to GCP and ISO14155, and that the protocol is followed. The trial specific monitoring program is based on the guidelines for on-site monitoring in relationship to the estimated risk of the study (Erasmus MC version 15 November 2012). According to these guidelines a negligible risk-monitoring program was set up for the trial.

Statistical considerations

Statistical analysis of endpoints. Categorical variables will be expressed as percentages and counts. Differences in categorical variables between randomly allocated treatment groups will be evaluated by applying chi-square tests or Fisher's exact tests. Continuous variables will be described as mean \pm one standard deviation, or as median and interquartile range, accordingly. Shapiro-Wilk tests will be applied to evaluate normality of continuous variables. Differences in continuous variables

between randomly allocated treatment groups will then be evaluated by applying Student's t-tests or Mann-Whitney tests. Parametric correlations will be assessed using the Pearson correlation coefficient while the Spearman's rank correlation coefficient is used if the correlation is non-parametric.

The operator strategy questionnaire will be evaluated using the McNemar's test.

Differences between the groups, both randomized and non-randomized, will be measured using the log-rank tests to evaluate differences in event-free survival. A univariate Cox proportional hazard regression will be used to quantify the relation between randomly allocated treatment arms and the incidence of clinical outcomes. In order to provide adjusted hazard ratios (HR), a multivariate Cox regression will be used, with adjustment for age, sex and (as far as allowed given the number of endpoint events) other confounders, possibly including stent size, previous coronary artery intervention, previous MI, multivessel disease, a history of CABG, dyslipidemia, hypertension, smoking, diabetes mellitus and renal function. Competing risks are taken into account for the analysis. Both primary and secondary study parameters are depicted in [Table II](#).

All tests will be 2-tailed, and a p-value of <0.05 will be considered statistically significant. The secondary outcomes are hypothesis generating and therefore no adjustment for multiple testing will be made. We will report estimates of population parameters together with their 95% confidence interval.

Sample size calculation. A recent meta-analysis showed that the incidence of MACE (heterogeneous definitions used) in patients with post PCI FFR <0.90 was 21.4% versus 5% in patients with post PCI FFR ≥ 0.90 .⁴ The average incidence of MACE in the latter study was 11%. The average incidence of MACE (comprised of cardiac death, any MI and TVR) at 1-year post PCI at the Erasmus MC is 10%. When these data are extrapolated, in the Erasmus MC patients with an FFR <0.90 will have an estimated MACE incidence of 19%. The MACE incidence of the patients who will be randomized to optimal care with IVUS is estimated at 7.5%: the average of the incidence at the EMC and the 5% that was found in the meta-analysis.

In summary, to determine the sample size we made the following assumptions/choices:

- Incidence of the study endpoint in those randomized to control/standard care: 19%
- Incidence of the study endpoint in those randomized to IVUS-directed stent placement: 7.5%
- type I error, two-sided: 0.05.
- type II error: 0.2 (i.e. power 80%)
- Allocation ratio $N2/N1 = 1$.

Then a sample size of 272 is required, 136 patients per treatment arm. The sample size should be enlarged by an additional 2–5% due to possible technical failures, lost to

follow-up or unsuitable FFR or IVUS acquisition. Finally 290 patients will be randomized.

Based on results of the FFR-SEARCH registry, 45% of the patients will have a post-procedural FFR <0.90 .¹⁰ This implies that a total of approximately 640 patients need to be enrolled in order find 290 patients with a post PCI FFR <0.90 .

Potential issues of concern

The use of FFR and IVUS in daily clinical practice has been shown to be safe with a low risk of complications. In the FFR SEARCH study, focusing on the predictive value of post-procedural FFR in almost 1000 patients, no complications due to the microcatheter were observed, while in only 2 patients a severe response to the intravenous adenosine occurred.¹⁰ In a study by van der Sijde et al in which the risk of periprocedural complications due to the use of IVUS was assessed in 2476 procedures, 12 complications (0.5%) occurred.²² All of these were self-limiting after retrieval of the imaging catheter and no major adverse events due to the use of IVUS were found. Furthermore, limited evidence is available at the moment on the homogeneity of post PCI FFR values in patients presenting with stable angina as compared to patients with unstable angina or non-ST elevation MI. Additionally, pre PCI FFR assessment using the Navvus microcatheter has proven to significantly overestimated the stenosis severity as compared to pressure wire based FFR measurements.^{23,24} However, this difference was mainly driven by a larger delta in vessels with a small minimal luminal area pre procedure. It is currently unknown if post PCI FFR assessment with the latter two methods will exemplify the same variance and direct extrapolation of the current study to pressure wire based post PCI FFR assessment and optimization is therefore not possible.

The sample size calculation presented the current study is based on a meta-analysis which included a heterogeneous cohort of studies with several outdated registries.⁴ The latter might result in an overestimation of the event rates and thus under-power the study design. Cumulative incidences are expected to diverge between the treatment and control group at longer follow-up if the luminal dimension and FFR can be increased, ensuring a hypothetical under-powered study at one year would be sufficiently powered at two or three years follow-up.^{4,5,25,26}

Study status and timeline

The FFR REACT trial is actively enrolling patients since October 31st, 2017 and has reached the milestone of enrolling 50% of the target population October 2018. At its current pace the study is expected to complete enrolment Q4 2019.

Summary

The FFR REACT study is an investigator initiated prospective, single-center randomized controlled trial

conducted at the Erasmus Medical Center designed to assess if FFR guided PCI optimization directed by IVUS in patients with an increased risk for MACE (post-PCI FFR below 0.90) will decrease target vessel failure at 1 year. Inclusion started in October 2017 and enrolment is expected to be complete in Q4 2019.

Public disclosure and publication policy

Findings of the study will be submitted for publication in a peer-reviewed international cardiology journal. Publication of the data will remain in the hands of the principal investigator and steering committee. The Erasmus MC received an unrestricted institutional grant from ACIST Medical Systems, Inc.

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